World Cancer Research Fund International Systematic Literature Review

The Associations between Food, Nutrition and Physical Activity and the Risk of Colorectal Cancer

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List of Abbreviations used in the CUP SLR

CUP	Continuous Update Project
WCRF/AICR	World Cancer Research Fund/American Institute for Cancer Research
SLR	Systematic Literature Review
RR	Relative Risk
LCI	Lower Limit Confidence Interval
UCI	Upper Limit Confidence Interval
HR	Hazard Ratio
CI	Confidence Interval

Other abbreviations used in Tables

Coeff	coefficient
FFQ	Food Frequency Questionnaire
hr	hour
HvL	highest vs.lowest
M	Men
RFS	Recommended Food Score
SEER	Surveillance Epidemiology End Results
W	women
wk	week
yr	year

List of Abbreviations of cohort study names used in the CUP SLR

AHS	Californian Seventh Day Adventists
Aichi	Aichi Cancer Registry Study
AMORIS	AMORIS study
ARIC	Atherosclerosis Risk in Communities (ARIC)
APC	Anderson Plan Cohort
ATBC	Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study
Basel Study	Basel Switzerland Study
BCDDP, 1973	Breast Cancer Detection Demonstration Project follow-up cohort
BIRNH	Belgian Interuniversity Research on Nutrition and Health
BOCS	Boyd Orr Cohort Study
BRHS	British Regional Heart Study
BUPA	BUPA Study
BWHS	Black Women's Health Study
CARET	Carotene and Retinol Efficacy Trial
Caerphilly	Caerphilly, South Wales, Cohort
CCCJ	Chiba Cancer Cohort, Japan

CCPS	Copenhagen Centre for Prospective Population Studies
CECS	Chinese Elderly Cohort Study
CHA	CHA Detection Project
CHS	Cardiovascular Health Study
CLUE	Campaign Against Cancer and Stroke, Washington County, Maryland
CMHS	California Men's Health Study
CMS	Copenhagen Male Study
CNBSS	Canadian National Breast Screening Study
CNRPCS	China Nationally Representative Prospective Cohort Study
COSM	Cohort of Swedish Men
COSMOS	Continuous Observation of Smoking Subjects
CLUE II	CLUE II
CPS	Cancer Prevention Study
CPRD	Clinical Practice Research Datalink
DCH	Danish Diet, Cancer and Health study
DOM	DOM Cohort
Dutch Cohort	Dutch Male Birth Cohort
E3N	*Étude Épidémiologique auprès des femmes de la Mutuelle Générale de l'Éducation Nationale*
EPIC	European Prospective Investigation into Cancer and Nutrition
ESTHER	Epidemiologische Studie zu Chancen der Verhütung, Früherkennung und optimierten Therapie chronischer Erkrankungen in der älteren Bevölkerung
Finnish Athletes	Cohort of Finnish Male Athletes
FinDrink	FinDrink Study
FMCHS	Finnish Mobile Clinic Health Examination Survey
FHS	Framingham Heart Study
FinRisk	The FinRisk Study
FRAM	Framingham study
French WWII	French Second World War Cohort
GEOL	GEOLynch Cohort Study
HAHS	Harvard Alumni Health Study
HES/ MFHS	Mini-Finland Health Survey
HFSS	Health Food Shoppers Study
HGSC/ Hokkaido	Hokkaido Government Cohort Study
HGS	Harvard Growth Study
HHCS	Hawaiian historical cohort study
HHCCS	Hitachi Health Care Centre Study
HHP	Honolulu Heart Program
Hiroshima Nagasaki	Hiroshima Nagasaki Study
HPFS	Health Professionals Follow-up Study
ICSS	Israel Civil Servant Study

ICRF	Icelandic Cardiovascular Risk Factor Study
IWHS	Iowa Women's Health Study
JACC	Japan Collaborative Cohort Study
Japan-Hawaii	Japan-Hawaii Cancer Study
JPHC	The Japan Public Health Centre-based Prospective Study
JPC	Japanese physicians cohort study
KPMCP	Kaiser Permanente Medical Care Program
KRIS	Kaunas Rotterdam Intervention Study and Multifactorial Ischemic Heart Disease Prevention Study
KIHD	Kuopio Ischaemic Heart Disease Risk Factor Study
KMICC/ KMIC	Korea Medical Insurance Corporation
KMCC	Korean Multi-Centre Cancer Cohort
KNHIC	Korea National Health Insurance Corporation Study
Korea 2004-2013	Korea Cohort 2004-2013
KRIS-MIHDPS	Kaunas Rotterdam Intervention Study (KRIS) and Multifactorial Ischemic Heart Disease Prevention Study (MIHDPS)
LBS	Lutheran Brotherhood Cohort Study
LSS	Life Span Study, atomic bomb survivors, Japan
LWS	Leisure World Study, Laguna Hills Study USA
Leisure World Cohort	Leisure World Cohort
MCCS	The Melbourne Collaborative Cohort Study
MCS	Miyagi Cohort Study
MEC	Multiethnic Cohort Study
MRFIT	The Multiple Risk Factor Intervention Trial
Monica10, Inter99, Health2006	MONICA 10 & Inter99 & Health 2006 Cohort Study
MVS	Male veteran study
MWS	Million Women Study
Nagoya 1983-2000	Nagoya 1983-2003 Cohort Study
NCC	Norwegian Composite Cohort consisting of 3 groups
NCS	Norwegian Counties Study
NHANES	National Health and Nutrition Examination Survey
NHEFS	Nutrition Examination Survey Epidemiology Follow-up Study
NHIS	National Health Interview Survey
NIH-AARP	NIH-AARP Diet and Health Study
NHS	Nurses' Health Study
NHSCD	Norwegian health survey for cardiovascular disease
NHSS	Norwegian national health screening service study
NHUNT	Norwegian HUNT study
NKP	North Karella Project
NLCS	The Netherlands Cohort Study on Diet and Cancer
Norway 1967-78	Norway 1967-1978 Cohort Study
NSC	Norway Study Cohort

NSHDC	Northern Sweden Health and Disease Cohort (NSHDC)
NSPT	Norwegian screening programme for tuberculosis
NYSC	New York State Cohort Study
NYUWHS	New York University Women's Health Study
Oahu	Oahu Cohort Study
Ohsaki/OCS	Ohsaki Cohort Study
OVS	Oxford Vegetarian Study
OCS	Ohsaki Cohort Study
PHS	Physicians Health Study
PLCO	Prostate, Lung, Colorectal, and Ovarian (PLCO) Cancer Screening Study
Reykjavik Study	Reykjavik Study Cohort
SCHS	Singapore Chinese Health Study
SCStudy	Shanghai Cohort Study
SECS	Shizuoka Elderly Cohort Study
SELECT	The Selenium and Vitamin E Cancer Prevention Trial (SELECT)
Shanghai China	Shanghai Study Cohort
SHOW	Smoking Health Study of Wisconsin
Shell Study	Shell Oil Company's Study
SFOSHCIC	Swedish Foundation for Occupational Safety and Health of the Construction Industry (Byggha¨ lsan)
SMHS	Shanghai Men's Health Study
SIMS	Swedish Intergenerational Mortality Study
SMART	Second Manifestations of ARTerial disease (SMART) study
SMC	Swedish Mammography Cohort
STC	Swedish Twin Cohort
SWHS	Shanghai Women's Health Study
SWSC	Sweden mammography screening cohort
TAC	Taiwan Arsenic Cohort, 1985-2000
TCCJ	Japan, Takayama cohort study
THIN	Health Improvement Network (THIN)
VHM&PP	The Vorarlberg Health Monitoring and Prevention Program
VIP	Västerbotten Intervention Project
VITAL	Vitamins And Lifestyle cohort
VCS	Vlaardingen cohort study
WES	Western Electric Company Study
WHI-DI & OS	Women's Health Initiative - Dietary Modification Trial and Observational Study
WS	Whitehall Study
UKWCS	UK Women Cohort Study
WWCCI	WWCCI Trial
WACS	Women's Antioxidant Cardiovascular Study

WLHS	Swedish Women Lifestyle Health Cohort Study
YTC/Chinese Miners	Chinese Miners, High Risk Population Study
Zutphen Study	Zutphen Study Cohort

Background

The main objective of the present systematic literature review is to update the evidence from prospective studies and randomised controlled trials on the association between foods, nutrients, physical activity, body adiposity and the risk of colorectal cancer in men and women.

This SLR does not present conclusions or judgements on the strength of the evidence. The CUP Panel will discuss and judge the evidence presented in this review.

The methods of the SLR are described in details in the protocol for the CUP review on colorectal cancer (in Annex).

Conclusions from the updated evidence for colorectal cancer. 2011 Report
(Based on the 2010 SLR and the Expert Panel discussion)

FOOD, NUTRITION, PHYSICAL ACTIVITY AND CANCERS OF THE COLON AND THE RECTUM 2011

	DECREASES RISK	INCREASES RISK
Convincing	**Physical activity**[1,2] **Foods containing dietary fibre**[3]	**Red meat**[4,5] **Processed meat**[4,6] **Alcoholic drinks (men)**[7] **Body fatness** **Abdominal fatness** **Adult attained height**[8]
Probable	Garlic Milk[9] Calcium[10]	**Alcoholic drinks (women)**[7]
Substantial effect on risk unlikely	None identified	

1 Physical activity of all types: occupational, household, transport and recreational.
2 The Panel judges that the evidence for colon cancer is convincing. No conclusion was drawn for rectal cancer.
3 Includes both foods naturally containing the constituent and foods which have the constituent added. Dietary fibre is contained in plant foods.
4 Although red and processed meats contain iron, the general category of 'foods containing iron' comprises many other foods, including those of plant origin.
5 The term 'red meat' refers to beef, pork, lamb, and goat from domesticated animals.
6 The term 'processed meat' refers to meats preserved by smoking, curing, or salting, or addition of chemical preservatives.
7 The judgements for men and women are different because there are fewer data for women. For colorectal and colon cancers the effect appears stronger in men than in women.
8 Adult attained height is unlikely directly to modify the risk of cancer. It is a marker for genetic, environmental, hormonal, and also nutritional factors affecting growth during the period from preconception to completion of linear growth (see chapter 6.2.13 – Second Expert Report).
9 Milk from cows. Most data are from high-income populations, where calcium can be taken to be a marker for milk/dairy consumption. The Panel judges that a higher intake of dietary calcium is one way in which milk could have a protective effect.
10 The evidence is derived from studies using supplements at a dose of 1200mg/day.

Notes on methods

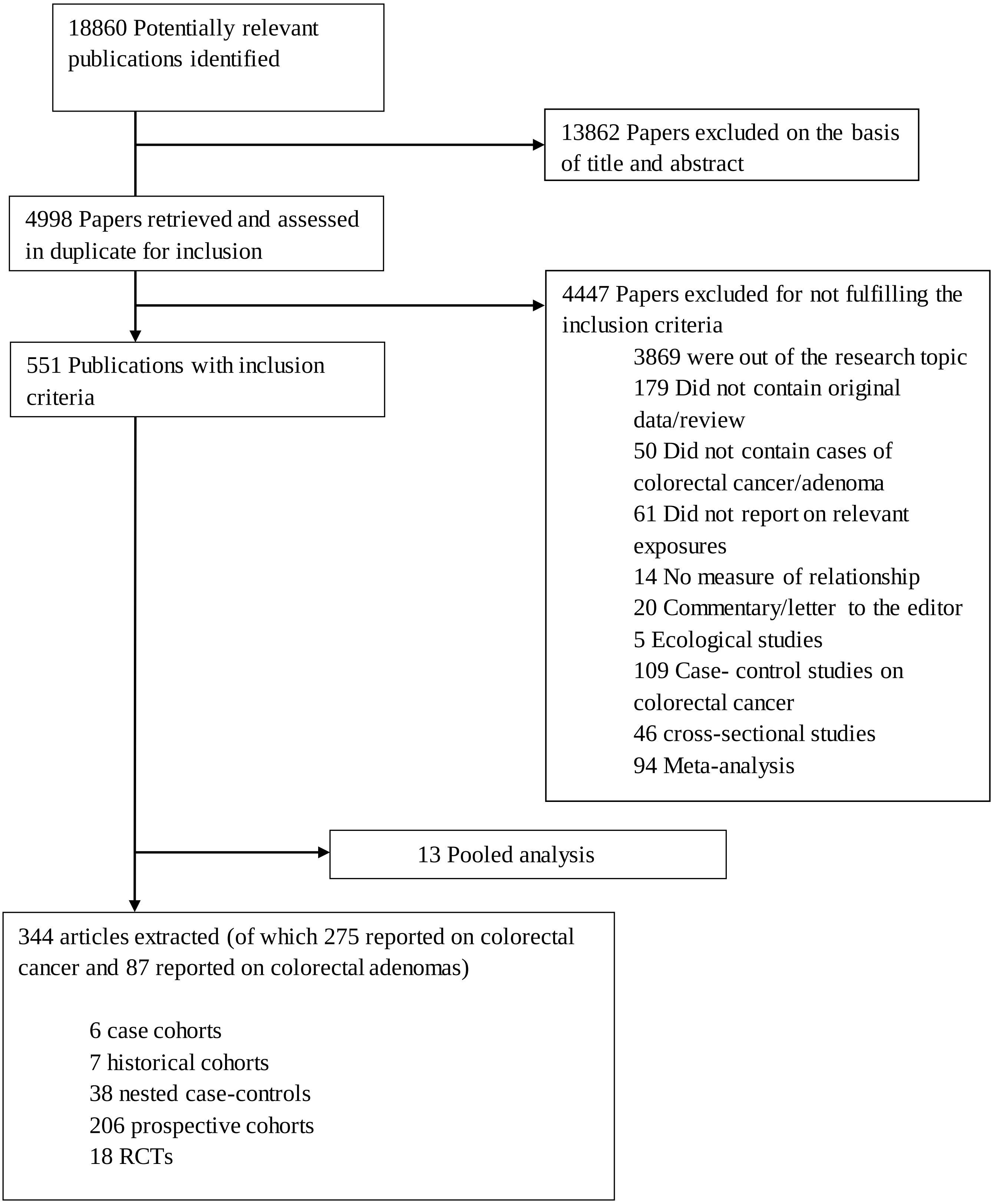
- The article search and WCRF database update for the 2010 CUP Report ended in December 31th 2009. The CUP team at IC updated the search from January 1st 2010 up to April 30th 2015 (See Flowchart).
- 2010 SLR refers to the first update of the 2005 SLR and CUP refers to the current update (2015 SLR).
- Dose-response meta-analysis were updated when at least two new publications with enough data for dose-response meta-analysis were identified during the update and if there were in total five relevant published cohort studies or five randomised controlled trials. The meta-analyses include all relevant published studies.
- Exposures for which the evidence was judged as convincing, probable or limited-suggestive in the Second Expert Report were reviewed even if the number of publications was below the previous figures; in most cases, the new data on these exposures are tabulated and no meta-analyses were conducted.
- Pooled analyses were included with other individual studies in the meta-analysis when possible.
- The term "dose-response meta-analysis" refers to meta-analysis conducted using log-linear dose-response models. Non-linear meta-analysis refers to meta-analysis using log-non-linear models.
- For comparability, the increment units for the dose-response analyses were those used in the meta-analyses in the CUP- SLR conducted for other cancers . However, if most of the identified studies reported in a different unit (servings or times/day instead of g/day) these were used as increment unit, as indicated in the Protocol. The units used may differ from those used in the 2010 SLR.
- The statistical methods to derive missing data are described in the protocol.
- Only summary relative risks estimated with random effect models are shown.
- The interpretation of heterogeneity tests should be cautious when the number of studies is low. Visual inspection of the forest plots and funnel plots is recommended.
- The I^2 statistic describes the proportion of total variation in study estimates that is due to heterogeneity. Low heterogeneity might account for less than 30 per cent of the variability in point estimates, and high heterogeneity for substantially more than 50 per cent. These values are tentative, because the practical impact of heterogeneity in a meta-analysis also depends on the size and direction of effects.
- Highest vs lowest forest plots show the relative risk estimates for the highest vs the reference category in each study. The overall summary estimate was not calculated except for exposures such as physical activity or multivitamin supplement use where dose-response analysis could not be conducted or when the pooling project results could be included in a highest compared to lowest analysis, but not in a dose-response analysis.
- The dose-response forest plots show the relative risk per unit of increase for each study (most often derived by the CUP review team from categorical data). The relative risk is denoted by a box (larger boxes indicate that the study has higher precision, and greater weight). Horizontal lines denote 95% confidence intervals

(CIs). Arrowheads indicate truncations. The diamond at the bottom shows the summary relative risk estimate and corresponding 95% CI. The unit of increase is indicated in each figure and in the summary table for each exposure.

- Dose-response plots showing the RR estimates for each exposure level in the studies are also presented for each reviewed exposure. The relative risks estimates were plotted in the mid-point of each category level (x-axis) and connected through lines.
- Exploratory non-linear dose-response meta-analyses were conducted only when there were five or more studies with three or more categories of exposure – a requirement of the method. Non-linear meta-analyses are not included in the sections for the other exposures. For exposures where the test for non-linearity is non-signification the non-linear figures are not displayed.
- The interpretation of the non-linear dose-response analyses should be mainly based on the shape of the curve and less on the p-value as the number of observations tended to be low, in particular in the extreme levels of exposure.

Continuous Update Project: Results of the search

Flow chart of the search for colorectal cancer – Continuous Update Project
Search period January 1st 2010-April 30th 2015



Cohort studies. Results by exposure

Table 1 Number of relevant publications identified during the 2010 SLR and the 2015 SLR and total number of publications by exposure.

The exposure code is the exposure identification in the database. Only exposures in publications identified during the CUP are shown. A number of publications higher than five does not necessarily mean that there are sufficient studies to conduct analysis for each cancer type.

Exposure Code	Exposure Name	Number of Publications			Total number of publications
		Cohort 2005 SLR	Cohort 2010 SLR	Cohort 2015 SLR	
1.1.1	Mediterranean diet	-	3	3	6
1.3.1	Vegetarianism	2	1	1	4
1.4	Dietary guideline index score	-	1	5	6
1.4	Healthy eating index	-	1	3	4
1.4	Healthy pattern	-	1	5	6
1.4	Individual level dietary patterns	-	6	4	10
2.1.1.4	Wholegrains	2	3	3	8
2.2.2	Total fruits	21	9	4	34
2.2	Total fruits and vegetables	11	6	4	21
2.2.1	Total vegetables	20	9	5	34
2.2.1.2	Cruciferous vegetables	8	3	3	14
2.2.1.3.1	Garlic	2	1	3	6
2.2.1.4	Green leafy vegetables	1	2	1	4
2.2.2.1	Citrus fruits	4	3	2	9
2.3	Legumes	7	4	3	14
2.4	Nuts	1	1	1	3
2.5.1	Red and processed meat	14	9	8	31
2.5.1.2	Processed meat	17	9	6	32
2.5.1.2.2	Fried meat	1	2	1	4
2.5.1.3	Red meat	15	7	7	29
2.5.1.3.1	Beef	4	3	2	9
2.5.1.3.3	Pork and other processed meat	6	3	2	11
2.5.1.4	Poultry	18	3	4	25
2.5.1.5	Liver	5	4	1	10
2.5.2	Fish	26	9	6	41
2.6.1.1	Butter	3	1	1	5
2.6.4	Fructose	2	2	1	5
2.6.4	Sugars (as foods)	-	1	1	2
2.7	Dairy products	11	5	3	19
2.7.1	Milk	17	6	2	25
2.7.2	Cheese	10	2	1	13

Exposure Code	Exposure Name	Number of Publications			Total number of publications
		Cohort 2005 SLR	Cohort 2010 SLR	Cohort 2015 SLR	
2.7.3	Yoghurt	5	2	2	9
3.6.1	Coffee	8	10	4	22
3.6.1	Decaffeinated coffee	-	1	2	3
3.6.2	Tea	7	5	4	16
3.6.2.2	Green tea	2	4	2	8
3.7.1	Alcoholism	7	1	2	10
3.7.1	Total alcoholic drinks	22	10	7	39
3.7.1.1	Beers	9	6	1	16
3.7.1.2	Wines	4	5	1	10
3.7.1.4	Liquor	5	5	1	11
4.1.2.9	Nitrate	-	1	1	2
4.2.5.1	Salt preference	-	1	1	2
4.3.5.4.1	Nitrite	1	1	1	3
4.4.2	Acrylamide	-	2	2	4
4.4.2.7	Bap	-	1	1	2
4.4.2.8	Heterocyclic amines	-	1	1	2
4.4.2.8	Meiqx	-	2	2	4
4.4.2.8	Phip	-	2	1	3
5.1	Carbohydrate	1	4	3	8
5.1.2	Dietary fibre	23	9	1	33
5.1.2.1	Cereal fibre	6	3	3	12
5.1.2.2	Vegetable fibre	7	6	1	14
5.1.2.3	Fruit fibre	7	6	1	14
5.1.4	Sucrose	2	3	1	6
5.1.5	Glycemic index	1	7	3	11
5.1.5	Glycemic load	2	8	3	13
5.2	N-3/n-6-ratio	-	2	1	3
5.2	Serum triglycerides	-	2	1	3
5.2	Total fat	-	7	1	8
5.2	Triglycerides	-	1	1	2
5.2.2	Saturated fatty acids	12	1	1	14
5.2.3	Monounsaturated fatty acids	9	8	1	18
5.2.4	Polyunsaturated fatty acids	6	4	1	11
5.2.4.1	Alpha-linolenic acid	-	2	2	4
5.2.4.1	Alpha-linolenic acid (18:3 n-3)	-	1	2	3
5.2.4.1	Dha (docosahexaenoic acid)	1	4	5	10
5.2.4.1	Docosapentaenoic acid	-	2	5	7
5.2.4.1	Eicosapentaenoic fatty acid	1	3	2	6
5.2.4.1	Linolenic acid	1	3	1	5
5.2.4.1	N-3 fatty acids	1	3	2	6
5.2.4.2	Arachidonic fatty acid (20:4)	-	1	3	4

Exposure Code	Exposure Name	Number of Publications			Total number of publications
		Cohort 2005 SLR	Cohort 2010 SLR	Cohort 2015 SLR	
5.2.4.2	Dihomo-gamma-linoleic	-	1	1	2
5.2.4.2	Gamma-linolenic acid (18:3 n-6)	-	1	1	2
5.2.4.2	N-6 fatty acids	1	7	1	9
5.2.5	Trans 18:1 fatty acid	-	1	1	2
5.2.5	Trans fatty acids	1	2	2	5
5.3	Protein	1	1	3	5
5.3.1	Methionine	8	9	7	24
5.4	Alcohol (as ethanol)	22	13	13	48
5.5.1	Total carotenoids, blood	-	1	1	2
5.5.1	Vitamin a	-	3	1	4
5.5.1.1	Serum retinol	-	2	1	3
5.5.1.2	Alpha-carotene	2	1	2	5
5.5.1.2	Beta-cryptoxanthin	1	1	1	3
5.5.1.2	Serum beta-carotene	-	2	1	3
5.5.10	Dietary vitamin d	13	1	2	16
5.5.10	Plasma 25-hydroxyvitamin d	1	1	4	6
5.5.10	Vitamin d supplement	-	1	1	2
5.5.11	Serum alpha-tocopherol	1	2	2	5
5.5.11	Vitamin E	9	3	1	13
5.5.11	Vitamin E from foods	2	1	3	6
5.5.11	Vitamin E from supplements	4	2	2	8
5.5.13	Multivitamin supplement	9	4	4	17
5.5.2	Lycopene	3	1	1	5
5.5.3	Dietary folate	10	6	5	21
5.5.3	Total folate	3	8	5	16
5.5.3	Plasma folate	-	5	5	10
5.5.4	Riboflavin	-	5	2	7
5.5.4	Riboflavin, biomarker	-	1	1	2
5.5.7	Dietary pyridoxine (vit B6)	1	4	2	7
5.5.7	Plasma pyridoxine (vitamin B6)	1	2	2	5
5.5.7	Pyridoxine (vitamin B6)	1	1	5	7
5.5.9	Dietary vitamin C	7	2	3	12
5.5.9	Vitamin c supplement	-	1	1	2
5.6.1	Sodium	-	1	3	4
5.6.2	Dietary heme iron	1	4	4	9
5.6.2	Iron	4	4	2	10
5.6.2	Iron, serum	-	1	2	3
5.6.3	Dietary calcium	27	8	2	37
5.6.4	Selenium	2	1	1	4
5.6.6	Magnesium	-	4	3	7
5.6.7	Zinc	1	1	2	4

Exposure Code	Exposure Name	Number of Publications			Total number of publications
		Cohort 2005 SLR	Cohort 2010 SLR	Cohort 2015 SLR	
5.8	Flavonoids	-	2	2	4
5.8	Isoflavones	-	5	1	6
6.1	Total Physical activity	9	7	5	21
6.1	Physical activity score	-	2	1	3
6.1.1.1	Occupational physical activity	6	4	1	11
6.1.1.2	Recreational physical activity	22	15	2	39
6.1.1.2	Walking	3	7	1	11
7.1	Energy intake	11	5	0	17
8.1.1	BMI	68	34	25	127
8.1.3	Weight	11	4	5	20
8.1.5	% body fat	-	1	2	3
8.1.5	Fat mass	2	2	2	6
8.1.6	BMI change	2	1	5	8
8.1.6	Weight change	-	3	4	7
8.2.1	Waist circumference	6	7	18	31
8.2.2	Hips circumference	1	2	2	5
8.2.3	Waist to hip ratio	8	7	7	22
8.3.1	Height	28	11	14	53
8.3.2	Leg length	2	2	1	5
8.4.1	Birth weight	1	2	3	6

1 Patterns of diet

Mediterranean diet

Five studies from five publications were identified on Mediterranean diet and colorectal cancer risk. The NHS and HPFS are included in one publication (Fung, 2010); EPIC-Italy (Agnoli, 2013) is included in EPIC (Bamia 2013) and not counted as a different study.

Inverse but not significant associations were observed in most studies.

In EPIC (Bamia, 2013) in analysis including 4,355 incident colorectal cancer cases, the RR estimate when comparing the highest score group (6–9) with the lowest score (0–3) of the Modified Mediterranean Score was 0.89 (95 % CI 0.80- 0.99) and the RR for 2-unit increment was 0.96 (95% CI 0.92- 1.00). The inverse association was somewhat more evident in women and for colon cancer risk. The association was of similar magnitude but not significant when centre-specific cut-off values were used instead of EPIC-wide cut-off points.

In a study in Sweden, adherence to a Modified Mediterranean Score was not related to mortality for colorectal cancer (RR for 1-unit increment: 0.99 (95% CI: 0.89-1.11, 127 cases) (Tognon, 2012).

In the NHS and the HPFS, alternate Mediterranean Diet was not related to colorectal cancer risk (Fung, 2010). The HR for the highest compared to the lowest quintile of the score were 0.88 (95% CI 0.74- 1.05, p-trend= 0.15) in men (1032 cases) and 0.89 (95% CI 0.77- 1.01, ptrend= 0.06) in women (1435 cases).

In an analysis in the NIH-AARP study (Reedy, 2008) including 3110 incident colorectal cancer cases, the Mediterranean Diet Score was inversely related to risk of colorectal cancer in men (RR for highest compared to lowest quintile= 0.72, 95% CI= 0.63- 0.83) but not in women (RR=0.89;95% CI= 0.72-1.11).

One meta-analysis on the effects of adherence to Mediterranean diet on colorectal cancer including 5 cohort studies and 2 case-controls showed an overall RR=0.86(95%CI=0.80-0.93, I^2=62%, highest vs lowest adherence score) (Schwingshackl, 2014). In this meta-analysis, one cohort study was on colorectal adenoma recurrence, not in colorectal cancer.

WCRF score

Two studies on adherence to WCRF recommendations (using a score) and colorectal cancer risk were identified. The Framingham Offspring cohort observed a non significant association betwee the score and colorectal cancer (HR per unit 0.87, 95 % CI: 0.68–1.12) (Makarem, 2015). The EPIC study observed that 1-point increment in the score was associated with a colorectal cancer risk reduction of 12% (95% CI: 9% - 16%) (Romaguera, 2012).

Vegetarian Dietary Pattern

The evidence comes from the studies in Adventists (mainly in North America) and in British vegetarians. In the Adventist Health Study 2 (Orlich, 2015) a vegetarian dietary pattern was significantly associated with lower risk of colorectal cancer (RR vegetarian vs nonvegetarian= 0.79 (95% CI 0.64-0.97; 490 cancer cases). The associations were inverse but not significant for colon and rectal cancers. Previous studies in Adventists showed reduced mortality for colorectal cancer in vegetarians compared to nonvegetarians (Frazer, 1999).
In British vegetarians, colorectal cancer risk was not lower in vegetarians compared to meat eaters (RR: 1.12; 95% CI: 0.87 -1.44) (Key, 2009). Similar results were observed in previous publications of the same study (SanJoaquin, 2004). The different results in Adventists vegetarians and British vegetarians had been explained by higher consumption of fruits and vegetables, dietary fibre and vitamin C in Adventists vegetarians than in British vegetarians (Orlich, 2015). Key, 1996).
In a pooled analysis of mortality in five prospective studies, comprising the Adventist Mortality Study, the Adventist Health Study, the Health Food Shoppers Study, the Oxford Vegetarian Study and the Heidelberg Study, there was no difference between vegetarians and non-vegetarians in mortality from colorectal cancer (Key et al, 1999).

Other Dietary Guideline Index Scores

Five studies explored different guidelines index scores. Some guidelines included components on physical activity, obesity and smoking. The different scores are described in the table.
In general all studies showed inverse associations of colorectal cancer with higher concordance with the guidelines. In the E3N French cohort in women (Dartois, 2014), colorectal cancer was inversely associated with higher concordance with the French lifestyle recommendations (the score included smoking, alcohol, fruits and vegetables consumption, BMI and physical activity). In the Women Health Initiative observational study, colorectal cancer incidence and mortality was inversely associated with higher adherence to the American Cancer Society (ACS) score including BMI, physical activity, fruit and vegetables, carotenoids, whole grains, red and processed meats, and alcohol (Thomson, 2014). In the NIH-AARP study (Kabat, 2015) higher ACS scores were associated with reduced risk of colon and rectal cancer in men and women.
The SCHS (Odegaard, 2013) an observational study of 50,466 Chinese men and women in Singapore showed a significant inverse association for colon and colorectal cancer, not for rectal cancer, for higher lifestyle factor index score (local dietary habits into account).
In the EPIC study (Aleksandrova, 2014) higher scores of a predefined healthy patterns was significantly associated with reduced risk of colon cancer in men and women, and of rectal cancer only in men.

The NIH-AARP study investigated other indexes (in addition to those described above). For men when comparing the highest scores with the lowest: Healthy Eating Index- 2005 (relative risk (RR) =0.72, 95%CI = 0.62-0.83); Alternate Healthy Eating Index (RR =0.70, 95% CI: 0.61, 0.81); and Recommended Food Score (RR = 0.75, 95% CI= 0.65, 0.87). For women, a significantly decreased risk was only found with the Healthy Eating Index-2005 (Reedy, 2008).

A posteriori-defined dietary patterns.

Studies on dietary patterns based on data (a posteriori) did not find significant associations of the identified patterns with colorectal cancer risk (Kumagai, 2014; Olberding, 2012; Engeset, 2009; Kim, 2005; Terry, 2001).

Table 2 Mediterranean diet and colorectal cancer risk. Main characteristics of studies identified in the CUP SLR

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors
Agnoli, 2013 COL40938 Italy	EPIC-Italy, Prospective Cohort, M/W	435/ 45 275 11.28 years	Cancer registry and hospital records	Semi-quantitative FFQ	Incidence, colorectal cancer	6-11 vs 0-1 score	0.49 (0.35-0.70) Ptrend:0.030	Age, BMI, educational level, gender, non-alcoholic beverage Intake, physical activity, smoking, study centre
		181/			Incidence, colorectal cancer, men		0.54 (0.30-0.96) Ptrend:0.085	
		254/			Incidence, colorectal cancer Women		0.46 (0.30-0.72) Ptrend:0.238	
		326/			Incidence, colon cancer		0.54 (0.36-0.81) Ptrend:0.110	
		159/			Incidence, distal colon cancer		0.44 (0.26-0.75) Ptrend:0.093	
		82/			Incidence, proximal colon cancer		0.73 (0.33-1.61) Ptrend:0.585	
		109/			Incidence, rectal cancer		0.41 (0.20-0.81) Ptrend:0.200	
Bamia, 2013 COL40964 Denmark, France, Germany,	EPIC, Prospective Cohort, Age: 25-70 years,	3 724/ 480 308 11.6 years	Cancer registry, record linkage, health Insurance rec, mortality registry,	FFQ in most centres. Modified Mediterranean score	Incidence, colorectal cancer	per 2 units	0.96 (0.92-1.00)	Age, sex, BMI, centre location, educational level, energy, physical
						6-9 vs 0-3 score	0.89 (0.80-0.99) Ptrend:0.02	

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors
Greece, Italy, Netherlands, Spain, Sweden, UK	M/W	2 753/	pathology and active follow up	Cut-offs were based on the centre-and-sex-specific medians	Incidence, colon cancer	per 2 units	0.95 (0.89-1.00)	activity, smoking
						6-9 vs 0-3 score	0.95 (0.84-1.07) Ptrend:0.23	
		2 479/			Incidence, colorectal cancer, women	per 2 units	0.95 (0.90-1.01)	
						6-9 vs 0-3 score	0.88 (0.77-1.01) Ptrend:0.05	
		1 876/			Men	per 2 units	0.97 (0.90-1.03)	
						6-9 vs 0-3 score	0.89 (0.76-1.04) Ptrend:0.14	
		1 602/			Incidence, rectal cancer	per 2 units	1.00 (0.93-1.07)	
						6-9 vs 0-3 score	0.97 (0.83-1.13) Ptrend:0.64	
		1 288/			Incidence, proximal cancer	per 2 units	0.97 (0.90-1.05)	
						6-9 vs 0-3 score	0.95 (0.80-1.12) Ptrend:0.36	
		1 212/			Incidence, distal cancer	per 2 units	0.97 (0.89-1.04)	
						6-9 vs 0-3 score	0.93 (0.78-1.11) Ptrend:0.31	
Tognon, 2012 COL41002 Sweden	VIP, Prospective Cohort, Age: 30-60	127/ 77 151 9 years	Vip database with the Swedish national cause-	Validated FFQ Modified Mediterranean score	Mortality, colorectal cancer, men and women	per 1 diet score	0.99 (0.89-1.11)	Age, educational level, obesity,

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors
	years, M/W	73/	of-death registry		Men	per 1 diet score	1.07 (0.93-1.24)	physical activity, smoking status
		54/			Women	per 1 diet score	0.91 (0.77-1.08)	
Fung, 2010 COL40828 USA	NHS+HPFS, Prospective Cohort, M/W	1 435/ 132 746	Self-report verified by medical record	FFQ Alternate Mediterranean score	Incidence, colorectal cancer, women	6-9 vs 1-2 score	0.88 (0.74-1.05) Ptrend:0.14	Age, alcohol Intake, aspirin use, BMI, colonoscopy, energy, family history, history of polyps, physical activity, smoking
		1 082/			Incidence, colon cancer, women	6-9 vs 1-2 score	0.91 (0.74-1.11) Ptrend:0.13	
		1 032/			Incidence, colorectal cancer, men	7-9 vs 0-2 score	0.88 (0.71-1.09) Ptrend:0.25	
		682/			Incidence, colon cancer, men	7-9 vs 0-2 score	0.87 (0.67-1.13) Ptrend:0.45	
		323/			Incidence, rectal cancer, women	6-9 vs 1-2 score	0.80 (0.55-1.15) Ptrend:0.64	
		218/			Men	7-9 vs 0-2 score	0.75 (0.46-1.23) Ptrend:0.19	
Reedy, 2010 COL40812 USA	NIH-AARP, Prospective Cohort, Age: 50-71 years, Retired	492 306 5 years	Cancer registry, national death Index, self-report, pathology reports	FFQ Mediterranean Diet Score	Incidence, colorectal cancer, women	highest quintile vs lowest quintile	0.89 (0.72-1.11)	Age, BMI, educational level, ethnicity, physical activity, smoking status, total energy
					Men	highest quintile vs lowest quintile	0.72 (0.63-0.83)	

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors
Reedy, 2008 COL40738 USA	NIH-AARP, Prospective Cohort, Age: 50-71 years, M/W	492 382 5 years	Cancer registry	FFQ Mediterranean Diet Score	Incidence, colorectal cancer, women	Mediterranean diet 6-9 vs 0-2 points	0.89 (0.72-1.11)	Age, BMI, educational level, energy Intake, physical activity, race, smoking status, menopausal hormone status
					Incidence, distal colon cancer, men	6-9 vs 0-2 points	0.68 (0.53-0.86)	
					Incidence, rectal cancer, women	56-88 vs 13-41 points	0.95 (0.61-1.48)	
					Incidence, colorectal cancer, men	Mediterranean diet 6-9 vs 0-2 points	0.72 (0.63-0.83)	
					Incidence, rectal cancer, women	6-9 vs 0-2 points	0.75 (0.50-1.21)	
					Incidence, colorectal cancer, men	16-38 vs 0-6 points	0.75 (0.65-0.87)	
					Incidence, proximal colon cancer, women	6-9 vs 0-2 points	0.84 (0.61-1.14)	
					Incidence, colorectal cancer, men	56-88 vs 15-41 points	0.71 (0.61-0.82)	
					Incidence, proximal colon	56-88 vs 13-41 points	0.75 (0.54-1.05)	

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors
					cancer, women			
					Incidence, distal colon cancer, men	56-88 vs 15-41 points	0.75 (0.75-0.96)	

Table 3 WCRF score and colorectal cancer risk. Main characteristics of studies identified in the CUP SLR

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors
Makarem, 2015 COL41060 USA	FHS-Offspring Cohort, Prospective Cohort, Age: 66 years, M/W	63/ 2 983 11.5 years	Death certificate and medical records	Semi-quantitative FFQ WCRF Score	Incidence, colorectal cancer	per 1 points	0.87 (0.68-1.12)	Age, sex, smoking status
Romaguera, 2012 COL41048 France, Italy, Spain, UK, Netherlands, Greece, Germany, Sweden, Denmark, Norway	EPIC, Prospective Cohort, Age: 25-70 years, M/W	3 880/ 386 355 11 years	Cancer registries, health Insurance records, pathology rec & active follow up	FFQ WCRF score	Incidence, colorectal cancer	per 1 points	0.88 (0.84-0.91)	Age, sex, disease at baseline, educational level, energy intake, smoking Intensity, smoking status, study centre

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors

Table 4 Dietary Guideline Index Score and colorectal cancer risk. Main characteristics of studies identified CUP SLR

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors
Dartois, 2014 COL41004 France	E3N EPIC-France, Prospective Cohort, Age: 43-68 years, W	481/ 64 732 8 years	Self-report verified by reviewing medical and pathological records by physicians	Self-administered questionnaire Index of compliance with the French and WHO guidelines	Incidence, colorectal cancer	4.5- 5 vs 0- 2	0.66 (0.45-0.97) Ptrend:0.013	Age at first child birth, age at menarche, educational level, family history of cancer In first degree relatives, menopausal estrogen use, menopausal status, number of children, professional activity, residence, use of oral contraception
Thomson, 2014 COL40998 USA	Women's Health Initiative (WHI) Observational	751/ 65 838 12.6 years	Mailed annual questionnaire, cancer	FFQ Adherence to American	Incidence, colorectal cancer	7-8 vs 0-2 score	0.48 (0.32-0.73) Ptrend:0.001	Age, aspirin use, colonoscopy, educational
						per 1 score	0.89 (0.85-0.94)	

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors
	Study, 1993, Prospective Cohort, Age: 50-79 years, W, Postmenopausal	190/	registries, national death Index and medical records	Cancer Society guidelines (including diet, smoking and physical activity)	Mortality, colorectal cancer	per 1 score	0.83 (0.75-0.91)	level, family history of cancer, having a healthcare provider, multivitamin supplement intake, NSAID use, parous/nulliparous, race/ethnicity, smoking, pack-years, total energy intake, unopposed estrogen use
						6-8 vs 0-3 score	0.39 (0.24-0.63) Ptrend:0.001	
Kabat, 2015 COL41063 USA	NIH-AARP, Prospective Cohort, Age: 50-71 years, M/W	2 844/ 476 396 10.5 years	Cancer registry	Semi-quantitative FFQ Adherence to American Cancer Society guidelines (including diet, smoking and physical activity)	Incidence, colon cancer, men	8-11 vs 0-3 score	0.52 (0.47-0.59)	Age, colonoscopy, educational level, energy intake, ethnicity, family history, marital status, smoking status
		1 417/			Incidence, rectal cancer, men	8-11 vs 0-3 score	0.60 (0.51-0.72)	
		1 287/			Incidence, colon cancer, women	8-11 vs 0-3 score	0.65 (0.54-0.78)	
		582/			Incidence, rectal cancer, women	8-11 vs 0-3 score	0.64 (0.49-0.83)	

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors
		228/			Incidence, small Intestinal cancer	8-11 vs 0-3 score	0.53 (0.36-0.79)	
Roswall, 2015 COL41039 Sweden	WLHS, Prospective Cohort, Age: 29-49 years, W	314/ 45 222 10 years	Cancer registry	Nordic Food Index (wholegrain bread, oatmeal, apples/pears, cabbages, root vegetables and fish/shellfish)	Incidence, colorectal cancer	per 1 points	1.04 (0.95-1.12)	Alcohol, BMI, educational level, energy, oral contraceptive history, red and processed meat, smoking, time since quitting smoking
						4-6 vs 0-1 points	1.09 (0.78-1.52)	
Aleksandrova, 2014 COL41051 Europe	EPIC, Prospective Cohort, Age: 25-70 years, M/W	3 759/ 347 237 12 years	Cancer registry	Healthy lifestyle index (includes diet, alcohol, BMI, smoking)	Incidence, colorectal cancer	5 vs 0-1 points	0.63 (0.54-0.74)	Age, sex, alcohol, body fat, educational level, physical activity, smoking, study centre, diet quality
						per 1 points	0.88 (0.86-0.92)	
						healthy vs unhealthy	0.88 (0.83-0.95)	
		2 369/			Incidence, colon cancer	5 vs 0-1 points	0.61 (0.50-0.74)	
						per 1 points	0.87 (0.84-0.91)	
						healthy vs unhealthy	0.88 (0.81-0.96)	
		2 002/			Incidence, colorectal cancer, women	healthy vs unhealthy	0.89 (0.81-0.98)	
						5 vs 0-1 points	0.76 (0.60-0.95)	
						per 1 points	0.91 (0.87-0.95)	
		1 757/			Men	healthy vs unhealthy	0.85 (0.77-0.95)	

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors
						5 vs 0-1 points	0.56 (0.44-0.69)	
						per 1 points	0.87 (0.83-0.90)	
		1 390/			Incidence, rectal cancer	5 vs 0-1 points	0.68 (0.53-0.88)	
						per 1 points	0.90 (0.85-0.94)	
						healthy vs unhealthy	0.89 (0.79-1.01)	
		1 340/			Incidence, colon cancer, women	healthy vs unhealthy	0.86 (0.77-0.97)	
						5 vs 0-1 points	0.65 (0.48-0.86)	
						per 1 points	0.88 (0.84-0.86)	
		1 029/			Men	5 vs 0-1 points	0.61 (0.46-0.81)	
						per 1 points	0.86 (0.82-0.91)	
		909/			Men	healthy vs unhealthy	0.89 (0.78-1.02)	
		728/			Incidence, rectal cancer, men	healthy vs unhealthy	0.80 (0.68-0.94)	
						5 vs 0-1 points	0.47 (0.32-0.68)	
						per 1 points	0.86 (0.80-0.91)	
		662/			Women	healthy vs unhealthy	1.00 (0.84-1.18)	
						5 vs 0-1 points	1.01 (0.68-1.49)	
						per 1 points	0.97 (0.99-1.04)	
Kyrø, 2013 COL40918 Denmark	DCH, Prospective Cohort, Age: 50-64 years, M/W	567/ 57 053 13 years	Cancer registry	FFQ Nordic Food Index (bread, wholegrain oatmeal,	Incidence, colorectal cancer, men	5-6 vs 0-1 points	0.87 (0.61-1.25)	Alcohol, educational level, energy, meat, smoking, sports/gymnastics, use of
						per 1 points	1.00 (0.93-1.07)	
		458/			Women	5-6 vs 0-1 points	0.65 (0.46-0.94)	
						per 1 points	0.91 (0.84-0.99)	

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors
		341/		apples/pears, cabbages, root vegetables and fish/shellfish)	Incidence, colon cancer, men	per 1 points	0.97 (0.88-1.06)	NSAID, waist circumference, Hormone replacement therapy
		324/			Women	per 1 points	0.95 (0.86-1.04)	
		226/			Incidence, rectal cancer, men	per 1 points	1.06 (0.95-1.19)	
		157/			Incidence, distal cancer, men	per 1 points	0.92 (0.80-1.06)	
		142/			Incidence, proximal cancer, women	per 1 points	1.00 (0.87-1.15)	
		134/			Incidence, distal cancer, women	per 1 points	0.94 (0.82-1.10)	
		133/			Incidence, proximal cancer, men	per 1 points	1.00 (0.87-1.16)	
Odegaard, 2013 COL40948 Singapore	SCHS, Prospective Cohort, Age: 45-74 years, M/W	969/ 50 466 579 628 person-years	Cancer registry and death registry	Higher score: higher intake of vegetables, fruit, and soy and lower intake	Incidence, colon cancer	highest 25th percentile vs lowest 25th percentile score	0.76 (0.59-0.98)	Age, sex, alcohol intake, BMI, diabetes, dialect group, educational level, energy intake, family history of

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors
				of meats, dim sum, western-style fast food and sugared soft drinks				colorectal cancer, physical activity, sleep, smoking, time of recruitment
Reedy, 2010 COL40812 USA (Same results in Reedy, 2008)	NIH-AARP, Prospective Cohort, Age: 50-71 years, M/W	2151 cases in men, 959 cases in women/ 492 306 5 years	Cancer registry, national death Index, self-report, pathology reports	FFQ Healthy Eating Index-2005	Incidence, colorectal cancer, men	highest quintile vs lowest quintile	0.70 (0.61-0.81)	Age, BMI, educational level, ethnicity, physical activity, smoking status, total energy
					Women	highest quintile vs lowest quintile	0.80 (0.64-0.98)	
				Alternate Healthy Eating Index	Men	highest quintile vs lowest quintile	0.72 (0.62-0.83)	
					Women	highest quintile vs lowest quintile	0.80 (0.64-1.00)	
				Recommended food score	Men	highest quintile vs lowest quintile	0.75 (0.65-0.87)	
					Women		1.01 (0.80-1.28)	
Engeset, 2009 COL40961 Norway	Norwegian European Prospective Investigation into Cancer and Nutrition (NEPIC), Prospective Cohort,	93/ 34 471 7 years	Cancer registry	FFQ FFQ labelled 5 clusters: 'traditional fish eaters' 'healthy' 'average, less fish, less	Incidence, colon cancer	bread pattern vs average	0.94 (0.45-1.95)	Age, educational level, energy Intake, fish Intake, fruit Intake, smoking, vegetable intake, physical activity
						healthy pattern vs average	0.89 (0.47-1.71)	
						fish pattern vs average	0.41 (0.13-1.30)	
						western pattern vs average	0.74 (0.31-1.78)	

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors
	Age: 48 years, W			healthy', 'western' 'traditional bread eaters' and 'alcohol users' based on the most dominant food groups in each cluster		alcohol pattern vs average	0.78 (0.34-1.80)	
		15			Incidence, colorectal cancer, postmenopausal	healthy pattern vs average	0.90 (0.44-1.83)	
		13				bread pattern vs average	0.94 (0.44-2.02)	
		8				western pattern vs average	0.88 (0.34-2.24)	
		8				fish pattern vs average	1.05 (0.40-2.72)	
		8				alcohol pattern vs average	1.07 (0.48-2.40)	
		40			Incidence, rectal cancer	alcohol pattern vs average	1.73 (0.59-5.06)	
						bread pattern vs average	1.41 (0.50-3.98)	
						western pattern vs average	1.09 (0.32-3.70)	
						healthy pattern vs average	0.51 (0.15-1.72)	
						fish pattern vs average	1.31 (0.35-4.98)	

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors
		9			Incidence, colorectal cancer, premenopausal	bread pattern vs average	1.24 (0.47-3.29)	
		7				healthy pattern vs average	0.65 (0.24-1.73)	
		6				western pattern vs average	0.81 (0.27-2.43)	
		5				alcohol pattern vs average	1.02 (0.33-3.14)	
Terry, 2001 COL00556 Sweden	SMC, Prospective Cohort, Age: 39-76 years, W	460/ 61 463 9.6 years	Computerized regional cancer registers	FFQ A posteriori defined dietary patterns "Healthy" dietary pattern	Incidence, colorectal cancer	Q 5 vs Q 1	0.79 (0.56-1.10)	Age, BMI, educational level, energy intake
				"Western" dietary pattern			0.97 (0.66-1.44)	
				"Drinker" dietary pattern			1.13 (0.84-1.53)	

Table 5 A posteriori derived dietary patterns and colorectal cancer risk. Main characteristics of studies identified CUP SLR

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors
Kumagai, 2014 COL41050 Japan	OCS, Prospective Cohort, Age: 40-79 years, M/W	854/ 44 097 11 years	Cancer registry	A posteriori derived dietary patterns DFA: high-dairy, high-fruit-and-vegetable, low-alcohol	Incidence, colorectal cancer	Q 4 vs Q 1	0.76 (0.60-0.97)	Age, sex, BMI, educational level, energy intake, family history of colorectal cancer, smoking status, walking
		554/			Incidence, colon cancer	Q 4 vs Q 1	0.89 (0.66-1.19)	
		323/			Incidence, rectal cancer	Q 4 vs Q 1	0.56 (0.37-0.84)	
Ollberding, 2012 COL40941 Hawaii, USA	MEC, Prospective Cohort, Age: 45-75 years, M/W	3 404/ 165 717 8.1 years	Cancer registry and national death Index	FFQ A posteriori derived patterns Meat and fat dietary pattern (factor score)	Incidence, colorectal cancer	1.33 vs -1.26 score	1.12 (0.94-1.33) Ptrend:0.099	Age, sex, age at cohort entry In log linear model, alcohol consumption, BMI, calcium, dietart fibre, energy Intake, ethnicity, family history of colorectal cancer, folate, history of diabetes, history of polyp diagnosis, HRT use, non-steriodal anti-inflammatory drug use, pack yrs of smoking, vigorous physical activity, vitamin d
Kim, 2005 COL01842 Japan	JPHC, Prospective Cohort, Age: 40-59 years, M/W	231 cases in men, 139 cases in women / 42 112 10 years	Cancer registry/death certificates/hospital records	FFQ A posteriori derived patterns Healthy pattern: high vegetables, fruits, soy products,	Incidence, colorectal cancer	Q 4 vs Q 1	Men 0.81 (0.52-1.24) Women 0.98 (0.58-1.65)	
					Incidence, colon cancer	Q 4 vs Q 1	Men 0.83 (0.49-1.41) Women 0.76 (0.39-1.50)	

				seaweeds, mushroom, milk, beans and yogurt	Incidence, rectal cancer	Q 4 vs Q 1	Men 0.76 (0.37-1.58) Women 1.43 (0.62-3.28)	
				Traditional pattern: high pickled vegetables, salted fish and roe, fish, rice and miso soup, low bread and butter and in men, high alcohol	Incidence, colorectal cancer	Q 4 vs Q 1	Men 0.88 (0.55-1.42) Women 1.53 (0.93-2.52)	
					Incidence, colon cancer	Q 4 vs Q 1	Men 1.05 (0.58-1.90) Women 2.06 91.10-3.84)	
					Incidence, rectal cancer	Q 4 vs Q 1	Men 0.62 (0.28-1.39) Women 0.85 90.36-2.02)	
				Western pattern: High meat, poultry, cheese, bread, butter	Incidence, colorectal cancer	Q 4 vs Q 1	Men 0.93 (0.62-1.41) Women 1.45 90.85-2.48)	
					Incidence, colon cancer	Q 4 vs Q 1	Men 1.05 (0.63-1.75) Women 2.21 (1.10-4.45)	
					Incidence, rectal cancer		Men 0.73 (0.36-1.43) Women 0.77 (0.32-1.83)	

Table 6 Vegetarian pattern and colorectal cancer risk. Main characteristics of studies identified CUP SLR

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Inclusion/exclu sion
Orlich, 2015 COL41043 USA	Adventist Health Study 2, Prospective Cohort, M/W	490/ 77 659 7.3 years	Cancer registry	FFQ	Incidence, colorectal cancer	vegetarian vs non-vegetarian	0.79 (0.64-0.97) Ptrend:0.03	Age, sex, alcohol, aspirin use, BMI, calcium supplement, colonoscopy, diabetes medication use, educational level, energy, family history of colorectal cancer, fibre Intake, history of Inflammatory bowel disease, history of peptic ulcer, HRT use, moderate activity, race, smoking, vitamin d supplement	
		380/			Incidence, colon cancer		0.83 (0.66-1.05) Ptrend:0.12		
		305/			Incidence, colorectal cancer, women		0.79 (0.61-1.03) Ptrend:0.08		
		185/			Men		0.81 (0.58-1.12) Ptrend:0.20		
		110/			Incidence, rectal cancer		0.66 (0.43-1.02) Ptrend:0.06		
		106/			Incidence, colorectal cancer, black		0.73 (0.47-1.14) Ptrend:0.16		
		384			Incidence, colorectal cancer, non-black		0.81 (0.65-1.03) Ptrend:0.08		
Key, 2009 COL40951	Oxford Vegetarian	384/ 61 566	UK national health service	Semi-quantitative FFQ	Incidence, colorectal cancer	vegetarian vs meat eater	1.49 (0.87, 1.44)	Age, sex, alcohol	

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Inclusion/exclusion
UK	Study 1980-1984 and EPIC-Oxford 1993-1999, Prospective Cohort, Age: 20-89 years, M/W	12.2 years	central register					consumption, BMI, physical activity level, smoking, study/method of recruitment	
		239/			Incidence, colon cancer	vegetarian vs meat eater	1.12 (0.81-1.54)		
		145/			Incidence, rectal cancer	vegetarian vs meat eater	1.12 (0.75-1.67)		
Sanjoaquin, 2004 COL01182 UK	Oxford Vegetarian Study 1980-1984, Prospective Cohort, Age: 18-89 years, M/W	95/ 10 998 17 years	Population/invitation	FFQ	Incidence, colorectal cancer	vegetarians vs non-vegetarians	0.85 (0.55-1.32) Ptrend:0.463	Age, sex, alcohol consumption, smoking habits	
Key, 1996 COL00418 UK	British Health Conscious and Vegetarian subjects 1973-1979, Prospective Cohort, Age: 16-79 years, M/W,	62/ 10 771 16.8 years	Public	Questionnaire	Mortality, colorectal cancer	health conscious cohort vs England and Wales	0.79 (0.47-1.33)	Age, sex, smoking	

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Inclusion/exclusion
	vegetarians and other health conscious subjects								

2 Foods

2.1.1.4 Whole grains

Cohort studies

Summary

Main results:

Seven studies on whole grain intake and colorectal cancer risk were identified, and one of these was a new publication since the 2010 SLR. Six studies investigated colorectal cancer, four investigated colon cancer, and three were on rectal cancer. Study characteristics and results for all cancer types are shown in the Table. For studies that reported whole grain intake in servings per day intakes were converted to grams per day by using a serving size of 30 grams.

Colorectal cancer:
Six studies (8320 cases) were included in the dose-response meta-analysis. The summary RR for a 90 g/d increase in whole grain intake was 0.83 (95% CI: 0.78-0.89) and there was low heterogeneity, I^2=18.2%, $p_{heterogeneity}$=0.30. There was no evidence of small study bias or publication bias with Egger's test, p=0.72. The summary RR ranged from 0.82 (95% CI: 0.77-0.88) when the Swedish Mammography Cohort (Larsson, 2005) was excluded to 0.86 (95% CI: 0.80-0.92) when the NIH-AARP Diet and Health study (Schatzkin, 2007) was excluded.

There was no indication of a nonlinear association, $p_{nonlinearity}$=0.33 in the analysis of colorectal cancer.

Colon cancer:
Four studies (3875 cases) were included in the dose-response meta-analysis of whole grain intake and colon cancer. The summary RR per 90 g/day increase in whole grain intake was 0.82 (95% CI: 0.73-0.92) and there was moderate heterogeneity, I^2=0%, $p_{heterogeneity}$=0.49.

Rectal cancer:
Three studies (1548 cases) were included in the dose-response meta-analysis of whole grain intake and postmenopausal colorectal cancer. The summary RR per 90 g/d increase in whole grain intake was 0.81 (95% CI: 0.54-1.20), with low heterogeneity, I^2=91.2%, $p_{heterogeneity}$<0.0001.

Study quality:
Whole grain intake was estimated from food intake assessed by FFQ in all studies.
Loss to follow-up was low for the studies that reported such data, although some studies did not provide data.

Cancers were identified by record linkages to health registries, cancer registries, mortality registries, or death indexes.

All studies adjusted for at least age, and most of the studies adjusted for most of the main colorectal cancer risk factors, including: age, physical activity, BMI, and alcohol consumption, smoking, red meat and hormone replacement therapy in women.

Table 7 Whole grain intake and colorectal cancer risk. Number of studies in the CUP SLR

	Number
Studies identified	7 studies (7 publications)
Studies included in forest plot of highest compared with lowest intake	Colorectal cancer: 4 studies Colon cancer: 4 Rectal cancer: 3
Studies included in linear dose-response meta-analysis	Colorectal cancer: 6 studies Colon cancer: 4 Rectal cancer: 3
Studies included in non-linear dose-response meta-analysis	Colorectal cancer: 4 studies Colon cancer: 4 Rectal cancer: not enough studies

Table 8 Whole grain intake and colorectal cancer risk. Summary of the linear dose-response meta-analysis in the 2010 SLR and 2015 SLR

	2010 SLR		
	Colorectal cancer	**Colon cancer**	**Rectal cancer**
Increment unit used	90 g/day		
Studies (n)	6	4	3
Cases (total number)	7941	3656	1393
RR (95%CI)	0.83 (0.79-0.89)	0.86 (0.79-0.94)	0.80 (0.56-1.14)
Heterogeneity (I^2, p-value)	18%, p=0.30	0%, p=0.42	91%, p<0.0001
P value Egger test	0.54	-	-

	2015 SLR		
	Colorectal cancer	**Colon cancer**	**Rectal cancer**
Increment unit used	90 g/day		
Studies (n)	6	4	3
Cases (total number)	8320	3875	1548
RR (95%CI)	0.83 (0.79-0.89)	0.82 (0.73-0.92)	0.82 (0.57-1.16)
Heterogeneity (I^2, p-value)	18.2%, p=0.30	0%, p=0.49	84%, p<0.0001
P value Egger test	0.72	-	-

Stratified analyses

Geographic location	**Asia**	**Europe**	**North-America**
Studies (n)	-	2	4
RR (95%CI)	-	0.89 (0.81-0.97)	0.79 (0.72-0.86)
Heterogeneity (I^2, p- value)	-	0%, p=0.50	0%, p=0.57

Table 9 Whole grains and colorectal cancer risk. Results of meta-analyses and pooled analyses of prospective studies published after the 2005 SLR.

Author, Year	Number of studies	Total number of cases	Studies country, area	Outcome	Comparison	RR (95%CI)	P trend	Heterogeneity (I^2, p value)
Meta-analyses								
Aune et al, 2012	6	7941	North America, Europe, Asia	Incidence	High vs. low Per 90 g/d	0.79 (0.72-0.86) 0.83 (0.78-0.89)	- -	0%, p=0.98 18%, p=0.30
Pooled analyses								
Park et al, 2005	13	8081	North America, Europe	Incidence	High vs. low	0.92 (0.84-1.00)	0.21	NA

Table 10 Whole grain intake and colorectal cancer risk. Main characteristics of studies included in the CUP SLR dose-response meta-analysis

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI)	Adjustment factors	Missing data derived for analysis
Kyrø, 2013 COL40963 Sweden, Norway	HELGA cohort, Prospective Cohort, Age: 40-63 years Includes the Norwegian Women and Cancer Cohort, the Northern Sweden Health and Disease Study Cohort, and the Danish Diet, Cancer, and Health cohort (all part of EPIC)	1 123/ 108 000 11 years	Cancer registry	Semi-quantitative FFQ	Total Whole grain intake			Age, alcohol, BMI, educational level, energy, HRT use, red and processed meat, smoking	Distribution of person-years, conversion of continuous units
					Incidence, colorectal cancer	≥71 vs 0-31 g/day	0.86 (0.69-1.06)		
					Incidence, colorectal cancer	per 25 g	0.94 (0.88-1.01)		
					Incidence, colon cancer, men	≥71 vs 0-31 g/day	0.76 (0.51-1.13)		
					Incidence, colon cancer, men	per 25 g	0.96 (0.84-1.09)		
					Incidence, proximal colon cancer, men	≥71 vs 0-31 g/day	0.99 (0.56-1.75)		
					Incidence, proximal colon cancer, men	per 25 g	0.99 (0.82-1.20)		
					Incidence, distal colon cancer, men	≥71 vs 0-31 g/day	0.65 (0.37-1.18)		
					Incidence, distal colon cancer, men	per 25 g	0.95 (0.79-1.15)		
					Incidence,	≥71 vs 0-31	0.76 (0.51-1.13)		

					rectal cancer, men	g/day			
					Incidence, rectal cancer, men	per 25 g	0.89 (0.76-1.04)		
					Incidence, colon cancer, women	≥68 vs 0-30 g/day	1.18 (0.80-1.73)		
					Incidence, colon cancer, women	per 25 g	0.99 (0.86-1.13)		
					Incidence, proximal colon cancer, women	≥68 vs 0-30 g/day	0.85 (0.49-1.50)		
					Incidence, proximal colon cancer, women	per 25 g	0.89 (0.73-1.08)		
					Incidence, distal colon cancer, women	≥68 vs 0-30 g/day	1.31 (0.73-2.33)		
					Incidence, distal colon cancer, women	per 25 g	1.00 (0.82-1.22)		
					Incidence, rectal cancer, women	≥68 vs 0-30 g/day	0.53 (0.30-0.91)		
					Incidence, rectal cancer, women	per 25 g	0.80 (0.66-0.98)		
					Whole grain products				
					Incidence, colorectal	≥189 vs 0-85 g/day	0.77 (0.63-0.93)		

					cancer				
					Incidence, colorectal cancer	per 50 g	0.94 (0.89-0.99)		
					Incidence, colon cancer, men	≥189 vs 0-85 g/day	0.67 (0.46-0.97)		
					Incidence, colon cancer, men	per 50 g	0.92 (0.84-1.00)		
					Incidence, proximal colon cancer, men	≥189 vs 0-85 g/day	0.55 (0.30-0.99)		
					Incidence, proximal colon cancer, men	per 50 g	0.89 (0.77-1.01)		
					Incidence, distal colon cancer, men	≥189 vs 0-85 g/day	0.71 (0.42-1.19)		
					Incidence, distal colon cancer, men	per 50 g	0.94 (0.82-1.06)		
					Incidence, rectal cancer, men	≥189 vs 0-85 g/day	0.77 (0.50-1.21)		
					Incidence, rectal cancer, men	per 50 g	0.92 (0.83-1.02)		
					Incidence, colon cancer, women	≥180 vs 0-90 g/day	0.82 (0.58-1.18)		
					Incidence, colon cancer, women	per 50 g	0.97 (0.88-1.06)		
					Incidence, proximal	≥180 vs 0-90 g/day	0.61 (0.36-1.03)		

					colon cancer, women				
					Incidence, proximal colon cancer, women	per 50 g	0.89 (0.77-1.03)		
					Incidence, distal colon cancer, women	≥180 vs 0-90 g/day	0.88 (0.52-1.50)		
					Incidence, distal colon cancer, women	per 50 g	0.98 (0.85-1.13)		
					Incidence, rectal cancer, women	≥180 vs 0-90 g/day	0.72 (0.45-1.16)		
					Incidence, rectal cancer, women	per 50 g	0.92 (0.80-1.06)		
Fung, 2010 COL40828 USA	HPFS, Prospective Cohort, M	132 746	Self report verified by medical record	FFQ	Incidence, colorectal cancer, men	per 1 serving/day	0.94 (0.88-0.99)	Age, alcohol intake, aspirin use, BMI, colonoscopy, energy, family history, history of polyps, physical activity, smoking	Conversion of continuous estimates
Fung, 2010 COL40828 USA	NHS, Prospective Cohort, W	132 746	Self report verified by medical record	FFQ	Incidence, colorectal cancer, women	per 1 serving/day	0.95 (0.89-1.02)	Age, alcohol intake, aspirin use, BMI, colonoscopy, energy, family history, history of polyps, physical activity, smoking	Conversion of continuous estimates

Schatzkin, 2007 COL40662 USA	NIH-AARP, Prospective Cohort, Age: 50-71 years, M/W	2 974/ 489 611 5 years	Cancer registry and national death Index	FFQ	Incidence, colorectal cancer	1.3 vs 0.2 g/1000kcal/day	0.79 (0.70-0.89)	Age, sex, calcium intake, folate intake, physical activity, red meat intake, smoking status, total energy intake	Conversion from g/1000 kcal/d to g/d
					Incidence, colon cancer	1.3 vs 0.2 g/1000kcal/day	0.86 (0.75-0.99)		
					Incidence, colorectal cancer, men	1.3 vs 0.2 g/1000kcal/day	0.79 (0.79-0.91)		
					Incidence, proximal colon cancer	1.3 vs 0.2 g/1000kcal/day	0.84 (0.69-1.01)		
					Incidence, colorectal cancer, women	1.3 vs 0.2 g/1000kcal/day	0.87 (0.70-1.07)		
					Incidence, distal colon cancer	1.3 vs 0.2 g/1000kcal/day	0.85 (0.69-1.06)		
					Incidence, rectal cancer	1.3 vs 0.2 g/1000kcal/day	0.64 (0.51-0.81)		
McCarl, 2006 COL40633 USA	IWHS, Prospective Cohort, Age: 55-69 years, W	954/ 35 197 15 years	SEER registry	FFQ	Incidence, colorectal cancer	≥19 vs ≤3.5 servings/week	0.81 (0.66-0.99)	Age	Midpoints, conversion from serv/wk to g/d
Larsson, 2005 COL01883 Sweden	SMC, Prospective Cohort, Age: 40-76 years, W	805/ 61 433 14.8 years	Cancer registry	FFQ	Incidence, colorectal cancer	≥4.5 vs ≤1.4 servings/day	0.80 (0.60-1.06)	Age, BMI, calcium intake, educational level, fruits, red meat intake, saturated fat intake, total energy intake, vegetable intake	Distribution of person-years, conversion from serv/d to g/d
					Incidence, colorectal cancer, excluding those with <2y follow-	≥4.5 vs ≤1.4 servings/day	0.76 (0.56-1.03)		

					up				
					Incidence, colon cancer	≥4.5 vs ≤1.4 servings/day	0.67 (0.47-0.96)		
					Incidence, colon cancer, women, excluding those with <2y follow-up	≥4.5 vs ≤1.4 servings/day	0.65 (0.45-0.94)		
					Incidence, proximal colon cancer	≥4.5 vs ≤1.4 servings/day	0.69 (0.40-1.20)		
					Incidence, distal colon cancer	≥4.5 vs ≤1.4 servings/day	0.54 (0.27-1.08)		
					Incidence, rectal cancer	≥4.5 vs ≤1.4 servings/day	1.11 (0.67-1.83)		
					Incidence, rectal cancer, women, excluding those with <2y follow-up	≥4.5 vs ≤1.4 servings/day	1.07 (0.62-1.82)		
McCullough, 2003 COL00367 USA	CPS II, Prospective Cohort, Age: 50-74 years, M/W	298/ 133 163 6 years	Cancer registry and death certificates and medical records	Semi-quantitative FFQ	Incidence, colon cancer, men	<0.46 vs 2+ serving/week	1.08 (0.67-1.74)	Age, aspirin use, BMI, calcium, educational level, energy intake, family history of colorectal cancer, multivitamin, physical activity, red meat intake, smoking habits	Distribution of person-years
					Incidence, colon cancer, men	≥11 vs 0-1.9 serving/week	0.95 (0.64-1.42)		
					Incidence, colon cancer, women	≥11.2 vs 0-2.4 serving/week	1.17 (0.73-1.87)		
					Incidence, colon cancer, women	<.58 vs 2.5+ serving/week	1.04 (0.59-1.83)		

Table 11 Whole grain intake and colorectal cancer risk. Main characteristics of studies excluded from the CUP SLR dose-response meta-analysis

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Reasons for exclusion
Egeberg, 2010 COL40841 Denmark	DCH, Prospective Cohort, Age: 50-64 years, M/W	244/ 55 819 10.6 years	Cancer registry	FFQ	Incidence, colon cancer, men	≥161 vs ≤75 g/day	0.61 (0.43-0.86)	Alcohol intake, BMI, educational level, leisure time physical activity, red and processed meat	Included in HELGA (Kyro, 2013)
					Incidence, colon cancer, men	per 50 g	0.85 (0.77-0.94)		
					Incidence, colon cancer, women	per 50 g	0.98 (0.88-1.10)		
					Incidence, colon cancer, women	≥161 vs ≤75 g/day	0.92 (0.63-1.35)		
					Incidence, rectal cancer, men	≥161 vs ≤75 g/day	0.88 (0.57-1.36)		
					Incidence, rectal cancer, men	per 50 g	0.90 (0.80-1.01)		
					Incidence, rectal cancer, women	per 50 g	1.02 (0.88-1.19)		
					Incidence, rectal cancer, women	≥161 vs ≤75 g/day	0.81 (0.50-1.30)		

Figure 1 RR estimates of colorectal cancer by levels of whole grain intake

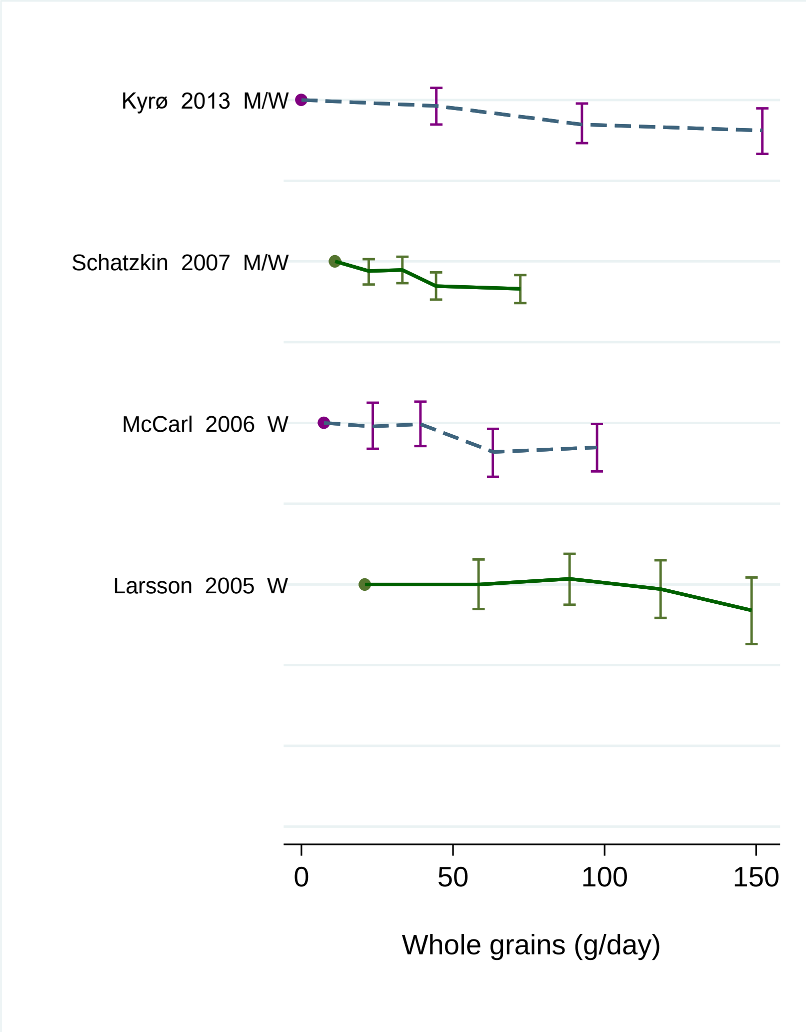


Figure 2 Relative risk of colorectal cancer for the highest compared with the lowest level of whole grain intake

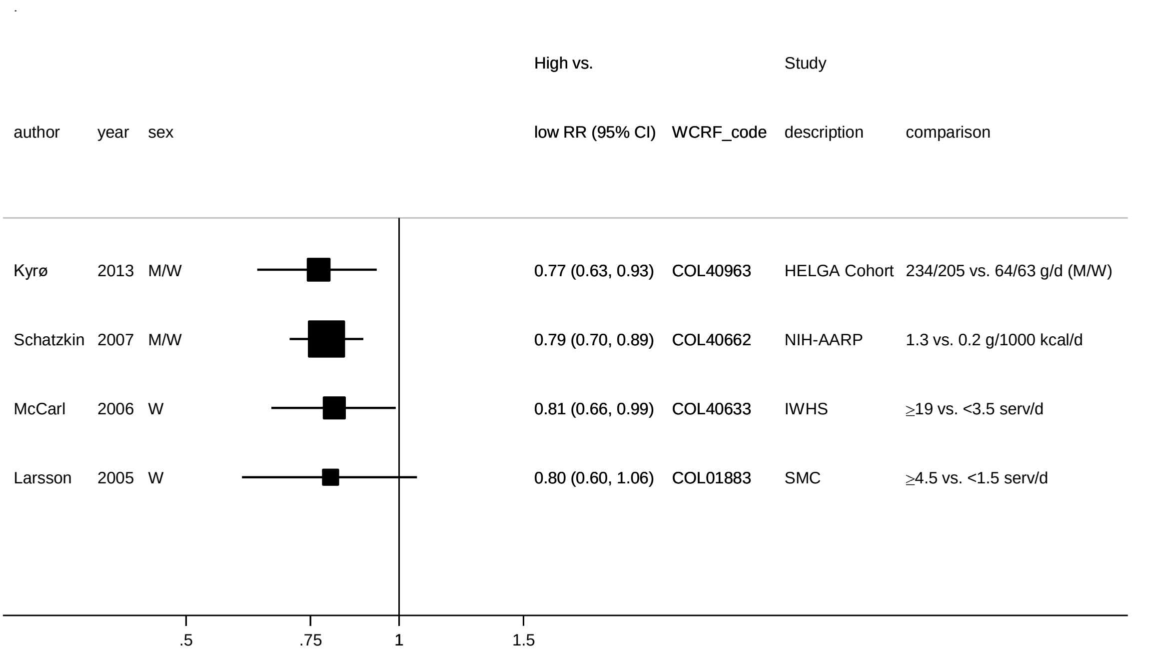


Figure 3 Relative risk of colorectal cancer for 90 g/day increase in whole grain intake

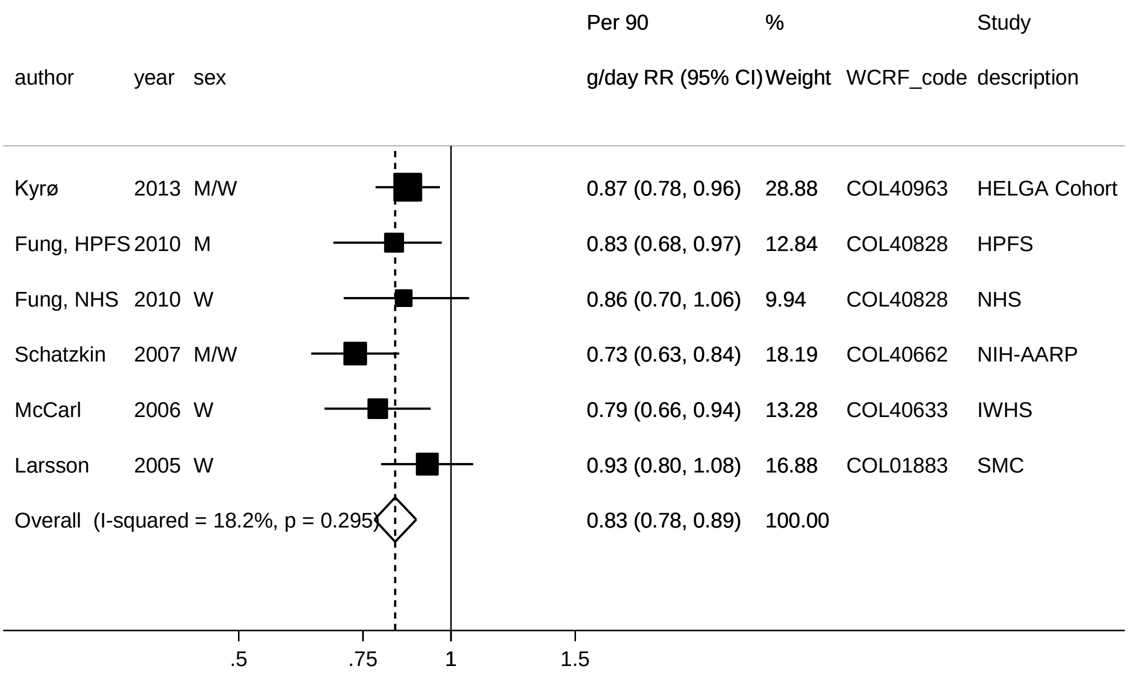
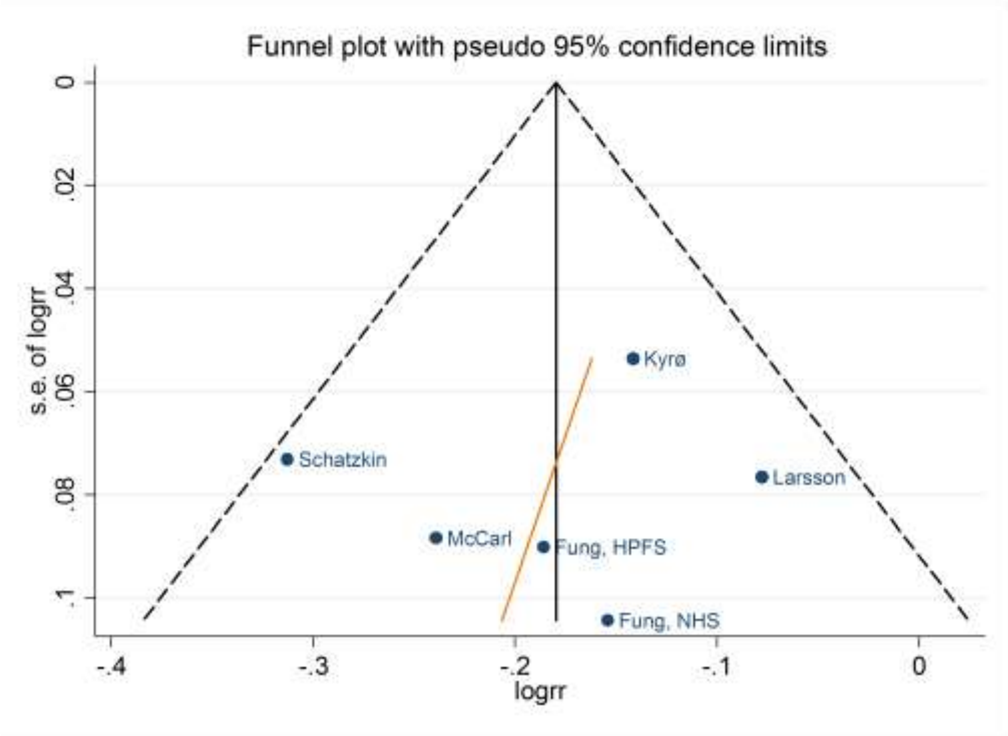
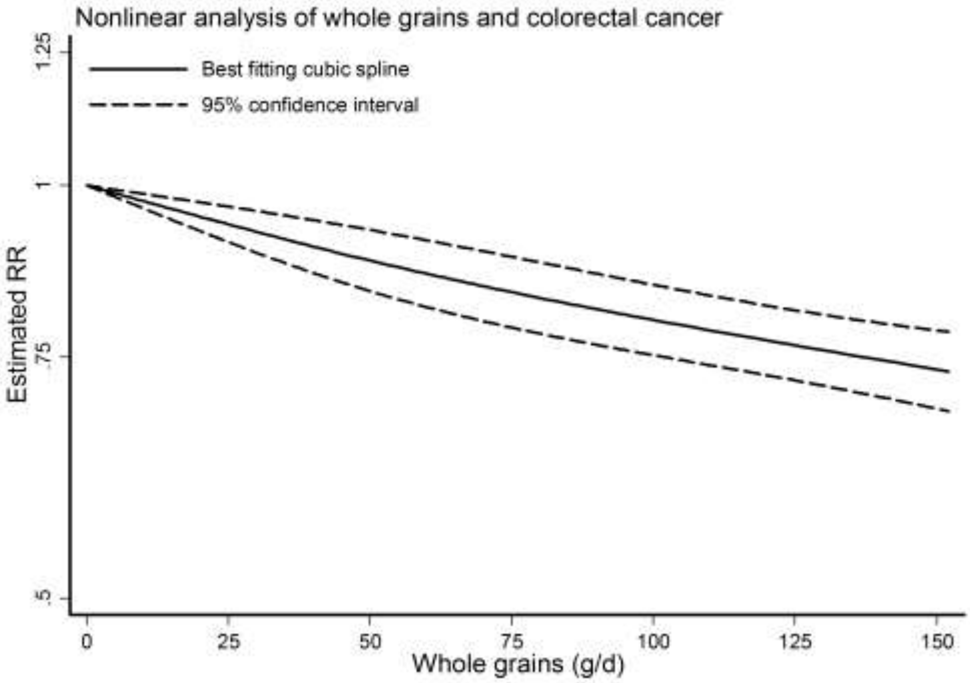


Figure 4 Funnel plot of studies included in the dose response meta-analysis of whole grain intake and colorectal cancer



p Egger's test =0.72

Figure 5 Whole grains and colorectal cancer, nonlinear dose-response analysis



p for non-linearity=0.33

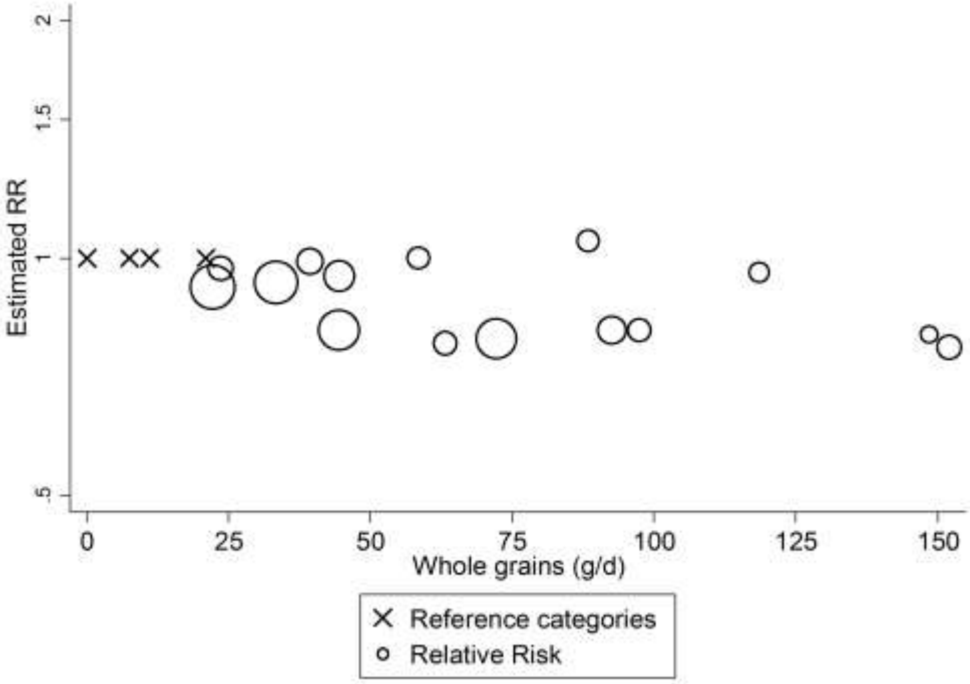


Table 12 Relative risk of colorectal cancer and whole grains estimated using non-linear models

Whole grains (g/day)	RR (95%CI)
0	1.00
25	0.94 (0.91-0.97)
50	0.88 (0.84-0.93)
75	0.84 (0.79-0.89)
100	0.80 (0.75-0.85)
125	0.76 (0.72-0.81)
150	0.73 (0.69-0.78)

Figure 6 RR estimates of colon cancer by levels of whole grain intake

Figure 7 Relative risk of colon cancer for the highest compared with the lowest level of whole grain intake

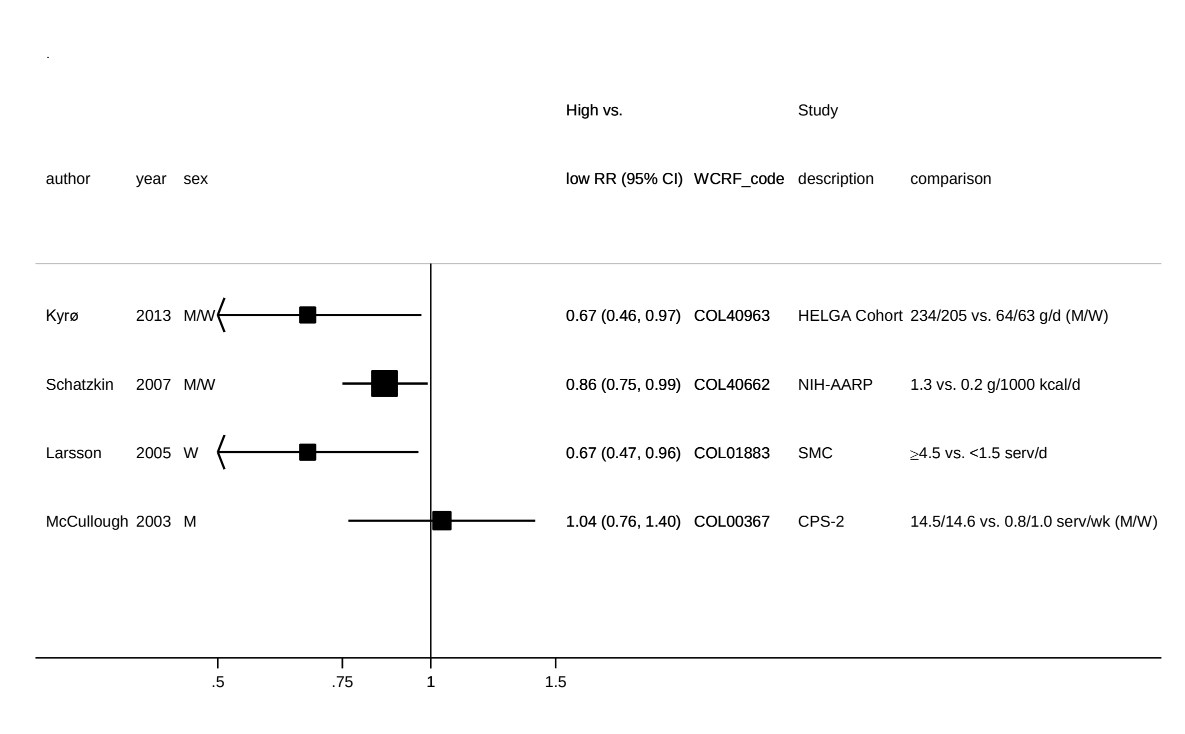


Figure 8 Relative risk of colon cancer for 90 g/day increase in whole grain intake

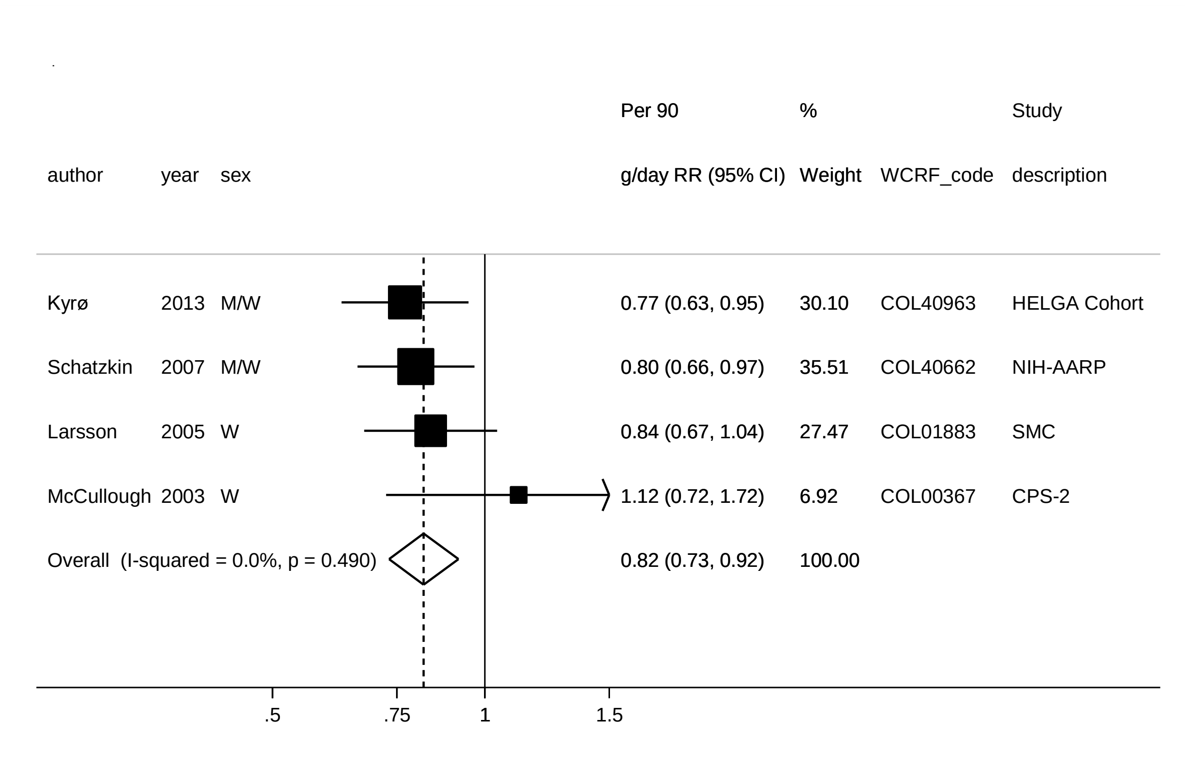
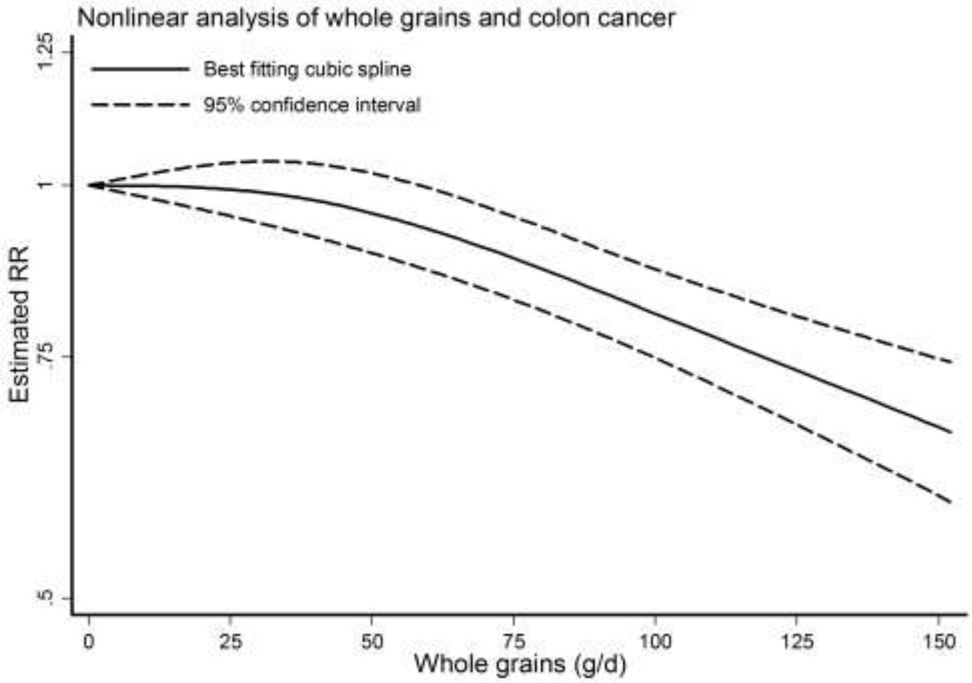


Figure 9 Whole grains and colon cancer, nonlinear dose-response analysis



P nonlinearity=0.01

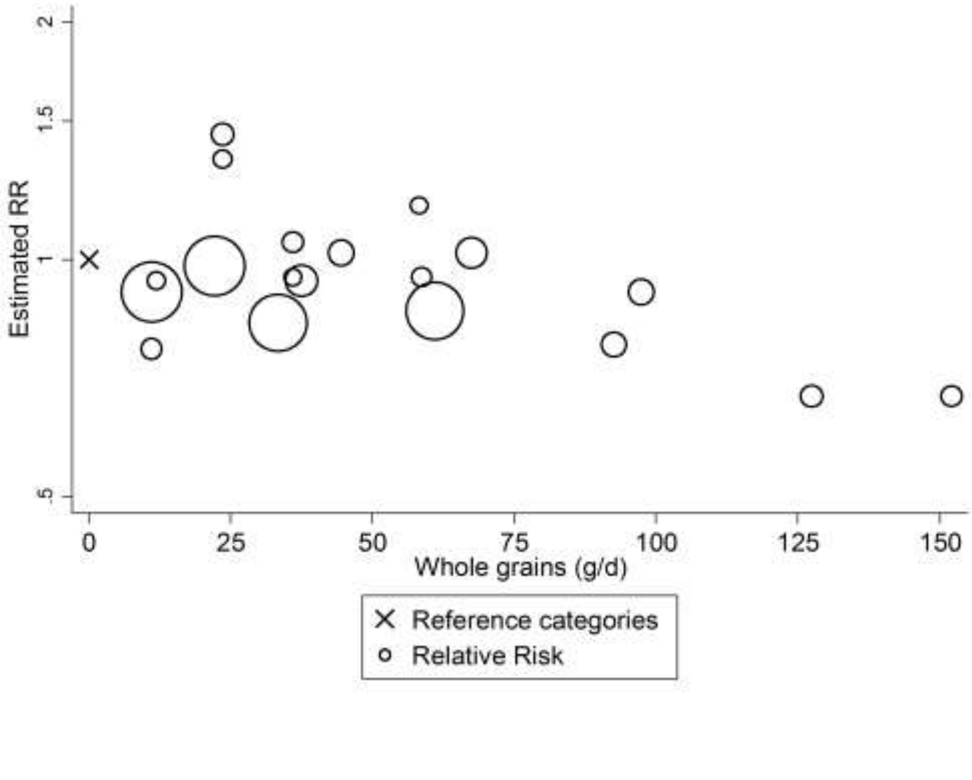


Table 13 Relative risk of colon cancer and whole grains estimated using non-linear models

Whole grains (g/day)	RR (95%CI)
0	1.00
25	0.99 (0.95-1.04)
50	0.95 (0.89-1.02)
75	0.89 (0.83-0.95)
100	0.81 (0.75-0.87)
125	0.73 (0.67-0.80)
150	0.67 (0.59-0.75)

Figure 10 RR estimates of rectal cancer by levels of whole grain intake

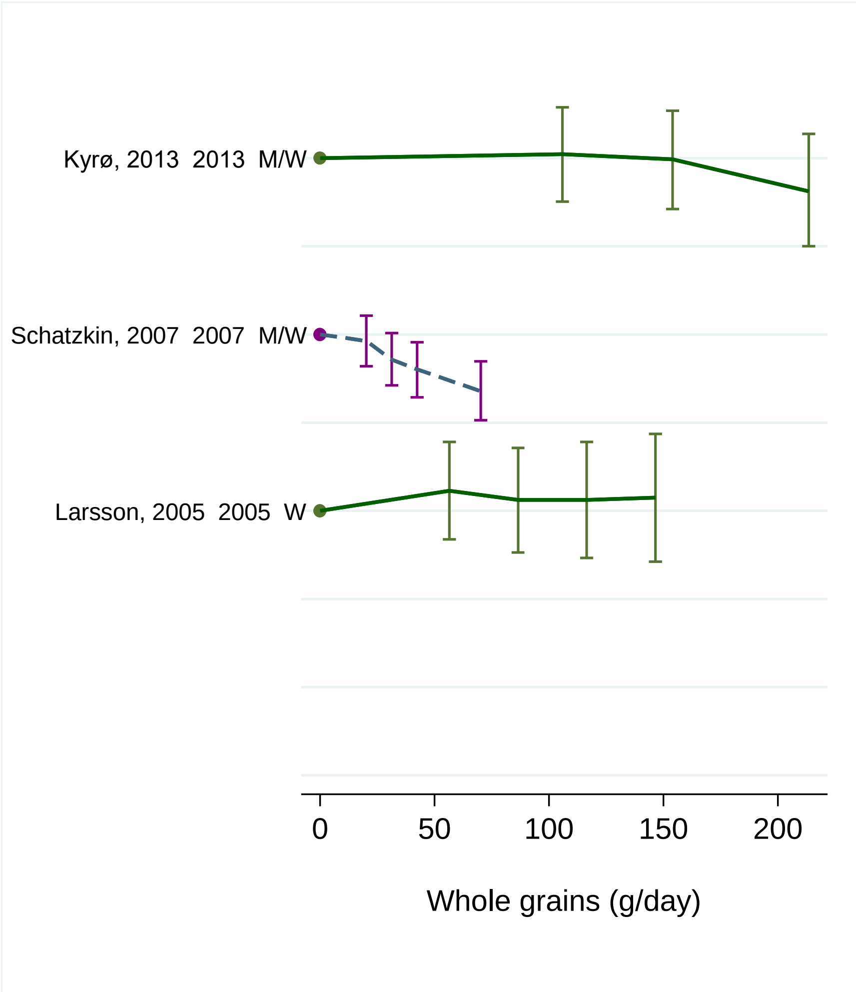


Figure 11 Relative risk of rectal cancer for the highest compared with the lowest level of whole grain intake

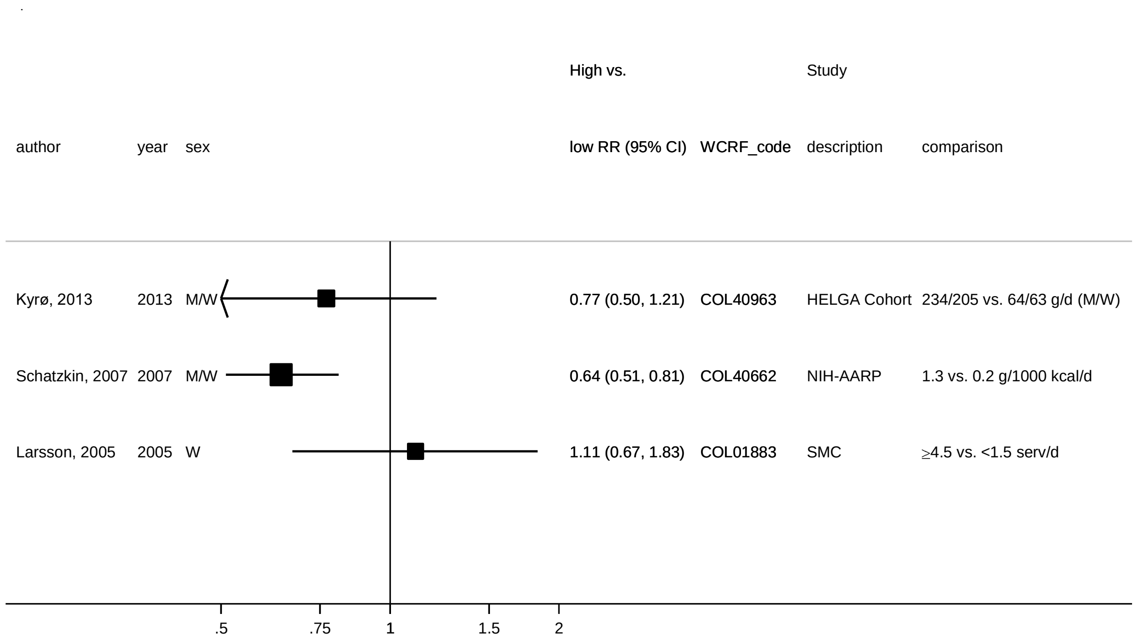
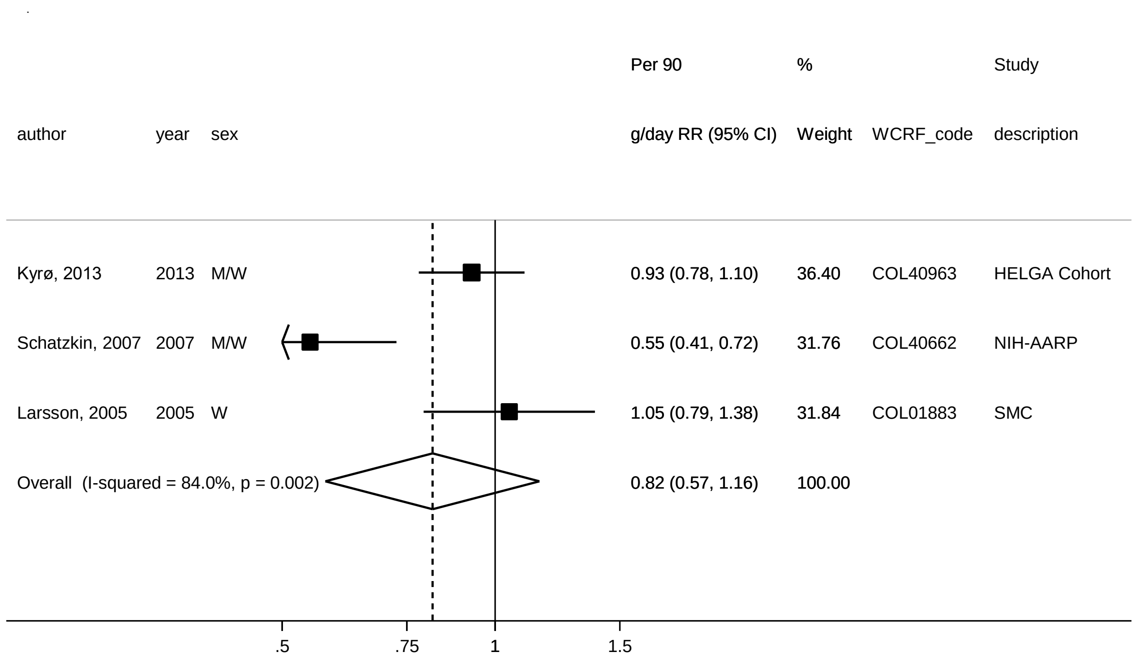


Figure 12 Relative risk of rectal cancer for 90 g/day increase in whole grain intake



2.2 Fruit and vegetables

Cohort studies

Summary

Main results:
Three new studies were identified (Vogtmann, 2013, Wie, 2014, and Makarem, 2015) since the 2010 SLR. In total 16 studies (21 publications) were identified on fruits and vegetables and colorectal cancer risk, and fifteen studies (14 publications) could be included in the dose-response analysis. Study characteristics and results for all cancer types are shown in the Table. For studies that reported fruit and vegetable intake in servings per day or other frequencies we used a serving size of 80 g for recalculation of the intakes to grams per day.

Colorectal cancer:
Ten studies (10999 cases) were included in the dose-response analysis. The summary RR for a 100 g/d increase in total fruit and vegetable intake was 0.98 (95% CI: 0.97-0.99) and there was no evidence of heterogeneity, I^2=13.8%, $p_{heterogeneity}$=0.32. There was no evidence of small study bias or publication bias with Egger's test, p=0.64. The summary RR ranged from 0.98 (95% CI: 0.97-0.99) when the NIH-AARP Diet and Health study (Park, 2007) was excluded to 0.99 (95% CI: 0.97-1.00) when the EPIC study (van Duijnhoven, 2009) was excluded.

The test for nonlinearity was significant, $p_{nonlinearity}$=0.009, and the association between fruits and vegetables and colorectal cancer was slightly stronger at lower levels of intake.

Colon cancer:
Eleven studies (>6045 cases) were included in the dose-response meta-analysis of total fruit and vegetable intake and colon cancer. The summary RR per 100 g/d was 0.99 (95% CI: 0.97-1.00) with low heterogeneity, I^2=0%, $p_{heterogeneity}$=0.50.

There was evidence of a nonlinear association between total fruit and vegetable intake and colon cancer, $p_{nonlinearity}$=0.01, with a stronger reduction in risk at lower levels of intake and no further reductions in risk with intakes above 700 grams per day.

Rectal cancer:
Ten studies (>2746 cases) were included in the dose-response meta-analysis of total fruit and vegetable intake intake and rectal cancer. The summary RR per 100 g/d was 0.99 (95% CI: 0.97-1.01) with moderate heterogeneity, I^2=0%, $p_{heterogeneity}$=0.56.

There was evidence of a nonlinear association between total fruit and vegetable intake and rectal cancer, $p_{nonlinearity}$=0.005, with a statistically significant association up to an intake of 600 grams per day, but no further reductions in risk with higher intakes.

Study quality

Total fruit and vegetable intake was assessed by FFQ in most studies. In EPIC, FFQ and food records were used depending on the cohort (van Duijnhoven, 2009).

Loss to follow-up was low for the studies that reported such data, although some studies did not provide data.

Cancers were identified by record linkages to health registries, cancer registries, mortality registries, or death indexes.

All studies adjusted for at least age, and most of the studies adjusted for most of the established colorectal cancer risk factors, including: age, physical activity, BMI, and alcohol consumption, smoking, red meat and hormone replacement therapy in women.

Table 14 Total fruit and vegetable intake and colorectal cancer risk. Number of studies in the CUP SLR

	Number
Studies identified	13 studies (17 publications)
Studies included in forest plot of highest compared with lowest intake	Colorectal cancer: 11 studies Colon cancer: 12 Rectal cancer: 10
Studies included in linear dose-response meta-analysis	Colorectal cancer: 13 studies Colon cancer: 11 Rectal cancer: 10
Studies included in non-linear dose-response meta-analysis	Colorectal cancer: 11 studies Colon cancer: 11 Rectal cancer: 10

Table 15 Total fruit and vegetable intake and colorectal cancer risk. Summary of the linear dose-response meta-analysis in the 2005 SLR, 2010 SLR and 2015 SLR

	2005 SLR		
	Colorectal cancer	**Colon cancer**	**Rectal cancer**
Increment unit used	Per 1 serving/day	Per 1 serving/day	Per 1 serving/day
Studies (n)	7	8	4
Cases (total number)	-	-	-
RR (95%CI)	0.99 (0.96-1.03)	0.99 (0.97-1.02)	0.98 (0.92-1.05)
Heterogeneity (I^2, p-value)	54.6%, p=0.03	45.2%, p=0.09	51.7%, p=0.10
P value Egger test	-	-	-

	2010 SLR		
	Colorectal cancer	**Colon cancer**	**Rectal cancer**

Increment unit used	100 g/day		
Studies (n)	7	10	9
Cases (total number)	9932	5827	2575
RR (95%CI)	0.99 (0.97-1.00)	0.99 (0.97-1.01)	0.99 (0.96-1.01)
Heterogeneity (I^2, p-value)	34.6%, p=0.16	25.4%, p=0.21	5.6%, p=0.39
P value Egger test			

	2015 SLR		
	Colorectal cancer	**Colon cancer**	**Rectal cancer**
Increment unit used	100 g/day		
Studies (n)	10	12	10
Cases (total number)	10999	>6045	>2746
RR (95%CI)	0.98 (0.97-0.99)	0.99 (0.97-1.00)	0.99 (0.97-1.01)
Heterogeneity (I^2, p-value)	13.8%, p=0.32	0%, p=0.50	0%, p=0.56
P value Egger test	0.64	0.75	0.22
Geographic location	**Asia**	**Europe**	**North-America**
Studies (n)	3	2	5
RR (95%CI)	1.00 (0.94-1.06)	0.96 (0.90-1.02)	0.99 (0.97-1.00)
Heterogeneity (I^2, p- value)	55.2%, p=0.11	61.6%, p=0.11	0%, p=0.79

Table 16 Fruit and vegetable intake and colorectal cancer risk. Results of meta-analyses and pooled analyses of prospective studies published after the 2005 SLR.

Author, Year	Number of studies	Total number of cases	Studies country, area	Outcome	Comparison	RR (95%CI)	P trend	Heterogeneity (I^2, p value)
Meta-analyses								
Aune et al, 2012	11 CRC 11 11 CC 7 RC	11853	North America, Europe, Asia	Incidence	High vs. low Per 100 g/d High vs. low High vs. low	0.92 (0.86-0.99) 0.99 (0.98-1.00) 0.91 (0.84-0.99) 0.97 (0.86-1.09)	- - - -	22%, p=0.24 38%, p=0.10 12.9%, p=0.32 0%, p=0.65
Pooled analyses								
Koushik, 2007	14	5838 CC	North America, Europe	Incidence	Quintile 5 vs. 1 ≥400 vs. <100 g/d	0.91 (0.82-1.01) 0.90 (0.77-1.05)	0.19 0.06	NA, p=0.31 NA, p=0.46

Table 17 Fruit and vegetable intake and colorectal cancer risk. Main characteristics of studies included in CUP SLR

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI)	Adjustment factors	Missing data derived for analysis
Makarem, 2015 COL41060 USA	FHS-Offspring Cohort, Prospective Cohort, Age: 66 years, M/W	63/ 2 983 11.5 years	Death certificate and medical records	Semi-quantitative FFQ	Incidence, colorectal cancer	per 1 points	0.96 (0.48-1.94)	Age, sex, smoking status	Conversion from WCRF score to g/d
Wie, 2014 COL41065 Korea	Cancer Screening Examination Cohort, Korea (CSECK), Prospective Cohort, M/W	53/ 8 024 7 years	Cancer registry and medical records	3-day food record	Incidence, colorectal cancer	≥600 vs <600 g/day	0.85 (0.38-1.92)	Age, sex, alcohol, BMI, educational level, energy Intake, Income, marital status, physical activity, smoking	None
					Incidence, colorectal cancer	per 100 g/day	1.00 (0.88-1.14)		
Vogtmann, 2013 COL40986 China	SMHS, Prospective Cohort, Age: 40-74 years, M	398/ 61 274 6.3 years	Cancer registry, shanghai vital statistics office, medical history	FFQ	Incidence, colorectal cancer	≥675.15 vs 0-284.34 g/day	0.71 (0.50-1.01)	Age, alcohol, BMI, diabetes, educational level, energy Intake, family history of colorectal cancer, Income, met-hours per week, occupation, red meat, smoking, total meat	Midpoints, distribution of person-years
					Incidence, colon cancer	≥675.15 vs 0-284.34 g/day	0.69 (0.43-1.09)		
					Incidence, rectal cancer	≥675.15 vs 0-284.34 g/day	0.75 (0.44-1.29)		
van Duijnhoven	EPIC, Prospective	2 819/ 452 755	Cancer registry,	FFQ	Incidence, colorectal	≥603.6 vs 0-	0.86 (0.75-	Age, sex, alcohol consumption, centre	Midpoints

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI)	Adjustment factors	Missing data derived for analysis
FJ, 2009COL40785 Denmark,France,Germany, Greece,Italy, Netherlands, Norway,Spain ,Sweden,UK	Cohort, Age: 35-70 years, M/W	8.8 years	health Insurance records, active follow up and mortality registry		cancer	221 g/day	1.00)	location, cereal fibre, energy from fat, energy from nonfat sources, fish, height, physical activity, processed meat, red meat Intake, smoking status, weight	
					Incidence, colorectal cancer	per 100 g/day	0.98 (0.97-1.00)		
					Incidence, colon cancer	≥603.6 vs 0-221 g/day	0.76 (0.63-0.91)		
					Incidence, colon cancer	per 100 g/day	0.96 (0.91-1.01)		
					Incidence, proximal colon cancer	≥603.6 vs 0-221 g/day	0.77 (0.58-1.02)		
					Incidence, distal colon cancer	≥603.6 vs 0-221 g/day	0.70 (0.53-0.93)		
					Incidence, rectal cancer	≥603.6 vs 0-221 g/day	1.09 (0.85-1.40)		
					Incidence, rectal cancer	per 100 g/day	1.00 (0.97-1.04)		
Lee, 2009 COL40764 China	SWHS, Prospective Cohort, Age: 40-70 years,	394/ 73 224 7.4 years	Cancer registry and death certificates and	Quantitative FFQ	Incidence, colorectal cancer	≥663 vs ≤324.9 g/day	1.20 (0.90-1.60)	Age, energy Intake	Midpoints
					Incidence, colon cancer	≥663 vs ≤324.9 g/day	1.30 (0.80-1.90)		

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI)	Adjustment factors	Missing data derived for analysis
	W		participant contact		Incidence, rectal cancer	≥663 vs ≤324.9 g/day	1.00 (0.60-1.70)		
Nomura, 2008 COL40663 USA	MEC, Prospective Cohort, Age: 45-75 years, M/W	1 023/ 191 011 7.3 years	Cancer registry	FFQ-quantitative	Incidence, colorectal cancer, men	483.2 vs 134.7 g1000 kcal/day	0.74 (0.59-0.93)	Age, alcohol Intake, aspirin use, BMI, calcium Intake, energy Intake, ethnicity, family history of colorectal cancer, folate Intake, history of polyps, multivitamin, pack-years of smoking, physical activity, red meat Intake, time, vitamin d	Distribution of cases and person-years, conversion of g/1000 kcal/d to g/d
					Incidence, colorectal cancer, women	608.1 vs 176.3 g1000 kcal/day	1.04 (0.81-1.33)		
					Incidence, colon cancer, men	483.2 vs 134.7 g1000 kcal/day	0.72 (0.55-0.94)		
					Incidence, colon cancer, women	608.1 vs 176.3 g1000 kcal/day	1.03 (0.78-1.38)		
					Incidence, rectal cancer, men	483.2 vs 134.7 g1000 kcal/day	0.72 (0.47-1.11)		
					Incidence, rectal cancer, women	608.1 vs 176.3 g1000 kcal/day	1.10 (0.65-1.85)		
Park, 2007 COL40697 USA	NIH-AARP, Prospective Cohort,	2 048/ 488 043 2 121 664	Cancer registry	FFQ	Incidence, colorectal cancer, men	5.2 vs 1.4 servings1000 kcal/day	0.91 (0.78-1.05)	Age, alcohol consumption, calcium Intake, educational level, physical activity, red	Distribution of person-years, conversion of

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI)	Adjustment factors	Missing data derived for analysis
	Age: 50-71 years, M/W	person-years			Incidence, colorectal cancer, women	6.5 vs 1.8 servings1000 kcal/day	1.08 (0.86-1.35)	meat Intake, smoking status, total energy Intake	serv/1000 kcal/d to g/d
					Incidence, distal colon cancer, women	6.5 vs 1.8 servings1000 kcal/day	1.12 (0.72-1.76)		
					Incidence, rectal cancer, women	6.5 vs 1.8 servings1000 kcal/day	1.26 (0.81-1.97)		
					Incidence, distal colon cancer, men	5.2 vs 1.4 servings1000 kcal/day	0.89 (0.69-1.15)		
					Incidence, rectal cancer, men	5.2 vs 1.4 servings1000 kcal/day	0.93 (0.71-1.22)		
					Incidence, colon cancer, men	5.2 vs 1.4 servings1000 kcal/day	0.92 (0.71-0.99)		
					Incidence, proximal colon cancer, men	5.2 vs 1.4 servings1000 kcal/day	0.92 (0.69-1.18)		

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI)	Adjustment factors	Missing data derived for analysis
					Incidence, colon cancer, women	6.5 vs 1.8 servings1000 kcal/day	1.04 (0.80-1.35)		
					Incidence, proximal colon cancer, women	6.5 vs 1.8 servings1000 kcal/day	1.01 (0.73-1.40)		
McCarl, 2006 COL40633 USA	IWHS, Prospective Cohort, Age: 55-69 years, W	954/ 35 197 15 years	Seer registry	FFQ	Incidence, colorectal cancer	≥58.01 vs ≤27.4 servings/week	0.90 (0.73-1.10)	Age	Midpoints, conversion of serv/wk to g/d
Lin, 2005 COL01831 USA	WHS, Prospective Cohort, Age: 45- years, W, professionals	223/ 36 976 10 years	Follow up questionnaires (self report), medical record and pathology reports	FFQ	Incidence, colorectal cancer, women	10 vs 2.6 serving/day	0.96 (0.58-1.62)	Age, alcohol consumption, aspirin use, BMI, family history of specific cancer, history of previous polyp and prior endoscopy, menopausal status, physical activity, postmenopausal hormone use, randomized treatment assignment, red meat Intake, smoking status, total energy	Distribution of person-years, conversion of serv/d to g/d
Sato, 2005 COL01930	MCS, Prospective	165/ 41 835	Population registry	Questionnaire	Incidence, colon cancer,	≥398 vs 0-543 g/day	1.13 (0.73-1.75)	Age, sex, alcohol consumption, BMI,	Midpoints

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI)	Adjustment factors	Missing data derived for analysis
Japan	Cohort, Age: 40-64 years, M	7 years			Incidence, rectal cancer,	≥398 vs 0-543 g/day	1.12 (0.67-1.89)	educational level, energy content, family history of specific cancer, meat consumption, physical activity, smoking status	
Terry, 2001 COL00059 Sweden	SMC, Prospective Cohort, Age: 40-74 years, W	460/ 61 463 588 270 person-years	Mammography screening program	FFQ	Incidence, colorectal cancer	≥5 vs 0-2.5 serving/day	0.73 (0.56-0.96)	Age, red meat & dairy product Intake, total caloric Intake	Midpoints, distribution of cases and person-years, conversion from serv/d to g/d
					Incidence, colon cancer,	≥5 vs 0-2.5 serving/day	0.81 (0.59-1.13)		
					Incidence, rectal cancer,	≥5 vs 0-2.5 serving/day	0.60 (0.38-0.96)		
					Incidence, proximal colon cancer,	≥5 vs 0-2.5 serving/day	0.91 (0.55-1.51)		
					Incidence, distal colon cancer,	≥5 vs 0-2.5 serving/day	0.87 (0.49-1.54)		
Michels, 2000 COL00365 USA	NHS, Prospective Cohort, Age: 30-55 years, W,	569/ 88 764 1 327 029 person-years	Population registries	Semi-quantitative FFQ	Incidence, colon cancer,	≥6 vs 0-2 serving/day	0.96	Age, alcohol consumption, aspirin use, BMI, family history of colorectal cancer, height, menopausal status, pack-years of smoking, physical activity,	Included in the dose-response analysis. No confidence intervals were provided for high
					Incidence, colon cancer,	per 1 serving/day	1.00 (0.96-1.04)		
					Incidence, rectal cancer,	≥6 vs 0-2 serving/day	0.88		

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI)	Adjustment factors	Missing data derived for analysis
	Registred nurses				Incidence, rectal cancer,	per 1 serving/day	1.00 (0.92-1.09)	postmenopausal hormone use, red meat Intake, sigmoidoscopy, supplement Intake, total caloric Intake	vs. low analysis
Michels, 2000 COL00365 USA	HPFS, Prospective Cohort, Age: 40-75 years, M, Health professionals	368/ 47 325 416 616 person-years		FFQ	Incidence, colon cancer,	≥6 vs 0-2 serving/day	1.28	Family history of specific cancer, smoking status, total energy, vitamin supplement	Included in the dose-response analysis. No confidence intervals were provided for high vs. low analysis
					Incidence, colon cancer,	per 1 serving/day	1.05 (0.99-1.11)		
					Incidence, rectal cancer,	≥6 vs 0-2 serving/day	1.20		
					Incidence, rectal cancer,	per 1 serving/day	1.06 (0.95-1.18)		
Voorrips, 2000 COL00578 Netherlands	NLCS, Case Cohort, Age: 55-69 years, M/W	266/ 120 852 6.3 years	Cancer registry	Semi-quantitative FFQ	Incidence, colon cancer, men	519 vs 177 g/day	0.95 (0.64-1.41)	Age, alcohol consumption, family history of colorectal cancer	None
					Incidence, colon cancer, women	578 vs 208 g/day	0.66 (0.44-1.01)		
					Incidence, proximal colon cancer, men	Q 5 vs Q 1	0.89 (0.51-1.56)		
					Incidence, distal colon	Q 5 vs Q 1	1.04 (0.62-1.75)		

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI)	Adjustment factors	Missing data derived for analysis
					cancer, men				
					Incidence, distal colon cancer, women	Q 5 vs Q 1	0.44 (0.23-0.82)		
					Incidence, proximal colon cancer, women	Q 5 vs Q 1	0.89 (0.52-1.51)		
					Incidence, rectal cancer, men	519 vs 177 g/day	0.88 (0.56-1.37)		
					Incidence, rectal cancer, women	578 vs 208 g/day	1.17 (0.63-2.17)		
Zheng, 1998 COL00209 USA	IWHS, Prospective Cohort, Age: 55-69 years, W, Postmenopausal	144/ 34 702 9 years	Population	Semi-quantitative FFQ	Incidence, rectal cancer,	≥48.6 vs ≤33.4 serving/week	0.97 (0.62-1.51)	Age	Midpoints, conversion from serv/wk to g/d
Steinmetz, 1994	IWHS, Prospective	212/ 35 216	Driving license	Semi-quantitative	Incidence, colon cancer,	≥47.1 vs 0-24.5	0.89 (0.57-1.40)	Age, energy Intake	Midpoints, conversion from

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI)	Adjustment factors	Missing data derived for analysis
COL00178 USA	Cohort, Age: 55-69 years, W, Postmenopausal	167 447 person-years		FFQ		serving/week			serv/wk to g/d, distribution of cases and person-years
					Incidence, proximal colon cancer,	≥47.1 vs 0-24.5 serving/week	0.78 (0.37-1.66)		
					Incidence, distal colon cancer,	≥47.1 vs 0-24.5 serving/week	0.91 (0.50-1.64)		
Shibata, 1992 COL00740 USA	Leisure World Cohort, Prospective Cohort, M/W, retirement community, uppermiddle social class	105/ 11 580 70 159 person-years	Community registry	FFQ	Incidence, colon cancer, women	≥8.3 vs 0-5.9 serving/day	0.63 (0.40-1.00)	Age, smoking habits	Conversion from serv/d to g/d, distribution of person-years
					Incidence, colon cancer, men	≥7.9 vs 0-5.5 serving/day	1.50 (0.91-2.46)		

Table 18 Fruit and vegetable intake and colorectal cancer risk. Main characteristics of studies excluded of the CUP SLR

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Reasons for exclusion
Hansen, 2009 COL40855 Denmark	DCH, Case Cohort, Age: 50-64 years	173/ 57 053	Cancer registry	FFQ	Incidence, colorectal cancer, gpx1 pro198leu cc	per 100 gday	0.93 (0.84-1.03)	Alcohol Intake, BMI, fibre, fruits and vegetables consumption, HRT use, smoking, pack-years	Duplicate, overlap with van Duijnhoven FJ, 2009 COL40785
					Incidence, colorectal cancer, gpx1 pro198leu ct	per 100 gday	1.00 (0.90-1.12)		
					Incidence, colorectal cancer, gpx1 pro198leu tt	per 100 gday	1.07 (0.89-1.29)		
McCullough, 2003 COL00367 USA	CPS II, Prospective Cohort, Age: 50-74 years, M/W	298/ 133 163 6 years	Cps-II cohort	Semi-quantitative FFQ	Incidence, colon cancer, men	Q 5 vs Q 1	1.23 (0.83-1.83)	Age, aspirin use, BMI, calcium, educational level, energy Intake, family history of colorectal cancer, multivitamin, physical activity, red meat Intake, smoking habits	Only high vs. low comparison
					Incidence, colon cancer, women	Q 5 vs Q 1	0.70 (0.43-1.15)		
Bueno-de-Mesquita, 2002 COL00950	EPIC, Prospective Cohort,	773/ 406 439	Not specified	FFQ	Incidence, colorectal cancer	Q 5 vs Q 1	0.74	Age, sex, body weight, centre location, energy Intake, ethanol Intake,	Duplicate, overlap with van Duijnhoven FJ,

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Reasons for exclusion
Europe	M/W				Incidence, colorectal cancer, women	≥658 vs 0-268 g/day	0.76	height, physical activity at work, smoking habits	2009 COL40785
					Incidence, colorectal cancer, without first 2 years of follow-up	Q 5 vs Q 1	0.72		
					Incidence, colorectal cancer, women, without first 2 yrs of follow-up	≥658 vs 0-268 g/day	0.81		
					Incidence, colorectal cancer, men	≥544 vs 0-184 g/day	0.68		
					Incidence, colorectal cancer, men, without first 2 yrs of follow-up	≥544 vs 0-184 g/day	0.53		

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Reasons for exclusion
Sellers, 1998 COL01974 USA	IWHS, Prospective Cohort, Age: 55-69 years, W, Postmenopausal	180/ 35 216 10 years	Seer registry	Semi-quantitative FFQ	Incidence, colon cancer, no family history of crc	≥48.1 vs ≤33 servings/week	0.80 (0.60-1.20)	Age, history of polyps, total energy Intake	Duplicate, overlap with McCarl, 2006 COL40633
					Incidence, colon cancer, family history of crc	≥48.1 vs ≤33 servings/week	1.80 (0.80-3.70)		

Figure 13RR estimates of colorectal cancer by levels of fruit and vegetable intake

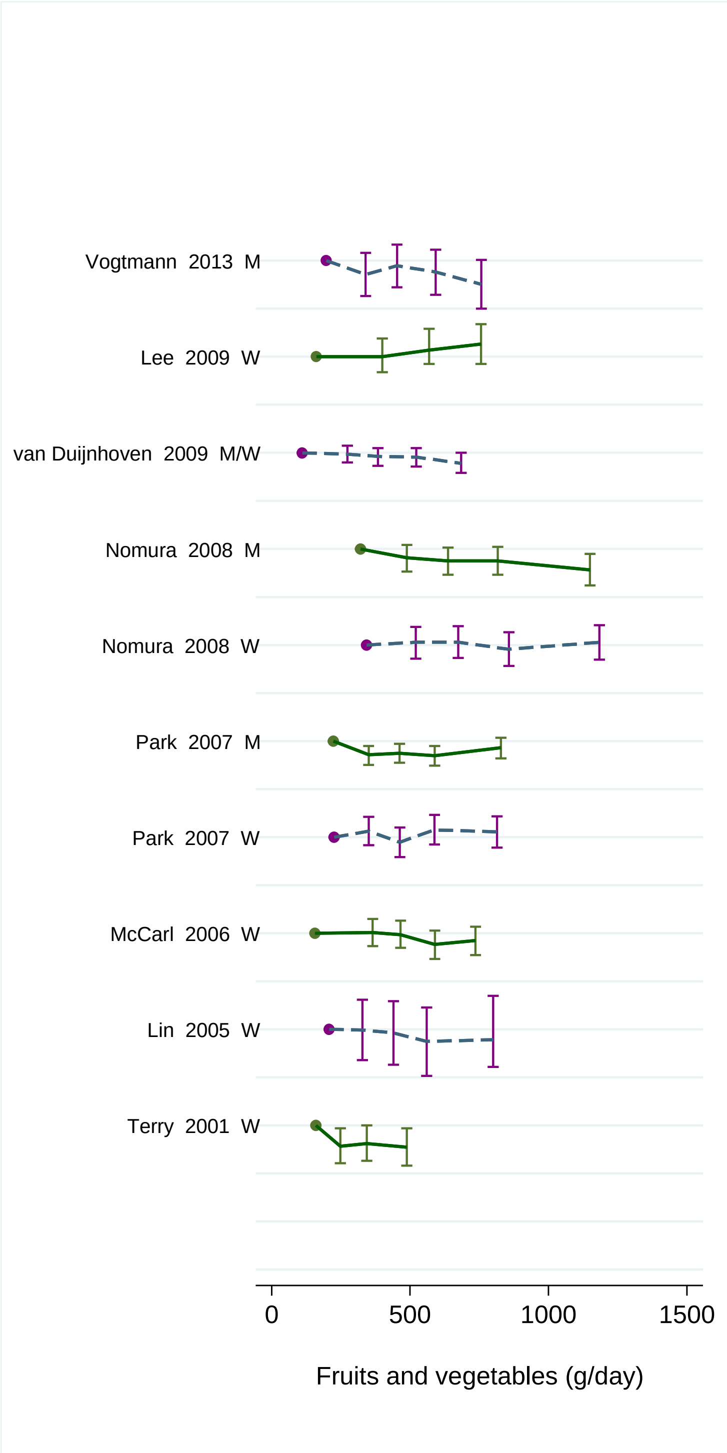


Figure 14Relative risk of colorectal cancer for the highest compared with the lowest level of fruit and vegetable intake

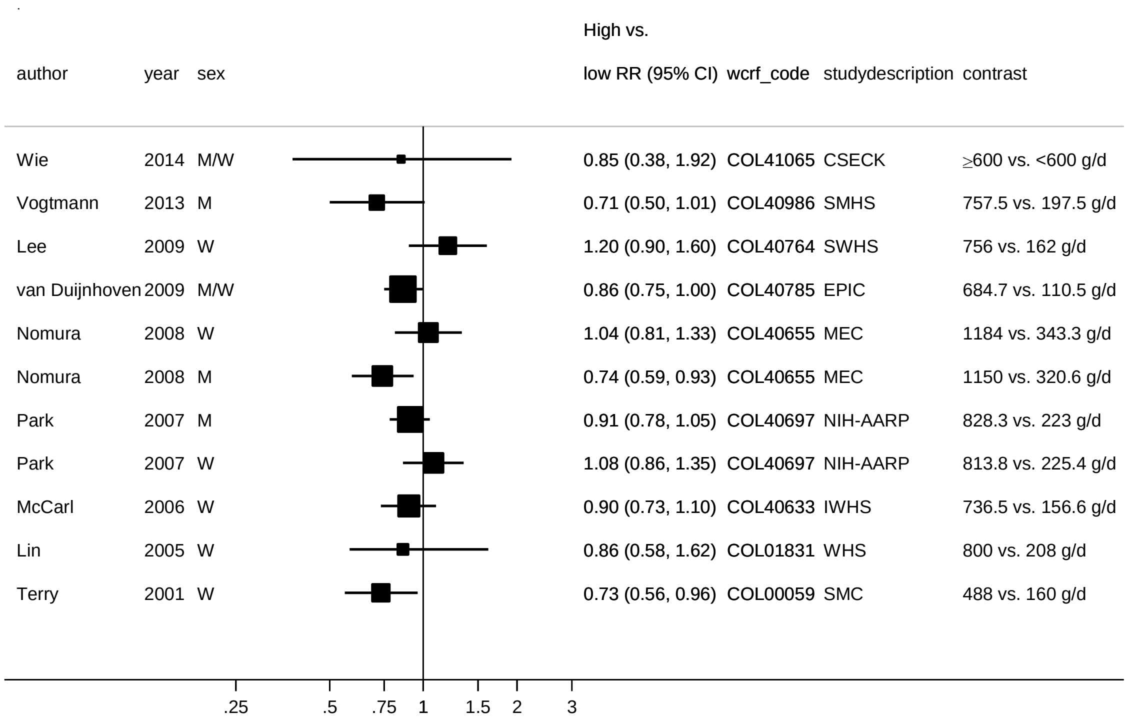


Figure 15 Relative risk of colorectal cancer for 100 g/day increase in fruit and vegetable intake

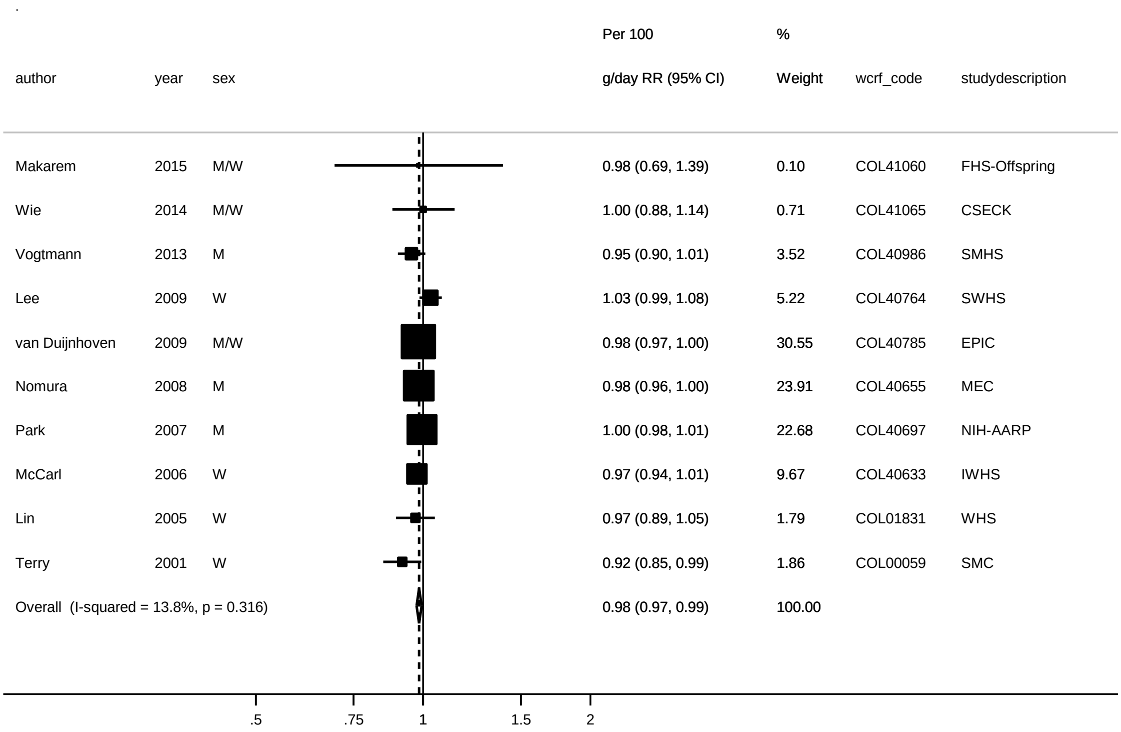


Figure 16 Relative risk of colorectal cancer for 100 g/day increase in fruit and vegetable intake, stratified by sex

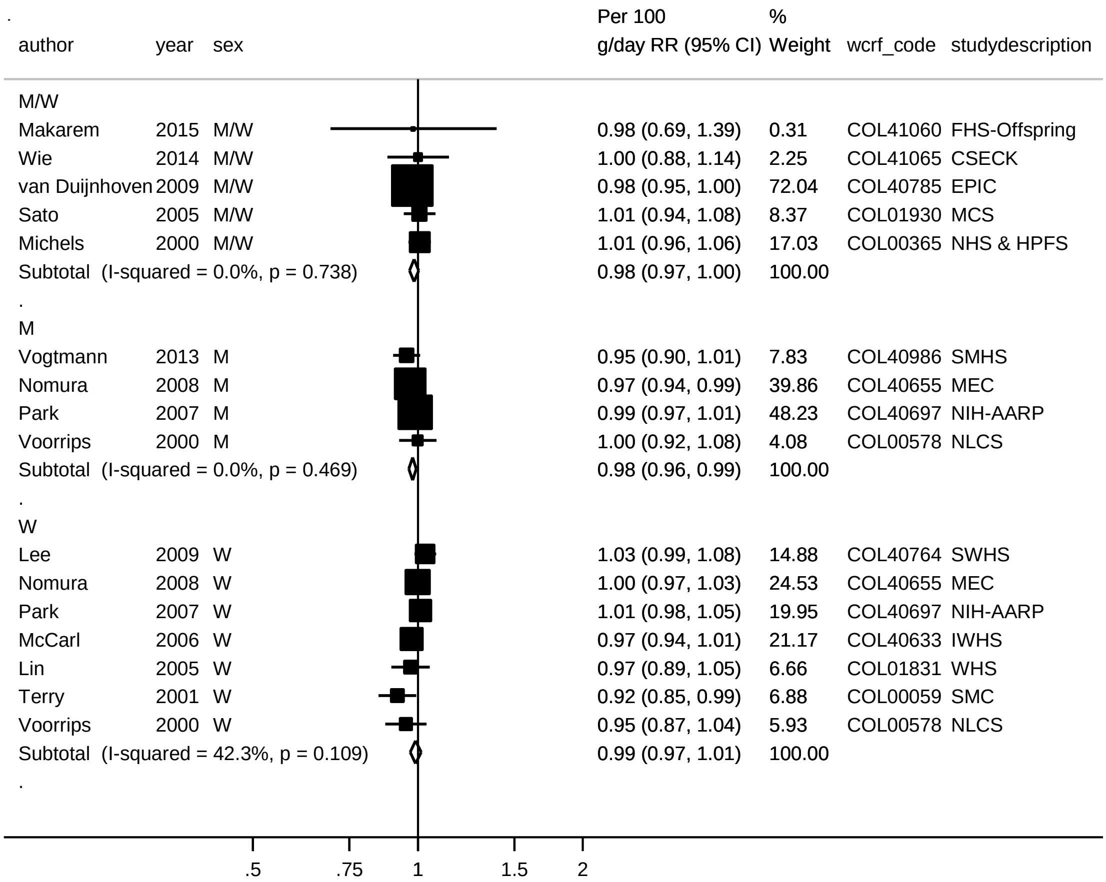


Figure 17 Relative risk of colorectal cancer for 100 g/day increase in fruit and vegetable intake, stratified by geographic location

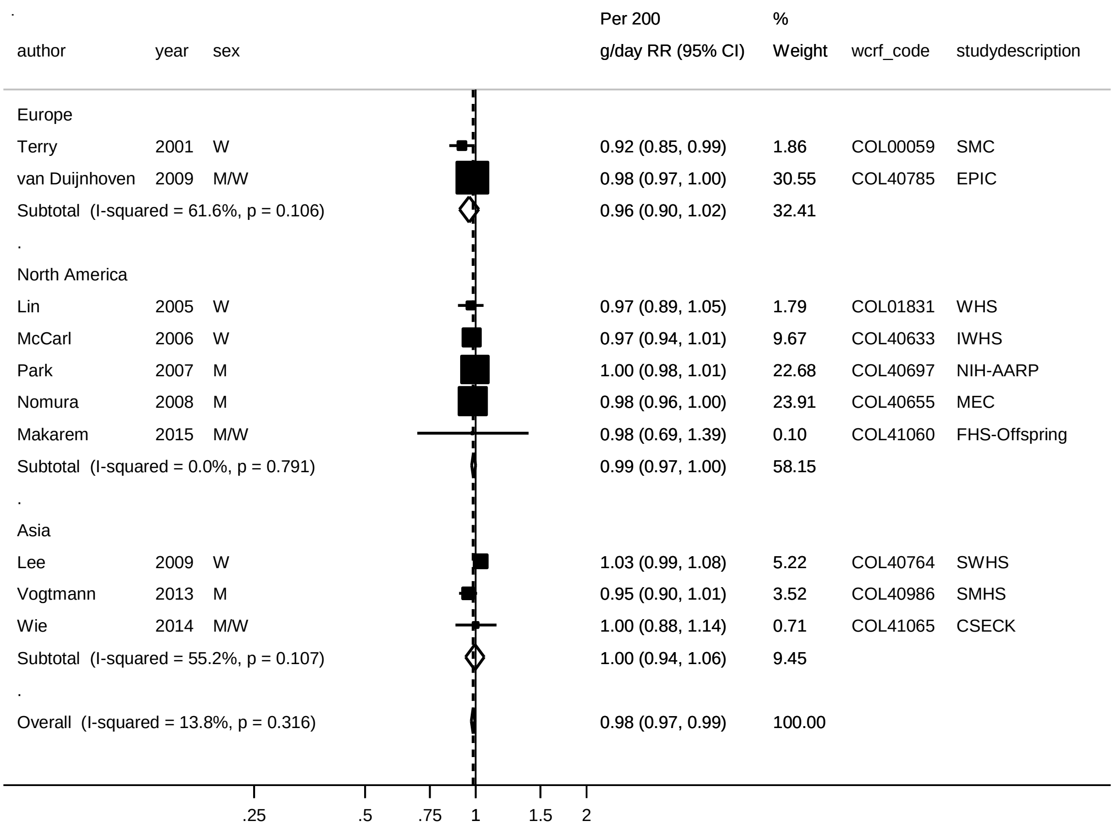
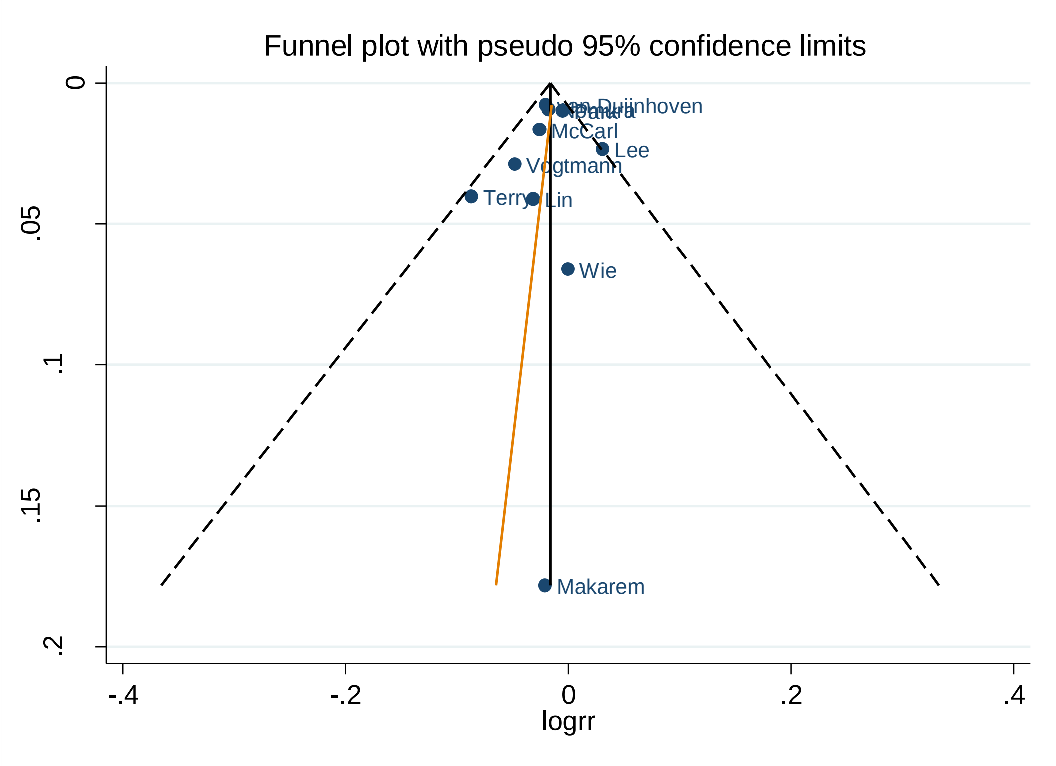
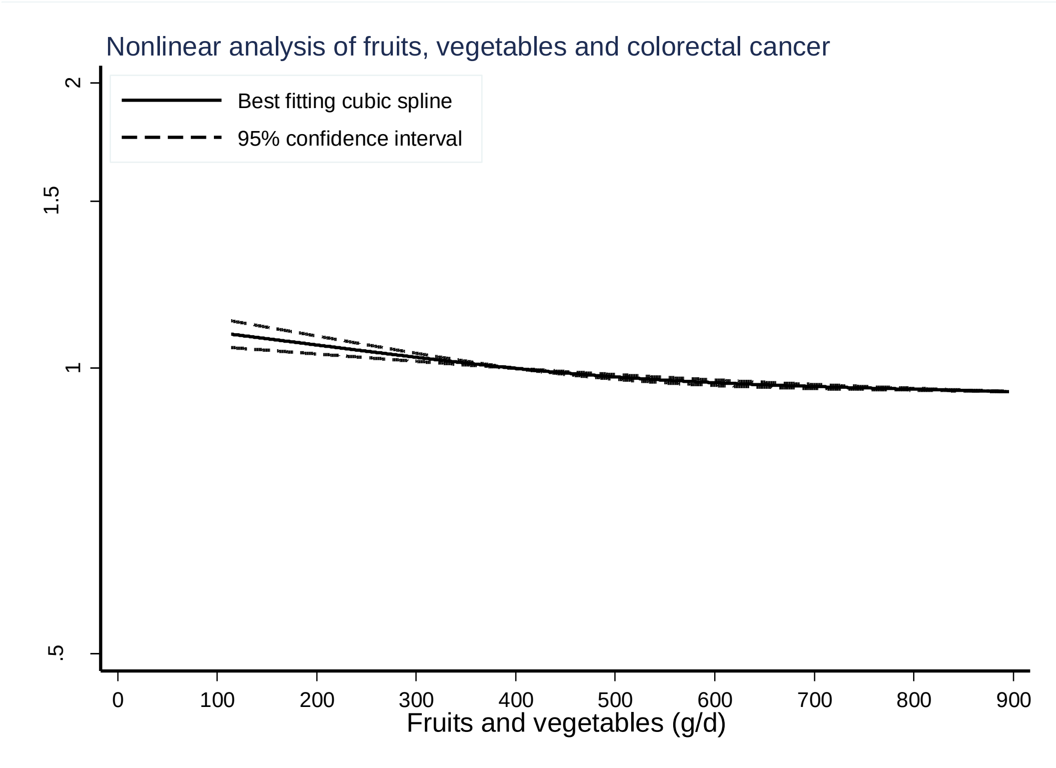


Figure 18 Funnel plot of studies included in the dose response meta-analysis of fruit and vegetable intake and colorectal cancer



p Egger's test=0.64

Figure 19 Relative risk of colorectal cancer and fruits and vegetables estimated using non-linear models



P nonlinearity=0.009

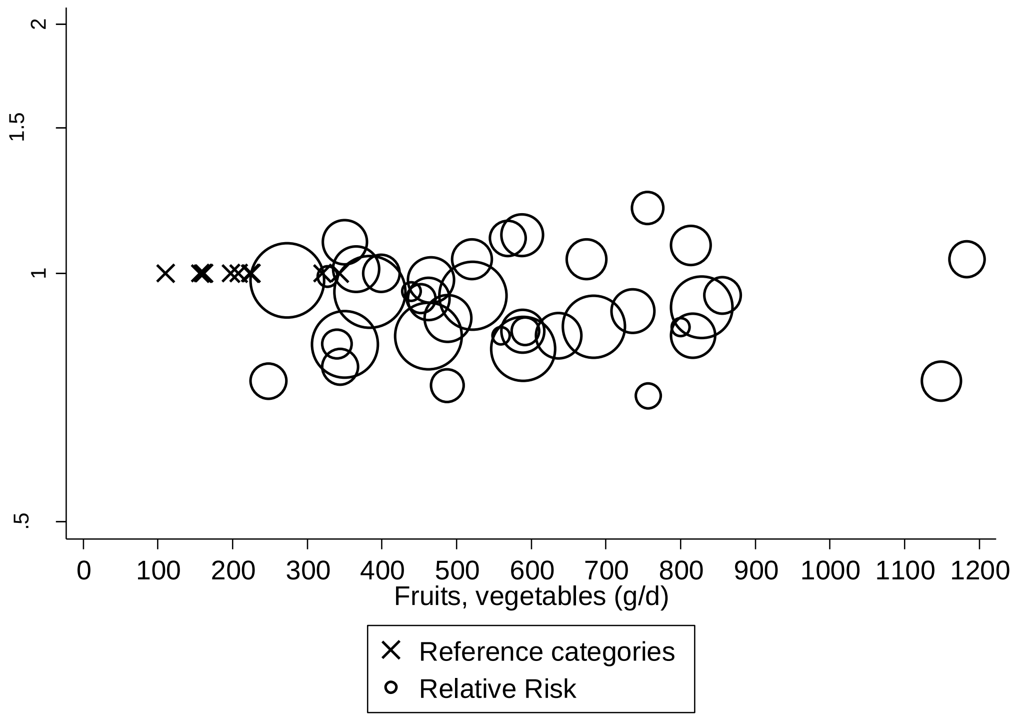


Table 19 Relative risk of colorectal cancer and fruit and vegetable intake estimated using non-linear models

g/day	RR (95% CI)
110.5	1.09 (1.05-1.12)
200	1.06 (1.04-1.08)
300	1.03 (1.02-1.04)
400	1.00
500	0.98 (0.97-0.99)
600	0.97 (0.96-0.97)
700	0.96 (0.95-0.96)
800	0.95 (0.95-0.95)
900	0.94 (0.94-0.94)

Figure 20RR estimates of colon cancer by levels of fruit and vegetable intake

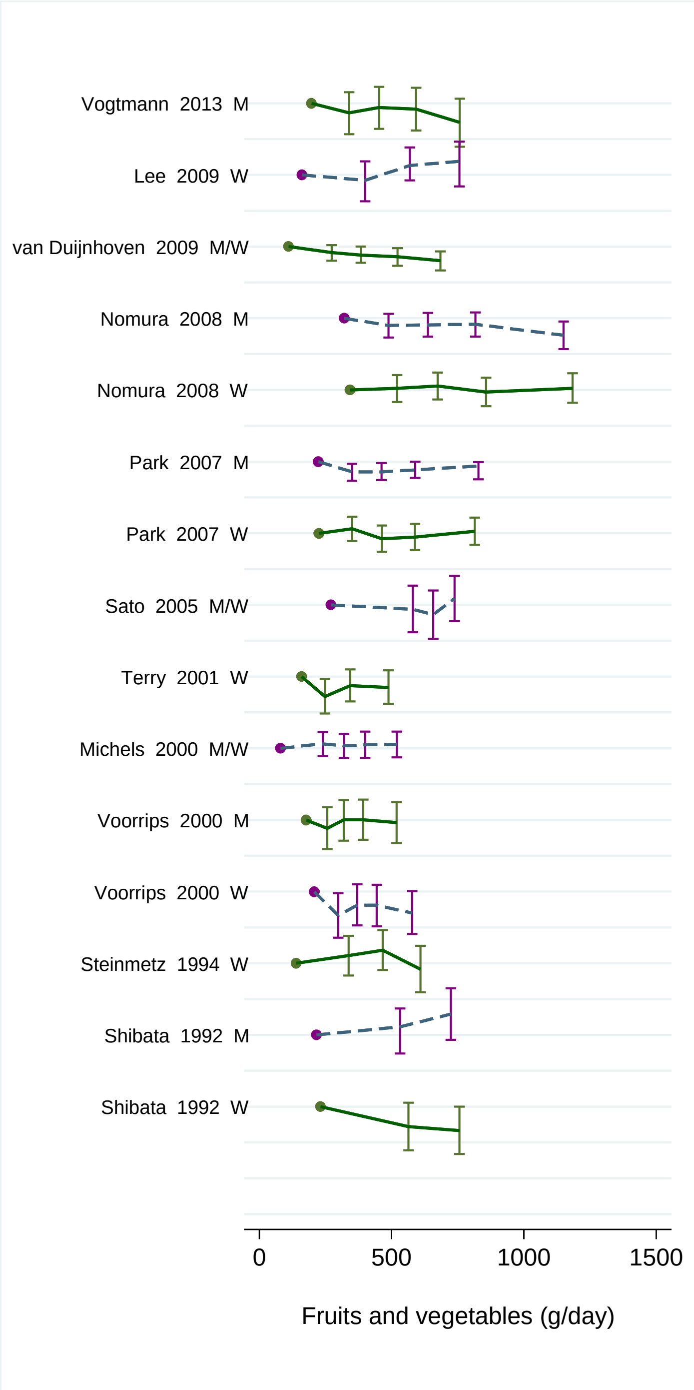


Figure 21 Relative risk of colon cancer for the highest compared with the lowest level of fruit and vegetable intake

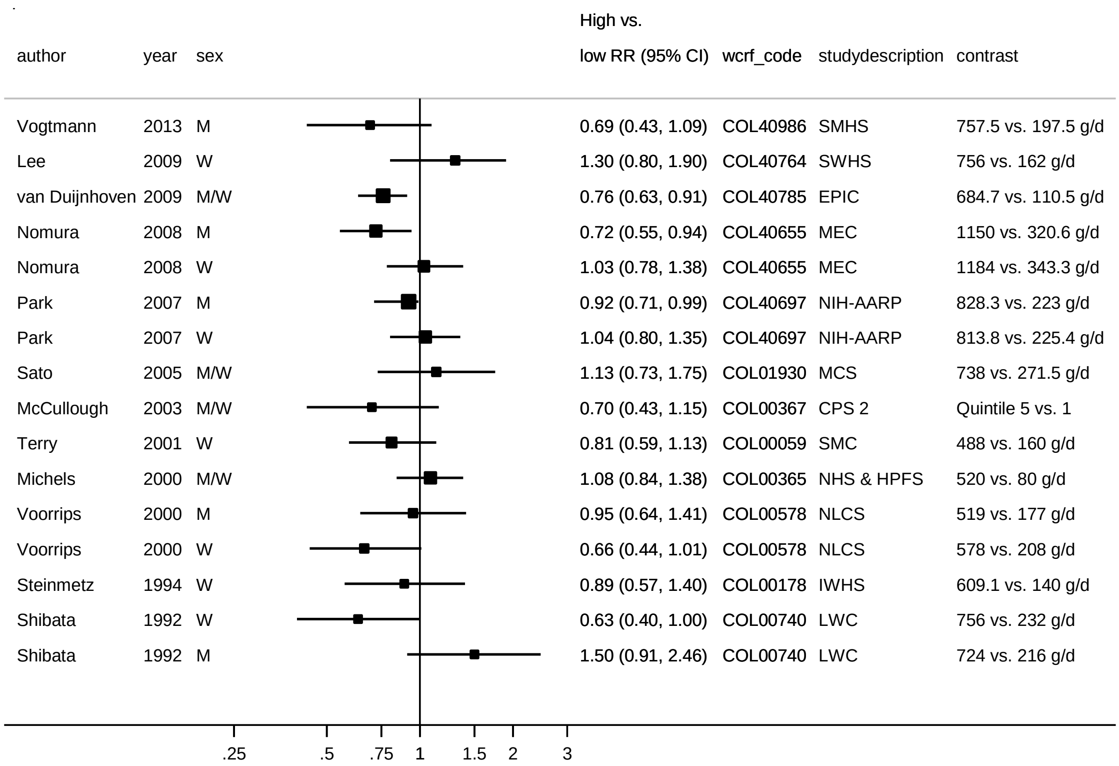


Figure 22 Relative risk of colon cancer for 100 g/day increase in fruit and vegetable intake

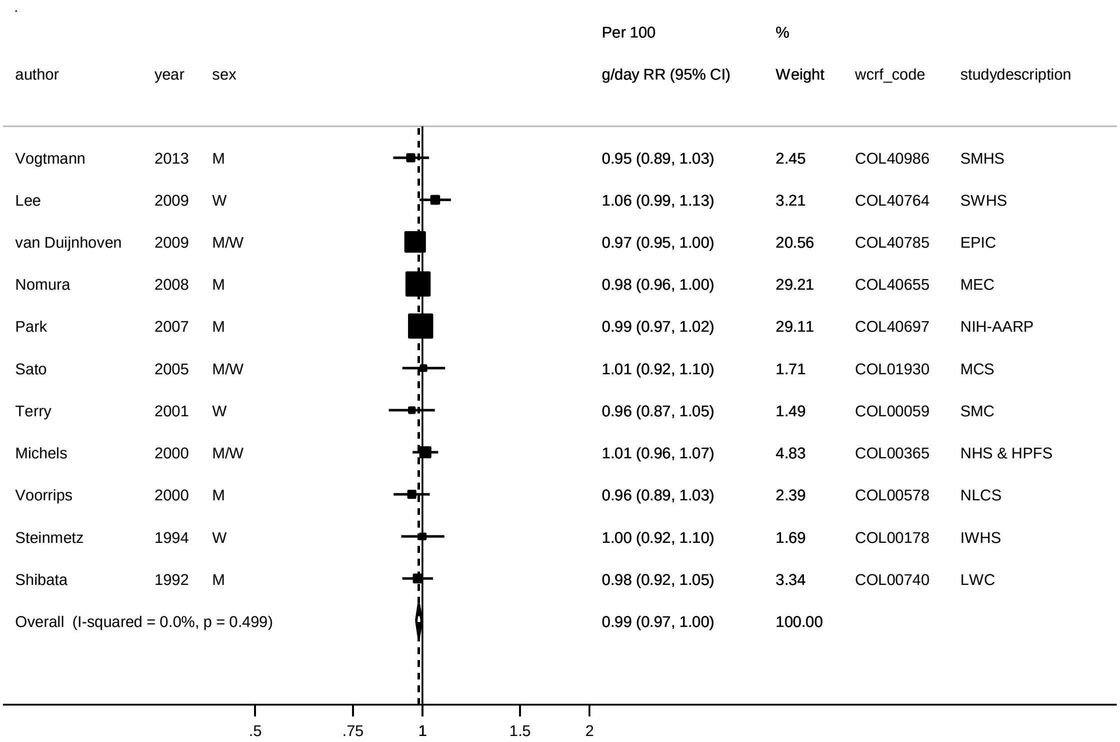


Figure 23 Relative risk of colon cancer for 100 g/day increase in fruit and vegetable intake, stratified by sex

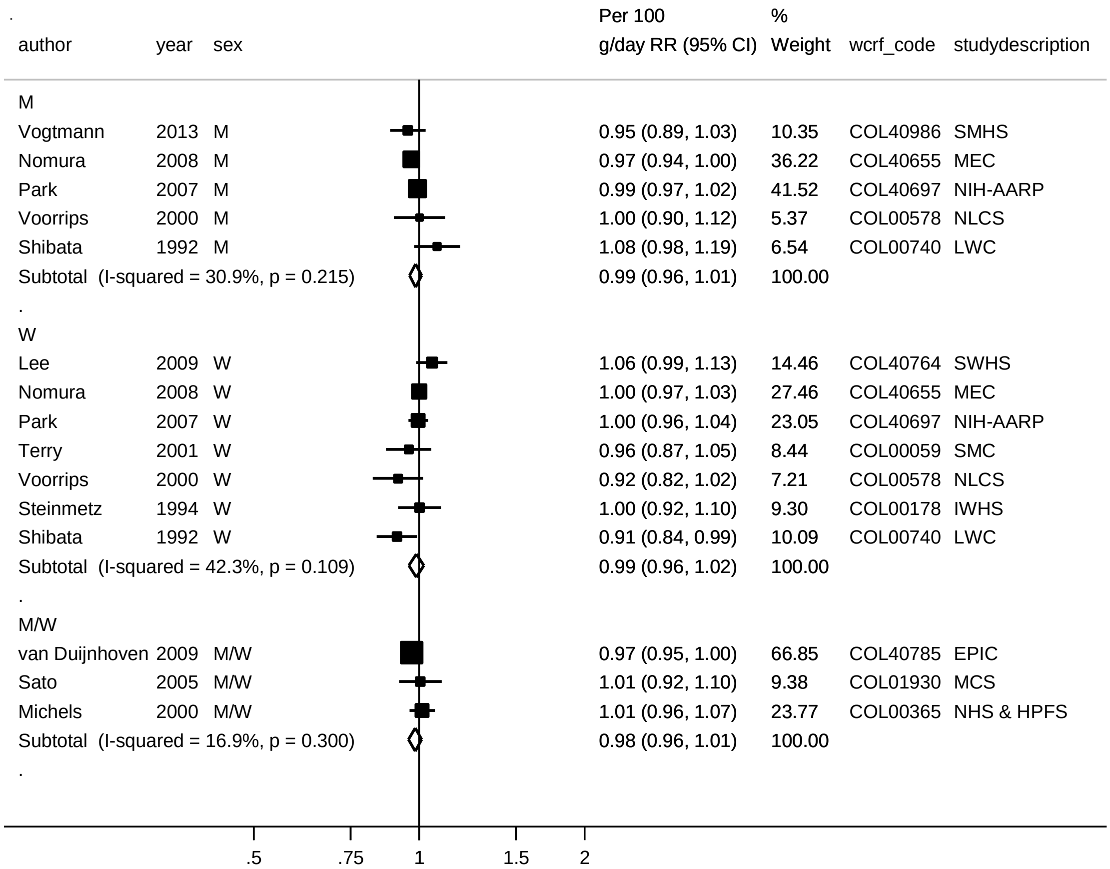


Figure 24 Funnel plot of studies included in the dose response meta-analysis of fruit and vegetable intake and colon cancer

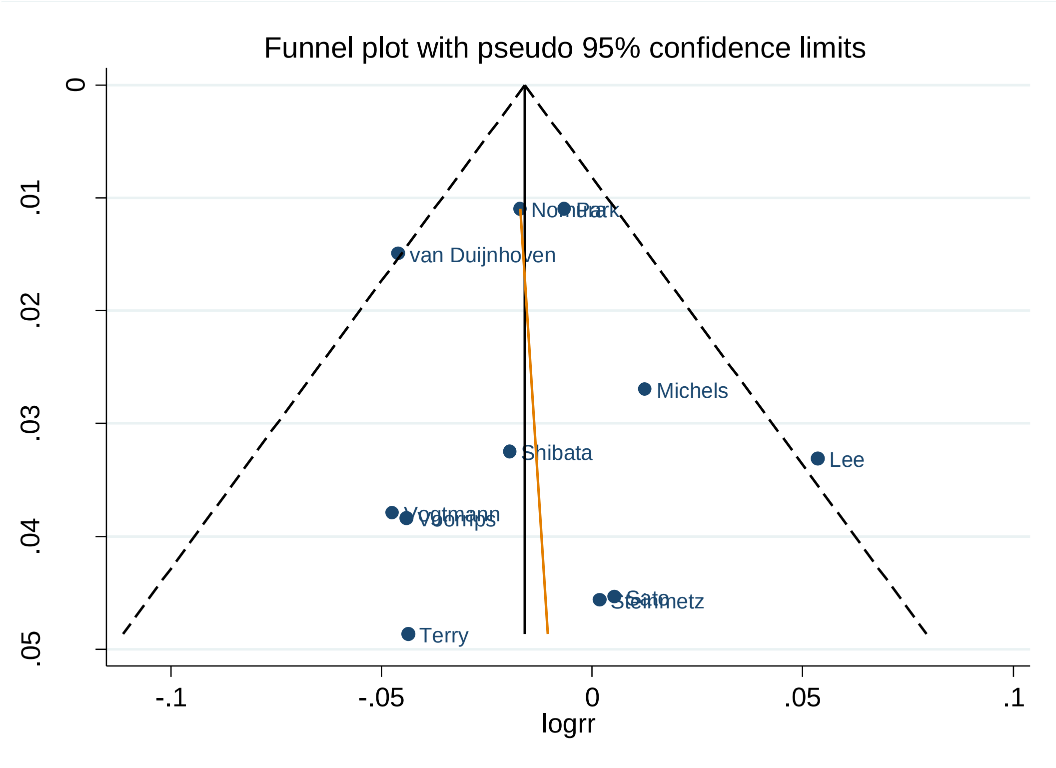
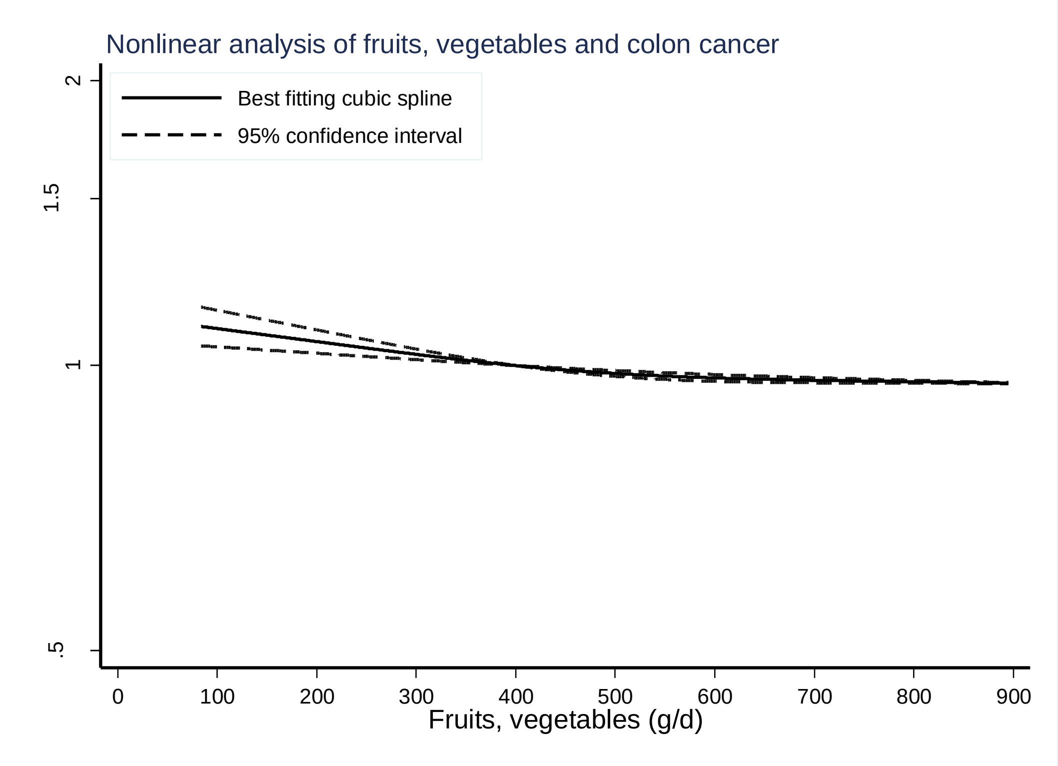


Figure 25 Relative risk of colon cancer and fruits and vegetables estimated using non-linear models



P nonlinearity=0.01

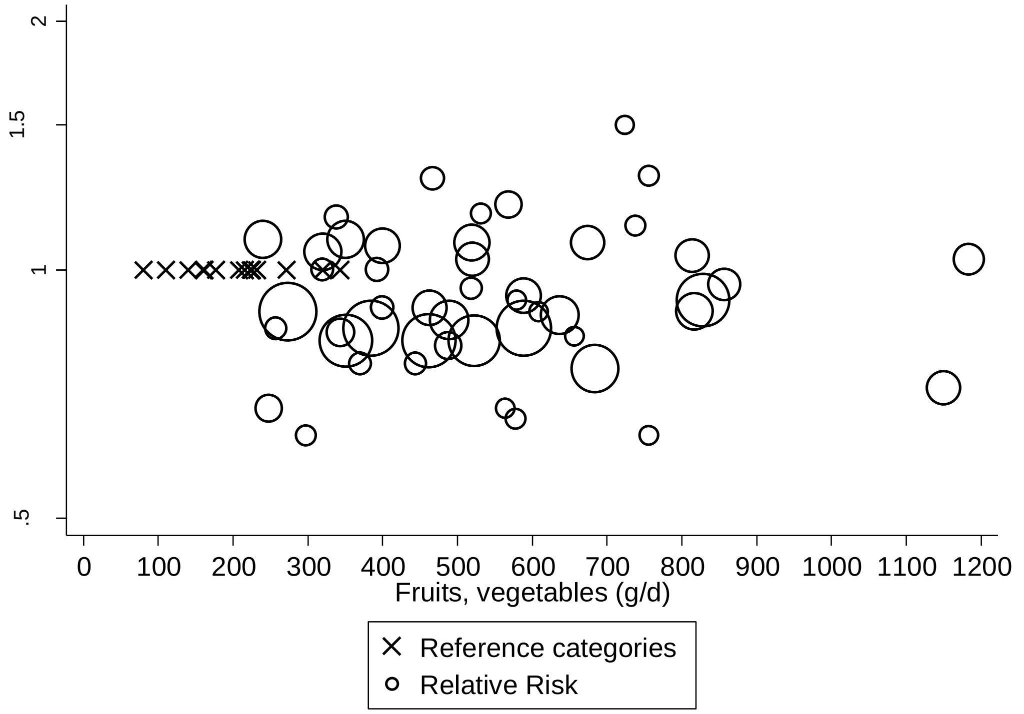


Table 20 Relative risk of colon cancer and fruit and vegetable intake estimated using non-linear models

80	1.10 (1.05-1.15)
100	1.09 (1.05-1.14)
200	1.06 (1.03-1.09)
300	1.03 (1.01-1.04)
400	1.00
500	0.98 (0.97-0.99)
600	0.97 (0.96-0.98)
700	0.96 (0.95-0.97)
800	0.96 (0.95-0.96)
900	0.96 (0.95-0.96)

Figure 26 RR estimates of rectal cancer by levels of fruit and vegetable intake

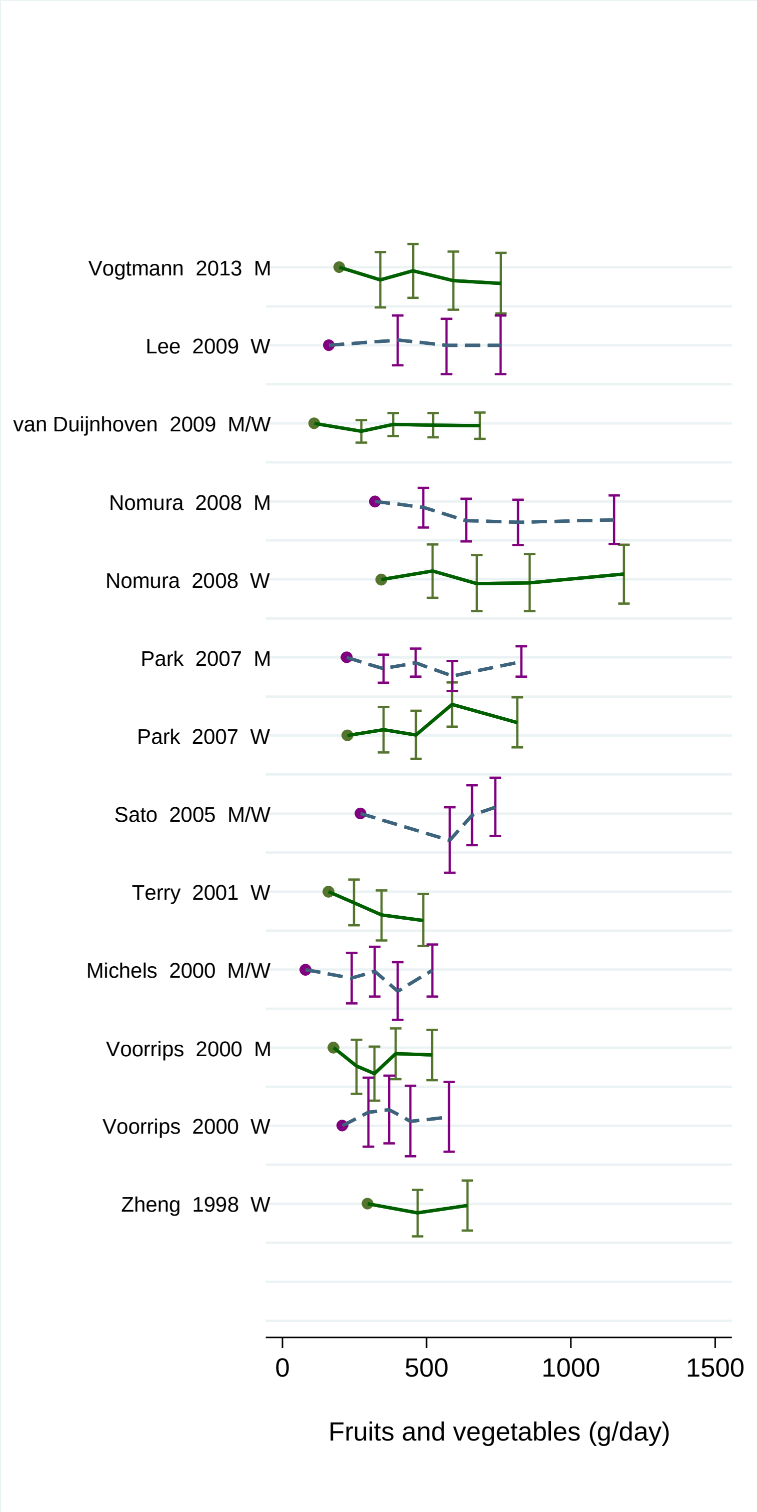


Figure 27 Relative risk of rectal cancer for the highest compared with the lowest level of fruit and vegetable intake

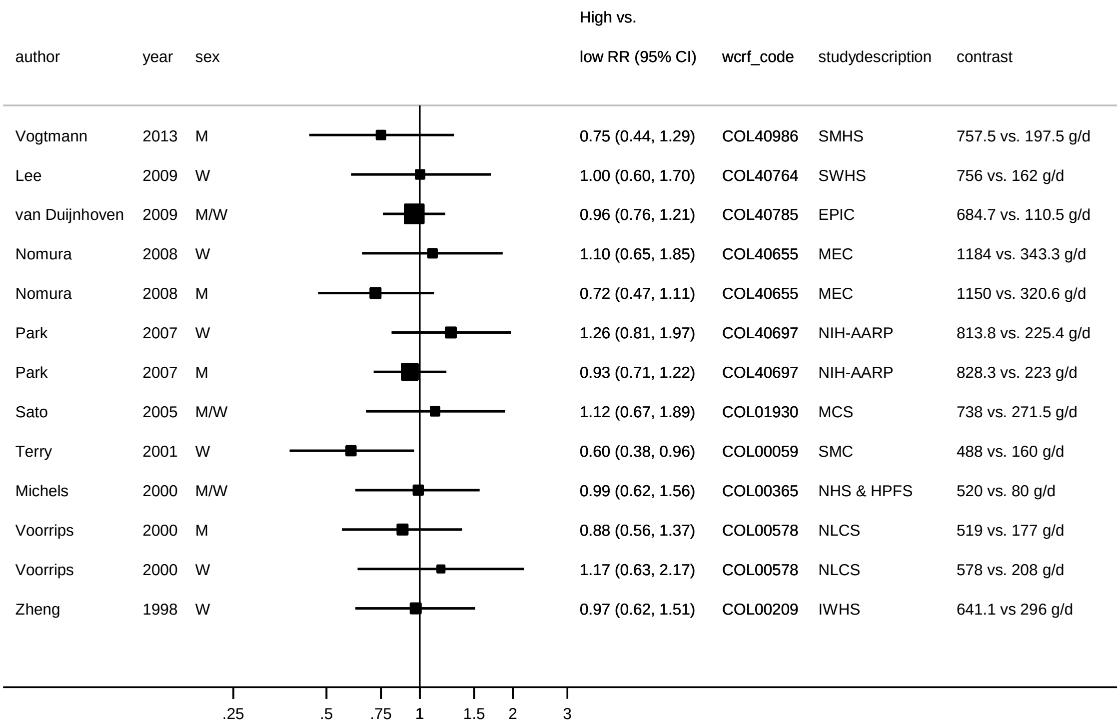


Figure 28 Relative risk of rectal cancer for 100 g/day increase in fruit and vegetable intake

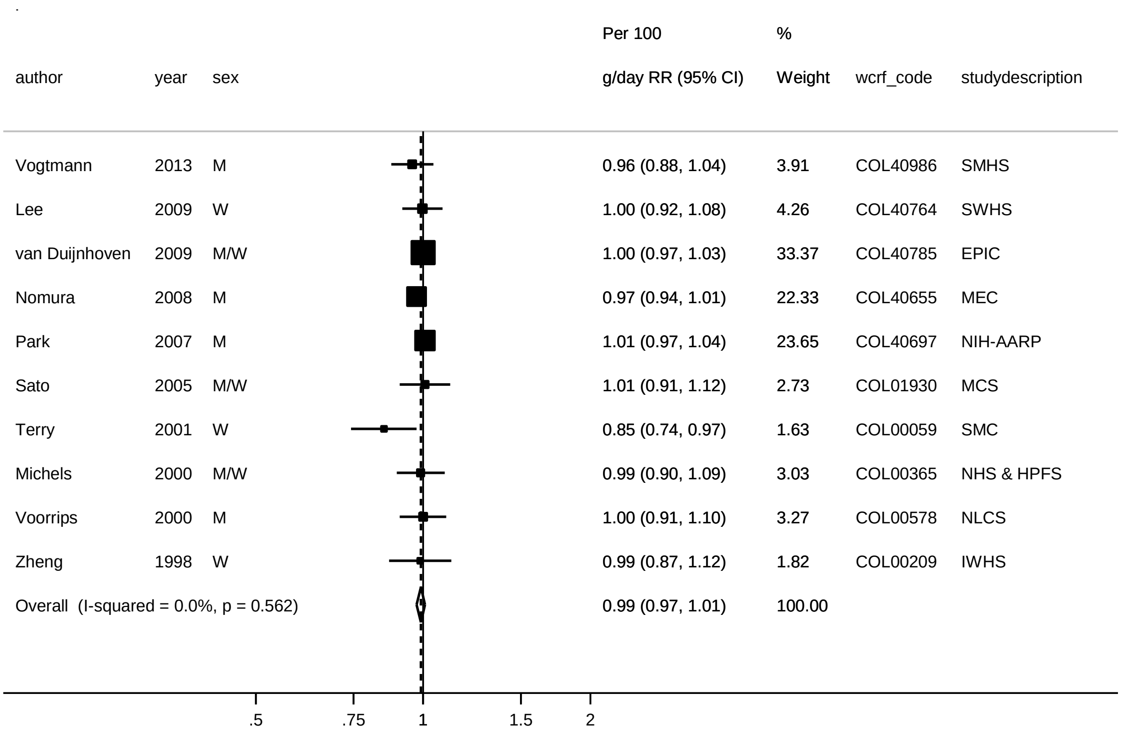


Figure 29Relative risk of rectal cancer for 100 g/day increase in fruit and vegetable intake, stratified by sex

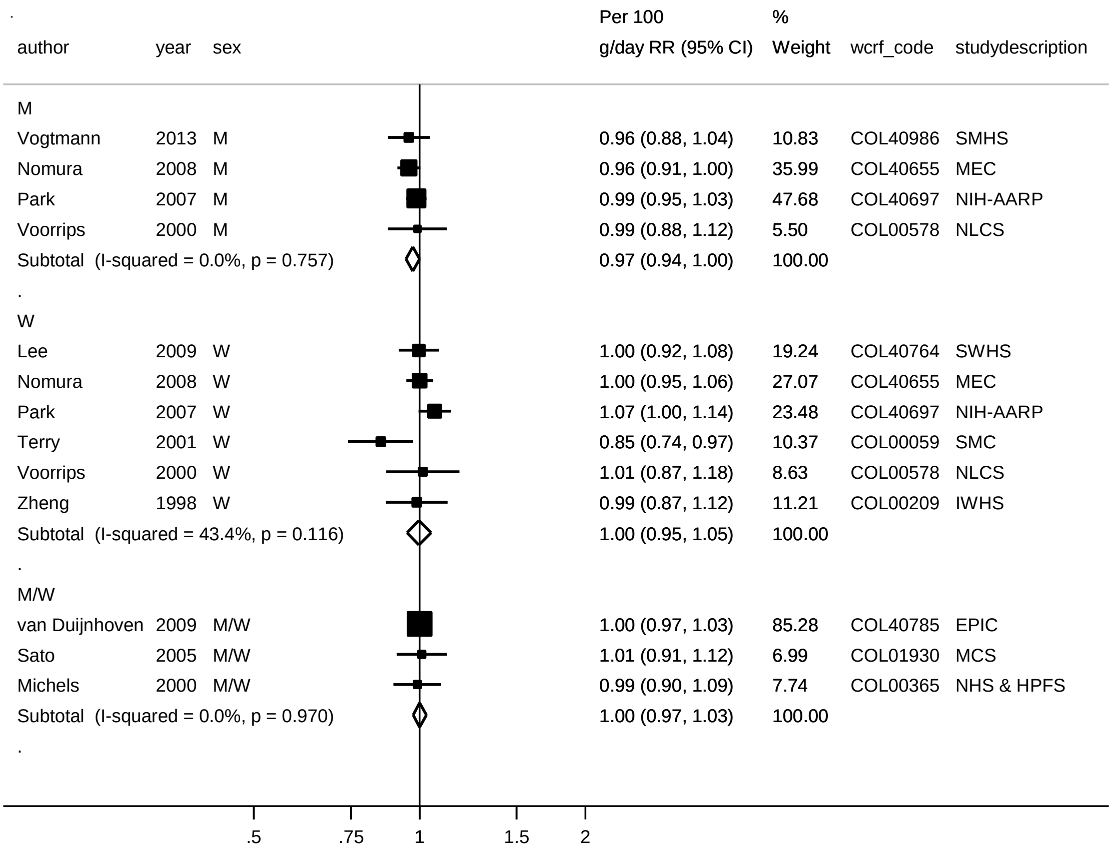


Figure 30 Funnel plot of studies included in the dose response meta-analysis of fruit and vegetable intake and rectal cancer

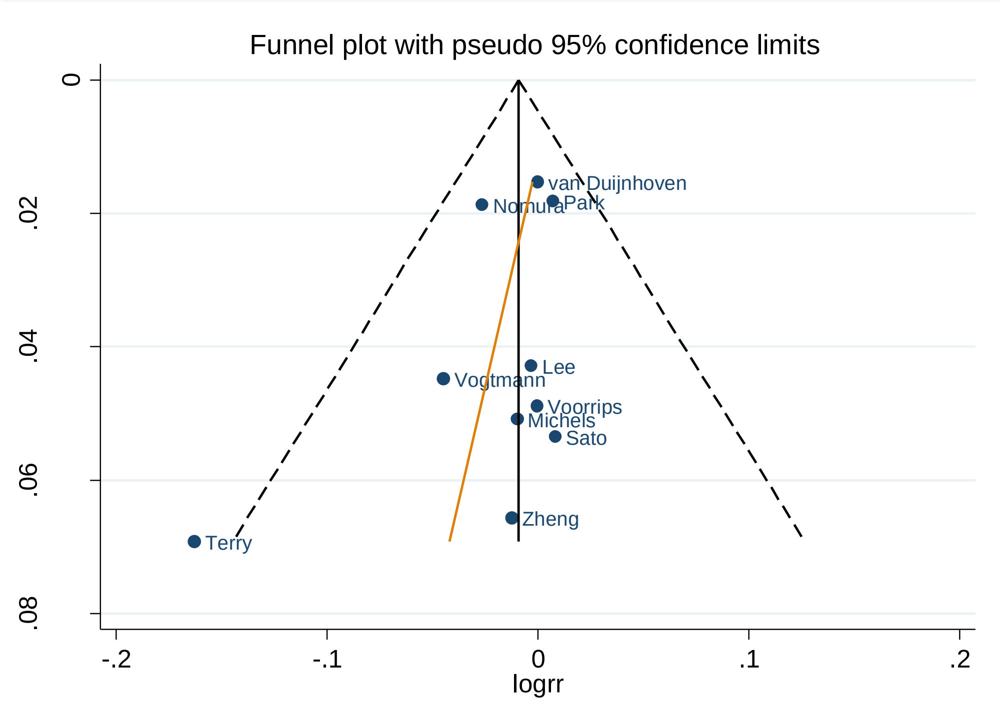
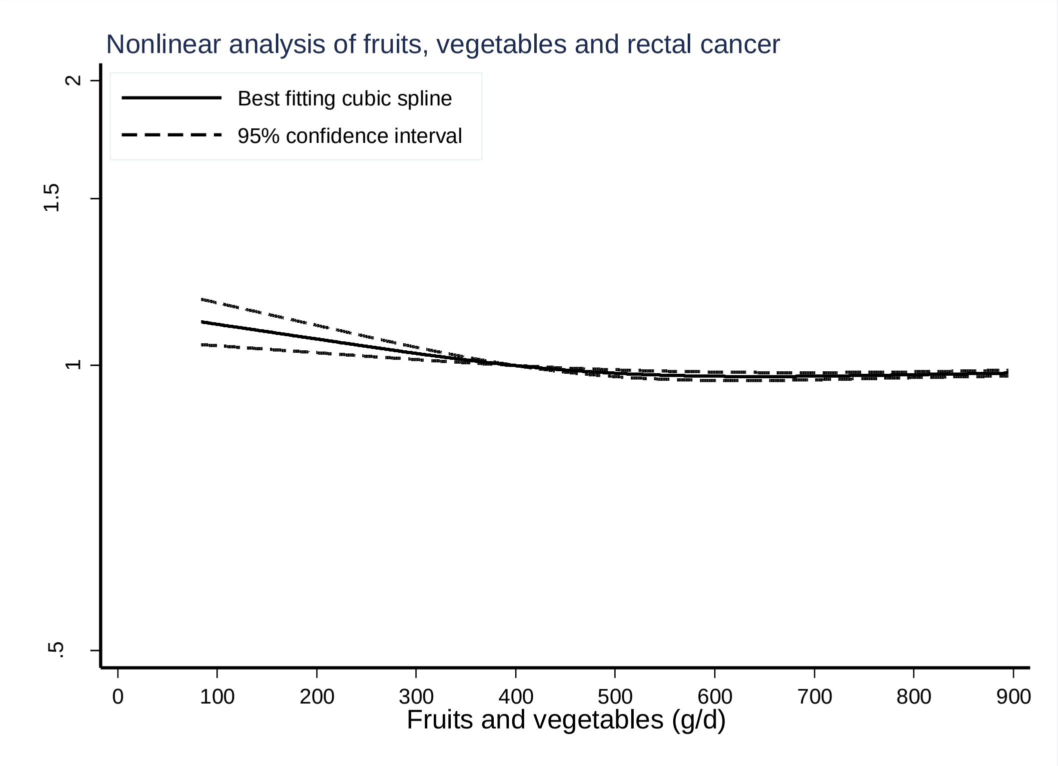


Figure 31 Relative risk of rectal cancer and fruits and vegetables estimated using non-linear models



P nonlinearity=0.005

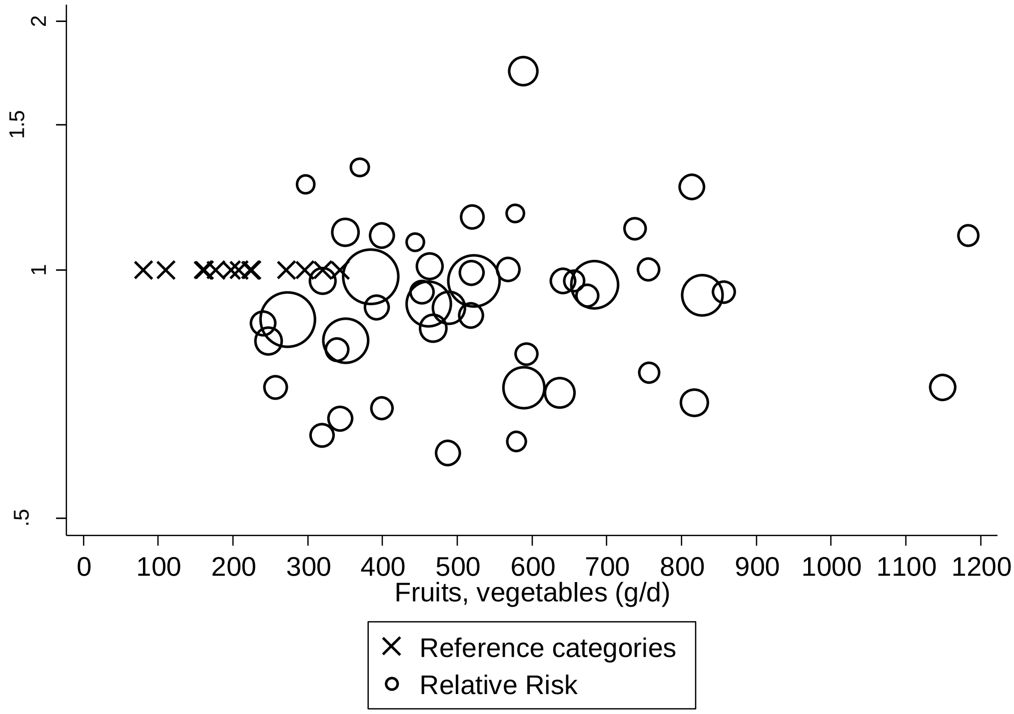


Table 21 Relative risk of rectal cancer and fruit and vegetable intake estimated using non-linear models

Fruit and vegetable (g/day)	RR (95%CI)
80	1.11 (1.05-1.18)
100	1.11 (1.05-1.16)
200	1.07 (1.03-1.10)
300	1.03 (1.01-1.05)
400	1.00
500	0.98 (0.97-0.99)
600	0.97 (0.96-0.98)
700	0.97 (0.96-0.98)
800	0.98 (0.97-0.99)
900	0.98 (0.97-0.99)

2.2.1 Total vegetables

Cohort studies

Summary

Main results:
Seven new publications were identified (Makarem, 2015, Bamia, 2013, Vogtmann, 2013, Fung, 2010, Aoyama, 2014, Agnoli, 2013, Ruder, 2011) and two of these were from new studies (Makarem, 2015, Vogtmann, 2013) since the 2010 SLR and five of these studies (four publications) could be included in the dose-response analyses (Makarem, 2015, Bamia, 2013, Vogtmann, 2013, Fung, 2010). In total 23 studies (34 publications) were identified on vegetables and colorectal cancer risk, and 18 of these studies (21 publications) could be included in the dose-response analysis. Study characteristics and results for all cancer types are shown in the Table. For studies that reported vegetable intake in servings per day or other frequencies we used a serving size of 80 g for recalculation of the intakes to grams per day.

Colorectal cancer:
Eleven studies (14136 cases) were included in the dose-response analysis. The summary RR for a 100 g/d increase in total vegetable intake was 0.98 (95% CI: 0.96-0.99) and there was no evidence of heterogeneity, I^2=0%, $p_{heterogeneity}$=0.48. There was no evidence of small study bias or publication bias with Egger's test, p=0.92. The summary RR ranged from 0.97 (95% CI: 0.96-0.99) when the Nurses' Health Study was excluded to 0.98 (95% CI: 0.97-1.00) when the NIH-AARP Diet and Health study (Park, 2007) was excluded.
The test for nonlinearity was significant, $p_{nonlinearity}$<0.0001, and the association between vegetables and colorectal cancer was slightly stronger at lower levels of intake.

Colon cancer:
Twelve studies (6308 cases) were included in the dose-response meta-analysis of total vegetable intake and colon cancer. The summary RR per 100 g/d was 0.98 (95% CI: 0.96-0.99) with no heterogeneity, I^2=0%, $p_{heterogeneity}$=0.48.

There was evidence of a nonlinear association between total vegetable intake and colon cancer, $p_{nonlinearity}$=0.02, with a statistically significant reduction up to 600 grams per day.

Rectal cancer:
Eight studies (2435 cases) were included in the dose-response meta-analysis of total vegetable intake intake and rectal cancer. The summary RR per 100 g/d was 0.99 (95% CI: 0.96-1.02) with moderate heterogeneity, I^2=0%, $p_{heterogeneity}$=0.73.

Although the test for nonlinearity was significant for the association between total vegetable intake and rectal cancer, $p_{nonlinearity}$<0.0001, there was no significant association.
Study quality:

Total vegetable intake was estimated from food intake assessed by FFQ or dietary history method in all studies, and in one of the studies a combination of FFQ, food records and 24 hour recalls were used (van Duijnhoven, 2009).
Loss to follow-up was low for the studies that reported such data, although some studies did not provide data.
Cancers were identified by record linkages to health registries, cancer registries, mortality registries, or death indexes.
All studies adjusted for at least age, and most of the studies adjusted for most of the established colorectal cancer risk factors, including: age, physical activity, BMI, and alcohol consumption, smoking, red meat and hormone replacement therapy in women.

Table 22 Total vegetable intake and colorectal cancer risk. Number of studies in the CUP SLR

	Number
Studies identified	23 studies (34 publications)
Studies included in forest plot of highest compared with lowest intake	Colorectal cancer: 9 studies Colon cancer: 5 Rectal cancer: 5
Studies included in linear dose-response meta-analysis	Colorectal cancer: 11 studies Colon cancer: 12 Rectal cancer: 8
Studies included in non-linear dose-response meta-analysis	Colorectal cancer: 9 studies Colon cancer: 10 Rectal cancer: 9

Table 23 Total vegetable intake and colorectal cancer risk. Summary of the linear dose-response meta-analysis in the 2005 SLR, 2010SLR and 2015 SLR

	2005 SLR		
	Colorectal cancer	**Colon cancer**	**Rectal cancer**
Increment unit used	Per 2 servings/day	Per 2 servings/day	Per 2 servings/day
Studies (n)	7	6	4
Cases (total number)	-	-	-
RR (95%CI)	1.00 (0.90-1.11)	0.96 (0.89-1.04)	0.99 (0.81-1.21)
Heterogeneity (I^2, p-value)	62.5%, p=0.006	8.6%, p=0.36	0%, p=0.51
P value Egger test	-	-	-

	2010 SLR		
	Colorectal cancer	**Colon cancer**	**Rectal cancer**
Increment unit used	100 g/day		
Studies (n)	8	10	7
Cases (total number)	12275	5772	2285
RR (95%CI)	0.98 (0.96-0.99)	0.97 (0.95-1.00)	1.00 (0.96-1.05)
Heterogeneity (I^2, p-value)	0%, p=0.78	0%, p=0.63	0%, p=0.82
P value Egger test	-	-	-

	2015 SLR		
	Colorectal cancer	**Colon cancer**	**Rectal cancer**
Increment unit used	100 g/day		
Studies (n)	11	12	8
Cases (total number)	14136	>6308	>2435
RR (95%CI)	0.98 (0.96-0.99)	0.97 (0.95-0.99)	0.99 (0.96-1.02)
Heterogeneity (I^2, p-value)	0%, p=0.48	0%, p=0.77	0%, p=0.78
P value Egger test	0.92	0.77	0.72

Stratified analysis by geopgraphic location

2015 SLR	**Asia**	**Europe**	**North-America**
Studies (n)	1	3	7
RR (95%CI)	0.87 (0.77-0.98)	0.99 (0.95-1.03)	0.98 (0.96-0.99)
Heterogeneity (I^2, p- value)	-	0%, p=0.56	0%, p=0.66

Table 24 Vegetable intake and colorectal cancer risk. Results of meta-analyses and pooled analyses of prospective studies published after the 2005 SLR.

Author, Year	Number of studies	Total number of cases	Studies country, area	Outcome	Comparison	RR (95%CI)	P trend	Heterogeneity (I^2, p value)
Meta-analyses								
Huxley et al, 2009	10 CC 8 RC 8 CRC	2651 CC 1005 RC 7916 CRC	North-America, Europe, Asia	Incidence/ mortality	High vs. low	0.93 (0.82-1.05) 0.88 (0.69-1.12) 0.95 (0.86-1.04)	- - -	19%, p=0.18 - -
Aune et al, 2012	15 12	16057 -	North America, Europe, Asia	Incidence	High vs. low Per 100 g/d High vs. low High vs. low	0.91 (0.86-0.96) 0.98 (0.97-0.99) 0.87 (0.81-0.94) 0.94 (0.85-1.04)	- - - -	0%, p=0.54 0%, p=0.69 0%, p=0.70 0%, p=0.59
Pooled analyses								
Koushik, 2007	14	5838 CC	North America, Europe	Incidence	Quintile 5 vs. 1 ≥300 vs. <100 g/d	0.94 (0.86-1.02) 0.96 (0.84-1.09)	0.21 0.24	NA, p=0.91 NA, p=0.33

Table 25 Vegetable intake and colorectal cancer risk. Main characteristics of studies included in the CUP SLR dose-response meta-analysis

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI)	Adjustment factors	Missing data derived for analysis
Bamia, 2013 COL40964 Denmark,France,Germany,Greece,Italy,Netherlands,Spain,Sweden,UK	EPIC, Prospective Cohort, Age: 25-70 years, M/W	4 355/ 480 308 11.6 years	Cancer registry, record linkage, health Insurance rec, mortality registry, pathology and active follow up	FFQ	Incidence, colorectal cancer	331 vs 88.6 g/day	0.98 (0.89-1.08)	Age, sex, BMI, centre location, cereal, dairy products consumption, educational level, ethanol, fish, fruits, legumes, lipids, meat, physical activity, smoking	Distribution of cases and person-years
					Incidence, colorectal cancer, women	331 vs 88.6 g/day	1.02 (0.90-1.16)		
					Incidence, colorectal cancer, men	331 vs 88.6 g/day	0.91 (0.80-1.06)		
Vogtmann, 2013 COL40986 China	SMHS, Prospective Cohort, Age: 40-74 years, M	398/ 61 274 6.3 years	Cancer registry, shanghai vital statistics office, medical history	FFQ	Incidence, colorectal cancer	≥466.64 vs 0-192.6 g/day	1.00 (0.72-1.41)	Age, alcohol, BMI, diabetes, educational level, energy Intake, family history of colorectal cancer, Income, met-hours per week, occupation, red meat, smoking, total meat	Midpoints, distribution of person-years
					Incidence, colon cancer	≥466.64 vs 0-192.6 g/day	0.95 (0.62-1.47)		
					Incidence, rectal cancer	≥466.64 vs 0-192.6 g/day	1.10 (0.64-1.89)		
Fung, 2010 COL40828 USA	HPFS, Prospective Cohort, M/W	132 746	Self report verified by medical record	FFQ	Incidence, colorectal cancer, men	per 1 serving/day	1.00 (0.96-1.04)	Age, alcohol Intake, aspirin use, BMI, colonoscopy, energy, family history, history of polyps, physical activity, smoking	Conversion of serv/d to g/d

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI)	Adjustment factors	Missing data derived for analysis
Fung, 2010 COL40828 USA	NHS, Prospective Cohort, M/W	132 746	Self report verified by medical record	FFQ	Incidence, colorectal cancer, women	per 1 serving/day	1.01 (0.96-1.05)	Age, alcohol Intake, aspirin use, BMI, colonoscopy, energy, family history, history of polyps, physical activity, smoking	Conversion of serv/d to g/d
George, 2009 COL40789 USA	NIH-AARP, Prospective Cohort, Age: 615 years, M/W, Retired	5 039/ 483 338 8 years	Cancer registry	FFQ	Incidence, colorectal cancer, women	1.43-4.38 vs 0-0.56 cups1000kcal/d	0.87 (0.74-1.02)	Age, alcohol, BMI, educational level, energy Intake, family history, fruits, marital status, menopausal hormone use, physical activity, race, smoking status	Midpoints, distribution of cases and person-years, conversion from cups/1000 kcal/d to g/d
					Incidence, colorectal cancer, women	1.43-4.38 vs 0-0.56 cups1000kcal/d	0.87 (0.74-1.02)		
van Duijnhoven FJ, 2009 COL40785 Denmark,France,Germany,Greece,Italy,Netherlands,Norway,Spain,Sweden,UK	EPIC, Prospective Cohort, Age: 35-70 years, M/W	2 819/ 452 755 8.8 years	Cancer registry, health Insurance records, active follow up and mortality registry	FFQ	Incidence, colorectal cancer	≥284.4 vs 0-95 g/day	0.92 (0.79-1.06)	Age, sex, alcohol consumption, centre location, cereal fibre, energy from fat, energy from nonfat sources, fish, fruits Intake, height, physical activity, processed meat, red meat Intake, smoking status, weight	Midpoints
					Incidence, colorectal cancer	per 100 g/day	0.99 (0.95-1.03)		
					Incidence, colon cancer	≥284.4 vs 0-95 g/day	0.85 (0.71-1.02)		
					Incidence, colon cancer	per 100 g/day	0.97 (0.93-1.02)		
					Incidence, distal colon cancer	≥284.4 vs 0-95 g/day	0.86 (0.66-1.14)		

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI)	Adjustment factors	Missing data derived for analysis
					Incidence, proximal colon cancer	≥284.4 vs 0-95 g/day	0.86 (0.65-1.14)		
					Incidence, rectal cancer	≥284.4 vs 0-95 g/day	1.04 (0.81-1.33)		
					Incidence, rectal cancer	per 100 g/day	1.04 (0.87-1.23)		
Nomura, 2008 COL40663 USA	MEC, Prospective Cohort, Age: 45-75 years, M/W	1 023/ 191 011 7.3 years	Cancer registry	FFQ-quantitative	Incidence, colorectal cancer, men	236.2 vs 71.9 g1000 kcal/day	0.85 (0.69-1.05)	Age, alcohol Intake, aspirin use, BMI, calcium Intake, energy Intake, ethnicity, family history of colorectal cancer, folate Intake, history of polyps, multivitamin, pack-years of smoking, physical activity, red meat Intake, time, vitamin d	Distribution of cases and person-years, conversion of g/1000 kcal/d to g/d
					Incidence, colorectal cancer, women	286.5 vs 85.5 g1000 kcal/day	0.94 (0.75-1.17)		
					Incidence, colon cancer, men	236.2 vs 71.9 g1000 kcal/day	0.80 (0.63-1.03)		
					Incidence, colon cancer, women	286.5 vs 85.5 g1000 kcal/day	0.90 (0.70-1.17)		
					Incidence, rectal cancer, men	236.2 vs 71.9 g1000 kcal/day	0.97 (0.64-1.46)		
					Incidence, rectal cancer, women	286.5 vs 85.5 g1000 kcal/day	1.09 (0.67-1.77)		
Park, 2007 COL40697	NIH-AARP, Prospective	2 048/ 488 043	Cancer registry	FFQ	Incidence, colorectal	2.8 vs 0.6 servings1000	0.82 (0.71-0.94)	Age, alcohol consumption,	Distribution of person-years,

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI)	Adjustment factors	Missing data derived for analysis
USA	Cohort, Age: 50-71 years, M/W	2 121 664 person-years			cancer, men	kcal/day		calcium Intake, educational level, physical activity, red meat Intake, smoking status, total energy Intake	conversion of serv/1000 kcal/d to g/d
					Incidence, colorectal cancer, women	3.6 vs 0.8 servings1000 kcal/day	1.12 (0.90-1.38)		
					Incidence, colon cancer, men	2.8 vs 0.6 servings1000 kcal/day	0.84 (0.71-0.99)		
					Incidence, proximal colon cancer, men	2.8 vs 0.6 servings1000 kcal/day	0.90 (0.72-1.14)		
					Incidence, distal colon cancer, men	2.8 vs 0.6 servings1000 kcal/day	0.76 (0.59-0.98)		
					Incidence, rectal cancer, men	2.8 vs 0.6 servings1000 kcal/day	0.81 (0.62-1.05)		
					Incidence, distal colon cancer, women	3.6 vs 0.8 servings1000 kcal/day	1.15 (0.76-1.73)		
					Incidence, rectal cancer, women	3.6 vs 0.8 servings1000 kcal/day	1.21 (0.80-1.83)		
					Incidence, colon cancer,	3.6 vs 0.8 servings1000	1.10 (0.86-1.40)		

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI)	Adjustment factors	Missing data derived for analysis
					women	kcal/day			
					Incidence, proximal colon cancer, women	3.6 vs 0.8 servings1000 kcal/day	1.06 (0.78-1.45)		
McCarl, 2006 COL40633 USA	IWHS, Prospective Cohort, Age: 55-69 years, W	954/ 35 197 15 years	Seer registry	FFQ	Incidence, colorectal cancer	≥34.5 vs ≤14.5 servings/week	0.89 (0.73-1.08)	Age	Midpoints, conversion of serv/wk to g/d
Lin, 2005 COL01831 USA	WHS, Prospective Cohort, Age: 45- years, W, professionals	223/ 36 976 10 years	Follow up questionnaires (self report), medical record and pathology reports	FFQ	Incidence, colorectal cancer, women	6.8 vs 1.5 serving/day	0.89 (0.56-1.41)	Age, alcohol consumption, aspirin use, BMI, family history of specific cancer, history of previous polyp and prior endoscopy, menopausal status, physical activity, postmenopausal hormone use, randomized treatment assignment, red meat Intake, smoking status, total energy	Distribution of person-years, conversion of serv/d to g/d

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI)	Adjustment factors	Missing data derived for analysis
Sato, 2005 COL01930 Japan	MCS, Prospective Cohort, Age: 40-64 years, M	165/41 835 7 years	Population registry	Questionnaire	Incidence, colon cancer,	≥313 vs 0-245 g/day	1.24 (0.79-1.95)	Age, sex, alcohol consumption,BMI, educational level, energy content, family history of specific cancer, meat consumption, physical activity, smoking status	Midpoints
					Incidence, rectal cancer,	≥313 vs 0-245 g/day	1.14 (0.67-1.93)		
McCullough, 2003 COL00367 USA	CPS II, Prospective Cohort, Age: 50-74 years, M/W	298/ 133 163 6 years	Cps-II cohort	Semi-quantitative FFQ	Incidence, colon cancer, men	≥3.3 vs 0-1.2 serving/day	0.69 (0.47-1.03)	Age, aspirin use, BMI, calcium, educational level, energy Intake, family history of colorectal cancer, multivitamin, physical activity, red meat Intake, smoking habits	Midpoints, distribution of person-years
					Incidence, colon cancer, men	<0.80 vs 1.3+ serving/day	1.79 (1.22-2.61)		
					Incidence, colon cancer, men	per 1 items/month	0.93 (0.87-1.00)		
					Incidence, colon cancer, women	≥3.3 vs 0-1.2 serving/day	0.91 (0.56-1.48)		
					Incidence, colon cancer, women	<0.81 vs 1.3+ serving/day	0.78 (0.42-1.44)		
					Incidence, colon cancer, women	per 1 items/month	0.99 (0.92-1.07)		
					Incidence, proximal colon cancer,	Q 2 vs Q 1	0.59 (0.31-1.11)		

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI)	Adjustment factors	Missing data derived for analysis
					men, proximal cancer				
					Incidence, distal colon cancer, men, distal cancer	Q 2 vs Q 1	0.71 (0.38-1.33)		
Flood, 2002 COL00410 USA	BCDDP, 1973, Prospective Cohort, W	485/ 45 490 386 142 person-years	Breast cancer screening centres	FFQ	Incidence, colorectal cancer,	≥0.79 vs 0-0.32 servingday/1000kj	0.95 (0.71-1.26)	Alcohol consumption, BMI, calcium, educational level, energy Intake, fruits, grains consumption, height, nsaid use, physical activity, red meat, smoking habits, supplements, vitamin d	Conversion of serv/d to g/d
Terry, 2001 COL00059 Sweden	SMC, Prospective Cohort, Age: 40-74 years, W	460/ 61 463 588 270 person-years	Mammography screening program	FFQ	Incidence, colorectal cancer	≥2 vs 0-1 serving/day	0.84 (0.65-1.09)	Age, red meat & dairy product Intake, total caloric Intake	Midpoints, distribution of cases and person-years, conversion from serv/d to g/d
					Incidence, colon cancer	≥2 vs 0-1 serving/day	0.90 (0.66-1.24)		
					Incidence, rectal cancer	≥2 vs 0-1 serving/day	0.71 (0.45-1.12)		
					Incidence, proximal colon cancer	≥2 vs 0-1 serving/day	0.72 (0.44-1.20)		
					Incidence, distal colon	≥2 vs 0-1 serving/day	1.13 (0.66-1.94)		

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI)	Adjustment factors	Missing data derived for analysis
					cancer				
Michels, 2000 COL00365 USA	NHS, Prospective Cohort, Age: 30-55 years, W, Registred nurses	569/ 88 764 1 327 029 person-years	Population registries	Semi-quantitative FFQ	Incidence, colon cancer,	≥5 vs 0-1 serving/day	0.96	Age, alcohol consumption, aspirin use, BMI, family history of colorectal cancer, height, menopausal status, pack-years of smoking, physical activity, postmenopausal hormone use, red meat Intake, sigmoidoscopy, supplement Intake, total caloric Intake	Conversion from serv/d to g/d, distribution of cases and person-years
					Incidence, colon cancer,	per 1 serving/day	1.03 (0.97-1.10)		
					Incidence, rectal cancer,	≥5 vs 0-1 serving/day	1.24		
					Incidence, rectal cancer,	per 1 serving/day	1.03 (0.91-1.17)		
Michels, 2000 COL00365 USA	HPFS, Prospective Cohort, Age: 40-75 years, M, Health professionals	368/ 47 325 416 616 person-years	Population registries	Semi-quantitative FFQ	Incidence, colon cancer,	≥5 vs 0-1 serving/day	1.24	Age, alcohol consumption, aspirin use, BMI, family history of colorectal cancer, height, menopausal status, pack-years of smoking, physical activity, red meat Intake, sigmoidoscopy, supplement Intake, total caloric Intake	Conversion from serv/d to g/d, distribution of cases and person-years
					Incidence, colon cancer,	per 1 serving/day	1.01 (0.90-1.14)		
					Incidence, rectal cancer,	≥5 vs 0-1 serving/day	0.67		
					Incidence, rectal cancer,	per 1 serving/day	1.01 (0.80-1.27)		

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI)	Adjustment factors	Missing data derived for analysis
Voorrips, 2000 COL00578 Netherlands	NLCS, Case Cohort, Age: 55-69 years, M/W	312/ 120 852 6.3 years	Cancer registry	Semi-quantitative FFQ	Incidence, colon cancer, men	285 vs 100 g/day	0.85 (0.57-1.27)	Age, alcohol consumption, family history of colorectal cancer	None
					Incidence, colon cancer, women	293 vs 107 g/day	0.83 (0.54-1.26)		
					Incidence, rectal cancer, men	285 vs 100 g/day	0.88 (0.55-1.41)		
					Incidence, distal colon cancer, men	Q 5 vs Q 1	0.76 (0.27-1.30)		
					Incidence, proximal colon cancer, men	Q 5 vs Q 1	1.03 (0.59-1.81)		
					Incidence, proximal colon cancer, women	Q 5 vs Q 1	0.99 (0.57-1.72)		
					Incidence, distal colon cancer, women	Q 5 vs Q 1	0.64 (0.36-1.17)		
					Incidence, rectal cancer, women	293 vs 107 g/day	1.78 (0.94-3.38)		
					Incidence, colon cancer,	per 25 g/day	0.98		

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI)	Adjustment factors	Missing data derived for analysis
					men				
					Incidence, colon cancer, women	per 25 g/day	0.97		
					Incidence, rectal cancer, men	per 25 g/day	0.99		
					Incidence, rectal cancer, women	per 25 g/day	1.05		
Pietinen, 1999 COL00176 Finland	ATBC, Prospective Cohort, Age: 50-69 years, M, Smokers	185/ 27 111 8 years	Population	Dietary history questionnaire	Incidence, colorectal cancer,	191 vs 44 g/day	1.20 (0.80-1.90)	Age, alcohol consumption, BMI, calcium Intake, educational level, energy Intake, physical activity, smoking years, supplement group	Distribution of person-years
Steinmetz, 1994 COL00178 USA	IWHS, Prospective Cohort, Age: 55-69 years, W, Postmenopausal	212/ 35 216 167 447 person-years	Driving license	Semi-quantitative FFQ	Incidence, colon cancer	Q 4 vs Q 1	0.74 (0.47-1.17)	Age, age at first child birth, alcohol consumption, BMI, educational level, energy Intake, history of polyps or colitis, parity, physical activity, smoking habits	Midpoints, conversion from serv/wk to g/d, distribution of cases and person-years
					Incidence, colon cancer	≥30.5 vs 0-15 serving/week	0.73 (0.47-1.13)		
					Incidence, distal colon cancer, distal sites	≥30.5 vs 0-15 serving/week	0.62 (0.35-1.09)		
					Incidence, proximal	≥30.5 vs 0-15 serving/week	0.90 (0.44-1.82)		

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI)	Adjustment factors	Missing data derived for analysis
					colon cancer, proximal sites				
Shibata, 1992 COL00740 USA	Leisure World Cohort, Prospective Cohort, M/W, retirement community, uppermiddle social class	105/ 11 580 70 159 person-years	Community registry	FFQ	Incidence, colon cancer, women	≥4.8 vs 0-3.2 serving/day	0.72 (0.45-1.16)	Age, smoking habits	Conversion from serv/d to g/d, distribution of person-years
					Incidence, colon cancer, men	≥4.5 vs 0-3 serving/day	1.39 (0.84-2.30)		

Table 26 Vegetable intake and colorectal cancer risk. Main characteristics of studies excluded from the linear dose-response meta-analysis

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI)	Adjustment factors	Reasons for exclusion
Makarem, 2015 COL41060 USA	FHS-Offspring Cohort, Prospective Cohort, Age: 66 years, M/W	63/ 2 983 11.5 years	Death certificate and medical records	Semi-quantitative FFQ	Incidence, colorectal cancer	per 1 points	0.44 (0.22-0.88)	Age, sex, smoking status	Not possible to convert WCRF score to intake in grams per day
Aoyama, 2014 COL41014 Japan	JACC study, Prospective Cohort, Age: 40-79 years, M/W	467/ 14 549 598 605 person-years	Cancer registry/ population register	Questionnaire	Incidence, colorectal cancer	Q 3 vs Q 3	1.00	Age, age, sex, beef, pork, or lamb, BMI, drinking amount, educational level, family history of colorectal cancer, local area, smoking, walking time	No quantities
					Incidence, colorectal cancer, men	≥1.8 vs ≥1.8 times/week	1.00		
					Incidence, colorectal cancer, women	≥2.2 vs ≥2.2 times/week	1.00		
					Incidence, colon cancer	Q 3 vs Q 3	1.00		
					Incidence, colon cancer, men	≥1.8 vs ≥1.8 times/week	1.00		
					Incidence, colon cancer, women	≥2.2 vs ≥2.2 times/week	1.00		
					Incidence,	Q 3 vs Q 3	1.00		

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI)	Adjustment factors	Reasons for exclusion
					rectal cancer				
					Incidence, rectal cancer, men	≥1.8 vs ≥1.8 times/week	1.00		
					Incidence, rectal cancer, women	≥2.2 vs ≥2.2 times/week	1.00		
Agnoli, 2013 COL40938 Italy	EPIC-Italy, Prospective Cohort, M/W	435/ 45 275 11.28 years	Cancer registry and hospital records	Semi-quantitative FFQ	Incidence, colorectal cancer	160.7-950.1 vs 0-96.6 g/day	0.89 (0.69-1.14)	Age, BMI, educational level, gender, non-alcoholic beverage Intake, physical activity, smoking, study center	Duplicate, overlap with Bamia et al, 2013 COL40964
Ruder, 2011 COL40896 USA	NIH-AARP, Prospective Cohort, Age: 50-71 years, Retired	2 819/ 292 797	Cancer registry and national health database	FFQ	Incidence, colon cancer	2.85 vs 0.53 times/day	0.88 (0.77-1.01)	Sex, age at baseline, alcohol consumption, aspirin use, BMI, educational level, energy, energy, history of colon cancer, HRT use, physical activity, race, smoking, vegetables	Duplicate, overlap with Park et al, 2007 COL40697
					Incidence, colon cancer	2.85 vs 0.53 times/day	0.87 (0.77-0.99)		
					Incidence, colon cancer	2.57 vs 0.39 times/day	0.81 (0.70-0.92)		
					Incidence, colon cancer	2.57 vs 0.39 times/day	0.80 (0.70-0.91)		
					Incidence, rectal cancer	2.85 vs 0.53 times/day	1.12 (0.88-1.41)		
					Incidence, rectal cancer	2.85 vs 0.53 times/day	1.14 (0.92-1.42)		
					Incidence, rectal cancer	2.57 vs 0.39 times/day	1.07 (0.84-1.36)		

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI)	Adjustment factors	Reasons for exclusion
					Incidence, rectal cancer	2.57 vs 0.39 times/day	1.10 (0.87-1.39)		
Butler, 2008 COL40639 Singapore	SCHS, Prospective Cohort, Age: 45-74 years, M/W	961/ 61 321 9.8 years	Cancer registry	FFQ	Incidence, colorectal cancer	Q 4 vs Q 1	0.98 (0.79-1.21)	Age, sex, alcohol Intake, BMI, diabetes, dialect group, educational level, energy Intake, exposure assessment, family history of colorectal cancer, physical activity, smoking habits	<3 categories of exposure
Iso, 2007 COL40707 Japan	JACC, Prospective Cohort, Age: 40-79 years, M/W	202/ 105 500 15 years	Municipal resident registration records, death certificates	FFQ	Mortality, colon cancer, men	3-4 vs ≤0 /week	0.83 (0.53-1.29)	Age, centre location	Mortality as outcome
					Mortality, colon cancer, women	3-4 vs ≤0 /week	1.35 (0.83-2.20)		
					Mortality, rectal cancer, men	3-4 vs ≤0 /week	1.24 (0.74-2.07)		
Wark, 2005 COL01807	, Case Cohort, Age: 55-69 years, M/W	368/ 120 852 7.3 years	Population registries	Semi-quantitative FFQ	Incidence, colon cancer, hmlh1+ cases	≥209.4 vs 0-150.5 g/day	0.94 (0.72-1.23)	Age, sex, family history of specific cancer, total energy	Duplicate, overlap with Voorrips et al, 2000 COL00578
					Incidence, colon cancer, hmlh1- cases	≥209.4 vs 0-150.5 g/day	0.86 (0.45-1.65)		
Tsubono, 2005 COL40746 Japan	JPHC, Prospective Cohort, Age: 40-59	377/ 88 658 694 074 person-years	Histology	FFQ	Incidence, colorectal cancer	Q 4 vs Q 1	1.00 (0.79-1.27)	Age, sex, alcohol consumption, BMI, centre location, cereal Intake, energy Intake, fish, meat Intake,	No quantities
					Incidence,	Q 4 vs Q 1	1.08 (0.80-		

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI)	Adjustment factors	Reasons for exclusion
	years, M/W				colon cancer		1.45)	physical activity, smoking status, vitamin use	
					Incidence, colorectal cancer, men	Q 4 vs Q 1	1.18 (0.88-1.59)		
					Incidence, colon cancer, men	Q 4 vs Q 1	1.24 (0.86-1.79)		
					Incidence, colorectal cancer, women	Q 4 vs Q 1	0.88 (0.57-1.35)		
					Incidence, rectal cancer	Q 4 vs Q 1	0.87 (0.58-1.31)		
					Incidence, colon cancer, women	Q 4 vs Q 1	1.01 (0.58-1.76)		
					Incidence, colon cancer, women	Q 4 vs Q 1	1.01 (0.58-1.76)		
					Incidence, rectal cancer, men	Q 4 vs Q 1	1.06 (0.63-1.78)		
Sanjoaquin, 2004 COL01182 UK	OVS, Prospective Cohort, Age: 18-89 years, M/W	95/ 10 998 17 years	Population/invitation	FFQ	Incidence, colorectal cancer,	Q 3 vs Q 1	0.86 (0.54-1.38)	Age, sex, alcohol consumption, smoking habits	No quantities

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI)	Adjustment factors	Reasons for exclusion
Bueno-de-Mesquita, 2002 COL00950 Europe	EPIC, Prospective Cohort, M/W	773/ 406 439	Not specified	FFQ	Incidence, colorectal cancer	Q 5 vs Q 1	0.71	Age, sex, body weight, centre location, energy Intake, ethanol Intake, fruit Intake, height, physical activity at work, smoking habits	Duplicate, overlap with Bamia et al, 2013 COL40964
					Incidence, colorectal cancer, women	≥316 vs 0-111 g/day	0.78		
					Incidence, colorectal cancer, men	≥252 vs 0-82 g/day	0.60		
Sellers, 1998 COL01974 USA	IWHS, Prospective Cohort, Age: 55-69 years, W, Postmenopausal	180/ 35 216 10 years	Seer registry	Semi-quantitative FFQ	Incidence, colon cancer, no family history of crc	≥27.1 vs ≤18 servings/week	1.10 (0.70-1.60)	Age, history of polyps, total energy Intake	Duplicate, overlap with Steinmetz et al, 1994 COL00178
					Incidence, colon cancer, family history of crc	≥27.1 vs ≤18 servings/week	2.00 (1.00-4.20)		
Hsing, 1998 COL00458 USA	Lutheran Brotherhood Study, Prospective Cohort, Age: 35- years, M, policyholders	120/ 17 633 286 731 person-years	Responding to mail survey	Questionnaire	Mortality, colon cancer,	≥4.6 vs ≤1.1 times/month	1.50 (0.80-2.80)	Age, alcohol consumption, smoking habits, total energy	Mortality as outcome

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI)	Adjustment factors	Reasons for exclusion
Kato, 1997 CRC00022 USA	New York University Women's Health Study, Prospective Cohort, Age: 34-65 years, W	100/ 14 272 105 044 person-years	Mammography screening program	Semi-quantitative FFQ	Incidence, colorectal cancer,	Q 4 vs Q 1	1.63 (0.92-2.89)	Age, educational level, place at enrollment, total calorie Intake	No quantities
Giovannucci, 1994 COL00119 USA	HPFS, Prospective Cohort, Age: 40-75 years, M, Health professionals	47 949 6 years	Mailing to health professionals	FFQ	Incidence, colon cancer,	≥5 vs ≤2 serving/day	1.02 (0.64-1.63)		Duplicate, overlap with Michels et al, 2000 COL00365
Thun, 1992 COL01224 USA, Puerto Rico	CPS II, Nested Case Control, Age: 30- years, M/W	611/ 3051 controls 6 years	Not specified	Questionnaire	Mortality, colon cancer, men	Q 5 vs Q 1	0.80	Age, sex, ethnicity	Mortality as outcome, duplicate, overlap with McCullough et al, 2003, COL00367
					Mortality, colon cancer, women	Q 5 vs Q 1	0.63 (0.45-0.89)		
					Mortality, colon cancer, women	Q 5 vs Q 1	0.66		
Hirayama, 1990 COL01508 Japan	Japan 6 prefectures cohort study, Prospective	563/ 265 118 17 years	Health centres	Interview	Mortality, rectal cancer,	daily consumption vs no daily consumption	1.05 (0.90-1.24)	Age, sex	Mortality as outcome

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI)	Adjustment factors	Reasons for exclusion
	Cohort, Age: 40- years, M/W				Mortality, colon cancer,	daily consumption vs no daily consumption	0.85 (0.73-0.99)		

Figure 32 RR estimates of colorectal cancer by levels of vegetable intake

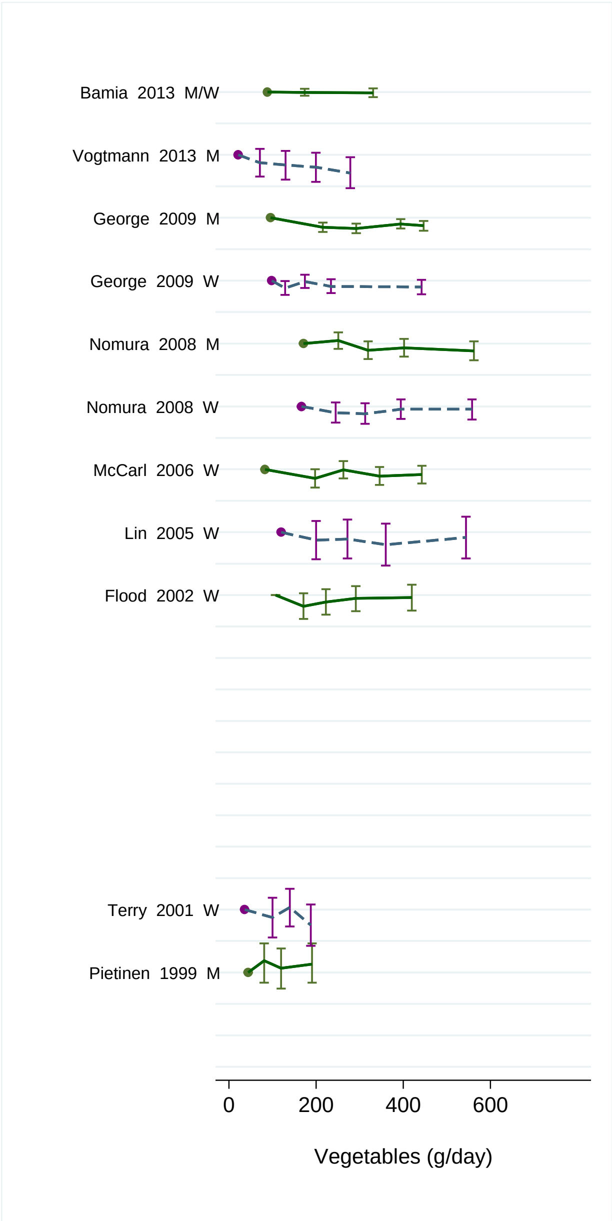


Figure 33 Relative risk of colorectal cancer for the highest compared with the lowest level of vegetable intake

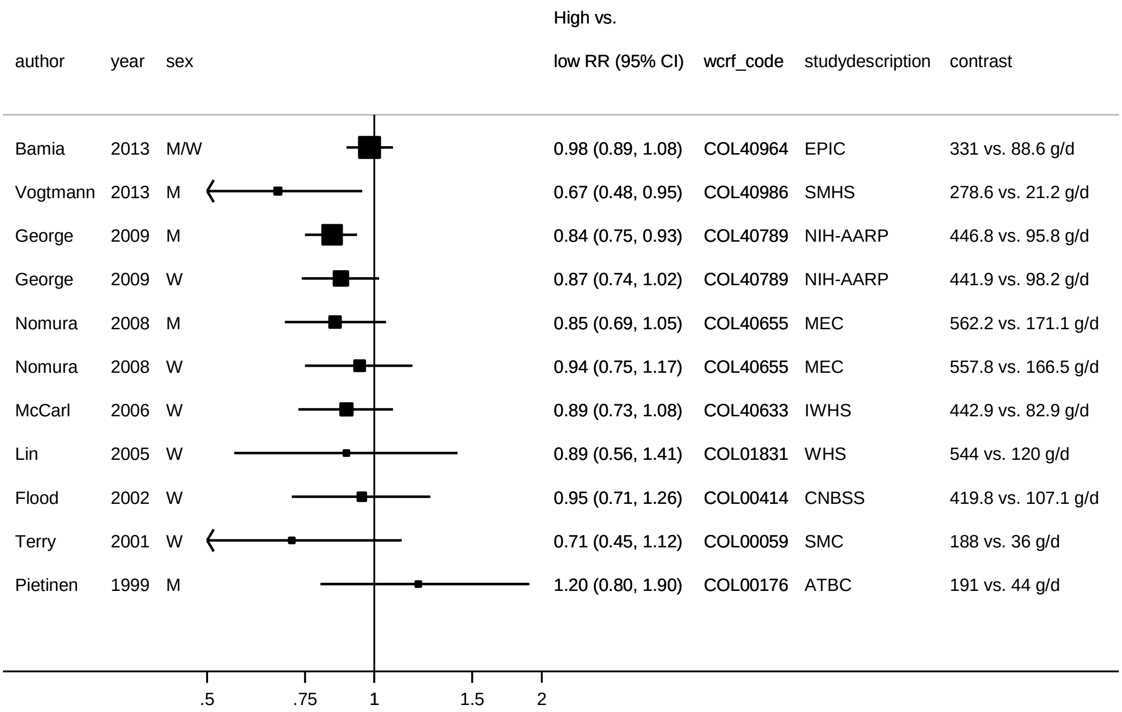


Figure 34 Relative risk of colorectal cancer for 100 g/day increase in vegetable intake

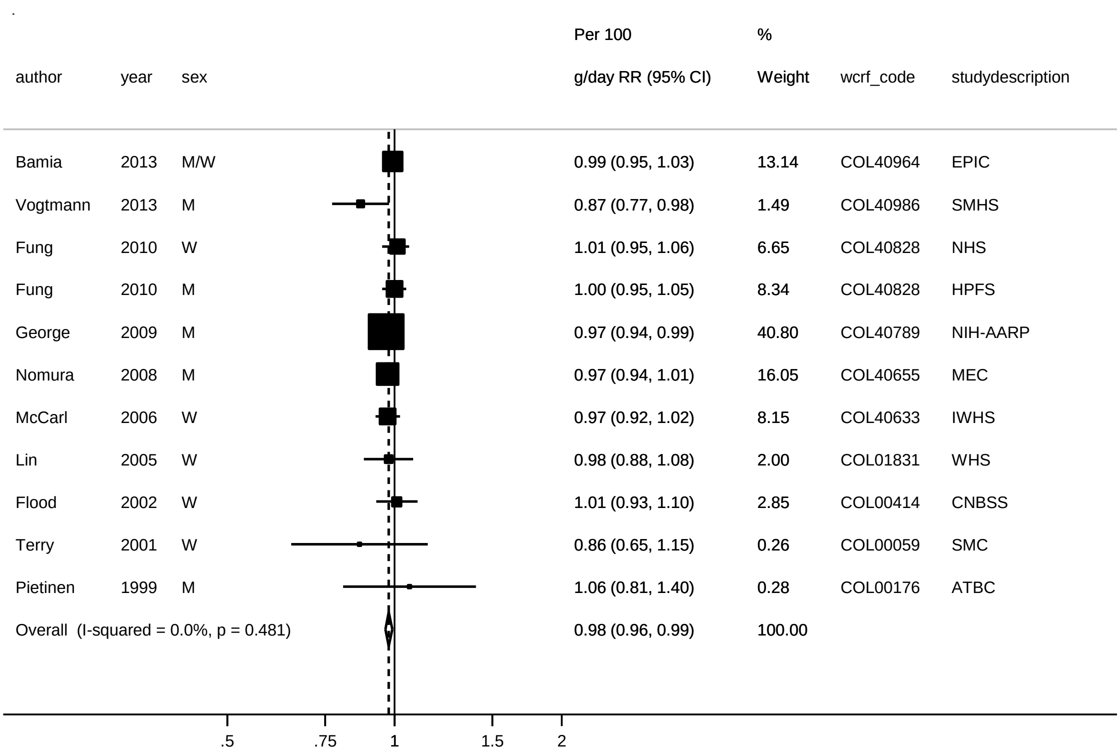


Figure 35 Relative risk of colorectal cancer for 100 g/day increase in vegetable intake, stratified by sex

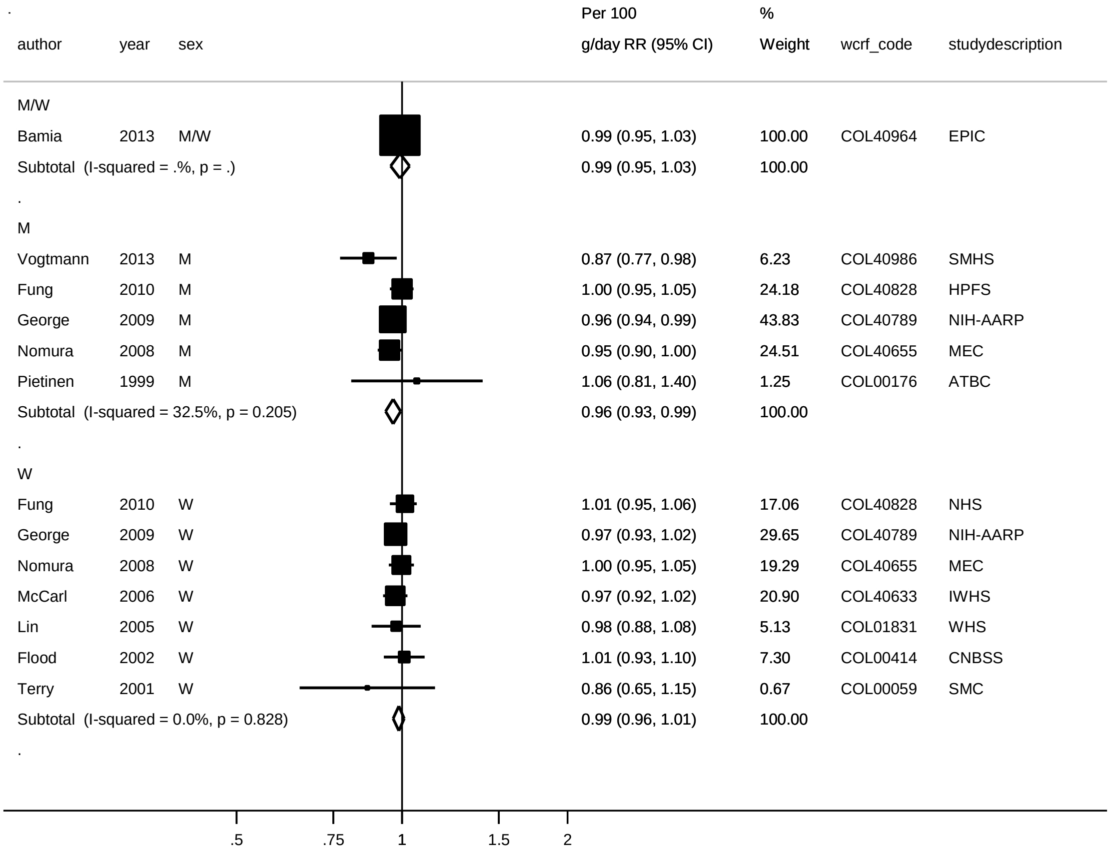


Figure 36 Relative risk of colorectal cancer for 100 g/day increase in vegetable intake, stratified by geographic location

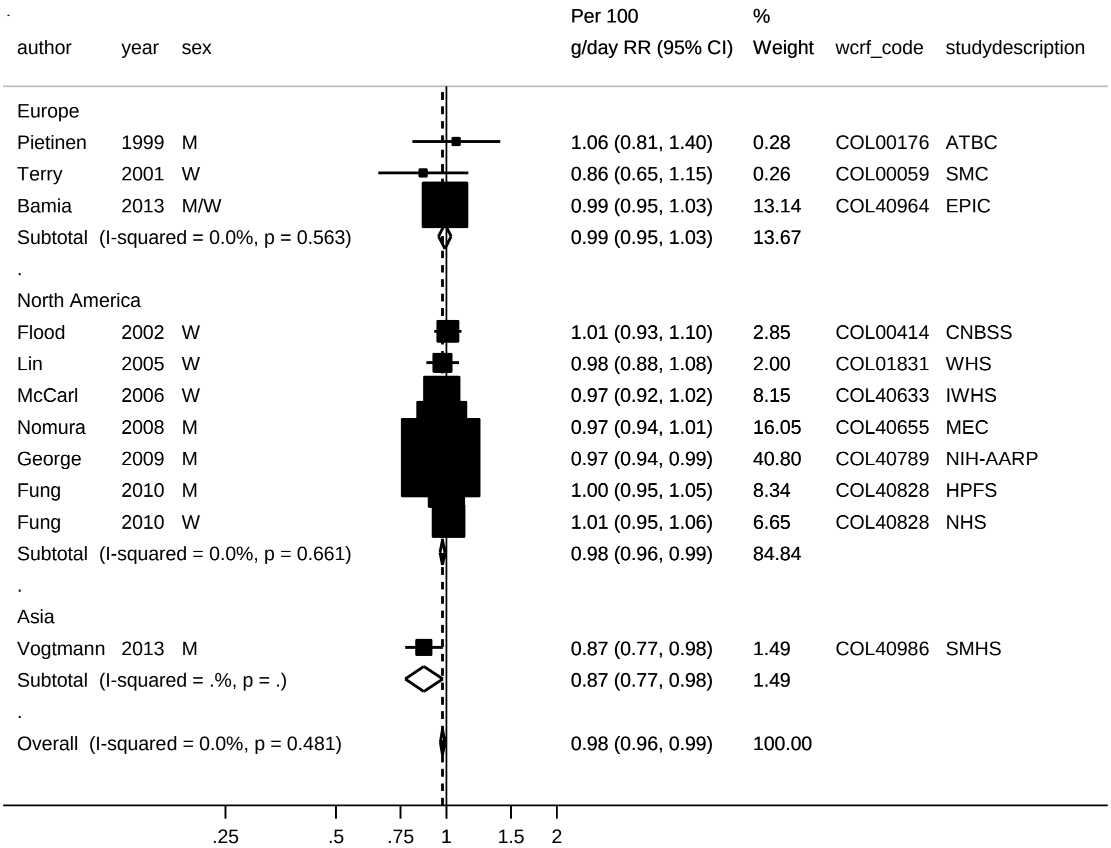
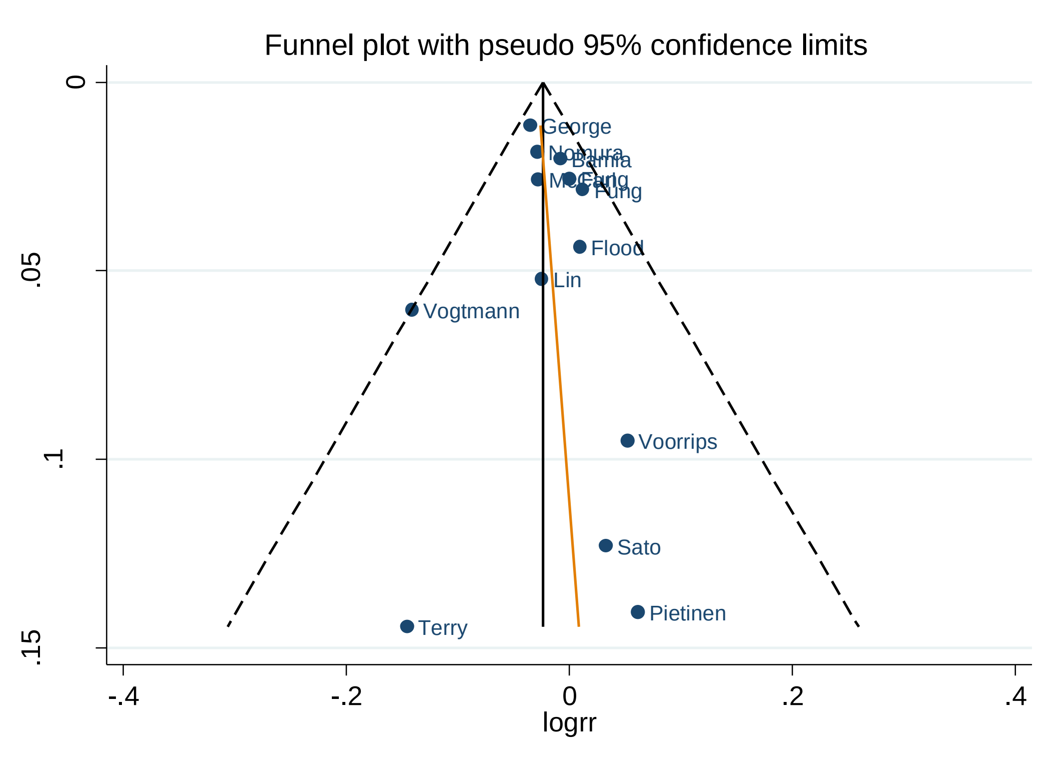
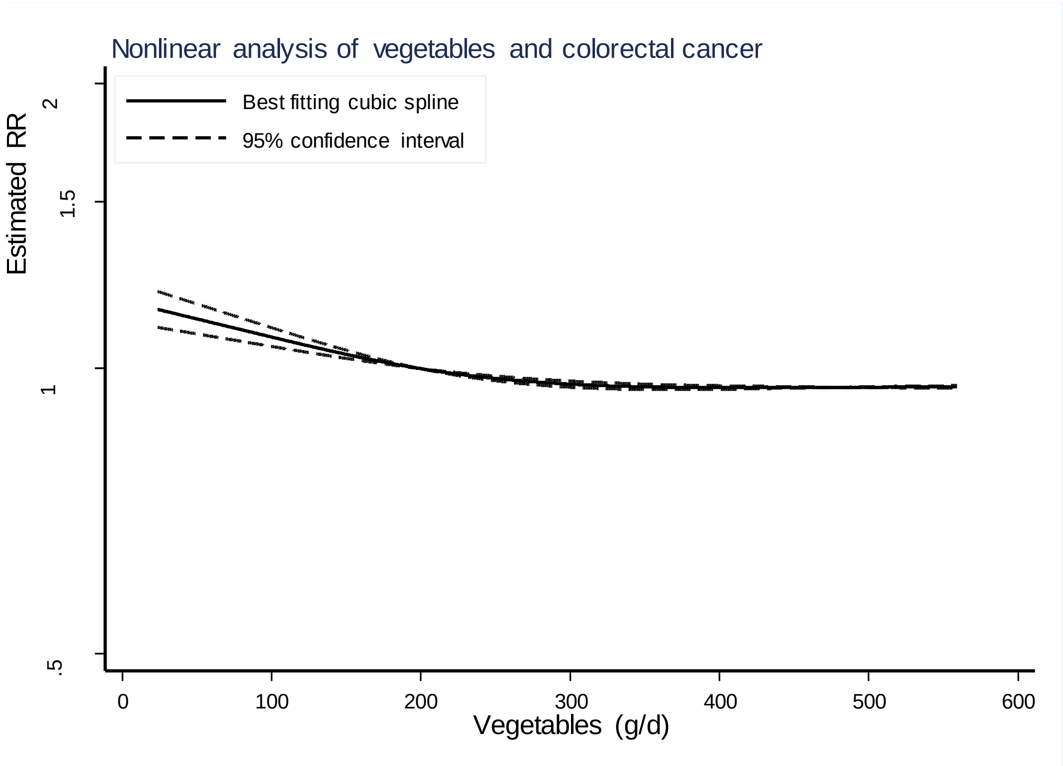


Figure 37 Funnel plot of studies included in the dose response meta-analysis of vegetable intake and colorectal cancer



p Egger's test =0.92

Figure 38 Relative risk of colorectal cancer and vegetables estimated using non-linear models



P nonlinearity<0.0001

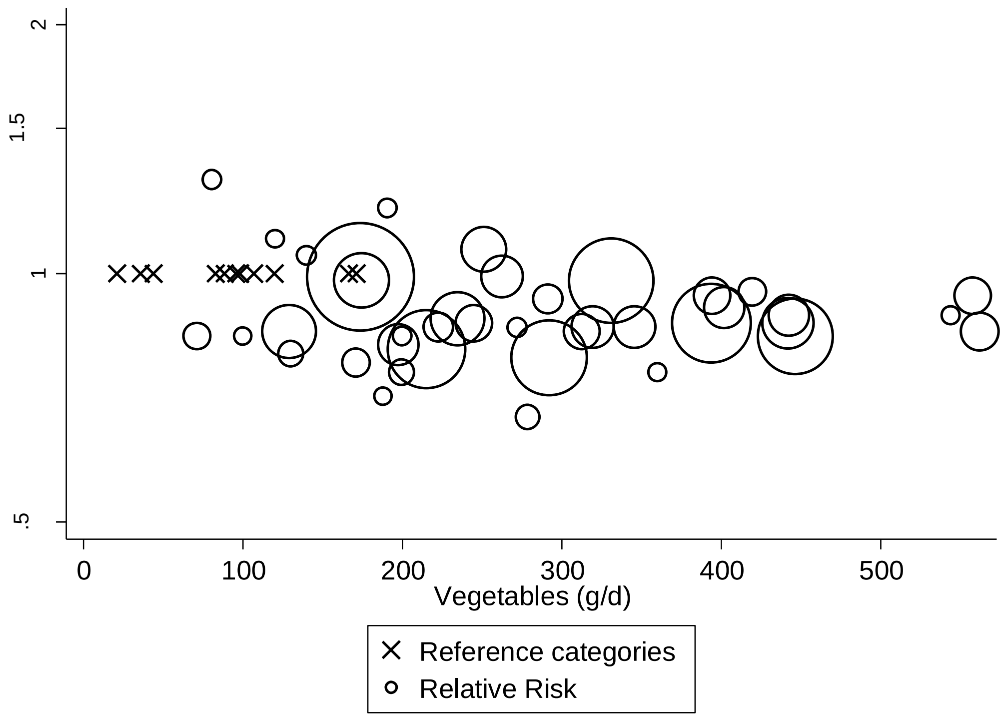


Table 27 Relative risk of colorectal cancer and vegetable intake estimated using non-linear models

g/day	RR (95% CI)
22	1.16 (1.11-1.21)
100	1.08 (1.06-1.10)
200	1.00
300	0.96 (0.95-0.97)
400	0.95 (0.95-0.96)
500	0.96 (0.96-0.96)

Figure 39 RR estimates of colon cancer by levels of vegetable intake

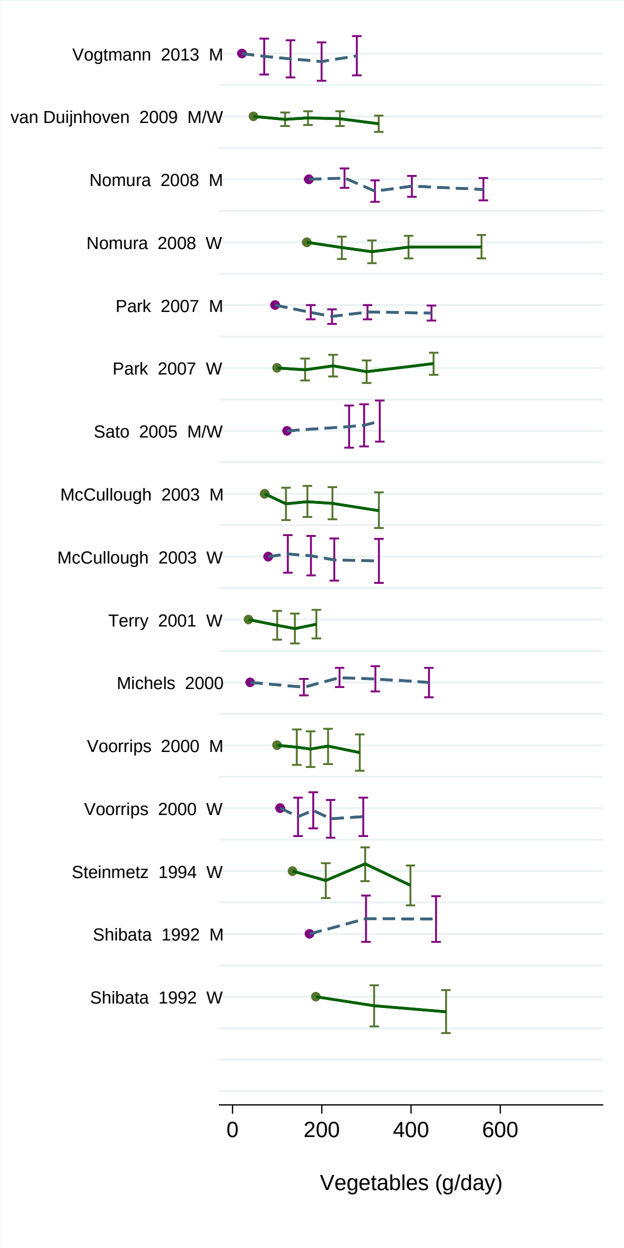


Figure 40 Relative risk of colon cancer for the highest compared with the lowest level of vegetable intake

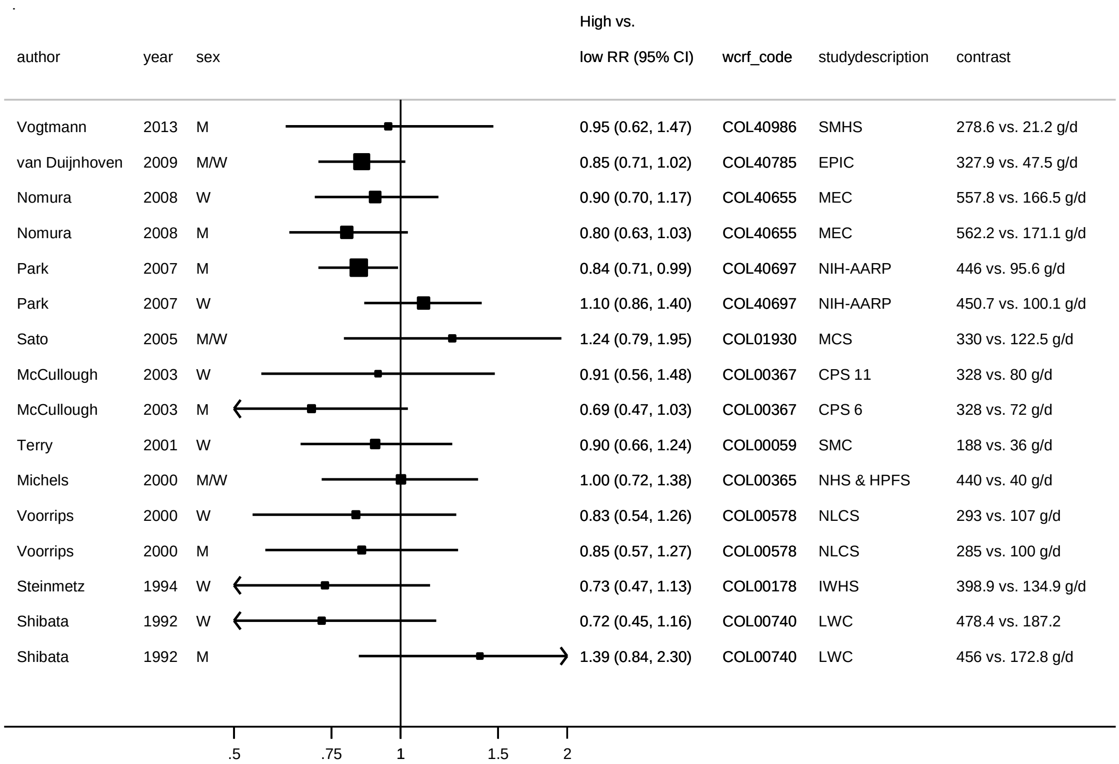


Figure 41 Relative risk of colon cancer for 100 g/day increase in vegetable intake

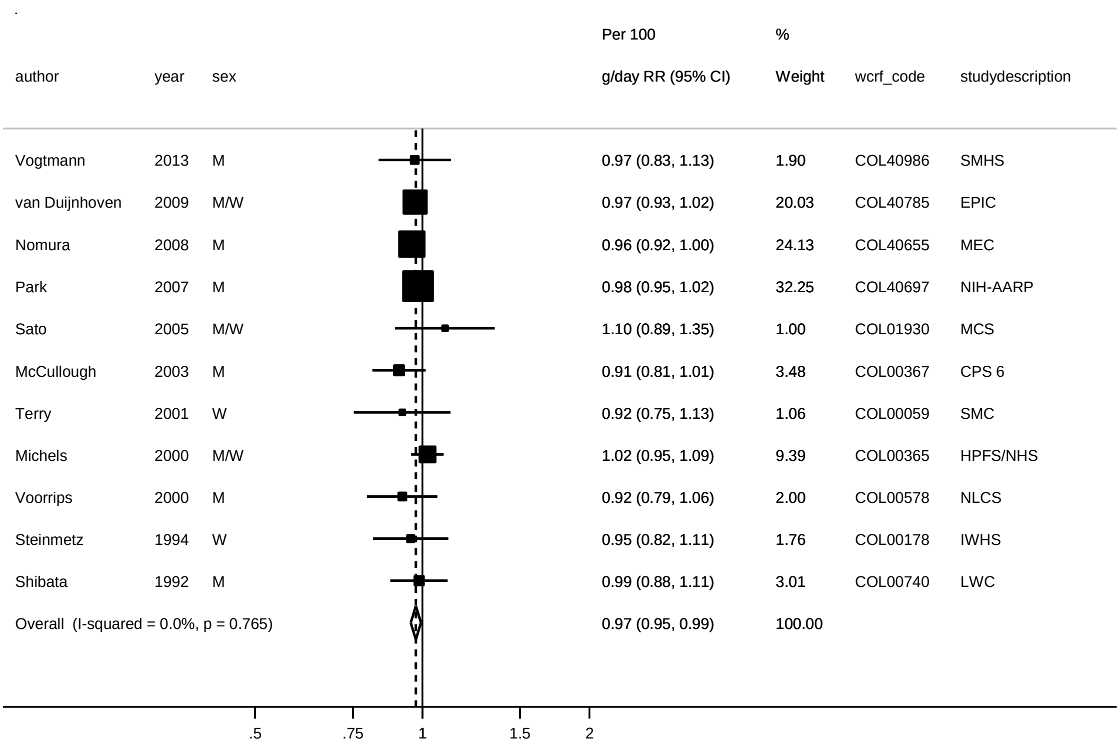


Figure 42 Relative risk of colon cancer for 100 g/day increase in vegetable intake, stratified by sex

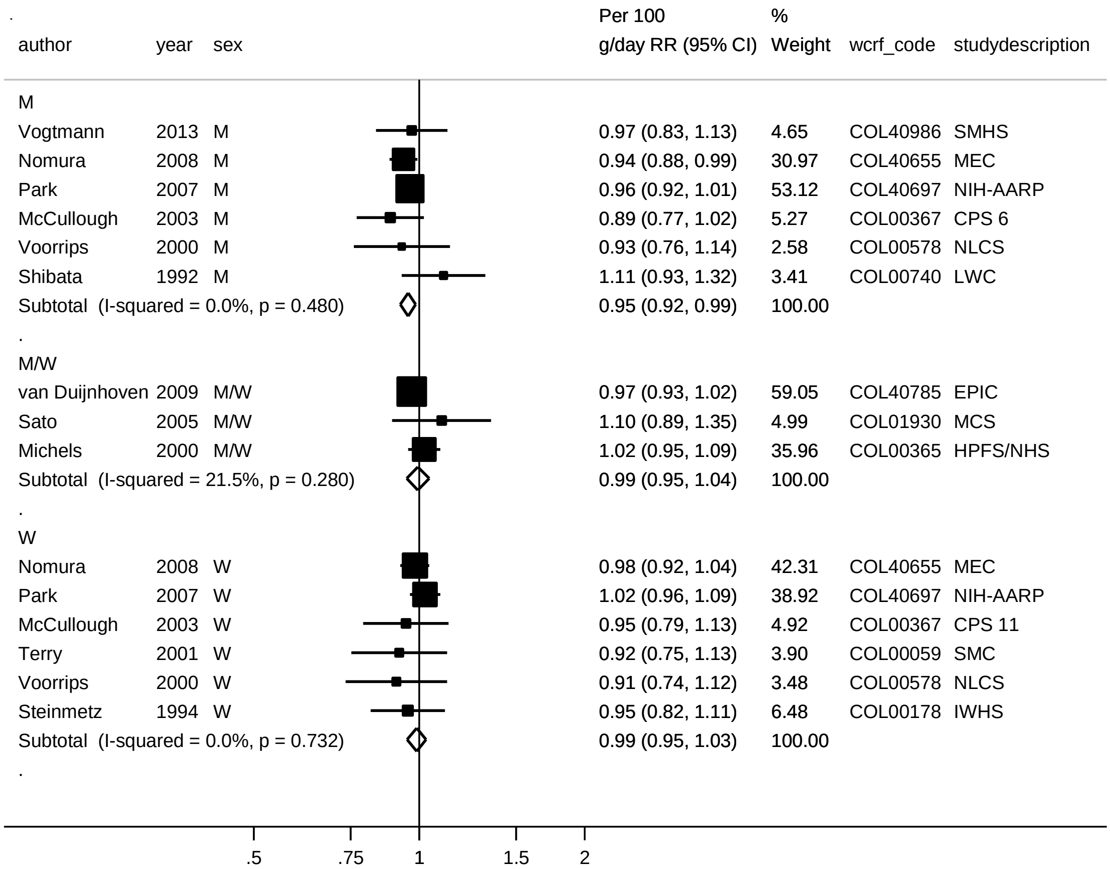


Figure 43 Funnel plot of studies included in the dose response meta-analysis of vegetable intake and colon cancer

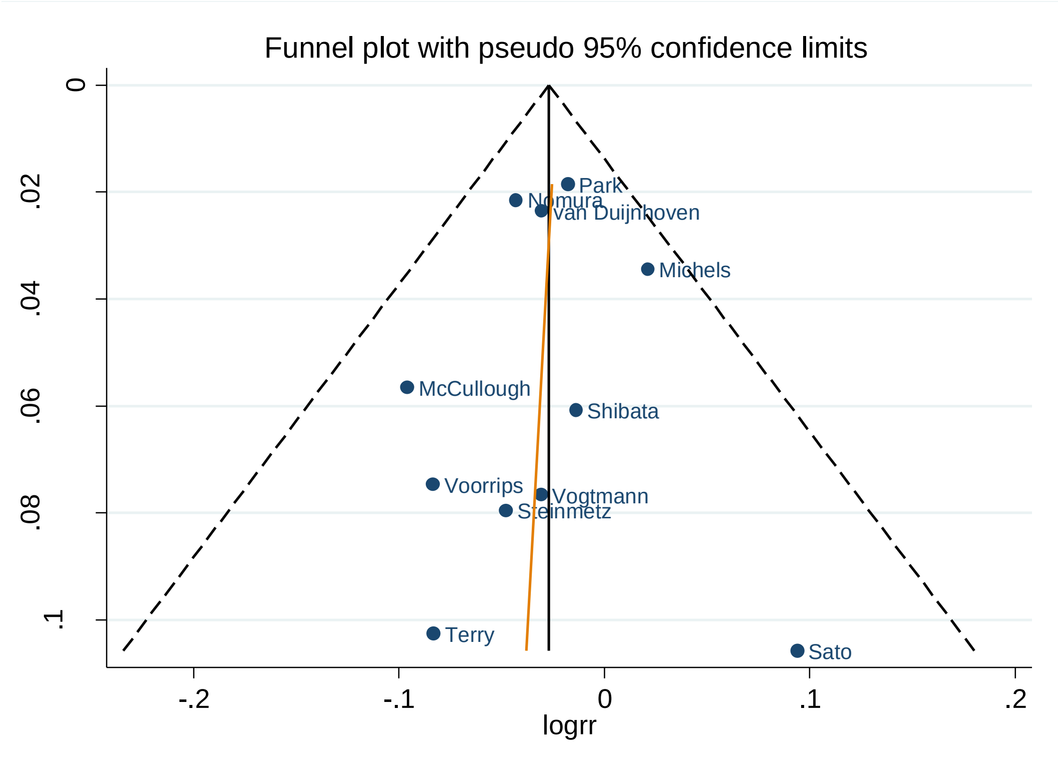
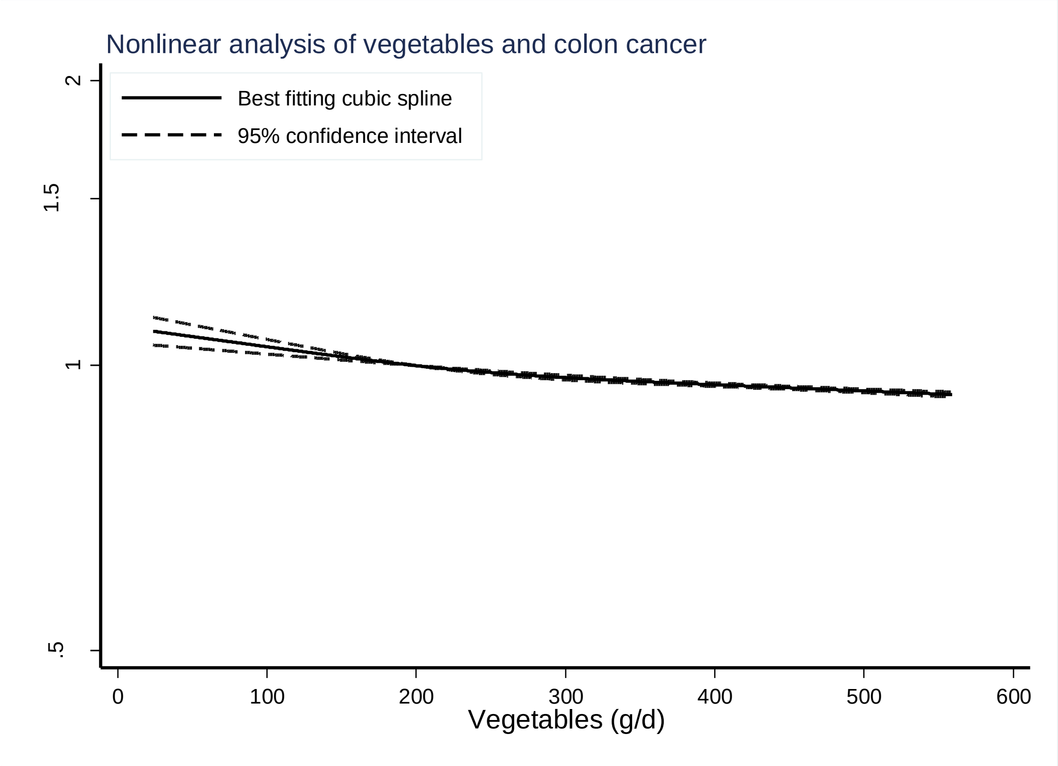


Figure 44 Relative risk of colon cancer and vegetables estimated using non-linear models



P nonlinearity=0.02

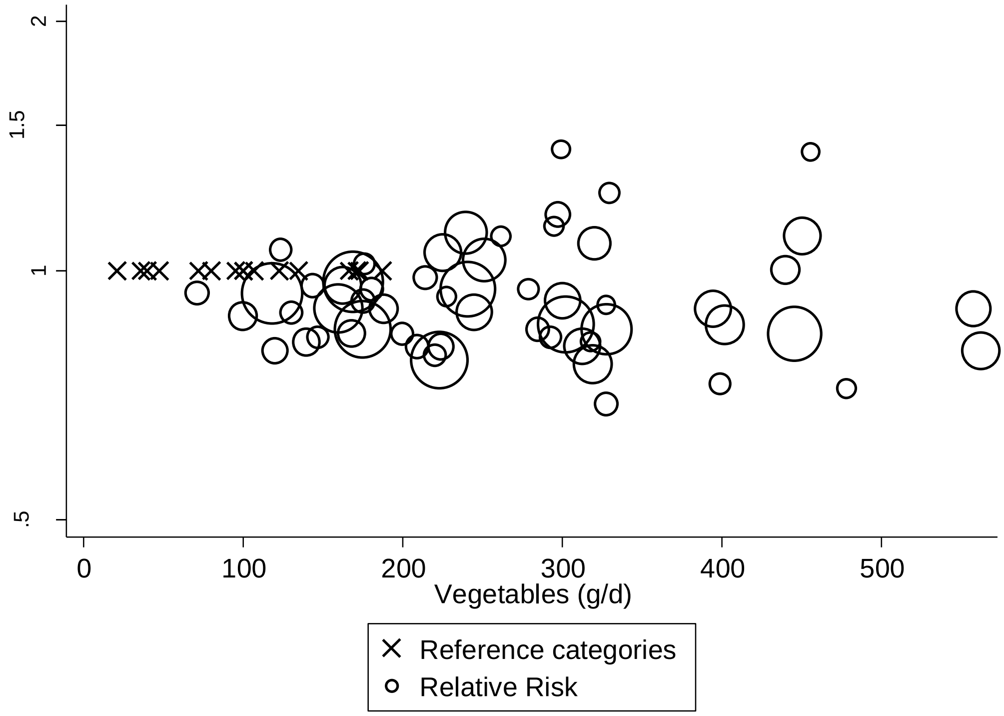


Table 28 Relative risk of colon cancer and vegetable intake estimated using non-linear models

Vegetable (g/day)	RR (95%CI)
21.2	1.09 (1.05-1.13)
100	1.05 (1.03-1.07)
200	1.00
300	0.97 (0.96-0.98)
400	0.95 (0.95-0.96)
500	0.94 (0.93-0.94)
21.2	1.09 (1.05-1.13)

Figure 45 RR estimates of rectal cancer by levels of vegetable intake

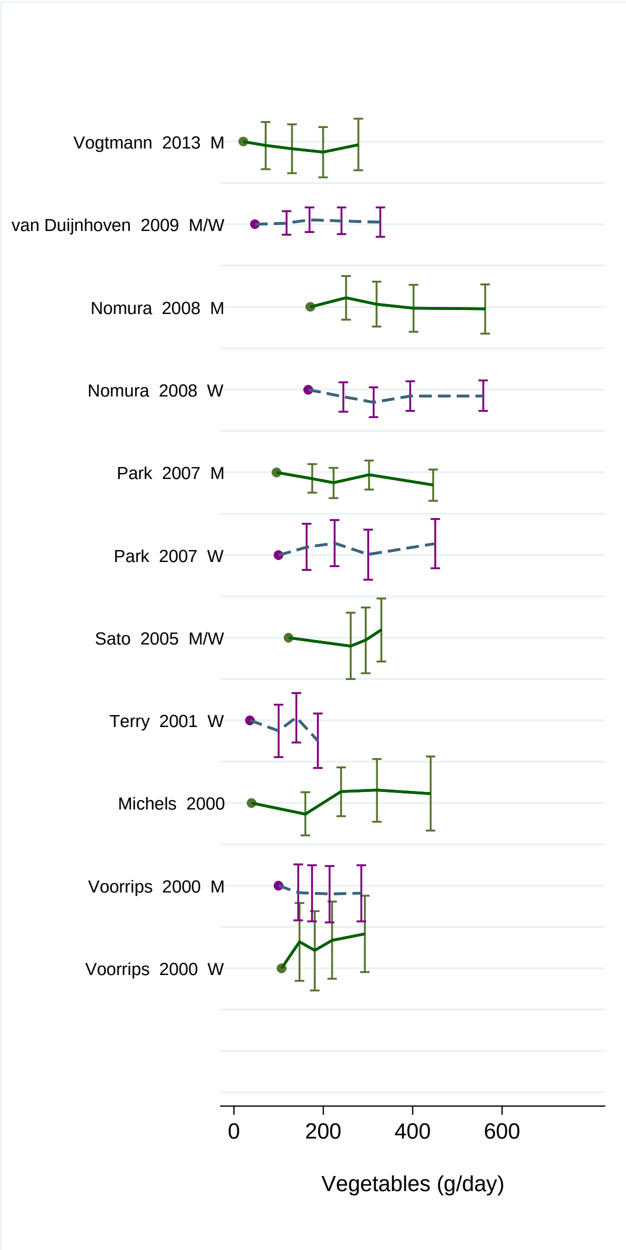


Figure 46 Relative risk of rectal cancer for the highest compared with the lowest level of vegetable intake

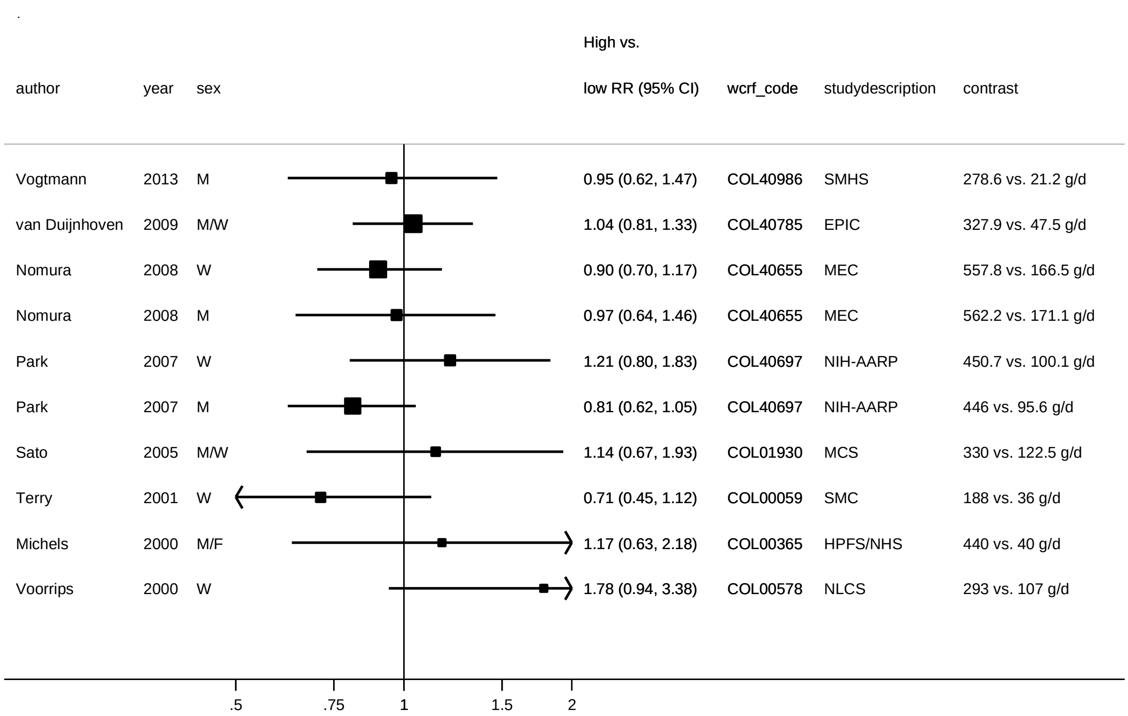


Figure 47 Relative risk of rectal cancer for 100 g/day increase in vegetable intake

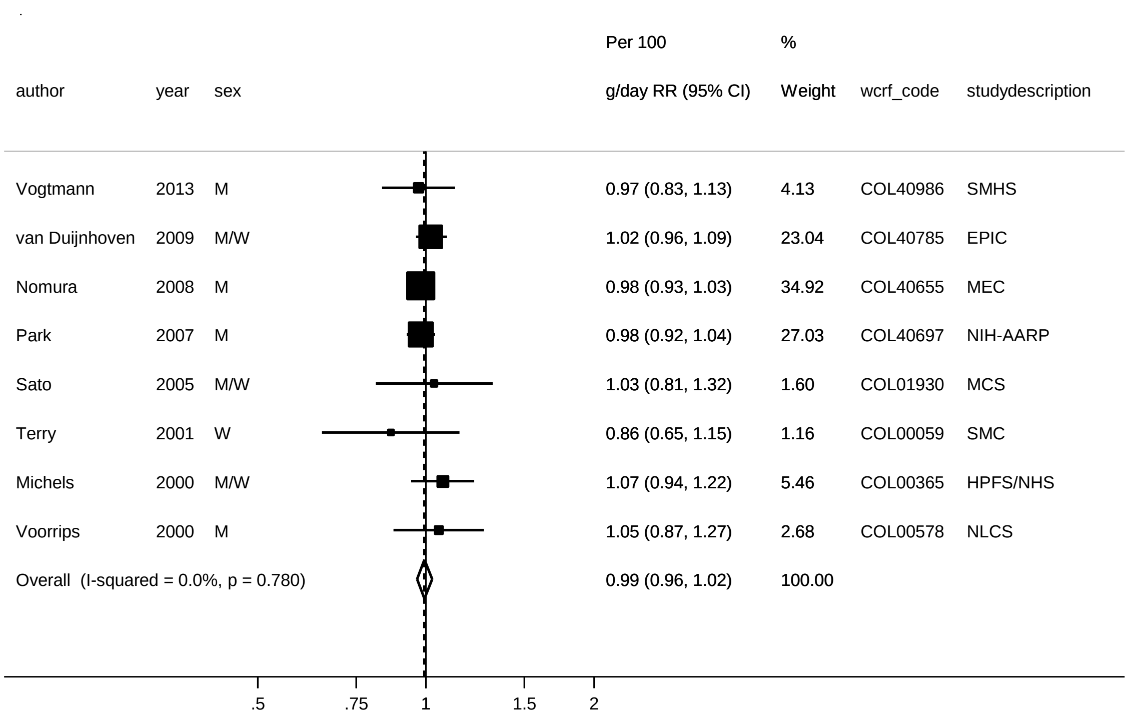


Figure 48 Relative risk of rectal cancer for 100 g/day increase in vegetable intake, stratified by sex

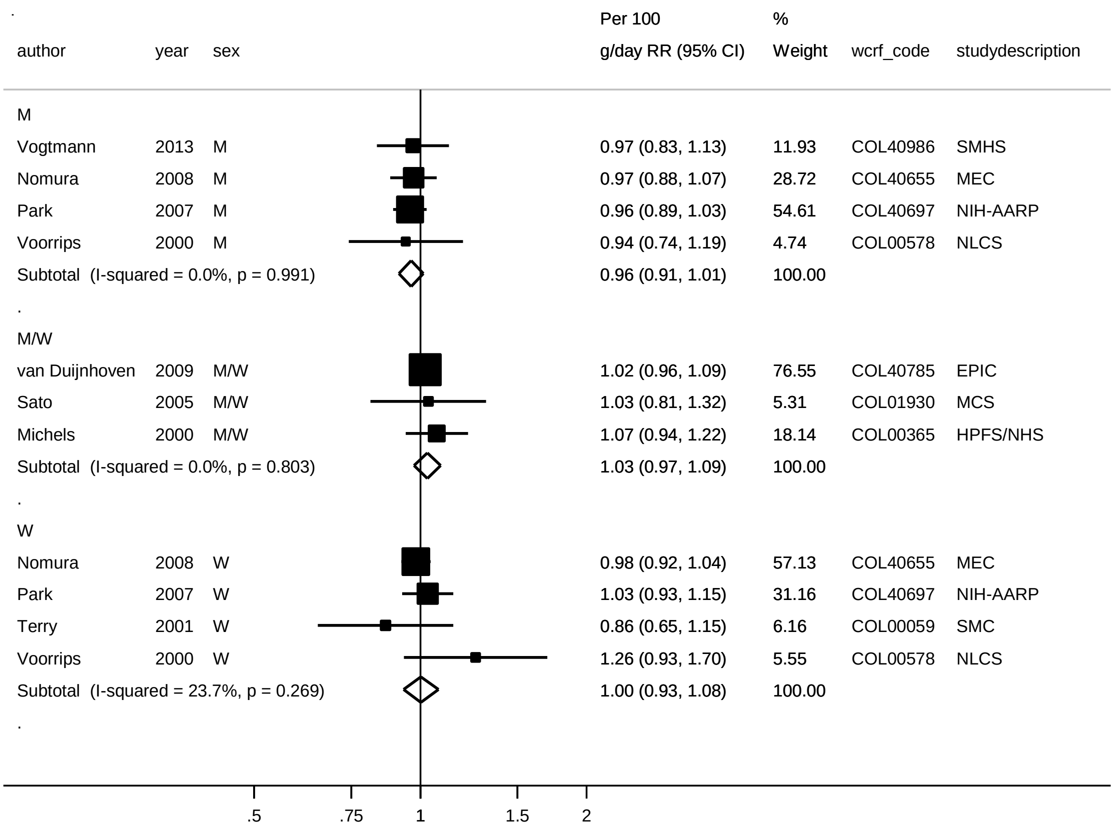


Figure 49 Funnel plot of studies included in the dose response meta-analysis of vegetable intake and rectal cancer

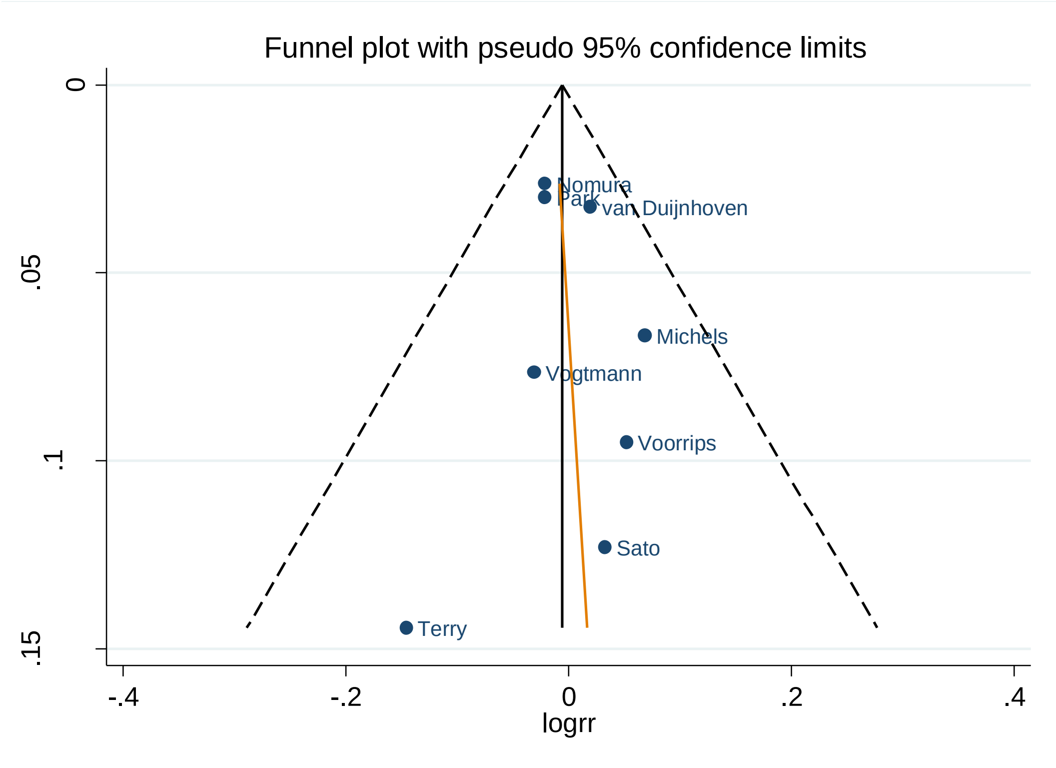
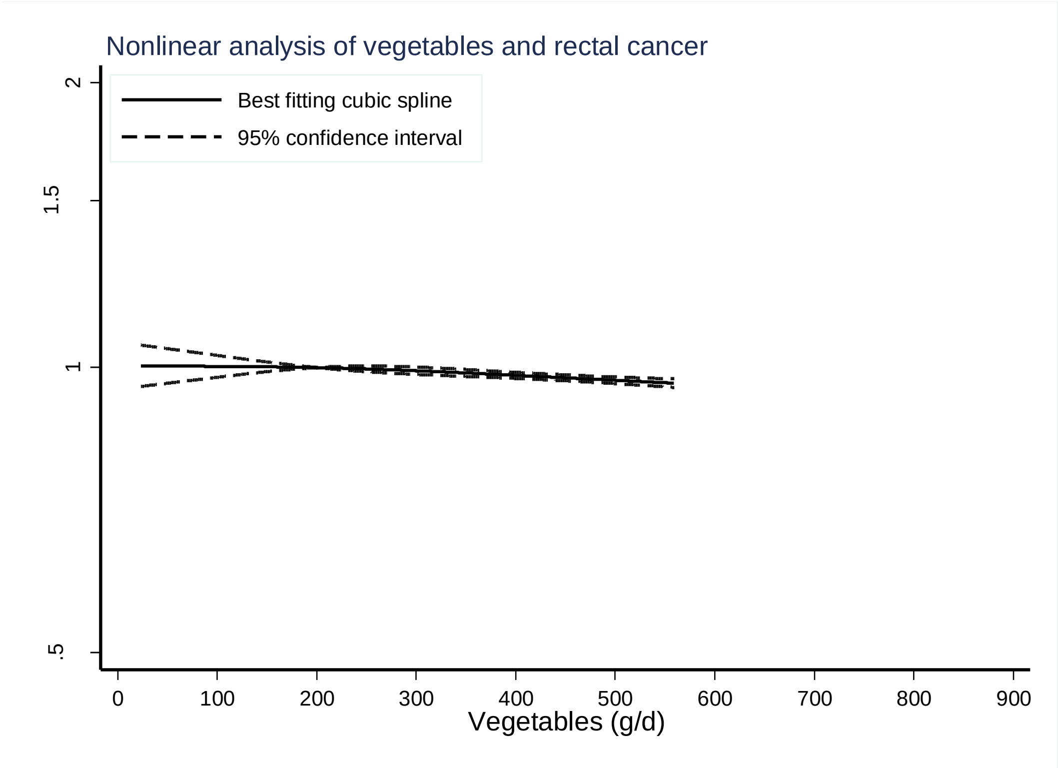


Figure 50 Relative risk of rectal cancer and vegetables estimated using non-linear models



P nonlinearity<0.0001

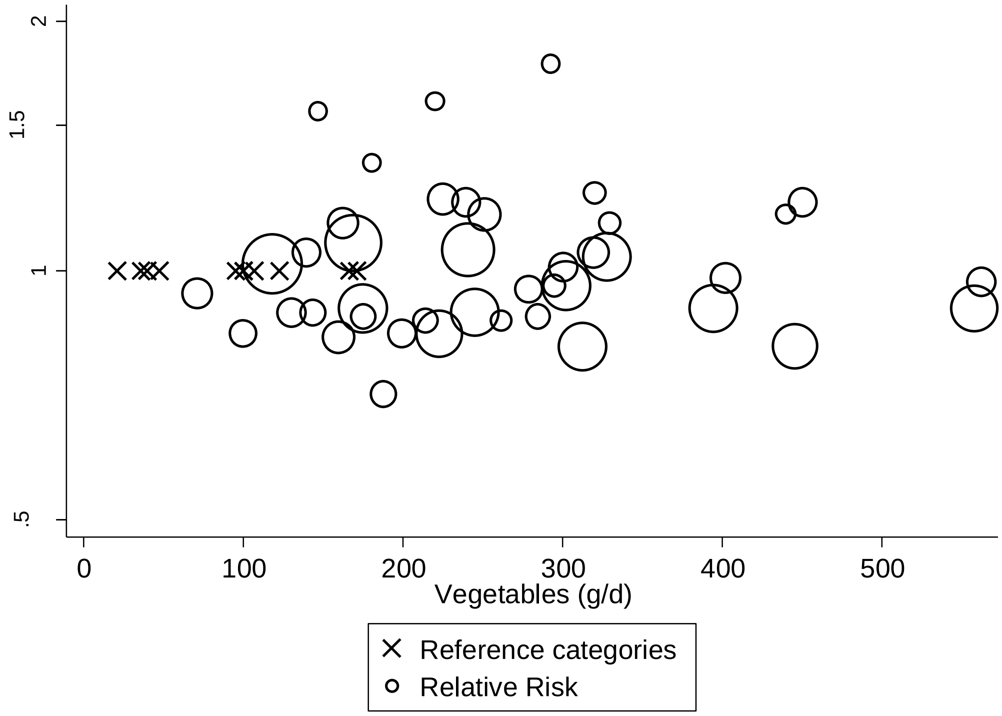


Table 29 Relative risk of rectal cancer and vegetable intake estimated using non-linear models

Vegetable (g/day)	RR (95%CI)
21.2	1.00 (0.95-1.06)
100	1.00 (0.98-1.03)
200	1.00
300	0.99 (0.98-1.00)
400	0.98 (0.97-0.99)
500	0.97 (0.96-0.98)

2.2.1.3.1 Garlic

Cohort studies

Summary

Main results:
No analysis on garlic and colorectal cancer was included in the 2010 SLR. The evidence that garlic intake probably decreases the risk of colorectal cancer comes from the 2005 SLR which identified a total of four case-control (with five OR estimates) and three cohort studies on garlic consumption and colorectal cancer. A meta-analysis including two cohort studies (IWHS and HPFS) was conducted and showed a RR estimate of 0.66 (95% CI: 0.48-0.91, pheterogeneity=0.67) for the highest category of garlic intake compared with the lowest category. A meta-analysis including five case-control studies showed a RR of 0.76 (0.58-0.98, pheterogeneity=0.06).
A table of the studies identified is included below. From the 4 studies identified (NHS, HPFS, IWHS and CPS II) all showed a not statistically significant association between garlic and colorectal, colon or rectal cancer.

2.2.1.3.1 Garlic supplements

The only study (NLCS) identified on garlic supplements and colon cancer in the 2005 SLR was described in the narrative review.
We identified 4 studies on colorectal cancer on garlic supplement use in the 2015 SLR that we could include in a highest compared to lowest analysis. The overall RR for the highest compared to lowest analysis on colorectal cancer was 1.07(95%CI=0.82-1.39, 56.2%, 0.07). Only three studies could be included in the analysis of colon and rectal cancer where the result of the highest compared to lowest analysis was 1.02(95% CI=0.70-1.48), 47.3%, 0.15) and (1.16, 95%= 0.74-1.83, 0%, 0.41), respectively.

Meta-analysis of cohort studies:
One meta-analysis (Heine Bröring, 2015) combined the results of colorectal, colon and rectal cancer from two studies (Satia, 2009 and Dorant, 1996) in a highest compared to lowest analysis which showed a non-statistically significant increased risk for garlic supplement use and colorectal cancer.

Table 30Garlic and colorectal cancer risk. Results of meta-analyses and pooled analyses of prospective studies published after the 2005 SLR.

Author, Year	Number of cohort studies	Total number of cases	Studies country, area	Outcome	Comparison	RR (95%CI)	P trend	Heterogeneity (I^2, p value)
Meta-analysis								
Heine Bröring, 2015	2	802	North America, Europe	Colorectal cancer	Highest vs Lowest	1.24(0.99-1.54)		0%, 0.36

Table 31 Garlic and colorectal cancer risk. Main characteristics of studies included in the CUP SLR dose-response meta-analysis

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors
Meng, 2013 COL40930	NHS, Prospective Cohort, Age: 30-55 years, W, nurses	634/ 76 208 24 years	Biennial follow-up questionnaires and medical records	Questionnaire	Incidence, proximal cancer	≥1/day vs <1/month	1.13 (0.78-1.64) Ptrend:0.33	Age, alcohol consumption, aspirin use, beef, pork or lamb as a main dish, BMI, calcium Intake, endoscopy, energy, folate, history of colorectal cancer, HRT use, physical
		397/			Incidence, distal cancer		1.39 (0.88-2.20) Ptrend:0.30	
		285/			Incidence, rectal cancer		1.14 (0.64-2.03) Ptrend:0.68	
		1 339			Incidence, colorectal cancer		1.21 (0.94-1.57) Ptrend:0.14	
		1 054/			Incidence, colon cancer		1.23 (0.92-1.64) Ptrend:0.15	

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors
								activity, processed meat, smoking, vitamin d
Meng, 2013 COL40931 USA	HPFS, Prospective Cohort, Age: 40-75 years, M, Health professionals	1 029/ 45 592 22 years		Questionnaire	Incidence, colorectal cancer	≥1/day vs <1/month	1.00 (0.71-1.42) Ptrend:0.89	Age, aspirin use, BMI, endoscopy, family history of colorectal cancer, physical activity, smoking Alcohol, beef, pork or lamb as a main dish, calcium, energy, folate, processed meat, vitamin d
		811/			Incidence, colon cancer		1.09 (0.76-1.58) Ptrend:0.90	
		345/		Questionnaire	Incidence, proximal cancer		1.35 (0.80-2.28) Ptrend:0.43	
		314/			Incidence, distal cancer		1.01 (0.55, 1.86)	
		218/		Questionnaire	Incidence, rectal cancer	≥1/day vs <1/month	0.60 (0.22-1.66) Ptrend:0.56	
McCullough, 2012 COL40919 USA	CPS II, Prospective Cohort, M/W	1 130/ 99 700 7 years	Cancer registry and death certificates and medical records	FFQ	Incidence, colorectal cancer	1+ vs <1 /month	1.03 (0.77-1.37) Ptrend:0.67	Age, alcohol, BMI, calcium, energy, fruits and vegetables consumption, gender, history of endoscopy,
		579/			Men	1+ vs <1 /month	1.10 (0.74-1.64) Ptrend:0.26	
		551/			Women	1+ vs <1 /month	0.87 (0.58-1.32)	

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors
							Ptrend:0.06	HRT use, NSAID use, physical activity, red and processed meat, smoking
Sellers, 1998 COL01974 USA	IWHS, Prospective Cohort, Age: 55-69 years, W, Postmenopausal	180/ 35 216 10 years	Seer registry	Semi-quantitative FFQ	Incidence, colon cancer, no family history of crc	≥1 vs ≤0 servings/week	1.20 (0.80-1.90) Ptrend:0.4	Age, history of polyps, total energy Intake
		61/			Family history of crc		1.00 (0.40-2.50) Ptrend:0.9	
Giovannucci, 1994 COL00119 USA	HPFS, Prospective Cohort, Age: 40-75 years, M, Health professionals	205/ 47 949 6 years	Mailing to health professionals	FFQ	Incidence, colon cancer,	≥2 vs ≤0 serving/week	0.77 (0.51-1.16) Ptrend:0.14	Age
					Incidence, distal colon cancer,	≥2 vs ≤0 serving/week	0.63 (0.38-1.65) Ptrend:0.07	
Steinmetz, 1994 COL00178 USA	IWHS, Prospective Cohort, Age: 55-69 years, W,	212/ 35 216 167 447 person-years	Seer registry	Semi-quantitative FFQ	Incidence, colon cancer,	≥1 vs 0-0.4 serving/week	0.68 (0.46-1.02) Ptrend:<0.1	Age, energy Intake
						Q 3 vs Q 1	0.70 (0.46-1.05)	Age, age at first child birth, alcohol consumption,

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors
	Postmenopausal							BMI, educational level, energy Intake, history of polyps or colitis, parity, physical activity, smoking habits
		120/			Incidence, distal colon cancer, distal sites	≥1 vs 0-0.4 serving/week	0.52 (0.30-0.93) Ptrend:<0.05	Age, energy Intake
		86/			Incidence, proximal colon cancer, proximal sites	≥1 vs 0-0.4 serving/week	1.00 (0.56-1.79)	

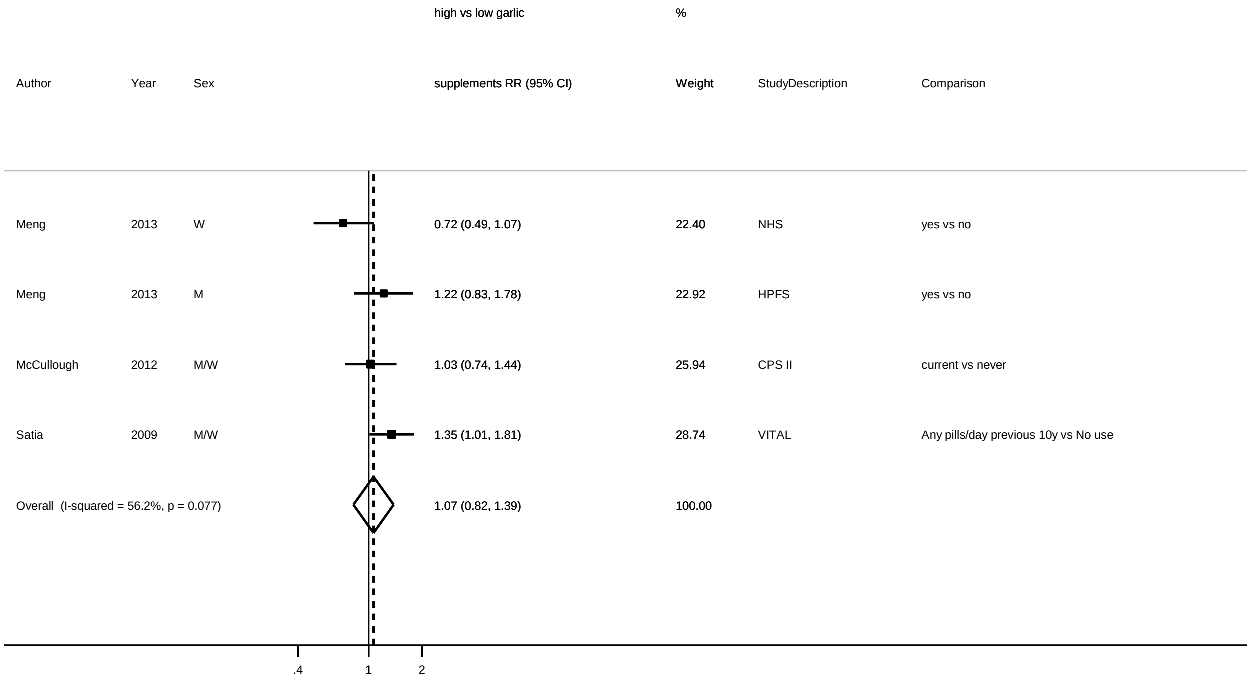
Table 32 Garlic supplements and colorectal cancer risk. Main characteristics of studies included in the CUP SLR dose-response meta-analysis

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors
Meng, 2013 COL40930	NHS, Prospective Cohort, Age: 30-55 years, W, nurses	302/ 76 208 24 years	Biennial follow-up questionnaires and medical records	Questionnaire	Incidence, proximal cancer	yes vs no	0.75 (0.44-1.27)	Age, alcohol consumption, aspirin use, beef, pork or lamb as a main dish, BMI, calcium Intake, endoscopy, energy, folate, history of colorectal cancer, HRT use, physical activity, processed meat, smoking, vitamin d
		153/			Incidence, distal cancer	yes vs no	0.68 (0.32-1.48)	
		115/			Incidence, rectal cancer	yes vs no	0.69 (0.28-1.71)	
		578/			Incidence, colon cancer	yes vs no	0.72 (0.46-1.11)	
Meng, 2013 COL40931 USA	HPFS, Prospective Cohort, Age: 40-75 years, M, Health professionals	559/ 45 592 22 years	Biennial follow-up questionnaires and medical records	Questionnaire	Incidence, colorectal cancer	yes vs no	1.22 (0.83-1.78)	Age, alcohol, aspirin use, beef, pork or lamb as a main dish, BMI, calcium, endoscopy, energy, family history of colorectal cancer, folate,
		431/			Incidence, colon cancer	yes vs no	1.16 (0.75-1.80)	
		200/			Incidence, proximal cancer	yes vs no	0.86 (0.40-1.85)	
		141/			Incidence, distal cancer	yes vs no	1.87 (1.01-3.46)	

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors
		128/			Incidence, rectal cancer	yes vs no	1.51 (0.71-3.21)	physical activity, processed meat, smoking, vitamin d
McCullough, 2012 COL40919 USA	CPS II, Prospective Cohort, M/W	764/ 99 700 7 years	Cancer registry and death certificates and medical records	FFQ	Incidence, colorectal cancer	current vs never	1.03 (0.74-1.44)	Age, alcohol, BMI, energy, gender, history of endoscopy, HRT use, NSAID use, physical activity, smoking, Calcium, fruits and vegetables consumption, red and processed meat
		390/			Men	current vs never	0.94 (0.57-1.53)	
		374/			Women	current vs never	1.09 (0.69-1.72)	
Satia, 2009 COL40962 USA	VITAL, Prospective Cohort, Age: 50-76 years, M/W	428/ 76 512 5 years	Seer registry	Questionnaire	Incidence, colorectal cancer	any pills/day during the previous 10y vs no use	1.35 (1.01-1.81)	Age, BMI, educational level, fruits and vegetables consumption, gender, nsaid use, phyisical activity, sigmoidoscopy
Dorant, 1996 COL00095	NLCS, Case Cohort,	252/ 120 852	Population registries	Semi-quantitative FFQ	Incidence, colon cancer,	exclusively garlic	1.36 (0.79-2.35)	Age, beta carotene,

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors
Netherlands	Age: 55-69 years, M/W	3.3 years				supplements vs no supplement		educational level, family history of large Intestinal cancer, gender, history of cholecystectomy, history of chronic Intestinal disease, smoking status, vitamin c
		147/			Incidence, rectal cancer,	exclusively garlic supplements vs no supplement	1.28 (0.63-2.60)	

Figure 51 RR (95% CI) of colorectal cancer for the highest compared with the lowest level of garlic supplements



2.2.2 Total Fruits

Cohort studies

Summary

Main results:
Six new publications were identified (Vogtmann, 2013, Bamia, 2013, Fung, 2010, Aoyama, 2014, Agnoli, 2013, Ruder, 2011) since the 2010 SLR. One of the publications was from a new study (Vogtmann, 2013) and four of these studies could be included in the dose-response analysis (Vogtmann, 2013, Bamia, 2013, Fung, 2010; the latter publication provided data from two different studies: the NHS and the HPFS). In total 24 studies (35 publications) were identified on fruits and colorectal cancer risk, and 17 of these studies (20 publications) could be included in the dose-response analyses. Study characteristics and results for all cancer types are shown in the Table. For studies that reported fruit intake in servings per day or other frequencies we used a serving size of 80 g for recalculation of the intakes to grams per day.

Colorectal cancer:

Thirteen studies (16355 cases) were included in the dose-response analysis. The summary RR for a 100 g/d increase in total fruit intake was 0.96 (95% CI: 0.93-1.00, $p_{association}$=0.03) and there was high heterogeneity, I^2=68.0%, $p_{heterogeneity}$<0.0001. Although the test for small study bias or publication bias was not significant, Egger's test, p=0.07, there was some suggestion of asymmetry which appeared to be driven by one study only (Sanjoaquin) and when excluded the Egger's test was attenuated, p=0.14. The summary RR ranged from 0.95 (95% CI: 0.92-0.99) when the EPIC study (Bamia, 2013) was excluded to 0.97 (95% CI: 0.94-1.00) when the Swedish Mammography study (Terry, 2001) was excluded.
The test for nonlinearity was significant, $p_{nonlinearity}$<0.0001, and there was no further reduction in risk above 300 grams per day.

Colon cancer:
Twelve studies (>6317 cases) were included in the dose-response meta-analysis of total fruit intake and colon cancer. The summary RR per 100 g/d was 0.98 (95% CI: 0.96-1.01) with low heterogeneity, I^2=25.4%, $p_{heterogeneity}$=0.09.
There was evidence of a nonlinear association between total fruit intake and colon cancer, $p_{nonlinearity}$<0.0001, and the association was strongest at lower intakes. There was no further reduction in risk above 600 grams per day.

Rectal cancer:
Nine studies (>2444 cases) were included in the dose-response meta-analysis of total fruit intake intake and rectal cancer. The summary RR per 100 g/d was 0.98 (95% CI: 0.93-1.03) with moderate heterogeneity, I^2=54.9%, $p_{heterogeneity}$=0.02.

There was evidence of a nonlinear association between total fruit intake and rectal cancer, $p_{nonlinearity}$<0.0001, with the strongest reduction in risk observed up to an intake of 300 grams per day. There was no further reduction in risk with higher intakes, and the association was weaker and lost significance from 600 grams per day and above.

Study quality:
Total fruit intake was estimated from food intake assessed by FFQ in all studies, and in one of the studies a combination of FFQ, food records and 24 hour recalls were used (van Duijnhoven, 2009).
Loss to follow-up was low for the studies that reported such data, although some studies did not provide data.
Cancers were identified by record linkages to health registries, cancer registries, mortality registries, or death indexes.
All studies adjusted for at least age, and most of the studies adjusted for most of the established colorectal cancer risk factors, including: age, physical activity, BMI, and alcohol consumption, smoking, red meat and hormone replacement therapy in women.

Table 33 Total fruit intake and colorectal cancer risk. Number of studies in the CUP SLR

	Number
Studies identified	24 studies (35 publications)
Studies included in forest plot of highest compared with lowest intake	Colorectal cancer: 11 studies Colon cancer: 10 Rectal cancer: 7
Studies included in linear dose-response meta-analysis	Colorectal cancer: 13 studies Colon cancer: 12 Rectal cancer: 9
Studies included in non-linear dose-response meta-analysis	Colorectal cancer: 9 studies Colon cancer: 10 Rectal cancer: 7

Table 34 Total fruit intake and colorectal cancer risk. Summary of the linear dose-response meta-analysis in the 2005 SLR, 2010 SLR and the 2015 SLR

	2005 SLR		
	Colorectal cancer	**Colon cancer**	**Rectal cancer**
Increment unit used	Per 1 serving/day	Per 1 serving/day	Per 1 serving/day
Studies (n)	8	7	3
Cases (total number)	-	-	-
RR (95%CI)	0.97 (0.92-1.03)	0.97 (0.92-1.02)	0.94 (0.78-1.13)
Heterogeneity (I^2, p-value)	68.9%, p=0.04	65.3%, p=0.003	72.0%, p=0.03
P value Egger test	-	-	-

	2010 SLR		
	Colorectal cancer	**Colon cancer**	**Rectal cancer**
Increment unit used	100 g/day		
Studies (n)	8	10	7
Cases (total number)	12775	6114	2303
RR (95%CI)	0.97 (0.94-0.99)	0.98 (0.95-1.01)	0.97 (0.92-1.02)
Heterogeneity (I^2, p-value)	51.2%, p=0.05	38.5%, p=0.10	38.4%, p=0.14
P value Egger test	-	-	-

	2015 SLR		
	Colorectal cancer	**Colon cancer**	**Rectal cancer**

Increment unit used	100 g/day		
Studies (n)	13	12	9
Cases (total number)	16355	>6317	>2444
RR (95%CI)	0.96 (0.93-1.00)	0.98 (0.96-1.01)	0.98 (0.93-1.03)
Heterogeneity (I^2, p-value)	68.0%, p<0.0001	37.9%, p=0.09	54.9%, p=0.02
P value Egger test	0.07	0.55	0.41

Stratified analysis by geographic location

2015 SLR	**Asia**	**Europe**	**North-America**
Studies (n)	2	4	7
RR (95%CI)	0.87 (0.78-0.98)	0.90 (0.75-1.07)	0.97 (0.94-1.00)
Heterogeneity (I^2, p- value)	0%, p=0.77	79.1%, p=0.002	37.8%, p=0.14

Table 35 Fruit intake and colorectal cancer risk. Results of meta-analyses and pooled analyses of prospective studies published after the 2005 SLR.

Author, Year	Number of studies	Total number of cases	Studies country, area	Outcome	Comparison	RR (95%CI)	P trend	Heterogeneity (I^2, p value)
Meta-analyses								
Huxley et al, 2009	8 CC 6 RC 8 CRC	2651 CC 1005 RC 7916 CRC	North-America, Europe, Asia	Incidence/ mortality	High vs. Low	0.99 (0.90-1.08) 0.78 (0.63-0.97) 1.01 (0.86-1.18)	- - -	25%, p=0.11 NA NA
Aune et al, 2012	14 CRC 13 11 CC 7 RC	14876	North America, Europe, Asia	Incidence	High vs. low Per 100 g/d High vs. low High vs. low	0.90 (0.83-0.98) 0.98 (0.94-1.01) 0.89 (0.81-0.97) 0.91 (0.76-1.09)	- - - -	41.6%, p=0.05 64%, p=0.001 30.2%, p=0.16 45.2%, p=0.09
Pooled analyses								
Koushik, 2007	14	5838 CC	North America, Europe	Incidence	Quintile 5 vs. 1 ≥400 vs. <100 g/d	0.93 (0.85-1.02) 0.87 (0.77-0.97)	0.28 0.04	NA, p=0.62 NA, p=0.90

Table 36 Fruit intake and colorectal cancer risk. Main characteristics of studies included in the CUP SLR dose-response meta-analysis

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI)	Adjustment factors	Missing data derived for analysis
Bamia, 2013 COL40964 Denmark,France,Germany,Greece,Italy,Netherlands,Spain, Sweden,UK	EPIC, Prospective Cohort, Age: 25-70 years, M/W	4 355/ 480 308 11.6 years	Cancer registry, record linkage, health Insurance rec, mortality registry , pathology and active follow up	FFQ	Incidence, colorectal cancer	384.8 vs 83.1 g/day	1.03 (0.97-1.08)	Age, sex, BMI, centre location, cereal, dairy products consumption, educational level, ethanol, fish, fruits, legumes, lipids, meat, physical activity, smoking	Distribution of cases and person-years
					Incidence, colorectal cancer, women	384.8 vs 83.1 g/day	1.01 (0.91-1.12)		
					Incidence, colorectal cancer, men	384.8 vs 83.1 g/day	1.02 (0.90-1.17)		
Vogtmann, 2013 COL40986 China	SMHS, Prospective Cohort, Age: 40-74 years, M	398/ 61 274 6.3 years	Cancer registry, shanghai vital statistics office, medical history	FFQ	Incidence, colorectal cancer	≥239.24 vs 0-42.38 g/day	0.67 (0.48-0.95)	Age, alcohol, BMI, diabetes, educational level, energy Intake, family history of colorectal cancer, Income, met-hours per week, occupation, red meat, smoking, total meat	Midpoints, distribution of person-years
					Incidence, colon cancer	≥239.24 vs 0-42.38 g/day	0.76 (0.49-1.20)		
					Incidence, colon cancer	per 20 g/day	0.98		
					Incidence, rectal cancer	≥239.24 vs 0-42.38 g/day	0.56 (0.33-0.97)		
					Incidence, rectal cancer	per 20 g/day	0.97		
Fung, 2010 COL40828 USA	HPFS, Prospective Cohort, M/W	132 746	Self report verified by medical record	FFQ	Incidence, colorectal cancer, men	per 1 serving/day	1.01 (0.96-1.05)	Age, alcohol Intake, aspirin use, BMI, colonoscopy, energy, family history, history of polyps, physical activity, smoking	Conversion of serv/d to g/d
Fung, 2010 COL40828	NHS, Prospective	132 746	Self report verified by	FFQ	Incidence, colorectal	per 1 serving/day	0.95 (0.90-0.99)		Conversion of serv/d to g/d

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI)	Adjustment factors	Missing data derived for analysis
USA	Cohort, M/W		medical record		cancer, women				
George, 2009 COL40789 USA	NIH-AARP, Prospective Cohort, Age: 615 years, M/W, Retired	5 039/ 483 338 8 years	Cancer registry	FFQ	Incidence, colorectal cancer, women	1.9-5.58 vs 0-0.6 cups1000kcal/d	0.93 (0.79-1.09)	Age, alcohol, BMI, educational level, energy Intake, family history, marital status, menopausal hormone use, physical activity, race, smoking status, vegetable Intake	Conversion of cups/1000 kcal/d to g/d, midpoints, distribution of cases and person-years
					Incidence, colorectal cancer, men	1.59-5.13 vs ≤0.44 cups1000kcal/d	0.94 (0.84-1.05)		
van Duijnhoven FJ, 2009 COL40785 Denmark,France,Germany,Greece,Italy,Netherlands,Norway,Spain,Sweden,UK	EPIC, Prospective Cohort, Age: 35-70 years, M/W	1 667/ 452 755 8.8 years	Cancer registry, health Insurance records, active follow up and mortality registry	FFQ	Incidence, colorectal cancer, women	≥342.7 vs 0-92.7 g/day	0.87 (0.72-1.04)	Age, alcohol consumption, centre location, cereal fibre, energy from fat, energy from nonfat sources, fish, height, physical activity, processed meat, red meat Intake, smoking status, vegetable Intake, weight	Midpoints
					Incidence, colorectal cancer, men	≥342.7 vs 0-92.7 g/day	0.89 (0.72-1.12)		
					Incidence, distal colon cancer	≥342.7 vs 0-92.7 g/day	0.84 (0.64-1.09)		
					Incidence, proximal colon cancer	≥342.7 vs 0-92.7 g/day	0.81 (0.62-1.05)		
					Incidence, colorectal cancer	≥342.7 vs 0-92.7 g/day	0.88 (0.76-1.01)		
					Incidence, colorectal cancer	per 100 g/day	0.97 (0.92-1.02)		
					Incidence,	per 100 g/day	0.98 (0.96-		

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI)	Adjustment factors	Missing data derived for analysis
					colorectal cancer		1.01)		
					Incidence, colon cancer	≥342.7 vs 0-92.7 g/day	0.84 (0.71-1.00)		
					Incidence, colon cancer	per 100 g/day	0.96 (0.90-1.02)		
					Incidence, colon cancer	per 100 g/day	0.97 (0.94-1.01)		
					Incidence, rectal cancer	≥342.7 vs 0-92.7 g/day	0.96 (0.76-1.21)		
					Incidence, rectal cancer	per 100 g/day	0.99 (0.95-1.04)		
					Incidence, rectal cancer	per 100 g/day	0.98 (0.89-1.07)		
Nomura, 2008 COL40663 USA	MEC, Prospective Cohort, Age: 45-75 years, M/W	1 023/ 191 011 7.3 years	Cancer registry	FFQ-quantitative	Incidence, colorectal cancer, men	295.9 vs 30.1 g1000 kcal/day	0.80 (0.64-0.99)	Age, alcohol Intake, aspirin use, BMI, calcium Intake, energy Intake, ethnicity, family history of colorectal cancer, folate Intake, history of polyps, multivitamin, pack-years of smoking, physical activity, red meat Intake, time, vitamin d	Distribution of cases and person-years, conversion of g/1000 kcal/d to g/d
					Incidence, colorectal cancer, women	381.5 vs 47.5 g1000 kcal/day	0.83 (0.65-1.06)		
					Incidence, colon cancer, men	295.9 vs 30.1 g1000 kcal/day	0.75 (0.58-0.97)		
					Incidence, colon cancer, women	381.5 vs 47.5 g1000 kcal/day	0.87 (0.65-1.15)		
					Incidence,	295.9 vs 30.1	0.80 (0.53-		

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI)	Adjustment factors	Missing data derived for analysis
					rectal cancer, men	g1000 kcal/day	1.21)		
					Incidence, rectal cancer, women	381.5 vs 47.5 g1000 kcal/day	0.77 (0.46-1.27)		
Park, 2007 COL40697 USA	NIH-AARP, Prospective Cohort, Age: 50-71 years, M/W	2 048/ 488 043 2 121 664 person-years	Cancer registry	FFQ	Incidence, colorectal cancer, men	0.24 vs ≥1 servings1000 kcal/day	1.24 (1.03-1.49)	Alcohol consumption, calcium Intake, educational level, physical activity, red meat Intake	Distribution of person-years, conversion of serv/1000 kcal/d to g/d
					Incidence, colorectal cancer, men	2.9 vs 0.4 servings1000 kcal/day	1.06 (0.91-1.23)		
					Incidence, colorectal cancer, women	0.24 vs ≥1 servings1000 kcal/day	1.06 (0.73-1.54)		
					Incidence, colorectal cancer, women	3.5 vs 0.6 servings1000 kcal/day	1.09 (0.88-1.36)		
					Incidence, distal colon cancer, men	2.9 vs 0.4 servings1000 kcal/day	1.14 (0.89-1.48)		
					Incidence, rectal cancer, men	2.9 vs 0.4 servings1000 kcal/day	0.99 (0.75-1.30)		
					Incidence, colon cancer, men	2.9 vs 0.4 servings1000 kcal/day	1.11 (0.93-1.32)		
					Incidence, proximal colon cancer, men	2.9 vs 0.4 servings1000 kcal/day	1.04 (0.81-1.34)		

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI)	Adjustment factors	Missing data derived for analysis
					Incidence, colon cancer, women	3.5 vs 0.6 servings1000 kcal/day	0.96 (0.75-1.24)		
					Incidence, proximal colon cancer, women	3.5 vs 0.6 servings1000 kcal/day	0.99 (0.72-1.36)		
					Incidence, distal colon cancer, women	3.5 vs 0.6 servings1000 kcal/day	0.97 (0.63-1.49)		
					Incidence, rectal cancer, women	3.5 vs 0.6 servings1000 kcal/day	1.59 (1.04-2.44)		
Akhter, 2007 COL40632 Japan	MCS, Prospective Cohort, Age: 40-64 years, M	307/ 21 199 11 years	Cancer registry	Self-administered questionnaire	Incidence, colorectal cancer	everyday vs ≤1-2times/month	1.06 (0.70-1.61)	Age	Midpoints, distribution of cases and person-years, conversion from frequency to g/d
McCarl, 2006 COL40633 USA	IWHS, Prospective Cohort, Age: 55-69 years, W	954/ 35 197 15 years	Seer registry	FFQ	Incidence, colorectal cancer	≥25.5 vs ≤9.8 servings/week	0.79 (0.65-0.97)	Age	Midpoints, conversion of serv/wk to g/d
Lin, 2005 COL01831 USA	WHS, Prospective Cohort, Age: 45- years, W,	223/ 36 976 10 years	Follow up questionnaires (self report), medical record and pathology	FFQ	Incidence, colorectal cancer, women	3.8 vs 0.6 serving/day	0.79 (0.48-1.30)	Age, alcohol consumption, aspirin use, BMI, family history of specific cancer, history of previous polyp and prior endoscopy, menopausal status,	Distribution of person-years, conversion of serv/d to g/d

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI)	Adjustment factors	Missing data derived for analysis
	professionals		reports					physical activity, postmenopausal hormone use, randomized treatment assignment, red meat Intake, smoking status, total energy	
Sato, 2005 COL01930 Japan	MCS, Prospective Cohort, Age: 40-64 years, M	165/ 41 835 7 years	Population registry	Questionnaire	Incidence, colon cancer,	≥242 vs 0-95 g/day	1.45 (0.85-2.47)	Age, sex, alcohol consumption, BMI, educational level, energy content, family history of specific cancer, meat consumption, physical activity, smoking status	Midpoints
					Incidence, rectal cancer,	≥242 vs 0-95 g/day	1.41 (0.73-2.73)		
Sanjoaquin, 2004 COL01182 UK	OVS, Prospective Cohort, Age: 18-89 years, M/W	91/ 10 998 17 years	Population/invitation	FFQ	Incidence, colorectal cancer,	≥10 vs ≤4 times/week	0.60 (0.35-1.02)	Age, sex, alcohol consumption, smoking habits	Midpoints, distribution of person-years
McCullough, 2003 COL00367 USA	CPS II, Prospective Cohort, Age: 50-74 years, M/W	298/ 133 163 6 years	Cps-II cohort	Semi-quantitative FFQ	Incidence, colon cancer, men	≥6.2 vs 0-1.1 serving/day	1.11 (0.76-1.62)	Age, aspirin use, BMI, calcium, educational level, energy Intake, family history of colorectal cancer, multivitamin, physical activity, red meat Intake, smoking habits	Midpoints, distribution of person-years
					Incidence, colon cancer, men	<0.39 vs 1.2+ serving/day	1.26 (0.83-1.90)		
					Incidence, colon cancer, women	≥6 vs 0-1.1 serving/day	0.74 (0.47-1.16)		
					Incidence, colon cancer, women	<0.46 vs 1.2+ serving/day	1.86 (1.18-2.94)		
Flood, 2002	BCDDP, 1973,	485/	Breast cancer	FFQ	Incidence,	≥0.38 vs 0-	1.15 (0.86-	Alcohol consumption, BMI,	Conversion of

Author, Year, WCRF Code, Country	Study name, characteristic s	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI)	Adjustment factors	Missing data derived for analysis
COL00410 USA	Prospective Cohort, W	45 490 386 142 person-years	screening centres		colorectal cancer,	0.09 servingday/1000kj	1.53)	calcium, educational level, energy Intake, grain Intake, height, nsaid use, physical activity, red meat Intake, smoking habits, supplement use, vegetable Intake, vitamin d	serv/d to g/d
Terry, 2001 COL00059 Sweden	SMC, Prospective Cohort, Age: 40-74 years, W	460/ 61 463 588 270 person-years	Mammography screening program	FFQ	Incidence, colorectal cancer	≥2 vs 0-1 serving/day	0.68 (0.52-0.89)	Age, red meat & dairy product Intake, total caloric Intake	Midpoints, distribution of cases and person-years, conversion from serv/d to g/d
					Incidence, colon cancer	≥2 vs 0-1 serving/day	0.76 (0.55-1.06)		
					Incidence, proximal colon cancer	≥2 vs 0-1 serving/day	0.97 (0.57-1.64)		
					Incidence, distal colon cancer	≥2 vs 0-1 serving/day	0.91 (0.53-1.55)		
					Incidence, rectal cancer	≥2 vs 0-1 serving/day	0.54 (0.33-0.89)		
Michels, 2000 COL00365 USA	HPFS, Prospective Cohort, Age: 40-75 years, M, Health	368/ 47 325 416 616 person-years	Population registries	Semi-quantitative FFQ	Incidence, colon cancer	≥5 vs 0-1 serving/day	1.35	Age, alcohol consumption, aspirin use, BMI, family history of colorectal cancer, height, pack-years of smoking, physical activity, red meat Intake, sigmoidoscopy, supplement Intake, total caloric Intake	Included in the dose-response analysis. No confidence intervals were provided for high vs. low analysis
					Incidence, colon cancer	per 1 serving/day	1.08 (1.00-1.16)		
					Incidence, rectal cancer,	≥5 vs 0-1 serving/day	2.04		
					Incidence,	per 1	1.09 (0.94-		

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI)	Adjustment factors	Missing data derived for analysis
	professionals				rectal cancer,	serving/day	1.26)		
Michels, 2000 COL00365 USA	NHS, Prospective Cohort, Age: 30-55 years, W, Registred nurses	569/ 88 764 1 327 029 person-years	Population registries	Semi-quantitative FFQ	Incidence, colon cancer	≥5 vs 0-1 serving/day	0.80	Age, alcohol consumption, aspirin use, BMI, family history of colorectal cancer, height, menopausal status, pack-years of smoking, physical activity, postmenopausal hormone use, red meat Intake, sigmoidoscopy, supplement Intake, total caloric Intake	Included in the dose-response analysis. No confidence intervals were provided for high vs. low analysis
					Incidence, colon cancer	per 1 serving/day	0.96 (0.89-1.03)		
					Incidence, rectal cancer,	≥5 vs 0-1 serving/day	0.66		
					Incidence, rectal cancer,	per 1 serving/day	0.96 (0.83-1.11)		
Voorrips, 2000 COL00578 Netherlands	NLCS, Case Cohort, Age: 55-69 years, M/W	331/ 120 852 6.3 years	Cancer registry	Semi-quantitative FFQ	Incidence, colon cancer, men	286 vs 34 g/day	1.33 (0.90-1.97)	Age, alcohol consumption, family history of colorectal cancer	None
					Incidence, colon cancer, women	343 vs 65 g/day	0.73 (0.48-1.11)		
					Incidence, rectal cancer, men	286 vs 34 g/day	0.85 (0.55-1.32)		
					Incidence, distal colon cancer, men	Q 5 vs Q 1	1.49 (0.88-2.54)		
					Incidence, proximal colon cancer, men	Q 5 vs Q 1	1.20 (0.71-2.05)		
					Incidence, proximal colon cancer, women	Q 5 vs Q 1	0.81 (0.47-1.39)		

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI)	Adjustment factors	Missing data derived for analysis
					Incidence, distal colon cancer, women	Q 5 vs Q 1	0.59 (0.30-1.13)		
					Incidence, rectal cancer, women	343 vs 65 g/day	0.67 (0.34-1.33)		
					Incidence, colon cancer, men	per 25 g/day	1.00		
					Incidence, colon cancer, women	per 25 g/day	0.98		
					Incidence, rectal cancer, men	per 25 g/day	1.00		
					Incidence, rectal cancer, women	per 25 g/day	1.00		
Pietinen, 1999 COL00176 Finland	ATBC, Prospective Cohort, Age: 50-69 years, M, Smokers	185/ 27 111 8 years	Population	Dietary history questionnaire	Incidence, colorectal cancer,	216 vs 30 g/day	1.10 (0.80-1.70)	Age, alcohol consumption, BMI, calcium Intake, educational level, energy Intake, physical activity, smoking years, supplement group	Distribution of person-years
Steinmetz, 1994 COL00178 USA	IWHS, Prospective Cohort, Age: 55-69	212/ 35 216 167 447 person-years	Driving license	Semi-quantitative FFQ	Incidence, colon cancer,	≥17.5 vs 0-7.4 serving/week	0.86 (0.58-1.29)	Age, energy Intake	Midpoints, conversion from serv/wk to g/d, distribution of
					Incidence, distal colon	≥17.5 vs 0-7.4 serving/week	0.97 (0.58-1.61)		

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI)	Adjustment factors	Missing data derived for analysis
	years, W, Postmenopausal				cancer, distal sites				cases and person-years
					Incidence, proximal colon cancer, proximal sites	≥17.5 vs 0-7.4 serving/week	0.80 (0.40-1.59)		
Shibata, 1992 COL00740 USA	Leisure World Cohort, Prospective Cohort, M/W, retirement community, uppermiddle social class	105/ 11 580 70 159 person-years	Community registry	FFQ	Incidence, colon cancer, women	≥3.7 vs 0-2.4 serving/day	0.50 (0.31-0.80)	Age, smoking habits	Conversion from serv/d to g/d, distribution of person-years
					Incidence, colon cancer, men	≥3.5 vs 0-2.2 serving/day	1.12 (0.69-1.81)		

Table 37 Fruit intake and colorectal cancer risk. Main characteristics of studies excluded from the CUP SLR

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI)	Adjustment factors	Reasons for exclusion
Aoyama, 2014 COL41014 Japan	JACC study, Prospective Cohort, Age: 40-79 years, M/W	806/ 14 549 598 605 person-years	Cancer registry/ population register	Questionnaire	Incidence, colorectal cancer	Q 3 vs Q 3	1.00	Age, age, sex, beef, pork, or lamb, BMI, drinking amount, educational level, family history of colorectal cancer, local area, smoking, walking time	No quantities
					Incidence, colon cancer	Q 3 vs Q 3	1.00		
					Incidence, colorectal cancer, women	≥3.2 vs ≥3.2 times/week	1.00		

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI)	Adjustment factors	Reasons for exclusion
					Incidence, colon cancer, men	≥1.7 vs ≥1.7 times/week	1.00		
					Incidence, rectal cancer	Q 3 vs Q 3	1.00		
					Incidence, colon cancer, women	≥3.2 vs ≥3.2 times/week	1.00		
					Incidence, rectal cancer, men	≥1.7 vs ≥1.7 times/week	1.00		
					Incidence, colorectal cancer, men	≥1.7 vs ≥1.7 times/week	1.00		
					Incidence, rectal cancer, women	≥3.2 vs ≥3.2 times/week	1.00		
Agnoli, 2013 COL40938 Italy	EPIC-Italy, Prospective Cohort, M/W	435/ 45 275 11.28 years	Cancer registry and hospital records	Semi-quantitative FFQ	Incidence, colorectal cancer	391.9-3790.5 vs 0-249.2 g/day	0.87 (0.68-1.12)	Age, BMI, educational level, gender, non-alcoholic beverage Intake, physical activity, smoking, study center	Overlap with Bamia, 2013 COL40964
Ruder, 2011 COL40896 USA	NIH-AARP, Prospective Cohort, Age: 50-71 years, Retired	2 819/ 292 797	Cancer registry and national health database	FFQ	Incidence, colon cancer	2.1 vs 0.16 times/day	0.84 (0.73-0.97)	Sex, age at baseline, alcohol consumption, aspirin use, BMI, educational level, energy, energy, fruits, history of colon cancer, HRT use, physical activity, race, smoking	Overlap with Park, 2007 COL40697
					Incidence, colon cancer	2.1 vs 0.16 times/day	0.82 (0.72-0.92)		
					Incidence, rectal cancer	2.1 vs 0.16 times/day	1.05 (0.82-1.34)		

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI)	Adjustment factors	Reasons for exclusion
					Incidence, rectal cancer	2.1 vs 0.16 times/day	0.91 (0.73-1.12)		
Butler, 2008 COL40639 Singapore	SCHS, Prospective Cohort, Age: 45-74 years, M/W	961/ 61 321 9.8 years	Cancer registry	FFQ	Incidence, colorectal cancer	Q 4 vs Q 1	0.89 (0.72-1.09)	Age, sex, alcohol Intake, BMI, diabetes, dialect group, educational level, energy Intake, exposure assessment, family history of colorectal cancer, physical activity, smoking habits	<3 categories
Tsubono, 2005 COL40746 Japan	JPHC, Prospective Cohort, Age: 40-59 years, M/W	377/ 88 658 694 074 person-years	Histology	FFQ	Incidence, colorectal cancer	Q 4 vs Q 1	0.92 (0.70-1.19)	Age, sex, alcohol consumption, BMI, centre location, cereal Intake, energy Intake, fish, meat Intake, physical activity, smoking status, vitamin use	No quantities
					Incidence, colon cancer	Q 4 vs Q 1	0.92 (0.66-1.28)		
					Incidence, colorectal cancer, men	Q 4 vs Q 1	1.06 (0.70-1.61)		
					Incidence, colon cancer, men	Q 4 vs Q 1	1.02 (0.61-1.70)		
					Incidence, colorectal cancer, women	Q 4 vs Q 1	0.93 (0.61-1.42)		
					Incidence, rectal cancer	Q 4 vs Q 1	0.91 (0.59-1.40)		
					Incidence, colon cancer,	Q 4 vs Q 1	0.87 (0.49-1.52)		

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI)	Adjustment factors	Reasons for exclusion
					women				
					Incidence, rectal cancer, men	Q 4 vs Q 1	1.19 (0.59-2.36)		
					Incidence, rectal cancer, women	Q 4 vs Q 1	0.84 (0.43-1.65)		
Wark, 2005 COL01807	NLCS, Case Cohort, Age: 55-69 years, M/W	387/ 120 852 7.3 years	Population registries	Semi-quantitative FFQ	Incidence, colon cancer, hmlh1+ cases	≥204.6 vs 0-115.9 g/day	1.03 (0.78-1.35)	Age, sex, family history of specific cancer, total energy	Overlap with Voorrips, 2000 COL00578
					Incidence, colon cancer, hmlh1- cases	≥204.6 vs 0-115.9 g/day	0.46 (0.23-0.90)		
Khan, 2004 COL01606 Japan	HCS, Prospective Cohort, Age: 40-97 years, M/W	15/ 3 458 14.3 years	Area residency lists	Questionnaire	Mortality, colorectal cancer, men	Q 2 vs Q 1	0.40 (0.10-1.50)	Age, smoking habits	Mortality
					Mortality, colorectal cancer, women	Q 2 vs Q 1	0.50 (0.10-3.80)	Health education, health screening, health status	
Kojima, 2004 COL01840 Japan	JACC, Prospective Cohort, Age: 40-79 years, M/W	115/ 107 824 10 years	Resident registry and death certificates	Questionnaire	Mortality, colon cancer, women	≥5 vs 0-2 times/week	1.62 (1.02-2.57)	Age, alcohol consumption, BMI, educational level, family history of specific cancer, physical activity, region of enrollment, smoking status	Mortality
					Mortality, colon cancer, men	≥5 vs 0-2 times/week	1.06 (0.64-1.75)		
					Mortality, rectal cancer, men	≥5 vs 0-2 times/week	0.80 (0.46-1.41)		

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI)	Adjustment factors	Reasons for exclusion
					Mortality, rectal cancer, women	≥5 vs 0-2 times/week	0.53 (0.22-1.26)		
Sauvaget, 2003 COL00521 Japan	Life Span Study, Prospective Cohort, Age: 34-103 years, M/W, subjects were atomic-bomb survivors	226/ 38 540 16 years	Population	FFQ	Mortality, colorectal cancer,	≥7 vs 0-1 serving/week	0.97 (0.73-1.29)	Age, sex, alcohol consumption, BMI, city, educational level, radiation dose, smoking habits	Mortality
Bueno-de-Mesquita, 2002 COL00950 Europe	EPIC, Prospective Cohort, M/W	773/ 406 439	Not specified	FFQ	Incidence, colorectal cancer,	Q 5 vs Q 1	0.83	Age, sex, body weight, centre location, energy Intake, ethanol Intake, height, physical activity at work, smoking habits, vegetables	Overlap with Bamia, 2013 COL40964
					Incidence, colorectal cancer, women	≥372 vs 0-114 g/day	0.86		
					Incidence, colorectal cancer, men	≥312 vs 0-68 g/day	0.79		
Sellers, 1998 COL01974 USA	IWHS, Prospective Cohort, Age: 55-69 years, W, Postmenopausal	180/ 35 216 10 years	Seer registry	Semi-quantitative FFQ	Incidence, colon cancer, no family history of crc	≥20.1 vs ≤13 servings/week	0.90 (0.60-1.20)	Age, history of polyps, total energy Intake	Overlap with McCarl, 2006 COL40633 USA
					Incidence, colon cancer, family history of crc	≥20.1 vs ≤13 servings/week	1.40 (0.70-2.80)		

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI)	Adjustment factors	Reasons for exclusion
Hsing, 1998 COL00458 USA	Lutheran Brotherhood Study, Prospective Cohort, Age: 35- years, M, Policyholders	145/ 17 633 286 731 person-years	Responding to mail survey	Questionnaire	Mortality, colorectal cancer,	≥67.1 vs ≤29.2 times/month	1.60 (0.90-2.80)	Age, alcohol consumption, smoking habits, total energy	Mortality
					Mortality, colon cancer,	≥67.1 vs ≤29.2 times/month	1.60 (0.90-2.90)		
Kato, 1997 CRC00022 USA	New York University Women's Health Study, Prospective Cohort, Age: 34-65 years, W	100/ 14 272 105 044 person-years	Mammography screening program	Semi-quantitative FFQ	Incidence, colorectal cancer,	Q 4 vs Q 1	1.49 (0.82-2.70)	Age, educational level, place at enrollment, total calorie Intake	No quantities
Key, 1996 COL00418 UK	British Health Conscious and Vegetarian subjects, Prospective Cohort, Age: 16-79 years, M/W, vegetarians ans other health conscious subjects	62/ 10 771 16.8 years	Public	Questionnaire	Mortality, colorectal cancer,	≥1 vs 0-1 serving/day	0.71 (0.40-1.27)	Age, sex, smoking habits	Mortality
					Mortality, colorectal cancer,	≥1 vs 0-1 serving/day	0.71 (0.40-1.27)		
Giovannucci, 1994	HPFS, Prospective	47 949	Mailing to health	FFQ	Incidence, colon cancer,	≥4 vs ≤1 serving/day	0.98 (0.54-1.77)		Overlap with Michels, 2000

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI)	Adjustment factors	Reasons for exclusion
COL00119 USA	Cohort, Age: 40-75 years, M, Health professionals	6 years	professionals						COL00365

Figure 52 RR estimates of colorectal cancer by levels of fruit intake

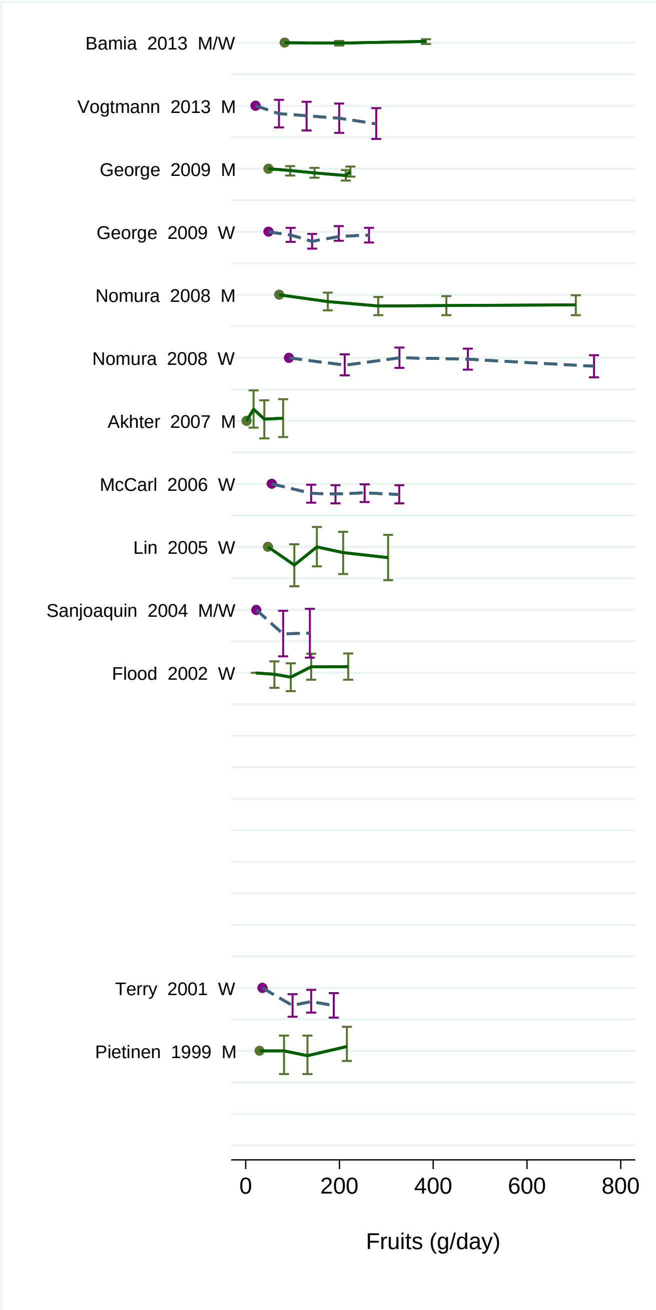


Figure 53 Relative risk of colorectal cancer for the highest compared with the lowest level of fruit intake

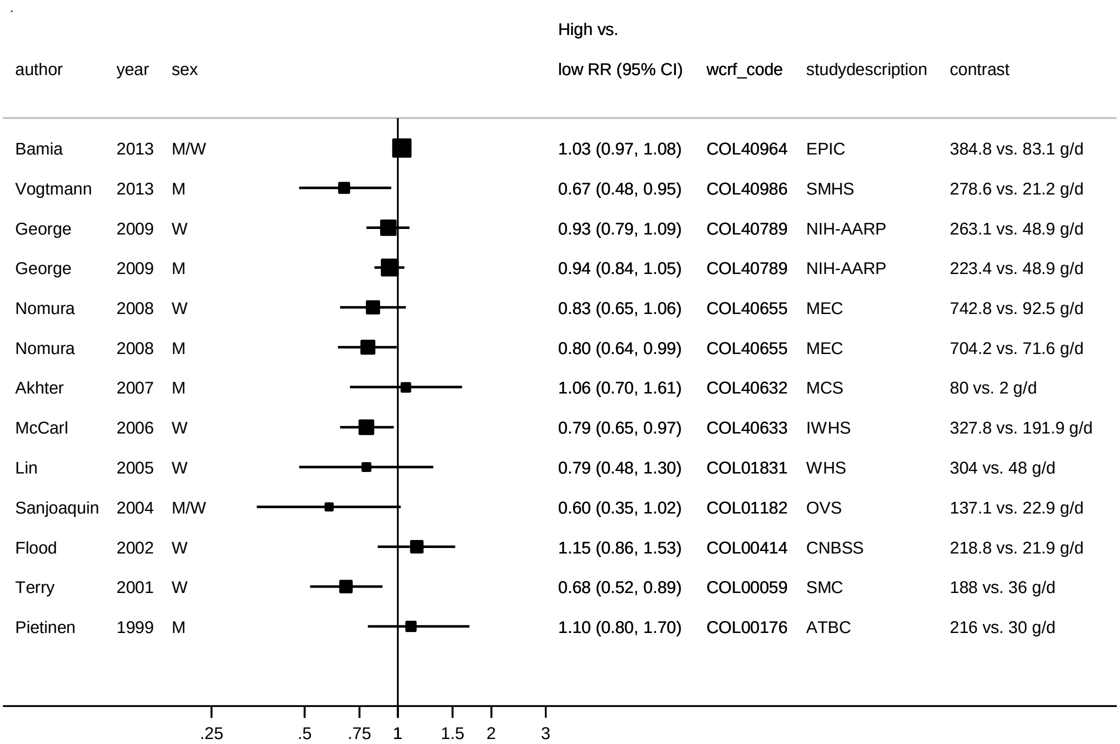


Figure 54 Relative risk of colorectal cancer for 100 g/day increase in fruit intake

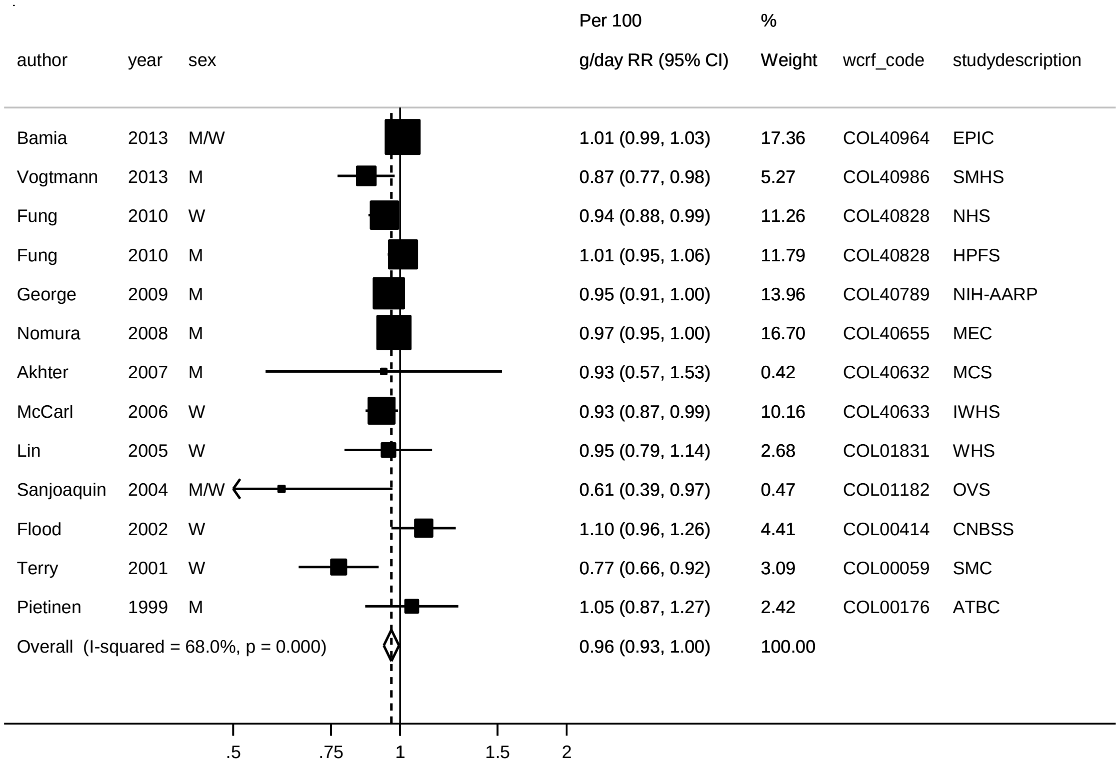


Figure 55 Relative risk of colorectal cancer for 100 g/day increase in fruit intake, stratified by sex

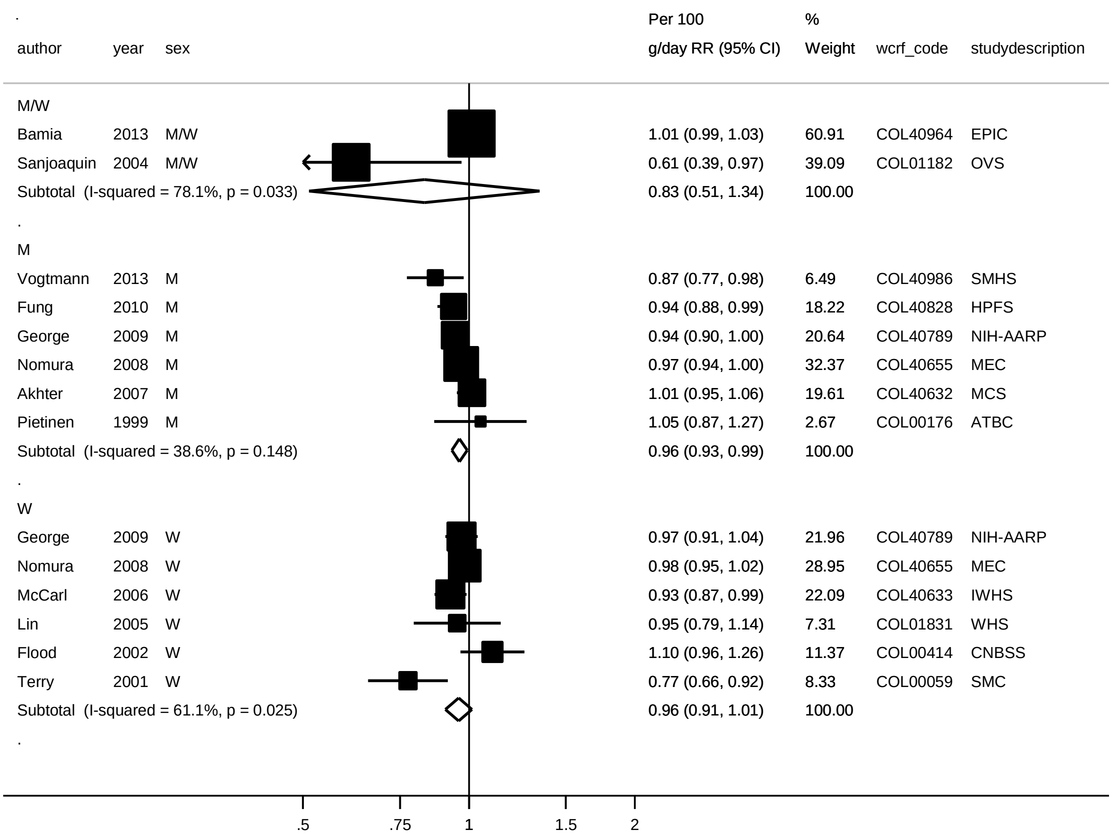


Figure 56 Relative risk of colorectal cancer for 100 g/day increase in fruit intake, stratified by geographic location

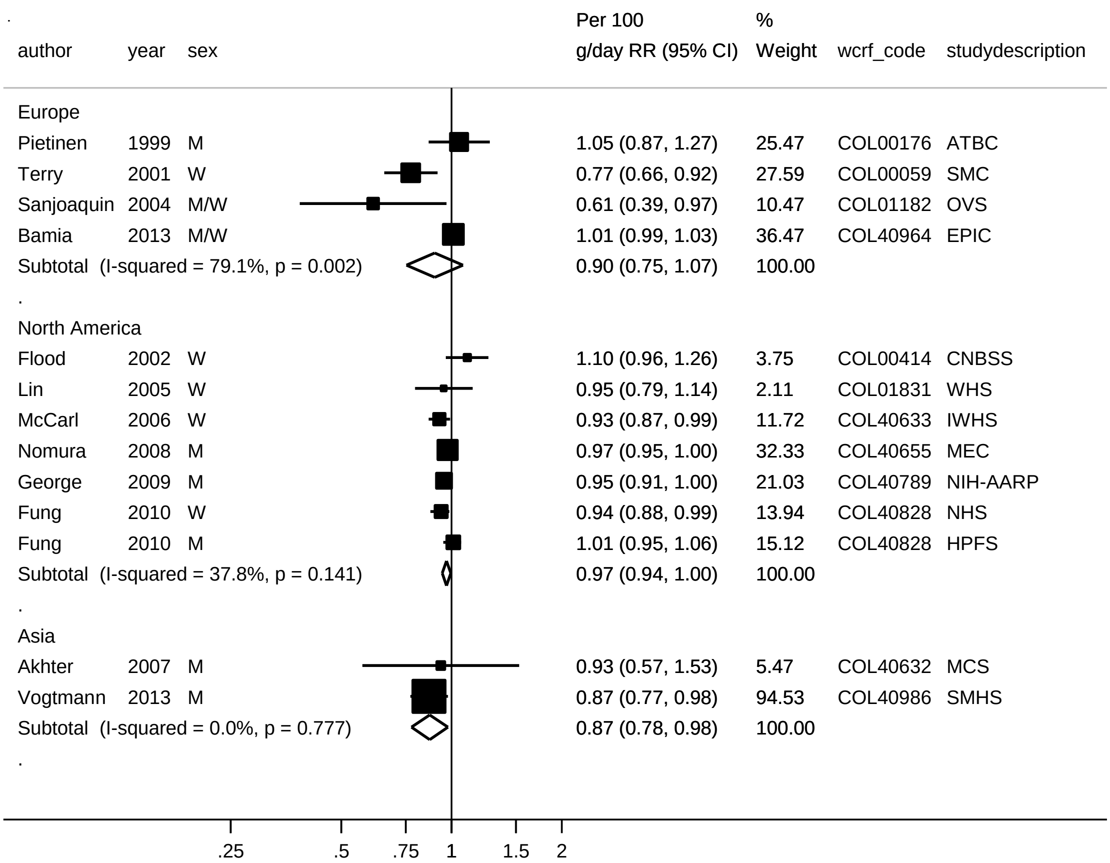
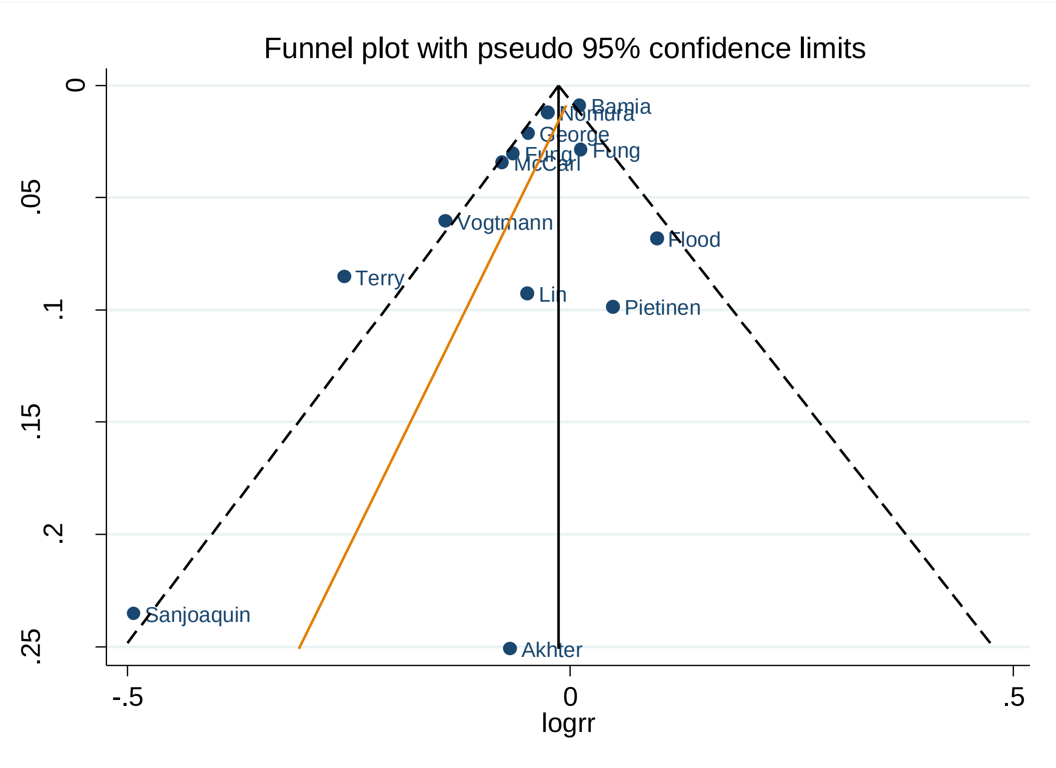
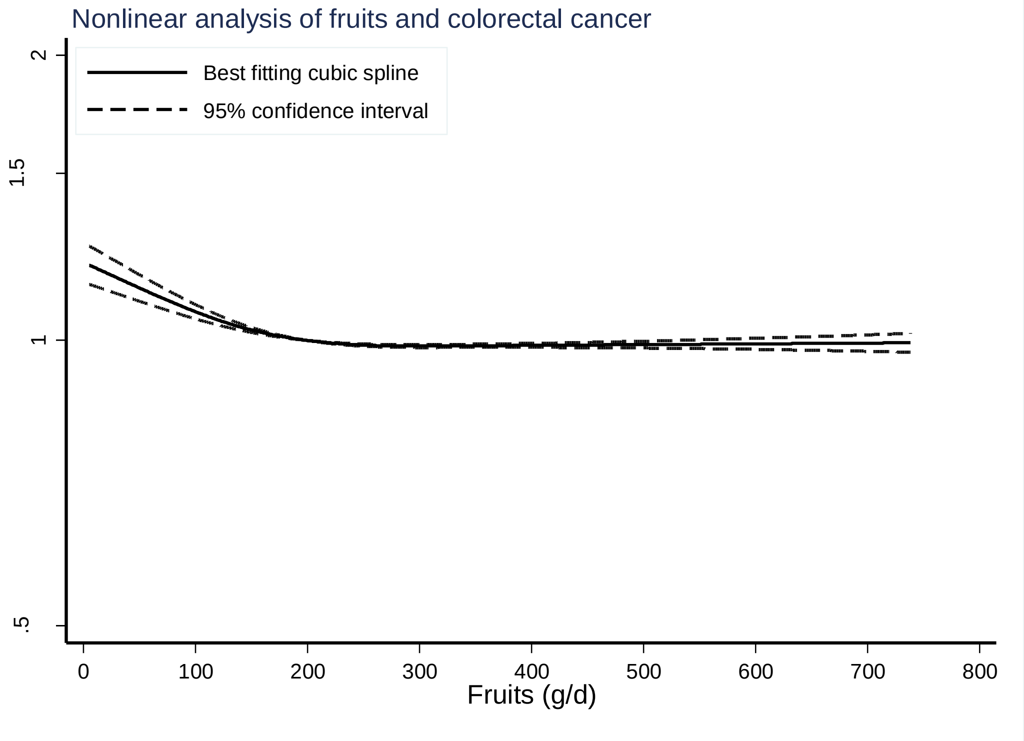


Figure 57 Funnel plot of studies included in the dose response meta-analysis of fruit intake and colorectal cancer



p Egger's test =0.07

Figure 58 Relative risk of colorectal cancer and fruits estimated using non-linear models



P nonlinearity<0.0001

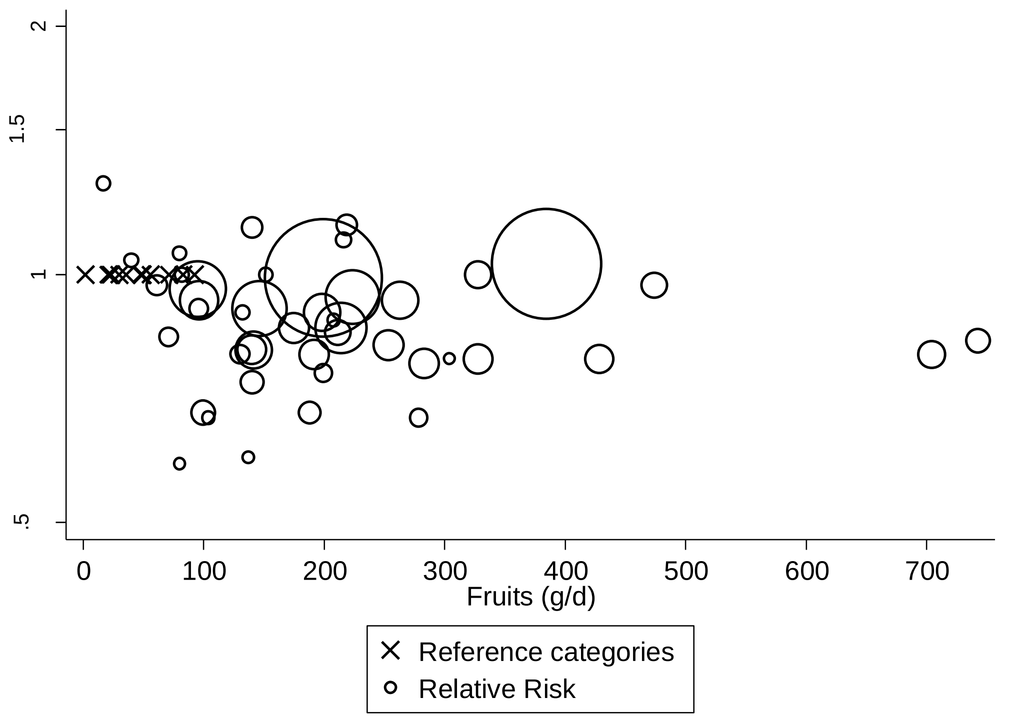


Figure 59 Relative risk of colorectal cancer and fruit intake estimated using non-linear models

Fruits g/day	RR (95% CI)
2	1.21 (1.15-1.26)
100	1.07 (1.05-1.09)
200	1.00
300	0.99 (0.98-0.99)
400	0.99 (0.98-0.99)
500	0.99 (0.98-1.00)
600	0.99 (0.98-1.01)
700	0.99 (0.97-1.01)

Figure 60 RR estimates of colon cancer by levels of fruit intake

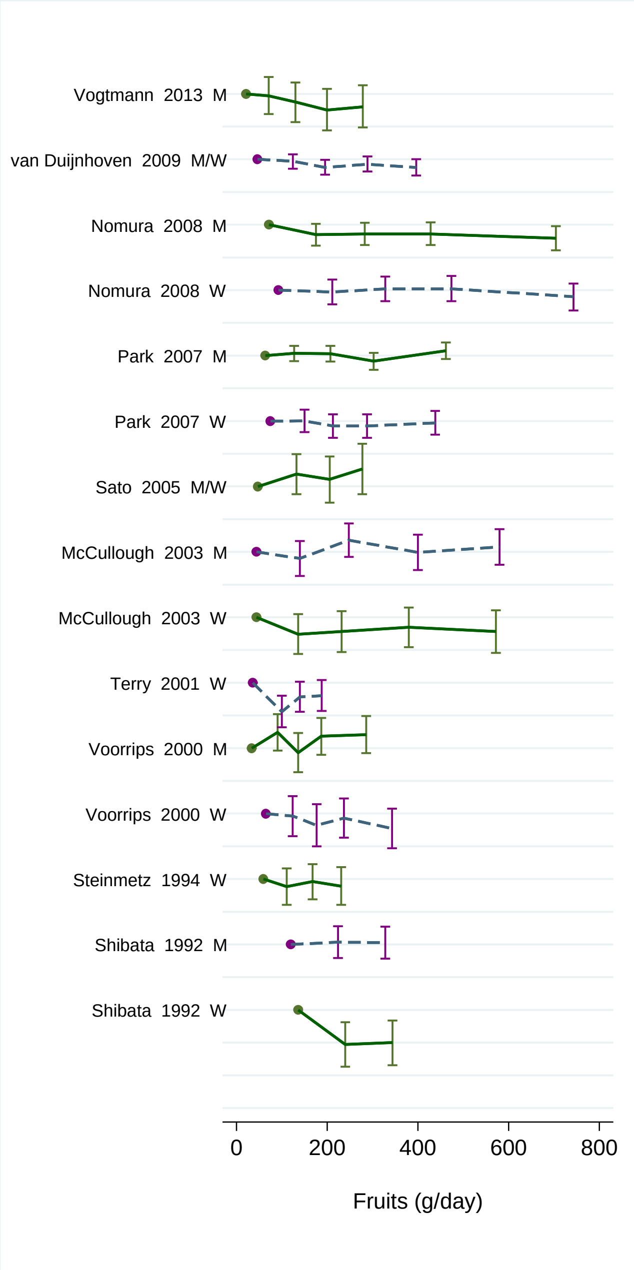


Figure 61 Relative risk of colon cancer for the highest compared with the lowest level of fruit intake

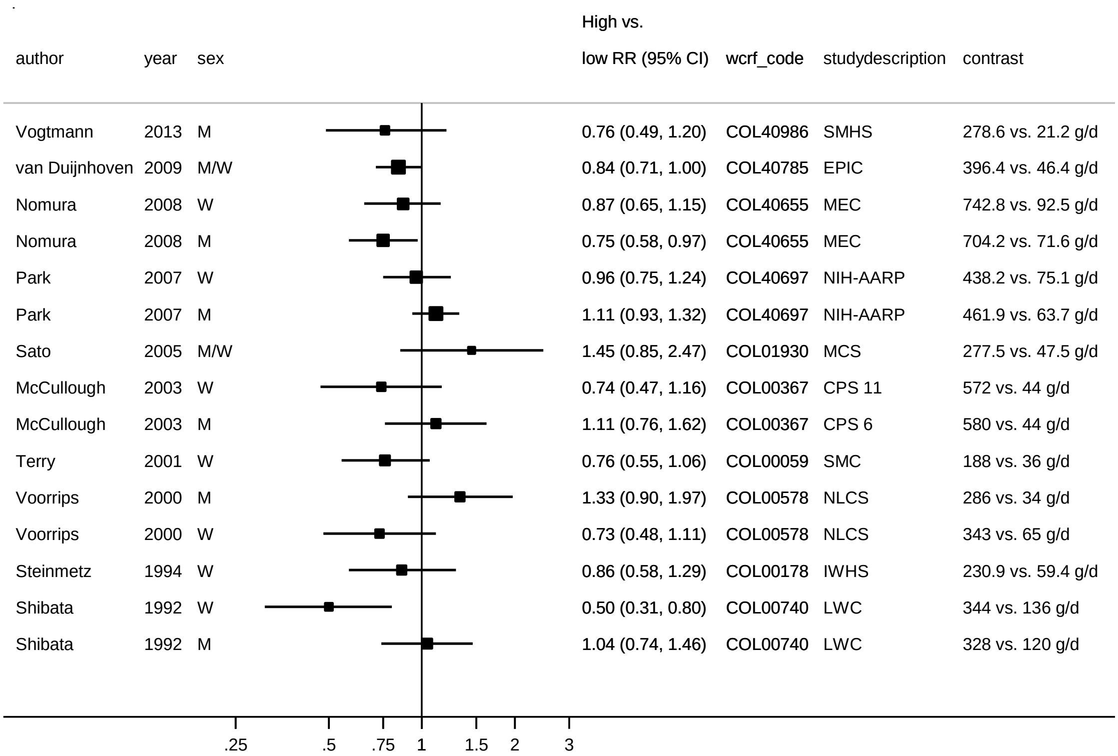


Figure 62 Relative risk of colon cancer for 100 g/day increase in fruit intake

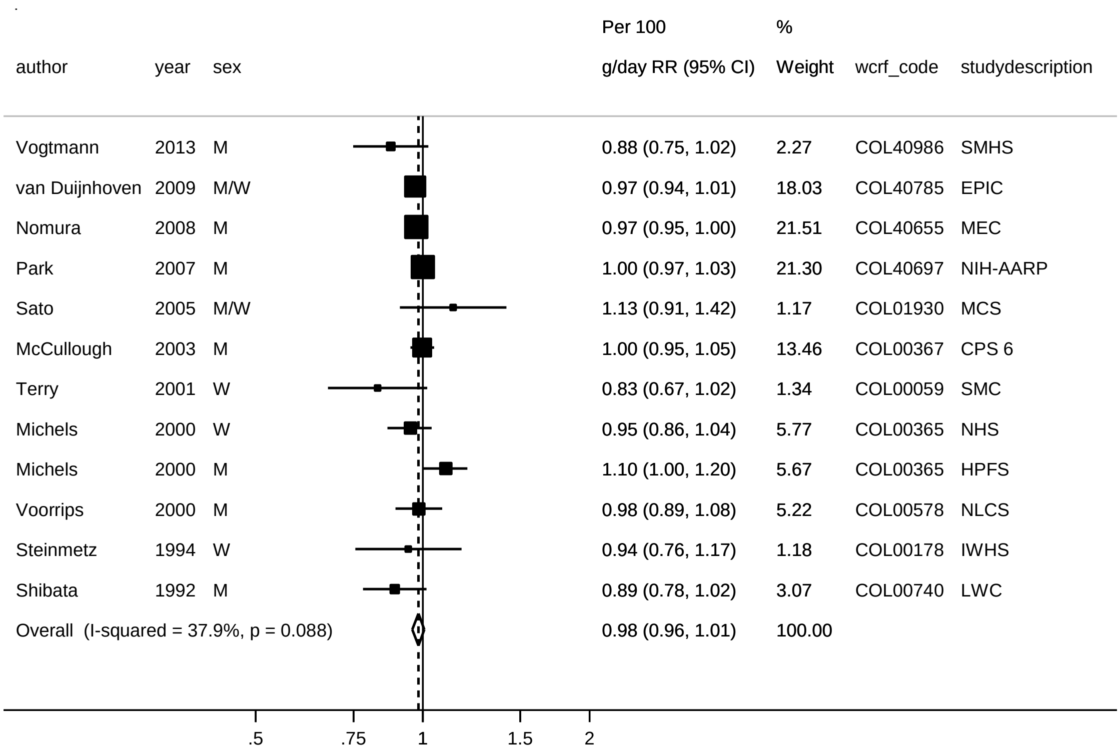


Figure 63 Relative risk of colon cancer for 100 g/day increase in fruit intake, stratified by sex

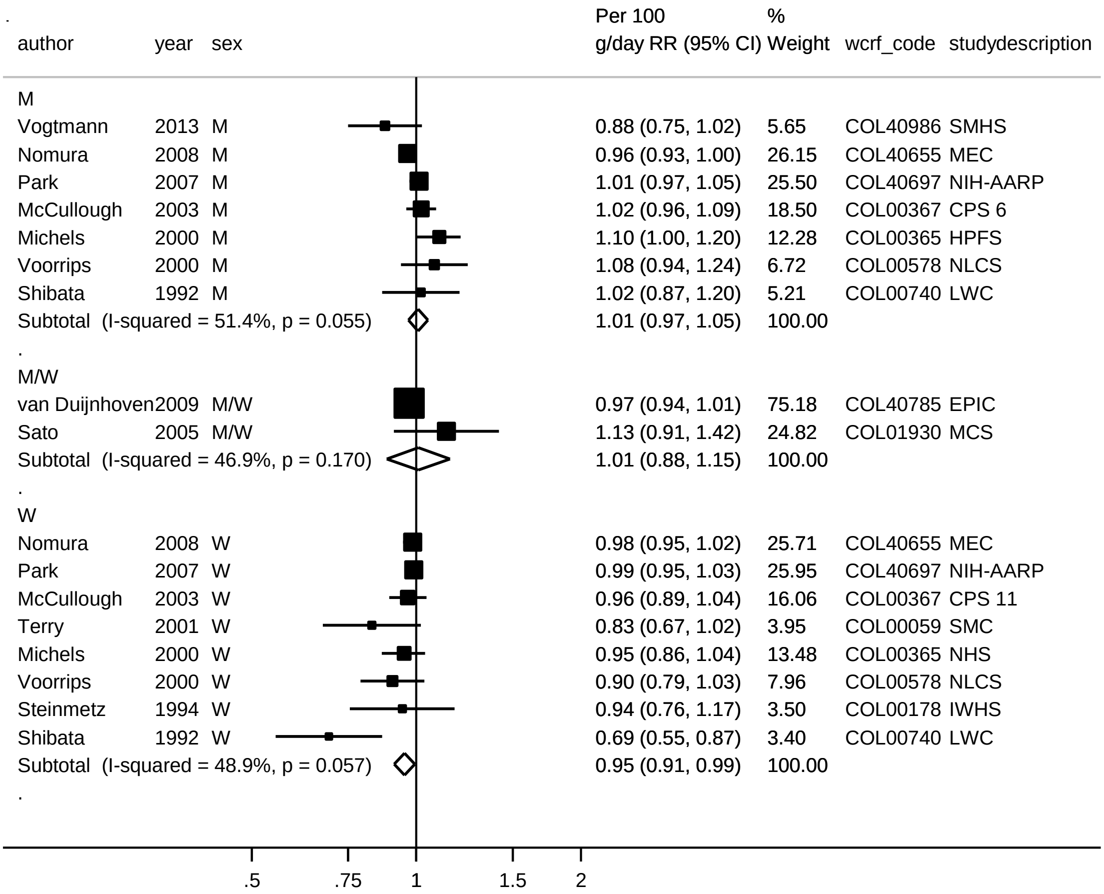


Figure 64 Funnel plot of studies included in the dose response meta-analysis of fruit intake and colon cancer

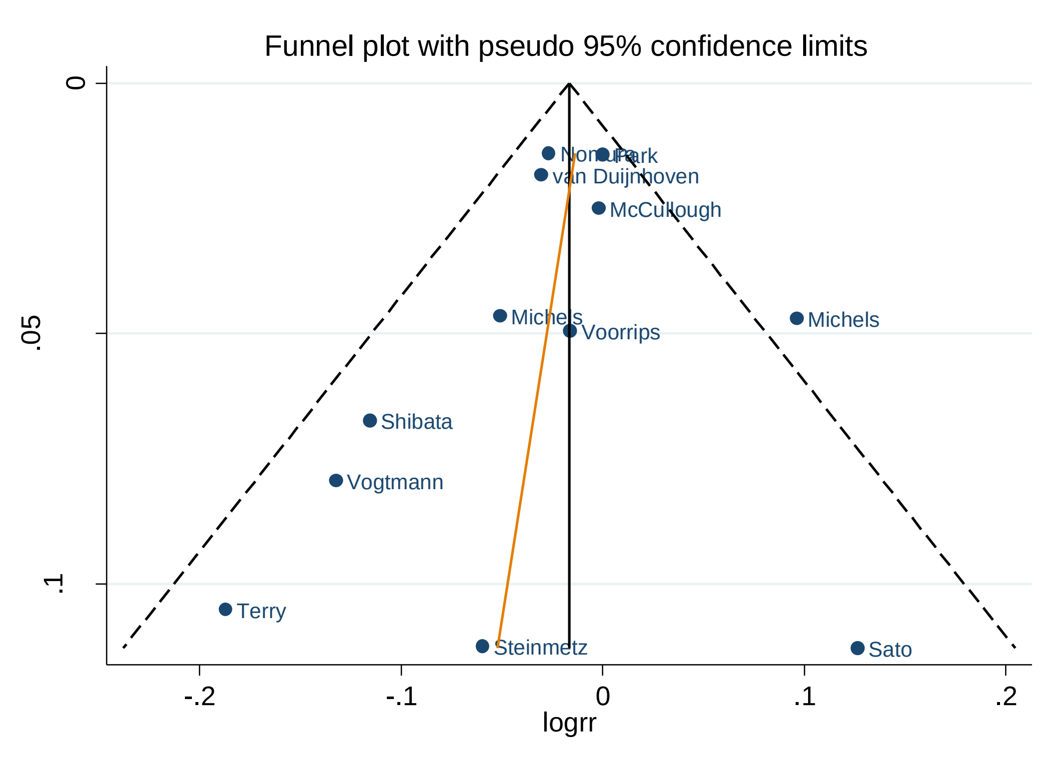
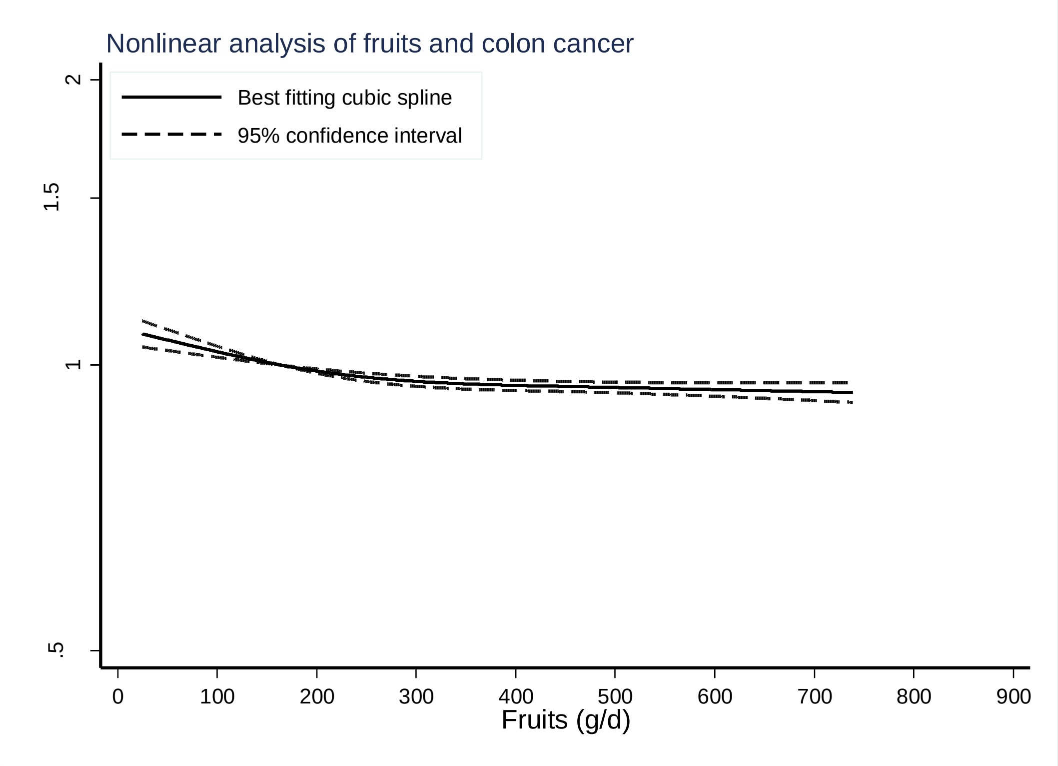


Figure 65 Relative risk of colon cancer and fruits estimated using non-linear models



P nonlinearity<0.0001

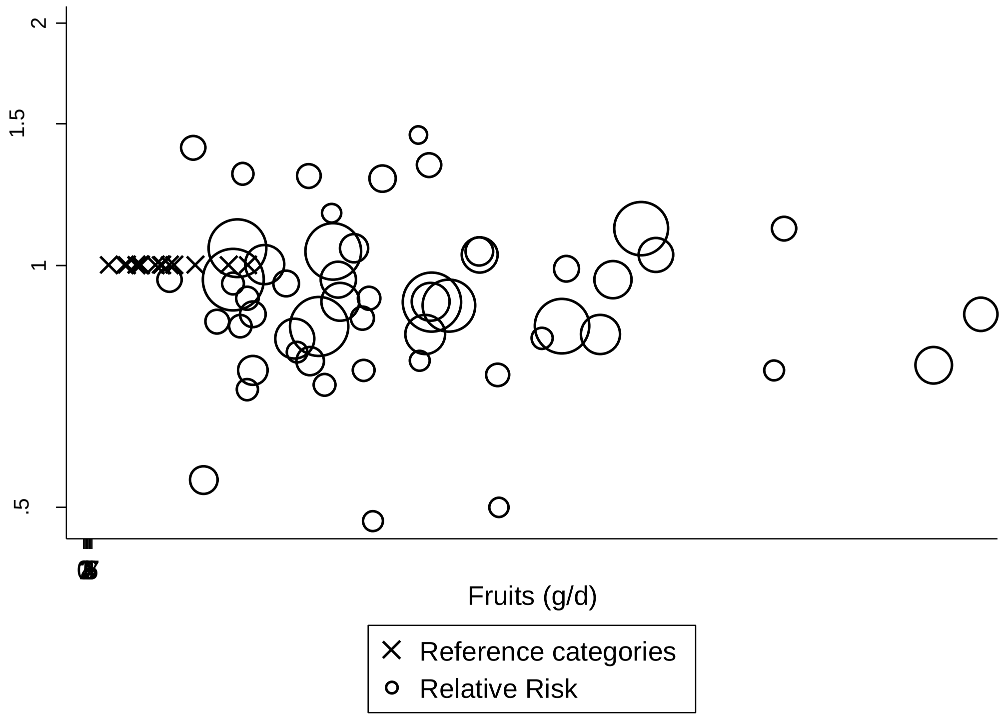


Table 38 Relative risk of colon cancer and fruit intake estimated using non-linear models

Fruit (g/day)	RR (95%CI)
21.2	1.10 (1.06-1.14)
100	1.05 (1.03-1.07)
200	1.00
300	0.98 (0.97-0.98)
400	0.97 (0.96-0.97)
500	0.96 (0.95-0.97)
600	0.96 (0.95-0.97)
700	0.95 (0.94-0.97)

Figure 66 RR estimates of rectal cancer by levels of fruit intake

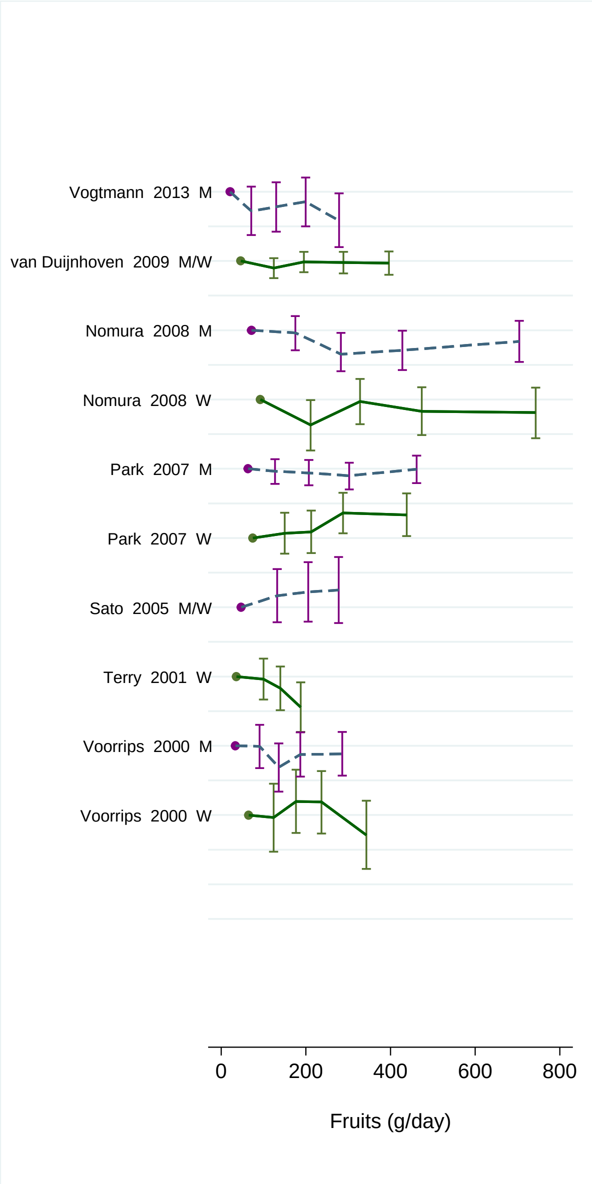


Figure 67 Relative risk of rectal cancer for the highest compared with the lowest level of fruit intake

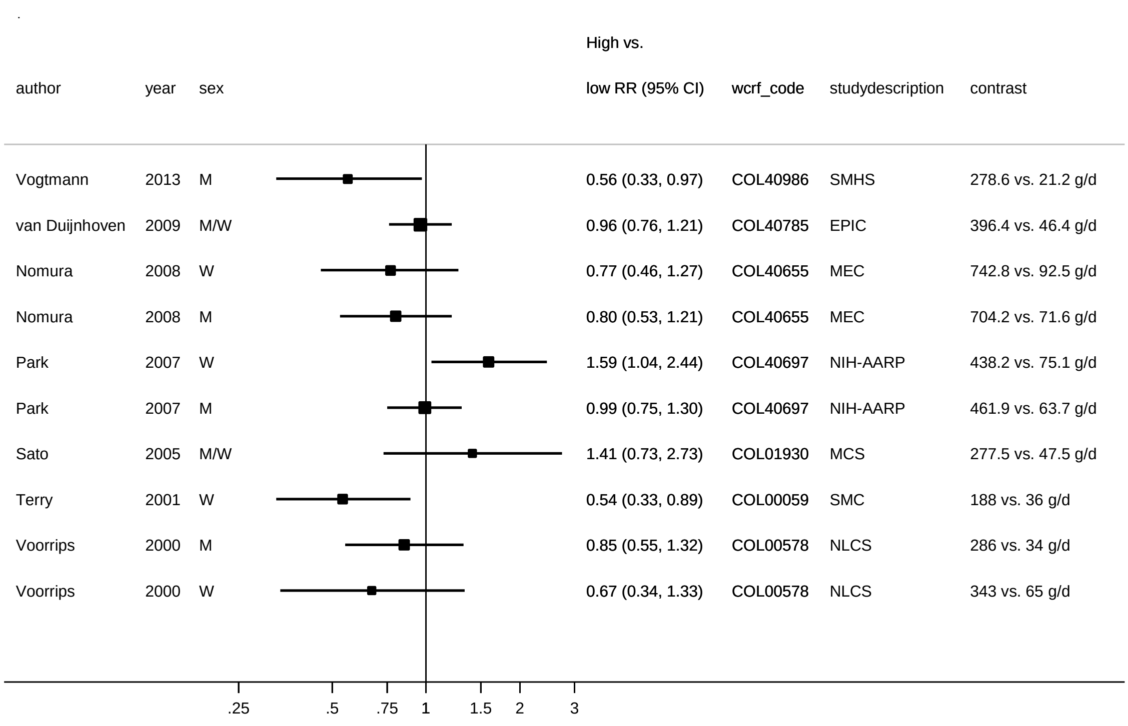


Figure 68 Relative risk of rectal cancer for 100 g/day increase in fruit intake

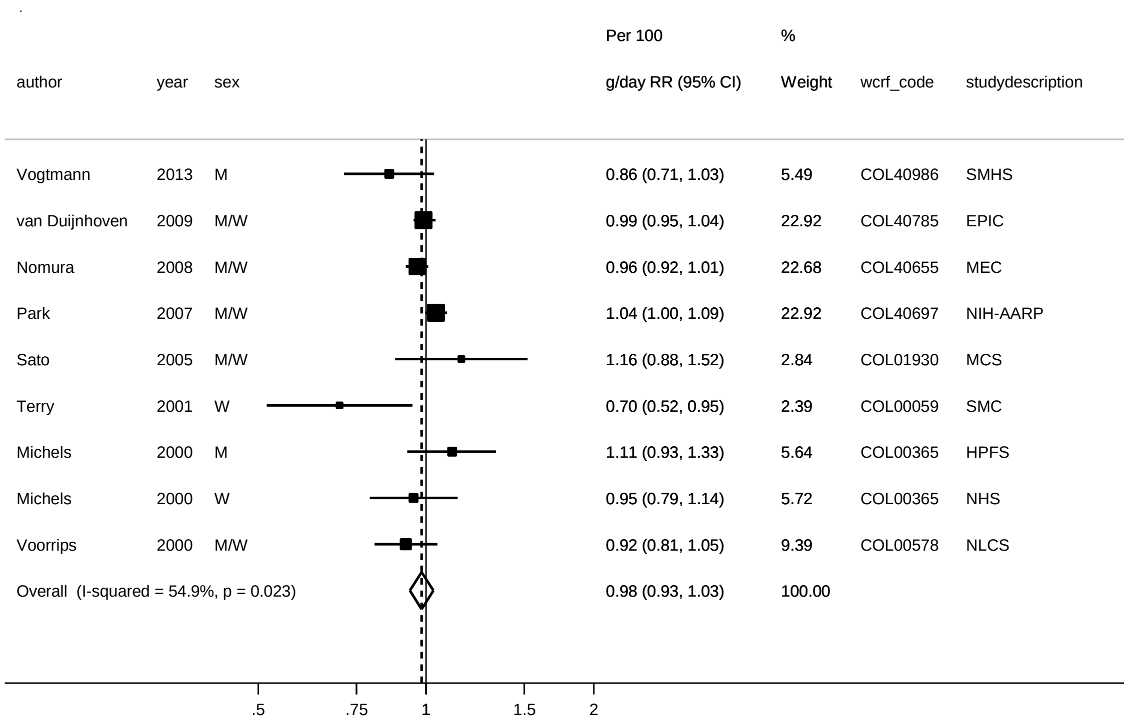


Figure 69 Relative risk of rectal cancer for 100 g/day increase in fruit intake, stratified by sex

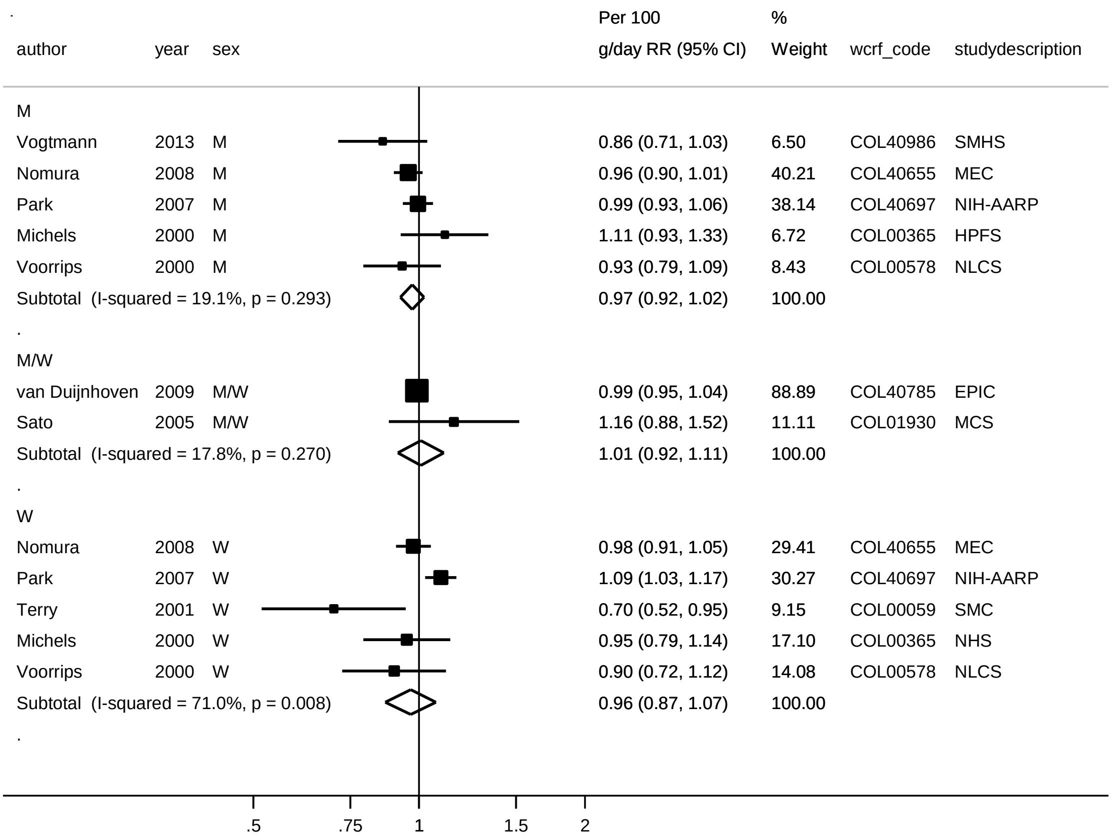


Figure 70 Funnel plot of studies included in the dose response meta-analysis of fruit intake and rectal cancer

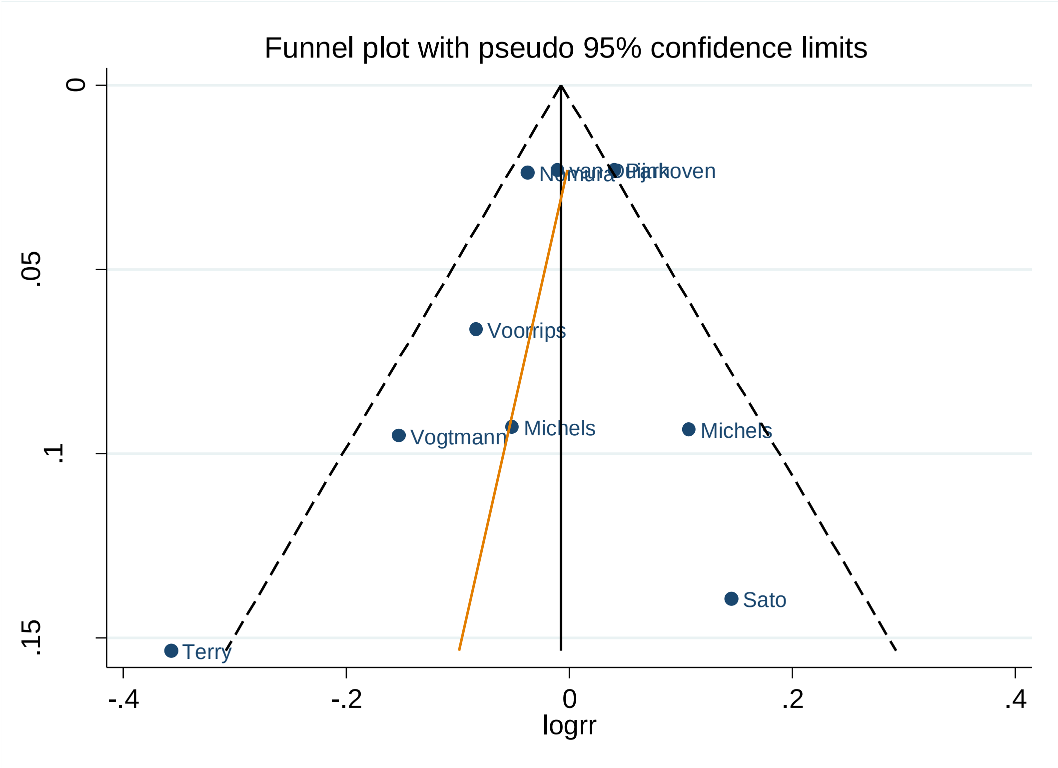
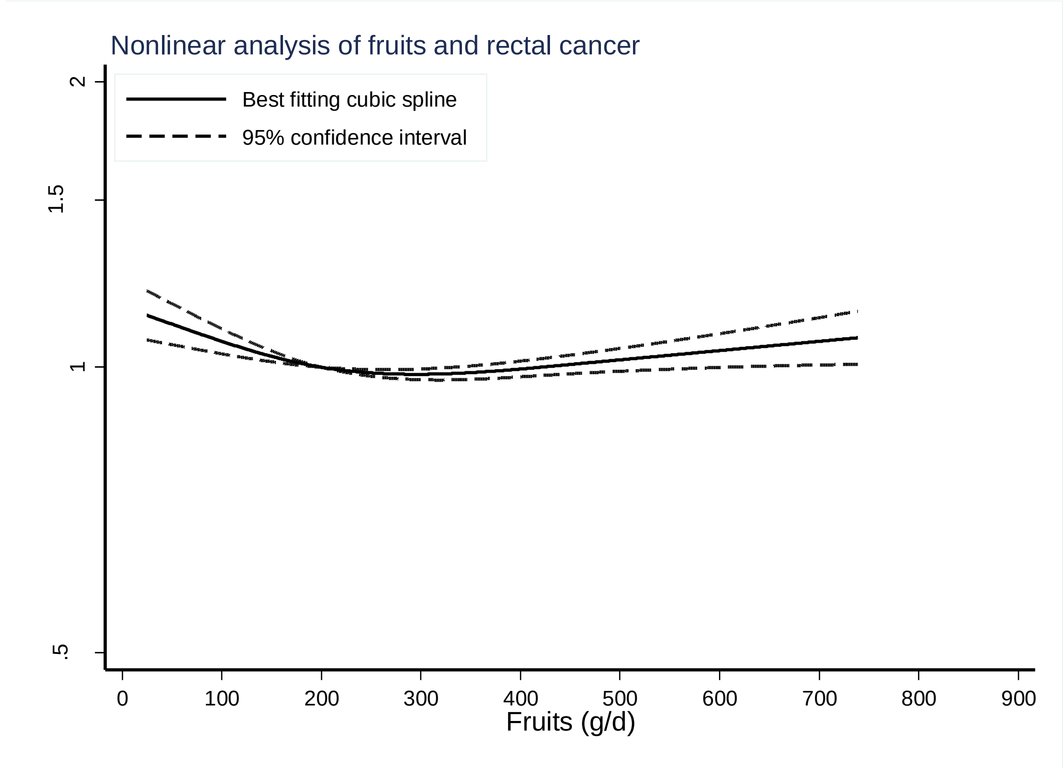


Figure 71 Relative risk of rectal cancer and fruits estimated using non-linear models



P nonlinearity<0.0001

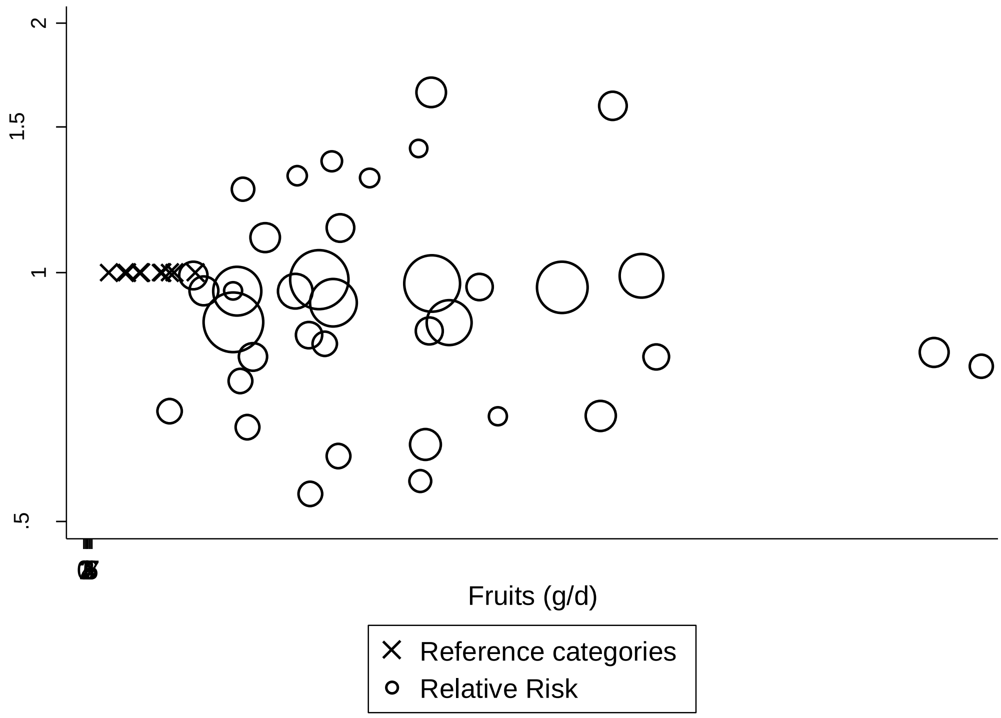


Table 39 Relative risk of rectal cancer and fruit intake estimated using non-linear models

Fruit (g/day)	RR (95%CI)
21.2	1.14 (1.07-1.21)
100	1.07 (1.03-1.10)
200	1.00
300	0.98 (0.97-0.99)
400	1.00 (0.98-1.02)
500	1.02 (0.99-1.05)
600	1.04 (1.00-1.08)
700	1.06 (1.01-1.13)

2.3 Legumes

Cohort studies

Summary

Main results:
Eight studies (twelve publications) were identified. In the 2010 SLR no analysis on legumes and colorectal cancer was conducted.

Colorectal cancer:
Four studies (7948 cases) were included in the dose-response meta-analysis of legumes and colorectal cancer. A non-significant association with moderate heterogeneity was observed. The results were inconsistent, with the only Asian study showing a stronger borderline inverse association per 50g of legumes a day.

Colon cancer:
Six studies (2145 cases) were included in the dose-response meta-analysis of legumes and colon cancer. A non-significant association with high heterogeneity was observed. The results were inconsistent, three studies showed non-significant inverse associations (AHS, NLCS and SMHS) and three studies non-significant positive associations (NHS, HPFS and IWHS).

Rectal cancer:
Four studies (729 cases) were included in the dose-response meta-analysis of legumes and rectal cancer. A non-significant association with moderate heterogeneity was observed. The results were inconsistent and non-significant.

Table 40 Legumes and colorectal cancer risk. Number of studies in the CUP SLR

	Number
Studies identified	4
Studies included in forest plot of highest compared with lowest exposure	4
Studies included in dose-response meta-analysis	4
Studies included in non-linear dose-response meta-analysis	NA

Note: Include cohort, nested case-control and case-cohort designs

Table 41 Legumes and colon cancer risk. Number of studies in the CUP SLR

	Number
Studies identified	6
Studies included in forest plot of highest compared with lowest exposure	6
Studies included in dose-response meta-analysis	6
Studies included in non-linear dose-response meta-analysis	NA

Note: Include cohort, nested case-control and case-cohort designs

Table 42 Legumes and rectal cancer risk. Number of studies in the CUP SLR

	Number
Studies identified	4
Studies included in forest plot of highest compared with lowest exposure	4
Studies included in dose-response meta-analysis	4
Studies included in non-linear dose-response meta-analysis	NA

Note: Include cohort, nested case-control and case-cohort designs

Table 43 Legumes and colorectal cancer risk. Summary of the dose-response meta-analysis in the 2010 SLR and 2015 SLR.

	2010 SLR	2015 SLR
Increment unit used		50g/day
Studies (n)		4
Cases (total number)		7948
RR (95%CI)		1.00(0.95-1.06)
Heterogeneity (I^2, p-value)		32.6%, 0.20

Table 44 Legumes and colon cancer risk. Summary of the dose-response meta-analysis in the 2010 SLR and CUP.

	2010 SLR	2015 SLR
Increment unit used		50g/day
Studies (n)		6
Cases (total number)		2145
RR (95%CI)		0.97(0.83-1.15)
Heterogeneity (I^2, p-value)		55%, 0.04

Table 45 Legumes and rectal cancer risk. Summary of the dose-response meta-analysis in the 2010 SLR and CUP.

	2010 SLR	2015 SLR
Increment unit used		50g/day
Studies (n)		4

Cases (total number)		729
RR (95%CI)		0.99(0.78-1.25)
Heterogeneity (I^2, p-value)		45.2%, 0.14

Table 46 Legumes and colorectal cancer risk. Main characteristics of studies included in the CUP SLR dose-response meta-analysis

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Missing data derived for analysis
Bamia, 2013 COL40964 Denmark, France, Germany, Greece, Italy, Netherlands, Spain, Sweden, UK	EPIC, Prospective Cohort, Age: 25-70 years, M/W	4 355/ 480 308 11.6 years	Cancer registry, record linkage, health Insurance rec, mortality registry , pathology and active follow up	FFQ	Incidence, colorectal cancer	30.1 vs 0 g/day	1.05 (0.95-1.17) Ptrend:0.32	Age, sex, BMI, centre location, cereal, dairy products consumption, educational level, ethanol, fish, fruits, legumes, lipids, meat, physical activity, smoking	Distribution of cases person-years by exposure category.
		2 479/			Women	30.1 vs 0 g/day	1.17 (1.01-1.34) Ptrend:0.03		
		1 876/			Men	30.1 vs 0 g/day	0.96 (0.81-1.13) Ptrend:0.62		
Vogtmann, 2013 COL40986 China	SMHS, Prospective Cohort, Age: 40-74 years, M	398/ 61 274 6.3 years	Cancer registry, shanghai vital statistics office, medical history	FFQ	Incidence, colorectal cancer	≥58.24 vs 0-16.99 g/day	0.82 (0.59-1.13) Ptrend:0.10	Age, alcohol, BMI, diabetes, educational level, energy intake, family history of colorectal cancer, Income, met-hours per week, occupation, red meat, smoking, total meat	Mid-points of exposure categories. Distribution of person-years by exposure category.
		236/			Incidence, colon cancer	≥58.24 vs 0-16.99 g/day	0.92 (0.60-1.40) Ptrend:0.39		
		162/			Incidence, rectal cancer	≥58.24 vs 0-16.99 g/day	0.69 (0.42-1.14) Ptrend:0.13		
Park, 2007 COL40697 USA	NIH-AARP, Prospective Cohort, Age: 50-71 years,	2972 488 043 2 121 664 person-years	Cancer registry	FFQ	Incidence, colorectal cancer, women	0.81 vs 0.09 servings1000 kcal/day	1.13 (0.91-1.40) Ptrend:0.22	Age, alcohol consumption, calcium intake, educational level, physical	Distribution of person-years by exposure category. Intakes in
					Men	0.69 vs 0.08	0.95 (0.83-1.09)		

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Missing data derived for analysis
	M/W					servings1000 kcal/day	Ptrend:0.85	activity, red meat intake, smoking status, total energy intake	servings/1000kcal/day converted to g/day using average energy intake per each quantile
Lin, 2005 COL01831 USA	WHS, Prospective Cohort, Age: 45- years, W, professionals	223/ 36 976 10 years	Follow up questionnaires (self-report), medical record and pathology reports	FFQ	Incidence, colorectal cancer, women	0.9 vs 0.1 serving/day	0.83 (0.54-1.28) Ptrend:0.19	Age, alcohol consumption, aspirin use, BMI, family history of specific cancer, history of previous polyp and prior endoscopy, menopausal status, physical activity, postmenopausal hormone use, randomized treatment assignment, red meat intake, smoking status, total energy	Distribution of person-years by exposure category. Intakes in servings/day converted to g/day
Michels, 2000 COL00365 USA	NHS, Prospective Cohort, Age: 30-55 years,	937/ 136089 1 743 645 person-years	Population registries	Semi-quantitative FFQ	Incidence, colon cancer,	per 1 serving/day ≥4 vs <1 servings/day	1.23 (0.93–1.63) 1.12 (0.89–1.42)	Age, alcohol consumption, aspirin use, BMI, family history of	Intakes in servings/day converted to g/day
		244/			Incidence, rectal	per 1	1.52 (0.99–2.32)		

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Missing data derived for analysis
	W, Registered nurses And HPFS, Prospective Cohort, Age: 40-75 years, M, Health professionals				cancer,	serving/day ≥4 vs <1 servings/day	1.38 (0.87–2.18)	colorectal cancer, height, menopausal status, pack-years of smoking, physical activity, postmenopausal hormone use, red meat intake, sigmoidoscopy, supplement intake, total caloric intake Family history of specific cancer, smoking status, total energy, vitamin supplement	
Voorrips, 2000 COL00578 Netherlands	NLCS, Case Cohort, Age: 55-69 years, M/W	313 120 852 6.3 years	Cancer registry	Semi-quantitative FFQ	Incidence, colon cancer, men	62 vs 11 g/day	1.13 (0.77-1.64) Ptrend:0.41	Age, alcohol consumption, family history of specific cancer	Distribution of person-years by exposure category.
		201/			Incidence, rectal cancer, men	62 vs 11 g/day	0.92 (0.58-1.47) Ptrend:0.97		
		274/			Incidence, colon cancer, women	58 vs 10 g/day	0.79 (0.52-1.20) Ptrend:0.58		
		122/			Incidence, rectal cancer, women	58 vs 10 g/day	1.01 (0.53-1.94) Ptrend:0,59		
Sellers, 1998	IWHS,	180/	SEER registry	Semi-	Incidence, colon	≥3.6 vs ≤2	1.00 (0.70-1.50)	Age, history of	Distribution of

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Missing data derived for analysis
COL01974 USA	Prospective Cohort, Age: 55-69 years, W, Postmenopausal	35 216 10 years		quantitative FFQ	cancer, no family history of crc	servings/week	Ptrend:0.9	polyps, total energy intake	person-years by exposure category. Intakes in servings/week converted to g/day
		61/			Family history of crc	≥3.6 vs ≤2 servings/week	1.50 (0.80-2.70) Ptrend:0.2		
Singh, 1998 COL00185 USA	AHS, Prospective Cohort, Age: 25- years, M/W, Seventh-day Adventists	144/ 32 051 178 544 person-years	Census list	FFQ	Incidence, colon cancer,	≥3 vs ≤1 times/week	0.53 (0.33-0.86) Ptrend:0.03	Age, sex, alcohol consumption, aspirin use, BMI, family history of specific cancer, physical activity, smoking habits	Intakes in times/week converted to g/day

Table 47 Legumes and colorectal cancer risk. Main characteristics of studies excluded from the CUP SLR dose-response meta-analysis

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Reasons for exclusion
Agnoli, 2013 COL40938 Italy	EPIC-Italy, Prospective Cohort, M/W	435/ 45 275 11.28 years	Cancer registry and hospital records	Semi-quantitative FFQ	Incidence, colorectal cancer	23.6-281.4 vs 0-11.8 g/day	0.89 (0.70-1.15) Ptrend:0.353	Age, BMI, educational level, gender, non-alcoholic beverage intake, physical activity, smoking, study centre	Superseded by Bamia, 2013 COL40964
Bueno-de-Mesquita, 2002 COL00950 Europe	EPIC, Prospective Cohort, M/W	773/ 406 439	Not specified	FFQ	Incidence, colorectal cancer,	Q 5 vs Q 1	1.41 Ptrend:0.54	Age, sex, body weight, centre location, energy intake, ethanol intake, height, physical activity at work, smoking habits	Superseded by Bamia, 2013 COL40964
		493/			Women	≥26 vs 0-1 g/day	1.66 Ptrend:0.35		
		279/			Men	≥23 vs 0-1 g/day	0.95 Ptrend:0.72		
Fraser, 1999 COL00102 USA	AHS, Prospective Cohort, Age: 25-100 years, M/W, Seventh-day Adventists	34 198 6 years	Census list	FFQ	Incidence, colon cancer, consumers of red meat	≥3 vs 0-1 times/week	0.33 (0.13-0.83)	Unadjusted	Superseded by Singh, 1998 COL00185 (adjusted results)
Steinmetz, 1994 COL00178 USA	IWHS, Prospective Cohort, Age: 55-69	212/ 35 216 167 447 person-years	SEER	Semi-quantitative FFQ	Incidence, colon cancer,	≥1 vs ≤0 serving/week	0.95 (0.66-1.36)	Age, energy intake	Superseded by Sellers, 1998 COL01974

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Reasons for exclusion
	years, W, Postmenopausal	120/			Incidence, distal colon cancer, distal sites	≥1 vs 0-0.4 serving/week	0.75 (0.46-1.22)		
		86/			Incidence, proximal colon cancer, proximal sites	≥1 vs 0-0.4 serving/week	1.27 (0.74-2.18)		

Figure 72 RR estimates of colorectal cancer by levels of legumes

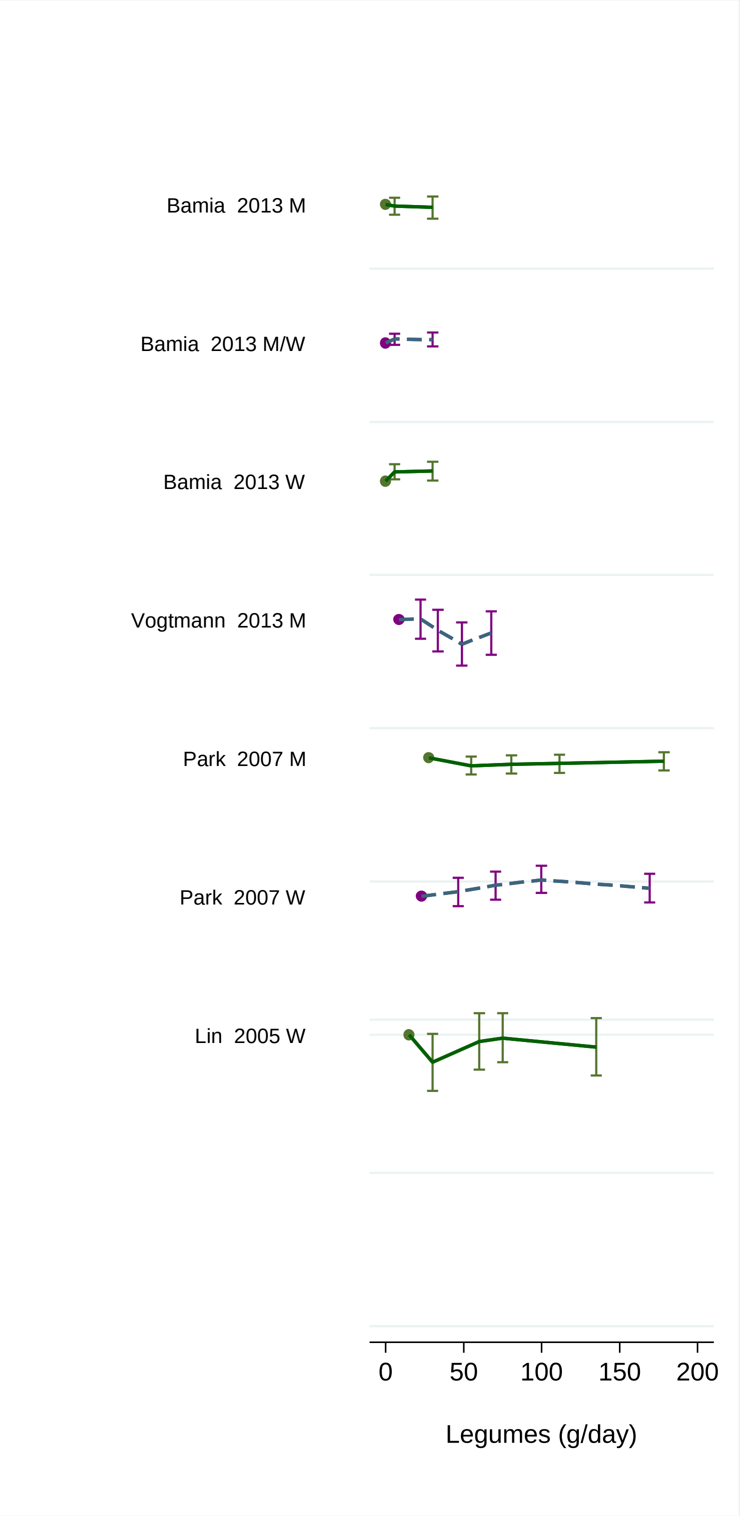


Figure 73 RR (95% CI) of colorectal cancer for the highest compared with the lowest level of legumes

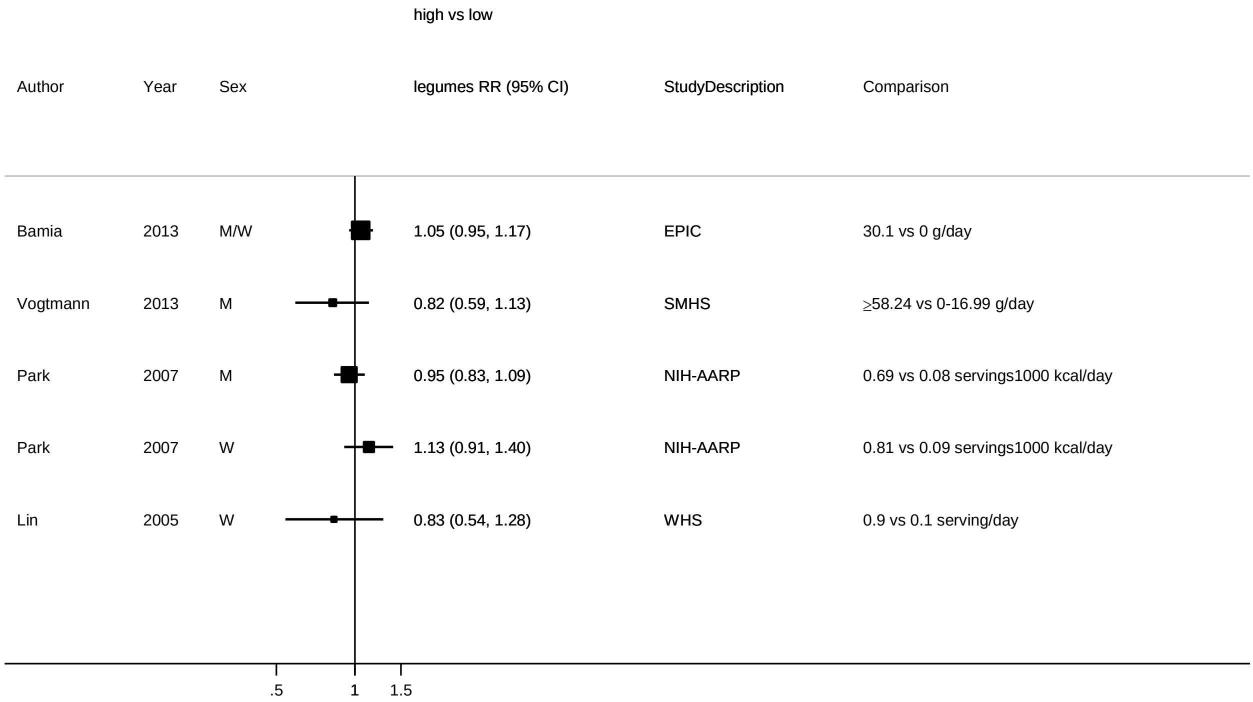


Figure 74 RR (95% CI) of colorectal cancer for 50g/day increase of legumes

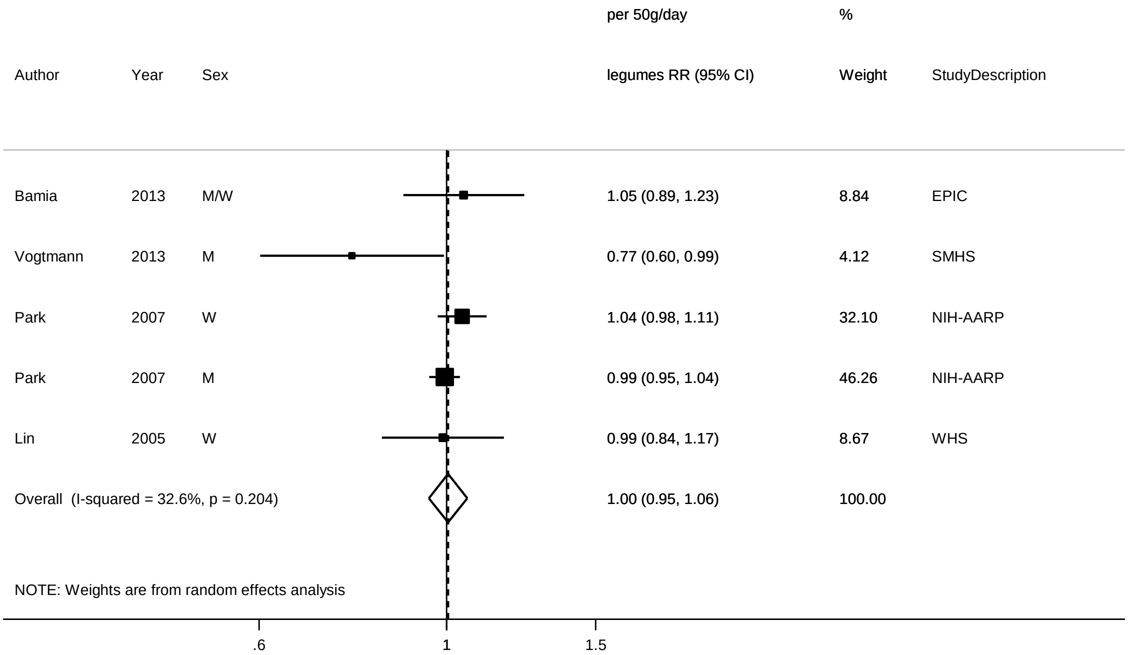


Figure 75 RR estimates of colon cancer by levels of legumes

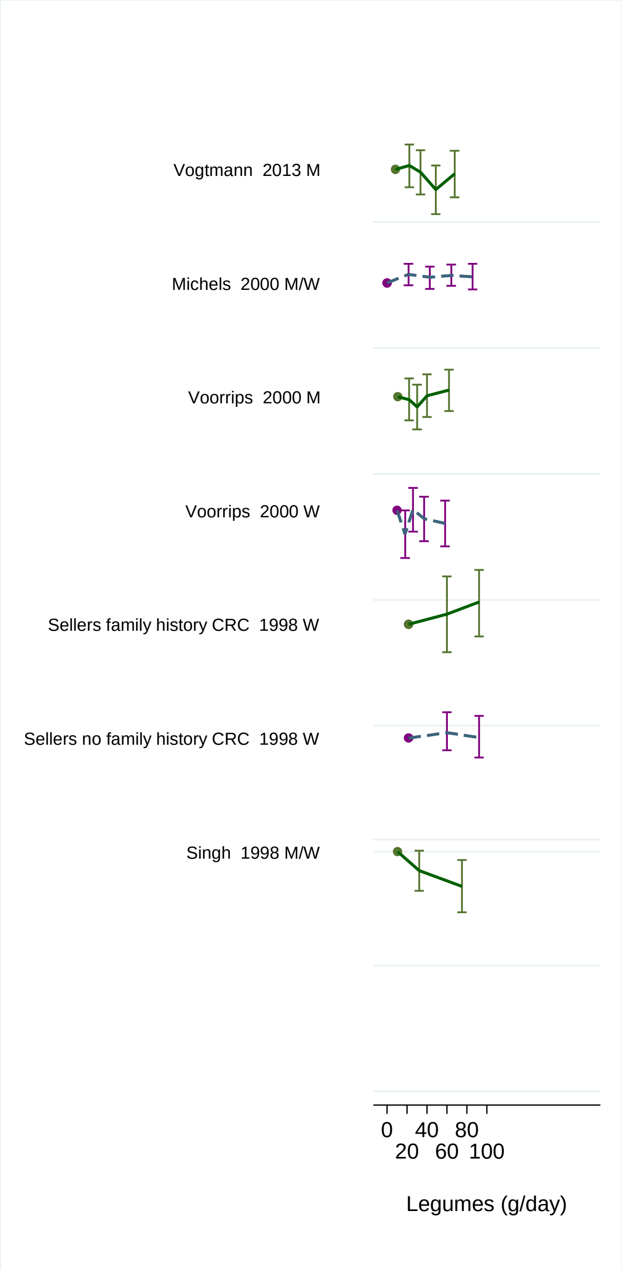


Figure 76 RR (95% CI) of colon cancer for the highest compared with the lowest level of legumes

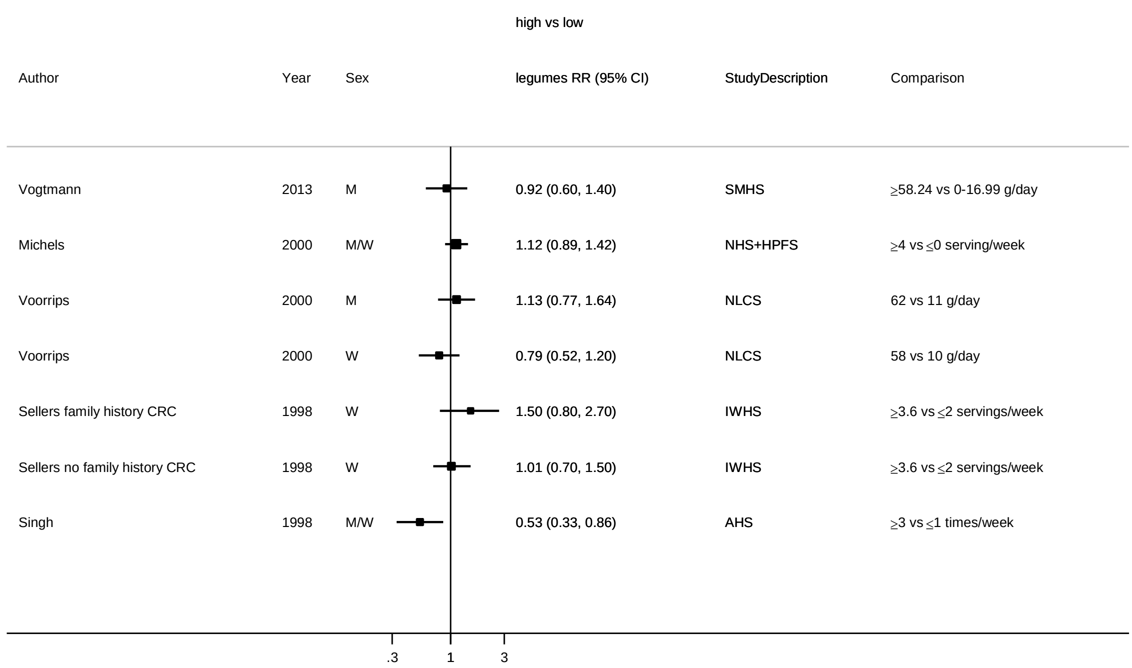


Figure 77 RR (95% CI) of colon cancer for 50g/day increase of legumes

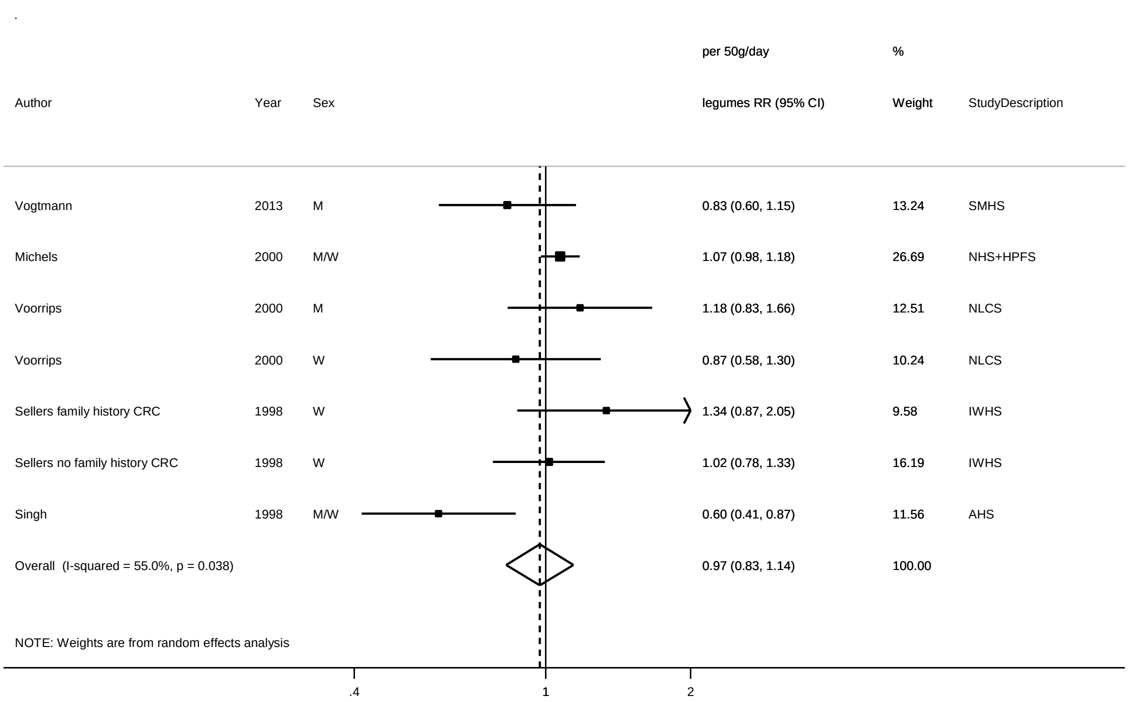


Figure 78 RR estimates of rectal cancer by levels of legumes

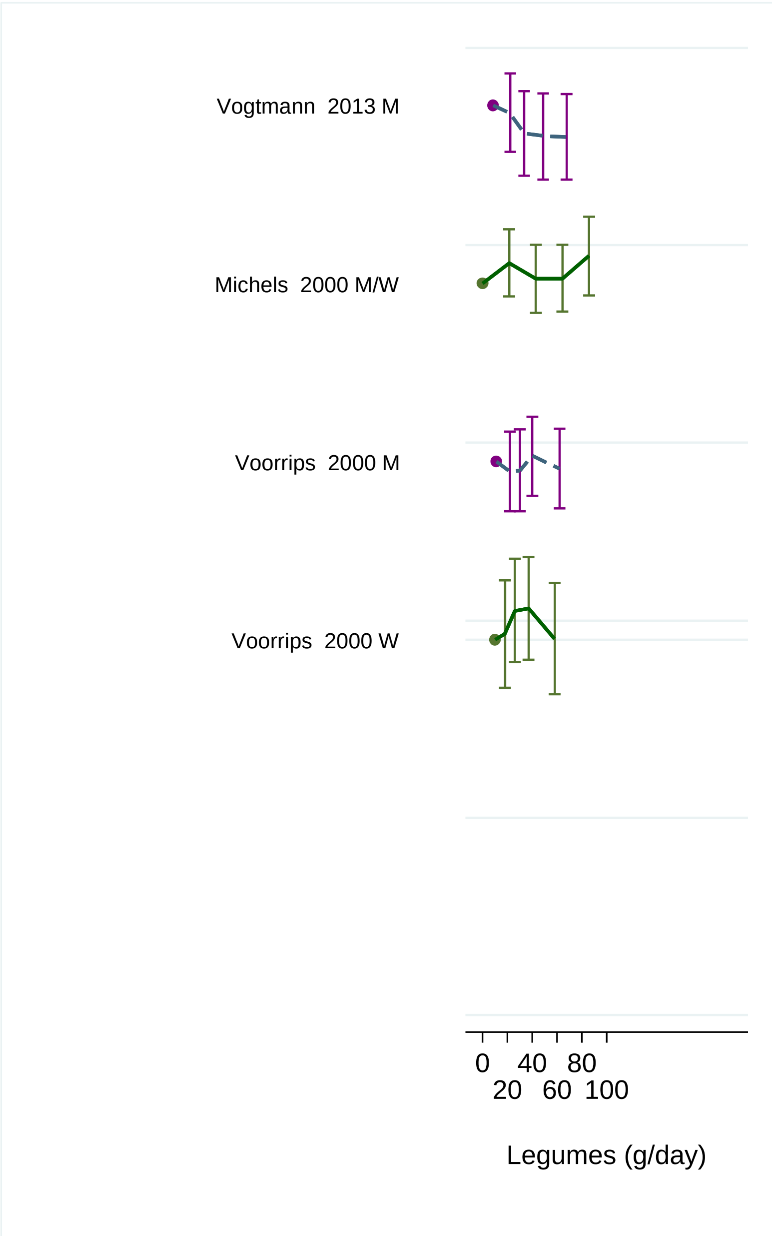


Figure 79 RR (95% CI) of rectal cancer for the highest compared with the lowest level of legumes

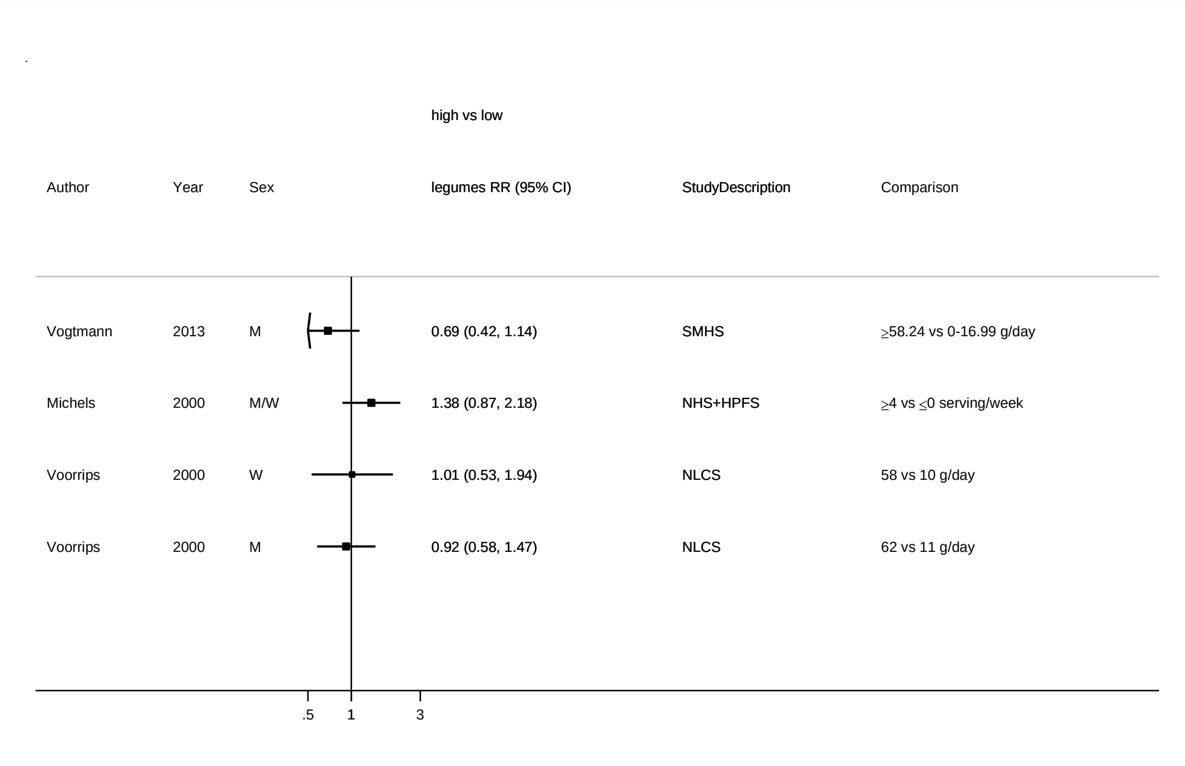
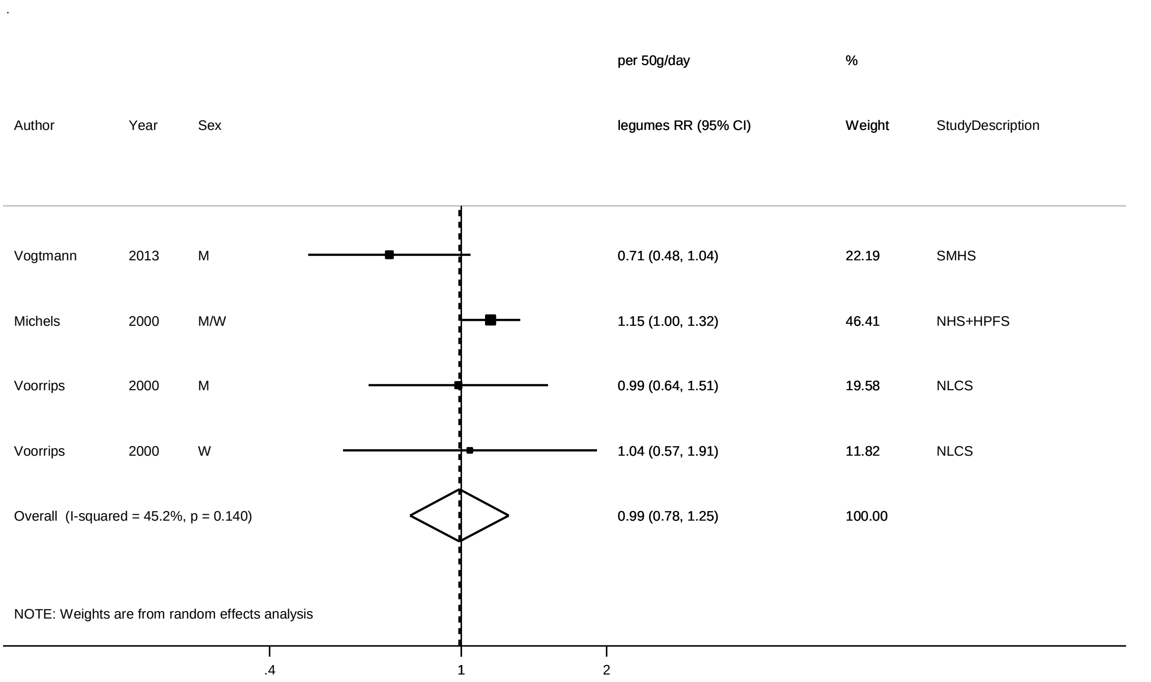


Figure 80 RR (95% CI) of rectal cancer for 50g/day increase of legumes



2.5.1 Red and processed meat

Cohort studies

Summary

Main results:
Eight new publications were identified, five were new studies and four were updates from the studies included in the 2010 SLR. There were no new studies on mortality, therefore all the analysis is on cancer incidence.

Colorectal cancer:
Fifteen studies (31551 cases) were included in the dose-response meta-analysis of red and processed meat and colorectal cancer. A significant association with high heterogeneity was observed. Only three studies (2 Asian and 1 American) showed a significant dose-response relationship. After stratification by sex, the association remained significant in men, but not in women where moderate heterogeneity persisted. After stratification by location, the results were significant for Asia and Europe, with no heterogeneity, and non-significant for North America. All studies from Asia were from Korea. There was no evidence of publication bias (p=0.46). There was no evidence of a non-linear association (p=0.75).
The summary RRs ranged from 1.10 (95% CI=1.02-1.18) when Cross, 2010 was omitted to 1.15 (95% CI=1.07-1.23) when Ollberding, 2012 was omitted.

Colon cancer:
Ten studies (10010) were included in the dose-response meta-analysis of red and processed meat and colon cancer. A significant association with high heterogeneity was observed. Four studies showed no significant associations and the remaining six (from Asia and North America) showed a significant dose-response association. After stratification by sex, the association remained significant in men, but not in women. After stratification by location, the results were significant for Asia and Europe, with no heterogeneity, and non-significant for North America. The high heterogeneity found in the subgroup of North American studies is mainly because of differences found in studies including men or women only.
There was evidence of publication bias (p=0.02). There was no evidence of a non-linear association (p=0.28).
The summary RRs ranged from 1.17 (95% CI=1.09-1.26) when Giovannucci, 1994 was omitted to 1.22 (95% CI=1.14-1.32) when Ruder, 2011 was omitted.

Rectal cancer:
Six studies (3455) were included in the dose-response meta-analysis of red and processed meat and rectal cancer. A non-significant association with moderate heterogeneity was observed. The Canadian National Breast Screening Study (NBSS) was the only study showing a significant association with a wide confidence interval. The remaining studies showed non-significant associations. There was a small number of studies in the stratified

analysis by sex and location. The high heterogeneity found in the subgroup of women and North American studies is explained by the result of NBSS.

There was no evidence of publication bias (p=0.12). There was no evidence of a non-linear association (p=0.40).
The summary RRs ranged from 1.10 (95% CI=1.00-1.21) when Kabat, 2007 was omitted to 1.22 (95% CI=1.00-1.49) when Ruder, 2011 was omitted.

Study quality:
The definition of red and processed meats varied between the studies. In general, the meat item was a combination of red meat, such as beef, pork and lamb, and processed meat, such as hotdogs, luncheon meat and bacon. Studies that reported data for a broad classification of meat, such as "total meat" categories, which included poultry or fish, were excluded.
It is possible that the difference amongst study results may be due to the differences in assessment of red and processed meats in the studies.
Adjustment may be another reason for heterogeneity. Although we cannot rule out residual confounding, most studies included in the meta-analyses adjusted results by smoking, alcohol consumption, BMI and physical activity in addition to age and sex.

Pooling project of cohort studies:
The UK Dietary Cohort Consortium reported no evidence of an association between red and processed meat consumption and colorectal cancer risk in a pooled analysis of food diary data from seven prospective studies (odd ratios for a 50g/day increase in red and processed meat = 0.97, 95% CI = 0.84-1.12). Similar relationships were observed for colon and rectal cancers (Spencer, 2010). The authors argued that the null results might be due to the relatively low meat intake in the cohorts (cut points of the highest quintiles of intake were only 80g/day, 50 g/day and 30 g/day for red and processed meat, red meat and processed meat respectively). Two of the cohorts (EPIC-Norfolk and EPIC-Oxford) participating in this consortium were included in our meta-analyses. Average red and processed meats intake was only 38.2 g/day among male and 28.7 g/day among female controls. EPIC-Oxford, the Oxford Vegetarian Study and the United Kingdom Women's Cohort Study included a high proportion of vegetarians and contributed with high number of cases.

Meta-analysis:
Two meta-analysis were published after the 2010 SLR. One showed a summary relative risk for the highest versus the lowest intake of red and processed meat of 1.22 (95% CI = 1.11-1.34) and a RR for every 100 g/day increase of 1.14 (95% CI=1.04-1.24) for colorectal cancer. Non-linear dose-response meta-analyses revealed that colorectal cancer risk increases approximately linearly with increasing intake of red and processed meats up to approximately 140 g/day, where the curve approaches its plateau (Chan, 2011).
Another meta-analysis (Alexander, 2015), combined 27 studies with different outcomes (colorectal, colon and rectal cancer) and obtained a RR of 1.11(1.03-1.19) for the highest versus lowest intake.

Table 48 Red and processed meat and colorectal cancer risk. Number of studies in the CUP SLR

	Number
Studies identified	19
Studies included in forest plot of highest compared with lowest exposure	14
Studies included in dose-response meta-analysis	15
Studies included in non-linear dose-response meta-analysis	8

Note: Include cohort, nested case-control and case-cohort designs

Table 49 Red and processed meat and colon cancer risk. Number of studies in the CUP SLR

	Number
Studies identified	15
Studies included in forest plot of highest compared with lowest exposure	11
Studies included in dose-response meta-analysis	10
Studies included in non-linear dose-response meta-analysis	9

Note: Include cohort, nested case-control and case-cohort designs

Table 50 Red and processed meat and rectal cancer risk. Number of studies in the CUP SLR

	Number
Studies identified	9
Studies included in forest plot of highest compared with lowest exposure	9
Studies included in dose-response meta-analysis	6
Studies included in non-linear dose-response meta-analysis	7

Note: Include cohort, nested case-control and case-cohort designs

Table 51 Red and processed meat and colorectal cancer risk. Summary of the dose-response meta-analysis in the 2010 SLR and 2015 SLR.

	2010 SLR	**2015 SLR**
Increment unit used	100g/day	100g/day
Studies (n)	9	15
Cases (total number)	8894	31551
RR (95%CI)	1.16 (1.04-1.30)	1.12(1.04-1.21)
Heterogeneity (I^2, p-value)	47%, 0.06	70.2%, <0.01

Stratified analysis by sex		
Men	**2010 SLR**	**2015 SLR**
Studies (n)	2	4
RR (95%CI)	1.08 (0.84 - 1.39)	1.10(1.02-1.18)
Heterogeneity (I^2, p-value)	0%, 0.83	0%, 0.66
Women		

Studies (n)	4	8
RR (95%CI)	1.02 (0.77-1.34)	1.13(1.00-1.29)
Heterogeneity (I^2, p-value)	61%, 0.05	46.8, 0.07

Stratified analysis by geographic location			
(no analysis in 2005 SLR or 2010 SLR)			
2015 SLR	**Asia**	**Europe**	**North America**
Studies (n)	3	3	9
RR (95%CI)	1.26(1.16-1.36)	1.09(1.01-1.17)	1.07(0.95-1.20)
Heterogeneity (I^2, p-value)	0%, 0.83	0%, 0.57	77.2%, <0.01

Table 52 Red and processed meat and colon cancer risk. Summary of the dose-response meta-analysis in the 2010 SLR and 2015 SLR.

	2010 SLR	**2015 SLR**
Increment unit used	100g/day	100g/day
Studies (n)	7	10
Cases (total number)	5037	10010
RR (95%CI)	1.21 (1.06-1.39)	1.19(1.10-1.30)
Heterogeneity (I^2, p-value)	56.0%, 0.04	62.9%, 0.004

Stratified analysis by sex		
Men	**2010 SLR**	**2015 SLR**
Studies (n)	2	5
RR (95%CI)	1.41 (0.98- 2.03)	1.32(1.13-1.53)
Heterogeneity (I^2, p-value)	71%, 0.06	27.6, 0.24
Women		
Studies (n)	4	8
RR (95%CI)	1.05(0.78-1.40)	1.18(0.98-1.43)
Heterogeneity (I^2, p-value)	57.0%, 0.08	44.3%, 0.08

Stratified analysis by geographic location			
(no analysis in 2005 SLR or 2010 SLR)			
2015 SLR	**Asia**	**Europe**	**North America**
Studies (n)	3	1	6
RR (95%CI)	1.23(1.16-1.31)	1.26 (1.07-1.48)	1.19(0.98-1.38)
Heterogeneity (I^2, p-value)	0%, 1.0		67.6%, <0.01

Table 53 Red and processed meat and rectal cancer risk. Summary of the dose-response meta-analysis in the 2010 SLR and 2015 SLR.

	2010 SLR	2015 SLR
Increment unit used	100g/day	100g/day
Studies (n)	5	6
Cases (total number)	2091	3455
RR (95%CI)	1.31 (1.13-1.52)	1.17(0.99-1.39)
Heterogeneity (I^2, p-value)	18.0%, 0.30	48.4%, 0.08

Stratified analysis by sex (no analysis 2010 SLR)		
2015 SLR	**Men**	**Women**
Studies (n)	1	3
RR (95%CI)	0.92(0.59-1.42)	1.34 (0.85-2.11)
Heterogeneity (I^2, p-value)		46.6%, 0.13

Stratified analysis by geographic location (no analysis in 2005 SLR or 2010 SLR)			
2015 SLR	**Asia**	**Europe**	**North America**
Studies (n)	1	2	3
RR (95%CI)	0.93(0.64-1.33)	1.23(1.01-1.50)	1.33(0.91-1.96)
Heterogeneity (I^2, p-value)		0%, 0.86	74.1%, 0.02

Table 54 Red and processed meat and colorectal cancer risk. Results of meta-analyses and pooled analyses of prospective studies published after the 2005 SLR.

Author, Year	Number of cohort studies	Total number of cases	Studies country, area	Outcome	Comparison	RR (95%CI)	P trend	Heterogeneity (I^2, p value)
Pooled analysis								
Spencer, 2010	7	579 cases 1996 controls	UK	Colorectal cancer	≥75 vs <25 g/day Per 50g/day	0.88 (0.65–1.20) 0.97 (0.84–1.12)	0.68	
				Colon cancer		0.88 (0.60–1.29) 1.03 (0.86–1.24)	0.74	
				Rectal cancer		0.83 (0.49–1.42) 0.85 (0.66–1.10)	0.22	
Meta-analysis								
Alexander, 2015	27		Europe, Asia and North America	Colorectal, colon and rectal cancer combined	Highest vs lowest	1.11(1.03-1.19)		33.6%, 0.01
Chan, 2011	10	11358	Europe, Asia and North America	Colorectal cancer	Highest vs lowest	1.22 (1.11-1.34)		56%, 0.01
					Per 100g/day	1.14(1.04-1.24)		
	8	5426		Colon cancer	Per 100g/day	1.25 (1.10–1.43)		60%, 0.02
	5	2091		Rectal cancer	Per 100g/day	1.31 (1.13–1.52)		18%, 0.30

Table 55 Red and processed meat and colorectal cancer risk. Main characteristics of studies included in the CUP SLR dose-response meta-analysis

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Missing data derived for analysis
Shin, 2014 COL41023 Korea	KNHIC, Prospective Cohort, Age: 30-80 years, M/W	9 084/ 1 326 058	Korean central cancer registry (kccr) & Insurance system	Self-administered questionnaire	Incidence, colorectal cancer, men	≥4 vs ≤1 times/week	1.26 (1.18-1.35)	Age, alcohol, BMI, cigarette smoking, family history of cancer, fasting blood sugar, height, serum cholesterol	Distribution of person-years and cases by exposure category. Mid-points of exposure categories. Conversion from times/week to g/day
		2 655/			Women		1.29 (1.12-1.49)		
		1252			Incidence, rectal cancer, women		1.39 (1.14-1.70)		
		1143			Incidence, rectal cancer, men		1.48 (1.10-1.99)		
		2868			Incidence, colon cancer, men		1.31 (1.19-1.45)		
		1210			Incidence, colon cancer, women		NA		
Wie, 2014 COL41065 Korea	Cancer Screening Examination Cohort, Korea (CSECK), Prospective Cohort, M/W	53/ 8 024 7 years	Cancer registry and medical records	3-day food record	Incidence, colorectal cancer	per 10 g/day	1.01 (0.90-1.14)	Age, sex, alcohol, BMI, educational level, energy intake, Income, marital status, physical activity, smoking	Conversion from 10g/day to 100g/day
Bamia, 2013 COL40964 Denmark,France ,Germany,Greec e,Italy,Netherlan	EPIC, Prospective Cohort, Age: 25-70 years,	4 355/ 480 308 11.6 years	Cancer registry, record linkage, health Insurance rec, mortality registry ,	FFQ	Incidence, colorectal cancer	151.5 vs 43.9 g/day	1.08 (0.99-1.18)	Age, sex, BMI, centre location, cereal, dairy products consumption,	
		2 479/			Women	151.5 vs 43.9 g/day	1.08 (0.97-1.20)		

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Missing data derived for analysis
ds,Spain,Sweden,UK	M/W	1 876/	pathology and active follow up		Men	151.5 vs 43.9 g/day	1.07 (0.94-1.22)	educational level, ethanol, fish, fruits, legumes, lipids, meat, physical activity, smoking	
Parr, 2013 COL40955 Norway	NOWAC, Prospective Cohort, Age: 41-70 years, W	666/ 84 538 11.1 years	Cancer registry	FFQ	Incidence, colorectal cancer	≥90 vs ≤30 g/day	1.40 (1.01-1.95)	Age, alcohol, BMI, calcium, energy, fibre, physical activity, smoking	Only included in subgroup analysis. Component of the EPIC study. Superseded by Norat, 2005 COL01698 and Bamia, 2013 COL40964. Mid-points of exposure categories.
		459			Incidence, colon cancer	≥90 vs ≤30 g/day	1.42 (0.95-2.14)		
		215/			Incidence, rectal cancer	≥90 vs ≤30 g/day	1.36 (0.77-2.38)		
Ollberding, 2012 COL40941 Hawaii, USA	MEC, Prospective Cohort, Age: 45-75 years, M/W	3 404/ 165 717 8.1 years	Cancer registry and national death Index	FFQ	Incidence, colorectal cancer	68.96 vs 16.18 g/1000 kcal/day	0.93 (0.83-1.05)	Age, sex, age at cohort entry, alcohol consumption, BMI, calcium, dietart fibre, energy intake, ethnicity, family history of colorectal cancer, folate,	Mid-points of exposure categories. Intakes in g/1000kcal/day converted to g/day using average energy intake per each quantile

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Missing data derived for analysis
								history of diabetes, history of polyp diagnosis, HRT use, non-steroidal anti-inflammatory drug use, pack yrs of smoking, vigorous physical activity, vitamin d	
Kim, 2011 COL40942 Korea	Korean Cohort Study, Prospective Cohort, Age: 30-80 years, M/W	6 444/ 2 248 129 7 years	Cancer registry	Questionnaire	Incidence, colorectal cancer	≥4 vs ≤1 times/week	1.23 (1.13-1.35)	Age, sex, alcohol consumption, BMI, family history of cancer, physical activity, smoking	Distribution of person-years by exposure category. Mid-points of exposure categories. Conversion from times/week to g/day
		4 501/			Men	≥4 vs ≤1 times/week	1.13 (1.02-1.26)		
		1 943/			Women	≥4 vs ≤1 times/week	1.42 (1.21-1.66)		
Ruder, 2011 COL40896 USA	NIH-AARP, Prospective Cohort, Age: 50-71 years, Retired	2 794/ 292 797	Cancer registry and national health database	FFQ	Incidence, colon cancer	1.49 vs 0.18 times/day	1.46 (1.26, 1.69)	Sex, age at baseline, alcohol consumption, aspirin use, BMI, educational level, energy, energy, history of colon cancer,	Used for colon and rectal cancer instead of Cross, 2010 because it has higher number of cases. Distribution of person-years by exposure
		985			Rectal cancer	1.49 vs 0.18 times/day	1.24 (0.97, 1.59)		

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Missing data derived for analysis
								HRT use, physical activity, race, red meat, smoking	category. Mid-points of exposure categories. Conversion from times/day to g/day.
Takachi, 2011 COL41056 Japan	JPHC, Prospective Cohort, Age: 45-74 years, M/W	481/ 80 658 9 years	Hospital records + cancer registry	FFQ	Incidence, colon cancer, men	117 vs 20 g/day	1.44 (1.06-1.98)	Age, alcohol consumption, area, BMI, calcium, diabetes, energy, fibre, folate, physical activity, salted fish consumption, screening exams, smoking status, vitamin b6, vitamin d	Distribution of person-years and cases by exposure category.
		307/			Women	107 vs 18 g/day	1.35 (0.92-1.98)		
		233/			Incidence, rectal cancer, men	117 vs 20 g/day	0.83 (0.52-1.30)		
		124/			Women	107 vs 18 g/day	0.78 (0.41-1.46)		
Cross, 2010 COL40794 USA	NIH-AARP, Prospective Cohort, Age: 50-71 years, M/W	2 719/ 300 948 7.2 years	Cancer registry and death certificates and questionnaires	FFQ	Incidence, colorectal cancer	61.6 vs 9.5 g/1000 kcal/day	1.24 (1.09-1.42)	Dietary calcium intake, dietary fibre intake, smoking habits, white meat	Used only for colorectal cancer, because reported baseline intake of meat and has higher number of cases than Ruder, 2011 COL40896. Distribution of

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Missing data derived for analysis
									person-years by exposure category. Mid-points of exposure categories. Intakes in g/1000kcal/day converted to g/day using average energy intake per each quantile
Fung, 2010 COL40828 USA	NHS+HPFS, Prospective Cohort, M/W	1432W 1032M 132 746	Self report verified by medical record	FFQ	Incidence, colorectal cancer, men	per 1 serving/day	1.08 (0.97-1.21)	Age, alcohol intake, aspirin use, BMI, colonoscopy, energy, family history, history of polyps, physical activity, smoking	Conversion 1 serving/day to 100g/day, used only in dose-response analysis.
					Women	per 1 serving/day	1.12 (0.99-1.26)		
Kabat, 2007 COL40637 Canada	CBSS, Prospective Cohort, Age: 40-59 years, W	617/ 48 666 16.4 years	Record linkages to cancer database and to the national mortality database	FFQ	Incidence, colorectal cancer	≥40.3 vs ≤14.24 g/day	1.12 (0.86-1.46)	Age, alcohol intake, BMI, educational level, fat intake, fibre, folic acid, HRT use, menopausal status, oral contraceptive	Distribution of person-years by exposure category. Mid-points of exposure categories.
		428/			Incidence, colon cancer	≥40.3 vs ≤14.24 g/day	0.88 (0.64-1.21)		
		195/			Incidence, rectal cancer	≥40.3 vs ≤14.24 g/day	1.95 (1.21-3.16)		

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Missing data derived for analysis
								use, pack-years of smoking, physical activity, total calories	
Berndt, 2006 COL40795 USA	CLUE II, Case Cohort, Age: 48 years, M/W	202/ 2 224 13.5 years	Cancer registry	FFQ	Incidence, colorectal cancer	≥86.3 vs ≤43.9 g/day	1.32 (0.86-2.02)	Age, energy intake, race	Distribution of person-years and cases by exposure category. Mid-points of exposure categories.
Oba, 2006 COL40626 Japan	TCCJ, Prospective Cohort, Age: 35-101 years, M/W	111/ 30 221 8 years	Hospital records and cancer registry	Semi-quantitative FFQ	Incidence, colon cancer, men	102.2 vs 33.3 g	1.56 (0.98-2.49)	Age, alcohol intake, BMI, energy intake, height, pack-years of smoking, physical activity	Distribution of person-years by exposure category.
		102/			Women	80.8 vs 22.4 g	0.94 (0.50-1.43)		
Chao, 2005 COL01689 USA	CPS II, Prospective Cohort, Age: 50-74 years, M/W	665/ 148 610 19 years	Cancer registry and death certificates and medical records	FFQ	Incidence, colon cancer, men	≥800 vs ≤180 g/week	1.30 (0.93-1.81)	Age, aspirin use, beer intake, BMI, educational level, fibre, fruits, liquor intake, multivitamin supplement intake, physical activity, smoking habits,	Distribution of person-years by exposure category. Mid-points of exposure categories. Conversion from g/week to g/day

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Missing data derived for analysis
								total energy, vegetable (total), wine intake	
		532/			Women	≥560 vs ≤90 g/week	0.98 (0.68-1.40)	HRT use	
Larsson, 2005 COL01849 Sweden	SMC, Prospective Cohort, Age: 40-75 years, W	733/ 61 433 855 585 person-years	Cancer registry	Questionnaire	Incidence, colorectal cancer,	≥94 vs 0-49 g/day	1.32 (1.03-1.68)	Age, alcohol consumption, BMI, calcium, educational level, energy intake, fish, folate, fruits, poultry, saturated fat, vegetables, whole-grain foods	Used continuous results
						per 100 g/day	1.20 (0.99-1.45)		
Norat, 2005 COL01698 Europe	EPIC, Prospective Cohort, Age: 21-83 years, M/W	855/ 478 040 2 279 075 person-years		Questionnaire	Incidence, colon cancer,	≥160 vs ≤10 g/day	1.17 (0.78-1.77)	Age, sex, alcohol consumption, body weight, centre location, energy from fat sources, energy from nonfat sources, fibre, height, physical activity, smoking status	Used for colon and rectal cancer. Superseded by Bamia, 2013 COL40964
		474/			Incidence, rectal cancer,	≥160 vs ≤10 g/day	1.75 (0.98-3.10)		
Lin, 2004 COL01834	WHS, Prospective	202/ 37 547	Self-report verified by	FFQ	Incidence, colorectal cancer	1.42 vs 0.13 servings/day	0.66 (0.40-1.09)	Age, alcohol consumption,	Distribution of person-years by

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Missing data derived for analysis
USA	Cohort, Age: 45- years, W	8.7 years	medical record					BMI, family history of colorectal cancer, history of polyps, physical activity, postmenopausal hormone use, randomized treatment assignment, smoking habits, total energy intake	exposure category. Mid-points of exposure categories. Conversion from servings/day to g/day
Flood, 2003 COL00412 USA	BCDDP, 1973, Prospective Cohort, Age: 62 years, W	487/ 45 496 386 716 person-years	Breast cancer screening centres	FFQ	Incidence, colorectal cancer,	52.2 vs 6.1 g/1000 kcal	1.04 (0.77-1.41)	Total energy, total meat	Distribution of person-years by exposure category. Mid-points of exposure categories. Intakes in g/1000kcal/day converted to g/day using average energy intake per each quantile
Pietinen, 1999 COL00176 Finland	ATBC, Prospective Cohort,	185/ 27 111 8 years	Cancer registry	Dietary history questionnaire	Incidence, colorectal cancer,	203 vs 79 g/day	1.10 (0.70-1.70)	Age, alcohol consumption, BMI, calcium	Distribution of person-years by exposure

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Missing data derived for analysis
	Age: 50-69 years, M, Smokers							intake, educational level, physical activity, smoking years, supplement group	category. Mid-points of exposure categories
Chen, 1998 COL01940 USA	PHS, Nested Case Control, M, physicians, 93% Caucasian	208/ 217 controls 13 years	Medical records	Questionnaire	Incidence, colorectal cancer, men	≥1.1 vs 0-0.5 serving/day	1.17 (0.68-2.02)	Alcohol consumption, BMI, physical activity	Distribution of person-years by exposure category. Mid-points of exposure categories. Conversion from servings/day to g/day
Bostick, 1994 COL00079 USA	IWHS, Prospective Cohort, Age: 55-69 years, W	212/ 35 216 167 447 person-years	SEER	Semi-quantitative FFQ	Incidence, colon cancer,	≥11 vs ≤4 serving/week	1.04 (0.62-1.76)	Age, energy intake, height, parity, total vitamin e intake, total vitamin e intake, vitamin a supplement	Mid-points of exposure categories. Conversion from servings/week to g/day
Willett, 1990 CRC00026 USA	NHS, Prospective Cohort, Age: 34-59 years, W, Registered nurses	150/ 88 751 512 488 person-years	Population	Semi-quantitative FFQ	Incidence, colon cancer,	≥134 vs ≤58 g/day	1.77 (1.09-2.88)	Age, energy intake	Mid-points of exposure categories.

Table 56 Red and processed meat and colorectal cancer risk. Main characteristics of studies excluded from the CUP SLR dose-response meta-analysis

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Reasons for exclusion
Lee, 2009 COL40764 China	SWHS, Prospective Cohort, Age: 40-70 years, W	394/ 73 224 7.4 years	Cancer registry and death certificates and participant contact	Quantitative FFQ	Incidence, colorectal cancer	≥89 vs ≤32.9 g/day	0.90 (0.70-1.40)	Age, educational level, energy intake, fibre intake, Income, NSAID use, season of Interview, tea consumption	Used only in highest versus lowest analysis
		236/			Incidence, colon cancer	≥89 vs ≤32.9 g/day	1.10 (0.70-1.80)		
		158/			Incidence, rectal cancer	≥89 vs ≤32.9 g/day	0.70 (0.40-1.30)		
Wei, 2009 COL40777 USA	NHS, Prospective Cohort, Age: 30-54 years, W	701/ 83 767 24 years	Self report verified by medical record	Semi-quantitative FFQ	Incidence, colon cancer	1 vs 0 serving/day	1.20 (0.95-1.51)	Age, aspirin use, BMI, family history of colorectal cancer, folate intake, height, pack-years of smoking, physical activity, postmenopausal hormone use, year of endoscopy	Used only in highest versus lowest analysis
Cross, 2008 COL40701 USA	NIH-AARP, Prospective Cohort,	80/ 494 000 7.5 years	Cancer registry	Semi-quantitative FFQ	Incidence, small Intestinal carcinoids	53.9 vs 14.2 g/1000 kcal	1.44 (0.78-2.69)	Sex, alcohol intake, BMI, educational	Superseded by Ruder, 2011 COL40896 and

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Reasons for exclusion
	Age: 50-71 years, M/W	60/			Incidence, small Intestinal adenocarcinomas	53.9 vs 14.2 g/1000 kcal	1.65 (0.80-3.38)	level, family history of cancer, fruit intake, marital status, person-years at risk, physical activity, race, smoking habits, total energy intake, vegetable intake	Cross, 2010 COL40794
Cross, 2007 COL40640 USA	NIH-AARP, Prospective Cohort, Age: 50-71 years, M/W	5 107/ 494 036 6.8 years	Cancer registry	FFQ	Incidence, colorectal cancer, men	62.7 vs 9.8 g/1000 kcal	1.24 (1.12-1.36)	Age, sex, alcohol consumption, BMI, educational level, energy intake, family history of cancer, fruits, marital status, physical activity, race, smoking habits, vegetable intake	Used only in highest compared to lowest analysis because it is the publication of NIH-AARP with higher number of cases. Superseded by Ruder, 2011 COL40896 and Cross, 2010 COL40794
		3 689/			Incidence, colon cancer, men	62.7 vs 9.8 g/1000 kcal	1.17 (1.05-1.31)		
		1 418/			Incidence, rectal cancer, men	62.7 vs 9.8 g/1000 kcal	1.45 (1.20-1.75)		
Khan, 2004 COL01606 Japan	HCS, Prospective Cohort, Age: 40-97 years,	15/ 3 458 14.3 years	Area residency lists	Questionnaire	Mortality, colorectal cancer, men	Q 2 vs Q 1	2.00 (0.60-6.30)	Age, smoking habits	Outcome is mortality
		14/			Women	Q 2 vs Q 1	1.00 (0.30-3.00)	Health education,	

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Reasons for exclusion
	M/W							health screening, health status	
Ma, 2001 COL00374 USA	PHS, Nested Case Control, Age: 40-84 years, M, Physicians	193/ 318 controls 13 years	Colorectal cancer diagnosis	Unknown	Incidence, colorectal cancer,	0.9-2.1 vs 0-0.5 serving/day	0.98 (0.60-1.60)	Age, alcohol consumption, aspirin use, BMI, molar ratio of Igf-i to Igfbp-3, physical activity, smoking habits, supplement intake	Superseded by Chen, 1998 COL01940
		55/ 106 controls			Tertile 1 of Igf-i/igfbp-3 molar ratio	0.9-2.1 vs 0-0.5 serving/day	1.14 (0.48-2.71)		
Hsing, 1998 COL00458 USA	Lutheran Brotherhood Study, Prospective Cohort, Age: 35- years, M, policyholders	145/ 17 633 286 731 person-years	Responding to mail survey	Questionnaire	Mortality, colorectal cancer,	≥60 vs ≤14 times/month	1.90 (0.90-4.30)	Age, alcohol consumption, smoking habits, total energy	Outcome is mortality
		120/			Mortality, colon cancer,	≥60 vs ≤14 times/month	1.80 (0.80-4.40)		
Sellers, 1998 COL01974 USA	IWHS, Prospective Cohort, Age: 55-69 years, W, Postmenopausal	180/ 35 216 10 years	SEER registry	Semi-quantitative FFQ	Incidence, colon cancer, no family history of crc	≥15.1 vs ≤10 servings/week	1.20 (0.80-1.90)	Age, history of polyps, total energy intake	Superseded by Bostick, 1994 COL00079
		61/			Family history of crc	≥15.1 vs ≤10 servings/week	0.80 (0.40-1.80)		
Giovannucci, 1994 COL00119	HPFS, Prospective Cohort,	251/ 47 949 6 years	Mailing to health professionals	FFQ	Incidence, colorectal cancer,	Q 5 vs Q 1	1.66 (1.14-2.42)	Age, energy intake	Used only in highest versus lowest analysis.

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Reasons for exclusion
USA	Age: 40-75 years, M, Health professionals	201/			Incidence, colon cancer,	129.5 vs 18.5 g/day	1.66 (1.04-2.65)	Age, alcohol consumption, aspirin use, BMI, dietary fibre intake, history of previous polyp and prior endoscopy, methionine intake, parental history of colon cancer, physical activity	Superseded by Fung, 2010 COL40828
		89/			Incidence, distal colon cancer,	Q 5 vs Q 1	1.78 (0.97-3.25)		
		69/			Incidence, proximal colon cancer,	Q 5 vs Q 1	0.87 (0.43-1.76)		
		46/			Incidence, rectal cancer,	Q 5 vs Q 1	1.22 (0.36-4.14)		
Thun, 1992 COL01224 USA, Puerto Rico	CPS II, Nested Case Control, Age: 30- years, M/W	611/ 3051 controls 6 years	Cancer registry and death certificates and medical records	Questionnaire	Mortality, colon cancer, men	Q 5 vs Q 1	1.21	Age, sex, ethnicity	Outcome is mortality
		539/ 2695 controls			Women	Q 5 vs Q 1	1.05		
						≥134 vs ≤58 g/day	1.77 (1.09-2.88)		

Figure 81 RR estimates of colorectal cancer by levels of red and processed meat

Figure 82 RR (95% CI) of colorectal cancer for the highest compared with the lowest level of red and processed meat

Author	Year	Sex	high vs low red and processed meat RR (95% CI)	studydescription	Comparison
Shin	2014	W	1.29 (1.12, 1.49)	KNHIC	≥4 vs ≤1 times/week
Shin	2014	M	1.15 (1.04, 1.27)	KNHIC	≥4 vs ≤1 times/week
Bamia	2013	M/W	1.08 (0.99, 1.18)	EPIC	151.5 vs 43.9 g/day
Ollberding	2012	M/W	0.93 (0.83, 1.05)	MEC	68.96 vs 16.18 g/1000 kcal/day
Kim	2011	M/W	1.23 (1.13, 1.35)	Korean Cohort Study	≥4 vs ≤1 times/week
Lee	2009	W	0.90 (0.70, 1.40)	SWHS	≥89 vs ≤32.9 g/day
Cross	2007	M/W	1.24 (1.12, 1.36)	NIH-AARP	62.7 vs 9.8 g/1000kcal/day
Kabat	2007	W	1.12 (0.86, 1.46)	NBSS	≥40.3 vs ≤14.24 g/day
Berndt	2006	M/W	1.32 (0.86, 2.02)	CLUE II study	≥86.3 vs <44.0
Larsson	2005	W	1.32 (1.03, 1.68)	SMC	≥94 vs ≤49 g/day
Lin	2004	W	0.66 (0.40, 1.09)	WHS	1.42 vs 0.13 servings/day
Flood	2003	W	1.10 (0.83, 1.45)	BCDDP	52.2 vs 6.1 g/1000kcal/day
Pietinen	1999	M	1.10 (0.70, 1.70)	ATBC	203 vs 79 g/day
Chen	1998	M	1.17 (0.68, 2.02)	PHS	>1 vs ≤0.5 servings/day
Giovannucci	1994	M	1.66 (1.14, 2.42)	HPFS	129.5 vs 18.5 g/day

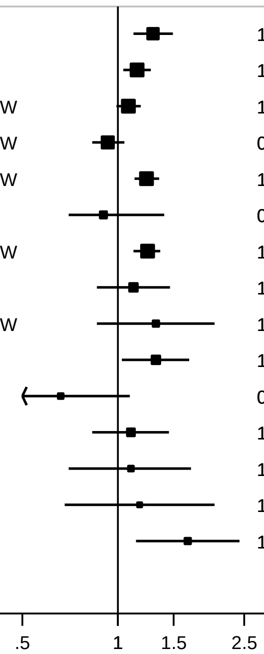


Figure 83 RR (95% CI) of colorectal cancer for 100g/day increase of red and processed meat

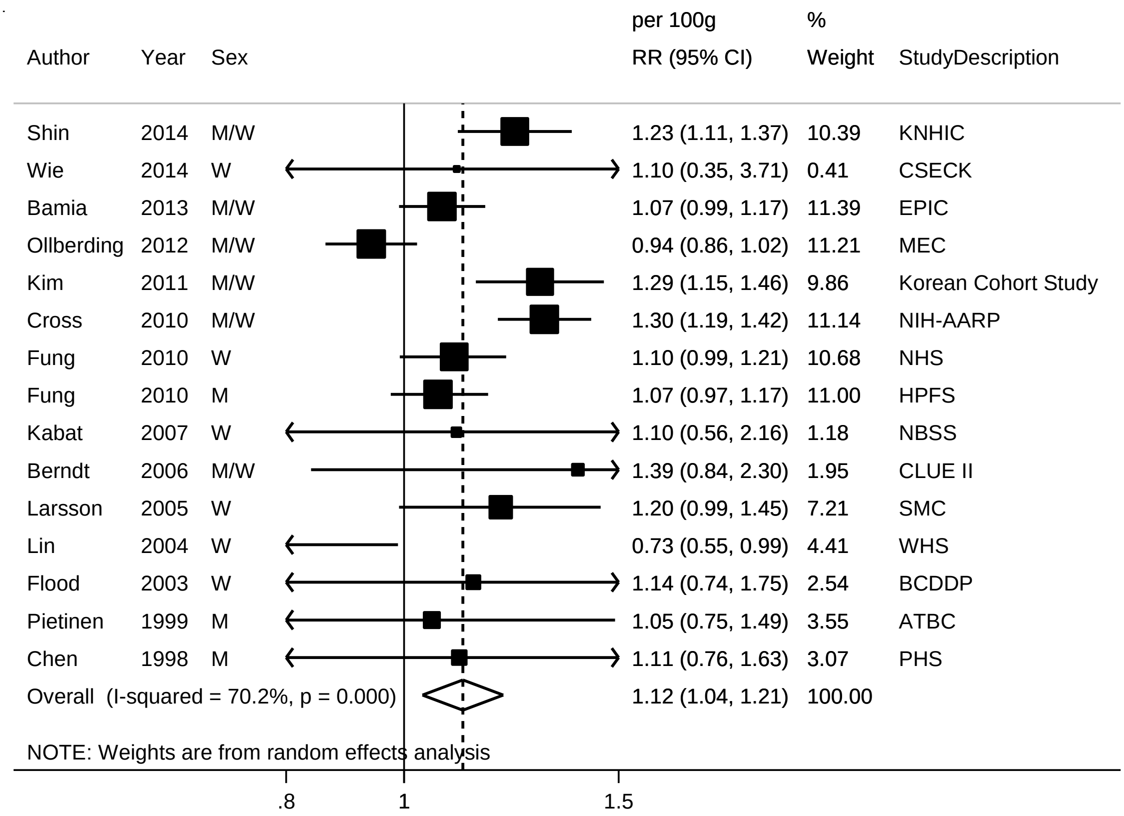


Figure 84 Funnel plot of studies included in the dose response meta-analysis of red and processed meat and colorectal cancer

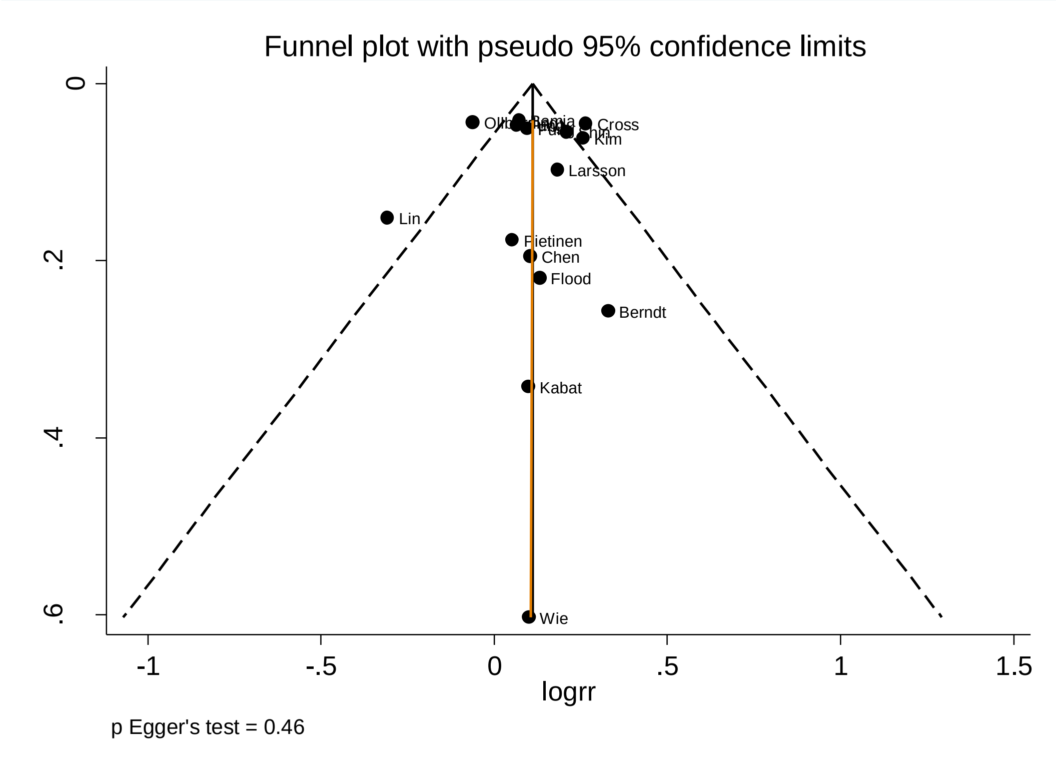


Figure 85 RR (95% CI) of colorectal cancer for 100g/day increase of red and processed meat by sex

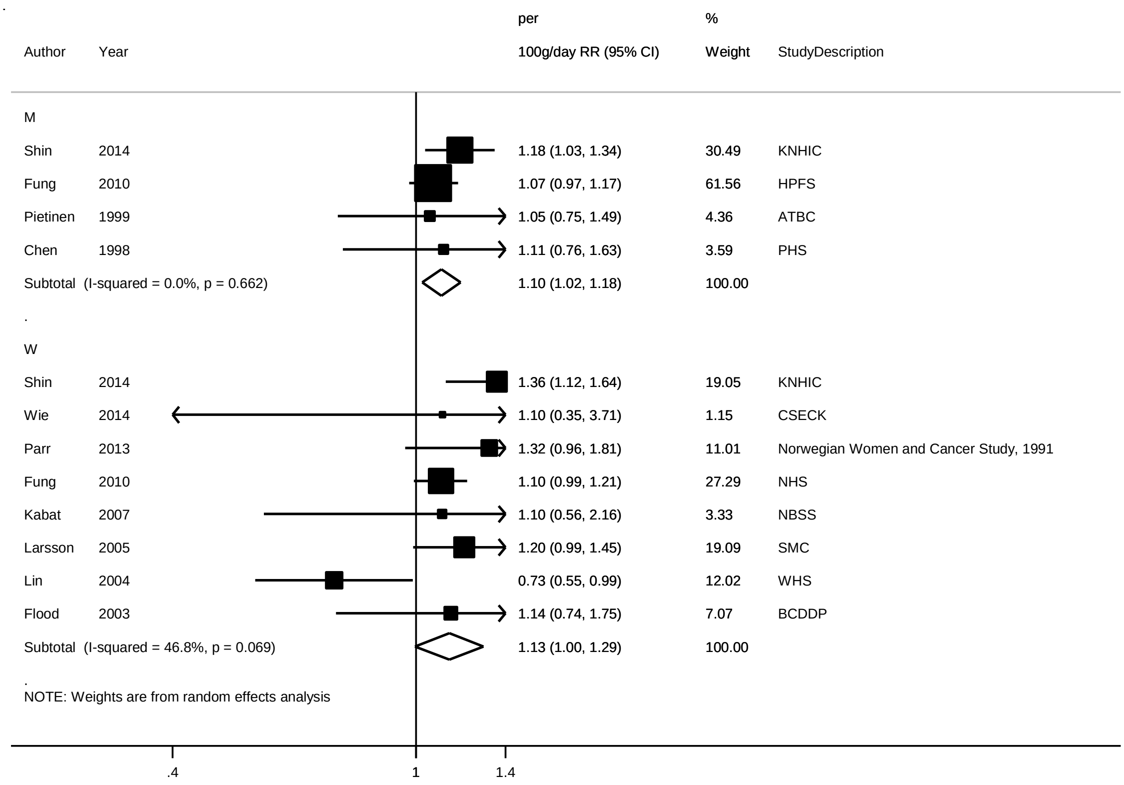


Figure 86 RR (95% CI) of colorectal cancer for 100g/day increase of red and processed meat by location

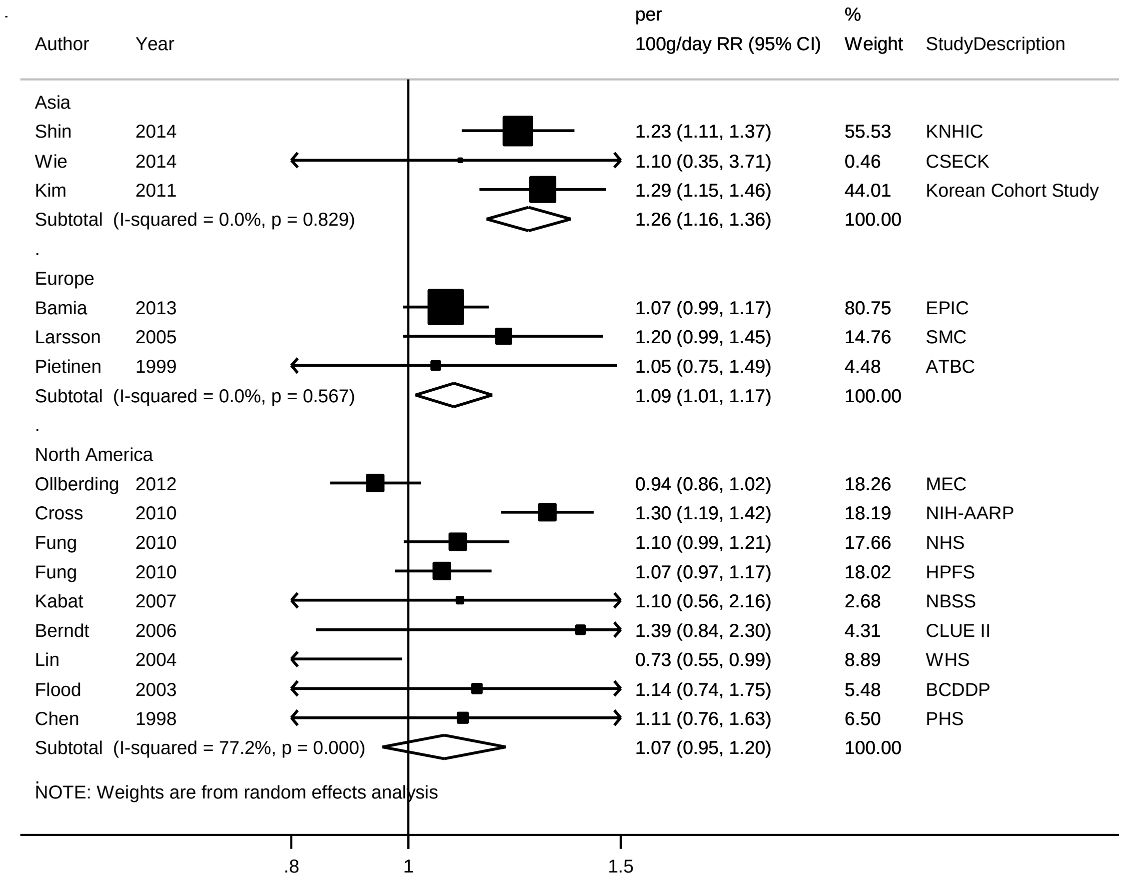


Figure 87 Relative risk of colorectal cancer and red and processed meat estimated using non-linear models

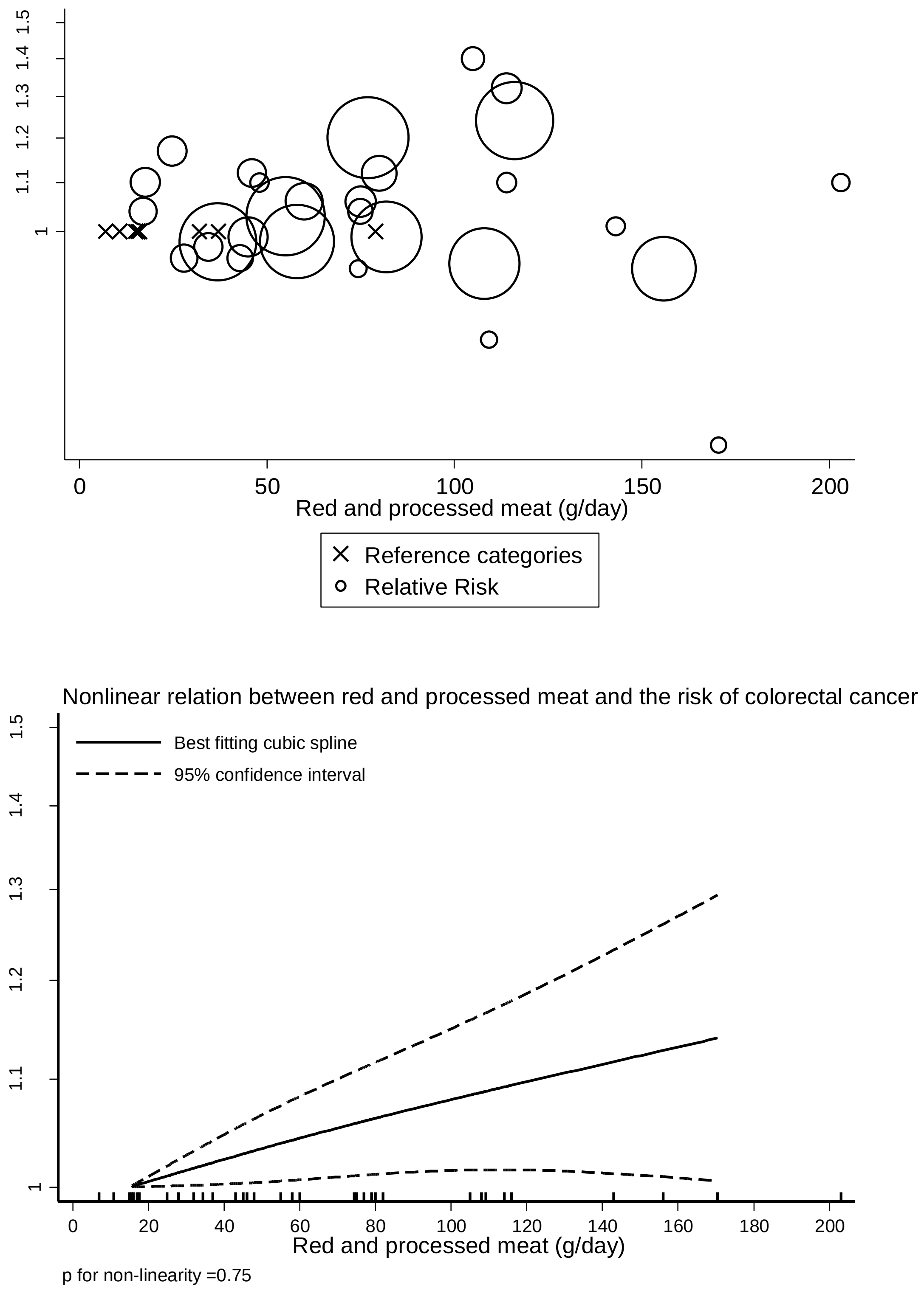


Table 57 Table with red and processed meat values and corresponding RRs (95% CIs) for non-linear analysis of red and processed meat and colorectal cancer

Red and processed meat(g/day)	RR (95%CI)
15	1
25	1.00(1.00-1.01)
45	1.02(1.00-1.05)
60	1.04(1.00-1.08)
100	1.08(1.02-1.16)
150	1.12(1.00-1.26)

Figure 88 RR estimates of colon cancer by levels of red and processed meat

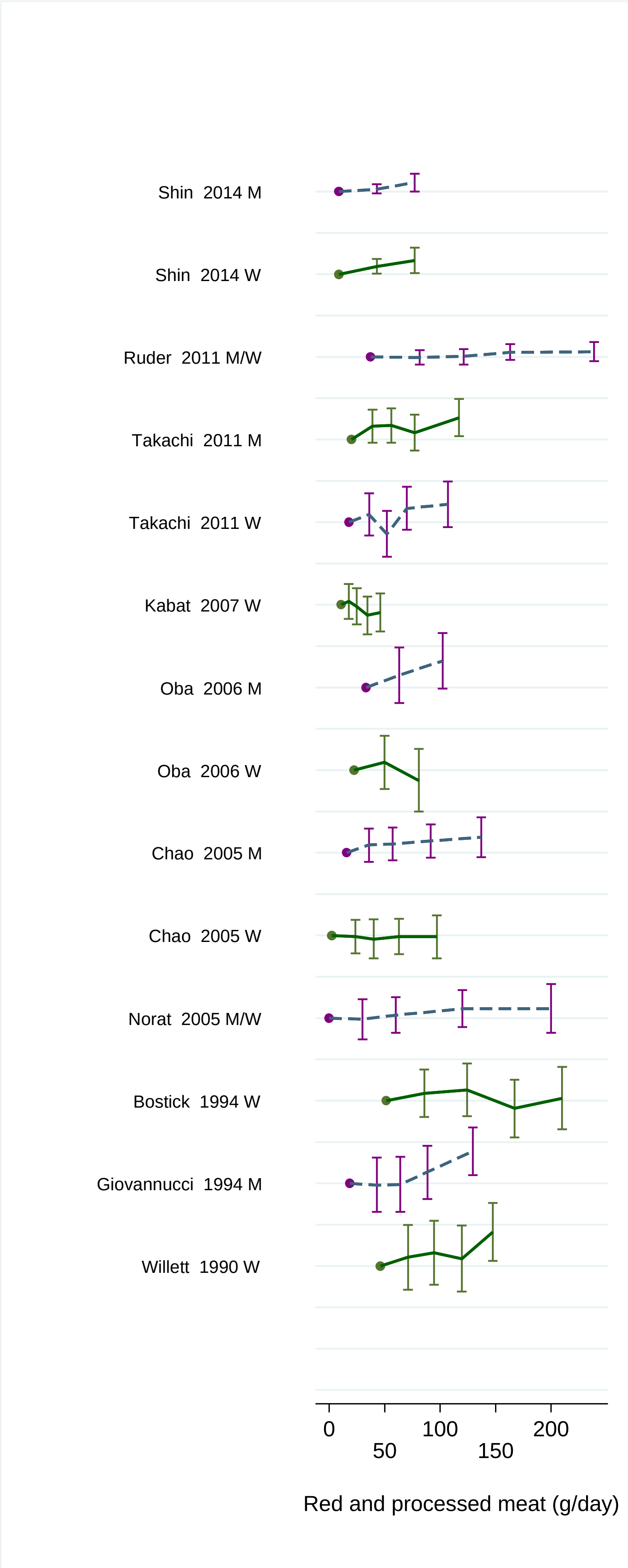


Figure 89 RR (95% CI) of colon cancer for the highest compared with the lowest level of red and processed meat

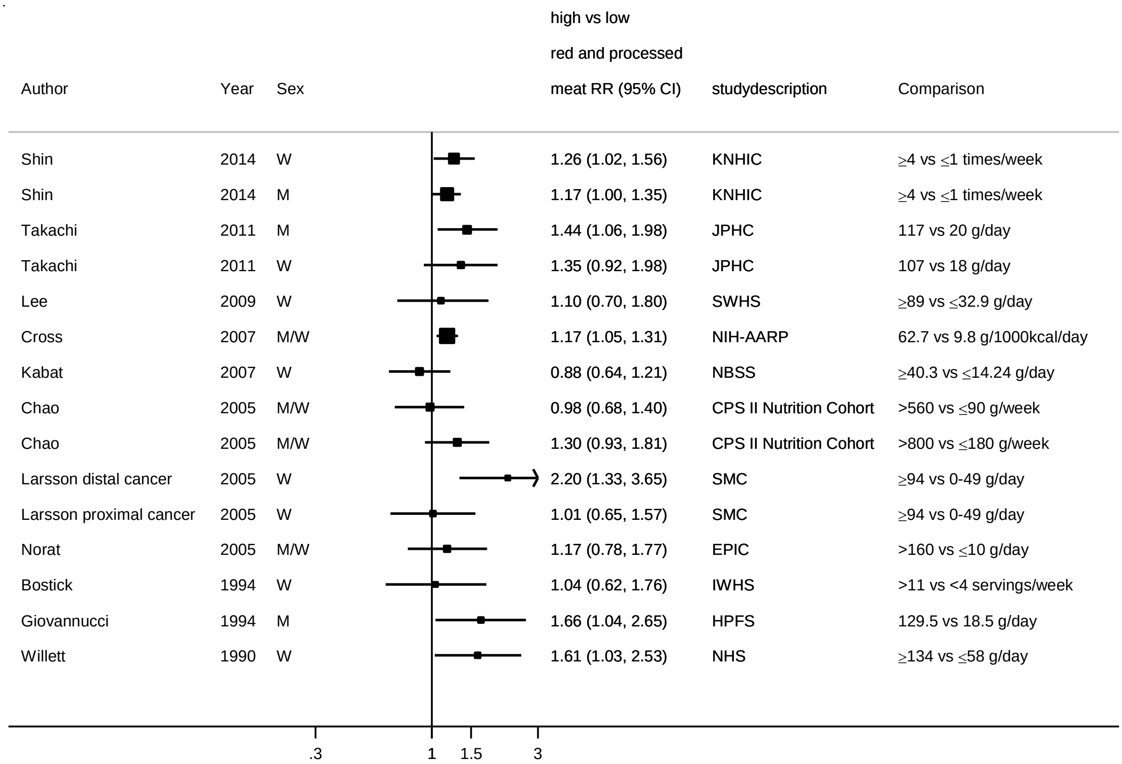


Figure 90 RR (95% CI) of colon cancer for 100g/day increase of red and processed meat

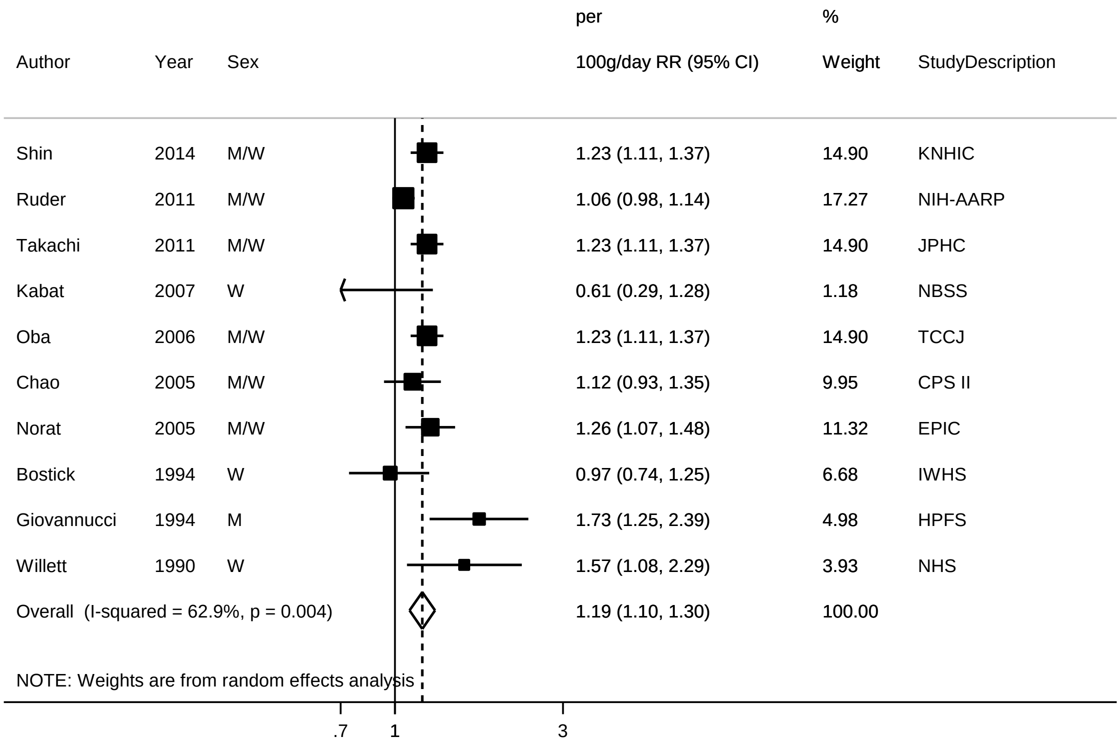


Figure 91 Funnel plot of studies included in the dose response meta-analysis of red and processed meat and colon cancer

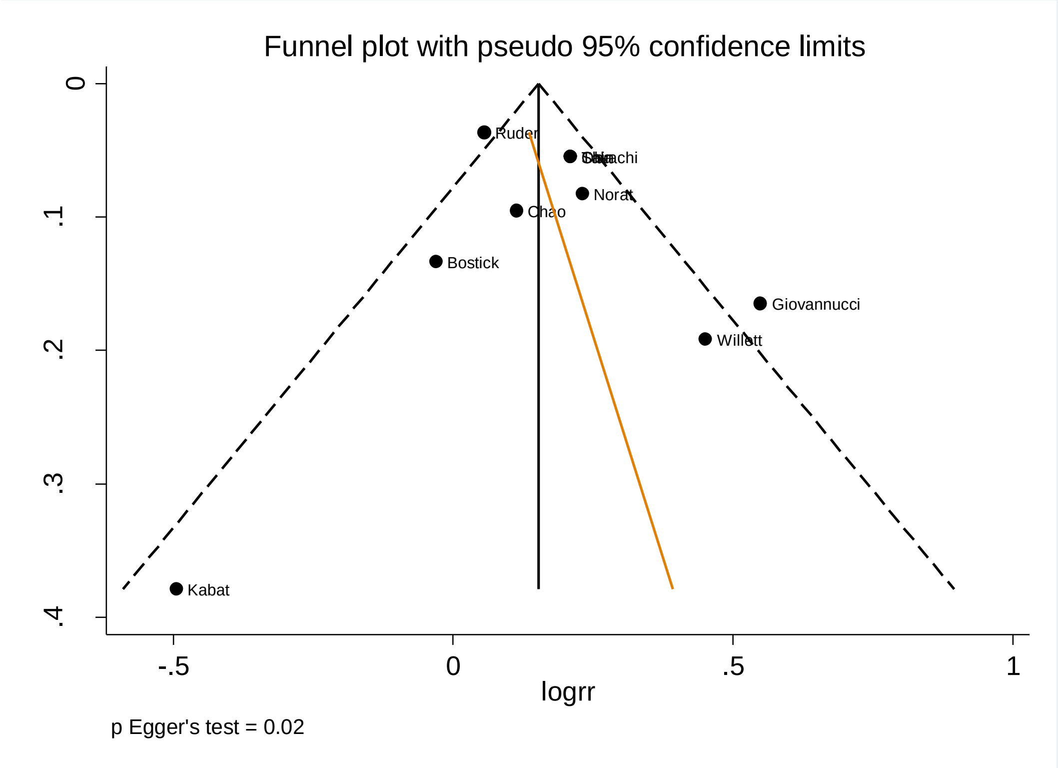


Figure 92 RR (95% CI) of colon cancer for 100g/day increase of red and processed meat by sex

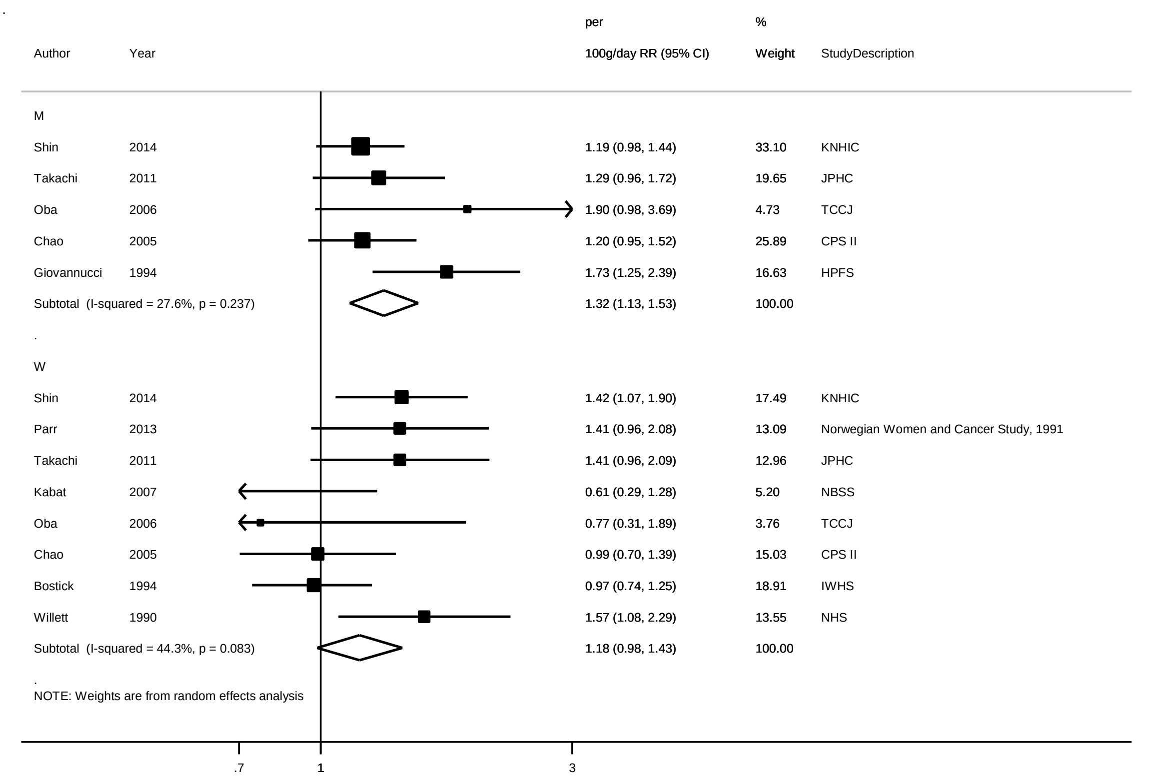


Figure 93 RR (95% CI) of colon cancer for 100g/day increase of red and processed meat by location

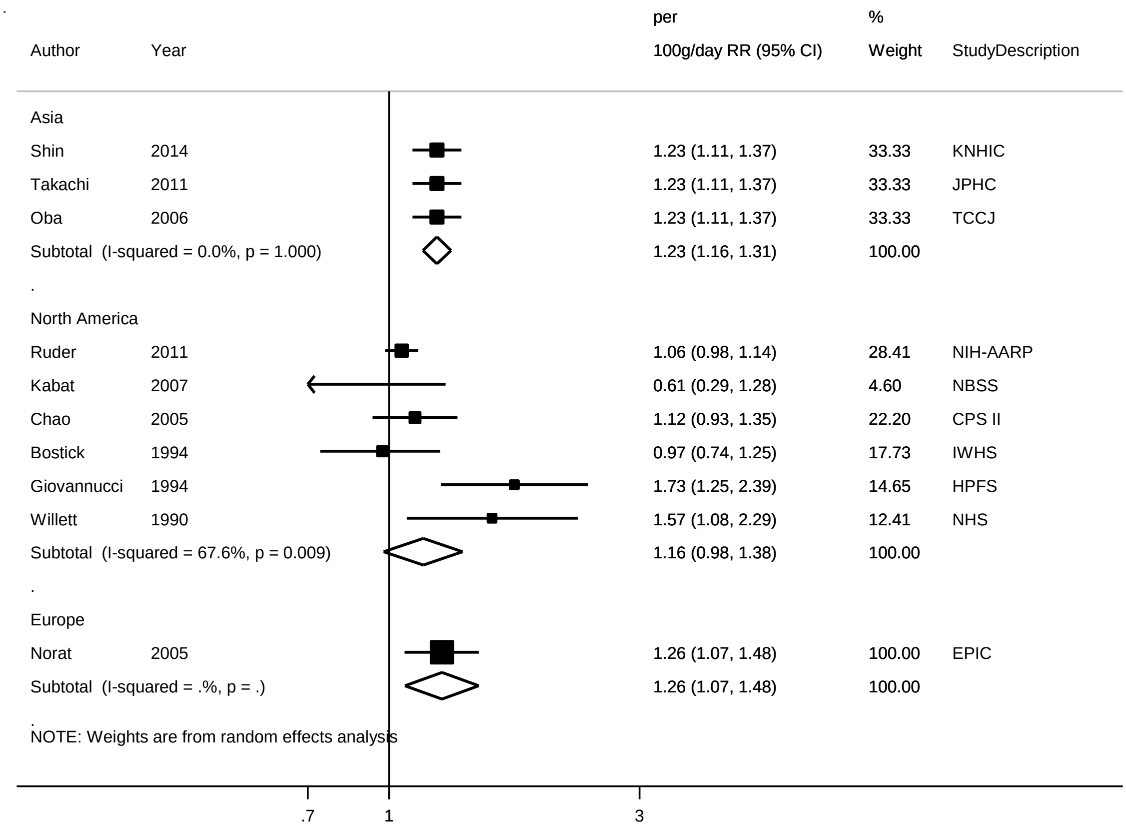
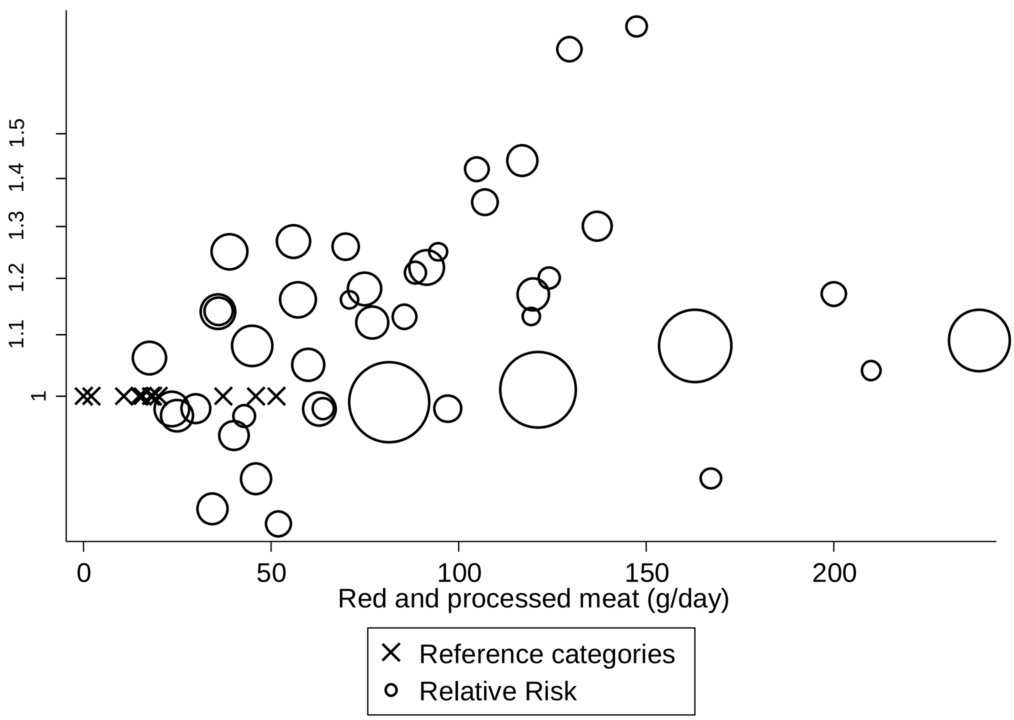


Figure 94 Relative risk of colon cancer and red and processed meat estimated using non-linear models



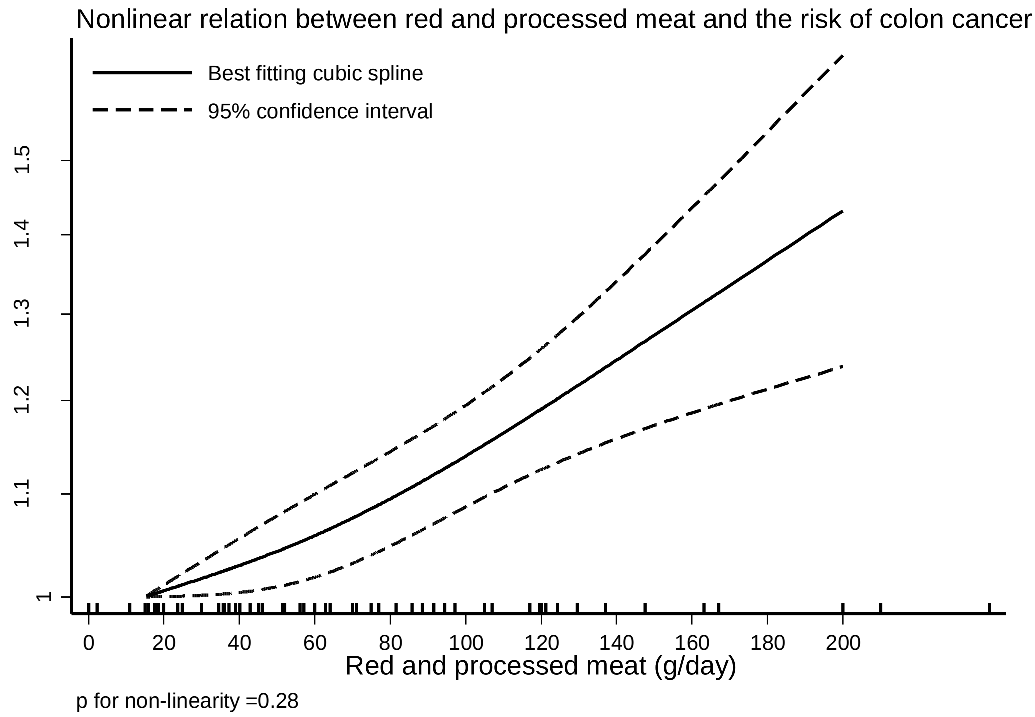


Table 58 Table with red and processed meat values and corresponding RRs (95% CIs) for non-linear analysis of red and processed meat and colon cancer

Red and processed meat(g/day)	RR (95%CI)
15	1
25	1.01(1.00-1.02)
45	1.03(1.00-1.06)
60	1.05(1.02-1.09)
100	1.15(1.09-1.20)
150	1.26(1.17-1.37)

Figure 95 RR estimates of rectal cancer by levels of red and processed meat

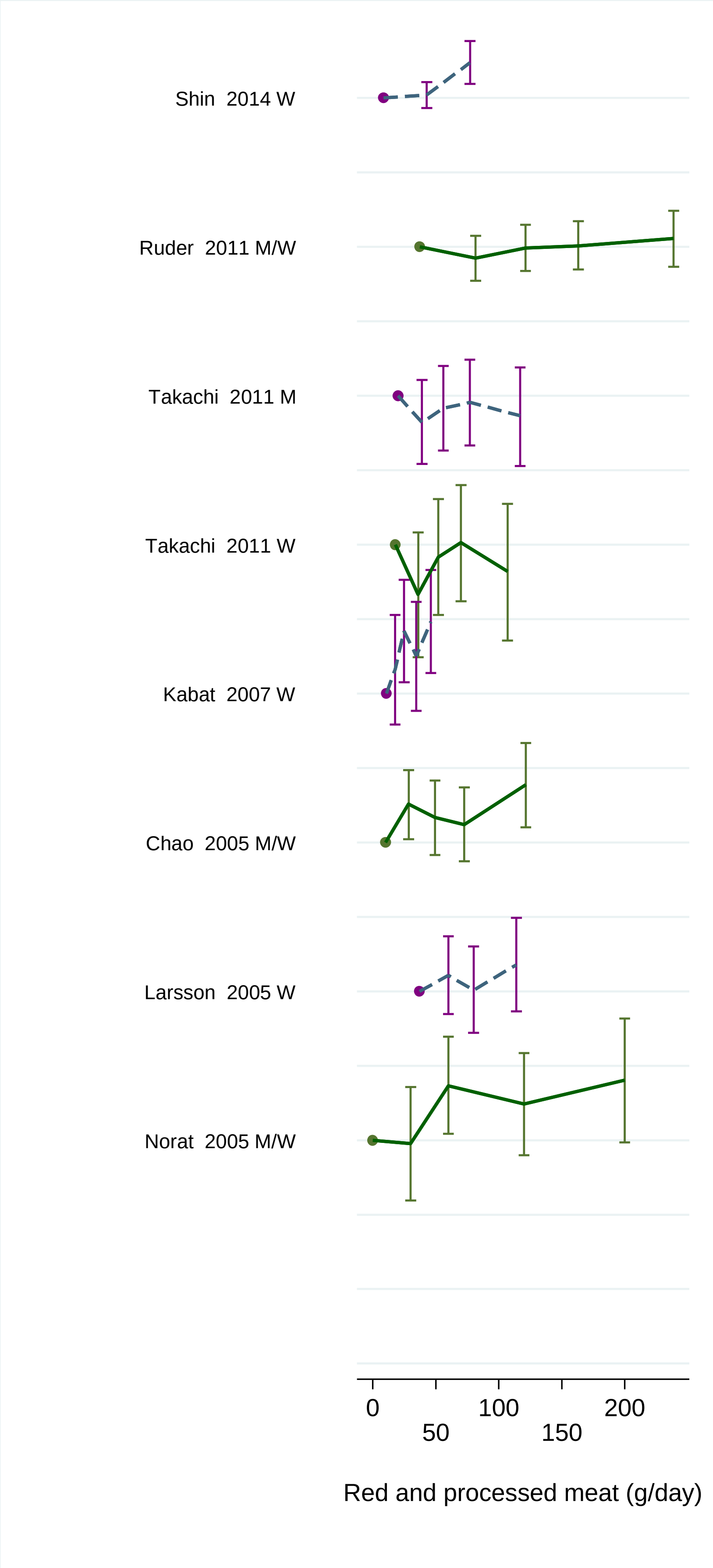


Figure 96 RR (95% CI) of rectal cancer for the highest compared with the lowest level of red and processed meat

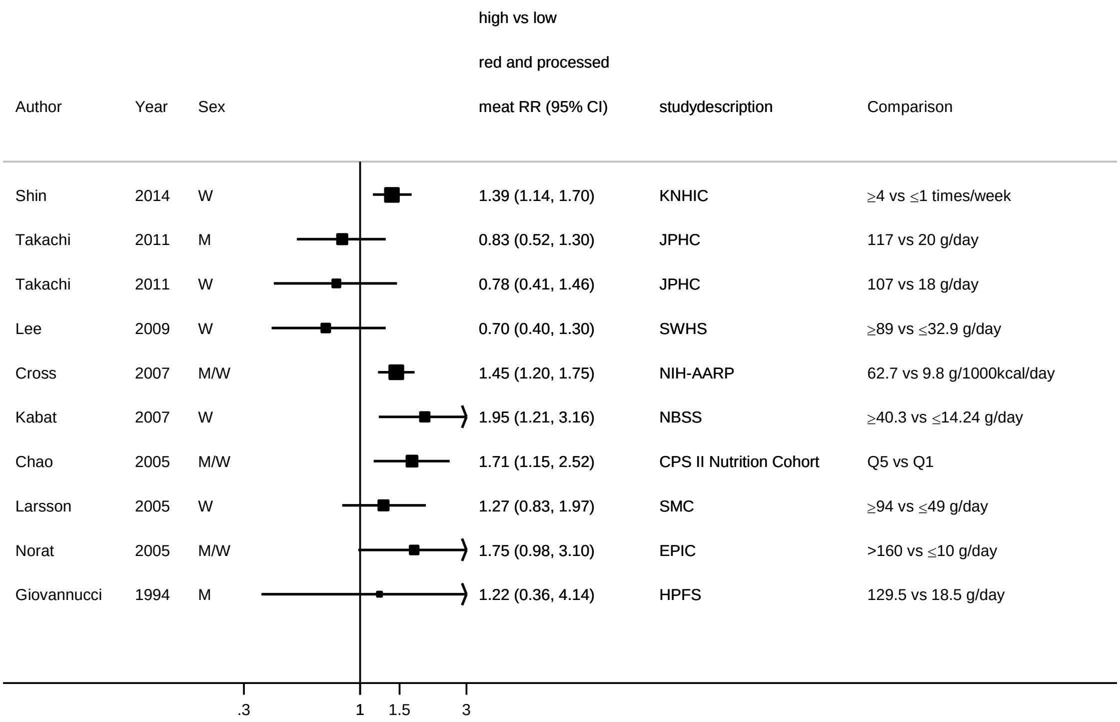


Figure 97 RR (95% CI) of rectal cancer for 100g/day increase of red and processed meat

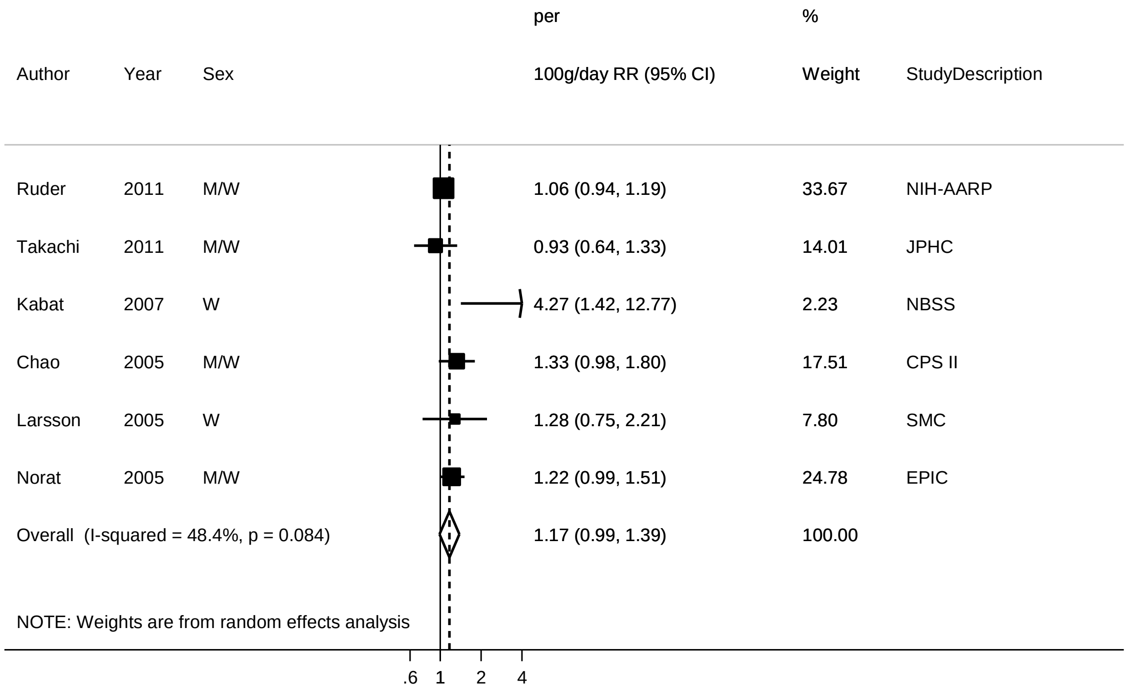


Figure 98 Funnel plot of studies included in the dose response meta-analysis of red and processed meat and rectal cancer

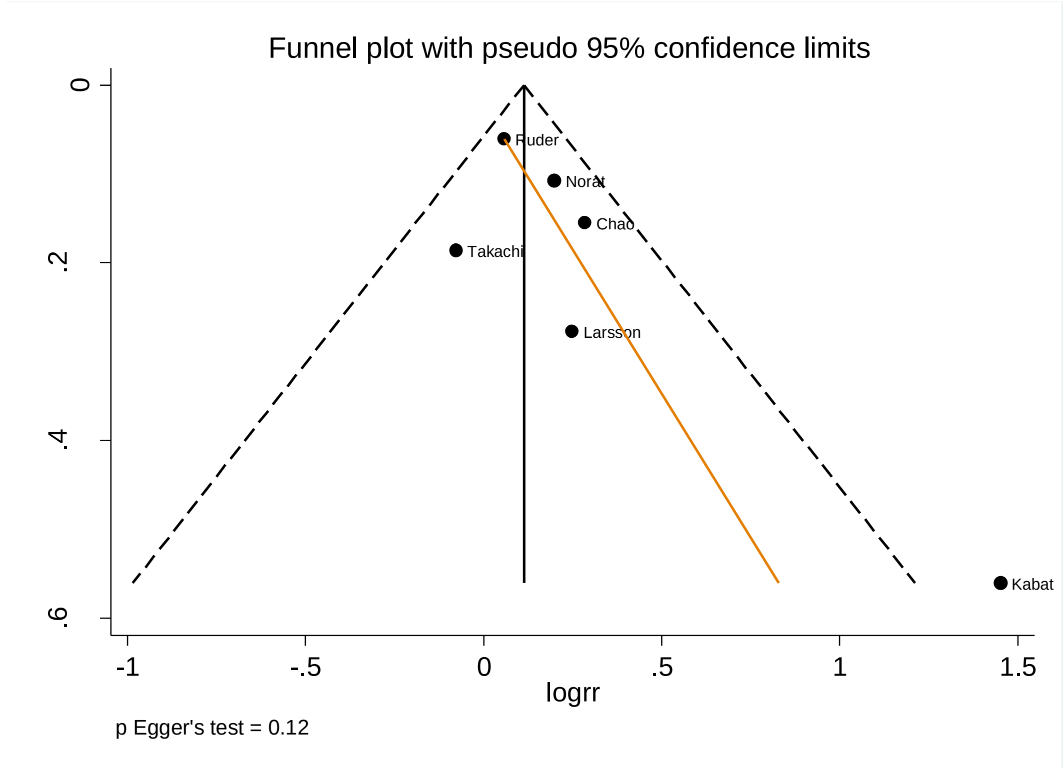


Figure 99 RR (95% CI) of rectal cancer for 100g/day increase of red and processed meat by sex

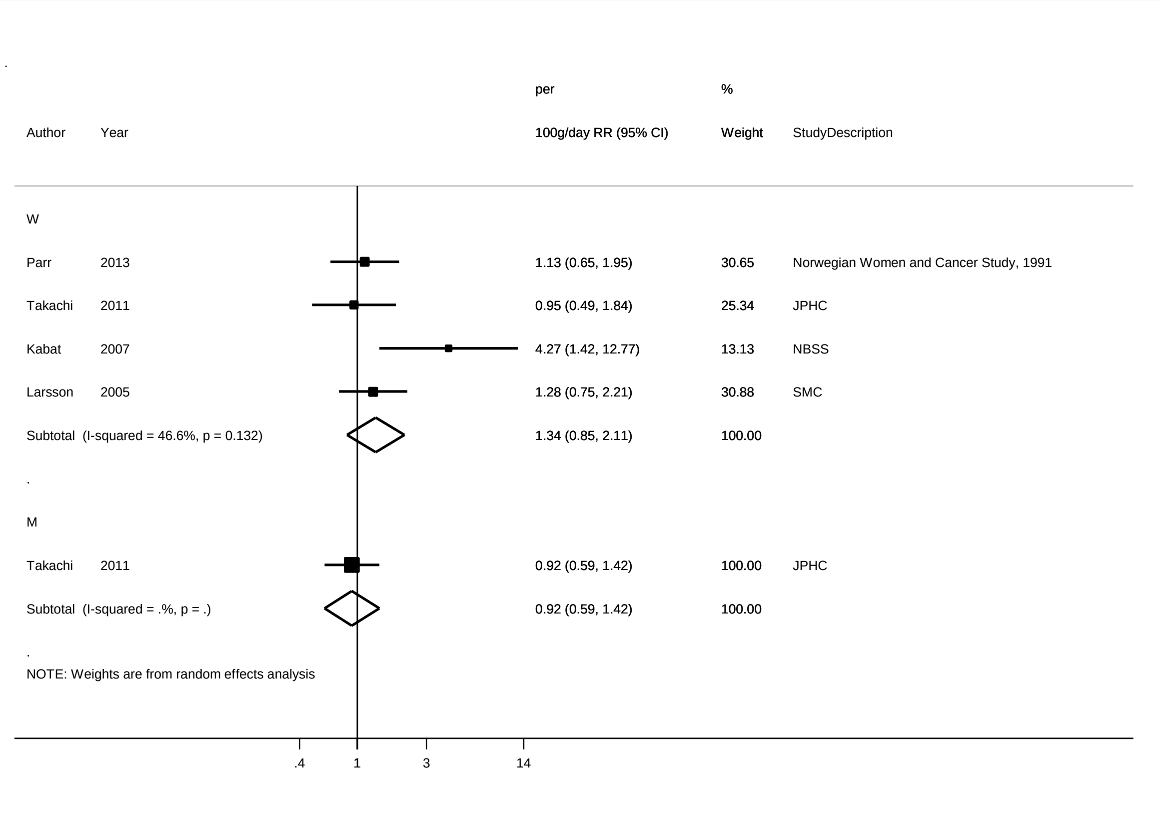


Figure 100 RR (95% CI) of rectal cancer for 100g/day increase of red and processed meat by location

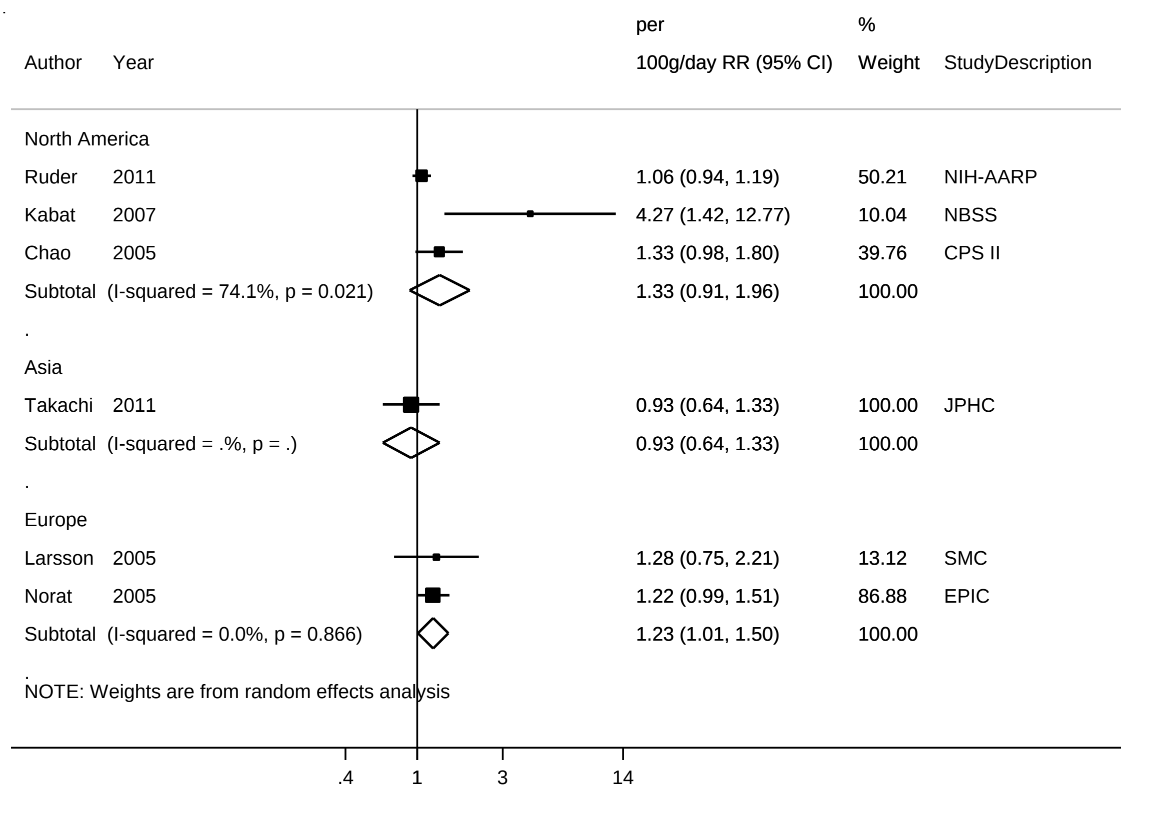
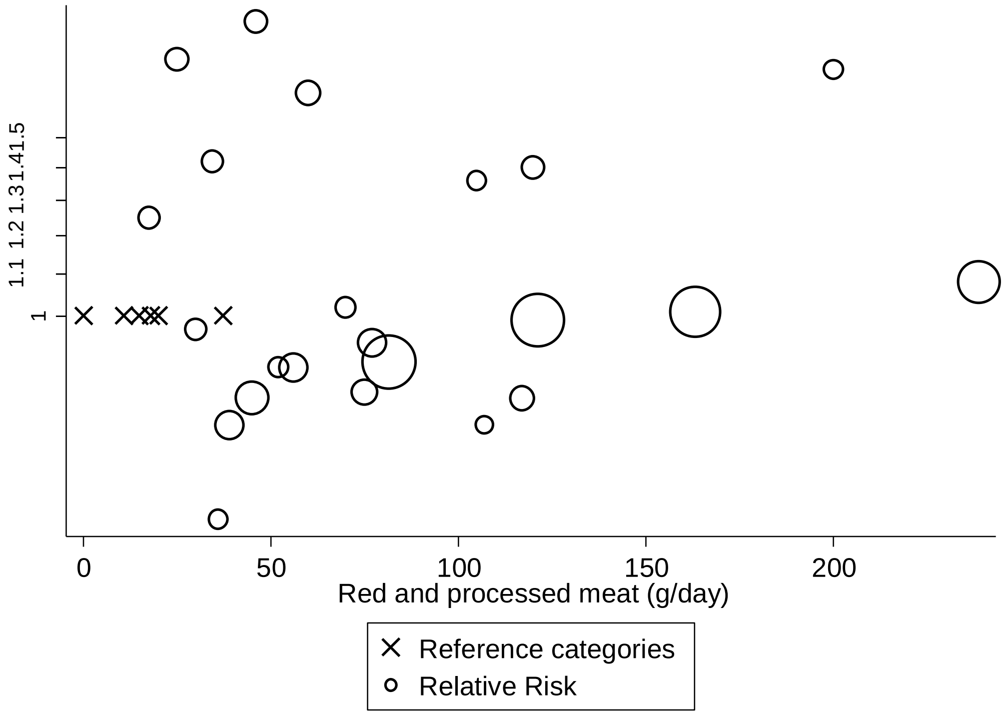


Figure 101 Relative risk of rectal cancer and red and processed meat estimated using non-linear models



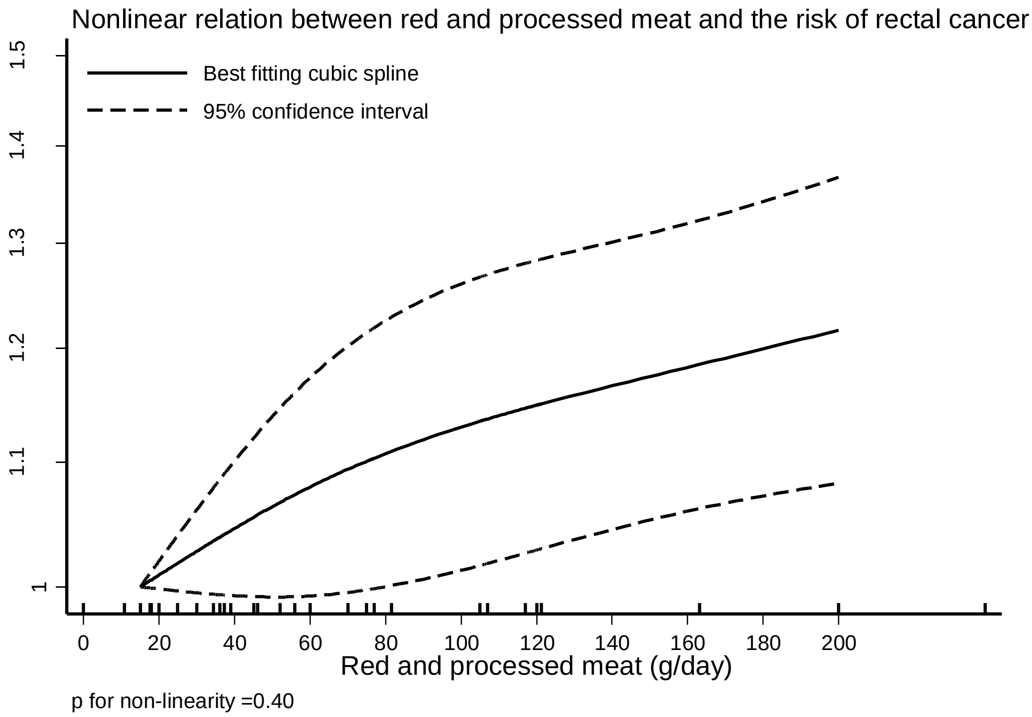


Table 59 Table with red and processed meat values and corresponding RRs (95% CIs) for non-linear analysis of red and processed meat and rectal cancer

Red and processed meat(g/day)	RR (95%CI)
15	1
25	1.00(1.00-1.02)
45	1.03(1.00-1.07)
60	1.06(1.01-1.09)
100	1.13(1.08-1.18)
150	1.27-1.17-1.37)

2.5.1.2 Processed meat

Cohort studies

For the dose-response analysis all results were converted to a common scale (grams per day) and 50 grams was used as a standard serving or portion size in studies that reported frequency of intake. The dose-response analyses were presented for an increment of 50 grams per day. For studies that presented the results in grams per 1000 kcal per day the intakes were converted to absolute intakes using the mean or median energy intake reported by the studies.

Summary

Main results:
Four new publications from four studies were identified, two superseded previous publications included in the 2010 SLR.

Colorectal cancer:
Ten studies (10738 cases) were included in the dose-response meta-analysis of processed meat and colorectal cancer. A significant association with low heterogeneity was observed. Three studies showed a significant association (EPIC, NIH-AARP and MCCS). After stratification by sex and location the relationship remained significant for European and North American studies. There was no evidence of publication bias (p=0.29). There was no evidence of a non-linear association (p=0.93).
The overall association remained statistically significant in influence analysis. The summary RRs ranged from 1.13(95% CI=1.04-1.22) when Cross, 2010 was omitted to 1.18(95% CI=1.09-1.28) when Pietinen, 1999 was omitted.

Colon cancer:
Twelve studies (8599 cases) were included in the dose-response meta-analysis of processed meat and colon cancer. A significant association with low heterogeneity was observed. After stratification by sex and location the relationship remained significant and with none or low heterogeneity in the subgroup of women, men, North American and European studies. There was evidence of publication bias (p<0.01). There was no evidence of a non-linear association (p=0.15).
The overall association remained statistically significant in influence analysis. The summary RRs ranged from 1.17(95% CI=1.09-1.26) when Oba, 2006was omitted to 1.27(95% CI=1.11-1.44) when Norat, 2005 was omitted.

Rectal cancer:
Ten studies (3029 cases) were included in the dose-response meta-analysis of processed meat and rectal cancer. A borderline significant association with no heterogeneity was observed. After stratification by sex and location the relationship was not significant in any of the subgroups. There was no evidence of publication bias (p=0.61). There was no evidence of a non-linear association (p=0.32).
The overall association remained statistically significant in influence analysis. The summary RRs ranged from 1.07(95% CI=0.99-1.17) when English, 2004 was omitted to 1.09(95% CI=0.95-1.25) when Ruder, 2011 was omitted.

Study quality:
Processed meat was generally described as processed meat, preserved meat or cured meat, but individual items included in the meat group could vary between the studies. Although we cannot rule out residual confounding, most studies included in the meta-analyses adjusted results by smoking, alcohol consumption, BMI and physical activity in addition to age and sex.

Pooling project of cohort studies:
In a pooled analysis of the Genetics and Epidemiology of Colorectal Cancer Consortium (GECCO) and the Colon Cancer Family Registry (CCFR) (Kantor, 2014) seven American cohort studies were included (HPFS, MEC, NHS, PHS, PLCO, VITAL, WHI; 3 488 cases) for each serving/day increase of processed meat the RR was 1.48 (95% CI 1.30–1.70).
In the UK Dietary Cohort Consortium (7 cohort studies), processed meat intake was not related to the risk of colorectal cancer in a nested case-control of 579 cases and 1,996 controls matched on age, sex and recruitment date (Spencer, 2010). The RR for the highest compared to the lowest intake was 0.76 (0.56–1.03). Similar relationships were observed for colon and rectal cancers.

Meta-analysis:
Two meta-analysis were published after the 2010 SLR. One showed that processed meat intake was significantly related to the risk of colorectal (RR highest vs lowest =1.17, 95% CI =1.09-1.25), colon (RR highest vs lowest = 1.19, 95% CI =1.11-1.29), and rectal cancer (RR highest vs lowest = 1.19, 95% CI = 1.02-1.39) (Chan, 2011).

Another meta-analysis (Alexander, 2015), combined 9 studies with different outcomes (colorectal, colon and rectal cancer) and obtained a RR of 1.10(1.05-1.15) per 30g/day.

Table 60 Processed meat and colorectal cancer risk. Number of studies in the CUP SLR

	Number
Studies identified	13
Studies included in forest plot of highest compared with lowest exposure	12
Studies included in dose-response meta-analysis	10
Studies included in non-linear dose-response meta-analysis	10

Note: Include cohort, nested case-control and case-cohort designs

Table 61 Processed meat and colon cancer risk. Number of studies in the CUP SLR

	Number
Studies identified	14
Studies included in forest plot of highest compared with lowest exposure	12
Studies included in dose-response meta-analysis	12
Studies included in non-linear dose-response meta-analysis	11

Note: Include cohort, nested case-control and case-cohort designs

Table 62 Processed meat and rectal cancer risk. Number of studies in the CUP SLR

	Number
Studies identified	12
Studies included in forest plot of highest compared with lowest exposure	10
Studies included in dose-response meta-analysis	10
Studies included in non-linear dose-response meta-analysis	11

Note: Include cohort, nested case-control and case-cohort designs

Table 63 Processed meat and colorectal cancer risk. Summary of the dose-response meta-analysis in the 2010 SLR and 2015 SLR.

	2010 SLR	**2015 SLR**
Increment unit used	50g/day	50g/day
Studies (n)	9	10
Cases (total number)	10863	10738
RR (95%CI)	1.18 (1.10-1.28)	1.16(1.08-1.26)
Heterogeneity (I^2, p-value)	12%, 0.33	20.1%,0.26

Stratified analysis by sex		
Men	**2010 SLR**	**2015 SLR**
Studies (n)	2	2
RR (95%CI)	1.11 (0.86- 1.44)	1.11(0.86-1.43)
Heterogeneity (I^2, p-value)	0.35, 0.22	33.6%, 0.22
Women		
Studies (n)	4	5

RR (95%CI)	1.09 (0.88- 1.33)	1.18(0.99-1.41)
Heterogeneity (I^2, p-value)	0%, 0.48	18.5%, 0.29

Stratified analysis by geographic location (no analysis in 2005 or 2010 SLR)			
2015 SLR	**Asia**	**Europe**	**North America**
Studies (n)	2	4	4
RR (95%CI)	1.37(0.76-2.49)	1.13(1.03-1.24)	1.15(0.98-1.34)
Heterogeneity (I^2, p-value)	30.9%, 0.23	0%, 0.74	48.7%, 0.12

Table 64 Processed meat and colon cancer risk. Summary of the dose-response meta-analysis in the 2010 SLR and 2015 SLR.

	2010 SLR	**2015 SLR**
Increment unit used	50g/day	50g/day
Studies (n)	9	12
Cases (total number)	6338	8599
RR (95%CI)	1.24 (1.13-1.36)	1.23(1.11-1.35)
Heterogeneity (I^2, p-value)	0%, 0.55	26.2%, 0.18

Stratified analysis by sex		
Men	**2010 SLR**	**2015 SLR**
Studies (n)	3	5
RR (95%CI)	1.64 (0.94- 2.84)	1.58(1.11-2.23)
Heterogeneity (I^2, p-value)	62%, 0.03	49.5%, 0.09
Women		
Studies (n)	4	8
RR (95%CI)	1.38 (1.06 -1.78)	1.32(1.13-1.55)
Heterogeneity (I^2, p-value)	0%, 0.65	0%, 0.91

Stratified analysis by geographic location (no analysis in 2005 or 2010 SLR)			
2015 SLR	**Asia**	**Europe**	**North America**
Studies (n)	4	3	5
RR (95%CI)	1.59(0.93-2.71)	1.19(1.05-1.35)	1.14(1.06-1.23)
Heterogeneity (I^2, p-value)	43.3%, 0.15	0%, 0.76	3.4%, 0.39

Table 65 Processed meat and rectal cancer risk. Summary of the dose-response meta-analysis in the 2010 SLR and 2015 SLR.

	2010 SLR	**2015 SLR**
Increment unit used	50g/day	50g/day
Studies (n)	8	10
Cases (total number)	2565	3029
RR (95%CI)	1.12 (0.99-1.28)	1.08(1.00-1.18)

Heterogeneity (I^2, p-value)	0%, 0.56	0%, 0.77

Stratified analysis by sex (no analysis in 2005 or 2010 SLR)		
2015 SLR	**Men**	**Women**
Studies (n)	3	5
RR (95%CI)	0.82(0.52-1.29)	1.12(0.86-1.46)
Heterogeneity (I^2, p-value)	0%, 0.63	0%, 0.82

Stratified analysis by geographic location (no analysis in 2005 or 2010 SLR)			
2015 SLR	**Asia**	**Europe**	**North America**
Studies (n)	3	3	3
RR (95%CI)	1.25(0.64-2.45)	1.08(0.92-1.26)	1.08(0.98-1.19)
Heterogeneity (I^2, p-value)	26.7%, 0.26	0%, 0.84	0%, 0.61

Table 66 Processed meat and colorectal cancer risk. Results of meta-analyses and pooled analyses of prospective studies published after the 2005 SLR.

Author, Year	Number of cohort studies	Total number of cases	Studies country, area	Outcome	Comparison	RR (95%CI)	P trend	Heterogeneity (I^2, p value)
Pooled analysis								
Kantor, 2014	7 nested case-control studies HPFS, MEC, NHS, PHS, PLCO, VITAL, WHI	3 488	North America	Colorectal cancer	Per 1 serving/day	1.48 (1.30–1.70)		
Spencer, 2010	7 Guernsey Study, EPIC- Norfolk, EPIC-Oxford, NSHD, Oxford Vegetarian Study Oxford Vegetarian Study, UKWCS, Whitehall II	579 cases 1996 controls	UK	Colorectal cancer	≥30 vs <5 g/day Per 50g/day	0.76 (0.56–1.03) 0.88 (0.68–1.15)	0.36	
				Colon cancer	≥30 vs <5 g/day Per 50g/day	0.90 (0.62–1.31) 1.01 (0.73–1.40)	0.94	
				Rectal cancer	≥30 vs <5 g/day Per 50g/day	0.50 (0.29–0.85) 0.65 (0.40–1.04)	0.07	
Meta-analysis								
Alexander, 2010	9		Europe, Asia and North America	Colorectal, colon and rectal cancer combined	30g/day	1.10 (1.05-1.15)		

Chan, 2011	9	11358	Europe, Asia and North America	Colorectal cancer	Per 50g/day	1.18(1.10-1.28)		12.2%, 0.33
	10	5426		Colon cancer	Per 50g/day	1.24(1.13-1.35)		0%, 0.65
	8	2091		Rectal cancer	Per 50g/day	1.12(0.99-1.28)		0%, 0.56

* Heterogeneity (I^2, p value) only reported when available

Table 67 Processed meat and colorectal cancer risk. Main characteristics of studies included in the CUP SLR dose-response meta-analysis

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Missing data derived for analysis
Parr, 2013 COL40955 Norway	NOWAC, Prospective Cohort, Age: 41-70 years, W	674/ 84 538 11.1 years	Cancer registry	FFQ	Incidence, colorectal cancer	≥60 vs ≤15 g/day	1.59 (1.19-2.12)	Age, alcohol, BMI, calcium, energy, fibre, physical activity, smoking	Only included in subgroup analysis. Component of the EPIC study. Superseded by Norat, 2005 COL01698
						per 50 g/day	1.21 (1.00-1.47)		
		459/			Incidence, colon cancer	≥60 vs ≤15 g/day	1.54 (1.08-2.19)		
						per 50 g/day	1.22 (0.97-1.54)		
		215/			Incidence, rectal cancer	≥60 vs ≤15 g/day	1.71 (1.02-2.85)		
						per 50 g/day	1.18 (0.84-1.67)		
Ollberding, 2012 COL40941 Hawaii, USA	MEC, Prospective Cohort, Age: 45-75 years, M/W	3 404/ 165 717 8.1 years	Cancer registry and national death Index	FFQ	Incidence, colorectal cancer	17.98 vs 1.7 g/1000 kcal/day	1.06 (0.94-1.19)	Age, sex, age at cohort entry In log linear model, alcohol consumption, BMI, calcium, dietary fibre, energy intake, ethnicity, family history of colorectal cancer, folate, history of diabetes, history of polyp diagnosis, HRT use, non-steroid	Distribution of person-years by exposure category. Mid-points of exposure categories. Intakes in g/1000kcal/day converted to g/day using average energy intake per each quantile

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Missing data derived for analysis
								anti-inflammatory drug use, pack yrs of smoking, vigorous physical activity, vitamin d	
Ruder, 2011 COL40896 USA	NIH-AARP, Prospective Cohort, Age: 50-71 years, Retired	2 819/ 292 797	Cancer registry and national health database	FFQ	Incidence, colon cancer	1.02 vs 0.05 times/day	1.24 (1.06-1.45)	Sex, age at baseline, alcohol consumption, aspirin use, BMI, educational level, energy, energy, history of colon cancer, HRT use, physical activity, processed meat, race, smoking	Distribution of person-years by exposure category. Mid-points of exposure categories. Conversion from times/day to g/day
		985/			Incidence, rectal cancer	1.02 vs 0.05 times/day	1.30 (0.99-1.70)		
Takachi, 2011 COL41056 Japan	JPHC, Prospective Cohort, Age: 45-74 years, M/W	481/ 80 658 9 years	Hospital records + cancer registry	FFQ	Incidence, colon cancer, men	16 vs 0.2 g/day	1.27 (0.95-1.71)	Age, alcohol consumption, area, BMI, calcium, diabetes, energy, fibre, folate, physical activity, salted fish consumption,	Distribution of person-years by exposure category.
		307/			Women	15 vs 0.4 g/day	1.19 (0.82-1.74)		
		233/			Incidence, rectal cancer, men	16 vs 0.2 g/day	0.70 (0.45-1.09)		
		124/			Women	15 vs 0.4 g/day	0.98 (0.53-1.79)		

Author, Year, WCRF Code, Country	**Study name, characteristics**	**Cases/ Study size Follow-up (years)**	**Case ascertainment**	**Exposure assessment**	**Outcome**	**Comparison**	**RR (95%CI) Ptrend**	**Adjustment factors**	**Missing data derived for analysis**
								screening exams, smoking status, vitamin b6, vitamin d	
Cross, 2010 COL40794 USA	NIH-AARP, Prospective Cohort, Age: 50-71 years, M/W	2 719/ 300 948 7.2 years	Cancer registry and death certificates and questionnaires	FFQ	Incidence, colorectal cancer	22.3 vs 1.6 g/1000 kcal/day	1.16 (1.01-1.32)	Sex, BMI, dietary calcium intake, educational level, non-processed meat, smoking habits, total energy intake	Used for colorectal cancer, superseded by Ruder, 2011 COL40896 Distribution of person-years by exposure category. Mid-points of exposure categories. Intakes in g/1000kcal/day converted to g/day using average energy intake per each quantile
Balder, 2006 COL40622 Netherlands	NLCS, Case Cohort, Age: 55-69 years, M/W	869/ 120 852 9.3 years	Cancer registry	Semi-quantitative FFQ	Incidence, colorectal cancer, men	≥20 vs ≤0 g/day	1.18 (0.84-1.64)	Age at entry, alcohol intake, BMI, family history of colorectal cancer, recreational activity,	
		666/			Women	≥20 vs ≤0 g/day	1.05 (0.74-1.48)		
		539/			Incidence, colon cancer, men	≥20 vs ≤0 g/day	1.33 (0.89-1.99)		

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Missing data derived for analysis
		484/			Women	≥20 vs ≤0 g/day	1.07 (0.73-1.57)	smoking status, total energy intake, vegetable intake	
		333/			Incidence, rectal cancer, men	≥20 vs ≤0 g/day	0.96 (0.60-1.53)		
		185/			Incidence, rectal cancer women	≥20 vs ≤0 g/day	1.01 (0.54-1.90)		
Oba, 2006 COL40626 Japan	TCCJ, Prospective Cohort, Age: 35-101 years, M/W	111/ 30 221 8 years	Hospital records and cancer registry	Semi-quantitative FFQ	Incidence, colon cancer, men	20.3 vs 3.9 g	1.98 (1.24-3.16)	Age, alcohol intake, BMI, energy intake, height, pack-years of smoking, physical activity	Distribution of person-years by exposure category.
		102/			Women	16.3 vs 3 g	0.85 (0.50-1.43)		
Sato, 2006 COL40671 Japan	MCS, Prospective Cohort, Age: 40-64 years, M/W	358/ 41 835 11 years	Cancer registry	FFQ	Incidence, colorectal cancer	3-4 times/wk vs almost never g/day	0.91 (0.61-1.35)	Age, sex, alcohol consumption, BMI, calcium intake, dietary fibre intake, educational level, energy intake, family history of cancer, fat consumption, physical activity, smoking status	Conversion from times/week to g/day
		217/			Incidence, colon cancer	3-4 times/wk vs almost never g/day	0.75 (0.45-1.27)		
		144/			Incidence, rectal cancer	3-4 times/wk vs almost never g/day	1.10 (0.60-2.03)		

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Missing data derived for analysis
Chao, 2005 COL01689 USA	CPS II, Prospective Cohort, Age: 50-74 years, M/W	665/ 148 610 19 years	Cancer registry and death certificates and medical records	FFQ	Incidence, colon cancer	≥240 vs ≤0 g/week	1.11 (0.80-1.54)	Age, aspirin use, beer intake, BMI, educational level, fibre, fruits, liquor intake, multivitamin supplement intake, physical activity, smoking habits, total energy, vegetable (total), wine intake	Distribution of person-years by exposure category. Conversion from g/week to g/day
					Incidence, rectal cancer		1.26(0.86-1.83)		
Larsson, 2005 COL01849 Sweden	SMC, Prospective Cohort, Age: 40-75 years, W	733/ 61 433 855 585 person-years	Cancer registry	Questionnaire	Incidence, colorectal cancer,	≥32 vs 0-11 g/day	1.07 (0.85-1.33)	Age, alcohol consumption, BMI, calcium, educational level, energy intake, fish, folate, fruits, poultry, saturated fat, vegetables, whole-grain foods	Distribution of person-years by exposure category. Mid-points of exposure categories. Conversion from servings/week to g/day.
		234/			Incidence, proximal cancer,	≥32 vs 0-11 g/day	1.02 (0.69-1.52)		
		230/			Incidence, rectal cancer,	≥32 vs 0-11 g/day	0.90 (0.60-1.34)		
		155/			Incidence, distal colon cancer,	≥32 vs 0-11 g/day	1.39 (0.86-2.24)		
Norat, 2005 COL01698 Europe	EPIC, Prospective Cohort, Age: 21-83 years,	1 329/ 478 040 2 279 075 person-years		Questionnaire	Incidence, colorectal cancer,	per 100 g/day	1.32 (1.07-1.63)	Age, sex, alcohol consumption, body weight, centre location,	Continuous results were directly used in dose-response analysis
						≥80 vs ≤10 g/day	1.42 (1.09-1.86)		
		855/			Incidence, colon	per 100 g/day	1.39 (1.06-1.82)		

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Missing data derived for analysis
	M/W				cancer,	≥80 vs ≤10 g/day	1.30 (0.92-1.84)	energy from fat sources, energy from nonfat sources, fibre, height, physical activity, smoking status	
		474/			Incidence, rectal cancer,	per 100 g/day	1.22 (0.87-1.71)		
						≥80 vs ≤10 g/day	1.62 (1.04-2.50)		
English, 2004 COL00019 australia	MCCS, Prospective Cohort, Age: 27-75 years, M/W	452/ 37 112 9 years	Population/electoral rolls	FFQ	Incidence, colorectal cancer,	≥4 vs ≤1.5 times/week	1.50 (1.10-2.00)	Sex, cereal intake, county of birth, energy intake, fat intake	Distribution of person-years by exposure category. Mid-points of exposure categories. Conversion from times/week to g/day
		283/			Incidence, colon cancer,	≥4 vs ≤1.5 times/week	1.30 (0.90-1.90)		
		169/			Incidence, rectal cancer,	≥4 vs ≤1.5 times/week	2.00 (1.10-3.40)		
Lin, 2004 COL01834 USA	WHS, Prospective Cohort, Age: 45- years, W	202/ 37 547 8.7 years	Self report verified by medical record	FFQ	Incidence, colorectal cancer	0.5 vs 0 servings/day	0.85 (0.53-1.35)	Age, alcohol consumption, BMI, family history of colorectal cancer, history of polyps, physical activity, postmenopausal hormone use, randomized treatment assignment, smoking habits,	Distribution of person-years by exposure category. Mid-points of exposure categories. Conversion from servings/day to g/day

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Missing data derived for analysis
								total energy intake	
Wei, 2004 COL00581 USA	NHS, Prospective Cohort, W, nurses	668/ 87 733 24 years	Self-reported verified by medical record and The National Death Index	Semi-quantitative FFQ	Incidence, colon cancer,	≥5 vs ≤0 serving/month	1.32 (0.95-1.83)	Age, alcohol consumption, beef, pork or lamb as a main dish, BMI, calcium, family history of colorectal cancer, folate, height, history of endoscopy, pack-years of smoking before age 30, physical activity	Distribution of person-years by exposure category. Mid-points of exposure categories. Conversion from servings/week to g/day
		202/ 87 733 24 years		Semi-quantitative FFQ	Incidence, rectal cancer,	≥5 vs ≤0 serving/month	0.73 (0.33-1.59)		
	HPFS, Prospective Cohort, M, Health professionals	467/ 46 632 14 years		Semi-quantitative FFQ	Incidence, colon cancer,	≥5 vs ≤0 times	1.27 (0.87-1.85)		
		135/ 46 632 14 years	Population registries	Semi-quantitative FFQ	Incidence, rectal cancer,	≥5 vs ≤0 times	1.06 (0.48-2.33)	Family history, folate intake, pack-years of smoking, total calcium	
Flood, 2003 COL00412 USA	BCDDP, 1973, Prospective Cohort, Age: 62 years, W	487/ 45 496 386 716 person-years	Breast cancer screening centres	FFQ	Incidence, colorectal cancer,	22.2 vs 0.02 g/1000 kcal	0.97 (0.73-1.28)	Total energy, total meat	Distribution of person-years by exposure category. Mid-points of exposure categories. intakes in g/1000kcal/day converted to

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Missing data derived for analysis
									g/day using average energy intake per each quantile
Pietinen, 1999 COL00176 Finland	ATBC, Prospective Cohort, Age: 50-69 years, M, Smokers	185/ 27 111 8 years	Cancer registry	Dietary history questionnaire	Incidence, colorectal cancer,	122 vs 26 g/day	1.20 (0.70-1.80)	Age, alcohol consumption, BMI, calcium intake, educational level, physical activity, smoking years, supplement group	Distribution of person-years by exposure category
Bostick, 1994 COL00079 USA	IWHS, Prospective Cohort, Age: 55-69 years, W	212/ 35 216 167 447 person-years	SEER	Semi-quantitative FFQ	Incidence, colon cancer,	≥3 vs ≤0 serving/week	1.51 (0.72-3.17)	Age, energy intake, height, parity, total vitamin e intake, total vitamin e intake age, vitamin a supplement	Distribution of person-years by exposure category. Mid-points of exposure categories. Conversion from servings/week to g/day

Table 68 Processed meat and colorectal cancer risk. Main characteristics of studies excluded from the CUP SLR dose-response meta-analysis

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Reasons for exclusion
Egeberg, 2013 COL40953 Denmark	DCH, Prospective Cohort, Age: 50-64 years, M/W	644/ 53 988 13.4 years	Cancer registry	FFQ	Incidence, colon cancer	≥42 vs 0-16 g/day	1.02 (0.78-1.34)	Age, alcohol, beef consumption, cold cuts, educational level, energy, fibre, fish, HRT use, lamb intake, liver, NSAID use, poultry, processed meat, red meat, sausages, smoking, sport, veal meat, waist circumference	Component of EPIC. Superseded by Norat, 2005 COL01698
						per 25 g/day	1.03 (0.94-1.13)		
					Incidence, rectal cancer	≥42 vs 0-16 g/day	0.88 (0.60-1.30)		
						per 25 g/day	0.93 (0.81-1.07)		
Gay, 2012 COL40920 UK	EPIC-Norfolk, Prospective Cohort, Age: 45-79 years, M/W	185/ 25 636 11 years	Cancer registry	7-day dietary recalls	Incidence, colorectal cancer, gc:at mutations	per 1 sd units	1.68 (1.03-2.75)	Age, sex, smoking	Superseded by Norat, 2005 COL01698
					Apc promoter methylation ≥20%	per 1 sd units	1.30 (0.91-1.85)		

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Reasons for exclusion
					Apc mutations	per 1 sd units	1.25 (0.91-1.72)		
						per 1 sd units	1.25 (0.91-1.72)		
Nöthlings, 2009 COL40763 USA	MEC, Nested Case Control, Age: 45-75 years, M/W	1 009/ 1522 controls	Surveillance registry/end results cancer registry	FFQ	Incidence, colorectal cancer	≥11 vs 0-3.4 g/1000kcal/day	1.08 (0.83-1.39)	BMI, calcium intake, ethanol, family history of colorectal cancer, fibre intake, folic acid intake, pack-years of smoking, physical activity, smoking status, vitamin d intake	Superseded by Ollberding, 2012 COL40941

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Reasons for exclusion
Cross, 2008 COL40701 USA	NIH-AARP, Prospective Cohort, Age: 50-71 years, M/W	80/ 494 000 7.5 years	Cancer registry	Semi-quantitative FFQ	Incidence, small Intestinal carcinoids	17.8 vs 2.6 g/1000 kcal	1.05 (0.58-1.89)	Alcohol intake, BMI, educational level, family history of cancer, fruit intake, marital status, person-years at risk, physical activity, race, smoking habits, total energy intake, vegetable intake	Superseded by Ruder, 2011 COL40896
		60/			Incidence, small Intestinal adenocarcinomas	17.8 vs 2.6 g/1000 kcal	1.20 (0.61-2.35)		
						17.8 vs 2.6 g/1000 kcal	1.36 (0.71-2.62)		
						per 10 g/1000 kcal	0.98 (0.76-1.26)		
						per 10 g/1000 kcal	0.94 (0.72-1.22)		
Sorensen, 2008 COL40690 Denmark	DCH, Case Cohort, Age: 50-64	379/ 57 000 10 years	Cancer registry	FFQ	Incidence, colorectal cancer	per 25 g/day	0.99 (0.86-1.13)	Alcohol intake, BMI, dietary fiber intake,	Component of EPIC. Superseded by
					Nat2 slow	per 25 g/day	1.04 (0.89-1.23)		

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Reasons for exclusion
	years, M/W				phenotype			HRT use, smoking status	Norat, 2005 COL01698
					Nat2 fast phenotype	per 25 g/day	0.92 (0.74-1.14)		
					Nat1 slow phenotype	per 25 g/day	1.01 (0.86-1.18)		
					Nat1 fast	per 25 g/day	0.96 (0.77-1.20)		
Cross, 2007 COL40640 USA	NIH-AARP, Prospective Cohort, Age: 50-71 years, M/W	5 107/ 494 036 6.8 years	Cancer registry	FFQ	Incidence, colorectal cancer, men	22.6 vs 1.6 g/1000 kcal	1.20 (1.09-1.32)	Age, sex, alcohol consumption, BMI, educational level, energy intake, family history of cancer, fruits, marital status, physical activity, race, smoking habits, vegetable intake	Superseded by Ruder, 2011 COL40896
					Incidence, rectal cancer, men	22.6 vs 1.6 g/1000 kcal	1.18 (1.06-1.32)		
Iso, 2007 COL40707 Japan	JACC, Prospective Cohort, Age: 40-79 years,	182/ 105 500 15 years	Municipal resident registration records, death certificates	FFQ	Mortality, colon cancer, men	3-4 vs ≤0 /week	1.41 (0.95-2.08)	Age, centre location	Outcome is mortality
		172			Women	3-4 vs ≤0 /week	0.90 (0.56-1.44)		

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Reasons for exclusion
	M/W	153/			Mortality, rectal cancer, men	3-4 vs ≤0 /week	0.89 (0.55-1.46)		
		71/			Women	3-4 vs ≤0 /week	1.30 (0.69-2.46)		
Brink, 2005 COL40717 Netherlands	NLCS, Case Cohort, Age: 55-69 years, M/W	448/ 2 948 7.3 years	Cancer registry	Semi-quantitative FFQ	Incidence, colon cancer	Q 4 vs Q 1	0.77 (0.57-1.04)	Age, sex, BMI, energy intake, family history of colorectal cancer, smoking habits	Superseded by Balder, 2006 COL40622
						per 30.3 g/day	0.93 (0.83-1.04)		
		160/			Incidence, rectal cancer	Q 4 vs Q 1	0.70 (0.43-1.13)		
						per 30.3 g/day	0.87 (0.72-1.03)		
Luchtenborg, 2005 COL01830	NLCS, Case Cohort, Age: 55-69 years, M/W	434/ 2 948 7.3 years	Population registries	Semi-quantitative FFQ	Incidence, colon cancer,	Q 4 vs Q 1	0.77 (0.57-1.04)	Age, sex, BMI, energy intake, family history of colorectal cancer, smoking status	Superseded by Balder, 2006 COL40622
						per 30.3 g/day	0.93 (0.84-1.04)		
		274/			Apc- cases	per 30.3 g/day	0.95 (0.83-1.08)		
						Q 4 vs Q 1	0.84 (0.58-1.20)		
		154/			Incidence, rectal cancer,	Q 4 vs Q 1	0.70 (0.44-1.13)		
						per 30.3 g/day	0.87 (0.73-1.03)		
		127/			Incidence, colon cancer, apc+ cases	per 30.3 g/day	0.93 (0.77-1.14)		
						Q 4 vs Q 1	0.69 (0.40-1.19)		
		73/			Incidence, rectal cancer, apc- cases	per 30.3 g/day	0.73 (0.57-0.93)		
						Q 4 vs Q 1	0.56 (0.27-1.16)		

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Reasons for exclusion
		57/			Apc+ cases	per 30.3 g/day	0.99 (0.74-1.31)		
						Q 4 vs Q 1	0.80 (0.39-1.67)		
Khan, 2004 COL01606 Japan	HCS, Prospective Cohort, Age: 40-97 years, M/W	15/ 3 458 14.3 years	Area residency lists	Questionnaire	Mortality, colorectal cancer, men	Q 2 vs Q 1	0.50 (0.10-2.20)	Age, smoking habits	Outcome is mortality
		14/			Women	Q 2 vs Q 1	1.40 (0.40-4.50)	Health education, health screening, health status	
Kojima, 2004 COL01840 Japan	JACC, Prospective Cohort, Age: 40-79 years, M/W	116/ 107 824 10 years	Resident registry and death certificates	Questionnaire	Mortality, colon cancer, men	3-7 vs 0-0.5 times/week	1.44 (0.90-2.31)	Age, alcohol consumption, BMI, educational level, family history of specific cancer, physical activity, region of enrolment, smoking status	Outcome is mortality
		111/			Women	3-7 vs 0-0.5 times/week	0.94 (0.53-1.66)		
		93/			Mortality, rectal cancer, men	3-7 vs 0-0.5 times/week	1.00 (0.56-1.78)		
		37/			Women	3-7 vs 0-0.5 times/week	1.56 (0.69-3.53)		
Knekt, 1999 COL01699 finland	FMCHES,Prospective Cohort, M/W	73/ 9 985 24 years	Social Insurance Institution	Diet history method	Incidence, colorectal cancer,	Q 4 vs Q 1	1.84 (0.98-3.47)	Age, sex, energy intake, municipality, smoking	Used only in highest vs lowest analysis
Kato, 1997 CRC00022	NY University Women's Health	100/ 14 272	Questionnaire, medical records,	Semi-quantitative FFQ	Incidence, colorectal	Q 4 vs Q 1	1.09 (0.59-2.02)	Age, educational level, place at	Used only in highest vs

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Reasons for exclusion
USA	Study, Prospective Cohort, Age: 34-65 years, W	105 044 person-years	cancer registries		cancer,			enrolment, total calorie intake	lowest analysis
Giovannucci, 1994 COL00119 USA	HPFS, Prospective Cohort, Age: 40-75 years, M, Health professionals	202/ 47 949 6 years	Self-reported verified by medical record and The National Death Index	FFQ	Incidence, colon cancer,	≥5 vs ≤0 serving/month	1.16 (0.44-3.04)	Age, total energy	Superseded by Wei, 2004 COL00581
Goldbohm, 1994 COL00025 Netherlands	NLCS, Case Cohort, Age: 55-69 years, M/W	215/ 120 852 3.3 years	Population registries	Semi-quantitative FFQ	Incidence, colon cancer,	≥20 vs ≤0 g/day	1.72 (1.03-2.87)	Age, sex, dietary fibre intake, energy intake	Superseded by Balder, 2006 COL40622
		110/			Women	≥20 vs ≤0 g/day per 15 g/day	1.66 (0.82-3.35) 0.99 (0.92-1.06)		
		105/			Men	≥20 vs ≤0 g/day per 15 g/day	1.84 (0.85-3.95) 1.17 (1.03-1.33)		

Figure 102 RR estimates of colorectal cancer by levels of processed meat

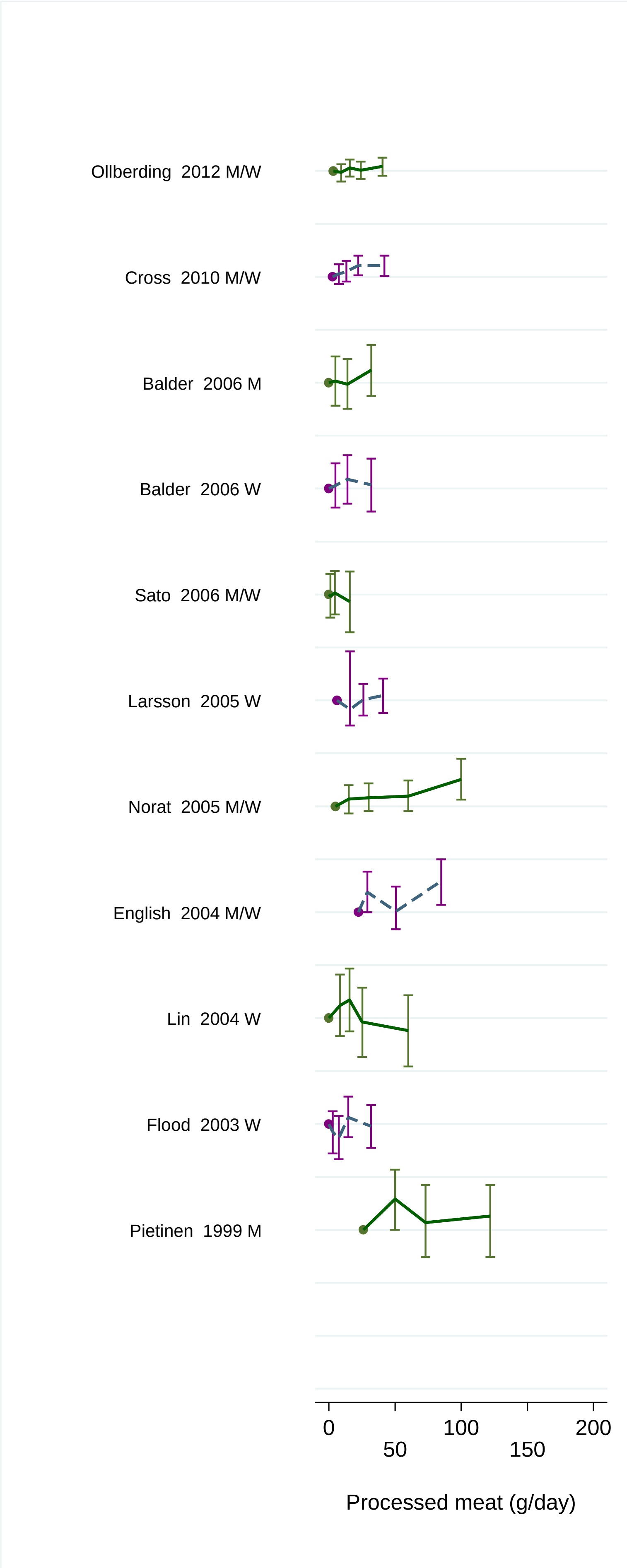


Figure 103 RR (95% CI) of colorectal cancer for the highest compared with the lowest level of processed meat

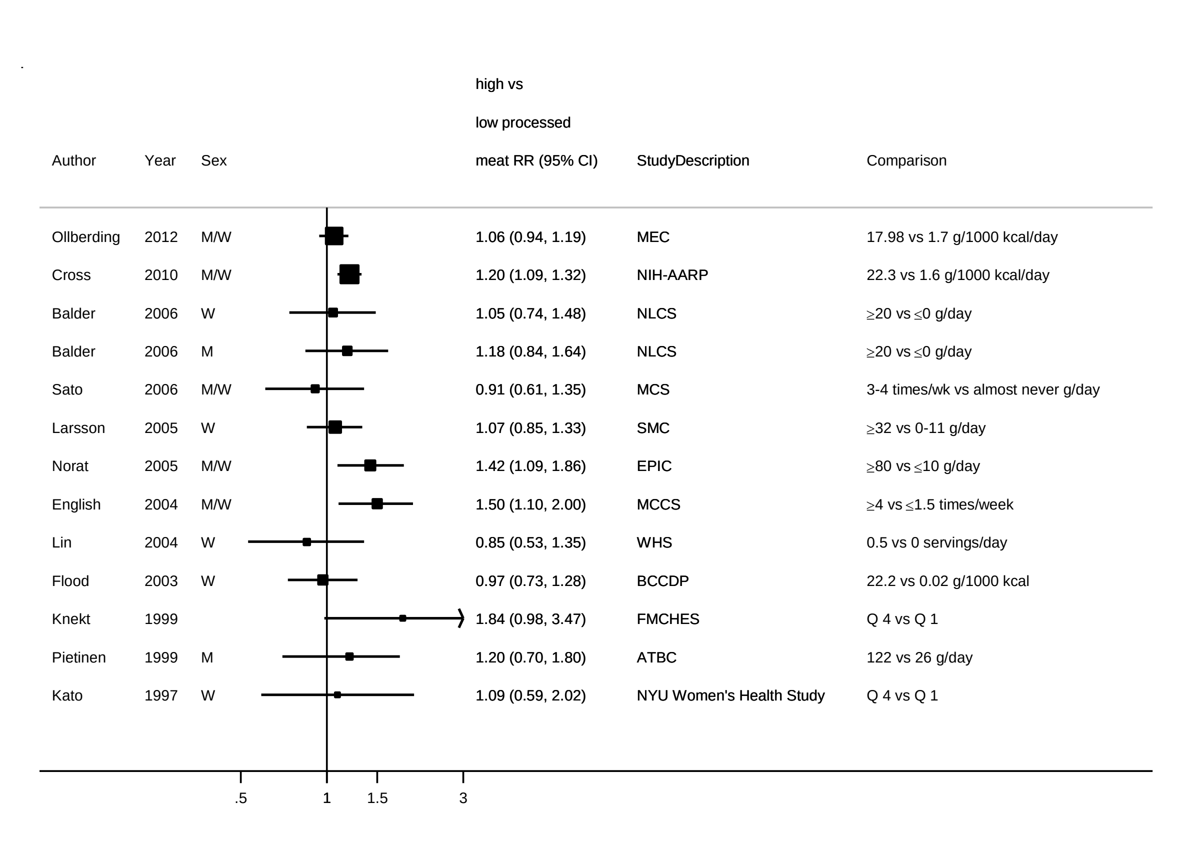


Figure 104 RR (95% CI) of colorectal cancer for 50g/day increase of processed meat

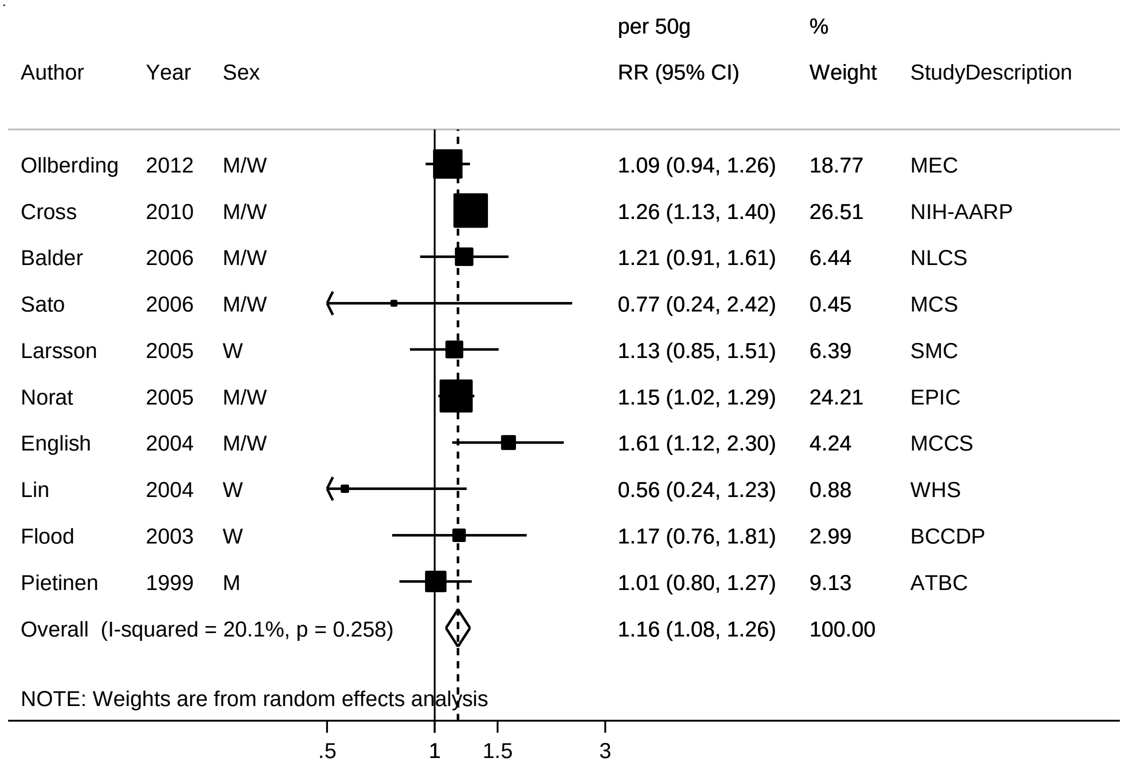


Figure 105 Funnel plot of studies included in the dose response meta-analysis processed meat and colorectal cancer

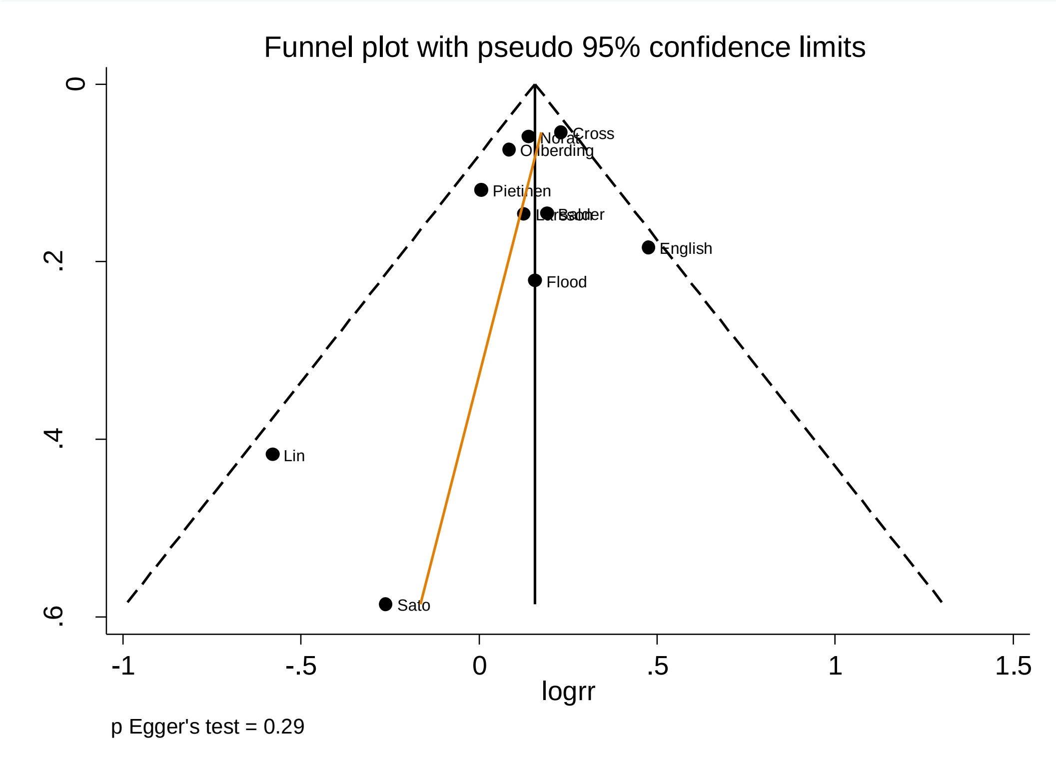


Figure 106 RR (95% CI) of colorectal cancer for 50g/day increase of processed meat by sex

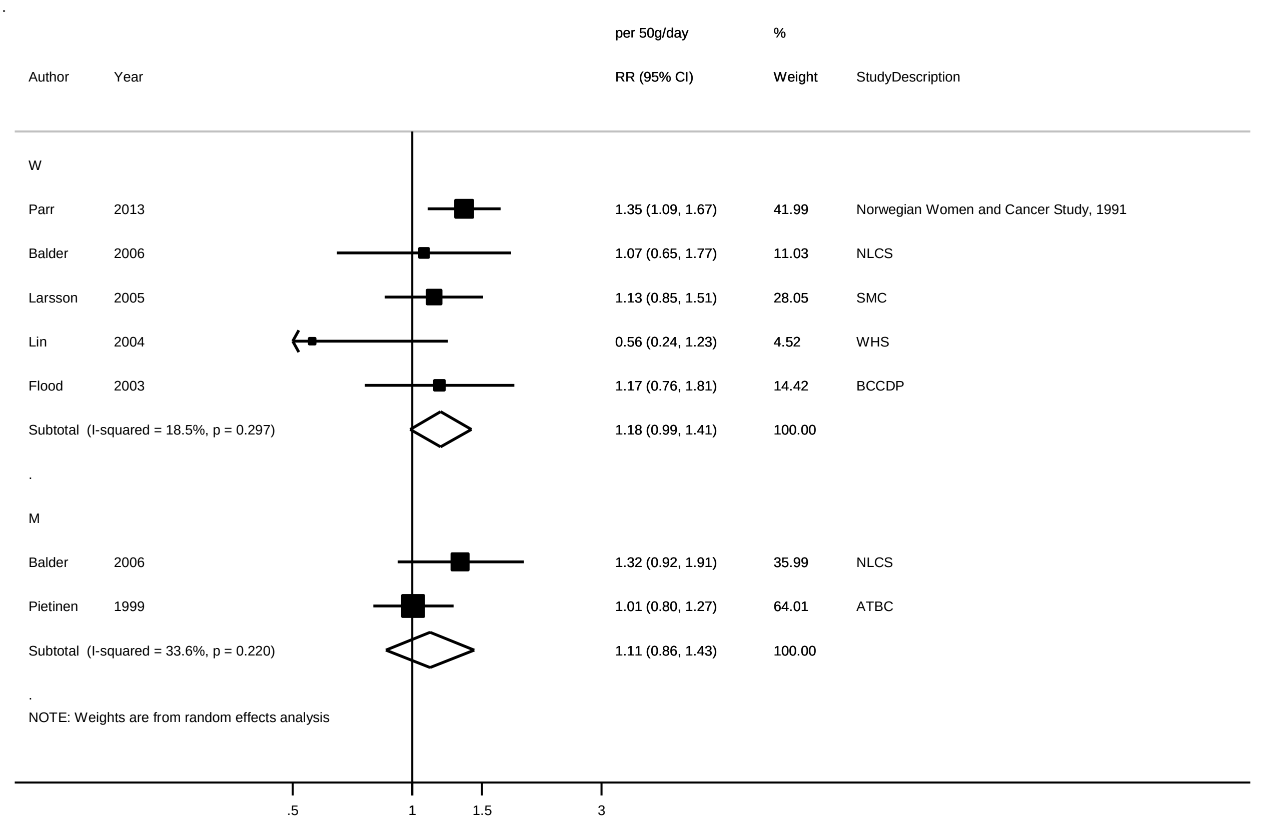


Figure 107 RR (95% CI) of colorectal cancer for 50g/day increase of processed meat by location

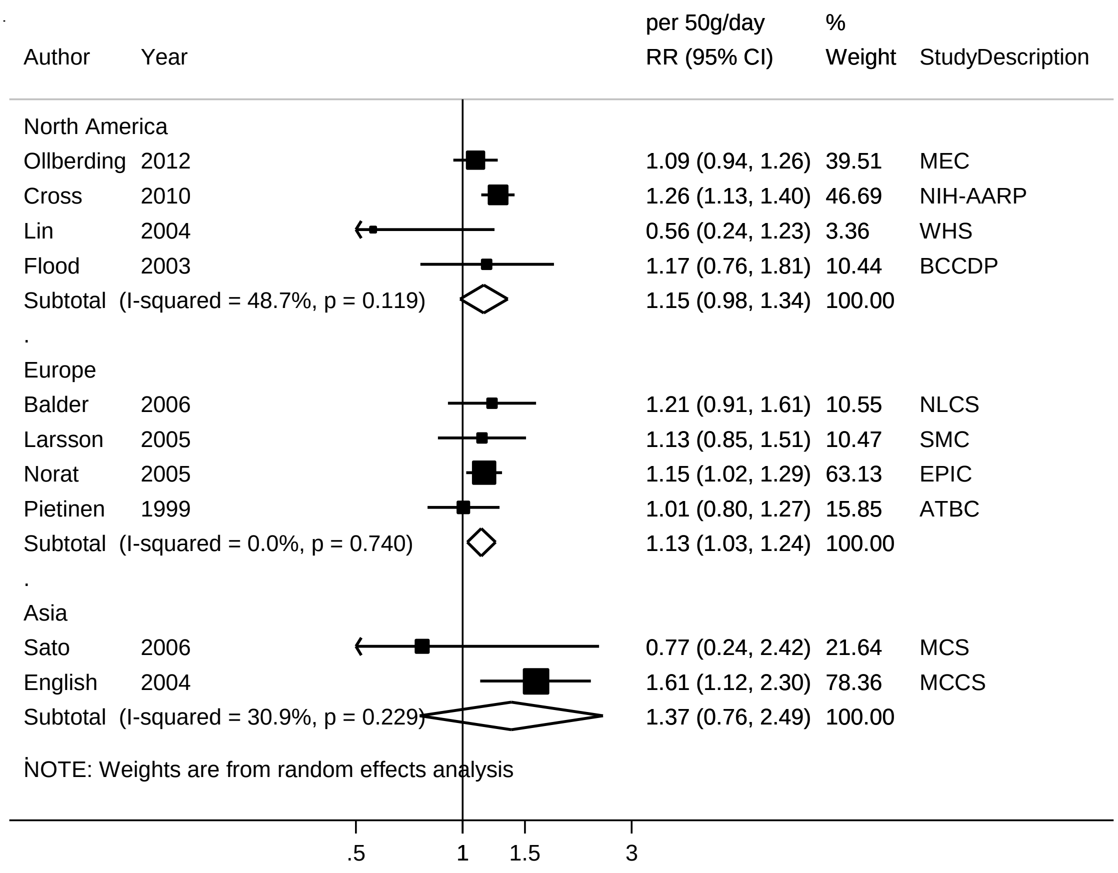


Figure 108 Relative risk of colorectal cancer and processed meat estimated using non-linear models

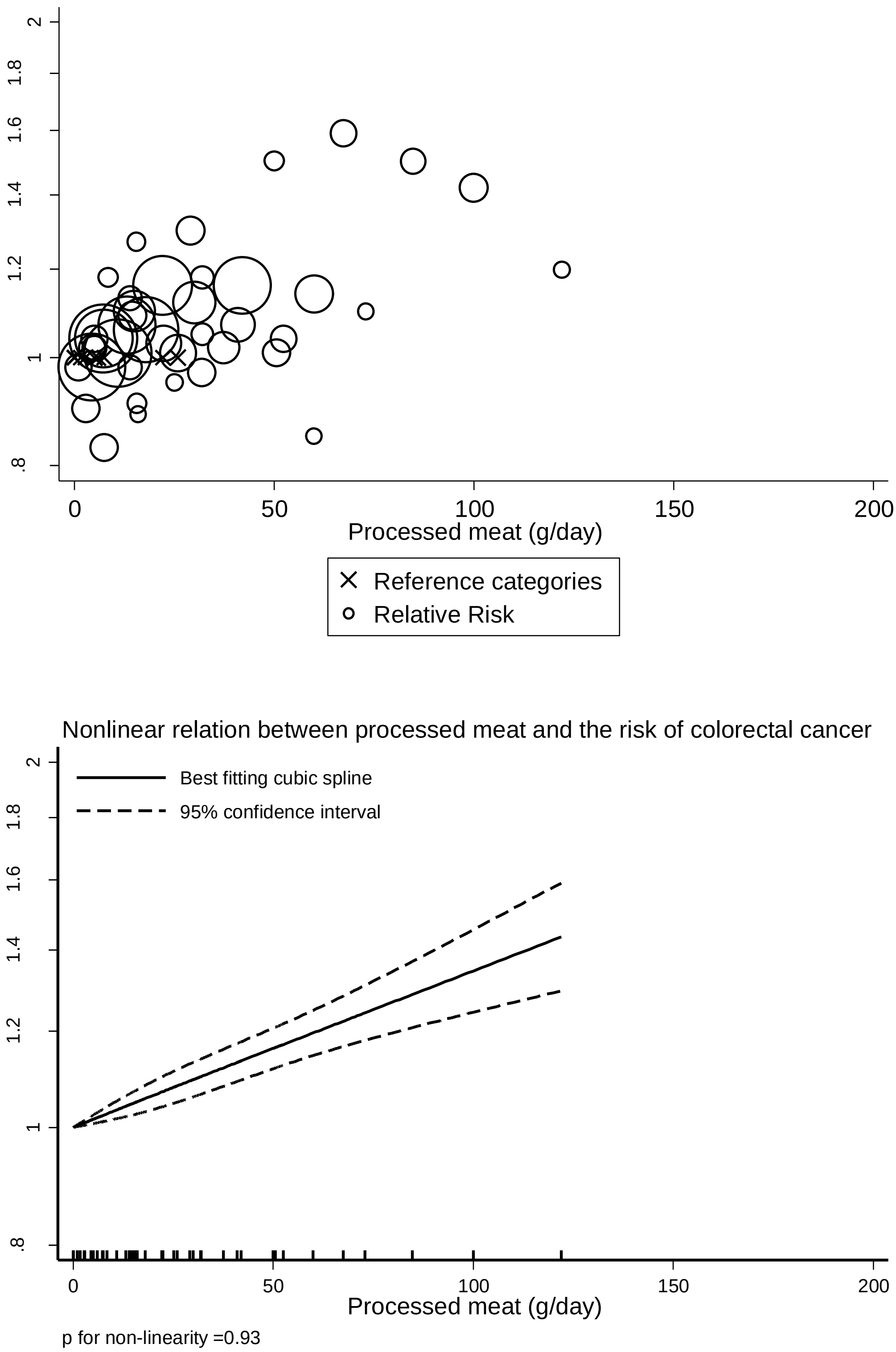


Table 69 Table with processed meat values and corresponding RRs (95% CIs) for non-linear analysis of processed meat and colorectal cancer

Processed meat (g/day)	RR(95%CI)
0	1
15	1.04(1.02-1.07)
30	1.09(1.06-1.13)
50	1.16(1.12-1.21)
100	1.34(1.24-1.45)

Figure 109 RR estimates of colon cancer by levels of processed meat

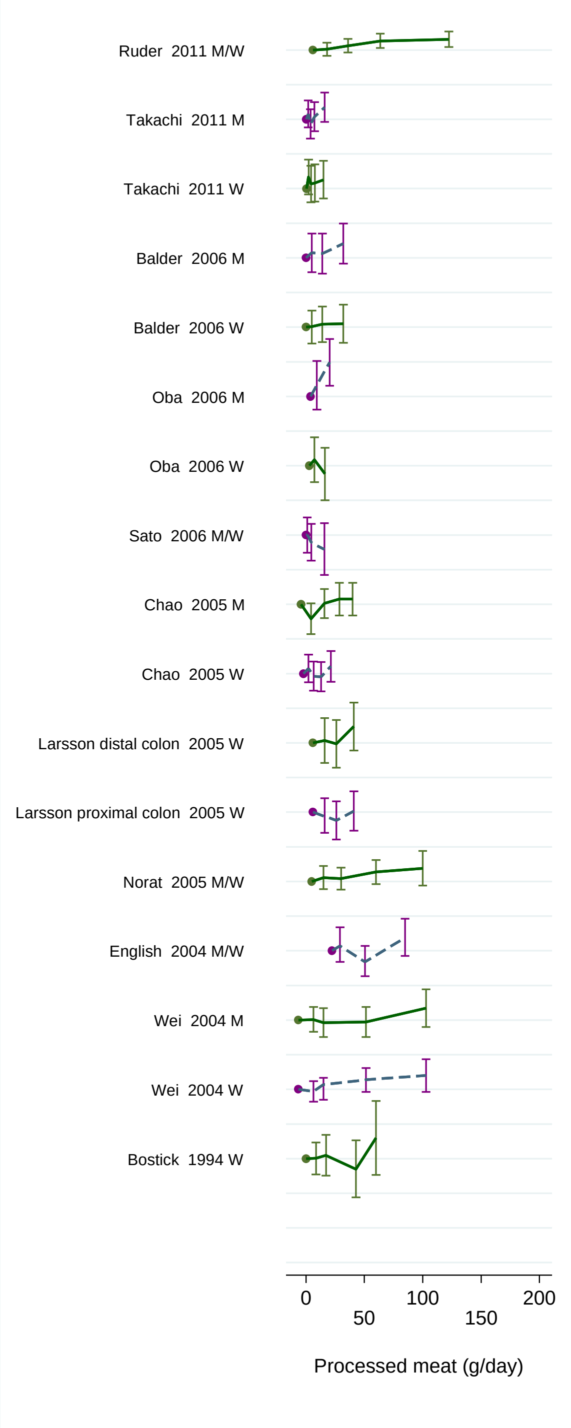


Figure 110 RR (95% CI) of colon cancer for the highest compared with the lowest level of processed meat

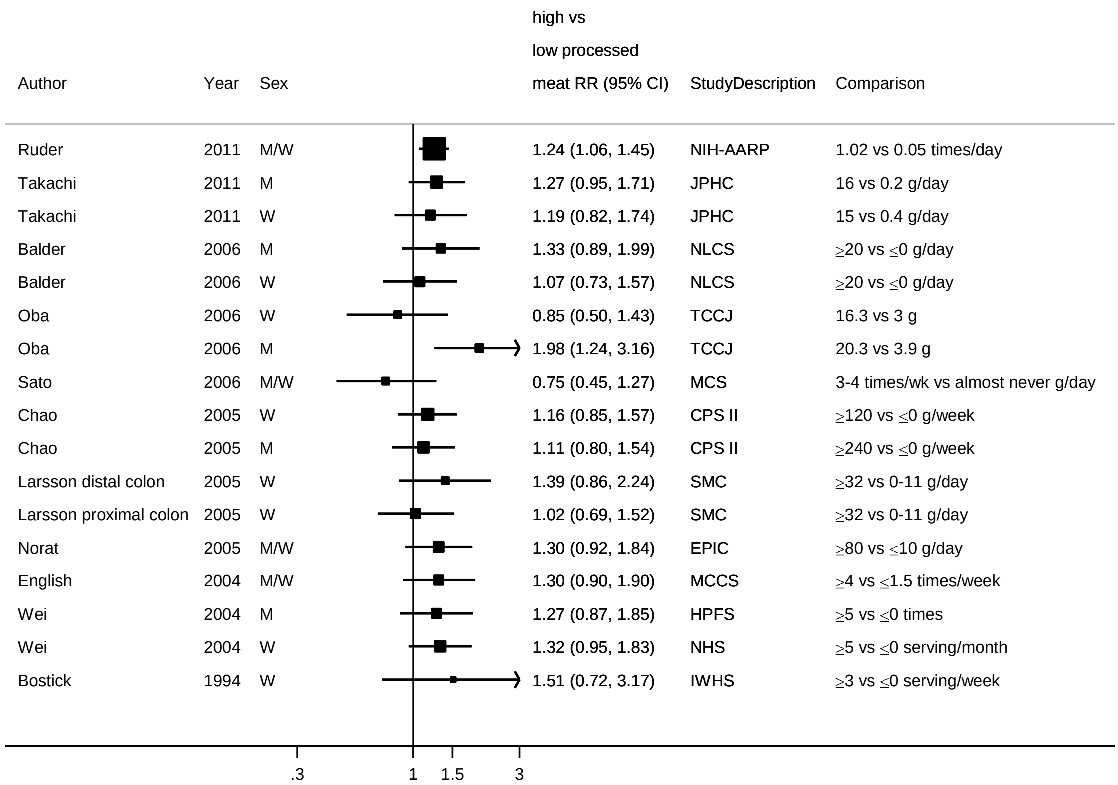


Figure 111 RR (95% CI) of colon cancer for 50g/day increase of processed meat

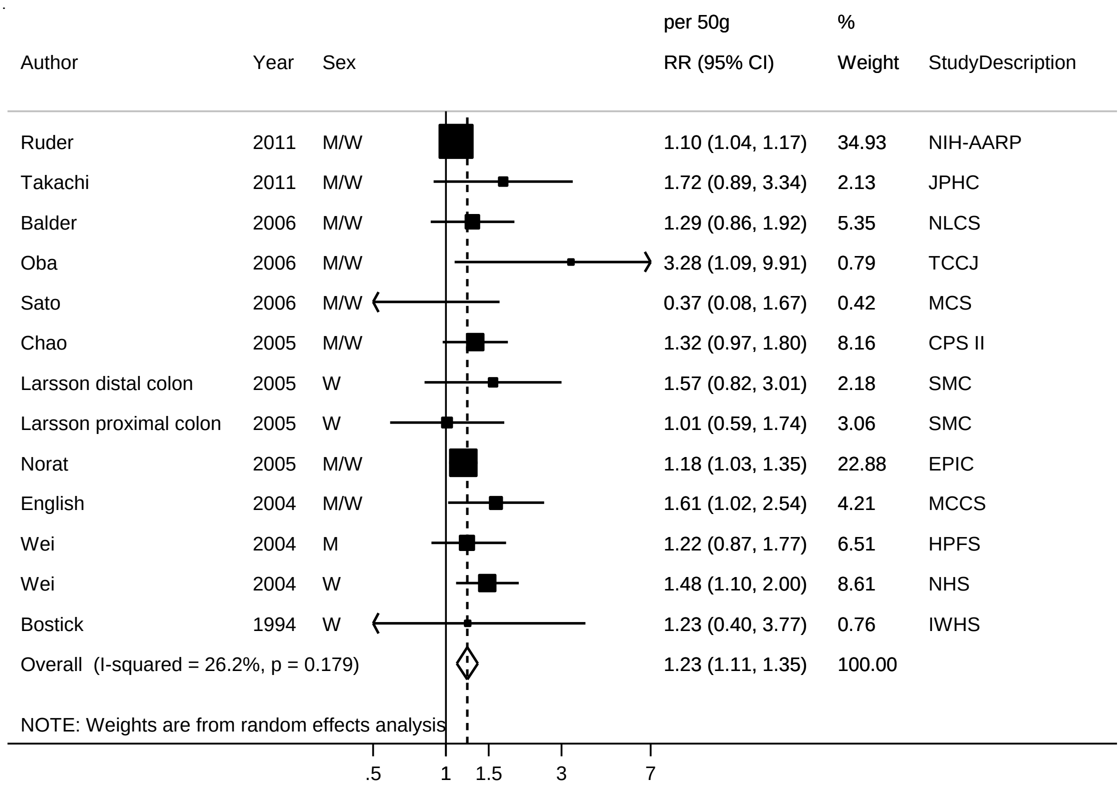


Figure 112 Funnel plot of studies included in the dose response meta-analysis of processed meat and colon cancer

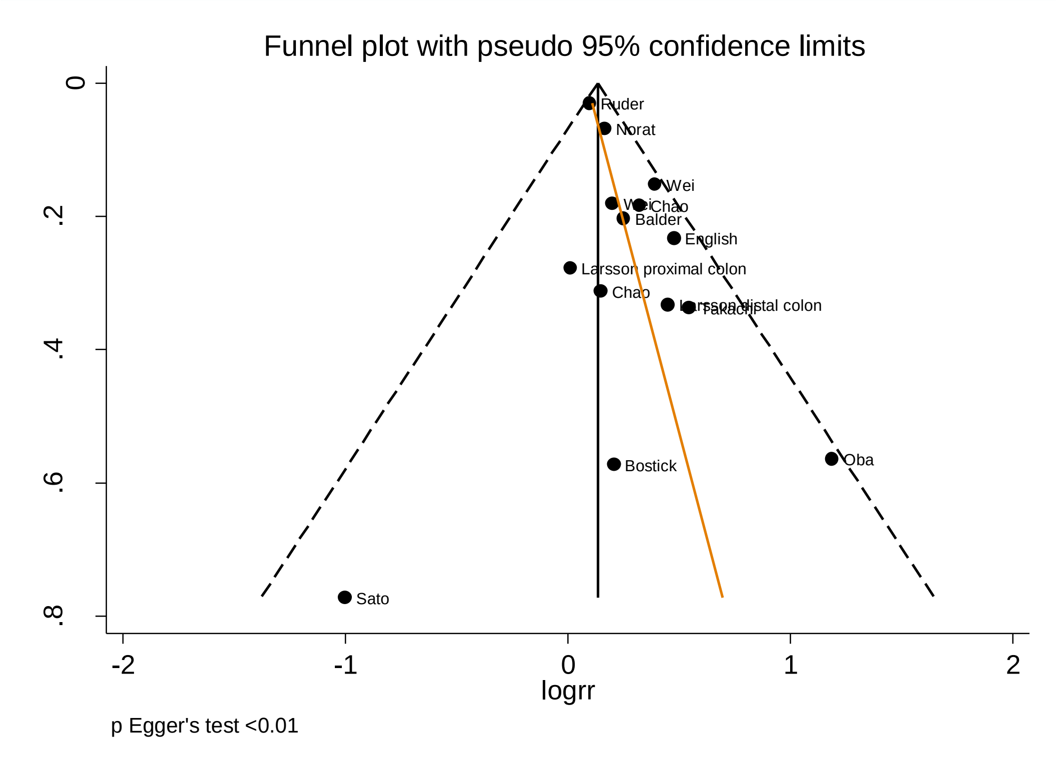


Figure 113 RR (95% CI) of colon cancer for 50g/day increase of processed meat by sex

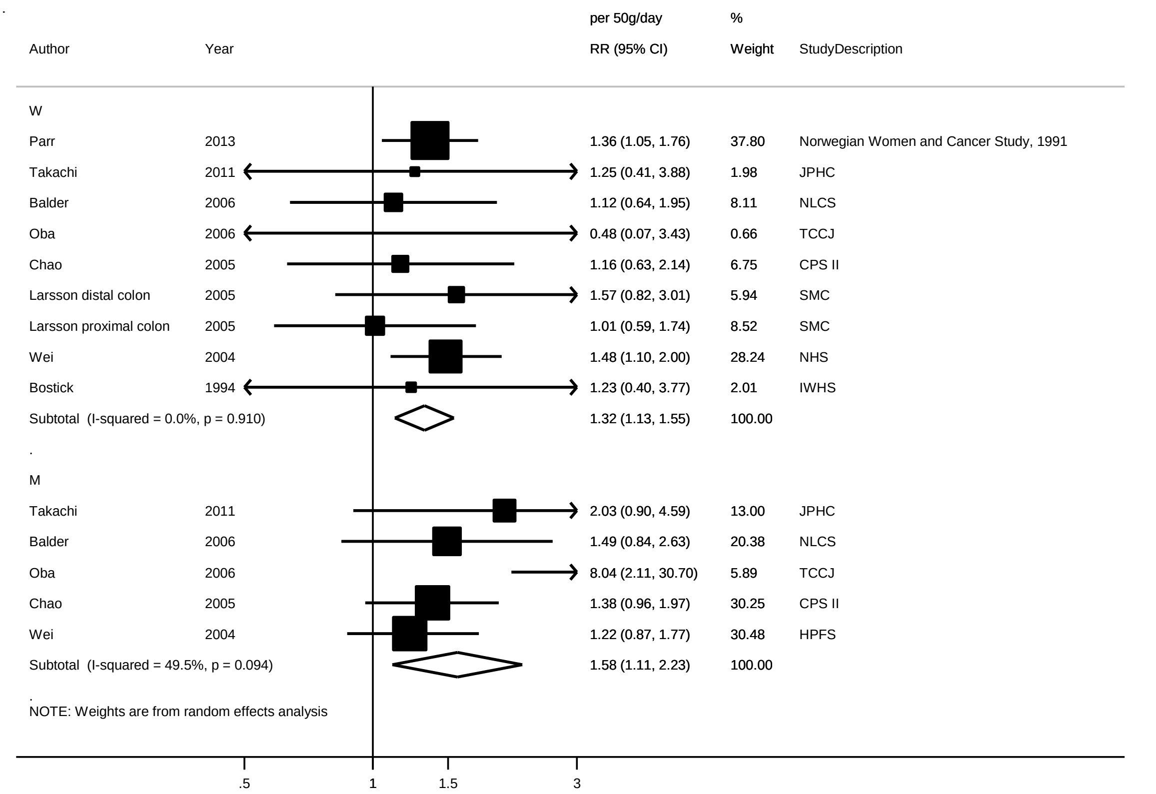


Figure 114 RR (95% CI) of colon cancer for 50g/day increase of processed meat by location

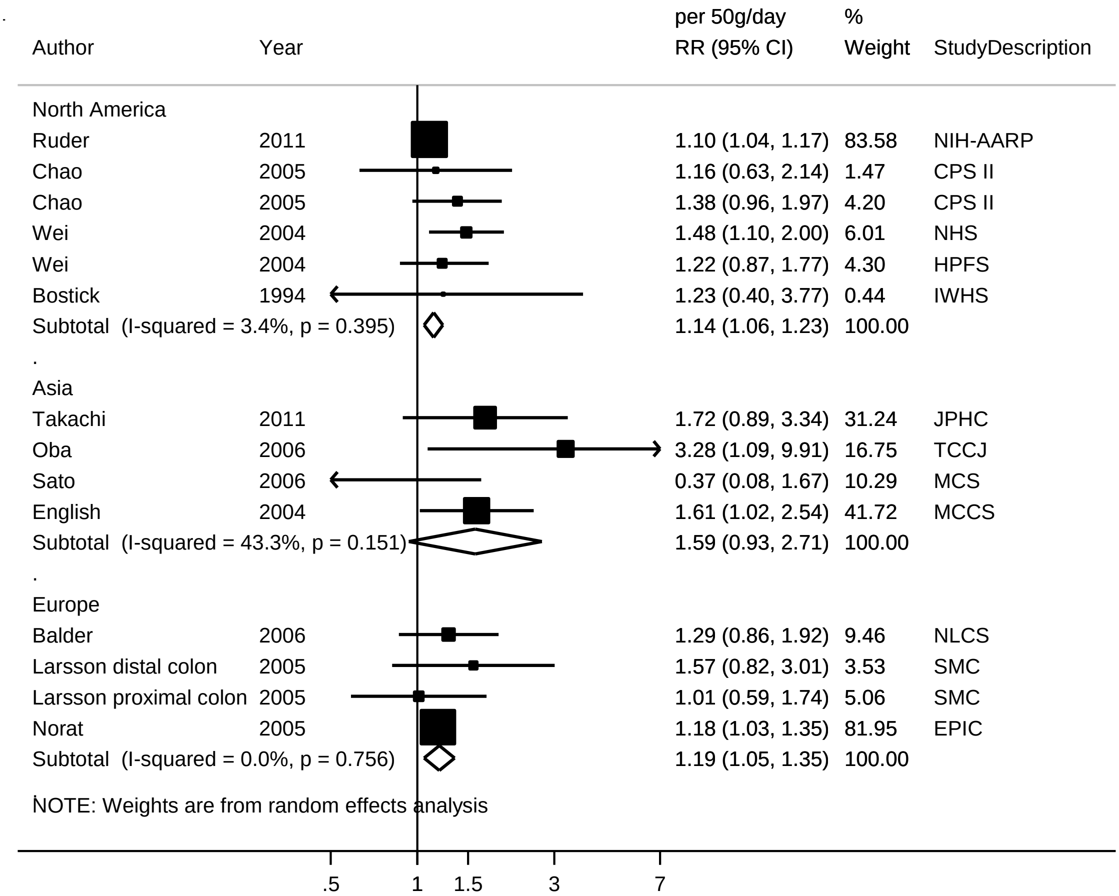
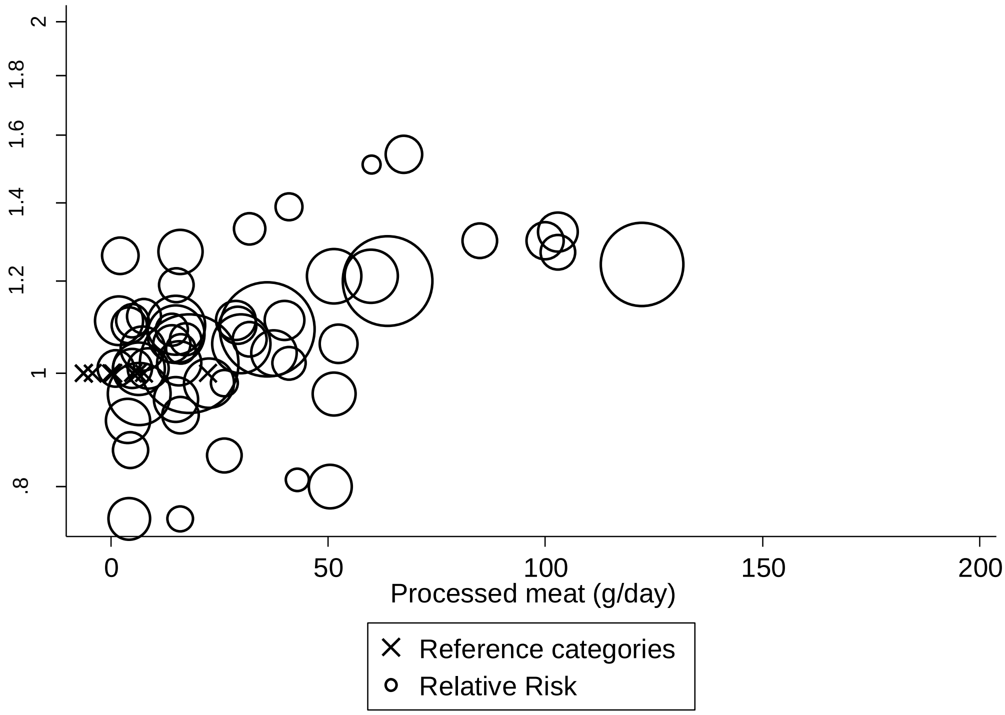


Figure 115 Relative risk of colon cancer and processed meat estimated using non-linear models



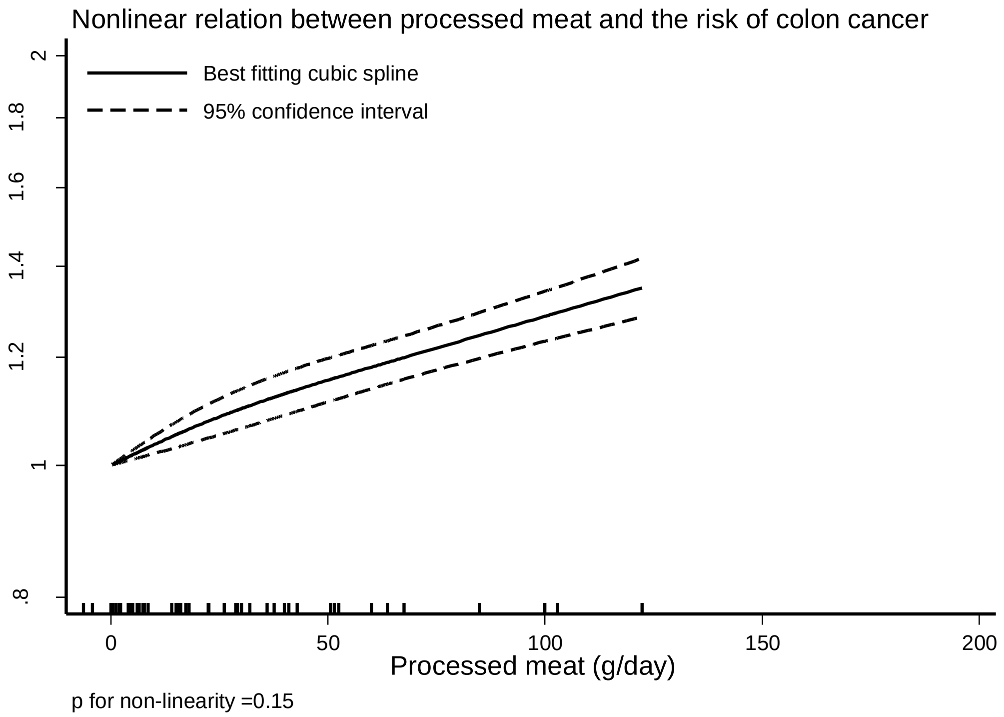


Table 70 Table with processed meat values and corresponding RRs (95% CIs) for non-linear analysis of processed meat and colon cancer

Processed meat (g/day)	RR (95%CI)
0	1
15	1.05(1.03-1.08)
30	1.10(1.06-1.14)
50	1.15(1.11-1.19
100	1.28(1.23-1.34)

Figure 116 RR estimates of rectal cancer by levels of processed meat

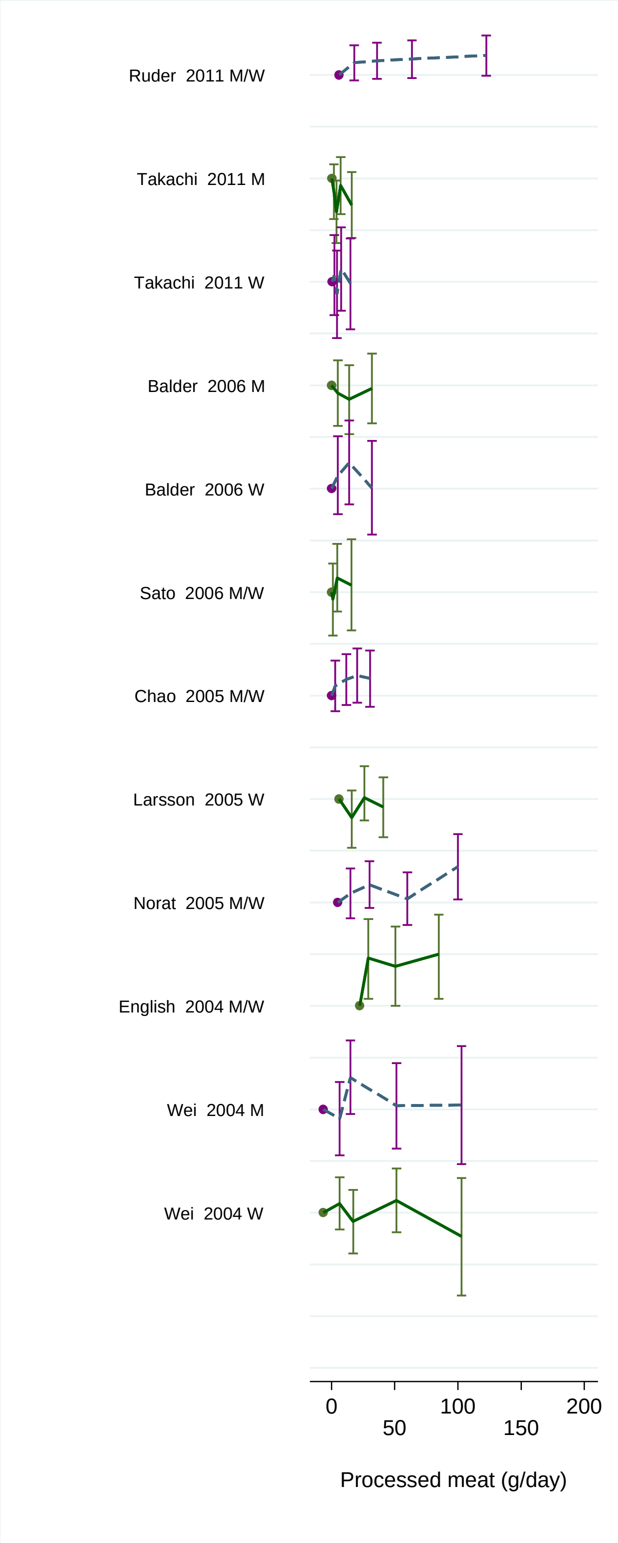


Figure 117 RR (95% CI) of rectal cancer for the highest compared with the lowest level of processed meat

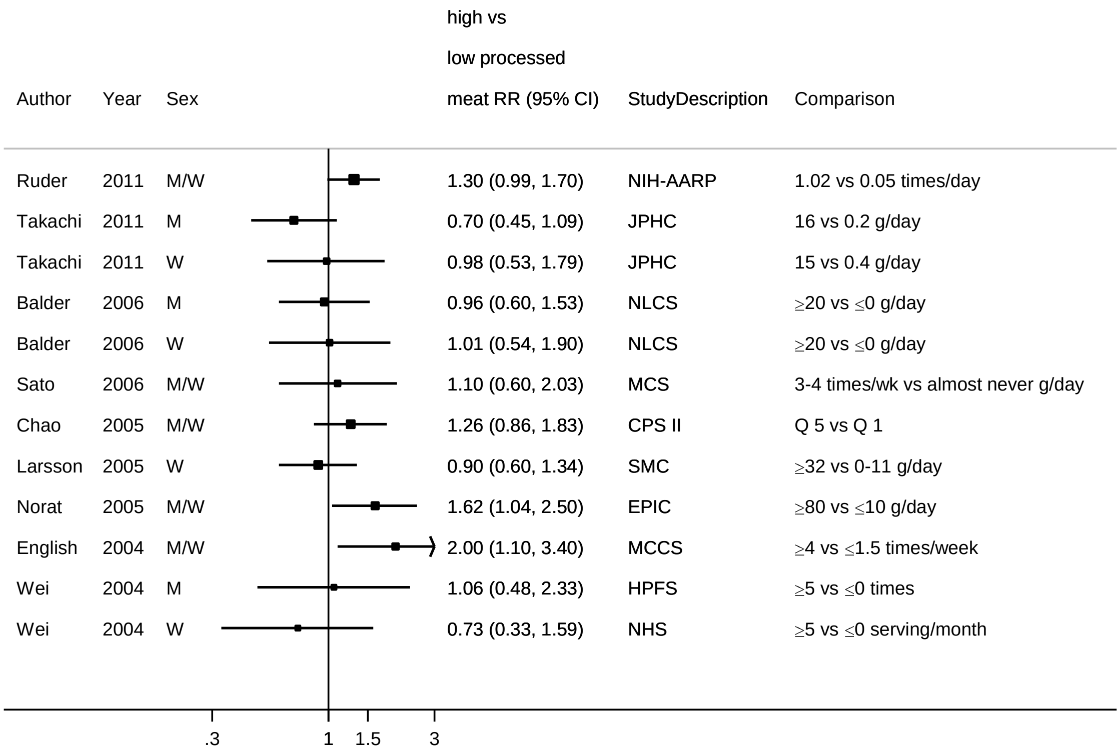


Figure 118 RR (95% CI) of rectal cancer for 50g/day increase of processed meat

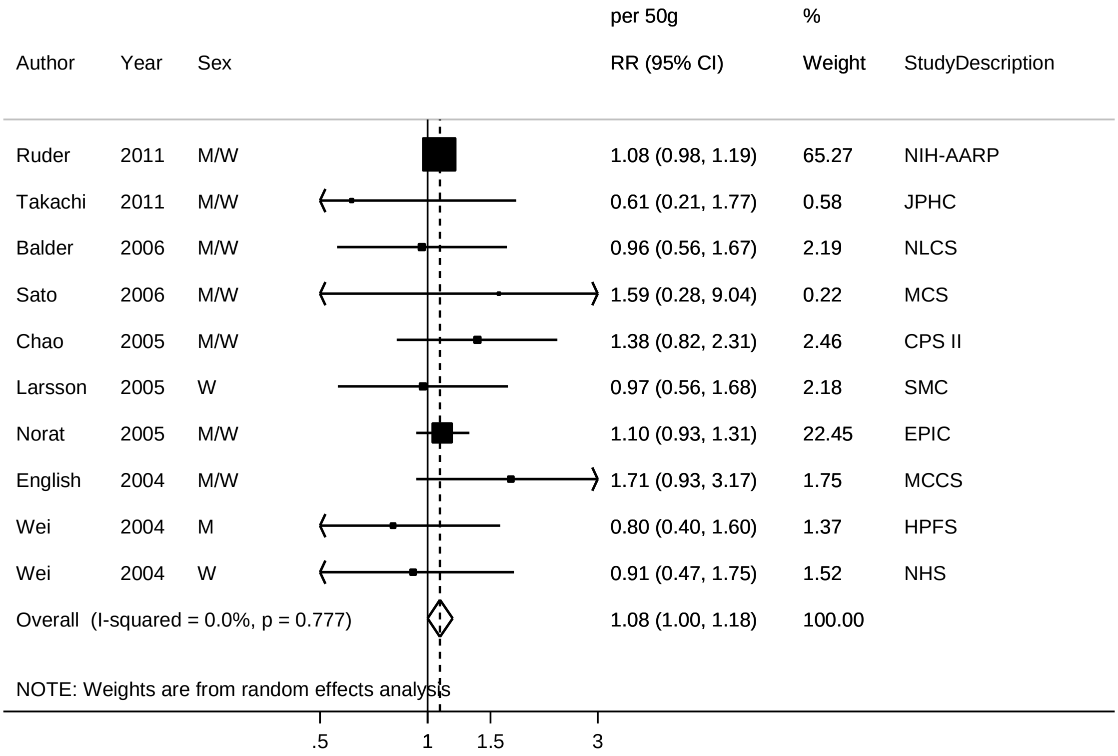


Figure 119 Funnel plot of studies included in the dose response meta-analysis of processed meat and rectal cancer

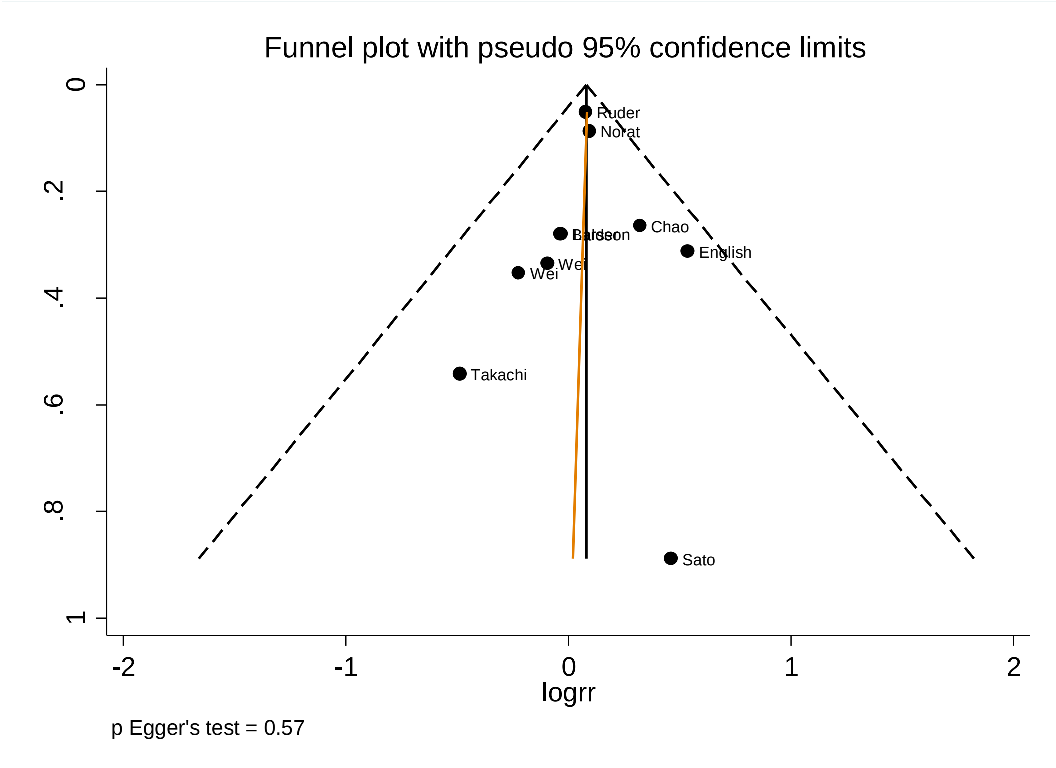


Figure 120 RR (95% CI) of rectal cancer for 50g/day increase of processed meat by sex

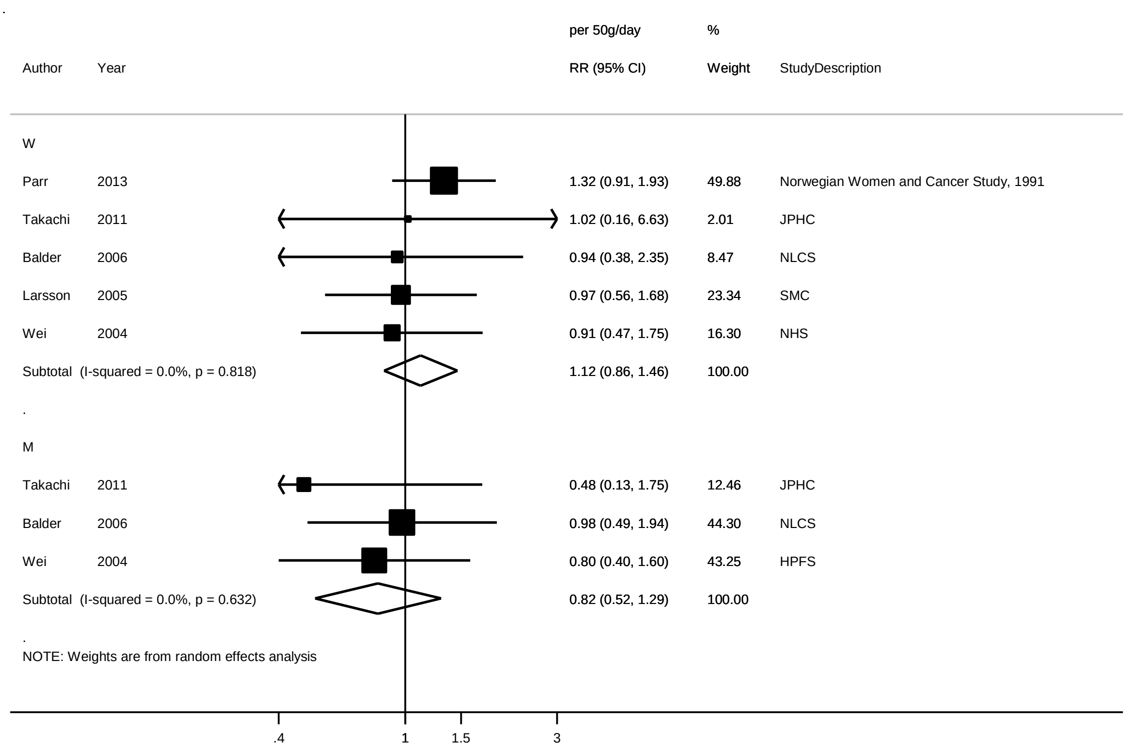


Figure 121 RR (95% CI) of rectal cancer for 50g/day increase of processed meat by location

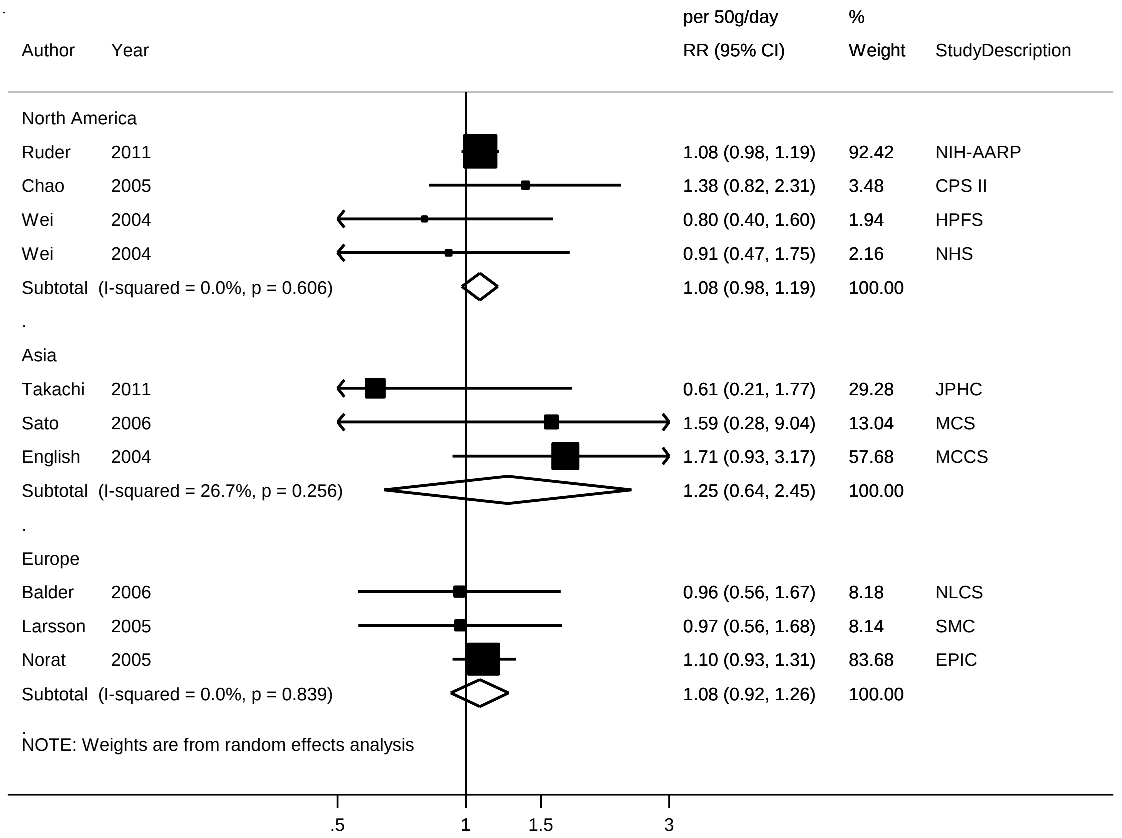
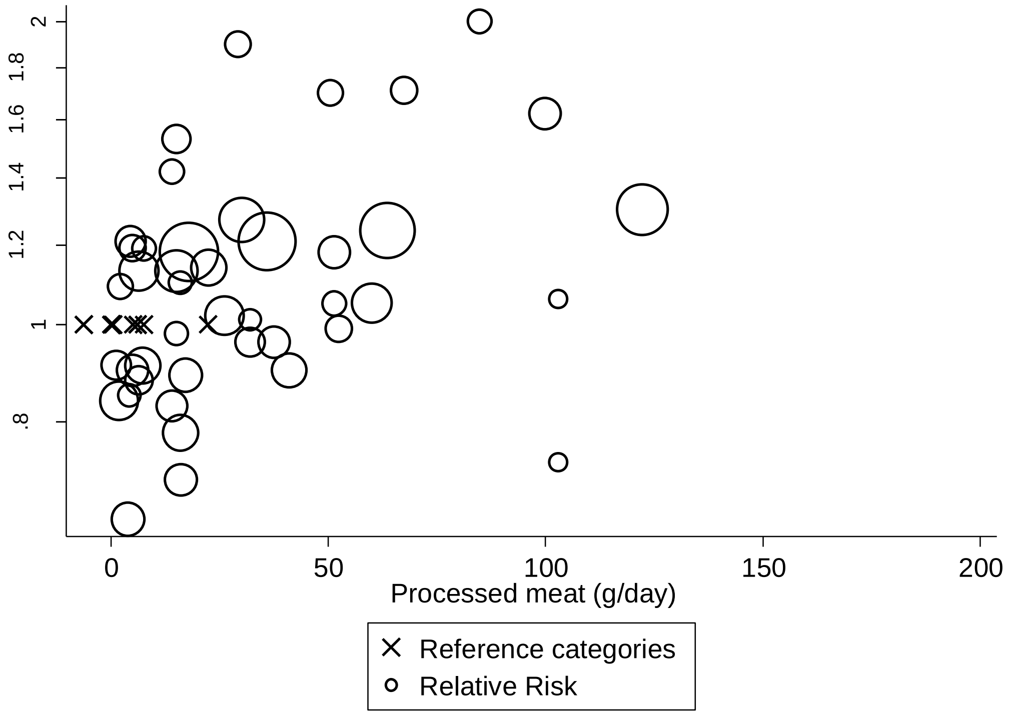


Figure 122 Relative risk of rectal cancer and processed meat estimated using non-linear models



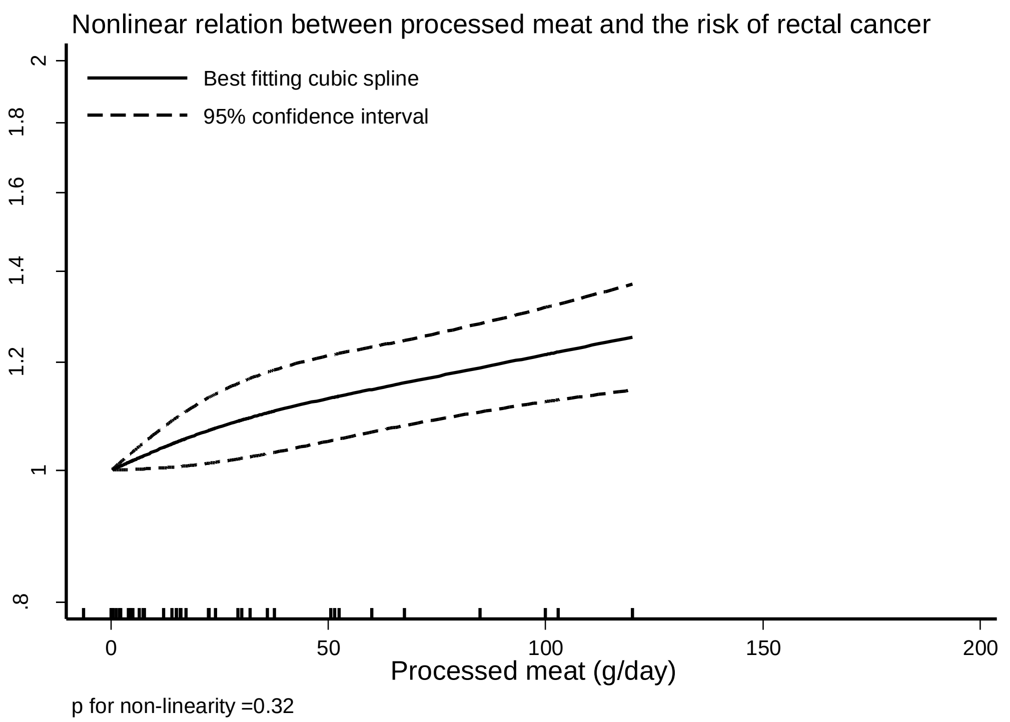


Table 71 Table with processed meat values and corresponding RRs (95% CIs) for non-linear analysis of processed meat and rectal cancer

Processed meat (g/day)	RR(95%CI)
0	1
15	1.04(1.00-1.09)
30	1.08(1.02-1.16)
50	1.12(1.05-1.21)
100	1.21(1.12-1.32)

2.5.1.3 Red meat

Cohort studies

Summary

Main results:
Three new publications were identified, one was an update of a study included in the 2010 SLR. There were no new studies on mortality.

Colorectal cancer:
Eight studies (6662 cases) were included in the dose-response meta-analysis of red meat and colorectal cancer. A borderline significant association with moderate heterogeneity was observed. No association of red meat intake and colorectal cancer risk was reported in most studies. The only evidence of an association is a significant dose-response relationship observed in the EPIC study. The European studies subgroup is the only subgroup showing a significant association. There was no evidence of publication bias (p=0.48). There was no evidence of a non-linear association (p=0.88).
The summary RRs ranged from 1.09 (95% CI=0.96-1.25) when EPIC (Norat, 2005) was omitted to 1.19 (95% CI=1.06-1.34) when MEC (Ollberding, 201) was omitted.

Colon cancer:
Eleven studies (4081 cases) were included in the dose-response meta-analysis of red meat and colon cancer. A significant association with moderate heterogeneity was observed. Only two studies (Larsson, 2005 and Takachi, 2011) showed significant increase risk with red meat consumption. In the Swedish Mammography Cohort (733 cases of colorectal cancer identified) consumption of unprocessed red meat (beef and pork) was associated almost 2-fold increased risk of distal colon cancer, whereas there was no apparent association with risks of proximal colon or rectal cancers. In the analysis in the large Japan Public Health Centre-based Prospective (JPHC) Study including 1145 colorectal cancer cases, a significant association of red meat intake with colon cancer was observed in women not in men (Takachi, 2011).

There was no evidence of publication bias (p=0.76). There was evidence of a non-linear association (p=0.02).
The summary RRs ranged from 1.09 (95% CI=1.03-1.16) when Larsson, 2005 was omitted to 1.24 (95% CI=1.08-1.43) when English, 2004 was omitted.

Rectal cancer:
Eight studies (1772 cases) were included in the dose-response meta-analysis of red meat and colon cancer. A non-significant association with no heterogeneity was observed. No association of red meat intake and rectal cancer risk was reported in all studies. There was no evidence of publication bias (p=0.45). There was no evidence of a non-linear association (p=0.94).
The summary RRs ranged from 1.05 (95% CI=0.94-1.17) when Norat, 2005 was omitted to 1.18 (95% CI=0.97-1.42) when Takachi, 2011 was omitted.

Study quality:
All studies used questionnaires self-reported FFQ or questionnaires to assess meat intake. In this analysis we included red meat was classified as beef, pork, lamb, hamburgers and fresh red meat. Studies which combined processed and unprocessed red meat where excluded from this analysis, and included in the red and processed meat analysis. All studies were multiple adjusted for different confounders. Cancer outcome was confirmed using cancer registry records in most studies.

Pooling project of cohort studies:
In a pooled analysis of the Genetics and Epidemiology of Colorectal Cancer Consortium (GECCO) and the Colon Cancer Family Registry (CCFR) (Kantor, 2014) seven American cohort studies were included (HPFS, MEC, NHS, PHS, PLCO, VITAL, WHI; 3 488 cases) for each serving/day increase of red meat the RR was 1.05 (95% CI 0.94–1.18).
In another publication of the Colon Cancer Family Registry and the Genetics and Epidemiology of Colorectal Cancer Consortium pooling individual data from case-control studies nested in five participating cohorts (HPFS, NHS, PLCO, VITAL, WHI; 3 091 cases and 4 209 controls), the OR for the highest compared to the lowest quartile of red meat was 1.06; 95% CI, 0.90–1.24 (Ananthakrishnan, 2014). The relationship was not modified by NAT2 enzyme activity (based on polymorphism at rs1495741). The OR in the nested case-control studies ranged from 0.97 (95% CI, 0.78-1.21) in the WHI (1429 cases and 1502 controls) to 1.37 (95% CI, 0.77-2.47) in the HPFS (174 cases and 322 controls).
In the UK Dietary Cohort Consortium (7 cohort studies), red meat intake was not related to the risk of colorectal cancer in a nested case-control of 579 cases and 1,996 controls matched on age, sex and recruitment date (Spencer, 2010). The RR for the highest compared to the lowest intake was 0.91 (0.66–1.24). Similar relationships were observed for colon and rectal cancers. The average intake of red and processed meat was low, 38.2 g/day in men and 28.7g/day in women controls and there was a high number of vegetarians in the cases.

Meta-analysis:
Two meta-analysis were published after the 2010 SLR. One showed that red meat intake was significantly related to the risk of colorectal (RR per 100g/day =1.17, 95% CI =1.05-1.31), and colon cancer (RR per 100g/day = 1.17, 95% CI =1.02-1.33). Not with rectal cancer (RR per 100g/day = 1.18, 95% CI = 0.98-1.42) (Chan, 2011).
Another meta-analysis (Alexander, 2015), combined 9 studies with different outcomes (colorectal, colon and rectal cancer) and obtained a RR of 1.05(0.98-1.12) for highest vs lowest.

Table 72 Red meat and colorectal cancer risk. Number of studies in the CUP SLR

	Number
Studies identified	14 (20 publications)
Studies included in forest plot of highest compared with lowest exposure	13
Studies included in dose-response meta-analysis	8
Studies included in non-linear dose-response meta-analysis	5

Note: Include cohort, nested case-control and case-cohort designs

Table 73 Red meat and colon cancer risk. Number of studies in the CUP SLR

	Number
Studies identified	14 (19 publications)
Studies included in forest plot of highest compared with lowest exposure	11
Studies included in dose-response meta-analysis	11
Studies included in non-linear dose-response meta-analysis	10

Note: Include cohort, nested case-control and case-cohort designs

Table 74 Red meat and rectal cancer risk. Number of studies in the CUP SLR

	Number
Studies identified	10 (13 publications)
Studies included in forest plot of highest compared with lowest exposure	8
Studies included in dose-response meta-analysis	8
Studies included in non-linear dose-response meta-analysis	7

Note: Include cohort, nested case-control and case-cohort designs

Table 75 Red meat and colorectal cancer risk. Summary of the dose-response meta-analysis in the 2010 SLR and 2015 SLR.

	2010 SLR	**2015 SLR**
Increment unit used	100g/day	100g/day
Studies (n)	8	8
Cases (total number)	4314	6662
RR (95%CI)	1.17 (1.05-1.31)	1.12(1.00-1.25)

Heterogeneity (I^2, p-value)	0%, 0.48	23.6%, 0.24

Stratified analysis by sex			
Men	**2010 SLR**	**2015 SLR**	
Studies (n)	2	2	
RR (95%CI)	1.28 (0.49 -3.35)	1.28(0.49-3.34)	
Heterogeneity (I^2, p-value)	64%, 0.09	64.2%, 0.09	
Women			
Studies (n)	3	4	
RR (95%CI)	1.05 (0.78 - 1.42)	1.02(0.78-1.33)	
Heterogeneity (I^2, p-value)	22%, 0.28	11.3%, 0.34	
Stratified analysis by geographic location			
(no analysis in 2005 or 2010 SLR)			
2015 SLR	**Asia**	**Europe**	**North America**
Studies (n)	2	6	1
RR (95%CI)	1.03(0.71-1.49)	1.20(1.05-1.37)	1.01(0.90-1.14)
Heterogeneity (I^2, p-value)	47.9%, 0.16	2.3%, 0.40	

Table 76 Red meat and colon cancer risk. Summary of the dose-response meta-analysis in the 2010 SLR and 2015 SLR.

	2010 SLR	2015 SLR
Increment unit used	100g/day	100g/day
Studies (n)	9	11
Cases (total number)	3172	4081
RR (95%CI)	1.12 (0.97-1.29)	1.22 (1.06-1.39)
Heterogeneity (I^2, p-value)	0%, 0.89	11.7%, 0.33

Stratified analysis by sex			
Men	**2010 SLR**	**2015 SLR**	
Studies (n)	2	2	
RR (95%CI)	1.06 (0.7-1.50)	1.07(0.74-1.56)	
Heterogeneity (I^2, p-value)	0%, 0.98	0%, 0.96	
Women			
Studies (n)	4	6	
RR (95%CI)	1.00 (0.72 - 1.38)	1.14(0.82-1.60)	
Heterogeneity (I^2, p-value)	0%, 0.60	39.1%, 0.13	
Stratified analysis by geographic location			
(no analysis in 2005 or 2010 SLR)			
2015 SLR	**Asia**	**Europe**	**North America**
Studies (n)	4	3	4
RR (95%CI)	1.14(0.90-	1.38 (1.02-1-87)	1.13 (0.86-1.48)

	1.44)		
Heterogeneity (I^2, p-value)	17.7%, 0.31	45.4%, 0.14	0%, 0.50

Table 77 Red meat and rectal cancer risk. Summary of the dose-response meta-analysis in the 2010 SLR and 2015 SLR.

	2010 SLR	2015 SLR
Increment unit used	100g/day	100g/day
Studies (n)	7	8
Cases (total number)	1477	1772
RR (95%CI)	1.18 (0.98-1.42)	1.13(0.96-1.34)
Heterogeneity (I^2, p-value)	0%, 0.67	0%, 0.52

Stratified analysis by sex		
(no analysis in 2005 or 2010 SLR)		
2015 SLR	**Men**	**Women**
Studies (n)	1	4
RR (95%CI)	0.90(0.92-1-92)	0.86(0.58-1.27)
Heterogeneity (I^2, p-value)		0%, 0.89

Stratified analysis by geographic location			
(no analysis in 2005 or 2010 SLR)			
2015 SLR	**Asia**	**Europe**	**North America**
Studies (n)	3	3	2
RR (95%CI)	1.10(0.74-1.64)	1.19 (0.95-1.50)	0.89 (0.51-1.56)
Heterogeneity (I^2, p-value)	45.4%, 0.16	0%, 0.74	0%

Table 78 Red meat and colorectal cancer risk. Results of meta-analyses and pooled analyses of prospective studies published after the 2005 SLR.

Author, Year	Number of cohort studies	Total number of cases	Studies country, area	Outcome	Comparison	RR (95%CI)	P trend	Heterogeneity (I^2, p value)*
Pooled analysis								
Kantor, 2014	7 nested case-control studies HPFS, MEC, NHS, PHS, PLCO, VITAL, WHI	3 488	North America	Colorectal cancer	Per 1 serving/day	1.05 (0.94–1.18)		
Ananthakrishnan, 2014	5 nested case-control studies HPFS, NHS, PLCO, VITAL, WHI	2564	North America	Colorectal cancer	Highest vs lowest	1.06 (0.90–1.24)		
Spencer, 2010	7 Guernsey Study, EPIC- Norfolk, EPIC-Oxford, NSHD, Oxford Vegetarian	579 cases 1996 controls	UK	Colorectal cancer	≥50 vs <5 g/day Per 50g/day	0.91 (0.66–1.24) 1.01 (0.84–1.22)	0.89	
				Colon cancer	≥50 vs <5 g/day Per 50g/day	0.92 (0.62–1.35) 1.04 (0.83–1.31)	0.72	
				Rectal cancer	≥50 vs <5 g/day Per 50g/day	0.87 (0.50–1.52) 0.96 (0.70–1.31)	0.78	

	Study Oxford Vegetarian Study, UKWCS, Whitehall II							
Meta-analysis								
Alexander, 2015	17		Europe, Asia and North America	Colorectal, colon and rectal cancer combined	Highest vs lowest	1.05(0.98-1.12)		8.45%, 0.33
Chan, 2011	8	11358	Europe, Asia and North America	Colorectal cancer	Per 100g/day	1.17(1.05-1.31)		0%, 0.48
	10	5426		Colon cancer	Per 100g/day	1.17(1.02-1.33)		0%, 0.64
	7	2091		Rectal cancer	Per 100g/day	1.18(0.98-1.42)		0%, 0.66

* Heterogeneity (I^2, p value) only reported when available

Table 79 Red meat and colorectal cancer risk. Main characteristics of studies included in the CUP SLR dose-response meta-analysis

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Missing data derived for analyses
Parr, 2013 COL40955 Norway	NOWAC, Prospective Cohort, Age: 41-70 years, W	666/ 84 538 11.1 years	Cancer registry	FFQ	Incidence, colorectal cancer	≥35 vs ≤5 g/day	0.92 (0.61-1.39)	Age, alcohol, BMI, calcium, energy, fibre, physical activity, smoking	Only included in subgroup analysis. Component of the EPIC study. Superseded by Norat, 2005 COL01698 and Bamia, 2013 COL40964
						per 100 g/day	0.70 (0.33-1.48)		
		455/			Incidence, colon cancer	25-35 vs ≤5 g/day	0.83 (0.58-1.18)		
						per 100 g/day	0.76 (0.31-1.86)		
		211/			Incidence, rectal cancer	per 100 g/day	0.59 (0.15-2.25)		
						25-35 vs ≤5 g/day	0.92 (0.53-1.59)		
Ollberding, 2012 COL40941 Hawaii, USA	MEC, Prospective Cohort, Age: 45-75 years, M/W	3 404/ 165 717 8.1 years	Cancer registry and national death Index	FFQ	Incidence, colorectal cancer	47.99 vs 7.41 g/1000 kcal/day	1.02 (0.91-1.16)	Age, sex, age at cohort entry In log linear model, alcohol consumption, BMI, calcium, dietary fibre, energy intake, ethnicity, family history of colorectal cancer, folate, history of diabetes, history of polyp diagnosis, HRT use, non-steroidal anti-inflammatory drug use, pack yrs of smoking,	Distribution of person-years by exposure category. Mid-points of exposure categories. Intakes in g/1000kcal/day converted to g/day using average energy intake per each quantile

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Missing data derived for analyses
								vigorous physical activity, vitamin d	
Takachi, 2011 COL41056 Japan	JPHC, Prospective Cohort, Age: 45-74 years, M/W	307/ 80 658 9 years	Hospital records + cancer registry	FFQ	Incidence, colon cancer, women	93 vs 14 g/day	1.48 (1.01-2.17)	Age, alcohol consumption, area, BMI, calcium, diabetes, energy, fibre, folate, physical activity, salted fish consumption, screening exams, smoking status, vitamin b6, vitamin d	Distribution of person-years by exposure category.
		259/			Men	117 vs 20 g/day	1.27 (0.93-1.74)		
		233/			Incidence, rectal cancer, men	117 vs 20 g/day	0.93 (0.58-1.49)		
		124/			Women	93 vs 14 g/day	0.81 (0.43-1.52)		
Lee, 2009 COL40764 China	SWHS, Prospective Cohort, Age: 40-70 years, W	394/ 73 224 7.4 years	Cancer registry and death certificates and participant contact	Quantitative FFQ	Incidence, colorectal cancer	≥67 vs ≤23.9 g/day	0.80 (0.60-1.10)	Age, educational level, energy intake, fibre intake, Income, NSAID use, season of Interview, tea consumption	Estimate confidence intervals, distribution of person-years by exposure category. Mid-points of exposure categories.
		236/			Incidence, colon cancer	≥67 vs ≤23.9 g/day	0.90 (0.60-1.50)		
		158/			Incidence, rectal cancer	≥67 vs ≤23.9 g/day	0.60 (0.30-1.10)		
Oba, 2006 COL40626 Japan	TCCJ, Prospective Cohort,	111/ 30 221 8 years	Hospital records and cancer registry	Semi-quantitative FFQ	Incidence, colon cancer, men	56.6 vs 18.7 g	1.03 (0.64-1.66)	Age, alcohol intake, BMI, energy intake,	Distribution of person-years by exposure

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Missing data derived for analyses
	Age: 35-101 years, M/W	102/			Women	42.3 vs 10.7 g	0.79 (0.49-1.28)	height, pack-years of smoking, physical activity	category.
Larsson, 2005 COL01849 Sweden	SMC, Prospective Cohort, Age: 40-75 years, W	733/ 61 433 855 585 person-years	Cancer registry	Questionnaire	Incidence, colorectal cancer,	≥4 vs 0-1.9 servings/week	1.22 (0.98-1.53)	Age, alcohol consumption, BMI, calcium, educational level, energy intake, fish, folate, fruits, poultry, saturated fat, vegetables, whole-grain foods	Distribution of person-years by exposure category. Mid-points of exposure categories. Conversion from servings/week to g/day.
		234/			Incidence, proximal colon cancer,	≥4 vs 0-1.9 servings/week	1.10 (0.74-1.64)		
		230/			Incidence, rectal cancer,	≥4 vs 0-1.9 servings/week	1.08 (0.72-1.62)		
		155/			Incidence, distal colon cancer,	≥4 vs 0-1.9 servings/week	1.99 (1.26-3.14)		
Norat, 2005 COL01698 Europe	EPIC, Prospective Cohort, Age: 21-83 years, M/W	1 329/ 478 040 2 279 075 person-years	Cancer registry	Questionnaire	Incidence, colorectal cancer,	per 100 g/day	1.21 (1.02-1.43)	Age, sex, alcohol consumption, body weight, centre location, energy from fat sources, energy from non-fat sources, fibre, height, physical activity, smoking status	Continuous results were directly used in dose-response analysis
						≥80 vs ≤10 g/day	1.17 (0.92-1.49)		
		855/			Incidence, colon cancer,	per 100 g/day	1.20 (0.96-1.48)		
						≥80 vs ≤10 g/day	1.20 (0.88-1.61)		
		474/			Incidence, rectal cancer,	per 100 g/day	1.23 (0.94-1.62)		
						≥80 vs ≤10 g/day	1.13 (0.74-1.71)		

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Missing data derived for analyses
English, 2004 COL00019 Australia	MCCS, Prospective Cohort, Age: 27-75 years, M/W	452/ 37 112 9 years	Population/electoral rolls	FFQ	Incidence, colorectal cancer,	≥6.5 vs ≤3 times/week	1.40 (1.00-1.90)	Age, sex, cereal product intake, country of birth, energy intake, fat intake	Distribution of person-years by exposure category. Mid-points of exposure categories. Conversion from times/week to g/day
		283/			Incidence, colon cancer,	≥6.5 vs ≤3 times/week	1.10 (0.70-1.60)		
		169/			Incidence, rectal cancer,	≥6.5 vs ≤3 times/week	2.30 (1.20-4.20)		
Wei, 2004 COL00581 USA	NHS, Prospective Cohort, W, nurses	670/ 87 733 24 years	Population registries	Semi-quantitative FFQ	Incidence, colon cancer,	≥5 vs ≤0 serving	1.31 (0.73-2.36)	Age, alcohol consumption, BMI, calcium, family history of colorectal cancer, folate, height, history of endoscopy, pack-years of smoking before age 30, physical activity, processed meat Family history, folate intake, pack-years of smoking, total calcium	Distribution of person-years by exposure category. Mid-points of exposure categories. Conversion from times/week to g/day
	HPFS, Prospective Cohort, M, Health professionals	467/ 46 632 14 years	Self-reported verified by medical record and The National Death Index	Semi-quantitative FFQ	Incidence, colon cancer,	≥5 vs ≤0 times	1.35 (0.80-2.27)		
	NHS	203/ 87 733 24 years		Semi-quantitative FFQ	Incidence, rectal cancer,	≥5 vs ≤0 serving/month	0.92 (0.31-2.71)		
	HPFS	135/ 46 632 14 years		Semi-quantitative FFQ	Incidence, rectal cancer,	≥5 vs ≤0 times	0.90 (0.34-2.45)		
Tiemersma, 2002 COL00563 Netherlands	Dutch prospective Monitoring Project on	54/ 292 controls 8.5 years	Population	FFQ	Incidence, colorectal cancer, men	≥5 vs 0-3 times/week	2.70 (1.10-6.70)	Age, alcohol consumption, body height, energy intake,	Distribution of person-years by exposure category. Mid-

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Missing data derived for analyses
	Cardiovascular Disease Risk Factors, Nested Case Control, Age: 20-59 years, M/W							study centre	points of exposure categories. Conversion from times/week to g/day
		48/ 245 controls			Women	≥5 vs 0-3 times/week	1.20 (0.50-2.80)		
Jarvinen, 2001 COL00852 Finland	Finnish Mobile Clinic Health Examination Survey, Prospective Cohort, Age: 39 years, M/W	109/ 9 959	Population/invitation	Questionnaire	Incidence, colorectal cancer,	Q 4 vs Q 1	1.50 (0.77-2.94)	Age, sex, BMI, cereal intake, energy intake, fruits intake, geographic location, occupational group, smoking, vegetable intake	Distribution of person-years by exposure category
		63/			Incidence, colon cancer,	Q 4 vs Q 1	1.34 (0.57-3.15)		
		46/			Incidence, rectal cancer,	Q 4 vs Q 1	1.82 (0.60-5.52)		
Pietinen, 1999 COL00176 Finland	ATBC, Prospective Cohort, Age: 50-69 years, M, Smokers	185/ 27 111 8 years	Cancer registry	Dietary history questionnaire	Incidence, colorectal cancer,	99 vs 35 g/day	0.80 (0.50-1.20)	Age, alcohol consumption, BMI, calcium intake, educational level, physical activity, smoking years, supplement group	Distribution of person-years by exposure category
Singh, 1998 COL00185	AHS, Prospective	127/ 32 051	Census list	FFQ	Incidence, colon cancer,	≥1 vs ≤0 times/week	1.41 (0.90-2.21)	Age, sex, alcohol	Mid-points of exposure

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Missing data derived for analyses
USA	Cohort, Age: 25- years, M/W, Seventh-day Adventists	178 544 person-years						consumption, aspirin use, BMI, family history of specific cancer, physical activity, smoking habits	categories. Conversion from times/week to g/day
Bostick, 1994 COL00079 USA	IWHS, Prospective Cohort, Age: 55-69 years, W	212/ 35 216 167 447 person-years	SEER	Semi-quantitative FFQ	Incidence, colon cancer,	≥3 vs ≤1 serving/week	1.21 (0.75-1.96)	Age, energy intake, height, parity, total vitamin e intake, total vitamin e intake, vitamin a supplement	Mid-points of exposure categories. Conversion from servings/week to g/day

Table 80 Red meat and colorectal cancer risk. Main characteristics of studies excluded from the CUP SLR dose-response meta-analysis

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Reasons for exclusion
Wie, 2014 COL41065 Korea	Cancer Screening Examination Cohort, Korea (CSECK), Prospective Cohort, M/W	53/ 8 024 7 years	Cancer registry and medical records	3-day food record	Incidence, colorectal cancer	≥43 vs <43 g/day	1.31 (0.60-2.61)	Age, sex, alcohol, BMI, educational level, energy intake, Income, marital status, physical activity, smoking	Used only in highest versus lowest analysis.
Agnoli, 2013 COL40938 Italy	EPIC-Italy, Prospective Cohort, M/W	435/ 45 275 11.28 years	Cancer registry and hospital records	Semi-quantitative FFQ	Incidence, colorectal cancer	112-665.6 vs 0-69 g/day	0.94 (0.72-1.23)	Age, BMI, educational level, gender, non-alcoholic beverage intake, physical activity, smoking, study center	Superseded by Norat, 2005 COL01698
						112-665.6 vs 0-69 g/day	0.97 (0.74-1.26)		
Egeberg, 2013 COL40953 Denmark	DCH, Prospective Cohort, Age: 50-64 years, M/W	644/ 53 988 13.4 years	Cancer registry	FFQ	Incidence, colon cancer	per 50 g/day	1.01 (0.87-1.19)	Age, alcohol, beef consumption, cold cuts, educational level, energy, fiber, fish, HRT use, lamb intake, liver, meat, nsaid use, pork, poultry,	Component of EPIC Superseded by Norat, 2005 COL01698
		345/			Incidence, rectal cancer	per 50 g/day	1.01 (0.87-1.19)		

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Reasons for exclusion
								processed meat, sausages, smoking, sport, veal meat, waist circumference	
Gay, 2012 COL40920 UK	EPIC-Norfolk, Prospective Cohort, Age: 45-79 years, M/W	185/ 25 636 11 years	Cancer registry	7-day dietary recalls	Incidence, colorectal cancer, gc:at mutations	per 1 sd units	0.68 (0.37-1.28)	Age, sex, smoking	Superseded by Norat, 2005 COL01698
					Apc promoter methylation ≥20%	per 1 sd units	1.07 (0.75-1.53)		
					Apc mutations	per 1 sd units	1.17 (0.85-1.59)		
Cross, 2010 COL40794 USA	NIH-AARP, Prospective Cohort, Age: 50-71 years, Retired	2719/ 300 948 7.0 years	Cancer registry and national health database	FFQ	Incidence, colorectal cancer	Q5 vs Q1	1.13(0.98-1.30)	Sex, age at baseline, alcohol consumption, aspirin use, BMI, educational level, energy, history of colon cancer, HRT use, physical activity, race, smoking	Used in highest compared to lowest analysis for colorectal cancer. NIH-AARP report most results on red and processed meat combined.
Nöthlings, 2009 COL40763 USA	MEC, Nested Case Control, Age: 45-75 years, M/W	1 009/ 1522 controls	Surveillance registry/end results cancer registry	FFQ	Incidence, colorectal cancer	≥26 vs 0-10.3 g/1000kcal/day	0.96 (0.74-1.23)	Age, sex, calcium intake, ethanol, ethnicity, folic acid intake, pack-years of	Superseded by Ollberding, 2012 COL40941
						≥26 vs 0-10.3 g/1000kcal/day	1.07 (0.84-1.35)		

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Reasons for exclusion
								smoking	
Butler, 2008 COL40639 Singapore	SCHS, Prospective Cohort, Age: 45-74 years, M/W	961/ 61 321 9.8 years	Cancer registry	FFQ	Incidence, colorectal cancer	Q 4 vs Q 1	1.01 (0.82-1.26)	Age, sex, alcohol intake, BMI, diabetes, dialect group, educational level, energy intake, exposure assessment, family history of colorectal cancer, physical activity, smoking habits	Used only in highest versus lowest analysis.
Sorensen, 2008 COL40690 Denmark	DCH, Case Cohort, Age: 50-64 years, M/W	379/ 57 000 10 years	Cancer registry	FFQ	Incidence, colorectal cancer, nat1 fast	per 25 g/day	1.06 (0.97-1.17)	Alcohol intake, BMI, dietary fiber intake, fish, HRT use, poultry, smoking status	Component of EPIC Superseded by Norat, 2005 COL01698
					Nat2 slow phenotype	per 25 g/day	1.06 (0.97-1.14)		
					Nat1 slow phenotype	per 25 g/day	1.02 (0.95-1.09)		
					Nat2 fast phenotype	per 25 g/day	1.01 (0.93-1.09)		
Iso, 2007 COL40707 Japan	JACC, Prospective Cohort, Age: 40-79 years, M/W	199/ 105 500 15 years	Municipal resident registration records, death certificates	FFQ	Mortality, colon cancer, women	3-4 vs ≤0 /week	0.80 (0.43-1.50)	Age, centre location	Outcome is mortality
		197/			Men	3-4 vs ≤0 /week	1.30 (0.74-2.29)		
		152/			Mortality, rectal	3-4 vs ≤0 /week	1.11 (0.55-2.20)		

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Reasons for exclusion
					cancer, men				
		75/			Women	3-4 vs ≤0 /week	0.78 (0.23-2.63)		
Feskanich, 2004 COL01680 USA	NHS, Nested Case Control, Age: 46-78 years, W	193/ 383 controls 11 years	Medical records and writing or by telephone	FFQ	Incidence, colorectal cancer,	(mean exposure)		Month of blood draw, year of birth	Reviewed in text, no RR. Superseded by Wei, 2004 COL00581
Khan, 2004 COL01606 Japan	HCS, Prospective Cohort, Age: 40-97 years, M/W	15/ 3 458 14.3 years	Area residency lists	Questionnaire	Mortality, colorectal cancer, men	Q 2 vs Q 1	2.00 (0.60-6.30)	Age, smoking habits	Outcome is mortality
		14/			Women	Q 2 vs Q 1	1.00 (0.30-3.00)	Health education, health screening, health status	
Kojima, 2004 COL01840 Japan	JACC, Prospective Cohort, Age: 40-79 years, M/W	110/ 107 824 10 years	Resident registry and death certificates	Questionnaire	Mortality, colon cancer, women	3-7 vs 0-0.5 times/week	1.11 (0.57-2.14)	Age, alcohol consumption, BMI, educational level, family history of specific cancer, physical activity, region of enrolment, smoking status	Outcome is mortality
		86/			Men	3-7 vs 0-0.5 times/week	1.46 (0.74-2.86)		
		81/			Mortality, rectal cancer, men	3-7 vs 0-0.5 times/week	1.38 (0.68-2.78)		
		30/			Women	3-7 vs 0-0.5 times/week	0.37 (0.05-2.84)		
Kato, 1997 CRC00022 USA	New York University Women's Health	100/ 14 272 105 044 person-	Questionnaire, medical records, cancer registries	Semi-quantitative FFQ	Incidence, colorectal cancer,	Q 4 vs Q 1	1.23 (0.68-2.22)	Age, educational level, place at enrolment, total	Used only in highest versus lowest analysis.

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Reasons for exclusion
	Study, Prospective Cohort, Age: 34-65 years, W	years						calorie intake	
Fraser, 1999 COL00102 USA	AHS, Prospective Cohort, Age: 25-100 years, M/W, Seventh-day Adventists	112/ 34 198 6 years	Census list	FFQ	Incidence, colon cancer, consumption white meat < 1 time/week	≥1 vs ≤0 times/day	1.86 (1.15-3.02)		Subgroup analysis only, superseded by Singh, 1998 COL00185
					Infrequent consumers of legumes	yes vs no times/week	2.68 (1.24-5.78)		
Hirayama, 1990 COL01508 Japan	Japan 6 prefectures cohort study, Prospective Cohort, Age: 40- years, M/W	563/ 265 118 17 years	Health centres	Interview	Mortality, rectal cancer,	daily consumption vs no daily consumption	0.73 (0.55-0.99)	Age, sex	Outcome is mortality
		558/			Mortality, colon cancer,	daily consumption vs no daily consumption	0.87 (0.66-1.14)		
Willett, 1990 CRC00026 USA	NHS, Prospective Cohort, Age: 34-59 years, W, Registered	150/ 88 751 512 488 person-years	Self-reported verified by medical record and The National Death Index	Semi-quantitative FFQ	Incidence, colon cancer,	≥7 vs ≤1 times/month	2.49 (1.24-5.03)	Age	Superseded by Wei, 2004 COL00581

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Reasons for exclusion
	nurses								

Figure 123 RR estimates of colorectal cancer by levels of red meat

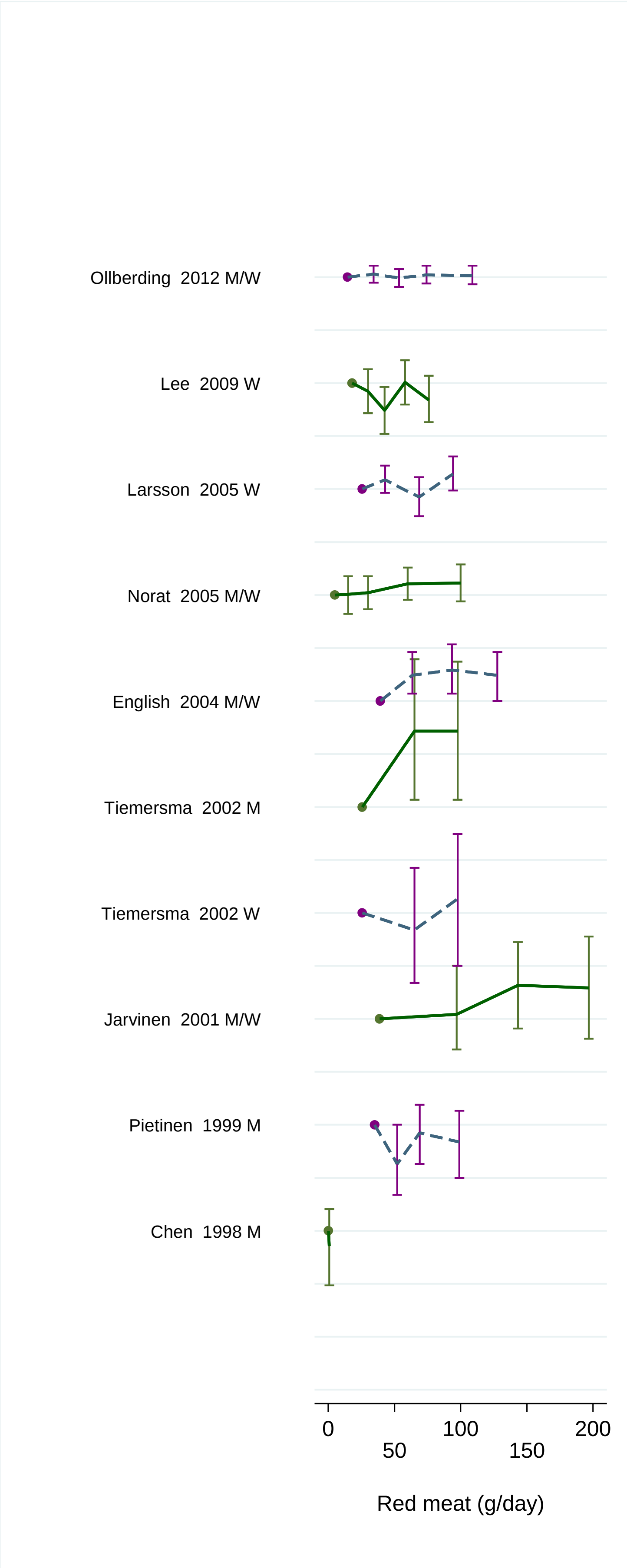


Figure 124 RR (95% CI) of colorectal cancer for the highest compared with the lowest level of red meat

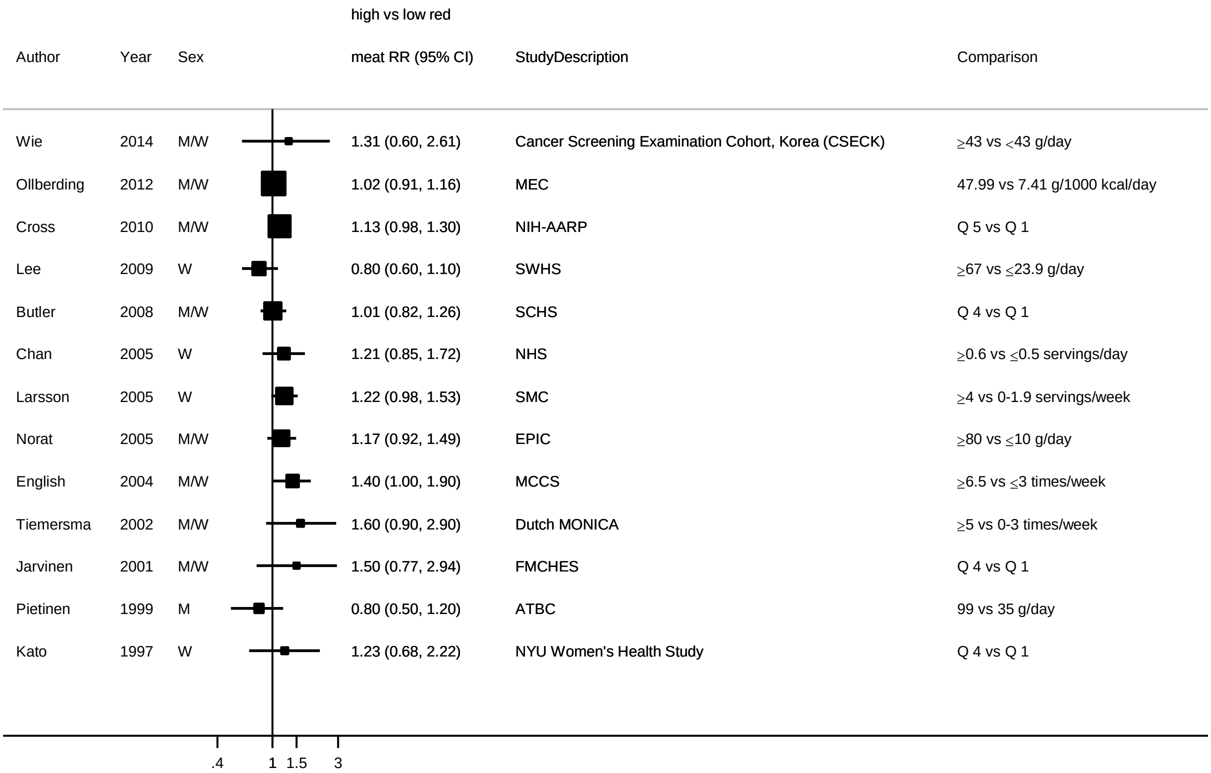
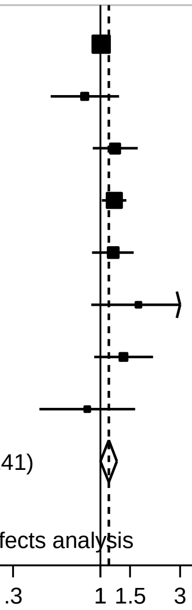


Figure 125 RR (95% CI) of colorectal cancer for 100g/day increase of red meat

Author	Year	Sex	per 100g RR (95% CI)	% Weight	StudyDescription
Ollberding	2012	M/W	1.01 (0.90, 1.14)	35.10	MEC
Lee	2009	W	0.81 (0.50, 1.29)	5.17	SWHS
Larsson	2005	W	1.23 (0.90, 1.67)	10.56	SMC
Norat	2005	M/W	1.21 (1.02, 1.43)	24.84	EPIC
English	2004	M/W	1.19 (0.89, 1.58)	12.02	MCCS
Tiemersma	2002	M/W	1.69 (0.88, 3.23)	2.82	Dutch MONICA
Jarvinen	2001	M/W	1.37 (0.92, 2.06)	6.75	FMCHES
Pietinen	1999	M	0.83 (0.43, 1.61)	2.75	ATBC
Overall (I-squared = 23.6%, p = 0.241)			1.12 (1.00, 1.25)	100.00	



NOTE: Weights are from random effects analysis

Figure 126 Funnel plot of studies included in the dose response meta-analysis red meat and colorectal cancer

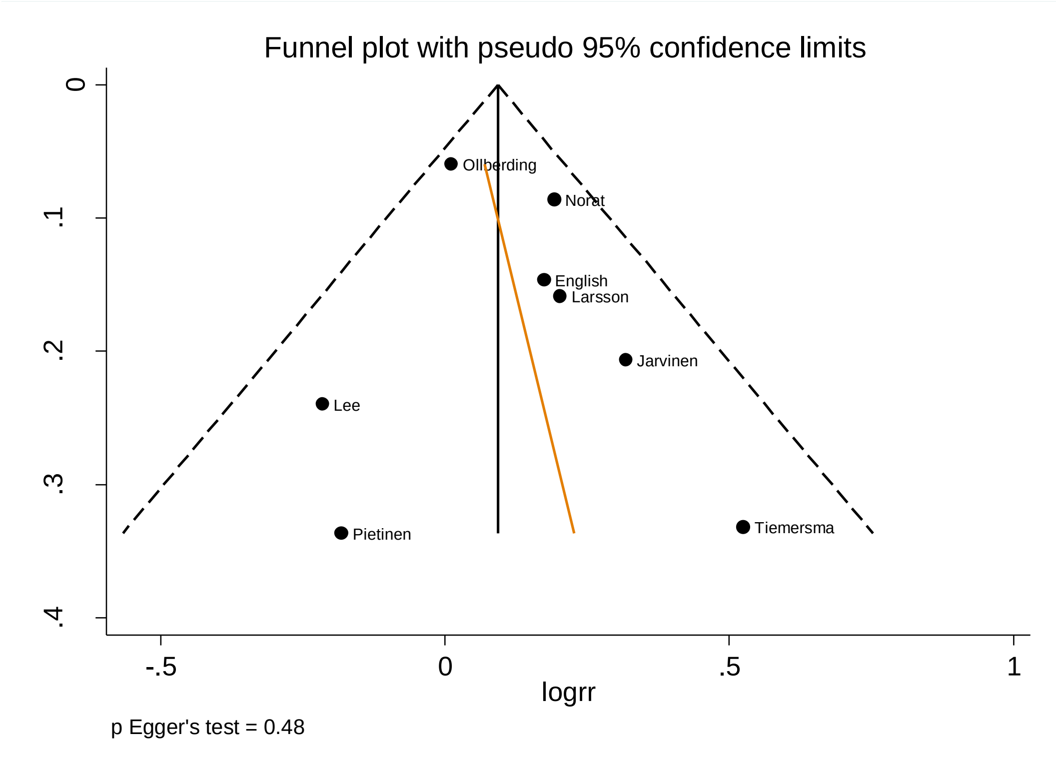


Figure 127 RR (95% CI) of colorectal cancer for 100g/day increase of red meat by sex

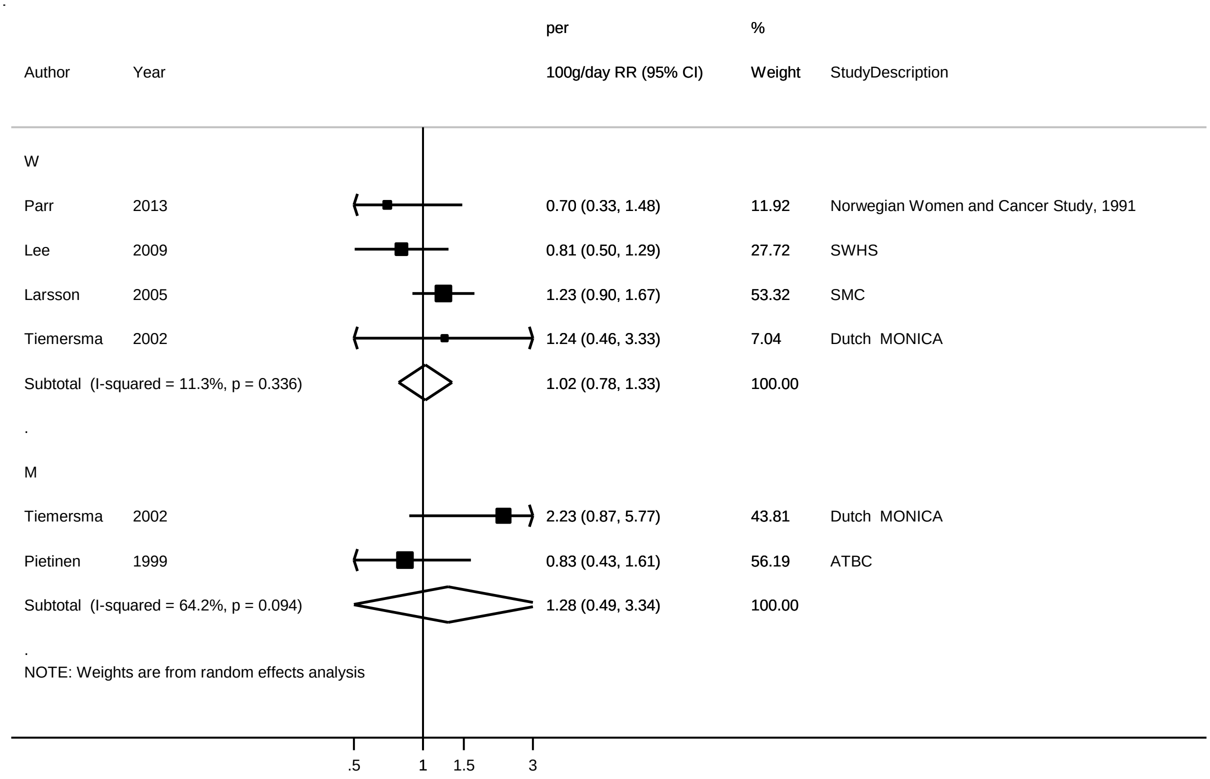


Figure 128 RR (95% CI) of colorectal cancer for 100g/day increase of red meat by location

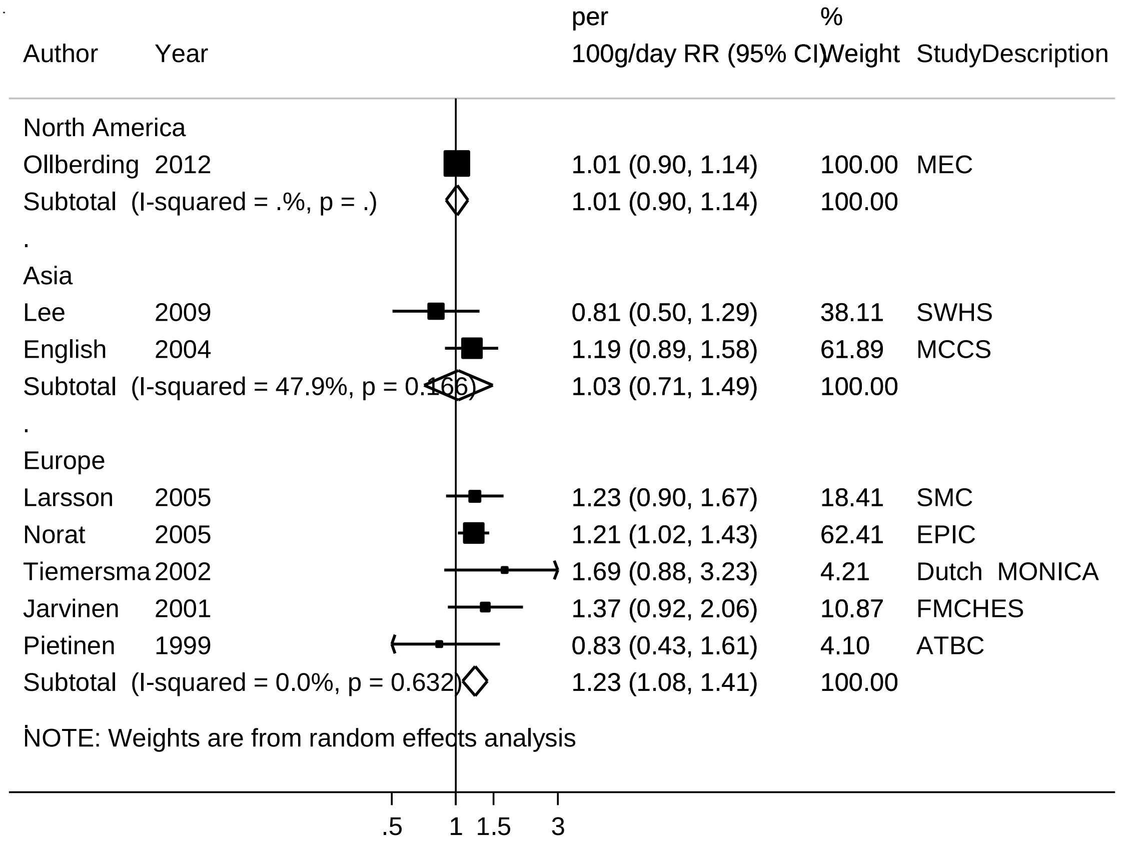
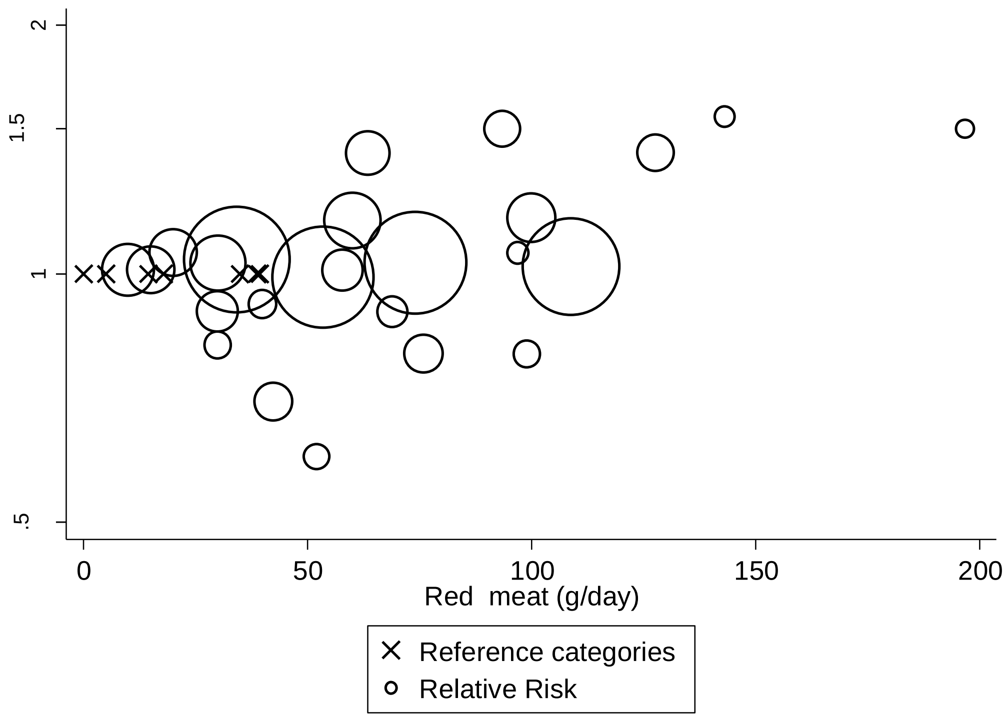


Figure 129 Relative risk of colorectal cancer and red meat estimated using non-linear models



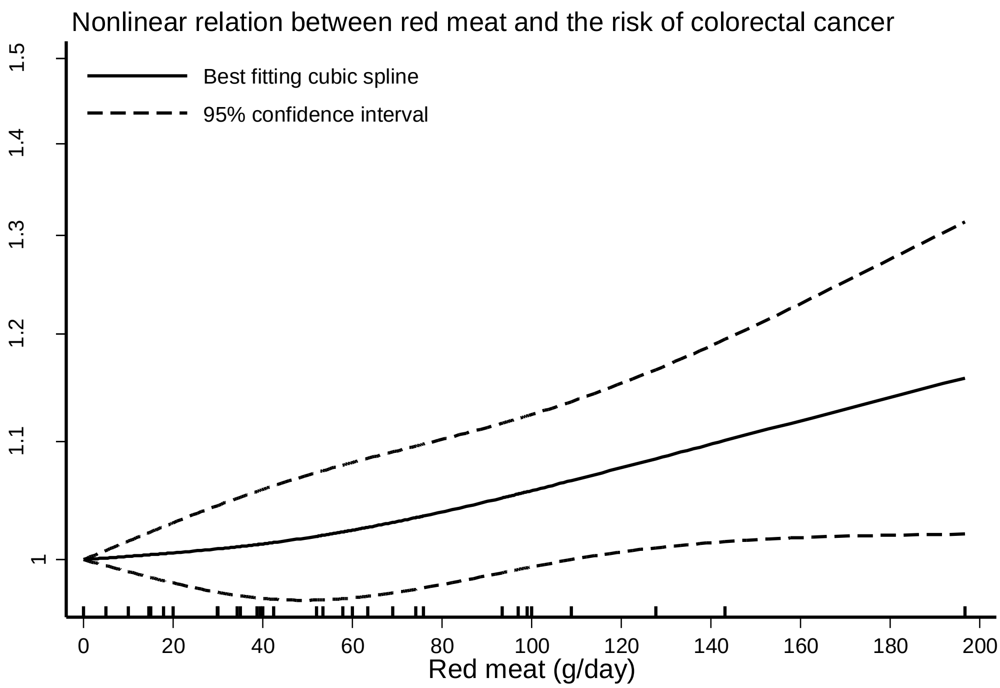


Table 81 Table with red meat values and corresponding RRs (95% CIs) for non-linear analysis of red meat and colorectal cancer

Red meat (g/day)	RR(95%CI)
0	1
15	1.00(0.99-1.02)
30	1.00(0.97-1.04)
50	1.01(0.96-1.07)
100	1.05(0.99-1.12)

Figure 130 RR estimates of colon cancer by levels of red meat

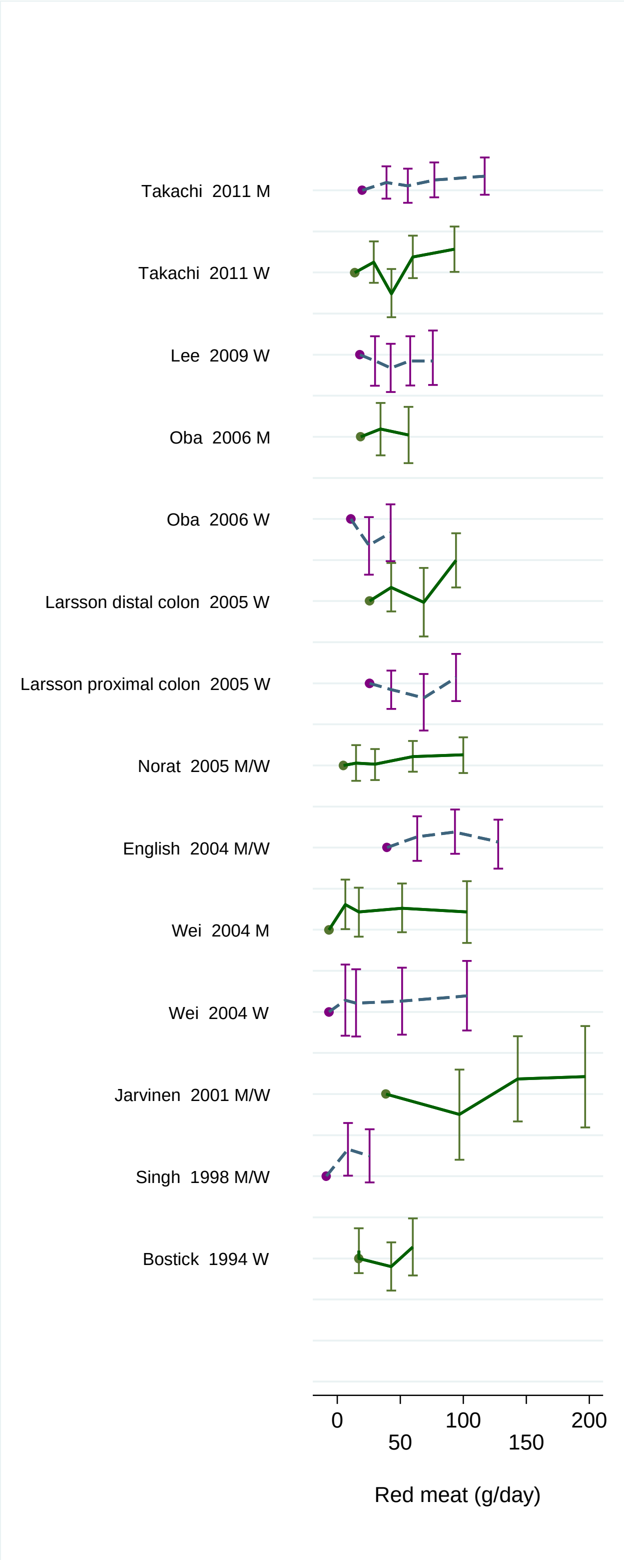


Figure 131 RR (95% CI) of colon cancer for the highest compared with the lowest level of red meat

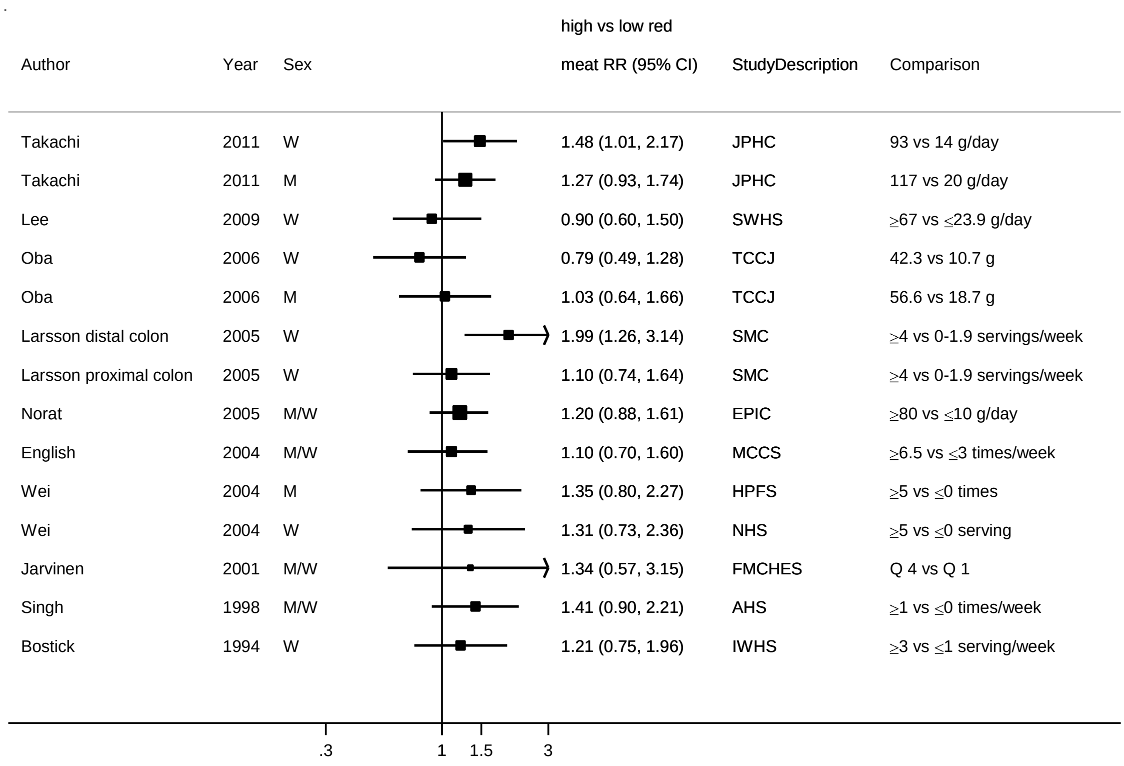


Figure 132 RR (95% CI) of colon cancer for 100g/day increase of red meat

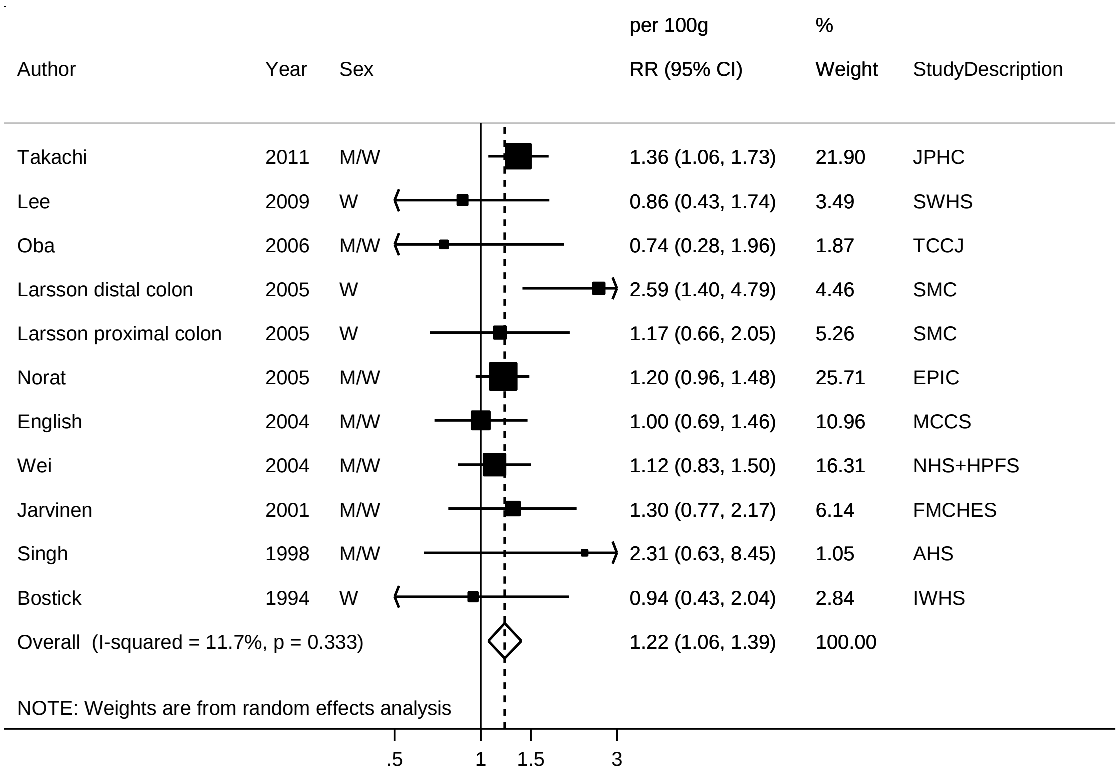


Figure 133 Funnel plot of studies included in the dose response meta-analysis red meat and colon cancer

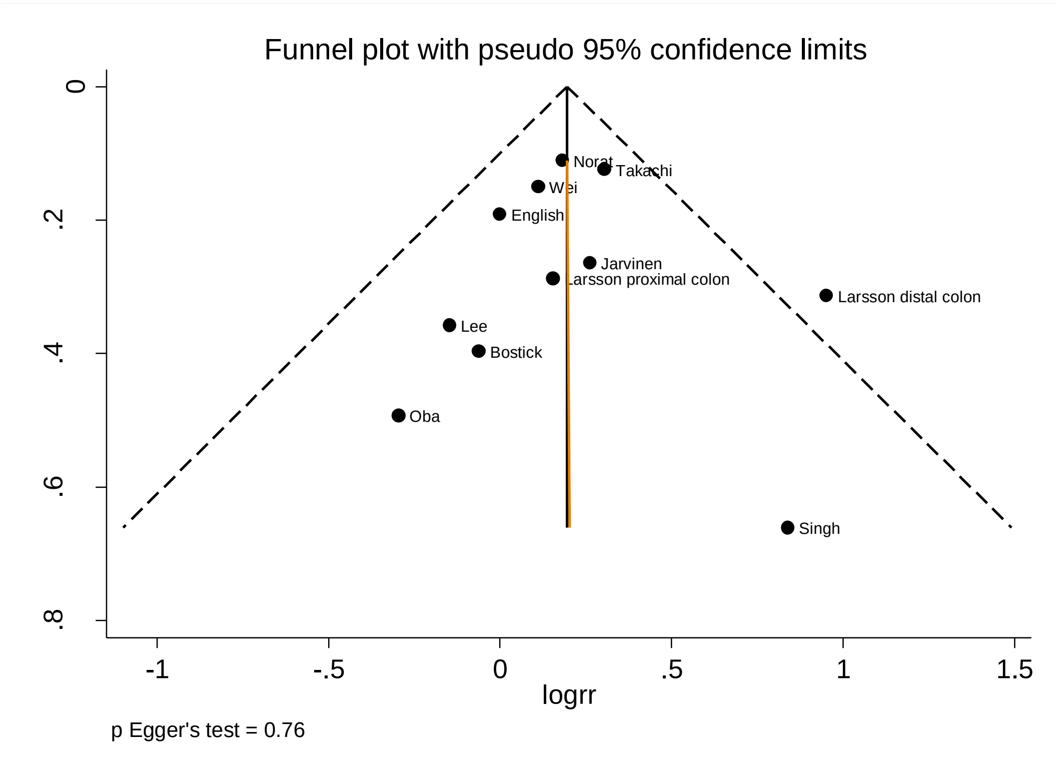


Figure 134 RR (95% CI) of colon cancer for 100g/day increase of red meat by sex

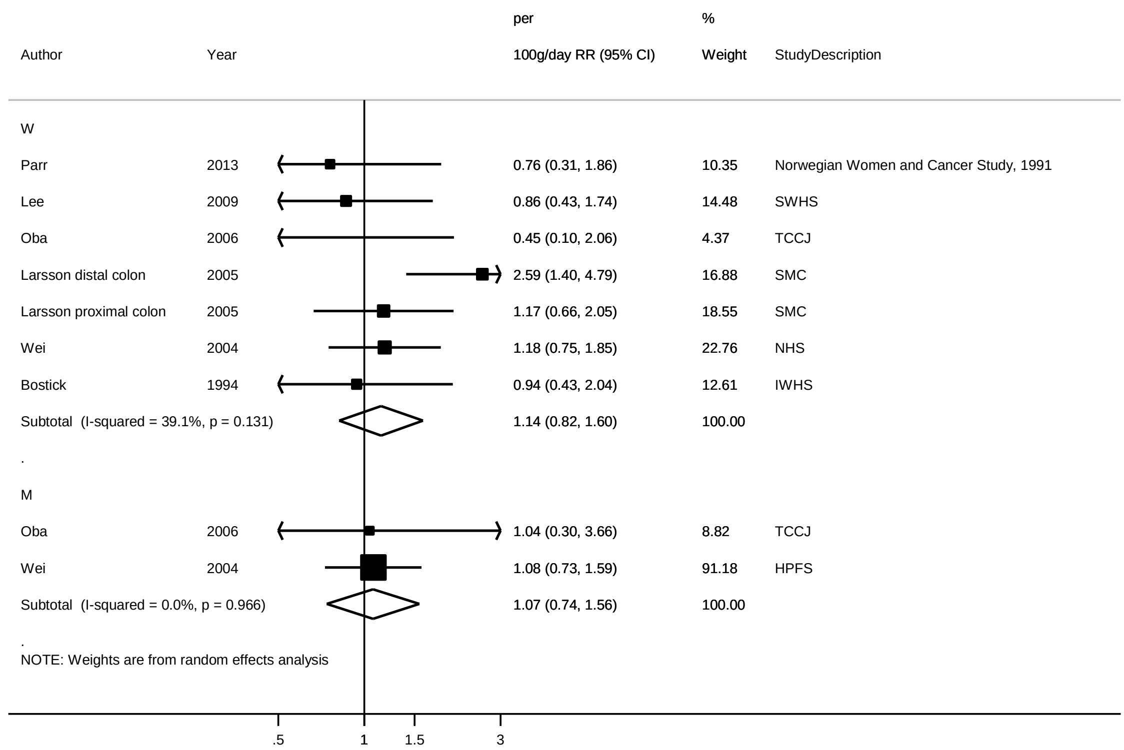


Figure 135 RR (95% CI) of colon cancer for 100g/day increase of red meat by location

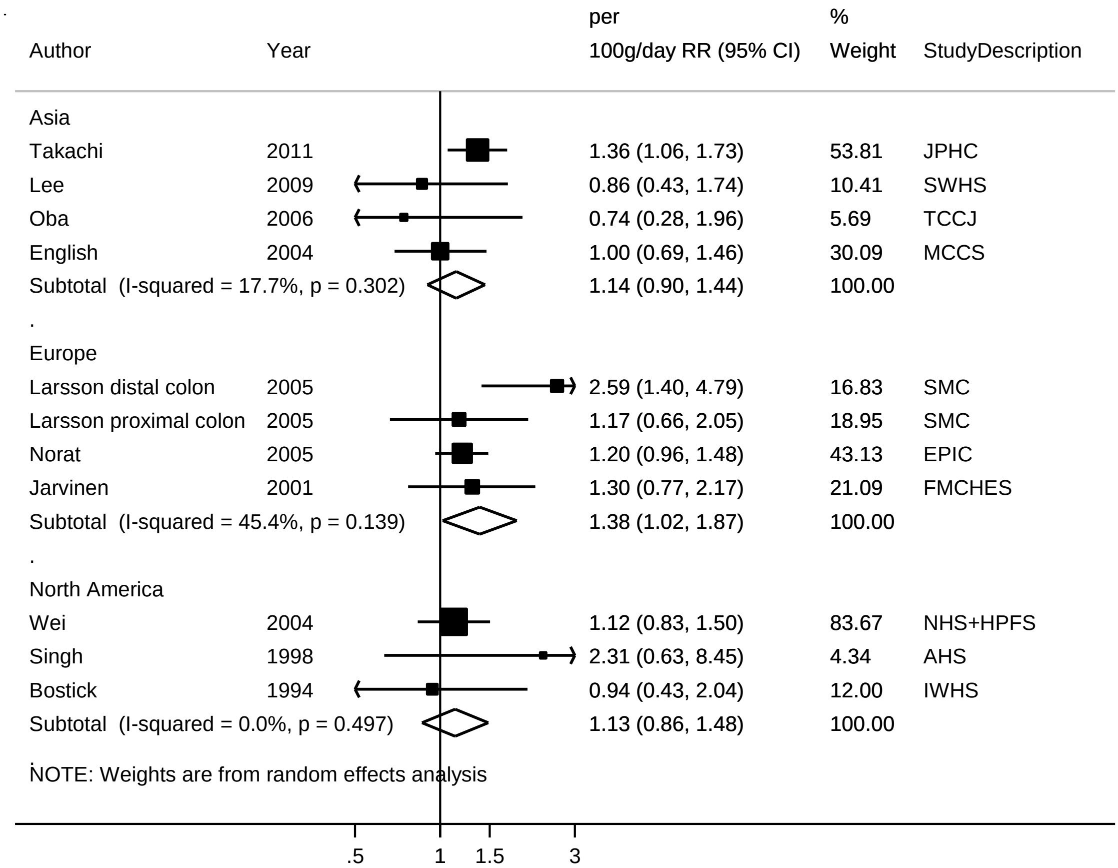
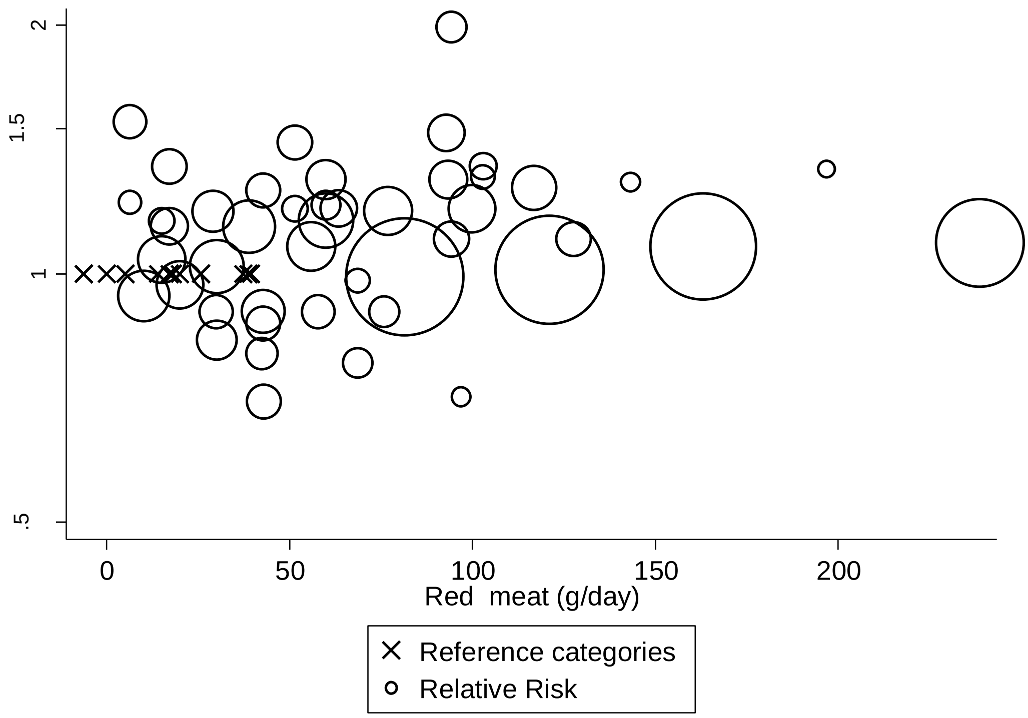
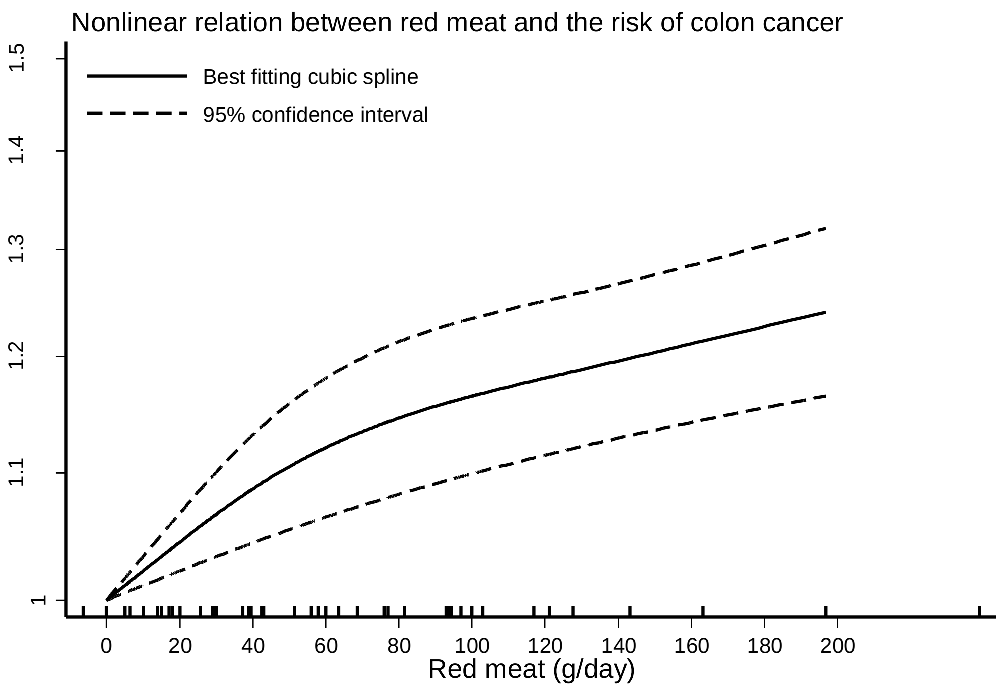


Figure 136 Relative risk of colon cancer and red meat estimated using non-linear models





p for non-linearity =0.02

Table 82 Table with red meat values and corresponding RRs (95% CIs) for non-linear analysis of red meat and colon cancer

Red meat (g/day)	RR(95%CI)
0	1
15	1.03(1.02-1.05)
30	1.06(1.03-1.10)
50	1.10(1.05-1.16)
100	1.16(1.09-1.23)

Figure 137 RR estimates of rectal cancer by levels of red meat

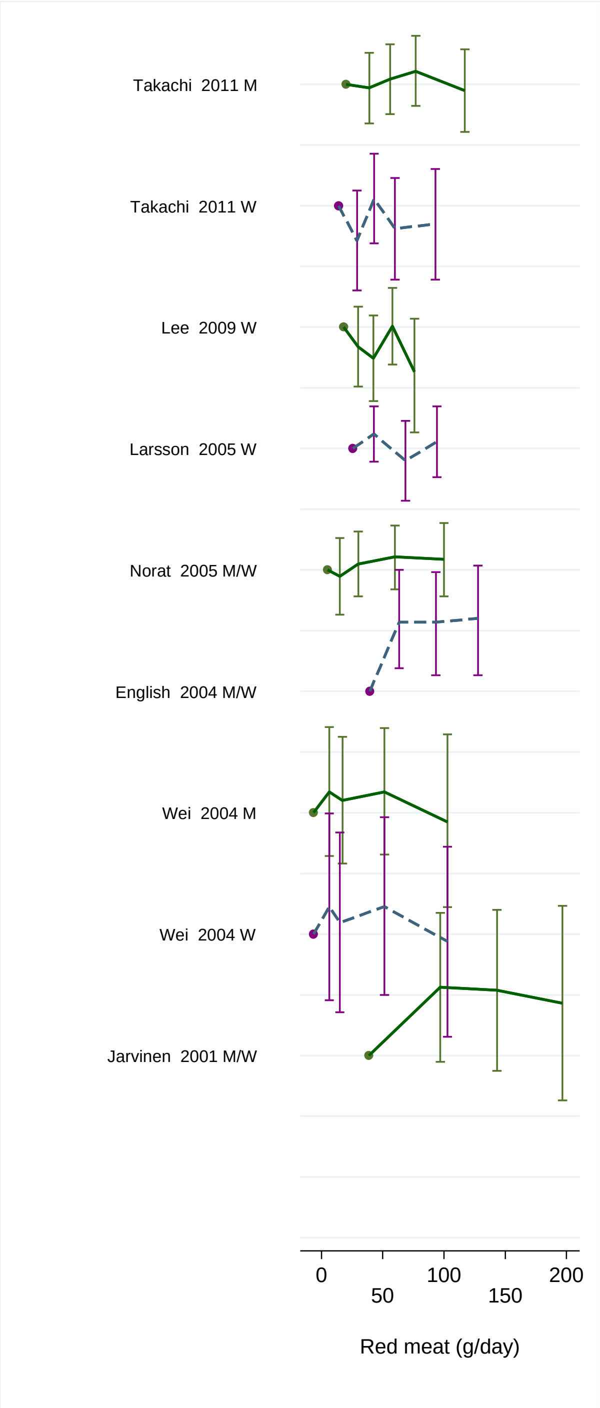


Figure 138 RR (95% CI) of rectal cancer for the highest compared with the lowest level of red meat

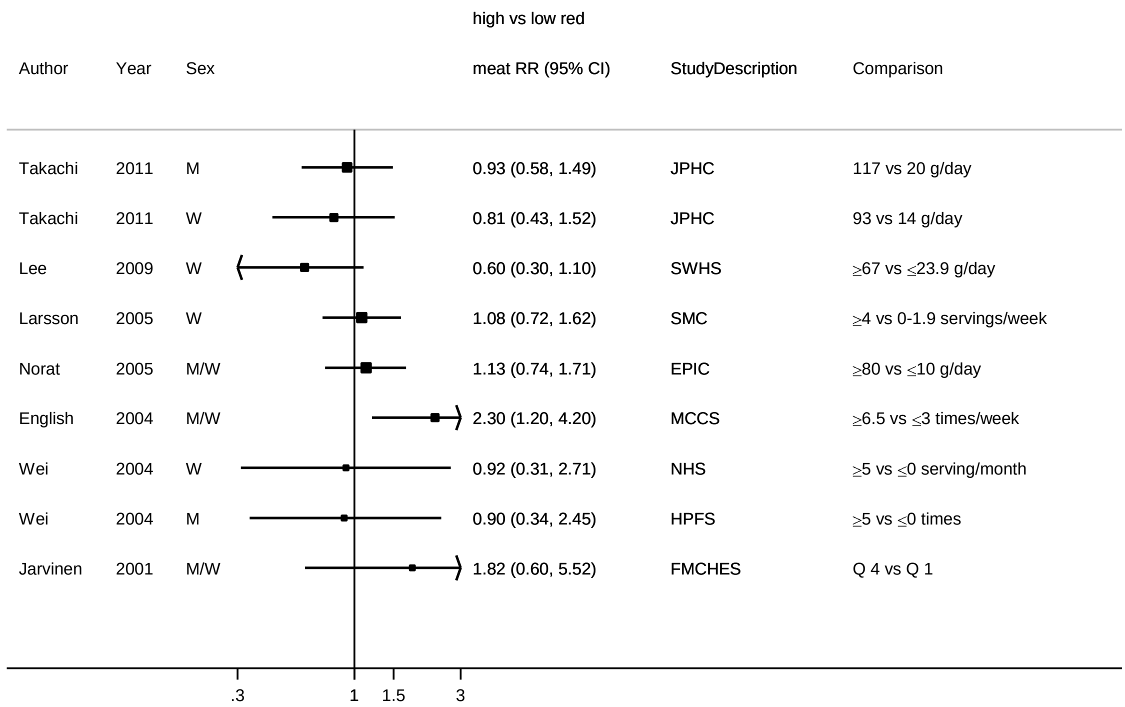


Figure 139 RR (95% CI) of rectal cancer for 100g/day increase of red meat

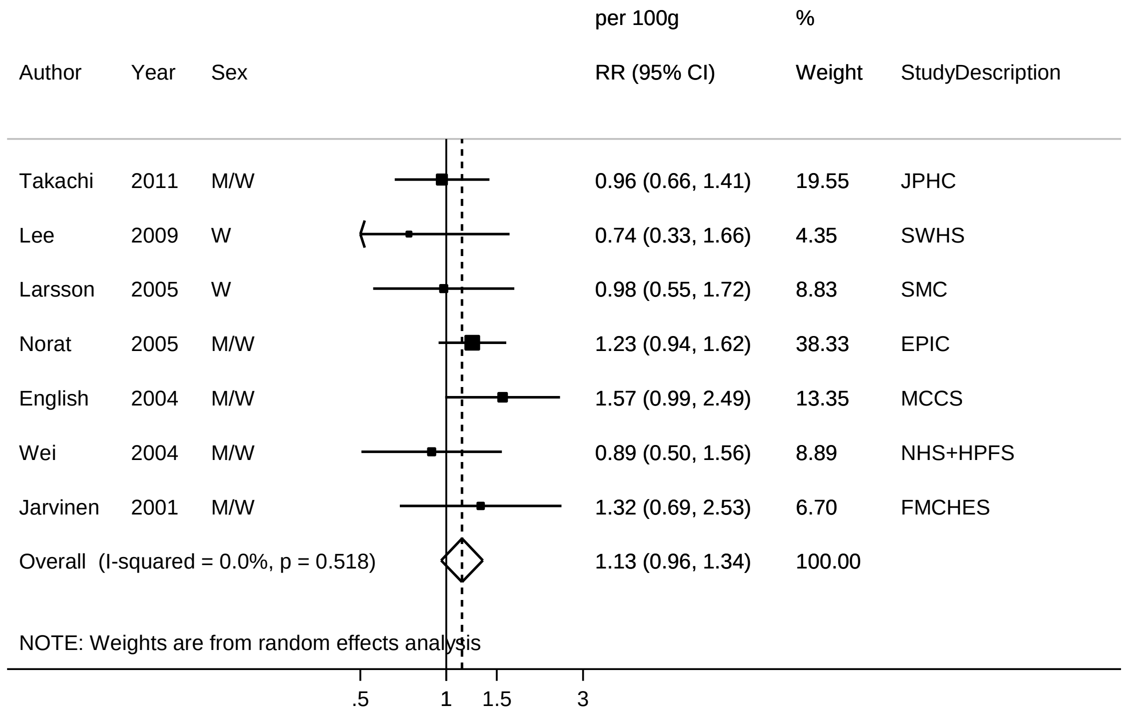


Figure 140 Funnel plot of studies included in the dose response meta-analysis of red meat and rectal cancer

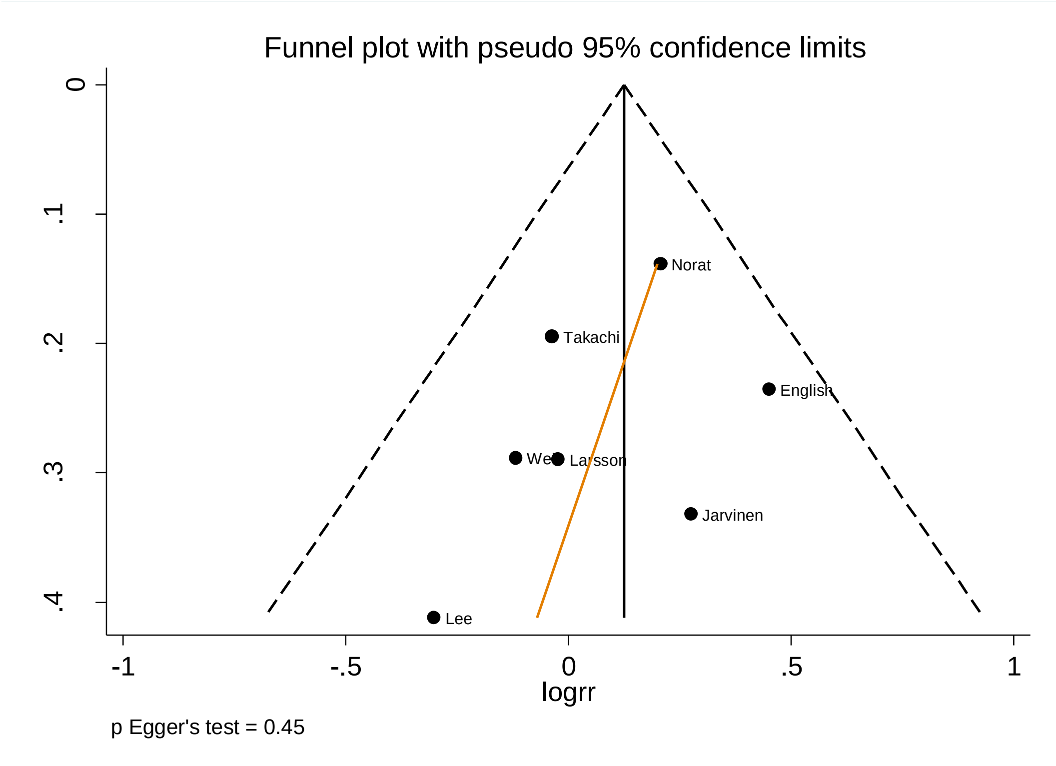


Figure 141 RR (95% CI) of rectal cancer for 100g/day increase of red meat by sex

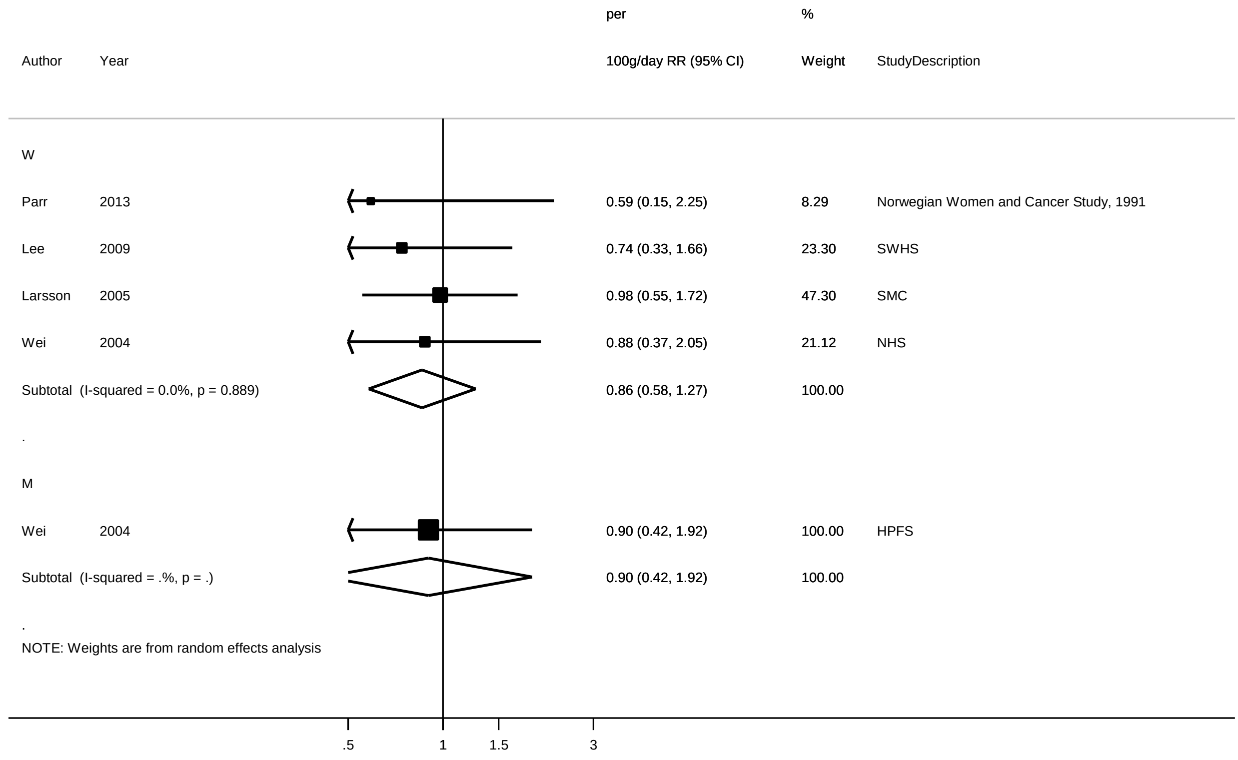


Figure 142 RR (95% CI) of rectal cancer for 100g/day increase of red meat by location

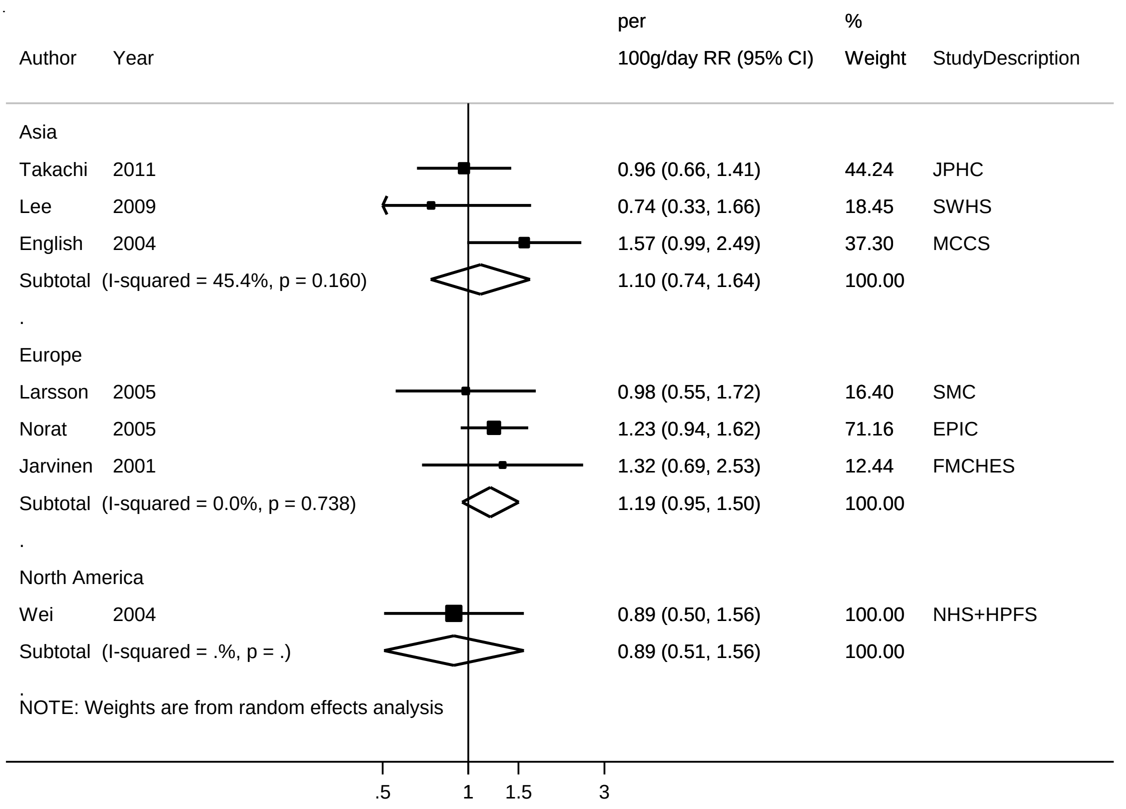
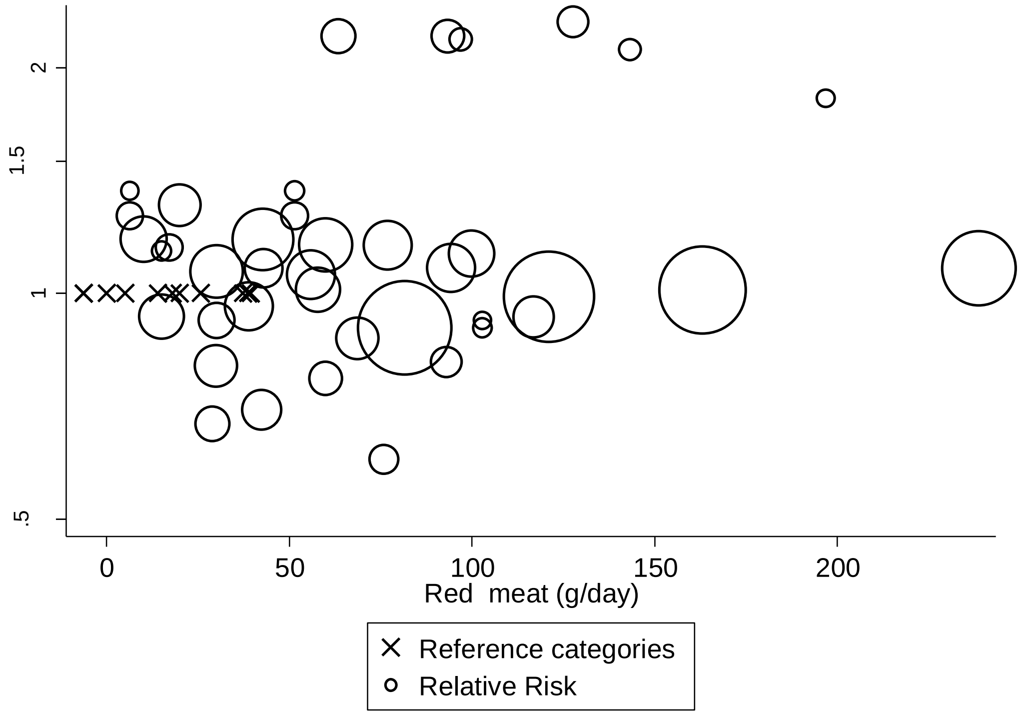


Figure 143 Relative risk of rectal cancer and red meat estimated using non-linear models



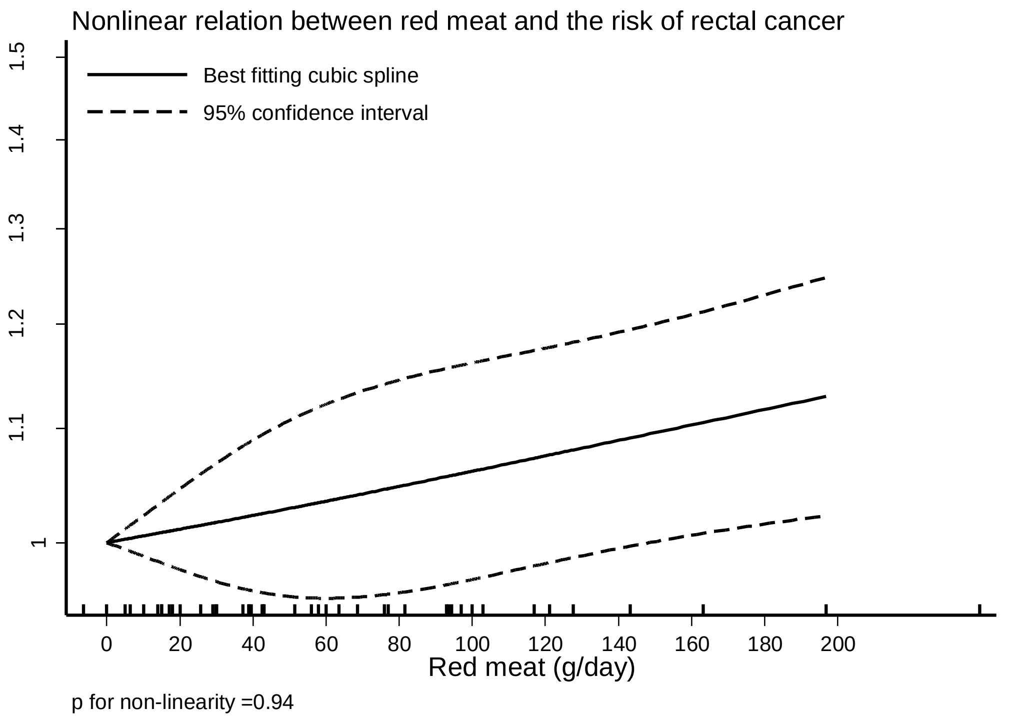


Table 83 Table with red meat values and corresponding RRs (95% CIs) for non-linear analysis of red meat and rectal cancer

Red meat (g/day)	RR(95%CI)
0	1
15	1.00(0.98-1.03)
30	1.01(0.97-1.07)
50	1.03(0.95-1.11)
100	1.06(0.97-1.16)

2.5.1.4 Poultry

Cohort studies

Summary

Main results:
Twenty studies (25 publications) were identified. No analysis was conducted in 2010 SLR. All the analyses were on cancer incidence. There were four studies on mortality, excluded from the analysis (Iso, 2007; Kojima, 2004; Khan, 2004; Hsing, 1998).

Colorectal cancer:
Seven studies (3429 cases) were included in the dose-response meta-analysis of poultry and colorectal cancer. A non-significant association with moderate heterogeneity was observed. Two studies were on chicken only and five on poultry. Only one study from Australia (English, 2004) observed a significant inverse association per 100g/day of chicken. After stratification by geographic location the result only remained the same. There was no evidence of publication bias (p=0.52).

Colon cancer:
Ten studies (8425 cases) were included in the dose-response meta-analysis of poultry and colon cancer. A non-significant association with moderate heterogeneity was observed. Five studies were on chicken only and five on poultry. Only one study from Australia (English, 2004) observed a significant inverse association per 100g/day of chicken. After stratification by sex and geographic location the result only remained the same. There was no evidence of publication bias (p=0.08).

Rectal cancer:
Six studies (3201 cases) were included in the dose-response meta-analysis of poultry and rectal cancer. A non-significant association with no heterogeneity was observed.

Four studies were on chicken only and two on poultry. After stratification by geographic location the result only remained the same. There was no evidence of publication bias (p=0.60).

Study quality:
The definition of poultry varied between studies. In general, total poultry intake included chicken, turkey, ground poultry, as well as the processed poultry components of turkey or chicken cold cuts and low-fat versions of hot dogs and sausage. Poultry queries included line items for breaded/deep-fried chicken, other chicken (baked, broiled, roasted or stewed), chicken casseroles, sandwiches, and mixtures, as well as general habits of consuming skin and light or dark meat.

Pooling project of cohort studies:
The UK Dietary Cohort Consortium reported no evidence of an association between poultry consumption and colorectal cancer risk in a pooled analysis of food diary data from seven prospective studies (odd ratios for ≥30 vs <1 g/day= 0.80, 95% CI = 0.62-1.04). Similar relationships were observed for colon and rectal cancers (Spencer, 2010).

Meta-analysis of cohort studies:
One meta-analysis of 16 cohort studies combined the outcomes colorectal and colon cancer incidence and observed a RR per 50g of poultry a day of 0.89 (0.81-0.97) and no evidence of a non-linear association (p non linearity=0.35). For colorectal mortality the RR per 50g of poultry a day was 0.97(95% CI = 0.79-1.20).

Table 84 Poultry and colorectal cancer risk. Number of studies in the CUP SLR

	Number
Studies identified	12
Studies included in forest plot of highest compared with lowest exposure	10
Studies included in dose-response meta-analysis	7
Studies included in non-linear dose-response meta-analysis	NA

Note: Include cohort, nested case-control and case-cohort designs

Table 85 Poultry and colon cancer risk. Number of studies in the CUP SLR

	Number
Studies identified	15
Studies included in forest plot of highest compared with lowest exposure	12
Studies included in dose-response meta-analysis	10
Studies included in non-linear dose-response meta-analysis	NA

Note: Include cohort, nested case-control and case-cohort designs

Table 86 Poultry and rectal cancer risk. Number of studies in the CUP SLR

	Number
Studies identified	10
Studies included in forest plot of highest compared with lowest exposure	9
Studies included in dose-response meta-analysis	6
Studies included in non-linear dose-response meta-analysis	NA

Note: Include cohort, nested case-control and case-cohort designs

Table 87 Poultry and colorectal cancer risk. Summary of the dose-response meta-analysis in the 2010 SLR and 2015 SLR.

	2010 SLR	**2015 SLR**
Increment unit used		100g/day
Studies (n)		7
Cases (total number)		3429
RR (95%CI)		0.81(0.53-1.25)
Heterogeneity (I^2, p-value)		48.0%, 0.05

Stratified analysis by geographic location (no analysis in 2005 SLR or 2010 SLR)			
2015 SLR	**Asia**	**Europe**	**North America**
Studies (n)	2	4	1
RR (95%CI)	0.76(0.26-2.23)	0.77(0.36- 1.64)	1.21(0.57-2.58)
Heterogeneity (I^2, p-value)	66.0%, 0.09	37.7%, 0.19	

Table 88 Poultry and colon cancer risk. Summary of the dose-response meta-analysis in the 2010 SLR and2015 SLR.

	2010 SLR	2015 SLR
Increment unit used		100g/day
Studies (n)		10
Cases (total number)		8425
RR (95%CI)		0.83(0.63-1.11)
Heterogeneity (I^2, p-value)		34.6%, 0.12

Stratified analysis by sex			
(no analysis in 2005 or 2010 SLR)			
2015 SLR	**Men**	**Women**	
Studies (n)	2	4	
RR (95%CI)	0.91(0.48-1.74)	0.64(0.17-2.49)	
Heterogeneity (I^2, p-value)	5.8%, 0.30	52.4%, 0.08	
Stratified analysis by geographic location			
(no analysis in 2005 or 2010 SLR)			
2015 SLR	**Asia**	**Europe**	**North America**
Studies (n)	3	3	4
RR (95%CI)	0.82(0.34-1.96)	0.76(0.51-1.12)	0.96(0.52-1.75)
Heterogeneity (I^2, p-value)	50.5%, 0.13	0%, 0.74	59.9%, 0.06

Table 89 Poultry and rectal cancer risk. Summary of the dose-response meta-analysis in the 2010 SLR and CUP.

	2010 SLR	2015 SLR
Increment unit used		100g/day
Studies (n)		6
Cases (total number)		3201
RR (95%CI)		0.86(0.72-1.01)
Heterogeneity (I^2, p-value)		0%, 0.96

Stratified analysis by geographic location			
(no analysis in 2005 or 2010 SLR)			
2015 SLR	**Asia**	**Europe**	**North America**
Studies (n)	3	2	1
RR (95%CI)	0.74(0.38-1.44)	0.99(0.56-1.74)	0.85(0.71-1.02)
Heterogeneity (I^2, p-value)	0%, 0.75	0%, 0.94	

Table 90 Poultry and colorectal cancer risk. Results of meta-analyses and pooled analyses of prospective studies published after the 2005 SLR.

Author, Year	Number of cohort studies	Total number of cases	Studies country, area	Outcome	Comparison	RR (95%CI)	P trend	Heterogeneity (I^2, p value)
Pooled analysis								
Spencer, 2010	7	579 cases 1996 controls	UK	Colorectal cancer	≥30 vs <1 g/day Per 30g/day	0.80 (0.62–1.04) 0.80(0.65-1.00)	0.05	
				Colon cancer		0.87 (0.63–1.19) 0.80 (0.61–1.05)	0.11	
				Rectal cancer		0.69 (0.44–1.09) 0.83 (0.57–1.20)	0.32	
Meta-analysis								
Shi, 2015	16	13949	North America, Europe, Australia, Japan	Colorectal cancer incidence	Per 50g/day	0.89(0.81-0.97)		41.2%, 0.04
	4			Colorectal cancer mortality		0.97(0.79-1.20)		0%, 0.70

* Heterogeneity (I^2, p value) only reported when available

Table 91 Poultry and colorectal cancer risk. Main characteristics of studies included in the CUP SLR dose-response meta-analysis

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Missing data derived for analysis
Daniel, 2011 COL40884 USA	NIH-AARP, Prospective Cohort, Age: 50-71 years, M/W	5 095/ 492 186 9.1 years	Cancer registry	FFQ (exposure: poultry)	Incidence, colon cancer	51.2 vs 5.3 g/1000 kcal	0.97 (0.89-1.07) Ptrend:0.43	Age, sex, BMI, educational level, energy intake, family history of cancer, fish intake, HRT use, marital status, race, red meat, smoking, vigorous activity	Distribution of person-years by exposure category. Intakes in g/1000kcal/day converted to g/day using average energy intake per each quantile
		1 884/			Incidence, rectal cancer	51.2 vs 5.3 g/1000 kcal	0.84 (0.72-0.98) Ptrend:0.08		
Takachi, 2011 COL41056 Japan	JPHC, Prospective Cohort, Age: 45-74 years, M/W	481/ 80 658 9 years	Hospital records + cancer registry	FFQ (exposure: chicken)	Incidence, colon cancer, men	21 vs 0.5 g/day	1.11 (0.83-1.49) Ptrend:0.44	Age, alcohol consumption, area, BMI, calcium, diabetes, energy, fibre, folate, physical activity, salted fish consumption, screening exams, smoking status, vitamin b6, vitamin d	Distribution of person-years by exposure category
		307/			Incidence, colon cancer, women	19 vs 0.5 g/day	1.01 (0.70-1.46) Ptrend:0.91		
		233/			Incidence, rectal cancer, men	21 vs 0.5 g/day	0.72 (0.47-1.09) Ptrend:0.22		
		124/			Incidence, rectal cancer, women	19 vs 0.5 g/day	1.27 (0.69-2.32) Ptrend:0.91		
Sato, 2006 COL40671 Japan	MCS, Prospective Cohort, Age: 40-64	381/ 41 835 11 years	Cancer registry	FFQ (exposure: chicken)	Incidence, colorectal cancer	3-4 times/wk vs almost never g/day	1.31 (0.83-2.06) Ptrend:0.06	Age, sex, alcohol consumption, BMI, calcium	Distribution of person-years by exposure category.
		238/			Incidence, colon	3-4 times/wk vs	1.58 (0.84-2.95)		

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Missing data derived for analysis
	years, M/W				cancer	almost never g/day	Ptrend:0.03	intake, dietary fibre intake, educational level, energy intake, family history of cancer, fat consumption, physical activity, smoking status	Conversion from times/wk to g/day
		157/			Incidence, rectal cancer	3-4 times/wk vs almost never g/day	0.97 (0.51-1.86) Ptrend:0.92		
Brink, 2005 COL40717 Netherlands	NLCS, Case Cohort, Age: 55-69 years, M/W	448/ 2 948 7.3 years	Cancer registry	Semi-quantitative FFQ (exposure: chicken)	Incidence, colon cancer	per 15.6 g/day	0.95 (0.85-1.07)	Age, sex, BMI, energy intake, family history of colorectal cancer, smoking habits	Mid-points of exposure categories.
						≥22.8 vs ≤0 g/day	0.87 (0.66-1.15) Ptrend:0.34		
		160/			Incidence, rectal cancer	per 15.6 g/day	0.98 (0.83-1.14)		
						≥22.8 vs ≤0 g/day	1.12 (0.70-1.79) Ptrend:0.96		
Larsson, 2005 COL01849 Sweden	SMC, Prospective Cohort, Age: 40-75 years, W	733/ 61 433 855 585 person-years	Cancer registry	Questionnaire (exposure: poultry)	Incidence, colorectal cancer,	≥0.5 vs ≤0 servings/week	0.75 (0.55-1.02) Ptrend:0.04	Age, alcohol consumption, BMI, calcium, educational level, energy intake, fish, folate, fruits, saturated fat, vegetables, whole-grain foods Red meat intake	Distribution of person-years by exposure category. Conversion from servings/wk to g/day
		234/			Incidence, proximal colon cancer,	≥0.5 vs ≤0 servings/week	0.77 (0.44-1.36) Ptrend:0.26		
		155/			Incidence, distal colon cancer,	≥0.5 vs ≤0 servings/week	0.86 (0.46-1.62) Ptrend:0.76		
Norat, 2005	EPIC,	1 329/		Questionnaire	Incidence,	per 100 g/day	0.92 (0.68-1.25)	Age, sex,	Distribution of

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Missing data derived for analysis
COL01698 Europe	Prospective Cohort, Age: 21-83 years, M/W	478 040 2 279 075 person-years		(exposure: poultry)	colorectal cancer,	≥40 vs ≤5 g/day	0.92 (0.76-1.12) Ptrend:.18	alcohol consumption, body weight, centre location, energy from fat sources, energy from non-fat sources, fibre, height, physical activity, smoking status	person-years by exposure category. Mid-points of exposure categories. Used continuous results.
		855/			Incidence, colon cancer,	per 100 g/day	0.92 (0.63-1.35)		
						≥40 vs ≤5 g/day	0.89 (0.70-1.13) Ptrend:0.19		
		474/			Incidence, rectal cancer,	per 100 g/day	0.92 (0.56-1.53)		
						≥40 vs ≤5 g/day	0.99 (0.71-1.37) Ptrend:.65		
English, 2004 COL00019 Australia	MCCS, Prospective Cohort, Age: 27-75 years, M/W	452/ 37 112 9 years	Population/electoral rolls	FFQ (exposure: chicken)	Incidence, colorectal cancer,	≥3.5 vs ≤1.5 times/week	0.70 (0.60-1.00) Ptrend:0.03	Sex, country of birth, and intake of energy, fat, and cereal products	Conversion from times/wk to g/day. Mid-points of exposure categories
		283/			Incidence, colon cancer,	≥3.5 vs ≤1.5 times/week	0.70 (0.50-1.10) Ptrend:0.08		
		169/			Incidence, rectal cancer,	≥3.5 vs ≤1.5 times/week	0.70 (0.50-1.20) Ptrend:0.2		
Tiemersma, 2002 COL00563 Netherlands	Dutch prospective Monitoring Project on Cardiovascular Disease Risk Factors, Nested Case Control, Age: 20-59 years, M/W	102/ 537 controls 8.5 years	Population	FFQ (exposure: poultry)	Incidence, colorectal cancer, women	≥4 vs 0-1 times/month	0.50 (0.20-1.10) Ptrend:0.07	Age, alcohol consumption, body height, energy intake, study centre	Conversion from times/month to g/day. Mid-points of exposure categories.
		54/ 292 controls			Incidence, colorectal cancer, men	≥4 vs 0-1 times/month	1.10 (0.50-2.40) Ptrend:0.68		

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Missing data derived for analysis
Ma, 2001 COL00374 USA	PHS, Nested Case Control, Age: 40-84 years, M, Physicians	193/ 318 controls 13 years	Colorectal cancer diagnosis	Unknown (exposure: poultry)	Incidence, colorectal cancer,	0.43-0.8 vs 0-0.07 serving/day	0.93 (0.52-1.68) Ptrend:0.36	Age, alcohol consumption, aspirin use, BMI, molar ratio of IGF-I to IGGBP-3, physical activity, smoking habits, supplement intake	Conversion from servings/day to g/day. Mid-points of exposure categories.
Pietinen, 1999 COL00176 Finland	ATBC, Prospective Cohort, Age: 50-69 years, M, Smokers	185/ 27 111 8 years	Cancer registry	Dietary history questionnaire (exposure: poultry)	Incidence, colorectal cancer,	27 vs 0 g/day	1.20 (0.80-1.80) Ptrend:0.40	Age, alcohol consumption, BMI, calcium intake, educational level, physical activity, smoking years, supplement group	Distribution of person-years by exposure category.
Bostick, 1994 COL00079 USA	IWHS, Prospective Cohort, Age: 55-69 years, W	212/ 35 216 167 447 person-years	SEER	Semi-quantitative FFQ (exposure: poultry)	Incidence, colon cancer,	≥1 vs ≤0 serving/week	1.52 (0.98-2.36) Ptrend:0.07	Age, energy intake, height, parity, total vitamin e intake, total vitamin e intake, age, vitamin a supplement	Conversion from servings/week to g/day. Mid-points of exposure categories.
Giovannucci, 1994 COL00119	HPFS, Prospective Cohort,	205/ 47 949 6 years	Mailing to health professionals	FFQ (exposure: poultry)	Incidence, colon cancer,	63.1 vs 8.8 g/day	0.82 (0.54-1.24) Ptrend:0.27	Age, total energy	

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Missing data derived for analysis
USA	Age: 40-75 years, M, Health professionals								
Willett, 1990 CRC00026 USA	NHS, Prospective Cohort, Age: 34-59 years, W, Registered nurses	150/ 88 751 512 488 person-years	Population	Semi-quantitative FFQ (exposure: chicken)	Incidence, colon cancer,	≥5 vs ≤1 times/month	0.47 (0.27-0.82) Ptrend:0.03	Age	Conversion times/month to g/day

Table 92 Poultry and colorectal cancer risk. Main characteristics of studies excluded from the CUP SLR dose-response meta-analysis

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Reasons for exclusion
Egeberg, 2013 COL40953 Denmark	DCH, Prospective Cohort, Age: 50-64 years, M/W	644/ 53 988 13.4 years	Cancer registry	FFQ	Incidence, colon cancer	poultry vs fish g/day	0.89 (0.78-1.03)	Age, alcohol, beef consumption, cold cuts, educational level, energy, fibre, fish, HRT use, lamb intake, liver, meat, NSAID use, pork, processed meat, sausages, smoking, sport, veal meat, waist circumference, red meat	Component of EPIC. Superseded by Norat, 2005 COL01698
						≥29 vs 0-10 g/day	1.11 (0.87-1.42) Ptrend:0.51		
						per 25 g/day	1.04 (0.93-1.15)		
		345/			Incidence, rectal cancer	per 25 g/day	0.94 (0.80-1.09)		
						≥29 vs 0-10 g/day	0.94 (0.69-1.29) Ptrend:0.39		
						poultry vs fish g/day	1.05 (0.86-1.29)		
Parr, 2013 COL40955 Norway	NOWAC, Prospective Cohort, Age: 41-70 years, W	625/ 84 538 11.1 years	Cancer registry	FFQ	Incidence, colorectal cancer	≥28 vs 0 g/day	0.91 (0.69-1.20) Ptrend:0.17	Age, alcohol, BMI, calcium, energy, fibre, physical activity, smoking	Component of EPIC. Superseded by Norat, 2005 COL01698
						≥28 vs 0 g/day	0.93 (0.71-1.22) Ptrend:0.24		
		428/			Incidence, colon cancer	≥28 vs 0 g/day	0.90 (0.65-1.25) Ptrend:0.16		
		227/			Incidence, proximal colon cancer	≥28 vs 0 g/day	1.04 (0.66-1.65) Ptrend:0.97		
		197/			Incidence, rectal cancer	≥28 vs 0 g/day	0.94 (0.56-1.56) Ptrend:0.71		

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Reasons for exclusion
		144/			Incidence, distal colon cancer	≥28 vs 0 g/day	0.83 (0.49-1.41) Ptrend:0.14		
Lee, 2009 COL40764 China	SWHS, Prospective Cohort, Age: 40-70 years, W	394/ 73 224 7.4 years	Cancer registry and death certificates and participant contact	Quantitative FFQ	Incidence, colorectal cancer	≥24 vs ≤3.9 g/day	1.20 (0.90-1.70) Ptrend:0.23	Age, educational level, energy intake, fibre intake, Income, NSAID use, season of Interview, tea consumption	Only included in highest compared to lowest analysis
		236/			Incidence, colon cancer	≥24 vs ≤3.9 g/day	1.20 (0.80-1.80) Ptrend:0.15		
		158/			Incidence, rectal cancer	≥24 vs ≤3.9 g/day	1.30 (0.70-2.10) Ptrend:0.90		
Iso, 2007 COL40707 Japan	JACC, Prospective Cohort, Age: 40-79 years, M/W	203/ 105 500 15 years	Municipal resident registration records, death certificates	FFQ	Mortality, colon cancer, men	3-4 vs ≤0 /week	1.05 (0.68-1.63)	Age, centre location	Outcome is mortality
		198/			Mortality, colon cancer, women	3-4 vs ≤0 /week	0.84 (0.53-1.32)		
		146/			Mortality, rectal cancer, men	3-4 vs ≤0 /week	0.86 (0.52-1.43)		
		74/			Mortality, rectal cancer, women	3-4 vs ≤0 /week	1.08 (0.51-2.29)		
Luchtenborg, 2005 COL01830	NLCS, Case Cohort, Age: 55-69 years, M/W	434/ 2 948 7.3 years	Population registries	Semi-quantitative FFQ	Incidence, colon cancer,	≥22.8 vs ≤0 g/day	0.87 (0.66-1.15) Ptrend:0.33	Age, sex, BMI, energy intake, family history of colorectal cancer, smoking status	Superseded by Brink, 2005 COL40717
					Incidence, colon cancer	per 15.5 g/day	0.95 (0.87-1.05)		
		274/			Incidence, colon cancer, apc-cases	≥22.8 vs ≤0 g/day	0.83 (0.58-1.18) Ptrend:0.19		
						per 15.5 g/day	0.90 (0.78-1.04)		
		154/			Incidence, rectal cancer,	≥22.8 vs ≤0 g/day	1.12 (0.70-1.79) Ptrend:0.96		

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Reasons for exclusion
					Incidence, rectal cancer	per 15.5 g/day	0.98 (0.83-1.14)		
		127/			Incidence, colon cancer, apc+ cases	≥22.8 vs ≤0 g/day	0.94 (0.59-1.50) Ptrend:0.95		
						per 15.5 g/day	1.06 (0.89-1.25)		
		73/			Incidence, rectal cancer, apc- cases	≥22.8 vs ≤0 g/day	1.29 (0.66-2.50) Ptrend:0.55		
						per 15.5 g/day	1.08 (0.88-1.32)		
		57/			Incidence, rectal cancer, apc+ cases	≥22.8 vs ≤0 g/day	0.90 (0.40-2.01) Ptrend:0.64		
						per 15.5 g/day	0.79 (0.59-1.05)		
		54/			Incidence, colon cancer, hmlh1- cases	≥22.8 vs ≤0 g/day	0.72 (0.34-1.50) Ptrend:0.34		
						per 15.5 g/day	0.93 (0.69-1.27)		
Khan, 2004 COL01606 Japan	HCS, Prospective Cohort, Age: 40-97 years, M/W	15/ 3 458 14.3 years	Area residency lists	Questionnaire	Mortality, colorectal cancer, men	Q 2 vs Q 1	1.00 (0.30-2.80)	Age, smoking habits	Outcome is mortality
		14/			Mortality, colorectal cancer, women	Q 2 vs Q 1	1.70 (0.60-5.20)	Health education, health screening, health status	
Kojima, 2004 COL01840 Japan	JACC, Prospective Cohort, Age: 40-79 years,	124/ 107 824 10 years	Resident registry and death certificates	Questionnaire	Mortality, colon cancer, women	3-7 vs 0-0.5 times/week	0.68 (0.38-1.21) Ptrend:0.60	Age, alcohol consumption, BMI, educational level, family	Outcome is mortality
		113/			Mortality, colon cancer, men	3-7 vs 0-0.5 times/week	1.55 (0.90-2.66) Ptrend:0.07		

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Reasons for exclusion
	M/W	89/			Mortality, rectal cancer, men	3-7 vs 0-0.5 times/week	0.80 (0.44-1.45) Ptrend:0.24	history of specific cancer, physical activity, region of enrolment, smoking status	
		33/			Mortality, rectal cancer, women	3-7 vs 0-0.5 times/week	0.71 (0.22-2.32) Ptrend:0.97		
Jarvinen, 2001 COL00852 Finland	Finnish Mobile Clinic Health Examination Survey, Prospective Cohort, Age: 39 years, M/W	109/ 9 959	Population/invitation	Questionnaire	Incidence, colorectal cancer,	yes vs no	1.59 (1.04-2.44)	Age, sex, BMI, cereal intake, energy intake, fruits intake, geographic location, occupational group, smoking, vegetable intake	Only included in highest compared to lowest analysis
		63/			Incidence, colon cancer,	yes vs no	1.93 (1.12-3.35)		
		46/			Incidence, rectal cancer,	yes vs no	1.20 (0.60-2.37)		
Hsing, 1998 COL00458 USA	Lutheran Brotherhood Study, Prospective Cohort, Age: 35- years, M, policyholders	145/ 17 633 286 731 person-years	Responding to mail survey	Questionnaire	Mortality, colorectal cancer,	≥4.1 vs ≤0.4 times/month	1.10 (0.50-2.20) Ptrend:0.70	Age, alcohol consumption, smoking habits, total energy	Outcome is mortality
		120/			Mortality, colon cancer,	≥4.1 vs ≤0.4 times/month	1.60 (0.70-3.60) Ptrend:0.20		
Kato, 1997 CRC00022 USA	New York University Women's Health Study, Prospective Cohort, Age: 34-65 years, W	100/ 14 272 105 044 person-years	Questionnaire, medical records, cancer registries	Semi-quantitative FFQ	Incidence, colorectal cancer,	Q 4 vs Q 1	0.79 (0.46-1.34) Ptrend:0.522	Age, educational level, place at enrolment, total calorie intake	Only included in highest compared to lowest analysis

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Reasons for exclusion
Goldbohm, 1994 COL00025 Netherlands	NLCS, Case Cohort, Age: 55-69 years, M/W	120 852 3.3 years	Population registries	Semi-quantitative FFQ	Incidence, colon cancer,	per 15 g/day	1.03 (0.90-1.17)	Age, sex, energy intake	Superseded by Brink, 2005 COL40717
Heilbrun, 1989 COL01555 USA	HHP, Nested Case Control, M	102/ 361 controls 16 years	Cancer registry & hospital surveillance	Recall questionnaire	Incidence, colon cancer,	(mean exposure)		Age	Mean exposure only
		60/ 361 controls			Incidence, rectal cancer,	(mean exposure)			

Figure 144 RR estimates of colorectal cancer by levels of poultry

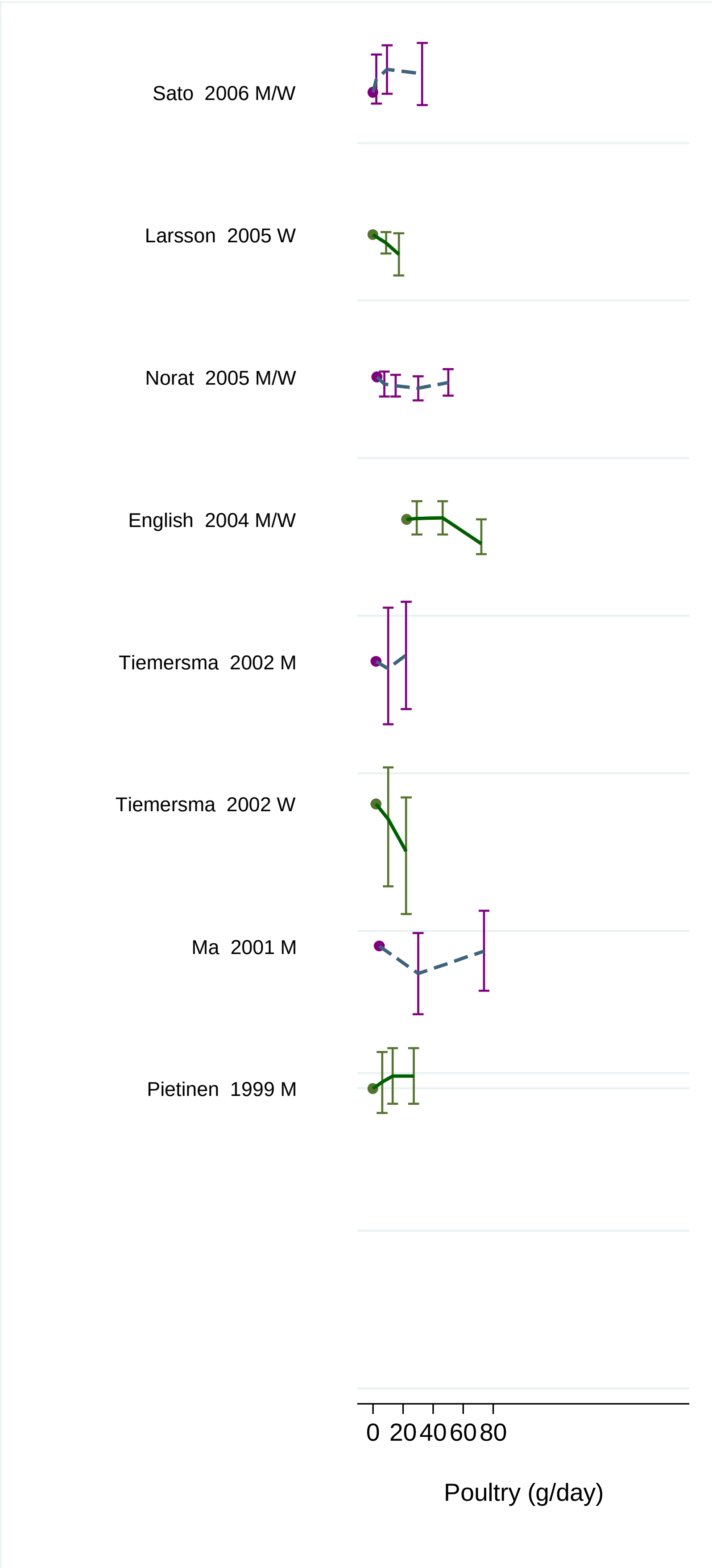


Figure 145 RR (95% CI) of colorectal cancer for the highest compared with the lowest level of poultry

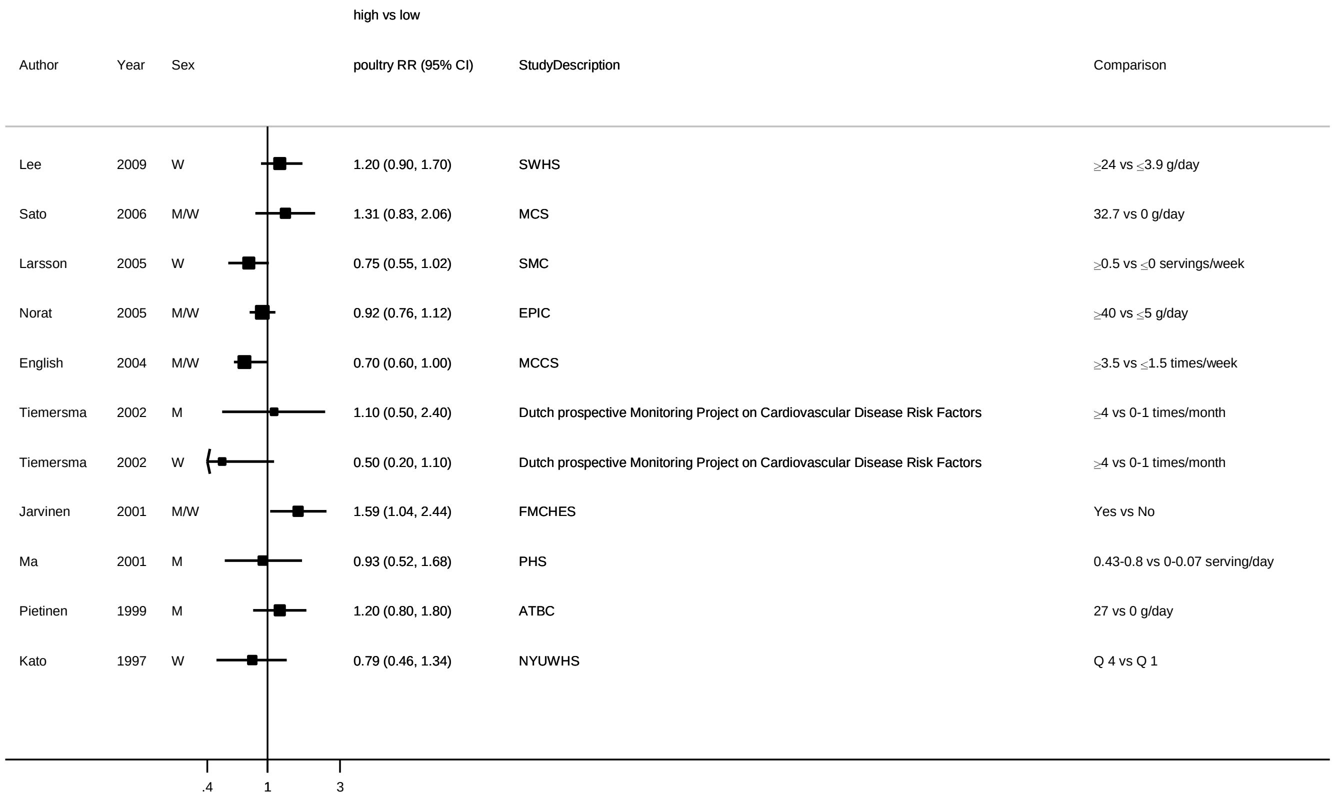


Figure 146 RR (95% CI) of colorectal cancer for 100g/day increase of poultry

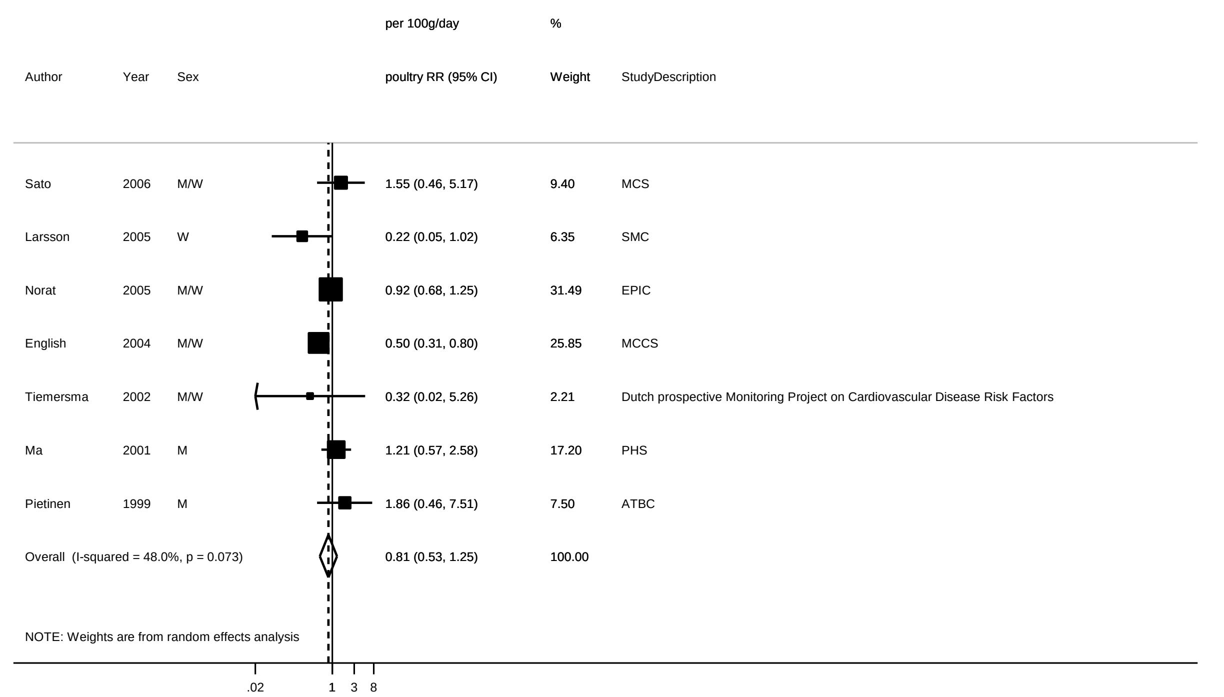


Figure 147 Funnel plot of studies included in the dose response meta-analysis poultry and colorectal cancer

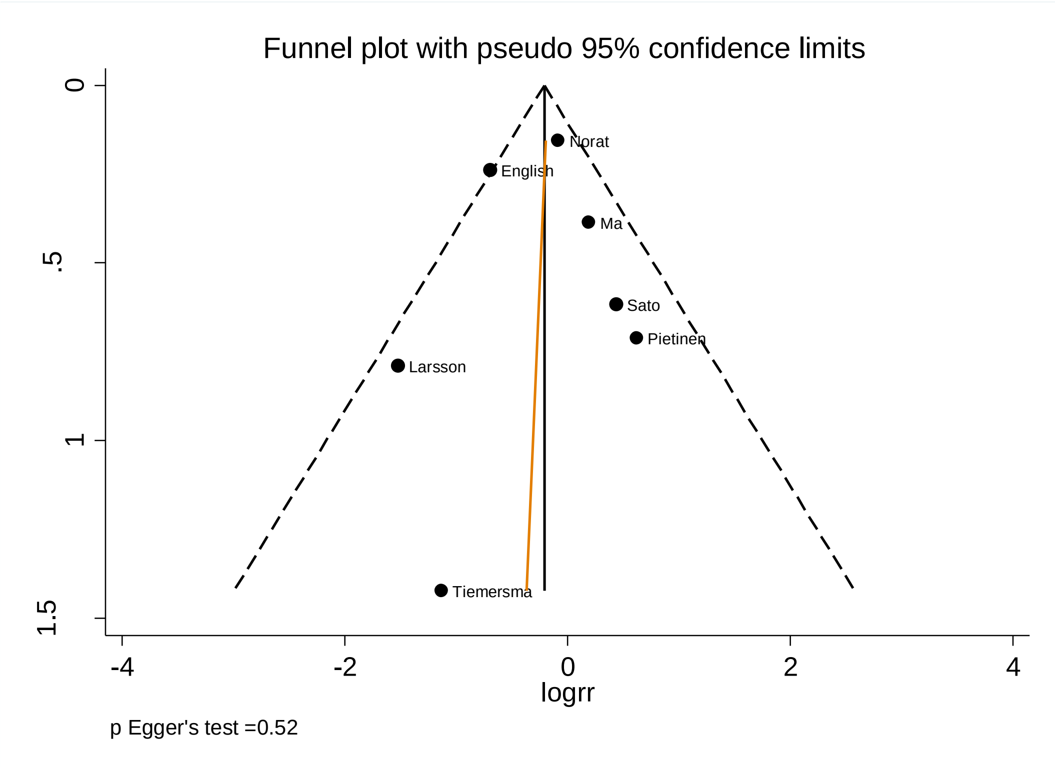


Figure 148 RR (95% CI) of colorectal cancer for 100g/day increase of poultry by location

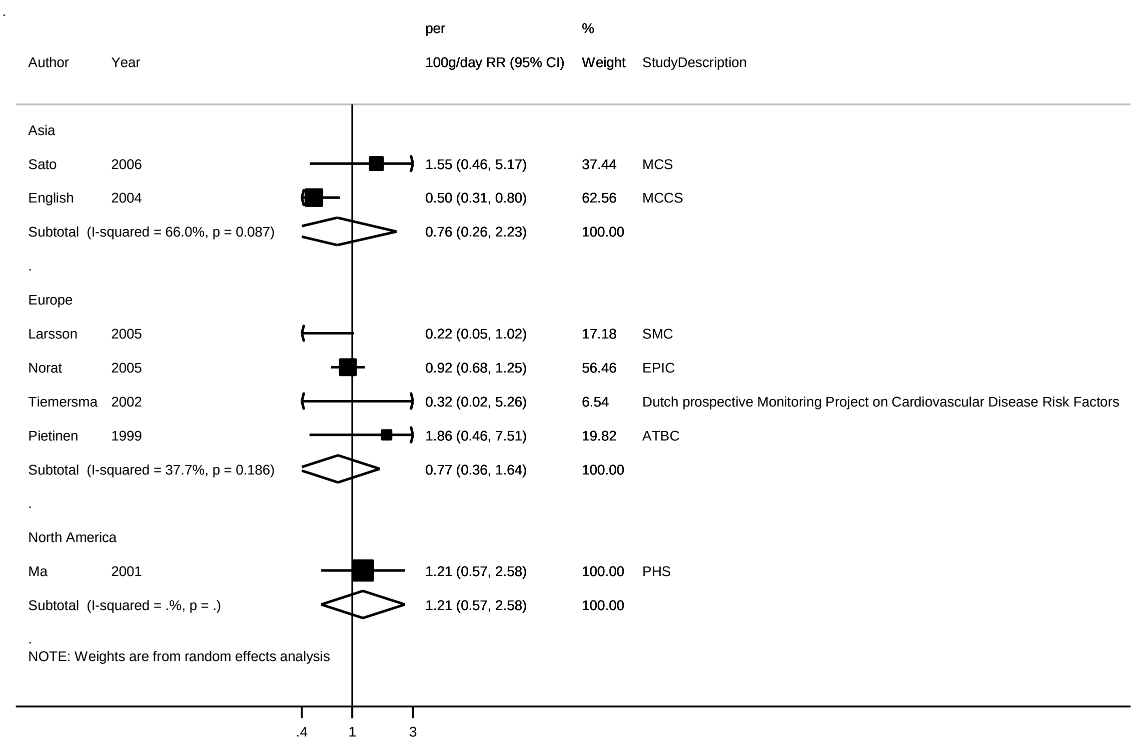


Figure 149 RR estimates of colon cancer by levels of poultry

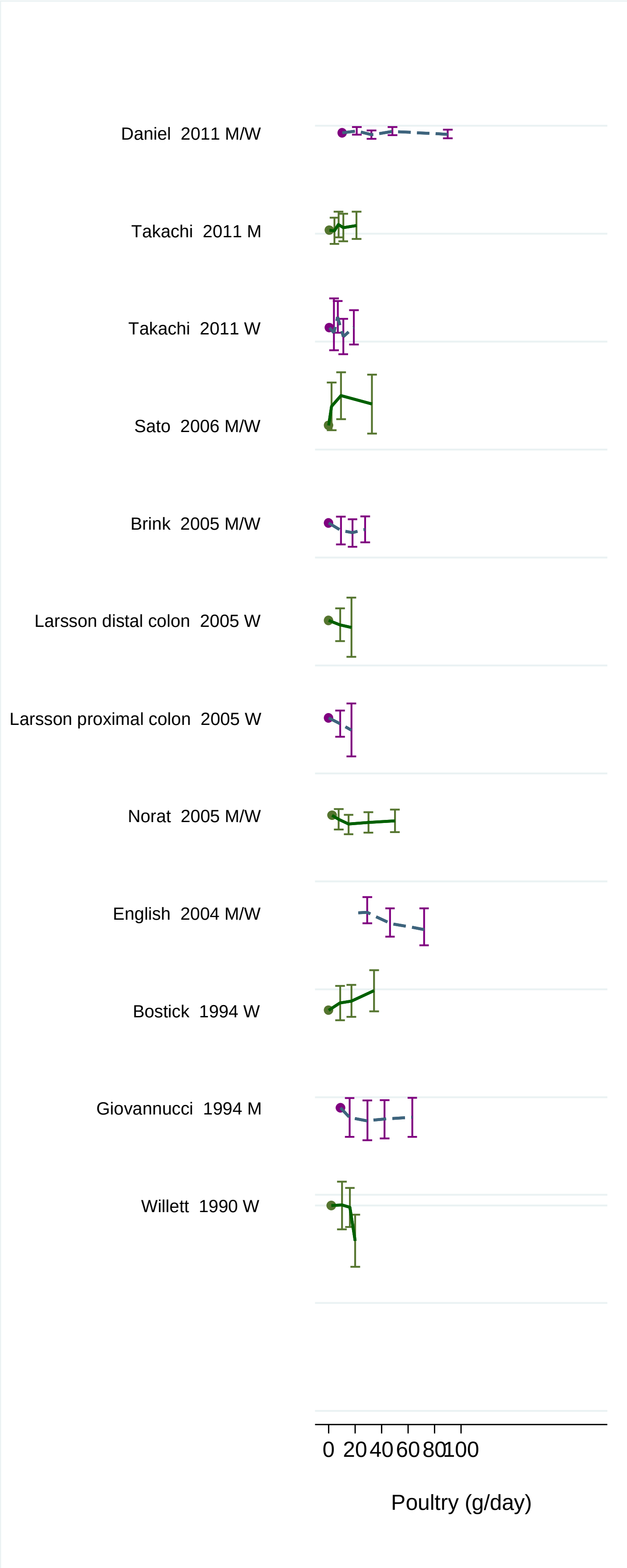


Figure 150 RR (95% CI) of colon cancer for the highest compared with the lowest level of poultry

Author	Year	Sex	high vs low poultry RR (95% CI)	StudyDescription	Comparison
Daniel	2011	M/W	0.97 (0.89, 1.07)	NIH-AARP	51.2 vs 5.3 g/1000 kcal
Takachi	2011	W	1.01 (0.70, 1.46)	JPHC	19 vs 0.5 g/day
Takachi	2011	M	1.11 (0.83, 1.49)	JPHC	21 vs 0.5 g/day
Lee	2009	W	1.20 (0.80, 1.80)	SWHS	≥24 vs ≤3.9 g/day
Sato	2006	M/W	1.58 (0.84, 2.95)	MCS	32.7 vs 0 g/day
Brink	2005	M/W	0.87 (0.66, 1.15)	NLCS	≥22.8 vs ≤0 g/day
Larsson distal colon	2005	W	0.86 (0.46, 1.62)	SMC	≥0.5 vs ≤0 servings/week
Larsson proximal colon	2005	W	0.77 (0.44, 1.36)	SMC	≥0.5 vs ≤0 servings/week
Norat	2005	M/W	0.89 (0.70, 1.13)	EPIC	≥40 vs ≤5 g/day
English	2004	M/W	0.70 (0.50, 1.10)	MCCS	≥3.5 vs ≤1.5 times/week
Jarvinen	2001	M/W	1.93 (1.12, 3.35)	FMCHES	Yes vs No
Bostick	1994	W	1.52 (0.98, 2.36)	IWHS	≥1 vs ≤0 serving/week
Giovannucci	1994	M	0.82 (0.54, 1.24)	HPFS	63.1 vs 8.8 g/day
Willett	1990	W	0.47 (0.27, 0.82)	NHS	≥5 vs ≤1 times/month

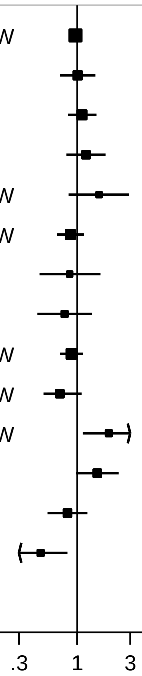


Figure 151 RR (95% CI) of colon cancer for 100g/day increase of poultry

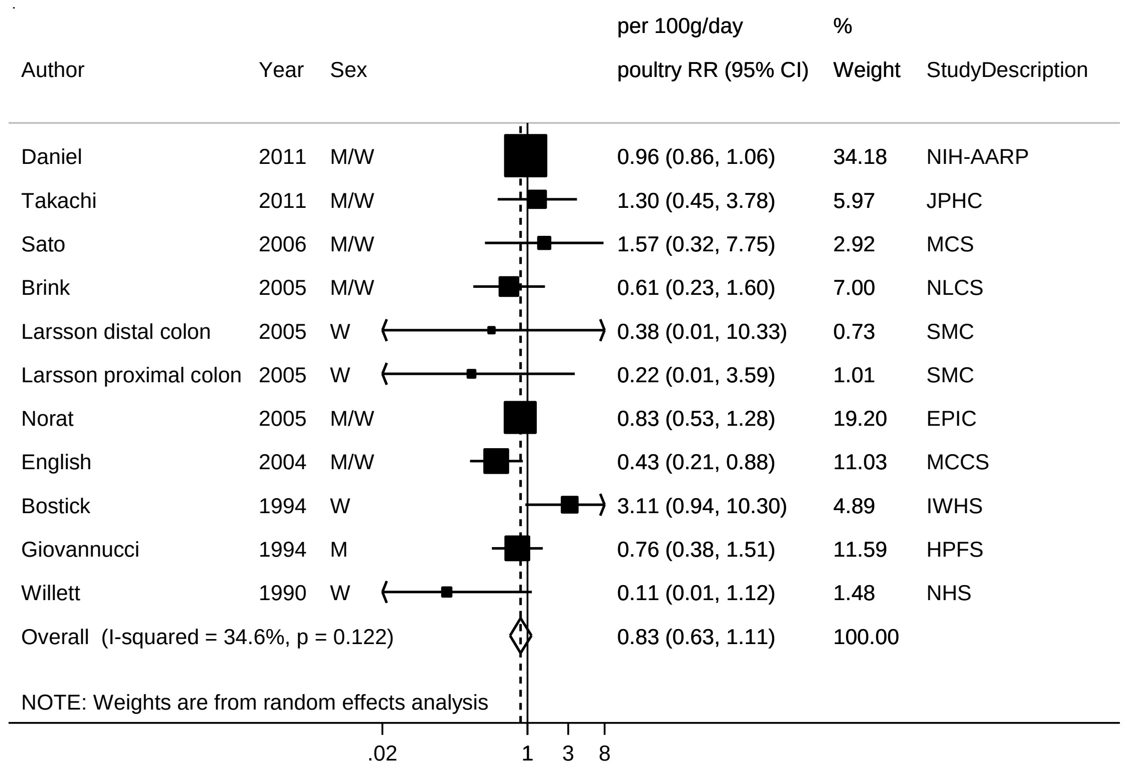


Figure 152 Funnel plot of studies included in the dose response meta-analysis poultry and colon cancer

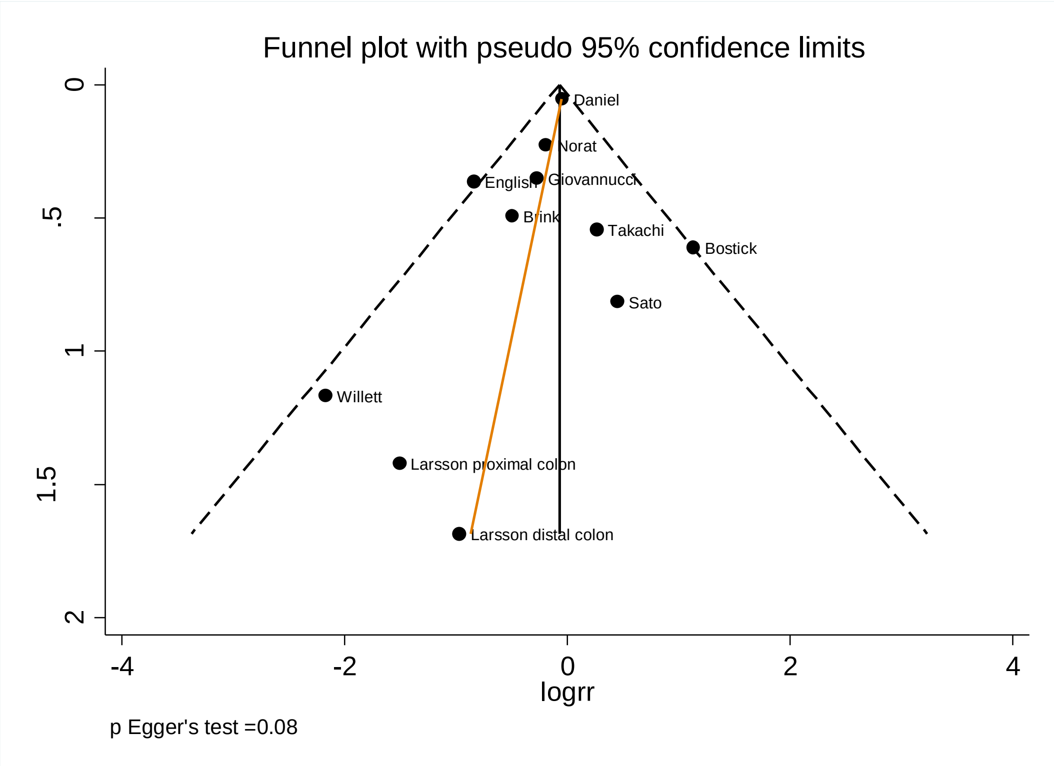


Figure 153 RR (95% CI) of colon cancer for 100g/day increase of poultry by sex

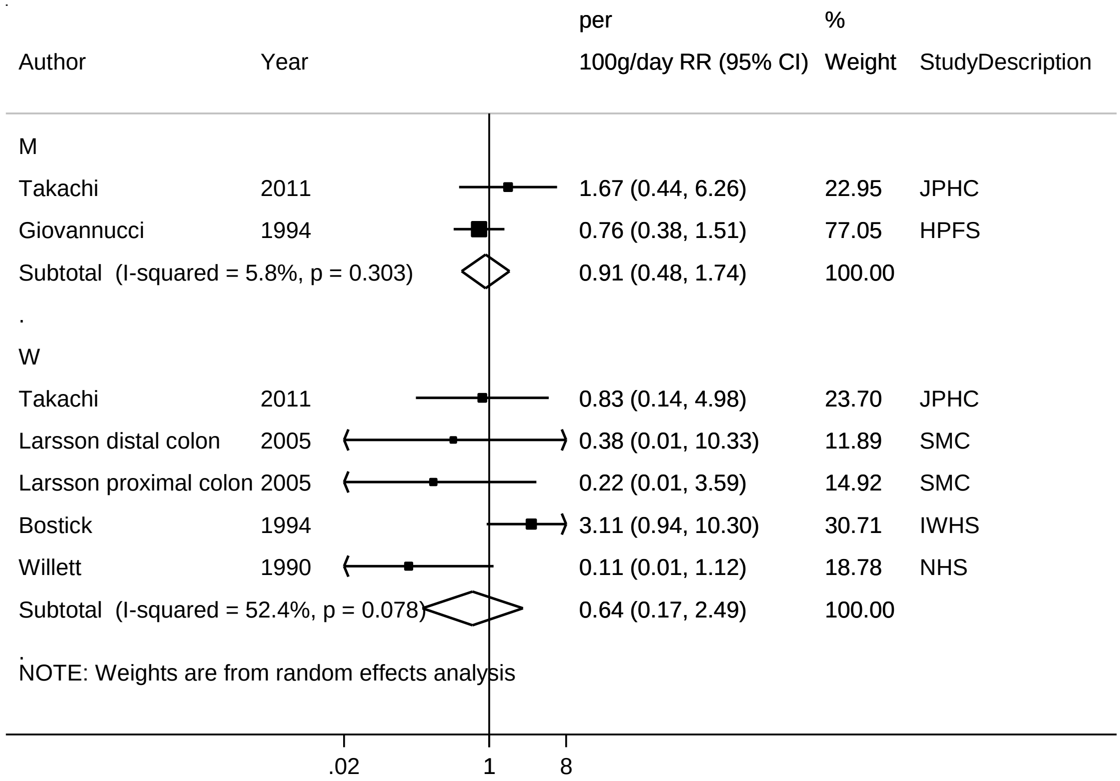


Figure 154 RR (95% CI) of colon cancer for 100g/day increase of poultry by location

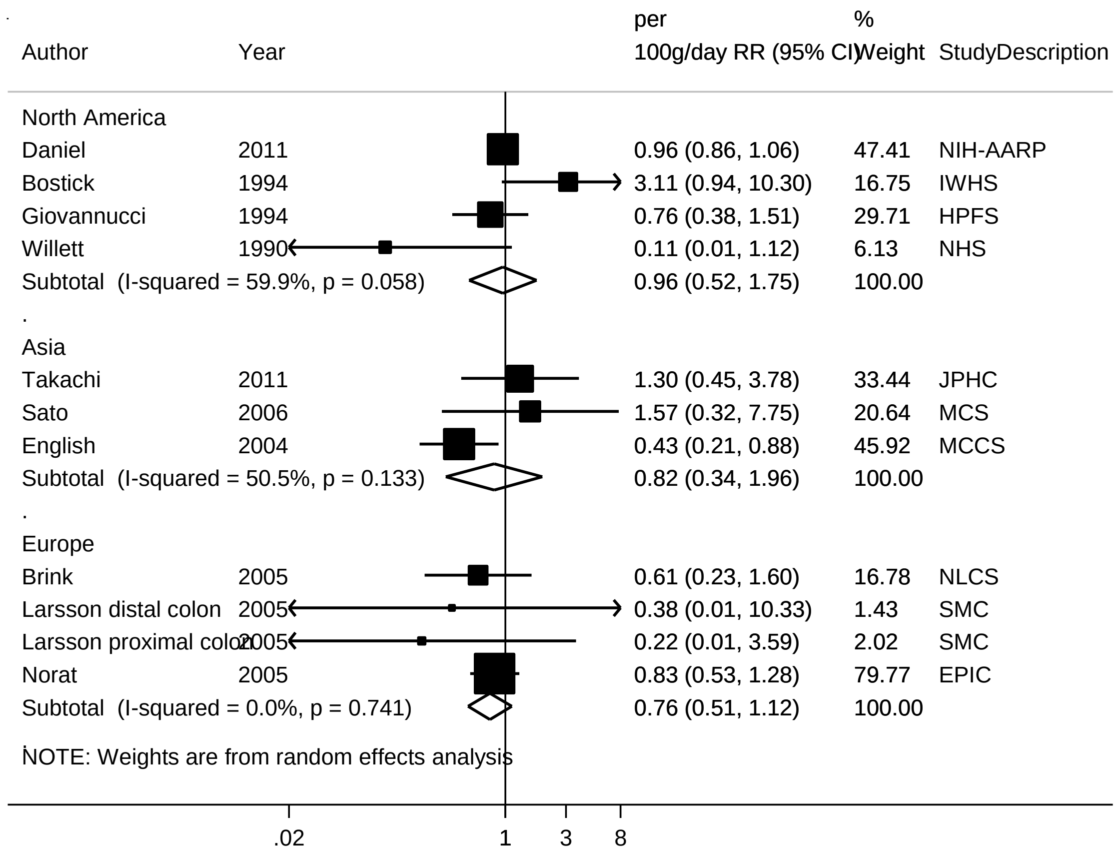


Figure 155 RR estimates of rectal cancer by levels of poultry

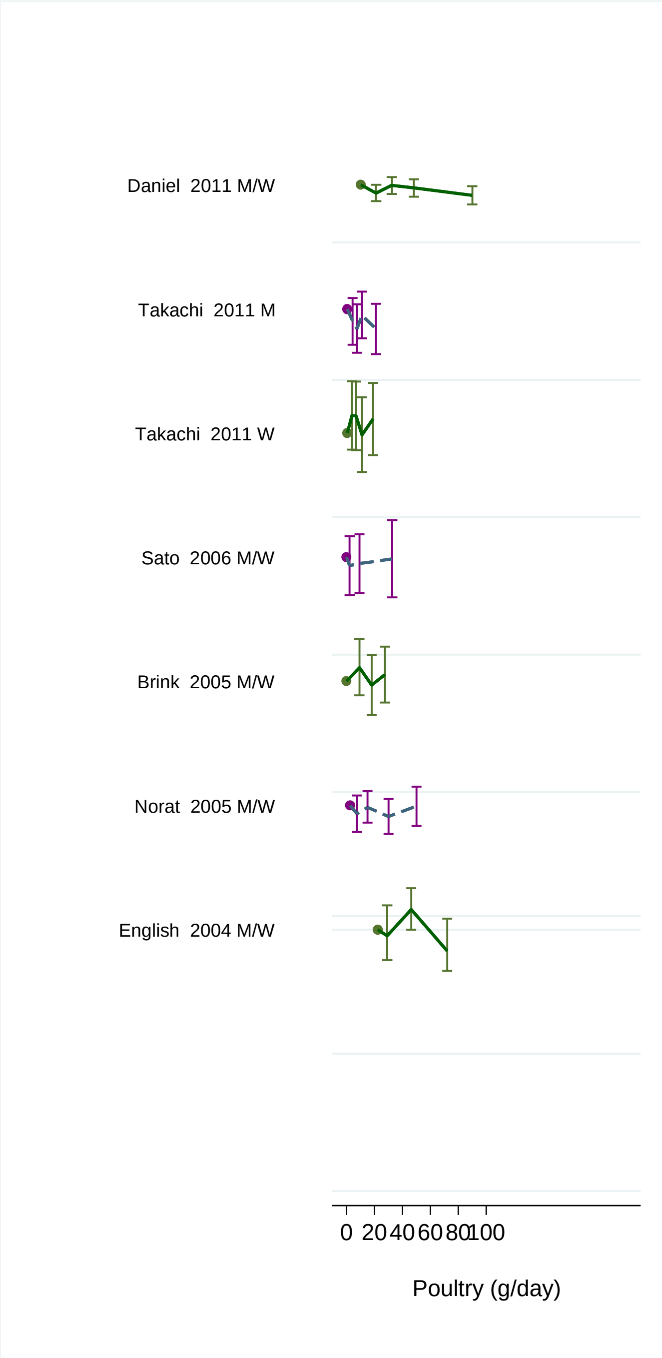


Figure 156 RR (95% CI) of rectal cancer for the highest compared with the lowest level of poultry

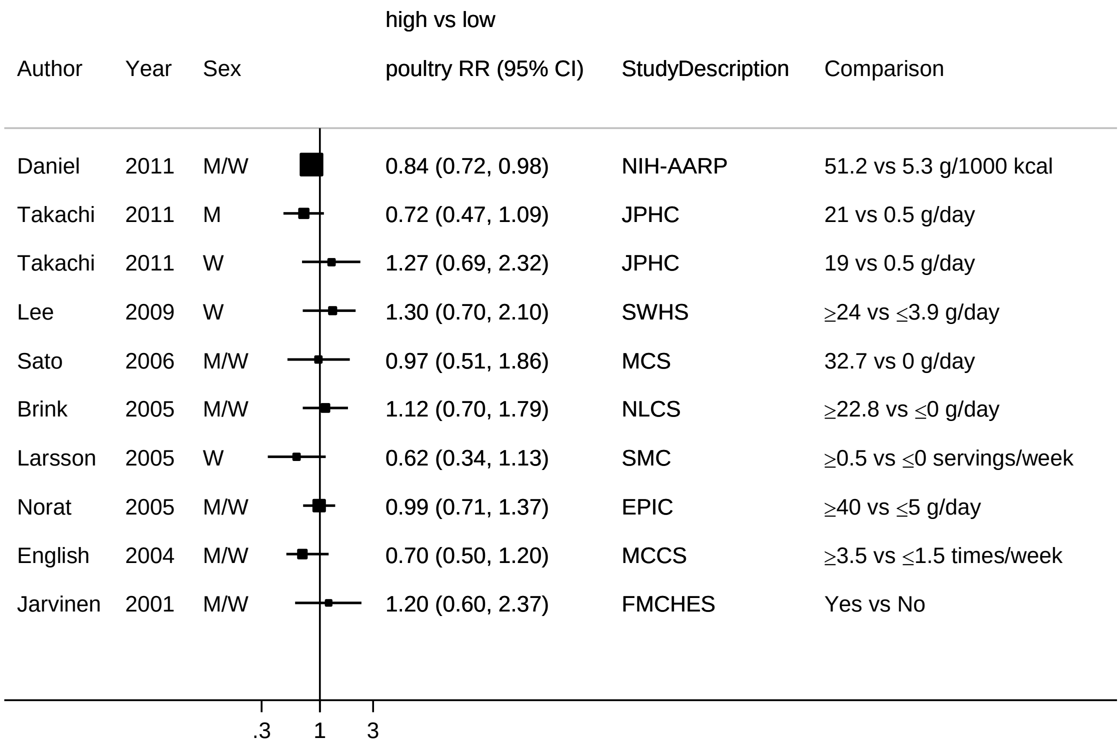


Figure 157 RR (95% CI) of rectal cancer for 100g/day increase of poultry

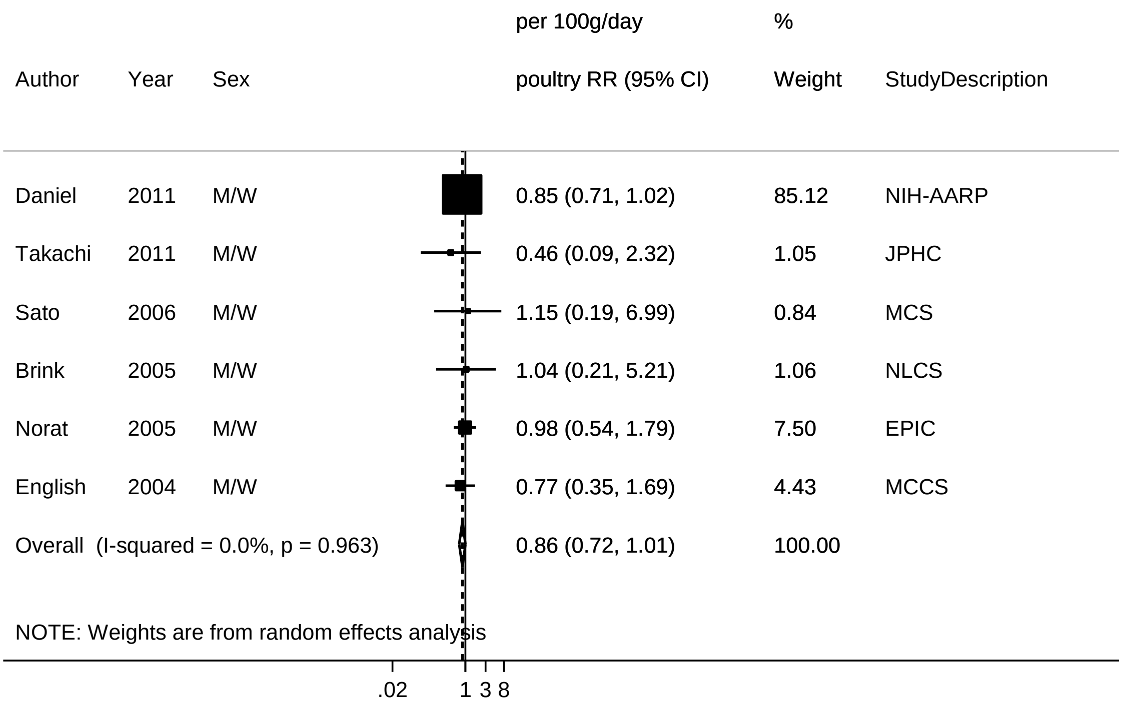


Figure 158 Funnel plot of studies included in the dose response meta-analysis poultry and rectal cancer

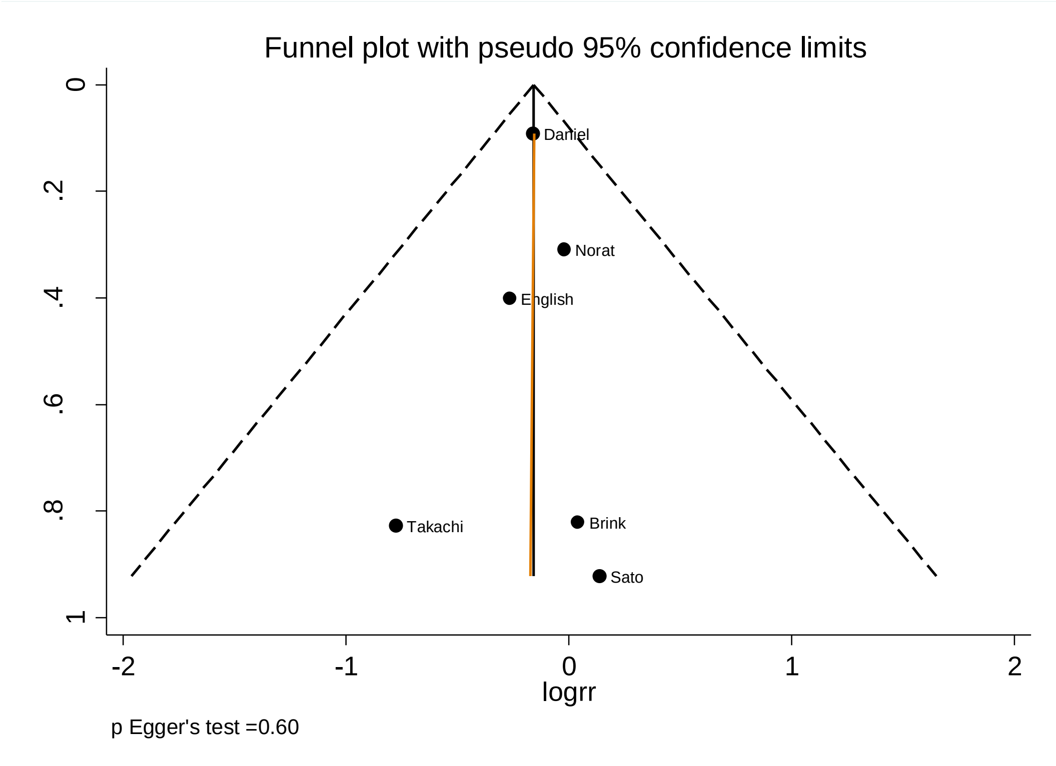
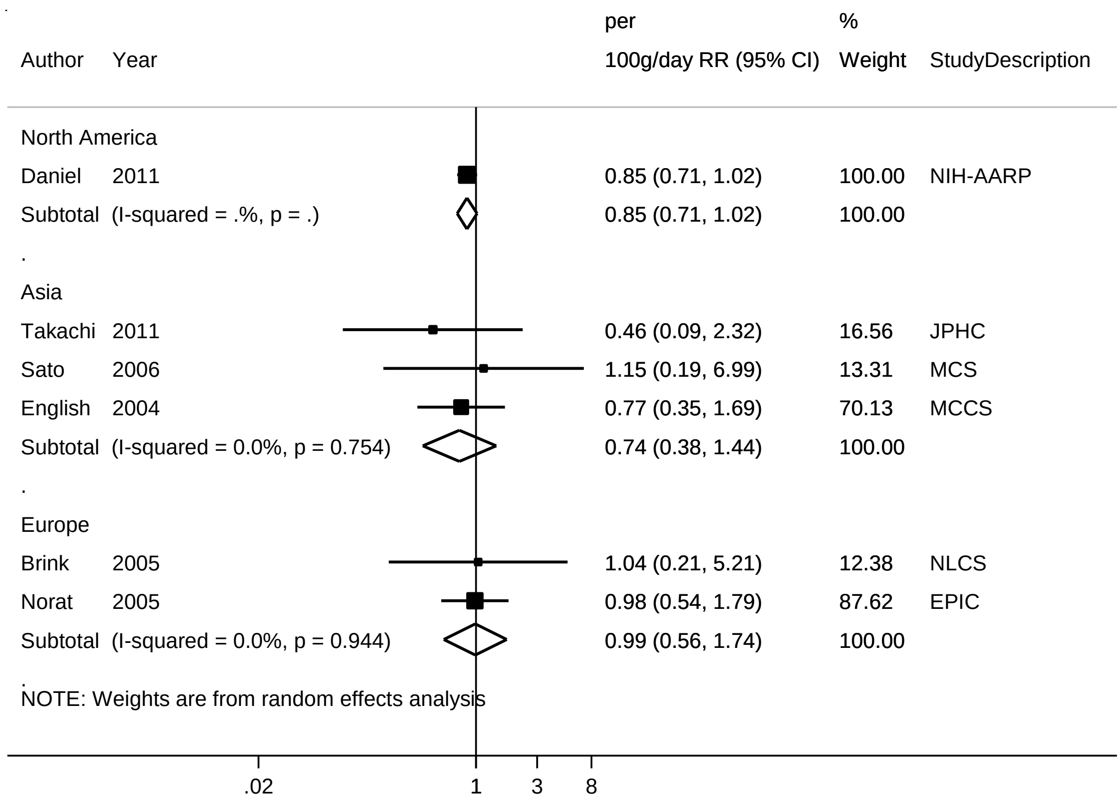


Figure 159 RR (95% CI) of rectal cancer for 100g/day increase of poultry by location



2.5.2 Fish

Cohort studies

Summary

Main results:
Twenty-six studies (37 publications) were identified. Four studies from 3 new publications were identified, one was a new study and three were updates from the studies included in the 2010 SLR. There were no new studies on mortality, therefore all the analyses are on cancer incidence.

Colorectal cancer:
Eleven studies (10356 cases) were included in the dose-response meta-analysis of fish and colorectal cancer. A significant inverse association with no heterogeneity was observed. The only two studies which showed an inverse association were the EPIC study (Bamia, 2013) and the PHS (Hall, 2008). The EPIC study had 40% weight in the analysis. In a sensitivity analysis we excluded the EPIC study and the overall result was not significant 0.94(95%CI=0.82-1.07). After stratification by sex and geographic location the result only remained significant in the subgroup of men. In a stratified analysis with the studies which adjusted for meat intake the result was not significant. There was no evidence of publication bias (p=0.27). There was no evidence of a non-linear association (p=0.55).

The summary RRs ranged from 0.86 (95% CI=0.76-0.97) when Sugawara, 2009 was omitted to 0.94 (95% CI=0.82-1.07) when EPIC (40% weight in the analysis, Bamia, 2013) was omitted.

Colon cancer:
Thirteen studies (10512 cases) were included in the dose-response meta-analysis of fish and colon cancer. A non-significant association with no heterogeneity was observed. The only study showing a significant inverse association was EPIC (Norat, 2005). After stratification by sex and geographic location results were not significant apart from in the European studies where a significant inverse association was observed. In the subgroup of studies that did not adjust for meat intake it was observed a significant inverse association. There was no evidence of publication bias (p=0.32). There was no evidence of a non-linear association (p=0.07).

The summary RRs ranged from 0.87 (95% CI=0.76-1.00) when Sugawara, 2009 was omitted to 0.95 (95% CI=0.83-1.09) when Norat, 2005 was omitted.

Rectal cancer:

Ten studies (3944 cases) were included in the dose-response meta-analysis of fish and rectal cancer. A non-significant association with no heterogeneity was observed. The only 2 studies showing an inverse association were the HPFS (Song, 2014) and the EPIC (Norat, 2005). After stratification by sex and geographic location the results remained not significant. In the subgroup of studies that did not adjust for meat intake a significant inverse association was observed. There was no evidence of publication bias (p=0.56). There was no evidence of a non-linear association (p=0.82).

The summary RRs ranged from 0.80 (95% CI=0.64-1.01) when Sugawara, 2009 was omitted to 0.92 (95% CI=0.75-1.13) when Norat, 2005 was omitted.

Study quality:
Exposure definition varied from general fish intake, fish meals, fish and shellfish intake to seafood consumption. Most studies could not differentiate amount of fish intake by n-3 fatty acids content. Most studies adjusted the results for multiple confounders. Three studies adjusted for fruit intake (EPIC, SMC and OCS) and three studies for vegetable intake (SMC, JPHC and EPIC). Cancer outcome was confirmed using cancer registry records and medical records in most studies.

Pooling Project of cohort studies:
The UK Dietary Cohort Consortium is a nested case-control of seven UK cohorts of 579 cases and 1,996 controls matched on age, sex and recruitment date (Spencer, 2010). It reported an inverse non- significant association per 50g/day of white fish or 50g/day of fatty fish intake. The RR for ≥30 vs < 1 g/day of white fish was 0.86 (0.64–1.16) and for fatty fish it was 0.73 (0.54–0.98), for colorectal cancer. Similar results were observed for colon and rectal cancer.

Meta-analysis of cohort studies:
One meta-analysis (Yu, 2014) including 20 cohort studies was identified. It showed a significant association between fish intake and colorectal cancer in the highest compared to lowest analysis and a non-significant association per 20g/day of fish intake.

Table 93 Fish and colorectal cancer risk. Number of studies in the CUP SLR

	Number
Studies identified	18
Studies included in forest plot of highest compared with lowest exposure	15
Studies included in dose-response meta-analysis	11
Studies included in non-linear dose-response meta-analysis	9

Note: Include cohort, nested case-control and case-cohort designs

Table 94 Fish and colon cancer risk. Number of studies in the CUP SLR

	Number
Studies identified	18
Studies included in forest plot of highest compared with lowest exposure	13
Studies included in dose-response meta-analysis	13
Studies included in non-linear dose-response meta-analysis	11

Note: Include cohort, nested case-control and case-cohort designs

Table 95 Fish and rectal cancer risk. Number of studies in the CUP SLR

	Number
Studies identified	15
Studies included in forest plot of highest compared with lowest exposure	12
Studies included in dose-response meta-analysis	10
Studies included in non-linear dose-response meta-analysis	8

Note: Include cohort, nested case-control and case-cohort designs

Table 96 Fish and colorectal cancer risk. Summary of the dose-response meta-analysis in the 2010 SLR and 2015 SLR.

	2010 SLR	**2015 SLR**
Increment unit used	100g/day	100g/day
Studies (n)	9	11
Cases (total number)	4503	10356
RR (95%CI)	0.88 (0.74-1.06)	0.89(0.80-0.99)
Heterogeneity (I^2, p-value)	38%, 0.12	0%, 0.52

Stratified analysis by sex		
Men	**2010 SLR**	**2015 SLR**
Studies (n)	4	6
RR (95%CI)	0.86 (0.64 - 1.16)	0.83(0.71-0.98)
Heterogeneity (I^2, p-value)	33%, 0.21	11.1%, 0.34
Women		
Studies (n)	5	7
RR (95%CI)	1.07 (0.82 - 1.41)	0.96(0.82-1.12)

Heterogeneity (I^2, p-value)	2%, 0.40	0%, 0.53	
Stratified analysis by geographic location			
(no analysis in 2005 SLR or 2010 SLR)			
2015 SLR	**Asia**	**Europe**	**North America**
Studies (n)	3	4	4
RR (95%CI)	1.03(0.84-1.26)	0.85(0.71-1.01)	0.83(0.68-1.03)
Heterogeneity (I^2, p-value)	0%, 0.90	2.0%, 0.38	0.5%, 0.39
Stratified analysis by adjustment for meat			
Yes			
Studies (n)	4	7	
RR (95%CI)	0.95(0.74-1.23)	0.89(0.79-1.01)	
Heterogeneity (I^2, p-value)	44.9%, 0.14	9.5%, 0.36	
No			
Studies (n)	5	4	
RR (95%CI)	0.78(0.62-0.97)	0.94(0.66-1.34)	
Heterogeneity (I^2, p-value)	9.2%, 0.35	0%, 0.50	

Table 97 Fish and colon cancer risk. Summary of the dose-response meta-analysis in the 2010 SLR and 2015 SLR.

	2010 SLR	2015 SLR
Increment unit used	100g/day	100g/day
Studies (n)	10	11
Cases (total number)	3156	10512
RR (95%CI)	0.90 (0.78-1.04)	0.91(0.80-1.03)
Heterogeneity (I^2, p-value)	0%, 0.61	0%, 0.76

Stratified analysis by sex			
Men	**2010 SLR**	**2015 SLR**	
Studies (n)	4	4	
RR (95%CI)	1.07 (0.85-1.35)	1.09(0.86-1.38)	
Heterogeneity (I^2, p-value)	0%, 0.76	0%, 0.80	
Women			
Studies (n)	6	7	
RR (95%CI)	0.85 (0.63-1.16)	0.94(0.72-1.22)	
Heterogeneity (I^2, p-value)	0%, 0.92	0%, 0.49	
Stratified analysis by geographic location			
(no analysis in 2005 SLR or 2010 SLR)			
2015 SLR	**Asia**	**Europe**	**North America**
Studies (n)	4	3	4
RR (95%CI)	1.04(0.85-1.28)	0.74(0.58-0.93)	0.91(0.74-1.13)

Heterogeneity (I^2, p-value)	0%, 0.99	0%, 0.81	0%, 0.43

Stratified analysis by adjustment for meat		
Yes		
Studies (n)	3	6
RR (95%CI)	1.04(0.84-1.29)	0.98(0.84-1.14)
Heterogeneity (I^2, p-value)	0%, 0.93	0%, 0.76
No		
Studies (n)	7	5
RR (95%CI)	0.80(0.65-0.97)	0.76(0.61-0.95)
Heterogeneity (I^2, p-value)	0%, 0.71	0%, 0.79

Table 98 Fish and rectal cancer risk. Summary of the dose-response meta-analysis in the 2010 SLR and 2015 SLR.

	2010 SLR	**2015 SLR**
Increment unit used	100g/day	100g/day
Studies (n)	7	10
Cases (total number)	1650	3944
RR (95%CI)	0.87 (0.69-1.10)	0.84(0.69-1.02)
Heterogeneity (I^2, p-value)	17%, 0.30	14.7%, 0.31

Stratified analysis by sex			
Men	**2010 SLR**	**2015 SLR**	
Studies (n)	2	3	
RR (95%CI)	1.11 (0.79 - 1.56)	0.88(0.50-1.55)	
Heterogeneity (I^2, p-value)	0%, 0.50	63.5%, 0.06	
Women			
Studies (n)	4	5	
RR (95%CI)	1.00 (0.65 - 1.54)	0.95(0.65-1.41)	
Heterogeneity (I^2, p-value)	0%, 0.72	0%, 0.81	
Stratified analysis by geographic location (no analysis in 2005 SLR or 2010 SLR)			
2015 SLR	**Asia**	**Europe**	**North America**
Studies (n)	4	3	3
RR (95%CI)	1.04(0.80-1.35)	0.64(0.46-0.88)	0.70(0.43-1.16)
Heterogeneity (I^2, p-value)	0%, 0.85	0%, 0.63	33.1%, 0.22
Stratified analysis by adjustment for meat			
Yes			
Studies (n)	4	7	
RR (95%CI)	1.07(0.82-1.39)	0.95(0.77-1.17)	
Heterogeneity (I^2, p-value)	0%, 0.91	0%, 0.45	
No			

Studies (n)	3	3
RR (95%CI)	0.64(0.47-0.87)	0.64(0.47-0.87)
Heterogeneity (I^2, p-value)	0%, 0.79	0%, 0.79

Table 99 Fish and colorectal cancer risk. Results of meta-analyses and pooled analyses of prospective studies published after the 2005 SLR.

Author, Year	Number of cohort studies	Total number of cases	Studies country, area	Outcome	Comparison	RR (95%CI)	P trend	Heterogeneity (I^2, p value)
Pooled-analysis								
Spencer, 2010	7 Guernsey Study, EPIC- Norfolk, EPIC-Oxford, NSHD, Oxford Vegetarian, UKWCS, Whitehall	579 cases 1996 controls	UK	Colorectal cancer	White fish			
					Per 50g/day	0.92 (0.70–1.21)	0.53	
					≥30 vs <1 g/day	0.86 (0.64–1.16)	0.33	
					Fatty fish			
					Per 50g/day	0.89 (0.70–1.13)		
					≥30 vs <1 g/day	0.73 (0.54–0.98)		
				Colon cancer	White fish			
					Per 50g/day	0.84 (0.59–1.19)	0.32	
					≥30 vs <1 g/day	0.80 (0.56–1.14)		
					Fatty fish			
					Per 50g/day	0.82 (0.61–1.11)	0.21	
					≥30 vs <1 g/day	0.73 (0.51–1.04)		
				Rectal cancer	White fish			
					Per 50g/day	1.12 (0.70–1.81)	0.63	
					≥30 vs <1 g/day	1.04 (0.61–1.78)		
					Fatty fish			
					Per 50g/day	0.99 (0.68–1.44)	0.95	
					≥30 vs <1 g/day	0.68 (0.39–1.18)		

Meta-analysis								
Yu, 2014	20 Europe (Denmark, France, Germany, Greece, Italy, the Netherlands, Norway, Spain, Sweden, Switzerland and the United Kingdom), North America (the United States), Asia (China and Japan) and Oceania (Australia)	14097	Europe, North America and Asia	Colorectal cancer	Fish consumers vs non/lowest consumers Per 20g/day	0.93 (0.87-0.99) 0.99(0.97-1.01)		64.7%, <0.001
				Colon cancer Rectal cancer	Fish consumers vs non/lowest consumers	0.95 (0.91-0.98) 0.85 (0.75-0.95)		33.5%, 0.16 58%, 0.02

* Heterogeneity (I^2, p value) only reported when available

Table 100 Fish and colorectal cancer risk. Main characteristics of studies included in the CUP SLR dose-response meta-analysis

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Missing data derived for analysis
Song, 2014 COL41015 USA	NHS, Prospective Cohort, Age: 30-55 years, W	1 469/ 76 386 26 years	Self-administered questionnaire, national death Index, pathology reports and medical records	FFQ	Incidence, colorectal cancer	≥40 vs ≤15 g/day	1.02 (0.86-1.20)	Age, alcohol, BMI, calendar year, calories intake, endoscopy, energy-adjusted calcium, energy-adjusted folate, energy-adjusted vitamin d, family history, fibre, HRT use, multivitamin supplement intake, NSAID use, pack years of smoking, physical activity, postmenopausal status, processed meat, red meat	Mid-points of exposure categories
		713/ 76 386 26 years	Self-administered questionnaire, national death Index, pathology reports and medical records	FFQ	Incidence, proximal colon cancer	≥40 vs ≤15 g/day	0.89 (0.70-1.14)		
		416/			Incidence, distal colon cancer	≥40 vs ≤15 g/day	1.36 (1.00-1.85)		
		310/ 76 386 26 years			Incidence, rectal cancer	≥40 vs ≤15 g/day	0.98 (0.69-1.40)		
Song, 2014 COL41016 USA	Health Professionals Follow-up Study (HPFS),	342/ 47 143 24 years	Self-report, medical records, pathology report, family	FFQ	Incidence, distal colon cancer	≥46 vs ≤16 g/day	1.12 (0.77-1.64)	Age, alcohol, BMI, endoscopy, energy-adjusted	
					Incidence, proximal colon	≥46 vs ≤16 g/day	0.95 (0.68-1.34)		

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Missing data derived for analysis
	Prospective Cohort, Age: 40-75 years, M, Health professionals		members, national death Index		cancer			calcium, energy-adjusted folate, energy-adjusted vitamin d, family history of colon cancer, fibre, multivitamin supplement intake, NSAID use, pack years of smoking, physical activity, red and processed meat, total calories, year	
		215/ 47 143 24 years			Incidence, rectal cancer	≥46 vs ≤16 g/day	0.60 (0.39-0.93)		
		987/ 47 143 24 years			Incidence, colorectal cancer	≥46 vs ≤16 g/day	0.88 (0.72-1.08)		
Bamia, 2013 COL40964 Denmark, France, Germany, Greece, Italy, Netherlands, Spain, Sweden, UK	EPIC, Prospective Cohort, Age: 25-70 years, M/W	4 355/ 480 308 11.6 years	Cancer registry, record linkage, health Insurance rec, mortality registry , pathology and active follow up	FFQ	Incidence, colorectal cancer	63.8 vs 8.6 g/day	0.90 (0.82-0.99)	Age, sex, BMI, centre location, cereal, dairy products consumption, educational level, ethanol, fish, fruits, legumes, lipids, meat, physical activity,	Distribution of person-years by exposure category.
		2 479/			Women	63.8 vs 8.6 g/day	0.94 (0.83-1.06)		
		1 876/			Men	63.8 vs 8.6 g/day	0.85 (0.74-0.97)		

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Missing data derived for analysis
								smoking	
Daniel, 2011 COL40884 USA	NIH-AARP, Prospective Cohort, Age: 50-71 years, M/W	5 095/ 492 186 9.1 years	Cancer registry	FFQ	Incidence, colon cancer	21.4 vs 3.6 g/1000 kcal	0.95 (0.87-1.04)	Age, sex, BMI, educational level, energy intake, family history of cancer, HRT use, marital status, poultry, race, red meat, smoking, vigorous activity	Intakes in g/1000kcal/day converted to g/day using average energy intake per each quantile
		1 884/			Incidence, rectal cancer	21.4 vs 3.6 g/1000 kcal	0.96 (0.83-1.11)		
		164/			Incidence, anal cancer	21.4 vs 3.6 g/1000 kcal	0.71 (0.41-1.23)		
Murff, 2009 COL40782 China	SWHS, Prospective Cohort, Age: 40-70 years, W	396/ 73 242 11 years	Cancer registry	FFQ	Incidence, colorectal cancer	104.52 vs 14.91 g/day	1.28 (0.87-1.90)	Age, alcohol consumption, aspirin use, BMI, energy intake, HRT use, menopausal status, multivitamin supplement intake, physical activity, polyunsaturated fat, red meat intake, smoking status	Distribution of person-years by exposure category.
		332/			>2 yrs follow-up	104.52 vs 14.91 g/day	1.05 (0.66-1.65)		
		200/			Incidence, colon cancer, >2 yrs follow-up	104.52 vs 14.91 g/day	0.94 (0.53-1.65)		
		132/			Incidence, rectal cancer, >2 yrs follow-up	104.52 vs 14.91 g/day	1.32 (0.61-2.84)		

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Missing data derived for analysis
Sugawara, 2009 COL40781 Japan	OCS, Prospective Cohort, Age: 40-79 years, M/W	379/ 39 498 9 years	Cancer registry and death certificates	FFQ	Incidence, colorectal cancer, men	≥96.4 vs 0-26.2 g/day	1.07 (0.78-1.46)	Alcohol consumption, BMI, educational level, employment status, energy intake, family history of cancer, fruit intake, history of diabetes, hypertension, marital status, meat intake, myocardial Infarction, physical activity, prevalent stroke, smoking status, vegetable intake	Mid-points of exposure categories
		229/			Incidence, colon cancer, men	≥96.4 vs 0-26.2 g/day	1.11 (0.75-1.64)		
		187/			Incidence, colorectal cancer, women	≥81.4 vs 0-26.6 g/day	0.96 (0.61-1.53)		
		163/			Incidence, rectal cancer, men	≥96.4 vs 0-26.2 g/day	0.99 (0.61-1.61)		
		118/			Incidence, colon cancer, women	≥81.4 vs 0-26.6 g/day	0.95 (0.53-1.71)		
		73/			Incidence, rectal cancer, women	≥81.4 vs 0-26.6 g/day	0.96 (0.47-1.96)		
Hall, 2008 COL40720 USA	PHS, Prospective Cohort, Age: 54 years, M	500/ 21 406 22 years	Self report verified by medical record	Semi-quantitative FFQ	Incidence, colorectal cancer	≥5 vs ≤0.9 times/week	0.63 (0.42-0.95)	Alcohol consumption, BMI, history of diabetes, multivitamin	Mid-points of exposure categories. Conversion from times/week to
		388/			Incidence, colon cancer	≥5 vs ≤0.9 times/week	0.62 (0.38-1.00)		

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Missing data derived for analysis
		112/			Incidence, rectal cancer	≥5 vs ≤0.9 times/week	0.65 (0.30-1.41)	supplement intake, physical activity, randomized treatment assignment, red meat intake, smoking habits	g/day
Brink, 2005 COL40717 Netherlands	NLCS, Case Cohort, Age: 55-69 years, M/W	448/ 2 948 7.3 years	Cancer registry	Semi-quantitative FFQ	Incidence, colon cancer	per 15 g/day	0.93 (0.83-1.04)	Age, sex, BMI, energy intake, family history of colorectal cancer, smoking habits	
						≥20 vs ≤0 g/day	1.03 (0.76-1.40)		
		290/			Ki-ras-	≥20 vs ≤0 g/day	0.87 (0.60-1.26)		
						per 15 g/day	0.88 (0.77-1.02)		
		160/			Incidence, rectal cancer	per 15 g/day	0.93 (0.80-1.08)		
						≥20 vs ≤0 g/day	0.94 (0.59-1.52)		
		144/			Incidence, colon cancer, ki-ras+	≥20 vs ≤0 g/day	1.38 (0.85-2.25)		
						per 15 g/day	1.00 (0.85-1.19)		
		89/			Incidence, rectal cancer, ki-ras-	≥20 vs ≤0 g/day	1.06 (0.58-1.94)		
						per 15 g/day	0.97 (0.81-1.17)		

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Missing data derived for analysis
		65/			Incidence, colon cancer, Ki-ras+	≥20 vs ≤0 g/day	0.78 (0.37-1.65)		
						per 15 g/day	0.86 (0.69-1.07)		
Larsson, 2005 COL01849 Sweden	SMC, Prospective Cohort, Age: 40-75 years, W	733/ 61 433 855 585 person-years	Cancer registry	Questionnaire	Incidence, colorectal cancer,	≥2 vs 0-0.4 serving/week	1.08 (0.81-1.43)	Age, alcohol consumption, BMI, calcium, educational level, energy intake, folate, fruits, poultry, red meat intake, saturated fat, vegetables, whole-grain foods	Distribution of person-years by exposure category. Conversion from servings/week to g/day
		234/			Incidence, proximal colon cancer,	≥2 vs 0-0.4 serving/week	1.03 (0.63-1.67)		
		230/			Incidence, rectal cancer,	≥2 vs 0-0.4 serving/week	1.08 (0.63-1.86)		
		155/			Incidence, distal colon cancer,	≥2 vs 0-0.4 serving/week	0.83 (0.45-1.51)		
Norat, 2005 COL01698 Europe	EPIC, Prospective Cohort, Age: 21-83 years, M/W	1 329/ 478 040 2 279 075 person-years		Questionnaire	Incidence, colorectal cancer,	per 100 g/day	0.70 (0.57-0.87)	Age, sex, alcohol consumption, body weight, centre location, energy from fat sources, energy from non-fat sources, fibre, height, physical activity,	Superseded by Bamia, 2013 COL40964 for colorectal cancer, used for colon and rectal cancer. Continuous results were used.
						≥80 vs ≤10 g/day	0.71 (0.55-0.91)		
		855/			Incidence, colon cancer,	per 100 g/day	0.76 (0.59-0.99)		
						≥80 vs ≤10 g/day	0.82 (0.60-1.11)		

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Missing data derived for analysis
		474/			Incidence, rectal cancer,	per 100 g/day	0.61 (0.43-0.87)	smoking status	
						≥80 vs ≤10 g/day	0.49 (0.32-0.76)		
		391/			Incidence, left colon cancer,	≥80 vs ≤10 g/day	0.70 (0.44-1.11)		
		351/			Incidence, right colon cancer,	≥80 vs ≤10 g/day	0.85 (0.53-1.37)		
					Incidence, colorectal cancer, low red and processed meat intake	Q 1 vs Q 3	1.46		
English, 2004 COL00019 Australia	MCCS, Prospective Cohort, Age: 27-75 years, M/W	452/ 37 112 9 years	Population/electoral rolls	FFQ	Incidence, colorectal cancer,	≥2.5 vs ≤1 times/week	0.90 (0.70-1.20)	Sex, country of birth, and intake of energy, fat, and cereal products	Conversion from times/week to g/day
						per 1 times/week	0.99 (0.91-1.08)		
		283/			Incidence, colon cancer,	≥2.5 vs ≤1 times/week	1.00 (0.70-1.40)		
						per 1 times/week	1.01 (0.90-1.12)		
		169/			Incidence, rectal cancer,	≥2.5 vs ≤1 times/week	0.90 (0.60-1.40)		

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Missing data derived for analysis
						per 1 times/week	0.97 (0.84-1.12)		
Kobayashi, 2004 COL01687 Japan	JPHC, Prospective Cohort, Age: 40-69 years, M/W	300/ 88 658 9 years	Cancer registry and death certificates	FFQ	Incidence, colon cancer, men	Q 4 vs Q 1	1.07 (0.72-1.58)	Age, alcohol intake, area, BMI, cereal intake, family history of colorectal cancer, meat intake, physical activity, smoking status, total energy intake, vegetable intake, vitamin use	Weighted average mid-exposure value per category from Cohort I and II
		156/			Women	Q 4 vs Q 1	1.05 (0.61-1.82)		
		154/			Incidence, rectal cancer, men	Q 4 vs Q 1	1.31 (0.78-2.22)		
		95/			Women	Q 4 vs Q 1	0.69 (0.35-1.36)		
Lin, 2004 COL01834 USA	WHS, Prospective Cohort, Age: 45- years, W	202/ 37 547 8.7 years	Self report verified by medical record	FFQ	Incidence, colorectal cancer	0.56 vs 0.07 servings/day	1.23 (0.77-1.91)	Age, alcohol consumption, BMI, family history of colorectal cancer, history of polyps, physical activity, postmenopausal hormone use,	Distribution of person-years by exposure category. Conversion from servings/day to g/day

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Missing data derived for analysis
								randomized treatment assignment, smoking habits, total energy intake	
Tiemersma, 2002 COL00563 Netherlands	Dutch prospective Monitoring Project on Cardiovascular Disease Risk Factors, Nested Case Control, Age: 20-59 years, M/W	102/ 537 controls 8.5 years	Population registry	FFQ	Incidence, colorectal cancer,	≥4 vs 0-1 times/month	0.70 (0.40-1.30)	Age, sex, alcohol consumption, body height, energy intake, study centre	Mid-points of exposure categories. Only included in highest compared to lowest to colon and rectal cancer
		54/ 292 controls			Men	≥4 vs 0-1 times/month	1.20 (0.60-2.40)		
		48/ 145 controls			Women	≥4 vs 0-1 times/month	0.50 (0.20-1.00)		
					Nat1 slow phenotype	≥4 vs 0-1 times/week	0.60 (0.30-1.20)		
					Nat2 slow phenotype	≥4 vs 0-1 times/week	0.90 (0.50-1.80)		
					Gstm1 present	≥4 vs 0-1 times/week	0.50 (0.20-1.10)		
		63			Incidence, colon cancer,	≥4 vs 0-1 times/month	0.50 (0.30-0.90)		
						≥4 vs 0-1 times/month	1.60 (0.70-3.60)		
					Women	≥4 vs 0-1	0.40 (0.10-0.90)		

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Missing data derived for analysis
						times/month			
Pietinen, 1999 COL00176 Finland	ATBC, Prospective Cohort, Age: 50-69 years, M, Smokers	185/ 27 111 8 years	Cancer registry	Dietary history questionnaire	Incidence, colorectal cancer,	68 vs 13 g/day	0.90 (0.60-1.40)	Alcohol consumption, BMI, calcium intake, educational level, physical activity, smoking years	Distribution of person-years by exposure category.
Gaard, 1996 CRC00008 Norway	Norwegian national health screening service study, Prospective Cohort, Age: 20-53 years, M/W	87/ 50 535 11.4 years	Enrolment by volunteers	FFQ	Incidence, colon cancer, men	≥5 vs 0-2 times/week	0.46 (0.19-1.11)	Age, attained age	Conversion from times/week to g/day
		63/			Women	≥5 vs ≤2 times/week	0.81 (0.30-1.94)		
Bostick, 1994 COL00079 USA	IWHS, Prospective Cohort, Age: 55-69 years, W	212/ 35 216 167 447 person-years	SEER	Semi-quantitative FFQ	Incidence, colon cancer	≥2.5 vs ≤1 serving/week	0.76 (0.49-1.19)	Energy intake, height, parity, total vitamin e intake, total vitamin e intake age, vitamin a supplement	Distribution of person-years by exposure category. Conversion from serving/week to g/day
						≥2.5 vs ≤1 serving/week	0.76 (0.49-1.19)		

Table 101 Fish and colorectal cancer risk. Main characteristics of studies excluded from the CUP SLR dose-response meta-analysis

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Reasons for exclusion
Egeberg, 2013 COL40953 Denmark	DCH, Prospective Cohort, Age: 50-64 years, M/W	644/ 53 988 13.4 years	Cancer registry	FFQ	Incidence, colon cancer	≥55 vs 0-27 g/day	0.86 (0.68-1.08)	Age, alcohol, beef consumption, cold cuts, educational level, energy, fiber, HRT use, lamb intake, liver, NSAIS use, pork, poultry, processed meat, red meat, sausages, smoking, sport, veal meat, waist circumference	Superseded by Norat, 2005 COL01698 (component of EPIC study)
						≥55 vs 0-27 g/day	0.87 (0.70-1.08)		
						per 25 g/day	0.93 (0.85-1.01)		
						per 25 g/day	0.94 (0.87-1.01)		
		345/			Incidence, rectal cancer	≥55 vs 0-27 g/day	1.01 (0.72-1.40)		
						≥55 vs 0-27 g/day	0.97 (0.71-1.32)		
						per 25 g/day	0.99 (0.88-1.10)		
						per 25 g/day	0.97 (0.88-1.08)		
Agnoli, 2013 COL40938 Italy	EPIC-Italy, Prospective Cohort, M/W	435/ 45 275 11.28 years	Cancer registry and hospital records	Semi-quantitative FFQ	Incidence, colorectal cancer	38.6-340.3 vs 0-20.1 g/day	0.88 (0.68-1.13)	Age, BMI, educational level, gender, non-alcoholic beverage intake, physical activity, smoking, study	Superseded by Bamia, 2013 COL40964

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Reasons for exclusion
								centre	
Cross, 2010 COL40794 USA	NIH-AARP, Prospective Cohort, Age: 50-71 years, M/W	2 719/ 300 948 7.2 years	Cancer registry and death certificates and questionnaires	FFQ	Incidence, colorectal cancer	Q 5 vs Q 1	0.95 (0.84-1.08)	Sex, BMI, dietary calcium intake, educational level, red meat intake, smoking habits, total energy intake	Only included in highest vs lowest analysis
Lee, 2009 COL40764 China	SWHS, Prospective Cohort, Age: 40-70 years, W	394/ 73 224 7.4 years	Cancer registry and death certificates and participant contact	Quantitative FFQ	Incidence, colorectal cancer	≥26 vs ≤3.9 g/day Fresh water fish	0.90 (0.60-1.20)	Age, educational level, energy intake, fibre intake, Income, NSAID use, season of Interview, tea consumption	Superseded by Murff, 2009 COL40782
						≥32 vs ≤3.9 g/day Marine fish	1.00 (0.70-1.40)		
						≥74 vs ≤19.9 g/day Total fish	1.30 (0.90-1.90)		
						≥3.5 vs ≤0 g/day Eel	1.30 (0.90-1.70)		
		236/			Incidence, colon	≥26 vs ≤3.9	0.80 (0.50-1.20)		

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Reasons for exclusion
					cancer	g/day Fresh water fish			
						≥32 vs ≤3.9 g/day	0.80 (0.50-1.20)		
						≥74 vs ≤19.9 g/day Total fish	1.40 (0.90-2.10)		
						≥3.5 vs ≤0 g/day Eel	1.40 (0.90-2.10)		
		158/			Incidence, rectal cancer	≥32 vs ≤3.9 g/day Marine fish	1.40 (0.80-2.30)		
						≥74 vs ≤19.9 g/day Total fish	1.30 (0.70-2.40)		
						≥3.5 vs ≤0 g/day Eel	1.10 (0.60-1.90)		
						≥26 vs ≤3.9 g/day Fresh water fish	1.00 (0.60-1.70)		
Butler, 2008 COL40639 Singapore	SCHS, Prospective Cohort, Age: 45-74 years,	961/ 61 321 9.8 years	Cancer registry	FFQ	Incidence, colorectal cancer	Q 4 vs Q 1	1.17 (0.96-1.43)	Age, sex, alcohol intake, BMI, diabetes, dialect group, educational	Only included in highest compared to lowest analysis

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Reasons for exclusion
	M/W							level, energy intake, exposure assessment, family history of colorectal cancer, physical activity, smoking habits	
Iso, 2007 COL40707 Japan	JACC, Prospective Cohort, Age: 40-79 years, M/W	211/ 105 500 15 years	Municipal resident registration records, death certificates	FFQ	Mortality, colon cancer, men	≥5 vs ≤2 /week	1.05 (0.73-1.50)	Age, centre location	Outcome is mortality
		198/			Women	≥5 vs ≤2 /week	1.00 (0.69-1.44)		
		156/			Mortality, rectal cancer, men	≥5 vs ≤2 /week	0.98 (0.65-1.48)		
		79/			Women	≥5 vs ≤2 /week	1.02 (0.58-1.80)		
Engeset, 2007 COL40696 Norway	NOWAC, Prospective Cohort, Age: 40-71 years, W	254/ 63 914 13 years	Cancer registry	Semi-quantitative FFQ	Incidence, colon cancer	≥118 vs ≤70.7 g/day	1.28 (0.90-1.81)	Age, added fats and sauces, energy intake, fibre intake, fish liver, fruits and vegetables consumption, smoking status	Superseded by Bamia, 2013 COL40964 Component study of EPIC
Siezen, 2006 COL40714	Dutch prospective	160/ 397 controls	Cancer registry	Semi-quantitative FFQ	Incidence, colorectal cancer	≥1 vs ≤0.9 times/week	0.83 (0.57-1.20)	Age, sex, centre location	Only included in highest

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Reasons for exclusion
Netherlands	Monitoring Project on Cardiovascular Disease Risk Factors, Nested Case Control, Age: 52 years, M/W	16 years							compared to lowest analysis
Luchtenborg, 2005 COL01830	NLCS, Case Cohort, Age: 55-69 years, M/W	434/ 2 948 7.3 years	Population registries	Semi-quantitative FFQ	Incidence, colon cancer,	≥20 vs ≤0 g/day	1.03 (0.76-1.40)	Age, sex, BMI, energy intake, family history of colorectal cancer, smoking status	Superseded by Brink, 2005 COL40717
						per 15.1 g/day	0.93 (0.84-1.04)		
		274/			Apc- cases	≥20 vs ≤0 g/day	1.13 (0.78-1.64)		
						per 15.1 g/day	0.95 (0.83-1.08)		
		154/			Incidence, rectal cancer,	≥20 vs ≤0 g/day	0.94 (0.59-1.52)		
						per 15.1 g/day	0.93 (0.81-1.07)		
		127/			Incidence, colon cancer, apc+ cases	≥20 vs ≤0 g/day	0.92 (0.54-1.56)		
						per 15.1 g/day	0.92 (0.76-1.12)		
		73/			Incidence, rectal cancer, apc- cases	≥20 vs ≤0 g/day	1.10 (0.56-2.18)		

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Reasons for exclusion
						per 15.1 g/day	0.99 (0.82-1.18)		
		57/			Apc+ cases	≥20 vs ≤0 g/day	0.56 (0.24-1.30)		
						per 15.1 g/day	0.83 (0.63-1.07)		
		54/			Incidence, colon cancer, hmlh1-cases	≥20 vs ≤0 g/day	0.73 (0.73-2.53)		
						per 15.1 g/day	0.81 (0.58-1.14)		
Sanjoaquin, 2004 COL01182 UK	OVS, Prospective Cohort, Age: 18-89 years, M/W	95/ 10 998 17 years	Population/invitation	FFQ	Incidence, colorectal cancer,	≥1 vs ≤0 times/week	1.17 (0.71-1.92)	Alcohol consumption, smoking habits	Only included in highest compared to lowest analysis
Khan, 2004 COL01606 Japan	HCS, Prospective Cohort, Age: 40-97 years, M/W	15/ 3 458 14.3 years	Area residency lists	Questionnaire	Mortality, colorectal cancer, men	Q 2 vs Q 1	0.30 (0.00-2.30)	Age, smoking habits	Outcome is mortality
		14/			Women	Q 2 vs Q 1	1.90 (0.50-6.90)	Health education, health screening, health status	Outcome is mortality
Kojima, 2004 COL01840 Japan	JACC, Prospective Cohort, Age: 40-79 years, M/W	129/ 107 824 10 years	Resident registry and death certificates	Questionnaire	Mortality, colon cancer, women	≥5 vs 0-2 times/week	0.97 (0.62-1.50)	Age, alcohol consumption, BMI, educational level, family history of specific cancer,	Outcome is mortality
		123/			Men	≥5 vs 0-2 times/week	1.04 (0.65-1.66)		
		103/			Mortality, rectal	≥5 vs 0-2	0.95 (0.60-1.51)		

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Reasons for exclusion
					cancer, men	times/week		physical activity, region of enrolment, smoking status	
		48/			Women	≥5 vs 0-2 times/week	0.90 (0.44-1.84)		
Ma, 2001 COL00374 USA	PHS, Nested Case Control, Age: 40-84 years, M, Physicians	193/ 318 controls 13 years	Colorectal cancer diagnosis	Unknown	Incidence, colorectal cancer,	0.35-2.03 vs 0-0.14 serving/day	0.92 (0.56-1.51)	Age, alcohol consumption, aspirin use, BMI, molar ratio of IGF-i to IGFbp-3, physical activity, smoking habits, supplement intake	Superseded Hall, 2008 COL40720
		55/ 106 controls			Tertile 1 of Igf-i/igfbp-3 molar ratio	0.35-2.03 vs 0-0.14 serving/day	0.86 (0.33-2.26)		
Knekt, 1999 COL01699 finland	Finnish follow up, Prospective Cohort, M/W	73/ 9 985 24 years	Social Insurance Institution	Diet history method	Incidence, colorectal cancer,	Q 4 vs Q 1	1.11 (0.55-2.28)	Age, sex, energy intake, municipality, smoking	Only included in highest compared to lowest
Hsing, 1998 COL00458 USA	Lutheran Brotherhood Study, Prospective Cohort, Age: 35- years, M, policyholders	145/ 17 633 286 731 person-years	Responding to mail survey	Questionnaire	Mortality, colorectal cancer,	≥4.1 vs ≤0.7 times/month	1.50 (0.90-2.60)	Age, alcohol consumption, smoking habits, total energy	Outcome is mortality
		120/			Mortality, colon cancer,	≥4.1 vs ≤0.7 times/month	1.40 (0.80-2.50)		
Kato, 1997 CRC00022	New York University	100/ 14 272	Questionnaire, medical records,	Semi-quantitative FFQ	Incidence, colorectal	Q 4 vs Q 1	0.49 (0.27-0.89)	Age, educational level, place at	Only included in highest

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Reasons for exclusion
USA	Women's Health Study, Prospective Cohort, Age: 34-65 years, W	105 044 person-years	cancer registries		cancer,			enrolment, total calorie intake	compared to lowest analysis
Kearney, 1996 COL00156 USA	HPFS, Prospective Cohort, Age: 40-75 years, M, Health professionals	203/ 47 935 6 years	Responding to mail survey	Semi-quantitative FFQ	Incidence, colon cancer,	≥2 vs ≤0 times/month	0.85 (0.48-1.51)	Age	Superseded by Giovannucci, 1994 COL00119
Giovannucci, 1994 COL00119 USA	HPFS, Prospective Cohort, Age: 40-75 years, M, Health professionals	205/ 47 949 6 years	Mailing to health professionals	FFQ	Incidence, colon cancer,	83.4 vs 8.4 g/day	1.06 (0.70-1.60)	Age, total energy	Song, 2014 COL41016
Goldbohm, 1994 COL00025 Netherlands	NLCS, Case Cohort, Age: 55-69 years, M/W	215/ 120 852 3.3 years	Population registries	Semi-quantitative FFQ	Incidence, colon cancer,	≥20 vs ≤0 g/day	0.81 (0.56-1.17)	Age, sex, dietary fiber intake, energy intake	Superseded by Brink, 2005 COL40717
		110/			Women	≥20 vs ≤0 g/day	0.87 (0.52-1.45)		

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Reasons for exclusion
		105/			Men	≥20 vs ≤0 g/day	0.73 (0.44-1.21)		
Willett, 1990 CRC00026 USA	NHS, Prospective Cohort, Age: 34-59 years, W, Registered nurses	150/ 88 751 512 488 person-years	Population registry	Semi-quantitative FFQ	Incidence, colon cancer,	≥5 vs ≤1 times/month	1.06 (0.36-3.12)	Age	Superseded by Song, 2014 COL41015
Hirayama, 1990 COL01508 Japan	Japan 6 prefectures cohort study, Prospective Cohort, Age: 40- years, M/W	563/ 265 118 17 years	Health centres	Interview	Mortality, rectal cancer,	daily consumption vs no daily consumption	0.90 (0.78-1.04)	Age, sex	Outcome is mortality
		558/			Mortality, colon cancer,	daily consumption vs no daily consumption	1.01 (0.87-1.16)		
Hirayama, 1989 COL01024 Japan	Japan 6 prefectures cohort study, Prospective Cohort, Age: 40- years, M/W	91/ 265 118 17 years	Population registry	Quantitative FFQ	Mortality, sigmoid cancer,	daily/occasional vs infrequent/never	0.76 (0.29-2.02)	Age	Outcome is mortality
					Mortality, proximal colon cancer,	daily/occasional vs infrequent/never	1.29 (0.74-2.26)		
Heilbrun, 1989 COL01555 USA	HHP, Nested Case Control,	102/ 361 controls 16 years	Cancer registry & hospital surveillance	Recall questionnaire	Incidence, colon cancer,	(mean exposure)		Age	Mean exposure values only

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Reasons for exclusion
	M	60/ 361 controls			Incidence, rectal cancer,	(mean exposure)			
Phillips, 1975 COL00717 USA	AHS, Nested Case Control, M/W, Seventh-day Adventists	41/ 105 controls 2 years	Hospital registry	Interview	Incidence, colon cancer,	any vs none	1.60	Age, sex, ethnicity	Unadjusted results
		35/ 82 controls				Q 3 vs Q 1	3.40		

Figure 160 RR estimates of colorectal cancer by levels of fish

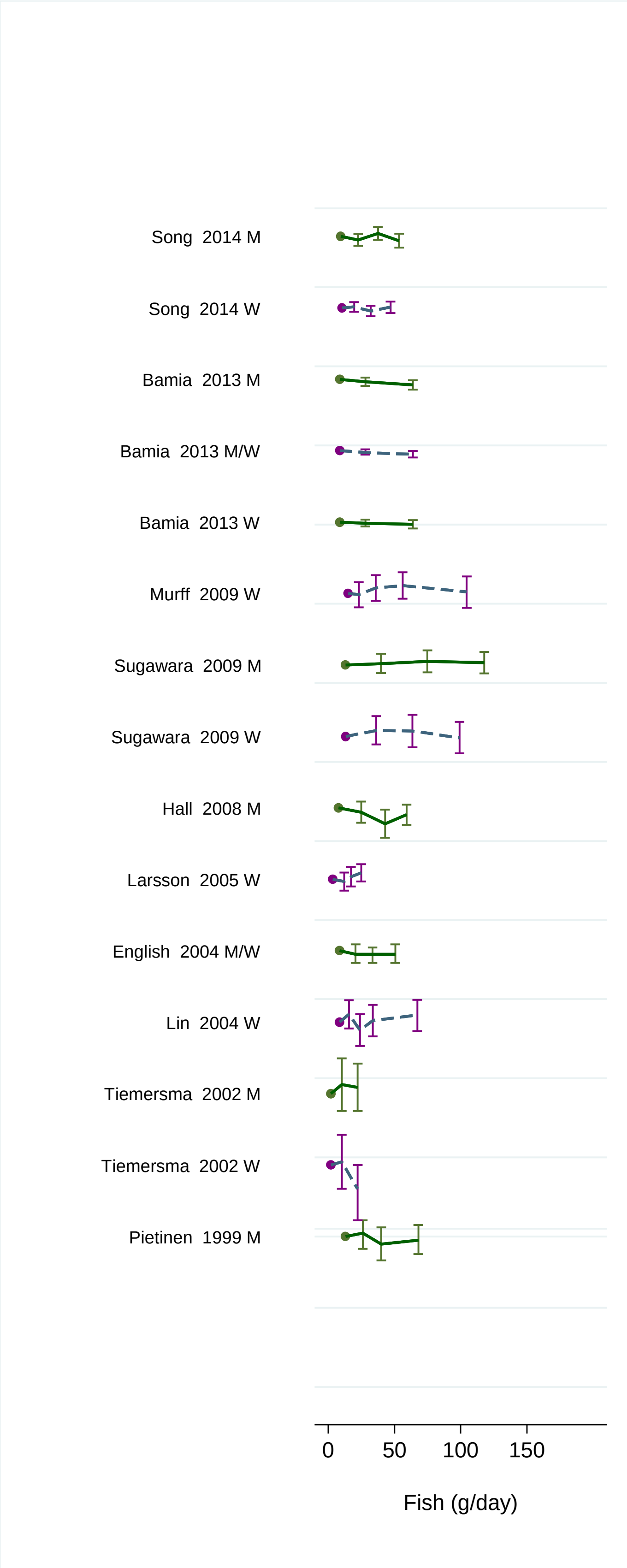


Figure 161 RR (95% CI) of colorectal cancer for the highest compared with the lowest level of fish

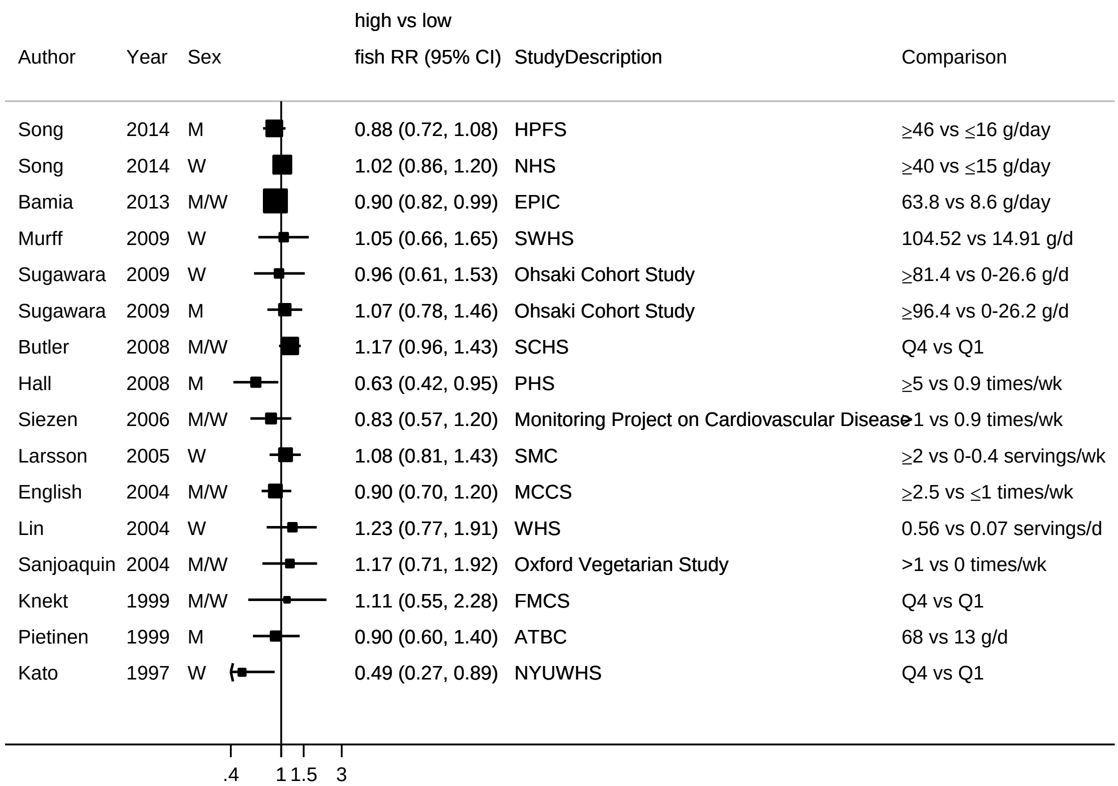


Figure 162 RR (95% CI) of colorectal cancer for 100g/day increase of fish

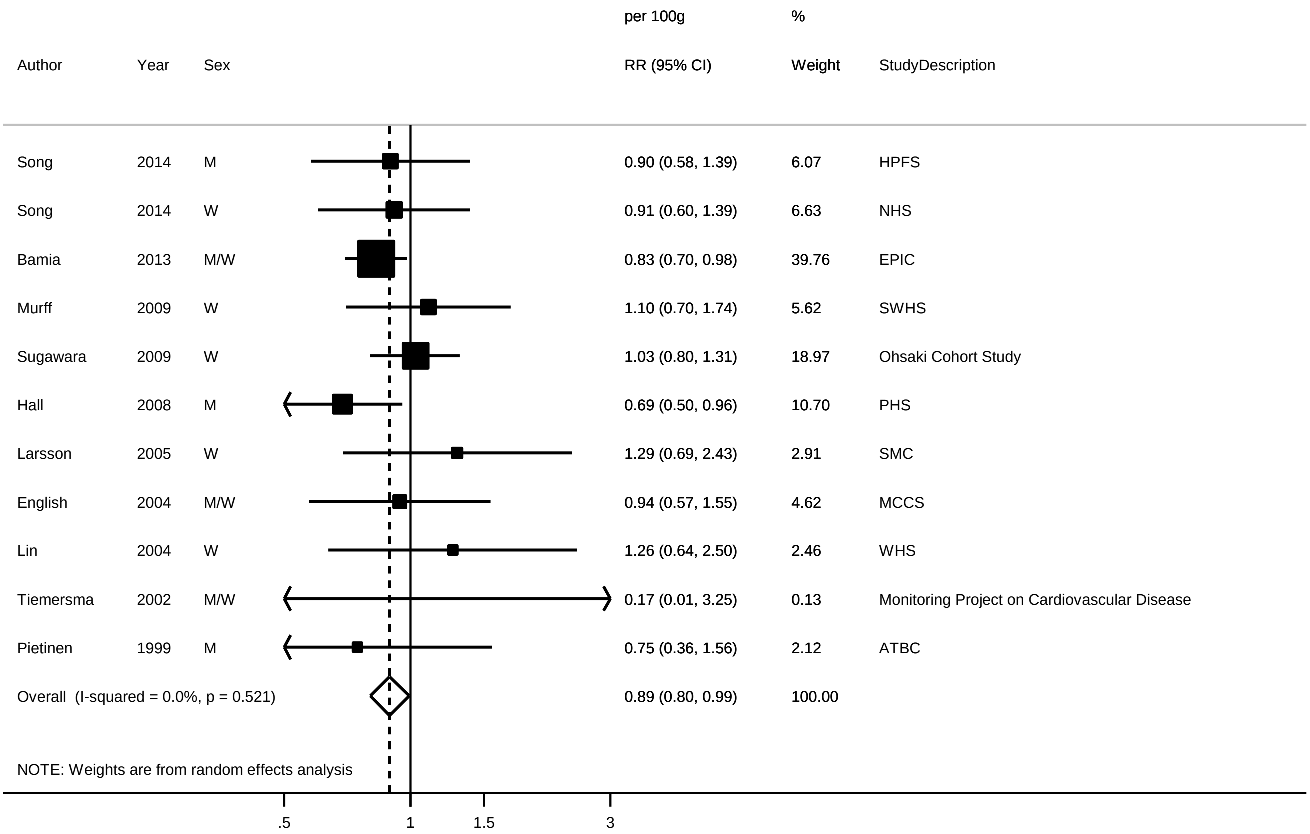


Figure 163 Funnel plot of studies included in the dose response meta-analysis of fish and colorectal cancer

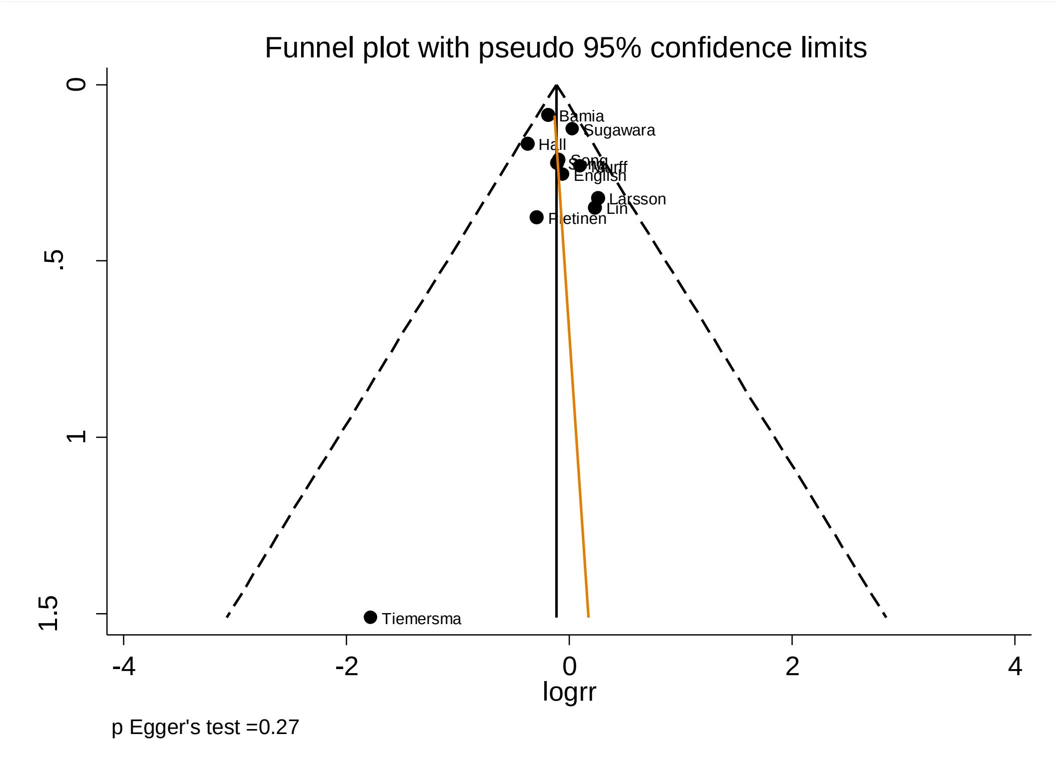


Figure 164 RR (95% CI) of colorectal cancer for 100g/day increase of fish by sex

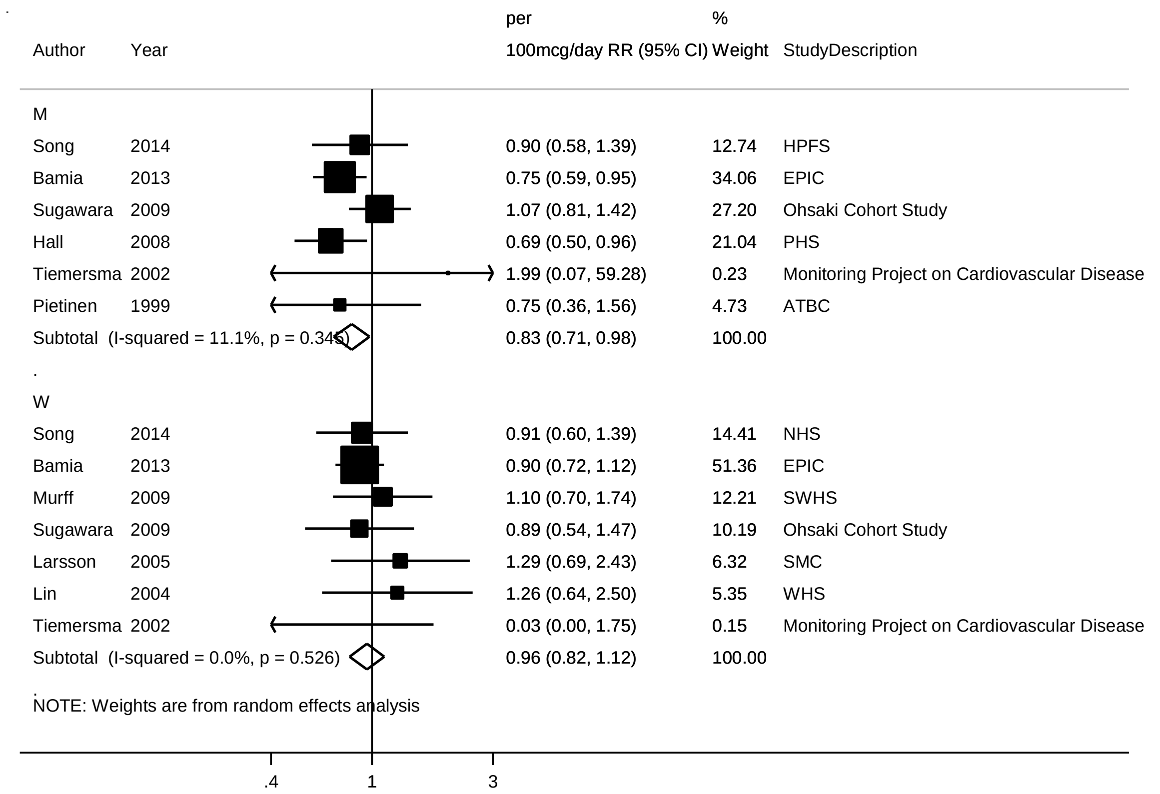


Figure 165 RR (95% CI) of colorectal cancer for 100g/day increase of fish by location

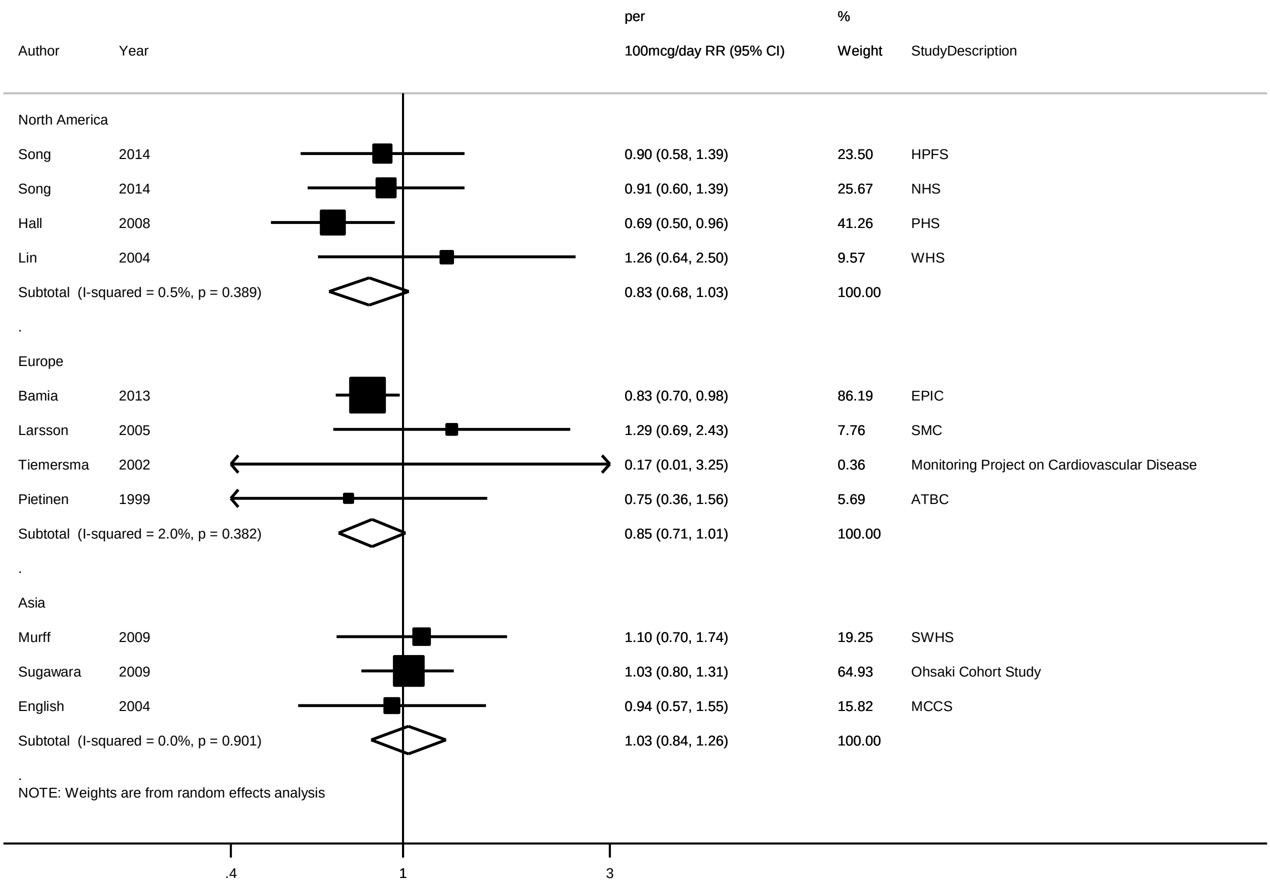


Figure 166 RR (95% CI) of colorectal cancer for 100g/day increase of fish by adjustment for meat

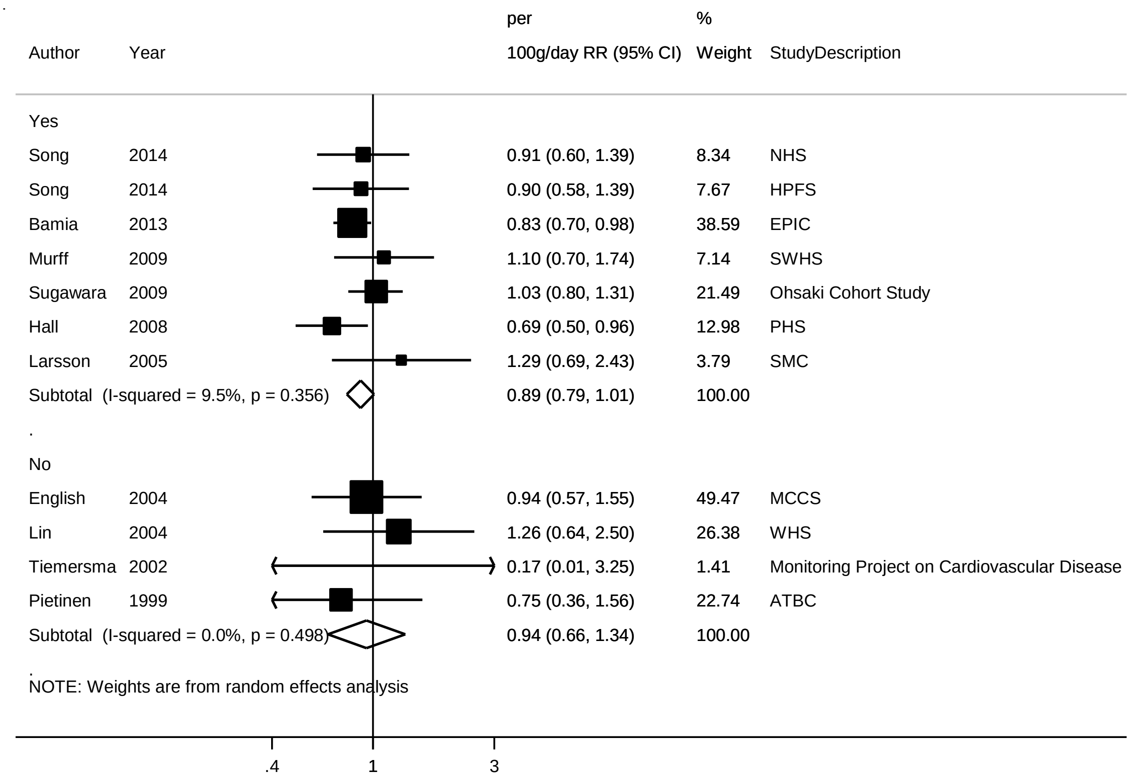


Figure 167 RR estimates of colon cancer by levels of fish

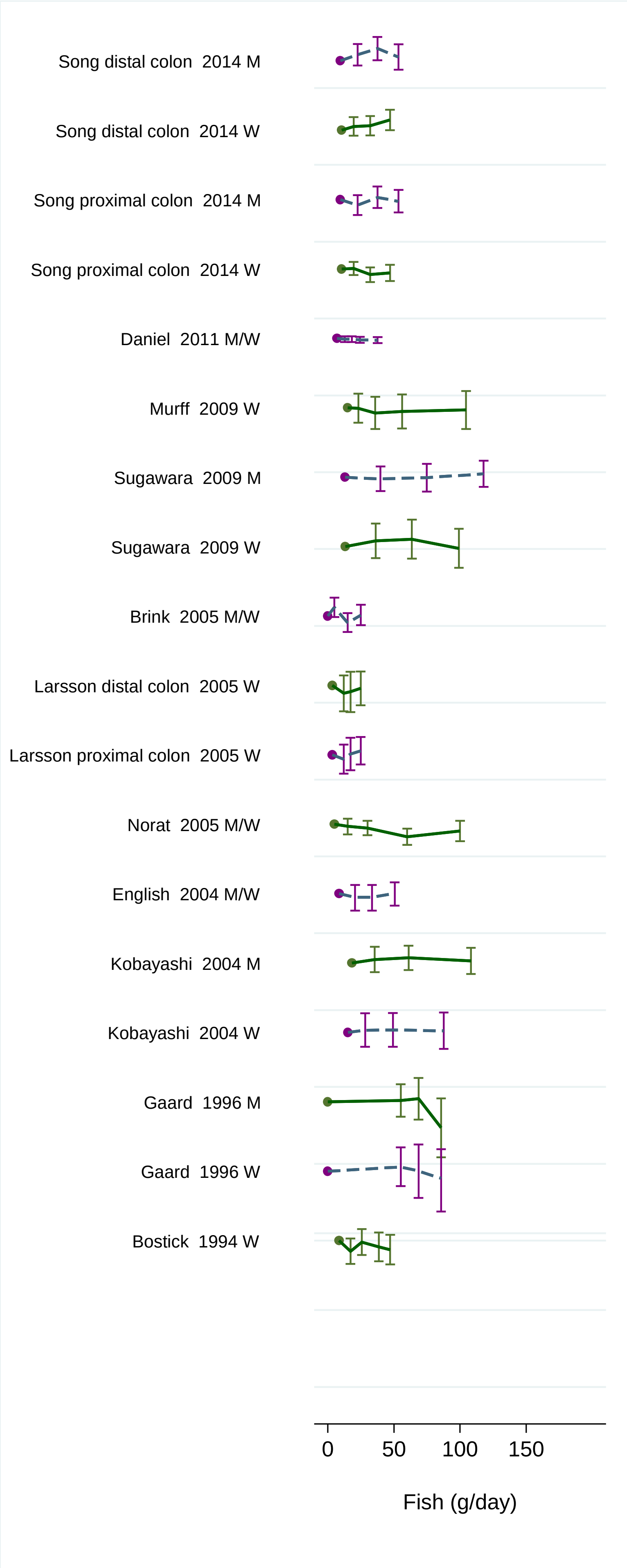


Figure 168 RR (95% CI) of colon cancer for the highest compared with the lowest level of fish

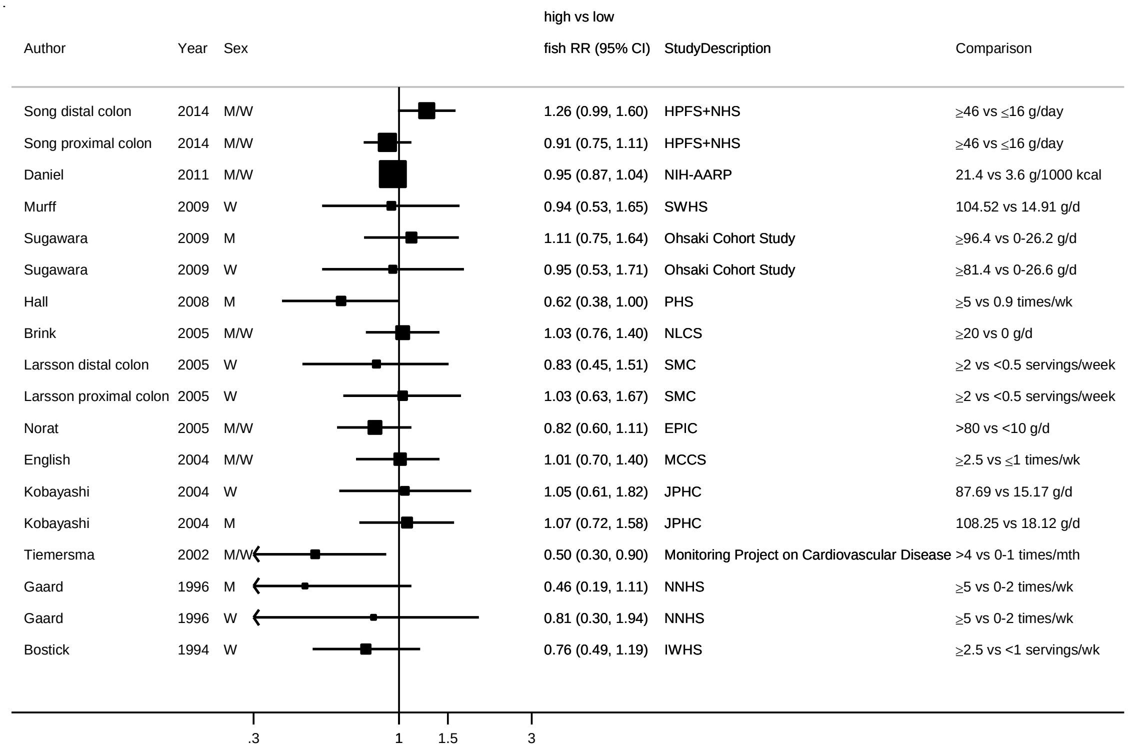


Figure 169 RR (95% CI) of colon cancer for 100g/day increase of fish

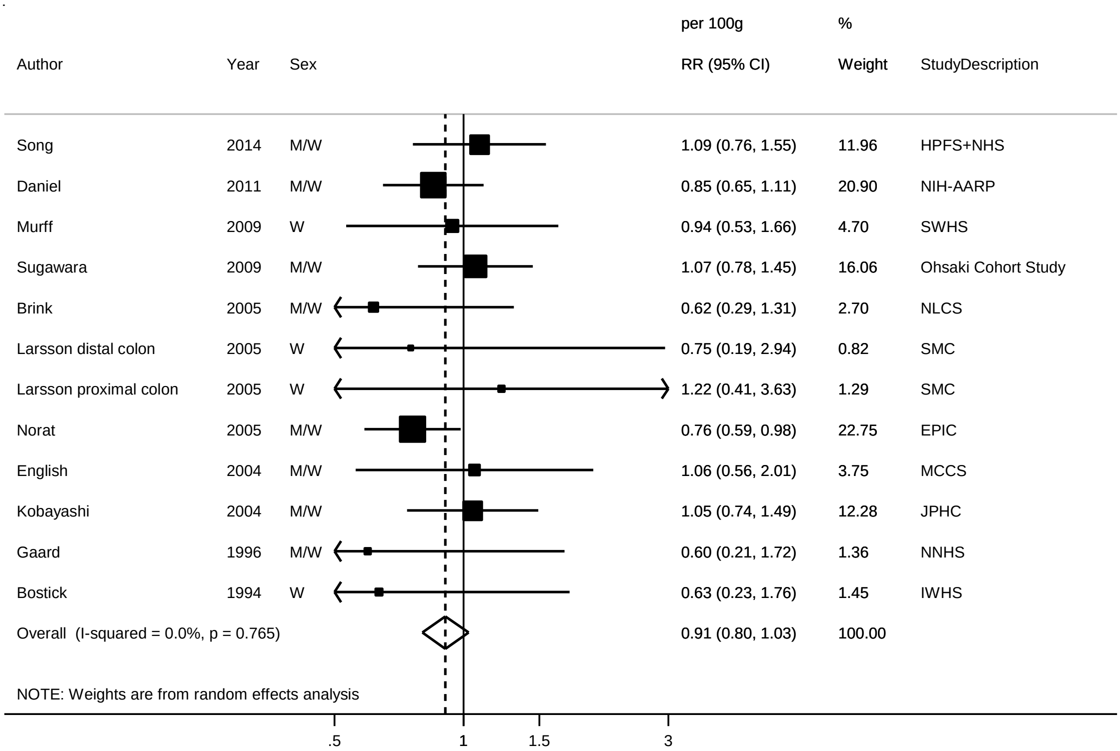


Figure 170 Funnel plot of studies included in the dose response meta-analysis of fish and colon cancer

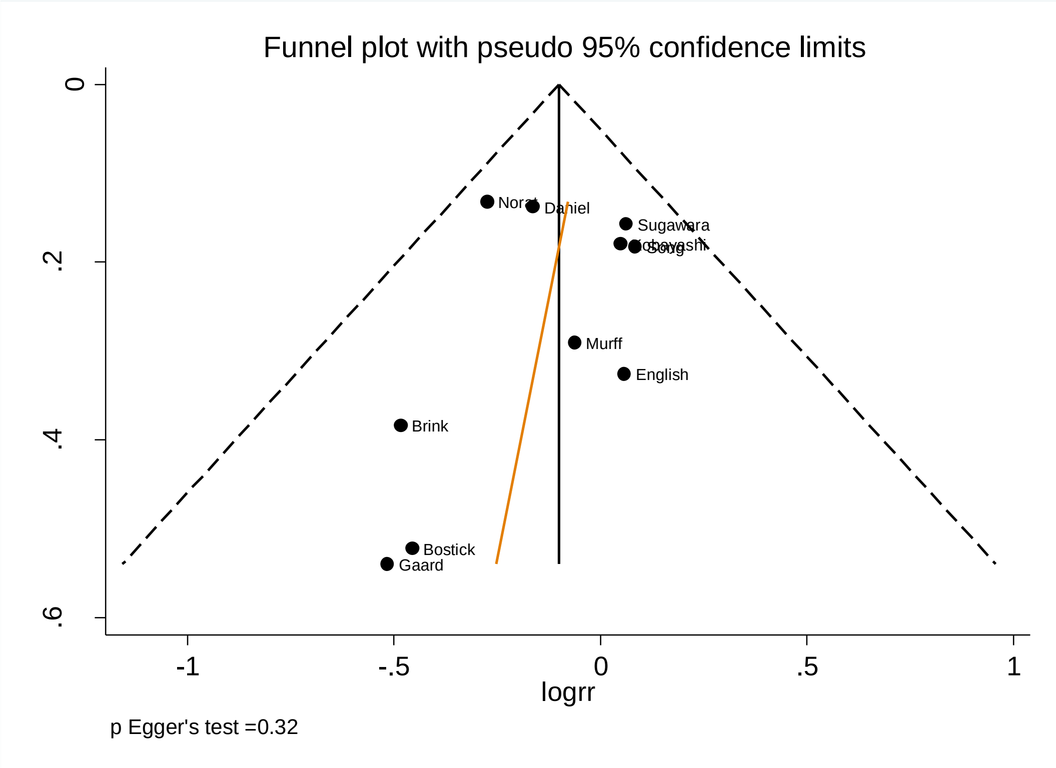


Figure 171 RR (95% CI) of colon cancer for 100g/day increase of fish by sex

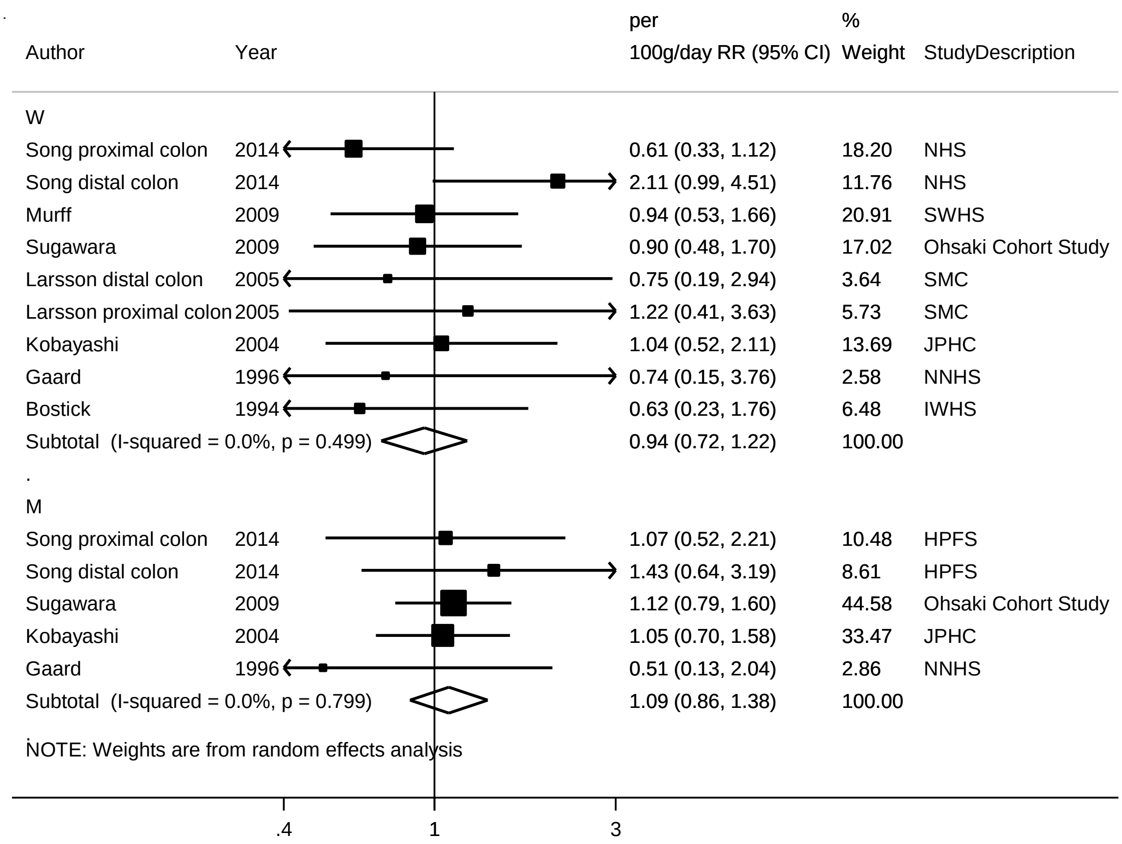


Figure 172 RR (95% CI) of colon cancer for 100g/day increase of fish by location

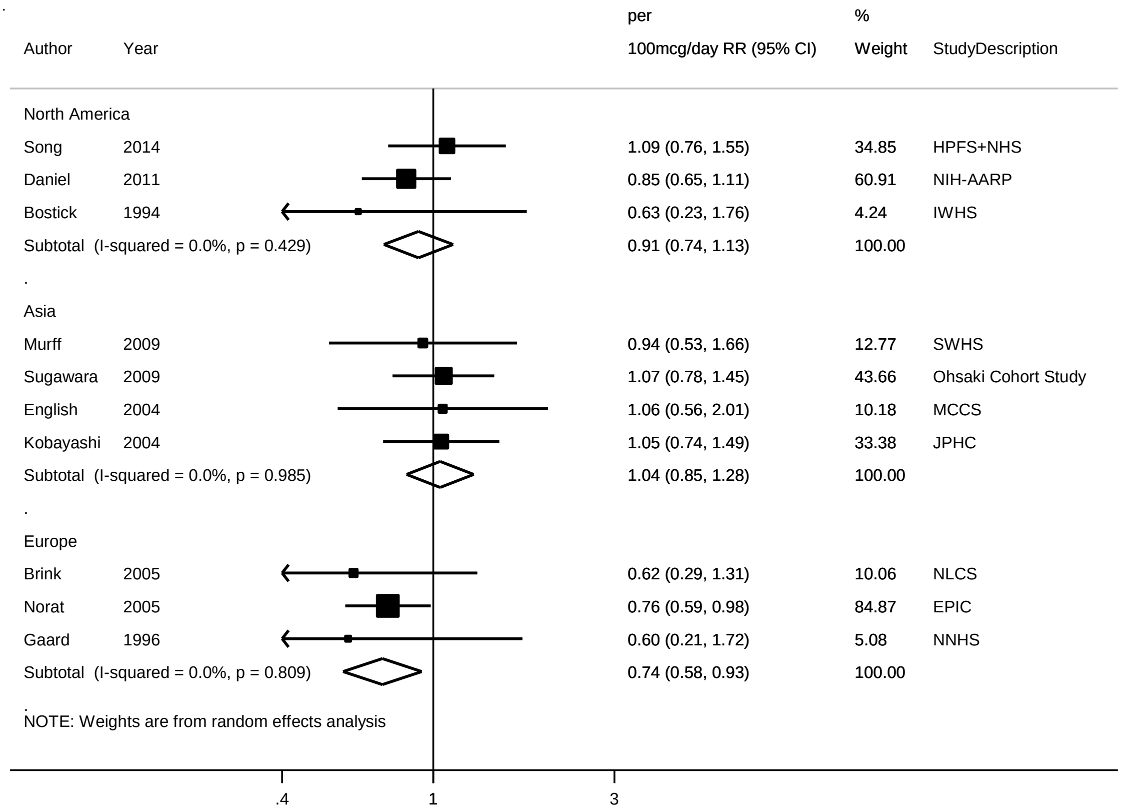


Figure 173 RR (95% CI) of colon cancer for 100g/day increase of fish by adjustment for meat

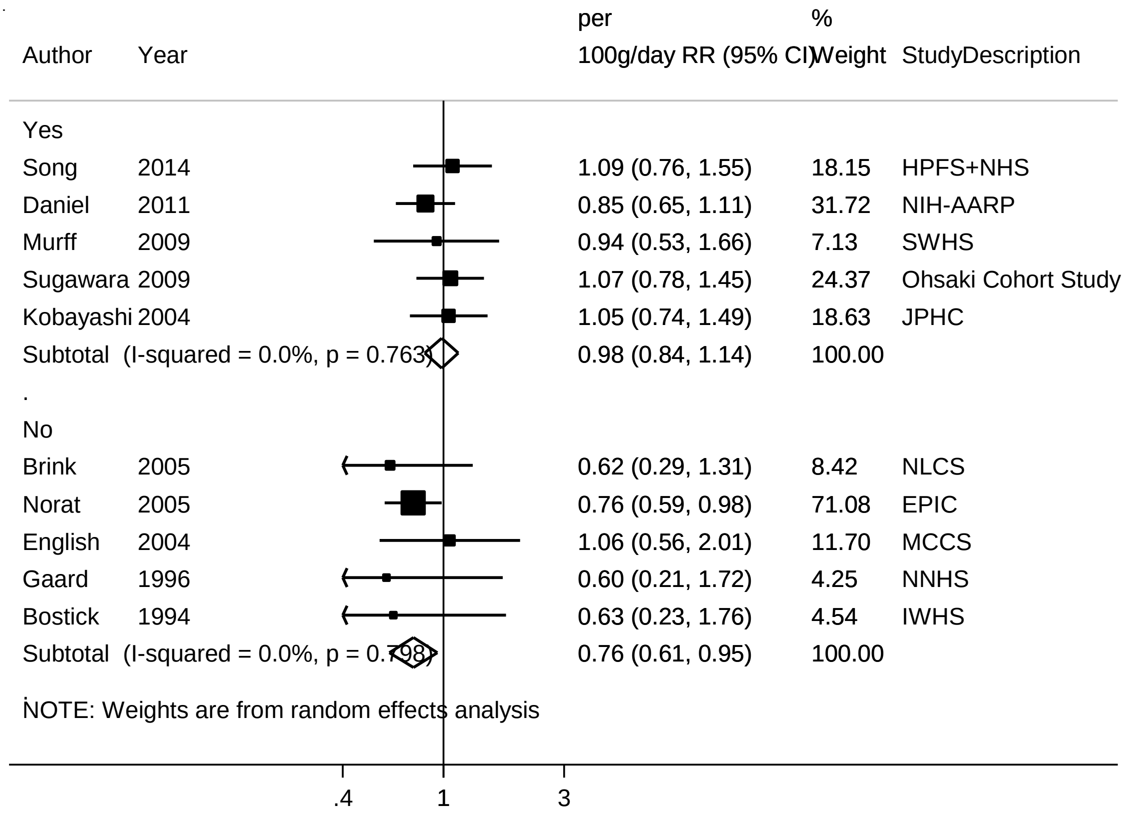


Figure 174 RR estimates of rectal cancer by levels of fish

Figure 175 RR (95% CI) of rectal cancer for the highest compared with the lowest level of fish

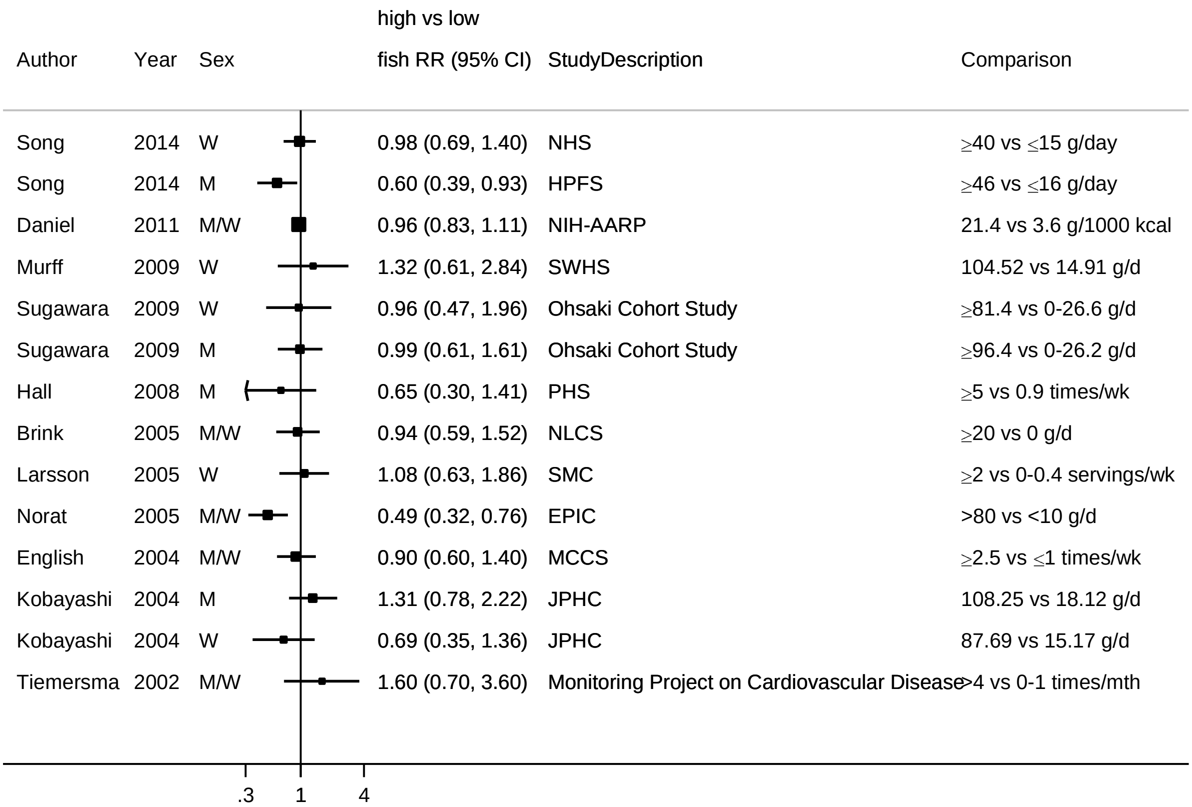


Figure 176 RR (95% CI) of rectal cancer for 100g/day increase of fish

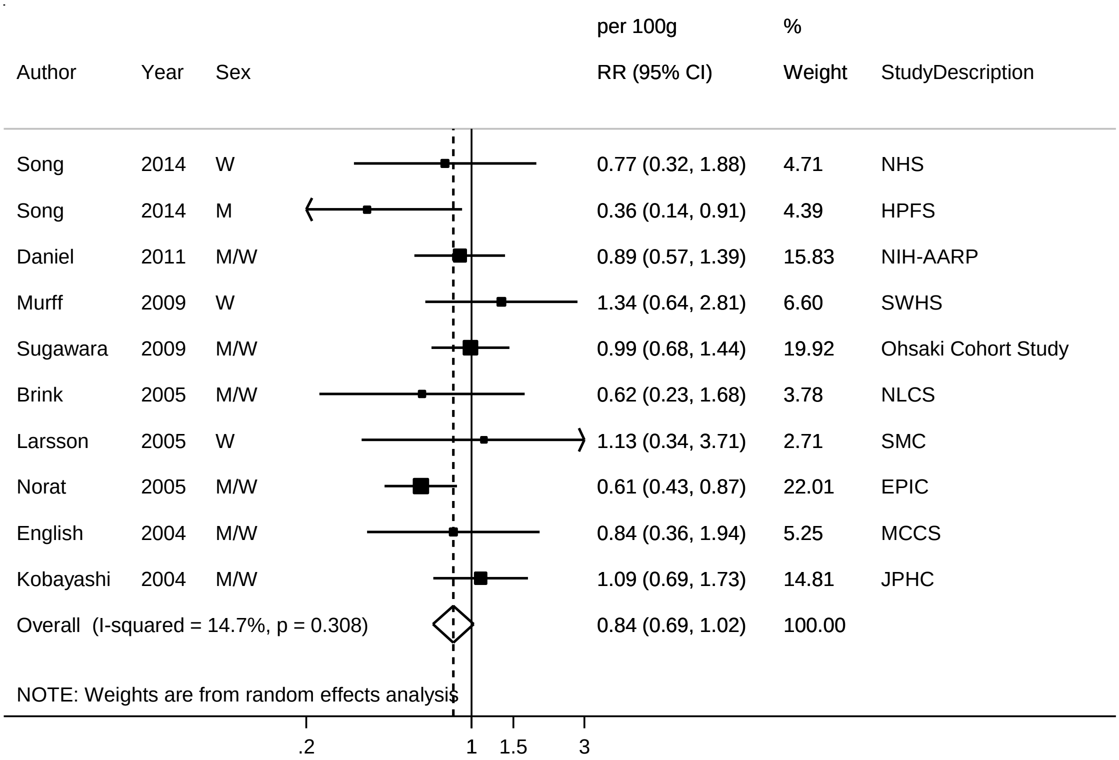


Figure 177 Funnel plot of studies included in the dose response meta-analysis of fish and rectal cancer

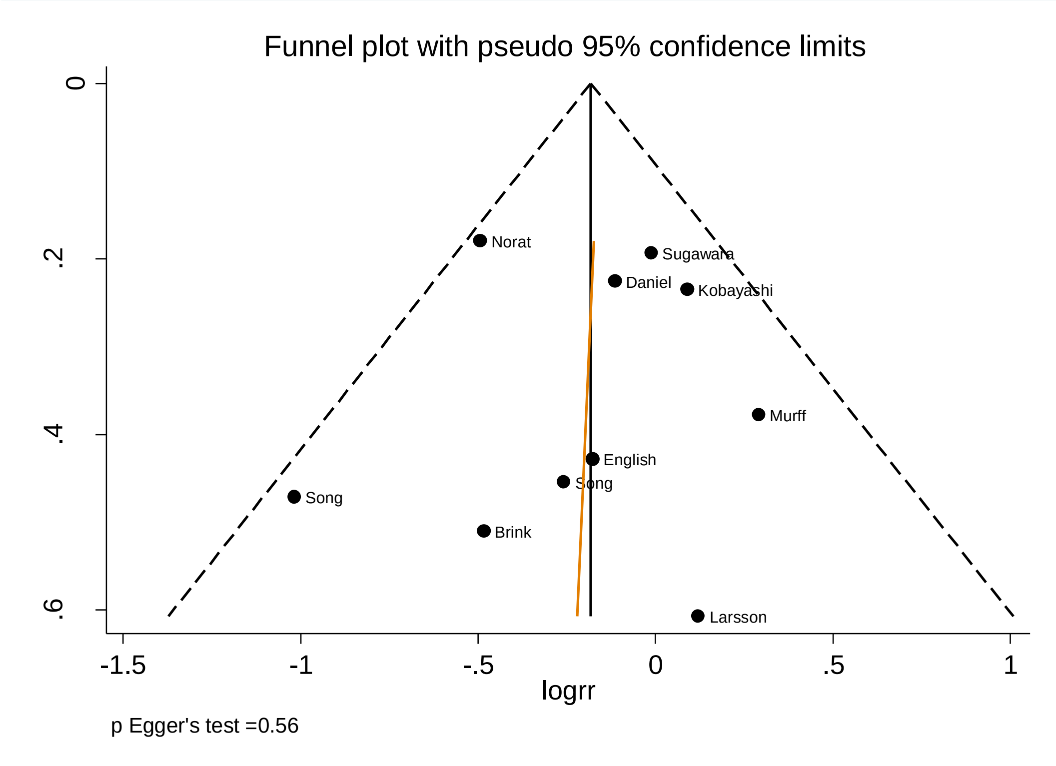


Figure 178 RR (95% CI) of rectal cancer for 100g/day increase of fish by sex

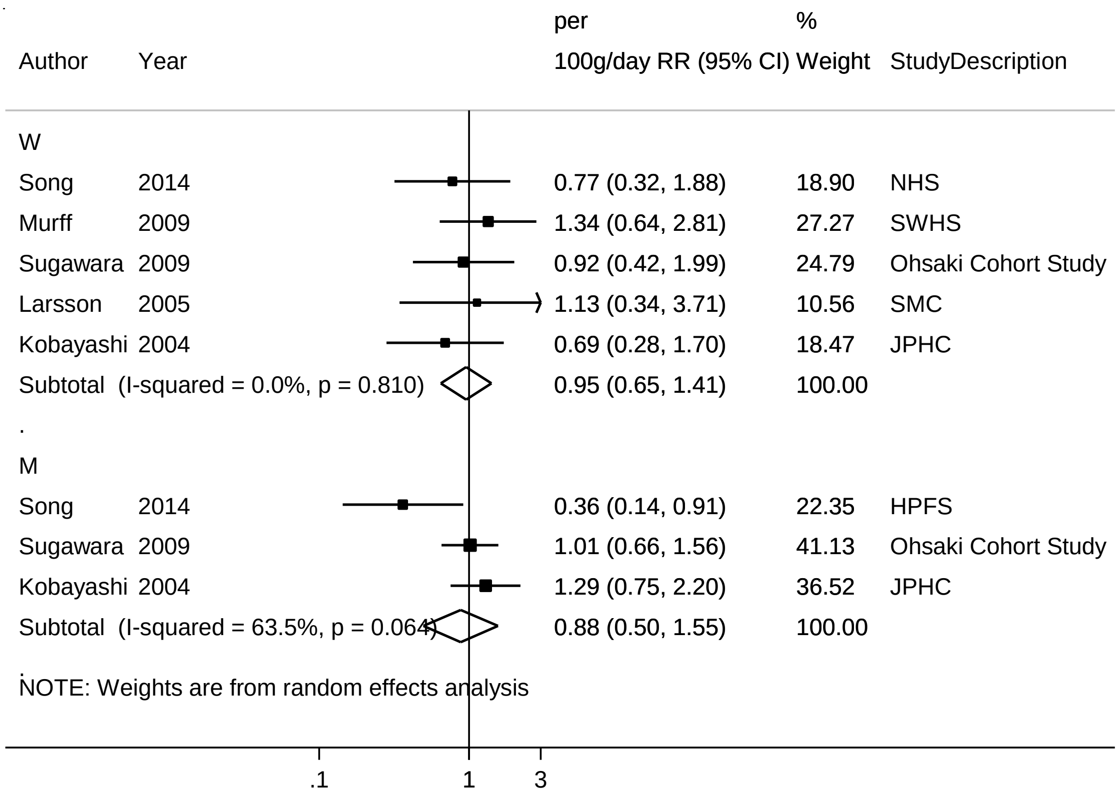


Figure 179 RR (95% CI) of rectal cancer for 100g/day increase of fish by location

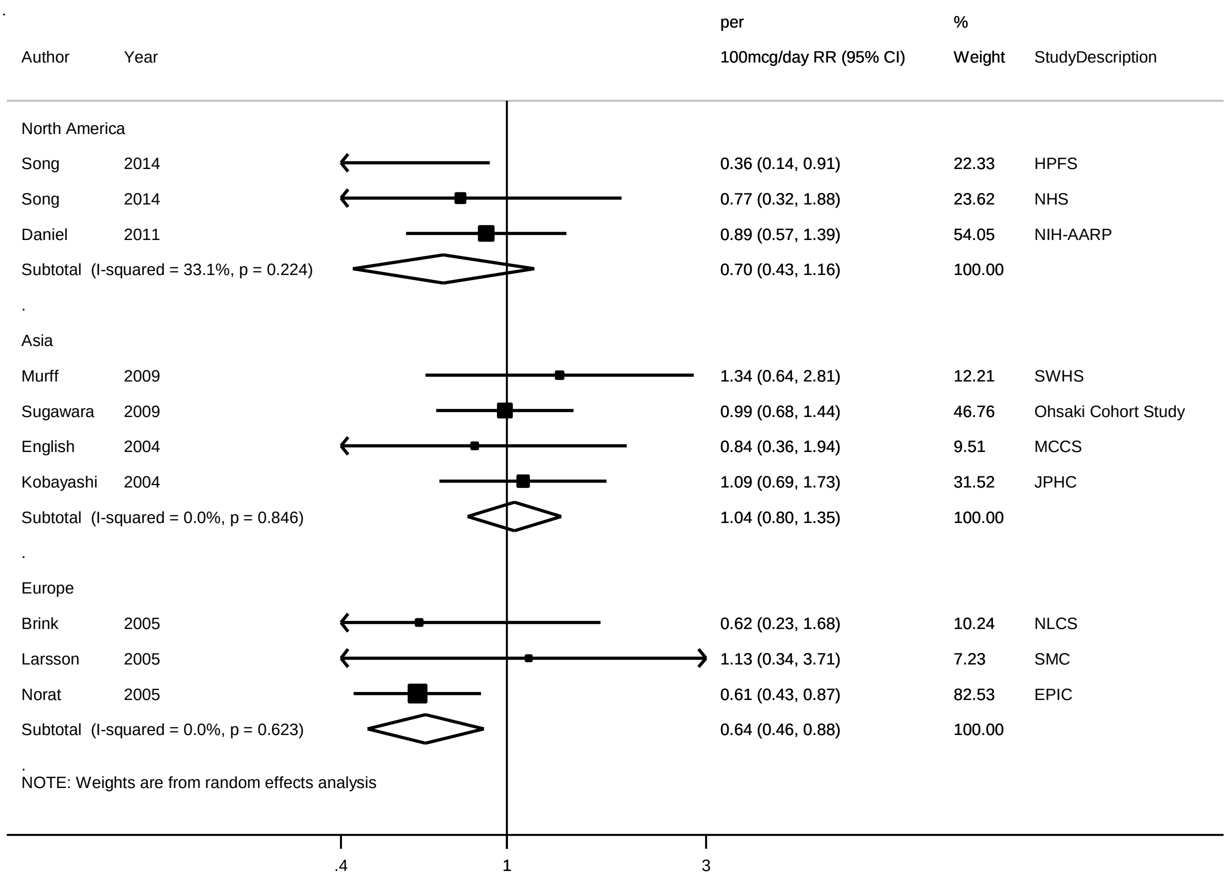
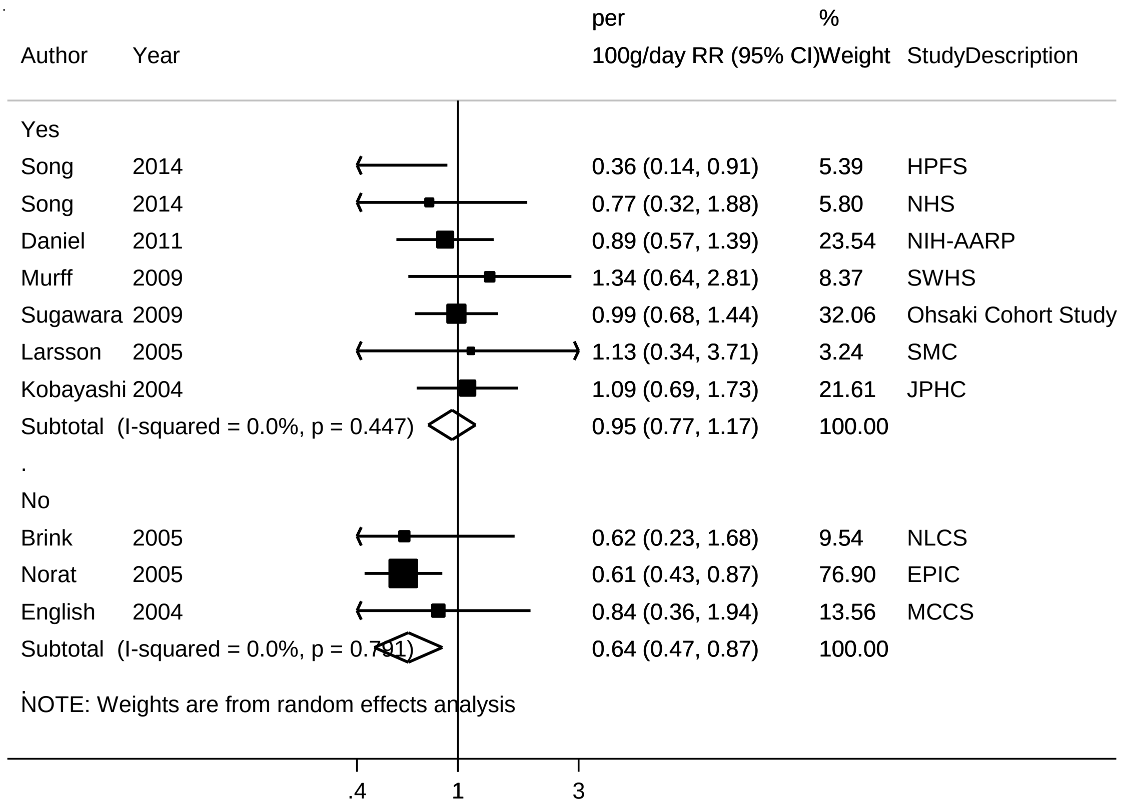


Figure 180 RR (95% CI) of rectal cancer for 100g/day increase of fish by adjustment for meat



2.6.1 Animal Fat

Overall, seven longitudinal studies on animal fat intake and risk of colon or colorectal cancer have been identified. The CUP identified one publication after the 2005 SLR of a Singaporean prospective study investigating the association between animal fat intake and colorectal cancer (Butler, 2009). The RR of colorectal cancer for the highest compared to the lowest quartile of intake of animal fat in men and women was 1.13 (95% CI: 0.94-1.35), p_{trend}=0.35. Another study, a 8.7 years follow-up of the Women's Health Study (WHS, Lin 2004), a randomized trial of low-dose aspirin and vitamin E in healthy US women aged 45 years or more, was not included in the 2005 SLR. The study reported a non-significant inverse association of animal fats and colorectal cancer risk [RR for animal fat as %energy (23% vs 10% of energy): 0.83 (95% CI: 0.53-1.29), p_{trend}=0.22]. None of the studies provided the data required for dose-response meta-analysis.

In the SLR 2005, five prospective studies were identified (see table and figures below) and a meta-analysis, including three studies was performed. The RR for 20g/day increment of fat intake was 1.13 (95% CI: 0.92-1.38), $p_{heterogeneity}$=0.167).

A published meta-analysis (Alexander, 2009) combined six of the studies mentioned before on colon or colorectal cancer did not support an association with animal fat intake [RR for high vs. low: 1.04 (95% CI: 0.83-1.31), $p_{heterogeneity}$=0.221), and RR per 20g/day: 1.02 (95% CI: 0.95-1.09)]. The study in Singapore (Butler, 2008) was not included in the meta-analysis and the %energy from fat in Lin, 2004 was approximated to g/day using mean energy intake in the first, third and fifth quintile. The RR for colon cancer (based on four studies) was 1.11 (95% CI: 0.81-1.52), $p_{heterogeneity}$=0.120 by comparing extreme categories.

Table 102 Animal fat intake and colorectal cancer risk. Main characteristics of studies included in the CUP SLR dose-response meta-analysis

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors
Butler, 2008 COL40639 Singapore	SCHS, Prospective Cohort, Age: 45-74 years, M/W	961/ 61 321 9.8 years	Cancer registry	FFQ	Incidence, colorectal cancer	q 4 vs q 1	1.13 (0.94-1.35) Ptrend:0.35	Age, sex, alcohol Intake, BMI, diabetes, dialect group, educational level, energy intake, exposure assessment, family history of colorectal cancer, physical activity, smoking habits
Lin, 2004 COL01834 USA	WHS, Prospective Cohort, Age: 45- years, W	202/ 37 547 8.7 years	Self-report verified by medical record	FFQ	Incidence, colorectal cancer	23 vs 10 % energy	0.83 (0.53-1.29) Ptrend:0.22	Age, alcohol consumption, BMI, family history of colorectal cancer, history of polyps, physical activity, postmenopausal hormone use, randomized treatment assignment, smoking habits, total energy Intake
Sanjoaquin, 2004 COL01182 UK	OVS, Prospective Cohort, Age: 18-89 years, M/W	76/ 10 998 17 years	Population/invitation	FFQ	Incidence, colorectal cancer	q 3 vs q 1	1.07 (0.58-1.97) Ptrend:0.66	Age, sex, alcohol consumption, smoking habits
Bostick, 1994 COL00079 USA	IWHS, Prospective Cohort, Age: 55-69 years, W	212/ 35 216 167 447 person-years	Driving license	Semi-quantitative FFQ	Incidence, colon cancer	≥51.8 vs ≤24.5 g/day	1.00 (0.64-1.54) Ptrend:0.97	Age, energy intake, height, parity, total vitamin e intake, total vitamin e intake, age, vitamin a supplement

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors
Giovannucci, 1994 COL00119 USA	HPFS, Prospective Cohort, Age: 40-75 years, M, Health professionals	205/ 47 949 6 years	Mailing to health professionals	FFQ	Incidence, colon cancer	56 vs 25 g/day	0.87 (0.55-1.38) Ptrend:0.67	Age, energy intake
Goldbohm, 1994 COL00025 Netherlands	NLCS, Case Cohort, Age: 55-69 years, M/W	215/ 120 852 3.3 years	Population registries	Semi-quantitative FFQ	Incidence, colon cancer	q 5 vs q 1	0.98 (0.64-1.49) Ptrend:0.67	Age, sex, dietary fibre intake, energy Intake
		110/			Women	25 vs 7 g/day	0.94 (0.52-1.72) Ptrend:0.47	
		105/			Men	31 vs 10 g/day	1.13 (0.63-2.02) Ptrend:0.72	
Willett, 1990 CRC00026 USA	NHS, Prospective Cohort, Age: 34-59 years, W, Registered nurses	189/ 88 751 512 488 person-years	Population	Semi-quantitative FFQ	Incidence, colorectal cancer	≥65 vs ≤38 g/day	1.64 (1.04-2.57) Ptrend:0.03	Age, energy intake
		150/			Incidence, colon cancer	≥65 vs ≤38 g/day	1.89 (1.13-3.15) Ptrend:0.01	
		103/			Incidence, colon cancer: Excluding first four years of follow-up	≥65 vs ≤38 g/day	2.52 (1.34-4.76) Ptrend:0.002	

Figure 181 RR (95% CI) of colorectal cancer for the highest compared with the lowest level of animal fat intake

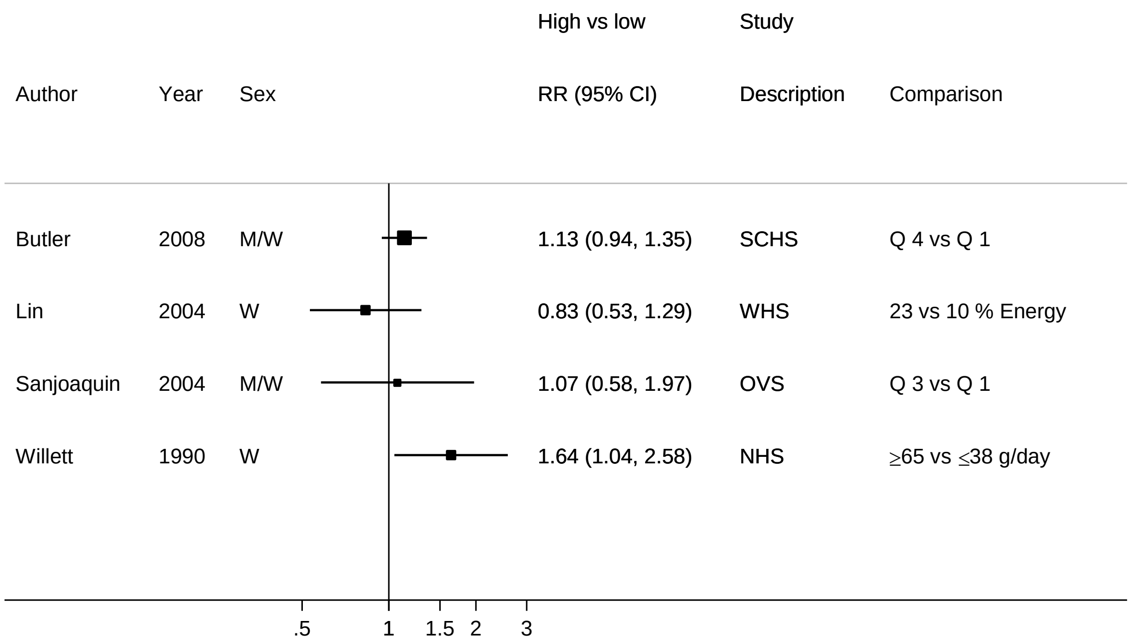
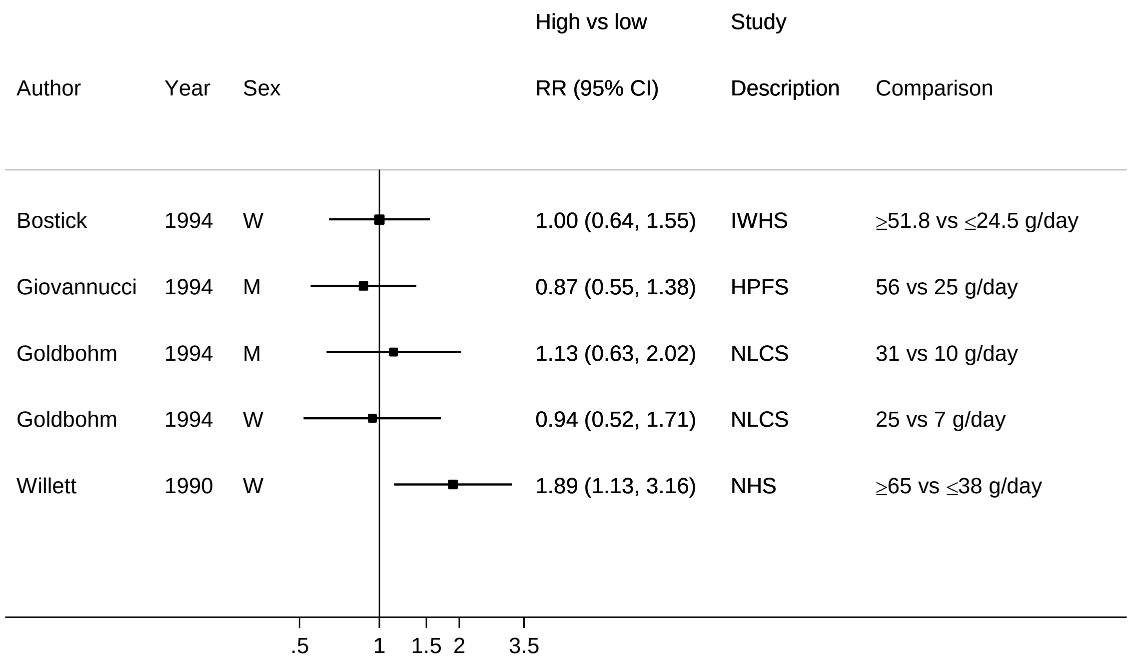


Figure 182 RR (95% CI) of colon cancer for the highest compared with the lowest level of animal fat intake



2.7 Dairy products

Cohort studies

Summary

Main results:
One new study (two publications) was identified (Murphy, 2013 and Bamia, 2013) since the 2010 SLR. In total 14 studies (19 publications) were identified on total dairy products and colorectal cancer risk, and ten of these could be included in the dose-response analysis. Study characteristics and results for all cancer types are shown in the Table. For studies that reported dairy intake in servings per day or other frequencies we used a serving size of 177 g for recalculation of the intakes to grams per day.

Colorectal cancer:
Ten studies (14859 cases) were included in the dose-response analysis. The summary RR for a 400 g/d increase in total dairy intake was 0.87 (95% CI: 0.83-0.90) and there was little evidence of heterogeneity, I^2=18.4%, $p_{heterogeneity}$=0.27. There was no evidence of small study bias or publication bias with Egger's test, p=0.63. The summary RR ranged from 0.86 (95% CI: 0.83-0.89) when the Swedish Mammography Cohort study (Terry, 2002) was excluded to 0.87 (95% CI: 0.84-0.91) when the Cohort of Swedish Men (Larsson, 2006) was excluded.

The test for nonlinearity was significant, $p_{nonlinearity}$=0.003, and the association between dairy products and colorectal cancer was slightly stronger at lower levels of intake.

Colon cancer:
Six studies (3991 cases) were included in the dose-response meta-analysis of total dairy intake and colon cancer. The summary RR per 400 g/d was 0.87 (95% CI: 0.81-94) with low heterogeneity, I^2=24%, $p_{heterogeneity}$=0.25.

There was no evidence of a nonlinear association between total dairy intake and colon cancer, $p_{nonlinearity}$=0.77.

Rectal cancer:
Five studies (2152 cases) were included in the dose-response meta-analysis of total dairy intake intake and rectal cancer. The summary RR per 400 g/d was 0.93 (95% CI: 0.82-1.06) with moderate heterogeneity, I^2=48.6%, $p_{heterogeneity}$=0.10.

There was evidence of a nonlinear association between total dairy intake and rectal cancer, $p_{nonlinearity}$=0.02, with a flattening of the dose-response slope at higher levels of intake.

Study quality:
Total dairy intake was estimated from food intake assessed by FFQ in all studies, and in one of the studies a combination of FFQ, food records and 24 hour recalls were used (Murphy et al, 2013).
Loss to follow-up was low for the studies that reported such data, although some studies did not provide data.
Cancers were identified by record linkages to health registries, cancer registries, mortality registries, or death indexes.
All studies adjusted for at least age, and most of the studies adjusted for most of the established colorectal cancer risk factors, including: age, physical activity, BMI, and alcohol consumption, smoking, red meat and hormone replacement therapy in women.

Table 103 Total dairy product intake and colorectal cancer risk. Number of studies in the CUP SLR

	Number
Studies identified	13 studies (18 publications)
Studies included in forest plot of highest compared with lowest intake	Colorectal cancer: 12 studies Colon cancer: 6 Rectal cancer: 6
Studies included in linear dose-response meta-analysis	Colorectal cancer: 10 studies Colon cancer: 6 Rectal cancer: 5
Studies included in non-linear dose-response meta-analysis	Colorectal cancer: 10 studies Colon cancer: 6 Rectal cancer: 5

Table 104 Total dairy product intake and colorectal cancer risk. Summary of the linear dose-response meta-analysis in the 2005 SLR, 2010 SLR and 2015 SLR

	2005 SLR			
	Colorectal cancer		**Colon cancer**	**Rectal cancer**
Increment unit used	Per 1 serving/day	Per 200 g/d	Per 1 serving/day	Per 1 serving/day
Studies (n)	8	2	5	-
Cases (total number)	-	-	-	-
RR (95%CI)	0.97 (0.93-1.01)	0.95 (0.82-1.10)	0.95 (0.86-1.06)	-
Heterogeneity (I^2, p-value)	11.5%, p=0.34	0%, p=0.86	49.5%, p=0.95	-
P value Egger test	-	-	-	-

	2010 SLR		
	Colorectal cancer	**Colon cancer**	**Rectal cancer**
Increment unit used	400 g/day		
Studies (n)	9	5	4
Cases (total number)	9807	-	-
RR (95%CI)	0.85 (0.81-0.90)	0.84 (0.72-0.97)	1.00 (0.77-1.28)
Heterogeneity (I^2, p-value)	0%, p=0.57	35.4%, p=0.19	68.9%, p=0.02
P value Egger test	0.86	-	-

	2015 SLR		
	Colorectal cancer	**Colon cancer**	**Rectal cancer**
Increment unit used	400 g/day		
Studies (n)	10	6	5
Cases (total number)	14859	3991	2152
RR (95%CI)	0.87 (0.83-0.90)	0.87 (0.81-0.94)	0.93 (0.82-1.06)
Heterogeneity (I^2, p-value)	18.4%, p=0.27	24.4%, p=0.25	48.6%, p=0.10
P value Egger test	0.63	-	-

	Colorectal cancer	**Colon cancer**	**Rectal cancer**
Increment unit used	400 g/day		
	Men		
Studies (n)	5	2	-
RR (95%CI)	0.84 (0.80-0.89)	0.77 (0.68-0.88)	-
Heterogeneity (I^2, p-value)	0%, p=0.69	0%, p=0.61	-
Increment unit used	**Women**		
Studies (n)	6	3	-
RR (95%CI)	0.86 (0.78-0.96)	0.98 (0.87-1.11)	-
Heterogeneity (I^2, p-value)	55.7%, p=0.05	0%, p=0.81	-

Stratified analyses by Geographic location			
	Asia	**Europe**	**North-America**
Studies (n)	-	5	5
RR (95%CI)	-	0.88 (0.82-0.95)	0.85 (0.80-0.89)
Heterogeneity (I^2, p- value)	-	53.8%, 0=0.07	0%, p=0.90

Table 105 Dairy intake and colorectal cancer risk. Results of meta-analyses and pooled analyses of prospective studies published after the 2005 SLR.

Author, Year	Number of studies	Total number of cases	Studies country, area	Outcome	Comparison	RR (95%CI)	P trend	Heterogeneity (I^2, p value)
Meta-analyses								
Huncharek, 2009	12	-	North America, Europe	Incidence, mortality	High vs. low	0.84 (0.75-0.95)	-	-
Aune et al, 2012	12 CRC 10 CRC 5 CC 4 RC	11579	North America, Europe	Incidence	High vs. low Per 400 g/d High vs. low Per 400 g/d High vs. low Per 400 g/d	0.81 (0.74-0.90) 0.83 (0.78-0.88) 0.72 (0.51-1.02) 0.84 (0.72-0.97) 0.96 (0.65-1.41) 1.00 (0.77-1.28)	- - - - - -	42%, p=0.06 24.8%, p=0.22 50%, p=0.09 35.4%, p=0.19 44%, p=0.13 68.9%, p=0.02

Table 106 Dairy intake and colorectal cancer risk. Main characteristics of studies included in the CUP SLR dose-response meta-analysis

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI)	Adjustment factors	Missing data derived for analysis
Murphy, 2013 COL41070 Denmark,France,Germany,Greece,Italy, Netherlands,Norway,Spain,Sweden,UK	EPIC, Prospective Cohort, Age: 30- years, M/W	4 513/ 477 122 11 years	Cancer registries, health Insurance records, pathology rec & active follow up	Dietary questionnaire	Incidence, colorectal cancer	≥490 vs 0-133.9 g/d	0.77 (0.70-0.86)	Age, alcohol consumption, BMI, centre location, educational level, fibre intake, menopausal hormone use, menopausal status, physical activity Index, red and processed meat, smoking status and dose, total energy intake, use of oral contraception	Midpoints
					Incidence, colorectal cancer	per 400 g/day	0.86 (0.79-0.93)		
					Incidence, colon cancer	≥490 vs 0-133.9 g/d	0.75 (0.66-0.86)		
					Incidence, colon cancer	per 400 g/day	0.94 (0.91-0.97)		
					Incidence, proximal colon cancer	≥490 vs 0-133.9 g/d	0.75 (0.62-0.91)		
					Incidence, proximal colon cancer	per 400 g/day	0.95 (0.89-1.01)		
					Incidence, distal colon cancer	≥490 vs 0-133.9 g/d	0.74 (0.61-0.90)		
					Incidence, distal colon cancer	per 400 g/day	0.94 (0.88-0.99)		
					Incidence, rectal cancer	≥490 vs 0-133.9 g/d	0.81 (0.69-0.96)		
					Incidence, rectal cancer	per 400 g/day	0.95 (0.90-1.00)		

Park, 2009 COL40783 USA	NIH-AARP, Prospective Cohort, Age: 50-71 years, M/W	3 463/ 492 810 7 years	Cancer registry	FFQ	Incidence, men	1.4 vs 0.2 servings per 1000kcal/day	0.85 (0.76-0.94)	Alcohol intake, BMI, educational level, ethnicity, family history of cancer, folate intake, fruits and vegetables intake, marital status, physical activity, red meat intake, smoking status, total energy, whole grain intake	Conversion of serv/1000 kcal/d to g/d, distribution of cases and person-years
					Incidence, women	1.6 vs 0.2 servings per 1000kcal/day	0.72 (0.61-0.84)		
Park, 2007 COL40668 USA	MEC, Prospective Cohort, Age: 45-75 years M/W	2110/ 7.3 years	Cancer registry	FFQ	Incidence, colorectal cancer, men	≥161 vs ≤32.9 g1000 kcal/day	0.80 (0.64-0.99)	Age, pack-years of cigarette smoking, family history of colorectal cancer, physical activity, history of intestinal polyps, use of NSAIDs, BMI, total energy, fiber, regular multivitamin use, hormone replacement therapy (women)	Midpoints, distribution of person-years
					Incidence, colorectal cancer, women	≥161 vs ≤32.9 g1000 kcal/day	0.81 (0.65-1.00)		
					Incidence, colorectal cancer, excluding men using calcium supplements	≥161 vs ≤32.9 g1000 kcal/day	0.77 (0.59-1.01)		
					Incidence, colorectal cancer, excluding women using calcium supplements	≥161 vs ≤32.9 g1000 kcal/day	0.66 (0.49-0.89)		

Larsson, 2006 COL40624 Sweden	COSM, Prospective Cohort, Age: 45-79 years, M	449/ 45 306 6.7 years	Cancer registry	FFQ	Incidence, colorectal cancer	≥7 vs ≤1.9 servings/day	0.46 (0.30-0.71)	Age, alcohol intake, aspirin use, educational level, family history of colorectal cancer, fruits, history of diabetes, multivitamin supplement intake, physical activity, red meat intake, saturated fat, smoking status, total energy intake, vegetable intake, vitamin d	Midpoints, conversion from serv/d to g/d, distribution of cases and person-years
					Incidence, colon cancer	≥7 vs ≤1.9 servings/day	0.44 (0.25-0.76)		
					Incidence, distal colon cancer	≥7 vs ≤1.9 servings/day	0.43 (0.20-0.93)		
					Incidence, proximal colon cancer	≥7 vs ≤1.9 servings/day	0.37 (0.16-0.88)		
					Incidence, rectal cancer	≥7 vs ≤1.9 servings/day	0.48 (0.23-0.99)		
McCarl, 2006 COL40633 USA	IWHS, Prospective Cohort, Age: 55-69 years, W	954/ 35 197 15 years	Seer registry	FFQ	Incidence, colorectal cancer	≥25.5 vs ≤7.5 servings/wee k	0.71 (0.58-0.87)	Age	Midpoints, conversion from serv/wk to g/d
Lin, 2005 COL01690 USA	WHS, Prospective Cohort, Age: 45- years, W,	223/ 36 976 10 years	SEER	FFQ	Incidence, colorectal cancer	≥3.1 vs ≤0.9 serving/day	0.89 (0.54-1.47)	Age, alcohol consumption, BMI, energy intake, family history of specific cancer, history of previous polyp and	Midpoints, conversion from serv/d to g/d, distribution of person-years
					Incidence, colorectal cancer	1.86 vs 0.13 servings/day	0.98 (0.65-1.59)		

	professionals				Incidence, colorectal cancer	2.71 vs 0.13 servings/day	1.02 (0.65-1.59)	prior endoscopy, menopausal status, multivitamin, physical activity, postmenopausal hormone use, randomized treatment assignment, red meat intake, saturated fat, smoking status	
McCullough, 2003 COL00366 USA	CPS II, Prospective Cohort, Age: 50-74 years, M/W, subgroup of CPS-II cohort	683/ 127 749 5 years	Cancer registry and death certificates and medical records	FFQ	Incidence, colorectal cancer, all	≥14 vs ≤2 serving/week	1.00 (0.75-1.34)	Age, sex, BMI, educational level, energy intake, family history of specific cancer, fruits, HRT use, multivitamin, physical activity, saturated fat, smoking habits, total vegetables	Midpoints, conversion from serv/wk to g/d, distribution of person-years
					Incidence, colorectal cancer, men	≥14 vs ≤2 serving/week	0.96 (0.67-1.38)		
					Incidence, colorectal cancer, women	≥14 vs ≤2 serving/week	1.11 (0.68-1.83)		
					Incidence, colon cancer, men	≥14 vs ≤2 serving/day	0.84 (0.54-1.29)		
					Incidence, proximal colon cancer, men	≥14 vs ≤2 serving/day	0.49 (0.24-1.03)		
					Incidence, distal colon cancer, men	≥14 vs ≤2 serving/day	1.18 (0.55-2.57)		
					Incidence, rectal cancer, men	≥14 vs ≤2 serving/day	1.22 (0.64-2.33)		

Terry, 2002 COL00560 Sweden	SMC, Prospective Cohort, Age: -76 years, W	572/ 61 463 695 438 person-years	Cancer registry	FFQ	Incidence, colorectal cancer	25-56 vs 0-12 serving/week	0.97 (0.73-1.29)	Age, alcohol consumption, BMI, educational level, folic acid, red meat intake, total energy, vitamin c	Midpoints, conversion from serv/wk to g/d, distribution of cases and person-years
					Incidence, colon cancer	25-56 vs 0-12 serving/week	1.03 (0.72-1.47)		
					Incidence, proximal colon cancer	25-56 vs 0-12 serving/week	1.32 (0.77-2.28)		
					Incidence, distal colon cancer	25-56 vs 0-12 serving/week	0.71 (0.38-1.30)		
					Incidence, rectal cancer	25-56 vs 0-12 serving/week	1.04 (0.64-1.71)		
Jarvinen, 2001 COL00314 Finland	Finnish Mobile Clinic Health Examination Survey, Prospective Cohort, Age: 39 years, M/W	72/ 9 959 19.6 years	Population	Questionnaire	Incidence, colorectal cancer	Q 4 vs Q 1	1.03 (0.46-2.32)	Age, sex, area of residence, BMI, energy intake, occupational group, smoking habits	Midpoints, distribution of person-years
					Incidence, colon cancer	Q 4 vs Q 1	0.37 (0.12-1.39)		
					Incidence, rectal cancer	Q 4 vs Q 1	2.52 (0.80-7.90)		
Pietinen, 1999 COL00176 Finland	ATBC, Prospective Cohort, Age: 50-69 years, M, Smokers	185/ 27 111 8 years	Cancer registry	Dietary history questionnaire	Incidence, colorectal cancer	1089 vs 318 g/day	0.60 (0.40-0.90)	Age, alcohol consumption, BMI, educational level, energy intake, physical activity, smoking years, supplement group	Distribution of person-years

Bostick, 1993 COL01450 USA	IWHS, Prospective Cohort, Age: 55-69 years, W	35 216 167 447 person-years	SEER	Semi-quantitative FFQ	Incidence, colon cancer	≥25 vs ≤8 serving/week	0.72 (0.38-1.36)	Energy intake, height, parity, seafood and skinless poultry intake, vitamin e, vitamin e x age	Midpoints
					Incidence, colon cancer	≥14 vs ≤4 serving/week	0.78 (0.45-1.36)		

Table 107 Dairy intake and colorectal cancer risk. Main characteristics of studies excluded from the CUP SLR dose-response meta-analysis

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Reasons for exclusion
Bamia, 2013 COL40964 Denmark,France,Germany,Greece,Italy,Netherlands,Spain,Sweden,UK	EPIC, Prospective Cohort, Age: 25-70 years, M/W	4 355/ 480 308 11.6 years	Cancer registry, record linkage, health Insurance rec, mortality registry , pathology and active follow up	FFQ	Incidence, colorectal cancer	529.8 vs 114 g/day	0.85 (0.78-0.92)	Age, sex, BMI, centre location, cereal, dairy products consumption, educational level, ethanol, fish, fruits, legumes, lipids, meat, physical activity, smoking	Duplicate, overlap with Murphy et al, 2013, COL41070
					Incidence, colorectal cancer, women	529.8 vs 114 g/day	0.84 (0.75-0.93)		
					Incidence, colorectal cancer, men	529.8 vs 114 g/day	0.88 (0.78-1.00)		
Butler, 2008 COL40639 Singapore	SCHS, Prospective Cohort, Age: 45-74 years, M/W	961/ 61 321 9.8 years	Cancer registry	FFQ	Incidence, colorectal cancer	Q 4 vs Q 1	0.98 (0.82-1.17)	Age, sex, alcohol intake, BMI, diabetes, dialect group, educational level, energy intake, exposure assessment, family history of colorectal cancer, physical activity, smoking habits	
van der Pols JC, 2007 COL40680 UK	BOCS, Historical Cohort, Age: 8 years, M/W	76/ 4 374 57 years	National health records	7-day food records	Incidence, colorectal cancer	471 vs 89 g/day	2.90 (1.26-6.65)	Age, sex, energy intake, fruit intake	Household dietary intake
Kesse, 2005 POL16753	EPIC-E3N, Prospective	516/ 5 320	National health Insurance	Questionnaire	Adenoma Incidence,	≥424.3 vs 0-184.82 g/day	0.80 (0.62-1.05)	Age at entry, alcohol	Duplicate, overlap with Murphy et al,

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Reasons for exclusion
France	Cohort, Age: 40-65 years, W, part of nat. health insurance scheme for teachers	3.7 years	scheme		colorectal adenoma, women			consumption, BMI, educational level, family history of specific cancer, physical activity, smoking status, total energy	2013, COL41070
					Adenoma Incidence, high-risk colorectal adenomas (>1cm), women	≥424.3 vs 0-184.82 g/day	0.85 (0.54-1.33)		
					Incidence, colorectal cancer, women	≥409.22 vs 0-179.46 g/day	0.78 (0.49-1.22)		
Hsing, 1998 COL00458 USA	Lutheran Brotherhood Study, Prospective Cohort, Age: 35- years, M, policyholders	145/ 17 633 286 731 person-years	Responding to mail survey	Questionnaire	Mortality, colorectal cancer	≥85.1 vs ≤25.9 times/month	0.60 (0.30-1.30)	Age, alcohol consumption, smoking habits, total energy	Mortality as outcome
					Mortality, colon cancer	≥85.1 vs ≤25.9 times/month	0.60 (0.30-1.30)		

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Reasons for exclusion
Zheng, 1998 COL00209 USA	IWHS, Prospective Cohort, Age: 55-69 years, W, Postmenopausal	144/ 34 702 9 years	SEER	Semi-quantitative FFQ	Incidence, rectal cancer,	Q 3 vs Q 1	0.72	Age, HRT use, pack-years of smoking, smoking habits, total energy	No quantities
Sellers, 1998 COL01974 USA	IWHS, Prospective Cohort, Age: 55-69 years, W, Postmenopausal	180/ 35 216 10 years	Seer registry	Semi-quantitative FFQ	Incidence, colon cancer, no family history of crc	≥20.1 vs ≤10 servings/week	0.70 (0.40-1.00)		Duplicate, Bostick et al, 1993 COL01450 was used as it provided results for colon cancer overall (not stratified by family history of CRC)
					Incidence, colon cancer, family history of crc	≥20.1 vs ≤10 servings/week	0.70 (0.40-1.40)		
Kato, 1997 CRC00022 USA	New York University Women's Health Study, Prospective	100/ 14 272 105 044 person-years	Mammography screening program	Semi-quantitative FFQ	Incidence, colorectal cancer,	Q 4 vs Q 1	0.69 (0.40-1.20)	Age, educational level, place at enrollment, total calorie intake	No quantities

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Reasons for exclusion
	Cohort, Age: 34-65 years, W								

Figure 183 RR estimates of colorectal cancer by levels of dairy product intake

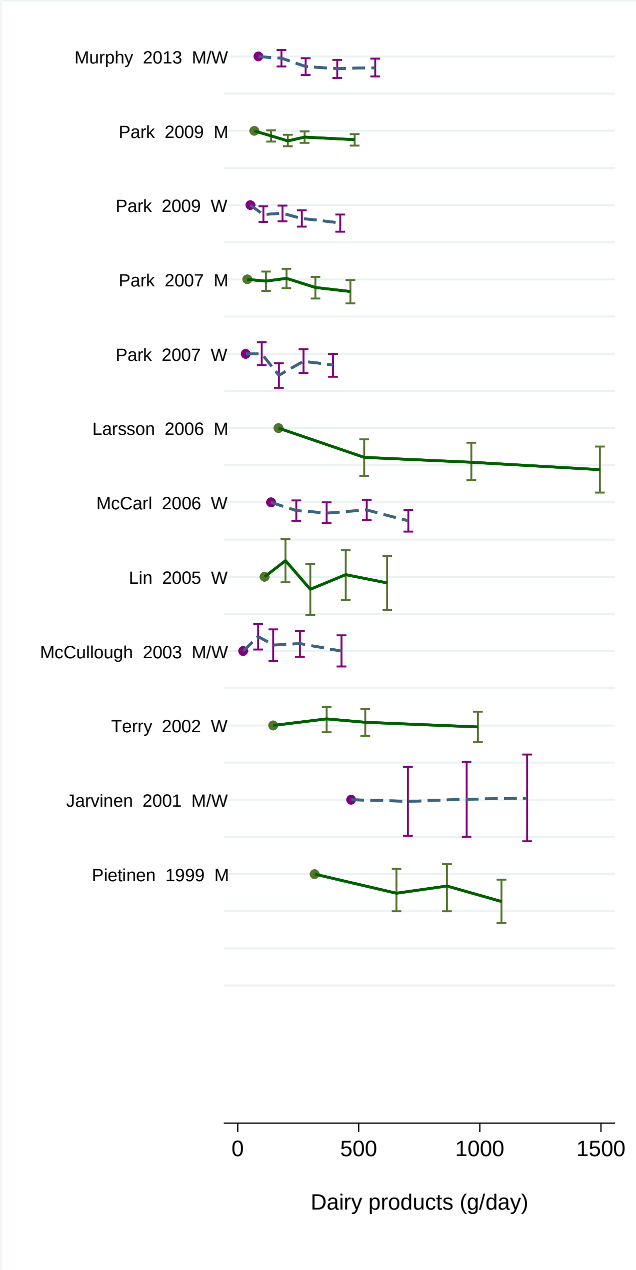


Figure 184 Relative risk of colorectal cancer for the highest compared with the lowest level of dairy product intake

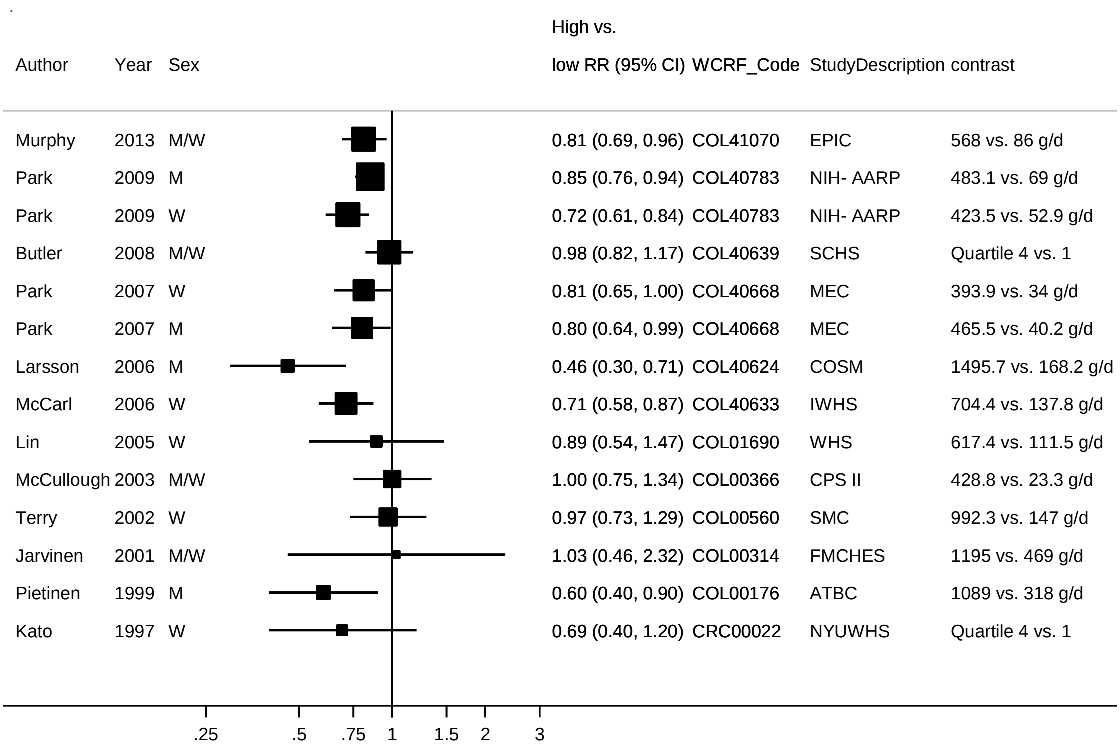


Figure 185 Relative risk of colorectal cancer for 400 g/day increase in dairy product intake

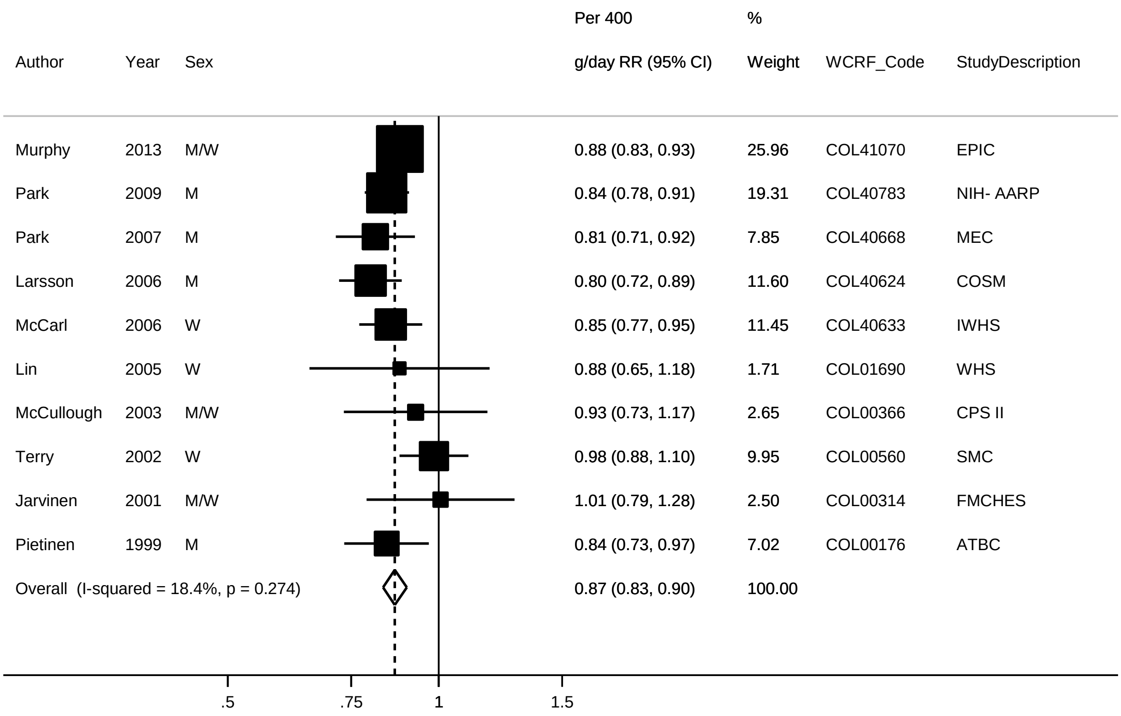


Figure 186 Relative risk of colorectal cancer for 400 g/day increase in dairy product intake, stratified by sex

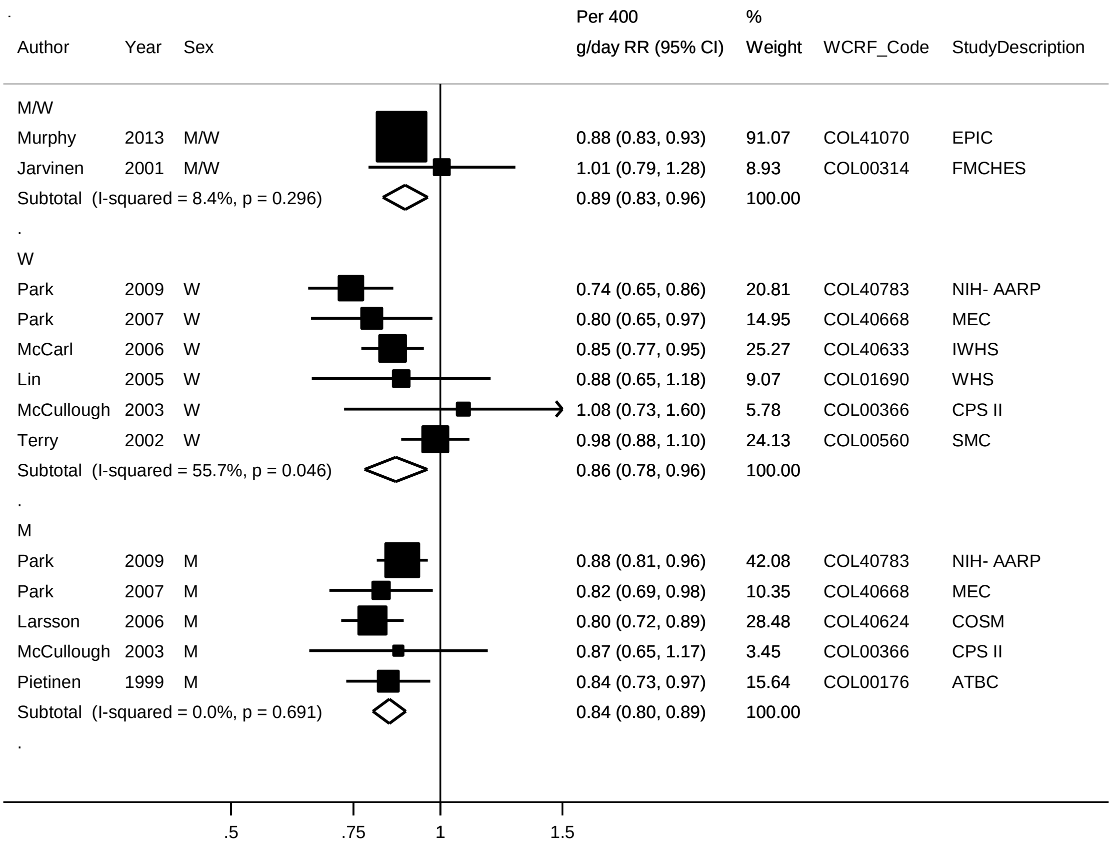


Figure 187Relative risk of colorectal cancer for 400 g/day increase in dairy product intake, stratified by geographic location

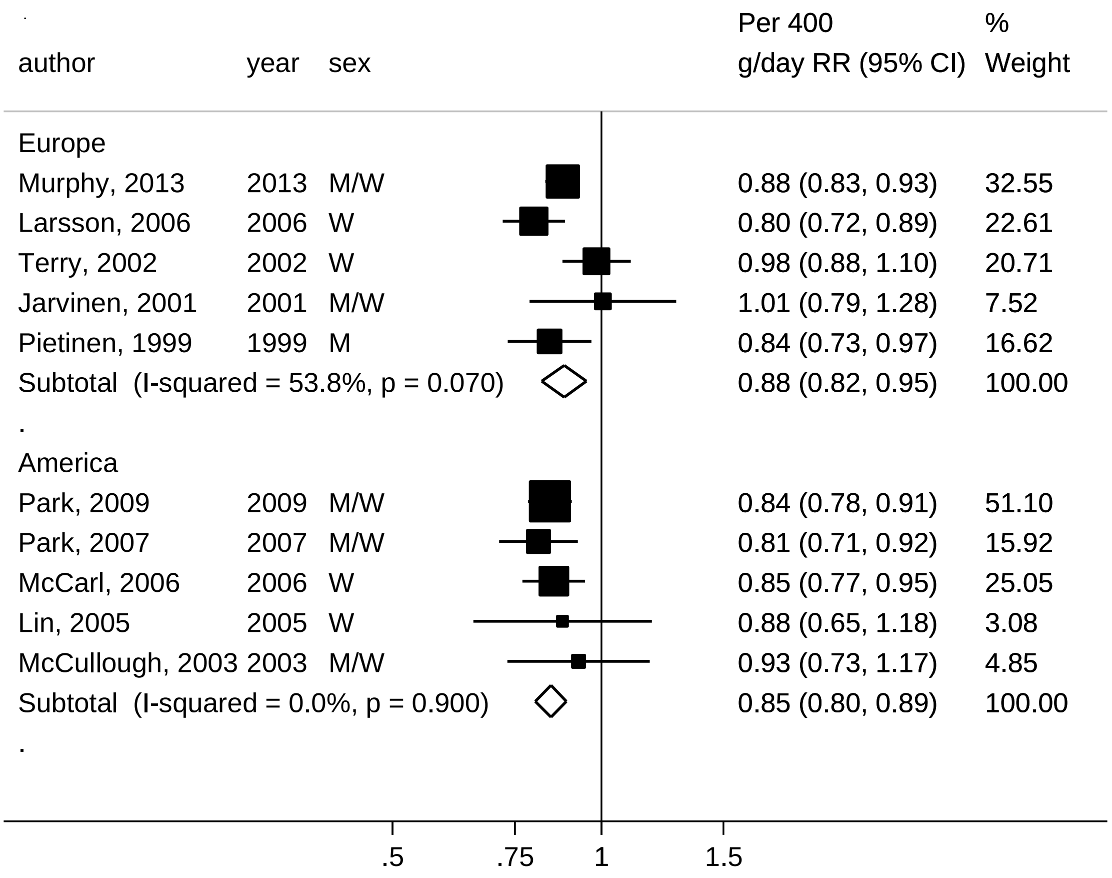
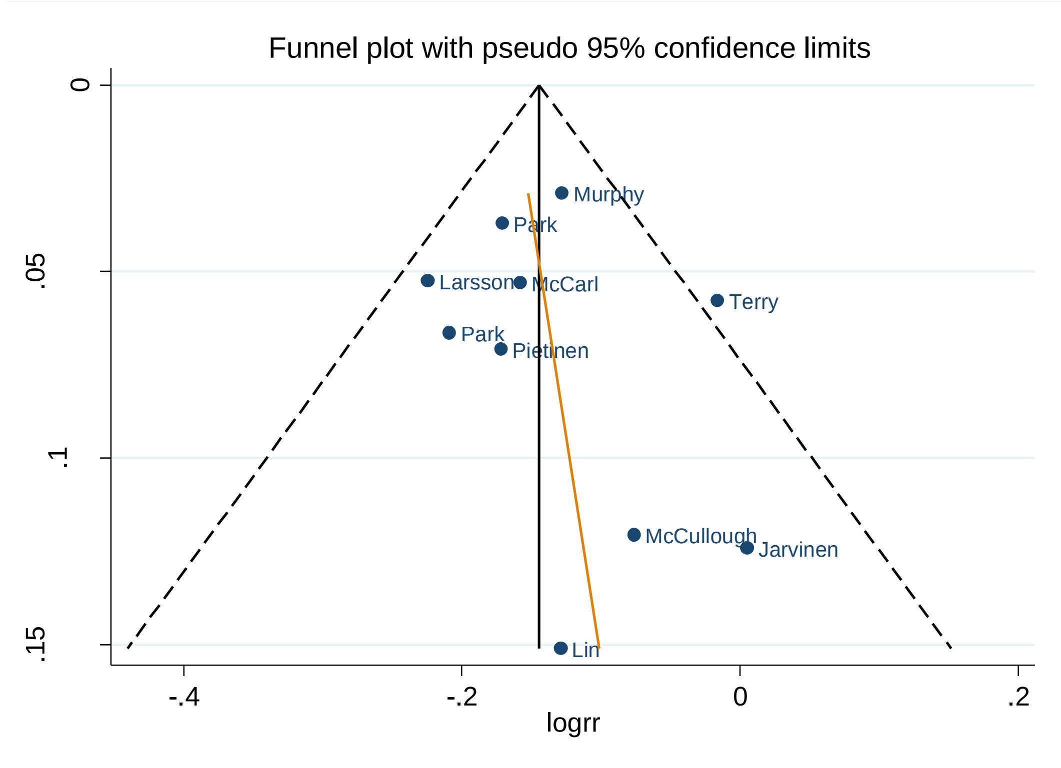
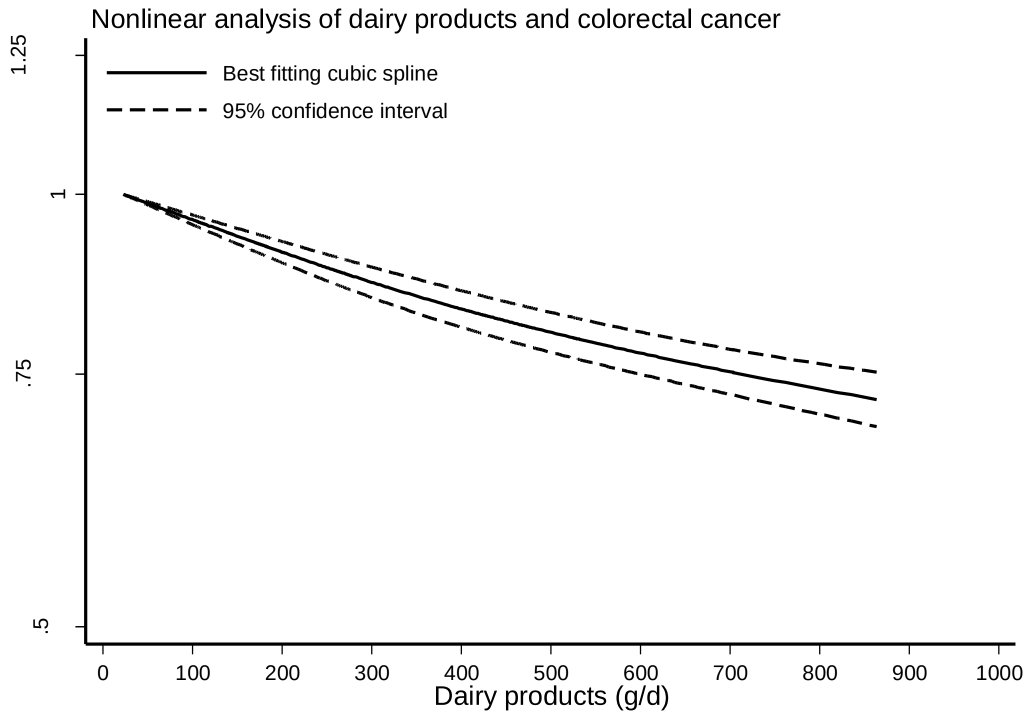


Figure 188 Funnel plot of studies included in the dose response meta-analysis of dairy product intake and colorectal cancer



p Egger's test=0.63

Figure 189 Dairy products and colorectal cancer, nonlinear dose-response analysis



p for non-linearity=0.003

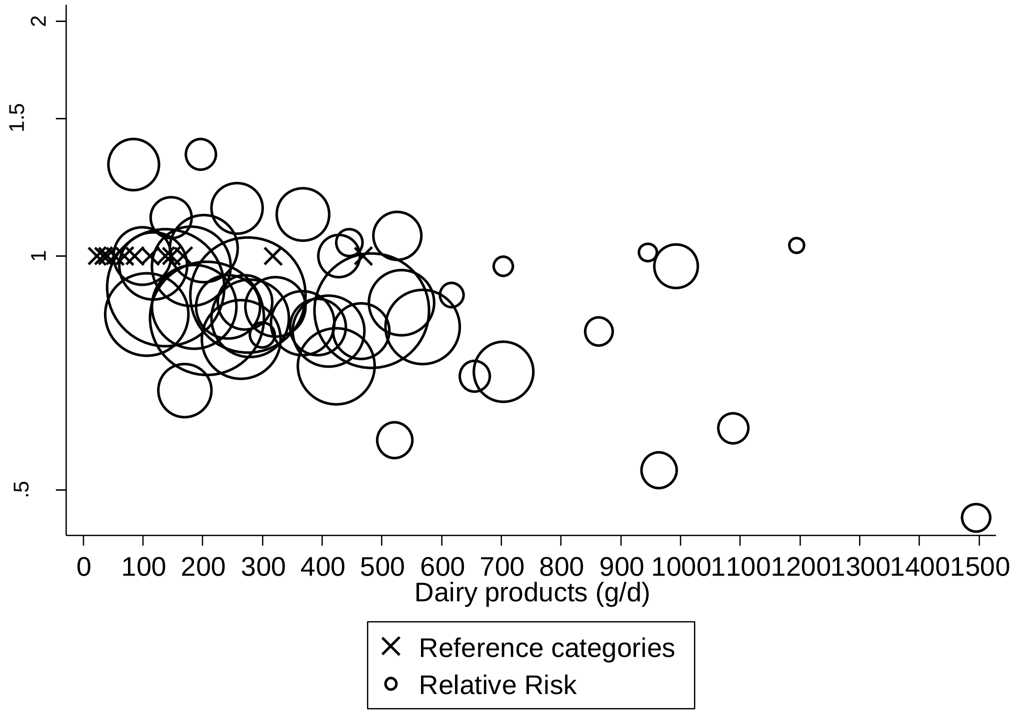


Table 108 Relative risk of colorectal cancer and dairy product intake estimated using non-linear models

Dairy products (g/day)	RR (95%CI)
23.3	1.00
100	0.95 (0.94-0.96)
200	0.90 (0.88-0.92)
300	0.86 (0.84-0.88)
400	0.82 (0.80-0.85)
500	0.79 (0.77-0.82)
600	0.77 (0.74-0.79)
700	0.74 (0.72-0.77)
800	0.72 (0.69-0.75)
900	0.70 (0.67-0.74)

Figure 190 RR estimates of colon cancer by levels of dairy product intake

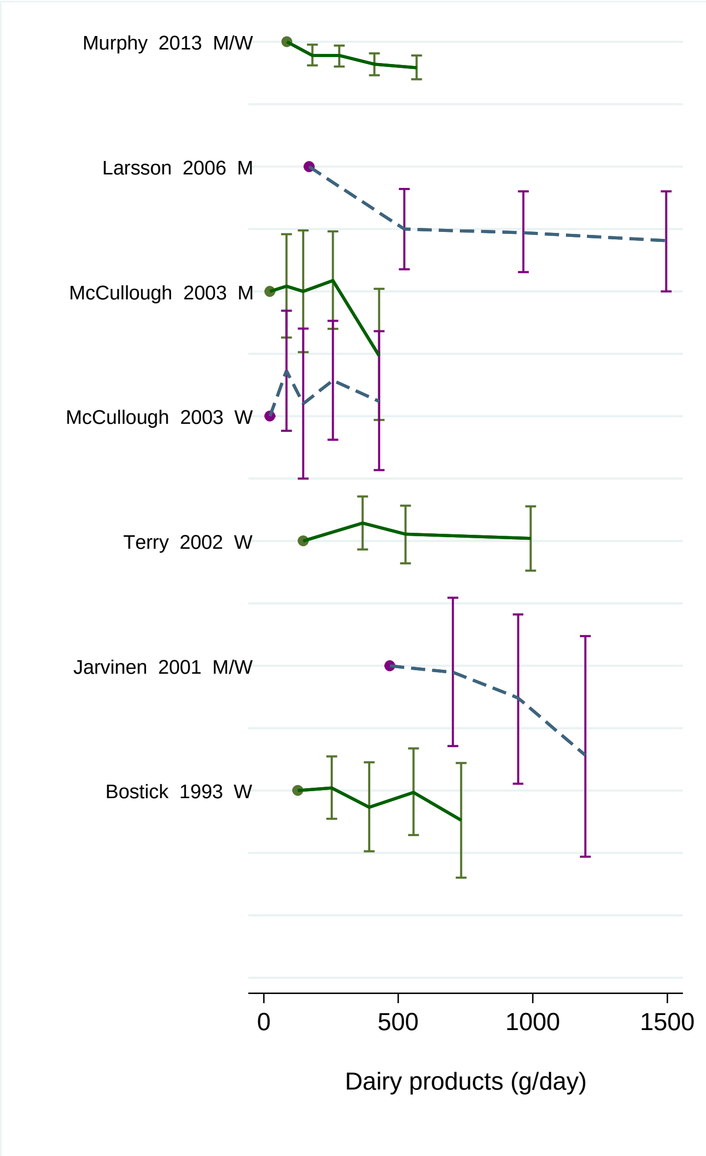


Figure 191 Relative risk of colon cancer for the highest compared with the lowest level of dairy product intake

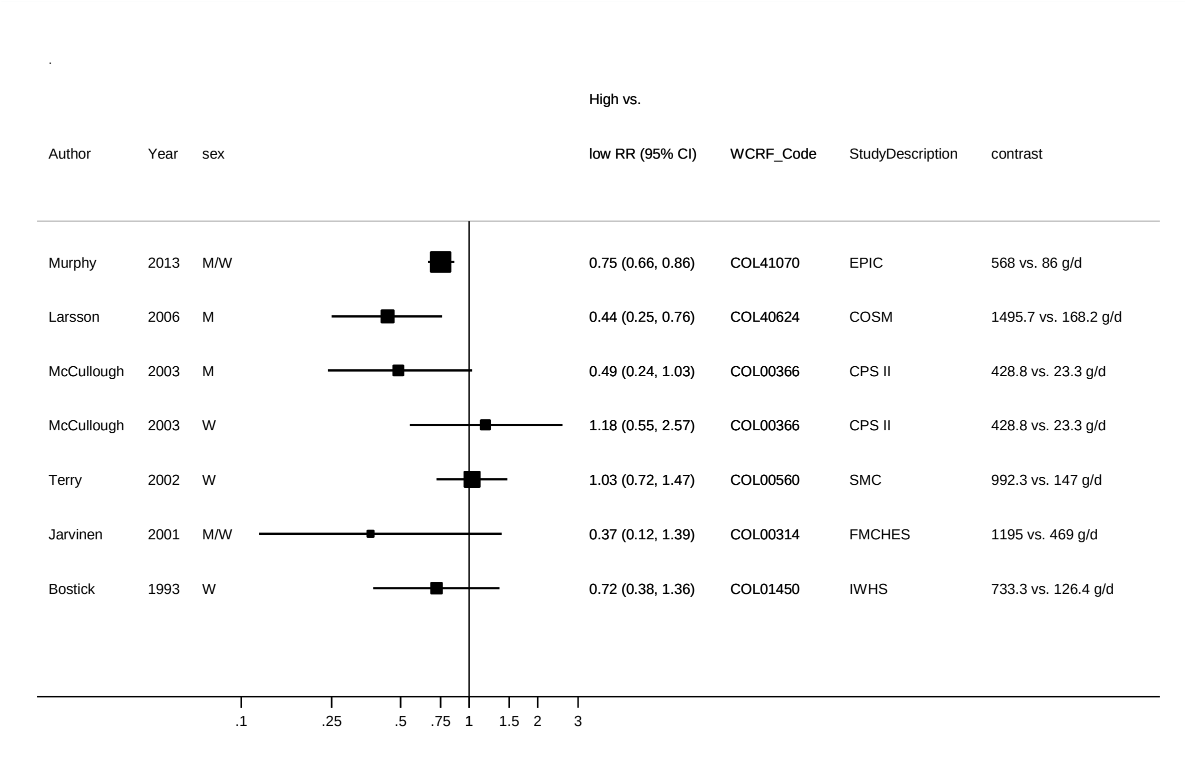


Figure 192 Relative risk of colon cancer for 400 g/day increase in dairy product intake

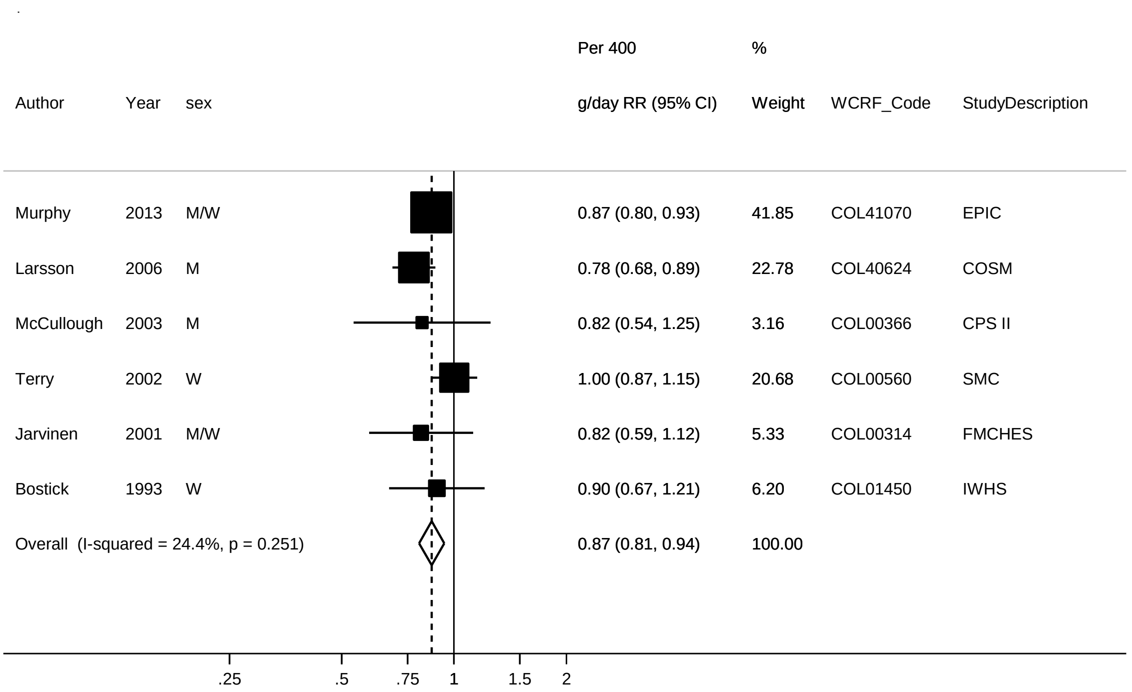


Figure 193 Relative risk of colon cancer for 400 g/day increase in dairy product intake, stratified by sex

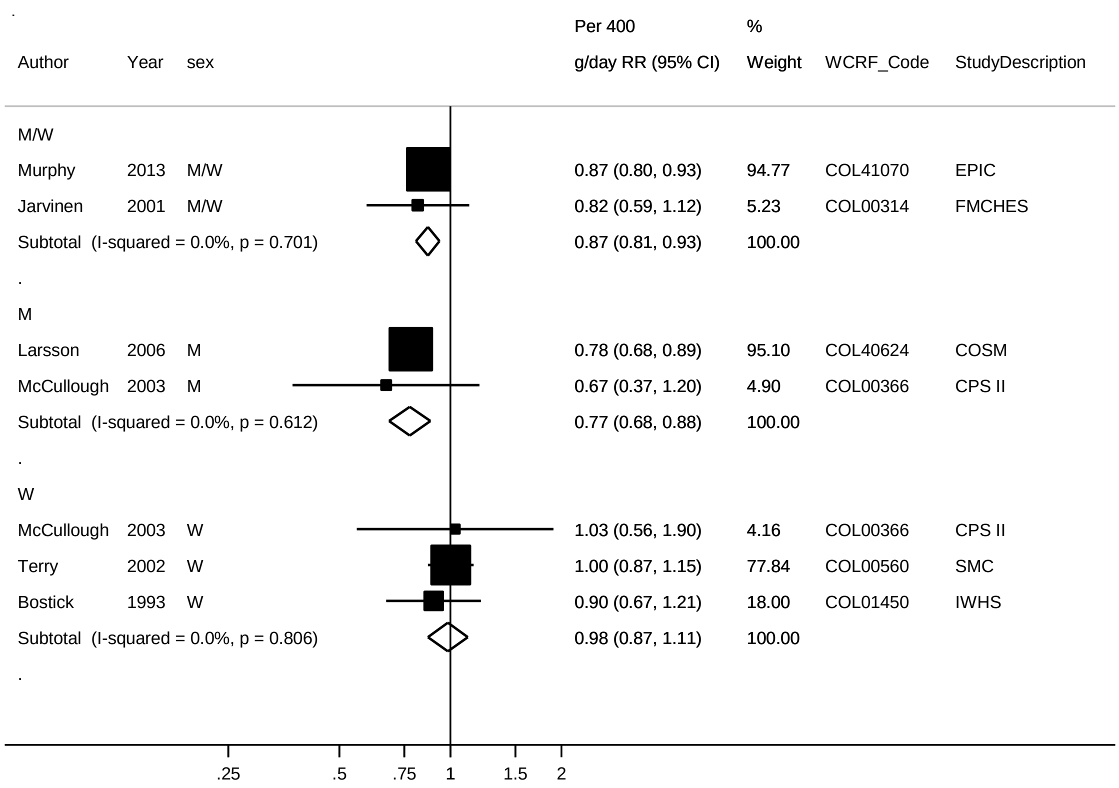
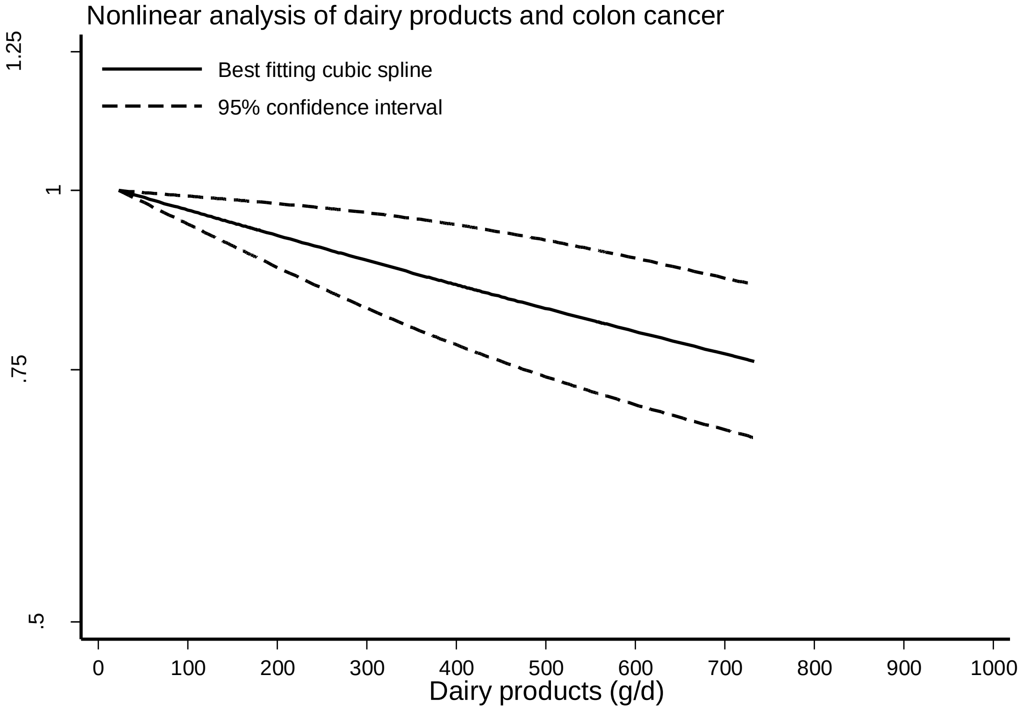


Figure 194 Dairy products and colon cancer, nonlinear dose-response analysis



p for non-linearity=0.77

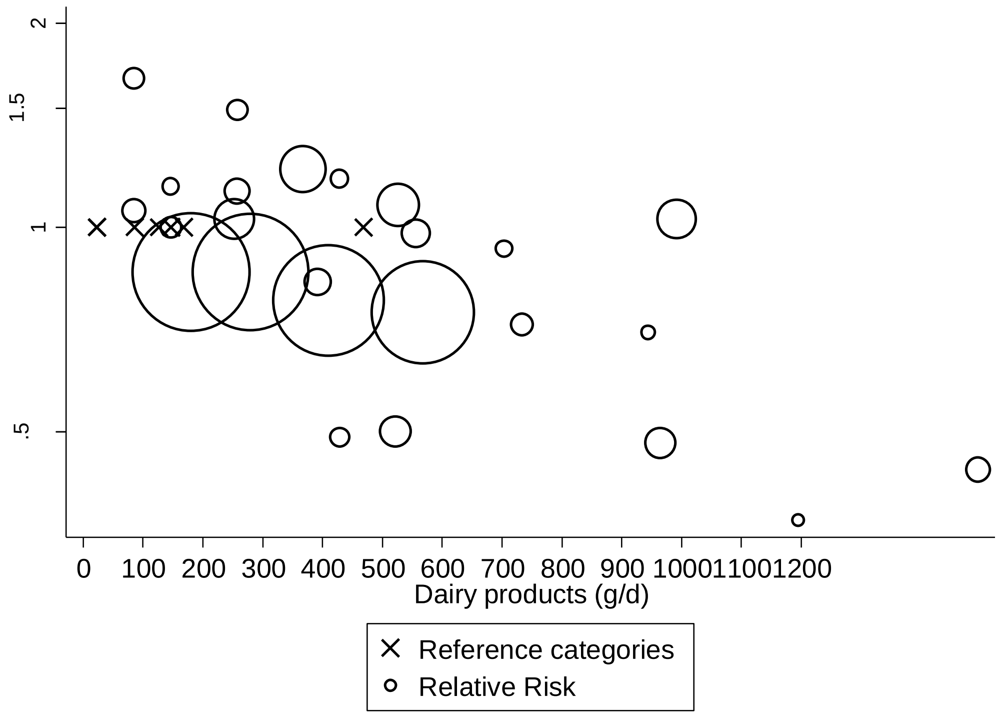


Table 109 Table x Relative risk of colon cancer and dairy product intake estimated using non-linear models

Dairy products (g/day)	RR (95%CI)
23.3	1.00
100	0.96 (0.93-0.99)
200	0.92 (0.87-0.98)
300	0.89 (0.81-0.96)
400	0.85 (0.77-0.94)
500	0.82 (0.73-0.92)
600	0.79 (0.70-0.89)
700	0.76 (0.67-0.87)
800	0.74 (0.65-0.84)
900	0.71 (0.62-0.81)

Figure 195 RR estimates of rectal cancer by levels of dairy product intake

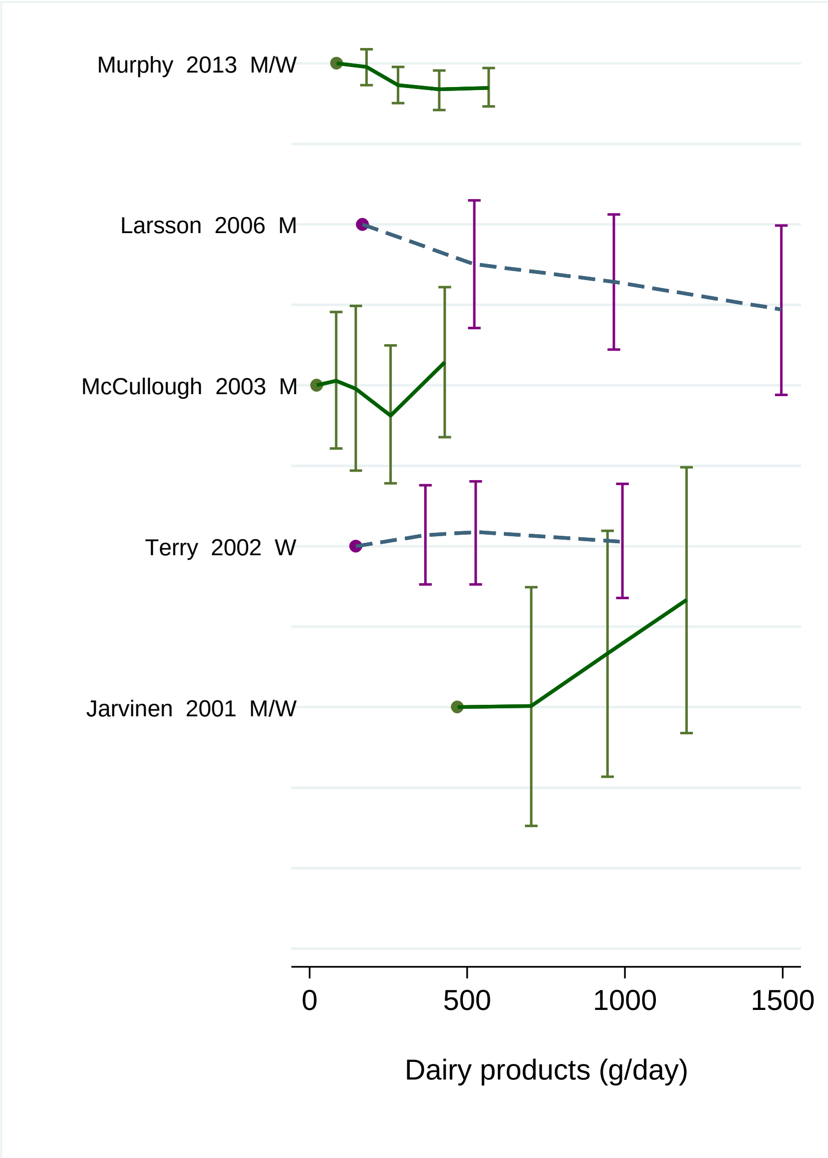


Figure 196 Relative risk of rectal cancer for the highest compared with the lowest level of dairy product intake

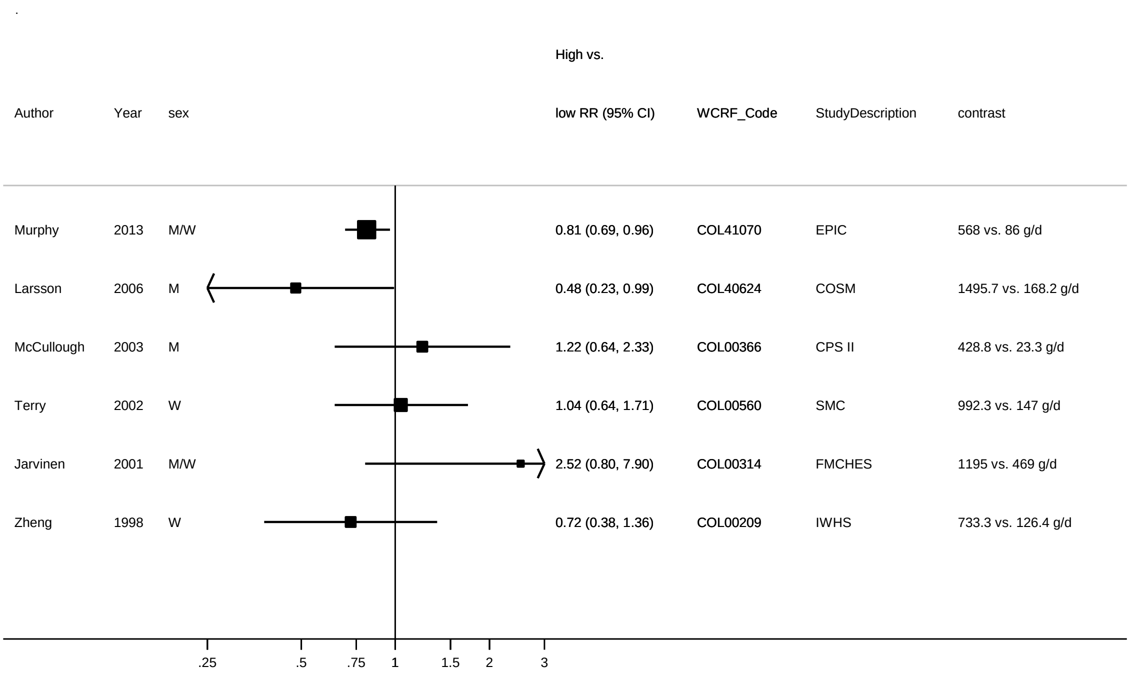


Figure 197 Relative risk of rectal cancer for 400 g/day increase in dairy product intake

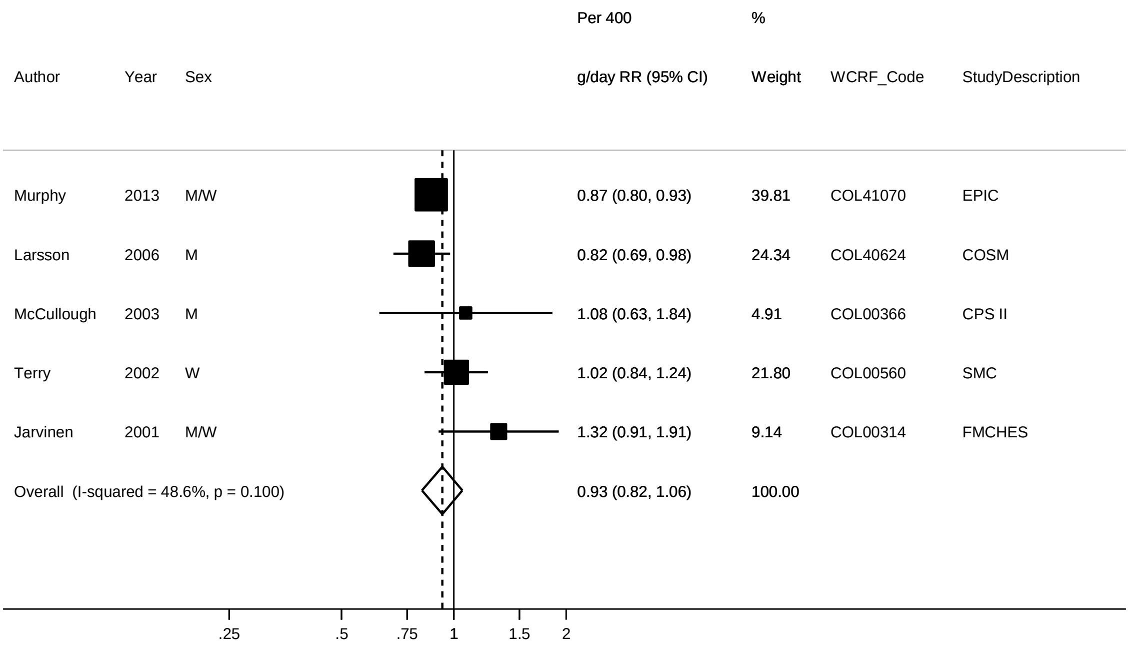
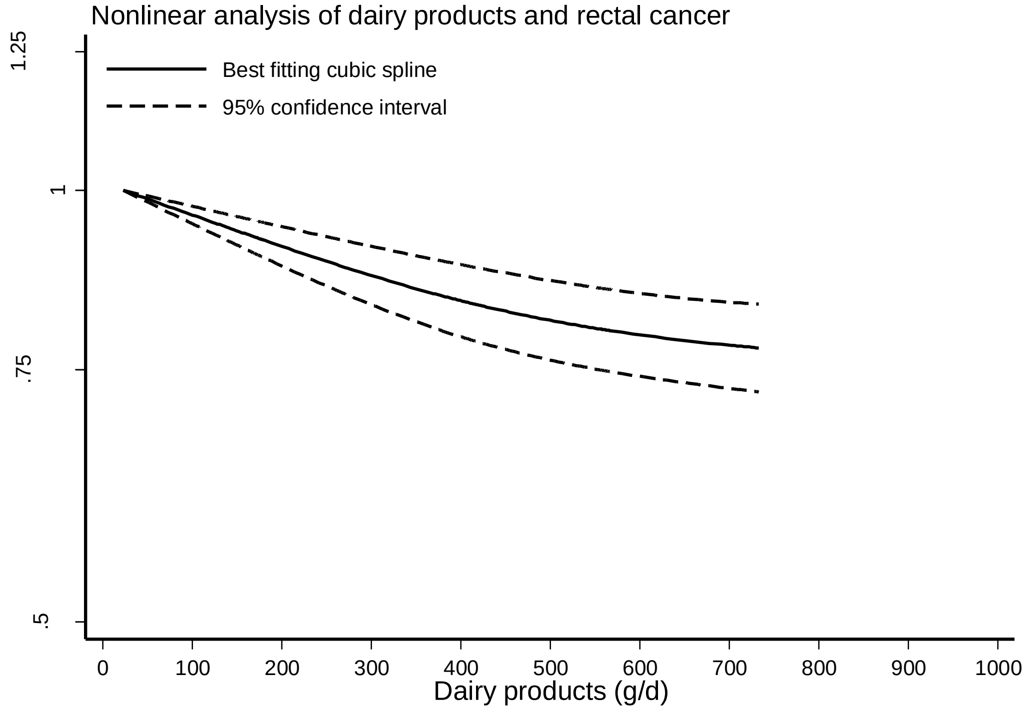


Figure 198 Dairy products and rectal cancer, nonlinear dose-response analysis



p for non-linearity=0.02

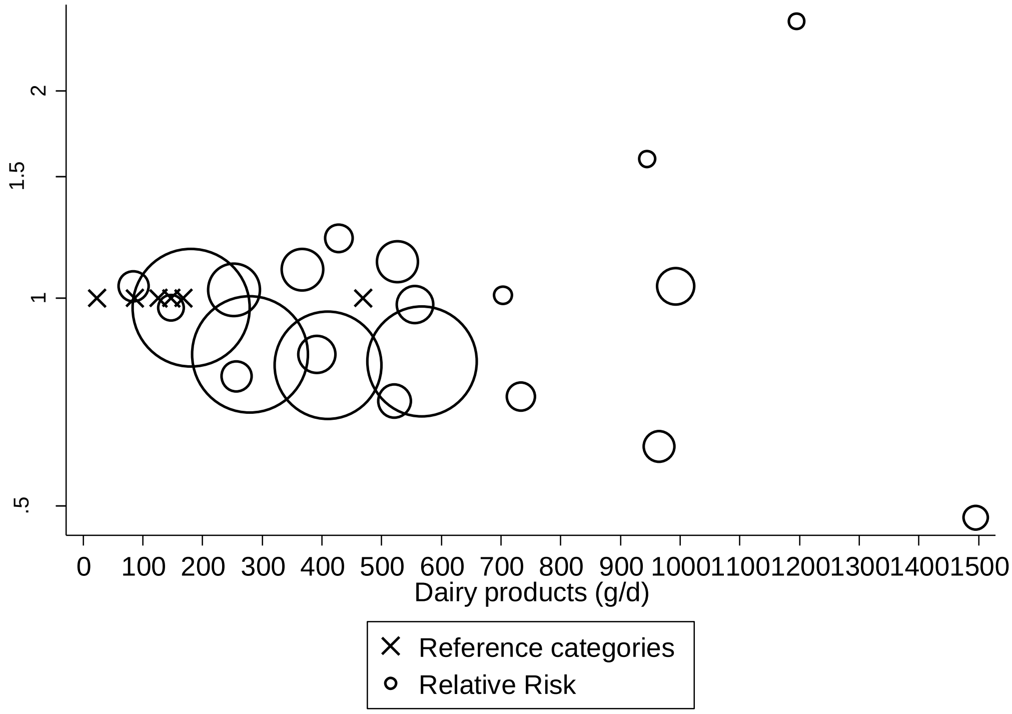


Table 110 Relative risk of rectal cancer and dairy product intake estimated using non-linear models

Dairy products (g/day)	RR (95%CI)
23.3	1.00
100	0.95 (0.93-0.97)
200	0.90 (0.87-0.94)
300	0.86 (0.82-0.91)
400	0.83 (0.78-0.88)
500	0.80 (0.75-0.86)
600	0.78 (0.73-0.84)
700	0.77 (0.72-0.83)
800	0.76 (0.71-0.82)
900	0.76 (0.69-0.82)

2.7.1 Total milk

Cohort studies

Summary

Main results:
Nineteen studies (24 publications) on total milk intake and colorectal cancer risk were identified, and three of these were new publications since the 2010 SLR. Nine studies investigated colorectal cancer, nine investigated colon cancer, and seven were on rectal cancer. Study characteristics and results for all cancer types are shown in the Table. For studies that reported total milk intake in servings per day intakes were converted to grams per day by using a serving size of 244 grams (244 mL), unless a serving size was provided in the publication.

Colorectal cancer:
Nine studies (10738 cases) were included in the dose-response meta-analysis. The summary RR for a 200 g/d increase in total milk intake was 0.94 (95% CI: 0.92-0.96) and there was no heterogeneity, I^2=0%, $p_{heterogeneity}$=0.97. There was no evidence of small study bias or publication bias with Egger's test, p=0.63. The summary RR ranged from 0.93 (95% CI: 0.89-0.97) when the EPIC study (Murphy, 2013) was excluded to 0.94 (95% CI: 0.0.92-0.96) when the Cohort of Swedish Men (Larsson, 2006) was excluded. When the Pooling Project is included in the analysis (excluding the overlapping studies) the association remains the same (RR: 0.94 (95% CI: 0.93-96).

There was no indication of a nonlinear association, $p_{nonlinearity}$=0.95 in the analysis of colorectal cancer.

Colon cancer:
Nine studies (8149 cases) were included in the dose-response meta-analysis of total milk intake and colon cancer. The summary RR per 200 g/day increase in total milk intake was 0.93 (95% CI: 0.91-0.96) and there was low heterogeneity, I^2=30.0%, $p_{heterogeneity}$=0.18.

There was indication of a nonlinear association, $p_{nonlinearity}$=0.002 in the analysis of total milk and colon cancer, and the association was steeper at the lower than the higher level of intake. In the Pooling Project (Cho, 2004), the association with milk intake was limited to cancers of distal colon and rectum (p=0.03). In other studies, the association with milk was similar for distal and proximal cancers (Murphy, 2013) or although not significantly different, it was more evident for distal than for proximal colon tumours (Simons, 2010; Larsson, 2006).

Rectal cancer:
Seven studies (3599 cases) were included in the dose-response meta-analysis of total milk intake and rectal cancer. The summary RR per 200 g/d increase in total milk intake was 0.94 (95% CI: 0.91-0.97), with no evidence of heterogeneity, I^2=0%, $p_{heterogeneity}$=0.93.
There was indication of a nonlinear association, $p_{nonlinearity}$<0.0001 in the analysis of total milk and rectal cancer, and the association was steeper at the lower than the higher level of intake.

Study quality:
Total milk intake was estimated from food intake assessed by FFQ in all studies, but one study used a combination of FFQs, dietary histories, and interviews.
Loss to follow-up was low for the studies that reported such data, although some studies did not provide data.
Cancers were identified by record linkages to health registries, cancer registries, mortality registries, or death indexes.
All studies adjusted for at least age, and most of the studies adjusted for most of the established colorectal cancer risk factors, including: age, physical activity, BMI, and alcohol consumption, smoking, red meat and hormone replacement therapy in women.

Table 111 Total milk intake and colorectal cancer risk. Number of studies in the CUP SLR

	Number
Studies identified	19 studies (24 publications)
Studies included in forest plot of highest compared with lowest intake	Colorectal cancer: 11 studies Colon cancer: 9 Rectal cancer: 7
Studies included in linear dose-response meta-analysis	Colorectal cancer: 9 studies Colon cancer: 9 Rectal cancer: 7
Studies included in non-linear dose-response meta-analysis	Colorectal cancer: 9 studies Colon cancer: 9 Rectal cancer: 7

Table 112 Total milk intake and colorectal cancer risk. Summary of the linear dose-response meta-analysis in the 2005 SLR, 2010 SLR and 2015SLR

	2005 SLR		
	Colorectal cancer	**Colon cancer**	**Rectal cancer**
Increment unit used	Per 1 serving/day	High vs. low	High vs. low
Studies (n)	6	6	2
Cases (total number)	-	-	-
RR (95%CI)	0.94 (0.85-1.03)	0.79 (0.65-0.96)	0.93 (0.59-1.46)
Heterogeneity (I^2, p-value)	12.4%, p=0.34	14.9%, p=0.32	0%, p=0.75
P value Egger test	-	0.19	-

	2010 SLR		
	Colorectal cancer	**Colon cancer**	**Rectal cancer**
Increment unit used	200 g/day		
Studies (n)	9	9	7
Cases (total number)	4510	-	-
RR (95%CI)	0.90 (0.85-0.94)	0.88 (0.79-0.97)	0.90 (0.79-1.02)
Heterogeneity (I^2, p-value)	24.6%, p=0.22	44.1%, p=0.11	0%, p=0.53
P value Egger test	0.86	-	-

	2015 SLR		
	Colorectal cancer	**Colon cancer**	**Rectal cancer**
Increment unit used	200 g/day		
Studies (n)	9	9	7
Cases (total number)	10738	8149	3599
RR (95%CI)	0.94 (0.92-0.96)	0.93 (0.90-0.96)	0.94 (0.91-0.97)
Heterogeneity (I^2, p-value)	0%, p=0.97	30.0%, p=0.18	0%, p=0.93
P value Egger test	0.63	0.49	0.62

Stratified analyses by geographic location			
2015 SLR	**Asia**	**Europe**	**North-America**
Studies (n)	1	5	3
RR (95%CI)	0.81 (0.59-1.10)	0.94 (0.91-0.96)	0.93 (0.88-0.99)
Heterogeneity (I^2, p- value)	-	0%, p=0.45	0%, p=0.72

Table 113 Total milk intake and colorectal cancer risk. Results of meta-analyses and pooled analyses of prospective studies published after the 2005 SLR.

Author, Year	Number of studies	Total number of cases	Studies country, area	Outcome	Comparison	RR (95%CI)	P trend	Heterogeneity (I^2, p value)
Meta-analyses								
Huncharek, 2009	14 CRC 8 CC 7 RC	-	North America, Europe, Asia	Incidence and mortality	High vs. low High vs. low High vs. low	0.90 (0.83-0.97) 0.78 (0.67-0.92) 0.95 (0.80-1.14)	-	- - -
Aune et al, 2012	10 CRC 6 CC 4 RC	5011	North America, Europe, Asia	Incidence	High vs. low Per 200 g/d High vs. low Per 200 g/d High vs. low Per 200 g/d	0.83 (0.74-0.93) 0.90 (0.85-0.94) 0.82 (0.72-0.94) 0.88 (0.79-0.97) 0.79 (0.60-1.06) 0.90 (0.79-1.02)	- - - - - -	14%, p=0.31 0%, p=0.62 0%, p=0.54 44.1%, p=0.11 0%, p=0.79 0%, p=0.53
Ralston et al, 2014	14 CRC 6 CRC 8 CRC 4 CC 3 CC 3 RC 2 RC	-	North America, Europe, Asia	Incidence and mortality	High vs. low, CRC, all High vs. low, CRC, men High vs. low, CRC, women High vs. low, CC, men High vs. low, CC, women High vs. low, RC, men High vs. low, RC, women	0.85 (0.77-0.93) 0.79 (0.69-0.91) 0.83 (0.68-1.02) 0.74 (0.60-0.91) 1.03 (0.78-1.36) 0.81 (0.60-1.09) 0.82 (0.56-1.21)	- - -	0%, p=NA 0%, p= NA 42%, p= NA 0%, p=NA 0%, p=NA 0%, p=NA 0%, p=NA
Pooled analyses								
Cho et al, 2004	10 CRC	7157	North	Incidence	≥250 vs. <70g/d	0.85 (0.78-0.94)	<0.001	NA, p=0.63

	CC	2912	America,		≥250 vs. <70g/d	0.88 (0.79-0.99)	0.01	NA, p=0.10
	PCC	1505	Europe		≥250 vs. <70g/d	0.99 (0.85-1.15)	0.56	NA, p=0.78
	DCC	1238			≥250 vs. <70g/d	0.73 (0.62-0.87)	<0.001	NA, p=0.61
	RC	1208			≥250 vs. <70g/d	0.80 (0.66-0.96)	0.02	NA, p=0.31

Table 114 Total milk intake and colorectal cancer risk. Main characteristics of studies included in the CUP SLR dose-response meta-analysis

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI)	Adjustment factors	Missing data derived for analysis
Murphy, 2013 COL41070 Denmark,France,Germany,Greece,Italy,Netherlands,Norway, Spain,Sweden, UK	EPIC, Prospective Cohort, Age: 30- years, M/W	4 513/ 477 122 11 years	Cancer registries, health Insurance records, pathology rec & active follow up	Dietary questionnaire	Incidence, colorectal cancer	≥325 vs 0-8.9 g/d	0.81 (0.73-0.90)	Age, alcohol consumption, BMI, centre location, educational level, fibre intake, menopausal hormone use, menopausal status, physical activity Index, red and processed meat, smoking status and dose, total energy intake, use of oral contraceptives	Midpoints
					Incidence, colorectal cancer	per 200 g/day	0.94 (0.91		
					Incidence, colon cancer	≥325 vs 0-8.9 g/d	0.80 (0.70-0.91)		
					Incidence, colon cancer	per 200 g/d	0.93 (0.90-0.97)		
					Incidence, proximal colon cancer	≥325 vs 0-8.9 g/d	0.84 (0.69-1.02)		
					Incidence, proximal colon cancer	per 200 g/day	0.95 (0.89-1.01)		
					Incidence, distal colon cancer	≥325 vs 0-8.9 g/d	0.78 (0.63-0.96)		
					Incidence, distal colon cancer	per 200 g/day	0.94 (0.88-0.99)		
					Incidence, rectal cancer	≥325 vs 0-8.9 g/d	0.84 (0.70-0.99)		
					Incidence,	per 200 g/day	0.95 (0.90-1.00)		

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI)	Adjustment factors	Missing data derived for analysis
					rectal cancer				
Ruder, 2011 COL40896 USA	NIH-AARP, Prospective Cohort, Age: 50-71 years, Retired	2 819/ 292 797	Cancer registry and national health database	FFQ	Incidence, colon cancer	2 vs 0.03 times/day	0.78 (0.67-0.90)	Sex, age at baseline, alcohol consumption, aspirin use, BMI, educational level, energy, energy, history of colon cancer, HRT use, milk, physical activity, race, smoking	Distribution of person-years, conversion from times/d to g/d
					Incidence, colon cancer	2 vs 0.03 times/day	0.70 (0.61-0.79)		
					Incidence, colon cancer	3 vs 0 times/day	0.92 (0.78-1.10)		
					Incidence, colon cancer	3 vs 0 times/day	0.84 (0.71-0.99)		
					Incidence, rectal cancer	2 vs 0.03 times/day	0.75 (0.58-0.96)		
					Incidence, rectal cancer	2 vs 0.03 times/day	0.74 (0.59-0.92)		
					Incidence, rectal cancer	3 vs 0 times/day	0.99 (0.73-1.34)		
					Incidence, rectal cancer	3 vs 0 times/day	0.94 (0.70-1.26)		
Simons, 2010 COL40821 Netherlands	NLCS, Prospective Cohort, Age: 55-69 years, M/W	1 260/ 120 852 13.3 years	Cancer registry and database of pathology reports	FFQ	Incidence, colorectal cancer, men	>2 vs 0 glasses/day	0.68 (0.50-0.92)	Age, BMI, educational level, ethanol intake, family history of colorectal cancer, fibre intake, folate intake, meat intake, non-occupational physical activity,	Conversion from glasses/d to g/d
					Incidence, colorectal cancer, women	>2 vs 0 glasses/day	0.94 (0.68-1.30)		
					Incidence, proximal colon cancer, women	>2 vs 0 glasses/day	1.08 (0.70-1.68)		

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI)	Adjustment factors	Missing data derived for analysis
					Incidence, proximal colon cancer, men	>2 vs 0 glasses/day	0.84 (0.53-1.32)	physical activity, processed meat consumption, smoking, total fluid intake, vitamin b6 intake	
					Incidence, distal colon cancer, men	>2 vs 0 glasses/day	0.67 (0.42-1.07)		
					Incidence, distal colon cancer, women	>2 vs 0 glasses/day	1.14 (0.66-1.94)		
					Incidence, rectal cancer, men	>2 vs 0 glasses/day	0.79 (0.49-1.27)		
					Incidence, rectal cancer, women	>2 vs 0 glasses/day	0.68 (0.38-1.23)		
Lee, 2009 COL40764 China	SWHS, Prospective Cohort, Age: 40-70 years, W	394/ 73 224 7.4 years	Cancer registry and death certificates and participant contact	Quantitative FFQ	Incidence, colorectal cancer	≥200 vs ≤0 g/day	0.80 (0.50-1.20)	Age, educational level, energy intake, fibre intake, Income, nsaid use, season of Interview, tea consumption	Midpoints, CIs for quartile 2 and 3
					Incidence, colon cancer	≥200 vs ≤0 g/day	0.80 (0.40-1.30)		
					Incidence, rectal cancer	≥200 vs ≤0 g/day	0.80 (0.40-1.70)		
Park, 2007 COL40668 USA	MEC, Prospective Cohort, Age: 45-75 years, M/W	1 138/ 191 011 7.3 years	Cancer registry	FFQ-quantitative	Incidence, colorectal cancer, men	≥122 vs ≤10.9 g1000 kcal/day	0.78 (0.63-0.96)	Age, BMI, energy intake, ethnicity, family history of colorectal cancer, fibre intake, history of polyps,	Midpoints, distribution of cases and person-years
					Incidence, colorectal cancer, women	≥122 vs ≤10.9 g1000 kcal/day	0.85 (0.68-1.06)		

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI)	Adjustment factors	Missing data derived for analysis
					Incidence, colorectal cancer, excluding men using calcium supplements	≥122 vs ≤10.9 g1000 kcal/day	0.81 (0.62-1.05)	multivitamin, nsaid use, physical activity, smoking, pack-years, time	
					Incidence, colorectal cancer, excluding women using calcium supplements	≥122 vs ≤10.9 g1000 kcal/day	0.67 (0.49-0.91)		
Larsson, 2006 COL40624 Sweden	COSM, Prospective Cohort, Age: 45-79 years, M	449/ 45 306 6.7 years	Cancer registry	FFQ	Incidence, colorectal cancer	≥1.5 vs ≤1.9 glasses/week	0.67 (0.51-0.87)	Age, alcohol intake, aspirin use, educational level, family history of colorectal cancer, fruits, history of diabetes, multivitamin supplement intake, physical activity, red meat intake, saturated fat, smoking status, total energy intake, vegetable intake, vitamin d	Midpoints, distribution of cases and person-years, conversion from serv/d to g/d
					Incidence, colorectal cancer	≥1.1 vs ≤0 servings/day	1.07 (0.86-1.34)		
					Incidence, colon cancer	≥1.5 vs ≤1.9 glasses/week	0.65 (0.46-0.91)		
					Incidence, colon cancer	≥1.1 vs ≤0 servings/day	1.17 (0.88-1.56)		
					Incidence, distal colon cancer	≥1.5 vs ≤1.9 glasses/week	0.53 (0.33-0.87)		
					Incidence, distal colon cancer	≥1.1 vs ≤0 servings/day	1.26 (0.84-1.91)		

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI)	Adjustment factors	Missing data derived for analysis
					Incidence, proximal colon cancer	≥1.5 vs ≤1.9 glasses/week	0.76 (0.45-1.30)		
					Incidence, proximal colon cancer	≥1.1 vs ≤0 servings/day	1.10 (0.72-1.69)		
					Incidence, rectal cancer	≥1.5 vs ≤1.9 glasses/week	0.69 (0.45-1.06)		
					Incidence, rectal cancer	≥1.1 vs ≤0 servings/day	0.94 (0.66-1.33)		
Lin, 2005 COL01690 USA	WHS, Prospective Cohort, Age: 45- years, W, professionals	223/ 36 976 10 years	SEER	FFQ	Incidence, colorectal cancer,	≥1 vs ≤0.1 serving/day	1.12 (0.72-1.74)	Age, alcohol consumption, BMI, energy intake, family history of specific cancer, history of previous polyp and prior endoscopy, menopausal status, multivitamin, physical activity, postmenopausal hormone use, randomized treatment assignment, red meat intake, saturated fat, smoking status	Midpoints, conversion from serv/d to g/d, distribution of person-years
Sanjoaquin, 2004	OVS, Prospective	93/ 10 998	Population/invitation	FFQ	Incidence, colorectal	≥0.5 vs ≤0.5 pints/day	1.10 (0.65-1.87)	Age, sex, alcohol consumption,	Midpoints, distribution of

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI)	Adjustment factors	Missing data derived for analysis
COL01182 UK	Cohort, Age: 18-89 years, M/W	17 years			cancer,			smoking habits	person-years, conversion from pints/d to g/d
McCullough, 2003 COL00366 USA	CPS II, Prospective Cohort, Age: 50-74 years, M/W, subgroup of CPS-II cohort	683/ 127 749 5 years	Cancer registry and death certificates and medical records	FFQ	Incidence, colorectal cancer,	≥1.1 vs ≤0 serving/day	0.96 (0.78-1.18)	Age, sex, BMI, educational level, energy intake, family history of specific cancer, fruits, HRT use, multivitamin, physical activity, saturated fat, smoking habits, total vegetables	Midpoints, conversion from serv/wk to g/d, distribution of person-years
					Incidence, colorectal cancer, men	≥1.1 vs ≤0 serving/day	0.86 (0.66-1.11)		
					Incidence, colon cancer, men	≥1.1 vs ≤0 serving/day	0.81 (0.60-1.10)		
					Incidence, colorectal cancer, women	≥1.1 vs ≤0 serving/day	1.18 (0.84-1.65)		
					Incidence, proximal colon cancer, men	≥1.1 vs ≤0 serving/day	0.68 (0.42-1.09)		
					Incidence, rectal cancer, men	≥1.1 vs ≤0 serving/day	0.89 (0.54-1.47)		
					Incidence, distal colon cancer, men	≥1.1 vs ≤0 serving/day	0.92 (0.54-1.58)		
Jarvinen, 2001 COL00314 Finland	Finnish Mobile Clinic Health Examination	72/ 9 959 19.6 years	Population	Questionnaire	Incidence, colorectal cancer,	Q 4 vs Q 1	0.72 (0.33-1.57)	Age, sex, area of residence, BMI, energy intake,	Midpoints, distribution of person-years

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI)	Adjustment factors	Missing data derived for analysis
	Survey, Prospective Cohort, Age: 39 years, M/W				Incidence, colon cancer,	Q 4 vs Q 1	0.46 (0.14-1.46)	occupational group, smoking habits	
					Incidence, rectal cancer,	Q 4 vs Q 1	1.13 (0.39-3.31)		
Gaard, 1996 CRC00008 Norway	norwegian national health screening service study, Prospective Cohort, Age: 20-53 years, M/W	84/ 50 535 11.4 years	Enrollment by volunteers	FFQ	Incidence, colon cancer, men	≥4 vs ≤1 glasses/day	0.72 (0.25-2.07)	Age, attained age	Midpoints, conversion of glasses/d to g/d
					Incidence, colon cancer, women	≥4 vs ≤1 glasses/day	1.24 (0.35-4.40)		
Kearney, 1996 COL00156 USA	HPFS, Prospective Cohort, Age: 40-75 years, M, Health professionals	203/ 47 935 6 years	Responding to mail survey	Semi-quantitative FFQ	Incidence, colon cancer,	≥1 vs 0-1 times/month	0.87 (0.52-1.44)	Age, alcohol consumption, aspirin use, BMI, dietary fiber, family history of colon cancer, past history of smoking, physical activity, previous polyps, red meat intake, saturated fat, screening, total calories	Conversion from frequency to g/d

Table 115 Total milk intake and colorectal cancer risk. Main characteristics of studies excluded from the CUP SLR dose-response meta-analysis

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI)	Adjustment factors	Inclusion/ exclusion
Iso, 2007 COL40707 Japan	JACC, Prospective Cohort, Age: 40-79 years, M/W	193/ 105 500 15 years	Municipal resident registration records, death certificates	FFQ	Mortality, colon cancer, women	≥5 vs ≤2 /week	1.00 (0.69-1.43)	Age, centre location	Mortality as outcome
					Mortality, colon cancer, men	≥5 vs ≤2 /week	1.17 (0.82-1.66)		
					Mortality, rectal cancer, men	≥5 vs ≤2 /week	1.16 (0.79-1.71)		
					Mortality, rectal cancer, women	≥5 vs ≤2 /week	1.13 (0.64-1.97)		
van der Pols JC, 2007 COL40680 UK	BOCS, Historical Cohort, Age: 8 years, M/W	76/ 4 374 57 years	National health records	7-day food records	Incidence, colorectal cancer	≥282 vs ≤117.9 ml/day	2.45 (1.11-5.41)	Age, sex, energy intake, fruit intake	Household dietary intake
Kesse, 2005 POL16753 France	EPIC-E3N, Prospective Cohort, Age: 40-65 years, W, part of nat. health insurance	516/ 5 320 3.7 years	National health Insurance scheme	Questionnaire	Adenoma Incidence, colorectal adenoma, women	≥211 vs ≤0 g/day	0.93 (0.73-1.19)	Alcohol consumption, BMI, educational level, family history of specific cancer, physical activity, smoking status, total energy	Duplicate, overlap with Murphy, 2013 COL41070
					Adenoma Incidence, high-risk colorectal	≥211 vs ≤0 g/day	0.80 (0.51-1.23)		

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI)	Adjustment factors	Inclusion/ exclusion
	scheme for teachers				adenomas (>1cm), women				
					Incidence, colorectal cancer, women	≥210 vs ≤0 g/day	0.54 (0.33-0.89)		
Khan, 2004 COL01606 Japan	HCS, Prospective Cohort, Age: 40-97 years, M/W	15/ 3 458 14.3 years	Area residency lists	Questionnaire	Mortality, colorectal cancer, men	Q 2 vs Q 1	0.70 (0.30-2.00)	Age, smoking habits	Mortality as outcome
					Mortality, colorectal cancer, women	Q 2 vs Q 1	0.50 (0.20-1.30)		
Kojima, 2004 COL01840 Japan	JACC, Prospective Cohort, Age: 40-79 years, M/W	132/ 107 824 10 years	Resident registry and death certificates	Questionnaire	Mortality, colon cancer, women	5-7 vs 0-0.4 times/week	1.16 (0.71-1.90)	Age, alcohol consumption, BMI, educational level, family history of specific cancer, physical activity, region of enrollment, smoking status	Mortality as outcome
					Mortality, colon cancer, men	5-7 vs 0-0.4 times/week	1.22 (0.74-2.02)		
					Mortality, rectal cancer, men	5-7 vs 0-0.4 times/week	1.05 (0.64-1.71)		
					Mortality, rectal cancer, women	5-7 vs 0-0.4 times/week	1.64 (0.70-3.82)		
Wu, 2002	NHS,		Nurses	FFQ	Incidence,	≥1.1 vs ≤0.5	0.93 (0.76-1.15)	Age, alcohol	<3 categories

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI)	Adjustment factors	Inclusion/ exclusion
COL00587 USA	Prospective Cohort, Age: 30-55 years, W	87 998 16 years	registry		colon cancer,	serving/day		consumption, aspirin use, BMI, family history of specific cancer, HRT use, menopausal status, physical activity, red meat intake, smoking habits	
Wu, 2002 COL00587 USA	HPFS, Prospective Cohort, Age: 40-75 years, M, Health professionals	47 344 10 years	Mailing to health professionals	FFQ	Incidence, colon cancer,	≥1.1 vs ≤0.5 serving/day	0.58 (0.27-1.17)	Age, alcohol consumption, aspirin use, BMI, family history of specific cancer, physical activity, red meat intake, smoking habits	<3 categories
Martinez, 1996 COL00131 USA	NHS, Prospective Cohort, Age: 30-55 years, W, Registred nurses	89 448 1 012 280 person-years	Nurses registry	Semi-quantitative FFQ	Incidence, colorectal cancer,	≥2 vs ≤1 serving/month	0.88 (0.65-1.19)	Age, alcohol consumption, aspirin use, BMI, family history of specific cancer, physical activity, red-meat intake, smoking habits	<3 categories
Kampman, 1994 COL00155 Netherlands	NLCS, Case Cohort, Age: 55-69 years, M/W	326/ 120 852 3.3 years	Population registries	Semi-quantitative FFQ	Incidence, colorectal cancer,	≥240 vs ≤0 g/day	0.86 (0.57-1.29)	Age, sex, BMI, energy intake, energy-adjusted intake of dietary fiber, energy-adjusted intake of fat, family history of specific cancer, history of gallbladder surgery	Duplicate, overlap with Simons

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI)	Adjustment factors	Inclusion/ exclusion
Ursin, 1990 COL41068 Norway	Combined Norwegian Cohorts, Prospective Cohort, Age: 35-75 years	92/ 15 914 11.5 years	Cancer registry	Questionnaire (general)	Mortality, colon cancer	≥2 vs 0.1-0.9 glasses/day	0.85	Age, sex, area of residence	No CIs, <3 categories
					Mortality, rectum	≥2 vs 0.1-0.9 glasses/day	0.85		
Hirayama, 1990 COL01508 Japan	Japan 6 prefectures cohort study, Prospective Cohort, Age: 40- years, M/W	563/ 265 118 17 years	Health centres	Interview	Mortality, colon cancer,	daily consumption vs no daily consumption	1.08 (0.19-1.28)	Age, sex	Mortality as outcome
					Mortality, rectal cancer,	daily consumption vs no daily consumption	1.02 (0.86-1.21)		
Hirayama, 1989 COL01024 Japan	Japan 6 prefectures cohort study, Prospective Cohort, Age: 40- years, M/W	91/ 265 118 17 years	Population	Quatitative FFQ	Mortality, sigmoid cancer,	daily/ occasional drinkers vs infrequent/ nondrinkers	2.20 (1.22-3.95)	Age, alcohol consumption	Mortality as outcome
					Mortality, proximal colon cancer,	daily/occasional vs infrequent/never	1.04 (0.83-1.32)		
					Mortality, sigmoid cancer, alcohol consumption : daily &	daily/ occasional drinkers vs infrequent/ nondrinkers	2.21 (1.16-4.21)		

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI)	Adjustment factors	Inclusion/ exclusion
					occasional				
					Mortality, sigmoid cancer, alcohol consumption : Infrequent & non drinkers	daily/ occasional drinkers vs infrequent/ nondrinkers	2.11 (0.50-8.87)		
Phillips, 1985 COL00719 USA	AHS, Prospective Cohort, Age: 30- years, M/W, Seventh-day Adventists	179/ 25 493 21 years		Quatitative FFQ	Mortality, colorectal cancer	≥3 vs ≤1 glasses/day	0.70 (0.40-1.20)	Age, sex	Mortality as outcome
					Mortality, colon cancer, women	≥3 vs ≤1 glasses/day	1.10 (0.50-2.20)		
					Mortality, colon cancer, men	≥3 vs ≤1 glasses/day	0.50 (0.20-1.10)		
					Mortality, rectal cancer,	≥1 vs ≤1 glasses/day	1.20 (0.60-2.70)		

Figure 199 RR estimates of colorectal cancer by levels of total milk intake

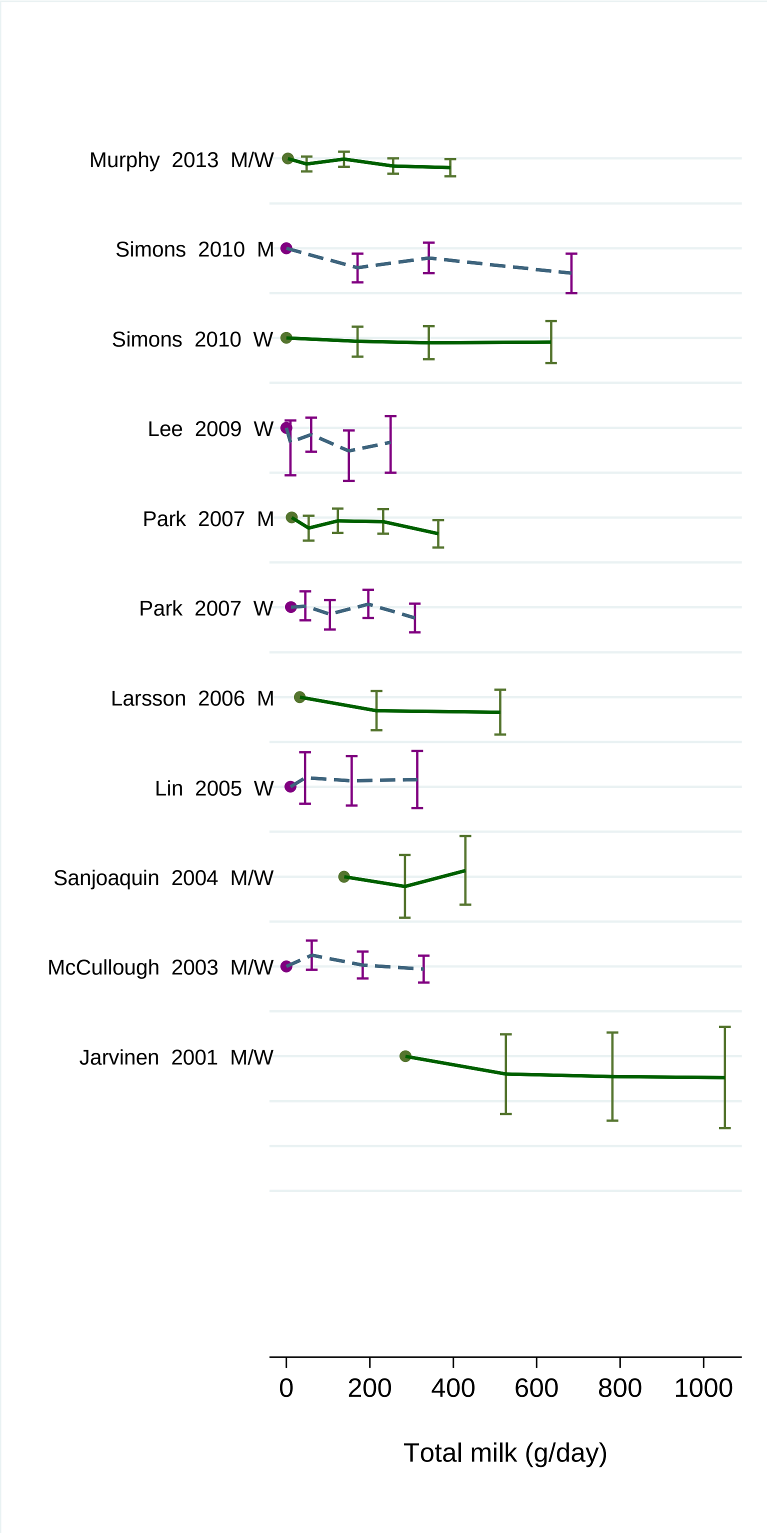


Figure 200 Relative risk of colorectal cancer for the highest compared with the lowest level of total milk intake

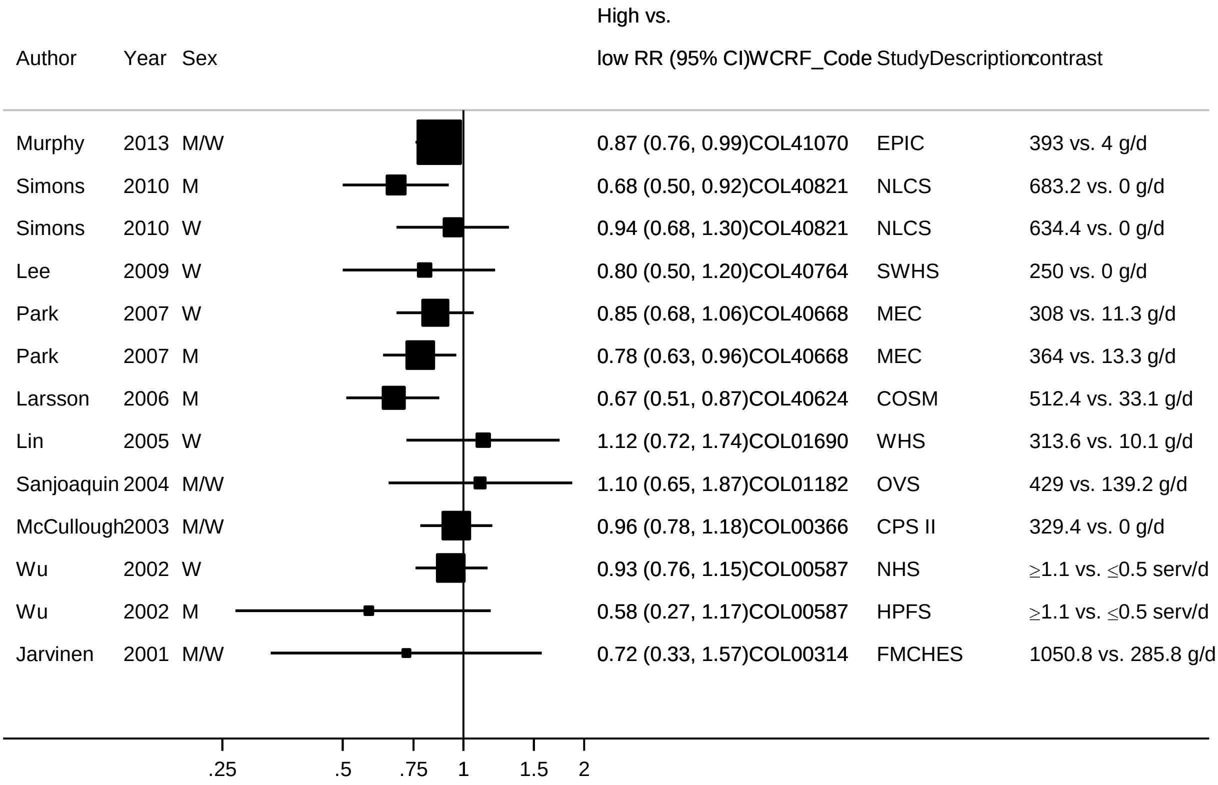
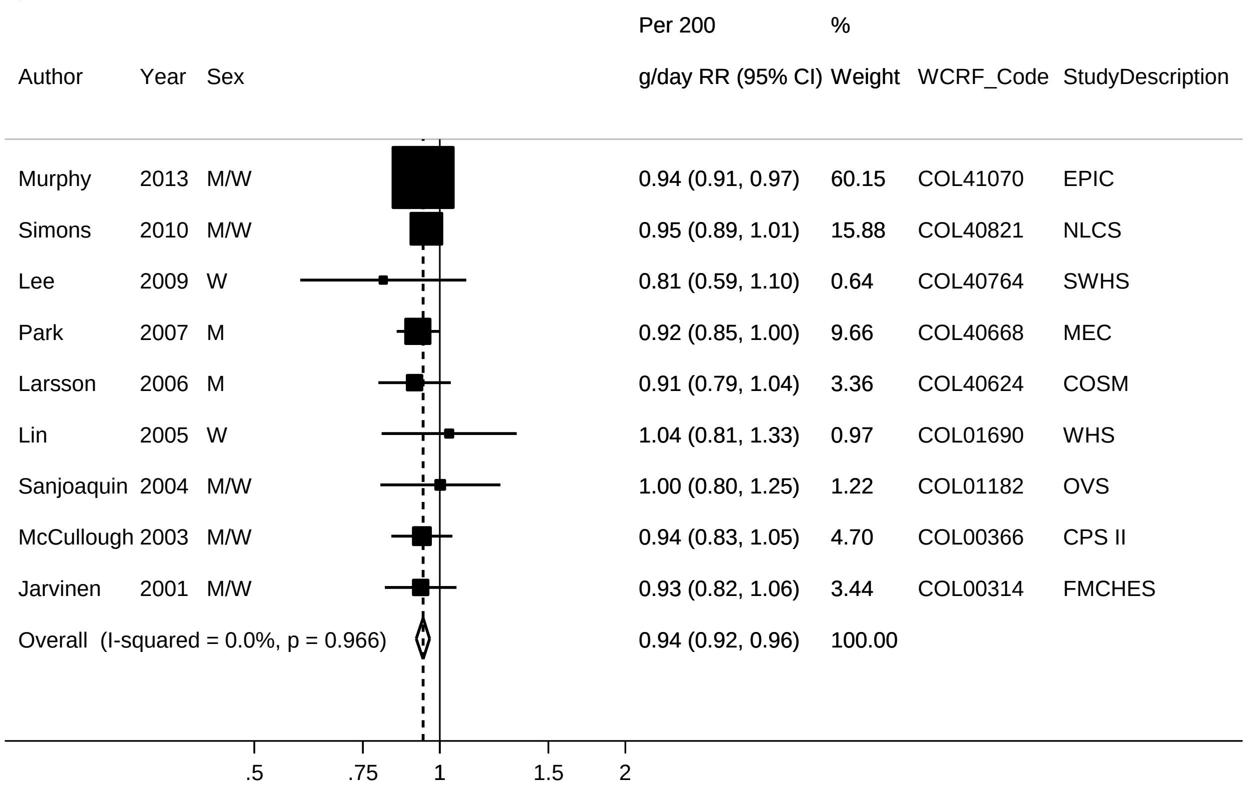


Figure 201 Relative risk of colorectal cancer for 200 g/day increase in total milk intake



Note: The Pooling Project of Prospective studies on Diet and Cancer (Cho, 2002) (10 cohort studies, 4992 colorectal cancer cases) reported a pooled RR for 500 g/day increase of milk intake of 0.88 (95% CI 0.82-0.95)
[0.95 (0.92-0.97) if rescaled to 200 g/day increase].
From the 10 cohorts, not included in the 2015 CUP SLR are: AHS, ATBC, CNBSS, IWHS, NYS, NYUWHS, SMC, NHS, HPFS (3895 cases).
When the Pooling Project is included in the meta-analysis and the NLCS (Simons, 2010) is excluded because it already included in the Pooling Project, the results remained the same.
(RR for 200 g/day: 0.94; 95% CI: 0.93-0.96, I^2:0% p=0.94, Egger test: 0.51. Total number of cohorts: 18, total number of colorectal cancer cases: 13 373)

Figure 202 Relative risk of colorectal cancer for 200 g/day increase in total milk intake, stratified by sex

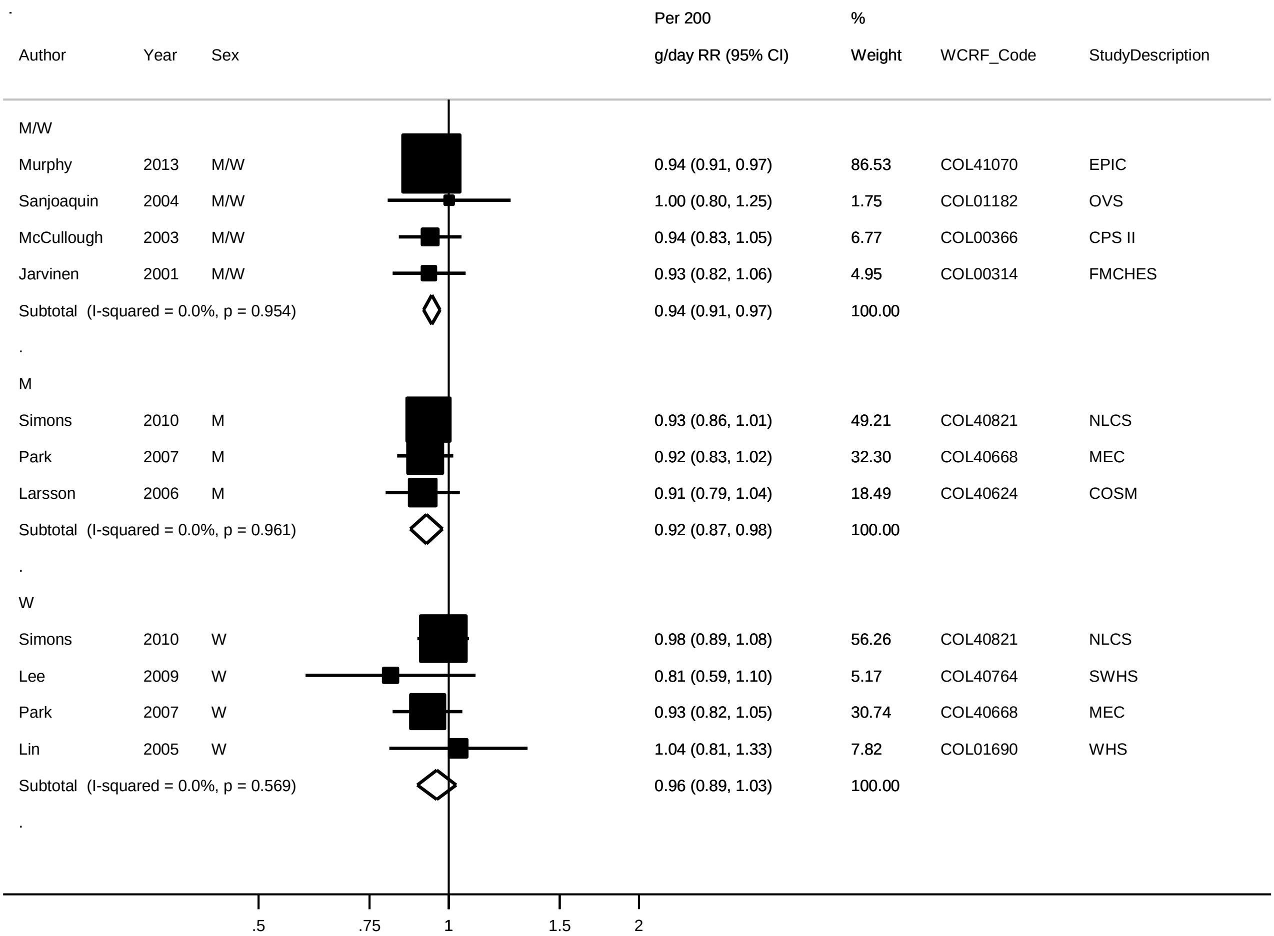


Figure 203 Relative risk of colorectal cancer for 200 g/day increase in total milk intake, stratified by geographic location

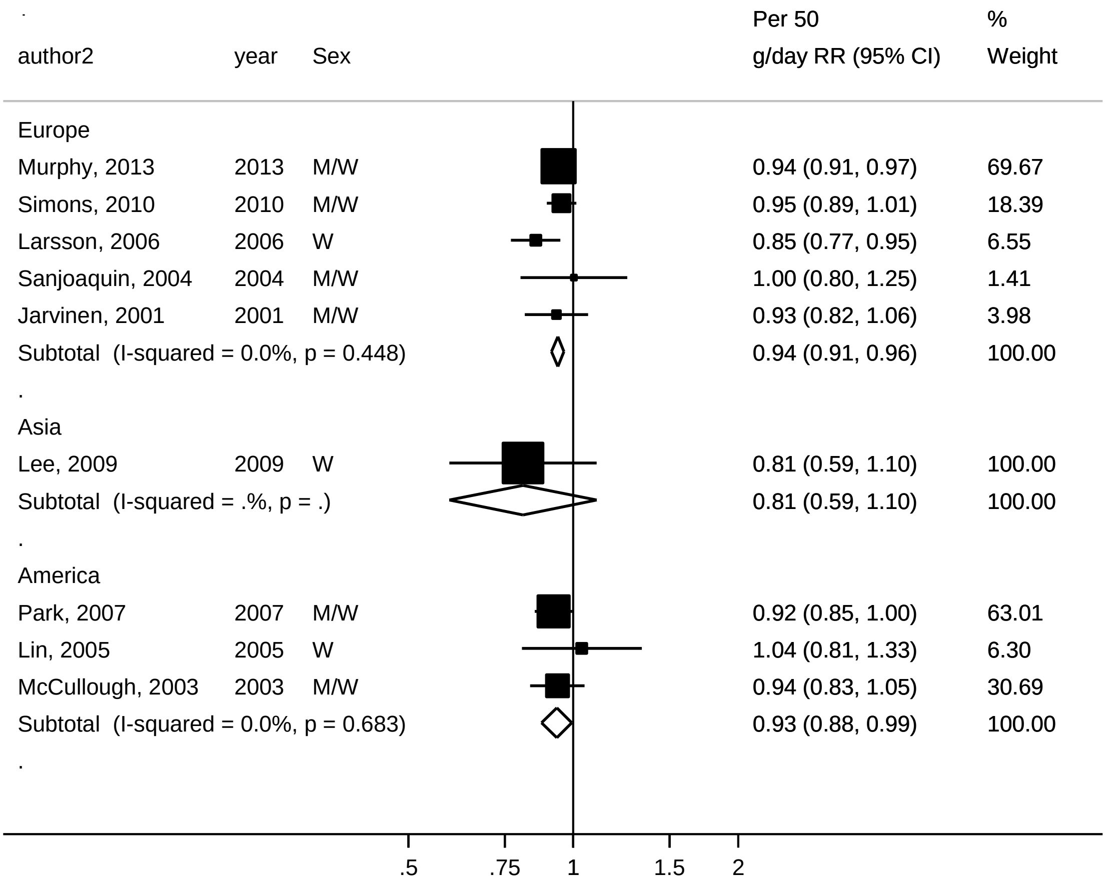
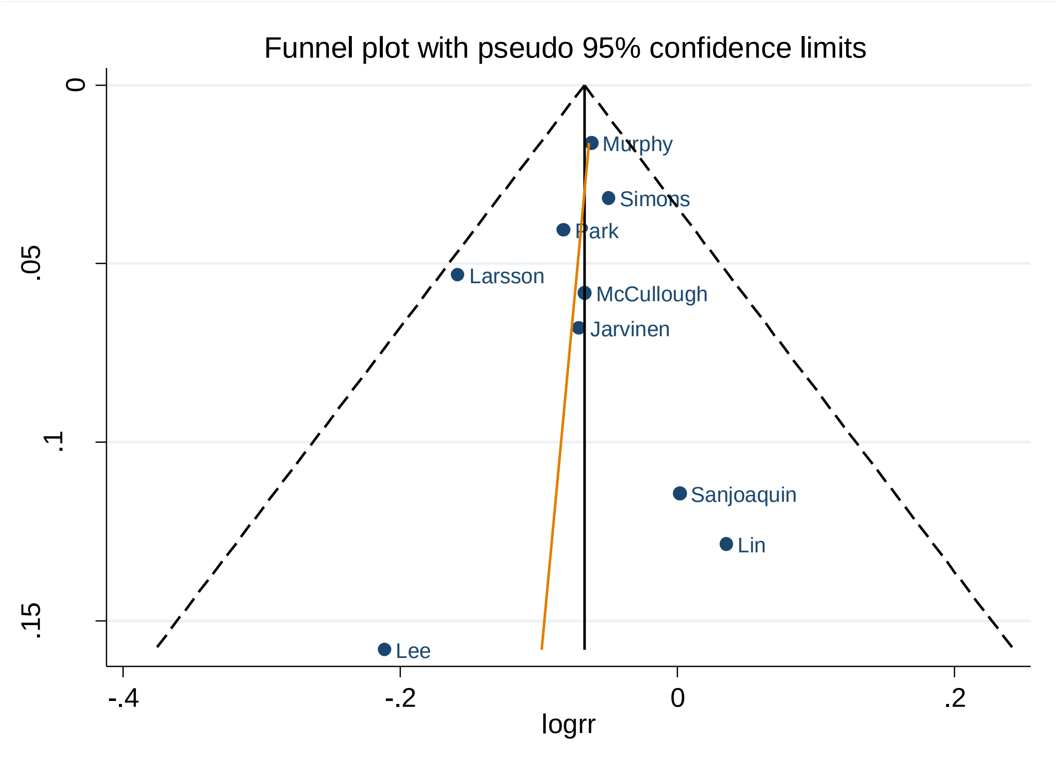
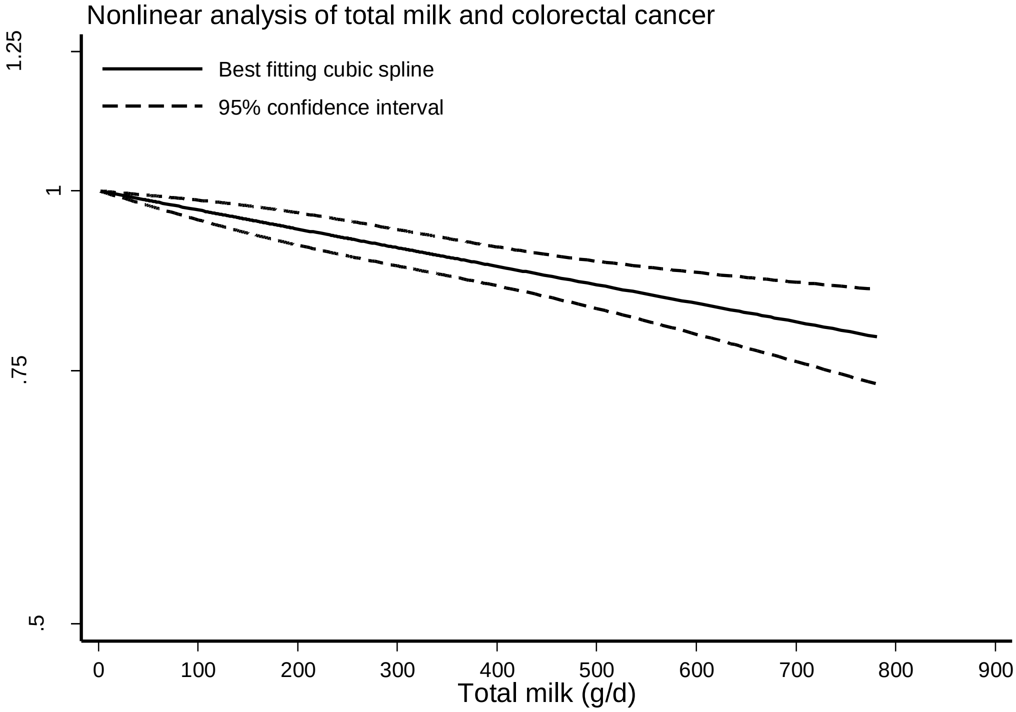


Figure 204 Funnel plot of studies included in the dose response meta-analysis of total milk intake and colorectal cancer



p Egger't test=0.63

Figure 205 Total milk and colorectal cancer, nonlinear dose-response analysis



p for non-linearity=0.95

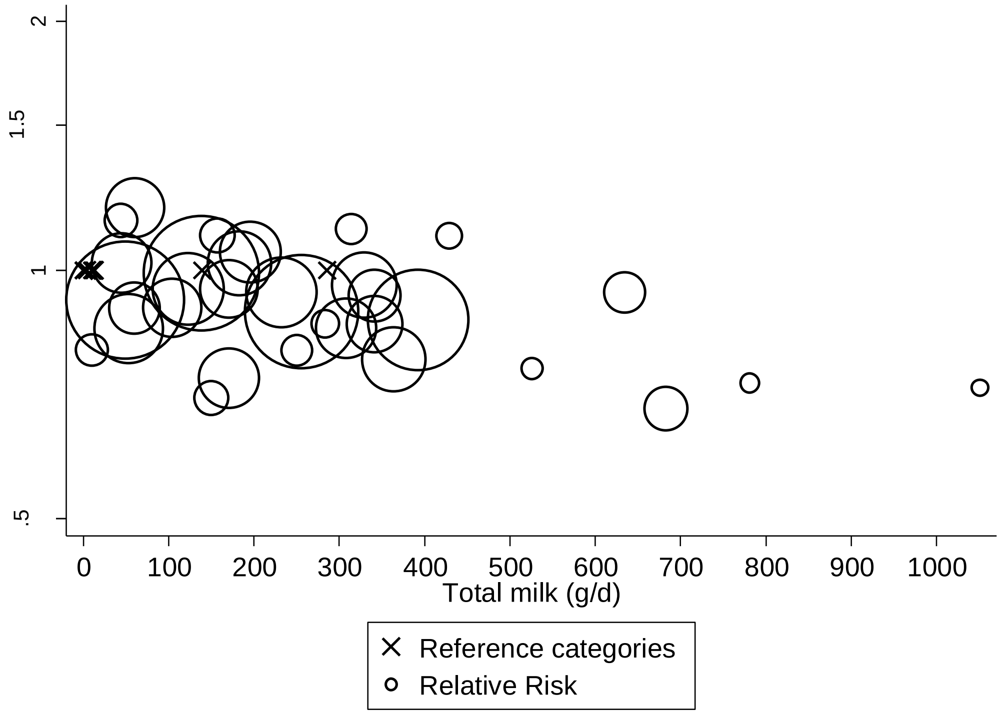


Table 116 Relative risk of colorectal cancer and total milk intake estimated using non-linear models

Total milk (g/day)	RR (95%CI)
0	1.00
100	0.97 (0.95-0.99)
200	0.94 (0.92-0.97)
300	0.91 (0.89-0.94)
400	0.89 (0.86-0.91)
500	0.86 (0.83-0.89)
600	0.84 (0.79-0.88)
700	0.81 (0.76-0.86)
800	0.79 (0.73-0.85)
900	0.76 (0.70-0.84)
1000	0.74 (0.66-0.83)

Figure 206 RR estimates of colon cancer by levels of total milk intake

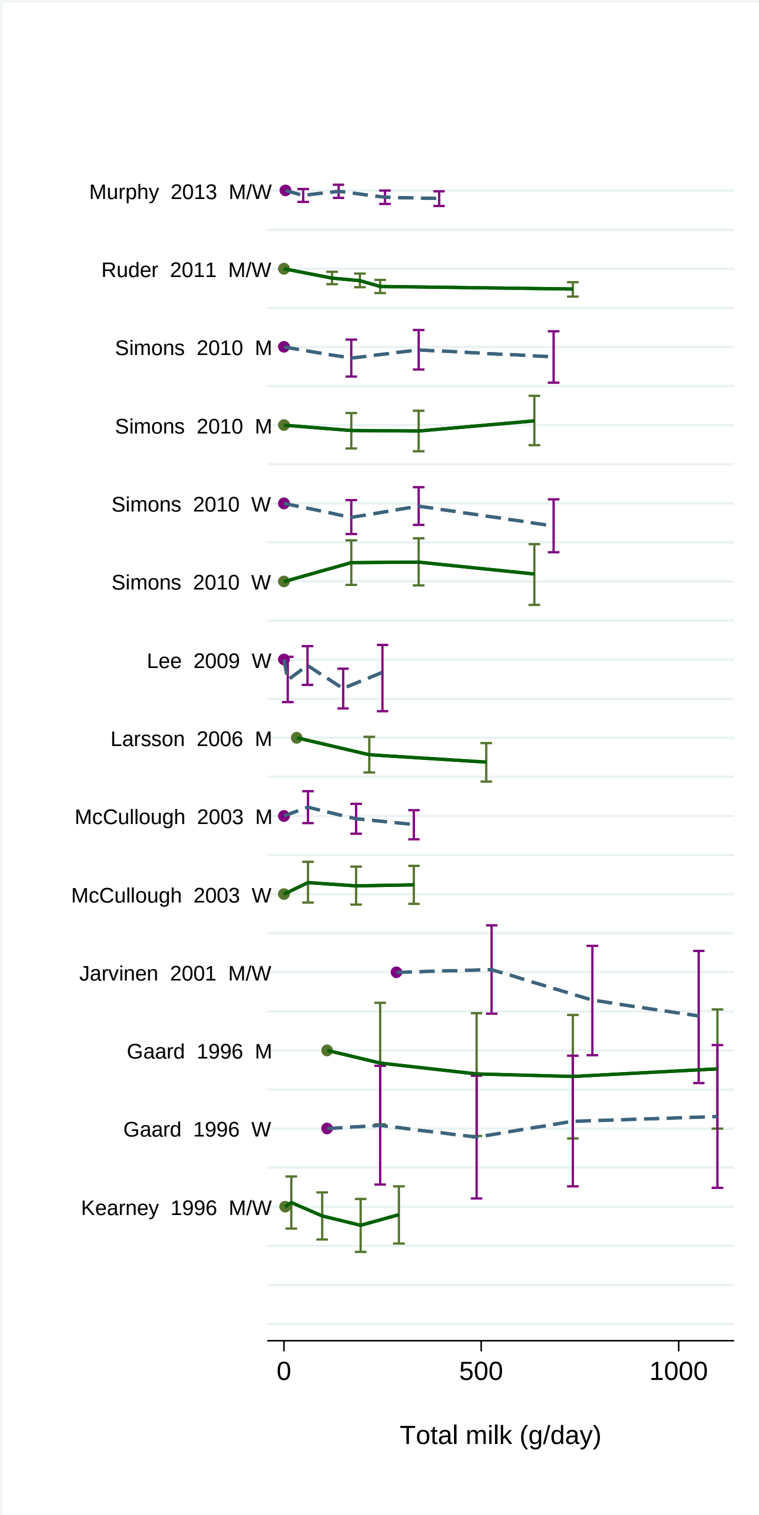


Figure 207 Relative risk of colon cancer for the highest compared with the lowest level of total milk intake

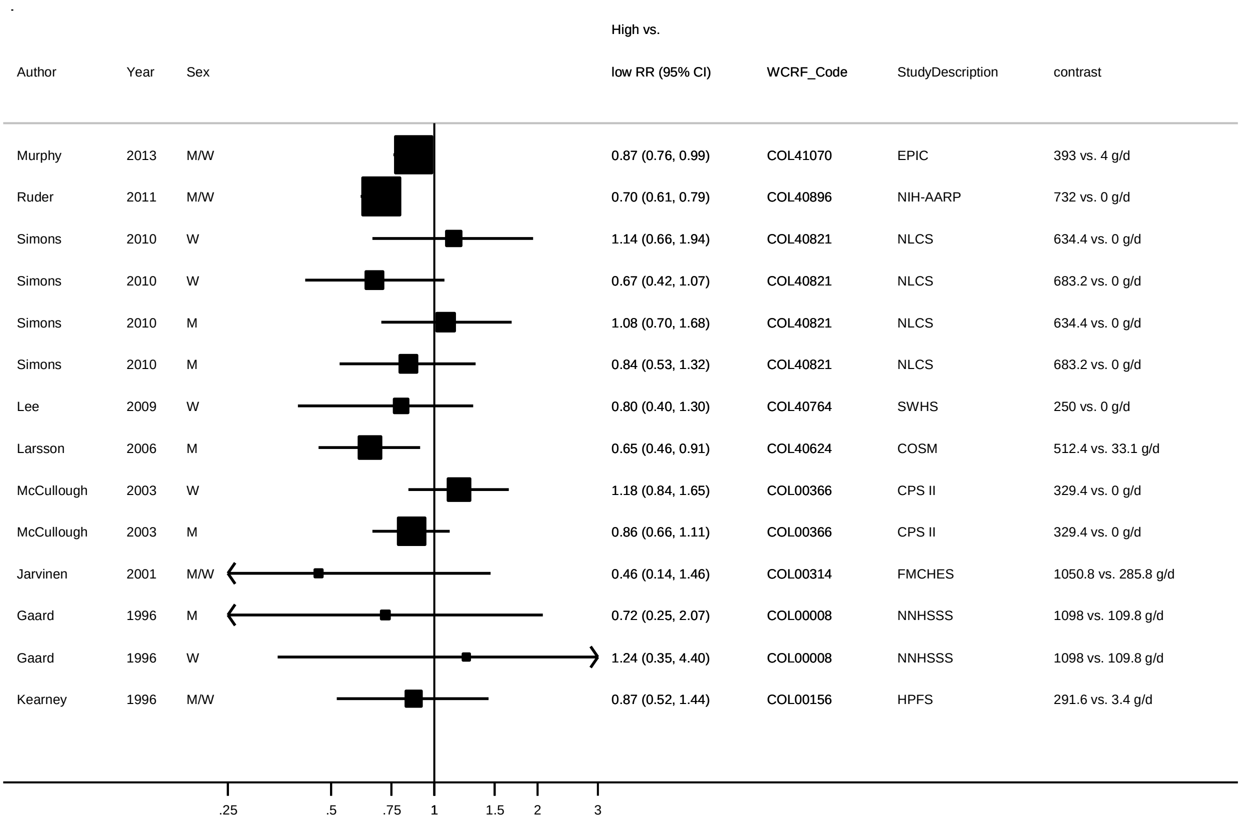
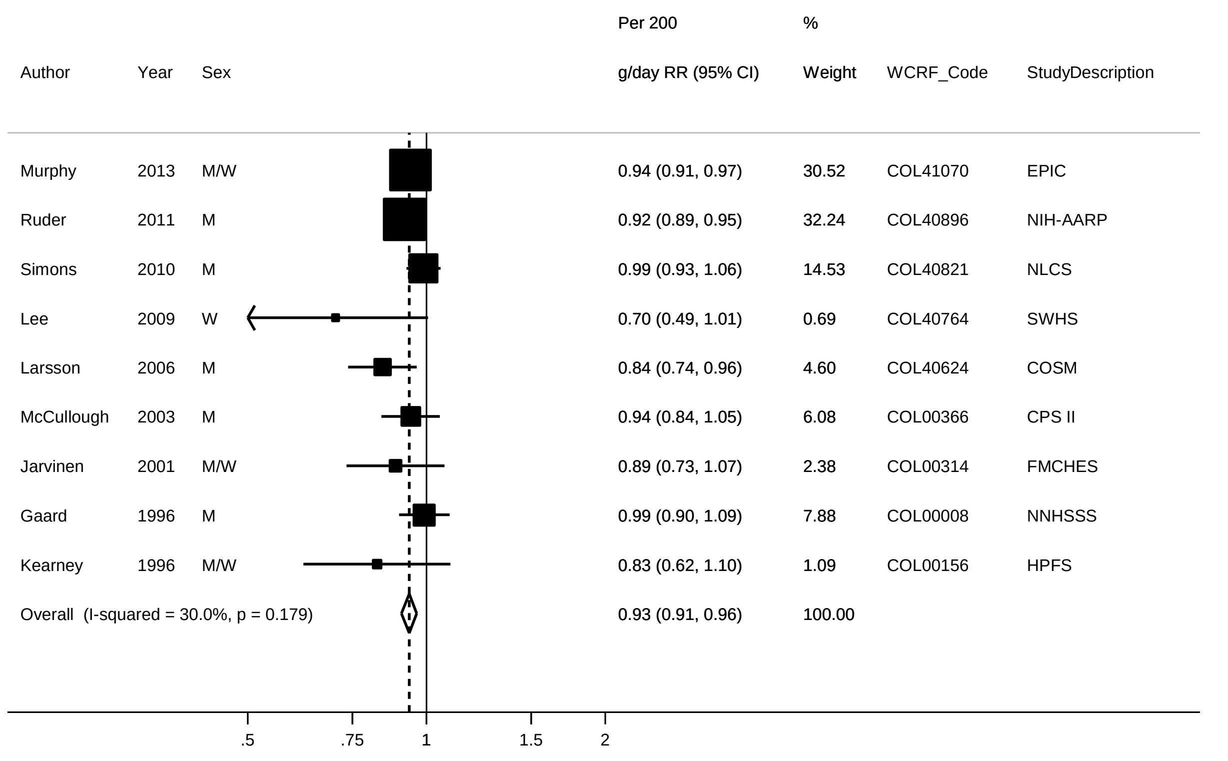


Figure 208 Relative risk of colon cancer for 200 g/day increase in total milk intake



Note: In the Pooling Project (Cho, 2004), the association with milk intake was limited to cancers of distal colon (p=0.03). For the highest compared to the lowest category of intake, the RR were 0.99 (95% CI 0.85-1.15) ptrend=0.56 for proximal colon and 0.73 (0.62-0.87) ptrend<0.001 for distal colon. In other studies, the RR for the highest compared to the lowest intake were 0.84 (0.69– 1.02) for proximal and 0.78 (0.63– 0.96) for distal colon (EPIC, Murphy, 2013); 0.84 (0.53–1.32) ptrend=0.82 for proximal and 0.67 (0.42–1.07) ptrend= 0.41 for distal colon (NLCS, Simons, 2010); and 0.76 (0.45, 1.30) p=0.27 for proximal and 0.53 (0.33, 0.87) p<0.01 for distal colon (COSM, Larsson, 2006).

Figure 209 Relative risk of colon cancer for 200 g/day increase in total milk intake, stratified by sex

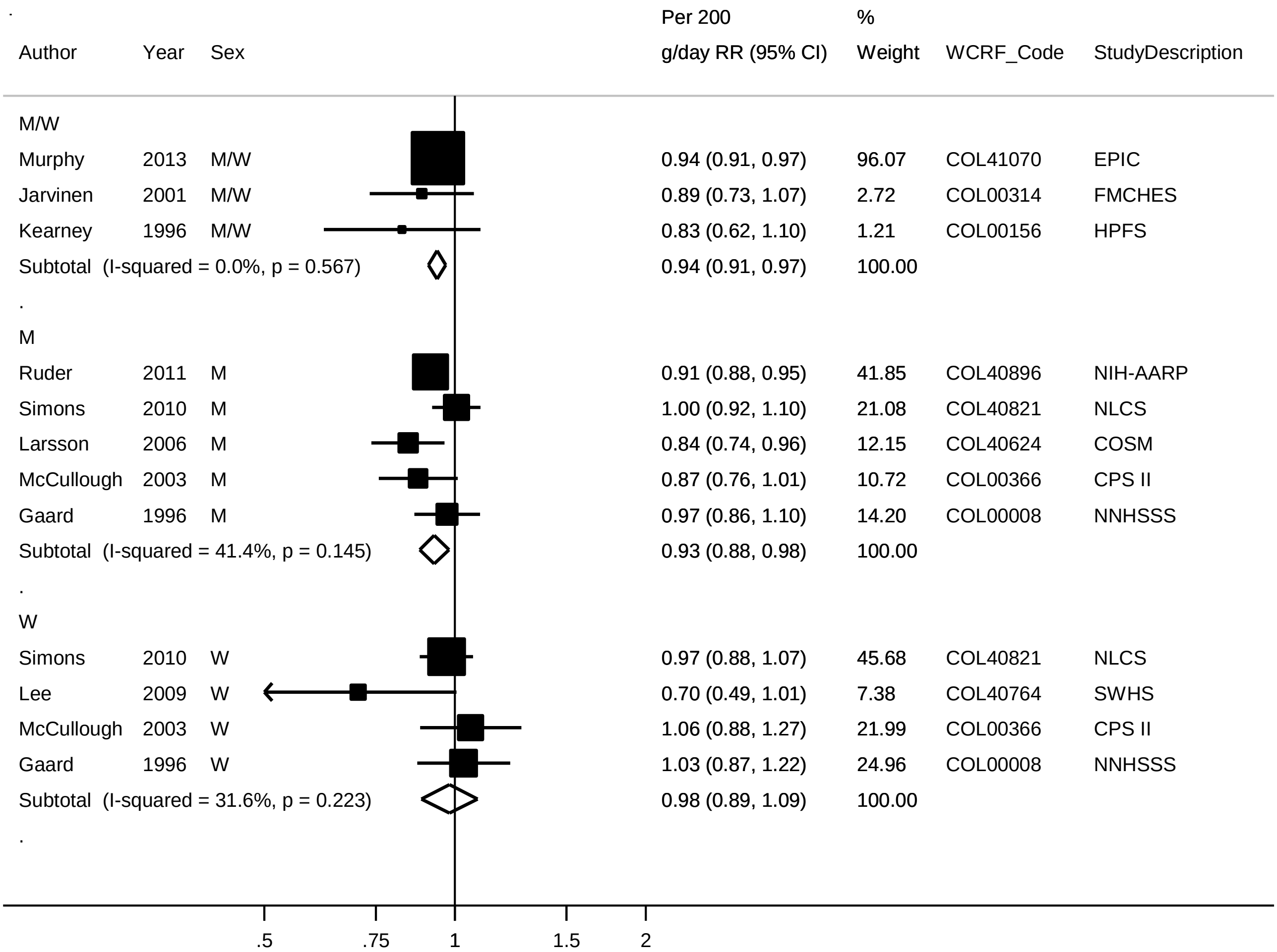
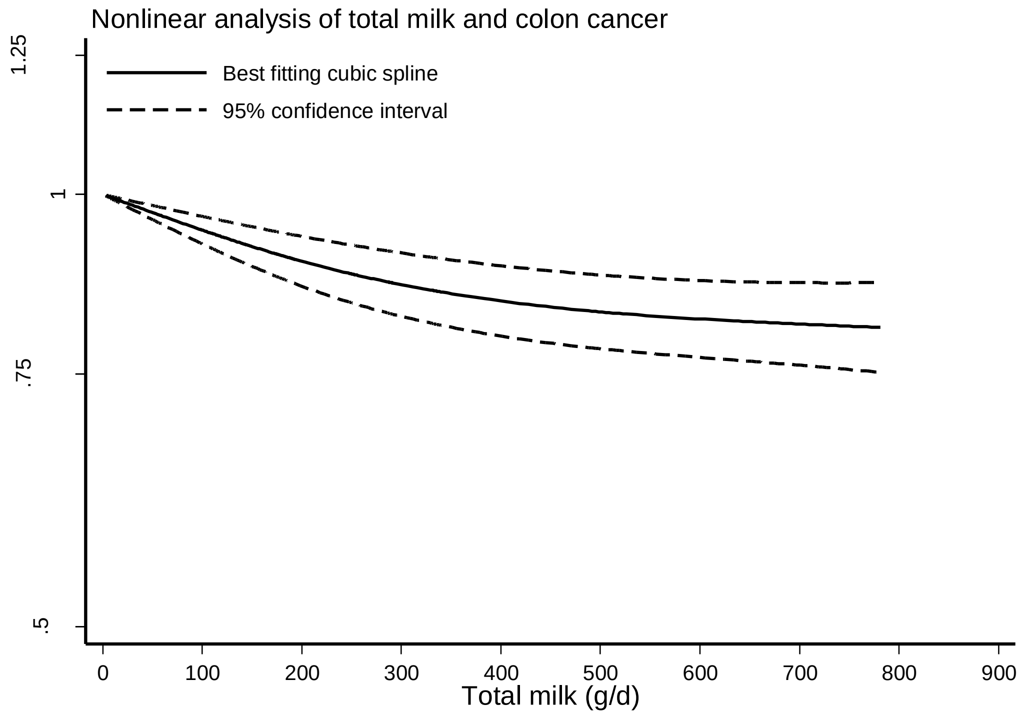


Figure 210 Total milk and colon cancer, nonlinear dose-response analysis



p for non linearity=0.002

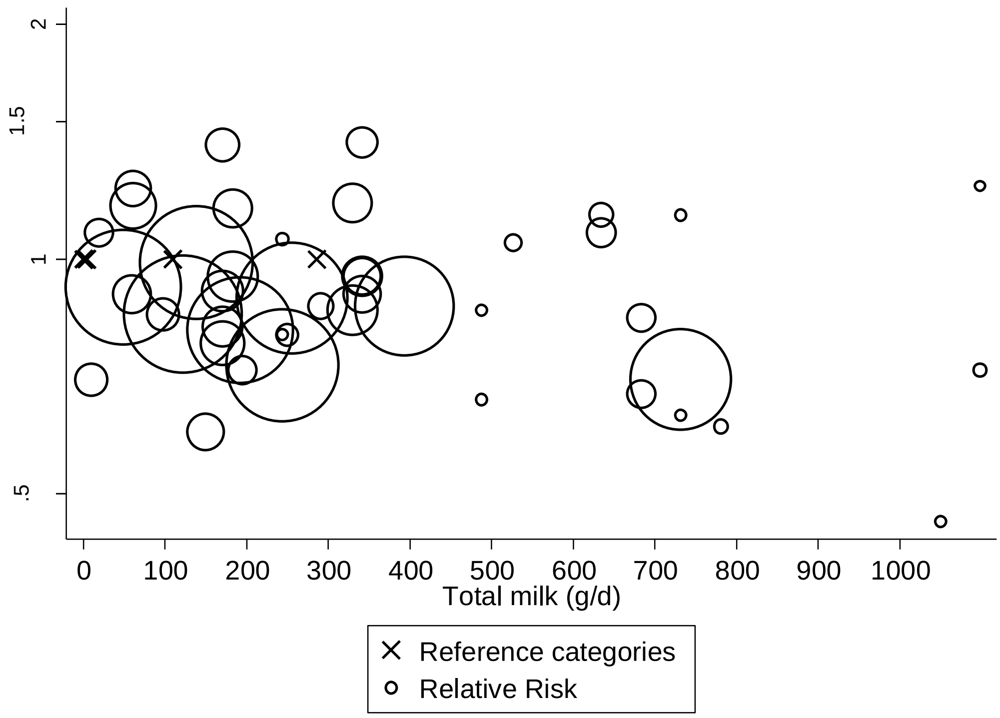


Table 117 Relative risk of colon cancer and total milk intake estimated using non-linear models

Total milk (g/day)	RR (95%CI)
0	1.00
100	0.94 (0.92-0.97)
200	0.90 (0.86-0.93)
300	0.87 (0.82-0.91)
400	0.84 (0.80-0.89)
500	0.83 (0.78-0.88)
600	0.82 (0.77-0.87)
700	0.81 (0.76-0.87)
800	0.81 (0.75-0.87)
900	0.80 (0.74-0.87)
1000	0.80 (0.72-0.87)

Figure 211 RR estimates of rectal cancer by levels of total milk intake

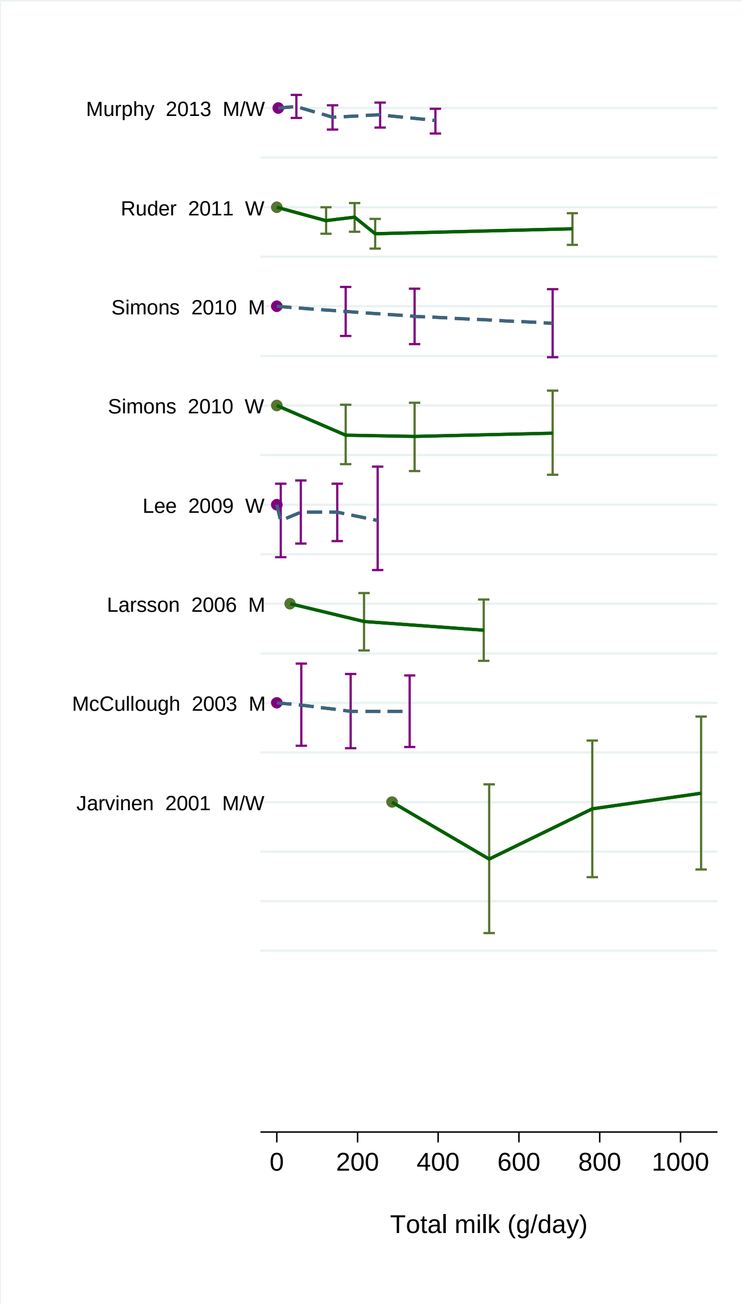


Figure 212 Relative risk of rectal cancer for the highest compared with the lowest level of total milk intake

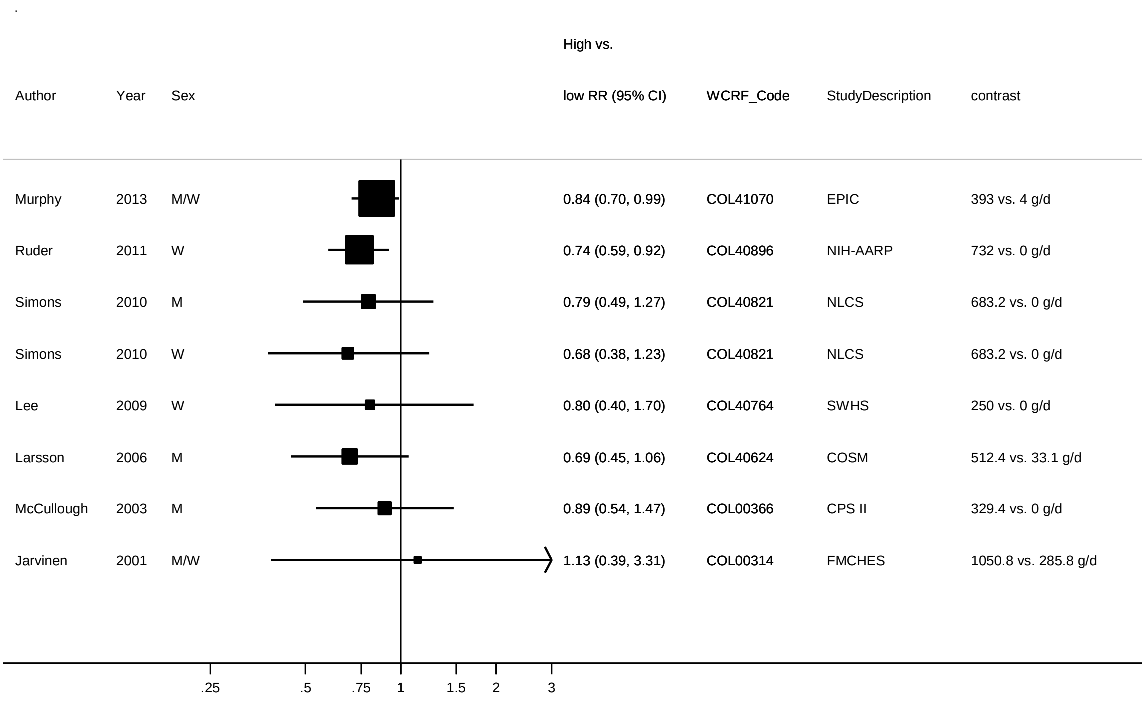


Figure 213 Relative risk of rectal cancer for 200 g/day increase in total milk intake

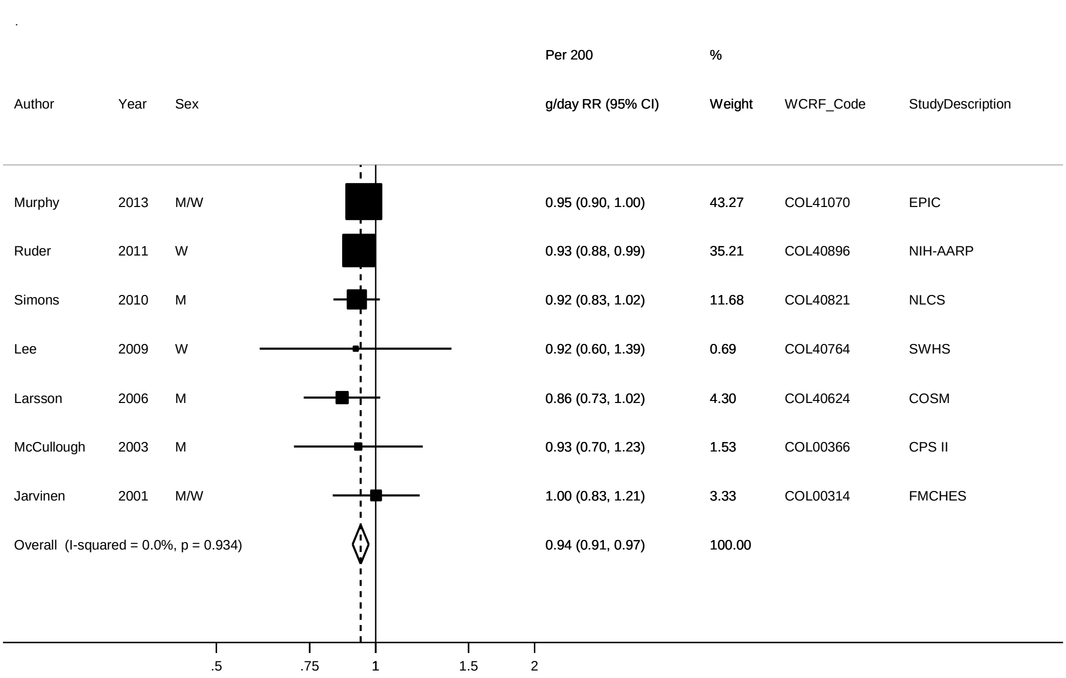


Figure 214 Relative risk of rectal cancer for 200 g/day increase in total milk intake, stratified by sex

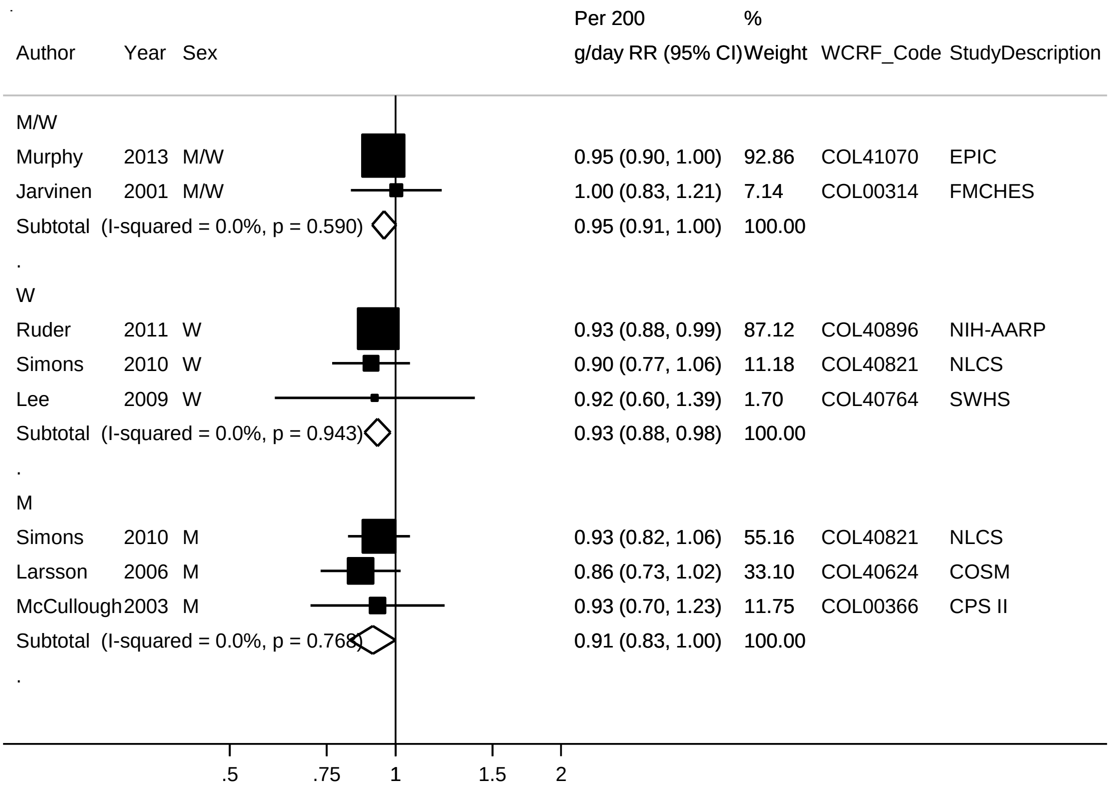
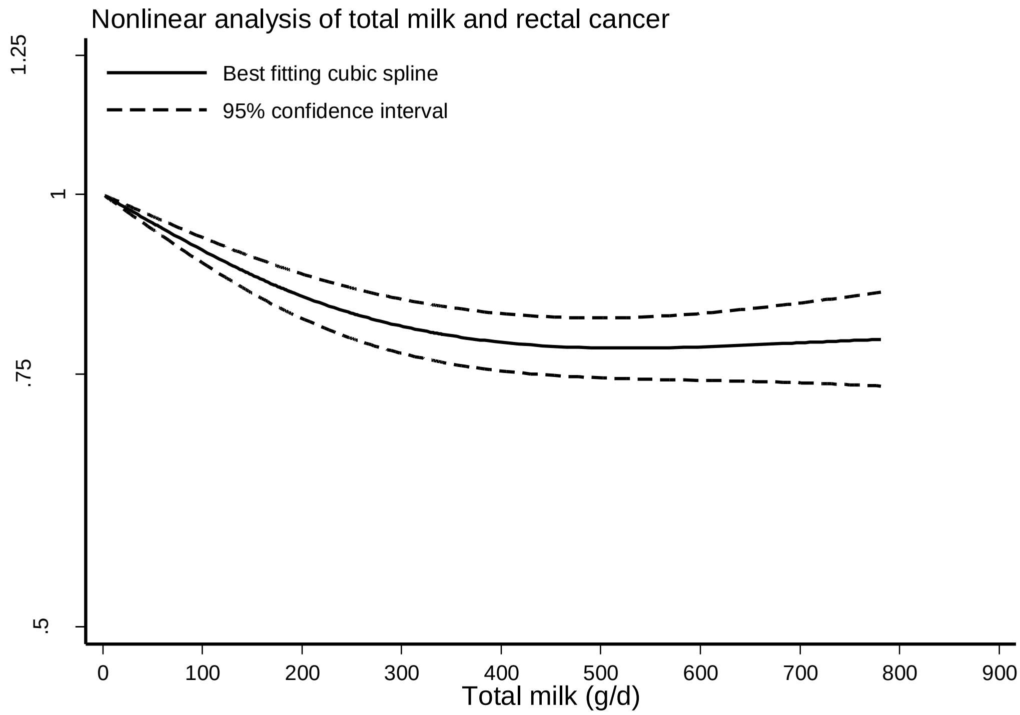


Figure 215 Total milk and rectal cancer, nonlinear dose-response analysis



p for non-linearity<0.0001

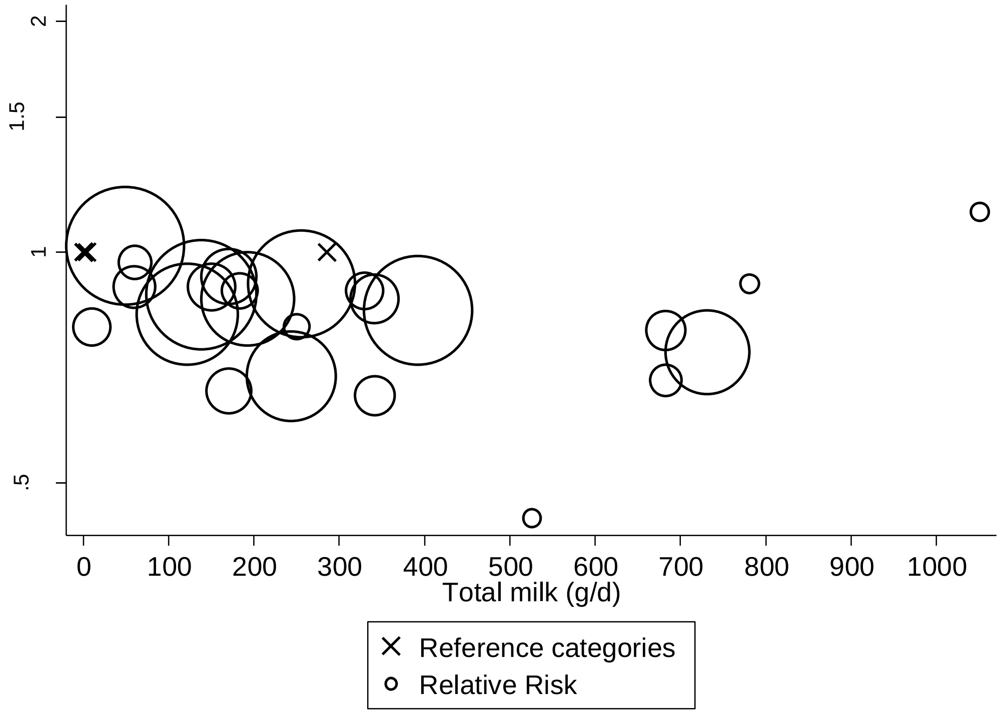


Table 118 Relative risk of rectal cancer and total milk intake estimated using non-linear models

Total milk (g/day)	RR (95%CI)
0	1.00
100	0.91 (0.90-0.93)
200	0.85 (0.82-0.88)
300	0.81 (0.78-0.85)
400	0.79 (0.75-0.83)
500	0.78 (0.75-0.82)
600	0.78 (0.74-0.83)
700	0.79 (0.74-0.84)
800	0.79 (0.73-0.86)
900	0.80 (0.73-0.88)
1000	0.81 (0.72-0.90)

2.7.2 Cheese

Cohort studies

Summary

Main results:
One new study (one publication) (Murphy, 2013) was published on cheese intake and colorectal cancer since the 2010 SLR. Seven studies investigated colorectal cancer, 6 investigated colon cancer and 4 investigated rectal cancer. Study characteristics and results for all cancer types are shown in the Table. For studies that reported cheese intake in servings per day we converted the intakes to grams per day by using a serving size of 43 grams (two slices).

Colorectal cancer
Seven studies (6462 cases) were included in the dose-response analysis. The summary RR for a 50 g/d increase in cheese intake was 0.94 (95% CI: 0.87-1.02) and there was little evidence of heterogeneity, I^2=9.5%, $p_{heterogeneity}$=0.36. There was no evidence of small study bias or publication bias with Egger's test, p=0.42. The summary RR ranged from 0.94 (95% CI: 0.85-1.03) when the Oxford Vegetarian Study (Sanjoaquin, 2004) was excluded to 0.97 (95% CI: 0.86-1.09) when the Cohort of Swedish Men (Larsson, 2006) was excluded.

Although the test for nonlinearity was significant, $p_{nonlinearity}$=0.047, the association between cheese and colorectal cancer was not significant.

Colon cancer

Six studies (3958 cases) were included in the dose-response meta-analysis of cheese intake and colon cancer. The summary RR per 50 g/d was 0.91 (95% CI: 0.80-1.03) with low heterogeneity, I^2=18.5%, $p_{heterogeneity}$=0.29.

In the Pooling Project (Cho, 2004) the pooled relative risks for ≥25 g/day compared to <5 g/day of cheese intake were 1.14 (0.95-1.36) ptrend=0.38 for colon cancer, 1.21 (1.00-1.45 for distal) ptrend=0.2 for proximal and 1.03 (0.84-1.26) ptrend=0.94 for distal colon cancer

There was no evidence of a nonlinear association between cheese intake and colon cancer, $p_{nonlinearity}$=0.95, and there was a significant inverse association for intakes of 40 g/d or higher.

Rectal cancer

Four studies (2101 cases) were included in the dose-response meta-analysis of cheese intake and rectal cancer. The summary RR per 50 g/d was 0.95 (95% CI: 0.90-1.00) with low heterogeneity, I^2=0%, $p_{heterogeneity}$=0.96.

In the Pooling Project (Cho, 2004) the pooled relative risk of cancer of the rectum for ≥25 g/day compared to <5 g/day of cheese intake was 1.08 (0.86-1.36) ptrend=0.28.

There was evidence of a nonlinear association between cheese intake and rectal cancer, $p_{nonlinearity}$=0.03, and there was a significant inverse association for intakes of 70 g/d or higher.

Study quality

Cheese intake was estimated from food intake assessed by FFQ in all studies, and in one of the studies a combination of FFQ, food records and 24 hour recalls were used (Murphy, 2013).

Loss to follow-up was low for the studies that reported such data, although some studies did not provide data.

Cancers were identified by record linkages to health registries, cancer registries, mortality registries, or death indexes.

All studies adjusted for at least age, and most of the studies adjusted for most of the established colorectal cancer risk factors, including: age, physical activity, BMI, and alcohol consumption, smoking, red meat and hormone replacement therapy in women.

Table 119 Cheese intake and colorectal cancer risk. Summary of the linear dose-response meta-analysis in the 2005 SLR, 2010SLR and 2015 SLR

	2005 SLR			
	Colorectal cancer	**Colorectal cancer**	**Colon cancer**	**Rectal cancer**
Increment unit used	Per 1 serving/day	Per 50 g/day	-	-
Studies (n)	3	2	-	-
Cases (total number)	583	484	-	-
RR (95%CI)	1.14 (0.82-	1.11 (0.88-1.39)	-	-

	1.58)			
Heterogeneity (I^2, p-value)	0%, p=0.44	0%, p=0.42	-	-
P value Egger test	-	-	-	-

	2010 SLR		
	Colorectal cancer	**Colon cancer**	**Rectal cancer**
Increment unit used	50 g/day		
Studies (n)	-	-	-
Cases (total number)	-	-	-
RR (95%CI)	-	-	-
Heterogeneity (I^2, p-value)	-	-	-
P value Egger test	-	-	-

	2015 SLR		
	Colorectal cancer	**Colon cancer**	**Rectal cancer**
Increment unit used	50 g/day		
Studies (n)	7	6	4
Cases (total number)	6462	3958	2101
RR (95%CI)	0.94 (0.87-1.02)	0.91 (0.80-1.03)	0.95 (0.90-1.00)
Heterogeneity (I^2, p-value)	9.5%, p=0.36	18.5%, p=0.29	0%, p=0.96
P value Egger test	0.72	-	-

Stratified analyses by geographic location			
2015 SLR	**Asia**	**Europe**	**North-America**
Studies (n)	-	6	1
RR (95%CI)	-	0.94 (0.85-1.04)	1.16 (0.63-2.13)
Heterogeneity (I^2, p- value)	-	19.2%, p=0.29	-

Table 120 Cheese intake and colorectal cancer risk. Results of meta-analyses and pooled analyses of prospective studies published after the 2005 SLR.

Author, Year	Number of studies	Total number of cases	Studies country, area	Outcome	Comparison	RR (95%CI)	P trend	Heterogeneity (I^2, p value)
Meta-analyses								
Aune et al, 2012	7 CRC	1635	North America, Europe	Incidence	High vs. low	0.94 (0.75-1.18)	-	39%, p=0.14
					Per 50 g/d	0.96 (0.83-1.12)	-	28%, p=0.22
	5 CC				High vs. low	1.04 (0.69-1.55)	-	58%, p=0.05
					Per 50 g/d	0.84 (0.68-1.04)	-	8.5%, p=0.36
	3 RC				High vs. low	0.88 (0.59-1.30)	-	0%, p=0.84
					Per 50 g/d	0.90 (0.70-1.15)	-	0%, p=0.93
Ralston et al, 2014	8		North America, Europe	Incidence	High vs. low, men	0.94 (0.58-1.54)	-	43%, p=0.81
					High vs. low, women	1.16 (0.82-1.63)	-	11%, p=0.41
					High vs. low, all	1.11 (0.90-1.36)	-	16%, p=0.34
Pooled analyses								
Cho et al, 2004	10 CRC	7157	North America, Europe	Incidence	≥25 vs. <5 g/d	1.10 (0.98-1.24)	0.21	NA, p=0.37
	CC	2912				1.14 (0.95-1.36)	0.38	NA, p=0.10
	PCC	1505				1.21 (1.00-1.45)	0.20	NA, p=0.78
	DCC	1238				1.03 (0.84-1.26)	0.94	NA, p=0.61
	RC	1208				1.08 (0.86-1.36)	0.28	NA, p=0.31

Table 121 Cheese intake and colorectal cancer risk. Main characteristics of studies included in the CUP SLR dose-response meta-analysis

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI)	Adjustment factors	Missing data derived for analysis
Murphy, 2013 COL41070 Denmark,France,Germany,Greece,Italy,Netherlands,Norway, Spain,Sweden, UK	EPIC, Prospective Cohort, Age: 30- years, M/W	4 513/ 477 122 11 years	Cancer registries, health Insurance records, pathology rec & active follow up	Dietary questionnaire	Incidence, colorectal cancer	≥56 vs 0-4.9 g/d	0.87 (0.76-0.99)	Age, alcohol consumption, BMI, centre location, educational level, fibre intake, menopausal hormone use, menopausal status, physical activity Index, red and processed meat, smoking status and dose, total energy intake, use of oral contraception	Midpoints
					Incidence, colorectal cancer	per 50 g/day	0.95 (0.90-1.00)		
					Incidence, colon cancer	≥56 vs 0-4.9 g/d	0.83 (0.71-0.97)		
					Incidence, colon cancer	per 50 g/day	0.93 (0.90-0.97)		
					Incidence, proximal cancer	≥56 vs 0-4.9 g/d	0.73 (0.58-0.93)		
					Incidence, proximal cancer	per 50 g/day	0.95 (0.89-1.01)		
					Incidence, distal colon cancer	≥56 vs 0-4.9 g/d	0.91 (0.71-1.17)		
					Incidence, distal colon cancer	per 50 g/day	0.94 (0.88-0.99)		
					Incidence, rectal cancer	≥56 vs 0-4.9 g/d	0.95 (0.76-1.18)		

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI)	Adjustment factors	Missing data derived for analysis
					Incidence, rectal cancer	per 50 g/day	0.95 (0.90-1.00)		
Larsson, 2006 COL40624 Sweden	COSM, Prospective Cohort, Age: 45-79 years, M	449/ 45 306 6.7 years	Cancer registry	FFQ	Incidence, colorectal cancer	≥3 slices/day vs <4 slices/wk slices	0.79 (0.56-1.12)	Age, alcohol intake, aspirin use, educational level, family history of colorectal cancer, fruits, history of diabetes, multivitamin supplement intake, physical activity, red meat intake, saturated fat, smoking status, total energy intake, vegetable intake, vitamin d	Midpoints, conversion from serv/d to g/d, distribution of cases and person-years
					Incidence, colon cancer	≥3 slices/day vs <4 slices/wk slices	0.78 (0.51-1.21)		
					Incidence, rectal cancer	≥3 slices/day vs <4 slices/wk slices	0.80 (0.45-1.41)		
					Incidence, distal colon cancer	≥3 slices/day vs <4 slices/wk slices	0.87 (0.45-1.70)		
					Incidence, proximal colon cancer	≥3 slices/day vs <4 slices/wk slices	0.76 (0.40-1.43)		
Larsson, 2005 COL01835 Sweden	SMC, Prospective Cohort, Age: 40-75 years, W	798/ 61 433 14.8 years	Mammography screening program	Questionnaire	Incidence, colorectal cancer	≥1 vs ≤0 servings/day	0.65 (0.44-0.96)	Age, BMI, cereal fibre, educational level, folate intake, red meat intake, total energy intake, vitamin b6 intake	Midpoints, conversion from serv/d to g/d, distribution of person-years
					Incidence, proximal colon cancer	≥1 vs ≤0 servings/day	0.76 (0.39-1.50)		
					Incidence, distal colon cancer	≥1 vs ≤0 servings/day	0.24 (0.07-0.82)		
					Incidence, rectal cancer	≥1 vs ≤0 servings/day	0.89 (0.46-1.71)		

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI)	Adjustment factors	Missing data derived for analysis
Lin, 2005 COL01690 USA	WHS, Prospective Cohort, Age: 45- years, W, professionals	223/ 36 976 10 years	SEER	FFQ	Incidence, colorectal cancer	≥0.7 vs ≤0.1 serving/day	1.38 (0.87-2.19)	Age, alcohol consumption, BMI, energy intake, family history of specific cancer, history of previous polyp and prior endoscopy, menopausal status, multivitamin, physical activity, postmenopausal hormone use, randomized treatment assignment, red meat intake, saturated fat, smoking status	Midpoints, conversion from serv/d to g/d, distribution of person-years
Sanjoaquin, 2004 COL01182 UK	OVS, Prospective Cohort, Age: 18-89 years, M/W	92/ 10 998 17 years	Population/invitation	FFQ	Incidence, colorectal cancer	≥10 vs ≤4 times/week	0.98 (0.48-2.03)	Age, sex, alcohol consumption, smoking habits	Midpoints, conversion from pints/d to g/d, distribution of person-years
Jarvinen, 2001 COL00314 Finland	Finnish Mobile Clinic Health Examination Survey, Prospective Cohort,	72/ 9 959 19.6 years	Population	Questionnaire	Incidence, colorectal cancer	Q 4 vs Q 1	1.65 (0.84-3.23)	Age, sex, area of residence, BMI, energy intake, occupational group, smoking habits	Midpoints, distribution of person-years
					Incidence, colon cancer	Q 4 vs Q 1	2.42 (0.91-6.43)		

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI)	Adjustment factors	Missing data derived for analysis
	Age: 39 years, M/W				Incidence, rectal cancer	Q 4 vs Q 1	1.12 (0.43-2.91)		
Singh, 1998 COL00185 USA	AHS, Prospective Cohort, Age: 25- years, M/W, Seventh-day Adventists	142/ 32 051 178 544 person-years	Census list	FFQ	Incidence, colon cancer,	≥2 vs ≤0.5 times/week	1.31 (0.84-2.03)	Age, sex, alcohol consumption, aspirin use, BMI, family history of specific cancer, physical activity, smoking habits	Midpoints, conversion from serv/wk to g/d
Kearney, 1996 COL00156 USA	HPFS, Prospective Cohort, Age: 40-75 years, M, Health professionals	203/ 47 935 6 years	Responding to mail survey	Semi-quantitative FFQ	Incidence, colon cancer	≥5 vs 0-1 times/month	1.35 (0.67-2.75)	Age, alcohol consumption, aspirin use, BMI, dietary fiber, family history of colon cancer, past history of smoking, physical activity, previous polyps, red meat intake, saturated fat, screening, total calories	Midpoints, conversion from serv/wk to g/d
Kampman, 1994 COL00155 Netherlands	NLCS, Case Cohort, Age: 55-69 years, M/W	326/ 120 852 3.3 years	Population registries	Semi-quantitative FFQ	Incidence, colorectal cancer, men	≥30 vs ≤0 g/day	0.88 (0.59-1.33)	Age, sex, BMI, energy intake, energy-adjusted intake of dietary fiber, energy-adjusted intake of fat, family history of specific cancer, history of	Midpoint, distribution of person-years
					Incidence, colorectal cancer, women	Q 4 vs Q 1	0.61 (0.34-1.09)		

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI)	Adjustment factors	Missing data derived for analysis
								gallbladder surgery	

Table 122 Cheese intake and colorectal cancer risk. Main characteristics of studies excluded from the CUP SLR dose-response meta-analysis

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI)	Adjustment factors	Reasons for exclusion
Iso, 2007 COL40707 Japan	JACC, Prospective Cohort, Age: 40-79 years, M/W	176/ 105 500 15 years	Municipal resident registration records, death certificates	FFQ	Mortality, colon cancer, women	≥5 vs ≤2 /week	0.81 (0.41-1.61)	Age, centre location	Mortality as outcome
					Mortality, colon cancer, men	≥5 vs ≤2 /week	1.10 (0.62-1.96)		
					Mortality, rectal cancer, men	≥5 vs ≤2 /week	1.48 (0.78-2.79)		
					Mortality, rectal cancer, women	≥5 vs ≤2 /week	0.80 (0.25-2.61)		

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI)	Adjustment factors	Reasons for exclusion
Kesse, 2005 POL16753 France	EPIC-E3N, Prospective Cohort, Age: 40-65 years, W, part of nat. health insurance scheme for teachers	516/ 5 320 3.7 years	National health Insurance scheme	Questionnaire	Incidence, colorectal cancer, women	≥70.12 vs 0-26.66 g/day	0.97 (0.61-1.54)	Age at entry, alcohol consumption, BMI, educational level, family history of specific cancer, physical activity, smoking status, total energy	Overlap with Murphy et al, 2013 COL41070
Khan, 2004 COL01606 Japan	HCS, Prospective Cohort, Age: 40-97 years, M/W	14/ 3 458 14.3 years	Area residency lists	Questionnaire	Mortality, colorectal cancer, women	Q 2 vs Q 1	1.50 (0.30-6.80)	Age, health education, health screening, health status, smoking habits	Mortality as outcome
Kojima, 2004 COL01840 Japan	JACC, Prospective Cohort, Age: 40-79 years, M/W	108/ 107 824 10 years	Resident registry and death certificates	Questionnaire	Mortality, colon cancer, women	0.5-7 vs ≤0 times/week	1.01 (0.61-1.69)	Age, alcohol consumption, BMI, educational level, family history of specific cancer, physical activity, region of enrollment, smoking status	Mortality as outcome
					Mortality, colon cancer, men	0.5-7 vs ≤0 times/week	1.17 (0.68-2.01)		
					Mortality, rectal cancer, men	0.5-7 vs ≤0 times/week	1.19 (0.70-2.02)		
					Mortality, rectal cancer, women	0.5-7 vs ≤0 times/week	2.52 (1.11-5.72)		
Phillips, 1985	AHS,	175/		Quatitative	Mortality,	≥3 vs ≤1	1.10 (0.80-1.60)	Age, sex	Mortality as

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI)	Adjustment factors	Reasons for exclusion
COL00719 USA	Prospective Cohort, Age: 30- years, M/W, Seventh-day Adventists	25 493 21 years		FFQ	colorectal cancer	days/week			outcome
					Mortality, colon cancer, women	≥3 vs ≤1 days/week	0.80 (0.50-1.40)		
					Mortality, colon cancer, women	≥3 vs ≤1 days/week	0.80 (0.50-1.40)		
					Mortality, rectal cancer	≥3 vs ≤1 days/week	1.00 (0.50-2.20)		
Phillips, 1975 COL00717 USA	AHS, Nested Case Control, M/W, Seventh-day Adventists	40/ 105 controls 2 years	Hospital	Interview	Incidence, colon cancer,	≥1 vs ≤1 times/week	2.30	Age, sex, ethnicity	Case-control study

Figure 216 RR estimates of colorectal cancer by levels of cheese intake

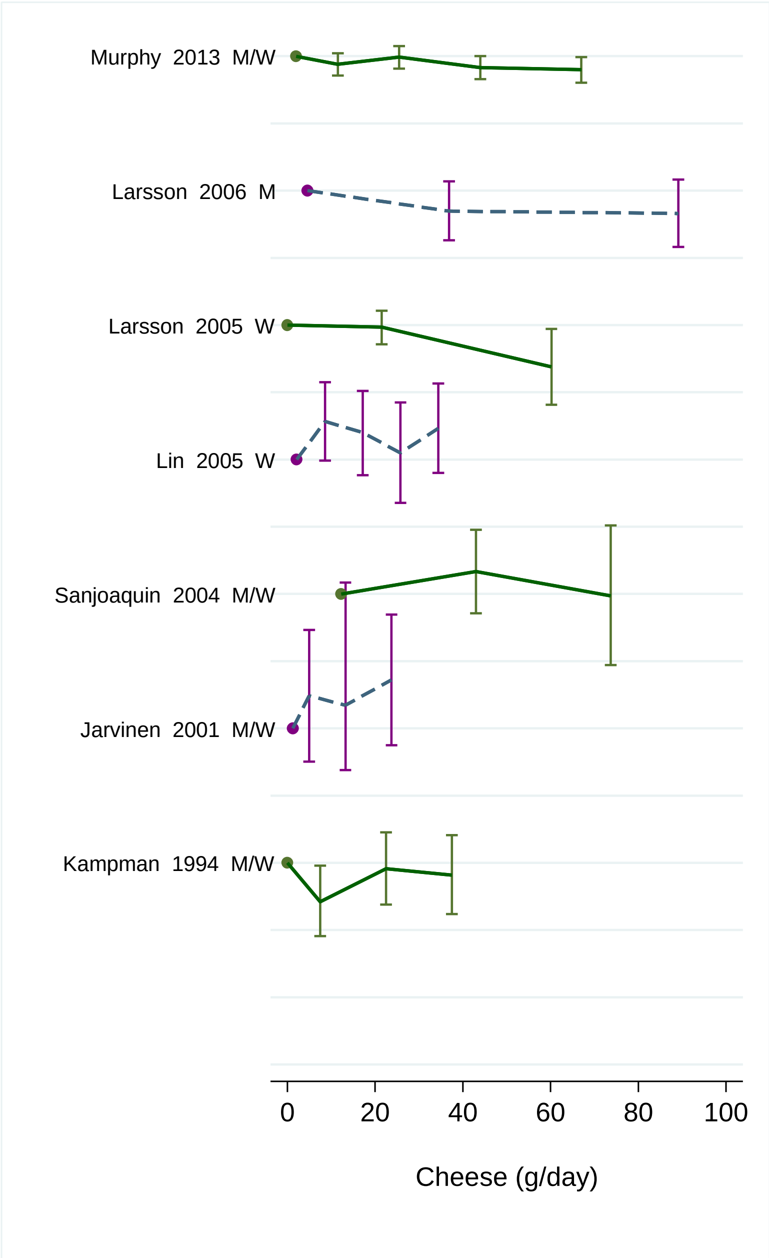


Figure 217 Relative risk of colorectal cancer for the highest compared with the lowest level of cheese intake

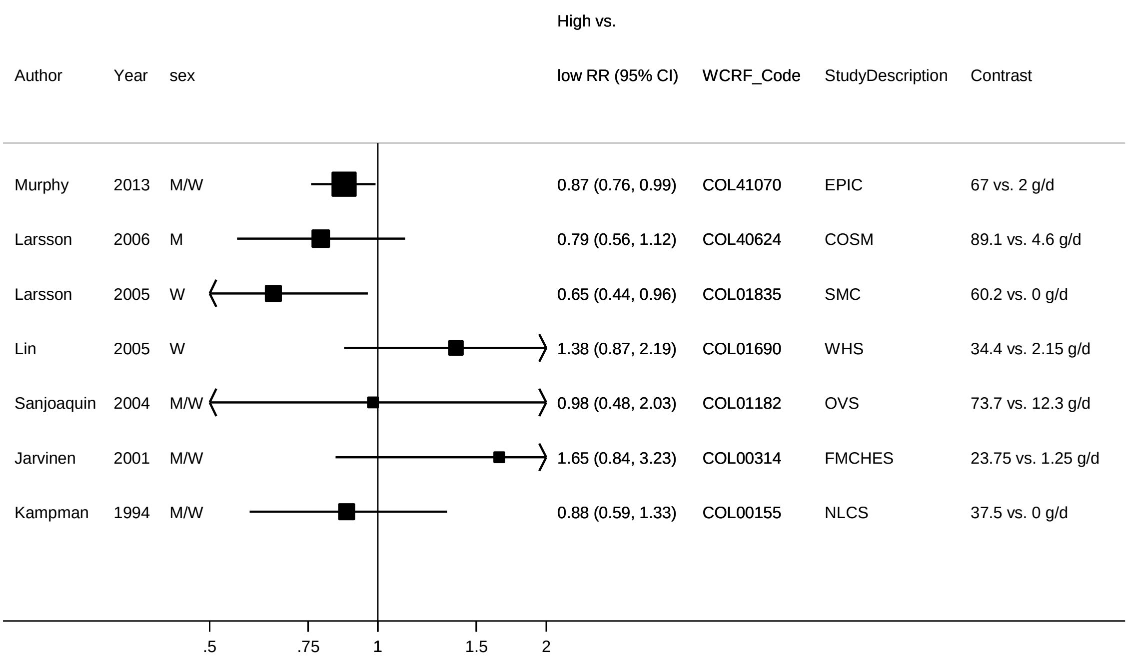


Figure 218 Relative risk of colorectal cancer for 50 g/day increase in cheese intake

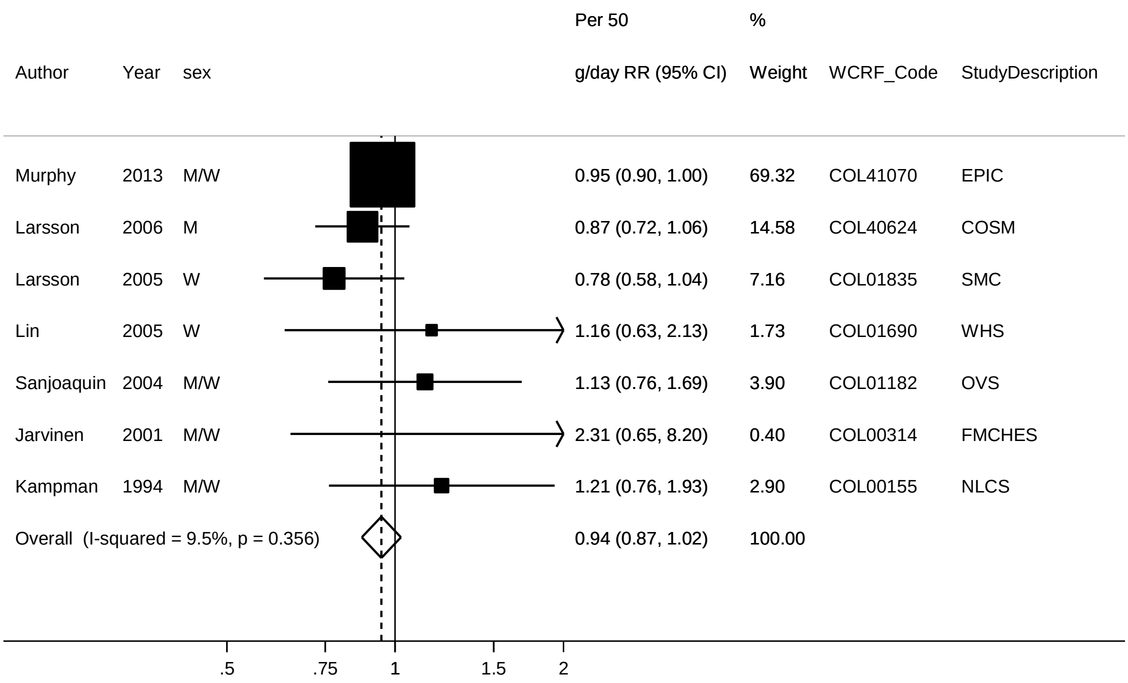


Figure 219 Relative risk of colorectal cancer for 50 g/day increase in cheese intake, stratified by sex

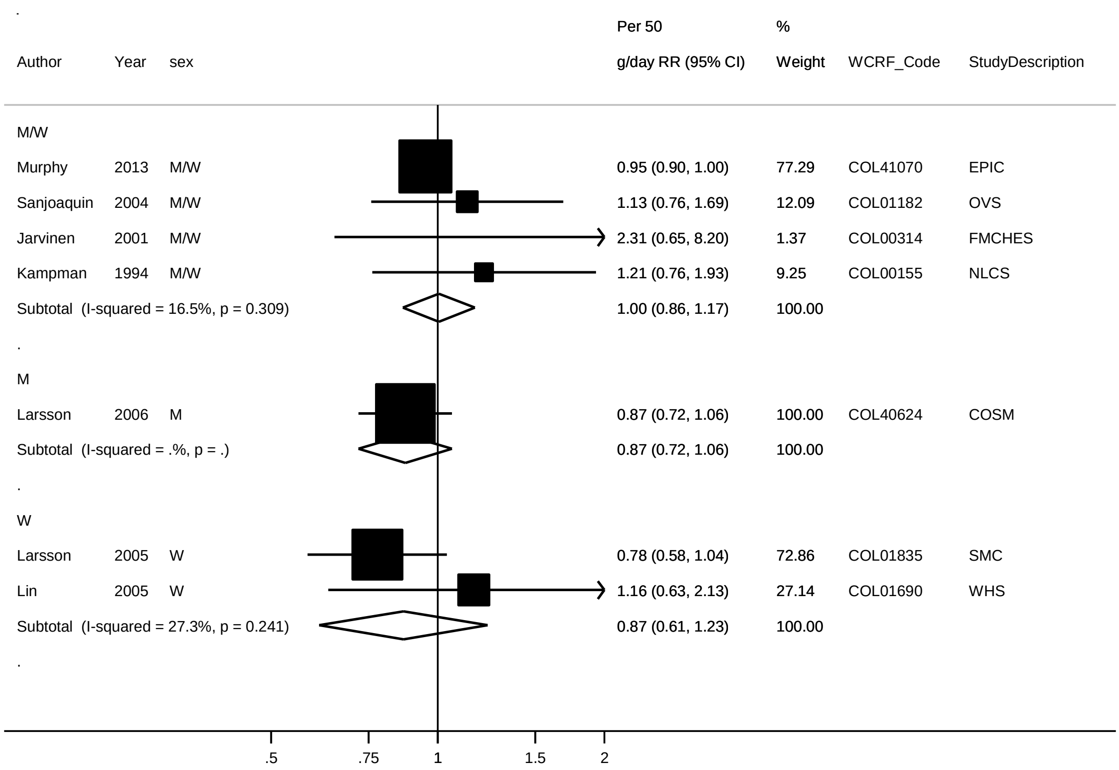
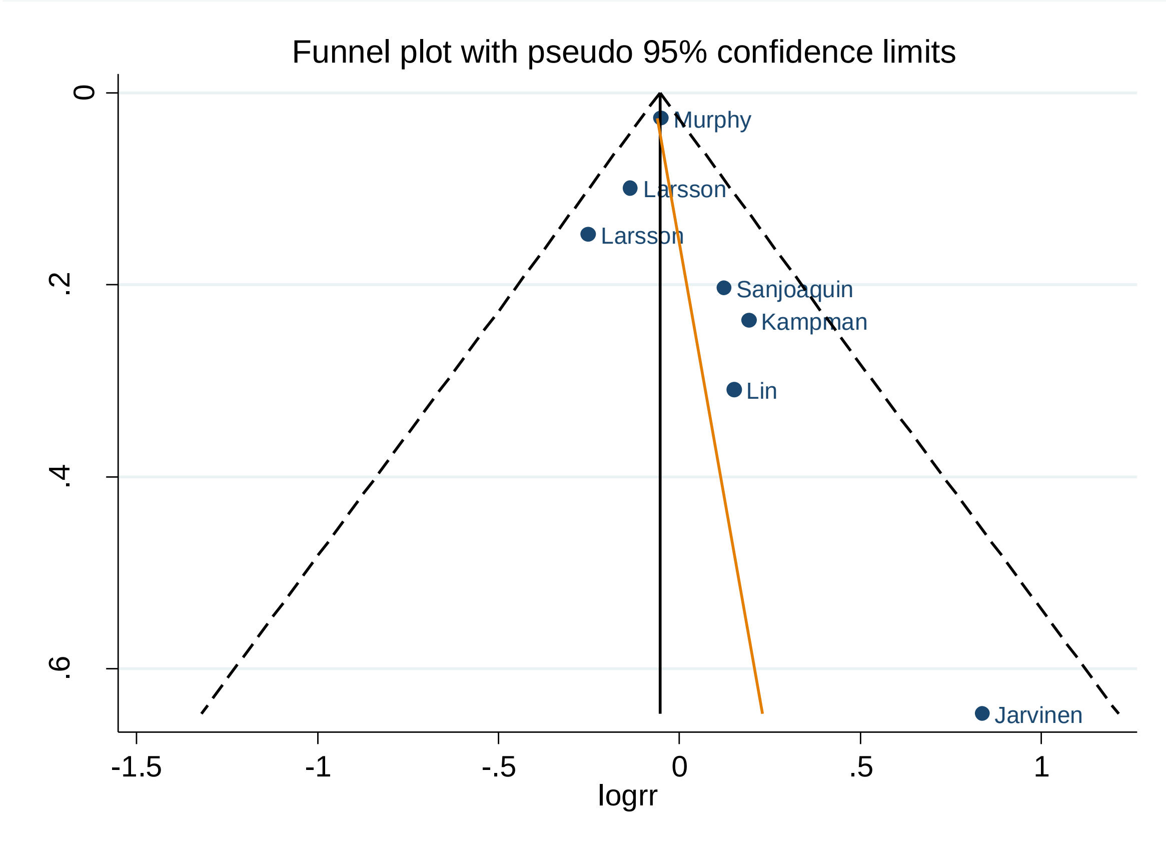
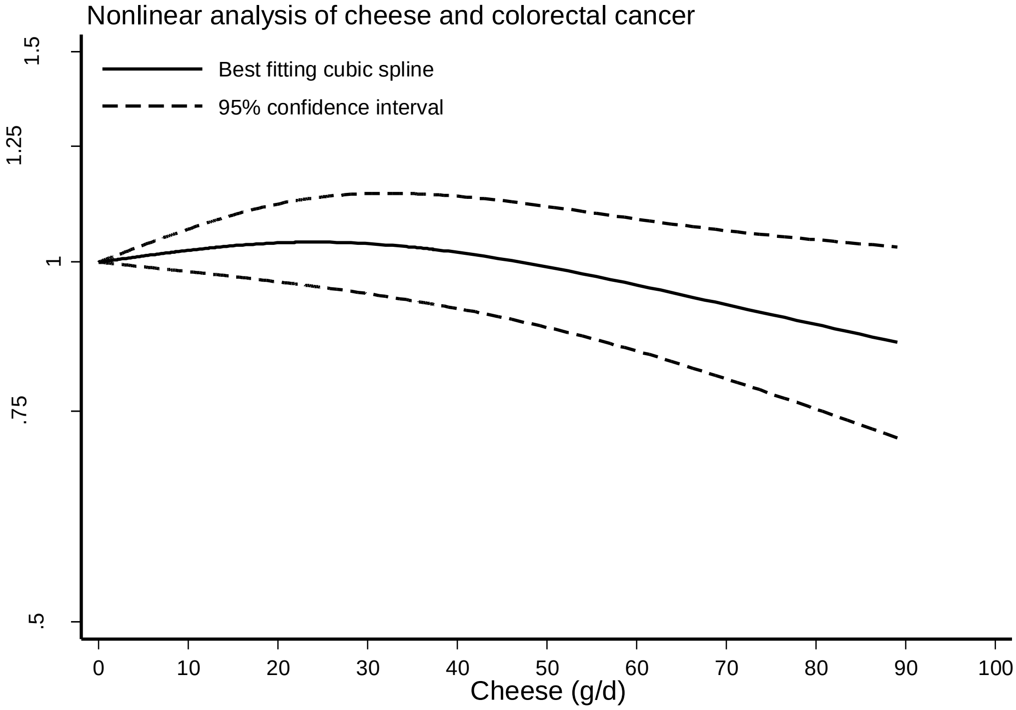


Figure 220 Funnel plot of studies included in the dose response meta-analysis of cheese intake and colorectal cancer



p for Egger's test=0.42

Figure 221 Cheese and colorectal cancer, nonlinear dose-response analysis



p for non-linearity=0.047

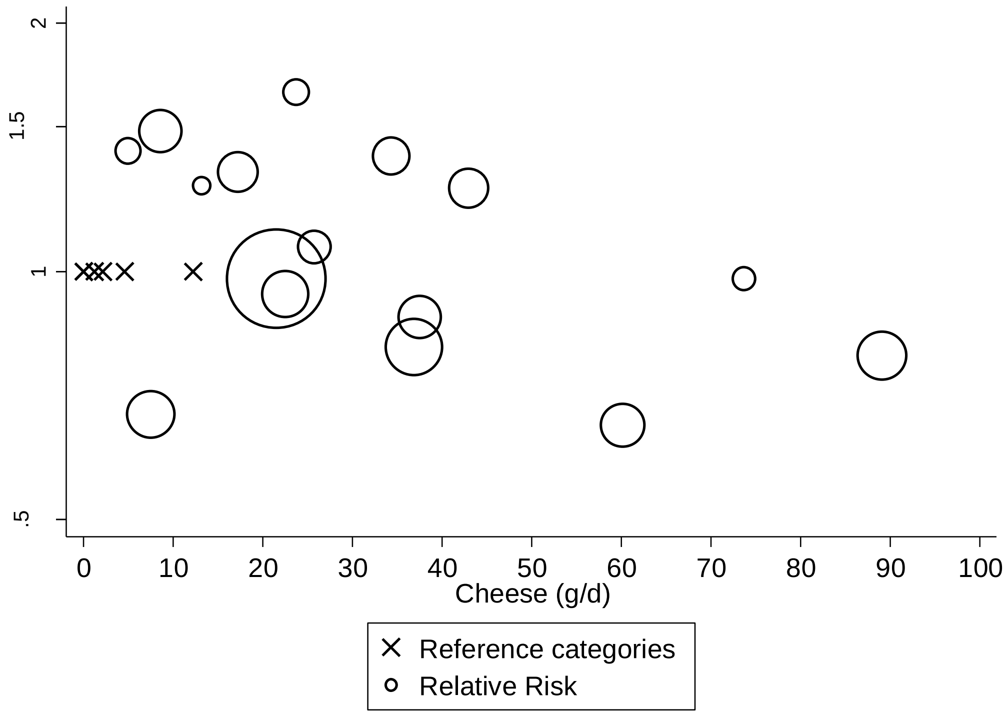
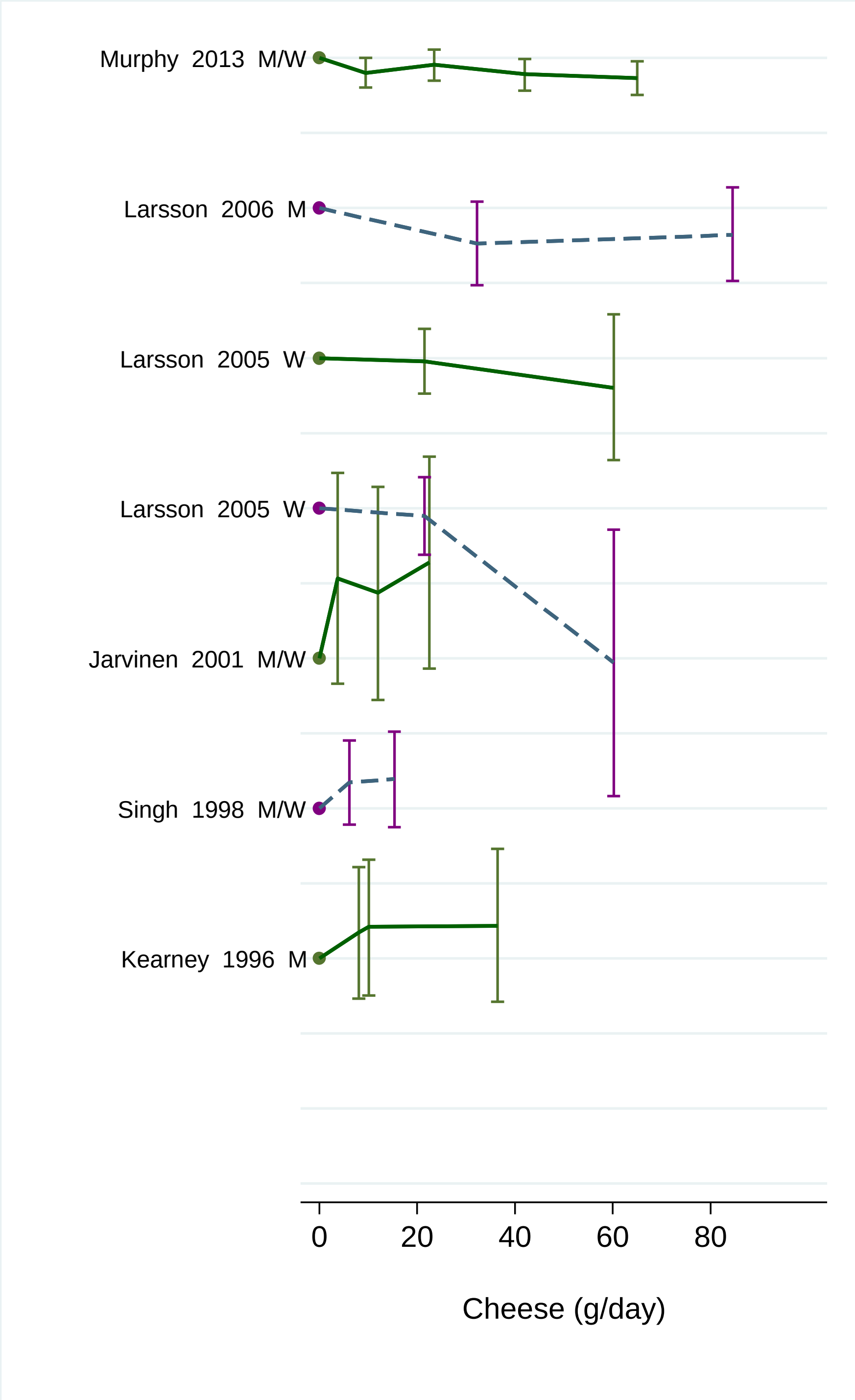


Figure 222 Relative risk of colorectal cancer and dairy product intake estimated using non-linear models

Cheese (g/day)	RR (95%CI)
0	1.00
10	1.02 (0.98-1.07)
20	1.04 (0.96-1.12)
30	1.04 (0.94-1.14)
40	1.02 (0.91-1.14)
50	0.99 (0.88-1.11)
60	0.96 (0.84-1.09)
70	0.92 (0.80-1.06)
80	0.89 (0.75-1.04)
90	0.86 (0.71-1.03)

Figure 223 RR estimates of colon cancer by levels of cheese intake



Larsson, 2005 top: distal colon cancer
Larsson, 2005 bottom: proximal colon cancer

Figure 224 Relative risk of colon cancer for the highest compared with the lowest level of cheese intake

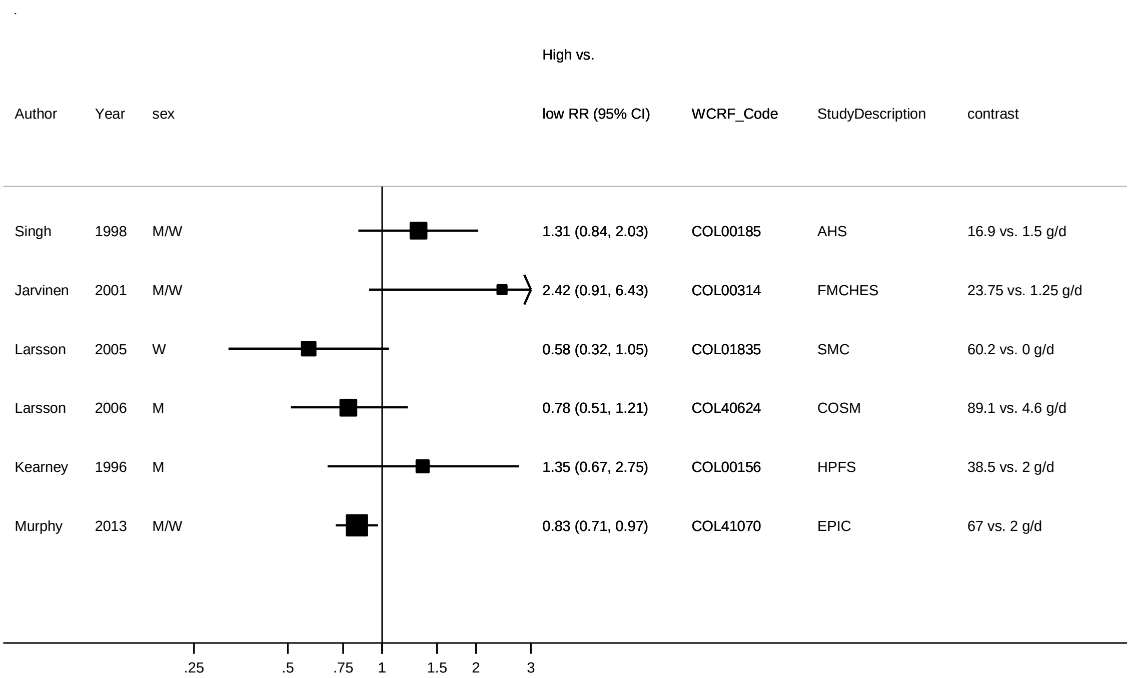


Figure 225 Relative risk of colon cancer for 50 g/day increase in cheese intake

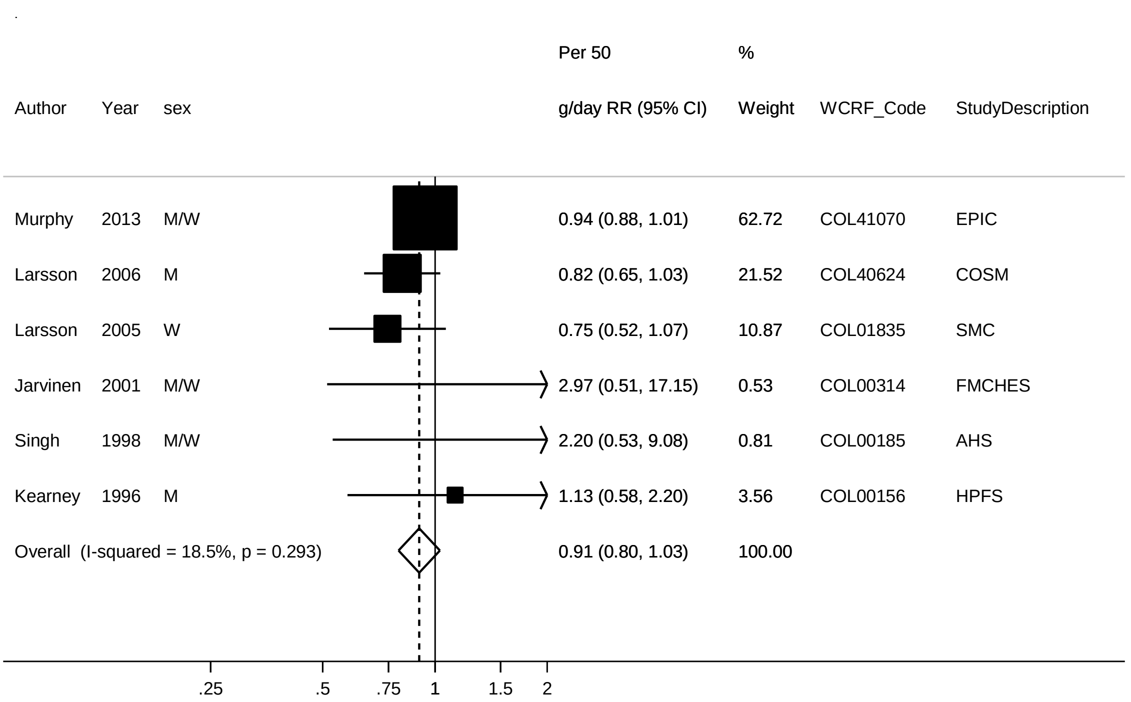


Figure 226 Relative risk of colon cancer for 50 g/day increase in cheese intake, stratified by sex

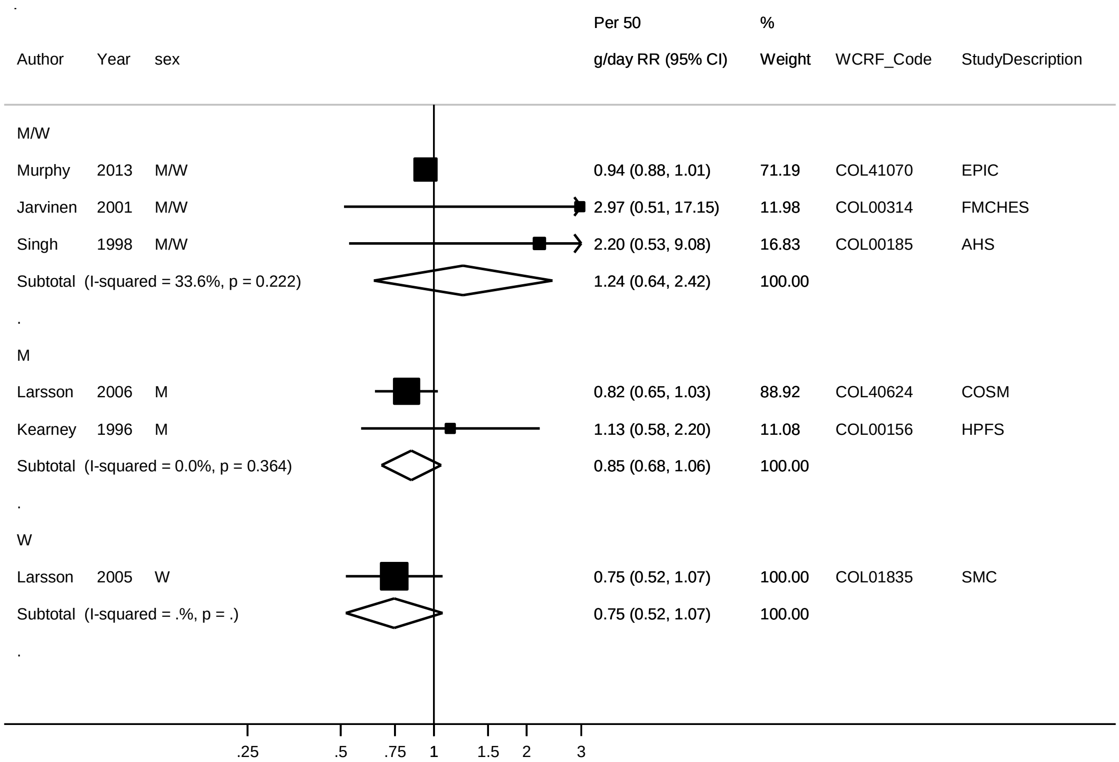


Figure 227 Funnel plot of studies included in the dose response meta-analysis of cheese intake and colon cancer

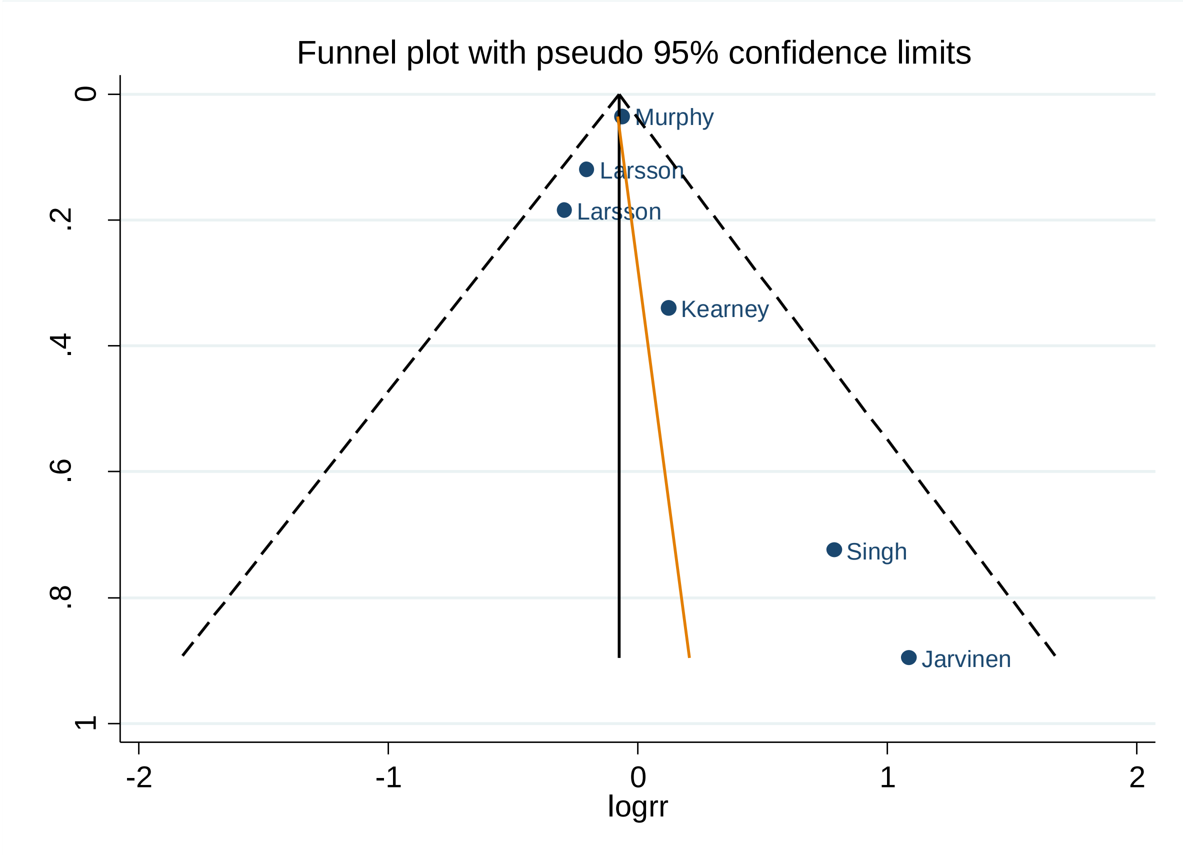
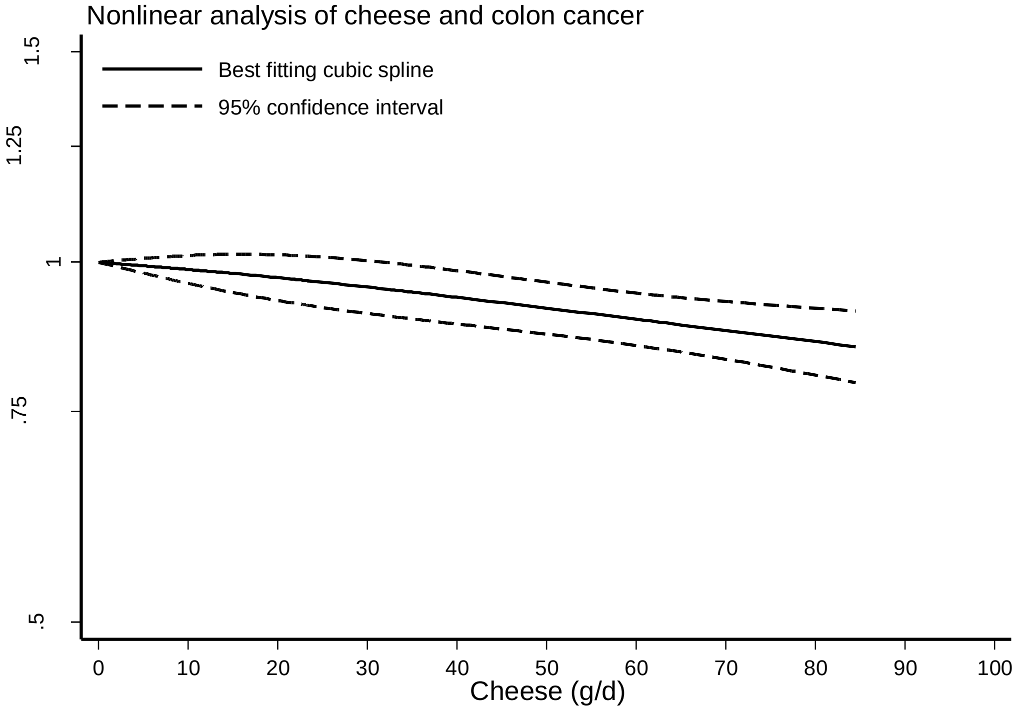


Figure 228 Cheese and colon cancer, nonlinear dose-response analysis



p non-linearity=0.95

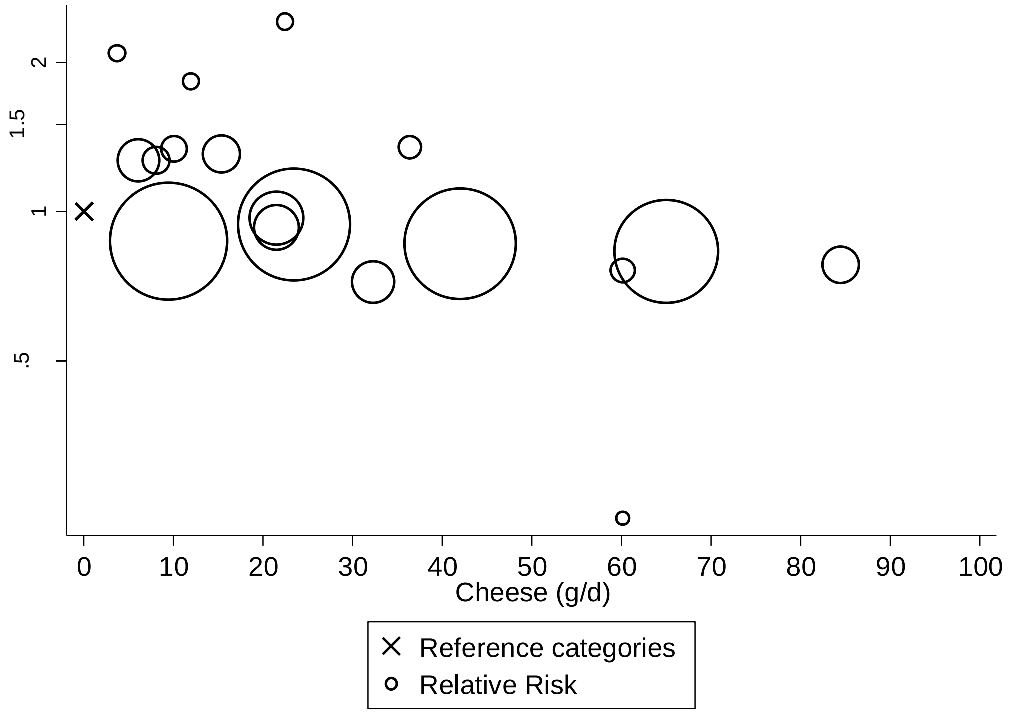


Table 123 Relative risk of colon cancer and dairy product intake estimated using non-linear models

Cheese (g/day)	RR (95%CI)
0	1.00
10	0.99 (0.96-1.01)
20	0.97 (0.93-1.01)
30	0.95 (0.91-1.00)
40	0.93 (0.89-0.98)
50	0.92 (0.87-0.96)
60	0.90 (0.85-0.94)
70	0.88 (0.83-0.93)
80	0.86 (0.80-0.92)
84	0.85 (0.79-0.91)

Figure 229 RR estimates of rectal cancer by levels of cheese intake

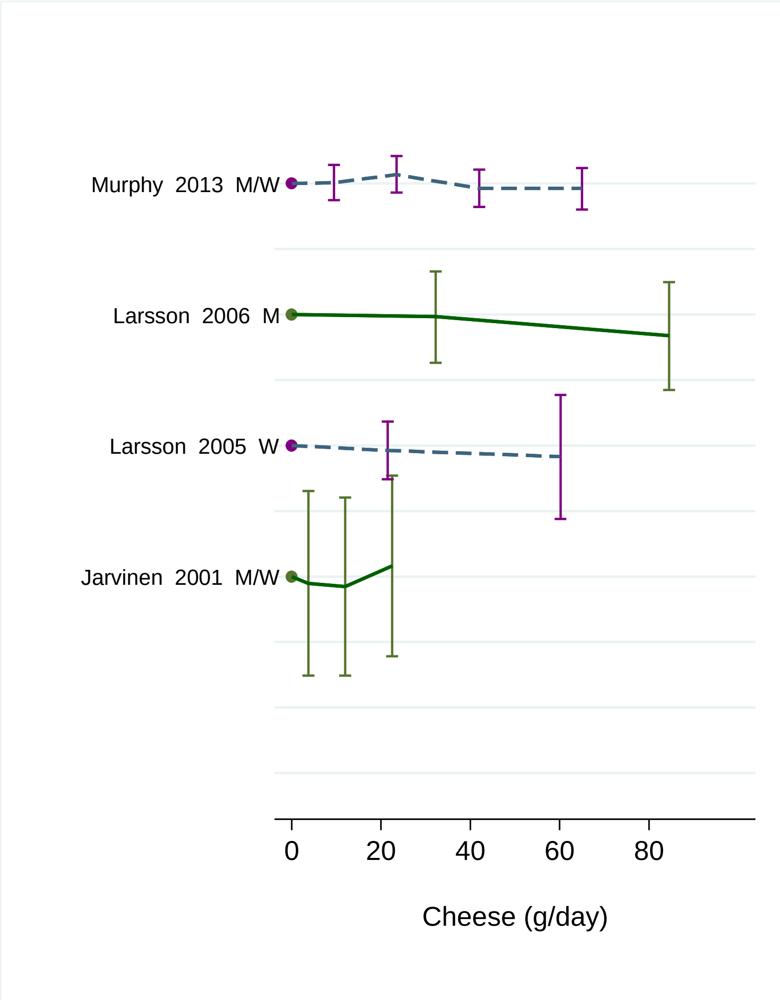


Figure 230 Relative risk of rectal cancer for the highest compared with the lowest level of cheese intake

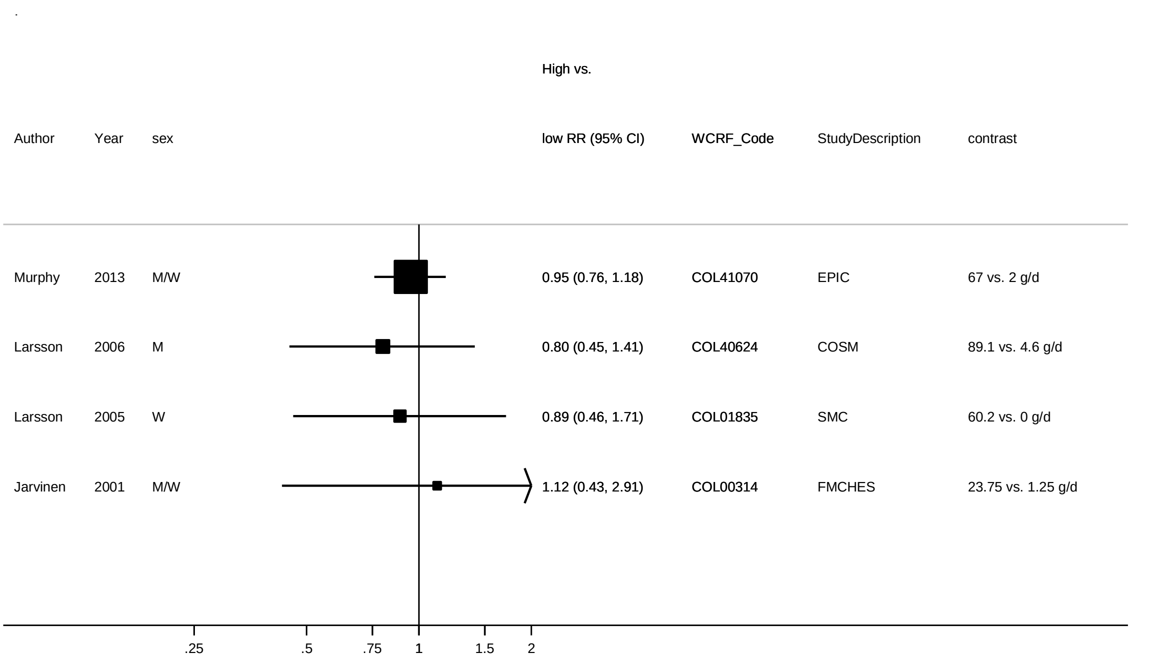


Figure 231 Relative risk of rectal cancer for 50 g/day increase in cheese intake

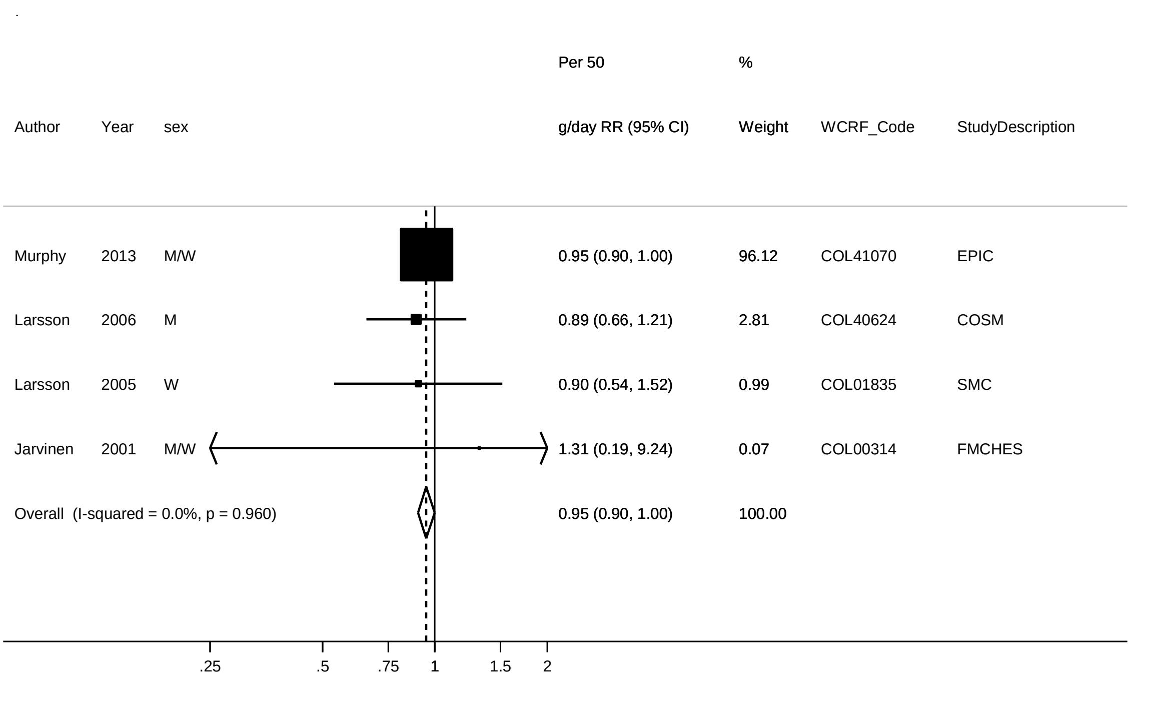
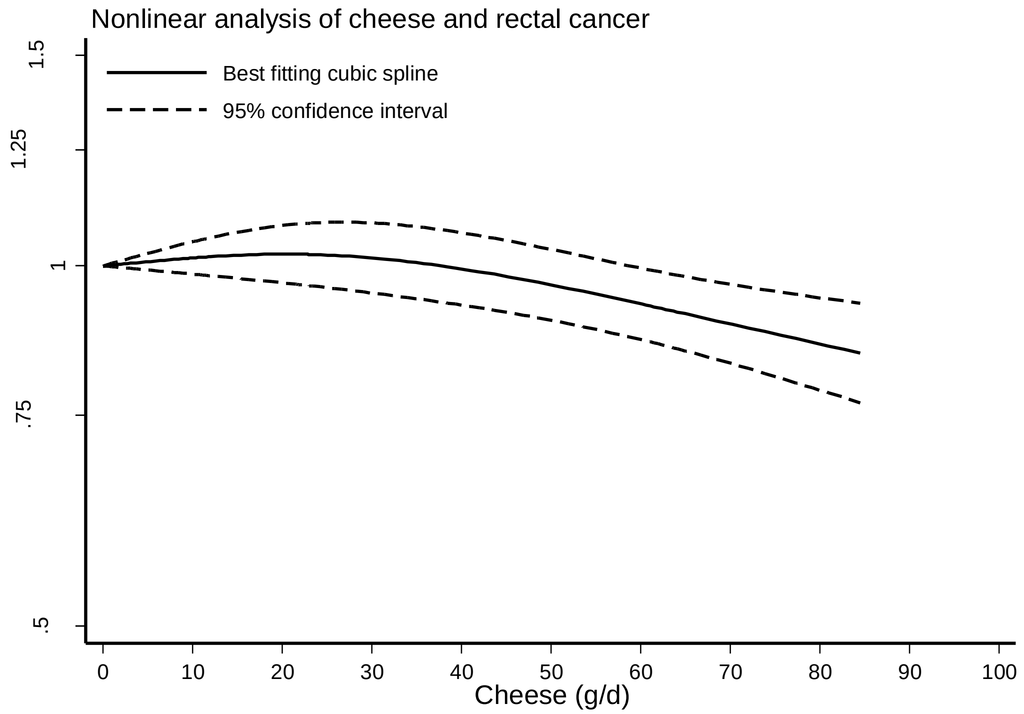


Figure 232 Cheese and rectal cancer, nonlinear dose-response analysis



p for non-linearity=0.03

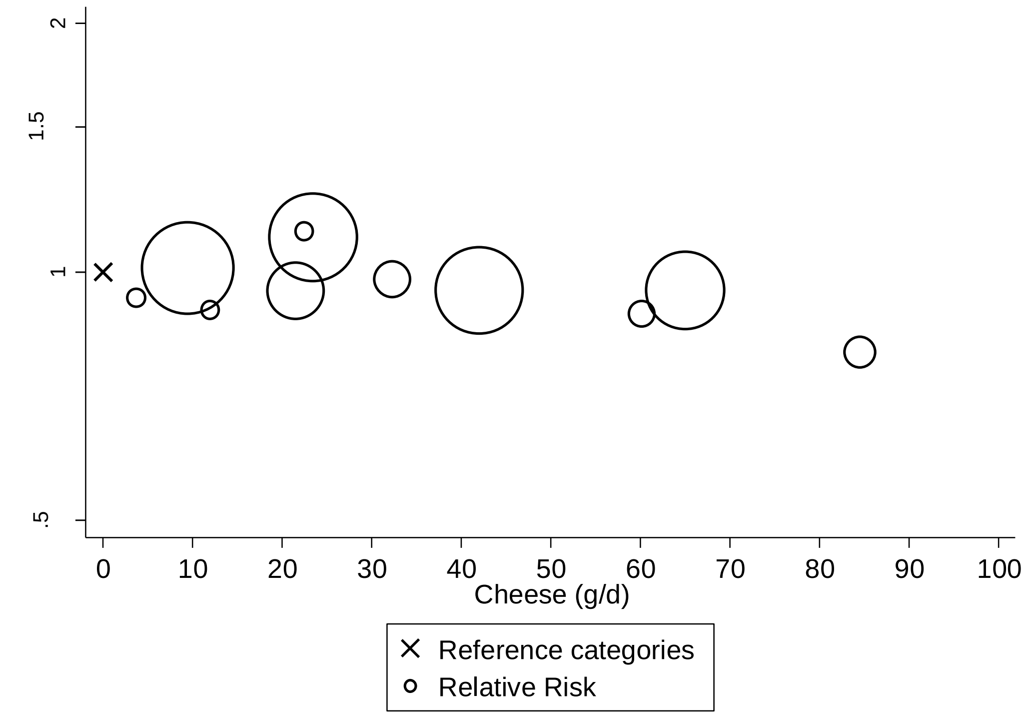


Table 124 Relative risk of rectal cancer and cheese intake estimated using non-linear models

Cheese (g/day)	RR (95%CI)
0	1.00
10	1.02 (0.98-1.05)
20	1.02 (0.97-1.08)
30	1.02 (0.95-1.09)
40	0.99 (0.93-1.07)
50	0.96 (0.90-1.03)
60	0.93 (0.87-1.00)
70	0.89 (0.83-0.96)
80	0.86 (0.79-0.94)
84	0.85 (0.77-0.93)

3.6.1 Coffee

Cohort studies

Summary

Colorectal cancer:
Fourteen studies (20 667 cases) were included in the dose-response meta-analysis of coffee consumption and colorectal cancer. No significant association was observed. Only one study showed an inverse association per 1 cup/day of coffee (NIH-AARP). In stratified analysis by sex and location, no significant association was observed.
There was evidence of small study bias (p=0.002). There was an evidence of a non-linear association (p=0.01).
In sensitivity analysis, the summary RRs did not change materially when excluding the studies in turn.

Colon cancer:
Twenty three studies (18 688 cases) were included in the dose-response meta-analysis. No significant association was observed. Thirteen cohort studies were included in the Pooling Project (Zhang, 2010). In stratified analysis by sex and location, no significant association was observed. There was no evidence of small study bias (p=0.55).
There was an evidence of a non-linear association (p=0.004). The non-linear association showed a decreased risk with higher consumption of coffee with amount above 3.5 cups/day.
In sensitivity analysis, the summary RRs did not change materially when excluding the studies in turn.
Five studies including 7 223 and 5 265 cases were included in the dose-response meta-analysis for proximal and distal colon cancer, respectively. No significant association was observed.

Rectal cancer:
Fifteen studies (7 605 cases) were included in the dose-response meta-analysis. No significant association was observed.
In stratified analysis by sex and location, no significant association was observed.
There was no evidence of small study bias (p=0.73). There was no evidence of a non-linear association (p=0.096).
The summary RRs did not change materially when excluding the studies in turn.

Study quality:
Cancer outcome was confirmed using cancer registry records in most studies and coffee intake was assessed using FFQ or questionnaire in all studies.

Table 125 Coffee consumption and colorectal cancer risk. Number of studies in the CUP SLR

	Number
Studies identified	14
Studies included in forest plot of highest compared with lowest exposure	14
Studies included in dose-response meta-analysis	14
Studies included in non-linear dose-response meta-analysis	12

Note: Include cohort, nested case-control and case-cohort designs

Table 126 Coffee consumption and colon cancer risk. Number of studies in the CUP SLR

	Number
Studies identified	27 (Including pooling project* study)
Studies included in forest plot of highest compared with lowest exposure	9
Studies included in dose-response meta-analysis	23
Studies included in non-linear dose-response meta-analysis	8

Note: Include cohort, nested case-control and case-cohort designs

*Pooling project study includes 13 cohort studies.

Table 127 Coffee consumption and rectal cancer risk. Number of studies in the CUP SLR

	Number
Studies identified	15
Studies included in forest plot of highest compared with lowest exposure	11
Studies included in dose-response meta-analysis	15
Studies included in non-linear dose-response meta-analysis	11

Note: Include cohort, nested case-control and case-cohort designs

Table 128 Coffee consumption and colorectal cancer risk. Summary of the dose-response meta-analysis in the 2010 SLR and 2015 SLR.

	2010 SLR (no analysis)	**2015 SLR**
Increment unit used		1 cup/day
Studies (n)		14
Cases (total number)		20 667
RR (95%CI)		1.00 (0.99-1.02)
Heterogeneity (I^2, p-value)		44.2%, 0.05

Stratified analysis by sex			
	Men		Women
Studies (n)	6		5
RR (95%CI)	1.01 (0.98-1.04)		1.00 (0.97-1.03)
Heterogeneity (I^2, p-value)	24.3%, 0.25		0%, 0.91
Stratified analysis by geographic location			
2015 SLR	**Asia**	**Europe**	**North America**
Studies (n)	3	6	4
RR (95%CI)	1.02 (0.95-1.09)	1.00 (0.99-1.02)	1.00 (0.96-1.03)
Heterogeneity (I^2, p-value)	52.9%, 0.11	0%, 0.78	60.7%, 0.05

Table 129 Coffee consumption and colon cancer risk. Summary of the dose-response meta-analysis in the 2010 SLR and 2015 SLR.

	2010 SLR (no analysis)	2015 SLR
Increment unit used		1 cup/day
Studies (n)		11
Cases (total number)		18 688
RR (95%CI)		0.99 (0.97-1.01)
Heterogeneity (I^2, p-value)		48.8%, 0.03

Stratified analysis by sex			
2015 SLR	**Men**		**Women**
Studies (n)	8		8
RR (95%CI)	0.98 (0.94-1.02)		0.98 (0.95-1.02)
Heterogeneity (I^2, p-value)	50.7%, 0.05		21.4%, 0.26
Stratified analysis by geographic location			
2015 SLR	**Asia**	**Europe**	**North America**
Studies (n)	4	3	3
RR (95%CI)	0.97 (0.87-1.08)	1.00 (0.98-1.01)	0.98 (0.93-1.04)
Heterogeneity (I^2, p-value)	67.9%, 0.02	0%, 0.62	60.8%, 0.08

Table 130 Coffee consumption and proximal and distal colon cancer risk. Summary of the dose-response meta-analysis in the 2010 SLR and 2015 SLR.

	Proximal	Distal
Increment unit used	1 cup/day	1 cup/day
Studies (n)	5	5
Cases (total number)	7 223	5 265
RR (95%CI)	0.99 (0.96-1.02)	0.99 (0.97-1.01)

Heterogeneity (I^2, p-value)	64.2%, 0.25	0%, 0.63

Table 131 Coffee consumption and rectal cancer risk. Summary of the dose-response meta-analysis in the 2010 SLR and 2015 SLR.

	2010 SLR (no analysis)	**2015 SLR**
Increment unit used		1 cup/day
Studies (n)		15
Cases (total number)		7 605
RR (95%CI)		1.01 (1.00-1.03)
Heterogeneity (I^2, p-value)		1.8%, 0.43

Stratified analysis by sex			
2015 SLR	**Men**	**Women**	
Studies (n)	7	5	
RR (95%CI)	1.01 (0.98-1.05)	1.02 (0.97-1.07)	
Heterogeneity (I^2, p-value)	0%, 0.58	0%, 0.55	
Stratified analysis by geographic location			
2015 SLR	**Asia**	**Europe**	**North America**
Studies (n)	3	7	5
RR (95%CI)	1.02 (0.95-1.10)	1.02 (1.00-1.04)	0.99 (0.96-1.03)
Heterogeneity (I^2, p-value)	0%, 0.59	0%, 0.45	8.1%, 0.35

Table 132 Coffee and colorectal cancer risk. Results of meta-analyses and pooled analyses of prospective studies published after the 2010 SLR.

Author, Year	Number of cohort studies	Total number of cases	Outcome	Comparison	RR (95%CI)	P trend	Heterogeneity (I^2, p value)
Pooled analysis							
Zhang, 2010	13	5 604	Incidence, colon cancer	> 1400 g/day (8-oz cups)	1.07 (0.89-1.30)	0.68	
		4 439		Per 250 g/day	0.99 (0.97-1.02)		0.45
		2 295	proximal colon cancer		0.99 (0.96-1.02)		0.98
		1 820	distal colon cancer		0.99 (0.96-1.03)		0.71
Meta-analysis							
Tian, 2013	12	NA	Incidence, colorectal cancer	For 1 cup/day increment	1.02 (0.97–1.07)	Non-linear models	NA
	8		Colon cancer		1.01 (0.94–1.08)		
	8		Rectal cancer		1.04 (0.93–1.16)		
Li, 2013	16	10 443	Incidence, colorectal cancer	Highest vs lowest	0.94 (0.88-1.01)		
			Incidence, colon cancer		0.93 (0.86-1.01)		

			Incidence, rectal cancer		0.98 (0.88-1.09)		
Yu, 2011	15		Incidence, colorectal cancer	Coffee drinkers vs non/lowest drinkers	0.89 (0.80-0.97)		75.3%, 0.000

Table 133 Coffee consumption and colorectal cancer risk. Main characteristics of studies included in the CUP SLR dose-response meta-analysis

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Missing data derived for analyses
Dik, 2014 COL40993 Denmark, France, Germany, Greece, Italy ,Netherlands, Norway, Spain, Sweden, UK	EPIC, Prospective Cohort, Age: 25-70 years, M/W	4 234/ 477 071 11.6 years	Cancer registry/ population register	Questionnaire	Incidence, colorectal cancer	per 100 ml/day	1.01 (0.99-1.02)	Age, sex, alcohol consumption, BMI, centre location, dairy products consumption, diabetes, educational level, energy from fat, energy from non-fat sources, fibre, HRT use, menopausal	Unit converted to cups/day
						High vs non/low consumption	1.06 (0.95-1.18)		
		2 691			Incidence, colon cancer	per 100 ml/day	1.00 (0.99-1.01)		
						High vs non/low consumption	0.99 (0.86-1.13)		
		1 242			Incidence, proximal colon cancer	per 100 ml/day	1.01 (0.99–1.03)		
						High vs non/low consumption	1.06 (0.87–1.30)		
		1 202			Incidence, distal colon cancer	per 100 ml/day	0.99 (0.97–1.01)		
						High vs non/low consumption	0.94 (0.76–1.15)		

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Missing data derived for analyses
		1 563/			Incidence, rectal cancer	per 100 ml/day	1.02 (1.00-1.03)	status, physical activity, red and processed meat, smoking	
						High vs non/low consumption	1.2 (1.00-1.44)		
Yamada, 2014 COL41013 Japan	JACC, Prospective Cohort, M/W	557/ 58 221 738 669 person-years	Cancer registry and hospital records	Self-administered questionnaire	Incidence, colorectal cancer, men	≥4 vs ≤1 cups/day	1.57 (0.97-2.55) Ptrend:0.03	Age, area, BMI, distillate consumption, drinking frequency, educational level, history of colorectal cancer, meat consumption, smoking, walking time	Mid-point categories
					Incidence, colorectal cancer, women		1.42 (0.57–3.50)		
					Incidence, colon, men		1.79 (1.01–3.18)		
					Incidence, colon, women		2.02 (0.81–5.03)		
					Incidence, rectal cancer, men		1.19 (0.48–2.95)		
					Incidence, rectal cancer, women	2-3 vs <1 cups/day	1.55 (0.89–2.69)		
Dominianni, 2013 COL40982 USA	PLCO, Prospective Cohort, Age: 55-74 years, M/W	681/ 57 398 11.4 years	Histology and medical records	FFQ	Incidence, colorectal cancer	≥4 cups/day vs none	1.08 (0.78-1.49)	Age, alcohol, alcohol intake, BMI, centre location, diabetes, educational	Mid-point categories Person-years of follow up in each category
					Incidence, proximal colon cancer		1.33 (0.86, 2.05		

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Missing data derived for analyses
					Incidence, distal colon cancer		1.11 (0.58, 2.13)	level, family history of colorectal cancer, fruit intake, gender, hormone use, meat intake, nsaid use, physical activity, race, sigmoidoscopy, smoking, vegetable intake	
					Incidence, rectal cancer		0.72 (0.36, 1.44)		
Sinha, 2012 COL40909 USA	NIH-AARP, Prospective Cohort, Age: 50-71 years, M/W, Retired	6 946/ 489 706 10.5 years	Cancer registry	FFQ	Incidence, colorectal cancer	≥6 cups/day vs <1 cups/week	0.80 (0.69-0.94)	Age, sex, alcohol, BMI, calcium, diabetes, educational level, energy intake, family history of colorectal cancer, fruits and vegetables consumption, HRT use, marital satus, nsaid use, race, red meat,	Mid-point categories Person-years of follow up in each category
		5 072			Incidence, colon cancer		0.74 (0.61, 0.89)		
		2 863			Incidence, proximal colon cancer		0.62 (0.48, 0.81)		
		1 993			Incidence, distal colon cancer		0.86 (0.64, 1.14)		
		1 874			Incidence, rectal cancer		1.01 (0.76, 1.34)		

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Missing data derived for analyses
								screening, smoking, time since quitting smoking, vigorous activity	
Nilsson LM, 2010 COL40816 Sweden	VIP, Prospective Cohort, M/W	321/ 64 603 15 years	Cancer registry	FFQ	Incidence, colorectal cancer	≥4 vs <1 servings/day	1.43 (0.86-2.38)	Age, sex, BMI, educational level, recreational physical activity, smoking	Mid-point categories
Bidel, 2010 COL40848 Sweden	Finland, 1972-2002, Prospective Cohort, Age: 25-74 years, M/W	538/ 62 013 34 years	Cancer registry	Questionnaire	Incidence, colorectal cancer	≥10 vs 0 cups/day	1.03 (0.58-1.83)	Age, alcohol consumption, BMI, diabetes mellitus, education years, leisure time physical activity, smoking, study, tea consumption	Mid-point categories
					Incidence, colon cancer		0.72 (0.35–1.47)		
					Incidence, rectal cancer		1.99 (0.71–5.55)		
Simons, 2010 COL40821 Netherlands	NLCS, Prospective Cohort, Age: 55-69 years,	1 260/ 120 852 13.3 years	Cancer registry and database of pathology reports	FFQ	Incidence, colorectal cancer, men	>6 vs ≤2 cups/day	1.00 (0.74-1.36)	Age, BMI, educational level, ethanol intake, family history of	
					Incidence, colorectal		1.07 (0.74–1.55)		

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Missing data derived for analyses
	M/W				cancer, women			colorectal cancer, fibre intake, folate intake, meat intake, non-occupational physical activity, physical activity, processed meat consumption, smoking, total fluid intake, vitamin b6 intake	
					Incidence, proximal colon cancer, men		0.91 (0.58–1.44)		
					Incidence, proximal colon cancer, women		1.12 (0.67–1.88)		
					Incidence, distal colon cancer, men		0.93 (0.59–1.47)		
					Incidence, distal colon cancer, women		0.96 (0.51–1.80)		
					Incidence, rectal cancer, men		1.60 (0.96–2.66)		
					Incidence, rectal cancer, women		1.41 (0.75–2.63)		
Lee, 2007 COL40654 Japan	JPHC, Prospective Cohort, Age: 52 years, M/W	726/ 96 162 10 years	Active patient notification from hospitals, cancer registries and death cert.	Questionnaire	Incidence, colorectal cancer, men	≥3 cups/day vs almost never	1.10 (0.82-1.47) Ptrend:0.91	Age, alcohol drinking, beef consumption, black tea consumption, BMI, chinese tea, family history of	Mid-point categories
		437/			Incidence, colorectal cancer, women		0.68 (0.40–1.15)		
		447/			Incidence, colon cancer, men		1.15 (0.80–1.66)		

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Missing data derived for analyses
		286/			Incidence, colon cancer, women		0.60(0.31–1.19)	colorectal cancer, green tea consumption, green vegetables, physical activity, pork, smoking status, study centre	
		249/			Incidence, rectal cancer, men		1.01 (0.61–1.66)		
		151/			Incidence, rectal cancer, women		0.84 (0.36–1.94)		
Naganuma, 2007 COL40650 Japan	MCS, Prospective Cohort, Age: 40-64 years, M/W	457/ 38 701 11 years	Cancer registry and death certificates and medical records	FFQ	Incidence, colorectal cancer	≥3 vs never cups/day	0.95 (0.65-1.39)	Age, sex, alcohol intake, black tea consumption, BMI, educational level, family history of colorectal cancer, fruits, green tea consumption, meat intake, smoking status, total caloric intake, vegetable intake	Mid-point categories
					Incidence, colon cancer		0.96 (0.58–1.59)		
					Incidence, proximal colon cancer		1.00 (0.52–1.94)		
					Incidence, distal colon cancer		0.88 (0.37–2.09)		
					Incidence, rectal cancer		0.94 (0.53–1.66)		
Larsson, 2006 COL40628	Cohort of Swedish men	1 279/ 106 739	Record linkage with cancer	FFQ	Incidence, colorectal cancer	per 1 cup/day	1.00 (0.97-1.04)	Age, BMI, educational	Mid-point categories
						≥4 vs <1	1.14 (0.90-1.44)		

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Missing data derived for analyses
Sweden	and Swedish Mammography Cohort, Prospective Cohort, M/W	1 240 597 person-years	registries			cups/day		level, fruits, milk, red meat intake, total energy intake, vegetable intake	
					Incidence, colon cancer	≥4 vs <1 cups/day	1.19 (0.89-1.60)		
						per 1 cup/day	1.00 (0.95-1.05)		
					Incidence, rectal cancer	≥4 vs <1 cups/day	1.06 (0.71-1.75)		
						per 1 cup/day	1.00 (0.94-1.07)		
Oba, 2006 COL40626 Japan	TCCJ, Prospective Cohort, Age: 35-101 years, M/W	111/ 30 221 8 years	Hospital records and cancer registry	Semi-quantitative FFQ	Incidence, colon cancer, men	1cup/day or more vs never-<1cup/mth	0.81 (0.46-1.42)	Age, alcohol intake, BMI, energy intake, height, pack-years of smoking, physical activity	Mid-point categories
					Incidence, colon cancer, women		0.43 (0.22–0.85)		
Michels, 2005 COL40754 USA	NHS-HPFS, Prospective Cohort, Age: 30-75 years, M/W	886/ 133 893 1 991 605 person-years	Self-report verified by medical record	Semi-quantitative FFQ	Incidence, colorectal cancer	> 5 cup/day vs never	0.98 (0.69-1.38)	Age, alcohol consumption, aspirin use, BMI, energy intake, family history of colorectal cancer, height, HRT use, menopausal	Mid-point categories
						Per 1 cup/day	0.99 (0.96-1.03)		
					Incidence, colon cancer	> 5 cup/day vs never	0.98 (0.68-1.41)		
						Per 1 cup/day	0.98 (0.95-1.02)		
					Incidence, rectal cancer	≥ 4-5 cup/day vs never	1.55 (0.97-2.45)		

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Missing data derived for analyses
						Per 1 cup/day	1.04 (0.96-1.13)	status, pack-years of smoking, physical activity, previous sigmoidoscopy, red meat intake, vitamin use	
Hartman, 1998 COL00214 Finland	ATBC, Nested Case Control, Age: 50-69 years, M, Male Smokers	106/ 27002 controls 6.1 years	Cancer registry	Recall questionnaire + FFQ	Incidence, colon cancer	> 6 vs ≤ 4 cups/day	0.84 (0.50-1.40)	Age, BMI, calcium, Intervention group, occupational physical activity	Mid-point categories
		79/			Incidence, rectal cancer		0.77 (0.43-1.40)		
Stensvold, 1994 COL00321 Norway	Norwegian health survey for cardiovascular disease, Prospective Cohort, Age: 35-54 years, M/W	78/ 42 973 432 773 person-years	Population registries	FFQ	Incidence, colon cancer, men	≥7 vs ≤2 cups/day	1.20	Age, county of residence, smoking habits	Confidence intervals were calculated
					Incidence, colon cancer, women		0.8		
					Incidence, rectal cancer, men		0.7		
					Incidence, rectal cancer, women		0.7		

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Missing data derived for analyses
Klatsky, 1988 COL00656 USA	KPMCP, Nested Case Control, M/W	203/ 2 410	Hospital records	Questionnaire	Incidence, colon cancer	per 1 cups/day	0.92 (0.80-1.06)	Age, sex, smoking, race, education	
		66/			Incidence, rectal cancer		0.84 (0.66-1.07)		
Wu, 1987 COL00774 USA	Leisure World Cohort, Prospective Cohort, M/W, Retirement community	68/ 11 644 4.5 years	Population registries	FFQ	Incidence, colorectal cancer, women	≥4 vs 0-1 cups/day	1.17 (0.40-3.10)	Age	Mid-point categories
					Incidence, colorectal cancer, men		1.54 (0.6-3.7)		

Table 134 Main characteristics of studies excluded from the CUP SLR dose-response meta-analysis.

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Reasons for exclusion
Peterson, 2010 COL40820 Singapore	SCHS, Prospective Cohort, Age: 45-74 years, M/W	325/ 61 321 9.8 years	Cancer registry and pathology register		Incidence, advanced colon cancer	>2 vs <1 cups/day	0.89 (0.66-1.19) Ptrend:0.40	Age, alcohol, BMI, diabetes, dialect group, educational level, family history of colorectal cancer, gender, green tea, physical activity, smoking, year	Advanced and localized colon cancer
		229/ 61 321 9.8 years			Incidence, localized colon cancer	>2 vs <1 cups/day	0.82 (0.59-1.14) Ptrend:0.24		
Mucci, 2006 COL40750 Sweden	SMC, Prospective Cohort, Age: 40-75 years, W	741/ 61 467 823 072 person-years	Cancer registry	FFQ	Incidence, colorectal cancer	≥4 vs ≤1 cups/day	1.00 (0.70-1.30)	Age, alcohol intake, BMI, educational level, energy intake, fibre intake, saturated fat	Superseded by Larsson, 2006 COL40628
		504/ 61 467 823 072 person-years			Incidence, colon cancer	≥4 vs ≤1 cups/day	1.10 (0.80-1.50)		
		237/ 61 467 823 072 person-years			Incidence, rectal cancer	≥4 vs ≤1 cups/day	0.90 (0.60-1.40)		
Terry, 2001	SMC,	460/	Cancer registry	Questionnaire	Incidence,	≥4 vs ≤1	1.04 (0.70-1.54)	Age, alcohol	Superseded by

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Reasons for exclusion
COL00553 Sweden	Prospective Cohort, Age: 40-74 years, W	61 463 588 270 person-years			colorectal cancer,	cups/day	Ptrend:0.95	consumption, BMI, calcium, dietary fibre, educational level, energy intake, folic acid, red meat intake, total fat, vitamin c, vitamin d	Larsson, 2006 COL40628
Suadicani, 1993 COL01085 Denmark	Denmark, Copenhagen fitness and risk of cvd study, Prospective Cohort, Age: 40-59 years, M	51/ 5 429 18 years	Public or private companies	Questionnaire	Incidence, colon cancer			Age	No RR reported
Jacobsen, 1986 COL01385 Norway, USA	Norwegian composite cohort consisting of 3 groups, Prospective Cohort, M/W	97/ 10 517 11.5 years	Questionnaire	Questionnaire	Incidence, colon cancer	≥7 vs 0-2 cups/day	0.54 Ptrend:0.10	Age, sex, alcohol consumption, residence	Description of cancer outcome is not the same as other studies included in the meta-analysis (colon cancer is including rectosigmoid
		63/ 10 517 11.5 years			Incidence, rectal cancer	≥7 vs 0-2 cups/day	1.07 Ptrend:0.94		

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Reasons for exclusion
									and rectal cancer excluding rectosigmiod)
Nomura, 1986 COL00708 USA	HHP, Prospective Cohort, Age: 45-68 years, M, Japanese ancestry	108/ 7 355	Population	Dietary history questionnaire	Incidence, colon cancer,	≥5 vs 0 cups/day	Ptrend:0.984	Age	No RR available

Figure 233 RR estimates of colorectal cancer by levels of coffee consumption

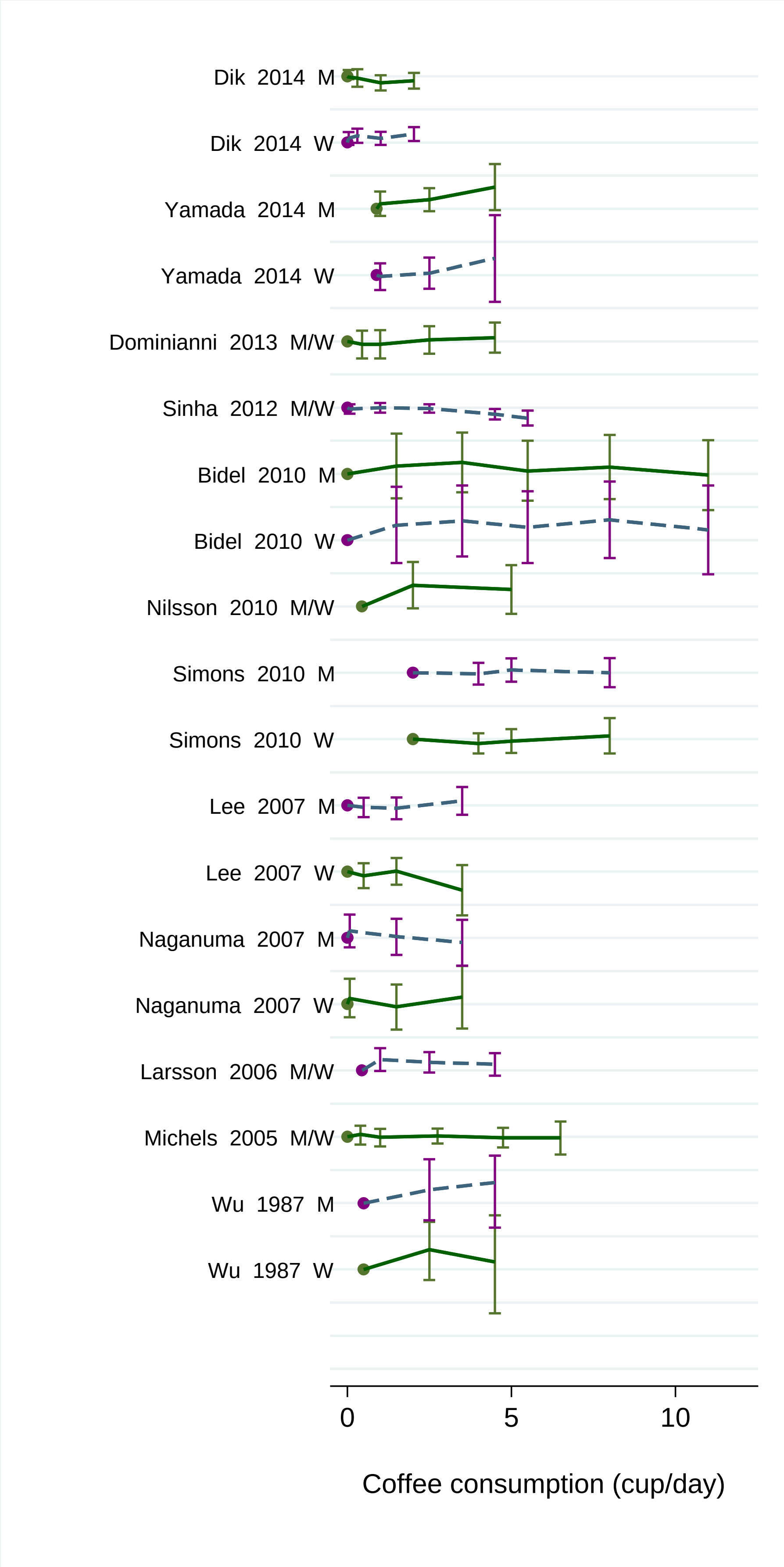


Figure 234 RR (95% CI) of colorectal cancer for the highest compared with the lowest level of coffee consumption

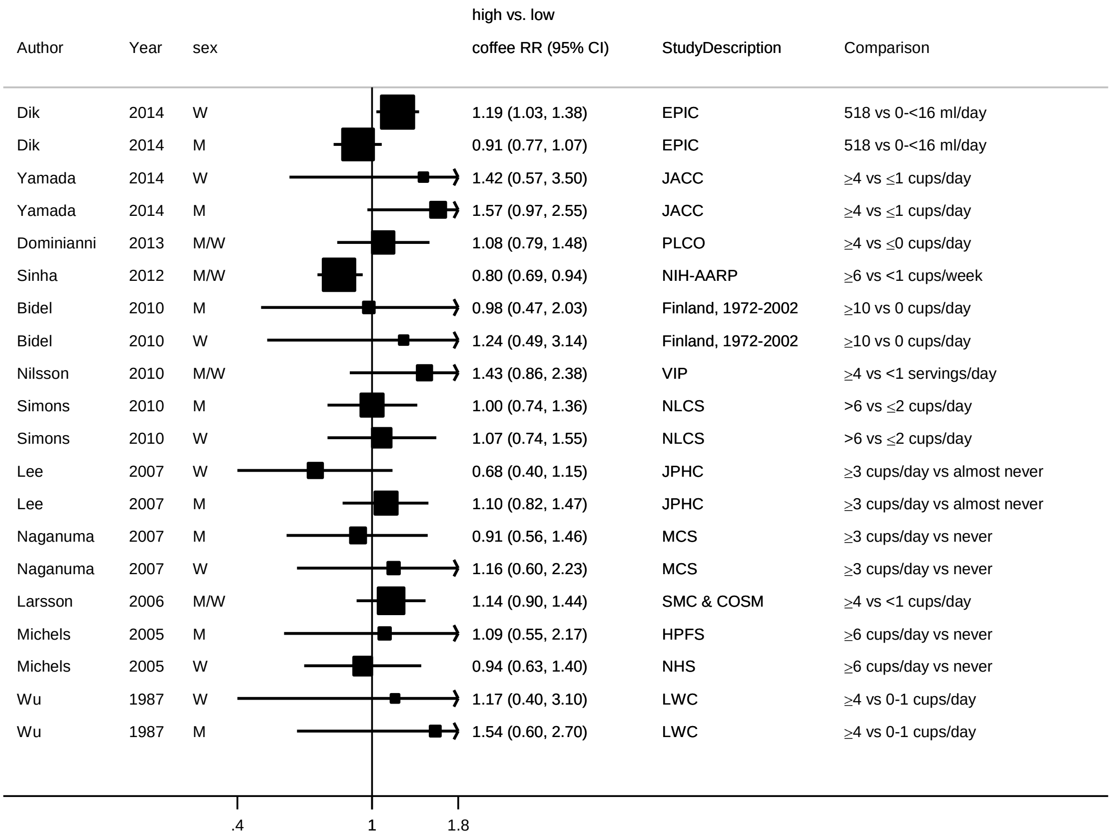


Figure 235 RR (95% CI) of colorectal cancer for 1 cup/day increase of coffee consumption

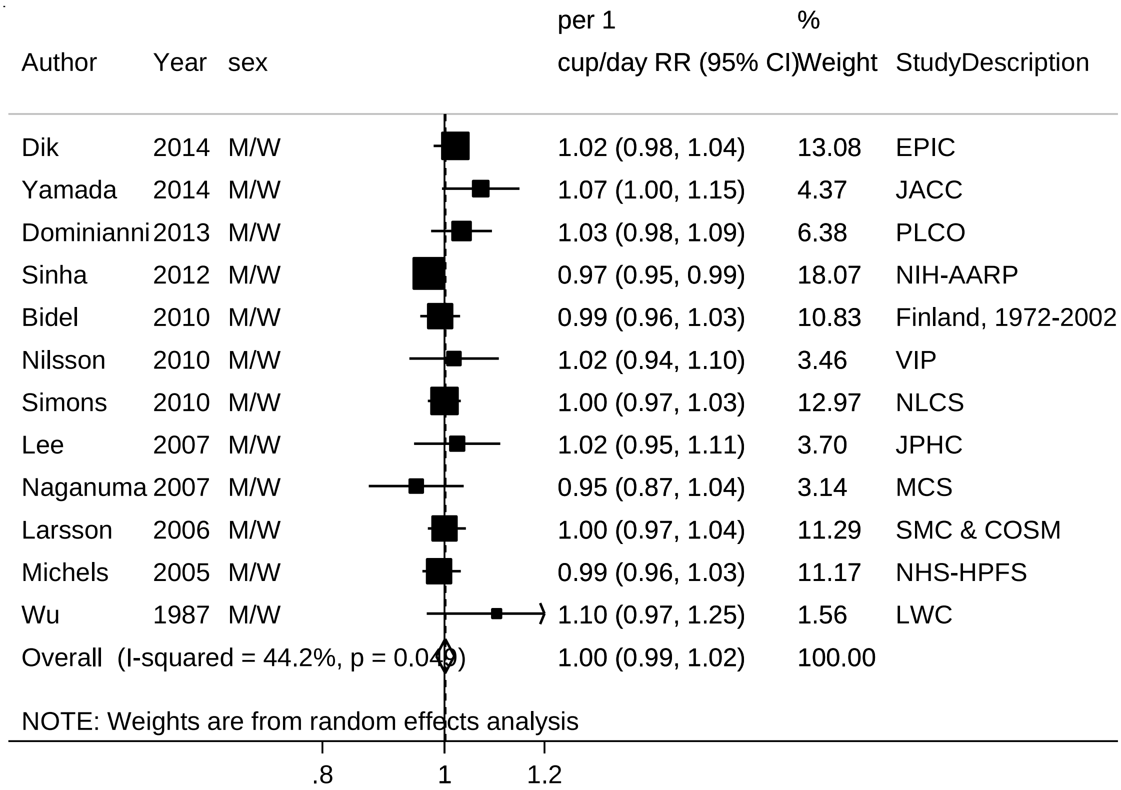


Figure 236 RR (95% CI) of colorectal cancer for 1 cup/day increase of coffee consumption by sex

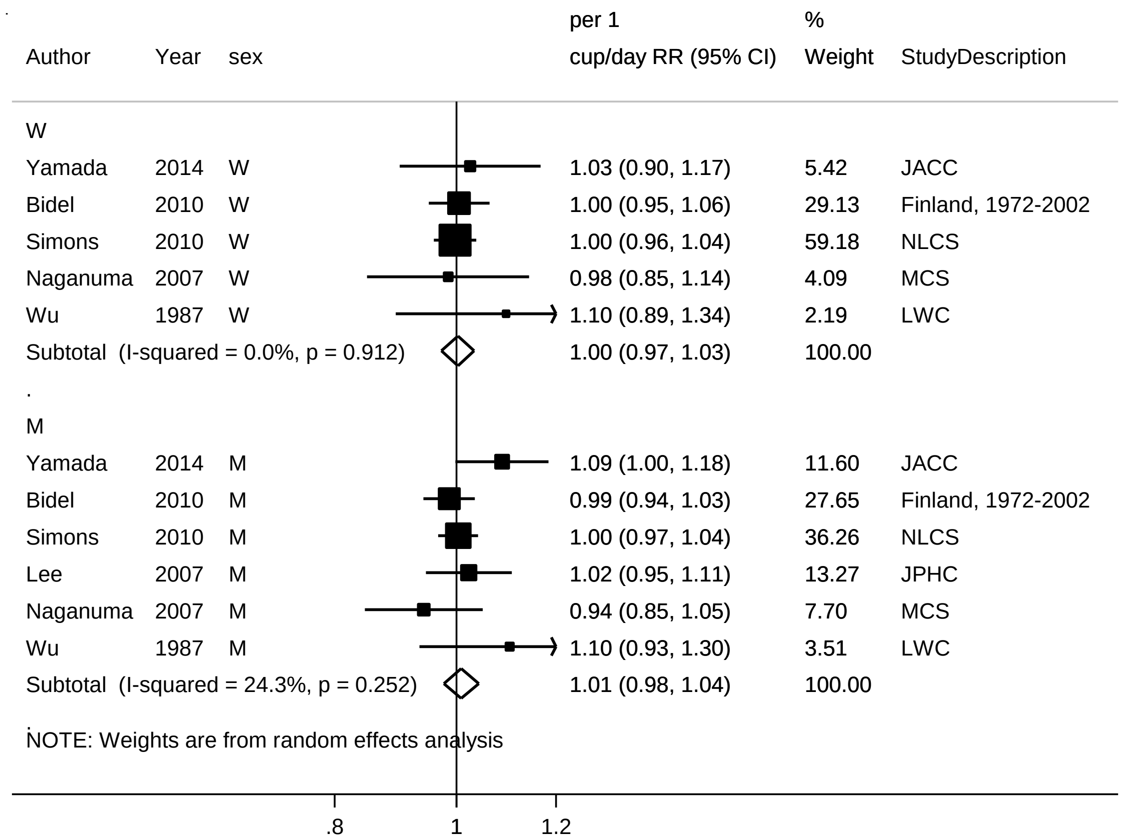
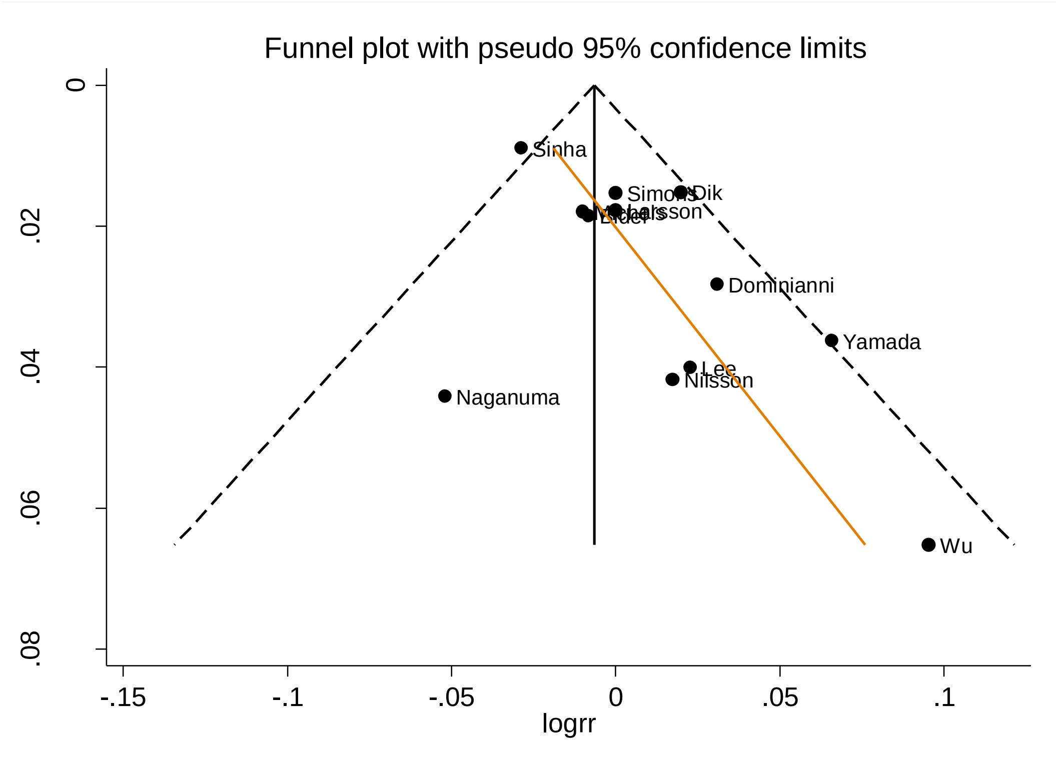


Figure 237 Funnel plot of studies included in the dose response meta-analysis coffee consumption and colorectal cancer



p for Egger's test=0.002

Figure 238 RR (95% CI) of colorectal cancer for 1 cup/day increase of coffee consumption by geographic location

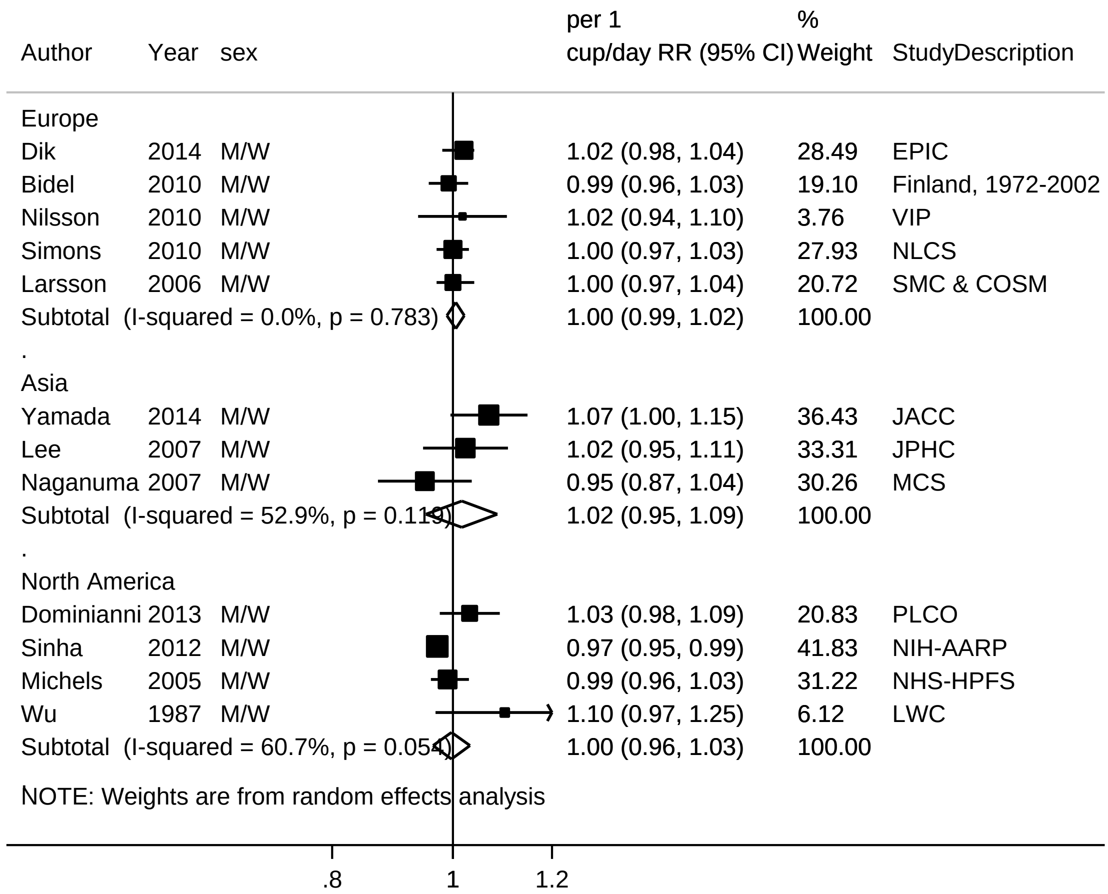
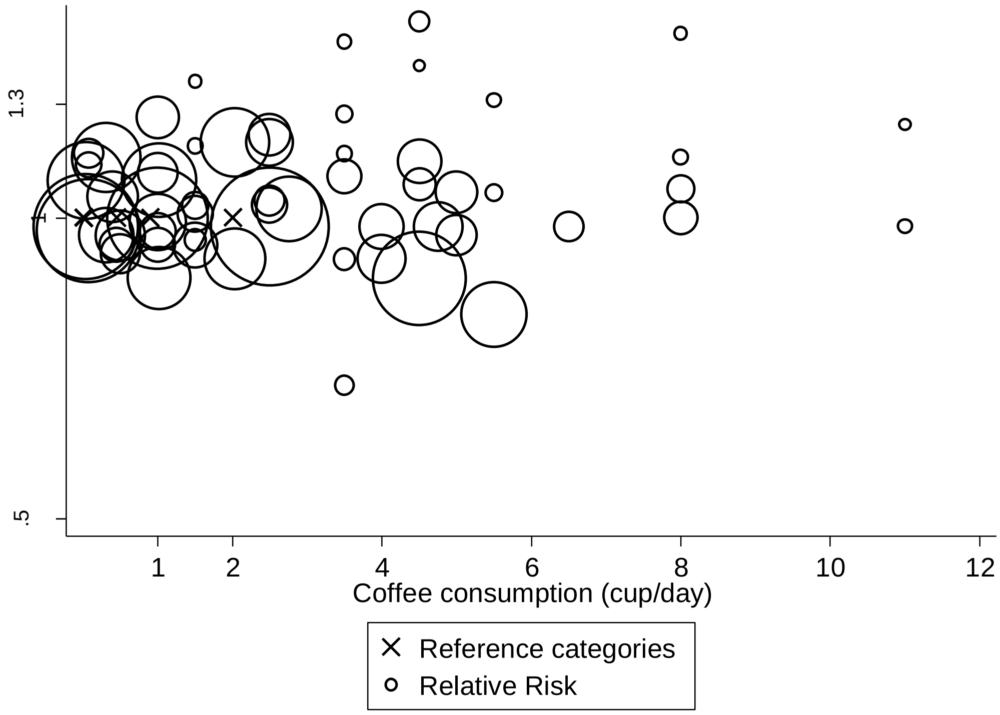
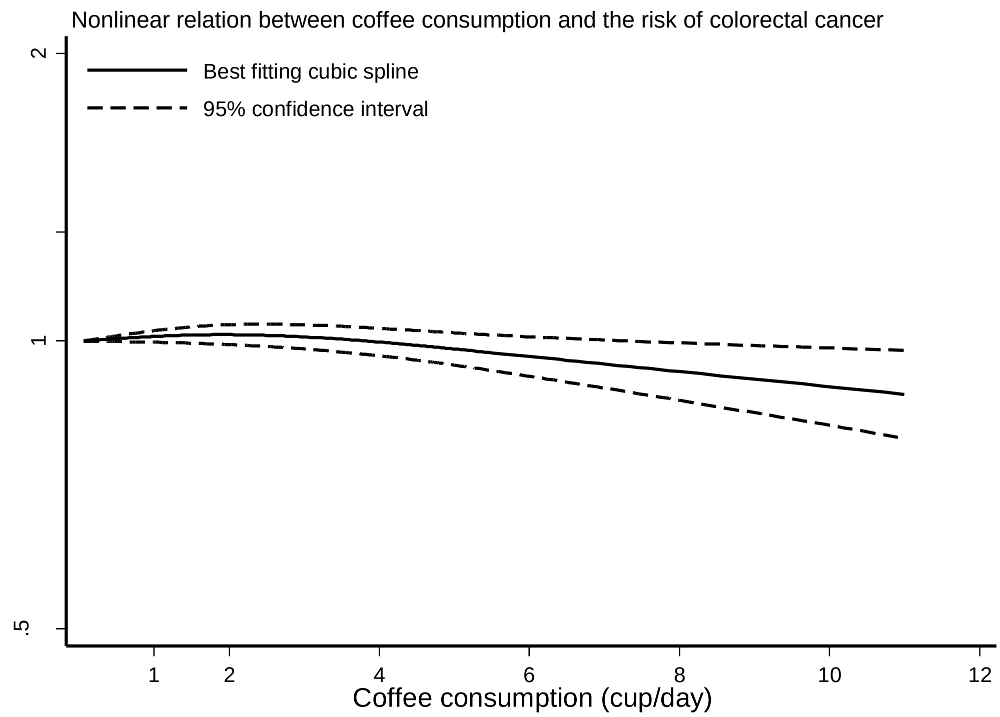


Figure 239 Relative risk of colorectal cancer and Coffee consumption estimated using non-linear models





p for non-linearity=0.011

Table 135 Table with coffee consumption values and corresponding RRs (95% CIs) for non-linear analysis of coffee consumption and colorectal cancer

Coffee consumption (cup/day)	RR (95%CI)
0	1.00
0.5	1.01 (1.00-1.01)
2.5	1.01 (0.99-1.04)
4.5	0.99 (0.96-1.03)
6.5	0.95 (0.91-1.01)
8.0	0.93 (0.87-1.00)
11	0.88 (0.79-0.98)

Figure 240 RR estimates of colon cancer by levels of coffee consumption

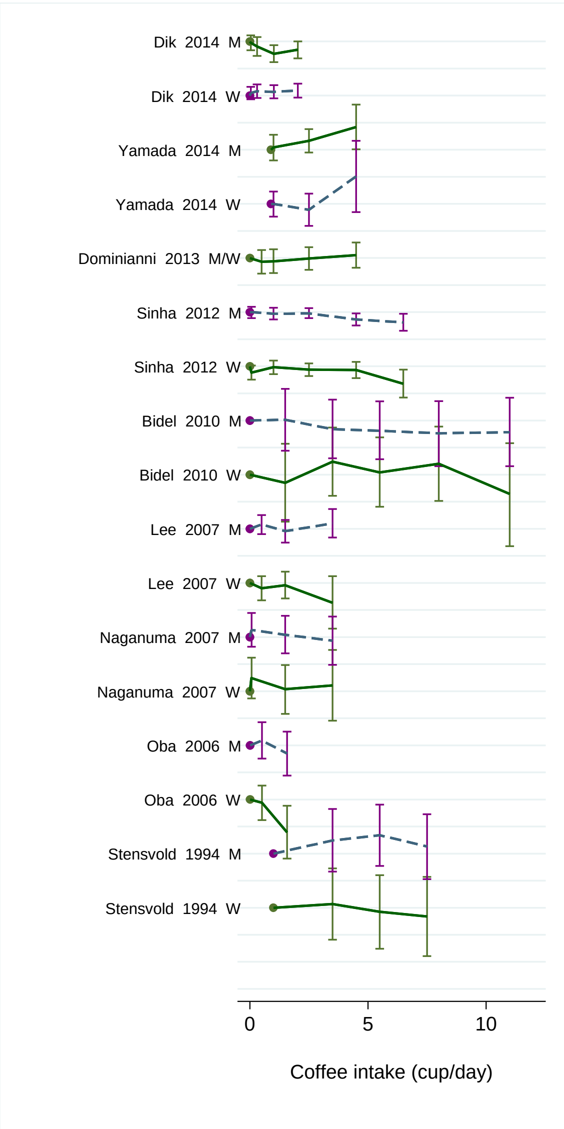


Figure 241 RR (95% CI) of colon cancer for the highest compared with the lowest level of coffee consumption

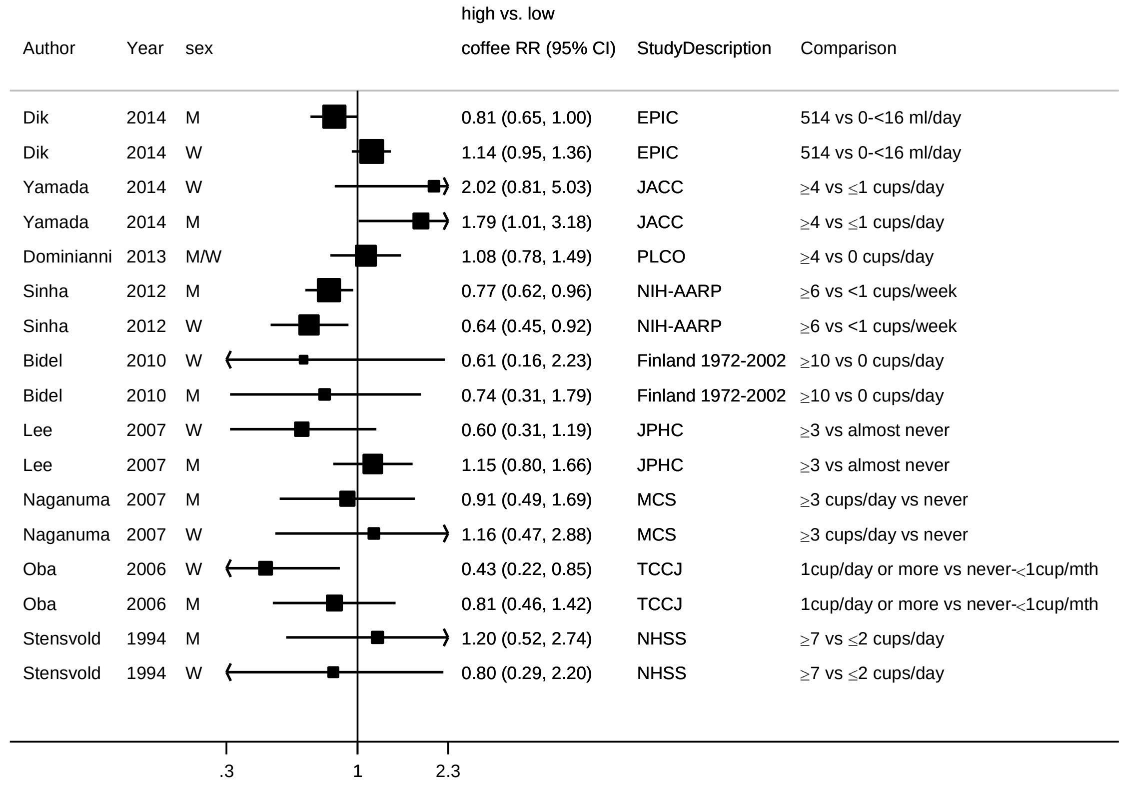


Figure 242 RR (95% CI) of colon cancer for 1 cup/day increase of coffee consumption

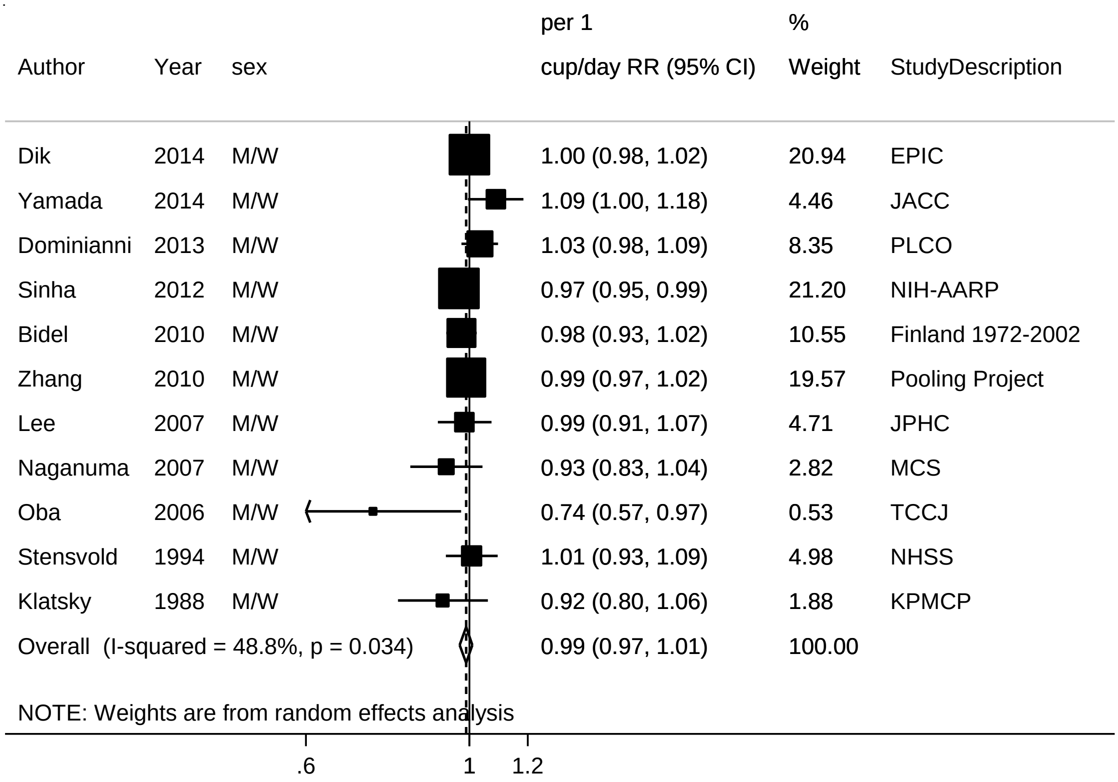
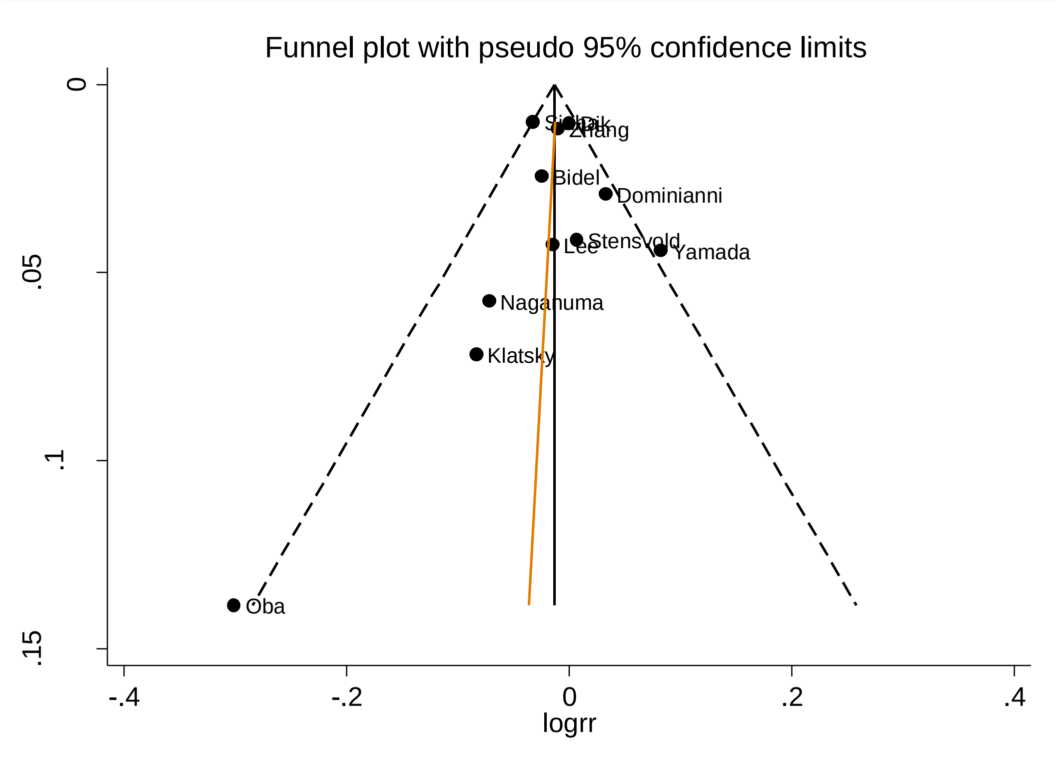


Figure 243 Funnel plot of studies included in the dose response meta-analysis Coffee consumption and colon cancer



p for Egger's test=0.55

Figure 244 RR (95% CI) of colon cancer for 1 cup/day increase of Coffee consumption by sex

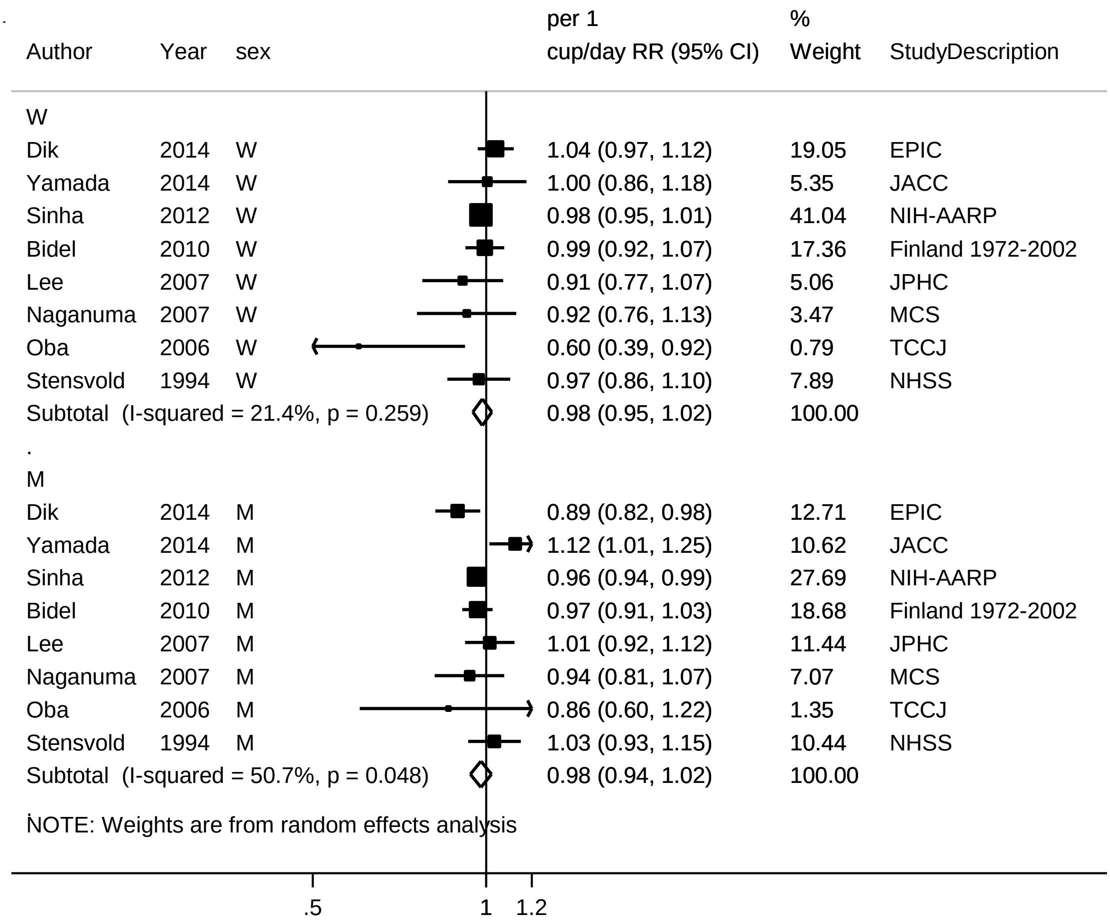


Figure 245 RR (95% CI) of colon cancer for 1 cup/day increase of coffee consumption by geographic location

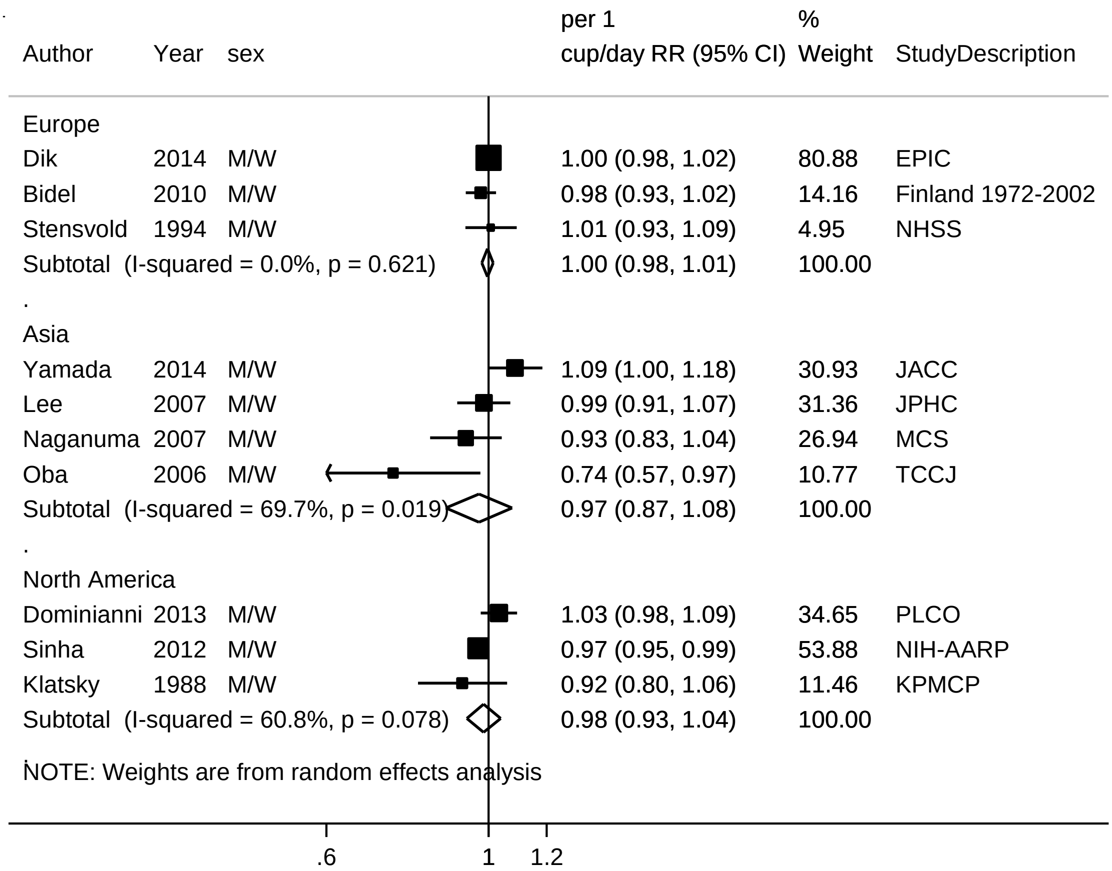
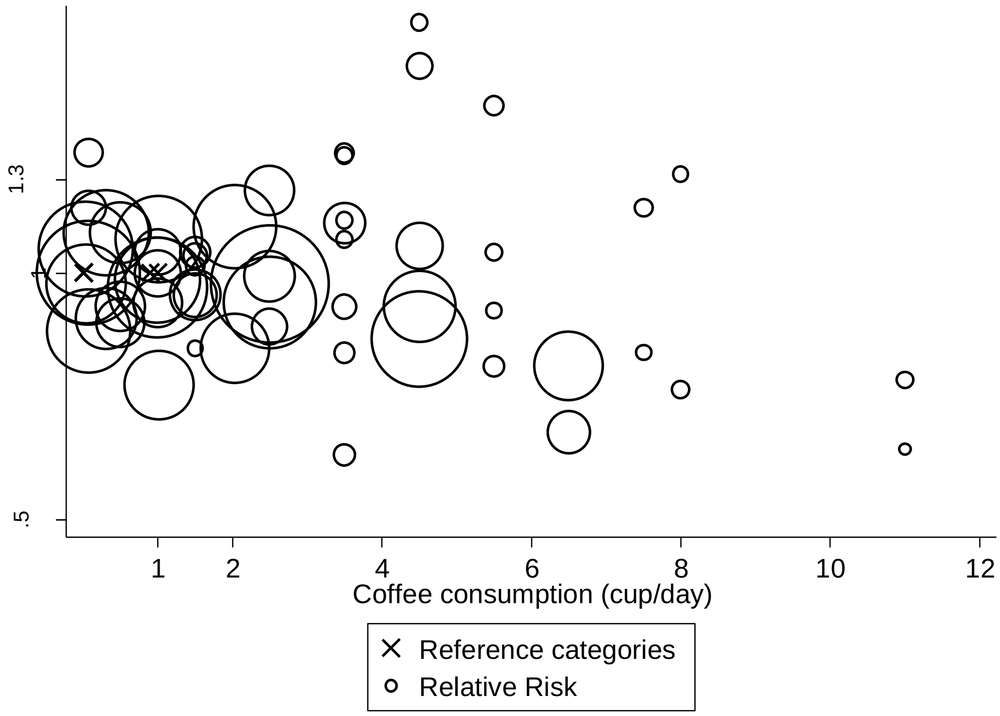
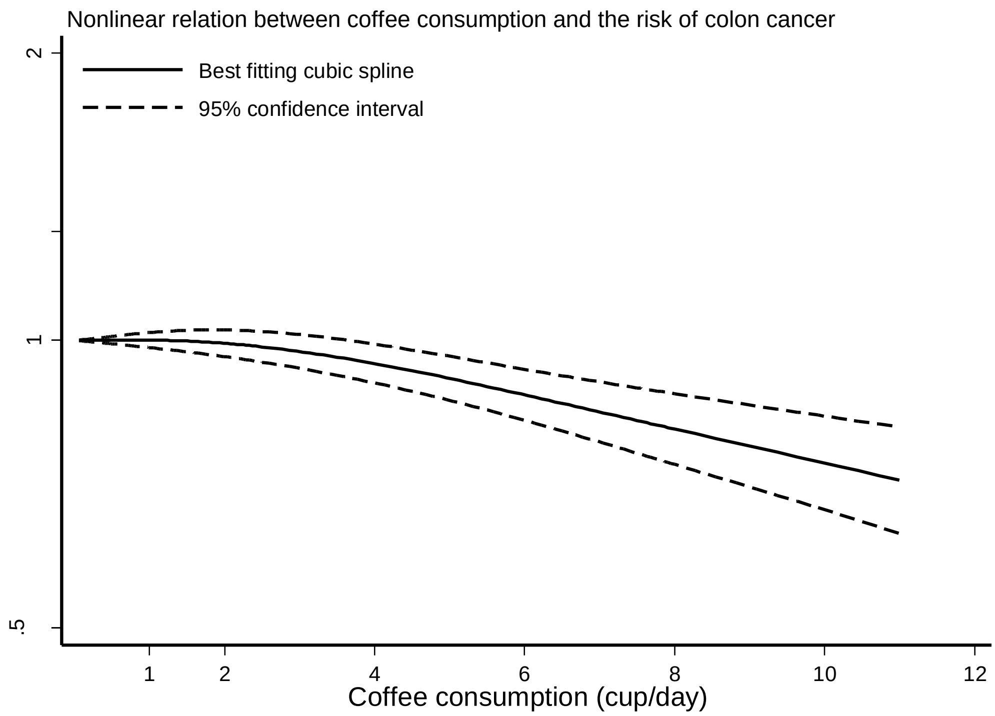


Figure 246 Relative risk of colon cancer and coffee consumption estimated using non-linear models





p for non-linearity=0.004

Table 136 Table with height values and corresponding RRs (95% CIs) for non-linear analysis of Coffee consumption and colon cancer

Coffee consumption (cup/day)	RR (95%CI)
0	1.00
0.5	1.00 (0.99-1.01)
2.5	0.98 (0.95-1.02)
4.5	0.93 (0.88-0.98)
6.5	0.86 (0.80-0.92)
8	0.81 (0.74-0.88)
11	0.71 (0.63-0.81)

Figure 247 RR (95% CI) of proximal colon cancer for 1 cup/day increase of coffee consumption

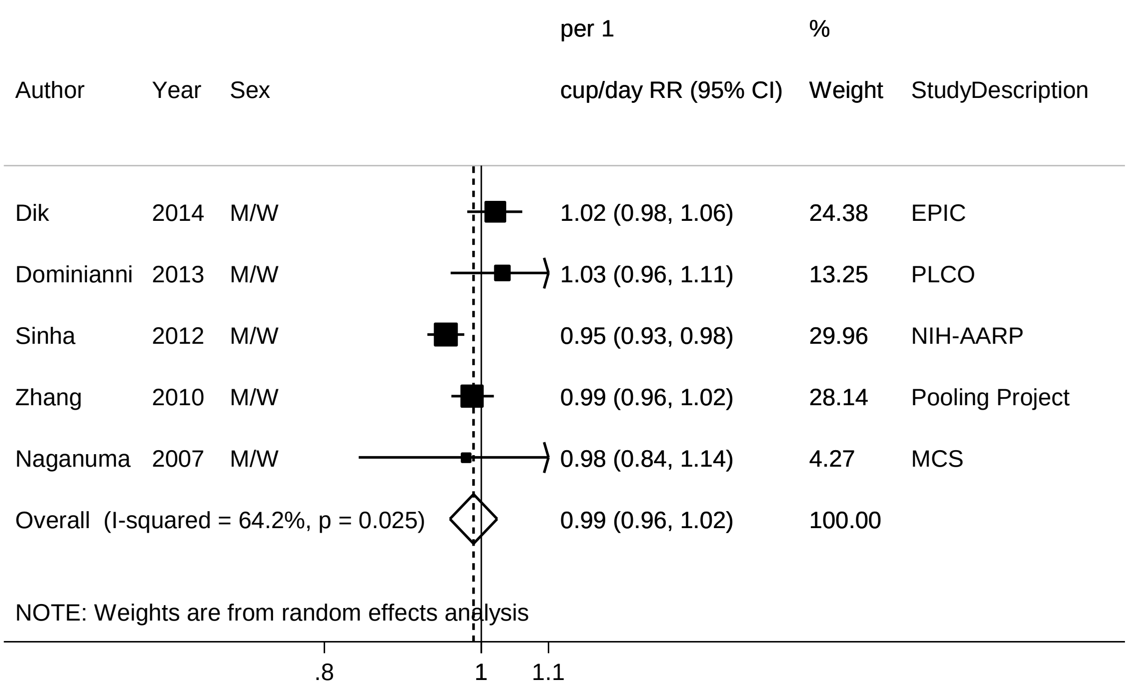


Figure 248 RR (95% CI) of distal colon cancer for 1 cup/day increase of coffee consumption

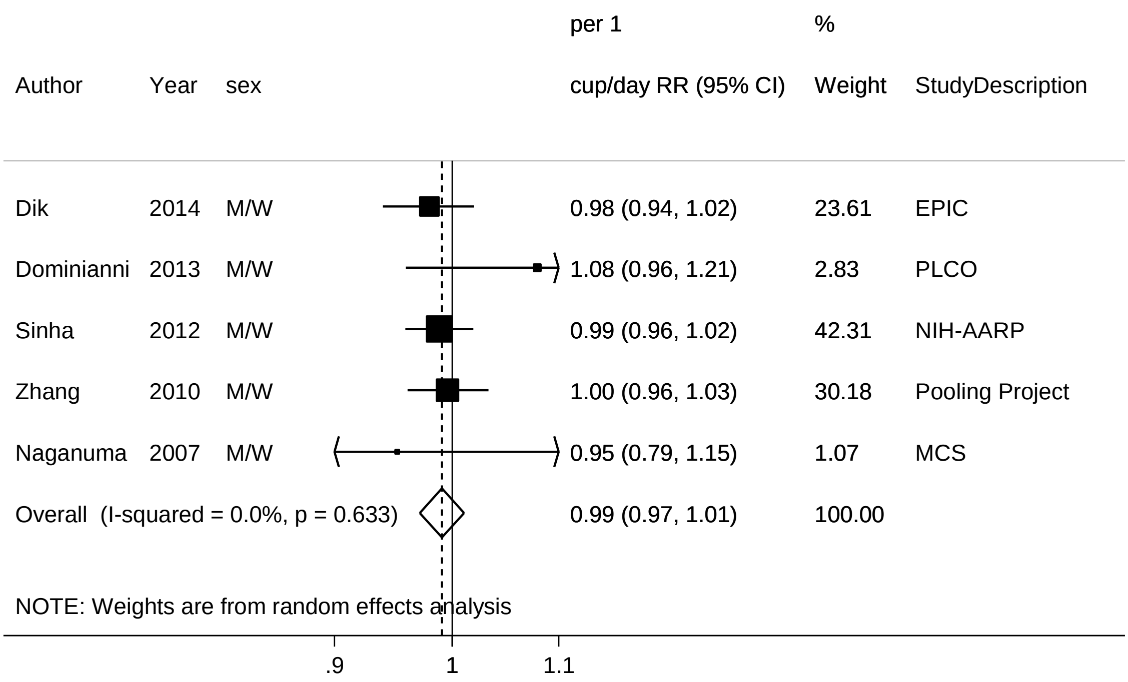


Figure 249 RR (95% CI) of rectal cancer for the highest compared with the lowest level of coffee consumption

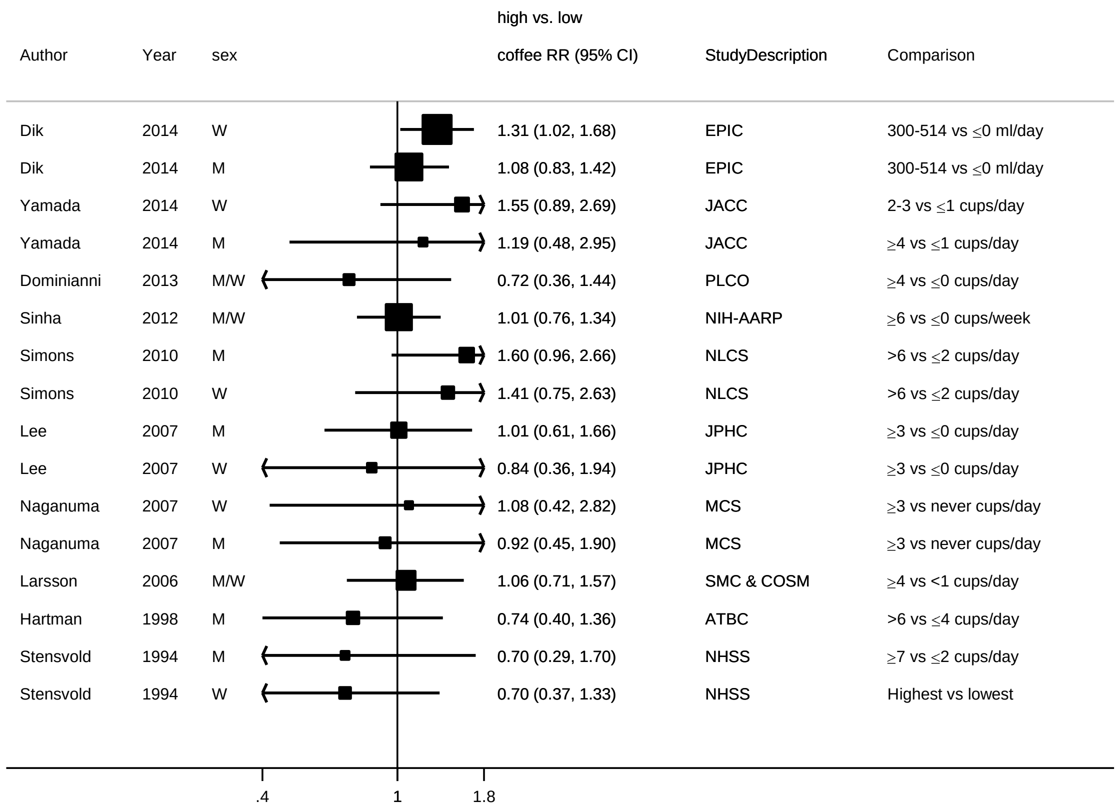


Figure 250 RR estimates of rectal cancer by levels of coffee consumption

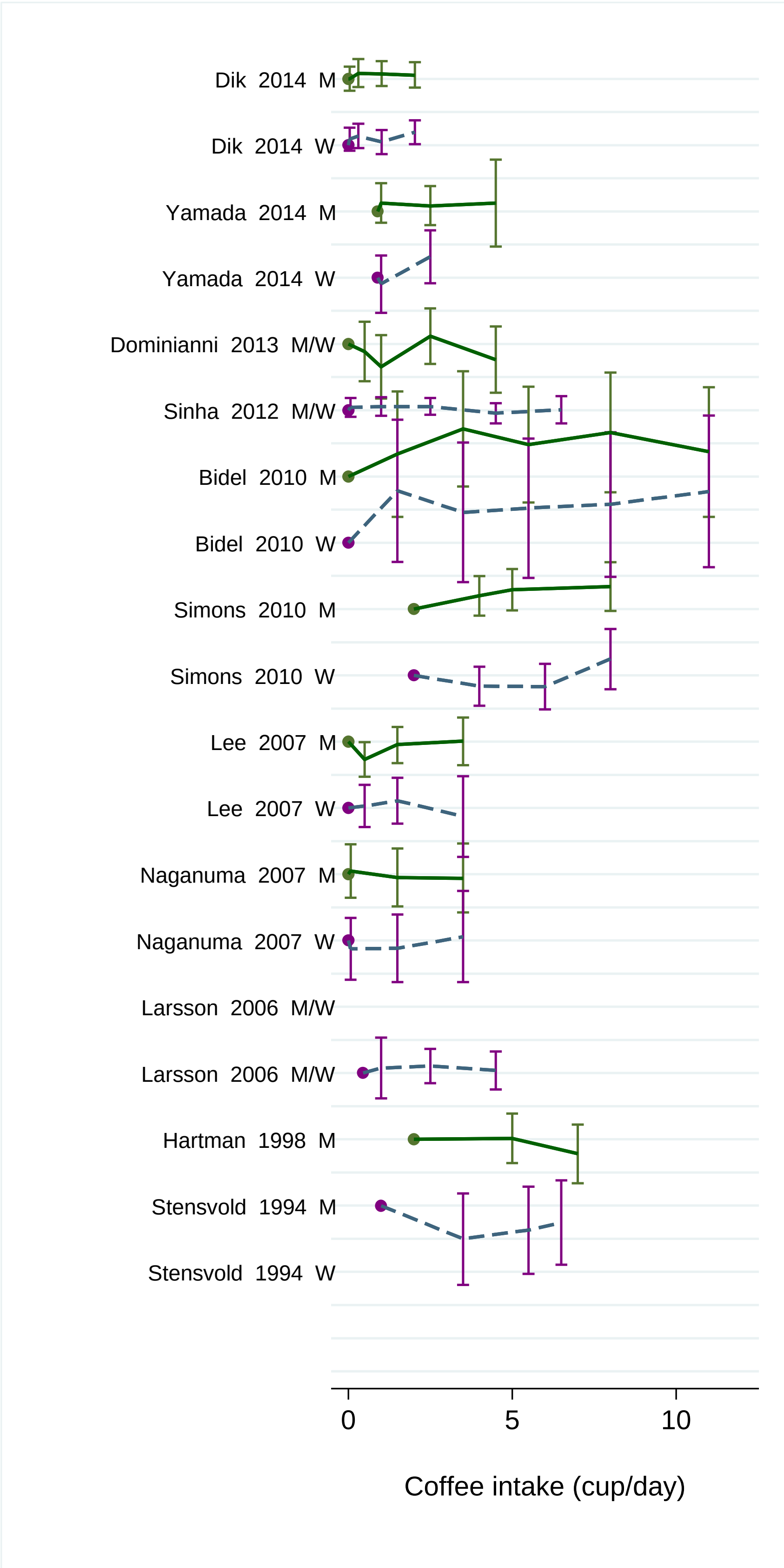


Figure 251 RR (95% CI) of rectal cancer for 1 cup/day increase of coffee consumption

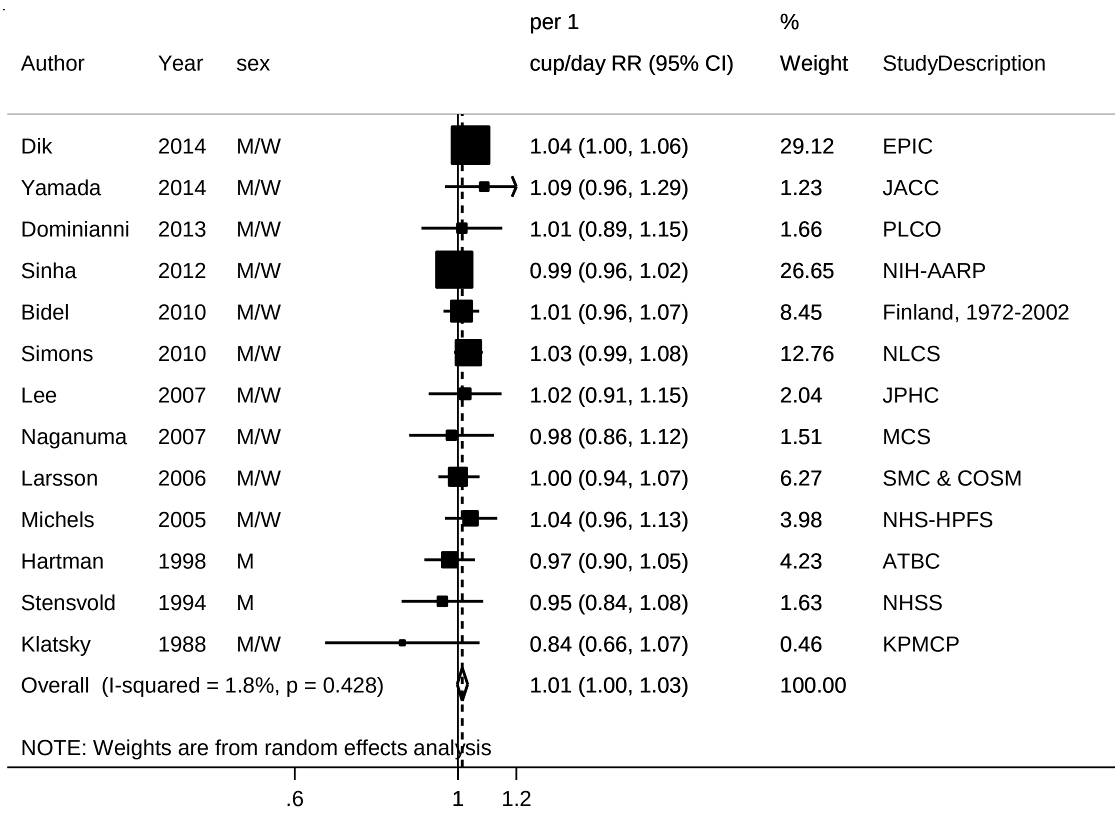
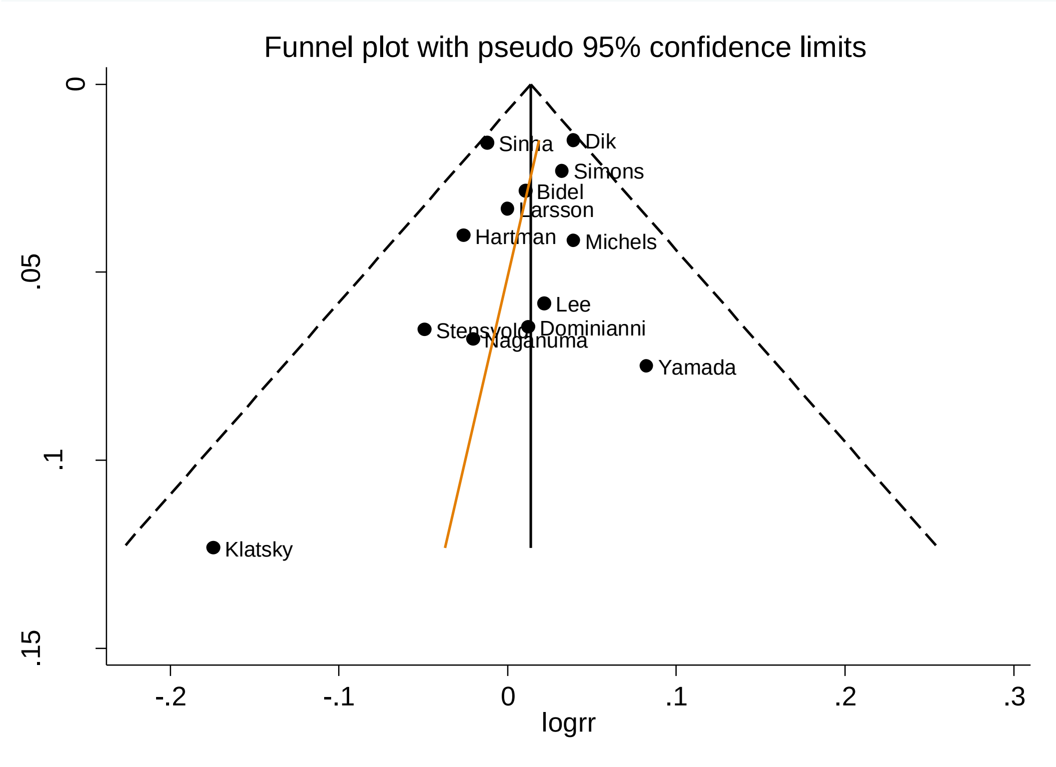


Figure 252 Funnel plot of studies included in the dose response meta-analysis coffee consumption and rectal cancer



p for Egger's test=0.73

Figure 253 RR (95% CI) of rectal cancer for 1 cup/day increase of coffee consumption by sex

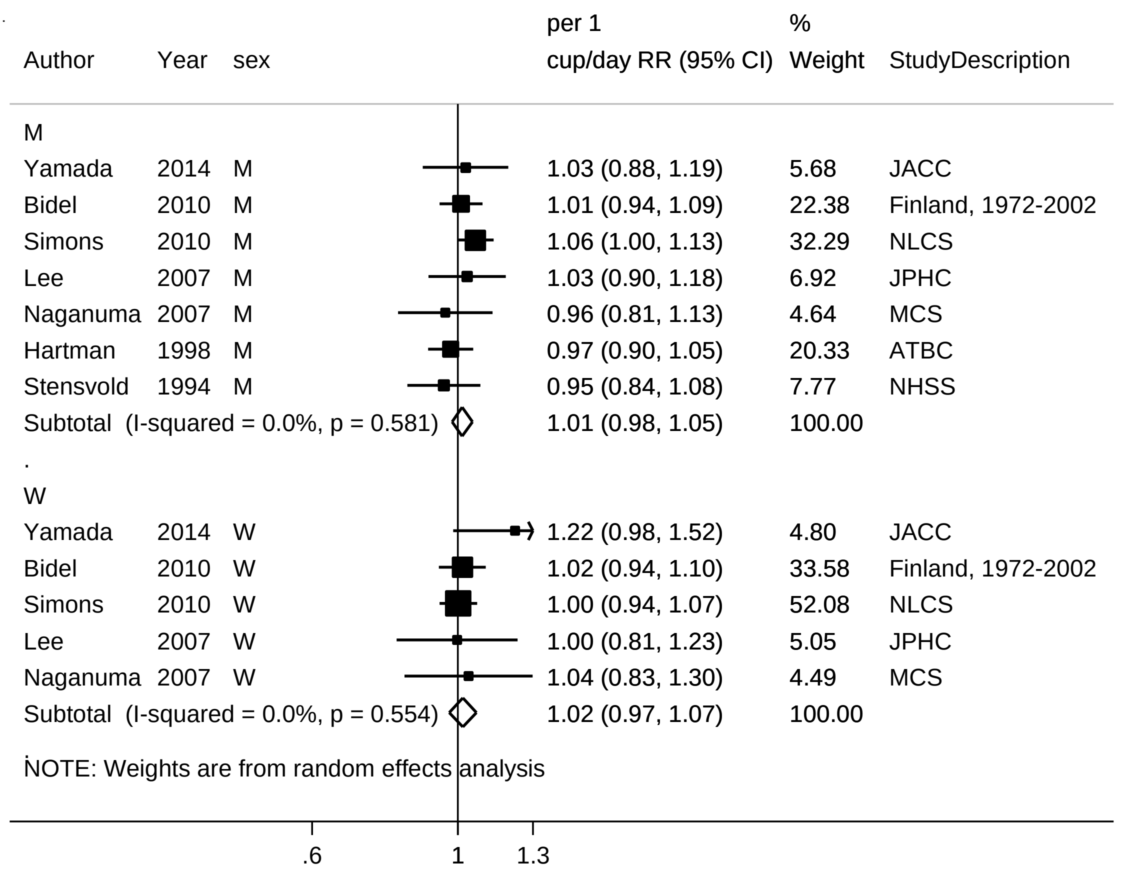
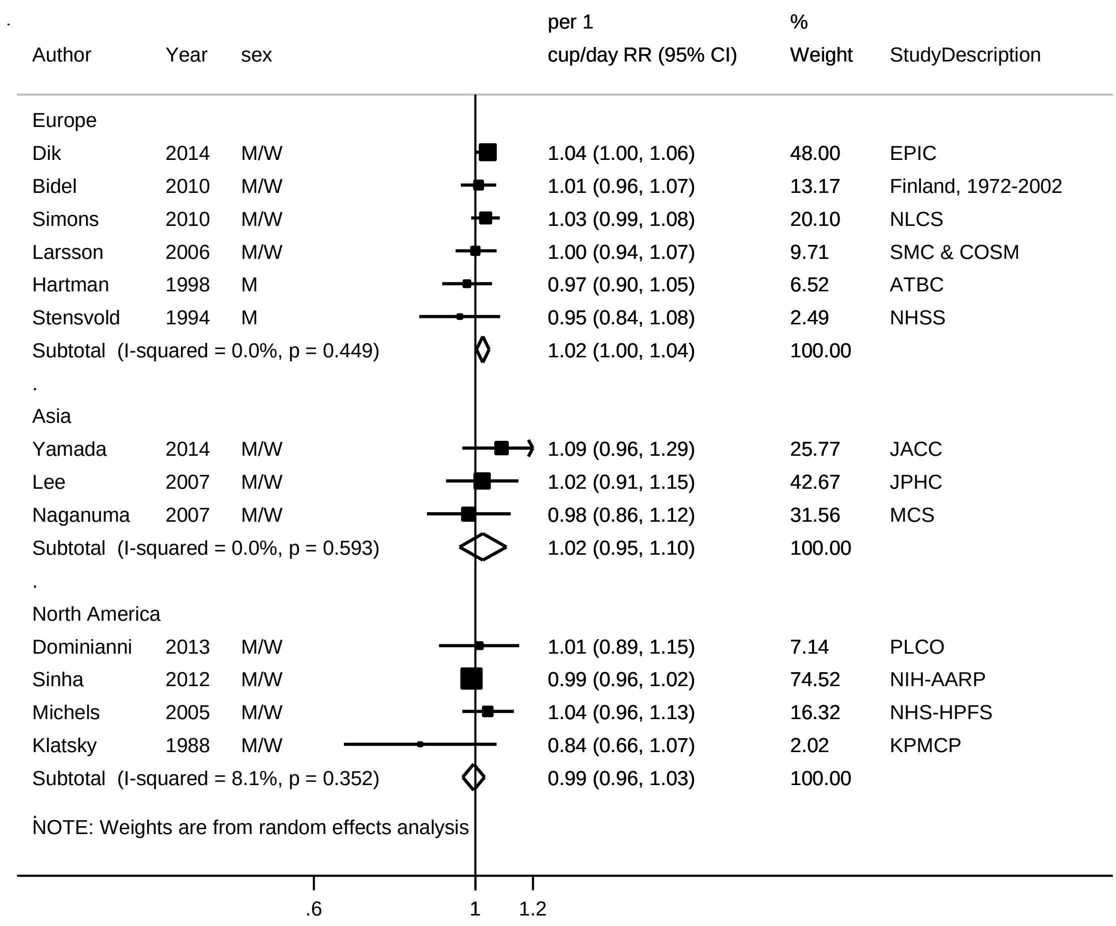


Figure 254 RR (95% CI) of rectal cancer for 1 cup/day increase of coffee consumption by geographic location



3.6.2 Tea

Cohort studies

Summary

Main results:
No meta-analysis was conducted in the CUP SLR 2010. In total, thirteen studies (sixteen publications) identified, including four new studies which were published after 2010. The Pooling Project of Prospective Studies of Diet and Cancer, including 11 studies, were included in the analysis. All the analyses are on cancer incidence.

Colorectal cancer:
Eight studies (16 251 cases) were included in the dose-response meta-analysis of tea consumption and colorectal cancer. No significant association was observed. In stratified analysis by location, no significant association was observed.
There was no evidence of small study bias (p=0.42). There was no evidence of a non-linear association (p=0.13).
In sensitivity analysis, the summary RRs did not change materially when excluding the studies in turn.

Colon cancer:
Sixteen studies (13 244) were included in the dose-response meta-analysis. No significant association was observed. Thirteen cohort studies were included in the Pooling Project (Zhang, 2010). There was no evidence of small study bias (p=0.33). The visual inspection of funnel plot shows the study of Su, 2002 was an outlier.
There was no evidence of a non-linear association (p=0.97).

In sensitivity analysis, the summary RRs did not change materially when excluding the studies in turn.
Four studies including 13 838 and 14 392 cases were included in the dose-response meta-analysis for proximal and distal colon cancer, respectively. No significant association was observed.

Rectal cancer:
Sixteen studies (4 621 cases), including 11 studies in the Pooling Project, were included in the dose-response meta-analysis. No significant association was observed.
In stratified analysis by location, no significant association was observed.
There was evidence of small study bias (p=0.04).
There was an evidence of a non-linear association (p=0.03). The non-linear analysis showed a decreased risk of rectal cancer with consumption of tea up to 3 cups/day.

The summary RRs ranged from 0.97 (95% CI: 0.93-1.01) when Dik, 2014 was omitted to 1.01 (95% CI: 0.98-1.05) when Simons, 2010 was omitted from the analysis.

Study quality:
Cancer outcome was confirmed using cancer registry records in most studies and tea intake was assessed using FFQ or questionnaire in all studies.

Table 137 Tea consumption and colorectal cancer risk. Number of studies in the CUP SLR

	Number
Studies identified	9
Studies included in forest plot of highest compared with lowest categories	8
Studies included in dose-response meta-analysis	8
Studies included in non-linear dose-response meta-analysis	7

Note: Include cohort, nested case-control and case-cohort designs

Table 138 Tea consumption and colon cancer risk. Number of studies in the CUP SLR

	Number
Studies identified	16* (including Pooling project study)
Studies included in forest plot of highest compared with lowest categories	16 (5 plus 11 studies included in the Pooling Project)
Studies included in dose-response meta-analysis	16
Studies included in non-linear dose-response meta-analysis	5

Note: Include cohort, nested case-control and case-cohort designs
*Pooling project study includes 13 cohort studies.

Table 139 Tea consumption and rectal cancer risk. Number of studies in the CUP SLR

	Number
Studies identified	16 (5 plus 11 studies included in the pooling project)
Studies included in forest plot of highest compared with lowest categories	16 (5 plus 11 studies included in the pooling project)
Studies included in dose-response meta-analysis	16 (5 plus 11 studies included

	in the pooling project)
Studies included in non-linear dose-response meta-analysis	7

Note: Include cohort, nested case-control and case-cohort designs

Table 140 Tea consumption and colorectal cancer risk. Summary of the dose-response meta-analysis in the 2010 SLR and 2015 SLR.

	2010 SLR (no analysis)	2015 SLR
Increment unit used		1 cup/day
Studies (n)		8
Cases (total number)		16 251
RR (95%CI)		0.99 (0.97-1.01)
Heterogeneity (I^2, p-value)		25.8%, 0.23

CUP Stratified analysis by sex			
CUP Stratified analysis by geographic location			
	Asia	**Europe**	**North America**
Studies (n)	1	3	4
RR (95%CI)	0.97 (0.93-1.02)	0.99 (0.97-1.01)	1.00 (0.94-1.06)
Heterogeneity (I^2, p-value)		13.3%, 0.32	53.1%, 0.12

Table 141 Tea consumption and colon cancer risk. Summary of the dose-response meta-analysis in the 2010 SLR and 2015 SLR.

	2010 SLR (no analysis)	2015 SLR
Increment unit used		1 cup/day
Studies (n)		6
Cases (total number)		13 244
RR (95%CI)		0.99 (0.94-1.03)
Heterogeneity (I^2, p-value)		75.1%, 0.001

Table 142 Tea consumption and proximal and distal colon cancer risk. Summary of the dose-response meta-analysis in the 2010 SLR and 2015 SLR.

	Proximal	Distal
Increment unit used	1 cup/day	1 cup/day
Studies (n)	4	4
Cases (total number)	13 838	14 392
RR (95%CI)	1.02 (0.99-1.05)	1.01 (0.97-1.05)
Heterogeneity (I^2, p-value)	0%, 0.74	25.3%, 0.26

Table 143 Tea consumption and rectal cancer risk. Summary of the dose-response meta-analysis in the 2010 SLR and 2015 SLR.

	2010 SLR (no analysis)	2015 SLR
Increment unit used		1 cup/day
Studies (n)		9
Cases (total number)		4 621
RR (95%CI)		0.99 (0.97-1.02)
Heterogeneity (I^2, p-value)		0%, 0.47

CUP Stratified analysis by geographic location			
	Asia	Europe	North America
Studies (n)	1	4	3
RR (95%CI)	0.96 (0.90-1.03)	1.00 (0.95-1.06)	0.97 (0.90-1.05)
Heterogeneity (I^2, p-value)		36.6%, 0.19	0%, 0.80

Table 144 Tea and colorectal cancer risk. Results of meta-analyses and pooled analyses of prospective studies published after the 2010 SLR.

Author, Year	Number of cohort studies	Total number of cases	Studies country, area	Outcome	Comparison	RR (95%CI)	P trend	Heterogeneity (I^2, p value)
Pooled-analysis								
Zhang, 2010	13	4 394	Worldwide	Incidence, colon cancer	> 1400 g/day (8-oz cups)	1.28 (1.02-1.61)		
					Per 250 g/day	1.04 (1.00-1.07)		0.50
		2 277		proximal colon cancer		1.04 (1.00-1.09)		0.64
		1 795		distal colon cancer		1.04 (0.99-1.10)		0.34
Meta-analysis								
Yu, 2014	15		Worldwide	Incidence, colorectal cancer		0.98 (0.93-1.03)		15%, 0.29
	12			Incidence, colon cancer		1.00 (0.95-1.07)		28.3%, 0.17
	10			Incidence, rectal cancer		0.96 (0.88-1.04)		17.5%, 0.28

Table 145Tea consumption and colorectal cancer risk. Main characteristics of studies included in the CUP SLR dose-response meta-analysis

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	categories assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Missing data derived for analyses
Dik, 2014 COL40993 Denmark, France, Germany, Greece, Italy , Netherlands, Norway, Spain, Sweden, UK	EPIC, Prospective Cohort, Age: 25-70 years, M/W	4 234/ 477 071 11.6 years	Cancer registry/ population register	Questionnaire	Incidence, colorectal cancer	per 100 ml/day	1.00 (0.99-1.01)	Age, sex, alcohol consumption, BMI, centre location, dairy products consumption, diabetes, educational level, energy from fat, energy from non-fat sources, fibre, HRT use, menopausal status, physical activity, red and processed meat, smoking	Unit converted to cups/day
						High vs non/low consumption	0.97 (0.86-1.09) Ptrend:0.56		
		2 691			Incidence, colon cancer	per 100 ml/day	0.99 (0.98-1.01)		
						High vs non/low consumption	0.88 (0.75-1.03) Ptrend:0.99		
		1 242			Incidence, proximal colon cancer	per 100 ml/day	1.00 (0.97-1.02)		
						High vs non/low consumption	0.85 (0.68-1.07) Ptrend:0.86		
		1 202			Incidence, distal colon cancer	per 100 ml/day			
						High vs non/low consumption	0.98 (0.78-1.24) Ptrend:0.18		
		1 563/			Incidence, rectal cancer	per 100 ml/day	1.01 (0.99-1.03)		
						High vs non/low consumption	1.13 (0.93-1.38) Ptrend:0.42		
Dominianni, 2013 COL40982 USA	PLCO, Prospective Cohort, Age: 55-74 years, M/W	681/ 57 398 11.4 years	Histology and medical records	FFQ	Incidence, colorectal cancer	≥2 cups/day vs none	0.79 (0.55, 1.13) Ptrend:0.19	Age, alcohol, alcohol intake, BMI, centre location, diabetes, educational	Mid-point categories Person-years of follow up in each category
		382/			Incidence, proximal colon cancer		0.84 (0.52, 1.36) Ptrend:0.36		

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	categories assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Missing data derived for analyses
		148/			Incidence, distal colon cancer		0.63 (0.30, 1.33) Ptrend:0.18	level, family history of colorectal cancer, fruit intake, gender, hormone use, meat intake, nsaid use, physical activity, race, sigmoidoscopy, smoking, vegetable intake	
		143/			Incidence, rectal cancer		0.70 (0.33, 1.46) Ptrend:0.60		
Nechuta, 2012 COL40923 China	SWHS, Prospective Cohort, Age: 40-70 years, W	586/ 69 310 11 years	Medical records and cancer registries	Interview	Incidence, colorectal cancer, Non-smoker/drinker	Current vs never	0.89 (0.73, 1.09)	Age, BMI, diabetes, educational level, exercise, family history of cancer, fruits and vegetables consumption, marital status, meat, occupation	Mid-point categories Person-years of follow up
						≥150 g/month vs never	0.86 (0.63, 1.18)		
		277/			Incidence, colon cancer	Current vs never	0.95 (0.74, 1.22)		
						≥150 g/month vs never	0.85 (0.56, 1.27)		
		177			Incidence, rectal cancer	Current vs never	0.82 (0.59, 1.13)		
						≥150 g/month vs never	0.89 (0.55, 1.43)		
Sinha, 2012	NIH-AARP,	6 946/	Cancer registry	FFQ	Incidence,	≥1 cup/day vs	0.97 (0.90, 1.05)	Age, sex,	Mid-point

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	categories assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Missing data derived for analyses
COL40909 USA	Prospective Cohort, Age: 50-71 years, M/W, Retired	489 706 10.5 years			colorectal cancer	none	Ptrend:0.700	alcohol, BMI, calcium, diabetes, educational level, energy intake, family history of colorectal cancer, fruits and vegetables consumption, HRT use, marital satus, nsaid use, race, red meat, screening, smoking, time since quitting smoking, vigorous activity	categories Person-years of follow up in each category
		5 072			Incidence, colon cancer		0.99 (0.91, 1.08) Ptrend:0.500		
		2 863			Incidence, proximal colon cancer		0.98 (0.88, 1.10) Ptrend:0.600		
		1 993			Incidence, distal colon cancer		1.02 (0.88, 1.17) Ptrend:0.600		
		1 874			Incidence, rectal cancer		0.92 (0.80, 1.07) Ptrend:0.800		
Simons, 2010 COL40821 Netherlands	NLCS, Prospective Cohort, Age: 55-69 years, M/W	1 260/ 120 852 13.3 years	Cancer registry and database of pathology reports	FFQ	Incidence, colorectal cancer, men	>6 vs ≤2 cups/day	0.92 (0.75-1.13) Ptrend:0.49	Age, BMI, educational level, ethanol intake, family history of colorectal cancer, fibre intake, folate	
		939/			Incidence, colorectal cancer, women		0.92 (0.74-1.14) Ptrend:0.66		
		361/			Incidence, proximal colon		1.03 (0.75-1.41) Ptrend:0.64		

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	categories assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Missing data derived for analyses
					cancer, men			intake, meat intake, non-occupational physical activity, physical activity, processed meat consumption, smoking, total fluid intake, vitamin b6 intake	
		380/			Incidence, proximal colon cancer, women		0.89 (0.67-1.20) Ptrend:0.65		
		417/			Incidence, distal colon cancer, men		0.99 (0.73-1.33) Ptrend:0.78		
		284/			Incidence, distal colon cancer, women		1.05 (0.74-1.49) Ptrend:0.87		
		322/			Incidence, rectal cancer, men		0.85 (0.63-1.16) Ptrend:0.36		
		173/			Incidence, rectal cancer, women		1.00 (0.66-1.51) Ptrend:0.98		
Michels, 2005 COL40754 USA	NHS-HPFS, Prospective Cohort, Age: 30-75 years, M/W	1 431/ 133 893 1 991 605 person-years	Self-report verified by medical record	Semi-quantitative FFQ	Incidence, colorectal cancer	> 5 cup/day vs never	0.98 (0.69-1.38)	Age, alcohol consumption, aspirin use, BMI, energy intake, family history of colorectal cancer, height, HRT use, menopausal status, pack-years of	Mid-point categories
						Per 1 cup/day	0.99 (0.96-1.03)		
		1170/			Incidence, colon cancer	> 5 cup/day vs never	0.98 (0.68-1.41)		
						Per 1 cup/day	0.98 (0.95-1.02)		
		260/			Incidence, rectal cancer	≥ 4-5 cup/day vs never	1.55 (0.97-2.45)		
						Per 1 cup/day	1.04		

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	categories assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Missing data derived for analyses
							(0.96 to 1.13)	smoking, physical activity, previous sigmoidoscopy, red meat intake, vitamin use	
Su, 2002 COL00548 USA	NHEFS I, Prospective Cohort, Age: 25-74 years, M/W	267/ 12 335 10 years	Population	Questionnaire	Incidence, colon cancer,	≥1.5 cups/day vs non-drinkers	0.85 (0.56-1.30) Ptrend:0.76	Age, alcohol consumption, aspirin use, BMI, calcium intake, educational level, energy intake, ethnicity, fat intake, fibre	Mid-point categories Person-years of follow up
	NHEFS II,	323/					0.59 (0.35-1.00) Ptrend: <0.01		
Terry, 2001 COL00555 Sweden	SMC, Prospective Cohort, Age: 40-74 years, W	460/ 61 463 588 270 person-years	Mammography screening program	Questionnaire	Incidence, colorectal cancer	≥2 cups/day vs <1 cups/week	0.98 (0.64–1.51)	Age, alcohol consumption, BMI, calcium, dietary fibre, educational level, energy intake, folic acid, red meat intake, total fat, vitamin c, vitamin d	Mid-point categories Person-years of follow up
		291/			Incidence, colon cancer		0.74 (0.42–1.31)		
		118/			Incidence, proximal colon cancer		0.92 (0.39–2.13)		
		101/			Incidence, distal colon cancer		0.85 (0.34–2.12)		

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	categories assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Missing data derived for analyses
		159			Incidence, rectal cancer		1.53 (0.77–3.03)		
Hartman, 1998 COL00214 Finland	ATBC, Nested Case Control, Age: 50-69 years, M, Male Smokers	106/ 27002 controls 6.1 years	Cancer registry	Recall questionnaire + FFQ	Incidence, colon cancer	≥1 vs 0 cups/day	2.09 (1.34-3.26)	Age, BMI, calcium, Intervention group, occupational physical activity	Mid-point categories
		79/			Incidence, rectal cancer		0.87 (0.47-1.60)		

Table 146Main characteristics of studies excluded from the CUP SLR dose-response meta-analysis.

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	categories assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Reasons for exclusion
Peterson, 2010 COL40820 Singapore	SCHS, Prospective Cohort, Age: 45-74 years, M/W	325/ 61 321 9.8 years	Cancer registry and pathology register		Incidence, advanced colon cancer	>2 vs <1 cups/day	0.89 (0.66-1.19) Ptrend:0.40	Age, alcohol, BMI, diabetes, dialect group, educational level, family history of colorectal cancer, gender, green tea, physical activity, smoking, year	Advanced and localized colon cancer
		229/ 61 321 9.8 years			Incidence, localized colon cancer	>2 vs <1 cups/day	0.82 (0.59-1.14) Ptrend:0.24		

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	categories assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Reasons for exclusion
Lee, 2009 COL40764 China	SWHS, Prospective Cohort, Age: 40-70 years, W	394/ 73 224 7.4 years	Cancer registry and death certificates and participant contact	Quantitative FFQ	Incidence, colorectal cancer	yes vs no	0.80 (0.60-1.00) Ptrend:0.03	Age, energy intake	Superseded by Nechuta, 2012 COL40923
		236			Incidence, colon cancer		0.80 (0.60-1.20)		
		158			Incidence, rectal cancer		0.70 (0.40-1.00)		
Sun, 2007 COL40660 Singapore	SCHS, Prospective Cohort, Age: 45-74 years, M/W	1 115/ 61 320 8.9 years	Cancer registry and mortality registry	FFQ	Incidence, colorectal cancer	daily vs non drinker	0.92 (0.73-1.16) Ptrend:0.50	Sex, age at Interview, black tea consumption, BMI, Calcium intake, coffee, dialect group, dietary fibre intake, educational level, family history of colorectal cancer, history of diabetes, moderate activity, smoking status, total energy, total fat, vitamin	No specific ranges Included in HvsL only
		794/			Incidence, localised colorectal cancer, men	daily vs non drinker	0.99 (0.64-1.55) Ptrend:0.59		
		648/			Incidence, colorectal cancer, men	daily vs non drinker	0.87 (0.66-1.15) Ptrend:0.41		
		467/			Incidence, colorectal cancer, women	daily vs non drinker	1.03 (0.67-1.57) Ptrend:0.95		
		355/			Incidence, advanced colorectal cancer, men	daily vs non drinker	0.83 (0.57-1.20) Ptrend:0.29		
		195/			Incidence,	daily vs non	0.84 (0.51-1.38)		

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	categories assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Reasons for exclusion
					advanced colon cancer, men	drinker	Ptrend:0.43	c, year of Interview	
		135/			Incidence, localized colon cancer, men	daily vs non drinker	0.75 (0.38-1.49) Ptrend:0.71		
Lin, 2006 COL40703 USA	NHS-HPFS, Prospective Cohort, Age: 30-75 years, M/W	498/ 107 401 10 years	Self-report verified by medical record	FFQ	Incidence, colorectal cancer, women	≥1 vs 0-0.5 servings/week	0.90 (0.72-1.13) Ptrend:0.65	Age, alcohol intake, aspirin use, BMI, calcium intake, family history of colorectal cancer, fibre intake, folate intake, history of polyps, multivitamin supplement intake, physical activity, postmenopausal hormone use, red meat intake, sigmoidoscopy, smoking status, total energy intake	Supersded by Michels, 2005 COL40754 & Zhang, 2010 (Pooling project study)
		380/			Incidence, colorectal cancer, men	≥1 vs 0-0.5 servings/week	1.15 (0.88-1.52) Ptrend:0.11		
Zheng, 1996 COL00210	IWHS, Prospective	350/ 35 369	SEER	Semi-quantitative FFQ	Incidence, colon cancer,	≥2 vs 0-3 cups/month	0.71 (0.45-1.11) Ptrend:0.16	Age, educational level, family	Superseded by Zhang, 2010

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	categories assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Reasons for exclusion
USA	Cohort, Age: 55-69 years, W, Postmenopausal	8 years						history of specific cancer, pack-years cigarette smoking, physical activity, smoking status, waist-hip circumference ratio Fruits and vegetables intake	(Pooling project study)
		124/ 35 369 8 years			Incidence, rectum and anus cancer,	≥2 vs 0-3 cups/month	0.70 (0.34-1.46) Ptrend:0.31		
Goldbohm, 1996 COL00120 Netherlands	NLCS, Case Cohort, Age: 55-69 years, M/W	564/ 120 852 4.3 years	Cancer registry and database of pathology reports	Semi-quantitative FFQ	Incidence, colorectal cancer,	≥5 cups/day vs 0	0.94 (0.66-1.34) Ptrend:0.748	Age, sex, alcohol consumption, BMI, coffee, family history of specific cancer, fibre intake, folate intake, gallbladder surgery	Superseded by Simon, 2010 COL40821
		184/			Incidence, colon cancer, men		1.01 (0.53-1.91) Ptrend:0.796		
		163/			Incidence, colon cancer, women		0.69 (0.37-1.29) Ptrend:0.264		
		140/			Incidence, rectal cancer, men		1.49 (0.78-2.85) Ptrend:0.212		
		127/			Incidence, colorectal cancer, 2 lowest quintiles of		0.96 (0.45-2.11) Ptrend:0.982		

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	categories assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Reasons for exclusion
					vegetable& fruit consumption				
		63/ 10 517 11.5 years			Incidence, rectal cancer	≥7 vs 0-2 cups/day	1.07 Ptrend:0.94		
Heilbrun, 1986 COL01022 USA	HHP, Prospective Cohort, Age: 45- years, M, Japanese ancestry	76/ 7 833 126 613 person-years	Unknown	Interview	Incidence, rectal cancer,	> once/day vs almost never times	4.20 Ptrend:0.0007	Alcohol consumption	The exposure is Black tea

Figure 255 RR estimates of colorectal cancer by levels of tea consumption

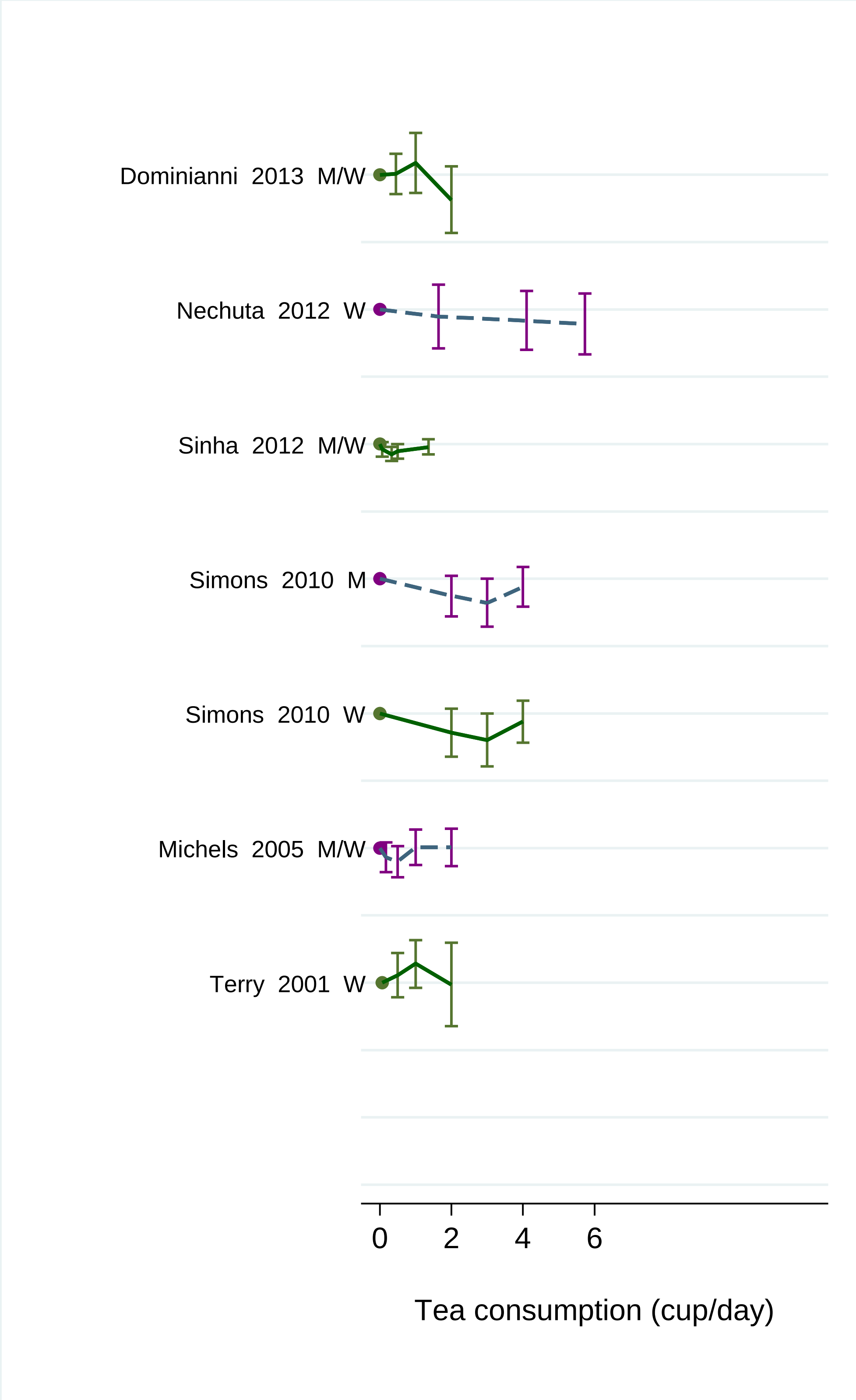


Figure 256 RR (95% CI) of colorectal cancer for the highest compared with the lowest level of tea consumption

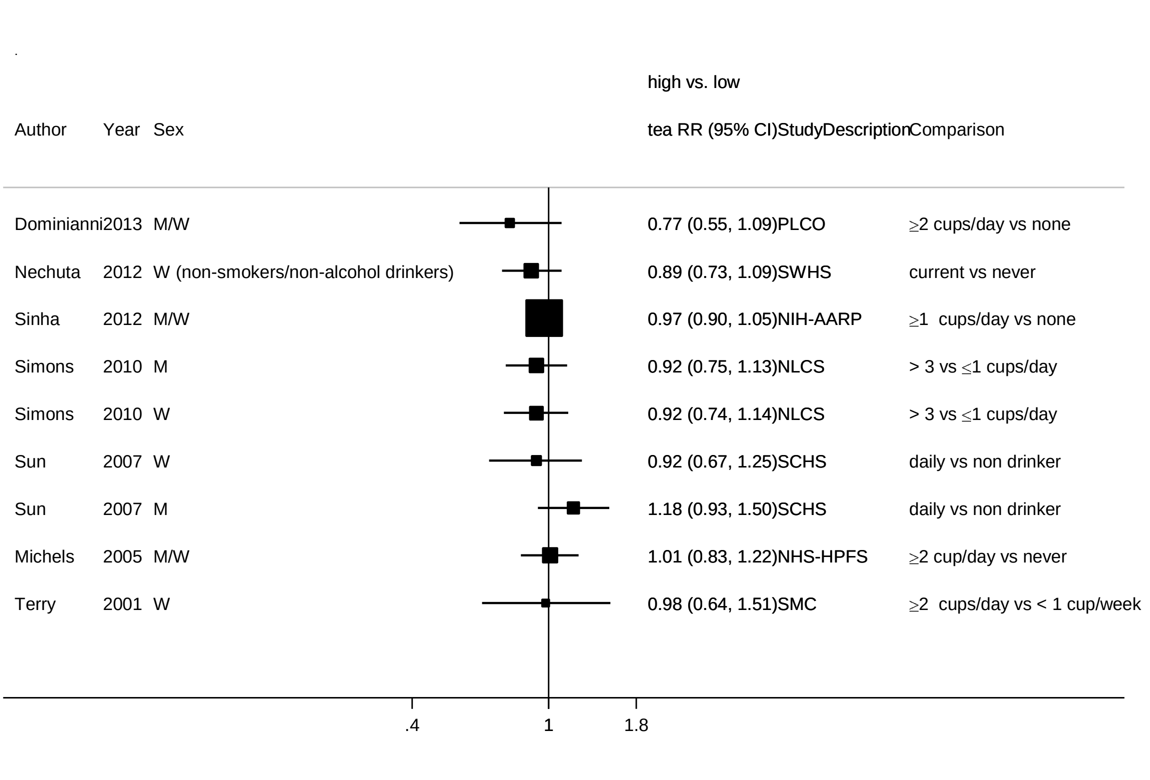


Figure 257 RR (95% CI) of colorectal cancer for 1 cup/day increase of tea consumption

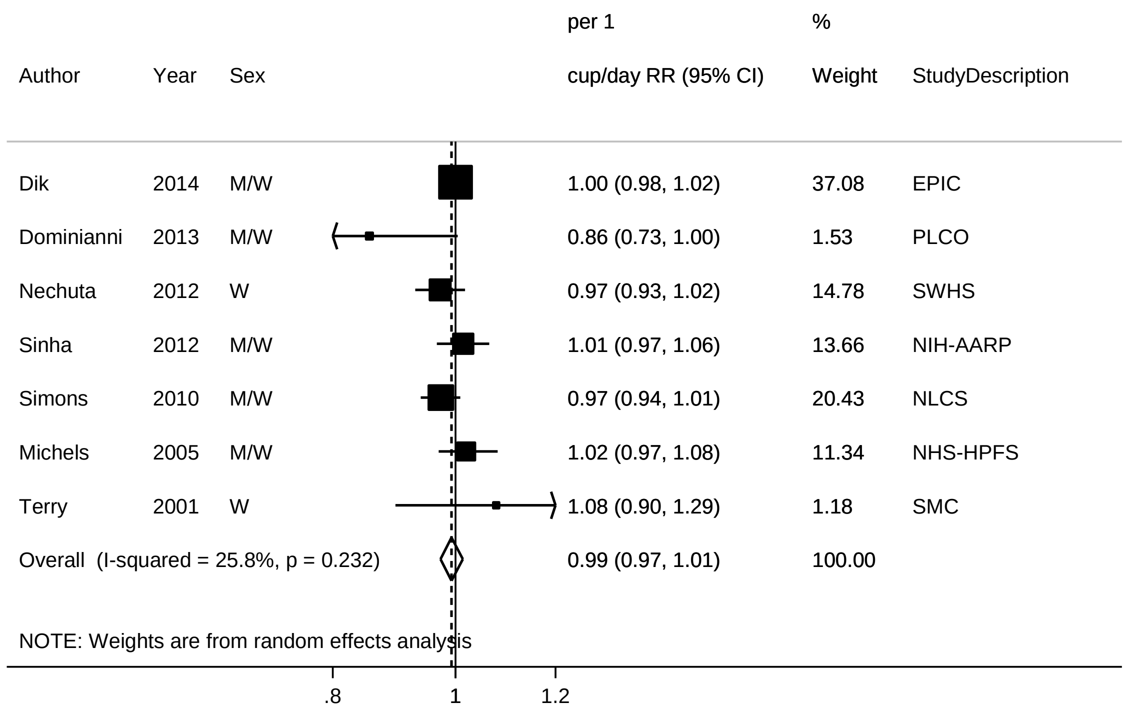
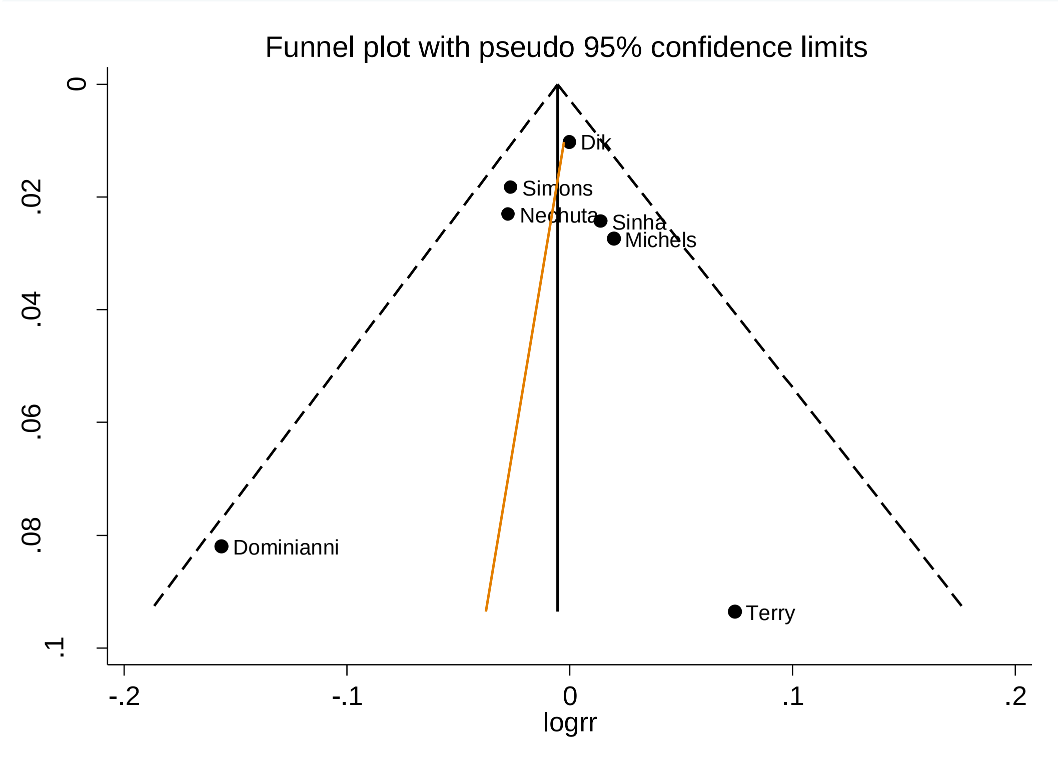


Figure 258 Funnel plot of studies included in the dose response meta-analysis tea consumption and colorectal cancer



p for Egger's test=0.42

Figure 259 RR (95% CI) of colorectal cancer for 1 cup/day increase of tea consumption by geographic location

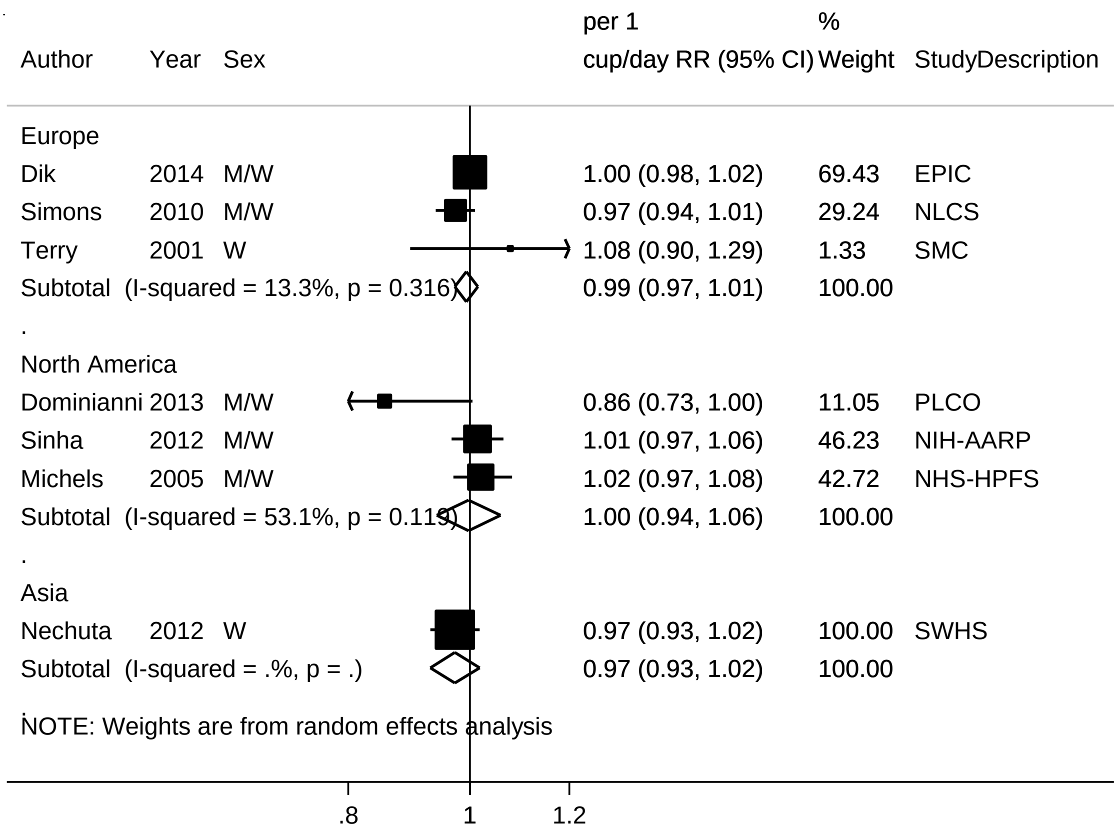


Figure 260 RR estimates of colon cancer by levels of tea consumption

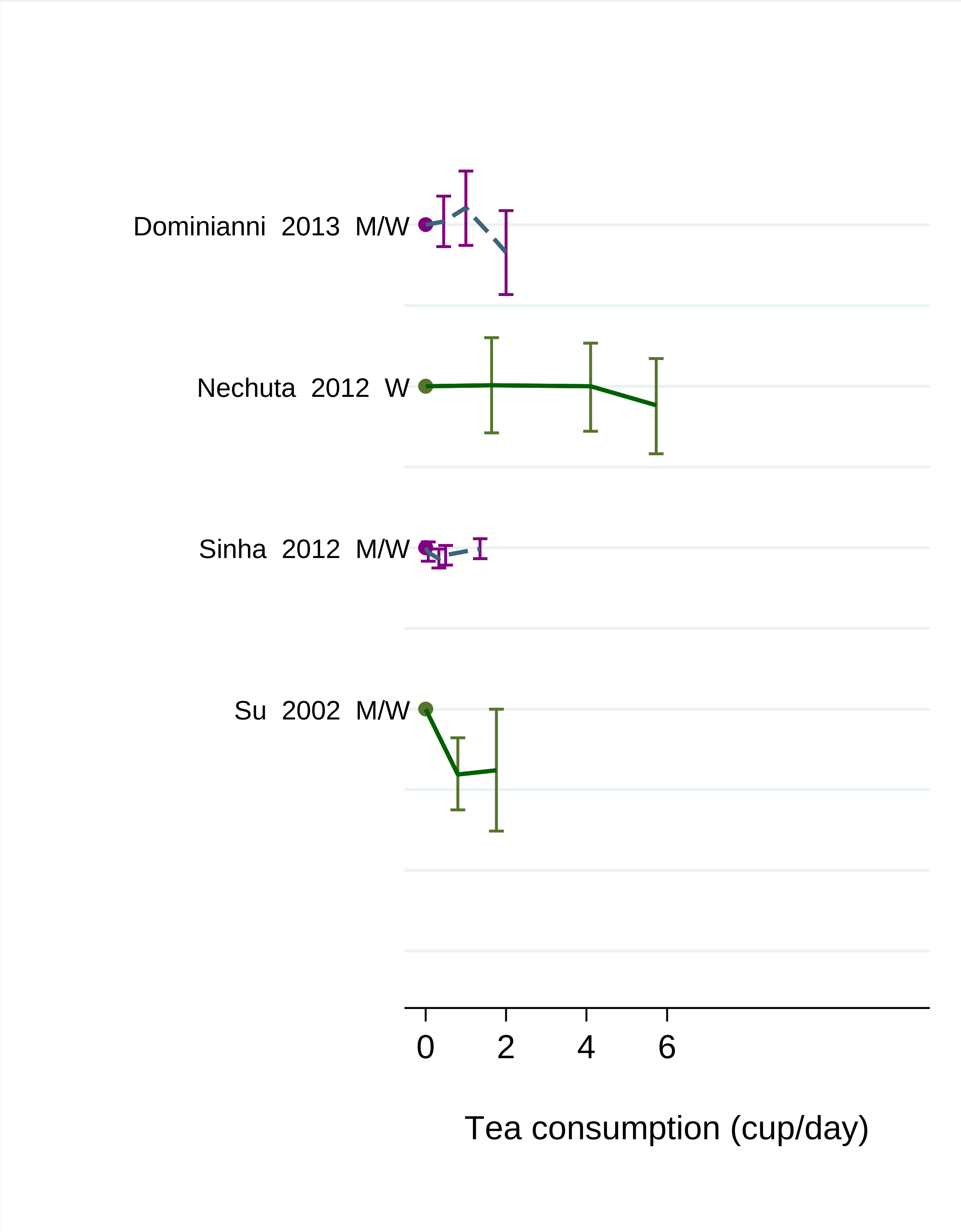


Figure 261 RR (95% CI) of colon cancer for the highest compared with the lowest level of tea consumption

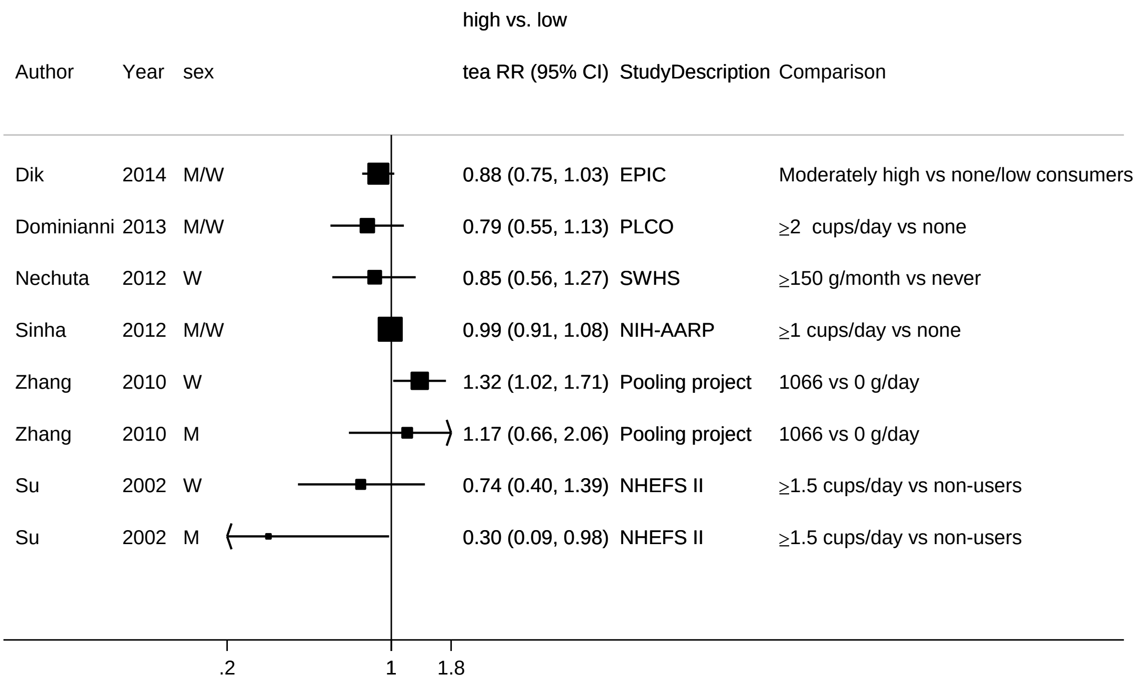


Figure 262 RR (95% CI) of colon cancer for 1 cup/day increase of tea consumption

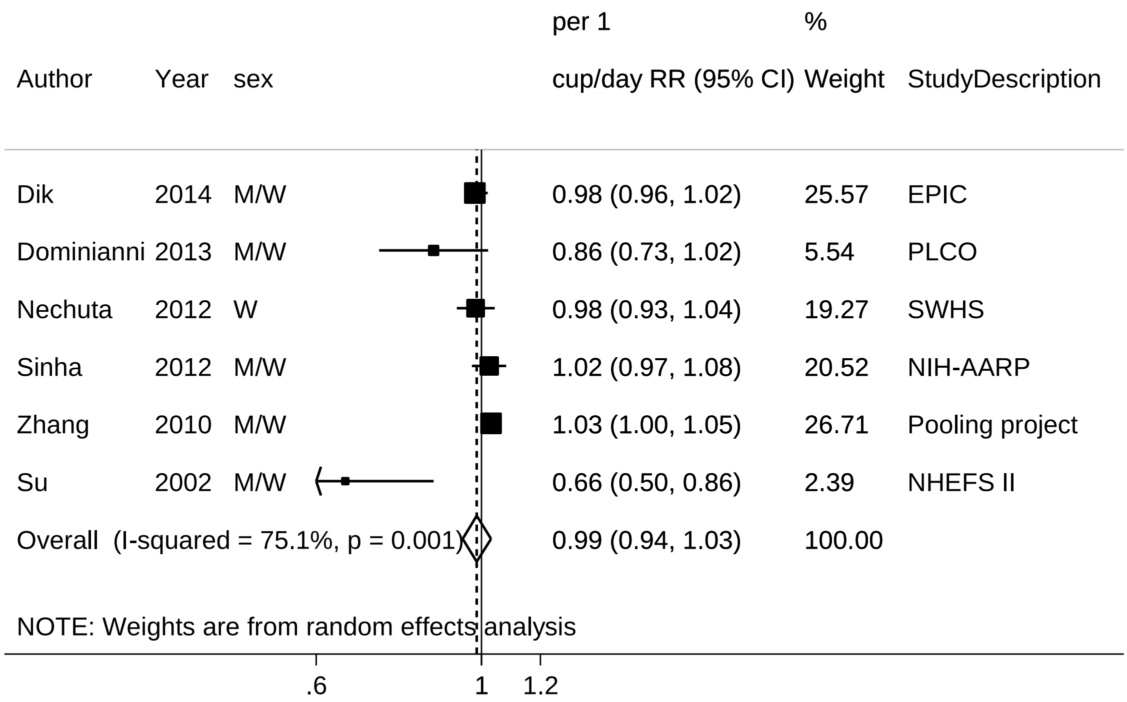
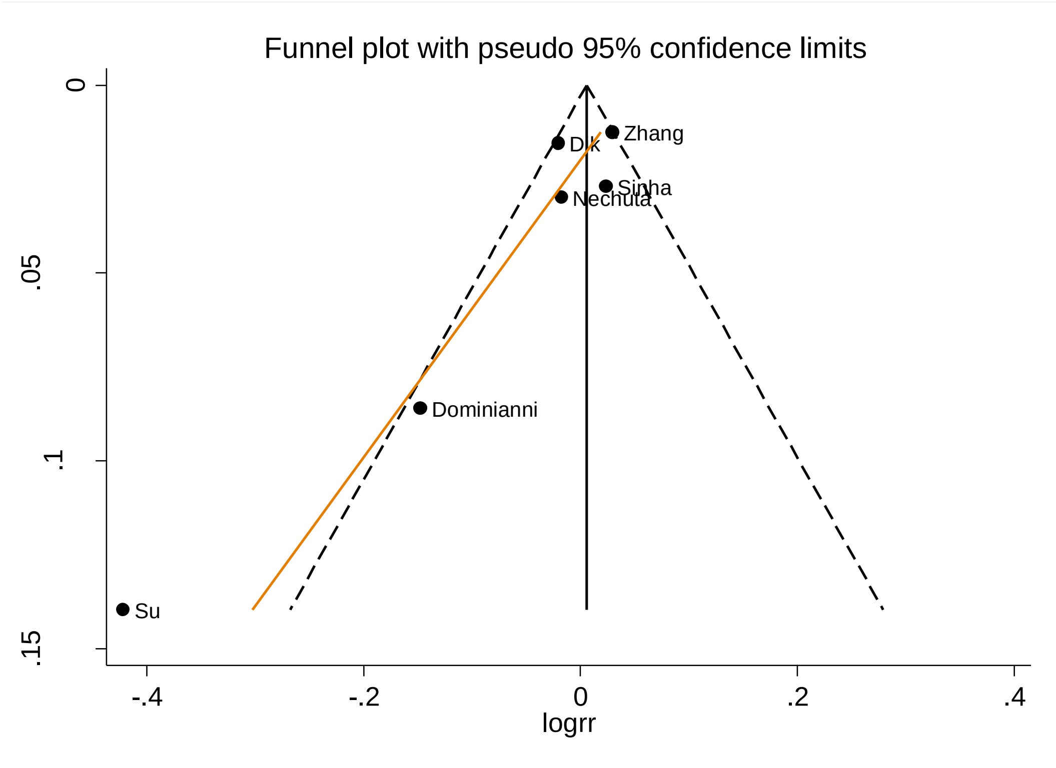


Figure 263 Funnel plot of studies included in the dose response meta-analysis tea consumption and colon cancer



p for Egger's test=0.33

Figure 264 RR (95% CI) of proximal colon cancer for 1 cup/day increase of tea consumption

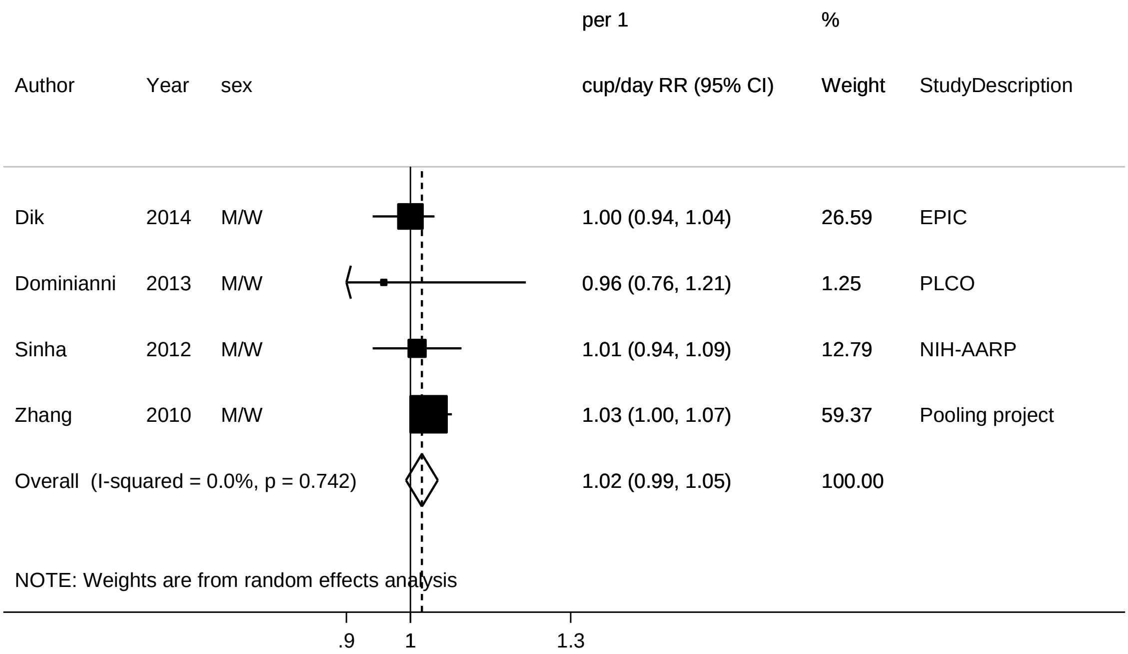


Figure 265 RR (95% CI) of distal colon cancer for 1 cup/day increase of tea consumption

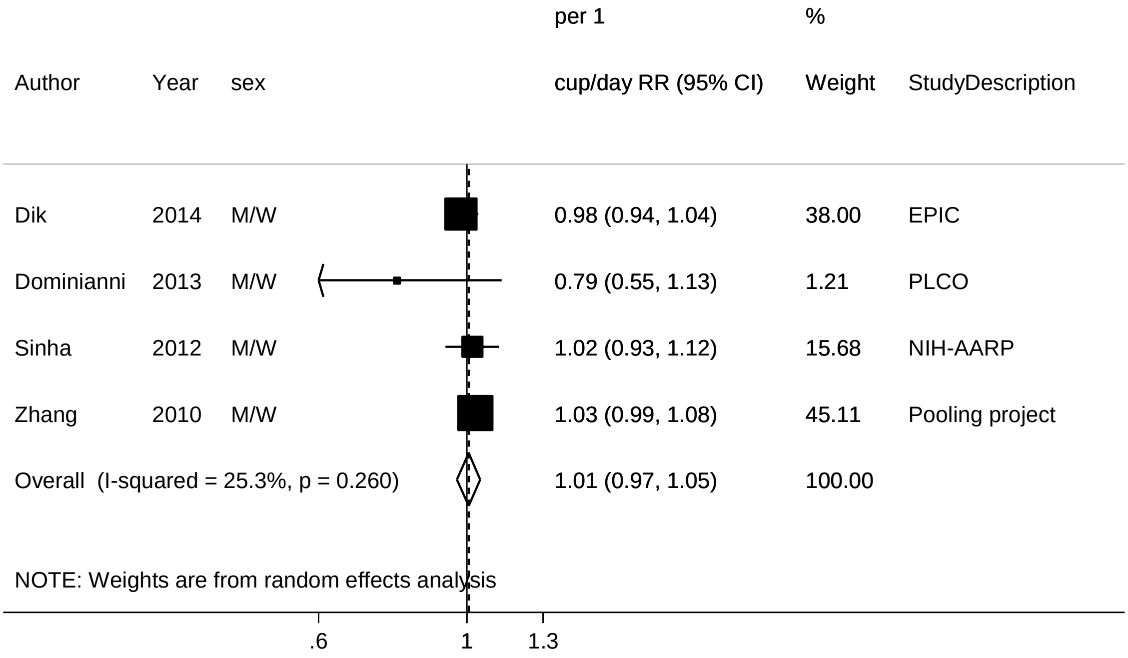


Figure 266 RR estimates of rectal cancer by levels of tea consumption

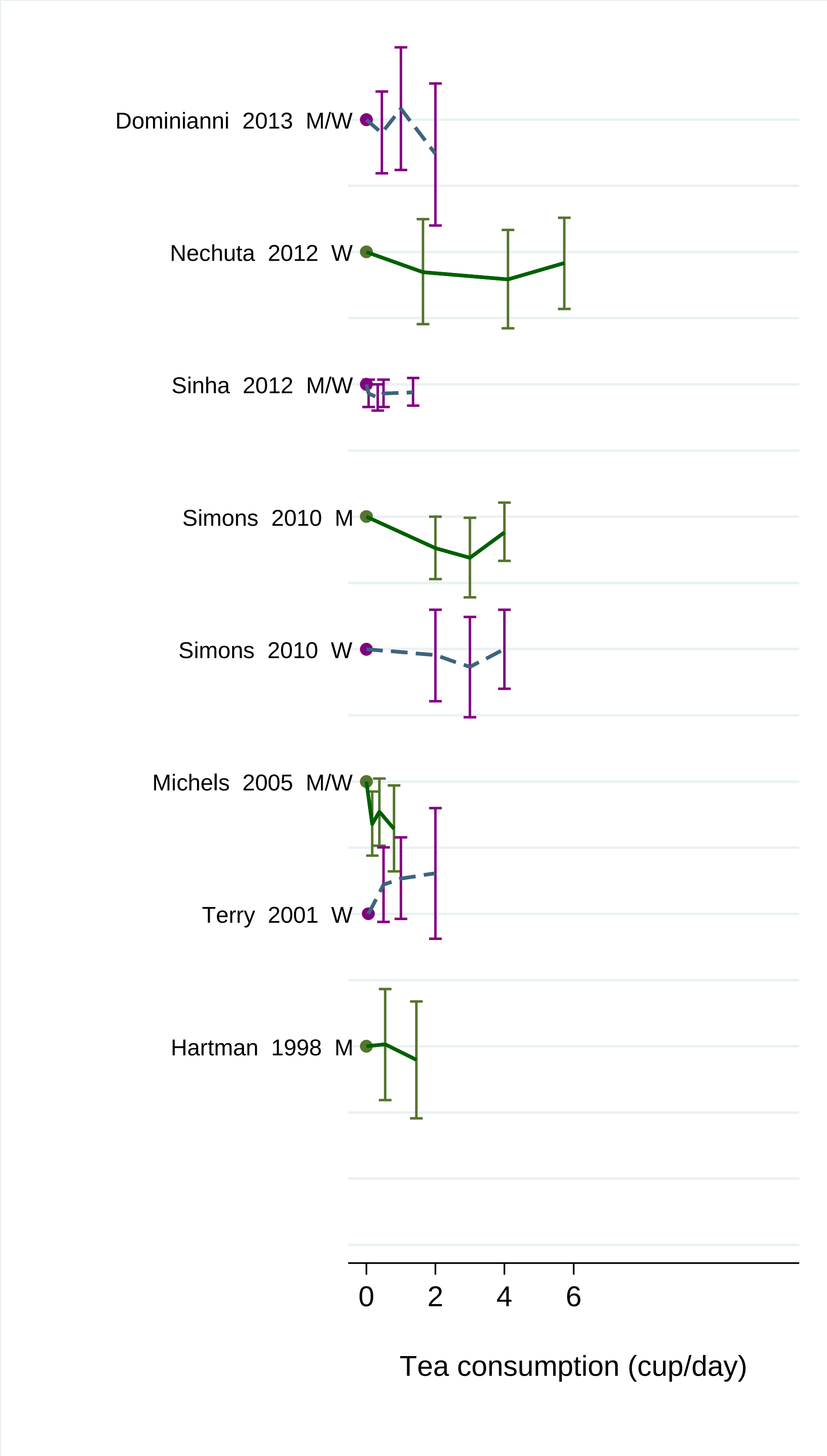


Figure 267 RR (95% CI) of rectal cancer for the highest compared with the lowest level of tea consumption

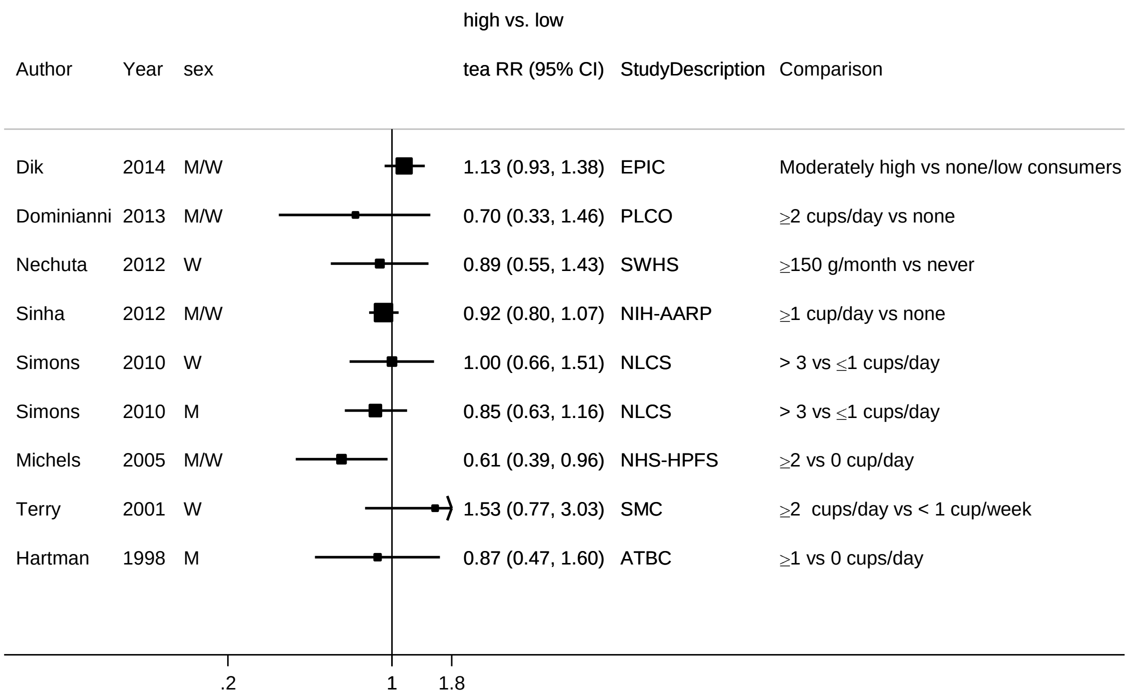


Figure 268 RR (95% CI) of rectal cancer for 1 cup/day increase of tea consumption

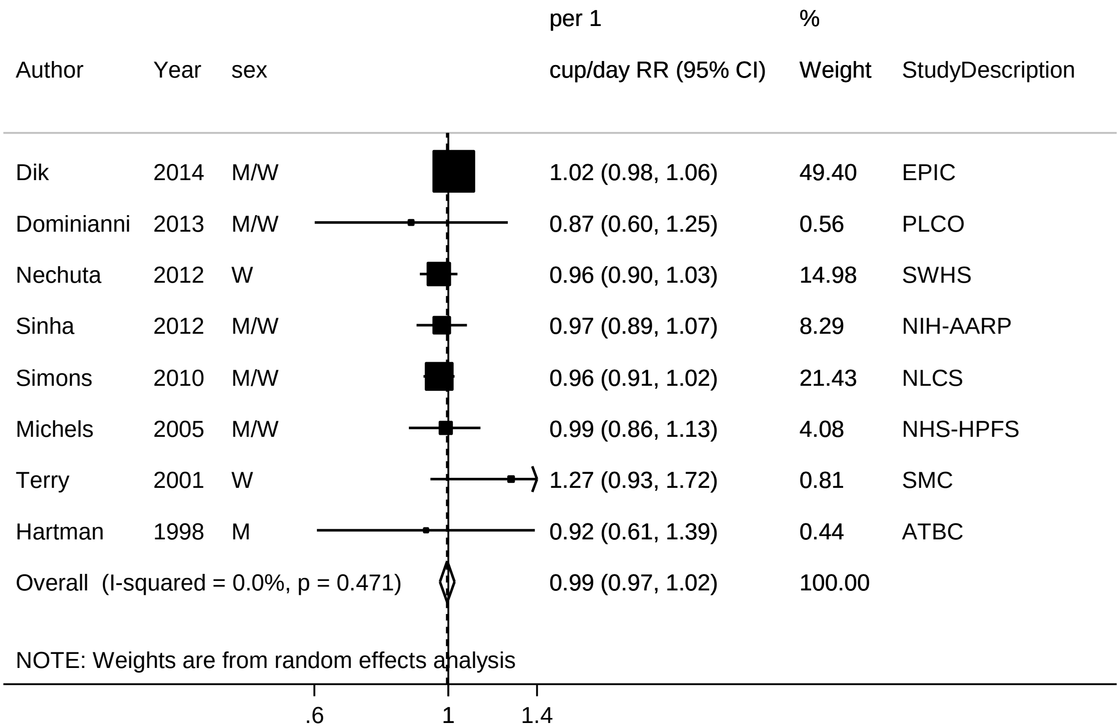
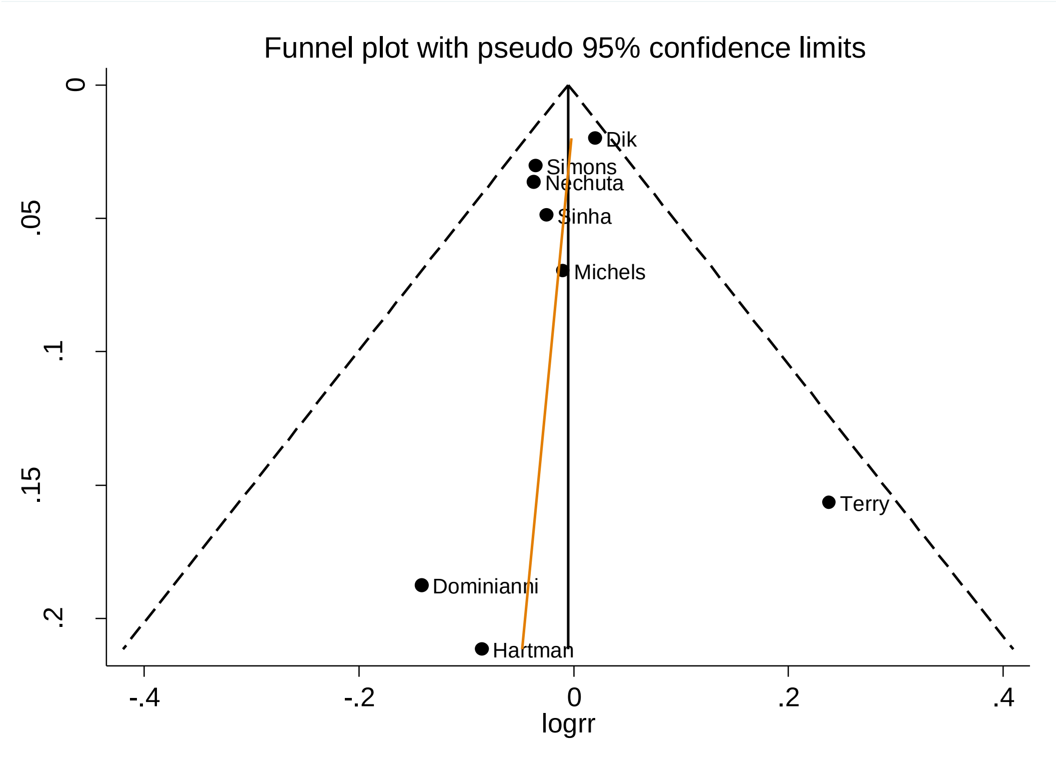


Figure 269 Funnel plot of studies included in the dose response meta-analysis tea consumption and rectal cancer



p for Egger's test=0.04

Figure 270 RR (95% CI) of rectal cancer for 1 cup/day increase of tea consumption by geographic location

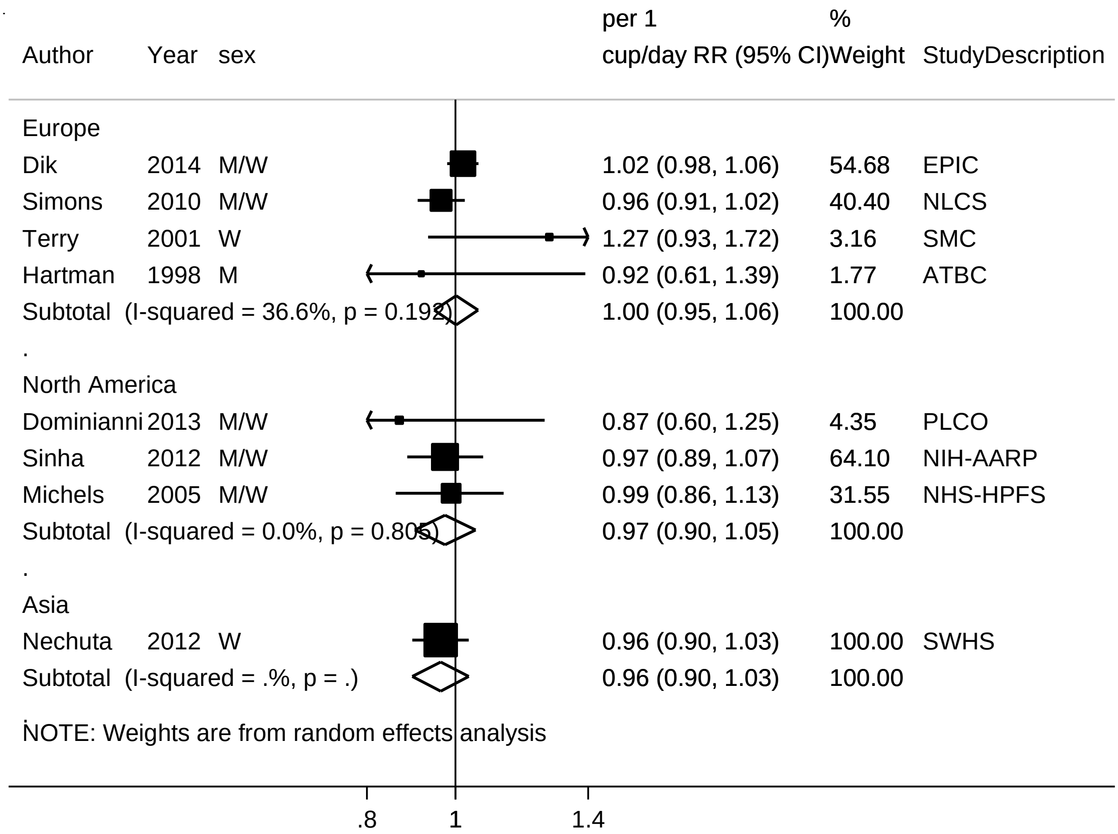
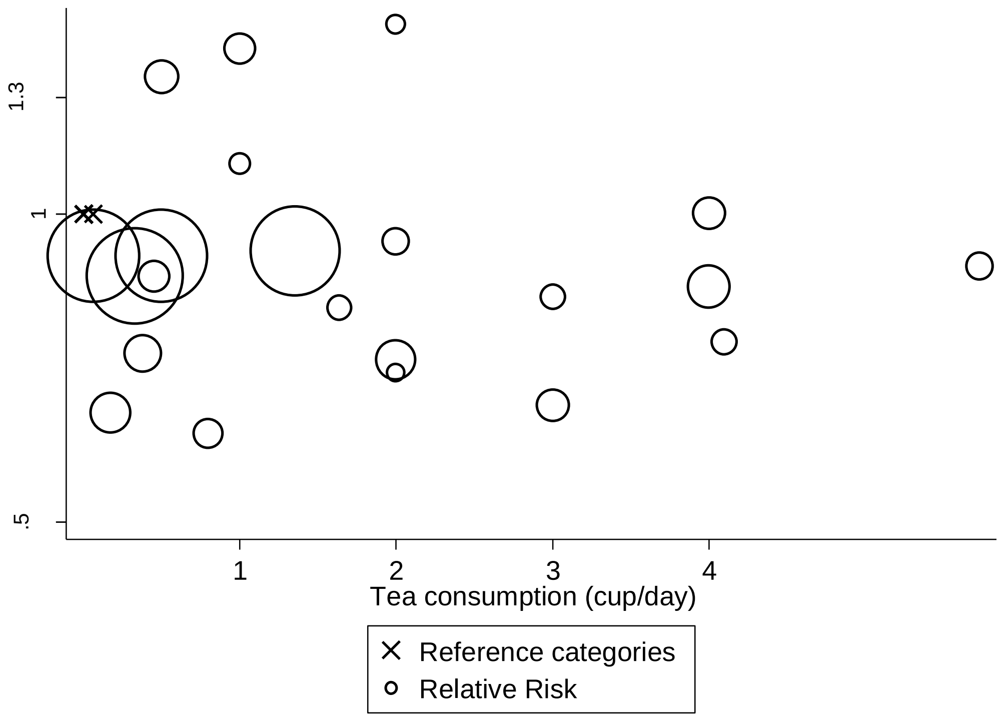
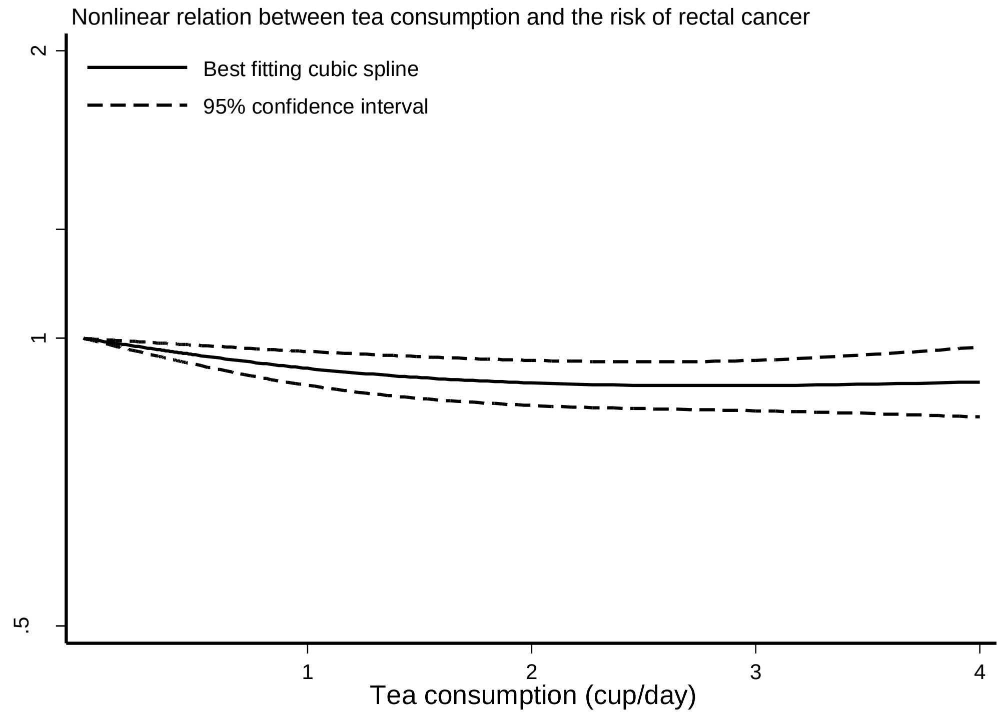


Figure 271 Relative risk of rectal cancer and tea consumption estimated using non-linear models





p for non-linearity=0.03

Table 147Table with tea consumption values and corresponding RRs (95% CIs) for non-linear analysis of tea consumption and rectal cancer

Tea consumption (cup/day)	RR (95%CI)
0	1.00
0.175	0.98 (0.97-0.99)
0.5	0.96 (0.94-0.99)
1.00	0.93 (0.89-0.97)
2.00	0.91 (0.86-0.96)
3.00	0.92 (0.86-0.99)
4.00	0.94 (0.84-1.05)

3.6.2.2 Green tea

Colon cancer:
Five studies (1 517 cases) were included in the dose-response meta-analysis of green tea consumption and colon cancer. No significant association was observed.
There was no evidence of small study bias (p=0.80).
All studies included in the dose-response et-analysis were conducted in Asia. In sensitivity analysis, the summary RRs did not change materially when excluding the studies in turn.

Study quality:
Cancer outcome was confirmed using cancer registry records in most studies and tea intake was assessed using FFQ or questionnaire in all studies.

Table 148 Green tea consumption and colon cancer risk. Number of studies in the CUP SLR

	Number
Studies identified	7
Studies included in forest plot of highest compared with lowest exposure	7
Studies included in dose-response meta-analysis	5
Studies included in non-linear dose-response meta-analysis	NA

Note: Include cohort, nested case-control and case-cohort designs

Table 149 Green tea consumption and colon cancer risk. Summary of the dose-response meta-analysis in the 2010 SLR and 2015 SLR.

	2010 SLR (no analysis)	**2015 SLR**
Increment unit used		1 cup/day
Studies (n)		5
Cases (total number)		1 517
RR (95%CI)		0.99 (0.97-1.01)
Heterogeneity (I^2, p-value)		0%, 0.74

Table 150 Green tea and colorectal cancer risk. Results of meta-analyses and pooled analyses of prospective studies published after the 2010 SLR.

Author, Year	Number of cohort studies	Total number of cases	Studies country, area	Outcome	Comparison	RR (95%CI)	P trend	Heterogeneity (I^2, p value)
Meta-analysis								
Wang, 2012	6	1 675	Worldwide	Incidence, colorectal cancer	Highest vs lowest	0.90 (0.72-1.08)		
					Per 1 cup/day	0.97 (0.91-1.03)		

Table 151 Green tea consumption and colon cancer risk. Main characteristics of studies included in the CUP SLR dose-response meta-analysis

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Missing data derived for analyses
Yang, 2011 COL40885 China	SMHS, Prospective Cohort, Age: 40-74 years, M	133/ 60 567 4.6 years	Cancer registry and medical records	Survey	Incidence, colon cancer	Yes vs no	0.69 (0.48-0.98)	Age, education, cigarette smoking, pack-years of cigarette smoking, alcohol consumption, regular exercise, Body Mass Index, history of diabetes, family history of colorectal cancer and intakes of vegetables, fruits and red meat	Mid-point exposure
						≥250 vs ≤0 g/month	0.85 (0.62-1.15) Ptrend:0.27		
Lee, 2007 COL40654 Japan	JPHC, Prospective Cohort, Age: 52 years, M/W	476/ 96 162 10 years	Active patient notification from hospitals, cancer registries and death cert.	Questionnaire FFQ	Incidence, colon cancer, men	≥5 cups/day vs almost never	0.92 (0.63–1.33)	Age, alcohol drinking, beef consumption, black tea consumption, BMI, Chinese tea, family	Mid-point exposure Person-years of follow up
		284/			Incidence, colon cancer, women		1.1 (0.7-1.73)		

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Missing data derived for analyses
								history of colorectal cancer, green tea consumption, green vegetables, physical activity, pork, smoking status, study centre	
Oba, 2006 COL40626 Japan	TCCJ, Prospective Cohort, Age: 35-101 years, M/W	111/ 30 221 8 years	Hospital records and cancer registry	Semi-quantitative FFQ	Incidence, colon cancer, men	1cup/day or more vs never-<1cup/month	0.75 (0.49-1.16)	Age, alcohol intake, BMI, energy intake, height, pack-years of smoking, physical activity	Mid-point exposure Person-years of follow up
		102/			Incidence, colon cancer, women		1.08 (0.67-1.76)		
Suzuki, 2005 COL01931 Japan	Miyagi perfecture cohort I, Prospective Cohort, Age: 40- years, M/W	158/ 65 915 9 years	Cancer registry/ population register	Questionnaire	Incidence, colon cancer, Cohort I	5 vs 0 cups/day	0.82 (0.49-1.39)	Age, sex, alcohol consumption, black tea intake, BMI, coffee intake, family history of colorectal cancer, fruits, green and yellow	Mid-point exposure
	Miyagi perfecture cohort II	147			Incidence, colon cancer, Cohort II		0.84 (0.48-1.45)		

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Missing data derived for analyses
								vegetables consumption, meat intake, other vegetables intake, smoking status	

Table 152 Green tea consumption and colon cancer risk. Main characteristics of studies excluded from the CUP SLR dose-response meta-analysis

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Inclusion/ exclusion reason
Nechuta, 2012 COL40923 China	SWHS, Prospective Cohort, Age: 40-70 years, W	586/ 69 310 11 years	Medical records and cancer registries	Interview	Incidence, colon cancer, non smoker/drinker	Current vs never	0.96 (0.74, 1.24)	Age, BMI, diabetes, educational level, exercise, family history of cancer, fruits and vegetables consumption, marital status, meat, occupation	Included in HvsL analysis only
Yang, 2007 COL40676 China	SWHS, Prospective Cohort,	255/ 69 710 6 years	Cancer registry	Questionnaire	Incidence, colon cancer	≥5 vs ≤0 g/day	0.56 (0.32-0.98) Ptrend:0.01		Superseded by Nechuta, 2012 COL40923

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Inclusion/ exclusion reason
	Age: 40-70 years, W								
Sun, 2007 COL40660 Singapore	SCHS, Prospective Cohort, Age: 45-74 years, M/W	1 208/ 61 320 8.9 years	Cancer registry and mortality registry		Incidence, localized colon cancer	daily vs non drinker	0.78 (0.4-1.5) Ptrend:0.08	Sex, age at Interview, black tea consumption, BMI, calcium intake, coffee, dialect group, dietary fibre intake, educational level, family history of colorectal cancer, history of diabetes, moderate activity, smoking status, total energy, total fat, vitamin c, year of Interview	Included in HvsL nalysis only No specific ranges
Nagano, 2001 COL00359 Japan	Life Span Study, Prospective Cohort,	412/ 38 540 403 412 person-	Responding to mail survey	Questionnaire	Incidence, colon cancer,	≥5 vs 0-1 times/day	1.00 (0.76-1.4)		Participants are Atomic Bomb Survivors

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Inclusion/ exclusion reason
	Age: 55 years, M/W, atomic-bomb survivors	years							

Figure 272 RR estimates of colon cancer by levels of green tea consumption

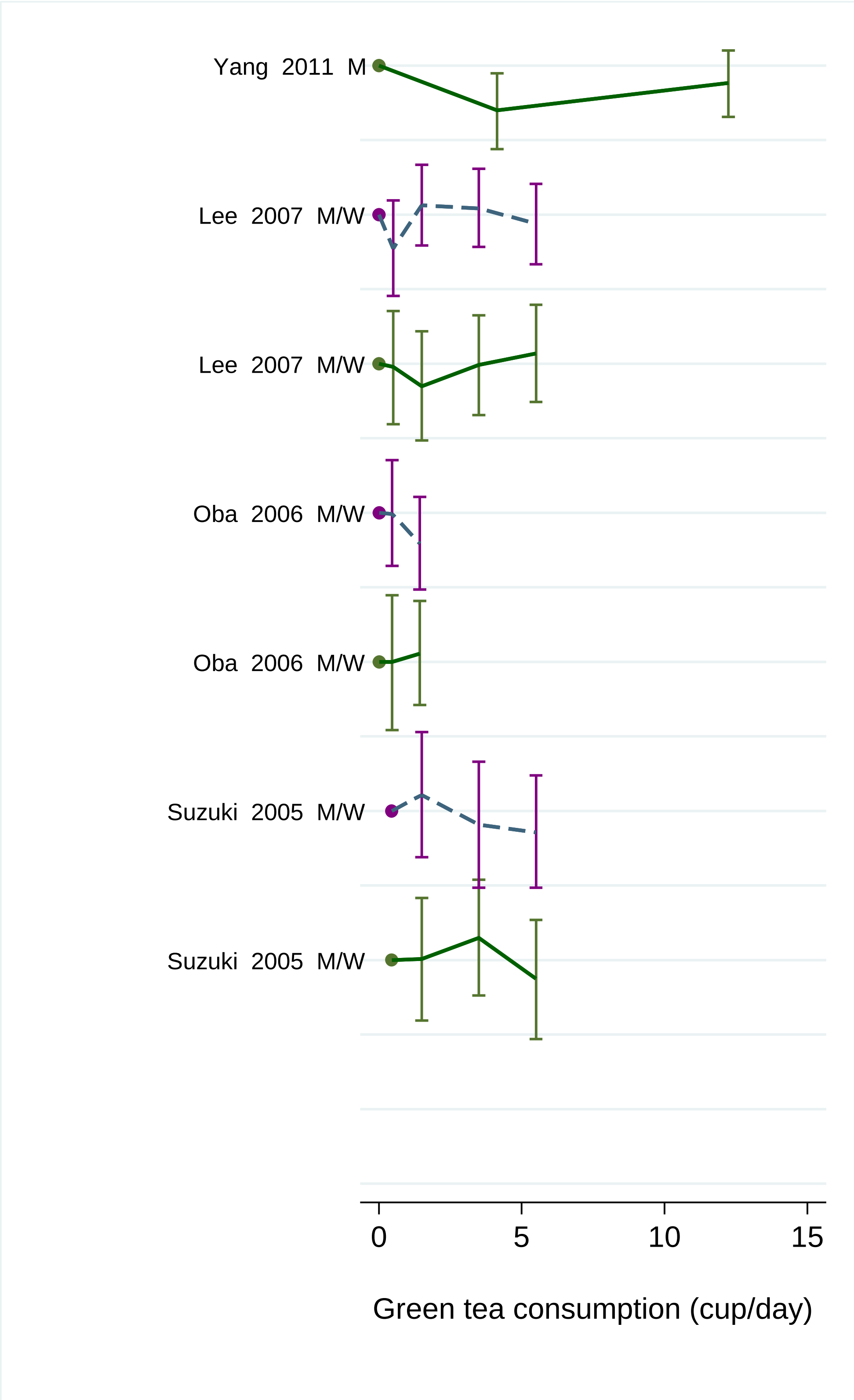


Figure 273 RR (95% CI) of colon cancer for the highest compared with the lowest level of green tea consumption

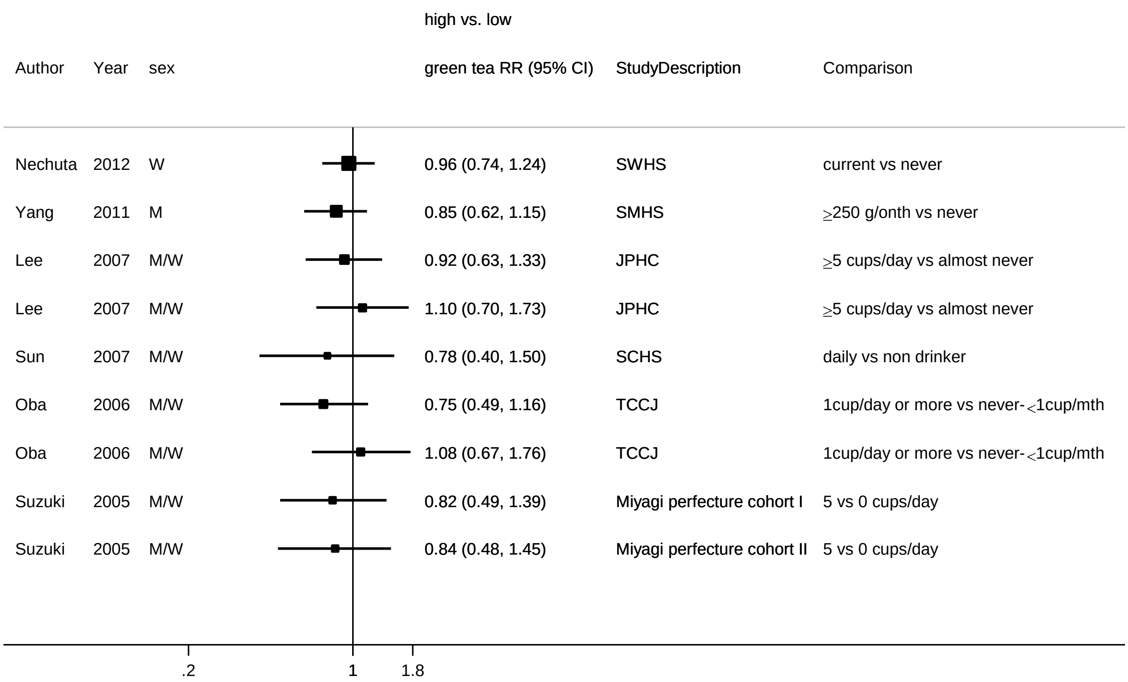


Figure 274 RR (95% CI) of colon cancer for 1 cup/day increase of green tea consumption

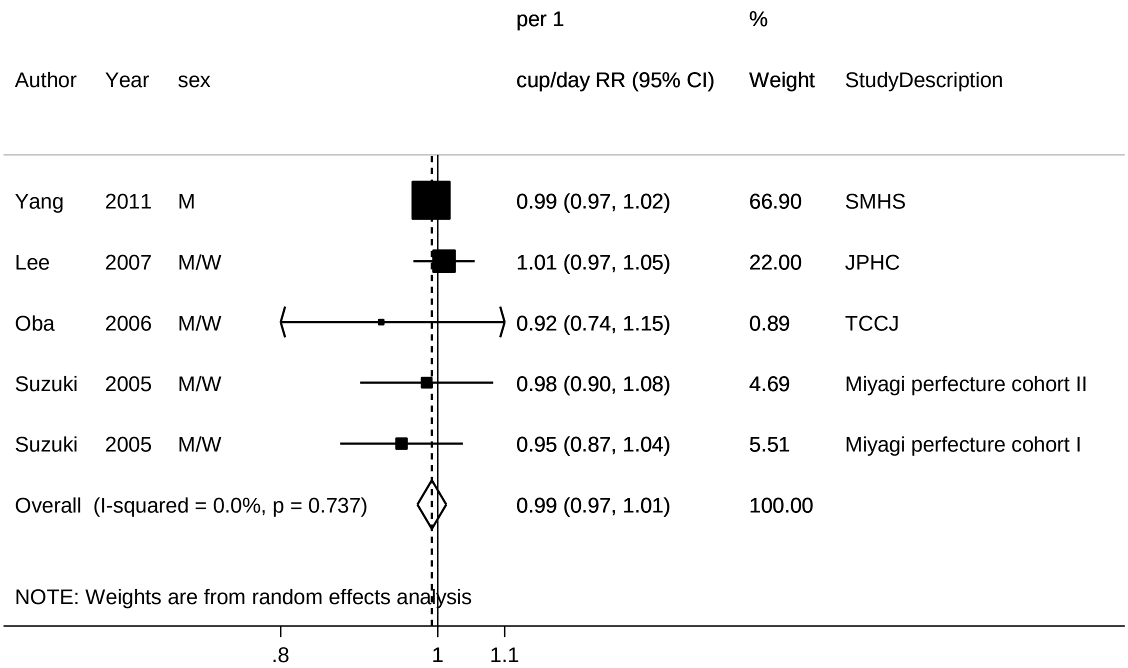
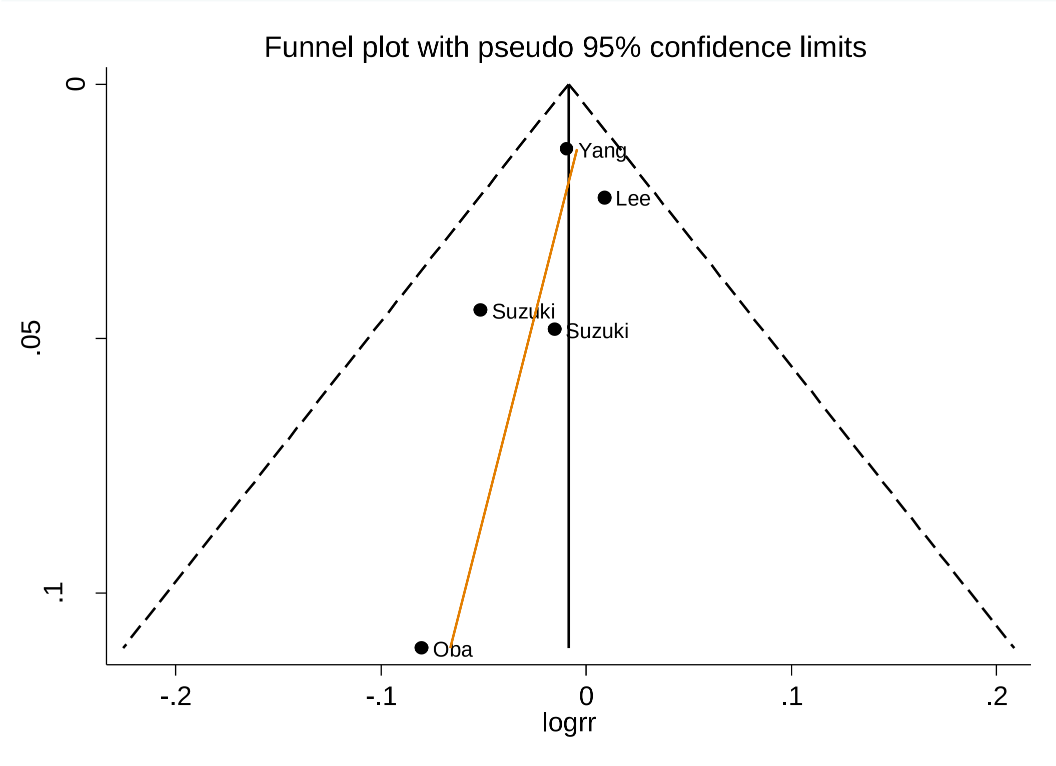


Figure 275 Funnel plot of studies included in the dose response meta-analysis green tea consumption and colon cancer



p for Egger's test=0.80

3.7.1 Total Alcoholic drinks

Cohort studies

Summary

Main results:
Six new studies were identified. Three on colorectal, three on colon cancer and one on rectal cancer. There were three new studies (Shen, 2013; Yang, 2012; Breslow, 2011) on mortality, but there was insufficient data to conduct dose-response meta-analysis on mortality. A highest compared to lowest analysis on colorectal cancer mortality was conducted, for this analysis alcohol as ethanol and total alcoholic drinks were combined.

Colorectal cancer:
Eight (36942 cases) were included in the dose-response meta-analysis of alcoholic drinks and colorectal cancer. A borderline significant association with high heterogeneity was observed. The heterogeneity was lower after stratification by sex. There was evidence of publication bias (p=0.008). There were not sufficient studies to test for a non-linear association.

Colon cancer:
Eight studies (5207 cases) were included in the dose-response meta-analysis of alcoholic drinks and colon cancer. A non-significant association with high heterogeneity was observed. After stratification by sex and geographic location, the heterogeneity persisted due to the opposite results from different studies. There was no evidence of publication bias (p=0.20). There were not sufficient studies to test for a non-linear association.

Rectal cancer:
Five studies (963 cases) were included in the dose-response meta-analysis of alcoholic drinks and rectal cancer. A borderline significant association with high heterogeneity (62.2%) was observed. After stratification by sex the result was not significant for the subgroup of men or women. There was evidence of publication bias (p=0.02). There were not sufficient studies to test for a non-linear association.

Study quality:
All studies used questionnaires self-reported FFQ or questionnaires to assess alcohol intake. All studies were multiple adjusted for different confounders. Cancer outcome was confirmed using cancer registry records in most studies.

Pooling project of cohort studies:
No pooling projects or meta-analyses were identified.

Table 153 Total alcoholic drinks and colorectal cancer risk. Number of studies in the CUP SLR

	Number
Studies identified	15 (17 publications)
Studies included in forest plot of highest compared with lowest exposure	15
Studies included in dose-response meta-analysis	8

Note: Include cohort, nested case-control and case-cohort designs

Table 154 Total alcoholic drinks and colon cancer risk. Number of studies in the CUP SLR

	Number
Studies identified	16
Studies included in forest plot of highest compared with lowest exposure	16
Studies included in dose-response meta-analysis	8

Note: Include cohort, nested case-control and case-cohort designs

Table 155 Total alcoholic drinks and rectal cancer risk. Number of studies in the CUP SLR

	Number
Studies identified	11
Studies included in forest plot of highest compared with lowest exposure	11
Studies included in dose-response meta-analysis	5

Note: Include cohort, nested case-control and case-cohort designs

Table 156 Total alcoholic drinks colorectal cancer risk. Summary of the dose-response meta-analysis in the 2010 SLR and 2015 SLR.

	2010 SLR	**2015 SLR**
Increment unit used	1 drink/ day	1 drink/ day
Studies (n)	4	8
Cases (total number)	1932	36942
RR (95%CI)	1.11 (0.90-1.38)	1.06 (1.00-1.11)
Heterogeneity (I^2, p-value)	76.6%, 0.004	60.4%, 0.01

Stratified analysis by sex (no analysis in 2005 or 2010 SLR)			
CUP	**Men**	**Women**	
Studies (n)		3	
RR (95%CI)	1.05(1.02-1.08)	1.02(1.01-1.03)	
Heterogeneity (I^2, p-value)	8.4%, 0.35	0%, 0.51	
Stratified analysis by geographic location (no analysis in 2005 or 2010 SLR)			
	Asia	**Europe**	**North America**

Studies (n)	1	4	3
RR (95%CI)	1.43 (1.15-1.77)	1.02(0.96-1.09)	1.08 (1.03-1.14)
Heterogeneity (I^2, p-value)	-	57.0%, 0.07	0%, 0.48

Table 157 Total alcoholic drinks and colon cancer risk. Summary of the dose-response meta-analysis in the 2010 SLR and 2015 SLR.

	2010 SLR	2015 SLR
Increment unit used	1 drink/ day	1 drink/ day
Studies (n)	5	8
Cases (total number)	1460	5207
RR (95%CI)	1.16 (0.97-1.39)	1.11 (0.90-1.36)
Heterogeneity (I^2, p-value)	85.5% <0.001	98.1%, <0.001

Stratified analysis by sex (no analysis in 2005 or 2010 SLR)		
CUP	**Men**	**Women**
Studies (n)	3	3
RR (95%CI)	1.04 (0.91-1.18)	0.88(0.67-1.16)
Heterogeneity (I^2, p-value)	45.6%, 0.16	69.1%, 0.04

Stratified analysis by geographic location (no analysis in 2005 or 2010 SLR)			
	Asia	**Europe**	**North America**
Studies (n)	2	3	3
RR (95%CI)	1.53(0.84-2.78)	0.99 (0.96-1.02)	0.96 (0.60-1.55)
Heterogeneity (I^2, p-value)	98.3%, <0.001	28.0%, 0.25	80.5%, <0.001

Table 158 Total alcoholic drinks and rectal cancer risk. Summary of the dose-response meta-analysis in the 2010 SLR and 2015 SLR.

	2010 SLR	2015 SLR
Increment unit used	1 drink/ day	1 drink/ day
Studies (n)	3	5
Cases (total number)	353	963
RR (95%CI)	1.11 (0.97-1.29)	1.08 (1.00-1.17)
Heterogeneity (I^2, p-value)	52.7%, 0.12	62.2%, 0.02

Stratified analysis by sex (no analysis in 2005 or 2010 SLR)		
CUP	**Men**	**Women**
Studies (n)	2	3

RR (95%CI)	1.11(0.97-1.26)	1.00 (0.84-1.19)
Heterogeneity (I^2, p-value)	0%, 0.44	17.9%, 0.30

Table 159 Total alcoholic drinks and colorectal cancer risk. Main characteristics of studies included in the CUP SLR dose-response meta-analysis

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Missing data derived for analyses
Hippisley-Cox, 2015 COL41058 England	QResearch database study, UK, Prospective Cohort, Age: 25-84 years, M/W	18 130/ 4 943 765 15 years	Cancer registry/death certificates/medical records	Medical records	Incidence, colorectal cancer, men	≥9.1 vs ≤0 units/day	1.56 (1.33-1.83)	Age, cancer diagnosis, ethnicity, family history of colorectal cancer, presence of other disease, smoking status, type 2 diabetes mellitus	Distribution of person-years by exposure category, mid-points of exposure categories.
		14 496/			Women	≥9.1 vs ≤0 units/day	1.36 (0.80-2.32)		
Klatsky, 2015 COL41059 USA	KPMCP, Prospective Cohort, Age: 41 years, M/W	2 148/ 124 193 17.8 years	Cancer registry	Questionnaire	Incidence, colorectal cancer	≥3 vs ≤0 drinks	1.40 (1.10-1.70)	Age, sex, BMI, educational level, marital status, race/ethnicity, smoking	Distribution of person-years by exposure category, mid-points of exposure categories.
Land, 2014 COL41062 USA	NSABP, Prospective Cohort, Age: 54 years, W, High Risk population	35/ 13 388 7 years	Follow-up visits	Questionnaire	Incidence, Invasive colon cancer	≥1.1 vs ≤0 drinks/day	0.61 (0.23-1.63)	Age, aspirin use, BMI, estrogen use, family history of cancer, leisure time physical activity, menstrual status, race, smoking duration, smoking Intensity, smoking status,	Distribution of person-years by exposure category, mid-points of exposure categories.

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Missing data derived for analyses
								treatment allocation	
Everatt, 2013 COL40967 Lithuania	KRIS-MIHDPS, Prospective Cohort, Age: 40-59 years, M	141/ 7 150 30 years	Cancer registry and death registry	Questionnaire	Incidence, colorectal cancer	2-7/week vs few times year times	1.62 (0.88-2.99)	Age, BMI, educational level, smoking, study	Conversion from drinks/week to drinks/day, mid-points of exposure categories.
Odegaard, 2013 COL40948 Singapore	SCHS, Prospective Cohort, Age: 45-74 years, M/W	969/ 50 466 579 628 person-years	Cancer registry and death registry		Incidence, colon cancer	8-14 vs >14 drinks/week	0.73 (0.40-1.33)	Age, sex, BMI, diabetes, dialect group, dietary pattern score, educational level, energy intake, family history of colorectal cancer, physical activity, sleep, smoking, time of recruitment	Distribution of person-years by exposure category, mid-points of exposure categories. Recalculate RR using Hamling's method
Allen, 2009 COL40762 UK	MWS, Prospective Cohort, Age: 55 years, W, midlife women	2129 1 280 296 7.2 years	Cancer registry	Questionnaire	Incidence, colon cancer	≥15 vs ≤2 drinks/day	1.00 (0.87-1.15)	Age, area of residence, BMI, hormone use, physical activity, smoking status, socio-economic status, use of oral contraception	Distribution of person-years by exposure category, mid-points of exposure categories. Recalculated floated RR's

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Missing data derived for analyses
		337			Incidence, rectal cancer	≥15 vs ≤2 drinks/day	1.25 (1.06-1.49)		
Park, 2009 COL40771 UK	EPIC-Norfolk, Prospective Cohort, Age: 40-79 years, M/W	386/ 24 244 11 years	Routine record linkage with cancer registration and death certification	FFQ	Incidence, colorectal cancer	≥21 vs ≤0 units/week	0.70 (0.44-1.13)	Age, sex, calcium intake, dietary fibre intake, educational level, energy intake, family history of colorectal cancer, fat intake, folate intake, height, physical activity, processed meat, smoking status, total meat intake, weight	Distribution of person-years by exposure category, mid-points of exposure categories. Conversion from drinks/week to drinks/day Aleksandrova, 2014 COL41051 used in highest vs lowest analysis for colon and rectal cancer
		256/			Incidence, colon cancer	≥21 vs ≤0 units/week	0.59 (0.32-1.09)		
		213/			Incidence, colorectal cancer, men	≥21 vs ≤0 units/week	0.85 (0.45-1.58)		
		173/			Women	14-20 vs ≤0 units/week	0.83 (0.44-1.56)		
		137/			Incidence, colon cancer, men	≥21 vs ≤0 units/week	0.69 (0.32-1.50)		
		122/			Incidence, rectal cancer	≥21 vs ≤0 units/week	0.94 (0.43-2.09)		
		119/			Incidence, colon cancer, women	14-20 vs ≤0 units/week	1.00 (0.48-2.08)		
		69/			Incidence, rectal cancer, men	≥21 vs ≤0 units/week	1.14 (0.38-3.43)		
		53/			Women	14-20 vs ≤0 units/week	0.55 (0.15-2.02)		
Tsong, 2007 COL40685 Singapore	SCHS, Prospective Cohort, Age: 45-74 years,	845/ 61 321 8.9 years	Cancer registry	FFQ	Incidence, colorectal cancer	≥7 vs ≤0 drinks/week	1.84 (1.31-2.58)	Age, sex, BMI, diabetes, dialect group, educational level, family	Mid-points of exposure categories. Conversion from drinks/week to
		516/			Incidence, colon cancer	≥7 vs ≤0 drinks/week	1.84 (1.31-2.35)		

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Missing data derived for analyses
	M/W	329/			Incidence, rectal cancer	≥7 vs ≤0 drinks/week	1.59 (1.07-2.35)	history of colorectal cancer, physical activity, smoking status, year of recruitment	drinks/day Superseded by Odegaard, 2013 COL40948 for colon cancer analysis
Wakai, 2005 COL40727 Japan	JACC, Prospective Cohort, Age: 40-79 years, M/W	382/ 57 736 7.6 years	Record linkage with cancer registries, population registries, death cert, medical records	Questionnaire	Incidence, colon cancer, men	≥3.0 vs 0 drinks/day	2.40 (1.31-4.40)	Age, area, beef consumption, BMI, educational level, family history of colorectal cancer, green vegetables, sedentary behaviour, smoking habits, walking time, walking time	Mid-points of exposure categories
		242/			Incidence, rectal cancer, men	≥3.0 vs 0 drinks/day	1.32 (0.67-2.63)		
		225/			Incidence, colon cancer, women	≥1.0 vs 0 drinks/day	1.22(0.49-3.03)		
		68/			Incidence, rectal cancer, women	≥1.0 vs 0 drinks/day	1.01 (0.67-1.51)		
Sanjoaquin, 2004 COL01182 UK	OVS, Prospective Cohort, Age: 18-89 years, M/W	95/ 10 998 17 years	Population/invitation	FFQ	Incidence, colorectal cancer,	≥8 vs ≤1 unit/week	1.53 (0.87-2.69)	Age, sex, alcohol consumption, smoking habits	Distribution of person-years by exposure category, mid-points of exposure categories. Mid-points of exposure categories. Conversion from

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Missing data derived for analyses
									drinks/week to drinks/day
Su, 2004 COL01929 USA	NHEFS, Prospective Cohort, Age: 25-74 years	111/ 10 220 10 years	General population (survey)	Semi-quantitative FFQ	Incidence, colon cancer	≥1 vs ≤0 drinks/day	1.69 (1.03-2.79)	Age, sex, BMI, educational level, meat intake, meat intake, multivitamin supplement intake, previous polyps, race, smoking status	Mid-points of exposure categories.
Pedersen, 2003 COL00350 Denmark	CCPPS, Prospective Cohort, M/W, based on 3 comprehensive Danish programmes	411/ 33 264 426 934 person-years	Population	Questionnaire	Incidence, colon cancer,	≥41 vs ≤1 drinks/week	0.80 (0.50-1.50)	Age, sex, BMI, smoking habits, study of origin	Distribution of person-years by exposure category, mid-points of exposure categories. Mid-points of exposure categories.
		202/			Incidence, rectal cancer,	≥41 vs ≤1 drinks/week	2.20 (1.00-4.60)		
Flood, 2002 COL00411 USA	Breast Cancer Detection Demonstration Project follow-up cohort, Prospective Cohort, Age: 40-93 years, W	490/ 45 264 8.5 years	Breast cancer screening centres	FFQ	Incidence, colorectal cancer,	≥2 vs ≤0 serving/day	1.16 (0.63-2.14)	Dietary folate, energy intake, methionine, smoking habits	Distribution of person-years by exposure category, mid-points of exposure categories. Mid-points of exposure categories.

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Missing data derived for analyses
Chen, 2001 COL00379 USA	PHS, Nested Case Control, M, physicians, 93% Caucasian	211/ 1104 controls 13 years	Medical records	Questionnaire	Incidence, colorectal cancer,	≥5 vs ≤1 drinks/week	1.25 (0.85-1.84)	Age, multivitamin, randomized treatment assignment, smoking status	Distribution of person-years by exposure category, mid-points of exposure categories. Mid-points of exposure categories. Conversion from drinks/week to drinks/day Driver, 2007 COL40711 Used in highest versus lowest analysis
Klatsky, 1988 COL00656 USA	KPMCP, Nested Case Control, M/W	173/ 2 410	Hospital records	Questionnaire	Incidence, colon cancer, excluding cases with history of bowel symptoms	≥3 vs never drinker drinks/day	1.20 (0.51-2.81)	Age, sex, BMI, cholesterol, coffee, educational level, ethnicity	Distribution of person-years by exposure category, mid-points of exposure categories. Mid-points of exposure categories.
		66			Rectal cancer		3.17(1.05-9.37)		

Table 160 Total alcoholic drinks and colorectal cancer risk. Main characteristics of studies excluded from the CUP SLR dose-response meta-analysis

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Reasons for exclusion
Aleksandrova, 2014 COL41051 Europe	EPIC, Prospective Cohort, Age: 25-70 years, M/W	728/ 347 237 12 years	Cancer registry		Incidence, colon men	limited vs heavy	0.85(0.74-0.97)	Age, sex, body fat, diet quality, educational level, physical activity, smoking	Only included in highest versus lowest analysis
					Incidence, colon, women		0.99(0.88-1.14)		
					Incidence, rectal cancer, men		0.76 (0.64-0.89)		
					Incidence, rectal cancer, women		0.91(0.76-1.09)		
Shen, 2013 COL40995 China	Chinese elderly cohort study HK, Prospective Cohort, Age: 65- years, M/W, Elderly	944/ 66 820 10.5 years	Hospital records and death register	Questionnaire	Mortality, colorectal cancer	High vs never	1.25 (0.68 to 2.30)	Age, sex, BMI, educational level, exercise, health status, housing, monthly expenditure, smoking status	Outcome is mortality
		516/			Men		1.48 (0.80 to 2.74)		
		428/			Women	Moderate vs never	0.46 (0.11 to 1.83)		
Yang, 2012 COL40922 China	CNRPCS, Prospective Cohort, Age: 40-79 years, M	193/ 218 189 15 years	Annual follow up by trained staff, death certificate and symptoms described by	Questionnaire	Mortality, colorectal cancer	≥700 vs non-drinkers g/week	1.06 (0.55-2.06) Ptrend:0.5	5-year age-group, educational level, geographic area, smoking	Outcome is mortality
						all drinkers vs non-drinkers	0.90 (0.65-1.24)		

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Reasons for exclusion
			family members						
Breslow, 2011 COL40892 USA	NHIS, Prospective Cohort, Age: 18- years, M/W	850/ 323 354 2 716 472 person-years	National center for health statistics & national death Index	Questionnaire	Mortality, colonrectal cancer	current drinker - heavier vs never drinker	1.01 (0.70-1.47)	Sex, BMI, educational level, marital status, race/ethnicity, region, smoking status	The outcome is mortality, only included on highest versus lowest analysis
		367/			Mortality, colorectal cancer, women	>7 vs 0 drinks/week	1.05 (0.61-1.80)		
					Men	>14 vs 0 drinks/week	1.08 (0.60-1.96)		
Cnattingius, 2009 COL40776 Sweden	Swedish Twin Cohort, Prospective Cohort, M/W, Twins	207/ 23 337 33 years	Population cancer registries and other procedures	FFQ	Incidence, colorectal cancer	moderately high vs none	1.01 (0.53-1.91)	Age	Included only in highest vs lowest analysis
Butler, 2008 COL40639 Singapore	SCHS, Prospective Cohort, Age: 45-74 years, M/W	961/ 61 321 9.8 years	Cancer registry	FFQ	Incidence, colorectal cancer	≥7 vs ≥0 drinks/week	1.58 (1.23-2.04) Ptrend:0.001	Age, sex, alcohol intake, BMI, diabetes, dialect group, educational level, energy intake, exposure assessment, family history of colorectal cancer, physical activity, smoking habits	Superseded by Odegaard, 2013 COL40948

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Reasons for exclusion
Akhter, 2007 COL40632 Japan	MCS, Prospective Cohort, Age: 40-64 years, M	131/ 21 199 11 years	Cancer registry	Self-administered questionnaire	Incidence, rectal cancer	current vs never	1.54 (0.91-2.61)	Age	Included only in highest vs lowest analysis
Driver, 2007 COL40711 USA	PHS, Prospective Cohort, Age: 40-84 years, M, Physicians	21 581 20 years	Follow up questionnaires (self-report), medical record and pathology reports	FFQ	Incidence, colorectal cancer	≥1 vs ≤0 /week	1.36 (1.08-1.71)	Age, BMI, cereal intake, history of diabetes, multivitamin, physical activity, smoking status, vegetable intake, vitamin c, vitamin e	Included only in highest vs lowest analysis, 2 categories only Chen, 2001 COL00379 Used in dose-response meta-analysis
Ozasa, 2007 COL40758 Japan	JACC, Prospective Cohort, M/W	203/		Unknown	Mortality, colon cancer, men	ex-drinkers vs rare/none	1.57 (0.90-2.75)	Age, study center	Outcome is mortality
		190/			Women	ex-drinkers vs rare/none	1.12 (0.41-3.03)		
		176/			Women	≥81 vs ≤0 ml/day	2.14 (0.29-15.40)		
		160/			Mortality, rectal cancer, men	ex-drinkers vs rare/none	1.89 (0.99-3.60)		
		158/			Mortality, colon cancer, men	≥81 vs ≤0 ml/day	1.75 (0.97-3.14)		

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Reasons for exclusion
		115/			Mortality, rectal cancer, men	≥81 vs ≤0 ml/day	2.25 (1.22-4.14)		
		77/			Women	ex-drinkers vs rare/none	1.51 (0.36-6.21)		
		68/			Women	1-53 vs ≤0 ml/day	0.62 (0.24-1.57)		
						ex-drinkers vs rare/none	1.57 (0.90-2.75)		
McCarl, 2006 COL40633 USA	IWHS, Prospective Cohort, Age: 55-69 years, W	954/ 35 197 15 years	SEER registry	FFQ	Incidence, colorectal cancer	yes vs no	1.00 (0.88-1.14)	Age	Included only in highest versus lowest analysis
Yeh, 2006 COL40675 Taiwan	Taiwanese Cohort, Prospective Cohort, Age: 30-65 years, M/W	68/ 23 943 10 years	Cancer registry and death certificates	Dietary record	Incidence, colorectal cancer, men	yes vs no	1.23 (0.71-2.16)	Age, BMI, cholesterol, smoking,	Included only in highest versus lowest analysis
Jiang, 2005 COL01846 China	China, Haining City of Zhejiang Province, Nested Case Control, Age: 40- years,	73/ 343 controls 12 years	Cancer registry	FFQ	Incidence, rectal cancer	current drinker vs non drinker	0.65 (0.30-1.41)	Age, sex, folate intake, methionine intake, smoking habits, total energy intake,	Included only in highest vs lowest analysis
					Incidence, colon cancer		1.04(0.46-2.39)		

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Reasons for exclusion
	M/W							zinc intake	
Chen, 2005 COL40724 China	Chinese Jiashan screening study, Prospective Cohort, Age: 30- years, M/W, Screening Program	121/ 64 100 10.6 years	Cancer registry and death registry	Questionnaire and Interview	Incidence, colorectal cancer, women	daily vs non-drinker (never or almost never)	1.06 (0.33-3.48)	Age, educational level, marital status, occupation, smoking status	Included only in highest vs lowest analysis
					Men	daily vs non-drinker (never or almost never)	1.03 (0.65-1.64)		
					Incidence, colon cancer, women	occasional vs non-drinker (never or almost never)	1.00		
					Incidence, rectal cancer, men	daily vs non-drinker (never or almost never)	1.37 (0.71-2.65)		
Wei, 2004 COL00581 USA	The Nurses's Health Study Cohort, Prospective Cohort, W, nurses	61/ 87 733 24 years	Self-reported verified by medical record and The National Death Index	Semi-quantitative FFQ	Incidence, rectal cancer,	past alcohol consumption vs no alcohol consumption	0.72 (0.29-1.81)	Age, beef, pork or lamb as a main dish, BMI, calcium, family history of colorectal cancer, folate, height, history of endoscopy, pack-years of smoking before	Only included in highest versus lowest analysis
	Health Professionals Study	135					1.06(0.5-2.27)		

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Reasons for exclusion
								age 30, physical activity, processed meat	
Koh, 2004 COL00053 China	SCHS, Nested Case Control, Age: 45-74 years, M/W	310/ 1177 controls	Cancer registry	Questionnaire	Incidence, colorectal cancer,	daily vs nondrinkers	Ptrend:0.14		Unadjusted results Superseded by Tsong, 2007 COL40685
Konings, 2002 COL01271 Netherlands	NLCS, Case Cohort, Age: 55-69 years, M/W	400/ 120 852 7.3 years	Cancer registry and database of pathology reports	Semi-quantitative FFQ	Incidence, colon cancer, men	alcohol drinkers vs nonalcohol drinkers			Unadjusted results
		360/			Women	alcohol drinkers vs nonalcohol drinkers			
		259/			Incidence, rectal cancer, men	alcohol drinkers vs nonalcohol drinkers			
		152/			Women	alcohol drinkers vs nonalcohol drinkers			
Hsing, 1998 COL00458 USA	Lutheran Brotherhood Study, Prospective Cohort, Age: 35- years, M, policyholders	87/ 17 633 286 731 person-years	Responding to mail survey	Questionnaire	Mortality, colorectal cancer,	≥14 vs ≤0 drinks/month	1.20 (0.60-2.70)	Age, alcohol intake, area of residence	Outcome is mortality, only included in highest versus lowest analysis

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Reasons for exclusion
Singh, 1998 COL00185 USA	AHS, Prospective Cohort, Age: 25- years, M/W, Seventh-day Adventists	146/ 32 051 178 544 person-years	Census list	FFQ	Incidence, colon cancer,	≥1 vs ≤1 times/week	2.05 (1.00-4.23)	Age, sex, family history of specific cancer	Included only in HvL analysis
Glynn, 1996 COL00431 Finland	ATBC, Prospective Cohort, Age: 50-69 years, M, Smokers	119/ 27 109 8 years	Cancer registry	Food-use questionnaire	Incidence, colorectal cancer, alcohol consumption:yes	Q 4 vs Q 1	1.70 (1.00-2.90)	Age	Included only in highest versus lowest analysis
Suadicani, 1993 COL01085 Denmark	Denmark, Copenhagen fitness and risk of cvd study, Prospective Cohort, Age: 40-59 years, M	51/ 5 429 18 years	Public or private companies	Questionnaire	Incidence, colon cancer,	(mean exposure)		Age	No measure of the relationship. Only mean values.
		42/			Incidence, rectal cancer,	(mean exposure)			
Hirayama, 1990 COL01508 Japan	Japan 6 prefectures cohort study, Prospective	563/ 265 118 17 years	Health centres	Interview	Mortality, rectal cancer,	daily consumption vs no daily consumption	1.30 (1.08-1.57)	Age, sex	Outcome is mortality, not enough studies to do analysis

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Reasons for exclusion
	Cohort, Age: 40- years, M/W	558/			Mortality, colon cancer,	daily consumption vs no daily consumption	1.01 (0.81-1.26)		
Stemmermann, 1990 COL00816 USA	HHP, Prospective Cohort, Age: 46-68 years, M	211/ 7 572 24 years	Population	Questionnaire + recall	Incidence, colon cancer,	≥40 vs ≤0 oz/month	1.44 (0.96-2.14) Ptrend:0.16	Age, age started smoking, current smoking status, ex smoker status, maximum number of cigarettes smoked per day, number of cigarettes smoked, number of years smoked maximum amount	Included only in highest versus lowest analysis
		101/			Incidence, rectal cancer,	≥40 vs ≤0 oz/month	1.86 (1.02-3.38) Ptrend:0.01		
Hirayama, 1989 COL01024 Japan	Japan 6 prefectures cohort study, Prospective Cohort, Age: 40- years, M/W	48/ 265 118 17 years	Population	Quantitative FFQ	Mortality, sigmoid cancer, women	drinkers vs non-drinkers	1.92 (1.13-3.26)	Age	Outcome is mortality, insufficient data to do analysis
		43/			Men	drinkers vs non-drinkers	4.38 (1.75-10.97)		
Sidney, 1986 COL01239 USA	KPMCP, Nested Case Control, M/W	245/ 1225 controls 348 000 person-years	Medical records	Questionnaire	Incidence, colorectal cancer,	current alcohol drinker vs no current alcohol use		Age, sex, race, time of examination	No risk estimate provided Superseded by Klatsky, 2015 COL41059

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Reasons for exclusion
Hirayama, 1985 COL01652 Japan	Japanese cohort study, Prospective Cohort, Age: 40- years, M	122 261 16 years	Population	Questionnaire	Mortality, colon cancer,	yes vs no	0.66		Outcome is mortality, insufficient data to do analysis
					Smokers	yes vs no	0.78		
Pollack, 1984 COL00720 Hawaii	HHP, Prospective Cohort, M, Honolulu Heart Study subjects	92/ 7 837 104 881 person-years	Hospital records + cancer registry	Questionnaire	Incidence, colon cancer,	≥40 vs ≤0 oz/month	Ptrend:0.480	Age, cigarette smoking	No risk estimate provided Superseded by Stemmermann, 1990 COL00816
Williams, 1981 COL01163 USA	FHS, Prospective Cohort, Age: 35-69 years, M	30/ 5 209 24 years	Population	Questionnaire	Incidence, colon cancer, women	yes vs no	1.35	Age, educational level, smoking status	Insufficient data to compute confidence intervals
		28/			Men	yes vs no	1.45	Metropolitan relative weight, serum cholesterol, systolic blood pressure	

Figure 276 RR estimates of colorectal cancer by levels of total alcoholic drinks

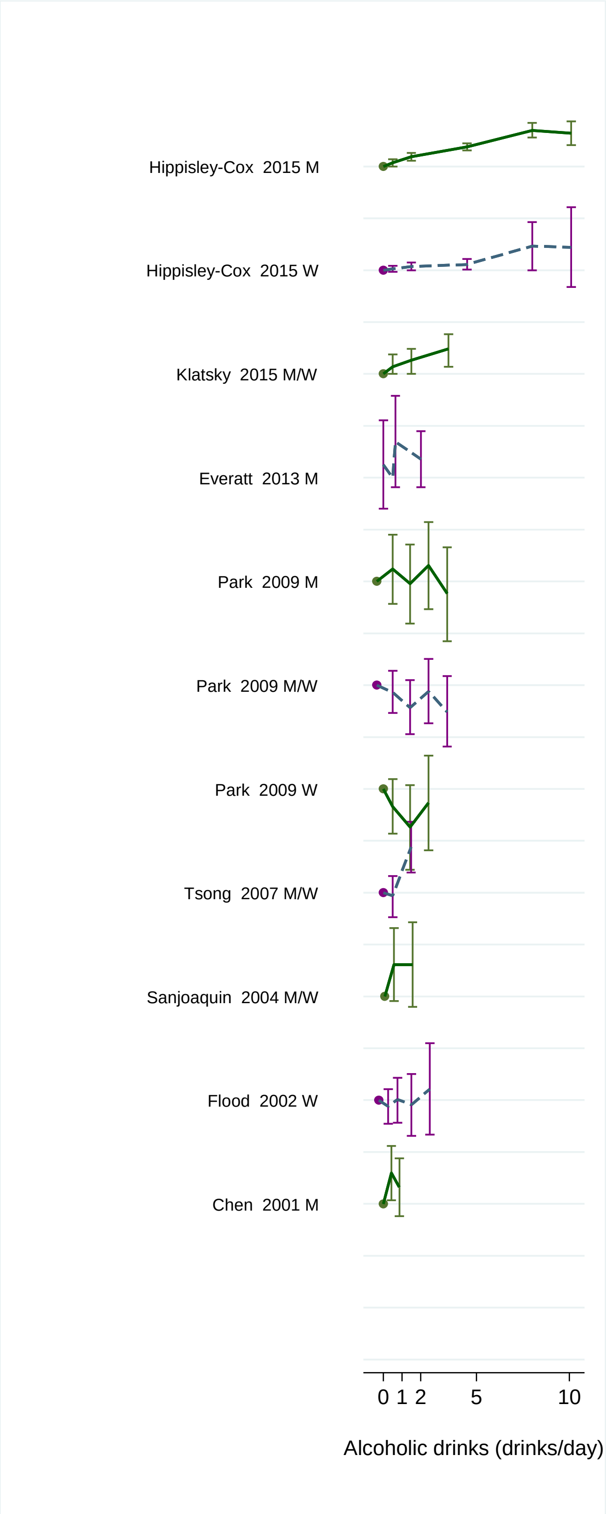


Figure 277 RR (95% CI) of colorectal cancer for the highest compared with the lowest level of total alcoholic drinks

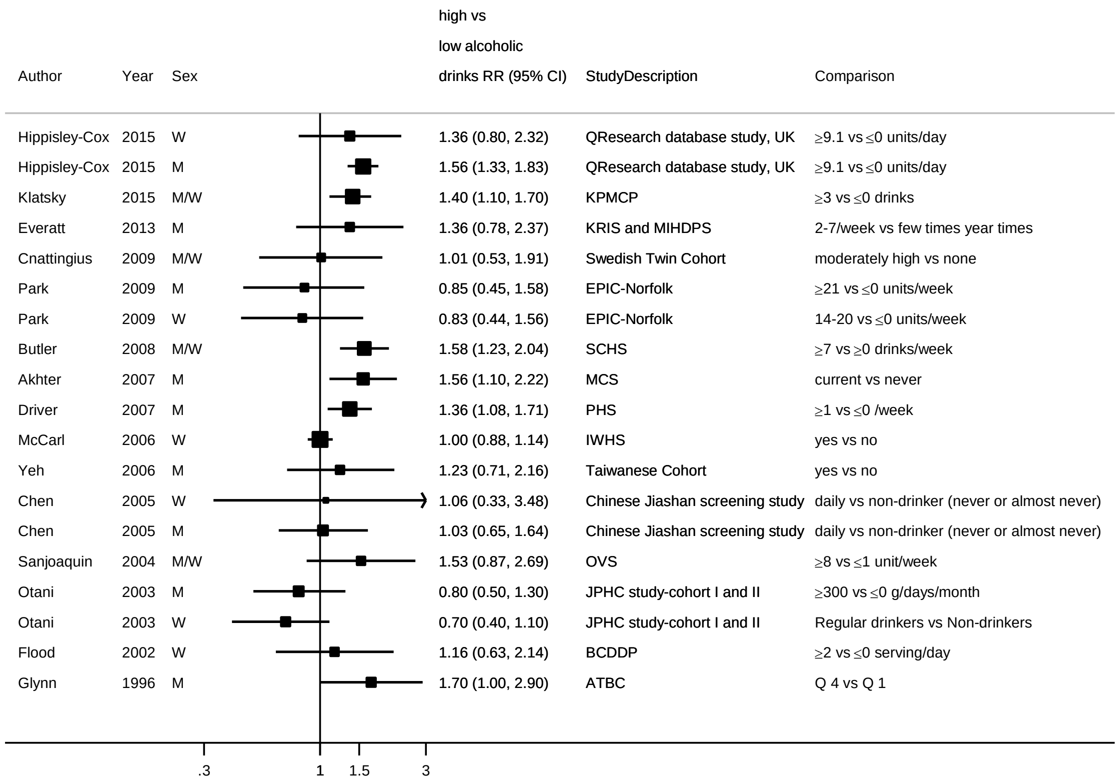


Figure 278 RR (95% CI) of colorectal cancer for 1 drink/day increase of total alcoholic drinks

Author	Year	Sex	per 1 drink/day RR (95% CI)	% Weight	StudyDescription
Hippisley-Cox	2015	M/W	1.05 (1.04, 1.05)	31.10	QResearch database study, UK
Klatsky	2015	M/W	1.09 (1.03, 1.15)	23.37	KPMCP
Everatt	2013	M	1.05 (0.96, 1.14)	16.50	KRIS and MIHDPS
Park	2009	M/W	0.92 (0.83, 1.02)	13.57	EPIC-Norfolk
Tsong	2007	M/W	1.43 (1.15, 1.77)	4.50	SCHS
Sanjoaquin	2004	M/W	1.29 (0.89, 1.87)	1.70	OVS
Flood	2002	W	1.01 (0.86, 1.17)	8.06	BCDDP
Chen	2001	M	1.28 (0.81, 2.00)	1.19	PHS
Overall (I-squared = 60.4%, p = 0.013)			1.06 (1.00, 1.11)	100.00	

NOTE: Weights are from random effects analysis

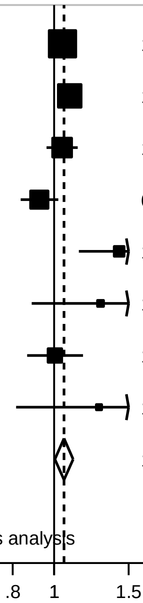


Figure 279 Funnel plot of studies included in the dose response meta-analysis of total alcoholic drinks and colorectal cancer

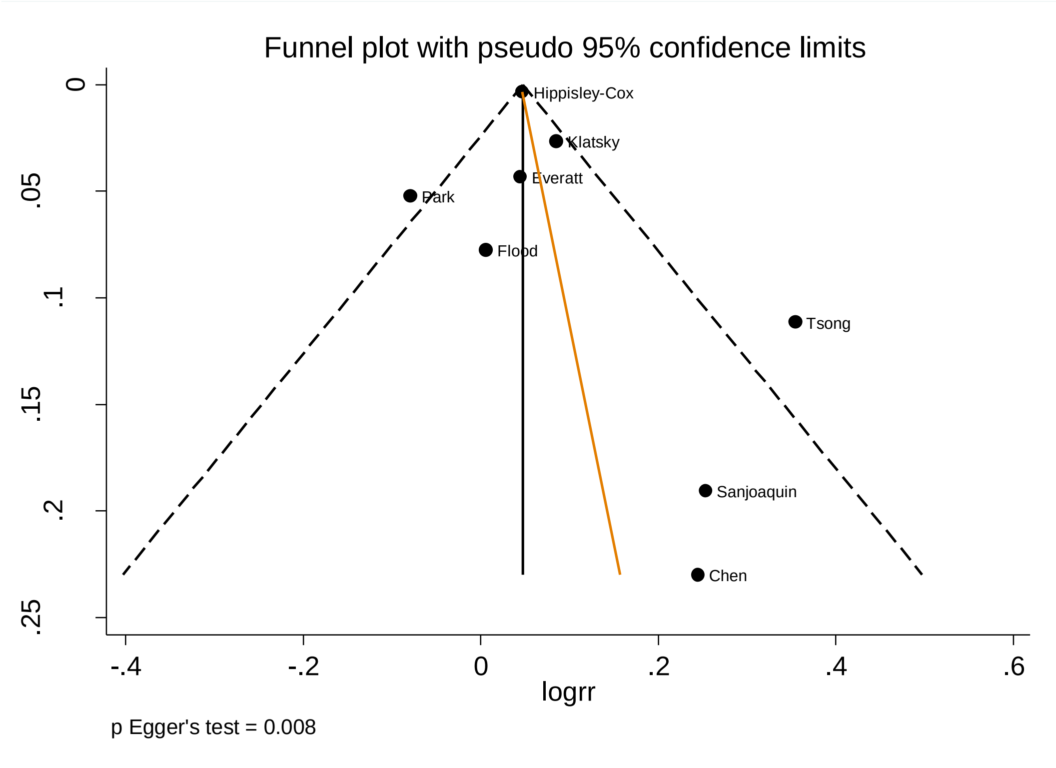


Figure 280 RR (95% CI) of colorectal cancer for 1 drink/day increase of total alcoholic drinks by sex

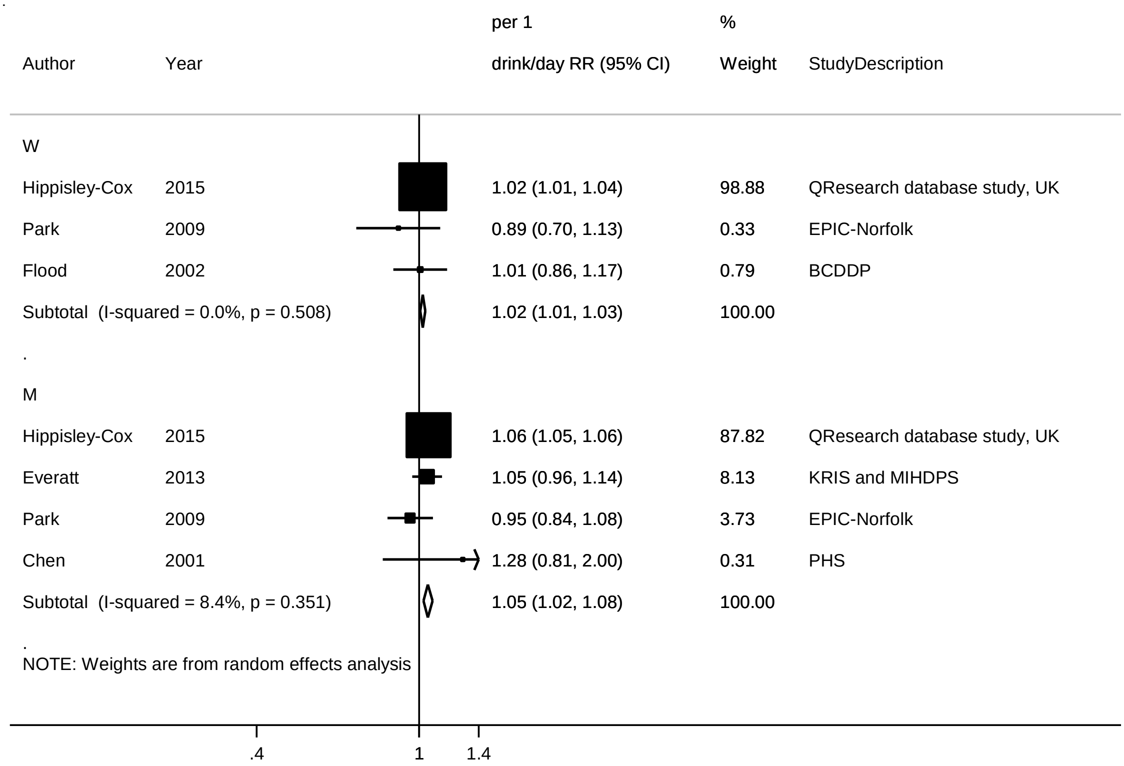


Figure 281 RR (95% CI) of colorectal cancer for 1 drink/day increase of total alcoholic drinks by geographic location

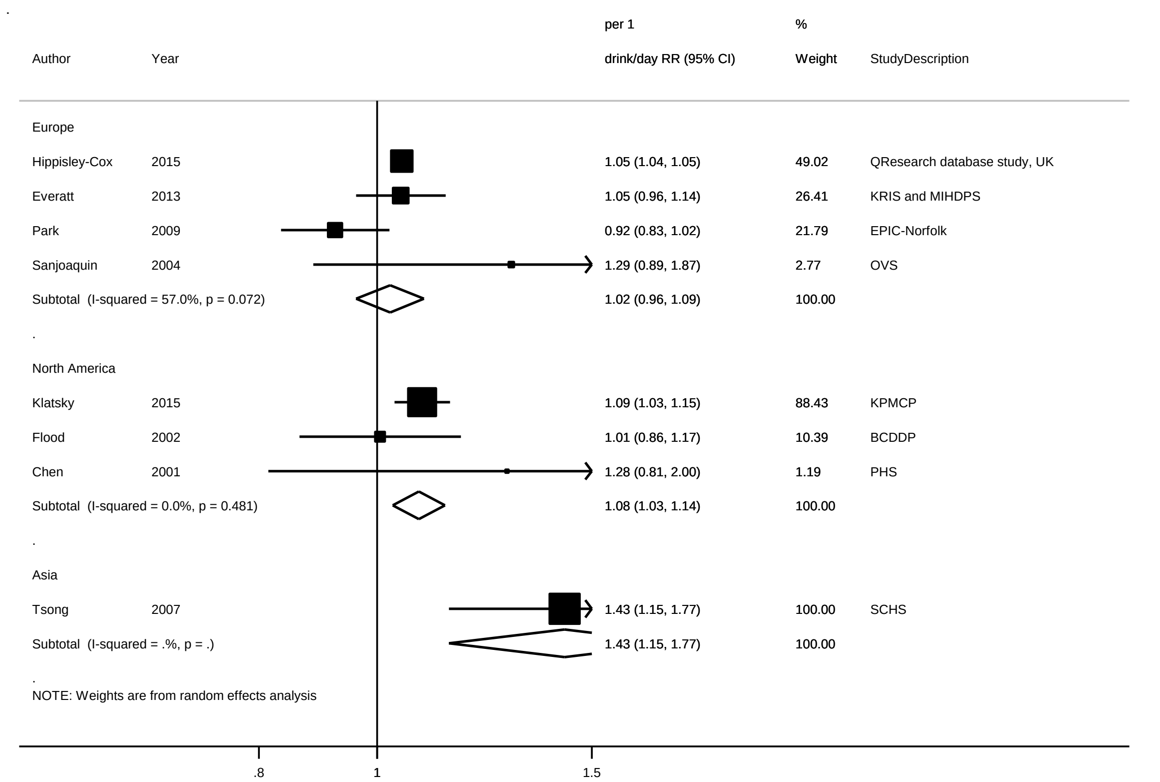


Figure 282 RR estimates of colon cancer by levels of total alcoholic drinks

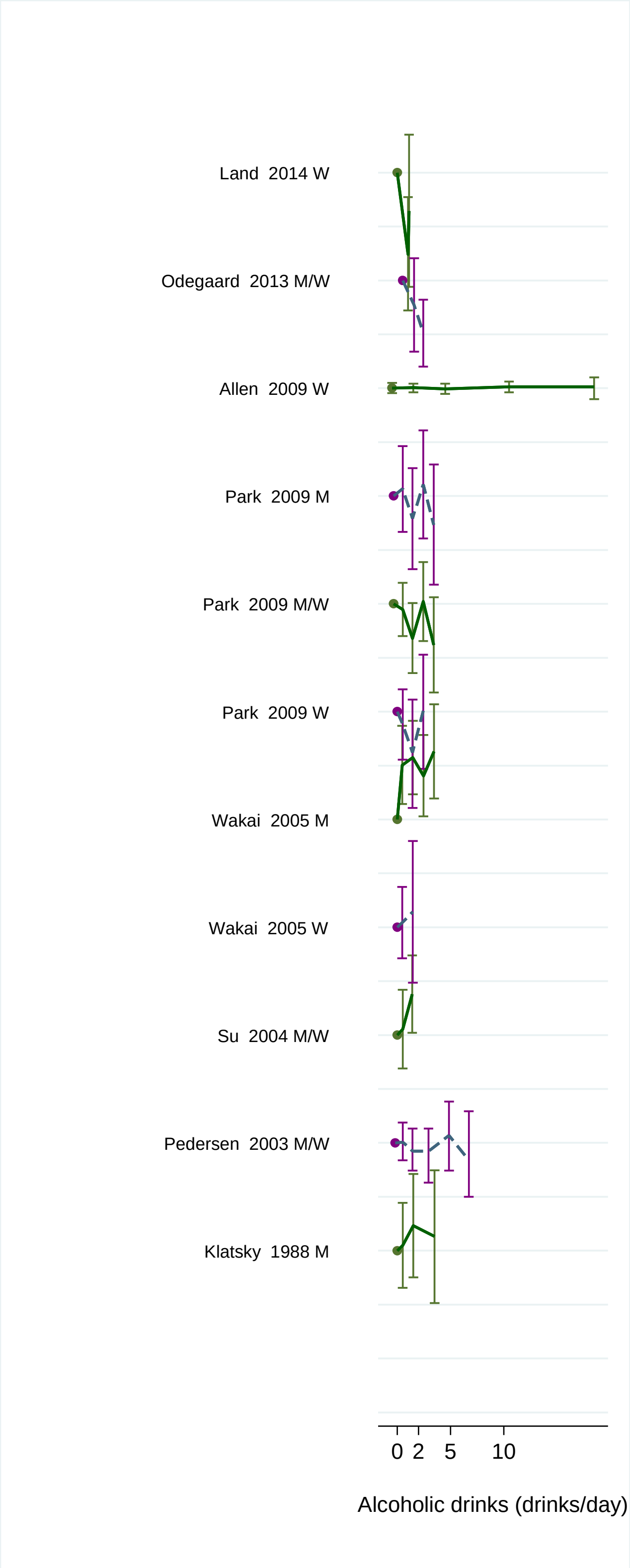


Figure 283 RR (95% CI) of colon cancer for the highest compared with the lowest level of total alcoholic drinks

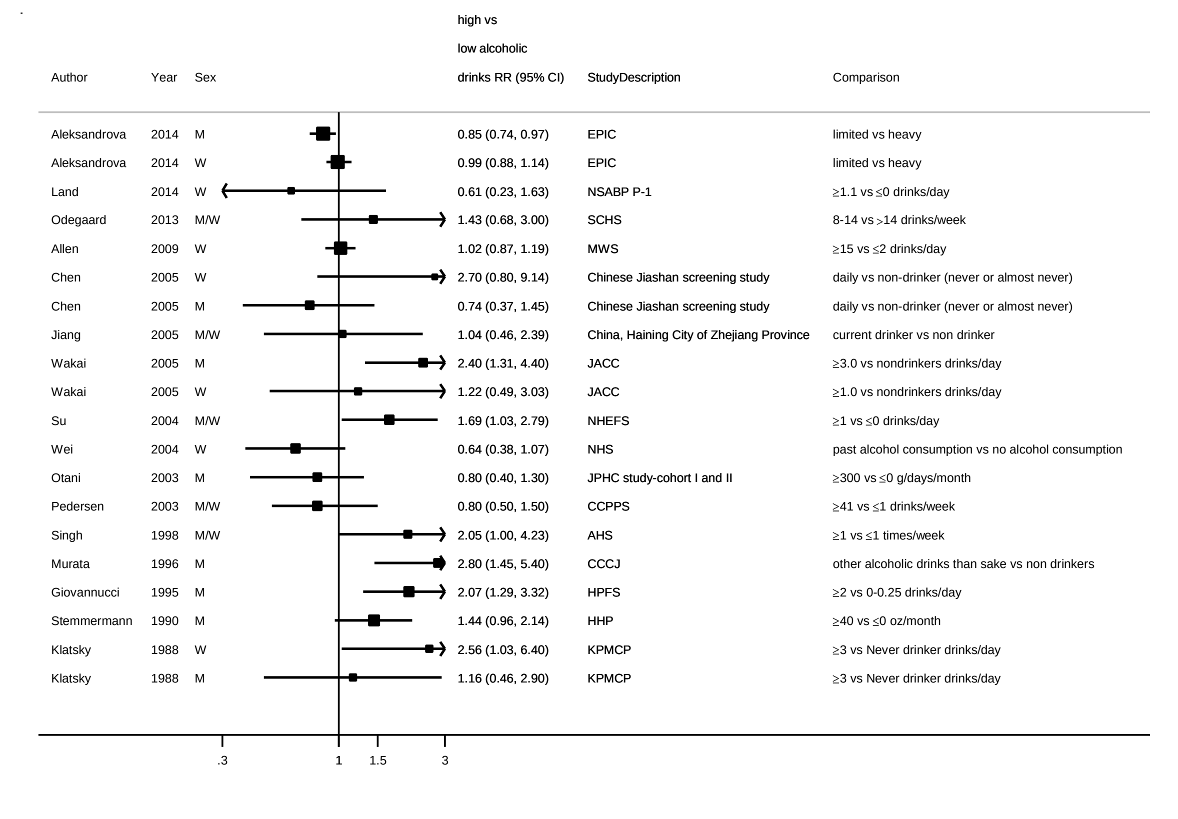
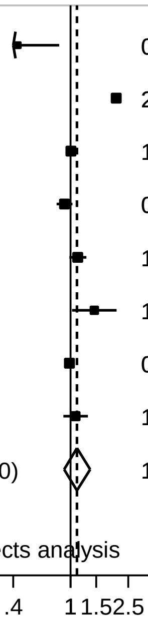


Figure 284 RR (95% CI) of colon cancer for 1 drink/day increase of total alcoholic drinks

Author	Year	Sex	per 1 drink/day RR (95% CI)	% Weight	StudyDescription
Land	2014	W	0.43 (0.22, 0.83)	5.92	NSABP P-1
Odegaard	2013	M/W	2.07 (1.92, 2.23)	14.32	SCHS
Allen	2009	W	1.00 (1.00, 1.01)	14.59	MWS
Park	2009	M/W	0.91 (0.80, 1.03)	13.83	EPIC-Norfolk
Wakai	2005	M	1.12 (0.98, 1.28)	13.74	JACC
Su	2004	M/W	1.46 (1.02, 2.08)	10.22	NHEFS
Pedersen	2003	M/W	0.98 (0.93, 1.04)	14.43	CCPPS
Klatsky	1988	M	1.08 (0.89, 1.31)	12.93	KPMCP
Overall (I-squared = 98.1%, p = 0.000)			1.11 (0.90, 1.36)	100.00	



NOTE: Weights are from random effects analysis

Figure 285 Funnel plot of studies included in the dose response meta-analysis of total alcoholic drinks and colon cancer

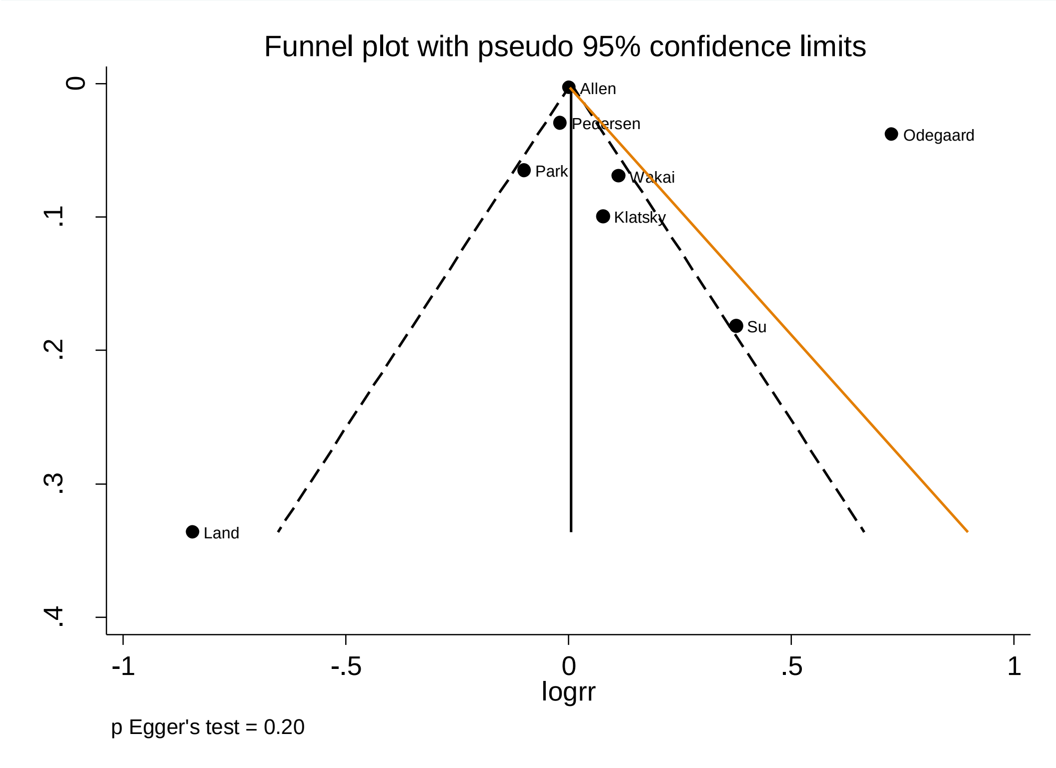


Figure 286 RR (95% CI) of colon cancer for 1 drink/day increase of total alcoholic drinks by sex

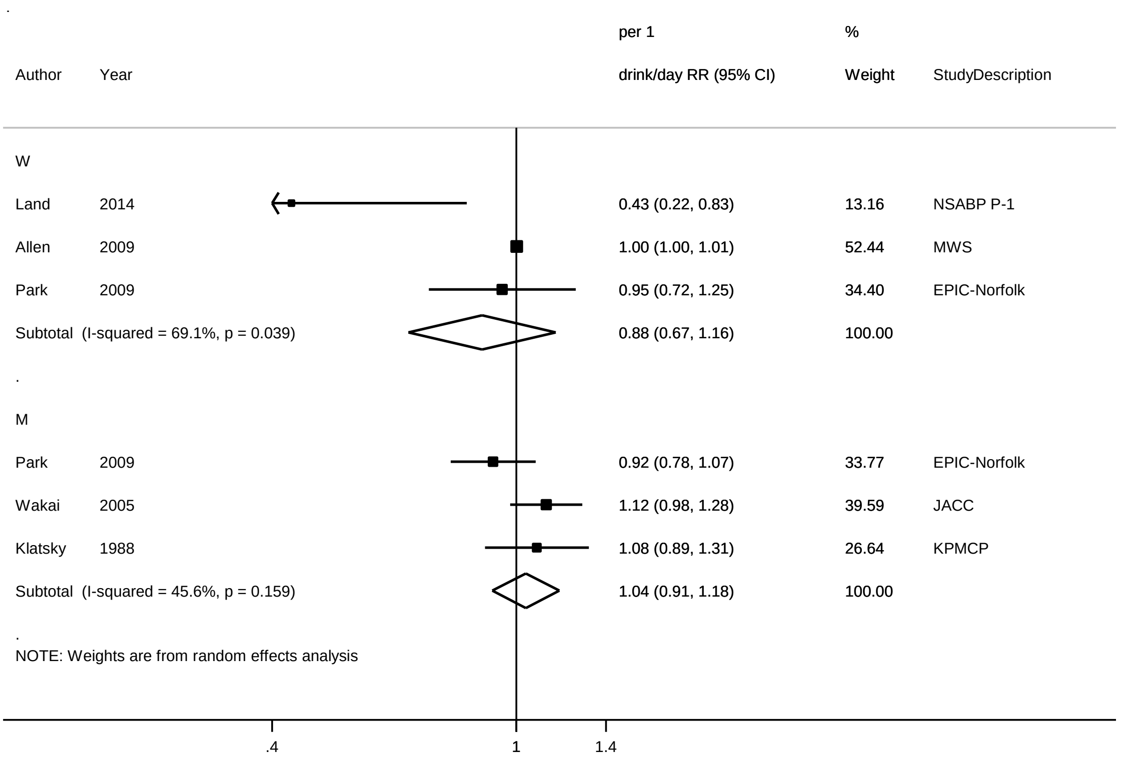


Figure 287 RR (95% CI) of colon cancer for 1 drink/day increase of total alcoholic drinks by geographic location

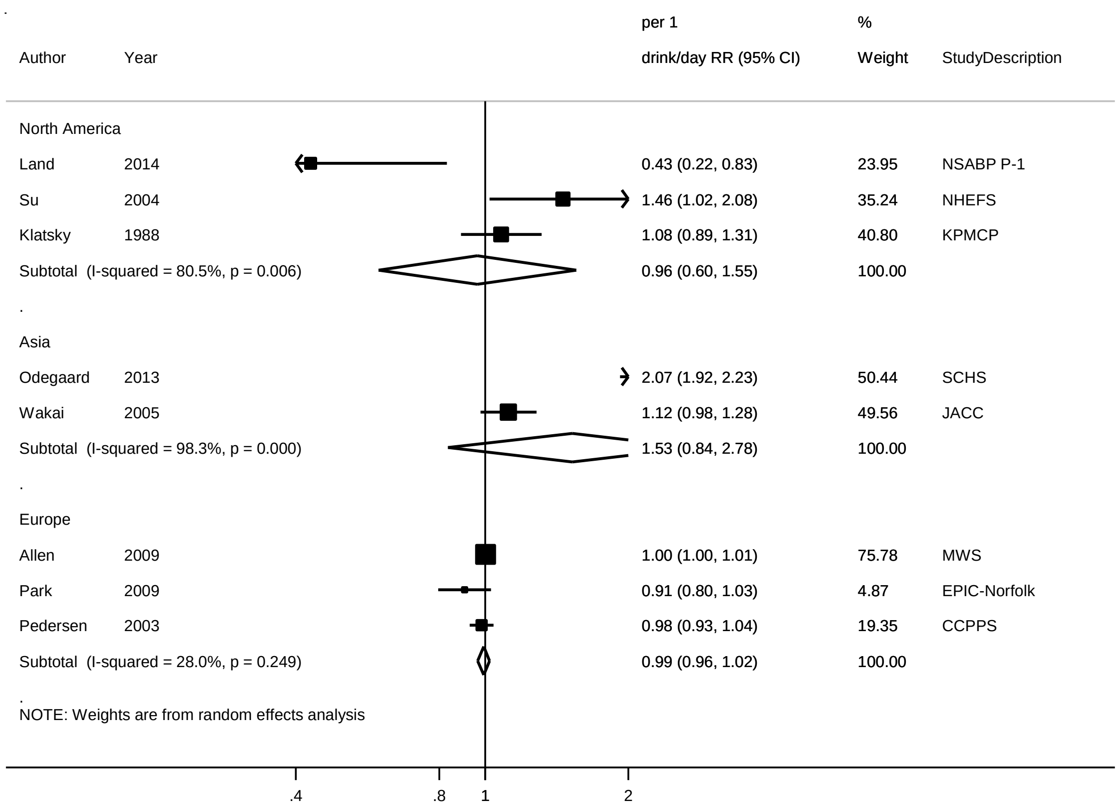


Figure 288 RR estimates of rectal cancer by levels of total alcoholic drinks

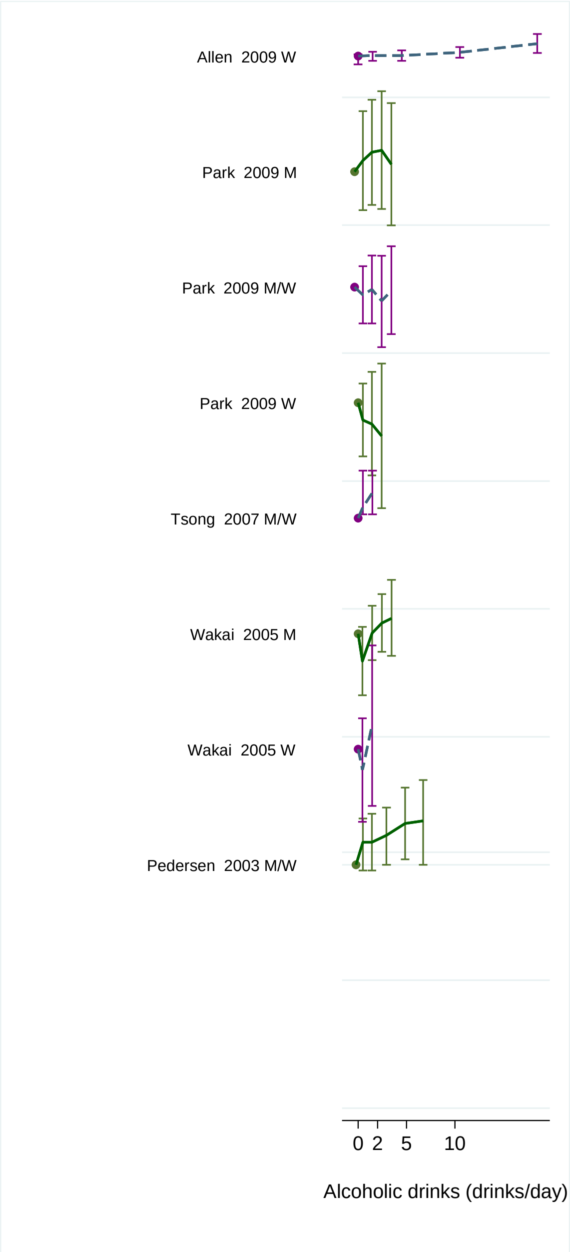


Figure 289 RR (95% CI) of rectal cancer for the highest compared with the lowest level of total alcoholic drinks

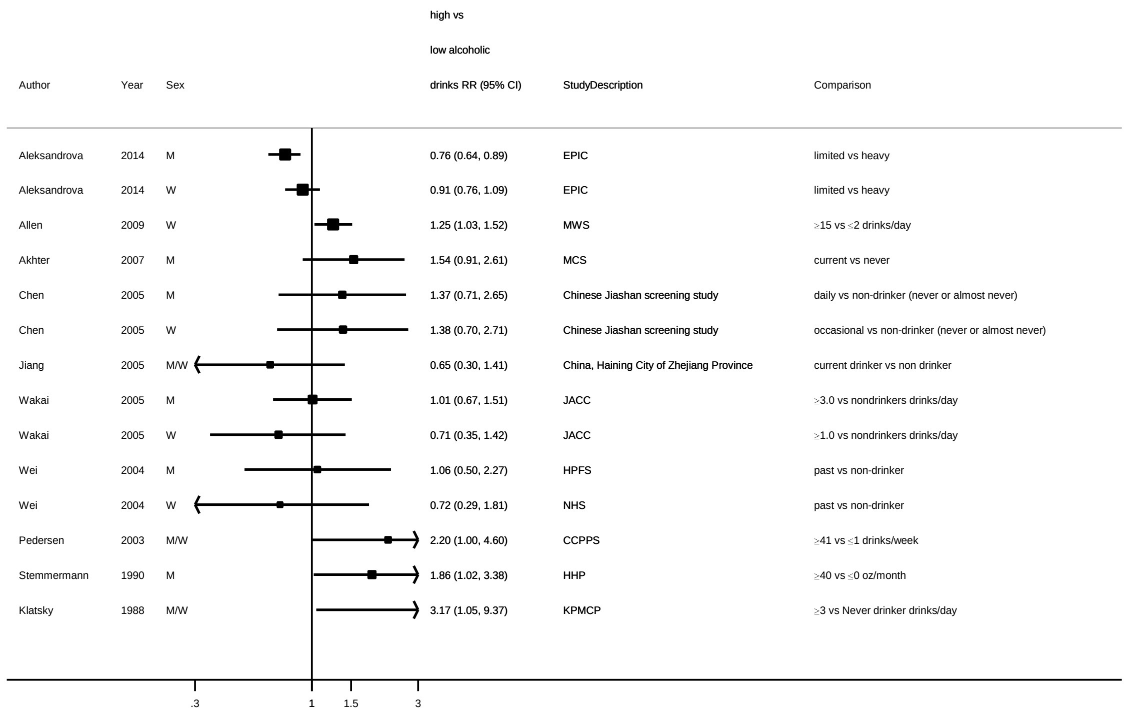


Figure 290 RR (95% CI) of rectal cancer for 1 drink/day increase of total alcoholic drinks

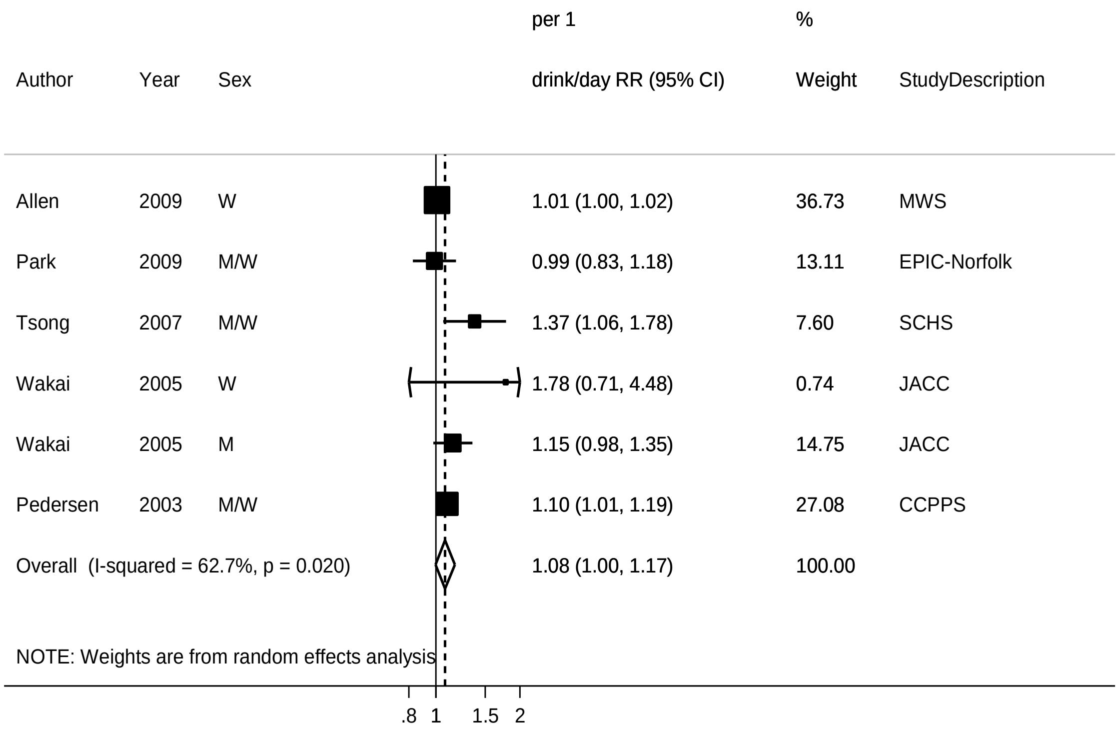


Figure 291 Funnel plot of studies included in the dose response meta-analysis of total alcoholic drinks and rectal cancer

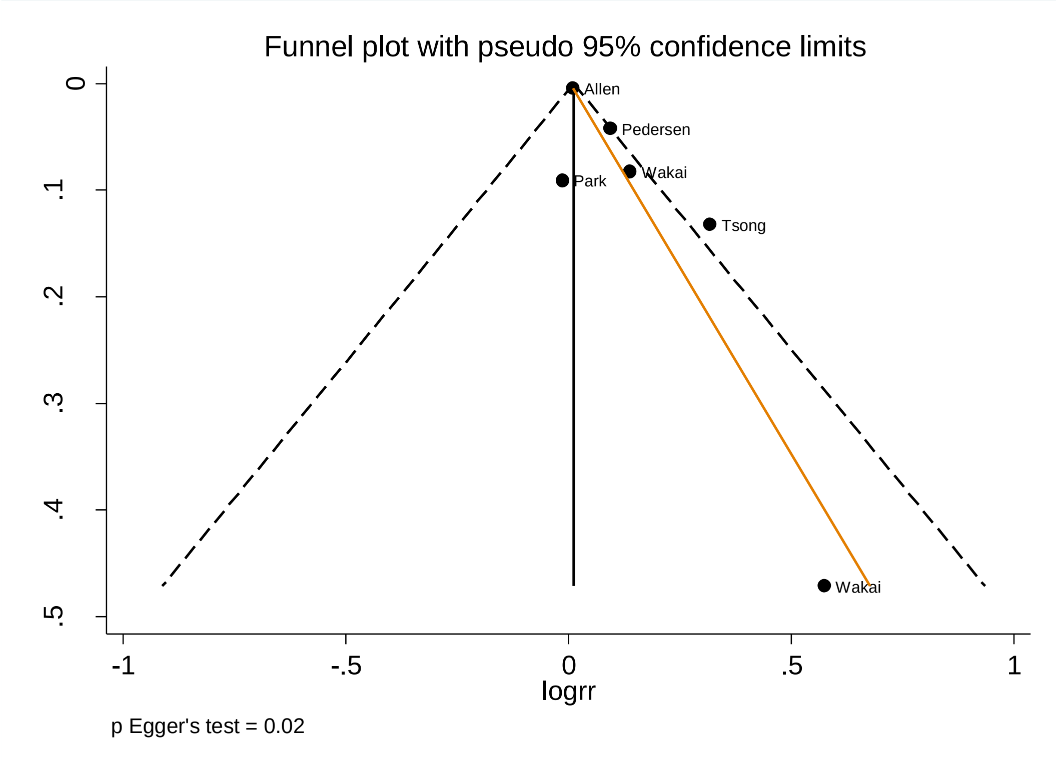
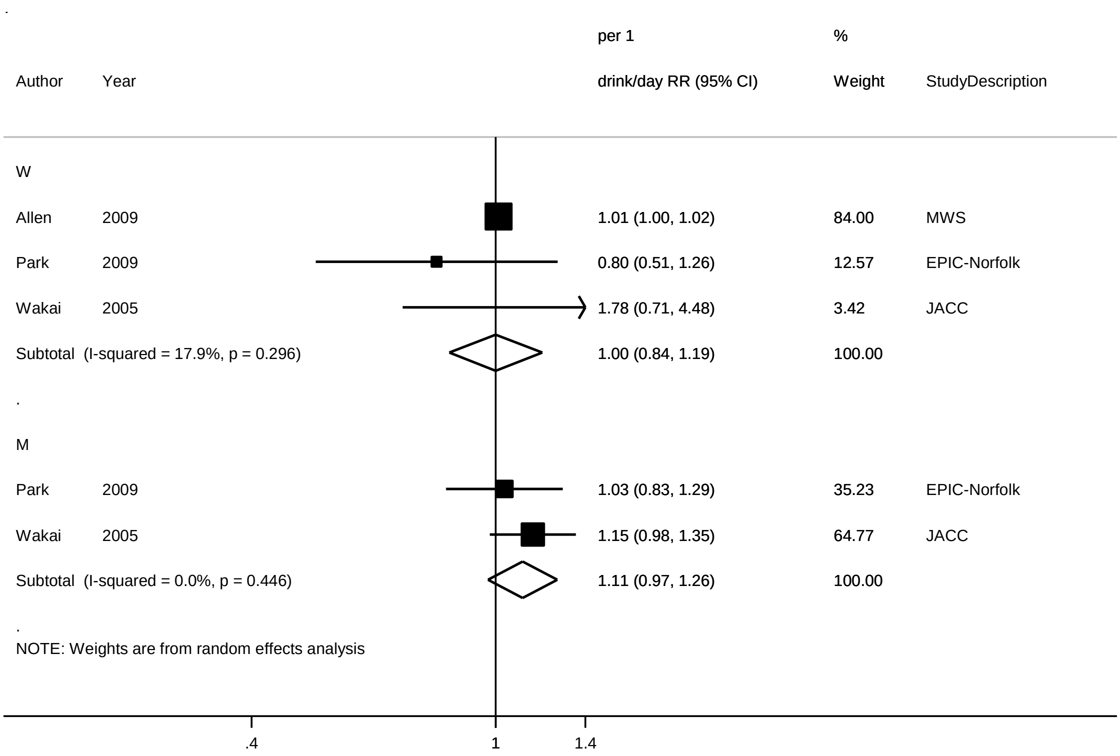


Figure 292 RR (95% CI) of rectal cancer for 1 drink/day increase of total alcoholic drink by sex



5.1.2 Dietary Fibre

Cohort studies

Summary

Main results:
Two studies (six publications) which superseded studies identified in 2010 SLR were identified. The Pooling Project of Prospective Studies of Diet and Cancer identified in the 2010 SLR could be included in the analysis. All the analyses are on cancer incidence. For the different types of fibre or distal and proximal colon cancer there was no update since the 2010 SLR.

Colorectal cancer:
Twenty one studies (16562 cases) were included in the dose-response meta-analysis of dietary fibre and colorectal cancer. Thirteen studies were included in the Pooling Project (Park, 2005). A borderline significant inverse association with high heterogeneity was observed. Only three studies showed a significant inverse association per 10g/day of dietary fibre (MEC, EPIC, JACC). After stratification by adjustment for folate intake the result was borderline significant for studies which adjusted for folate and non-significant for the three studies not adjusting for folate intake. For the stratified analysis by sex and location, the individual studies overlapping with the Pooling Project were used instead of the Pooling Project (Park, 2005). A significant inverse association with null to low heterogeneity was observed for men, women, European and North American studies.

There was evidence of small study bias (p=0.002). There was no evidence of a non-linear association (p=0.06).
The summary RRs was stronger when Park, 2005 was omitted 0.91 (95% CI=0.86-0.96) and non-significant 0.95 (95% CI=0.88-1.02) when Nomura, 2007 was omitted.
We conducted an analysis using the results of individual studies instead of using the Pooling Project. In this analysis fifteen studies (14876 cases) could be included and the overall result was similar to the result observed in the 2010 SLR, RR per 10g/day=0.91 (95%CI=0.88-0.94, 0%,ph=0.70)

Colon cancer:
Twenty one studies (12601 cases) were included in the dose-response meta-analysis of dietary fibre and colon cancer. Thirteen studies were included in the Pooling Project (Park, 2005). A borderline significant association with high heterogeneity was observed. Only three studies showed a significant inverse association per 10g/day of dietary fibre (MEC, EPIC, JACC). After stratification by adjustment for folate intake the result was borderline significant for studies which adjusted for folate and not significant for the studies without adjustement for folate. For the stratified analysis by sex and location, the individual studies overlapping with the Pooling Project were used instead of the Pooling Project (Park, 2005). A

significant inverse association with low or no heterogeneity was observed for men, North American and European studies.

There was evidence of small study bias (p=0.001). There was evidence of a non-linear association (p<0.001) with higher intakes of dietary fibre showing a reduced risk of colon cancer. The curve is steeper for lower intakes, hence a greater reduction in risk as intake increases from very low levels.
The summary RRs ranged from 0.88 (95% CI=0.81-0.98) when Park, 2005 was omitted to 0.94 (95% CI=0.87-1.00) when Wakai, 2007 was omitted.
We conducted an analysis using the results of individual studies instead of using the Pooling Project. In this analysis twelve studies (9297 cases) could be included and the overall result was similar to the result observed in the 2010 SLR, RR per 10g/day =0.91 (95%CI=0.84-0.97, 22.8%, ph=0.23)

Rectal cancer:
Twenty one studies (5809 cases) were included in the dose-response meta-analysis of dietary fibre and rectal cancer. Thirteen studies were included in the Pooling Project (Park, 2005). A non-significant association with low/modetate heterogeneity was observed. Only one study showed a significant inverse association per 10g/day of dietary fibre (MEC study). After stratification by adjustment for folate intake the result remained non-significant in both subgroups. For the stratified analysis by sex and location, the individual studies overlapping with the Pooling Project were used instead of the Pooling Project (Park, 2005). The results remained unchanged.

There was no evidence of publication bias (p=0.10). There was no evidence of a non-linear association (p=0.75).
The summary RRs ranged from 0.89 (95% CI=0.83-0.96) when Schatzkin, 2007 was omitted to 0.96 (95% CI=0.90-1.02) when Nomura, 2007 was omitted.

We conducted an analysis using the results of individual studies instead of using the Pooling Project. In this analysis ten studies (4149 cases) could be included and the overall result was similar to the result observed in the 2010 SLR, RR per 10g/day=0.94 (95%CI=0.85-1.03, 48.4%, ph=0.04)

Study quality:
The exposure definition and assessment of non-starch polysaccharides or dietary fibre was not detailed in the articles. It has been suggested that the folate intake might confound the inverse association observed between dietary fibre intake and colorectal cancer risk, therefore we stratified the analysis for studies by adjustment for folate intake.
The NHS and HPFS assessed dietary fibre intake using two methods, the AOAC and the Englyst method, and observed similar results. The EPIC study took into account the different analytical methods used by the different countries by using the EPIC Nutrient Data Base (ENDB); in which the nutritional composition of foods across the different countries has been standardized. The EPIC study (Murphy, 2012) was the only one using calibrated intakes and

observed a 13% lower (95% CI: 0.79–0.96) colorectal cancer risk per 10 g/day increase in total fibre intake in calibrated models.

Pooling Project of cohort studies:
The Pooling Project of Prospective Studies of Diet and Cancer had examined the association between dietary fibre intake and risk of colorectal cancer (Park, 2005). Results from a total of 13 cohort studies, 7 328 414 person-years and 8081 colorectal cancer cases were analysed. Study-specific food frequency questionnaires were used to assess fibre intake. For the association between dietary fibre intake and risk of colorectal cancer, a statistical significant 16% decreased risk was observed in the age adjusted model comparing the highest with the lowest quintile (pooled RR = 0.84, 95% CI = 0.77-0.92); but the association was attenuated when potential colorectal cancer risk factors were accounted for(pooled multivariate RR = 0.94, 95% CI = 0.86-1.03).When intakes of dietary fibre were examined separately by specific food sources, none were associated with risk of colorectal cancer, for cereal fibre the RR for Q5 vs Q1 was 1.00(95% CI = 0.93-1.08), for vegetables fibre it was 1.02(95% CI = 0.94-1.11) and for fruit fibre it was 0.96(95% CI = 0.89-1.04). We updated the results of the 2010 SLR on the types of fibres by including the Pooling Project in highest versus lowest figures below, no new study was identified.

A total of 579 cases and 1996 matched controls were included in the UK Dietary Cohort Consortium which includes seven cohort studies (EPIC Norfolk, EPIC-Oxford, the Guernsey Study, the Medical Research Council National Survey of Health and Development, the Oxford Vegetarian Study, the UK Women Cohort Study and Whitehall II) (Dahm, 2010). Four- to 7-day food diaries and food frequency questionnaires (FFQ) were used to assess dietary fibre intake. The multivariable-adjusted odds ratio of colorectal cancer for highest versus lowest quintile of fibre intake density, assessed by food dairies was 0.66 (95% CI = 0.45-0.96) (P trend = 0.01). For the same analysis, but using FFQ to assess dietary fibre, failed to show a statistically significant inverse association (OR highest versus lowest quintile intake = 0.88, 95% CI = 0.57 -1.36) (P trend = 0.6). The authors suggested that methodological differences in studies may account for the inconsistent relationships observed in previous studies. This study was excluded from our analysis because EPIC Norfolk and EPIC Oxford were superseded by recent EPIC study publications.

Table 161 Dietary fibre and colorectal cancer risk. Number of studies in the CUP SLR

	Number
Studies identified	23 (27 publications)
Studies included in forest plot of highest compared with lowest exposure	23
Studies included in dose-response meta-analysis	21
Studies included in non-linear dose-response meta-analysis	20

Note: Include cohort, nested case-control and case-cohort designs

Table 162 Dietary fibre and colon cancer risk. Number of studies in the CUP SLR

	Number
Studies identified	21 (8+13 PP) (20 publications)
Studies included in forest plot of highest compared with lowest exposure	21
Studies included in dose-response meta-analysis	21
Studies included in non-linear dose-response meta-analysis	21

Note: Include cohort, nested case-control and case-cohort designs

Table 163 Dietary fibre and rectal cancer risk. Number of studies in the CUP SLR

	Number
Studies identified	21 (8+13 PP) (12 publications)
Studies included in forest plot of highest compared with lowest exposure	21
Studies included in dose-response meta-analysis	21
Studies included in non-linear dose-response meta-analysis	21

Note: Include cohort, nested case-control and case-cohort designs

Table 164 Dietary fibre and colorectal cancer risk. Summary of the dose-response meta-analysis in the 2010 SLR and 2015 SLR.

	2010 SLR	**2015 SLR**
Increment unit used	10g/day	10g/day
Studies (n)	15	21
Cases (total number)	13122	16562
RR (95%CI)	0.90 (0.86-0.94)	0.93(0.87-1.00)
Heterogeneity (I^2, p-value)	4.2%, 0.41	72.2%, <0.001

Stratified analysis by sex		
Men	**2010 SLR**	**2015 SLR**
Studies (n)	5	6
RR (95%CI)	0.88 (0.78-0.99)	0.89(0.82-0.96)
Heterogeneity (I^2, p-value)	35%, 0.19	24.9%. 0.25
Women		

Studies (n)	10	11
RR (95%CI)	0.92 (0.87-0.98)	0.91(0.87-0.96
Heterogeneity (I^2, p-value)	0%, 0.87	0%, 0.89
Stratified analysis by geographic location		
(no analysis in 2005 SLR or 2010 SLR)		

2015 SLR	**Asia**	**Europe**	**North America**
Studies (n)	3	3	9
RR (95%CI)	0.79(0.60-1.03)	0.90(0.85-0.96)	0.92(0.88-0.96)
Heterogeneity (I^2, p-value)	25%, 0.26	0%, 0.85	0%, 0.61

Stratified analysis by adjustment for folate		
Yes		
Studies (n)	8	18
RR (95%CI)	0.89 (0.83-0.95)	0.92(0.85-1.00)
Heterogeneity (I^2, p-value)	35%, 0.15	82.3%, <0.001
No		
Studies (n)	7	3
RR (95%CI)	0.93 (0.87-0.99)	0.99(0.85-1.16)
Heterogeneity (I^2, p-value)	0%, 0.85	0%, 0.79

Table 165 Dietary fibre and colon cancer risk. Summary of the dose-response meta-analysis in the 2010 SLR and 2015 SLR.

	2010 SLR	**2015 SLR**
Increment unit used	10g/day	10g/day
Studies (n)	12	21
Cases (total number)	7558	12601
RR (95%CI)	0.89 (0.81-0.97)	0.91(0.84-1.00)
Heterogeneity (I^2, p-value)	35%, 0.11	69.2%, 0.001

Stratified analysis by sex		
Men	**2010 SLR**	**2015 SLR**
Studies (n)	7	8
RR (95%CI)	0.86 (0.76-0.96)	0.88(0.81-0.95)
Heterogeneity (I^2, p-value)	20%, 0.28	11.3%, 0.34
Women		
Studies (n)	8	9
RR (95%CI)	0.94 (0.82-1.08)	0.92(0.83-1.02)
Heterogeneity (I^2, p-value)	30%, 0.19	27.7%, 0.20
Stratified analysis by geographic location		
(no analysis in 2005 SLR or 2010 SLR)		

2015 SLR	**Asia**	**Europe**	**North America**
Studies (n)	3	2	7

RR (95%CI)	0.70(0.39-1.27)	0.90(0.82-0.98)	0.92(0.86-0.98)
Heterogeneity (I^2, p-value)	75.1%, 0.02	0%, 0.47	0%, 0.89
Stratified analysis by adjustment for folate			
Yes			
Studies (n)	8	18	
RR (95%CI)	0.87 (0.78-0.97)	0.91(0.82-1.00)	
Heterogeneity (I^2, p-value)	52%, 0.04	79%, <0.001	
No			
Studies (n)	4	3	
RR (95%CI)	0.94 (0.79-1.11)	0.97(0.73-1.28)	
Heterogeneity (I^2, p-value)	0%, 0.54	5.0%, 0.35	

Table 166 Dietary fibre and rectal cancer risk. Summary of the dose-response meta-analysis in the 2010 SLR and 2015 SLR.

	2010 SLR	2015 SLR
Increment unit used	10g/day	10g/day
Studies (n)	10	21
Cases (total number)	2977	5809
RR (95%CI)	0.91 (0.81-1.03)	0.93(0.85-1.01)
Heterogeneity (I^2, p-value)	15%, 0.31	31%, 0.17

Stratified analysis by sex			
Men	**2010 SLR**	**2015 SLR**	
Studies (n)	5	6	
RR (95%CI)	0.90 (0.69-1.19)	0.89(0.74-1.06)	
Heterogeneity (I^2, p-value)	43%, 0.14	39.7%, 0.14	
Women			
Studies (n)	6	7	
RR (95%CI)	0.91 (0.76-1.08)	0.93(0.80-1.08)	
Heterogeneity (I^2, p-value)	0%, 0.61	18.2%, 0.29	
Stratified analysis by geographic location (no analysis in 2005 SLR or 2010 SLR)			
2015 SLR	**Asia**	**Europe**	**North America**
Studies (n)	3	1	6
RR (95%CI)	0.88(0.60-1.29)	0.92(0.82-1.03)	0.94(0.81-1.08)
Heterogeneity (I^2, p-value)	0%, 0.42		46.5%, 0.09
Stratified analysis by adjustment for folate			
Yes			
Studies (n)	7	18	
RR (95%CI)	0.91 (0.80-1.03)	0.93(0.85-1.01)	
Heterogeneity (I^2, p-value)	12%, 0.34	37.2%, 0.16	

No		
Studies (n)	3	3
RR (95%CI)	0.94 (0.61-1.44)	0.94(0.62-1.44)
Heterogeneity (I^2, p-value)	45%, 0.16	44.9%, 0.16

Table 167 Dietary Fibre and colorectal cancer risk. Results of meta-analyses and pooled analyses of prospective studies published after the 2005 SLR.

Author, Year	Number of cohort studies	Total number of cases	Studies country, area	Outcome	Comparison	RR (95%CI)	P trend	Heterogeneity (I^2, p value)
Meta-analysis								
Aune, 2011	16	14514 colorectal cancer	North America, Europe and Asia	Colorectal cancer	Per 10 g/day	0.90 (0.86–0.94)		0%, 0.48
	13			Colon cancer		0.89(0.81-0.97)		35%, 0.11
	10			Rectal cancer		0.91(0.83-1.03)		15%, 0.31

Table 168 Dietary fibre and colorectal cancer risk. Main characteristics of studies included in the CUP SLR dose-response meta-analysis

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Missing data derived for analysis
Bradbury, 2014 COL41009 Europe	EPIC, Prospective Cohort	4 517/ 470 000	Cancer registry	Questionnaire	Incidence, colorectal cancer	highest vs lowest	0.83 (0.72-0.96) Ptrend:0.013	Age, sex, alcohol, BMI, calcium, centre location, contraception, educational level, energy intake, folate, hormone replacement therapy, menopausal status, physical activity, red and processed meat, smoking	Only used in colorectal highest versus lowest analysis. Murphy, 2012 COL40914 Used for colon and rectal analysis
						≥28.5 vs ≤16.4 g/day	0.86 Ptrend:0.04		
		2 819/				per 10 g/day	0.87 (0.79-0.96)		
Murphy, 2012 COL40914 Europe	EPIC, Prospective Cohort, Age: 35- years, M/W	4 517/ 477 312 11 years	Cancer registry and pathology reports	Questionnaire and 24hr recall	Incidence, colorectal cancer	≥28.5 vs ≤16.4 g/day	0.83 (0.72-0.96) Ptrend:0.013		Distribution of person-years by exposure category. Continuous results used.
						per 10 g/day	0.90 (0.84-0.96)		
		2 869/			Incidence, colon cancer	per 10 g/day	0.89 (0.81-0.97)		
		1 648/			Incidence, rectal cancer	per 10 g/day	0.92 (0.82-1.02)		
		1 298/			Incidence, proximal colon cancer	≥28.5 vs ≤16.4 g/day	0.92 (0.71-1.20) Ptrend:0.51		
						per 10 g/day	0.91 (0.80-1.03)		
		1 266/			Incidence, distal colon cancer	≥28.5 vs ≤16.4 g/day	0.70 (0.53-0.92) Ptrend:0.021		
						per 10 g/day	0.88 (0.77-1.00)		
		820/			Incidence, proximal colon cancer, women	≥27.5 vs ≤16.1 g/day	0.88 (0.63-1.23) Ptrend:0.32		
						per 10 g/day	0.87 (0.74-1.03)		

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Missing data derived for analysis
		746/			Incidence, distal colon cancer, women	≥27.5 vs ≤16.1 g/day	0.76 (0.53-1.09) Ptrend:0.12		
						per 10 g/day	0.87 (0.73-1.05)		
		520/			Incidence, distal colon cancer, Men	per 10 g/day	0.89 (0.73-1.08)		
						≥30.6 vs ≤17.3 g/day	0.68 (0.44-1.05) Ptrend:0.061		
		478/			Incidence, proximal colon cancer, men	per 10 g/day	0.96 (0.79-1.16)		
						≥30.6 vs ≤17.3 g/day	0.95 (0.62-1.47) Ptrend:0.77		
Kabat, 2008 COL40722 USA	Women's Health Initiative - Observational study, Prospective Cohort, W, Postmenopausal	1 470/ 158 800 7.8 years	Mail or telephone questionnaires verified by trained physician adjudicators	FFQ	Incidence, colorectal cancer	≥21.3 vs ≤9.8 g/day	1.06 (0.67-1.70) Ptrend:0.97	Age, BMI, dietary calcium, educational level, energy intake, family history of colorectal cancer, fibre, height, history of diabetes, hormone use, number of cigarettes smoked, observational study participants, physical activity	Mid-points of exposure categories
		798/			Incidence, proximal colon cancer	≥21.3 vs ≤9.8 g/day	1.20 (0.73-1.95) Ptrend:0.97		
		351/			Incidence, distal colon cancer	≥21.3 vs ≤9.8 g/day	0.97 (0.46-2.05) Ptrend:0.94		
		303/			Incidence, rectal cancer	≥21.3 vs ≤9.8 g/day	0.88 (0.39-2.01) Ptrend:0.39		
Schatzkin, 2007 COL40662	NIH-AARP, Prospective	2 974/ 489 611	Cancer registry and national	FFQ	Incidence, colorectal cancer	15.9 vs 6.6 g/1000kcal/day	0.99 (0.85-1.15) Ptrend:0.96	Calcium intake, folate intake,	Distribution of person-years by

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Missing data derived for analysis
USA	Cohort, Age: 50-71 years, M/W	5 years	death Index					physical activity, red meat intake, smoking status, total energy intake Hormone use	exposure category. intakes in g/1000kcal/day converted to g/day using average energy intake per each quantile
		2 049/			Incidence, colorectal cancer Men	15 vs 6 g/1000kcal/day	1.06 (0.88-1.25) Ptrend:0.55		
		1 139/			Incidence, proximal colon cancer	15.9 vs 6.6 g/1000kcal/day	0.93 (0.72-1.18) Ptrend:0.68		
		925/			Incidence, colorectal cancer, women	17 vs 7 g/1000kcal/day	1.10 (0.84-1.43) Ptrend:0.45		
		914/			Incidence, distal colon cancer	15.9 vs 6.6 g/1000kcal/day	0.97 (0.73-1.28) Ptrend:0.80		
Nomura, 2007 COL40655 USA	MEC, Prospective Cohort, Age: 45-75 years, M/W	1 138/ 191 011 7.3 years	Cancer registry, death certificate and national death Index	Quantitative FFQ	Incidence, colorectal cancer, men	16.5 vs 6.1 g/kcal/day	0.62 (0.48-0.79) Ptrend:0.002	Alcohol intake, aspirin use, BMI, calcium intake, family history of colorectal cancer, folate intake, history of polyps, multivitamin supplement intake, pack-years of smoking, physical activity, red meat intake, vitamin d, hormone use	Distribution of person-years by exposure category. intakes in g/1000kcal/day converted to g/day using average energy intake per each quantile
		1 023/							
		972/			Women	18.6 vs 7.5 g/kcal/day	0.88 (0.67–1.14) Ptrend:0.245		
		812/			Incidence, colon cancer, men	16.5 vs 6.1 g/kcal/day	0.64 (0.48–0.86) Ptrend:<0.0001		
		802/			Women	18.6 vs 7.5 g/kcal/day	0.92 (0.68–1.25) Ptrend:0.361		
		308/			Incidence, rectal cancer, men	16.5 vs 6.1 g/kcal/day	0.52 (0.32-0.84) Ptrend:0.004		
		207/			Women	18.6 vs 7.5 g/kcal/day	0.82 (0.48-1.43) Ptrend:0.639		

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Missing data derived for analysis
Wakai, 2007 COL40674 Japan	JACC, Prospective Cohort, Age: 40-79 years, M/W	443/ 43 115 7.6 years	Cancer registry and death certificates and medical records	FFQ	Incidence, colorectal cancer	Q 4 vs Q 1	0.73 (0.51-1.03) Ptrend:0.028	Age, sex, alcohol consumption, area, beef consumption, BMI, calcium intake, daily walking habits, educational level, energy intake, family history of colorectal cancer, folate, energy adjusted, physical activity, pork, sedentary behaviour, vitamin d	Estimated weighted average exposure values from sex-specific cut-points.
		291/			Incidence, colon cancer	Q 4 vs Q 1	0.74 (0.53-1.03) Ptrend:0.019		
						Q 4 vs Q 1	0.58 (0.38-0.88) Ptrend:0.002		
		142/			Incidence, rectal cancer	Q 4 vs Q 1	1.10 (0.59-2.07) Ptrend:0.67		
Otani, 2006 COL40623 Japan	JPHC, Prospective Cohort, Age: 40-69 years, M/W	567/ 86 412 10 years	Cancer registry and death certificates	FFQ	Incidence, colorectal cancer, men	Q 5 vs Q 1	0.92 (0.67-1.30) Ptrend:0.30	Age, alcohol consumption, BMI, calcium intake, energy intake, folate intake, follow-up time, physical activity, red meat intake, smoking habits, study area, vitamin d	
		340/			Women	Q 5 vs Q 1	1.40 (0.95-2.20) Ptrend:0.90		
						Q 5 vs Q 1	1.40 (0.94-2.20) Ptrend:0.087		
		335/			Men	18.7 vs 6.4 g/day	0.85 (0.53-1.40) Ptrend:0.48		
						18.7 vs 6.4 g/day	0.68 (0.48-0.96) Ptrend:0.021		

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Missing data derived for analysis
		231/			Incidence, colon cancer, men	18.7 vs 6.4 g/day	0.80 (0.45-1.40) Ptrend:0.39		
		187/			Incidence, colorectal cancer, women	20 vs 8.3 g/day	0.86 (0.54-1.40) Ptrend:0.95		
						20 vs 8.3 g/day	0.58 (0.31-1.10) Ptrend:0.21		
		136/			Incidence, colon cancer, women	20 vs 8.3 g/day	0.48 (0.23-1.00) Ptrend:0.12		
		104/			Incidence, rectal cancer, men	18.7 vs 6.4 g/day	0.95 (0.40-2.30) Ptrend:0.99		
		51/			Incidence, rectal cancer, Women	20 vs 8.3 g/day	1.00 (0.32-3.30) Ptrend:0.82		
Shin, 2006 COL40665 China	SWHS, Prospective Cohort, Age: 40-70 years, W	283/ 73 314 5.74 years	Follow up survey/cancer registry/vital statistics registry	FFQ	Incidence, colorectal cancer	≥13.46 vs 0-7.3 g/day	1.10 (0.60-1.80) Ptrend:0.652	Age, alcohol, calories intake, educational level, family history of colorectal cancer, menopausal status, multivitamin supplement intake, physical activity, smoking status	Distribution of person-years by exposure category. Mid-points of exposure categories
		129/			Incidence, colon cancer	≥13.46 vs 0-7.3 g/day	1.20 (0.60-2.40) Ptrend:0.835		
		91/			Incidence, rectal cancer	≥13.46 vs 0-7.3 g/day	0.90 (0.40-2.10) Ptrend:0.335		

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Missing data derived for analysis
Park, 2005 Pooling Project	13 cohort studies ATBC CPS II HPFS NLCS NYSC BCDDP CNBSS IWHS NYUWHS NHS ORDET SMC WHS	6-20 years 8081 cases 321 720+479 597 646+501 492+296 436 612 1010 127 220+648 61 714 201	Self-administrated questionnaire, medical record, cancer registry	Study specific FFQ	Incidence, colorectal cancer	Highest vs Lowest ≥30 vs <10 g/day	0.94(0.86-1.03) 1.00(0.85-1.17) Ptrend:0.68	Age; body mass index; education; physical activity; family history of colorectal cancer; use of postmenopausal hormone therapy; oral contraceptive use; use of nonsteroidal anti-inflammatory drugs; multivitamin use; smoking habits; alcohol; dietary intake of folate, red meat, total milk, and total energy	Distribution of person-years by exposure category. Mid-points of exposure categories
					Incidence, colon cancer (5724 cases)	≥30 vs <10 g/day	1.04(0.86-1.26) Ptrend:0.17		
					Incidence, rectal cancer (2031 cases)	≥25 vs <10 g/day	0.87(0.68-1.09) Ptrend:0.27		
Sanjoaquin, 2004 COL01182 UK	OVS, Prospective Cohort, Age: 18-89 years, M/W	63/ 10 998 17 years	Population/invitation	FFQ	Incidence, colorectal cancer,	Q 3 vs Q 1	0.82 (0.43-1.56) Ptrend:0.424	Age, sex, alcohol consumption, smoking habits	
Gaard, 1996 COL00008	Norwegian national health	83/ 50 535	Enrolment by volunteers	FFQ	Incidence, colon cancer, men	≥17.9 vs ≤13.5 g/day	0.82 (0.46-1.46) Ptrend:.6	Age, attained age, BMI,	Mid-points of exposure

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Missing data derived for analysis
Norway	screening service study(NNHS), Prospective Cohort, Age: 20-53 years, M/W	11.4 years						energy intake, height, smoking status	categories
		59/			Women	≥11.3 vs ≤8.5 g/day	2.10 (0.90-4.87) Ptrend:.12		
Heilbrun, 1989 COL01555 USA	HHP, Nested Case Control, M	102/ 361 controls 16 years	Cancer registry & hospital surveillance	Recall questionnaire	Incidence, colon cancer,	≤7.5 vs ≥14.8 g/day	1.40 Ptrend:0.354	Age Alcohol consumption	Estimation of confidence intervals. Mid-points of exposure categories
		60/ 361 controls			Incidence, rectal cancer,	≤7.5 vs ≥14.8 g/day	0.83 Ptrend:0.192		
		51/			Incidence, colon cancer, fat intake, ≥61 g/day	≤7.5 vs ≥14.8 g/day	0.82 Ptrend:0.237		
					Fat intake, <61 g/day	≤7.5 vs ≥14.8 g/day	2.28 Ptrend:0.042		

Table 169 Dietary fibre and colorectal cancer risk. Main characteristics of studies excluded from the CUP SLR dose-response meta-analysis

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Reasons for exclusion
Gay, 2012 COL40920 UK	EPIC-Norfolk, Prospective Cohort, Age: 45-79 years, M/W	185/ 25 636 11 years	Cancer registry	7-day dietary recalls	Incidence, colorectal cancer, apc mutations	per 1 sd units	1.03 (0.75-1.43)	Age, sex, smoking	Case-only study, interaction results only
					Gc:at mutations	per 1 sd units	1.23 (0.74-2.06)		
					Apc promoter methylation ≥20%	per 1 sd units	0.54 (0.34-0.86)		
Hansen, 2012 COL40886	HELGA cohort, Prospective Cohort, Age: 30-64 years, M/W	379/ 108 081 11.3 years	Cancer registry and death registry	FFQ	Incidence, colon cancer, women	≥24.5 vs ≤15.4 g/day	0.87 (0.65-1.18)	Alcohol, BMI, educational level, HRT use, red and processed meat, smoking	Component of the EPIC study, Superseded by Murphy, 2012 COL40914 and Bradbury, 2014 COL41009
						per 10 g/day	0.99 (0.86-1.14)		
		312/			Men	≥28.1 vs ≤16.8 g/day	0.55 (0.38-0.79)		
						per 10 g/day	0.74 (0.64-0.86)		
		257/			Incidence, rectal cancer, men	per 10 g/day	1.02 (0.87-1.19)		
						≥28.1 vs ≤16.8 g/day	1.11 (0.87-1.19)		
		220/			Women	≥24.5 vs ≤15.4 g/day	0.97 (0.66-1.42)		
						per 10 g/day	0.99 (0.82-1.19)		
Ruder, 2011 COL40896 USA	NIH-AARP, Prospective Cohort,	2 819/ 292 797	Cancer registry and national health database	FFQ	Incidence, colon cancer	13 vs 5 g/1000 kcal	0.97 (0.85-1.10) Ptrend:0.75	Sex, age at baseline, alcohol	Only provided fibre intake 10 years before

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Reasons for exclusion
	Age: 50-71 years, Retired	985/			Incidence, rectal cancer	13 vs 5 g/1000 kcal	1.26 (1.00-1.58) Ptrend:0.06	consumption, aspirin use, BMI, educational level, energy, energy, fibre, history of colon cancer, HRT use, physical activity, race, smoking	baseline. Schatzkin, 2007 COL40662 was used.
Dahm, 2010 COL40866 UK	UK Dietary Cohort Consortium 7 UK cohort studies, Guernsey Study, EPIC- Norfolk, EPIC-Oxford, NSHD, Oxford Vegetarian, UKWCS, Whitehall M/W	579/ 1996 controls	Cancer registry	Food diary and FFQ	Incidence, colorectal cancer	per 1 quintile	0.92 (0.83 to 1.01)	Alcohol intake, dietary folate, energy from fat, energy from non-fat sources, height, weight	Includes EPIC Norfolk and EPIC Oxford. Superseded by by Murphy, 2012 COL40914 and Bradbury, 2014 COL41009
						Q5 vs Q1	0.67 (0.42 to 1.05)		
Hansen, 2009 COL40855 Denmark	DCH, Case Cohort, Age: 50-64 years	173/ 57 053	Cancer registry	FFQ	Incidence, colorectal cancer, gpx1 pro198leu cc	per 10 g/day	0.78 (0.55-1.10)	Alcohol intake, BMI, fibre, fruits and vegetables consumption, HRT use,	Component of the EPIC study, Superseded by Murphy, 2012 COL40914 and Bradbury, 2014
		164/			Gpx1 pro198leu ct	per 10 g/day	0.93 (0.66-1.31)		

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Reasons for exclusion
		38/			Gpx1 pro198leu tt	per 10 g/day	1.02 (0.53-1.97)	smoking, pack-years	COL41009
Butler, 2008 COL40639 Singapore	SCHS, Prospective Cohort, Age: 45-74 years, M/W	961/ 61 321 9.8 years	Cancer registry	FFQ	Incidence, colorectal cancer	Q 4 vs Q 1	0.98 (0.81-1.19) Ptrend:0.78	Age, sex, alcohol intake, BMI, diabetes, dialect group, educational level, energy intake, exposure assessment, family history of colorectal cancer, physical activity, smoking habits	Only included in highest versus lowest analysis
McCarl, 2006 COL40633 USA	IWHS, Prospective Cohort, Age: 55-69 years, W	954/ 35 197 15 years	SEER registry	FFQ	Incidence, colorectal cancer	≥25.4 vs ≤13.2 g/day	0.75 (0.61-0.92)	Age	Included in Pooling Project (Park, 2005)
Bingham, 2005 COL40747 Europe	EPIC, Prospective Cohort, Age: 25-70 years, M/W	1 118/ 519 978 2 279 075 person-years	Cancer/patholog y registries, mortality registries, health Insurance records, active follow up	FFQ	Incidence, colon cancer, men	≥29.5 vs ≤15.9 g/day	0.77 (0.58-1.02) Ptrend:0.01	Age, sex, alcohol consumption, centre location, educational level, energy from fat, energy from non-fat sources, folate intake, height,	Superseded by Murphy, 2012 COL40914 and Bradbury, 2014 COL41009
		603/			Incidence, rectal cancer, men	≥29.5 vs ≤15.9 g/day	0.81 (0.55-1.21) Ptrend:0.5		
		496/			Incidence, left colon cancer, men	≥29.5 vs ≤15.9 g/day	0.58 (0.39-0.86) Ptrend:<0.001		

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Reasons for exclusion
		452/			Incidence, right colon cancer, men	≥29.5 vs ≤15.9 g/day	0.93 (0.59-1.47) Ptrend:0.47	physical activity, processed meat, red meat intake, smoking status, total energy, weight	
Lin, 2005 COL01831 USA	WHS, Prospective Cohort, Age: 45- years, W, professionals	223/ 36 976 10 years	Follow up questionnaires (self-report), medical record and pathology reports	FFQ	Incidence, colorectal cancer, women	26 vs 12 g/day	0.75 (0.47-1.18) Ptrend:0.11	Age, alcohol consumption, aspirin use, BMI, family history of specific cancer, history of previous polyp and prior endoscopy, menopausal status, physical activity, postmenopausal hormone use, randomized treatment assignment, red meat intake, smoking status, total energy	Included in Pooling Project (Park, 2005)
Michels, 2005 COL01823 USA	NHS-HPFS, Prospective Cohort, Age: 30-75	919/ 124 226 1 776 498 person-years	Self-report verified by medical record	FFQ	Incidence, colorectal cancer, women	per 5 g	0.98 (0.88-1.08)	Age, alcohol consumption, aspirin use, BMI, calcium	Included in Pooling Project (Park, 2005)

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Reasons for exclusion
	years, M/W	593/			Men	per 5 g	0.97 (0.89-1.05)	intake, family history of colorectal cancer, folate intake, glycaemic load intake, height, HRT use, menopausal status, methionine intake, multivitamin supplement intake, pack-years of smoking, physical activity, previous endoscopic screening, processed meat, red meat intake, time period, total caloric intake	
					Incidence, rectal cancer, women	per 5 g	0.95 (0.75-1.20)		
					Men	per 5 g	0.99 (0.83-1.18)		
					Incidence, colon cancer, women	per 5 g	0.98 (0.88-1.10)		
					Men	per 5 g	0.96 (0.87-1.06)		
Norat, 2005 COL01698 Europe	EPIC, Prospective Cohort, Age: 21-83 years,	478 040 2 279 075 person-years		Questionnaire	Incidence, colorectal cancer, low red and processed meat intake	Q 1 vs Q 3	1.30	Age, sex, alcohol consumption, body weight, centre location,	Superseded by Murphy, 2012 COL40914

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Reasons for exclusion
	M/W							energy from fat sources, energy from non-fat sources, fibre, height, physical activity, smoking status	
Higginbotham, 2004 COL00299 USA	WHS, Prospective Cohort, Age: 45- years, W, nurses	174/ 38 451 7.9 years	Cancer registry	FFQ	Incidence, colorectal cancer,	Q 5 vs Q 1	0.79 (0.45-1.38) Ptrend:0.50	Age, alcohol consumption, BMI, energy-adjusted calcium, energy-adjusted folate, energy-adjusted total fat, energy-adjusted vitamin d, family history of specific cancer, history of oral contraceptive use, HRT use, NSAID use, physical activity, smoking habits, total energy	Included in Pooling Project (Park, 2005)
						per 10 g/day	0.83 (0.61-1.14)		

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Reasons for exclusion
Koh, 2004 COL00053 China	SCHS, Nested Case Control, Age: 45-74 years, M/W	310/ 1177 controls	Cancer registry	Questionnaire	Incidence, colorectal cancer,	(mean exposure)			Superseded by Butler, 2008 COL40639
Mai, 2003 COL00335 USA	BCDDP, 1973, Prospective Cohort, Age: 62 years, W, cohort was a subset of BCDDP	487/ 45 491 386 186 person-years	Subset of original bcddp cohort	FFQ	Incidence, colorectal cancer,	≥12 vs ≤6.3 g/1000 kcal/day	0.94 (0.70-1.26)	Alcohol consumption, BMI, calcium, educational level, height, NSAID use, red meat intake, smoking habits, vitamin d	Included in Pooling Project (Park, 2005)
McCullough, 2003 COL00367 USA	CPS II, Prospective Cohort, Age: 50-74 years, M/W	298/ 133 163 6 years	Cancer registry and death certificates and medical records	Semi-quantitative FFQ	Incidence, colon cancer, men	≥16.6 vs 0-9.2 g/day	0.92 (0.64-1.32) Ptrend:0,95	Age, aspirin use, BMI, calcium, educational level, energy intake, family history of colorectal cancer, multivitamin, physical activity, red meat intake, smoking habits	Included in Pooling Project (Park, 2005)
		210/			Women	≥14.4 vs 0-7.9 g/day	0.86 (0.52-1.42) Ptrend:0,71	+ HRT use	

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Reasons for exclusion
Konings, 2002 COL01271 Netherlands	NLCS, Case Cohort, Age: 55-69 years, M/W	120 852 7.3 years	Cancer registry and database of pathology reports	Semi-quantitative FFQ	Incidence, colon and rectal cancer		Mean exposure		Included in Pooling Project (Park, 2005)
Terry, 2001 COL00059 Sweden	SMC, Prospective Cohort, Age: 40-74 years, W	460/ 61 463 588 270 person-years	Mammography screening program	FFQ	Incidence, colorectal cancer,	21.8 vs 12.3 g/day	0.96 (0.70-1.33) Ptrend:0.98	Age, alcohol consumption, BMI, calcium, educational level, energy intake, folic acid intake, red meat intake, total fat intake, vitamin c, vitamin d	Included in Pooling Project (Park, 2005)
Colbert, 2001 COL00384 Finland	ATBC, Prospective Cohort, Age: 50-69 years, M, Male Smokers	152/ 29 133 12 years	Cancer registry	Food-use questionnaire	Incidence, colon cancer		Mean exposure		Included in Pooling Project (Park, 2005)
		104/							
Fuchs, 1999 COL00103 USA	NHS, Prospective Cohort, Age: 34-59 years, W	281/ 88 757 1 408 232 person-years	Nurses registry	Semi-quantitative FFQ	Incidence, proximal colon cancer,	24.9 vs 9.8 g/day	1.00 (0.61-1.61) Ptrend:0.96	Age, alcohol consumption, aspirin use, BMI, consumption of beef pork, lamb as main dish,	Included in Pooling Project (Park, 2005)
		255/			Incidence, distal colon cancer,	24.9 vs 9.8 g/day	1.08 (0.67-1.72) Ptrend:0.99		

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Reasons for exclusion
								energy intake, energy-adjusted intake, family history of specific cancer, history of colorectal adenoma, physical activity, screening endoscopy during study period, smoking status	
Pietinen, 1999 COL00176 Finland	ATBC, Prospective Cohort, Age: 50-69 years, M, Smokers	185/ 27 111 8 years	Cancer registry	Dietary history questionnaire	Incidence, colorectal cancer,	34.1 vs 16 g/day	1.00 (0.60-1.50) Ptrend:0.79	Age, alcohol consumption, BMI, calcium intake, educational level, energy intake, physical activity, smoking years, supplement group	Included in Pooling Project (Park, 2005)
Sellers, 1998 COL01974 USA	IWHS, Prospective Cohort, Age: 55-69	180/ 35 216 10 years	SEER registry	Semi-quantitative FFQ	Incidence, colon cancer, no family history of crc	≥22.6 vs ≤16.17 servings/week	0.80 (0.50-1.20) Ptrend:0.3	Age, history of polyps, total energy intake	Included in Pooling Project (Park, 2005)

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Reasons for exclusion
	years, W, Postmenopausal	/65			Family history of crc	≥22.6 vs ≤16.17 servings/week	1.20 (0.60-2.60) Ptrend:0.6		
Kato, 1997 COL00022 USA	New York University Women's Health Study, Prospective Cohort, Age: 34-65 years, W	100/ 14 272 105 044 person-years	Questionnaire, medical records, cancer registries	Semi-quantitative FFQ	Incidence, colorectal cancer	Q 4 vs Q 1	1.51 (0.85-2.68) Ptrend:0.137	Age, educational level, place at enrolment, total calorie intake	Included in Pooling Project (Park, 2005)
Tangrea, 1997 COL00267 Finland	ATBC, Nested Case Control, Age: 50-69 years, M, Smokers	146/ 292 controls	Cancer registry	Questionnaire	Incidence, colorectal cancer,	(mean exposure)		Age, clinic site, date of blood draw	Included in Pooling Project (Park, 2005)
Glynn, 1996 COL00161 Finland	ATBC, Nested Case Control, Age: 50-69 years, M, Male Smokers	136/ 249 controls 8 years	Cancer registry	FFQ	Incidence, colorectal cancer,	(mean exposure)		Age, clinic site, date of blood collection	Included in Pooling Project (Park, 2005)
Steinmetz, 1994	IWHS,	212/	SEER	Semi-	Incidence, colon	≥24.8 vs 0-14.4	0.80 (0.49-1.31)	Age, energy	Included in

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Reasons for exclusion
COL00178 USA	Prospective Cohort, Age: 55-69 years, W, Postmenopausal	35 216 167 447 person-years		quantitative FFQ	cancer,	g/day		intake	Pooling Project (Park, 2005)
		120/			Incidence, distal colon cancer	≥24.8 vs 0-14.4 g/day	0.66 (0.34-1.29)		
		86/			Incidence, proximal colon cancer	≥24.8 vs 0-14.4 g/day	1.03 (0.48-2.22)		
Giovannucci, 1994 COL00119 USA	HPFS, Prospective Cohort, Age: 40-75 years, M, Health professionals	205/ 47 949 6 years	Mailing to health professionals	FFQ	Incidence, colon cancer	32.8 vs 14.2 g/day	1.08 (0.68-1.70) Ptrend:0.12	Age, alcohol consumption, aspirin use, energy intake, family history of specific cancer, methionine, pack-years of smoking, previous endoscopic screening, previous polyps, red meat intake	Included in Pooling Project (Park, 2005)
Bostick, 1993 COL01450 USA	IWHS, Prospective Cohort, Age: 55-69	35 216 167 447 person-years	SEER	Semi-quantitative FFQ	Incidence, colon cancer	(mean exposure)			Included in Pooling Project (Park, 2005)

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Reasons for exclusion
	years, W								
Willett, 1990 COL00026 USA	NHS, Prospective Cohort, Age: 34-59 years, W, Registered nurses	150/ 88 751 512 488 person-years	Population	Semi-quantitative FFQ	Incidence, colon cancer,	≥21.3 vs ≤11.5 g/day	0.90 (0.54-1.49) Ptrend:0.70	Age, energy intake	Included in Pooling Project (Park, 2005)
Wu, 1987 COL00774 USA	Leisure World Cohort, Prospective Cohort, M/W, Retirement community	68/ 11 644 4.5 years	Population registries	FFQ	Incidence, colorectal cancer, women	Q 3 vs Q 1	0.64 (0.40-1.20)	Age	Only included in highest compared to lowest analysis
		58/			Men	Q 3 vs Q 1	1.13 (0.60-2.10)		

Figure 293 RR estimates of colorectal cancer by levels of dietary fibre

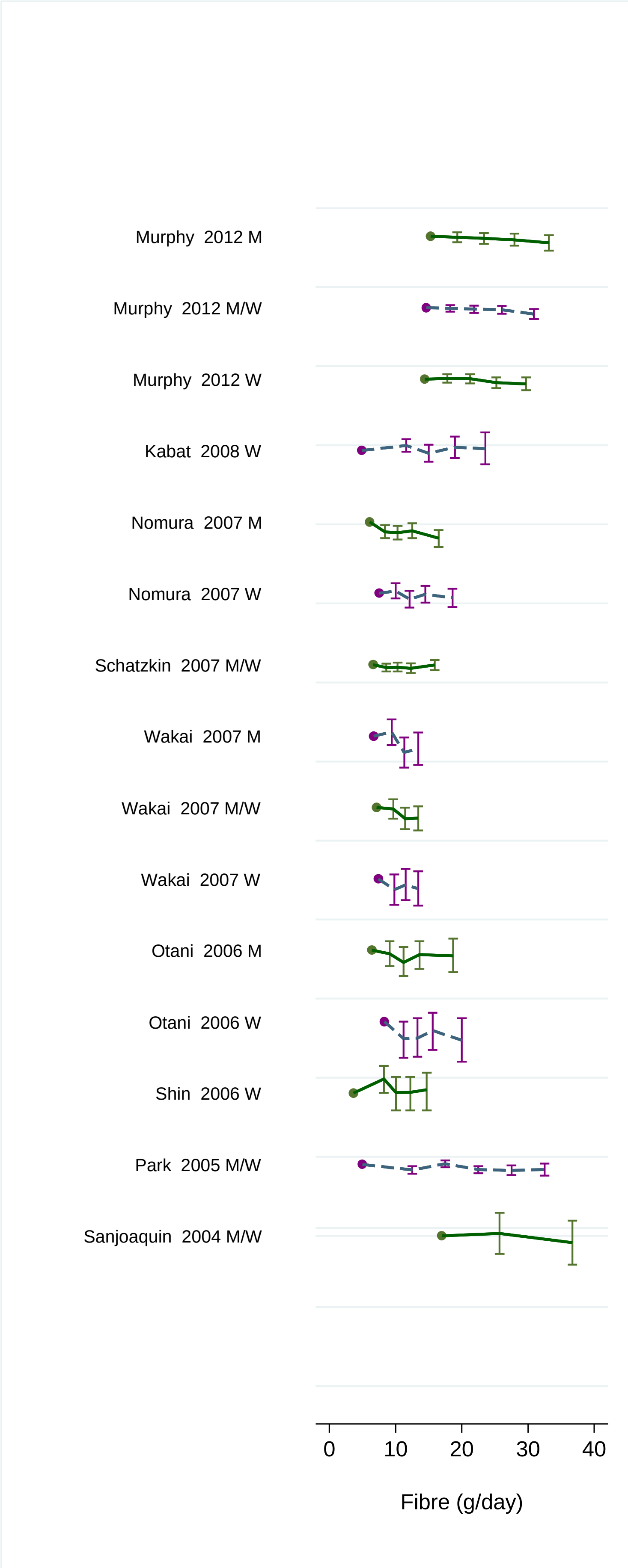


Figure 294 RR (95% CI) of colorectal cancer for the highest compared with the lowest level of dietary fibre

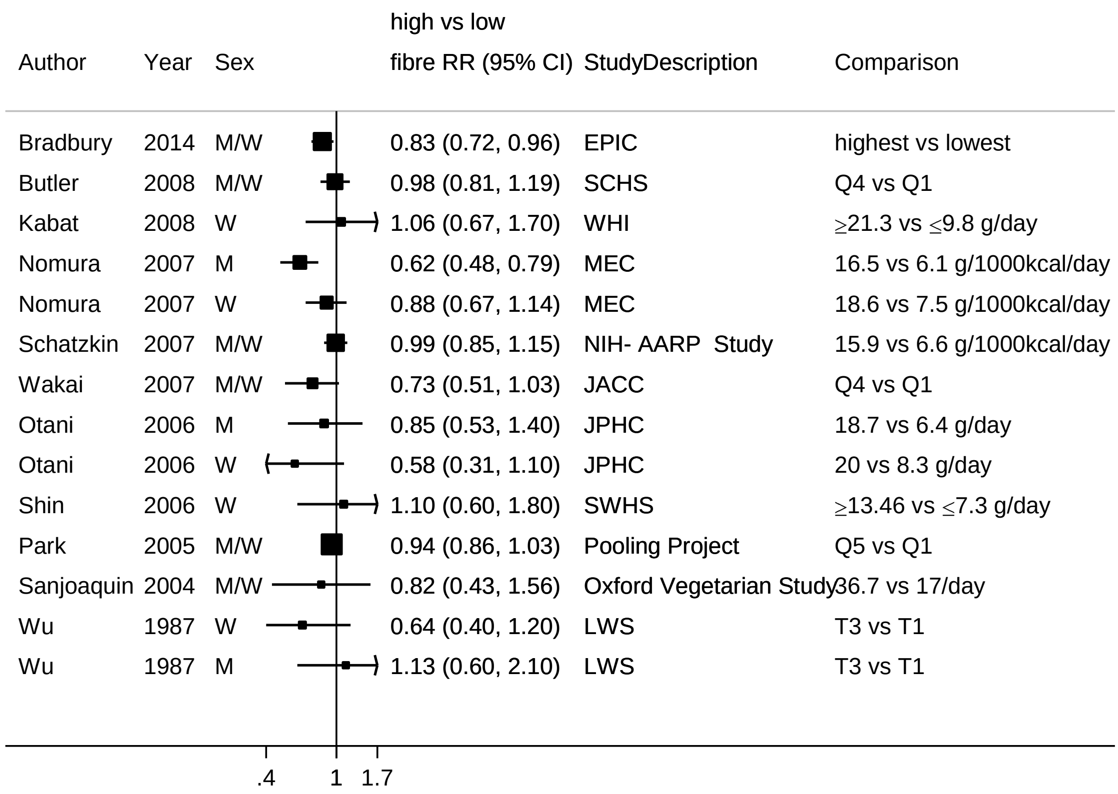


Figure 295 RR (95% CI) of colorectal cancer for 10g/day increase of dietary fibre

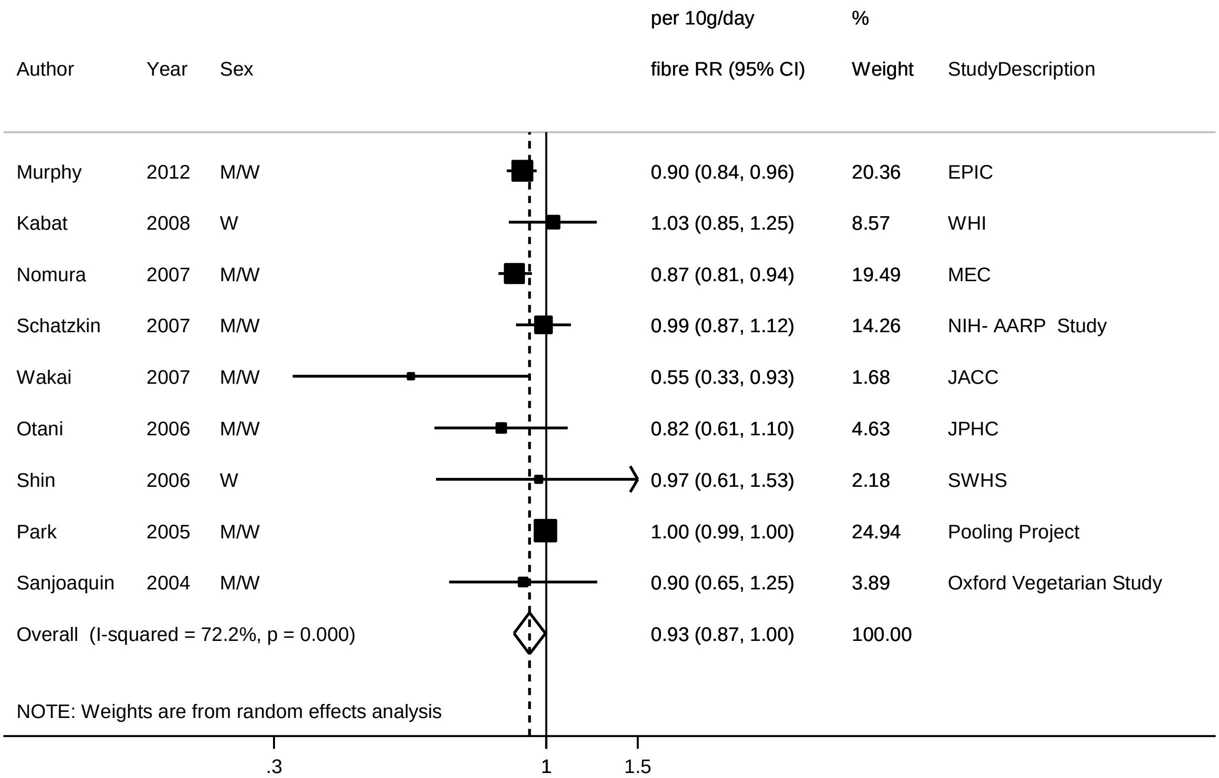


Figure 296 Funnel plot of studies included in the dose response meta-analysis dietary fibre and colorectal cancer

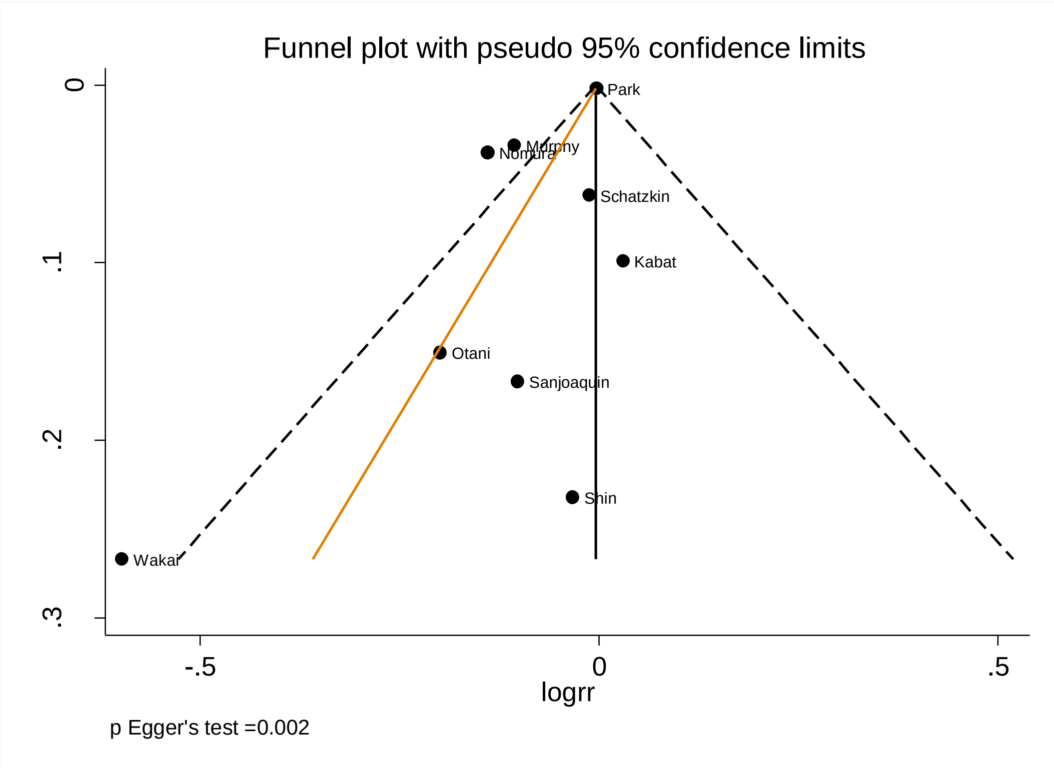
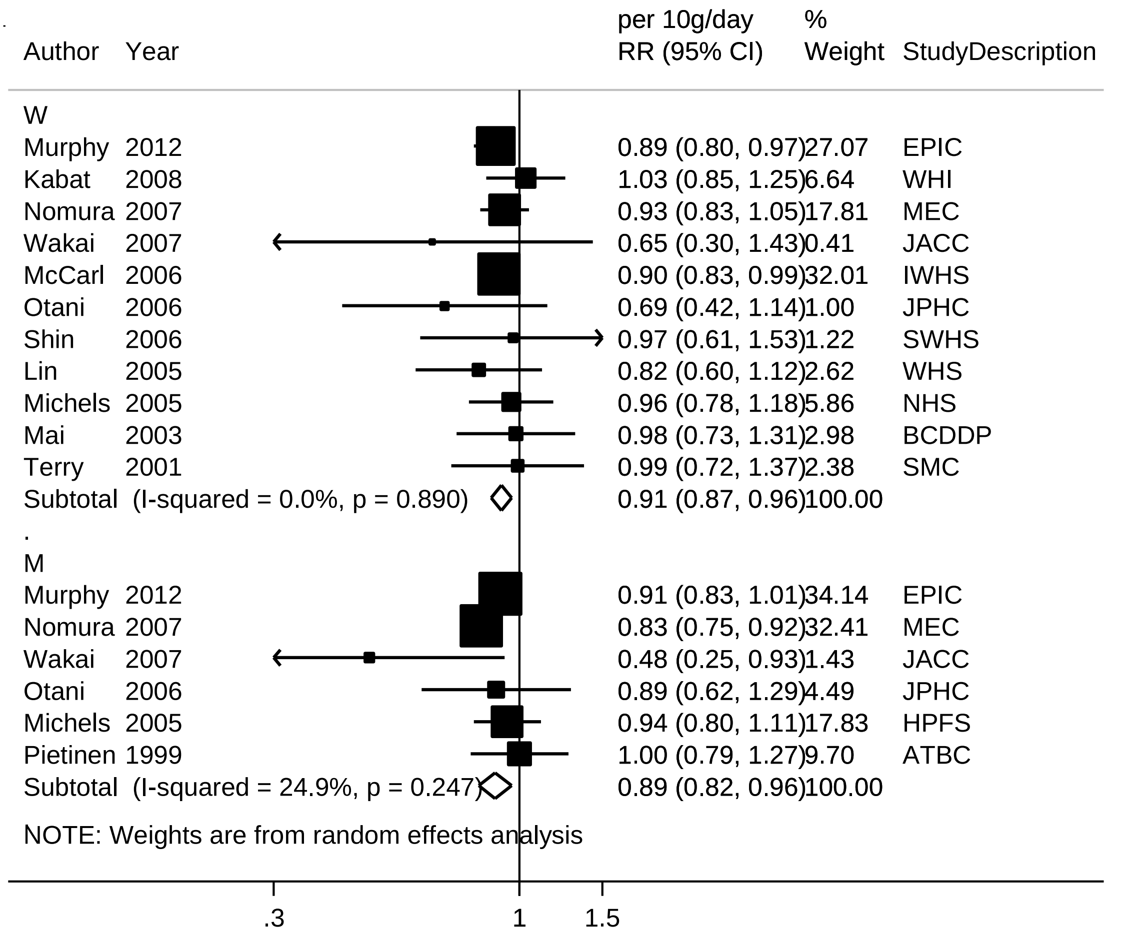
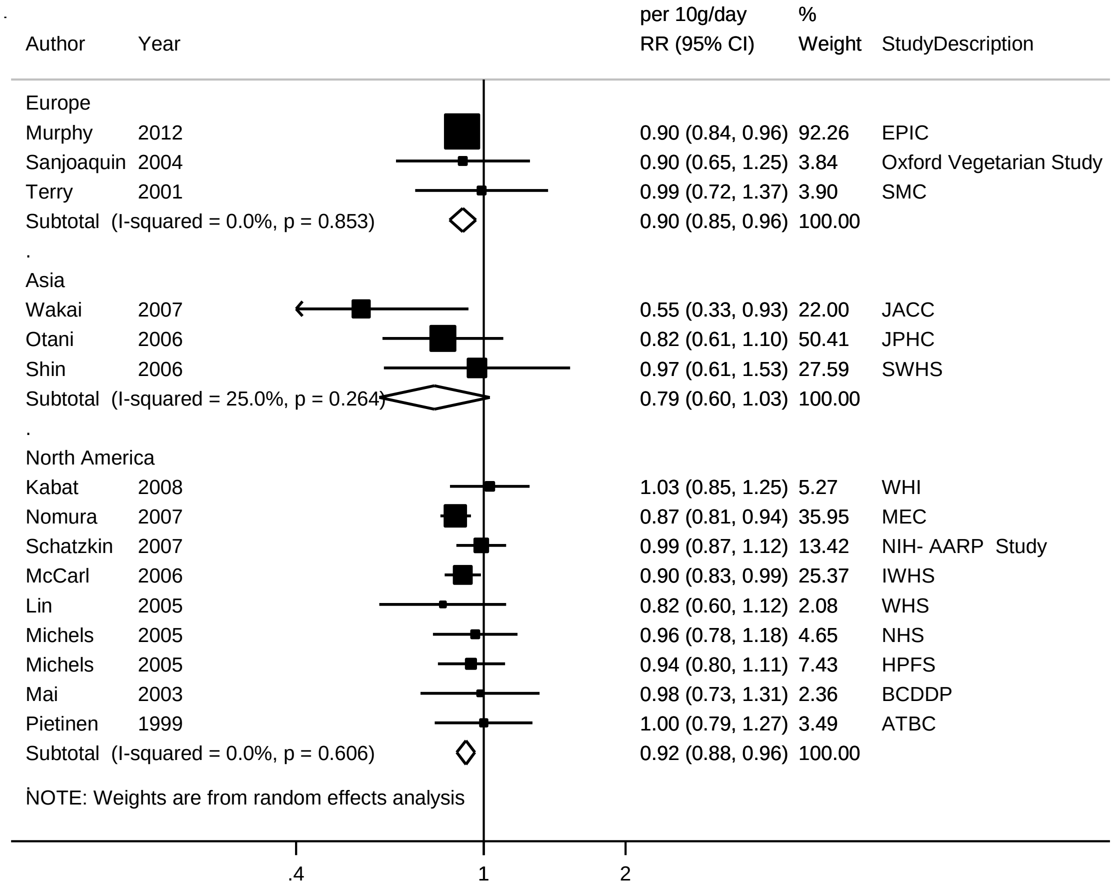


Figure 297 RR (95% CI) of colorectal cancer for 10g/day increase of dietary fibre by sex



The individual studies in the Pooling project were used in this analysis and not the overall Pooling Project result (Park, 2005).

Figure 298 RR (95% CI) of colorectal cancer for 10g/day increase of dietary fibre by location



The individual studies were used in this analysis and not the Pooling Project (Park, 2005).

Figure 299 RR (95% CI) of colorectal cancer for 10g/day increase of dietary fibre by adjustment for folate

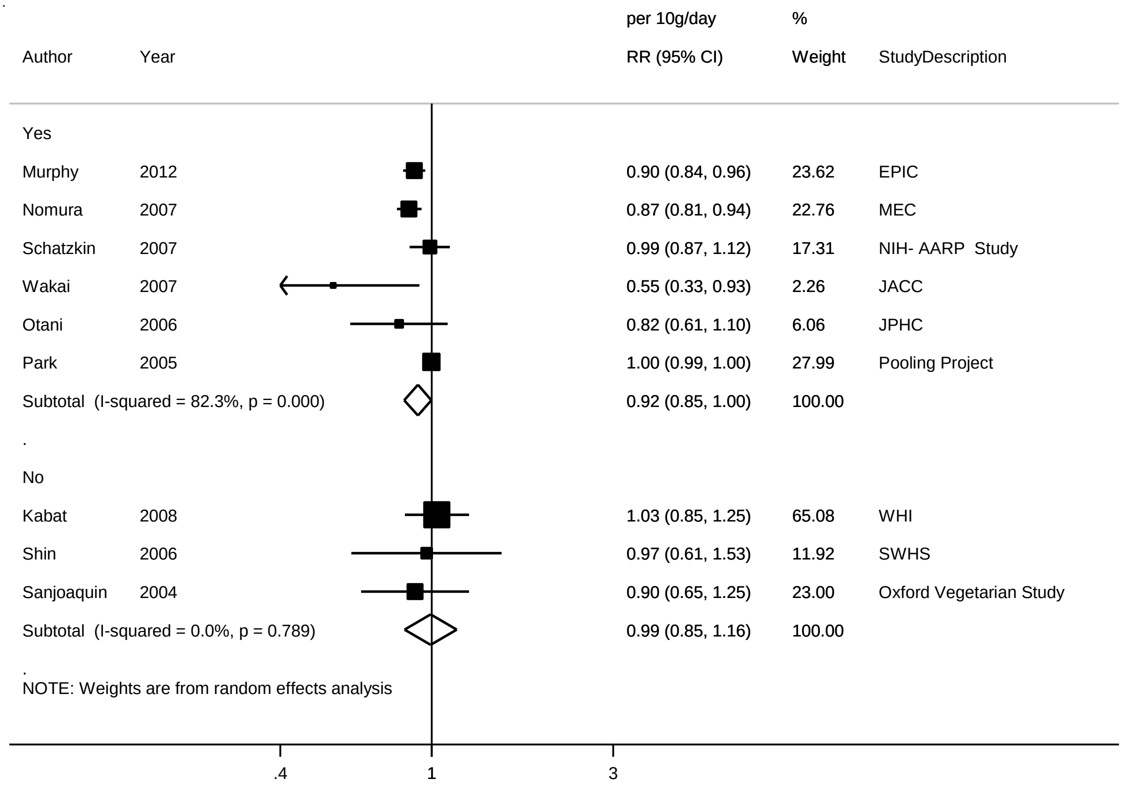
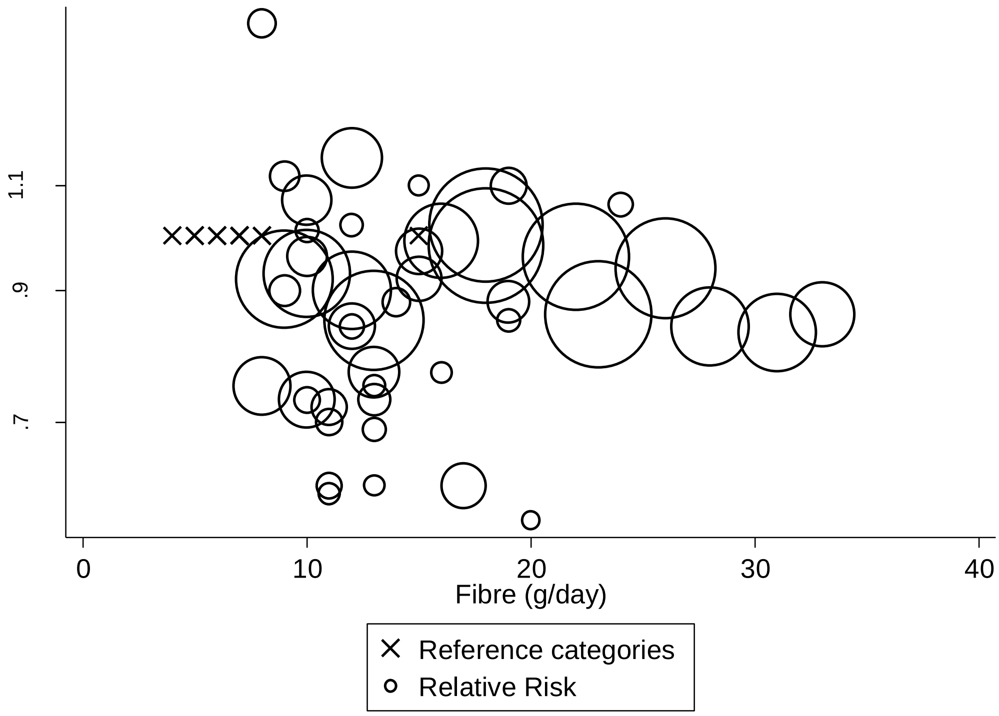


Figure 300 Relative risk of colorectal cancer and dietary fibre estimated using non-linear models



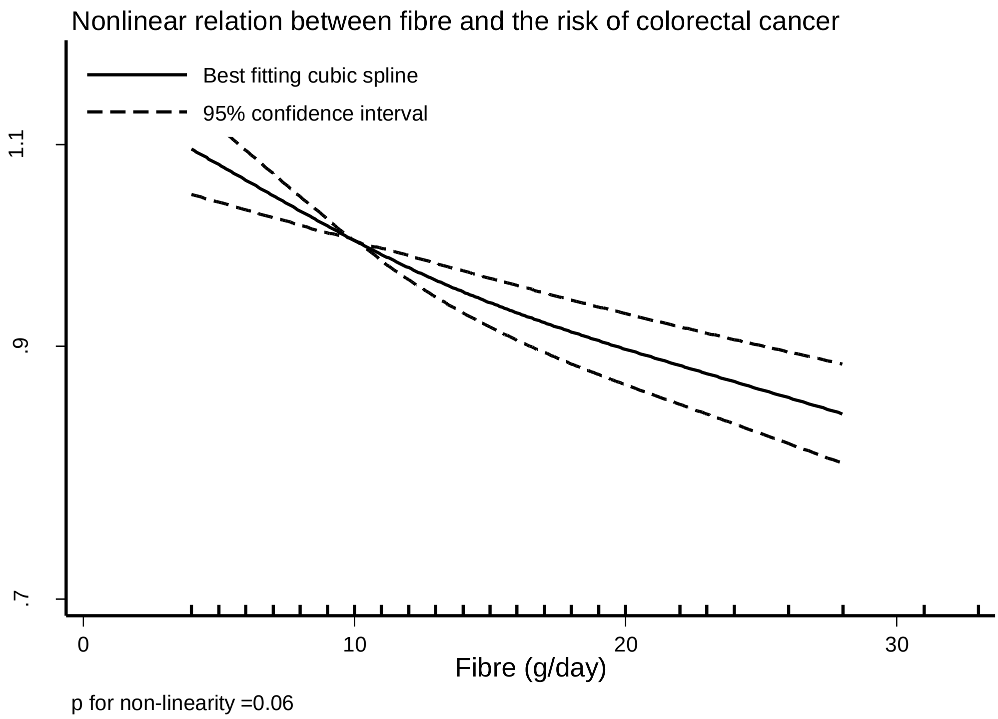


Table 170 Table with dietary fibre values and corresponding RRs (95% CIs) for non-linear analysis of dietary fibre and colorectal cancer

Dietary fibre(g/day)	RR (95%CI)
4	1.09(1.04-1.14)
7	1.04(1.02-1.06)
10	1
15	0.94(0.92-0.96)
20	0.89(0.86-0.93)
30	0.82(0. 67-0.87)

Figure 301 RR (95% CI) of colorectal cancer for 10g/day increase of dietary fibre including individual study results and not the Pooling Project

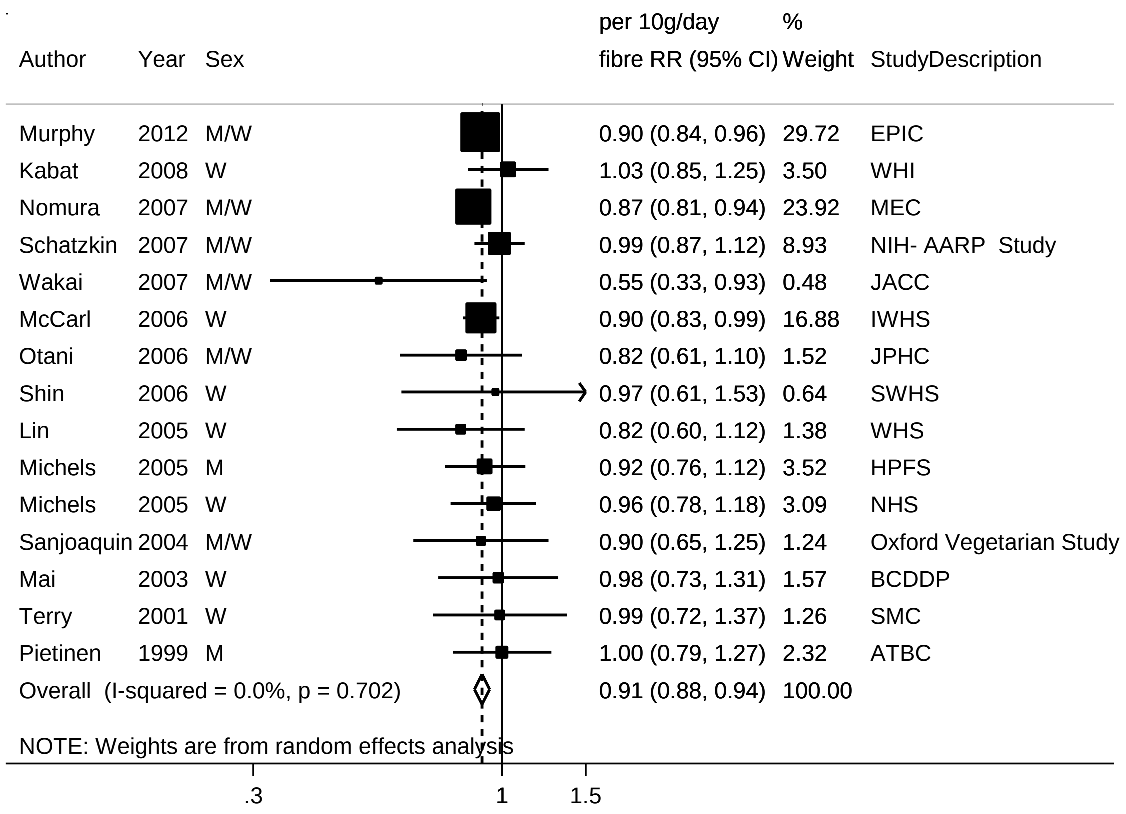


Figure 302 RR estimates of colon cancer by levels of dietary fibre

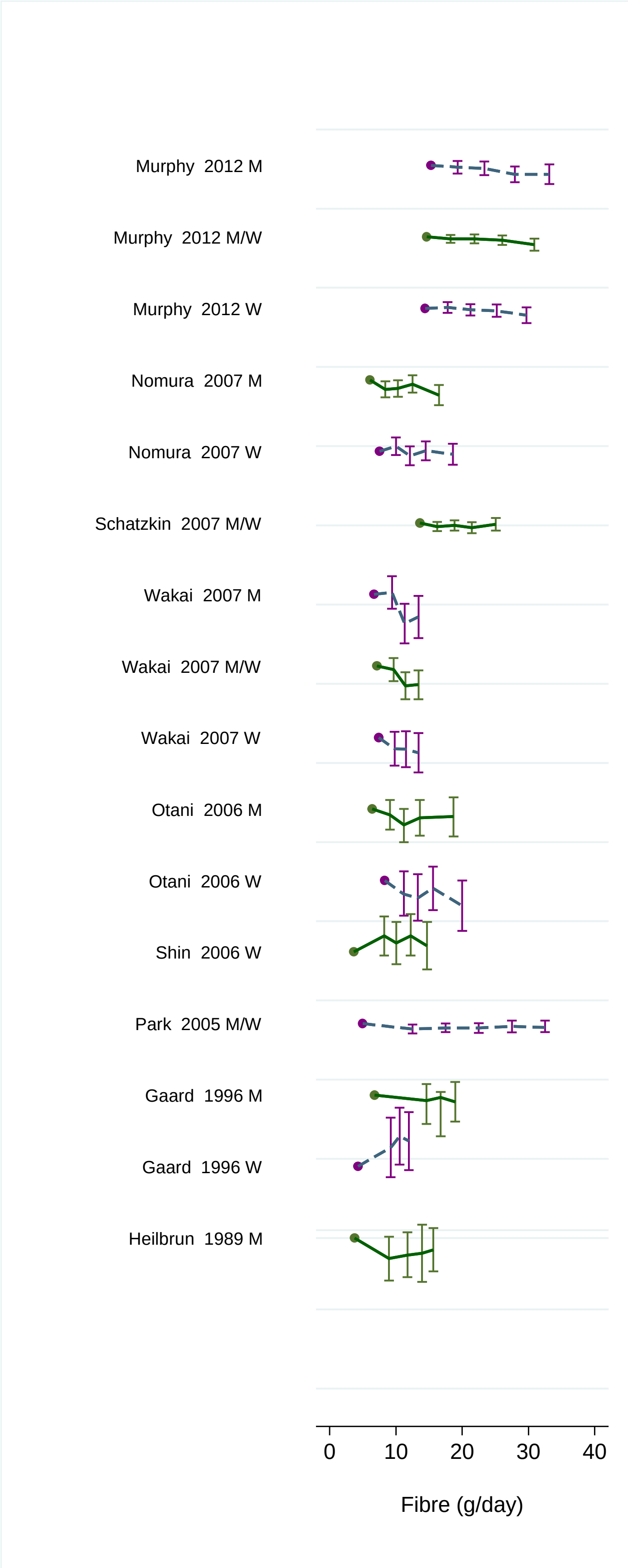


Figure 303 RR (95% CI) of colon cancer for the highest compared with the lowest level of dietary fibre

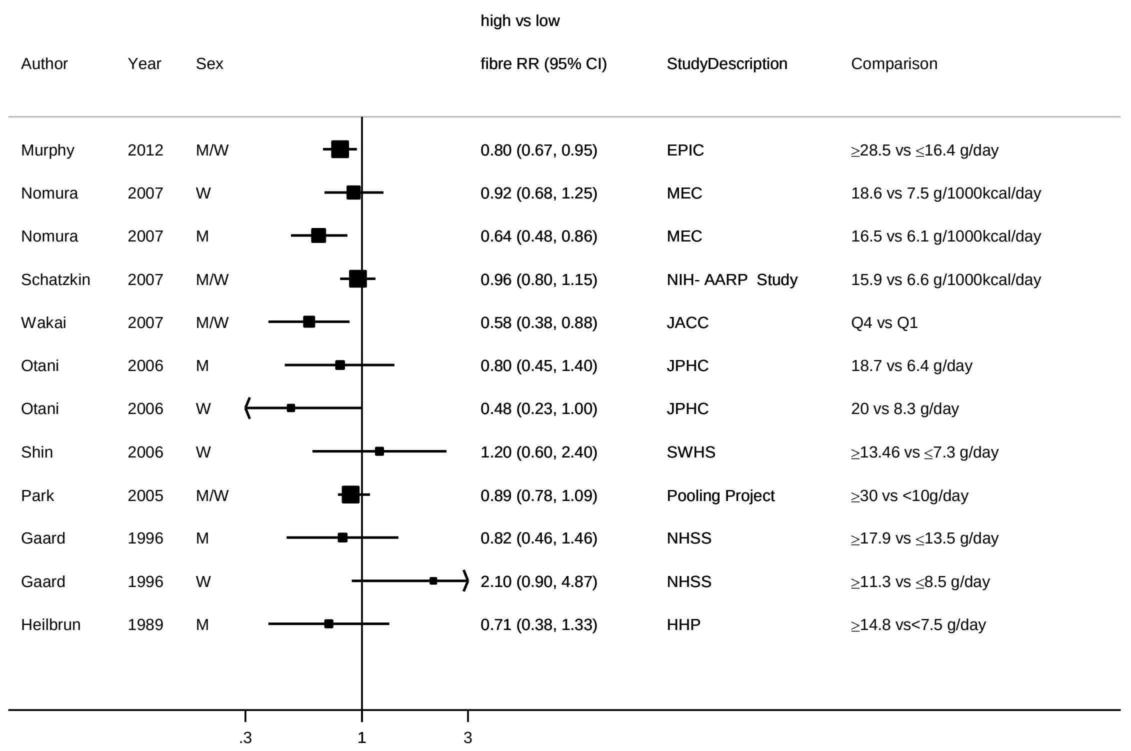


Figure 304 RR (95% CI) of colon cancer for 10g/day increase of dietary fibre

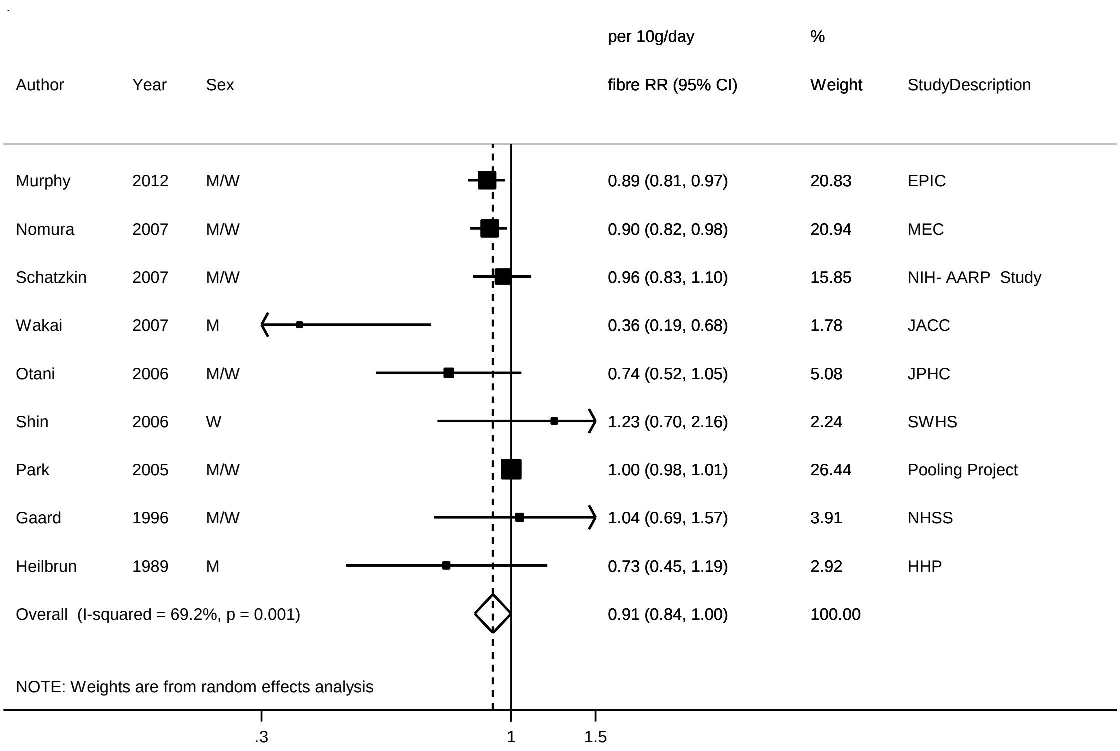


Figure 305 Funnel plot of studies included in the dose response meta-analysis dietary fibre and colon cancer

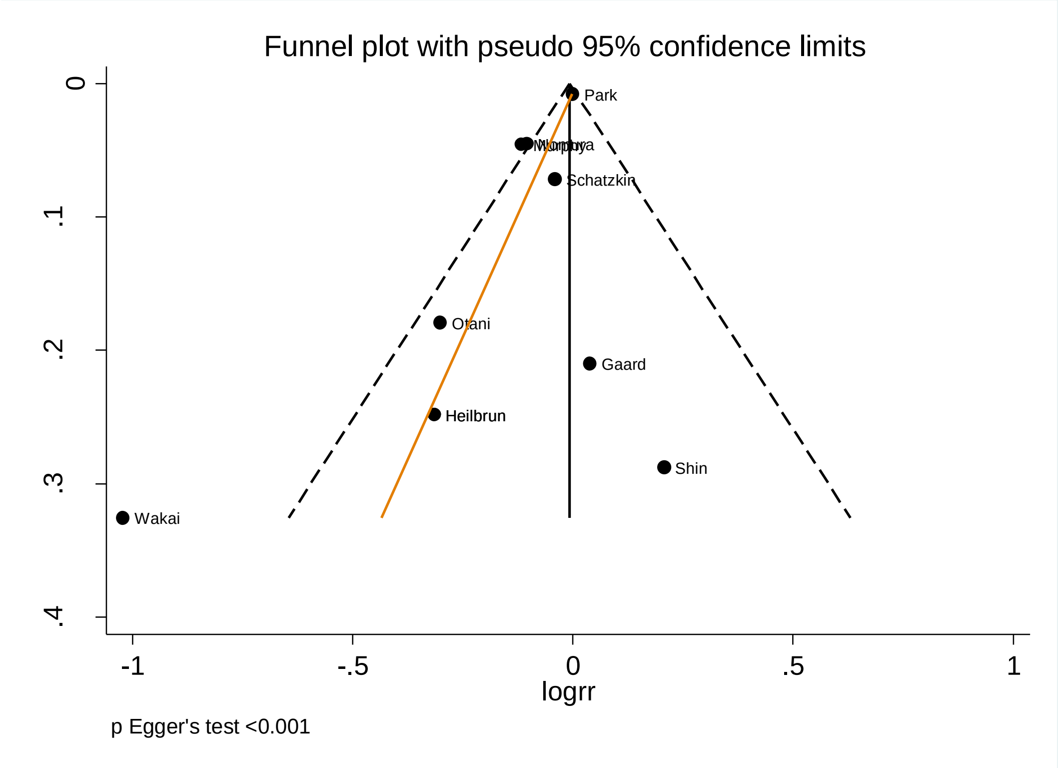
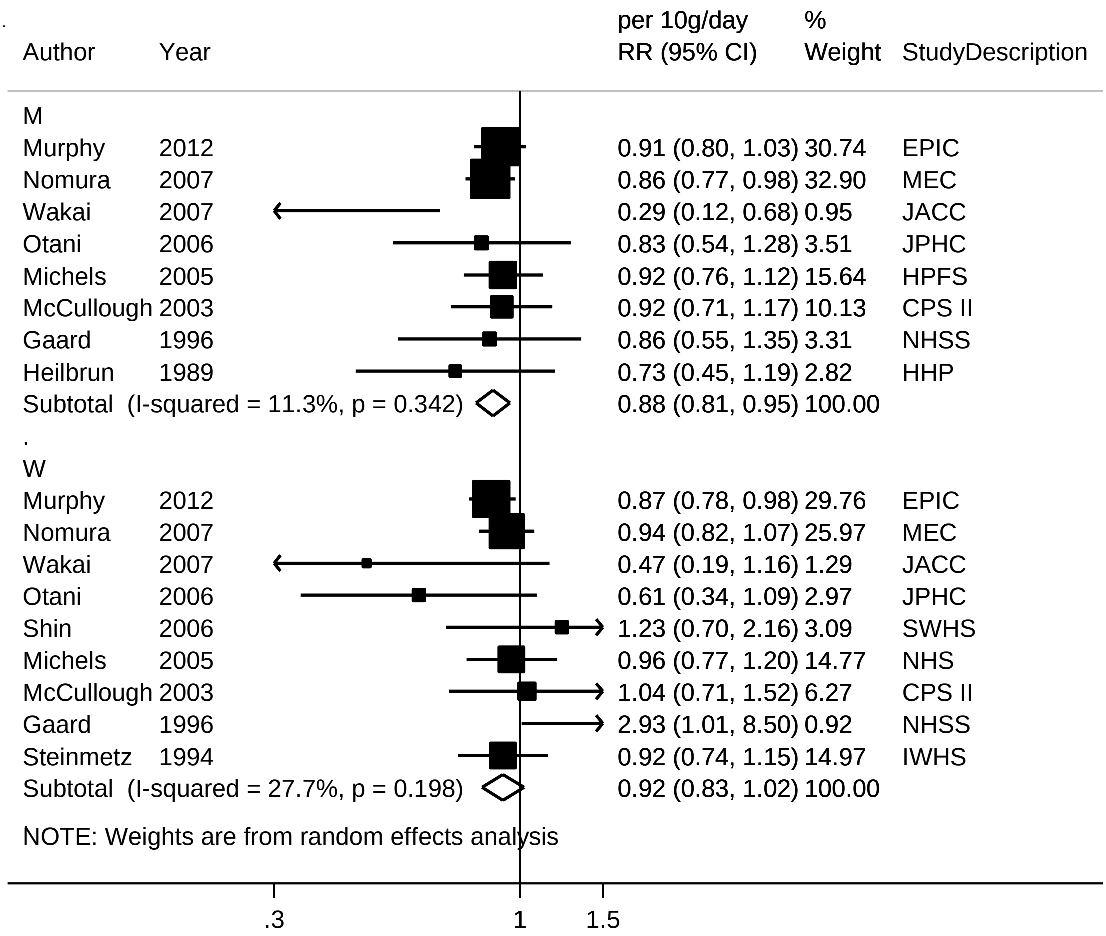
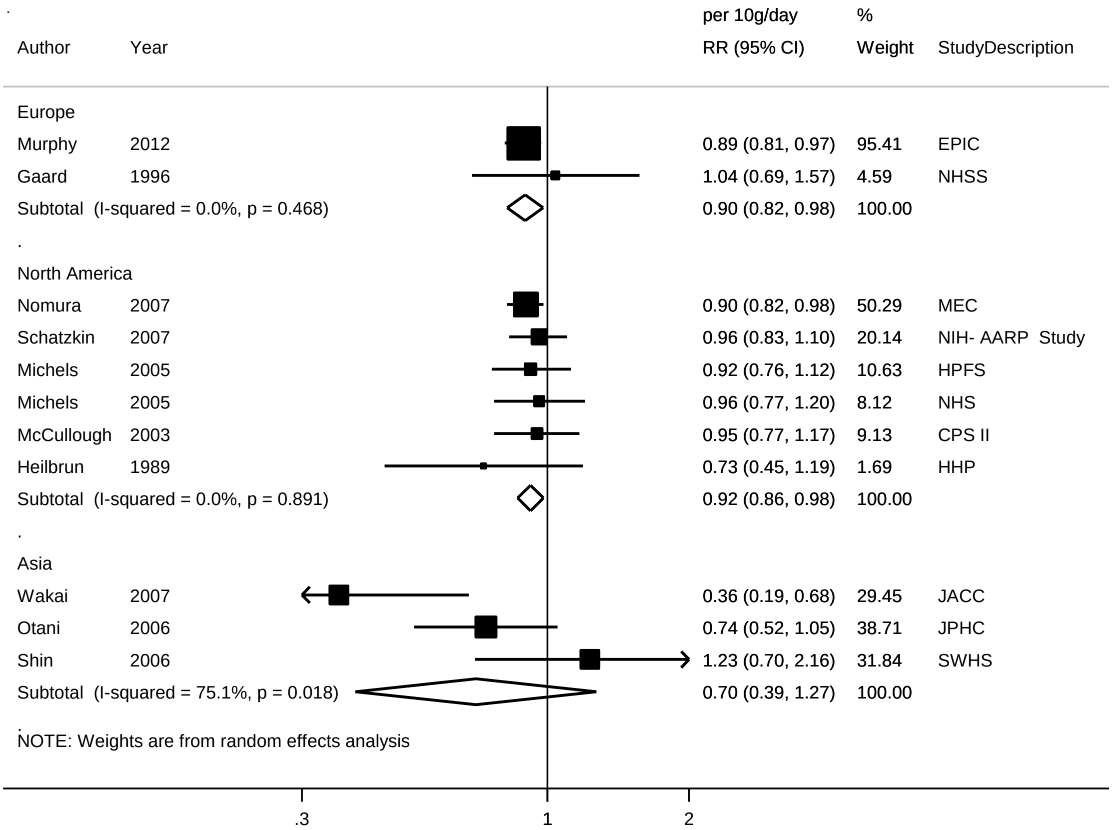


Figure 306 RR (95% CI) of colon cancer for 10g/day increase of dietary fibre by sex



The individual studies were used in this analysis and not the Pooling Project (Park, 2005).

Figure 307 RR (95% CI) of colon cancer for 10g/day increase of dietary fibre by location



The individual studies were used in this analysis and not the Pooling Project (Park, 2005).

Figure 308 RR (95% CI) of colon cancer for 10g/day increase of dietary fibre by adjustment for folate

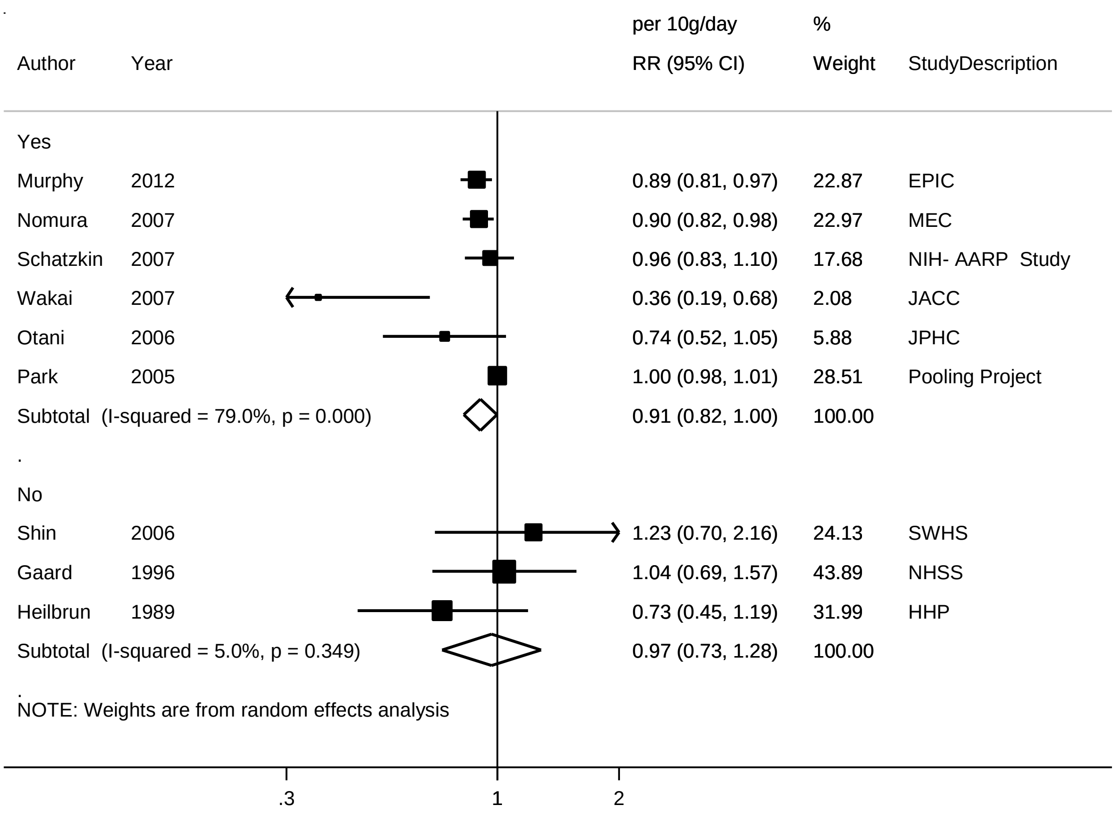
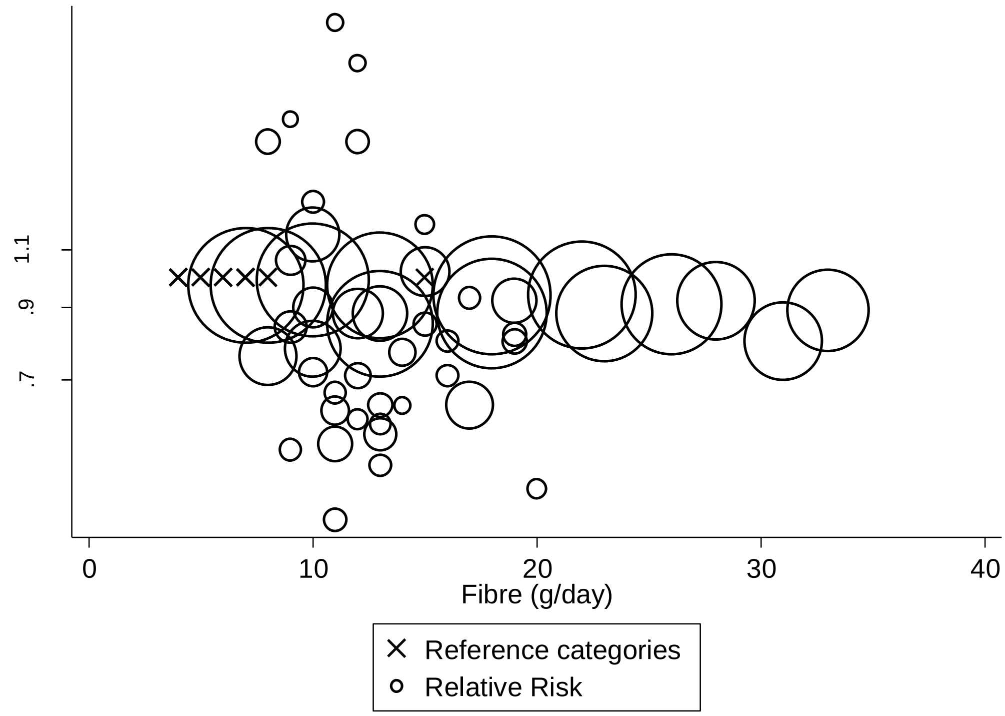


Figure 309 Relative risk of colon cancer and dietary fibre estimated using non-linear models



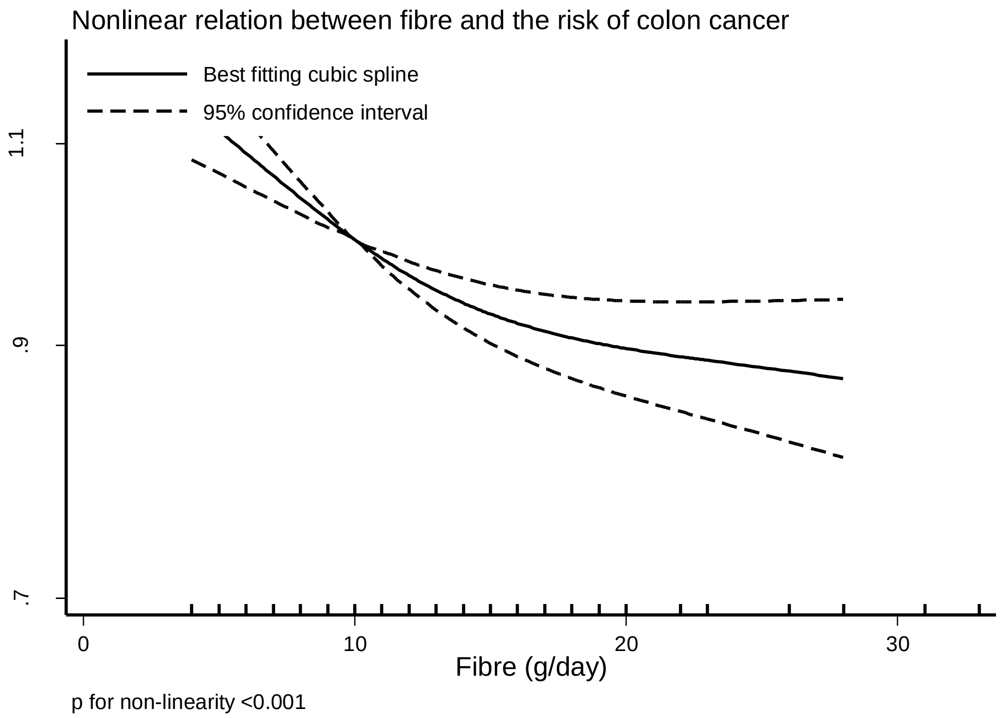


Table 171 Table with dietary fibre values and corresponding RRs (95% CIs) for non-linear analysis of dietary fibre and colon cancer

Dietary fibre(g/day)	RR (95%CI)
4	1.13(1.08-1.20)
7	1.06(1.04-1.09)
0	1
15	0.92(0.90-0.96)
20	0.89(0.85-0.94)
30	0.86(0. 78-0.94)

Figure 310 RR (95% CI) of colon cancer for 10g/day increase of dietary fibre including individual study results and not the Pooling Project

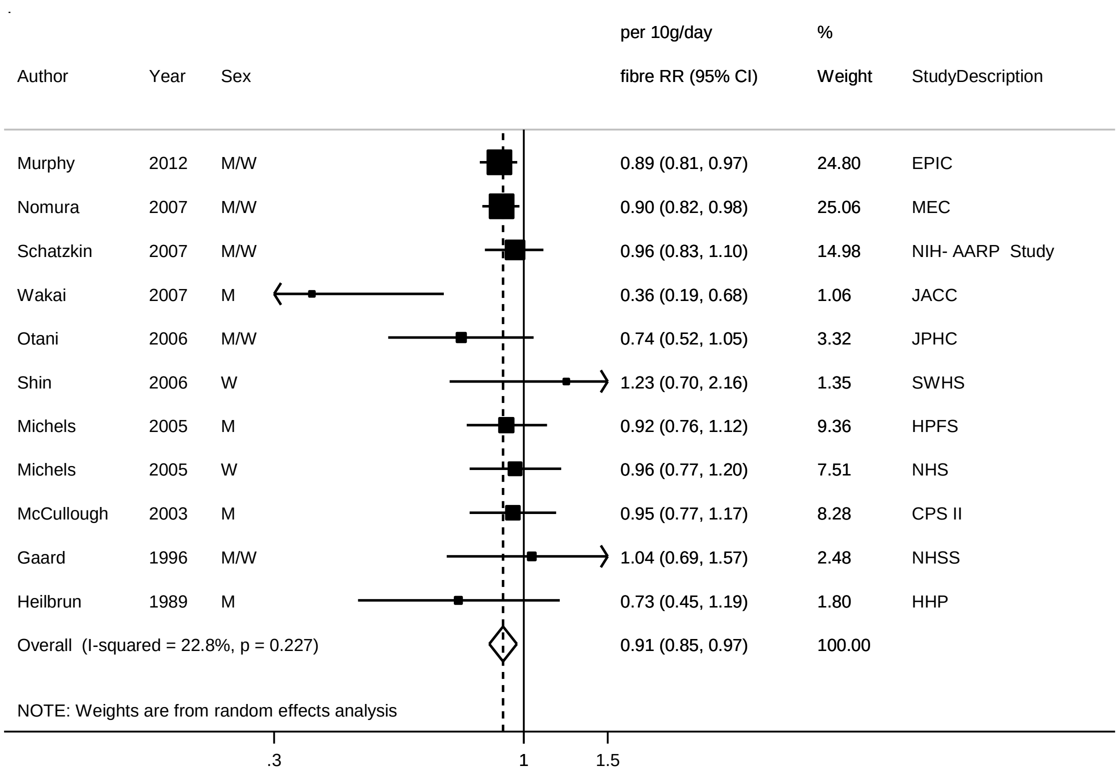


Figure 311 RR estimates of rectal cancer by levels of dietary fibre

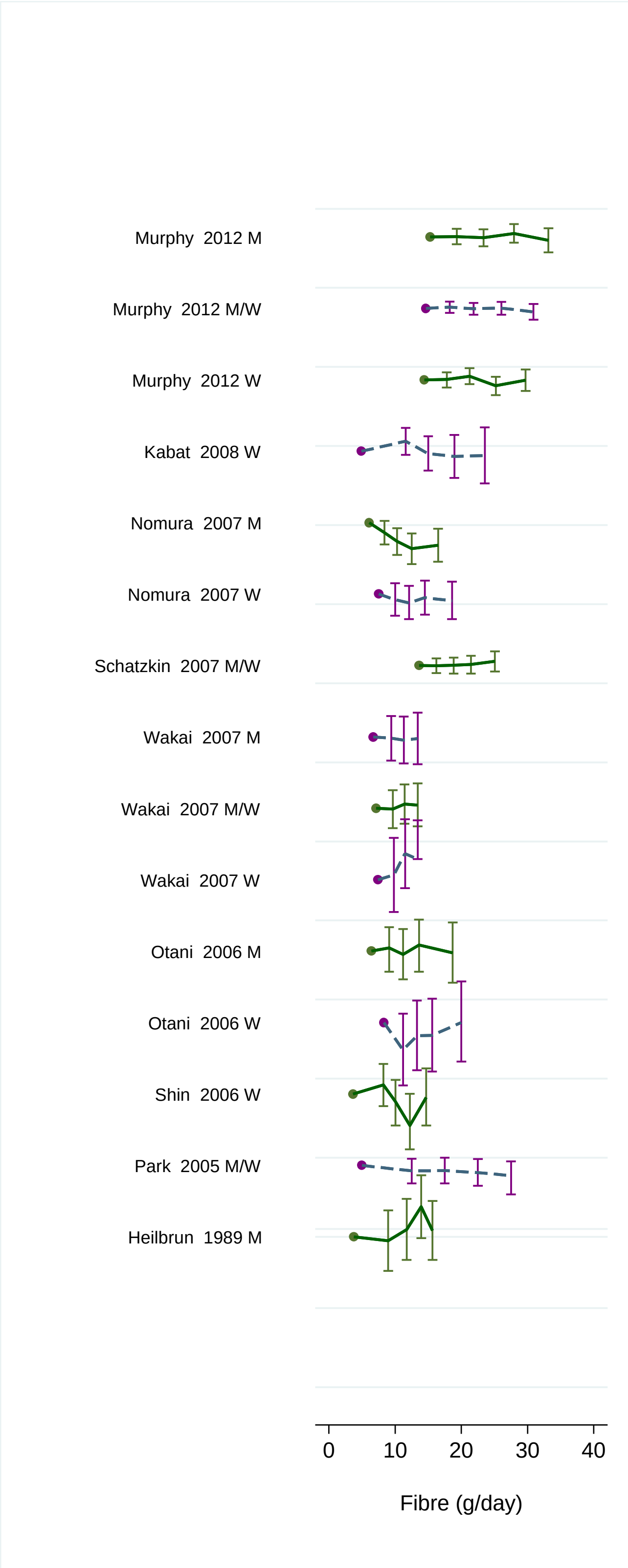


Figure 312 RR (95% CI) of rectal cancer for the highest compared with the lowest level of dietary fibre

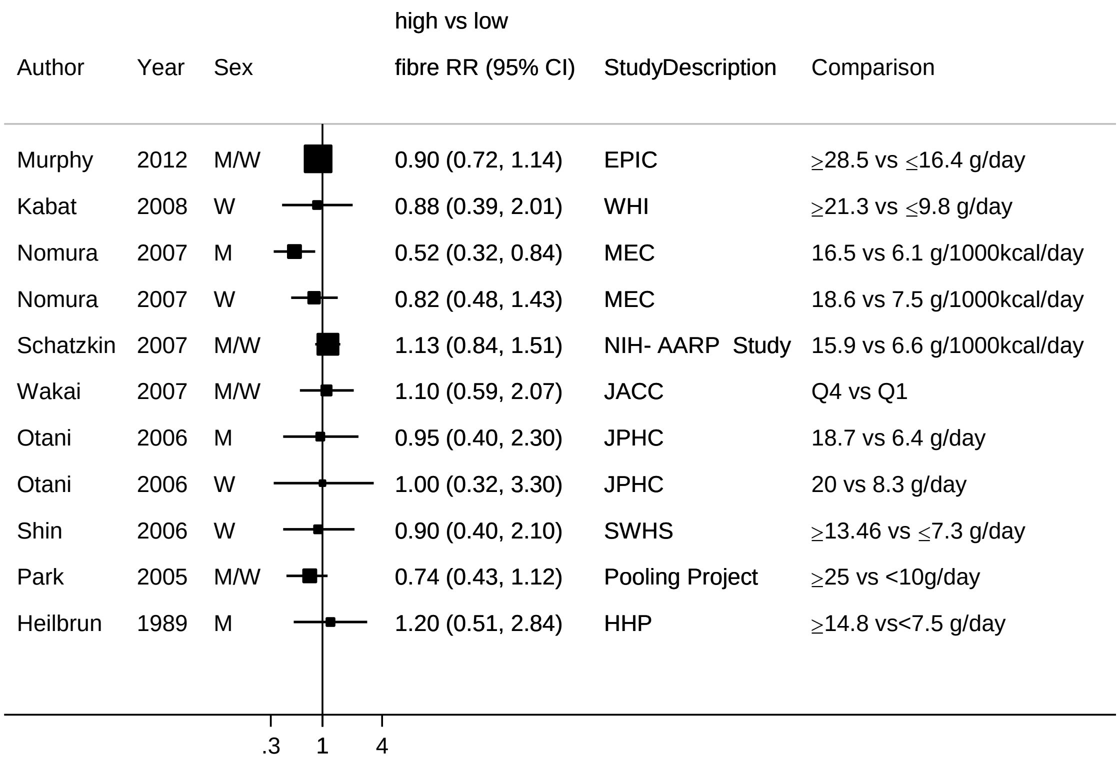


Figure 313 RR (95% CI) of rectal cancer for 10g/day increase of dietary fibre

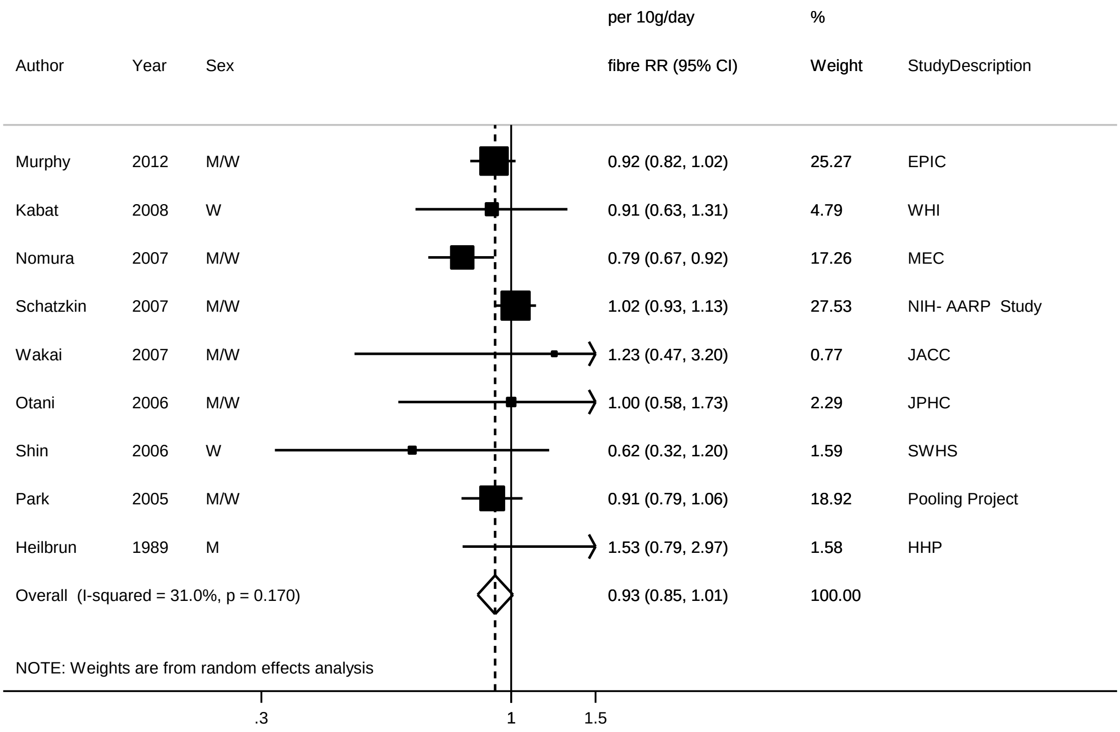


Figure 314 Funnel plot of studies included in the dose response meta-analysis dietary fibre and rectal cancer

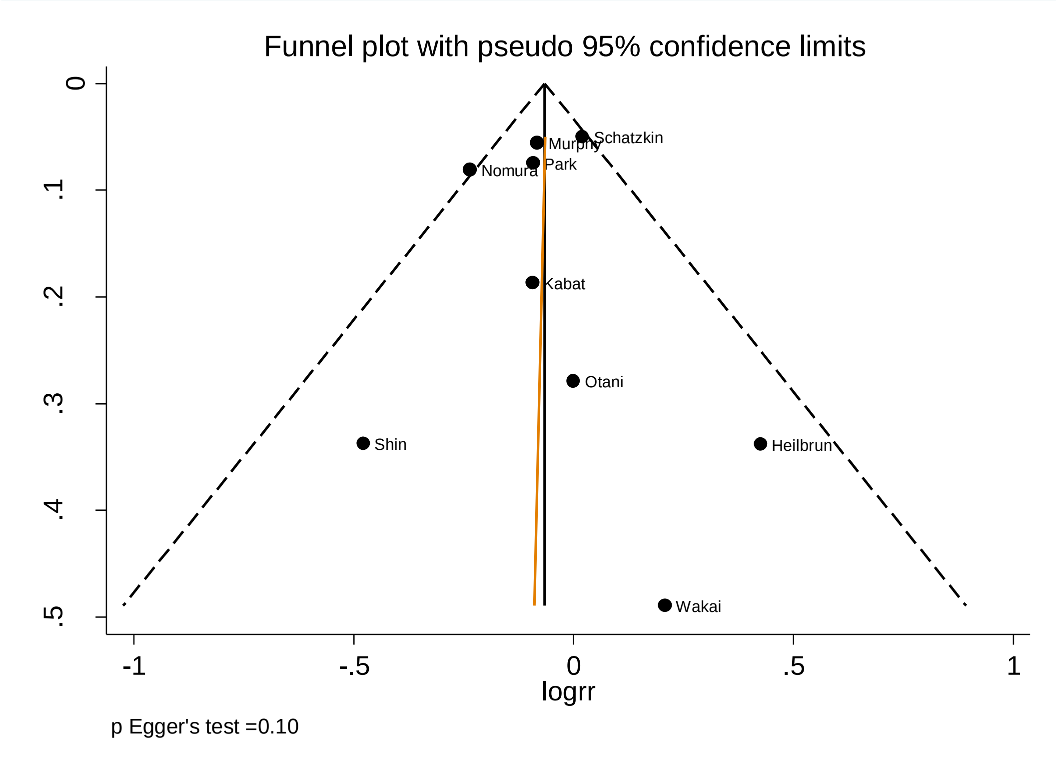
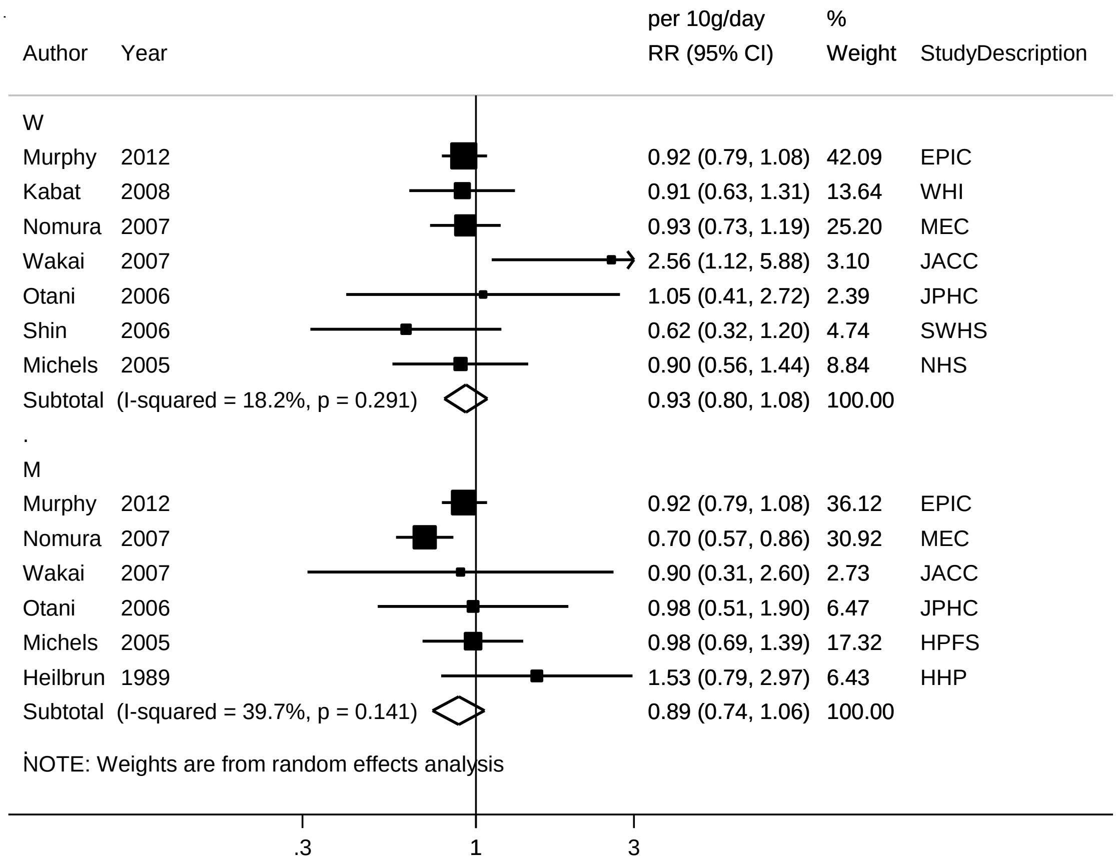
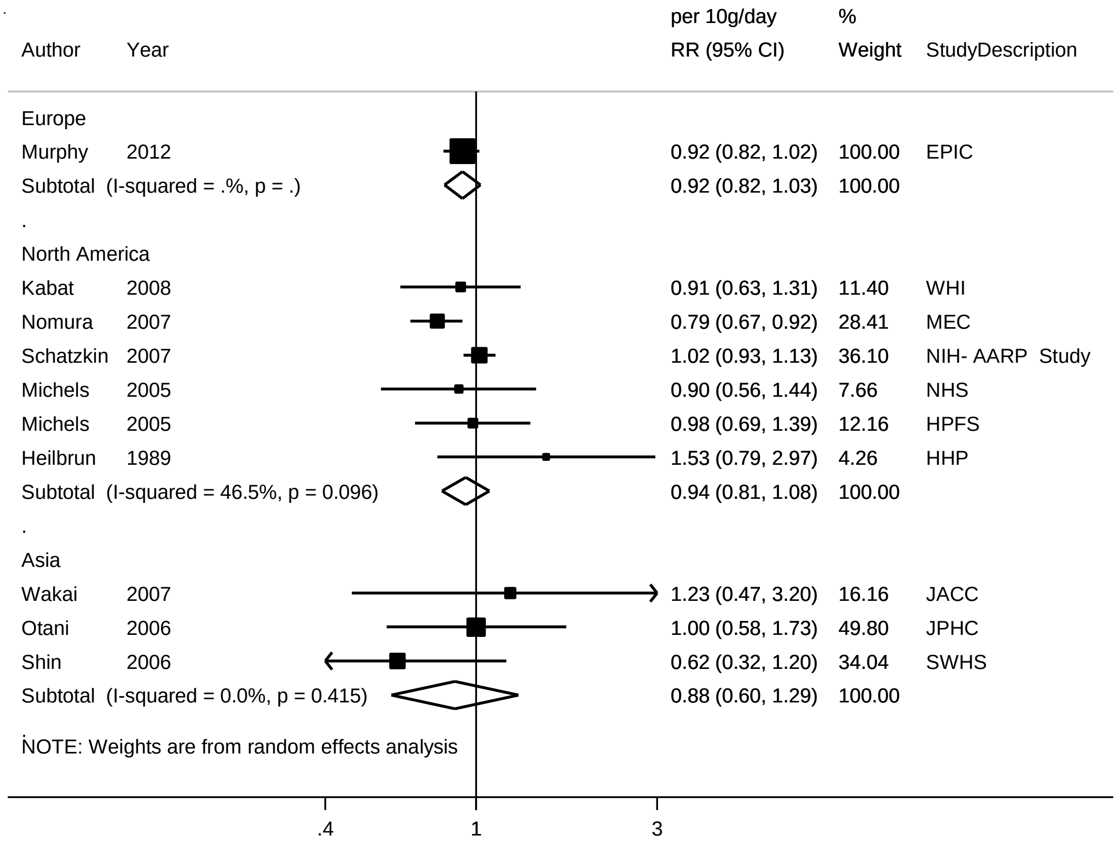


Figure 315 RR (95% CI) of rectal cancer for 10g/day increase of dietary fibre by sex



The individual studies were used in this analysis and not the Pooling Project (Park, 2005).

Figure 316 RR (95% CI) of rectal cancer for 10g/day increase of dietary fibre by location



The individual studies were used in this analysis and not the Pooling Project (Park, 2005).

Figure 317 RR (95% CI) of rectal cancer for 10g/day increase of dietary fibre by adjustment for folate

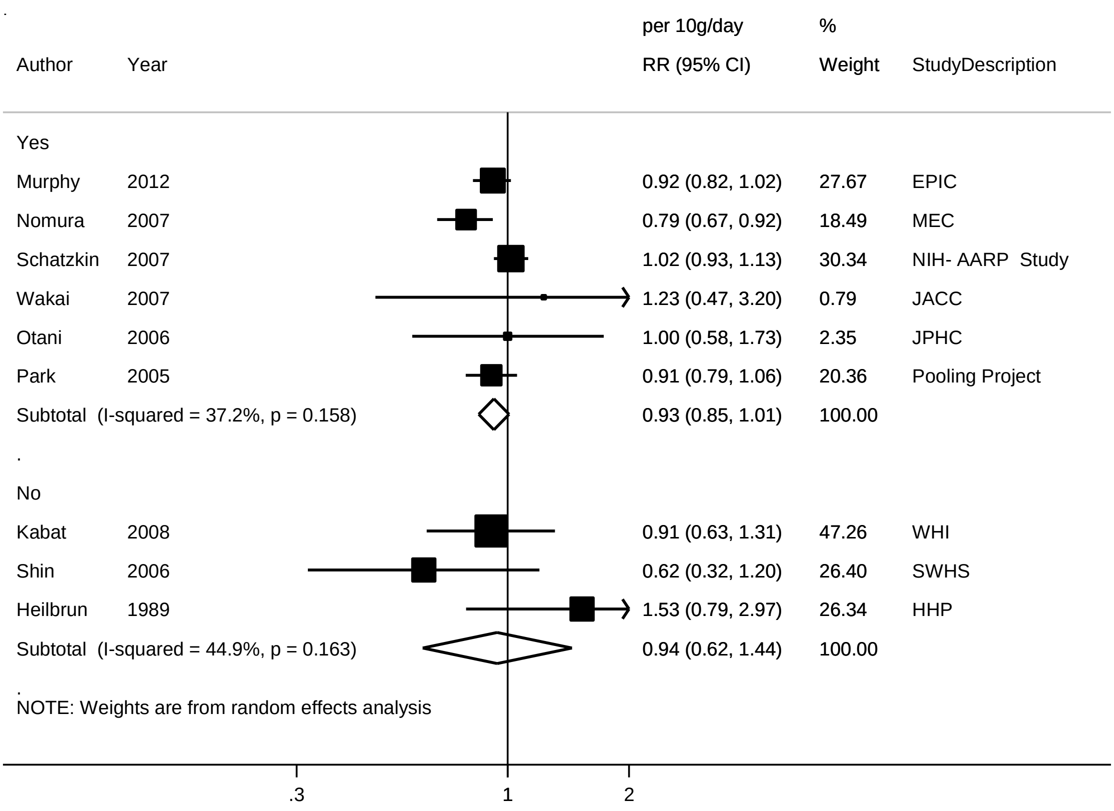


Figure 318 RR (95% CI) of colorectal cancer for the highest compared with the lowest level of cereal fibre (including the Pooling Project)

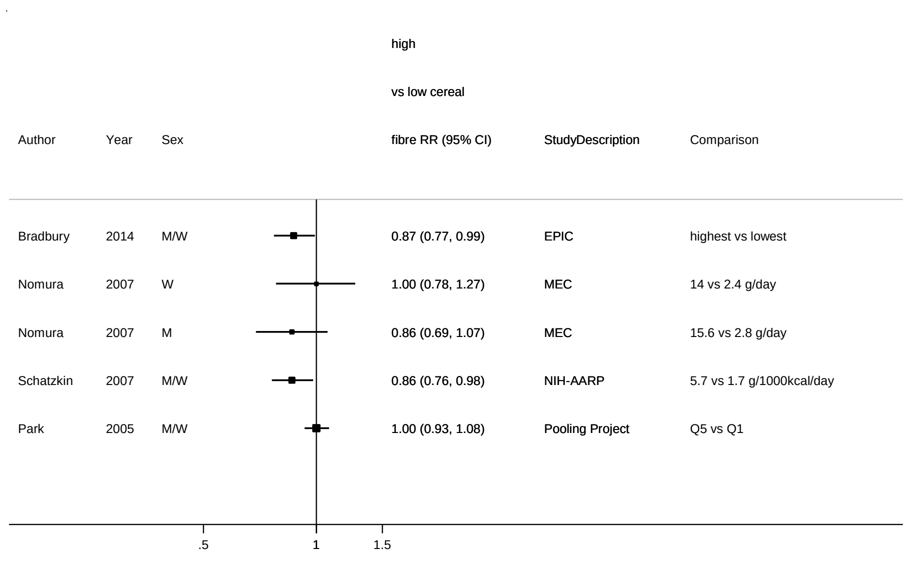


Figure 319 RR (95% CI) of colorectal cancer for the highest compared with the lowest level of vegetable fibre (including the Pooling Project)

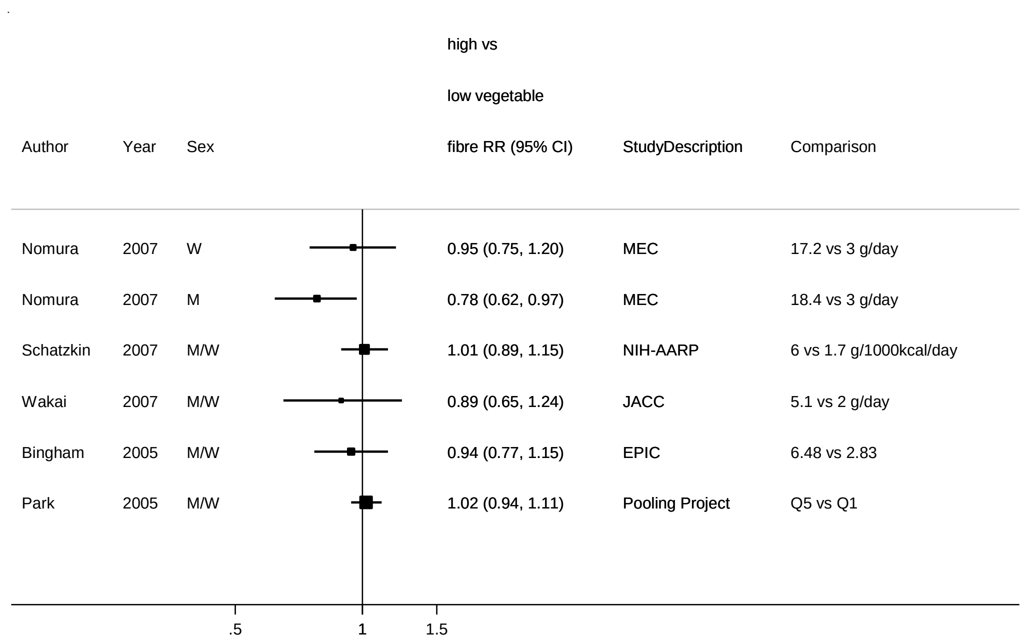
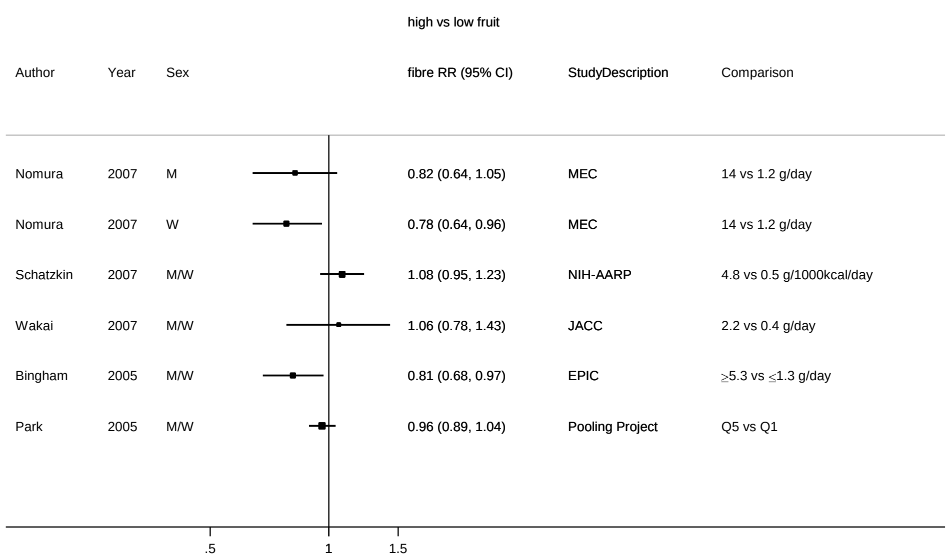


Figure 320 RR (95% CI) of colorectal cancer for the highest compared with the lowest level of fruit fibre (including the Pooling Project)



5.1.4 Foods containing sugars

In total, two prospective studies in three publications investigated the association between foods containing sugars and risk of colorectal cancer (Tasevka, 2012; Sellers, 1998 and Bostick, 1994).

The CUP identified one large prospective study (NIH-AARP diet and health study, Tasevska, 2012) after the 2005 SLR investigating the intake of added sugars (including sugars as ingredients in processed and prepared food, drinks, jams/jellies, candies, ice-creams, and as sugar eaten separately or added to foods) and colorectal cancer among men and women (COL40854). The RR of colorectal cancer for the highest compared to the lowest quintile of added sugars was 1.02 (95% CI: 0.89-1.16), p_{trend}=0.55 for men (2601 cases), and 0.99 (95% CI: 0.81-1.19), p_{trend}=0.87 for women (1296 cases), respectively. A smaller study (212 cases) included in the 2005 SLR (COL00079, Bostick 1994) investigated the association between sucrose-rich foods (including sucrose-containing beverages, chocolate, candies, cookies, cakes, pies, pastries, jelly, ice milk and ice cream) and colon cancer among postmenopausal women, the Iowa Women's Health Study (IWHS). The study reported a positive association of sucrose-rich foods and colon cancer risk [RR for high vs. low: 1.74 (95% CI: 1.60-2.87), p_{trend}=0.12].

The CUP identified another publication within this study (IWHS, COL01974, Sellers, 1998) not included in the 2005 SLR, investigating the association between sucrose-rich foods and colon cancer stratified by family history of colorectal cancer. After stratification, a positive non-significant increased risk of colon cancer of sucrose-rich foods for women with a family history of colorectal cancer was reported [RR for high vs. low: 1.20 (95% CI: 0.60-2.50), p_{trend}=0.6], whereas findings did not support an association for women without a family history of colorectal cancer [RR for high vs. low: 1.00 (95% CI: 0.70-1.50), p_{trend}=0.9].

Table 172 Foods containing sugars and colorectal cancer risk. Main characteristics of studies included in the CUP SLR dose-response meta-analysis

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors
Tasevska, 2012 COL40854 USA	NIH-AARP, Prospective Cohort, Age: 50-71 years, M/W, Retired	2 601/ 435 686	US social security administration death master file/national death Index	Semi-quantitative FFQ	Incidence, colorectal cancer, men	q 5 vs q 1	1.02 (0.89-1.16) Ptrend:0.55	Alcohol intake, BMI, calcium Intake, calcium supplement, educational level, energy intake, family history of colon cancer, fibre intake, fruit juice, fruits intake, height, marital status, physical activity, race, red meat intake, smoking
		1 296/			Incidence, colorectal cancer, women	q 5 vs q 1	0.99 (0.81-1.19) Ptrend:0.87	
Sellers, 1998 COL01974 USA	IWHS, Prospective Cohort, Age: 55-69 years, W, Postmenopausal	180/ 35 216 10 years	Seer registry	Semi-quantitative FFQ	Incidence, colon cancer, no family history of colorectal cancer	≥21.1 vs ≤14 servings/week	1.00 (0.70-1.50) Ptrend:0.9	Age, history of polyps, total energy Intake
		61/			Incidence, colon cancer, Family history of colorectal cancer	≥21.1 vs ≤14 servings/week	1.20 (0.60-2.50) Ptrend:0.6	
Bostick, 1994 COL00079 USA	IWHS, Prospective Cohort, Age: 55-69 years, W	212/ 35 216 167 447 person-years	Driving license	Semi-quantitative FFQ	Incidence, colon cancer	≥20.5 vs ≤5.5 serving/week	1.74 (1.06-2.87) Ptrend:0.12	Age, energy intake, height, parity, total vitamin e Intake, total vitamin e Intake * age, vitamin a supplement

5.1.4 Sugar as food

The CUP identified four new prospective studies on sugar intake and colorectal cancer after the 2005 SLR (Tasevska, 2012, Howarth, 2008, Kabat, 2008, and McCarl, 2006).
Overall, three studies investigated total sugar intake (Tasevska, 2012, Kabat, 2008, and Terry, 2003), six studies sucrose intake (Tasevska, 2012, Howarth, 2008, McCarl, 2006, Michaud, 2005, Higginbotham, 2004, and Bostick, 1994), five studies fructose intake (Tasevska, 2012, McCarl, 2006, Michaud, 2005, Higginbotham, 2004, and Bostick, 1994), one study glucose intake (McCarl, 2006), and two studies lactose intake (Jarvinen, 2001, and Kearney, 1996) with risk of colorectal cancer (see tables below).

Total sugar intake

Two new prospective studies on total sugar intake and colorectal cancer were identified after the 2005 SLR (Tasevska, 2012, and Kabat, 2008). The two large cohort studies (NIH-AARP diet and health study, Tasevka 2012, and the Women's Health Initiative Observational Study (WHI), Kabat 2008) did not show a statistically significant association between total sugar intake and risk of colorectal cancer. In the NIH-AARP study (including 3897 cases) the RR (95% CI) of colorectal cancer for the highest compared to the lowest quintile of total sugar intake was 0.95 (95% CI: 0.83-1.09), p_{trend}=0.54 for men, and 1.06 (95% CI: 0.87-1.29), p_{trend}=0.38 for women, respectively (Tasevska, 2012). In the WHI study (including 1470 cases) the RR of colorectal cancer was 1.16 (95% CI: 0.91-1.49), p_{trend}=0.87, by comparing high vs low intake of total sugar (Kabat, 2008).
Included in the 2005 SLR, the Canadian National Breast Screening Study (CNBSS, Terry 2003) including 616 cases, did not report an association between sugar intake and colorectal cancer as well [RR for high vs. low: 1.03 (95% CI: 0.73-1.44), p_{trend}=0.71] (Terry, 2003).

Sucrose intake

The CUP identified three new prospective studies after the 2005 SLR (Tasevska, 2012, Howarth, 2008, and McCarl, 2006).
A total of five studies investigated colorectal cancer (Tasevska, 2012, Howarth, 2008, McCarl, 2006, Michaud, 2005, and Higginbotham, 2004), three studies colon cancer (Howarth, 2008, Michaud, 2005, and Bostick, 1994) and one study rectal cancer (Michaud, 2005). None of the studies showed a statistically significant association of sucrose intake with colorectal or colon cancer, respectively, except for one study. The study by Michaud *et al.*, 2005 (NHS-HPFS) reported a borderline statistically significant increased risk of colorectal cancer for men (683 cases) by comparing high versus low sucrose intake [RR for high vs. low: 1.30 (95% CI: 0.99-1.69), p_{trend}=0.03] (Figure 171, and Figure 172). The NHS-HPFS study reported a statistically significant decreased risk of rectal cancer for women [RR for high vs. low: 0.62 (95% CI: 0.39-0.99), p_{trend}=0.17], but not for men [RR: 1.47 (95% CI: 0.81-2.66), p_{trend}=0.11] (Michaud, 2005).

Fructose intake

Two new studies were identified by the CUP after the 2005 SLR investigating fructose intake and colorectal cancer (Tasevska, 2012, and McCarl, 2006).

In total, four studies focused on colorectal (Tasevska, 2012, McCarl, 2006, Michaud, 2005, and Higginbotham, 2004), two on colon (Michaud, 2005, and Bostick, 1994), and one on rectal cancer (Michaud, 2005).

The two new studies (NIH-AARP, including 3897 cases and IWHS, including 954 cases) did not support a statistically significant association between fructose intake and colorectal cancer (Tasevska, 2012 and McCarl, 2006). In the 2005 SLR, the results were inconsistent. The NHS-HPFS reported a significant increased risk of fructose intake (high vs low) of colorectal cancer for men (683 cases), but not for women (1096 cases) (Michaud, 2005), whereas another smaller study (WHS, including 174 cases) showed a positive association for women as well (Higginbotham, 2004) (Figure 173). Studies on fructose intake and colon (Michaud, 2005, and Bostick, 1994), or rectal cancer (Michaud, 2005), respectively, reported similar findings.

Glucose intake

The CUP identified one prospective study on glucose intake and risk of colorectal cancer in women, including 954 cases (IWHS, McCarl 2006) after the 2005 SLR. The age-adjusted model did not show a statistically significant association between glucose intake and risk of colorectal cancer, by comparing high vs low glucose intake [RR: 0.85 (95% CI: 0.70-1.03)].

Lactose intake

No new study was identified during the CUP. The total number of studies remained at two prospective studies (Jarvinen, 2001, and Kearney, 1996). The studies reported a non-significant decreased risk of high compared with low lactose intake of colorectal, or colon cancer, respectively.

Table 173 Total sugar intake and colorectal cancer risk. Main characteristics of studies included in the CUP SLR dose-response meta-analysis

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors
Tasevska, 2012 COL40854 USA	NIH-AARP, Prospective Cohort, Age: 50-71 years, M/W, Retired	2 601/ 435 686	US social security administration death master file/national death Index	Semi-quantitative FFQ	Incidence colorectal cancer, men	q 5 vs q 1	0.95 (0.83-1.09) Ptrend:0.54	Alcohol intake, BMI, calcium intake, calcium supplement, educational level, energy intake, family history of colon cancer, fibre intake, height, marital status, physical activity, race, red meat intake, smoking
		1 296/			Incidence colorectal cancer, women	q 5 vs q 1	1.06 (0.87-1.29) Ptrend:0.38	
Kabat, 2008 COL40722 USA	Women's Health Initiative - Observational study, Prospective Cohort, W, Postmenopausal	1 470/ 158 800 7.8 years	Mail or telephone questionnaires verified by trained physician adjudicators	FFQ	Incidence, colorectal cancer	≥129.8 vs ≤58.7 g/day	1.16 (0.91-1.49) Ptrend:0.87	Age, BMI, dietary calcium, educational level, energy intake, family history of colorectal cancer, fibre, height, history of diabetes, hormone use, number of cigarettes smoked, observational study participants, physical activity
		798/			Incidence, proximal colon cancer	≥129.8 vs ≤58.7 g/day	0.95 (0.73-1.24) Ptrend:0.81	
		351/			Incidence, distal colon cancer	≥129.8 vs ≤58.7 g/day	1.15 (0.77-1.72) Ptrend:0.38	
		303/			Incidence, rectal cancer	≥129.8 vs ≤58.7 g/day	1.26 (0.82-1.93) Ptrend:0.24	
Terry, 2003 COL00561 Canada	CNBSS, Prospective Cohort, Age: 40-59 years, W	616/ 49 124 810 649 person-years	Breast cancer screening centres	Quantitative FFQ	Incidence, colorectal cancer	≥104 vs ≤52 g/day	1.03 (0.73-1.44) Ptrend:0.71	Age, alcohol consumption, BMI, educational level, energy intake, folic acid intake, hormone replacement therapy, oral contraceptive use, parity, physical activity, red meat intake, smoking habits, study centre, treatment allocation

Table 174 Sucrose intake and colorectal cancer risk. Main characteristics of studies included in the CUP SLR dose-response meta-analysis

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors
Tasevska, 2012 COL40854 USA	NIH-AARP, Prospective Cohort, Age: 50-71 years, M/W, Retired	2 601/ 435 686	US social security administration death master file/national death Index	Semi-quantitative FFQ	Incidence colorectal cancer, men	q 5 vs q 1	1.06 (0.93-1.21) Ptrend:0.91	Alcohol intake, BMI, calcium intake, calcium supplement, educational level, energy intake, family history of colon cancer, fibre intake, height, marital status, physical activity, race, red meat intake, smoking
		1 296/			Incidence colorectal cancer, women	q 5 vs q 1	1.11 (0.92-1.33) Ptrend:0.13	
Howarth, 2008 COL40653 USA	MEC, Prospective Cohort, Age: 45-75 years	920/ 191 004 8 years	Cancer registry and death certificates	FFQ-quantitative	Incidence, colorectal cancer, women	q 5 vs q 1	0.88 (0.70-1.11) Ptrend:0.158	Age, alcohol intake, BMI, calcium intake, dietary fiber, ethnicity, family history of colorectal cancer, folate intake, history of polyps, HRT use, multivitamin, nsaid use, physical activity, red meat intake, smoking, pack-years, time, vitamin d, energy intake
		717/			Incidence, colon cancer, women	q 5 vs q 1	0.85 (0.66-1.11) Ptrend:0.155	
McCarl, 2006 COL40633 USA	IWHS, Prospective Cohort, Age: 55-69 years, W	954/ 35 197 15 years	Seer registry	FFQ	Incidence, colorectal cancer	≥55.2 vs ≤24.5 g	0.83 (0.68-1.01)	Age
Michaud, 2005 COL01824 USA	NHS-HPFS, Prospective Cohort, M/W	1 096/ 130 719 20 years	Self-report, medical record and pathology report reviewed by centrally trained physician	FFQ	Incidence, colorectal cancer, women	55 vs 17 g/day	0.89 (0.72-1.11) Ptrend:0.10	Age, alcohol, aspirin use, beef, pork or lamb as a main dish, BMI, calcium intake, cereal fibre, family history of colon cancer, folate intake, height, history of endoscopy, pack-years of smoking,
		858/			Incidence, colon cancer, women	55 vs 17 g/day	0.99 (0.78-1.26) Ptrend:0.49	

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors
		238/			Incidence, rectal cancer, women	55 vs 17 g/day	0.62 (0.39-0.99) Ptrend:0.17	physical activity, processed meat
		683/			Incidence, colorectal cancer, men	67 vs 26 g/day	1.30 (0.99-1.69) Ptrend:0.03	
		552/			Incidence, colon cancer, men	67 vs 26 g/day	1.25 (0.93-1.68) Ptrend:0.13	
		131/			Incidence, rectal cancer, men	67 vs 26 g/day	1.47 (0.81-2.66) Ptrend:0.11	
Higginbotham , 2004 COL00299 USA	WHS, Prospective Cohort, Age: 45- years, W, nurses	174/ 38 451 7.9 years	Cancer registry	FFQ	Incidence, colorectal cancer	q 5 vs q 1	1.51 (0.90-2.54) Ptrend:0.06	Age, alcohol consumption, BMI, energy-adjusted calcium, energy-adjusted folate, energy-adjusted total fat, energy-adjusted vitamin d, energy-adjusted total fiber, family history of specific cancer, history of oral contraceptive use, HRT use, nsaid use, physical activity, smoking habits, total energy
						per 10 g/day	1.08 (0.96-1.21)	
Bostick, 1994 COL00079 USA	IWHS, Prospective Cohort, Age: 55-69 years, W	212/ 35 216 167 447 person-years	Driving license	Semi-quantitative FFQ	Incidence, colon cancer	≥62.5 vs ≤25.8 g/day	1.45 (0.88-2.39) Ptrend:0.14	Age, energy intake, height, parity, total vitamin e intake, total vitamin e intake * age, vitamin a supplement

Table 175 Fructose intake and colorectal cancer risk. Main characteristics of studies included in the CUP SLR dose-response meta-analysis

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors
Tasevska, 2012 COL40854 USA	NIH-AARP, Prospective Cohort, Age: 50-71 years, M/W, Retired	2 601/ 435 686	US social security administration death master file/national death Index	Semi-quantitative FFQ	Incidence colorectal cancer, men	q 5 vs q 1	0.99 (0.87-1.14) Ptrend:0.91	Alcohol intake, BMI, calcium intake, calcium supplement, educational level, energy intake, family history of colon cancer, fibre intake, height, marital status, physical activity, race, red meat intake, smoking
		1 296/			Incidence colorectal cancer, women	q 5 vs q 1	1.05 (0.87-1.27) Ptrend:0.20	
McCarl, 2006 COL40633 USA	IWHS, Prospective Cohort, Age: 55-69 years, W	954/ 35 197 15 years	Seer registry	FFQ	Incidence, colorectal cancer	≥31.6 vs ≤13.9 g	0.87 (0.71-1.07)	Age
Michaud, 2005 COL01824 USA	NHS-HPFS, Prospective Cohort, M/W	1 096/ 130 719 20 years	Self-report, medical record and pathology report reviewed by centrally trained physician	FFQ	Incidence, colorectal cancer, women	68 vs 22 g/day	0.87 (0.71-1.07) Ptrend:0.2	Age, alcohol, aspirin use, beef, pork or lamb as a main dish, BMI, calcium intake, cereal fibre, family history of colon cancer, folate intake, height, history of endoscopy, pack-years of smoking, physical activity, processed meat
		858/			Incidence, colon cancer, women	68 vs 22 g/day	0.86 (0.68-1.09) Ptrend:0.15	
		238/			Incidence, rectal cancer, women	68 vs 22 g/day	0.92 (0.59-1.44) Ptrend:0.47	
		683/			Incidence, colorectal cancer, men	72 vs 29 g/day	1.37 (1.05-1.78) Ptrend:0.008	
		552/			Incidence, colon cancer, men	72 vs 29 g/day	1.38 (1.03-1.86) Ptrend:0.02	

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors
		131/			Incidence, rectal cancer, men	72 vs 29 g/day	1.31 (0.72-2.38) Ptrend:0.33	
Higginbotham, 2004 COL00299 USA	WHS, Prospective Cohort, Age: 45- years, W, nurses	174/ 38 451 7.9 years	Cancer registry	FFQ	Incidence, colorectal cancer	q 5 vs q 1	2.09 (1.13-3.87) Ptrend:0.08	Age, alcohol consumption, BMI, energy-adjusted calcium, energy-adjusted folate, energy-adjusted total fat, energy-adjusted vitamin d, energy-adjusted total fiber, family history of specific cancer, history of oral contraceptive use, HRT use, nsaid use, physical activity, smoking habits, total energy
						per 10 g/day	1.04 (0.91-1.18)	
Bostick, 1994 COL00079 USA	IWHS, Prospective Cohort, Age: 55-69 years, W	212/ 35 216 167 447 person-years	Driving license	Semi-quantitative FFQ	Incidence, colon cancer	≥30.6 vs ≤13.4 g/day	0.93 (0.61-1.42) Ptrend:0.78	Age, energy intake, height, parity, total vitamin e intake, total vitamin e Intake * age, vitamin a supplement

Table 176 Glucose intake and colorectal cancer risk. Main characteristics of studies included in the CUP SLR dose-response meta-analysis

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors
McCarl, 2006 COL40633 USA	IWHS, Prospective Cohort, Age: 55-69 years, W	954/ 35 197 15 years	Seer registry	FFQ	Incidence, colorectal cancer	≥27.1 vs ≤11.9 g	0.85 (0.70-1.03)	Age

Table 177 Lactose intake and colorectal cancer risk. Main characteristics of studies included in the CUP SLR dose-response meta-analysis

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors
Jarvinen, 2001 COL00314 Finland	Finnish Mobile Clinic Health Examination Survey, Prospective Cohort, Age: 39 years, M/W	72/ 9 959 19.6 years	Population	Questionnaire	Incidence, colorectal cancer	q 4 vs q 1	0.91 (0.40-2.07) Ptrend:0.38	Age, sex, area of residence, BMI, energy intake, occupational group, smoking habits
		38/			Incidence, colon cancer	q 4 vs q 1	0.31 (0.08-1.15) Ptrend:0.03	
		34/			Incidence, rectal cancer	q 4 vs q 1	2.36 (0.75-7.40) Ptrend:0.40	
Kearney, 1996 COL00156 USA	HPFS, Prospective Cohort, Age: 40-75 years, M, Health professionals	47 935 6 years	Responding to mail survey	Semi-quantitative FFQ	Incidence, colon cancer, colon cancer	q 5 vs q 1	0.84 (0.54-1.29) Ptrend:0.74 Result Number:50410	Age, alcohol consumption, aspirin use, BMI, dietary fiber, family history of colon cancer, past history of smoking, physical activity, previous polyps, red meat intake, saturated fat, screening, total calories

Figure 321 RR (95% CI) of colorectal cancer for the highest compared with the lowest level of sucrose intake

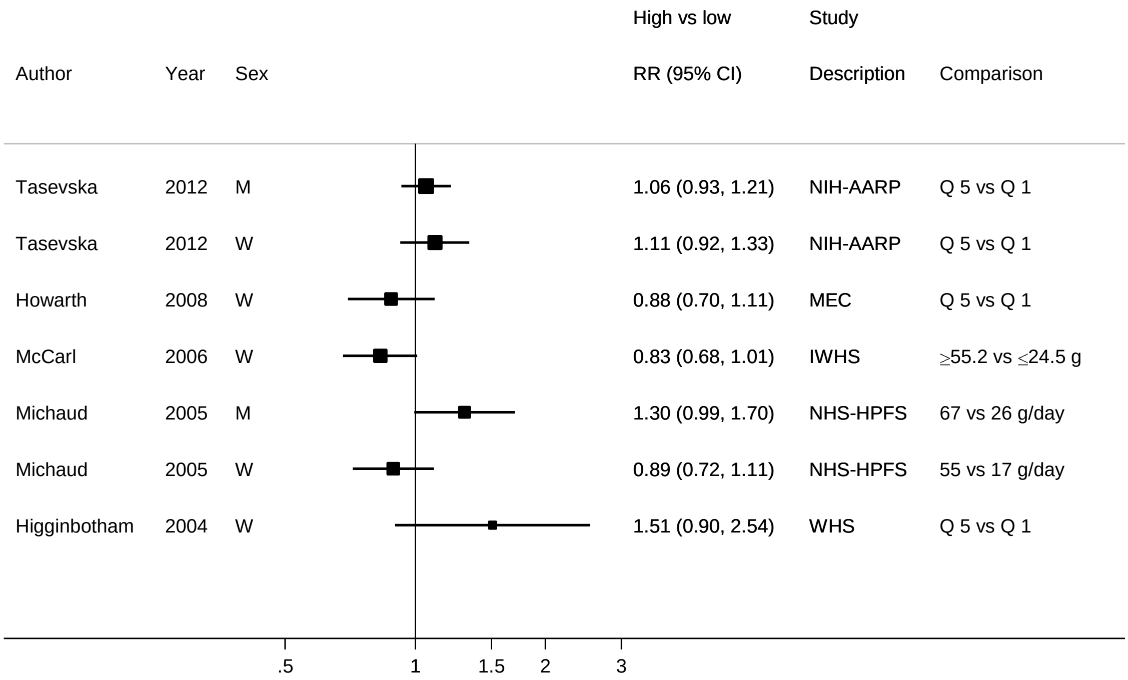


Figure 322 RR (95% CI) of colon cancer for the highest compared with the lowest level of sucrose intake

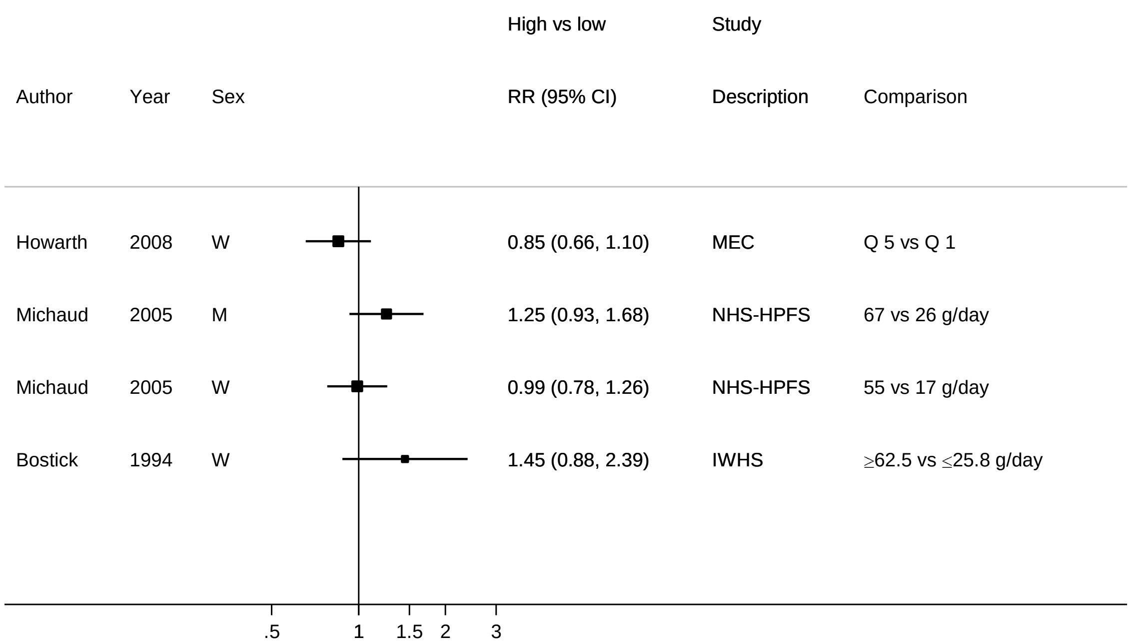
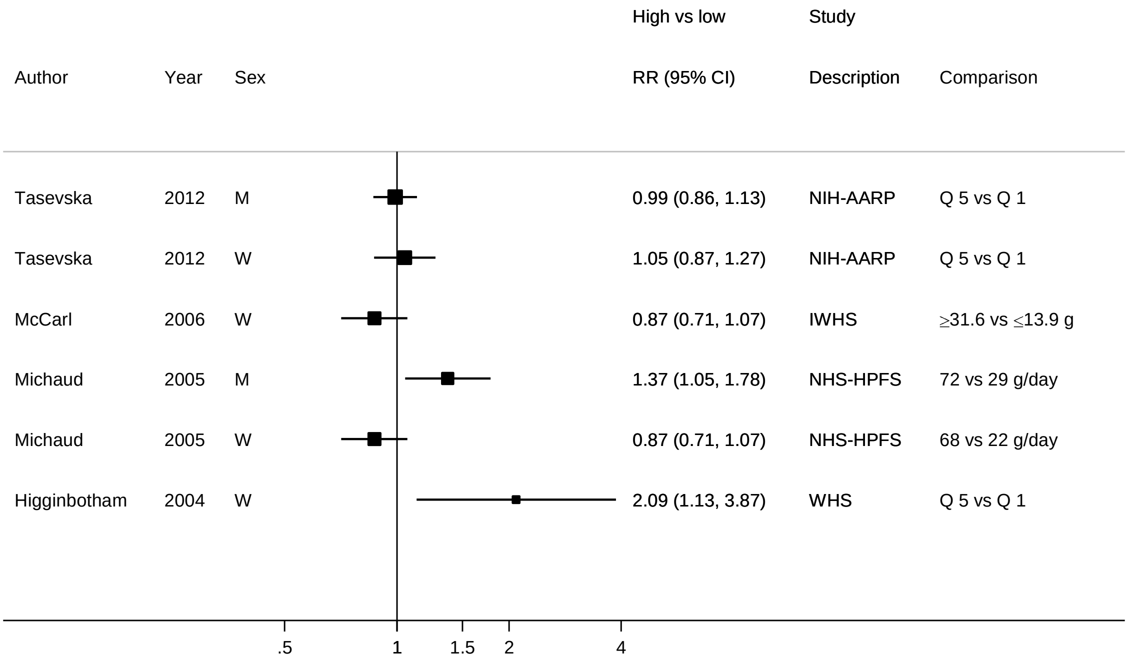


Figure 323 RR (95% CI) of colorectal cancer for the highest compared with the lowest level of fructose intake



5.1. Total Carbohydrate

Cohort studies

Summary

Main results:
Three new publications, two new studies and an updated publication of a study identified in 2010 SLR were identified. For distal and proximal colon cancer there was no update since the 2010 SLR.

Colorectal cancer:
Ten studies (7925 cases) were included in the dose-response meta-analysis of total carbohydrate and colorectal cancer. A non-significant association with moderate heterogeneity was observed. Only one study on women showed a positive association per 100g/day (WHS). After stratification by sex or geographic location the results remained non-significant. There was evidence of small study bias (p=0.03). There was no evidence of a non-linear association (p=0.10).

Colon cancer:
Nine studies (7819 cases) were included in the dose-response meta-analysis of total carbohydrate and colon cancer. A non-significant association with no heterogeneity was observed. All studies showed non-significant associations. After stratification by sex or geographic location the results remained non-significant. There was evidence of small study bias (p=0.48). There was evidence of a non-linear association (p=0.29).

Rectal cancer:
Nine studies (2717 cases) were included in the dose-response meta-analysis of total carbohydrate and rectal cancer. A non-significant association with no heterogeneity was observed. All studies showed non-significant associations. After stratification by sex or geographic location the results remained non-significant. There was evidence of small study bias (p=0.69). There was evidence of a non-linear association (p=0.19).

Study quality:

All studies were fully adjusted for different confounders. Measurement errors in the assessment of dietary intake are known to bias effect estimates; however, none of the studies included in the analysis made any corrections for measurement errors. Most studies used FFQ to assess carbohydrate intake.

Pooling Project of cohort studies
No Pooling Project was identified.

Meta-analysis
One meta-analysis (Aune, 2012) was published after the 2010 SLR. It did not support an independent association between diets high in carbohydrate, glycemic index, or glycemic load and colorectal cancer risk. The summary RR for high versus low intake was 0.93 (95% CI: 0.84–1.04, I^2 = 40%) for total carbohydrate.

Table 178 Total carbohydrate and colorectal cancer risk. Number of studies in the CUP SLR

	Number
Studies identified	11 (11 publications)
Studies included in forest plot of highest compared with lowest exposure	10
Studies included in dose-response meta-analysis	10
Studies included in non-linear dose-response meta-analysis	10

Note: Include cohort, nested case-control and case-cohort designs

Table 179 Total carbohydrate and colon cancer risk. Number of studies in the CUP SLR

	Number
Studies identified	11 (13 publications)
Studies included in forest plot of highest compared with lowest exposure	9
Studies included in dose-response meta-analysis	9
Studies included in non-linear dose-response meta-analysis	9

Note: Include cohort, nested case-control and case-cohort designs

Table 180 Total carbohydrate and rectal cancer risk. Number of studies in the CUP SLR

	Number
Studies identified	11 (13 publications)
Studies included in forest plot of highest compared with lowest exposure	9
Studies included in dose-response meta-analysis	9
Studies included in non-linear dose-response meta-analysis	9

Note: Include cohort, nested case-control and case-cohort designs

Table 181 Total carbohydrate and colorectal cancer risk. Summary of the dose-response meta-analysis 2015 SLR (no analysis in 2005 SLR or 2010 SLR).

	2015 SLR
Increment unit used	100g/day
Studies (n)	10
Cases (total number)	7925
RR (95%CI)	1.00(0.89-1.12)
Heterogeneity (I^2, p-value)	48.6%, 0.04

Stratified analysis by sex			
2015 SLR	**Men**		**Women**
Studies (n)	2		7
RR (95%CI)	1.08(0.82-1.44)		0.95(0.83-1.08)
Heterogeneity (I^2, p-value)	72.6%, 0.06		40.6%, 0.12
Stratified analysis by geographic location			
2015 SLR	**Asia**	**Europe**	**North America**
Studies (n)	1	2	7
RR (95%CI)	0.76 (0.49-1.16)	1.20(0.91-1.58)	0.99(0.87-1.12)
Heterogeneity (I^2, p-value)		0%, 0.98	56.4%, 0.03

Table 182 Total carbohydrate and colon cancer risk. Summary of the dose-response meta-analysis 2015 SLR (no analysis in 2005 SLR or 2010 SLR).

	2015 SLR
Increment unit used	100g/day
Studies (n)	9
Cases (total number)	7819
RR (95%CI)	0.99 (0.88-1.10)
Heterogeneity (I^2, p-value)	36.9%, 0.12

Stratified analysis by sex			
2015 SLR	**Men**		**Women**
Studies (n)	2		5
RR (95%CI)	1.08(0.83-1.39)		0.86(0.76-0.98)
Heterogeneity (I^2, p-value)	57.2%, 0.13		0%, 0.69
Stratified analysis by geographic location			
2015 SLR	**Asia**	**Europe**	**North America**
Studies (n)	1	2	6
RR (95%CI)	0.64(0.37-1.11)	1.11(0.84-0.46)	0.99(0.87-1.12)
Heterogeneity (I^2, p-value)		0%, 0.95	48%, 0.09

Table 183 Total carbohydrate and rectal cancer risk. Summary of the dose-response meta-analysis 2015 SLR (no analysis in 2005 SLR or 2010 SLR).

	2015 SLR
Increment unit used	100g/day
Studies (n)	10
Cases (total number)	2727
RR (95%CI)	1.02(0.89-1.17)
Heterogeneity (I^2, p-value)	0%, 0.76

Stratified analysis by sex		
2015 SLR	**Men**	**Women**
Studies (n)	2	6
RR (95%CI)	1.06 (0.76-1.48)	1.03 (0.83-1.27)
Heterogeneity (I^2, p-value)	18.3%, 0.27	0%, 0.58

Stratified analysis by geographic location			
2015 SLR	**Asia**	**Europe**	**North America**
Studies (n)	1	2	6
RR (95%CI)	0.91(0.46-1.78)	0.95(0.55-1.63)	1.03(0.89-1.20)
Heterogeneity (I^2, p-value)		0%, 0.49	0%, 0.51

Table 184 Total carbohydrate and colorectal cancer risk. Results of meta-analyses and pooled analyses of prospective studies published after the 2005 SLR.

Author, Year	Number of cohort studies	Total number of cases	Studies country, area	Outcome	Comparison	RR (95%CI)	P trend	Heterogeneity (I^2, p value)
Meta-analysis								
Aune, 2012	10	12382	North America, Europe and Asia	Colorectal cancer	Highest vs Lowest	0.93 (0.84–1.04)		40%, 0.08
					Per 10 units/day	0.95 (0.84-1.07)		57%, 0.01

Table 185 Total carbohydrate and colorectal cancer risk. Main characteristics of studies included in the CUP SLR dose-response meta-analysis

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Missing data derived for analysis
Sieri, 2015 COL41035 Italy	EPIC, Prospective Cohort, M/W	421/ 47 749 11.7 years	Cancer registry and hospital discharge records	FFQ	Incidence, colorectal cancer	350 vs 237 g/day	1.51 (0.97-2.34) Ptrend:0.10	Sex, alcohol intake, BMI, calcium intake, educational level, energy, folate intake, non-alcohol energy, physical activity, saturated fat intake, smoking status	Distribution of person-years
		314/			Incidence, colon cancer	350 vs 237 g/day	1.20 (0.81-1.79) Ptrend:0.77		
		107/			Incidence, rectal cancer	350 vs 237 g/day	1.14 (0.47-2.78) Ptrend:0.06		
Li, 2011 COL40806 China	SWHS, Prospective Cohort, Age: 40-70 years, W	475/ 73 061 9.1 years	Cancer registry and medical records	Dietary recall	Incidence, colorectal cancer	302.3 vs 242.2 g/day	0.87 (0.66-1.15) Ptrend:0.41	Age, birth year, BMI, educational level, family history of colorectal cancer, HRT use, income, physical activity, total energy	
		188/			Incidence, rectal cancer	302.3 vs 242.2 g/day	1.02 (0.66-1.59) Ptrend:0.76		
		287/			Incidence, colon cancer	302.3 vs 242.2 g/day	0.79 (0.55-1.12) Ptrend:0.20		
Ruder, 2011 COL40896 USA	NIH-AARP, Prospective Cohort, Age: 50-71 years, Retired	2 794/ 292 797	Cancer registry and national health database	FFQ	Incidence, colon cancer	109 vs 71 g/1000 kcal	1.07 (0.95-1.21) Ptrend:0.13	Sex, age at baseline, alcohol consumption, aspirin use, BMI, educational	Intakes in g/1000kcal/day converted to g/day using average energy intake per each
		979/			Incidence, rectal cancer	109 vs 71 g/1000 kcal	1.07 (0.87-1.32) Ptrend:0.82		

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Missing data derived for analysis
								level, energy, history of colon cancer, HRT use, physical activity, race, smoking	quantile
Howarth, 2008 COL40653 USA	MEC, Prospective Cohort, Age: 45-75 years	1 166/ 191 004 8 years	Cancer registry and death certificates	FFQ-quantitative	Incidence, colorectal cancer, men	≥331.2 vs ≤243.8 g/day	1.09 (0.84-1.40) Ptrend:0.603	Age, alcohol intake, BMI, calcium intake, dietary fibre, energy intake, ethnicity, family history of colorectal cancer, folate intake, history of polyps, multivitamin, NSAID use, physical activity, red meat intake, smoking, pack-years, time, vitamin d HRT use	
		920/			Women	≥281.1 vs ≤210.6 g/day	0.71 (0.53-0.95) Ptrend:0.025		
		835/			Incidence, colon cancer, men	≥331.2 vs ≤243.8 g/day	1.10 (0.81-1.49) Ptrend:0.452		
		717/			Women	≥281.1 vs ≤210.6 g/day	0.69 (0.50-0.96) Ptrend:0.038		
		318/			Incidence, rectal cancer, men	≥331.2 vs ≤243.8 g/day	0.98 (0.60-1.59) Ptrend:0.642		
		198/			Women	≥281.1 vs ≤210.6 g/day	0.78 (0.42-1.44) Ptrend:0.337		
Kabat, 2008 COL40722 USA	Women's Health Initiative - Observational study, Prospective Cohort,	1 470/ 158 800 7.8 years	Mail or telephone questionnaires verified by trained physician	FFQ	Incidence, colorectal cancer	≥260.2 vs ≤131.5 g/day	0.89 (0.64-1.25) Ptrend:0.97	Age, BMI, dietary calcium, educational level, energy intake, family history of	
		798/			Incidence, proximal colon cancer	≥260.2 vs ≤131.5 g/day	0.78 (0.49-1.25) Ptrend:0.28		

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Missing data derived for analysis
	W, Postmenopausal	351/	adjudicators		Incidence, distal colon cancer	≥260.2 vs ≤131.5 g/day	0.66 (0.32-1.37) Ptrend:0.93	colorectal cancer, fibre, height, history of diabetes, hormone use, number of cigarettes smoked, observational study participants, physical activity	
		303/			Incidence, rectal cancer	≥260.2 vs ≤131.5 g/day	1.33 (0.62-2.85) Ptrend:0.15		
Larsson, 2007 COL40705 Sweden	SMC, Prospective Cohort, Age: 40-76 years, W	870/ 61 433 15.7 years	Record linkage with cancer registries	FFQ	Incidence, colorectal cancer	≥246 vs ≤210 g/day	1.10 (0.85-1.44) Ptrend:0.45	Age, alcohol consumption, BMI, calcium intake, cereal fibre, date of enrolment, educational level, folate intake, magnesium, red meat intake, total energy intake	Midpoints
		594/			Incidence, colon cancer	≥246 vs ≤210 g/day	1.14 (0.83-1.57) Ptrend:0.64		
		283/			Incidence, rectal cancer	≥246 vs ≤210 g/day	0.94 (0.59-1.50) Ptrend:0.78		
McCarl, 2006 COL40633 USA	IWHS, Prospective Cohort, Age: 55-69 years, W	954/ 35 197 15 years	Seer registry	FFQ	Incidence, colorectal cancer	≥275.6 vs ≤153 g/day	0.79 (0.65-0.97)	Age	Midpoints, distribution of person-years
Michaud, 2005	NHS-HPFS,	1 096/	Self-report,	FFQ	Incidence,	202 vs 110	0.87 (0.68-1.11)	Age, alcohol,	

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Missing data derived for analysis
COL01824 USA	Prospective Cohort, M/W	130 719 20 years	medical record and pathology report reviewed by centrally trained physician		colorectal cancer, women	g/day	Ptrend:0.15	aspirin use, beef, pork or lamb as a main dish, BMI, calcium intake, cereal fibre, family history of colon cancer, folate intake, height, history of endoscopy, pack-years of smoking, physical activity, processed meat	
		858/			Incidence, colon cancer, women	202 vs 110 g/day	0.86 (0.65-1.13) Ptrend:0.14		
		683/			Incidence, colorectal cancer, men	288 vs 182 g/day	1.27 (0.93-1.72) Ptrend:0.11		
		552/			Incidence, colon cancer, men	288 vs 182 g/day	1.21 (0.85-1.71) Ptrend:0.2		
		238/			Incidence, rectal cancer, women	202 vs 110 g/day	0.91 (0.53-1.55) Ptrend:0.78		
		131/			Men	288 vs 182 g/day	1.45 (0.73-2.38) Ptrend:0.34		
Higginbotham, 2004 COL00299 USA	WHS, Prospective Cohort, Age: 45- years, W, nurses	174/ 38 451 7.9 years	Cancer registry	FFQ	Incidence, colorectal cancer	Q5 vs Q1	2.41 (1.10-5.27) Ptrend:0.02	Age, alcohol consumption, BMI, energy-adjusted calcium, energy-adjusted folate, energy-adjusted total fat, energy-adjusted vitamin d, energy adjusted total fibre, family history of specific cancer, history of oral contraceptive use, HRT use,	

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Missing data derived for analysis
								NSAID use, physical activity, smoking habits, total energy	
Terry, 2003 COL00561 Canada	CNBSS, Prospective Cohort, Age: 40-59 years, W	616/ 49 124 810 649 person-years	Breast cancer screening centres	Quantitative FFQ	Incidence, colorectal cancer	≥249 vs ≤142 g/day	1.01 (0.68-1.51) Ptrend:0.66	Age, alcohol consumption, BMI, educational level, energy intake, folic acid intake, hormone replacement therapy, oral contraceptive use, parity, physical activity, red meat intake, smoking habits, study centre, treatment allocation	
		436/			Incidence, colon cancer	≥249 vs ≤142 g/day	1.04 (0.63-1.72) Ptrend:0.80		
		180/			Incidence, rectal cancer	≥249 vs ≤142 g/day	0.98 (0.49-1.97) Ptrend:0.85		

Table 186 Total carbohydrate and colorectal cancer risk. Main characteristics of studies excluded from the CUP SLR dose-response meta-analysis

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Reasons for exclusion
Kato, 1997 CRC00022 USA	New York University Women's Health Study, Prospective Cohort, Age: 34-65 years, W	100/ 14 272 105 044 person-years	Mammography screening program	Semi-quantitative FFQ	Incidence, colorectal cancer	Q 4 vs Q 1	1.21 (0.67-2.17) Ptrend:0.7	Age, educational level, place at enrolment, total calorie Intake	Only used in highest vs lowest analysis
Chyou, 1996 COL00087 USA	HHP, Prospective Cohort, M, Japanese ancestry	330/ 8 006 19 years	Selective service draft registration file	Recall	Incidence, colon cancer	Highest vs Lowest	0.87 (0.67-1.12)	Age	Only used in highest vs lowest analysis
Bostick, 1994 COL00079 USA	IWHS, Prospective Cohort, Age: 55-69 years, W	212/ 35 216 167 447 person-years	Driving license	Semi-quantitative FFQ	Incidence, colon cancer	≥274 vs ≤152 g/day	1.30 Ptrend:0.50	Age, energy Intake, height, parity, total vitamin e Intake, total vitamin e Intake, age, vitamin a supplement	Superseded by McCarl, 2006 COL40633

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Reasons for exclusion
Heilbrun, 1989 COL01555 USA	HHP, Nested Case Control, M	102/ 361 controls 16 years	Cancer registry & hospital surveillance	Recall questionnaire	Incidence, colon cancer			Age	Superseded by Chyou, 1996 COL00087
		60/ 361 controls			Incidence, rectal cancer				
Stemmermann, 1984 COL01232 USA	HHP, Prospective Cohort, Age: 45-68 years, M	106/ 7 074 15 years	Selective service draft registration file	Dietary history questionnaire	Incidence, colon cancer			Age	Superseded by Chyou, 1996 COL00087
		59/			Incidence, rectal cancer				

Figure 324 RR estimates of colorectal cancer by levels of total carbohydrate

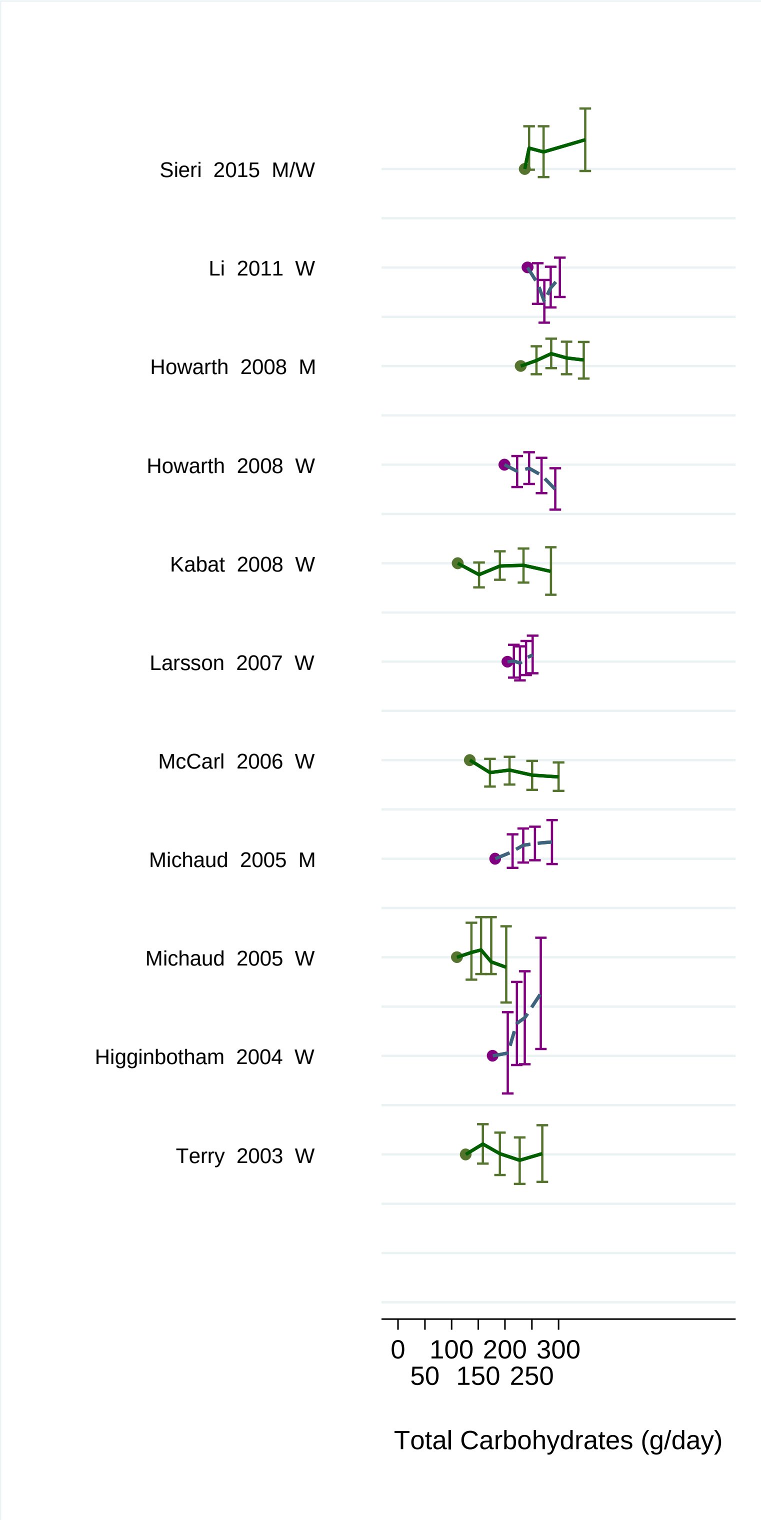


Figure 325 RR (95% CI) of colorectal cancer for the highest compared with the lowest level of total carbohydrate

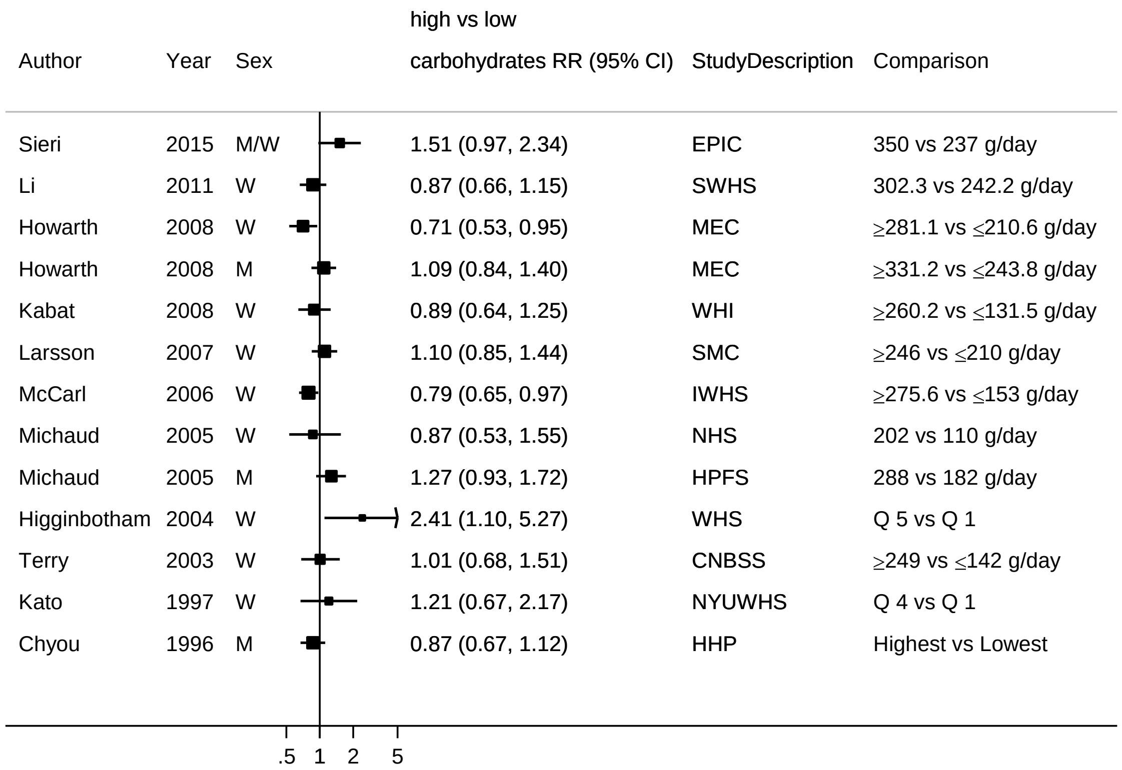


Figure 326 RR (95% CI) of colorectal cancer for 100g/day increase of total carbohydrates

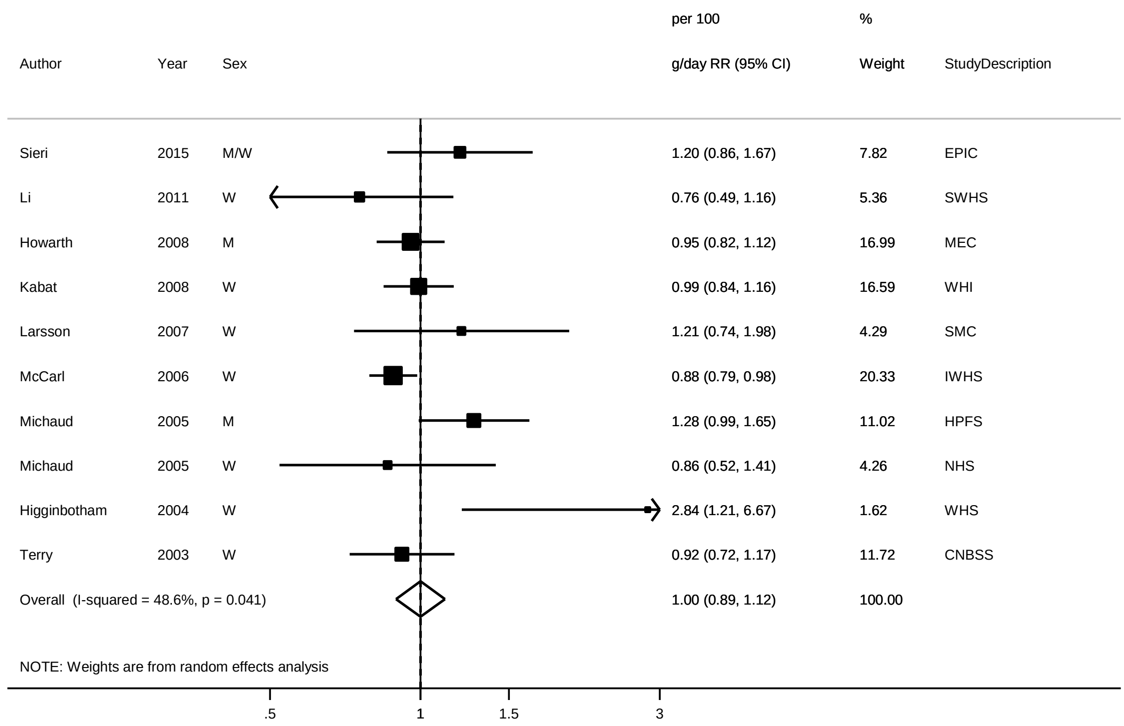


Figure 327 Funnel plot of studies included in the dose response meta-analysis total carbohydrate and colorectal cancer

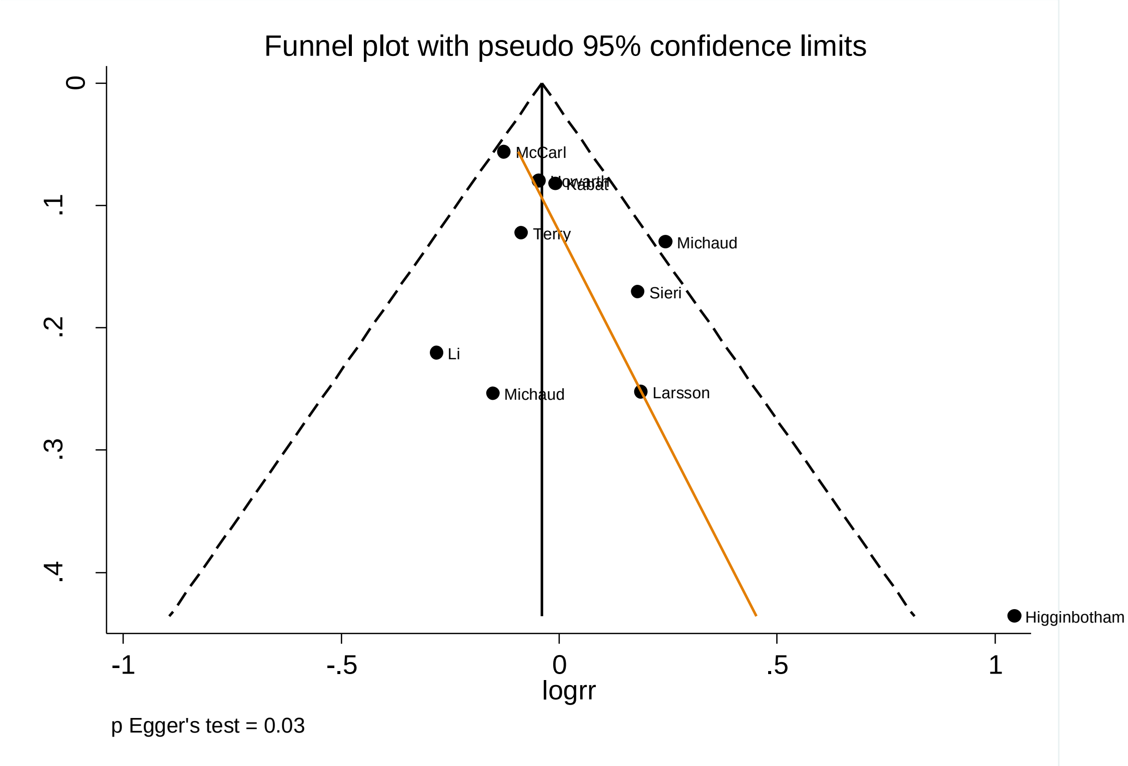


Figure 328 RR (95% CI) of colorectal cancer for 100g/day increase of total carbohydrate by sex

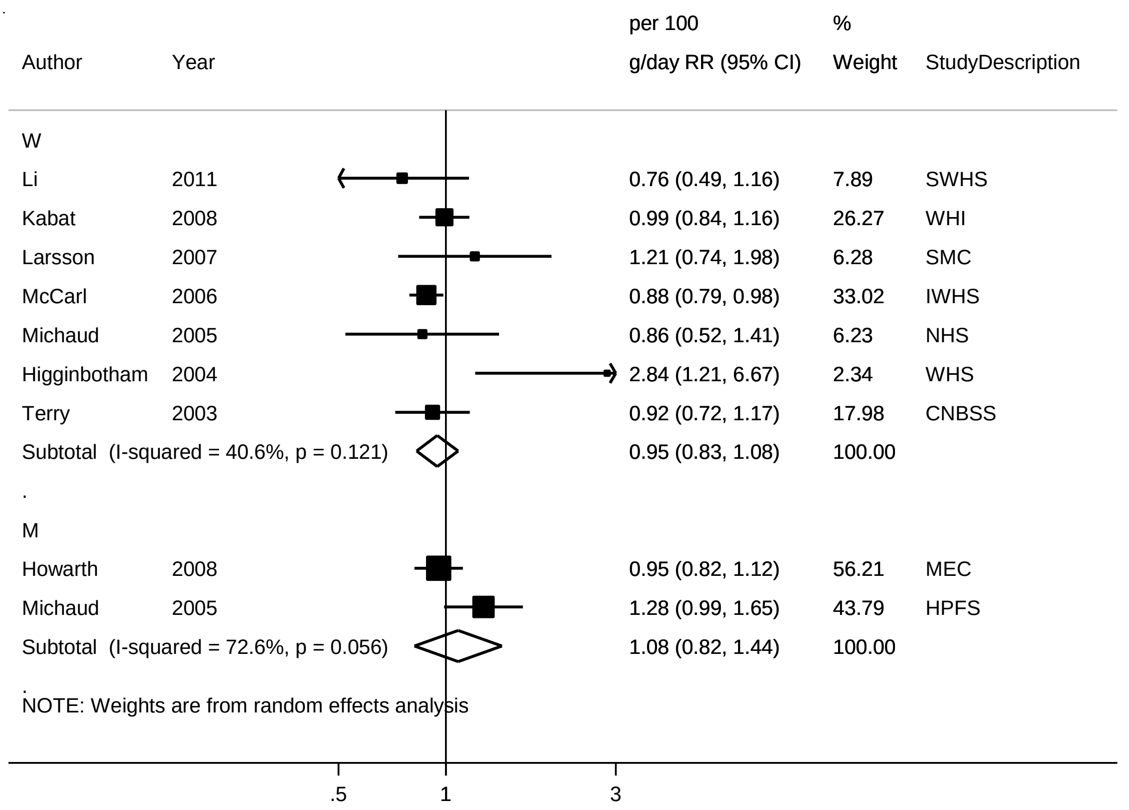


Figure 329 RR (95% CI) of colorectal cancer for 100g/day increase of total carbohydrate by location

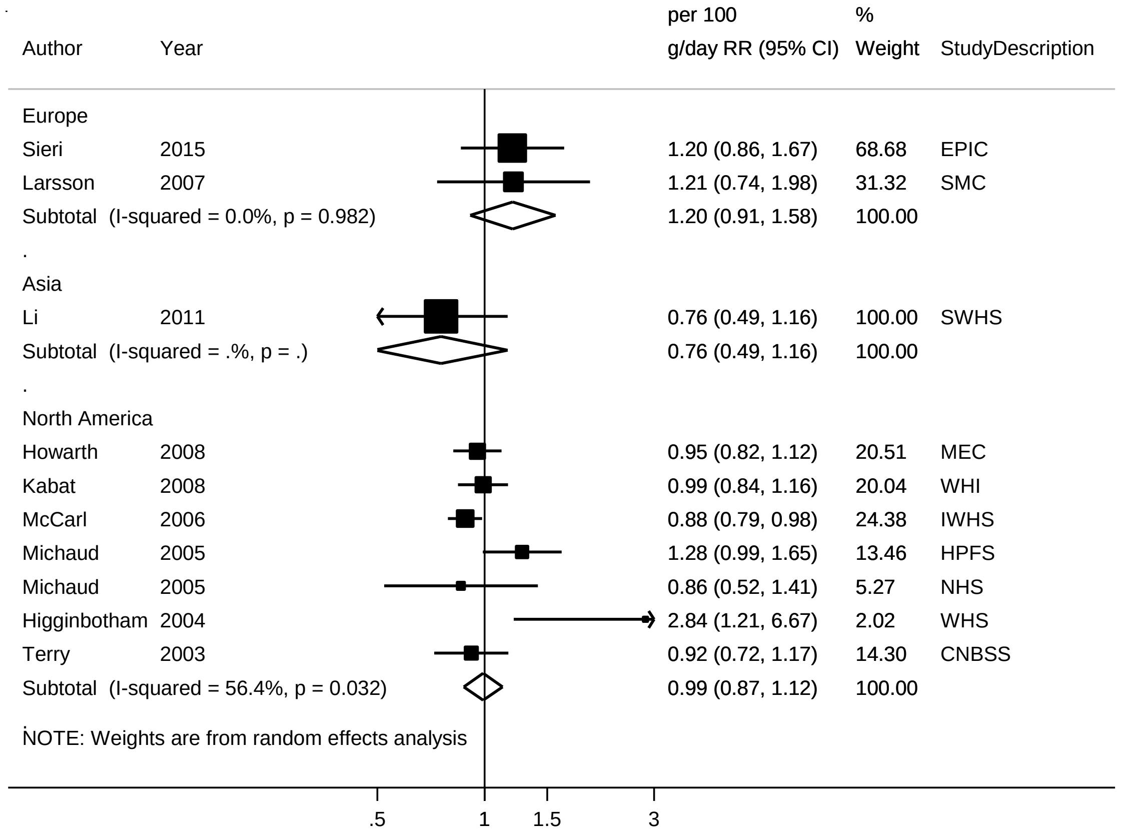


Figure 330 RR estimates of colon cancer by levels of total carbohydrate

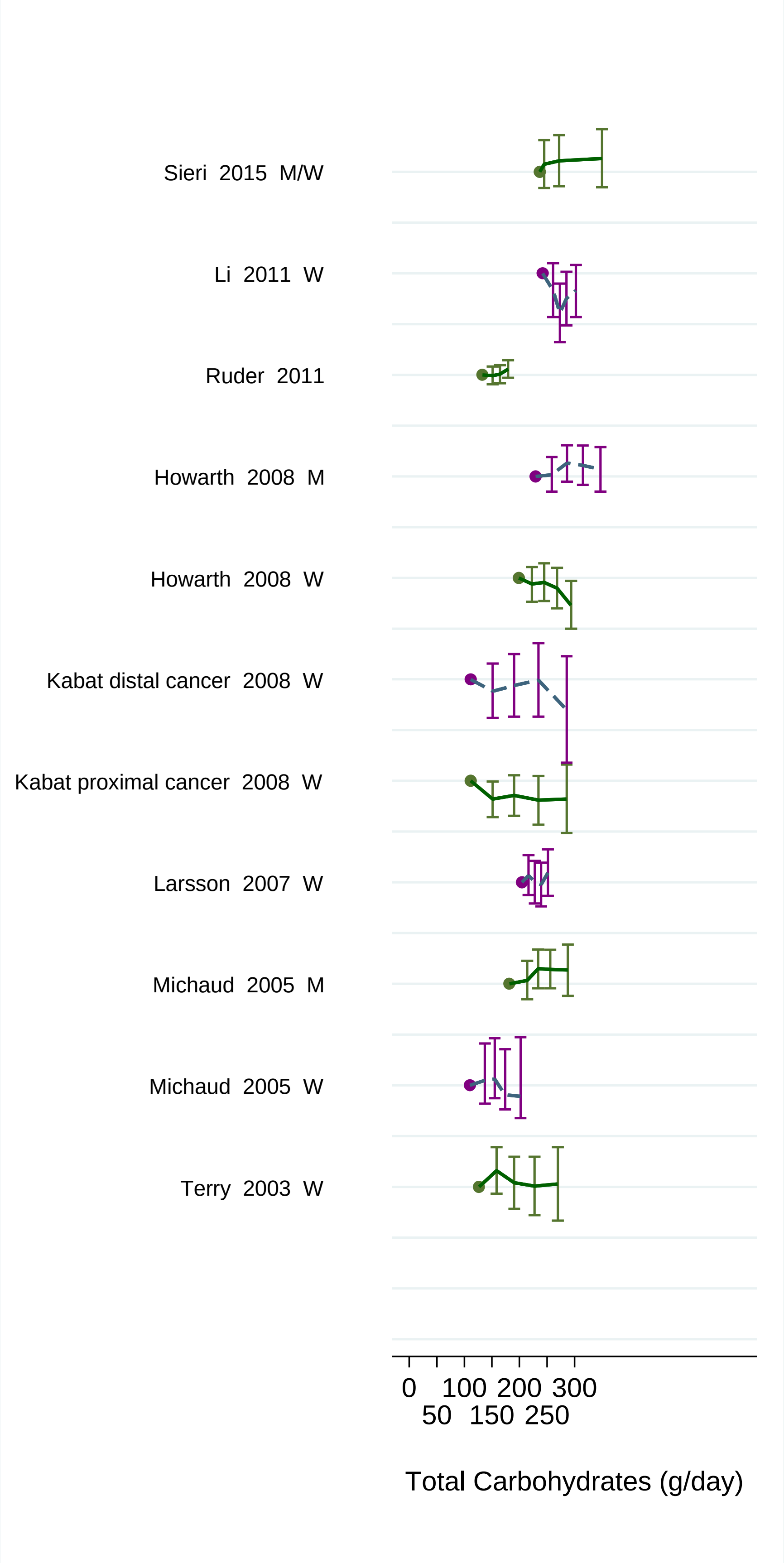


Figure 331 RR (95% CI) of colon cancer for the highest compared with the lowest level of total carbohydrate

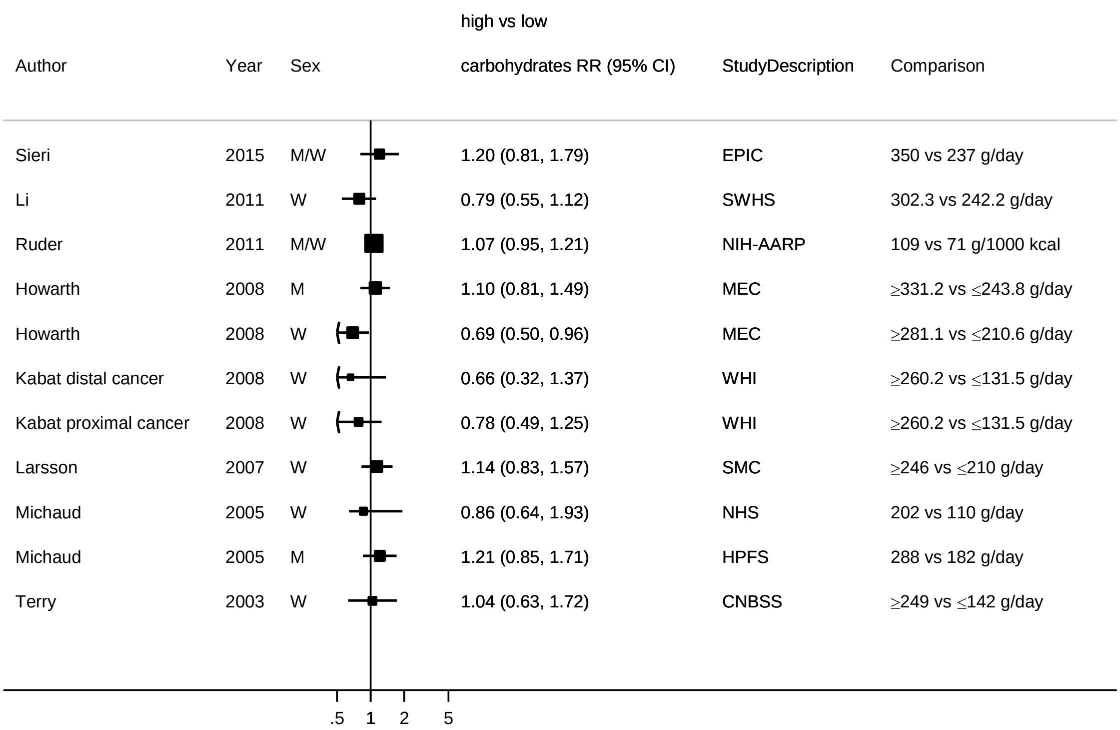


Figure 332RR (95% CI) of colon cancer for 100g/day increase of total carbohydrates

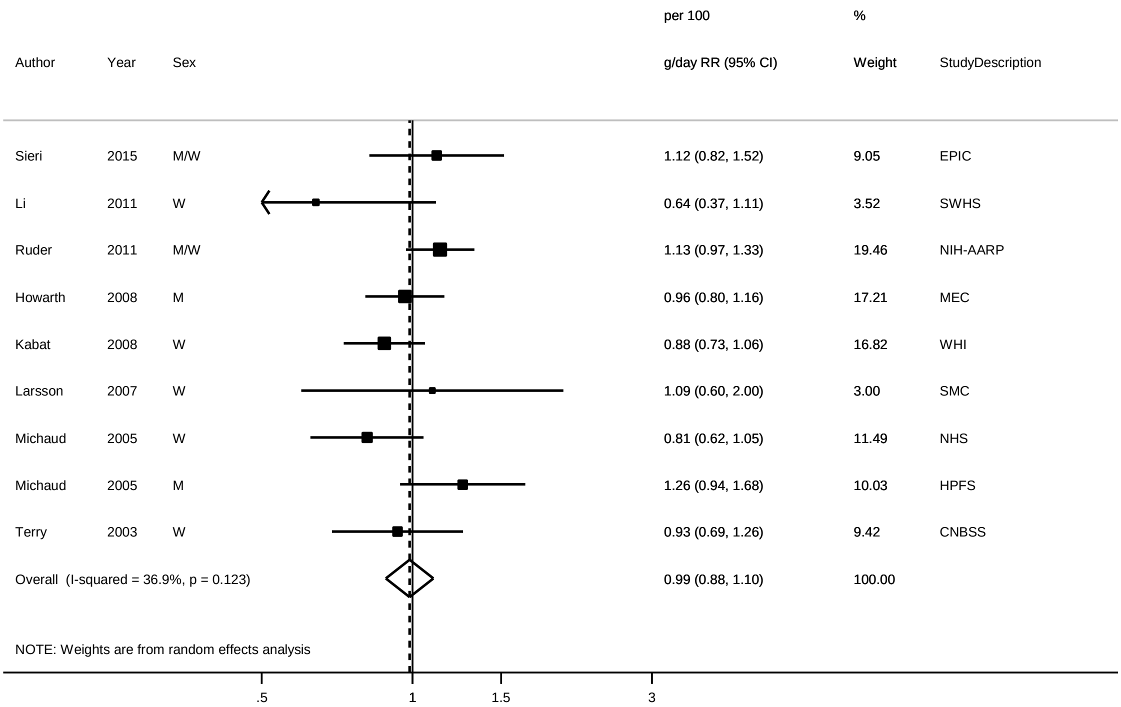


Figure 333 Funnel plot of studies included in the dose response meta-analysis total carbohydrate and colon cancer

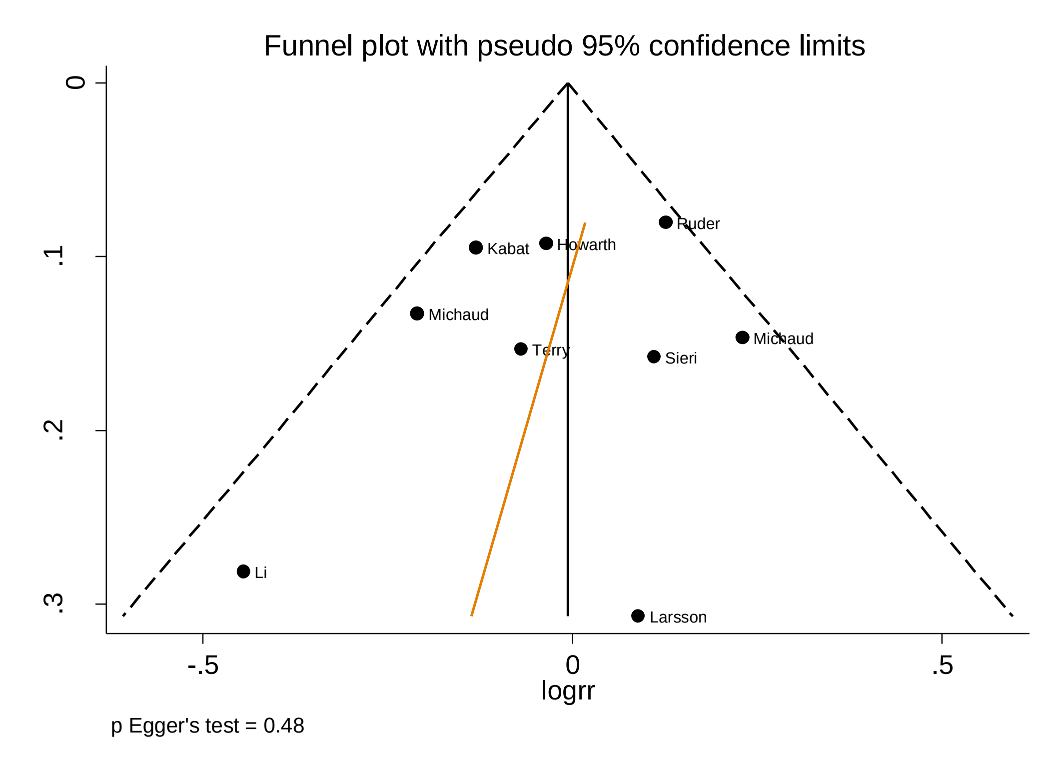


Figure 334 RR (95% CI) of colon cancer for 100g/day increase of total carbohydrates by sex

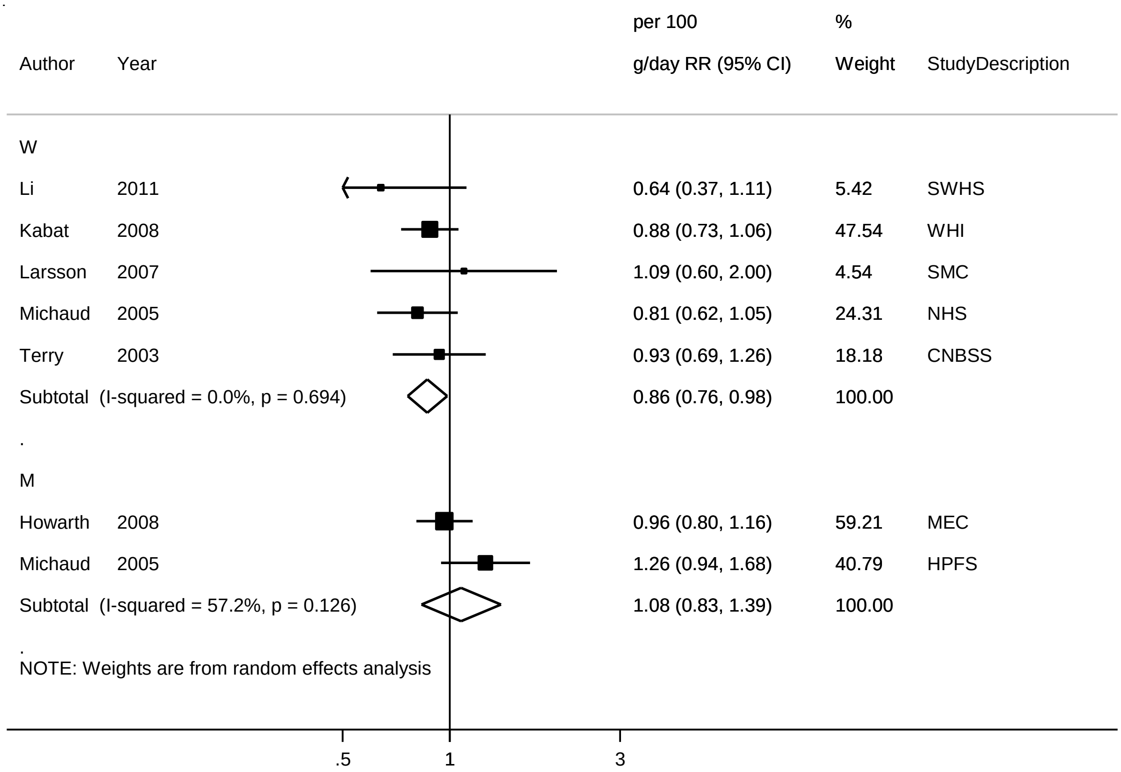


Figure 335 RR (95% CI) of colon cancer for 100g/day increase of total carbohydrates by location

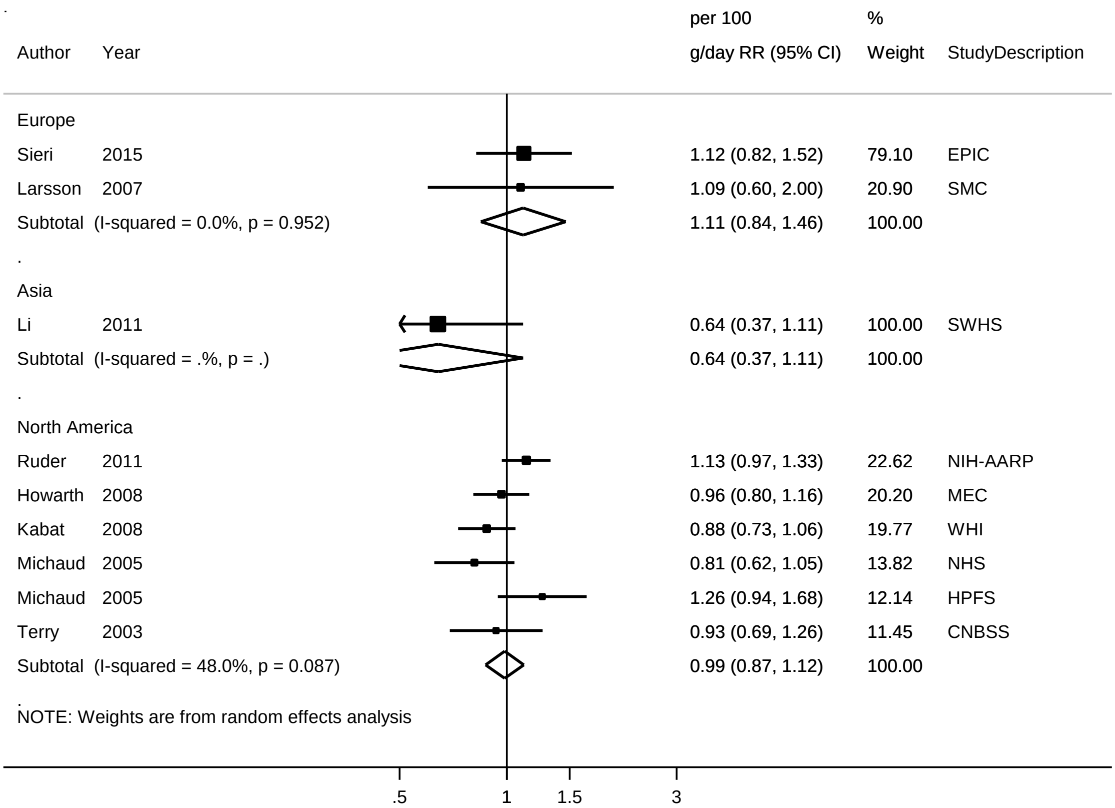


Figure 336 RR estimates of rectal cancer by levels of total carbohydrate

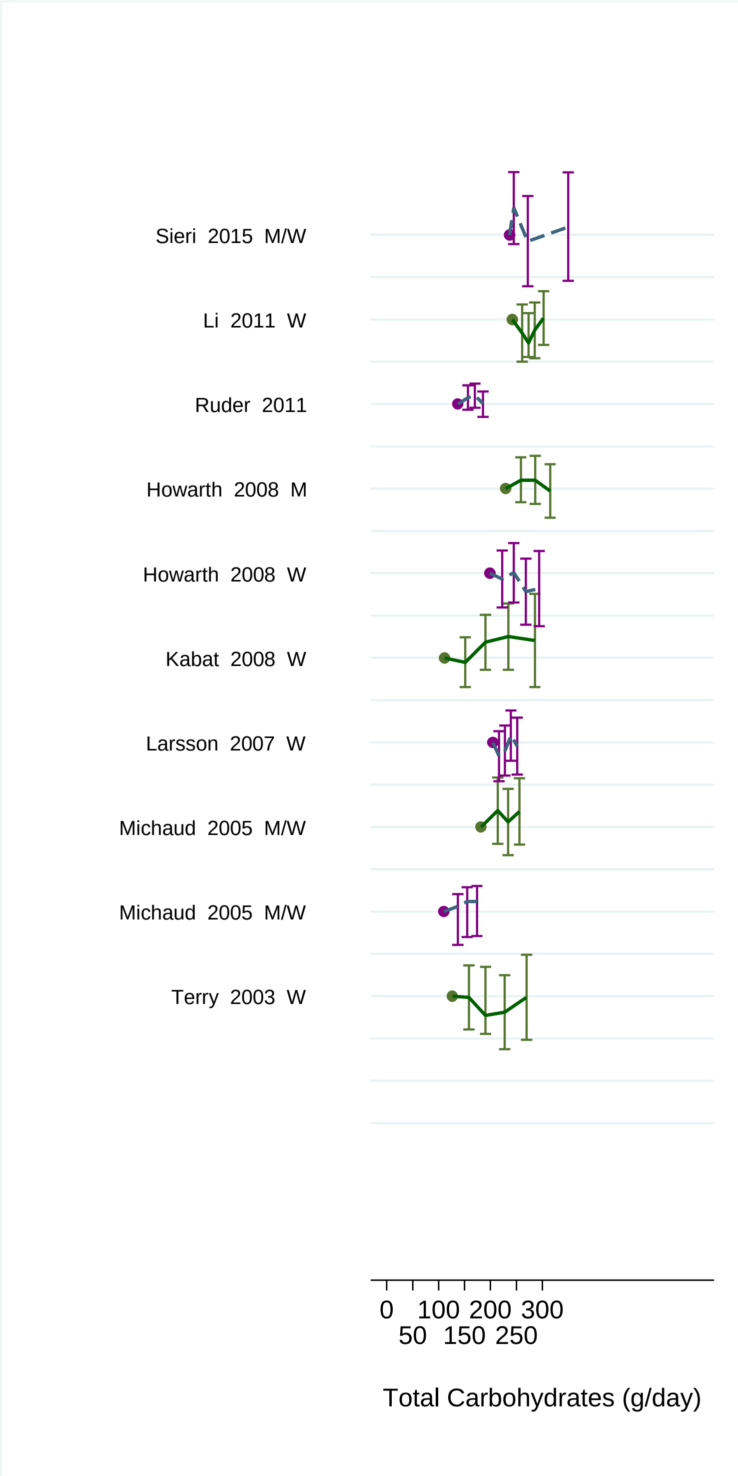


Figure 337 RR (95% CI) of rectal cancer for the highest compared with the lowest level of total carbohydrate

Author	Year	Sex	high vs low carbohydrates RR (95% CI)	StudyDescription	Comparison
Sieri	2015	M/W	1.14 (0.47, 2.78)	EPIC	350 vs 237 g/day
Li	2011	W	1.02 (0.66, 1.59)	SWHS	302.3 vs 242.2 g/day
Ruder	2011	M/W	1.07 (0.87, 1.32)	NIH-AARP	109 vs 71 g/1000 kcal
Howarth	2008	W	0.78 (0.42, 1.44)	MEC	≥281.1 vs ≤210.6 g/day
Howarth	2008	M	0.98 (0.60, 1.59)	MEC	≥331.2 vs ≤243.8 g/day
Kabat	2008	W	1.33 (0.62, 2.85)	WHI	≥260.2 vs ≤131.5 g/day
Larsson	2007	W	0.94 (0.59, 1.50)	SMC	≥246 vs ≤210 g/day
Michaud	2005	W	0.91 (0.50, 1.47)	NHS	202 vs 110 g/day
Michaud	2005	M	1.45 (0.73, 2.38)	HPFS	288 vs 182 g/day
Terry	2003	W	0.98 (0.49, 1.97)	CNBSS	≥249 vs ≤142 g/day

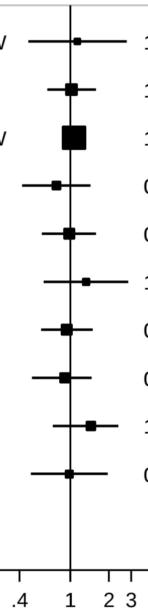


Figure 338 RR (95% CI) of rectal cancer for 100g/day increase of total carbohydrates

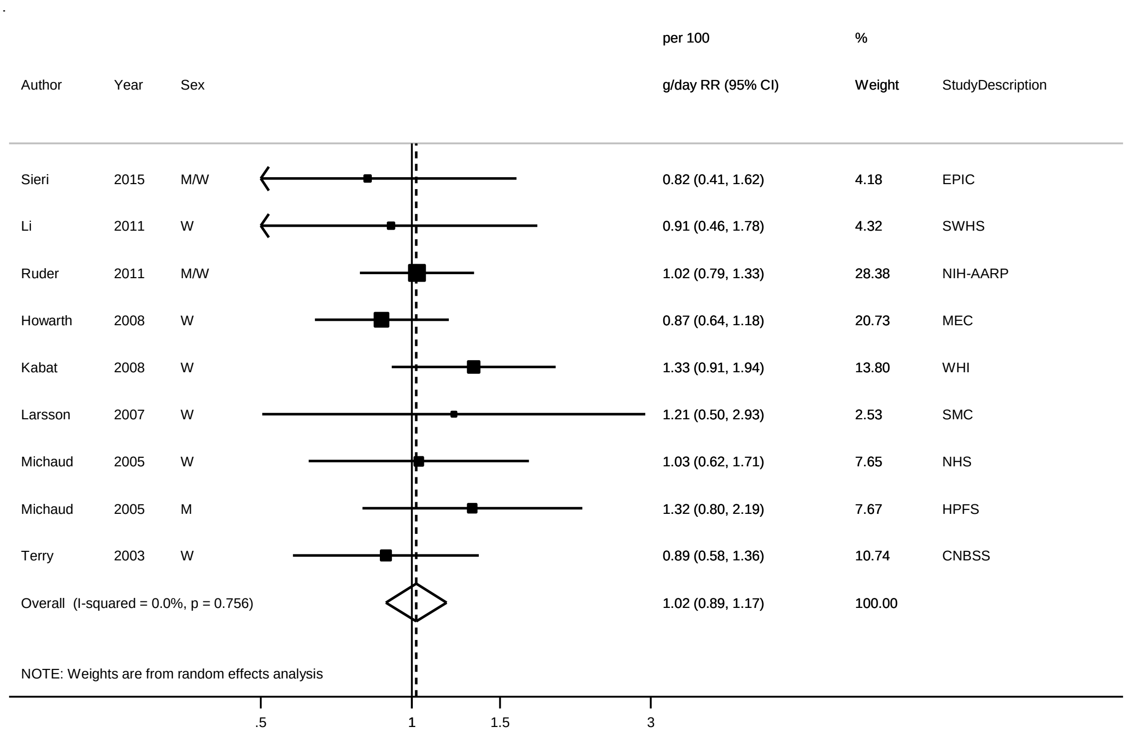


Figure 339 Funnel plot of studies included in the dose response meta-analysis total carbohydrate and rectal cancer

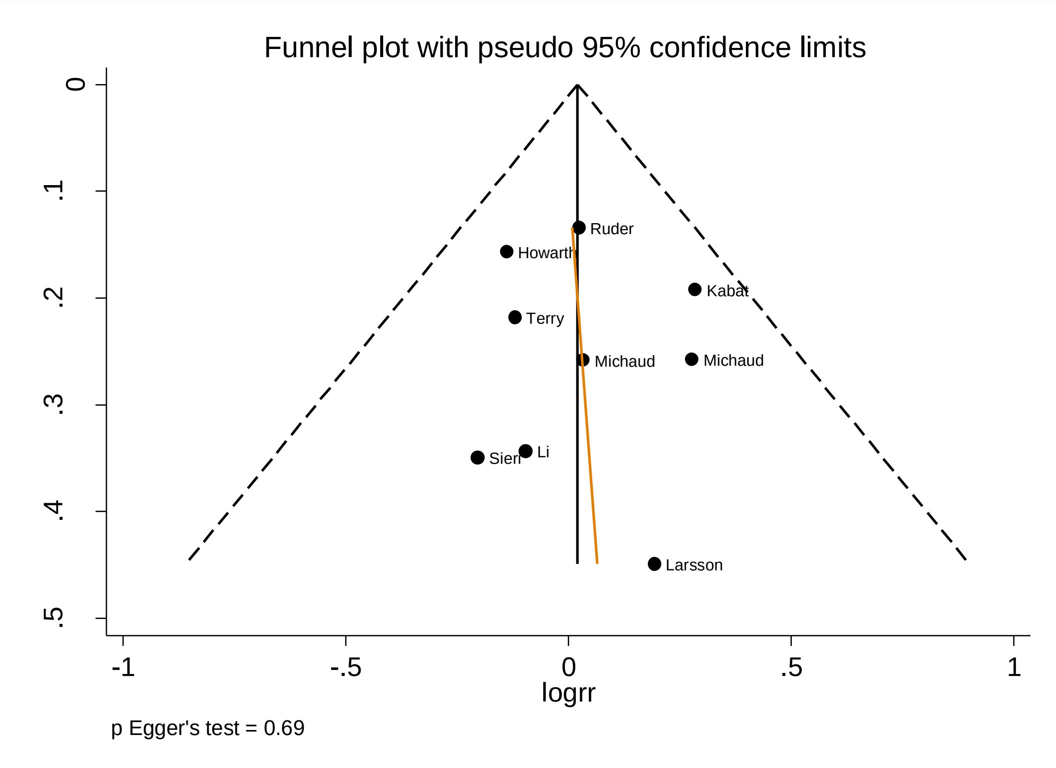


Figure 340 RR (95% CI) of rectal cancer for 100g/day increase of total carbohydrates by sex

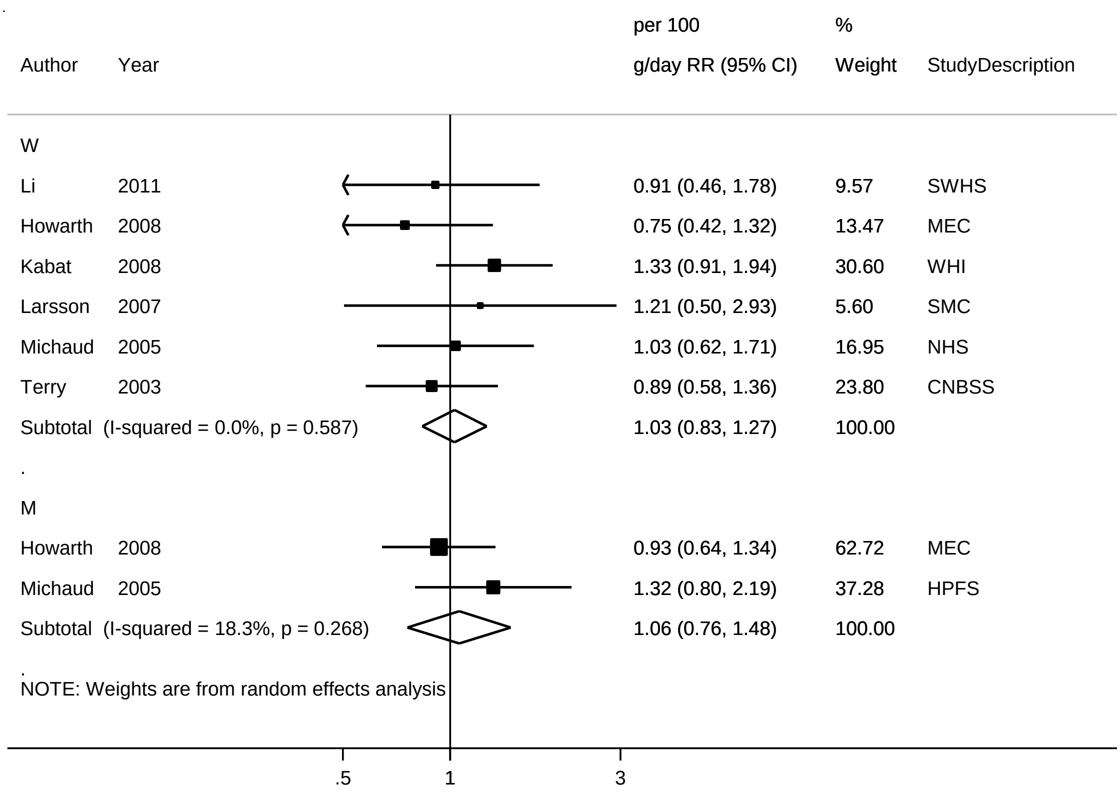
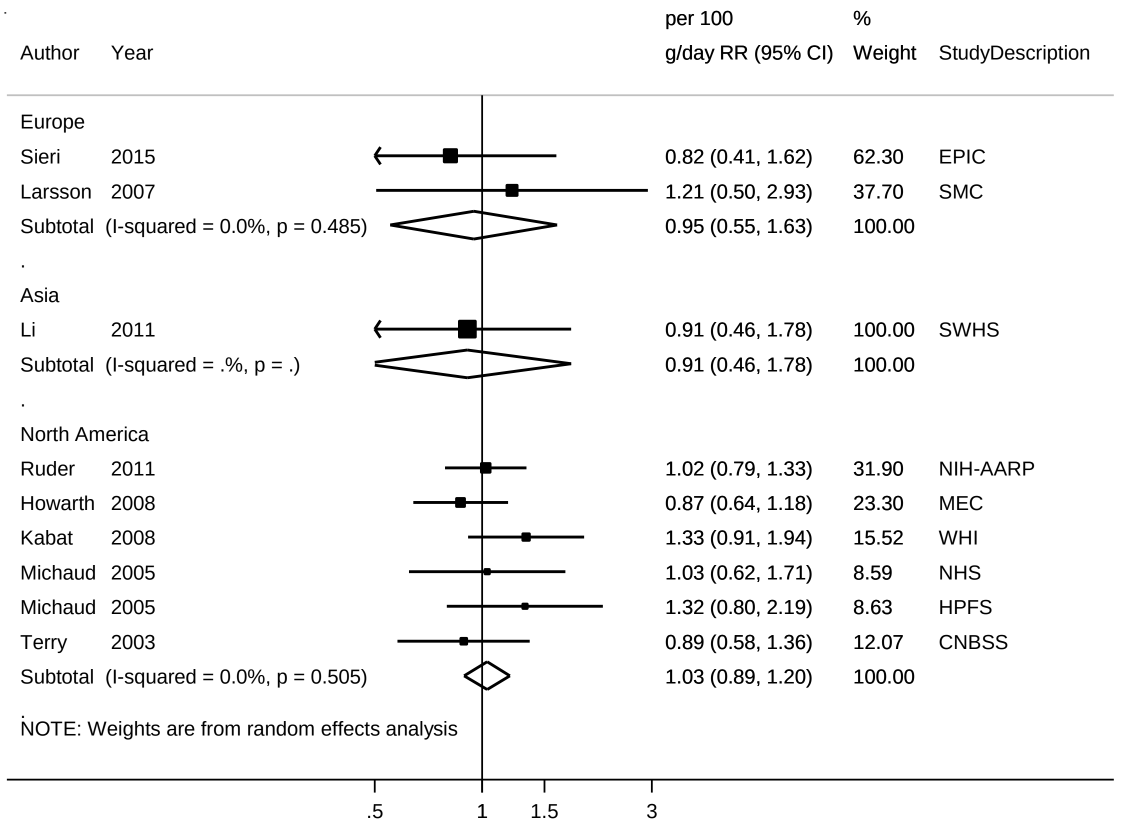


Figure 341 RR (95% CI) of rectal cancer for 100g/day increase of total carbohydrates by location



5.1.5 Glycemic Index

Cohort studies

Summary

Main results:
Three new publications, two new studies and an updated publication of a study identified in 2010 SLR were identified. For distal and proximal colon cancer there was no update since the 2010 SLR.

Colorectal cancer:
Eleven studies (12910 cases) were included in the dose-response meta-analysis of glycemic index and colorectal cancer. A non-significant association with high heterogeneity was observed. Only two studies showed a positive association per 10 units/day (EPIC and NIH-AARP). After stratification by sex or geographic the results remained non-significant. There was evidence of small study bias (p=0.04). There was no evidence of a non-linear association (p=0.17).

Colon cancer:
Eight studies (5800 cases) were included in the dose-response meta-analysis of glycemic index and colon cancer. A non-significant association with low heterogeneity was observed. Only one study showed a positive association per 10 units/day (EPIC). After stratification by sex or geographic the results remained non-significant. There was evidence of small study bias (p=0.76). There was evidence of a non-linear association (p=0.01).

Rectal cancer:
Eight studies (1627 cases) were included in the dose-response meta-analysis of glycemic index and rectal cancer. A non-significant association with no heterogeneity was observed. All studies showed non-significant associations. After stratification by sex or geographic the results remained non-significant. There was evidence of small study bias (p=0.35). There was evidence of a non-linear association (p=0.06).

Study quality:

All studies were fully adjusted for different confounders. Measurement errors in the assessment of dietary intake are known to bias effect estimates; however, none of the studies included in the analysis made any corrections for measurement errors. Assessment of glycemic index or glycemic load are based on their postprandial blood glucose response and are not concentration values of nutrients in the foods consumed. There is some variability in glycemic index measured between studies, ranging from 34 to 89 units.

Pooling Project of cohort studies
No Pooling Project was identified.

Meta-analysis
One meta-analysis (Aune, 2012) was published after the 2010 SLR. It did not support an independent association between diets high in carbohydrate, glycemic index, or glycemic load and colorectal cancer risk. The summary RR for high versus low intake was 1.00 (95% CI: 0.87–1.14, I2 = 31%) for carbohydrate, 1.07 (95% CI: 0.99–1.16, I2 = 28%) for glycemic index, and 1.00 (95% CI: 0.91–1.10, I2 = 39%) for glycemic load. There was a significant positive association between glycemic index and colorectal cancer in studies that adjusted for physical activity, but a non-significant inverse association among studies that did not adjust for physical activity.

Table 187 Glycemic index and colorectal cancer risk. Number of studies in the CUP SLR

	Number
Studies identified	11 (12 publications)
Studies included in forest plot of highest compared with lowest exposure	11
Studies included in dose-response meta-analysis	11
Studies included in non-linear dose-response meta-analysis	11

Note: Include cohort, nested case-control and case-cohort designs

Table 188 Glycemic index and colon cancer risk. Number of studies in the CUP SLR

	Number
Studies identified	8 (9 publications)
Studies included in forest plot of highest compared with lowest exposure	8
Studies included in dose-response meta-analysis	8
Studies included in non-linear dose-response meta-analysis	8

Note: Include cohort, nested case-control and case-cohort designs

Table 189 Glycemic index and rectal cancer risk. Number of studies in the CUP SLR

	Number
Studies identified	8 (9 publications)
Studies included in forest plot of highest compared with lowest exposure	8
Studies included in dose-response meta-analysis	8
Studies included in non-linear dose-response meta-analysis	8

Note: Include cohort, nested case-control and case-cohort designs

Table 190 Glycemic index and colorectal cancer risk. Summary of the dose-response meta-analysis in the 2010 SLR and 2015 SLR.

	2010 SLR	2015 SLR
Increment unit used	10 units/day	10 units/day
Studies (n)	9	11
Cases (total number)	11884	12910
RR (95%CI)	1.07 (0.99-1.06)	1.05(0.95-1.15)
Heterogeneity (I^2, p-value)	44.5%, 0.06	57.4%, 0.009

Stratified analysis by sex		
Men	**2010 SLR**	**2015 SLR**
Studies (n)	3	3
RR (95%CI)	1.09 (0.93-1.27)	1.01(0.83-1.23)
Heterogeneity (I^2, p-value)	48.4%, 0.14	72.0%, 0.02
Women		
Studies (n)	8	9
RR (95%CI)	1.08 (0.98-1.18)	1.05(0.95-1.15)
Heterogeneity (I^2, p-value)	39.6%, 0.12	43.2%, 0.08

Stratified analysis by geographic location (no analysis in 2005 SLR or 2010 SLR)			
2015 SLR	**Asia**	**Europe**	**North America**
Studies (n)	1	3	7
RR (95%CI)	1.01(0.81-1.29)	1.08(0.82-1.41)	1.05(0.94-1.17)
Heterogeneity (I^2, p-value)		59.6%, 0.08	67.0%, 0.006

Table 191 Glycemic index and colon cancer risk. Summary of the dose-response meta-analysis in the 2010 SLR and 2015 SLR.

	2010 SLR	2015 SLR
Increment unit used	10 units/day	10 units/day
Studies (n)	6	8
Cases (total number)	5135	5800
RR (95%CI)	1.05 (0.96-1.14)	1.00(0.90-1.10)
Heterogeneity (I^2, p-value)	5.4%, 0.38	24.2%, 0.23

Stratified analysis by sex		
Men	**2010 SLR**	**2015 SLR**
Studies (n)	2	2
RR (95%CI)	0.84 (0.47-1.49)	0.79(0.52-1.19)
Heterogeneity (I^2, p-value)	85.6%, 0.008	75.3%, 0.04
Women		
Studies (n)	5	6

RR (95%CI)	1.07 (0.97-1.18)	1.03(0.93-1.14)
Heterogeneity (I^2, p-value)	7.1%, 0.37	6.1%, 0.38

Stratified analysis by geographic location (no analysis in 2005 SLR or 2010 SLR)			
2015 SLR	**Asia**	**Europe**	**North America**
Studies (n)	1	3	4
RR (95%CI)	0.96(0.70-1.30)	1.01(0.71-1.43)	1.02 (0.92-1.12)
Heterogeneity (I^2, p-value)		67.7%, 0.05	0%, 0.44

Table 192 Glycemic index and rectal cancer risk. Summary of the dose-response meta-analysis in the 2010 SLR and 2015 SLR.

	2010 SLR	**2015 SLR**
Increment unit used	10 units/day	10 units/day
Studies (n)	6	8
Cases (total number)	1344	1627
RR (95%CI)	1.08(0.93-1.06)	1.10(0.95-1.26)
Heterogeneity (I^2, p-value)	0%, 0.85	0%, 0.92

Stratified analysis by sex		
Men	**2010 SLR**	**2015 SLR**
Studies (n)	2	2
RR (95%CI)	1.29 (0.88-1.89)	1.20(0.72-2.01)
Heterogeneity (I^2, p-value)	19.6%, 0.27	59.3%, 0.12
Women		
Studies (n)	5	6
RR (95%CI)	1.04 (0.88-1.23)	1.08(0.92-1.27)
Heterogeneity (I^2, p-value)	0.0%, 0.89	0.0%, 0.95

Stratified analysis by geographic location (no analysis in 2005 SLR or 2010 SLR)			
2015 SLR	**Asia**	**Europe**	**North America**
Studies (n)	1	3	4
RR (95%CI)	1.11(0.77-1.61)	1.27 (0.94-1.70)	1.04(0.87-1.24)
Heterogeneity (I^2, p-value)		0%, 0.83	0%, 0.81

Table 193 Glycemic index and colorectal cancer risk. Results of meta-analyses and pooled analyses of prospective studies published after the 2005 SLR.

Author, Year	Number of cohort studies	Total number of cases	Studies country, area	Outcome	Comparison	RR (95%CI)	P trend	Heterogeneity (I^2, p value)
Meta-analysis								
Aune, 2012	10	12382	North America, Europe and Asia	Colorectal cancer	Highest vs Lowest	1.07 (0.99–1.16)		28%, 0.19
					Per 10 units/day	1.07 (0.99–1.15)		39%, 0.10

Table 194 Glycemic index and colorectal cancer risk. Main characteristics of studies included in the CUP SLR dose-response meta-analysis

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Missing data derived for analysis
Sieri, 2015 COL41035 Italy	EPIC, Prospective Cohort, M/W	426/ 47 749 11.7 years	Cancer registry and hospital discharge records	FFQ	Incidence, colorectal cancer	56.5 vs 50.4	1.35 (1.03-1.78) Ptrend:0.031	Sex, alcohol intake, BMI, calcium intake, educational level, energy, folate intake, non-alcohol energy, physical activity, saturated fat intake, smoking status	Distribution of person-years
		314/			Incidence, colon cancer	56.5 vs 50.4	1.37 (1.00-1.88) Ptrend:0.047		
		241/			Incidence, colorectal cancer, whr ≥ 0.83	56.5 vs 50.4	1.69 (1.15-2.46) Ptrend:0.011		
		167/			Whr < 0.83	56.5 vs 50.4	0.99 (0.64-1.52) Ptrend:0.996		
		122/			Incidence, proximal colon cancer	56.5 vs 50.4	1.38 (0.92-2.07) Ptrend:0.199		
					Incidence, distal colon cancer	56.5 vs 50.4	1.36 (0.83-2.25) Ptrend:0.199		
		107/			Incidence, rectal cancer	56.5 vs 50.4	1.34 (0.76-2.34) Ptrend:0.341		
Li, 2011 COL40806 China	SWHS, Prospective Cohort, Age: 40-70 years, W	475/ 73 061 9.1 years	Cancer registry and medical records	Dietary recall	Incidence, colorectal cancer	76 vs 64.4	1.09 (0.81-1.46) Ptrend:0.86	Age, birth year, BMI, educational level, family history of colorectal cancer, hormone use, Income,	
		287/			Incidence, colon cancer	76 vs 64.4	1.05 (0.71-1.54) Ptrend:0.77		
		188/			Incidence, rectal	76 vs 64.4	1.16 (0.73-1.84)		

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Missing data derived for analysis
					cancer		Ptrend:0.53	physical activity, total energy	
Bao, 2010 COL40837 USA	NHS+HPFS, Prospective Cohort, M/W	1 420/ 132 886	Self reported/death certificate/ medical records	FFQ	Incidence, colorectal cancer, women	46 vs 34	0.95 (0.79-1.13) Ptrend:0.22	Age, alcohol intake, aspirin use, BMI, endoscopy, energy intake, family history of colorectal cancer, history of polyps or colitis, multivitamin supplement intake, physical activity, smoking	
		1 067/			Incidence, colon cancer, women	46 vs 34	0.93 (0.75-1.15) Ptrend:0.13		
		1 061/			Incidence, colorectal cancer, men	47 vs 34	0.92 (0.74-1.15) Ptrend:0.41		
		694/			Incidence, colon cancer, men	47 vs 34	0.88 (0.67-1.16) Ptrend:0.44		
		323/			Incidence, rectal cancer, women	46 vs 34	1.14 (0.79-1.66) Ptrend:0.50		
		222/			Men	47 vs 34	1.05 (0.65-1.69) Ptrend:0.95		
George, 2009 COL40791 USA	NIH-AARP, Prospective Cohort, Age: 50-71 years, M/W	3 031/ 446 177 8 years	Cancer registry	FFQ	Incidence, colorectal cancer, men	57.02-84.13 vs 33.51-51.26	1.16 (1.04-1.30)	Age, sex, alcohol intake, BMI, educational level, ethnicity, family history of cancer, marital status, physical activity, smoking status, total energy intake	Midpoints, distribution of person-years and cases

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Missing data derived for analysis
		1 457/			Women	56.56-83.94 vs 33.61-50.43	1.16 (0.98-1.37)		
Kabat, 2008 COL40722 USA	Women's Health Initiative - Observational study, Prospective Cohort, W, Postmenopausal	1 470/ 158 800 7.8 years	Mail or telephone questionnaires verified by trained physician adjudicators	FFQ	Incidence, colorectal cancer	≥55.5 vs ≤49.3	1.10 (0.92-1.32) Ptrend:0.27	Age, BMI, dietary calcium, educational level, energy intake, family history of colorectal cancer, fibre, height, history of diabetes, hormone use, number of cigarettes smoked, observational study participants, physical activity	
		798/			Incidence, proximal colon cancer	≥55.5 vs ≤49.3	1.17 (0.90-1.51) Ptrend:0.45		
		351/			Incidence, distal colon cancer	≥55.5 vs ≤49.3	0.95 (0.64-1.41) Ptrend:0.9		
		303/			Incidence, rectal cancer	≥55.5 vs ≤49.3	1.07 (0.71-1.62) Ptrend:0.35		
Weijenberg, 2008 COL40686 Netherlands	NLCS, Case Cohort, Age: 55-69 years, M/W	1 082/ 120 852 11.3 years	Cancer registry and database of pathology reports	Semi-quantitative FFQ	Incidence, colorectal cancer, men	64.5 vs 56.6	0.81 (0.61-1.08) Ptrend:0.27	Age, alcohol, BMI, calcium intake, educational level, family history of colon cancer, physical activity, processed meat, smoking status, total energy intake	

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Missing data derived for analysis
		755/			Women	61.9 vs 53.7	1.20 (0.85-1.67) Ptrend:0.53		
		674/			Incidence, colon cancer, men	64.5 vs 56.6	0.64 (0.46-0.89) Ptrend:0.01		
		551/			Women	61.9 vs 53.7	1.34 (0.91-1.96) Ptrend:0.22		
		361/			Incidence, distal colon cancer, men	64.5 vs 56.6	0.58 (0.38-0.89) Ptrend:0.03		
		313/			Incidence, proximal colon cancer, men	64.5 vs 56.6	0.71 (0.45-1.12) Ptrend:0.1		
		310/			Women	61.9 vs 53.7	1.40 (0.87-2.24) Ptrend:0.08		
		280/			Incidence, rectal cancer, men	64.5 vs 56.6	1.38 (0.85-2.23) Ptrend:0.08		
		241/			Incidence, distal colon cancer, women	61.9 vs 53.7	1.18 (0.69-1.99) Ptrend:0.80		
		138/			Incidence, rectal cancer, women	61.9 vs 53.7	1.01 (0.52-1.98) Ptrend:0.81		
Larsson, 2007 COL40705 Sweden	SMC, Prospective Cohort, Age: 40-76 years, W	870/ 61 433 15.7 years	Record linkage with cancer registries	FFQ	Incidence, colorectal cancer	≥83.4 vs ≤75.7	1.00 (0.75-1.33) Ptrend:0.55	Age, alcohol consumption, BMI, calcium intake, cereal fibre, date of enrolment, educational	Midpoints
		594/			Incidence, colon cancer	≥83.4 vs ≤75.7	0.84 (0.60-1.18) Ptrend:0.21		
		297/			Incidence,	≥83.4 vs ≤75.7	1.95 (1.19-3.20)		

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Missing data derived for analysis
					colorectal cancer		Ptrend:0.01	level, folate intake, magnesium, red meat intake, total energy intake	
		286/			Incidence, proximal colon cancer	≥83.4 vs ≤75.7	0.97 (0.58-1.63) Ptrend:0.41		
		283/			Incidence, rectal cancer	≥83.4 vs ≤75.7	1.32 (0.80-2.17) Ptrend:0.62		
		210/				≥83.4 vs ≤75.7	0.81 (0.46-1.40) Ptrend:0.25		
					Incidence, colorectal cancer	≥83.4 vs ≤75.7	1.70 (0.93-3.11) Ptrend:0.04		
						≥83.4 vs ≤75.7	1.58 (0.88-2.85)		
Strayer, 2007 COL40678 USA	BCDDP, Prospective Cohort, Age: 62 years, W	490/ 45 561 8.5 years	Self-report, cancer registry, death report	FFQ	Incidence, colorectal cancer	55 vs 42.8	0.75 (0.56-1.00) Ptrend:0.03	Age, BMI, calcium intake, energy intake, health screening, HRT use, NSAID use, smoking status	
		183/			BMI-normal, phy act-high	55 vs 42.8	1.00 (0.60-1.67) Ptrend:0.71		
		114/			BMI-overwt, phy act-high	55 vs 42.8	0.62 (0.36-1.07) Ptrend:0.13		
		113/			BMI-normal, phy act-low	55 vs 42.8	0.77 (0.42-1.44) Ptrend:0.42		
		80/			BMI-overwt, phy act-low	55 vs 42.8	0.47 (0.22-1.01) Ptrend:0.06		
						per 1 unit	0.98 (0.96-1.00)	Fibre intake	
McCarl, 2006 COL40633 USA	IWHS, Prospective Cohort,	954/ 35 197 15 years	Seer registry	FFQ	Incidence, colorectal cancer	≥89.4 vs ≤80.9	1.08 (0.88-1.32) Ptrend:0.15	Age, BMI, diabetes, energy intake,	Midpoints, distribution of person-years

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Missing data derived for analysis
	Age: 55-69 years, W	362/			BMI 25-30	≥89.4 vs ≤80.9	0.85 (0.60-1.18) Ptrend:0.59	multivitamin supplement intake, physical activity, smoking, pack-years, waist to hip ratio	
		323/			BMI < 25	≥89.4 vs ≤80.9	0.94 (0.66-1.33) Ptrend:0.57		
		291/			Incidence, colon cancer, BMI 25-30	≥89.4 vs ≤80.9	0.93 (0.64-1.34) Ptrend:0.82		
		269/			Incidence, colorectal cancer, BMI ≥30	≥89.4 vs ≤80.9	1.66 (1.13-2.43) Ptrend:0.02		
		250/			Incidence, colon cancer, BMI < 25	≥89.4 vs ≤80.9	1.03 (0.70-1.51) Ptrend:0.23		
		228/			Incidence, colorectal cancer, no diabetes & BMI ≥30	≥89.4 vs ≤80.9	1.82 (1.20-2.76) Ptrend:<0.01		
		216/			Incidence, colon cancer, BMI ≥30	≥89.4 vs ≤80.9	1.45 (0.96-2.19) Ptrend:0.21		
		184/			No diabetes & BMI ≥30	≥89.4 vs ≤80.9	1.60 (1.02-2.51) Ptrend:0.07		
		77/			Incidence, rectal cancer, BMI 25-30	≥89.4 vs ≤80.9	0.58 (0.25-1.33) Ptrend:0.12		
		76/			BMI < 25	≥89.4 vs ≤80.9	0.52 (0.22-1.23) Ptrend:0.16		

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Missing data derived for analysis
		56/			BMI >=30	≥89.4 vs ≤80.9	3.34 (1.09-10.20) Ptrend:0.02		
		47/			No diabetes & BMI ≥30	≥89.4 vs ≤80.9	4.22 (1.19-14.90) Ptrend:0.01		
Higginbotham, 2004 COL00299 USA	WHS, Prospective Cohort, Age: 45- years, W, nurses	174/ 38 451 7.9 years	Cancer registry	FFQ	Incidence, colorectal cancer	per 1 unit/day	1.05 (1.00-1.11)	Age, alcohol consumption, BMI, energy-adjusted calcium, energy-adjusted folate, energy-adjusted total fat, energy-adjusted vitamin d, energy adjusted total fibre, family history of specific cancer, history of oral contraceptive use, HRT use, NSAID use, physical activity, smoking habits, total energy	
						57 vs 49	1.71 (0.98-2.98) Ptrend:0.04		

Table 195 Glycemic index and colorectal cancer risk. Main characteristics of studies excluded from the CUP SLR dose-response meta-analysis

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Reasons for exclusion
Michaud, 2005 COL01824 USA	NHS-HPFS, Prospective Cohort, M/W	1 096/ 130 719 20 years	Self-report, medical record and pathology report reviewed by centrally trained physician	FFQ	Incidence, colorectal cancer, women	81 vs 65	1.08 (0.87-1.34) Ptrend:0.27	Age, alcohol, aspirin use, beef, pork or lamb as a main dish, BMI, calcium intake, cereal fibre, family history of colon cancer, folate intake, height, history of endoscopy, pack-years of smoking, physical activity, processed meat	Superseded by Bao, 2010 COL40837
		858/			Incidence, colon cancer, women	81 vs 65	1.06 (0.83-1.36) Ptrend:0.29		
		683/			Incidence, colorectal cancer, men	82 vs 69	1.14 (0.88-1.48) Ptrend:0.33		
		552/			Incidence, colon cancer, men	82 vs 69	1.13 (0.84-1.51) Ptrend:0.40		
		403/			Incidence, proximal colon cancer, women	81 vs 65	1.11 (0.77-1.58) Ptrend:0.27		
		326/			Incidence, distal colon cancer, women	81 vs 65	0.91 (0.63-1.34) Ptrend:0.82		
		238/			Incidence, rectal cancer, women	81 vs 65	1.14 (0.73-1.78) Ptrend:0.7		
		228/			Incidence, distal colon cancer, men	82 vs 69	1.06 (0.67-1.68) Ptrend:0.91		
		227/			Incidence, proximal colon cancer, men	82 vs 69	0.99 (0.63-1.57) Ptrend:0.72		
		131/			Incidence, rectal cancer, men	82 vs 69	1.21 (0.68-2.15) Ptrend:0.65		

Figure 342 RR estimates of colorectal cancer by levels of glycemic index

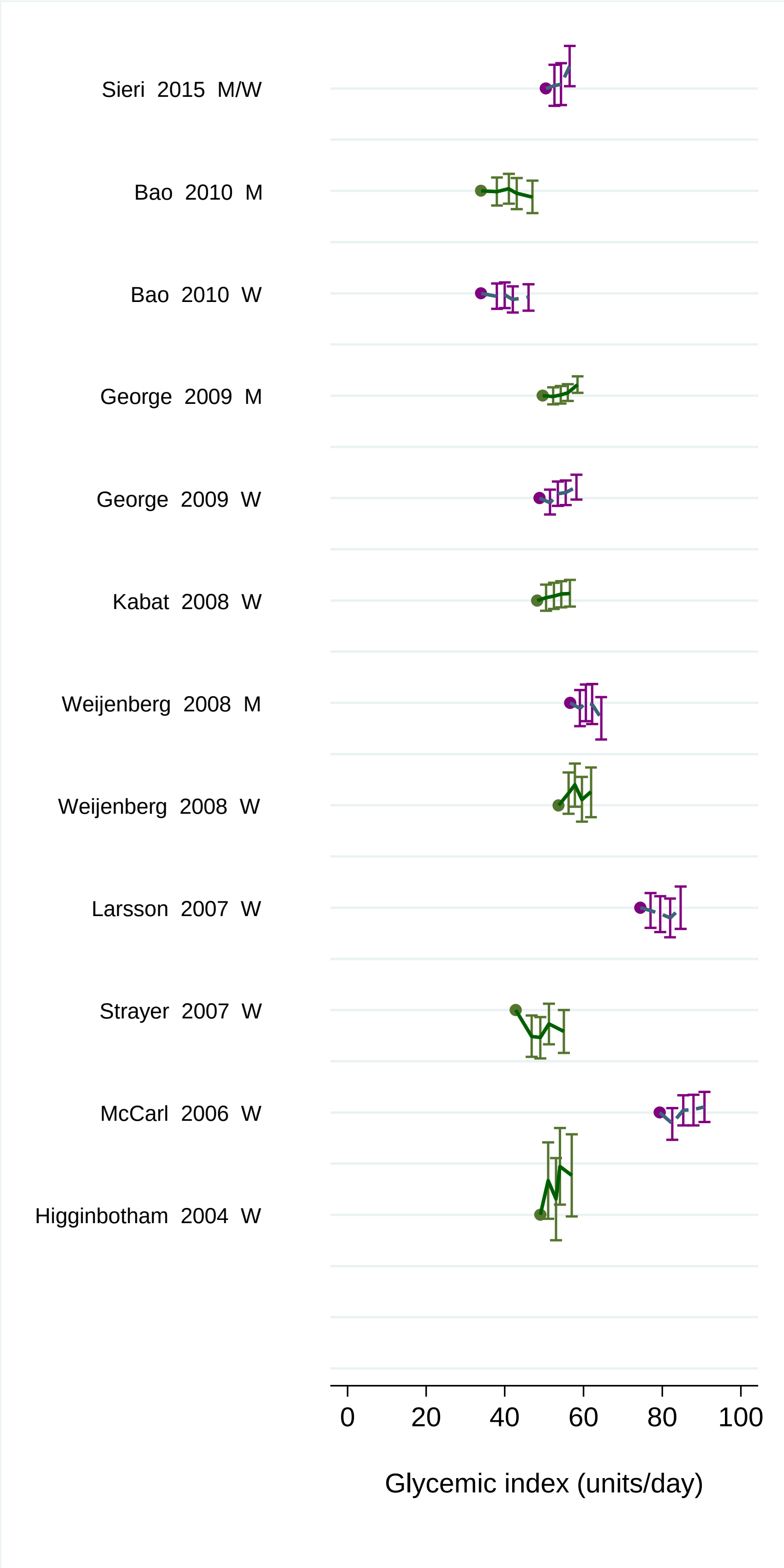


Figure 343 RR (95% CI) of colorectal cancer for the highest compared with the lowest level of glycemic index

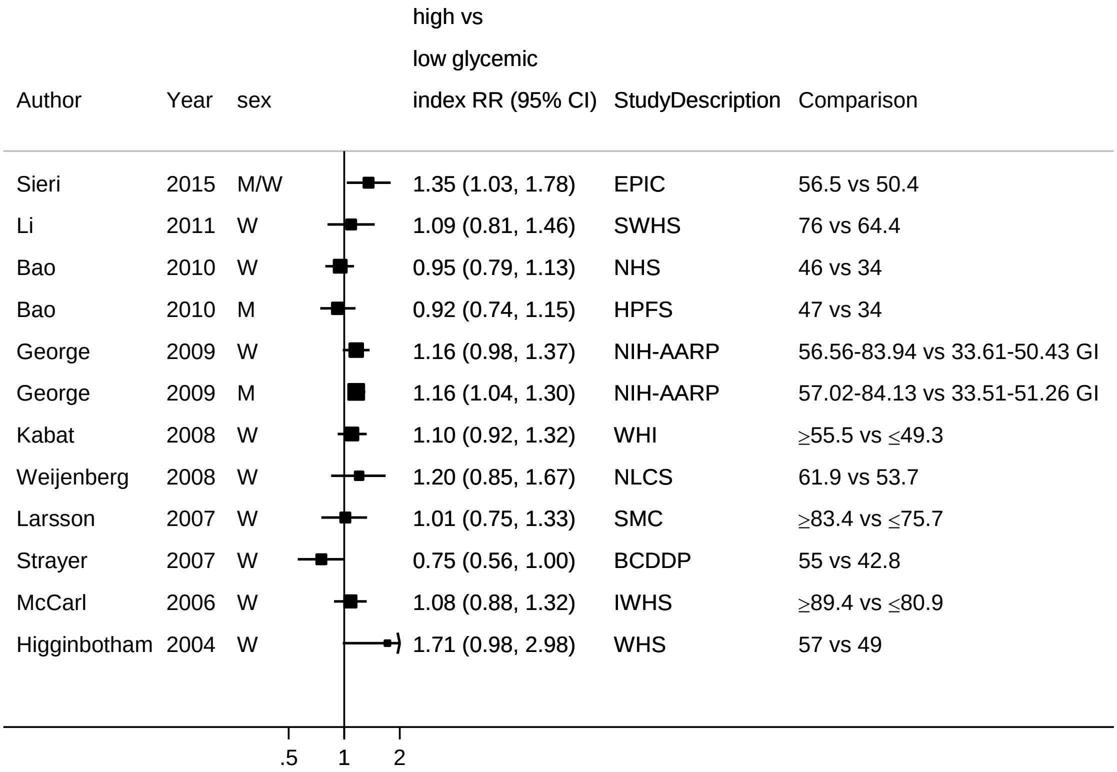


Figure 344 RR (95% CI) of colorectal cancer for 10units/day increase of glycemic index

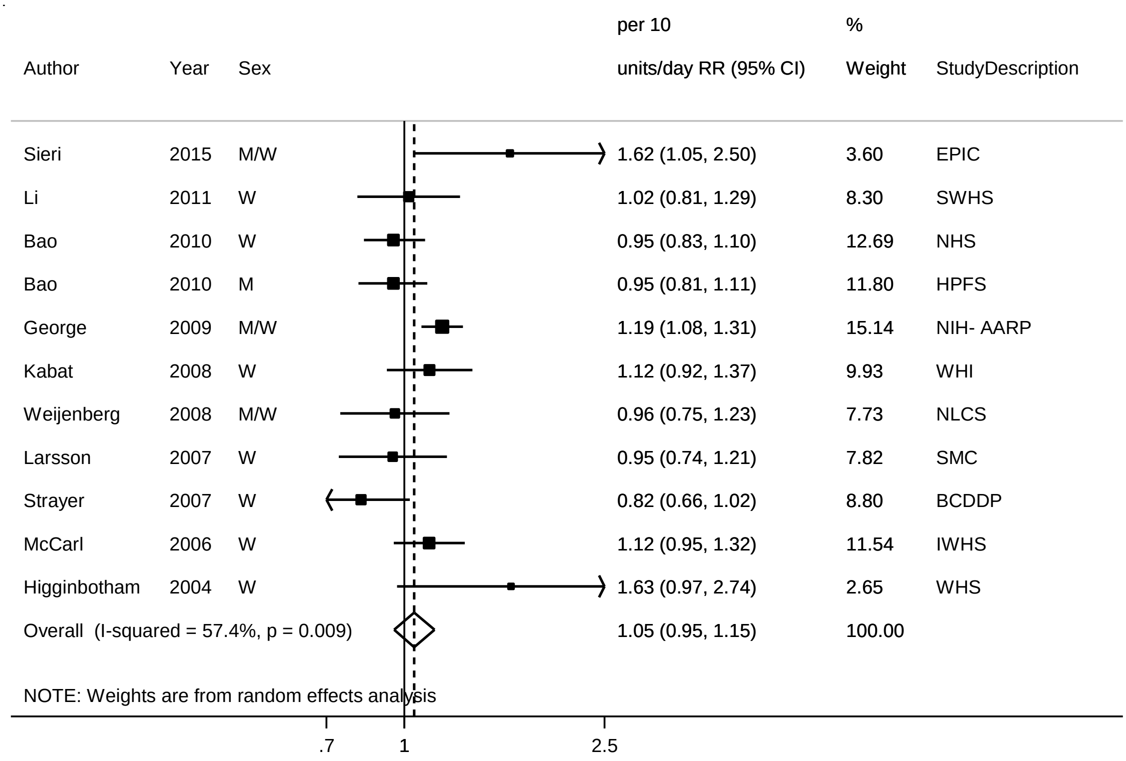


Figure 345 Funnel plot of studies included in the dose response meta-analysis glycemic index and colorectal cancer

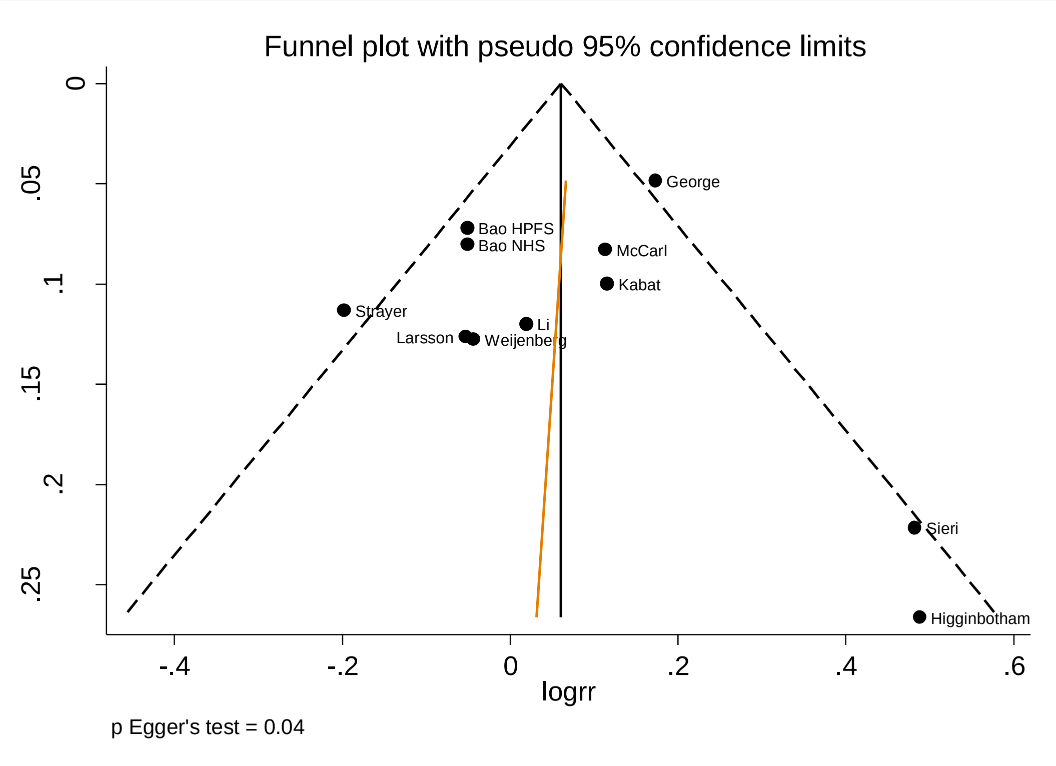


Figure 346 RR (95% CI) of colorectal cancer for 10 units/day increase of glycemic index by sex

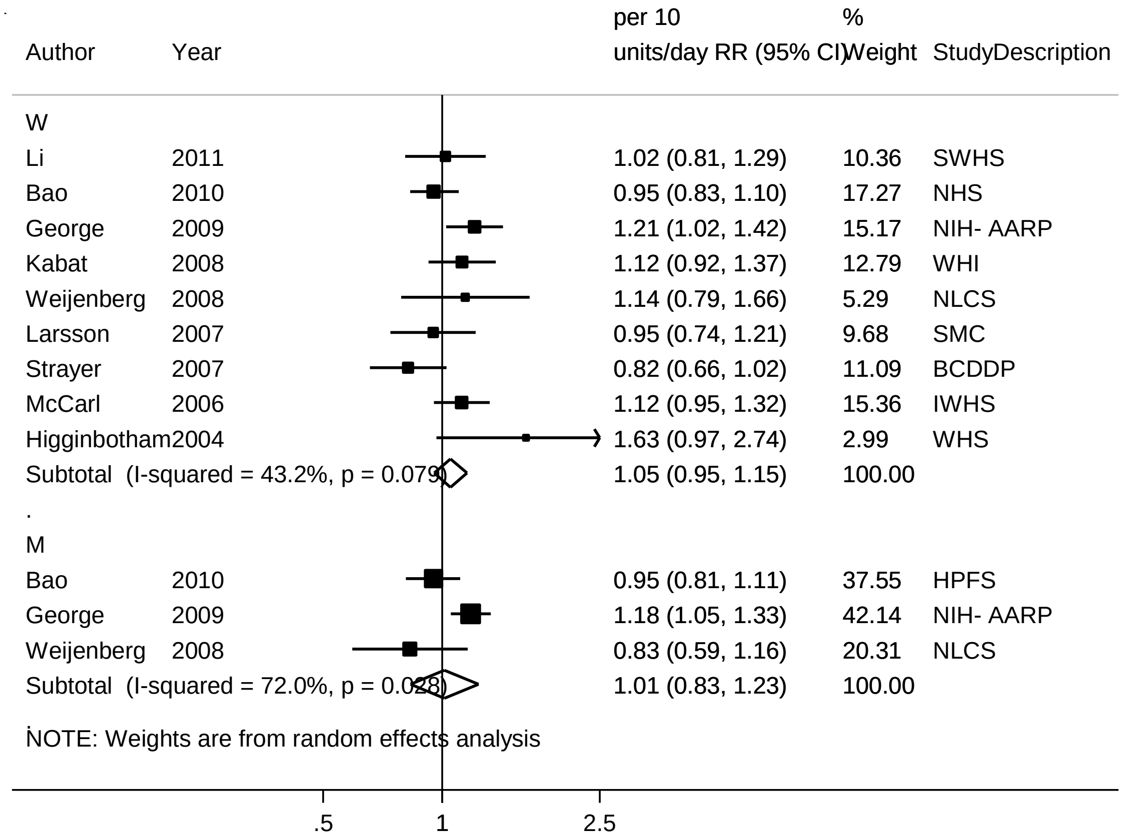


Figure 347 RR (95% CI) of colorectal cancer for 10 units/day increase of glycemic index by location

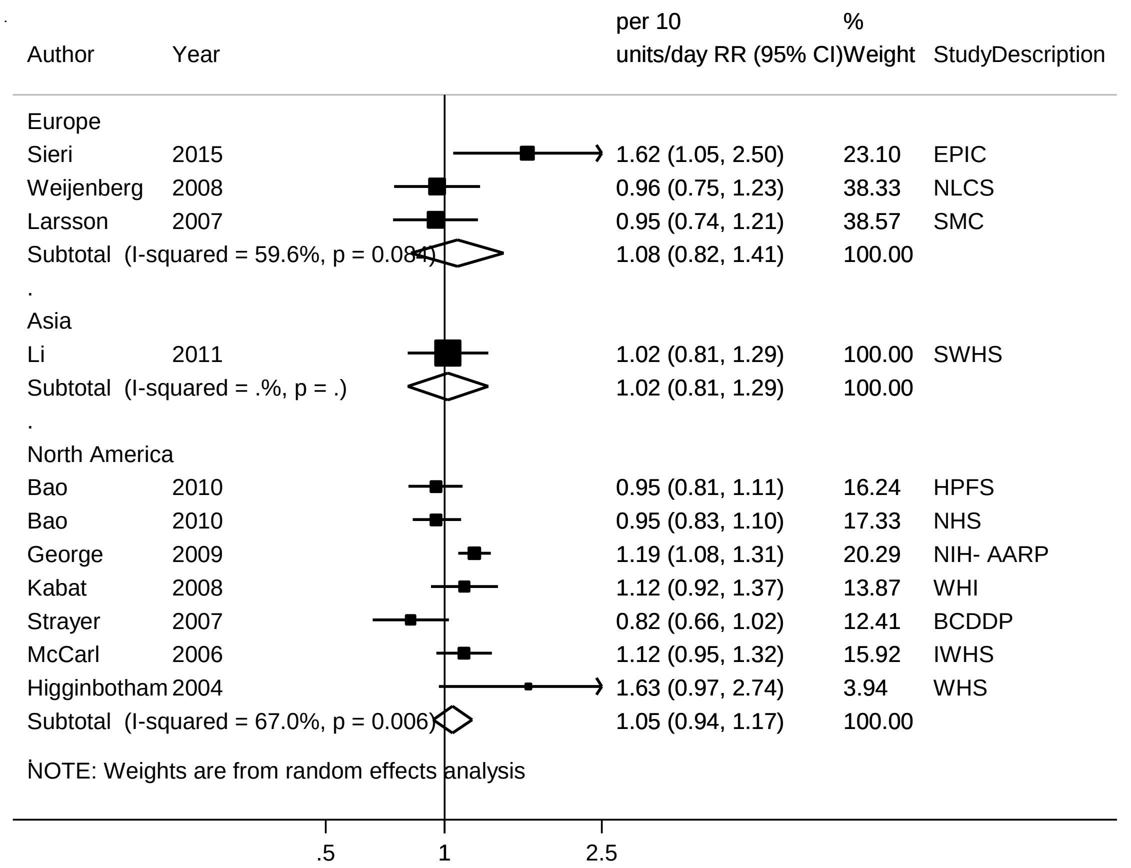


Figure 348 RR estimates of colon cancer by levels of glycemic index

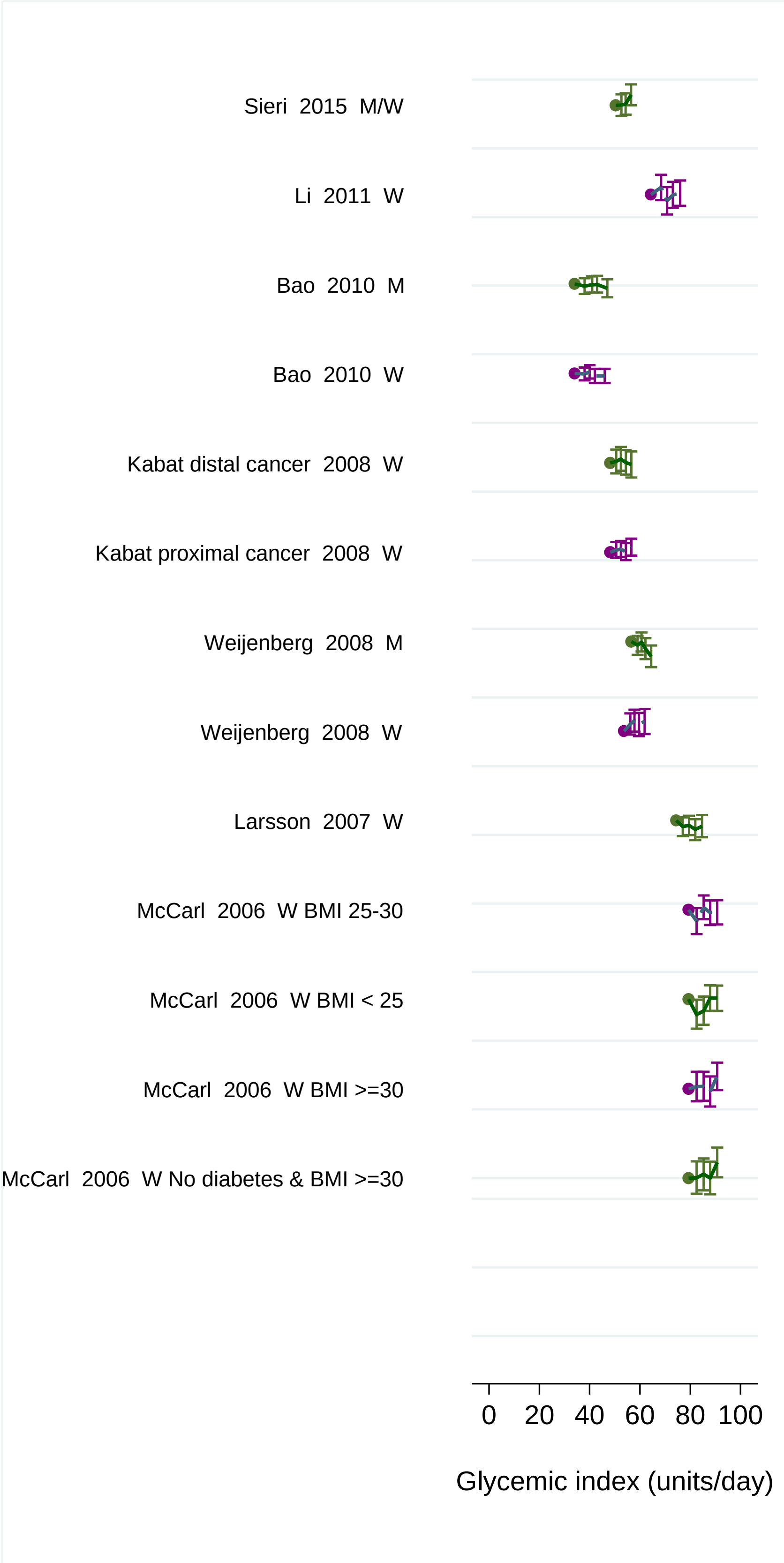


Figure 349 RR (95% CI) of colon cancer for the highest compared with the lowest level of glycemic index

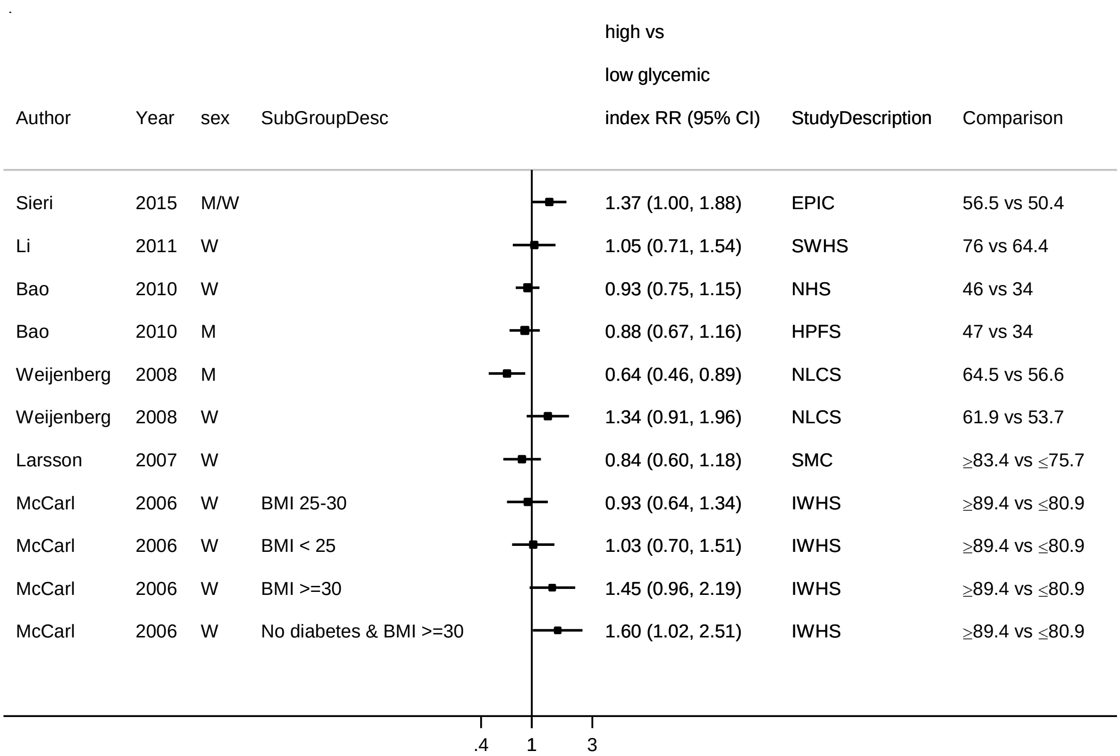


Figure 350 RR (95% CI) of colon cancer for 10 units/day increase of glycemic index

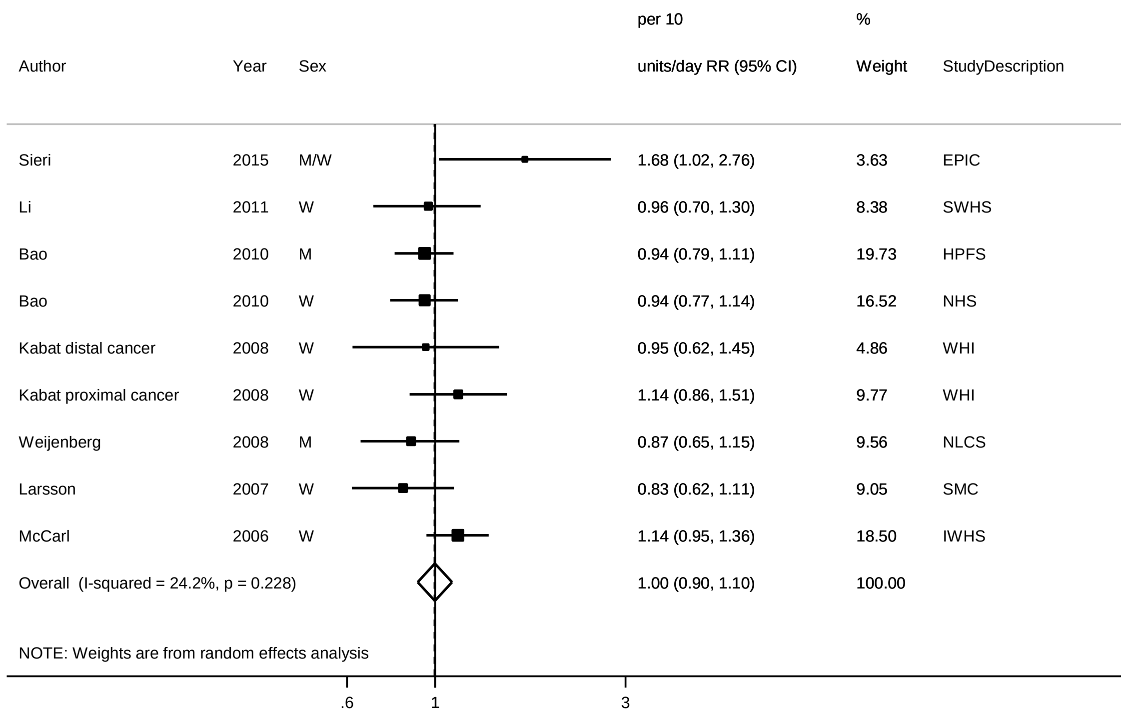


Figure 351 Funnel plot of studies included in the dose response meta-analysis glycemic index and colon cancer

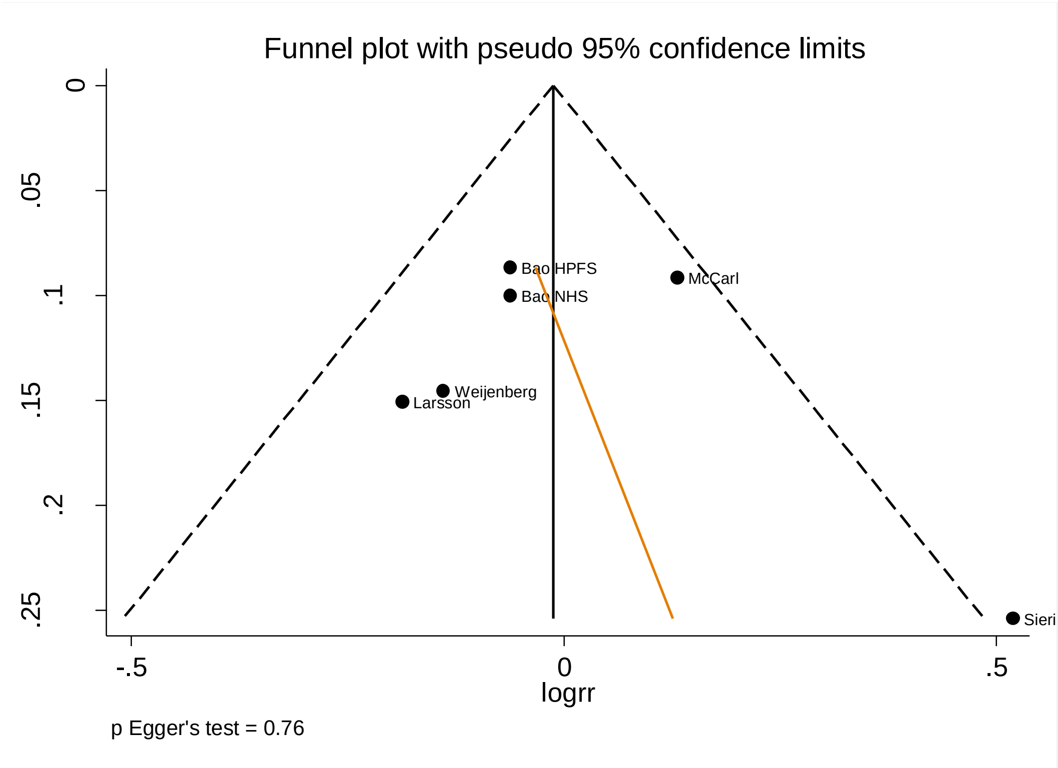


Figure 352 RR (95% CI) of colon cancer for 10 units/day increase of glycemic index by sex

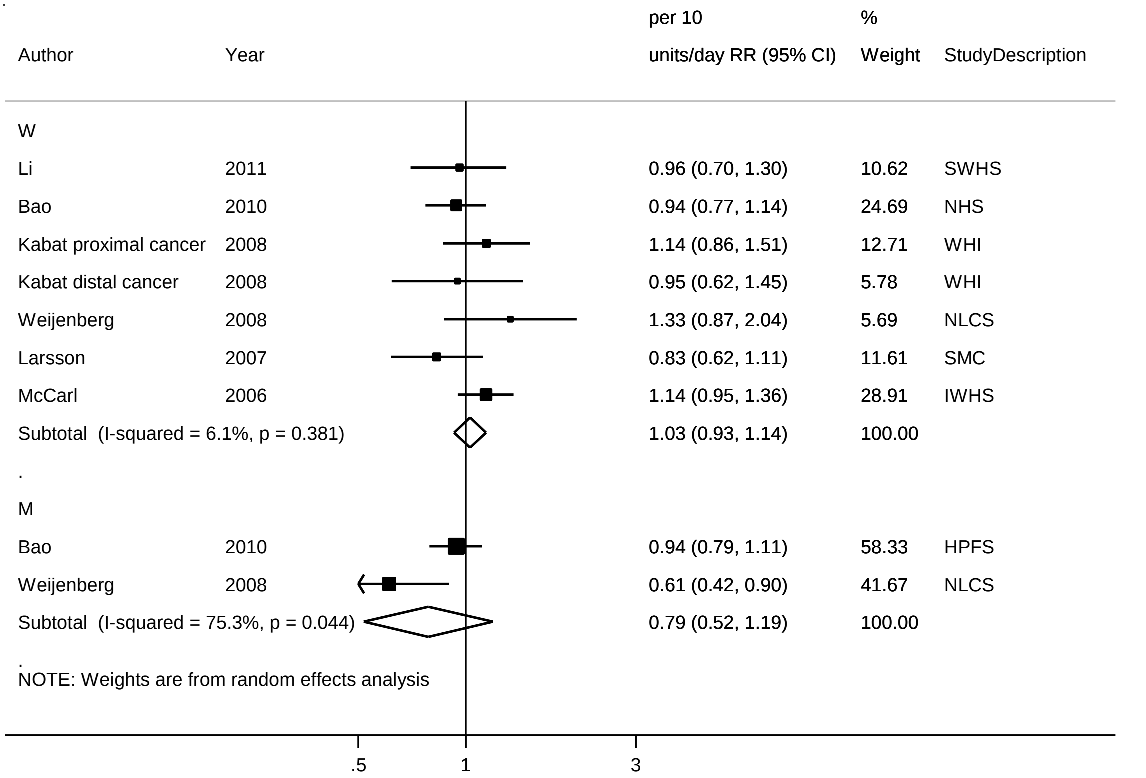


Figure 353 RR (95% CI) of colon cancer for 10 units/day increase of glycemic index by location

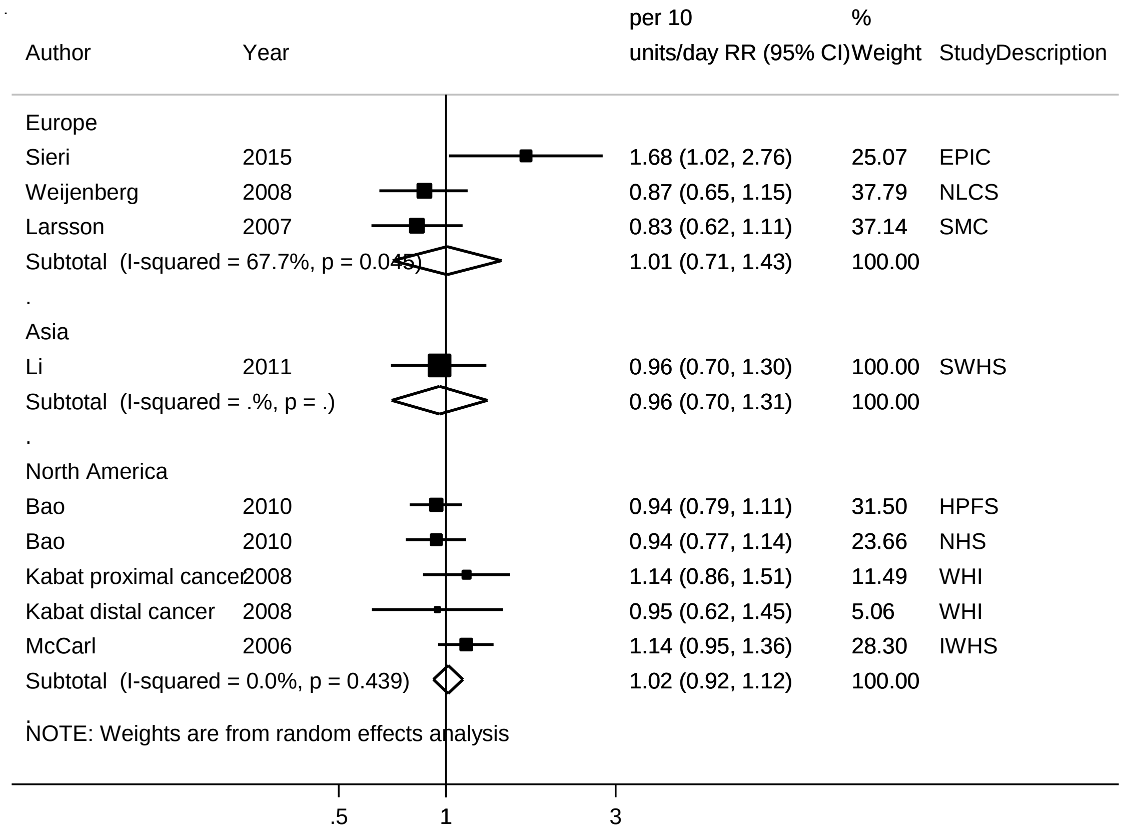
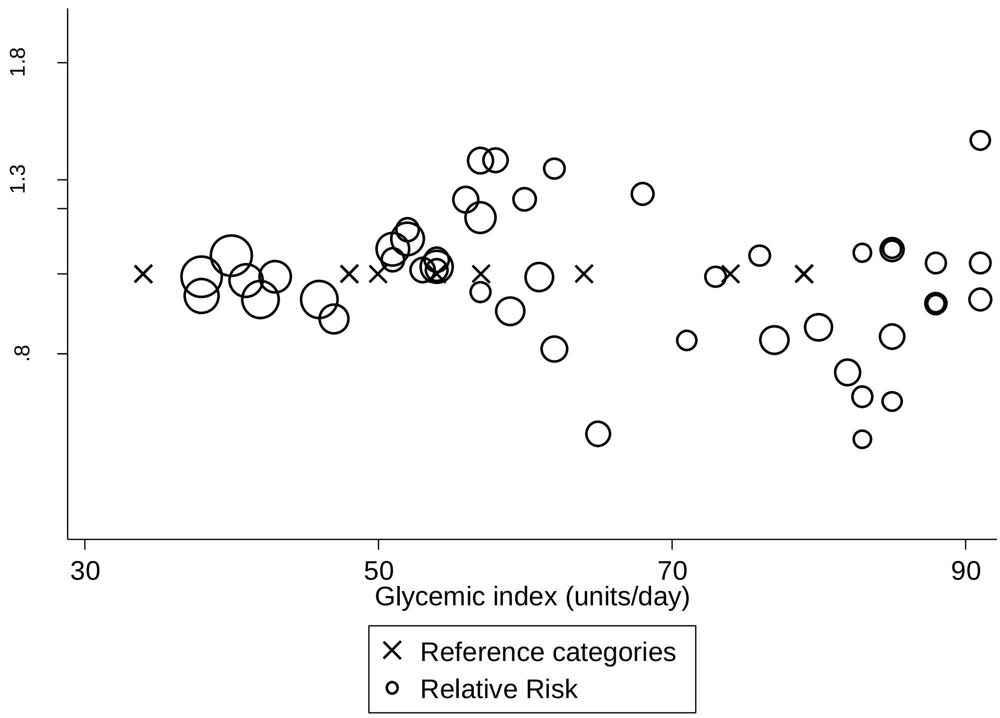


Figure 354 Relative risk of colon cancer and glycemic index estimated using non-linear models



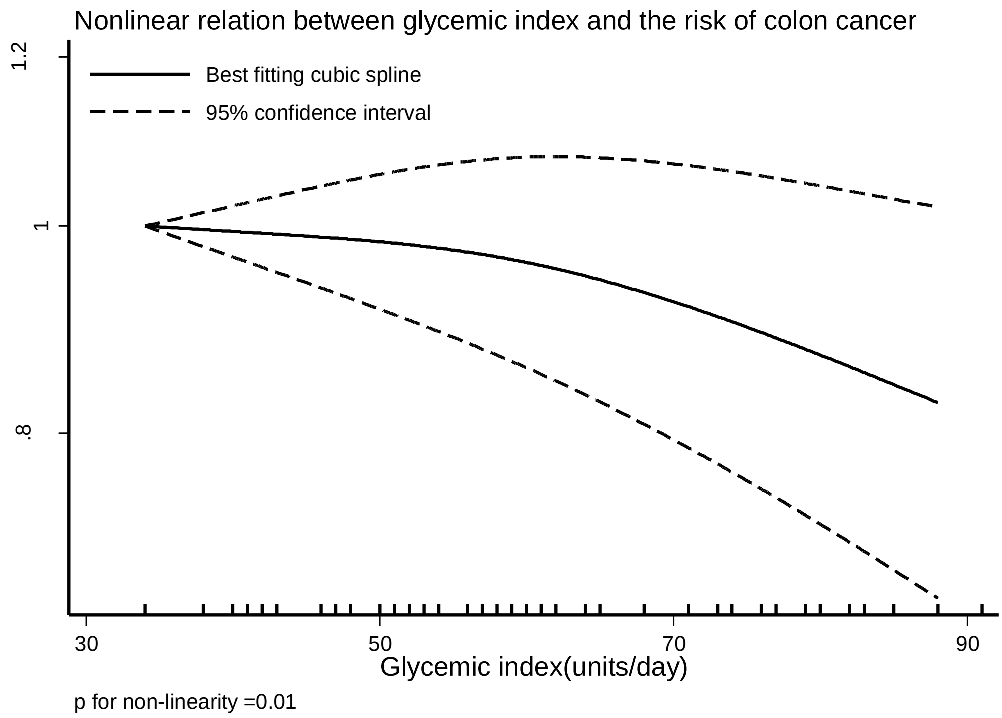


Table 196 Table with glycemic index values and corresponding RRs (95% CIs) for non-linear analysis of glycemic index and colon cancer

Glycemic index(units/day)	RR (95%CI)
34	1
50	0.98(0.91-1.05)
60	0.96(0.85-1.07)
70	0.93(0.80-1.07)
88	0.83(0.67-1.02)

Figure 355 RR estimates of rectal cancer by levels of glycemic index

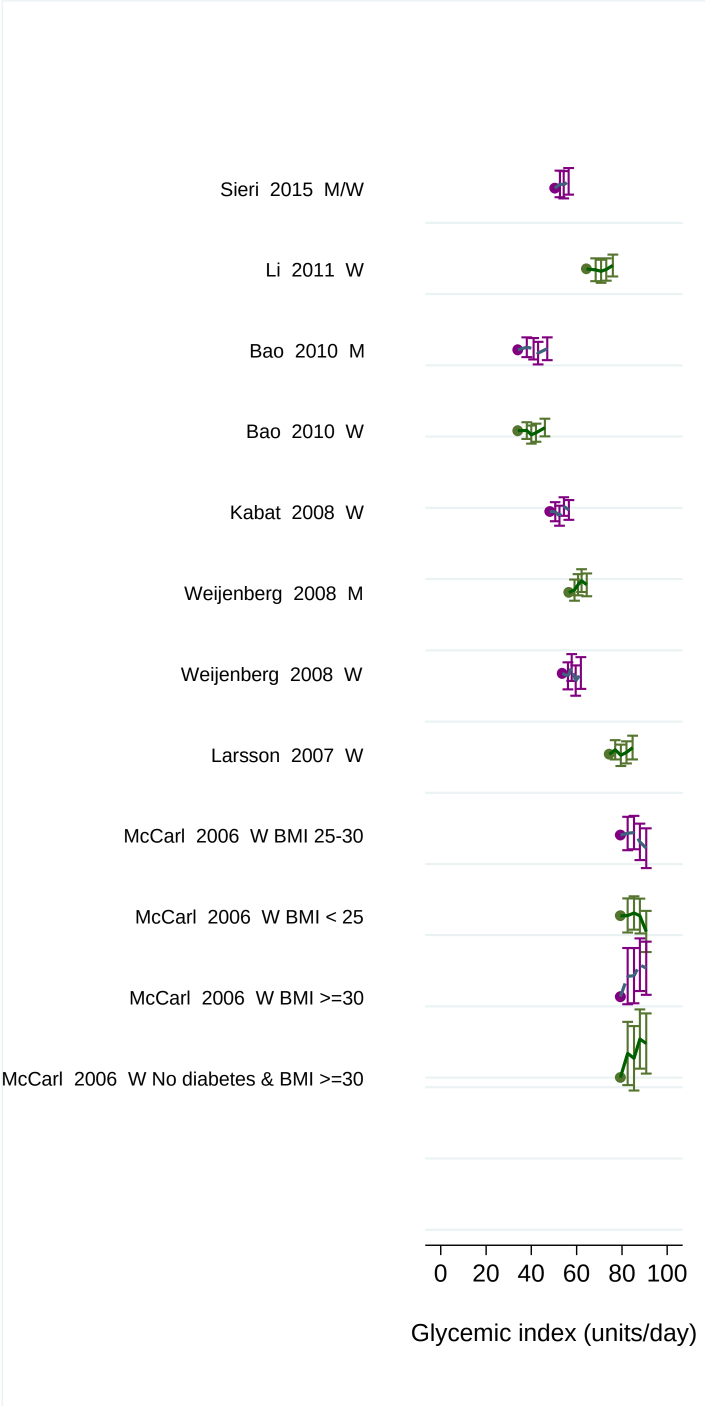


Figure 356 RR (95% CI) of rectal cancer for the highest compared with the lowest level of glycemic index

Author	Year	sex	SubGroupDesc	high vs low glycemic index RR (95% CI)	StudyDescription	Comparison
Sieri	2015	M/W		1.34 (0.76, 2.34)	EPIC	56.5 vs 50.4
Li	2011	W		1.16 (0.73, 1.84)	SWHS	76 vs 64.4
Bao	2010	W		1.14 (0.79, 1.66)	NHS	46 vs 34
Bao	2010	M		1.05 (0.65, 1.69)	HPFS	47 vs 34
Kabat	2008	W		1.07 (0.71, 1.62)	WHI	≥55.5 vs ≤49.3
Weijenberg	2008	W		1.01 (0.52, 1.98)	NLCS	61.9 vs 53.7
Weijenberg	2008	M		1.38 (0.85, 2.23)	NLCS	64.5 vs 56.6
Larsson	2007	W		1.32 (0.80, 2.17)	SMC	≥83.4 vs ≤75.7
McCarl	2006	W	No diabetes & BMI >=30	4.22 (1.19, 14.90)	IWHS	≥89.4 vs ≤80.9
McCarl	2006	W	BMI 25-30	0.58 (0.25, 1.33)	IWHS	≥89.4 vs ≤80.9
McCarl	2006	W	BMI < 25	0.52 (0.22, 1.23)	IWHS	≥89.4 vs ≤80.9
McCarl	2006	W	BMI >=30	3.34 (1.09, 10.20)	IWHS	≥89.4 vs ≤80.9

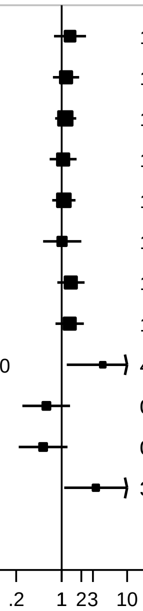


Figure 357 RR (95% CI) of rectal cancer for 10 units/day increase of glycemic index

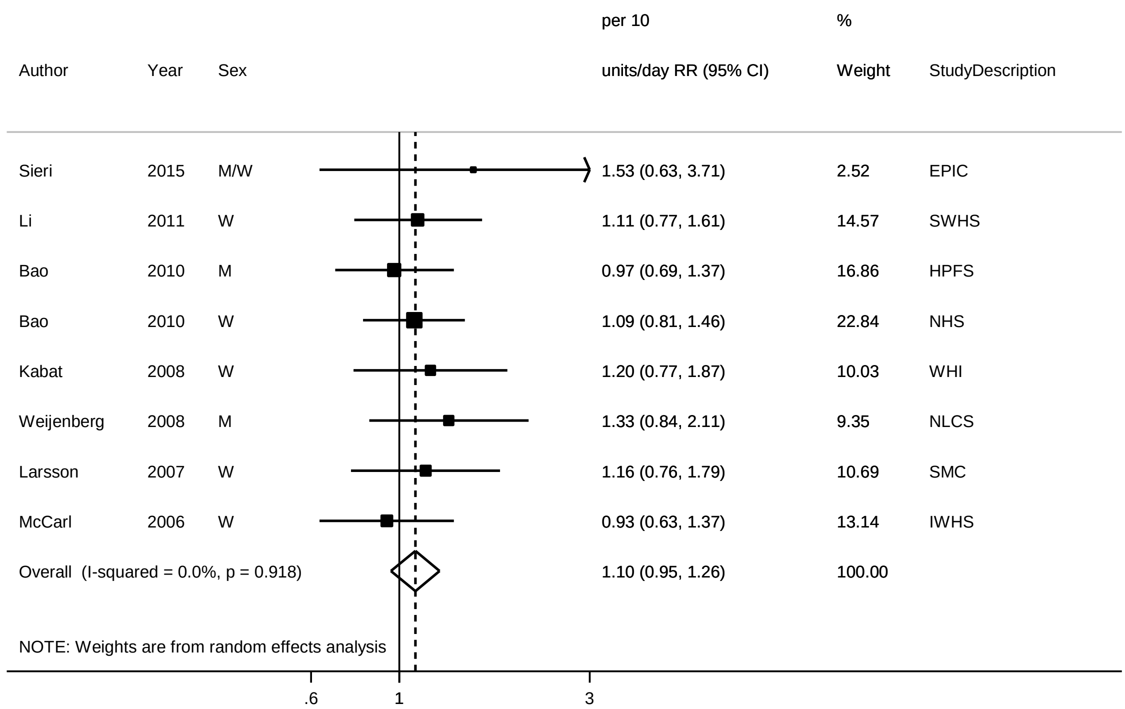


Figure 358 Funnel plot of studies included in the dose response meta-analysis glycemic index and rectal cancer

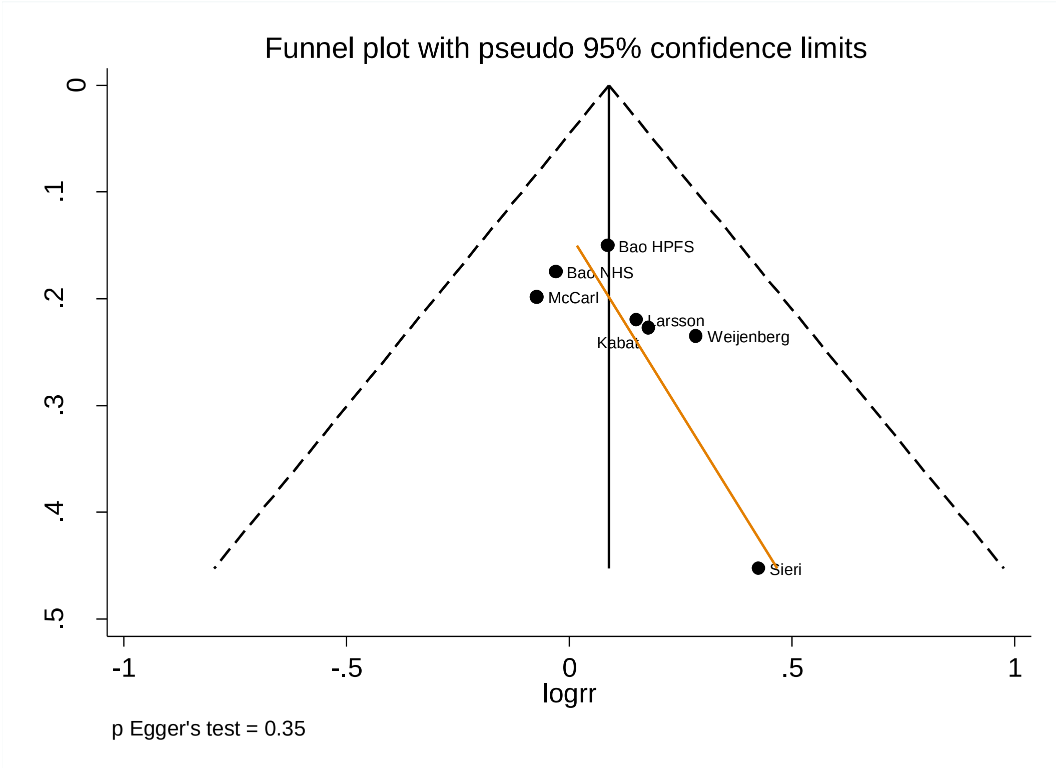


Figure 359 RR (95% CI) of rectal cancer for 10 units/day increase of glycemic index by sex

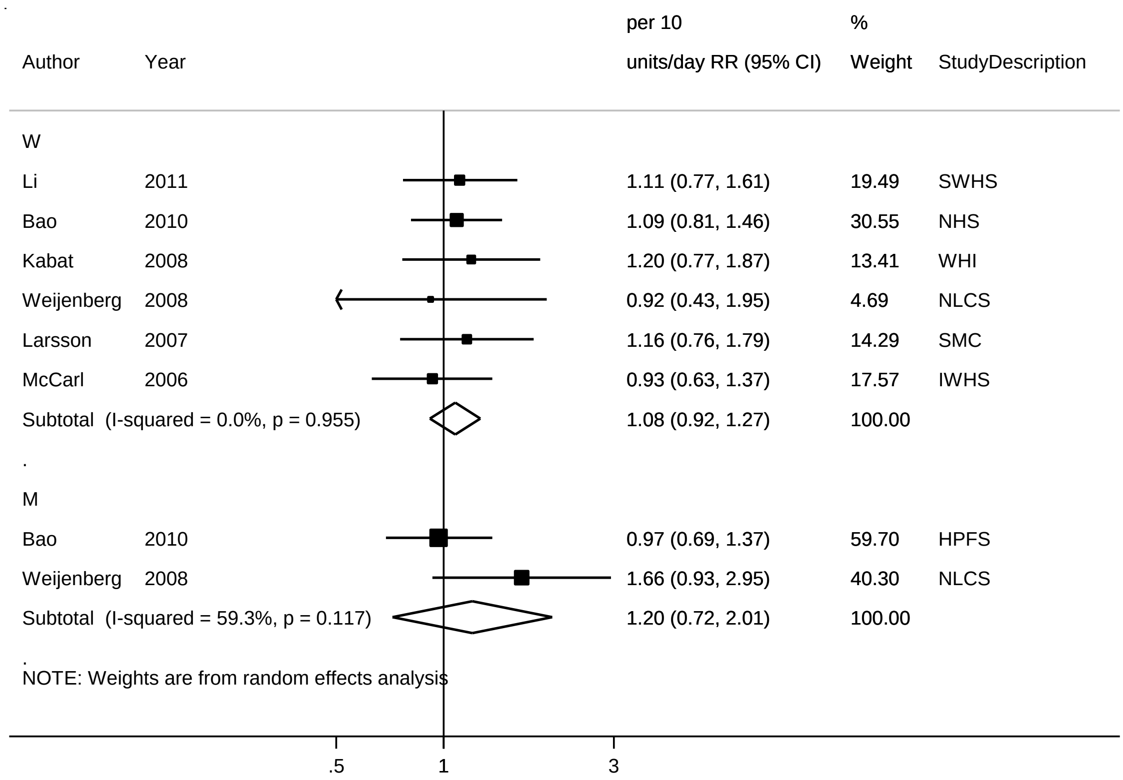
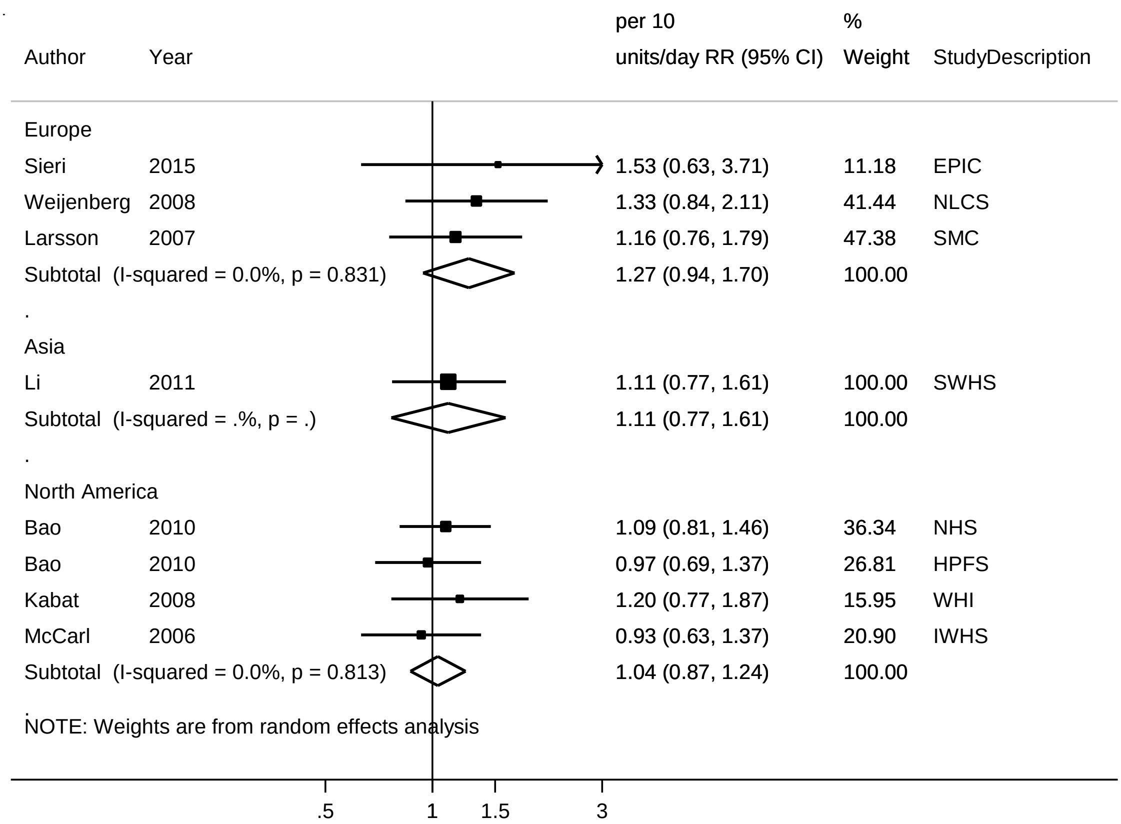


Figure 360 RR (95% CI) of rectal cancer for 10 units/day increase of glycemic index by location



5.1.5 Glycemic load

Cohort studies

Summary

Main results:
Three new publications, two new studies and an updated publication of a study identified in 2010 SLR were identified. For distal and proximal colon cancer there was no update since the 2010 SLR.

Colorectal cancer:
Thirteen studies (16482 cases) were included in the dose-response meta-analysis of glycemic load and colorectal cancer. A non-significant association with low heterogeneity was observed. Only one study on women showed a positive association per 50 units/day (WHS). After stratification by sex or geographic the results remained non-significant. There was evidence of small study bias (p=0.69). There was no evidence of a non-linear association (p=0.09).

Colon cancer:
Ten studies (8075 cases) were included in the dose-response meta-analysis of glycemic load and colon cancer. A non-significant association with no heterogeneity was observed. Only one study showed a positive association per 50 units/day in obese women(IWHS). After stratification by sex or geographic the results remained non-significant. There was evidence of small study bias (p=0.78). There was evidence of a non-linear association (p=0.49).

Rectal cancer:
Ten studies (2749 cases) were included in the dose-response meta-analysis of glycemic load and rectal cancer. A non-significant association with no heterogeneity was observed. Only one study on women showed a positive association per 50 units/day (WHS). After stratification by sex or geographic the results remained non-significant. There was evidence of small study bias (p=0.35). There was evidence of a non-linear association (p=0.98).

Study quality:

All studies were fully adjusted for different confounders. Measurement errors in the assessment of dietary intake are known to bias effect estimates; however, none of the studies included in the analysis made any corrections for measurement errors. Assessment of glycemic index or glycemic load are based on their postprandial blood glucose response and are not concentration values of nutrients in the foods consumed. There is some variability in glycemic load measured between studies, ranging from 46 to 930 units.

Pooling Project of cohort studies
No Pooling Project was identified.

Meta-analysis
One meta-analysis (Aune, 2012) was published after the 2010 SLR. It did not support an independent association between diets high in carbohydrate, glycemic index, or glycemic load and colorectal cancer risk. The summary RR for high versus low intake was 1.00 (95% CI: 0.91–1.10, I^2 = 39%) for glycemic load.

Table 197 Glycemic load and colorectal cancer risk. Number of studies in the CUP SLR

	Number
Studies identified	13 (14 publications)
Studies included in forest plot of highest compared with lowest exposure	13
Studies included in dose-response meta-analysis	13
Studies included in non-linear dose-response meta-analysis	13

Note: Include cohort, nested case-control and case-cohort designs

Table 198 Glycemic load and colon cancer risk. Number of studies in the CUP SLR

	Number
Studies identified	10 (11 publications)
Studies included in forest plot of highest compared with lowest exposure	10
Studies included in dose-response meta-analysis	10
Studies included in non-linear dose-response meta-analysis	10

Note: Include cohort, nested case-control and case-cohort designs

Table 199 Glycemic load and rectal cancer risk. Number of studies in the CUP SLR

	Number
Studies identified	10 (11 publications)
Studies included in forest plot of highest compared with lowest exposure	10
Studies included in dose-response meta-analysis	10
Studies included in non-linear dose-response meta-analysis	10

Note: Include cohort, nested case-control and case-cohort designs

Table 200 Glycemic load and colorectal cancer risk. Summary of the dose-response meta-analysis in the 2010 SLR and 2015 SLR.

	2010 SLR	**2015 SLR**
Increment unit used	50 units/day	50 units/day
Studies (n)	11	13
Cases (total number)	14879	16482
RR (95%CI)	1.00(0.94-1.07)	0.98(0.95-1.01)
Heterogeneity (I^2, p-value)	54.2%, 0.02	15.5%, 0.28

Stratified analysis by sex		
Men	**2010 SLR**	**2015 SLR**
Studies (n)	4	4
RR (95%CI)	1.03 (0.90-1.18)	0.98(0.93-1.04)
Heterogeneity (I^2, p-value)	75.2%, 0.007	41.1%, 0.16
Women		
Studies (n)	10	11
RR (95%CI)	0.97 (0.90-1.05)	0.98(0.92-1.04)
Heterogeneity (I^2, p-value)	46.3%, 0.053	37.7%, 0.09

Stratified analysis by geographic location (no analysis in 2005 SLR or 2010 SLR)			
2015 SLR	**Asia**	**Europe**	**North America**
Studies (n)	1	3	9
RR (95%CI)	0.94(0.77-1.15)	0.98(0.86-1.12)	0.98(0.95-1.02)
Heterogeneity (I^2, p-value)		0%, 0.54	37.6%, 0.12

Table 201 Glycemic load and colon cancer risk. Summary of the dose-response meta-analysis in the 2010 SLR and 2015 SLR.

	2010 SLR	**2015 SLR**
Increment unit used	50 units/day	50 units/day
Studies (n)	7	10
Cases (total number)	7123	8075
RR (95%CI)	0.98 (0.91-1.06)	0.97(0.94-1.01)
Heterogeneity (I^2, p-value)	37.6%, 0.13	0%, 0.76

Stratified analysis by sex		
Men	**2010 SLR**	**2015 SLR**
Studies (n)	3	3
RR (95%CI)	1.07 (0.87-1.30)	1.00(0.85-1.18)
Heterogeneity (I^2, p-value)	68.9%, 0.04	69.6%,0.04
Women		
Studies (n)	7	8

RR (95%CI)	0.93 (0.86-1.01)	0.96(0.92-1.00)
Heterogeneity (I^2, p-value)	19.5%, 0.28	0%, 0.46

Stratified analysis by geographic location (no analysis in 2005 SLR or 2010 SLR)			
2015 SLR	**Asia**	**Europe**	**North America**
Studies (n)	1	3	6
RR (95%CI)	0.89(0.69-1.15)	0.97(0.81-1.16)	0.98(0.95-1.01)
Heterogeneity (I^2, p-value)		20.5%, 0.28	0%, 0.73

Table 202 Glycemic load and rectal cancer risk. Summary of the dose-response meta-analysis in the 2010 SLR and 2015 SLR.

	2010 SLR	**2015 SLR**
Increment unit used	50 units/day	50 units/day
Studies (n)	7	10
Cases (total number)	2278	2749
RR (95%CI)	1.10 (0.99-1.22)	1.03(0.97-1.09)
Heterogeneity (I^2, p-value)	0%, 0.58	0%, 0.69

Stratified analysis by sex		
Men	**2010 SLR**	**2015 SLR**
Studies (n)	7	3
RR (95%CI)	1.08 (0.91-1.29)	1.00(0.92-1.08)
Heterogeneity (I^2, p-value)	0%, 0.45	0%, 0.82
Women		
Studies (n)	3	8
RR (95%CI)	1.10 (0.97-1.25)	1.06(0.98-1.14)
Heterogeneity (I^2, p-value)	0%, 0.52	0%, 0.57

Stratified analysis by geographic location (no analysis in 2005 SLR or 2010 SLR)			
2015 SLR	**Asia**	**Europe**	**North America**
Studies (n)	1	3	6
RR (95%CI)	1.03(0.76-1.41)	1.03(0.82-1.30)	1.03(0.97-1.10)
Heterogeneity (I^2, p-value)		0%, 0.71	13.3%, 0.33

Table 203 Glycemic load and colorectal cancer risk. Results of meta-analyses and pooled analyses of prospective studies published after the 2005 SLR.

Author, Year	Number of cohort studies	Total number of cases	Studies country, area	Outcome	Comparison	RR (95%CI)	P trend	Heterogeneity (I^2, p value)
Meta-analysis								
Aune, 2012	10	12382	North America, Europe and Asia	Colorectal cancer	Highest vs Lowest	1.00 (0.91–1.10)		39%, 0.08
					Per 10 units/day	1.01 (0.95–1.08)		47%, 0.04

Table 204 Glycemic load and colorectal cancer risk. Main characteristics of studies included in the CUP SLR dose-response meta-analysis

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Missing data derived for analysis
Sieri, 2015 COL41035 Italy	EPIC, Prospective Cohort, M/W	426/ 47 749 11.7 years	Cancer registry and hospital discharge records	FFQ	Incidence, colorectal cancer	191 vs 125	1.43 (0.94-2.18) Ptrend:0.153	Sex, alcohol intake, BMI, calcium intake, educational level, energy, folate intake, non-alcohol energy, physical activity, saturated fat intake, smoking status	Distribution of person-years
		314/			Incidence, colon cancer	191 vs 125	1.60 (0.98-2.60) Ptrend:0.071		
		107/			Incidence, rectal cancer	191 vs 125	1.03 (0.45-2.37) Ptrend:0.769		
Li, 2011 COL40806 China	SWHS, Prospective Cohort, Age: 40-70 years, W	475/ 73 061 9.1 years	Cancer registry and medical records	Dietary recall	Incidence, colorectal cancer	225.9 vs 159.7	0.94 (0.71-1.24) Ptrend:0.84	Age, birth year, BMI, educational level, family history of colorectal cancer, HRT use, income, physical activity, total energy	
		287/			Incidence, colon cancer	225.9 vs 159.7	0.92 (0.64-1.32) Ptrend:0.45		
		188/			Incidence, rectal cancer	225.9 vs 159.7	0.99 (0.64-1.52) Ptrend:0.55		
Bao, 2010 COL40837 USA	HPFS+NHS, Prospective Cohort, M/W	1 420/ 132 886	Self-reported/death certificate/ medical records	FFQ	Incidence, colorectal cancer, women	745 vs 547	0.92 (0.77-1.11) Ptrend:0.17	Age, alcohol intake, aspirin use, BMI, endoscopy, energy intake,	
		1 067/			Incidence, colon cancer, women	745 vs 547	0.86 (0.70-1.07) Ptrend:0.09		

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Missing data derived for analysis
		1 061/			Incidence, colorectal cancer, men	930 vs 673	0.90 (0.72-1.12) Ptrend:0.29	family history of colorectal cancer, history of polyps or colitis, multivitamin supplement intake, physical activity, smoking	
		694/			Incidence, colon cancer, men	930 vs 673	0.85 (0.65-1.12) Ptrend:0.34		
		323/			Incidence, rectal cancer, women	745 vs 547	1.21 (0.82-1.77) Ptrend:0.63		
		222/			Men	930 vs 673	1.11 (0.69-1.77) Ptrend:0.81		
George, 2009 COL40791 USA	NIH-AARP, Prospective Cohort, Age: 50-71 years, M/W	3 031/ 446 177 8 years	Cancer registry	FFQ	Incidence, colorectal cancer, men	164.44-740.24 vs 7.08-83.2	0.88 (0.72-1.08)	Age, sex, alcohol intake, BMI, educational level, ethnicity, family history of cancer, marital status, menopausal hormone use, physical activity, smoking status, total energy intake	Midpoints, distribution of person-years and cases
		1 457/			Women	135.31-583.68 vs 4.61-66.91	0.87 (0.64-1.18)		
Howarth, 2008 COL40653 USA	MEC, Prospective Cohort, Age: 45-75 years	1 166/ 191 004 8 years	Cancer registry and death certificates	FFQ-quantitative	Incidence, colorectal cancer, men	≥188.5 vs ≤130.4	1.15 (0.89-1.48) Ptrend:0.193	Age, alcohol intake, BMI, calcium intake, dietary fibre, energy intake,	
		920/			Women	≥156.9 vs ≤113.8	0.75 (0.57-0.97) Ptrend:0.017		

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Missing data derived for analysis
		835/			Incidence, colon cancer, men	≥188.5 vs ≤130.4	1.22 (0.90-1.65) Ptrend:0.082	ethnicity, family history of colorectal cancer, folate intake, history of polyps, multivitamin, NSIAD use, physical activity, red meat intake, smoking, pack-years, time, vitamin d, HRT use	
		717/			Women	≥156.9 vs ≤113.8	0.77 (0.57-1.04) Ptrend:0.038		
		318/			Incidence, rectal cancer, men	≥188.5 vs ≤130.4	0.97 (0.60-1.56) Ptrend:0.689		
		198/			Women	≥156.9 vs ≤113.8	0.70 (0.39-1.25) Ptrend:0.297		
Kabat, 2008 COL40722 USA	Women's Health Initiative - Observational study, Prospective Cohort, W, Postmenopausal	1 470/ 158 800 7.8 years	Mail or telephone questionnaires verified by trained physician adjudicators	FFQ	Incidence, colorectal cancer	≥126.7 vs ≤62.3	1.11 (0.82-1.49) Ptrend:0.47	Age, BMI, dietary calcium, educational level, energy intake, family history of colorectal cancer, fibre, height, history of diabetes, hormone use, number of cigarettes smoked, observational study participants, physical activity	
		798/			Incidence, proximal colon cancer	≥126.7 vs ≤62.3	0.86 (0.56-1.31) Ptrend:0.41		
		351/			Incidence, distal colon cancer	≥126.7 vs ≤62.3	1.11 (0.59-2.11) Ptrend:0.50		
		303/			Incidence, rectal cancer	≥126.7 vs ≤62.3	1.84 (0.95-3.56) Ptrend:0.05		

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Missing data derived for analysis
Weijenberg, 2008 COL40686 Netherlands	NLCS, Case Cohort, Age: 55-69 years, M/W	1 082/ 120 852 11.3 years	Cancer registry and database of pathology reports	Semi-quantitative FFQ	Incidence, colorectal cancer, men	165.4 vs 108.7	0.83 (0.64-1.08) Ptrend:0.37	Age, alcohol, BMI, calcium intake, educational level, family history of colon cancer, physical activity, processed meat, smoking status, total energy intake	
		755/			Women	123.6 vs 82.5	1.00 (0.73-1.36) Ptrend:0.81		
		674/			Incidence, colon cancer, men	165.4 vs 108.7	0.72 (0.51-1.00) Ptrend:0.1		
		551/			Women	123.6 vs 82.5	1.13 (0.79-1.60) Ptrend:0.32		
		280/			Incidence, rectal cancer, men	165.4 vs 108.7	1.01 (0.68-1.51) Ptrend:0.37		
		138/			Women	123.6 vs 82.5	0.79 (0.43-1.43) Ptrend:0.55		
Larsson, 2007 COL40705 Sweden	SMC, Prospective Cohort, Age: 40-76 years, W	870/ 61 433 15.7 years	Record linkage with cancer registries	FFQ	Incidence, colorectal cancer	≥200 vs ≤163	1.06 (0.81-1.39) Ptrend:0.78	Age, alcohol consumption, BMI, calcium intake, cereal fibre, date of enrolment, educational level, folate intake, magnesium, red meat intake, total energy intake	Midpoints
		594/			Incidence, colon cancer	≥200 vs ≤163	0.97 (0.70-1.32) Ptrend:0.66		
		283/			Incidence, rectal cancer	≥200 vs ≤163	1.20 (0.74-1.95) Ptrend:0.45		
Strayer, 2007 COL40678 USA	BCDDP, Prospective Cohort,	490/ 45 561 8.5 years	Self-report, cancer registry, death report	FFQ	Incidence, colorectal cancer	89.4 vs 46.5	0.91 (0.70-1.20) Ptrend:0.32	Age, BMI, energy intake, health screening,	

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Missing data derived for analysis
	Age: 62 years, W							HRT use, NSAID use, smoking status	
McCarl, 2006 COL40633 USA	IWHS, Prospective Cohort, Age: 55-69 years, W	954/ 35 197 15 years	Seer registry	FFQ	Incidence, colorectal cancer	≥193 vs ≤146	1.09 (0.88-1.35) Ptrend:0.33	Age, BMI, diabetes, energy intake, multivitamin supplement intake, physical activity, smoking, pack-years, waist to hip ratio	Midpoints, distribution of person-years
		291/			Incidence, colon cancer, BMI 25-30	≥193 vs ≤146	1.10 (0.76-1.58) Ptrend:0.81		
		250/			BMI < 25	≥193 vs ≤146	0.74 (0.47-1.14) Ptrend:0.26		
		216/			BMI >=30	≥193 vs ≤146	1.68 (1.06-2.67) Ptrend:<0.01		
		77/			Incidence, rectal cancer, BMI 25-30	≥193 vs ≤146	0.66 (0.30-1.44) Ptrend:0.54		
		76/			BMI < 25	≥193 vs ≤146	0.88 (0.41-1.86) Ptrend:0.54		
		56/			BMI >=30	≥193 vs ≤146	2.23 (0.91-5.45) Ptrend:0.04		
Higginbotham, 2004 COL00299 USA	WHS, Prospective Cohort, Age: 45- years, W, nurses	174/ 38 451 7.9 years	Cancer registry	FFQ	Incidence, colorectal cancer	143 vs 92	2.85 (1.40-5.80) Ptrend:0.004	Age, alcohol consumption, BMI, energy-adjusted calcium, energy-adjusted folate, energy-adjusted total fat, energy-adjusted vitamin	

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Missing data derived for analysis
								d, energy adjusted total fibre, family history of specific cancer, history of oral contraceptive use, HRT use, NSAID use, physical activity, smoking habits, total energy	
Terry, 2003 COL00561 Canada	CNBSS, Prospective Cohort, Age: 40-59 years, W	616/ 49 124 810 649 person-years	Breast cancer screening centres	Quantitative FFQ	Incidence, colon cancer	≥185 vs ≤98	0.95 (0.61-1.50) Ptrend:0.49	Age, alcohol consumption, BMI, educational level, energy intake, folic acid intake, hormone replacement therapy, oral contraceptive use, parity, physical activity, red meat intake, smoking habits, study centre, treatment allocation	
					Incidence, colorectal cancer	≥185 vs ≤98	1.05 (0.73-1.53) Ptrend:0.94		
					Incidence, rectal cancer	≥185 vs ≤98	1.34 (0.70-2.58) Ptrend:0.31		

Table 205 Glycemic load and colorectal cancer risk. Main characteristics of studies excluded from the CUP SLR dose-response meta-analysis

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Inclusion/exclusion
Michaud, 2005 COL01824 USA	NHS-HPFS, Prospective Cohort, M/W	1 096/ 130 719 20 years	Self-report, medical record and pathology report reviewed by centrally trained physician	FFQ	Incidence, colorectal cancer, women	81 vs 65	1.08 (0.87-1.34) Ptrend:0.27	Age, alcohol, aspirin use, beef, pork or lamb as a main dish, BMI, calcium intake, cereal fibre, family history of colon cancer, folate intake, height, history of endoscopy, pack-years of smoking, physical activity, processed meat	Superseded by Bao, 2010 COL40837
						167 vs 80	0.89 (0.71-1.11) Ptrend:0.15		
		858/			Incidence, colon cancer, women	81 vs 65	1.06 (0.83-1.36) Ptrend:0.29		
						167 vs 80	0.89 (0.69-1.15) Ptrend:0.11		
		683/			Incidence, colorectal cancer, men	82 vs 69	1.14 (0.88-1.48) Ptrend:0.33		
						223 vs 131	1.32 (0.98-1.79) Ptrend:0.04		
		552/			Incidence, colon cancer, men	223 vs 131	1.25 (0.88-1.25) Ptrend:0.11		
						82 vs 69	1.13 (0.84-1.51) Ptrend:0.40		
		403/			Incidence, proximal colon cancer, women	81 vs 65	1.11 (0.77-1.58) Ptrend:0.27		
						167 vs 80	0.77 (0.53-1.11) Ptrend:0.02		
		326/			Incidence, distal colon cancer,	167 vs 80	0.90 (0.60-1.36) Ptrend:0.59		

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Inclusion/exclusion
					women	81 vs 65	0.91 (0.63-1.34) Ptrend:0.82		
		238/			Incidence, rectal cancer, women	81 vs 65	1.14 (0.73-1.78) Ptrend:0.7		
						167 vs 80	0.87 (0.52-1.44) Ptrend:0.95		
		228/			Incidence, distal colon cancer, men	82 vs 69	1.06 (0.67-1.68) Ptrend:0.91		
						223 vs 131	0.87 (0.51-1.49) Ptrend:0.85		
		227/			Incidence, proximal colon cancer, men	82 vs 69	0.99 (0.63-1.57) Ptrend:0.72		
						223 vs 131	1.10 (0.64-1.88) Ptrend:0.67		
		131/			Incidence, rectal cancer, men	223 vs 131	1.61 (0.82-3.17) Ptrend:0.17		
						82 vs 69	1.21 (0.68-2.15) Ptrend:0.65		

Figure 361 RR estimates of colorectal cancer by levels of glycemic load

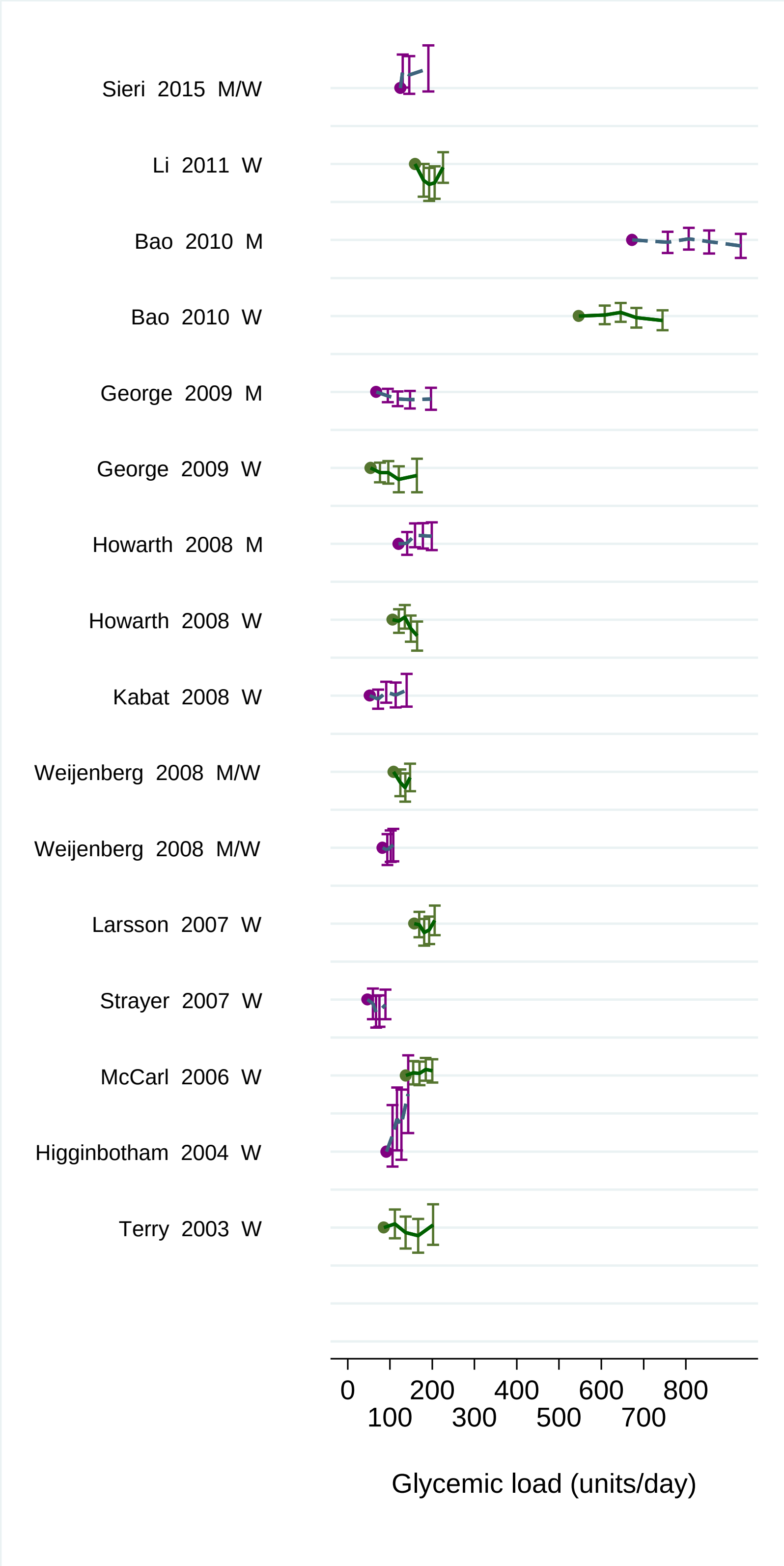


Figure 362 RR (95% CI) of colorectal cancer for the highest compared with the lowest level of glycemic load

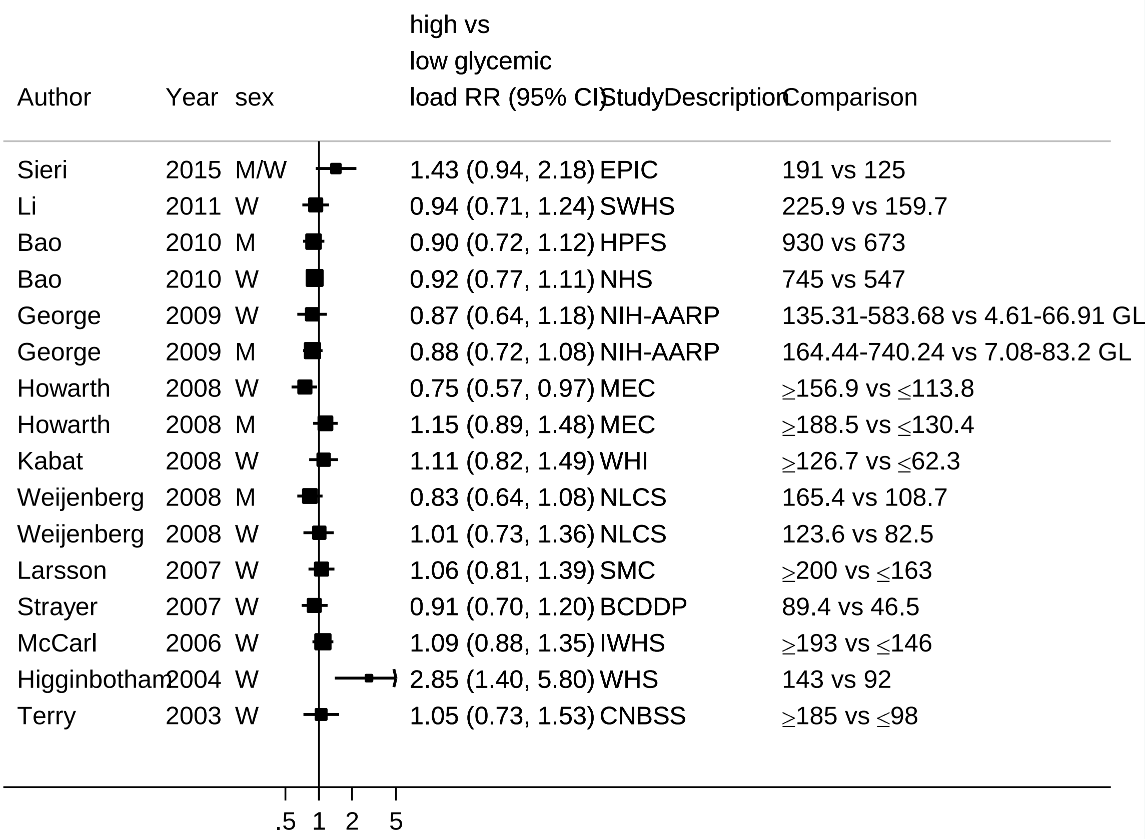


Figure 363 RR (95% CI) of colorectal cancer for 50 units/day increase of glycemic load

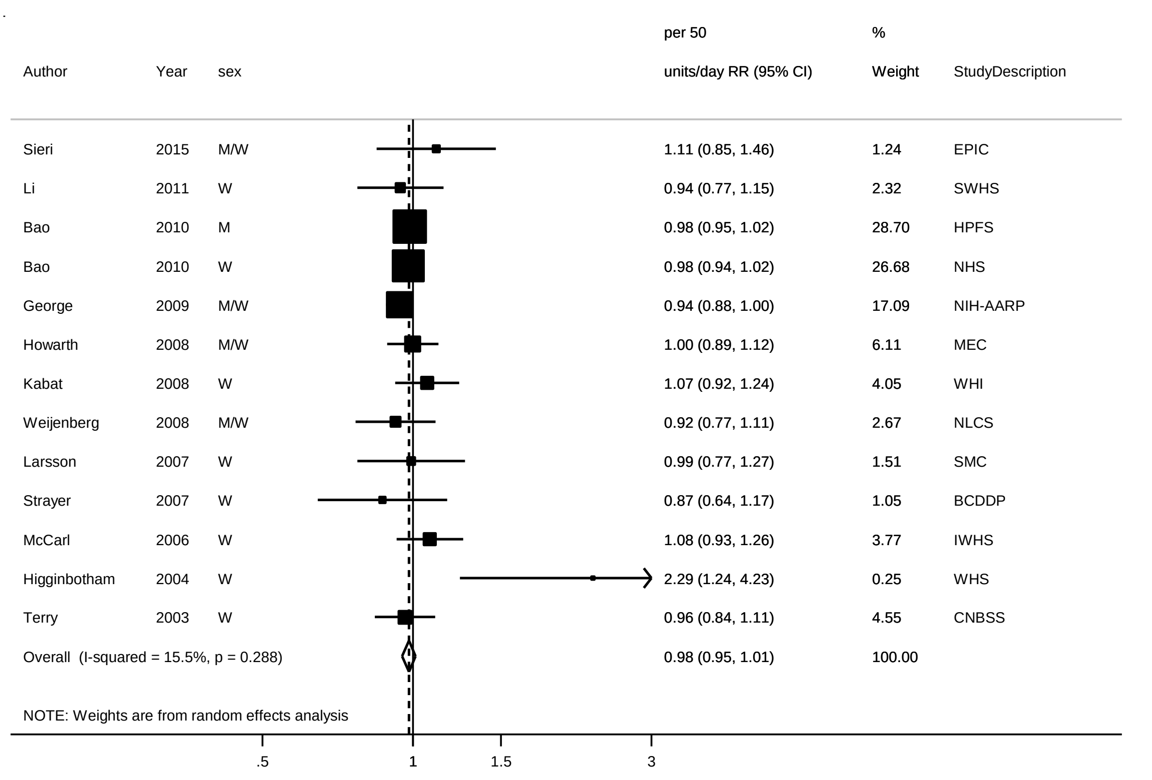


Figure 364 Funnel plot of studies included in the dose response meta-analysis glycemic load and colorectal cancer

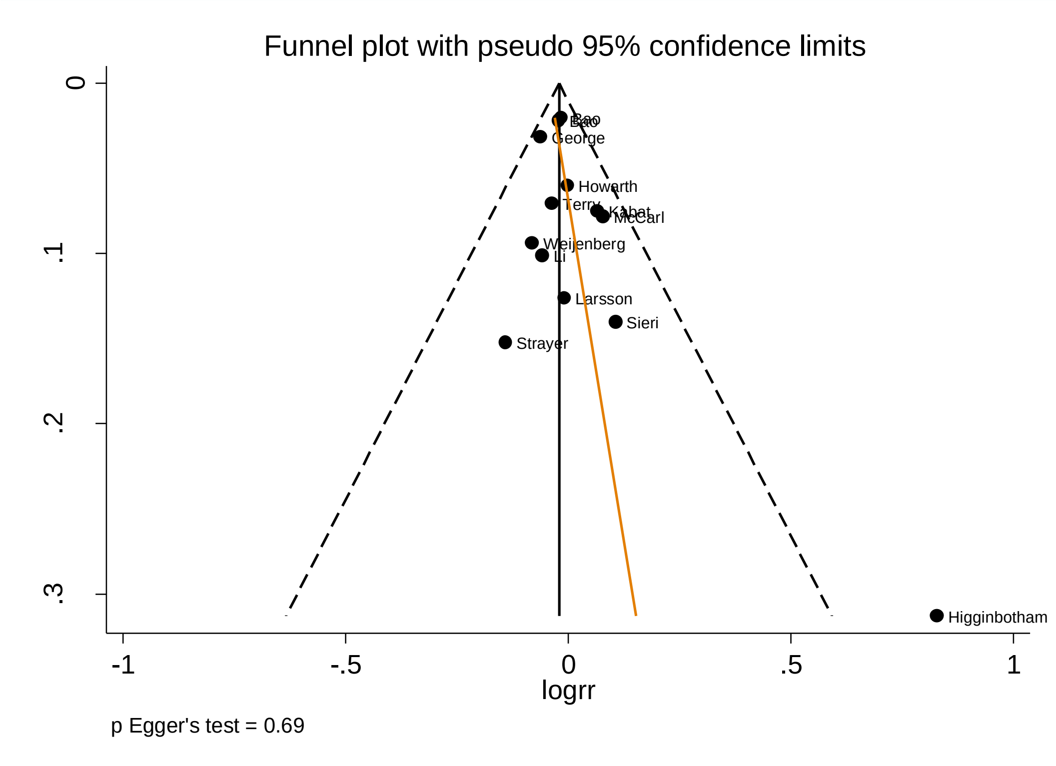


Figure 365 RR (95% CI) of colorectal cancer for 50 units/day increase of glycemic load by sex

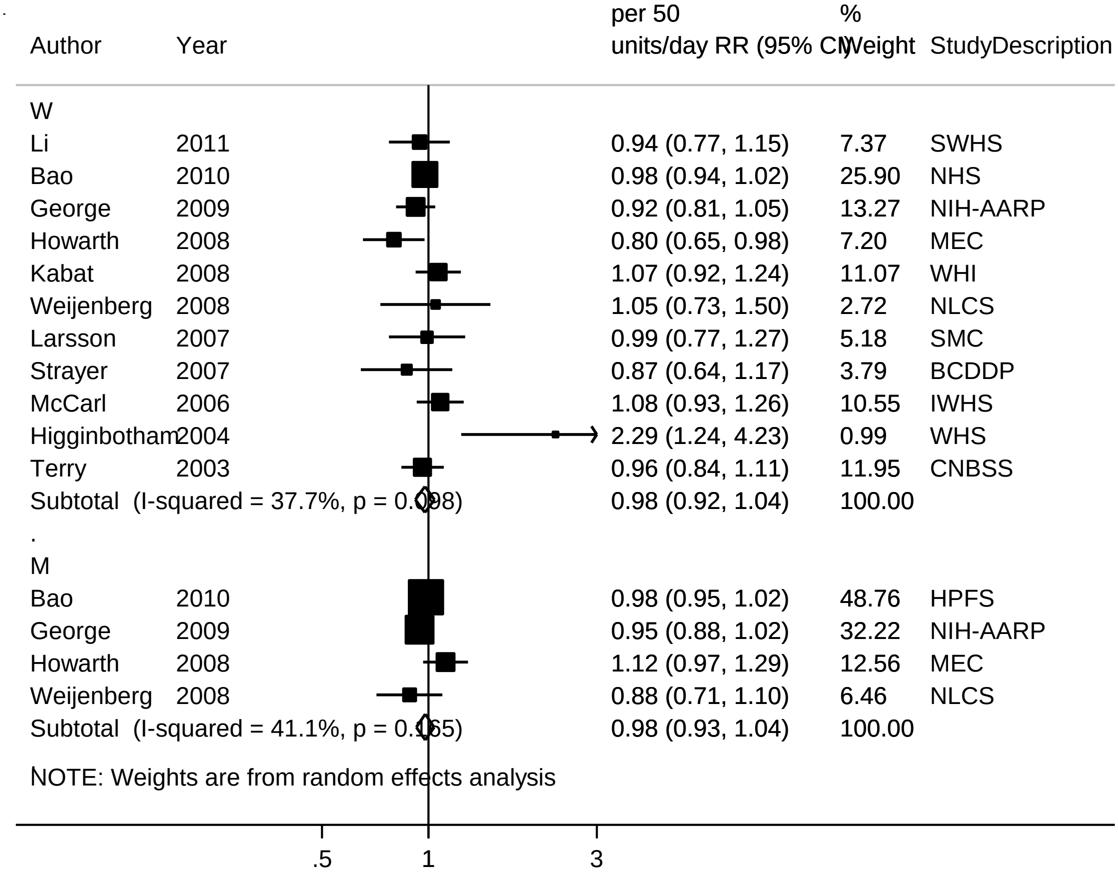


Figure 366 RR (95% CI) of colorectal cancer for 50 units/day increase of glycemic load by location

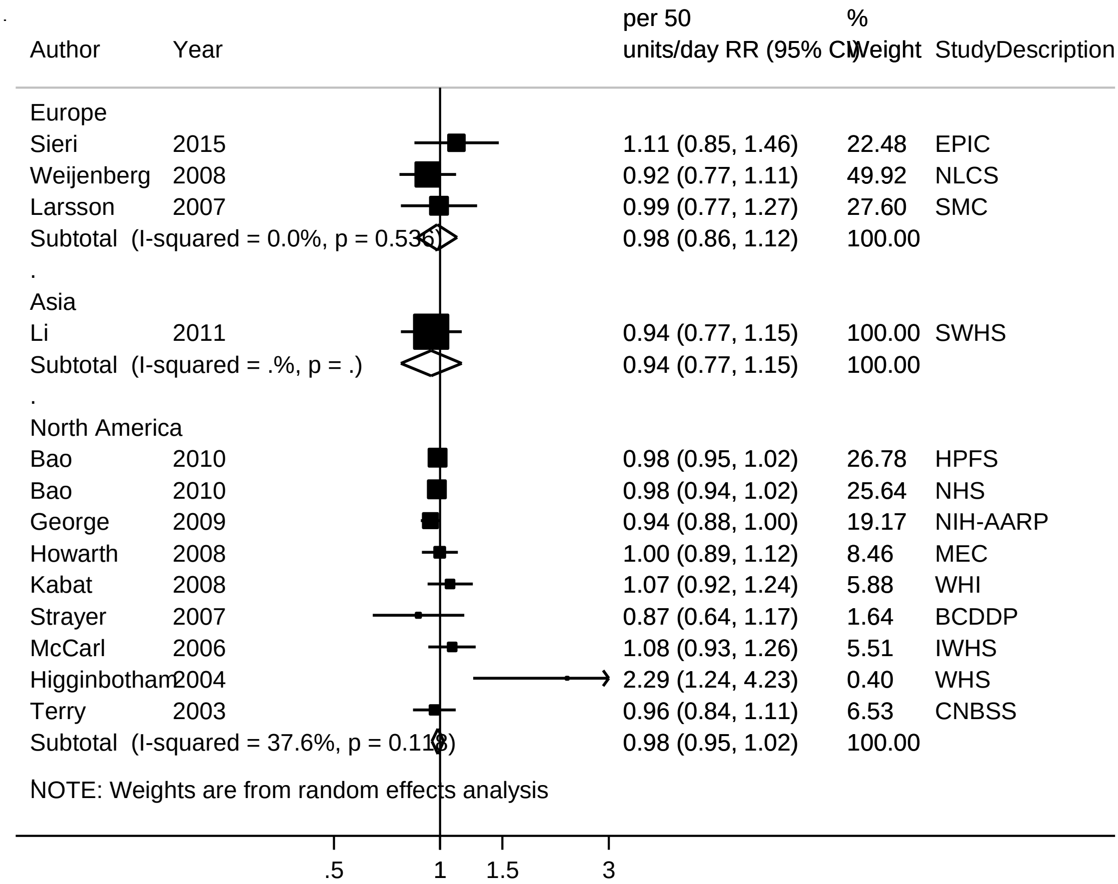


Figure 367 RR estimates of colon cancer by levels of glycemic load

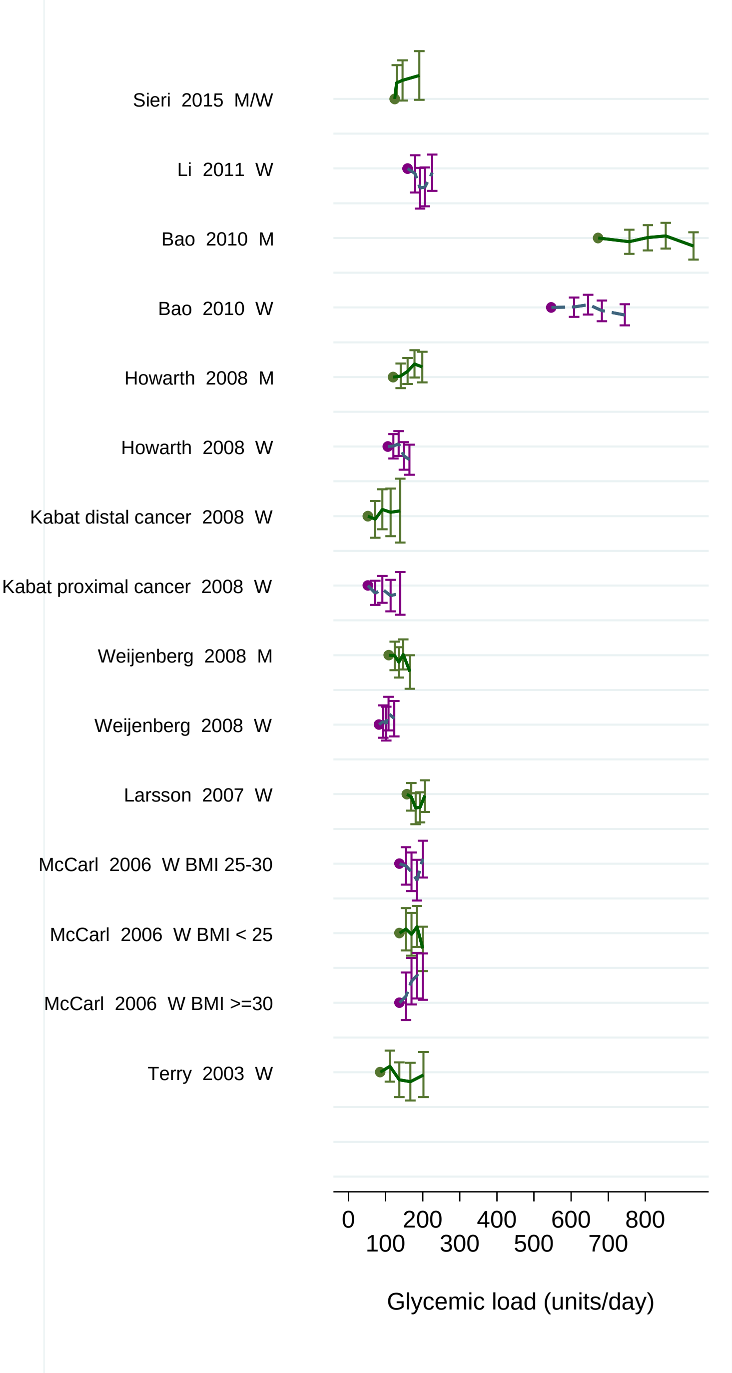


Figure 368 RR (95% CI) of colon cancer for the highest compared with the lowest level of glycemic load

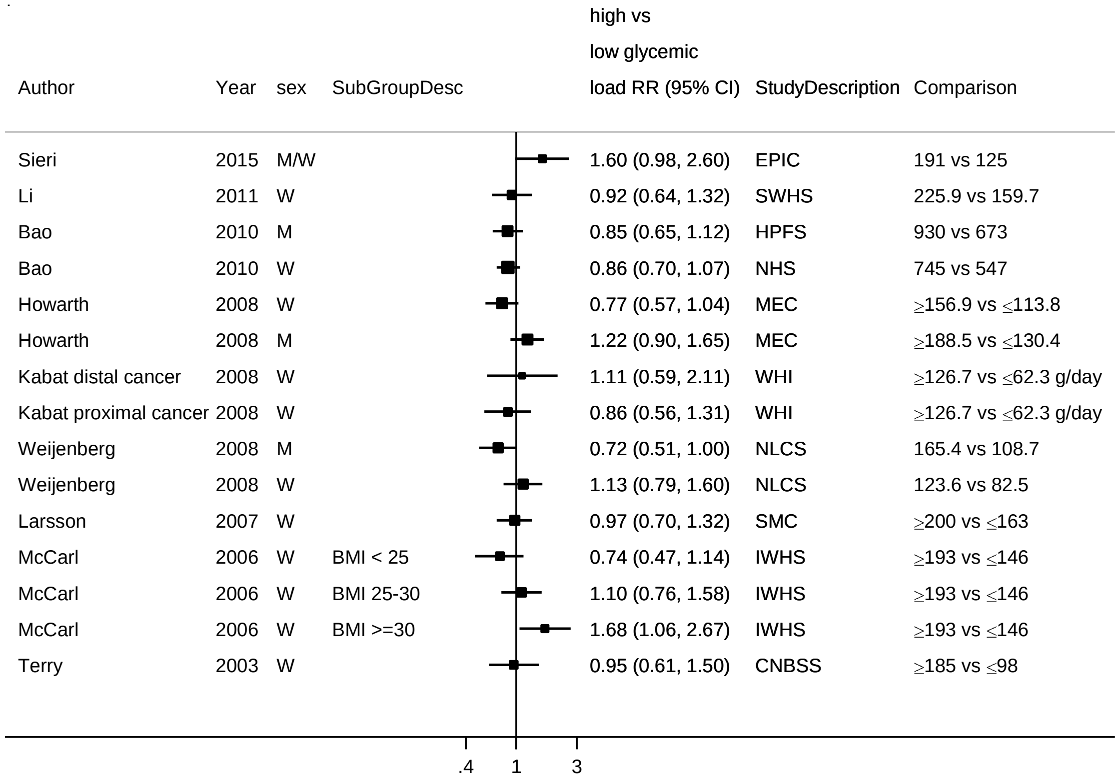


Figure 369 RR (95% CI) of colon cancer for 50 units/day increase of glycemic load

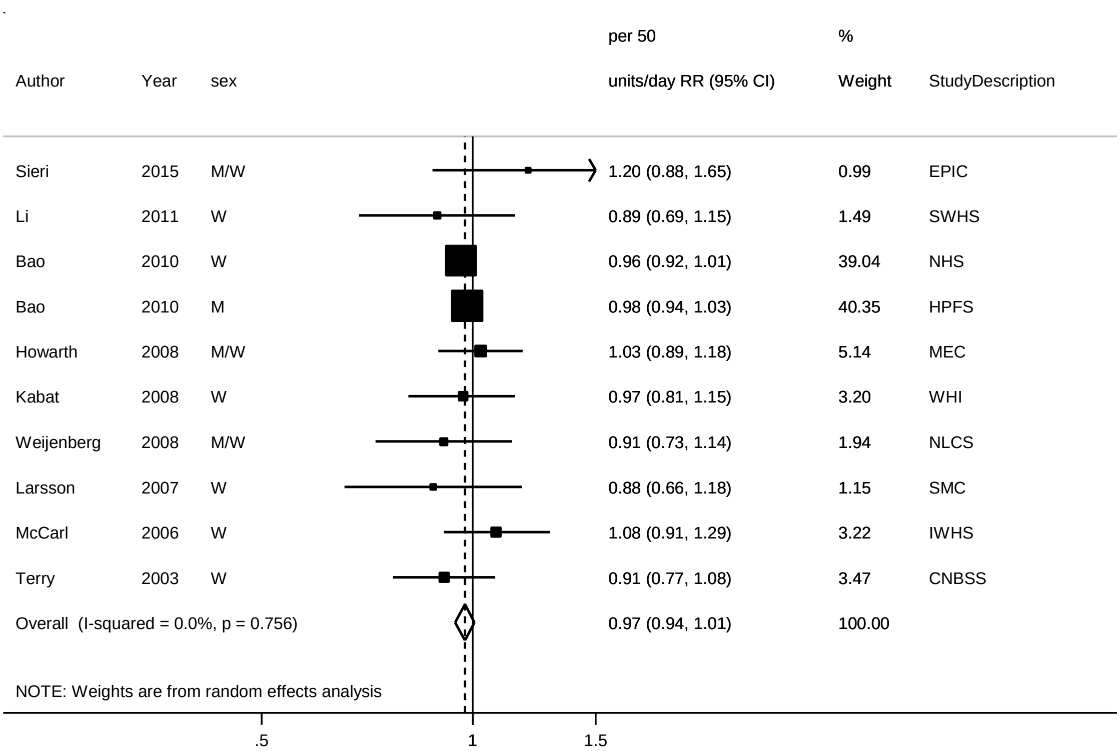


Figure 370 Funnel plot of studies included in the dose response meta-analysis glycemic load and colon cancer

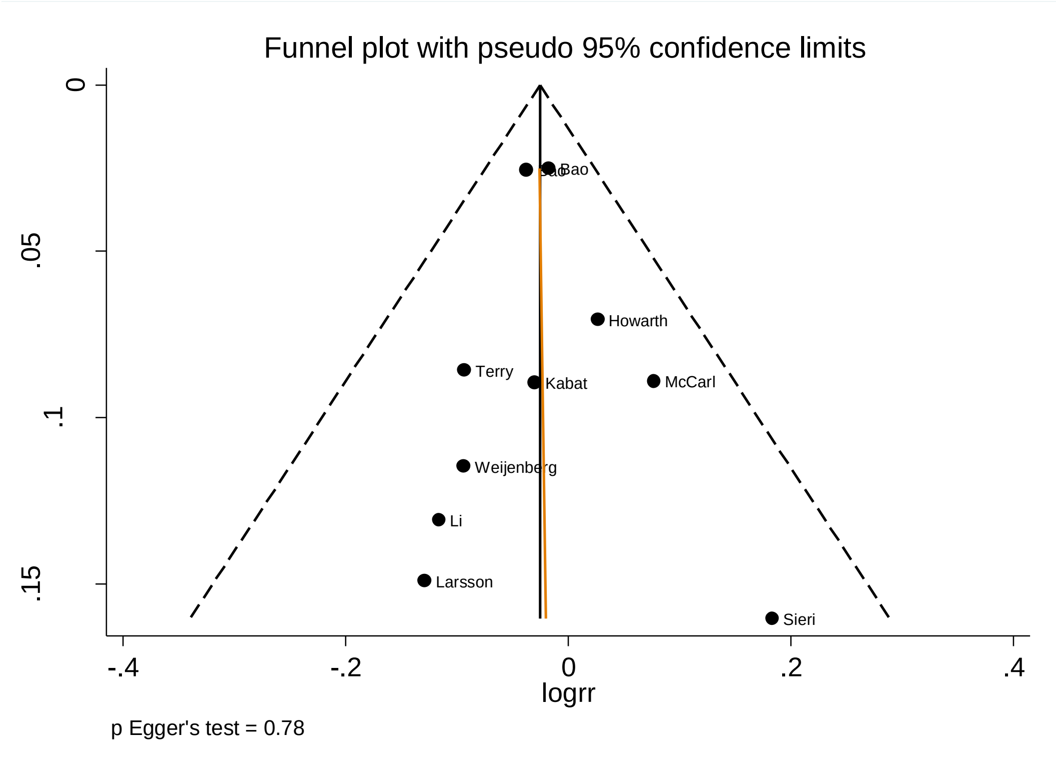


Figure 371 RR (95% CI) of colon cancer for 50 units/day increase of glycemic load by sex

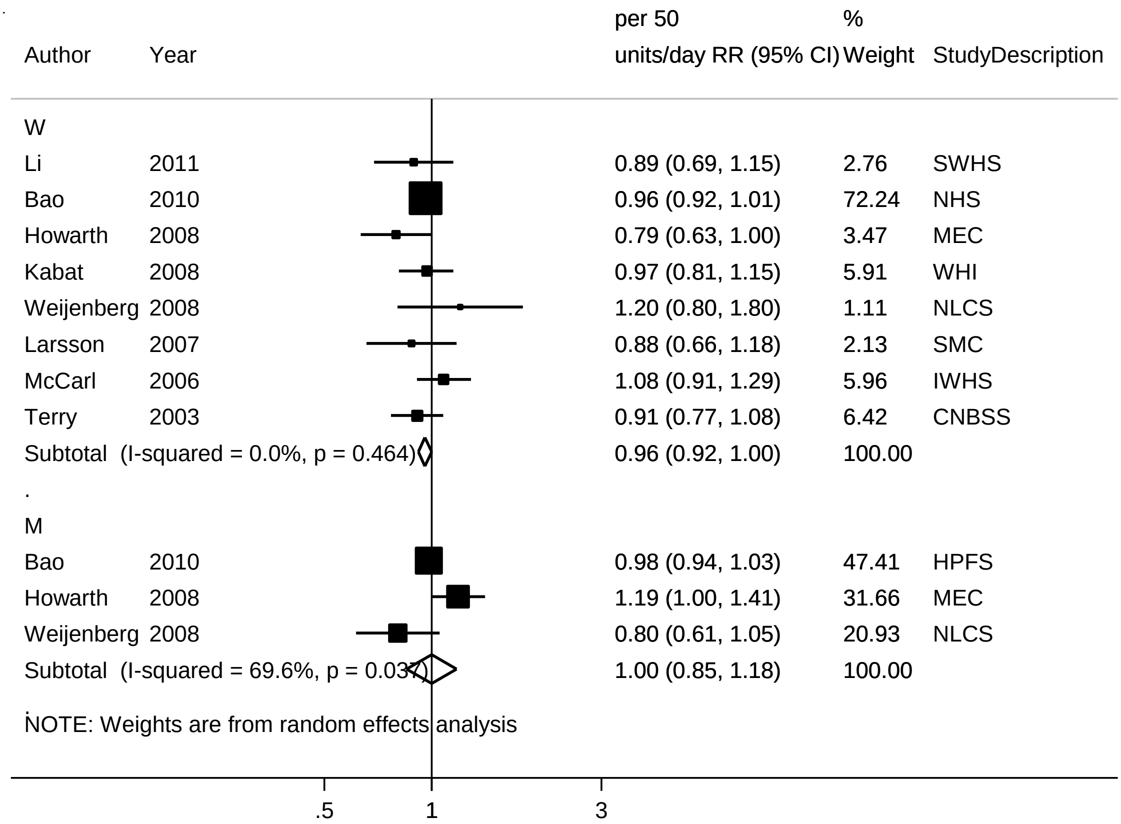


Figure 372 RR (95% CI) of colon cancer for 50 units/day increase of glycemic load by location

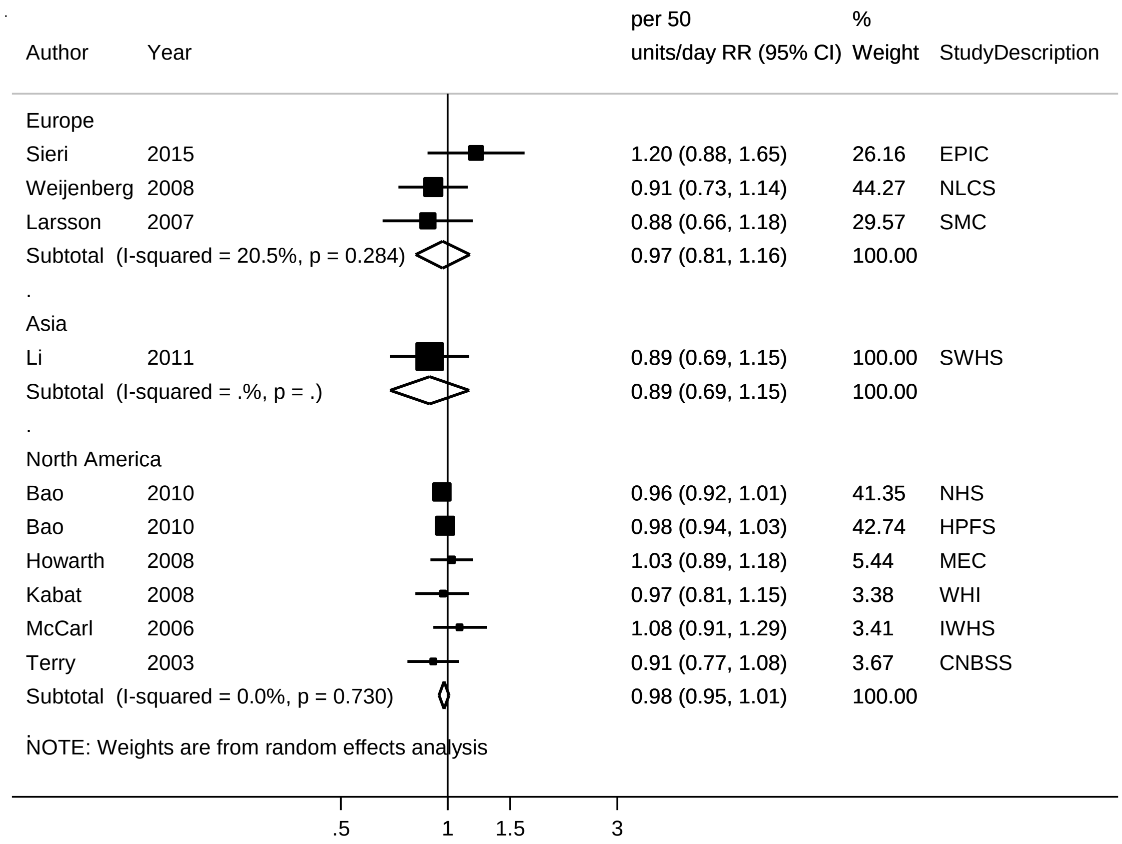


Figure 373 RR estimates of rectal cancer by levels of glycemic load

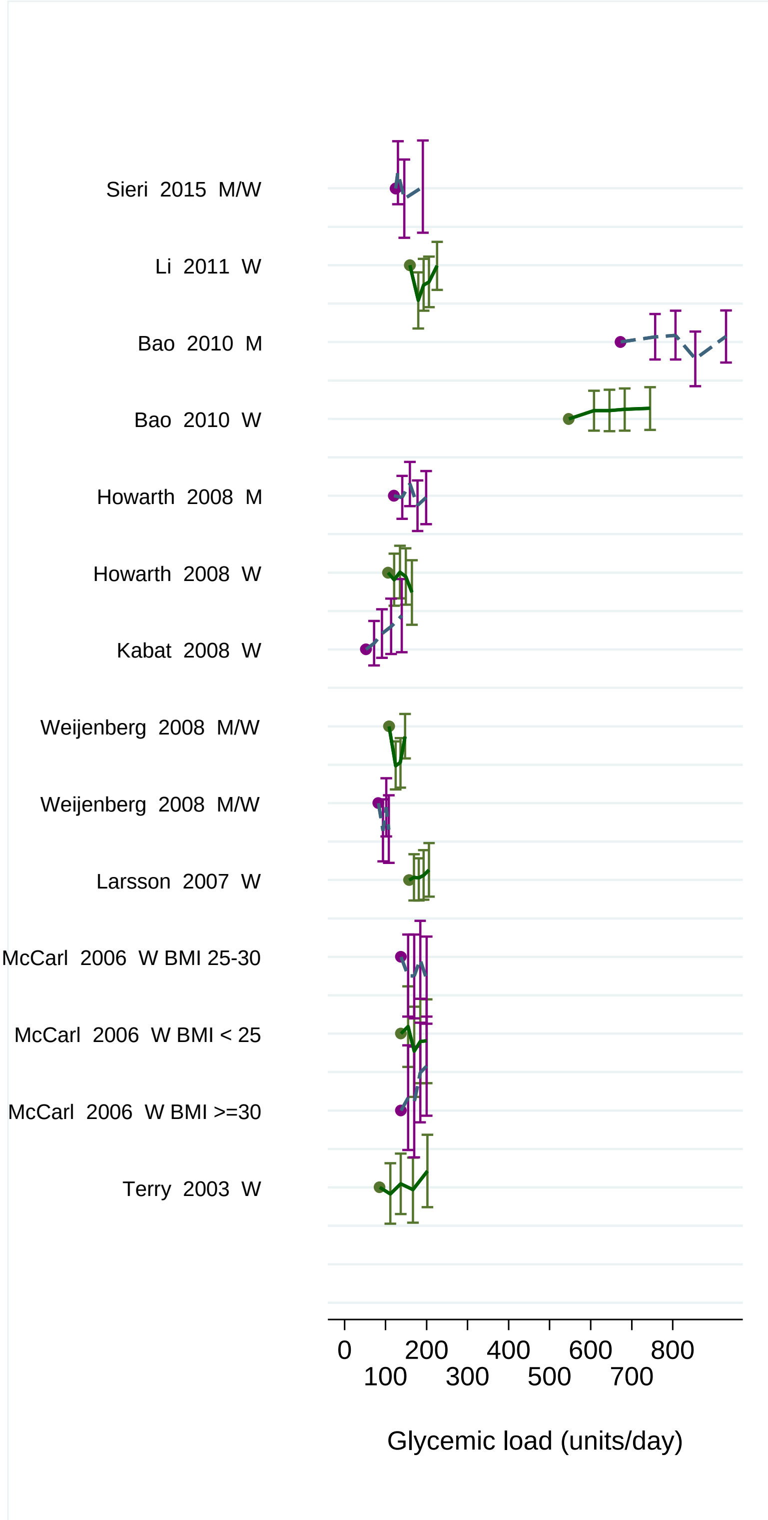


Figure 374 RR (95% CI) of rectal cancer for the highest compared with the lowest level of glycemic load

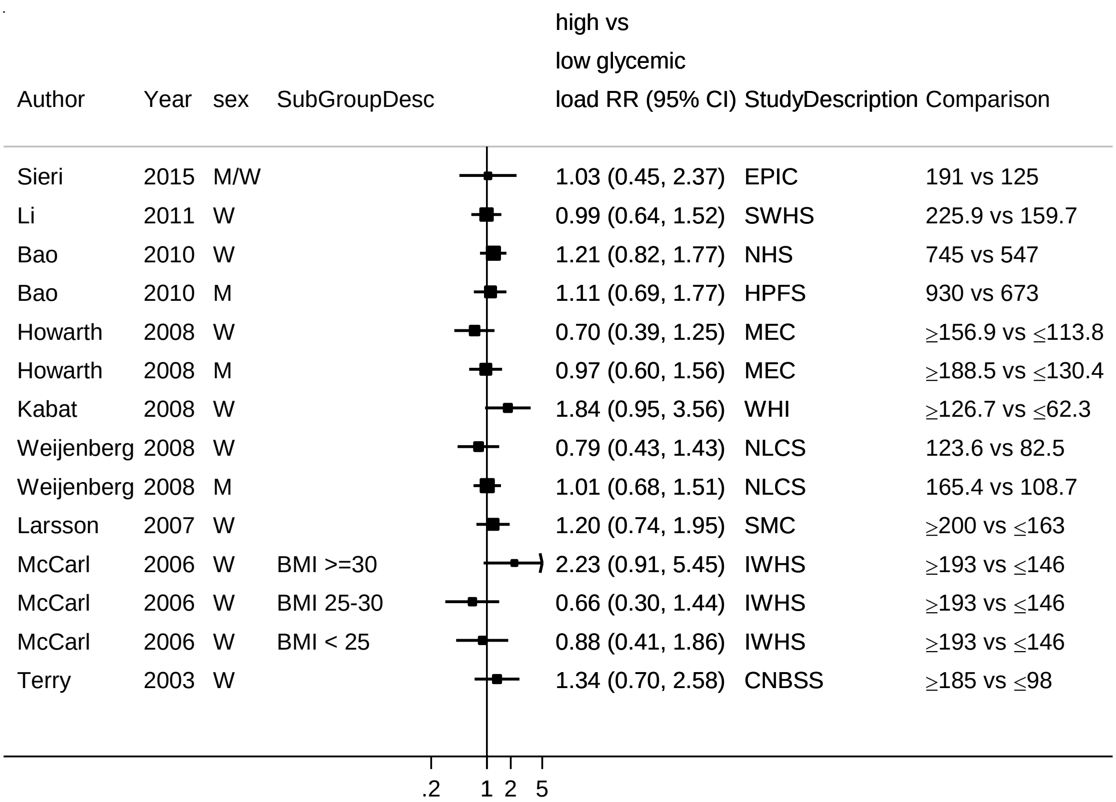


Figure 375 RR (95% CI) of rectal cancer for 50 units/day increase of glycemic load

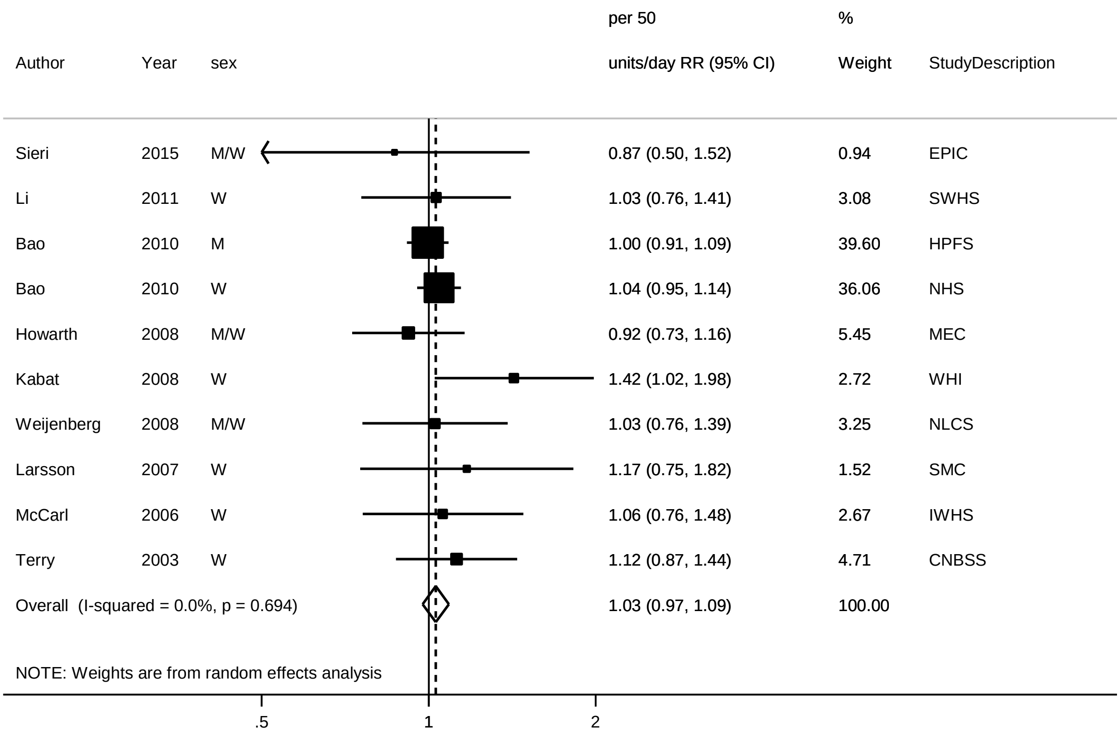


Figure 376 Funnel plot of studies included in the dose response meta-analysis glycemic load and rectal cancer

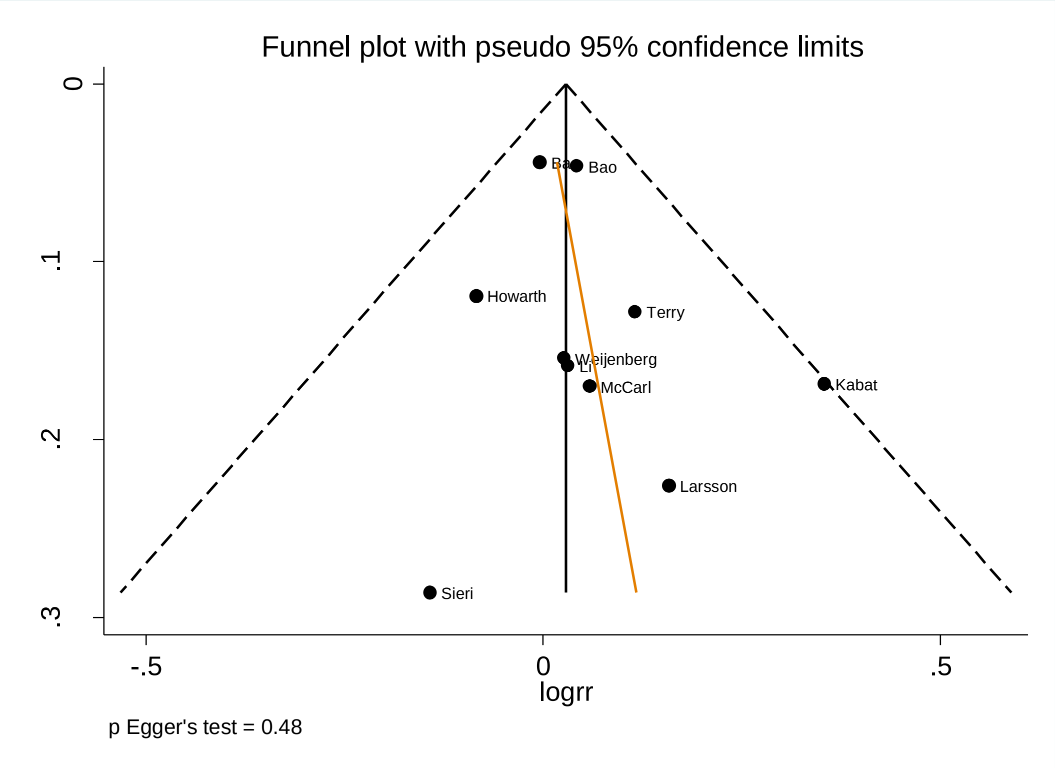


Figure 377 RR (95% CI) of rectal cancer for 50 units/day increase of glycemic load by sex

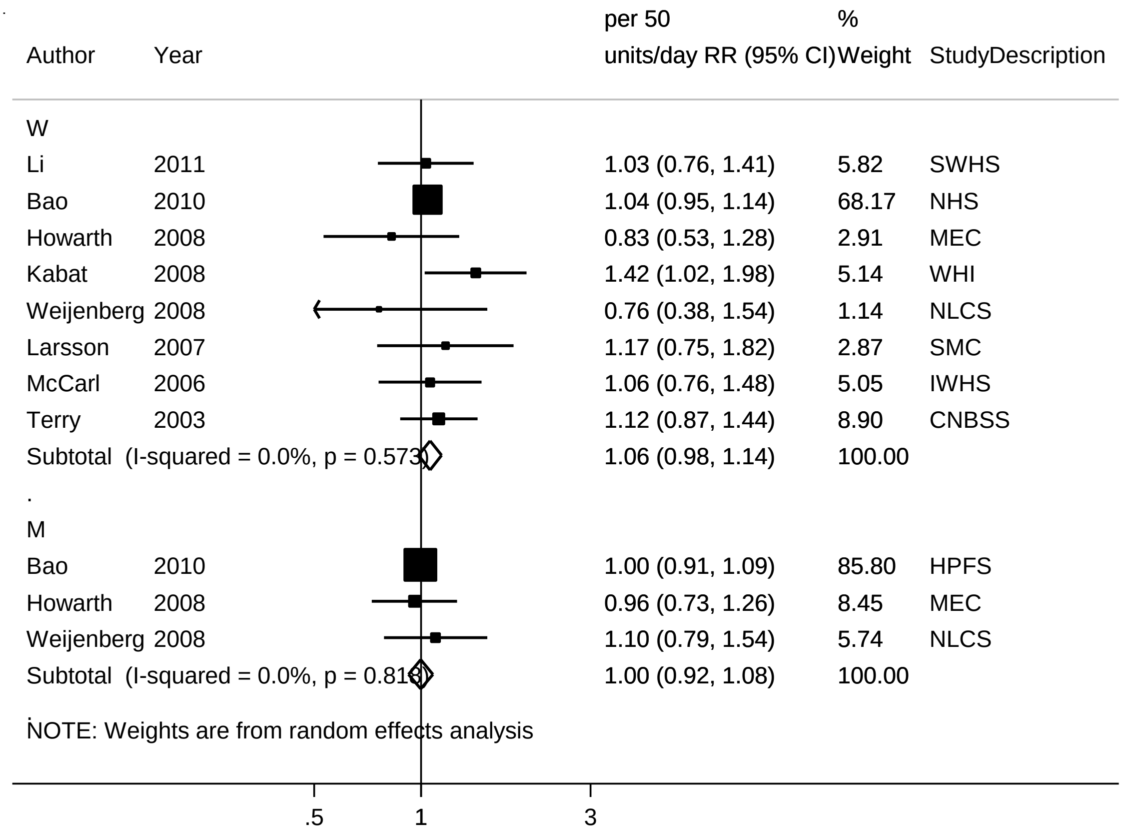
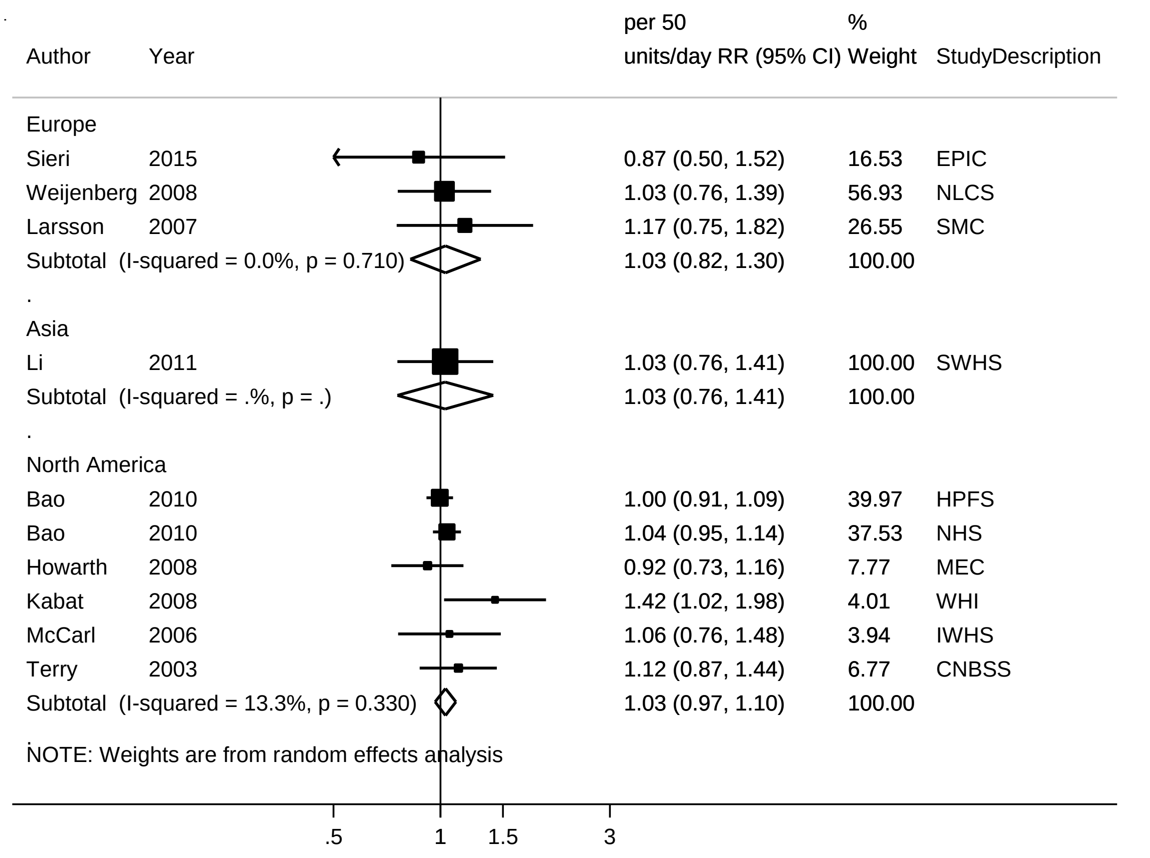


Figure 378 RR (95% CI) of rectal cancer for 50 units/day increase of glycemic load by location



5.2.4.1 Dietary n-3 fatty acid from fish

Cohort studies

Summary

Main results:
No meta-analysis was conducted in the SLR 2010. In total, five studies identified, including two new studies which were published after 2010. All the analyses are on cancer incidence. There were not enough studies to conduct the dose-response meta-analysis for colon and rectal cancer.

Colorectal cancer:
Five studies (3 647 cases) were included in the dose-response meta-analysis of dietary n-3 fatty acid from fish and colorectal cancer. No significant association was observed.
After stratification by sex and geographic location, no significant associations were observed.
There was no evidence of publication bias (p=0.35). There was evidence of a non-linear association (p=<0.001) only significant increased risk up to 0.43 g/day.

The summary RRs ranged from 1.00 (95% CI=0.93-1.08) when Song, 2014 (HPFS) was omitted to 1.03 (95% CI=0.96-1.11) when Butler, 2009 was omitted.

Study quality:
Marine n-3 fatty acid intake was estimated using FFQ. The studies adjusted for most known confounding factors. Cancer outcome was confirmed using cancer registry records and medical records in most studies.

No pooled analysis or meta-analysis were identified.

Table 206 Dietary n-3 fatty acid from fish and colorectal cancer risk. Number of studies in the CUP SLR

	Number
Studies identified	5 (6 publications)
Studies included in forest plot of highest compared with lowest exposure	5
Studies included in dose-response meta-analysis	5
Studies included in non-linear dose-response meta-analysis	5

Note: Include cohort, nested case-control and case-cohort designs

Table 207 Dietary n-3 fatty acid from fish and colorectal cancer risk. Summary of the dose-response meta-analysis in the 2010 SLR and 2015 SLR

	2010 SLR (no analysis)	**2015 SLR**
Increment unit used		0.3 g/day
Studies (n)		5
Cases (total number)		3 647
RR (95%CI)		1.02 (0.96-1.09)
Heterogeneity (I^2, p-value)		0%,0.88

Stratified analysis by sex			
2015 SLR	**Men**	**Women**	
Studies (n)	3	2	
RR (95%CI)	1.05 (0.96-1.16)	1.01 (0.90-1.13)	
Heterogeneity (I^2, p-value)	0%, 0.86	0%, 0.49	
Stratified analysis by geographic location			
2015 SLR	**Asia**	**Europe**	**North America**
Studies (n)	1	1	3
RR (95%CI)	0.97 (0.84-1.12)	1.01 (0.85-1.20)	1.04 (0.96-1.12)
Heterogeneity (I^2, p-value)			0%, 0.77

Table 208 Dietary n-3 fatty acid from fish and colorectal cancer risk. Main characteristics of studies included in the CUP SLR dose-response meta-analysis

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Missing data derived for analyses
Song, 2014 COL41015 USA	NHS, Prospective Cohort, Age: 30-55 years, W	1 295/ 76 386 26 years	Self-administered questionnaire, national death Index, pathology reports and medical records	FFQ	Incidence, colorectal cancer	≥0.3 vs ≤0.15 g/day	1.03 (0.89-1.20)	Age, alcohol, BMI, calendar year, calories intake, endoscopy, energy-adjusted calcium, energy-adjusted folate, energy-adjusted vitamin d, family history, fibre, HRT use, multivitamin supplement intake, nsaid use, pack years of smoking, physical activity, postmenopausal status, processed meat, red meat	Mid-point exposure
Song, 2014 COL41016 USA	Health Professionals Follow-up Study (HPFS), Prospective	847/ 47 143 24 years	Self-report, medical records, pathology report, family members,		Incidence, colorectal cancer	≥0.41 vs ≤0.16 g/day	1.05 (0.85-1.30)	Age, alcohol, BMI, endoscopy, energy-adjusted calcium, energy-	Mid-point exposure

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Missing data derived for analyses
	Cohort, Age: 40-75 years, M, Health professionals		national death Index					adjusted folate, energy-adjusted vitamin d, family history of colon cancer, fibre, multivitamin supplement intake, nsaid use, pack years of smoking, physical activity, red and processed meat, total calories, year	
Butler, 2009 COL40769 Singapore	SCHS, Prospective Cohort, Age: 45-74 years, M/W	375/ 61 321 >10 years	Cancer registry	Quantitative FFQ	Incidence, advanced colorectal cancer, men	0.67 vs 0.36 g/1000 kcal/day	0.77 (0.47-1.26) Ptrend:0.42	Age, alcohol intake, BMI, diabetes, dialect group, educational level, energy intake, family history of colorectal cancer, physical activity, smoking habits, year of	Unit converted to g/day

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Missing data derived for analyses
								Interview	
Daniel, 2009 COL40784 USA	CPS II, Prospective Cohort, Age: 69 years, M/W	452/ 99 080	Cancer registry and death certificates and medical records	FFQ	Incidence, colorectal cancer, men	≥0.25 vs ≤0.09 g/day	1.00 (0.75-1.33) Ptrend:0.90	Age, BMI, dairy products consumption, energy intake, fruits intake, health screening, HRT use, nsaid use, recreational activity, red and processed meat, vegetable intake	Mid-point exposure
		417/ 99 080			Incidence, colorectal cancer, women	≥0.24 vs ≤0.09 g/day	0.94 (0.72-1.24) Ptrend:0.83		
Pietinen, 1999 COL00176 Finland	ATBC, Prospective Cohort, Age: 50-69 years, M, Smokers	185/ 27 111 8 years	Population	Dietary history questionnaire	Incidence, colorectal cancer,	0.70 vs 0.20 g/day	1.20 (0.80-1.90)	Age, alcohol consumption, BMI, calcium intake, educational level, energy intake, physical activity, smoking years, supplement group	

Table 209 Dietary n-3 fatty acid from fish and colorectal cancer risk. Main characteristics of studies excluded from the CUP SLR dose-response meta-analysis

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Reasons for exclusion
Butler, 2008 COL40639 Singapore	SCHS, Prospective Cohort, Age: 45-74 years, M/W	961/ 61 321 9.8 years	Cancer registry	FFQ	Incidence, colorectal cancer	Q 4 vs Q 1	1.21 (1.01-1.45) Ptrend:0.03	Age, sex, alcohol intake, BMI, diabetes, dialect group, educational level, energy intake, exposure assessment, family history of colorectal cancer, physical activity, smoking habits	Superseded by Butler, 2009 COL40769

Figure 379 RR estimates of colorectal cancer by levels of dietary n-3 fatty acid from fish

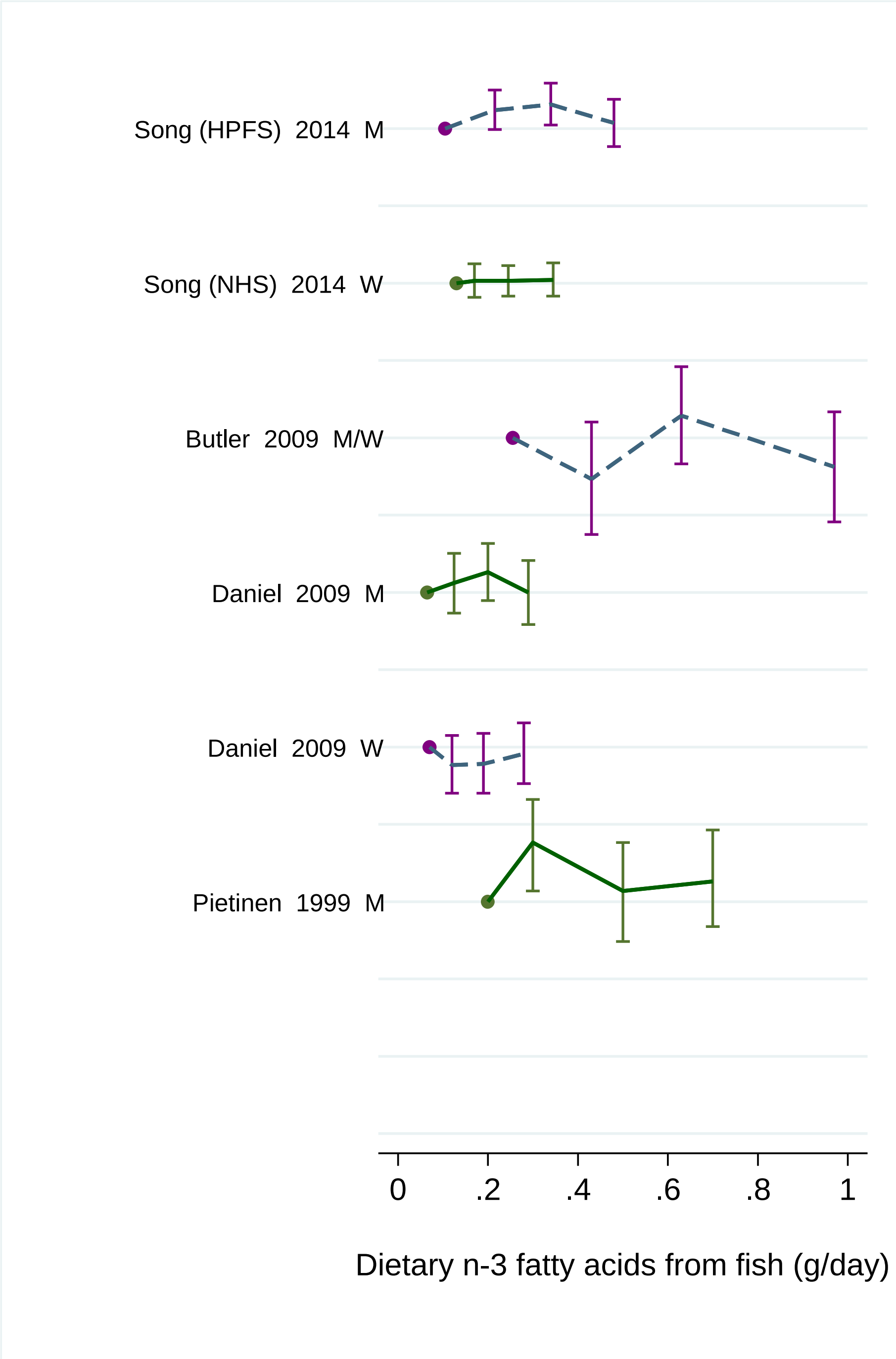


Figure 380 RR (95% CI) of colorectal cancer for the highest compared with the lowest level of dietary n-3 fatty acid from fish

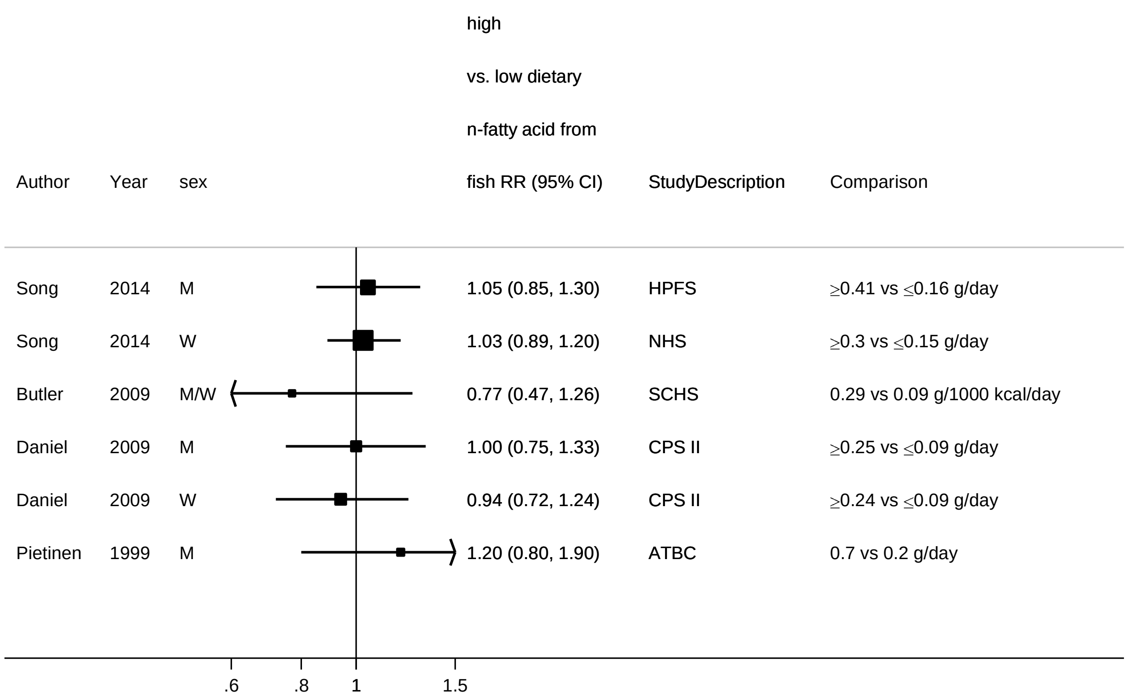


Figure 381 RR (95% CI) of colorectal cancer for 0.3g/day increase of dietary n-3 fatty acid from fish

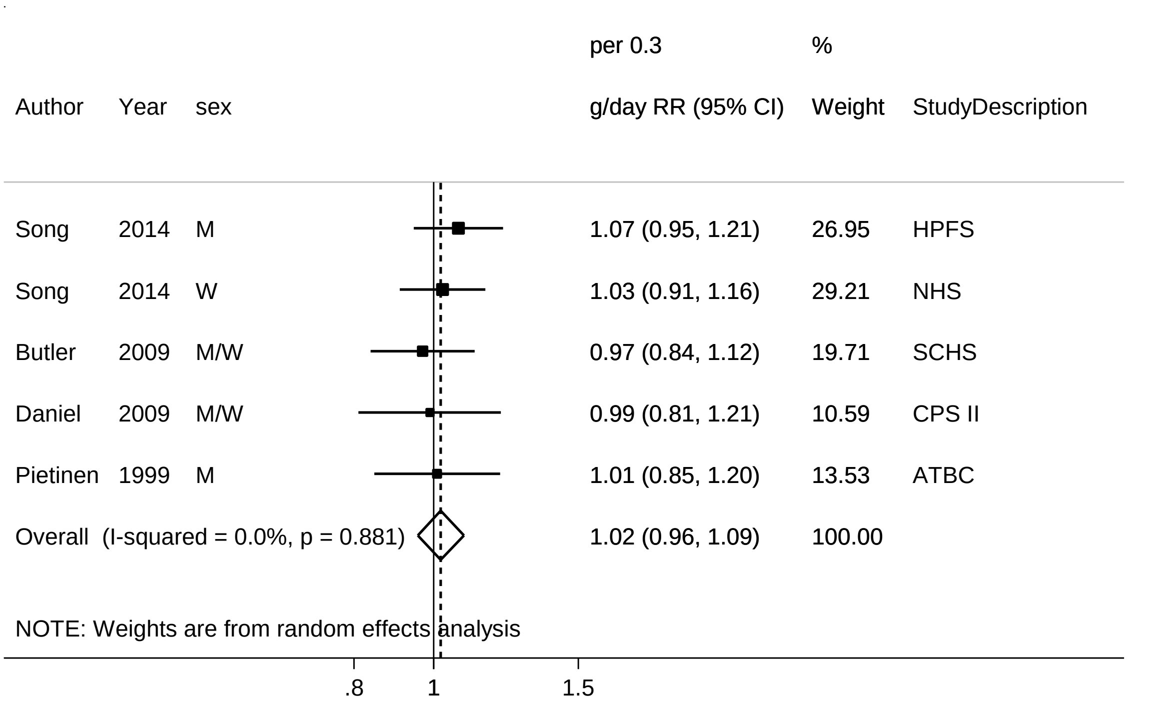
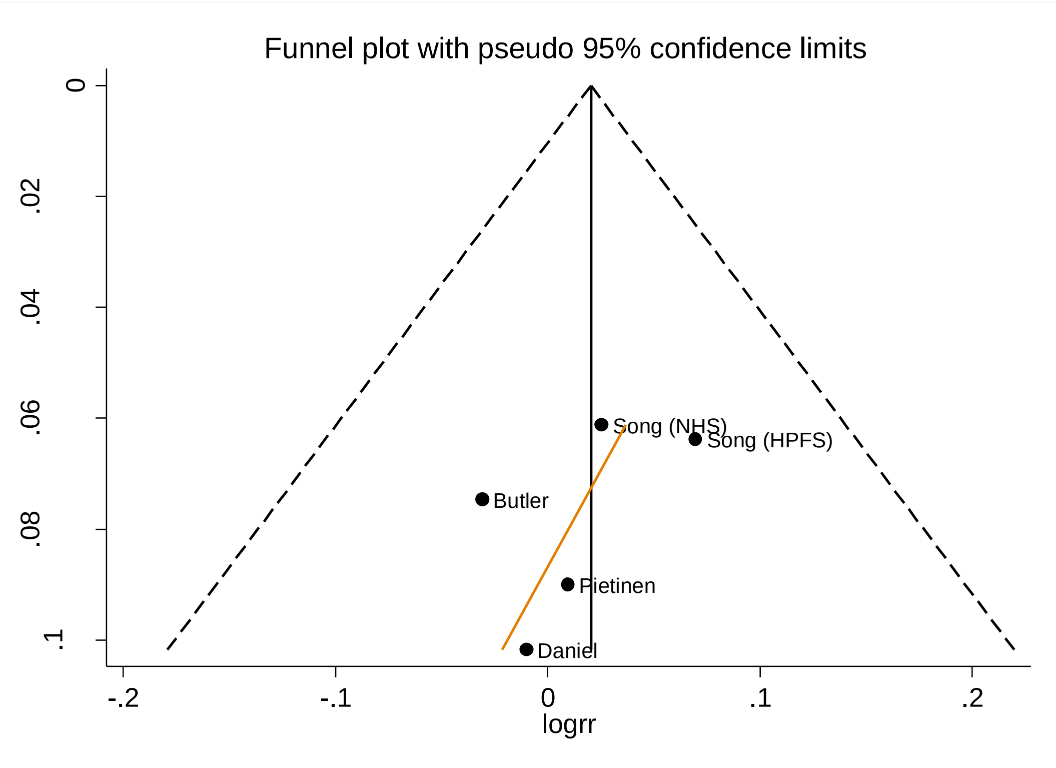


Figure 382 Funnel plot of studies included in the dose response meta-analysis of dietary n-3 fatty acid from fish and colorectal cancer



p for Egger's test=0.35

Figure 383 RR (95% CI) of colorectal cancer for 1mg/day increase of dietary n-3 fatty acid from fish by sex

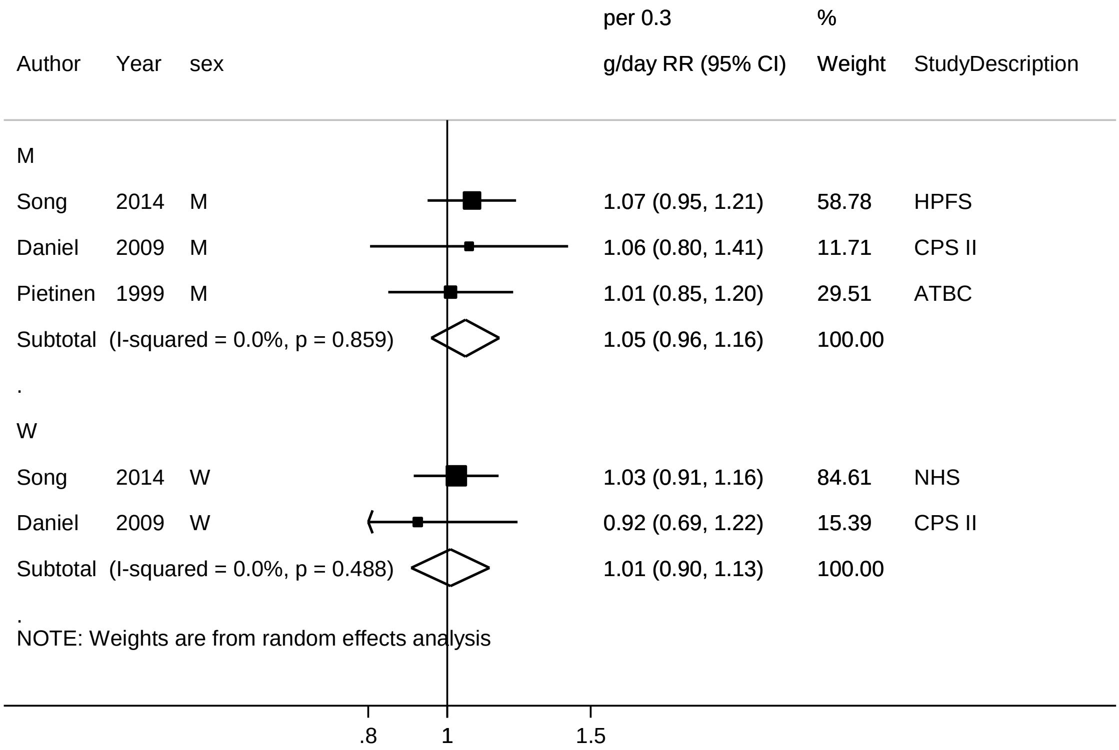


Figure 384 RR (95% CI) of colorectal cancer for 1mg/day increase of dietary n-3 fatty acid from fish by geographic location

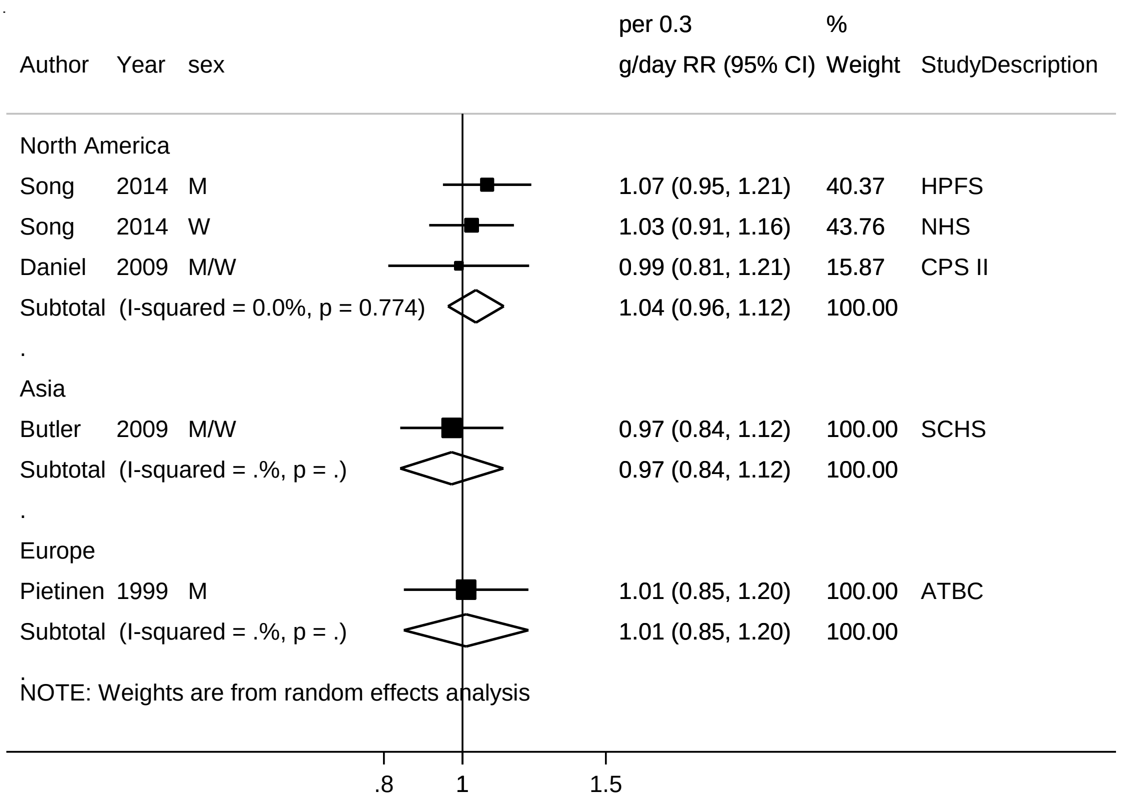
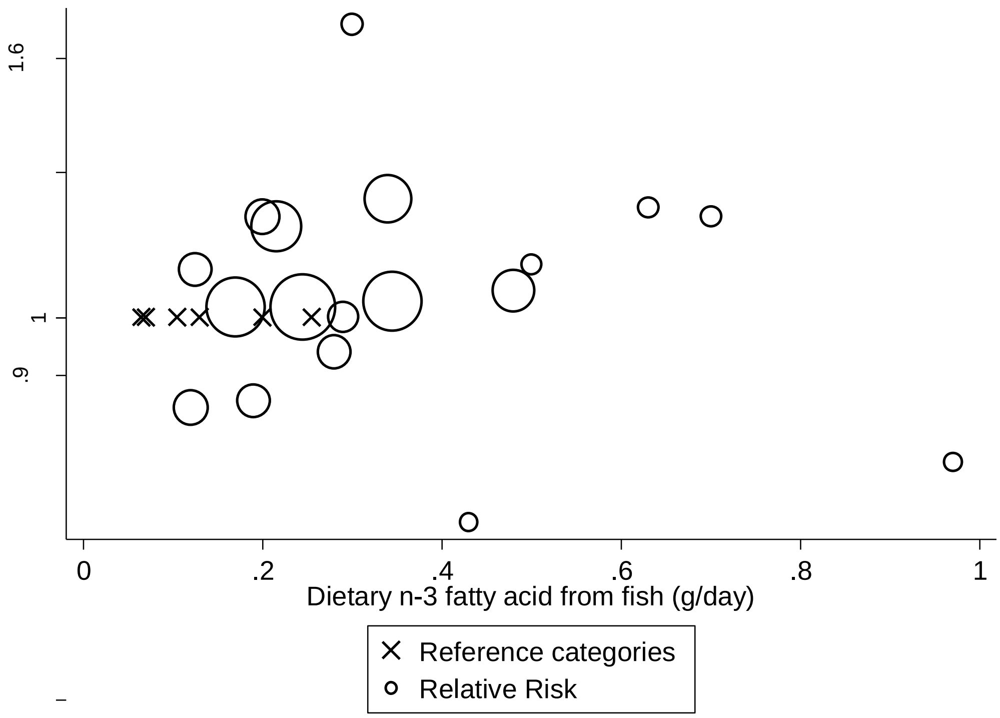
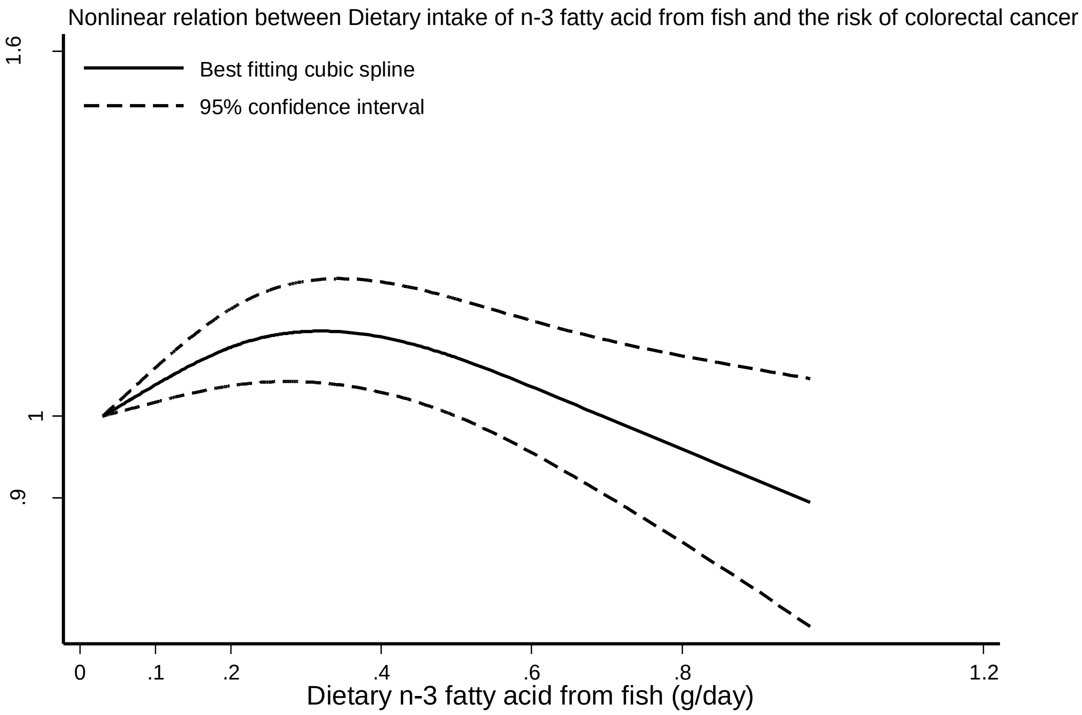


Figure 385 Relative risk of colorectal cancer and dietary intake of n-3 fatty acid from fish estimated using non-linear models





p for non-linearity=0.000

Table 210 Table with dietary intake of n-3 fatty acid values and corresponding RRs (95% CIs) for non-linear analysis of dietary intake of n-3 fatty acid from fish and colorectal cancer

Dietary intake of n-3 fatty acid from fish (g/day)	RR (95%CI)
0.03	1.00
0.10	1.04 (1.02-1.07)
0.19	1.09 (1.04-1.14)
0.25	1.11 (1.05-1.18)
0.43	1.10 (1.02-1.18)
0.70	1.00 (0.90-1.10)
0.97	0.89 (0.76-1.05)

5.4 Alcohol (as ethanol)

Cohort studies

Summary

Main results:
Eight new studies were identified since the publication of the 2010 CUP SLR, seven studies on colorectal, four on colon cancer and two on rectal cancer. There were five studies (Shen, 2013; Yang, 2012; Breslow, 2011; Kim, 2010 and Yi 2010) on mortality, but there was insufficient data to conduct dose-response meta-analysis on mortality. A highest compared to lowest analysis on colorectal cancer mortality was conducted, for this analysis alcohol as ethanol and total alcoholic drinks were combined.

Colorectal cancer:
Sixteen studies (15896 cases) were included in the dose-response meta-analysis of alcohol and colorectal cancer. A significant association with moderate heterogeneity was observed (7% risk increase for 10 g increase of alcohol intake). The significant association was observed in men after stratification by sex. Significant associations were observed in analyses by geographic location; the heterogeneity was reduced but persisted within the three North American studies which was explained by the lack of association in a cohort of postmenopausal women (IWHS, Razzak, 2011).
The overall association remained statistically significant in influence analysis. The summary RRs ranged from 1.06 (95% CI=1.05-1.08) when Nan, 2013 was omitted to 1.07 (95% CI=1.05-1.09) when Bamia, 2013 was omitted.
There was no significant evidence of publication bias (p=0.33). There was evidence of a non-linear association (p<0.01). No significant risk increase is observed at low intake levels

(about less than 20 g/day). The relationship is positive and linear above this level. Only six studies could be included in the analysis.

In the 2010 SLR there was only analysis on beer (drinks/day), no analysis on wine or liquor.

We conducted a dose-response analysis per 10g/day of wine combining colorectal and colon cancer the RR was 1.04(95%CI=1.01-1.08, 0%, p=0.65, 6 studies), which was driven by the EPIC study (Ferrari, 2007). When we excluded this study the result was not significant 1.04 (95%CI=0.96-1.13).
In a dose-response analysis per 10g/day of beer and colorectal cancer the RR was 1.08(95%CI=1.05-1.11, 0%, p=0.96, 5 studies). In a dose-response analysis per 10g/day of liquors and colorectal cancer the RR was 1.08(95%CI=1.02-1.14, 0%, p=0.74, 4 studies).

Colon cancer:
Eighteen studies (12051 cases) were included in the dose-response meta-analysis of alcohol and colon cancer. A significant 7% risk increase for 10 g increase of alcohol intake was observed, with moderate heterogeneity. A significant association was consistently observed in women, and men for whom the results were also heterogeneous. In analysis by geographic location, weaker and overall heterogeneous associations were observed in North American studies compared to European and Asian studies opposite results. More studies could be included in the subgroup of Asian studies. There was no evidence of publication bias (p=0.31). There was no evidence of a non-linear association (p=0.24) from the 11 studies included in the analysis.
The overall association remained statistically significant in influence analysis. The summary RRs ranged from 1.06 (95% CI=1.04-1.09) when Akhter, 2007 was omitted to 1.07 (95% CI=1.06-1.09) when Ferrari, 2007 was omitted.

Rectal cancer:
Eleven studies (7763 cases) were included in the dose-response meta-analysis of alcohol and rectal cancer. A significant 7% risk increase for 10 g increase of alcohol intake was observed with high heterogeneity was observed. After stratification by sex and geographic location the associations remained significant and the heterogeneity persisted in men. There was no evidence of small study bias (p=0.07). There was no evidence of a non-linear association (p=0.85) from the 11 studies included in the analysis.
The overall association remained statistically significant in influence analysis. The summary RRs ranged from 1.05 (95% CI=1.01-1.09) when Murata, 1996 was omitted to 1.07 (95% CI=1.03-1.10) when Chyou, 1996 was omitted.

Study quality:
All studies used questionnaires self-reported FFQ or questionnaires to assess alcohol intake. All studies were multiple adjusted for different confounders. Cancer outcome was confirmed using cancer registry records in most studies.

Pooling project of cohort studies:

Two Pooling Projects were identified. One was a pooled analysis of Japanese studies (Mizoue, 2008) and the other was a pooled analysis of UK studies part of the UK Dietary Cohort Consortium (Park, 2010). Both were identified in the 2010 SLR, but were not included in the analysis. The Japanese analysis showed a significant positive association in men and women. The pooled analysis from the UK showed non-significant results. Asian studies tend to use higher categories of alcohol intake than European and American studies. Because the UK Dietary Cohort Consortium includes the EPIC-Norfolk and EPIC-Oxford studies for the analysis on colorectal cancer it was not combine with the studies identified in the CUP SLR in order to avoid the overlap with the EPIC study (Bamia, 2013).

Table 211 Alcohol (as ethanol) and colorectal cancer risk. Number of studies in the CUP SLR (this table related to incidence only)

	Number
Studies identified	19 studies (26 publications)
Studies included in forest plot of highest compared with lowest exposure	17
Studies included in dose-response meta-analysis	16
Studies included in non-linear dose-response meta-analysis	16

Note: Include cohort, nested case-control and case-cohort designs

Table 212 Alcohol (as ethanol) and colon cancer risk. Number of studies in the CUP SLR

	Number
Studies identified	18 studies (27 publications)
Studies included in forest plot of highest compared with lowest exposure	15
Studies included in dose-response meta-analysis	14
Studies included in non-linear dose-response meta-analysis	11

Note: Include cohort, nested case-control and case-cohort designs

Table 213Alcohol (as ethanol) and rectal cancer risk. Number of studies in the CUP SLR

	Number
Studies identified	16 (22 publications)
Studies included in forest plot of highest compared with lowest exposure	14
Studies included in dose-response meta-analysis	11
Studies included in non-linear dose-response meta-analysis	11

Note: Include cohort, nested case-control and case-cohort designs

Table 214Alcohol (as ethanol) colorectal cancer risk. Summary of the dose-response meta-analysis in the 2010 SLR and 2015 SLR.

	2010 SLR	**2015 SLR**
Increment unit used	Per 10g/day	Per 10g/day
Studies (n)	8	16
Cases (total number)	5261	15896
RR (95%CI)	1.10(1.06-1.13)	1.07(1.05-1.09)
Heterogeneity (I^2, p-value)	50.7%; 0.05	24.5%, 0.21

Stratified analysis by sex		
Men	**2010 SLR**	**2015 SLR**
Studies (n)	**7**	14

RR (95%CI)	1.11(1.08-1.15)	1.08(1.06-1.10)
Heterogeneity (I^2, p-value)	21.1%, 0.27	13.9%, 0.32
Women		
Studies (n)	2	10
RR (95%CI)	1.07(0.98-1.17)	1.04 (1.00-1.08)
Heterogeneity (I^2, p-value)	0%, 0.62	42.9%, 0.12
Stratified analysis by geographic location		
2005 SLR (no analysis in 2010 SLR)		
Asia	**2005 SLR**	**2015 SLR**
Studies (n)	2	7
RR (95%CI)	1.17(1.05-1.31)	1.07 (1.06-1.08)
Heterogeneity (I^2, p-value)	9.3%, 0.29	10.7%, 0.33
Europe		
Studies (n)	4	5
RR (95%CI)	1.05(0.99-1.12)	1.05(1.02-1.08)
Heterogeneity (I^2, p-value)	0%, 0.82	0%, 0.53
North America		
Studies (n)	2	4
RR (95%CI)	1.07(0.98-1.17)	1.06 (1.01-1.12)
Heterogeneity (I^2, p-value)	57.2%, 0.04	63.1%, 0.04

Table 215Alcohol (as ethanol) and colon cancer risk. Summary of the dose-response meta-analysis in the 2010 SLR and 2015 SLR.

	2010 SLR	2015 SLR
Increment unit used	Per 10g/day	Per 10g/day
Studies (n)	12	14
Cases (total number)	7782	12051
RR (95%CI)	1.08(1.04-1.13)	1.07 (1.05-1.09)
Heterogeneity (I^2, p-value)	60.1%, ≤0.01	34.2%, 0.13

Stratified analysis by sex		
Men	**2010 SLR**	**2015 SLR**
Studies (n)	**10**	12
RR (95%CI)	1.10(1.06-1.14)	1.08(1.06-1.10)
Heterogeneity (I^2, p-value)	62.4%, <0.01	36.9%, 0.13
Women		
Studies (n)	8	10
RR (95%CI)	1.03(0.96-1.10)	1.05(1.02-1.09)
Heterogeneity (I^2, p-value)	34.2%, =0.16	0%, 0.46
Stratified analysis by geographic location		
Asia	**2010 SLR**	

Studies (n)	5	8
RR (95%CI)	1.13(1.09-1.17)	1.08(1.07-1.10)
Heterogeneity (I^2, p-value)	0%, 0.97	0%, 0.61
Europe		
Studies (n)	3	3
RR (95%CI)	1.03(1.00-1.06)	1.03(1.00-1.07)
Heterogeneity (I^2, p-value)	0%, 0.44)	0%, 0.52
North America		
Studies (n)	4	3
RR (95%CI)	1.07(0.93-1.23)	1.07(0.99-1.16)
Heterogeneity (I^2, p-value)	70.6%, 0.02	0%, 0.52

Table 216 Alcohol (as ethanol) and rectal cancer risk. Summary of the dose-response meta-analysis in the 2010 SLR and 2015 SLR.

	2010 SLR	**2015 SLR**
Increment unit used	Per 10g/day	Per 10g/day
Studies (n)	11	11
Cases (total number)	3584	7763
RR (95%CI)	1.10(1.07-1.12)	1.08(1.07-1.10)
Heterogeneity (I^2, p-value)	0%, 0.64	0%, 0.54

Stratified analysis by sex		
Men	**2010 SLR**	**2015 SLR**
Studies (n)	**9**	10
RR (95%CI)	1.10(1.07-1.13)	1.09(1.06-1.12)
Heterogeneity (I^2, p-value)	6.1%, 0.39	24.6%, 0.25
Women		
Studies (n)	7	8
RR (95%CI)	1.09(1.03-1.16)	1.09(1.04-1.15)
Heterogeneity (I^2, p-value)	0%, 0.54	0%, 0.58
Stratified analysis by geographic location		
Asia	**2010 SLR**	**2015 SLR**
Studies (n)	5	7
RR (95%CI)	1.09(1.05-1.14)	1.07(1.05-1.10)
Heterogeneity (I^2, p-value)	0%, 0.70	0%, 0.92
Europe		
Studies (n)	3	3
RR (95%CI)	1.09(1.07-1.12)	1.09 (1.05-1.12)
Heterogeneity (I^2, p-value)	0%, 0.61	0%, 0.61
North America		
Studies (n)	3	1

RR (95%CI)	1.08(0.94-1.24)	1.13 (1.08-1.19)
Heterogeneity (I^2, p-value)	42.2%, 0.18	-

Table 217 Alcohol (as ethanol) and colorectal cancer risk. Results of meta-analyses and pooled analyses of prospective studies published after the 2005 SLR.

Author, Year	Number of cohort studies	Total number of cases	Studies country, area	Outcome	Comparison	RR (95%CI)	P trend	Heterogeneity (I^2, p value)
Pooled analyses								
Park, 2010	7	579	UK	Colorectal cancer	≥45 vs 0 g/day	Men 1.24(0.69-2.22) Women 1.52(0.56-4.10)	0.97 0.72	
		380		Colon cancer	≥30 vs <5 g/day	1.21(0.77-1.90)	0.85	
		174		Proximal colon		1.03 (0.57-1.86)	0.54	
		146		Distal colon		1.60 (0.85-3.01)	0.46	
		199		Rectal cancer		0.93(0.48-1.78)	0.76	
Mizoue, 2008	5	M 1724 W 1078	Japan	Colorectal cancer	Per 15g/day	Men 1.11 (1.09-1.14) Women 1.13 (1.06-1.20)	<0.001 <0.001	
		M 1093 W 736		Colon cancer		Men 1.12 (1.09-1.15) Women 1.14 (1.05-1.23)	<0.001 0.001	
		M 629 W 338		Rectal cancer		Men 1.11 (1.07-1.15) Women 1.14 (1.02-1.29)	<0.001 0.027	

Table 218 Alcohol (as ethanol) and colorectal cancer risk. Main characteristics of studies included in the CUP SLR dose-response meta-analysis

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Missing data derived for analyses
Shin, 2014 COL41023 Korea	KNHIC, Prospective Cohort, Age: 30-80 years, M/W	2655 1 326 058	Korean central cancer registry (kccr) & Insurance system	Self-administered questionnaire	Incidence, rectal cancer, women	≥25 vs ≤0 g/day	1.48 (1.10-1.99)	Age, BMI, cigarette smoking, family history of cancer, fasting blood sugar, height, meat consumption, serum cholesterol	Distribution of person-years by exposure category, mid-points of exposure categories.
		6492			Incidence, colon cancer, men		1.31 (1.19-1.45)		
		3555			Incidence, colorectal cancer, men		1.26 (1.18, 1.35)		
		3146			Incidence, rectal cancer, men		1.26 (1.18-1.35)		
Nan, 2013 COL40971 USA	NHS, Prospective Cohort, Age: 30-55 years, W, Registered nurses	1 628/ 87 856 28 years	Medical records, pathology reports, next of kin, death certificate, ndi	FFQ	Incidence, colorectal cancer	≥30 vs ≤0 g/day	1.30 (1.00-1.69) Ptrend:0.15	Age, aspirin use, BMI, dietary calcium, endoscopy, energy intake, family history of colorectal cancer, height, multivitamin supplement intake, pack-yrs of smoking, physical activity, postmenopausal hormone use,	Midpoints

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Missing data derived for analyses
								red meat	
Nan, 2013 COL40972 USA	HPFS, Prospective Cohort, Age: 40-75 years, M, Health professionals	1 165/ 46 874 22 years	Medical records, pathology reports, next of kin, death certificate, ndi		Incidence, colorectal cancer	≥30 vs ≤0 g/day	1.38 (1.11-1.72) Ptrend:<0.001	Age, aspirin use, BMI, dietary calcium, energy intake, family history of colorectal cancer, height, multivitamin supplement intake, physical activity, postmenopausal hormone use, red meat	Midpoints
Bamia, 2013 COL40964 Denmark, France, Germany, Greece, Italy, Netherlands, Spain, Sweden, UK	EPIC, Prospective Cohort, Age: 25-70 years, M/W	2 479/ 480 308 11.6 years	Cancer registry, record linkage, health Insurance rec, mortality registry , pathology and active follow up	FFQ	Incidence, colorectal cancer, women	23.1 vs 0.4 g/day	0.98 (0.88-1.08)	Age, sex, BMI, centre location, cereal, dairy products consumption, educational level, ethanol, fish, fruits, legumes, lipids, meat, physical activity, smoking	Distribution of person-years by exposure category.
		1 876/			Men	23.1 vs 0.4 g/day	1.20 (1.06-1.35)		
Everatt, 2013 COL40967 Lithuania	KRIS-MIHDPS, Prospective Cohort,	248/ 7 150 30 years	Cancer registry and death registry	Questionnaire	Incidence, colorectal cancer	≥140.1 vs 0.1-10 g/week	1.67 (0.98-2.84)	Age, BMI, educational level, smoking,	Rescale reference category using

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Missing data derived for analyses
	Age: 40-59 years, M							study	the Hamling's method
Cho, 2012 COL40902 U.S	NHS-HPFS, Prospective Cohort, M/W, Health professionals	1801/ 135 151 26 years	Questionnaire and mortality register	FFQ	Incidence, colon cancer, family history of crc	30 vs 0 g/day	2.03 (1.11-3.71) Ptrend:0.69	Age, aspirin use, BMI, calcium, calendar period, endoscopy, energy intake, folate, HRT use, menopausal status, pack yrs of smoking, red meat	Midpoints
Razzak, 2011 COL40889 USA	IWHS, Prospective Cohort, Age: 55-69 years, W	1 255/ 41 836 16 years	Cancer registry and pathology register	Semi-quantitative FFQ	Incidence, colorectal cancer	≥31 vs ≤0 g/day	1.00 (0.71-1.40)	Age, BMI, calcium, energy intake, exogenous female hormones, fat intake, folate, methionine, physical activity, red meat, smoking status, sucrose, vitamin e, whr	Mid-points of exposure categories.
		633/			Incidence, proximal colon cancer	≥31 vs ≤0 g/day	1.12 (0.71-1.77)		
		594/			Incidence, distal colon cancer	≥31 vs ≤0 g/day	0.89 (0.54-1.50)		
Allen, 2009 COL40762 UK	MWS, Prospective Cohort,	1 914/ 1 280 296 7.2 years	Cancer registry	Questionnaire	Incidence, colon cancer	per 10 g/day	0.97 (0.96-1.11)	Age, area of residence, BMI, hormone use,	

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Missing data derived for analyses
	Age: 55 years, W, midlife women				Incidence, rectal cancer		1.10(1.02-1.18)	physical activity, smoking status, socio-economic status, use of oral contraception	
Bongaerts, 2008 COL40635 Netherlands	NLCS, Case Cohort, Age: 55-69 years, M/W	557/ 4 774 13.3 years	Cancer registry	Semi-quantitative FFQ	Incidence, colon cancer, men	≥30 vs ≤0 g/day	1.40 (0.95-2.09)	Age, sex, BMI, calcium intake, family history of colorectal cancer, fat intake, fibre intake, physical activity, total energy intake	Used for colon and rectal cancer. Mid-points of exposure categories.
		460/			Women	≥30 vs ≤0 g/day	1.87 (1.03-3.38)		
		232/			Incidence, rectal cancer, men	≥30 vs ≤0 g/day	2.08 (1.20-3.59)		
		108/			Women	≥30 vs ≤0 g/day	0.72 (0.16-3.10)		
Toriola, 2008 COL40664 Finland	KIHD, Prospective Cohort, Age: 53 years, M	54/ 2 627 16.7 years	Cancer registry	Questionnaire	Incidence, colorectal cancer, men, without first 2 yrs of follow-up	115.5-2853.1 vs 0-3.2 g/week	3.50 (1.20-9.80)	Age, family history of cancer, fibre, leisure time physical activity, smoking status, socio-economic status, vegetable intake, year of Interview	Mid-points of exposure categories. Conversion from g/week to g/day
Mizoue, 2008	Pooled Analysis Japanese Studies				Incidence, colorectal cancer	Per 15g/day	1.11(1.09-1.14)	Area, age, smoking, body mass index	Mid-points of exposure categories.
	JPHC I	61595/ 694			Incidence, colon		1.12(1.09-115)		

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Missing data derived for analyses
					cancer			,energy, red meat, calcium, fiber and folate	
	JPHC II	78825/781			Incidence, rectal cancer		1.11(1.07-1.15)		
	JCCS	110792/ 662							
	Miyagi Cohort	47605/ 482							
	Takayana Study	31552/ 283							
Ferrari, 2007 COL40648 Europe	EPIC, Prospective Cohort, Age: 35-70 years, M/W	1 833/ 478 732 6.2 years	Cancer registry / database / pathology reports	FFQ	Incidence, colorectal cancer	≥60 vs 0.1-4.9 g/day	1.64 (1.29-2.08) Ptrend:<0.001	Age, sex, centre location, educational level, height, non-alcohol energy, physical activity, smoking status, weight	Superseded by Bamia, 2013 COL40964 for colorectal cancer. Used for colon and rectal cancer. Conversion 15g/day to 10g/day
						per 15 g/day	1.09 (1.05-1.13)		
		1 184/			Incidence, colon cancer	≥60 vs 0.1-4.9 g/day	1.43 (1.04-1.97) Ptrend:0.201		
						per 15 g/day	1.07 (1.02-1.12)		
		649/			Incidence, rectal cancer	≥60 vs 0.1-4.9 g/day	1.93 (1.35-2.78) Ptrend:0.003		
						per 15 g/day	1.11 (1.05-1.17)		
		528/			Incidence, distal colon cancer	≥60 vs 0.1-4.9 g/day	1.68 (1.08-2.62) Ptrend:0.073		
						per 15 g/day	1.08 (1.01-1.16)		
		476/			Incidence, proximal colon cancer	≥60 vs 0.1-4.9 g/day	0.92 (0.51-1.66) Ptrend:0.323		
						per 15 g/day	1.03 (0.95-1.12)		
					Incidence, colorectal	per 15 g/day	1.15 (1.03-1.28)		

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Missing data derived for analyses
					cancer, never smoker				
					Former smoker	per 15 g/day	1.11 (0.97-1.28)		
					Current smoker	per 15 g/day	1.23 (1.12-1.36)		
					Incidence, colon cancer, men	per 15 g/day	1.04 (0.98-1.10)		
					Women	per 15 g/day	1.10 (0.96-1.26)		
					Incidence, rectal cancer, men	per 15 g/day	1.11 (1.04-1.17)		
					Women	per 15 g/day	1.20 (0.97-1.49)		
Akhter, 2007 COL40632 Japan	MCS, Prospective Cohort, Age: 40-64 years, M	285/ 21 199 11 years	Cancer registry	Self-administered questionnaire	Incidence, colorectal cancer	≥45.6 vs ≤0 g/day	1.91 (1.32-2.78)	Age, BMI, educational level, family history of colorectal cancer, fruits, green and yellow vegetables consumption, meat intake, physical activity, smoking status	Mid-points of exposure categories.
		164/			Incidence, colon cancer	≥45.6 vs ≤0 g/day	2.03 (1.23-3.33)		
		124/			Incidence, rectal cancer	≥45.6 vs ≤0 g/day	1.84 (1.05-3.21)		
		73/			Incidence, distal colon cancer	≥45.6 vs ≤0 g/day	4.17 (1.63-10.66)		
		70/			Incidence, proximal cancer	≥45.6 vs ≤0 g/day	1.40 (0.72-2.75)		
		285			Incidence, colorectal cancer	Current vs never	1.56 (1.10-2.22)		
		124			Incidence, rectal		1.54 (0.91-2.61)		

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Missing data derived for analyses
Chyou, 1996 COL00087 USA	HHP, Prospective Cohort, M, Japanese ancestry	123/ 8 006 19 years	Selective service draft registration file	Recall	Incidence, rectal cancer, rectal cancer	≥24 vs ≤0 oz/month	2.30 (1.43-3.69)	Age	Distribution of person-years by exposure category. Mid-points of exposure categories. Conversion from oz/month to g/day
Glynn, 1996 COL00431 Finland	ATBC, Prospective Cohort, Age: 50-69 years, M, Smokers	140/ 27 109 8 years	Cancer registry	Food-use questionnaire	Incidence, colorectal cancer,	per 1 g/day	1.01 (1.00-1.02)	Age, calcium, coffee, energy intake, physical activity during work, starch, sweet and sugar	Exposure units rescaled to 10g/day
					Incidence, colon cancer	27.7 vs 5.3 g/day	3.60(1.60-10.40)		
					Incidence, rectal cancer		1.50(0.30-6.70)		
Murata, 1996 COL04060 Japan	Japan, Chiba cancer association cohort, Nested Case Control, M	61/ 122 controls 9 years	Screening examinations	Questionnaire	Incidence, colon cancer,	≥56.7 vs ≤0 g/day	3.20	Age, sex, address	Distribution of person-years by exposure category. Confidence intervals estimation. Mid-points of exposure categories.
		43/ 86 controls			Incidence, rectal cancer,	≥56.7 vs ≤0 g/day	1.40		
Wu, 1987 COL00774 USA	Leisure World Cohort, Prospective	68/ 11 644 4.5 years	Population registries	FFQ	Incidence, right colon cancer, women	≥31 vs ≤0 ml/day	1.00 (0.40-2.80)	Age	Distribution of person-years by exposure
						≥31 vs ≤0	1.66 (0.80-3.60)		

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Missing data derived for analyses
	Cohort, M/W, Retirement community					ml/day			category. Conversion from ml/day to g/day. Mid-points of exposure categories.
		58/			Men	≥31 vs ≤0 ml/day	2.84 (1.20-6.50)		
						≥31 vs ≤0 ml/day	2.21 (0.80-6.00)		
						≥31 vs ≤0 ml/day	2.42 (1.30-4.50)		
					Incidence, colorectal cancer, women	≥31 vs ≤0 ml/day	1.45 (0.80-2.60)		

Table 219 Alcohol (as ethanol) and colorectal cancer risk. Main characteristics of studies excluded from the CUP SLR dose-response meta-analysis

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Reasons for exclusion
Makarem, 2015 COL41060 USA	Framingham Heart Study - Offspring Cohort, Prospective Cohort, Age: 66 years, M/W	63/ 2 983 11.5 years	Death certificate and medical records	Semi-quantitative FFQ	Incidence, colorectal cancer	per 1 points WCRF score	0.29 (0.15-0.56)	Age, sex, smoking status	Insufficient data to include in analysis (include in dietary patterns section)
Nishihara, 2014 COL41036 USA	NHS-HPFS, Prospective Cohort, Age: 30-75 years, M/W, nurses & health professionals	573/	Medical records and death registries	Semi-quantitative FFQ	Incidence, colorectal cancer, women	≥15 vs ≤0 g/day	1.10 (0.83-1.45)	Age, aspirin use, BMI, calcium, endoscopy, family history of colorectal cancer, folate, methionine, multivitamin, pack yrs of smoking, physical activity, red meat, total caloric intake, vitamin b12, vitamin b6, year	Nan, 2013 COL40971 was used because has higher number of cases
		420/			Men	≥15 vs ≤0 g/day	1.39 (1.04-1.84)		
Aleksandrova, 2014	EPIC, Prospective	2 002/ 347 237	Cancer registry		Incidence, colorectal	limited vs heavy	0.96 (0.87-1.07)	Age, sex, body fat, diet quality,	Used Bamia, 2013 which
						limited vs heavy	0.96 (0.87-1.06)		

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Reasons for exclusion
COL41051 Europe	Cohort, Age: 25-70 years, M/W	12 years			cancer, women			educational level, physical activity, smoking	provides category range
		1 757/			Men	limited vs heavy	0.81 (0.73-0.89)		
						limited vs heavy	0.79 (0.72-0.88)		
Shen, 2013 COL40995 China	Elderly Health Centre Hong-Kong 1998-2001, Prospective Cohort, Age: 65- years, M/W, Elderly	944/ 66 820 10.5 years	Hospital records and death register	Questionnaire	Mortality, colorectal cancer	High vs never	1.25 (0.68 -2.3)	Age, sex, BMI, educational level, exercise, health status, housing, monthly expenditure, smoking status	Outcome is mortality, only included on highest versus lowest analysis
		516/ 66 820 10.5 years			Mortality, colorectal cancer, women	Moderate vs never	0.46 (0.11-1.43)		
		428/ 66 820 10.5 years			Mortality, colorectal cancer, men	High vs never	1.48(0.8-2.44)		
Agnoli, 2013 COL40938 Italy	EPIC-Italy, Prospective Cohort, M/W	435/ 45 275 11.28 years	Cancer registry and hospital records	Semi-quantitative FFQ	Incidence, colorectal cancer	12.3-198.6 vs 0-0.71 g/day	1.23 (0.96-1.58) Ptrend:0.090	Age, gender, non-alcoholic beverage intake, study center	Superseded by Bamia, 2013 COL40964
Yang, 2012 COL40922 China	CNRPCS, Prospective Cohort, Age: 40-79 years, M	193/ 218 189 15 years	Annual follow up by trained staff, death certificate and symptoms described by family members		Mortality, colorectal cancer	≥700 vs non-drinkers g/week	1.06 (0.55-2.06) Ptrend:0.5	5-year age-group, educational level, geographic location, smoking	The outcome is mortality, only included on highest versus lowest analysis
Gay, 2012 COL40920	EPIC-Norfolk, Prospective	185/ 25 636	Cancer registry	7-day dietary recalls	Incidence, colorectal	per 1 sd units	1.83 (1.10-3.04)	Age, sex, smoking	Superseded by Bamia, 2013

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Reasons for exclusion
UK	Cohort, Age: 45-79 years, M/W	11 years			cancer, gc:at mutations				COL40964
					Apc promoter methylation ≥20%	per 1 sd units	1.10 (0.75-1.61)		
					Apc mutations	per 1 sd units	1.63 (1.13-2.35)		
Bongaerts, 2011 COL40825 Netherlands	NLCS, Prospective Cohort, Age: 55-69 years, M/W	594/ 120 852 7.3 years	Cancer registry and database of pathology reports	FFQ	Incidence, colorectal cancer	≥30 vs abstainers g/day	0.91 (0.59-1.41)	Age, BMI, calcium, energy intake, energy-adjusted intake of fat, family history of colorectal cancer, fibre, gender, non-occupational physical activity	Bongaerts, 2008 was used because it has higher number of cases

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Reasons for exclusion
Schernhammer, 2011 COL40882 USA	NHS, Prospective Cohort, Age: 30-55 years, W, Registered nurses	386/ 88 691 20 years	Questionnaire/ medical records/death record	Semi-quantitative FFQ	Incidence, colon cancer	15-11 vs ≤0 g/day	1.11 (0.79-1.58) Ptrend:0.87	Age, alcohol, aspirin use, beef intake, BMI, calcium, energy intake, family history of colon cancer, gender, history of polyps, methionine, multivitamin, phyisical activity, sigmoidoscopy, smoking, vitamin b12, vitamin b6	Superseded by Nan, 2013 COL40971
Breslow, 2011 COL40892 USA	NHIS, Prospective Cohort, Age: 18- years, M/W	850/ 323 354 2 716 472 person-years	National center for health statistics & national death Index	Questionnaire	Mortality, colonrectal cancer	current drinker - heavier vs never drinker	1.01 (0.70-1.47) Ptrend:0.24	Sex, BMI, educational level, marital status, race/ethnicity, region, smoking status	Outcome is mortality. Included only in high versus lowest analysis
		367/			Mortality, colorectal cancer, women	current drinker - heavier vs never drinker	1.05 (0.61-1.80) Ptrend:0.33		
					Men	current drinker - heavier vs never	1.08 (0.60-1.96) Ptrend:0.40		

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Reasons for exclusion
						drinker			
Park, 2010	UK Dietary Cohort Consortium	380 7 studies			Incidence, colon cancer	≥30 vs <5 g/day	1.21(0.77-1.90)	Age, weight, height, smoking status, social class, intakes of energy, fibre, folate, red meat and processed meat.	Mid-points of exposure categories. Overlaps with EPIC Study (Bamia, 2013) and Ferrari, 2007 COL40648
	EPIC Norfolk	25000/318			Incidence, rectal cancer		0.93 (0.48-1.78)		
	EPIC Oxford	65249/121			Incidence, colorectal cancer, men	≥45 vs 0 g/day	1.24(0.69-2.22)		
	Guemsey Study	6127/28			Incidence, colorectal cancer, women		1.52(0.56-4.10)		
	Oxford Vegetarian Study	11140/31							
	NSHD	5362/ 7							
	UKWCS	35792/ 25							
	Whitehall II	10308/ 49							
Yi, 2010 COL40798 Korea	Kangwha Cohort, Prospective Cohort, Age: 55- years, M/W	26/ 6 291 20.8 years	Death records/calls or follow up visits/death certificates	Questionnaire and Interview	Mortality, colorectal cancer, men	≥540 vs ≤0 g/week	2.61 (0.88-7.78)	Age, BMI, educational level, ginseng intake, history of chronic disease, pesticide use, smoking habits	Outcome is mortality. Included only in high versus lowest analysis
		17/			Mortality, colon cancer, men	≥540 vs ≤0 g/week	4.59 (1.10-19.20)		
		9/			Mortality, rectal cancer, men	≥540 vs ≤0 g/week	1.01 (0.16-6.25)		
Simons, 2010 COL40821 Netherlands	NLCS, Prospective Cohort,	1 260/ 120 852 13.3 years	Cancer registry and database of pathology	FFQ	Incidence, colorectal cancer, men	>200 vs 0 ml/day	1.32 (0.94-1.85) Ptrend:0.16	Age, BMI, educational level, ethanol intake,	Superseded by Bongaerts, 2011

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Reasons for exclusion
	Age: 55-69 years, M/W	939/	reports		Women	>200 vs 0 ml/day	0.72 (0.37-1.41) Ptrend:0.14	family history of colorectal cancer, fibre intake, folate intake, meat intake, non-occupational physical activity, physical activity, processed meat consumption, smoking, total fluid intake, vitamin b6 intake	COL40825 and Bongaerts, 2008 COL40635
		417/			Incidence, distal colon cancer, men	>200 vs 0 ml/day	0.94 (0.57-1.53) Ptrend:0.96		
		380/			Incidence, proximal colon cancer, women	>200 vs 0 ml/day	1.28 (0.80-2.03) Ptrend:0.84		
		361/			Men	>200 vs 0 ml/day	1.16 (0.79-1.70) Ptrend:0.95		
		322/			Incidence, rectal cancer, men	>200 vs 0 ml/day	1.33 (0.80-2.20) Ptrend:0.28		
		284/			Incidence, distal colon cancer, women	>200 vs 0 ml/day	0.45 (0.16-1.26) Ptrend:0.23		
		173/			Incidence, rectal cancer, women	>200 vs 0 ml/day	1.00 (0.50-2.02) Ptrend:0.86		
Kim, 2010 COL40834/ COL40827 Korea	KNHIC, Prospective Cohort, Age: 40-69 years, M/W	466/ 1 341 393 5 years	National death Index		Mortality, colorectal cancer, men	≥90 vs ≤0 g/day	1.31 (0.90-1.91)	Age, blood pressure, BMI, fasting serum glucose, physical activity, residential space, smoking, total cholesterol	The outcome is mortality, only included on highest versus lowest analysis
		153/			Women	≥15 vs ≤0 g/day	2.51 (1.31-4.82)		
Key, 2009 COL40775	EPIC, Prospective	228/ 63 550	National cancer registers	FFQ	Incidence, colorectal cancer	≥16 vs 1-7 g/day	1.24 (0.84-1.83)	Age, sex, method of recruitment,	Superseded by Bamia, 2013

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Reasons for exclusion
UK	Cohort, Age: 20-89 years, M/W, Vegetarians							smoking status	COL40964
Schernhammer, 2008 COL40729 USA	NHS-HPFS, Prospective Cohort, M/W	389/ 136 062 2 566 968 person-years	Self report verified by medical record	Semi-quantitative FFQ	Incidence, colon cancer, women	≥15 vs ≤0 g/day	1.14 (0.80-1.61) Ptrend:0.91	Age, aspirin use, beef consumption, BMI, calcium intake, energy intake, family history of colorectal cancer, folate intake, methionine intake, multivitamin supplement intake, physical activity, previous polyps, sigmoidoscopy, smoking status, vitamin b12 intake, vitamin B6 intake	Superseded by Cho, 2012 COL40902
		310/			Women, msi-low/mss	≥15 vs ≤0 g/day	1.17 (0.79-1.73) Ptrend:0.52		
		277/			Men	≥15 vs ≤0 g/day	1.44 (1.03-2.01) Ptrend:0.01		
		238/ 136 062 2 566 968 person-years			Incidence, colon cancer, men, msi-low/mss	≥15 vs ≤0 g/day	1.52 (1.06-2.17) Ptrend:0.002		
		79/ 136 062 2 566 968 person-years			Incidence, colon cancer, women, msi-high	≥15 vs ≤0 g/day	1.01 (0.51-2.04) Ptrend:0.26		
		39/			Men, msi-high	≥15 vs ≤0 g/day	0.99 (0.40-2.43) Ptrend:0.78		
Thygesen, 2008 COL40723 USA	HPFS, Prospective Cohort,	868/ 47 432 16 years	Follow up questionnaires, medical records	FFQ	Incidence, colorectal cancer	per 10 g/day	1.08 (1.03-1.13)	Age, aspirin use, BMI, calcium intake,	Superseded by Nan, 2013

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Reasons for exclusion
	Age: 40-75 years, M, Health professionals							colonoscopy, family history, folate intake, methionine, multivitamin, physical activity, processed and red meat, sigmoidoscopy, smoking status, total calories, vitamin d	COL40971
Hansen, 2008 COL40736 Denmark	DCH, Case Cohort, Age: 50-64 years, M/W	164/ 1 215 10 years	Cancer registry	Unknown	Incidence, colorectal cancer, men, no homozygous carrier	per 10 g/day	1.04 (0.97-1.12)	Age, BMI, dietary fibre intake, fish intake, fruits and vegetables consumption, HRT use, red meat intake	Superseded by Bamia, 2013 COL40964 (component study of EPIC)
		121/			Women, no homzygous carrier	per 10 g/day	1.15 (0.98-1.36)		
		51/			Men, homozygous carrier - yes	per 10 g/day	1.20 (1.00-1.43)		
		47/			Women, homozygous carrier - yes	per 10 gday	0.87 (0.61-1.25)		
Schernhammer, 2008	The Nurses's Health Study	399/ 88 691	Self report verified by	Semi-quantitative FFQ	Incidence, colon cancer	≥15 vs ≤0 g/day	1.19 (0.86-1.65) Ptrend:0.72	Age	Superseded by Cho, 2012

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Reasons for exclusion
COL40730 USA	Cohort, Prospective Cohort, Age: 30-55 years, W	22 years	medical record			≥15 vs ≤0 g/day	1.19 (0.85-1.67) Ptrend:0.67	Alcohol intake, beef, pork or lamb as a main dish, BMI, family history of colorectal cancer, history of polyps, multivitamin supplement intake, physical activity, postmenopausal hormone use, previous endoscopic screening, smoking habits	COL40902
de Vogel S, 2008 COL40734 Netherlands	NLCS, Case Cohort, Age: 55-69 years, M/W	32/ 4 717 7.3	Record linkage to cancer registry/histo- and cyto-pathology reports	FFQ	Incidence, colorectal cancer, women, no mlh1 protein	≥30 vs ≤0 g/day	3.38 (0.97-11.87) Ptrend:0.64	Age, BMI, calcium intake, energy intake, family history of colorectal cancer, fat intake, fibre, Iron intake, meat intake, smoking habits, vitamin c	Superseded Bongaerts, 2008 COL40635
Kabat, 2008 COL40636	CNBSS, Prospective	617/ 49 654	Record linkages to cancer	FFQ	Incidence, colorectal cancer	≥30 vs ≤0 g/day	1.02 (0.72-1.44) Ptrend:0.48	Age, BMI, calories Intake,	Only included in highest vs

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Reasons for exclusion
Canada	Cohort, Age: 40-59 years, W, Screening Program	16.4 years	database and to the national mortality database					educational level, HRT use, menopausal status, oral contraceptive use, pack-years of smoking	lowest analysis
Bongaerts, 2006 COL40619 Netherlands	NLCS, Case Cohort Age: 55-69 years, M/W	417/ 4 076 7.3 years	Cancer registry	Semi-quantitative FFQ	Incidence, colon and rectosigmoid junction cancer, ki-ras-	≥30 vs ≤0 g/day	1.25 (0.80-1.80)	Age, BMI, calcium intake, family history of colorectal cancer, nutrients, smoking status	Superseded Bongaerts, 2008 COL40635
		231/			Ki-ras+	≥30 vs ≤0 g/day	1.13 (0.70-1.90)		
		148/			Incidence, colon cancer, men, ki-ras-	≥30 vs ≤0 g/day	1.24 (0.70-2.30)		
		140/			Women, ki-ras+	≥30 vs ≤0 g/day	1.83 (0.80-4.10)	Age, BMI, calcium intake, family history of colorectal cancer, nutrients, smoking status	
					Women, ki-ras-	≥30 vs ≤0 g/day	0.65 (0.10-5.50)		
		63/			Incidence, rectal cancer, men, ki-ras-	≥30 vs ≤0 g/day	2.00 (0.80-5.30)		
		27/			Women, ki-ras+	≥30 vs ≤0 g/day	1.25 (0.10-11.70)		

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Reasons for exclusion
		24/			Women, ki-ras-	0.1-29.9 vs ≤0 g/day	0.98 (0.40-2.20)		
		82			Incidence, colon cancer, men, ki-ras+	≥30 vs ≤0 g/day	1.15 (0.50-2.60)		
					Incidence, rectal cancer, men, ki-ras+		0.98 (0.20-4.00)		

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Reasons for exclusions
Nakaya, 2005 COL01872 Japan	MCS, Prospective Cohort, Age: 40-64 years, M	191/ 21 201 153 389 person-years	Cancer registry	Questionnaire	Incidence, colon cancer,	≥22.8 vs ≤0 g/day	1.90 (1.20-3.70) Ptrend:0.03	Age, educational level, smoking status, vegetable consumption	Superseded by Athker, 2007 COL40632
		122/			Incidence, rectal cancer,	≥22.8 vs ≤0 g/day	1.50 (0.70-3.10) Ptrend:0.23		
Wei, 2004 COL00581 USA	NHS, Prospective Cohort, W, nurses	672/ 87 733 24 years	Self-reported verified by medical record and The National Death Index	Semi-quantitative FFQ	Incidence, colon cancer,	≥20 vs ≤0 g/day	1.14 (0.86-1.52)	Age, beef, pork or lamb as a main dish, BMI, calcium, family history of colorectal cancer, folate, height, history of endoscopy, pack-years of smoking before age 30, physical activity, processed meat, calcium	Superseded by Schernhammer, 2008 COL40729. Used only in highest vs lowest analysis of rectal cancer
	HPFS, Prospective Cohort, M, Health professionals	395/ 46 632 14 years			Incidence, colon cancer,	≥20 vs ≤0 g/day	1.55 (1.05-2.27)		
	NHS,	204/ 87 733 24 years			Incidence, rectal cancer,	≥20 vs ≤0 g/day	1.48 (0.90-2.44)		
	HPFS,	117/ 46 632 14 years			Incidence, rectal cancer,	≥20 vs ≤0 g/day	1.11 (0.54-2.29)		
Otani, 2003 COL00352 Japan	JPHC, Prospective Cohort, Age: 40-59	299/ 41 374 10 years	Cancer registry and death certificate	Questionnaire	Incidence, colon cancer, men	≥300 vs ≤0 g/days/month	1.90 (1.40-2.73) Ptrend:<0.001	Age, BMI, family history of specific cancer, physical	Superseded by Mizoue, 2008
		195/			Incidence,	≥300 vs ≤0	2.00 (1.30-3.00)		

	years, M/W				colorectal cancer, men	g/week	Ptrend:0.024	activity, public health center, smoking status	
		148/			Incidence, rectal cancer, men	≥300 vs ≤0 g/days/month	2.40 (1.50-4.00) Ptrend:0.015		
Shimizu, 2003 COL00529 Japan	TCCJ, Prospective Cohort, Age: 35- years, M/W	108/ 29 051 8 years	Hospital records and cancer registry	Semi-quantitative FFQ	Incidence, colon cancer, men	≥36.8 vs ≤0 g/day	2.67 (1.06-6.76) Ptrend:0.01	Age, alcohol consumption, BMI, educational level, height, smoking habits	Superseded by Mizoue, 2008
		94/			Women	≥3.76 vs ≤0 g/day	1.78 (1.00-3.18) Ptrend:0.03		
		59/			Incidence, rectal cancer, men	≥36.8 vs ≤0 g/day	1.17 (0.50-2.73) Ptrend:0.06		
Harnack, 2002 COL00312 USA	IWHS, Prospective Cohort, Age: 55-69 years, W	598/ 41 836 13 years	SEER	Semi-quantitative FFQ	Incidence, colon cancer,	≥20 vs 0-20 g/day	1.08 (0.72-1.62)	Age, BMI, calcium Intake, energy Intake, estrogen use, pack-years of smoking, vitamin e Oral. contraceptive use	Used only in highest vs lowest analysis
		123/ 41 836 13 years			Incidence, rectal cancer,	≥20 vs 0-20 g/day	0.91 (0.39-2.10)		
Fuchs, 2002 COL00415 USA	The Nurses's Health Study Cohort, Prospective Cohort, Age: 30-55 years, W, nurses	428/ 88 758 1 375 165 person-years	Nurses registry	FFQ	Incidence, colon cancer, no family history of crc	≥30 vs ≤0 g/day	0.88 (0.56-1.39)	Age, alcohol consumption, aspirin use, beef, pork, or lamb, BMI, energy-adjusted levels of methionine, physical activity, screening endoscopy, smoking habits	Superseded Nishihara, 2014 COL41036

Malila, 2002 COL00336 Finland	ATBC, Prospective Cohort, Age: 50-69 years, M, Male Smokers	184/ 26 951 8 years	Hospital records	Dietary history questionnaire	Incidence, colorectal cancer,	(mean exposure)			Only has mean exposure
Colbert, 2001 col00384 Finland	ATBC, Prospective Cohort, Age: 50-69 years, M, Male Smokers	152/ 29 133 12 years	Unknown	Food-use questionnaire	Incidence, colon cancer, colon cancer	(mean exposure)			Only has mean exposure
		104/			Incidence, rectal cancer, rectal cancer	(mean exposure)			
Pietinen, 1999 COL00176 Finland	ATBC, Prospective Cohort, Age: 50-69 years, M, Smokers	185/ 27 111 8 years	Hospital records	Dietary history questionnaire	Incidence, colorectal cancer,	(mean exposure)		Energy intake	Only has mean exposure
Hsing, 1998 COL00458 USA	Lutheran Brotherhood Study, Prospective Cohort, Age: 35- years, M, policyholders	73/ 17 633 286 731 person-years	Responding to mail survey	Questionnaire	Mortality, colon cancer,	ever vs never	1.30 (0.80-2.00)	Age, alcohol Intake, area of residence	Outcome is mortality
Giovannucci, 1995 COL00112 USA	HPFS, Prospective Cohort, Age: 40-75 years, M,	35/ 47 931 261 916 person-years	Voluntarily responded to mailed questionnaire	Semi-quantitative FFQ	Incidence, colon cancer, folate intake >646 mcg/day	≥20 vs ≤20 g/day	1.03 (0.52-2.06)	Age, aspirin use, BMI, energy intake, family history of specific cancer, folate, history of	Superseded by Nan, 2013 COL40971

	Health professionals							endoscopy, history of previous polyp and prior endoscopy, methionine, physical activity, red meat intake, smoking habits	
Gapstur, 1994 COL00212 USA	IWHS, Prospective Cohort, Age: 55-69 years, W, Postmenopausal	75/ 38 006 5 years	SEER	Semi-quantitative FFQ	Incidence, rectal cancer,	≥4 vs ≤0 g/day	1.27 (0.72-2.24) Ptrend:0.46	Age	Superseded by Razzak, 2011 COL40889
					Excluding first year of follow up	≥4 vs ≤0 g/day	0.83 Ptrend:0.23		
Goldbohm, 1994 COL00427 Netherlands	NLCS, Case Cohort, Age: 55-69 years, M/W	104/ 120 852 3.3 years	Cancer registry and pathology reports	Semi-quantitative FFQ	Incidence, colon cancer, women	≥30 vs ≤0 g/day	1.30 Ptrend:0.76	Age, BMI, educational level, energy intake, energy-adjusted intake of dietary fiber, energy-adjusted intake of fat, energy-adjusted intake of meat, energy-adjusted intake of protein, history of gallbladder surgery, smoking habits	Superseded by Bongaerts, 2011 COL40825
		101/			Men	≥30 vs ≤0 g/day	0.90 Ptrend:0.77		
		73/			Incidence, rectal cancer, men	≥30 vs ≤0 g/day	2.80 Ptrend:0.04		
		33/			Women	≥30 vs ≤0 g/day	1.30 Ptrend:0.97		
Kreger, 1992 COL00665 USA	FHS, Prospective Cohort,	66/ 5 209 40 years	Hospital records	Questionnaire	Incidence, colon cancer, women	per 1 oz/week	0.95 (0.87-1.04)		Unadjusted results

	Age: 30-62 years, M/W	56/			Men	per 1 oz/week	1.00 (0.97-1.04)		
		20/			Incidence, rectal cancer, women	per 1 oz/week	0.92 (0.74-1.13)		
		19/			Men	per 1 oz/week	0.99 (0.92-1.05)		
Garland, 1985 COL01050 USA	Western Electric Study 1959-78, Prospective Cohort, Age: 40-55 years, M	49/ 1 954 20 years	Hospital records	Diet history method	Incidence, colorectal cancer,	(mean exposure)			Only has mean exposure
Stemmermann, 1984 COL01232 USA	HHP, Prospective Cohort, Age: 45-68 years, M	106/ 7 074 15 years	Cancer registry	Dietary history questionnaire	Incidence, colon cancer,	(mean exposure)		Age	Only has mean exposure
		59/			Incidence, rectal cancer,	(mean exposure)			

Figure 386 RR estimates of colorectal cancer by levels of alcohol (as ethanol)

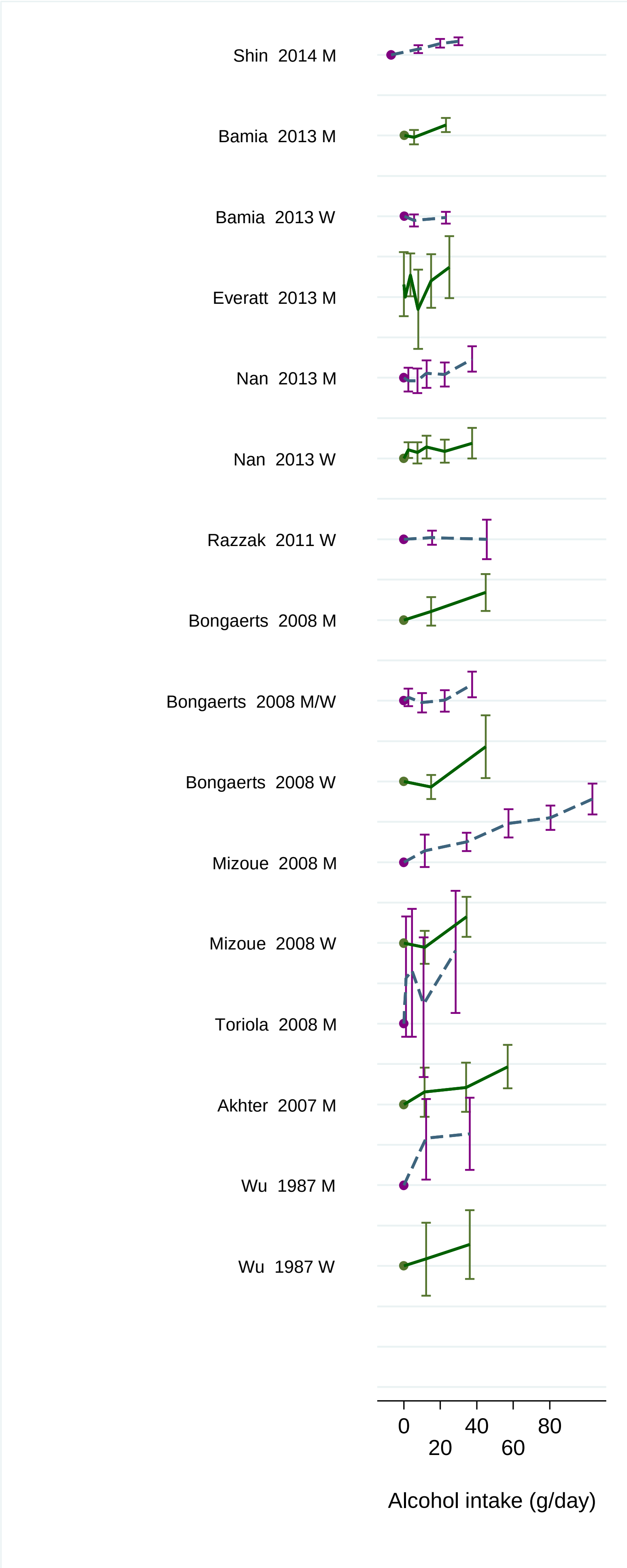


Figure 387 RR (95% CI) of colorectal cancer for the highest compared with the lowest level of alcohol (as ethanol)

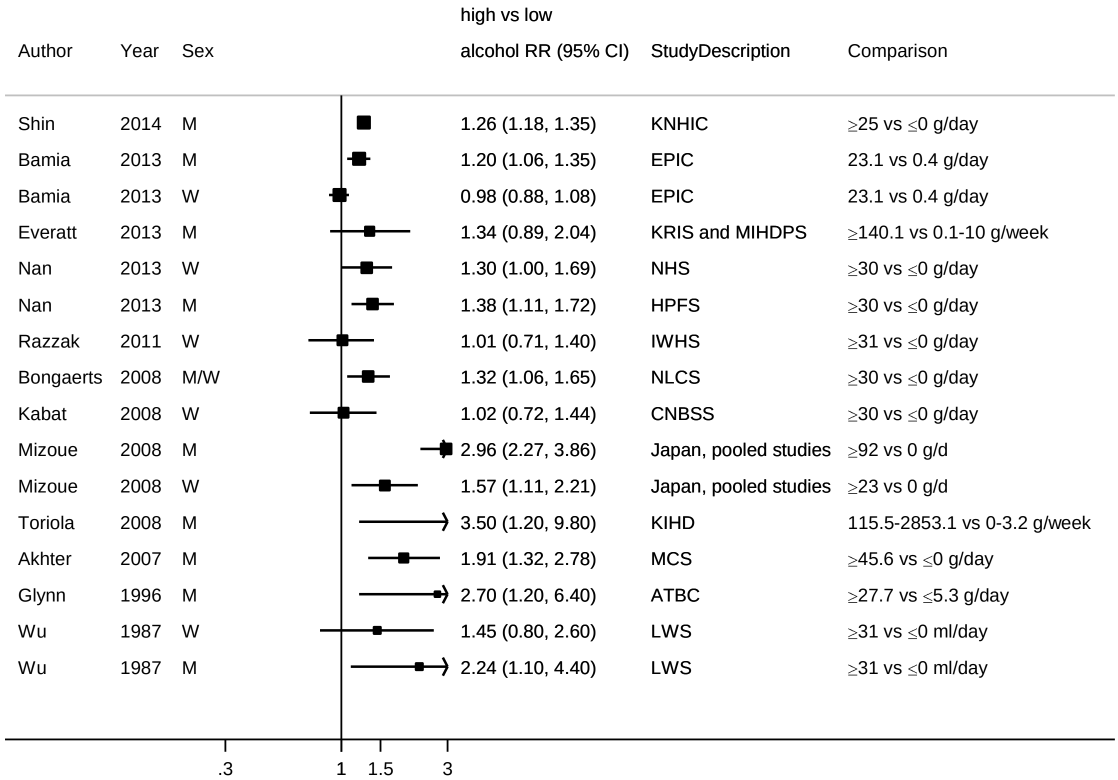


Figure 388 RR (95% CI) of colorectal cancer for 10g/day increase of alcohol (as ethanol)

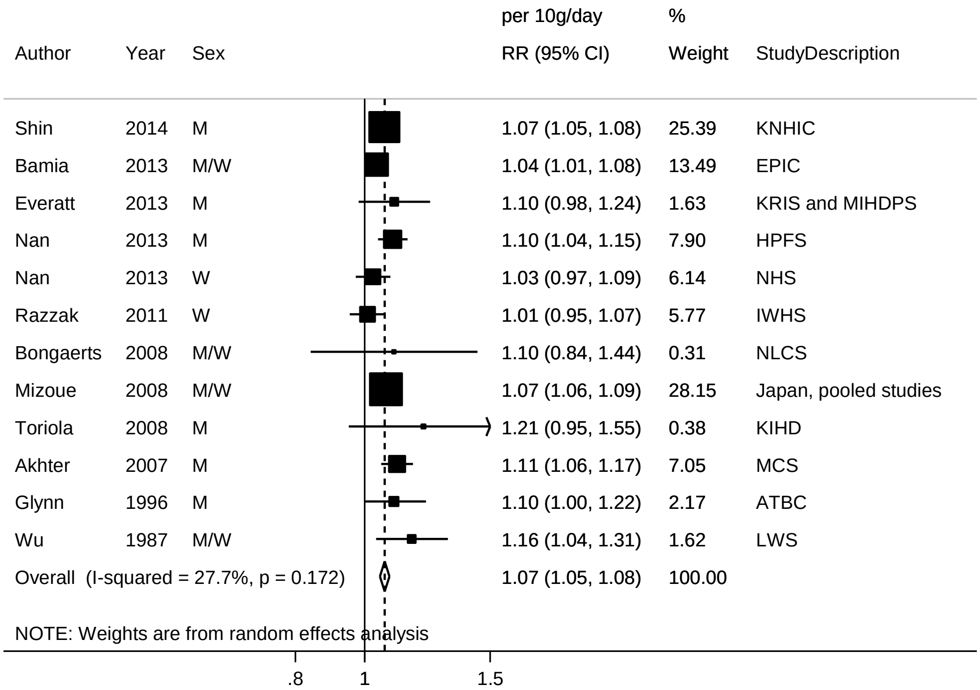


Figure 389 Funnel plot of studies included in the dose response meta-analysis of alcohol (as ethanol) and colorectal cancer

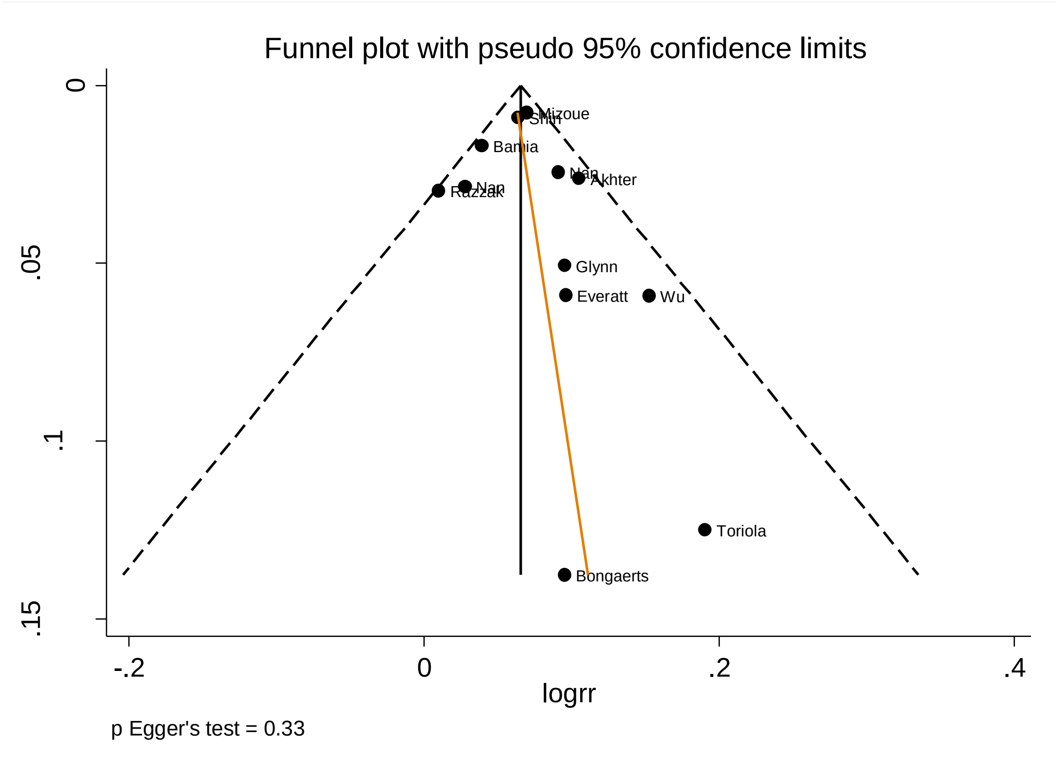


Figure 390 RR (95% CI) of colorectal cancer for 10g/day increase of alcohol (as ethanol) by sex

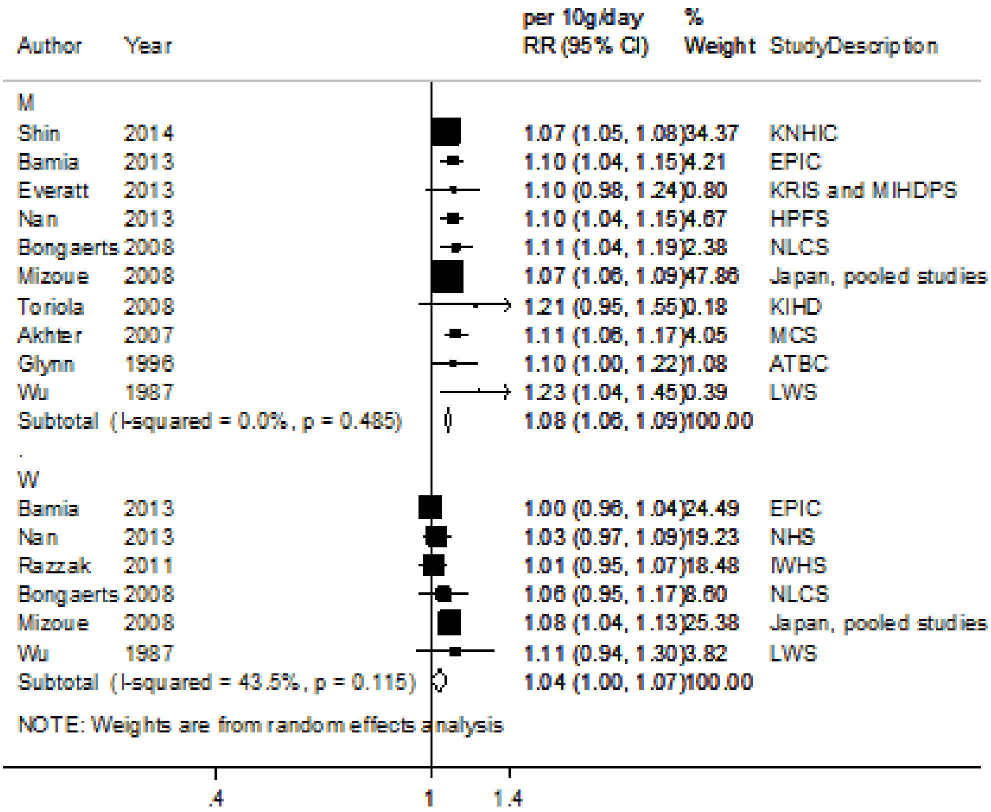
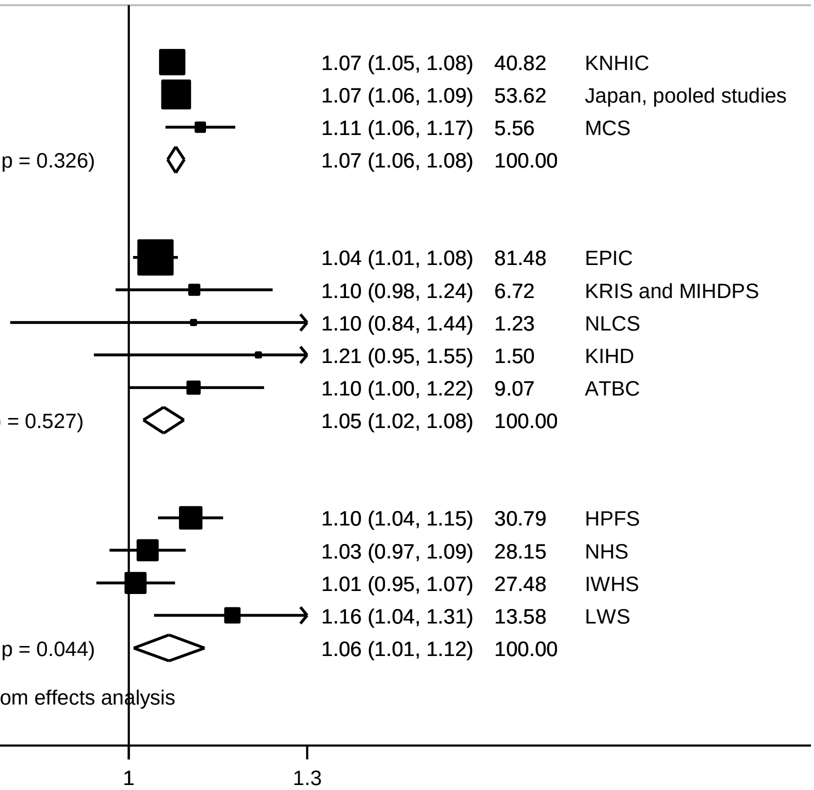


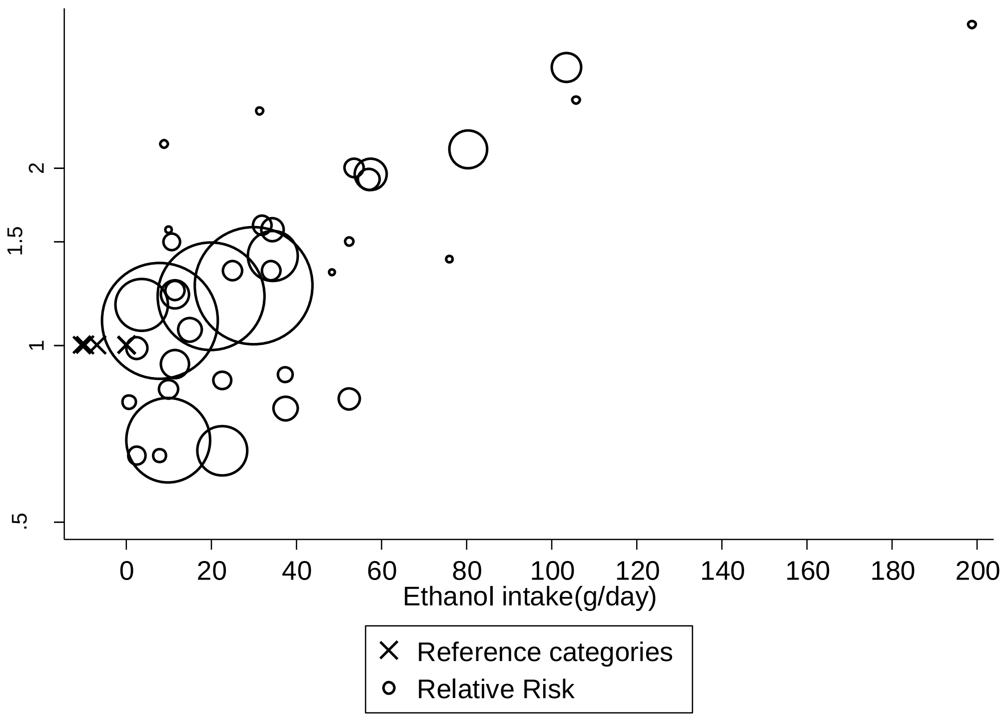
Figure 391 RR (95% CI) of colorectal cancer for 10g/day increase of alcohol (as ethanol) by geographic location



Author	Year	per 10g/day RR (95% CI)	% Weight	StudyDescription
Asia				
Shin	2014	1.07 (1.05, 1.08)	40.82	KNHIC
Mizoue	2008	1.07 (1.06, 1.09)	53.62	Japan, pooled studies
Akhter	2007	1.11 (1.06, 1.17)	5.56	MCS
Subtotal (I-squared = 10.7%, p = 0.326)		1.07 (1.06, 1.08)	100.00	
.				
Europe				
Bamia	2013	1.04 (1.01, 1.08)	81.48	EPIC
Everatt	2013	1.10 (0.98, 1.24)	6.72	KRIS and MIHDPS
Bongaerts	2008	1.10 (0.84, 1.44)	1.23	NLCS
Toriola	2008	1.21 (0.95, 1.55)	1.50	KIHD
Glynn	1996	1.10 (1.00, 1.22)	9.07	ATBC
Subtotal (I-squared = 0.0%, p = 0.527)		1.05 (1.02, 1.08)	100.00	
.				
North America				
Nan	2013	1.10 (1.04, 1.15)	30.79	HPFS
Nan	2013	1.03 (0.97, 1.09)	28.15	NHS
Razzak	2011	1.01 (0.95, 1.07)	27.48	IWHS
Wu	1987	1.16 (1.04, 1.31)	13.58	LWS
Subtotal (I-squared = 63.1%, p = 0.044)		1.06 (1.01, 1.12)	100.00	

NOTE: Weights are from random effects analysis

Figure 392 Relative risk of colorectal cancer and alcohol (as ethanol) estimated using non-linear models



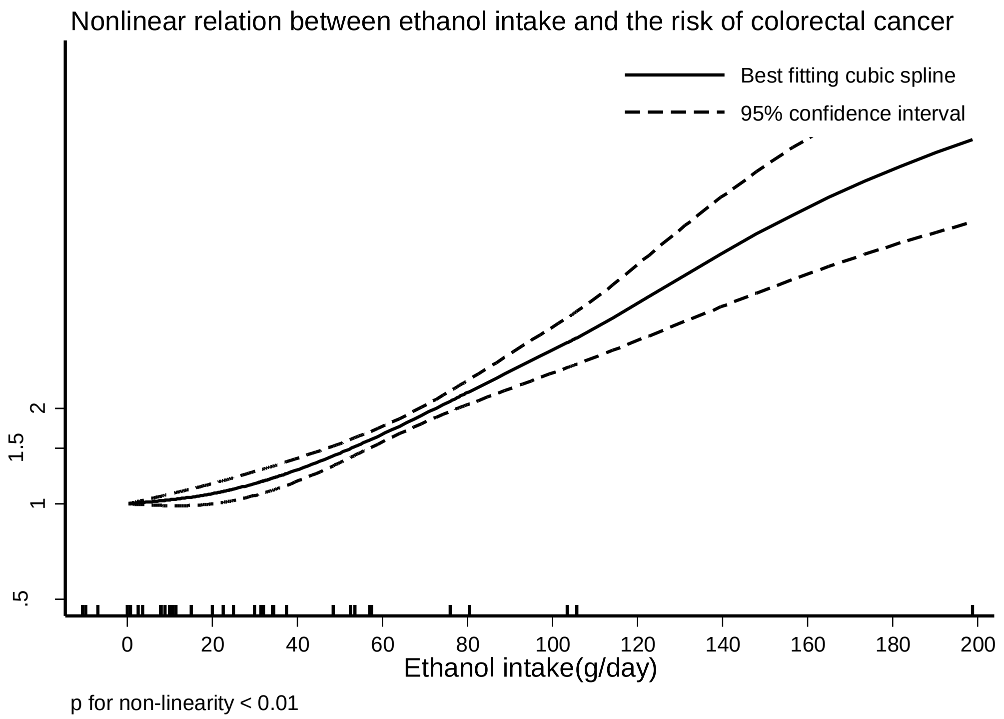


Table 220 Table with alcohol (as ethanol) values and corresponding RRs (95% CIs) for non-linear analysis of alcohol (as ethanol) and colorectal cancer

Alcohol (g/day)	RR (95%CI)
0	1
10	1.02(0.98-1.07)
20	1.07(1.00-1.16)
30	1.15(1.06-1.26)
40	1.25(1.14-1.36)
50	1.41(1.31-1.52)
60	1.60(1.51-1.69)

Figure 393RR (95% CI) of colorectal <u>cancer mortality</u> for the highest compared with the lowest level of alcohol (as ethanol)

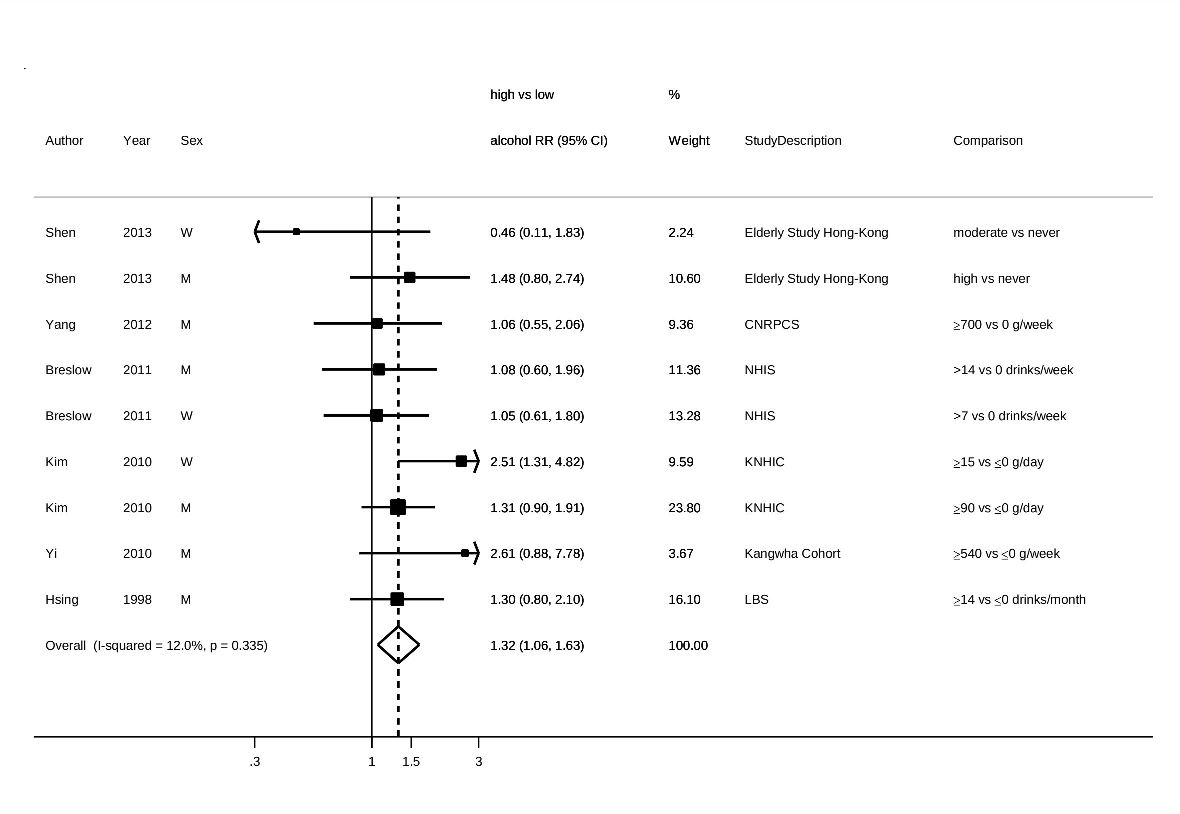


Figure 394 RR estimates of colon cancer by levels of alcohol (as ethanol)

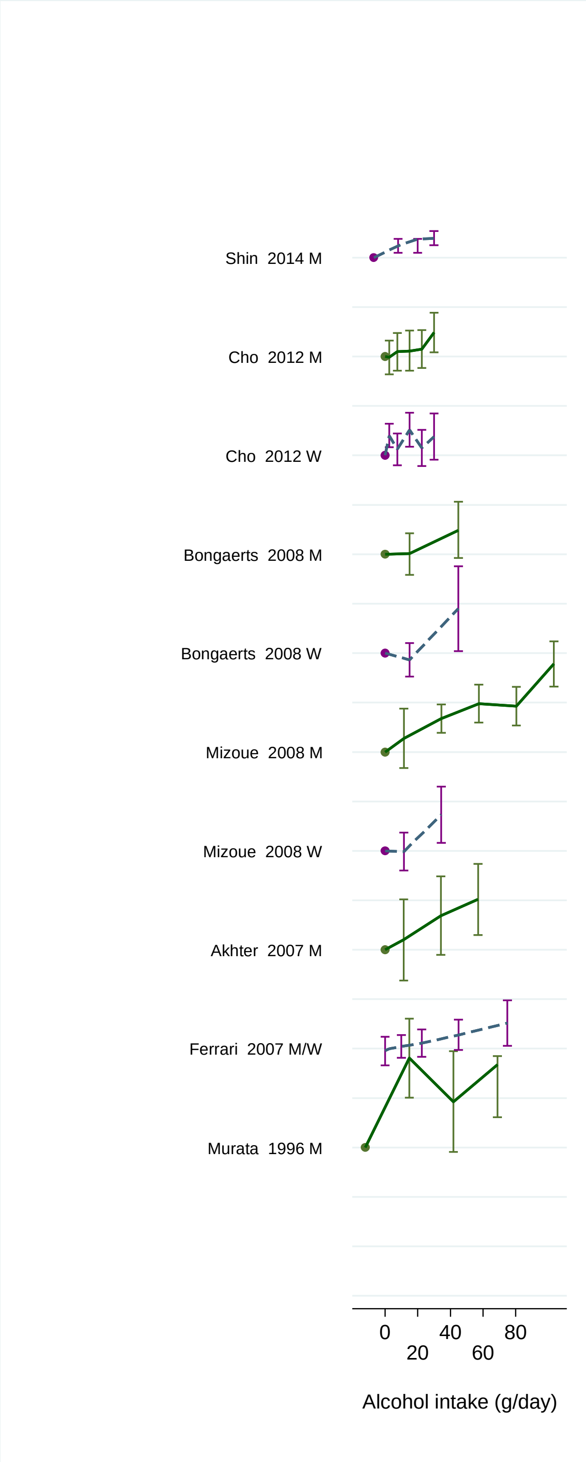


Figure 395 RR (95% CI) of colon cancer for the highest compared with the lowest level of alcohol (as ethanol)

Author	Year	Sex	high vs low alcohol RR (95% CI)	StudyDescription	Comparison
Shin	2014	M	1.31 (1.19, 1.45)	KNHIC	≥25 vs ≤0 g/day
Cho	2012	W	1.30 (0.94, 1.80)	NHS	30 vs 0 g/day
Cho	2012	M	1.40 (1.06, 1.85)	HPFS	30 vs 0 g/day
Bongaerts	2008	W	1.87 (1.03, 3.38)	NLCS	≥30 vs ≤0 g/day
Bongaerts	2008	M	1.40 (0.95, 2.09)	NLCS	≥30 vs ≤0 g/day
Mizoue	2008	W	1.66 (1.12, 2.46)	Japan, pooled studies	≥23 vs 0 g/d
Mizoue	2008	M	3.44 (2.50, 4.72)	Japan, pooled studies	≥92 vs 0 g/d
Akhter	2007	M	2.03 (1.23, 3.33)	MCS	≥45.6 vs ≤0 g/day
Ferrari	2007	M/W	1.43 (1.04, 1.97)	EPIC	≥60 vs 0.1-4.9 g/day
Harnack	2002	W	1.08 (0.72, 1.62)	IWHS	≥20 vs 0-20 g/day
Glynn	1996	M	3.60 (1.30, 10.40)	ATBC	≥27.7 vs ≤5.3 g/day
Murata	1996	M	3.20 (1.53, 6.70)	CCCJ	≥56.7 vs ≤0 g/day
Wu (left colon)	1987	M	2.21 (0.80, 6.00)	LWS	≥31 vs ≤0 ml/day
Wu (right colon)	1987	W	1.66 (0.80, 3.60)	LWS	≥31 vs ≤0 ml/day

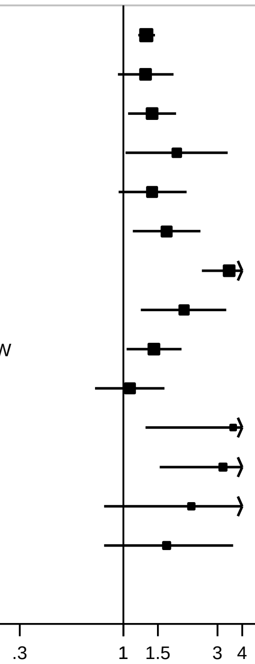


Figure 396 RR (95% CI) of colon cancer for 10g/day increase of alcohol (as ethanol)

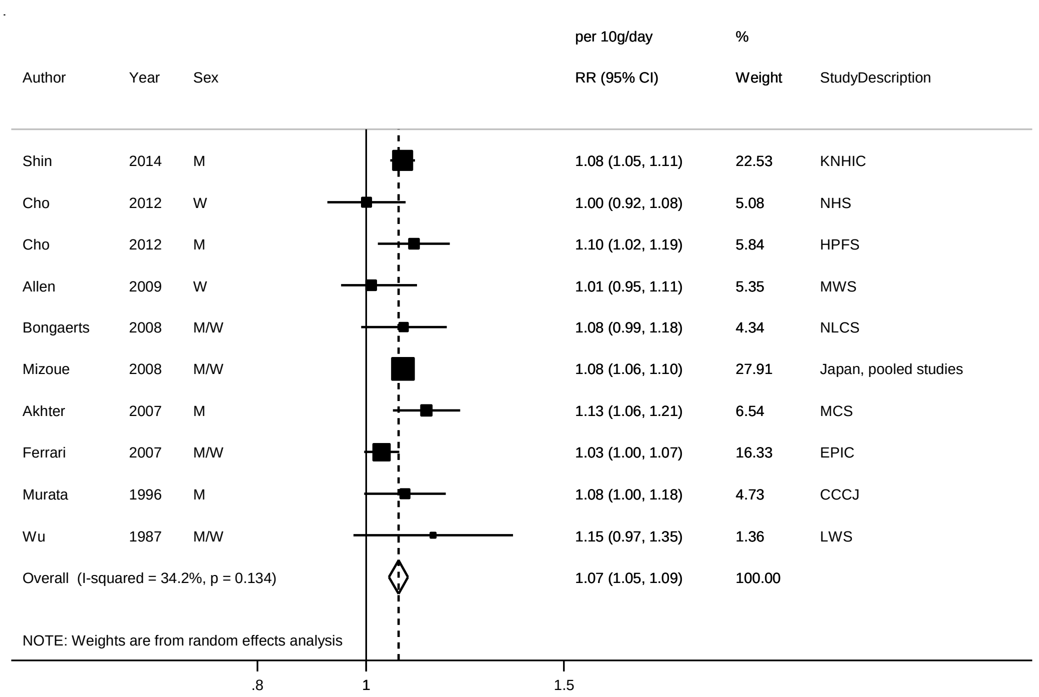


Figure 397 Funnel plot of studies included in the dose response meta-analysis of alcohol (as ethanol) and colon cancer

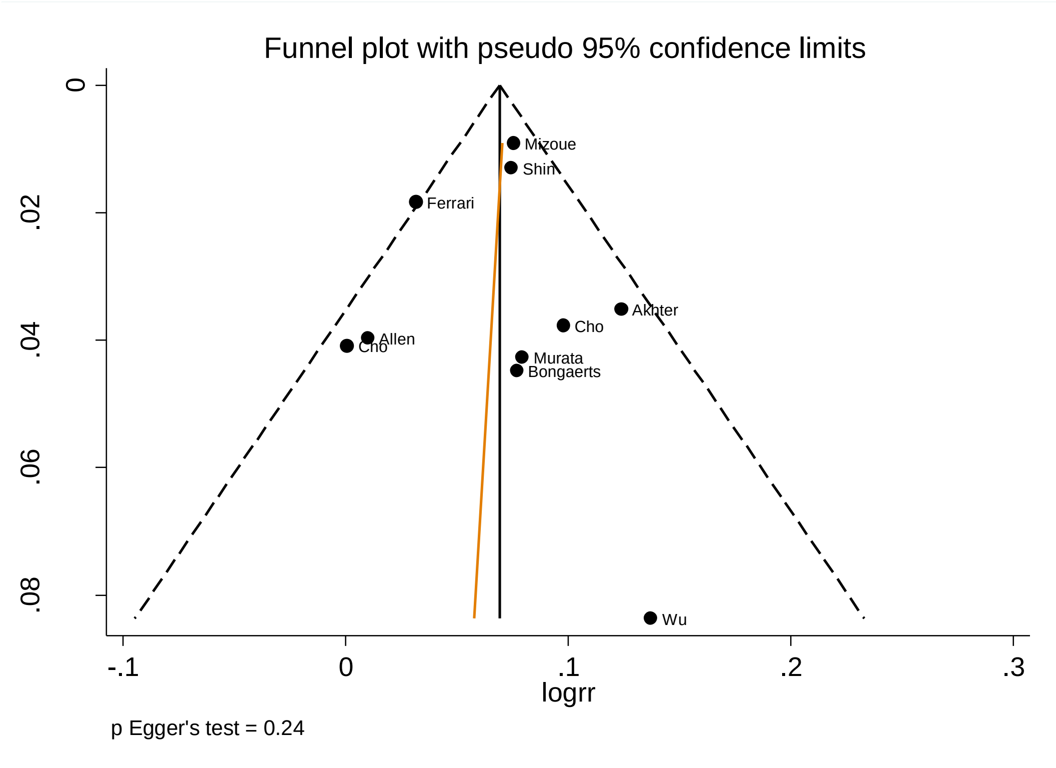


Figure 398 RR (95% CI) of colon cancer for 10g/day increase of alcohol (as ethanol) by sex

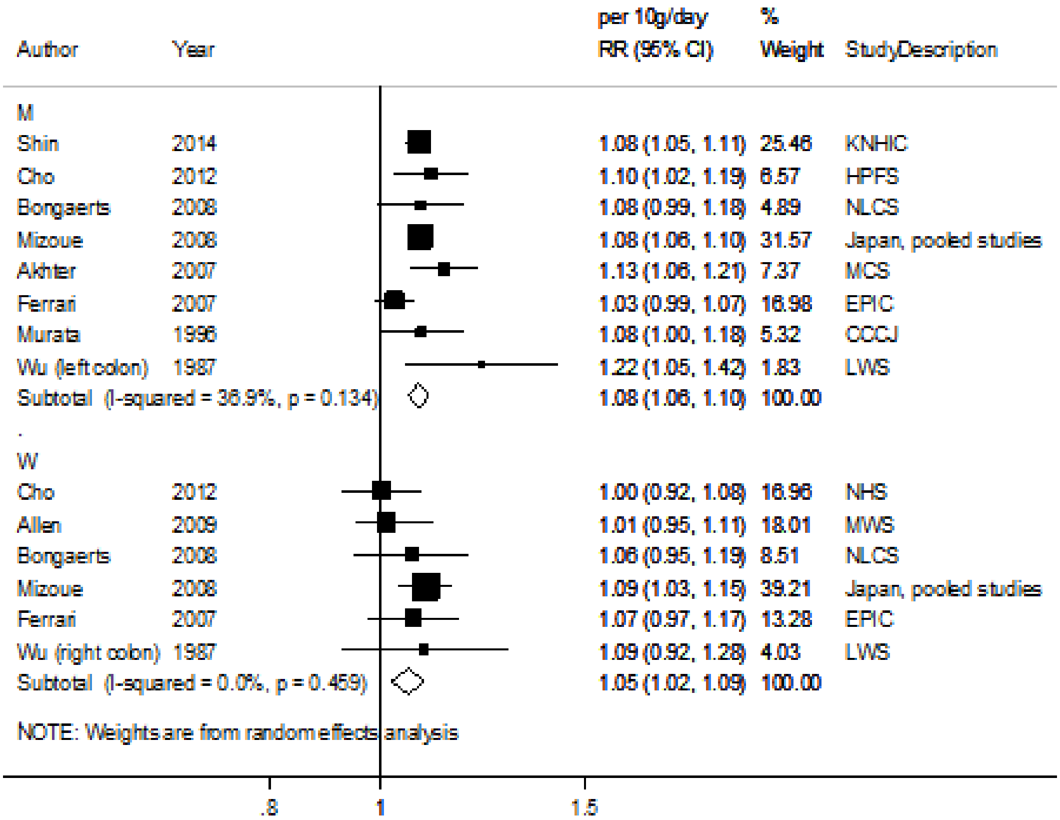


Figure 399 RR (95% CI) of colon cancer for 10g/day increase of alcohol (as ethanol) by geographic location

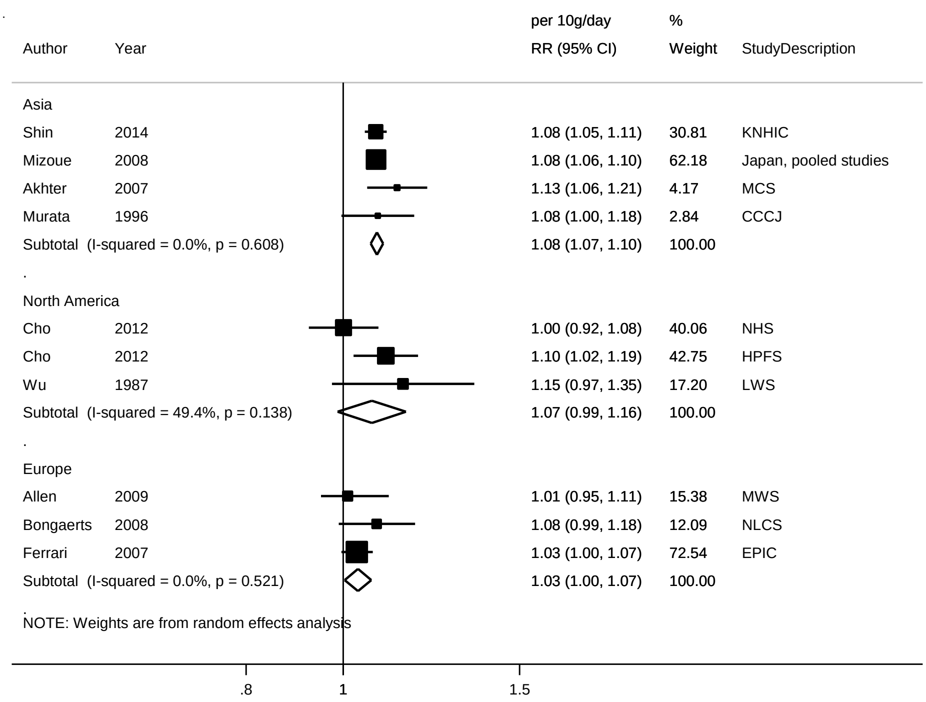


Figure 400 RR estimates of rectal cancer by levels of alcohol (as ethanol)

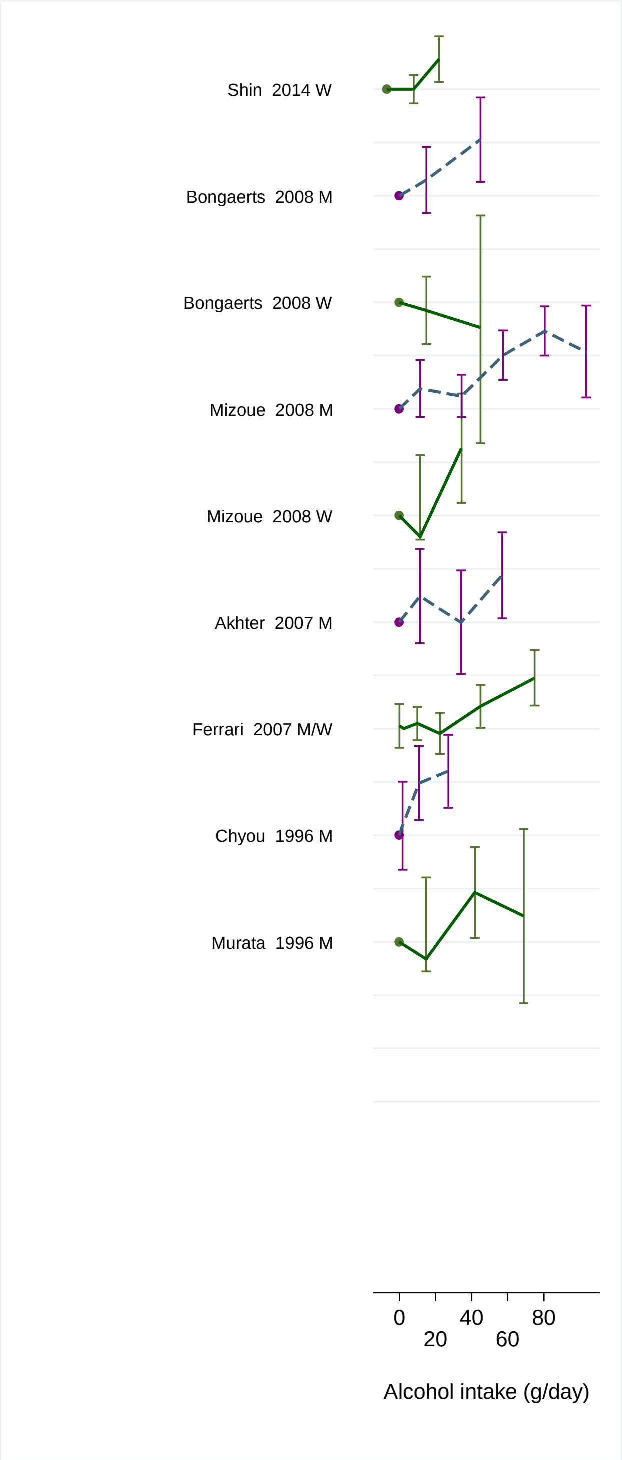


Figure 401RR (95% CI) of rectal cancer for the highest compared with the lowest level of alcohol (as ethanol)

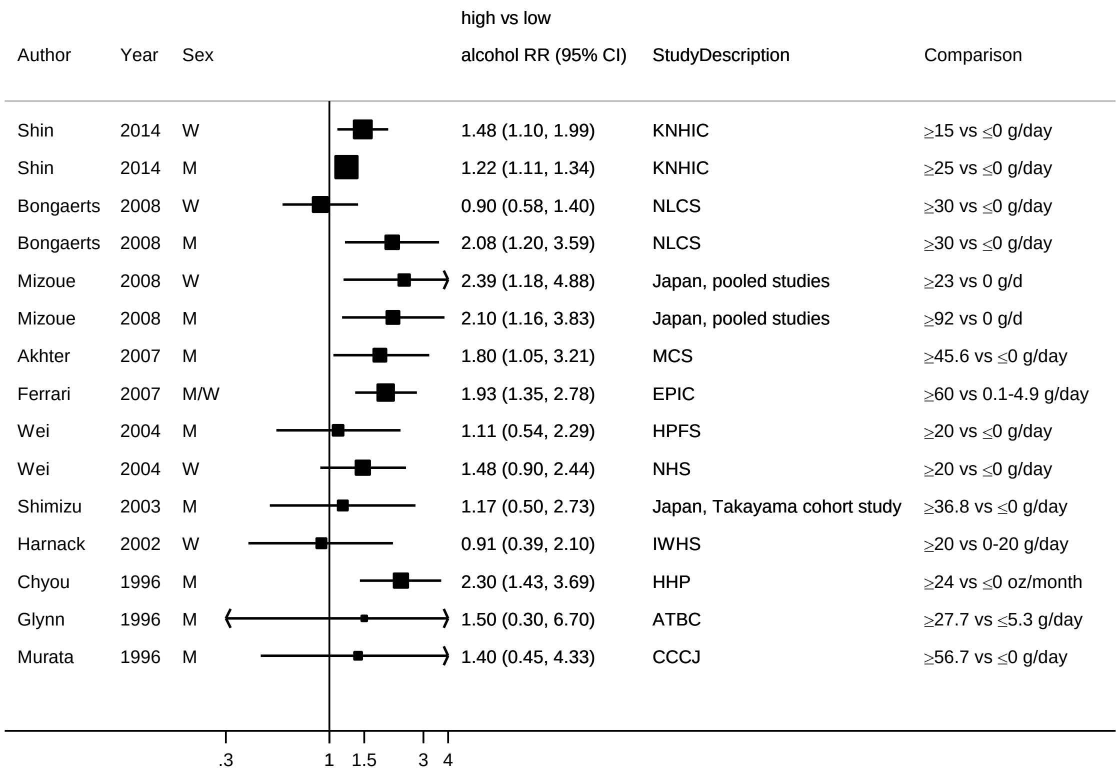


Figure 402 RR (95% CI) of rectal cancer for 10g/day increase of alcohol (as ethanol)

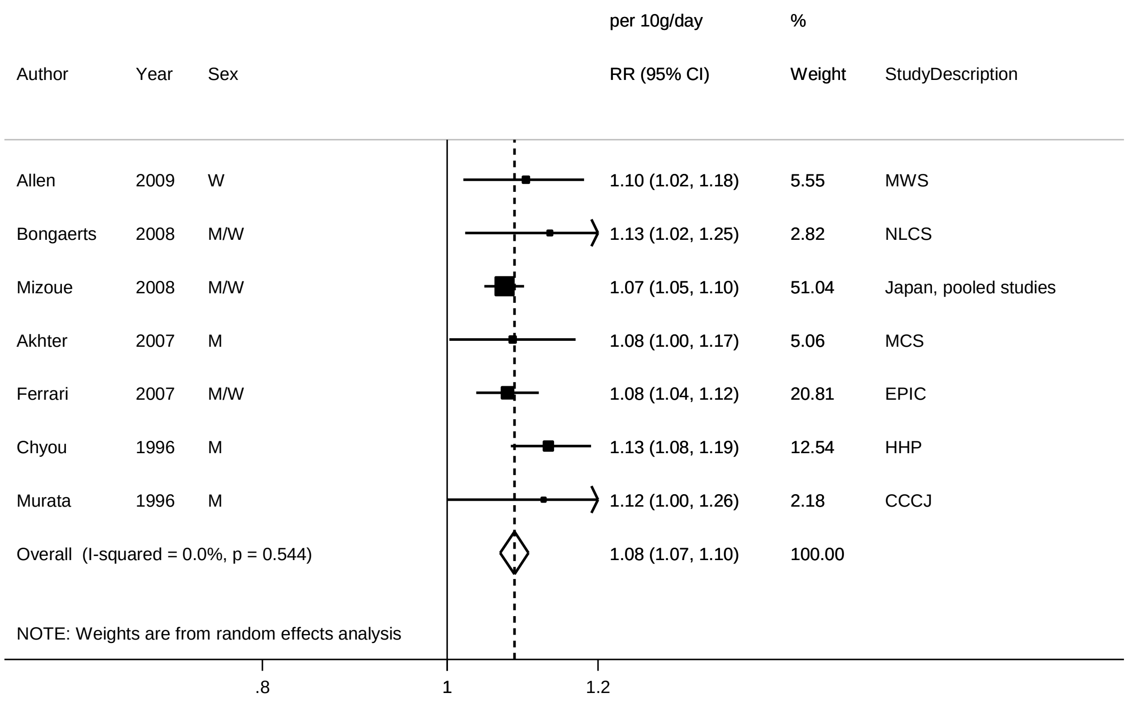


Figure 403 Funnel plot of studies included in the dose response meta-analysis of alcohol (as ethanol) and rectal cancer

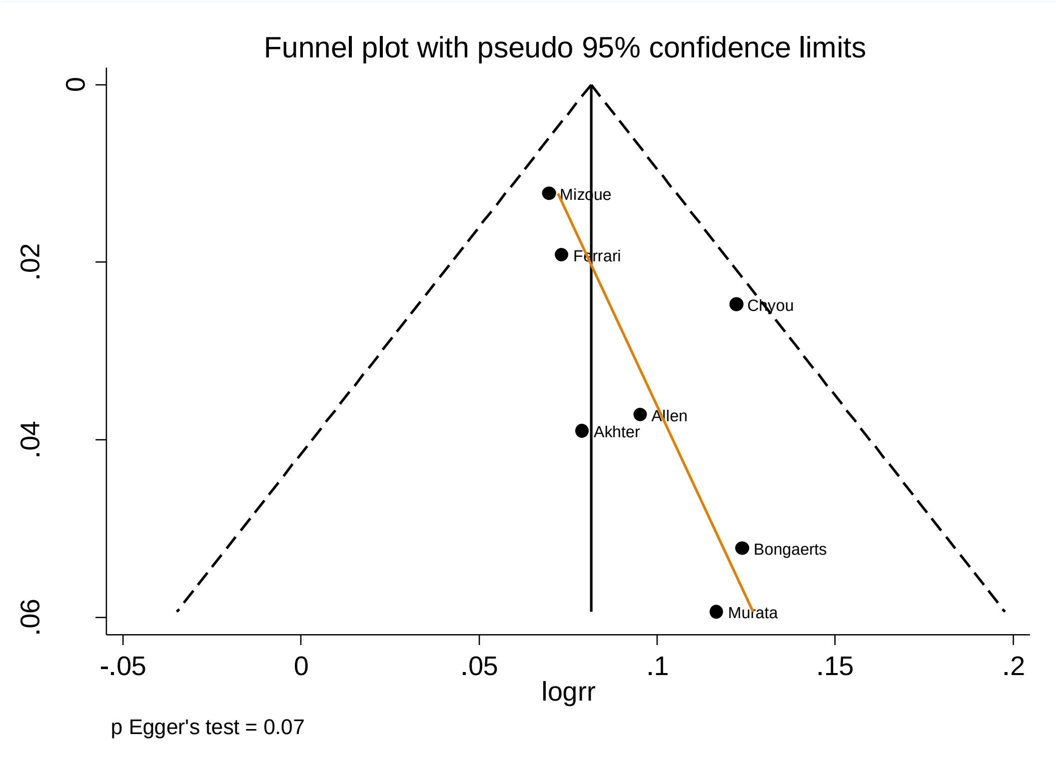


Figure 404 RR (95% CI) of rectal cancer for 10g/day increase of alcohol (as ethanol) by sex

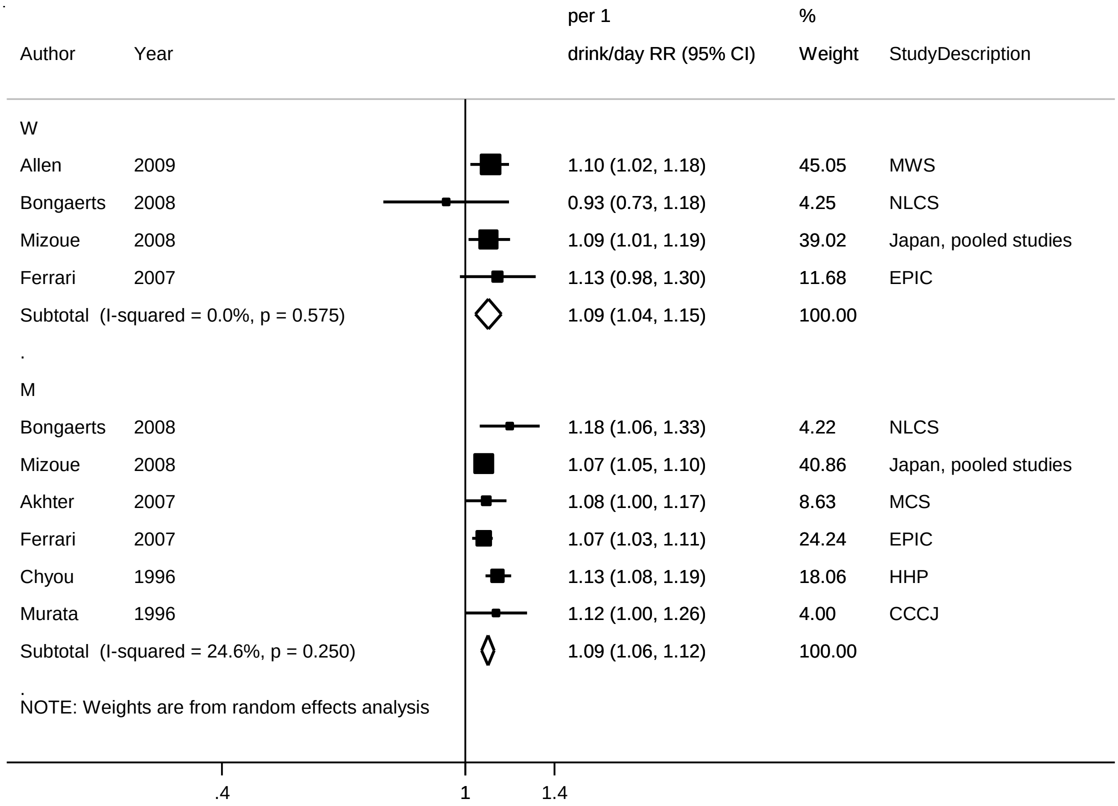


Figure 405 RR (95% CI) of rectal cancer for 10g/day increase of alcohol (as ethanol) by geographic location

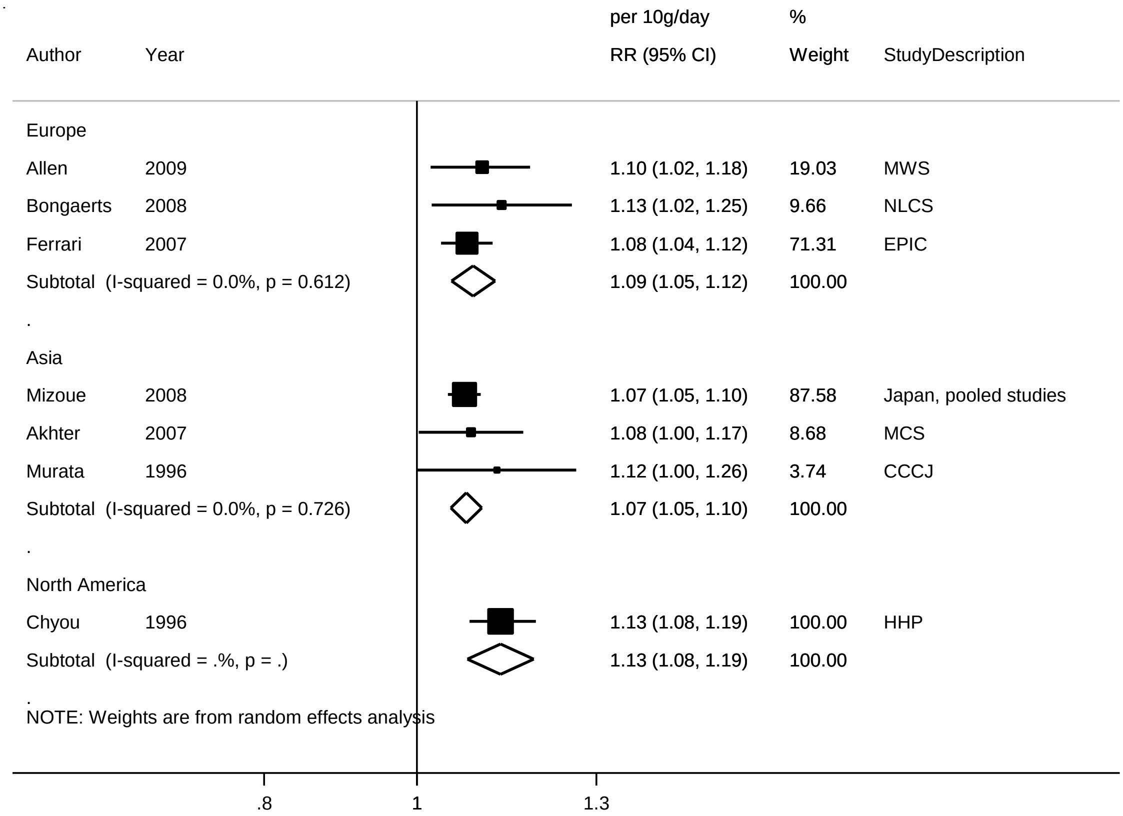


Figure 406 RR (95% CI) of colorectal cancer for the highest compared with the lowest level of wine

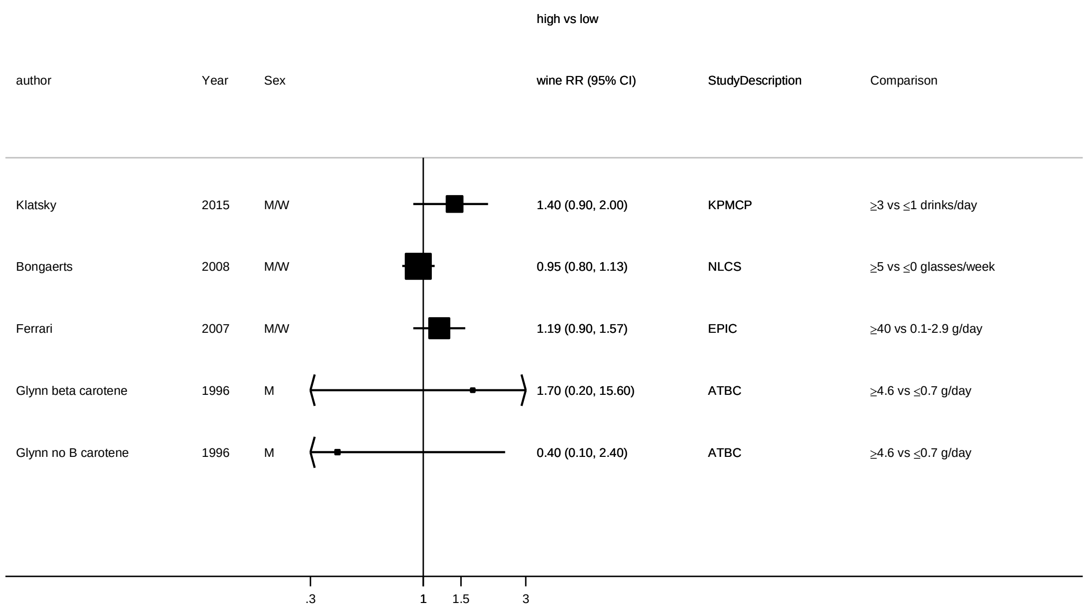
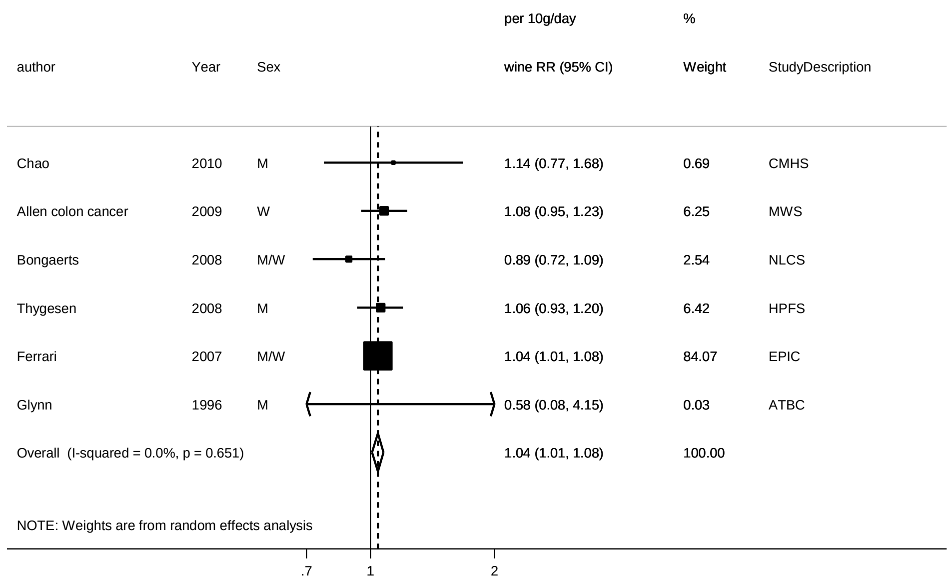


Figure 407 RR (95% CI) of colorectal and colon cancer for 10g/day increase of wine



Note: When EPIC study is excluded the overall is 1.04 (0.96-1.13)

Figure 408 RR (95% CI) of colorectal cancer for the highest compared with the lowest level of beers

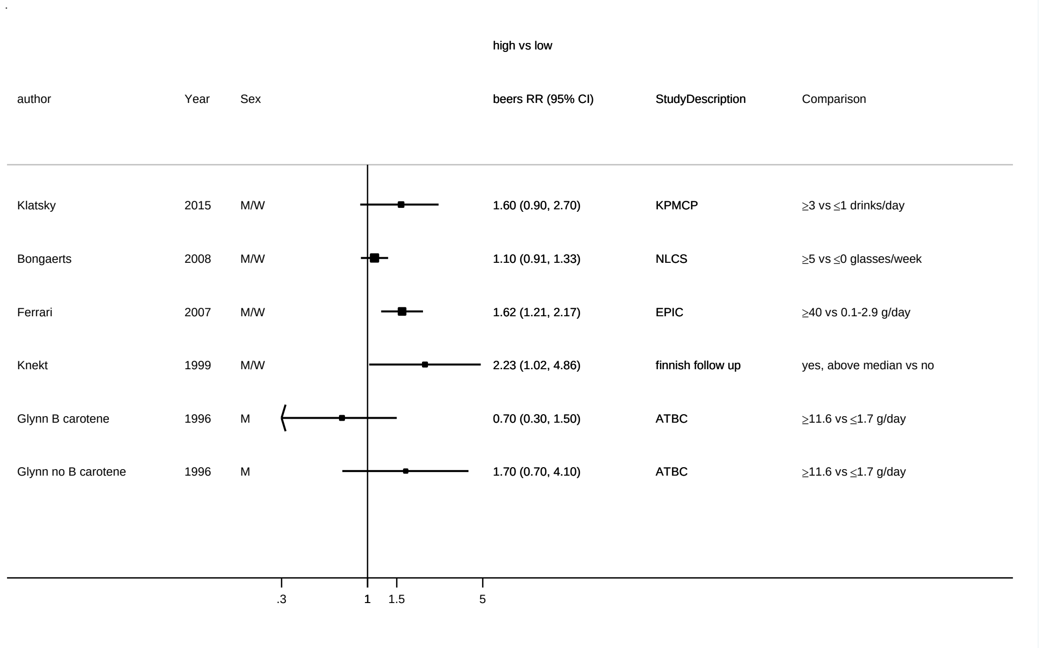
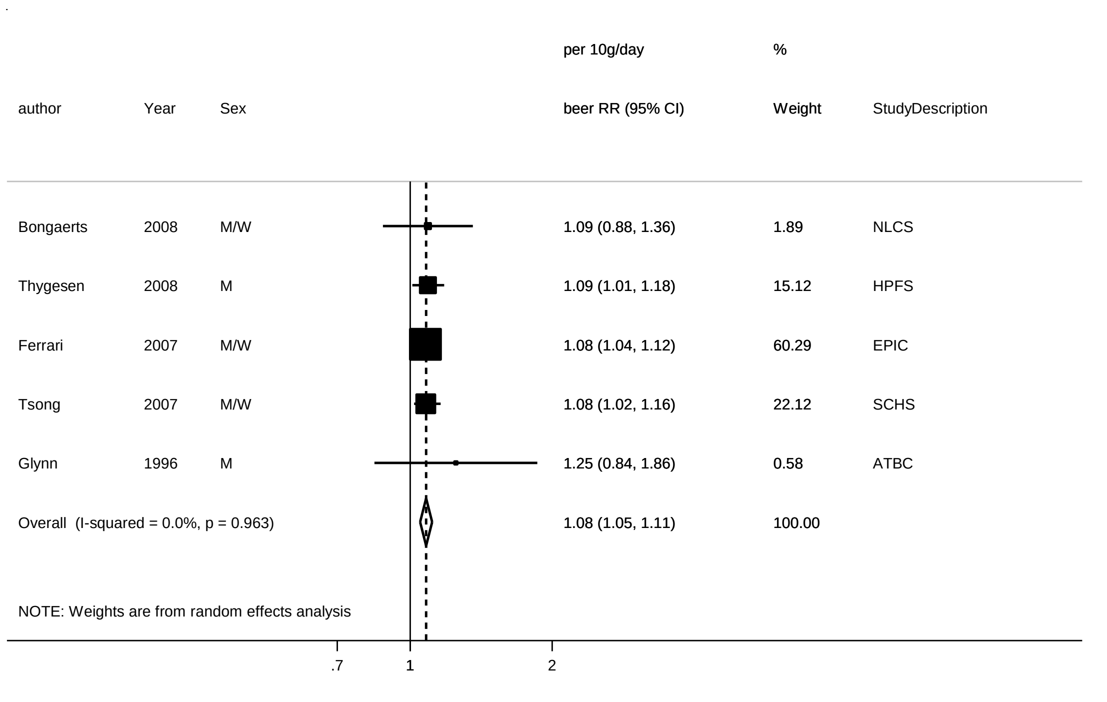


Figure 409 RR (95% CI) of colorectal cancer for 10g/day increase of beers



Note: When EPIC study excluded the overall is 1.08 (1.04-1.14)

Figure 410 RR (95% CI) of colorectal cancer for the highest compared with the lowest level of liquors

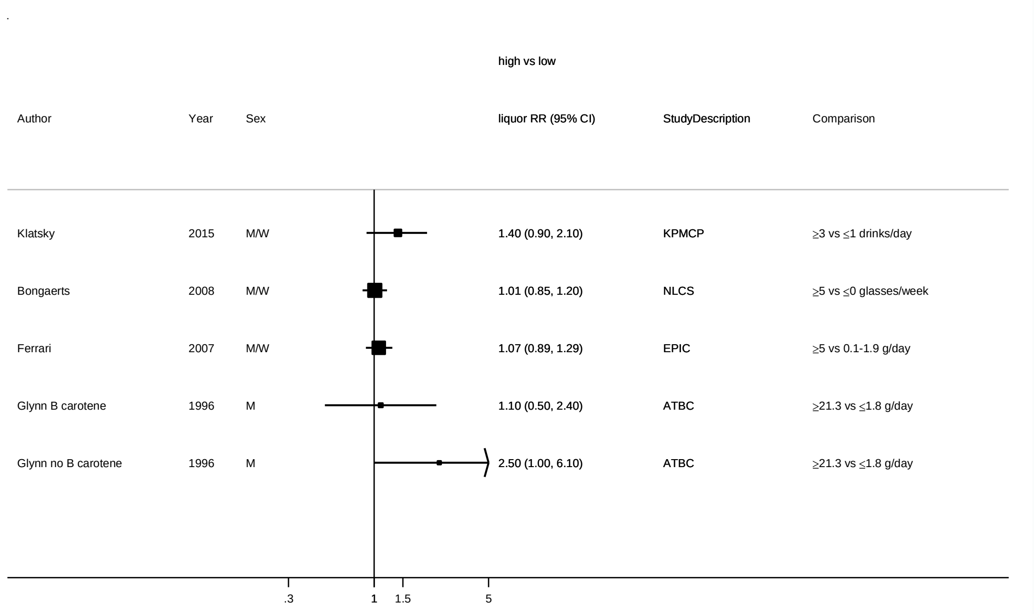
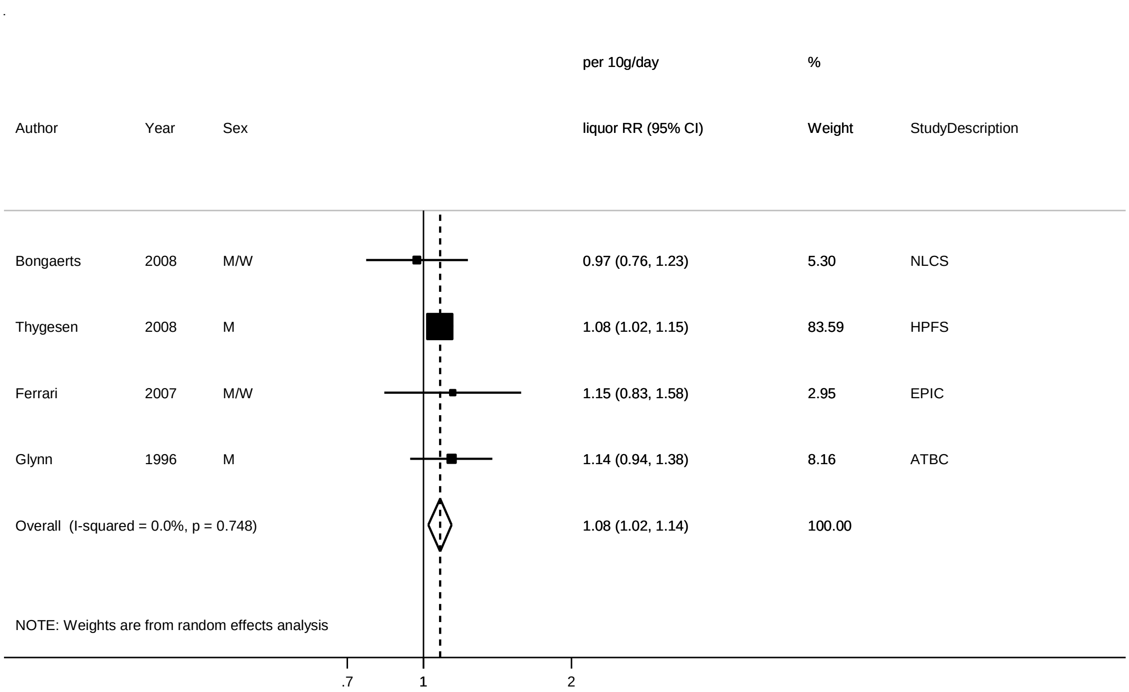


Figure 411 RR (95% CI) of colorectal cancer for 10g/day increase of liquors



5.5.10 Dietary vitamin D

Only one new study (Yang, 2011) was identified after SLR 2010. No dose-response meta-analysis was conducted.

In the 2010 SLR, the summary relative risk for 100 IU/day increment of Vitamin D in foods was 0.95 (95% CI 0.93-0.98; I^2=11%, p=0.34) for colorectal cancer (10 studies, 5171 cases). No significant association with colon cancer (RR=0.99; 95% CI 0.93-1.06; I^2=0%, p=0.68 ; 6 studies 1991 cases) or rectal cancer (RR=0.87; 95% CI 0.72-1.05; I^2=57%, p=0.05 ; 5 studies 925 cases) was observed.

In the Swedish Women's Lifestyle and Health cohort (Yang, 2011), dietary vitamin D was not related to colorectal cancer risk. The RR estimate for the comparison of Vitamin D intake in diet ≥5.1 µg/day compared to <2.9 µg/day was 1.13 (95% CI 0.73-1.73), ptrend=0.75.

5.5.10 Supplemental vitamin D

Only one new study (Prentice, 2013) was identified after SLR 2010. No dose-response meta-analysis was conducted.

In the 2010 SLR, the summary relative risk of colorectal cancer for 100 IU/day increment of Vitamin D in supplements was 0.93 (95% CI 0.88-0.99) (2 studies, 415 cases).

The Women's Health Initiative observational study is a cohort study including 36 282 postmenopausal women (Prentice, 2013). The hazard ratio of colorectal cancer for vitamin D supplementation (number of cases=9) compared to no supplement use (number of cases=174) was 0.67 (95% 0.33-1.36).

5.5.10 Vitamin D and calcium supplement

Randomized controlled trials.

The Women's Health Initiative was a double blind, placebo-controlled clinical trial of 1,000 mg elemental calcium carbonate plus 400 IU of vitamin D3 daily, with average intervention period of 7.0 years in postmenopausal women in US. The main outcome was hip fracture, and secondarily, total fracture and colorectal cancer. Vitamin D and calcium supplement had no effect of colorectal cancer risk. The hazard ratio of colorectal cancer for calcium and vitamin D supplementation compared to placebo use was 1.06 (95% CI 0.85- 1.32) in all trial participants and 0.81 (95% CI 0.58- 1.13) after excluding women using personal calcium or vitamin D supplements at baseline.

Prospective cohort studies

Only one new study (Prentice, 2013) was identified after SLR 2010. No dose-response meta-analysis was conducted.
In the Women's Health Initiative observational study in postmenopausal women (Prentice, 2013), the age-adjusted incidence was 0.11% in non users of supplements (174 incident cases) and 0.08 % (88 incident cases) in Vitamin D and calcium supplement users after 7.2 years of follow-up on average. The hazard ratio of colorectal cancer for calcium and vitamin D supplementation compared to no supplement use was 0.83 (95% 0.61-1.12).

5.5.10 Plasma or serum vitamin D

Summary

Main results:
In total 11 studies (13 publications) were identified on serum vitamin D and colorectal cancer risk. Eight new studies (Seven publications) were identified since the 2010 SLR. One study (2 publications) were on colorectal cancer mortality (Freedman, 2007 & 2010).

Cohort studies

Colorectal cancer:
Eleven studies (4 801 cases) were included in the dose-response meta-analysis of plasma or serum 25-hydroxy vitamin D. There was a borderline significant inverse association between higher level of vitamin D and colorectal cancer risk. High heterogeneity was observed. There was no evidence of publication bias (P=0.90). The visual inspection of funnel plot shows that the studies of WHI (Wactawski-Wende, 2013) and ATBC study (Anic, 2014) were outliers.
After stratification by location, the results were significant for North American studies with no heterogeneity and non-significant for Europe.

The summary RR's ranged from 0.90 (95% CI=0.84-0.96) when Anic, 2014 was omitted to 0.94 (95% CI=0.88-1.00) when Wactawski-Wende, 2013 was omitted.
There was no evidence of a non-linear inverse association (n=9).

Colon cancer:
Nine studies (2 037 cases) were included in the dose-response meta-analysis. No significant association was observed. There was no evidence of small study bias (p=0.07).

In stratified analysis by location, only studies in Europe showed a significant inverse association. No significant association was observed when data stratified by sex.

There was an evidence of a non-linear association (p=<0.001). The non-linear association showed a decreased risk with higher levels of serum with amount above 28.7 nmol/l.

In sensitivity analysis, the summary RRs ranged from 0.87 (95% CI=0.78-0.96) when Otani, 2007 was excluded to 0.91 (95% CI=0.81-1.03) when Braun, 1995 was eliminated.

Rectal cancer:
Seven studies (1 579 cases) were included in the dose-response meta-analysis. A borderline significant inverse association was observed.
Medium heterogeneity was observed. There was no evidence of small study bias (p=0.12).

In stratified analysis by sex and location, only studies in women and studies in Asia showed a significant inverse association.
There was no evidence of a non-linear association (p=0.64).
In sensitivity analysis, the summary RRs ranged from 0.77 (95% CI=0.63-0.95) when Jenab, 2010 was excluded to 0.91 (95% CI=0.79-1.05) when Otani, 2007 was eliminated.

Study quality:
All studies were multiple adjusted for different confounders. Cancer outcome was confirmed medical records and cancer registry records in most studies. Wactawski-Wende, 2013 was a case-control nested in a RCT of Vitamin D + Calcium; there was no interaction between serum 25-hydroxyvitamin D levels at baseline and treatment assignment (P = 0.54).

Table 221 Serum vitamin D and colorectal cancer risk. Number of studies in the CUP SLR

	Number
Studies identified	12 studies (15 publications)
Studies included in forest plot of highest compared with lowest exposure	11
Studies included in dose-response meta-analysis	11
Studies included in non-linear dose-response meta-analysis	9

Note: Include cohort, nested case-control and case-cohort designs

Table 222Serum vitamin D and colon cancer risk. Number of studies in the CUP SLR

	Number
Studies identified	10 studies (10 publications)
Studies included in forest plot of highest compared with lowest exposure	9
Studies included in dose-response meta-analysis	9
Studies included in non-linear dose-response meta-analysis	8

Note: Include cohort, nested case-control and case-cohort designs

Table 223 Serum vitamin D and rectal cancer risk. Number of studies in the CUP SLR

	Number
Studies identified	8 studies (8

	publications)
Studies included in forest plot of highest compared with lowest exposure	7
Studies included in dose-response meta-analysis	7
Studies included in non-linear dose-response meta-analysis	5

Note: Include cohort, nested case-control and case-cohort designs

Table 224 Serum vitamin D and colorectal cancer risk. Summary of the dose-response meta-analysis in the 2010 SLR and 2015 SLR.

	2010 SLR	2015 SLR
Increment unit used	Per 100 IU/l	30 nmol/l
Studies (n)	6	11
Cases (total number)	2 318	4 801
RR (95%CI)	0.96 (0.94-0.97)	0.92 (0.85-1.00)
Heterogeneity (I^2, p-value)	0%, 0.81	54.1%, 0.02
Stratified analysis by sex		
Men		
Studies (n)		3
RR (95%CI)		1.05 (0.88-1.26)
Heterogeneity (I^2, p-value)		60.2%, 0.08
Women		
Studies (n)		2
RR (95%CI)		0.83 (0.53-1.26)
Heterogeneity (I^2, p-value)		60.2%, 0.08
Stratified analysis by geographic location		
Asia		
Studies (n)		1
RR (95%CI)		0.95 (0.81-1.13)
Heterogeneity (I^2, p-value)		
Europe		
Studies (n)		4
RR (95%CI)		0.97 (0.83-1.13)
Heterogeneity (I^2, p-value)		0.64%, 0.04
North America		
Studies (n)		6
RR (95%CI)		0.89 (0.79-1.00)
Heterogeneity (I^2, p-value)		61.4%, 0.03
Stratified analysis by BMI adjustment		
BMI adjusted		
Studies (n)		10
RR (95%CI)		0.94 (0.88-1.01)

Heterogeneity (I^2, p-value)		33.6%, 0.15
BMI not adjusted		
Studies (n)		1
RR (95%CI)		0.67 (0.53-0.85)
Heterogeneity (I^2, p-value)		

Table 225 Serum vitamin D and colon cancer risk. Summary of the dose-response meta-analysis in the 2010 SLR and 2015 SLR.

	2010 SLR	**2015 SLR**
Increment unit used	Per 100 IU/l	30 nmol/l
Studies (n)	6	9
Cases (total number)	1 444	2 037
RR (95%CI)	0.95 (0.92-1.00)	0.90 (0.81-1.01)
Heterogeneity (I^2, p-value)	47.9%, 0.09	62.5%, 0.009
Stratified analysis by sex		
Men		
Studies (n)		4
RR (95%CI)		0.94 (0.77-1.14)
Heterogeneity (I^2, p-value)		64.3%, 0.04
Women		
Studies (n)		2
RR (95%CI)		1.07 (0.69-1.66)
Heterogeneity (I^2, p-value)		80.7%, 0.02
Stratified analysis by geographic location		
Asia		
Studies (n)		1
RR (95%CI)		1.14 (0.93-1.40)
Heterogeneity (I^2, p-value)		
Europe		
Studies (n)		2
RR (95%CI)		0.77 (0.68-0.87)
Heterogeneity (I^2, p-value)		0%, 0.48
North America		
Studies (n)		6
RR (95%CI)		0.90 (0.80-1.02)
Heterogeneity (I^2, p-value)		47%, 0.11

Table Serum vitamin D and rectal cancer risk. Summary of the dose-response meta-analysis in the 2010 SLR and 2015 SLR.

	2010 SLR	2015 SLR
Increment unit used	Per 100 IU/l	30 nmol/l
Studies (n)	5	7
Cases (total number)	700	1 579
RR (95%CI)	0.95 (0.86-1.05)	0.83 (0.69-1.00)
Heterogeneity (I^2, p-value)	66.7%, 0.02	43.3%, 0.12
Stratified analysis by sex		
Men		
Studies (n)		4
RR (95%CI)		0.81 (0.54-1.22)
Heterogeneity (I^2, p-value)		69.1%, 0.02
Women		
Studies (n)		2
RR (95%CI)		0.62 (0.44-0.88)
Heterogeneity (I^2, p-value)		0%, 0.86
Asia		
Studies (n)		1
RR (95%CI)		0.58(0.41-0.83)
Heterogeneity (I^2, p-value)		
Europe		
Studies (n)		2
RR (95%CI)		0.94(0.75-1.19)
Heterogeneity (I^2, p-value)		10%, 0.29
North America		
Studies (n)		4
RR (95%CI)		0.87 (0.71-1.07)
Heterogeneity (I^2, p-value)		4.5%, 0.35

Table 226 Serum vitamin D and colorectal cancer risk. Results of meta-analyses and pooled analyses of prospective studies published after the 2010 SLR.

Author, Year	Number of cohort studies	Total number of cases	Studies country, area	Outcome	Comparison	RR (95%CI)	P trend	Heterogeneity (I^2, p value)
Meta-analysis								
Lee, 2011	8	2 690	North America, Europe, Asia	Incidence, colorectal cancer	Highest vs lowest	0.66 (0.54-0.81)		
	9	1 822		Incidence, colon cancer		0.77 (0.56-1.07)		
	8	868		Incidence, rectal cancer		0.50 (0.28-0.88)		
Gandini, 2011	9 (case-control and cohort studies)	2 630	USA	Incidence, colorectal cancer		0.85 (0.79-0.91)		55%, <0.01

Table 227 Serum vitamin D and colorectal cancer risk. Main characteristics of studies included in the CUP SLR dose-response meta-analysis

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Missing data derived for analyses
Weinstein, 2015 COL41025 USA	PLCO, Nested Case Control, Age: 55-74	476/ 474 controls 5.6 years	Self-report verified by medical record		Incidence, colorectal cancer	≥100 vs 50-75 nmol/l	0.40 (0.17-0.92)	Alcohol, aspirin use, BMI, educational level, family	
						Q 5 vs Q 1	0.59 (0.36-0.95)		
						per 25 nmol/l	0.77 (0.65-0.91)		

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Missing data derived for analyses
	years, M/W	421/ 419 controls			Incidence, colon cancer	Q 4 vs Q 1	0.61 (0.40-0.93)	history of colorectal cancer, Ibuprofen use, matching variables, physical activity, smoking habits	
		365/			Incidence, colorectal cancer	Q5 vs Q1	0.60 (0.35-1.01)		
		300/ 299 controls			Incidence, proximal colon cancer	Q 4 vs Q 1	0.49 (0.30-0.82)		
		273/ 271 controls			Incidence, colorectal cancer stage I-II	Q 4 vs Q 1	0.62 (0.37-1.03)		
		174/ 173 controls			Incidence, distal colon & rectal cancer	Q 4 vs Q 1	0.74 (0.39-1.41)		
		119/ 118 controls			Incidence, distal colon cancer	Q 4 vs Q 1	0.96 (0.42-2.18)		
		55/ 54 controls			Incidence, rectal cancer	Q 4 vs Q 1	0.52 (0.17-1.59)		
Anic, 2014 COL41008 Finland	ATBC, Nested Case Control, Age: 50-69 years, M	416/ 416 controls	Cancer registry		Incidence, colorectal cancer	Q 4 vs Q 1	1.56 (1.02-2.36)	Age at randomization, BMI, date of blood collection, height, physical activity, serum alpha tocopherol,	

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Missing data derived for analyses
								serum beta-carotene, serum retinol, years of smoking	
Skaaby, 2014 COL41019 Denmark	Monica10, Inter99, Health2006, Prospective Cohort, Age: 18-71 years, M/W	141/ 12 204 11.3 years	Cancer registry		Incidence, colorectal cancer	Q 4 vs Q 1	0.82 (0.51-1.35)	Alcohol, BMI, educational level, fish, gender, physical activity, season, smoking, study	
					Incidence, colorectal cancer, women	per 10 nmol/l	0.89 (0.79-1.01)		
					Incidence, colorectal cancer, men	per 10 nmol/l	0.95 (0.90-1.08)		
Song, 2014 COL41026 USA	NHS, Nested Case Control, Age: 30-55 years, W, nurses	341/ 678 controls 20 years	Questionnaire/medical records/death record		Incidence, colorectal cancer	35.3-44.5 vs 12.8-18.3 ng/ml	0.64 (0.42-0.99)	Age, alcohol, BMI, dash score, endoscopy, family history of colorectal cancer, Infection with HBV and/or HCV, Inflammatory score, matching variables, multivitamin supplement intake, pack	Unit converted to nmol/l

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Missing data derived for analyses
								years of smoking, physical activity, regular aspirin use	
Song, 2014 COL41027 USA	HPFS, Nested Case Control, Age: 40-75 years, M, Health professionals	274/ 531 controls	Questionnaire/medical records/death record		Incidence, colorectal cancer	36.6-43.1 vs 14.9-20.8 ng/ml	0.81 (0.50-1.30)	Age, alcohol, BMI, dash score, endoscopy, family history of colorectal cancer, Inflammatory score, matching variables, multivitamin supplement intake, pack years of smoking, physical activity, regular aspirin use	Unit converted to nmol/l
Wactawski-Wende, 2013 COL40667	WHI, Case Control nested in a RCT of Vit D + Calcium,	306/ 306 controls 11 years	Self-report, verified by medical records		Incidence, colorectal cancer	≥58.4 vs <31 nmol/l	2.53 (1.49–4.32)	Age, center, race or ethnic group, date of blood sampling	Hamling method used to recalculate RR's

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Missing data derived for analyses
	Age:50-79 years, W								
Ordonez-Mena, 2013 COL40960 Germany	ESTHER, Prospective Cohort, Age: 50-74 years, M/W	136/ 9 482 8 years	Self-report, linkage to cancer registries, medical and pathology records		Incidence, colorectal cancer	Q 4 vs Q 2+3	0.77 (0.50-1.20)	Age, sex, BMI, educational level, family history of cancer, fish consumption, fruit intake, multivitamin supplement intake, physical activity, red meat, smoking, vegetables intake	Hamling method used to recalculate RR's
Lee, 2011 COL40861	PHS, Nested Case Control, Age: 40-84 years, M	229/ 389 controls 8.9 years	Follow up questionnaire, medical records		Incidence, colorectal cancer	37.9 vs 15.7 ng/ml	1.08 (0.62-1.87)	Age, race, smoking status, season, fasting status, vigorous exercise, dairy calcium intake, BMI	Unit converted
		172/ 287 controls			Incidence, colon cancer		1.38 (0.73-2.64)		
		57/ 102 controls			Incidence, rectal cancer		0.45 (0.14-1.46)		

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Missing data derived for analyses
Jenab, 2010 COL40823 multi-national	EPIC, Nested Case Control, Age: 35-70 years, M/W	1 248/ 1248 controls 7 years	Record linkage to cancer registry/histo- and cyto- pathology reports	Dietary recall	Incidence, colorectal cancer	≥100 vs 50-74.9 nmol/l	0.77 (0.56-1.06)	Age, sex, alcohol intake, BMI, centre location, educational level, fasting condition, fruits intake, meat intake, menopausal status, phase of menstrual cycle at time of blood collection, smoking status, time, total dietary energy consumption, total physical activity, use of HRT, vegetable intake	Hamling method used to recalculate RR's
		785/ 785 controls			Incidence, colon cancer	100-123.5 vs 50-60.9 nmol/l	0.71 (0.46-1.08)		
Woolcott, 2010 COL40799 USA	MEC, Nested Case Control, Age: 45-75 years, M/W	229/ 434 controls	Cancer registry and national death Index	Dietary recall	Incidence, colorectal cancer	≥32.8 vs ≤16.7 ng/ml	0.60 (0.33-1.07)	Age, sex, area of residence, BMI, family history of colon cancer, fasting condition,	Unit converted to nmol/l
						per 2 ngml	0.71 (0.53-0.95)		
						per 2 ngml	0.68 (0.51-0.92)		
		170/			Incidence, colon	per 2 ngml	0.79 (0.56-1.10)		

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Missing data derived for analyses
		319 controls			cancer			processed meat, race, time, year of birth Calcium intake	
		43/ 83 controls			Incidence, rectal cancer	per 2 ngml	0.40 (0.19-0.85)		
Otani, 2007 COL40672 Japan	JPHC, Nested Case Control, Age: 40-69 years, M/W	163/ 324 controls 11.5 years	Cancer registry and death certificates	FFQ	Incidence, colorectal cancer, men	≥32.1 vs ≤22.8 ng/ml	0.73 (0.35-1.50)	Age, alcohol consumption, BMI, date of blood collection, family history of colorectal cancer, fasting condition, physical activity, smoking, pack-years, study area, vitamin use	Unit converted to nmol/l
		160/ 297 controls			Incidence, colorectal cancer women	≥27 vs ≤18.6 ng/ml	1.10 (0.50-2.30)		
		119/ 237 controls			Incidence, colon cancer, men	≥32.1 vs ≤22.8 ng/ml	1.20 (0.51-2.70)		
		106/ 195 controls			Incidence, colon cancer, women	≥27 vs ≤18.6 ng/ml	2.10 (0.78-5.60)		
		54/ 102 controls			Incidence, rectal cancer, women	≥27 vs ≤18.6 ng/ml	2.70 (0.94-7.60)		
						≥27 vs ≤18.6 ng/ml	0.33 (0.08-1.30)		
		44/ 87 controls			Incidence, rectal cancer, men	≥32.1 vs ≤22.8 ng/ml	0.07 (0.01-0.99)		
						≥32.1 vs ≤22.8 ng/ml	4.60 (1.00-20.00)		

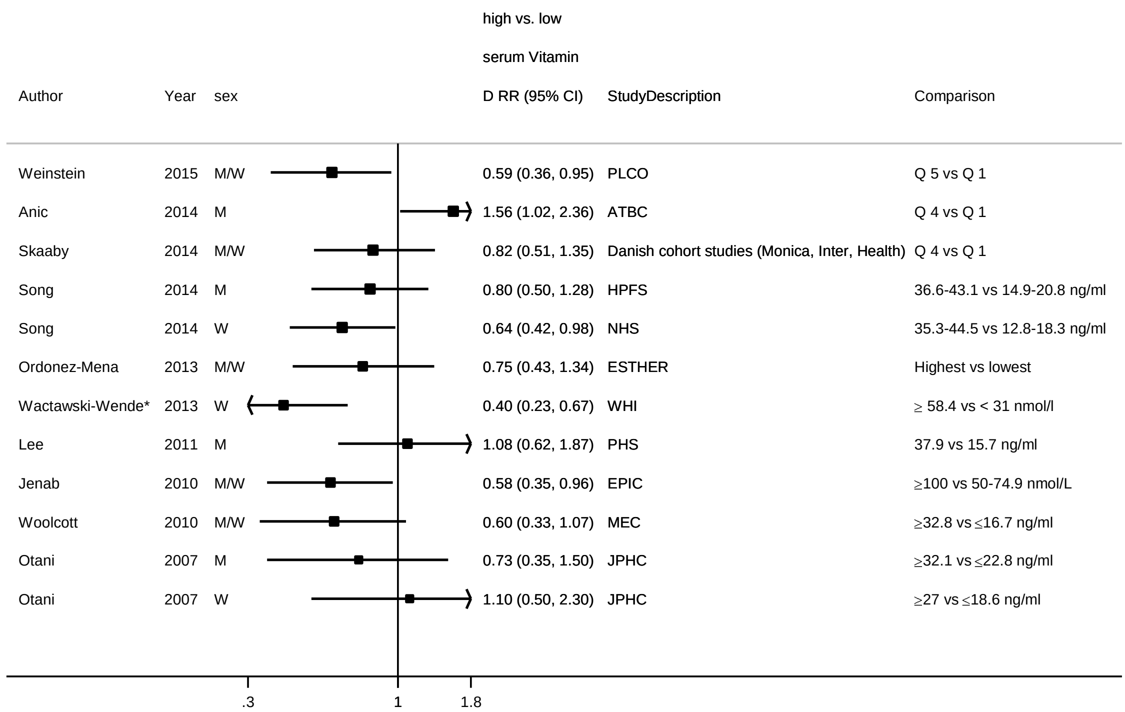
Table 228 Serum vitamin D and colorectal cancer risk. Main characteristics of studies excluded from the CUP SLR dose-response meta-analysis

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Reasons for exclusion
Jung, 2014 COL41053 USA	NHS-HPFS, Prospective Cohort, Age: 30-75 years, M/W, Health professionals	1 059/ 140 418	Self-report verified by medical record and pathology report		Incidence, colorectal cancer	Q 5 vs Q 1	0.55 (0.43-0.71)	Age, sex, alcohol, aspirin use, BMI, calcium, endoscopy, family history of colorectal cancer, height, physical activity, red meat, smoking, total calories, total fruit and vegetable consumption	The exposure was predicted vitamin D score
Freedman, 2010 COL40843 USA	NHANES III, Prospective Cohort, Age: 17- years, M/W	95/ 16 819 225 212 person-years	National death Index		Mortality, colorectal cancer	≥100 vs ≤50 nmol/liter	0.35 (0.11-1.14)	Age, BMI, ethnicity, gender, smoking	Mortality
		61/			Men	≥80 vs ≤50 nmol/liter	0.71 (0.25-1.99)		
		44/			Women	≥80 vs ≤50 nmol/liter	0.37 (0.11-1.27)		

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Reasons for exclusion
Freedman, 2007 COL40709 USA	NHANES III, Prospective Cohort, Age: 17- years, M/W	66/ 16 818 146 578 person-years	National death Index	24 hour recall	Mortality, colorectal cancer	≥80 vs ≤49 nmol/l	0.28 (0.11-0.68)	Age, sex, pack-years of smoking, race	Mortality
Wu, 2007 COL40683 USA	HPFS, Nested Case Control, Age: 66 years, M	179/ 356 controls 8 years	Medical records	FFQ	Incidence, colorectal cancer	39.4 vs 18.4 ng/ml	0.83 (0.45-1.52)	Age, alcohol consumption, aspirin use, family history, folate intake, meat intake, pack-years of smoking, year of Interview	Superseded by Song, 2014
		139/ 276 controls			Incidence, colon cancer	38.8 vs 19.3 ng/ml	0.46 (0.24-0.89)		
		40/ 70 controls			Incidence, rectal cancer	37.4 vs 21.2 ng/ml	3.32 (0.87 to 12.69)		
	NHS, Nested Case Control, Age: 66 years, W	193/ 383 controls			Incidence, colorectal cancer	Q5 vs Q1	0.51 (0.26 to 1.00)		
		149/ 295 controls			Incidence, colon cancer	Q4 vs Q1	0.64 (0.33 to 1.26)		
		44/ 88 controls			Incidence, rectal cancer	T3 vs T1	0.15 (0.02 to 1.05)		
	HPFS & NHS	373/ 739 controls			Incidence, colorectal cancer	Q5 vs Q1	0.66 (0.42 to 1.05)		
		288/ 571 controls			Incidence, colon cancer	T3 vs T1	0.54 (0.34 to 0.86)		
Tangrea, 1997	ATBC,	146/	Hospital records	Questionnaire	Incidence,	≥43.2 vs ≤31.7	0.90 (0.50-1.70)	Age, clinic site,	Superseded by

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Reasons for exclusion
COL00267 Finland	Nested Case Control, Age: 50-69 years, M, Smokers	292 controls			colorectal cancer,	ng/l		date of blood draw	Anic, 2014 COL41008
						≥19.4 vs ≤9.8 ng/l	0.60 (0.30-1.10)		
		103/ 204 controls			Incidence, distal colon & rectal cancer	≥19.4 vs ≤9.8 ng/l	0.50 (0.20-0.90)		
		91/ 181 controls			Incidence, colon cancer	≥43.2 vs ≤31.7 ng/l	1.20 (0.60-2.60)		
						≥19.4 vs ≤9.8 ng/l	0.80 (0.40-1.60)		
		55/ 109 controls			Incidence, rectal cancer	≥43.2 vs ≤31.7 ng/l	0.50 (0.20-1.50)		
						≥19.4 vs ≤9.8 ng/l	0.40 (0.10-1.10)		
		48/ 95 controls			Incidence, distal colon cancer	≥19.4 vs ≤9.8 ng/l	0.60 (0.20-1.50)		
		43/ 86 controls			Incidence, proximal colon cancer	≥19.4 vs ≤9.8 ng/l	1.30 (0.40-4.20)		

Figure 412 RR (95% CI) of colorectal cancer for the highest compared with the lowest level serum Vitamin D



*The RR's in EPIC and ESTHER studies were recalculated using Hamling method.

Figure 413 RR estimates of colorectal cancer by levels of serum Vitamin D

Figure 414 RR (95% CI) of colorectal cancer for 30 nmol/l unit increase

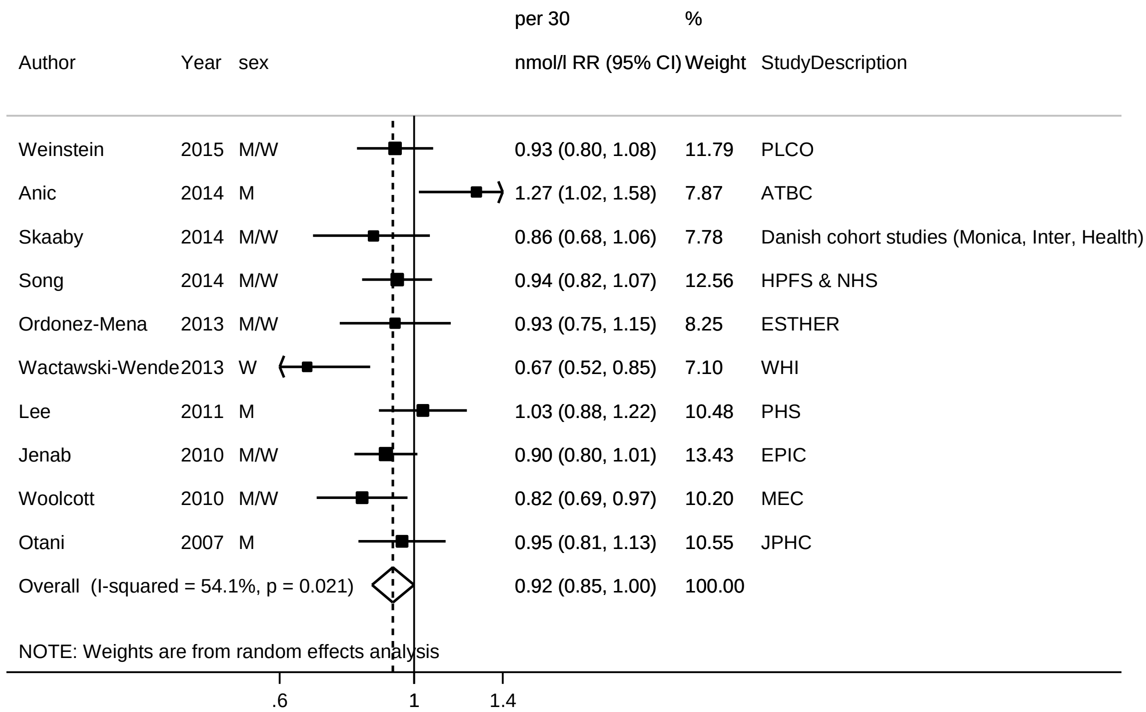
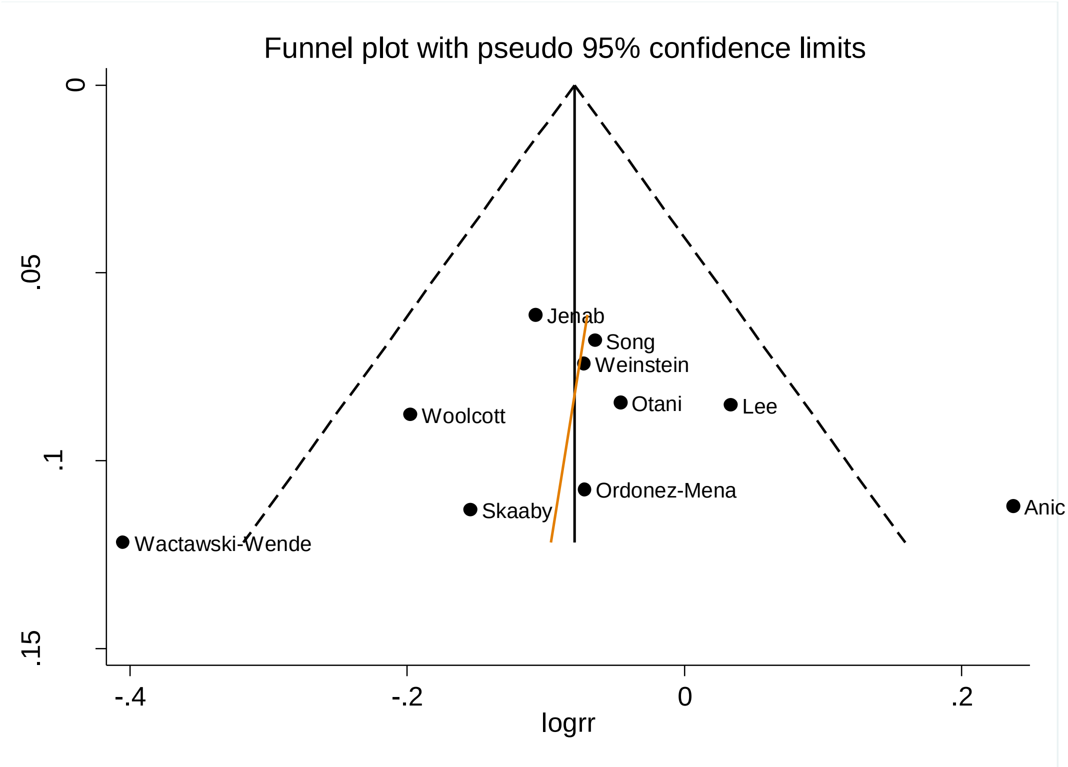


Figure 415 Funnel plot of studies included in the dose response meta-analysis of serum Vitamin D and colorectal cancer



p for Egger's test=0.90

Figure 416 RR (95% CI) of colorectal cancer for 30 nmol/l unit increase by sex

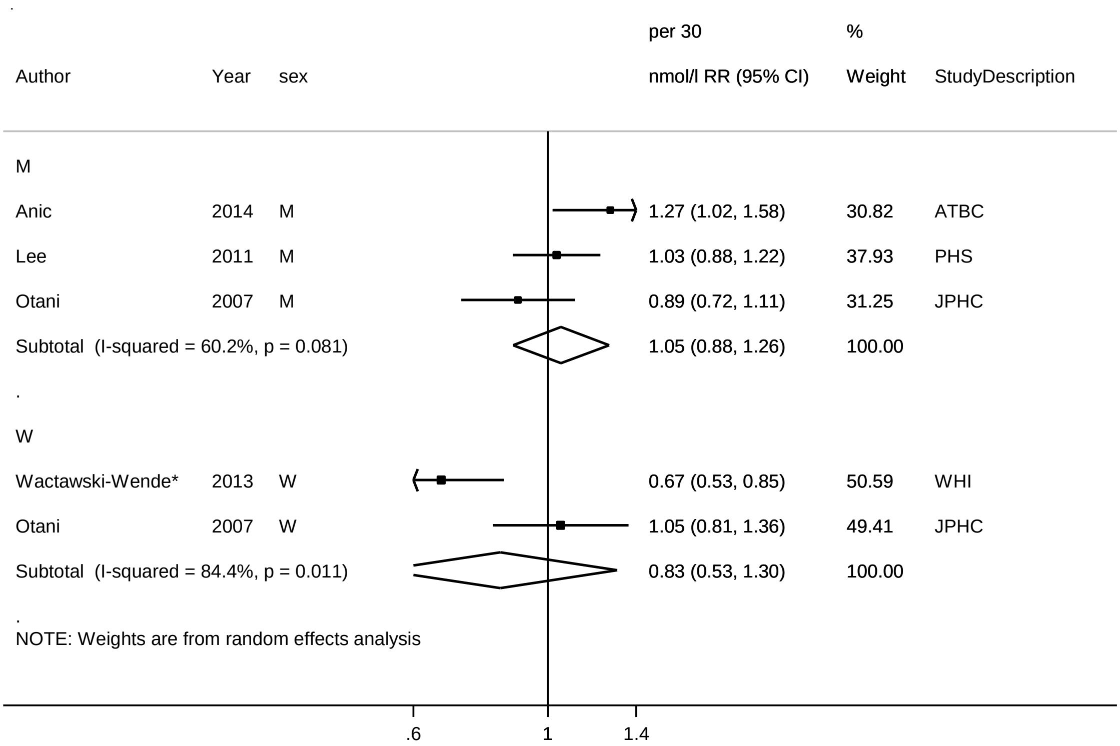


Figure 417 RR (95% CI) of colorectal cancer for 30 nmol/l unit increase by geographical location

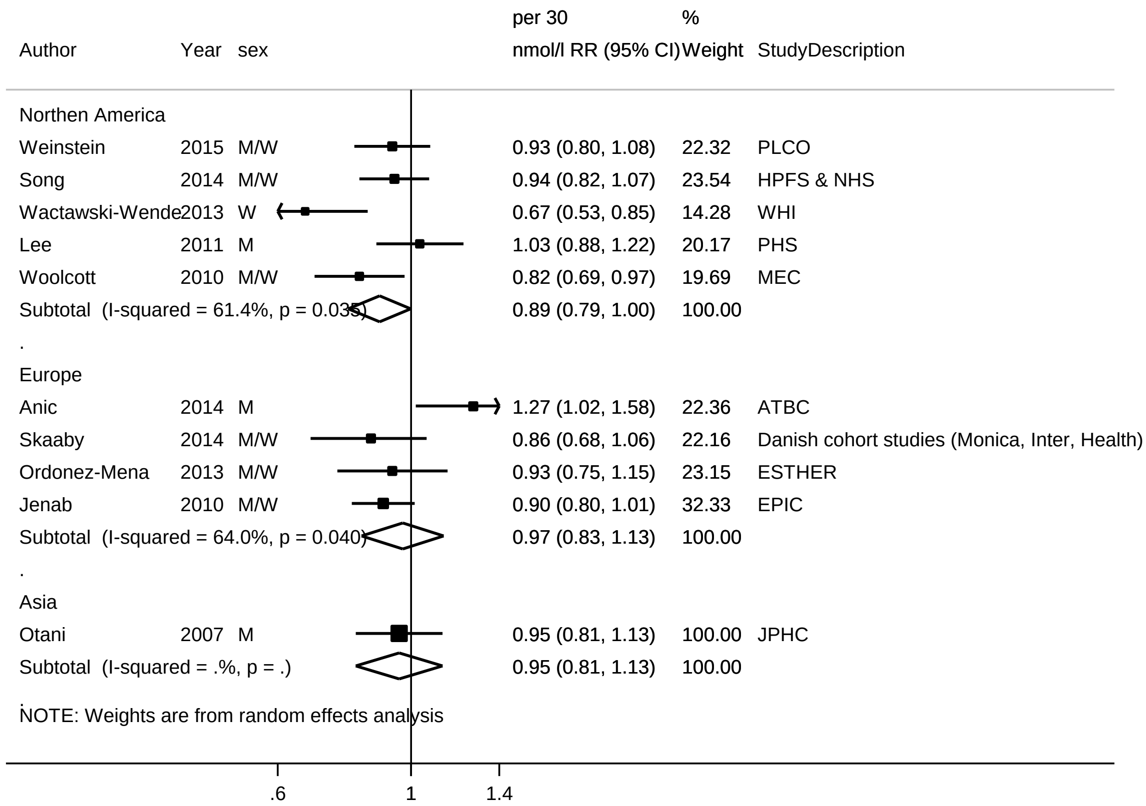


Figure 418 RR (95% CI) of colorectal cancer for 30 nmol/l unit increase by BMI adjustment

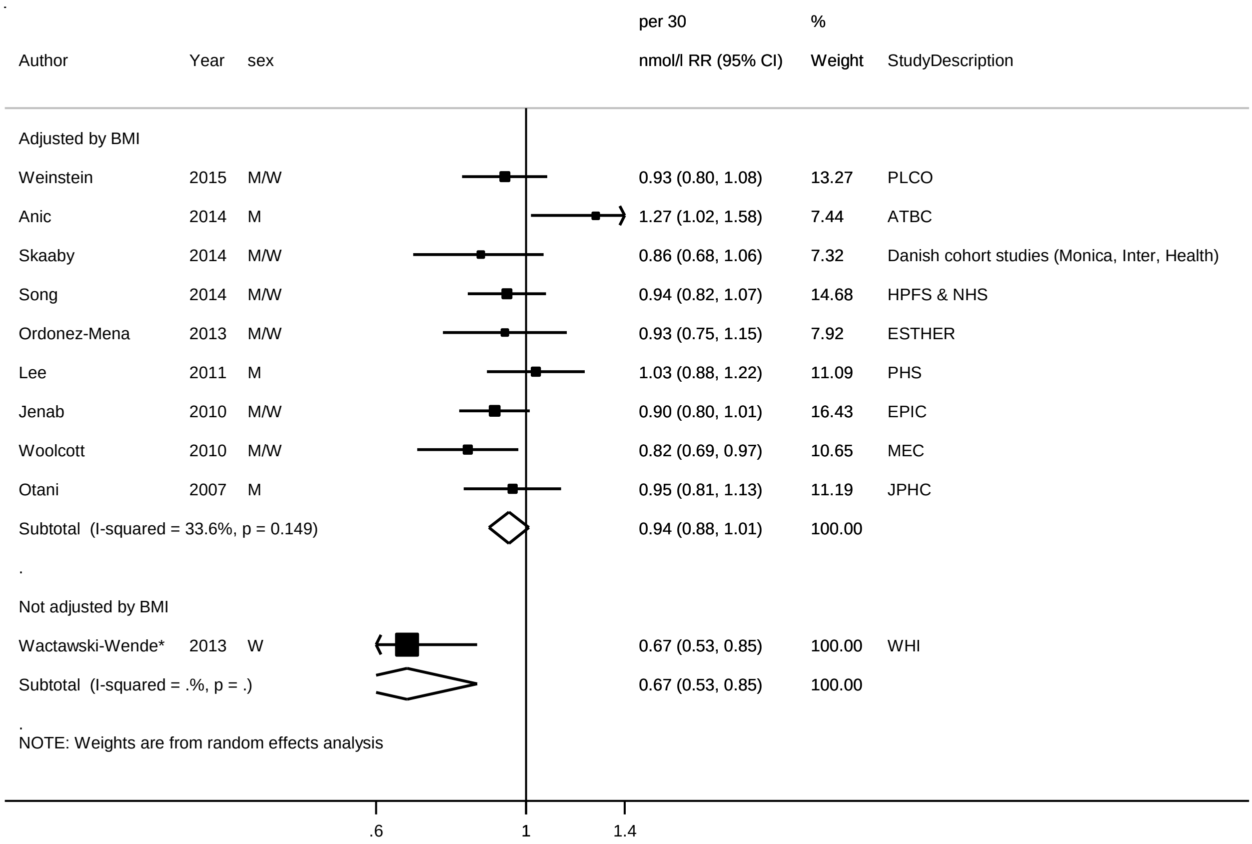
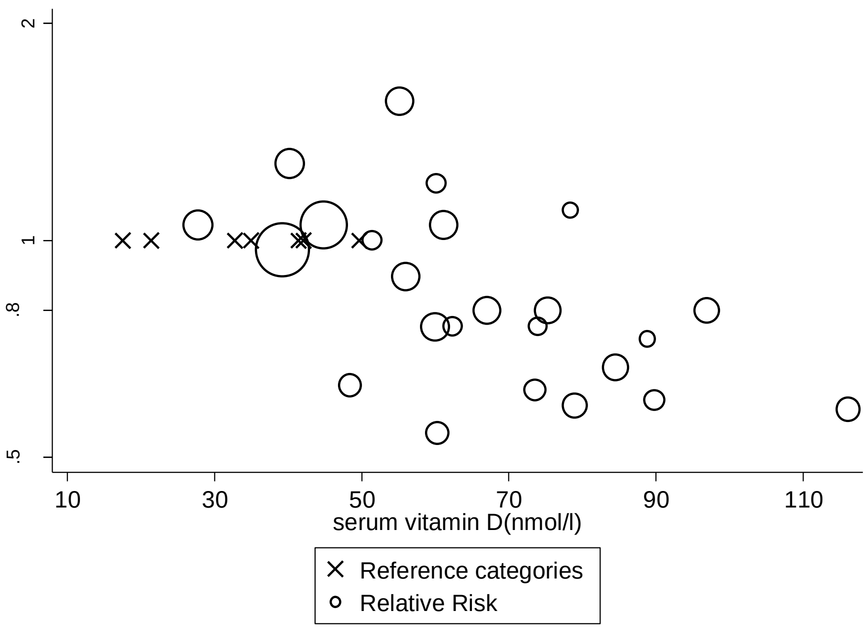
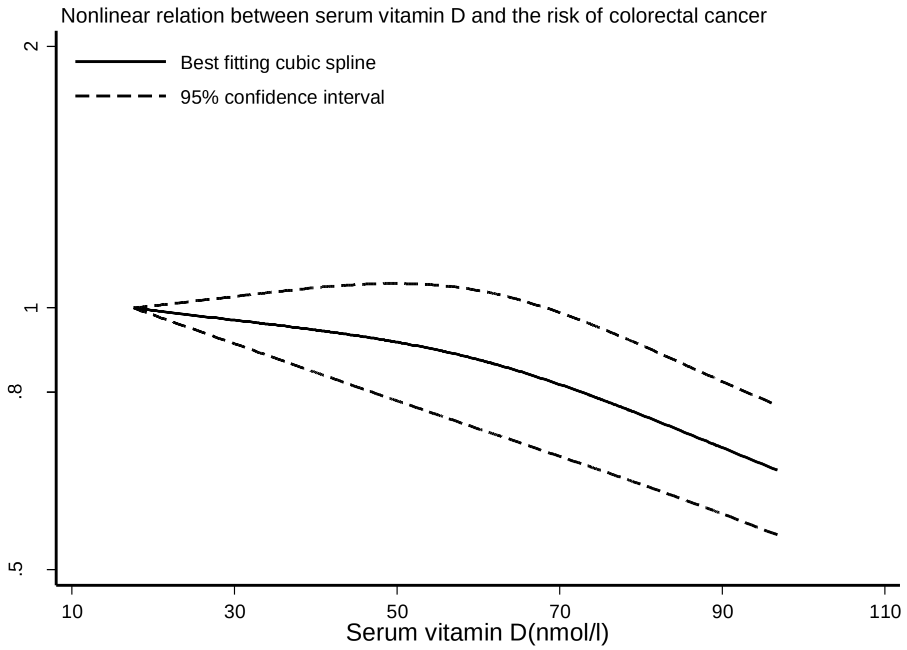


Figure 419 Relative risk of colorectal cancer and serum vitamin D estimated using non-linear models





p for non-linearity=0.09

Table 229 Table with values and corresponding RRs (95% CIs) for non-linear analysis of serum vitamin D and colorectal cancer

Serum Vitamin D (nmol/l)	RR (95%CI)
17.58	1.00
32.8	0.96 (0.89-1.04)
48.42	0.92 (0.79-1.07)
60.3	0.87 (0.72-1.05)
73.50	0.80 (0.66-0.96)
78.99	0.76 (0.63-0.92)
84.5	0.73 (0.61-0.87)

Figure 420 RR (95% CI) of colon cancer for the highest compared with the lowest level serum Vitamin D

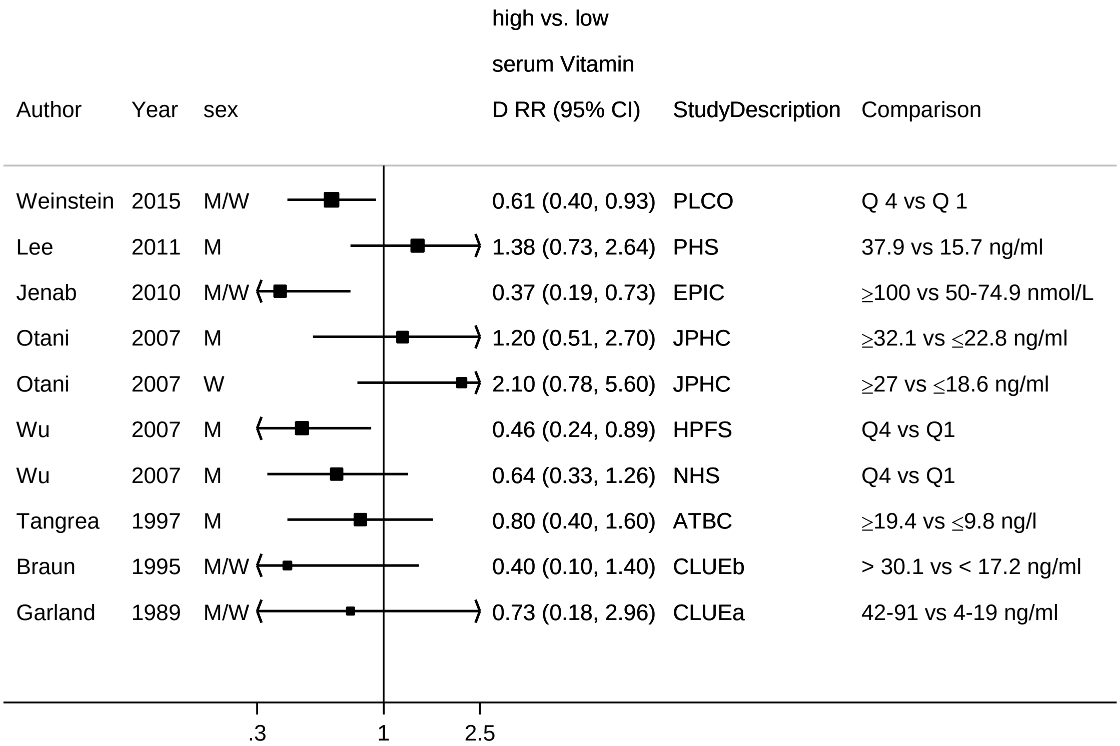


Figure 421 RR estimates of colon cancer by levels of serum Vitamin D

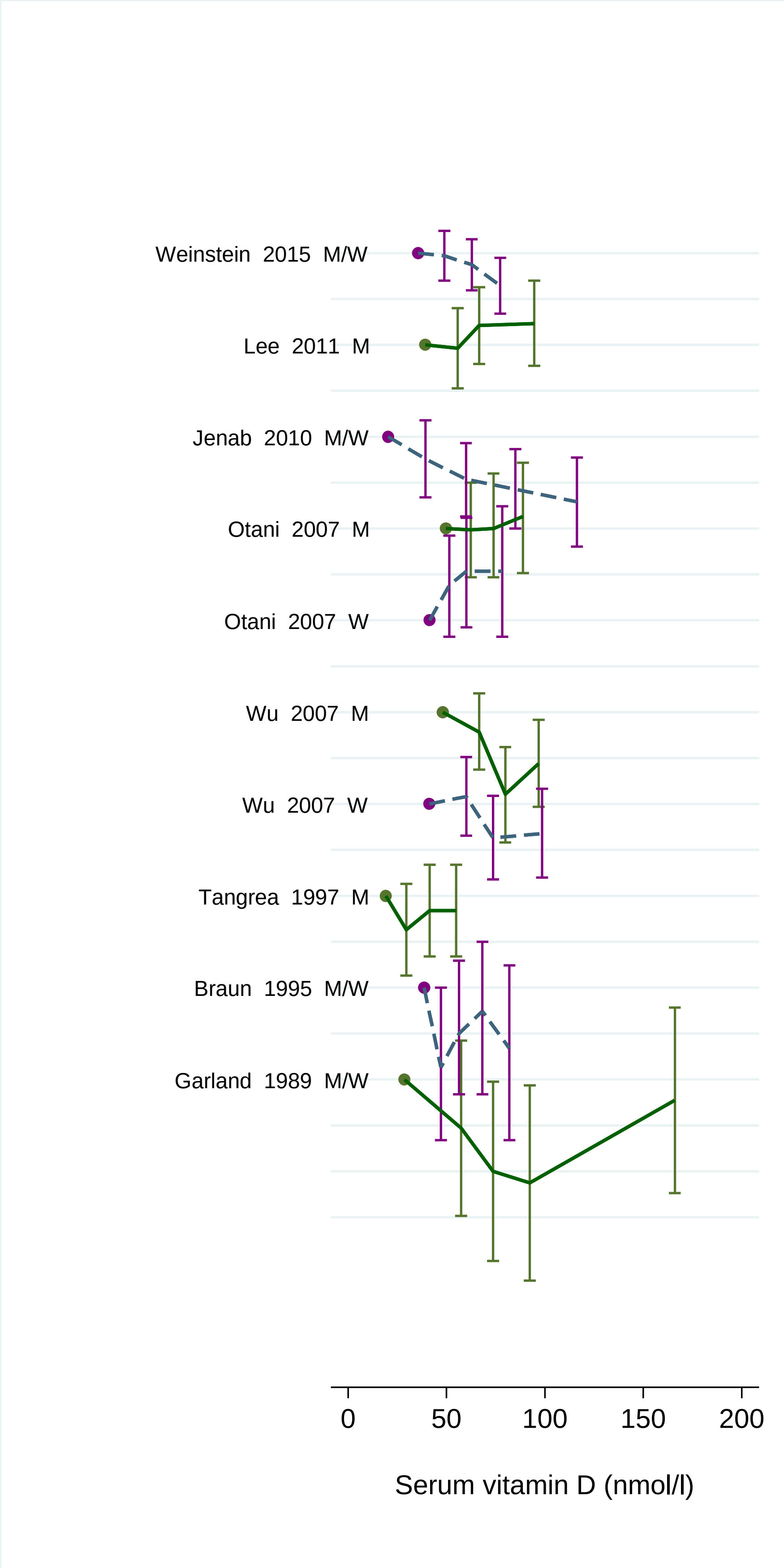


Figure 422 RR (95% CI) of colon cancer for 30 nmol/l unit increase

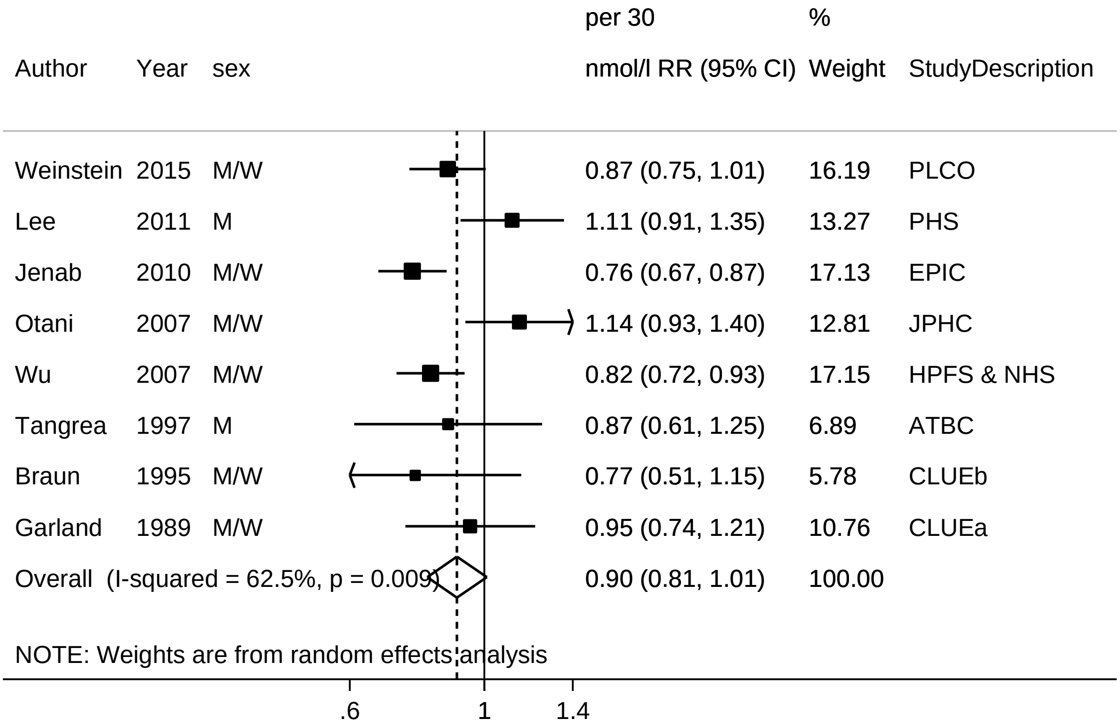


Figure 423 Funnel plot of studies included in the dose response meta-analysis of serum Vitamin D and colon cancer

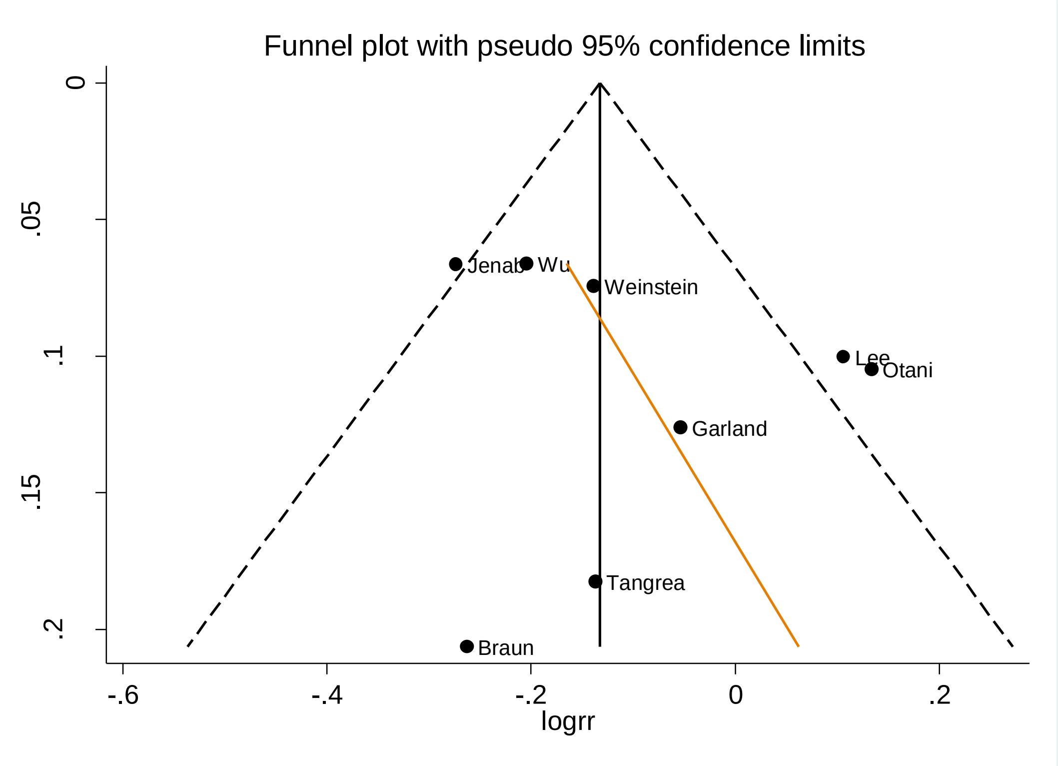


Figure 424 RR (95% CI) of colon cancer for 30 nmol/l unit increase by geographical location

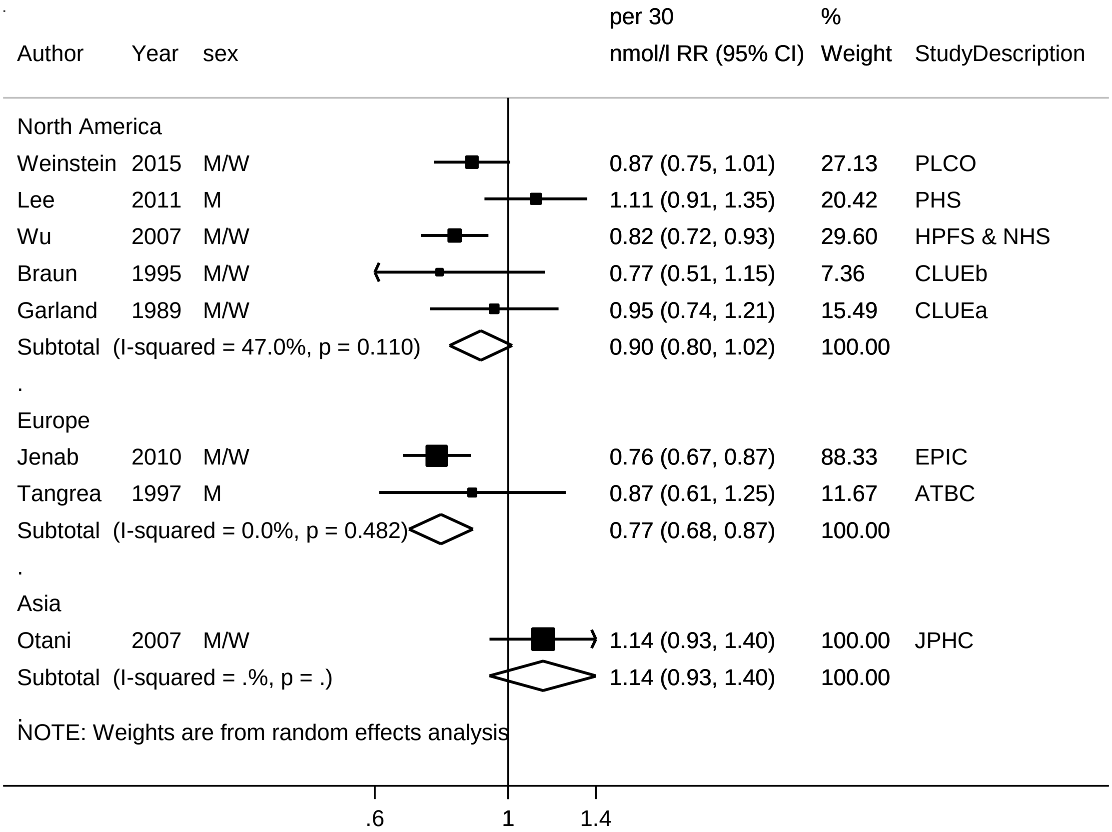


Figure 425 RR (95% CI) of rectal cancer for the highest compared with the lowest level serum Vitamin D

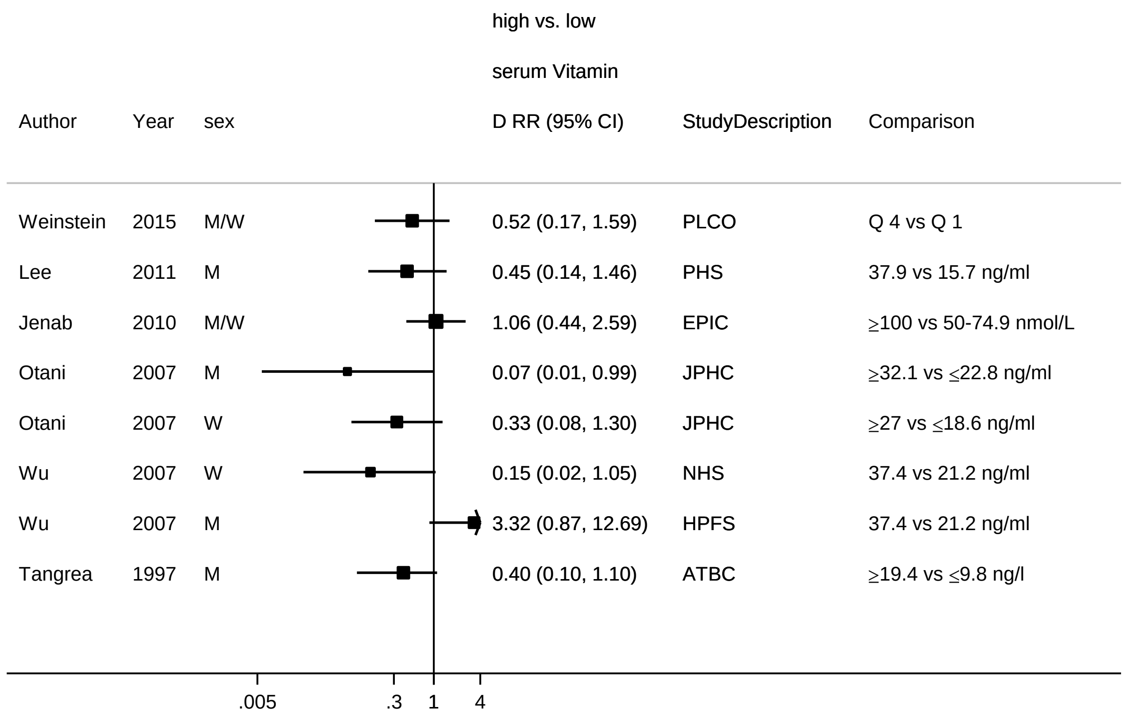


Figure 426 RR estimates of rectal cancer by levels of serum Vitamin D

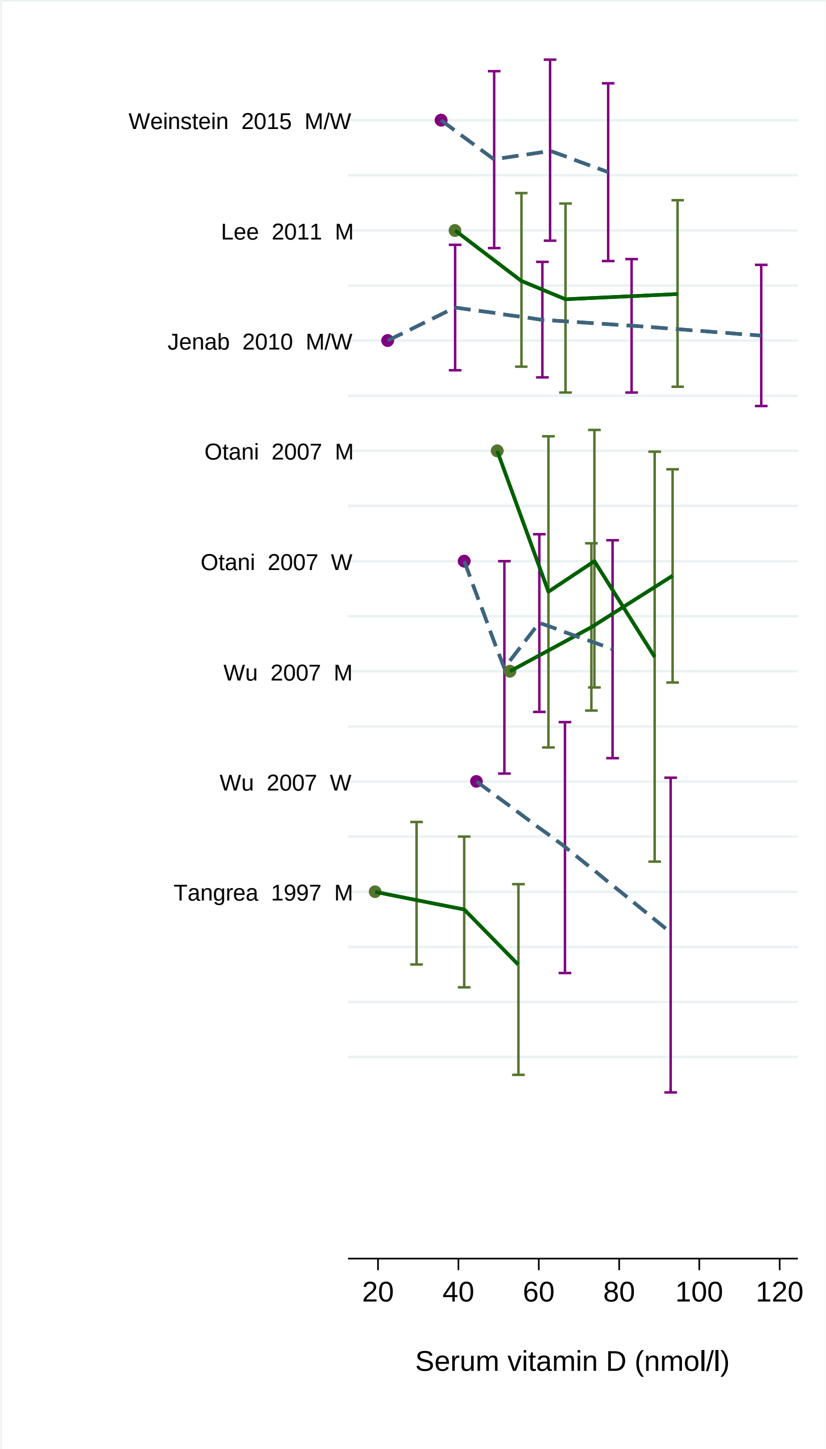


Figure 427 RR (95% CI) of rectal cancer for 30 nmol/l unit increase

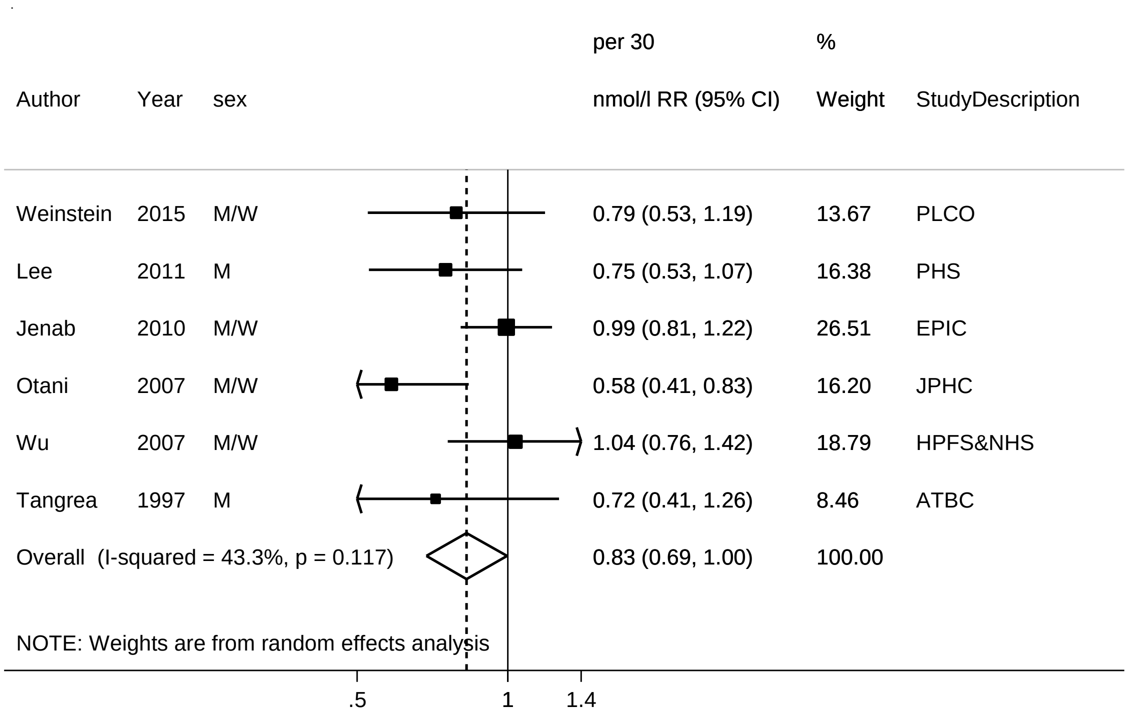


Figure 428 Funnel plot of studies included in the dose response meta-analysis of serum Vitamin D and rectal cancer

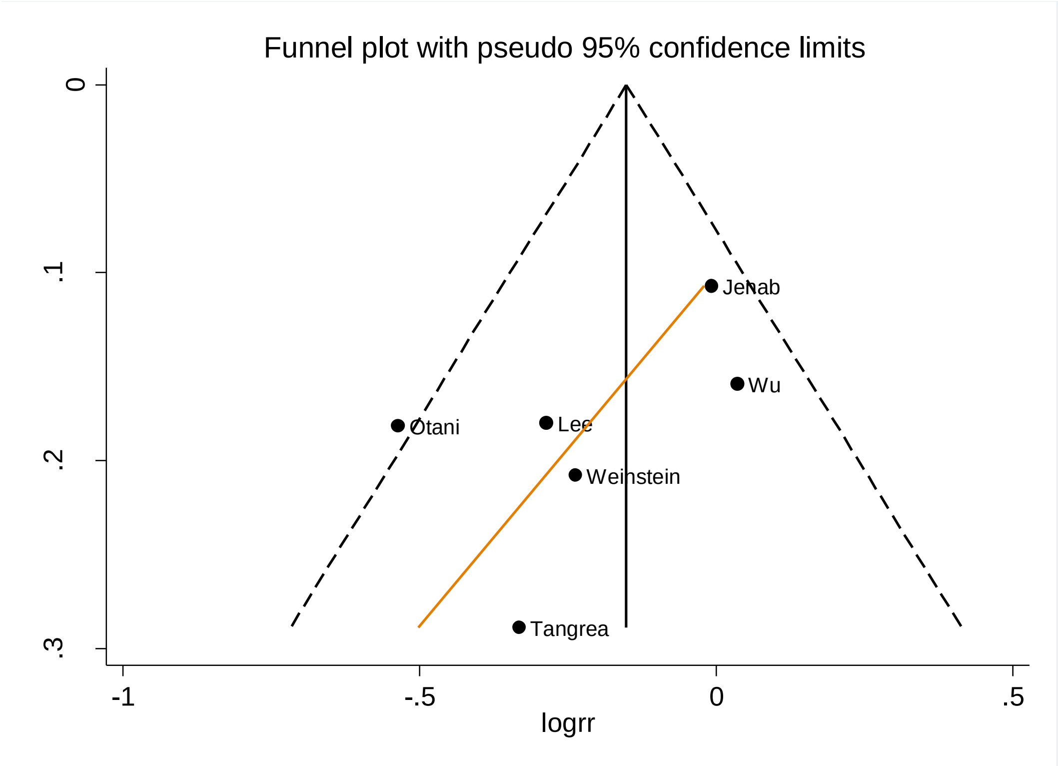
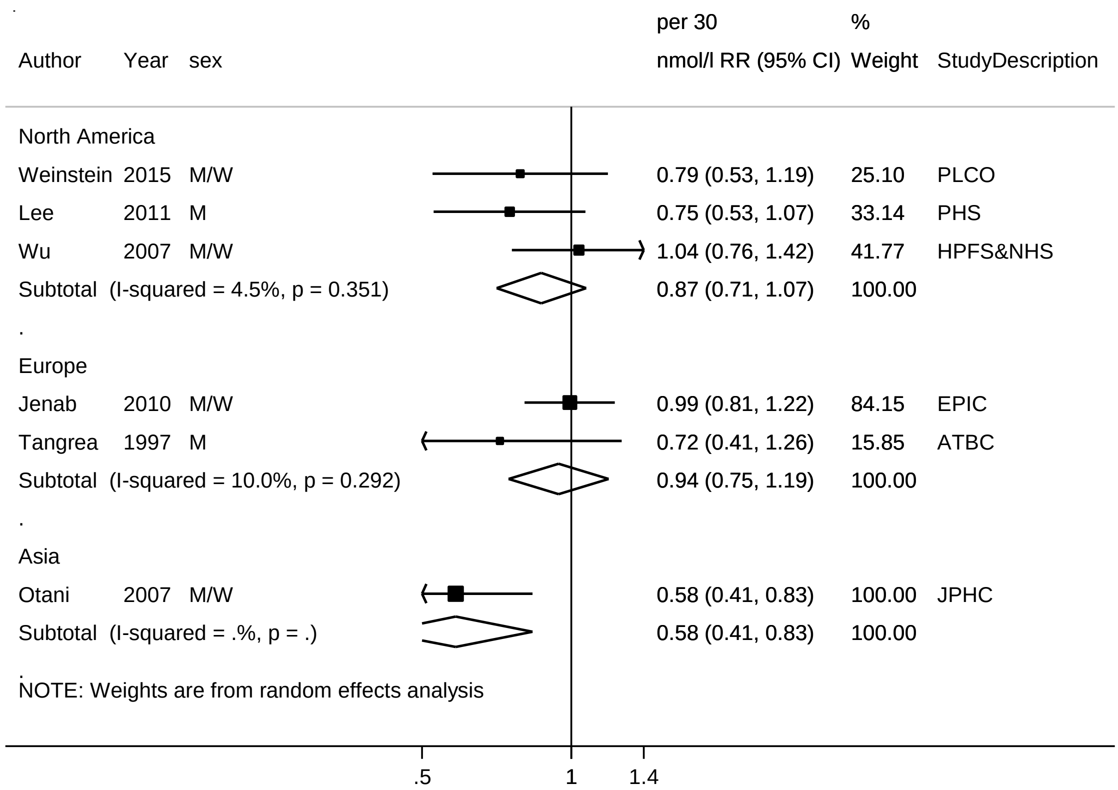


Figure 429 RR (95% CI) of rectal cancer for 30 nmol/l unit increase by geographical location



5.5.11 Dietary vitamin E

Cohort studies

Summary

Main results:
two studies and a pooled analysis of 13 studies (9 publications) were identified in the CUP. No analysis was conducted in 2010 SLR. There were only enough studies to conduct analysis on colon cancer incidence.
The three studies on colorectal cancer (Shin 2006, McCarl 2006 and Malila 2002) showed a non-significant association in highest compared to lowest analysis of dietary vitamin E.

The three studies on rectal cancer (Leenders 2014, Shin 2006, Zheng 1998) showed a non-significant association in highest compared to lowest analysis of dietary vitamin E.

Colon cancer:
Thirteen studies from the Pooling Project and 2 studies identified in the CUP (6635 cases) were included in the highest compared to lowest meta-analysis of dietary vitamin E and colon cancer. Four of the studies identified were included in the Pooling Project. A non-significant association with no heterogeneity was observed.

Pooling Project of Cohort studies:
The Pooling Project of Prospective Studies of Diet and Cancer had examined the association between dietary vitamin E intake and risk of colon cancer (Park, 2010). Results from a total of 13 cohort studies, 676141 men and women and 5454 colon cancer cases were analysed. Study-specific food frequency questionnaires were used to assess dietary vitamin E intake. For the association between dietary vitamin E intake and risk of colon cancer, a non-significant association risk was observed in the multivariate adjusted model comparing the highest with the lowest quintile (pooled RR = 0.99, 95% CI = 0.89-1.11). For total vitamin E the result was borderline significant (RR=0.83(95% CI = 0.70-0.99, >200 vs ≤6mg/day).

Table 230 Dietary vitamin E and colon cancer risk. Number of studies in the CUP SLR

	Number
Studies identified	2+13PP (9 publications)
Studies included in forest plot of highest compared with lowest exposure	15
Studies included in dose-response meta-analysis	NA
Studies included in non-linear dose-response meta-analysis	NA

Note: Include cohort, nested case-control and case-cohort designs

Table 231 Dietary vitamin E and colon cancer risk. Summary of the dose-response meta-analysis in the 2010 SLR and 2015 SLR.

	2010 SLR	**2015 SLR**
Increment unit used		Highest vs Lowest
Studies (n)		15
Cases (total number)		6635
RR (95%CI)		0.99(0.89-1.09)
Heterogeneity (I^2, p-value)		0%, 0.96

Table 232 Dietary vitamin E and colorectal cancer risk. Main characteristics of studies included in the CUP SLR dose-response meta-analysis

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Missing data derived for analysis
Leenders, 2014 COL41012 Europe	EPIC, Nested Case Control, Age: 35-70 years, M/W	898/ 898 controls	Cancer registry	FFQ	Incidence, colon cancer	≥13 vs ≤8 mg/day	0.99 (0.74-1.33)	Alcohol consumption, educational level, matching variables, number of cigarettes smoked, physical activity, smoking duration, smoking status, time since smoking cessation, waist circumference	
		501/ 501 controls			Incidence, rectal cancer	≥13 vs ≤8 mg/day	1.11 (0.74-1.65)		
Park, 2010 Pooling Project	Studies ATBC CPS II HPFS NLCS NYSC BCDDP CNBSS IWHS NLCS NYUWHS NHS	5454/676141 44 467+349 456 393 335+223 349 431 799 353 96 162+429	Self-reported questionnaire and medical record	FFQ	Incidence, colon cancer	Q5 vs Q1	0.99(0.89-1.11)	Age, body mass index, education, physical activity, family history of colorectal cancer, use of nonsteroidal anti-inflammatory drugs, multivitamin use, smoking,	

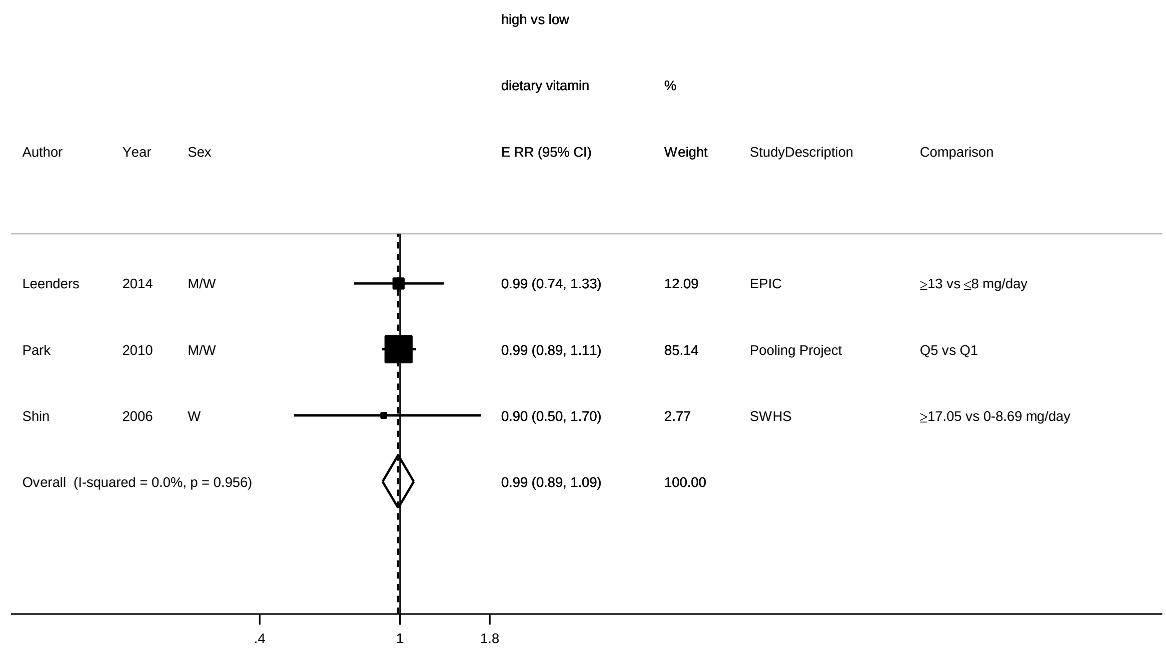
Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Missing data derived for analysis
	ORDET SMC WHS	43 485 40						alcohol consumption, intakes of red meat, total milk, dietary folate and total energy, and use of postmenopausal hormone therapy (premenopausal, never, ever) and oral contraceptive use (never, ever) in women	
Shin, 2006 COL40665 China	SWHS, Prospective Cohort, Age: 40-70 years, W	283/ 73 314 5.74 years	Follow up survey/cancer registry/vital statistics registry	FFQ	Incidence, colorectal cancer	≥17.05 vs 0-8.69 mg/day	1.00 (0.60-1.50)	Age, alcohol, calories intake, educational level, family history of colorectal cancer, menopausal status, multivitamin supplement intake, physical activity, smoking status	
		129/			Incidence, colon cancer	≥17.05 vs 0-8.69 mg/day	0.90 (0.50-1.70)		
					Incidence, rectal cancer	≥17.05 vs 0-8.69 mg/day	0.50(0.20-1.30)		

Table 233 Dietary vitamin E and colorectal cancer risk. Main characteristics of studies excluded from the CUP SLR dose-response meta-analysis

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Reasons for exclusion
McCarl, 2006 COL40633 USA	IWHS, Prospective Cohort, Age: 55-69 years, W	954/ 35 197 15 years	SEER registry	FFQ	Incidence, colorectal cancer	≥37.5 vs ≤5.9 mg/day	0.70 (0.57-0.87)	Age	Included in the Pooling Project. Park, 2010
Malila, 2002 COL00336 Finland	ATBC, Prospective Cohort, Age: 50-69 years, M, Male Smokers	184/ 26 951 8 years	Hospital records	Dietary history questionnaire	Incidence, colorectal cancer,	17.7 vs 7.5 mg/day	1.26 (0.83-1.89)	Age, alcohol consumption, BMI, energy intake, physical activity, serum cholesterol, smoking habits, trial supplementation	Included in the Pooling Project. Park, 2010
Wu, 2002 COL00905 USA	NHS, Prospective Cohort, Age: 30-55 years, W, nurses	336/ 87 998 16 years	Self-reported, hospital records and National Death Index	Semi-quantitative FFQ	Incidence, colon cancer, nhs (women) and no supplemental vit e	Q 5 vs Q 1	0.78 (0.55-1.11)	Age, alcohol consumption, aspirin use, BMI, family history of colorectal cancer, menopausal status, pack-years of smoking, physical activity, postmenopausal hormone use,	Included in the Pooling Project. Park, 2010

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Reasons for exclusion
								red meat intake	
Wu, 2002 COL00905 USA	HPFS, Prospective Cohort, Age: 40-75 years, M, Health professionals	207/ 47 344 10 years			Incidence, colon cancer, no supplemental vit e	Q 5 vs Q 1	1.18 (0.76-1.83)		Included in the Pooling Project. Park, 2010
Sellers, 1998 COL01974 USA	IWHS, Prospective Cohort, Age: 55-69 years, W, Postmenopausal	180/ 35 216 10 years	SEER	Semi-quantitative FFQ	Incidence, colon cancer, no family history of crc	≥8.33 vs ≤5.91 mg/day	0.80 (0.50-1.30)	Age, history of polyps, total energy intake	Included in the Pooling Project. Park, 2010
		61/			Family history of crc	≥8.33 vs ≤5.91 mg/day	1.20 (0.50-2.60)		
Zheng, 1998 COL00209 USA	IWHS, Prospective Cohort, Age: 55-69 years, W, Postmenopausal	144/ 34 702 9 years	SEER	Semi-quantitative FFQ	Incidence, rectal cancer,	Q 3 vs Q 1	0.93 (0.59-1.44)	Age, HRT use, pack-years of smoking, smoking habits, total energy	Included in the Pooling Project. Park, 2010
Bostick, 1993 COL00483 USA	IWHS, Prospective Cohort, Age: 55-69 years, W	212/ 35 216 167 447 person-years	SEER	Semi-quantitative FFQ	Incidence, colon cancer,	≥9.8 vs ≤4.9 iu/day	1.05 (0.55-1.88)	Age, calories intake, height, low-fat meat intake, parity, vitamin a supplement intake	Included in the Pooling Project. Park, 2010

Figure 430 RR (95% CI) of colon cancer for the highest compared with the lowest level of vitamin E



5.5.11 Supplemental vitamin E

Randomised Controlled Trials

Five RCT's (7 publications) were identified.

The ATBC Study (Virtamo, 2013 and Albanes 2000) is a randomized, double-blinded, placebo-controlled trial testing the effect of a-tocopherol and b-carotene supplementation on the incidence of lung cancer and other cancers in male smokers. 29,133 individuals were recruited from the total male population aged 50–69 years living in south-western Finland and were followed for 18 years post-trial. Subjects who were eligible and willing to participate in the trial were randomly assigned to one of the four intervention regimens: a-tocopherol (dl-a-tocopheryl acetate 50 mg daily) alone, beta-carotene (20 mg daily) alone, both a-tocopherol and beta-carotene, or placebo.
For colorectal cancer incidence, no significant association was observed when comparing the intervention group receiving alpha-tocopherol supplement and the group not receiving alpha-tocopherol supplement (676 cases).

SELECT (Klein, 2011 and Lippman, 2009) is a phase 3 double-blind randomized placebo controlled trial of selenium (200 mcg daily from L-selenomethionine) and/or vitamin E (400 IU daily of all-rac-α-tocopheryl acetate) for prostate cancer prevention with a planned minimum and maximum follow up of 7 and 12 years respectively.
The trial included 34,888 men (54 464 person-years of follow up) randomly assigned to 4 groups (selenium, vitamin E, selenium plus vitamin E and placebo) between August 22, 2001 and June 24, 2004. During a mean follow-up of 5.46 years, until October 2008, a total of 85 colorectal cancers were diagnosed when comparing the use of vitamin E supplement with placebo (75 cases). Compared to the placebo group (75), the hazard ratios of colorectal cancer in the treatment group were 1.09 (99% CI= 0.72 – 1.64, 85 cases).

The Physician's Health Study II (Gaziano, 2009) is a randomized double-blind, placebo-controlled, factorial trial of vitamin E (synthetic α-tocoperol 400 IU on alternate days) and vitamin C (500 mg daily) supplementation. The study included 14,641 male physicians in the United States of 50 year of age or older. During a mean follow-up of 8 years, a total of 1008 prostate cancer cases were confirmed. Compared to the placebo group (45 cases), there were no significant difference in colorectal cancer incidence in the group receiving vitamin E (42 cases, HR: 0.88, 0.64-1.19).

The Women's Antioxidant Cardiovascular Study (Lin, 2009) is a double-blind, placebo-controlled 2 × 2 × 2 factorial trial of vitamin C (500 mg of ascorbic acid daily), natural-source vitamin E (600 IU of alpha-tocopherol every other day), and beta carotene (50 mg every other day), 7627 women who were free of cancer before random assignment were selected for this study. The average duration of follow-up from random assignment to the end of the trial was 9.4 years. Comparting to the placebo group (27 cases) there were no significant difference in colorectal cancer incidence in the group receiving vitamin E (17 cases, RR=0.63 (95% CI=0.34 to 1.15).

In the Women's Health Study (Lee, 2005) conducted between 1992 and 2004, 39 876 apparently healthy US women aged at least 45 years were randomly assigned to receive vitamin E (600 IU of natural-source vitamin E on alternate days) or placebo and aspirin or placebo, using a 2x2 factorial design, and were followed up for an average of 10.1 years. There was no significant effect on the incidences colon cancers (RR= 1.00; 95%CI= 0.77-1.31; P=0.99).

Cohort studies

Summary

Main results:
Five studies on colon cancer incidence and two studies on colorectal mortality were identified. Only highest compared to lowest analysis was conducted. No analysis was conducted in the 2010 SLR.

Colon cancer:
Five studies were included in the highest compared to lowest meta-analysis of supplemental vitamin E and colon cancer. All studies on colon cancer incidence, except one (IWHS) observed a non-significant association with vitamin E supplementation. The IWHS (Sellers, 1998) observed a significant decrease risk in a subgroup of individual without a family history of colorectal cancer when comparing supplementation with more than 30mg/day with no supplementation.

Two studies on colorectal cancer mortality (Iso, 2007 and Hansen, 2009) reported non-siginificant associations when comparing the use versus non use and the use of 10mg/day of vitamin E supplement, respectively.

Table 234 Supplemental vitamin E and colon cancer risk. Number of studies in the CUP SLR

	Number
Studies identified	5 (5 publications)
Studies included in forest plot of highest compared with lowest exposure	5
Studies included in dose-response meta-analysis	NA
Studies included in non-linear dose-response meta-analysis	NA

Note: Include cohort, nested case-control and case-cohort designs

Table 235 Supplemental vitamin E and colon cancer risk. Summary of the dose-response meta-analysis in the 2010 SLR and 2015 SLR.

	2010 SLR	2015 SLR
Increment unit used		Highest vs Lowest
Studies (n)		5
Cases (total number)		1904
RR (95%CI)		0.83(0.73-0.95)
Heterogeneity (I^2, p-value)		0%, 0.47

Table 236 Supplemental vitamin E and colorectal cancer risk. Main characteristics of RCT studies identified in the CUP SLR

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors
Virtamo, 2013 COL41003 Finland	ATBC, Randomised Control Trial, Age: 50-69 years, M, Male Smokers	676/ 25 563 18 years	Finnish cancer registry and death certificates		Incidence, colorectal cancer	alpha-tocopherol vs no alpha-tocopherol	1.02 (0.87-1.18)	
		347/				alpha-tocopherol vs placebo	1.03 (0.83-1.27)	
Klein, 2011 COL40894 North America	SELECT, Randomised Control Trial, Age: 50- years, M, healthy men	160/ 34 887 54 646 person-years	Self-report verified by medical record and pathology report	Questionnaire	Incidence	vitamin e supplement vs placebo	1.09 (0.72-1.64) Ptrend:0.60	
Lippman, 2009 COL40767 USA	SELECT, Randomised Control Trial, Age: 50- years, M	137/ 35 533 5.46 years	Self-report/hospital record/patholog y reports	FFQ	Incidence, colorectal cancer	vit e and selenium vs placebo	1.28 (0.82-2.00)	
		126/				vitamin e from suppl vs placebo	1.09 (0.69-1.73)	
		23/			Mortality, colorectal cancer	vitamin e from suppl vs placebo	1.30 (0.44-3.83)	
Gaziano, 2009 COL40770 USA	PHS II, Randomised Control Trial, Age: 50- years, M,	162/ 13 983 8 years	Self report verified by medical record	FFQ	Incidence, colorectal cancer	vit e assignment vs placebo	0.88 (0.64-1.19)	Age, other design Issue, randomized treatment assignment,
		53/			Mortality, colorectal cancer	vit e assignment vs placebo	0.68 (0.39-1.18)	

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors
	Physicians							salad intake, study
Lin, 2009 COL41000 USA	WACS, Randomised Control Trial, Age: 40- years, W	44/ 7 627 9.4 years	Multiple methods		Incidence, colorectal cancer	vitamin e vs placebo	0.63 (0.34-1.15)	Age, alcohol consumption, BMI, smoking status, treatment allocation
Lee, 2005 COL40761 USA	WHS, Randomised Control Trial, Age: 45- years, W	214/ 39 876 10.1 years	Self-reported and National Death Index	Questionnaire	Incidence, colon cancer	intervention vs placebo	1.00 (0.77-1.31)	Age, randomization group
Albanes, 2000 COL01969 Finland	ATBC, Randomised Control Trial, Age: 50-69 years, M, Smokers	135/ 29 133 6.1 years	Cancer registry and death certificates	Diet history questionnaire	Mortality, colorectal cancer	intervention vs no intervention	0.92 (0.51-1.64)	Intervention group, age, BMI, and serum cholesterol
		66/			Incidence, colorectal cancer	intervention vs placebo	0.79 (0.48-1.28)	

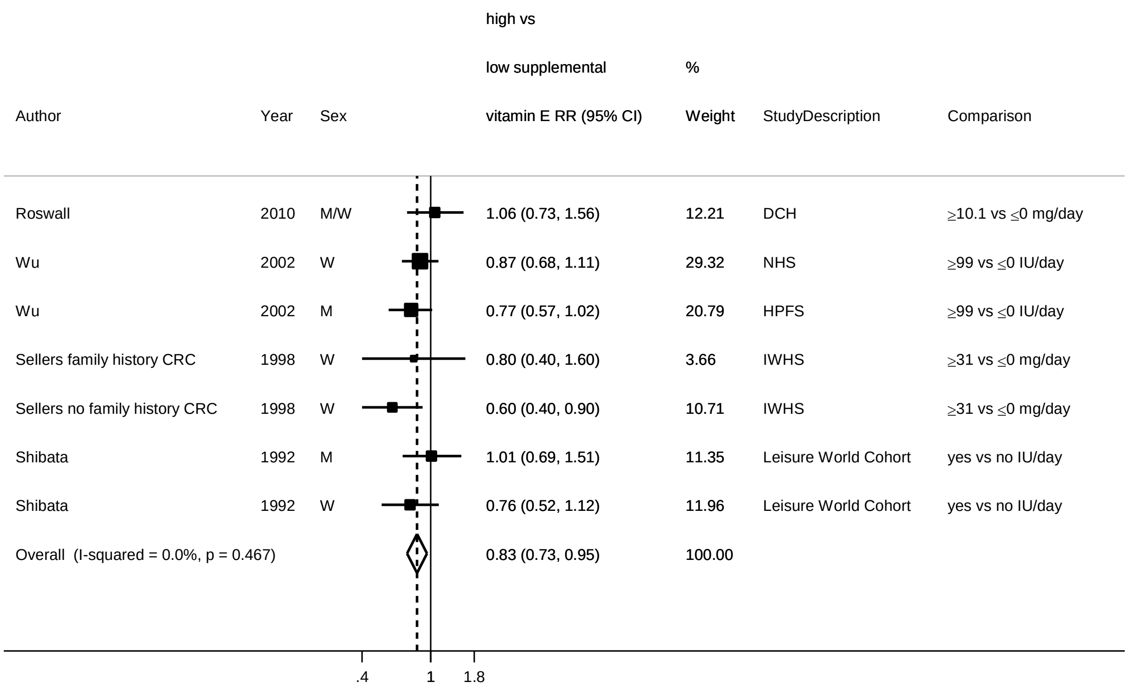
Table 237 Supplemental vitamin E and colorectal cancer risk. Main characteristics of cohort studies identified in the CUP SLR

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors
Roswall, 2010 COL40797 Denmark	DCH, Prospective Cohort, Age: 50-64 years, M/W	465 56 332 10.6 years	Cancer registry	FFQ	Incidence, colon cancer	≥10.1 vs ≤0 mg/day	1.06 (0.73-1.56) Ptrend:0.15	Age, alcohol intake, beta carotene, BMI, educational level, folate intake, hormone use, physical activity, processed meat, red meat intake, smoking status, smoking status, vitamin c, vitamin e supplement
						per 10 mg/day	1.01 (1.00-1.03)	+Vitamin e intake
Hansen, 2009 COL40855 Denmark	DCH, Case Cohort, Age: 50-64 years	73/ 57 053	Cancer registry	FFQ	Incidence, colorectal cancer, gpx1 pro198leu ct	per 10 mg/day	0.96 (0.89-1.03)	Alcohol intake, BMI, fibre, fruits and vegetables consumption, HRT use, smoking, pack-years
		72/			Gpx1 pro198leu cc	per 10 mg/day	0.99 (0.94-1.04)	
		22/			Gpx1 pro198leu tt	per 10 mg/day	1.26 (0.98-1.62)	
Iso, 2007 COL40707	JACC, Prospective	209/ 105 500	Municipal resident	FFQ	Mortality, colon cancer, men	use vs no use	1.76 (0.98-3.17)	Age, centre location

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors
Japan	Cohort, Age: 40-79 years, M/W	15 years	registration records, death certificates		Women	use vs no use	0.86 (0.46-1.59)	
		158/			Mortality, rectal cancer, men	use vs no use	0.61 (0.19-1.92)	
		84/			Women	use vs no use	1.36 (0.62-3.00)	
Wu, 2002 COL00905 USA	NHS, Prospective Cohort, Age: 30-55 years, W, nurses	626/ 87 998 16 years	Self-reported, hospital records and National Death Index	Semi-quantitative FFQ	Incidence, colon cancer	vitamin E suppl and multivitamin vs never users	0.88 (0.66-1.16)	Alcohol consumption, aspirin use, BMI, family history of colorectal cancer, menopausal status, pack-years of smoking, physical activity, postmenopausal hormone use, red meat intake
						≥99 vs ≤0 iu/day	0.87 (0.68-1.11) Ptrend:37	
						≥600 vs ≤0 iu/day	0.78 (0.43-1.42) Ptrend:0.29	
	HPFS, Prospective Cohort, Age: 40-75 years, M, Health professionals	370/ 47 344 10 years		Semi-quantitative FFQ	Incidence, colon cancer	vitamin E suppl and multivitamin vs never users	0.82 (0.60–1.11)	
		355/				≥99 vs ≤0 iu/day	0.77 (0.57-1.02) Ptrend:0.06	
						≥600 vs ≤0 iu/day	0.70 (0.38-1.29) Ptrend:0.06	
Jacobs, 2001 COL00296 USA, Puerto Rico	CPS II, Prospective Cohort, Age: 30- years, M/W	4 336/ 711 891 14 years	Self-reported and National Death Index	Questionnaire	Mortality, colorectal cancer,	≥10 vs ≤0 year	1.08 (0.85-1.38)	Age, sex, aspirin use, BMI, BMI x sex, educational level, high-fiber grain food consumption,
		2 430/			Men	≥10 vs ≤0 year	1.13 (0.82-1.57)	
		1 906/			Women	≥10 vs ≤0 year	1.05 (0.73-1.49)	

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors
								HRT use, vegetable consumption, vitamin supplement uses
		264/			Mortality, colon cancer,	≥10 vs ≤0 year	1.02 (0.79-1.31)	
		37/			Mortality, rectal cancer,	≥10 vs ≤0 year	1.78 (0.94-3.35)	
Sellers, 1998 COL01974 USA	IWHS, Prospective Cohort, Age: 55-69 years, W, Postmenopausal	180/ 35 216 10 years	SEER registry	Semi-quantitative FFQ	Incidence, colon cancer, no family history of crc	≥31 vs ≤0 mg/day	0.60 (0.40-0.90) Ptrend:0.03	Age, history of polyps, total energy intake
		61/			Family history of crc	≥31 vs ≤0 mg/day	0.80 (0.40-1.60) Ptrend:0.5	
Bostick, 1993 COL00483 USA	IWHS, Prospective Cohort, Age: 55-69 years, W	212/ 35 216 167 447 person-years	SEER	Semi-quantitative FFQ	Incidence, colon cancer,	≥31 vs ≤0 iu/day	0.44 (0.28-0.71) Ptrend:0.0002	Age
						≥31 vs ≤0 iu/day	0.50 (0.28-0.87) Ptrend:0.01	Age, calories intake, height, low-fat meat intake, parity, vitamin a supplement intake
Shibata, 1992 COL00740 USA	Leisure World Cohort, Prospective Cohort, M/W, retirement community, upper-middle social class	105/ 11 580 70 159 person-years	Hospital records and National Death Index	FFQ	Incidence, colon cancer, women	yes vs no	0.76 (0.52-1.12)	Age, smoking habits
		97/			Men	yes vs no	1.01 (0.69-1.51)	

Figure 431 RR (95% CI) of colon cancer for the highest compared with the lowest level of supplemental vitamin E



5.5.13 Multivitamin supplement

Randomised Controlled Trials

One RCT (Gaziano, 2012) was identified during the CUP. The Physician's Health Study II was a randomised, double-blind, placebo-controlled, 2 x 2 x 2 x 2 factorial trial of daily multivitamin supplementation, vitamin E (400-IU synthetic -tocopherol), vitamin C (500 mg synthetic ascorbic acid) and beta carotene (50-mg Lurotin) including 14 641 male physicians in the United States of 50 year of age or older. The trial investigated benefits and risk of supplementation on cancer, cardiovascular disease, eye disease, and cognitive function. Treatment started in 2001 and the multivitamin component continued until 2011. . Lung cancer mortality was not the main outcome. Men taking multivitamin did not have a reduction on colorectal cancer risk in 2011 (HR= 0.95; 95% CI= 0.60-1.48 comparing active treatment -37 cases- with placebo - 39 cases).

Cohort studies

Summary

Main results:
Eleven studies on colorectal cancer incidence and multivitamin use were identified. There were three studies on colon and rectal cancer and two studies on cancer mortality which were excluded. Only highest compared to lowest analysis was conducted. No analysis was conducted in 2010 SLR.

Colorectal cancer:
Eleven studies (8072 cases) were included in the highest compared to lowest meta-analysis of multivitamin supplement and colorectal cancer. A borderline significant association with high heterogeneity was observed.

Pooling Project of cohort studies
The Pooling Project of Prospective Studies of Diet and Cancer had examined the association between multivitamin use and risk of colon cancer (Park, 2010). Results from a total of 13 cohort studies, 676141 men and women and 5454 colon cancer cases were analysed (follow up 7-20 years). Study-specific food frequency questionnaires were used to assess the use of multivitamins. For the association between use of multivitamins and risk of colon cancer, an inverse significant association risk was observed when comparing users vs non users (pooled RR = 0.88, 95% CI = 0.81-0.96). The authors argue that multivitamin users may be more health conscious and have a healthier lifestyle than nonusers, which may confound the association observed between multivitamin use and risk of colon cancer therefore they adjusted for several lifestyle and other dietary factors and observed no substantial confounding by these factors. However, most studies did not provide information on

screening practices and non-steroid anti-inflammatory drug use which may confound the association.

Meta-analysis of cohort studies

A meta-analysis of 7 cohort studies (Heine-Broring, 2015) observed a statistically significant inverse association between use of multivitamin supplements and colorectal cancer RR=0.92, 95% CI= 0.87-0.97; use vs no use). This analysis includes 5 out of 13 cohorts from the Pooling Project while three cohorts of the analysis were not included in the Pooling Project. A summary estimate of the Pooling Project and the three cohorts combined also showed a statistically significant decreased risk for colorectal cancer in "use vs no use" meta-analysis of multivitamin supplements (RR=0.92; 95% CI= 0.86-0.98). No heterogeneity was present (I^2=0%, p=0.43).

Table 238 Multivitamin supplement and colorectal cancer risk. Number of studies in the CUP SLR

	Number
Studies identified	11 (12 publications)
Studies included in forest plot of highest compared with lowest exposure	11
Studies included in dose-response meta-analysis	NA
Studies included in non-linear dose-response meta-analysis	NA

Note: Include cohort, nested case-control and case-cohort designs

Table 239Multivitamin supplement and colorectal cancer risk. Summary of the dose-response meta-analysis in the 2010 SLR and 2015 SLR.

	2010 SLR	2015 SLR
Increment unit used		Highest vs Lowest
Studies (n)		11
Cases (total number)		8072
RR (95%CI)		0.88(0.76-0.98)
Heterogeneity (I^2, p-value)		46.7%, 0.05

Table 240 Multivitamin use and colorectal cancer risk. Results of meta-analyses and pooled analyses of prospective studies published after the 2005 SLR.

Author, Year	Number of cohort studies	Total number of cases	Studies country, area	Outcome	Comparison	RR (95%CI)	P trend	Heterogeneity (I^2, p value)
Pooled analysis								
Park, 2010	13 ATBC CPS II HPFS NLCS NYSC BCDDP CNBSS IWHS NLCS NYUWHS NHS ORDET SMC WHS	5454 44 467+349 456 393 335+223 349 431 799 353 96 162+429 43 485 40	North America and Europe	Colon cancer incidence	Users vs non users	0.88(0.81-0.96)		0.17
Meta-analysis								
Heine-Broring,2015	7	8737	North America and Europe	Colorectal and colon cancer incidence	Users vs non users	0.92(0.87-0.97)		4.9%, 0.39

	16	14191		Including pooling project		0.92(0.86-0.98)		0%, 0.43

Table 241 Multivitamin supplements and colorectal cancer risk. Main characteristics of studies included in the CUP SLR dose-response meta-analysis

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors
Hutchinson, 2014 COL41052 UK	UKWCS, Prospective Cohort, Age: 33-74 years, W	362/ 32 665 15 years	National statistics office	Questionnaire Vitamins, minerals, fish oils or other food supplements (14% of the 8915 women who were currently taking supplements at the second survey, were taking calcium supplements on a daily basis)	Incidence, colorectal cancer	users vs non users	1.13 (0.87-1.46)	Age, alcohol, BMI, educational level, exercise, smoking
Park, 2011 COL40853 USA	MEC, Prospective Cohort, Age: 45-75 years, M/W, Japanese, Caucasian, or Hawaiian	1 494/ 182 099	Surveillance registry/end results cancer registry	Questionnaire Multivitamins: with or without minerals, at least weekly Single supplement use: one or more of vitamin A, vitamin C, vitamin E, b-carotene, calcium, selenium, or iron at least once a week during the past year.	Incidence colorectal cancer, men	use vs no use	1.08 (0.66-1.75)	Age at baseline, BMI, educational level, energy from fat, ethnicity, family history of colorectal cancer, fruit intake, HRT use, menopausal status, physical activity, pre-existing disease, smoking status, single supplement use, vegetable intake, yogurt consumption
		1 292/			Women	use vs no use	0.71 (0.43-1.18)	
Lee, 2011 USA	NHS+HPFS	2299/ 87891men and 47290 women	Self-reported and medical records	FFQ Multivitamins (no details)	Incidence, colorectal cancer	≥20 years vs never	0.77(0.64-0.94)	Age, calendar year, pack-years of smoking before age 30 y, physical activity, aspirin dose,

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors
								height, BMI, family history of colorectal cancer in parents and siblings, menopausal status and hormone therapy use, history of endoscopy, and intakes of red meat, alcohol, calcium from foods, and total energy.
Yang, 2011 COL40876 Sweden	WLHS, Prospective Cohort, W	133/ 49 259 15 years	Cancer registry	Semi-quantitative FFQ	Incidence, colorectal cancer	yes vs no	1.05 (0.64-1.71)	Age, alcohol, BMI, educational level, physical activity, smoking
Neuhouser, 2009 COL40813 USA	WHI, Prospective Cohort, Age: 50-79 years, W, Postmenopausal	1 590/ 161 808 7.95 years	Self-report verified by medical record	Questionnaire, women brought supplement bottles to clinic *multivitamins (alone):*=>10 vitamins and no minerals, nutrient levels were at least 100% of US RDA *multivitamins with minerals:* 20 to 30 vitamins and minerals and nutrient levels <= 100% US RDA *Stress supplement*	Incidence, colorectal cancer	yes vs no	Any multivitamin (vitamins or vitaminerals or stress vitamins) (n yes= 635) 0.99 (0.88-1.11) Multivitamin (n yes=60) 1.05 (0.79-1.41) Multivitamins with mineral (n yes=60) 0.98 (0.86-1.11)	Age at examination, blood pressure, cholesterol plasma, energy from fat, estrogen replacement therapy, family history of cancer, family history of obesity, fruits and vegetables consumption, randomization group, study center, unopposed estrogen use, supplements of vitamin c, vitamin e supplement, calcium as single supplement

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors
				higher doses (often>200% of US RDA) of several B vitamins and often large doses of vitamin C or selected minerals, such as selenium or zinc. *Supplement mixtures :* < 10 components, such as B complex or antioxidant mixtures, were not considered multivitamins			Stress supplements (nyes=30) 0.89 (0.57-1.37)	(including antacids)
McCarl, 2006 COL40633 USA	IWHS, Prospective Cohort, Age: 55-69 years, W	936/ 35 197 15 years	SEER registry	FFQ Multivitamins (no details)	Incidence, colorectal cancer	yes vs no	0.82 (0.71-0.94)	Age
Zhang, 2006 COL40742 USA	WHS, Prospective Cohort, Age: 45- years, W, Health professionals	220/ 37 916 10.1 years	Self-report, death report, national death Index, medical records reviewed by physicians	FFQ Multivitamins (no details)	Incidence, colorectal cancer	current use vs never use	1.07 (0.72-1.61)	Age, alcohol abuse, aspirin use, BMI, family history of colorectal cancer In first degree relatives, folate intake, history of polyps, menopausal status, physical activity,

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors
								postmenopausal hormone use, randomized treatment assignment, red meat intake, smoking status, total energy intake, vitamin b6 intake
Jacobs, 2003 COL00313 USA	CPS II, Prospective Cohort, Age: 30- years, M/W, subgroup of CPS-II cohort	797/ 145 260 5 years	Self-reported and National Death Index	FFQ Multivitamins (no details)	Incidence, colorectal cancer,	≥16 vs ≤0 times/month	0.71 (0.57-0.89)	Age, sex, BMI, calcium supplement, educational level, fibre, physical activity, saturated fat, vitamin c supplement
		564/			Incidence, colon cancer,	≥16 vs ≤0 times/month	0.72 (0.55-0.94)	
		232/			Incidence, rectal cancer,	≥16 vs ≤0 times/month	0.69 (0.46-1.04)	
Sanjoaquin, 2004 COL01182 UK	OVS, Prospective Cohort, Age: 18-89 years, M/W	91/ 10 998 17 years	Cancer registry	FFQ Vitamin supplements (no details)	Incidence, colorectal cancer,	used vs not used	1.00 (0.63-1.59) Ptrend:0.993	Age, sex, alcohol consumption, smoking habits
Kato, 1999 COL00436 USA	New York University Women's Health Study, Nested Case Control, Age: 62 years, W	150/ 81	Follow-up questionnaire	Semi-quantitative FFQ Any vitamin/mineral (no details)	Incidence, colorectal cancer,	any vs none	0.67 (0.42-1.06)	Age, beer consumption, date of enrolment, date of subsequent blood, family history of specific cancer, menopausal status, occult blood testing,

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors
								physical activity

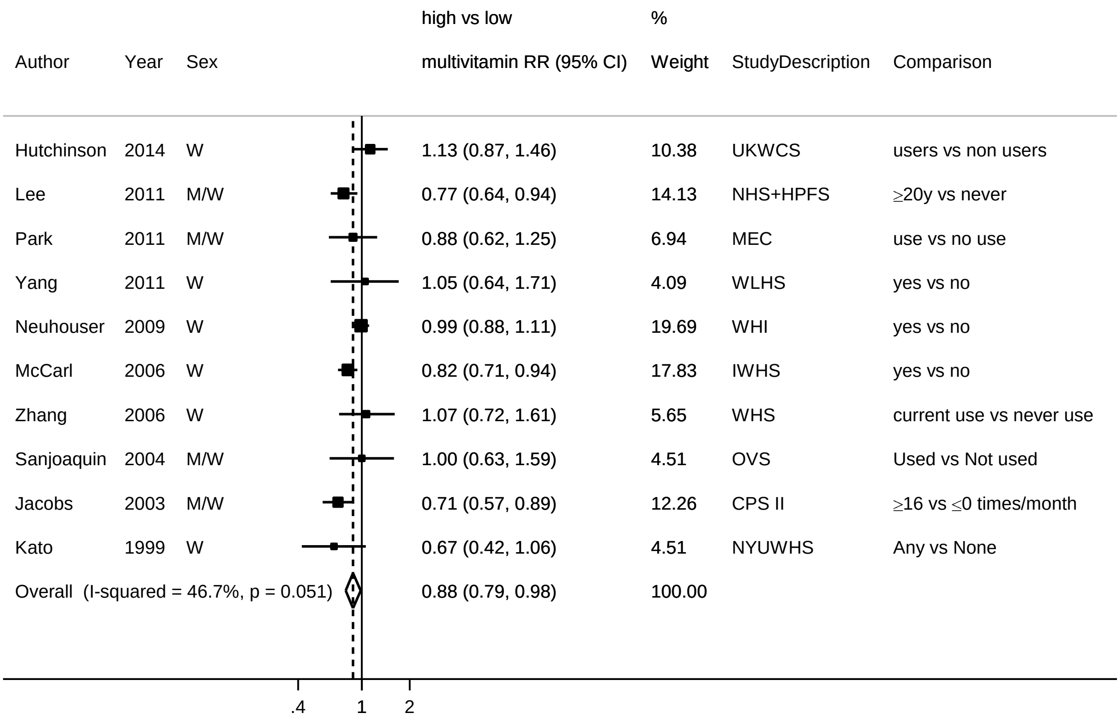
Table 242 Multivitamin supplements and colorectal cancer risk. Main characteristics of studies excluded from the CUP SLR dose-response meta-analysis

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Reasons for exclusion
Iso, 2007 COL40707 Japan	JACC, Prospective Cohort, Age: 40-79 years, M/W	214/ 105 500 15 years	Municipal resident registration records, death certificates	FFQ Multivitamin	Mortality, colon cancer, men	use vs no use	1.52 (1.03-2.27)	Age, centre location	Outcome is mortality
		179/			Women	use vs no use	1.42 (0.92-2.19)		
		159/			Mortality, rectal cancer, men	use vs no use	1.09 (0.64-1.86)		
		84/			Women	use vs no use	0.96 (0.41-2.24)		
Feskanich, 2004 COL01680 USA	NHS, Nested Case Control, Age: 46-78 years, W	193/ 383 controls 11 years	Medical records and writing or by telephone	FFQ	Incidence, colorectal cancer,	user vs non-user	39% and 36% users in cases and non-cases respectively	Month of blood draw, year of birth	Superseded by Fuchs, 2002 COL00415
Wu, 2002 COL00905 USA	HPFS, Prospective Cohort, Age: 40-75 years, M, Health professionals	328/ 47 344 10 years	Hospital and pathology reports National Death Index	Semi-quantitative FFQ Multivitamins and individual vitamins	Incidence, colon cancer, no past users	Vitamin E supplement and multivitamin users vs never users Multivitamin only users vs never users	0.82 (0.60-1.11) 0.97 (0.75–1.24)	Age, family history of colorectal cancer, BMI, physical activity , pack-years of smoking before age 30, aspirin use , red meat intake, alcohol consumption	Not enough studies to conduct analysis on colon cancer only

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Reasons for exclusion
Fuchs, 2002 COL00415 USA	NHS, Prospective Cohort, Age: 30-55 years, W, nurses	428/ 88 758 1 375 165 person-years	Hospital and pathology reports National Death Index	FFQ Multivitamin use (no details)	Incidence, colon cancer, no family history of crc	yes vs no	0.89 (0.72-1.10)	Age, alcohol consumption, aspirin use, beef, pork, or lamb, BMI, energy-adjusted levels of methionine, physical activity, screening endoscopy, smoking habits	Not enough studies to conduct analysis on colon cancer only
Wu, 2002 COL00905 USA	NHS, Prospective Cohort, Age: 30-55 years, W, nurses	600/ 87 998 16 years	Hospital and pathology reports National Death Index	FFQ Multivitamins and individual vitamins	Incidence, colon cancer, no past users	Vitamin E supplement and multivitamin users vs never users Multivitamin only users vs never users	0.88 (0.66-1.16) 0.83 (0.68–1.01)	Age, alcohol consumption, aspirin use, BMI, family history of colorectal cancer, menopausal status, pack-years of smoking, physical activity, postmenopausal hormone use, red meat intake	Not enough studies to conduct analysis on colon cancer only
Jacobs, 2001 COL00295 USA, Puerto	CPS II, Prospective Cohort,	5 093/ 806 379 16 years	Self-reported and National Death Index	Questionnaire Multivitamin use	Mortality, colon cancer,	Daily users vs nonusers	0.92 (0.86-1.00)	Age, sex, aspirin use, BMI,	Outcome is mortality

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Reasons for exclusion
Rico	Age: 30- years, M/W	2 740/			Men	Daily users vs nonusers	0.91 (0.82-1.00)	educational level, high-fiber grain food consumption, HRT use, vegetable consumption, vitamin c supplement use, vitamin e supplement use	
		2 353/			Women	users vs nonusers	0.93 (0.84-1.00) Number:53151		
Giovannucci, 1998 COL00113 USA	NHS, Prospective Cohort, Age: 30-55 years, W, nurses	655/ 88 756 1 215 392 person-years	Hospital and pathology reports National Death Index	Semi-quantitative FFQ Multivitamins containing folic acid	Incidence, colorectal cancer,	≥15 vs ≤15 year	0.53 (0.35-0.80)	Age, alcohol consumption, aspirin use, beef, pork, or lamb as main dish intake, BMI, family history of specific cancer, fibre, methionine, physical activity, smoking habits	Superseded by Lee, 2011 USA
		224/			Incidence, distal colon cancer,	≥15 vs ≤15 year	0.37 (0.15-0.90)		
		218/			Incidence, proximal colon cancer,	≥15 vs ≤15 year	0.16 (0.06-0.52)		
		143/			Incidence, rectal cancer,	≥15 vs ≤15 year	1.27 (0.67-2.46)		

Figure 432 RR (95% CI) of colorectal cancer for the highest compared with the lowest level of multivitamin supplement use



5.5.3 Dietary folate

Cohort studies

Main results

Colorectal cancer:

Twelve studies (8284 cases) were included in the dose-response meta-analysis of dietary folate and colorectal cancer. with a non-significant inverse association with low heterogeneity was observed. In the stratified analysis by sex the heterogeneity persisted in the subgroup of women, but not in men. In the stratified analysis by geographic location, the moderate heterogeneity persisted in the subgroup of three European studies, no heterogeneity was observed for Asian (3 studies) or American studies (6 studies).

There was no evidence of publication bias (p=0.32). There was no evidence of non-linear association (p=0.60).

The overall association remained similar in influence analysis. The summary RRs ranged from 0.98(95% CI=0.96-1.00) when the Australian study (Bassett, 2013) was omitted to 0.99(95% CI=0.96-1.01) when the WHI (Zschäbitz, 2013) was omitted.

Colon cancer:

Seventeen studies (7038) were included in the dose-response meta-analysis of dietary folate and colon cancer. The the Pooling Project of Prospective Studies of Diet and Cancer (Kim, 2010) included thirteen of the studies identified in the CUP. Therefore it was combined, in the dose-response analysis and highest compared to lowest analysis, with the four other studies identified. The dose-response figure 418 shows the results of each cohort identified in the CUP only because the Pooling Project (Kim, 2010) did not report the results of each cohort in the consortium. No significant association was observed. There was moderate heterogeneity, mainly due to the results of two small studies. Within the Pooling project, there was no evidence of heterogeneity across study results (test for heterogeneity = 0.85; Kim, 2010). In the CUP, the results were similar in stratified analysis by sex or geographic location. The number of studies in each strata was low. There was no evidence of publication bias (p=0.75). The overall association remained not statistically significant in influence analysis. The summary RRs ranged from 0.96(95% CI=0.92-1.02) when Kim, 2010 was omitted to 0.98(95% CI=0.96-1.01) when Roswall, 2010 was omitted.

Among the North American studies in the Pooling Project, the authors did not observe attenuation of the effect estimates for dietary folate in analyses of the pre- fortification period (data not shown; Kim, 2010).

Also, in the Pooling project, the nonparametric regression analyses did not detect nonlinearity in the association between dietary folate intake and colon cancer risk (p-value, test for nonlinearity<0.05). The Australian study (Bassett, 2013) reported no departure from linearity for colorectal cancer (p>0.1) and the Danish study (Roswall, 2010), reported no deviation from linearity for all the micronutrients investigated in the study. Since most of the cohort studies identified in the Cup are in the Pooling project, nonlinearity was not further explored in the CUP.

Rectal cancer:
Seven studies (1786cases) were included in the dose-response meta-analysis of dietary folate and rectal cancer. No association with no heterogeneity was observed. The results persisted in men and stratified analysis geographic location and showed a significant inverse association for the four studies in women. There was no evidence of non-linear association (p=0.66).

Study quality:
Most studies used questionnaires self-reported FFQ to assess diet. The NHANES (Su, 2001) assessed the folate intake by 24h-recall and reported a 43% risk reduction (RR = 0.57, 95% CI=0.34–0.97) for colon cancer for the highest vs. lowest quartile of dietary folate intake during 20 years of follow-up among 10,011 participants. Means of dietary folate and total energy intake in the case-control study nested in the Chinese cohort was higher than in other studies (608 mcg/day and 4177 kcal/day, respectively)(Jiang, 2005) . Two North-American studies indicated that folate fortification was included in the estimates of dietary folate (Zschabitz, 2013, Stevens, 2011).
All studies were multiple adjusted for different confounders. Cancer outcome was confirmed using cancer registry and medical records in most studies.

Pooling project of cohort studies:
The the Pooling Project of Prospective Studies of Diet and Cancer (Kim, 2010) included thirteen studies (BCDDP, CPS II, HPFS IWHS, NYS, NYUWHS, NHS, WHS, NLCS, ORDET, SMC, CNBSS, ATBC) on dietary folate and colon cancer and reported a RR per 100 mcg/day 0.98(95%CI=0.95-1.01, ph=0.31).
A total of 5,720 individuals were diagnosed with incident colon cancers over follow-up times ranging from up to 7–20 years among the 229,466 men and 495,668 women in the thirteen cohort studies. Median energy adjusted dietary folate intake ranged from 184 to 409 mcg/ day across studies. The characteristics of the studies included in the Pooling Project are in the inclusion table below.

Meta-analysis
A meta-analysis of ten cohort studies reported a summary risk estimate of colorectal cancer for the comparison of the high versus low ‘‘quantile’’ of folate intake of 0.92 (CI 95% 0.81–1.05), 10 cohort studies; I^2 = 42% with no significant heterogeneity (Kennedy , 2011).

Table 243 Dietary folate and colorectal cancer risk. Number of studies in the CUP SLR

	Number
Studies identified	14 (15publications)
Studies included in forest plot of highest compared with lowest exposure	11
Studies included in dose-response meta-analysis	10

Studies included in non-linear dose-response meta-analysis	10

Note: Include cohort, nested case-control and case-cohort designs

Table 244 Dietary folate and colon cancer risk. Number of studies in the CUP SLR

	Number
Studies identified	17 (17 publications)
Studies included in forest plot of highest compared with lowest exposure	17
Studies included in dose-response meta-analysis	17 (13PP+4)
Studies included in non-linear dose-response meta-analysis	NA

Note: Include cohort, nested case-control and case-cohort designs

Table 245 Dietary folate and rectal cancer risk. Number of studies in the CUP SLR

	Number
Studies identified	7 (8 publications)
Studies included in forest plot of highest compared with lowest exposure	7
Studies included in dose-response meta-analysis	6
Studies included in non-linear dose-response meta-analysis	6

Note: Include cohort, nested case-control and case-cohort designs

Table 246 Dietary folate and colorectal cancer risk. Summary of the dose-response meta-analysis in the 2010 SLR and 2015 SLR.

	2010 SLR	**2015 SLR**
Increment unit used	100mcg/day	100mcg/day
Studies (n)	7	10
Cases (total number)	5401	6986
RR (95%CI)	0.99 (0.93-1.05)	0.99(0.96-1.02)
Heterogeneity (I^2, p-value)	26%, 0.23	31.4%, 0.16

Stratified analysis by sex			
Men	**2010 SLR**	**2015 SLR**	
Studies (n)	2	3	
RR (95%CI)	1.00 (0.89-1.13)	0.99(0.95-1.04)	
Heterogeneity (I^2, p-value)	27%, 0.24	0%, 0.44	
Women			
Studies (n)	7	9	
RR (95%CI)	0.99 (0.91-1.08)	0.98(0.93-1.02)	
Heterogeneity (I^2, p-value)	45%, 0.09	36.9%, 0.12	
Stratified analysis by geographic location			
(no analysis in 2005 SLR or 2010 SLR)			
2015 SLR	**Asia**	**Europe**	**North America**

Studies (n)	3	2	5
RR (95%CI)	1.03(0.99-1.07)	0.89(0.64-1.23)	0.96(0.94-0.99)
Heterogeneity (I^2, p-value)	0%, 0.61	73.1%, 0.05	0%, 0.92

Table 247 Dietary folate and colon cancer risk. Summary of the dose-response meta-analysis in the 2010 SLR and 2015 SLR.

	2010 SLR	2015 SLR
Increment unit used	100mcg/day	100mcg/day
Studies (n)	6	17
Cases (total number)	2767	7038
RR (95%CI)	0.90 (0.80-1.01)	0.97(0.93-1.02)
Heterogeneity (I^2, p-value)	60%, 0.03	50.9%, 0.09

Stratified analysis by sex			
Men	**2010 SLR**	**2015 SLR**	
Studies (n)	2	3	
RR (95%CI)	0.76 (0.57-1.02)	0.85 (0.70-1.05)	
Heterogeneity (I^2, p-value)	59%, 0.12	71.6%, 0.03	
Women			
Studies (n)	5	6	
RR (95%CI)	0.90 (0.73-1.11)	0.93(0.81-1.07)	
Heterogeneity (I^2, p-value)	65%, 0.02	58.6%, 0.03	
Stratified analysis by geographic location			
(no analysis in 2005 or 2010 SLR)			
2015 SLR	**Asia**	**Europe**	**North America**
Studies (n)	2	3	4
RR (95%CI)	1.00(0.96-1.05)	0.84(0.66-1.06)	0.92(0.83-1.01)
Heterogeneity (I^2, p-value)	0%, 0.82	73%, 0.03	35.7%, 0.20

Table 248 Dietary folate and rectal cancer risk. Summary of the dose-response meta-analysis in the 2010 SLR and 2015 SLR.

	2010 SLR	2015 SLR
Increment unit used	100mcg/day	100mcg/day
Studies (n)	4	7
Cases (total number)	958	1786
RR (95%CI)	1.02(0.87-1.19)	1.00(0.95-1.06)
Heterogeneity (I^2, p-value)	0%, 0.66	0%, 0.51

Stratified analysis by sex.

(no analysis in 2005 or 2010 SLR)			
2015 SLR	**Women**	**Men**	
Studies (n)	4	1	
RR (95%CI)	0.88(0.79-0.97)	1.04(0.92-1.17)	
Heterogeneity (I^2, p-value)	0%, 0.68		
Stratified analysis by geographic location			
(no analysis in 2005 or 2010 SLR)			
2015 SLR	**Asia**	**Europe**	**North America**
Studies (n)	2	3	2
RR (95%CI)	1.06(0.98-1.14)	1.00(0.88-1.18)	0.94(0.86-1.02)
Heterogeneity (I^2, p-value)	0%, 0.62	0%, 0.94	0%, 0.60

Table 249 Dietary folate and colorectal cancer risk. Main characteristics of studies included in the CUP SLR dose-response meta-analysis

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Missing data derived for analyses
Bassett, 2013 COL40980 Australia	MCCS, Prospective Cohort, Age: 27-80 years, M/W	910/ 37 109 15 years	Cancer registry and death registry	121 items FFQ	Incidence, colorectal cancer	445 vs 212 mcg/day	1.08 (0.86-1.35)	Sex, alcohol, cereal fibre, country of birth, educational level, family history of cancer, physical activity, smoking. Age in time axis	
		581/			Incidence, colon cancer	445 vs 212 mcg/day	0.98 (0.74-1.31)		
		326/			Incidence, rectal cancer	445 vs 212 mcg/day	1.26 (0.87-1.83)		
Zschäbitz, 2013 COL40934 USA	Women's Health Initiative - Observational study, Prospective Cohort, W, Postmenopausal	808/ 88 045 11 years	Self-report verified by medical record	122 items FFQ Natural folate and folic acid from fortification	Incidence, colorectal cancer	≥343 vs ≤189	0.83 (0.68-1.01)	Age, BMI, history of colonoscopy, ethnicity, hormone use, physical activity, smoking	Distribution of person-years by exposure category. Mid-points of exposure categories.
Stevens, 2011 COL40887 USA	CPS II-Nutrition Cohort, Prospective Cohort, Age: 50-74 years, M/W	1 023/ 99 523 15 years	Cancer registry and medical records	152 items modified Willett FFQ	Incidence, colorectal cancer	>446 vs <197 mcg/day	0.81 (0.66–0.99)	Age, sex, alcohol, BMI, educational level, endoscopy, energy intake, family history of colorectal cancer, HRT use, low-fat dairy products, non-steriodal	Mid-points of exposure categories.
		219			Incidence, rectal cancer		0.84 (0.54–1.30)		
		799			Incidence, colon cancer		0.80 (0.63–1.01)		Superseded by Pooling Project Kim, 2010 for colon cancer dose response meta-analysis.

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Missing data derived for analyses
								anti-inflammatory drug use, race, red meat, smoking	
Kim, 2010 Pooling Project	BCDDP CPS II HPFS IWHS NYS NYUWHS NHS WHS NLCS ORDET SMC CNBSS ATBC	349 816 456 799 558 96 591 163 746 43 485 349 187	Follow-up questionnaires and medical records	FFQ	Incidence, colon cancer	Highest vs lowest	0.92 (0.84-1.00)	Education, BMI, height, smoking, energy intake, alcohol, red meat, milk intake, multivitamin, history of colorectal cancer, NSAID, physical activity, HRT, age	Used continuous results in dose-response meta-analysis of colon cancer.
						Per 100mcg/day	0.98(0.95-1.01)		
Roswall, 2010 COL40797 Denmark	DCH, Prospective Cohort, Age: 50-64 years, M/W	465 56 332 10.6 years	Cancer registry	192-items FFQ	Incidence, colon cancer	≥386.95 vs 0-254.86 mcg/day	0.83 (0.57-1.21)	Age, BMI, smoking status, educational level, hormone use, physical activity, and intakes of alcohol, red meat, processed meat, vitamin C, vitamin E beta carotene,	
						per 100 mcg/day	0.85 (0.73-0.99)		
		283/			Incidence, rectal cancer	≥398.43 vs 0-270.11 mcg/day	1.25 (0.78-2.00)		
						per 100 mcg/day	0.95 (0.83-1.09)		

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Missing data derived for analyses
								folate supplement	
Shrubsole, 2009 COL40773 China	SWHS, Prospective Cohort, Age: 40-70 years, W	394/ 72 861	Cancer registry/death certificates/questionnaires	FFQ	Incidence, colorectal cancer	419 vs 213 mcg/day	1.10 (0.80-1.70)	Age, educational level, household income, BMI, smoking, HRT use, drinking status, physical activity, menopausal status, family history colorectal cancer, NSAID use, B vitamin supplement, history of colorectal polyps, diabetes, intakes of energy, fruits, vegetables, red meats, and calcium	Distribution of person-years by exposure category.
Kabat, 2008 COL40636 Canada	CNBSS, Prospective Cohort, Age: 40-59 years, W, Screening Program	617/ 49 654 16.4 years	Record linkages to cancer database and to the national mortality database	86 items FFQ	Incidence, colorectal cancer	≥374 vs ≤236 mcg/day	0.89 (0.68-1.17)	Age, alcohol, BMI, calories intake, educational level, HRT use, menopausal status, oral contraceptive	Distribution of person-years by exposure category. Mid-points of exposure categories.

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Missing data derived for analyses
								use, pack-years of smoking	
de Vogel S, 2008 COL40646 Netherlands	NLCS, Prospective Cohort, Age: 55-69 years, M/W	1 389/ 4 774 13.3 years	Cancer registry	Semi-quantitative FFQ	Incidence, Colorectal cancer, men	297.2 vs 160.8 mcg/day	0.87 (0.65-1.15)	Age, alcohol intake, BMI, smoking status, family history of colorectal cancer, and daily intakes of energy, calcium, fat, fibre, iron, meat, methionine, riboflavin, vitamin b6 intake	Superseded by Pooling Project Kim, 2010 for colon cancer dose response meta-analysis.
		960/			Colorectal, Women	267.3 vs 139 mcg/day	1.25 (0.89-1.76)		
		467/			Distal colon cancer, men	297.2 vs 160.8 mcg/day	0.71 (0.46-1.08)		
		296/			Distal colon cancer, women	267.3 vs 139 mcg/day	1.34 (0.81-2.22)		
		386/			Proximal colon cancer, women	267.3 vs 139 mcg/day	1.24 (0.76-2.02)		
		382/			Proximal colon cancer, men	297.2 vs 160.8 mcg/day	0.97 (0.62-1.52)		
		360/			Rectal cancer, men	297.2 vs 160.8 mcg/day	1.01 (0.64-1.60)		
		176/			Rectal cancer, women	267.3 vs 139 mcg/day	1.06 (0.53-2.11)		
Ishihara, 2007 COL40641 Japan	JPHC, Prospective Cohort, M/W	335/ 81 184 5.8 years	Periodic Institutional reports from hospitals, cancer registries, death cert.	138 items FFQ	Incidence, colorectal cancer, men	Q 4 vs Q 1	1.20 (0.85-1.71)	Age, BMI, physical activity, smoking status, study area, alcohol consumption, intakes of calcium, meat,	Mid-points of exposure categories.
		191/			Women	Q 4 vs Q 1	1.33 (0.85-2.09)		

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Missing data derived for analyses
								vitamin D supplements	
Zhang, 2006 COL40742 USA	WHS, Prospective Cohort, Age: 45- years, W, Health professionals	220/ 37 916 10.1 years	Self-report, death report, national death Index, medical records reviewed by physicians	131-item FFQ	Incidence, colorectal cancer	≥385 vs ≤243 mcg/day	0.67 (0.43-1.03)	Age, alcohol consumption, aspirin use, BMI, family history of colorectal cancer in first degree relatives, history of polyps, menopausal status, physical activity, postmenopausal hormone use, randomized treatment assignment, red meat intake, smoking status, total energy intake	Distribution of person-years by exposure category. Mid-points of exposure categories.
Jiang, 2005 COL01846 China	China, Haining City of Zhejiang Province, Nested Case Control, Age: 40- years, M/W	73/ 343 controls 12 years	Cancer registry	FFQ	Incidence, rectal cancer	≥172.08 vs ≤115.63 mcg/1000 kcal/day	1.39 (0.56-3.50)	Age, sex, alcohol intake, methionine intake, smoking habits, zinc intake	Distribution of Non-cases. Mid-points of exposure categories. intakes in mcg/1000kcal/day converted to mcg/day using

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Missing data derived for analyses
									average energy intake per each quantile
		53/ 343 controls			Incidence, colon cancer	≥172.08 vs ≤115.63 mcg1000 kcal/day	0.91 (0.69-1.19)		
Larsson, 2005 COL01852 Sweden	SMC, Prospective Cohort, Age: 40-75 years, W	805/ 61 433 911 042 person-years	Cancer registry	Questionnaire	Incidence, colorectal cancer	≥212 vs 0-149 mcg/day	0.80 (0.60-1.06)	Age, beta carotene, BMI, calcium, cereal fibre, educational level, methionine, red meat intake, saturated fat, total energy, vitamin b6	Distribution of person-years by exposure category. Mid-points of exposure categories
		252/			Incidence, rectal cancer	≥212 vs 0-149 mcg/day	0.93 (0.55-1.56)		
		547/			Incidence, colon cancer	≥212 vs 0-149 mcg/day	0.61 (0.41-0.91)		Superseded by Pooling Project Kim, 2010 for colon cancer dose response meta-analysis
Flood, 2002 COL00411 USA	BCDDP, 1973, Prospective Cohort, Age: 40-93 years, W	485 45 264 8.5 years	Breast cancer screening centres	FFQ	Incidence, colorectal cancer,	≥272 vs ≤142 mcg/1000 kcal	0.86 (0.65-1.13)	Alcohol consumption, energy intake, methionine	
Terry, 2002 COL01158 Canada	CNBSS, Case Cohort, Age: 40-59 years,	198/ 56 837 10.4 years	Breast cancer screening centres	Quantitative FFQ	Incidence, colon cancer,	≥367 vs ≤233 mcg/day	0.60 (0.30-1.10)	Age, BMI, educational level, energy intake, physical	Superseded by Pooling Project Kim, 2010 for colon cancer

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Missing data derived for analyses
	W							activity, smoking habits, total fat intake	dose response meta-analysis
		97/			Incidence, rectal cancer,	≥367 vs ≤233 mcg/day	0.70 (0.30-1.80)		Distribution of person-years by exposure category.
Su, 2001 COL00547 USA	NHANES I, Prospective Cohort, Age: 25-74 years, M/W	219/ 10 011	Population registry	24h-Recall questionnaire	Incidence, colon cancer,	≥249 vs ≤103.3 mcg/day	0.57 (0.34-0.97)	Age, sex, alcohol consumption, educational level, ethnicity, intakes of energy, fat, vitamin B12, vitamin B6	Distribution of person-years by exposure category. Mid-points of exposure categories.
		120/			Women	≥249 vs ≤103.3 mcg/day	0.74 (0.36-1.51)		
		99/			Men	≥249 vs ≤103.3 mcg/day	0.40 (0.18-0.88)		
Giovannucci, 1998 COL00113 USA	NHS, Prospective Cohort, Age: 30-55 years, W, nurses	219/ 88 756 1 215 392 person-years	Hospital rectods and National Death Index	Semi-quantitative FFQ	Incidence, colon cancer, using supplements <15 years	≥300 vs ≤200 mcg/day	0.82 (0.56-1.20)	Age, alcohol consumption, aspirin use, beef, pork or lamb intake, BMI, family history of specific cancer, methionine, physical activity, smoking habits	Superseded by Pooling Project Kim, 2010 for colon cancer dose response meta-analysis.

Table 250 Dietary folate and colorectal cancer risk. Main characteristics of studies excluded from the CUP SLR dose-response meta-analysis

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Reasons for exclusion
Gay, 2012 COL40920 UK	EPIC-Norfolk, Prospective Cohort, Age: 45-79 years, M/W	185/ 25 636 11 years	Cancer registry	7-day dietary recalls	Incidence, colorectal cancer, gc:at mutations	per 1 sd units	0.92 (0.52-1.65)	Age, sex, smoking	Case-only study, only interaction results
					Apc promoter methylation ≥20%	per 1 sd units	0.55 (0.35-0.85)		
					Apc mutations	per 1 sd units	0.91 (0.65-1.27)		
Lee, 2011 USA	NHS+HPFS	2299/ 87891men and 47290 women	Self-reported and medical records	FFQ	Incidence, colorectal cancer	≥500 years vs <250 mcg/d	1.02 (0.84, 1.24)	Age, calendar year, pack-years of smoking before age 30 y, physical activity, aspirin dose, height, BMI, family history of colorectal cancer in parents and siblings, menopausal status and hormone therapy use, history of endoscopy, and intakes of red meat, alcohol,	Superseded by Pooling Project Kim, 2010

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Reasons for exclusion
								calcium from foods, and total energy.	
de Vogel S, 2011 COL40867 Netherlands	Netherlands Cohort Study on Diet and Cancer, 1986-1997, Nested Case Control, Age: 55-69 years, M/W	502/ 1 663	Cancer registry / database / pathology reports	FFQ	Incidence colorectal cancer, more than 3 variant alleles of folate metabolizing enzymes	255 vs 162 mcg/day	0.89 (0.51–1.54)	Age, sex, alcohol consumption, BMI, family history of colon cancer, methionine, smoking status, total energy intake, vitamin B2, vitamin B6	Superseded by Pooling Project Kim, 2010 for colon cancer dose response meta-analysis.
Wei, 2009 COL40777 USA	NHS, Prospective Cohort, Age: 30-54 years, W	701/ 83 767 24 years	Self- report verified by medical record	Semi-quantitative FFQ	Incidence, colon cancer	600 vs 150 mcg/day	0.84 (0.69-1.02)	Age, aspirin use, BMI, family history of colorectal cancer, height, pack-years of smoking, physical activity, postmenopausal hormone use, red or processed meat intake, year of endoscopy	Superseded by Pooling Project Kim, 2010 for colon cancer dose response meta-analysis.
Butler, 2008 COL40639 Singapore	SCHS, Prospective Cohort,	961/ 61 321 9.8 years	Cancer registry	FFQ	Incidence, colorectal cancer	Q 4 vs Q 1	0.86 (0.71-1.04)	Age, sex, alcohol intake, BMI, diabetes,	Used only in highest compared to

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Reasons for exclusion
	Age: 45-74 years, M/W							dialect group, educational level, energy intake, exposure assessment, family history of colorectal cancer, physical activity, smoking habits	lowest analysis
Schernhammer, 2008 COL40730 USA	NHS, Prospective Cohort, Age: 30-55 years, W	399/ 88 691 22 years	Self report verified by medical record	Semi-quantitative FFQ	Incidence, colon cancer	≥400 vs ≤199 mcg/day	0.80 (0.61-1.06)	Age, BMI, intakes of energy, alcohol beef, pork or lamb as a main dish, family history of colorectal cancer, history of polyps, multivitamin supplement use, physical activity, postmenopausal hormone use, previous endoscopic screening, smoking habits	Superseded by Schernhammer, 2011 COL40882 and the Pooling Project Kim, 2010 for colon cancer dose response meta-analysis.
de Vogel S, 2008	NLCS, Case Cohort,	367/ 4 717	Record linkage to cancer	FFQ	Incidence, colorectal	279.9 vs 163.2 mcg/day	0.97 (0.65-1.44)	Age, BMI, calcium intake,	Superseded by de Vogel S,

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Reasons for exclusion
COL40734 Netherlands	Age: 55-69 years, M/W	7.3	registry/histo- and cyto- pathology reports		cancer, men			energy intake, family history of colorectal cancer, fat intake, fibre, Iron intake, meat intake, smoking habits, vitamin c	2008 COL40646
		281/			Women	247.9 vs 142.4 mcg/day	0.92 (0.57-1.48)		
		73/			Women, mlh1 hypermethylatio n	247.9 vs 142.4 mcg/day	0.88 (0.33-2.32)		
		65/			Men, mlh1 hypermethylatio n	279.9 vs 163.2 mcg/day	0.88 (0.36-2.14)		
		52/			Women, braf mutation	247.9 vs 142.4 mcg/day	1.42 (0.51-3.95)		
		49/			Men, braf mutations	279.9 vs 163.2 mcg/day	3.04 (1.13-8.20)		
		38/			Men, msi mutations	279.9 vs 163.2 mcg/day	0.78 (0.23-2.67)		
		38/			Women, msi mutation	247.9 vs 142.4 mcg/day	0.72 (0.19-2.72)		
		32/			Women, no mlh1 protein	247.9 vs 142.4 mcg/day	1.22 (0.31-4.74)		
		24/			Men, no mlh1 protein	279.9 vs 163.2 mcg/day	1.00 (0.20-5.10)		
de Vogel S, 2006 COL40616 Netherlands	NLCS, Prospective Cohort, Age: 55-69 years, M/W	213/ 4 673 7.3 years	Record linkage with cancer registries	Semi-quantitative FFQ	Incidence, colon carcinoma, men	279.9 vs 162.7 mcg/day	0.96 (0.61-1.54)	Age, BMI, family history, fibre, intakes of energy, iron, methionine, riboflavin, vitamin B6,	Superseded by de Vogel S, 2008 COL40646
		186/			Women	248 vs 142.5 mcg/day	0.82 (0.45-1.49)		

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Reasons for exclusion
								vitamin C	
Brink, 2005 COL40743 Netherlands	NLCS, Case Cohort, Age: 55-69 years, M/W	231/ 3 048 7.3 years	Cancer registry	Semi-quantitative FFQ	Incidence, colon cancer, men	per 100 mcg/day	0.87 (0.66-1.14)	Age, alcohol consumption, BMI, family history of colorectal cancer, smoking habits, intakes of energy, fibre , iron meat, vitamin C	Superseded by de Vogel S, 2008 COL40646
		199/			Colon cancer, women	per 100 mcg/day	0.98 (0.62-1.56)		
		99/			Incidence, rectal cancer, men	per 100 mcg/day	0.58 (0.36-0.93)		
		51/			Incidence, rectal cancer, women	per 100 mcg/day	1.85 (1.13-3.02)		
Wark, 2005 COL01807	NLCS, Case Cohort, Age: 55-69 years, M/W	387/ 120 852 7.3 years	Cancer registry and database of pathology reports	Semi-quantitative FFQ	Incidence, colon cancer, hmlh1+ cases	≥225.6 vs 0-177.1 mcg/day	1.04 (0.78-1.39)	Age, sex, family history of specific cancer, total energy	Superseded by de Vogel S, 2008 COL40646
		54/			Hmlh1- cases	≥225.6 vs 0-177.1 mcg/day	0.92 (0.43-2.00)		
Fuchs, 2002 COL00415 USA	NHS, Prospective Cohort, Age: 30-55 years, W, nurses	368/ 88 758 1 375 165 person-years	Self-reported and National Death Index	FFQ	Incidence, colon cancer, no family history of crc	≥400 vs ≤200 mcg/day	0.98 (0.72-1.33)	Age, alcohol consumption, aspirin use, beef, pork, or lamb, BMI, energy-adjusted levels of methionine, physical activity, screening endoscopy, smoking habits	Superseded by the Pooling Project Kim, 2010 for colon cancer dose response meta-analysis.
		295/			No family history of crc	≥5 vs ≤0 year	1.12 (0.83-1.50)		
Konings, 2002	NLCS,	400/	Cancer registries	Semi-	Incidence, colon	per 50 mcg/day	0.88 (0.78-0.99)	Age, alcohol	Superseded by

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Reasons for exclusion
COL01271 Netherlands	Case Cohort, Age: 55-69 years, M/W	120 852 7.3 years		quantitative FFQ	cancer, men			consumption, family history of colorectal cancer, intakes of energy, dietary fibre, iron, vitamin C	de Vogel S, 2008 COL40646
						≥266 vs ≤168 mcg/day	0.73 (0.46-1.17)		
		360/			Colon cancer, women	≥243 vs ≤150 mcg/day	0.68 (0.39-1.20)		
						per 50 mcg/day	0.96 (0.81-1.13)		
		259/			Incidence, rectal cancer, men	≥266 vs ≤168 mcg/day	0.66 (0.35-1.21)		
						per 50 mcg/day	0.87 (0.74-1.02)		
		194/			Distal colon cancer, men	≥266 vs ≤168 mcg/day	0.74 (0.40-1.35)		
		186/			Proximal colon cancer, men	≥266 vs ≤168 mcg/day	0.75 (0.39-1.44)		
		185/			Proximal colon cancer , women	≥266 vs ≤168 mcg/day	0.72 (0.33-1.54)		
		152/			Rectal cancer, women	≥243 vs ≤150 mcg/day	1.26 (0.58-2.76) 7		
						per 50 mcg/day	1.10 (0.92-1.32)		
						≥266 vs ≤168 mcg/day	0.69 (0.31-1.52)		
Sellers, 1998 COL01974 USA	IWHS, Prospective Cohort, Age: 55-69	180/ 35 216 10 years	SEER registry	Semi-quantitative FFQ	Incidence, colon cancer, no family history of crc	≥413.5 vs ≤255.38 iu/day	0.70 (0.50-1.00)	Age, history of polyps, total energy intake	Superseded by Razzak, 2012 COL40928

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Reasons for exclusion
	years, W, Postmenopausal	62/			Family history of crc	≥413.5 vs ≤255.38 iu/day	0.90 (0.50-1.70)		

Figure 433 RR estimates of colorectal cancer by levels of dietary folate

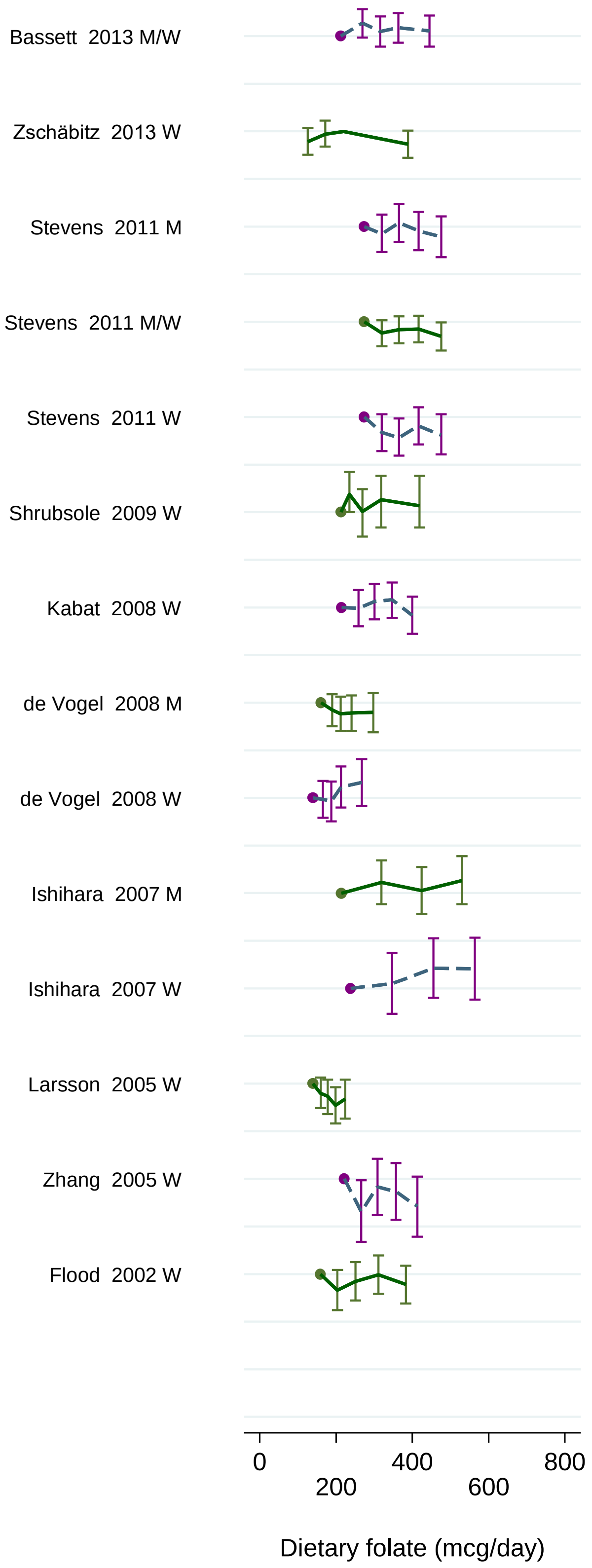


Figure 434 RR (95% CI) of colorectal cancer for the highest compared with the lowest level of dietary folate

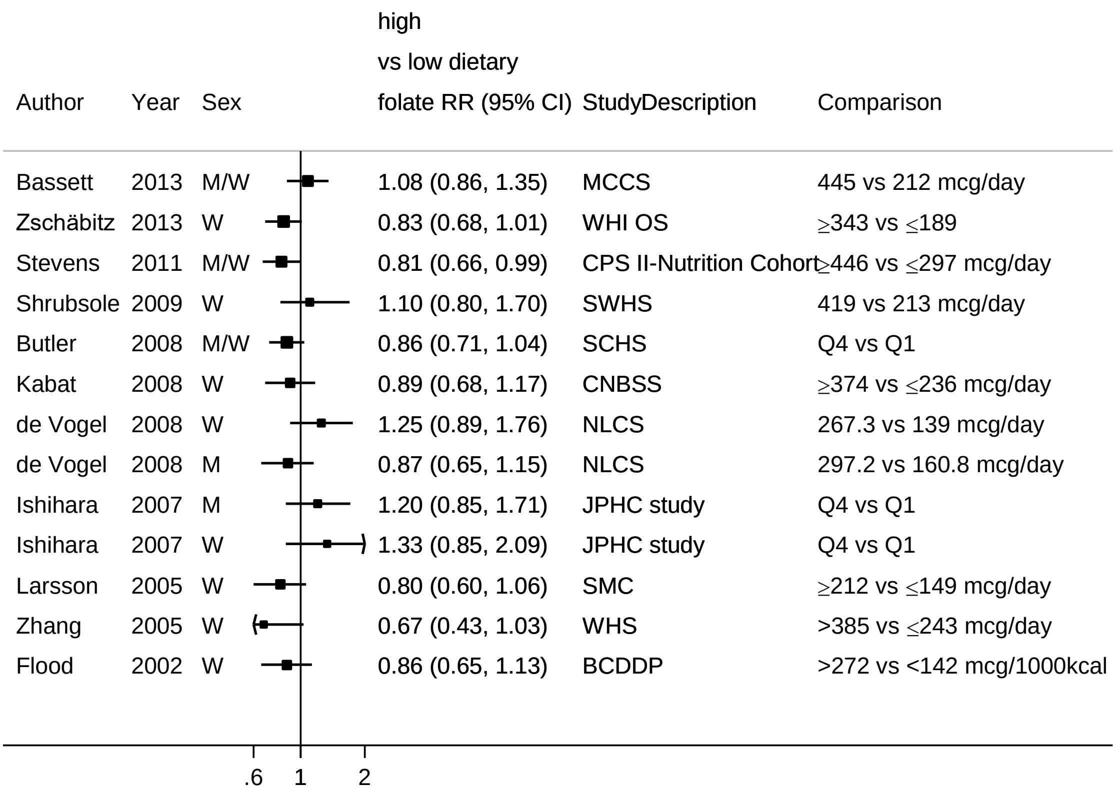


Figure 435 RR (95% CI) of colorectal cancer for 100mcg/day increase of dietary folate

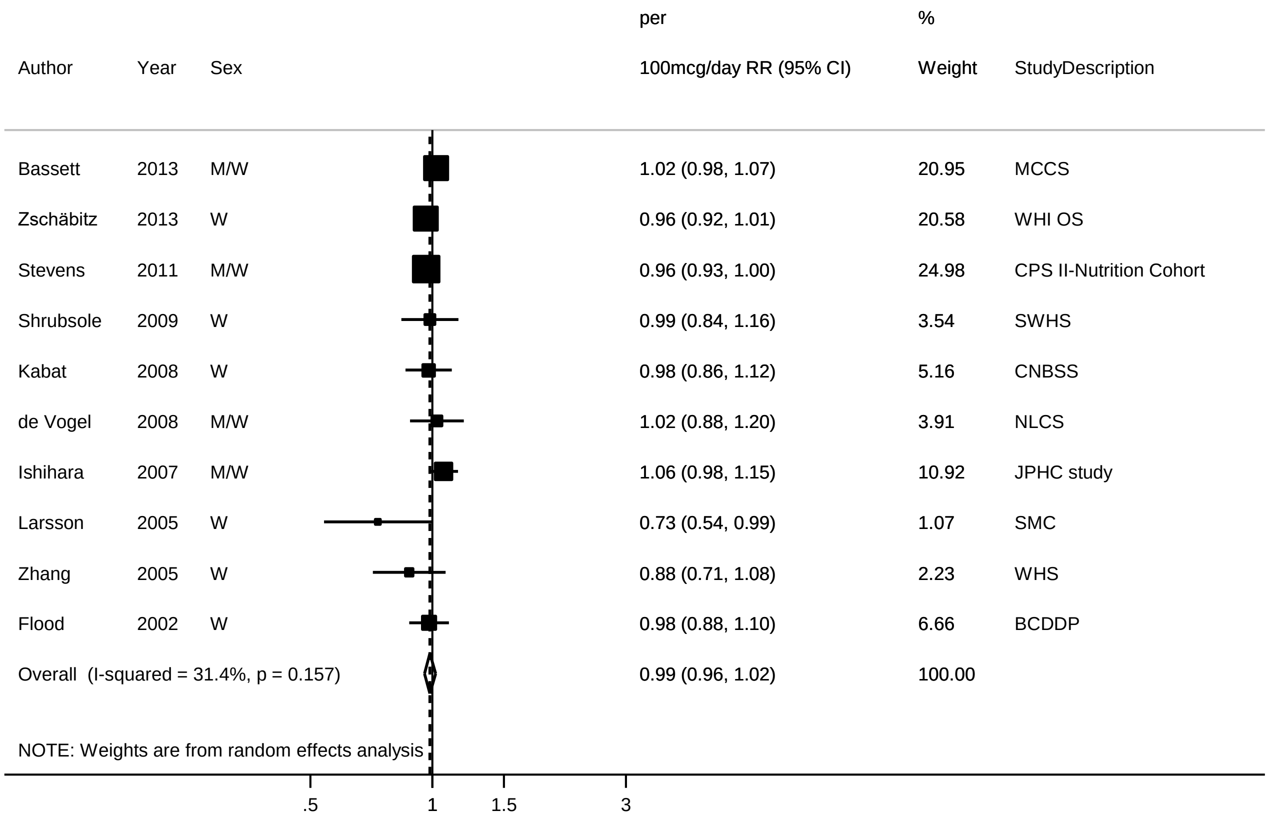


Figure 436 Funnel plot of studies included in the dose response meta-analysis dietary folate and colorectal cancer

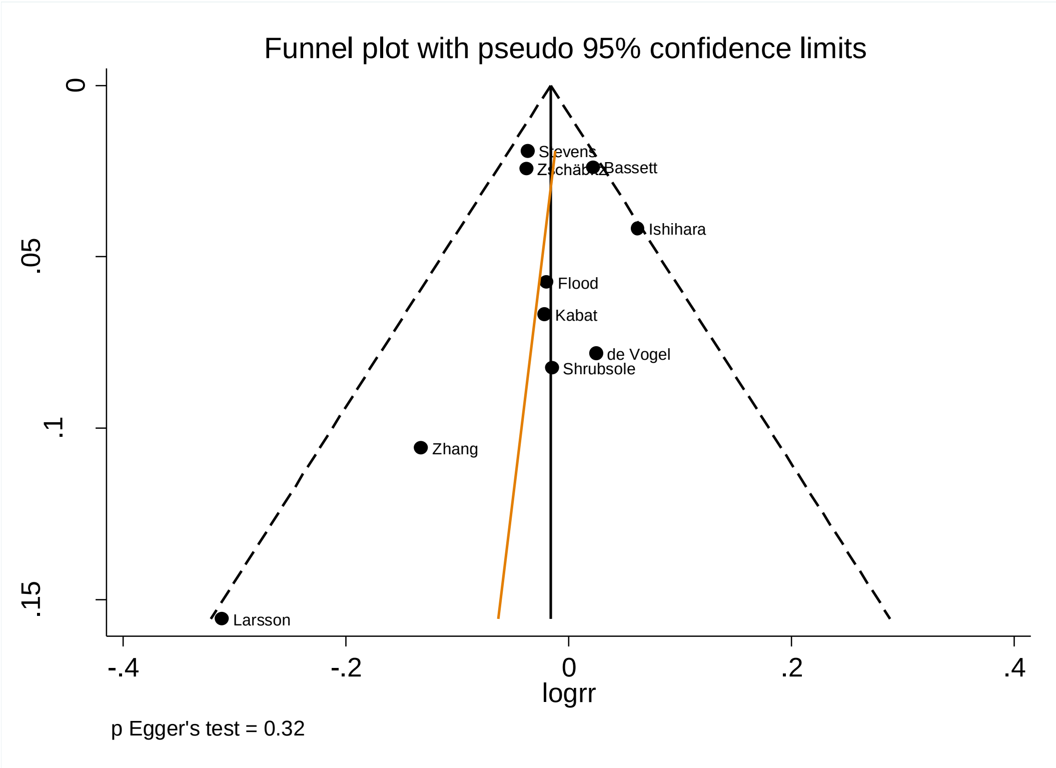


Figure 437 RR (95% CI) of colorectal cancer for 100mcg/day increase of dietary folate by sex

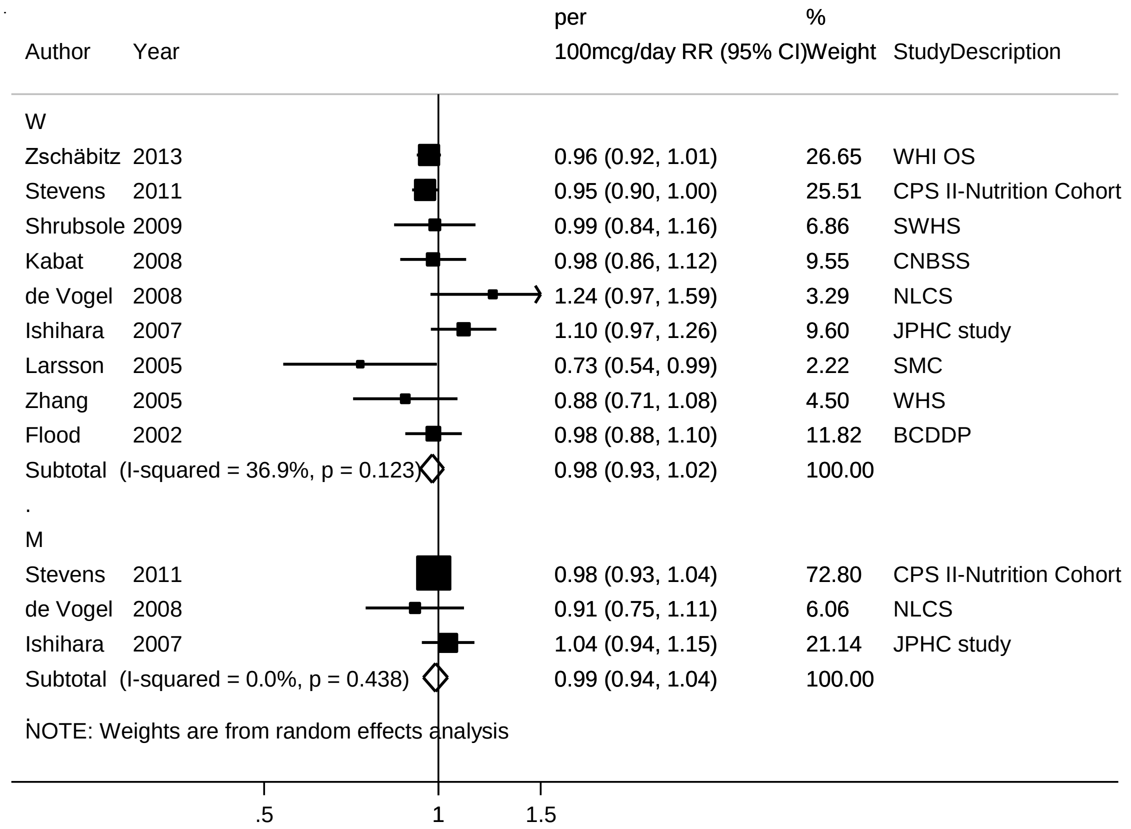


Figure 438 RR (95% CI) of colorectal cancer for 100mcg/day increase of dietary folate by location

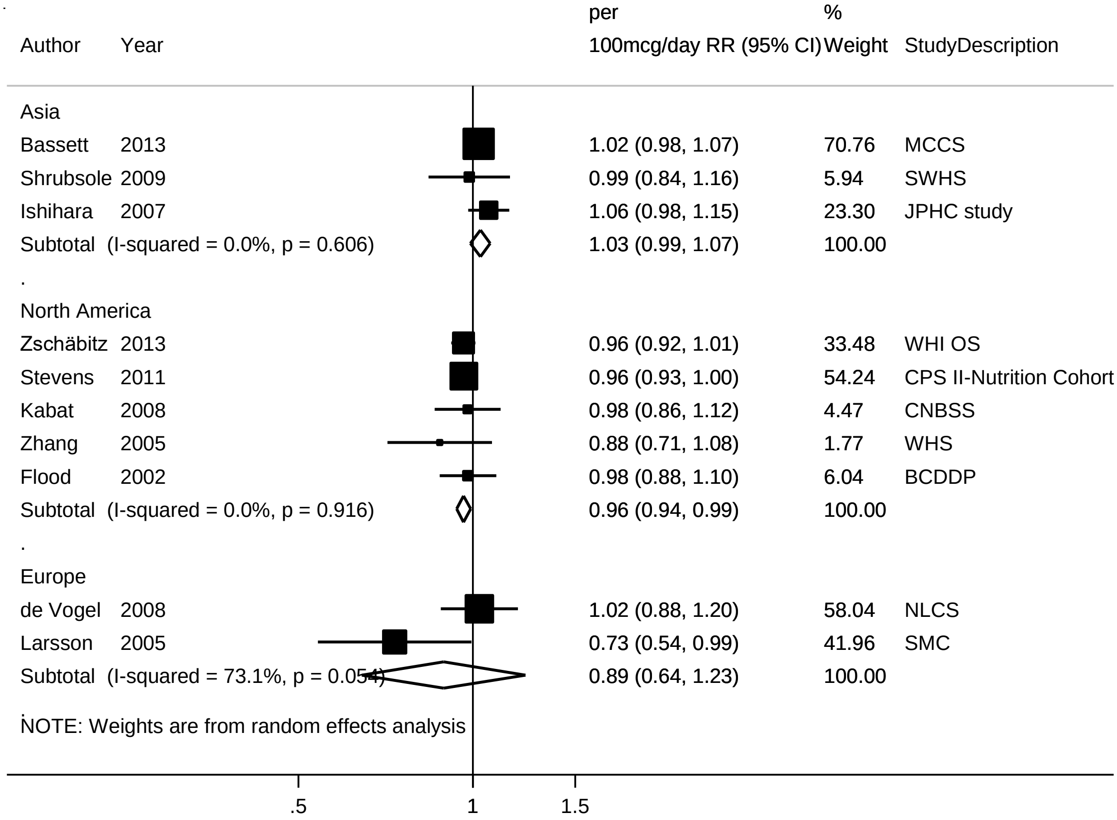


Figure 439 RR estimates of colon cancer by levels of dietary folate

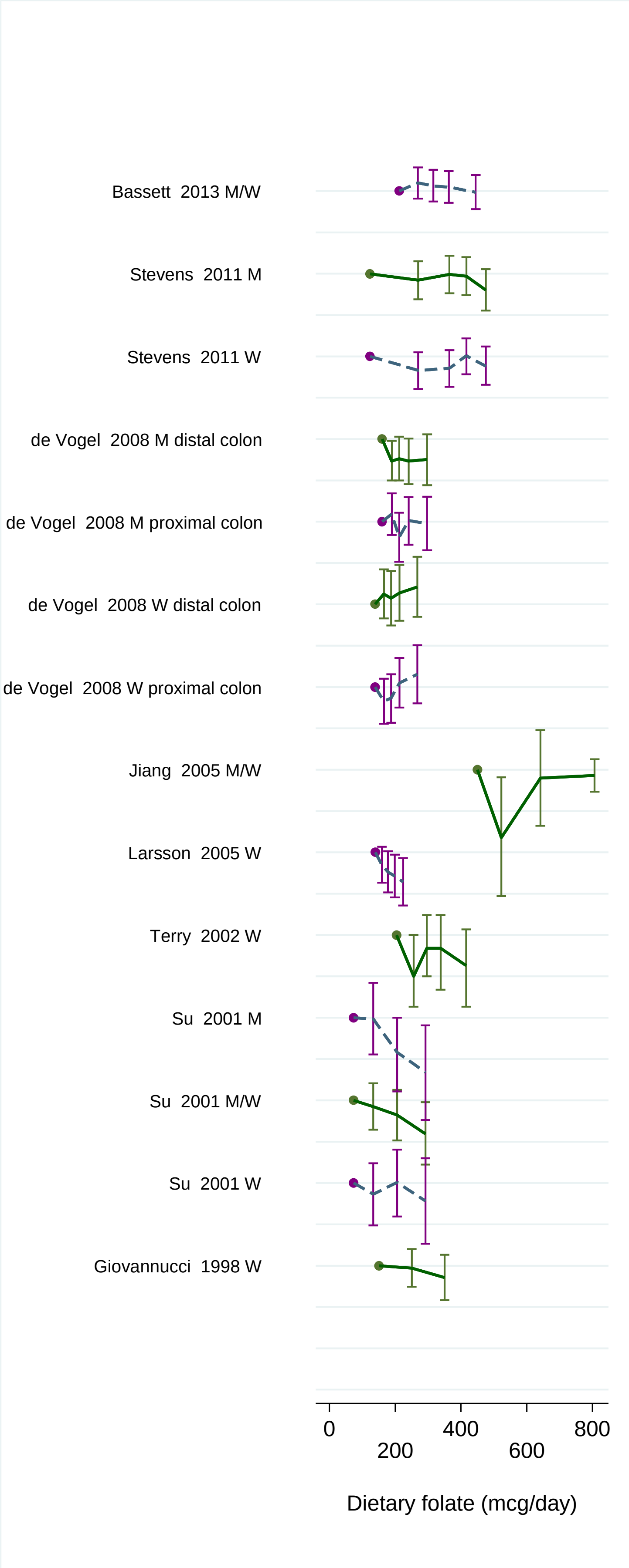
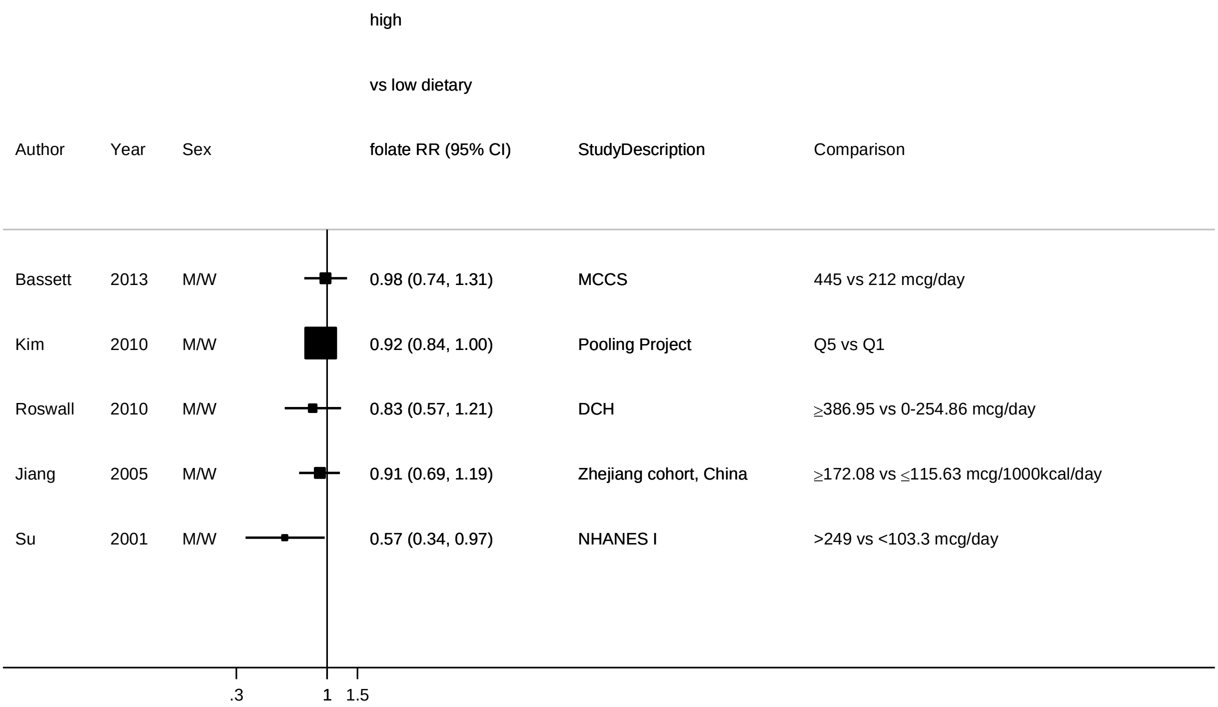


Figure 440 RR (95% CI) of colon cancer for the highest compared with the lowest level of dietary folate



Note: The studies included in the Pooling project (Kim, 2010) are in women in North America (BCDDP, IWHS, NYUWHS, NHS, WHS); in men and women in North America (CPS II, HPFS, NYS); in women in Europe (ORDET, SMC) and in men in Europe (ATBC).

Figure 441 RR (95% CI) of colon cancer for 100mcg/day increase of dietary folate

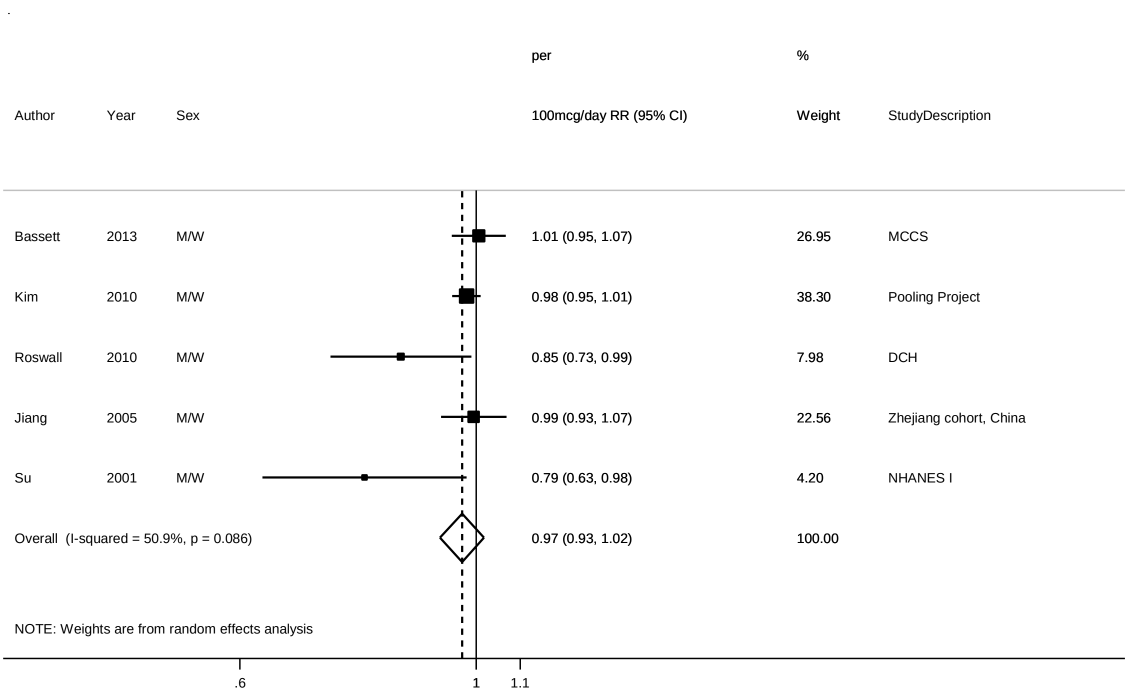


Figure 442 Funnel plot of studies included in the dose response meta-analysis dietary folate and colon cancer

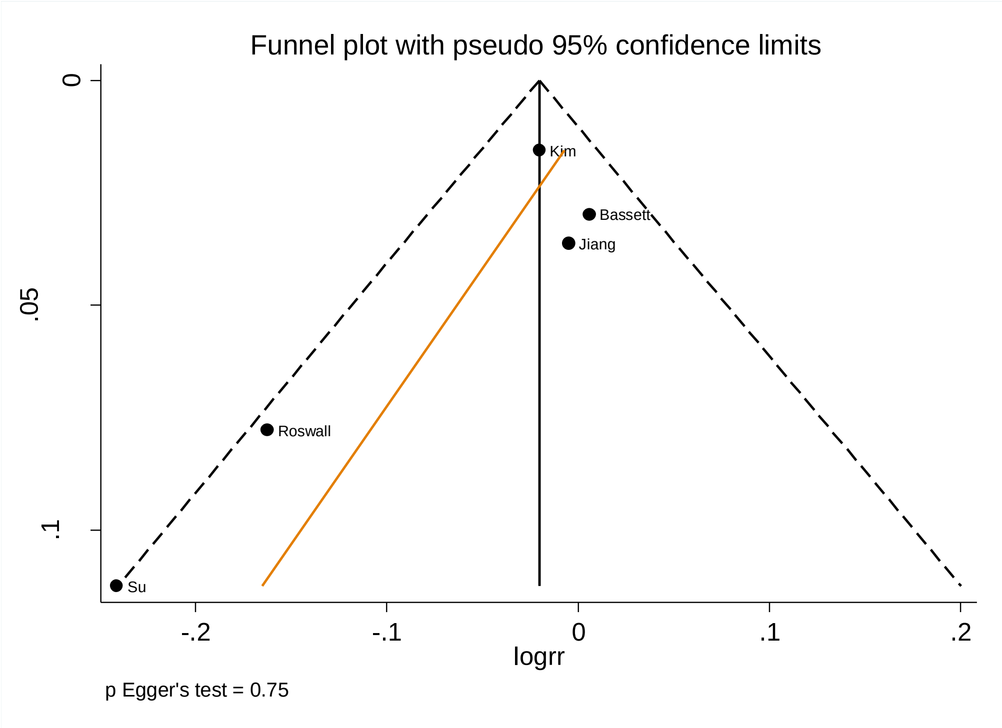


Figure 443 RR (95% CI) of colon cancer for 100mcg/day increase of dietary folate by sex

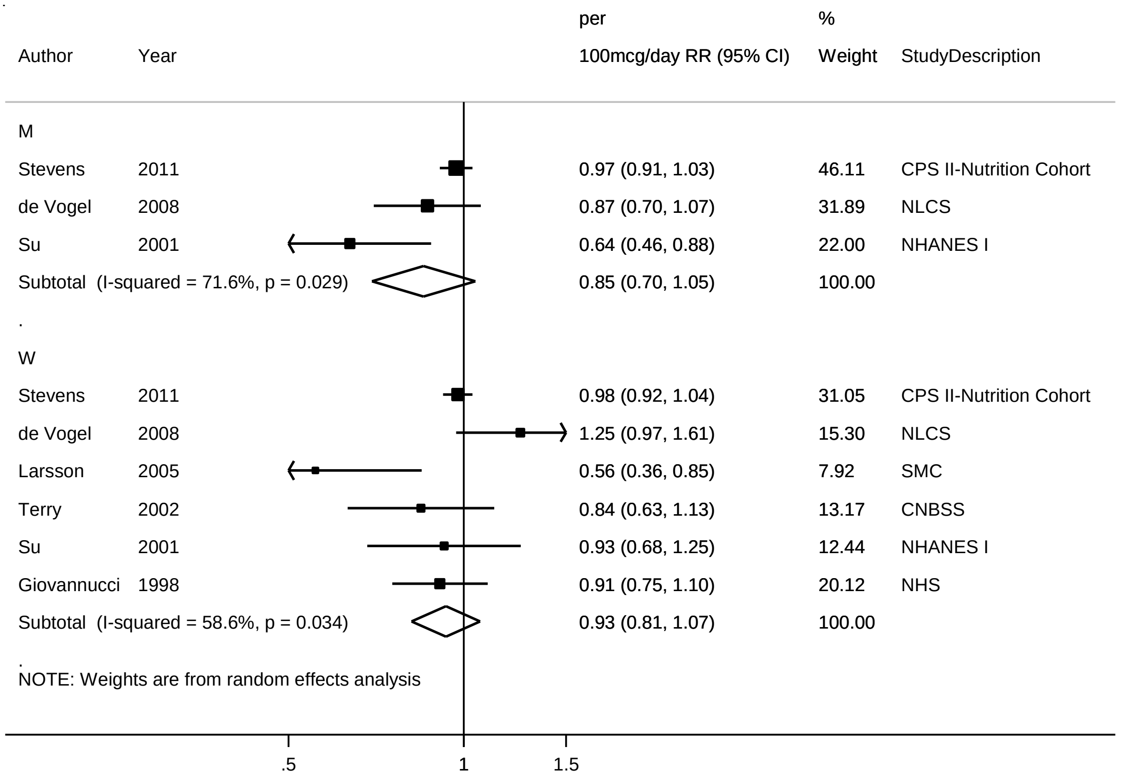
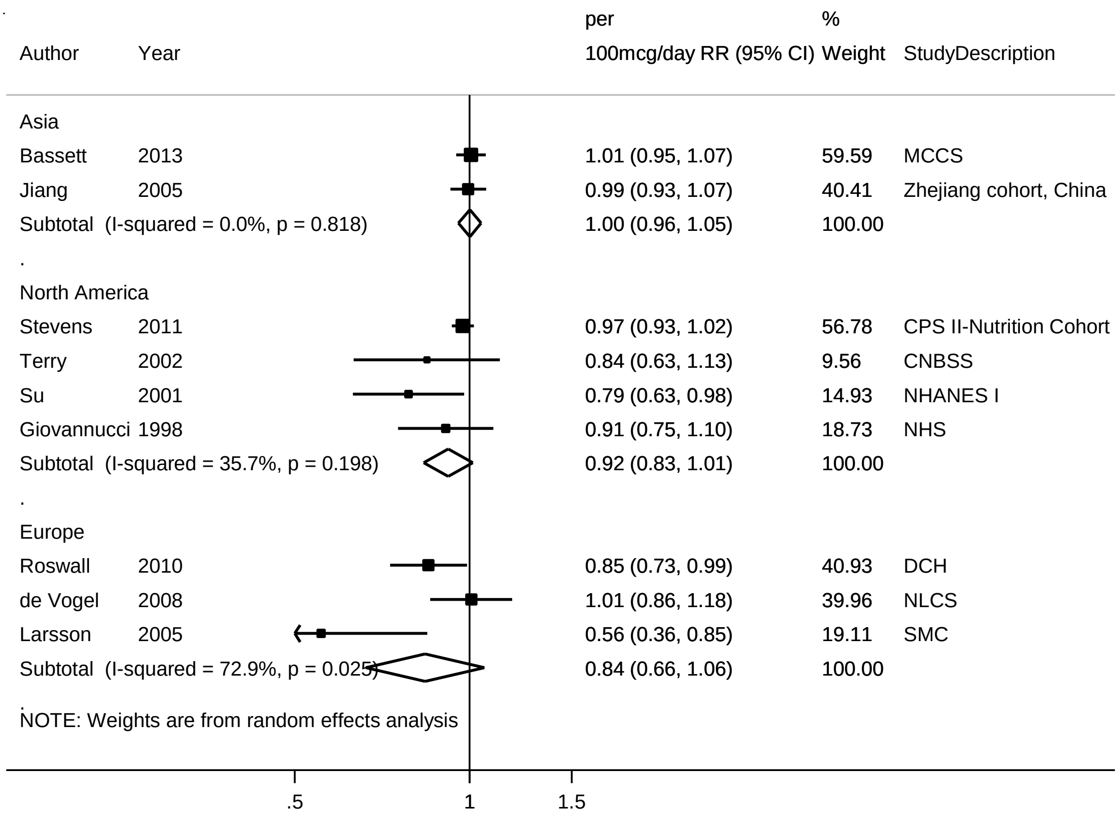


Figure 444 RR (95% CI) of colon cancer for 100mcg/day increase of dietary folate by location



For the stratified analysis the individual studies were used, not the Pooling Project (Kim, 2010).

Figure 445 RR estimates of rectal cancer by levels of dietary folate

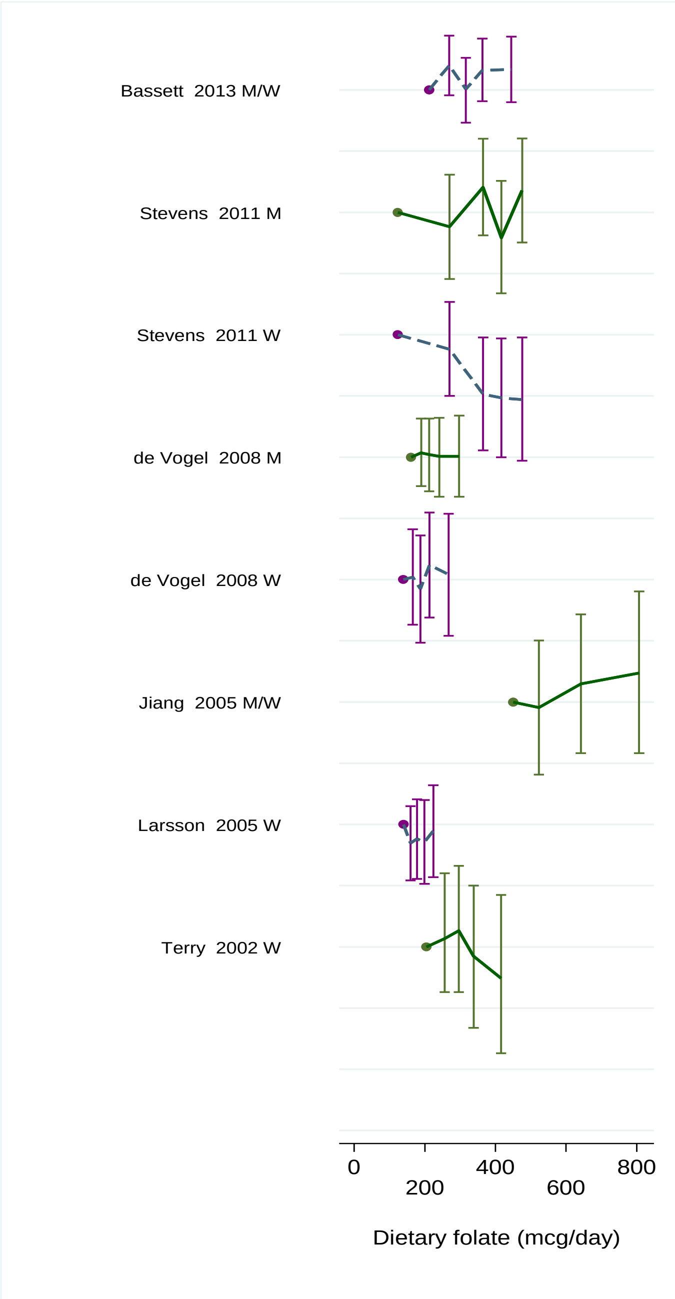


Figure 446 RR (95% CI) of rectal cancer for the highest compared with the lowest level of dietary folate

Author	Year	Sex	high vs low dietary folate RR (95% CI)	StudyDescription	Comparison
Bassett	2013	M/W	1.26 (0.87, 1.83)	MCCS	445 vs 212 mcg/day
Stevens	2011	W	0.48 (0.24, 0.97)	CPS II-Nutrition Cohort	≥446 vs ≤197 mcg/day
Stevens	2011	M	1.28 (0.71, 2.31)	CPS II-Nutrition Cohort	≥446 vs ≤197 mcg/day
Roswall	2010	M/W	1.25 (0.78, 2.00)	DCH	≥398.43 vs 0-270.11 mcg/day
de Vogel	2008	W	1.06 (0.53, 2.11)	NLCS	267.3 vs 139 mcg/day
de Vogel	2008	M	1.01 (0.64, 1.60)	NLCS	297.2 vs 160.8 mcg/day
Jiang	2005	M/W	1.39 (0.56, 3.50)	Zhejiang cohort, China	≥172.08 vs ≤115.63 mcg/1000kcal/day
Larsson	2005	W	0.93 (0.55, 1.56)	SMC	≥212 vs ≤149 mcg/day
Terry	2002	W	0.70 (0.30, 1.80)	CNBSS	>367 vs <233 mcg/day

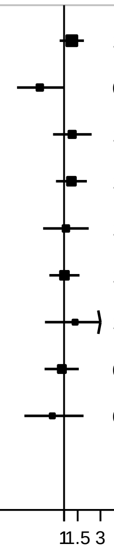


Figure 447 RR (95% CI) of rectal cancer for 100mcg/day increase of dietary folate

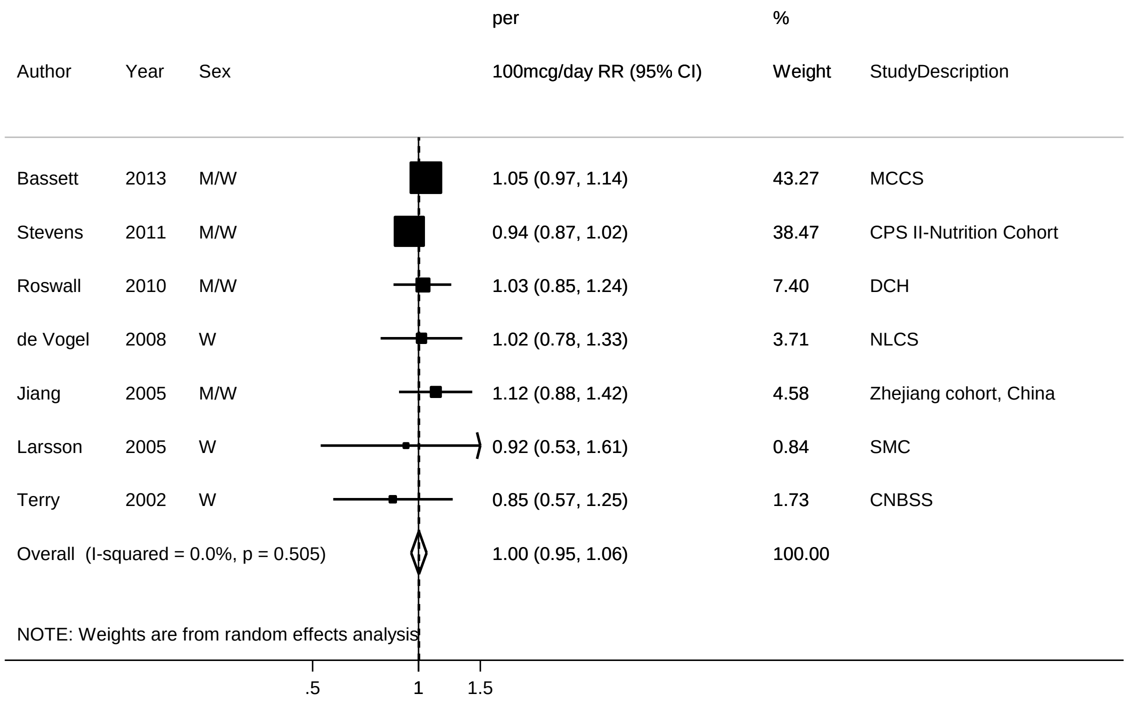


Figure 448 Funnel plot of studies included in the dose response meta-analysis dietary folate and rectal cancer

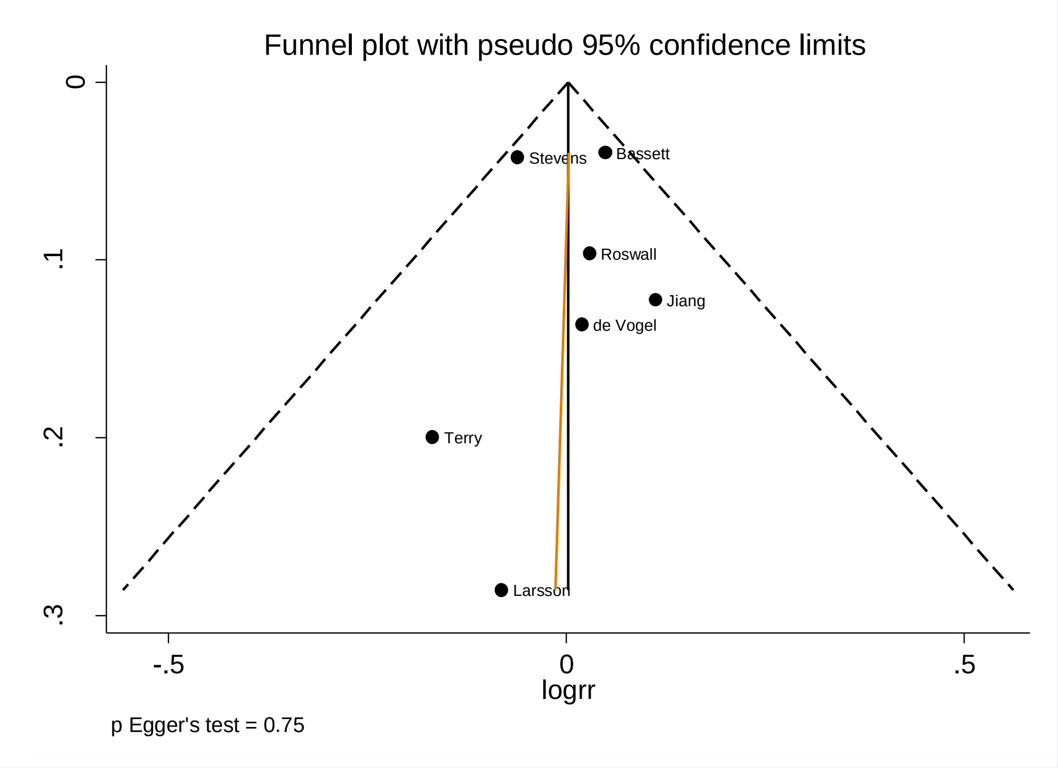


Figure 449 RR (95% CI) of rectal cancer for 100mcg/day increase of dietary folate by sex

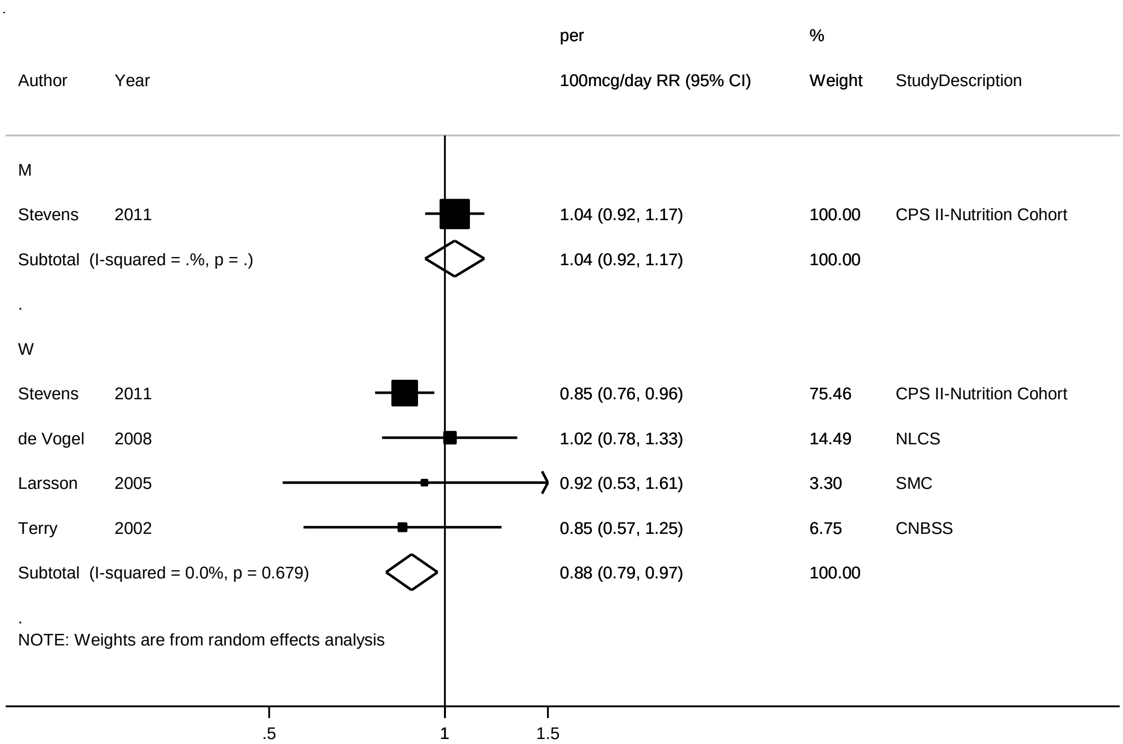
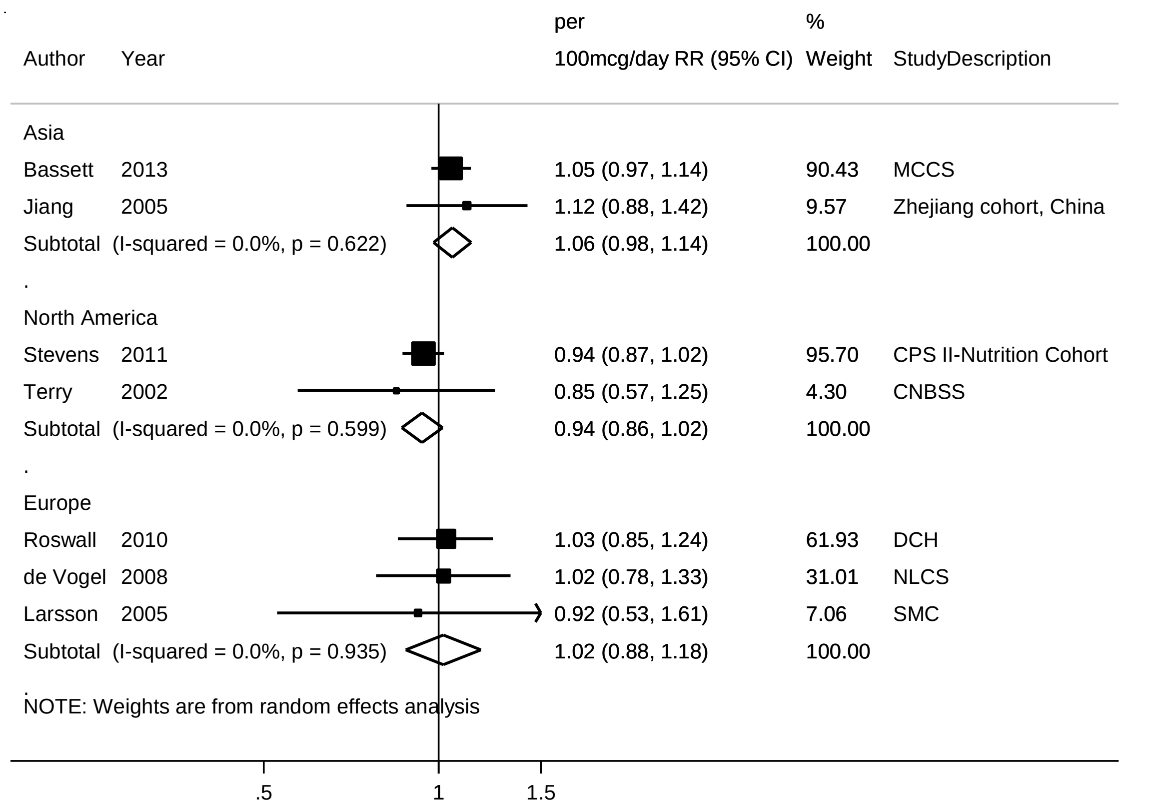


Figure 450 RR (95% CI) of rectal cancer for 100mcg/day increase of dietary folate by location



5.5.3 Total folate intake

Cohort studies

Colorectal cancer:

Eight publications from eight different cohorts were identified, from which five publications from six cohort studies were published after the 2005 SLR. Some cohorts reported results in more than one publication.

Seven studies (4633 cases) were included in the dose-response meta-analysis of total folate and colorectal cancer. No association was observed. All the included studies were from North-America. Six studies were on women only and one study in men and women. No stratified analysis by sex or location was conducted. There was no heterogeneity and no evidence of publication bias (p=0.15). There was no significant evidence of non-linear association (p=0.06).

The overall association remained statistically not significant in influence analysis. The summary RRs ranged from 0.98(95% CI=0.97-1.00) when the BCDDP study (Flood, 2002) was omitted to 0.99(95% CI=0.98-1.00) when the IWHS (McCarl, 2006) was omitted.

Colon cancer:

Thirteen publications from seven different cohorts were identified, from which four publications from three cohort studies were published after the 2005 SLR. Some cohorts reported results in more than one publication. In addition, the Pooling Project of Cohort Studies on Diet and Cancer including data on total folate intake and colon cancer from eight cohort studies was published in 2010 (Kim, 2010).

Ten studies (4765 cases) were included in the dose-response meta-analysis of total folate and colon cancer. The Pooling Project (Kim, 2010) included eight of the studies identified in the CUP and it was combined, in the dose-response analysis and highest compared to lowest meta-analysis, with the two other studies identified. The figure of dose-response by study shows the results of each individual study identified in the CUP; the Pooling Project (Kim, 2010) did not report individual study estimates.

No association was observed. There was low heterogeneity (29.8%). The results are mainly driven by the Pooling Project (75.6% weight in the analysis).

The Pooling Project (Kim, 2010) included eight studies (BCDDP, CPS II, HPFS WHS, NYS, NYUWHS, NHS, WHS) on total folate and colon cancer risk. The data was harmonised across studies and analyses carefully adjusted for potential confounders. In the Pooling project, the pooled multivariate RR for highest vs lowest quintile of total folate intake was 0.87(95% CI 0.78–0.98, p-value, test for trend = 0.02). Analyses excluding the New York State Cohort, which used regression weight methods to calculate nutrient intakes to compensate for their shorter dietary questionnaire, did not modify the results. There was no difference of association by duration of follow-up; therefore the study does not support that high-dose folic acid supplementation may increase the risk of recurrence of colorectal adenomas. The association did not vary by participant age.

A stronger association was observed among men (RR for highest vs. lowest quintile = 0.77, 95% CI 0.57–1.03) than women (RR =0.89, 95% CI 0.78–1.01) but the difference was not significant (p-value, test for between-studies heterogeneity due to sex for the highest quintile = 0.30). No difference across sex was observed in the dose response meta-analysis of three studies in the CUP.

The summary dose-response estimate of the two European studies identified in the CUP is lower than for North American studies, but this was influenced by the study in Finnish male smokers (Glynn 1996) in which supplement folate intake was very low and the range of intake was lower than in other studies.

Departure from non-linearity was not explored because the association between total folate intake and colon cancer risk was consistent with a linear association (p-value, test for nonlinearity<0.1) in the Pooling project and this analyses include most of the existing data.

Rectal cancer:
Seven studies were identified, from which three were published after the 2005 SLR.
Six studies (909 cases) were included in the dose-response meta-analysis of total folate and rectal cancer. No significant association with no heterogeneity was observed. Similar results were observed after stratification by sex and geographic location . There were no studies from Asia. There was no evidence of publication bias (p=0.25). There was not enough data to conduct non-linear analysis.

Meta-analysis:
No meta-analysis of cohort studies and total folate intake was identified.

Table 251 Total folate and colorectal cancer risk. Number of studies in the CUP SLR

	Number
Studies identified	8 (10 publications)
Studies included in forest plot of highest compared with lowest exposure	8
Studies included in dose-response meta-analysis	8
Studies included in non-linear dose-response meta-analysis	8

Note: Include cohort, nested case-control and case-cohort designs

Table 252 Total folate and colon cancer risk. Number of studies in the CUP SLR

	Number
Studies identified	10 (12 publications)
Studies included in forest plot of highest compared with lowest exposure	10*
Studies included in dose-response meta-analysis	10*
Studies included in non-linear dose-response meta-analysis	Pooling project (Kim, 2010)

Note: 8 cohort studies in the Pooling Project (Kim, 2010)

Table 253 Total folate and rectal cancer risk. Number of studies in the CUP SLR

	Number
Studies identified	7 (6 publications)
Studies included in forest plot of highest compared with lowest exposure	7
Studies included in dose-response meta-analysis	6
Studies included in non-linear dose-response meta-analysis	NA

Note: Include cohort, nested case-control and case-cohort designs

Table 254 Total folate and colorectal cancer risk. Summary of the dose-response meta-analysis in the 2010 SLR and 2015 SLR.

	2010 SLR *	**2015 SLR**
Increment unit used	100mcg/day	100mcg/day
Studies (n)	4	8
Cases (total number)	1422	4633
RR (95%CI)	0.98 (0.94-1.03)	0.99(0.98-1.00)
Heterogeneity (I^2, p-value)	61.2%, 0.05	0%, 0.92

*The summary RR for an increment of 100 mcg/day of colorectal and colon cancers (in the same analysis) was 0.98 (0.95-1.01) for 9 cohort studies, from which 4 were on colorectal cancer.

Table 255 Total folate and colon cancer risk. Summary of the dose-response meta-analysis in the 2010 SLR and 2015 SLR.

	2010 SLR	2015 SLR
Increment unit used	100mcg/day	100mcg/day
Studies (n)	4	10
Cases (total number)	1823	4765
RR (95%CI)	0.97 (0.91-1.03)	0.97(0.91-1.03)
Heterogeneity (I^2, p-value)	57%, 0.07	29.8%, 0.24

Stratified analysis by sex			
Men	**2010 SLR**	**2015 SLR**	**Pooling project (Kim, 2010)**
Increment unit used	100mcg/day	100mcg/day	Highest vs lowest
Studies (n)	2	3	4
RR (95%CI)	0.83 (0.52 - 1.34)	0.96(0.90-1.03)	0.77(0.57–1.03)
Heterogeneity (I^2, p-value)	49%, 0.16	6.0%, 0.35	NA
Women			
Studies (n)	2	3	7
RR (95%CI)	0.98 (0.91 - 1.05)	0.97(0.94-1.00)	0.89 (0.78–1.01)
Heterogeneity (I^2, p-value)	76%, 0.04	6.8%, 0.34	NA/ P het. sex=0.30

Stratified analysis by geographic location (no analysis in 2005 SLR)		
2015 SLR	**Europe**	**North America**
Increment unit used	100mcg/day	100mcg/day
Studies (n)	2	4
RR (95%CI)	0.83(0.53-1.29)	0.97 (0.95-1.00)
Heterogeneity (I^2, p-value)	46.7%, 0.17	0%, 0.54

Table 256 Total folate and rectal cancer risk. Summary of the dose-response meta-analysis in the 2010 SLR and 2015 SLR.

	2010 SLR	2015 SLR
Increment unit used	100mcg/day	100mcg/day
Studies (n)	4	6
Cases (total number)	512	909
RR (95%CI)	1.00(0.96-1.03)	0.99(0.96-1.02)
Heterogeneity (I^2, p-value)	0%, 0.48	0%, 0.63

Stratified analysis by sex		
Men	**2010 SLR**	**2015 SLR**
Studies (n)	2	3
RR (95%CI)	1.09 (0.54 - 2.19)	1.02(0.84-1.24)
Heterogeneity (I^2, p-value)	39%, 0.20	40.7%, 0.19
Women		
Studies (n)	2	3
RR (95%CI)	1.00 (0.96 - 1.04)	0.96(0.86-1.07)
Heterogeneity (I^2, p-value)	0%, 0.58	69.3%, 0.04
Stratified analysis by geographic location		
(no analysis in 2005 or 2010 SLR)		
2015 SLR	**North America**	**Europe**
Studies (n)	4	2
RR (95%CI)	0.99(0.96-1.03)	1.09(0.60-2.00)
Heterogeneity (I^2, p-value)	0%, 0.62	32.6%, 0.22

Table 257 Total folate and colorectal cancer risk. Main characteristics of studies included in the CUP SLR dose-response meta-analysis

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Missing data derived for analyses
Nishihara, 2014 COL41036 USA	NHS-HPFS, Prospective Cohort, Age: 30-75 years, M/W, nurses & health professionals	993/	Medical records and death registries	Semi-quantitative FFQ	Incidence, colorectal cancer	≥400 vs ≤200 mcg/day	1.00 (0.76-1.32)	Age, sex, year of questionnaire return, regular aspirin use, BMI, endoscopy status, family history of colorectal cancer, multivitamin use, pack years smoked, physical activity, red meat, vitamin B12, vitamin B6, calcium, methionine, total caloric intake	Mid-points of exposure categories. The Pooling Project Kim, 2010 was used for dose response meta-analysis on colon cancer
Zschäbitz, 2013 COL40934 USA	Women's Health Initiative - Observational study, Prospective Cohort, W, Postmenopausal	808/ 88 045 11 years	Self report verified by medical record	FFQ	Incidence, colorectal cancer	≥939 vs 0-242	0.90 (0.74-1.10)	Age, BMI, colonoscopy, ethnicity, hormone use, physical activity, smoking	Distribution of person-years by exposure category The Pooling Project Kim, 2010 was used for dose response meta-analysis on colon cancer

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Missing data derived for analyses
Razzak, 2012 COL40928 USA	IWHS, Prospective Cohort, Age: 55-69 years, W	1 298/ 35 216	Cancer registry and national death Index	126 items Willett FFQ	Incidence, colorectal cancer	≥573.5 vs ≤250 mcg/day	0.95 (0.76-1.20)	Age, BMI, waist to hip ratio, diabetes, exogenous estrogen use, physical activity, smoking status, and daily intakes of total energy, total fat, sucrose, red meat, calcium, vitamin E and alcohol	Mid-points of exposure categories.
		673/			Incidence, proximal colon cancer	≥573.5 vs ≤250 mcg/day	0.81 (0.59-1.11)		Superseded by Pooling Project Kim, 2010 for colon cancer dose response meta-analysis.
		597/			Incidence, distal colon cancer	≥573.5 vs ≤250 mcg/day	1.08 (0.77-1.49)		
Schernhammer, 2011 COL40882 USA	NHS, Prospective Cohort, Age: 30-55 years, W, Registered nurses	386/ 88 691 20 years	Questionnaire/medical records/death record	Semi-quantitative FFQ	Incidence, colon cancer	≥400 vs ≤200 mcg	0.81 (0.61-1.08)	Age, alcohol, aspirin use, beef intake, BMI, calcium, energy intake, family history of colon cancer, gender, history of polyps, methionine, multivitamin, physical activity, sigmoidoscopy, smoking, vitamin b12,	Superseded by Pooling Project Kim, 2010 for dose response meta-analysis on colon cancer.

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Missing data derived for analyses
								vitamin b6	
Stevens, 2011 COL40887 USA	CPS II-Nutrition Cohort, Prospective Cohort, Age: 50-74 years, M/W	1 023/ 99 523 15 years	Cancer registry and medical records	FFQ	Incidence, colorectal cancer	≥1224 vs <422 mcg/day	0.81 (0.66–0.99)	Age, sex, alcohol, BMI, educational level, endoscopy, energy intake, family history of colorectal cancer, HRT use, low-fat dairy products, non-steriodal anti-inflammatory drug use, race, red meat, smoking	Superseded by Pooling Project Kim, 2010 for colon cancer dose response meta-analysis.
		799			Incidence, colon cancer		0.83 (0.66–1.04)		
		219			Incidence, rectal cancer		0.73 (0.47–1.16)		
Kim, 2010 Pooling Project	BCDDP CPS II HPFS IWHS NYS	349 816 456 799 558	Follow-up questionnaires and medical records	FFQ	Incidence, colon cancer	≥560 vs <240 mcg/day	0.87 (0.78-0.98)	Education, BMI, height, smoking, energy intake, alcohol, red meat, milk	Reported dose-response for colon cancer in continuous increment.

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Missing data derived for analyses
	NYUWHS NHS WHS	96 591 163				Per 100mcg/day	0.99(0.96-1.02)	intake, multivitamin, history of colorectal cancer, NSAID, physical activity, HRT, age	
Roswall, 2010 COL40797 Denmark	DCH, Prospective Cohort, Age: 50-64 years, M/W	178/ 56 332 10.6 years	Cancer registry	FFQ	Incidence, rectal cancer	≥461.23 vs 0-282.8 mcg/day	1.06 (0.67-1.70)	Age, alcohol intake, beta carotene, BMI, educational level, hormone use, physical activity, processed meat, red meat intake, smoking status, smoking status, vitamin c, vitamin e	Reported dose-response for colon cancer in continuous increment.
		105/				per 100 mcg/day	0.95 (0.83-1.09)		
					Incidence, colon cancer	≥441.67 vs 0-273.71 mcg/day	0.67 (0.46-1.00)		
						per 100 mcg/day	0.94 (0.85-1.04)		
Zhang, 2005 COL40742 USA	WHS, Prospective Cohort, Age: 45- years, W, Health professionals	220/ 37 916 10.1 years	Self-report, death report, national death Index, medical records reviewed by physicians	FFQ	Incidence, colorectal cancer	≥614 vs ≤258 mcg/day	1.16 (0.76-1.79)	Age, alcohol consumption, aspirin use, BMI, family history of colorectal cancer In first degree relatives, history	Distribution of person-years by exposure category. Mid-points of exposure categories.

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Missing data derived for analyses
		44			Incidence, rectal cancer		0.94(0.43-2.03)	of polyps, menopausal status, physical activity, postmenopausal hormone use, randomized treatment assignment, red meat intake, smoking status, total energy intake	
Wei, 2004 COL00581 USA	NHS, Prospective Cohort, W, nurses	672/ 87 733 24 years	Self-reported verified by medical records and National Death Index	Semi-quantitative FFQ	Incidence, colon cancer, women	≥401 vs ≤200 mcg/day	0.82 (0.66-1.03)	Age, alcohol consumption, beef, pork or lamb as a main dish, BMI, calcium, family history of colorectal cancer, height, history of endoscopy, pack-years of smoking before age 30, physical activity, processed meat	Schernhammer, 2011 was used COL40882 The Pooling Project Kim, 2010 was used for dose response meta-analysis on colon cancer
	HPFS, Prospective Cohort, M, Health professionals	467/ 46 632 14 years			Incidence, colon cancer, men	≥400 vs ≤200 mcg/day	0.72 (0.45-1.16)		
	NHS	204/			Incidence, rectal cancer, women	≥401 vs ≤200 mcg/day	1.32 (0.86-2.05)		Distribution of person-years by exposure category.
	HPFS	135/			Incidence, rectal cancer, men	≥400 vs ≤200 mcg/day	0.67 (0.26-1.72)		
Flood, 2002 COL00411 USA	BCDDP, 1973, Prospective Cohort,	485 45 264 8.5 years	Breast cancer screening centres	FFQ	Incidence, colorectal cancer,	≥633 vs ≤188 mcg/day	1.01 (0.75-1.35)	Alcohol consumption, energy intake,	Distribution of person-years by exposure

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Missing data derived for analyses
	Age: 40-93 years, W							methionine, total fat	category. Mid-points of exposure categories.
Harnack, 2002 COL00312 USA	IWHS, Prospective Cohort, Age: 55-69 years, W	598/ 41 836 13 years	SEER	Semi-quantitative FFQ	Incidence, colon cancer,	634.03-2555.2 vs 32.14-231.12 mcg/day	1.12 (0.77-1.63)	Age, BMI, calcium intake, energy intake, estrogen use, pack-years of smoking, vitamin e Oral contraceptive use	The Pooling Project Kim, 2010 was used for dose response meta-analysis on colon cancer
		123/			Incidence, rectal cancer,	463.37-2555.2 vs 32.14-281.85 mcg/day	0.89 (0.52-1.51)		Mid-points of exposure categories.
Kato, 1999 COL00436 USA	New York University Women's Health Study, Nested Case Control, Age: 62 years, W	150/ 81	Follow-up questionnaire	Semi-quantitative FFQ	Incidence, colorectal cancer,	≥626 vs ≤224 mcg/day	0.88 (0.46-1.69)	Age, beer consumption, date of enrolment, date of subsequent blood, family history of specific cancer, menopausal status, occult blood testing, physical activity	Mid-points of exposure categories.
Glynn, 1996 COL00161 Finland	ATBC, Nested Case Control, Age: 50-69 years,	86/ 159 controls 8 years	Cancer registry	FFQ	Incidence, colon cancer	388 vs 268 mcg/day	0.51 (0.20-1.31)	Age, clinic site, date of blood collection, energy intake, physical	Distribution of non cases by exposure category.
		50/ 90 controls			Incidence, rectal cancer	388 vs 268 mcg/day	2.12 (0.43-10.54)		

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Missing data derived for analyses
	M, Male Smokers							activity, starch, vitamin a intake	

Table 258 Total folate and colorectal cancer risk. Main characteristics of studies excluded from the CUP SLR dose-response meta-analysis

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Reasons for exclusion
Lee, 2011 USA	NHS+HPFS	2299/ 87891men and 47290 women	Self-reported and medical records	FFQ	Incidence, colorectal cancer	≥800 years vs <250 mcg/d	0.89 (0.74, 1.06)	Age, calendar year, pack-years of smoking before age 30 y, physical activity, aspirin dose, height, BMI, family history of colorectal cancer in parents and siblings, menopausal status and hormone therapy use, history of endoscopy, and intakes of red meat, alcohol, calcium from foods, and total energy.	Superseded by Pooling Project Kim, 2010
Schernhammer, 2008 COL40729 USA	NHS-HPFS, Prospective Cohort, M/W	277/ 136 062 2 566 968 person-years	Self-report verified by medical record	Semi-quantitative FFQ	Incidence, colon cancer, men	≥662 vs ≤284 mcg/day	0.80 (0.54-1.19)	Age, aspirin use, BMI, intakes of calcium, beef, methionine,	Superseded by Wei, 2004

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Reasons for exclusion
								vitamin B12, vitamin B6, total energy intake, family history of colorectal cancer, multivitamin supplement use, physical activity, previous polyps, sigmoidoscopy, smoking status	
McCarl, 2006 COL40633 USA	IWHS, Prospective Cohort, Age: 55-69 years, W	954/ 35 197 15 years	SEER registry	FFQ	Incidence, colorectal cancer	≥634.61 vs ≤231.78 mcg	0.73 (0.59-0.89)	Age	Superseded by Razzak, 2012 COL40928
Feskanich, 2004 COL01680 USA	NHS, Nested Case Control, Age: 46-78 years, W	193/ 383 controls 11 years	Medical records and writing or by telephone	FFQ	Incidence, colorectal cancer,	(mean exposure)		Month of blood draw, year of birth	Mean exposure only Superseded by Wei, 2004
Fuchs, 2002 COL00415 USA	NHS, Prospective Cohort, Age: 30-55 years,	428/ 88 758 1 375 165 person-years	Self-reported verified by medical records and National Death Index	FFQ	Incidence, colon cancer, no family history of crc	≥400 vs ≤200 mcg/day	0.91 (0.69-1.19)	Age, alcohol consumption, aspirin use, beef, pork, or lamb, BMI,	Superseded by Wei, 2004, COL00581 and Kim, 2010

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Reasons for exclusion
	W, nurses							energy-adjusted levels of methionine, physical activity, screening endoscopy, smoking habits	
Giovannucci, 1998 COL00113 USA	NHS, Prospective Cohort, Age: 30-55 years, W, nurses	442/ 88 756 1 215 392 person-years	Self-reported verified by medical records and National Death Index	Semi-quantitative FFQ	Incidence, colon cancer,	≥401 vs ≤200 mcg/day	0.69 (0.52-0.93)	Age, alcohol consumption, aspirin use, beef, pork, or lamb as main dish intake, BMI, family history of specific cancer, fibre, methionine, physical activity, smoking habits	Superseded by Wei, 2004, COL00581 and Kim, 2010
Giovannucci, 1995 COL00112 USA	HPFS, Prospective Cohort, Age: 40-75 years, M, Health professionals	205/ 47 931 261 916 person-years		Semi-quantitative FFQ	Incidence, colon cancer,	Q 5 vs Q 1	0.86 (0.54-1.36)	Age, aspirin use, BMI, energy intake, family history of specific cancer, folate, history of endoscopy, history of previous polyp	Only highest compared to lowest and interaction results. Superseded by Kim, 2010
		149/			Aspirin non-users	≥646 vs ≤269 mcg/day	0.86 (0.50-1.47)		
		56/			Aspirin use	≥646 vs ≤269 mcg/day	0.82 (0.33-2.08)		

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Reasons for exclusion
								and prior endoscopy, methionine, physical activity, red meat intake, smoking habits	

Figure 451 RR estimates of colorectal cancer by levels of total folate

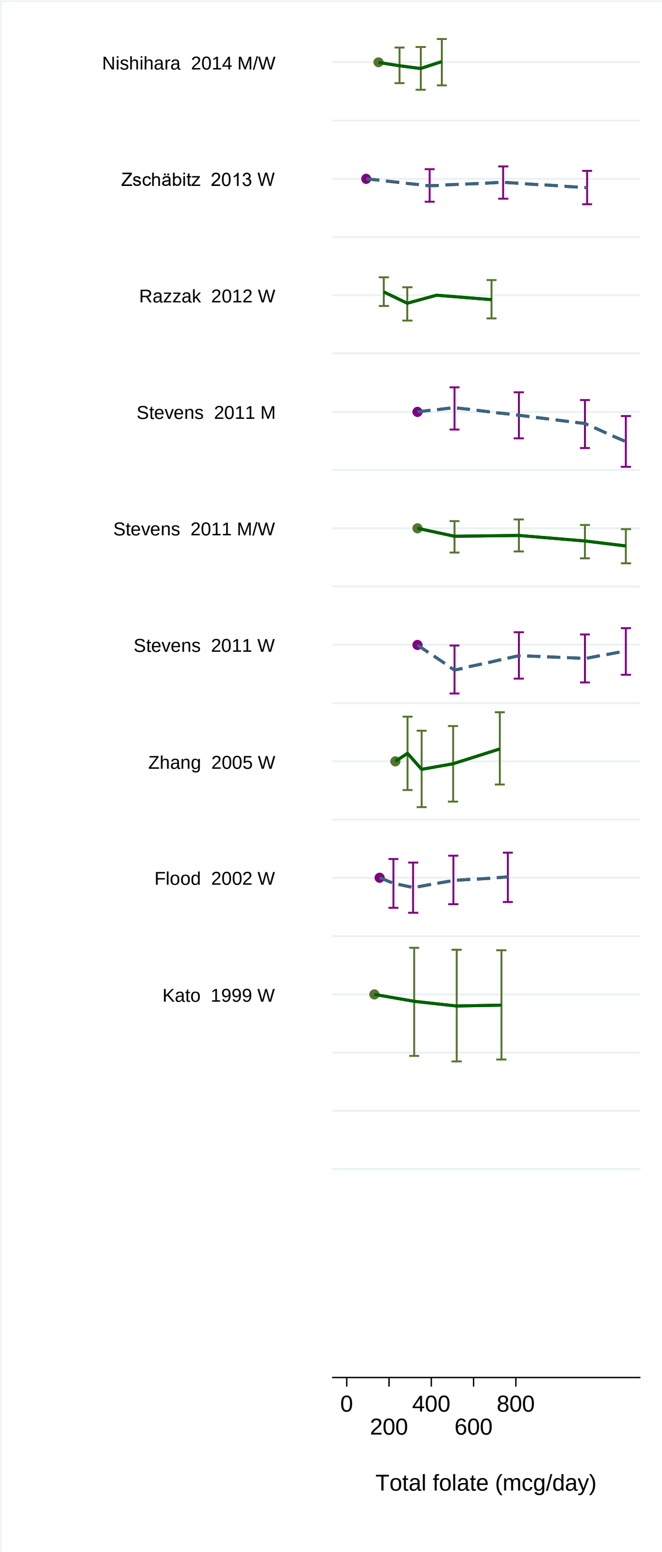


Figure 452 RR (95% CI) of colorectal cancer for the highest compared with the lowest level of total folate

Author	Year	sex	high vs low total folate RR (95% CI)	StudyDescription	Comparison
Nishihara	2014	M/W	1.01 (0.76, 1.32)	NHS-HPFS	≥400 vs ≤200 mcg/day
Zschäbitz	2013	W	0.90 (0.74, 1.10)	WHI OS	≥939 vs 0-242
Razzak	2012	W	0.95 (0.76, 1.20)	IWHS	≥573.5 vs ≤250 mcg/day
Stevens	2011	M/W	0.81 (0.66, 0.99)	CPS II-Nutrition Cohort	≥1224 vs ≤422
Zhang	2005	W	1.16 (0.76, 1.79)	WHS	>614 vs ≤258 mcg/day
Flood	2002	W	1.01 (0.75, 1.35)	BCDDP	>633 vs <188 mcg/day
Kato	1999	W	0.88 (0.46, 1.69)	NYWHS	≥626 vs ≤224 mcg/day

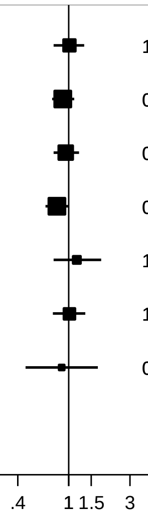


Figure 453 RR (95% CI) of colorectal cancer for 100mcg/day increase of total folate

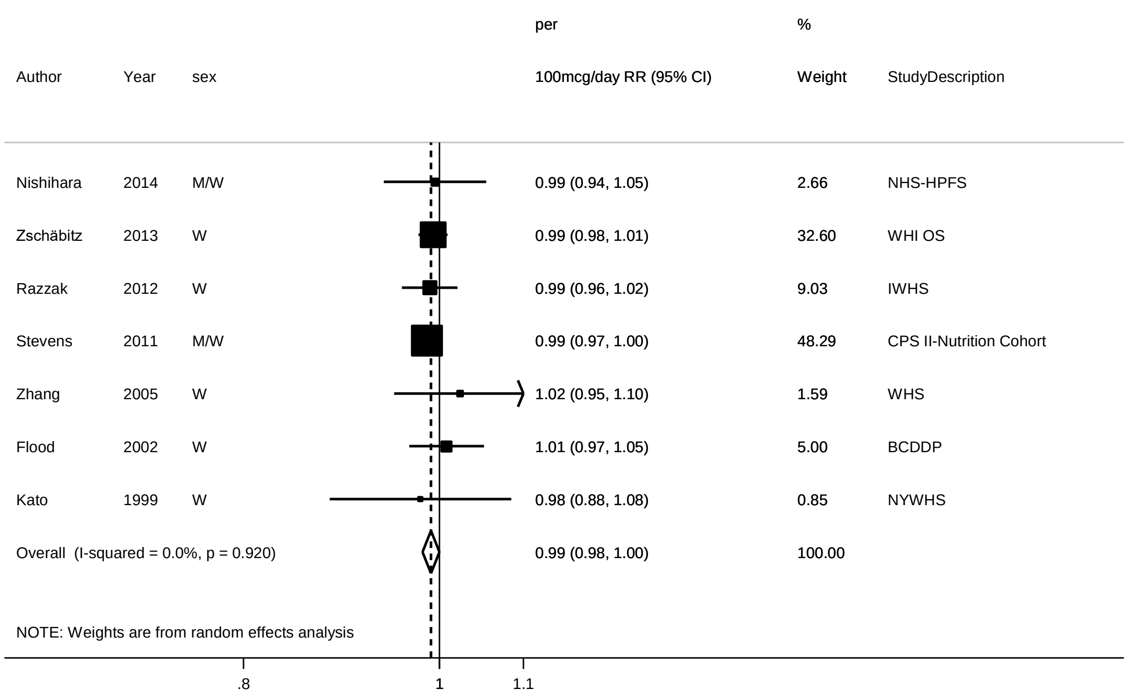


Figure 454 Funnel plot of studies included in the dose response meta-analysis total folate and colorectal cancer

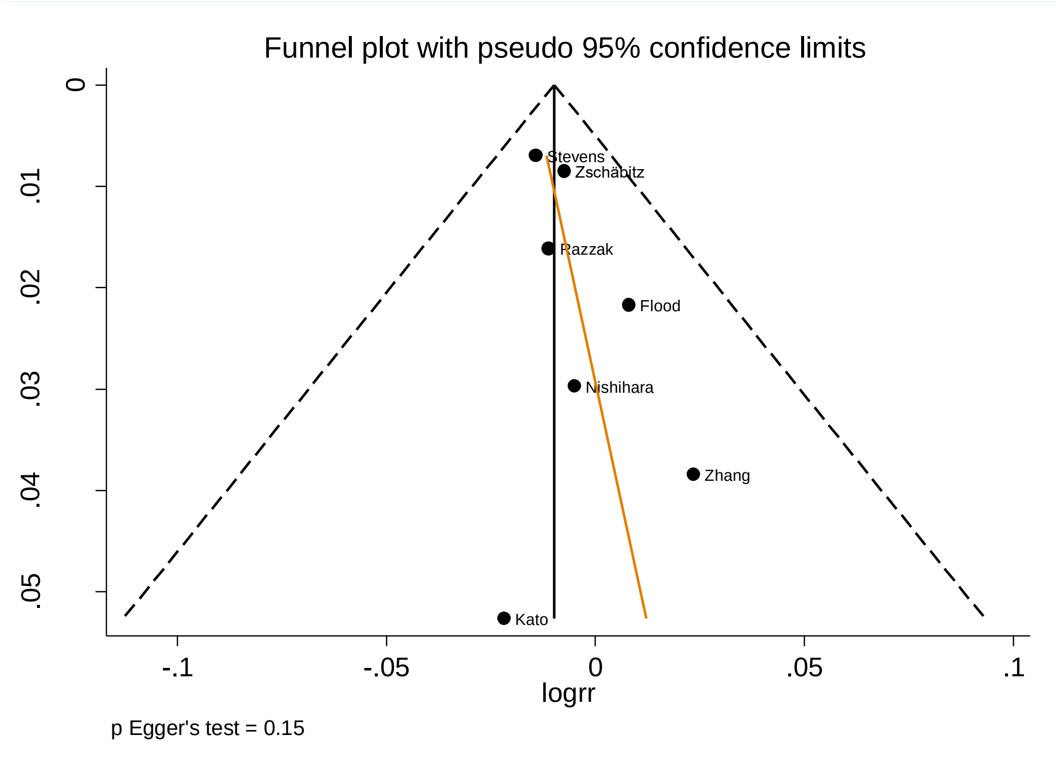
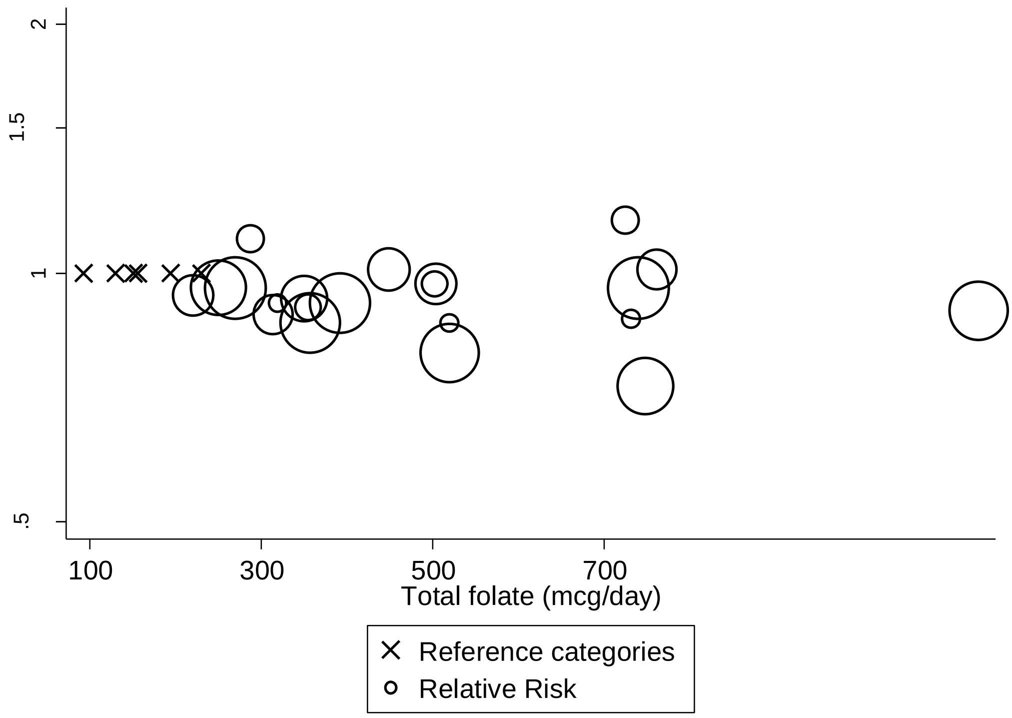


Figure 455 Relative risk of colorectal cancer and total folate estimated using non-linear models



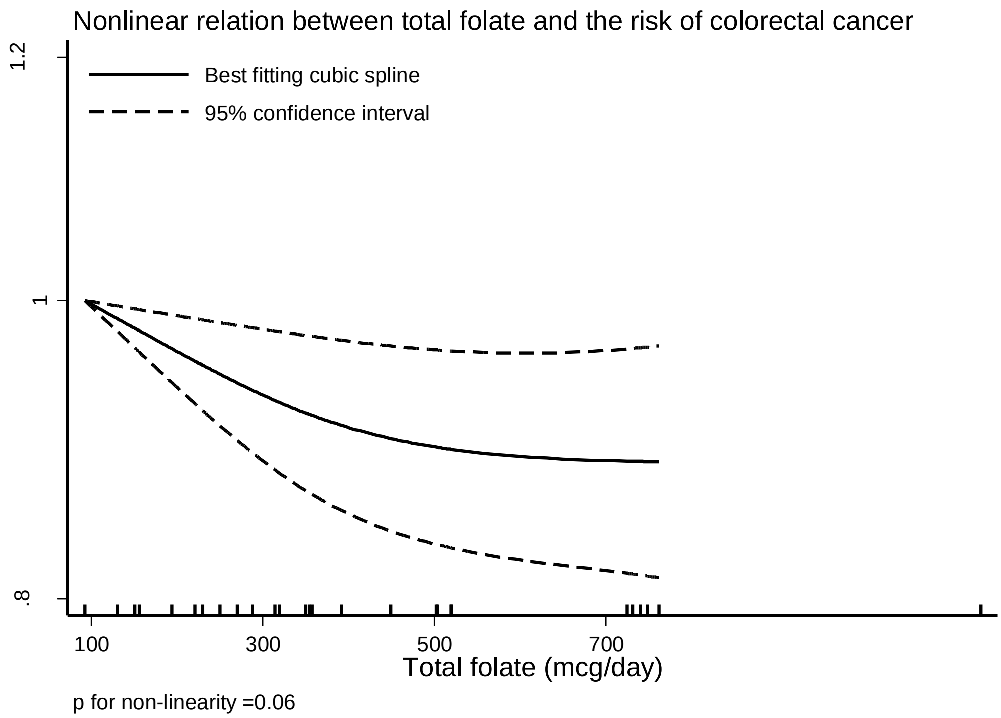


Table 259 Table with total folate values and corresponding RRs (95% CIs) for non-linear analysis of total folate and colorectal cancer

Total folate (mcg/day)	RR(95%CI)
92	1
130	0.8(0.97-0.99)
250	0.95(0.91-0.98)
400	0.91 (0.85-0.97)
520	0.89(0.83-0.96)
760	0.88(0.81-0.96)

Figure 456 RR estimates of colon cancer by levels of total folate

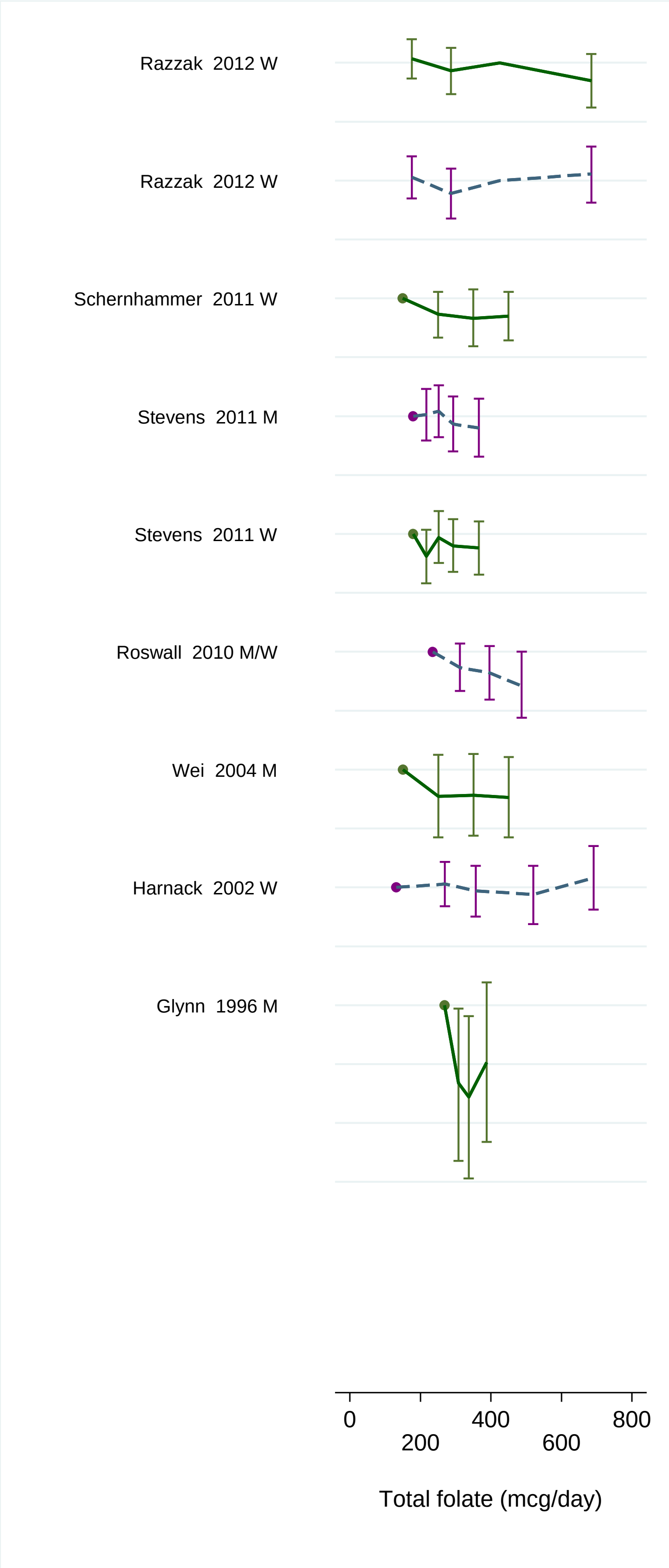
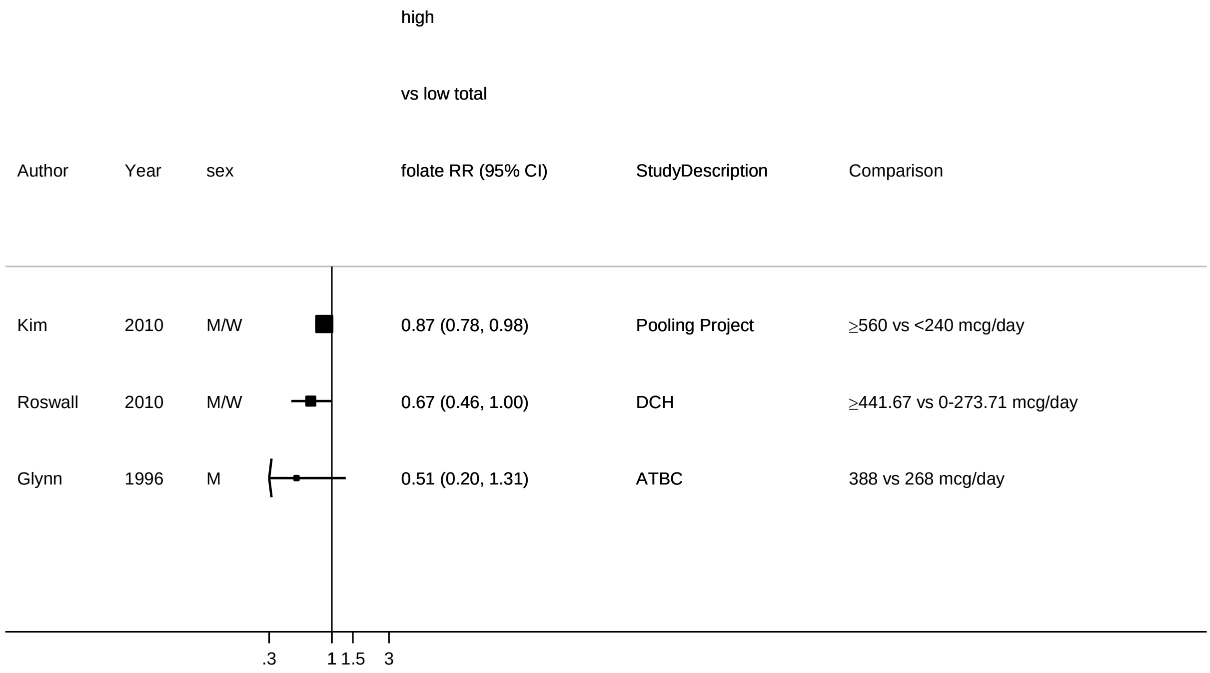
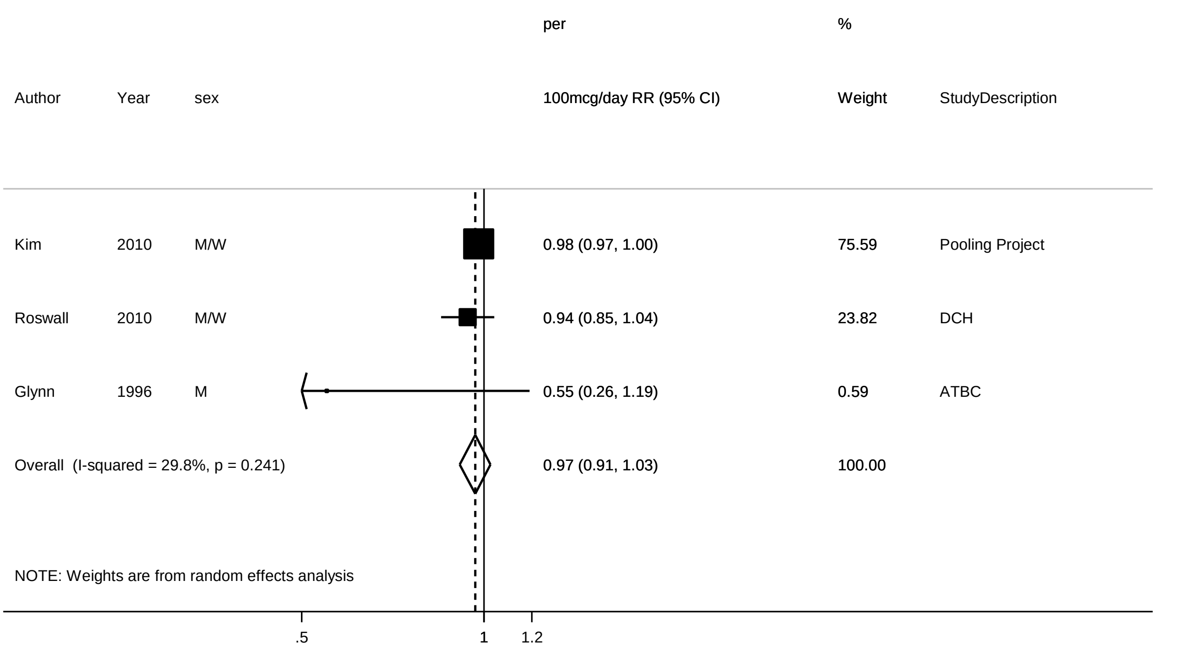


Figure 457 RR (95% CI) of colon cancer for the highest compared with the lowest level of total folate



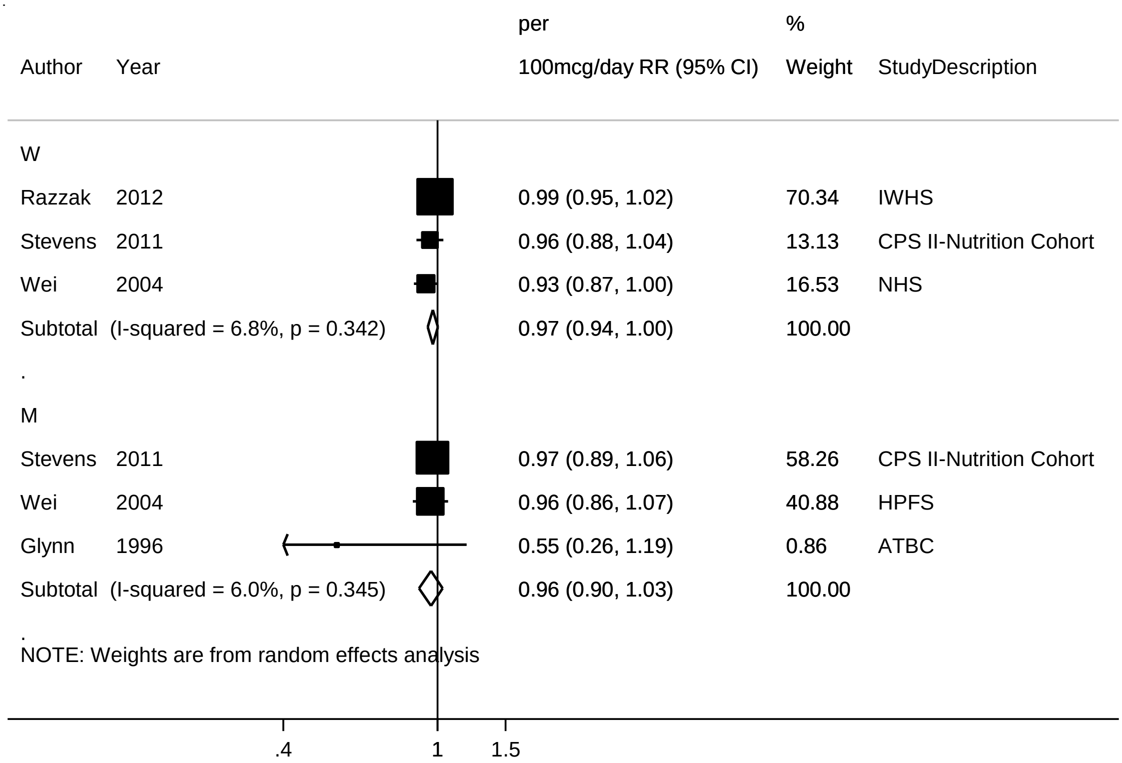
Note: The ATBC study was not included in the Pooling Project (Kim, 2010) for total folate because of the low prevalence of supplement users (< 8%).

Figure 458 RR (95% CI) of colon cancer for 100mcg/day increase of total folate



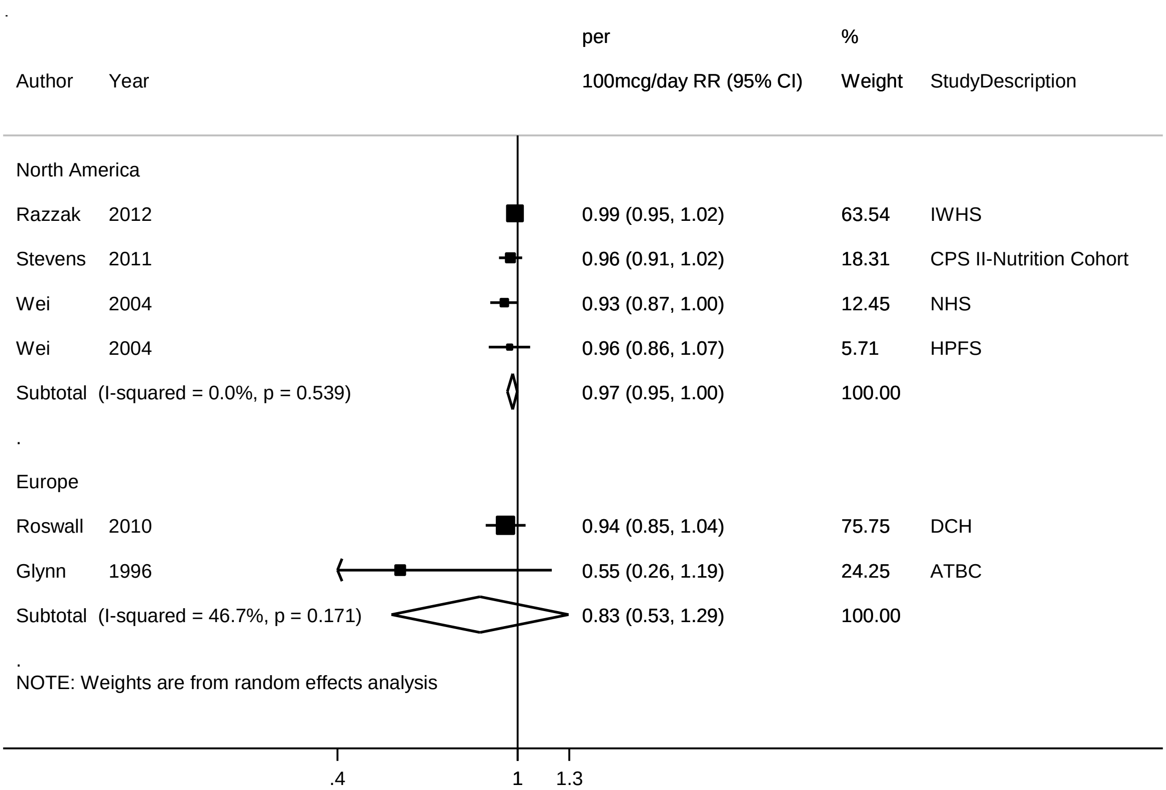
Note: The ATBC study was not included in the Pooling Project (Kim, 2010) for total folate because the low prevalence of supplement users (< 8%).

Figure 459 RR (95% CI) of colon cancer for 100mcg/day increase of total folate by sex



Note: In the Pooling project (Kim, 2010), the associations for men and women were not significantly different from each other (p-value, test for between-studies heterogeneity due to sex for the highest quintile = 0.30) although a stronger association was observed among men (pooled multivariate RR for highest vs. lowest quintile = 0.77, 95% CI 0.57–1.03) than women (pooled multivariate RR = 0.89, 95% CI 0.78–1.01).

Figure 460 RR (95% CI) of colon cancer for 100mcg/day increase of total folate by location



Note: Only North American cohorts were included in the Pooling Project (Kim, 2010) for total folate.

Figure 461 RR estimates of rectal cancer by levels of total folate

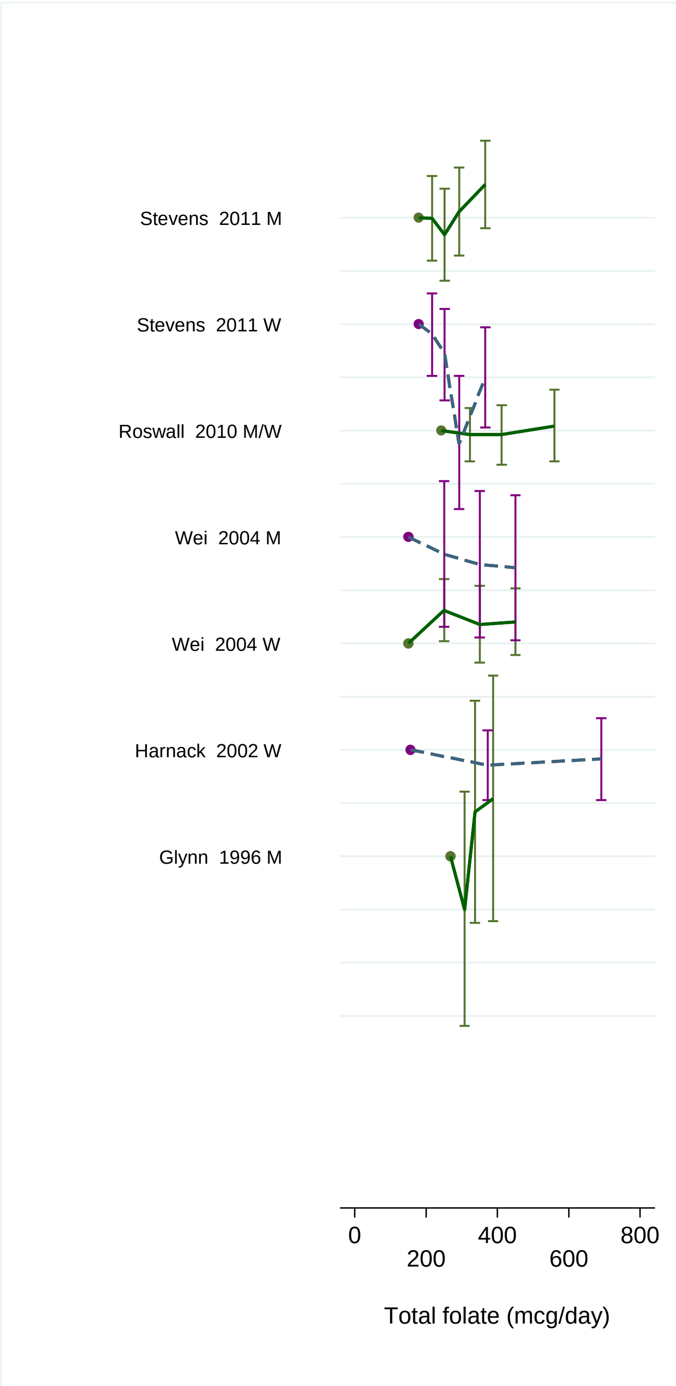


Figure 462 RR (95% CI) of rectal cancer for the highest compared with the lowest level of total folate

Author	Year	sex	high vs low total folate RR (95% CI)	StudyDescription	Comparison
Stevens	2011	W	0.50 (0.26, 0.96)	CPS II-Nutrition Cohort	≥316 vs ≤198 mcg/day
Stevens	2011	M	1.54 (0.87, 2.72)	CPS II-Nutrition Cohort	≥316 vs ≤198 mcg/day
Roswall	2010	M/W	1.06 (0.67, 1.70)	DCH	≥461.23 vs 0-282.8 mcg/day
Zhang	2005	W	0.94 (0.43, 2.03)	WHS	>614 vs ≤258 mcg/day
Wei	2004	W	1.32 (0.86, 2.05)	NHS	>400 vs ≤200 mcg/day
Wei	2004	M	0.67 (0.26, 1.72)	HPFS	>400 vs ≤200 mcg/day
Harnack	2002	W	0.89 (0.52, 1.51)	IWHS	463-2555 vs 32-282
Glynn	1996	M	2.12 (0.43, 10.54)	ATBC	388 vs 268 mcg/day

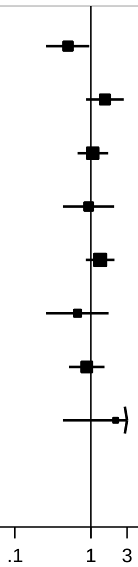


Figure 463 RR (95% CI) of rectal cancer for 100mcg/day increase of total folate

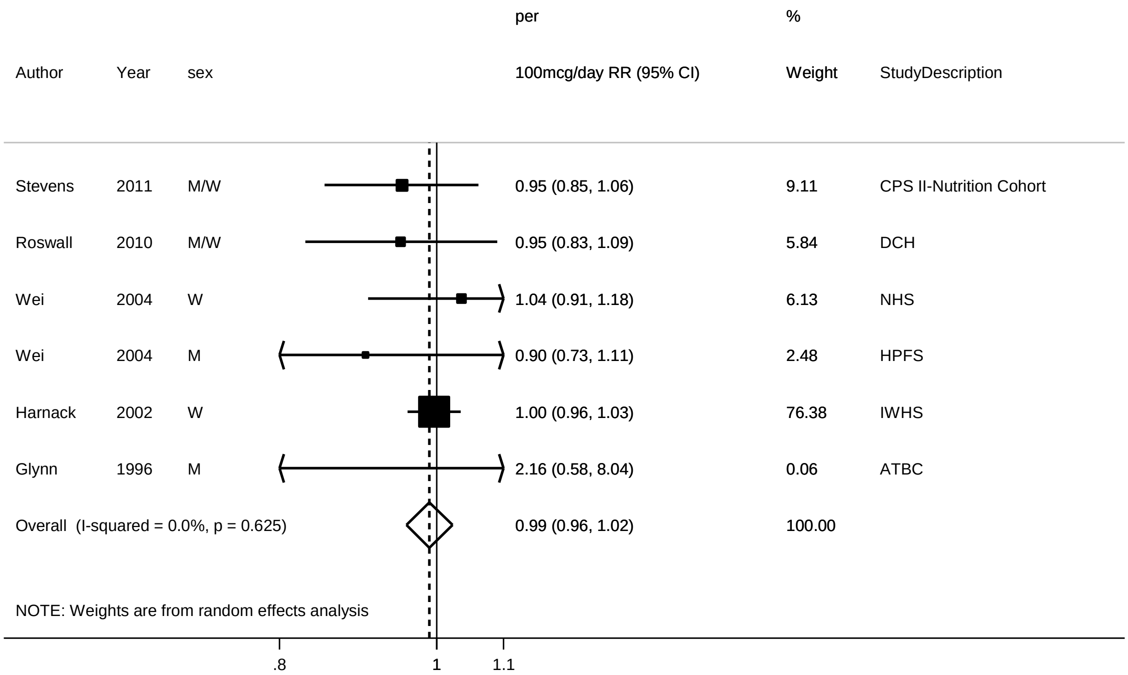


Figure 464 Funnel plot of studies included in the dose response meta-analysis total folate and rectal cancer

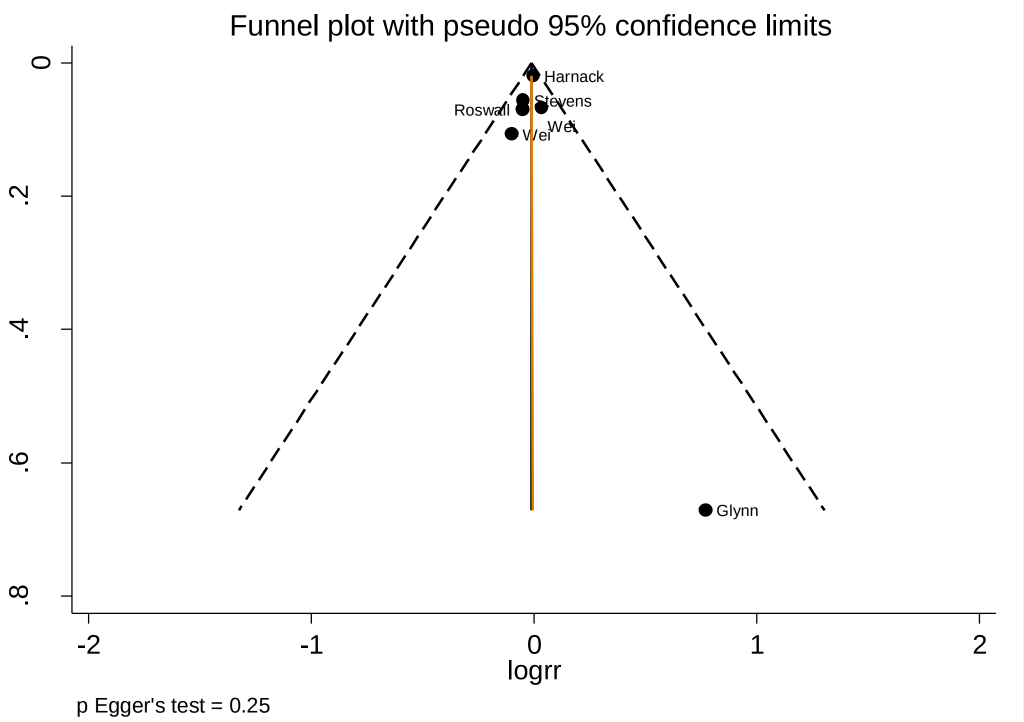


Figure 465 RR (95% CI) of rectal cancer for 100mcg/day increase of total folate by sex

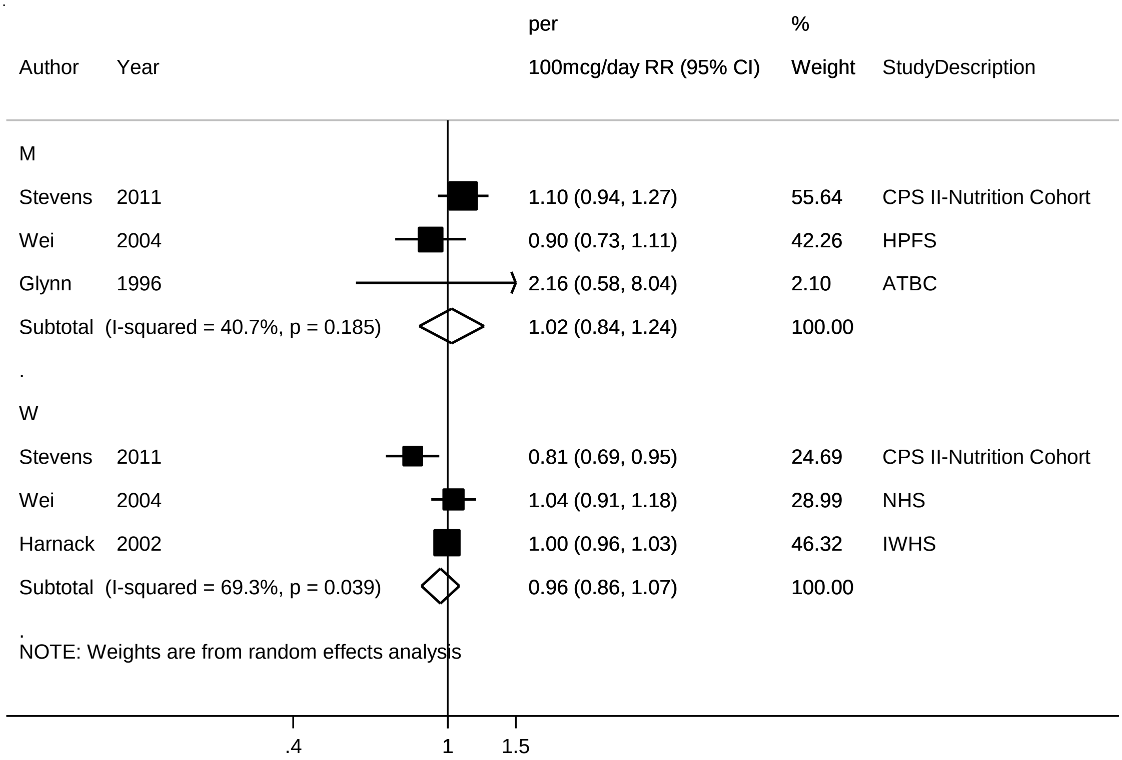
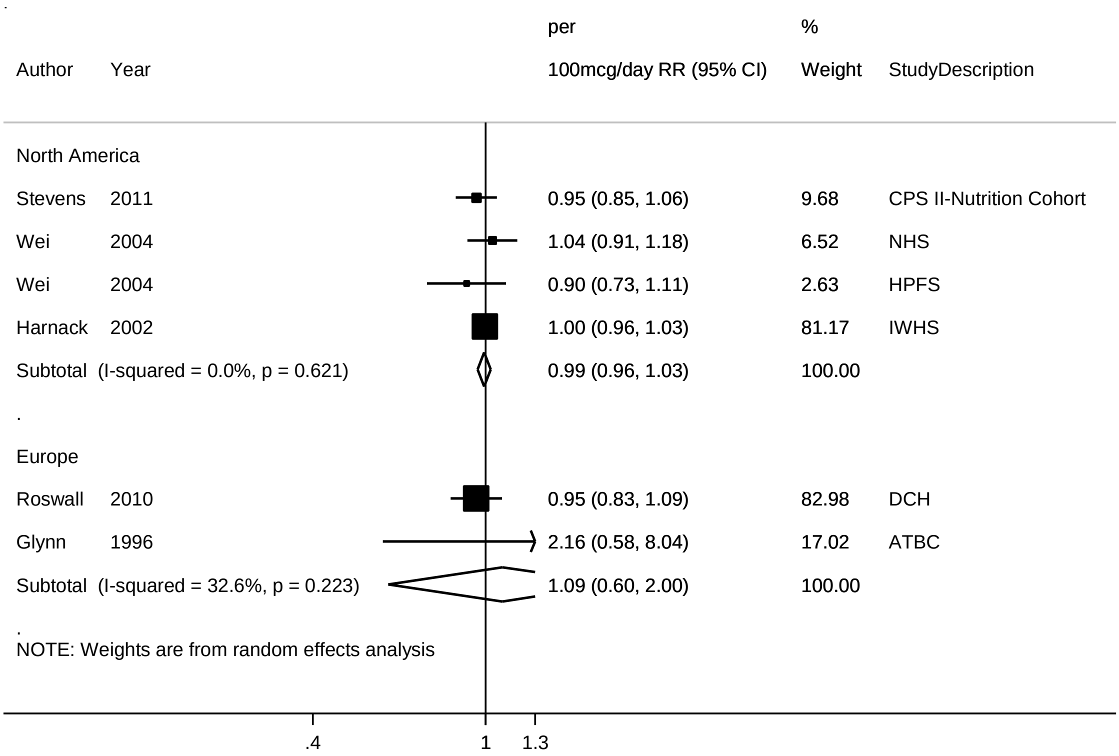


Figure 466 RR (95% CI) of rectal cancer for 100mcg/day increase of total folate by location



5.5.3 Serum/plasma folate

Cohort studies

Summary

Main results:
Five new publications were identified, one superseded a previous publication included in the 2010 SLR the other 4 were new studies.

Colorectal cancer:
Twelve studies (4261 cases) were included in the dose-response meta-analysis of serum/plasma folate and colorectal cancer. A non-significant association with low heterogeneity was observed. All studies showed non-significant results. The association remained not significant after stratification by sex and location. There was no evidence of publication bias (p=0.59). There was evidence of a non-linear association (p<0.001), however this was only significant for very high levels of blood folate which are above the normal range of 20ng/ml of blood folate.
The overall association remained not statistically significant in influence analysis. The summary RRs ranged from 0.99(95% CI=0.97-1.00) when Neuhouser, 2015 was omitted to 0.99(95% CI=0.98-1.00) when Le Marchand, 2009 was omitted.

Colon cancer:
Three studies (1132 cases) were included in the dose-response meta-analysis of serum/plasma and colon cancer. A non-significant association with no heterogeneity was observed. One American study (WHI) represented 98% of the analysis. No stratified analysis was conducted.

Rectal cancer:
Four studies (1620 cases) were included in the dose-response meta-analysis of serum/plasma and rectal cancer. A non-significant association with no heterogeneity was observed. One American study (WHI) represented 96% of the analysis. No stratified analysis was conducted.

Study quality:
Nine studies were on plasma folate and three studies were on serum folate. All studies were multiple adjusted for different confounders. Cancer outcome was confirmed medical records and cancer registry records in most studies. The analysis included studies from North America, were enriched cereal grains are fortified with 140 mg of folic acid per 100 g of flour (Neuhouser, 2015), Asia and Europe were fortification is not mandatory. The results were similar in studies from different countries.

Pooling project of cohort studies:
No Pooling Project was identified.

Meta-analysis of cohort studies:
One meta-analysis of 10 cohorts, representing 3,477 cases and 7,039 controls was identified (Chuang, 2013). The linear and nonlinear models corresponded to relative risks of 0.96 (95% CI= 0.91-1.02) and 0.99 (95% CI=0.96-1.02), respectively, per 10 nmol/L. The pooled relative risks when comparing the highest with the lowest category were 0.80 (95% CI: 0.61, 0.99) for radioimmunoassay and 1.03 (95% CI: 0.83, 1.22) for microbiological assay. The authors suggest that the stronger association for the radioimmunoassay-based studies could reflect differences in cohorts and study designs rather than assay performance. The results from this meta-analysis are comparable with the results found in the CUP.

Table 260 Serum/plasma folate and colorectal cancer risk. Results of meta-analyses and pooled analyses of prospective studies published after the 2010 SLR.

Author, Year	Number of cohort studies	Total number of cases	Studies country, area	Outcome	Comparison	RR (95%CI)	P trend	Heterogeneity (I^2, p value)
Meta-analysis								
Chuang, 2013	10	3,477 cases and 7,039 controls	North America, Europe, Asia	Colorectal cancer	Per 10 nmol/L	0.96 (0.91-1.02)		

Table 261 Serum/plasma folate and colorectal cancer risk. Number of studies in the CUP SLR

	Number
Studies identified	12
Studies included in forest plot of highest compared with lowest exposure	12
Studies included in dose-response meta-analysis	12
Studies included in non-linear dose-response meta-analysis	11

Note: Include cohort, nested case-control and case-cohort designs

Table 262 Serum/plasma folate and colon cancer risk. Number of studies in the CUP SLR

	Number
Studies identified	4
Studies included in forest plot of highest compared with lowest exposure	4
Studies included in dose-response meta-analysis	3
Studies included in non-linear dose-response meta-analysis	NA

Note: Include cohort, nested case-control and case-cohort designs

Table 263 Serum/plasma folate and rectal cancer risk. Number of studies in the CUP SLR

	Number
Studies identified	4
Studies included in forest plot of highest compared with lowest exposure	4
Studies included in dose-response meta-analysis	4
Studies included in non-linear dose-response meta-analysis	NA

Note: Include cohort, nested case-control and case-cohort designs

Table 264 Serum/plasma folate and colorectal cancer risk. Summary of the dose-response meta-analysis in the 2010 SLR and 2015 SLR.

	2010 SLR	**2015 SLR**
Increment unit used	2ng/ml	2ng/ml
Studies (n)	7	12
Cases (total number)	1491	4261
RR (95%CI)	0.97 (0.93-1.00)	0.99(0.98-1.01)
Heterogeneity (I^2, p-value)	0%, 0.46	3.6%, 0.41

Stratified analysis by sex		
Men	**2010 SLR**	**2015 SLR**
Studies (n)	3	5
RR (95%CI)	1.01 (0.86 - 1.20)	1.03(0.98-1.10)
Heterogeneity (I^2, p-value)	0%, 0.94	0%, 0.98
Women		
Studies (n)	4	6

RR (95%CI)	0.97 (0.90 - 1.04)		0.99(0.97-1.02)
Heterogeneity (I^2, p-value)	27%, 0.25		19.3%, 0.29
Stratified analysis by geographic location			
(no analysis in 2005 or 2010 SLR)			
	Asia	**Europe**	**North America**
Studies (n)	3	3	6
RR (95%CI)	0.99(0.90-1.09)	0.99(0.96-1.02)	0.99(0.96-1.02)
Heterogeneity (I^2, p-value)	24.7%, 0.27	0%, 0.92	41.0%,0.13

Table 265 Serum/plasma folate and colon cancer risk. Summary of the dose-response meta-analysis in the 2010 SLR and 2015 SLR.

	2010 SLR	**2015 SLR***
Increment unit used	2ng/ml	2ng/ml
Studies (n)	2	3
Cases (total number)	376	1132
RR (95%CI)	0.98 (0.85-1.14)	1.01(0.99-1.03)
Heterogeneity (I^2, p-value)	0%, 0.44	0%, 0.71

*No Stratified analysis was conducted.

Table 266 Serum/plasma folate and rectal cancer risk. Summary of the dose-response meta-analysis in the 2010 SLR and 2015 SLR.

	2010 SLR	**2015 SLR ***
Increment unit used	2ng/ml	2ng/ml
Studies (n)	3	4
Cases (total number)	306	1620
RR (95%CI)	0.87 (0.70-1.09)	0.96(0.92-1.00)
Heterogeneity (I^2, p-value)	0%, 0.71	0%, 0.72

*No Stratified analysis was conducted.

Table 267 Serum/plasma folate and colorectal cancer risk. Main characteristics of studies included in the CUP SLR dose-response meta-analysis

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Reasons for exclusion
Neuhouser, 2015 COL41054 USA	Women's Health Initiative, Nested Case Control, Age: 50-79 years, W, Postmenopausal	956/ 959 controls	Self-report verified by medical record	Plasma and RBC folate concentrations were determined by radio assay	Incidence, colorectal cancer	≥26.85 vs ≤9.72 ng/ml	0.91 (0.67-1.23)	Age, BMI, colonoscopy, family history of colorectal cancer, postmenopausal hormone use	Mid-points of exposure categories.
		558/ 559 controls			Incidence, proximal colon cancer	≥26.85 vs ≤9.72 ng/ml	0.97 (0.65-1.43)		
		198/ 203 controls			Incidence, distal colon cancer	≥26.85 vs ≤9.72 ng/ml	1.54 (0.71-3.34)		
		182/ 181 controls			Incidence, rectal cancer	≥26.85 vs ≤9.72 ng/ml	0.58 (0.27-1.25)		
Lee, 2012 COL40917 USA	PHS, Nested Case Control, Age: 40-84 years, M, Physicians	240/ 408 controls	Self-reported verified by medical record review	Plasma folate measured using a microbiological method	Incidence, colorectal cancer	11 vs 3.5 ng/ml	1.40 (0.88-2.24)	Age, smoking	Distribution of cases and non-cases by exposure category
Lee, 2012 COL40916 USA	NHS, Nested Case Control, Age: 30-55 years, W, Registered nurses	189/ 377 controls	Self-report verified by medical record	Plasma folate was measured using a radioassay kit (Bio-Rad, Richmond, CA)	Incidence, colorectal cancer	17.6 vs 3.8 ng/ml	1.26 (0.75-2.12)	Age, fasting status at time of blood collection, month of blood draw	Distribution of cases and non-cases by exposure category
Lee, 2012 COL40905 USA	HPFS, Nested Case Control,	173/ 345 controls	Self -report verified by medical record	Plasma folate was measured using a	Incidence, colorectal cancer	11.3 vs 2.9 ng/ml	1.22 (0.71-2.10)	Age, month of blood draw	Distribution of cases and non-cases by

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Reasons for exclusion
	Age: 40-75 years, M, Health professionals			radioassay kit (Bio-Rad, Richmond, CA)					exposure category
Eussen, 2010 COL40822 multi-national	EPIC, Nested Case Control, Age: 35-70 years, M/W	1 327/ 2239 controls	Cancer registry, contact with cancer and pathology registries and active contact of study subjects	Plasma folate was determinated by lactobacillus casei microbiological assay.	Incidence, colorectal cancer	>18.3 vs <7.6 nmol/L	0.91 (0.73-1.14)	Age, sex, alcohol, BMI, date of blood draw, educational level, fibre intake, physical activity, red and processed meat, smoking status, study centre	Distribution of person-years by exposure category. Mid-points of exposure categories.
Le Marchand L, 2009 COL40774 USA	MEC, Nested Case Control, Age: 45-75 years, M/W	223/ 407 controls	SEER registry	Plasma folate, radioimmunoassay method using a commercially available kit from Biorad.	Incidence, colorectal cancer	≥26.2 vs ≤9.94 ng/ml	0.61 (0.33-1.13)	Age, sex, BMI, date of blood collection, ethanol intake, ethnicity, family history of colorectal cancer, fasting condition, health screening, laboratory batch, physical activity, processed meat, smoking, pack-years, study	Mid-points of exposure categories.

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Reasons for exclusion
								centre	
Shrubsole, 2009 COL40772 China	SWHS, Nested Case Control, Age: 40-70 years, W	303/ 1188 controls	Cancer registry/death certificates/questionnaires	Plasma folate level were analysed using microbiological assay	Incidence, colorectal cancer	11.1-304 vs 2.04-7.54 ng/ml	1.20 (0.80-1.70)	Age, alcohol consumption, BMI, calcium intake, diabetes, educational attainment, energy intake, family history of colorectal cancer, fruit intake, history of polyps, HRT use, Income, menopausal status, nsaid use, physical activity, red meat intake, smoking status, vegetable intake, vitamin use	Mid-points of exposure categories.
Otani, 2008 COL40673 Japan	JPHC, Nested Case Control, Age: 40-69 years, M/W	163/ 324 controls 11.5 years	Cancer registry and death certificates	Plasma folate measured by chemiluminescence immunoassay,	Incidence, colorectal cancer, men	≥8.6 vs ≤5.5 ng/ml	0.86 (0.45-1.60)	Age, alcohol intake, BMI, date of blood collection, family history of colorectal cancer, fasting condition, pack-years of smoking,	
		160/ 297 controls			Women	≥10.6 vs ≤6.7 ng/ml	1.00 (0.56-1.90)		
		119/ 237 controls			Incidence, colon cancer, men	≥8.6 vs ≤5.5 ng/ml	0.82 (0.39-1.70)		
		106/ 195 controls			Women	≥10.6 vs ≤6.7 ng/ml	0.97 (0.47-2.00)		

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Reasons for exclusion
		54/ 102 controls			Incidence, rectal cancer, women	≥10.6 vs ≤6.7 ng/ml	1.50 (0.38-5.50)	physical activity, study area, vitamin use	
		44/ 87 controls			Men	≥8.6 vs ≤5.5 ng/ml	0.63 (0.11-3.60)		
Weinstein, 2008 COL40687 Finland	ATBC, Nested Case Control, Age: 50-69 years, M	275/ 275 controls 14.2 years	Cancer registry	Serum folate by radioassay	Incidence, colorectal cancer	12.9 vs 5.7 nmol/l	1.07 (0.60-1.91)	Age, BMI, date of blood collection, Iron intake, physical activity, vitamin d	Exposure unit in nmol/l, divided by conversion factor 2.266 to convert to ng/ml
		151/ 151 controls			Incidence, colon cancer	12.9 vs 5.7 nmol/l	1.41 (0.62-3.23)		
		126/ 126 controls			Incidence, rectal cancer	12.9 vs 5.7 nmol/l	0.67 (0.27-1.71)		
Rossi, 2006 COL40759 Australia	Busselton (Western Australia) Health Survey, 1969, Prospective Cohort, Age: 40-90 years, M/W	41/ 1 988 29 years	Death register	Serum folate By microbiological assay system	Incidence, colorectal cancer	per 2 mcg/litre	0.83 (0.62-1.10)	Age, sex, alcohol intake, BMI, smoking habits	
Van Guelpen B, 2006 COL40681 Sweden	NSHDC, Nested Case Control, Age: 25-74 years, M/W	221/ 432 controls 4.2 years	Cancer registry	Plasma folate by Quantaphase II radioassay	Incidence, colorectal cancer	≥15 vs ≤4.9 nmol/l	1.01 (0.47-2.19)	Age, sex, alcohol intake, BMI, date of enrolment, fasting condition, physical activity, smoking status,	Mid-points of exposure categories.
		82/ 157 controls			Incidence, rectal cancer	Q 5 vs Q 1	0.50 (0.15-1.55)		

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Reasons for exclusion
								study centre	
Kato, 1999 COL00436 USA	New York University Women's Health Study, Nested Case Control, Age: 62 years, W	150/ 81	Follow-up questionnaire	Serum folate was measure by immunoassay	Incidence, colorectal cancer,	≥31.04 vs ≤12.23 nmol/l	0.52 (0.27-0.97)	Age, beer consumption, date of enrolment, date of subsequent blood, family history of specific cancer, menopausal status, occult blood testing, physical activity	Distribution of cases and non cases by exposure category. Mid-points of exposure categories.

Table 268 Serum/plasma folate and colorectal cancer risk. Main characteristics of studies excluded from the CUP SLR dose-response meta-analysis

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Reasons for exclusion
Ma, 1997 COL40780 USA	PHS, Nested Case Control, Age: 40-84 years, M	202/ 326 controls 12 years	Medical records	Plasma measured microbiologically	Incidence, colorectal cancer	deficient vs adequate ng/ml	1.78 (0.93-3.42)	Age, alcohol consumption, aspirin use, BMI, multivitamin supplement intake, physical activity, smoking status	Binary result only. Superseded by Lee, 2012 COL40917
Glynn, 1996 COL00161 Finland	ATBC, Nested Case Control, Age: 50-69 years, M, Male Smokers	86/ 159 controls 8 years	Cancer registry	Serum folate	Incidence, colon cancer	>2.9 vs ≤ 2.9ng/ml	0.73	Unadjusted	Superseded by Weinstein, 2008 COL40687. Reviewed in text, CI mentioned to include 1.0
		50/ 90 controls			Incidence, rectal cancer		2.43		

Figure 467 RR estimates of colorectal cancer by levels of serum/plasma folate

Figure 468 RR (95% CI) of colorectal cancer for the highest compared with the lowest level of serum/plasma folate

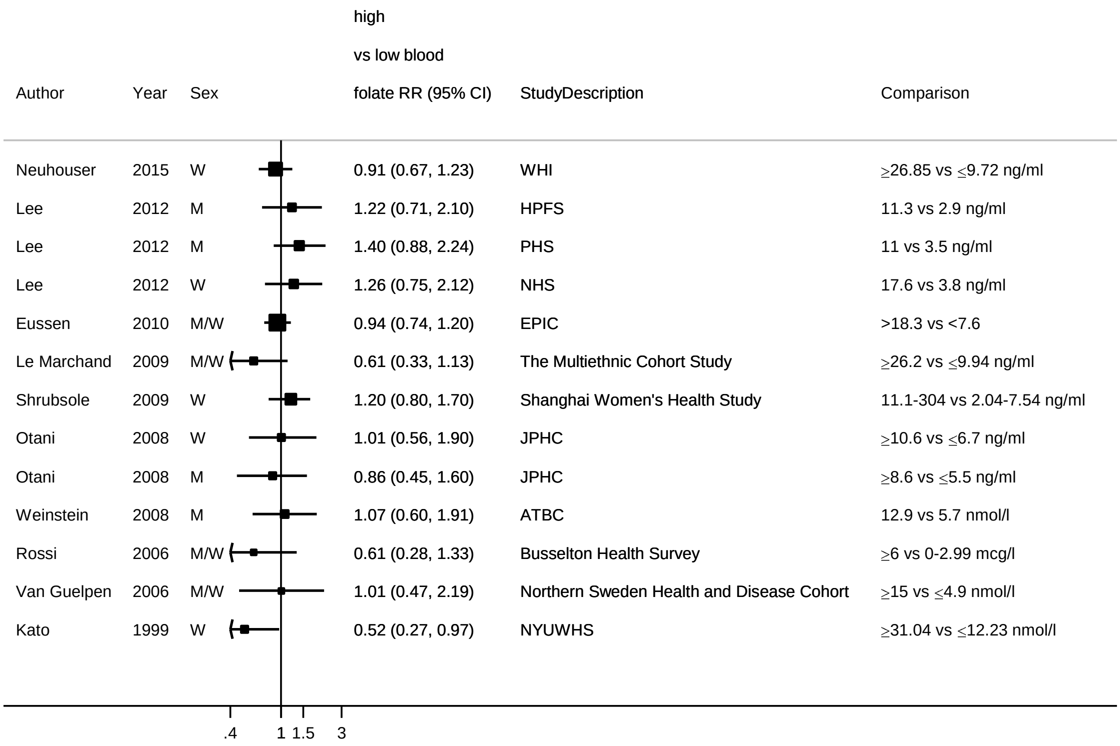


Figure 469 RR (95% CI) of colorectal cancer for 2ng/ml increase of serum/plasma folate

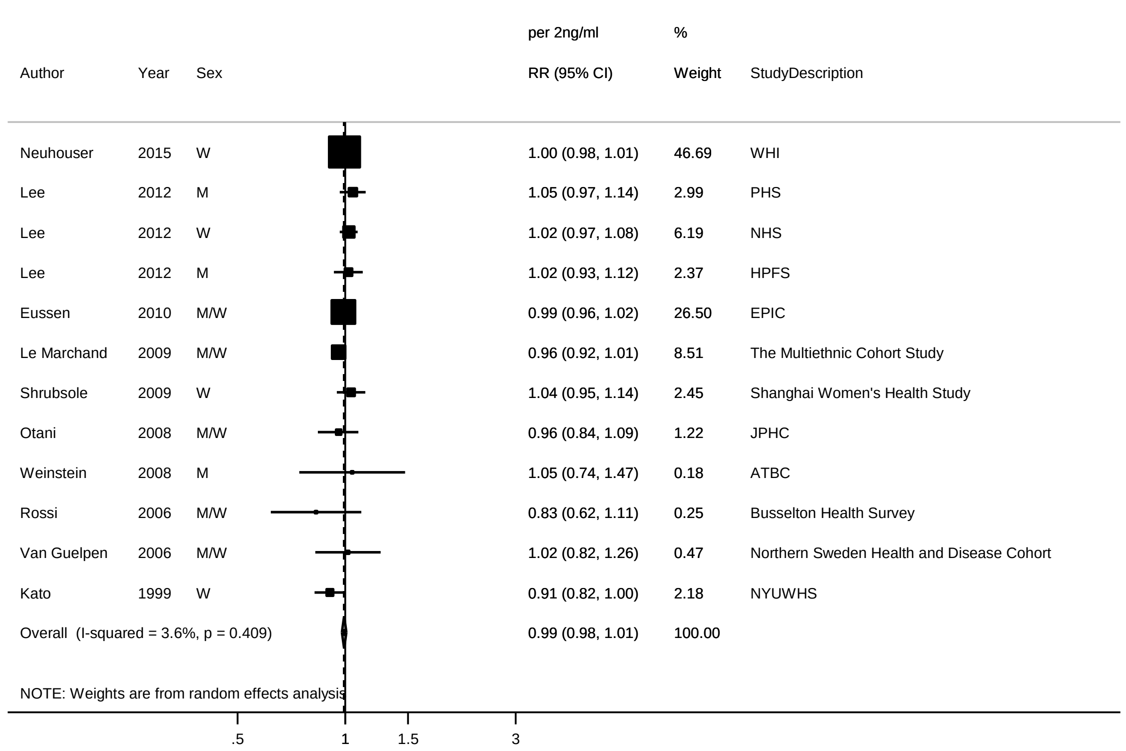


Figure 470 Funnel plot of studies included in the dose response meta-analysis serum/plasma folate and colorectal cancer

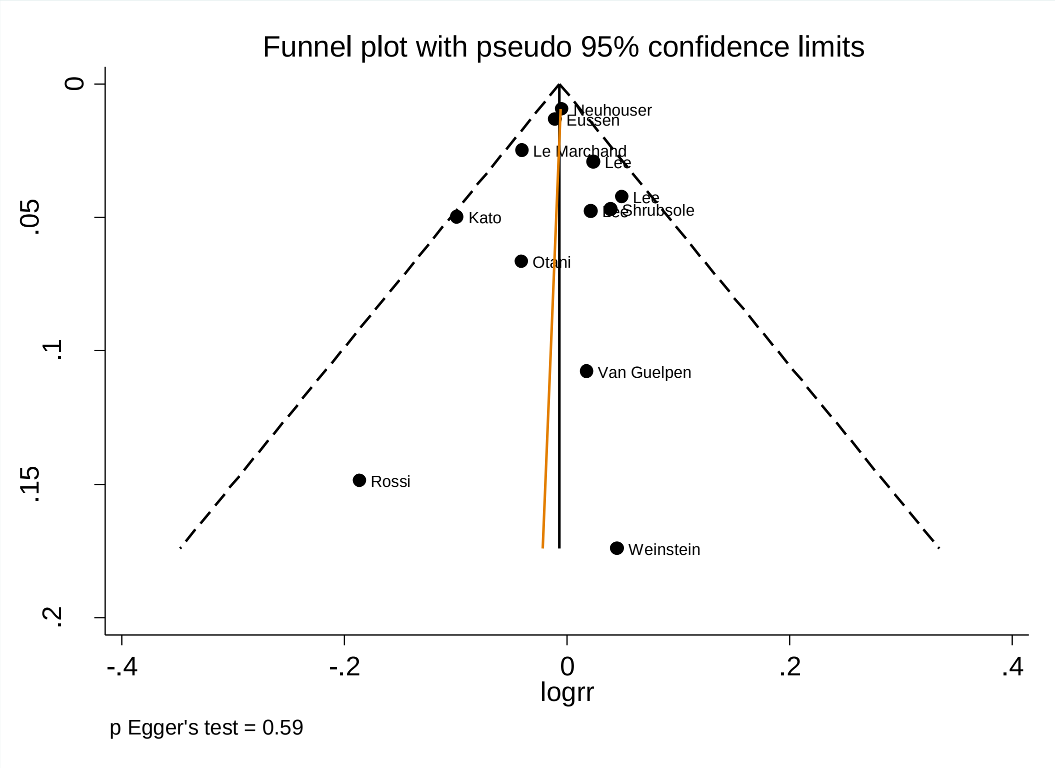


Figure 471 RR (95% CI) of colorectal cancer for 2ng/ml increase of serum/plasma folate by sex

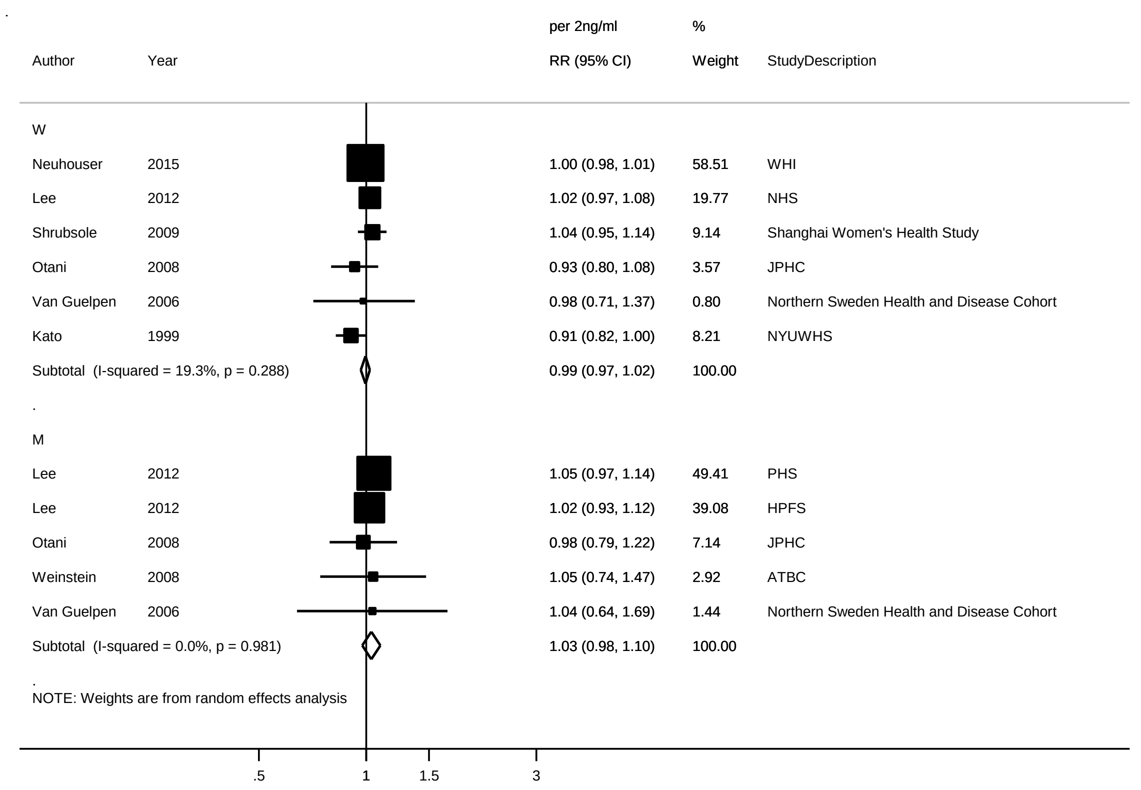


Figure 472 RR (95% CI) of colorectal cancer for 2ng/ml increase of serum/plasma folate by location

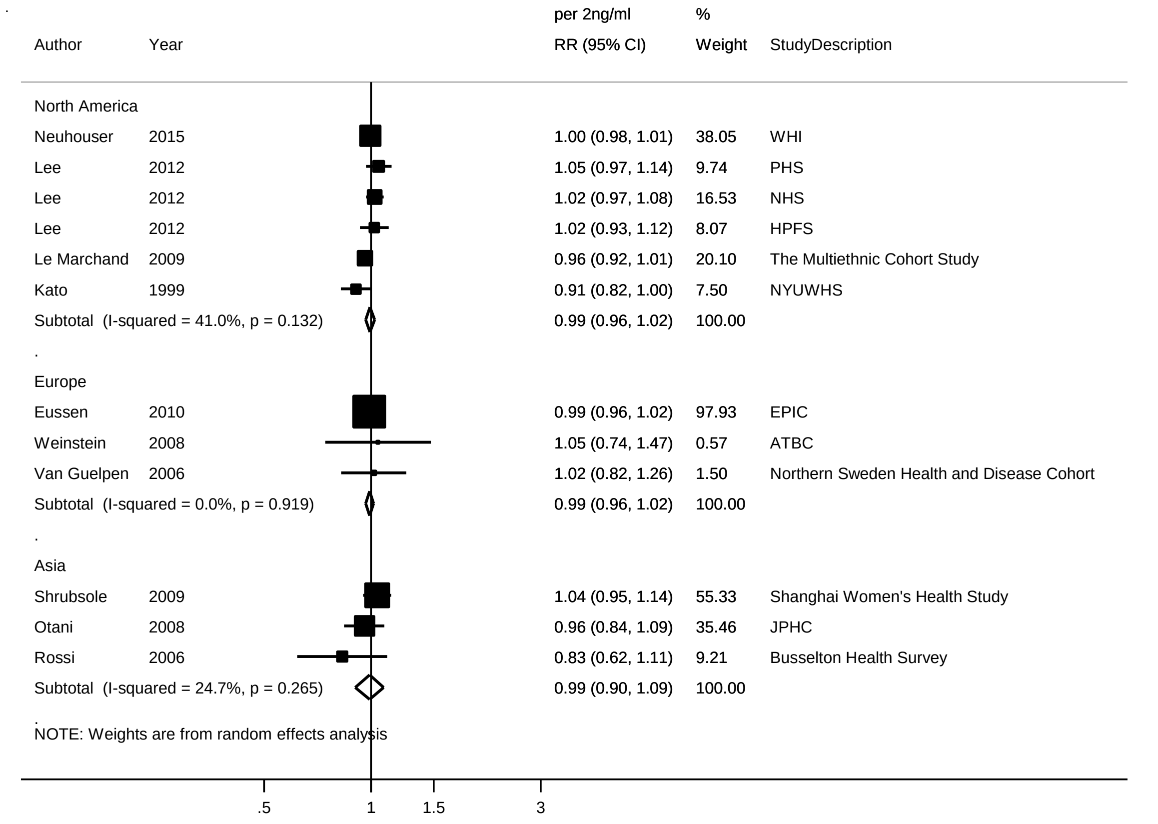
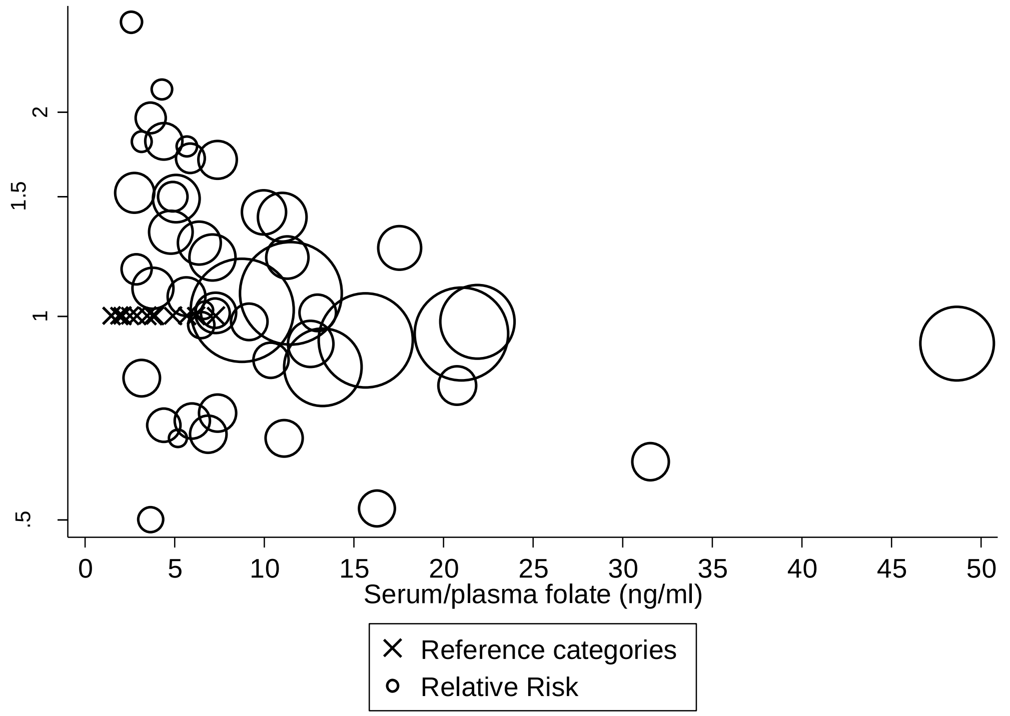


Figure 473 Relative risk of colorectal cancer and serum/plasma folate estimated using non-linear models



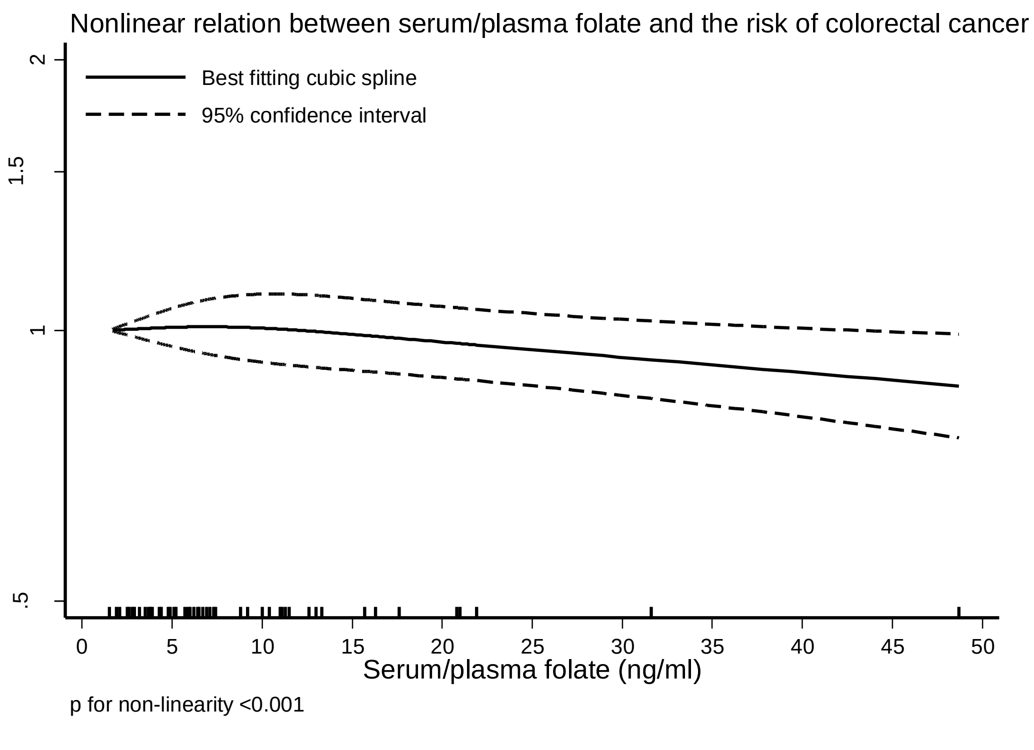


Table 269 Table with serum/plasma folate values and corresponding RRs (95% CIs) for non-linear analysis of serum/plasma folate and colorectal cancer

Serum/plasma folate (ng/ml)	RR(95%CI)
1.5	1
5	1.00(0.96-1.06)
10	1.00(0.92-1.09)
15	0.98(0.90-1.08)
30	0.92(0.84-1.02)
50	0.87(0.76-0.99)

Figure 474 RR estimates of colon cancer by levels of serum/plasma folate

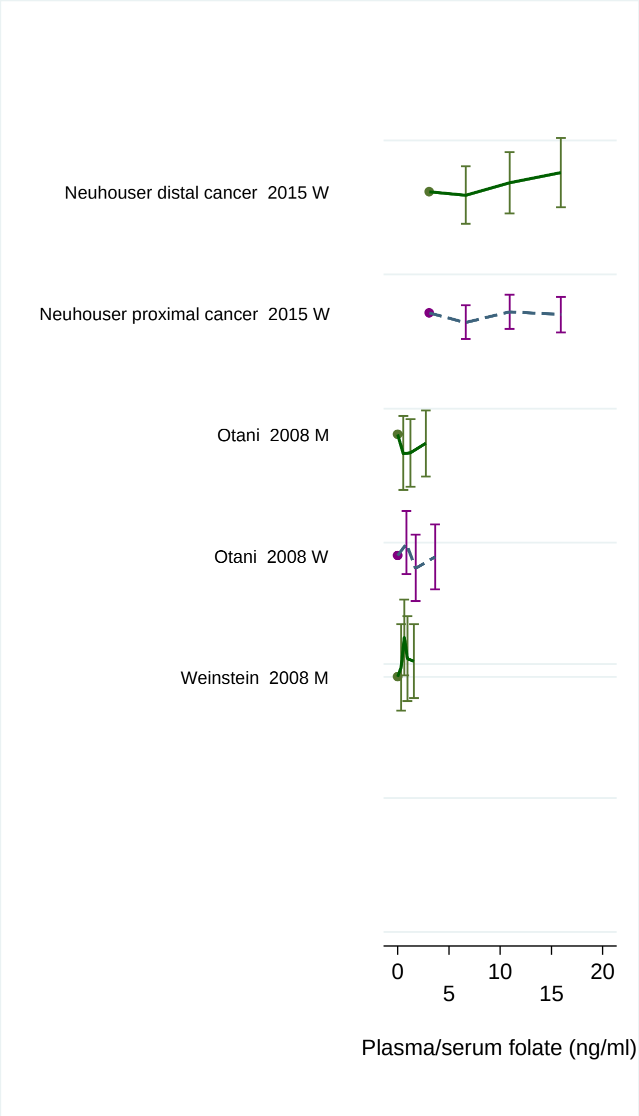


Figure 475 RR (95% CI) of colon cancer for the highest compared with the lowest level of serum/plasma folate

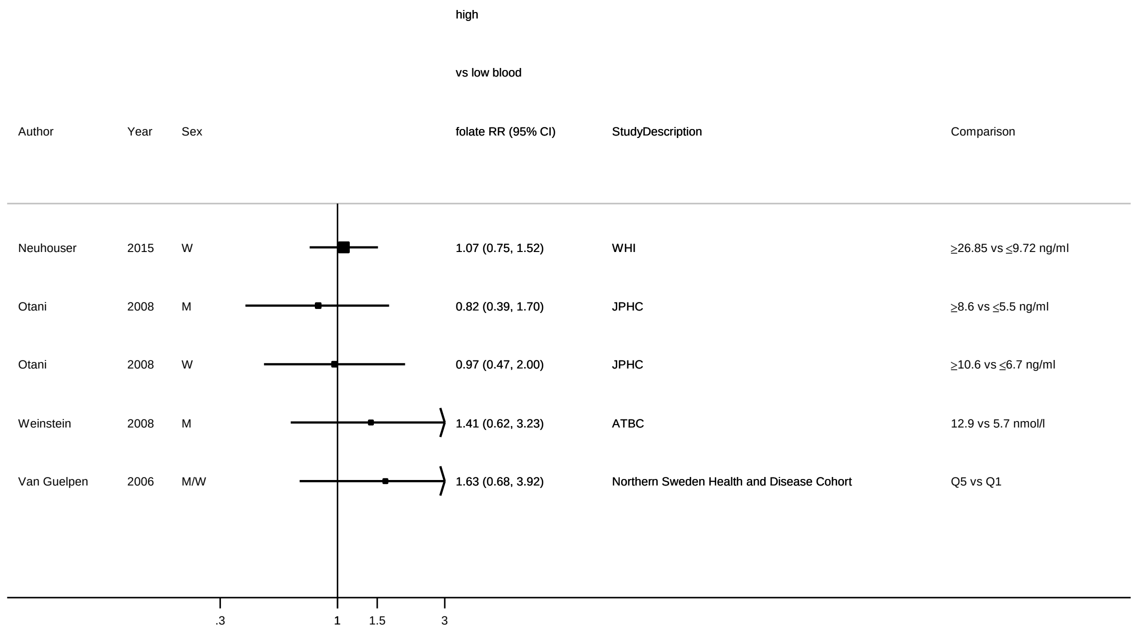


Figure 476 RR (95% CI) of colon cancer for 2ng/ml increase of serum/plasma folate

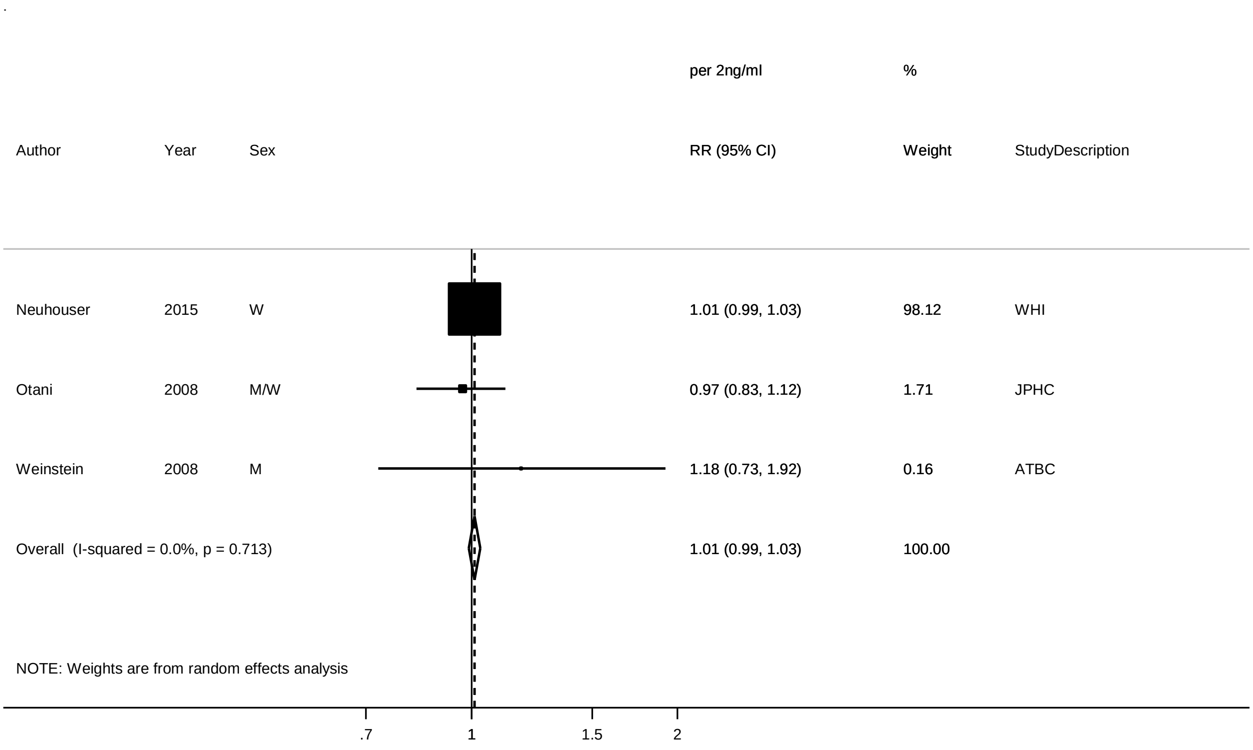


Figure 477 RR estimates of rectal cancer by levels of serum/plasma folate

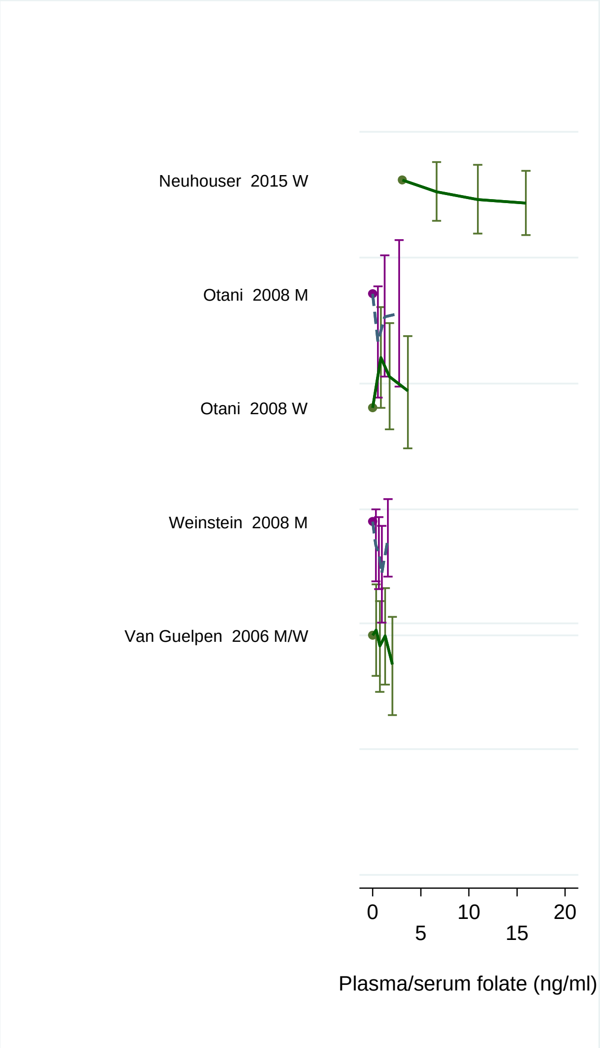


Figure 478 RR (95% CI) of rectal cancer for the highest compared with the lowest level of serum/plasma folate

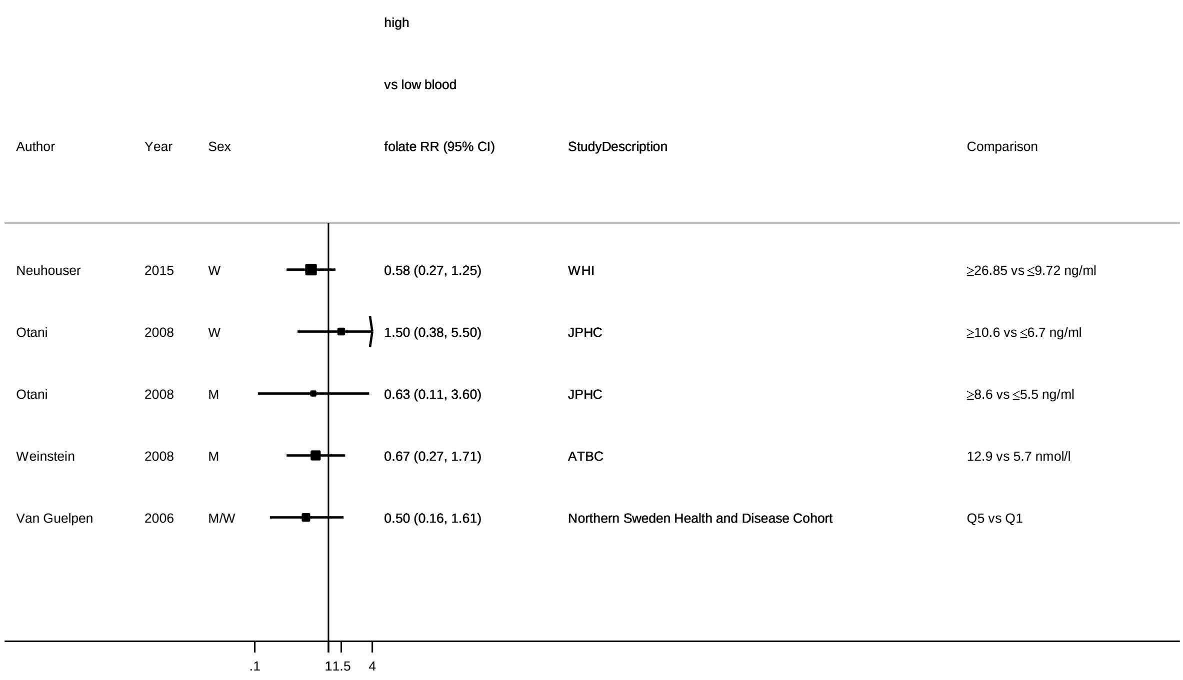
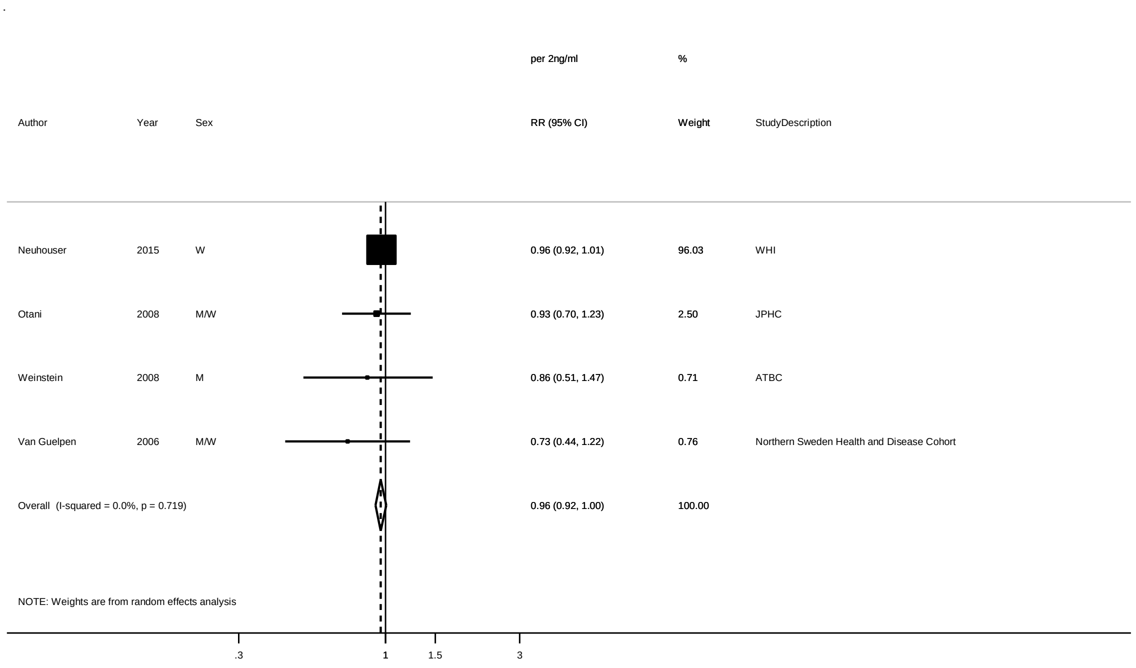


Figure 479 RR (95% CI) of rectal cancer for 2ng/ml increase of serum/plasma folate



5.5.7 Dietary vitamin B6

Colorectal cancer:
Six new studies were identified after the SLR 2010. No analysis was conducted during the SLR 2010. In total, 8 studies (7 047 cases) were included in the dose-response meta-analysis. No significant association was observed. High heterogeneity was observed. There was no evidence of publication bias (p=0.08). The visual inspection of funnel plot shows that the study of de Vogel, 2008 was an outlier.
In influence analysis, the summary RR's ranged from 0.88 (95% CI: 79-0.98) when de Vogel, 2008 was omitted to 0.93 (95% CI: 0.83-1.04) when Ishihara, 2007 was omitted.
There was evidence of a non-linear association between higher intakes of dietary vitamin B6 and colorectal cancer risk (p=0.05). However, the inverse association was not significant with intakes of more than 1.60 mg/day.

Colon cancer:
Four studies were identified including one new study (Bassette, 2013). No dose-response meta-analysis was conducted. Three studies showed no significant association between vitamin B6 intake and colon cancer (Schenhammer, 2008; Larsson, 2005; Harnack, 2002). The study of Bassett, 2013 suggested a U-shaped association between colon cancer risk and vitamin B6 intake.

Four studies were identified for proximal and distal colon cancer and dietary vitamin B6 intake, including one new study (Razzak, 2012). No met-analysis was conducted. Four studies reported no significant associations of proximal and distal colon cancer with dietary vitamin B6 intake (Razzak, 2012; de Vogel, 2008; Zhang, 2006; Harnack, 2002).

Rectal cancer:
Five studies were identified including one new study (Bassette, 2013). No dose-response meta-analysis was conducted. Four studies reported no significant associations (Bassette, 2013; de Vogel, 2008; Zhang, 2006; Harnack, 2002). The study of Larsson, 2005 showed an inverse dose-response relationship between vitamin B6 intake and rectal cancer.

Study quality:
Cancer outcome was confirmed using records in cancer registries in most studies. The relative risks estimates in all studies were adjusted for potential confounders.

Pooled analysis of cohort studies:
No pooled analysis was identified.

Meta-analysis:
A meta-analysis (Larsson, 2010) of 9 cohort studies found no significant association for dietary vitamin B6 intake and colorectal cancer risk. However, in sensitivity analyses

excluding one cohort study (de Vogel, 2008) a significant inverse association was found for the highest vs lowest categories of vitamin B6 intake (0.80 (95% CI:0.69-0.92)).

Table 270 Dietary vitamin B6 and colorectal cancer risk. Number of studies in the CUP SLR

	Number
Studies identified	12
Studies included in forest plot of highest compared with lowest exposure	10
Studies included in dose-response meta-analysis	8
Studies included in non-linear dose-response meta-analysis	8

Note: Include cohort, nested case-control and case-cohort designs

Table 271 Dietary vitamin B6 and colorectal cancer risk. Summary of the dose-response meta-analysis in the 2010 SLR and 2015 SLR.

	2010 SLR (no analysis)	**2015 SLR**
Increment unit used		2 mg/day
Studies (n)		8
Cases (total number)		7 047
RR (95%CI)		0.91 (0.81-1.02)
Heterogeneity (I^2, p-value)		67.1%, 0.003

Stratified analysis by geographic location (no analysis in 2005 SLR or 2010 SLR)				
2015 SLR	**Asia**	**Australia**	**Europe**	**North America**
Studies (n)	2	1	2	3
RR (95%CI)	0.77 (0.62-0.96)	1.00 (0.90-1.11)	0.96 (0.591.57)	0.91 (0.76-1.09)
Heterogeneity (I^2, p-value)	0%, 0.62		89.8%, 0.002	70.9, 0.03

Table 272 Dietary vitamin B6 and colorectal cancer risk. Results of meta-analyses and pooled analyses of prospective studies published after the 2010 SLR.

Author, Year	Number of cohort studies	Total number of cases	Studies country, area	Outcome	Comparison	RR (95%CI)	P trend	Heterogeneity (I^2, p value)
Meta-analysis								
Larsson, 2010	8		Worldwide	Incidence, colorectal cancer	Highest vs lowest	0.90 (0.75-1.07)		56.2%, 0.01

Table 273 Dietary vitamin B6 and colorectal cancer risk. Main characteristics of studies included in the CUP SLR dose-response meta-analysis

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Missing data derived for analyses
Bassett, 2013 COL40980 Australia	MCCS, Prospective Cohort, Age: 27-80 years, M/W	910/ 37 109 15 years	Cancer registry and death registry	121 items FFQ	Incidence, colorectal cancer	3.88 vs 1.33 mg/day	1.01 (0.82,1.23)	Sex, alcohol, cereal fibre, country of birth, educational level, family history of cancer, physical activity, smoking. Age in time axis	
						Per 1 SD	1.01 (0.94,1.08)		
		581/			Incidence, colon cancer	3.88 vs 1.33 mg/day	0.97 (0.76,1.24)		
						Per 1 SD	1.01 (0.93,1.10)		
		326/			Incidence, rectal cancer	3.88 vs 1.33 mg/day	1.08 (0.75,1.56)		
						Per 1 SD	0.99 (0.89,1.11)		
Zschäbitz, 2013 COL40934 USA	Women's Health Initiative - Observational study, Prospective Cohort, W, Postmenopausal	808/ 88 045 11 years	Self-report verified by medical record	122 items FFQ Natural folate and folic acid from fortification	Incidence, colorectal cancer	1.16 vs > 1.99 mcg/day	0.80 (0.66-0.97)	Age, BMI, history of colonoscopy, ethnicity, hormone use, physical activity, smoking	Distribution of person-years by exposure category Mid-points of exposure categories
Razzak, 2012 COL40928 USA	IWHS, Prospective Cohort, Age: 55-69 years, W	1 298/ 35 216	Cancer registry and national death Index	126 items Willett FFQ	Incidence, colorectal cancer	≥3.89 vs ≤1.72 mg/day	1.08 (0.86–1.35)	Age, BMI, waist to hip ratio, diabetes, exogenous estrogen use, physical activity, smoking status, and daily intakes	Mid-points of exposure categories
		673/			Incidence, proximal colon cancer		0.96 (0.69–1.32)		
		597/			Incidence, distal colon cancer		1.23 (0.88–1.70)		

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Missing data derived for analyses
								of total energy, total fat, sucrose, red meat, calcium, vitamin E and alcohol	
Shrubsole, 2009 COL40773 China	SWHS, Prospective Cohort, Age: 40-70 years, W	394/ 72 861	Cancer registry/death certificates/questionnaires	FFQ	Incidence, colorectal cancer	2.33 vs 1.36 mg/day	0.7 (0.4-1.2)	Age, educational level, household income, BMI, smoking, HRT use,drinking status, physical activity, menopausal status, family history colorectal cancer, NSAID use, B vitamin supplement, history of colorectal polyps, diabetes, intakes of energy, fruits, vegetables, red meats, and calcium	Distribution of person-years by exposure category
de Vogel, 2008 COL40646 Netherlands	NLCS, Prospective Cohort, Age: 55-69	1 389/ 4 774 13.3 years	Cancer registry	Semi-quantitative FFQ	Incidence, Colorectal cancer, men	1.88 vs 1.22 mg/day	1.29 (0.90–1.84)	Age, alcohol intake, BMI, smoking status, family history of	
		960/			Colorectal,	1.63 vs 1.05	1.39 (0.92-2.08)		

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Missing data derived for analyses
	years, M/W				Women	mg/day		colorectal cancer, and dialy intakes of energy, calcium, fat, fibre, iron, meat, methionine, riboflavin, vitamin b6 intake	
		467/			Distal colon cancer, men	1.88 vs 1.22 mg/day	1.03 (0.60–1.76)		
		296/			Distal colon cancer, women	1.63 vs 1.05 mg/day	1.06 (0.56–2.03)		
		386/			Proximal colon cancer, women	1.63 vs 1.05 mg/day	1.15 (0.65–2.04)		
		382/			Proximal colon cancer, men	1.88 vs 1.22 mg/day	1.50 (0.86–2.62)		
		360/			Rectal cancer, men	1.88 vs 1.22 mg/day	1.35 (0.76–2.41)		
		176/			Rectal cancer, women	1.63 vs 1.05 mg/day	3.57 (1.56–8.17)		
Ishihara, 2007 COL40641 Japan	JPHC, Prospective Cohort, M/W	335/ 81 184 5.8 years	Periodic Institutional reports from hospitals, cancer registries, death cert.	138 items FFQ	Incidence, colorectal cancer, men	1.91 vs 1.09 mg/day	0.69 (0.48-0.98)	Age, BMI, physical activity, smoking status, study area, alcohol consumption, intakes of calcium, meat, vitamin D supplements	
		191/			Incidence, colorectal cancer, women	1.8 vs 1.02 mg/day	1.10 (0.67-1.83)		
Zhang, 2006 COL40742 USA	WHS, Prospective Cohort, Age: 45- years, W,	220/ 37 916 10.1 years	Self-report, death report, national death Index, medical records	131-item FFQ	Incidence, colorectal cancer	≥2.40 vs <1.69 mg/day	0.84 (0.56-1.27)	Age, alcohol consumption, aspirin use, BMI, family history of	Distribution of person-years by exposure category

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Missing data derived for analyses
	Health professionals		reviewed by physicians					colorectal cancer in first degree relatives, history of polyps, menopausal status, physical activity, postmenopausal hormone use, randomized treatment assignment, red meat intake, smoking status, total energy intake	Mid-points of exposure categories
Larsson, 2005 COL01852 Sweden	SMC, Prospective Cohort, Age: 40-75 years, W	805/ 61 433 911 042 person-years	Cancer registry	Questionnaire	Incidence, colorectal cancer	≥2.05 vs <1.53 mg/day	0.66 (0.50–0.86)	Age, beta carotene, BMI, calcium, cereal fibre, educational level, methionine, red meat intake, saturated fat, total energy, vitamin b6	Distribution of person-years by exposure category Mid-points of exposure categories
		252/			Incidence, rectal cancer		0.75 (0.54–1.04)		
		547/			Incidence, colon cancer		0.50 (0.31–0.82)		

Table 274 Main characteristics of studies excluded from the CUP SLR dose-response meta-analysis.

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Reasons for exclusion
Jung, 2014 COL41011 Netherlands	GEOL, Prospective Cohort, Age: 18-20 years, M/W	122/ 470 28 months	colonoscopy examination	FFQ	Incidence, colorectal cancer	> 2 vs ≤ 1.75 mg/day	0.98 (0.59-1.62) MMR mutation carriers	Age, sex, number of colonoscopies during person-time, NSAID use, and physical activity	Genotyping data
Nishahara, 2014 COL41036 USA	NHS-HPFS Prospective Cohort, Age: 30-75 years, M/W	993/ 3 206 985 person-years	medical records and national death index	FFQ	Incidence, colorectal cancer	Q5 vs Q1	0.98 (0.74-1.31)	Age, year, sex	Used in HvsL analysis only No specific quintiles
Le Marchand, 2005	MEC, Nested case-control study	822 cases/ 2 021 controls		FFQ	Incidence, colorectal cancer	2.46 vs 1.63 mg/day	0.68 (0.51-0.91) MTHFR CC 0.87 (0.64-1.20) MTHFR CT 0.53 (0.32-0.86) MTHFR TT	Age at blood draw, sex, race/ethnicity	Genotype data

Figure 480 RR estimates of colorectal cancer by levels of dietary vitamin B6

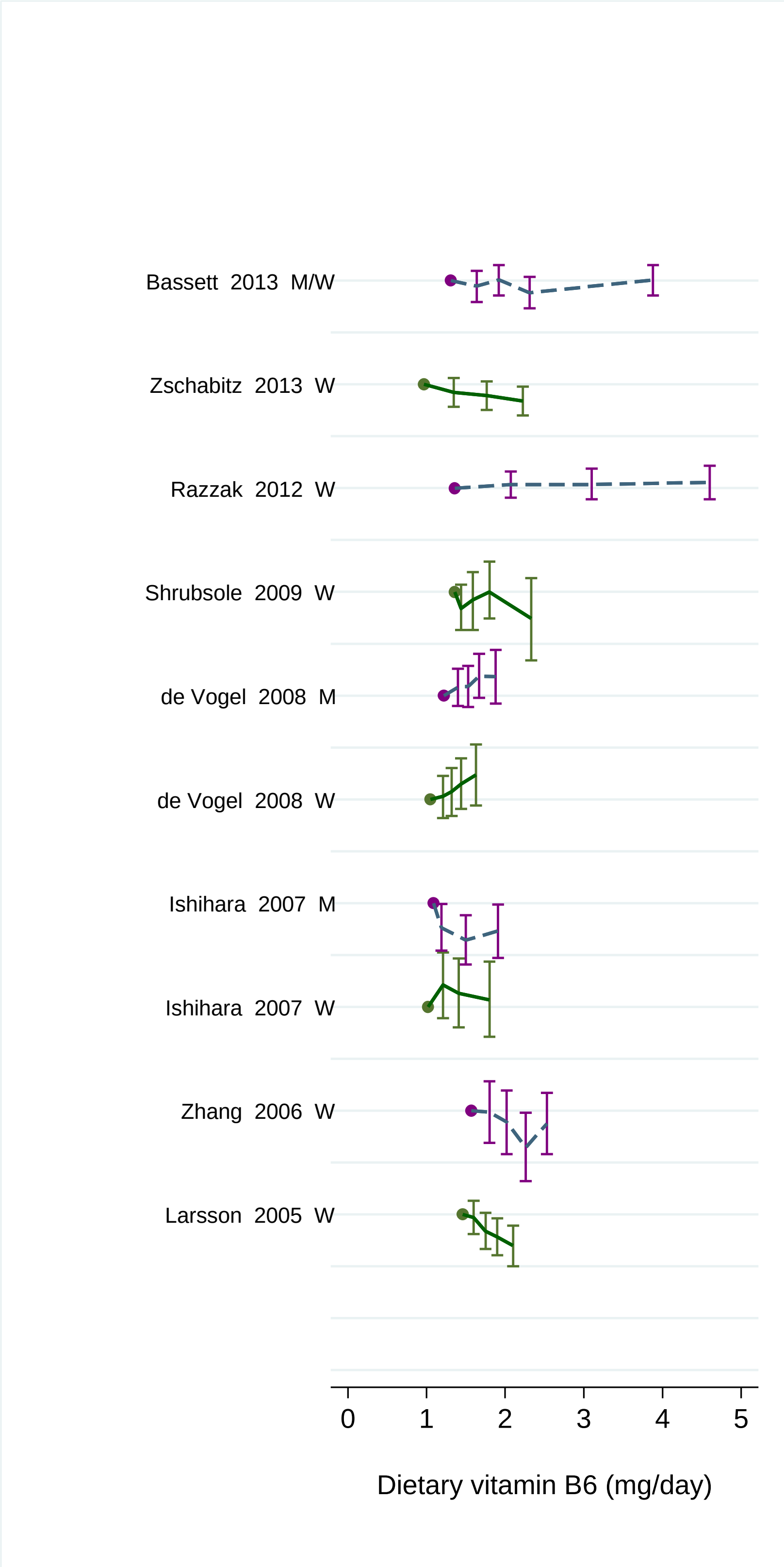


Figure 481 RR (95% CI) of colorectal cancer for the highest compared with the lowest level of dietary vitamin B6

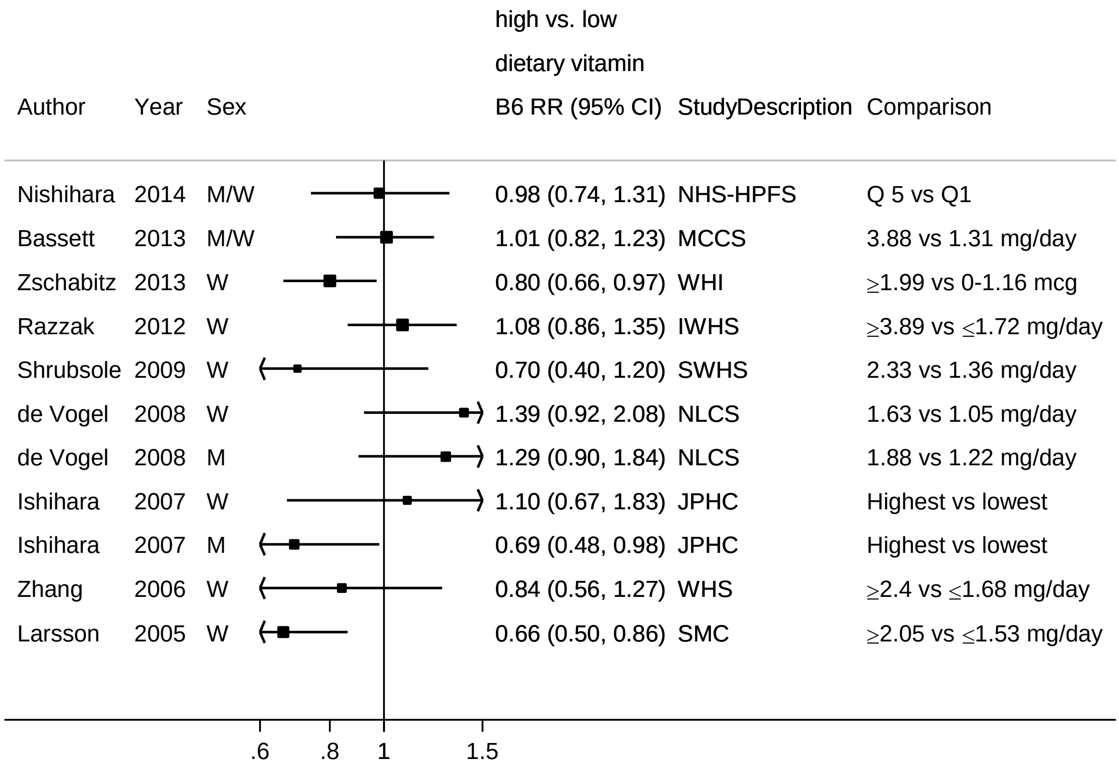


Figure 482 RR (95% CI) of colorectal cancer for 2 mg/day increase of dietary vitamin B6

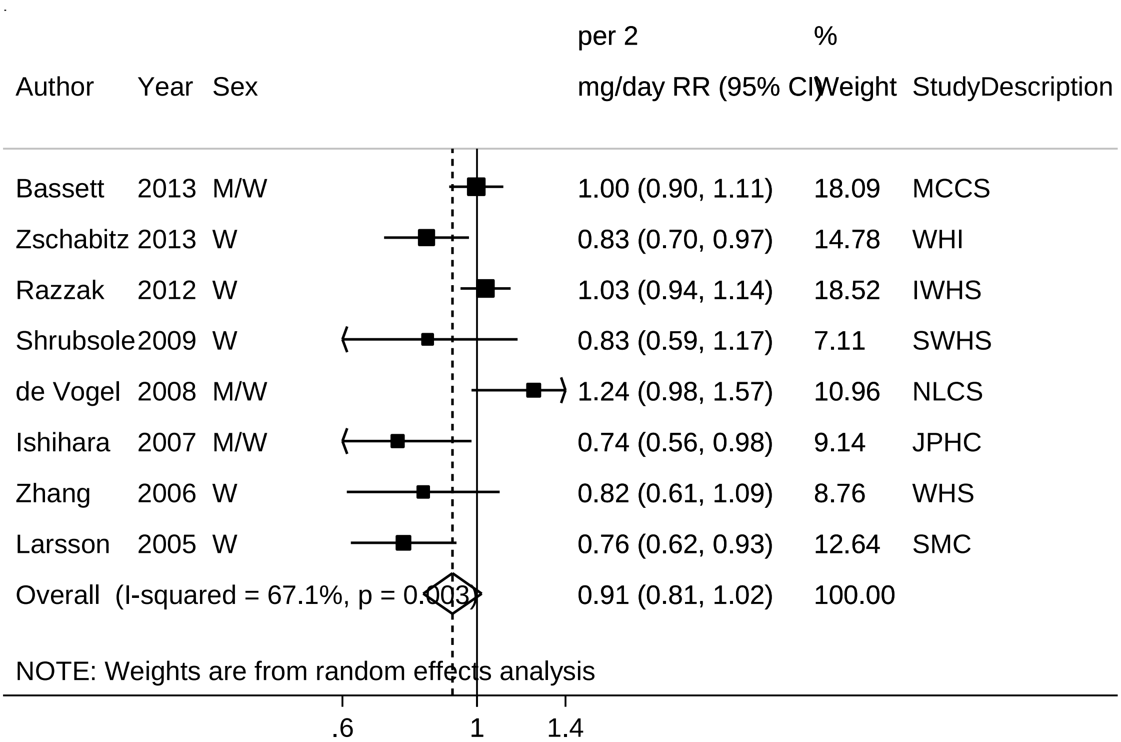
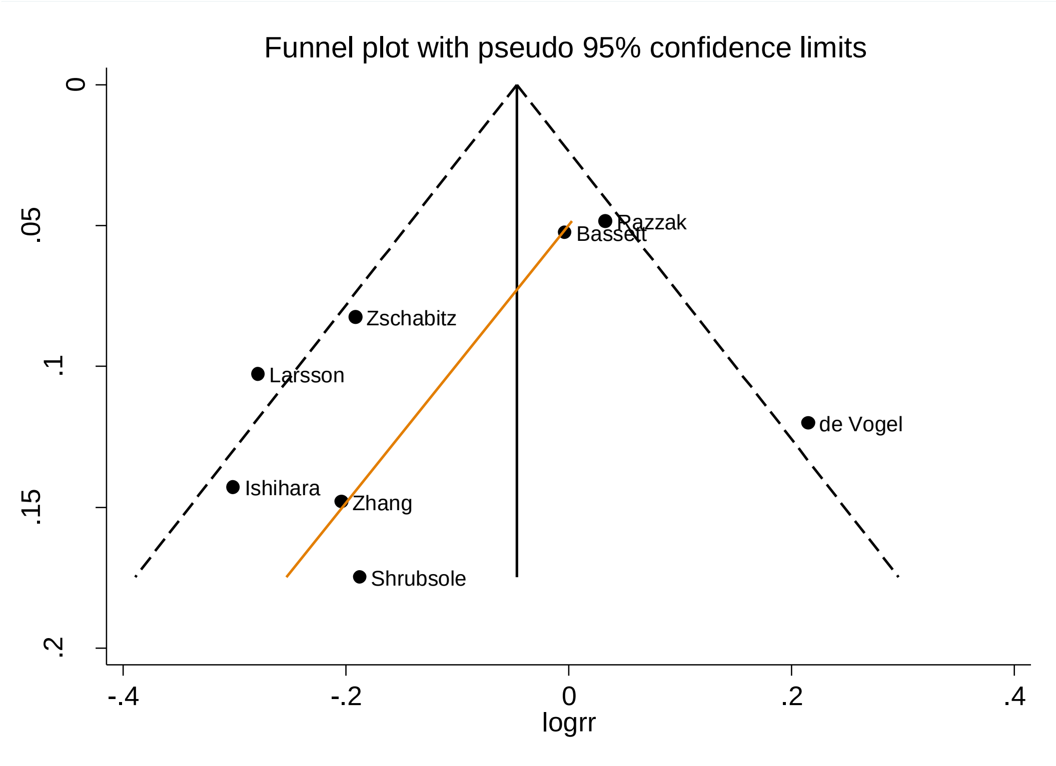


Figure 483 Funnel plot of studies included in the dose response meta-analysis dietary vitamin B6 and colorectal cancer



p for Egger's test =0.08

Figure 484 RR (95% CI) of colorectal cancer for 2 mg/day increase of dietary vitamin B6 by geographic location

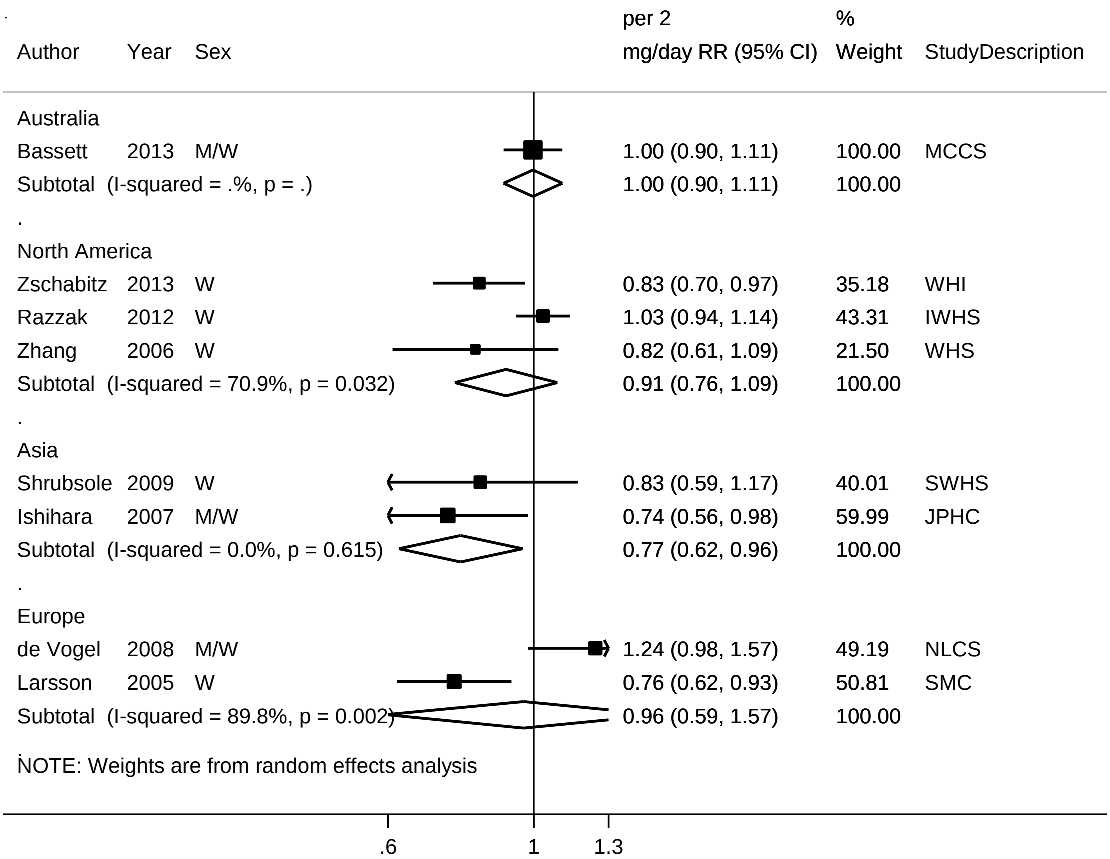
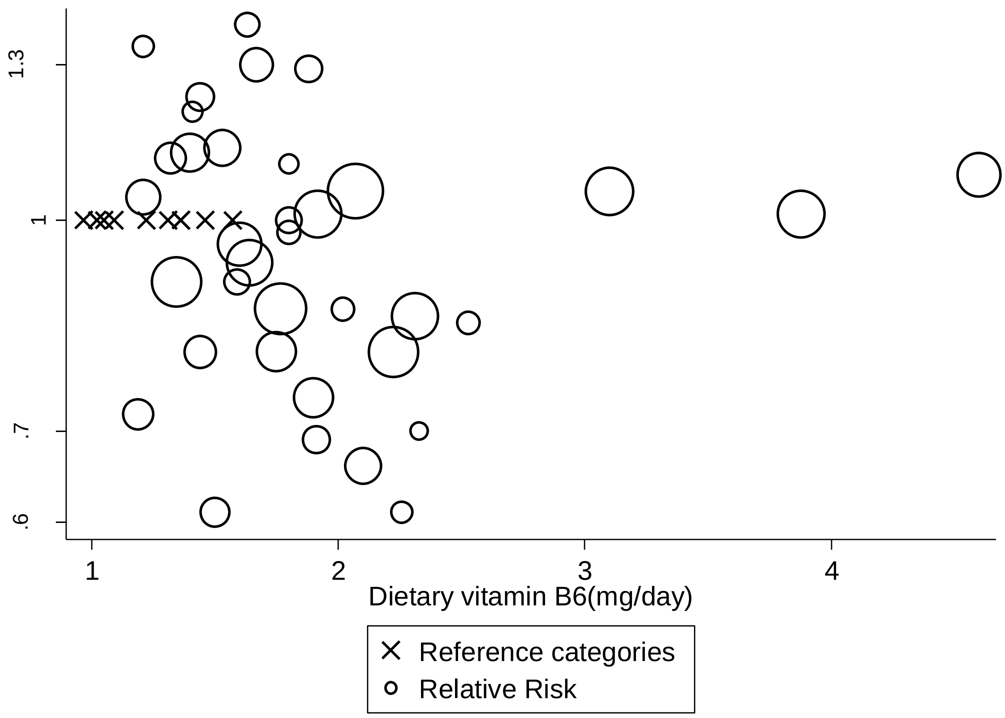
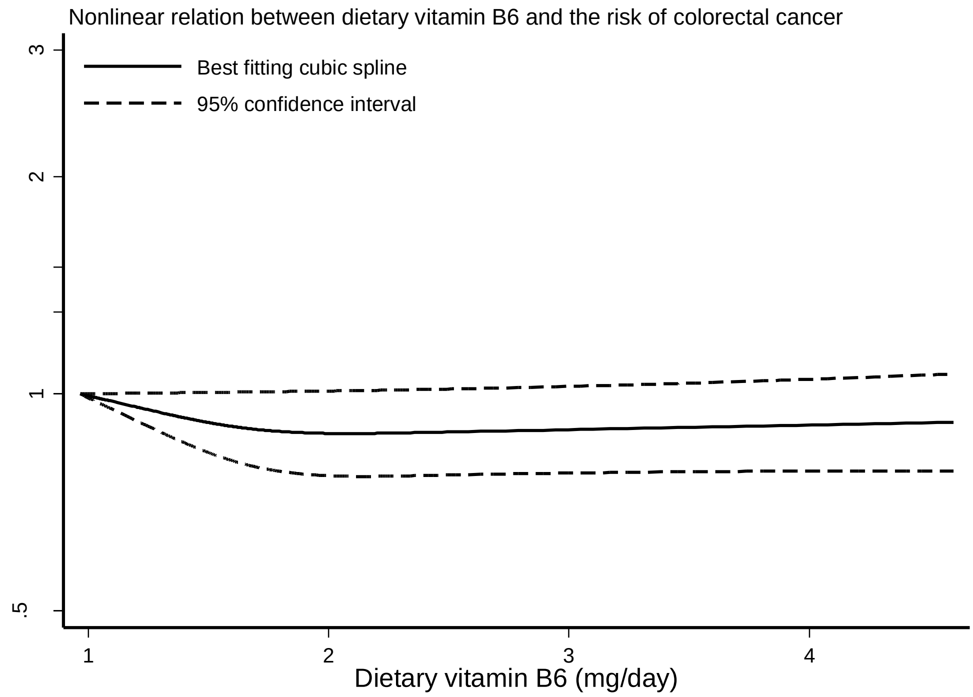


Figure 485 Relative risk of colorectal cancer and dietary vitamin B6 estimated using non-linear models





p for non-linearity=0.05

Table 275 Table with dietary vitamin B6 values and corresponding RRs (95% CIs) for non-linear analysis of dietary vitamin B6 and colorectal cancer

Dietary vitamin B6 (mg/day)	RR (95%CI)
0.96	1.00
1.05	0.98 (0.97-1.00)
1.41	0.92 (0.85-1.00)
1.53	0.91 (0.82-1.00)
1.60	0.90 (0.80-1.01)
2.07	0.88 (0.77-1.01)
4.6	0.91 (0.78-1.07)

5.5.9 Dietary vitamin C

Cohort studies

Summary

Main results:
Eight studies (12 publications) were identified in the CUP. One pooled analysis of 13 studies was identified (Park, 2010). No analysis was conducted in 2010 SLR. There were only enough studies to conduct analysis on colon cancer incidence.

Colon cancer:
Six studies (4391cases) were included in the dose-response meta-analysis of dietary vitamin C and colon cancer. A significant inverse association with moderate heterogeneity was observed. Only one study of Japanese-American men from Hawaii observed a significant association. There was no evidence of publication bias (p=0.06).
Eighteen studies could be included in the highest compared to lowest analysis which included 13 studies from the Pooling Project and 5 studies identified in the CUP.

Pooling Project of Cohort studies:
The Pooling Project of Prospective Studies of Diet and Cancer had examined the association between dietary vitamin C intake and risk of colon cancer (Park, 2010). Results from a total of 13 cohort studies, 676141 men and women and 5454 colon cancer cases were analysed. Study-specific food frequency questionnaires were used to assess dietary vitamin C intake. For the association between dietary vitamin C intake and risk of colon cancer, a non-significant association risk was observed in the multivariate adjusted model comparing the highest with the lowest quintile (pooled RR = 1.06, 95% CI = 0.95-1.18). For total vitamin C

the result was borderline significant (RR=0.86(95% CI = 0.74-1.00, >600 vs ≤100mg/day).

Table 276 Dietary vitamin C and colon cancer risk. Number of studies in the CUP SLR

	Number
Studies identified	18 (5+13PP)
Studies included in forest plot of highest compared with lowest exposure	18
Studies included in dose-response meta-analysis	6
Studies included in non-linear dose-response meta-analysis	NA

Note: Include cohort, nested case-control and case-cohort designs

Table 277 Dietary vitamin C and colon cancer risk. Summary of the dose-response meta-analysis in the 2010 SLR and 2015 SLR.

	2010 SLR	2015 SLR
Increment unit used		40mg/day
Studies (n)		6
Cases (total number)		4391
RR (95%CI)		0.94(0.89-0.99)
Heterogeneity (I^2, p-value)		49.6%, 0.08

Table 278 Dietary vitamin C and colorectal cancer risk. Main characteristics of studies included in the CUP SLR dose-response meta-analysis

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Missing data derived for analysis
Leenders, 2014 COL41012 Europe	EPIC, Nested Case Control, Age: 35-70 years, M/W	898/ 898 controls	Cancer registry	FFQ	Incidence, colon cancer	≥151 vs ≤79 mg/day	0.76 (0.57-1.01) Ptrend:0.05	Alcohol consumption, educational level, matching variables, number of cigarettes smoked, physical activity, smoking duration, smoking status, time since smoking cessation, waist circumference	Distribution of person-years by exposure categories. Mid-points of exposure categories.
		501/ 501 controls			Incidence, rectal cancer	≥151 vs ≤79 mg/day	1.01 (0.68-1.51) Ptrend:0.90		
Ruder, 2011 COL40896 USA	NIH-AARP, Prospective Cohort, Age: 50-71 years, Retired	2 819/ 292 797 985/	Cancer registry and national health database	FFQ	Incidence, colon cancer	169 vs 31 mg/1000kcal	0.83 (0.72-0.95) Ptrend:0.02	Sex, age at baseline, alcohol consumption, aspirin use, BMI, educational level, energy, energy, history of colon cancer, HRT use, physical activity, race,	Distribution of person-years by exposure category. Intakes in mg/1000kcal/da y converted to mg/day using average energy intake per each quantile
					Incidence, rectal cancer	169 vs 31 mg/1000kcal	0.96 (0.77-1.21) Ptrend:0.48		

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Missing data derived for analysis
								smoking, vitamin c	
Shin, 2006 COL40665 China	SWHS, Prospective Cohort, Age: 40-70 years, W	283/ 73 314 5.74 years	Follow up survey/cancer registry/vital statistics registry	FFQ	Incidence, colorectal cancer	≥127.2 vs 0-53.4 mg/day	1.10 (0.70-1.60) Ptrend:0.681	Age, alcohol, calories intake, educational level, family history of colorectal cancer, menopausal status, multivitamin supplement intake, physical activity, smoking status	Distribution of person-years by exposure categories. Mid-points of exposure categories.
		129/			Incidence, colon cancer	≥127.2 vs 0-53.4 mg/day	1.00 (0.50-1.90) Ptrend:0.976		
		91/			Incidence, rectal cancer	≥127.2 vs 0-53.4 mg/day	1.20 (0.60-2.40) Ptrend:0.662		
Sellers, 1998 COL01974 USA	IWHS, Prospective Cohort, Age: 55-69 years, W, Postmenopausal	180/ 35 216 10 years	SEER registry	Semi-quantitative FFQ	Incidence, colon cancer, no family history of crc	≥168.4 vs ≤115 mg/day	0.80 (0.60-1.20) Ptrend:0.3	Age, history of polyps, total energy intake	Distribution of person-years by exposure categories.
		61/			Family history of crc	≥168.4 vs ≤115 mg/day	1.10 (0.50-2.20) Ptrend:0.8		
Shibata, 1992 COL00740 USA	Leisure World Cohort, Prospective Cohort, M/W, retirement community, upper middle social class	105/ 11 580 70 159 person-years	Community registry	FFQ	Incidence, colon cancer, women	≥225 vs 0-155 mg/day	0.61 (0.38-0.99) Ptrend:<0.05	Age, smoking habits	Mid-points of exposure categories.
		97/			Men	≥210 vs 0-145 mg/day	1.15 (0.70-1.88)		

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Missing data derived for analysis
Heilbrun, 1989 COL01555 USA	HHP, Nested Case Control, M	102/ 361 controls 16 years	Cancer registry & hospital surveillance	Recall questionnaire	Incidence, colon cancer,	≤37 vs ≥160 mg/day	1.87 Ptrend:0.011	Age, alcohol consumption	Distribution of person-years by exposure categories. Estimation of confidence intervals. RRs with the lowest category as reference was calculated using the Hamling's method
		60/ 361 controls			Incidence, rectal cancer,	≤37 vs ≥160 mg/day	0.80 Ptrend:0.713		

Table 279 Dietary vitamin C and colorectal cancer risk. Main characteristics of studies excluded from the CUP SLR dose-response meta-analysis

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Reasons for exclusion
Park, 2010 Pooling Project	Studies ATBC CPS II HPFS NLCS NYSC BCDDP CNBSS IWHS NLCS NYUWHS NHS ORDET SMC WHS	5454/676141 44 467+349 456 393 335+223 349 431 799 353 96 162+429 43 485 40	Self-reported questionnaire and medical record	FFQ	Incidence, colon cancer	Q5 vs Q1	1.06(0.95-1.18) P trend: 0.12	Age, body mass index, education, physical activity, family history of colorectal cancer, use of nonsteroidal anti-inflammatory drugs, multivitamin use, smoking, alcohol consumption, intakes of red meat, total milk, dietary folate and total energy, and use of postmenopausal hormone therapy (premenopausal, never, ever) and oral	Only included in highest compared to lowest analysis

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Reasons for exclusion
								contraceptive use (never, ever) in women	
Roswall, 2010 COL40797 Denmark	DCH, Prospective Cohort, Age: 50-64 years, M/W	56 332 10.6 years	Cancer registry	FFQ	Incidence, colon cancer	≥172.89 vs ≤83.92 mg/day	1.33 (0.87–2.03)	Age, alcohol intake, BMI, educational level, hormone use, physical activity, processed meat, red meat intake, smoking status, vitamin e	Component of EPIC study Superseded by Leenders, 2014 COL41012
						per 100 mg/day	1.09 (0.82-1.44)		
Hansen, 2009 COL40855 Denmark	DCH, Case Cohort, Age: 50-64 years	173/ 57 053	Cancer registry	FFQ	Incidence, colorectal cancer, gpx1 pro198leu cc	per 100 mg/day	0.58 (0.34-0.98)	Alcohol intake, BMI, fibre, fruits and vegetables consumption, HRT use, smoking, pack-years	Component of EPIC study Superseded by Leenders, 2014 COL41012
		164/			Gpx1 pro198leu ct	per 100 mg/day	0.98 (0.60-1.62)		
		38/			Gpx1 pro198leu tt	per 100 mg/day	1.31 (0.49-3.49)		
Wark, 2005 COL01807	NLCS, Case Cohort, Age: 55-69 years, M/W	387/ 120 852 7.3 years	Cancer registry and database of pathology reports	Semi-quantitative FFQ	Incidence, colon cancer, hmlh1+ cases	≥115.7 vs 0-80.6 mg/day	1.08 (0.81-1.43) Ptrend:0.67	Age, sex, family history of specific cancer, total energy	Case-only study

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Reasons for exclusion
		54/			Hmlh1- cases	≥115.7 vs 0-80.6 mg/day	0.81 (0.39-1.68) Ptrend:0.51		
Glynn, 1996 COL00161 Finland	ATBC, Nested Case Control, Age: 50-69 years, M, Male Smokers	136/ 249 controls 8 years	Cancer registry	FFQ	Incidence, colorectal cancer,	(mean exposure)		Age, clinic site, date of blood collection	Only mean exposure
Bostick, 1993 COL00483 USA	IWHS, Prospective Cohort, Age: 55-69 years, W	212/ 35 216 167 447 person-years	SEER	Semi-quantitative FFQ	Incidence, colon cancer,	≥202 vs ≤90 mg/day	1.32 (0.83-2.09) Ptrend:0.47	Age, calories intake, height, low-fat meat intake, parity, total vitamin e intake, total vitamin e x age, vitamin a supplement intake	Superseded by Sellers, 1998 COL01974
Wu, 1987 COL00774 USA	Leisure World Cohort, Prospective Cohort, M/W, Retirement community	68/ 11 644 4.5 years	Population registries	FFQ	Incidence, colorectal cancer, women	Q 3 vs Q 1	0.50 (0.30-0.90)	Age	Superseded by Shibata, 1992 COL00740
		58/			Men	Q 3 vs Q 1	0.88 (0.50-1.70)		

Figure 486 RR estimates of colon cancer by levels of dietary vitamin C

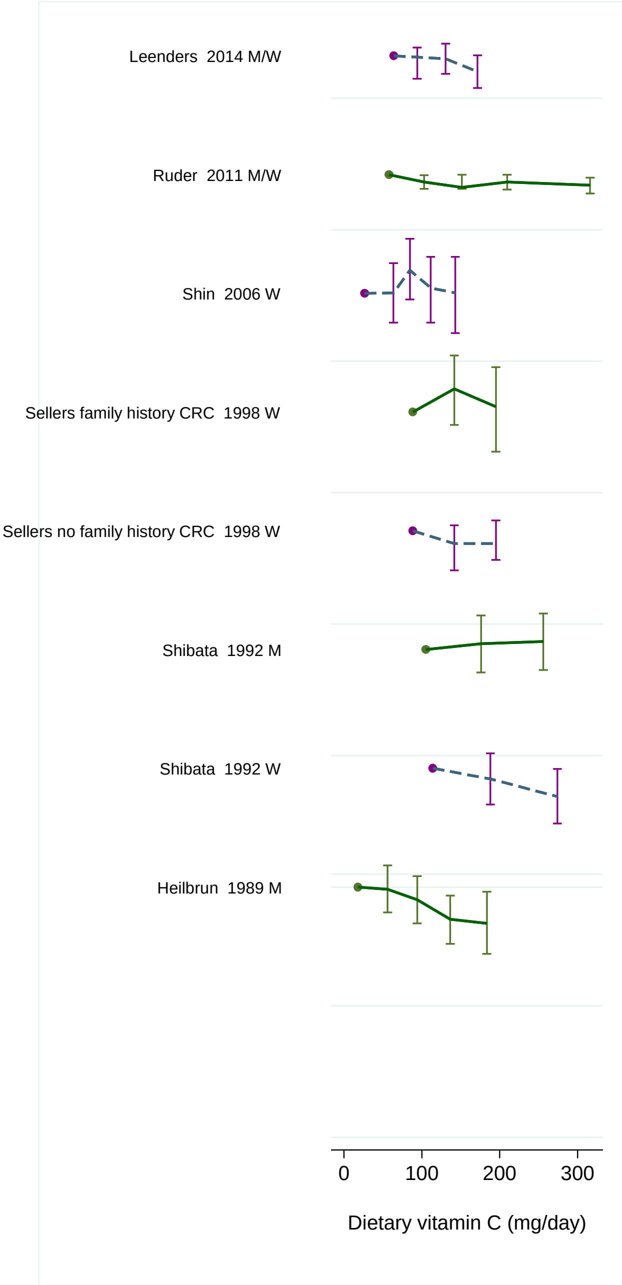


Figure 487 RR (95% CI) of colon cancer for the highest compared with the lowest level of vitamin C

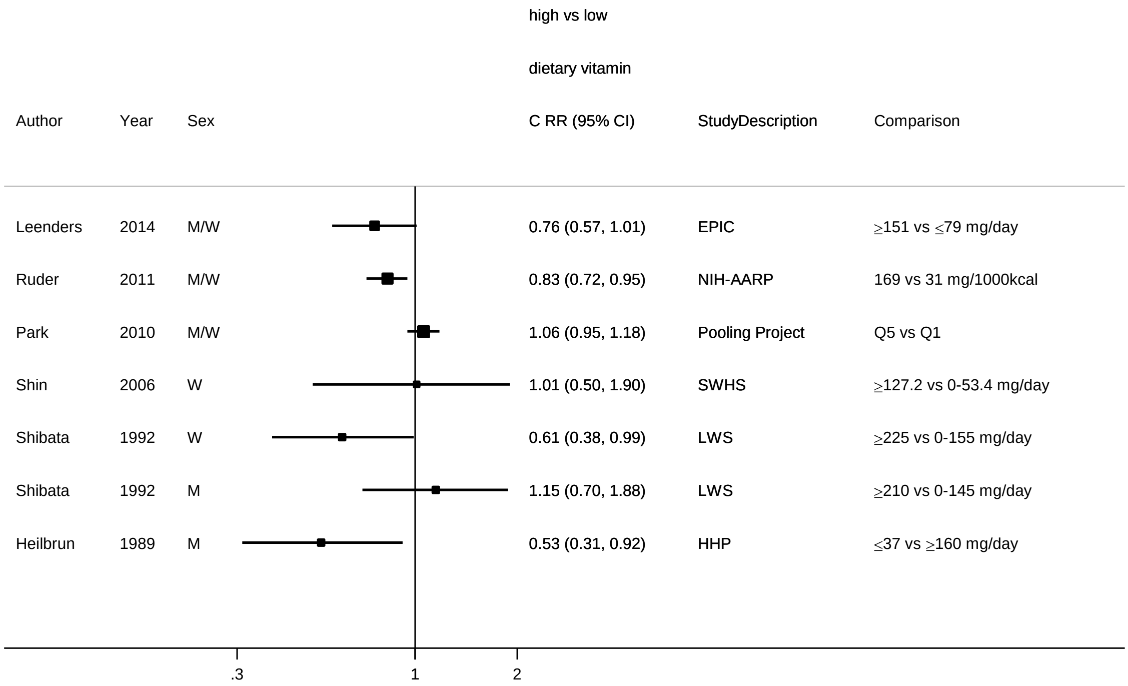


Figure 488 RR (95% CI) of colon cancer for 40mg/day increase of dietary vitamin C

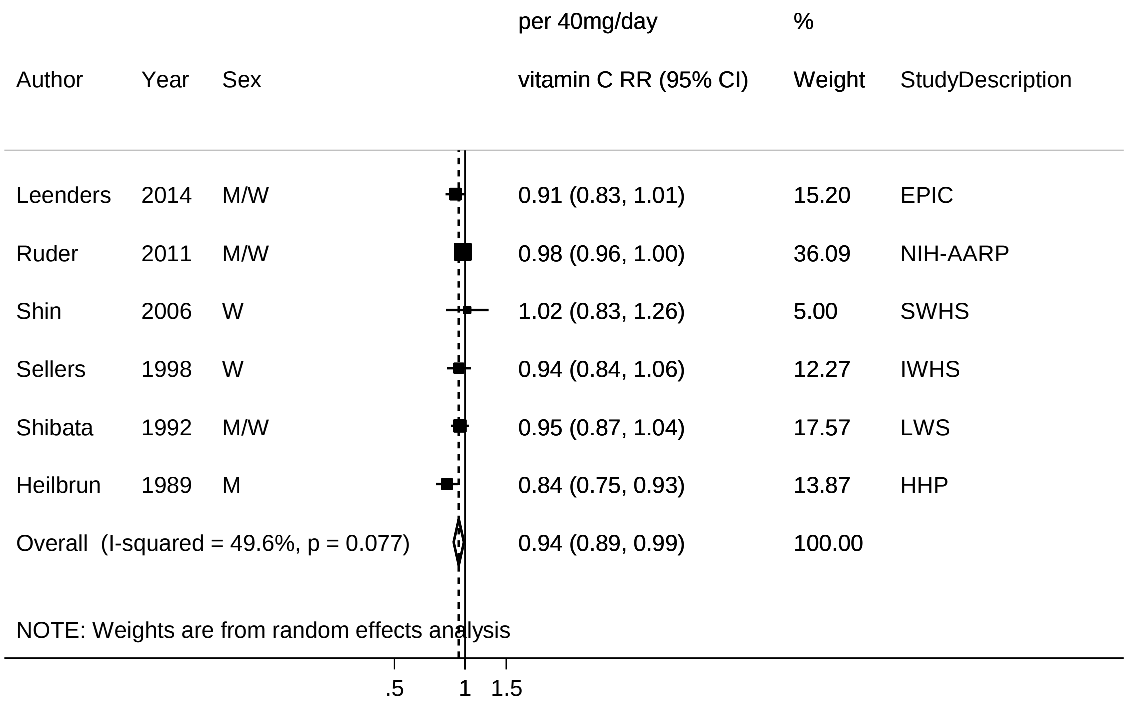
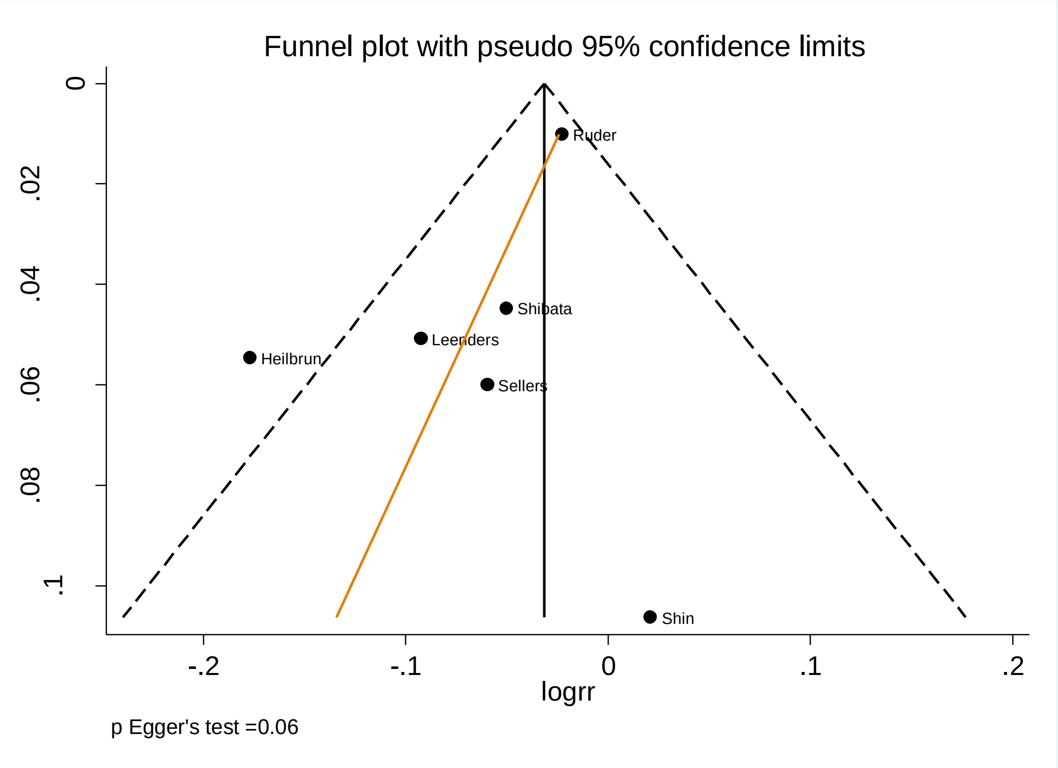


Figure 489 Funnel plot of studies included in the dose response meta-analysis dietary vitamin C and colon cancer



5.6.2 Total iron intake (diet and supplement)

Two new studies from one publication were identified (Zhang, 2011). There were 5studies (4 publications) in total in total iron intake. The results of each study are in the table below. All studies showed non-significant associations except the NIH-AARP (Cross, 2010) which showed an inverse association for colorectal and colon cancer.

Table 280 Total iron and colorectal cancer risk. Main characteristics of studies identified in the CUP SLR

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors
Gay, 2012 COL40920 UK	EPIC-Norfolk, Case-only study, Age: 45-79 years, M/W	185/ 25 636 11 years	Cancer registry	7-day dietary recalls	Incidence, colorectal cancer, gc:at mutations	per 1 sd units	1.05 (0.59-1.88)	Age, sex, smoking
					Apc promoter methylation ≥20%	per 1 sd units	0.77 (0.51-1.16)	
					Apc mutations	per 1 sd units	1.18 (0.84-1.69)	
Zhang, 2011 COL40891 USA	NHS-HPFS, Prospective Cohort, M/W, nurses & health professionals	1 079/ 115 061 22 years	Medical records and pathology reports	FFQ	Incidence, colorectal cancer, women	≥22.7 vs 0-10.9 mg/day	1.11 (0.88-1.41) Ptrend:0.44	Age, alcohol consumption, aspirin use, BMI, calcium Intake, endoscopy, energy-adjusted folate, history of colorectal cancer, HRT use, physical activity, smoking, vitamin d, zinc intake
		1 035/			Men	≥24.6 vs 0-12.6 mg/day	1.08 (0.84-1.38) Ptrend:0.61	
		837/			Incidence, colon cancer, women	≥22.7 vs 0-10.9 mg/day	1.03 (0.79-1.36) Ptrend:0.87	
		815/			Men	≥24.6 vs 0-12.6 mg/day	1.14 (0.85-1.51) Ptrend:0.59	
		242/			Incidence, rectal cancer, women	≥22.7 vs 0-10.9 mg/day	1.44 (0.90-2.33) Ptrend:0.05	
		208/			Men	≥24.6 vs 0-12.6 mg/day	0.94 (0.55-1.60) Ptrend:0.91	
Cross, 2010	NIH-AARP,	2 719/	Cancer registry	FFQ	Incidence,	36.1 vs 10.8	0.75 (0.66-0.86)	Sex, BMI,

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors
COL40794 USA	Prospective Cohort, Age: 50-71 years, M/W	300 948 7.2 years	and death certificates and questionnaires		colorectal cancer	mg/day	Ptrend:<0.001	dietary calcium intake, dietary fiber intake, educational level, smoking habits, total energy intake
		1 995/			Incidence, colon cancer	36.1 vs 10.8 mg/day	0.73 (0.62-0.84) Ptrend:<0.001	
		724/			Incidence, rectal cancer	36.1 vs 10.8 mg/day	0.84 (0.65-1.08) Ptrend:0.070	
Kato, 1999 COL00434 USA	New York University Women's Health Study, Nested Case Control, Age: 34-65 years, W	105/ 523 controls 4.7 years	Questionnaires	FFQ	Incidence, colorectal cancer,	Q 4 vs Q 1	1.17 (0.60-2.30) Ptrend:0.44	Beer consumption, family history of colorectal cancer, hours spent In sports In their early thirties, prior occult blood testing
		49/			Incidence, distal colon cancer,	Q 4 vs Q 1	0.95 (0.30-2.80) Ptrend:0.82	
		33/			Incidence, proximal colon cancer,	Q 4 vs Q 1	3.29 (0.70-14.60) Ptrend:0.04	
		17/			Incidence, rectal cancer,	Q 4 vs Q 1	0.85 (0.20-4.70) Ptrend:0.87	

5.6.2 Dietary iron intake

No new studies were identified in the CUP, there were 5 studies in totalThe results of each study are in the table below. The results were inconsistent, one study showed an inverse significant association (Cross, 2010), one study a positive significant association (Wurzelmann, 1996) for colon and proximal colon cancer, and three studies were non-significant.

Table 281 Dietary iron and colorectal cancer risk. Main characteristics of studies identified in the CUP SLR

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors
Cross, 2010 COL40794 USA	NIH-AARP, Prospective Cohort, Age: 50-71 years, M/W	2 719/ 300 948 7.2 years	Cancer registry and death certificates and questionnaires	FFQ	Incidence, colorectal cancer	11.4 vs 5.9 mg/1000 kcal/day	0.75 (0.65-0.87) Ptrend:<0.001	Sex, BMI, dietary calcium intake, dietary fiber intake, educational level, smoking habits, total energy intake
		1 995/			Incidence, colon cancer	11.4 vs 5.9 mg/1000 kcal/day	0.78 (0.66-0.92) Ptrend:0.009	
		724/			Incidence, rectal cancer	11.4 vs 5.9 mg/1000 kcal/day	0.68 (0.52-0.90) Ptrend:0.017	
Kabat, 2007 COL40637 Canada	NBSS, Prospective Cohort, Age: 40-59 years, W	617/ 48 666 16.4 years	Record linkages to cancer database and to the national mortality database	FFQ	Incidence, colorectal cancer	≥14.99 vs ≤11.8 mg/day	1.07 (0.80-1.43) Ptrend:0.94	Age, alcohol intake, BMI, educational level, fat intake, fibre, folic acid, HRT use, menopausal status, oral contraceptive use, pack-years of smoking, physical activity, total calories
		428/			Incidence, colon cancer	≥14.99 vs ≤11.8 mg/day	1.07 (0.75-1.53) Ptrend:0.96	
		195/			Incidence, rectal cancer	≥14.99 vs ≤11.8 mg/day	1.12 (0.67-1.88) Ptrend:0.62	
Balder, 2006 COL40622 Netherlands	NLCS, Case Cohort, Age: 55-69 years, M/W	869/ 120 852 9.3 years	Cancer registry	Semi-quantitative FFQ	Incidence, colorectal cancer, men	17 vs 9.5 mg/day	1.34 (0.93-1.93) Ptrend:0.12	Age at entry, alcohol intake, BMI, family history of colorectal cancer, recreational
		666/			Women	15 vs 8.5 mg/day	1.08 (0.72-1.62) Ptrend:0.90	
		539/			Incidence, colon	17 vs 9.5	1.30 (0.84-2.01)	

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors
					cancer, men	mg/day	Ptrend:0.43	activity, smoking status, total energy intake, vegetable intake
		484/			Women	15 vs 8.5 mg/day	1.14 (0.73-1.80) Ptrend:0.91	
		333/			Incidence, rectal cancer, men	17 vs 9.5 mg/day	1.44 (0.85-2.45) Ptrend:0.08	
		185/			Women	15 vs 8.5 mg/day	1.11 (0.53-2.30) Ptrend:0.63	
Cross, 2006 COL40621 Finland	ATBC, Nested Case Control, Age: 50-69 years, M	117/ 260 controls 14.2 years	Cancer registry	FFQ	Incidence, colorectal cancer	≥22.1 vs ≤14.4 mg/day	0.40 (0.10-1.10) Ptrend:0.06	Age, alcohol consumption, aspirin use, BMI, educational level, energy intake, other laboratory factors, physical activity, smoking habits
Wurzelmann, 1996 COL00221 USA	NHANES I, Prospective Cohort, Age: 31- years, M/W	98/ 11 317 15 years	Population registry	Recall questionnaire + FFQ	Incidence, colon cancer,	Q 4 vs Q 1	3.35 (1.74-6.46) Ptrend:<0.001	Age, sex
		57/			Incidence, distal colon cancer,	Q 4 vs Q 1	1.03 (0.80-1.32)	
		52/			Incidence, proximal colon cancer,	Q 4 vs Q 1	1.44 (1.23-1.69)	
		38/			Incidence, rectal cancer,	Q 4 vs Q 1	1.01 (0.42-2.42) Ptrend:0.98	

5.6.3 Dietary calcium

Cohort studies

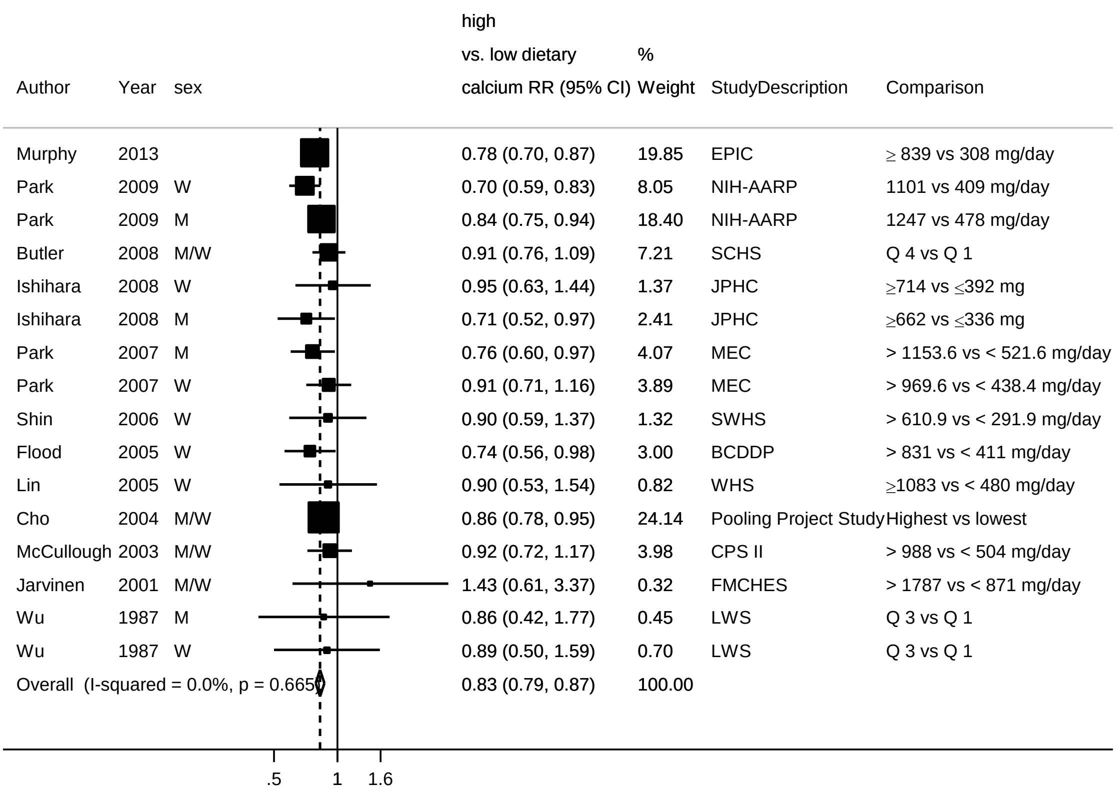
Summary

One new study (EPIC & EPIC-Heidelberg) (2 publications) was identified after the 2010 SLR. No meta-analysis was conducted. Previousley in the 2010 SLR, the dose-response analysis of 13 cohort studies showed a significant inverse association for dietary calcium intake and colorectal cancer risk.The summary RR was (0.94, 95% CI = 0.93-0.96, I^2=0%, p =0.52) per 200 mg/day.

Colorectal cancer:

A high vs low analysis was conducted. The Pooling Project of Prospective Studies of Diet and Cancer (Cho, 2004), including 10 studies (4 992 cases), was included in the high vs low analysis. A significant inverse association was observed for dietary calcium intake and colorectal cancer risk.

Figure 490 RR (95% CI) of colorectal cancer for the highest compared with the lowest level of dietary calcium intake



5.6.2 Heme-iron

Cohort studies

Summary

Main results:
Three studies from 2 new publications were identified. There were no new studies on mortality, therefore all the analyses are on cancer incidence.

Colorectal cancer:
Six studies (6070 cases) were included in the dose-response meta-analysis of heme-iron and colorectal cancer. A non-significant association with no heterogeneity was observed. All studies included showed non-significant associations. After stratification by sex and geographic location the result remained non-significant. There was no evidence of publication bias (p=0.53). There was evidence of a non-linear association (p=0.001) with a significant increase in risk for higher levels of heme-iron. The slope is steeper at lower levels and then starts to plateau.

The summary RRs ranged from 1.03 (95% CI=0.96-1.09) when Cross, 2010 was omitted to 1.05 (95% CI=0.98-1.13) when Kabat, 2007 was omitted.

Colon cancer:
Eight studies (6780 cases) were included in the dose-response meta-analysis of heme-iron and colon cancer. A non-significant association with lmoderate heterogeneity was observed. One study on women (SMC and IWHS) showed a significant association per 1mg/day of heme-iron and another was borderline significant, overall the result remained non-significant in the subgroup analysis including only women. There was no evidence of publication bias (p=0.12). There was no evidence of a non-linear association (p=0.78).

The summary RRs ranged from 1.03 (95% CI=0.98-1.11) when Larsson, 2005 was omitted to 1.09 (95% CI=0.98-1.23) when Zhang, 2011 was omitted.

Rectal cancer:
Six studies (2293 cases) were included in the dose-response meta-analysis of heme-iron and rectal cancer. A non-significant association with no heterogeneity was observed. All studies included showed non-significant associations. After stratification by sex and geographic location the result remained non-significant. There was no evidence of publication bias (p=0.31). There was evidence of a non-linear association (p=0.02) with a significant increase in risk for higher levels of heme-iron. The slope is steeper at lower levels and then starts to plateau.

The summary RRs ranged from 1.07 (95% CI=0.97-1.20) when Cross, 2010 was omitted to 1.09 (95% CI=0.97-1.25) when Kabat, 2007 was omitted.

Study quality:
Heme-iron intake was estimated using percentages of the total iron content in meat and fish in six of the studies, while a more detailed database that takes into account the influence of various cooking methods on the heme-iron content of the meats was used in the NIH-AARP study (Cross, 2010). The studies adjusted for most known confounding factors. Cancer outcome was confirmed using cancer registry records and medical records in most studies.

Pooling Project of cohort studies:
No Pooling Project was identified.

Meta-analysis of cohort studies:
A meta-analysis of 8 cohort studies that we also included in the CUP analysis observed a RR for the highest versus the lowest intake of 1.14 (95 % CI = 1.04–1.24) (Qiao, 2013). In the subgroup analysis, the positive association of heme-iron intake with risk for colorectal cancer was not significantly modified by subsites within the colorectal, sex, geographic location, study duration, the number of cases, or the range of intake (p-interaction = 0.18), but apparently stronger in women (RR = 1.18, 95 % CI = 1.01–1.38), in the European studies (RR = 1.28, 95 % CI = 1.07–1.53), and in the studies with a wider range of exposure (RR = 1.25, 95 % CI = 1.06–1.47).

Table 282 Heme-iron and colorectal cancer risk. Number of studies in the CUP SLR

	Number
Studies identified	7 (7 publications)
Studies included in forest plot of highest compared with lowest exposure	6
Studies included in dose-response meta-analysis	6
Studies included in non-linear dose-response meta-analysis	6

Note: Include cohort, nested case-control and case-cohort designs

Table 283 Heme-iron and colon cancer risk. Number of studies in the CUP SLR

	Number
Studies identified	8 (8 publications)
Studies included in forest plot of highest compared with lowest exposure	8
Studies included in dose-response meta-analysis	8
Studies included in non-linear dose-response meta-analysis	8

Note: Include cohort, nested case-control and case-cohort designs

Table 284 Heme-iron and rectal cancer risk. Number of studies in the CUP SLR

	Number
Studies identified	6 (6 publications)
Studies included in forest plot of highest compared with lowest exposure	6
Studies included in dose-response meta-analysis	6
Studies included in non-linear dose-response meta-analysis	6

Note: Include cohort, nested case-control and case-cohort designs

Table 285 Heme-iron and colorectal cancer risk. Summary of the dose-response meta-analysis in the 2010 SLR and 2015 SLR.

	2010 SLR	**2015 SLR**
Increment unit used	1mg/day	1mg/day
Studies (n)	3	6
Cases (total number)	4871	6070
RR (95%CI)	1.04 (0.97-1.12)	1.04(0.98-1.10)
Heterogeneity (I^2, p-value)	0%, 0.53	0%, 0.81

Stratified analysis by sex (no analysis in 2005 SLR or 2010 SLR)			
2015 SLR	**Men**	**Women**	
Studies (n)	3	4	
RR (95%CI)	1.02(0.92-1.13)	1.04(0.96-1.12)	
Heterogeneity (I^2, p-value)	0%, 0.57	0%, 0.48	
Stratified analysis by geographic location			
(no analysis in 2005 SLR or 2010 SLR)			
2015 SLR	**Asia**	**Europe**	**North America**

Studies (n)	1	1	4
RR (95%CI)	0.96(0.71-1.28)	1.06(0.92-1.22)	1.04(0.97-1.11)
Heterogeneity (I^2, p-value)			0%, 0.54

Table 286 Heme-iron and colon cancer risk. Summary of the dose-response meta-analysis in the 2010 SLR and 2015 SLR.

	2010 SLR	2015 SLR
Increment unit used	1mg/day	1mg/day
Studies (n)	5	8
Cases (total number)	4734	6780
RR (95%CI)	1.12 (0.99-1.27)	1.07(0.99-1.17)
Heterogeneity (I^2, p-value)	54%, 0.07	37.4%, 0.14

Stratified analysis by sex		
Men	**2010 SLR**	**2015 SLR**
Studies (n)		3
RR (95%CI)		1.06(0.90-1.25)
Heterogeneity (I^2, p-value)		31.4%, 0.23
Women		
Studies (n)	4	6
RR (95%CI)	1.11 (0.93 -1.33)	1.10(0.97-1.24)
Heterogeneity (I^2, p-value)	68%, 0.03	43%, 0.12

Stratified analysis by geographic location (no analysis in 2005 SLR or 2010 SLR)			
2015 SLR	**Asia**	**Europe**	**North America**
Studies (n)	1	2	5
RR (95%CI)	0.92(0.65-1.31)	1.22(0.89-1.69)	1.05(0.96-1.14)
Heterogeneity (I^2, p-value)		74.3%, 0.05	25.7%, 0.26

Table 287 Heme-iron and rectal cancer risk. Summary of the dose-response meta-analysis in the 2010 SLR and 2015 SLR.

	2010 SLR	2015 SLR
Increment unit used	1mg/day	1mg/day
Studies (n)	3	6
Cases (total number)	1437	2293
RR (95%CI)	1.09 (0.96-1.23)	1.09(0.98-1.21)
Heterogeneity (I^2, p-value)	0%, 0.80	0%, 0.97

Stratified analysis by sex		
2015 SLR	**Men**	**Women**
Studies (n)	3	4
RR (95%CI)	0.99(0.81-1.20)	1.12(0.97-1.31)
Heterogeneity (I^2, p-value)	0%, 0.80	0%, 0.50

Stratified analysis by geographic location (no analysis in 2005 SLR or 2010 SLR)			
2015 SLR	**Asia**	**Europe**	**North America**
Studies (n)	1	1	4
RR (95%CI)	1.02(0.61-1.73)	1.08(0.90-1.30)	1.10(0.96-1.25)
Heterogeneity (I^2, p-value)			0%, 0.80

Table 288 Heme-iron and colorectal cancer risk. Results of meta-analyses and pooled analyses of prospective studies published after the 2005 SLR.

Author, Year	Number of cohort studies	Total number of cases	Studies country, area	Outcome	Comparison	RR (95%CI)	P trend	Heterogeneity (I^2, p value)
Meta-analysis								
Qiao, 2013	8 JPHC, NHS, HPFS, NIH-AARP, NBSS, NLCS, SMC, IWHS	8269	North America, Europe and Asia	Colorectal cancer	Highest vs Lowest 1mg/day	1.14(1.04–1.24) 1.11(1.03-1.18)		11.5%, 0.34
				Men (3)	Highest vs Lowest	1.09 (0.92–1.29)		8.1%, 0.34
				Women (6)	Highest vs Lowest	1.18 (1.01–1.38)		29.6%, 0.20
	8			Colon cancer	Highest vs Lowest	1.14 (1.03–1.26)		11.9%, 0.69
	6			Rectal cancer		1.18 (1.00–1.38)		0%, 0.86

Table 289 Heme-iron and colorectal cancer risk. Main characteristics of studies included in the CUP SLR dose-response meta-analysis

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Missing data derived for analyses
Hara, 2012 COL40921 Japan	JPHC, Prospective Cohort, Age: 45-74 years, M/W	786/ 85 097 808 053 person-years	Hospital records	FFQ	Incidence, colorectal cancer, men	0.77 vs 0.24 mg/day	1.06 (0.79-1.42) Ptrend:0.6	Age, area, BMI, calcium, diabetes, ethanol, fiber, folate, magnesium intake, metabolic equivalents, omega3pufa, screening, smoking, vitamin b12, vitamin b6, vitamin d, zinc	
		527/			Incidence, colon cancer, men		1.02 (0.71-1.46) Ptrend:0.7		
		498/			Incidence, colorectal cancer, women	0.67 vs 0.23 mg/day	0.88 (0.61-1.29) Ptrend:0.4		
		351/			Incidence, colon cancer, women		0.94 (0.60-1.46) Ptrend:0.6		
		259/			Incidence, rectal cancer, men	0.77 vs 0.24 mg/day	1.17 (0.69-1.98) Ptrend:0.6		
		147/			Women		0.78 (0.39-1.58) Ptrend:0.6		
Zhang, 2011 COL40891 USA	NHS-HPFS, Prospective Cohort, M/W, nurses & health professionals	1 079/ 115 061 22 years	Medical records and pathology reports	FFQ	Incidence, colorectal cancer, women	≥1.3 vs 0-0.78 mg/day	1.21 (0.96-1.52) Ptrend:0.10	Age, alcohol consumption, aspirin use, BMI, calcium intake, endoscopy, energy-adjusted folate, history of colorectal cancer, HRT use, physical activity, smoking,	Distribution of person-years by exposure category. Mid-points of
		1 035/			Men	≥1.6 vs 0-0.9 mg/day	0.98 (0.77-1.26) Ptrend:0.80		
		837/			Incidence, colon cancer, women	≥1.3 vs 0-0.78 mg/day	1.13 (0.87-1.47) Ptrend:0.30		
		815/			Men	≥1.6 vs 0-0.9 mg/day	0.99 (0.75-1.31) Ptrend:0.97		
		242/			Incidence, rectal cancer, women	≥1.3 vs 0-0.78 mg/day	1.50 (0.90-2.49) Ptrend:0.17		

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Missing data derived for analyses
		208/			Men	≥1.6 vs 0-0.9 mg/day	0.93 (0.53-1.62) Ptrend:0.62	vitamin d, zinc intake	
Cross, 2010 COL40794 USA	NIH-AARP, Prospective Cohort, Age: 50-71 years, M/W	2 719/ 300 948 7.2 years	Cancer registry and death certificates and questionnaires	FFQ	Incidence, colorectal cancer	335.8 vs 48.1 mcg/1000kcal/day	1.13 (0.99-1.29) Ptrend:0.022	Sex, BMI, dietary calcium intake, dietary fiber intake, educational level, smoking habits, total energy intake	Conversion from mcg/1000kcal/day to mg/day
		1 995/			Incidence, colon cancer		1.10 (0.94-1.28) Ptrend:0.138		
		724/			Incidence, rectal cancer		1.24 (0.96-1.60) Ptrend:0.049		
Kabat, 2007 COL40637 Canada	NBSS, Prospective Cohort, Age: 40-59 years, W	617/ 48 666 16.4 years	Record linkages to cancer database and to the national mortality database	FFQ	Incidence, colorectal cancer	≥2.95 vs ≤1.57 mg/day	1.06 (0.80-1.42) Ptrend:0.99	Age, alcohol intake, BMI, educational level, fat intake, fibre, folic acid, HRT use, menopausal status, oral contraceptive use, pack-years of smoking, physical activity, total calories	Mid-points of exposure categories.
		428/			Incidence, colon cancer		0.99 (0.70-1.40) Ptrend:0.99		
		195/			Incidence, rectal cancer		1.27 (0.74-2.19) Ptrend:0.71		
Balder, 2006 COL40622 Netherlands	NLCS, Case Cohort, Age: 55-69 years, M/W	869/ 120 852 9.3 years	Cancer registry	Semi-quantitative FFQ	Incidence, colorectal cancer, men	1.85 vs 0.6 mg/day	1.16 (0.87-1.55) Ptrend:0.27	Age at entry, alcohol intake, BMI, family history of colorectal cancer, recreational	
		666/			Women	1.54 vs 0.47 mg/day	1.22 (0.89-1.68) Ptrend:0.22		
		539/			Incidence, colon	1.85 vs 0.6	1.29 (0.92-1.81)		

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Missing data derived for analyses
					cancer, men	mg/day	Ptrend:0.10	activity, smoking status, total energy intake, vegetable intake	
		484/			Women	1.54 vs 0.47 mg/day	1.20 (0.83-1.74) Ptrend:0.56		
		333/			Incidence, rectal cancer, men	1.85 vs 0.6 mg/day	0.98 (0.64-1.50) Ptrend:0.84		
		185/			Women	1.54 vs 0.47 mg/day	1.23 (0.73-2.07) Ptrend:0.11		
Larsson, 2005 COL40745 Sweden	SMC, Prospective Cohort, Age: 40-75 years, W	547/ 61 433 14.8 years	Cancer Registry	FFQ	Incidence, colon cancer	≥2.06 vs ≤0.66 mg/day	1.31 (0.98-1.75) Ptrend:0.03	Age, BMI, calcium intake, calendar period, dietary fibre intake, educational level, folate intake, saturated fat, total energy intake, zinc intake	Distribution of person-years by exposure category. Mid-points of exposure categories
					Alcohol intake ≥20g/week		2.29 (1.25- 4.21) Ptrend:0.007		
Lee, 2004 COL00285 USA	IWHS, Prospective Cohort, Age: 55-69 years, W, Postmenopausal	438/ 34 708 15 years	SEER	FFQ	Incidence, proximal colon cancer,	≥2.05 vs ≤0.76 mg/day	2.18 (1.24-3.86) Ptrend:0.01	Age, alcohol consumption, BMI, calcium, diabetes, fibre, folate, HRT use, multivitamin supplement intake, physical activity, saturated fat, smoking habits, total caloric intake, vitamin	Mid-points of exposure categories
		303/			Incidence, distal colon cancer,	≥2.05 vs ≤0.76 mg/day	0.90 (0.45-1.81) Ptrend:0.77		

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Missing data derived for analyses
								e, zinc	

Table 290 Heme-iron and colorectal cancer risk. Main characteristics of studies excluded from the CUP SLR dose-response meta-analysis

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Reasons for exclusion
Gilsing, 2013 COL40987 Netherlands	Netherlands Cohort Study on Diet and Cancer (NLCS), Case Cohort, Age: 55-69 years, M/W	644/ 4 026 7.3 years	Cancer registry and pathology register	FFQ	Incidence, colorectal cancer, kras negative	per 1 mg/day	1.27 (0.86-1.69)	Age, sex, alcohol consumption, BMI, energy intake, family history of colorectal cancer, meat intake, non-occupational physical activity, physical activity, processed meat, smoking, vegetable consumption	Only has interaction results. Superseded by Balder, 2006 COL40622 (higher number cases)
					Kras positive		1.35 (0.93–1.94)		
		435			Incidence, colon cancer, kras negative	per 1 mg/day	1.31 (0.92–1.87)		
					Kras positive		1.43 (0.98–2.09)		
		140			Incidence, rectal cancer, kras negative	per 1 mg/day	1.41 (0.85–2.35)		
					Kras positive		0.58 (0.27–1.25)		
Gay, 2012 COL40920 UK	EPIC-Norfolk, Prospective Cohort, Age: 45-79 years, M/W	185/ 25 636 11 years	Cancer registry	7-day dietary recalls	Incidence, colorectal cancer, gc:at mutations	per 1 sd units	1.64 (0.97-2.75)	Age, sex, smoking	Case-only study with interaction results
					Apc promoter methylation ≥20%	per 1 sd units	1.13 (0.79-1.62)		
					Apc mutations	per 1 sd units	1.50 (1.09-2.09)		

Figure 491 RR estimates of colorectal cancer by levels of heme-iron

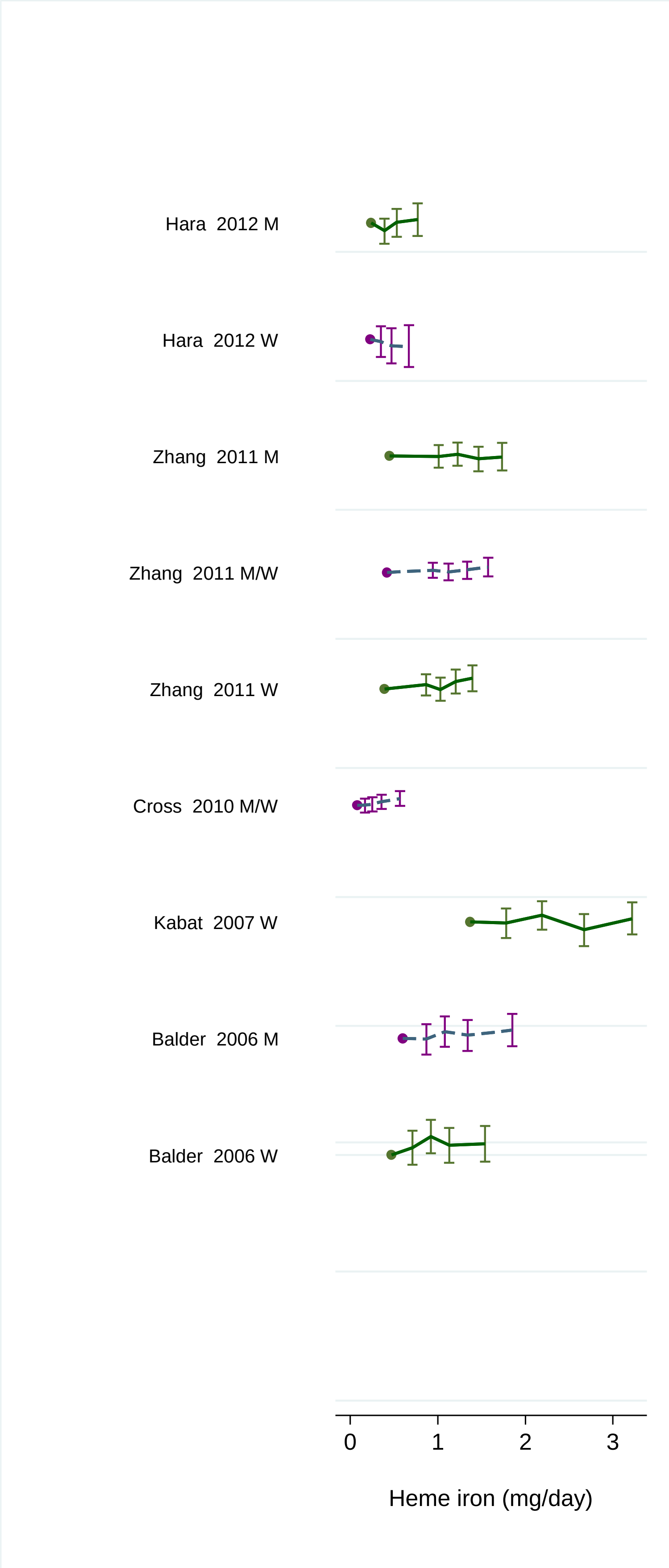


Figure 492 RR (95% CI) of colorectal cancer for the highest compared with the lowest level of heme-iron

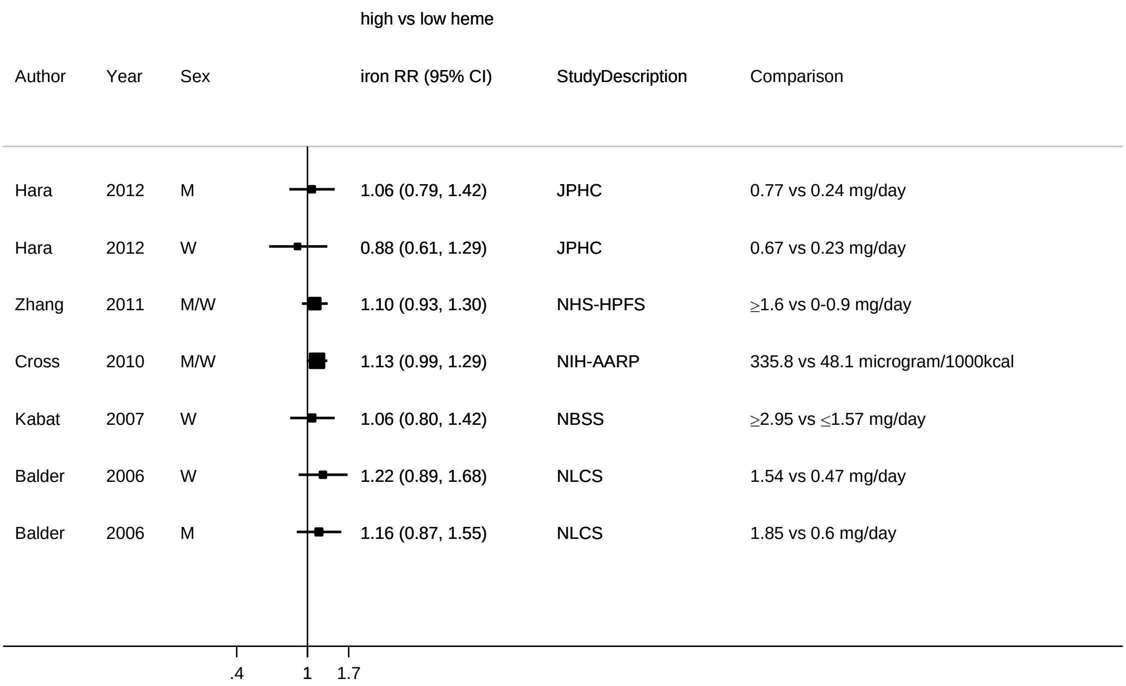


Figure 493 RR (95% CI) of colorectal cancer for 1mg/day increase of heme-iron

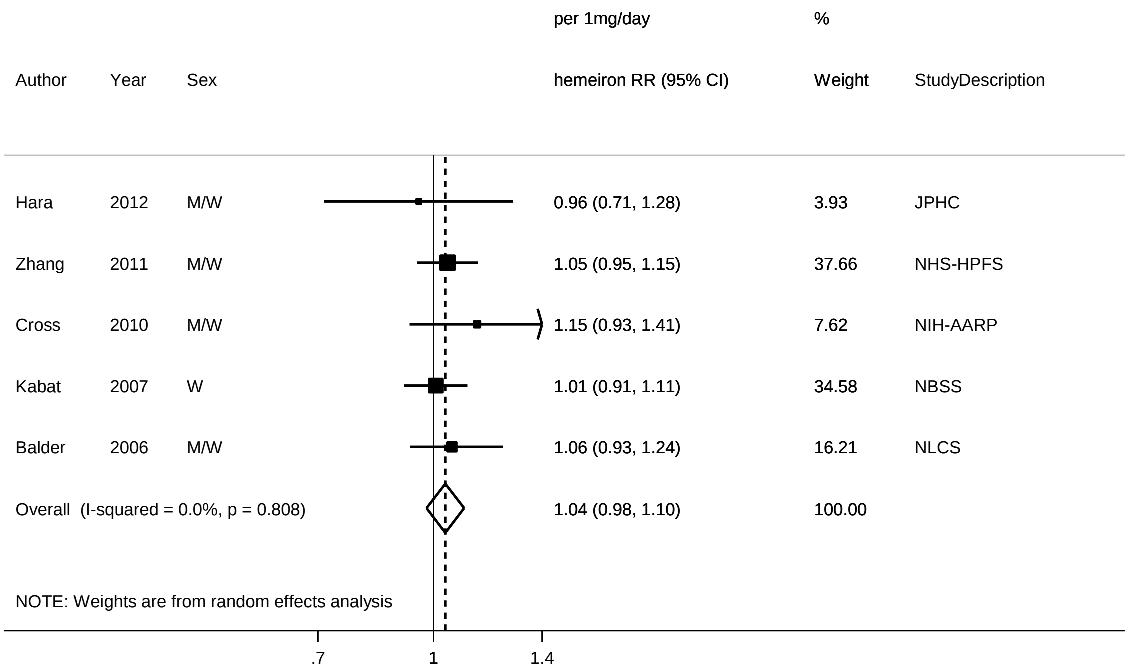


Figure 494 Funnel plot of studies included in the dose response meta-analysis of heme-iron and colorectal cancer

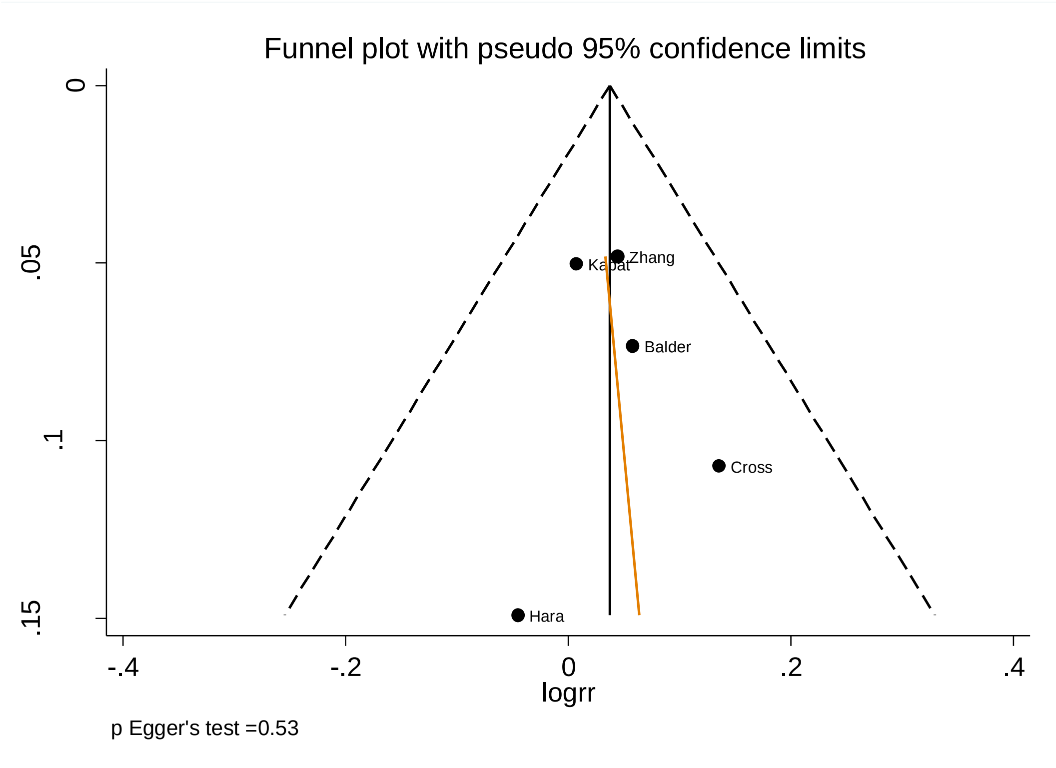


Figure 495 RR (95% CI) of colorectal cancer for 1mg/day increase of heme-iron by sex

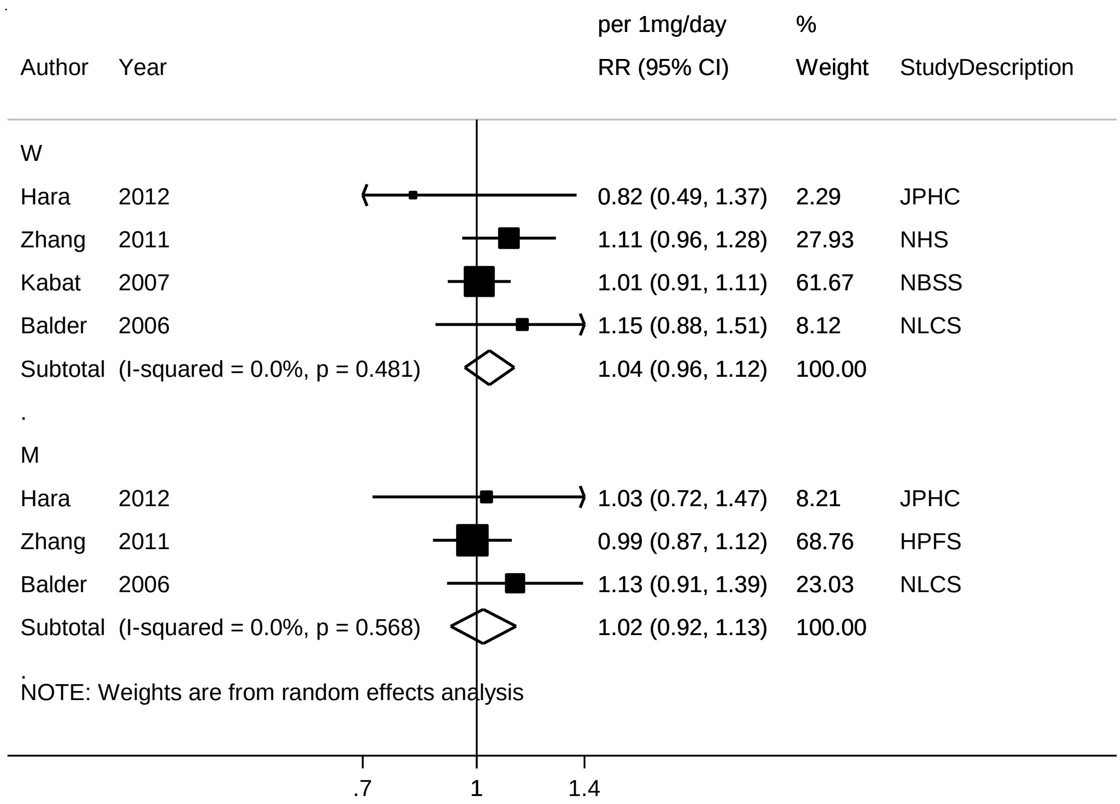


Figure 496 RR (95% CI) of colorectal cancer for 1mg/day increase of heme-iron by location

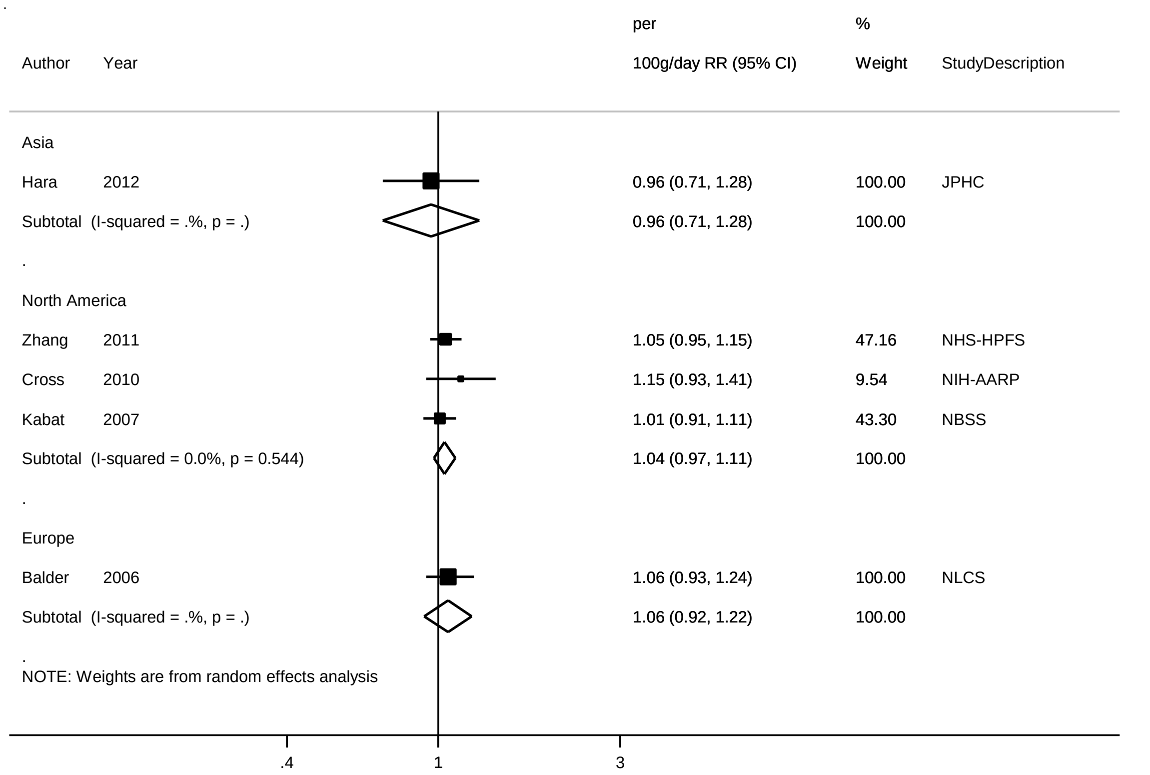
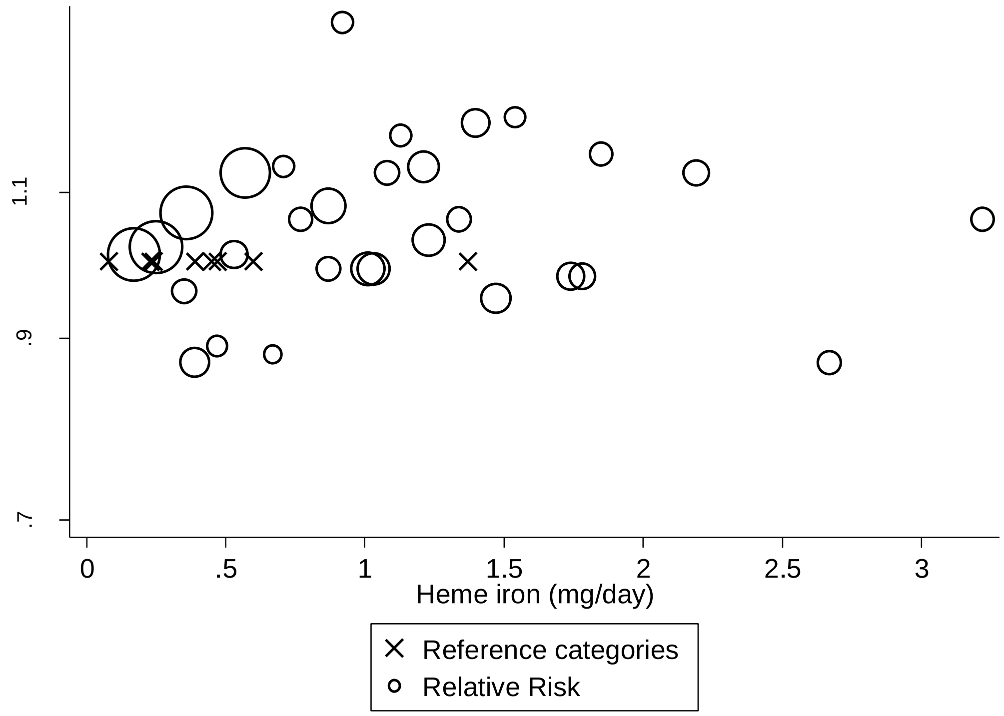


Figure 497 Relative risk of colorectal cancer and heme-iron estimated using non-linear models



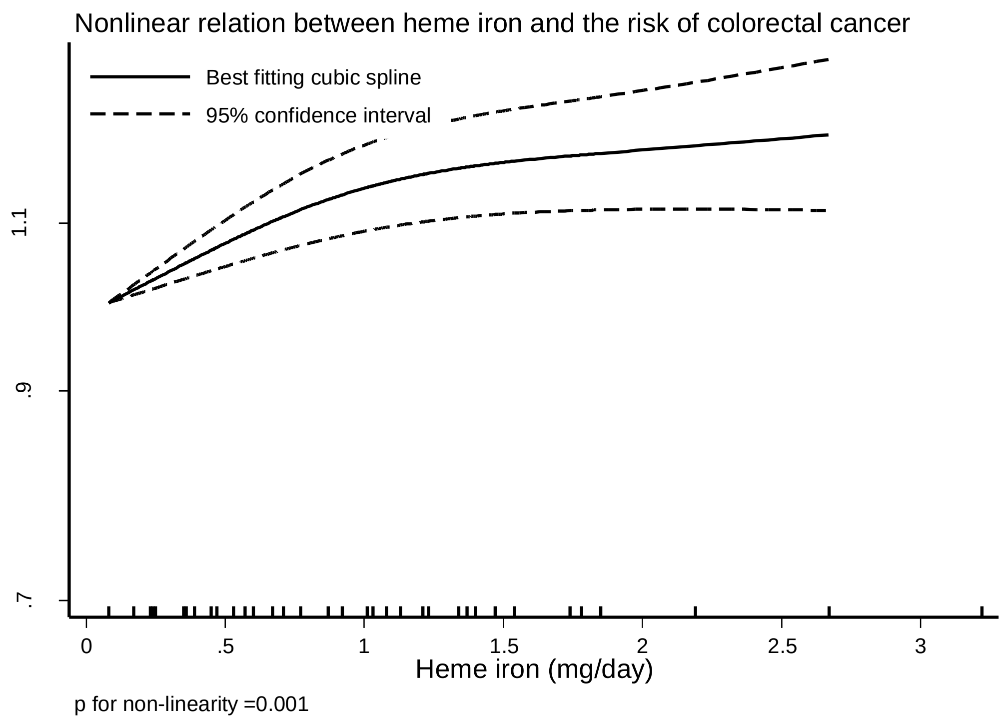


Table 291 Table with heme-iron values and corresponding RRs (95% CIs) for non-linear analysis of heme-iron and colorectal cancer

Heme-iron (mg/day)	RR(95%CI)
0	
0.6	1.09(1.05-1.13)
1.01	1.15(1.09-1.21)
1.4	1.18(1.11-1.25)
2.19	1.21(1.12-1.30)

Figure 498 RR estimates of colon cancer by levels of heme-iron

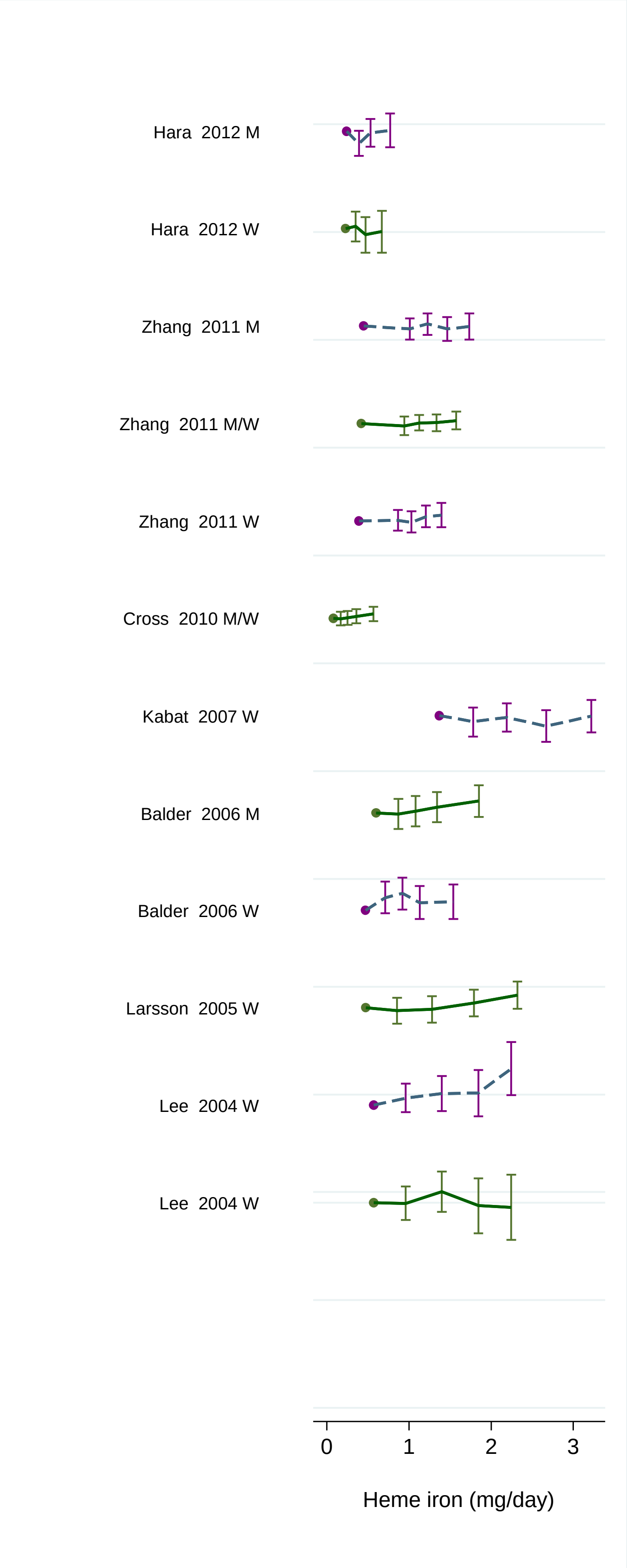


Figure 499 RR (95% CI) of colon cancer for the highest compared with the lowest level of heme-iron

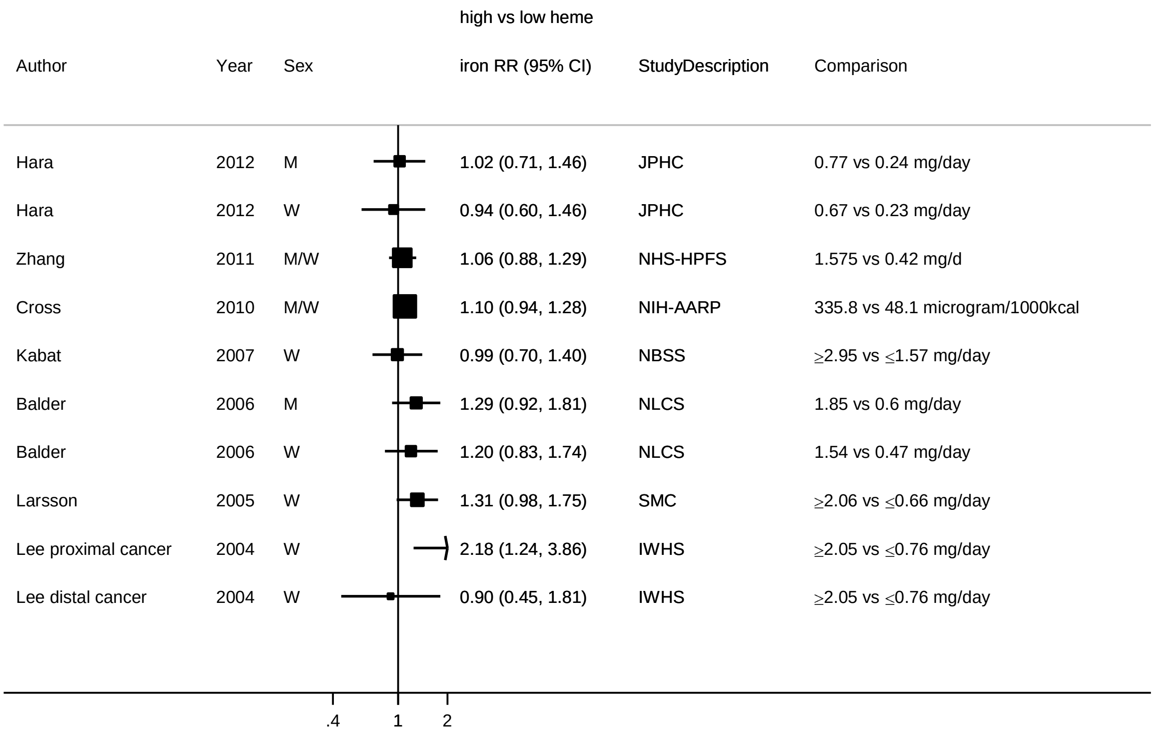


Figure 500 RR (95% CI) of colon cancer for 1mg/day increase of heme-iron

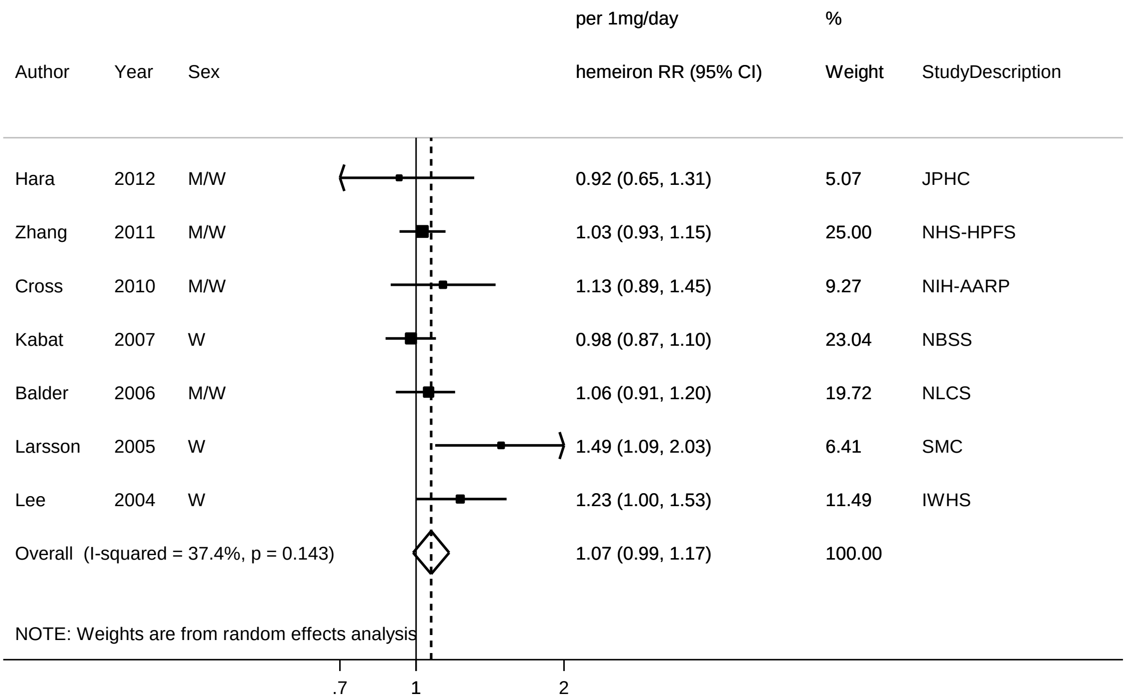


Figure 501 Funnel plot of studies included in the dose response meta-analysis of heme-iron and colon cancer

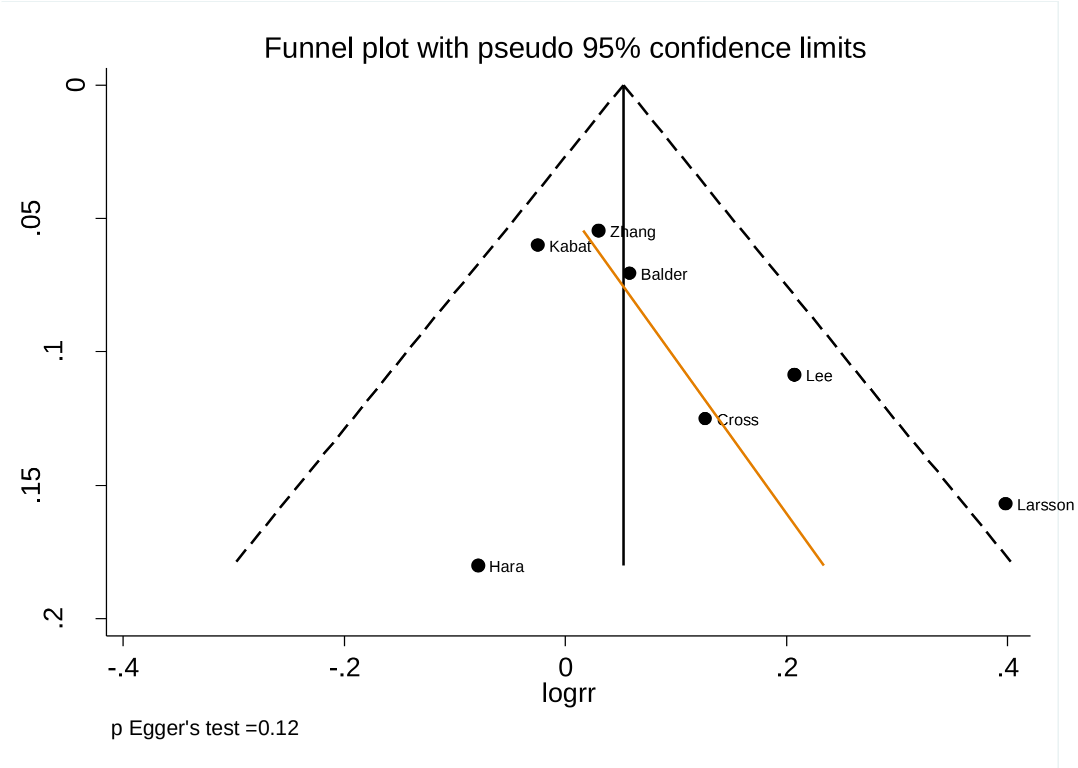


Figure 502 RR (95% CI) of colon cancer for 1mg/day increase of heme-iron by sex

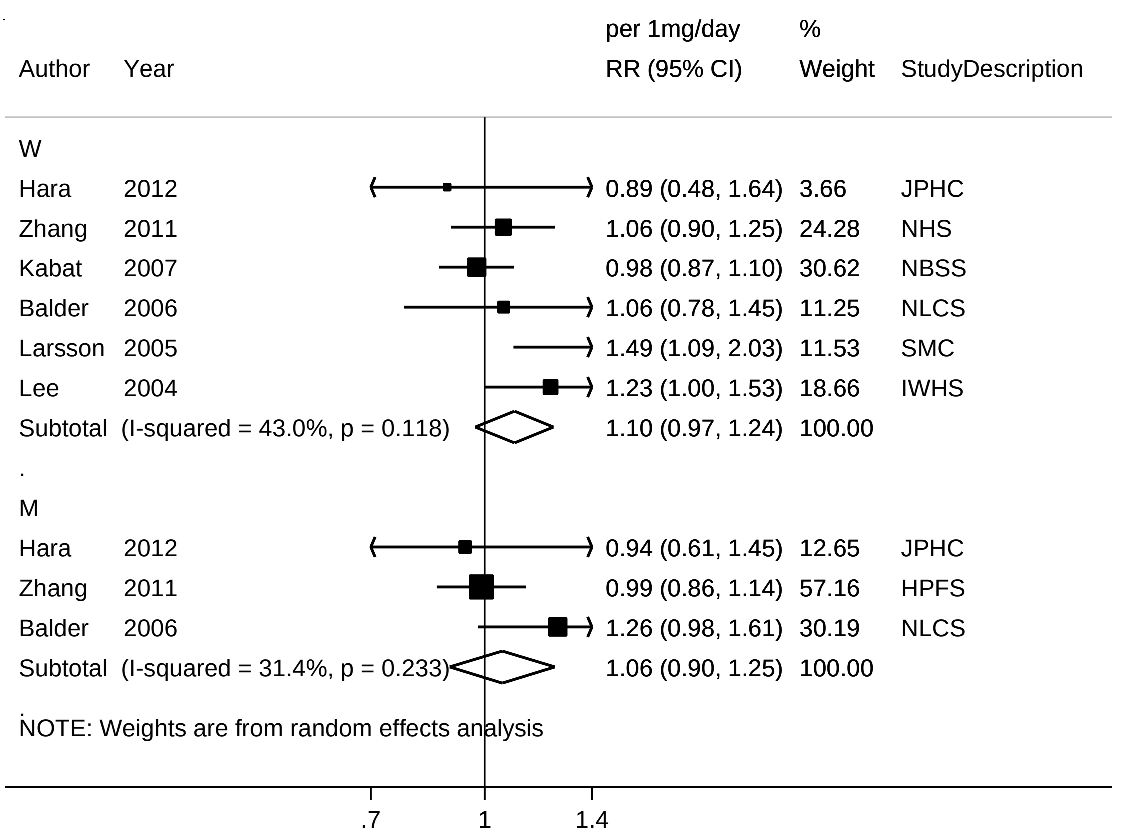


Figure 503 RR (95% CI) of colon cancer for 1mg/day increase of heme-iron by location

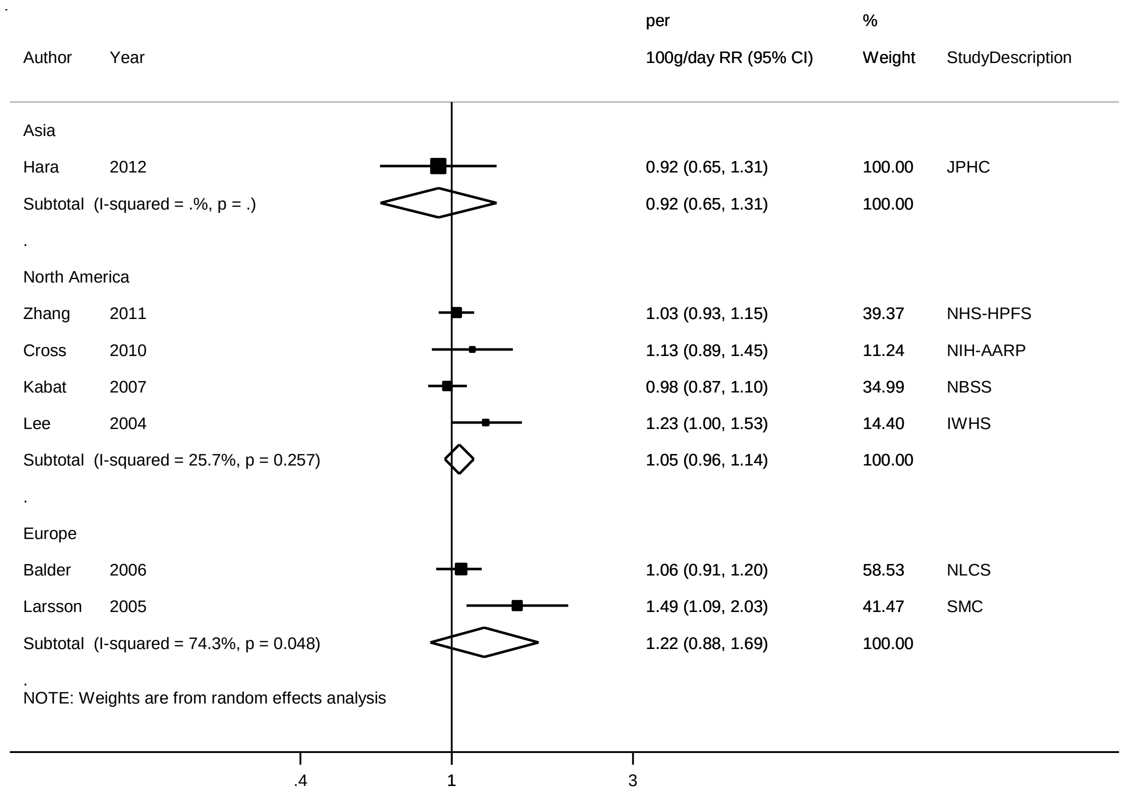


Figure 504 RR estimates of rectal cancer by levels of heme-iron

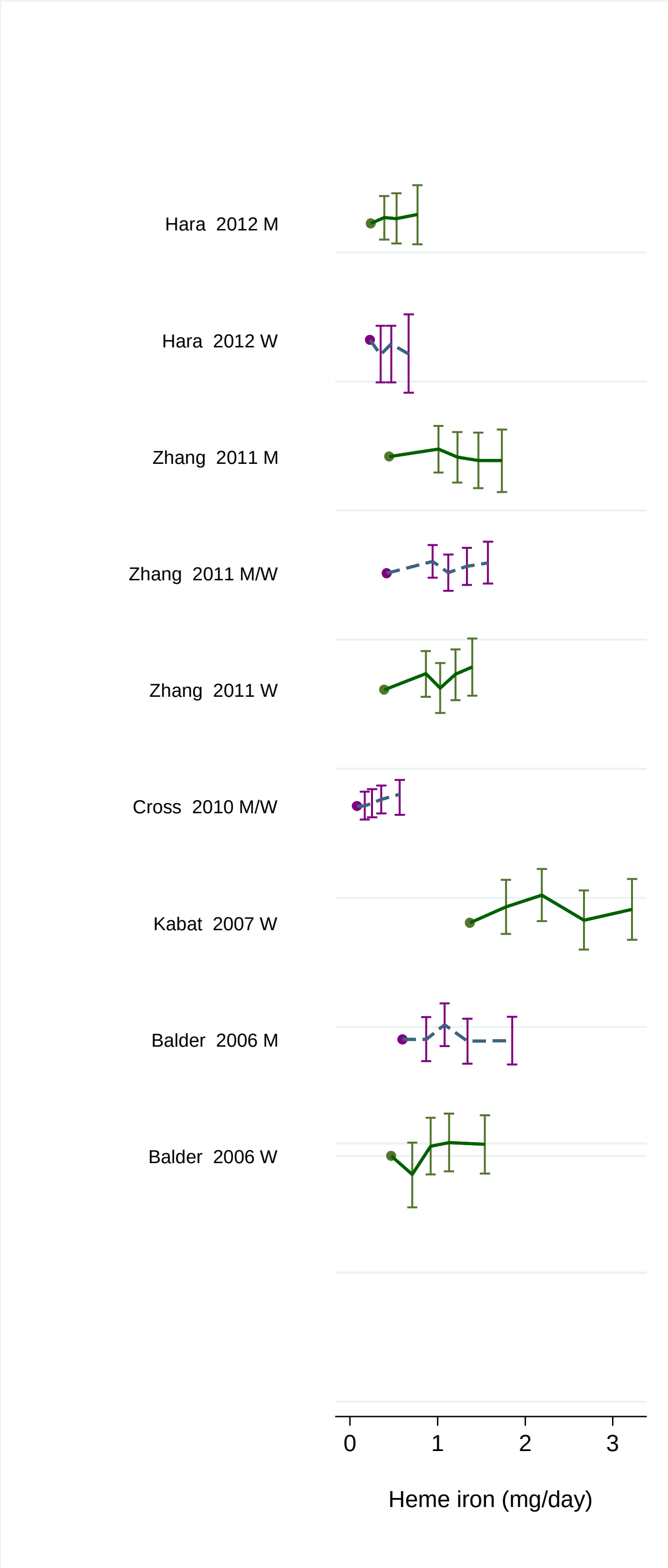


Figure 505 RR (95% CI) of rectal cancer for the highest compared with the lowest level of heme-iron

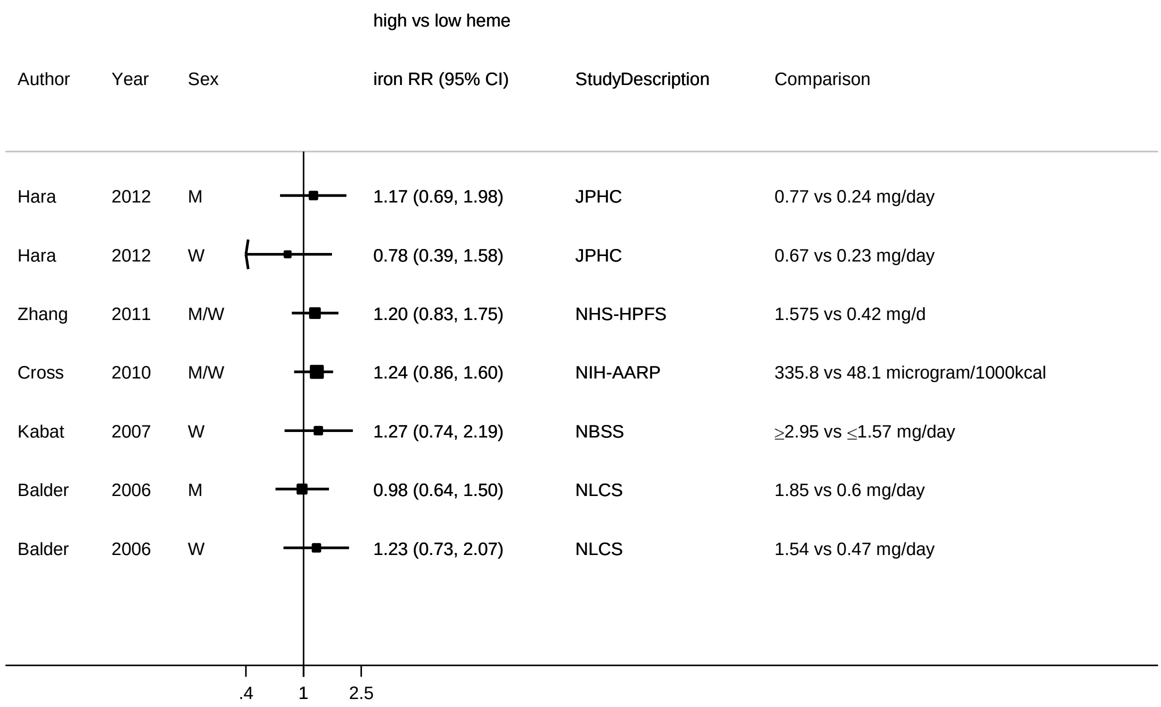


Figure 506 RR (95% CI) of rectal cancer for 1mg/day increase of heme-iron

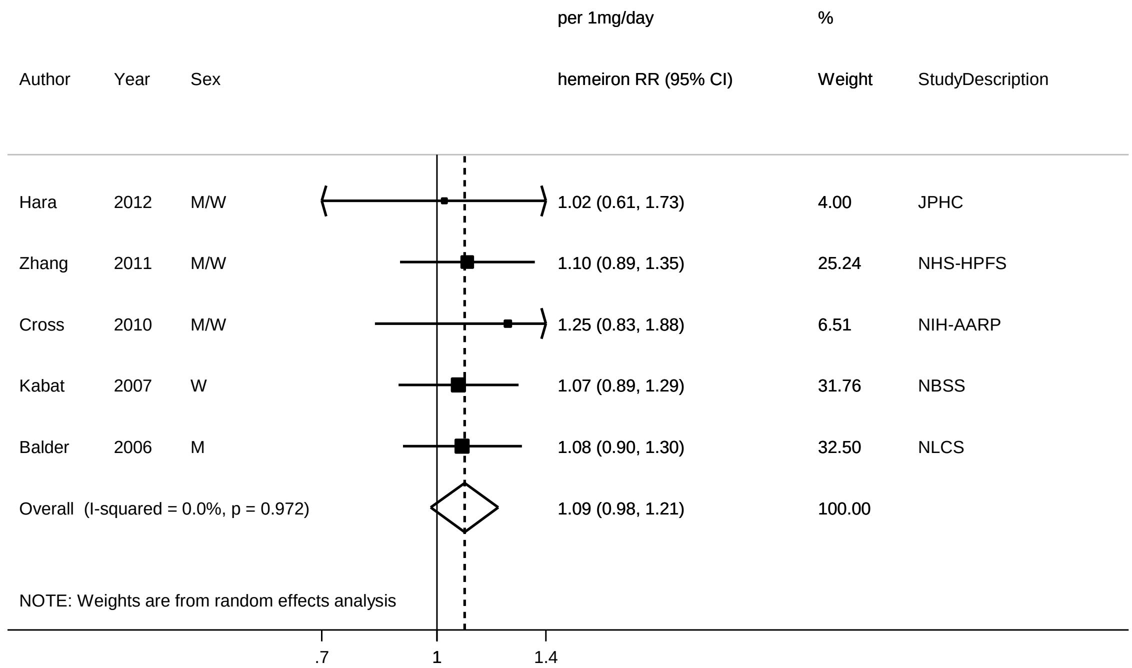


Figure 507 Funnel plot of studies included in the dose response meta-analysis of heme-iron and rectal cancer

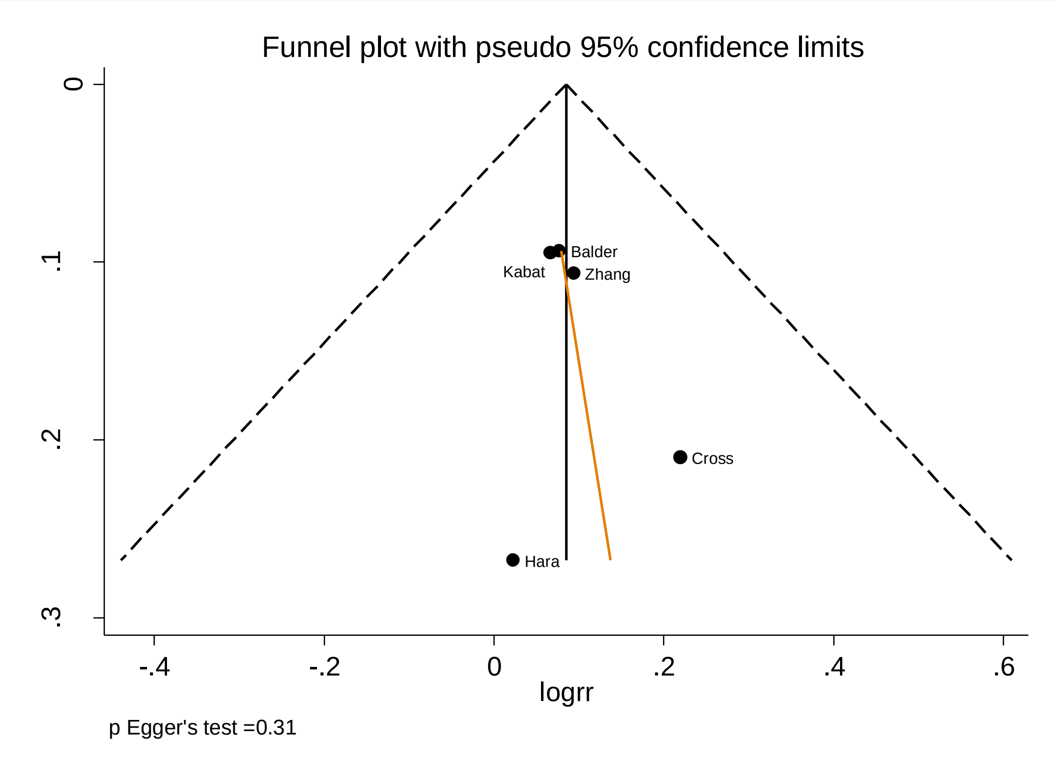


Figure 508 RR (95% CI) of rectal cancer for 1mg/day increase of heme-iron by sex

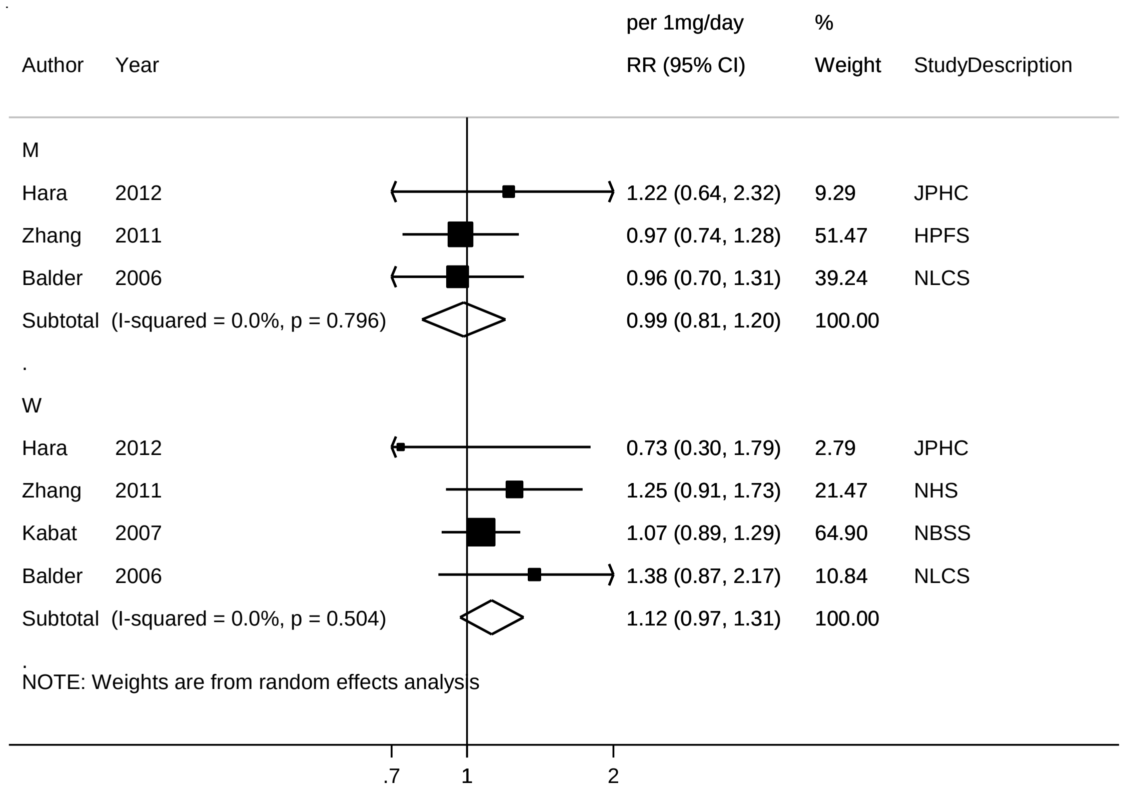


Figure 509 RR (95% CI) of rectal cancer for 1mg/day increase of heme-iron by location

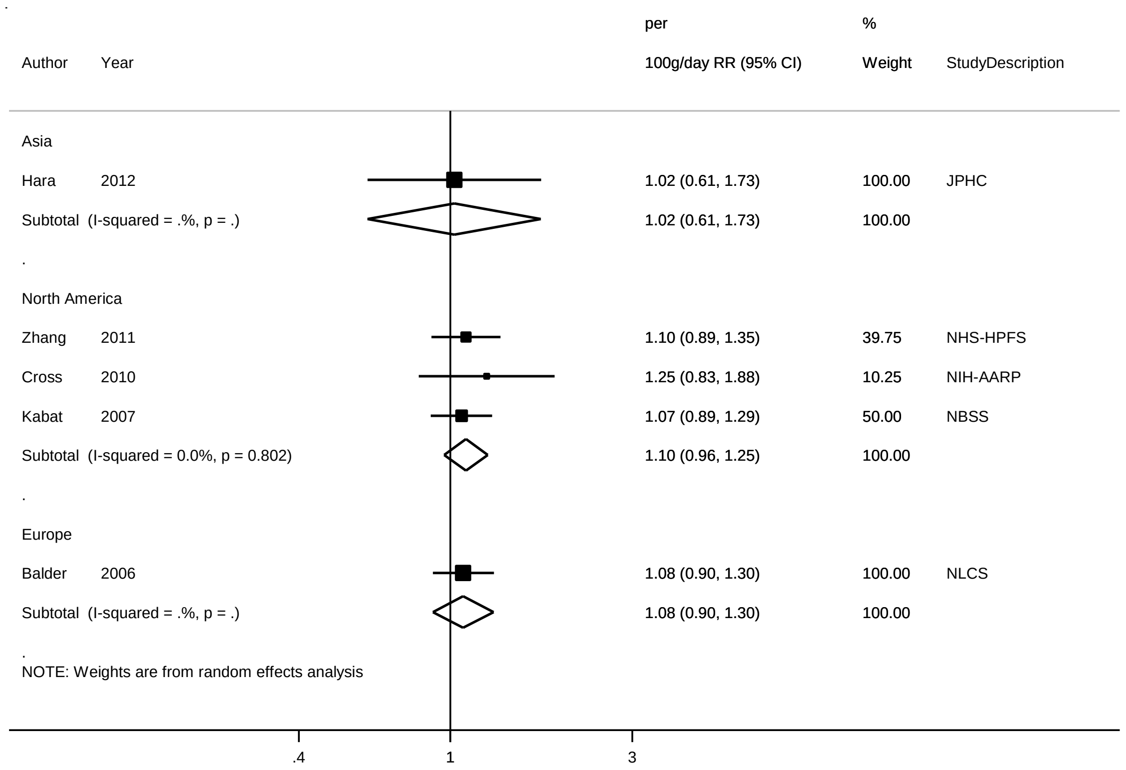
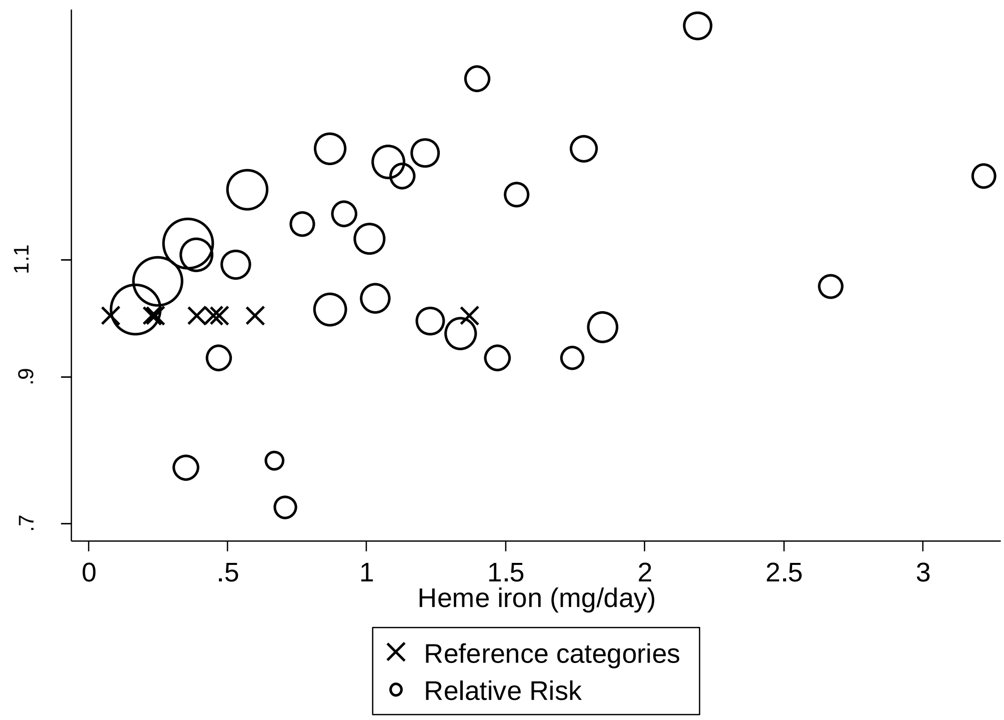


Figure 510 Relative risk of rectal cancer and heme-iron estimated using non-linear models



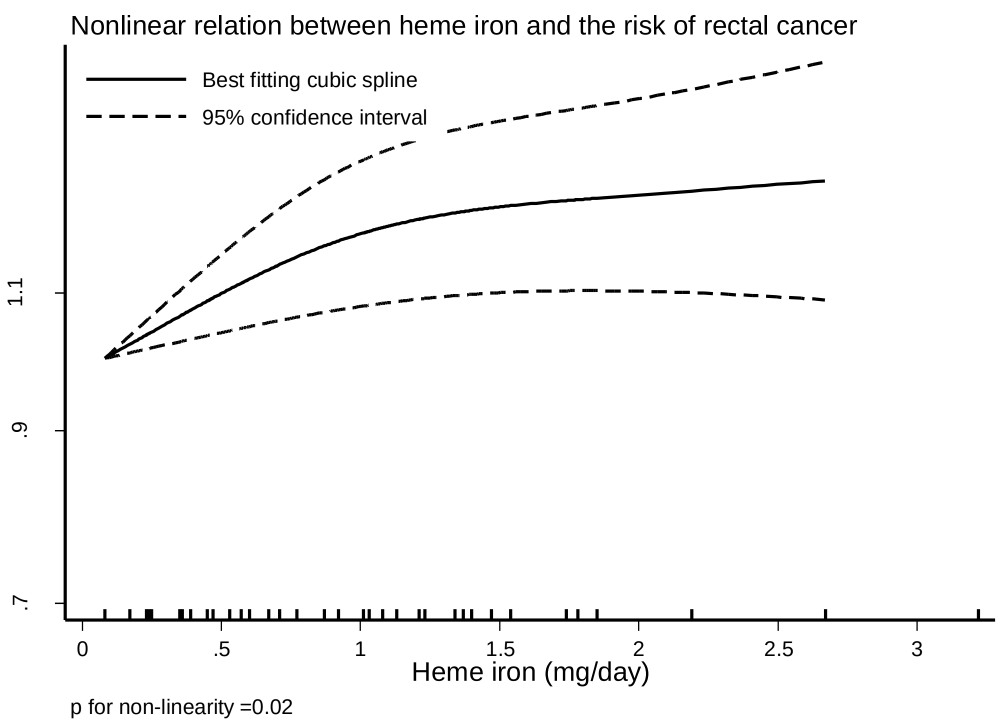


Table 292Table with heme-iron values and corresponding RRs (95% CIs) for non-linear analysis of heme-iron and rectal cancer

Heme-iron (mg/day)	RR(95%CI)
0	
0.6	1.02(1.00-1.03)
1.01	1.20(1.07-1.33)
1.4	1.24(1.09-1.40)
2.19	1.28(1.10-1.48)

5.6.4 Selenium supplements

Cohort studies

Summary

Main results:

No analysis on selenium and colorectal cancer was included in the 2010 SLR. One RCT (SELECT, Lippman, 2009) was described in the narrative review. An updated publication of the SELECT study was identified in the 2015 SLR (Klein, 2001).

A total of 35 533 men from 427 study sites in the United States, Canada, and Puerto Rico were randomized between August 22, 2001, and June 24, 2004. The primary analysis included 34 887 men who were randomly assigned to 1 of 4 treatment groups: 8752 to receive selenium; 8737, vitamin E; 8702, both agents, and 8696, placebo. Oral selenium (200 µg/d from *L*-selenomethionine) with matched vitamin E placebo, vitamin E (400 IU/d of all *rac*-_-tocopheryl acetate) with matched selenium placebo, both agents, or both matched placebos for a planned follow-up of a minimum of 7 and maximum of 12 years.
327 colorectal cases were identified. The RR for vitamin E+ selenium vs placebo was 1.21 (95%CI=0.81-1.81), the RR for selenium supplement vs placebo was 0.96 (95%CI=0.63-1.46) (Klein, 2011).

A cohort study (IWHS) identified in the 2010 SLR compared the use vs non-use of selenium supplements. The results are shown in the table below.

Table 293 Selenium supplements and colorectal cancer risk. Main characteristics of studies included in the CUP SLR dose-response meta-analysis

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors
Klein, 2011 COL40894 North America	SELECT, Randomised Control Trial, Age: 50- years, M, healthy men	168/ 34 887 54 646 person-years	Self report verified by medical record and pathology report	Questionnaire	Incidence	selenium and vit e supplement vs placebo	1.21 (0.81-1.81) Ptrend:0.22	
		149/				selenium supplement vs placebo	0.96 (0.63-1.46) Ptrend:0.79	
Lippman, 2009 COL40767 USA	SELECT, Randomised Control Trial, Age: 50- years, M	123/ 35 533 5.46 years	Self report/hospital record/patholog y reports	FFQ	Incidence, colorectal cancer	selenium from supp vs placebo	1.05 (0.66-1.67)	
		20/			Mortality, colorectal cancer	selenium from suppl vs placebo	1.00 (0.32-3.16)	
						selenium and vit e vs placebo	1.49 (0.52-4.28)	
Bostick, 1993 COL00483 USA	IWHS, Prospective Cohort, Age: 55-69 years, W	212/ 35 216 167 447 person-years	Population	Semi-quantitative FFQ	Incidence, colon cancer,	yes vs no	0.60 (0.27-1.32)	Age, calories Intake, height, low-fat meat Intake, parity, total vitamin e Intake, total vitamin e x age, vitamin a supplement Intake

5.6.4 Dietary and total selenium

One study (Butler, 2008) from Singapore reported a not statistically significant association between dietary selenium and colorectal cancer. The RR for the highest vs lowest was 1.14 (95%CI=0.95-1.37).

One study (Hansen, 2009) from Denmark reported a not statistically significant association on interactions between different polymorphisms, total selenium and colorectal cancer.

6 Physical Activity

Table 294 Main characteristics of physical activity assessment in studies included in the review of CRC

Study	Domains	Description of assessment	Validation
European Prospective Investigation into Nutrition and Cancer (EPIC)	Total (Aleksandrova, 2014) Recreational (Friedenreich, 2006)	Self-administered questionnaire in most centres and interview in a few. Questionnaire on occupational activity, walking, cycling, gardening, sports, do-it-yourself work, housework and stair climbing	Relative validity and reproducibility undertaken; the questionnaire was found to be satisfactory for the ranking of subjects, less suitable for estimation of energy expenditure. Construct validity by correlation with BMI (from other publication)
Secondary analysis of National Surgical Adjuvant Breast and Bowel Project (NSABP) Breast Cancer Prevention Trial USA	Recreational (Land, 2014)	Questions on physical inactivity, and light, moderate or vigorous leisure time physical activity	Not indicated
Nurses's Health Study Cohort	Recreational (Wolin, 2007; Wei, 2004; Wei, 2009)	Self-reported questionnaires on usual walking pace and number of flights of stairs climbed daily; average in 8 leisure-time activities: walking or hiking outdoors, jogging, running, bicycling, lap swimming, playing tennis, squash or racquetball, calisthenics, aerobics, aerobic dance or use of a rowing machine. Activity converted to METs	Instrument reliable and valid in a similar cohort of younger nurses. Questionnaire had good correlation with a weekly recall (r = 0.79) and the average of four, 7-day activity diaries administered over 1 year (r = 0.56) .

Singapore Chinese Health Study	Total physical activity (Odegaard, 2013)	Interview; 8 continuous categories ranging from never to 31 hours or more in an average week spent doing strenuous sports (e.g. jogging, bicycling on hills, tennis, squash,swimming laps or aerobics); vigorous work (e.g. moving heavy furniture, loading or unloading trucks, shoveling or equivalent manual labour); and moderate activities (e.g. brisk walking, bowling, bicycling on level ground, tai chi and chi kung)	
The Netherlands's Cohort Study	Total Recreational (Simons, 2013)	Self-administered questionnaire: occupational sitting time and nonoccupational physical activity time (walking/cycling, gardening/doing odd jobs, and sports/gymnastics)	
Norwegian World Class Athletes	Recreational (Robsahm, 2010)	Hours and type of exercises	Not indicated in the paper
Shanghai Women's Health Study	Recreational (Lee, 2009)	Regular exercise (no details)	Not indicated in the paper
NIH- AARP Diet and Health Study, US	Total physical activity Recreational (Howard, 2008)	Self-administered questionnaire. Times per week of physical activity or sports that lasted at least 20 min and caused increases in breathing or heart rate, or caused them to work up a sweat (i.e., current exercise/sports). Daily routine activity at home or work: sitting, sitting and walking, standing or walking but not lifting or carrying things, carrying light loads or climbing stairs, and carrying heavy loads or doing heavy work.	Reliability and validity evaluated in similar U.S. cohorts and found to provide useful information
Japan Public Health Center-based Prospective Study (JPHC Study) I and II	Total physical activity (Lee, 2007; Inoue, 2008)	Self-administered questionnaire: frequency of heavy physical work or strenuous exercise, sedentary activity and walking or standing. MET-hour assigned to activities	Validity of MET-hour score assessed in 55 men and 55 women from the cohort using a 4-day 24-h physical activity record . Rank correlation coefficient between MET-hour score and physical activity records was 0.64 ($p < 0.0001$)

California Teachers Study USA	Recreational (Mai, 2007)	Time spent participating in all moderate activities (brisk walking, recreational tennis, volleyball, golf, softball, and cycling on level street) and strenuous activities (swimming laps, aerobics, calisthenics, running, jogging, cycling on hills, and racquetball)	Not indicated
Breast Cancer Detection Demonstration Project (BCDDP)	Total physical activity (Calton, 2006)	Hours spent sleeping and engaged in light, moderate and vigorous activities on a typical weekday and weekend day (examples of light activity: sitting, working in an office, watching TV and driving a car; moderate activity: light housework, hiking and golf; of vigorous activity: heavy housework, strenuous sports/exercise and aerobics). Frequency of regular activity similar to brisk walking ,bicycling, long enough to the point of sweating. MET-hour assigned to activities	Not validated but predicts cardiovascular mortality in this cohort. Instrument resembles other validated questionnaires (Framingham Heart Study, College Alumnus Physical Activity Questionnaire)
Cohort of Swedish men (COSM)	Total physical activity Recreational (Larsson, 2006)	Self-administered questionnaire: activity at work (mostly sitting down; sitting down about half of the time; mostly standing up; mostly walking, lifts, carry little; mostly walking,lifts, carry much; heavy manual labor), time of home/housework. Leisure time: walking/bicycling and exercise . Physical inactivity: time watching TV/reading, sleeping and sitting/lying down. MET-hour assigned to activities.	Validated in 111 men. Spearman correlation coefficients between the questionnaire and 7- day activity records: 0.4 for leisure-time physical activity, 0.6 for home/housework, 0.4 for work/occupation, and 0.6 for total activity score.
Schnohr, 2005 COL01986 Denmark	CCPPS, Prospective Cohort, Age: 20-93 years, M/W	Self-administered questionnaire including frequency of entirely sedentary activities (reading, TV, cinema), light physical activity (walking, cycling, light gardening), vigorous physical activity (brisk walking, fast cycling, heavy gardening, sports where you get sweaty or exhausted, regular heavy exercise or competitive sports)	The questionnaire discriminates sedentary persons well from their more active counterparts with regard to maximal oxygen uptake
Norwegian Nord-Trondelag Health Study	Total physical activity (Nilsen, 2002)	Not described in Nilsen 2002 In Nilsen 2008: frequency, duration, and intensity of recreational physical activity in a week (walking, skiing, swimming, or other sports). (In lung SLR: Questionnaire.	Not indicated

Norway	Recreational (Nilsen, 2008)	Frequency of recreational physical exercise during a week (walking, skiing, swimming, other sports), duration per occasion, and intensity of activity.	
CPS II Nutrition Cohort	Recreational (Chao, 2004)	Self-reported time spent at seven recreational activities (walking, jogging/running, lap swimming, tennis or racquetball, bicycling/stationary bike, aerobics/calisthenics, and dancing) in the year before study enrolment	Not validated
British Regional Heart Study (BRHS)	Total physical activity (Wannamethee, 2001)	Questionnaire on walking, cycling, gardening, do-it-yourself, and sporting (vigorous) activity. Physical activity at work was excluded because it was considered low	Validated in men free of coronary heart disease using heart rate and forced expiratory volume
Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study, Finland	Recreational (Colbert, 2001)	Usual leisure-time activity in the past year as: *(i)* sedentary (*e.g.*, reading, watching television); *(ii)* moderate (*e.g.*, walking, hunting, gardening) fairly regularly; or *(iii)* heavy (*e.g.*, running, skiing, swimming) fairly regularly**.**	Not indicated
Adventists Health Study	Total physical activity (Singh, 1998)	Physical activity index calculated from questionnaire about vigorous leisure-time or occupational activities	Not indicated
Physicians' Health Study	Recreational (Lee, 1997)	Time spent in activity vigorously enough to work up a sweat. Occupational activity excluded	Not indicated
Norwegian National Health Screening Service study	Total physical activity Recreational (Thune, 1996)	Self-reported. Combined score of occupational activity and physical activity during recreational hours(reading, watching TV or other sedentary activities; walking, bicycling or other physical activities, exercise, sport)	Not indicated
Harvard Alumni Study	Total physical activity (Lee,	Number of flights of stairs climbed and city blocks walked, and time spent in active sport play and kind of sports in previous week	Reliability and validity reported in other publication (no data in the

	1991) Recreational (Lee, 1994)	and year	paper)
Framingham Study USA	Total physical activity Ballard-Barbash, 1990	Self-reported weighted sum of time sleeping, sitting or standing, walking, moderate activity (as gardening), heavy (as shoveling).	Not indicated
Honolulu Heart Program	Total physical activity (Severson, 1989)	Same as Framingham study: time sleeping, sitting or standing, walking, moderate activity (as gardening), heavy (as shoveling).	Not indicated
Iowa Women's Health Study USA	Recreational (Bostick, 1994)	Two questions on frequency of free-time activities: moderate (bowlimg, golf, light sports, exercise, gardening, long walks) and vigorous (jogging, racket sports, swimming, aerobics, strenuous sports)	Not indicated
Swedish Twin Follow-up Study	Total physical activity Recreational (Gerhardsson, 1988)	Self-reported. Combination of time and intensity of occupational and recreational activities	Not indicated
Leisure World Cohort	(Wu, 1987)	Mailed questionnaire; time spent on physical activity (swimming, biking, dancing)	Not indicated

6.1. Total physical activity

Cohort studies

Summary

Main results:
From the 2010 SLR, two new studies on colorectal cancer, three on colon cancer , one on distal and proximal colon cancer and two on rectal cancer were published. The new studies presented the results in different units, therefore a dose-response meta-analysis was not conducted.
A dose-response meta-analysis was conducted in the 2010 SLR and the results are included in the tables below.

Fifteen studies out of seventeen published studies) were included in highest compared to lowest analysis. Six studies (5607 cases) were included in the highest compared to lowest analysis on colorectal cancer, twelve studies (8996 cases) in the analysis on colon cancer and nine studies (2326 cases) in the analysis on rectal cancer. All studies were on incidence. No analysis on mortality was conducted.

Total physical activity was significantly inversely associated to the risk of colorectal cancer (RR for the highest compared to the lowest=0.81; 95%CI=0.69-0.95) and colon cancer (for the same comparison, RR=0.80; 95%CI=0.72-0.88). No significant association was observed between total physical activity and rectal cancer.

Study quality:
Cancer outcome was confirmed using cancer registry records in most studies. Physical activity was assessed using different questionnaires. Most studies adjusted for multiple confounders, three studies adjusted for age only (Ballard-Barbash, 1990; Lee, 1991; Nilsen, 2002), one study adjusted for age and BMI (Severson, 1989) and one study for age and sex (Gerhardsson, 1988).

Meta-analysis and pooled analysis:
None on total physical activity identified after 2010.

Table 295 Total physical activity and colorectal cancer risk. Number of studies in the CUP SLR

	Number
Studies identified	7 (8 publications)
Studies included in forest plot of highest compared with lowest exposure	6
Studies included in dose-response meta-analysis	NA

Note: Include cohort, nested case-control and case-cohort designs

Table 296 Total physical activity and colon cancer risk. Number of studies in the CUP SLR

	Number
Studies identified	13(15 publications)
Studies included in forest plot of highest compared with lowest exposure	12
Studies included in dose-response meta-analysis	NA

Note: Include cohort, nested case-control and case-cohort designs

Table 297 Total physical activity and rectal cancer risk. Number of studies in the CUP SLR

	Number
Studies identified	10 (12 publications)
Studies included in forest plot of highest compared with lowest exposure	9
Studies included in dose-response meta-analysis	NA

Note: Include cohort, nested case-control and case-cohort designs

Table 298 Total physical activity and colorectal cancer risk. Summary of the dose-response meta-analysis in the 2010 SLR and 2015 SLR.

	2010 SLR	**2015 SLR**
Increment unit used	5 METS-hours/week	Highest vs lowest
Colorectal cancer		
Studies (n)	3	6
Cases (total number)	924	5607
RR (95%CI)	0.97(0.94-0.99)	0.81(0.69-0.95)
Heterogeneity (I^2, p-value)	0%, 0.54	47.9%, 0.05
Colon cancer		
Studies (n)	5	12
Cases (total number)	3153	8396
RR (95%CI)	0.92(0.86-0.99)	0.80(0.72-0.88)
Heterogeneity (I^2, p-value)	80.3%, <0.001	39.1%, 0.06

Rectum cancer		
Studies (n)	3	9
Cases (total number)	483	2326
RR (95%CI)	1.02(0.95-1.10)	1.04(0.92-1.18)
Heterogeneity (I^2, p-value)	33.7%, 0.22	9.2%, 0.36

Table 299 Total physical activity and colorectal cancer risk. Main characteristics of studies included in the CUP SLR dose-response meta-analysis

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors
Aleksandrova, 2014 COL41051 Europe	EPIC, Prospective Cohort, Age: 25-70 years, M/W	3 759/ 347 237 12 years	Cancer registry (in a few centres, combination of methods)	Questionnaire on occupational activity, walking, cycling, gardening, sports, do-it-yourself work, housework and stair climbing	Incidence, colorectal cancer	high vs low	0.94 (0.87-1.00)	Age, sex, overweight and obesity, study centre, alcohol consumption, diet quality index, education, smoking
		1390/			Incidence, rectal cancer	high vs low	1.03 (0.92-1.15)	
		2369/			Incidence, colon cancer	high vs low	0.88 (0.81-0.96)	
Odegaard, 2013 COL40948 Singapore	SCHS, Prospective Cohort, Age: 45-74 years, M/W	969/ 50 466 579 628 person-years	Cancer registry and death registry	Interview on strenuous sports vigorous work and moderate activities (e.g., walking, bicycling)	Incidence, colon cancer	≥1.5 vs <1.5 hours/week	0.61 (0.42-0.88)	Age, sex, BMI, diabetes, dialect group, dietary pattern score, energy intake, sleep time, alcohol intake, education, family history of colorectal cancer, smoking
Simons, 2013	NLCS,	1 026/	Cancer registry	Self-	Incidence, colon	active vs low	0.65 (0.43-0.99)	Age, BMI, family

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors
COL40956 Netherlands	Prospective Cohort, Age: 55-69 years, M/W	4 416 16 years		administered questionnaire: occupational sitting time and nonoccupational physical activity time (walking/cycling, gardening/doing odd jobs, and sports/gymnastics	cancer, men			history of colon cancer, meat intake, processed meat, alcohol, energy, smoking
		530/			Incidence, distal colon cancer, men	active vs low	0.71 (0.42-1.21)	
		454/			Incidence, proximal colon cancer, men	active vs low	0.60 (0.36-1.00)	
		399/			Incidence, rectal cancer, men	active vs low	0.99 (0.53-1.83)	
Howard, 2008 COL40715 USA	NIH- AARP Diet and Health Study, Prospective Cohort, Age: 50-71 years, M/W	1 264/ 488 720 6.9 years	Cancer registry	Questionnaire	Incidence, colon cancer, men	66.08 vs 5.53 met-hours/week	0.79 (0.66-0.94)	Age, alcohol consumption, BMI, calcium intake, educational level, fruit intake, race, red meat intake, smoking status, vegetable intake, whole grain intake, family history of colorectal cancer, total energy
		672/			Women	66.08 vs 8.07 met-hours/week	0.92 (0.71-1.18)	
Inoue, 2008 COL40647 Japan	JPHC, Prospective Cohort, Age: 45-74	328/ 79 771	Active patient notification from hospitals, cancer registries and		Incidence, colon cancer, men	36.25-46.25 vs 21.6-27.1 mets/day	0.58 (0.43-0.79)	Age, alcohol intake, BMI, history of diabetes, recreational activity, smoking status,
		228/			Women	35.45-46.25 vs	0.82 (0.56-1.21)	

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors
	years, M/W		death cert.			21.6-27.1 mets/day		total energy intake, area
		162/			Incidence, rectal cancer, men	36.25-46.25 vs 21.6-27.1 mets/day	0.88 (0.57-1.36)	
		86/			Women	35.45-46.25 vs 21.6-27.1 mets/day	1.79 (0.99-3.23)	
Lee, 2007 COL40644 Japan	JPHC study-cohort I and II, Prospective Cohort, Age: 40-69 years, M/W	290/ 65 022 6 years	Active patient notification from hospitals, cancer registries and death cert.	Self-administered questionnaire	Incidence, colorectal cancer, men	43.75 vs 28.25 met/hours/day	0.69 (0.49-0.97)	Age, alcohol intake, BMI, folate intake, red meat intake, smoking habits, study area, family history of colorectal cancer, fibre
		196/			Women	43.75 vs 28.5 met/hours/day	1.16 (0.76-1.77)	
		140/			Incidence, colon cancer, women	43.75 vs 28.5 met/hours/day	0.89 (0.54-1.49)	
		93/			Incidence, rectal cancer, men	43.75 vs 28.25 met/hours/day	1.06 (0.56-2.00)	
		56/			Women	43.75 vs 28.5 met/hours/day	2.23 (0.99-5.01)	
Calton, 2006 COL40618 USA	BCDDP, Prospective Cohort, W	243/ 31 783 270 325 person-years	Self-report, pathology report, national death index, death cert, state cancer registries	Questionnaire	Incidence, colon cancer	65-98.1 vs 34-48.5 met hr/day	1.15 (0.76-1.75)	Age, alcohol intake, aspirin use, BMI, calcium intake, educational level, hormone use, red meat intake, smoking status,

Author, Year, WCRF Code, Country	**Study name, characteristics**	**Cases/ Study size Follow-up (years)**	**Case ascertainment**	**Exposure assessment**	**Outcome**	**Comparison**	**RR (95%CI) Ptrend**	**Adjustment factors**
								family history of colorectal cancer
Larsson, 2006 COL40625 Sweden	COSM, Prospective Cohort, Age: 45-79 years, M	365/ 45 906 7.1 years	Cancer registry	Postal questionnaire	Incidence, colorectal cancer	≥44.9 vs ≤37.8 met-hours/day	0.82 (0.60-1.10)	Age, aspirin use, BMI, educational level, history of diabetes, smoking status, family history of colorectal cancer
		227/			Incidence, colon cancer	≥44.9 vs ≤37.8 met-hours/day	0.79 (0.53-1.17)	
		140/			Incidence, rectal cancer	≥44.9 vs ≤37.8 met-hours/day	0.86 (0.53-1.37)	
Nilsen, 2002 COL00306 Norway	Norwegian Nord-Trondelag Health Study, Prospective Cohort, Age: 20- years, M/W	368/ 75 219 12 years	Cancer registry		Incidence, colorectal cancer, women	high vs low	0.81 (0.54-1.23)	Age
		362/			Men	high vs low	0.54 (0.37-0.79)	
					Incidence, rectal cancer	high vs low	0.63 (0.36-1.12)	
Wannamethee, 2001 COL01187 UK	BRHS, Prospective Cohort, Age: 40-59 years, M	135/ 7 588 18.8 years	General practioners	Questionnaire	Incidence, colorectal cancer,	vigorous vs none to moderate	0.95 (0.48-1.88)	Age, alcohol consumption, BMI, social class, cigarette smoking
Thune, 1996 COL00269	Norwegian national health	228/ 81 516	Cancer registry	Questionnaire	Incidence, colon cancer, men,	active (o2-4 + r2-4) vs	0.97 (0.63-1.50)	Age, BMI, geographic region

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors
Norway	screening service study, Prospective Cohort, Age: 20-69 years, M/W	1 305 607 person-years			Rectal cancer	sedentary (r1+o1-2)	1.20 (0.72-2.02)	
		98/			Female, colon cancer	active (o2-4 + r2-4) vs sedentary (r1+o1-2)	0.63 (0.39-1.04)	Age, BMI, geographic region
					Rectal cancer		1.27 (0.59-2.72)	
Lee, 1991 COL00678 USA	Harvard Alumni Cohort, Prospective Cohort, Age: 30-79 years, M, Harvard Alumni	225/ 17 148 26 years	Harvard alumni questionnaires and death certificates		Incidence, colon cancer,	Highly active vs inactive	0.85 (0.64-1.12)	Age
					Rectal cancer		1.43 (0.78-2.60)	
Ballard-Barbash, 1990 COL00488 USA	FHS, Prospective Cohort, Age: 30-62 years, M/W	73/ 4 124 28 years	Hospital records	Questionnaire	Incidence, colorectal cancer, men	25-29 vs 34-84	1.80 (1.00-3.20)	Age
		59/			Female	25-29 vs 31-55	1.10 (0.60-1.80)	
Severson, 1989 COL00738 USA	Honolulu Heart Program, Prospective Cohort, Age: 46-68 years,	191/ 7 925 31 years	Cancer registry & hospital surveillance	Interview	Incidence, colon cancer,	≥34.3 vs 0-30.1	0.71 (0.51-0.99)	Age, BMI

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors
	M							
Gerhardsson, 1988 COL01044 Sweden	Swedish Twin Follow-up Study, Prospective Cohort, M/W, twin individuals	36/ 16 477 14 years	Cancer and Death Registries	Questionnaire	Incidence, colon cancer,	$Q_2$1 vs $Q_2$2	3.60 (1.30-9.80)	Age, sex
					Rectal cancer		0.83 (0.45-1.43)	
Singh, 1998 COL00185 USA	AHS, Prospective Cohort, Age: 25- years, M/W, Seventh-day Adventists	152/ 32 051 178 544 person-years	Medical records	Questionnaire	Incidence, colon cancer,	high vs low vigorous physical activity	1.04 (0.72-1.51)	Age, sex, family history of specific cancer

Table 300 Total physical activity and colorectal cancer risk. Main characteristics of studies excluded from the CUP SLR dose-response meta-analysis

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Exclusion reason
Makarem, 2015 COL41060 USA	Framingham Heart Study - Offspring Cohort, Prospective Cohort, Age: 66.00years, M/W	63/ 2 983 11.5 years	Death certificate and medical records	Questionnaire	Incidence, colorectal cancer	per 1 points	0.95 (0.47-1.93)	Age, sex, smoking status	Only continuous results
						per 1 points	0.88 (0.43-1.78)	Age	
Hughes, 2011 COL40873 Netherlands	Netherlands Cohort Study on Diet and Cancer, 1986-1997, Case Cohort, Age: 55-69 years, M/W	321/ 5 000 7.3 years	Cancer registry	Questionnaire	Incidence, colorectal cancer, non-cimp	high vs low	0.69 (0.47-1.01)	Age, sex, education level, energy intake, smoking status, socio-economic status, alcohol intake, family history of colorectal cancer, fruit and vegetable, grains intake, physical activity, red meat consumption	Superseded by Simmons, 2013
						high vs low	0.67 (0.47-0.96)	Age, sex	

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Exclusion reason
								Age, sex	
		155/			2-3 genes methylated	high vs low	0.54 (0.31-0.94)		
		122/			0-1 genes methylated	high vs low	0.72 (0.41-1.28)		
		108/			Island methylator phenotype (cimp)	high vs low	0.81 (0.48-1.36)	Age, sex, education level, energy intake, smoking status, socio-economic status, alcohol intake, family history of colorectal cancer, fruit and vegetable, grains intake, phyisical activity, red meat consumption	
		93/			4-7 genes methylated	high vs low	0.88 (0.50-1.54)	Age, sex	
Friedenreich, 2006	EPIC, Prospective	1 075/ 413 044	Cancer registry, record linkage,	Questionnaire/interview	Incidence, colon cancer	active vs inactive	0.78 (0.59-1.03)	Age, center, educational	Superseded by Aleksandrova,

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Exclusion reason
COL40620 Europe	Cohort, Age: 35-70 years, M/W	6.38 years	health insurance rec, pathology and active follow up					level, energy intake, fiber intake, height, smoking status, weight	2014
		587/			Incidence, rectal cancer	active vs inactive	1.02 (0.73-1.44)		
Pukkala, 1993 COL01117 Finland	Finland, female teachers, Prospective Cohort, W, teachers	26/ 10 118 141 092 person-years	Cancer Registries		Incidence, colon cancer, language teachers	Language teachers vs Finnish population	1.25 (0.81-1.81)	Age	No level of physical activity measured. Comparison between physical activity teachers and Finnish general population
		15/			Incidence, rectal cancer, language teachers	Language teachers vs Finnish population	1.10 (0.62-1.81)		
		9/			Incidence, colon cancer, Physical education teachers	Physical education teachers vs Finnish population	1.61 (0.74-3.05)		
		1/			Incidence, rectal cancer, Physical education teachers	Physical education teachers vs Finnish population	0.27 (0.01-1.52)		

Figure 511 RR (95% CI) of colorectal cancer for the highest compared with the lowest level of total physical activity

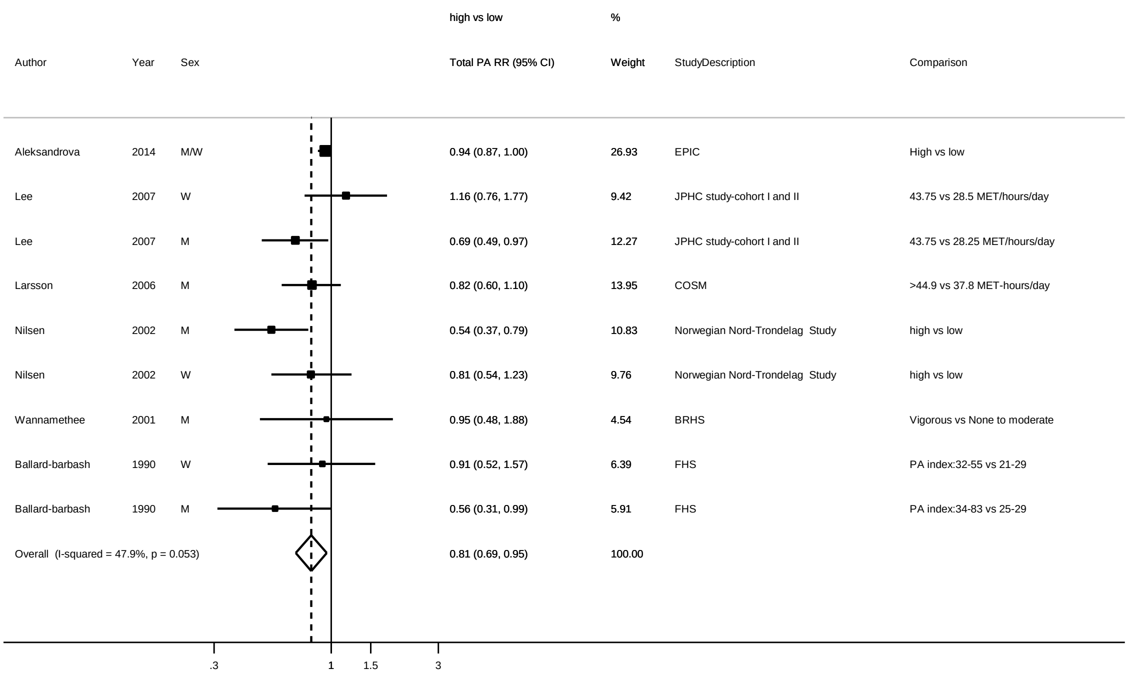


Figure 512 RR (95% CI) of colon cancer for the highest compared with the lowest level of total physical activity

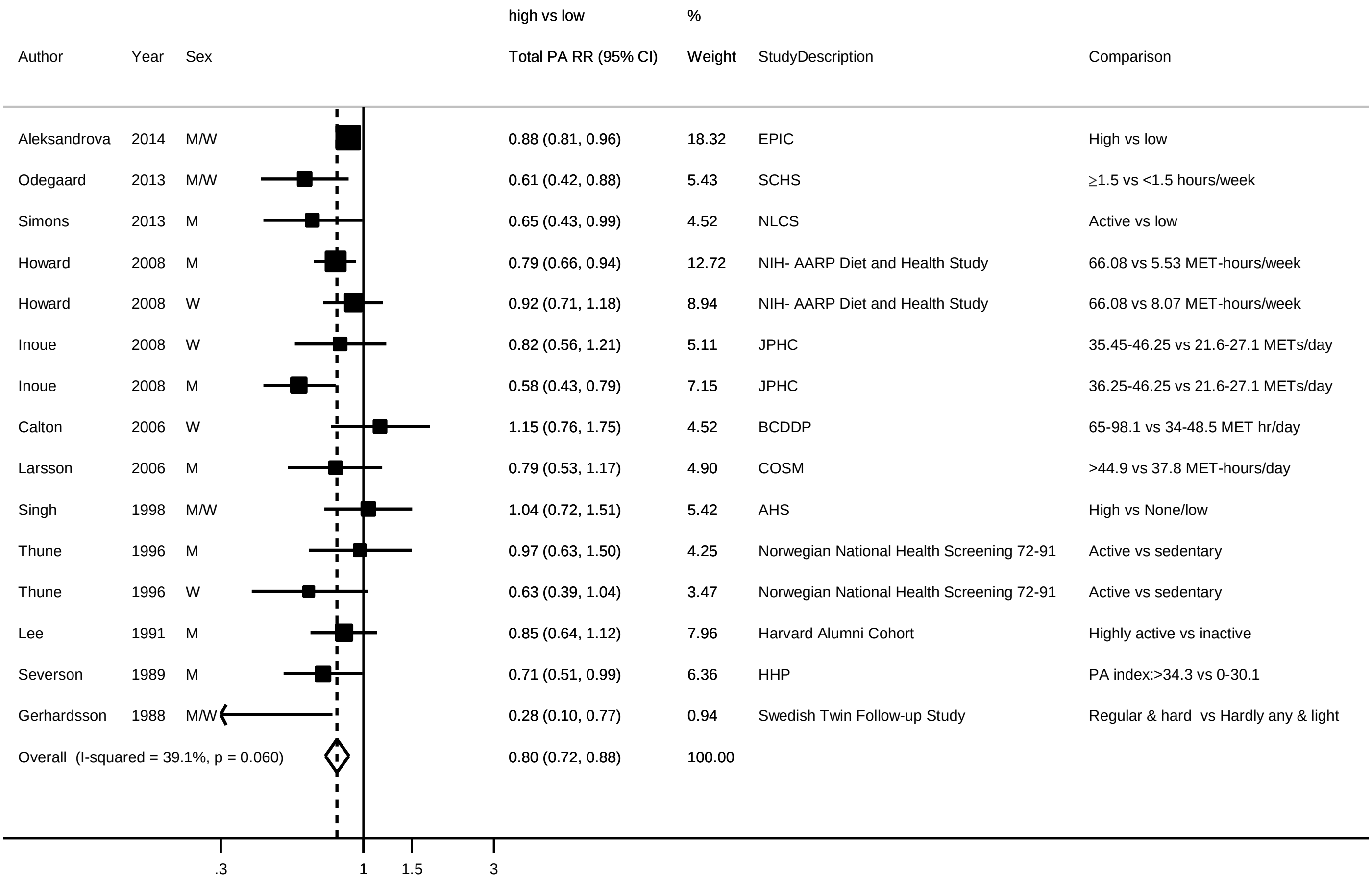
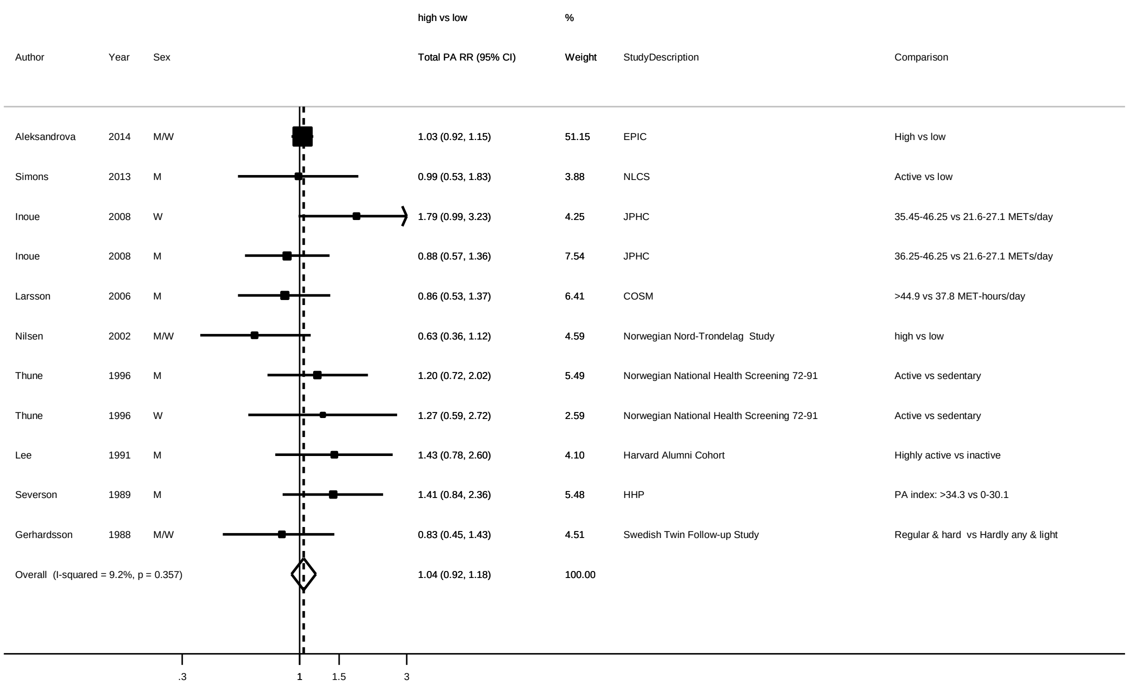


Figure 513 RR (95% CI) of rectal cancer for the highest compared with the lowest level of total physical activity



6.1.1.2 Recreational physical activity

Cohort studies

Summary

Main results:
There were no new studies on colorectal cancer, 3 new studies on colon cancer, one new study on rectal cancer, one new study on distal and proximal colon cancer. The new studies identified presented the results in different units, therefore a dose-response meta-analysis was not conducted.
A dose-response meta-analysis was conducted in the 2010 SLR and the results are included in the tables below.

Twenty studies (20 publications) out of 31 studies (39 publications) were included in highest compared to lowest analysis. Two studies (Batty, 2010 and Suzuki, 2007) were on cancer mortality and were excluded. Six studies included in the 2010 SLR in the colorectal cancer analysis were excluded from this analysis because there were not new studies on colorectal cancer to update the analysis.

Nineteen studies (10258 cases) were included in the highest compared to lowest analysis of colon cancer and fourteen studies (4560 cases) were included in the highest compared to lowest analysis of rectal cancer. A significant inverse association was observed for colon cancer and recreational physical activity, RR=0.84(95%CI=0.78-0.91), and a non-significant association was observed for rectal cancer and recreational physical activity, RR=0.95(95%CI=0.85-1.07).

Study quality:
Cancer outcome was confirmed using cancer registry records in most studies. Physical activity was assessed using different questionnaires. Most studies adjusted for multiple confounders, four studies adjusted for age only (McCarl, 2006; Lee, 1997; Wu, 1987; Albanes, 1989), one study adjusted for age and sex (Gerhardsson, 1988), one study for age and race (Mai, 2007) and one study adjusted for age and energy intake (Lee, 2009).

Pooling project of cohort studies:
No Pooling Project was identified.

Table 301 Recreational physical activity and colon cancer risk. Number of studies in the CUP SLR

	Number
Studies identified	21 (26 publications)
Studies included in forest plot of highest compared with lowest exposure	20
Studies included in dose-response meta-analysis	NA

Note: Include cohort, nested case-control and case-cohort designs

Table 302 Recreational physical activity and rectal cancer risk. Number of studies in the CUP SLR

	Number
Studies identified	14(15 publications)
Studies included in forest plot of highest compared with lowest exposure	14
Studies included in dose-response meta-analysis	NA

Note: Include cohort, nested case-control and case-cohort designs

Table 303 Recreational physical activity and colorectal cancer risk. Summary of the dose-response meta-analysis in the 2010 SLR (no analysis was conducted in the 2015 SLR).

	2010 SLR	**2015 SLR**
Increment unit used	5 METS-hours/week	-
Studies (n)	3	
Cases (total number)	2220	
RR (95%CI)	0.97 (0.94-1.00)	
Heterogeneity (I^2, p-value)	66.2%, 0.05	

Table 304Recreational physical activity and colon cancer risk. Summary of the dose-response meta-analysis in the 2010 SLR and 2015 SLR.

	2010 SLR	**2015 SLR**
Increment unit used	5 METS-hours/week	Highest vs lowest
Studies (n)	5	20
Cases (total number)	2650	10258
RR (95%CI)	0.98 (0.96-1.00)	0.84(0.78-0.91)
Heterogeneity (I^2, p-value)	51.7%, 0.08	32.9%, 0.05

Table 305 Recreational physical activity and rectal cancer risk. Summary of the dose-response meta-analysis in the 2010 SLR and 2015 SLR.

	2010 SLR	**2015 SLR**
Increment unit used	5 METS-hours/week	Highest vs lowest
Studies (n)	5	14
Cases (total number)	1275	4560
RR (95%CI)	1.00 (0.97-1.03)	0.95(0.85-1.07)
Heterogeneity (I^2, p-value)	44.9%, 0.123	26.8%, 0.15

Table 306 Recreational physical activity and colorectal cancer risk. Results of pooled analyses of prospective studies published after the 2010 SLR.

Author, Year	Number of cohort studies	Total number of cases	Studies country, area	Outcome	Comparison	RR (95%CI)	P trend	Heterogeneity (p value)
Boyle, 2012	21 cohort and case-control studies	9512	Europe, North America, Japan, Australia	Proximal colon cancer	Highest vs lowest	0.73(0.66-0.81)		31.3%, 0.06
		8171		Distal colon cancer		0.74(0.68-0.80)		0%, 0.47
Yang, 2010	28 cohort studies		Europe, North America, Asia	Colon cancer	Highest vs lowest Men	0.74(0.61 - 0.90)	0.14	
					Highest vs lowest Women	0.99(0.95 – 1.02)	0.41	
Harris, 2009	15	7873	Europe, North America, Japan	Colon cancer	Highest vs lowest Men	0.80 (0.67-0.96)		54.1%, 0.01
					Highest vs lowest Women	0.86 (0.76-0.98)		0%, 0.88
				Rectal cancer	Highest vs lowest Men	1.02 (0.83-1.26)		8.1%, 0.37
					Highest vs lowest Women	1.29 (0.82-2.01)		29.5%, 0.24

Table 307 Recreational physical activity and colorectal cancer risk. Main characteristics of studies included in the CUP SLR dose-response meta-analysis

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Reasons for exclusion
Land, 2014 COL41062 USA	NSABP P-1, Prospective Cohort, Age: 54 years, W, High Risk population	35/ 13 388 7 years	Follow-up visits	Questionnaire	Incidence, invasive colon cancer	low/no activity vs more active	0.90	Age, alcohol consumption, estrogen use, family history of cancer, menstrual status, race, smoking status, treatment allocation, asprine use, smoking duration, smoking intensity	
Simons, 2013 COL40956 Netherlands	NLCS, Prospective Cohort, Age: 55-69 years, M/W	377/ 4 416 16 years	Cancer registry	Self-report	Incidence, distal colon cancer, women	>90 vs ≤30 /day	0.69 (0.50-0.96)	Age, BMI, family history of colon cancer, meat intake, processed meat, alcohol, energy, smoking	
		227/			Incidence, rectal cancer, women		0.59 (0.39-0.90)		
		1 107/			Incidence, colon cancer, men		1.06 (0.84-1.33)		
		438/			Incidence, rectal cancer, men		1.10 (0.80-1.52)		
		581/			Incidence,		1.18 (0.88-1.60)		

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Reasons for exclusion
					distal colon cancer, men				
		480/			Incidence, proximal colon cancer, men		0.92 (0.68-1.25)		
		517/			Women		0.71 (0.53-0.96)		
		924/			Incidence, colon cancer, women		0.70 (0.55-0.88)		
Robsahm, 2010 COL40835 Norway	Norwegian World Class Athletes, Prospective Cohort, Age: 17- years, M/W	22/ 3 428	Cancer registry	Questionnaire	Incidence, colon cancer	athlete vs not athlete	0.89(0.56-1.34)	Age, sex, birth cohort	
Wei, 2009 COL40777 USA	The Nurses's Health Study Cohort, Prospective Cohort, Age: 30-54 years, W	701/ 83 767 24 years	Self-report verified by medical record	Self-completed questionnaire every 4 years (no details)	Incidence, colon cancer	21 vs 2 met-hours/week	0.51 (0.33-0.78)	Age, aspirin use, BMI, folate intake, height, pack-years of smoking, year of endoscopy, family history of colorectal cancer, postmenopausal	

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Reasons for exclusion
								hormone use, red or processed meat intake	
Lee, 2009 COL40764 China	SWHS, Prospective Cohort, Age: 40-70 years, W	236/ 73 224 7.4 years	Cancer registry and death certificates and participant contact		Incidence, colon cancer	≥13.6 vs ≤0 met-hours/week	1.20 (0.80-1.70)	Age, energy intake	
		158/			Incidence, rectal cancer	≥13.6 vs ≤0 met-hours/week	1.10 (0.70-1.70)		
Howard, 2008 COL40715 USA	NIH- AARP Diet and Health Study, Prospective Cohort, Age: 50-71 years, M/W	1 090/ 488 720 6.9 years	Cancer registry	Questionnaire	Incidence, colon cancer, women	≥5 times/week vs never/rarely	0.87 (0.71-1.06)	Age, alcohol consumption, BMI, calcium intake, educational level, fruit intake, menopausal hormone use, physical activity, race, red meat intake, smoking status, vegetable intake, whole grain intake, family history of colorectal cancer, total energy	
		2 257/			Men	≥5 times/week vs never/rarely	0.82 (0.71-0.95)		
		1 190/			Incidence, proximal colon cancer, men	≥5 times/week vs never/rarely	0.83 (0.68-1.02)		
		923/			Incidence, rectosigmoid and rectum cancer, men	≥5 times/week vs never/rarely	0.76 (0.61-0.95)		
		971/			Incidence, distal colon cancer, men	≥5 times/week vs never/rarely	0.83 (0.67-1.03)		
		361/			Incidence, rectosigmoid and rectum	≥5 times/week vs never/rarely	0.97 (0.67-1.41)		

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Reasons for exclusion
					cancer, women				
		389/			Incidence, distal colon cancer, women	≥5 times/week vs never/rarely	0.82 (0.58-1.14)		
		670/			Incidence, proximal colon cancer, women	≥5 times/week vs never/rarely	0.91 (0.70-1.17)		
Nilsen, 2008 COL40731 Norway	Norwegian Nord-Trondelag Health Study, Prospective Cohort, Age: 20- years, M/W	124/ 59 369 17 years	Cancer registry	Questionnaire	Incidence, rectal cancer, women	high vs no activity	1.01 (0.58-1.75)	Age, alcohol consumption, BMI, educational level, marital status, smoking status	
		170/			Men	high vs no activity	1.12 (0.65-1.96)	Age, alcohol consumption, BMI, educational level, marital status, smoking status	
		346/			Incidence, colon cancer, men	≥4 vs ≤0 times/week	0.77 (0.54-1.09)	Age, alcohol consumption, BMI, educational level, marital status, smoking status	

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Reasons for exclusion
					Incidence, distal colon cancer, women	high vs low	0.56 (0.37-0.83)	Age, alcohol consumption, BMI, educational level, marital status, smoking status	
						high vs low	0.81 (0.59-1.10)	Age, alcohol consumption, BMI, educational level, marital status, smoking status	
Mai, 2007 COL40658 USA	California Teachers Study, 1995, Prospective Cohort, Age: 22-84 years, W	107/ 120 147 6.6 years	Cancer registry	Self completed questionnaire	Incidence, distal colon cancer	≥4 vs 0-0.5 hrs/week for 1 year	0.78 (0.48-1.25)	Age, race	
		395/			Incidence, invasive colon cancer	≥4 vs 0-0.5 hrs/week for 1 year	0.81 (0.63-1.05)		
		272/			Incidence, proximal colon cancer	≥4 vs 0-0.5 hrs/week for 1 year	0.81 (0.59-1.11)		
Friedenreich, 2006 COL40620 Europe	EPIC, Prospective Cohort, Age: 35-70 years, M/W	1 094/ 413 044 6.38 years	Cancer registry, record linkage, health insurance rec, pathology	Questionnaire /interview	Incidence, colon cancer	≥42.8 vs ≤11.9 met-hour/week	0.88 (0.74-1.05)	Age, center, educational level, energy intake, fiber intake, height, smoking status, weight	
		599/			Incidence, rectal cancer	≥42.8 vs ≤11.9 met-hour/week	1.21 (0.94-1.54)		

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Reasons for exclusion
			and active follow up						
Larsson, 2006 COL40625 Sweden	COSM, Prospective Cohort, Age: 45-79 years, M	307/ 45 906 7.1 years	Cancer registry	Postal questionnaire	Incidence, colon cancer	≥60 vs ≤9 minutes/day	0.56 (0.37-0.83)	Age, aspirin use, BMI, educational level, history of diabetes, occupational activity, smoking status, family history of colorectal cancer, household physical activity	
		132/			Incidence, proximal colon cancer	≥60 vs ≤9 minutes/day	0.72 (0.37-1.40)	Age, aspirin use, BMI, educational level, history of diabetes, occupational activity, smoking status, family history of colorectal cancer, household physical activity	
		491/			Incidence, colorectal cancer		0.57 (0.41-0.79)		
		137/			Incidence, distal colon cancer		0.40 (0.22-0.70)		
		187			Incidence, rectal cancer		0.59 (0.34–1.02)		
Schnohr, 2005 COL01986	CCPPS, Prospective	215/ 28 259		Questionnaire	Incidence, colon cancer,	vigorous vs low	0.72 (0.47-1.11)	Age, alcohol consumption,	

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Reasons for exclusion
Denmark	Cohort, Age: 20-93 years, M/W	14 years			men			BMI, educational level, occupational physical activity, other design issue, smoking habits, birth cohort	
		127/			Incidence, rectal cancer, men	vigorous vs low	0.89 (0.53-1.49)	Age, alcohol consumption, BMI, educational level, occupational physical activity, other design issue, smoking habits, birth cohort	
		180/			Incidence, colon cancer, women	vigorous vs low	0.90 (0.56-1.46)	Age, alcohol consumption, BMI, educational level, occupational physical activity, other design issue, smoking habits, birth cohort	
		127/	Cancer	Questionnaire	Incidence,	vigorous vs low	0.89 (0.53-1.49)	Age, alcohol	

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Reasons for exclusion
		28 259 14 years	registry		rectal cancer, men			consumption, BMI, educational level, occupational physical activity, smoking habits, study, birth cohort	
Chao, 2004 COL01942 USA	CPS II, Prospective Cohort, Age: 50-74 years, M/W	536/ 151 174 19 years	Cancer registry and medical records		Incidence, colorectal cancer, men	≥30 vs ≤0 met-hours/week	0.60 (0.41-0.87)	Age, alcohol consumption, educational level, multivitamin use in 1982, red meat intake, smoking status, exercise level in 1982, fiber, folate	Only included in rectal cancer analysis
		390/			Incidence, rectosigmoid and rectum cancer, men	≥7 vs ≤0 hours/week	0.83 (0.59-1.16)	Age, alcohol consumption, educational level, multivitamin use in 1982, red meat intake, smoking status, exercise level in 1982, fiber, folate	

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Reasons for exclusion
		505/			Incidence, proximal colon cancer, men	≥7 vs ≤0 hours/week	0.63 (0.45-0.88)	Age, alcohol consumption, educational level, multivitamin use in 1982, red meat intake, smoking status, exercise level in 1982, fiber, folate	
		339/			Incidence, distal colon cancer, men	≥7 vs ≤0 hours/week	0.82 (0.55-1.24)	Age, alcohol consumption, educational level, multivitamin use in 1982, red meat intake, smoking status, exercise level in 1982, fiber, folate	
Wei, 2004 COL00581 USA	The Nurses's Health Study Cohort, Prospective Cohort, W, nurses	196/ 87 733 24 years	Self-reported verified by medical record and The National Death Index	Questionnaire	Incidence, rectal cancer,	$Q_6$5 vs $Q_6$1	1.28 (0.77-2.12)	Age, alcohol consumption, BMI, beef, pork or lamb as a main dish, calcium, family history of	

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Reasons for exclusion
	Health Professionals Follow-up Study, Prospective Cohort, M, Health professionals	466/ 46 632 14 years			Incidence, colon cancer,	$Q_6$5 vs $Q_6$1	0.71 (0.52-0.96) Ptrend:0.04	colorectal cancer, folate, height, history of endoscopy, pack-years of smoking before age 30, processed meat	
					Incidence, rectal cancer		0.95 (0.56-1.60) Ptrend:0.37		
Colbert, 2001 col00384 Finland	Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study, Prospective Cohort, Age: 50-69 years, M, Male Smokers	152/ 29 133 12 years	Unknown	Questionnaire	Incidence, colon cancer	Active vs sedentary	0.82 (0.59-1.13)	Age, BMI, smoking habits, supplement group	
		104/			Incidence, rectal cancer,	Active vs sedentary	0.93 (0.63-1.37)	Age, supplement group	
Lee, 1997 COL00150 USA	PHS, Prospective Cohort, Age: 40-84 years, M, Physicians	217/ 21 807 10.9 years		Questionnaire	Incidence, colon cancer,	≥5 vs ≤1 times/week	1.10 (0.70-1.60)	Age	
Thune, 1996 COL00269	Norwegian national health	230/ 81 516	Personal identificatio	Questionnaire	Incidence, colon cancer,	regular training (r3+r4) vs	1.33 (0.90-1.98)	Age, BMI, civil status,	

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Reasons for exclusion
Norway	screening service study, Prospective Cohort, Age: 20-69 years, M/W	1 305 607 person-years	n number		male, colon cancer	sedentary (r1)		geographical region	
		169/			Incidence, rectal cancer, male, rectal cancer	regular training (r3+r4) vs sedentary (r1)	0.98 (0.60-1.61)		
		99/			Incidence, colon cancer, women, colon cancer	regular training (r3+r4) vs sedentary (r1)	0.84 (0.43-1.65)		
		55/			Incidence, rectal cancer, women, rectal cancer	regular training (r3+r4) vs sedentary (r1)	1.49 (0.53-4.22)		
		90/			Incidence, proximal colon cancer, male, proximal sites	active (r2-4) vs sedentary (r1)	1.05 (0.62-1.78)		
		128/			Incidence, distal colon cancer, male, distal sites	active (r2-4) vs sedentary (r1)	1.19 (0.75-1.89)		
		48/			Incidence, proximal colon cancer, women, proximal sites	active (r2-4) vs sedentary (r1)	0.51 (0.28-0.93)		
		45/			Incidence,	active (r2-4) vs	0.80 (0.41-1.56)		

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Reasons for exclusion
					distal colon cancer, women, distal sites	sedentary (r1)			
Bostick, 1994 COL00079 USA	IWHS, Prospective Cohort, Age: 55-69 years, W	212/ 35 216 167 447 person-years	SEER	Questionnaire	Incidence, colon cancer	vigorous vs low	0.95 (0.68-1.39)	Age, total energy intake, height, parity, total vitamin E, vitamin A intake	
Lee, 1994 COL40790 USA	Harvard Alumni Health Study 1962-1966, Prospective Cohort, Age: 30-79 years, M	280/ 17 607	Harvard alumni questionnaires and death certificates	Questionnaire	Incidence, colon cancer	≥2500 vs ≤999	1.08 (0.81-1.46)	Age, family history of cancer	
		53/			Incidence, rectal cancer	≥2500 vs ≤999	1.71 (0.88-3.31)		
Gerhardsson, 1988 COL01044 Sweden	Swedish Twin Follow-up Study, Prospective Cohort, M/W, twin individuals	16 477 14 years	Cancer registry	Questionnaire	Incidence, rectal cancer,	hardly any & light vs regular & hard	1.20 (0.70-2.20)	Age, sex	
		121/			Incidence, colon cancer,	hardly any or light vs regular & hard	1.60 (1.00-2.70)		
Wu, 1987 COL00774 USA	Leisure World Cohort, Prospective Cohort, M/W,	58/ 11 644 4.5 years	Population registries		Incidence, colorectal cancer, male	≥2 vs ≤0 hours/day	0.40 (0.20-0.80)	Age	
		68/			Female	≥2 vs ≤0 hours/day	0.89 (0.50-1.60)		

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Reasons for exclusion
	Retirement community					≥2 vs ≤0 hours/day	0.68 (0.30-1.50)		
		58/			Incidence, right colon cancer, male	≥2 vs ≤0 hours/day	0.50 (0.20-1.30)		
		68/			Female	≥2 vs ≤0 hours/day	1.16 (0.40-2.50)		
		58/			Incidence, left colon cancer, male	≥2 vs ≤0 hours/day	0.36 (0.10-1.10)		

Table 308 Recreational physical activity and colorectal cancer risk. Main characteristics of studies excluded from the CUP SLR dose-response meta-analysis

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Reasons for exclusion
Batty, 2010 COL40838 UK	Whitehall Study, Prospective Cohort, Age: 40-69 years, M, Employed men	104/ 6 928 40 years	NHS central registry	Questionnaire	Mortality, colon cancer	Inactive vs active	1.00 (0.64-1.8)	Age, BMI, job classification, forced expiratory volume in 1 second, smoking	Outcome is mortality, insufficient number of studies
					Mortality, rectal cancer	Inactive vs active	1.80 (0.79-4.12)		
Yun, 2008 COL40946 Korea	KNHIC, Prospective Cohort, Age: 40- years, M	1 827/ 444 963 6 years	Cancer registry	Self-report	Incidence, colorectal cancer	moderate-high vs low	0.98 (0.90-1.08)	Age, BMI, dietary preference, employment, fasting blood sugar, smoking status, alcohol drinking	Outcome is colorectal cancer not enough studies to update analysis
Wolin, 2007 COL40700 USA	The Nurses's Health Study Cohort, Prospective Cohort, Age: 40-65 years, W, nurses	302/ 79 295 1 230 354 person-years	Follow up questionnaires; medical records; pathology reports; national death index	Questionnaire	Incidence, proximal colon cancer	≥21.5 vs ≤2 met-hours/week	0.97 (0.68-1.38)	Age, alcohol intake, aspirin use, BMI, calcium intake, family history of colon cancer, history of endoscopy, history of polyps, multivitamin use, red meat intake, smoking status, vitamin d	Superseded by Wei, 2009
		245/			Incidence, distal colon cancer	≥21.5 vs ≤2 met-hours/week	0.54 (0.34-0.84)		
		547/			Incidence, colon cancer	≥21.5 vs 2.1-4.5 met-hours/week	0.77 (0.58-1.01)		

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Reasons for exclusion
Driver, 2007 COL40711 USA	PHS, Prospective Cohort, Age: 40-84 years, M, Physicians	21 581 20 years	Follow up questionnaires (self report), medical record and pathology reports		Incidence, colorectal cancer	rarely exercise vs exercise/active /week	1.06 (0.83-1.36)	Age, BMI, history of diabetes, multivitamin, physical activity, smoking status, vegetable intake, vitamin c, vitamin e, cereals intake	Outcome is colorectal cancer not enough studies to update analysis
Suzuki, 2007 COL40949 Japan	JACC, Prospective Cohort, Age: 40-79 years, M/W	127/ 109 778	Death certificate	Questionnaire	Mortality, rectal cancer, men	<1 vs >3 hours/week	1.39 (0.82-2.35)	Age, study area	Outcome is mortality, insufficient number of studies
		177/			Mortality, colon cancer, men	<1 vs >3 hours/week	0.67 (0.46-0.98)		
McCarl, 2006 COL40633 USA	IWHS, Prospective Cohort, Age: 55-69 years, W	948/ 35 197 15 years	SEER registry		Incidence, colorectal cancer	high vs low	0.83 (0.71-0.97)	Age	Outcome is colorectal cancer not enough studies to update analysis
Johnsen, 2006 COL40629 Denmark	DCH, Prospective Cohort, Age: 50-64 years, M/W	157/ 54 478 7.6 years	Cancer registry	Questionnaire	Incidence, colon cancer, men	per 1 hours	1.00 (0.91-1.10)	Age, alcohol, BMI, fat consumption, hrt use, nsaids, recreational activity, red	Component of the EPIC study
						per 10 met score	0.97 (0.93-1.01)		
		140/			Women	per 1 hours	1.03 (0.93-1.14		

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Reasons for exclusion
						per 10 met score	1.00 (0.96-1.04)	meat intake, smoking status, total energy intake, educational attainment, fibre	
Sanjoaquin, 2004 COL01182 UK	OVS, Prospective Cohort, Age: 18-89 years, M/W	95/ 10 998 17 years	Population/invitation		Incidence, colorectal cancer,	≥2 vs ≤2 times/week	0.82 (0.49-1.36)	Age, sex, alcohol consumption, smoking habits	Outcome is colorectal cancer not enough studies to update analysis
Malila, 2002 COL00336 Finland	Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study, Prospective Cohort, Age: 50-69 years, M, Male Smokers	184/ 26 951 8 years	Population		Incidence, colorectal cancer,	active vs not active			Superseded by Colbert, 2001
Wannamethee, 2001 COL01187 UK	BRHS, Prospective Cohort, Age: 40-59 years, M	135/ 7 588 18.8 years	General practioners	Questionnaire	Incidence, colorectal cancer,	≥1 vs ≤1 times/month	0.90 (0.60-1.35)	Age, alcohol consumption, BMI, social class, cigarette smoking	Outcome is colorectal cancer not enough studies to update analysis
Pukkala, 2000	Finland, world	23/	Athletes registry	Athletes	Incidence,	athletes vs	(0.00-1.27)		Unadjusted

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Reasons for exclusion
COL00980 Finland	class male athletes, Prospective Cohort, M, male athletes	2 269 53 501 person-years			colon cancer, men	population	Sports, endurance		results
						athletes vs population	1.37 (0.59-2.69) Sports, power		
						athletes vs population	1.74 (0.90-3.04) Sports, speed		
						athletes vs population	1.60 (0.33-4.67) Sports, shooting		
						athletes vs population	2.92 (1.07-6.32) Sports, wrestlers		
Ford, 1999 COL00097 USA	NHANES I, Prospective Cohort, Age: 25-74 years, M/W	222/ 13 420 19 years	Multistage stratified sampling design	Questionnaire	Incidence, colon cancer,	little or no exercise vs much exercise			No measure of association
Martínez, 1997 COL00139 USA	The Nurses's Health Study Cohort, Prospective Cohort, Age: 30-55 years, W, Registred nurses	161/ 89 448 1 012 375 person-years	Nurses registry	Questionnaire	Incidence, colon cancer, 1986-1992 follow-up	≥21 vs ≤2 met-hours/week	0.52	Age	Superseded by Wolin 2007 and Wei 2004
						≥21 vs ≤2 met-hours/week	0.54 (0.33-0.90)	Age, alcohol consumption, BMI, cigarette smoking, family history of specific cancer, aspirin use, postmenopausal	

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Reasons for exclusion
								hormone use, red meat intake	
		73/			Incidence, distal colon cancer, 1986-1992 follow-up, distal cancer	≥21 vs ≤2 met-hours/week	0.31	Age	
						≥21 vs ≤2 met-hours/week	0.31 (0.12-0.77)	Age, alcohol consumption, BMI, cigarette smoking, family history of specific cancer, aspirin use, postmenopausal hormone use, red meat intake	
		66/			Incidence, proximal colon cancer, 1986-1992 follow-up, proximal cancer	≥21 vs ≤2 met-hours/week	0.77 (0.38-1.58)	Age, alcohol consumption, BMI, cigarette smoking, family history of specific cancer, aspirin use, postmenopausal hormone use, red meat intake	
						≥21 vs ≤2 met-hours/week	0.73	Age	
Glynn, 1996 COL00161 Finland	Alpha-Tocopherol, Beta-Carotene Cancer Prevention	144/ 29 133 8 years	Cancer registry	Questionnaire	Incidence, colorectal cancer,	exercise vs reading		Age, clinic site, date of blood collection	Superseded by Colbert, 2001

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Reasons for exclusion
	Study, Nested Case Control, Age: 50-69 years, M, Male Smokers								
Giovannucci, 1995 COL00110 USA	Health Professionals Follow-up Study, Prospective Cohort, Age: 40-75 years, M	203/ 31 055 6 years	Voluntarily responded to mailed questionnaire	Questionnaire	Incidence, colon cancer	46.8 vs 0.9 met-hours/week	0.44 (0.27-0.71)	Age	Superseded by Wei, 2004
						46.8 vs 0.9 met-hours/week	0.53 (0.32-0.88)	Age, aspirin use, BMI, energy intake, family history of specific cancer, history of screening, methione intake, smoking habits, alcohol intake, dietary fiber intake, folate intake, red meat intake	
		46/			Incidence, rectal cancer, rectal cancer	46.8 vs 0.9 met-hours/week	1.83 (0.83-3.84)	Age	
					Incidence, distal colon cancer, distal sites	46.8 vs 0.9 met-hours/week	0.50 (0.25-1.00)	Age	
					Incidence,	46.8 vs 0.9 met-	0.75 (0.36-1.55)	Age	

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Reasons for exclusion
					proximal colon cancer, proximal sites	hours/week			
					Incidence, colon cancer, colon cancer	46.8 vs 0.9 met-hours/week	0.41 (0.22-0.74)	Age, aspirin use, BMI, energy intake, family history of specific cancer, history of screening, methione intake, physical activity, smoking habits, alcohol intake, dietary fiber intake, folate intake, history of polyp diagnosis, red meat intake	
Suadicani, 1993 COL01085 Denmark	Denmark, Copenhagen fitness and risk of cvd study, Prospective Cohort, Age: 40-59 years, M	51/ 5 429 18 years	Public or private companies	questionnaire	Incidence, colon cancer				No measure of association Superseded by Schnohr 2005
					Incidence, rectal cancer				

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Reasons for exclusion
Albanes, 1989 COL00497 USA	NHANES I, Prospective Cohort, Age: 25-74 years, M/W, 84% White	66/ 12 554	NHANES I	Questionnaire	Incidence, colorectal cancer, women	quite inactive vs very active	1.20 (0.60-2.80)	Age	Outcome is colorectal cancer not enough studies to update analysis
		62/			Men	quite inactive vs very active	1.00 (0.50-1.90)		
Garfinkel, 1988 COL01049 USA	CPS II, Prospective Cohort, Age: 30- years, M/W	254/ 56 683	Death certificate, self-reported and records	Questionnaire	Mortality, colorectal cancer	sports play ≥ 5 hr/wk vs sports play ≤ 5 hr/wk	0.80 Sports	Age, sex, birth year	Superseded by Chao, 2004
		201/			Mortality, colon cancer	sports play ≥ 5 hr/wk vs sports play ≤ 5 hr/wk	0.91 Sports		
		53/			Mortality, rectal cancer	sports play ≥ 5 hr/wk vs sports play ≤ 5 hr/wk	0.46 Sports		
Polednak, 1976 COL01612 USA	US, athletic cohort, Prospective Cohort, M	8 393	Registries		Mortality, colon cancer	major athlete vs non-athlete			Mortality rates results, unadjusted results

Figure 514 RR (95% CI) of colon cancer for the highest compared with the lowest level of recreational physical activity

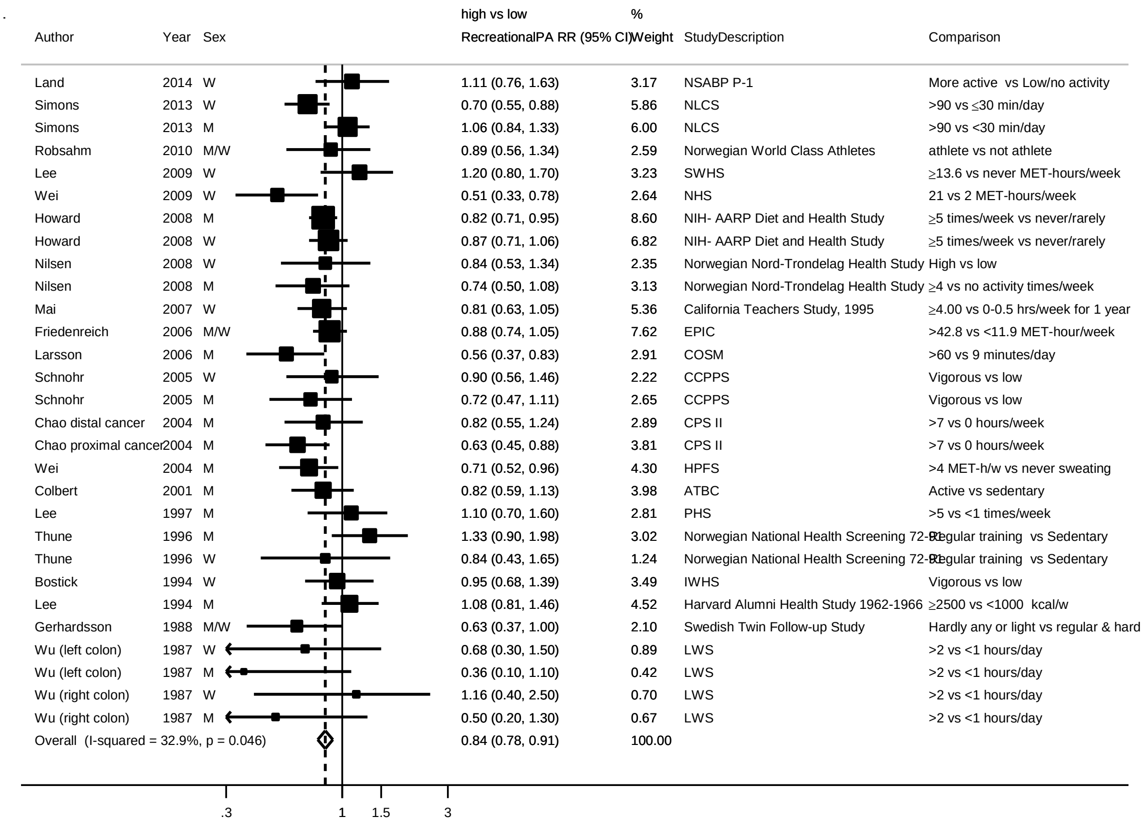
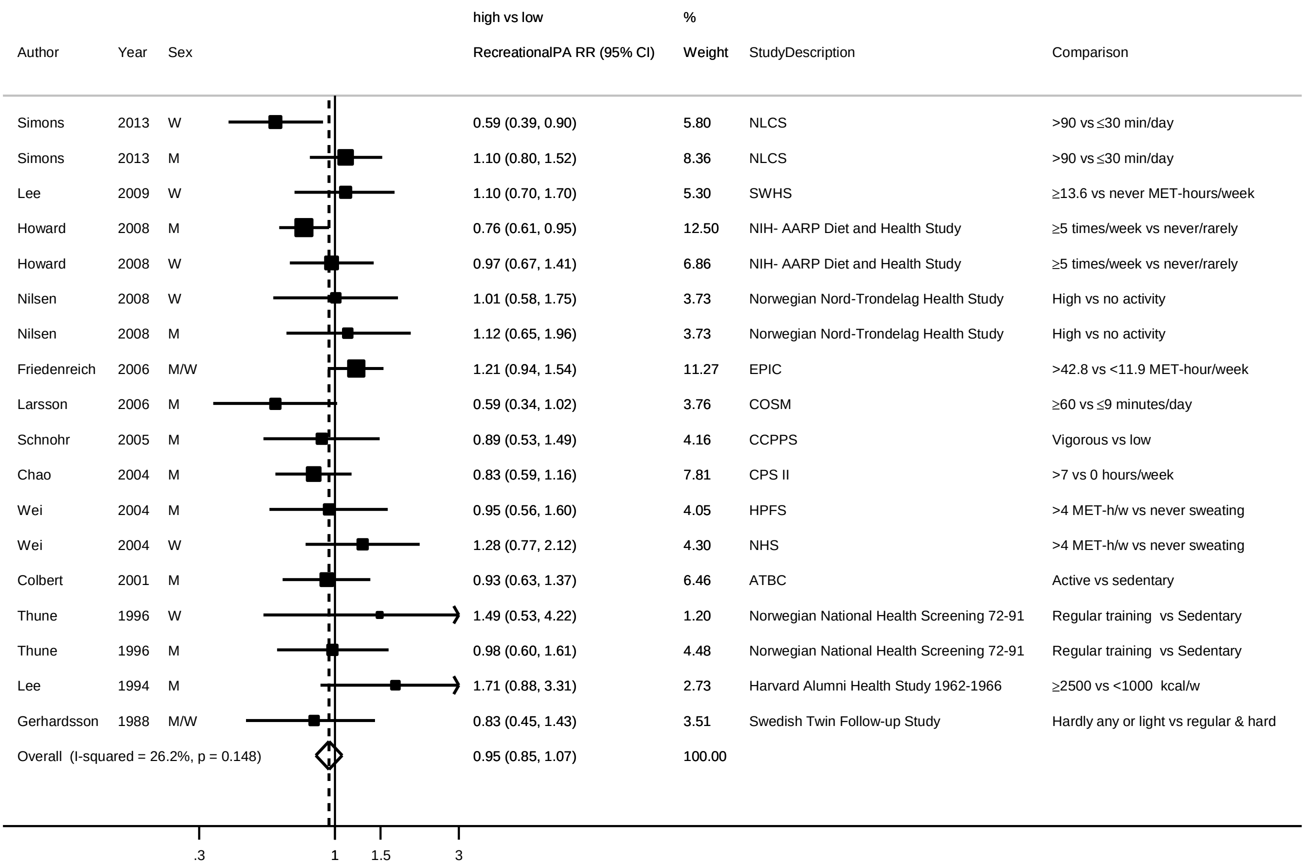


Figure 515 RR (95% CI) of rectal cancer for the highest compared with the lowest level of recreational physical activity



6.1.1.2 Walking

Cohort studies

Summary

Main results:

Nine studies from 11 publications were identified. No new studies on colorectal cancer, 3 new studies on colon cancer and rectal cancer (two studies were on mortality and one on incidence) and one new study on distal and proximal colon cancer. The new studies identified presented the results in different units, therefore a dose-response meta-analysis was not conducted. Because there were not enough studies to conducted analysis on mortality and there is only one new study on incidence (Simmons, 2013) the highest compared to lowest analysis could only include four studies, therefore it was not conducted.

No dose-response meta-analysis was conducted in the 2010 SLR due to the small number of studies, the highest compared to lowest analysis was not conducted. Results from individual studies are included in the tables below. From the four studies that could be included in a highest compared to lowest analysis for colon cancer only one (Takahashi, 2007) showed an inverse significant association for men who walked more than1.1 hours vs 0.4 hours/day. For rectal cancer only one study (Simons, 2013) from the four studies showed an inverse association for women when comparing >60 to ≤10 minutes/day of walking.

Study quality:
Cancer outcome was confirmed using cancer registry records in most studies. Physical activity was assessed using different questionnaires. Most studies adjusted for multiple confounders.

Pooling project of cohort studies:
No Pooling Project was identified.

Meta-analysis of cohort studies:
No meta-analysis was identified.

Table 309 Walking and colorectal cancer risk. Main characteristics of studies identified in the CUP SLR

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors
Simons, 2013 COL40956 Netherlands	NLCS, Prospective Cohort, Age: 55-69 years, M/W	1 107/ 4 416 16 years	Cancer registry	Self-report	Incidence, colon cancer, men	>60 vs <10 /day	0.94 (0.76-1.17)	Age, BMI, family history of colon cancer, meat intake, processed meat, alcohol, energy, smoking
		924/			Women	>60 vs ≤10	0.79 (0.60-1.04)	
		581/			Incidence, distal colon cancer, men	>60 vs <10 /day	1.09 (0.83-1.42)	
		517/			Incidence, proximal colon cancer, women	>60 vs ≤10	0.85 (0.60-1.19)	
		480/			Men	>60 vs <10 /day	0.83 (0.62-1.10)	
		438/			Incidence, rectal cancer, men	>60 vs <10 /day	1.03 (0.77-1.38)	
		377/			Incidence, distal colon cancer, women	>60 vs ≤10	0.75 (0.52-1.10)	
		227/			Incidence, rectal cancer, women	>60 vs ≤10	0.47 (0.27-0.83)	
Lee, 2007 COL40644	JPHC study- cohort I and II,	290/ 65 022	Active patient notification from	Self- administered	Incidence, colorectal	≥3 vs ≤2.9 hours/day	0.82 (0.65-1.05)	Age, alcohol intake, BMI,

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors
Japan	Prospective Cohort, Age: 40-69 years, M/W	6 years	hospitals, cancer registries and death cert.	questionnaire	cancer, men			folate intake, red meat intake, smoking habits, study area, family history of colorectal cancer, fibre
		197/			Incidence, colon cancer, men	≥3 vs ≤2.9 hours/day	0.79 (0.59-1.06)	
		166/			Incidence, colorectal cancer, women	≥3 vs ≤2.9 hours/day	1.06 (0.78-1.45)	
		140/			Incidence, colon cancer, women	≥3 vs ≤2.9 hours/day	1.02 (0.70-1.47)	
		107/			Incidence, distal colon cancer, men	≥3 vs ≤2.9 hours/day	1.02 (0.68-1.52)	
		93/			Incidence, rectum cancer, men	≥3 vs ≤2.9 hours/day	0.88 (0.57-1.36)	
		82/			Incidence, proximal colon cancer, men	≥3 vs ≤2.9 hours/day	0.62 (0.40-0.98)	
		72/			Women	≥3 vs ≤2.9 hours/day	1.03 (0.62-1.72)	
		59/			Incidence, distal colon cancer, women	≥3 vs ≤2.9 hours/day	1.03 (0.58-1.83)	
		56/			Incidence, rectum cancer,	≥3 vs ≤2.9 hours/day	1.20 (0.65-2.19)	

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors
					women			
Takahashi, 2007 COL40704 Japan	MCS, Prospective Cohort, Age: 40-64 years, M/W	166/ 41 988 7 years	Record linkage with cancer registries	Questionnaire	Incidence, colorectal cancer, men	≥1.1 vs ≤0.4 hours/day	0.57 (0.38-0.83)	Age, alcohol consumption, BMI, educational level, meat intake, physical activity, smoking status, vegetable intake, family history of colorectal cancer, oranges
		101/			Incidence, colon cancer, men	≥1.1 vs ≤0.4 hours/day	0.38 (0.23-0.64)	
		94/			Incidence, colorectal cancer, women	≥1.1 vs ≤0.4 hours/day	1.02 (0.60-1.75)	
		65/			Incidence, rectal cancer, men	≥1.1 vs ≤0.4 hours/day	1.07 (0.55-2.06)	
		50/			Incidence, colon cancer, women	≥1.1 vs ≤0.4 hours/day	1.33 (0.60-2.94)	
		44/			Incidence, rectal cancer, women	≥1.1 vs ≤0.4 hours/day	0.82 (0.39-1.71)	
Wolin, 2007 COL40700 USA	The Nurses's Health Study Cohort, Prospective Cohort, Age: 40-65 years, W, nurses	265/ 79 295 1 230 354 person-years	Follow up questionnaires; medical records; pathology reports; national death index	Questionnaire	Incidence, colon cancer	≥4 vs ≤0 hours/week	0.73 (0.48-1.10)	Age, alcohol intake, aspirin use, BMI, calcium intake, family history of colon cancer, history of endoscopy, history of polyps,
		141/			Incidence, proximal polyps	≥4 vs ≤0 hours/week	0.89 (0.52-1.51)	
		124/			Incidence, distal colon cancer	≥4 vs ≤0 hours/week	0.54 (0.28-1.06)	

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors
								multivitamin use, red meat intake, smoking status, vitamin d
Chao, 2004 COL01942 USA	CPS II, Prospective Cohort, Age: 50-74 years, M/W	594/ 151 174 19 years	Cancer registry and medical records		Incidence, colorectal cancer, men	≥7 vs ≤0 hours/week	0.96 (0.72-1.29)	Age, alcohol consumption, educational level, multivitamin use in 1982, red meat intake, smoking status, exercise level in 1982, fiber, folate
		320/			Incidence, proximal colon cancer, men	≥7 vs ≤0 hours/week	0.83 (0.56-1.25)	
		240/			Incidence, rectosigmoid and rectum cancer, men	≥7 vs ≤0 hours/week	0.89 (0.59-1.34)	
		214/			Incidence, distal colon cancer, men	≥7 vs ≤0 hours/week	1.08 (0.67-1.73)	
Wannamethee, 2001 COL01187 UK	BRHS, Prospective Cohort, Age: 40-59 years, M	135/ 7 588 18.8 years	General practitioners	Questionnaire	Incidence, colorectal cancer,	≥60 vs ≤20 minutes/day	0.76 (0.28-2.07) pace	Age, alcohol consumption, BMI, social class, cigarette smoking

Table 310 Walking and colorectal cancer risk. Main characteristics of studies excluded from the CUP SLR dose-response meta-analysis

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Exclusion reason
Batty, 2010 COL40838 UK	Whitehall Study, Prospective Cohort, Age: 40-69 years, M, Employed men	104/ 6 928 40 years	UKNHS central registry	Questionnaire	Mortality, colon cancer	slower vs faster	1.22 (0.47-3.19)	Age, BMI, job classification, forced expiratory volume in 1 second, smoking	Outcome is mortality not enough studies to update analysis
		43/			Mortality, rectal cancer		4.85 (1.7-13.8)		
Akhter, 2007 COL40632 Japan	MCS, Prospective Cohort, Age: 40-64 years, M	307/ 21 199 11 years	Cancer registry		Incidence, colorectal cancer	>1h/day vs <30min/day	1.35 (1.02-1.79)	Age	Outcome is colorectal cancer not enough studies to update analysis
Suzuki, 2007 COL40949 Japan	JACC, Prospective Cohort, Age: 40-79 years, M/W	167/ 109 778	Death certificate	Questionnaire	Mortality, colon cancer, women	<1 vs >3 hours/day	1.28 (0.88-1.84)	Age, study area	Outcome is mortality not enough studies to update analysis
		165/			Men	<1 vs >3 hours/day	0.96 (0.67-1.38)		
		117/			Mortality, rectum cancer, men	<1 vs >3 hours/day	1.01 (0.66-1.54)		
		61/			Women	<1 vs >3 hours/day	0.68 (0.34-1.33)		

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Exclusion reason
Johnsen, 2006 COL40629 Denmark	DCH, Prospective Cohort, Age: 50-64 years, M/W	157/ 54 478 7.6 years	Cancer registry	Questionnaire	Incidence, colon cancer, men	per 1 hours	1.01 (0.98-1.04)	Age, alcohol, BMI, fat consumption, hrt use, nsaids, recreational activity, red meat intake, smoking status, total energy intake, educational attainment, fibre	
		140/			Women	per 1 hours	0.99 (0.95-1.03)		
Davey Smith G, 2000 COL00391 UK	Whitehall Study, Prospective Cohort, Age: 40-64 years, M, civil servants	89/ 6 702 25 years	UKNHS central registry	Questionnaire	Mortality, colorectal cancer,	slower vs faster	2.35 (1.10-5.10)	Age	Outcome is mortality not enough studies to update analysis
						slower vs faster	2.46 (1.10-5.40)	Age, BMI, smoking habits, forced expiratory volume in 1 second, grade	
		64/			Apparently healthy at study entry	slower vs faster	1.98 (0.60-6.80)		

7.1 Energy intake

Cohort studies

Summary

Main results:
Eleven studies (sixteen publications) were identified. Only highest compared to lowest analysis was conducted. No analysis was conducted in 2010 SLR.

Colorectal cancer:
Six studies (2703 cases) were included in the highest compared to lowest meta-analysis of energy intake and colorectal cancer. A non-significant association with high heterogeneity was observed.

Colon cancer:
Eight studies (1602 cases) were included in the highest compared to lowest meta-analysis of energy intake and colon cancer. A non-significant association with high heterogeneity was observed.

Meta-analysis of cohort studies
One meta-analysis of 11 studies observed that energy intake was associated with a reduced risk of colon and colorectal cancer combined (RR 0.90, 95%CI= 0.81-0.99, highest vs lowest) (Yu, 2012).

Table 311 Energy intake and colorectal cancer risk. Number of studies in the CUP SLR

	Number
Studies identified	6
Studies included in forest plot of highest compared with lowest exposure	6
Studies included in dose-response meta-analysis	NA
Studies included in non-linear dose-response meta-analysis	NA

Note: Include cohort, nested case-control and case-cohort designs

Table 312 Energy intake and colon cancer risk. Number of studies in the CUP SLR

	Number
Studies identified	8 (11 publications)
Studies included in forest plot of highest compared with lowest exposure	8
Studies included in dose-response meta-analysis	NA
Studies included in non-linear dose-response meta-analysis	NA

Note: Include cohort, nested case-control and case-cohort designs

Table 313 Energy intake and colorectal cancer risk. Summary of the dose-response meta-analysis in the 2010 SLR and 2015 SLR.

	2010 SLR	**2015 SLR**
Increment unit used		Highest vs Lowest
Studies (n)		6
Cases (total number)		2703
RR (95%CI)		1.02(0.84-1.25)
Heterogeneity (I^2, p-value)		55.6%, 0.05

Table 314 Energy intake and colon cancer risk. Summary of the dose-response meta-analysis in the 2010 SLR and 2015 SLR.

	2010 SLR	**2015 SLR**
Increment unit used		Highest vs Lowest
Studies (n)		8
Cases (total number)		1602
RR (95%CI)		1.02(0.83-1.27)
Heterogeneity (I^2, p-value)		51.6%, 0.06

Table 315 Energy intake and colorectal cancer risk. Main characteristics of studies included in the CUP SLR dose-response meta-analysis

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors
Lee, 2009 COL40764 China	SWHS, Prospective Cohort, Age: 40-70 years, W	394/ 73 224 7.4 years	Cancer registry and death certificates and participant contact	Quantitative FFQ	Incidence, colorectal cancer	≥1844 vs ≤1406.9 kcal/day	1.20 (0.90-1.60) Ptrend:0.08	Age, energy intake
		236/			Incidence, colon cancer	≥1844 vs ≤1406.9 kcal/day	1.40 (1.00-2.00) Ptrend:0.06	
		158/			Incidence, rectal cancer	≥1844 vs ≤1406.9 kcal/day	1.00 (0.60-1.50) Ptrend:0.69	
Prentice, 2009 COL40811 USA	WHI, Prospective Cohort, Age: 50-79 years, W, Postmenopausal	363/ 80 816 11.3 years	Self-report, medical record and pathology report reviewed by centrally trained physician	FFQ	Incidence, colon cancer, dm trial and observation study	Q 4 vs Q 1	1.51 (1.03-2.21)	Age-underlying cox models, alcohol, family history of colon cancer, history of polyp diagnosis, Intervention assignment, physical activity, race, smoking status
						per 20 % kcal/day	1.47 (1.11-1.94)	
Butler, 2008 COL40639 Singapore	SCHS, Prospective Cohort, Age: 45-74 years, M/W	961/ 61 321 9.8 years	Cancer registry	FFQ	Incidence, colorectal cancer	Q 4 vs Q 1	0.97 (0.80-1.18) Ptrend:0.77	Age, sex, alcohol intake, BMI, diabetes, dialect group, educational level, energy intake, exposure

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors
								assessment, family history of colorectal cancer, physical activity, smoking habits
McCarl, 2006 COL40633 USA	IWHS, Prospective Cohort, Age: 55-69 years, W	954/ 35 197 15 years	SEER registry	FFQ	Incidence, colorectal cancer	≥2232 vs ≤1298.3 kcal/day	0.80 (0.66-0.97)	Age
Oba, 2006 COL40626 Japan	TCCJ, Prospective Cohort, Age: 35-101 years, M/W	111/ 30 221 8 years	Hospital records and cancer registry	Semi-quantitative FFQ	Incidence, colon cancer, men	3339.6 vs 1814.6 kcal	1.00 (0.60-1.69)	Age, alcohol intake, BMI, height, pack-years of smoking, physical activity
		102/			Women	2782.7 vs 1423.9 kcal	0.77 (0.47-1.27)	
Jarvinen, 2001 COL00852 Finland	Finnish Mobile Clinic Health Examination Survey, Prospective Cohort, Age: 39 years, M/W	109/ 9 959	Population/invitation	Questionnaire	Incidence, colorectal cancer,	Q 4 vs Q 1	0.78 (0.42-1.44)	Age, sex, BMI, geographic location, occupational group, smoking
		63/			Incidence, colon cancer,	Q 4 vs Q 1	0.74 (0.32-1.71)	
		46/			Incidence, rectal cancer,	Q 4 vs Q 1	0.82 (0.33-2.04)	
Pietinen, 1999 COL00176 Finland	ATBC, Prospective Cohort, Age: 50-69 years,	185/ 27 111 8 years	Cancer registry	Dietary history questionnaire	Incidence, colorectal cancer,	3696 vs 1984 kcal/day	1.70 (1.00-2.90) Ptrend:0.05	Age, alcohol consumption, BMI, calcium intake, educational

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors
	M, Smokers							level, physical activity, smoking years, supplement group
Kato, 1997 CRC00022 USA	New York University Women's Health Study, Prospective Cohort, Age: 34-65 years, W	100/ 14 272 105 044 person-years	Questionnaire, medical records, cancer registries	Semi-quantitative FFQ	Incidence, colorectal cancer,	Q 4 vs Q 1	1.20 (0.69-2.08) Ptrend:0.788	Age, educational level, place at enrolment
Gaard, 1996 CRC00008 Norway	Norwegian national health screening service study, Prospective Cohort, Age: 20-53 years, M/W	83/ 50 535 11.4 years	Enrolment by volunteers	FFQ	Incidence, colon cancer, men	≥9999 vs ≤6857 kj/day	1.13 (0.58-2.22) Ptrend:0.83	Age, attained age, BMI, height, smoking status
		60/			Women	≥6654 vs ≤4453 kj/day	1.49 (0.70-3.19) Ptrend:0.72	
Martinez, 1996 COL00131 USA	NHS, Prospective Cohort, Age: 30-55 years, W, Registered nurses	157 89 448 1 012 280 person-years	Nurses registry	Semi-quantitative FFQ	Incidence, colon cancer,	Q 5 vs Q 1	1.18 (0.89-1.57)	Age

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors
Bostick, 1994 COL00079 USA	IWHS, Prospective Cohort, Age: 55-69 years, W	212/ 35 216 167 447 person-years	SEER	Semi-quantitative FFQ	Incidence, colon cancer	≥2239 vs ≤1300 kcal/day	0.60 (0.39-0.92) Ptrend:0.05	Age, height, parity, total vitamin e intake, total vitamin e intake age, vitamin a supplement
Goldbohm, 1994 COL00025 Netherlands	NLCS, Case Cohort, Age: 55-69 years, M/W	215/ 120 852 3.3 years	Population registries	Semi-quantitative FFQ	Incidence, colon cancer,	Q 5 vs Q 1	0.74 (0.47-1.18) Ptrend:0.24	Age, sex, dietary fibre intake
		110/			Women	2200 vs 1163 kcal/day	0.75 (0.40-1.41) Ptrend:0.23	
		105/			Men	2791 vs 1510 kcal/day	0.72 (0.36-1.45) Ptrend:0.62	

Table 316 Energy intake and colorectal cancer risk. Main characteristics of studies excluded from the CUP SLR dose-response meta-analysis

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Reasons for exclusion
Zheng, 1998 COL00209 USA	IWHS, Prospective Cohort, Age: 55-69 years, W, Postmenopausal	144/ 34 702 9 years	SEER	Semi-quantitative FFQ	Incidence, rectal cancer,	≥1940.4 vs ≤1499 kcal/day	0.89 (0.60-1.32) Ptrend:0.56	Age	Outcome is rectal cancer, not enough studies
Steinmetz, 1994 COL00178 USA	IWHS, Prospective Cohort, Age: 55-69 years, W, Postmenopausal	212/ 35 216 167 447 person-years	SEER	Semi-quantitative FFQ	Incidence, colon cancer,	Q 4 vs Q 1	0.66 (0.44-0.98)	Age	Superseded by Bostick, 1994 COL00079
Bostick, 1993 COL00483 USA	IWHS, Prospective Cohort, Age: 55-69 years, W	212/ 35 216 167 447 person-years	SEER	Semi-quantitative FFQ	Incidence, colon cancer,	≥2239 vs ≤1300 kcal/day	0.62 (0.40-0.95) Ptrend:0.06	Age	Superseded by Bostick, 1994 COL00079
Willett, 1990 CRC00026 USA	NHS, Prospective Cohort, Age: 34-59 years, W, Registered nurses	150/ 88 751 512 488 person-years	Cancer register	Semi-quantitative FFQ	Incidence, colon cancer,	≥1960 vs ≤1129 kcal/day	0.94 (0.57-1.56) Ptrend:0.80	Age	Superseded by Martinez, 1996 COL00131

Figure 516 RR (95% CI) of colorectal cancer for the highest compared with the lowest level of energy intake

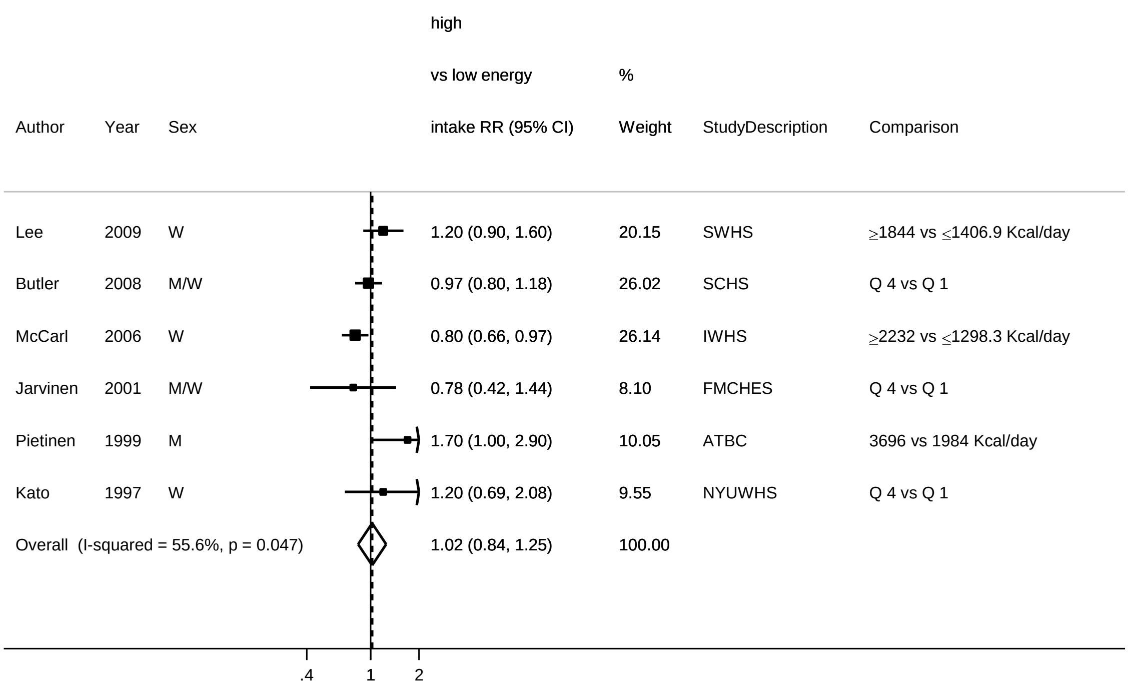
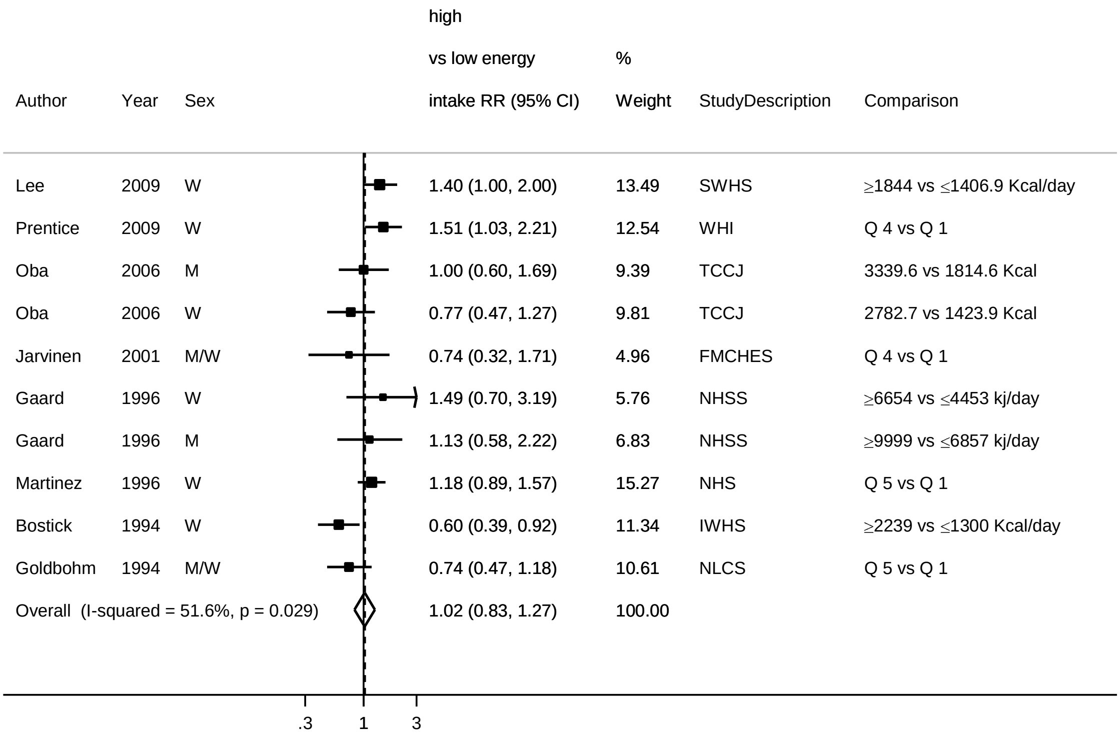


Figure 517 RR (95% CI) of colon cancer for the highest compared with the lowest level of energy intake



8 Anthropometry

8.1.1 BMI

Cohort studies

Summary

Thirty seven new publications (27 studies) were identified after the 2010 SLR, twenty four new studies on colorectal, 17 on colon and 13 new studies on rectal cancer. From these, four new studies (Taghizadeh, 2015; Gray, 2012; Dehal, 2011; Fiscella, 2011) were on colorectal cancer mortality.

In 14 studies, the lowest category of BMI (usually including underweight individuals) was not used as the referent category(Guo et al, 2014; Bhaskaran et al, 2014; Song et al, 2014; Morikawa et al, 2013; Renehan et al, 2012; Odegaard et al, 2011; Matsuo et al, 2011; Bassett et al, 2010; Song et al, 2008; Thygesen et al, 2008; Jee et al, 2008; Reeves et al, 2007; Bowers et al, 2006; Engeland et al, 2005). For these studies the relative risks were recalculated using the lowest category for their inclusion in dose-response meta-analysis using the Hamling method.

Cancer outcome was confirmed using records in cancer registries in most studies. All studies were multiple adjusted for different confounders. About half of the studies used measured height and weight to calculate BMI (n=31), 27 studies used self-reported BMI and 6 studies used BMI from medical records.

Pooling project of cohort studies:
One Pooling Projects was identified, including a pooled analysis of 8 Japanese studies (Matsuo, 2012), which included in the analysis. Asian studies tend to use different categories of BMI than European and American studies.

Table 317 Summary RR (95% CI) of colorectal cancer for 5 kg/m^2 in BMI by cancer site and sex

	Colorectal	Colon	Proximal colon	Distal colon	Rectal
All studies					
RR (95%CI)	1.05 (1.03-1.07)	1.07 (1.05-1.09)	1.05 (1.03-1.08)	1.08 (1.04-1.11)	1.02 (1.01-1.04)
Studies (n)	38*	41	20	20	35
Cases (total number)	71 089	72 605	8 437	14 985	67 732
I^2, p-heterogeneity	74.2%, < 0.001	72.1%, < 0.001	44.0%, 0.04	51.6%, 0.02	59.4%, < 0.001
P value Egger test	0.16	<0.001	0.06	0.08	0.78
Men					
RR (95%CI)	1.08 (1.04-1.11)	1.10 (1.07-1.13)	1.13 (1.05-1.21)	1.23 (1.08-1.38)	1.02 (1.01-1.04)
Studies (n)	20	26	12	12	24
I^2, p-heterogeneity	83.3%, < 0.001	74.2%, < 0.001	33.2%, 0.20	77.0%, 0.002	21.8%, 0.20
Women					
RR (95%CI)	1.05 (1.02-1.08)	1.04 (1.02-1.06)	1.04 (1.01-1.07)	1.05 (1.03-1.08)	1.01 (0.99-1.03)
Studies (n)	24	29	16	16	24
I^2, p-heterogeneity	82.5%, < 0.001	48.2%, < 0.01	30.4%, 0.18	0%, 0.60	44.1%, 0.03

- 30 publications; one publication is a pooled analysis of 8 Japanese cohorts and two other publications included two cohorts each

Colorectal cancer:
Thirty eight studies (71 089 cases) were included in the dose-response meta-analysis. A 5% increase of colorectal cancer risk for an increment of 5 kg/m^2 of BMI was observed. There was high heterogeneityand although there was no significant statistical evidence of publication or small study bias (p=0.16), the funnel plot was asymmetric. Visual inspection of the funnel and forest plot shows that the asymmetry is driven by the smaller studies (Tulinius,1997; Schoen ,1999, Yamamoto, 2010) a study in Northern China (Guo, 2014) and the Japanese pooled analysis of 8 cohorts (Matsuo, 2012) that reported stronger associations than the average.

Significant associations with colorectal cancer were observed in analyses stratified by study size, years of follow-up, lowest and highest categories of BMI ranges and in studies in which weight and height were self-assessed and in those in which they were measured. Several differences in associations emerged in stratified analyses, but none of them was statistically significant. The associations tended to be stronger in men than in women but the difference was not statistically significant (p homogeneity= 0.34) and when the analysis was restricted to studies that reported in both sexes, the summary RR were 1.06 (95% CI 1.01-1.11) in women and 1.08 (95% CI 1.04-1.11) in men (p homogeneity =0.60). The summary associations were stronger in studies in Asia compared to studies in Europe and North America (p homogeneity =0.43), in studies in which weight and height were self-reported compared to measured (p homogeneity =0.63), and in studies with higher number of cases (>3000) or longer follow-up. Also, studies in which the lowest category of BMI was <18.5 kg/m^2 and those in which the highest category was >30 kg/m^2 reported on average stronger associations than studies with lower range of BMI in the study populations. However, none of these variables independently explained the significant heterogeneity.
In sensitivity analysis, the summary RR did not change when the categories of BMI corresponding to underweight were omitted from the dose-response meta-analysis (RR= 1.05 (95% CI: 1.03-1.06; I^2=77.2%, p=<0.001).

There was statistical evidence of non-linear relationship (p= <0.01). Colorectal cancer risk increased with BMI increases the risk increase appears to be stronger from BMI increases above 27 kg/m^2 approximately. In seven other studies the outcome investigated was mortality from colorectal cancer. The summary RR for an increment of 5 kg/m2 in these studies was 1.03 (95% CI 1.02-1.05).

Stratified analysis by Mortality as outcome		
Studies (n)		7
RR (95%CI)		1.03 (1.02-1.05)
Heterogeneity (I^2, p-value)		6.2%, 0.38

Colon cancer:

Forty one studies (72 605 cases) from 33 publications were included in the dose-response meta-analysis. A 7% increase of colon cancer risk for each 5 kg/m^2 increment of BMI was observed. There was high heterogeneityand significant evidence of publication or small study bias (p<0.001). The funnel plot shows that smaller studies with lower than expected associations are not in the figure.

In stratified analysis by sex and geographical location, the summary RR showed stronger associations in studies in men than women (p homogeneity =0.059) but similar associations in studies in Asia, North America and Europe (p homogeneity =0.59).

There was statistical evidence of non-linear association (p=0.02) but the curve looks linear in all the range of BMI investigated.

Proximal and distal colon cancer:

Twenty studies were included in dose-response meta-analysis for proximal (8 437 cases) and distal (14 985 cases) colon cancer. There was evidence of positive significant association between BMI and both proximal and distal colon cancer risk, that was slightly stronger for distal than for proximal cancer but not statistically different (p homogeneity =0.26). Medium to high heterogeneity was observed. There was marginal evidence of publication or small study bias (proximal: p=0.06; distal: p=0.08). In analysis stratified by sex, the association of BMI with both proximal and distal colon cancer were stronger in men than in women.

Rectal cancer:

Thirty five studies (67 732 cases) were included in the dose-response meta-analysis. A 2% of rectal cancer risk for an increment of 5 kg/m^2 was observed. The association of BMI with rectal cancer was weaker than the association with colon cancer (p homogeneity =0.003). High heterogeneitywas observed between studies. There was no evidence of a significant publication or small study bias (p=0.78).

In stratified analysis, the summary RR was statistically significant in men but not in women, and of similar magnitude across geographic locations.

There was evidence of a non-linear association (p=< 0.001). The curve shows that there is no evidence of association for BMI<27.5 kg/m^2 approximately and the risk increase for BMI values above this level.

Table 318 BMI and colorectal cancer risk. Number of studies in the CUP SLR

	Number		
	Colorectal	Colon	Rectal
Studies identified	*57 (75 publications)	*55 (79 publications)	*46 (49 publications)

Studies included in forest plot of highest compared with lowest exposure	44	44	38
Studies included in dose-response meta-analysis	38	41	35
Studies included in non-linear dose-response meta-analysis	20	33	28

Note: Include cohort, nested case-control and case-cohort designs
* One publication is a pooled analysis of 8 Japanese cohorts and two other publications included two cohorts each

Table 319 BMI and colorectal cancer risk. Summary of the dose-response meta-analysis in the 2005 SLR and 2015 SLR.

Colorectal cancer		
	2010 SLR	**2015 SLR**
Increment unit used	1 kg/m^2	5 kg/m^2
All studies		
Studies (n)	23	38
Cases (total number)	62 344	71 089
RR (95%CI)	1.02 (1.02-1.03)	1.05 (1.03-1.07)
Heterogeneity (I^2, p-value)	59.9%, < 0.001	74.2%, < 0.001
P value Egger test		0.16
Stratified analysis by sex		
Men	**2010 SLR**	**2015 SLR**
Studies (n)	12	20
RR (95%CI)	1.03 (1.03-1.04)	1.08 (1.04-1.11)
Heterogeneity (I^2, p-value)	0%, 0.90	83.3%, < 0.001
Women		
Studies (n)	16	24
RR (95%CI)	1.02 (1.01-1.03)	1.05 (1.02-1.08)
Heterogeneity (I^2, p-value)	66.9%, < 0.001	82.5%, < 0.001
Stratified analysis by geographic location		
Asia	**2010 SLR**	**2015 SLR**
Studies (n)	4	15
RR (95%CI)	1.03 (1.02-1.05)	1.10 (1.00-1.20)
Heterogeneity (I^2, p-value)	0%, 0.64	91.5%; p=< 0.001
Europe		
Studies (n)	9	10

RR (95%CI)	1.02 (1.01-1.03)	1.05 (1.03-1.06)
Heterogeneity (I^2, p-value)	50.1%, 0.000	23.3%, 0.23
North America		
Studies (n)	10	13
RR (95%CI)	1.03 (1.02-1.03)	1.04 (1.02-1.06)
Heterogeneity (I^2, p-value)	28.9%, 0.18	48.8%, 0.03
Stratified analysis by exposure assessment		
2015 SLR	**Measured**	**|Self-reported**
Studies (n)	13	26
RR (95%CI)	1.04 (1.01-1.07)	1.05 (1.03-1.08)
Heterogeneity (I^2, p-value)	61.9%, < 0.01	80.7%, < 0.001

Other stratified analyses of colorectal cancer in the 2015 SLR			
By number of cases	**< 1000 cases**	**1000-3000 cases**	**≥ 3000 cases**
Studies (n)	23	3	11
RR (95%CI)	1.03 (1.02-1.04)	1.04 (1.02-1.06	1.10 (1.02-1.18)
Heterogeneity (I^2, p- value)	17.9 %, 0.22	4.6%, 0.35	94.6%, < 0.001
By years of follow up	**< 10 years**	**10 - < 15 years**	**≥ 15 years**
Studies (n)	15	17	6
RR (95%CI)	1.04 (1.02-1.07)	1.06 (1.02-1.10)	1.04 (1.02-1.06)
Heterogeneity (I^2, p- value)	42.7%, 0.05	88.4%, < 0.001	9.2%, 0.35
By highest category of BMI	**≥ 25 - ≥ 29.9 kg/m²**	**≥ 30 - ≥ 34.9 kg/m²**	**≥ 35 kg/m²**
Studies (n)	11	20	2
RR (95%CI)	1.03 (1.01-1.05)	1.06 (1.03-1.09	1.06 (0.99-1.13)
Heterogeneity (I^2, p- value)	0%, 0.84	87.1%, < 0.001	89.9%, < 0.01
By lowest category of BMI	**< 18.5 kg/m²**	**18.5 - ≤ 24.9 kg/m²**	**≥ 25 kg/m²**
Studies (n)	5	27	1
RR (95%CI)	1.07 (1.03-1.11)	1.04 (1.02-1.06)	1.00 (0.55-1.81)
Heterogeneity (I^2, p- value)	70.5%, < 0.01	78.5%, < 0.001	

BMI and colon cancer risk. Summary of the dose-response meta-analysis in the CUP.

Colon cancer		
	2010 SLR	**2015 SLR**
Increment unit used	1 kg/m²	5 kg/m²
All studies		
Studies (n)	29	41
Cases (total number)	44 256	72 605

RR (95%CI)	1.03 (1.03-1.04)	1.07 (1.05-1.09)
Heterogeneity (I^2, p-value)	68.2%, < 0.001	72.1%, < 0.001
P value Egger test		<0.001
Stratified analysis by sex		
	2010 SLR	**2015 SLR**
Men		
Studies (n)	22	26
RR (95%CI)	1.04 (1.03-1.05)	1.10 (1.07-1.13)
Heterogeneity (I^2, p-value)	49.9%, < 0.01	74.2%, < 0.001
Women		
Studies (n)	24	29
RR (95%CI)	1.02 (1.01-1.03)	1.04 (1.02-1.06)
Heterogeneity (I^2, p-value)	52.7%, 0.001	48.2%, < 0.01
Stratified analysis by geographic location		
Asia		
Studies (n)	6	14
RR (95%CI)	1.04 (1.02-1.07)	1.09 (1.03-1.16)
Heterogeneity (I^2, p-value)	43.3%, 0.12	82.5%, < 0.001
Europe		
Studies (n)	10	12
RR (95%CI)	1.03 (1.02-1.04)	1.05 (1.03-1.08)
Heterogeneity (I^2, p-value)	63.7%, <0.01	67.2%, <0.001
North America		
Studies (n)	12	14
RR (95%CI)	1.04 (1.03-1.05)	1.08 (1.05-1.11)
Heterogeneity (I^2, p-value)	58.0%, < 0.01	74.9%, < 0.001

Proximal colon		
	2010 SLR	**2015 SLR**
Increment unit used	1 kg/m^2	5 kg/m^2
Studies (n)	9	20
Cases (total number)	1364	8 437
RR (95%CI)	1.03 (1.01-1.05)	1.05 (1.03-1.08)
Heterogeneity (I^2, p-value)	45.7%, 0.07	44.0%, 0.04
P value Egger test	0.12	0.06
Stratified analysis by sex		
Men		
Studies (n)	4	12
RR (95%CI)	1.06 (1.02-1.09)	1.13 (1.05-1.21)
Heterogeneity (I^2, p-value)	0%, 0.50	33.2%, 0.20
Women		
Studies (n)	7	16

RR (95%CI)	1.02 (0.99-1.04)	1.04 (1.01-1.07)
Heterogeneity (I^2, p-value)	42.1%, 0.11	30.4%, 0.18

Distal colon		
	2010 SLR	**2015 SLR**
Increment unit used	1 kg/m^2	5 kg/m^2
Studies (n)	9	20
Cases (total number)	1332	14 985
RR (95%CI)	1.04 (1.02-1.05)	1.08 (1.04-1.11)
Heterogeneity (I^2, p-value)	0%, 0.95	51.6%, 0.02
P value Egger test	0.84	0.08
Stratified analysis by sex		
Men		
Studies (n)	4	12
RR (95%CI)	1.05 (1.02-1.08)	1.23 (1.08-1.38)
Heterogeneity (I^2, p-value)	0%, 0.93	77.0%, 0.002
Women		
Studies (n)	7	16
RR (95%CI)	1.03 (1.01-1.05)	1.05 (1.03-1.08)
Heterogeneity (I^2, p-value)	0%, 0.73	0%, 0.60

Table 320 BMI and rectal cancer risk. Summary of the dose-response meta-analysis in the CUP.

Rectal cancer		
	2010 SLR	**2015 SLR**
Increment unit used	1 kg/m^2	5 kg/m^2
All studies		
Studies (n)	22	35
Cases (total number)	22 615	67 732
RR (95%CI)	1.01 (1.01-1.02)	1.02 (1.01-1.04)
Heterogeneity (I^2, p-value)	13.8%, 0.28	59.4%, < 0.001
P value Egger test		0.78

Stratified analysis by sex		
	2010 SLR	**2015 SLR**
Men		
Studies (n)	18	24
RR (95%CI)	1.02 (1.01-1.02)	1.02 (1.01-1.04)
Heterogeneity (I^2, p-value)	0%, 0.48	21.8%, 0.20
Women		
Studies (n)	18	24
RR (95%CI)	1.01 (1.00-1.02)	1.01 (0.99-1.03)

Heterogeneity (I^2, p-value)	32.0%, 0.10	44.1%, 0.03
Stratified analysis by geographic location		
Asia		
Studies (n)	5	13
RR (95%CI)	1.01 (0.97-1.05)	1.03 (1.01-1.05)
Heterogeneity (I^2, p-value)	50.3%, 0.09	0%, 0.50
Europe		
Studies (n)	10	12
RR (95%CI)	1.01 (1.00-1.01)	1.02 (0.99-1.06)
Heterogeneity (I^2, p-value)	0%, 0.49	77.1%, < 0.001
North America		
Studies (n)	6	9
RR (95%CI)	1.02 (1.01-1.03)	1.02 (0.99-1.05)
Heterogeneity (I^2, p-value)	2.5%, 0.40	23.9%, 0.24
Australia		
Studies (n)	1	1
RR (95%CI)	1.01 (0.97-1.04)	1.02 (0.97-1.08)
Heterogeneity (I^2, p-value)		

Table 321 BMI and colorectal cancer risk. Results of meta-analyses and pooled analyses of prospective studies published after the 2010 SLR.

Author, Year	Number of cohort studies	Cancer site	Comparison	RR (95%CI)	P trend	Heterogeneity (I^2, p value)
Robsahm, 2013	20	Distal colon	High vs normal BMI	1.59 (1.34-1.89)		
	20	Proximal colon		1.24 (1.08-1.42)		
	11	Rectum		1.23 (1.02-1.48)		
Ma, 2013	41	Colorectal	Obese vs normal BMI	1.33 (1.25–1.42)		< 0.001, 68.9%
		Colon		1.47 (1.34–1.60)		< 0.001, 71.3%
		Distal colon		1.29 (1.10–1.51)		0.058, 40.5%
		Proximal		1.36 (1.16–1.60)		0.798, 0%
		Rectum		1.14 (1.09–1.20)		0.048, 29.3%
	USA	Colorectal cancer		1.46 (1.32–1.61)		0.052, 34.8%
	Europe			1.25 (1.14–1.36)		< 0.001, 77.5%
	Asia			1.35 (1.18–1.54)		0.165, 25.1%
	Australia			1.20 (1.00–1.44)		0.350, 10.3%
		Colorectal, Men		1.46 (1.36–1.57)		0.043, 31.9%
		Colorectal , Women		1.15 (1.07–1,23)		0.026, 37.2%

		Colon, Men		1.54 (1.46–1.63)		0.585, 0%
		Colon, Women		1.22 (1.09–1.37)		0.014, 46.4%
		Rectal, Men		1.23 (1.11–1.37)		0.154, 25.1%
		Rectal, Women		1.07 (1.00–1.13)		0.727, 0%
Matsuo, 2012	8	Colorectal, men 3 055 cases	Per 1 kg/m^2	1.03 (1.02-1.04)	< 0.001	0.64, 0%
			30 vs 23-<25 kg/m^2	1.24 (1.06-1.44)		0.01, 69.8%
		Colorectal, women 1 924 cases	Per 1 kg/m^2	1.07 (1.05-1.08)	<0.001	< 0.001, 97.9%
			30 vs 23-<25 kg/m^2	1.17 (0.87-1.57)		0.85, 0%
		Colon , men 1 919 cases	Per 1 kg/m^2	1.04 (1.02-1.06)	< 0.001	0.36, 9.1%
			30 vs 23-<25 kg/m^2	1.47 (0.99-2.18)		0.096, 52.7%
		Colon, women 1 534 cases	Per 1 kg/m^2	1.03 (1.01-1.05)	0.003	0.83, 0%
			30 vs 23-<25 kg/m^2	1.18 (0.83-1.68)		0.98, 0%
		Proximal colon, men 710 cases	Per 1 kg/m^2	1.03 (1.00-1.06)	0.09	0.90, 0%
			30 vs 23-<25 kg/m^2	1.61 (0.83-3.09)		0.76, 0%

		Proximal colon, women 710 cases	Per 1 kg/m^2	1.03 (1.01-1.06)	0.009	0.76,0%
			30 vs 23-<25 kg/m^2	1.26 (0.79-1.99)		0.63, 0%
		Distal colon, men 946 cases	Per 1 kg/m^2	1.05 (1.03-1.08)	< 0.001	0.63, 0%
			30 vs 23-<25 kg/m^2	1.77 (1.06-3.00)		0.13, 47.5%
		Distal colon, women 609 cases	Per 1 kg/m^2	1.02 (0.99-1.05)	0.26	0.63, 0%
			30 vs 23-<25 kg/m^2	1.42 (0.76-2.66)		0.74, 0%
		Rectum, men 1111 cases	Per 1 kg/m^2	1.02 (0.99-1.04)	0.20	0.92, 0%
			30 vs 23-<25 kg/m^2	1.57 (0.97-2.53)		0.26, 24.9%
		Rectum, women, 735 cases	Per 1 kg/m^2	1.00 (0.97-1.03)	0.78	0.29, 18.5%
			30 vs 23-<25 kg/m^2	1.39 (0.81-2.39)		0.397, 0%

Table 322 BMI and colorectal cancer risk. Main characteristics of studies included in the CUP SLR dose-response meta-analysis

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Missing data derived for analyses
Taghizadeh, 2015 COL41055 Netherlands	Vlaardingen cohort study, Prospective Cohort, Age: 20-65 years, M/W	113/ 8 645 40 years	National death certificate	Data obtained from the survey	Mortality, colorectal cancer	obese vs normal kg/m²	1.28 (0.73-2.25)	Age, residence, smoking	Mid-point categories Person-years of follow up
Bhaskaran, 2014 COL41010 UK	CPRD, Prospective Cohort, Age: 16- years, M/W	13 465/ 5 243 978 25 years	Medical records	Weight and height were measured	Incidence, colon cancer	per 5 kg/m²	1.10 (1.07-1.13)	Age, sex, diabetes, socio-economic status, alcohol, calendar year	Mid-point categories Hamling method used to recalculate the RR's
						35 vs 18.5-24.9 kg/m²	1.36 (1.23-1.51)		
		6 123/			Incidence, rectal cancer	per 5 kg/m²	1.04 (1.00-1.08)		
		5 819/				35 vs 18.5-24.9 kg/m²	1.18 (1.01-1.38)		
					Never smokers	per 5 kg/m²	1.05 (0.99-1.12)		
Guo, 2014 COL41041 China	Northern China 2006-2011, Prospective Cohort, Age: 18- years, M/W	149/ 133 273 4.28 years	Self-report, next of kin, medical and pathological records	Weight and height were measured	Incidence, colorectal cancer	≥ 28 vs <18.5kg/m²	1.39 (0.83-2.34)	Age, alcohol consumption, education level, smoking	Mid-point categories Person-years of follow up
		62/			Colon cancer	≥ 28 vs 18.5-23.9 kg/m²	2.75 (1.25-6.06)		

		86/			Rectal cancer	≥ 28 vs <18.5kg/m²	0.86 (0.42-1.80)		
Wie, 2014 COL41065 Korea	Korea 2004-2008, Prospective Cohort, M/W	53/ 8024 7 years	Cancer registry and medical records	Weight and height were measured	Incidence, Colorectal cancer	Per 1 kg/m²	1.00 (0.89-1.13)	Age, sex, energy intake, smoking, physical activity, alcohol use, income, education and marital status	Mid-point Increment unit converted to 5 kg/m²
						≥ 25 vs < 25 kg/m²	0.64 (0.32-1.26)		
Song, 2014 COL41018 Finland	FINRISK, Prospective Cohort, Age: 24-74 years, M/W	203/ 54 725 20.6 years	Cancer and mortality registries	Height and weight were measured on site by specially trained nurses	Incidence Colon cancer, men	≥ 35 vs < 18.5 kg/m²	3.24 (1.45-7.24)	Age, leisure - physical activity, area, education, smoking	Mid-point categories, number of cases per quintiles, person years Hamling method used to recalculate the RR's
		184/							
		203/			Colon, women		2.02 (1.13-3.62)		
		184/			Rectum, men		1.14 (0.34-3.81)		
		103/			Rectum, women		1.14 (0.40-3.24)		
Kabat, 2013 COL40965 USA	WHI, Prospective Cohort, Age: 50-79 years, W, Post-menopausal	166/ 11 124 12.9 years	Self-report verified by reviewing medical and pathological records by physicians	Weight, height, and waist and hip circumferences measured by trained staff	Incidence, colorectal cancer	≥ 31.4 vs ≤ 24 kg/m²	1.07 (0.66-1.75) Ptrend:0.55	Diabetes, ethnicity, HRT use, physical activity, alcohol, education, family history colorectal cancer, pack years smoking randomisation group	Mid-point categories

Kitahara, 2013 COL40966 USA	PLCO, Prospective Cohort, Age: 55-74 years, M/W	962/ 74 474 11.9 years	Self-reported/death certificate/ medical records	Questionnaire	Incidence, colorectal cancer, all	≥ 30 vs 18.5-24.9 kg/m²	1.24 (1.04-1.47) Ptrend:0.02	Sex, HRT use, race, study centre, age at baseline, screening, smoking	Mid-point categories Person-years of follow up
		546/			Colorectal, men		1.48 (1.16-1.89) Ptrend:0.002		
		416/			Colorectal, women		1.03 (0.80-1.33) Ptrend:0.74		
		529/			Proximal colon, all		1.32 (1.04-1.66) Ptrend:0.02		
		275/			Proximal colon, men		1.48 (1.05-2.09) Ptrend:0.02		
		254/			Proximal colon, women		1.23 (0.89-1.69) Ptrend:0.21		
		219/			Distal colon, all		1.07 (0.73-1.55) Ptrend:0.70		
		131/			Distal colon, men		1.48 (0.90-2.42) Ptrend:0.12		
		85/			Distal colon, women		0.66 (0.36-1.21) Ptrend:0.25		
		200/			Rectum, all		1.20 (0.81-1.78) Ptrend:0.35		
		134/			Rectum, men		1.38 (0.83-2.27) Ptrend:0.21		
		66/			Rectum, women		0.95 (0.50-1.79) Ptrend:0.89		
Morikawa, 2013 COL40958	NHS & HPFS, Pooled analysis,	861/ 156 703	Self-report (provided	Weight measured,	Incidence, colorectal cancer	≥ 30 vs < 18.5 kg/m²	1.52 (1.19-1.93) Ptrend:0.0001	Age, aspirin, calcium, caloric	Used in stratified

& COL40959 USA	(W) nurses and (M) health professionals	2 631 423 person-years	evidence of treatment), medical records and pathology reports, national death Index	height was self-reported in 1976				intake, folate, red meat, vit D, multivitamin, smoking status, alcohol, family history CRC, sigmoidoscopy, physical activity smoking, HRT use (women)	analysis by sex only Mid-point categories Hamling method used to recalculate the RR's
	NHS, Prospective Cohort, W	493/ 109 046					1.55 (1.16-2.06) Ptrend:0.001		
	HPFS, Prospective Cohort, M	368/ 47 684					1.30 (0.83-2.03) Ptrend:0.14		
Poynter, 2013 COL40952 USA	IWHS, Prospective Cohort, Age: 55-71 years, W, Post-menopausal	707/ 37 459 22 years	SEER	BMI was calculated from self-reported current weight and height	Incidence, colon cancer, aged ≥75 years	≥ 30 vs < 25 kg/m²	1.38 (1.13-1.69) Ptrend:0.001	Estrogen use, physical activity, age at baseline, smoking	Mid-point categories
		604/			Incidence, colon cancer, aged < 75 years	≥ 30 vs < 25 kg/m²	1.44 (1.16-1.78) Ptrend:0.0006		
Li, 2012 COL40937 China	SWHS, Prospective Cohort, Age: 40-70 years, W	621/ 72 972 11 years	Follow up survey/cancer registry/vital statistics registry	Anthropometric measurements, measured by trained Interviewers at baseline	Incidence, colorectal cancer	≥ 26.71 vs ≤ 21.1 kg/m²	1.08 (0.82-1.43) Ptrend:0.75	Alcohol consumption, energy intake, fruit, Income, menopausal status, physical activity, tea consumption, age at baseline, cigarette, education, family history of	Mid-point categories
						≥ 30 vs ≤ 25 kg/m²	0.89 (0.63-1.25) Ptrend:0.73		
		381/			Incidence, colon cancer	≥ 26.71 vs ≤ 21.1 kg/m²	1.00 (0.70-1.43) Ptrend:0.97		
						≥ 30 vs ≤ 25 kg/m²	0.78 (0.50-1.23) Ptrend:0.43		

		240/			Incidence, rectal cancer	≥ 26.71 vs ≤ 21.1 kg/m^2	1.22 (0.78-1.90) Ptrend:0.64	colorectal cancer, red meat, vegetables	
						≥ 30 vs ≤ 25 kg/m^2	1.07 (0.63-1.81) Ptrend:0.66		
Li, 2012 COL40936 China	SMHS, Prospective Cohort, Age: 40-74 years, M	313/ 61 283 5.5 years	Follow up survey/cancer registry/vital statistics registry	Anthropometric measurements, measured by trained Interviewers at baseline	Incidence, colorectal cancer	≥ 26.2 vs ≤ 21.13 kg/m^2	1.71 (1.20-2.44) Ptrend:0.003	Alcohol consumption, energy intake, fruits, Income, physical activity, tea consumption, age at baseline, education, family history of colorectal cancer, pack years of smoking, red meat, vegetables	Mid-point categories
						≥ 30 vs < 25 kg/m^2	1.74 (1.01-3.01) Ptrend:0.014		
		180/			Incidence, colon cancer	≥ 26.2 vs ≤ 21.13 kg/m^2	2.15 (1.35-3.43) Ptrend:0.0006		
		133/			Incidence, rectal cancer	≥ 30 vs < 25 kg/m^2	1.84 (0.85-3.99) Ptrend:0.88		
						≥ 26.2 vs ≤ 21.13 kg/m^2	1.20 (0.69-2.10) Ptrend:0.61		
Renehan, 2012 COL40925 USA	NIH-AARP, Prospective Cohort, Age: 50-71 years, M/W	4 076/ 273 679 2 509 662 person years	Cancer registry	Assessed by questionnaire, recalled weights at ages 18, 35, and 50 years and self-reported height	Incidence, colorectal cancer, men	per 5 kg/m^2	1.14 (1.08-1.20)	Age, physical activity, race, alcohol, education, smoking, alcohol consumption, HRT use (in women)	Hamling method used to recalculate the RR's Person-years of follow up in each category
		2 804/				≥ 35 vs < 18.5 kg/m^2	1.50 (1.18-1.91) Ptrend:<0.0001		
		1 240/			Incidence, colorectal	≥ 35 vs < 18.5 kg/m^2	1.25 (0.97-1.60) Ptrend:0.13		

					cancer, women	per 5 kg/m^2	1.05 (0.99-1.11)		
		2 070/			Incidence, colon cancer, men	≥ 35 vs < 18.5 kg/m^2	1.53 (1.16-2.03) Ptrend:<0.0001		
						per 5 kg/m^2	1.18 (1.11-1.25)		
		1 145/			Incidence, proximal colon cancer, men	≥ 35 vs < 18.5 kg/m^2	1.57 (1.09-2.25) Ptrend:< 0.0001		
						per 5 kg/m^2	1.20 (1.11-1.30)		
		855/			Incidence, distal colon cancer, men	≥ 35 vs < 18.5 kg/m^2	1.68 (1.05-2.68) Ptrend:0.003		
						per 5 kg/m^2	1.15 (1.05-1.27)		
		962/			Incidence, colon cancer, women	≥ 35 vs < 18.5 kg/m^2	1.23 (0.93-1.64) Ptrend:0.20		
						per 5 kg/m^2	1.05 (0.98-1.12)		
		607/			Incidence, proximal colon cancer, women	≥ 35 vs < 18.5 kg/m^2	1.15 (0.82-1.63) Ptrend: 0.67		
						per 5 kg/m^2	1.02 (0.93-1.11)		
		329/			Incidence, distal colon cancer, women	≥ 35 vs < 18.5 kg/m^2	1.35 (0.812.25) Ptrend: 0.23		
						per 5 kg/m^2	1.07 (0.96-1.20)		
		762/			Incidence, rectal cancer, men	≥ 35 vs < 18.5 kg/m^2	1.43 (0.90-2.28) Ptrend:0.51		
						per 5 kg/m^2	1.03 (0.93-1.14)		
		282/			Incidence, rectal	≥ 35 vs < 18.5	1.28 (0.76-2.16)		

					cancer, women	kg/m²	Ptrend:0.45		
						per 5 kg/m²	1.05 (0.92-1.19)		
Gray, 2012 COL40981 USA	HAHS, Prospective Cohort, Age: 46.1 (mean age) years, M/W	228/ 19 593 56.5 years	Death certificate	Height and weight were measured	Mortality, Colorectal cancer	Per 2.55 kg/m²	1.12 (1.00-1.26)	Age	
Hughes, 2011 COL40895 Netherlands	NLCS, Prospective Cohort, Age: 55-69 years, M/W	1 211/ 120 852 16.3 years	Cancer registry	Self-reported height and weight	Incidence, colorectal cancer, men	27.1-39.6 vs 16.1-23 kg/m²	1.25 (0.96-1.62) Ptrend:0.08	Age, alcohol consumption, energy intake, occupational activity, education, family history of colorectal cancer, smoking	Mid-point categories Number of non-cases in each category
		1 211/				per 5 kg/m²	1.25 (1.05-1.46)		
		1 106/			Incidence, colorectal cancer, women	27.6-41.4 vs 15.4-22.1 kg/m²	0.97 (0.76-1.24) Ptrend:0.90		
						per 5 kg/m²	0.98 (0.88-1.10)		
		327/			Incidence, proximal colon cancer, men	27.1-39.6 vs 16.1-23 kg/m²	1.35 (0.90-1.98) Ptrend: 0.43		
						per 5 kg/m²	1.19 (0.92-1.54)		
		427			Incidence, distal colon cancer, men	27.1-39.6 vs 16.1-23 kg/m²	1.38 (0.95-1.98) Ptrend: 0.05		
						per 5 kg/m²	1.42 (1.13-1.79)		
		459/			Incidence, proximal colon cancer, women	27.6-41.4 vs 15.4-22.1 kg/m²	0.91 (0.65-1.28) Ptrend: 0.84		

						per 5 kg/m^2	1.02 (0.87-1.18)		
		327/			Incidence, distal colon cancer, women	27.6-41.4 vs 15.4-22.1 kg/m^2	1.04 (0.72-1.50) Ptrend: 0.84		
						per 5 kg/m^2	0.95 (0.79-1.14)		
		299/			Incidence, rectal cancer, men	27.1-39.6 vs 16.1-23 kg/m^2	1.01 (0.67-1.51) Ptrend:0.96		
						per 5 kg/m^2	1.02 (0.79-1.32)		
		205/			Incidence, rectal cancer, women	27.6-41.4 vs 15.4-22.1 kg/m^2	1.07 (0.67-1.60) Ptrend:0.90		
						per 5 kg/m^2	1.05 (0.83-1.31)		
Dehal, 2011 COL40893 USA	NHEFS, Prospective Cohort, Age: 25-75 years, M/W	52/ 7 016 118 998 person-years	Death index & social security administration death file	Weight and height were measured	Mortality, colorectal cancer	obese vs normal weight kg/m^2	2.04 (1.08-3.83) Ptrend:0.02	Marital status, race/ethnicity, alcohol, baseline residence type area, education, family income, smoking	
Park, 2011 COL41069 UK	EPIC-Norfolk, Prospective Cohort, Age: 40-79 years, M/W	357/ 20 608 11 years	Record linkage to cancer registration and death certificates	Self-reported and measured	Incidence, colorectal cancer, men (measured BMI)	$\geq$ 28.9 vs < 23.9 kg/m^2	1.06 (0.67-1.69) Ptrend:0.52	Age, sex, smoking, alcohol, education, exercise, family history of CRC, energy intake, folate, fibre,	Mid-point categories Person-years of follow up
					Incidence, colorectal		0.97 (0.61-1.54) Ptrend:0.85		

					cancer, men (self-reported BMI)			total meat and processed meat, intakes	
					Incidence, colorectal cancer, women (measured BMI)	≥ 29.4 vs < 22.6 kg/m²	1.57 (0.91–2.73) Ptrend:0.05		
					Incidence, colorectal cancer, women (self-reported BMI)		1.97 (1.18–3.30) Ptrend:0.02		
					Men (measured BMI)	Per 4 unit increase	0.86 (0.60-1.24)	Age, sex, s moking, alcohol, education, exercise, family history of CRC, energy intake, folate, fibre, total meat and processed meat, intakes, waist and hip circumferences	
					Men (self-reported BMI)		0.97 (0.70-1.34)		
					Women (measured BMI)		0.84 (0.58-1.19)		
					Women (self-reported BMI)		1.16 (0.90-1.51)		
Odegaard, 2011 COL40883 Singapore	SCHS, Prospective Cohort, Age: 45-74	980/ 51 251 11.5 years	Cancer registry and death registry	Self-reported height and weight	Incidence, colorectal cancer	≥ 27.5 vs < 18.5 kg/m²	1.25 (1.01-1.55) Ptrend:0.44	Age, sex, diabetes, dialect group, dietary pattern score,	Mid-point categories Hamling method
		596/			Incidence, colon		1.48 (1.13-1.92)		

	years, M/W, middle-aged adults				cancer		Ptrend:0.31	family history of cancer, physical activity, sleep, alcohol intake, education, energy, smoking, year	used to recalculate the RR's Person-years of follow up in each category
		384/			Incidence, rectal cancer		0.93 (0.64-1.36) Ptrend:0.92		
		589/			Incidence, colorectal cancer, never smokers		1.35 (1.04-1.76) Ptrend:0.46		
					Ever smokers		1.08 (0.74-1.58) Ptrend:0.61		
		391/			Incidence, colon cancer, never smokers		1.59 (1.16-2.16) Ptrend: 0.58		
		205/			Incidence, colon cancer, ever smokers		1.26 (0.76-2.08) Ptrend: 0.35		
		198/			Incidence, rectal cancer, never smokers		0.96 (0.59-1.56) Ptrend:0.63		
		176/			Ever smokers		0.90 (0.50-1.61) Ptrend:0.80		
Oxentenko, 2010 COL40849 USA	IWHS, Prospective Cohort, Age: 55-69 years, W	1 464/ 36 941 619 961 person-years	SEER	Self-reported height and weight at baseline	Incidence, colorectal cancer	≥ 29.52 vs ≤ 23.45 kg/m²	1.29 (1.10-1.51) Ptrend:0.001	Age, age at menopause, calcium, contraception, diabetes, energy intake, estrogen use, folate, smoking status,	Mid-point categories
						obese III vs normal	1.56 (1.10-2.22) Ptrend:<0.001		
		771/			Incidence, proximal colorectal cancer	≥ 29.52 vs ≤ 23.45 kg/m²	1.17 (0.94-1.46) Ptrend:0.15		

						obese III vs normal	1.30 (0.78-2.18) Ptrend:0.06	total fat, vitamin E, alcohol, cigarette consumption, fruit and vegetable, physical activity level, red meat	
		660/			Incidence, distal colorectal cancer	≥ 29.52 vs ≤ 23.45 kg/m^2	1.44 (1.14-1.83) Ptrend:0.001		
						obese III vs normal	1.86 (1.14-3.05)		
Yamamoto, 2010 COL40807 Japan	HHCCS, Nested case-control study, Age: 54 years, M/W	22 cases/ 69 controls 3 years	Histology	Measured height and weight	Incidence, colorectal cancer	≥ 24.9 vs ≤ 22.1 kg/m^2	4.38 (0.82-23.25) Ptrend:0.09	Age, sex, alcohol consumption, smoking status, year of examination	
Bassett, 2010 COL40836 Australia	MCCS, Prospective Cohort, Age: 40-69 years, M/W	569/ 41 154 14 years	Cancer registry	Self-reported	Incidence, colon cancer, women	≥ 30 vs < 23 kg/m^2	1.00 (0.70-1.44) Ptrend:0.90	Country of birth, energy intake, fat intake, fruit and vegetable consumption, education, processed and red meat, smoking	Mid-point categories Hamling method used to recalculate the RR's
		292/				per 5 kg/m^2	1.01 (0.86-1.18)		
		277/			Incidence, colon cancer, men	≥ 30 vs < 23 kg/m^2	1.51 (1.00-2.28) Ptrend: < 0.01		
						per 5 kg/m^2	1.39 (1.12-1.71)		
Laake, 2010 COL40796 Norway	NCS, Prospective Cohort, Age: 20-49 years,	450/ 76 179 23.2 years	Cancer registry	Height and weight was measured at examinations up to three times	Incidence, colon cancer, men	≥ 30 vs 18.5-22.99 kg/m^2	1.80 (1.25-2.59) Ptrend:0.004	Age, area of residence, educational level, energy intake, height,	Mid-point categories
						per 5 kg/m^2	1.25 (1.08-1.45)		
		419/			Incidence, colon	per 5 kg/m^2	1.17 (1.04-1.31)		

	M/W, Screening Program			between 1974 and 1988	cancer, women	≥ 30 vs 18.5-22.99 kg/m²	1.48 (1.09-2.02) Ptrend:0.01	physical activity, smoking status	
		228/			Incidence, proximal colon cancer, men	≥ 30 vs 18.5-22.99 kg/m²	1.17 (0.68-2.00) Ptrend:		
						per 5 kg/m²	1.07 (0.86-1.33)		
		174/			Incidence, distal colon cancer, men	≥ 30 vs 18.5-22.99 kg/m²	3.26 (1.79-5.95) Ptrend:<0.01		
						per 5 kg/m²	1.49 (1.19-1.87)		
		237/			Incidence, proximal colon cancer, women	≥ 30 vs 18.5-22.99 kg/m²	1.43 (0.94-2.19) Ptrend:0.07		
						per 5 kg/m²	1.15 (0.99-1.34)		
		159/			Incidence, distal colon cancer, women	≥ 30 vs 18.5-22.99 kg/m²	1.65 (1.01-2.70) Ptrend:0.01		
						per 5 kg/m²	1.25 (1.05-1.49)		
Prentice, 2009 COL40811 USA	WHI Prospective Cohort, Age: 50-79 years, W, postmenopausal women	363/ 80 816 11 years 87/	Self-report, medical record and pathology report reviewed by centrally trained physician		Incidence, colon cancer	per 10 units	1.81 (1.19-2.76)	Age, family history of colon cancer, physical activity, smoking status, alcohol, total energy intake	
					Incidence, rectal cancer	per 10 units	0.62 (0.26-1.52)		
Jee, 2008 COL40643	KNHIC, Prospective	4 671/ 1 213 829	National cancer registries,	Weight and height	Incidence, colon cancer, men	≥ 30 vs < 20 kg/m²	1.42 (1.02-1.98) Ptrend:<0.0001	Age, smoking status	Mid-point categories

Korea	Cohort, Age: 30-95 years, M/W	10.8 years	hospitalisation records and admission files	measurements were recorded during health examination at hospital		per 1 kg/m^2	1.06		Person-years of follow up
		4 032/			Incidence, rectum cancer, men	≥ 30 vs < 20 kg/m^2	1.16 (0.77-1.74) Ptrend:0.001		
						per 1 kg/m^2	1.03		
		1 959/			Incidence, colon cancer, women	≥ 30 vs < 20 kg/m^2	1.01 (0.72-1.42) Ptrend:0.0114		
		1 681/			Incidence, rectum cancer, women	per 1 kg/m^2	1.03		
						≥ 30 vs < 20 kg/m^2	1.14 (0.78-1.68) Ptrend:0.0184		
						per 1 kg/m^2	1.03		
Song, 2008 COL40659 Korea	KNHIC, Prospective Cohort, Age: 40-64 years, W, Post-menopausal	453/ 170 481 8.75 years	Self-report, cancer registry, death report	Weights and heights were measured	Incidence, colon cancer	≥ 30 vs <18.5 kg/m^2	2.43 (1.40-4.23)	Age, alcohol, height, physical activity, smoking status, pay level at study entry	Mid-point categories Person-years of follow up
						per 1 kg/m^2	1.05 (1.02-1.09)		
Thygesen, 2008 COL40728 USA	HPFS, Prospective Cohort, Age: 40-75 years, M	693/ 46 349 18 years	Self-report verified by medical record	Self-reported data	Incidence, colon cancer	> 35.1 vs ≤ 20 kg/m^2	2.29 (1.23-4.26)	Age, alcohol consumption, aspirin use, intakes of calcium, energy, folate, methionine, and multivitamin, physical activity, previous	Mid-point categories Hamling method used to recalculate the RR's.

								endoscopic screening, processed meat, red meat intake, smoking habits, vitamin d, family history of colorectal cancer	
Wang, 2008 COL40666 USA	CPS II, Prospective Cohort, M/W	546/ 95 151 7.7 years	Self-report, pathology report, national death Index, death cert, state cancer registries	Self-reported data	Incidence, colorectal cancer, men	≥ 35 vs 18.5-24.9 kg/m²	1.76 (1.12-2.76) Ptrend:0.02	Age, alcohol, educational level, height, history of endoscopy, multivitamin use, NSAID use, physical activity, smoking status	Mid-point categories
							1.32 (0.73-2.40) Ptrend:0.62 (adjusted for WC)		
		407/			Incidence, colorectal cancer, Women		1.62 (1.04-2.54) Ptrend:0.006		
							1.21 (0.68-2.17) Ptrend:0.39 (adjusted for WC)	HRT use, waist circumference	
		402/			Incidence, colon cancer, men		1.93 (1.14-3.28) Ptrend:0.01		
							1.18 (0.59–2.38) Ptrend:0.92 (adjusted for WC)		
		314/			Incidence, colon cancer, women		1.40 (0.84-2.36) Ptrend:0.18		

							1.07 (0.54–2.09) Ptrend:0.88 (adjusted for WC)		
		142/			Incidence, rectal cancer, men		1.38 (0.58-3.28) Ptrend:0.7		
							1.74 (0.55-5.50) Ptrend:0.5 (adjusted for WC)		
		93/			Incidence, rectal cancer, women		2.67 (1.09-6.54) Ptrend:0.001		
							1.88 (0.60–5.93) Ptrend:0.13 (adjusted for WC)		
Reeves, 2007 COL40670 UK	MWS, Prospective Cohort, Age: 50-64 years, W	4 008/ 1 222 630 5 years	National health records	Self-reported	Incidence, colorectal cancer	$\geq$ 30 vs < 22.5 kg/m^2	1.01 (0.94-1.09)	Age, alcohol consumption, geographical area, physical activity, reproductive factors, smoking status, socio-economic status	Mid-point categories Person-years of follow up
						per 10 unit	1.00 (0.92-1.08)		
		1 884/			Never smoked	per 10 unit	1.04 (0.92-1.18)		
		1 743/			Postmenopausal never users of HRT	per 10 unit	0.99 (0.88-1.12)		
		1 548/			Mortality, colorectal cancer	per 10 unit	0.99 (0.87-1.13)		
						$\geq$ 30 vs < 22.5 kg/m^2	1.03 (0.92-1.16)		

		136/			Incidence, colorectal cancer, premenopausal never users of HRT	per 10 unit	1.61 (1.05-2.48)		
Bowers, 2006 COL40699 Finland	ATBC, Prospective Cohort, Age: 58 years, M, Smokers	410/ 28 983 14.1 years	Cancer registry	Measured by trained staff	Incidence, colorectal cancer	> 30 vs < 18.5 kg/m^2	1.66 (1.27-2.18)	Age, no of cigarettes smoked	Mid-point categories
						29.21-54.36 vs 12.97-23.11 kg/m^2	1.70 (1.01-2.85) Ptrend:0.01		
		227/			Incidence, colon cancer	> 30 vs < 18.5 kg/m^2	1.78 (1.25-2.55)		
						29.21-54.36 vs 12.97-23.11 kg/m^2	2.03 (1.00-4.13) Ptrend:0.02		
		183/			Incidence, rectal cancer	29.21-54.36 vs 12.97-23.11 kg/m^2	1.38 (0.65-2.96) Ptrend:0.21		
						> 30 vs < 18.5 kg/m^2	1.51 (0.99-2.29)		
Larsson, 2006 COL40625 Sweden	COSM, Prospective Cohort, Age: 45-79 years, M	461/ 45 906 7.1 years	Cancer registry	Self-reported height and weight at age 20, weight and waist circum. at baseline	Incidence, colorectal cancer	≥ 30 vs < 23 kg/m^2	1.54 (1.08-2.21) Ptrend:0.01	Age, aspirin use, BMI, educational level, history of diabetes, recreational activity, smoking status,	Mid-point categories
							1.71 (1.20-2.42) Ptrend:0.001		
		284/			Incidence, colon cancer		1.60 (1.03-2.48) Ptrend:0.08		
		180/			Incidence,		1.44 (0.79-2.61)		

					rectum cancer		Ptrend:0.06	family history of colorectal cancer	
		129/			Incidence, distal colon cancer		1.49 (0.78-2.84) Ptrend:0.16		
		120/			Incidence, proximal colon cancer		1.43 (0.71-2.88) Ptrend:0.32		
Lukanova, 2006 COL40752 Sweden	NSHDC, Prospective Cohort, Age: 29-61 years, M/W	136/ 68 786 8.2 years	Medical records	Weight and height measured by nurse	Incidence, colorectal cancer, men	≥ 27.7 vs 18.5-23.4 kg/m^2	1.20 (0.76-1.94) Ptrend:0.25	Age, smoking habits, calendar year	Mid-point categories Person-years of follow up
						≥ 30 vs 18.5-24.9 kg/m^2	1.61 (0.95-2.65) Ptrend:0.08		
		108/			Women	≥ 27 vs 18.5-22.1 kg/m^2	1.54 (0.90-2.74) Ptrend:0.04		
						≥ 30 vs 18.5-24.9 kg/m^2	2.01 (1.22-3.27) Ptrend:0.005		
		76/			Incidence, colon cancer, women	≥ 27.1 vs 18.5-22.1 kg/m^2	2.05 (1.04-4.41) Ptrend:0.02		
		73/			Men	≥ 27.7 vs 18.5-23.4 kg/m^2	1.28 (0.66-2.60) Ptrend:0.42		
		58/			Incidence, rectal cancer, men	≥ 27.7 vs 18.5-23.4 kg/m^2	1.23 (0.63-2.51) Ptrend:0.36		
						≥ 30 vs 18.5-24.9 kg/m^2	1.96 (0.96-3.86) Ptrend:0.13		
		31/			Women	≥ 27 vs 18.5-22.1 kg/m^2	0.86 (0.33-2.30) Ptrend:0.93		
						≥ 30 vs 18.5-24.9 kg/m^2	1.30 (0.42-3.45) Ptrend:0.54		
MacInnis, 2006	MCCS,	117/	Cancer registry	Height, weight,	Incidence,	≥ 30 vs < 25	1.0 (0.7–1.4)	Age-underlying	Person-years of

COL40751 Australia	Prospective Cohort, Age: 27-75 years, W	24 072 10.4 years		waist and hip were measured	proximal colon cancer	kg/m^2		cox models, country of birth, educational level, HRT use	follow up
		79/			Incidence, distal colon cancer	per 5 kg/m^2	1.04 (0.90–1.20)		
MacInnis, 2006 COL40627 Australia	MCCS, Prospective Cohort, Age: 27-75 years, M/W	229/ 41 114 10.3 person-years	Cancer registry	Measured	Incidence, rectal cancer	≥ 30 vs < 25 kg/m^2	1.20 (0.80-1.70)	Age, sex, country of birth	Person-years of follow up
						per 5 kg/m^2	1.03 (0.88-1.21)		
		134/			Incidence, rectal cancer , men	≥ 30 vs < 25 kg/m^2	1.30 (0.80-2.40)		
						per 5 kg/m^2	1.09 (0.86-1.38)		
		120/			Incidence, stage I/II rectal cancer	per 5 kg/m^2	1.07 (0.86-1.34)		
		102/			Incidence, stage III/iv rectal cancer	per 5 kg/m^2	1.02 (0.80-1.29)		
		95/			Incidence, rectal cancer, women	≥ 30 vs < 25 kg/m^2	1.10 (0.70-1.90)		
						per 5 kg/m^2	0.98 (0.80-1.22)		
Pischon, 2006 COL01985 Europe	EPIC, Prospective Cohort, Age: 25-70 years, M/W	563/ 368 277 2 254 727 person-years	Population registries	Self-reported questionnaires	Incidence, colon cancer, women	≥ 28.9 vs < 21.7 kg/m^2	1.06 (0.79-1.42) Ptrend:0.40	Alcohol consumption, centre, educational level, physical activity, smoking status,	Person-years of follow up
		421/			Incidence, colon cancer, men	≥ 29.4 vs < 23.6 kg/m^2	1.55 (1.12-2.15) Ptrend:0.06		
		295/			Incidence, rectal	≥ 29.4 vs < 23.6	1.05 (0.72-1.55)		

					cancer, men	kg/m²	Ptrend:0.47	age at recruitment, fibre, fish and shellfish, fruits and vegetables, red and processed meat	
		291/			Incidence, rectal cancer, women	≥ 28.9 vs < 21.7 kg/m²	1.06 (0.71-1.58) Ptrend:0.51		
Samanic, 2006 COL40708 Sweden	SFOSHCIC, Historical Cohort, Age: 18-67 years, M	1 795/ 362 552 19 years	Health screening programme	From health records	Incidence, colon cancer	> 30 vs 18.5-24.9 kg/m²	1.74 (1.48-2.04) Ptrend:<0.001	Age, calendar year, smoking status	Mid-point categories Person-years of follow up
		1 362/			Incidence, rectal cancer	> 30 vs 18.5-24.9 kg/m²	1.36 (1.13-1.66) Ptrend:<0.01		
		379/			Never smokers	> 30 vs 18.5-24.9 kg/m²	1.70 (1.23-2.35) Ptrend:0.01		
Yeh, 2006 COL40675 Taiwan	Taiwan cohort, Prospective Cohort, Age: 30-65 years, M/W	68/ 23 943 10 years	Cancer registry and death certificates	Height and weight were measured	Incidence, colorectal cancer, men	≥ 28.6 vs ≤ 24.2 kg/m²	1.87 (0.86-4.04) Ptrend:0.11	Age, nutritional factors (nos), residence, smoking status	Mid-point categories Person-years of follow up
		39/			Incidence, colorectal cancer, women	≥ 28.6 vs ≤ 24.2 kg/m²	2.19 (0.77-6.23) Ptrend:0.012		
Tsai, 2006 COL41001 USA	Shell employees cohort study, Prospective Cohort, Age: 30-69 years	43/ 7 139 20 years	Death index & social security administration death file	Recorded through the shell health surveillance system	Mortality, colorectal cancer	≥ 30 vs 18.5-24.9 kg/m²	1.84 (0.76-4.45)	Age, sex, blood pressure, cholesterol, fasting blood sugar, smoking	Mid-point categories Person years of follow up
Engeland, 2005 COL01941 Norway	norwegian composite cohort	24 130/ 1 999 978 23 years	Health survey, cancer registry, death registry	Height and weight measured by trained staff	Incidence, colorectal cancer, women	≥ 30 vs < 18.5 kg/m²	1.06 (1.02-1.10) Ptrend:0.01	Age, birth cohort	Mid-point categories

	consisting of 3 groups, Prospective Cohort, Age: 20-74 years, M/W	22 987/			Men		1.40 (1.32-1.48) Ptrend:<0.001		
		16 638/			Incidence, colon cancer, women		1.07 (1.02-1.12) Ptrend:0.006		
		13 805/			Incidence, colon cancer, men		1.49 (1.39-1.60) Ptrend:<0.001		
		9 182/			Incidence, rectum cancer, men		1.27 (1.16-1.38) Ptrend:<0.001		
		7 492/			Incidence, rectum cancer, women		1.04 (0.97-1.11) Ptrend:0.6		
		6 145/			Men, 45-74 years		1.26 (1.14-1.39)		
		5 013/			Women, 45-74 years		1.03 (0.95-1.11)		
		3 037/			Men, 20-44 years		1.24 (1.03-1.49)		
		2 479/			Women, 20-44 years		1.05 (0.90-1.23)		
Rapp, 2005 COL01878 Austria	VHM&PP, Prospective Cohort, Age: 19-94 years, M/W	271/ 1 450 000 person-years	Local physicians	Recorded by medical staff	Incidence, colon cancer, women	≥ 35 vs 18.5-24.9 kg/m^2	0.88 (0.43-1.81) Ptrend:0.73	Age, smoking status, occupational group	Mid-point categories
		260/			Incidence, colon cancer, men	≥ 35 vs 18.5-24.9 kg/m^2	2.48 (1.15-5.39) Ptrend:0.005		
		138/			Incidence, rectal cancer, men	≥ 30 vs 18.5-24.9 kg/m^2	1.66 (1.01-2.73) Ptrend:0.053		

		133/			Incidence, rectal cancer, women	$\geq$ 35 vs 18.5-24.9 kg/m^2	0.96 (0.38-2.39) Ptrend:0.005		
Lin, 2004 COL01832 USA	WHS, Prospective Cohort, Age: 45- years, W, professionals	202/ 36 876 8.7 years			Incidence, colorectal cancer, women	$\geq$ 30 vs < 23 kg/m^2	1.67 (1.08-2.59) Ptrend:0.018	Age, alcohol consumption, family history of specific cancer, history of previous polyp and prior endoscopy, menopausal status, physical activity, randomized treatment assignment, red meat intake, smoking status, aspirin use, postmenopausal hormone use, total energy	Mid-point categories
		158/			Incidence, colon cancer		1.73 (1.05-2.85) Ptrend:0.029		
		83/			Incidence, colon, proximal		2.59 (1.34–5.01) Ptrend:0.004		
		75/			Incidence, colon, distal		0.93 (0.41–2.14) Ptrend:0.91		
		67/			Post-menop & HRT nonusers		2.91 (1.40-6.06) Ptrend:0.018		
		62/			Post-menop & HRT users		1.41 (0.65-3.06) Ptrend:0.128		
		40/			Incidence, rectal cancer		1.55 (0.64-3.77) Ptrend:0.25		
					Incidence, colorectal cancer, ER+		1.36 (0.69-2.68) Ptrend:0.11		
					Er-		2.42 (1.31-4.49) Ptrend:0.02		
Moore, 2004 COL00362 US	FHS, Prospective Cohort, Age: 30-79 years, M/W,	306/	Self-report, health check, National Death Index	Height and weight were measured	Incidence, colon cancer	$\geq$ 30 vs 18.5-< 25 kg/m^2	1.60 (1.00-2.50)	Age, sex, alcohol consumption, educational level, physical activity,	Mid-point categories
		97/			Incidence, proximal colon cancer, age: 30-		1.60 (0.90-3.00)		

	members of original Framingham study				54 yrs			smoking habits, height	
		91/			Age: 55-79 yr		2.90 (1.60-5.20)		
		56/			Incidence, distal colon cancer, age: 30-54 yrs		1.40 (0.55-3.60)		
		53/			Age: 55-79 yr		1.80 (0.75-4.30)		
Sanjoaquin, 2004 COL01182 UK	OVS, Prospective Cohort, Age: 18-89 years, M/W	92/ 10 998 17 years	Population/invitation	Self-reported	Incidence, colorectal cancer,	≥ 25 vs < 20 kg/m²	0.83 (0.40-1.70) Ptrend:0.535	Age, sex	Mid-point categories Person-years of follow up
						≥ 25 vs < 20 kg/m²	0.74 (0.36-1.53) Ptrend:0.791	Alcohol consumption, smoking habits	
Wei, 2004 COL00581 USA	NHS, Prospective Cohort, W, nurses	672/ 87 733 24 years	Self-report, medical records and National Death Index	Self-reported	Incidence, colon cancer,	> 30 vs < 23 kg/m²	1.28 (1.10-1.62) Ptrend:0.05	Age, family history, BMI, physical activity, beef, pork or lamb as a main dish, processed meat, alcohol, calcium, folate, height, pack-years smoking before age 30, history of endoscopy	Mid-point categories Person-years of follow up
		204/			Incidence, rectal cancer		1.56 (1.01-2.42) Ptrend:0.04		
	HPFS, Prospective Cohort, M, Health professionals	135/ 46 632 14 years			Incidence, rectal cancer		1.03 (0.49-2.14) Ptrend:0.70		
		467/			Incidence, colon cancer		1.85 (1.26-2.72) Ptrend:0.001		
	HPFS & NHS	1123/ 134 356			Incidence, colon cancer,		1.39 (1.14-1.69) Ptrend:0.001		
		336/			Incidence, rectal		1.40 (0.96-2.03)		

					cancer		Ptrend:0.11		
		1459/			Incidence, colorectal cancer	Per 5 kg/m^2	1.06 (1.03-1.10)		
Saydah, 2003 COL00522 USA	CLUE II, Nested Case Control, Age: 45- years, M/W	173/ 346 controls	Cancer registry	Self-report	Incidence, colorectal cancer,	≥ 30 vs < 25 kg/m^2	1.70 (1.01-2.86) Ptrend:0.08	Age, sex, date of blood draw, race, time since last meal	Mid-point categories
		132/			Incidence, colon cancer,		1.79 (1.02-3.13) Ptrend:0.06		
					Incidence, proximal colon cancer		1.46 (0.71–2.98) Ptrend:0.52		
					Incidence, distal colon cancer		2.60 (1.18–5.70) Ptrend:0.02		
					Incidence, rectal cancer		1.64 (0.68-3.94) Ptrend:0.41		
Calle, 2003 COL00375 Colombia, USA, Puerto Rico	CPS II, Prospective Cohort, Age: 30- years, M/W	3 494/ 900 053 16 years	Hospital records and death certificates	Self-reported	Mortality, colorectal cancer, men	≥35.0-39.9 vs 18.5-24.9 kg/m^2	1.84 (1.39-2.41) Ptrend:<0.001	Age, alcohol consumption, educational level, number of cigarettes smoked, physical activity, aspirin use, fat consumption, marital status, race, smoking status, vegetable consumption Estrogen-	Mid-point categories Person-years of follow up
		3 012/			Women	≥ 40.0 vs 18.5-24.9 kg/m^2	1.46 (0.94-2.24) Ptrend:<0.001		

								replacement therapy	
Colangelo, 2002 COL00383 USA	CHA Detection Project in Industry, Prospective Cohort, Age: ≥ 40 years	191/ 35 582 866 926 person-years	National Death Index	Height and weight were measured	Mortality, colorectal cancer	Q4 vs Q1	0.91 (0.52-1.61) Ptrend:0.76	Age,race, education, sex	Mid-point categories
		126/					1.22 (0.87-1.72) Ptrend:0.22		
		362/			Incidence, colorectal cancer, men	> 27.1 vs < 23 kg/m^2	1.07 (0.80-1.42) Ptrend:0.51		
Terry, 2002 COL00558 Canada	CNBSS, Prospective Cohort, Age: 40-59 years, W	527/ 89 835 936 433 person-years	National Mortality Database and to the Canadian Cancer Database	Self-reported	Incidence, colorectal cancer	> 30 vs < 25 kg/m^2	1.08 (0.82-1.41) Ptrend:0.57	Age, educational level, oral contraceptive use, parity, physical activity, smoking habits, HRT	Mid-point categories Person-years of follow up
		363/			Incidence, colon cancer		0.95 (0.67-1.34) Ptrend:0.97		
		172/			Incidence, proximal colon cancer		0.81 (0.48-1.38) Ptrend:0.61		
		164/			Incidence, rectal cancer		1.35 (0.87-2.07) Ptrend:0.35		
		148/			Incidence, distal colon cancer		1.31 (0.79-2.16) Ptrend:0.22		
Terry, 2001 COL00554 Sweden	SWSC, Prospective Cohort, Age: 40-76	460/ 61 463 588 270 person-years	Cancer registry	Self-reported	Incidence, colorectal cancer,	> 26.7 vs < 22 kg/m^2	1.24 (0.95-1.62) Ptrend:0.06	Age, alcohol consumption, educational level, energy	Mid-point categories Person-years of

	years, W	291/			Incidence, colon cancer,		1.21 (0.86-1.70) Ptrend:0.25	intake, red meat intake, vitamin d, calcium, folate, total fat, vitamin c	follow up
		159/			Incidence, rectal cancer,		1.32 (0.83-2.08) Ptrend:0.13		
		118/			Incidence, proximal colon cancer,		1.13 (0.66-1.94) Ptrend:0.53		
		101/			Incidence, distal colon cancer,		1.21 (0.67-2.19) Ptrend:0.45		
Kaaks, 2000 COL40787 USA	NYUWHS, Nested Case Control, Age: 35-65 years, W, Screening Program	100/ 196 controls	Active follow up by questionnaire; cancer registry and national death Index	Self-reported height and weight	Incidence, colorectal cancer	31.98 vs 20.91 kg/m²	2.83 (1.23-6.54) Ptrend:0.006	Age, menopausal status, reproductive factors, smoking status, time	Mid-point categories
		73/ 144 controls			Incidence, colon cancer	32.81 vs 21.25 kg/m²	3.07 (1.12-8.41) Ptrend:0.01		
Ford, 1999 COL00097 USA	NHANES I, Prospective Cohort, Age: 25-74 years, M/W	222/ 13 420 19 years	Multistage stratified sampling design	Weight and height were measured	Incidence, colon cancer	≥ 30 vs < 22 kg/m²	2.79 (1.22,6.35)	Age	Mid-point categories
					Incidence, colon cancer, men		2.95 (0.99, 8.74)		
					Incidence, colon cancer, women		2.74(1.04, 7.25)		
Schoen, 1999 COL00183 USA	CHS, Prospective Cohort, Age: 65- years, M/W	102/ 5 849	Medicare enrolment lists	Weight and height were measured	Incidence, colorectal cancer	Q 4 vs Q 1	1.40 (0.80-2.50)	Age, sex, physical activity	Mid-point categories Person-years of follow up
Singh, 1998	AHS,	142/	Hospital records	Self-reported	Incidence, colon	> 25 vs < 22.5	1.33 (0.88-2.06)	Age, sex, family	Mid-point

COL00185 USA	Prospective Cohort, Age: 25- years, M/W, Seventh-day Adventists	32 051 178 544 person-years	and cancer registry		cancer	kg/m²		history of specific cancer	categories
		83/			Incidence, colon cancer, women		1.05 (0.63-1.75)		
		59/			Incidence, colon cancer, men		2.63 (1.12-6.13)		
Tulinius, 1997 COL00622 Iceland	ICRF, Prospective Cohort, M/W	193/ 22 946	Population registry	Anthropometrics measured	Incidence, colorectal cancer, men	per 1 kg/m²	1.04 (0.99-1.08)	Age	
Chyou, 1996 COL00087 USA	HHP, Prospective Cohort, M, Japanese ancestry	330/ 8 006 19 years	Hospital records + cancer registry	Self-reported	Incidence, colon cancer	≥ 25.8 vs < 21.7 kg/m²	1.38 (1.01-1.90) Ptrend:0.0046	Age	Mid-point categories
		123/			Incidence, rectal cancer		0.63 (0.38-1.04) Ptrend:0.1697		
Thune, 1996 COL00269 Norway	NHSCD, Prospective Cohort, Age: 20-69 years, M/W	230/ 81 516 1 305 607 person-years	Cancer registry	Height and weight were measured	Incidence, colon cancer, men	per 1 g/cm²	1.25 (1.01-1.53)	Age	Unit converted to kg/m²
		169/			Incidence, rectal cancer, men	per 1 g/cm²	0.99 (0.60-1.63)		
		99/			Incidence, colon cancer, women	per 1 g/cm²	0.93 (0.57-1.52)		
		55/			Incidence, rectal cancer, women	per 1 g/cm²	0.96 (0.51-1.82)		
Lee, 1992 COL00679	HAHS, Prospective	290/ 17 595	Health examination	Height and weight were	Incidence, colon cancer,	≥ 26 vs < 22.5 kg/m²	1.52 (1.06-2.17) Ptrend:0.03	Age, physical activity, parental	Mid-point categories

USA	Cohort, Age: 48 years, M	26 years	check	measured		per 1 kg/m^2	1.08 (1.04-1.13)	history of cancer	
Wu, 1987 COL00774 USA	LWC, Prospective Cohort, M/W, Retirement community	68/ 11 644 4.5 years	Population registries	self- administered	Incidence, colorectal cancer, women	$\geq$ 34 vs $\leq$ 29 lbs/m^2	1.19 (0.70-2.20)	Age	Mid-point categories
							1.80 (1.00-3.20)		
		58/			Incidence, colorectal cancer, men	$\geq$ 35 vs $\leq$ 31 lbs/m^2	2.40 (1.10-5.40)		
							2.65 (1.25-5.60)	Alcohol consumption, physical activity, smoking habits	

Table 323 BMI and colorectal cancer risk. Main characteristics of studies excluded from the CUP SLR dose-response meta-analysis

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Reasons for exclusion
Heo, 2015 COL41057 USA	WHI, Prospective Cohort, Age: 50-79 years, W, postmenopausal	1 904/ 144 701 12 years	Self-report verified by medical record and pathology report	Height and weight were measured	Incidence, colorectal cancer	per 1 score	1.12 (1.06-1.17)	Age, diabetes, ethnicity, folate intake, height, HRT use, physical activity, randomisation, red meat intake, alcohol, Asprine use, education, family history of colorectal cancer, smoking	z-scores of BMI reported Kabat, 2013 COL40965 Used instead
						high risk vs low risk kg/m²	1.12 (1.02-1.24)		
		1 516/			Incidence, colon cancer	per 1 score	1.12 (1.06-1.18)		
						high risk vs low risk kg/m²	1.18 (1.05-1.33)		
		257/			Incidence, rectal cancer	per 1 score	1.07 (0.94-1.22)		
Shin, 2014 COL41023 Korea	KNHIC, Prospective Cohort, Age: 30-80 years, M/W	9 084/ 1 326 058	Cancer registry & Insurance system	Height and weight were measured	Incidence, colorectal cancer, male	≥ 25 vs ≤ 25 kg/m²	1.13 (1.07-1.19)	Age, cigarette smoking, family history of cancer, fasting blood sugar, height, alcohol, meat consumption, serum cholesterol	Used in HvL analysis, only 2 categories
Kabat, 2015 COL41034	WHI Prospective	1 908/ 143 901	Self-report verified by	Weight and height were	Incidence, colorectal cancer	Q_5 vs Q_1	1.28 (1.10-1.50) Ptrend:0.001	Age, aspirin, diabetes, family	No specific ranges of

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Reasons for exclusion
USA	Cohort, Age: 50-79 years, W, postmenopausal women	13 years	medical record and pathology report	measured by trained staff at baseline	Ever used HRT	Q_5 vs Q_1	1.60 (1.26-2.03) Ptrend:<0.001	history of colon cancer, HRT use, met-hours per week, treatment allocation, waist circumference, alcohol, education, ethnic origin, smoking	quintiles No number of cases in each quintile Kabat, 2013 Col40965 used instead
					Never used HRT	Q_2 vs Q_2	1.10 (0.90-1.36)		
					Never used HRT	Q_5 vs Q_1	1.25 (1.02-1.54) Ptrend:< 0.01		
Brändstedt, 2014 COL41022 Sweden	Malmo Diet and Cancer, 1991, Prospective Cohort, Age: 44-74 years, M/W	422/ 28 098 18 years	Cancer registry	Weight and height were measured	Incidence, colorectal cancer, braf negative	> 27.1 vs < 23.8 kg/m^2	1.53 (1.20-1.97) Ptrend:<0.001	Age, sex, alcohol, education, smoking	Only has gene interactions results
		214/			Women, braf negative	> 26.6 vs < 23.2 kg/m^2	1.38 (0.97-1.96) Ptrend:0.08		
		208/			Men braf negative	> 27.5 vs < 24.7 kg/m^2	1.67 (1.19-2.35) Ptrend:0.001		
		179/			Kras positive	> 27.1 vs < 23.8 kg/m^2	2.11 (1.38-3.22) Ptrend:<0.001		
		166/			Women kras negative	> 26.6 vs < 23.2 kg/m^2	1.40 (0.92-2.14) Ptrend:0.16		
		148/			Men kras negative	> 27.5 vs < 24.7 kg/m^2	1.21 (0.82-1.80) Ptrend:0.29		

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Reasons for exclusion
		94/			Women kras mutated	> 26.6 vs < 23.2 kg/m²	1.28 (0.76-2.15) Ptrend:0.33		
		85/			Men kras mutated	> 27.5 vs < 24.7 kg/m²	2.44 (1.41-4.23) Ptrend:0.001		
		71/			Kras negative	> 27.1 vs < 23.8 kg/m²	1.32 (0.99-1.76) Ptrend:0.05		
		65/			Braf mutated	> 27.1 vs < 23.8 kg/m²	1.15 (0.64-2.08)		
						> 27.1 vs < 23.8 kg/m²	1.15 (0.64-2.08) Ptrend:0.63		
		45/			Women braf mutated	> 26.6 vs < 23.2 kg/m²	1.20 (0.50-2.87) Ptrend:0.94		
		26/			Men braf mutated	> 27.5 vs < 24.7 kg/m²	0.97 (0.39-2.44) Ptrend:0.94		
Miao Jonasson, 2014 COL41049 Sweden	Swedish National Diabetes Register Cohort Study, Prospective Cohort, Age: 30-90 years, M/W,	591/ 11 093 9 years	Swedish cancer registry & record linkage with swedish cause-of-death registry	From registry records	Incidence, colorectal cancer	per 5 kg/m²	1.11 (1.01-1.21)	Age, diabetes, diabetes medication use, hba1c, smoking	Participants are type 2 diabetes patients
						≥ 30 vs 18.5-24.9 kg/m²	1.52 (1.20-1.93)		
		357/			Incidence, colorectal cancer, men	per 5 kg/m²	1.10 (0.96-1.25)		
		263/				≥ 30 vs 18.5-24.9 kg/m²	1.62 (1.17-2.24)		
		234/			Incidence, colorectal	≥ 30 vs 18.5-24.9 kg/m²	1.39 (0.98-1.96)		

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Reasons for exclusion
	Other				cancer, women	per 5 kg/m²	1.11 (0.99-1.26)		
Simons, 2014 COL41029 Netherlands	NLCS, Case Cohort, Age: 55-69 years	204/	Cancer registry		Incidence, colorectal cancer, igfbp 2 genes methylated	Q3 vs Q1	1.67 (1.17-2.38) Ptrend:< 0.01	Age, sex, non-occupational physical activity	Only has gene interactions results Hughes, 2011 COL40895 used instead
						per 5 kg/m²	1.39 (1.11-1.74)		
		178/			Igfbp 1 gene methylated	Q3 vs Q1	1.11 (0.77-1.62) Ptrend:0.57		
						per 5 kg/m²	1.19 (0.93-1.71)		
		121/			Igfbp 3 genes methylated	Q3 vs Q1	2.07 (1.29-3.33) Ptrend:0.27		
						per 5 kg/m²	1.34 (1.07-1.67)		
		112/			Igfbp 0 genes methylated	Q33 vs Q31	1.39 (0.88-2.19) Ptrend:0.16		
						per 5 kg/m²	1.26 (0.93-1.71)		
Semmens, 2013 COL40929 Japan	Life Span Study, Prospective Cohort, M/W	1 142/ 56 064	Cancer registry	Self-reported	Incidence, colon cancer	Q3 vs Q1	1.30 (1.09-1.54)	Sex, city Age, attained age	Participants are atomic bomb survivors
						per 5 kg/m²	1.14 (1.03-1.26)		
		577/			Incidence, colon cancer, women	21.65-24 vs < 19.63 kg/m²	1.16 (0.92-1.46)		
						per 5 kg/m²	1.07 (0.94-1.22)		
		565/			Incidence, colon cancer,	21.64-23.71 vs < 19.74 kg/m²	1.46 (1.14-1.88)		

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Reasons for exclusion
					men	per 5 kg/m²	1.25 (1.07-1.45)		
van Kruijsdijk RC, 2013 COL40974 Netherlands	SMART, Prospective Cohort, Age: 18-80 years, M/W, High Risk population	71/ 6 172 6 years	Cancer registry	Height and weight measured	Incidence, colorectal cancer	per 4 kg/m²	0.96 (0.76-1.22)	Age, sex, alcohol consumption, smoking status, pack years of smoking	Participants are CVD patients
Hartz, 2012 COL40901 USA	WHI, Prospective Cohort, Age: 50-79 years, W, Post-menopausal	1 181/ 141 652 8 years		Measured	Incidence, colon cancer	per 1 sd units	1.15	Age, income, physical activity, race, treatment allocation, alcohol, education, region, smoking	No Confidence Intervals
Hughes, 2012 COL40943 Netherlands	NLCS, Case Cohort, Age: 55-69 years, M/W	550/ 4 654 7 years	Cancer registry and pathology database	Self-reported	Incidence, colorectal cancer, braf wildtype	per 5 kg/m²	1.28 (1.12-1.45)	Sex, ethnicity	Only has gene interactions results Hughes, 2011 COL40895 used instead
						Q4 vs Q1	1.40 (1.09-1.80) Ptrend:<0.001		
		544/			Ms-stable	per 5 kg/m²	1.22 (1.08-1.39)		
						Q4 vs Q1	1.33 (1.03-1.70) Ptrend:0.04		
Hughes, 2012	MCCS,	495/	Cancer	Height (cm),	Incidence,	per 5 kg/m²	1.10 (1.00-1.22)	Sex, ethnicity	Only has gene

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Reasons for exclusion
COL40944 Australia	Prospective Cohort, Age: 27-75 years, M/W	40 154	registry/death records/national death index	weight (kg) and waist circumference (cm) were measured	colorectal cancer, ms-stable	Q4 vs Q1	1.31 (1.01-1.71) Ptrend:0.04		interactions results
		487/			Braf wildtype	per 5 kg/m^2	1.10 (0.99-1.21)		
						Q4 vs Q1	1.35 (1.03-1.78) Ptrend:0.04		
Kuchiba, 2012 COL40903 USA	NHS, Prospective Cohort, W, nurses	536/ 109 051 18 years	Questionnaire and mortality register	Self-reported	Incidence, colorectal cancer	30 vs 18.5-22.9 kg/m^2	1.61 (1.22-2.13) Ptrend:0.001	Age, aspirin use, calcium, energy intake, folate intake, HRT use, multi-vitamin supplements, physical activity, family history of colorectal cancer, menopause status, red meat, sigmoidoscopy, vitamin D	Superseded by Morikawa, 2013 COL40958 & Wei, 2004 COL00581
Lee, 2012 COL40877 Korea	HIH, Historical Cohort, Age: 35-80 years, W,	15/ 5 517 7 years	Colonoscopy examination	Body weight was measured	Incidence, colorectal cancer	$\geq$ 27 vs < 27 kg/m^2	0.75 (0.21-2.74)	Age, cardiovascular disease risk score, smoking	Used in HvL analysis, only 2 categories

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Reasons for exclusion
	Health Insurance Holders								
Fiscella, 2011 COL40833	NHANES III, Historical Cohort	91/ 15 772	National death index		Mortality, colorectal cancer	≥ 30 vs < 20 kg/m²	1.52 (0.69-3.35)	Sex, alcohol consumption, calcium intake, diabetes, educational level, health insurance, meat intake, physical activity, race, smoking status, fibre intake, history of colorectal cancer, month of blood draw, region, saturated fat intake,	No number of cases in categories
Hughes, 2011 COL40873 Netherlands	NLCS, Case Cohort, Age: 55-69 years, M/W	318/ 5 000 7 years	Cancer registry	Self-reported	Incidence, colorectal cancer, non-CIMP	Q4 vs Q1	1.22 (0.84-1.75) Ptrend:0.18	Age, sex, education level, energy intake, smoking status, socio-economic status, alcohol intake, family history of colorectal	Only has phenotype results Hughes, 2011 COL40895 used
						per 5 kg/m²	1.19 (0.98-1.14)		

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Reasons for exclusion
								cancer, fruit and vegetable, grains intake, phyisical activity, red meat consumption	
Levi, 2011 COL40897 Israel	Jewish Israeli male study, Prospective Cohort, Age: 16-19 years, M	537/ 1 109 864 18 years	Cancer registry	Weight and height were measured	Incidence, colorectal non-mucinous cancer	> 23.63 vs < 19.01 kg/m²	1.43 (1.09-1.89) Ptrend:< 0.01	Country of birth, height, immigration period, residence, year of birth, age at baseline, SES	Outcome is mucinous cancer
		445/			Incidence, colon cancer	> 23.63 vs < 19.01 kg/m²	1.69 (1.24-2.29) Ptrend:0.001		
		193/			Incidence, rectal cancer	> 23.63 vs < 19.01 kg/m²	0.86 (0.54-1.34) Ptrend:0.12		
		171/							
		101/			Incidence, colorectal mucinous carcinoma	>23.63 vs <19.01 kg/m²	1.12 (0.62-2.02) Ptrend:0.132		
Andreotti, 2010 COL40846 USA	AHS, Prospective Cohort, M/W,	230/ 67 947 10 years	Cancer registry	Self-reported	Incidence, colon cancer, men	≥ 35 vs < 18.5 kg/m²	2.03 (1.05-3.93)	Race, educational level, family history of cancer	Participants are pesticide applicators and their spouses
						per 1 kg/m²	1.05 (1.02-1.09)		
		113/			Incidence, colon	30-34.9 vs <	1.36 (0.79-2.36)		

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Reasons for exclusion
	Pesticide applicators and their spouses				cancer, women	18.5 kg/m²			
						per 1 kg/m²	0.99 (0.95-1.04)		
		102/			Incidence, rectal cancer, men	≥ 35 vs < 18.5 kg/m²	3.21 (1.34-7.71)		
						per 1 kg/m²	1.06 (0.99-1.12)		
		34/			Incidence, rectal cancer, women	30-34.9 vs < 18.5 kg/m²	1.15 (0.45-2.98)		
						per 1 kg/m²	1.03 (0.96-1.11)		
Cnattingius, 2009 COL40776 Sweden	STC, Prospective Cohort, M/W, Twins	210/ 23 337 33 years	Population cancer registries and other procedures	Self-reported by questionnaires	Incidence, colorectal cancer	≥ 25 vs 18.5-24.9 kg/m²	1.60 (1.15-2.23)	Age	Used in HvL analysis
Key, 2009 COL40775 UK	EPIC-Oxford, Prospective Cohort, Age: 20-89 years, M/W, Vegetarians	218/ 63 550	National cancer registers	Self-reported height and weight	Incidence, colorectal cancer	> 27.5 vs 20-22.4 kg/m²	0.85 (0.54-1.33)	Age, sex, smoking status, method of recruitment	No specific range of quintiles reported Used in HvL analysis
Lee, 2009 COL40764 China	SWHS, Prospective Cohort,	394/ 73 224 7 years	Cancer registry and death certificates and		Incidence, colorectal cancer	> 26.1 vs < 21.5 kg/m²	1.10 (0.80-1.50) Ptrend:0.50	Age, energy intake Age-underlying	Superseded by Li, 2012 COL40937

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Reasons for exclusion
	Age: 40-70 years, W	236/	participant contact		Incidence, colon cancer		0.90 (0.60-1.30) Ptrend:0.98	cox models, family history of colon cancer, physical activity, race, smoking status, alcohol, history of polyp diagnosis, intervention assignment	
		158/			Incidence, rectal cancer		1.40 (0.90-2.20) Ptrend:0.27		
Wei, 2009 COL40777 USA	NHS, Prospective Cohort, Age: 30-54 years, W	701/ 83 767 24 years	Self-report verified by medical record		Incidence, colon cancer	30 vs 20 kg/m²	1.16 (0.98-1.38)	Age, aspirin use, folate intake, height, pack-years of smoking, year of endoscopy, family history of colorectal cancer, postmenopausal hormone use, red or processed meat intake	Cumulative risk estimates reported Wei, 2004 COL00581 used
						consistently high vs average kg/m²	1.68 (1.39-2.03)		
Stocks, 2008 COL40691 Sweden	NSHDC, Nested Case Control,	218/ 901 4 years	Cancer registry	Measured	Incidence, colorectal cancer	> 28.3 vs < 23.4 kg/m²	1.20 (0.75-1.93) Ptrend:0.41	Age, sex, date of blood collection, fasting condition	Supersede by Lukanova, 2006 COL40752
						obese vs under	1.79 (1.09-2.95)		

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Reasons for exclusion
	Age: 60.00years, M/W					to normal weight kg/m²	Ptrend:0.07		
						yes vs no kg/m²	1.77 (1.11-2.82) Ptrend:0.02		
Adams, 2007 COL40630 USA	NIH- AARP Diet and Health Study, Prospective Cohort, Age: 50-71 years, M/W	2 314/ 517 144 5 years	Cancer registry	Self-administered questionnaire	Incidence, colorectal cancer, men	≥ 40 vs 18.5-< 23 kg/m²	2.05 (1.45-2.91) Ptrend:<0.0005	Age-underlying cox models, alcohol, calcium intake, red meat intake, smoking status HRT use	Superseded by Renehan, 2012 COL40925
		1 676/			Incidence, colon cancer, men		2.39 (1.59-3.58) Ptrend:<0.0005		
		1 029/			Incidence, colorectal cancer, women		1.28 (0.88-1.85) Ptrend:0.03		
		769/			Incidence, colon cancer, women		1.49 (0.98-2.25) Ptrend:0.02		
		677/			Incidence, rectal cancer, men	≥ 35 vs 18.5-< 23 kg/m²	1.00 (0.68-1.58) Ptrend:0.31		
		278/			Incidence, rectal cancer, women		1.44 (0.92-2.25) Ptrend:0.20		
Akhter, 2007 COL40632 Japan	MCS, Prospective Cohort, Age: 40-64 years, M	307/ 21 199 11 years	Cancer registry		Incidence, colorectal cancer	≥ 25.0 vs < 18.5 kg/m²	1.61 (0.59-4.40)	Age	Superseded by Matsuo, 20122012

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Reasons for exclusion
Wang, 2007 COL40679 USA	CPS II, Prospective Cohort, Age: 63 years, W, postmenopausal women	814/ 73 842 11 years	Medical records, cancer registries, national death Index	Self-administered questionnaire -	Incidence, colorectal cancer, postmenopausal women	≥ 30 vs 18.5-24.9 kg/m²	1.19 (0.97-1.45) Ptrend:0.04	Age, educational level, HRT use, history of diabetes, history of endoscopy, multivitamin use, NSAID use, physical activity, smoking status	Superseded by Wang, 2008 COL40666
						per 5 unit	1.08 (1.00-1.17)		
		386/			Postmenopausal years without HRT ≥ 15	≥ 30 vs 18.5-24.9 kg/m²	1.20 (0.92-1.57)		
						per 5 unit	1.07 (0.96-1.19)		
		365/			HRT never	≥ 30 vs 18.5-24.9 kg/m²	1.36 (1.04-1.79)		
						per 5 unit	1.13 (1.02-1.25)		
		216/			HRT former	≥ 30 vs 18.5-24.9 kg/m²	0.92 (0.61-1.39)		
Lundqvist, 2007 COL40692 &COL40693 Sweden, Finland	Sweden, Finland Co-twin study,1975, Prospective Cohort, Age: 44.00years, M/W	513/ 68 149 25 years	National cancer registers	Measured	Incidence, colon cancer, older subjects	≥ 30.0 vs 18.5-< 25.0 kg/m²	1.30 (0.90-1.80)	Age, sex, county of residence, diabetes, educational level, physical activity, smoking status	This study has 2 different designs
						per 1 kg/m²	1.02 (0.99-1.05)		
		327/			Incidence, colon cancer, older subjects	≥ 30.0 vs 18.5-< 25.0 kg/m²	1.90 (0.80-4.50)		
						per 1 kg/m²	1.09 (1.02-1.17)		
		324/			Incidence, rectal	≥ 30.0 vs 18.5-<	0.70 (0.40-1.20)		

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Reasons for exclusion
		68 149 25 years			cancer, older subjects	25.0 kg/m²			
						per 1 kg/m²	1.00 (0.97-1.04)		
		226/			Incidence, rectal cancer, older subjects	≥ 30.0 vs 18.5-< 25.0 kg/m²	3.80 (1.00-15.20)		
						per 1 kg/m²	1.06 (0.97-1.15)		
						per 1 kg/m²	1.01 (0.89-1.15)		
Driver, 2007 COL40711 USA	PHS, Prospective Cohort, Age: 40-84 years, M, Physicians	21 581 20 years	Follow up questionnaires (self-report), medical record and pathology reports	Height and weight assessed by questionnaire	Incidence, colorectal cancer	≥ 30 vs ≤ 25 kg/m²	1.62 (1.09-2.42)	Age, alcohol, history of diabetes, multivitamin, physical activity, smoking status, vegetable intake, vitamin c, vitamin e, cereals intake	Used in HvL analysis
							1.60 (1.07-2.38)		
Ahmed, 2006 COL40617 USA	Atherosclerosis Risk in Communities (ARIC) Study, 1987, Prospective Cohort, Age: 45-64 years,	194/ 14 109 12 years	Cancer registry & hospital surveillance	Measured	Incidence, colorectal cancer	Highest vs lowest	1.54 (0.90-2.80)	Age, sex, alcohol consumption, aspirin use, HRT use, NSAID use, pack-years of smoking, physical activity, family	Used in HvsL analysis
		107/			Incidence, colorectal cancer, men		1.52 (0.90-2.70)		
		87/			Incidence, colorectal		1.26 (0.60-2.60)		

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Reasons for exclusion
	M/W				cancer, women			history of colorectal cancer	
Berndt, 2006 COL40795 USA	CLUE II, Case Cohort, Age: 48.00years, M/W	250/ 2 224 14 years	Cancer registry		Incidence, colorectal cancer	> 25 vs 24.9 kg/m^2	1.18 (0.88-1.56)	Age, race	Results on genotype Superseded by Saydah, 2003 COL00522 which included in HvsL analysis only
McCarl, 2006 COL40633 USA	IWHS, Prospective Cohort, Age: 55-69 years, W	954/ 35 197 15 years	SEER registry		Incidence, colorectal cancer	> 30.64 vs < 22.8 kg/m^2	1.43 (1.17-1.76)	Age	Superseded by Poynter, 2013 COL40952
Stürmer, 2006 COL40710 USA	PHS, Prospective Cohort, Age: 40-84 years, M, Health professionals	494/ 22 071 19 years	Self-report verified by medical record	Self-reported	Incidence, colorectal cancer	≥ 27 vs < 27 kg/m^2	1.40 (1.10-1.70)	Alcohol consumption, fruit and vegetable intake, multivitamin use, NSAID use, physical activity, pre-existing disease, smoking habits	Superseded by Driver, 2007 COL40711

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Reasons for exclusion
Yeh, 2006 COL40675 Taiwan	7 township Taiwanese cohort, Prospective Cohort, Age: 30-65 years, M/W	68/ 23 943 10 years	Cancer registry and death certificates		Incidence, colorectal cancer, men	≥ 28.6 vs < 24.2 kg/m²	1.98 (0.91-4.30)	Age, nutritional factors (nos), residence, smoking status	Used in HvsL analysis
Kuriyama, 2005 COL01837 Japan	MCS, Prospective Cohort, Age: 40-64 years, M/W	155/ 27 539 9 years	Population registry	Self-administered questionnaire	Incidence, colorectal cancer, men	≥ 30 vs 18.5-24.9 kg/m²	1.78 (0.73-4.38) Ptrend:0.10	Age, alcohol consumption, fruit (total), smoking status, bean-paste soup consumption, fish consumption, green en yellow vegetable consumption, meat consumption, type of health Insurance	Superseded by Matsuo, 20122012
		115/			Incidence, colorectal cancer, women		2.06 (1.03-4.13) Ptrend:0.06	Age at menarche, menopausal status, age at	
		88/			Incidence, colon		1.30 (0.32-5.37)		

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Reasons for exclusion
					cancer, men		Ptrend:0.37	end of first pregnancy	
		82/			Incidence, colorectal cancer, postmenopausal women		2.08 (0.88-4.90) Ptrend:0.06		
		72/			Incidence, colon cancer, women		2.25 (0.95-5.33) Ptrend:0.06		
		67/			Incidence, rectal cancer, men		2.41 (0.74-7.85) Ptrend:0.09		
		42/			Incidence, rectal cancer, women		1.21 (0.29-5.14) Ptrend:0.77		
					Incidence, distal colon cancer, men		1.41 (0.19-10.52) Ptrend:0.54		
		35/			Incidence, distal colon cancer, women		2.86 (0.98-8.37) Ptrend:0.48		
		34/			Incidence, proximal colon cancer, men		1.71 (0.23-12.92) Ptrend:0.29		
		30/			Incidence, rectal cancer, postmenopausal women		2.07 (0.47-9.09) Ptrend:0.33		

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Reasons for exclusion
		28/			Incidence, proximal colon cancer, women		1.03 (0.13-8.01) Ptrend:0.11		
Oh, 2005 COL01868 Korea	KNHIC, Prospective Cohort, Age: 20- years, M	1 563/ 781 283 10 years	General health status examinations		Incidence, rectosigmoid cancer, men	> 30 vs 18.5-22.9 kg/m²	1.08 (0.56-2.10) Ptrend:0.025	Age, alcohol consumption, area of residence, family history of specific cancer, physical activity, smoking status	Superseded by Jee, 2008 COL40643
		997/			Incidence, adenocarcinoma of colon and rectum, men		1.20 (0.62-2.32) Ptrend:0.006		
		953/			Incidence, colon cancer, men		1.92 (1.15-3.22) Ptrend:0.003		
		487/			Incidence, adenocarcinoma of colon, men		1.64 (0.90-2.98) Ptrend:0.007		
		291/			Incidence, colon cancer, nonsmokers		1.75 (0.64-4.78) Ptrend:0.04		
		272/			Incidence, rectosigmoid cancer, nonsmokers		1.72 (1.21-2.48) Ptrend:0.168		
		204/			Incidence, adenocarcinoma of colon,		1.89 (0.55-5.63) Ptrend:0.039		

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Reasons for exclusion
					nonsmokers				
Otani, 2005 COL01891 Japan	JPHC study-cohort I and II, Prospective Cohort, Age: 40-69 years, M/W	626/ 102 949 9 years	Population registries		Incidence, colorectal cancer, men	> 30 vs < 25 kg/m²	1.50 (0.90-2.50) Ptrend:0.004	Age, alcohol consumption, smoking status, miso soup intake, public health centre area, refraining from salty foods and animal fats	Superseded by Matsuo, 2012
		424/			Incidence, colon cancer, men		1.40 (0.70-2.80) Ptrend:0.003		
		418/			Incidence, invasive colorectal cancer, men		1.90 (1.05-3.40) Ptrend:0.001		
		360/			Incidence, colorectal cancer, women		0.80 (0.40-1.50) Ptrend:0.94		
		262/			Incidence, invasive colon cancer, men		2.20 (1.10-4.40) Ptrend:<0.001		
		244/			Incidence, distal colon cancer, men		1.30 (0.50-3.20) Ptrend:0.13		
		229/			Incidence, colon cancer, women		0.50 (0.20-1.40) Ptrend:0.73		
		202/			Incidence, rectal cancer, men		1.60 (0.60-3.90) Ptrend:0.40		
		165/			Incidence,		1.80 (0.70-5.00)		

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Reasons for exclusion
					proximal colon cancer, men		Ptrend:0.003		
		156/			Incidence, invasive rectal cancer, men		1.50 (0.50-4.10) Ptrend:0.39		
		151/			Incidence, invasive distal colon cancer, men		1.80 (0.70-5.00) Ptrend:0.006		
		131/			Incidence, rectal cancer, women		1.30 (0.50-3.10) Ptrend:0.56		
		112/			Incidence, proximal colon cancer, women		0.50 (0.10-2.10) Ptrend:0.47		
		108/			Incidence, distal colon cancer, women		0.60 (0.10-2.50) Ptrend:0.87		
		106/			Incidence, invasive proximal colon cancer, men		2.70 (0.99-7.60) Ptrend:0.01		
Samanic, 2004 COL00516 USA	MVS, Historical Cohort, Age: 18-100	18 122/ 12 years	Medical records	Data obtained from clinical records	Incidence, colon cancer, white men	obese vs non-obese	1.47 (1.39-1.55)	Age, calendar years	Used in HvsL analysis
		10 568/			Incidence, rectal	obese vs non-	1.23 (1.14-1.33)		

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Reasons for exclusion
	years, M, veterans				cancer, white men	obese			
		4 092/			Incidence, colon cancer, black men	obese vs non-obese	1.45 (1.28-1.64)		
		1 866/			Incidence, rectal cancer, black men	obese vs non-obese	1.11 (0.90-1.37)		
Feskanich, 2004 COL01680 USA	NHS, Nested Case Control, Age: 46-78 years, W	193/ 121 700 11 years	Medical records and writing or by telephone	Self-reported	Incidence, colorectal cancer	(mean exposure)		Month of blood draw, year of birth	Supersede by Morikawa, 2013 COL40958
Koh, 2004 COL00053 China	SCHS, Nested Case Control, Age: 45-74 years, M/W	310/ 63 257	Cancer registry		Incidence, colorectal cancer	≥ 28 vs ≤ 20 kg/m²	Ptrend:0.04		No RR available
MacInnis, 2004 COL00373 Australia	MCCS, Prospective Cohort, Age: 27-75 years, M	153/ 16 566 145 433 person-years		Measured by interviewer	Incidence, colon cancer,	> 29.3 vs < 24.7 kg/m²	1.70 (1.10-2.80)	Age, educational level, country of birth	Superseded by Bassett, 2010 COL40836 & MacInnis, 2006 COL40751
						per 5 kg/m²	1.29 (1.04-1.60)	Age, educational level, country of birth	

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Reasons for exclusion
		78/			Incidence, distal colon cancer,	per 5 kg/m²	1.38 (1.03-1.84)	Age, country of birth, educational level	
		70/			Incidence, proximal colon cancer	per 5 kg/m²	1.18 (0.86-1.62)	Age, country of birth, educational level	
Shimizu, 2003 COL00529 Japan	Japan, Takayama cohort study, Prospective Cohort, Age: 35- years, M/W	104/ 29 051 8 years		Self-reported	Incidence, colon cancer, men	≥ 23.6 vs ≤ 21.2 kg/m²	2.11 (1.26-3.53) Ptrend:0.005	Age, alcohol consumption, educational level, physical activity, smoking habits, height	Superseded by Matsuo, 2012
		89/			Incidence, colon cancer, women	≥ 23.1 vs ≤ 21.6 kg/m²	1.22 (0.69-2.15) Ptrend:0.48		
		58/			Incidence, rectal cancer, men	≥ 23.6 vs ≤ 21.2 kg/m²	0.85 (0.45-1.60) Ptrend:0.60		
		41/			Incidence, rectal cancer, women	≥ 23.1 vs ≤ 21.6 kg/m²	0.92 (0.44-1.92) Ptrend:0.86		
Kmet, 2003 COL00308 USA	Washington SEER colorectal cancer following breast cancer study, Nested Case Control, Age: 40-84 years, W, Breast cancer	130/ 14 900	Western Washington population-based SEER	Hospital records	Incidence, colon cancer	≥ 30 vs < 30 kg/m²	2.20 (1.20-3.90)	Age, family history of specific cancer, calendar year, stage of breast cancer	Breast cancer patients (Colon cancer is not the primary cancer)

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Reasons for exclusion
	patients								
Meyerhardt, 2003 COL00898 USA	Intergroup Trial 0089, Historical Cohort, Age: 62.00years, M/W	3 438 9 years	Hospital	Measured by clinicians	Recurrence, colon cancer, men	> 30 vs 21-24.9 kg/m²	0.98 (0.79-1.23)	Age, sex, baseline performance status, bowel obstruction, ethnicity/race, bowel perforation, completion of chemotherapy, duke stage of disease, predominant macroscopic pathologic feature, presence of peritoneal implants	Recurrence
						> 30 vs 21-24.9 kg/m²	1.11 (0.94-1.30)		
					Recurrence, colon cancer, women	>3 0 vs 21-24.9 kg/m²	1.24 (0.98-1.59)		
Wong, 2003 COL00586 China	SCHS, Nested Case Control, Age: 45-74 years, M/W	217/ 63 257	Cancer registry	Self-reported	Incidence, colorectal cancer	≥ 28 vs < 22 kg/m²			No RR available
Tiemersma COL00563	Dutch prospective	102 cases/ 537 controls	Population register		Incidence, colorectal cancer	Mean exposure	26.9 (cases)		Mean exposure Reported only

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Reasons for exclusion
Netherlands	Monitoring Project on Cardiovascular Disease Risk Factors, Nested Case Control, Age:20-59 years, M/W	36 000 8.5 years					25.9 (controls)		
Nilsen, 2002 COL00306 Norway	NHUNT, Prospective Cohort, Age: 20- years, M/W	368/ 75 219 12 years	Cancer registry	Not specified	Incidence, colorectal cancer, women	> 27.4 vs < 21.8 kg/m²	0.98 (0.71-1.34) Ptrend:0.96	Age	It was included in the Engeland, 2005 study COL00306
Malila, 2002 COL00336 Finland	ATBC, Prospective Cohort, Age: 50-69 years, M, Male Smokers	184/ 26 951 8 years	Cancer registry		Incidence, colorectal cancer				Mean exposure Reported only Superseded by Bowers, 2006 COL40699
Okasha, 2002 COL00351 Scotland	Glasgow Alumni Cohort study, Prospective	64/ 10 675 41 years	Glasgow university alumni registry	Measured by a physician	Mortality, colorectal cancer, men	22.8-35.08 vs < 19.71 kg/m²	0.98 (0.47-2.05)	Age	Only 2 categories of results

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Reasons for exclusion
	Cohort, Age: 20.00years, M/W, Glasgow University alumni								
Colbert, 2001 col00384 Finland	ATBC, Prospective Cohort, Age: 50-69 years, M, Male Smokers	152/ 29 133 12 years	Cancer registry		Incidence, colon cancer				Mean exposure reported only Superseded by Bowers, 2006 COL40699
		104/			Incidence, rectal cancer				
Field, 2001 COL00407 USA	NHS, Prospective Cohort, Age: 30-55 years, W	521/ 77 690 10 years	Medical records, National Death Index	Self-reported	Incidence, colon cancer	> 35 vs 18.5-21.9 kg/m²	2.10 (1.40-3.10)	Age, ethnicity/race, smoking habits	Superseded by Wei, 2004 COL00581
Nilsen, 2001 COL00361 Norway	Norwegian Nord-Trondelag Health Study, Prospective Cohort, Age: 20- years, M/W	358/ 75 219 12 years	Cancer registry	Measured	Incidence, colorectal cancer, women	≥ 27.5 vs ≤ 21.8 kg/m²	0.98 (0.71-1.34) Ptrend:0.96	Age	Superseded by Nilsen, 2002 COL00306
		354/			Incidence, colorectal cancer, men	≥ 27.2 vs ≤ 23 kg/m²	1.07 (0.80-1.42) Ptrend:0.51		
Field, 2001	HPFS,	387/	Medical records,	Self-reported	Incidence, colon	> 35 vs 18.5-	2.20 (0.80-6.00)		Superseded by

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Reasons for exclusion
COL00407 USA	Prospective Cohort, Age: 40-75 years, M	46 060 10 years	National Death Index		cancer	21.9 kg/m²			Thygesen, 2008 COL40728
Jarvinen, 2001 COL00314 Finland	FMCHES, Prospective Cohort, Age: 39.00years, M/W	72/ 9 959 20 years			Incidence, colorectal cancer			Age, sex	Mean exposure reported only
Wolk, 2001 COL00585 Sweden	Obesity cohort, Prospective Cohort, Age: 46 years, M/W	142/ 28 129 10 years	Inpatient register		Incidence, colon cancer	obese vs population	1.30 (1.10-1.50)		Unadjusted RR
		109/			Incidence, colon cancer women	obese vs population kg/m2	1.30 (1.10-1.60)		
		74/			Incidence, rectal cancer	obese vs population	1.20 (0.90-1.40)		
		44/			Incidence, rectal cancer, women	obese vs population kg/m2	1.00 (0.70-2.90)		
		33/			Incidence, colon cancer, men	obese vs population kg/m2	1.20 (0.80-1.60)		
		30/			Incidence, rectal	obese vs	1.50 (1.00-2.10)		

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Reasons for exclusion
					cancer, men	population kg/m2			
Folsom, 2000 COL01688 USA	IWHS, Prospective Cohort, Age: 55-69 years, W	462/ 31 702 10 years	SEER	Self-reported	Incidence, colon cancer	> 30.21 vs < 22.8 kg/m²	1.70 (1.20-2.40)	Age, alcohol consumption, educational level, energy intake, physical activity, red meat intake, age of first live birth, estrogen use, fish intake, fruit intake, pack-years of cigarette smoking, smoking status, vegetable intake, vitamin use, waist-hip ratio, whole grain intake	Superseded by Poynter, 2013 COL40952
Pietinen, 1999 COL00176 Finland	ATBC, Prospective Cohort, Age:50-69 years M	185/ 27 111 8 years	Cancer registry		Incidence, colorectal	Mean exposure	26.3 (Cases) 26.0 (Non-cases)		Mean exposure reported only Bowers, 2006 COL40699 used instead

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Reasons for exclusion
Hara, 1999 COL01012 Japan	Japan, Saga prefecture study, Prospective Cohort, Age: 40-69 years, M/W	16/ 2 073 14 years	Population	Self-reported	Incidence, colorectal cancer, women	> 24.2 vs 19.8-24.2 kg/m²	1.39 (0.46-4.15) Ptrend:0.47	Age, alcohol consumption, physical activity, smoking habits	Superseded by Matsuo, 2012
						19.8 vs 19.8-24.2 kg/m2	0.81 (0.17-3.73) Ptrend:0.47		
		6/			Men	> 24.2 vs 19.8-24.2 kg/m²	6.39 (1.21-33.81) Ptrend:<0.05		
Robsahm, 1999 COL00180 Norway	NSPT, Prospective Cohort, Age: 30-69 years, M/W, participants of a nation-wide screening programme	7 620/ 1 122 852 19 479 236 person-years	Cancer registry		Incidence, colon cancer, women	Q 5 vs Q 1	1.07 (0.99-1.15)	Attained age, birth cohort, county of residence	Used in HvsL analysis only
		6 397/			Incidence, colon cancer, men	Q 5 vs Q 1	1.39 (1.39-1.50)		
		4 393/			Incidence, rectal cancer, men	Q 5 vs Q 1	1.16 (1.07-1.27)		
		3 482/			Incidence, rectal cancer, women	Q 5 vs Q 1	1.03 (0.93-1.14)		
Kato, 1999 COL00436 USA	NYUWHS, Nested Case Control, Age: 62.00years, W	105/ 15 785	Questionnaire, medical records, cancer registries	Questionnaire, medical records, National Death Index	Incidence, colorectal cancer			Age, date of enrolment, date of subsequent blood, menopausal status	Mean exposure reported only Kaaks, 2000 COL40787 Used in HvsL analysis

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Reasons for exclusion
Gaard, 1997 COL00163 Norway	NHSCD, Prospective Cohort, Age: 20-54 years, M/W	62 173 702 010 person-years	Cardiovascular screening	Measured	Incidence, colon cancer, men	> 2.71 vs < 2.3 g/cm2	1.64 (0.92-2.92) Ptrend:0.04	Age	Thune, 1996 COL00269 used instead
						> 2.71 vs < 2.3 g/cm2	1.61 (0.76-3.44) Ptrend:0.21		
					Incidence, colon cancer, women	> 2.66 vs < 2.17 g/cm2	1.02 (0.53-1.97) Ptrend:0.88		
						> 2.66 vs < 2.17 g/cm2	0.64 (0.31-1.33) Ptrend:0.8		
Kato, 1997 CRC00022 USA	NYUWHS, Prospective Cohort, Age: 34-65 years, W	100/ 14 272 105 044 person-years	Questionnaire, medical records, cancer registries	Self-reported	Incidence, colorectal cancer	Q_4 vs Q_4	1.19 (0.68-2.08)	Age, place at enrolment	Superseded by Kaaks, 2000 COL40787
Martínez, 1997 COL00139 USA	NHS, Prospective Cohort, Age: 30-55 years, W	393/ 89 448 1 012 375 person-years	Medical records, National Death Index	Self-reported	Incidence, colon cancer	≥ 29 vs < 21 kg/m²	1.45 (1.02-2.07) Ptrend:0.04	Age, alcohol consumption, cigarette smoking, family history of specific cancer, aspirin use, postmenopausal hormone use, red meat intake	Superseded by Wei, 2004 COL00581
		184/			Incidence, distal colon cancer,		1.96 (1.18-3.25) Ptrend:0.004	BMI	

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Reasons for exclusion
					distal sites				
		157/			Incidence, proximal colon cancer, proximal sites		1.26 (0.71-2.23) Ptrend:0.54		
Tangrea, 1997 COL00267 Finland	ATBC, Nested Case Control, Age: 50-69 years, M, Smokers	146/	Cancer registries		Incidence, colorectal cancer			Age, clinic site, date of blood drawn	Mean exposure reported only Bowers, 2006 COL40699 used instead
Giovannucci, 1995 COL00110 USA	HPFS, Prospective Cohort, Age: 40-75 years, M	203/ 31 055 6 years	Medical records, National Death Index		Incidence, colon cancer, colon cancer	> 29 vs < 21.9 kg/m^2	1.48 (0.89-2.46) Ptrend:0.02	Age, alcohol consumption, energy intake, family history of specific cancer, physical activity, smoking habits, aspirin use, dietary fibre intake, folate intake, history endoscopic screening, history polyp	Supersede by Thygesen, 2008 COL40728

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Reasons for exclusion
								diagnosis, methione intake, red meat intake	
Bostick, 1994 COL00079 USA	IWHS, Prospective Cohort, Age: 55-69 years, W	212/ 35 216 167 447 person-years	SEER		Incidence, colon cancer	> 30.62 vs < 22.9 kg/m²	1.41 (0.90-2.23) Ptrend:0.03	Age, energy intake, parity, vitamin A supplement, vitamin E intake	Superseded by Poynter, 2013 COL40952
Chyou, 1994 COL00086 USA	HHP, Prospective Cohort, M, Japanese ancestry	289/ 7 945 19 years	Cancer registry & hospital surveillance		Incidence, colon cancer, colon cancer	≥ 26.0 vs < 22.0 kg/m²	1.21 (0.87-1.68) Ptrend:0.006	Age	Superseded by Chyou, 1996 COL00087
		108/			Incidence, rectal cancer, rectal cancer	(mean exposure)			
Moller, 1994 COL01056 Denmark	Danish record-linkage study, Historical Cohort, Age: 0- years, M/W, Obese	195/ 43 965 5 years	Hospital records	Clinical records	Incidence, colon cancer	obese vs danish population (expected)	1.20 (1.00-1.40)	Age, period	Used in HvsL only
		136/			Incidence, colon cancer, women	obese vs danish population (expected)	1.20 (1.00-1.40)		
		59/			Incidence, colon cancer, men	obese vs danish population (expected)	1.30 (1.00-1.70)		
		58/			Incidence, rectal	obese vs danish	1.20 (0.90-1.50)		

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Reasons for exclusion
					cancer, women	population (expected)			
		33/			Incidence, rectal cancer, men	obese vs danish population (expected)	1.00 (0.70-1.40)		
Bostick, 1993 COL00483 USA	IWHS, Prospective Cohort, Age: 55-69 years, W	212/ 35 216 167 447 person-years	SEER	Self-reported	Incidence, colon cancer			Age	Mean exposure Reported only Superseded by Poynter, 2013 COL40952
Suadicani, 1993 COL01085 Denmark	Denmark, Copenhagen fitness and risk of CVD study, Prospective Cohort, Age: 40-59 years, M	51/ 5 429 18 years	Public or private companies	Measured	Incidence, colon cancer			Age	Mean exposure reported only
		42/			Incidence, rectal cancer				
Le Marchand, 1992 COL00676 USA	HHCS, Historical Cohort, Age: 15-29 years, M	203/ 3 501 15 years	Population registries		Incidence, colon cancer	Q 3 vs Q 1	1.4 (1.10-1.80)	Socio-economic status, ethnic origin of parents, month and year of birth	Used in HvsL analysis
					Incidence, rectal cancer		0.80 (0.52-1.24) Ptrend:0.37		

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Reasons for exclusion
Must, 1992 COL00703 USA	HGS, Prospective Cohort, Age: 73 years, M/W, third Harvard Growth Study	5/ 508 55 years	National Death Index	Height and weight were measured	Incidence, colorectal cancer, men	22-25 vs < 22 kg/m^2	5.60 (0.60-57.50)	BMI	Used in HvsL analysis
Kreger, 1992 COL00665 USA	FHS, Prospective Cohort, Age: 30-62 years, M/W	66/ 5 209 40 years	Population	BMI was used as exposure but nothing was specified about assessment technique	Incidence, colon cancer, women	per 1 kg/m^2	1.03 (0.98-1.07)	Alcohol consumption, hypertension, sf 0-20, cigarette smoking, glucose intolerance	Unadjusted RR Superseded by Moore, 2004 COL00362
		56/			Men	per 1 kg/m^2	1.09 (1.00-1.18)		
		20/			Incidence, rectal cancer, women	per 1 kg/m^2	0.99 (0.90-1.10)		
		19/			Men	per 1 kg/m^2	0.91 (0.80-1.05)		
Lee, 1992 COL00679 USA	Harvard Alumni Cohort, Prospective Cohort, Age: 48.00years, M, Harvard Alumni	290/ 17 595 26 years	Harvard alumni questionnaires and death certificates	Measured/self-reported	Incidence, colon cancer	> 26 vs 0-22.5 kg/m^2	1.52 (1.06-2.17) Ptrend:0.03	Age, physical activity, parental history of cancer	Used in HvsL analysis only
Chute, 1991 COL00475 USA	NHS, Prospective Cohort, Age: 30-55 years,	126/ 118 404 8 years	Medical records, National Death Index	Self-reported	Incidence, colon cancer	> 28 vs 21 kg/m^2	1.50 (0.80-2.70) Ptrend:0.45	Age	Superseded by Wei, 2004 COL00581

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Reasons for exclusion
	W, nurses								
Gerhardsson, 1988 COL01044 Sweden	Swedish Twin Follow-up Study, Prospective Cohort, M/W, twin individuals	16 477 14 years	Cancer registry		Incidence, colon cancer	yes vs no	1.00 (0.60-1.50)		Unadjusted RRs
						yes vs no	0.80 (0.50-1.30)		
						yes vs no	1.00 (0.50-1.70)		
Klatsky, 1988 COL00656 USA	KPMCP, Nested Case Control, M/W	203/ 106 203	Hospital records		Incidence, colon cancer	per 0.1 kg/m²	1.04 (1.02-1.06)		Unadjusted RRs
		66/			Incidence, rectal cancer	per 0.1 kg/m²	1.00 (0.96-1.04)		
Sidney, 1986 COL01239 USA	KPMCP, Nested Case Control, M/W	245/ 48 314 348 000 person-years	Medical records		Incidence, colorectal cancer			Age, sex, race, time of examination	Mean exposure reported only
Garland, 1985 COL01050 USA	Western Electric Health Study, Prospective Cohort, Age: 40-55 years, M	49/ 1 954 20 years	Medical records		Incidence, colorectal cancer				Mean exposure reported only
Nomura, 1985	HHP,	101/	Cancer registry	Measured and	Incidence, colon	26.32-44.59 vs		Age	No RRs

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Reasons for exclusion
COL00709 USA	Prospective Cohort, Age: 45-68 years, M	7 868	& hospital surveillance	self-reported	cancer	14.31-21.25 kg/m^2	Ptrend:0.167		available Chyou, 1996 COL00087 used instead
		63/			Incidence, rectal cancer	26.32-44.59 vs 14.31-21.25 kg/m^2	Ptrend:0.294		
Tartter, 1984 COL01088 USA	New York Mount Sinai Medical Centre Study, Prospective Cohort, M/W	63/ 279	Hospital records		Recurrence, colorectal cancer	above median vs median and below			No RRs available
		37/			Recurrence, colorectal cancer, men	above median vs median and below			
		26/			Recurrence, colorectal cancer, women	above median vs median and below			

Figure 518 RR estimates of colorectal cancer by levels of BMI

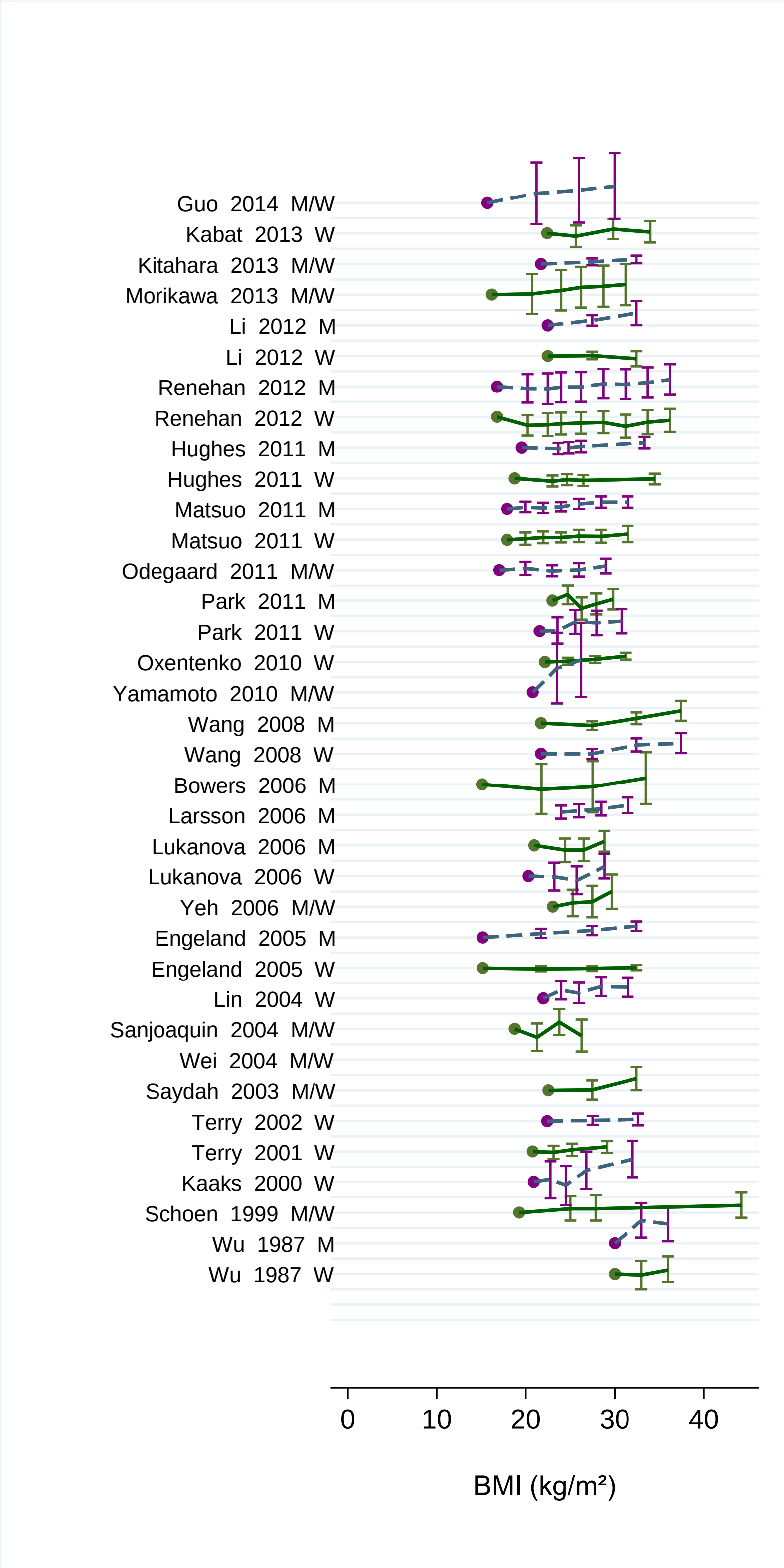


Figure 519 RR (95% CI) of colorectal cancer for the highest compared with the lowest level of BMI

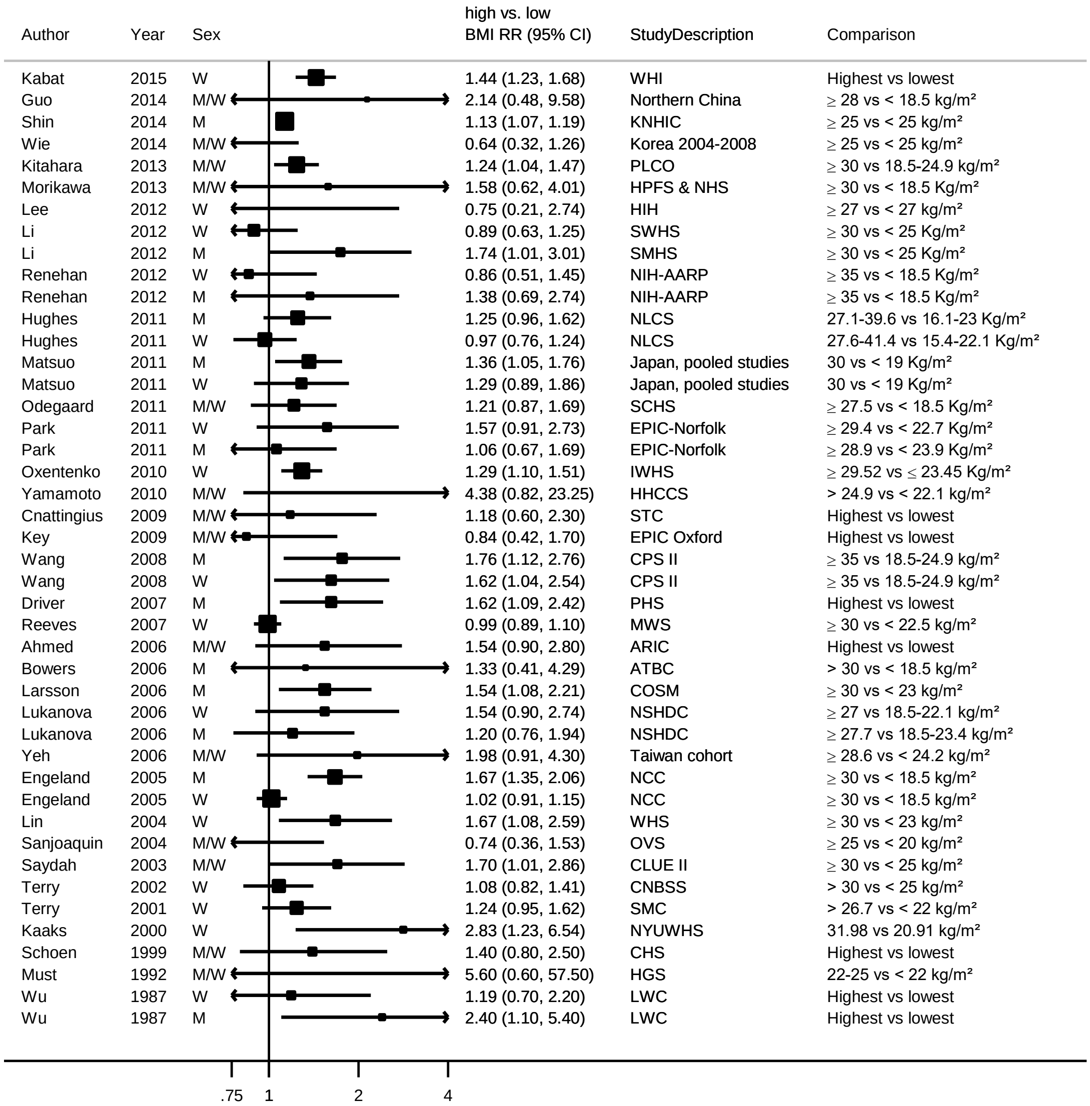


Figure 520 RR (95% CI) of colorectal cancer for 5 kg/m^2 increase of BMI

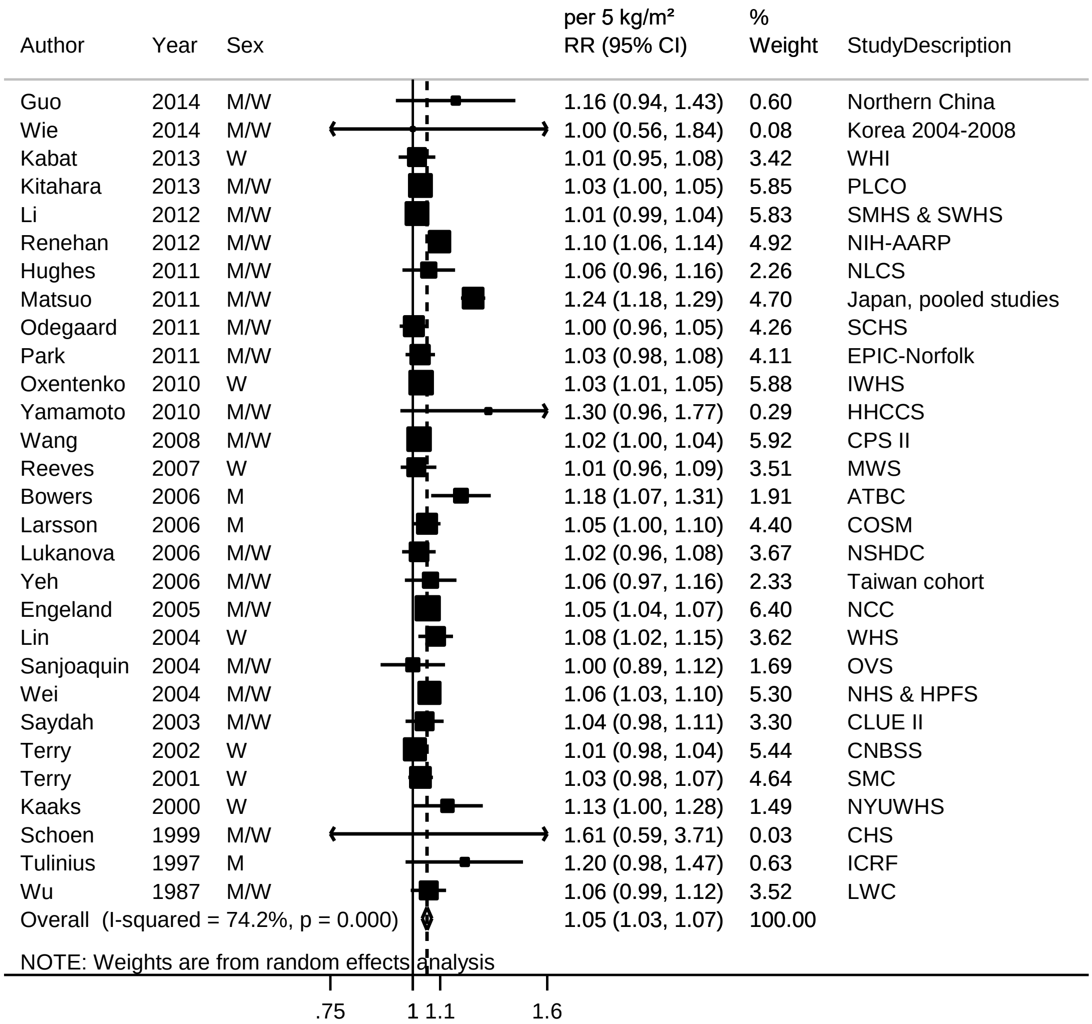
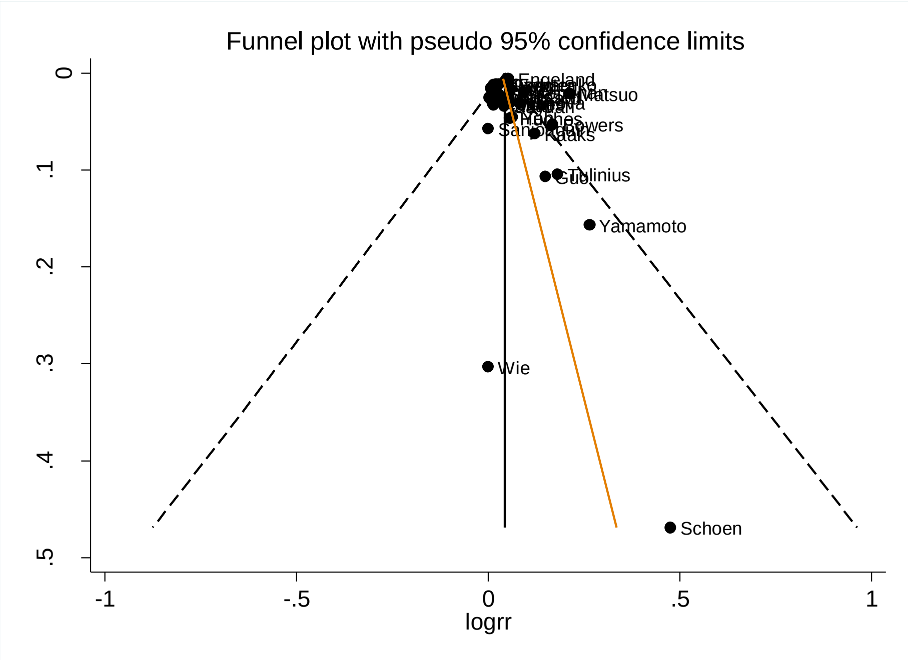
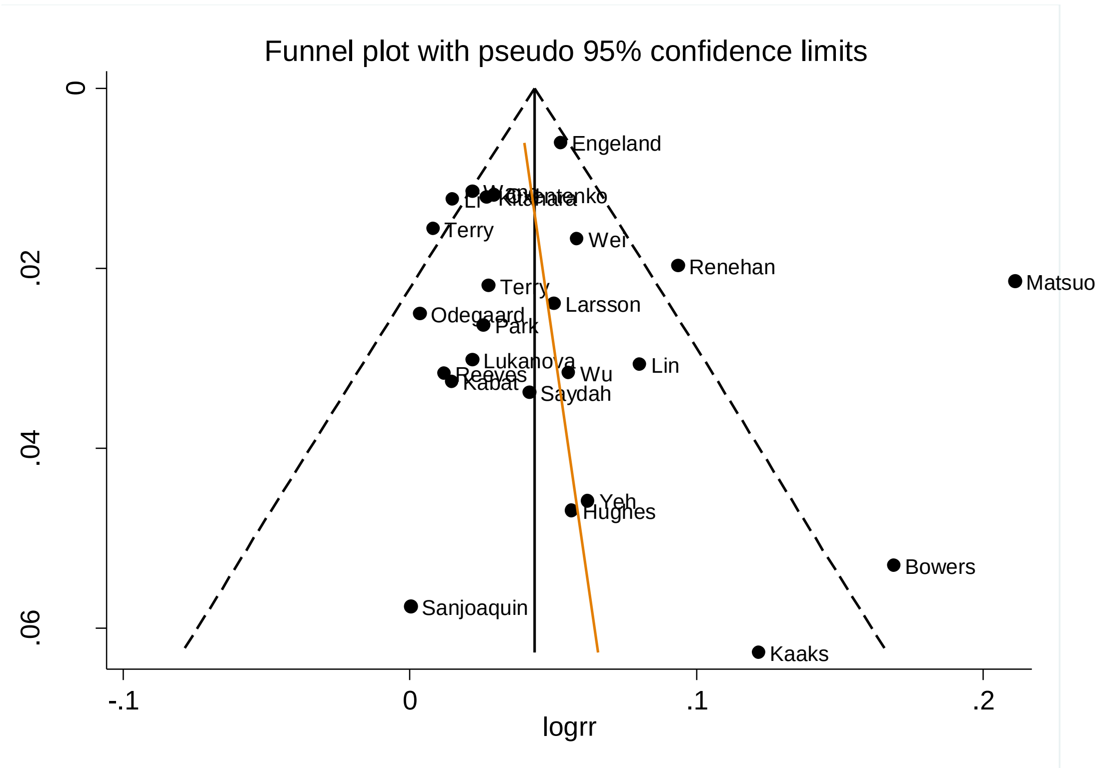


Figure 521 Funnel plot of studies included in the dose response meta-analysis of BMI and colorectal cancer

A) All studies



B) After exclusion of less precise studies (Guo, Tulinius, Yamamoto, Wie, Schoen)



p-value Egger test: 0.20

Figure 522 RR (95% CI) of colorectal cancer for 5 kg/m^2 increase of BMI by sex

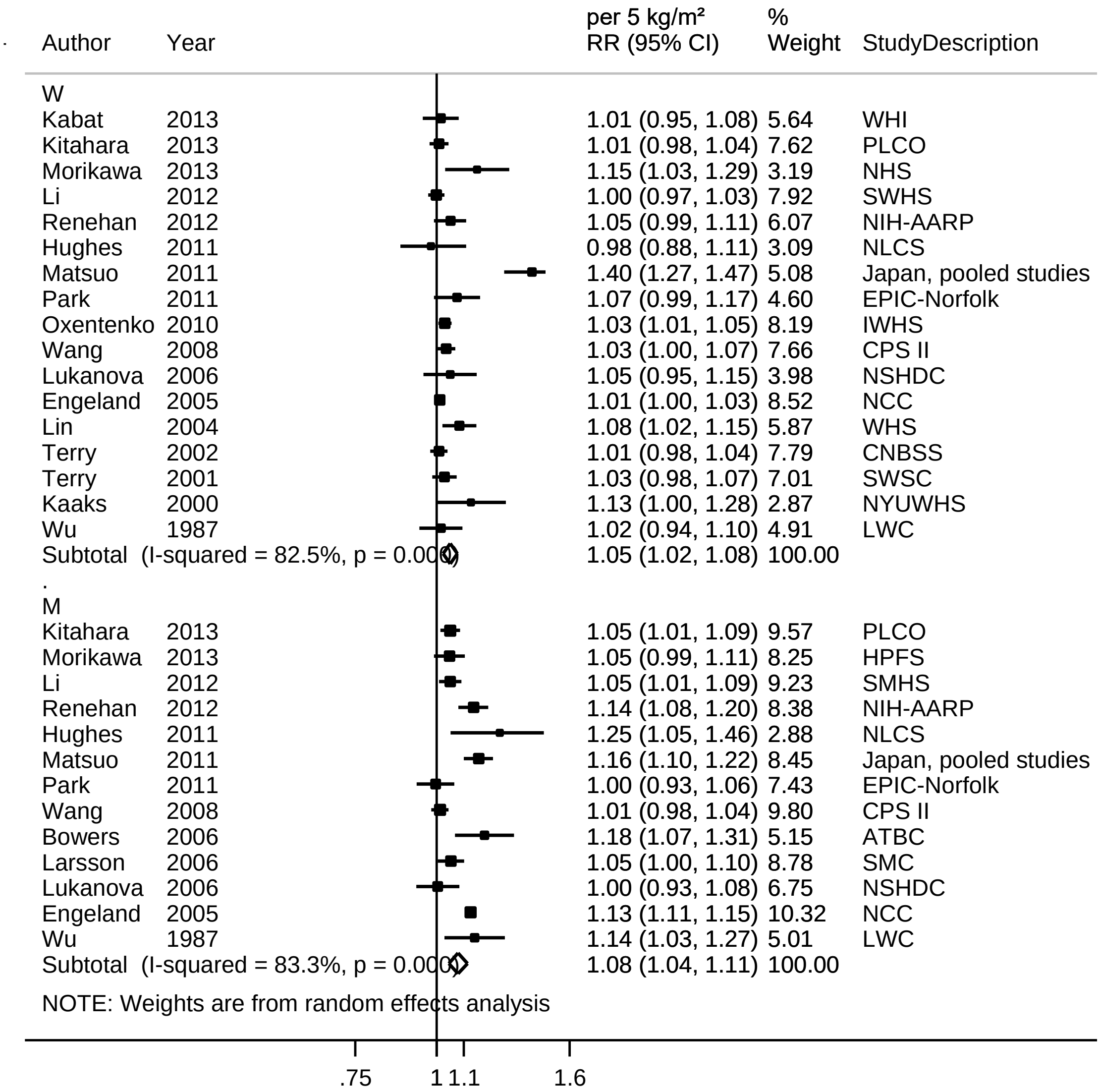


Figure 523 RR (95% CI) of colorectal cancer for 5 kg/m^2 increase of BMI by geographic location

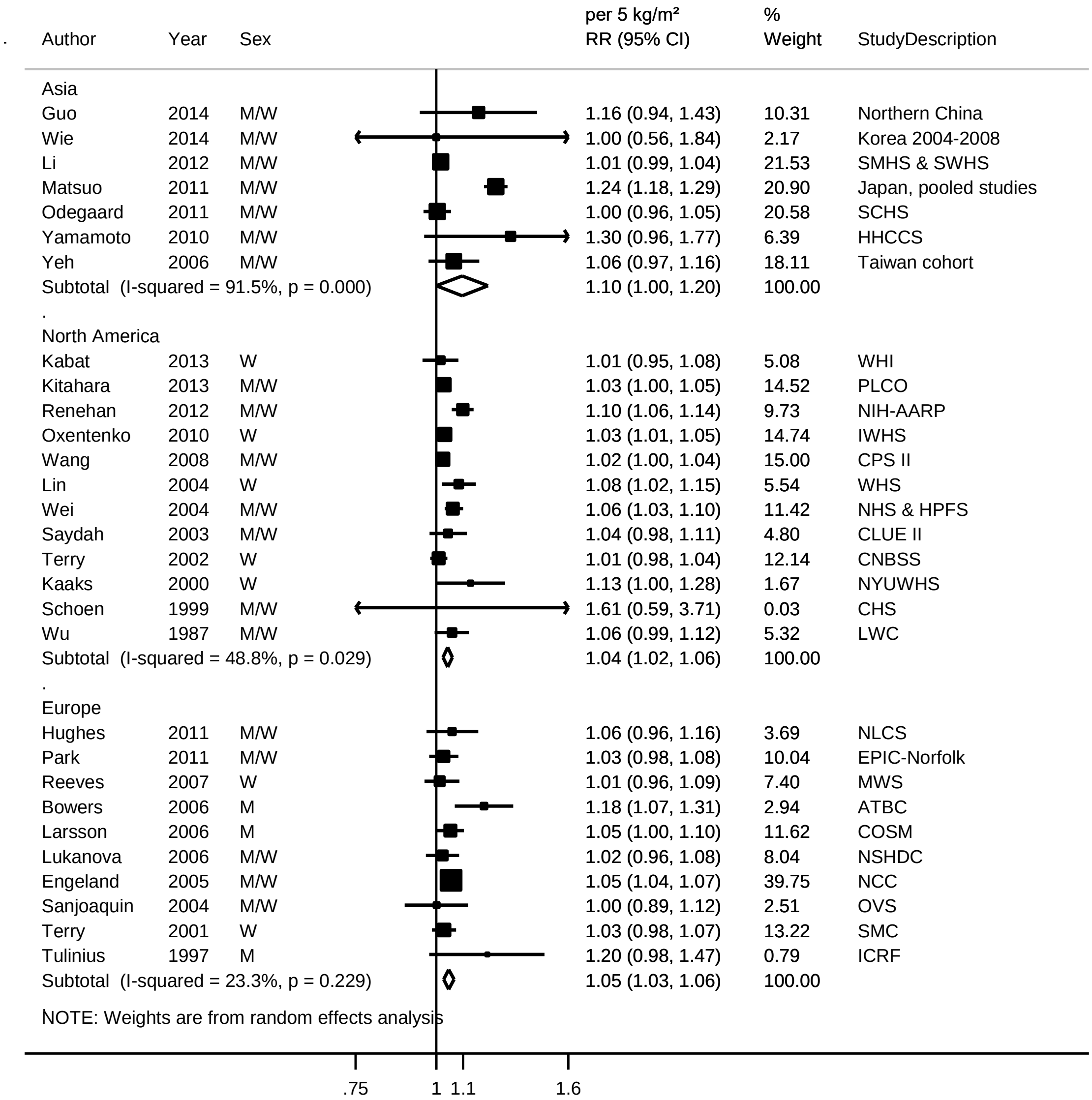
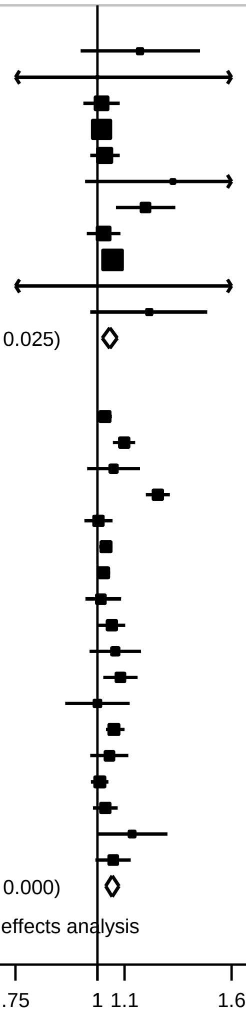


Figure 524 RR (95% CI) of colorectal cancer for 5 kg/m^2 increase of BMI by exposure assessment methods

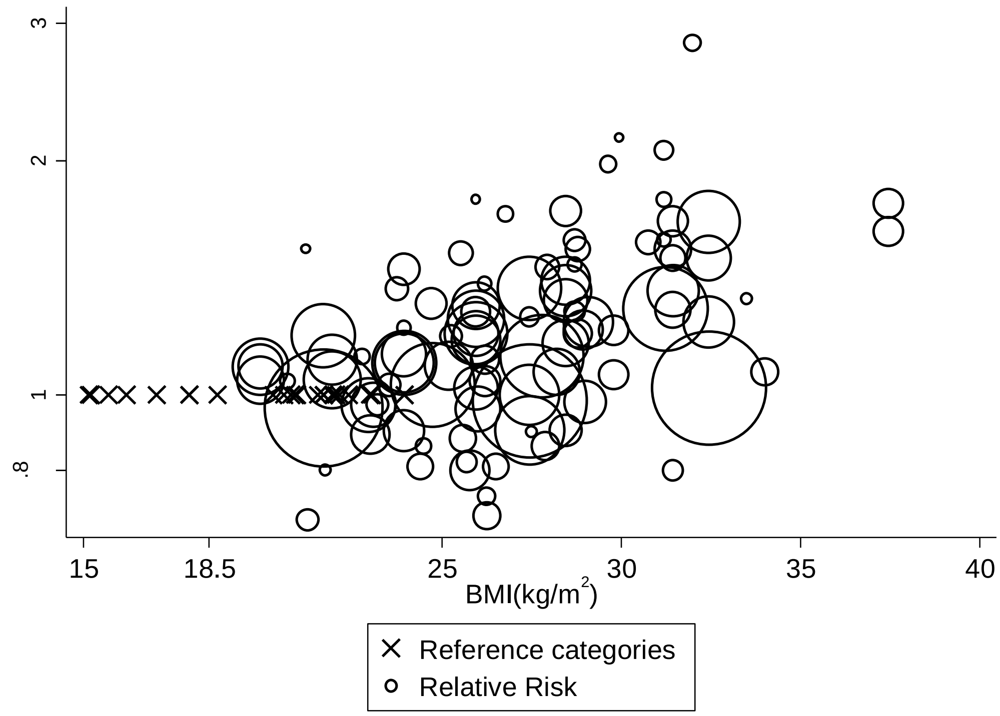
1=Measured, 2=self-reported

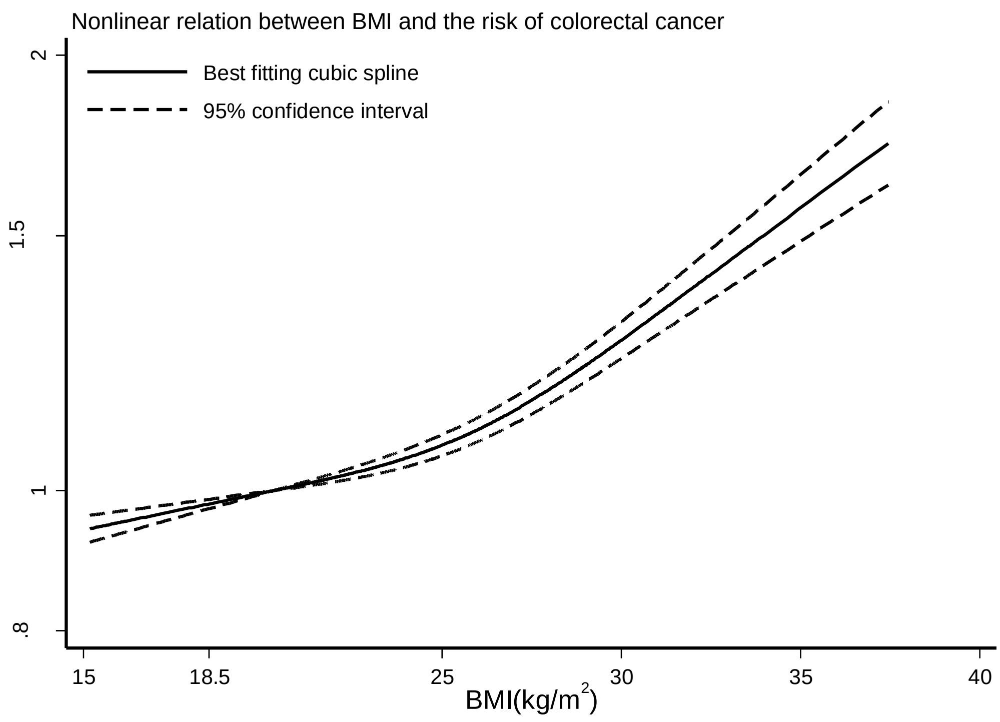


Author	Year	Sex	per 5 kg/m² RR (95% CI)	% Weight	StudyDescription
1					
Guo	2014	M/W	1.16 (0.94, 1.43)	1.55	Northern China
Wie	2014	M/W	1.00 (0.56, 1.84)	0.20	Korea 2004-2008
Kabat	2013	W	1.01 (0.95, 1.08)	11.09	WHI
Li	2012	M/W	1.01 (0.99, 1.04)	24.29	SMHS & SWHS
Park	2011	M/W	1.03 (0.98, 1.08)	14.23	EPIC-Norfolk
Yamamoto	2010	M/W	1.30 (0.96, 1.77)	0.74	HHCCS
Bowers	2006	M	1.18 (1.07, 1.31)	5.42	ATBC
Lukanova	2006	M/W	1.02 (0.96, 1.08)	12.19	NSHDC
Engeland	2005	M/W	1.05 (1.04, 1.07)	28.59	NCC
Schoen	1999	M/W	1.61 (0.59, 3.71)	0.08	CHS
Tulinius	1997	M	1.20 (0.98, 1.47)	1.61	ICRF
Subtotal (I-squared = 51.2%, p = 0.025)			1.04 (1.02, 1.07)	100.00	
.					
2					
Kitahara	2013	M/W	1.03 (1.00, 1.05)	7.37	PLCO
Renehan	2012	M/W	1.10 (1.06, 1.14)	6.55	NIH-AARP
Hughes	2011	M/W	1.06 (0.96, 1.16)	3.57	NLCS
Matsuo	2011	M/W	1.24 (1.18, 1.29)	6.34	Japan, pooled studies
Odegaard	2011	M/W	1.00 (0.96, 1.05)	5.90	SCHS
Oxentenko	2010	W	1.03 (1.01, 1.05)	7.40	IWHS
Wang	2008	M/W	1.02 (1.00, 1.04)	7.43	CPS II
Reeves	2007	W	1.01 (0.96, 1.09)	5.10	MWS
Larsson	2006	M	1.05 (1.00, 1.10)	6.04	COSM
Yeh	2006	M/W	1.06 (0.97, 1.16)	3.66	Taiwan cohort
Lin	2004	W	1.08 (1.02, 1.15)	5.21	WHS
Sanjoaquin	2004	M/W	1.00 (0.89, 1.12)	2.78	OVS
Wei	2004	M/W	1.06 (1.03, 1.10)	6.89	NHS & HPFS
Saydah	2003	M/W	1.04 (0.98, 1.11)	4.86	CLUE II
Terry	2002	W	1.01 (0.98, 1.04)	7.02	CNBSS
Terry	2001	W	1.03 (0.98, 1.07)	6.28	SMC
Kaaks	2000	W	1.13 (1.00, 1.28)	2.49	NYUWHS
Wu	1987	M/W	1.06 (0.99, 1.12)	5.11	LWC
Subtotal (I-squared = 80.7%, p = 0.000)			1.05 (1.03, 1.08)	100.00	

NOTE: Weights are from random effects analysis

Figure 525 Relative risk of colorectal cancer and BMI estimated using non-linear models





p for non-linearity$\leq$ 0.01

Table 324 Table with BMI values and corresponding RRs (95% CIs) for non-linear analysis of BMI and colorectal cancer

BMI (Kg/m^2)	RR (95%CI)
18.75	0.98 (0.98-0.99)
20.29	1.00
23.75	1.05 (1.03-1.06)
25.25	1.08 (1.06-1.10)
27.50	1.15 (1.13-1.18)
31.20	1.34 (1.29-1.38)

Figure 526 RR estimates of colon cancer by levels of BMI

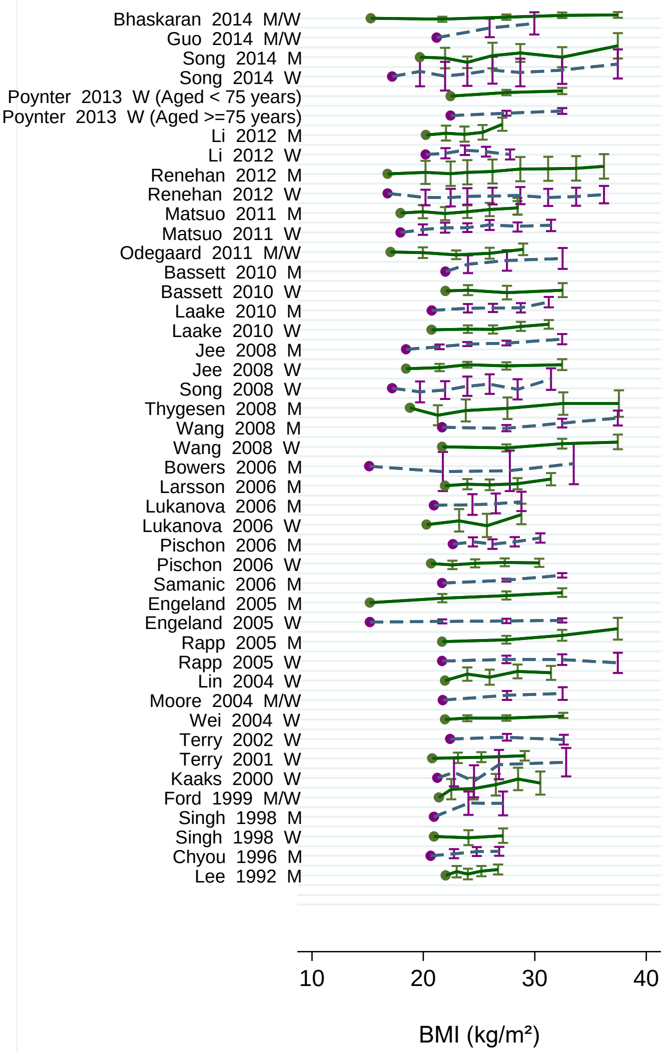


Figure 527 RR (95% CI) of colon cancer for the highest compared with the lowest level of BMI

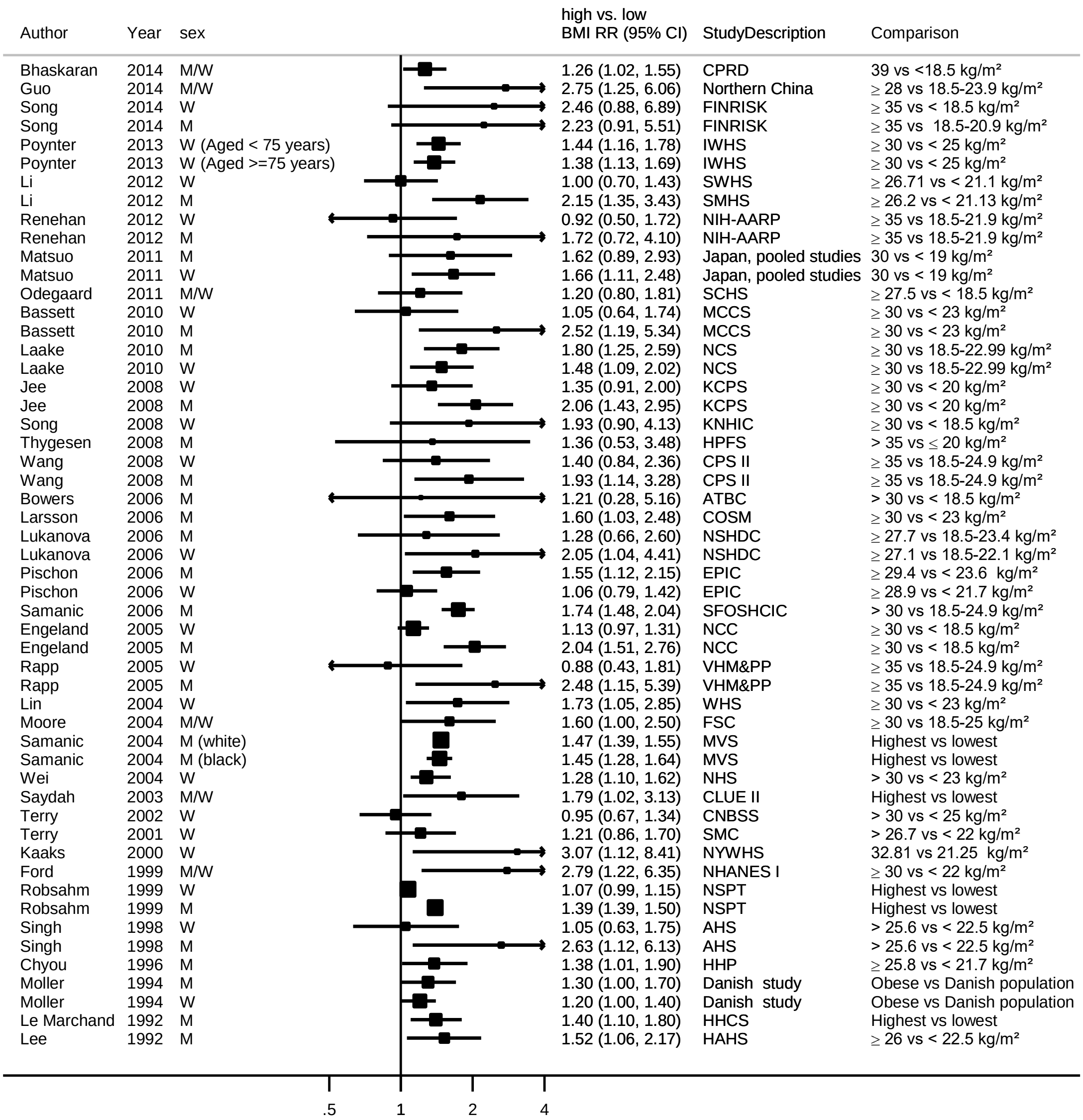
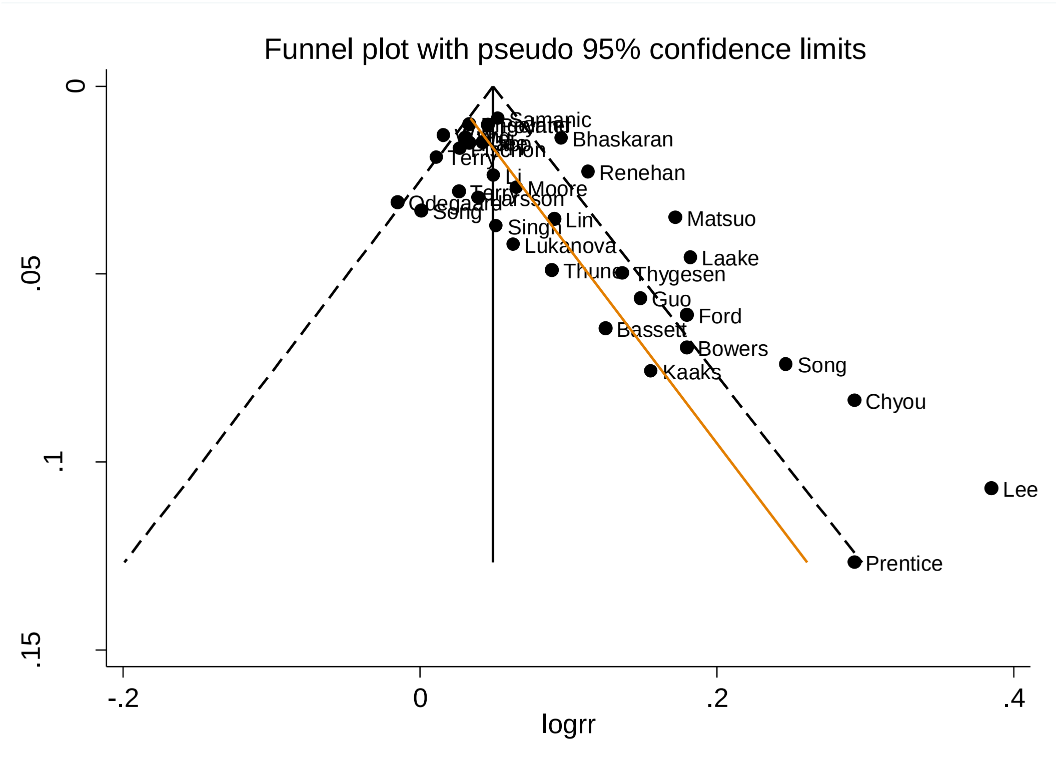


Figure 528 RR (95% CI) of colon cancer for 5 kg/m^2 increase of BMI

Author	Year	sex	per 5 kg/m² RR (95% CI)	% Weight	StudyDescription
Bhaskaran	2014	M/W	1.10 (1.07, 1.13)	5.01	CPRD
Guo	2014	M/W	1.16 (1.04, 1.30)	1.53	Northern China
Song	2014	M/W	1.00 (0.94, 1.07)	2.97	FINRISK
Poynter	2013	W	1.05 (1.03, 1.07)	5.37	IWHS
Li	2012	M/W	1.05 (1.00, 1.10)	3.91	SMHS & SWHS
Renehan	2012	M/W	1.12 (1.07, 1.17)	4.02	NIH-AARP
Matsuo	2011	M/W	1.19 (1.11, 1.27)	2.81	Japan, pooled studies
Odegaard	2011	M/W	0.98 (0.93, 1.05)	3.18	SCHS
Bassett	2010	M/W	1.13 (1.00, 1.28)	1.25	MCCS
Laake	2010	M/W	1.20 (1.10, 1.31)	2.07	NCS
Prentice	2009	W	1.34 (1.01, 1.66)	0.38	WHI
Jee	2008	M/W	1.04 (1.01, 1.07)	4.90	KCPS
Song	2008	W	1.28 (1.10, 1.47)	1.00	KNHIC
Thygesen	2008	M	1.15 (1.04, 1.26)	1.83	HPFS
Wang	2008	M/W	1.02 (0.99, 1.04)	5.10	CPS II
Bowers	2006	M	1.20 (1.04, 1.37)	1.11	ATBC
Larsson	2006	M	1.04 (0.98, 1.10)	3.30	COSM
Lukanova	2006	M/W	1.07 (0.98, 1.16)	2.28	NSHDC
Pischon	2006	M/W	1.03 (0.99, 1.06)	4.71	EPIC
Samanic	2006	M	1.05 (1.04, 1.07)	5.51	SFOSHCIC
Engeland	2005	M/W	1.03 (1.01, 1.05)	5.38	NCC
Rapp	2005	M/W	1.03 (1.00, 1.07)	4.88	VHM&PP
Lin	2004	W	1.09 (1.02, 1.17)	2.79	WHS
Moore	2004	M/W	1.07 (1.01, 1.13)	3.57	FSC
Wei	2004	W	1.03 (1.00, 1.06)	5.03	NHS
Terry	2002	W	1.01 (0.97, 1.05)	4.46	CNBSS
Terry	2001	W	1.03 (0.97, 1.08)	3.47	SMC
Kaaks	2000	W	1.17 (1.01, 1.36)	0.96	NYWHS
Ford	1999	M/W	1.20 (1.06, 1.35)	1.37	NHANES I
Singh	1998	M/W	1.05 (0.98, 1.13)	2.64	AHS
Chyou	1996	M	1.34 (1.16, 1.61)	0.81	HHP
Thune	1996	M/W	1.09 (0.99, 1.20)	1.88	NHSCD
Lee	1992	M	1.47 (1.21, 1.84)	0.53	HAHS
Overall (I-squared = 72.1%, p = 0.000)			1.07 (1.05, 1.09)	100.00	

NOTE: Weights are from random effects analysis

Figure 529 Funnel plot of studies included in the dose response meta-analysis of BMI and colon cancer



p for Egger's test<0.001

Figure 530 RR (95% CI) of colon cancer for 5 kg/m^2 increase of BMI by sex

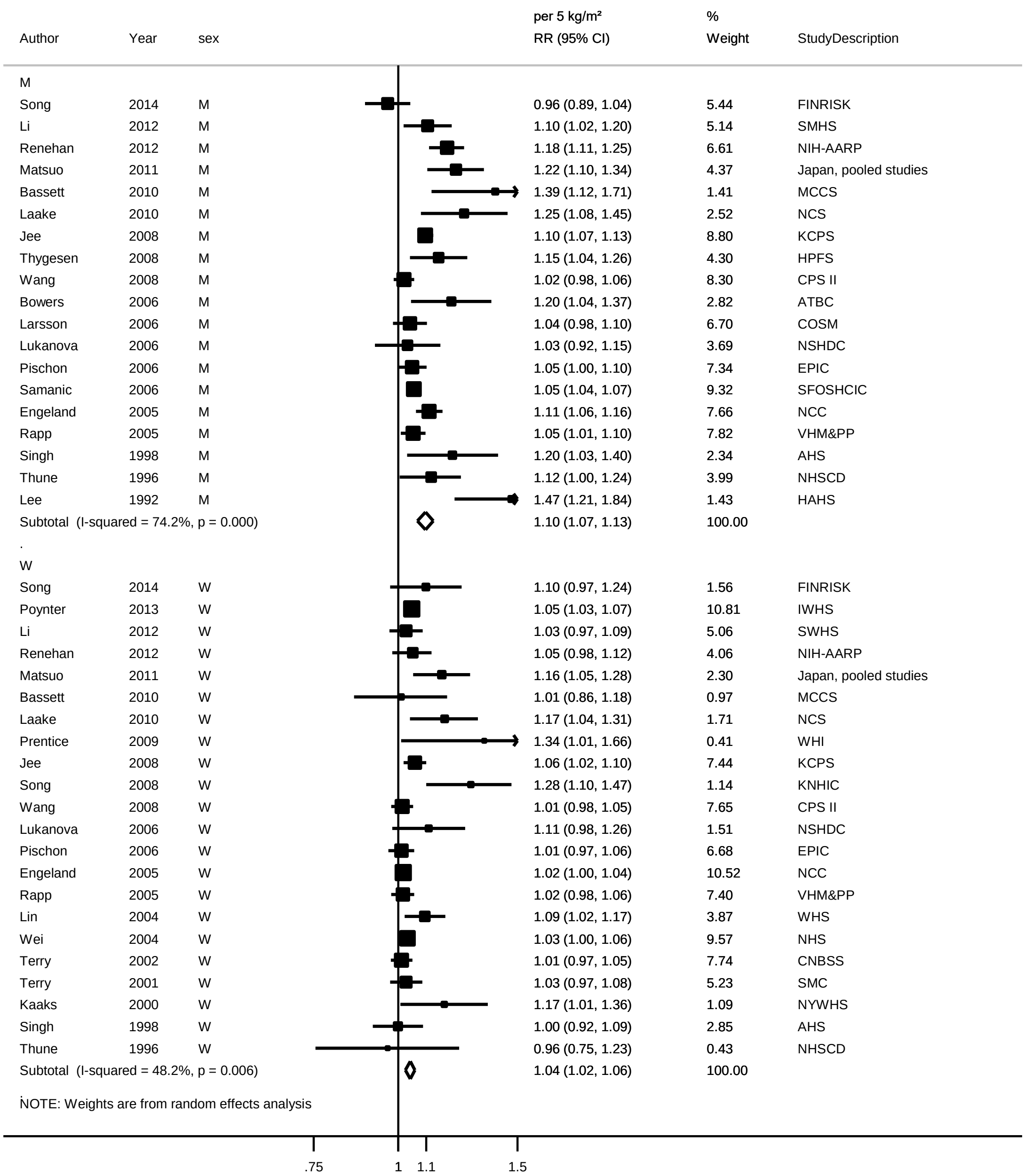


Figure 531 RR (95% CI) of colon cancer for 5 kg/m^2 increase of BMI by geographic location

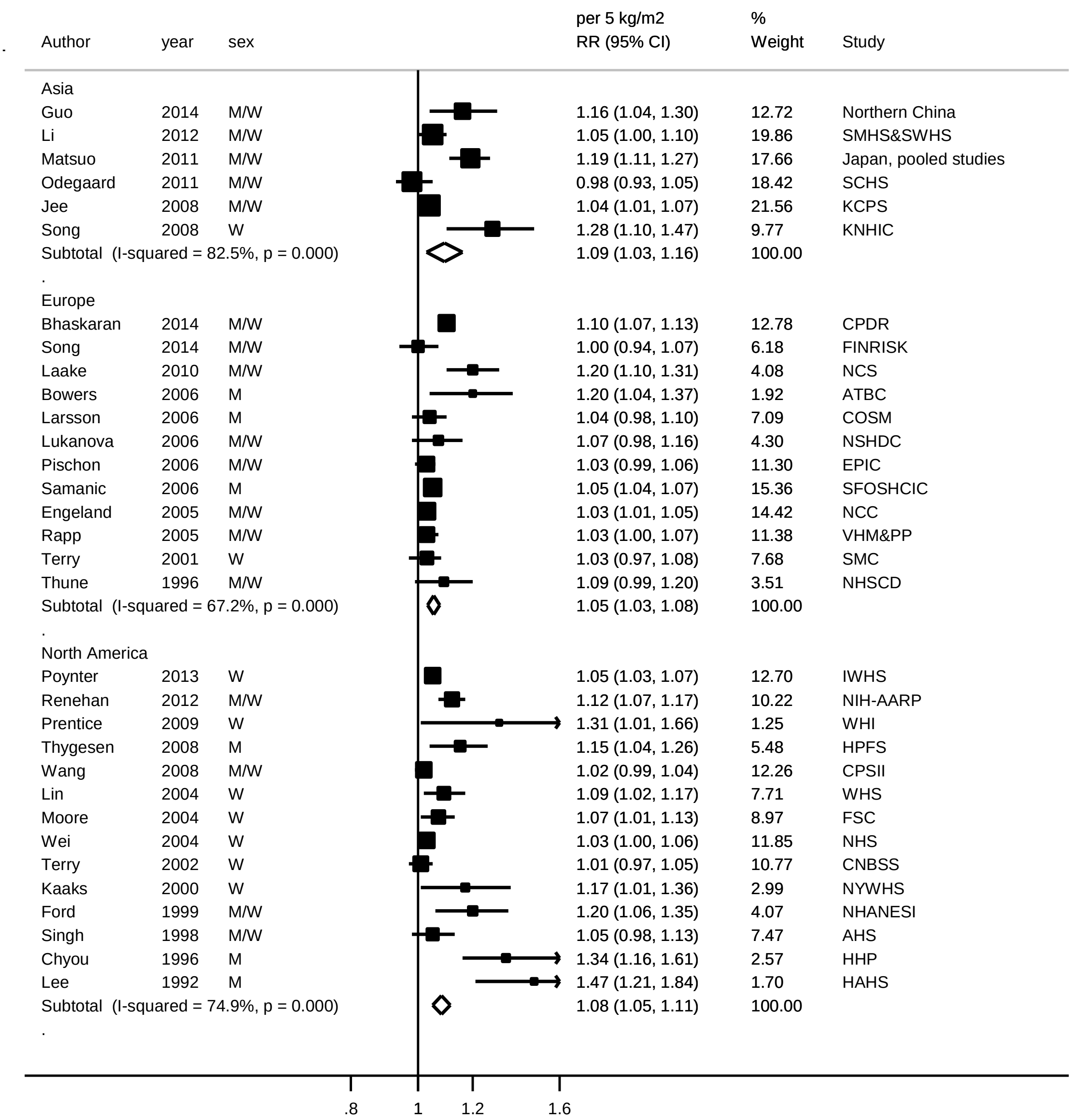


Figure 532 RR (95% CI) of colon cancer for the highest compared with the lowest level of BMI and proximal colon cancer

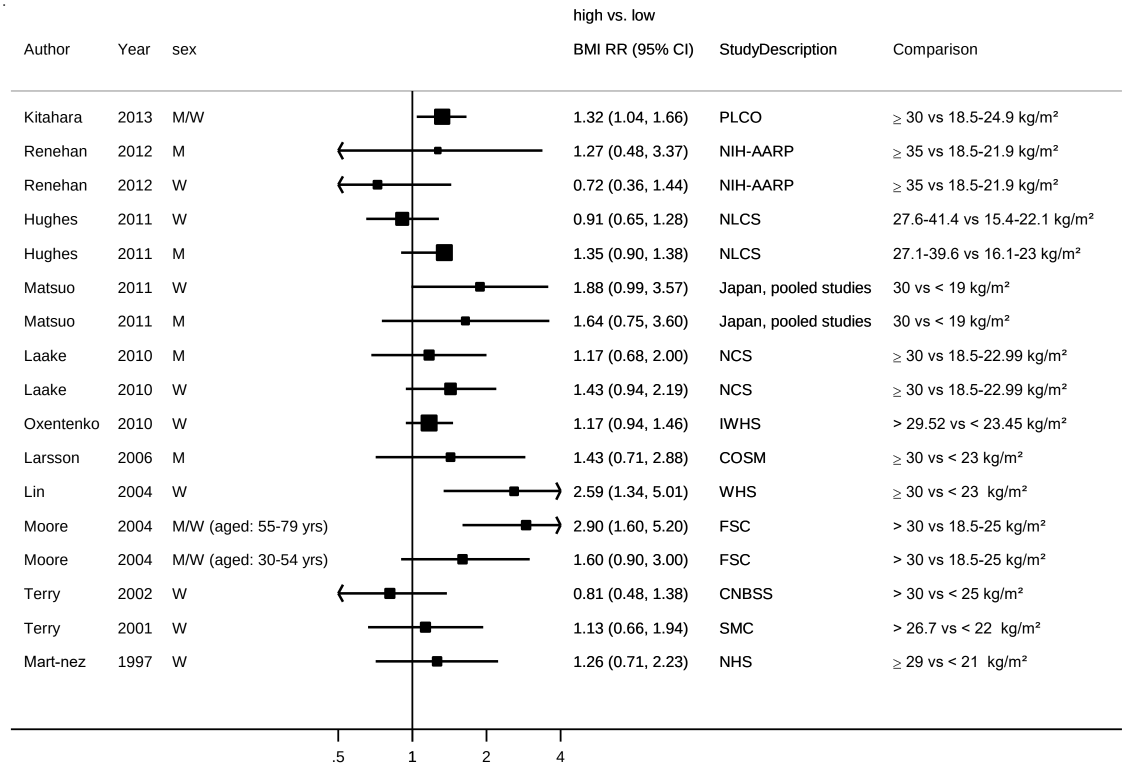


Figure 533 RR (95% CI) of colon cancer for 5 kg/m^2 increase of BMI and proximal colon cancer

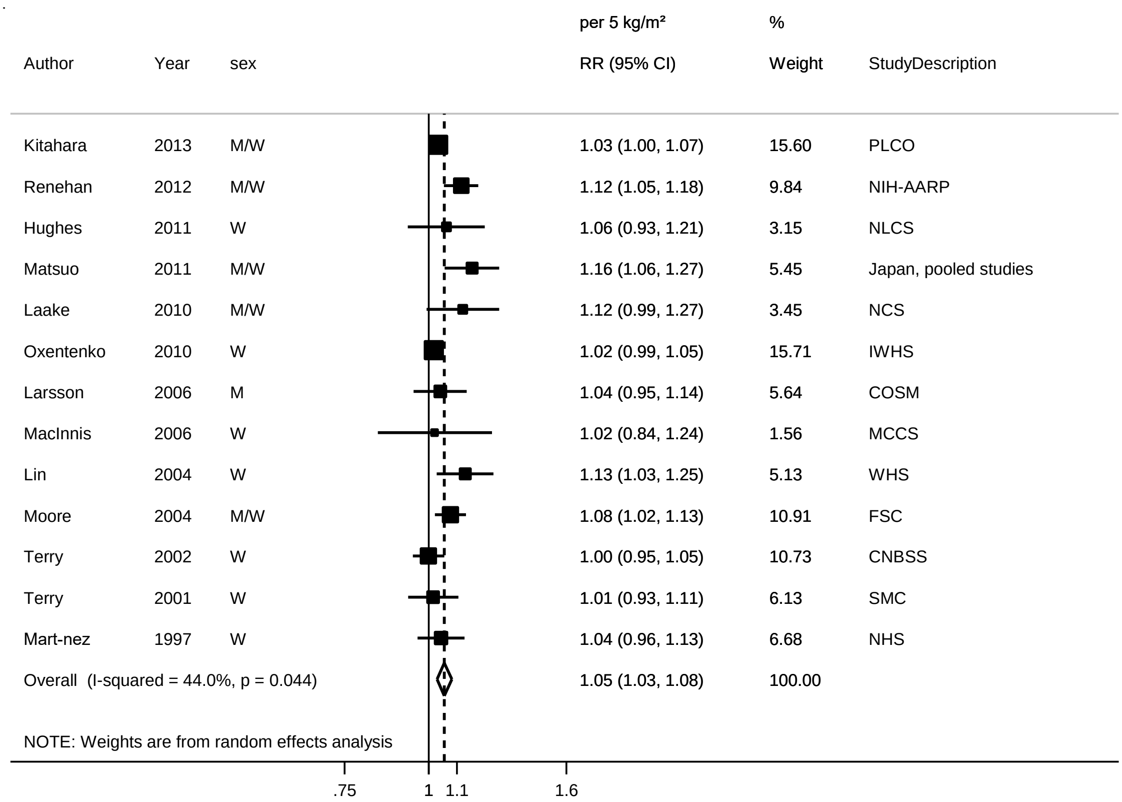


Figure 534 RR (95% CI) of colon cancer for 5 kg/m² increase of BMI and Proximal colon cancer by sex

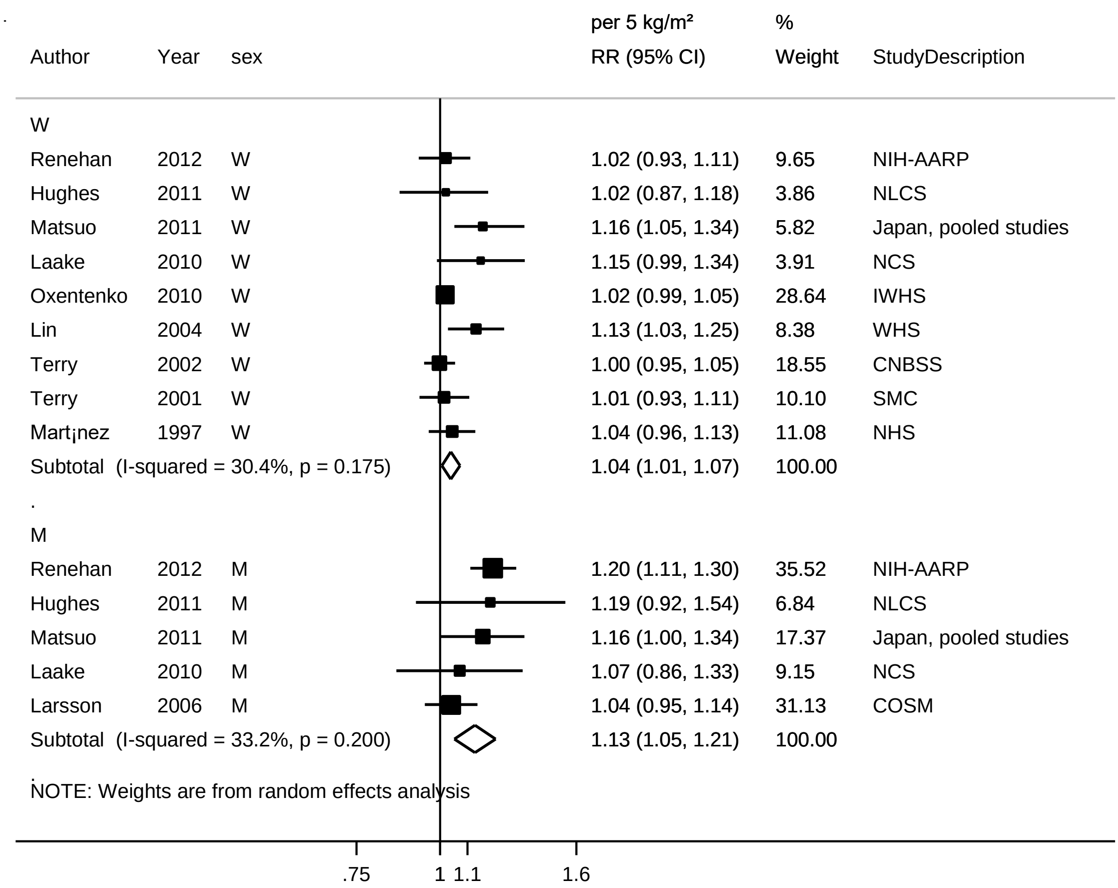


Figure 535 RR (95% CI) of colon cancer for the highest compared with the lowest level of BMI and distal colon cancer

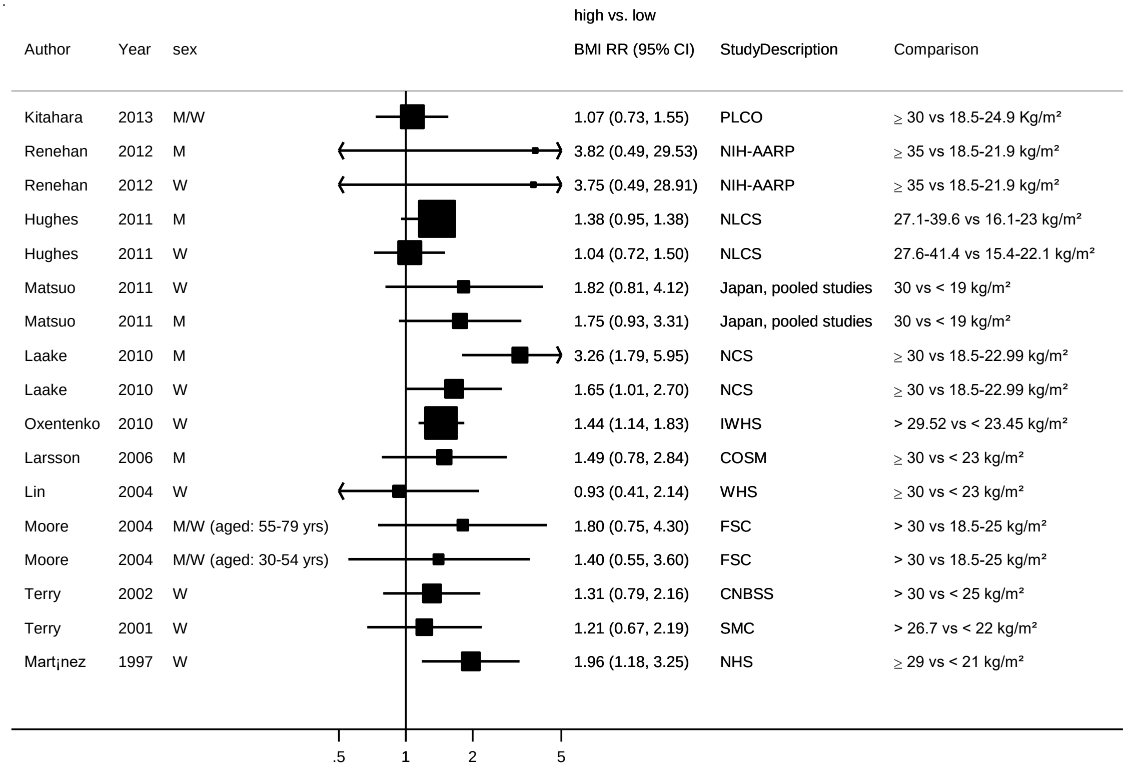


Figure 536 RR (95% CI) of colon cancer for 5 kg/m^2 increase of BMI and distal colon cancer

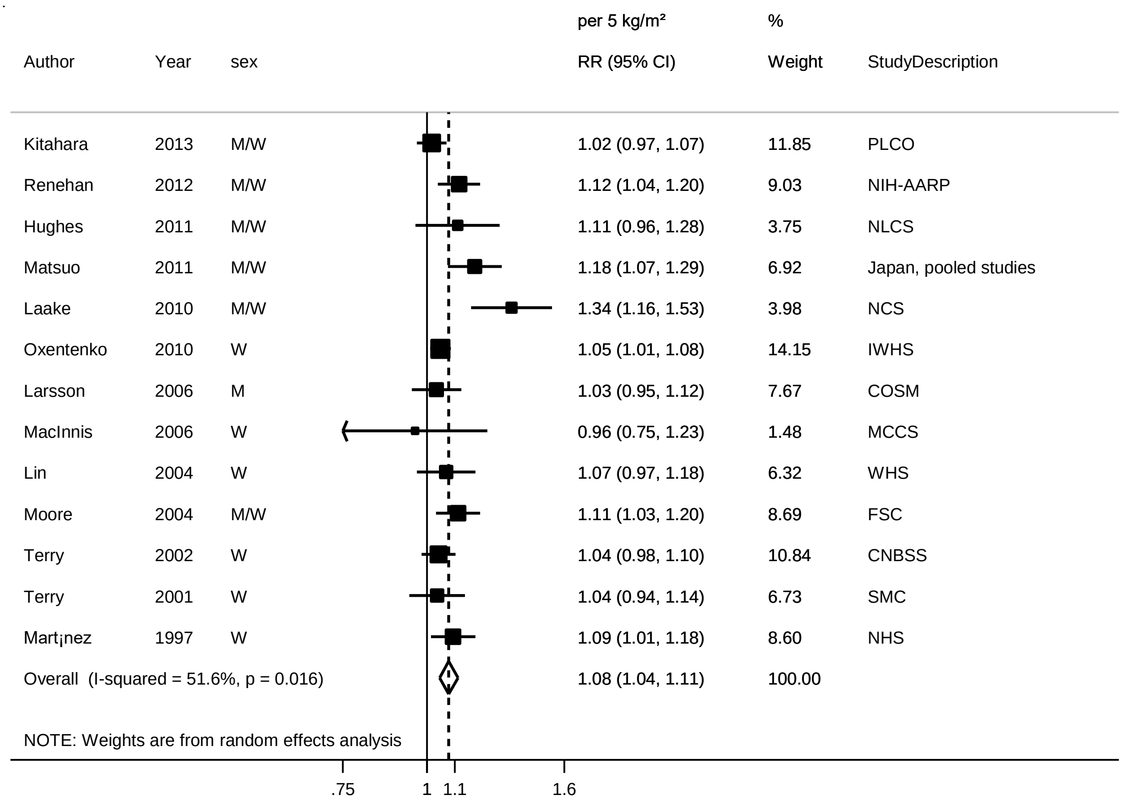


Figure 537 RR (95% CI) of colon cancer for 5 kg/m^2 increase of BMI and distal colon cancer by sex

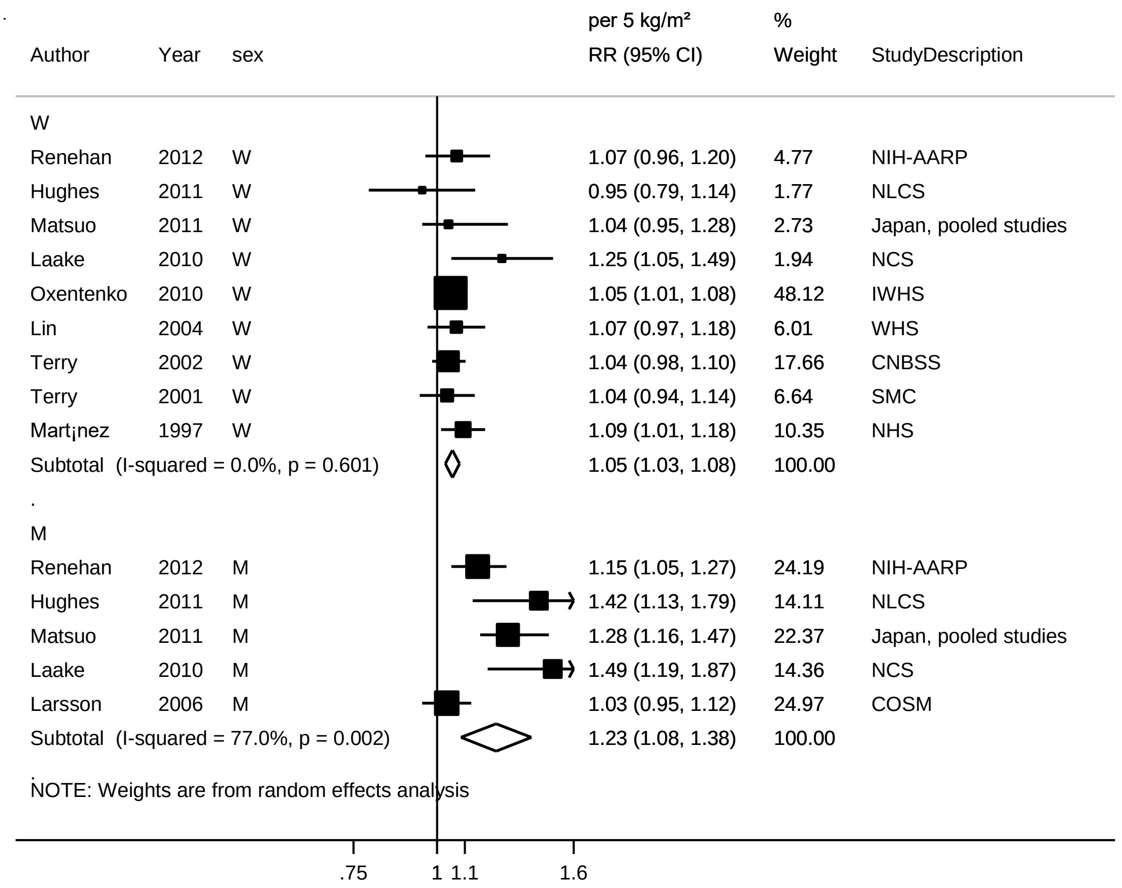
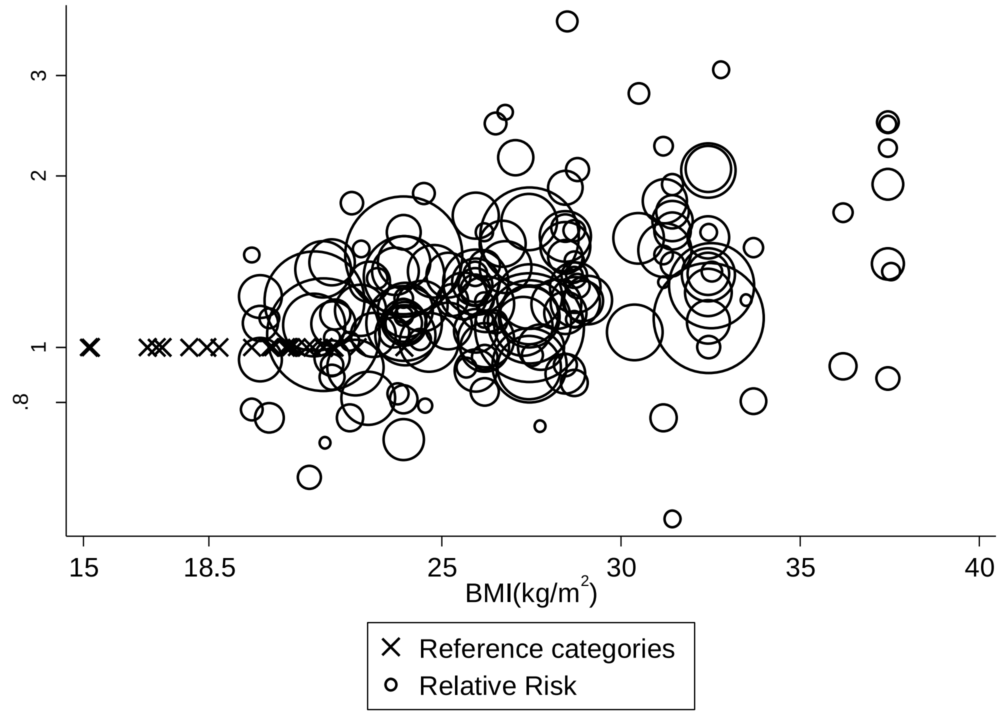
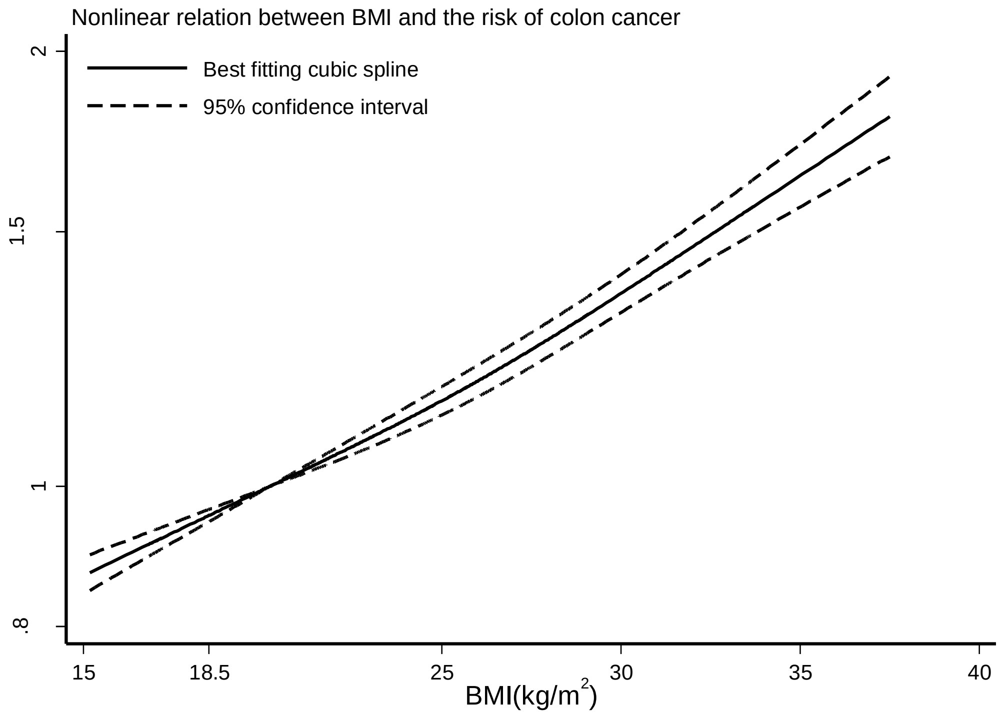


Figure 538 Relative risk of colon cancer and BMI estimated using non-linear models





p for non-linearity=0.02

Table 325 Table with BMI values and corresponding RRs (95% CIs) for non-linear analysis of BMI and colon cancer

BMI (Kg/m^2)	RR (95%CI)
18.79	0.96 (0.95-0.97)
20.2	1.00
23.80	1.11 (1.09-1.13)
25.70	1.17 (1.14-1.20)
27.5	1.25 (1.21-1.28)
31.2	1.42 (1.38-1.47)

Figure 539 RR estimates of rectal cancer by levels of BMI

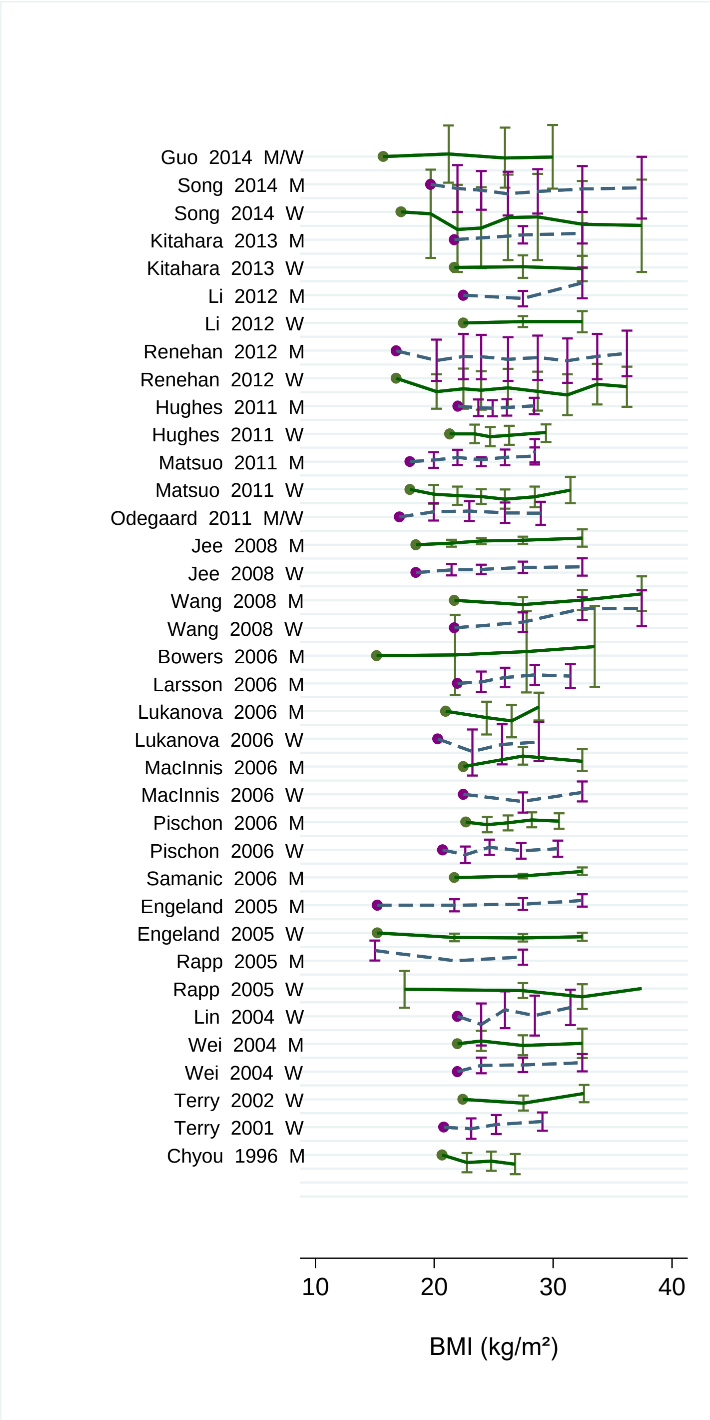


Figure 540 RR (95% CI) of rectal cancer for the highest compared with the lowest level of BMI

Author	Year	sex	high vs. low BMI RR (95% CI)	StudyDescription	Comparison
Bhaskaran	2014	M/W	1.07 (0.78, 1.48)	CPRD	39 vs <18.5 kg/m²
Guo	2014	M/W	0.98 (0.20, 4.86)	Northern China	≥ 28 vs < 18.5 kg/m²
Shin	2014	M	1.07 (0.99, 1.15)	KNHIC	≥ 25 vs < 25 kg/m²
Song	2014	W	0.51 (0.05, 5.04)	FINRISK	≥ 35 vs <18.5 kg/m²
Song	2014	M	0.84 (0.18, 3.96)	FINRISK	≥ 35 vs 18.5-20.9 kg/m²
Kitahara	2013	M	1.38 (0.83, 2.27)	PLCO	≥30 vs 18.5-24.9 kg/m²
Kitahara	2013	W	0.95 (0.50, 1.79)	PLCO	≥30 vs 18.5-24.9 kg/m²
Li	2012	W	1.07 (0.63, 1.81)	SWHS	≥ 30 vs < 25 kg/m²
Li	2012	M	1.84 (0.85, 3.99)	SMHS	≥ 30 vs < 25 kg/m²
Renehan	2012	M	0.88 (0.28, 2.73)	NIH-AARP	≥ 35 vs < 18.5 kg/m²
Renehan	2012	W	0.66 (0.24, 1.80)	NIH-AARP	≥ 35 vs < 18.5 kg/m²
Hughes	2011	M	1.01 (0.67, 1.51)	NLCS	27.1-39.6 vs 16.1-23 kg/m²
Hughes	2011	W	1.07 (0.67, 1.60)	NLCS	27.6-41.4 vs 15.4-22.1 kg/m²
Matsuo	2011	M	1.73 (0.96, 3.09)	Japan, pooled studies	30 vs < 19 kg/m²
Matsuo	2011	W	0.97 (0.50, 1.86)	Japan, pooled studies	30 vs < 19 kg/m²
Odegaard	2011	M/W	1.21 (0.68, 2.14)	SCHS	≥ 27.5 vs 21.5-24.4 kg/m²
Wang	2008	W	2.67 (1.09, 6.54)	CPS II	≥ 35 vs 18.5-24.9 kg/m²
Wang	2008	M	1.38 (0.58, 3.28)	CPS II	≥ 35 vs 18.5-24.9 kg/m²
Bowers	2006	M	1.57 (0.21, 12.02)	ATBC	> 30 vs < 18.5 kg/m²
Larsson	2006	M	1.44 (0.79, 2.61)	COSM	≥ 30 vs < 23 kg/m²
Lukanova	2006	M	1.23 (0.63, 2.51)	NSHDC	≥ 27.7 vs 18.5-23.4 kg/m²
Lukanova	2006	W	0.86 (0.33, 2.30)	NSHDC	≥ 27 vs 18.5-22.1 kg/m²
MacInnis	2006	M	1.30 (0.80, 2.40)	MCCS	≥ 30 vs < 25 kg/m²
MacInnis	2006	W	1.10 (0.70, 1.90)	MCCS	≥ 30 vs < 25 kg/m²
Pischon	2006	W	1.06 (0.71, 1.58)	EPIC	≥ 29.4 vs < 23.6 kg/m²
Pischon	2006	M	1.05 (0.72, 1.55)	EPIC	≥ 29.4 vs < 23.6 kg/m²
Samanic	2006	M	1.36 (1.13, 1.66)	SFOSHCIC	> 30 vs 18.5-24.9 kg/m²
Engeland	2005	M	1.27 (0.93, 1.73)	NCC	≥ 30 vs < 18.5 kg/m²
Engeland	2005	W	0.83 (0.68, 1.01)	NCC	≥ 30 vs 18.5-24.9 kg/m²
Rapp	2005	W	0.96 (0.38, 2.39)	VHM&PP	≥ 35 vs 18.5-24.9 kg/m²
Rapp	2005	M	1.66 (1.01, 2.73)	VHM&PP	≥ 35 vs 18.5-24.9 kg/m²
Lin	2004	W	1.55 (0.64, 3.77)	WHS	≥ 30 vs < 23 kg/m²
Samanic	2004	M (white)	1.23 (1.14, 1.33)	MVS	Highest vs lowest
Samanic	2004	M (black)	1.11 (0.90, 1.37)	MVS	Highest vs lowest
Wei	2004	M	1.03 (0.49, 2.14)	HPFS	>=30 vs. <23
Wei	2004	W	1.56 (1.01, 2.42)	NHS	≥ 30 vs < 23 kg/m²
Saydah	2003	M/W	1.64 (0.68, 3.94)	CLUE II	Highest vs lowest
Terry	2002	W	1.35 (0.87, 2.07)	CNBSS	> 30 vs < 25 kg/m²
Terry	2001	W	1.32 (0.83, 2.08)	SMC	> 26.7 vs < 22 kg/m²
Robsahm	1999	M	1.16 (1.07, 1.27)	NSPT	Highest vs lowest
Robsahm	1999	W	1.03 (0.93, 1.14)	NSPT	Highest vs lowest
Chyou	1996	M	0.63 (0.38, 1.04)	HHP	≥ 25.8 vs < 21.7 kg/m²
Moller	1994	M/W	1.10 (0.90, 1.30)	Danish study	Obese vs Danish population
Le Marchand	1992	M	0.80 (0.52, 1.24)	HHCS	Highest vs lowest

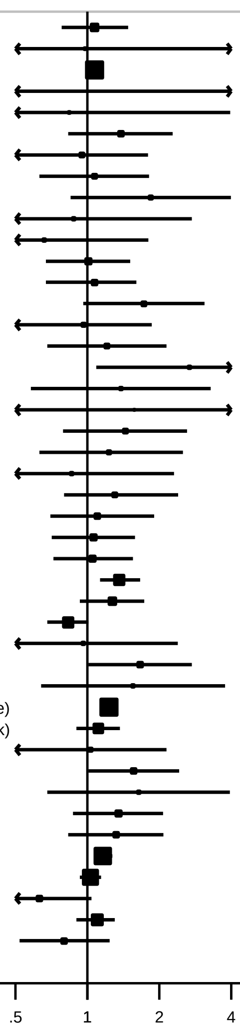


Figure 541 RR (95% CI) of rectal cancer for 5 kg/m^2 increase of BMI

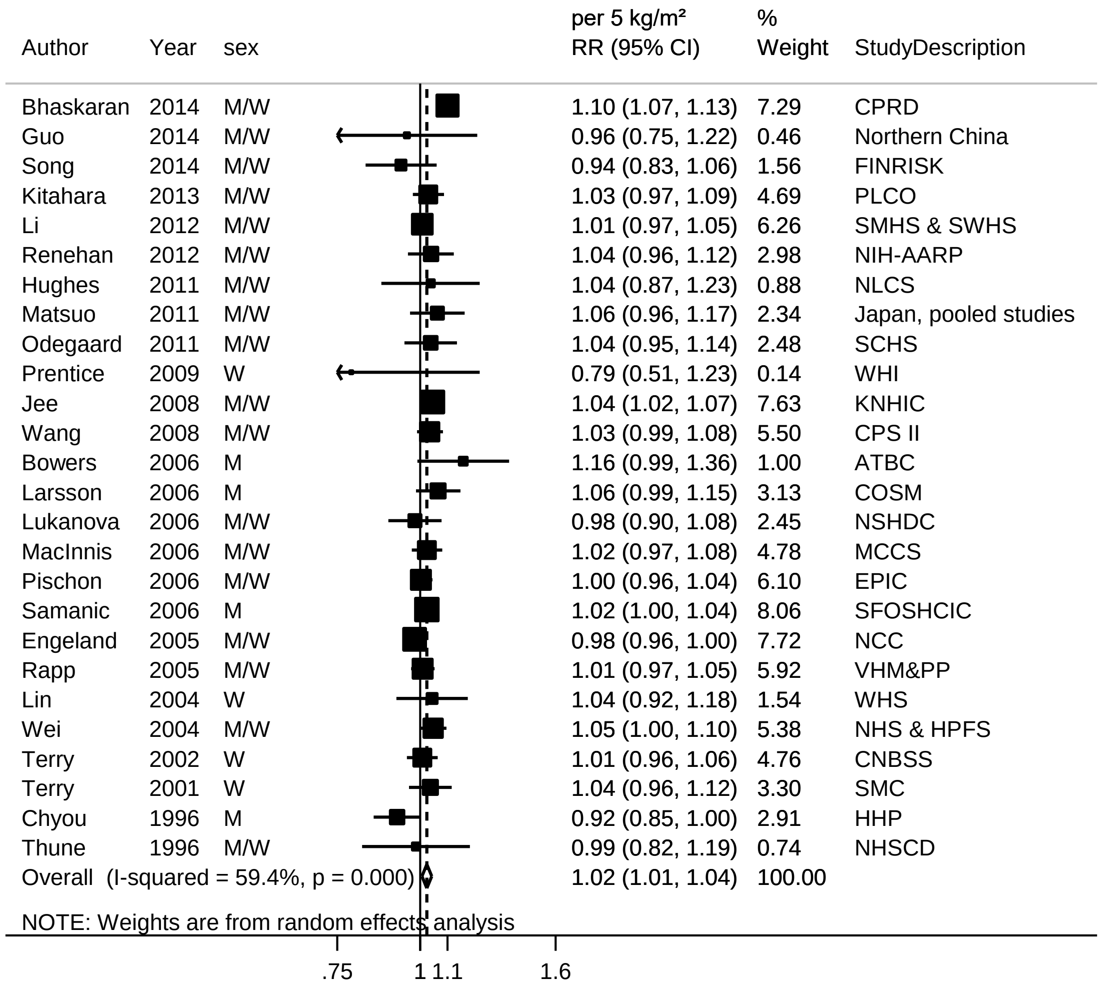
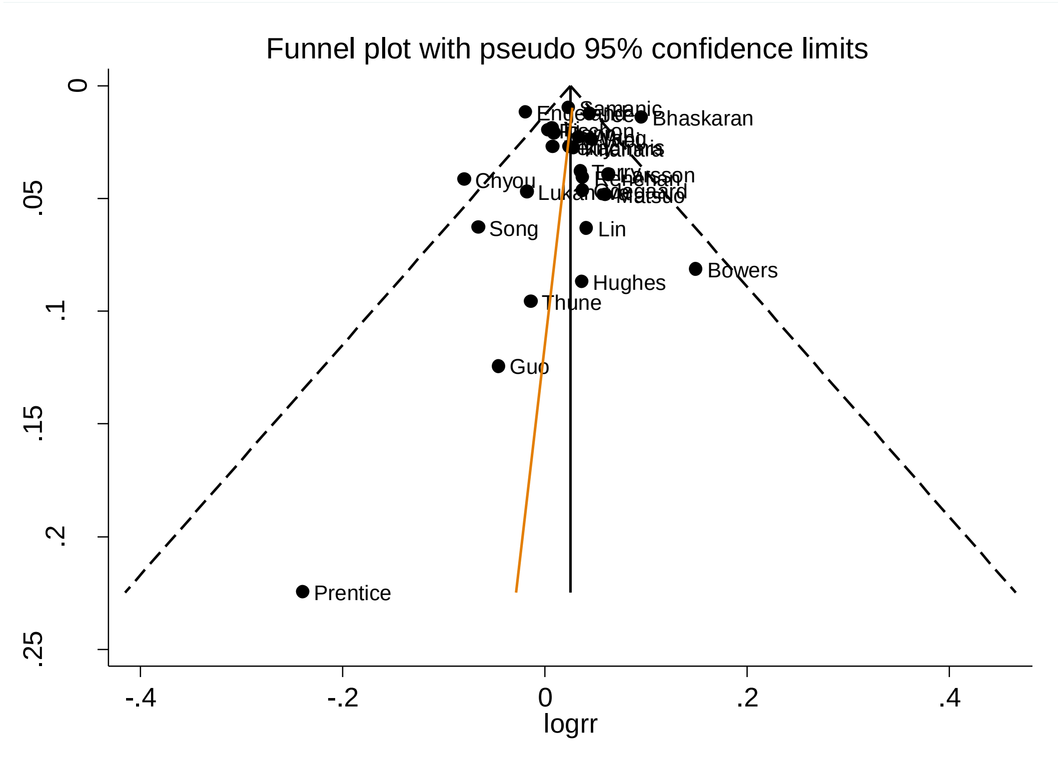


Figure 542 Funnel plot of studies included in the dose response meta-analysis of BMI and rectal cancer



p Egger's test =0.78

Figure 543 RR (95% CI) of rectal cancer for 5 kg/m² increase of BMI by sex

Author	Year	per 5 kg/m² RR (95% CI)	% Weight	StudyDescription
W				
Song	2014	0.90 (0.71, 1.16)	0.79	FINRISK
Kitahara	2013	1.00 (0.92, 1.09)	4.86	PLCO
Li	2012	1.01 (0.97, 1.06)	9.70	SWHS
Renehan	2012	0.99 (0.88, 1.11)	3.22	NIH-AARP
Matsuo	2011	1.00 (0.86, 1.16)	1.98	Japan, pooled studies
Prentice	2009	0.79 (0.51, 1.23)	0.26	WHI
Jee	2008	1.04 (1.00, 1.09)	10.04	KNHIC
Wang	2008	1.11 (1.04, 1.20)	6.18	CPS II
Lukanova	2006	0.96 (0.82, 1.12)	1.86	NSHDC
MacInnis	2006	0.99 (0.92, 1.06)	6.35	MCCS
Pischon	2006	1.00 (0.95, 1.06)	8.20	EPIC
Engeland	2005	0.96 (0.94, 0.99)	13.09	NCC
Rapp	2005	0.97 (0.92, 1.03)	8.19	VHM&PP
Lin	2004	1.04 (0.92, 1.18)	2.75	WHS
Wei	2004	1.07 (1.01, 1.13)	8.13	NHS
Terry	2002	1.01 (0.96, 1.06)	8.52	CNBSS
Terry	2001	1.04 (0.96, 1.12)	5.88	SMC
Subtotal (I-squared = 44.1%, p = 0.027)		1.01 (0.99, 1.03)	100.00	
.				
M				
Song	2014	0.95 (0.82, 1.09)	1.24	FINRISK
Kitahara	2013	1.05 (0.98, 1.12)	4.61	PLCO
Li	2012	1.00 (0.94, 1.06)	5.29	SMHS
Renehan	2012	1.01 (0.92, 1.11)	2.71	NIH-AARP
Matsuo	2011	1.10 (0.95, 1.22)	1.64	Japan, pooled studies
Jee	2008	1.05 (1.02, 1.08)	16.19	KNHIC
Wang	2008	0.99 (0.93, 1.04)	6.36	CPS II
Bowers	2006	1.16 (0.99, 1.36)	1.00	ATBC
Larsson	2006	1.06 (0.99, 1.15)	3.87	COSM
Lukanova	2006	1.00 (0.89, 1.12)	1.89	NSHDC
MacInnis	2006	1.07 (1.00, 1.16)	4.07	MCCS
Pischon	2006	1.01 (0.95, 1.06)	6.78	EPIC
Samanic	2006	1.02 (1.00, 1.04)	21.90	SFOSHCIC
Engeland	2005	1.03 (0.98, 1.07)	9.45	NCC
Rapp	2005	1.05 (0.99, 1.12)	6.13	VHM&PP
Wei	2004	1.00 (0.92, 1.09)	3.37	HPFS
Chyou	1996	0.92 (0.85, 1.00)	3.52	HHP
Subtotal (I-squared = 21.8%, p = 0.200)		1.02 (1.01, 1.04)	100.00	

NOTE: Weights are from random effects analysis

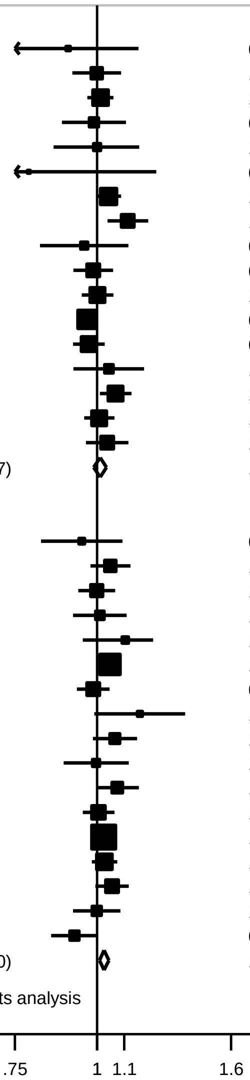


Figure 544 RR (95% CI) of rectal cancer for 5 kg/m^2 increase of BMI by geographic location

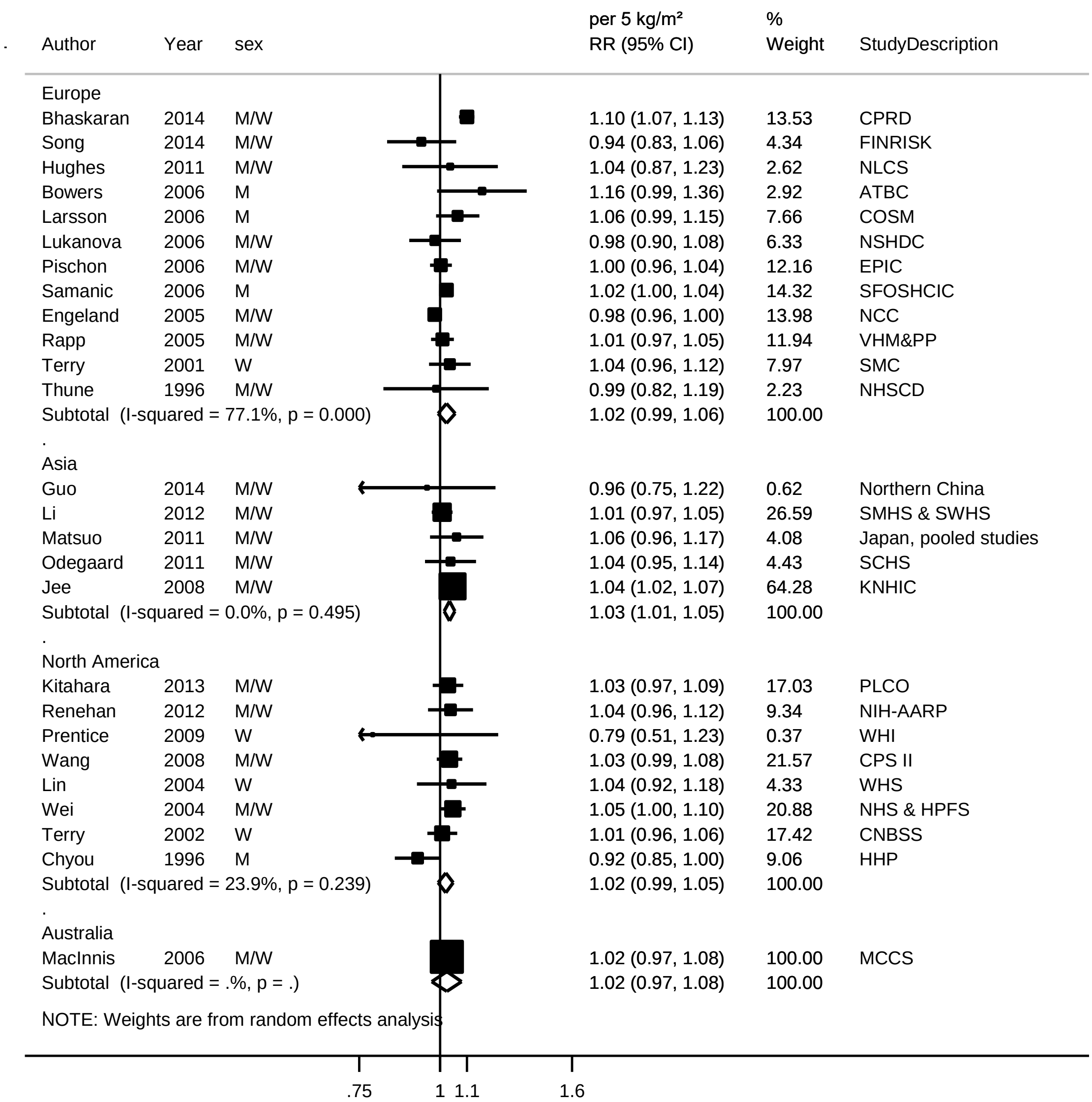
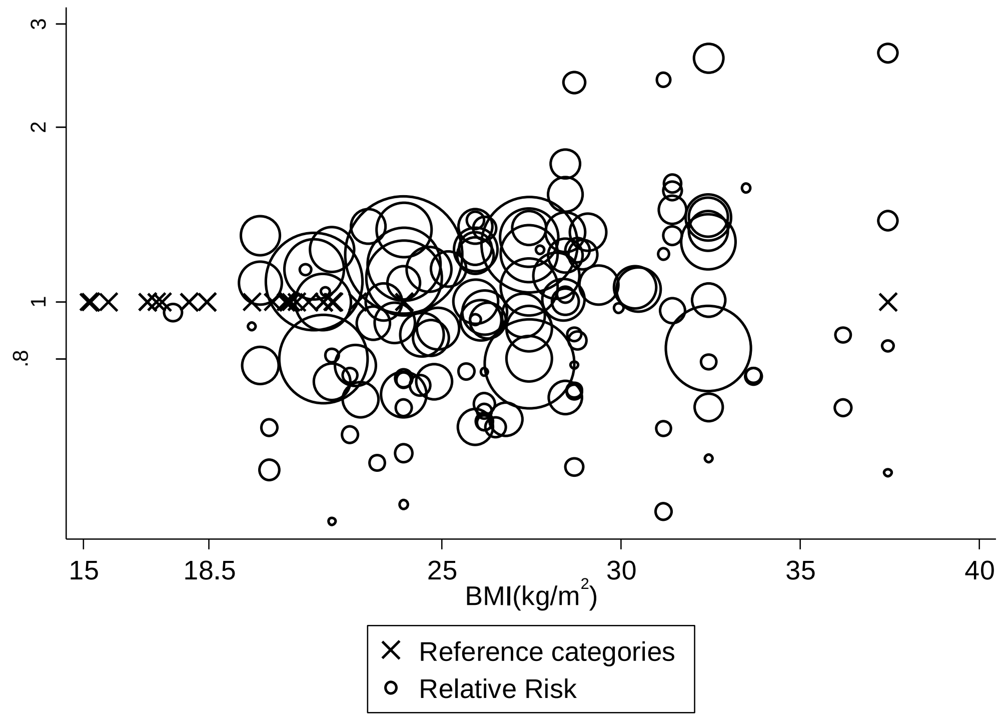
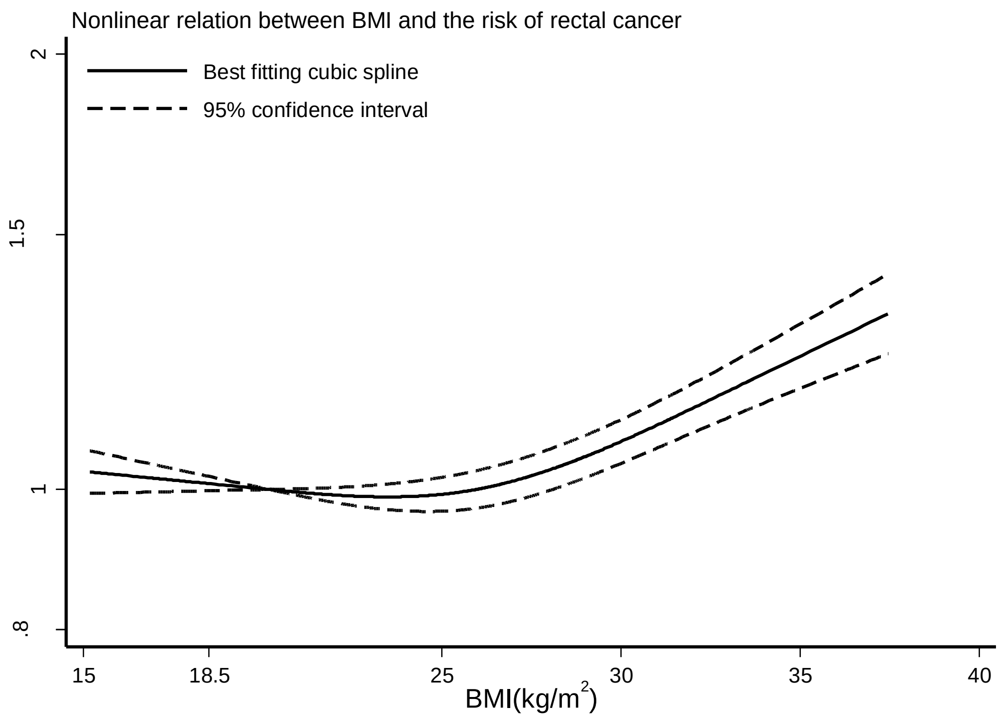


Figure 545 Relative risk of rectal cancer and BMI estimated using non-linear models





p for non-linearity$\leq$ 0.001

Table 326 Table with BMI values and corresponding RRs (95% CIs) for non-linear analysis of BMI and rectal cancer

BMI (Kg/m^2)	RR (95%CI)
18.45	1.01 (1.00-1.02)
20.2	1.00
24.40	0.99 (0.97-1.01)
27.30	1.02 (0.99-1.05)
29.95	1.08 (1.04-1.12)
32.45	1.15 (1.11-1.20)

8.2.1 Waist Circumference

Cohort studies

Summary

Main results:
Ten new studies (16 publications) were identified since the publication of the 2010 CUP SLR.

Colorectal cancer:
Eight studies (4301 cases) were included in the dose-response meta-analysis. A significant association was observed (2% risk increase for 10 cm increase of waist circumference). There was no significant evidence of publication bias (p=0.45). The significant association were borderline significant in men and significant in women (p homogeneity= 0.51). In all studies the RR estimates were adjusted for main potential confounders. In onestudy (MacInnis, 2006) only age, education country of birth and in women HRT use, remained in the final models after testing multiple covariates. Two studies reported RR's with further adjustment for BMI (Park, 2011; Wang, 2008).
There was no evidence of non-linear association (p=0.17)

Colon cancer:
Ten studies (3613 cases) were included in the dose-response meta-analysis. A significant 4% risk increase was observed for an increase of 10 cm of waist circumference. High heterogeneity was observed. There was evidence of publication bias (p=<0.01).
The significant associations were observed both in men and women (p homogeneity=0.51).
In stratified analysis by geographic location, the studies in Asia showed a stronger association compared to the studies conducted in Europe and North America, but no statistically significant difference was detected (p=0.69).

There were not enough studies with the data required to conduct dose-response meta-analysis for proximal and distal colon cancer. Three studies were included in the highest vs lowest analysis for proximal colon cancer.

Rectal cancer:
Six studies (1579 cases) were included in the dose-response meta-analysis of waist circumference and rectal cancer. A marginal significant increased risk of 2% was observed for an increase of 10 cm of waist circumference. No heterogeneity was observed. There was no evidence of publication bias (p=0.70).
A significant association was observed in women.
In influence analysis, the summary RRs ranged from 1.01 (95% CI=1.00-1.03) when Larsson, 2006 was omitted to 1.02 (95% CI=1.00-1.04) when Li, 2013 was omitted.

Study quality:
Most studies used measured waist circumference. All studies adjusted for main potential confounders. Three studies reported RR's with further adjustment for BMI (Park, 2001; Wang, 2008; Moore, 2004).

Table 327 Waist circumference and colorectal cancer risk. Number of studies in the CUP SLR

	Number		
	Colorectal	Colon	Rectum
Studies identified	13 (18 publications)	12 (17 publications)	7 studies (7 publications)
Studies included in forest plot of highest compared with lowest exposure	10	11	6
Studies included in dose-response meta-analysis	8	10	6
Studies included in non-linear dose-response meta-analysis	7	8	6

Note: Include cohort, nested case-control and case-cohort designs

Table 328 Waist circumference and colorectal cancer risk. Summary of the dose-response meta-analysis in the 2010 SLR and 2015 SLR.

	2010 SLR	**2015 SLR**
Increment unit used	Per inch	10 cm
Studies (n)	3	8
Cases (total number)	1798	4301
RR (95%CI)	1.03 (1.02-1.04)	1.02 (1.01-1.03)
Heterogeneity (I^2, p-value)	0%, 0.57	0%, 0.74

CUP Stratified analysis			
Sex	**Women**		**Men**
Studies (n)	5		4
RR (95%CI)	1.03 (1.02-1.04)		1.02 (1.00-1.04)
Heterogeneity (I^2, p-value)	0%, 0.85		47.2%, 0.13
Geographic location	**Europe**	**North America**	**Asia**
Studies (n)	2	3	3
RR (95%CI)	1.01 (0.99-1.04)	1.02 (1.01-1.03)	1.03 (1.01-1.05)
Heterogeneity (I^2, p-value)	34.4%, 0.22	0%, 0.72	0%, 0.79

Table 329 Waist circumference and colon cancer risk. Summary of the dose-response meta-analysis in the 2010 SLR and 2015 SLR.

	2010 SLR	**2015 SLR**
Increment unit used	Per inch	10 cm
Studies (n)	**6**	10
Cases (total number)	3202	3613
RR (95%CI)	1.05 (1.03-1.06)	1.04 (1.02-1.06)
Heterogeneity (I^2, p-value)	63%, 0.02	62.9%, 0.006

Stratified analysis by sex		
Men	**2010 SLR**	**2015 SLR**
Studies (n)	**6**	7
RR (95%CI)	1.06 (1.04-1.08)	1.07 (1.02-1.12)
Heterogeneity (I^2, p-value)	53%, 0.06	95%, < 0.001
Women		
Studies (n)	5	7
RR (95%CI)	1.03 (1.02-1.04)	1.03 (1.01-1.04)
Heterogeneity (I^2, p-value)	0%, 0.44	7.8%, 0.37

CUP Stratified analysis			
	Europe	**North America**	**Asia**
Studies (n)	2	5	2
RR (95%CI)	1.02 (1.01-1.04)	1.03 (1.01-1.05)	1.05 (1.02-1.08)
Heterogeneity (I^2, p-value)	0%, 0.88	31.2%, 0.21	

Table 330 Waist circumference and rectal cancer risk. Summary of the dose-response meta-analysis in the 2010 SLR and 2015 SLR.

	2010 SLR	2015 SLR
Increment unit used	Per inch	10 cm
Studies (n)	4	6
Cases (total number)	1206	1579
RR (95%CI)	1.03 (1.01-1.04)	1.02 (1.00-1.03)
Heterogeneity (I^2, p-value)	0%, 0.84	0%, 0.49
CUP Stratified analysis by sex		
Sex	**Women**	**Men**
Studies (n)	4	5
RR (95%CI)	1.03 (1.01-1.06)	1.01 (0.98-1.03)
Heterogeneity (I^2, p-value)	0%, 0.44	28.7%, 0.23

Table 331 Waist circumference and colorectal cancer risk. Results of meta- of prospective studies published after the 2010 SLR.

Author, Year	Number of cohort studies	Studies country, area	Outcome	Comparison	RR (95%CI)	Heterogeneity (I^2, p value)
Ma, 2013	54		Colorectal cancer	Highest vs lowest	1.45 (1.33-1.60)	10.8%, 0.32
			Colon cancer		1.613 (1.417–1.837)	0.573, 0%
			Colon cancer, proximal		1.873 (1.118–3.136)	0.773, 0%
			Colon cancer, distal		1.942 (1.250–3.017)	0.507, 0%
			Rectal cancer		1.349 (1.114–1.634)	0.582, 0%
		USA	Colorectal cancer		1.612 (1.379–1.885)	0.227, 24.3%
		Europe	Colorectal cancer		1.368 (1.215–1.541)	0.520, 0%
			Colorectal cancer, men		1.477 (1.300–1.677)	0.135, 30.2%
			Colorectal cancer, women		1.442 (1.296–1.604)	0.834, 0%
			Colon cancer, men		1.812 (1.464–2.242)	0.308, 15.9%
			Colon cancer, women		1.498 (1.253–1.791)	0.955, 0%
			Rectal cancer, men		1.281 (0.990–1.657)	0.934, 0%
			Rectal cancer, women		1.495 (1.025–2.181)	0.224, 33.1%

Table 332 Waist circumference and colorectal cancer risk. Main characteristics of studies included in the CUP SLR dose-response meta-analysis

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Missing data derived for analyses
Kabat, 2013 COL40965 USA	WHI, Prospective Cohort, Age: 50-79 years, W, Postmenopausal	169/ 11 124 12.9 years	Self-report verified by reviewing medical and pathological records by physicians	Measured	Incidence, colorectal cancer	≥ 94.1 vs ≤ 75.9 cm	1.30 (0.82-2.07) Ptrend:0.23	Age, alcohol, diabetes, educational level, energy, ethnicity, family history of colorectal cancer, HRT use, pack yrs of smoking, physical activity, randomisation	Mid-point categories
Li, 2013 COL40937 China	SWHS, Prospective Cohort, Age: 40-70 years, W	622/ 72 962 11 years	Follow up survey/cancer registry/vital statistics registry	Measured	Incidence, colorectal cancer	≥ 85 vs < 70 cm	1.26 (0.93-1.72) Ptrend:0.43	Age at baseline, alcohol consumption, cigarette, educational level, energy intake, family history of colorectal cancer, fruits, Income, menopausal status, physical	Mid-point categories
		382/			Incidence, colon cancer		1.34 (0.89-2.00) Ptrend:0.46		
		240/			Incidence, rectal cancer		1.17 (0.73-1.88) Ptrend:0.73		

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Missing data derived for analyses
								activity, red meat, tea consumption, vegetables	
Li, 2013 COL40936 China	SMHS, Prospective Cohort, Age: 40-74 years, M	313/ 61 240 5.5 years	Follow up survey/cancer registry/vital statistics registry	Measured	Incidence, colorectal cancer	≥ 92 vs < 78 cm	1.38 (0.97-1.97) Ptrend:0.004	Age at baseline, alcohol consumption, cigarette, educational level, energy intake, family history of colorectal cancer, fruits, Income, menopausal status, physical activity, red meat, tea consumption, vegetables	Mid-point categories
		180/			Incidence, colon cancer		2.00 (1.21-3.29) Ptrend:0.0002		
		133/			Incidence, rectal cancer		0.88 (0.52-1.49) Ptrend:0.95		
Park, 2011 COL41069 UK	EPIC-Norfolk, Prospective Cohort, Age: 40-79 years, M/W	357/ 20 608 11 years	Record linkage to cancer registration and death certificates	Self-reported and measured	Incidence, colorectal cancer, men (measured WC)	≥ 103.3 vs < 88 cm	0.86 (0.55-1.36) Ptrend:0.53	Age, sex, smoking, alcohol, education, exercise, family history of CRC, energy intake,	Mid-point categories Person-years of follow up
					Incidence,		0.95 (0.54-1.64)		

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Missing data derived for analyses
					colorectal cancer, men (self-reported WC)		Ptrend:0.86	folate, fibre, total meat and processed meat, intakes	
					Incidence, colorectal cancer, women (measured WC)	≥ 90.5 vs < 73 cm	1.65 (0.97–2.86) Ptrend:0.009		
					Incidence, colorectal cancer, women (self-reported WC)		1.42 (0.85–2.35) Ptrend:0.12		
					Incidence, colorectal cancer, men (measured WC)	Per 10 unit increase	1.06 (0.77-1.46)	Age, sex, smoking, alcohol, education, exercise, family history of CRC, energy intake, folate, fibre, total meat and processed meat, intakes, height and weight	
					Incidence, colorectal cancer, men (self-reported WC)		0.99 (0.74-1.32)		
					Incidence, colorectal		1.41 (1.06-1.87)		

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Missing data derived for analyses
					cancer, women (measured WC)				
					Incidence, colorectal cancer, women (self-reported WC)		0.97 (0.76-1.22)		
Kabat, 2012 COL40898 USA	WHI, Prospective Cohort, Age: 50-79 years, W, Postmenopausal	81/ 4 862 11.9 years	Self-reported validated by pathology report	Waist circumference measured	Incidence, colorectal cancer	per 1 cm	1.00 (0.97-1.04)	Age, alcohol, BMI, ethnicity, family history of colorectal cancer, participant type, physical activity	Mid-point categories Person-years of follow up
		80/			Incidence, colorectal cancer	≥ 88 vs < 79 cm	1.08 (0.50-2.34) Ptrend:0.84		
		65/			Incidence, colon cancer	per 1 cm	1.00 (0.97-1.03)		
		65/			Incidence, colon cancer	≥ 88 vs < 79 cm	1.01 (0.43-2.37) Ptrend:0.99		
Oxentenko, 2010 COL40849 USA	IWHS, Prospective Cohort, Age: 55-69 years, W	1 464/ 36 941 619 961 person-years	SEER	Self-reported	Incidence, colorectal cancer	≥ 96.53 vs ≤ 77.15 cm	1.32 (1.11-1.56) Ptrend:<0.001	Age, age at menopause, alcohol, calcium, cigarette consumption, contraception, diabetes, energy	Mid-point categories
					Incidence, proximal		1.27 (1.01-1.60) Ptrend:0.02		
					Incidence distal		1.37 (1.07-1.77) Ptrend:0.008		

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Missing data derived for analyses
								intake, Oestrogen use, red meat, folate, fruits and vegetables consumption, physical activity level, smoking status, total fat, vitamin E	
Yamamoto, 2010 COL40807 Japan	HHCCS, Nested case-control study, Age: 54 years, M/W	22 cases/ 69 controls 3 years	Histology	Measured	Incidence, colorectal cancer	≥89 vs ≤79 cm	2.03 (0.57-7.25) Ptrend:0.2	Age, sex, alcohol consumption, smoking status, year of examination	
Wang, 2008 COL40666 USA	CPS II, Prospective Cohort, M/W	546/ 95 151 7.7 years	Self-report, pathology report, national death Index, death cert, state cancer registries	Self-report	Incidence, colorectal cancer, men	≥ 120 vs ≤ 94 cm	1.68 (1.12-2.53) Ptrend:0.006	Age, alcohol, educational level, height, history of endoscopy, multivitamin supplement intake, NSAID use, physical activity, smoking status	Mid-point categories
		407/			Incidence, colorectal cancer, women	≥ 110 vs ≤ 84 cm	1.75 (1.20-2.54) Ptrend:0.003		
		402/			Incidence, colon cancer, men	≥ 120 vs ≤ 94 cm	2.05 (1.29-3.25) Ptrend:<0.001		
		314/			Incidence, colon cancer, women	≥ 110 vs ≤ 84 cm	1.54 (1.00-2.37) Ptrend:0.09		

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Missing data derived for analyses
		142/			Incidence, rectal cancer, men	≥ 120 vs ≤ 94 cm	1.02 (0.43-2.42) Ptrend:0.88	HRT use	
		93/			Incidence, rectal cancer, women	≥ 110 vs ≤ 84 cm	2.65 (1.23-5.71) Ptrend:0.002		
Larsson, 2006 COL40625 Sweden	COSM, Prospective Cohort, Age: 45-79 years, M	407/ 45 906 7.1 years	Cancer registry	Self-reported	Incidence, colorectal cancer	≥ 104 vs < 88 cm ≥104 vs ≤87 cm	1.29 (0.90-1.85) Ptrend:0.03	Age, aspirin use, height, educational level, family history of colorectal cancer, history of diabetes, recreational activity, recreational activity, smoking status	Mid-point categories
		252/			Incidence, colon cancer		1.44 (0.93-2.24) Ptrend:0.09		
		158/			Incidence, rectal cancer		1.24 (0.68-2.25) Ptrend:0.16		
		112/			Incidence, distal colon cancer		1.62 (0.80-3.27) Ptrend:0.47		
		110/			Incidence, proximal colon cancer		1.66 (0.84-3.27) Ptrend:0.08		
Pischon, 2006 COL01985	EPIC, Prospective Cohort,	418/ 368 277 6.1 years	Population registries	Measured	Incidence, colon, men	≥ 103 vs < 86	1.39 (1.01-1.93) Ptrend:0.001	Age, centre, height, smoking status education alcohol intake physical activity fibre intake, consumption of red and processed meat , fish and shell fish and	Mid-categories Person-years of follow up
		562/			Incidence, colon, women	≥ 89 vs < 70.2	1.48 (1.08-2.03) Ptrend:0.008		
		293/			Incidence,	≥ 103 vs < 86	1.27 (0.84-1.91)		

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Missing data derived for analyses
					rectal, men		Ptrend:0.21	fruits and vegetables	
		291/			Incidence, rectal, women	≥ 89 vs < 70.2	1.23 (0.81-1.86) Ptrend:0.22		
MacInnis, 2006 COL40751 Australia	MCCS, Prospective Cohort, Age: 27-75 years, W	212/ 24 072 10.4 years	Cancer registry, medical records	Measured	Incidence, colon	Per 10 cm increase	1.14 (1.02-1.28)	Age, country of birth, education level, HRT use ((main potential confounders tested and not retained in the final models)	
						≥ 88 vs < 80 cm	1.4 (1.0-1.9)		
		117/			Incidence, proximal colon cancer	Per 10 cm increase	1.16 (1.00-1.36)		
		79/			Incidence, distal Colon cancer		1.02 (0.84-1.24)		
MacInnis, 2006 COL40627 Australia	MCCS, Prospective Cohort, Age: 27-75 years, M/W	229/ 41 114 10.3 person-years	Cancer registry	Measured	Incidence, rectal cancer	Q 3 vs Q 1	1.40 (1.00-1.90)	Age, sex, country of birth	
		229/				per 10 cm	1.12 (0.99-1.27)		
		134/			Incidence, rectal cancer, men	≥ 102 vs < 94 cm	1.40 (0.90-2.20)		
		134/				per 10 cm	1.15 (0.97-1.36)		

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Missing data derived for analyses
		95/			Incidence, rectal cancer, women	≥ 88 vs < 80 cm	1.40 (0.80-2.20)		
		95/				per 10 cm	1.10 (0.93-1.30)		
MacInnis, 2004 COL00373 Australia	MCCS, Prospective Cohort, Age: 27-75 years, M	153/ 16 566 145 433 years	Cancer registry, medical records	Measured	Incidence, colon cancer	per 10 cm	1.37 (1.18-1.60)	Age, country of birth, educational level (main potential confounders tested and not retained in the final models)	
						≥ 99.3vs < 87 cm	2.1 (1.3-3.5)		
		70/			Incidence, proximal colon cancer	per 10 cm	1.24 (0.99-1.56)		
		78/			Incidence, distal colon cancer	per 10 cm	1.46 (1.18-1.80)		
Moore, 2004 COL00362	FRAM, Prospective Cohort, Age: 30-79 years, M/W, members of original Framingham study	157/			Incidence, colon cancer, age: 30-54 yrs	x-large vs small	2.00 (1.1-3.7)	Age, sex, alcohol consumption, educational level, height, physical activity, smoking habits	
		149/			Incidence, colon cancer, age: 55-79 yrs		2.6 (1.3-5.2)		
		71/			Incidence, colon cancer, men age: 30-54 yrs		2.4 (0.99-5.7)		
		69/			Incidence, colon		3.3 (1.3-8.8)		

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Missing data derived for analyses
					cancer, men age: 55-79 yrs				
		86/			Incidence, colon cancer, women age: 30-54 yrs		1.8 (0.78-4.3)		
		80/			Incidence, colon cancer, women age: 55-79 yrs		2.3 (0.86-6.3)		
		157/			Incidence, colon cancer, age: 30-54 yrs		2.9 (1.2-6.7)	Age, BMI, sex, alcohol consumption, height, educational level, height, physical activity, smoking habits	
		149/			Incidence, colon cancer, age: 55-79 yrs		2.4 (1.00-5.6)		
Folsom, 2000 COL01688 USA	IWHS, Prospective Cohort, Age: 55-69 years, W	462/ 31 702 10 years	SEER		Incidence, colon cancer	≥ 96 vs < 74.4 cm	1.60 (1.20-2.20)	Age, age at first child birth, alcohol consumption, educational level, energy intake, oestrogen use, fish intake, fruit intake, pack-	Mid-point categories Person-years of follow up

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Missing data derived for analyses
								years of cigarette smoking, physical activity, red meat intake, smoking status, vegetable intake, vitamin use, whole grain intake	
Giovannucci, 1995 COL00110 USA	HPFS, Prospective Cohort, Age: 40-75 years, M	117/ 31 055 6 years	Medical records, national Death Index		Incidence, colon cancer, 65% who completed 1987 questionnaire	≥43 vs ≤34.9 inch	2.56 (1.33-4.96) Ptrend:<0.0001	Age, alcohol consumption, aspirin use, dietary fibre intake, energy intake, family history of specific cancer, folate intake, history endoscopic screening, methionine intake, physical activity, previous polyp diagnosis, red	Inch converted to cm Mid-point categories

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Missing data derived for analyses
								meat intake, smoking habits	

Table 333 Waist circumference and colorectal cancer risk. Main characteristics of studies excluded from the CUP SLR dose-response meta-analysis

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Reasons for exclusion
Heo, 2015 COL41057 USA USA	WHI, Prospective Cohort, Age: 50-79 years, W	1 904/ 144 701 12 years	Self-report verified by medical record and pathology report	Measured	Incidence, colorectal cancer	per 1 z-score	1.18 (1.12-1.23)	Age, alcohol, aspirin use, diabetes, educational level, ethnicity, family history of colorectal cancer, folate intake, height, hormone use, physical activity, randomisation, red meat intake, smoking	z-scores reported
		1 904/			Incidence, colorectal cancer	≥ 87 vs < 87 cm	1.20 (1.08-1.32)		
		1 516/			Incidence, colon cancer	per 1 score	1.19 (1.12-1.26)		
		1 516/			Incidence, colon cancer	≥ 76 vs < 76 cm	1.27 (1.13-1.43)		
		257/			Incidence, rectal cancer	per 1 score	1.06 (0.93-1.22)		
		257/			Incidence, rectal cancer	per 1 score	1.06 (0.93-1.21)		
Kabat, 2015 COL41034 USA	WHI, Prospective Cohort,	1 908/ 143 901 12.7 years	Self-report verified by medical record	Weight, height, and waist and hip	Incidence, colorectal cancer, never	Q 5 vs Q 1	2.50 (1.73-3.63) Ptrend:<0.0001	Age, alcohol, aspirin use, diabetes,	No range of categories

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Reasons for exclusion
	Age: 50-79 years, W		and pathology report	circumferences measured	HRT users			educational level, ethnicity, family history of colon cancer, HRT use, met-hours per week, smoking, treatment allocation	
					Incidence, colorectal cancer	Q 5 vs Q 1	1.74 (1.48-2.05) Ptrend:<0.0001	Age, BMI, alcohol, aspirin use, diabetes, educational level, ethnicity, family history of colon cancer, HRT use, met-hours per week, smoking, treatment allocation	
					Incidence, colorectal cancer, ever used HRT	Q 5 vs Q 1	2.39 (1.64-3.49) Ptrend:<0.0001	Age, alcohol, aspirin use, diabetes, educational level, ethnicity, family history of colon cancer,	
					Incidence, colorectal	Q 2 vs Q 1	1.58 (1.26-1.97)		

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Reasons for exclusion
					cancer, HRT never			HRT use, met-hours per week, smoking, treatment allocation	
Brändstedt, 2014 COL41022 Sweden	MDCS, Prospective Cohort, Age: 44-74 years, M/W	422/ 28 098 18 years	Cancer registry		Incidence, colorectal cancer, braf negative	≥ 101 vs ≤ 95 cm	1.60 (1.18-2.16) Ptrend:0.001	Age, sex, alcohol, educational level, smoking	Gene-mutation data
		314/			Incidence, colorectal cancer, kras negative		1.29 (0.91-1.83) Ptrend:0.120		
		179/			Incidence, colorectal cancer, kras positive	≥ 101 vs ≤ 95 cm	1.98 (1.20-3.28) Ptrend:0.004		
Simons, 2014 COL41029 Netherlands	NLCS, Case Cohort, Age: 55-69 years	188/	Cancer registry		Incidence, colorectal cancer, Igfbp 2 genes methylated	> median vs < median	1.22 (0.84-1.75)	Age, sex, BMI, non-occupational physical activity	Gene-methylation data
		169/			Incidence, colorectal cancer, Igfbp 1 gene methylated		1.25 (0.86-1.82)		

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Reasons for exclusion
		112/			Incidence, colorectal cancer, Igfbp 3 genes methylated		1.26 (0.78-2.04)		
		104/			Incidence, colorectal cancer, Igfbp 0 genes methylated		0.91 (0.57-1.43)		
Parekh, 2013 COL40991 USA	FHS-Offspring Cohort, Prospective Cohort, Age: 20- years, M/W	93/ 4 615 37 years	Death certificate and medical records	Waist circumference was measured by trained personnel	Incidence, colon cancer	substantially increased risk vs normal	1.08 (0.50-2.35)	Age, sex, alcohol, BMI, smoking status	Used in HvsL analysis only
Hartz, 2012 COL40901 USA	WHI, Prospective Cohort, Age: 50-79 years, W	1 181/ 141 652 8 years	Self-reported verified by medical record	Measured	Incidence, colon cancer	per 1 SD units	1.28	Age, alcohol, BMI, educational level, Income, physical activity, race, region, smoking, treatment allocation	Superseded by Kabat, 2012 COL40898
Hughes, 2012 COL40943	NLCS, Case Cohort,	541/ 4 654	Cancer registry and pathology		Incidence, colorectal	Q 4 vs Q 1	1.59 (1.23-2.06) Ptrend:0.009	Sex, ethnicity	Gene-interaction data

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Reasons for exclusion
Netherlands	Age: 55-69 years, M/W	7.3 years	database		cancer, braf wildtype				
Hughes, 2012 COL40944 Australia	MCCS, Prospective Cohort, Age: 27-75 years, M/W	480/ 40 154	Cancer registry and National Death index	.	Incidence, colorectal cancer, braf wildtype	Q 4 vs Q 1	1.66 (1.27-2.18) Ptrend:<0.001	Sex, ethnicity	Gene-interaction data
Aleksandrova, 2011 COL40878 Denmark, France, Germany, Greece, Italy, Netherlands, Spain, Sweden, UK	EPIC, Nested Case Control, Age: 25-70 years, M/W	438 case/ 364 controls 9.3 years	Cancer registry and pathology register		Incidence, colon cancer	high vs low (by criteria of International Diabetes Federation (IDF))	1.68 (1.31-2.15)	Alcohol, educational level, fibre, matching variables, physical activity, smoking	Pischon, 2006 COL01985 Used instead
		231 cases/ 175 controls			Incidence, colon cancer	high vs low (by criteria of National Cholesterol Education Program/Adult Treatment Panel III (NCEP/ATPIII))	1.55 (1.19-2.02)		
		239 cases/ 231 controls			Incidence, rectal cancer	high vs low (by criteria of IDF)	1.07 (0.79-1.45)		

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Reasons for exclusion
		127 cases/ 105 controls			Incidence, rectal cancer	high vs low (by criteria of (NCEP/ATPIII))	1.34 (0.96-1.87)		
Hughes, 2011 COL40895 Netherlands	NLCS, Prospective Cohort, Age: 55-69 years, M/W	1 211/ 120 852 16.3 years	Cancer registry	Self-reported height and weight	Incidence, colorectal cancer, men	56-68 vs 28-48 trouser/skirt size	1.63 (1.17-2.29) Ptrend:0.02	Age, alcohol consumption, educational level, energy intake, family history of colorectal cancer, occupational activity, smoking	The exposure is rouser/skirt size
Gunter, 2008 COL40737 USA	WHI, Case-cohort study, Age:50-79 years W	438 cases/ 805 controls 6.42 years	Colonoscopy examination	Examined at baseline	Incidence, colorectal cancer	< 75 vs ≥ 93 Kg/m²	1.82 (1.22-2.7)	Age, smoking status, ethnicity, family history of colorectal cancer, previous endoscopic screening, physical activity, NSAID use, alcohol consumption	Superseded by Kabat, 2013 COL40965

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Reasons for exclusion
Ahmed, 2006 COL40617 USA	ARIC, Prospective Cohort, Age: 45-64 years, M/W	194/ 14 109 11.5 years	Cancer registry & hospital surveillance	waist and hip were measured once using anthropometric tape	Incidence, colorectal cancer	high vs low	1.40 (1.00-1.90)	Age, sex, alcohol consumption, aspirin use, family history of colorectal cancer, HRT use, NSAID use, pack-years of smoking, physical activity	Used in HvsL analysis
Schoen, 1999 COL00183 USA	Cardiovascular Health Study, Prospective Cohort, Age: > 65 years, M/W	102/ 5849	Medical enrolment list		Incidence, colorectal cancer	Q4 vs Q1	2.2 (1.2-4.1)	Age, sex, physical activity	Sex-specific quintiles Used in HvsL analysis
Martínez, 1997 COL00139 USA	NHS, Prospective Cohort, Age: 30-55 years, W	/ 89 448 1 012 375 person-years	Cancer registry	Self-reported	Incidence, colon cancer	> 34 vs < 27.5 inch	1.48 (1.89-2.46)	Age, alcohol consumption, cigarette smoking, family history of specific cancer, aspirin use, postmenopausal hormone use,	Used in HvsL analysis

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Reasons for exclusion
								red meat intake	

Figure 546 RR estimates of colorectal cancer by levels of waist circumference

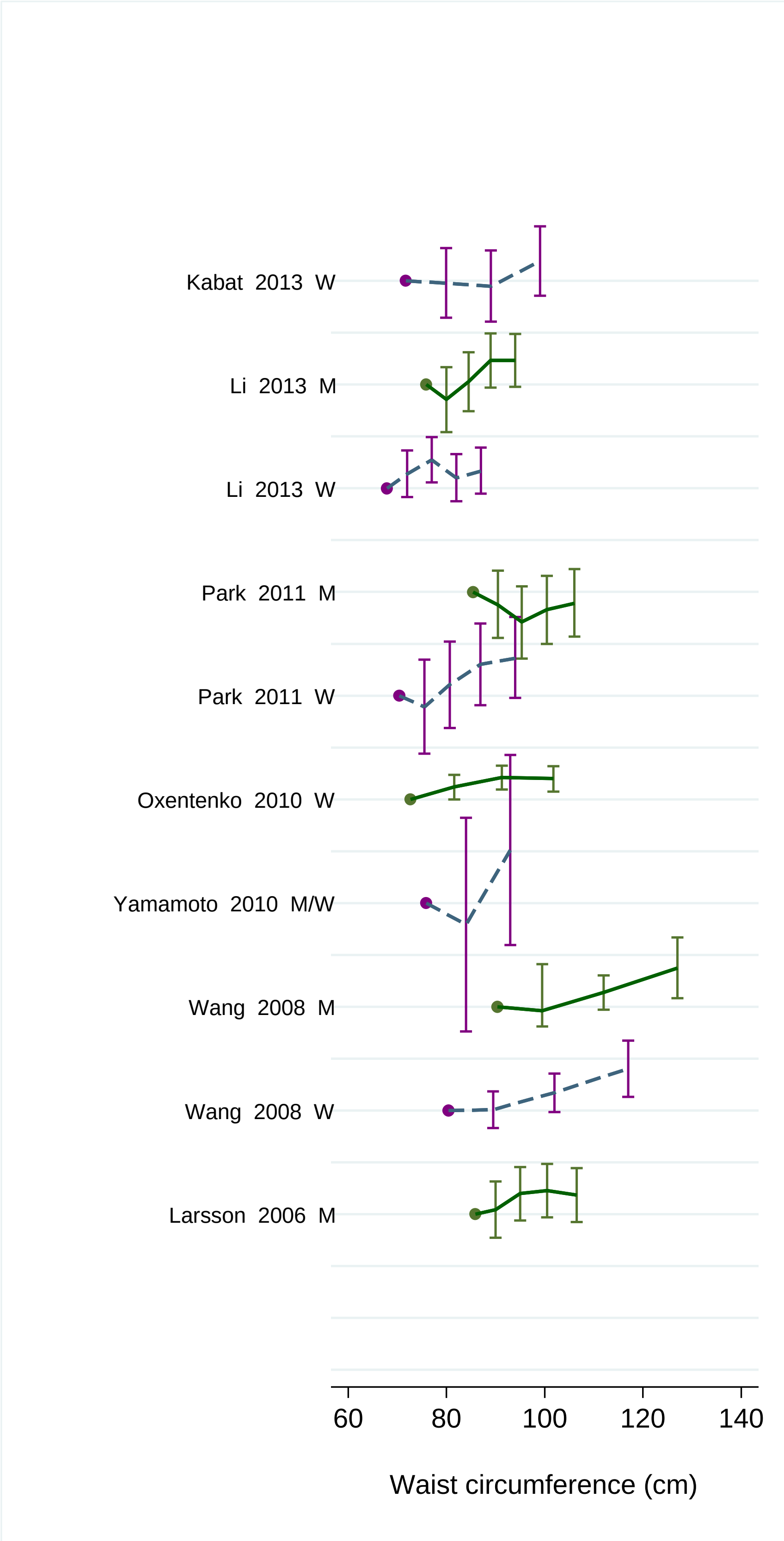


Figure 547 RR (95% CI) of colorectal cancer for the highest compared with the lowest level of waist circumference

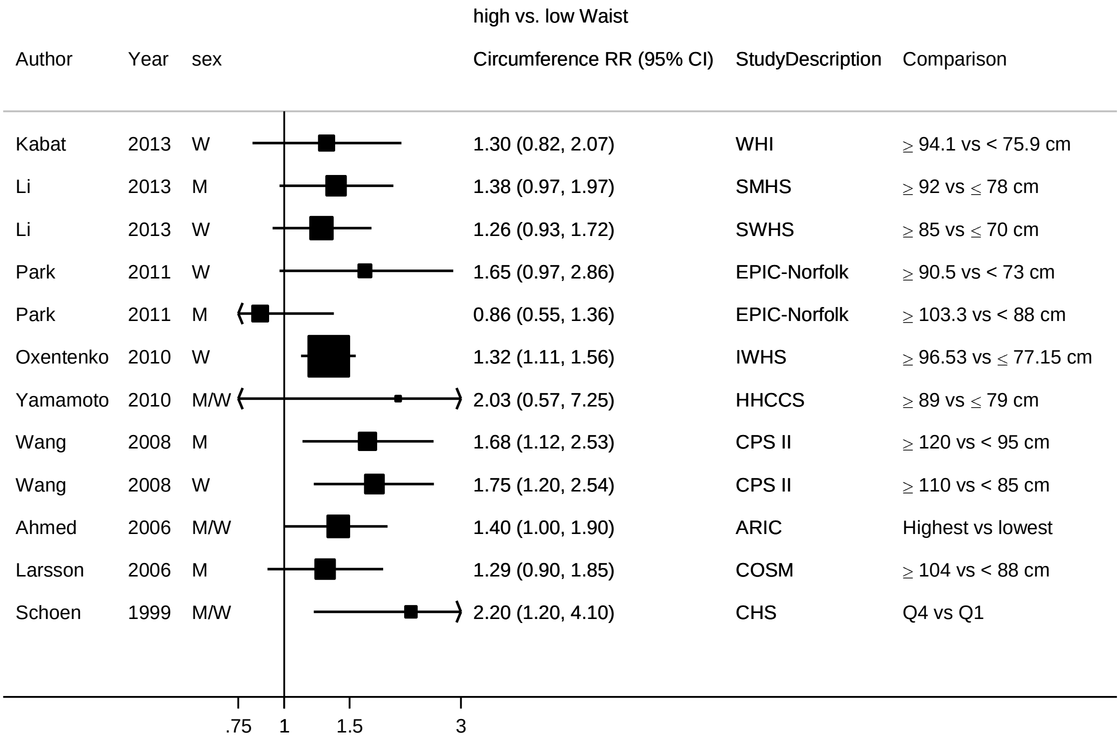


Figure 548 RR (95% CI) of colorectal cancer for 10 cm increase of waist circumference

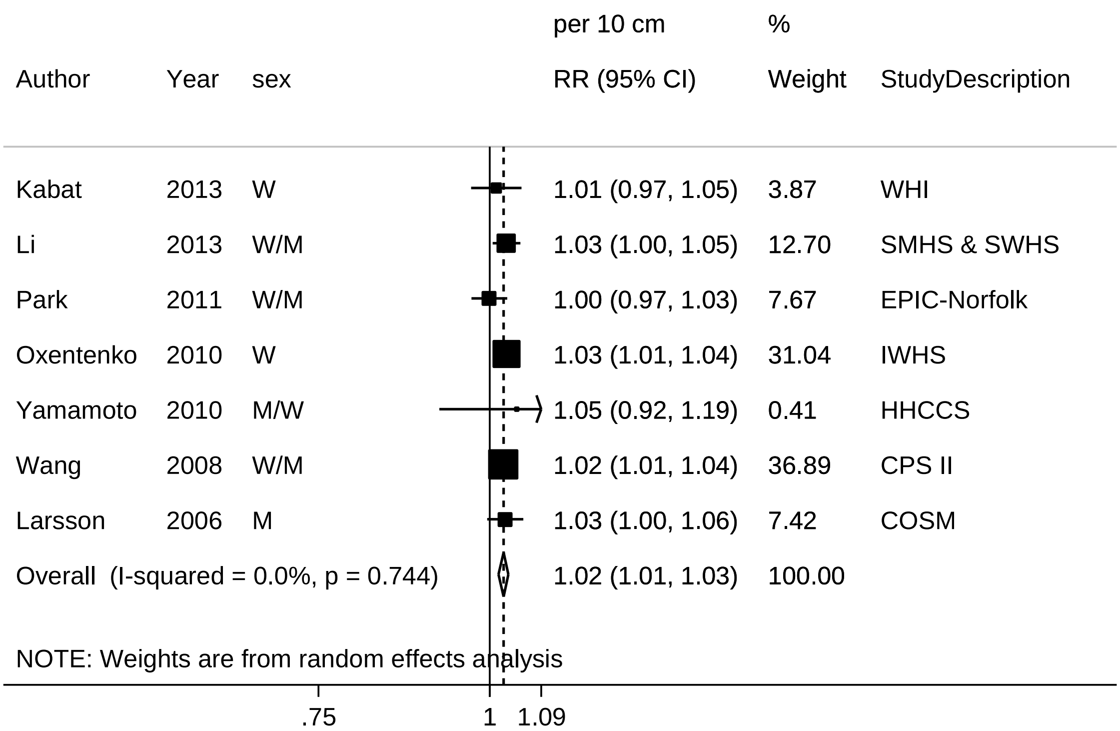
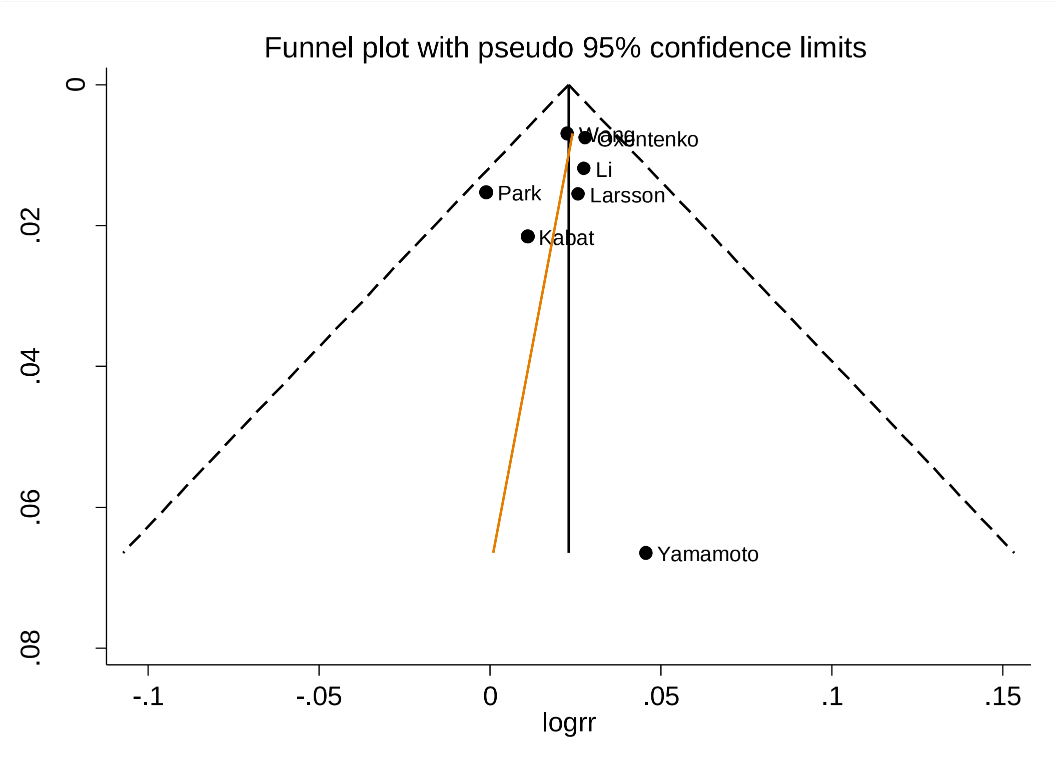


Figure 549 Funnel plot of studies included in the dose response meta-analysis of waist circumference and colorectal cancer



p for Egger's test=0.45

Figure 550 RR (95% CI) of colorectal cancer for 10 cm increase of waist circumference by sex

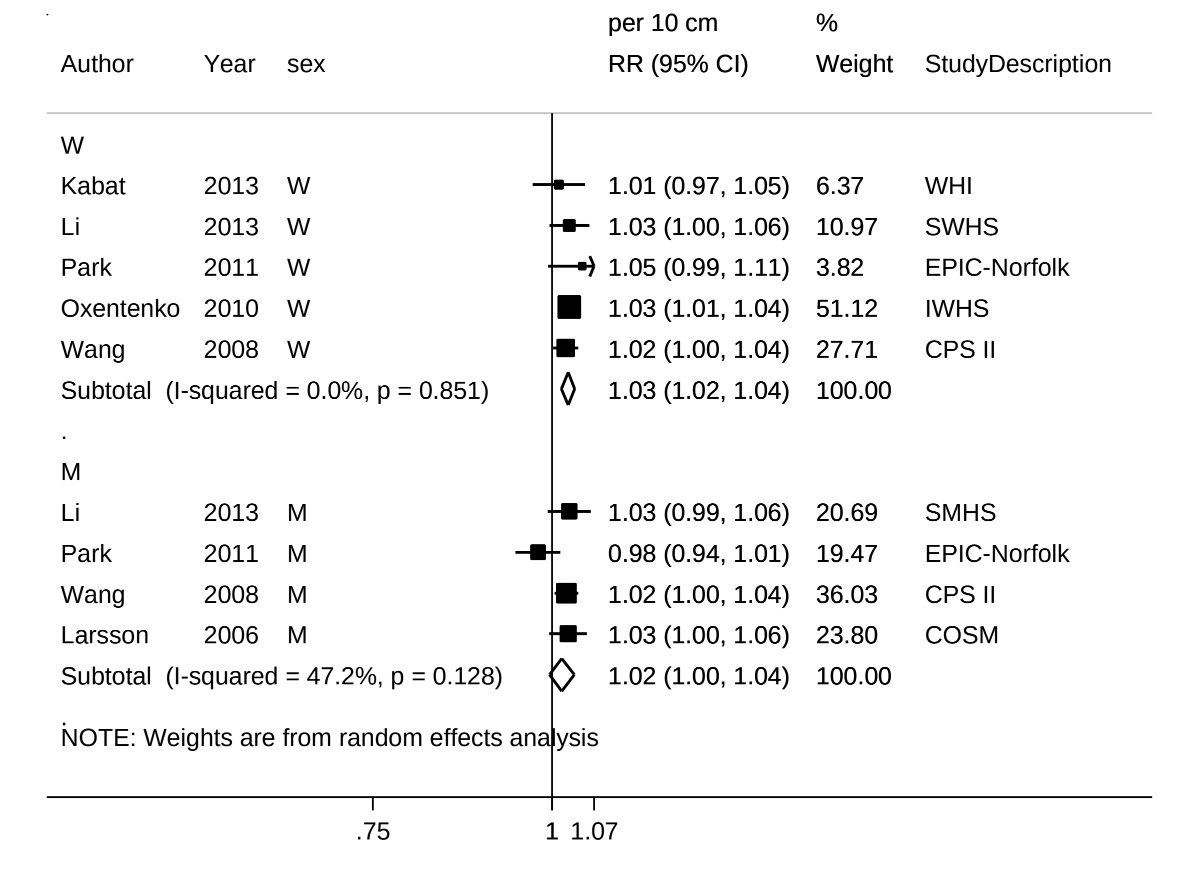


Figure 551 RR (95% CI) of colorectal cancer for 10 cm increase of waist circumference by geographical location

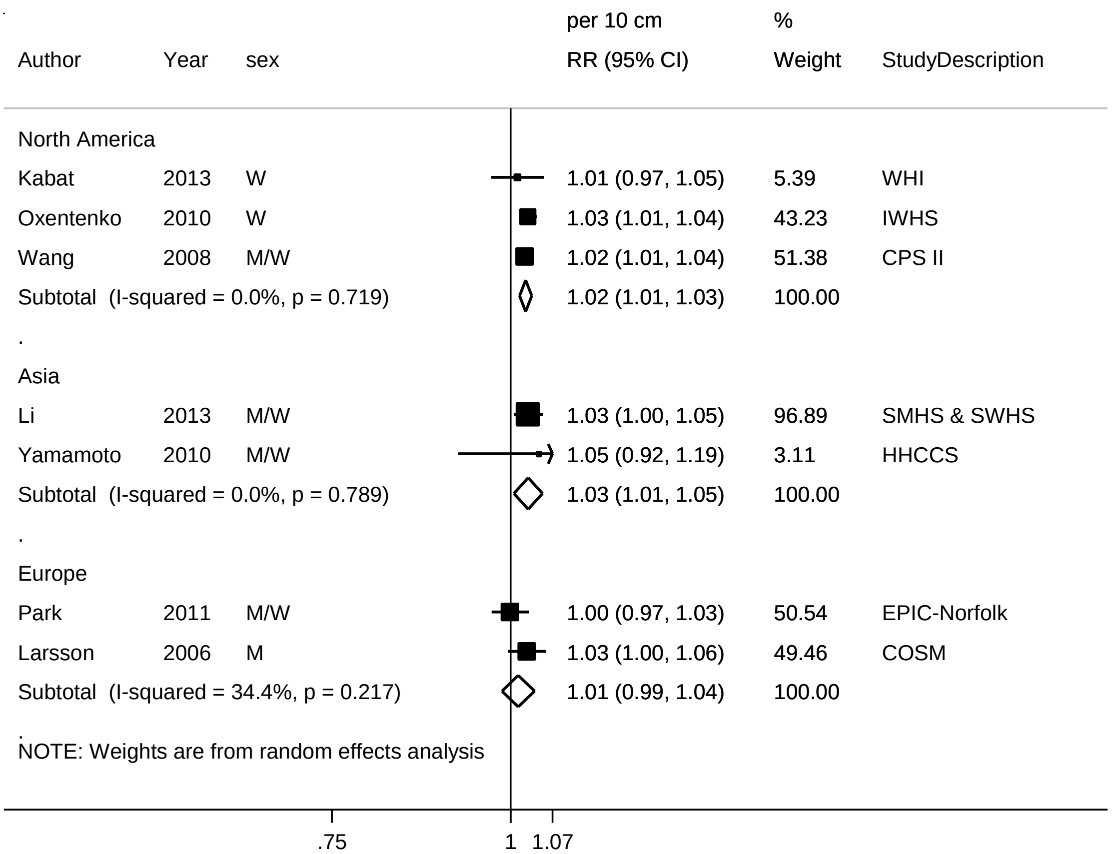


Figure 552 RR estimates of colon cancer by levels of waist circumference

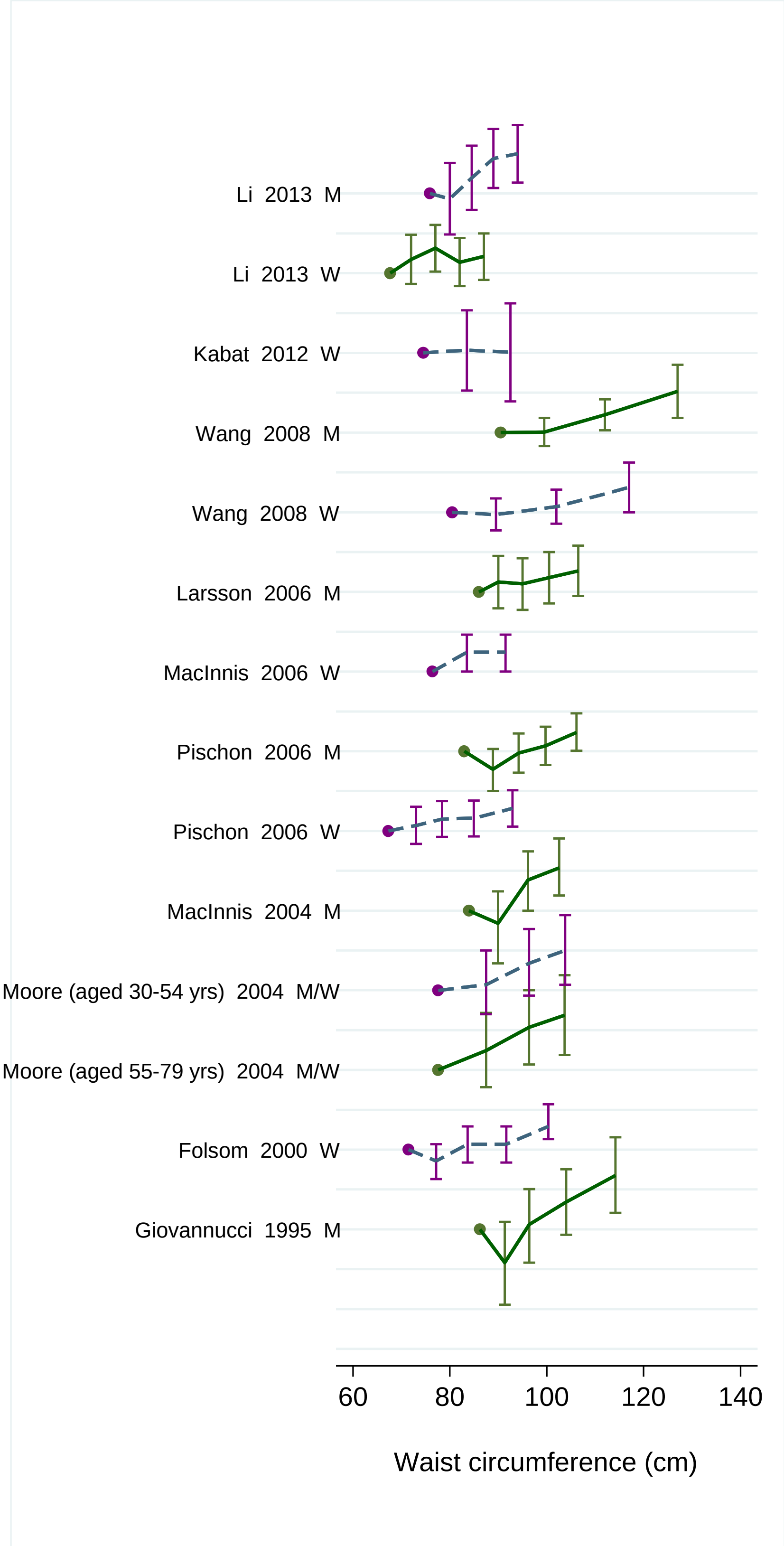


Figure 553 RR (95% CI) of colon cancer for the highest compared with the lowest level of waist circumference

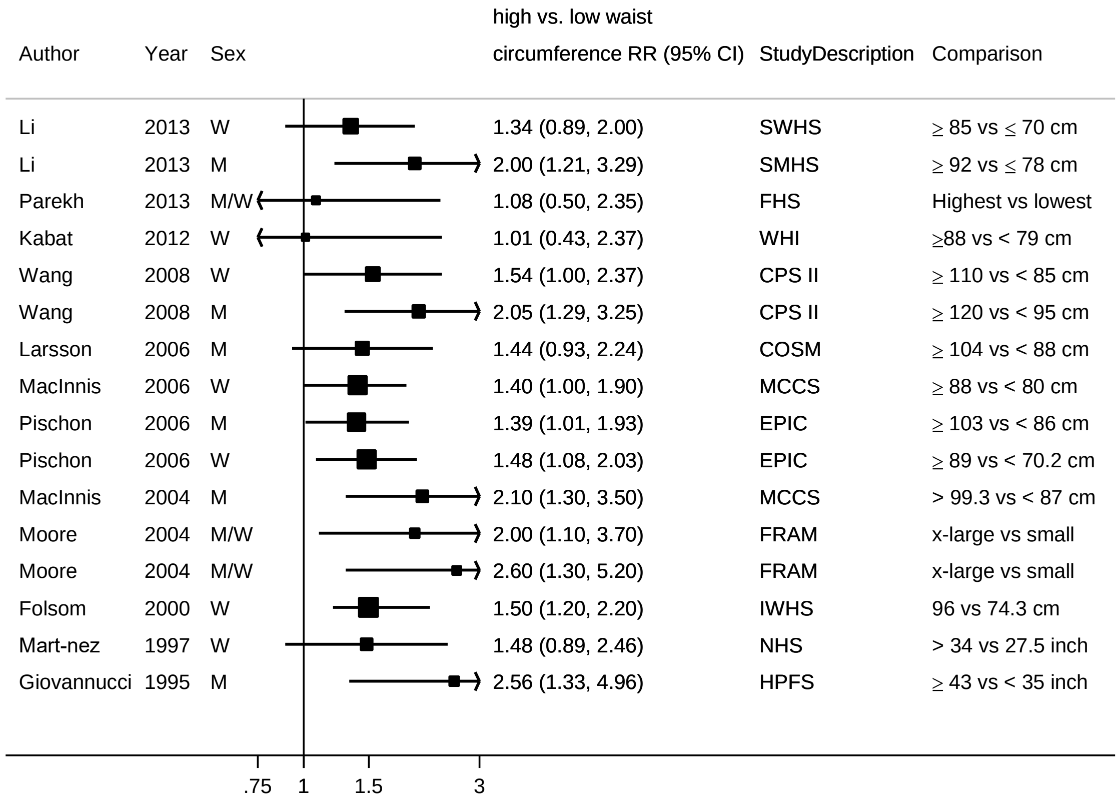


Figure 554 RR (95% CI) of colon cancer for 10 cm increase of waist circumference

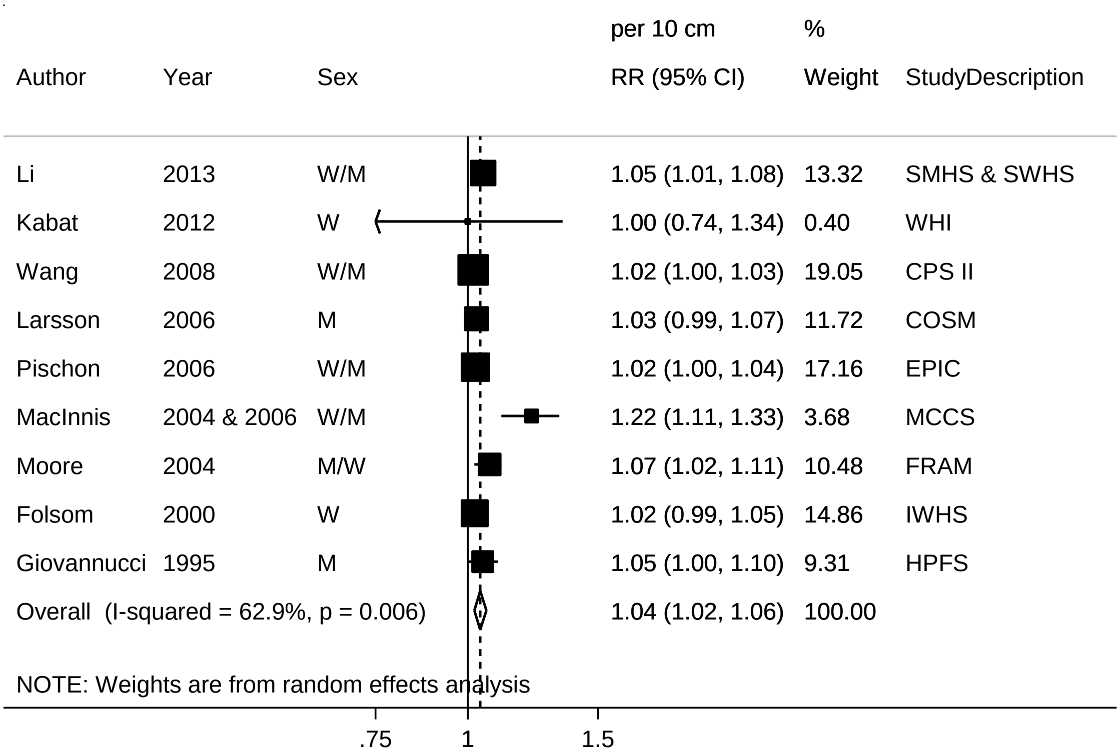
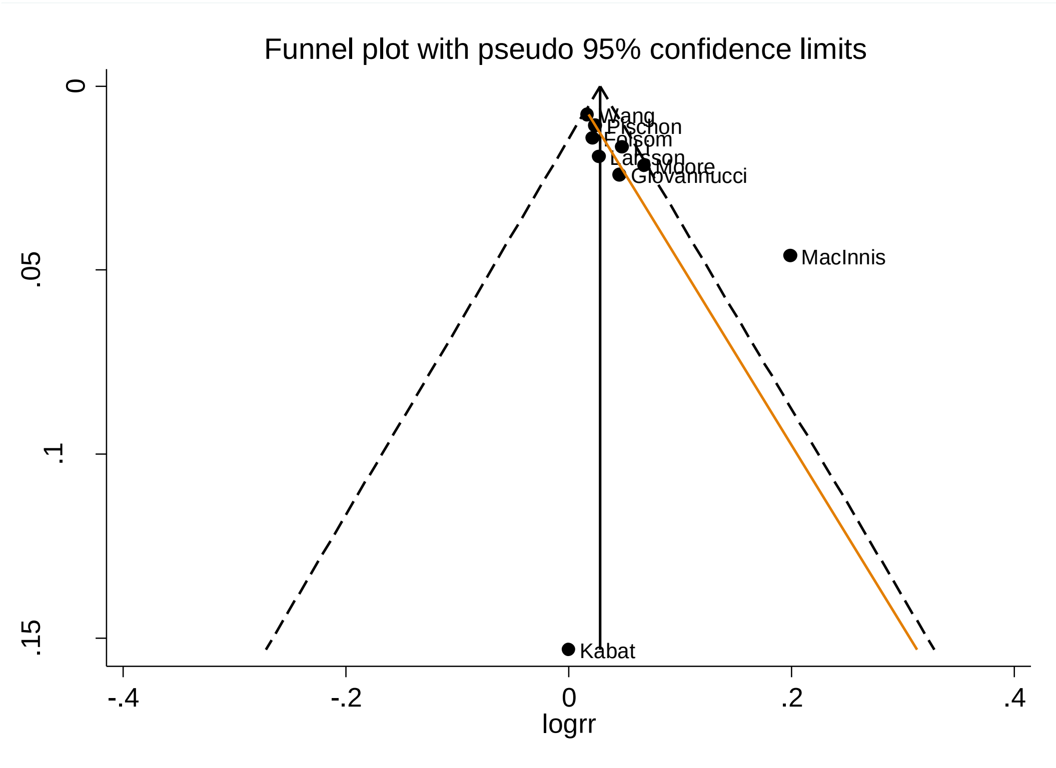


Figure 555 Funnel plot of studies included in the dose response meta-analysis of waist circumference and colon cancer



P value for Egger's test=<0.01

Figure 556 RR (95% CI) of colon cancer for 10 cm increase of waist circumference by sex

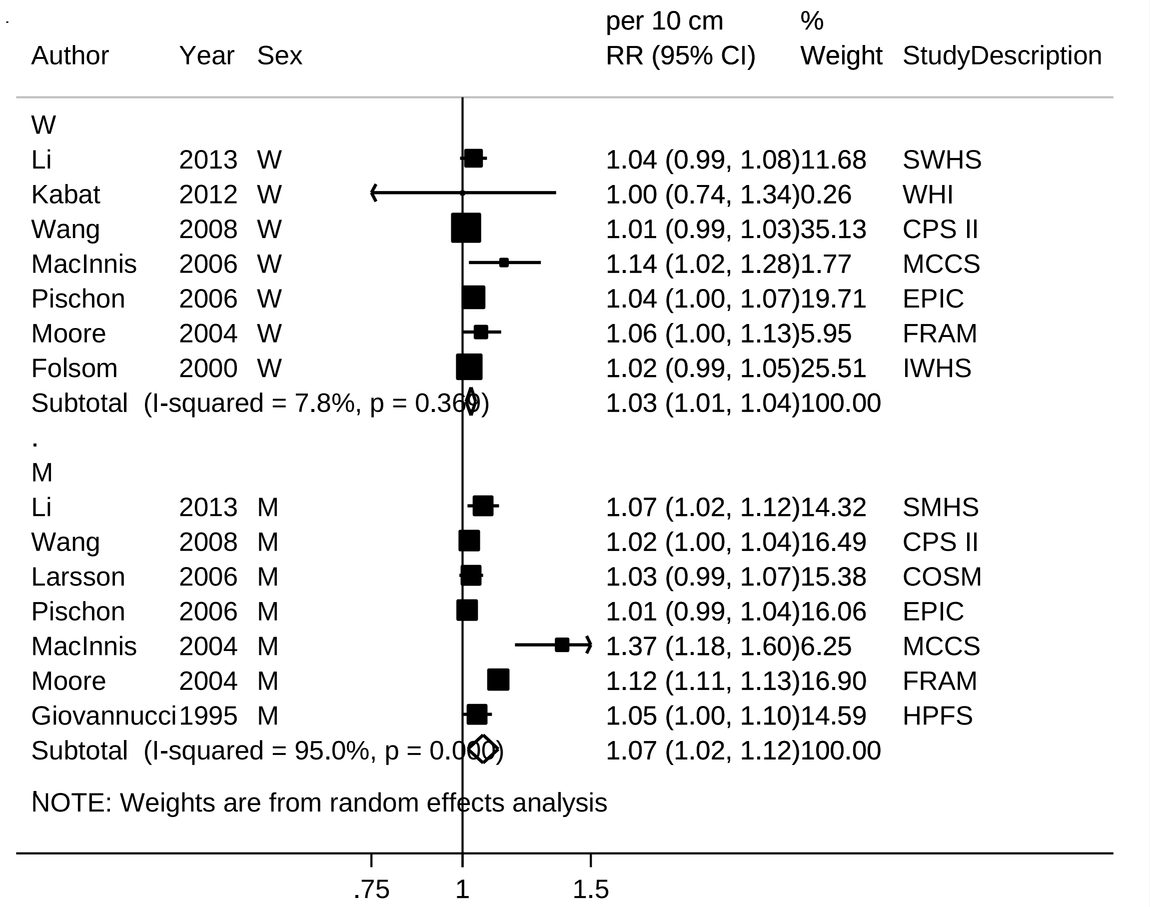


Figure 557 RR (95% CI) of colon cancer for 10 cm increase of waist circumference by geographical location

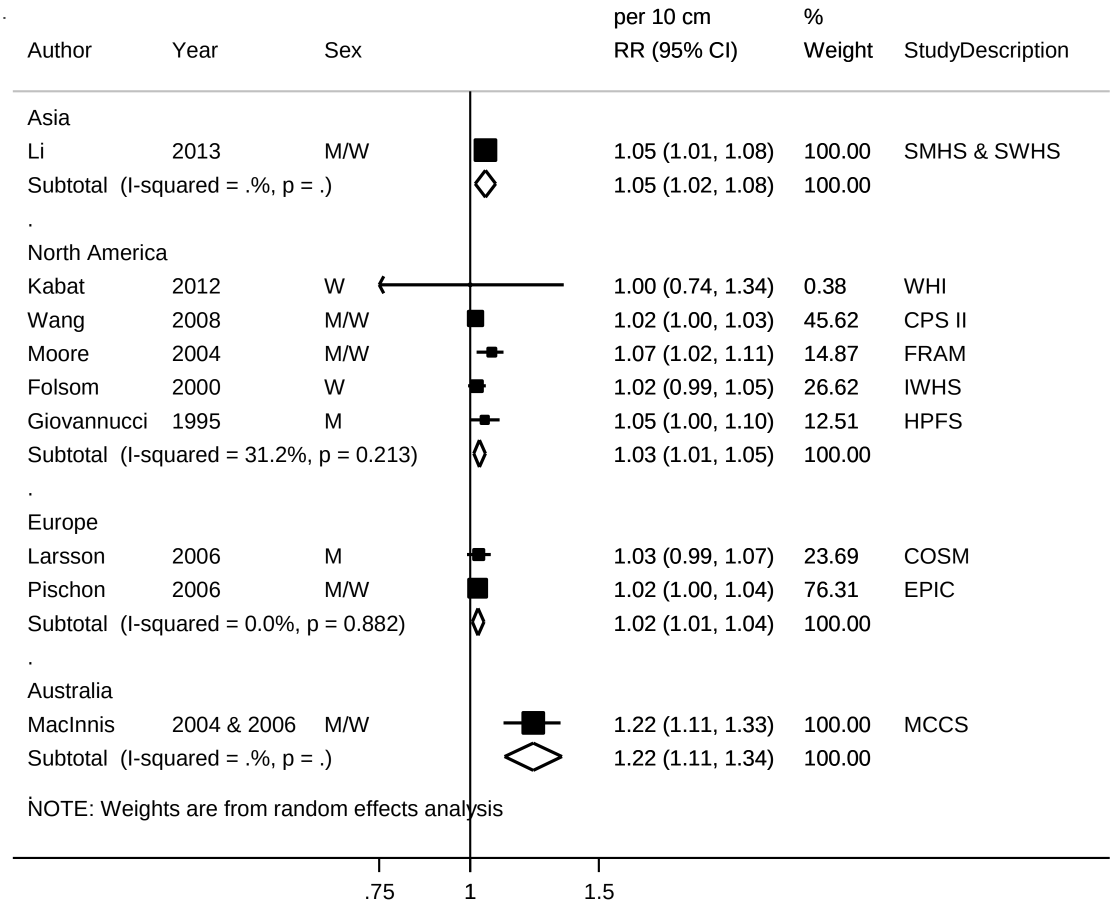


Figure 558 RR (95% CI) of proximal colon cancer for the highest compared with the lowest level of waist circumference

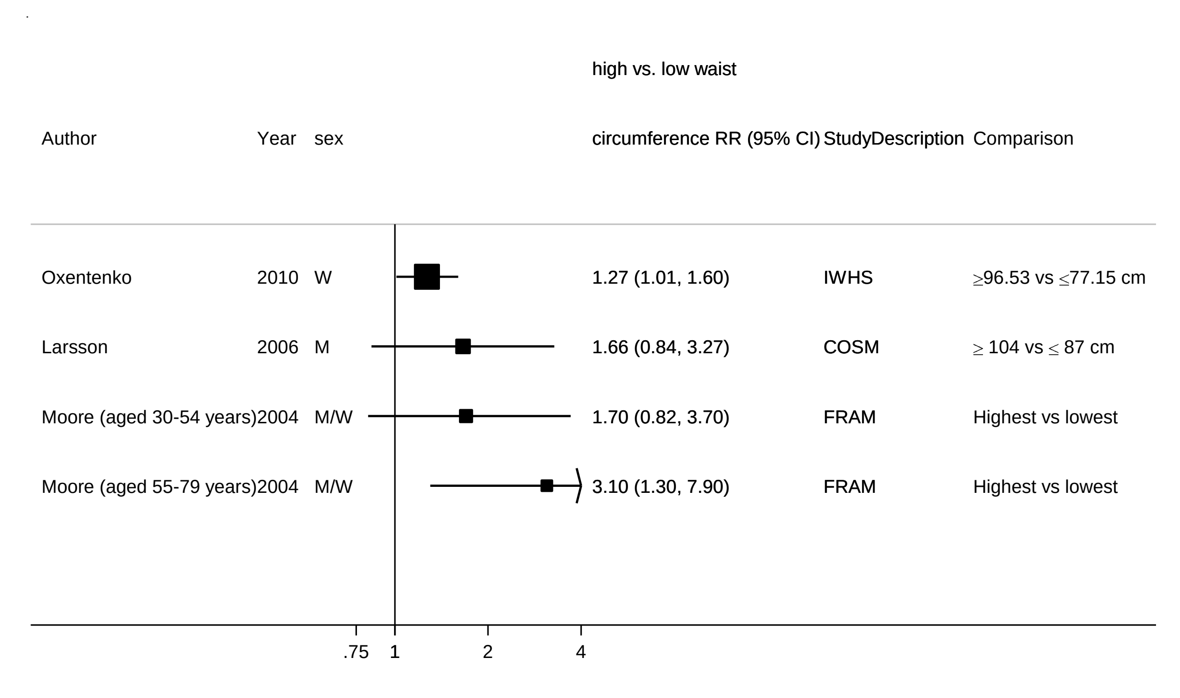


Figure 559 RR estimates of rectal cancer by levels of waist circumference

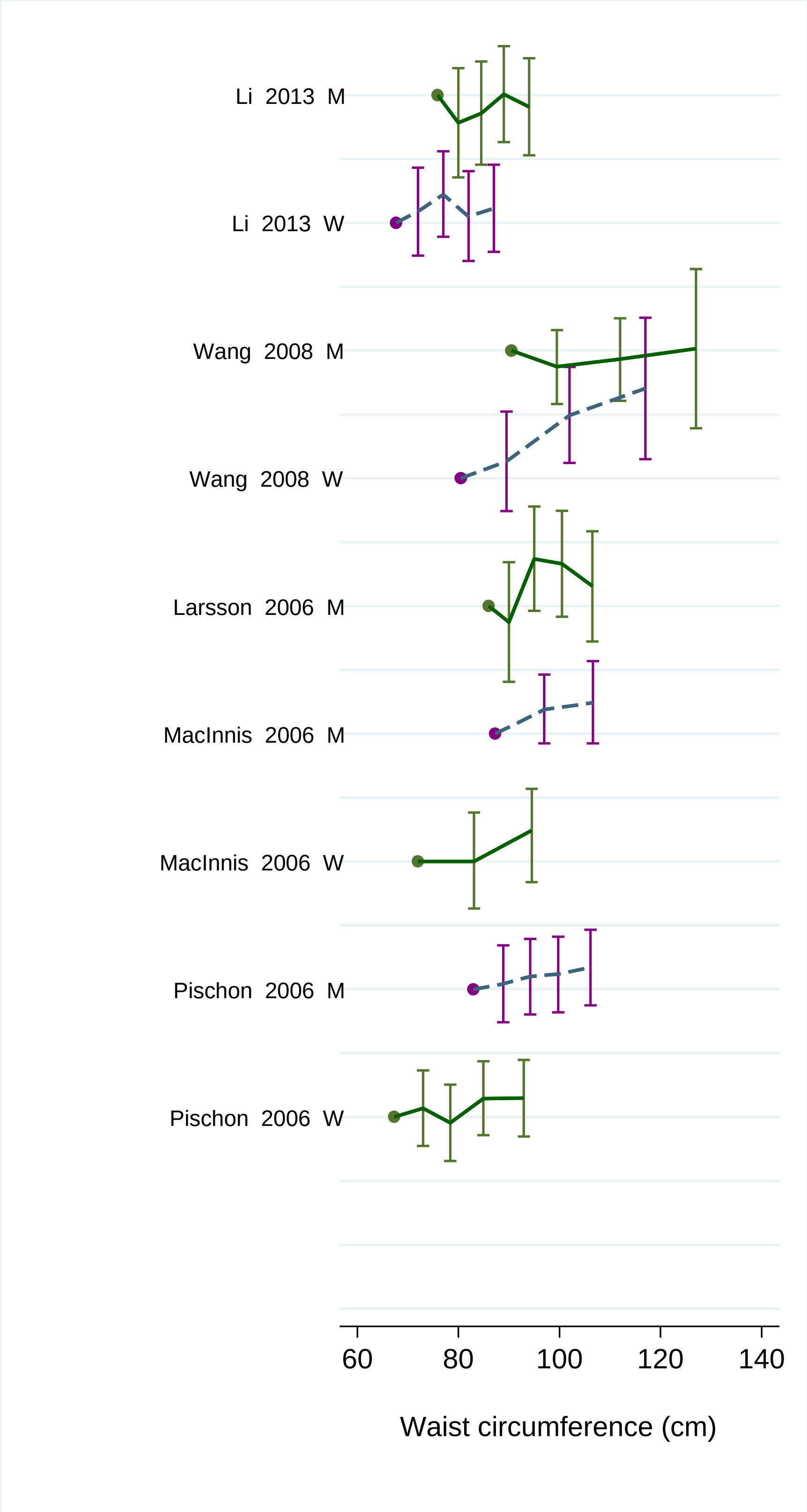


Figure 560 RR (95% CI) of rectal cancer for the highest compared with the lowest level of waist circumference

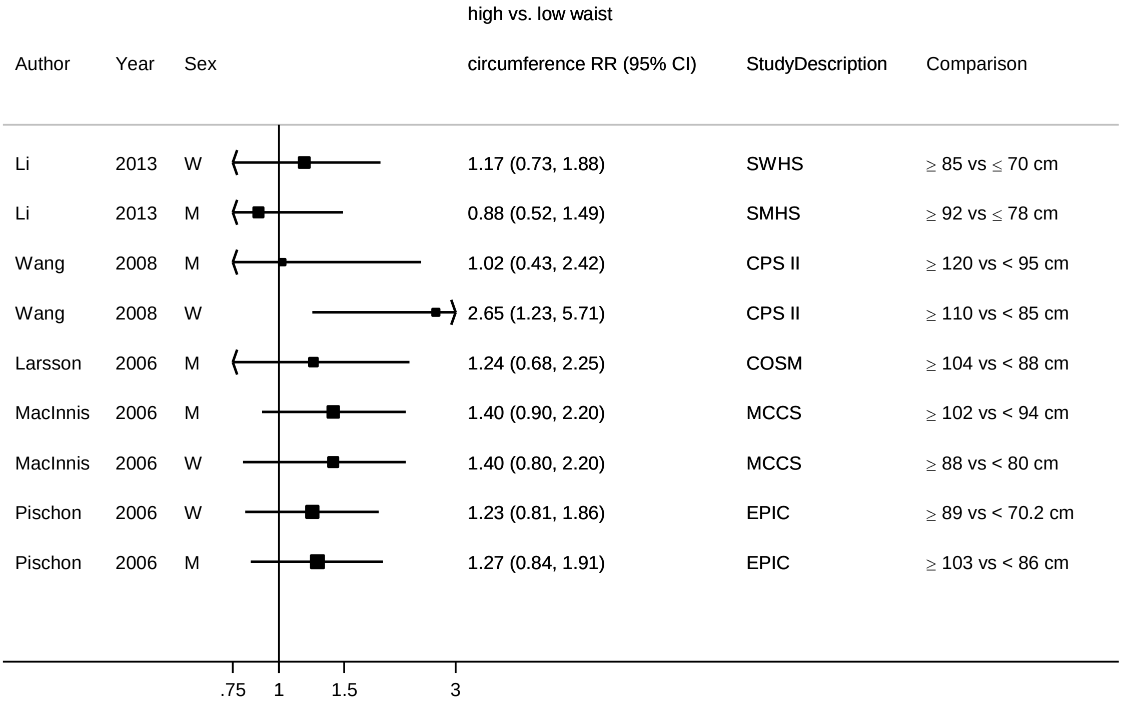


Figure 561 RR (95% CI) of rectal cancer for 10 cm increase of waist circumference

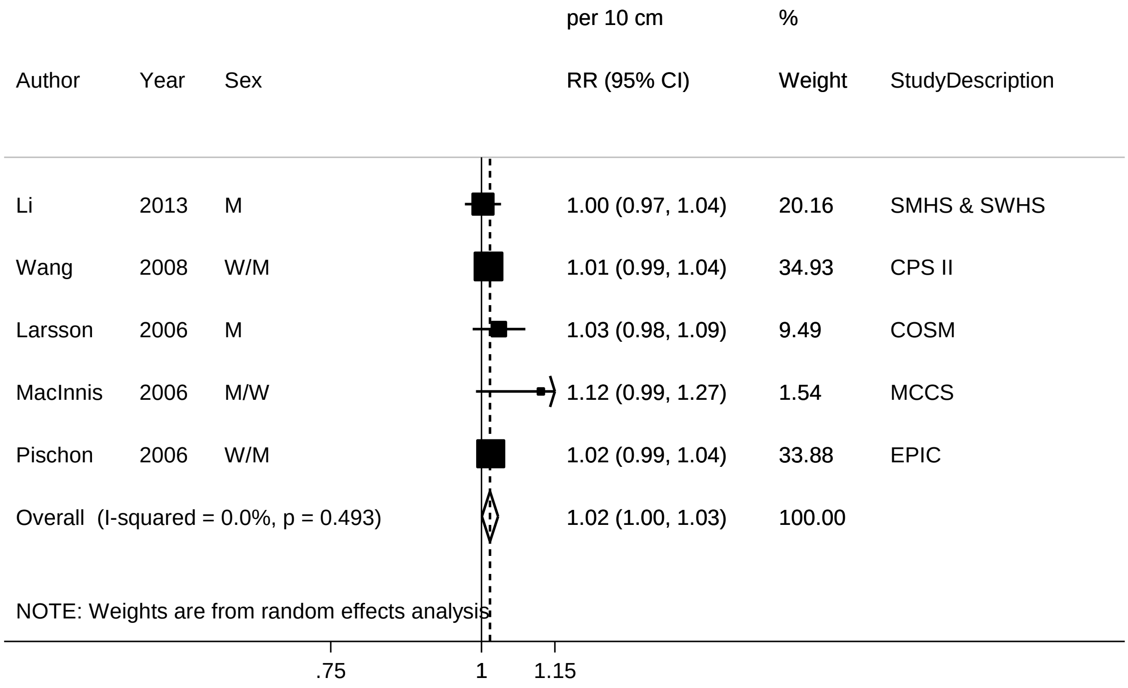
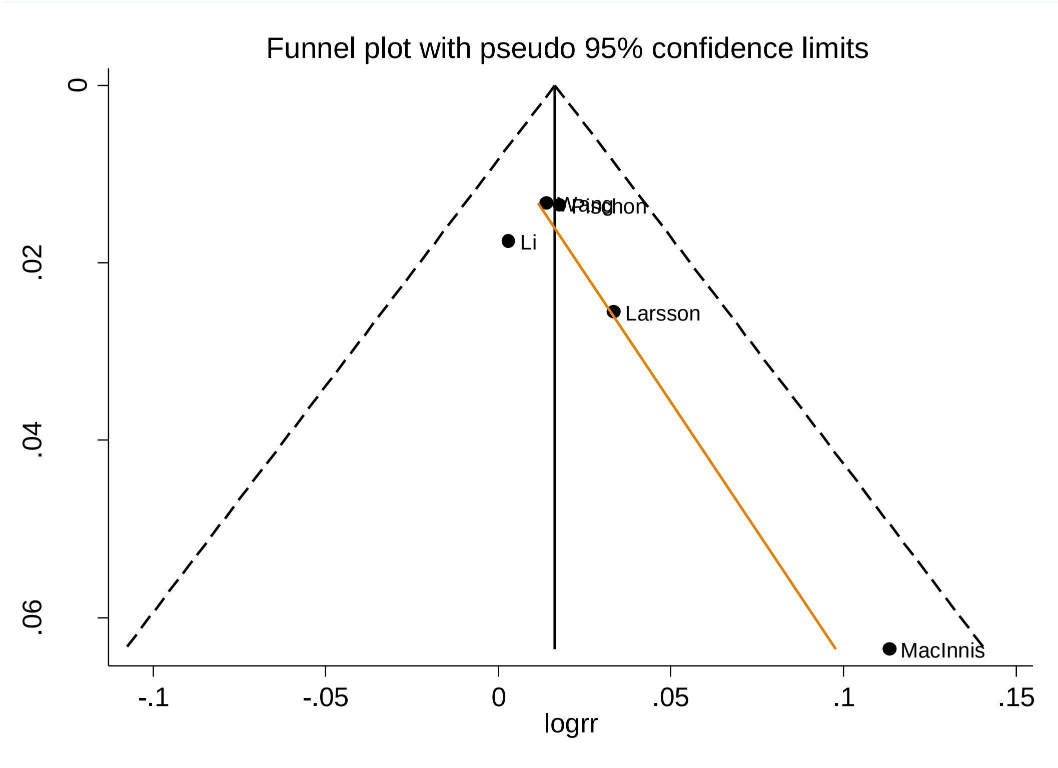
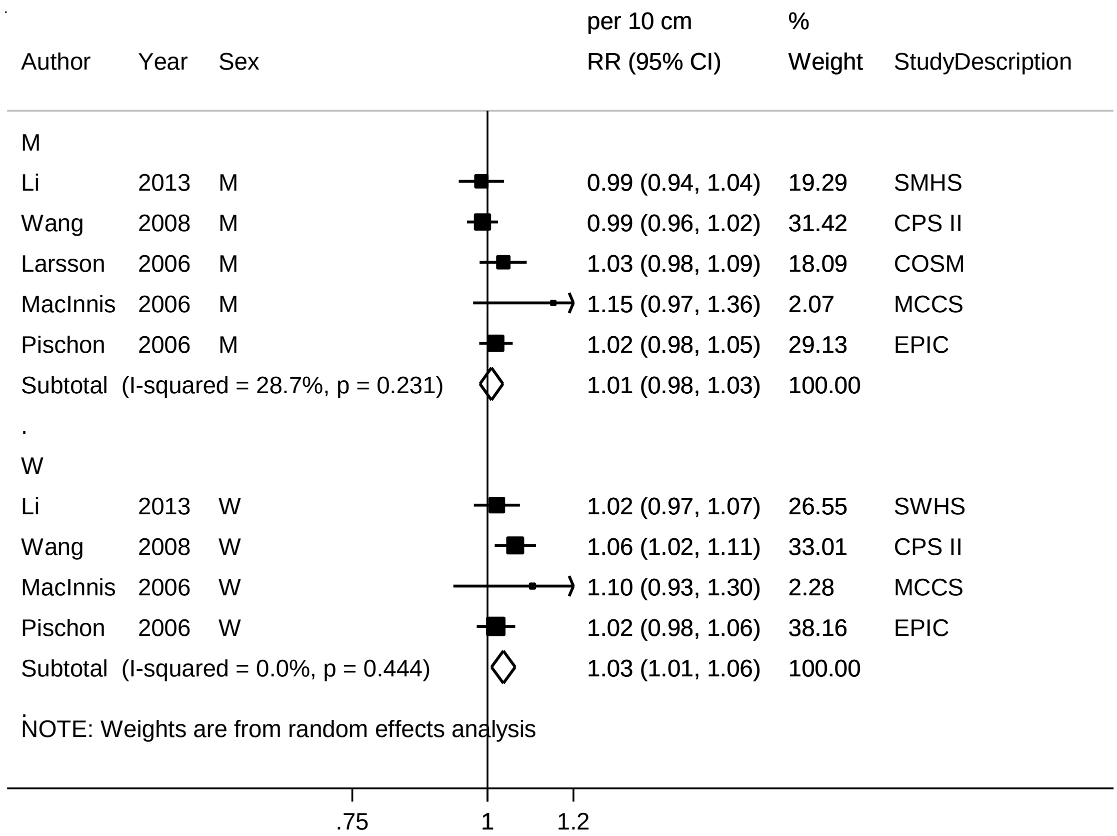


Figure 562 Funnel plot of studies included in the dose response meta-analysis of waist circumference and rectal cancer



p for Egger’s test=0.70

Figure 563 RR (95% CI) of rectal cancer for 10 cm increase of waist circumference by sex



8.2.3 Waist to hip ratio

Cohort studies

Summary

Five new studies (8 publications) were identified after the SLR 2010. Overall, eight cohort studies were included in the analyses described below.

Colorectal cancer:
Four studies (2 564 cases), which were all identified after the SLR 2010, were included in the dose-response meta-analysis of waist to hip ratio and colorectal cancer. Three studies were in women and one study in men. A significant association was observed for all studies combined (2% risk increase for 0.1 unit increase of waist to hip ratio).
Low heterogeneity was observed. There was no evidence of publication bias (p=0.56).

Colon cancer:
Seven studies (2 481 cases) were included in the dose-response meta-analysis of waist to hip ratio and colon cancer. A significant association (20% risk increase) with high heterogeneity was observed. The heterogeneity was explained by the lack of association in two Asian studies (Li, 2013). The association was significant in men and borderline significant in women. There was significant statistical evidence of publication bias (p=<0.001). Smaller studies on the left side of the funnel plot appear to be missing.
Only one study (Martinez, 1997) reported results in proximal and distal colon cancer and another study (Oxentenko, 2010) reported on proximal colon and distal colorectal cancer (including rectosigmoid junction and rectum). Similar associations were observed across cancer sites. No dose-response meta-analysis was performed.

Rectal cancer:
Four studies were identified. No dose-response meta-analysis was conducted. Three studies reported positive no significant associations of rectal cancer in men and women or the highest compared to the lowest level of waist to hip ratio. Only one study (EPIC, Pischon, 2006) reported a significant positive association in men but not in women.

Study quality:
Cancer outcome was confirmed using records in cancer registries in most studies. The relative risks estimates in all studies were adjusted for potential confounders and in two studies also adjusted for BMI (Folsom, 2000; Martinez, 1997). In one study (MCCS) the covariates were only age, sex ad country of birth. In five of the cohort studies, waist and hip circumferences were measured and in three, they were self-reported.

Table 334 Waist to hip ratio and colorectal cancer risk. Number of studies in the CUP SLR

	Colorectal	Colon	Rectum
	Number of studies		
Studies identified	6 (10 publications)	9 (12 publications)	4 (3 publications)
Studies included in forest plot of highest compared with lowest exposure	5	8	4
Studies included in dose-response meta-analysis	4	7	NA
Studies included in non-linear dose-response meta-analysis	NA	7	NA

Note: Include cohort, nested case-control and case-cohort designs

Table 335 Waist to hip ratio and colorectal cancer risk. Summary of the dose-response meta-analysis in the 2010 SLR and 2015 SLR.

	2010 SLR	**2015 SLR**
Increment unit used	Per 0.1 unit	Per 0.1 unit
	Colorectal cancer	
Studies (n)	3	4
Cases (total number)	1785	2 564
RR (95%CI)	1.17 (1.09-1.25)	1.02 (1.01-1.04)
Heterogeneity (I^2, p-value)	0%, 0.67	16.8%, 0.307
	Colon cancer	
Studies (n)	6	7
Cases (total number)	2 325	2 481
RR (95%CI)	1.27 (1.15-1.41)	1.20 (1.09-1.32)
Heterogeneity (I^2, p-value)	48.5%,0.08	87.3%, <0.001
	Rectal cancer	
Studies (n)	3	-
Cases (total number)	970	-
RR (95%CI)	1.20 (1.07-1.34)	-
Heterogeneity (I^2, p-value)	0%, 0.72	-

Table 336 Waist to hip ratio and colorectal cancer risk. Main characteristics of studies included in the CUP SLR dose-response meta-analysis

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Missing data derived for analyses
Li, 2013 COL40937 China	SWHS, Prospective Cohort, Age: 40-70 years, W	621/ 72 972 11 years	Follow up survey/cancer registry/vital statistics registry	Measured	Incidence, colorectal cancer	≥0.85 vs ≤0.77	1.01 (0.79-1.31) Ptrend:0.65	Age at baseline, alcohol consumption, cigarette, educational level, energy intake, family history of colorectal cancer, income, menopausal status, physical activity, intakes of red meat, tea, vegetables, fruits	Mid-point categories
		381/			Incidence, colon cancer		0.96 (0.69-1.34) Ptrend:0.92		
		240/			Incidence, rectal cancer		1.11 (0.74-1.66) Ptrend:0.40		
Li, 2013 COL40936 China	SMHS, Prospective Cohort, Age: 40-74 years, M	313/ 61 283 5.5 years	Follow up survey/cancer registry/vital statistics registry	Measured	Incidence, colorectal cancer	≥0.95 vs ≤0.85	1.65 (1.12-2.41) Ptrend:0.0004	Age at baseline, alcohol consumption, cigarette, educational level, energy intake, family history of colorectal cancer, income, physical activity, intakes of red meat, tea, vegetables,fruits	Mid-point categories
		169/			Incidence, colon cancer		1.97 (1.19-3.24) Ptrend:0.0004		
		133/			Incidence, rectal cancer		1.24 (0.69-2.26) Ptrend:0.20		

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Missing data derived for analyses
Kabat, 2013 COL40965 USA	WHI, Prospective Cohort, Age: 50-79 years, W, Postmenopausal	166/ 11 124 12.9 years	Self-report verified by reviewing medical and pathological records by physicians	Measured	Incidence, colorectal cancer	≥0.85 vs ≤0.75	1.18 (0.74-1.90) Ptrend:0.40	Age, alcohol, diabetes, educational level, energy, ethnicity, family history of colorectal cancer, HRT use, pack yrs of smoking, physical activity, randomisation	Mid-point categories
Oxentenko, 2010 COL40849 USA	IWHS, Prospective Cohort, Age: 55-69 years, W	1 464/ 36 941 619 961 person-years	SEER	Self-reported	Incidence, colorectal cancer	≥0.9 vs ≤0.78	1.28 (1.08-1.50) Ptrend:0.003	Age, age at menopause, estrogen use, alcohol, physical activity, smoking status and intensity, diabetes, energy intake, intakes of folate, fruits and vegetables, red meat, total fat, vitamin E,calcium	Mid-point categories
Pischon, 2006 COL01985	EPIC, Prospective Cohort,	416/ 368 277 6.1 years	Population registries	Measured	Incidence, colon, men	≥ 0.990 vs < 0.887	1.51 (1.06 to 2.15) Ptrend:0.006	Age, centre, height, smoking status education alcohol intake physical activity	Mid-categories Person-years of follow up in quintiles
		560/			Incidence,	≥ 0.846 vs <	1.52 (1.12 to		

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Missing data derived for analyses
					colon, women	0.734	2.05) Ptrend:0.002	fibre intake, consumption of red and processed meat , fish and shell fish, fruits and vegetables	
		292/			Incidence, rectal, men	≥ 103 vs < 86	1.93 (1.19 to 3.13) Ptrend:0.16		
		291/			Incidence, rectal, women		1.20 (0.81 to 1.79) Ptrend:0.17		
MacInnis, 2006 COL40751 Australia	MCCS, Prospective Cohort, Age: 27-75 years, W	212/ 24 072 10.4 years	Cancer registry, medical records	Measured	Incidence, colon cancer	Per 0.1 unit increase	1.31 (1.08-1.58)	Country of birth, education level, HRT use	
						≥ 0.80 vs < 0.75	1.7 (1.1-2.4)		
MacInnis, 2006 COL40627 Australia	MCCS, Prospective Cohort, Age: 27-75 years, M/W	229/ 41 114 10.3 person-years	Cancer registry	Measured	Incidence, rectal cancer	Q 3 vs Q 1	1.30 (0.9-1.8)	Age, sex, country of birth	
						Per 0.1 unit	1.24 (1.02-1.51)		
		134/			Incidence, rectal cancer, men	Per 0.1 unit	1.18 (0.90-1.55)		
						Q 3 vs Q 1	1.25 (0.80-1.80)		
		95/			Incidence, rectal cancer, women	Per 0.1 unit	1.31 (1.0-1.72)		
						Q 3 vs Q 1	1.40 (0.80-2.40)		
MacInnis, 2004 COL00373 Australia	MCCS, Prospective Cohort,	153/ 16 566 145 433 years	Cancer registry, medical records	Measured	Incidence, colon cancer	≥0.96 vs <0.88	2.1 (1.30-3.40)	Age, country of birth, educational level	
						Per 0.1 unit	1.78 (1.4-2.24)		

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Missing data derived for analyses
	Age: 27-75 years, M	70/			Incidence, proximal colon cancer		1.51 (1.04–2.17)		
		78/			Incidence, distal colon cancer		1.96 (1.41–2.73)		
Folsom, 2000 COL01688 USA	IWHS, Prospective Cohort, Age: 55-69 years, W	462/ 31 702 10 years	SEER	Self-reported	Incidence, colon cancer	≥0.9 vs ≤0.76	1.00 (0.70-1.40)	Age, BMI, age at first child birth, alcohol consumption, estrogen use, educational level, smoking status, physical activity, pack-years of cigarette, energy intake, intakes of fish, fruit, red meat, vegetables whole grain, vitamin use	Mid-point categories
Martínez, 1997 COL00139 USA	NHS, Prospective Cohort, Age: 30-55 years, W, Registered nurses	161/ 89 448 1 012 375 person-years	Cancer registry	Self-reported	Incidence, colon cancer, 1986-1992 follow-up	≥0.83 vs ≤0.73	1.48 (0.88-2.49) Ptrend:0.16	Age, alcohol consumption, aspirin use, BMI, cigarette smoking, family history of specific cancer, postmenopausal hormone use, red meat intake	Mid-point categories

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Missing data derived for analyses
Giovannucci, 1995 COL00110 USA	HPFS, Prospective Cohort, Age: 40-75 years, M	117/ 31 055 6 years		Self-reported	Incidence, colon cancer, 65% who completed 1987 questionnaire	≥0.99 vs ≤0.89	3.41 (1.52-7.66) Ptrend:0.01	Age, alcohol consumption, aspirin use, dietary fiber intake, energy intake, family history of specific cancer, folate intake, history endoscopic screening, methionine intake, physical activity, previous polyp diagnosis, red meat intake, smoking habits	Mid-point categories

Table 337 Waist to hip ratio and colorectal cancer risk. Main characteristics of studies excluded from the CUP SLR dose-response meta-analysis

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Inclusion/ exclusion reasons
Kabat, 2015 COL41034 USA	WHI, Prospective Cohort, Age: 50-79 years,	1 908/ 143 901 12.7 years	Self-report verified by medical record and pathology report	Measured	Incidence, colorectal cancer		1.65 (1.40-1.93)	Age, alcohol, aspirin use, smoking, HRT use, diabetes, educational level, ethnicity, family history of colorectal	No specific quintile ranges
Heo, 2015 COL41057 USA	WHI, Prospective Cohort, Age: 50-79 years, W Postmenopausal	1 904/ 144 701 12 years	Self-report verified by medical record and pathology report	Measured	Incidence, colorectal cancer	per 1 score	1.12 (1.08-1.16)	Age, alcohol, aspirin use, diabetes, educational level, ethnicity, family history of colorectal cancer, folate intake, height, hormone use, physical activity, randomisation, red meat intake, smoking	Exposure is z-WHR
						≥0.75 vs ≤0.74	1.18 (1.07-1.30)		
Brändstedt, 2014 COL41022 Sweden	MDCS, Prospective Cohort, Age: 44-74 years, M/W	26/ 28 098 18 years	Cancer registry		Incidence, colorectal cancer, men braf mutated	≥0.9 vs ≤0.8	1.20 (0.43-3.34) Ptrend:0.697		Gene interaction data
Hartz, 2012	WHI,	1 181/		Measured	Incidence, colon	per 1 sd units	1.14	Age, alcohol,	No specific

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Inclusion/ exclusion reasons
COL40901 USA	Prospective Cohort, Age: 50-79 years, W, Postmenopausal	141 652 8 years			cancer			BMI, educational level, Income, physical activity, race, region, smoking, treatment allocation	increment
Lee, 2009 COL40764 China	SWHS, Prospective Cohort, Age: 40-70 years, W	394/ 73 224 7.4 years	Cancer registry and death certificates and participant contact		Incidence, colorectal cancer	≥0.84 vs ≤0.77	1.20 (0.90-1.60) Ptrend:0.27	Age, energy intake	Superseded by Li, 2013 COL40937
Gunter, 2008 COL40737 USA	WHI, Case-cohort study, Age:50-79 years	438/ 1 247	Self-reported verified by medical record	Examined at baseline	Incidence, colorectal cancer	0.85 vs 0.74	1.47 (1.04-2.09) Ptrend: 0.01	Age	Superseded by Kabat, 2013 COL40965
Ahmed, 2006 COL40617 USA	ARIC, Prospective Cohort, Age: 45-64 years, M/W	107/ 14 109 11.5 years	Cancer registry & hospital surveillance	Measured	Incidence, colorectal cancer, men	≥1 vs ≤0.92	2.38 (1.30-4.20)		Used in HvsL analysis only
McCarl, 2006 COL40633 USA	IWHS, Prospective Cohort, Age: 55-69 years, W	954/ 35 197 15 years	SEER registry		Incidence, colorectal cancer	≥0.91 vs ≤0.75	1.46 (1.19-1.80)	Age	Superseded by Oxentenko, 2010 COL40849

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Inclusion/ exclusion reasons
Bostick, 1994 COL00079 USA	IWHS, Prospective Cohort, Age: 55-69 years, W	212/ 35 216 167 447 person-years	SEER	Self-reported	Incidence, colon cancer	≥0.91 vs ≤0.76	1.25 (0.83-1.88) Ptrend:0.30	Age, energy intake, height, parity, vitamin a supplement, vitamin e intake, vitamin e intake age	Superseded by Folsom, 2000 COL01688
Bostick, 1993 COL00483 USA	IWHS, Prospective Cohort, Age: 55-69 years, W	212/ 35 216 167 447 person-years	SEER	Self-reported	Incidence, colon cancer		0.84		Mean exposure reported
Bostick, 1993 COL01450 USA	IWHS, Prospective Cohort, Age: 55-69 years, W	212/ 35 216 167 447 person-years	SEER	Self-reported	Incidence, colon cancer				Mean exposure reported
Schoen, 1990 COL00183 USA	Cardiovascular Health Study, Prospective Cohort, Age: >65 years	102/ 5 849	Hospital record	Measured	Incidence, colon cancer	Q4 vs Q1	2.6 (1.4-4.8)	Age, sex, physical activity	Used in HvsL analysis

Figure 564 RR estimates of colorectal cancer by levels of waist to hip ratio

Figure 565 RR (95% CI) of colorectal cancer for the highest compared with the lowest level of waist to hip ratio

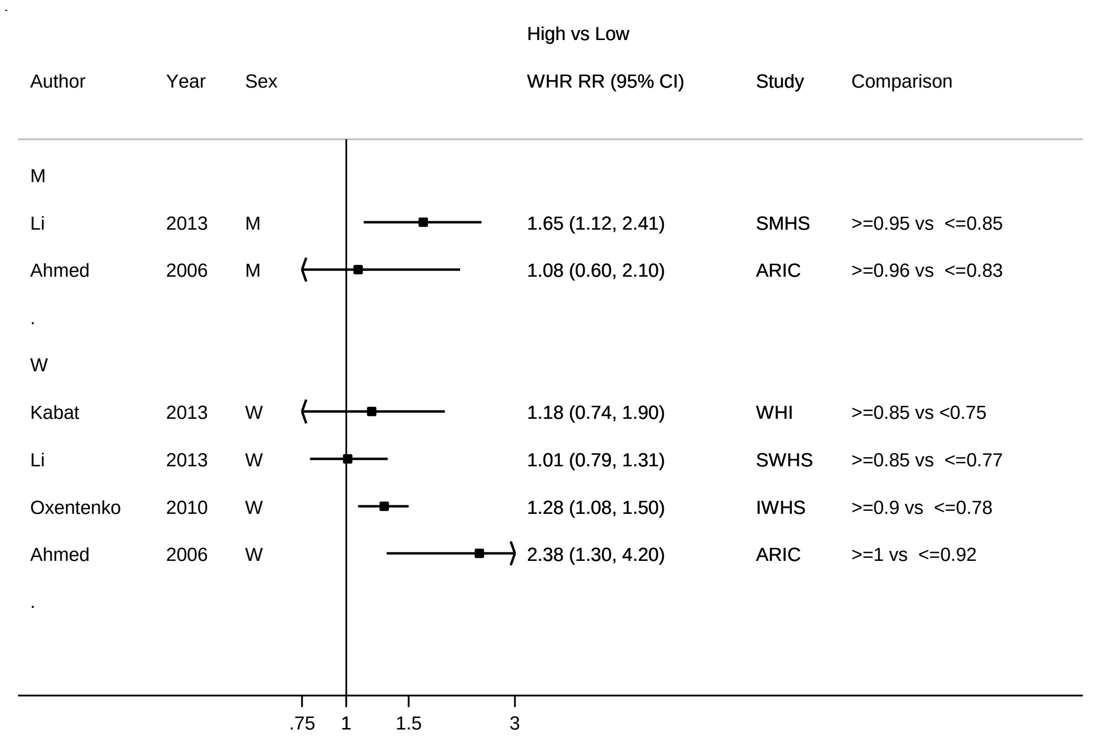


Figure 566 RR (95% CI) of colorectal cancer for 0.1 unit increase of waist to hip ratio

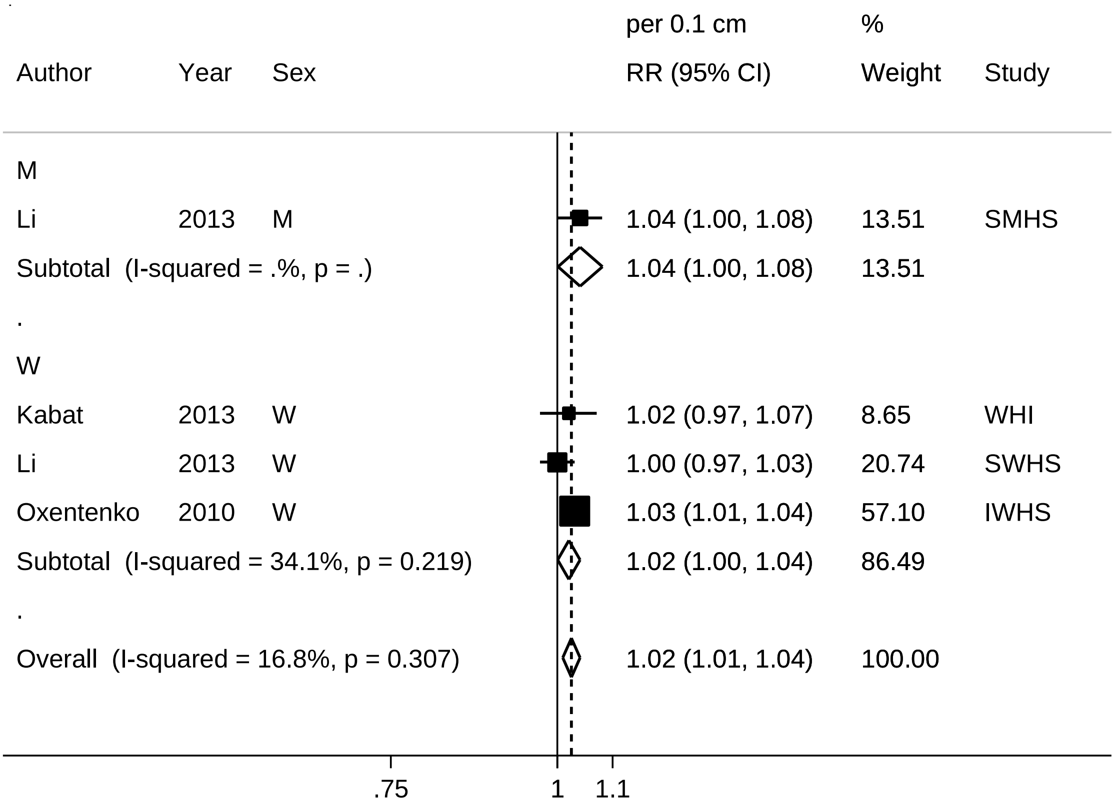
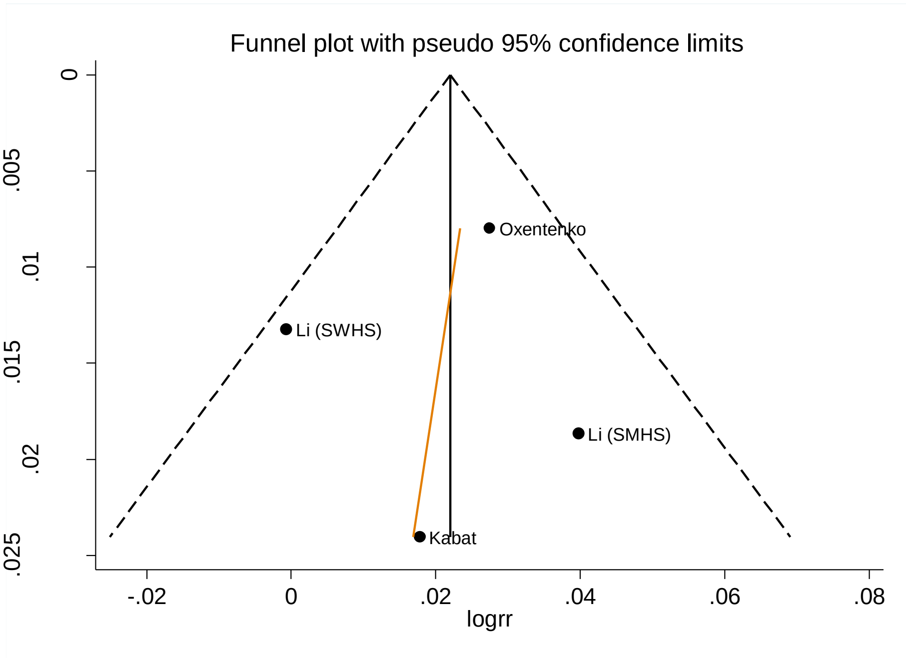


Figure 567 Funnel plot of studies included in the dose response meta-analysis of waist to hip ratio and colorectal cancer



p for Egger's test=0.56

Figure 568 RR (95% CI) of colon cancer for the highest compared with the lowest level of waist to hip ratio

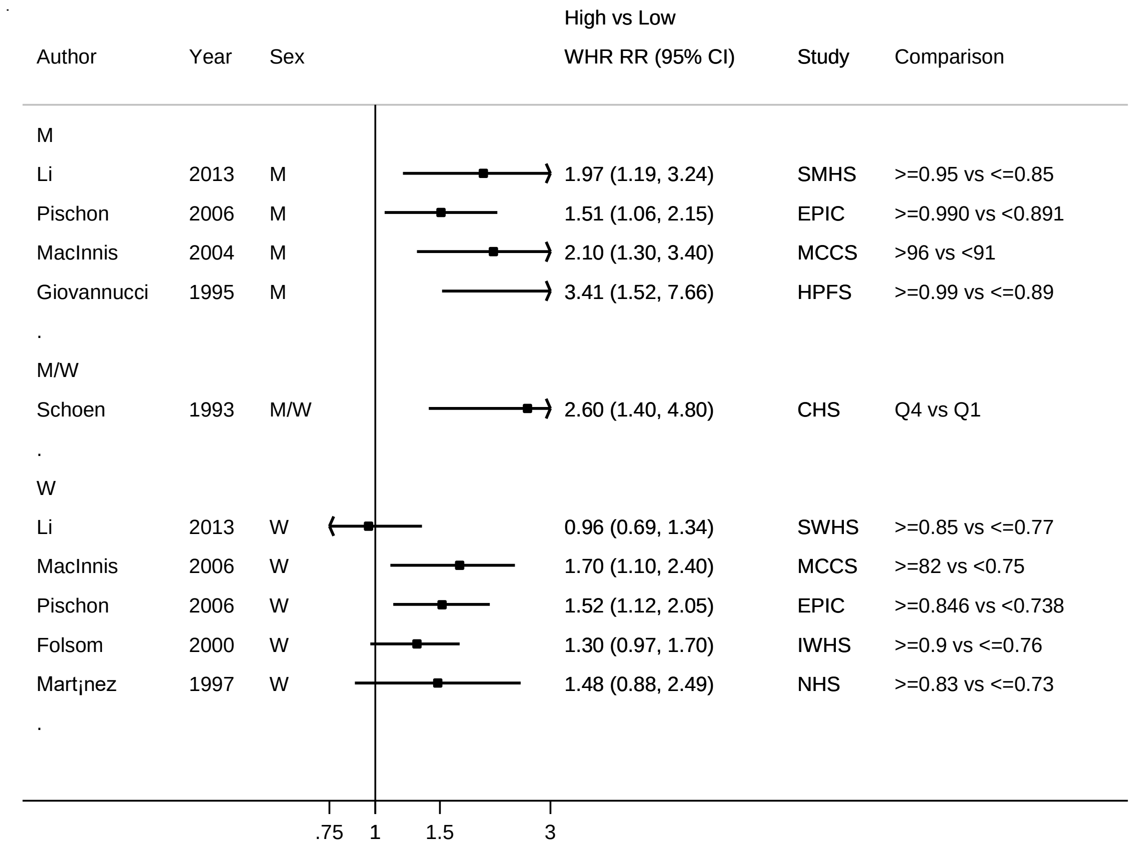


Figure 569 RR estimates of colon cancer by levels of waist to hip ratio

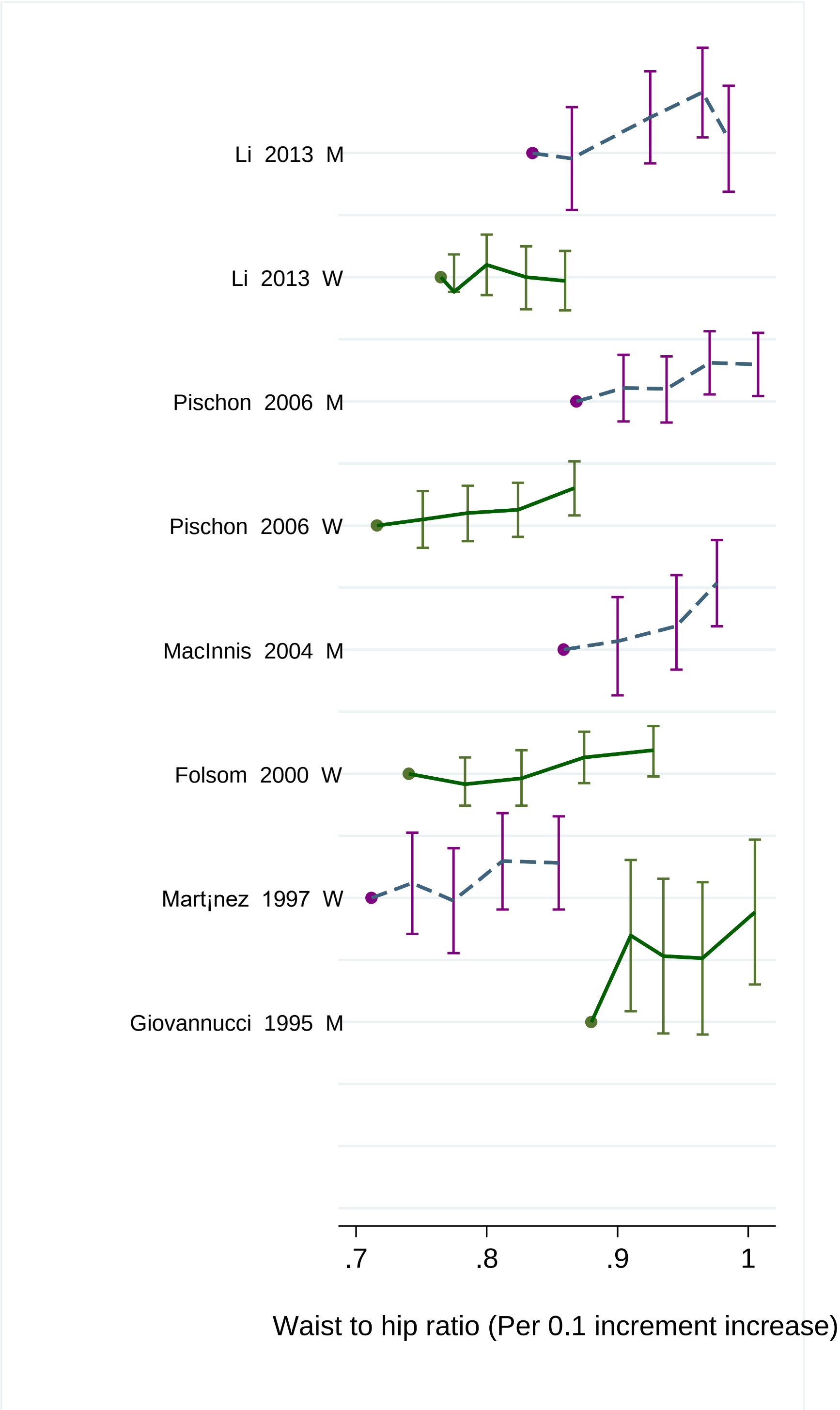


Figure 570 RR (95% CI) of colon cancer for 0.1 unit increase of waist to hip ratio

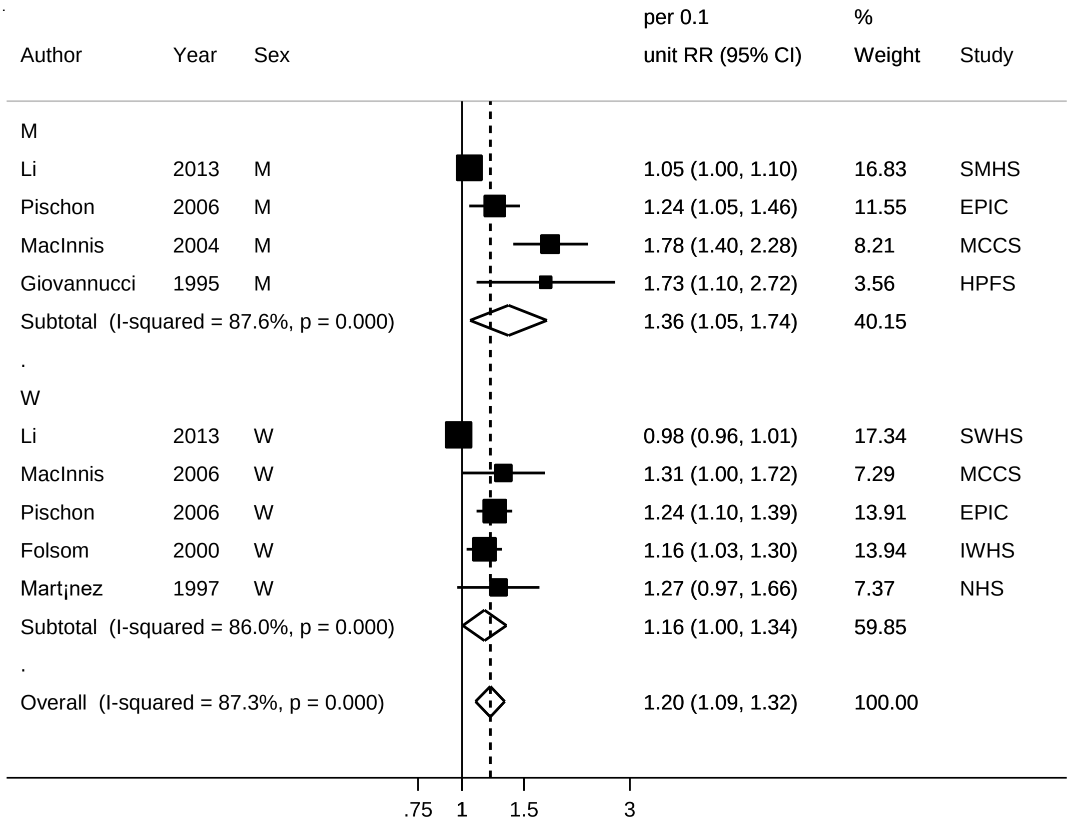
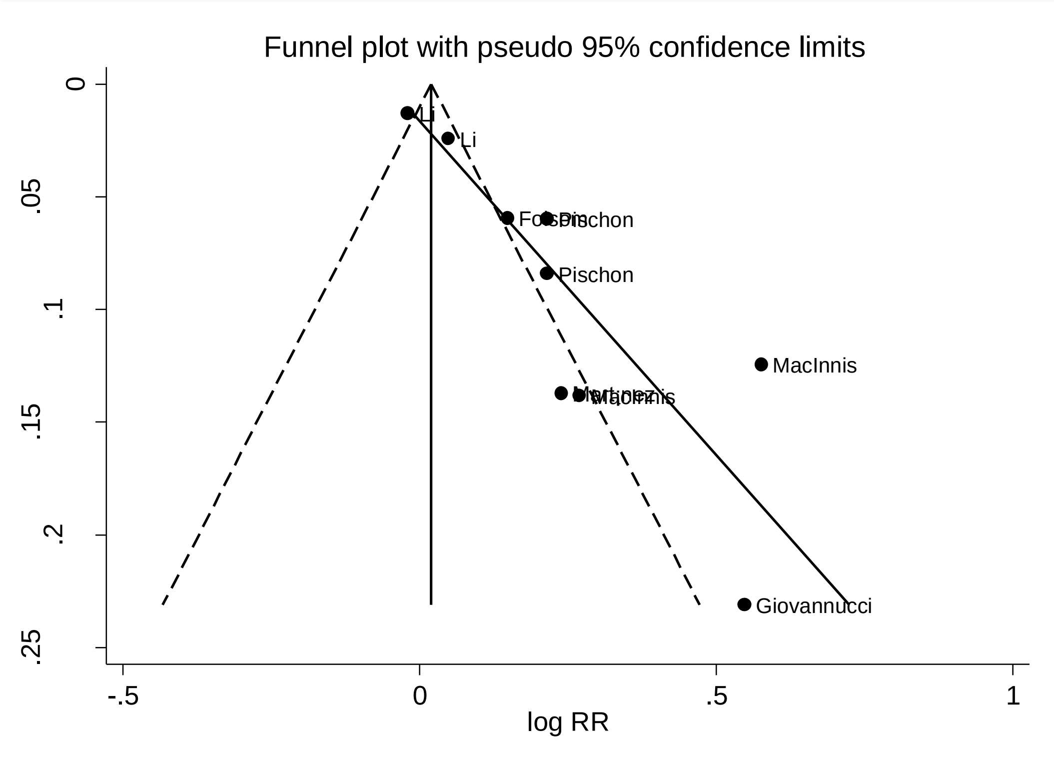
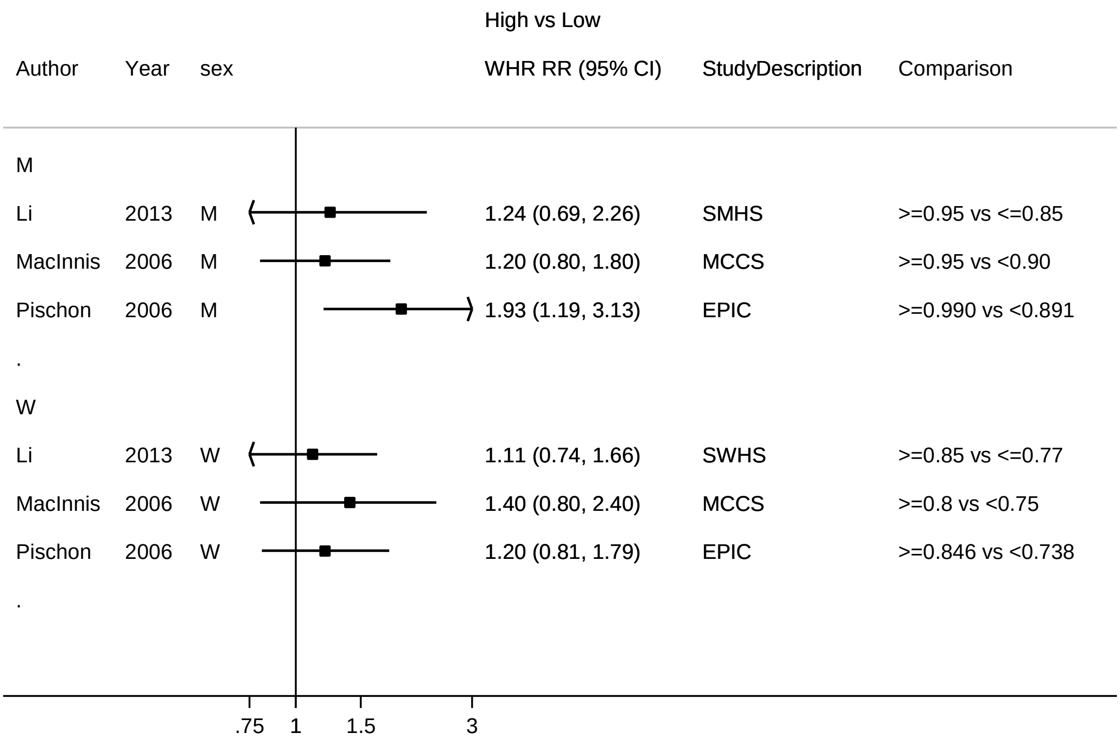


Figure 571 Funnel plot of studies included in the dose response meta-analysis of waist to hip ratio and colon cancer



p for Egger's test<0.001

Figure 572 RR (95% CI) of rectal cancer for the highest compared with the lowest level of waist to hip ratio



8.3.1 Height

Cohort studies

Summary

Main results:
Twelve new studies (fourteen publications) were identified after the 2010 SLR. All the analyses are on cancer incidence.

Main results:

Colorectal cancer:
Thirteen studies (65 880cases) were included in the dose-response meta-analysis. A 5% increase of colorectal cancer risk for an increase of 5 cm of height was observed. There was high heterogeneity and significant evidence of publication or small study bias (p=<0.001).
In stratified analysis the association tended to be stronger in women than in men and slightly stronger in studies in North America compared to studies in Europe.
The summary RR's did not change materially when excluding the studies in turn.

There was no evidence of non-linear relationships (p= 0.12).

Colon cancer:
Fourteen studies (85 589 cases) were included in the dose-response meta-analysis. A significant positive association was observed for height and colon cancer risk. High heterogeneity was observed between studies. There was no evidence of a significant publication or small study bias (p=0.99).
In stratified analysis by sex and geographical location, the summary RR showed stronger associations in studies in women than men and in studies in North America than studies in Asia, Europe and Australia.

In influence analysis, the summary RR's ranged from 1.00 (95% CI: 1.03-1.05) when Green, 2011 was omitted to 1.07 (95% CI: 1.04-1.08) when Wei, 2004 was omitted.
There was evidence of a significant non-linear association (p=0.006), showing a significant risk increase with increasing height. Only eight studies could be included in the analysis.

There were not enough studies to include in dose-response meta-analysis for proximal and distal colon cancer.

Rectal cancer:
Thirteen studies (25 005 cases) were included in the dose-response meta-analysis. A borderline significant positive association of height with rectal cancer risk was observed.

High heterogeneity was observed between studies. There was evidence of a significant publication or small study bias (p=0.002).

In stratified analysis, the summary RR showed stronger associations in studies in women than men and in studies in North America than studies in Asia and Europe.

The summary RR's ranged from 1.02 (95% CI: 1.00-1.05) when Kabat, 2013 was omitted to 1.04 (95% CI: 1.01-1.07) when Engeland, 2005 was omitted in influence analysis.

There was no evidence of a non-linear association (p=0.75).

Study quality:
Cancer outcome was confirmed using records in cancer registries in most studies. All studies were multiple adjusted for different confounders.

Table 338 Height and colorectal cancer risk. Number of studies in the CUP SLR

	Number
Studies identified	20 (24 publications)
Studies included in forest plot of highest compared with lowest exposure	11
Studies included in dose-response meta-analysis	13
Studies included in non-linear dose-response meta-analysis	9

Note: Include cohort, nested case-control and case-cohort designs

Table 339 Height and colon cancer risk. Number of studies in the CUP SLR

	Number
Studies identified	19 (24 publications)
Studies included in forest plot of highest compared with lowest exposure	13
Studies included in dose-response meta-analysis	14
Studies included in non-linear dose-response meta-analysis	8

Note: Include cohort, nested case-control and case-cohort designs

Table 340 Height and rectal cancer risk. Number of studies in the CUP SLR

	Number
Studies identified	18 (20 publications)
Studies included in forest plot of highest compared with lowest exposure	14
Studies included in dose-response meta-analysis	13
Studies included in non-linear dose-response meta-analysis	8

Note: Include cohort, nested case-control and case-cohort designs

Table 341 Height and colorectal cancer risk. Summary of the dose-response meta-analysis in the 2010 SLR and 2015 SLR.

	2010 SLR	2015 SLR
Increment unit used	5 cm	5 cm
Studies (n)	8	13
Cases (total number)	50075	65 880
RR (95%CI)	1.05 (1.03-1.08)	1.05 (1.02-1.07)
Heterogeneity (I^2, p-value)	10.7%, 0.35	89.7%, < 0.001

Stratified analysis by sex		
Men	**2010 SLR**	**2015 SLR**
Studies (n)	6	8
RR (95%CI)	1.04 (1.03-1.06)	1.04 (1.03-1.05)
Heterogeneity (I^2, p-value)	0%, 0.80	0%, 0.46
Women		
Studies (n)	5	9
RR (95%CI)	1.06 (1.04-1.09)	1.06 (1.02-1.09)
Heterogeneity (I^2, p-value)	15.8%, 0.31	91.5%, < 0.001
Stratified analysis by geographic location		
Asia		
Studies (n)		1
RR (95%CI)		1.03 (0.95-1.10)
Heterogeneity (I^2, p-value)		
Europe		
Studies (n)		5
RR (95%CI)		1.05 (1.04-1.06)
Heterogeneity (I^2, p-value)		0%, 0.64
North America		
Studies (n)		7
RR (95%CI)		1.06 (1.01-1.11)
Heterogeneity (I^2, p-value)		79.7%, <0.001

Table 342 Height and colon cancer risk. Summary of the dose-response meta-analysis in the 2010 SLR and 2015 SLR.

	2010 SLR	2015 SLR
Increment unit used	5 cm	5 cm
Studies (n)	**9**	14
Cases (total number)	6984	85 589
RR (95%CI)	1.09 (1.05-1.12)	1.05 (1.04-1.07)
Heterogeneity (I^2, p-value)	42%, 0.09	89.6%, <0.001

Stratified analysis by sex		
Men	**2010 SLR**	**2015 SLR**
Studies (n)	**7**	9
RR (95%CI)	1.08 (1.03-1.13)	1.02 (1.01-1.04)
Heterogeneity (I^2, p-value)	55.5%, 0.04	75.3%, <0.001
Women		
Studies (n)	7	12
RR (95%CI)	1.09 (1.06-1.13)	1.06(1.04-1.09)
Heterogeneity (I^2, p-value)	0%, 0.86	88.5%, <0.001
Stratified analysis by geographic location		
Asia		
Studies (n)		2
RR (95%CI)		1.12 (0.96-1.32)
Heterogeneity (I^2, p-value)		79.2%, 0.03
Europe		
Studies (n)		5
RR (95%CI)		1.06 (1.00-1.12)
Heterogeneity (I^2, p-value)		93%, <0.001
North America		
Studies (n)		6
RR (95%CI)		1.05 (1.01-1.10)
Heterogeneity (I^2, p-value)		89.7%, <0.001
Australia		
Studies (n)		1
RR (95%CI)		1.13 (1.04-1.23)
Heterogeneity (I^2, p-value)		

Table 343 Height and rectal cancer risk. Summary of the dose-response meta-analysis in the 2010 SLR and 2015 SLR.

	2010 SLR	**2015 SLR**
Increment unit used	5 cm	5 cm
Studies (n)	8	13
Cases (total number)	5062	25 005
RR (95%CI)	1.03 (0.99, 1.07)	1.03 (1.01-1.06)
Heterogeneity (I^2, p-value)	24.8%, 0.231	59.9%, 0.004

Stratified analysis by sex		
Men	**2010 SLR**	**2015 SLR**
Studies (n)	**7**	10
RR (95%CI)	1.05(1.01-1.08)	1.02 (1.00-1.05)

Heterogeneity (I^2, p-value)	0%, 0.69	39.7%, 0.09
Women		
Studies (n)	6	11
RR (95%CI)	1.00 (0.95-1.06)	1.04 (1.00-1.08)
Heterogeneity (I^2, p-value)	19.6%,0.29	56.3%, 0.01

Stratified analysis by geographic location				
2015 SLR	**Asia**	**Europe**	**North America**	**Australia**
Studies (n)	2	5	5	1
RR (95%CI)	1.04 (1.00-1.09)	1.00 (1.00-1.00)	1.06 (1.02-1.10)	1.11 (1.01-1.23)
Heterogeneity (I^2, p-value)	0%, 0.61	0%, 0.76	28.5%, 0.24	

Published pooled analysis

One published pooled analysis on height and colorectal cancer risk was identified (Wormser, 2012).

Height colorectal cancer risk. Results of pooled analysis of prospective studies published after the 2005 SLR.

Author, Year	Number of cohort studies	Total number of deaths	Studies country, area	Outcome	Comparison	RR (95%CI)	P trend	Heterogeneity (I^2, p value)*
Pooled analysis								
Wormser, 2012	130 population based prospective studies	4,855		Colorectal cancer mortality	Per 6.5cm	1.07 (1.03-1.11)	-	12%

Table 344Height and colorectal cancer risk. Main characteristics of studies included in the CUP SLR dose-response meta-analysis

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Missing data derived for analyses
Boursi, 2014 COL41032 UK	THIN, Nested Case Control, Age: 40- years, M/W	5 617/ 15122 controls	Medical records	Medical records	Incidence, colorectal cancer, men	> 179 vs < 170 cm	1.25 (1.14-1.3	Alcohol, BMI, colonoscopy, connective tissues disease, diabetes, heart disease, NSAID use, smoking	Mid-point categories
						Per 10 cm increase	1.1 (1.05-1.15)		
		4 361/ 11725 controls			Incidence, colorectal cancer, women	>165 vs <156 cm	1.25 (1.12-1.39)		
						Per 10 cm increase	1.16 (1.1-1.23)		
Kabat, 2014 COL41031 USA	NIH-AARP, Prospective Cohort, Age: 50-71 years, M/W, Retired	1 311/ 481 197 10.5 years	Cancer registry and national death Index	Self-reported height	Incidence, colon cancer, women	per 10 cm	1.19 (1.10-1.29)	Age, age at menarche, alcohol, BMI, colonoscopy, educational level, family history of cancer, physical activity, race, smoking	
		2 860/		Self-reported height	Incidence, colon cancer, men		1.10 (1.05-1.16)		
		1 427/		Self-reported height	Incidence, rectal cancer, men		1.09 (1.02-1.17)		
		591/		Self-reported height	Incidence, rectal cancer, women		1.12 (0.99-1.26)		
Kabat, 2013 COL40979 USA	WHI, Prospective Cohort,	1 516/ 144 701 12 years	Cancer registry and national death Index	Self-reported height	Incidence, colorectal cancer	per 10 cm	1.19 (1.10-1.28)	Age, age at menarche, alcohol, aspirin	

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Missing data derived for analyses
	Age: 50-79 years, W	1 904/ 144 701 12 years			Incidence, colon cancer		1.18 (1.08-1.29)	use, diabetes, educational level, ethnicity, family history of colorectal cancer, folate intake, HRT use, pack-years of cigarette smoking, physical activity, randomisation, red meat	
		257/ 481 197 10.5 years			Incidence, rectal cancer		1.37 (1.1-1.7)		
Kabat, 2013 COL40945 Canada	CNBSS, Prospective Cohort, Age: 40-59 years, W	1 096/ 88 256 16.2 years	Record linkages to cancer database and to the national mortality database	Height and weight measured at the Initial examination.	Incidence, colorectal cancer	per 10 cm	1.13 (1.02-1.24)	Age, BMI, hormone replacement therapy, menopausal status, oral contraceptive use, pack yrs of smoking, years of education	
		769/			Incidence, colon cancer	per 10 cm	1.12 (1.00-1.26)		
		338/			Incidence, rectal cancer	per 10 cm	1.15 (0.97-1.37)		
Walter, 2013 COL40999 USA	VITAL, Prospective Cohort, Age: 50-76	491/ 65 038 7.3 years	Cancer registry	Questionnaire	Incidence, colorectal cancer	per 5 inch	1.12 (0.94-1.32)	Age, sex, race	Increment converted to 5 cm

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Missing data derived for analyses
	years, M/W								
Green, 2011 COL40879 UK	MWS, Prospective Cohort, Age: 56 years, W	6 281/ 1 297 124 9.4 years	Cancer registry	Questionnaire	Incidence, colon cancer	per 10 cm	1.25 (1.17-1.32)	Age, age at first child birth, age at menarche, alcohol, BMI, parity, region, smoking, socio-economic status, strenuous exercise	
Hughes, 2011 COL40895 Netherlands	NLCS, Prospective Cohort, Age: 55-69 years, M/W	1 211/ 120 852 16.3 years	Cancer registry	Self-reported height and	Incidence, colorectal cancer, men	183-200 vs 158-172 cm	0.80 (0.60-1.08) Ptrend:0.16	Age, alcohol consumption, educational level, energy intake, family history of colorectal cancer, occupational activity, smoking, weight	Mid-point categories
		1 211/			Incidence, colorectal cancer, men	per 5 cm	0.96 (0.89-1.04)		
		1 106/			Incidence, colorectal cancer, women	171-186 vs 143-160 cm	1.32 (1.03-1.71) Ptrend:0.05		
		1 106/			Incidence, colorectal cancer, women	per 5 cm	1.09 (1.01-1.17)		
		459/			Incidence, proximal colon cancer, women	171-186 vs 143-160 cm	1.19 (0.84-1.70) Ptrend:0.67		

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Missing data derived for analyses
		459/			Incidence, proximal colon cancer, women	per 5 cm	1.04 (0.95-1.15)		
		427/			Incidence, distal colon cancer, men	183-200 vs 158-172 cm	0.97 (0.63-1.48) Ptrend:0.70		
		427/			Incidence, distal colon cancer, men	per 5 cm	0.99 (0.89-1.11)		
		327/			Incidence, proximal colon cancer, men	183-200 vs 158-172 cm	0.90 (0.59-1.37) Ptrend:0.66		
		327/			Incidence, proximal colon cancer, men	per 5 cm	1.01 (0.90-1.13)		
		327/			Incidence, distal colon cancer, women	171-186 vs 143-160 cm	1.53 (1.03-2.27) Ptrend:0.05		
		327/			Incidence, distal colon cancer, women	per 5 cm	1.11 (0.99-1.24)		
		205/			Incidence, rectal cancer, women	171-186 vs 143-160 cm	1.49 0.98, 2.27		
						per 5 cm	1.14 0.98, 1.32		

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Missing data derived for analyses
		299/			Incidence, rectal cancer, men	per 5 cm	0.95 (0.85-1.07)		
						183-200 vs 158-172 cm	0.71 (0.43-1.17)		
Oxentenko, 2010 COL40849 USA	IWHS, Prospective Cohort, Age: 55-69 years, W	1 464/ 36 941 619 961 person-years	Health registers	Self-reported height and weight at baseline	Incidence, colorectal cancer	≥169 vs ≤157 cm	1.38 (1.17-1.64) Ptrend:<0.001	Age, age at menopause, alcohol, calcium, cigarette consumption, contraception, diabetes, energy intake, Estrogen use, folate, fruits and vegetables consumption, physical activity level, red meat, smoking status, total fat, vitamin E	Mid-point categories
Sung, 2009 COL40778 Korea	KNHIC, Prospective Cohort, Age: 40-64 years, M/W, middle-class	2 499/ 788 789 8.72 years	Cancer registry and death records	Weight and height were measured	Incidence, colon cancer, men	≥171.1 vs ≤164.5 cm	1.10 (0.98-1.24)	Age, alcohol consumption, area of residence, BMI, occupation, physical activity, salary,	Mid-point categories
						Per 5 cm	1.04 (1.00-1.08)		
		1007/			Incidence, colon cancer, women	≥171.1 vs ≤164.5 cm	1.21 (1.01-1.46)		

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Missing data derived for analyses
	adults					Per 5 cm	1.08 (1.01-1.15)	smoking habits	
		2281/			Incidence, rectal cancer, men	≥158.1 vs ≤151 cm	1.16 (1.03-1.31)		
						Per 5 cm	1.06 (1.01-1.1)		
		892/			Incidence, rectal cancer, women		0.92 (0.75-1.12)		
						Per 5 cm	1.00 (0.94-1.08)		
Bowers, 2006 COL40699 Finland	ATBC, Prospective Cohort, Age: 58 years, M, Smokers	410/ 28 983 14.1 years	Cancer registry	Measured by trained staff	Incidence, colorectal cancer	179-200 vs 136-168 cm	0.90 (0.64-1.27) Ptrend:0.17	Age, number of cigarettes smoked, weight	Mid-point categories
		227/			Incidence, colon cancer		0.82 (0.78-1.53)		
		183/			Incidence, rectal cancer		1.02 (0.61-1.7)		
Pischon, 2006 COL01985 Europe	EPIC, Prospective Cohort, Age: 25-70 years, M/W	421/ 368 277 2 254 727 person-years	Population registries	Self-reported questionnaires	Incidence, colon cancer, women	≥180.5 vs <167 cm	1.79 (1.3-2.46)	Alcohol consumption, centre, educational level, physical activity, smoking status, age at	Person-years of follow up
		563/			Incidence, colon cancer, men	≥167.5 vs <155 cm	1.4 (0.99-1.98)		
		295/			Incidence, rectal	≥180.5 vs 0-	1.00 (0.66-1.52)		

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Missing data derived for analyses
					cancer, men	167.9 cm		recruitment, fibre, fish and shellfish, fruits and vegetables, red and processed meat	
		291/			Incidence, rectal cancer, women	≥167.5 vs 0-155.9 cm	0.78 (0.5-1.21)		
MacInnis, 2006 COL40627 Australia	MCCS, Prospective Cohort, Age: 27-75 years, M/W	229/ 41 114 10.3 person-years	Cancer registry	Measured following a standard protocol, fat mass and fat free mass estimated by bio-electrical Impedance, validated and reproducibility checked	Incidence, rectal cancer	Q 3 vs Q 1	1.20 (0.90-1.80)	Age, sex, country of birth	Person-years of follow up
						Per 10 cm	1.23 (1.00-1.51)		
		134/			Incidence, rectal cancer, men	Per 10 cm	1.15 (0.89-1.48)		
						≥176 vs ≤168.9 cm	1.1 (0.7-1.8)		
		95/			Incidence, rectal cancer, women	Per 10 cm	1.38 (1.00-1.09)		
						≥163 vs ≤156.9 cm	1.4 (0.8-2.3)		
MacInnis, 2006 COL40751 Australia	MCCS, Prospective Cohort, Age: 27-75 years, W	212/ 24 072 10.4 years	Cancer registry		Incidence, colon cancer	Per 10 cm	1.17 (0.93-1.48)	Age, sex, country of birth, HRT use	Person-years of follow up
						≥161 vs ≤155 cm	1.1 (0.8-1.5)		

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Missing data derived for analyses
MacInnis, 2004 COL00373 Australia	MCCS, Prospective Cohort, Age: 27-75 years, M	153/ 16 566 145 433 Person years	Cancer registry		Incidence, colon cancer	Per 10 cm	1.43 (1.12-1.83)	Age, sex, country of birth,	
						>177.4 vs <167.5 cm	1.9 (1.1-3.1)		
Engeland, 2005 COL01941 Norway	NCC, Prospective Cohort, Age: 20-74 years, M/W	22 987/ 1 999 978 23 years	Health survey, cancer registry, death registry	Height and weight measured by trained staff	Incidence, colorectal cancer, men	≥180 vs <160 cm	1.14 (1.10-1.18)	Age, birth cohort	Mid-point categories Hamling method used
		24 130/			Incidence, colorectal cancer, women	≥170 vs <150 cm	1.14 (1.09-1.19)		
		13 805/			Incidence, colon cancer, men	≥180 vs <160 cm	1.18 (1.13-1.23)		
		16 638/			Incidence, colon cancer, women	≥170 vs <150 cm	1.18 (1.12-1.24)		
		9 182/			Incidence, rectal cancer, men	≥180 vs <160 cm	1.08 (1.03-1.14)		
		7 492/			Incidence, rectal cancer, women	≥170 vs <150 cm	1.06 (0.97-1.15)		
Otani, 2005 COL01891 Japan	JPHC study-cohort I and II, Prospective Cohort,	626/ 102 949 9 years	Population registries		Incidence, colorectal cancer, men	≥170 vs < 160 cm	1.1 (0.8-1.5)	Age, alcohol consumption, smoking status, miso soup	Mid-point categories
		360/			Incidence,	≥157 vs <148	1.1 (0.7-1.6)		

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Missing data derived for analyses
	Age: 40-69 years, M/W				colorectal cancer, women	cm		intake, public health centre area, refraining from salty foods and animal fats	
Wei, 2004 COL00581 USA	NHS, Prospective Cohort, W, nurses	672/ 87 733 24 years	Self-reported verified by medical record and The National Death Index	Self-reported	Incidence, colon cancer		1.48 (1.18-1.88)	Age, family history, BMI, physical activity, beef, pork or lamb as a main dish, processed meat, alcohol, calcium, folate, height, pack-years smoking before age 30, history of endoscopy	Mid-point categories Person-years of follow up
		166/			Incidence, rectal cancer		1.08 (0.7-1.69)		
	HPFS, Prospective Cohort, M, Health professionals	134/ 46 632 14 years			Incidence, rectal cancer		1.42 (0.85-2.35)		
		467/			Incidence, colon cancer		1.5 (1.13-2.00)		
	HPFS & NHS	984/ 134 356			Incidence, colon cancer		1.5 (1.25-1.79)		
		298/			Incidence, rectal cancer		1.18 (0.84-1.64)		
Shimizu, 2003 COL00529 Japan	TCCJ, Prospective Cohort, Age: 35- years,	108/ 29 051 8 years	Hospital records and cancer registry	Self-reported	Incidence, colon cancer, men	≥168 vs ≤162 cm	2.13 (1.26-3.58)	Age, alcohol consumption, educational level, physical	Mid-point categories
		93/			Incidence, colon	≥155 vs ≤150	1.48 (0.81-2.7)		

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Missing data derived for analyses
	M/W				cancer, women	cm		activity, smoking habits, height	
		59/			Incidence, rectal cancer, men	≥168 vs ≤162 cm	1.21 (0.57-2.61)		
		41/			Incidence, rectal cancer, women	≥155 vs ≤150 cm	1.3 (0.52-3.21)		
Gunnell, 2003 COL40757 UK	Caerphily study, Prospective cohort study, Age:45-59 years	38/ 2512 21 years	Central personal register	Measured	Incidence, colorectal cancer	Per 6 cm	0.96 (0.69-1.34)	Age, smoking status, BMI, occupation, household size,unemployment	
Kato, 1997 CRC00022 USA	NYUWHS, Prospective Cohort, Age: 34-65 years, W	100/ 14 272 105 044 person-years	Questionnaire, medical records, cancer registries		Incidence, colorectal cancer	Q_4 vs Q_4	1.03 (0.55-1.95)	Age, place at enrolment	
Thune, 1996 COL00269 Norway	NHSCD, Prospective Cohort, Age: 20-69 years, M/W	224/ 81 516 1 305 607 person-years	Cancer registry	Height and weight were measured	Incidence, colon cancer, men	Per 10 cm	1.13 (0.94-1.35)	Age	
		99/			Incidence, colon cancer, women		1.08 (0.8-1.47)		

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Missing data derived for analyses
		169			Incidence, colon cancer, men		1.02 (0.82-1.25)		
		55/			Incidence, colon cancer, women		0.88 (0.59-1.32)		
Bostick, 1994 COL00079 USA	IWHS, Prospective Cohort, Age: 55-69 years, W	212/ 35 216 167 447 person-years	SEER		Incidence, colon cancer	≥67 vs ≤63 inch	1.23 (0.83-1.84)	Age, energy intake, parity, vitamin a supplement, vitamin E intake	
Albanes, 1988 COL00495 USA	NHANES I Age: 25-74 years, M/W	62/ 12 554 10 years	Hospital records, death certificate	Measured	Incidence, colorectal cancer, men	Q4 vs Q1	2.1 (1.00-4.5)	Age	
		67/			Incidence, colorectal cancer, women		1.6 (0.8-3.0)		
Hebert, 1997 COL00430 USA	PHS Age: 40-84 years M	341/ 22 071 12 years	Medical records	Self-reported	Incidence, colorectal cancer	≥73 vs <68inch	1.53 (1.04-2.25)	Age, beta-carotene, BMI, Aspirin use, smoking, alcohol consumption, physical activity	
					Incidence, colon cancer		1.70 (1.08-2.66)		

Table 345 Height and colorectal cancer risk. Main characteristics of studies excluded from the CUP SLR dose-response meta-analysis

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Reasons for exclusion
Brändstedt, 2014 COL41022 Sweden	MDCS, Prospective Cohort, Age: 44-74 years, M/W	422/ 28 098 18 years	Cancer registry	Estimated	Incidence, colorectal cancer, braf negative	≥172 vs ≤164 cm	1.21 (0.85-1.71) Ptrend:	Age, sex, alcohol, educational level, smoking	Gene interaction data
Shin, 2014 COL41023 Korea	KNHIC, Prospective Cohort, Age: 30-80 years, M/W	2 655/ 1 326 058	Korean central cancer registry (kccr) & Insurance system	Height and weight were measured	Incidence, colorectal cancer, women	≥159 vs ≤151 cm	1.22 (1.09-1.37)	Age, alcohol, BMI, cigarette smoking, family history of cancer, fasting blood sugar, meat consumption, serum cholesterol	Used in Hvsl analysis only
					Incidence, rectal cancer, women	≥159 vs ≤151 cm	1.23 (1.04-1.45)		
					Incidence, left colon cancer, women	≥159 vs ≤151 cm	1.41 (1.12-1.79)		
					Incidence, colorectal cancer, men	≥173 vs ≤165 cm	1.21 (1.13-1.30)		
					Incidence, rectal cancer, men	≥173 vs ≤165 cm	1.16 (1.06-1.29)		
					Incidence, left colon, men	≥173 vs ≤165 cm	1.38 (1.20-1.58)		
					Incidence, colon cancer, men	≥173 vs ≤165 cm	1.26 (1.13-1.40)		
					Incidence, right colon, women	≥159 vs ≤151 cm	1.04 (0.80-1.36)		

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Reasons for exclusion
					Incidence, colon cancer, women	≥159 vs ≤151 cm	1.24 (1.04-1.47)		
Simons, 2014 COL41029 Netherlands	NLCS, Case Cohort, Age: 55-69 years	204/	Cancer registry	Questionnaire	Incidence, colorectal cancer, Igfbp 2 genes methylated	Q 3 vs Q 1	1.23 (0.84-1.79) Ptrend:0.28	Age, sex, non-occupational physical activity, weight	Gene methylation data
					Incidence, colorectal cancer, Igfbp 2 genes methylated	per 5 cm	1.05 (0.93-1.19)		
Semmens, 2013 COL40929 Japan	Life Span Study, Prospective Cohort, M/W	1 142/ 56 064	Cancer registry	Self-reported	Incidence, colon cancer	Q 3 vs Q 1	1.24 (1.05-1.47)	Age, sex, city attained age	Participants are atomic bomb survivors
					Incidence, colon cancer	per 10 cm	1.10 (0.99-1.22)		
		577/			Incidence, colon cancer, women	153-155 vs ≤149 cm	1.27 (0.99-1.63)		
		565/			Incidence, colon cancer, men	164-168 vs ≤160 cm	1.23 (0.97-1.55)		
		565/			Incidence, colon cancer, men	per 10 cm	1.06 (0.92-1.23)		
Hughes, 2012 COL40943 Netherlands	NLCS, Case Cohort, Age: 55-69	561/ 4 654 7.3 years	Cancer registry and pathology database	Height (cm) and body weight (kg) were self-	Incidence, colorectal cancer, braf	per 5 cm	1.08 (1.01-1.15)	Sex, ethnicity	Gene interaction data

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Reasons for exclusion
	years, M/W			reported	wildtype				
Hughes, 2012 COL40944 Australia	MCCS, Prospective Cohort, Age: 27-75 years, M/W	495/ 40 154	Cancer registry/death records/national death Index	Measured	Incidence, colorectal cancer, ms-stable	per 5 cm	1.07 (0.99-1.15)	Sex, ethnicity	Gene interaction data
Cnattingius, 2009 COL40776 Sweden	STC, Prospective Cohort, Age:	248/ 2 337 33 year	Population cancer registries	Questionnaire	Incidence, colorectal cancer	Q4 vs Q2	1.00 (0.70-1.44)	Age	Used in HvsL analysis only
Whitley, 2009 COL40677	Boyd Orr Cohort	59/ 2 642 59 years	Cancer registry and death certificates	Measured	Incidence/ mortality, colorectal cancer	Per 1 SD	1.06 (0.84-1.33)	Age, sex	Childhood stature The level of increment is not specified
Lundqvist, 2007 COL40692 Sweden, Finland	Sweden, Finland Co-twin study, 1975, Prospective Cohort, Age: 44 years, M/W	717/ 68 149 25.2 years	National cancer registers	Measured, BMI & height	Incidence, colon cancer	Highest vs lowest	1.12 (1.00-1.50)	Age, county of residence, diabetes, educational level, physical activity, smoking status	Used in HvsL analysis only
		479/			Incidence, rectal cancer		1.00 (0.70-1.20)		
McCarl, 2006	IWHS,	954/	SEER registry		Incidence,	≥67 vs <62 inch	1.42 (1.17-1.72)	Age	Superseded by

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Reasons for exclusion
COL40633 USA	Prospective Cohort, Age: 55-69 years, W	35 197 15 years			colorectal cancer				Oxentenko, 2010 COL40849
Norat, 2005 COL01698 Europe	EPIC, Prospective Cohort, Age:21-83 Years M/W	1 329 /478 040 2 279 075 person years	Cancer registry		Incidence, colorectal cancer				Mean exposure reported Pischon, 2006 used COL01985
Giovannucci, 2004 COL00615 USA	HPFS, Prospective Cohort, Age:40-75 Years M	494/ 47 690 12 years	Cancer registry		Incidence, colon cancer	Per 9 inch	1.68 (1.18-2.38)	Age, race, smoking status, alcohol consumption	Wei, 2004 Used COL00581
Tamakoshi, 2004 COL00551	JACC, Prospective Cohort, Age: 40-79 years M/W	249/ 74 320 1 016 485 Person years	Cancer registry	Self-reported	Incidence, colon cancer, men	≥165 vs <161 cm	1.58 (0.91-2.73)	Age, race, smoking status, alcohol consumption, meat, intake, green leafy vegetables intake, family history of cancer	Mortality
					Incidence, colon cancer, women	≥153 vs <150	1.38 (0.77-2.48)		
Colangelo, 2002	CHA Detection	191/	National Death	Height and	Mortality,	Per 7 cm	1.24 (1.07-1.43)		Mortality

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Reasons for exclusion
COL00383 USA	Project in Industry, Prospective Cohort, Age: ≥ 40 years	35 582 866 926 person-years	Index	weight were measured	colorectal cancer, men			Age, race, education, sex	
		126/			Mortality, colorectal cancer, women		0.95 (0.79-1.16)		
Davey Smith, 2000 COL00390 Scotland	The Renfrew/Paisley General Population Study, Prospective Cohort, Age: 45-64 years	201/ 15 393 20 years	Area residency list	Measured	Mortality, colorectal cancer	Per -10 cm	0.7 (0.56-0.88)	Age, social class, deprivation category	Mortality
Robsahm, 1999 COL00180 Norway	NSPT, Prospective Cohort, Age: M/W	/ 112 2852			Incidence, colon cancer, men	Q5 vs Q1	1.37 (1.27-1.49)		Used in HvsL analysis only
					Incidence, colon cancer, women		1.35 (1.26-1.45)		
					Incidence, rectal cancer, men		1.17 (1.06-1.29)		
					Incidence, rectal cancer, women		1.18 (1.06-1.03)		
Tangrea, 1997 COL00267	ATBC, Nested Case	146/	Population registries		Incidence, colorectal cancer			Age, clinic site, date of blood	No RR reported

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Reasons for exclusion
Finland	Control, Age: 50-69 years, M, Smokers							drawn	
Gaard, 1997 COL00163 Norway	NHSCD, Prospective Cohort, Age: M/W	292/ 62 173			Incidence, colon cancer, men	Highest vs lowest	0.89 (0.48-1.61)		Used in HvsL analysis only
					Incidence, colon cancer, women		0.83 (0.43-1.64)		
		106 (M+W)			Incidence, rectal cancer, men		1.44 (0.67-3.12)		
					Incidence, rectal cancer, women		0.91 (0.36-2.29)		
Giovannucci, 1995 COL00110 USA	HPFS, Prospective Cohort, Age: 40-75 years, M	203/ 31 055 6 years	Self-reported verified by medical record and The National Death Index		Incidence, colon cancer, colon cancer	≥73 vs <69 cm	1.76 (1.13-2.74)	Age, alcohol consumption, energy intake, family history of specific cancer, physical activity, smoking habits, aspirin use, dietary fibre intake, folate intake, history endoscopic	Superseded by Wei, 2004 COL00581

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Reasons for exclusion
								screening, history polyp diagnosis, methione intake, red meat intake	
Chyou, 1994 COL00086 USA	HHP, Prospective Cohort, M, Japanese ancestry	289/ 7 945 19 years	Selective service draft registration file		Incidence, colon cancer	Mean exposure	86.9 cm		Mean exposure reported
		108/			Incidence, rectal cancer		86.7 cm		
Suadicani, 1993 COL01085 Denmark	Copenhagen CVD Study, Prospective Cohort, Age: M	93/ 5429			Incidence, rectal cancer	178-198 vs 151-171 cm	0.32 (0.11-1.00)		Used in HvsL analysis only
Le Marchand, 1992 COL00676 USA	HHCS, Prospective Cohort, Age: M	203/ 3 501			Incidence, rectal cancer	Q3 vs Q1	0.8 (0.5-1.3)		Used in HvsL analysis only
Chute, 1991 COL00475 USA	NHS, Prospective Cohort,	191/ 118 404 8 years	Self-reported verified by medical record	Self-reported	Incidence, colon cancer	≥168 vs <161	1.6 (1.1-2.5)	Age	Superseded by Wei, 2004 COL00581

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Reasons for exclusion
	Age: 30-55 years, W, nurses	49/	and The National Death Index		Incidence, rectal cancer		1.2 (0.6-2.6)		
Tartter, 1984 COL01088 USA	New York Mount Sinai Medical Centre Study, Prospective Cohort, M/W	63/ 279	Hospital		Recurrence, colorectal cancer				Recurrence No RR reported

Figure 573 RR estimates of colorectal cancer by levels of height

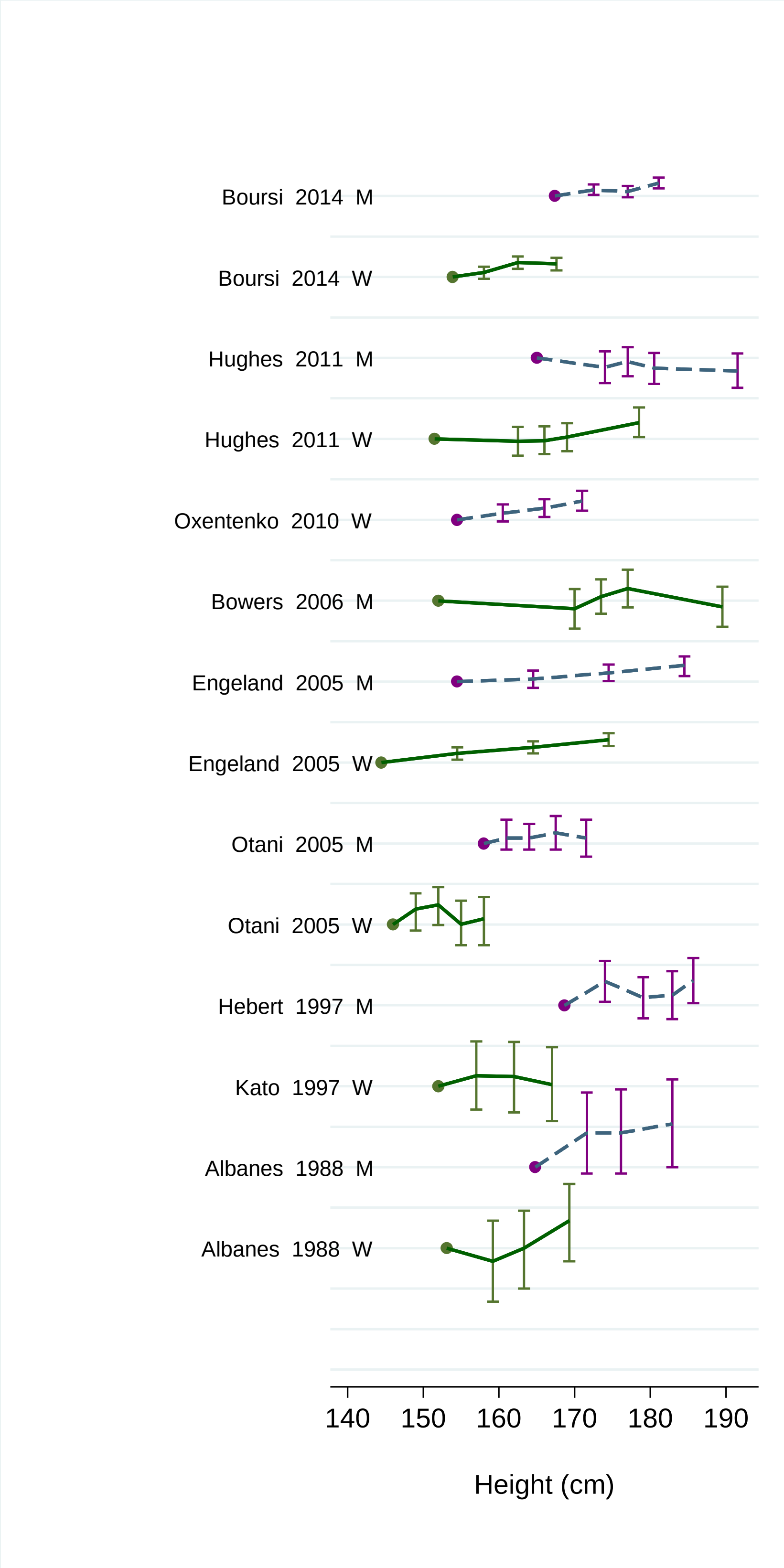


Figure 574 RR (95% CI) of colorectal cancer for the highest compared with the lowest level of height

Author	Year	sex	high vs. low Height RR (95% CI)	StudyDescription	Comparison
Boursi	2014	M/W	1.25 (1.12, 1.39)	THIN	>165 vs <156 cm
Boursi	2014	M/W	1.25 (1.14, 1.37)	THIN	> 179 vs < 170 cm
Shin	2014	M	1.21 (1.13, 1.30)	KNHIC	≥173 vs ≤165 cm
Shin	2014	W	1.22 (1.09, 1.37)	KNHIC	≥159 vs ≤151 cm
Hughes	2011	W	1.32 (1.03, 1.71)	NLCS	171-186 vs 143-160 cm
Hughes	2011	M	0.80 (0.60, 1.08)	NLCS	183-200 vs 158-172 cm
Oxentenko	2010	W	1.38 (1.17, 1.64)	IWHS	≥169 vs ≤157 cm
Cnattingius	2009	M/W	1.00 (0.70, 1.44)	STC	Q 4 vs Q 2
Bowers	2006	M	0.90 (0.64, 1.27)	ATBC	179-200 vs 136-168 cm
Engeland	2005	W	1.48 (1.33, 1.65)	NCC	≥170 vs < 150 cm
Engeland	2005	M	1.32 (1.10, 1.54)	NCC	≥180 vs < 170 cm
Otani	2005	W	1.10 (0.70, 1.60)	JPHC	≥157 vs< 148 cm
Otani	2005	M	1.10 (0.80, 1.50)	JPHC	≥170 vs < 160 cm
Hebert	1997	M	1.53 (1.04, 2.25)	PHS	≥73 vs < 67 inch
Kato	1997	W	1.03 (0.55, 1.95)	NYUWHS	≥165 vs < 155 cm
Albanes	1988	M	2.10 (1.00, 4.50)	NHANES I	>178.6 vs ≤169 cm
Albanes	1988	W	1.60 (0.80, 3.00)	NHANES I	>165.5 vs ≤157 cm

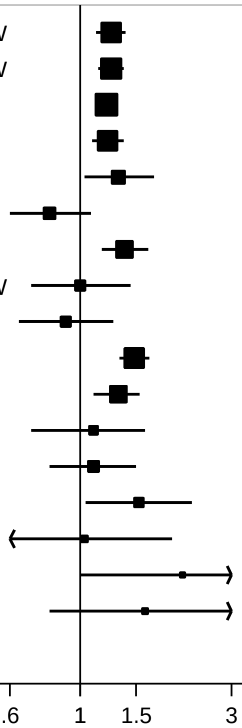


Figure 575 RR (95% CI) of colorectal cancer for 5 cm increase of height

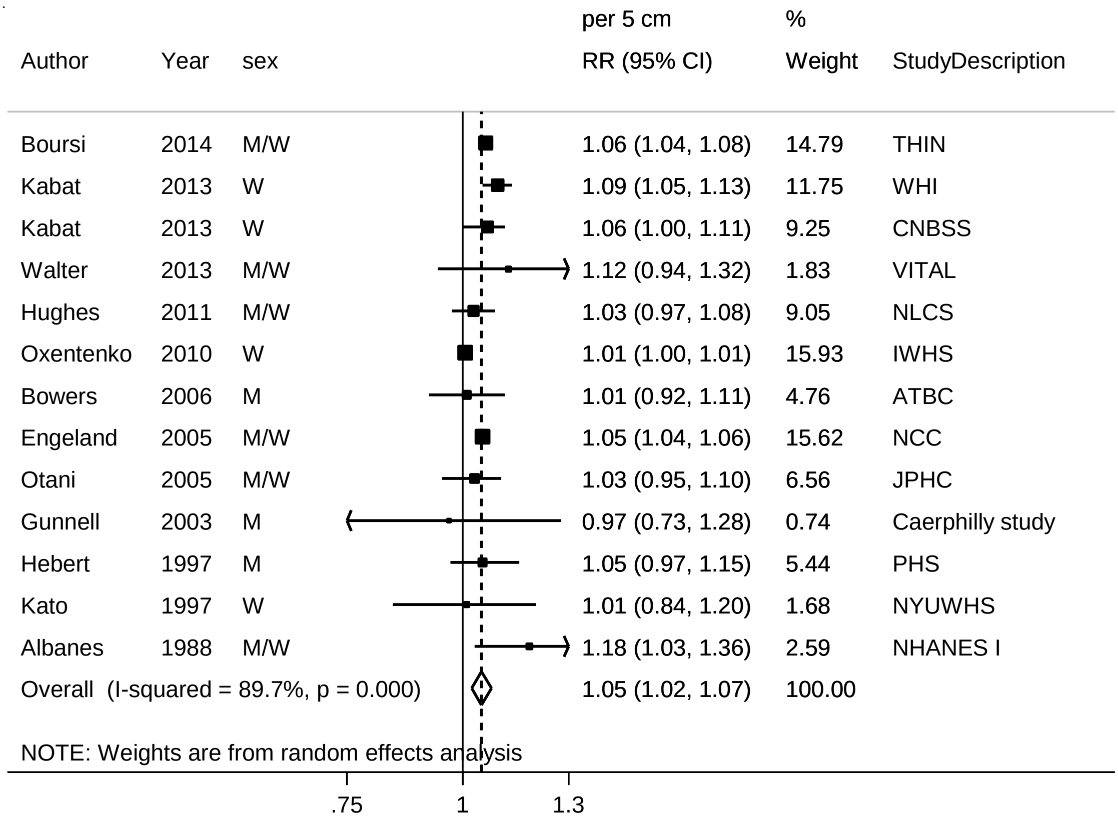
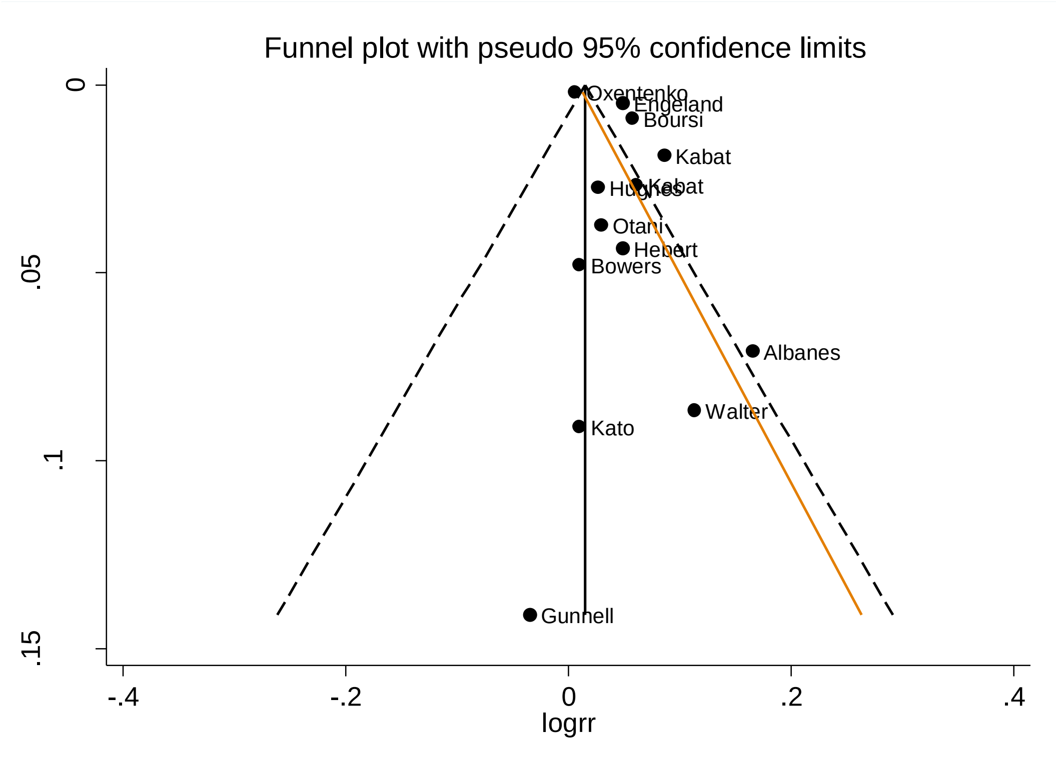


Figure 576 Funnel plot of studies included in the dose response meta-analysis of height and colorectal cancer



p for Egger's test<0.001

Figure 577 RR (95% CI) of colorectal cancer for 5 cm increase of height by sex

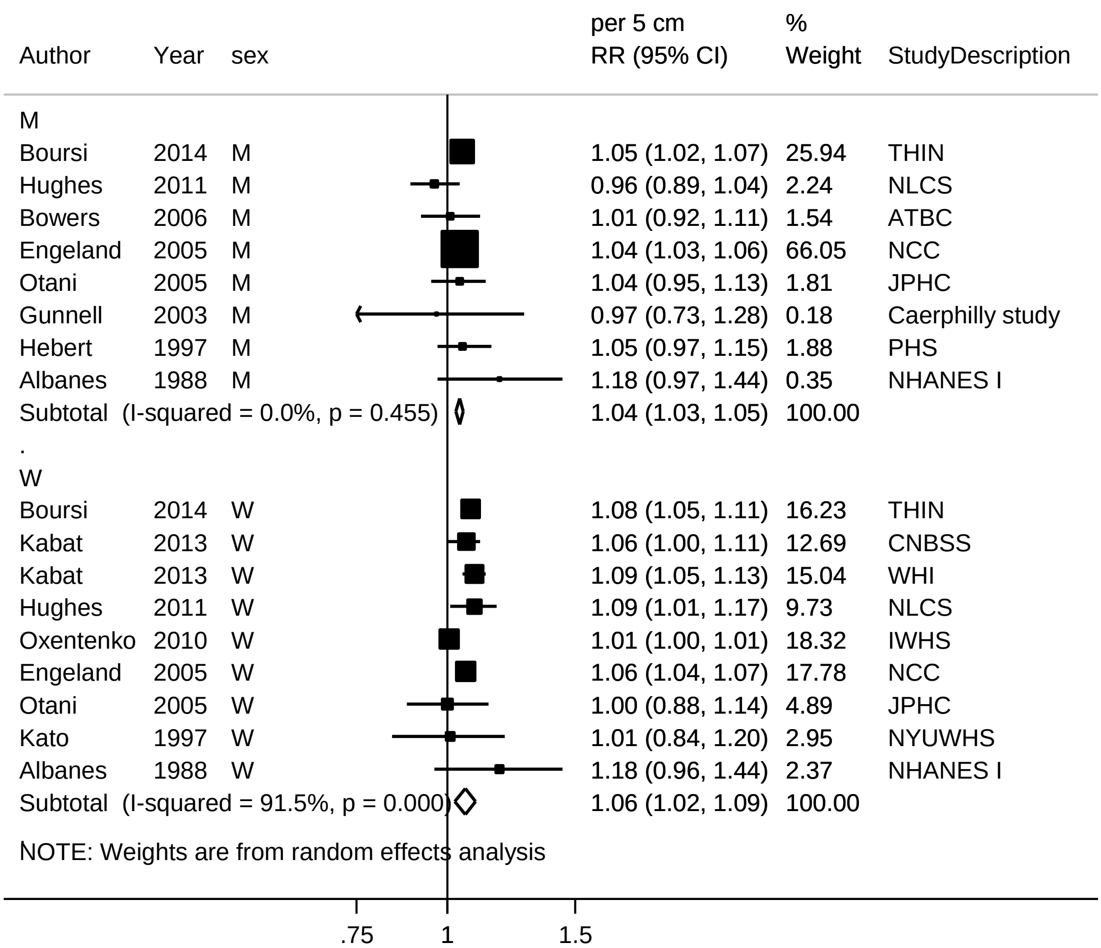


Figure 578 RR (95% CI) of colorectal cancer for 5 cm increase of height by geographical location

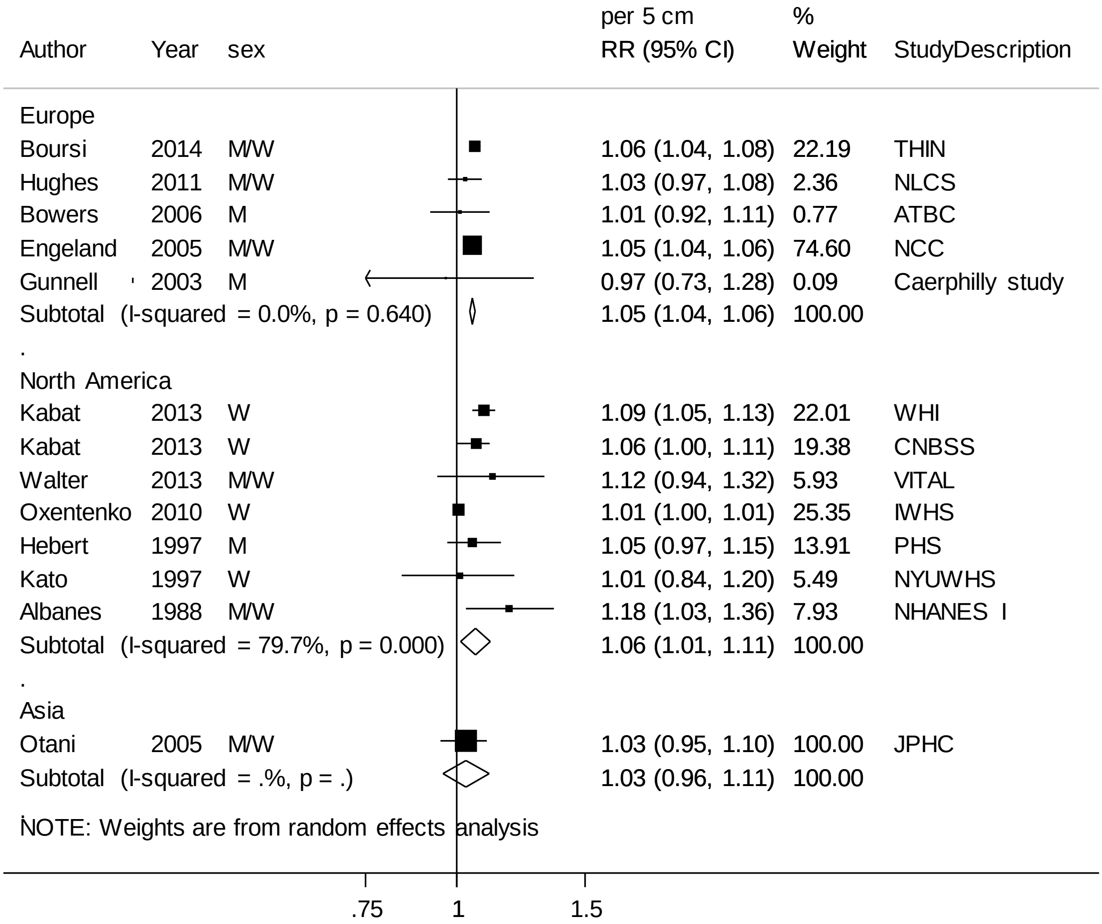
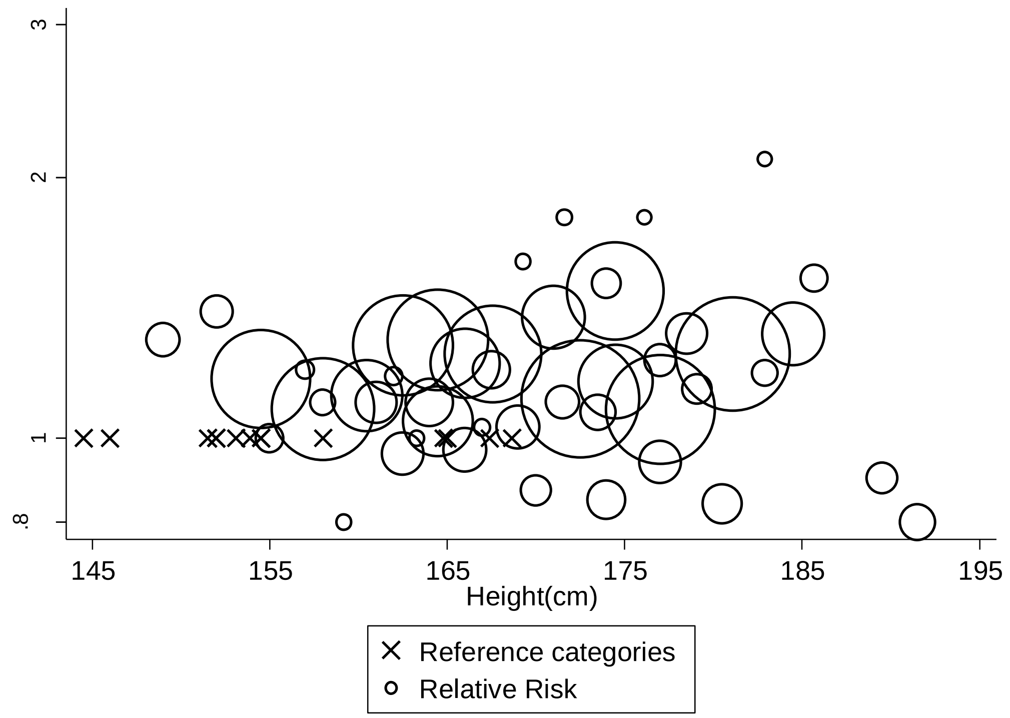
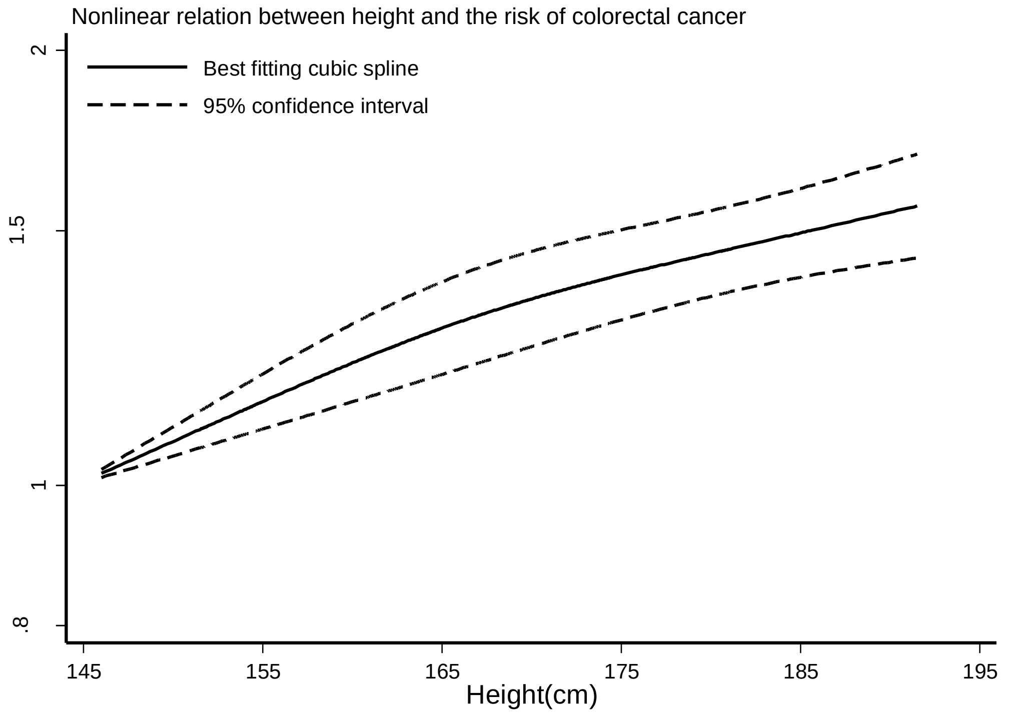


Figure 579 Relative risk of colorectal cancer and height estimated using non-linear models





p for non-linearity=0.12

Table 346 Table with height values and corresponding RRs (95% CIs) for non-linear analysis of height and colorectal cancer

Height (cm)	RR (95%CI)
144.5	1.00
155	1.14 (1.09-1.19)
165	1.2 (1.19-1.38)
170	1.35 (1.25-1.45)
174.5	1.39 (1.30-1.50)
185	1.50 (1.40-1.61)
191.5	1.56 (1.44-1.70)

Figure 580 Figure RR estimates of colon cancer by levels of height

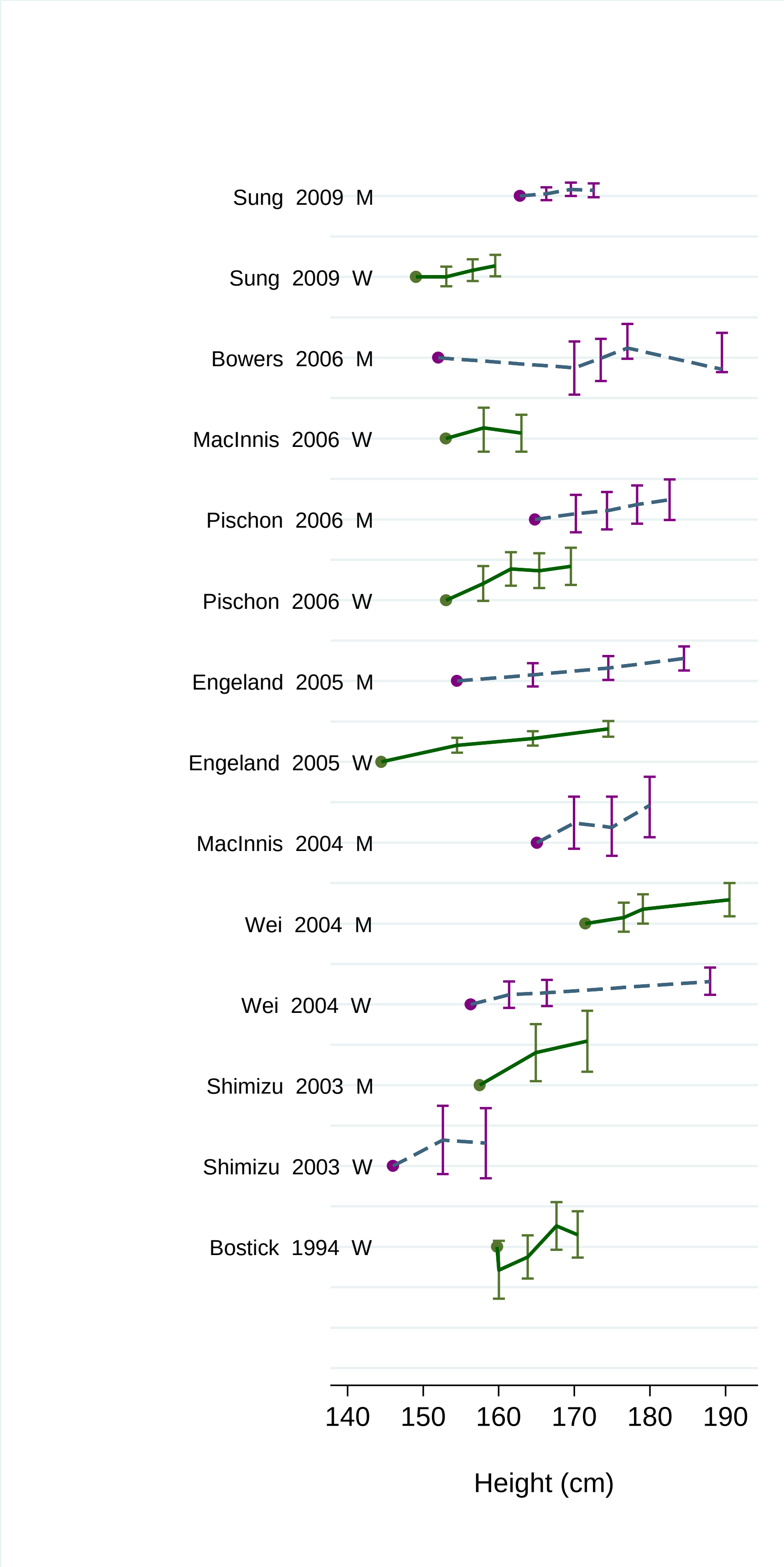


Figure 581 RR (95% CI) of colon cancer for the highest compared with the lowest level of height

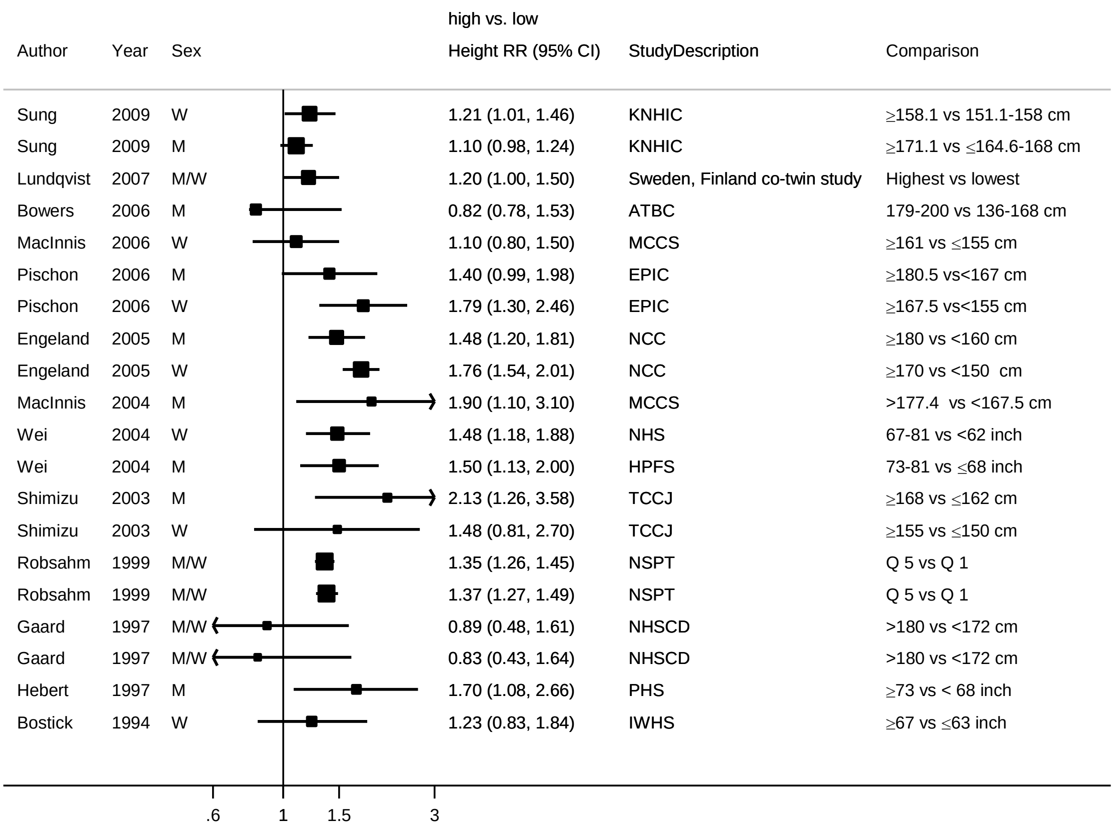


Figure 582 RR (95% CI) of colon cancer for 5 cm increase of height

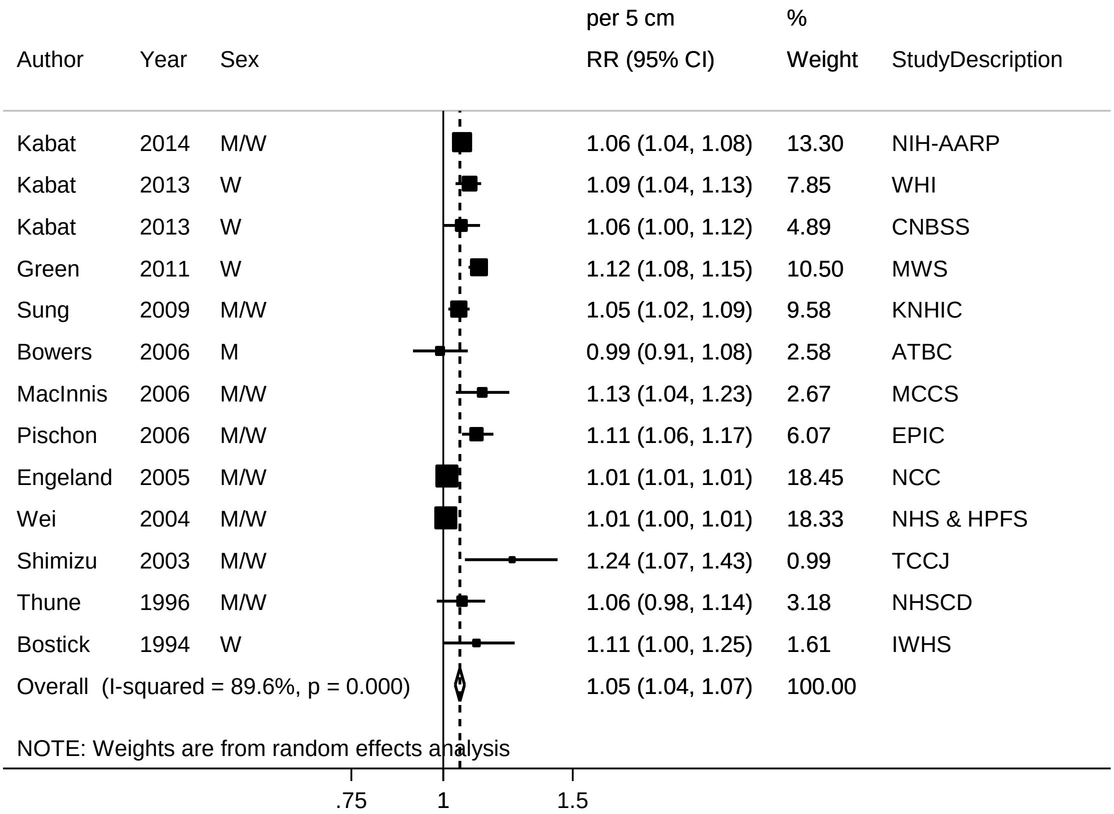
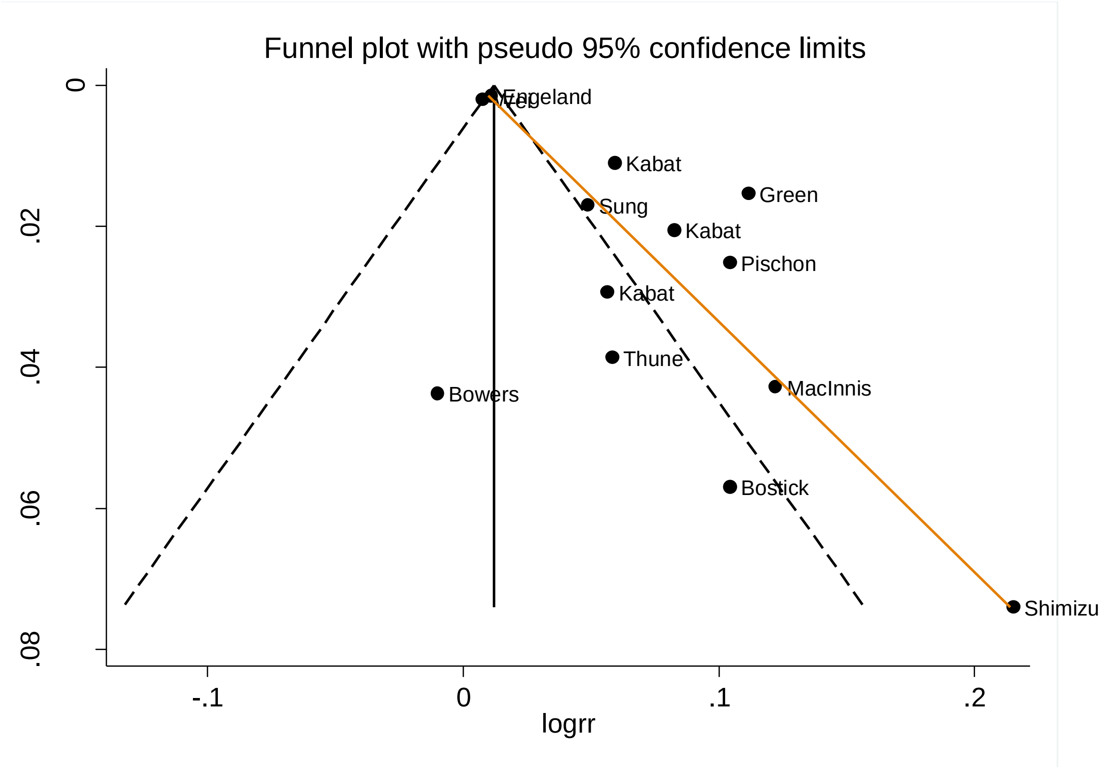


Figure 583 Funnel plot of studies included in the dose response meta-analysis of height and colon cancer



p for Egger's test=0.99

Figure 584 RR (95% CI) of colon cancer for 5 cm increase of height by sex

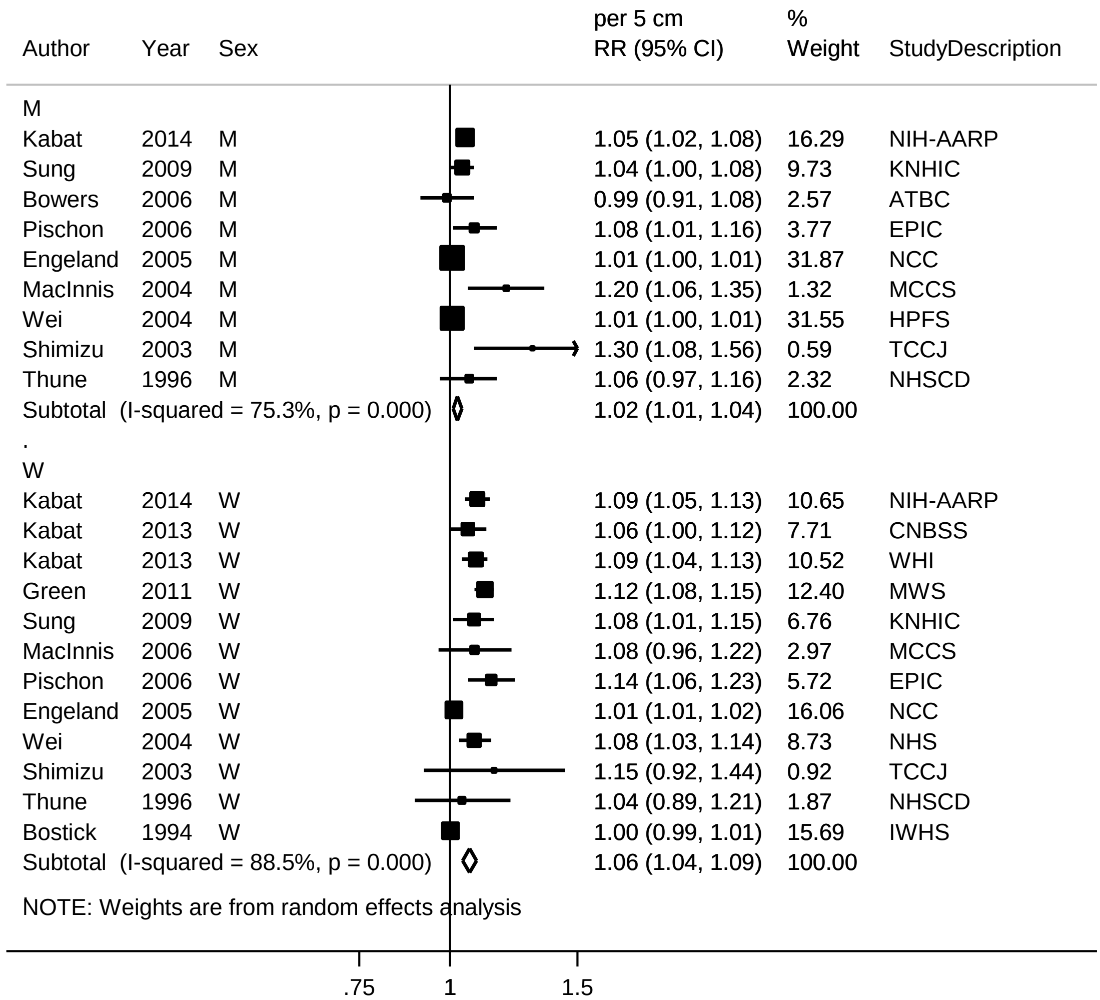


Figure 585 RR (95% CI) of colon cancer for 5 cm increase of height by geographic location

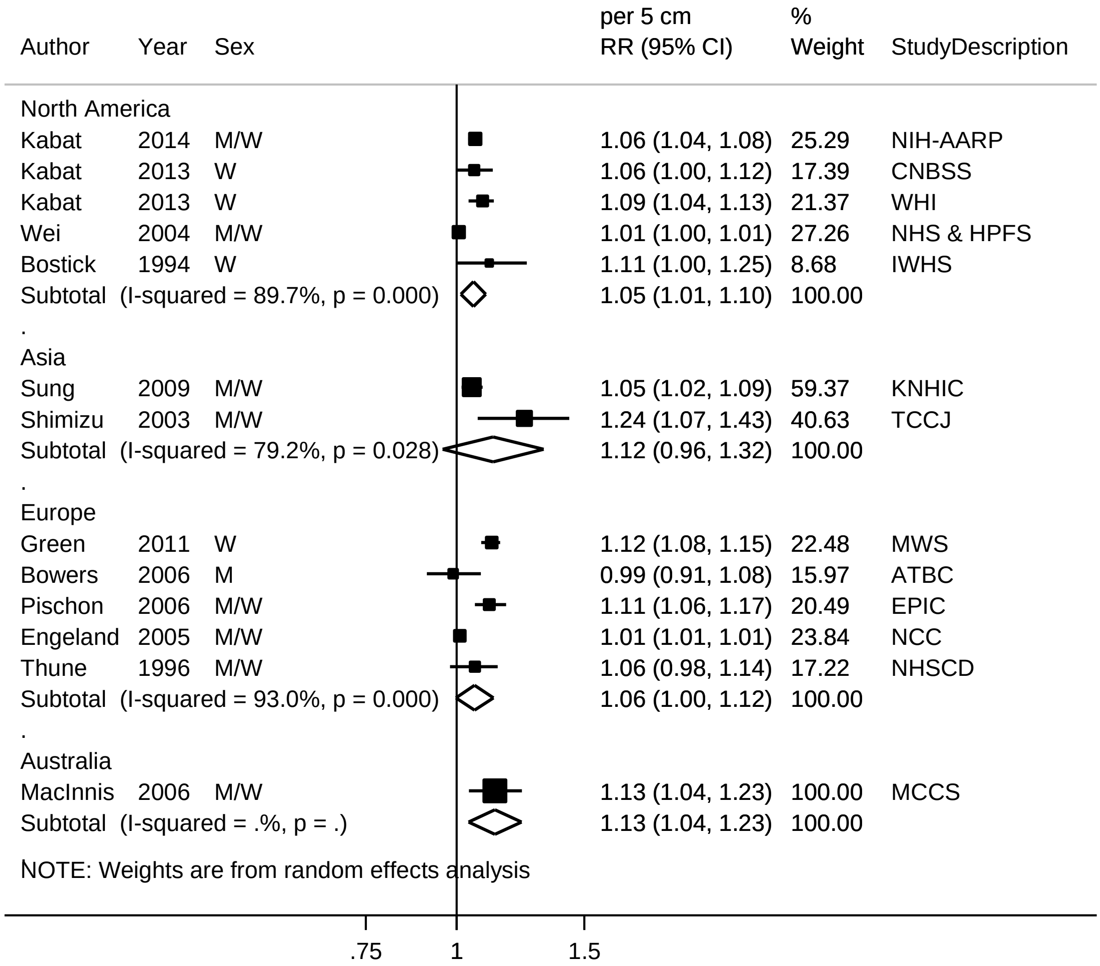
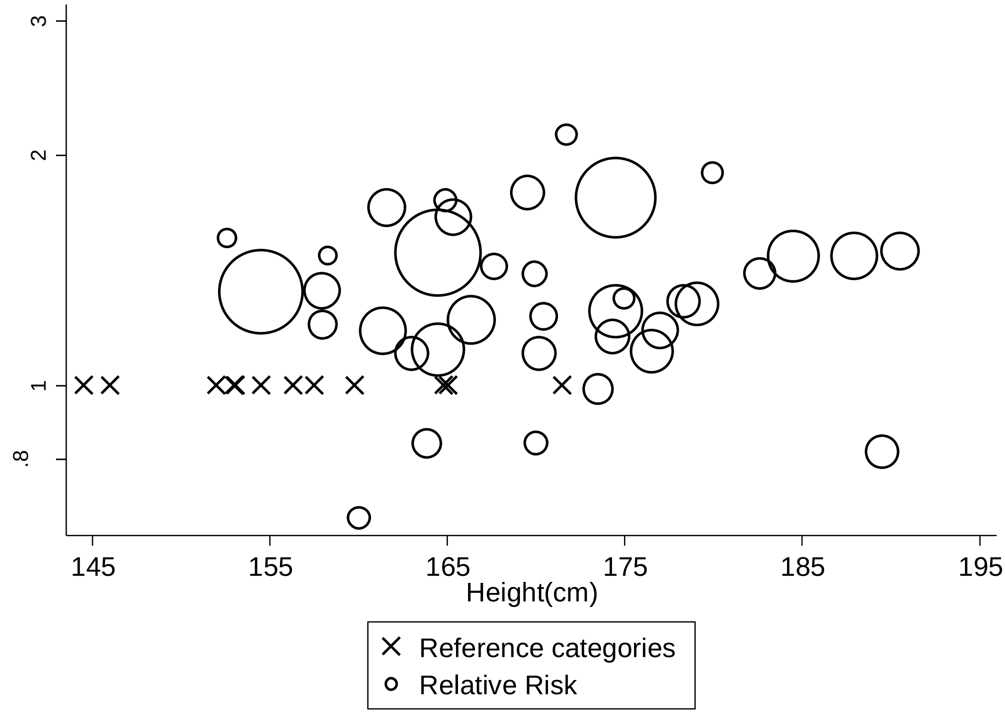
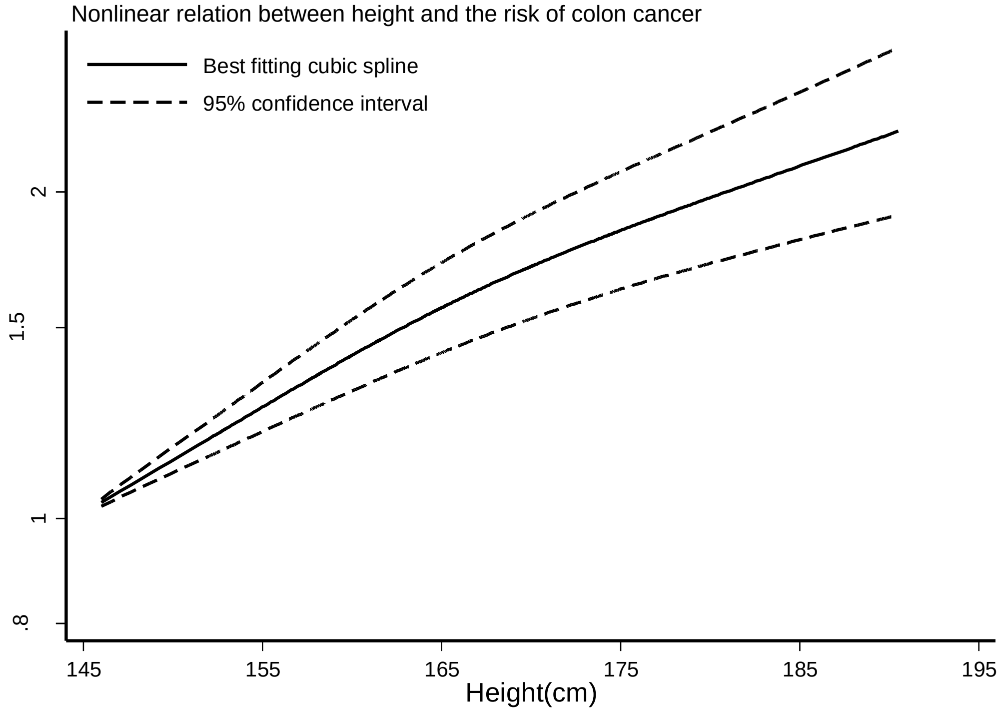


Figure 586 Relative risk of colon cancer and height estimated using non-linear models





P=0.006

Table 347 Table with height values and corresponding RRs (95% CIs) for non-linear analysis of height and colon cancer

Height (cm)	RR (95%CI)
144.5	1.00
154.5	1.25 (1.19-1.32)
164.5	1.55 (1.41-1.70)
170	1.71 (1.53-1.91)
174.5	1.83 (1.62-2.07)
184.5	2.10 (1.80-2.45)
190.5	2.28 (1.91-2.72)

Figure 587 RR estimates of rectal cancer by levels of height

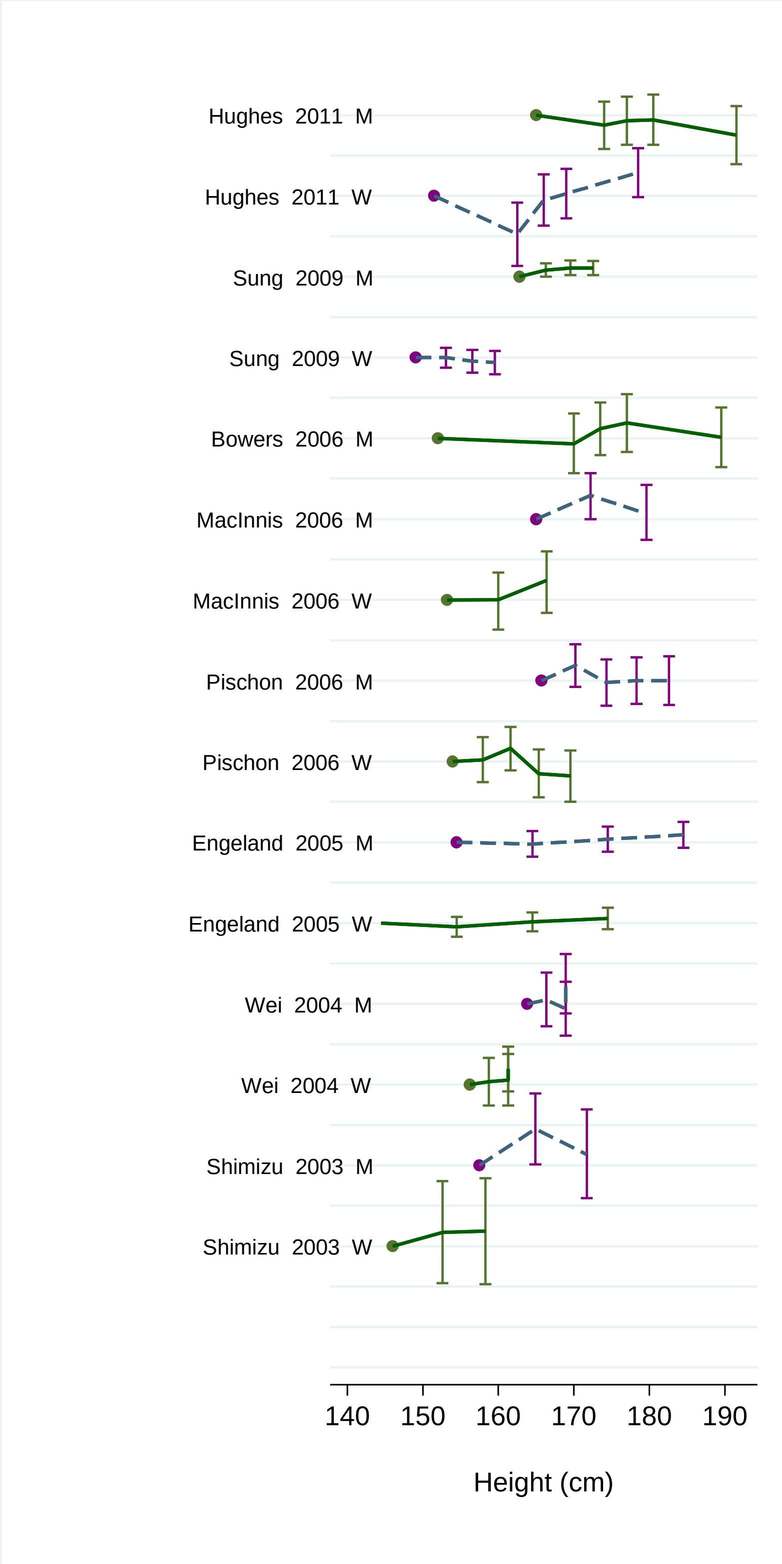


Figure 588 RR (95% CI) of rectal cancer for the highest compared with the lowest level of height

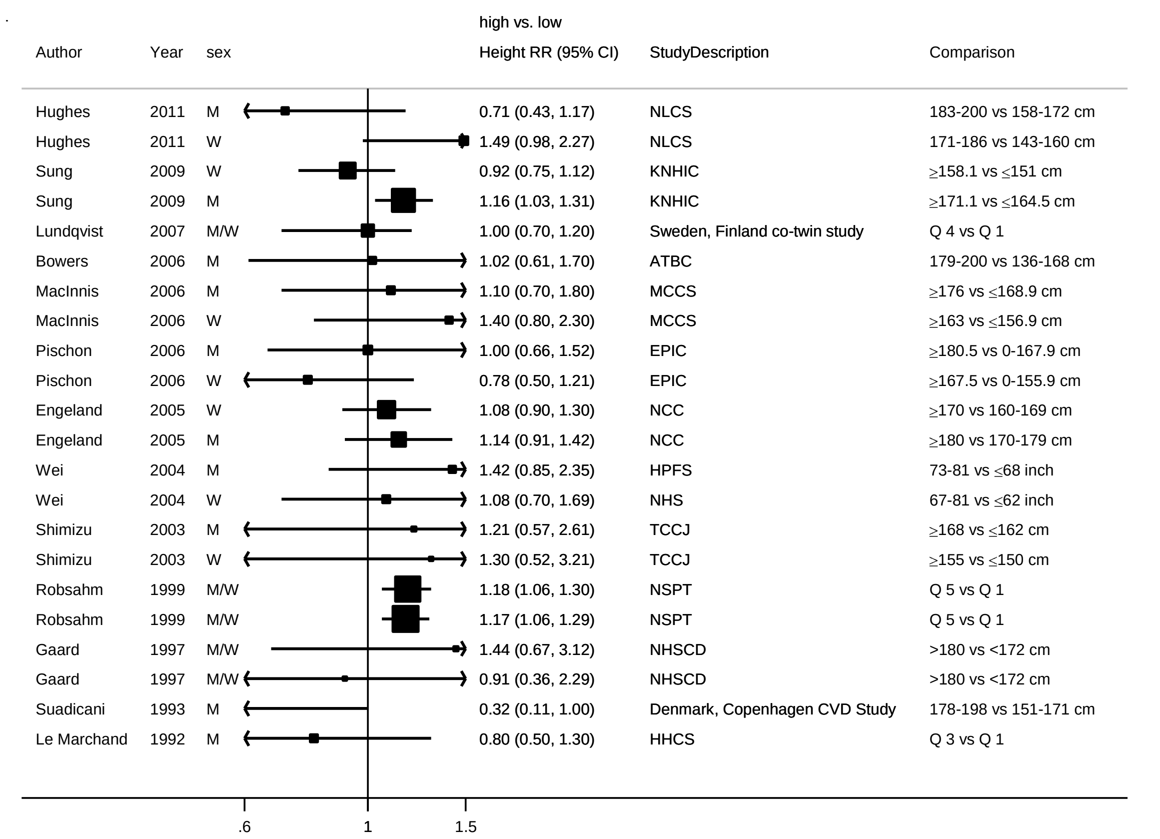


Figure 589 RR (95% CI) of rectal cancer for 5 cm increase of height

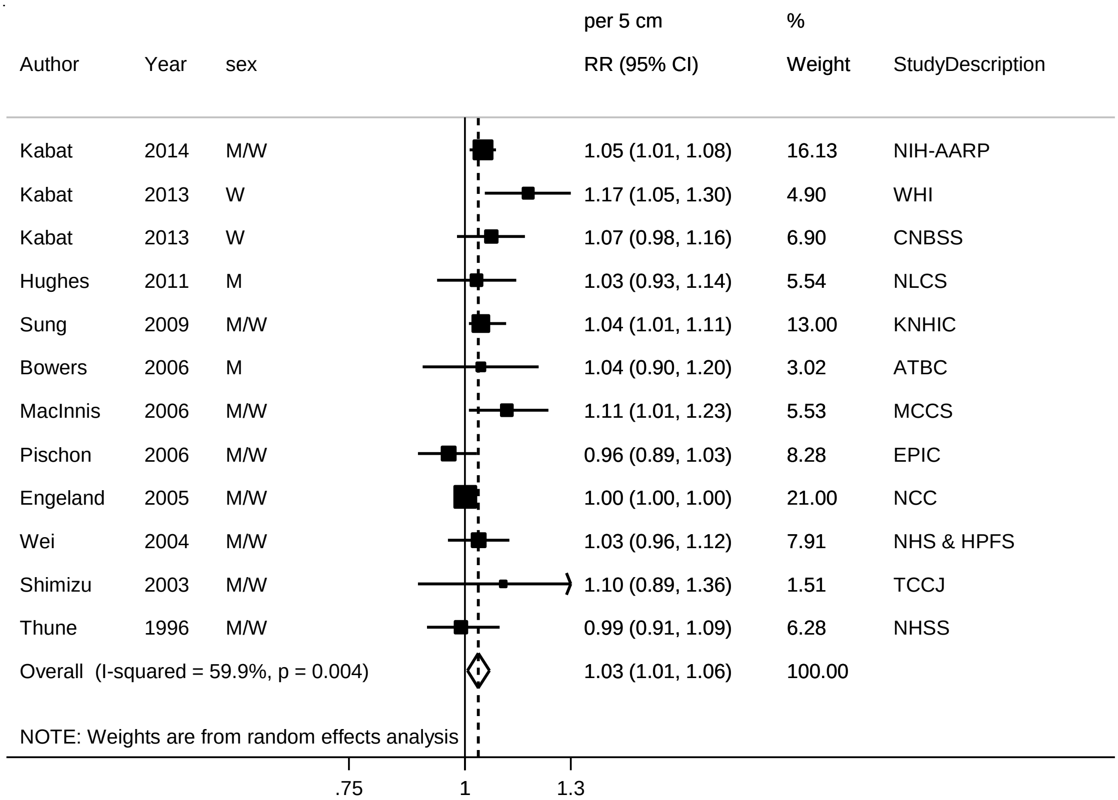
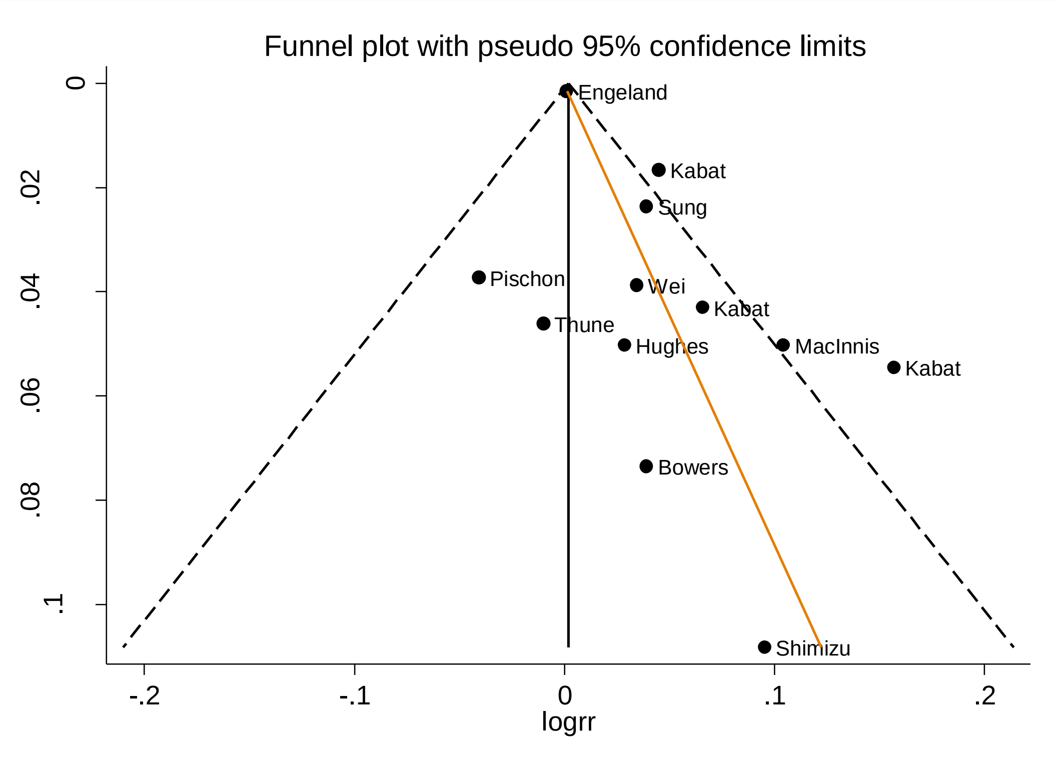


Figure 590 Funnel plot of studies included in the dose response meta-analysis of height and rectal cancer



p for Egger's test=0.002

Figure 591 RR (95% CI) of rectal cancer for 5 cm increase of height by sex

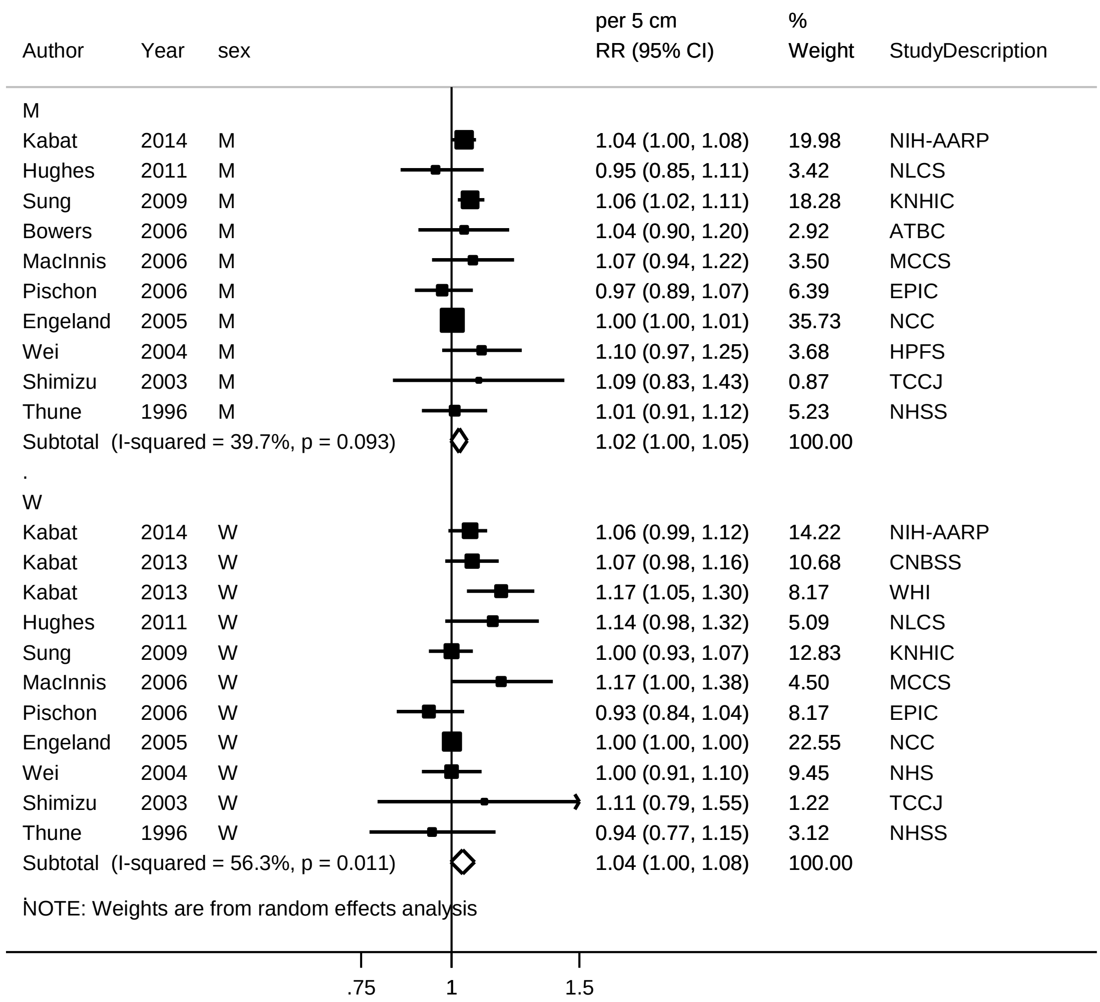


Figure 592 RR (95% CI) of rectal cancer for 5 cm increase of height by geographic location

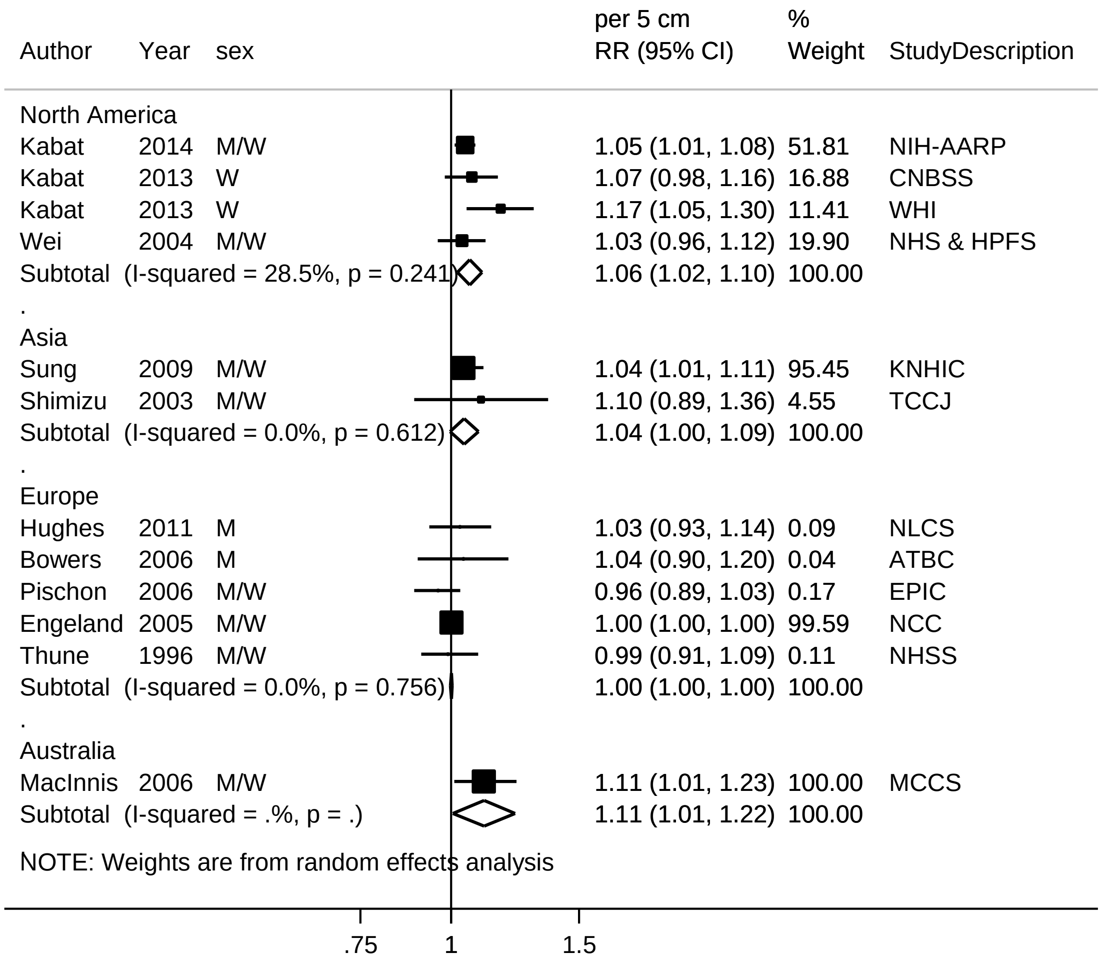
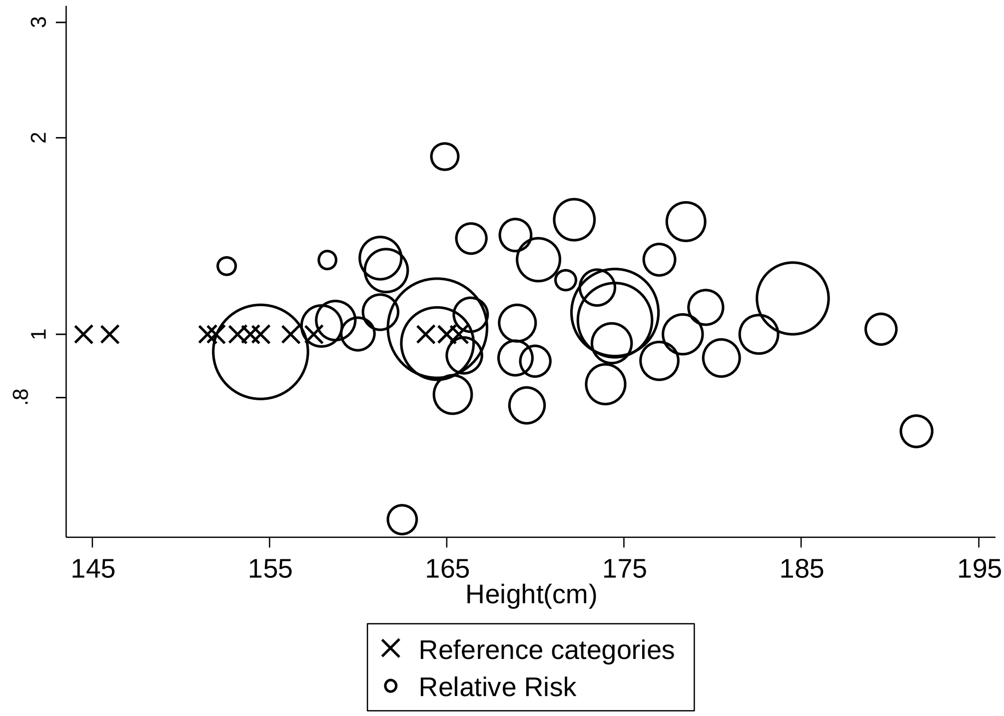
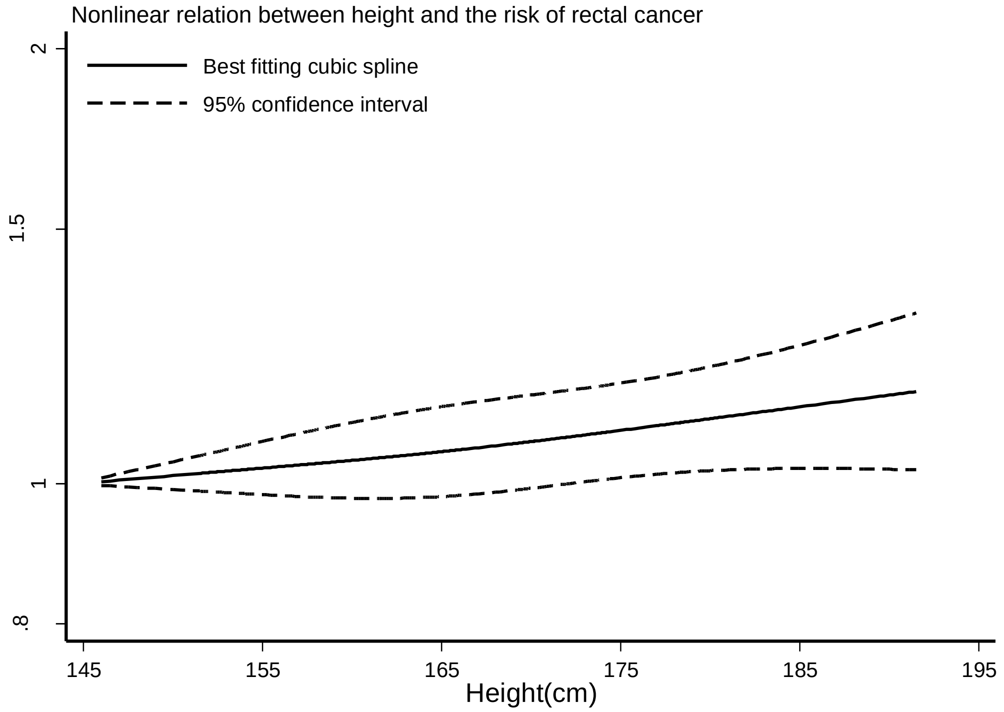


Figure 593 Relative risk of rectal cancer and height estimated using non-linear models





p for non-linearity=0.75

Table 348 Table with height values and corresponding RRs (95% CIs) for non-linear analysis of height and rectal cancer

Height (cm)	RR (95%CI)
144.5	1.00
154.5	1.02 (0.98-1.07)
165	1.05 (0.98-1.13)
170	1.07 (0.99-1.15)
174.5	1.09 (1.01-1.17)
184.5	1.13 (1.02-1.24)
191.5	1.16 (1.02-1.31)

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Appendix 1

a) Anthropometric characteristics investigated by each study

Several studies investigated BMI, weight, height, waist circumference, and waist-to-hip ratio and colorectal cancer risk. The anthropometric characteristics investigated by each study are indicated with a cross in the list below:

WCRF Code	Author	Year	Country	Study Description	BMI	Height	Weight	Waist circumference	Waist-to-hip-ratio
COL41055	Taghizadeh	2015	Netherlands	VCS	X				
COL41010	Bhaskaran	2014	UK	CPRD	X				
COL41041	Guo	2014	China	Northern China 2006-2011	X				
COL41018	Song	2014	Finland	FINRISK	X				
COL41065	Wie	2014	Korea	Cancer Screening Examination Cohort, Korea (CSECK)	X				
COL40965	Kabat	2013	USA	Women's Health Initiative	X			X	X
COL40966	Kitahara	2013	USA	PLCO	X				
COL40936	Li	2013	China	SMHS	X		X	X	X
COL40937	Li	2013	China	SWHS	X		X	X	X
COL40958	Morikawa	2013	USA	HPFS	X				
COL40959	Morikawa	2013	USA	NHS	X				
COL40952	Poynter	2013	USA	IWHS	X				
COL40981	Gray	2012	USA	HAHS	X				
COL41069	Park	2012	UK	EPIC-Norfolk	X			X	
COL40925	Renehan	2012	USA	NIH-AARP	X		X		
COL40893	Dehal	2011	USA	NHEFS	X				
COL40895	Hughes	2011	Netherlands	NLCS	X	X		X	

WCRF Code	Author	Year	Country	Study Description	BMI	Height	Weight	Waist circumference	Waist-to-hip-ratio
COL40883	Odegaard	2011	Singapore	SCHS	X				
COL40836	Bassett	2010	Australia	MCCS	X		X		
COL40796	Laake	2010	Norway	NCS	X		X		
COL40849	Oxentenko	2010	USA	IWHS	X	X	X	X	X
COL40807	Yamamoto	2010	Japan		X			X	
COL40811	Prentice	2009	USA	WHI	X				
COL40643	Jee	2008	Korea	KNHIC	X				
COL40659	Song	2008	Korea	KNHIC	X				
COL40728	Thygesen	2008	USA	HPFS	X		X		
COL40666	Wang	2008	USA	CPS II	X			X	
COL40670	Reeves	2007	UK	MWS	X				
COL40699	Bowers	2006	Finland	ATBC	X	X	X		
COL40625	Larsson	2006	Sweden	COSM	X		X	X	
COL40752	Lukanova	2006	Sweden	NSHDC	X				
COL40751	MacInnis	2006	Australia	MCCS	X	X	X	X	X
COL40627	MacInnis	2006	Australia	MCCS	X	X	X	X	X
COL01985	Pischon	2006	Europe		X	X	X	X	X
COL40708	Samanic	2006	Sweden		X				
COL41001	Tsai	2006	USA	Shell employees cohort study	X				
COL40675	Yeh	2006	Taiwan		X				
COL01941	Engeland	2005	Norway	norwegian composite cohort consisting of 3 groups	X	X			
COL01878	Rapp	2005	Austria	VHM-PP	X				
COL01832	Lin	2004	USA	WHS	X				
COL00362	Moore	2004		FHS	X			X	

WCRF Code	Author	Year	Country	Study Description	BMI	Height	Weight	Waist circumference	Waist-to-hip-ratio
COL01182	Sanjoaquin	2004	UK	OVS	X				
COL00581	Wei	2004	USA	NHS	X	X			
COL00375	Calle	2003	Colombia, USA, Puerto Rico	CPS II	X				
COL00522	Saydah	2003	USA	CLUE II	X				
COL00383	Colangelo	2002	USA	CHA	X	X			
COL00306	Lund Nilsen TI	2002	Norway	Norwegian Nord-Trondelag Health Study	X				
COL00558	Terry	2002	Canada	CNBSS	X				
COL00554	Terry	2001	Sweden	SMC	X				
COL40787	Kaaks	2000	USA	New York University Women's Health Study	X				
COL00097	Ford	1999	USA	NHANES I	X				
COL00183	Schoen	1999	USA	Cardiovascular Health Study	X			X	X
COL00185	Singh	1998	USA	AHS	X				
COL00622	Tulinius	1997	Iceland	Icelandic Cardiovascular Risk Factor Study	X		X		
COL00087	Chyou	1996	USA	HHP	X				
COL00269	Thune	1996	Norway	Norwegian national health screening service study	X	X			
COL00679	Lee	1992	USA	HAHS	X				
COL00774	Wu	1987	USA	Leisure World Cohort	X				

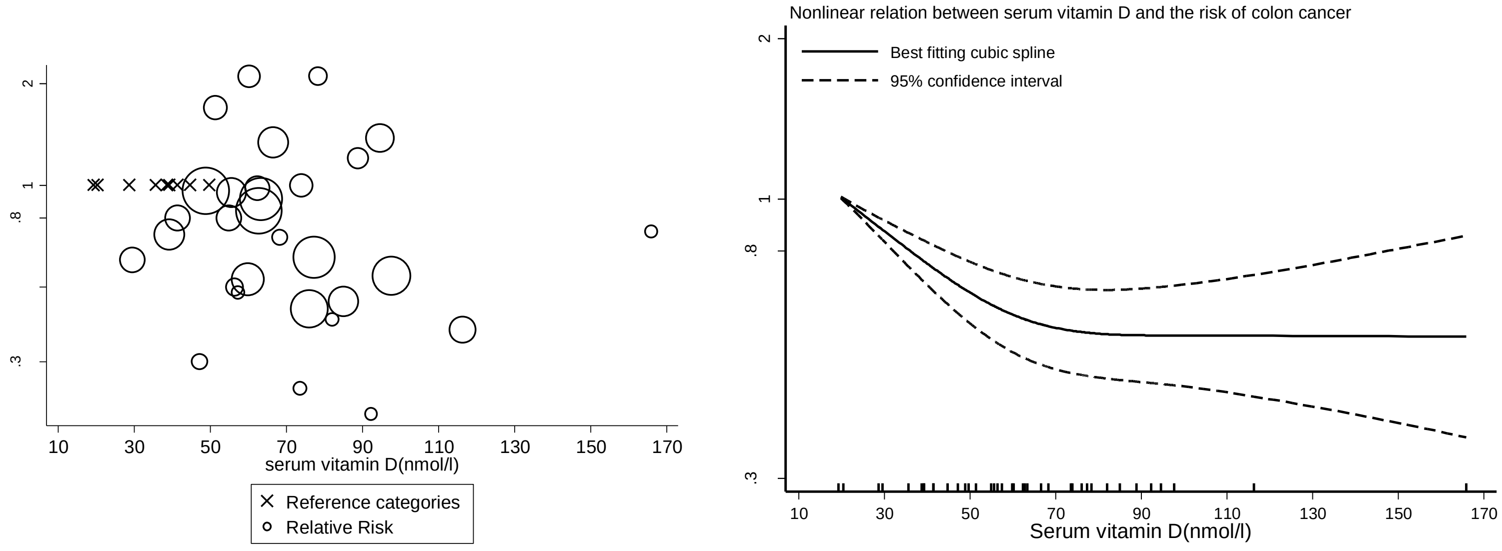
b) Fruit and vegetable characteristics investigated by each study

Several studies investigated fruit and vegetable and colorectal cancer risk. The types investigated by each study are indicated with a cross in the list below:

Author	WCRF code	Year	Country	StudyDescription	Fruit and vegetables	Vegetables	Cruciferous Vegetables	Green leafy vegetables	Fruits	Citrus fruit
Makarem	COL41060	2015	USA	FHS-Offspring Cohort	X	X				
Wie	COL41065	2014	Korea	Cancer Screening Examination Cohort, Korea (CSECK)	X					
Vogtmann	COL40986	2013	China	SMHS	X	X	X	X	X	X
Lee	COL40785	2009	China	SWHS	X					
van Duijnhoven FJ	COL40764	2009	Denmark,France,Germany,Greece,Italy,Netherlands,Norway,Spain,Sweden,UK	EPIC	X	X			X	
Nomura	COL40663	2008	USA	MEC	X	X	X		X	X
Park	COL40697	2007	USA	NIH-AARP	X	X	X	X	X	X
McCarl	COL40633	2006	USA	IWHS	X	X			X	
Lin	COL01831	2005	USA	WHS	X	X	X	X	X	X
Sato	COL01930	2005	Japan	MCS	X	X			X	
McCullough	COL00367	2003	USA	CPS II	X	X	X		X	X
Terry	COL00059	2001	Sweden	SMC	X	X			X	
Michels	COL00365	2000	USA	NHS	X	X	X	X	X	X
Michels	COL00365	2000	USA	HPFS	X	X	X	X	X	X
Voorrips	COL00578	2000	Netherlands	NLCS	X	X		X	X	X
Zheng	COL00209	1998	USA	IWHS	X					
Steinmetz	COL00178	1994	USA	IWHS	X	X	X	X	X	
Shibata	COL00740	1992	USA	Leisure World Cohort	X	X			X	

c) Supplementary figures and tables of nonlinear dose-reponse meta-analysis of colon and plasma/serum vitamin D

Suplementary figure: Relative risk of colon cancer and serum vitamin D estimated using non-linear models



p for non-linearity=< 0.001

Supplementary table Table with values and corresponding RRs (95% CIs) for non-linear analysis of serum vitamin D and colon cancer

Serum Vitamin D (nmol/l)	RR (95%CI)
20.4	1.00
28.7	0.89 (0.85-0.92)
39.19	0.77 (0.70-0.84)
51.42	0.66 (0.57-0.76)
66.64	0.58 (0.49-0.69)
85	0.56 (0.46-0.68)
94.60	0.56 (0.45-0.69)
165.99	0.55 (0.36-0.85)

Appendix 2 Colorectal adenomas. Recent meta-analyses on colorectal adenomas and relevant exposures

(Only the most recent or larger meta-analysis is shown)

2.2.1.3 Total allium vegetables

Author, Year	Number of studies	Comparison	RR (95%CI)	Heterogeneity (I^2, p value)*
Turati, 2014	3 Case-control studies	Highest vs lowest	0.88(0.80-0.98)	0%, 0.81

2.3Legumes

Author, Year	Number of studies	Comparison	RR (95%CI)	Heterogeneity (I^2, p value)*
Keum, 2014	13	Highest vs lowest	0.83(0.75-0.93)	26%, 0.15
	Case-control:10		0.86 (0.76–0.98)	25%, 0.18
	Prospective:3		0.73 (0.61–0.88)	0%, 0.64

2.5 White meat and fish

Author, Year	Number of studies	Comparison	RR (95%CI)	Heterogeneity (I^2, p value)*
Xu, 2013				
White meat	12	Highest vs lowest	0.96(0.84-1.09)	33%, 0.12
	Case-control:8		0.84 (0.67–1.06)	41%, 0.10
	Prospective:4		0.73 (0.61–0.88)	0%, 0.64
Fish	11		0.97(0.80-1.19)	42%, 0.07
	Case-control:10		0.94(0.76-1.17)	42%, 0.08
	Prospective:1		1.25(0.85-1.84)	-
Poultry	7		0.96(0.82-1.18)	38%, 0.14
	Case-control:5		0.96(0.72-1.29)	54%, 0.07
	Prospective:2		0.97(0.78-1.21)	0%, 0.35

2.5.1.2 Processed meat

Author, Year	Number of studies	Comparison	RR (95%CI)	Heterogeneity (I^2, p value)*
Aune, 2013	All: 10	Per 50 g/day	1.29 (1.10-1.53)	27%
	Case-control: 8		1.23 (0.99-1.52)	37 %
	Prospective: 2		1.45 (1.10-1.90)	0 %

2.5.1.3 Red meat

Author, Year	Number of studies	Comparison	RR (95%CI)	Heterogeneity (I^2, p value)*
Aune, 2013	All: 16	Per 100 g/day	1.27 (1.16-1.40)	5%
	Case-control: 10		1.34 (1.12-1.59)	31 %
	Prospective: 6		1.20 (1.06-1.36)	0 %

5.1.2 Dietary Fibre

Author, Year	Number of studies	Comparison	RR (95%CI)	Heterogeneity (I^2, p value)*
Ben , 2012	20	Per 10g/day	0.91 (0.87- 0.95),	54%, 0.008
	Case control:11		0.88(0.83-0.94)	49%, 0.03
	Prospective:3		0.96(0.90-1.01)	43%, 0.17
	Cereal fibre 8		0.70(0.51–0.96)	75%, 0.001
	Vegetable fibre 5		0.85 (0.71–1.03)	58%,0.05
	Fruit fibre 5		0.79 (0.66–0.94)	28%, 0.24

5.4 Alcohol

Author, Year	Number of studies	Comparison	RR (95%CI)	Heterogeneity (I^2, p value)*
Ben , 2015	30	Per 25g/day	1.27(1.17-1.37)	77%, <0.001
	Case control:27		1.28 (1.16−1.41)	76%, <0.001
	Prospective:3		1.29 (1.06-1.57)	77%, <0.001
Zhu, 2014	25	Highest vs lowest	1.16 (1.10, 1.22)	44%, 0.01
	Case control:23		1.17 (1.11, 1.22)	35%, 0.05
	Prospective:2		1.08 (0.88, 1.33)	71%, .06

5.5.1 Dietary vitamin A, beta-carotene and retinol

Author, Year	Number of studies	Comparison	RR (95%CI)	Heterogeneity (I^2, p value)*
Xu, 2012	8 (1 nested case-control and 7 case-control studies)	Highest vs lowest Dietary vitamin A	0.87 (0.67-1.13)	44%, 0.08
	4	Highest vs lowest Dietary beta-carotene	0.47 (0.24-0.91)	74%, 0.009
	3	Highest vs lowest Dietary retinol	0.84 (0.50-1.39)	46%, 0.16

5.5.9 Dietary vitamin C

Author, Year	Number of studies	Comparison	RR (95%CI)	Heterogeneity (I^2, p value)*
Xu, 2012	12 (1 nested case-control and 11 case-control studies)	Highest vs lowest	0.78 (0.62-0.98)	59%, 0.005

5.5.11 Dietary vitamin E

Author, Year	Number of studies	Comparison	RR (95%CI)	Heterogeneity (I^2, p value)*
Xu, 2012	10 (1 nested case-control and 9 case-control studies)	Highest vs lowest	0.87 (0.69-1.10)	55%, 0.017

5.5.10 Serum vitamin D

Author, Year	Number of studies	Comparison	RR (95%CI)	Heterogeneity (I^2, p value)*
Lee, 2011	9 (5 case-control and 4 cohort studies)	Per 10 ng/mL	0.93 (0.87-0.98)	63%, 0.006
Yin, 2011	Adenoma incidence 8	20 ng/ml	0.82 (0.69–0.97)	0.02
	Adenoma recurrence 2		0.87 (0.56–1.35)	0.52
	Adenoma incidence and recurrence10		0.84 (0.72–0.97)	0.02

5.6.3 Total Calcium

Author, Year	Number of studies	Comparison	RR (95%CI)	Heterogeneity (I^2, p value)*
Keum, 2014	13	Per 300mg/day	0.93(0.90-0.97)	49%, 0.02
	Retrospective:5		0.91 (0.82–1.01)	58%, 0.05
	Prospective:8		0.95 (0.92–0.98)	45%, 0.08
	High risk adenoma 6		0.89(0.85-0.94)	17%, 0.30
	Small adenoma 3		0.97(0.94-1.01)	0%, 0.91

5.6.4 Total selenium

Author, Year	Number of studies	Comparison	RR (95%CI)	Heterogeneity (I^2, p value)*
Cai, 2012	10 (4 case-control, 2 nested case-control, 2 cohort and 2 RCT studies)	Highest vs lowest	0.88(0.67-1.17)	55.1%, 0.009

6. Physical activity

Author, Year	Number of studies	Comparison	RR (95%CI)	Heterogeneity (I^2, p value)*
Wolin, 2011	20	Highest vs lowest	0.84 (0.77, 0.92)	46%, <0.001

8.1.1 BMI

Author, Year	Number of studies	Comparison	RR (95%CI)	Heterogeneity (I^2, p value)*
Ben, 2012	Case-control: 7	Per 5 kg/m^2	1.09 (1.05–1.15)	34.3%
	Prospective:16		1.28 (1.08–1.51)	73.4%
	Cross-sectional: 13		1.20 (1.11–1.29)	81.1

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(Only the most recent publication of a trial, or that with the larger number of cases is shown).

1. Pattern of diet (Low fat, high fibre, fruits and vegetables)

Author, Year, Country Study name	**Study name, characteristics**	**Cases** Treatment/ control	**Case ascertainment**	**Outcome**	**Treatment/ comparison**	**RR (95%CI) Ptrend**
Sansbury, 2009 Polyp Prevention Trial USA	Randomised Control Trial, 947 control group, *958* intervention group Age at least 35- years, M/W with at least one histologically confirmed colorectal adenoma identified 4 years follow-up	65/347	Full colonoscopies at baseline, their 1-year visit, and the end of the trial intervention, about 4 years after randomization	Adenoma recurrence	Supercompliers intervention (20% energy intake from fats, at least 18 g of fibre and 3.5 servings of fruits and vegetables per 1,000 kcal) vs no intervention	0.65 (0.47-0.92)
		7/66		Advanced adenoma		0.44 (0.18-1.05)

2.1.1.1 Dietary fibre and Lactobacillus casei

Author, Year, Country Study name	Study name, characteristics	Cases Treatment/ control	Case ascertainment	Outcome	Treatment/ comparison	RR (95%CI) Ptrend
Ishikawa, 2005 Japan	Randomised Control Trial, Age: 40-65 years, at least two colorectal tumours M/W 95, 96, 96, 93 were assigned to wheat bran, lactobacillus casei, both or no intervention	106/93	Colonoscopy 2 or 4 years after start treatment	Adenoma recurrence (principal outcome)	Wheat bread vs dietary information	1.31 (0.87–1.97)
		107/118			L.caseii Lactobacillus vs dietary information	0.76 (0.50–1.15)
					Tumour occurrence in the group with wheat brand and Lcassei was higher than in the group with any of the two groups and lower than in the no intervention group	

5.5.3 Folic acid

Author, Year, Country Study name	Study name, characteristics	Cases Treatment/ control	Case ascertainment	Outcome	Treatment/ comparison	RR (95%CI) Ptrend
Gao, 2013 China	980 men and women (> 50 years) confirmed no adenoma by colonoscopy in past 5 years Average 37.8 months of follow-up	64/132	Colonoscopy examination (Colorectal adenoma occurrence was primary outcome)	Any adenoma	1 mg/day folic acid supplement or treatment without folic acid	0.74 (0.65-0.85)
		42/78		|Left colon adenoma		0.40 (0.33-0.49)
		16/29		Right colon adenoma		0.77 (0.55-1.09)
		8/22		Advanced adenoma		0.67 (0.58-0.76)
Figuereido, 2009 US, Canada, UK Aspirin/Folate Polyp Prevention Study (AFPPS) NHS/HPFS Polyp Prevention Study, United Kingdom Colorectal Adenoma Prevention (ukCAP) Trial	Pooled analyses of 3 trials: 1,324 participants treatment, 1,308 placebo Up to 3.5 years of treatment	343/339	Large bowel endoscopy and pathology review	Adenoma recurrence	0.5 or 1.0 mg/ day of folic acid or placebo	0.98 (0.82–1.17) P=0.81
		105/97		Advanced lesions		1.06 (0.81–1.39) P=0.65
Jaszewski, 2008	49 treated, 45	49/45	Colonoscopy	Any adenoma	5 mg/day	Lower number of

Author, Year, Country Study name	Study name, characteristics	Cases Treatment/ control	Case ascertainment	Outcome	Treatment/ comparison	RR (95%CI) Ptrend
USA	placebo 3 year follow-up				folic acid for 3 years vs placebo	adenomas/ patient in the intervention group (0.36 ± 0.69) compared to placebo group (0.82 ± 1.17) P=0.02

5.6.3 Calcitriol, acetylsalicylic acid, and calcium carbonate

Author, Year, Country Study name	Study name, characteristics	Cases Treatment/ control	Case ascertainment	Outcome	Treatment/ comparison	RR (95%CI) Ptrend
Pommergaard, 2015 Europe, USA, Russia,	Men and women aged 40-75 years with previous adenoma, 209 assigned to 0.5 µg calcitriol, 75 mg acetylsalicylic acid, and 1250 mg calcium carbonate each day for 3 years, 218 with placebo	52/58	colonoscopy after 3 years	Adenoma recurrence assessed	Treatment vs placebo	0.94 (0.60–1.48)

5.6.3 Calcium and Vitamin D

Author, Year, Country Study name	**Study name, characteristics**	**Cases** Treatment/ control	**Case ascertainment**	**Outcome**	**Treatment/ comparison**	**RR (95%CI) Ptrend**
Baron, 2015 USA Calcium Polyp Prevention Study	Patients with past diagnosed adenomas and no known colorectal polyps remaining after complete colonoscopy Partial 2x2 factorial design: 2259 participants to receive daily vitamin D3 (1000 IU), calcium as carbonate (1200 mg), both, or neither	438/442	Colonoscopy was anticipated to be performed after 3 or 5 years	Adenomas (primary end point)	Vitamin D vs no Vitamin D	0.99 (0.89–1.09)
		345/362			Calcium vs no calcium	0.95 (0.85–1.06)
		259/259			Calcium and Vit D vs calcium alone	1.01 (0.88–1.15)
		174/183			Calcium and Vitamin D vs placebo	0.93 (0.80–1.08)

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Appendix 3 Protocol

Continuous update of the WCRF-AICR report on diet and cancer

Protocol: Colorectal Cancer

Prepared by: Imperial College Team

The current protocol for the continuous update should ensure consistency of approach to the evidence, common approach to the analysis and format for displaying the evidence used as in the literature reviews for the Second Expert Report[1].

The starting point for this protocol are:

- The convention for conducting systematic reviews developed by WCRF International for the Second Expert Report [1]
- The protocol developed by the SLR group on colorectal cancer for the Second Expert Report (Wageningen University, the Netherlands) [1]

The peer-reviewed protocol will represent the agreed plan for the Continuous Update. Should departure from the agreed plan be considered necessary at a later stage, this must be agreed by the Continuous Update Panel (CUP) and the reasons documented.

Background.

In the judgment of the Panel of the WCRF-AICR Second Expert Report [2], the factors listed below modify the risk of colon and rectum cancers. Judgments are graded according to the strength of the evidence.

FOOD, NUTRITION, PHYSICAL ACTIVITY, AND CANCERS OF THE COLON AND THE RECTUM		
In the judgement of the Panel, the factors listed below modify the risk of cancers of the colon and the rectum. Judgements are graded according to the strength of the evidence.		
	DECREASES RISK	INCREASES RISK

Convincing	Physical activity [1,2]	Red meat [3,4] Processed meat [4,5] Alcoholic drinks (men)[6] Body fatness Abdominal fatness Adult attained height[7]
Probable	Foods containing dietary fibre[8] Garlic[9] Milk [10,11] Calcium[12]	Alcoholic drinks (women) [6]
Limited –suggestive	Non-starchy vegetables[9] Fruits[9] Foods containing folate[8] Foods containing selenium[8] Fish Foods containing vitamin D [8,13] Selenium[14]	Foods containing iron [4,8] Cheese[10] Foods containing animal fats[8] Foods containing sugars[15]
Limited –no conclusion	Cereals (grains) and their products; potatoes; poultry; shellfish and other seafood; other dairy products; total fat; fatty acid composition; cholesterol; sugar (sucrose); coffee; tea; caffeine; total carbohydrate; starch; vitamin A; retinol; vitamin C; vitamin E; multivitamins; non-dairy sources of calcium; methionine; beta-carotene; alpha-carotene; lycopene; meal frequency; energy intake	
	None identified	

1 Physical activity of all types: occupational, household, transport, and recreational.
2 Much of the evidence reviewed grouped colon cancer and rectal cancer together as 'colorectal' cancer. ***The Panel judges*** that the evidence is stronger for colon than for rectum.
3 The term 'red meat' refers to beef, pork, lamb, and goat from domesticated animals.
4 Although red and processed meats contain iron, the general category of 'foods containing iron' comprises many other foods, including those of plant origin.
5 The term 'processed meat' refers to meats preserved by smoking, curing, or salting, or addition of chemical preservatives.
6 The judgements for men and women are different because there are fewer data

for women. Increased risk is only apparent above a threshold of 30 g/day of ethanol for both sexes.
7 Adult attained height is unlikely directly to modify the risk of cancer. It is a marker for genetic, environmental, hormonal, and also nutritional factors affecting growth during the period from preconception to completion of linear growth (see chapter 6.2.1.3).
8 Includes both foods naturally containing the constituent and foods which have the constituent added (see chapter 3.5.3). Dietary fibre is contained in plant foods (see box 4.1.2 and chapter 4.2).
9 Judgements on vegetables and fruits do not include those preserved by salting and/or pickling.
10 Although both milk and cheese are included in the general category of dairy products, their different nutritional composition and consumption patterns may result in different findings.
11 Milk from cows. Most data are from high-income populations, where calcium can be taken to be a marker for milk/dairy consumption. ***The Panel judges*** that a higher intake of dietary calcium is one way in which milk could have a protective effect.
12 The evidence is derived from studies using supplements at a dose of 1200 mg/day.
13 Found mostly in fortified foods and animal foods.
14 The evidence is derived from studies using supplements at a dose of 200 μg/day. Selenium is toxic at high doses.
15 'Sugars' here means all 'non-milk extrinsic' sugars, including refined and other added sugars, honey, and as contained in fruit juices and syrups. It does not include sugars naturally present in whole foods such as fruits. It also does not include lactose as contained in animal or human milks.

1. Research question

The research topic is:

The associations between food, nutrition and physical activity and the risk of colorectal cancer.

2. Review team

3. Timeline

The review for the Second Expert Report[1] ended in December 30th 2005. A pre-publication update extended the search to June 30th 2006 for exposures and cancer sites with suggestive, probable and convincing associations with the exposure of interest. In order to ensure the completeness of the database, the ICL will conduct the search with starting date January 1st 2010. The reviewer will verify that there are not duplicities in the database. With that purpose, a module for article search has been implemented in the interface for data entry.

List of tasks and deadlines for the continuous update on colorectal cancer:

Task	Deadline
Start Medline search of relevant articles	1st March, 2015
Review abstracts and citations identified in initial electronic search. Select papers for complete review	30th April 2015
Review relevant papers. Select papers for data extraction*	30th June, 2015
Data extraction	30th June, 2015
Start quantitative analysis	1st July, 2015
End of quantitative analysis	30th September, 2015
Send report to WCRF-AICR	18th December, 2015
Transfer Endnote files to WCRF	18th December, 2015

4. Search strategy

The Continuous update team will use the search strategy established in the SLR Guidelines with the modifications implemented by the SLR centre (Wageningen University) for the 2nd Expert Report[1] .

The complete search strategy and the modifications are in Annex 1.

5. Selection of articles

Only articles that match the inclusion criteria will be updated in the database. Pooled analysis and meta-analysis will be identified in the search, but they will not be included in the database. The results of these studies will be used for support in the preparation of the report.

5.1 Inclusion criteria

The articles to be included in the review:

- Have to be included in Medline from January 1st 2006.
- Have to present results from an epidemiologic study of one of the following types[†]:
    - Randomized controlled trial
    - Group randomized controlled trial (Community trial)
    - Prospective cohort study

- Nested case-control study
- Case-cohort study
- Historical cohort study

- Must have as outcome of interest, incidence of colorectal, colon or rectum cancers, or mortality for these cancers.
- Have to present results on the relevant exposures
- Published in English language*

† It was agreed between the SLR centre and WCRF secretariat to focus on cohort studies . The decision was based on the high number of cohort studies existing. Therefore evidence for exposures graded convincing, probable and limited suggestive in the 2nd Expert Report was based on the results of cohort studies. Filters for study design will not be implemented in the search strategy.

** The extent of the update has to be adequate to time and resources. For this reason the proposal is to give priority to articles published in English language. Most, if not all, high quality studies will be published in peer-reviewed journals in English language and referenced in the Medline database.*

5.2 Exclusion criteria

The articles to be excluded from the review:

- Are out of the research topic
- Studies focusing on pre-malignant colorectal conditions, for example colorectal adenomas (that will be the topic of a different review)
- Do not report measure of association between the exposure and the risk of colorectal, colon or rectum cancers
- The measure of the relationship between exposure and outcome is only the mean difference of exposure
- Are supplement to the main manuscript (e.g. Authors' Reply).
- Are published on-line as "Epub ahead of print" or "In Press". The data of these articles will be extracted after the definitive version is released.
- Are not in English language

Pooled analysis and meta-analysis will be used as support for interpretation, but the data will not be included in the database.

6. Exposures

The continuous update will use the labels and exposure codes listed in the SLR Guidelines for the Second Expert Report[1].

6.1 Biomarkers of exposure

In the SLR for the Second Expert Report[1], biomarkers of exposure were included under the heading and with the code of the corresponding exposure. Some review centres decided to include only biomarkers for which there was some evidence on reliability or validity, while other centres included in the database results on all the biomarkers retrieved in the search, independently of their validity. During the process of evaluation of the evidence, the Panel of Experts took in consideration the validity of the reported biomarkers.

The SLR centre on prostate cancer (Bristol University) prepared a list of biomarkers to be included and excluded, based on data of studies on validity and repeatability of the biomarkers. The continuous update on colorectal cancer will use these guidelines for exclusion of biomarkers. The list of included and excluded biomarkers and the reasons for exclusion prepared by the SLR centre Bristol is in Annex 2.

Biomarkers of effect of exposure and biomarkers of cancer are not included in this review.

7. Outcome

The outcome of interest is colorectal, colon or rectal cancer encompassing incidence and mortality. Results of studies on incidence and mortality will be presented separately.

Due to colorectal cancer screening, a proportion of colorectal cancer diagnoses can be of early localised disease. The information on whether the study population was undergoing screening and any other information provided in the papers related to screening practices for colorectal cancer or colorectal adenomas will be extracted and included in the database.

8. Databases

Only the Medline database will be searched. Data provided from the SLR Colorectal cancer for the Second Expert Report[1] indicates that 90 % of the articles included in the review have been retrieved from the Medline database.

9. Hand searching for cited references

For feasibility reasons, journals will not be hand searched in the continuous update.

Hand searching, and searching in other databases will be done after recommendation of the Continuous Update Panel or if there is some evidence that an important study has been missed by the search strategy. In the SLR 3% of the articles were retrieved by hand seraching. The CU team will review the references of meta-analyses and pooling projects that will be published during the update period.

10. Retrieving papers

The abstracts from the initial search results from PubMed will be reviewed by one person to assess each reference as to whether it is relevant and potentially relevant.

The complete papers of relevant and potentially relevant references and of references that cannot be excluded upon reading the title and abstracts will be retrieved. A second assessment will be done after review of the complete papers.

The assessment of papers will be checked by a second reviewer. It is envisaged that 10% of the assessment should be checked.

The IC team uses resources at Imperial College to retrieve the papers identified as satisfying the inclusion criteria. This should cover most of the online journal. For articles not accessible through the IC library, funds provided by WCRF-AICR will be required.

11. Labelling of references

For consistency with the previous data collected during the SLR process for the Second Expert Report[1], the Imperial College team will use the same labelling of references: the unique identifier for a particular reference will be constructed using a 3-letter code to represent the cancer site (e.g. COL for colorectal cancer), followed by a 5-digit number that will be allocated in sequence. For consistency with the SLR, the identification COL will be used for studies on colorectal, colon or rectal cancers, and for cancer subsites along the colon (ascendant, descendent, transverse colon, proximal or distal). The cancer sub-site will be extracted and the information included in the database.

12. Reference Manager Files

Reference Manager databases are generated in the continuous update containing the references of the initial search.

1) One of the customized fields (User Def 1) is named ‘inclusion’ and this field is marked ‘included’, ‘excluded’ for each paper, thereby indicating which papers are deemed potentially relevant based on an assessment of the title and abstract.
2) One of the customized fields (User Def 2) is named ‘reasons’ and this field should include the reason for exclusion for each paper.

3) The study identifier should be entered under the field titled ‘label’.

4) One of the customized fields (User Def 3) is named “study design”. This field indicates the study design of each paper:

Case-study / case series
Cross-sectional study
Randomised controlled trial
Group randomised control trial
Uncontrolled trial
Ecologic study

Case-control study
Non-randomised control trial
Prospective cohort study
Nested case-control study
Historical cohort study
Case-cohort study
Time series with multiple measurements
Case only study with prospective exposure measurement
Case only study with retrospective exposure measurement

The Reference Management databases will be converted to EndNote and sent to WCRF Secretariat.

13. Data extraction

The Access databases generated during the SLR for the Second Expert Report[1] have been merged into one database at Imperial College.

The IC team will update the merged database using a new interface created at Imperial College. The interface allows the update of all variables included in the Access databases for the SLR for the Second Expert Report[1], including quality characteristics and results, the variables for which the exposure – disease association was adjusted for, the strategy of analysis, the validity of the measurements and whether analyses were performed that attempted to correct for the likely effect of measurement error in the exposure variable.

The study design algorithm devised for use of the SLR centres for the Second Expert Report[1] will be used to allocate study designs to papers (SLR specification manual – version 15 pp 123). In some cases it will be appropriate to assign more than one design to a particular paper because the methods for assessment of different exposures may vary, because the data analyses correspond to more than one study design (e.g. analyses in the entire cohort and nested case-control).

13.1 Quality control

Ideally, data extraction should be performed in duplicate for all papers. This is not feasible with the available resources. Instead, 10% of the data extracted from the studies that are included throughout the year of continuous update will be checked by a second reviewer at Imperial College.

Similarly 10% of the studies indicated as excluded will be checked by a second reviewer.

Some automatic checks will be conducted in the data:

- the confidence interval contains the effect estimate and is symmetrical
- the sum of cases and non case individuals in the categories of exposures add up to the total number of cases and non case individuals (for analysis that are not in subgroups). If these exceed the total number of cases and controls or are lower than 20% the study will be flagged and checked.

13.2 Choice of Result

The effect measure estimated with all the models reported in the paper should be extracted. The models should be labelled as not adjusted, minimally adjusted, intermediately adjusted and maximally adjusted. In addition, the IC reviewer should indicate a "best model" for inclusion in reports. Unadjusted results will be used only when no others were given.

The best model has to be controlled for confounding by age. The control of confounding by age can be done by adjustment or by matching. Where there is more than one model adjusting for age, the most adjusted one will be considered to be the best model. Exception to this criterion will be "mechanistic" models, adjusting for variables likely to be in the causal pathway. Examples of mechanistic models are:

1) results for meat adjusted for saturated fatty acids
2) results for fish adjusted for n-3 fatty acids
3) results for milk and dairy products adjusted for calcium
4) results for BMI adjusted for weight
5) results for waist-to-hip ratio adjusted for either waist or hip circumference

When such results (over adjusted results) are reported, the most adjusted results that are not over adjusted will be extracted.

Potential risk factors of colorectal cancer are:

- Age
- Sex
- Smoking habits
- Social class/ living conditions/ income
- Physical activity
- Body mass index
- Total energy intake
- Alcohol consumption
- Ethnicity
- Supplement use

Family history of colorectal cancer (first degree relatives sufficient)
NSAID usage
Hormone replacement therapy (in women)

Sometimes, some of the potential risk factors are not kept in the model because their inclusion does not modify the risk estimates. If this is specified in the article text, this model should also be considered the "best model".

13.3 Effect modification

The IC team should report whether interaction terms were included in models and extract the results, in particular any statistical tests of heterogeneity across strata. This information was not collected in a standardized way in the SLR. In many cases, a note was added in the database indicating that an interaction term was reported in the article. The IC team envisage developing a module for data entry of results of analysis on effect modifiers and interactions, but this facility is at its early stage of development.

13.4 Gene-nutrient interaction

No attempt was made to critically appraise or analyse the studies that reported gene-nutrient interactions in the Second Expert Report[1]. The results of these studies were described in the narrative under the relevant exposures.
A separate protocol to handle gene-nutrient interactions is in the process of being developed.

13.5 Multiple articles

Data should be extracted for each individual paper, even if there is more than one paper from any one study, unless the information is identical. The most appropriate set of data on a particular exposure will be selected amongst the papers published on a study to ensure there is no duplication of data from the same study in an analysis. To facilitate the detection of multiple reports from the same study, the study name in each article should be extracted.

If needed, the IC team should contact the authors for clarification. If the matter remains unresolved the review coordinator of the continuous update will discuss the issue with the WCRF Secretariat and the CUP, if necessary.

14. Reports

14.1 Content of the report:

14.1.1 Results of the search

Information on number of records downloaded, number of papers thought potentially relevant after reading titles and abstracts and number of included relevant papers. The reasons for excluding papers should also be described.

14.1.2 Description of studies identified in the continuous update

Amount of data and study types (i.e. numbers of different types of studies)
Populations studied
Exposures identified
Outcomes identified

14.1.3 Summary of number of studies by exposure and study type, separated on new (studies identified in the continuous update) and total.

14.1.4 Tabulation of study characteristics

Information on the characteristics (e.g. population, exposure, outcome, study design) and results of the study (e.g. direction and magnitude) of the new studies should be summarised in tables using the same format as for the SLR for the Second Expert Report[1].
Within this table the studies should be ordered according to design (trials, cohort studies). The results will be presented separately for advanced/aggressive colorectal cancer.

A summary table with number of studies by exposure should be produced:

Exposure Code	Name	Outcome	Number of controlled trials			Number of cohort studies		
			Total	SLR	Continuous update	Total	SLR	Continuous update

A table of study characteristics, in two parts below, should be produced:

Author, Year, country, WCRF Code	Study design	Country, Ethnicity, other characteristics	Age (mean)	Cases (n)	Non cases (n/person-years)	Case ascertainment	Follow-up (years)

Assessment details	Category of exposure	Subgroup	No cat	OR	(95% CI)	p trend	Adjustment factors						
							A	B	C	D	E	F	G

Where
A : Age
B : Socioeconomic status
C : Colorectal cancer screening
D : Anthropometry: Height or BMI
E : Energy intake, other dietary factors
F : Race
G : Others, e.g. family history, smoking, physical activity, marital status

14.2 Data analysis

Meta-analytic and narrative aspects of the data analysis will complement each other. The meta-analyses will not solely focus on simple binary (''high-low'') comparisons but also examine the evidence for dose-response effects. Exposure effect estimates from observational studies may be affected by confounding, selection bias, and error in measurement of exposure variables. The existence of a dose-response relation between exposure and outcome can help address uncertainties about misclassification effects and helps strengthen causal reasoning.

14.2.1 When to do a meta-analysis

A meta-analysis for a particular exposure and outcome will be conducted when 3 or more trials or cohort studies has been published after the publication of the 2nd expert report, and if the new and the previous results totalise to more than 3 trials or 5 cohort studies.

The meta-analysis will include also the study results extracted during the SLR and included in the merged database. Special care will be taken to avoid including more than once the results of the same study (e.g. previous analyses and re-analyses after a longer follow-up).

14.2.2 Methods

The methods that will be used to do meta-analyses will be the same methods used for the Second Expert Report[1].

In meta-analysis of ''high-low'' comparisons, summary RR estimates with their corresponding 95% CIs will be derived with the method of DerSimonian and Laird [3] using the assumption of a random effects model that incorporated between-study variability.

To estimate the dose-response relationship, category-specific risk estimates will be transformed into estimates of the relative risk (RR) associated with a unit of increase in exposure by use of the method of generalised least-squares for trend estimation [4]. The unit of increment will be kept as the same unit used in the SLR. We will assign to each exposure category the mid-point for closed categories, and the median for open categories (assuming a normal distribution for exposure) [5]. The relative risk estimates for each unit of increase of the exposure will be combined by use of random-effect meta-analysis[3].

We will use the "best" (most adjusted risk estimate) from each study. Heterogeneity between studies will be assessed with the I^2 statistic as a measure of the proportion of total variation in estimates that is due to heterogeneity, where I^2 values of 25%, 50%, and 75% correspond to cut-off points for low, moderate, and high degrees of heterogeneity [6].

When possible, meta-regression should be performed to investigate sources of heterogeneity. The variables that will be examined as sources of heterogeneity are geographic area (North-America –Non black population, North-America –Black population, Europe, Asia, Other); year of publication, outcome (incidence or mortality), stage of disease (all combined or not specified and aggressive/advanced staged).

Other variables that may be considered as source of heterogeneity are characterisation of the exposure (FFQ, recall, diary, anthropometry etc.), exposure range (including correction for measurement error, length of intervention), adjustment for confounders, age at recruitment and time of follow-up. However, the interpretation should be cautious. If a considerable number of study characteristics are considered as possible explanations for heterogeneity in a meta-analysis containing only a small number of studies, then there is a high probability that one or more will be found to explain heterogeneity, even in the absence of real associations with between the study characteristics and the size of associations.

A usual method of assessing and displaying heterogeneity, we will construct and examine forest plots. Publication bias will be examined in funnel plots.

We will use STATA version 9.0 (College Station, TX, USA) to analyse data.

14.2.3 Missing values

The data needed to estimate the dose-response associations are often incompletely reported, which may result in exclusion of results from meta-analyses. Failure to include all available evidence will reduce precision of summary estimates and may also lead to bias if propensity to report results in sufficient detail is associated with the magnitude and/or direction of associations.

A recent review showed that only 64% of the results of cohort studies provide enough data to be included in dose-response meta-analysis[7]. Moreover, results that showed evidence of an association were more likely to be usable in dose-response meta-analysis than results that found no such evidence. Insufficient detail in reporting of results of observational studies can lead to exclusion of these results from meta-analyses and is an important threat to the validity of systematic reviews of such research.

We will therefore use methods to compute missing data recently summarized[7] . The information required for data to be usable for meta-analysis, for each type of result is:

Dose-response data (regression coefficients)

Estimated odds, risk, or hazard ratio per unit increase in exposure with confidence interval (or standard error of log ratio or p value)
Unit of measurement

Quantile-based or category data

No. of cases and non cases (or person-time denominator for cohort studies) in each group; or total number of cases and non cases (or study size) plus explicitly defined equal-sized groups (for quantile-based data)
Estimated odds, risk, or hazard ratios with confidence intervals (or standard error of log ratio or p value) compared with the baseline group, for each non baseline group (if these are not reported, unadjusted odds ratios can be calculated from the numbers of cases and controls)
Range, mean, or median of exposure in each group
Unit of measurement

The most frequently occurring problems in reporting and suggested solutions to make results usable in a dose-response meta-analysis are in the next table.

Type of data	Problem	Assumptions
Dose-response data	Serving size is not quantified or ranges are missing, but group descriptions are given	Use serving size recommended in SLR Prostate[1] (Annex 3. Same as SLR prostate for consistency in the analyses)
	Standard error missing	The p value (either exact or the upper bound) is used to estimate the standard error
Quantile-based data	Numbers of controls (or the denominator in cohort studies) are missing	Group sizes are assumed to be approximately equal
	Odds ratio is missing	Unadjusted odds ratios are calculated by using numbers of cases and controls in each group
	Confidence interval is missing	Standard error and hence confidence interval were calculated from raw numbers (although doing so may result in a somewhat smaller standard error than would be obtained in an adjusted analysis)
	Group mean are missing	This information may be estimated by using the method of Chene and Thompson [5] with a normal or lognormal distribution, as appropriate, or by taking midpoints (scaled in unbounded groups according to group numbers) if the number of groups is too small to calculate a distribution
Category data	Numbers of cases and controls (or the denominator in cohort studies) is missing	These numbers may be inferred based on numbers of cases and the reported odds ratio (proportions will be correct unless adjustment for confounding factors considerably alter the crude odds ratios)

14.2.4 Influence of updated studies in the overall results

We will do influence-analyses to assess the effect of each updated study on the summary risk estimates[8] .

References

1. World Cancer Research Fund/ American Institute for Cancer Research. Systematic Literature Review – Support Resource. In : Food, Nutrition, Physical Activity and the Prevention of Cancer: A Global Perspective.Washington DC: AICR , 2007

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3. DerSimonian R, Laird N (1986) Meta-analysis in clinical trials. Control Clin Trials 7:177–188

4. N Orsini, R Bellocco and S Greenland, Generalized least squares for trend estimation of summarized dose-response data, Stata *J* 6 (2006), pp. 40–57

5. Chêne G, Thompson SG. Methods for summarizing the risk associations of quantitative variables in epidemiologic studies in a consistent form.Am J Epidemiol. 1996;144(6):610-21.

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8. A Tobias, Assessing the influence of a single study in meta-analysis, Stata Tech Bull 47 (1999), pp. 15–17.

Protocol: Colorectal cancer

Prepared by: Imperial College Team

Annex 1: Search strategy

We will use the standard search strategy for systematic literature review in PubMed developed by WCRF.
This standard search uses a combination of subject heading terms e.g. MeSH in PubMed and has been structured to include all the exposures cited in the SLR Specification Manual (see below).

This search strategy will be combined with the following search questions:

#1 Colorectal neoplasms [MeSH] OR intestinal polyps [MeSH]
#2 malign* [tiab] OR neoplasm* [tiab] OR carcinoma* [tiab] OR cancer* [tiab] OR tumor* [tiab] OR tumour* [tiab] OR polyp* [tiab]
#3 colon [tiab] OR rectum [tiab] OR rectal [tiab] OR colorectum [tiab] OR colorectal [tiab] OR large bowel [tiab] OR large intestine [tiab] OR gut [tiab]
#4 #1 OR (#2 AND #3)

Search strategy from WCRF Guidelines (version 15)[1] for search literature review (relating to food, nutrition and physical activity):

#1 diet therapy[MeSH Terms] OR nutrition[MeSH Terms]

#2 diet[tiab] OR diets[tiab] OR dietetic[tiab] OR dietary[tiab] OR eating[tiab] OR intake[tiab] OR nutrient*[tiab] OR nutrition[tiab] OR vegetarian*[tiab] OR vegan*[tiab] OR "seventh day adventist"[tiab] OR macrobiotic[tiab] OR breastfeed*[tiab] OR breast feed*[tiab] OR breastfed[tiab] OR breast fed[tiab] OR breastmilk[tiab] OR breast milk[tiab]

#3 food and beverages[MeSH Terms]

#4 food*[tiab] OR cereal*[tiab] OR grain*[tiab] OR granary[tiab] OR wholegrain[tiab] OR wholewheat[tiab] OR roots[tiab] OR plantain*[tiab] OR tuber[tiab] OR tubers[tiab] OR vegetable*[tiab] OR fruit*[tiab] OR pulses[tiab] OR beans[tiab] OR lentils[tiab] OR chickpeas[tiab] OR legume*[tiab] OR soy[tiab] OR soya[tiab] OR nut[tiab] OR nuts[tiab] OR peanut*[tiab] OR groundnut*[tiab] OR seeds[tiab] OR meat[tiab] OR beef[tiab] OR pork[tiab] OR lamb[tiab] OR poultry[tiab] OR chicken[tiab] OR turkey[tiab] OR duck[tiab] OR fish[tiab] OR fat[tiab] OR fats[tiab] OR fatty[tiab] OR egg[tiab] OR eggs[tiab] OR bread[tiab] OR oils[tiab] OR shellfish[tiab] OR seafood[tiab] OR sugar[tiab] OR syrup[tiab] OR dairy[tiab] OR milk[tiab] OR herbs[tiab] OR spices[tiab] OR chilli[tiab] OR chillis[tiab] OR pepper*[tiab] OR condiments[tiab]

#5 fluid intake[tiab] OR water[tiab] OR drinks[tiab] OR drinking[tiab] OR tea[tiab] OR coffee[tiab] OR caffeine[tiab] OR juice[tiab] OR beer[tiab] OR spirits[tiab] OR liquor[tiab] OR wine[tiab] OR alcohol[tiab] OR alcoholic[tiab] OR beverage*[tiab] OR ethanol[tiab] OR yerba mate[tiab] OR ilex paraguariensis[tiab]

#6 pesticides[MeSH Terms] OR fertilizers[MeSH Terms] OR "veterinary drugs"[MeSH Terms]

#7 pesticide*[tiab] OR herbicide*[tiab] OR DDT[tiab] OR fertiliser*[tiab] OR fertilizer*[tiab] OR organic[tiab] OR contaminants[tiab] OR contaminate*[tiab] OR veterinary drug*[tiab] OR polychlorinated dibenzofuran*[tiab] OR PCDF*[tiab] OR polychlorinated dibenzodioxin*[tiab] OR PCDD*[tiab] OR polychlorinated biphenyl*[tiab] OR PCB*[tiab] OR cadmium[tiab] OR arsenic[tiab] OR chlorinated hydrocarbon*[tiab] OR microbial contamination*[tiab]

#8 food preservation[MeSH Terms]

#9 mycotoxin*[tiab] OR aflatoxin*[tiab] OR pickled[tiab] OR bottled[tiab] OR bottling[tiab] OR canned[tiab] OR canning[tiab] OR vacuum pack*[tiab] OR refrigerate*[tiab] OR refrigeration[tiab] OR cured[tiab] OR smoked[tiab] OR preserved[tiab] OR preservatives[tiab] OR nitrosamine[tiab] OR hydrogenation[tiab] OR fortified[tiab] OR additive*[tiab] OR colouring*[tiab] OR coloring*[tiab] OR flavouring*[tiab] OR flavoring*[tiab] OR nitrates[tiab] OR nitrites[tiab] OR solvent[tiab] OR solvents[tiab] OR ferment*[tiab] OR processed[tiab] OR antioxidant*[tiab] OR genetic modif*[tiab] OR genetically modif*[tiab] OR vinyl chloride[tiab] OR packaging[tiab] OR labelling[tiab] OR phthalates[tiab]

#10 cookery[MeSH Terms]

#11 cooking[tiab] OR cooked[tiab] OR grill[tiab] OR grilled[tiab] OR fried[tiab] OR fry[tiab] OR roast[tiab] OR bake[tiab] OR baked[tiab] OR stewing[tiab] OR stewed[tiab] OR casserol*[tiab] OR broil[tiab] OR broiled[tiab] OR boiled[tiab] OR microwave[tiab]

OR microwaved[tiab] OR re-heating[tiab] OR reheating[tiab] OR heating[tiab] OR re-heated[tiab] OR heated[tiab] OR poach[tiab] OR poached[tiab] OR steamed[tiab] OR barbecue*[tiab] OR chargrill*[tiab] OR heterocyclic amines[tiab] OR polycyclic aromatic hydrocarbons[tiab]

#12 dietary carbohydrates[MeSH Terms] OR dietary proteins[MeSH Terms] OR sweetening agents[MeSH Terms]

#13 salt[tiab] OR salting[tiab] OR salted[tiab] OR fiber[tiab] OR fibre[tiab] OR polysaccharide*[tiab] OR starch[tiab] OR starchy[tiab] OR carbohydrate*[tiab] OR lipid*[tiab] OR linoleic acid*[tiab] OR sterols[tiab] OR stanols[tiab] OR sugar*[tiab] OR sweetener*[tiab] OR saccharin*[tiab] OR aspartame[tiab] OR acesulfame[tiab] OR cyclamates[tiab] OR maltose[tiab] OR mannitol[tiab] OR sorbitol[tiab] OR sucrose[tiab] OR xylitol[tiab] OR cholesterol[tiab] OR protein[tiab] OR proteins[tiab] OR hydrogenated dietary oils[tiab] OR hydrogenated lard[tiab] OR hydrogenated oils[tiab]

#14 vitamins[MeSH Terms]

#15 supplements[tiab] OR supplement[tiab] OR vitamin*[tiab] OR retinol[tiab] OR carotenoid*[tiab] OR tocopherol[tiab] OR folate*[tiab] OR folic acid[tiab] OR methionine[tiab] OR riboflavin[tiab] OR thiamine[tiab] OR niacin[tiab] OR pyridoxine[tiab] OR cobalamin[tiab] OR mineral*[tiab] OR sodium[tiab] OR iron[tiab] OR calcium[tiab] OR selenium[tiab] OR iodine[tiab] OR magnesium[tiab] OR potassium[tiab] OR zinc[tiab] OR copper[tiab] OR phosphorus[tiab] OR manganese[tiab] OR chromium[tiab] OR phytochemical[tiab] OR allium[tiab] OR isothiocyanate*[tiab] OR glucosinolate*[tiab] OR indoles[tiab] OR polyphenol*[tiab] OR phytoestrogen*[tiab] OR genistein[tiab] OR saponin*[tiab] OR coumarin*[tiab]

#16 physical fitness[MeSH Terms] OR exertion[MeSH Terms] OR physical endurance[MeSH Terms] or walking[MeSH Terms]

#17 recreational activit*[tiab] OR household activit*[tiab] OR occupational activit*[tiab] OR physical activit*[tiab] OR physical inactivit*[tiab] OR exercise[tiab] OR exercising[tiab] OR energy intake[tiab] OR energy expenditure[tiab] OR energy balance[tiab] OR energy density[tiab]

#18 growth[MeSH Terms] OR anthropometry[MeSH Terms] OR body composition[MeSH Terms] OR body constitution[MeSH Terms]

#19 weight loss[tiab] or weight gain[tiab] OR anthropometry[tiab] OR birth weight[tiab] OR birthweight[tiab] OR birth-weight[tiab] OR child development[tiab] OR height[tiab] OR body composition[tiab] OR body mass[tiab] OR BMI[tiab] OR obesity[tiab] OR obese[tiab] OR overweight[tiab] OR over-weight[tiab] OR over weight[tiab] OR skinfold measurement*[tiab] OR skinfold thickness[tiab] OR DEXA[tiab] OR bio-impedence[tiab] OR waist circumference[tiab] OR hip circumference[tiab] OR waist hip ratio*[tiab]

#20 #1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19

Optional:
#21 animal[MeSH Terms] NOT human[MeSH Terms]

#22 #20 NOT #21

Annex 2. Tables of excluded and included biomarkers proposed by the SLR centre Bristol (SLR prostate cancer).

Extracted from: Food, Nutrition, Physical Activity and the Prevention of Cancer: A Global Perspective
Systematic Literature Review – Support Resource
SLR Prostate Cancer (pp 1185-1186)

The reviewers of the SLR centre Bristol used two chapters (Willet: Nutritional epidemiology (Chapter 9), 1998; Margetts and Nelson: Design concepts in nutritional epidemiology (Chapter 7), 1997) to guide their decisions. If there was no info, the biomarker was excluded. If one of the chapters stated the biomarker was useful, the data on validity were checked. Biomarkers with a correlation >0.20 were included. If the chapters stated that there were no good biomarkers for a nutrient or that the biomarker was valid for certain range of intake only, the biomarker was excluded. It was assumed that if biomarkers measured in plasma were valid, this would also be true for serum and vice versa.

The reviewers of the SLR centre Bristol have been more inclusive with respect to the validation required for biomarkers of important nutrients and have therefore added serum/plasma retinol, retinol binding protein, vit B6, ferritin, magnesium, erythrocyte superoxide dismutase (more details below). They have also included biomarkers where validity is not possible: this happens in the case of toxins and phytochemicals where dietary data are sparse. Various contaminants, such as cadmium, lead, PCBs in the serum are also included now although validity data are not available. The level of these chemicals in human tissues is often the only available measure of ingestion.

Measured in	**Include**	**Exclude**
Serum	Provit A carotenoids: Carotene, B-carotene, Alpha-carotene Nonprovit A carotenoids: Carotenoids, Lycopene, Cryptoxanthin (B-), Lutein+zeaxanthin Vit E: alpha-tocopherol, gamma tocopherol Selenium n-3 fatty acids: EPA (Eicosapentaenoic), DHA (Docosahexaenoic) Magnesium Vit A: Retinol &Retinol Binding Protein Pyridoxic acid (vit B6) Phytoestrogen: Genistein, Daidzein Chemical food contaminants Polychlorinated biphenyls (PCBs) Phytochemicals	Prealbumin Minerals: Zinc, Copper, Copper/zinc ratio, Zinc/retinol ratio Other dietary lipids: Cholesterol, Triglycerides Saturated fatty acids, Monounsaturated fatty acids, Polyunsaturated fatty acids Lipids (as nutrients), Total fat (as nutrients), Total protein
Urine	4-pyridoxic acid (vit B6) in 24-h urine	Nitrosamines Xanthurenic acid in 24-h urine Arsenic Ferritin
Saliva		Other dietary lipids: Cholesterol, Triglycerides
Erythrocyte	Linoleic acid Selenium Superoxide dismutase Cadmium	Minerals: Zinc, Copper Monounsaturated fatty acids n-3 fatty acids: EPA (Eicosapentaenoic), DHA (Docosahexaenoic) n-6 fatty acids (other than linoleic acid) Polyunsaturated fatty acids, Saturated fatty acids Glutathione peroxidase

Measured in	Include	Exclude
Plasma	Vit D Vit E: alpha-tocopherol, gamma tocopherol Vit C Provit A carotenoids: Carotene, Alpha-carotene, B-carotene Nonprovit A carotenoids: Lycopene, Cryptoxanthin (B-), zeaxanthin, Lutein Selenium, Selenoprotein Folate, Iron: ferritin Vit A Retinol: Retinol Binding Protein Cadmium, Cadmium/zinc ratio EPA DHA fatty acids	Alkaline phosphatase Minerals: Zinc, Copper, caeruloplasmin Other dietary lipids: Cholesterol, Triglycerides, LDL, HDL
Adipose tissue	n-3 fatty acids: EPA (Eicosapentaenoic), DHA (Docosahexaenoic) n-6 fatty acids Trans fatty acids , Polyunsaturated fatty acids, Saturated fatty acids	Unsaturated fat, Monounsaturated fatty acids n-9 fatty acids other measures of polyunsat fa: M:S ratio, M:P ratio, n3-n6 ratio
leucocyte	Vit C	Zinc
Erythrocyte membrane	n-6 fatty acids: linoleic	n-6 fatty acids (other than linoleic) n-3 fatty acids: EPA (Eicosapentaenoic), DHA (Docosahexaenoic)
Hair		Minerals: Zinc, Copper, Manganese, Iron Cadmium
Toenails or fingernails	Selenium	Cadmium, zinc

Reasons for exclusion and inclusion of biomarkers proposed by the SLR centre Bristol.

Extracted from: Food, Nutrition, Physical Activity and the Prevention of Cancer: A Global Perspective
Systematic Literature Review – Support Resource
SLR Prostate Cancer (pp 1187-1189)
(Source: Willet: Nutritional epidemiology (Chapter 9), 1998; Margetts and Nelson: Design concepts in nutritional epidemiology (Chapter 7), 1997)

Exposure	Measured in	Valid?	Reason (Willett)	Reason (Margetts / Nelson)
Retinol	Plasma/serum	Yes	Can be measured adequately, but limited interpretability in well-nourished population (p 190).	Main biochemical marker of vit A intake is serum retinol (p 194) although in western countries dietary intake of this vitamin is only a very minor determinant of its plasma levels.
Retinol-Binding protein	Serum	Yes	Retinol levels are highly correlated to RBP(p192).	May be measure of physiologically available form. Not if certain disease processes exist (p 192).
Beta-carotene	Plasma	Yes	Yes (p 194) although blood levels much more responsive to supplemental beta-carotene than beta-carotene from food sources (p 193)	Yes (p 197)
Alpha-carotene Beta-cryptoxanthin Lutein+zeaxanthin Lycopene	Plasma	Yes	Yes (p 194)	There is some evidence for interaction between carotenoids during intestinal absorption, which may complicate relationship between intake and blood levels (p 198)
Vit E	Plasma	Yes	Yes (p 196) NB. Strong confounding with serum cholesterol and total lipid concentrations (p 196).	Plasma, red and white blood cells. Yes, if used for vit E supplements. Yes, although if used for diet, associations are only moderate (p199)

Exposure	Measured in	Valid?	Reason (Willett)	Reason (Margetts / Nelson)
Vit D: D25 (OH)D	Plasma Serum	Yes	Yes (P 198/199) NB. Seasonal variation exists, especially in elderly populations, decreasing in winter and rising during summer (p 198) Sunshine exposure is most important determinant; level is better marker of dietary intake in subjects with low sun exposure	Both can be used to measure vit D status, but the higher plasma concentration and lesser metabolic control of d25 makes this, by far, the better option (p 198).
Vit D: 1.25 (OH)2D		No	No. Influenced by calcium and phosphate levels and parathyroid hormone (p 199).	
Vit D: Alkaline phosphatase activity	Serum	No	No. Is indirect measure of vit D status and is susceptible to other disease processes (p 199)	No info
Vit C	Plasma Leukocyt e Serum	Yes	Yes (p 200). Leukocyte may be preferred for long-term intake and plasma and serum reflects more recent intake (p 201)	Yes (p 209), vit C exhibits the strongest and most significant correlation between intake and biochemical indices. Known confounders are: gender, smoking
Vitamin B6	Plasma	Yes	Yes response to supplementation shows response in PLP. PLP better measure of short term rather than long term	Recent studies show that there is unlikely to be a strong correlation between dietary intake and plasma pyridoxal phosphate levels (PPL)
PLP and 4 Pyridoxic acid	Urinary	Yes	Urinary B6 may be more responsive to recent dietary intake than plasma PLP. Random samples of urine 4 –pyridoxic acid correlate well with 24 hour collections	
Folacin (folate)	Serum Erythrocy te	Yes	Yes good correlation with dietary folate in both serum and erythrocytes	Used for assessing folate status Table 7.11p
Magnesium	Serum	Yes	Yes stronger correlation with supplement users than with dietary Mg	
Iron	Serum Hair/nails	No No	No, short-term variability is very high (p 208). No, remains to be determined	

Iron: Ferritin	Serum	Yes	Meat intake predicts serum ferritin level (p 208)	No marker of iron intake is satisfactory (p. 192)
Exposure	**Measured in**	**Valid?**	**Reason (Willett)**	**Reason (Margetts / Nelson)**
Copper : Superoxide dismutase	Erythrocyte	Yes	Among four men fed a copper deficient diet for 4 months, erythrocyte S.O.D declined for all 4. Copper repletion restored S.O.D levels	
Copper	Plasma/serum	No	No (p 211): large number of lifestyle factors/pathologic conditions probably alter blood copper concentrations (smoking, infections)	
Copper	Hair	No	No evidence (212) and data suggests influenced by external contamination	No. Copper-dependent enzyme superoxide dismutase in erythrocytes and copper-protein complex caeroplasmin in serum have been shown to be associated with copper intake, but these markers may be influenced by nondietary factors (p 193)
Selenium	Blood components Toenails	Yes	Yes. Erythrocyte is probably superior to serum as measure of long-term intake (p 206). Lower influence of environment in countries where wearing shoes is norm (toenails). Selenium status is reduced by smoking, also in older persons (p 207); Relationship of selenium with disease may be modified by other antioxidants (vit E and C)	Yes (p 193). Relationship between selenium intake and biomarkers is reasonably good. Urine: reasonable marker, plasma reflects intake provided that the range of variation is large. Red cell and glutathione perioxidase are markers of longer-term intakes. Hair and toenails are alternative possibilities, although contamination of hair samples with shampoo must be controlled for
Glutathione perioxidase	Plasma Serum Erythrocytes	No	Is poor measure of selenium intake among persons with moderate and high exposure (p 206)	

	Blood			
Exposure	**Measured in**	**Valid?**	**Reason (Willett)**	**Reason (Margetts / Nelson)**
Zinc Metallothionein levels	Any	No No	No (p 212) May be marker of short-term intake (p 213)	No biochemical marker is a good indicator of zinc intake (p 192/193). This is, in general terms, also true for other trace metal nutrients such as copper, manganese, chromium, etc
Lipids: total fats	Any	No	No (p 213)	No, there are no markers of total fat intake (p 215)
Cholesterol, LDL Lipoprotein levels	Serum	No	No, but may be useful to predict dietary changes but not for dietary intake (p 215)	No, relationship dietary cholesterol and lipoprotein levels of cholesterol are complex and appears to vary across range of intake (p218)
Linoleic acid	Plasma Adipose tissue	No Yes	Plasma linoleic acid can discriminate between groups with relatively large differences in intake but performs less well on an individual basis (p 220) Yes (p 220)	No consistent relation between dietary linoleic acid intake and plasma linoleic acid (p 220). Across the range of fatty acids in the diet, fatty acids levels in blood and other tissue (adipose tissue) reflect the dietary levels. NB levels are not comparable across tissues
Marine omega-3 fatty acids (EPA, DHA)	Serum Plasma Adipose tissue	Yes	Yes (p 222/223), although dose-response relation remains to be determined	
Monounsat fatty acids (oleic acid)	Plasma Adipose tissue	No No	No, plasma levels are poor predictors of oleic acid intake, but adipose tissue may weakly reflect oleic acid intake (p. 224). Validity is too low	
Polyunsat fatty acids	Adipose tissue	Yes	Yes (p 220)	No info

Exposure	Measured in	Valid?	Reason (Willett)	Reason (Margetts / Nelson)
Saturated fatty acids (Palmitic acid, stearic acids)	Adipose tissue Plasma	Yes No	Yes, long term sat fatty acid intake may be reflected in adipose tissue levels (p 224) No, levels of palmitic and stearic acids in plasma do not provide a simple index of intake (p 224).	No info
Trans-fatty acids	Adipose tissue	Yes	Yes (p 225)	No info
Protein	Any	No	No (p 226)	No info
Nitrogen	Urine	Yes	Yes, but several 24-h samples are needed to provide a stable estimate of nitrogen intake (p 227) Nitrogen excretion increases with body size and exercise and decreased caloric intake	Yes (p 219) One assumes that subjects are in nitrogen Balance

Data on validity and reliability of included biomarkers

Extracted from: Food, Nutrition, Physical Activity and the Prevention of Cancer: A Global Perspective Systematic Literature Review – Support Resource

SLR Prostate Cancer (pp 1187-1189)

Nutrient	**Biologic tissue**	**Val./reproduc**	**Coef**	**Details**
Retinol	Plasma	Validity	0.17	Borderline Correlation between pre-formed vit A intake and plasma retinol. However plasma retinol is a recognized marker of vit A nutritional status for undernourished populations
Beta-carotene			0.51	Correlation between plasma beta-carotene level (averaged from 2 samples taken 1 week apart) and a 7-day diet record estimate of beta-carotene in 98 non-smoking women (Willett, p 194).
			0.38	Cross-sectional correlation between dietary intake of carotene and plasma betacarotene in 902 adult females. In males (n=880): r=0.20 (Margetts, table 7.9a).
	Plasma	Reproducibility	0.45	Correlation for carotene (80% beta-carotene, 20% alpha-carotene) between two measurements taken 6 years apart (Willett, p 194).
Beta-cryptoxanthin	Plasma	Validity	0.49	Correlation between plasma beta-carotene level (averaged from 2 samples taken 1 week apart) and a 7-day diet record estimate of beta carotene in 98 non-smoking women (Willett, p 194)
Lutein+zeaxanthin	Plasma	Validity	0.31	
Lycopene	Plasma	Validity	0.50	
Alpha-carotene	Plasma	Validity	0.58	
Alpha-carotene	Plasma	Validity	0.43	Cross-sectional correlation between dietary intake of carotene and plasma alphacarotene in 902 adult females. In males (n=880): r=0.41 (Margetts, table 7.9a).
Carotenoids	Plasma	Reproducibility	≥080	Within-person variability of plasma levels over 1 week (Willett, p 194).
Vitamin E	Plasma	Validity	0.53	Lipid-adjusted alpha-tocopherol measurements and estimated intake (incl. supplements). After excluding supplement users: r=0.35 (Willett, p 196)
	Plasma	Reproducibility	0.65	Unadjusted repeated measures over a 6-year period (p 188). Adjusting for serum cholesterol reduced correlation to r=0.46 (p 188). Also r=0.65 was found over a 4-year period in 105 adults in Finland

				(Willett, p 196).
	Plasma	Validity	0.20	Cross-sectional correlation between dietary intake of vit E and plasma vit E in 880 adult males. In females (n=906): r=0.14 (Margetts, table 7.9a)
Nutrient	**Biologic tissue**	**Val./reproduc**	**Coef**	**Details**
Vitamin D: D25 (OH)D	Plasma	Validity	0.35	Correlation between FFQ estimate of vit D intake (including supplements) with plasma D25 (OH)D (n=139). Correlation excluding supplement users: r=0.25 (Willett, p 199)
			0.18	Cross-sectional correlation between dietary intake of nutrients and biochemical markers in UK pre-school child study in females (n=350). In males (n=365) r=0.06 (Margetts, table 7.9b).
	Serum	Validity	0.24	Correlation between estimated vit D intake from food and supplements (based on 24 h recall) and serum D25 (OH)D (n=373 healthy women). Food only: r=0.11 (Willett, p 199).
Vitamin C	Plasma	Validity	0.43	Unadjusted correlation between questionnaire-derived dietary ascorbic acid intake and plasma ascorbic acid concentration in a heterogeneous population. Diet only: r=38 (Table 9.1). Correlation is 0.31 for leukocyte ascorbic acid concentration.(Willett, p 200)
		Reproducibility	0.28	Repeated measures in men obtained 6 years apart (Willett, p 201)
		Validity	0.43	Cross-sectional correlation between dietary intake of nutrients and biochemical markers in UK pre-school child study in males (n=369). In females (n=354) r=0.39 (Margetts, table 7.9b).
	Serum	Validity	0.55	Correlation between food-frequency questionnaire estimate of vit C intake and serum vit C values (in smokers) in 196 men in Scotland (adjusted for total energy intake, BMI and serum cholesterol level). Non-smokers: 0.58 (Willett, p 200/201)
	Leukocyte	Validity	0.49	Correlation between one week of intake data and a single leukocyte ascorbate measurement for men. For women:

				r=0.36. Nutrition survey of elderly in UK (Margetts, p 211)
Vitamin B6	Plasma Urinary	Validity Validity	0.37 -	Correlation between B6 and plasma pyridoxal phosphate levels in 280 healthy men =0.37 (Willett p203)
Folacin	Serum Erythrocyte	Validity	0.56 0.51	Correlation of 0.56 in Framington Heart study 385 subjects (serum) Correlation in 19 elderly subjects (erythrocyte) (Willet p204)
Magnesium	Serum	Validity	0.27	Correlation between intake with supplements 0.27 in 139 men and 0.15 without supplements (Willett p211)
Iron (ferritin)	Serum	Validity	0.16	Borderline 0.16 correlation with heme intake but only r-0.15 with total iron intake (Willett p 208). Included as marker of iron storage
Copper (Superoxide dismutase)	Erythrocyte	-	-	S.O.D levels reflect both depletion and repletion of Cu (Willett p 212)
Selenium	Serum	Validity	0.63	Correlation between selenium intake and serum selenium in South Dakotans (n=44)(Willett, p 186)
		Reproducibility	0.76	Average correlation between repeated measurements at four 3-month intervals in 78 adults (Willett, p 188)
	Toenails	Validity	0.59	Correlation between selenium intake and toenail selenium level in South Dakotans (n=44) (Willett, p 186)`
		Reproducibility	0.48	Correlation for selenium levels in toenails collected 6 years apart from 127 US women (Willett, p 206)
	Whole blood	Validity	0.62	Correlation between selenium intake and whole blood selenium in South Dakotans (n=44) (Willett, p 186)
		Reproducibility	0.95	Average correlation between repeated measurements at four 3-month intervals in 78 adults (Willett, p 188)
Linoleic acid	Adipose tissue	Validity	0.57	Correlation between dietary linoleic acid intakes determined from 7-day weighted diet records and the relative proportion of linoleic acid in adipose tissue in Scottish men (n=164). Also correlation between linoleic acid measured in adipose tissue and calculated from FFQ in 118 Boston-area men (Willett, p 220)
Eicosapentaenoic	Adipose	Validity	0.40	Correlation with intake estimated from

(n-3)	tissue			three 7-day weighted food records (Willett, p 223).
		Reproducibility	0.68	Correlation over 8 months in 27 men and women aged 20-29 (Willett, p 223).
	Plasma	Validity	0.23	Correlation of cholesterol ester fraction and intake in 3,570 adults (Willett, p 223)
		Reproducibility	0.38	Correlation of two measurements taken 6 years apart in study of 759 Finnish youths (Willett, p 219)

Nutrient	**Biologic tissue**	**Val./reproduc**	**Coef**	**Details**
Docosahexaenoic (n-3)	Adipose Tissue	Validity	0.66	Correlation with intake estimated from three 7-day weighted food records (Willett, p 223)
		Reproducibility	0.93	Correlation over 8 months in 27 men and women aged 20-29 (Willett, p 223).
	Plasma	Validity	0.42	Correlation of cholesterol ester fraction and intake in 3,570 adults (Willett, p 223)
		Reproducibility	0.38	Correlation of two measurements taken 6 years apart in study of 759 Finnish youths (Willett, p 219)
Polyunsaturated fatty acids	Adipose tissue	Validity	0.80	Correlation between % of polyunsaturated fatty acid relative to total fatty acid intake and relative % of adipose tissue polyunsaturated fatty acid (Willett, p 220)
Palmitic acid	Adipose tissue	Validity	0.27	Correlation adipose tissue measurement with a FFQ estimate among 118 men. A correlation of 0.14 was reported among women. Among 20 healthy subjects, correlations between normal intake of total saturated fatty acids and fatty acid composition of triglycerides in adipose tissue was 0.57 (Willett, p 224)
Stearic acid	Adipose tissue	Validity	0.56	Among 20 healthy subjects, correlations between normal intake of total saturated fatty acids and fatty acid composition of triglycerides in adipose tissue (Willett, p 224)
Trans fatty acids	Adipose tissue	Validity	0.40	Correlation between adipose trans and intake estimated from the average of two FFQ among 140 Boston-area women. Previous study: 115 Boston area women, correlation of 0.51 between trans intake estimated from a single FFQ and a fatty acid measurement. Among 118 Boston-area men: correlation of 0.29 between trans fatty acid measured in adipose and by FFQ (Willett, p 225)
Nitrogen	Urine	Validity	0.69	Correlation between nitrogen intakes estimated from weighted food records of 16 days and the average of six 24-h urine nitrogen levels (160 women) (Willett, p 227)
Phyto Oestrogens Genistein, daidzein	Plasma 24 hr urine	Validity	0.97 0.92	Urinary excretion (24 h) and plasma concentrations of PO were significantly

				related to measured dietary PO intake (r 0.97, P<0.001 and r 0.92, P<0.001 respectively). These findings validate the PO database and indicate that 24 h urinary excretion and timed plasma concentrations can be used as biomarkers of PO intake. Br J Nutr. 2004 Mar;91(3):447-57

Nutrient	**Biologic tissue**	**Val./reproduc**	**Coef**	**Details**
Enterodiol Enterolactone	Serum Urine	Validity	0.13 to 0.29	Urinary enterodiol and enterolactone and serum enterolactone were significantly correlated with dietary fiber intake (r = 0.13-0.29) Cancer Epidemiol Biomarkers Prev. 2004 May;13(5):698-708

Annex 3. List of conversion units (as used in the SLR prostate, Bristol)

In cases where the units of measurement differed between results the units would be converted, where possible, such that all results used the same measurement. Where assumptions had to be made on portion or serving sizes an agreement was reached after discussion between team members and consultation of various sources. The following general sizes were agreed upon:

Beer	400ml serving
Cereals	60g serving
Cheese	35g serving
Dried fish	10g serving
Eggs	55g serving (1 egg)
Fats	10g serving
Fruit & Vegetables	80g serving
Fruit Juice	125ml serving
General drinks inc soft & hot drinks	200ml serving
Meat & Fish	120g serving
Milk	50ml serving
Milk as beverage	200ml serving
Processed cheese slice	10g serving
Processed meat	50g serving
Shellfish	60g serving
Spirits	25ml serving
Staple foods (rice, pasta, potatoes, beans & lentils, foods boiled in soy sauce)	150g serving
Water & Fluid intake	8oz cup
Wine	125ml serving

Appendix 4

Dietary Calcium (data from 2010 SLR)

Summary

The CUP team is aware that since December 2009, the end date of the literature search for this report, one cohort study has been published. This study is included in the review.

Twenty-two different prospective studies were accumulated until June 2010, among which were six new studies identified during the CUP. Dose-response meta-analyses on dietary calcium and colorectal, colon, and its sub-sites and rectal cancer incidence were performed. Highest versus lowest forest plots were also generated to examine the same associations. The analysis on colorectal cancer was further stratified by sex.

For the dose-response analyses all results were converted to a common scale (milligrams per day). The dose-response results are presented for an increment of 200 mg per day. For studies that presented the results in mg per 1000 kcal per day the intakes were converted to absolute intakes using the mean or median energy intake. E.g. if the median energy intake was 2000 kcal/day the intake in mg per 1000 kcal per day was multiplied by a factor of 2 (2000/1000=2).

Main results

Colorectal cancer

Thirteen studies were included in the dose-response analysis of dietary calcium and colorectal cancer risk. There was a statistically significant reduction in risk (summary RR=0.94, 95% CI = 0.93-0.96) per 200 mg/d, with little evidence of heterogeneity, I^2=0.0%, p=0.52. Analyses stratified by sex showed similar results for both genders. There was no evidence of publication bias with Egger‟s test, p=0.91. Sensitivity analyses excluding one study at a time did not materially alter these results.

Colon cancer

Ten studies were included in the dose-response analysis of dietary calcium and colon cancer risk. There was no significant association, summary RR=0.93 (95% CI = 0.89-0.97) per 200 mg/d, with no evidence of heterogeneity, I^2=9.5%, p=0.36. The Egger‟s test suggests a light publication bias, p=0.049 and checking the funnel plot visually suggested small studies with positive association may be missing.

Sensitivity analyses excluding one study at a time did not materially alter these results.

Rectal cancer

Eight studies were included in the dose-response analysis of dietary calcium and rectal cancer risk. There was no significant association, summary RR was 0.94 (95% CI = 0.86-1.02) per 200 mg/d, with little evidence of heterogeneity, I^2=34.9%, p=0.15. In sensitivity analyses excluding one study at a time the summary RRs ranged from 0.90 (95% CI = 0.84-0.96) when excluding the study by Jarvinen et al, 2001 to 0.96 (95% CI = 0.87-1.06) when excluding the study by Jenab et al, 2010.

Proximal colon cancer

Four studies were included in the dose-response analysis of dietary calcium and colon cancer risk. There was a statistically significant reduction in risk, summary RR=0.89 (95% CI = 0.80-0.98) per 200 mg/d, with little evidence of heterogeneity, I^2=2.03%, p=0.57. The summary RR became statistically non-significant (summary RR = 0.94, 95% CI = 0.82-1.08) when the study by Flood et al, 2005 was omitted in an influence testing.

Distal colon cancer

Four studies were included in the dose-response analysis of dietary calcium and colon cancer risk. There was no significant association, summary RR=0.88 (95% CI = 0.75-1.02) per 200 mg/d, with little evidence of heterogeneity, I^2=40.4%, p=0.17. There was no evidence of publication bias with Egger‟s test, p=0.48. In sensitivity analyses excluding one study at a time the summary RR ranged from 0.83 (95% CI = 0.74-0.95) when excluding the study by Stemmermann et al, 1990 to 0.90 (95% CI = 0.71- 1.14) when excluding the study by Ishiara et al, 2008.

Published pooling project/meta-analysis

Cho et al. performed a pooled analysis of ten cohort studies on the association of dietary calcium intake and risk of colorectal cancer incidence (Cho, E et al., 2004). After 6 – 16 years of follow-up of 534536 individuals, 4992 colorectal cancer cases were ascertained. For the highest versus the lowest quintile of dietary calcium intake, the multivariate adjusted RR was 0.86 (95% CI = 0.78-0.95, P_{trend} = 0.02).

Huncharek et al. conducted a meta-analysis of dietary/total calcium intake and colorectal cancer (Huncharek, M. et al., 2009). The summary RR for the highest versus lowest intake was 0.76 (95% CI = 0.69-0.84, $P_{heterogeneity}$ = 0.70, 10 cohort studies) for colon and 0.72 (95% CI = 0.60-0.86, $P_{heterogeneity}$ 0.92, seven cohort studies) for rectum. Consistent results were observed in the analysis on either colorectal or colon cancer risk (summary RR = 0.77, 95% CI = 0.71-0.81, $P_{heterogeneity}$ = 0.21).

Table 1 Appendix 4 Studies on dietary calcium identified during the CUP

Author/year	Study name	Number of cases	Years of follow-up	Comparison	RR (95% CI)
Jenab, 2010	EPIC	1220 CRC 772 COL 448 REC	3	>1425.3 vs <573.45 mg/d >1425.3 vs <573.45 mg/d >1425.3 vs <573.45 mg/d	0.69 (0.50-0.96), CRC 0.72 (0.47-1.10), COL 0.63 (0.36-1.11), REC
Park, 2009	NIH- AARP Diet and Health Study	5098 CRC	7.0	1247 vs 478 mg/d 1101 vs 409 mg/d	0.84 (0.75-0.94), CRC, men 0.70 (0.59-0.82), CRC, women
Ishiara, 2008	JPHC	761 CRC 312 COL 146 REC	7.8	>662 vs <336 mg/d >714 vs <392 mg/d >662 vs <336 mg/d >662 vs <336 mg/d >662 vs <336 mg/d	0.71 (0.52-0.98), CRC, men 0.95 (0.63-1.44), CRC, women 0.78 (0.42-1.44), PRO, men 0.60 (0.35-1.01), DIS, men 0.88 (0.48-1.61), REC men
Butler, 2008	Singapore Chinese Health study	961 CRC	9.8	Q4 vs Q1 but no cut-off provided	0.91 (0.76-1.09), CRC
Park, 2007	Hawaii-Los Angeles Multiethnic Cohort (MEC) Study	2110 CRC	7.3	>1153.6 vs <521.6 mg/d >969.6 vs <438.4 mg/d	0.76 (0.59-0.96), CRC, men 0.91 (0.72-1.17), CRC, women
McCarl, 2006	Iowa Women's Health study	954 CRC	15	>1532.1 vs <603.2 mg/d	0.68 (0.55-0.83), CRC
Shin, 2006	Shanghai Women's Health Study	283 CRC 129 COL 91 REC	5.7	>610.9 vs <291.9 mg/d >610.9 vs <291.9 mg/d >610.9 vs <291.9 mg/d	0.90 (0.60-1.40), CRC 0.60 (0.30-1.10), COL 0.60 (0.20-1.40), REC
Kesse, 2005	EPIC-E3N	172 CRC	6.9	>1201.8 vs. <766.2 mg/d	0.72 (0.47-1.10), CRC

Flood, 2005	BCDDP	482 CRC 284 COL 74 REC	8.5	>831 vs <411 mg/d >831 vs <411 mg/d >831 vs <411 mg/d >831 vs <411 mg/d >831 vs <411 mg/d	0.74 (0.56-0.98), CRC 0.62 (0.43-0.90), COL 0.60 (0.38-0.97), PRO 0.66 (0.37-1.16), DIS 0.87 (0.43-1.77), REC
Sellers, 1998	Iowa Women's Health Study	241 COL	10.0	>964.8 vs <615 mg/d >964.8 vs <615 mg/d	0.70 (0.40-1.00), COL, no family history of CRC 0.80 (0.40-1.70), COL, family history of CRC

Table 2 Appendix 4 Overall evidence on dietary calcium and colorectal cancer

SLR	Summary of evidence
2005 SLR	Twelve publications reported on dietary calcium and colorectal cancer risk[1]. Three of these studies reported statistically significant reductions in risk, which was restricted to women ≥55y in one study. The other studies reported non-significant associations.
Continuous Update Project	Eight new publications on different cohort studies were identified; Six of these studies found statistically significant decreased risk of colorectal cancer associated with dietary calcium intake, while two others reported non-significant RRs of 0.90 and 0.91. The study of Kesse 2005 was missed for dietary calcium in previous SLR; it reported a statistically non-significant RR of 0.72. In the Continuous Update Project project, the publication of Sellers et al 1998 has been considered (more recent than the previously included publication of Bostick et al 1993 for the same study); they observed a borderline non-significant decreased risk of colon cancer in women associated with dietary calcium intake, but only in those with no family history of colorectal cancer.

[1] Five other publications on colon cancer were included in the analysis of colorectal (if not available colon) cancer.

Tabl 3 Appemdix 4 Summary of results of the dose-response meta-analysis of dietary calcium and colorectal cancer

Colorectal cancer			
		2005 SLR	Continuous Update Project
Studies (n)		10	13
Cases (n)		-	11519
RR (95% CI)		0.98 (0.95-1.00)	0.94 (0.93-0.96)
Quantity		Per 200 mg/d	Per 200 mg/d
Heterogeneity (I^2, p-value)		25%, p=0.19	0%, p=0.52
Stratified analyses			
Sex	Men	0.97 (0.93-1.01) I^2=0%, p=0.682	0.93 (0.88-0.99) I2=51.6%, p=0.13
	Women	0.96 (0.92-0.99) I^2=0%, p=0.43	0.93 (0.91-0.95) I^2=0%, p=0.78
Colon cancer			
		2005 SLR	Continuous Update Project
Studies (n)		8	10
Cases (n)		-	2738
RR (95% CI)		0.95 (0.92-0.98)	0.93 (0.89-0.97)
Quantity		Per 200 mg/d	Per 200 mg/d
Heterogeneity (I^2, p-value)		0%, p=0.92	9.5%, p=0.36

Rectal cancer		
	2005 SLR	Continuous Update Project
Studies (n)	6	8
Cases (n)	-	1173
RR (95% CI)	0.96 (0.91-1.01)	0.94 (0.86-1.02)
Quantity	Per 200 mg/d	Per 200 mg/d
Heterogeneity (I^2, p-value)	5%, p=0.15	34.9%, p=0.15

Table 4 Inclusion/exclusion table for meta-analysis of dietary calcium and colorectal cancer

WCRFCode	Author	Year	Study Design	Study Name	Subgroup	Cancer outcome	SLR	CUP dose-response	CUP H vs. L forest plot	Estimated values	Exclusion reason
COLnew2	Jenab M	2010	Nested case control	EPIC	No Sub-Group	colorectal cancer	New	Yes	Yes	Mid-exposure values	
						colon cancer	New	Yes	Yes	Mid-exposure values	
						rectal cancer	New	Yes	Yes	Mid-exposure values	
COL40783	Park et al	2009	Prospective Cohort	NIH- AARP Diet and Health Study	Men	colorectal cancer	New	Yes	Yes	nb of cases and PY per quantile	
					Women	colorectal cancer	New	Yes	Yes		
COL40638	Ishihara J	2008	Prospective Cohort	JPHC, 1990	Men	colorectal cancer	New	Yes	Yes	Mid-exposure values	
					Women	colorectal cancer	New	Yes	Yes		
					Men	proximal colon cancer	New	Yes	Yes		
					Men	distal colon cancer	New	Yes	Yes		
					Men	rectum cancer	New	Yes	Yes		
COL40639	Butler LM	2008	Prospective Cohort	Singapore Chinese Health study	Mixed	colorectal cancer	New	No	Yes		No information for a dose-response analysis
COL40668	Park SY	2007	Prospective Cohort	Hawaii-Los Angeles Multiethnic Cohort (MEC) Study	Men	colorectal cancer	New	No	Yes		Missing PY
					Women	colorectal cancer	New	No	Yes		Missing PY
COL40668	Park SY	2007	Prospective Cohort	Hawaii-Los Angeles Multiethnic Cohort (MEC) Study	Men	colorectal cancer	New	No	Yes		Missing PY
					Women	colorectal cancer	New	No	Yes		Missing PY
COL40633	McCarl M	2006	Prospective Cohort	Iowa Women's Health study	Women	colorectal cancer	New	Yes	Yes	Mid-exposure values	
COL40665	Shin A	2006	Prospective Cohort	Shanghai Women's Health Study	Women	colorectal cancer	New	Yes	Yes	Mid-exposure values + nb of cases and PY per quantile	
						colon cancer	New	Yes	Yes		
						rectum cancer	New	Yes	Yes		

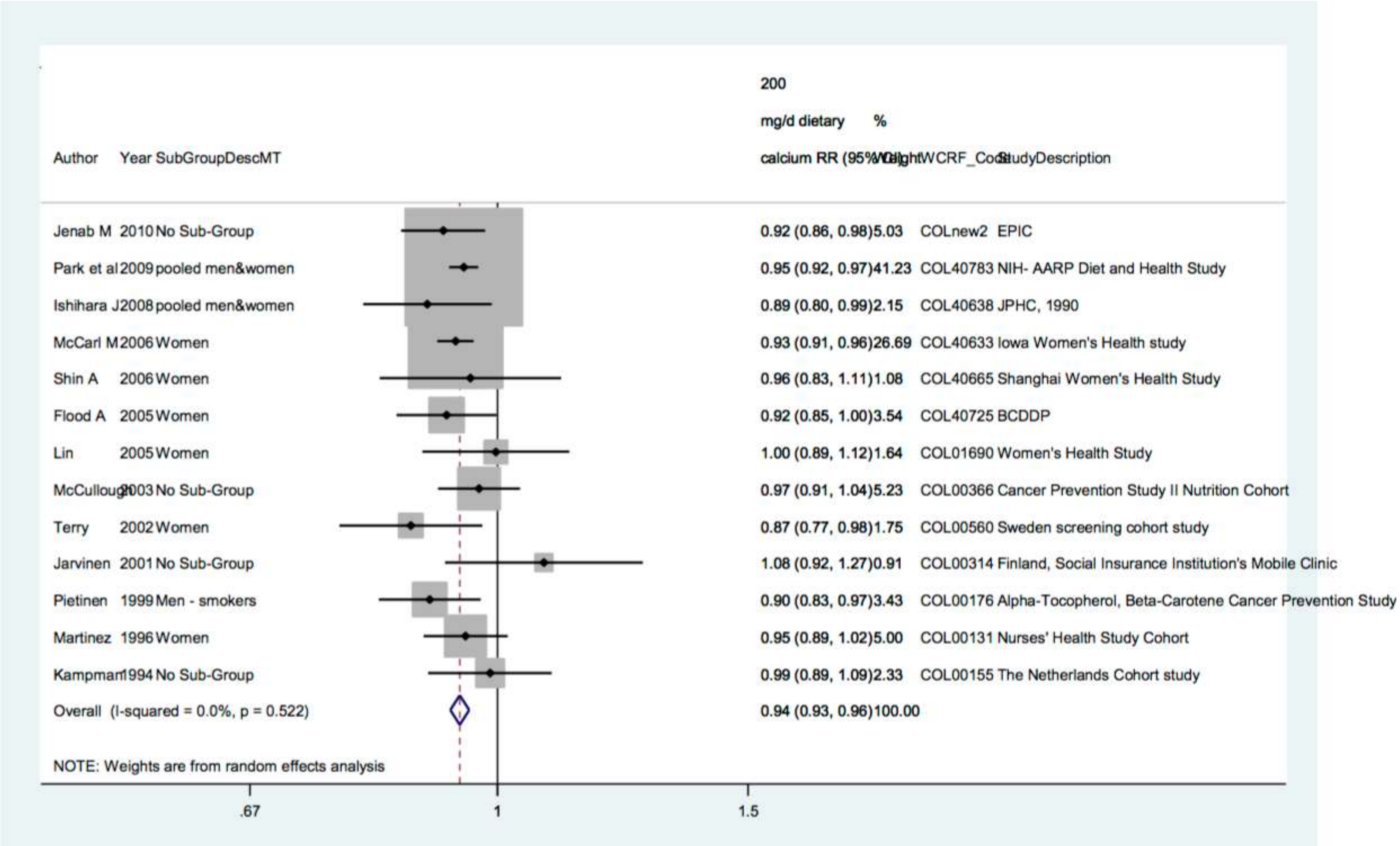
COL40725	Flood A	2005	Prospective Cohort	BCDDP	Women	colorectal cancer	New	Yes	Yes	Mid-exposure values + PY per quantile	
						rectum cancer	New	Yes	Yes	Mid-exposure values + nb of cases and PY per quantile	
						colon cancer	New	Yes	Yes		
						distal colon cancer	New	Yes	Yes		
						proximal colon cancer	New	Yes	Yes		
COL01690	Lin	2005	Prospective Cohort	Women's Health Study	Women	colorectal cancer	Yes (Dose ; Hvs.L)	Yes	Yes	Mid-exposure values + PY per quantile	
COL01843	Kesse	2005	Prospective Cohort	EPIC-E3N	Women	colorectal cancer	New	No	No		Results from Jenab 2010 are more recent
COL00053	Koh	2004	Nested Case Control	Singapore Chinese Health study	Mixed	colorectal cancer	Yes (Dose	No	No		No result
COL00581	Wei E.K.	2004	Prospective Cohort	health professionals follow-up study	Men	colon cancer	Yes (Hvs.L)	No	Yes		Missing PY==>even if less recent, the result from COL00156 is retained
						rectum cancer	Yes (Hvs.L)	No	Yes		
COL00581	Wei E.K.	2004	Prospective Cohort	Nurses' Health Study Cohort	Women	colon cancer	Yes (Hvs.L)	No	Yes		Missing PY==>even if less recent, the result from COL00131 is retained
						rectum cancer	Yes (Hvs.L)	No	Yes		
COL00366	McCullough	2003	Prospective Cohort	Cancer Prevention Study II Nutrition Cohort	Men/Women	colorectal cancer	Yes (Dose ; Hvs.L)	Yes	Yes	Mid-exposure values + PY per quantile	
					Men	proximal colon cancer	Yes (Dose ; Hvs.L)	No	Yes		Missing PY
					Men	distal colon cancer	Yes (Dose ; Hvs.L)	No	Yes		
					Men	colon cancer	Yes (Dose ; Hvs.L)	No	Yes		
					Men	rectum cancer	Yes (Dose ; Hvs.L)	No	Yes		
COL00560	Terry	2002	Prospective Cohort	Sweden screening cohort study	Women	colorectal cancer	Yes (Dose ; Hvs.L)	Yes	Yes	PY per quantile	
						colon cancer	Yes (Dose ; Hvs.L)	Yes	Yes		
						proximal colon	Yes (Dose ; Hvs.L)	Yes	Yes		

						cancer					
						distal colon cancer	Yes (Dose ; Hvs.L)	Yes	Yes		
						rectum cancer	Yes (Dose ; Hvs.L)	Yes	Yes		
COL00587	Wu	2002	Prospective Cohort	Nurses' Health Study Cohort	Women - no calcium supplement	distal colon cancer	Yes (Hvs.L)	No	Yes		No information for a dose-response analysis Subgroup, but retained for main analysis because max number of cases
					Women	colon cancer	Reviewed in text	No	No		There are more recent results for the same cohort/exposure/outcome - Only H vs L
COL00587	Wu	2002	Prospective Cohort	health professionals follow-up study	Men	colon cancer	Reviewed int ext	No	No		There are more recent results for the same cohort/exposure/outcome
					Men - no calcium supplement	distal colon cancer	Yes (Hvs.L)	No	Yes		No information for a dose-response analysis Subgroup, but retained for main analysis because max number of cases
col00384	Colbert	2001	Prospective Cohort	Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study	Men - smokers	colon cancer	Yes (Dose)	No	No		No result
						rectum cancer	Yes (Dose)	No	No		No result
COL00314	Jarvinen	2001	Prospective Cohort	Finland, Social Insurance Institution's Mobile Clinic	Mixed	colon cancer	Yes (Hvs.L)	Yes	Yes	weighted means for exposure + PY per quantile	
						rectum cancer	Yes (Hvs.L)	Yes	Yes		
						colorectal cancer	Yes (Hvs.L)	Yes	Yes		
COL00176	Pietinen	1999	Prospective Cohort	Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study	Men - smokers	colorectal cancer	Yes (Hvs.L)	Yes	Yes	PY per quantile	
COL01974	Sellers TA	1998	Prospective Cohort	Iowa Women's Health Study	Women - no family history of CRC	colon cancer	No	No	Yes		Missing PY ==> even if less recent, COL01450 is retained
					Women - family history of CRC	colon cancer	No	No	Yes		
COL00209	Zheng W. et al	1998	Prospective Cohort	Iowa Women's Health Study	Women - no calcium supplement	rectum cancer	Yes (Dose ; Hvs.L)	Yes	Yes	Mid-exposure values + PY per quantile	
COL00267	Tangrea	1997	Nested Case Control	Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study	Men - smokers	colorectal cancer	Yes (Dose)	No	No		There are more recent results for the same cohort/exposure/outcome
CRC00022	Kato	1997	Prospective Cohort	New York University Women Health's Study	Women	colorectal cancer	Yes (Hvs.L)	No	Yes		Missing data (exposure doses)
CRC00008	Gaard	1996	Prospective Cohort	norwegian national health screening service study	Men	colon cancer	Yes (Dose ; Hvs.L)	Yes	Yes	Mid-exposure values + PY per quantile	
COL00087	Chyou	1996	Prospective Cohort	Honolulu Heart program	Men	colon cancer	Revieweed in text	No	No		No result
						rectum	Reviewed in	No	No		No result

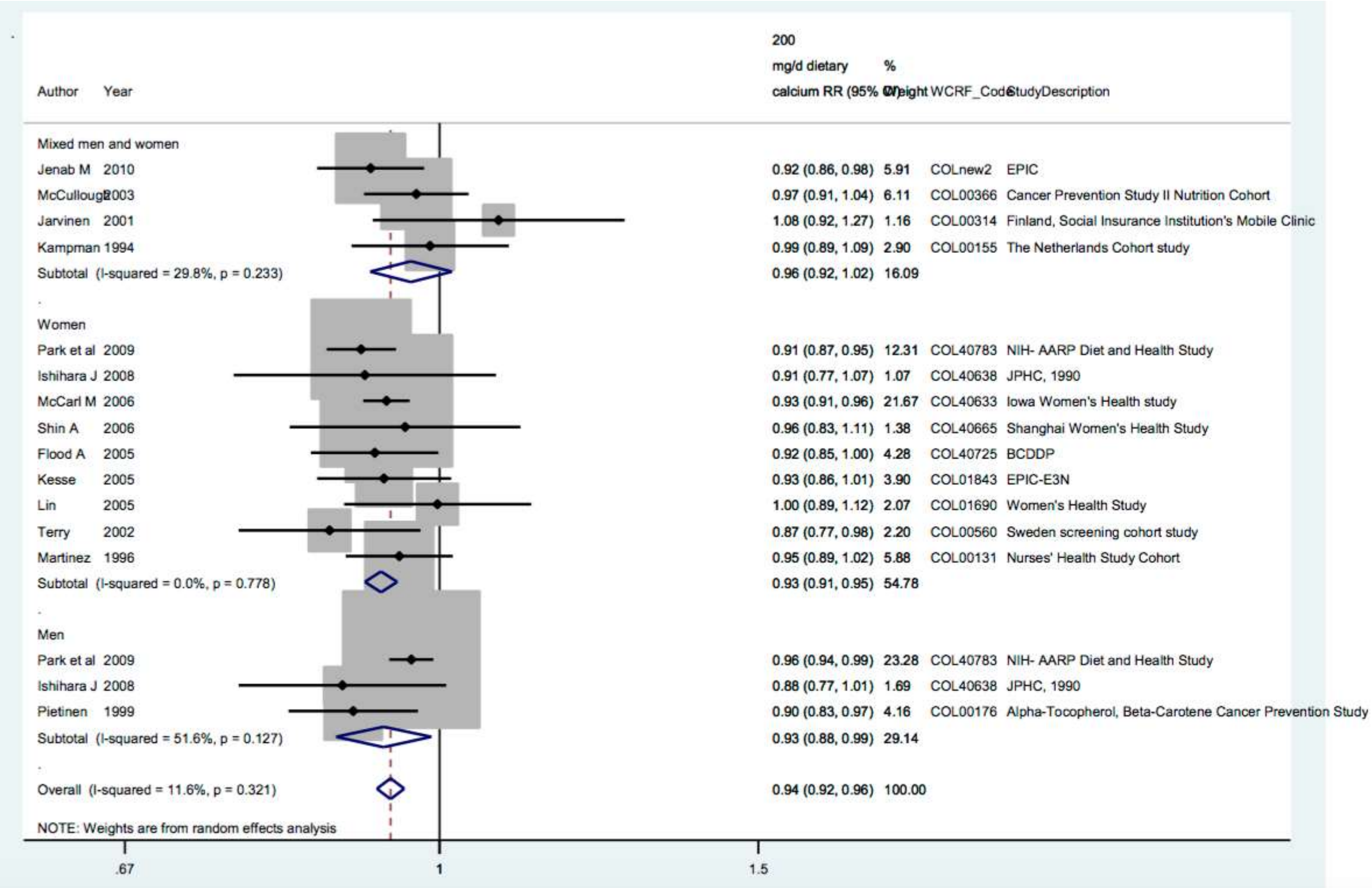
						cancer	text				
COL00131	Martinez	1996	Prospective Cohort	Nurses' Health Study Cohort	Women	colorectal cancer	Yes (Dose ; Hvs.L)	Yes	Yes	Conversion : increase of 200 instead of 800 mg/d	
						colon cancer	Yes (Dose)	Yes	No		For H vs L, the result from COL00581 was more recent
						rectum cancer	Yes (Dose)	Yes	No		For H vs L, the result from COL00581 was more recent
COL00156	Kearney J et al	1996	Prospective Cohort	health professionals follow-up study	Men	colon cancer	Yes (Dose)	Yes	No	Mid-exposure	For H vs L, the result from COL00581 was more recent
COL00161	Glynn	1996	Nested Case Control	Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study	Men - smokers	colorectal cancer	Reviewed in text	No	No		There are more recent results for the same cohort/exposure/outcome
COL00155	Kampman	1994	Case Cohort	The Netherlands Cohort study	Mixed	colorectal cancer	Yes (Hvs.L)	Yes	Yes	PY per quantile	
COL01450	Bostick	1993	Prospective Cohort	Iowa Women's Health Study	Women	colon cancer	Yes (Dose ; Hvs.L)	Yes	No	Mid-exposure values + PY per quantile + nb of cases taken from the age-ajusted model	For H vs L, the result from COL01974 was more recent
COL01102	Slob	1993	Prospective Cohort	Dutch Civil servants study	Men	colorectal cancer	Reviewed in text	No	No		No result
COL00750	Stemmer mann	1990	Prospective Cohort	Honolulu Heart program	Men	Colorectal cancer	Yes (Dose)	No	No	Tertiles of exposure determined by simulation of a normal distribution, based on mean-se + Hamling	Mean values only
						colon cancer	Yes (Dose; Hvs.L)	Yes	Yes		
						Cecum ascending colon	Yes (Dose ; Hvs.L)	Yes	Yes		
						transverse & descending colon cancer	Yes (Dose ; Hvs.L)	Yes	Yes		
						Rectum	Yes (Dose)	No	No		Mean values only
COL01555	Heilbrun	1989	Nested Case Control	Honolulu Heart program	Men	colon cancer	Revieweed in text	No	No		No result
						rectum cancer	Yes	No	No		No result

COL00774	Wu	1987	Prospective Cohort	Leisure World Cohort	Men	colorectal cancer	Yes (Hvs.L)	No	Yes		Missing data for exposure ("tertiles" without any dose precision)
					Women	colorectal cancer	Yes (Hvs.L)	No	Yes		
COL01383	Heilbrun	1986	Nested Case Control	Honolulu Heart program	Men	colon cancer	Reviewed in text	No	No		No result
COL01050	Garland	1985	Prospective Cohort	Western Electric Health study	Men	colorectal cancer	Yes (Hvs.L)	No	No		Missing data (RR 95%CI)
Total no. of articles = 35				**Total no. of individual cohort studies = 22**			**Total no. of individual cohort studies included = 16 (10 & 14 in CRC/COL; 8 & 8 in COL; 6 & 6 in REC; 3 & 3 in PRO; 3 & 5 in DIS; dose-response and H vs. L meta-analysis respectively)**	**Total no. of studies included = 13 in CRC; 10 in COL; 8 in REC; 4 in PRO; 4 in DIS**	**Total no. of studies included = 17 in CRC; 11 in COL; 10 in REC; 5 in PRO; 7 in DIS**		

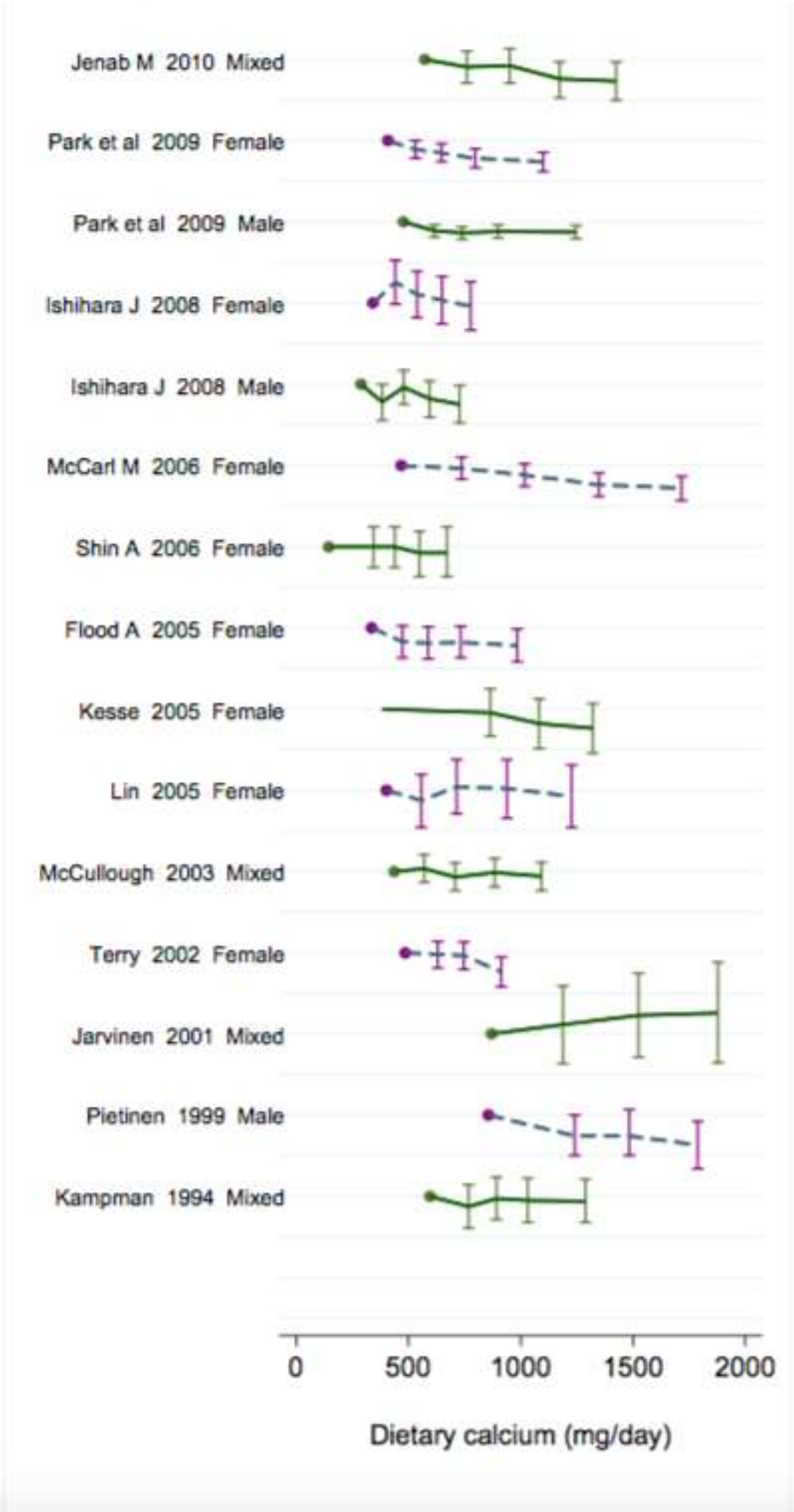
Dose-response meta-analysis of dietary calcium and colorectal cancer – per 200mg/d



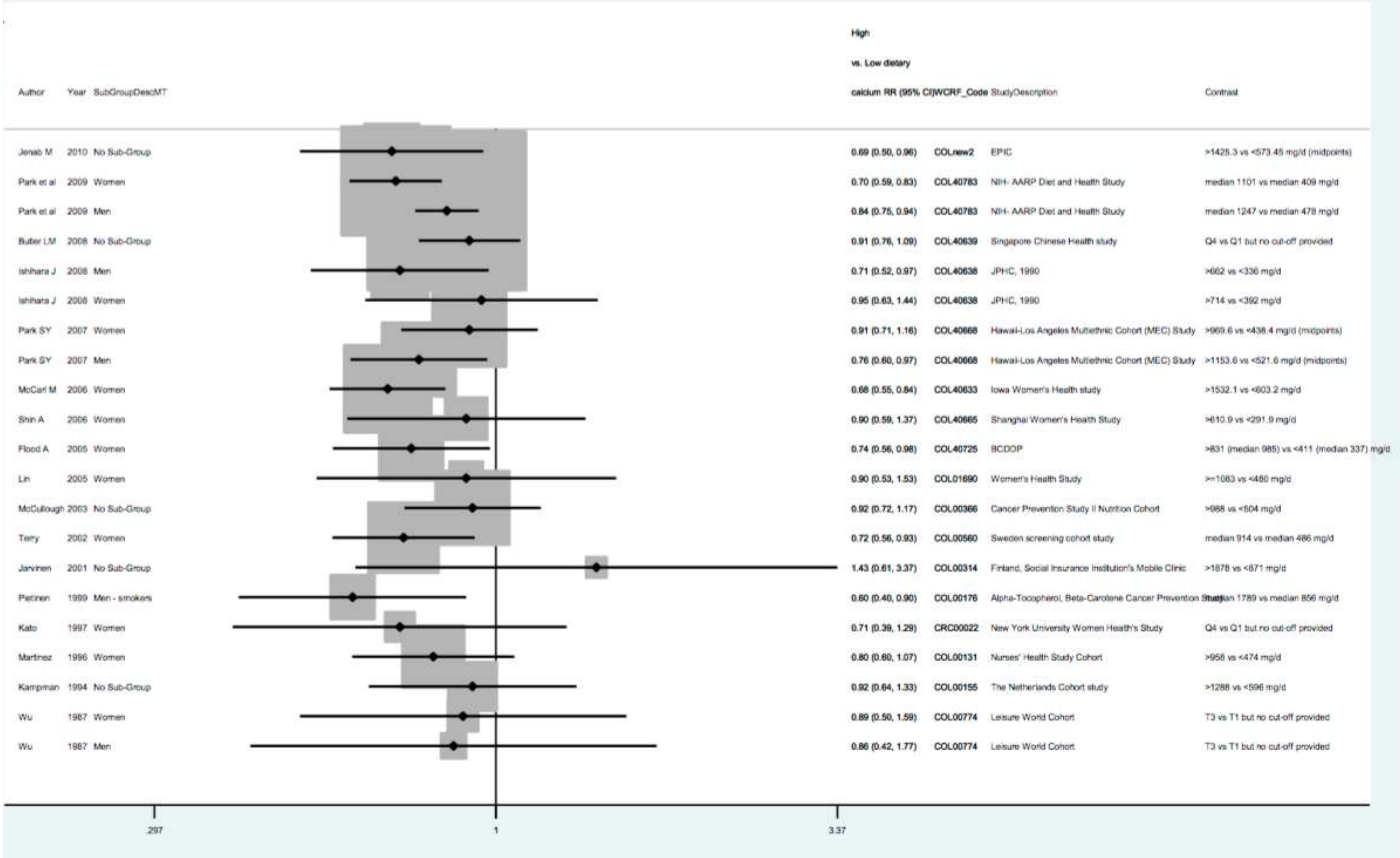
Dose-response meta-analysis of dietary calcium and colorectal cancer, stratified by sex - per 200 mg/d



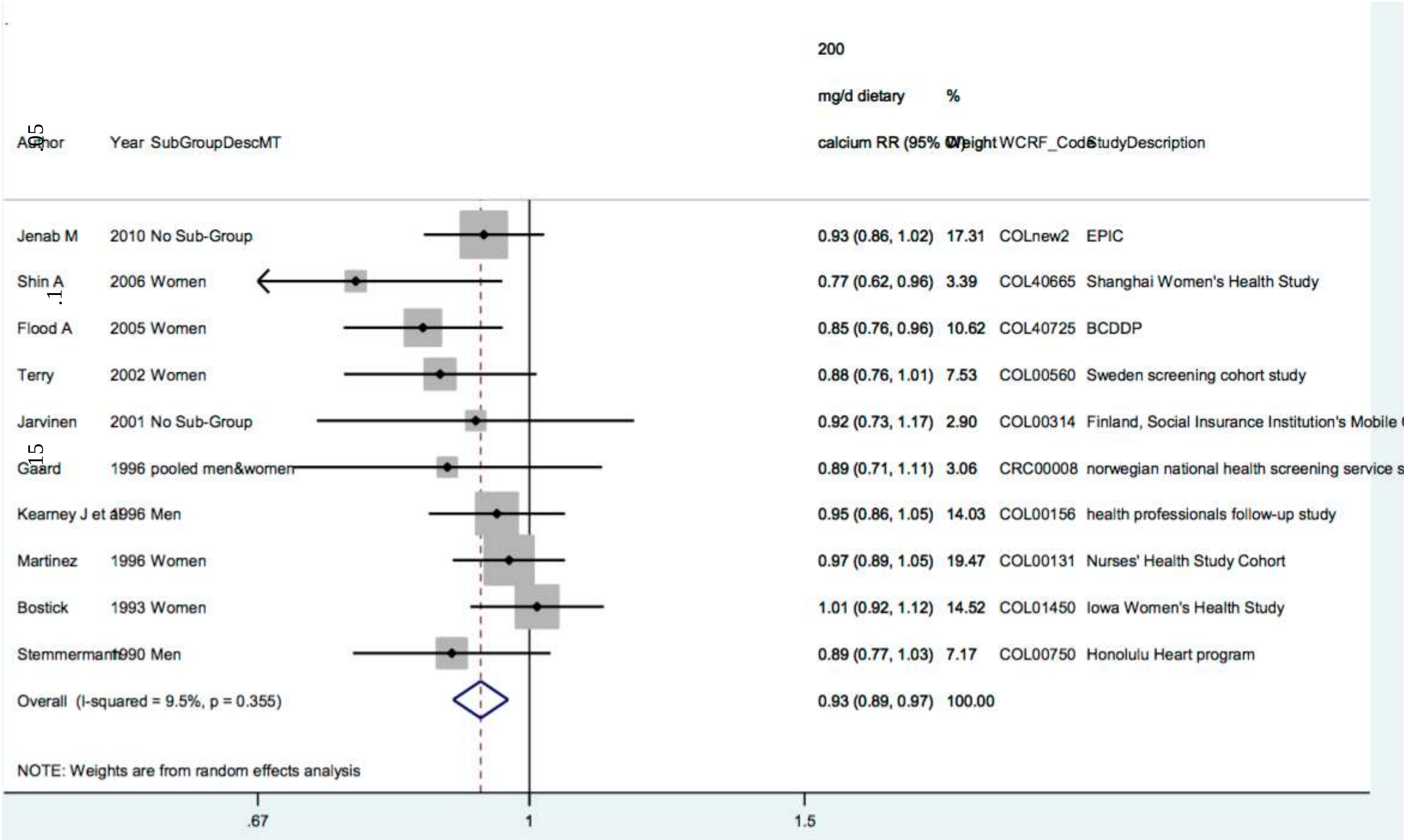
Dose-response graph on dietary calcium and colorectal cancer



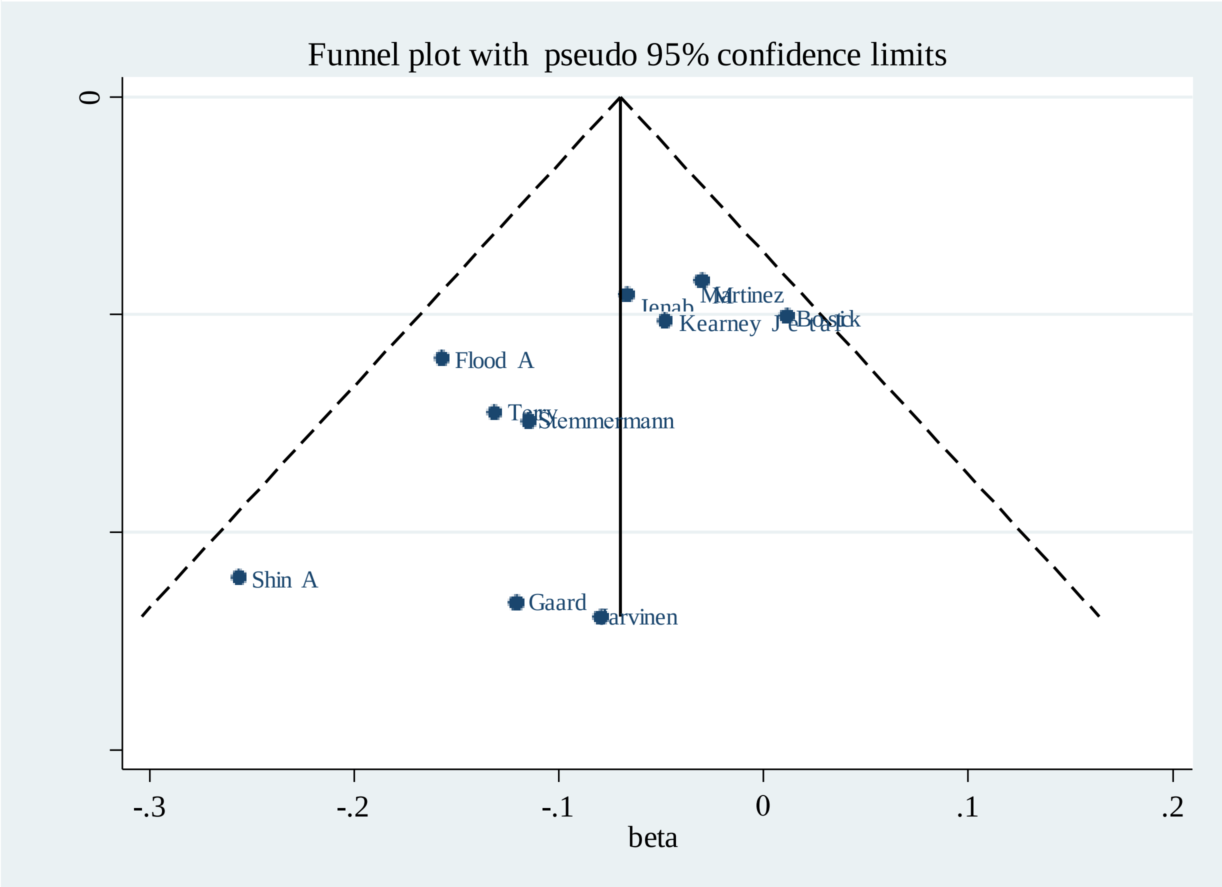
Highest versus lowest forest plot of dietary calcium and colorectal cancer



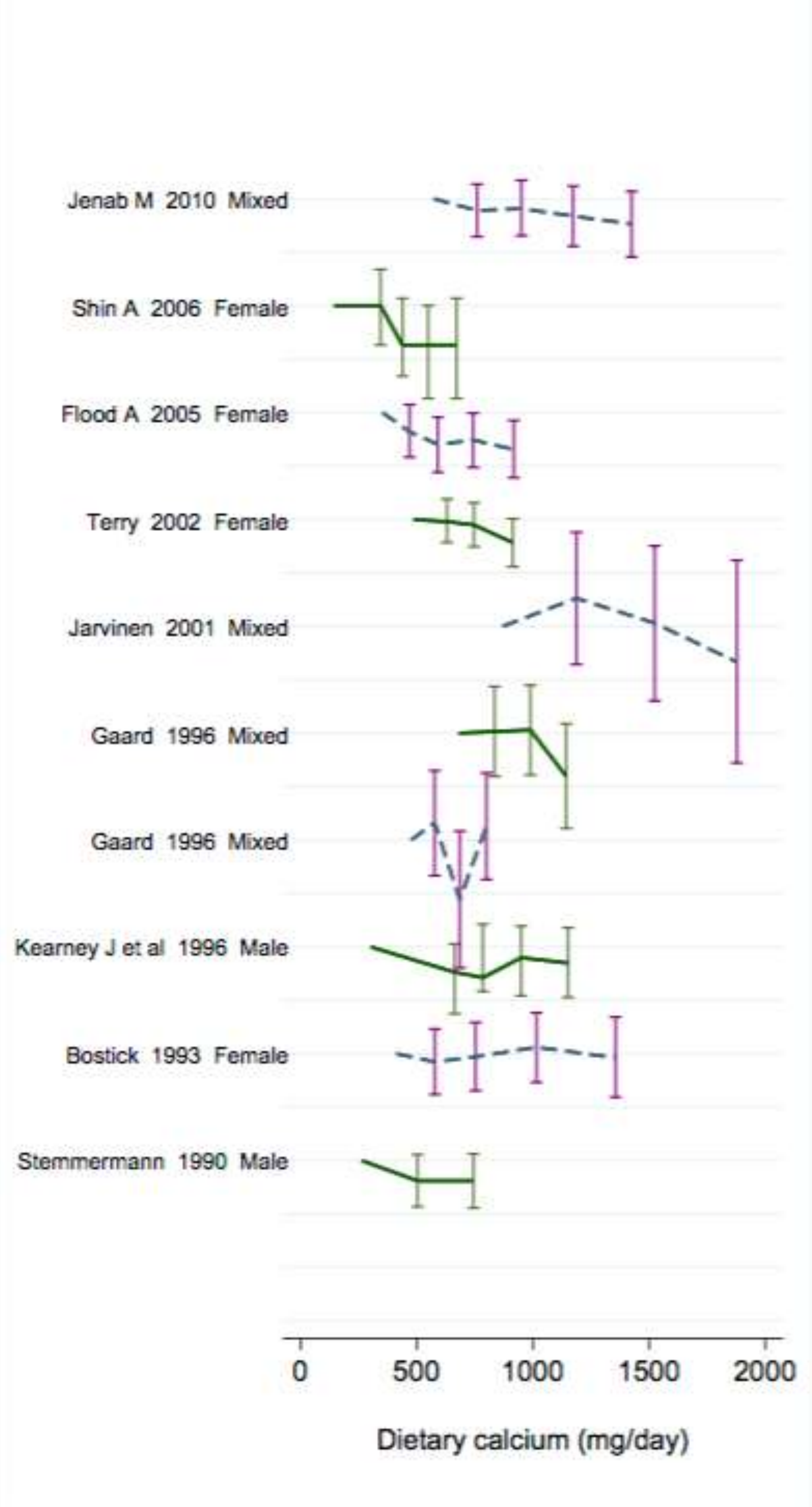
Dose-response meta-analysis of dietary calcium and colon cancer - per 200 mg/d



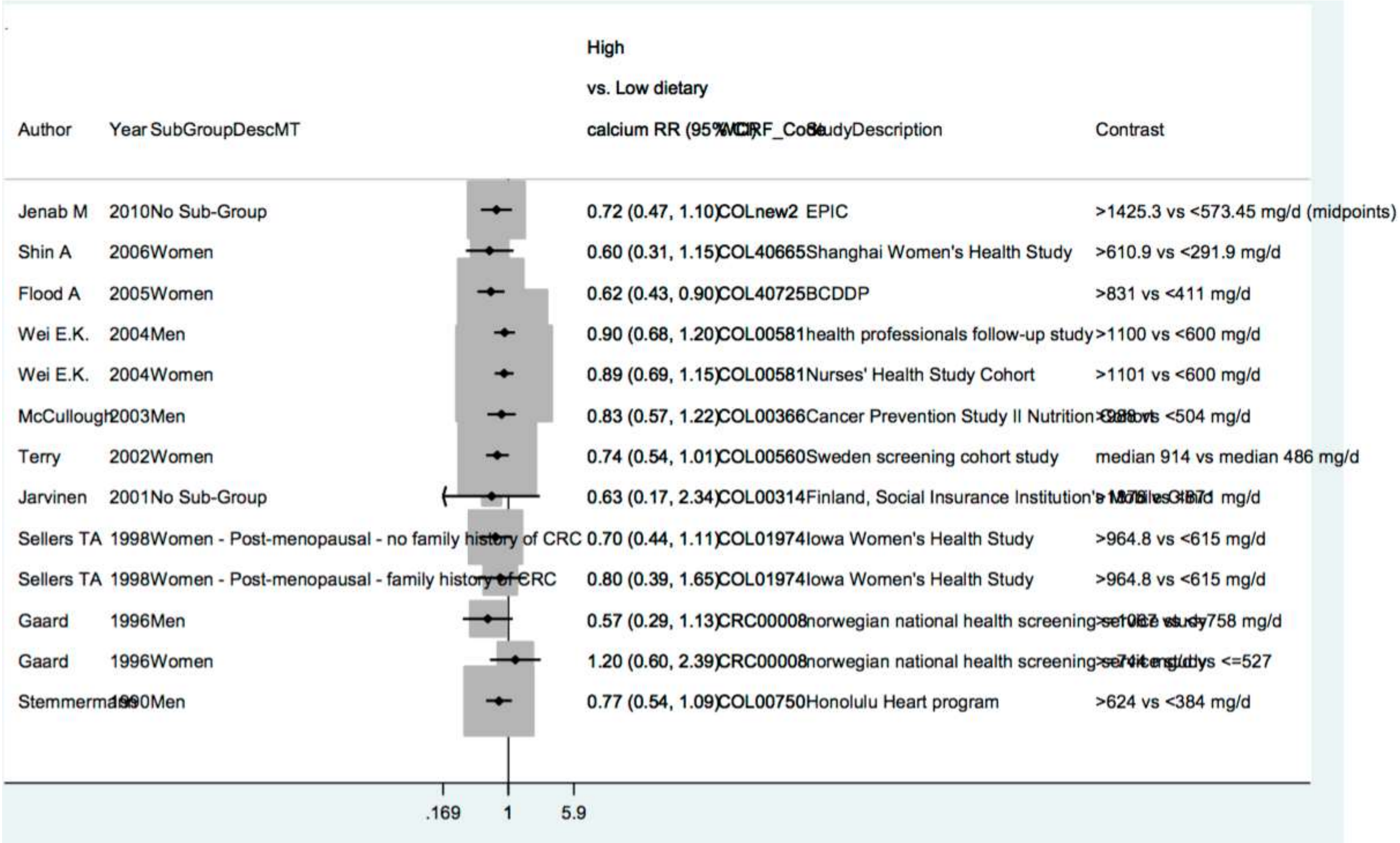
Funnel plot of dietary calcium and colon cancer



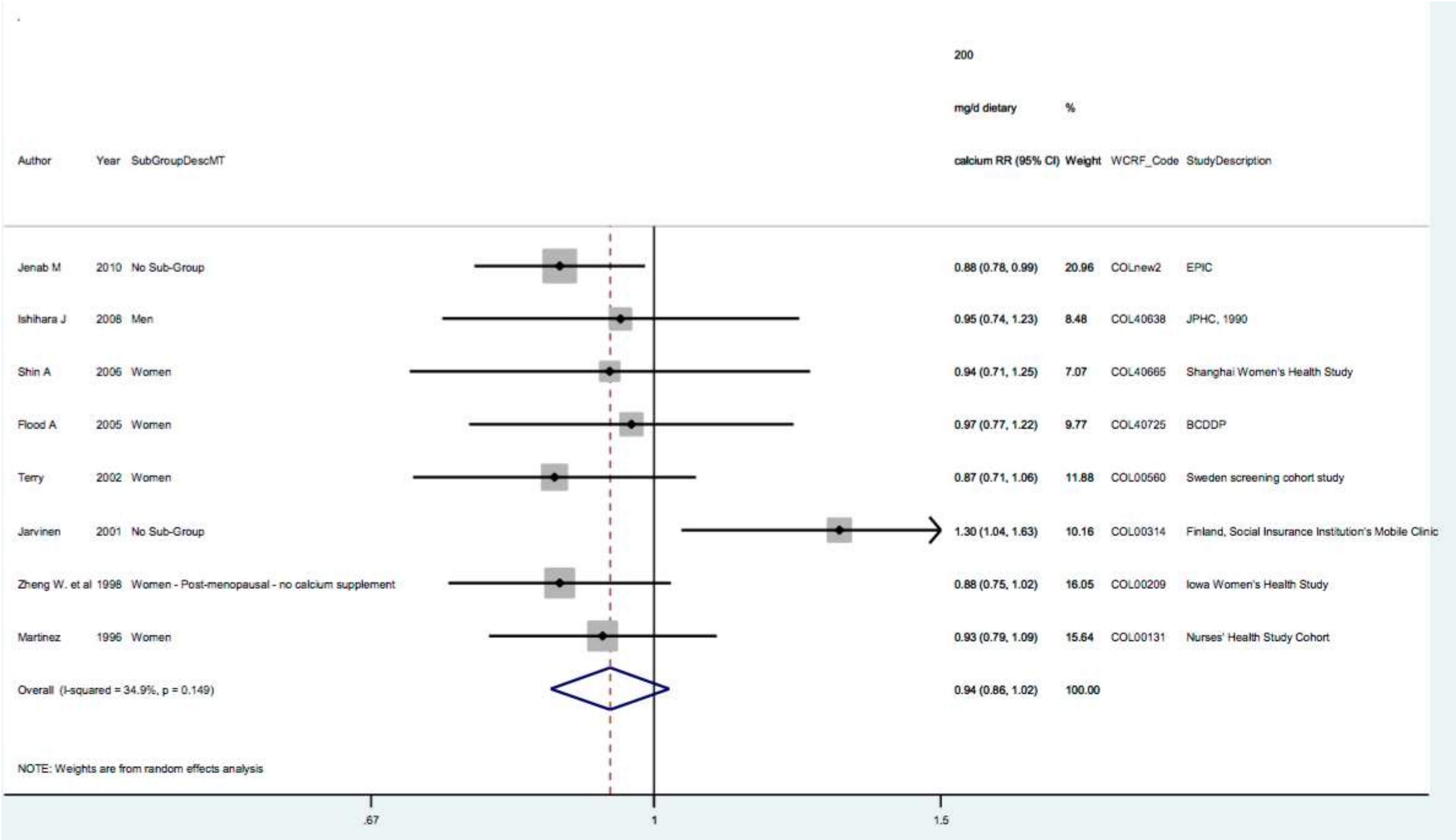
Dose-response graph of dietary calcium and colon cancer



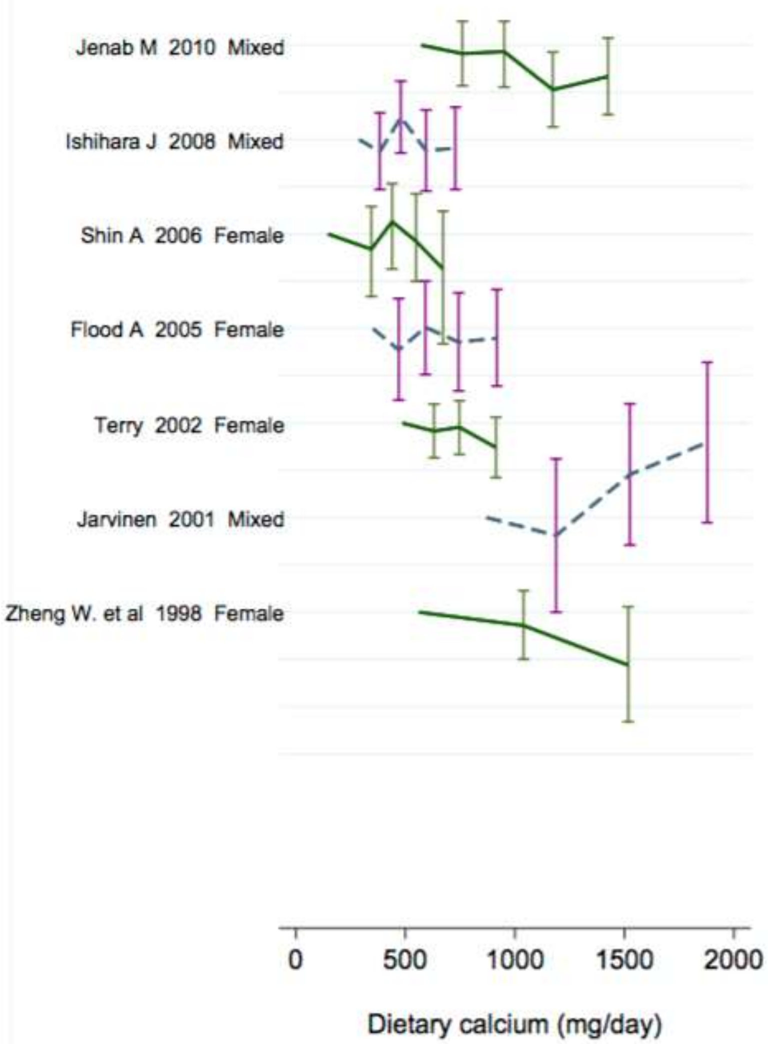
Highest versus lowest forest plot of dietary calcium and colon cancer



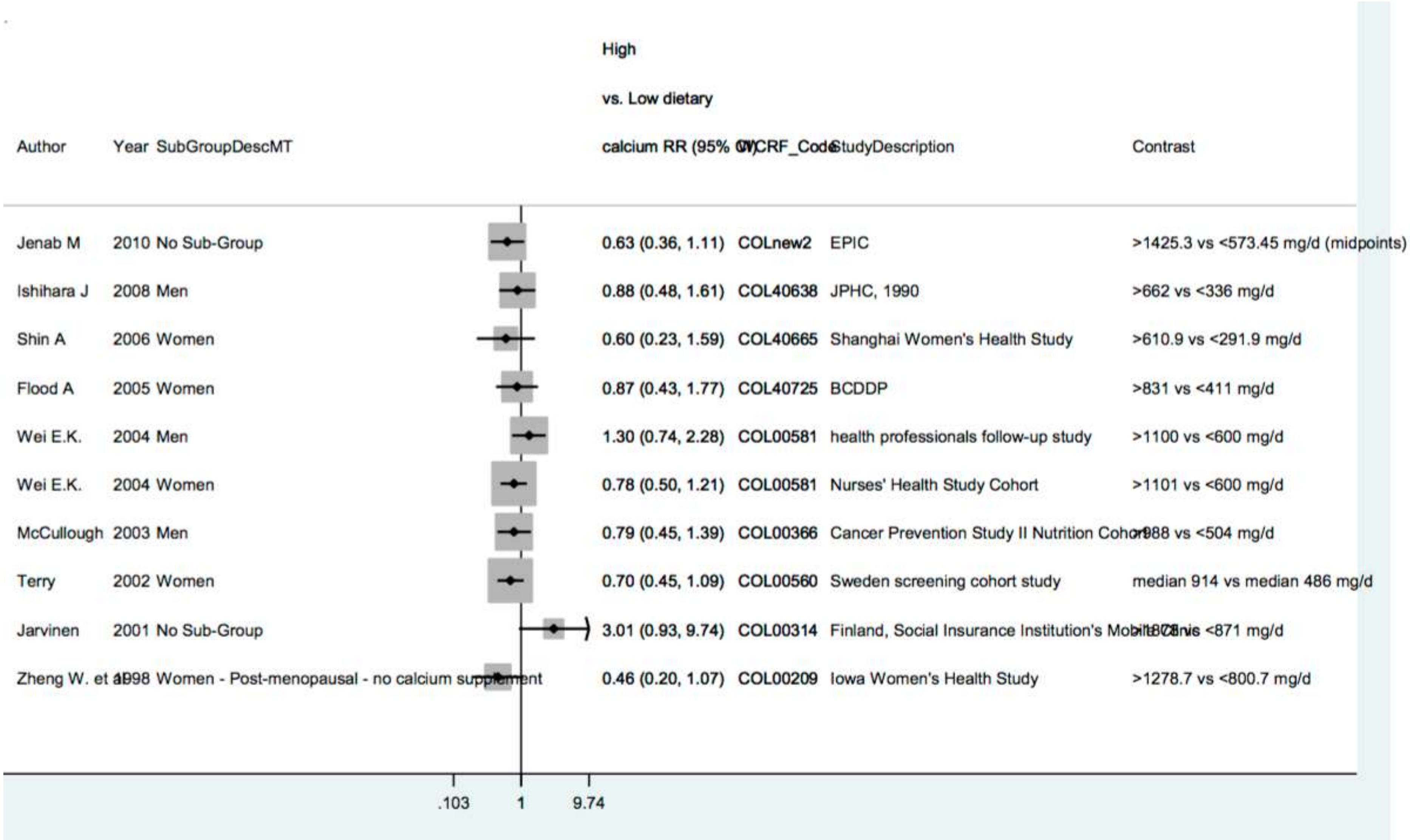
Dose-response meta-analysis of dietary calcium and rectal cancer - per 200 mg/d



Dose-response graph of dietary calcium and rectal cancer



Highest versus lowest forest plot of dietary calcium and rectal cancer



Dose-response meta-analysis of dietary calcium and proximal colon cancer - per 200 mg/d

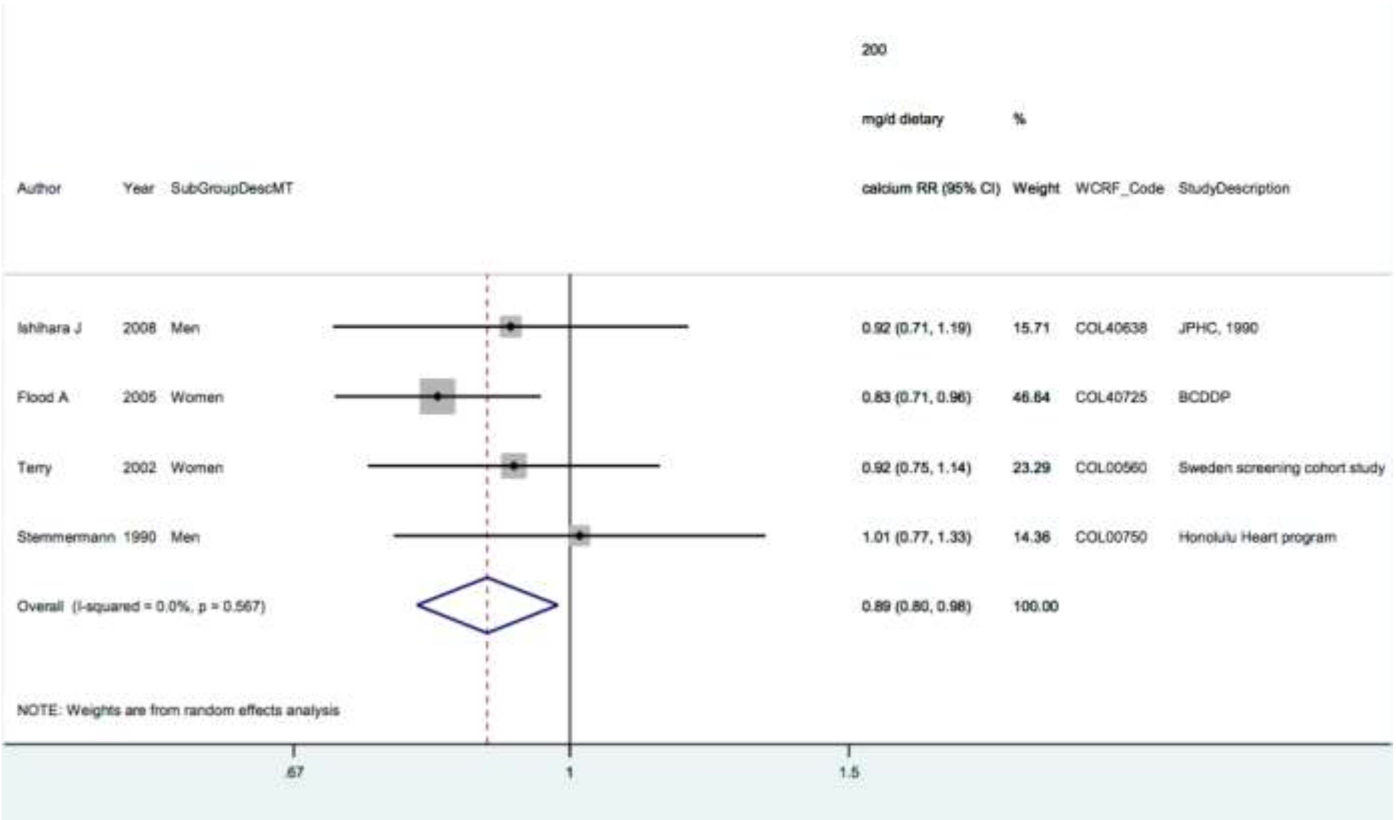
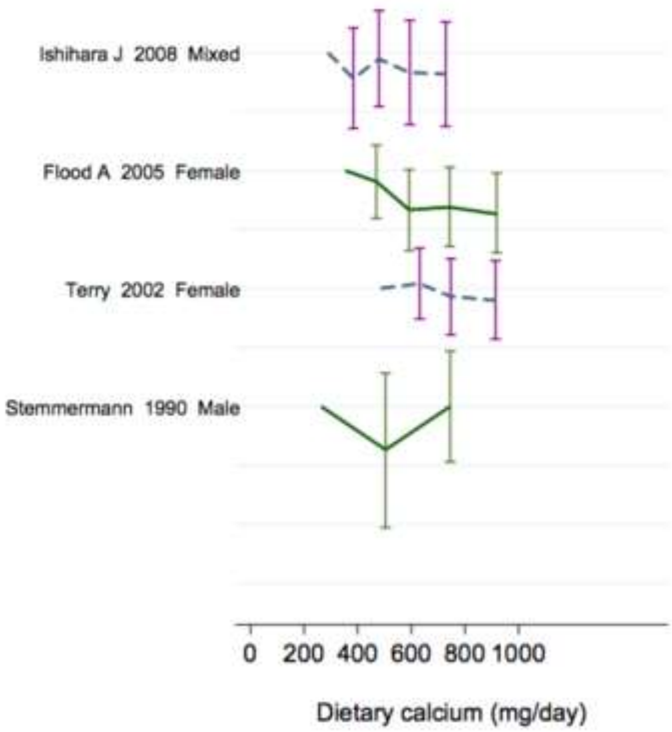
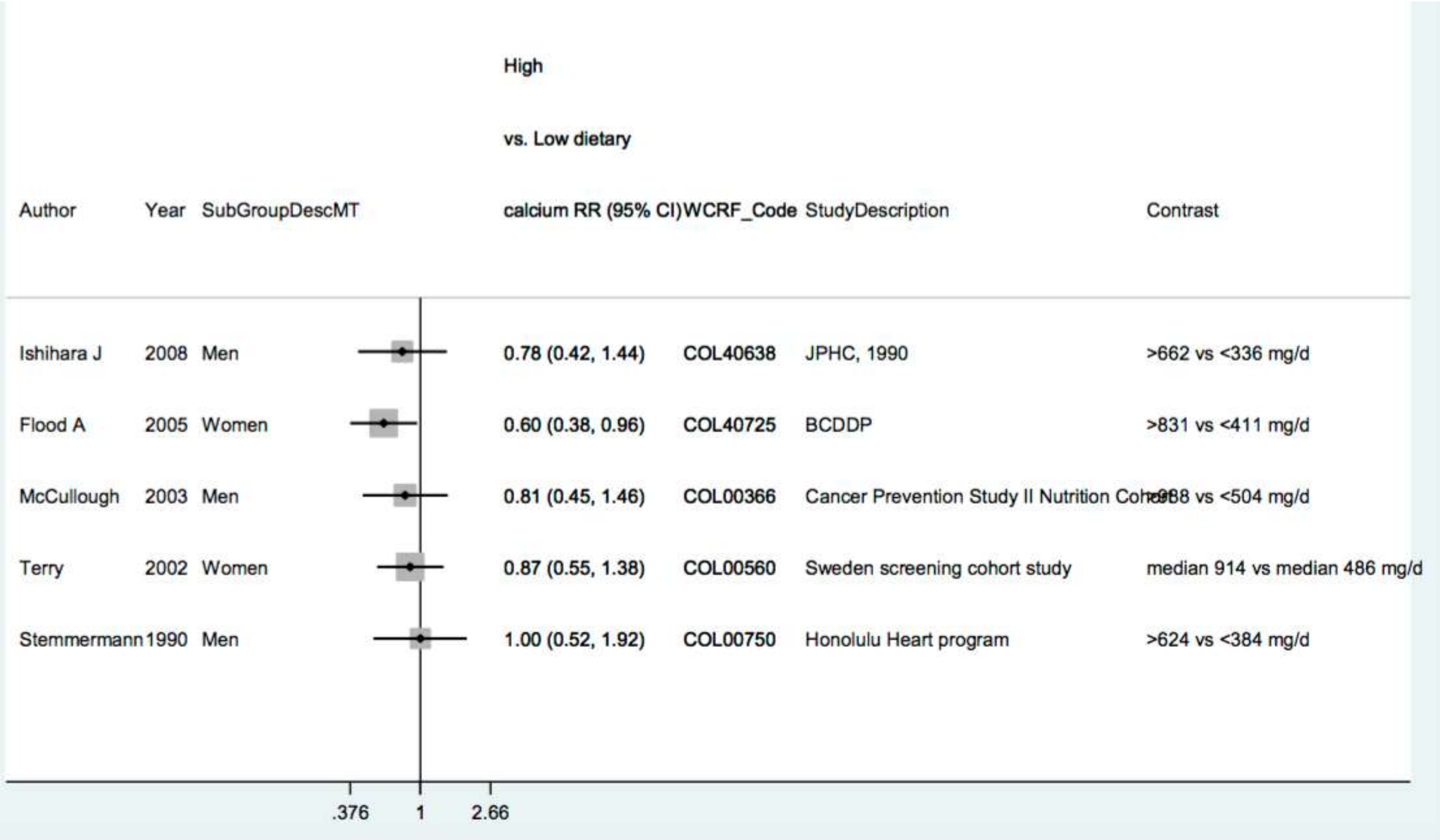


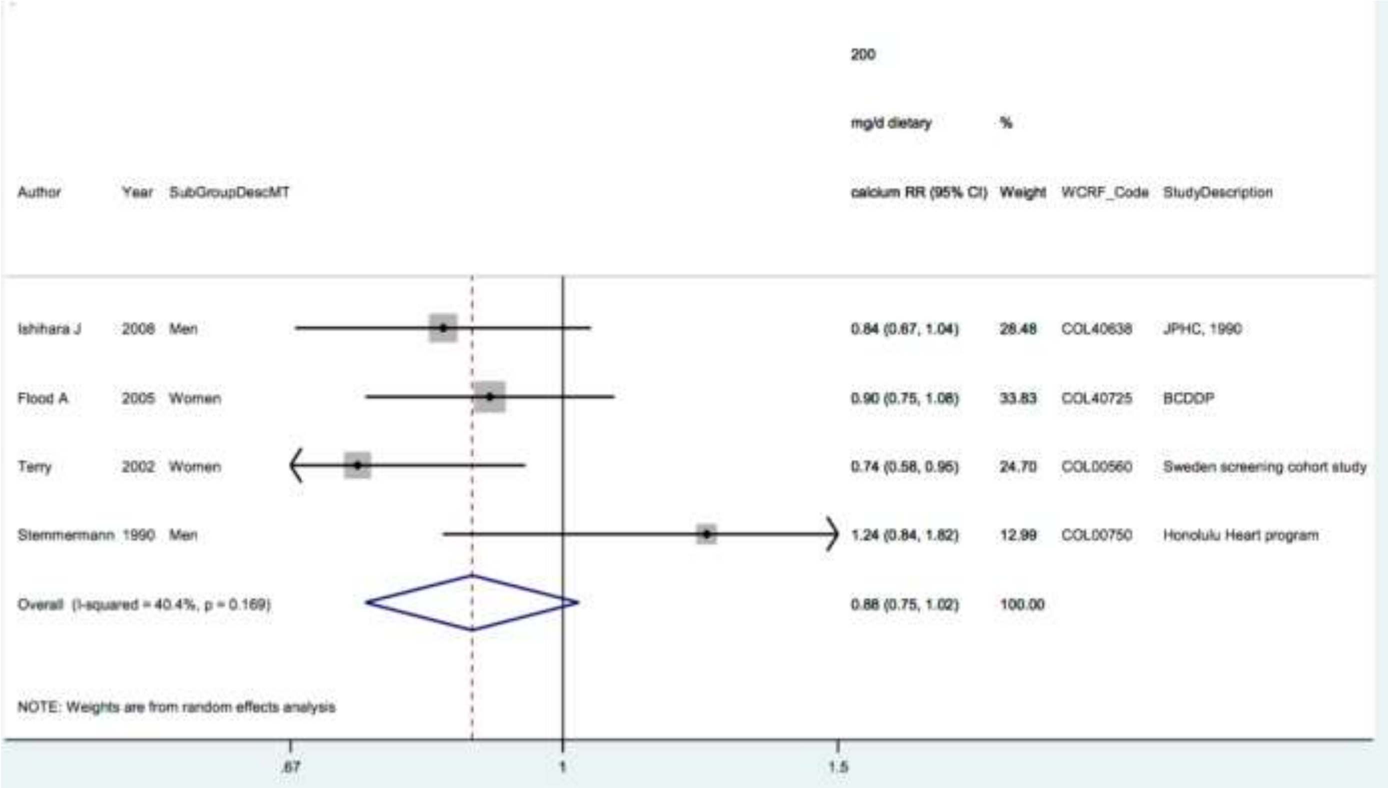
Figure 330 Dose-response graph of dietary calcium and proximal colon cancer



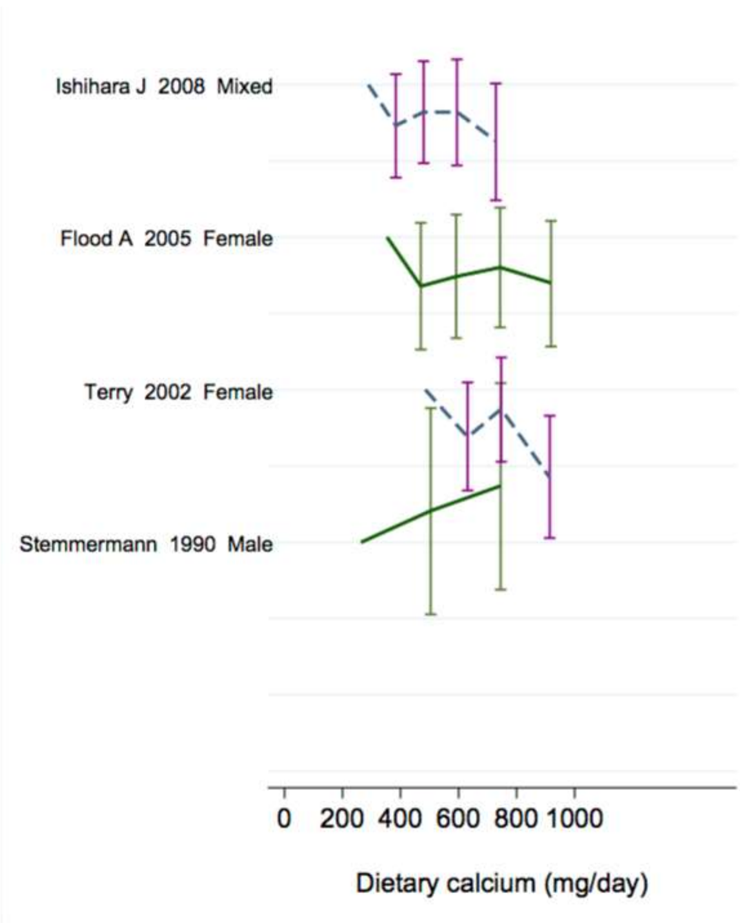
Highest versus lowest forest plot of dietary calcium and proximal colon cancer



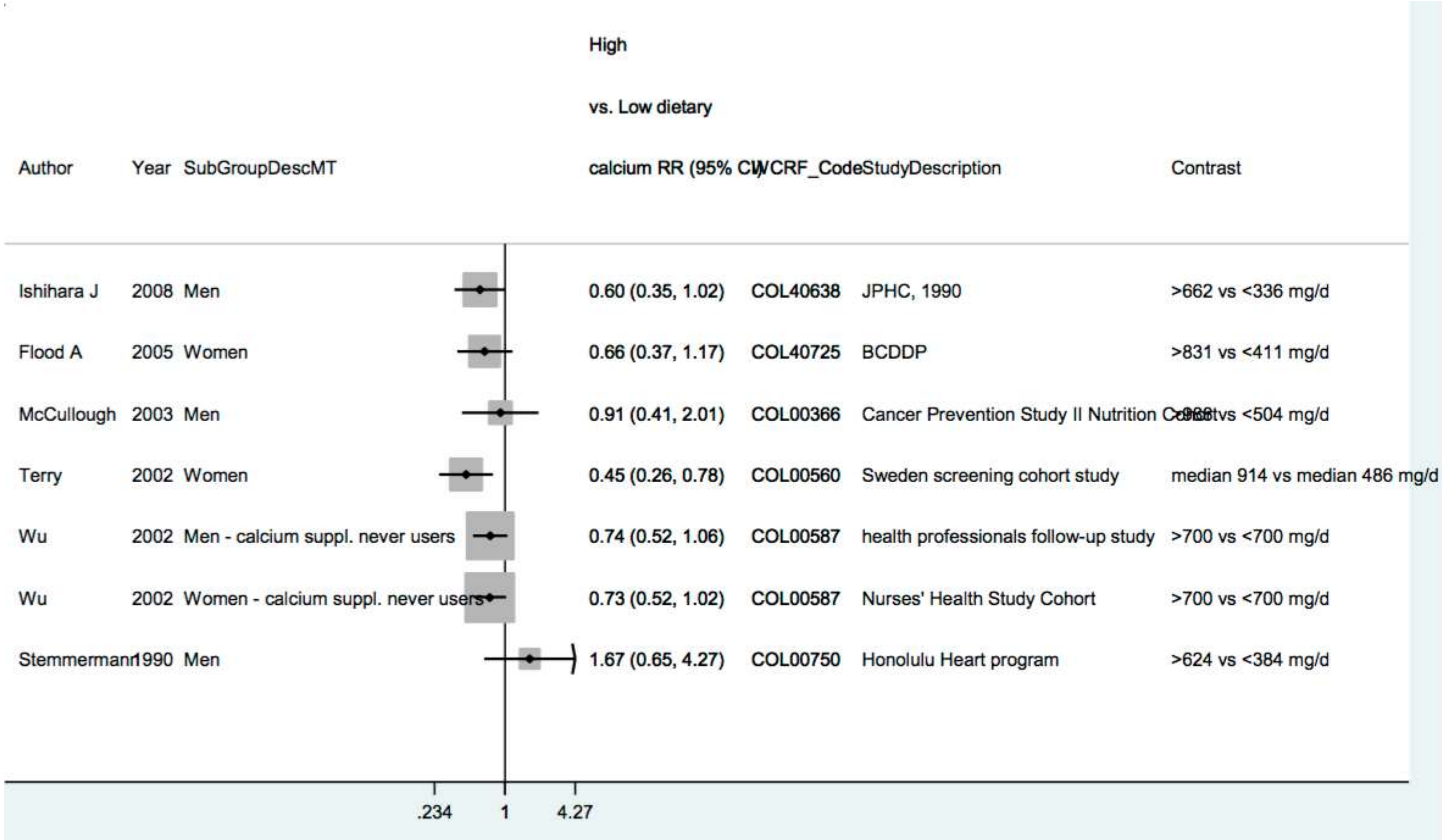
Dose-response meta-analysis of dietary calcium and distal colon cancer - per 200 mg/d



Dose-response graph on dietary calcium and distal colon cancer



Highest versus lowest forest plot of dietary calcium and distal colon cancer



Appendix 5

Calcium supplements

Summary

A total of nine prospective studies were accumulated until June 2010, of which three were identified during the CUP. A highest versus lowest forest plot on colorectal cancer incidence was constructed. Less than three new studies had provided sufficient format of data to be included in a dose-response meta- analysis.

Main results

Six out of seven cohort studies observed a decreased risk in colorectal cancer for a high consumption compared with a low consumption of supplemental calcium. Three of these results were either statistically significant or borderline significant. One subgroup analysis on men was also significant. The remaining study reported a non-significant elevated risk.

Published meta-analysis

Weingarten et al. conducted a Cochrane review on dietary calcium supplementation for preventing colorectal cancer and adenomatous polyps (Weingarten, M.A.M.A. et al., 2008). Two trials were identified with new diagnosis of colorectal cancer as a primary outcome. However as authors pointed out, there were too few events (a total of five cases among 1346 participants) for any meaningful conclusion.

Huncharek et al. conducted a meta-analysis of calcium supplements and colorectal cancer (Huncharek, M. et al., 2009). The summary RR for the highest versus lowest intake was 0.76 (95% CI = 0.65-0.89, $P_{heterogeneity}$ = 0.23, five cohort studies) for colorectal or colon risk.

Table 1 Appendix 5 Studies on supplemental calcium identified during the CUP

Author/year	Study name	Number of cases	Years of follow-up	Comparison	RR (95% CI)
Park, 2009	NIH- AARP Diet and Health Study	5098 CRC	7.0	>1000 vs 0 mg/d >1000 vs 0 mg/d	0.74 (0.58-0.94), CRC, men 0.86 (0.72-1.02), CRC, women
Flood, 2005	BCDDP	482 CRC	8.5	>801 vs 0 mg/d	0.76 (0.56-0.98), CRC
Park, 2007	Hawaii-Los Angeles Multiethnic Cohort (MEC) Study	2110 CRC	7.3	>200 vs 0 mg/d >200 vs 0 mg/d	0.74 (0.60-0.90), CRC, men 0.82 (0.69-0.98), CRC, women

Table 2 Appendix 5 Overall evidence on supplemental calcium and colorectal cancer

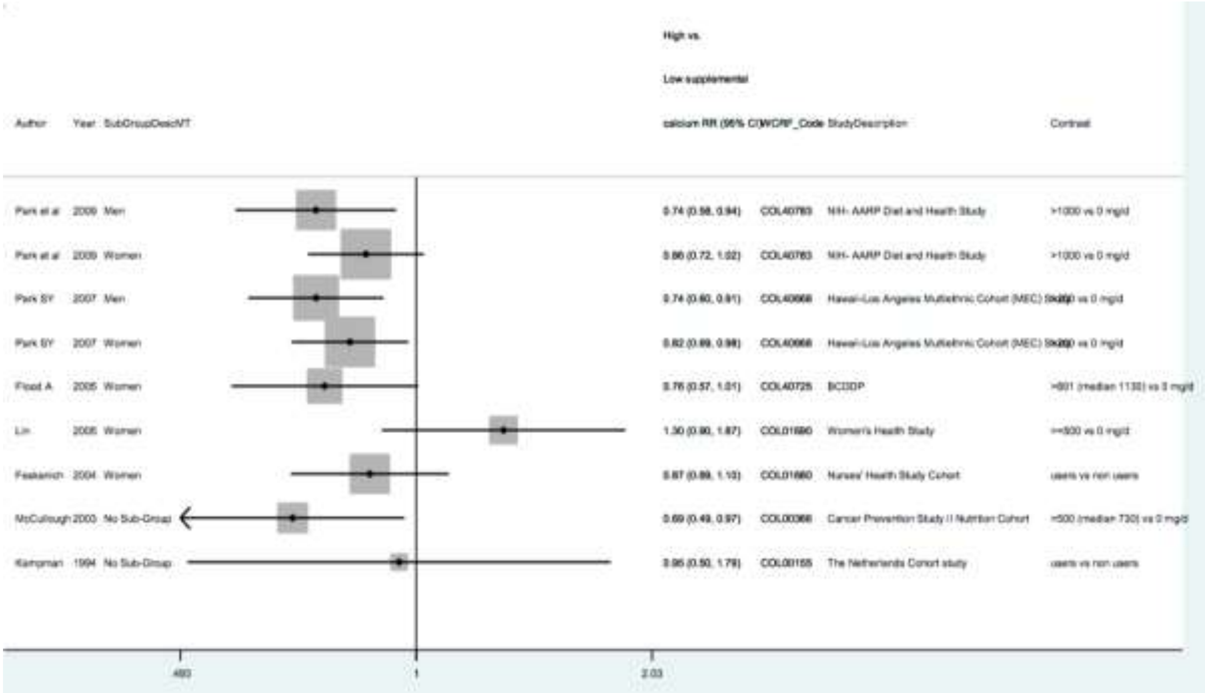
SLR	Summary of evidence
2005 SLR	Six studies reported on supplemental calcium and colorectal cancer risk; all found no significant association.
Continuous Update Project	Three new prospective studies were identified. One (Park et al., 2009) found a significant inverse association among men, but not women. The two other studies (Flood, A. et al., 2005 and Park, S.Y. et al., 2007) found a significant inverse association.

Table 3 Appendix 5 Inclusion/exclusion table for meta-analysis of supplemental calcium and colorectal cancer

WCRFCode	Author	Year	Study Design	Study Name	Subgroup	Cancer outcome	SLR	CUP dose-response	CUP H vs. L forest plot	Exclusion reason	Remarks
COL40783	Park et al	2009	Prospective Cohort	NIH- AARP Diet and Health Study	Men	colorectal cancer	New	No	Yes	Missing data (n for cases and PY)	
					Women	colorectal cancer	New	No	Yes	Missing data (n for cases and PY)	
COL40668	Park SY	2007	Prospective Cohort	Hawaii-Los Angeles Multiethnic Cohort (MEC) Study	Men	colorectal cancer	New	No	Yes	Missing PY	
COL01690	Lin	2005	Prospective Cohort	Women's Health Study	Women	colorectal cancer	Yes (Hvs.L)	No	Yes	Missing PY	
COL40725	Flood A	2005	Prospective Cohort	BCDDP	Women	colorectal cancer	New	No	No	Dose-response meta-analysis not performed as only one new study was identified	Can be included in a dose-response meta-analysis
COL01680	Feskanich	2004	Nested Case Control	Nurses' Health Study Cohort	Women	colorectal cancer	Yes (H vs.L)	No	Yes	Data format not sufficient for a dose-response meta-analysis	
COL00366	McCullough	2003	Prospective Cohort	Cancer Prevention Study II Nutrition Cohort	No Sub-group	colorectal cancer	Yes (Hvs.L M/F)	No	Yes	Missing PY	
COL00587	Wu	2002	Prospective Cohort	Nurses' Health Study Cohort	Women - past supplement users excluded	distal colon cancer	Reviewed in text	No	No	Data format not sufficient for a dose-response meta-analysis; H vs. L analysis not performed as only one new study was identified	Can be included in a H vs. L analysis
				health professionals follow-up study	Men	distal colon cancer	Yes (Hvs.L)	No	No	Data format not sufficient for a dose-response meta-analysis; H vs. L analysis not performed as only one new study was identified	Can be included in a H vs. L analysis
COL01974	Sellers TA	1998	Prospective Cohort	Iowa Women's Health Study	Women - Post-menopausal - no family history of CRC	colon cancer	No	No	No	H vs. L analysis not performed as only one new study was identified	Can be included in a H vs. L analysis
					Women - Post-menopausal - family history of CRC	colon cancer	No	No	No	H vs. L analysis not performed as only one new study was identified	Can be included in a H vs. L analysis
COL01974	Sellers TA	1998	Prospective Cohort	Iowa Women's Health Study	Women - Post-menopausal - no family history of CRC	colon cancer	No	No	No	H vs. L analysis not performed as only one new study was identified	Can be included in a H vs. L analysis
					Women - Post-	colon cancer	No	No	No	H vs. L analysis not	Can be

					menopausal - family history of CRC					performed as only one new study was identified	included in a H vs. L analysis
COL00209	Zheng W. et al	1998	Prospective Cohort	Iowa Women's Health Study	Women - Post-menopausal	rectum cancer	Reviewed in text	No	No	Data format not sufficient for a dose-response meta-analysis; H vs. L analysis not performed as only one new study was identified	Can be included in a H vs. L analysis
COL00155	Kampman	1994	Case Cohort	The Netherlands Cohort study	No Sub-Group	colorectal cancer	Yes (Hvs.L)	No	Yes	Data format not sufficient for a dose-response meta-analysis	
COL01450	Bostick	1993	Prospective Cohort	Iowa Women's Health Study	Women	colon cancer	Yes (Hvs.L)	No	No	Superseded by Sellers et al, 1998, COL01974 on the highest versus lowest analysis; dose-response meta-analysis not performed as only one new study was identified	Can be included in a dose-response meta-analysis ; overall results were on women instead of subgroup by family history of colorectal cancer as in Sellers et al., 1998, COL01974
Total no. of articles = 11				**Total no. of individual cohort studies = 9**			**Total no. of individual cohort studies included = 6 (6 CRC/COL and 3 COL in H vs. L meta-analysis)**	**-**	**Total no. of studies included = 7 in CRC; 1 in COL**		

Highest versus lowest forest plot of supplemental calcium and colorectal cancer



Appendix 6

Vitmain D

Dietary vitamin D

The CUP team is aware that since December 2009, the end date of the literature search for this report, one cohort study has been published. This study is included in the review.

Fourteen prospective studies were accumulated until June 2010 (in 20 publications), among which were five new studies identified during the CUP (6 publications). Dose-response meta-analyses on dietary vitamin D and colorectal, colon, and its sub-sites and rectal cancer incidence were performed. Highest versus lowest forest plots were also generated to examine the same associations.

For the dose-response analyses all results were converted to a common scale (IU per day). The dose-response results are presented for an increment of 100 IU per day. For studies that presented the results in IU per 1000 kcal per day the intakes were converted to absolute intakes using the mean or median energy intake. E.g. if the median energy intake was 2000 kcal/day the intake in IU per 1000 kcal per day was multiplied by a factor of 2 (2000/1000=2).

Main results

Colorectal cancer

Ten studies were included in the dose-response analysis of dietary vitamin D and colorectal cancer risk. There was a statistically significant reduction in risk (summary RR=0.95, 95% CI = 0.93-0.98) per 100 IU/d, with no evidence of heterogeneity, I^2=11%, p=0.34. Sensitivity analyses excluding one study at a time did not materially alter these results.

Colon cancer

Six studies were included in the dose-response analysis of dietary vitamin D and colon cancer risk. There was no significant association, summary RR=0.99 (95% CI = 0.93-1.06) per 100 IU/d, with no evidence of heterogeneity, I^2=0%, p=0.68. Sensitivity analyses excluding one study at a time did not materially alter these results.

Rectal cancer

Five studies were included in the dose-response analysis of dietary vitamin D and rectal cancer risk. There was no significant association, summary RR was 0.87 (95% CI = 0.72-1.05) per 100 IU/d, with evidence of heterogeneity, I^2=57.4% p=0.052. In sensitivity analyses excluding one study at a time the summary RRs ranged from 0.85 (95% CI = 0.74-0.97) when excluding the study by Jarvinen et al, 2001 to 0.92 (95% CI = 0.75-1.13) when excluding the study by Martinez et al, 1996.

Proximal colon cancer

Two studies were included in the dose-response analysis of dietary vitamin D and proximal colon cancer risk. There was no significant association, summary RR=1.03 (95% CI = 0.89-1.19) per 100 IU/d, with no evidence of heterogeneity, I^2=0%, p=0.34.

Distal colon cancer

Two studies were included in the dose-response analysis of dietary vitamin D and distal colon cancer risk. There was no significant association, summary RR=1.07 (95% CI = 0.72-1.59) per 100 IU/d, with evidence of heterogeneity, I^2=75.1%, p=0.045.

Published meta-analysis

Huncharek et al. conducted a meta-analysis of dietary vitamin D intake and colorectal cancer (Huncharek,M. et al., 2009). The summary RR for the highest versus lowest intake was 0.94 (95% CI =0.83–1.06, P heterogeneity = 0.13, 10 cohort studies) for colon/colorectal and 0.83 (95% CI = 0.70–1.04, P heterogeneity 0.66, five cohort studies) for rectum.

Table 1 Appendix 6 Studies on dietary vitamin D identified during the CUP

Author/year	Study name	Number of cases	Years of follow-up	Comparison	RR (95% CI)
Jenab, 2010	EPIC	1220 CRC 772 COL 448 REC	3	>264 vs <64 IU/d >264 vs <64 IU/d >264 vs <64 IU/d	0.84 (0.60-1.17), CRC 1.00 (0.66-1.53), COL 0.61 (0.34-1.09), REC
Ishiara, 2008	JPHC	761 CRC 312 COL 146 REC	7.8	>670 vs <172 IU/d >654 vs <182 IU/d >670 vs <172 IU/d >670 vs <172 IU/d >670 vs <172 IU/d	0.92 (0.60-1.42), CRC, men 1.49 (0.86-2.60), CRC, women 1.23 (0.50-3.02), PRO, men 0.67 (0.32-1.43), DIS, men 1.09 (0.48-2.52), REC, men
Butler, 2008	Singapore Chinese Health study	961 CRC	9.8	Q4 vs Q1 but no cut-off provided	1.09 (0.92-1.31), CRC
Park, 2007	Hawaii-Los Angeles Multiethnic Cohort (MEC) Study	2110 CRC	7.3	>96.0 vs <30.9 IU/1000kcal/d >96.0 vs <30.9 IU/1000kcal/d	0.91 (0.73-1.13), CRC, men 0.78 (0.63-0.96), CRC, women
McCarl, 2006	Iowa Women's Health study	954 CRC	15	>617.3 vs <161.3 IU/d	0.68 (0.56-0.83), CRC
Kesse, 2005	EPIC-E3N	172 CRC	6.9	>129.2 vs <68.4 IU/d	0.89 (0.58-1.36), CRC

Table 2 Appendix 6 Overall evidence on dietary vitamin D and colorectal cancer

SLR	Summary of evidence
2005 SLR	Eight[1] publications reported on dietary vitamin D and colorectal cancer risk[1]. All of these studies reported non-significant associations.
Continuous Update Project	Six new publications on different cohort studies were identified; four of these studies found statistically significant decreased risk of colorectal cancer associated with dietary vitamin D intake (one only in men), while two others reported non-significant associations.

[1] Three other publications on colon cancer were included in the analysis of colorectal cancer.

Table 3 Appendix 6 Summary of results of the dose-response meta-analysis of dietary vitamin D and colorectal cancer

Colorectal cancer		
	2005 SLR	Continuous Update Project
Studies (n)	9 (including 3 on colon only)	10
Cases (n)	-	5171
RR (95% CI)	0.99 (0.97-1.00)	0.95 (0.93-0.98)
Quantity	Per 100 IU/d	Per 100 IU/d
Heterogeneity (I^2, p-value)	0%, p=0.62	11%, p=0.34
Colon cancer		
	2005 SLR	Continuous Update Project
Studies (n)	3	6
Cases (n)	-	1991
RR (95% CI)	0.99 (0.98-1.01)	0.99 (0.93-1.06)
Quantity	Per 100 IU/d	Per 100 IU/d
Heterogeneity (I^2, p-value)	0%, p=0.98	0%, p=0.68
Rectal cancer		
	2005 SLR	Continuous Update Project
Studies (n)	2	5
Cases (n)	-	925
RR (95% CI)	0.77 (0.63-0.94)	0.87 (0.72-1.05)
Quantity	Per 100 IU/d	Per 100 IU/d
Heterogeneity (I^2, p-value)	0%, p=0.37	57.4%, p=0.052
Proximal colon		
	2005 SLR	Continuous Update Project
Studies (n)	-	2
Cases (n)	-	293
RR (95% CI)	-	1.03 (0.89-1.19)
Quantity	-	Per 100 IU/d
Heterogeneity (I^2, p-value)	-	0%, p=0.34
Distal colon		
	2005 SLR	Continuous Update Project
Studies (n)	-	2
Cases (n)	-	303
RR (95% CI)	-	1.07 (0.72-1.59)
Quantity	-	Per 100 IU/d
Heterogeneity (I^2, p-value)	-	75.1%, p=0.045

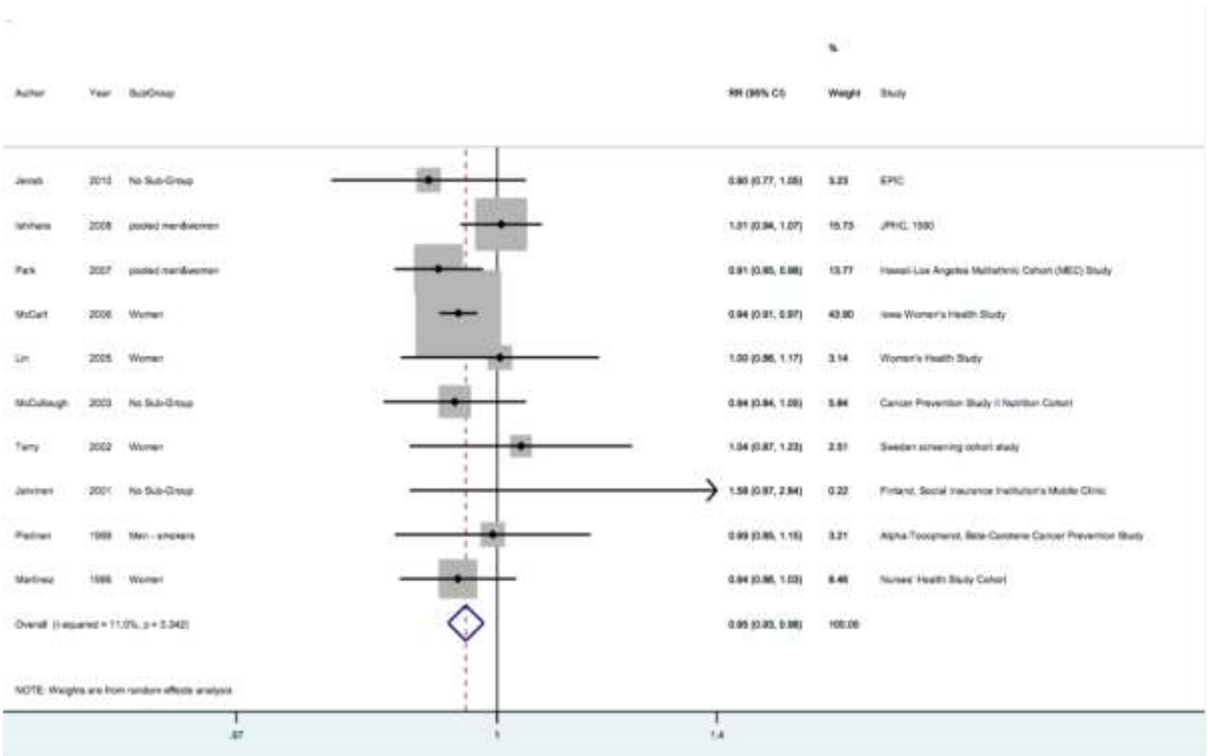
Inclusion/exclusion table for meta-analysis of dietary vitamin D and colorectal cancer

WCRFCode	Author	Year	Study Design	Study Name	Subgroup	Cancer outcome	SLR	CUP dose-response	CUP H vs. L forest plot	Estimated values	Exclusion reason
COLnew2	Jenab M	2010	Nested case control	EPIC	No Sub-Group	colorectal cancer	New	Yes	Yes	Mid-exposure values	
						colon cancer	New	Yes	Yes	Mid-exposure values	
						rectal cancer	New	Yes	Yes	Mid-exposure values	
COL40638	Ishihara J	2008	Prospective Cohort	JPHC, 1990	Men	colorectal cancer	New	Yes	Yes	Mid-exposure values	
					Women	colorectal cancer	New	Yes	Yes	Mid-exposure values	
					Men	distal colon cancer	New	Yes	Yes	Mid-exposure values	
					Men	proximal colon cancer	New	Yes	Yes	Mid-exposure values	
					Men	rectal cancer	New	Yes	Yes	Mid-exposure values	
COL40639	Butler LM	2008	Prospective Cohort	Singapore Chinese Health study	No Sub-Group	colorectal cancer	New	No	Yes		No information for a dose-response analysis
COL40668	Park SY	2007	Prospective Cohort	Hawaii-Los Angeles Multiethnic Cohort (MEC) Study	Men	colorectal cancer	New	No	Yes		Missing PY
					Women	colorectal cancer	New	No	Yes		Missing PY
COL40633	McCarl M	2006	Prospective Cohort	Iowa Women's Health Study	Women	colorectal cancer	New	Yes	Yes	Mid-exposure values	
COL01690	Lin	2005	Prospective Cohort	Women's Health Study	Women	colorectal cancer	Yes (Dose; H. vs.L)	Yes	Yes	Mid-exposure values + PY per quantile	
COL01843	Kesse	2005	Prospective Cohort	EPIC-E3N	Women	colorectal cancer	New	No	No		Results from Jenab 2010 are more recent
COL00366	McCullough	2003	Prospective Cohort	Cancer Prevention Study II Nutrition Cohort	Men	colon cancer	Yes (H. vs L.)	No	Yes		Missing PY
					No Sub-Group	colorectal cancer	Yes (Dose; H. vs.L)	Yes	Yes	Mid-exposure values + PY per quantile	
					Men	distal colon cancer	Yes (H. vs L.)	No	Yes		Missing PY
					Men	proximal colon cancer	Yes (H. vs L.)	No	Yes		Missing PY
					Men	rectal cancer	Yes (H. vs L.)	No	Yes		Missing PY
COL00560	Terry	2002	Prospective Cohort	Sweden screening cohort study	Women	colon cancer	Yes (H. vs L.)	Yes	Yes	Mid-exposure values + PY + nb of cases per quantile	
						colorectal cancer	Yes (Dose;H. vs L.)	Yes	Yes	Mid-exposure values + PY + nb of cases per quantile	
						distal colon cancer	Yes (H. vs L.)	Yes	Yes	Mid-exposure values + PY + nb of cases per quantile	

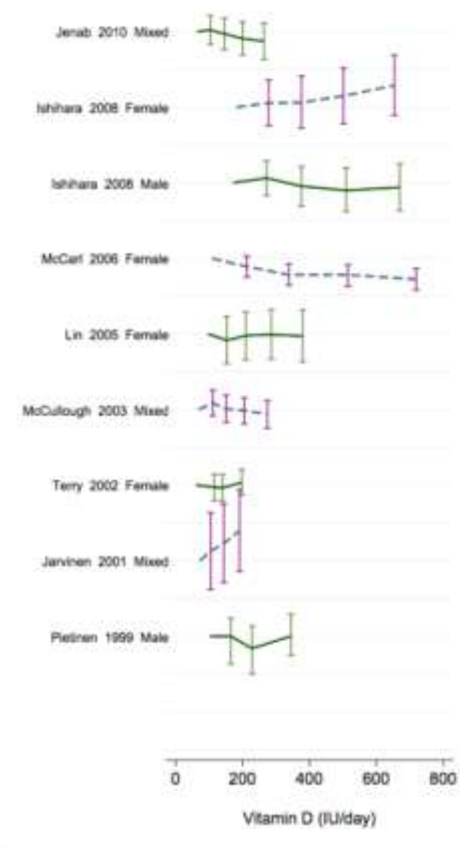
						proximal	Yes (H. vs L.)	Yes	Yes	Mid-exposure values + PY + nb of cases	

						colon cancer				per quantile	
COL00314	Jarvinen	2001	Prospective Cohort	Finland, Social Insurance Institution's Mobile Clinic	No Sub-Group	colon cancer	Yes (H. vs L.)	Yes	Yes	Mid-exposure values + weighted means for exposure + PY per quantile	
						colorectal cancer	Yes (H. vs L.)	Yes	Yes	Mid-exposure values + weighted means for exposure + PY per quantile	
						rectal cancer	Yes (H. vs L.)	Yes	Yes	Mid-exposure values + weighted means for exposure + PY per quantile	
COL00176	Pietinen	1999	Prospective Cohort	Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study	Men - smokers	colorectal cancer	Yes (Dose; Hvs.L)	Yes	Yes	PY per quantile	
COL01974	Sellers TA	1998	Prospective Cohort	Iowa Women's Health Study	Women - post menopausal - no family history of CRC	colon cancer	Reviewed in text	No	Yes		Missing PY
					Women - post menopausal - family history of CRC	colon cancer	Reviewed in text	No	Yes		Missing PY
COL00209	Zheng W	1998	Prospective Cohort	Iowa Women's Health Study	Women - post menopausal	rectal cancer	Reviewed in text	No	Yes		Missing exposure
COL00267	Tangrea	1997	Nested Case Control	Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study	Men - smokers	colorectal cancer	Yes (Dose)	No	No		Only mean exposure
COL00131	Martinez	1996	Prospective Cohort	Nurses' Health Study Cohort	Women	colon cancer	Yes (Dose)	Yes	No	Conversion for 250 IU ==> for 100 IU	Continuous result, no suitable for H vs L.
						colorectal cancer	Yes (Dose; H. vs.L)	Yes	Yes	Mid-exposure values + PY per quantile	
						rectal cancer	Yes (Dose)	Yes	No	Conversion for 250 IU ==> for 100 IU	Continuous result, no suitable for H vs L.
COL00156	Kearney J	1996	Prospective Cohort	health professionals follow-up study	Men	colon cancer	Yes (H. vs L.)	Yes	Yes	Mid-exposure values + PY per quantile	
COL00161	Glynn	1996	Nested Case Control	Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study	Men - smokers	colorectal cancer	Reviewed in text	No	No		Only mean exposure
COL01450	Bostick	1993	Prospective Cohort	Iowa Women's Health Study	Women	colon cancer	Yes (Dose; H. vs.L)	Yes	No	Mid-exposure values + PY per quantile	For H vs L, results from Sellers 1998 are more recent
COL01555	Heilbrun	1989	Nested Case Control	Honolulu Heart program	Men	colon cancer	Yes (Dose)	No	No		Only mean exposure
						rectal cancer	Yes (Dose)	No	No		Only mean exposure
COL01050	Garland	1985	Prospective Cohort	Western Electric Health study	Men	colorectal cancer	Yes (H. vs. L)	No	No		Only mean exposure
Total no. of articles = 20				**Total no. of individual cohort studies = 14**			**Total no. of ndividual cohort studies included = 10 (9 & 9 in CRC/COL; 3 & 5 in COL; 2 & 3 in REC, dose-response and H vs. L meta-analysis respectively; 2 PRO and 2 DIS in H vs. L meta-analysis)**	**Total no. of studies included = 9 in CRC; 6 in COL; 5 in REC; 2 in PRO; 2 in DIS**	**Total no. of studies included = 11 in CRC; 6 in COL; 6 in REC; 3 in PRO; 3 in DIS**		

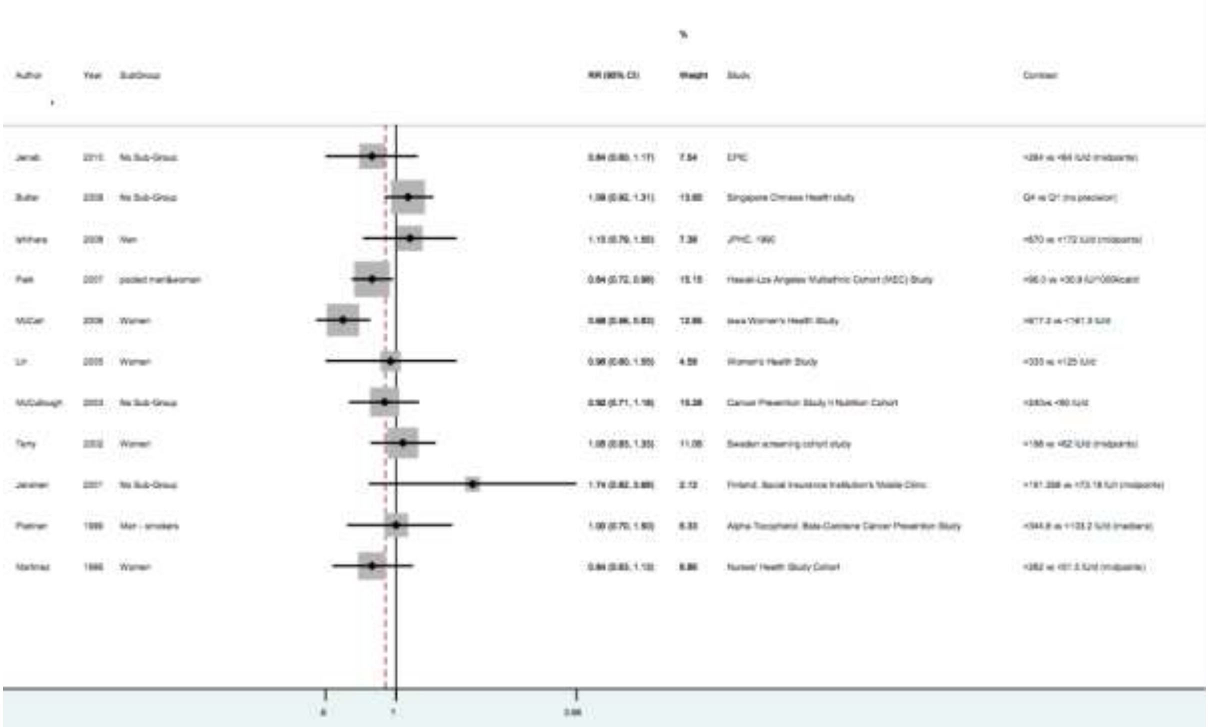
Dose--response meta-analysis of dietary vitamin D and colorectal cancer – per 100 IU/d



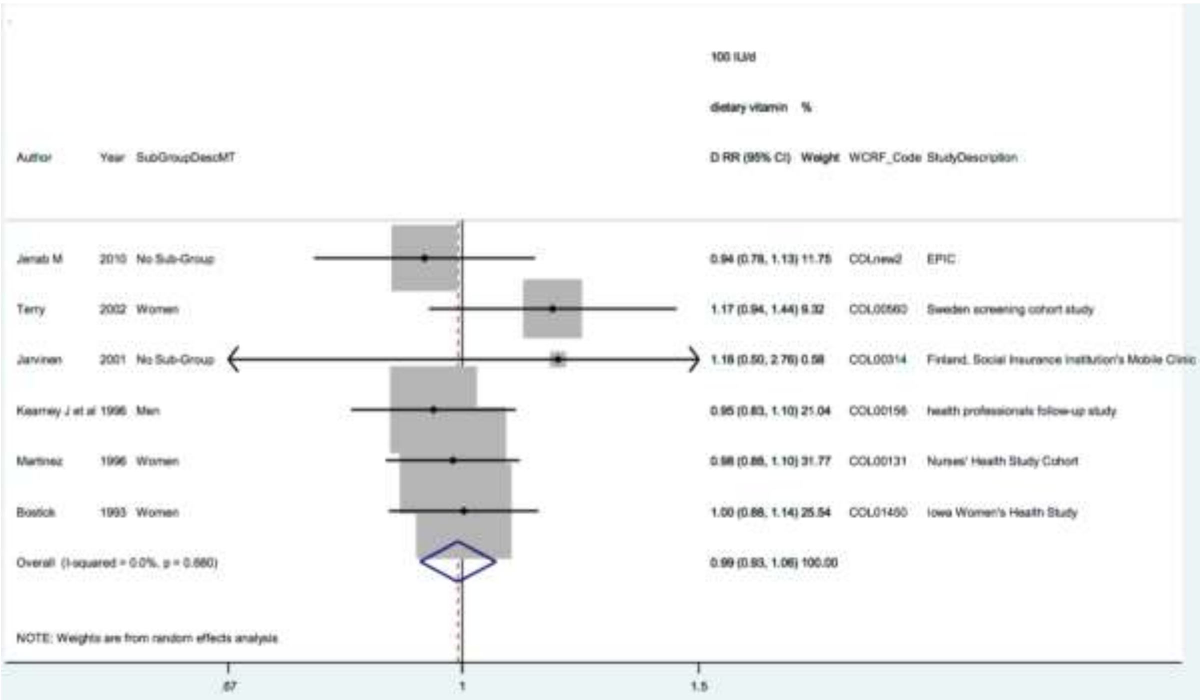
Dose-response graph of dietary vitamin D and colorectal cancer



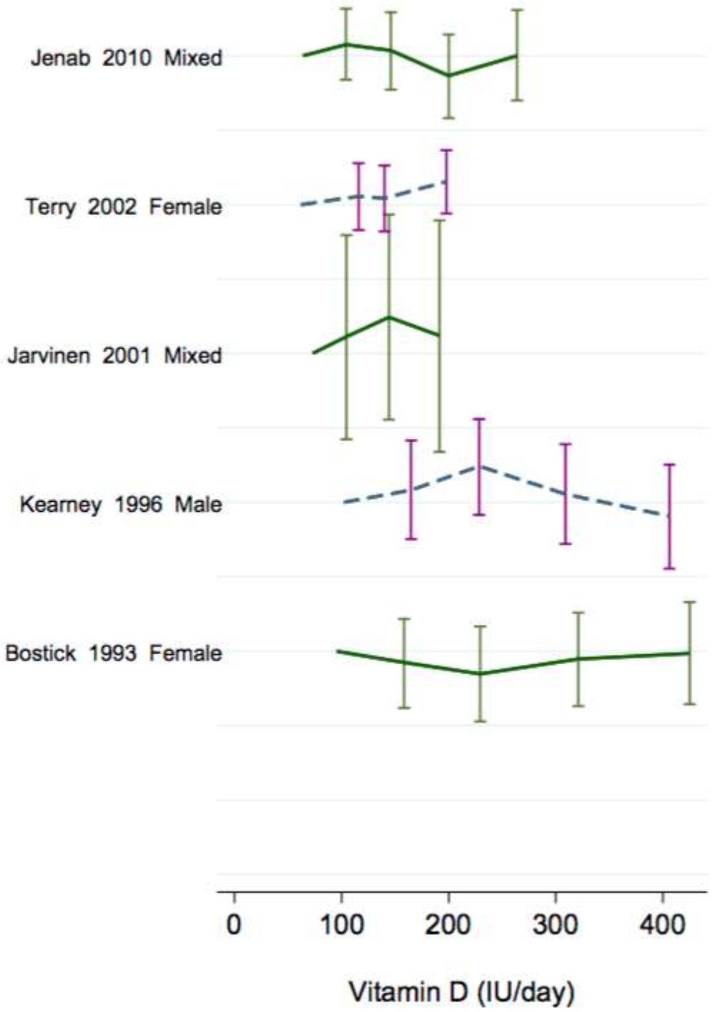
Highest versus lowest forest plot of dietary vitamin D and colorectal cancer



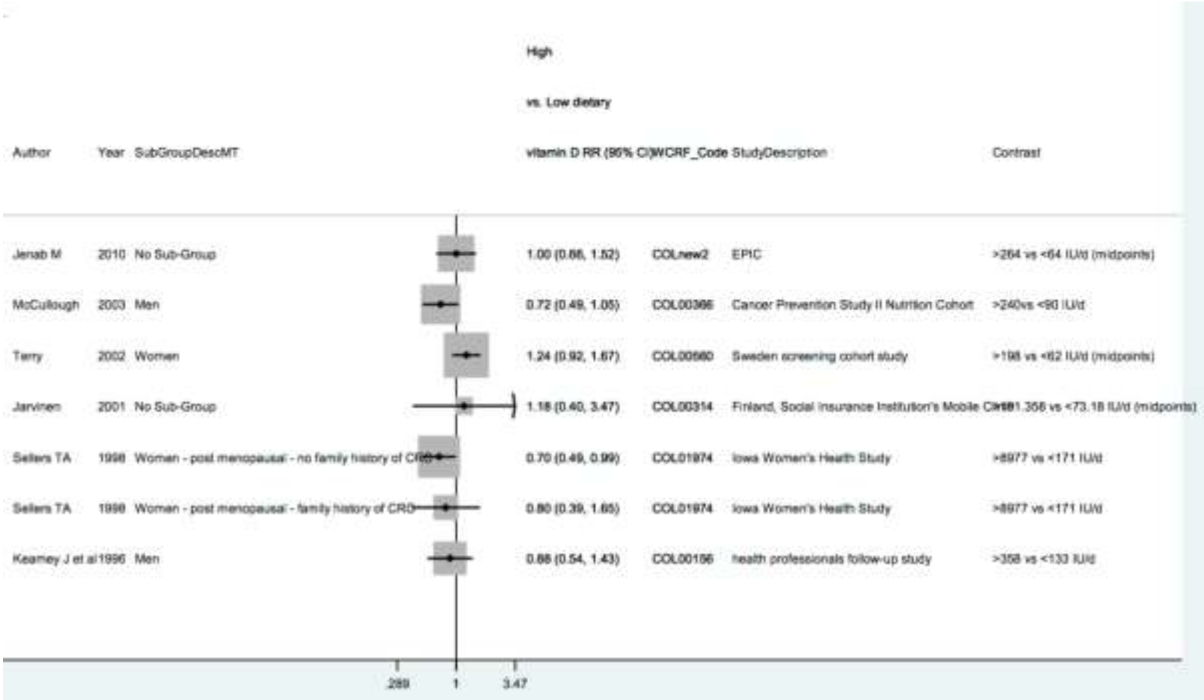
Dose-response meta-analysis of dietary vitamin D and colon cancer - per 100 IU/d



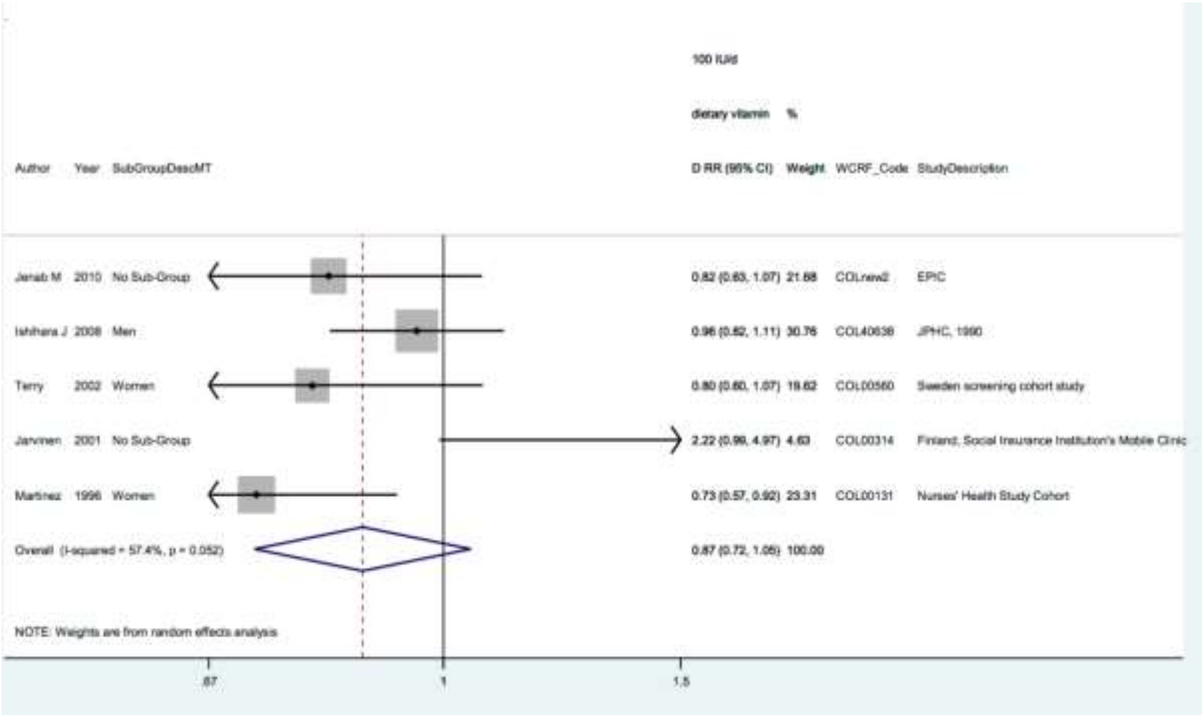
Dose-response graph of dietary vitamin D and colon cancer



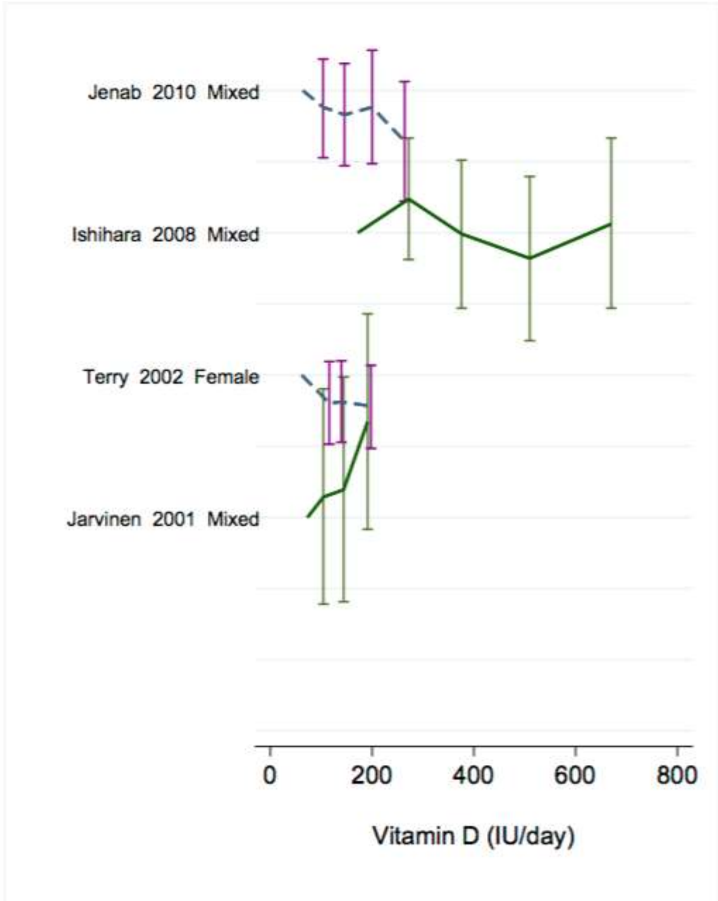
Highest versus lowest forest plot of dietary vitamin D and colon cancer



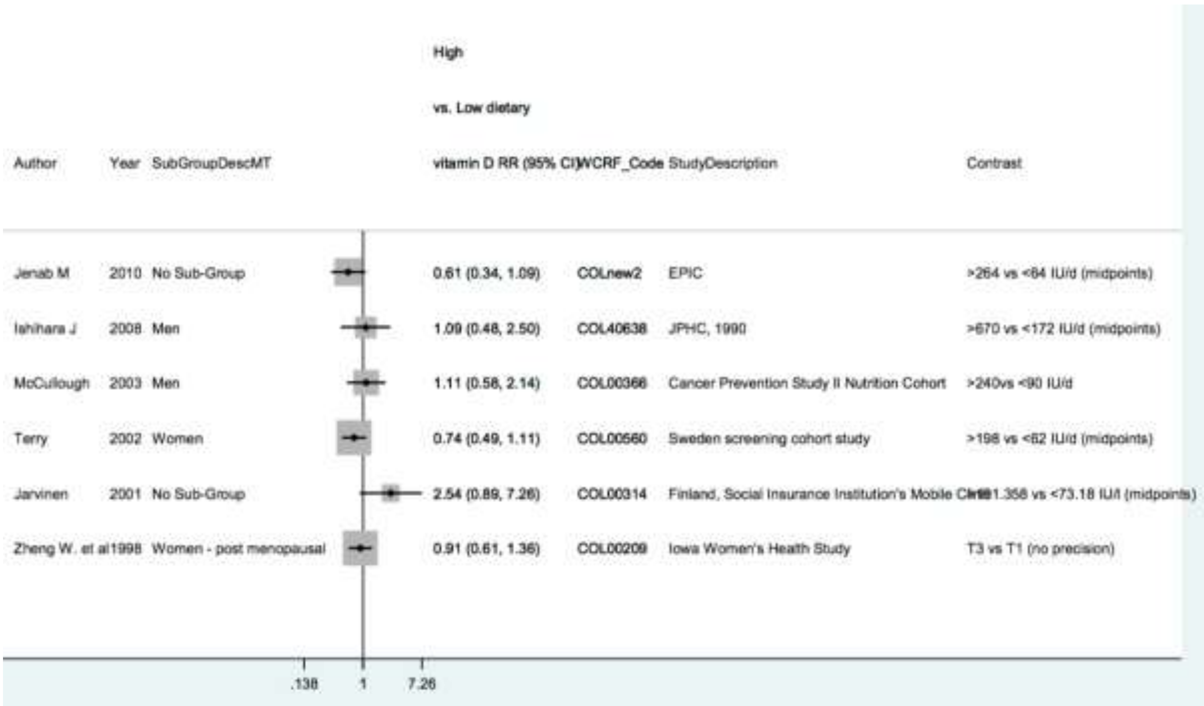
Dose-response meta-analysis of dietary vitamin D and rectal cancer - per 100 IU/d



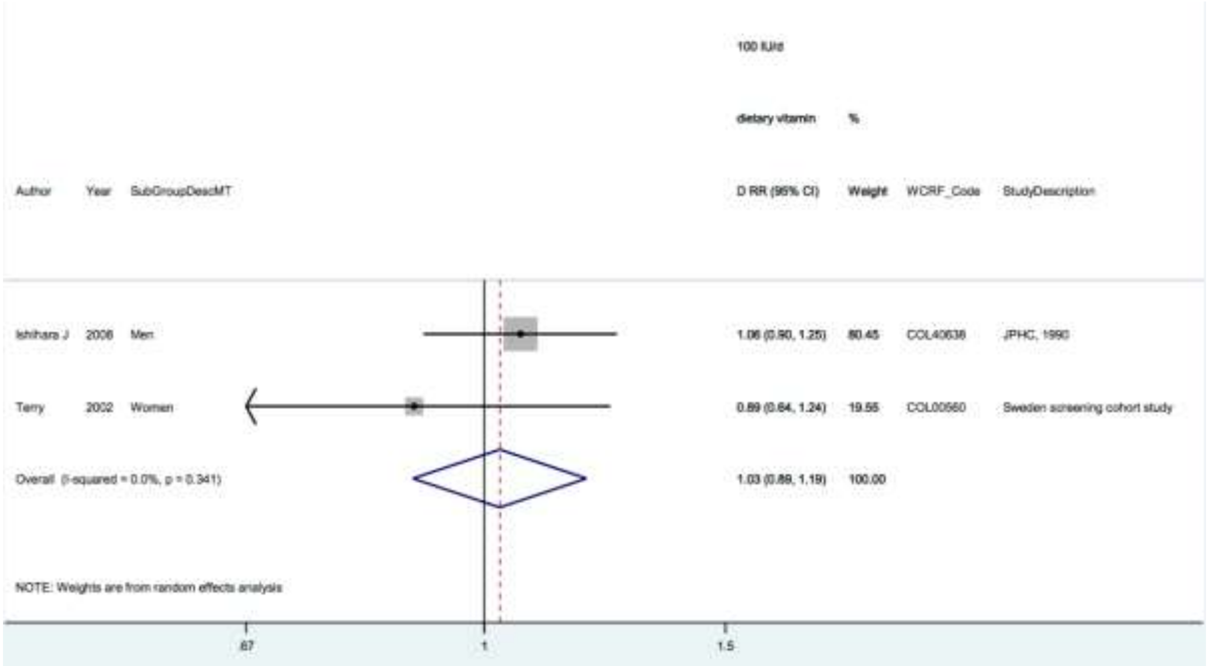
Dose-response graph of dietary vitamin D and rectal cancer]



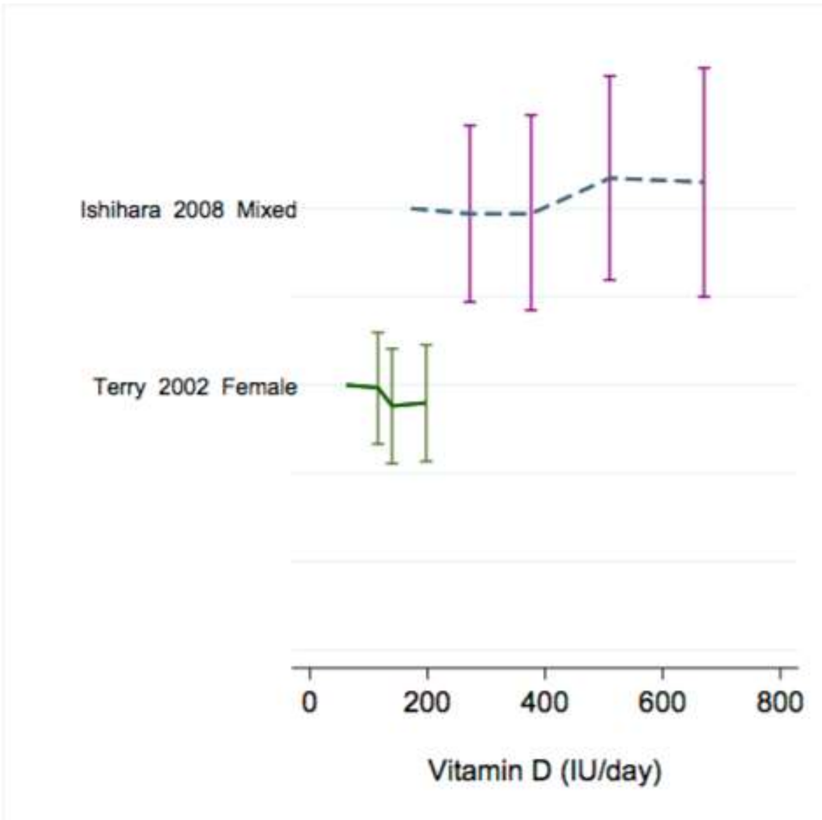
Highest versus lowest forest plot of dietary vitamin D and rectal cancer



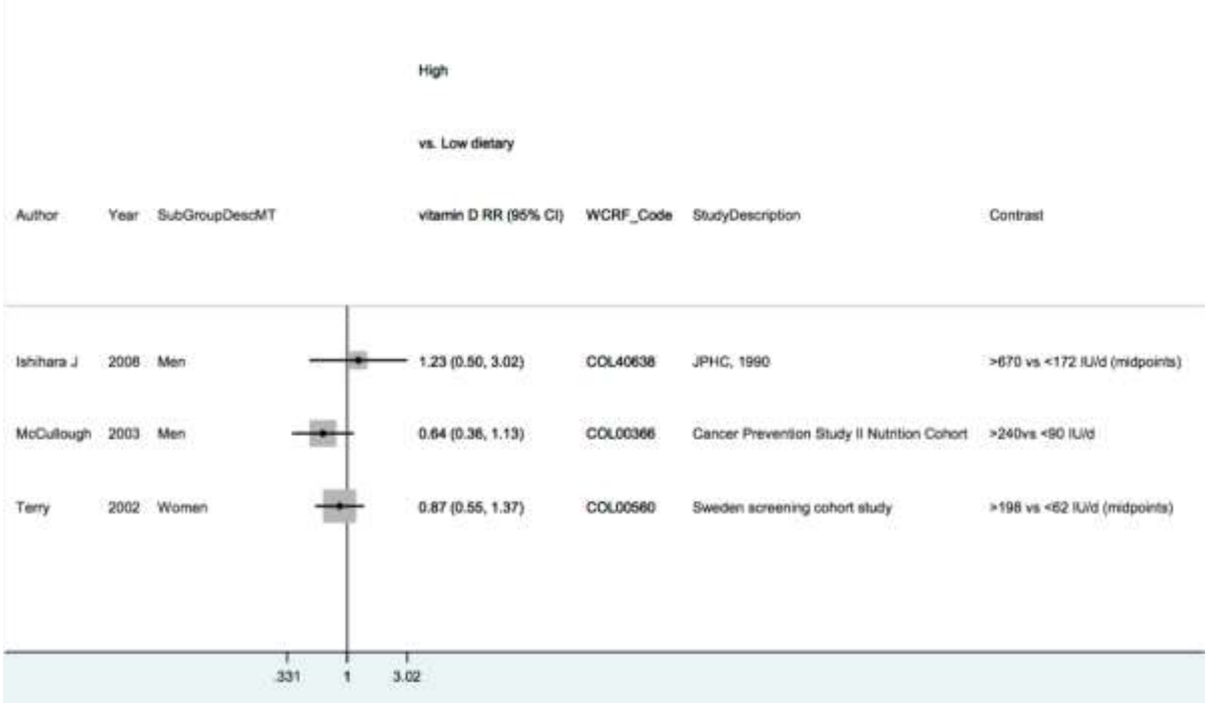
Dose-response meta-analysis of dietary vitamin D and proximal colon cancer - per 100 IU/d



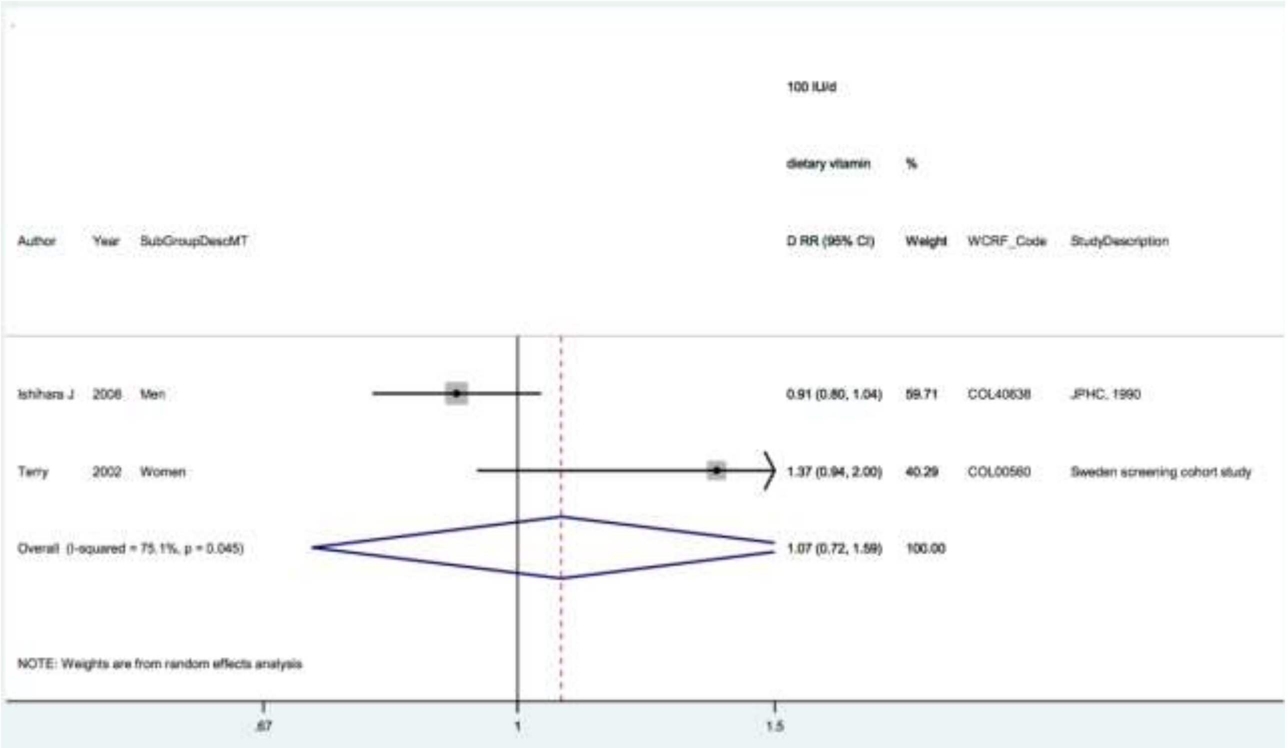
Dose-response graph of dietary vitamin D and proximal colon cancer



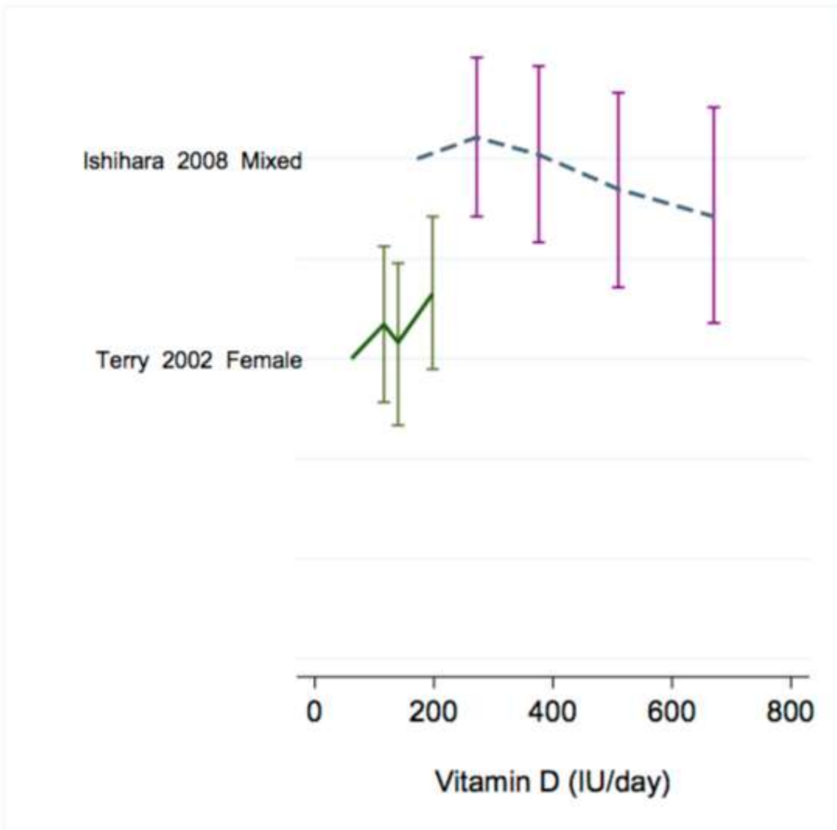
Highest versus lowest forest plot of dietary vitamin D and proximal colon cancer



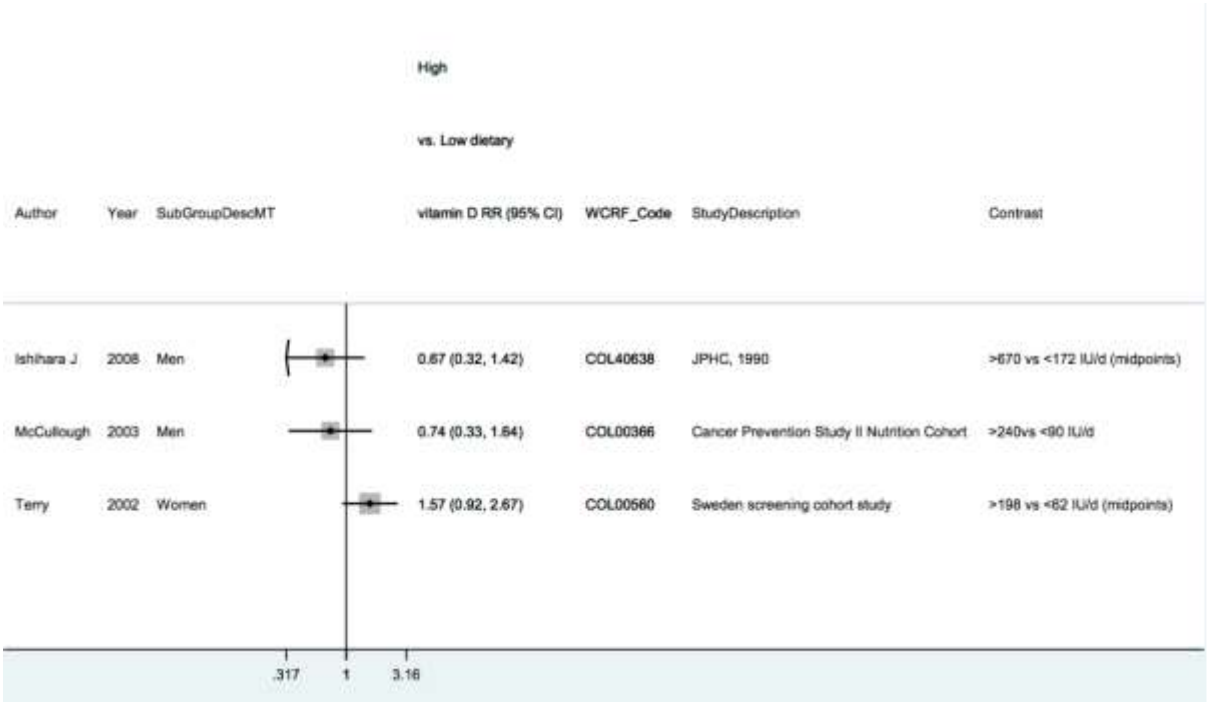
Dose-response meta-analysis of dietary vitamin D and distal colon cancer - per 100 IU/d



Dose-response graph of dietary vitamin D and distal colon cancer



Highest versus lowest forest plot of dietary vitamin D and distal colon cancer



Supplemental vitamin D

Summary

A total of six prospective studies were accumulated till June 2010 (from eight publications). Only one new study was identified during the CUP. However, even for previously identified studies, choices of analyses were made in the Continuous Update Project were different from 2005 SLR (such as not including studies that reported on colon cancer in the colorectal cancer analyses).

Dose-response meta-analyses on supplemental vitamin D intake and colon cancer incidence were performed. Highest versus lowest forest plots were constructed for colorectal and colon cancer.

Main results

Colon cancer

Two studies were included in the dose-response analysis of total vitamin D and colon cancer risk. There was a significant reduction in risk (summary RR=0.93, 95% CI = 0.88-0.99) per 100 IU/d, with no evidence of heterogeneity, I^2=0%, p=0.98.

Table 4 Appendix 6 Studies on supplemental vitamin D identified during the CUP

Author/year	Study name	Number of cases	Years of follow-up	Comparison	RR (95% CI)
Park, 2007	Hawaii-Los Angeles Multiethnic Cohort (MEC) Study	2110 CRC	7.3	>400 vs <400 IU/d >400 vs <400 IU/d	0.65 (0.49-0.84), CRC, men 0.97 (0.75-1.26), CRC, women

Table 5 Appendix 6 Overall evidence on supplemental vitamin D and colorectal cancer

SLR	Summary of evidence
2005 SLR	Three studies reported on supplemental vitamin D and colorectal cancer risk; all found no significant association.
Continuous Update Project	One new prospective study was identified (Park et al., 2009) and found a significant inverse association among men, but not women.

[1] Two other publications on colon cancer were included in the analysis of colorectal cancer.

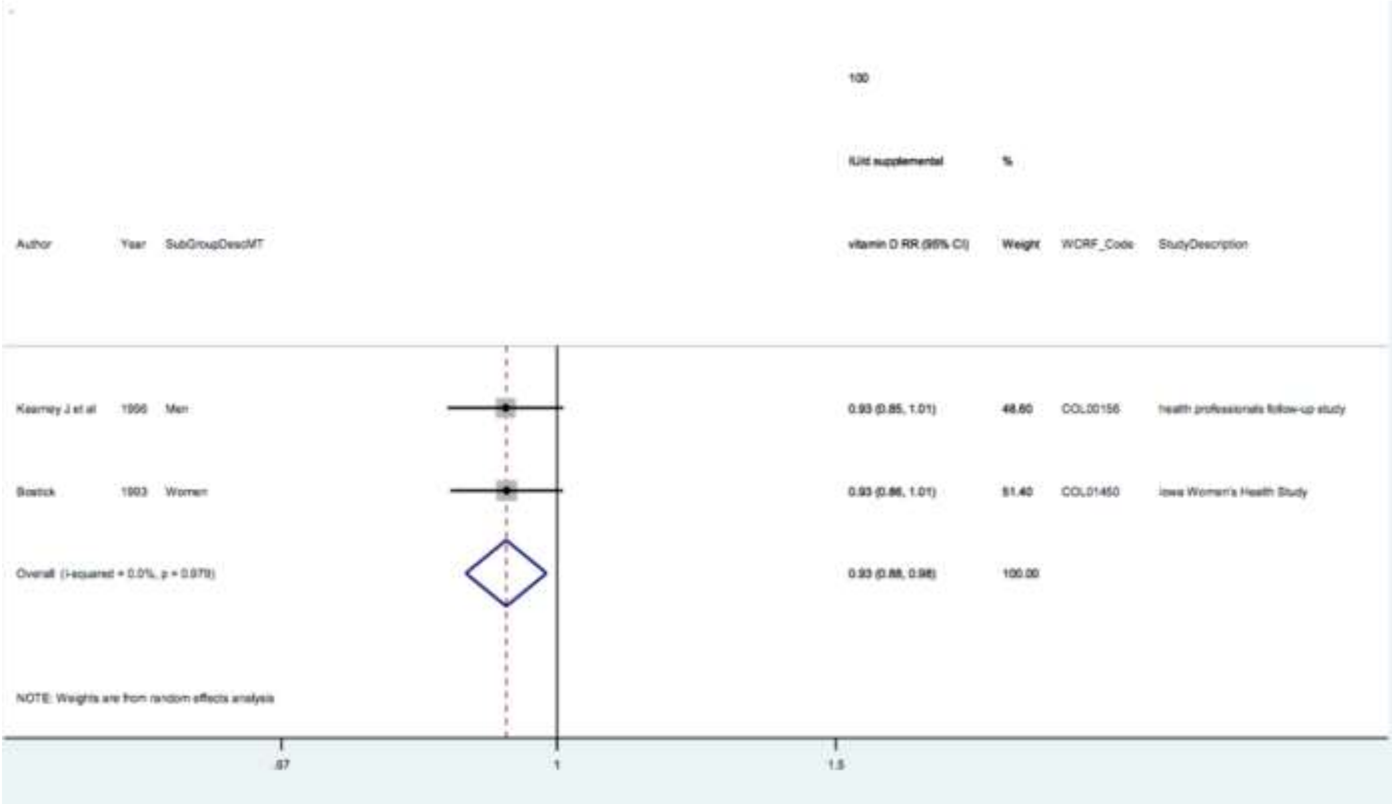
Table 6 Appendix 6 Summary of results of the dose-response meta-analysis of supplemental vitamin D and colon cancer

Colon cancer		
	2005 SLR	Continuous Update Project
Studies (n)	3	2
Cases (n)	-	415
RR (95% CI)	0.97 (0.86-1.09)	0.93 (0.88-0.99)
Quantity	-	Per 100 IU/d
Heterogeneity (I^2, p-value)	51%, p=0.038,	0%, p=0.98

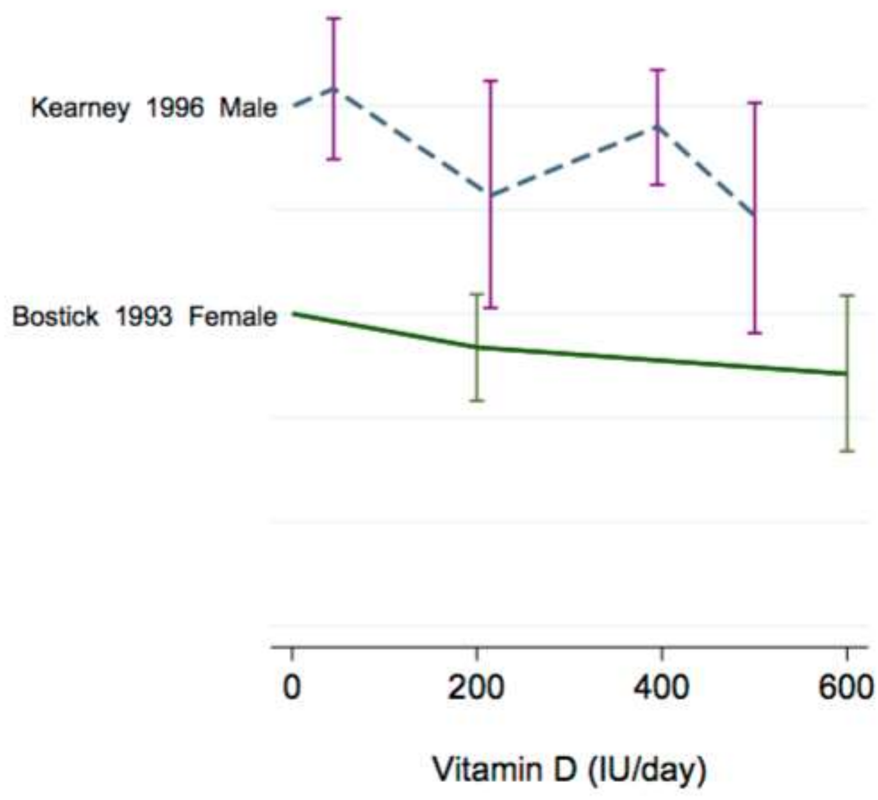
Table 7 Appendix 6 Inclusion/exclusion table for meta-analysis of supplemental vitamin D and colorectal cancer

WCRFCode	Author	Year	Study Design	Study Name	Subgroup	Cancer outcome	SLR	CUP dose-response	CUP H vs. L forest plot	Estimated values	Exclusion reason
COL40668	Park SY	2007	Prospective Cohort	Hawaii-Los Angeles Multiethnic Cohort (MEC) Study	Men	colorectal cancer	New	No	Yes		Missing PY
					Women	colorectal cancer	New	No	Yes		Missing PY
COL01690	Lin	2005	Prospective Cohort	Women's Health Study	Women	colorectal cancer	Yes (Dose; H. vs.L)	No	Yes		Missing standard deviation value
COL00314	Jarvinen	2001	Prospective Cohort	Finland, Social Insurance Institution's Mobile Clinic	No Sub-Group	colorectal cancer	Yes (H. vs L.)	No	Yes		No information for a dose-response analysis
COL00209	Zheng W. et al	1998	Prospective Cohort	Iowa Women's Health Study	Women - post menopausal	rectal cancer	Reviewed in text	No	Yes (but only result available)		Missing exposure
COL01974	Sellers TA	1998	Prospective Cohort	Iowa Women's Health Study	Women - no family history of CRC	colon cancer	Reviewed in text	No	Yes		Missing PY
					Women - family history of CRC	colon cancer	Reviewed in text	No	Yes		Missing PY
COL00156	Kearney J et al	1996	Prospective Cohort	health professionals follow-up study	Men	colon cancer	Yes (Dose; H. vs.L)	Yes	Yes	Mid-exposure values + PY per quantile	
COL00131	Martinez	1996	Prospective Cohort	Nurses' Health Study Cohort	Women	colorectal cancer	Yes (H. vs.L)	No	Yes		No information for a dose-response analysis
COL01450	Bostick	1993	Prospective Cohort	Iowa Women's Health Study	Women	colon cancer	Yes (Dose; H. vs.L)	Yes	No	Mid-exposure values + nb of cases and PY not provided for the multivariate model ==>taken from the age-ajusted model	For H vs L, results from Sellers 1998 are more recent.
Total no. of articles = 8				**Total no. of individual cohort studies = 6**			**Total no. of individual cohort studies included = 5 (3 & 5 in CRC/COL dose-response and H vs. L meta-analysis respectively)**	**Total no. of studies included = 2 in COL**	**Total no. of studies included = 4 in CRC; 2 in COL; 1 in REC**		

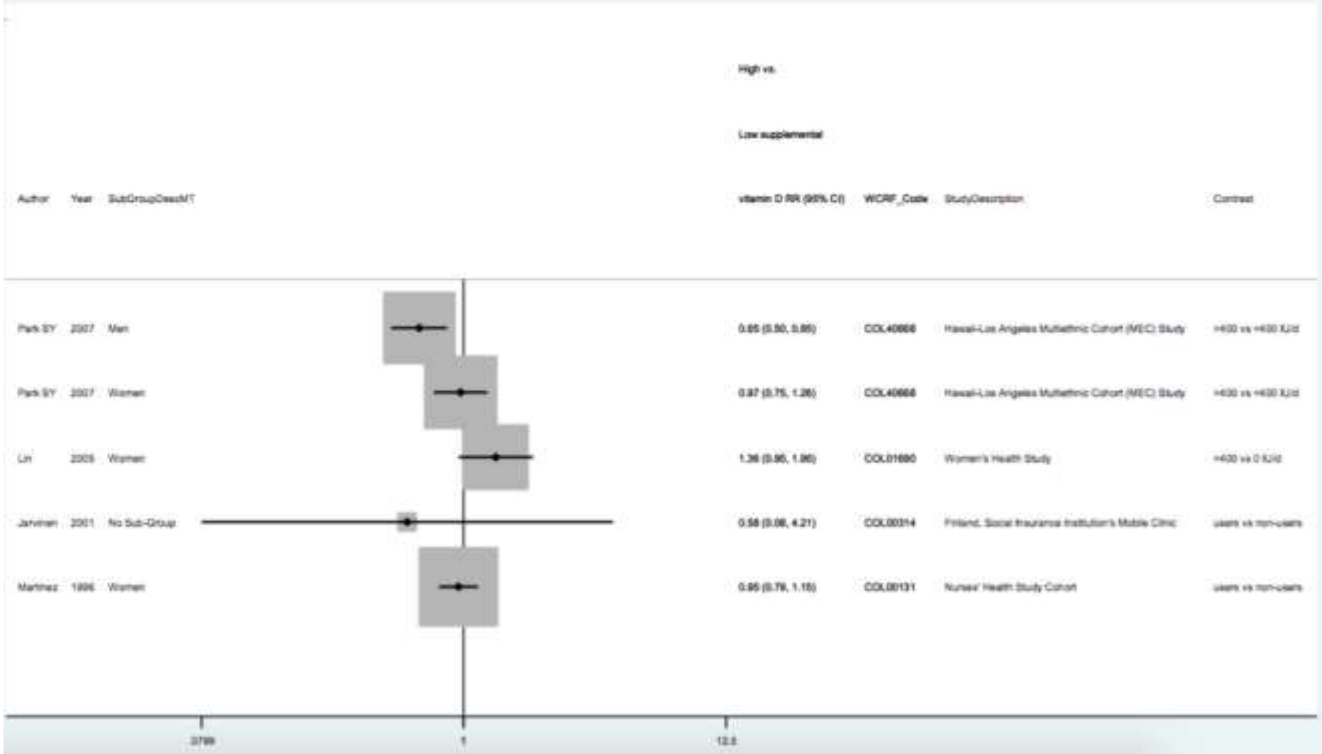
Dose-response meta-analysis of supplemental vitamin D and colon cancer - per 100 IU/d



Dose-response graph of supplemental vitamin D and colon cancer



Highest versus lowest forest plot of supplemental vitamin D and colorectal cancer



Highest versus lowest forest plot of supplemental vitamin D and colon cancer