WCRF/AICR Systematic Literature Review Continuous Update Project Report

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

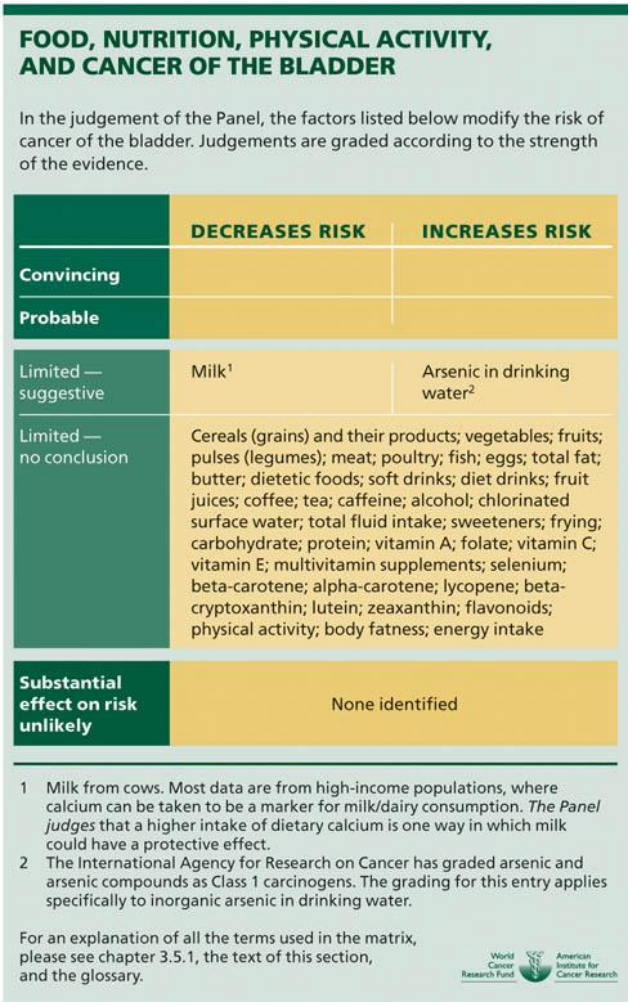
List of Abbreviations of cohort study names used in the CUP SLR

AHS	Californian Seventh Day Adventists
AMS	Adventists Mortality Study
ATBC	Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study
BRHS	British Regional Heart Study
CCPS	Copenhagen City Heart Study, the Copenhagen County Centre of Preventive Medicine and the Copenhagen Male Study
CHS	Copenhagen City Heart Study
CPS	Cancer Prevention Study
CSM	Cohort of Swedish Men
DCS	Danish Diet, Cancer and Health study
EPIC	European Prospective Investigation into Cancer and Nutrition
FHS	Framingham Heart Study
HPFS	Health Professionals Follow-up Study
HPP	Honolulu Heart Program
IWHS	Iowa Women's Health Study
JACC	Japan Collaborative Cohort Study
JPHC	The Japan Public Health Centre-based Prospective Study
NHICS	Korea National Health Insurance Study
LWS	Leisure World Study, Laguna Hills Study USA
LSS	Life Span Study, atomic bomb survivors, Japan
MEC	Multiethnic Cohort Study
MWS	The Million Women Study
NHS	The Nurses' Health Study
NIH-AARP	NIH-AARP Diet and Health Study
NCS	The Netherlands Cohort Study
PLCO	Prostate, Lung, Colorectal, and Ovarian (PLCO) Cancer Screening Study
SELECT	The Selenium and Vitamin E Cancer Prevention Trial
SMC	Swedish Mammography Cohort

STC	Swedish Twin Cohort
WHI	Women's Health Initiative
VITAL	VITamins And Lifestyle cohort

Background

Matrices presented in the WCRF/AICR 2007 Expert Report



FOOD, NUTRITION, PHYSICAL ACTIVITY, AND CANCER OF THE BLADDER

In the judgement of the Panel, the factors listed below modify the risk of cancer of the bladder. Judgements are graded according to the strength of the evidence.

	DECREASES RISK	INCREASES RISK
Convincing		
Probable		
Limited — suggestive	Milk[1]	Arsenic in drinking water[2]
Limited — no conclusion	Cereals (grains) and their products; vegetables; fruits; pulses (legumes); meat; poultry; fish; eggs; total fat; butter; dietetic foods; soft drinks; diet drinks; fruit juices; coffee; tea; caffeine; alcohol; chlorinated surface water; total fluid intake; sweeteners; frying; carbohydrate; protein; vitamin A; folate; vitamin C; vitamin E; multivitamin supplements; selenium; beta-carotene; alpha-carotene; lycopene; beta-cryptoxanthin; lutein; zeaxanthin; flavonoids; physical activity; body fatness; energy intake	
Substantial effect on risk unlikely	None identified	

1 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.
2 The International Agency for Research on Cancer has graded arsenic and arsenic compounds as Class 1 carcinogens. The grading for this entry applies specifically to inorganic arsenic in drinking water.

For an explanation of all the terms used in the matrix, please see chapter 3.5.1, the text of this section, and the glossary.

World Cancer Research Fund | American Institute for Cancer Research

Modifications to the existing protocol

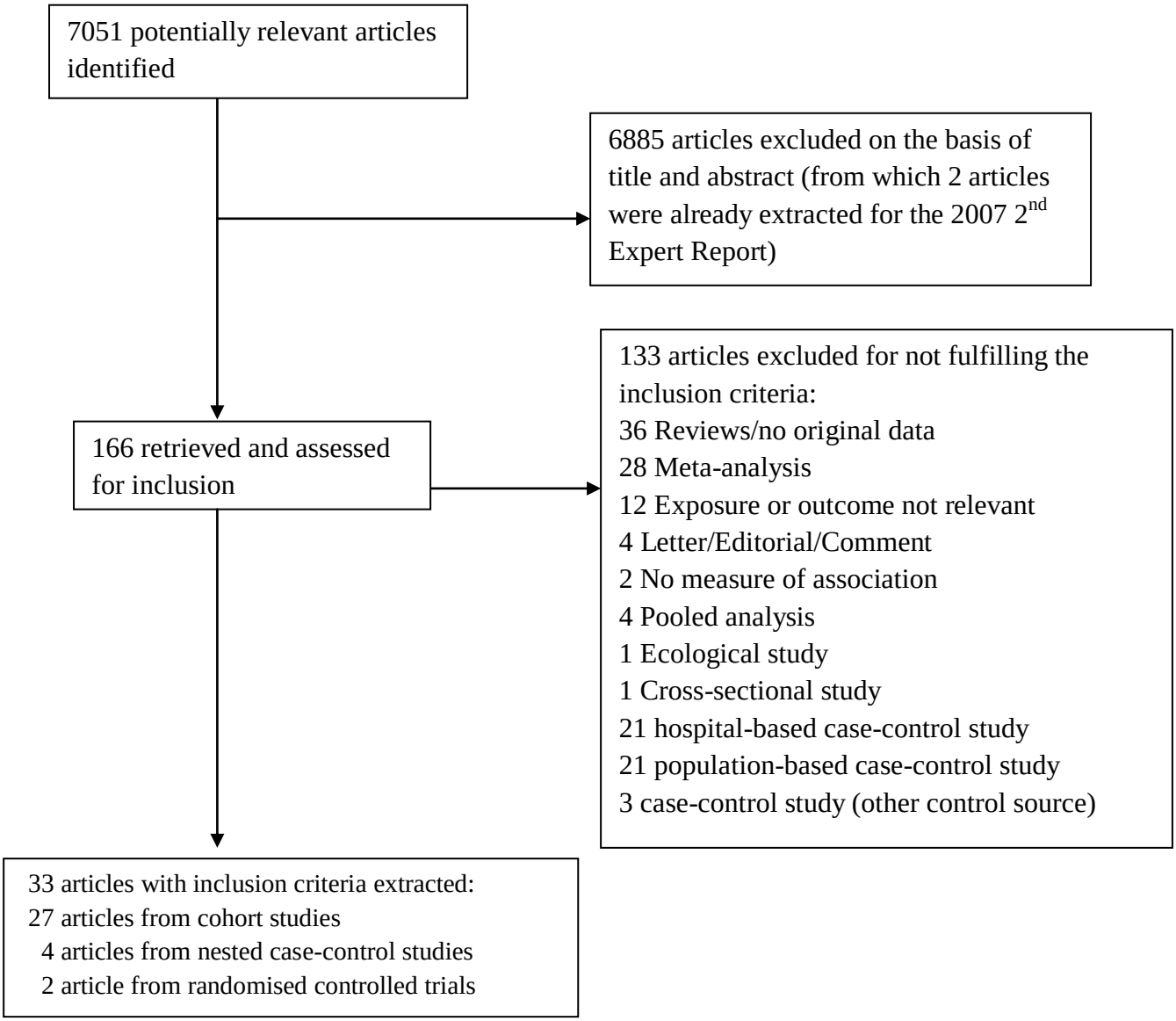
The research team composition was modified. The literature search and data extraction was conducted by Snieguole Vingeliene and Leila Abar. Ana Rita Vieira and Dagfinn Aune did the data analyses. Ana Rita Vieira prepared the first draft of the report.
The timeline was modified. The search was finished on July 2013 and the SLR report ready to be sent to WCRF Secretariat on November 1st 2013.

Notes on figures and statistics used

- The statistical methods used are described in the protocol.
- The method by Hamling et al, 2008 was used to convert risk estimates when the reference category was not the lowest category
- 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 (Higgins and Thompson, 2002). 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.
- Heterogeneity test and I^2 statistics are shown for a "Highest vs. Lowest" meta-analysis when this is the only type of meta-analysis conducted.
- Only summary relative risks estimated with random effect models are shown.
- The dose-response forest plots show the relative risk estimate for each study, expressed per unit of increase. 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 table.
- Highest vs. lowest forest plots show the relative risk estimate for the highest vs. the reference category used in each study. The comparisons in each study are shown. The overall summary estimate was not calculated (except for physical activity domains).
- The dose-response plot shows the results for each study included in the review. The relative risks estimates are plotted in the mid-point of each category level (x-axis) and are connected through lines.
- Nonlinearity was explored when there were at least five studies and their results suggested a non-linear association. Nonlinear dose–response curves were plotted using restricted cubic splines for each study, using knots fixed at percentiles 10%, 50%, and 90% through the distribution. These were combined using multivariate meta-analysis.
- The non-linear graphs are only presented when the p-value for non-linearity is statistically significant. Otherwise only the p-value is reported in the text.

Continuous Update Project: Results of the search

Flow chart of the search for bladder cancer – Continuous update project Search period January 1st 2006-July 31st 2013



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Randomised controlled trials (RCT). Results by exposure.

Two randomised controlled trials on bladder cancer (as secondary outcome) were identified: The Selenium and Vitamin E Cancer Prevention Trial (SELECT) (Lotan, 2012) and the Women's Health Initiative (WHI) trial (Brunner R. 2011). A meta-analysis of RCTs, which compared folic acid supplementation versus placebo, was identified (Vollsett, 2013).

Selenium and Vitamin E

SELECT is a phase 3 double-blind randomized placebo controlled trial of selenium (200 μg 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 34,887 men randomly assigned to 4 groups (selenium, vitamin E, selenium plus vitamin E and placebo) between August 22, 2001 and June 24, 2004. Compared to the placebo group (53 cases), there were no significant differences in bladder cancer incidence in the groups receiving vitamin E (56 cases, HR 1.05, IQR 0.64–1.73, p=0.79), selenium (60 cases, HR 1.13, 0.70–1.84, p=0.52) or vitamin E plus selenium (55 cases, HR 1.05, 0.63–1.70, p=0.86).

5.6.3 Calcium and vitamin D

One randomised controlled trial was identified. The Women's Health Initiative (WHI) trial of calcium plus vitamin D (Brunner R. 2011) where women were randomized to 1,000 mg of elemental calcium with 400 IU vitamin D3 or placebo showed that calcium plus vitamin D supplementation was not associated with bladder cancer risk, RR =1.49 (95%CI: 0.88, 2.53).

5.5.3 Folic acid supplements

A meta-analysis of 13 RCT showed that during a weighted average scheduled treatment duration of 5.2 years, allocation to folic acid quadrupled plasma concentrations of folic acid (57·3 nmol/L for the folic acid groups vs. 13·5 nmol/L for the placebo groups), but had no significant effect on overall cancer incidence. The RR of bladder cancer in the intervention group (102 bladder cancer cases, 24 799 participants) compared to the control (105 bladder cancer cases, 24 8220 participants was 0.97 (95% CI: 0.68–1.39). The daily doses of folic acid used in the trials ranged from 0.5 mg to 5 mg, except in one trial of a 40 mg daily dose (Vollsett, 2013).

Cohort studies. Results by exposure.

Table 1 Number of relevant articles identified during the 2005 SLR and the CUP and total number of articles by exposure.

The exposure code is the exposure identification in the database. Only exposures identified during the CUP are shown. **The numbers in the table refer to the number of articles identified in the SLR and in the CUP.**

Exposure code	Exposure name	Number of articles		Total number of articles
		SLR 2005	CUP	
1.4	Type of breakfast	0	1	1
1.4	Preference for salty foods	0	1	1
1.4	Individual level dietary patterns	0	1	1
1.5	Other dietary patterns	0	1	1
1.7	Other dietary pattern issues	0	2	2
2.1.1.2.3	Rice	2	1	3
2.1.2	Root vegetables	0	2	2
2.1.2.1	Potatoes	0	1	1
2.2	Fruit and (non-starchy) vegetables	6	2	8
2.2.1	Total vegetables	4	5	9
2.2.1	Fruiting vegetables	0	2	2
2.2.1	Fried vegetables	1	1	2
2.2.1.3	Garlic and Onion	0	2	2
2.2.1.1.1	Carrots	3	1	4
2.2.1.2	Cruciferous vegetables	4	2	6
2.2.1.2.2	Chinese cabbage	1	1	2
2.2.1.2.3	Cabbage	3	2	5
2.2.1.4	Green leafy vegetables	3	2	5
2.2.1.4.2	Spinach	3	1	4
2.2.1.4.4	Seaweed	2	1	3
2.2.1.5	Wild plants	0	1	1
2.2.1.5	Pickles	0	1	1
2.2.1.5	Mushrooms	2	3	5
2.2.1.5	Lettuce, cabbage	0	1	1
2.2.1.5	Leafy vegetables	0	2	2
2.2.1.5	All vegetables	6	1	7
2.2.1.5.13	Tomatoes	6	1	7
2.2.2	Total fruits	7	4	11
2.2.2.1	Citrus fruits	2	3	5
2.2.2.2	Stone fruits	0	2	2
2.2.2.2	Other fruits	2	1	3
2.2.2.2	Berries	4	2	6

2.2.2.2.11	Grape	1	2	3
2.3.1.1	Miso soup	2	1	3
2.3.2	Beans	0	1	1
2.3.2.2	Tofu	3	1	4
2.5.1	Total meat	4	2	6
2.5.1	White meat	0	1	1
2.5.1.2	Processed meat	3	5	8
4.4.2.5	Fried meat	1	1	2
2.5.1.2.8	Bacon	0	1	1
2.5.1.2.9	Sausages	0	1	1
2.5.1.2.9	Hot dog	0	1	1
2.5.1.3	Red meat	0	5	5
2.5.1.3.1	Beef	3	1	4
2.5.1.3.3	Pork	3	1	4
2.5.1.4	Poultry	2	4	6
2.5.1.5	Liver	0	1	1
2.5. 1.7	Hamburger	0	2	2
2.5.2	Fish paste	1	1	2
2.5.2	Fish	4	3	7
2.5.2	Dark meat fish	0	1	1
2.5.2.3	Dried and salted fish	3	1	4
2.5.3	Shellfish	0	1	1
2.5.4	Eggs	6	1	7
2.6	Fat preference	0	1	1
2.6.1.1	Butter	4	2	6
2.6.1.4	Fish oil	0	2	2
2.6.3	Margarine	0	1	1
2.6.4	Sugars (as foods)	1	1	2
2.6.4	Fructose	0	1	1
2.7	Dairy products	0	3	3
2.7	Non fermented milk and milk products	0	1	1
2.7	Cultured milk	0	1	1
2.7.1	Milk	5	5	10
2.7.2	Cheese	2	3	5
2.7.3	Yoghurt and fermented milk products	1	3	4
2.9.13	Sweets	0	1	1
3.1	Total fluid intake	4	2	6
3.2	Well or spring water (public water supply)	0	1	1
3.2	Water as beverage	4	2	6
3.4	Soft drinks	3	1	4
3.4.2	Carbonated beverages	1	0	1
3.5	Fruit juices	2	1	3
3.5	Fruit and vegetable juices	0	1	1
3.6.1	Coffee	12	3	15
3.6.2	Tea	3	1	4

3.6.2	Black tea	2	1	3
3.6.2.2	Green tea	2	2	4
3.7.1	Alcohol consumption	0	3	3
3.7.1	Alcoholic drinks	0	2	2
3.7.1	Frequency alcohol consumption	0	1	1
3.7.1	Alcoholism	0	2	2
3.7.1	Alcoholic drinks - years since stopping	0	1	1
3.7.1	Alcoholic drinks - duration of use	0	1	1
3.7.1	Age start alcohol consumption	0	1	1
4.1.2.7.2	Arsenic	6	4	10
4.1.2.9	Other contaminants	0	1	1
4.1.2.9	DiMeIQx	0	1	1
4.2	Preserved foods	0	1	1
4.2.5.1	Salt	0	1	1
4.3.5.4.1	Nitrites and nitrates (as food additives)	1	1	2
4.3.5.4.1	Nitrate from public water	0	1	1
4.3.5.4.1	NDMA (N-nitrosodimethylamine)	0	1	1
4.3.5.4.1	Dietary nitrite	0	1	1
4.3.5.4.1	Dietary nitrate	0	2	2
4.3.5.4.1	Total nitroso compounds	0	1	1
4.4.2	Acrylamide	0	2	2
4.4.2.5	Fried foods	0	1	1
4.4.2.5	MelQx	0	1	1
4.4.2.7	BaP	0	1	1
4.4.2.8	PhIP	0	1	1
4.4.2.9	Mutagen index, meat	0	1	1
5.1.2	Fibre	0	1	1
5.1.4	Sugars (as nutrients)	0	1	1
5.1.4	Sucrose	0	1	1
5.1.4	Mono/disaccharides	0	1	1
5.1.4	Lactose	0	1	1
5.1.5	Glycaemic load	0	1	1
5.1.5	Glycaemic index	0	1	1
5.2	Fat	0	1	1
5.2.4.1	Fish fatty acids (EPA and DHA)	0	1	1
5.2.5	Trans fatty acids	1	1	2
5.3	Protein	1	1	2
5.4	Alcohol (as ethanol)	8	2	10
5.5.1.1	Retinol supplement	0	1	1
5.5.1.2	Plasma beta-cryptoxanthin	0	1	1
5.5.1.2	Plasma beta-carotene	0	1	1
5.5.1.2	Plasma alpha-carotene	0	1	1
5.5.1.2	Beta-carotene, total (supplemental & dietary)	0	1	1
5.5.1.2	Beta-carotene, dietary	0	2	2

5.5.1.2	Beta-carotene supplements	0	2	2
5.5.1.2	Beta-carotene	15	0	15
5.5.1.2	Alpha-carotene	6	0	6
5.5.2	Plasma zeaxanthin	0	1	1
5.5.2	Plasma total carotenoids	0	1	1
5.5.2	Plasma lycopene	0	1	1
5.5.2	Plasma lutein	0	1	1
5.5.3	Total folate intake	0	1	1
5.5.3	Total folate	5	1	6
5.5.3	Folate supplement	0	2	2
5.5.3	Dietary folate	0	1	1
5.5.3	Thiamine (vitamin B1) supplement	0	2	2
5.5.6	Nicotinic acid	0	1	1
5.5.7	Pyridoxine (vitamin B6) supplement	0	1	1
5.5.8	Cobalamin (vitamin B12) supplement	0	1	1
5.5.9	Total vitamin C	3	1	4
5.5.9	Supplemental vitamin C	5	3	8
5.5.9	Plasma vitamin C	0	1	1
5.5.9	Dietary vitamin C	4	2	6
5.6.2	Heme iron	0	1	1
5.6.3	Total calcium	0	1	1
5.6.3	Supplemental calcium	0	2	2
5.6.3	Dietary calcium	1	3	4
5.6.3	Calcium	1	2	3
5.6.4	Selenium, supplements	0	1	1
5.7.6	Caffeine	2	1	3
5.7.7	Total physical activity (overall summary measures)	4	5	9
5.5.10	Blood 25-Hydroxyvitamin D	0	3	3
5.5.10	Vitamin D supplement	0	1	1
5.5.11	Supplemental Vitamin E	5	3	8
5.5.11	Vitamin E from foods	0	1	1
5.5.11	Total vitamin E (diet and supplements)	0	1	1
5.5.13	Other vitamins (including multivitamins)	0	1	1
5.5.13	Multivitamin supplement	2	3	5
5.5.13	Duration of multivitamin use	0	1	1
6.1.1.1	Occupational physical activity	1	0	1
6.1.1.2	Recreational activity	2	2	4
6.1.1.2	Leisure time physical activity score	0	1	1
6.1.1.2	Leisure physical activity	0	1	1
6.1.1.4	Walking pace	0	1	1
6.1. 2	Frequency of physical activity	1	0	1
6.1.3	Vigorous activity	0	1	1
6.1.3.2	Vigorous recreational activity	0	1	1
6.1.3.2	Moderate recreational activity	0	2	2

6. 2	Television watching	0	1	1
6.2	Physical inactivity	0	1	1
7.1	Energy Intake	2	3	5
7.1.0.1	Percent of energy from saturated fat	0	1	1
7.1.0.1	Percent of energy from polyunsaturated fat	0	1	1
7.1.0.1	Percent of energy from fat	0	1	1
7.1.0.2	Percent of energy from protein	0	1	1
7.1.0.2	Percent of energy from animal protein	0	1	1
7.1.0.2	Energy from protein	0	1	1
7.1.0.3	Percent of energy from carbohydrate	0	1	1
8.1.1	BMI	13	12	25
8.1.1	BMI in adolescence	0	1	1
8.1.1	BMI at 18 yrs	0	2	2
8.1.1	Obesity	0	1	1
8.1.2	Body surface	1	0	1
8.1.3	Weight	3	2	5
8.1.3	Weight at 20 yrs	0	1	1
8.1.5	Body fat	1	0	1
8.1.6	Weight change	0	1	1
8.2.1	Waist circumference	1	1	2
8.3.1	Height (and proxy measures)	4	6	10
8.4.1	Birth weight	0	1	1

2 Foods

2.2 Fruit and non-starchy vegetables

Methods

The eight studies identified, three of them in the CUP, were included in the meta-analysis. The unit used in the dose-response analysis was one serving/day because the majority of the studies reported the intake in servings. Studies reporting in grams of fruit and vegetables were converted to servings, using 80g as conversion unit for 1 serving of fruit and vegetables. One study (Park SY, 2013) reported the intake of fruit and vegetables in grams per 1000 calories per day, which was converted to servings/day using the median energy intake reported in the study.

Two studies investigated invasive bladder cancer (Park SY, 2013; Larsson, 2008b), one study included invasive and in situ bladder cancers (Michaud, 2002a), one study included also cancers of the ureters, renal pelvis or urethra -35 cases out of 619 cases- (Zeegers, 2001b) and in three studies bladder cancer was the outcome but no more detail was given (Shibata, 1992; Michaud, 1999a; Holick 2005).One study was on urothelial cancer and the consumption of fruit and vegetables (Steineck, 1988).

All studies adjusted for smoking status, intensity and duration except a study in elderly that adjusted for smoking status only (Shibata, 1992). The study in male smokers adjusted for duration and intensity of smoking (Michaud, 2002a).

Main results

The summary RR per 1 serving per day (80 grams) was 0.97 (95% CI: 0.95-0.99, I^2=0%, pheterogeneity=0.76, n=8). There was no significant evidence of publication bias with Egger's test, p=0.09. The asymmetry in the funnel plot appears to be driven by the inverse association study observed in a large study (Park, 2013) that reported intake in grams/1000kcal/d (MEC, Park, 2013). After excluding this study from the analysis the relationship was no longer significant (RR per 1 serving per day: 0.98 (95% CI: 0.95-1.01). The summary RR per 100g/day of fruit and non-starchy vegetables was 0.96 (95% CI: 0.94-1.00, I^2=0%, pheterogeneity=0.76, n=8).

It was not possible to stratify the meta-analysis by smoking status. After excluding the only study on male smokers (Michaud, 2002a) the result remained the same, 0.97(95% CI: 0.95-0.99, I^2=0%, pheterogeneity=0.98, n=7). The only study that stratified the analysis by smoking status (Park SY, 2009) concluded that the association of bladder cancer with fruits and vegetables did not vary across smoking status (never, former, current smoker) at baseline. The only difference in association by smoking status was for a dietary pattern rich in vegetables for which a significant inverse association was observed in men smokers, but not in men never or former smokers.

After stratification by sex, the RR per 1 serving per day was 0.99 (95% CI: 0.96-1.01, I^2=0%, pheterogeneity=0.59, n=4) for men and 0.93 (95% CI: 0.81-1.07, n=2, I^2=86.9%, pheterogeneity<0.01, n=2) for women. Only two studies in women were identified. One study reported a significant association (MEC, Park SY, 2013) and the other study (NHS; Holick C, 2005) reported a non-significant association.

There was no significant evidence of non-linear association between fruit and vegetables intake and bladder cancer (p for non-linearity=0.06). The spline model suggests a decrease in risk from approximately 6 servings/day, which is mainly driven by a few extreme points.

Heterogeneity

Overall, there was no evidence of heterogeneity, I^2=0%, pheterogeneity=0.76.

Comparison with the Second Expert Report

In the 2005 SLR the evidence relating fruit and vegetables to bladder cancer was considered limited – no conclusion.

Published meta-analyses or pooled analyses

No published meta-analyses or pooled analyses were identified.

Table 2 Studies on fruit and vegetables intake identified during the CUP

Author/year	Country	Study name	Number of cases	Years of follow-up	Sex	RR	LCI	UCI	Contrast
Park SY, 2013	USA and Hawaii	Multiethnic Cohort Study	429 men and 152 women	12.5 years	M	0.87	0.64	1.17	≥426 vs. <216 g/1000kcal/d
					F	0.35	0.22	0.56	
Larsson SC, 2008 (b)	Sweden	Swedish Mammography Cohort and Cohort of Swedish men	485	9.4 years	M/F	0.80	0.60	1.05	≥5.8 vs. <2.7 servings/d

Table 3 Overall evidence on fruit and vegetables intake and bladder cancer

SLR	Summary of evidence
2005 SLR	5 studies were included in the meta analysis and found a non-significant association between fruit and vegetables intake and bladder cancer.
CUP	Three cohort studies reported on fruit and vegetables intake and bladder cancer. One showed no significant association and the other showed a significant inverse association in women in the highest category of consumption compared to those in the lowest ≥426 vs. <216 g/1000kcal/d), but not in men.

Table 4 Summary of results of the dose-response meta-analysis of fruit and vegetables intake and bladder cancer

Bladder cancer		
	2005 SLR	CUP
Studies (n)	5	8
Cases (n)	1442	2508
Increment unit	Per 1 serving/day	Per 1 serving/day
RR (95% CI)	1.00 (0.96-1.03)	0.97 (0.95-0.99)
Heterogeneity (I^2, p-value)	I^2=22.9%, p=0.27	0%, p=0.76

Stratified analysis		
Men		0.99 (0.96-1.01)
Heterogeneity (I^2, p-value)		I^2=0%, p=0.59, n=4
Women		0.93 (0.81-1.07)
Heterogeneity (I^2, p-value)		I^2=86.9%, p<0.01, n=2

Table 5 Inclusion/exclusion table for meta-analysis of fruit and vegetables intake and bladder cancer

WCRF code	Author	Year	Study design	Study name	Sex	Cancer outcome	2005 SLR	CU dose-response	CU H vs. L forest plot	Estimated values	Exclusion reason
BLA97217	Park SY	2013	Prospective cohort study	Multiethnic Cohort Study	M/F	Incidence	No	Yes	Yes	Midpoints. Person-years. Conversion from g/100kcal to servings/day	
BLA97158	Larsson SC	2008(b)	Prospective cohort study	Swedish Mammography Cohort and Cohort of Swedish men	M/F	Incidence	No	Yes	Yes	Midpoints	
BLA11803	Holick C	2005	Prospective cohort study	Nurses' Health Study	F	Incidence	Yes	Yes	Yes		
BLA00185	Michaud D	2002(a)	Prospective cohort study	ATBC study	M	Incidence/Mortality	Yes	Yes	Yes	Person-years. Conversion from g/day to servings/day	
BLA03992	Zeegers M	2001(b)	Prospective cohort study	Netherlands Cohort Study	M/F	Incidence	Yes	Yes	Yes	Midpoints. Conversion from g/day to servings/day	
BLA02843	Michaud D	1999(a)	Prospective cohort study	Health Professionals Follow-up Study	M	Incidence/Mortality	Yes	Yes	Yes		
BLA00922	Shibata A	1992	Prospective cohort study	Laguna Hills Study USA	M	Incidence	Yes	Yes	Yes	Person-years	
BLA01325	Steineck G	1988	Prospective cohort study	Swedish Twin Cohort	M/F	Incidence/Mortality	Yes	No	Yes		Only high vs. low results

Figure 1 Highest versus lowest forest plot of fruit and vegetables intake and bladder cancer

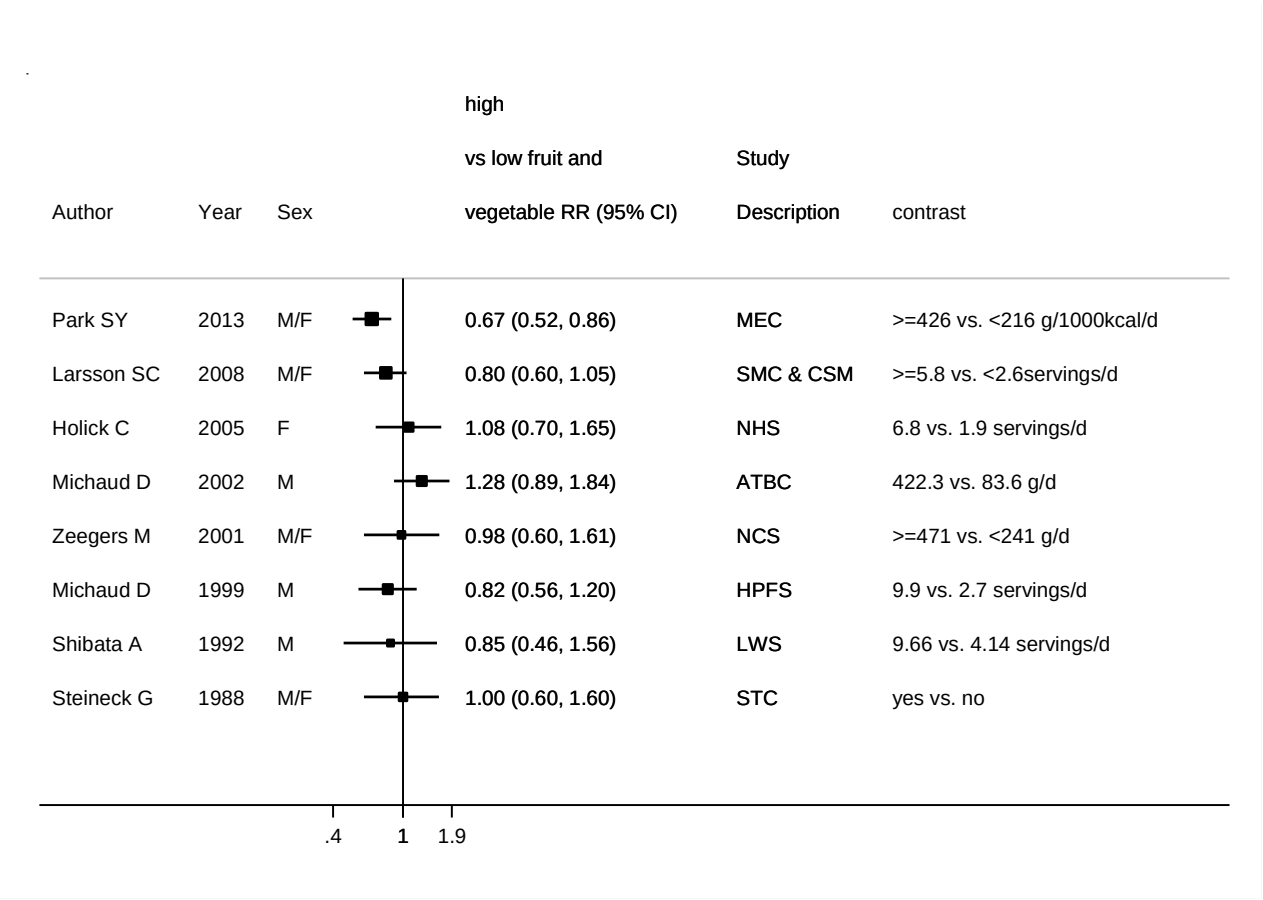


Figure 2 Dose-response meta-analysis of fruit and vegetables intake and bladder cancer, per 1 serving /day

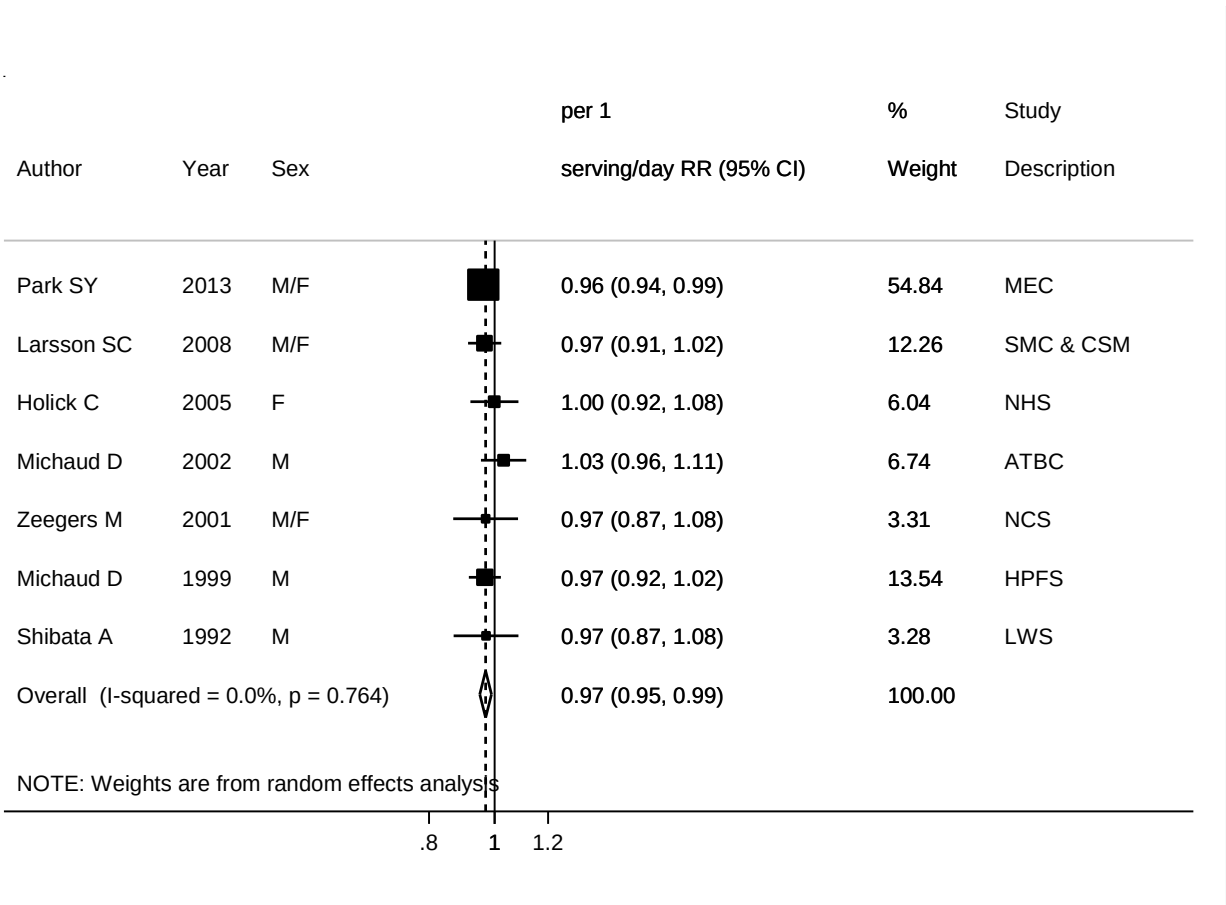
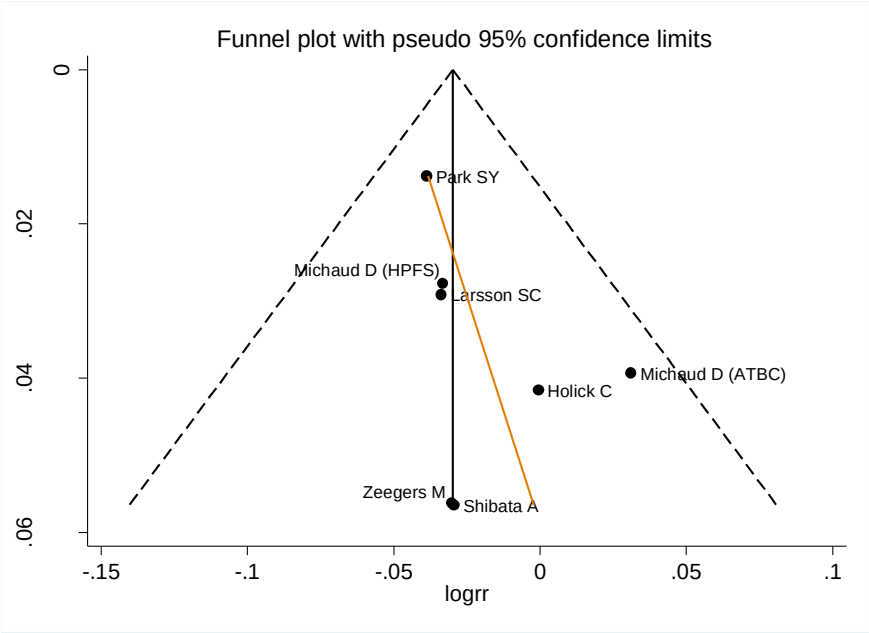


Figure 3 Funnel plot of fruit and vegetables intake and bladder cancer



Egger's test p=0.09

Figure 4 Dose-response graph of fruit and vegetables intake and bladder cancer

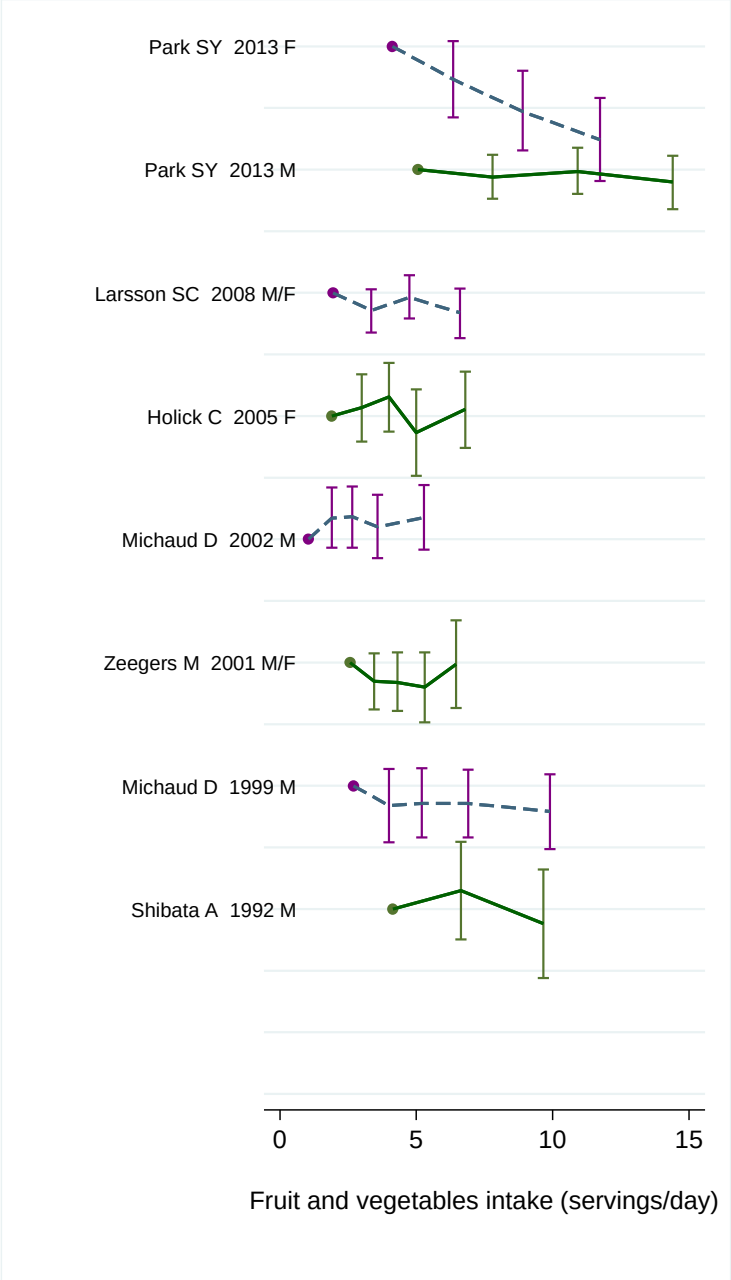


Figure 5 Dose-response meta-analysis of fruit and vegetables intake and bladder cancer, per 1 serving /day, stratified by sex

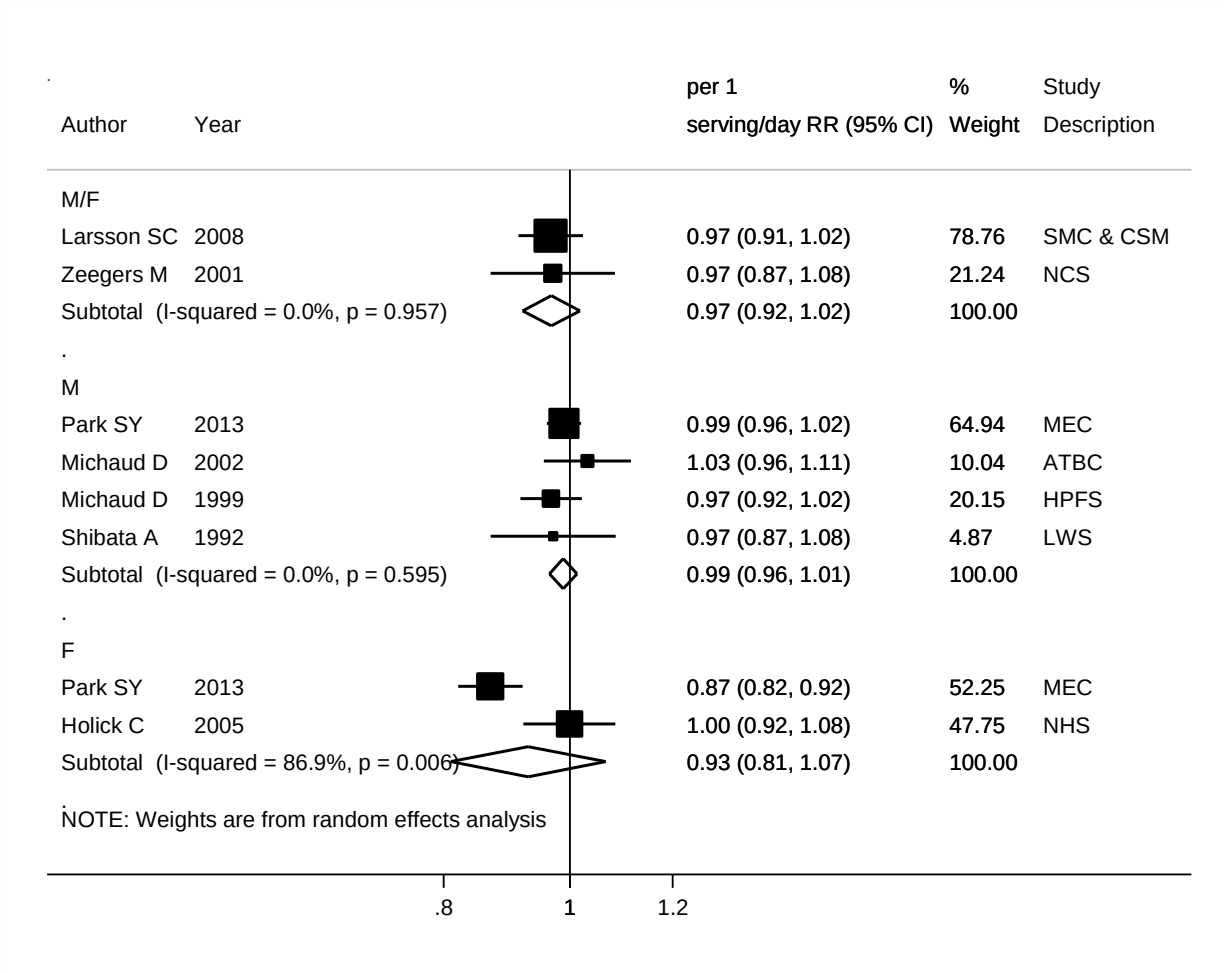
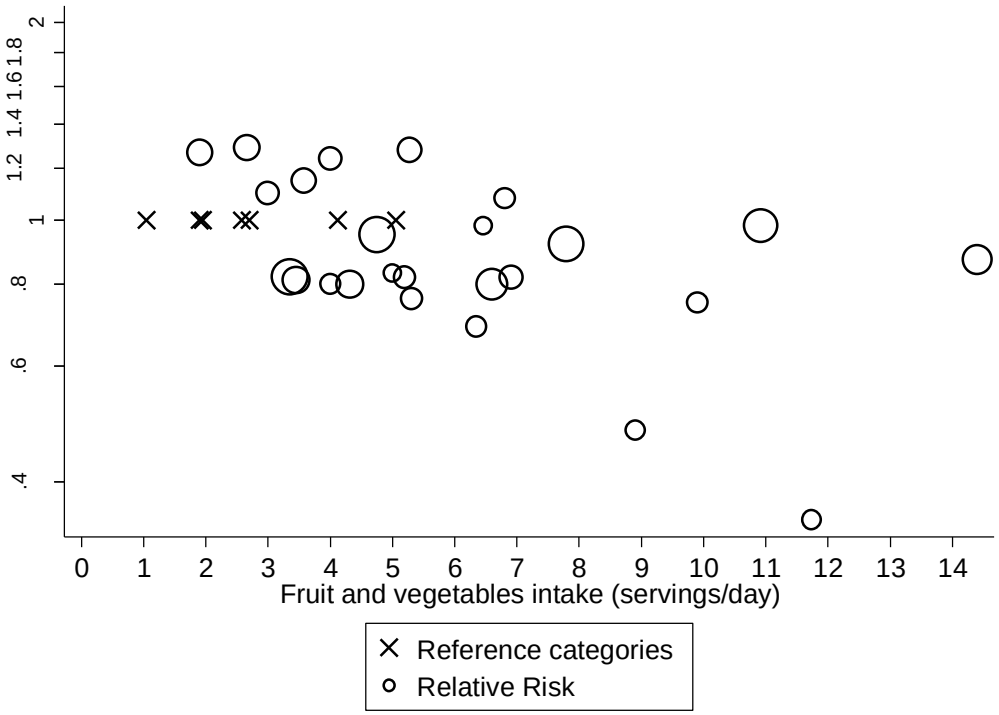
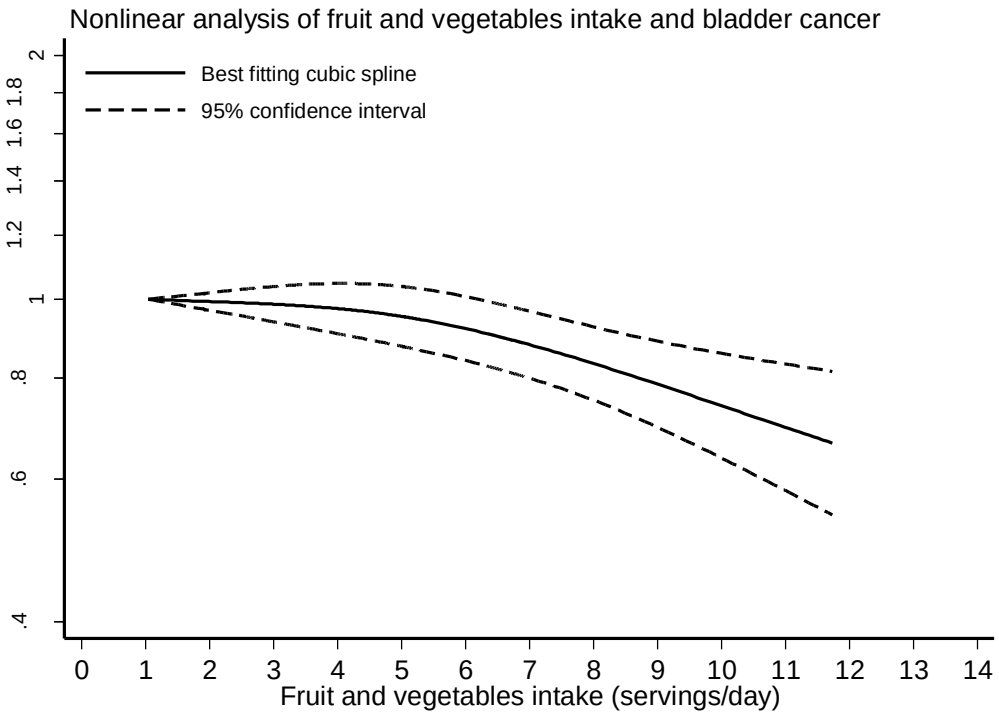


Figure 6 Nonlinear dose-response analysis of fruit and vegetables intake and bladder cancer





P for non-linearity= 0.06

Table 6 Table with fruit and vegetables values and corresponding RRs (95% CIs) for nonlinear analysis of fruit and vegetables intake and bladder cancer

Fruit and Vegetable intake (servings/day)	RR (95%CI)
1	1
2.5	0.98 (0.95-1.08)
5	0.95 (0.87-1.03)
6.6	0.91 (0.83-0.99)
7	0.88 (0.80-0.97)

2.2.1 Non-starchy vegetables

Methods

The ten studies identified, from which 5 identified in the CUP were included in the meta-analysis. The unit used in the dose-response analysis was one serving/day because the majority of the studies reported the intake in servings. Studies reporting in grams of vegetables were converted to servings, using as conversion unit 80g equivalent to 1 serving of vegetables. One study (George SM, 2009) reported the intake of vegetables in cup equivalent per 1000 calories and another study (Park SY, 2013) reported the intake of vegetables in grams per 1000 calories per day that were converted to total intake per day using the median energy intake reported in the studies.

Five studies (four articles) investigated invasive bladder cancer (Park, 2013; Ros, 2012; George, 2009; Larsson, 2008b), one study included invasive and in situ bladder cancers (Michaud, 2002a), one study included also cancers of the ureters, renal pelvis or urethra -35 cases out of 619 cases- (Zeegers, 2001b) and in three studies bladder cancer was the outcome but no more detail was given (Shibata, 1992; Michaud, 1999a; Holick 2005).

All studies adjusted for smoking status, intensity and duration except a study in elderly that adjusted for smoking status only (Shibata, 1992). The study in male smokers adjusted for duration and intensity of smoking (Michaud, 2002a).

Main results

The summary RR per 1 serving per day was 0.97 (95% CI: 0.94-1.00, I^2=10.1%, pheterogeneity=0.35, n=10). After stratification by sex, the RR per 1 serving per day was 0.98 (95% CI: 0.93-1.02, I^2=20%, pheterogeneity=0.28, n=5) for men and 0.97 (95% CI: 0.80-1.18, I^2=75.9%, pheterogeneity=0.02, n=3) for women.

There was evidence of publication bias with Egger's test, p=0.02. The funnel plot shows that the three smaller studies reported positive associations and no studies of similar size reported inverse associations. The summary RR per 100g/day of non-starchy vegetables was 0.96 (95% CI: 0.93-1.00, I^2=10.1%, pheterogeneity=0.35, n=10).

Only in two studies results were stratified by smoking status and the results were inconsistent. In the MEC study (Park, 2013) the associations were similar across smoking strata in women. A significant inverse association was observed in male current smokers (RR highest vs. lowest: 0.43; 95% CI: 0.18, 1.02; ptrend=0.03) but not in never or former smokers. In the EPIC study (Ros, 2012), the inverse association was observed in never and former smokers, but not in current smokers. The multiplicative interaction test was not significant in both studies. There was no evidence of non-linearity (p=0.17).

Heterogeneity

There was no evidence of heterogeneity, I^2=10.1%, pheterogeneity=0.35.

Comparison with the Second Expert Report

In the 2005 SLR the evidence relating vegetables intake to bladder cancer was considered limited-no conclusion.

Published pooled analysis or meta-analysis

In a meta-analysis of 3 cohort studies, low consumption of vegetables was not related to bladder cancer (RR=1.09, 95% CI: 0.76-1.54) (Steinmaus, 2000). Another meta-analysis of cohort and case-control studies showed inconsistent results for fruit and vegetables consumption and bladder cancer. The overall RR per 100g of vegetables per day was 0.91, 95% CI: 0.82-1.00, p=0.12 when including 6 cohort and case-control studies. When the analysis was restricted to 2 cohort studies the overall RR was (RR= 0.92, 95% CI: 0.75-0.99, p=0.14) (Riboli, 2003).

Table 7 Studies on vegetables intake identified during the CUP

Author/year	Country	Study name	Number of cases	Years of follow-up	Sex	RR	LCI	UCI	Contrast
Park SY, 2013	USA and Hawaii	Multiethnic Cohort Study	429 men and 152 women	12.5 years	M	0.89	0.66	1.19	≥201 vs. <107 g/1000kcal/d
					F	0.49	0.29	0.83	
Ros MM, 2012	Europe	EPIC	947	8.9 years	M/F	0.88	0.72	1.08	≥234 vs. <129 g/d
George SM, 2009	USA	NIH-AARP	1664	8 years	M	0.92	0.77	1.09	1.10–3.25 vs. 0-0.44 cup equivalent/1000kcal
					F	1.07	0.71	1.60	1.43-4.38 vs. 0-0.56 cup equivalent/1000kcal
Larsson SC, 2008 (b)	Sweden	Swedish Mammography Cohort and Cohort of Swedish men	485	9.4 years	M/F	0.89	0.67	1.19	≥3.7 vs. <1.6 servings/d
Holick, 2005	USA	Nurses' Health Study	237	20 years	F	1.29	0.87	1.91	3.7 vs. 1.1 servings/d

Table 8 Overall evidence on vegetables intake and bladder cancer

SLR	Summary of evidence
2005 SLR	4 studies were included in the meta analysis and found no significant association between vegetables intake and bladder cancer.
CUP	Five new cohort studies reported on vegetables intake and bladder cancer. Only one study showed a protective effect for women with the highest vegetable consumption compared to the lowest (≥201 vs. <107 g/1000kcal/d).

Table 9 Summary of results of the dose-response meta-analysis of vegetables intake and bladder cancer

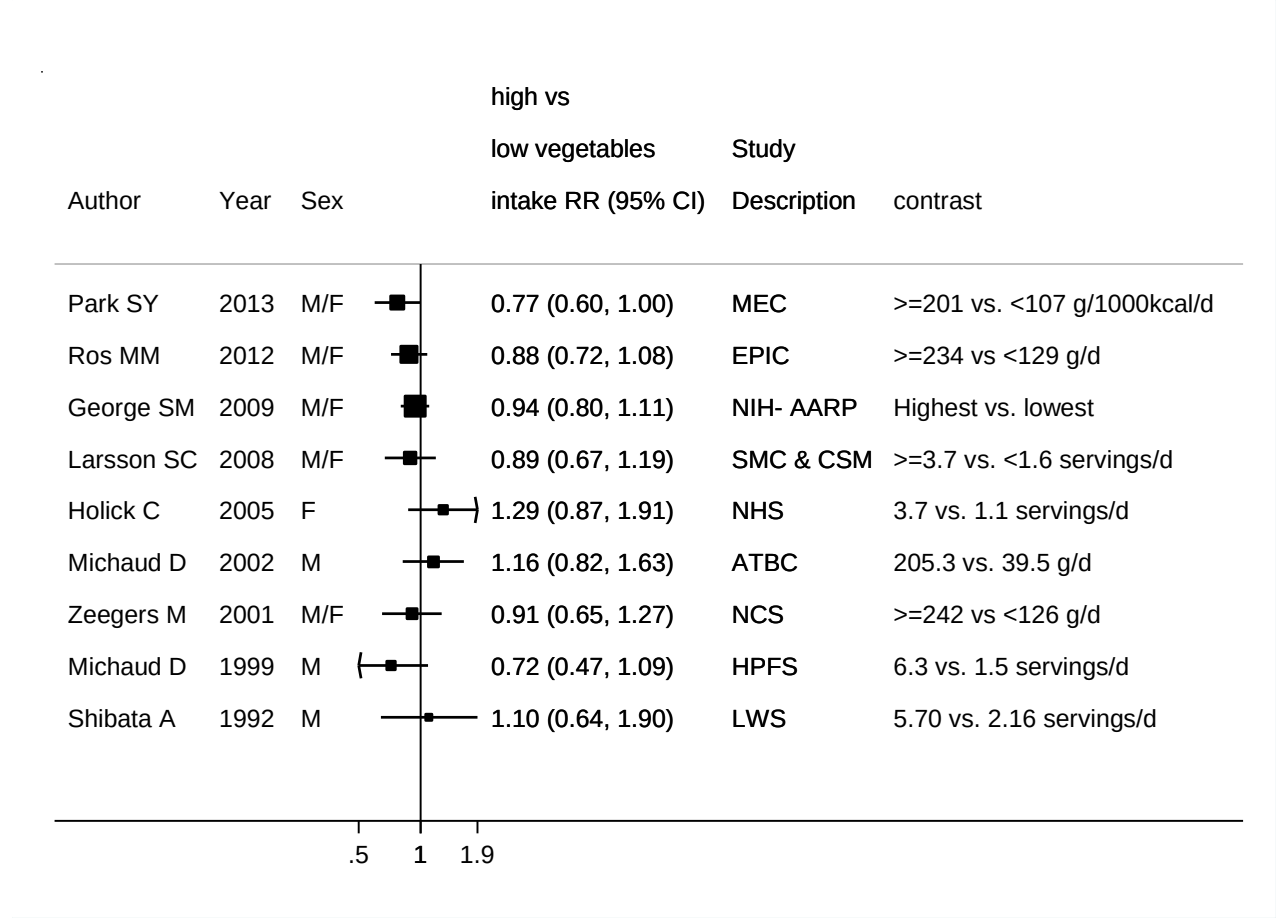
Bladder cancer		
	2005 SLR	CUP
Studies (n)	4	10
Cases (n)	1205	5119
Increment unit	Per 1 serving/day	Per 1 serving/day
RR (95% CI)	0.98 (0.92-1.04)	0.97 (0.94-1.00)
Heterogeneity (I^2, p-value)	I^2=21.6%, p=0.28	10.1%, p=0.35
Stratified analysis		
Men		0.98 (0.93-1.02)
Heterogeneity (I^2, p-value)		I^2=20%, p=0.28, n=5
Women		0.97 (0.80-1.18)
Heterogeneity (I^2, p-value)		I^2=75.9%, p=0.02, n=3

Table 10 Inclusion/exclusion table for meta-analysis of vegetables intake and bladder cancer

WCRF code	Author	Year	Study design	Study name	Sex	Cancer outcome	2005 SLR	CU dose-response	CU H vs. L forest plot	Estimated values	Exclusion reason
BLA97217	Park SY	2013	Prospective cohort study	Multiethnic Cohort Study	M/F	Incidence	No	Yes	Yes	Midpoints. Person-years. Conversion to servings/day	
BLA97202	Ros MM	2012	Prospective cohort study	EPIC	M/F	Incidence	No	Yes	Yes	Person-years. Midpoints. Conversion to servings/day	
BLA97201	George SM	2009	Prospective cohort study	NIH-AARP	M/F	Incidence	No	Yes	Yes	Person-years and cases per quintile. Midpoints. Conversion to servings/day	
BLA97158	Larsson SC	2008(b)	Prospective cohort study	Swedish Mammography Cohort and Cohort of Swedish men	M/F	Incidence	No	Yes	Yes	Midpoints	
BLA11803	Holick C	2005	Prospective cohort study	Nurses' Health Study	F	Incidence	No	Yes	Yes		In the 2005 SLR only included in the green vegetables and cruciferous vegetables analysis.
BLA00185	Michaud D	2002 (a)	Prospective cohort study	ATBC study	M	Incidence/Mortality	Yes	Yes	Yes	Person-years. Conversion to servings/day	
BLA03992	Zeegers M	2001(b)	Prospective cohort study	Netherlands Cohort Study	M/F	Incidence	Yes	Yes	Yes	Midpoints. Conversion to servings/day	
BLA02843	Michaud D	1999 (a)	Prospective cohort study	Health Professionals Follow-up	M	Incidence/Mortality	Yes	Yes	Yes		

				Study							
BLA00922	Shibata A	1992	Prospective cohort study	Laguna Hills Study USA	M	Incidence	Yes	Yes	Yes	Person-years	

Figure 7 Highest versus lowest forest plot of vegetables intake and bladder cancer



For George SM, 2009 the contrast was 1.4 vs. 0.4 cup equivalent/1000kcal for women and 1.3 vs. 0.8 cup equivalent/1000kcal for men.

Figure 8 Dose-response meta-analysis of vegetables intake and bladder cancer, per 1 serving /day

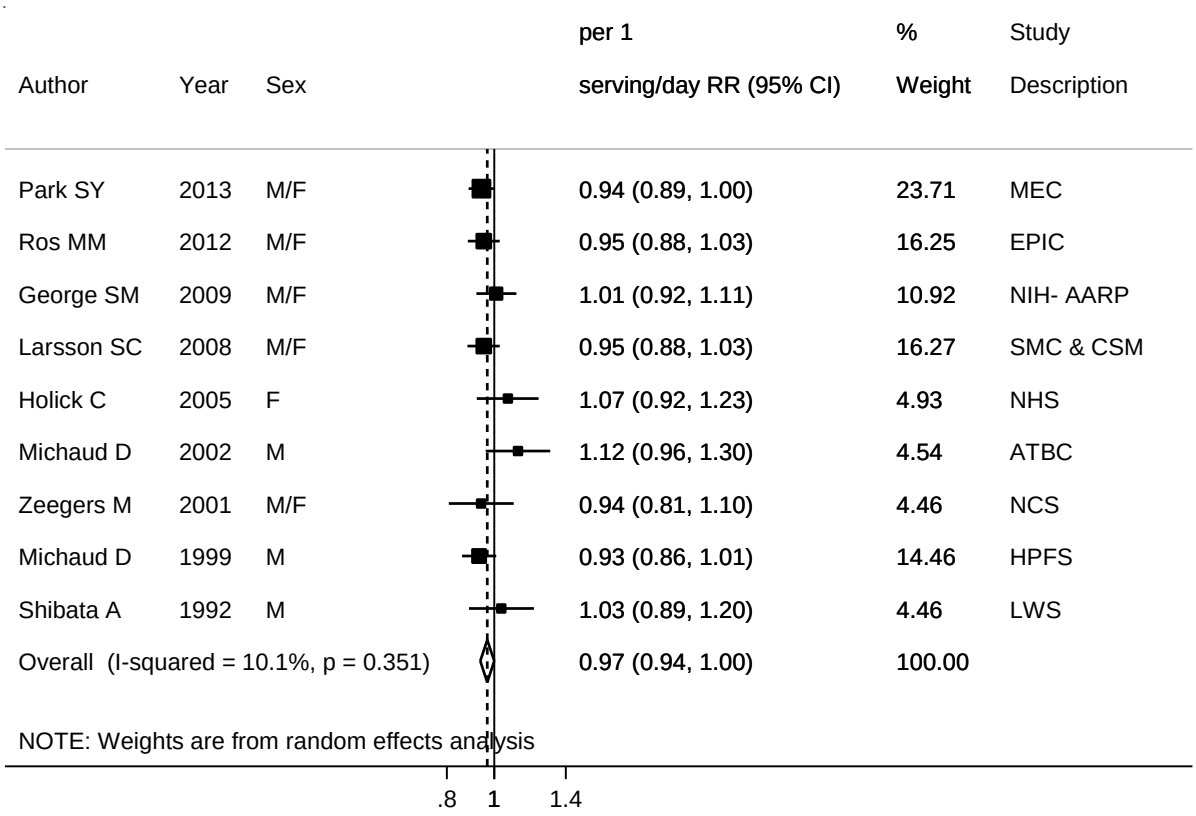
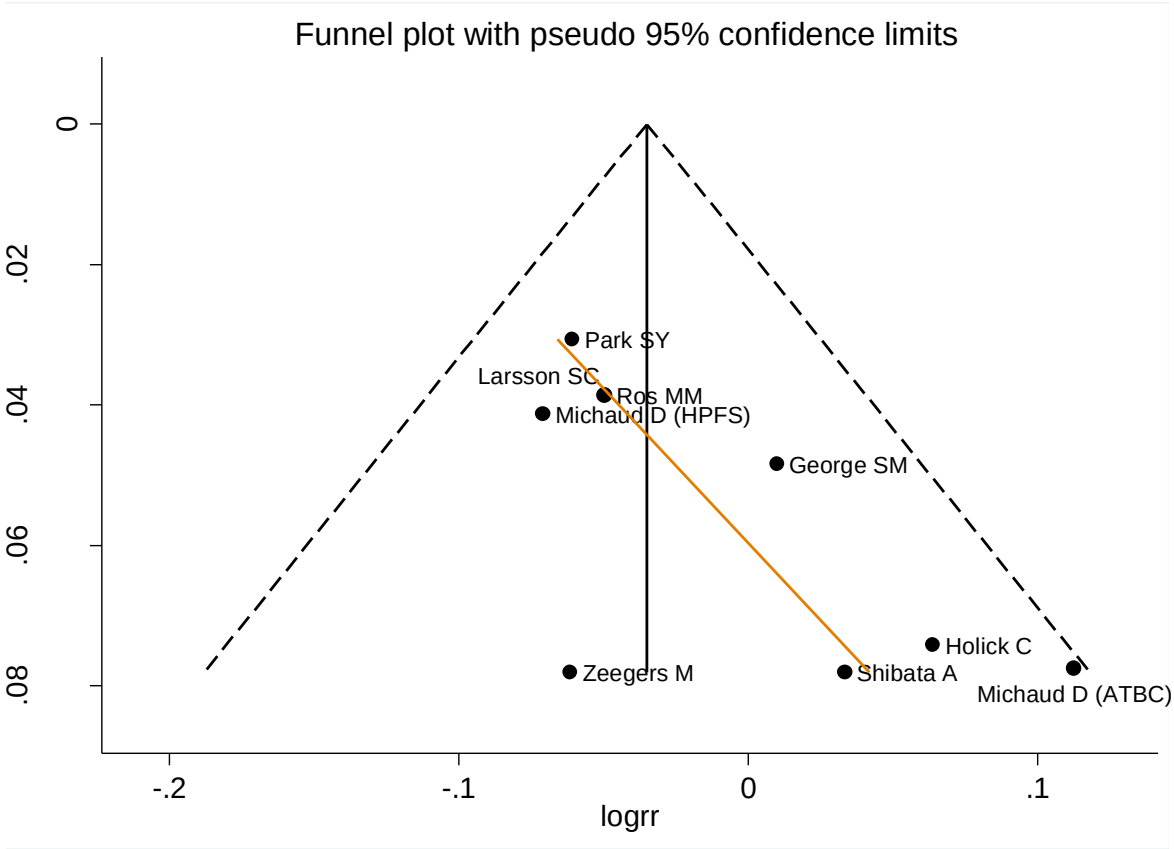


Figure 9 Funnel plot of vegetables intake and bladder cancer



Egger's test p=0.02

Figure 10 Dose-response graph of vegetables intake and bladder cancer

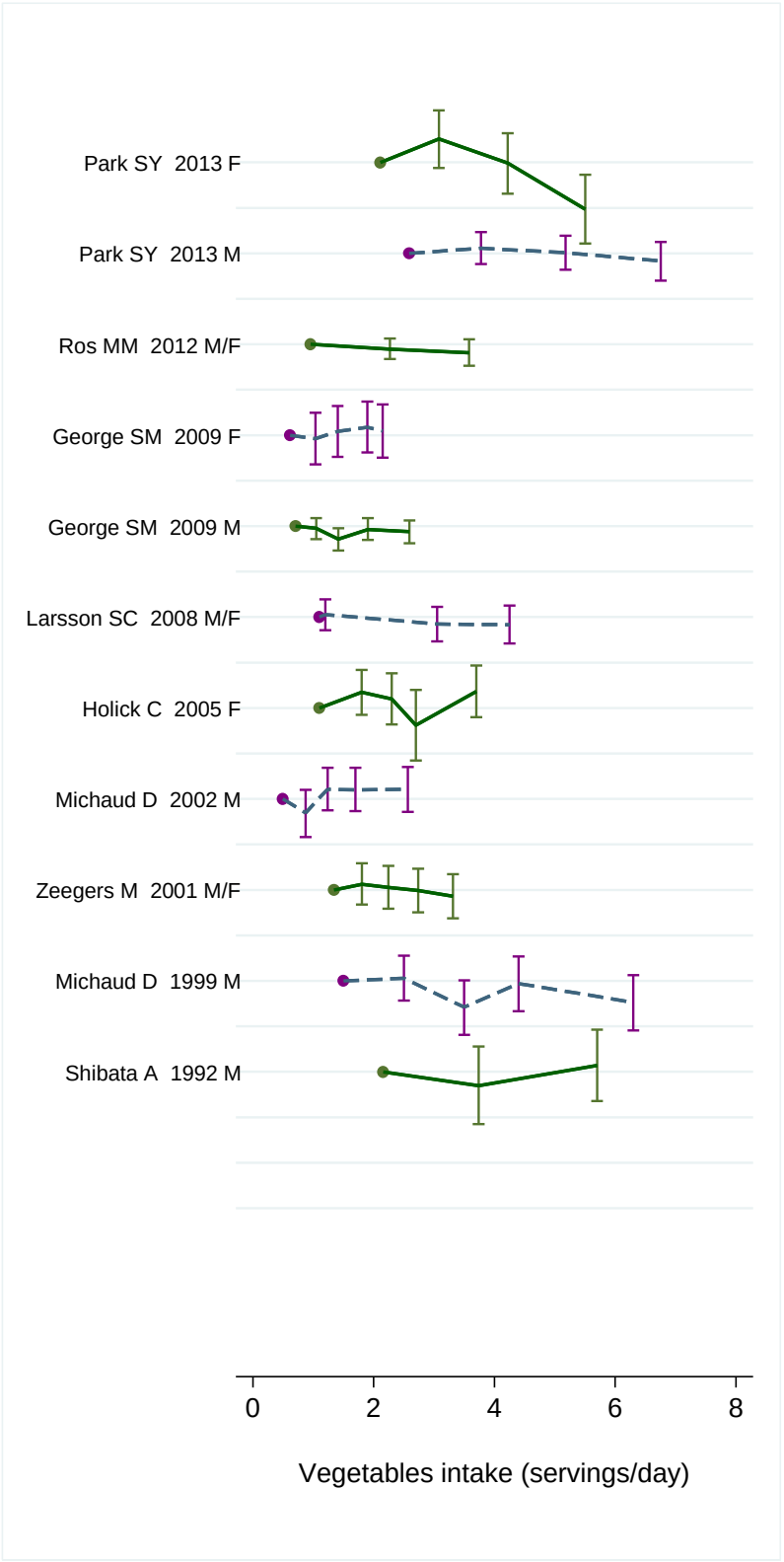
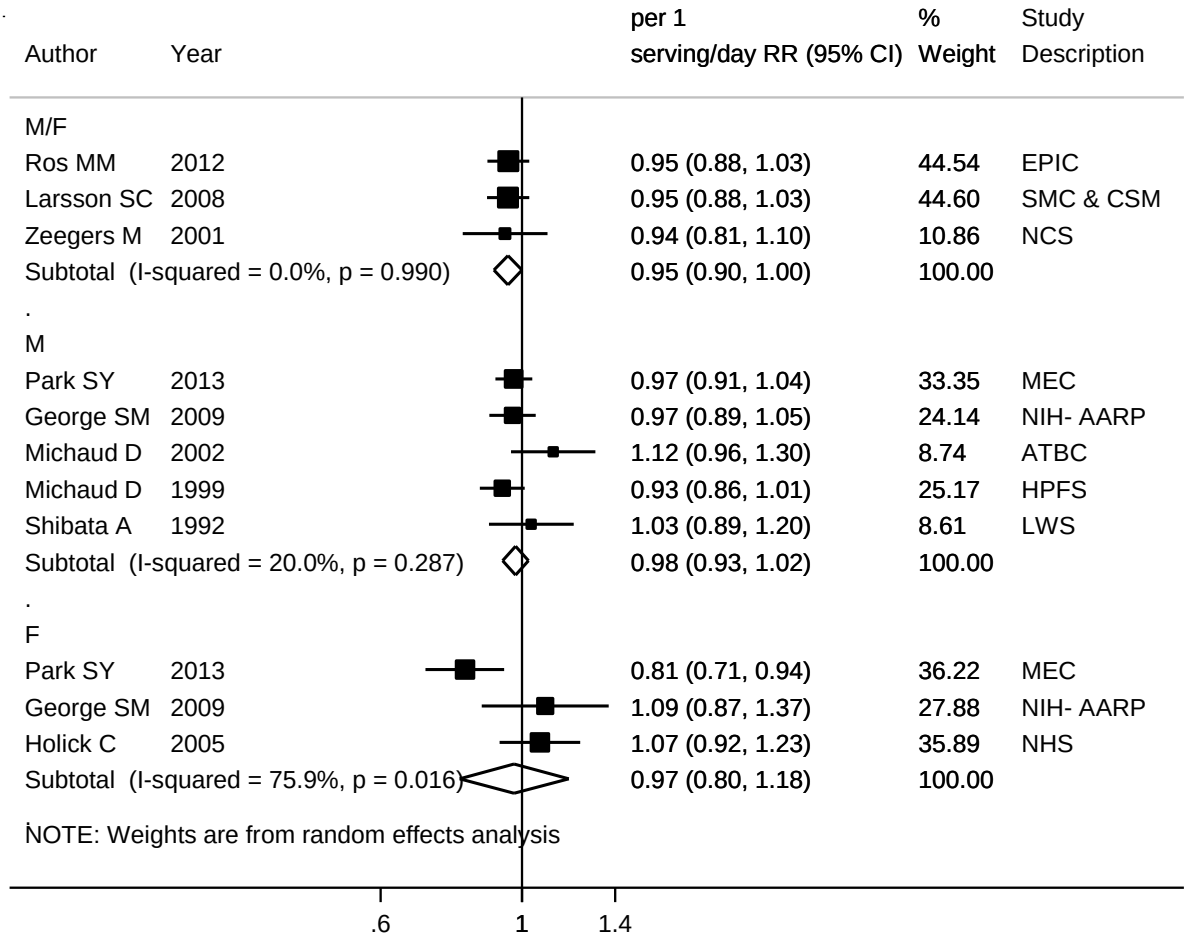


Figure 11 Dose-response meta-analysis of vegetables intake and bladder cancer, per 1serving /day, stratified by sex



2.2.1.2 Cruciferous vegetables

Methods

The seven studies identified, from which three identified in the CUP, were included in meta-analysis. The unit used in the dose-response analysis was one serving/week because the majority of the studies reported the intake in servings. Studies reporting in grams of cruciferous vegetables were converted to servings, using as conversion unit 80g equivalent to 1 serving of cruciferous vegetables. One study (Park SY, 2013) reported the intake of cruciferous vegetables in grams per 1000 calories per day, which was converted to servings/day using the median energy intake reported in the study.

Two studies investigated only invasive bladder cancer (Park, 2013; Larsson, 2008b -2 studies in one publication-), one study included invasive and in situ bladder cancers (Michaud, 2002a), one study included also cancers of the ureters, renal pelvis or urethra -35 cases out of 619 cases- (Zeegers, 2001b) and in two studies bladder cancer was the outcome but no more detail was given (Holick 2005; Michaud, 1999a).

All studies adjusted for smoking status, intensity and duration. The study in male smokers adjusted for duration and intensity of smoking (Michaud, 2002a).

Main results

The summary RR per 1 serving per week was 0.98 (95% CI: 0.94-1.02, I^2=58.2%, pheterogeneity=0.04, n=7). There was no evidence of publication bias with Egger's test, p=0.50. It was not possible to stratify the analysis by smoking status. After excluding the only study on male smokers (Michaud, 2002a) the overall RR was 0.96 (95% CI: 0.93-0.99, I^2=25.9%, pheterogeneity=0.25, n=6). The summary RR per 100g/day of cruciferous vegetables 0.98 (95% CI: 0.93-1.03, I^2=58.2%, pheterogeneity=0.04, n=7).

There was evidence of non-linear relationship between cruciferous vegetables intake and bladder cancer (p for non-linearity<0.001, with higher risk reductions at intakes higher than 6 servings per week). Results are driven by a low number of points as shown in the figure.

Heterogeneity

There was evidence of high heterogeneity, I^2=58.2%, pheterogeneity=0.04. Visual inspection of the forest plot suggest this is explained by a study in Finnish male smokers (Michaud, 2002a) that found a borderline increased risk (p trend=0.05) of bladder cancer for increasing cruciferous vegetable consumption, although none of the categorical risk estimates were significant.

Comparison with the Second Expert Report

In the 2005 SLR the evidence relating cruciferous vegetables intake to bladder cancer was considered limited- no conclusion.

Published meta-analysis or pooled analysis

A meta-analysis reported a summary relative risk for the highest compared to the lowest intake of cruciferous vegetables of 0.86 (95% CI: 0.61-1.11; I^2: 73.0%; pheterogeneity: 0.005) for 5 cohort studies and 0.78 (0.67, 0.89; I^2: 0%; pheterogeneity: 0.768) for 5 case-control studies (Liu, 2013). The MEC (Park, 2013) was not included in the meta-analyses.

Table 11 Studies on cruciferous vegetables intake identified during the CUP

Author/year	Country	Study name	Number of cases	Years of follow-up	Sex	RR	LCI	UCI	Contrast
Park SY, 2013	USA and Hawaii	Multiethnic Cohort Study	429 men and 152 women	12.5 years	M	0.81	0.60	1.10	≥30.9 vs. <10.1 g/1000kcal/d
					F	0.70	0.42	1.15	
Larsson SC, 2008 (b)	Sweden	Swedish Mammography Cohort and Cohort of Swedish men	485	9.4 years	M/F	0.97	0.74	1.27	≥3.5 vs. <0.9 servings/week

Table 12 Overall evidence on cruciferous vegetables intake and bladder cancer

SLR	Summary of evidence
2005 SLR	4 studies were included in the meta analysis and found a non-significant association between cruciferous vegetables intake and bladder cancer.
CUP	Three new cohort studies reported on cruciferous vegetables intake and bladder cancer and showed no significant association.

Table 13 Summary of results of the dose-response meta-analysis of cruciferous vegetables intake and bladder cancer

Bladder cancer		
	2005 SLR	CUP
Studies (n)	4	7
Cases (n)	1371	2437
Increment unit	Per 1 serving/week	Per 1 serving/week
RR (95% CI)	0.98 (0.91-1.03)	0.98 (0.94-1.02)
Heterogeneity (I^2, p-value)	I^2=67%, p=0.03	58.2%, p=0.04

Table 14 Inclusion/exclusion table for meta-analysis of cruciferous vegetables intake and bladder cancer

WCRF code	Author	Year	Study design	Study name	Sex	Cancer outcome	2005 SLR	CU dose-response	CU H vs. L forest plot	Estimated values	Exclusion reason
BLA97217	Park SY	2013	Prospective cohort study	Multiethnic Cohort Study	M/F	Incidence	No	Yes	Yes	Midpoints. Person-years. Conversion to servings/day	
BLA97158	Larsson SC	2008(b)	Prospective cohort study	Swedish Mammography Cohort and Cohort of Swedish men	M/F	Incidence	No	Yes	Yes	Midpoints	
BLA11803	Holick C	2005	Prospective cohort study	Nurses' Health Study	F	Incidence	Yes	Yes	Yes		
BLA00185	Michaud D	2002 (a)	Prospective cohort study	ATBC study	M	Incidence/Mortality	Yes	Yes	Yes	Person-years. Conversion to servings/day	
BLA03992	Zeegers M	2001(b)	Prospective cohort study	Netherlands Cohort Study	M/F	Incidence	Yes	Yes	Yes	Midpoints. Conversion to servings/day	
BLA02843	Michaud D	1999(a)	Prospective cohort study	Health Professionals Follow-up Study	M	Incidence/Mortality	Yes	Yes	Yes		

Figure 12 Highest versus lowest forest plot of cruciferous vegetables intake and bladder cancer

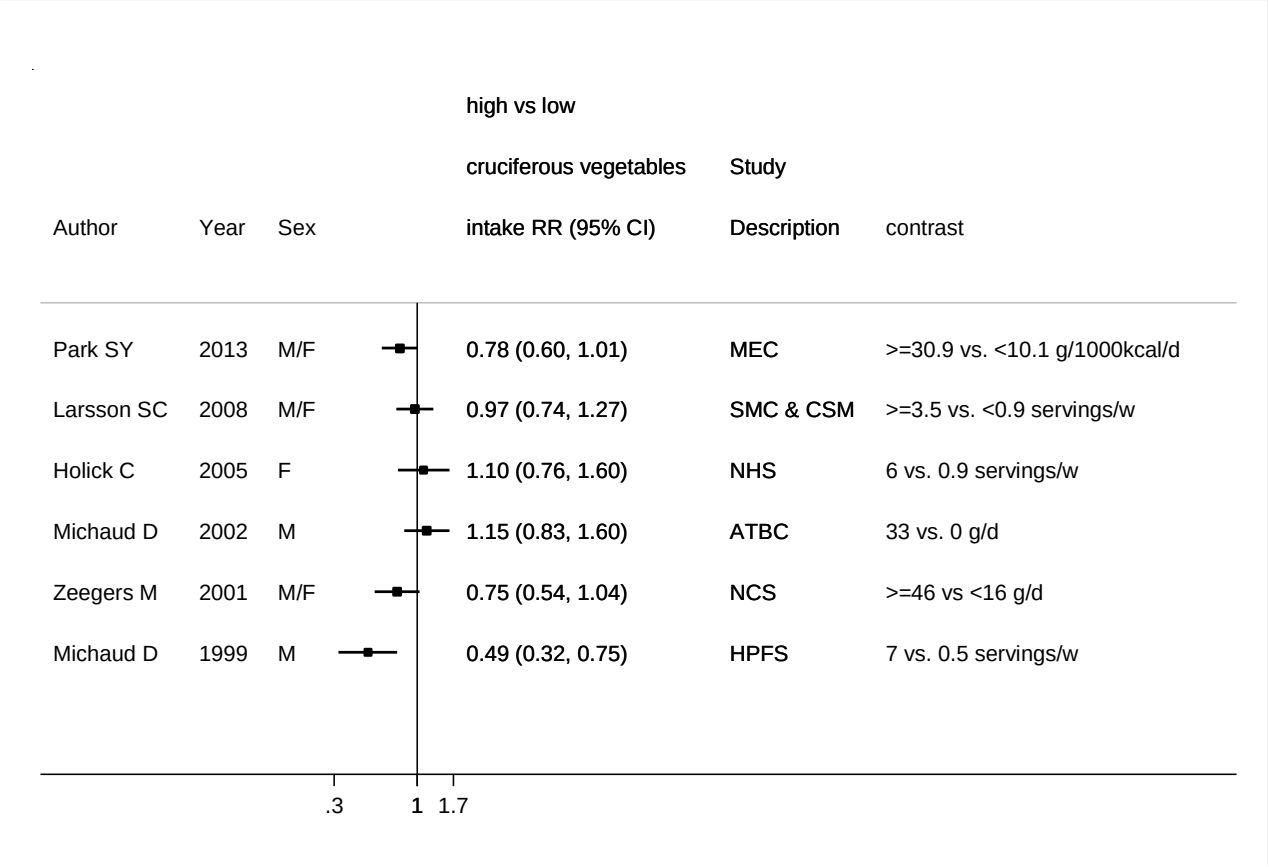


Figure 13 Dose-response meta-analysis of cruciferous vegetables intake and bladder cancer, per 1serving /week

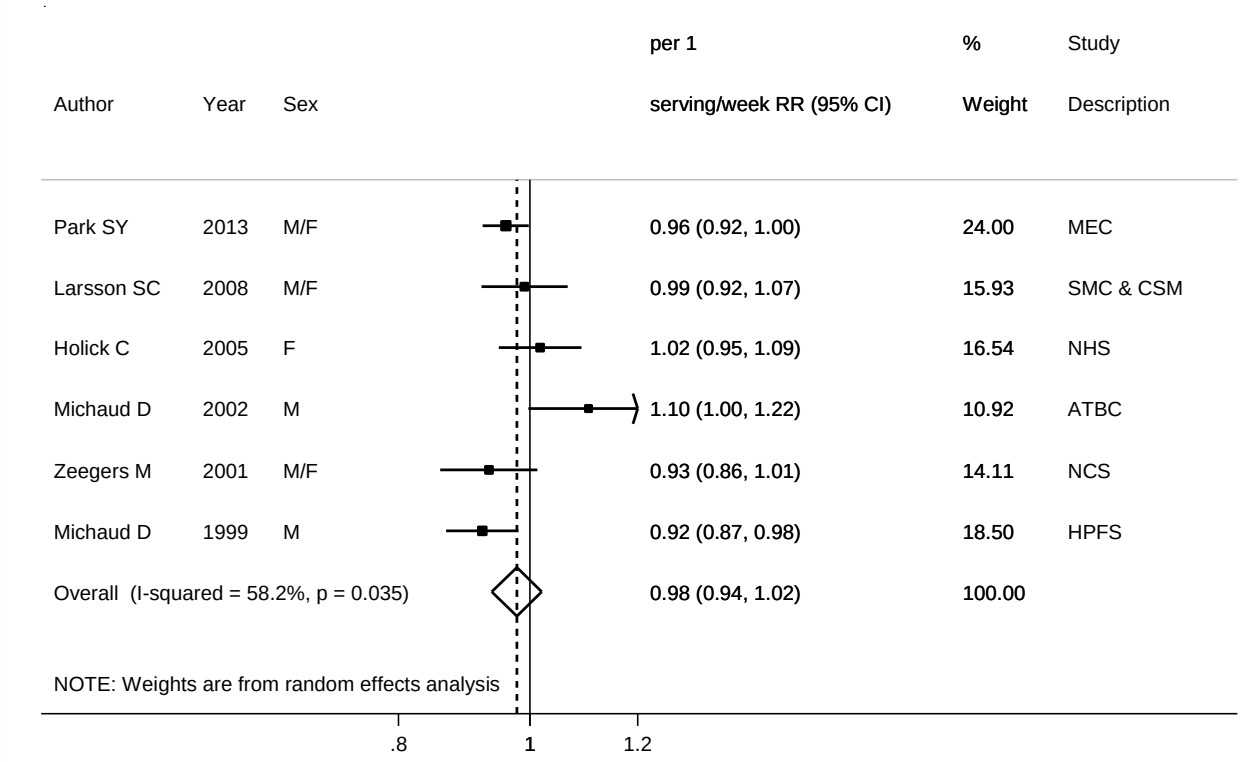
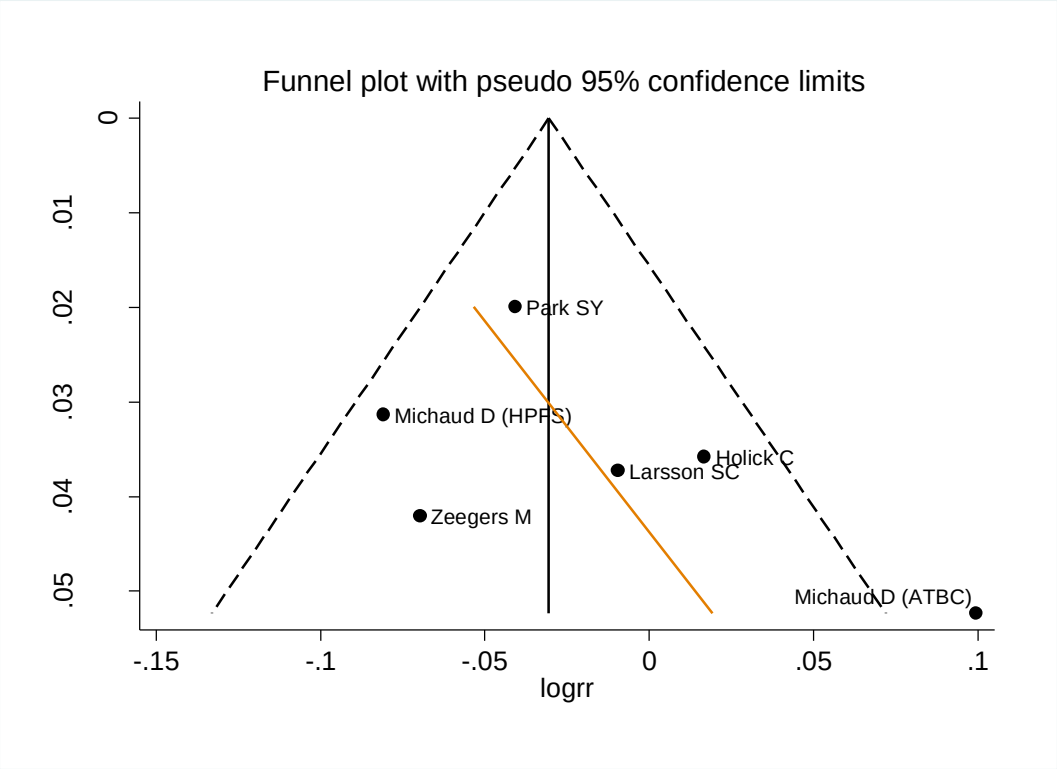


Figure 14 Funnel plot of cruciferous vegetables intake and bladder cancer



Egger's test p=0.50

Figure 15 Dose-response graph of cruciferous vegetables intake and bladder cancer

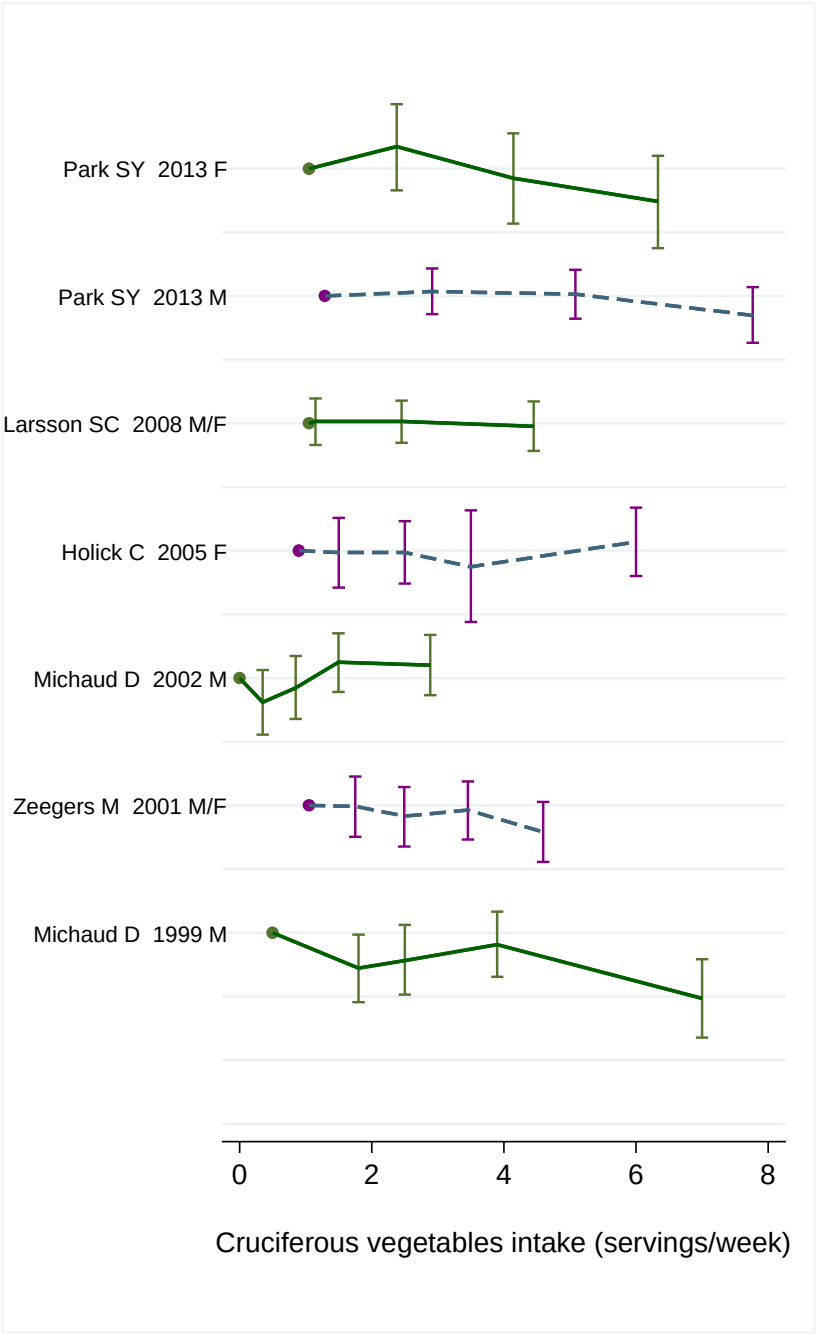
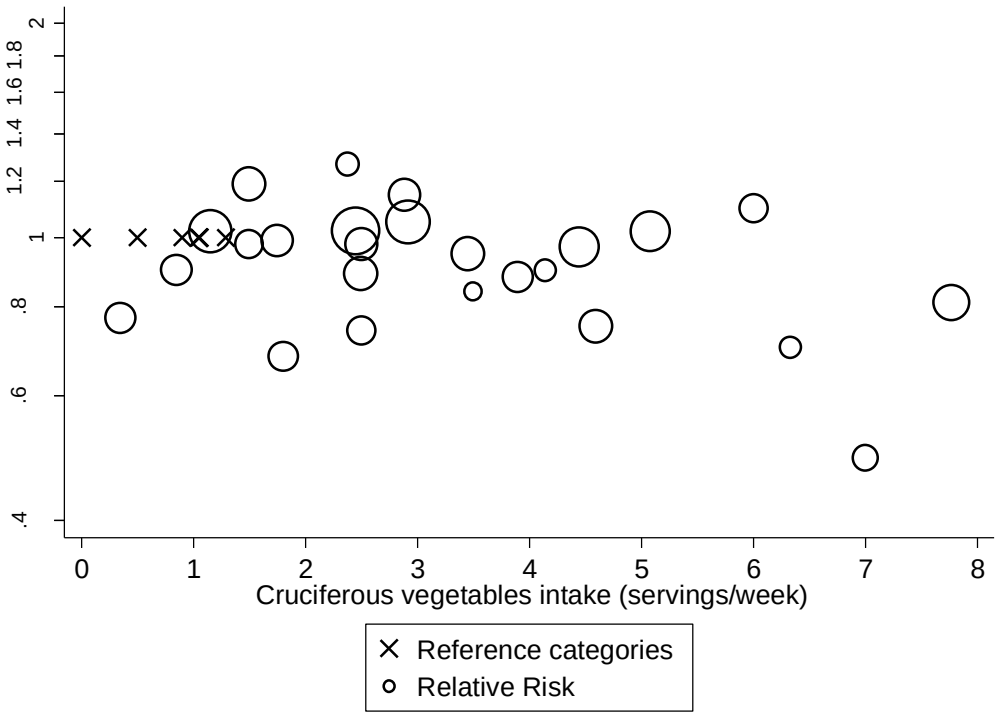
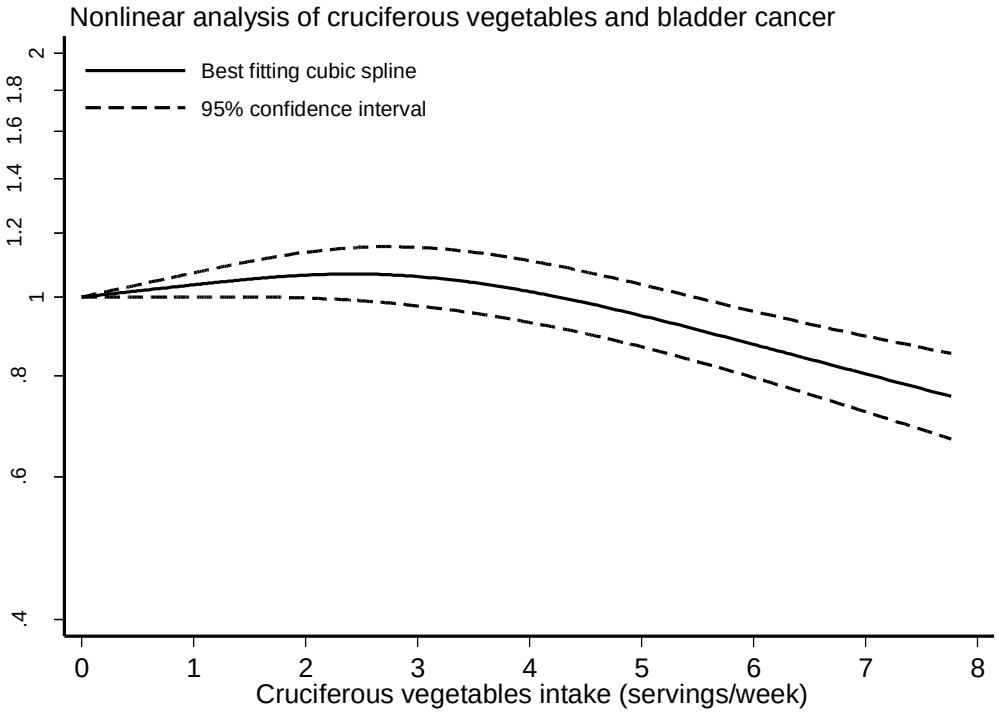


Figure 16 Nonlinear dose-response analysis of cruciferous vegetables intake and bladder cancer





P for non-linearity< 0.001

Table 15 Table with cruciferous vegetables values and corresponding RRs (95% CIs) for nonlinear analysis of cruciferous vegetables intake and bladder cancer

Cruciferous vegetables intake (servings/week)	RR (95%CI)
0	1
0.9	1.03 (1.0-1.06)
1.5	1.05 (1.0-1.10)
2.45	1.06 (0.99-1.15)
3.9	1.02 (0.93-1.11)
6	0.87 (0.79-0.96)
7.76	0.75 (0.66-0.85)

2.2.1.4 Green leafy vegetables

Methods

The six studies identified, from which three identified in the CUP were included in meta-analysis. The unit used in the dose-response analysis was one servings/week. Studies reporting in grams of leafy vegetables were converted to servings, using as conversion unit 80g equivalent to 1 serving of leafy vegetables.

Two studies investigated only invasive bladder cancer incidence (Ros, 2012; Larsson, 2008b), one study included also cancers of the ureters, renal pelvis or urethra -35 cases out of 619 cases- (Zeegers, 2001b) and in one study bladder cancer was the outcome but no more detail was given (Michaud, 1999a). One study in Japanese investigated mortality for urothelial cell carcinoma (including bladder, renal pelvis and ureter).

All studies adjusted for smoking status, intensity and duration.

Main results

The summary RR per 1 serving per week was 0.98 (95% CI: 0.95-1.01, I^2=0%, pheterogeneity=0.74, n=6). There was no evidence of publication bias with Egger's test, p=0.17. The overall result remained the same after excluding the only study which reported on mortality (Sakauchi, 2004) RR=0.98 (95% CI: 0.95-1.01, I^2=0%, pheterogeneity=0.66, n=5). The summary RR per 100g/day of green leafy vegetables was 0.98 (95% CI: 0.94-1.01, I^2=0%, pheterogeneity=0.74, n=6). It was not possible to stratify the analysis by smoking status. There was no evidence on non-linearity (p=0.29).

Heterogeneity

There was no evidence heterogeneity, I^2=0%, pheterogeneity=0.74.

Comparison with the Second Expert Report

In the 2005 SLR the evidence relating green leafy vegetables to bladder cancer was considered limited- no conclusion.

Published meta-analyses or pooled analyses

No published meta-analyses or pooled analyses were identified.

Table 16 Studies on green leafy vegetables intake identified during the CUP

Author/year	Country	Study name	Number of cases	Years of follow-up	Sex	RR	LCI	UCI	Contrast
Ros MM, 2012	Europe	EPIC	947	8.9 years	M/F	0.80	0.62	1.03	≥30.77 vs. <7.60 g/day
Larsson SC, 2008 (b)	Sweden	Swedish Mammography Cohort and Cohort of Swedish men	485	9.4 years	M/F	0.97	0.74	1.27	≥4 vs. <0.9 servings/week

Table 17 Overall evidence on green leafy vegetables intake and bladder cancer

SLR	Summary of evidence
2005 SLR	3 studies were included in the meta analysis and found a non-significant association between green leafy vegetables intake and bladder cancer.
CUP	Three new cohort studies (2 articles) reported on green leafy vegetables intake and bladder cancer and showed no significant association.

Table 18 Summary of results of the dose-response meta-analysis of green leafy vegetables intake and bladder cancer

Bladder cancer		
	2005 SLR	CUP
Studies (n)	3	6
Cases (n)	878	2310
Increment unit	Per 1 serving/week	Per 1 serving/week
RR (95% CI)	0.98 (0.93-1.04)	0.98 (0.95-1.01)
Heterogeneity (I^2, p-value)	I^2=0%, p=0.62	0%, p=0.74

Table 19 Inclusion/exclusion table for meta-analysis of green leafy vegetables intake and bladder cancer

WCRF code	Author	Year	Study design	Study name	Sex	Cancer outcome	2005 SLR	CU dose-response	CU H vs. L forest plot	Estimated values	Exclusion reason
BLA97202	Ros MM	2012	Prospective cohort study	EPIC	M/F	Incidence	No	Yes	Yes	Person-years. Midpoints. Conversion to servings/day	
BLA97158	Larsson SC	2008(b)	Prospective cohort study	Swedish Mammography Cohort and Cohort of Swedish men	M/F	Incidence	No	Yes	Yes	Midpoints	
BLA10545	Sakauchi F	2004	Prospective cohort study	Japan Collaborative Cohort Study (JACC)	M/F	Mortality	Yes	Yes	Yes	Midpoints	
BLA03992	Zeegers M	2001(b)	Prospective cohort study	Netherlands Cohort Study	M/F	Incidence	Yes	Yes	Yes	Midpoints. Conversion to servings/day	
BLA02843	Michaud D	1999(a)	Prospective cohort study	Health Professionals Follow-up Study	M	Incidence/Mortality	Yes	Yes	Yes		

Figure 17 Highest versus lowest forest plot of green leafy vegetables intake and bladder cancer

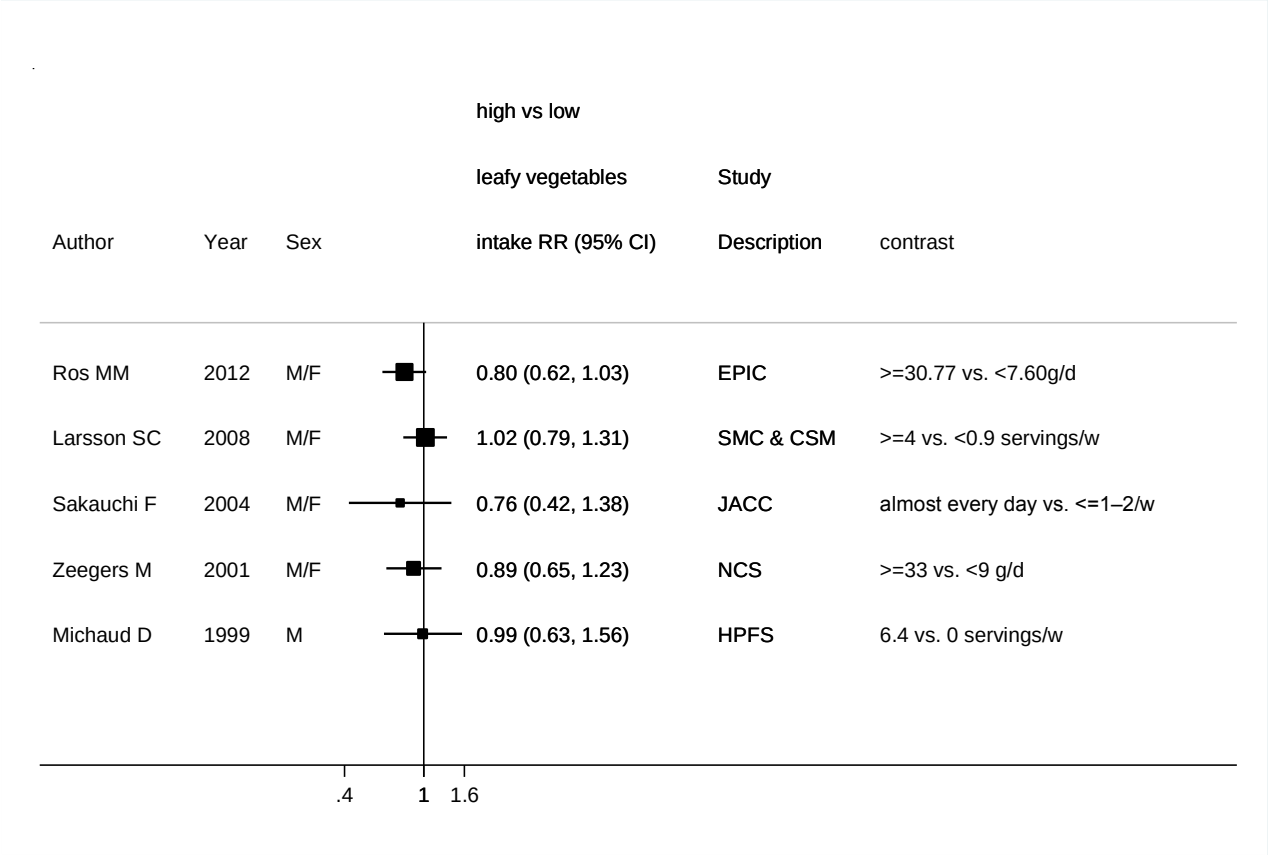


Figure 18 Dose-response meta-analysis of green leafy vegetables intake and bladder cancer, per 1serving /week

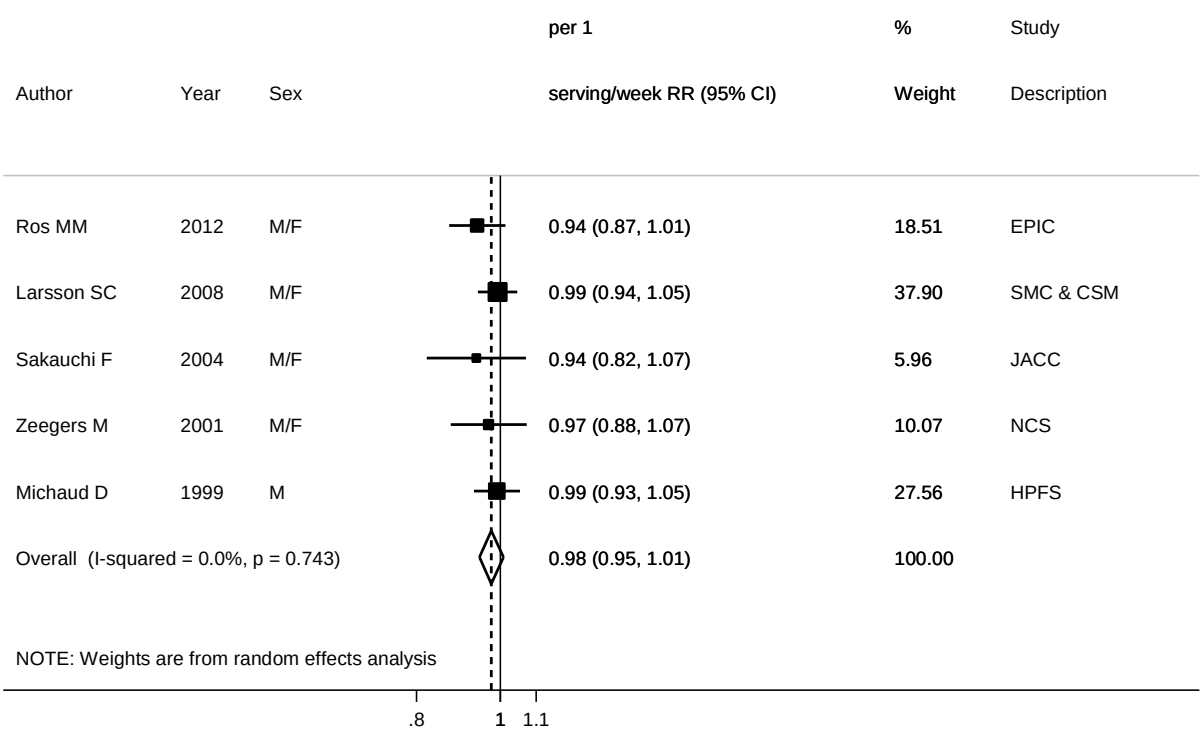
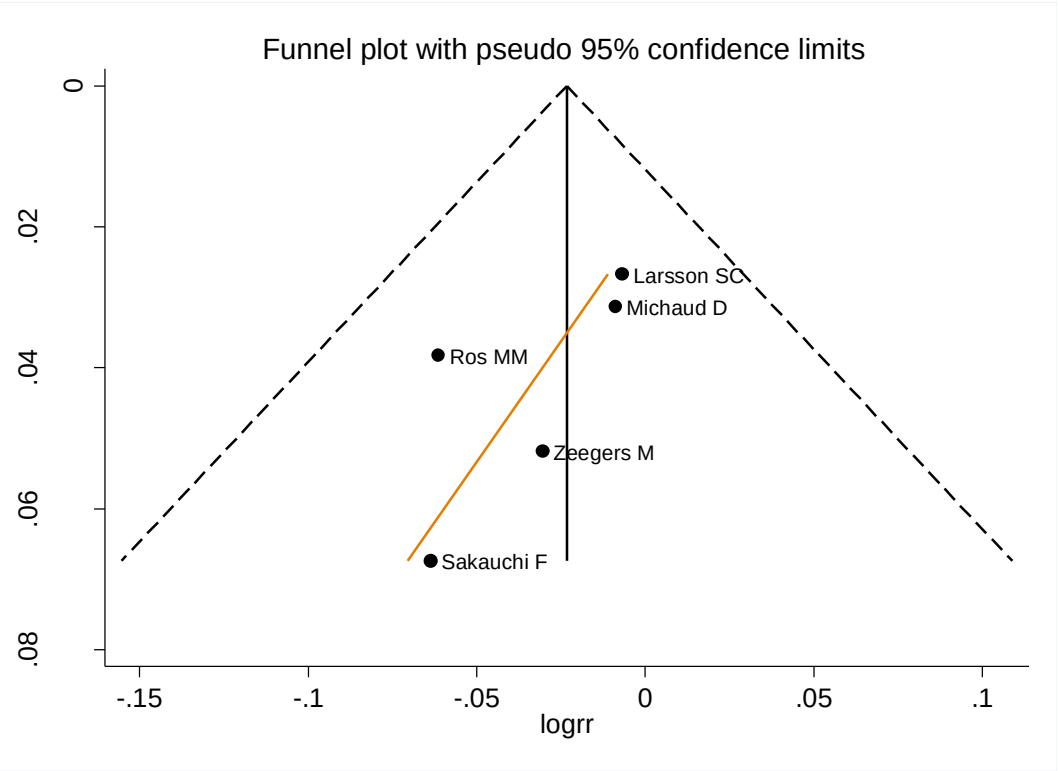
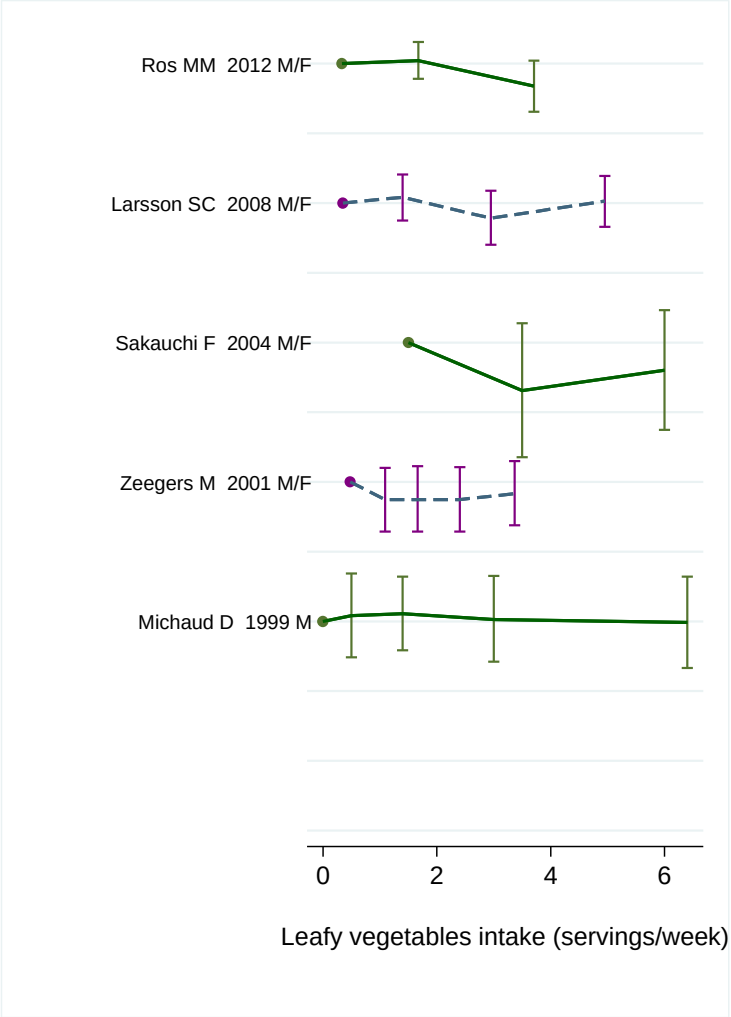


Figure 19 Funnel plot of green leafy vegetables intake and bladder cancer



Egger's test p=0.17

Figure 20 Dose-response graph of green leafy vegetables intake and bladder cancer



2.2.2 Fruits

Methods

The twelve studies identified, from which five identified in the CUP were included in the meta-analysis. The unit used in the dose-response analysis was one serving/day because the majority of the studies reported the intake in servings. Studies reporting in grams of fruits were converted to servings, using as conversion unit 80g equivalent to 1 serving of fruits. One study (George SM, 2009) reported the intake of fruits in cup equivalent per 1000 calories, which was converted to servings/day using the median energy intake reported in the study. Another study (Park SY, 2013) reported the intake of fruits in grams per 1000 calories per day, which was converted to servings/day using the median energy intake reported in the study.

Four studies investigated invasive bladder cancer (Park, 2013; Ros, 2012; George, 2009; Larsson, 2008b), one study included invasive and in situ bladder cancers (Michaud, 2002a), one study included also cancers of the ureters, renal pelvis or urethra -35 cases out of 619 cases- (Zeegers, 2001b), in four studies bladder cancer was the outcome but no more detail was given (Shibata, 1992; Michaud, 1999a; Nagano, 2000; Holick, 2005) and one cohort investigated lower urinary tract cancer (70 bladder cancer cases out of 83 cases in the study) (Chyou, 1993).

All studies adjusted for smoking status, intensity and duration except two studies that adjusted for smoking status only (Shibata, 1992, Nagano, 2000) and one study that adjusted by pack-years (Chyou, 1993). The study in male smokers adjusted for duration and intensity of smoking (Michaud, 2002a).

Main results

The summary RR per 1 serving per day was 0.98 (95% CI: 0.96-1.00, I^2=0%, pheterogeneity=0.51, n=12). There was no evidence of publication bias with Egger's test, p=0.48.

In a sensitivity analysis excluding the studies that reported intake per 1000 kcal/day (Park, 2013; George, 2009) the summary RR per 1 serving per day was 0.97 (95% CI: 0.93-1.01, I^2=8.3%, pheterogeneity= 0.36). The summary RR per 100g/day of fruits was 0.98 (95% CI: 0.95-1.00, I^2=0%, pheterogeneity=0.51, n=12).

After stratification by sex, the RR per 1 serving per day was 0.98 (95% CI: 0.94-1.02, I^2=19.2%, pheterogeneity=0.29, n=6) for men and 0.97 (95% CI: 0.87-1.09, I^2=70.2%, pheterogeneity=0.04, n=3) for women. It was not possible to stratify the analysis by smoking status. Only one study showed results stratified by smoking status. In the EPIC study (Ros, 2012), the inverse associations were observed among never and former smokers but not in current smokers. The multiplicative interaction test was no significant. There was no evidence of non-linearity (p=0.43).

Heterogeneity

No evidence of heterogeneity, I^2=0%, pheterogeneity=0.50.

Comparison with the Second Expert Report

In the 2005 SLR the evidence relating fruit to bladder cancer was considered limited- no conclusion.

Published pooled analysis or meta-analysis

A meta-analysis of 4 cohort studies showed that a low consumption of fruit was not associated with an increased risk of bladder cancer (RR = 1.40, 95% CI: 1.08-1.83) (Steinmaus, 2000). Another meta-analysis of cohort and case-control studies showed inconsistent results for fruit and vegetables consumption and bladder cancer. The overall RR per 100g of fruit per day was 0.81, 95% CI: 0.73-0.91, p<0.01 when including 8 cohort and case-control studies. When the analysis was restricted to cohort studies the overall RR became weaker (RR= 0.80, 95% CI: 0.65-0.99, p=0.13) (Riboli, 2003).

Table 20 Studies on fruit intake identified during the CUP

Author/year	Country	Study name	Number of cases	Years of follow-up	Sex	RR	LCI	UCI	Contrast
Park SY, 2013	USA and Hawaii	Multiethnic Cohort Study	429 men and 152 women	12.5 years	M	0.89	0.66	1.19	≥239 vs. <77.4 g/1000kcal/d
					F	0.54	0.34	0.85	
Ros MM, 2012	Europe	EPIC	947	8.9 years	M/F	1.01	0.82	1.21	≥267 vs. <131 g/d
George SM, 2009	USA	NIH-AARP	1664	8 years	M	0.90	0.75	1.08	1.59–5.13 vs. 0-0.44 cup equivalent/1000kcal
					F	1.52	1.00	2.33	1.90–5.5 vs. 0–0.60 cup equivalent/1000kcal
					M/F	0.98	0.83	1.15	2.4 vs. 0.4 cup equivalent/1000kcal
Larsson SC, 2008 (b)	Sweden	Swedish Mammography Cohort and Cohort of Swedish men	485	9.4 years	M/F	0.93	0.69	1.25	≥2.3 vs. <0.8 servings/d

Table 21 Overall evidence on fruit intake and bladder cancer

SLR	Summary of evidence
2005 SLR	7 studies were included in the meta analysis and found a non-significant association between fruit intake and bladder cancer.
CUP	Five new cohort studies reported on fruit intake and bladder cancer. Only one showed a protective effect for women who consume high amounts of fruit (≈ >554g/day).

Table 22 Summary of results of the dose-response meta-analysis of fruit intake and bladder cancer

Bladder cancer		
	2005 SLR	CUP
Studies (n)	7	12
Cases (n)	1652	5329
Increment unit	Per 1 serving/day	Per 1 serving/day
RR (95% CI)	0.98 (0.93-1.03)	0.98 (0.96-1.00)
Heterogeneity (I^2, p-value)	I^2=0%, p=0.45	0%, p=0.51
Stratified analysis		
Men		0.98 (0.94-1.02)
Heterogeneity (I^2, p-value)		I^2=19.2%, p=0.29, n=6
Women		0.97 (0.87-1.09)
Heterogeneity (I^2, p-value)		I^2=70.2%, p=0.04, n=3

Table 23 Inclusion/exclusion table for meta-analysis of fruit intake and bladder cancer

WCRF code	Author	Year	Study design	Study name	Sex	Cancer outcome	2005 SLR	CUP dose-response	CUP H vs. L forest plot	Estimated values	Exclusion reason
BLA97217	Park SY	2013	Prospective cohort study	Multiethnic Cohort Study	M/F	Incidence	No	Yes	Yes	Midpoints. Person-years. Conversion to servings/day	
BLA97202	Ros MM	2012	Prospective cohort study	EPIC	M/F	Incidence	No	Yes	Yes	Person-years. Midpoints. Conversion to servings/day	
BLA97201	George SM	2009	Prospective cohort study	NIH-AARP	M/F	Incidence	No	Yes	Yes	Person-years and cases per quintile. Midpoints. Conversion to servings/day	
BLA97158	Larsson SC	2008(b)	Prospective cohort study	Swedish Mammography Cohort and Cohort of Swedish men	M/F	Incidence	No	Yes	Yes	Midpoints	
BLA11803	Holick C	2005	Prospective cohort study	Nurses' Health Study	F	Incidence	Yes	Yes	Yes		
BLA00185	Michaud D	2002 (a)	Prospective cohort study	ATBC study	M	Incidence/Mortality	Yes	Yes	Yes	Person-years. Conversion to servings/day	
BLA03992	Zeegers M	2001(b)	Prospective cohort study	Netherlands Cohort Study	M/F	Incidence	Yes	Yes	Yes	Midpoints. Conversion to servings/day	
BLA02708	Nagano J	2000	Prospective cohort study	Life Span Study, atomic bomb survivors, Japan	M/F	Incidence/Mortality	Yes	Yes	Yes	Midpoints. Conversion to servings/day	
BLA02843	Michaud D	1999(a)	Prospective cohort	Health Professionals	M	Incidence/Mortality	Yes	Yes	Yes		

			study	Follow-up Study							
BLA00777	Chyou PH	1993	Prospective cohort study	Honolulu Heart Program	M	Incidence/ Mortality	Yes	Yes	Yes	Person-years. Midpoints. Conversion to servings/day	
BLA00922	Shibata A	1992	Prospective cohort study	Laguna Hills Study USA	M	Incidence	Yes	Yes	Yes	Person-years	

Figure 21 Highest versus lowest forest plot of fruit intake and bladder cancer

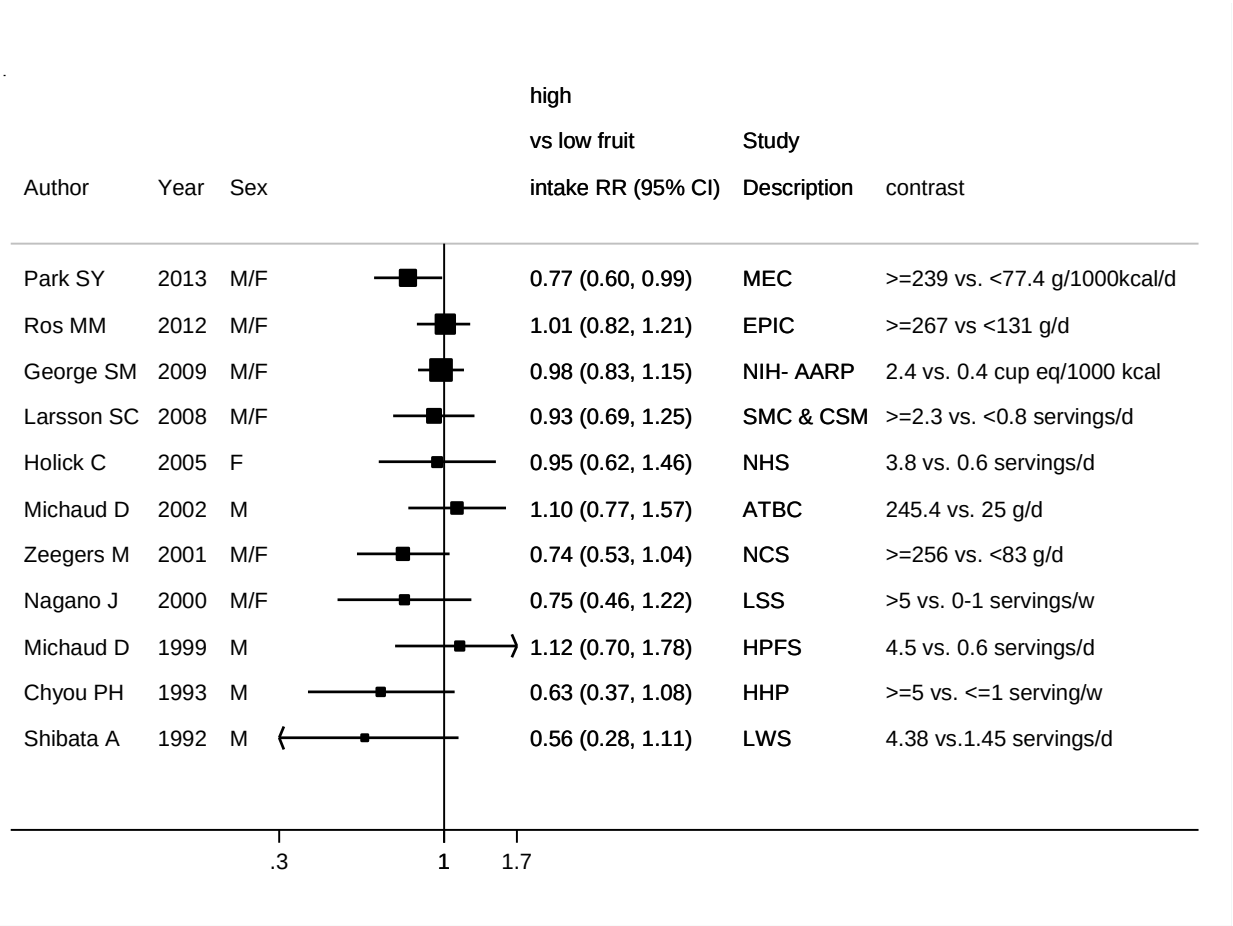


Figure 22 Dose-response meta-analysis of fruit intake and bladder cancer, per 1serving /day

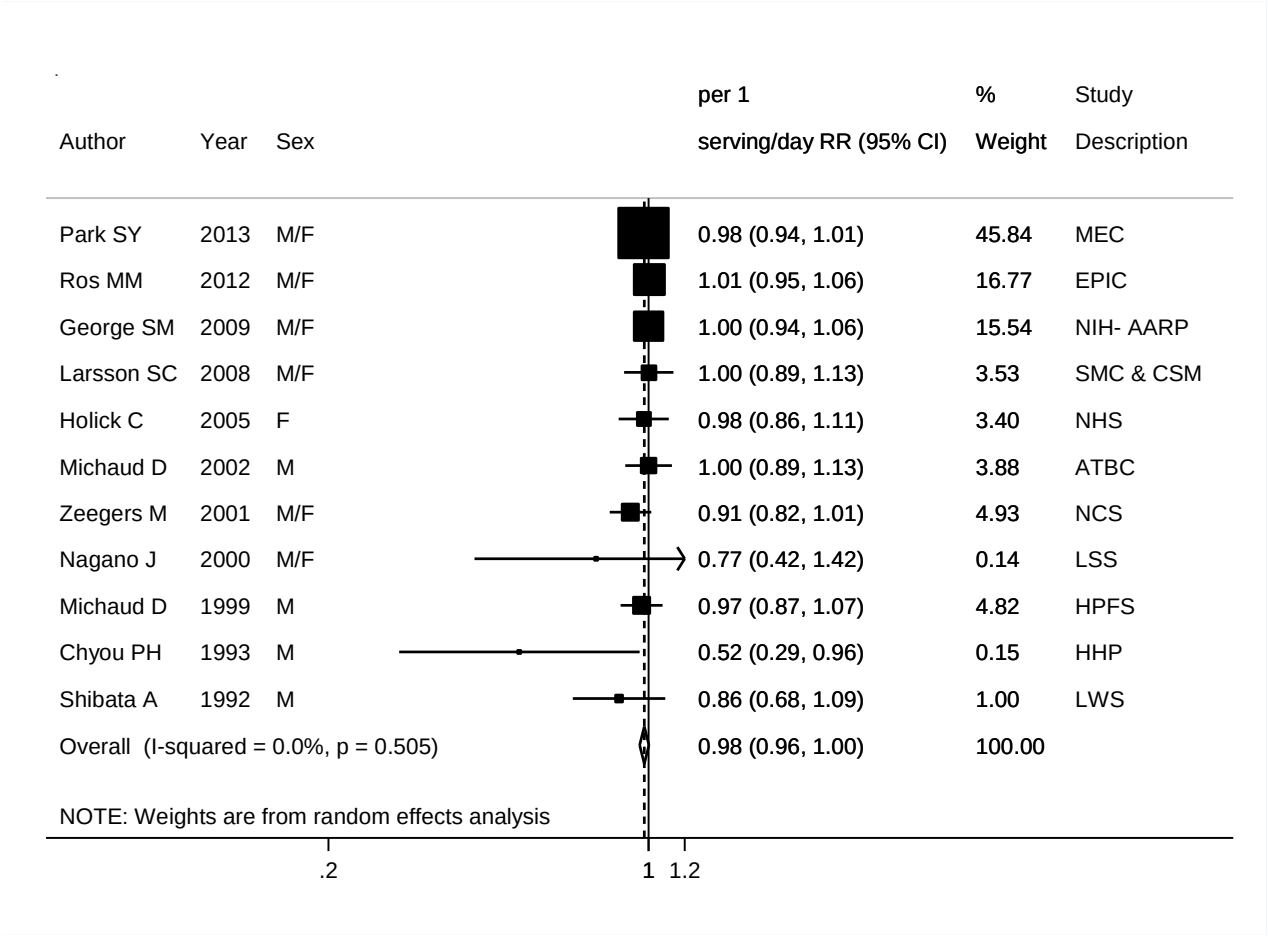
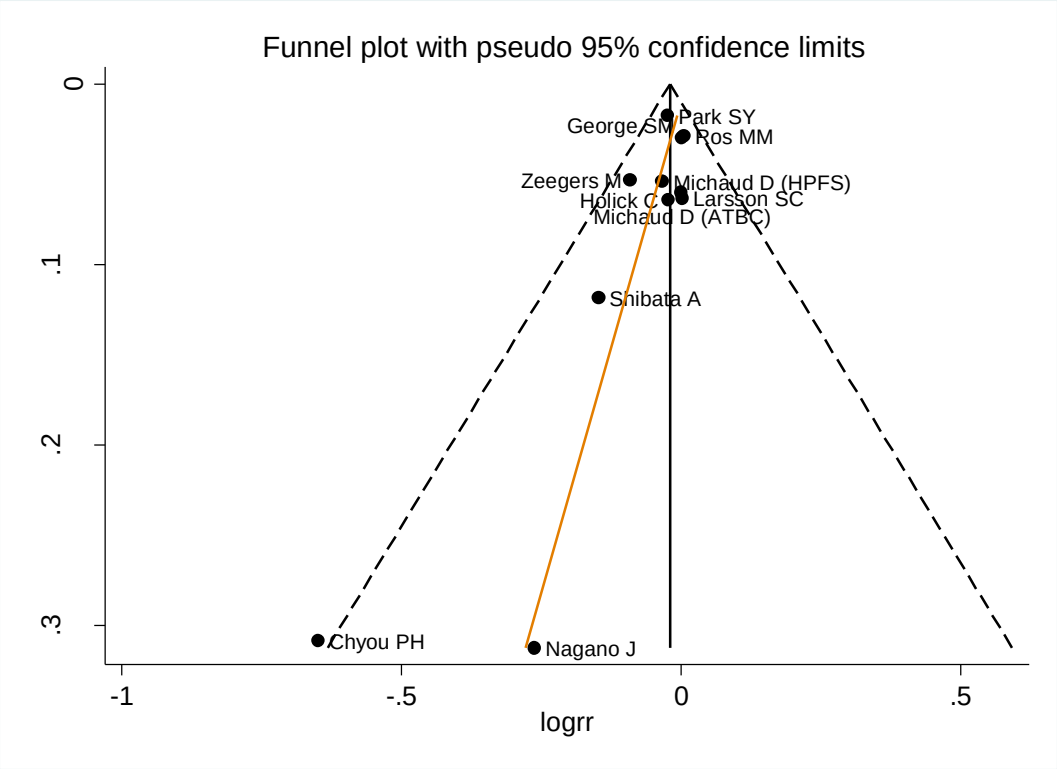


Figure 23 Funnel plot of fruit intake and bladder cancer



Egger's test p=0.48

Figure 24 Dose-response graph of fruit intake and bladder cancer

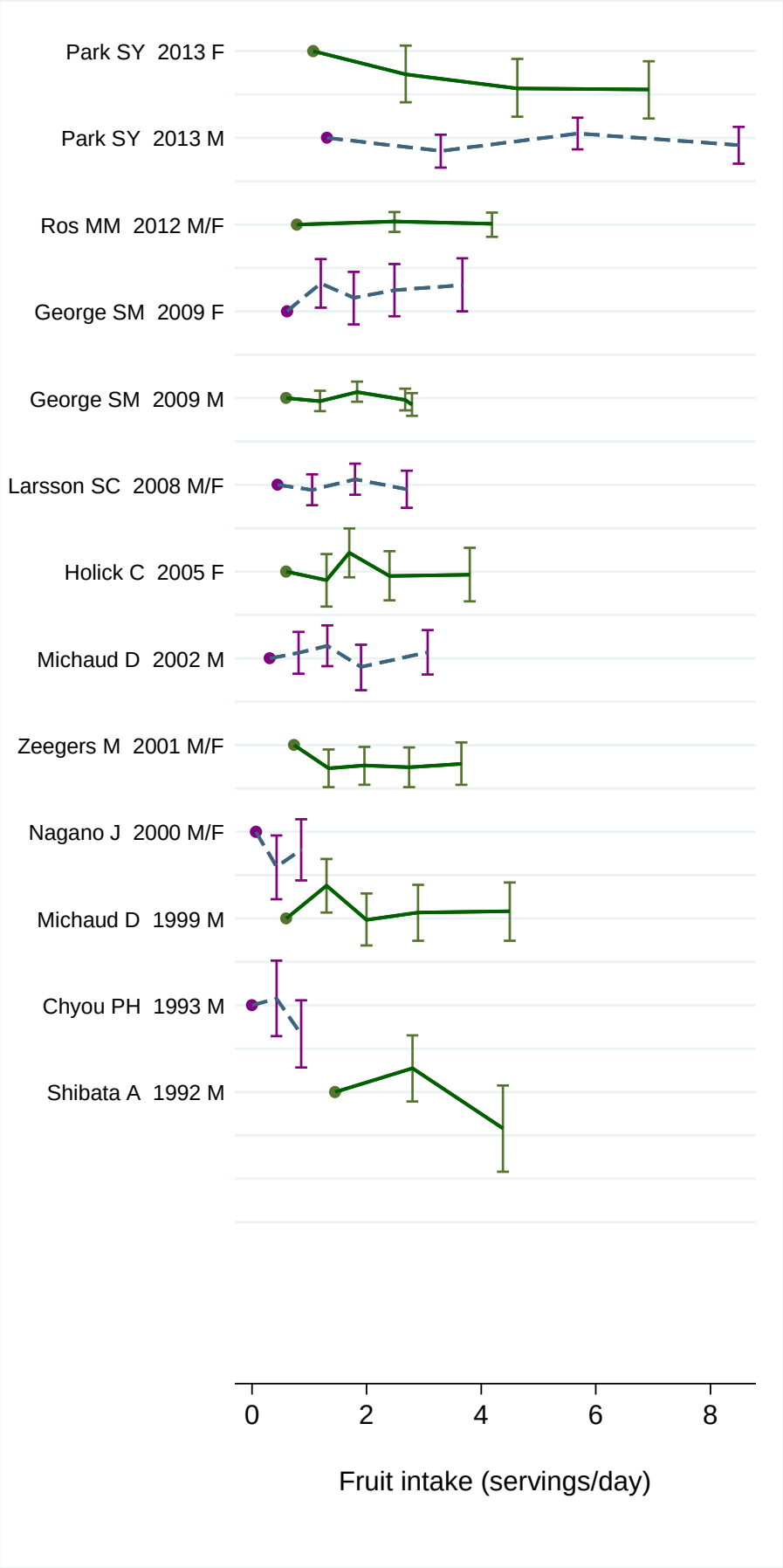
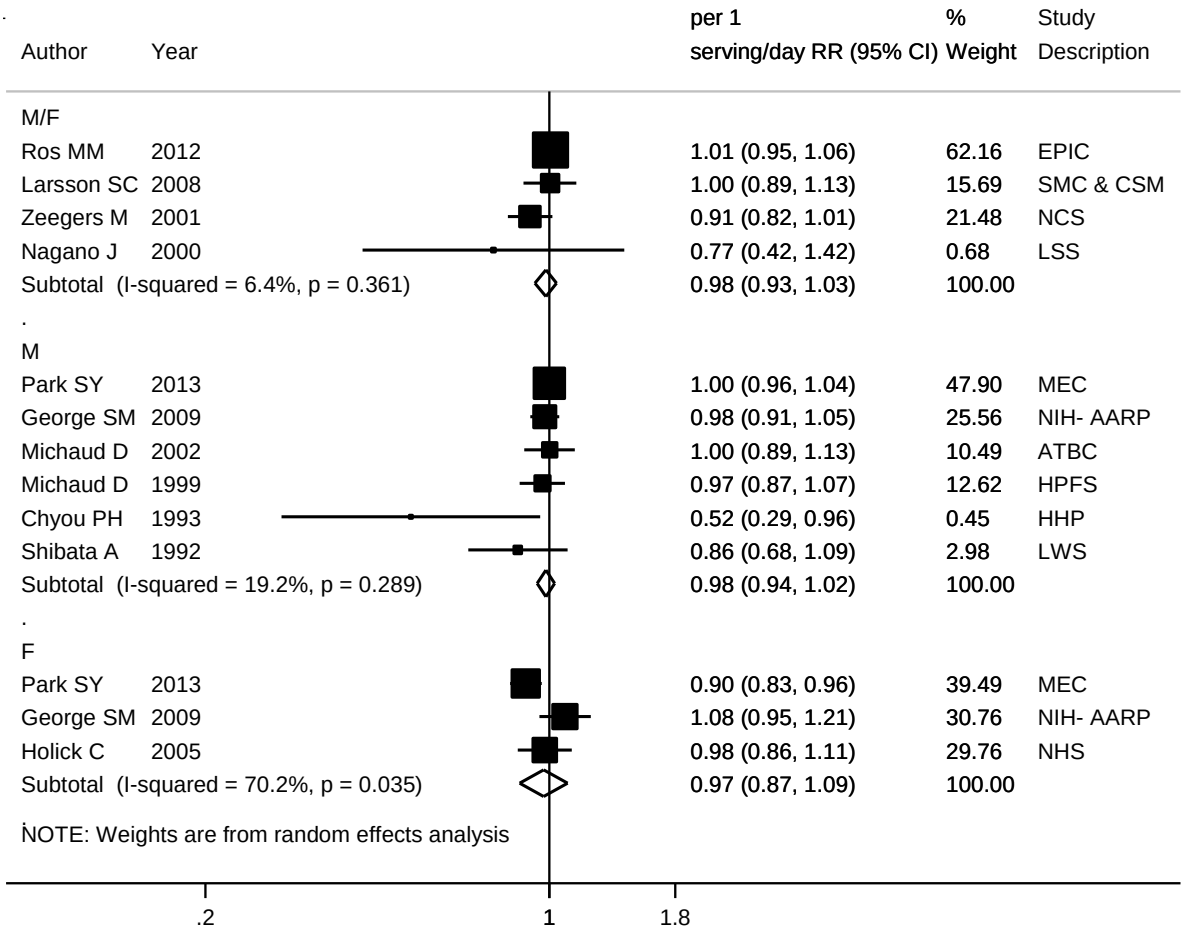


Figure 25 Dose-response meta-analysis of fruit intake and bladder cancer, per 1serving /day, stratified by sex



2.2.2.1 Citrus fruit

Methods

Six studies (five publications) had been identified, four of them in the CUP. The unit used in the dose-response analysis was one serving/day because the majority of the studies reported the intake in servings. Studies reporting in grams of citrus fruits were converted to servings, using as conversion unit 80g equivalent to 1 serving of citrus fruits. One study (Park SY, 2013) reported the intake of citrus fruit in grams per 1000 calories per day that was converted to servings/day using the median energy intake reported in the study.

Two studies investigated invasive bladder cancer (Park, 2013; Larsson, 2008b), one study was on bladder cancer but no details (Holick, 2005) and two studies investigated urothelial cell cancer - including also cancers of the ureters, renal pelvis- (Zeegers, 2001b; Iso, 2007). One study had mortality as outcome (Iso, 2007).

All studies adjusted for smoking status, intensity and duration except one study in which results are only age-adjusted (Iso, 2007).

Main results

The summary RR per 1 serving per day was 0.96 (95% CI: 0.91-1.02, I^2=0%, pheterogeneity=0.56, n=6). It was not possible to stratify the meta-analysis by smoking status.

After excluding the study with mortality as outcome (Iso, 2007) the overall result remained the same, 0.97 (95% CI: 0.91-1.02, I^2=0%, pheterogeneity=0.94, n=4). There was no evidence of publication bias with Egger test (p=0.68) although the funnel plot shows that small studies with positive associations are missing. There was no evidence of non-linearity (p=0.15).

Heterogeneity

There was no evidence of heterogeneity, I^2=0%, pheterogeneity=0.56.

Comparison with the Second Expert Report

In the 2005 SLR the evidence relating citrus fruit to bladder cancer was considered limited- no conclusion.

Published meta-analyses or pooled analyses

No published meta-analyses or pooled analyses were identified.

Table 24 Studies on citrus fruit intake identified during the CUP

Author/year	Country	Study name	Number of cases	Years of follow-up	Sex	RR	LCI	UCI	Contrast
Park SY, 2013	USA and Hawaii	Multiethnic Cohort Study	429 men and 152 women	12.5 years	M	0.97	0.74	1.28	≥94 vs. <13.4 g/1000kcal/d
					F	0.56	0.34	0.90	
Larsson SC, 2008 (b)	Sweden	Swedish Mammography Cohort and	485	9.4 years	M/F	0.88	0.68	1.16	≥5.1 vs. <0.5 servings/week

		Cohort of Swedish men							
Iso H, 2007	Japan	JACC Study	127	12 years	M	0.81	0.43	1.49	≥5 vs. <3 servings/week
					F	0.29	0.10	0.83	

Table 25 Overall evidence on citrus fruit intake and bladder cancer

SLR	Summary of evidence
2005 SLR	2 studies were included in the meta analysis and found a non-significant association between citrus fruit intake and bladder cancer.
CUP	Four new cohort studies reported on citrus fruit intake and bladder cancer. One showed a protective effect of citrus fruit consumption against bladder cancer mortality in women (Iso, 2007) and another study showed a protective effect against bladder cancer incidence for women who consume more than ≈234g/d of citrus fruit a day (Park SY, 2013).

Table 26 Summary of results of the dose-response meta-analysis of citrus fruit intake and bladder cancer

Bladder cancer		
	2005 SLR	CUP
Studies (n)	2	6
Cases (n)	775	1968
Increment unit	Per 1 serving/day	Per 1 serving/day
RR (95% CI)	0.92 (0.82-1.03)	0.96 (0.91-1.02)
Heterogeneity (I^2, p-value)	I^2=0%, p=0.39	0%, p=0.56

Table 27 Inclusion/exclusion table for meta-analysis of citrus fruit intake and bladder cancer

WCRF code	Author	Year	Study design	Study name	Sex	Cancer outcome	SLR	CUP dose-response	CUP H vs. L forest plot	Estimated values	Exclusion reason
BLA97217	Park SY	2013	Prospective cohort study	Multiethnic Cohort Study	M/F	Incidence	No	Yes	Yes	Midpoints. Person-years. Conversion to servings/day	
BLA97158	Larsson SC	2008(b)	Prospective cohort study	Swedish Mammography Cohort and Cohort of Swedish men	M/F	Incidence	No	Yes	Yes	Midpoints. Conversion to servings/day	
BLA97203	Iso H	2007	Prospective cohort study	Japan Collaborative Cohort Study (JACC Study)	M/F	Mortality	No	Yes	Yes	Midpoints. Conversion to servings/day	
BLA11803	Holick C	2005	Prospective cohort study	Nurses' Health Study	F	Incidence	Yes	Yes	Yes	Conversion to servings/day	
BLA03992	Zeegers M	2001(b)	Prospective cohort study	Netherlands Cohort Study	M/F	Incidence	Yes	Yes	Yes	Midpoints. Conversion to servings/day	

Figure 26 Highest versus lowest forest plot of citrus fruit intake and bladder cancer

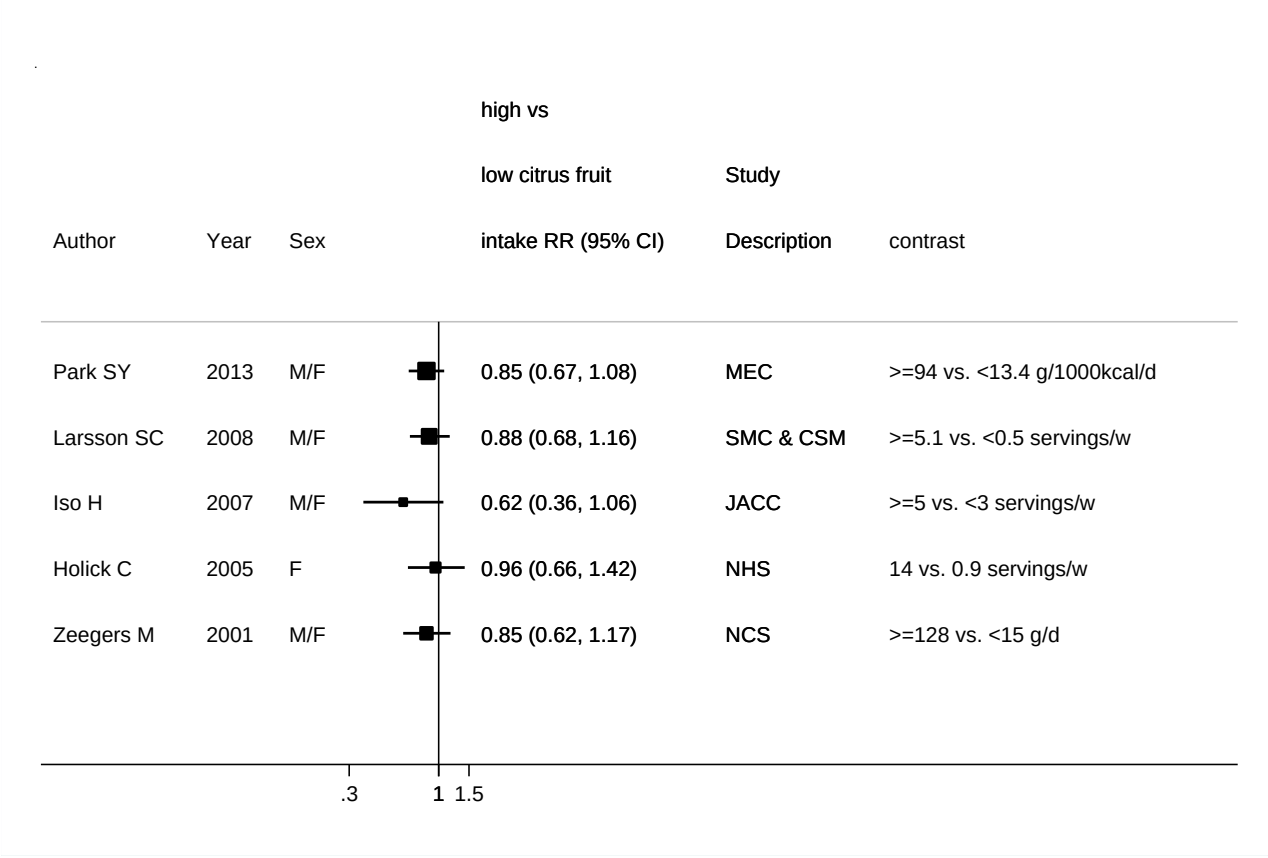


Figure 27 Dose-response meta-analysis of citrus fruit intake and bladder cancer, per 1serving /day

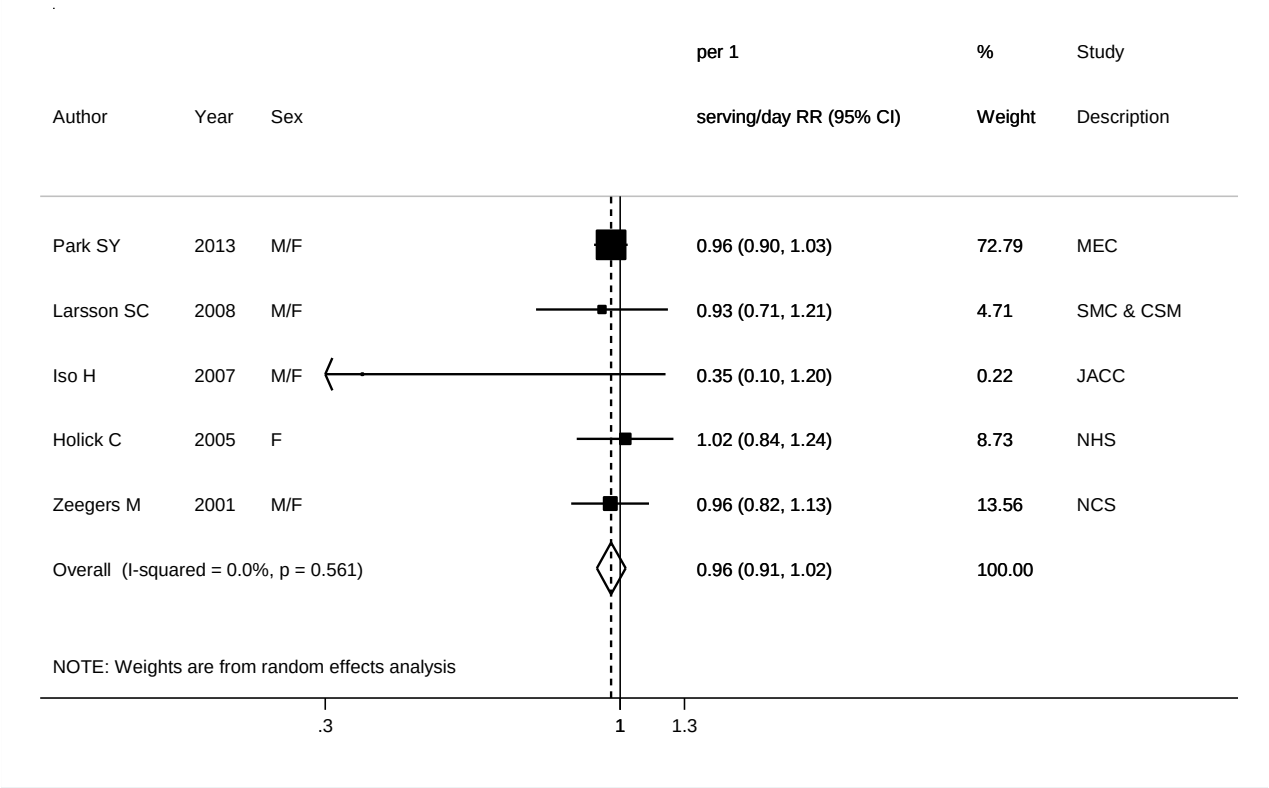
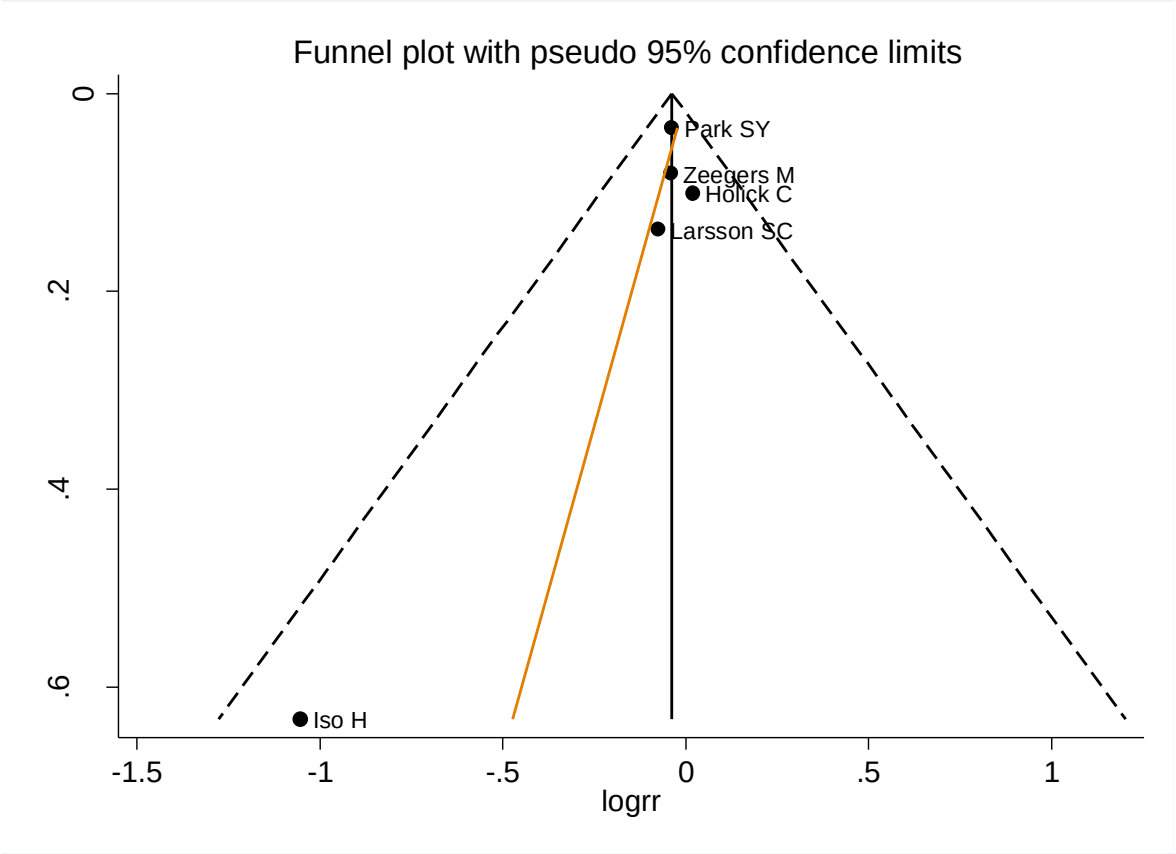


Figure 28 Funnel plot of citrus fruit and bladder cancer



Egger's test p=0.68

Figure 29 Dose-response graph of citrus fruit intake and bladder cancer

2.5.1 Total meat

Methods

Seven studies from 6 articles were identified. Three studies from two articles were identified in the CUP. The unit used in the dose-response analysis was 100g/day. Servings were rescaled to grams assuming that 1 serving of meat was equivalent to 120g. Total meat included red meats, processed meats and poultry. In one study in non-smokers at study enrollment (Lumbreras, 2008), the results were adjusted by smoking status (never or former smoker). Two studies were adjusted by smoking status (Mills, 1991; Nagano, 2000) and the remaining by smoking status and pack-years.

Main results

The summary RR per 100g/day increase of total meat intake was 1.01 (95% CI: 0.82-1.26, I^2=0%, pheterogeneity=0.70, n=5). It was not possible to stratify the analysis by smoking status.

Heterogeneity

There was no evidence of heterogeneity, I^2=0%, pheterogeneity=0.70.

Comparison with the Second Expert Report

In the 2005 SLR the evidence relating meat to bladder cancer was considered limited- no conclusion.

Published meta-analyses or pooled analyses

A meta-analysis of four cohort studies (Wang, 2012) reported a non-significant association of meat intake and bladder cancer (RR = 1.17, 95% CI = 0.83–1.50) when comparing the highest with the lowest category of meat intake. The summary estimate for the same comparison from 7 case-control studies was 0.98 (95% CI= 0.69-1.28).

Table 28 Studies on total meat identified during the CUP

Author/year	Country	Study name	Number of cases	Years of follow-up	Sex	RR	LCI	UCI	Contrast
Larsson SC, 2009	Sweden	Swedish Mammography Cohort and Cohort of Swedish men	485	9.4 years	M/F	1.05	0.71	1.55	≥1.5 servings/day vs. ≤2 servings/week
Lumbreras B, 2008	Europe	Gen Air nested with EPIC	118	-	M/F (slow acetylators)	0.7	0.3	1.9	180 vs. 32g/day
					M/F (rapid acetylators)	3.5	1.2	9.7	

Table 29 Overall evidence on total meat and bladder cancer

SLR	Summary of evidence
2005 SLR	4 studies were identified and found a non-significant association between total meat and bladder cancer.
CUP	Three new cohort studies reported on total meat and bladder cancer and with the exception of the study on individuals with NAT2 rapid genotype (rapid acetylators), all showed a non-significant association.

Table 30 Summary of results of the dose-response meta-analysis of total meat and bladder cancer

Bladder cancer		
	2005 SLR*	CUP
Studies (n)		5
Cases (n)		813
Increment unit		Per 100g/day
RR (95% CI)		1.01 (0.82-1.26)
Heterogeneity (I^2, p-value)		I^2=0%, p=0.70

* No meta-analysis was conducted in the SLR.

Table 31 Inclusion/exclusion table for meta-analysis of total meat intake and bladder cancer

WCRF code	Author	Year	Study design	Study name	Sex	Cancer outcome	2005 SLR	CUP dose-response	CUP H vs. L forest plot	Estimated values	Exclusion reason
BLA97160	Larsson SC	2009	Prospective cohort study	Swedish Mammography Cohort and Cohort of Swedish men	M/F	Incidence	No	Yes	Yes	Midpoints. Conversion to g/d	
BLA97166	Lumbreras B	2008	Nested case-control study	Gen Air nested with EPIC	M/F	Incidence	No	Yes	Yes		
BLA10545	Sakauchi F	2004	Prospective cohort study	Japan Collaborative Cohort Study (JACC)	M/F	Mortality	Yes	No	No		Identified in the 2005 SLR, relationship not quantified, only reported in the text that meat intake was not related to bladder cancer mortality
BLA02708	Nagano J	2000	Prospective cohort study	Life Span Study, atomic bomb survivors, Japan	M/F	Incidence/Mortality	Yes	Yes	Yes	Midpoints. Conversion to g/day	
BLA00777	Chyou PH	1993	Prospective cohort study	Honolulu Heart Program	M	Incidence/ Mortality	Yes	Yes	Yes	Person-years. Midpoints. Conversion to g/day	
BLA01090	Mills P	1991	Prospective cohort study	Adventists Health Study	M/F	Incidence	Yes	No	Yes		Only high versus low results

Figure 30 Highest versus lowest forest plot of total meat intake and bladder cancer

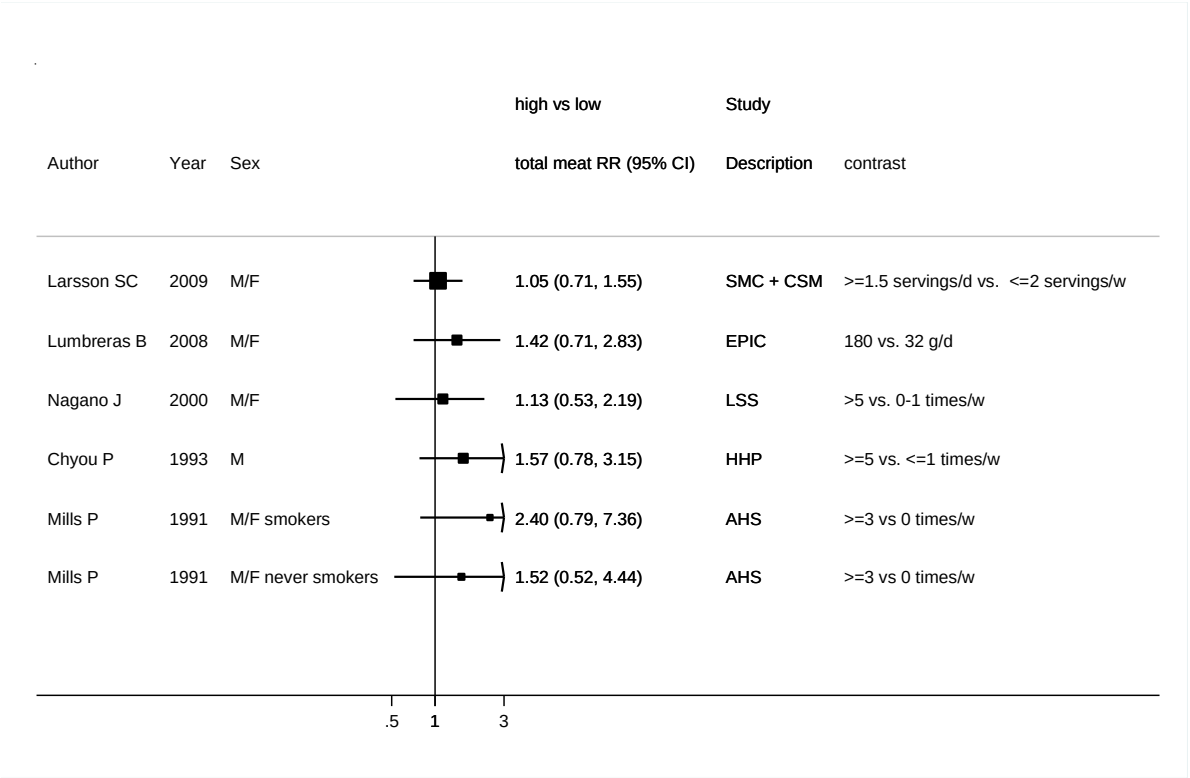


Figure 31 Dose-response meta-analysis of total meat intake and bladder cancer, per 100g /day

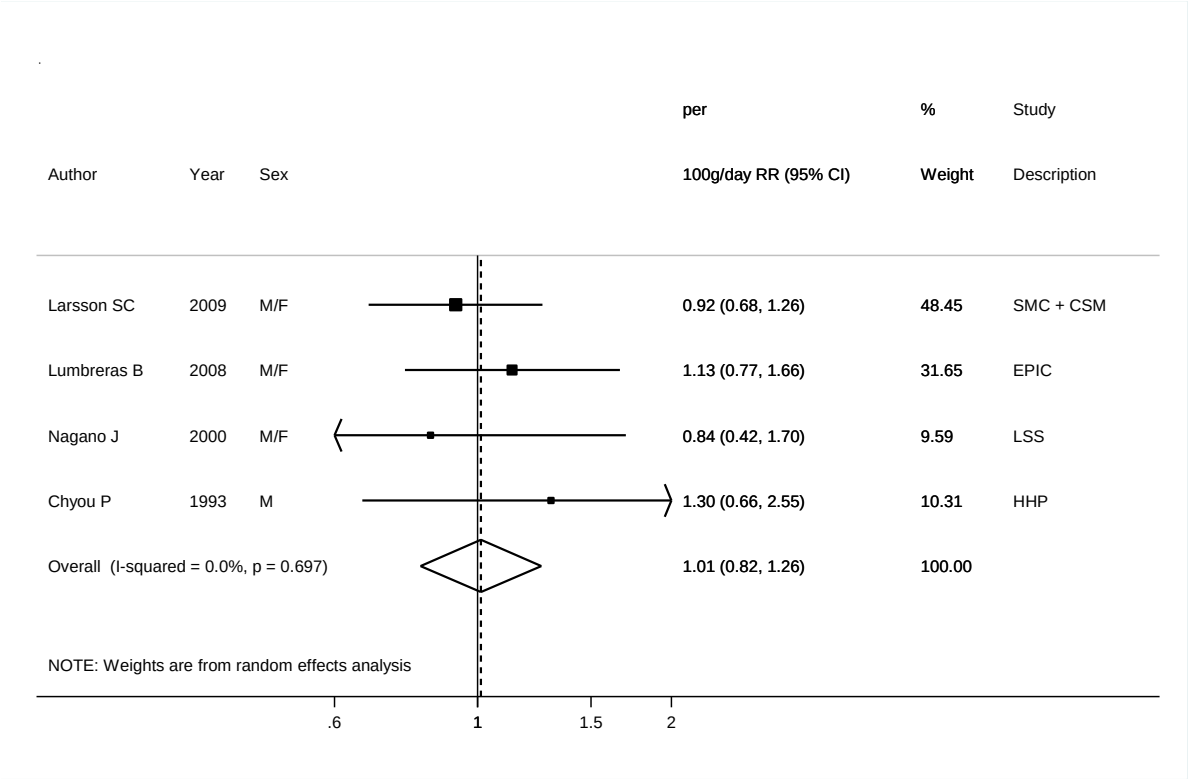
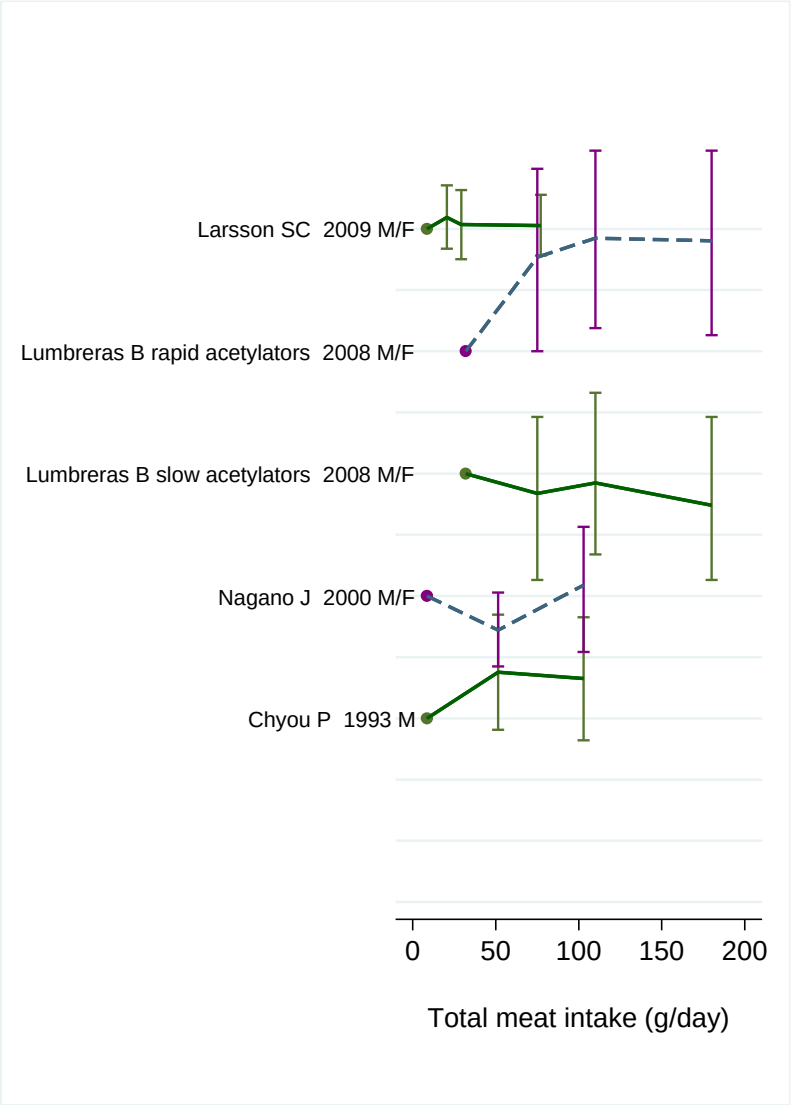


Figure 32 Dose-response graph of total meat intake and bladder cancer



2.5.1.2 Processed meat

Methods

Eight studies from 8 articles were identified; six studies from 5 articles were identified in the CUP. One updated publication of the JACC study was also identified in the CUP. The unit used in the dose-response analysis was 50g/day; 1 serving of processed meat was approximated to 50g of meat. In the European and American studies (Michaud, 2006; Ferrucci, 2010; Larson, 2009) processed meat included bacon, sausage, cold cuts, ham, hotdogs and salami. In the Japanese studies it included ham and sausages (Nagano, 2000; Sakauchi, 2004; Iso, 2007) and in a study in Honolulu it included ham, bacon and sausages (Chyou, 1993).

Outcome was incidence of bladder cancer in all studies except one study that investigated urothelial cancer death -including cancers of the bladder, renal pelvis or urethers- (Sakauchi, 2004) and one study on cancers of the lower urinary tract (70 bladder cancer cases out of 83 cases, Chyou, 1993). All results were adjusted for smoking status and dose except one that showed only age-adjusted results (Iso, 2007).

Main results

The summary RR per 50g of processed meat per day was 1.06 (95% CI: 0.92-1.24, I^2=0%, pheterogeneity=0.942, n=8) with no evidence of publication bias, Egger's test, p=0.51. It was not possible to stratify the analysis by smoking status. There was no evidence of non-linearity (p=0.09).

Heterogeneity

There was no evidence of heterogeneity, I^2=0%, pheterogeneity=0.942.

Comparison with the Second Expert Report

In the 2005 SLR the three studies which reported on ham, bacon and sausage and bladder cancer showed a not significant relationship, no conclusion.

Published meta-analyses or pooled analyses

No published meta-analyses or pooled analyses were identified.

Table 32 Studies on processed meat identified during the CUP

Author/year	Country	Study name	Number of cases	Years of follow-up	Sex	RR	LCI	UCI	Contrast
Ferrucci LM, 2010	USA	NIH-AARP Diet and Health Study	854	7 years	M/F	1.10	0.86	1.40	22.3 vs. 1.6 g/1000kcal/d
Larsson SC,	Sweden	Swedish	485	9.4	M/F	1.01	0.80	1.28	≥5

2009		Mammography Cohort and Cohort of Swedish men		years					servings/week vs. 0-3 servings/month
Michaud D, 2006	USA	NHS	304	22 years	F	0.81	0.40	1.63	≥5 vs. 0 servings/w
		HPFS	504	16 years	M	1.09	0.71	1.69	
Iso H, 2007	Japan	JACC study	118	12 years	M	0.97	0.51	1.86	≥3-4 vs. <1 times/w
					F	1.36	0.52	3.59	
Cross, 2007	USA	NIH-AARP	1666	8.2 years	M/F	1.16	0.98	1.38	22.6 vs. 1.6 g/1000kcal/d

Table 33 Overall evidence on processed meat and bladder cancer

SLR	Summary of evidence
2005 SLR	3 studies were included in the meta analysis and found a non-significant association between ham, bacon or sausage and bladder cancer.
CUP	Five new cohort studies reported on processed meat and bladder cancer and showed no significant association.

Table 34 Summary of results of the dose-response meta-analysis of processed meat and bladder cancer

Bladder cancer		
	2005 SLR*	CUP
Studies (n)	3	8
Cases (n)	298	2357
Increment unit	Per 1 serving/week	Per 50g/day
RR (95% CI)	1.0 (0.92-1.08)	1.06 (0.92-1.24)
Heterogeneity (I^2, p-value)	I^2=0%, p=0.45	I^2=0%, p=0.94

* Meta-analysis on ham/bacon/sausage and bladder cancer risk

Table 35 Inclusion/exclusion table for meta-analysis of processed meat intake and bladder cancer

WCRF code	Author	Year	Study design	Study name	Sex	Cancer outcome	2005 SLR	CUP dose-response	CUP H vs. L forest plot	Estimated values	Exclusion reason
BLA97205	Ferrucci LM	2010	Prospective cohort study	NIH-AARP Diet and Health Study	M/F	Incidence	No	Yes	Yes	Midpoints. Person-years. Conversion to g/d	
BLA97160	Larsson SC	2009	Prospective cohort study	Swedish Mammography Cohort and Cohort of Swedish men	M/F	Incidence	No	Yes	Yes	Midpoints. Conversion to g/day	
BLA97203	Iso H	2007	Prospective cohort study	Japan Collaborative Cohort Study (JACC Study)	M/F	Mortality	No	Yes	Yes	Midpoints. Conversion to g/day	
BLA97187	Cross A	2007	Prospective cohort study	NIH-AARP Diet and Health Study	M/F	Incidence	No	No	No		Superseded by Ferrucci LM, 2010
BLA97213	Michaud D	2006	Prospective cohort study	Health Professionals Follow-up Study and Nurses' Health Study	M/F	Incidence	No	Yes	Yes	Midpoints. Conversion to g/day	
BLA10545	Sakauchi F	2004	Prospective cohort study	Japan Collaborative Cohort Study (JACC)	M/F	Mortality	Yes	No	No		Superseded by Iso, 2007
BLA02708	Nagano J	2000	Prospective cohort study	Life Span Study, atomic bomb survivors, Japan	M/F	Incidence/Mortality	Yes	Yes	Yes	Midpoints. Conversion to g/day	

BLA00777	Chyou PH	1993	Prospective cohort study	Honolulu Heart Program	M	Incidence/ Mortality	Yes	Yes	Yes	Person-years. Midpoints. Conversion to g/day	

Figure 33 Highest versus lowest forest plot of processed meat intake and bladder cancer

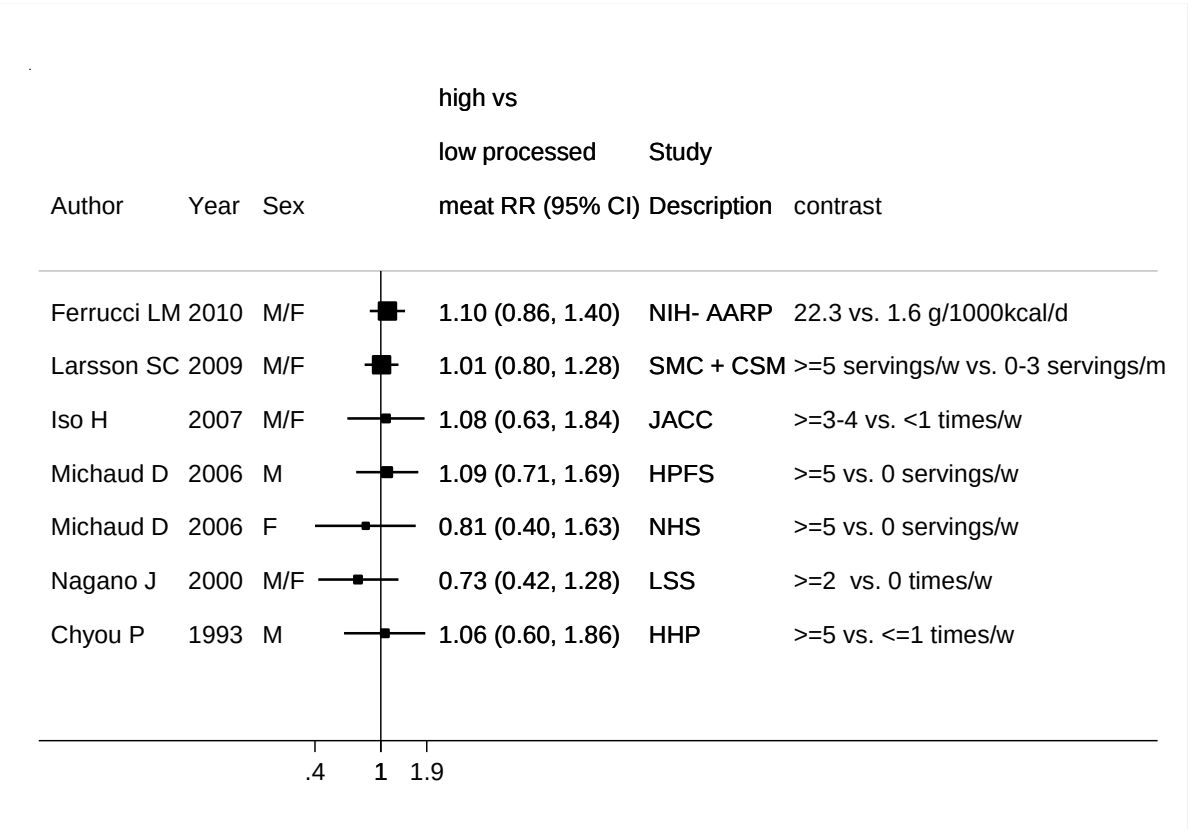


Figure 34 Dose-response meta-analysis of processed meat intake and bladder cancer, per 50g/day

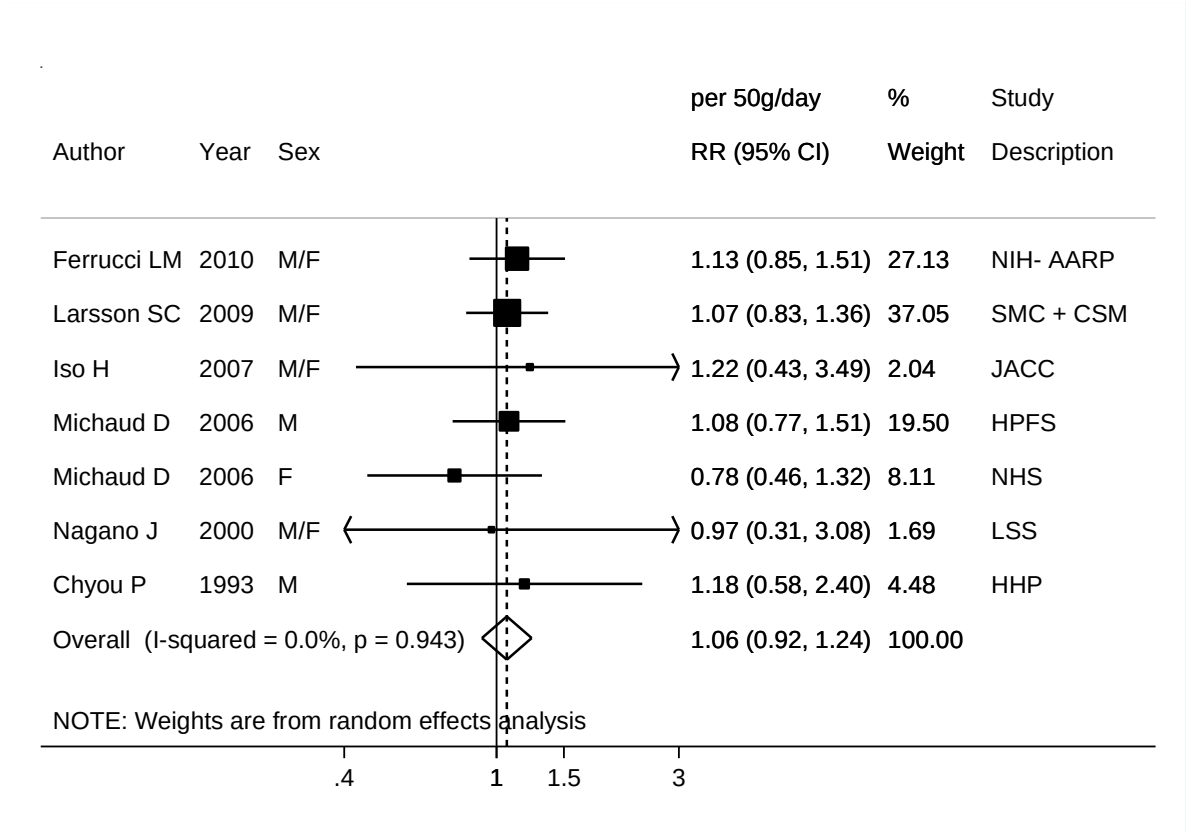
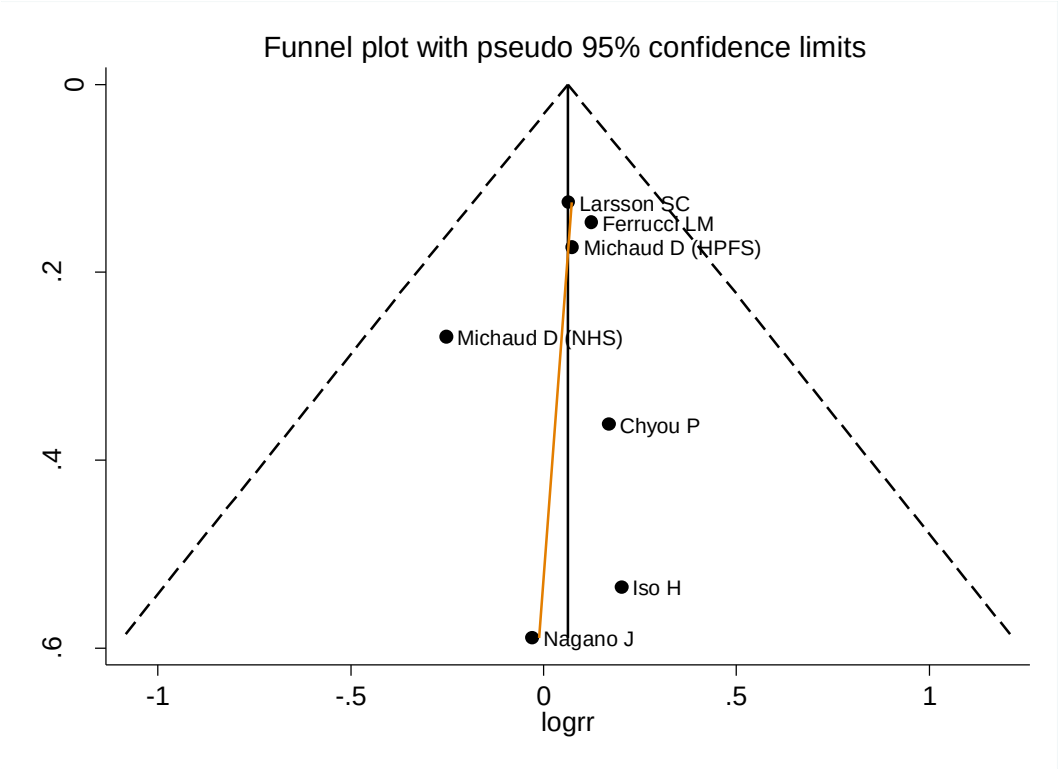
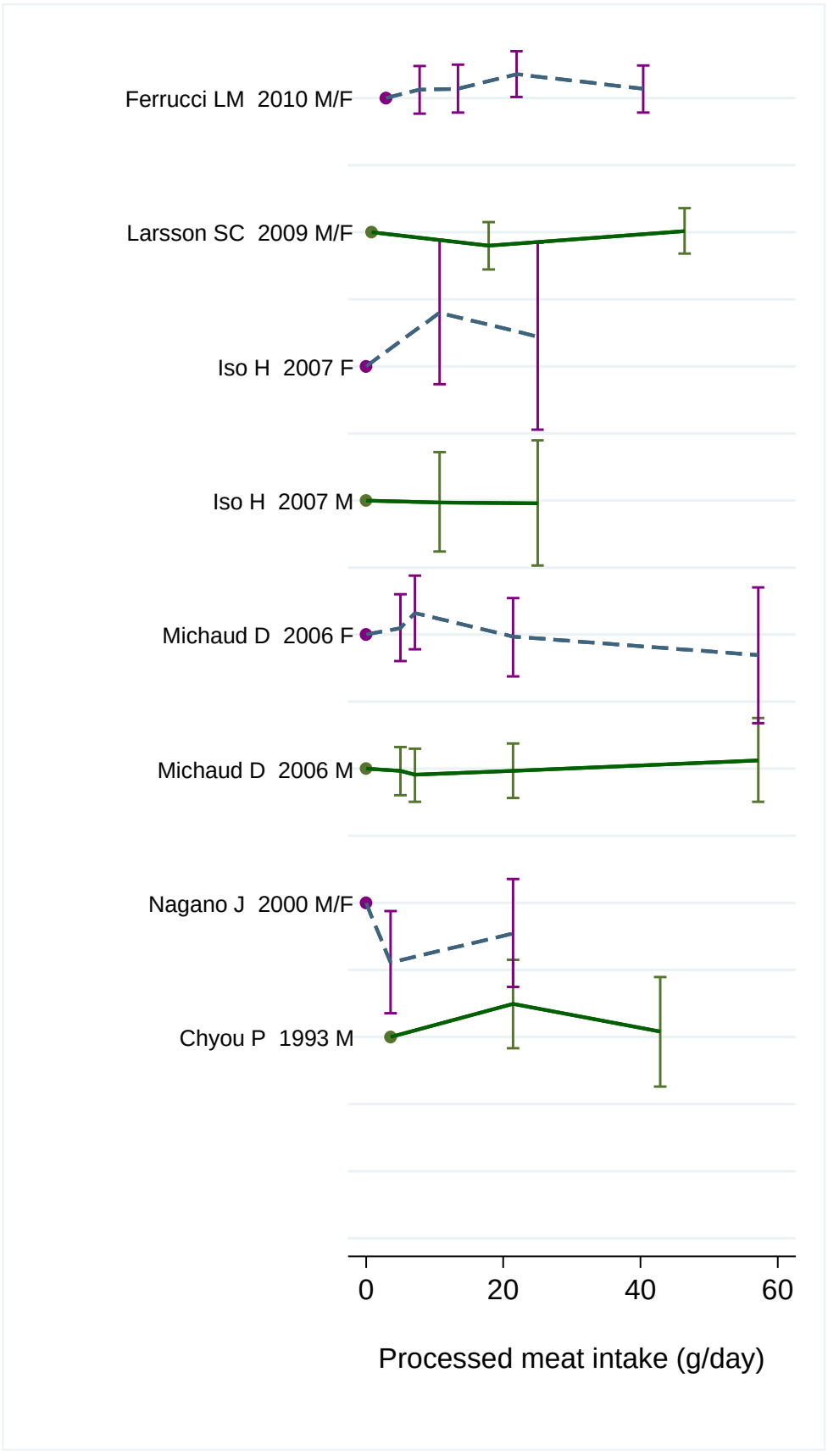


Figure 35 Funnel plot of processed meat intake and bladder cancer



Egger's test p=0.51

Figure 36 Dose-response graph of processed meat intake and bladder cancer



2.5.1.3 Red meat

Methods

Six studies (5 articles) were identified, all of them in the CUP. The unit used in the dose-response analysis was 100g/day (1 serving of red meat was approximated to 120g of meat). The definition of red meat varies across studies. Red meat included: beef, veal and lamb as main dish (Michaud, 2006), fresh and processed red meats (Ferruci, 2010; Jacszyn, 2011) or fresh red meats, hamburgers, meatballs and liver (Larsson, 2009). All studies adjusted results by smoking status, duration and dose.

Main results

The summary RR per 100g increase of red meat per day was 1.02 (95% CI: 0.97-1.06, I^2=0%, pheterogeneity=0.54, n=6). There was no evidence of publication bias, Egger's test p=0.44. It was not possible to stratify the analysis by smoking status. The test for non-linearity was non-significant (p=0.26).

Heterogeneity

There was evidence of moderate heterogeneity, I^2=0%, pheterogeneity=0.54.

Comparison with the Second Expert Report

No studies on red meat and bladder cancer were identified in the 2005 SLR.

Published meta-analyses or pooled analyses

No published meta-analyses or pooled analyses were identified.

Table 36 Studies on red meat identified during the CUP

Author/year	Country	Study name	Number of cases	Years of follow-up	Sex	RR	LCI	UCI	Contrast
Jakszyn P, 2011	Europe	EPIC	1001	8.7 years	M/F	1.15	0.90	1.45	130.63–754.79 vs. 0–57.86 g/day
Ferrucci LM, 2010	USA	NIH-AARP Diet and Health Study	854	7 years	M/F	1.22	0.96	1.54	61.6 vs. 9.5 g/1000kcal/d
Larsson SC, 2009	Sweden	Swedish Mammography Cohort and Cohort of Swedish men	485	9.4 years	M/F	1.01	0.71	1.41	≥5 servings/week vs. 0-3 servings/month
Cross, 2007	USA	NIH-AARP Diet and Health Study	1666	8.2 years	M/F	1.12	0.94	1.33	62.7 vs. 9.8 g/1000kcal/d

Michaud D, 2006	USA	NHS	304	22 years	F	1.01	0.56	1.85	≥5 servings/week vs. 1-3 servings/month
		HPFS	504	16 years	M	0.93	0.57	1.52	

Table 37 Overall evidence on red meat and bladder cancer

SLR	Summary of evidence
2005 SLR	No studies were identified.
CUP	Six new cohort studies reported on red meat and bladder cancer and showed no significant association.

Table 38 Summary of results of the dose-response meta-analysis of red meat and bladder cancer

Bladder cancer		
	2005 SLR*	CUP
Studies (n)		6
Cases (n)		3148
Increment unit		Per 100g/day
RR (95% CI)		1.02 (0.97-1.06)
Heterogeneity (I^2, p-value)		I^2=0%, p=0.54

* No meta-analysis was conducted in the SLR.

Table 39 Inclusion/exclusion table for meta-analysis of red meat intake and bladder cancer

WCRF code	Author	Year	Study design	Study name	Sex	Cancer outcome	2005 SLR	CUP dose-response	CUP H vs. L forest plot	Estimated values	Exclusion reason
BLA97181	Jakszyn P	2011	Prospective cohort study	EPIC	M/F	Incidence	No	Yes	Yes	Midpoints. Person-years	
BLA97205	Ferrucci LM	2010	Prospective cohort study	NIH-AARP Diet and Health Study	M/F	Incidence	No	Yes	Yes	Midpoints. Person-years. Conversion to g/d	
BLA97160	Larsson SC	2009	Prospective cohort study	Swedish Mammography Cohort and Cohort of Swedish men	M/F	Incidence	No	Yes	Yes	Midpoints. Conversion to g/d	
BLA97187	Cross A	2007	Prospective cohort study	NIH-AARP Diet and Health Study	M/F	Incidence	No	No	No		Superseded by Ferrucci LM, 2010
BLA97213	Michaud D	2006	Prospective cohort study	Health Professionals Follow-up Study and Nurses' Health Study	M/F	Incidence	No	Yes	Yes	Midpoints. Conversion to g/day	

Figure 37 Highest versus lowest forest plot of red meat intake and bladder cancer

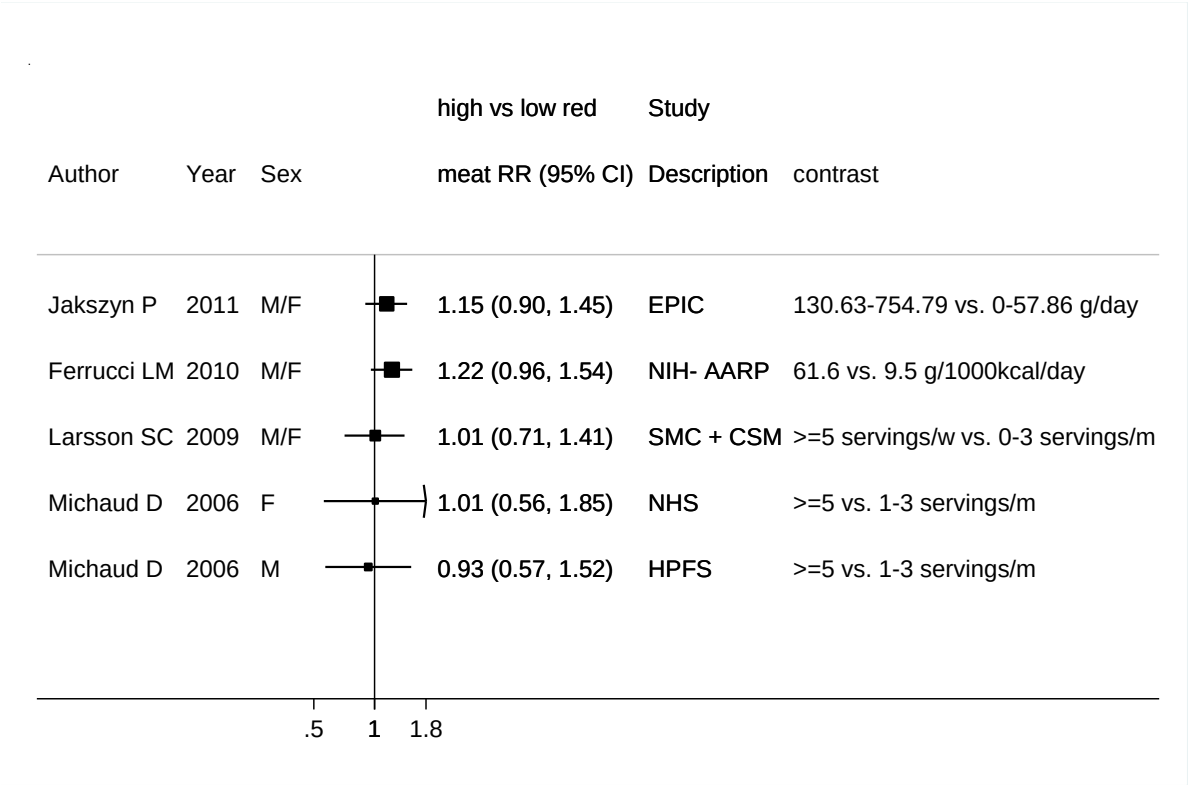


Figure 38 Dose-response meta-analysis of red meat intake and bladder cancer, per 100g /day

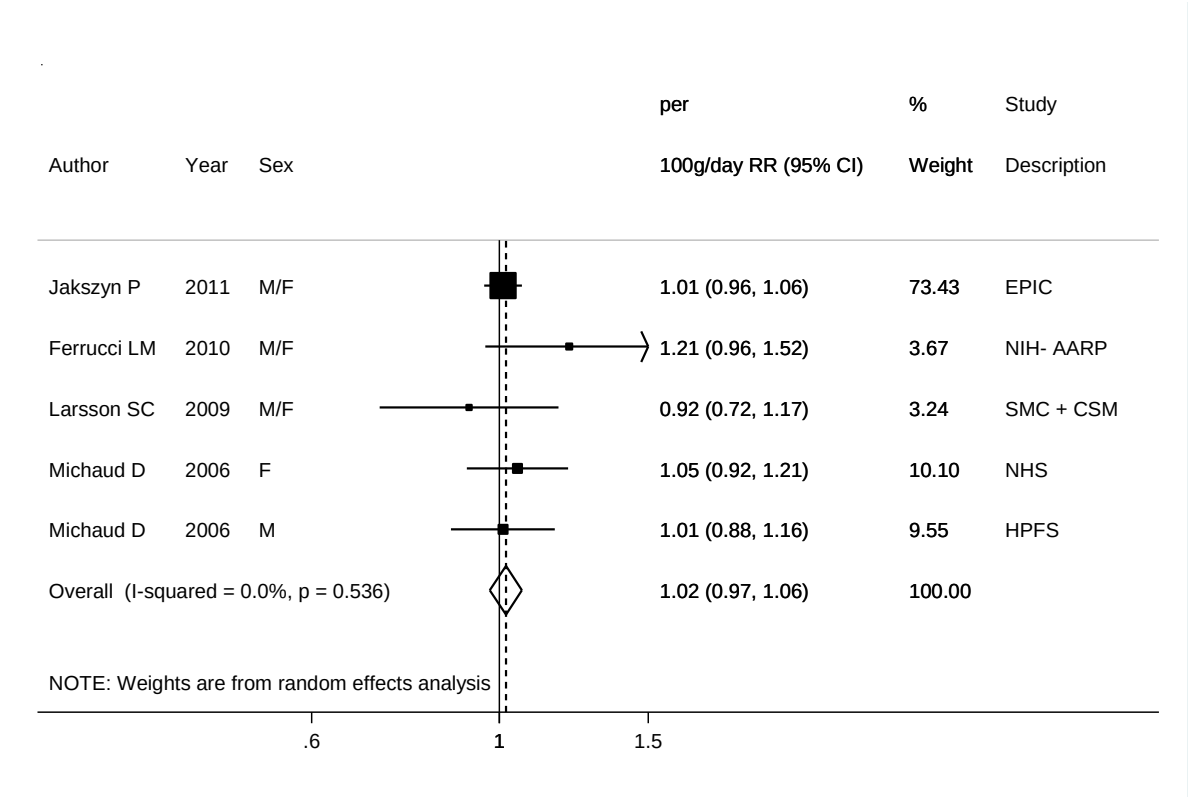
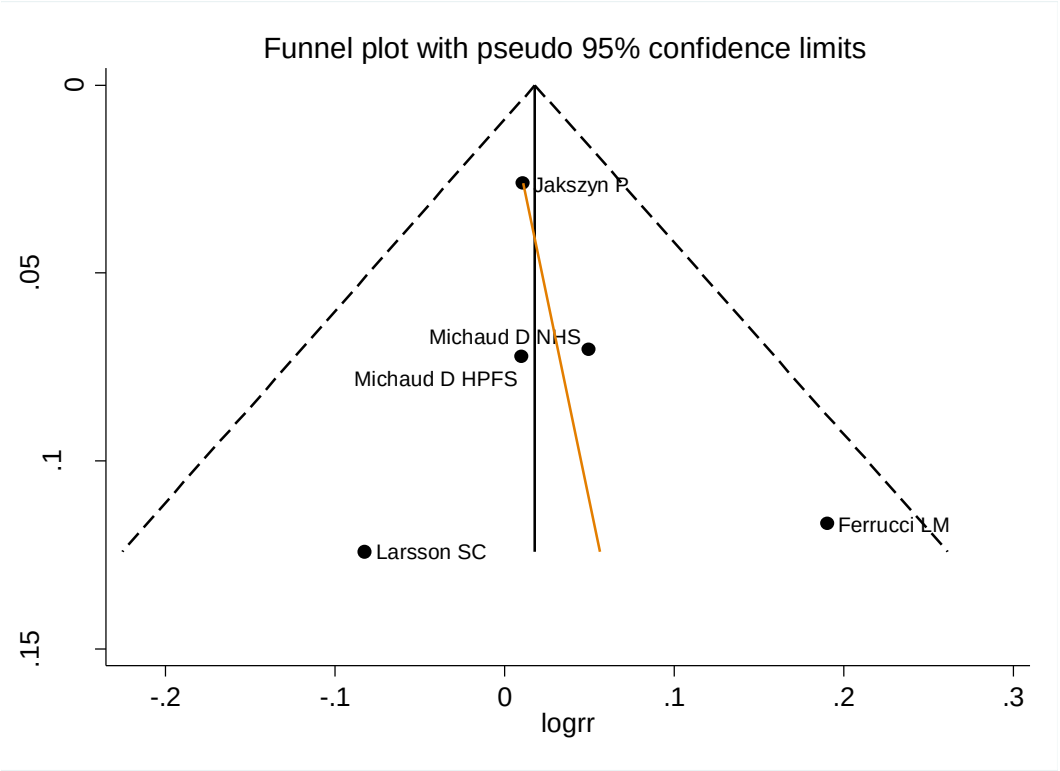
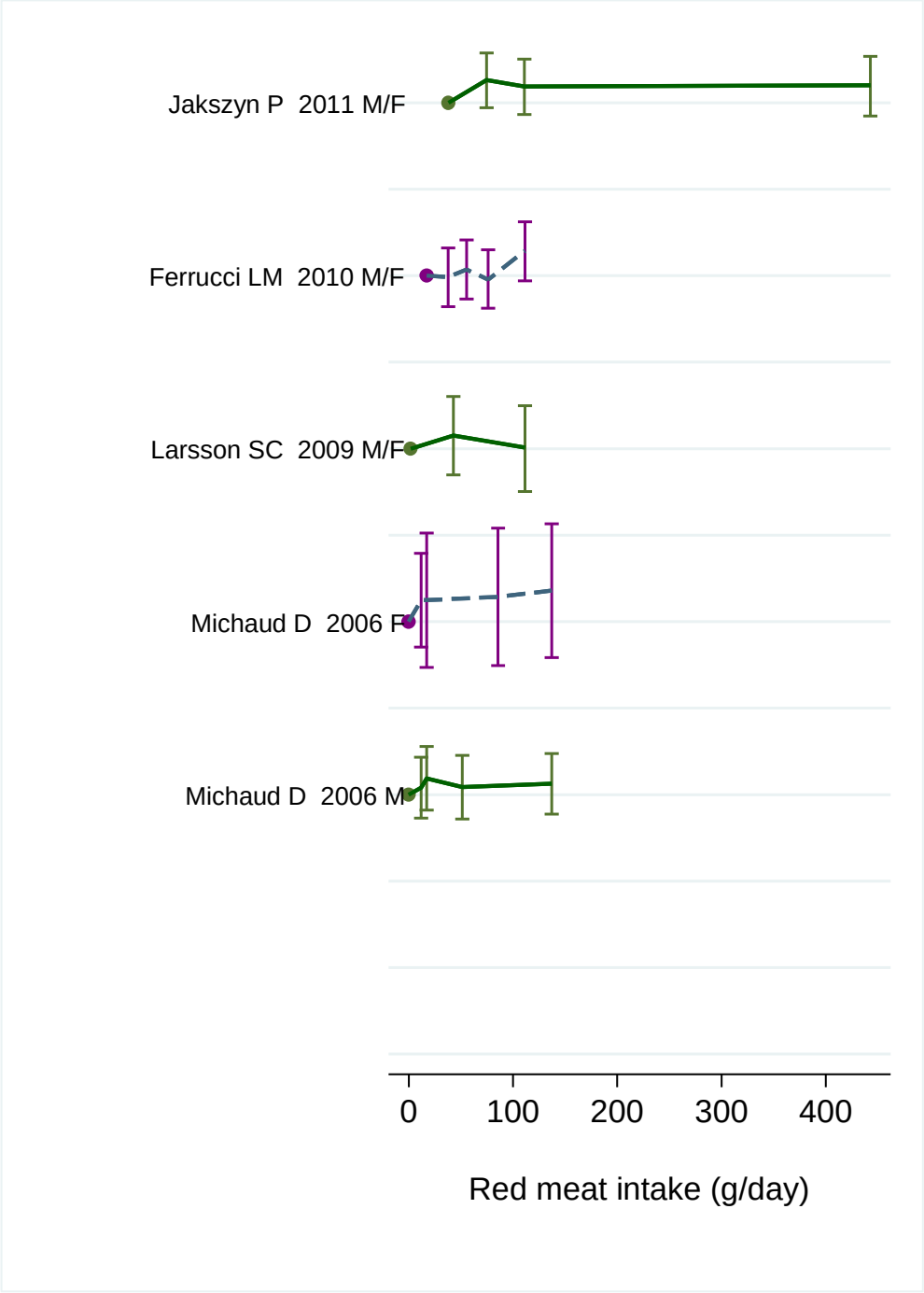


Figure 39 Funnel plot of red meat intake and bladder cancer



Egger's test p=0.44

Figure 40 Dose-response graph of red meat intake and bladder cancer



2.5.1.4 Poultry

Methods

Five cohort studies (three articles) were identified in the CUP. Two other cohort studies had been identified in the 2005 SLR for the Second Expert Report. The Japan Collaborative Cohort Study (JACC) has three articles. Overall, there are data from five distinct cohort studies.

The unit used in the dose-response analysis was 100g/day; 1 serving of poultry was considered equivalent to 120g of white meat. Two studies were on intake of chicken (Nagano, 2000; Iso, 2007), two studies on chicken and poultry (Larsson, 2009; Daniel, 2011), including processed poultry in one of them (Daniel, 2011). In one study, relative risks were reported separately for chicken with or without skin (Michaud, 2006). Only results of chicken with skin were used (for comparability with other studies).

Outcome was incidence of bladder cancer in all studies except one study that investigated urothelial cancer death -including cancers of the bladder, renal pelvis or urethers- (Sakauchi, 2004). All results were adjusted for smoking status and dose except one that showed only age-adjusted results (Iso, 2007).

Main results

The summary RR per 100g of poultry per day was 0.91 (95% CI: 0.81-1.03, I^2=0%, pheterogeneity=0.60, n=7). Egger's test suggested no evidence of publication bias (0.32). There was no evidence of non-linearity (p=0.13).

Heterogeneity

There was evidence of low heterogeneity, I^2=33.9%, pheterogeneity=0.20.

Comparison with the Second Expert Report

Two studies on chicken and bladder cancer risk were identified in the 2005 SLR that provided no evidence of association.

Published meta-analyses or pooled analyses

No published meta-analyses or pooled analyses were identified.

Table 40 Studies on poultry/chicken intake identified during the CUP

Author/year	Country	Study name	Number of cases	Years of follow-up	Sex		RR	LCI	UCI	Contrast
Daniel C, 2011	USA	NIH-AARP Diet and Health Study	2296	9 years	M/F		0.83	0.73	0.96	26.6 vs. 5.3 g/1000kcal/day
Larsson SC, 2009	Sweden	Swedish Mammography Cohort and Cohort of Swedish men	485	9.4 years	M/F		0.96	0.70	1.30	≥2 servings/week vs. never
Iso H, 2007	Japan	JACC study	118	12 years	M		1.24	0.60	2.53	≥3-4 vs. <1 times/w
					F		0.38	0.12	1.17	
Michaud D, 2006	USA	NHS	304	22 years	F	Chicken without skin	1.66	0.94	2.95	≥5 vs. 0 servings/w
						Chicken with skin	1.01	0.72	1.43	2-4 vs. 0 servings/week
		HPFS	504	16 years	M	Chicken without skin	1.45	0.96	2.17	≥5 vs. 0 servings/w
						Chicken with skin	1.10	0.86	1.41	2-4 vs. 0 servings/week

Table 41 Overall evidence on poultry/chicken and bladder cancer

SLR	Summary of evidence
2005 SLR	Two studies were included in the meta analysis; there was no evidence of association between chicken and bladder cancer.
CUP	Five new cohort studies reported on poultry/chicken and bladder cancer and showed no significant association.

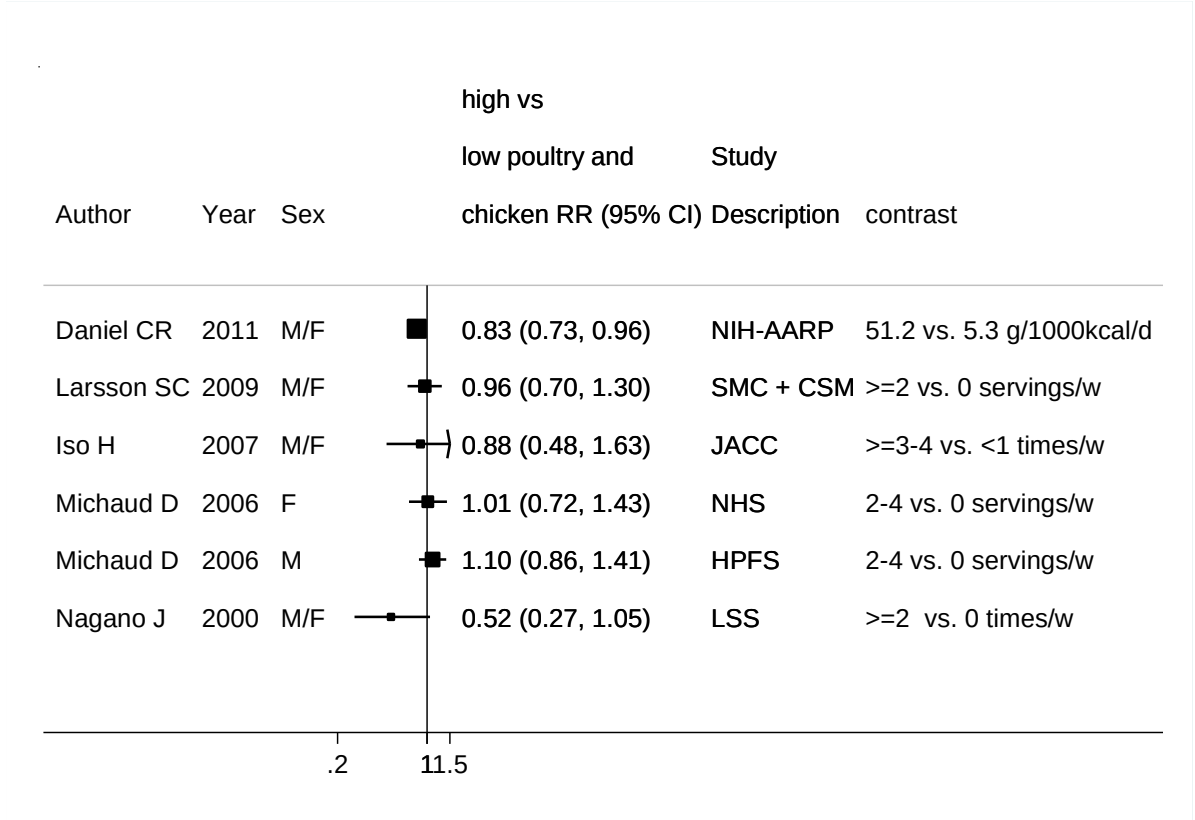
Table 42 Summary of results of the dose-response meta-analysis of poultry/chicken and bladder cancer

Bladder cancer		
	2005 SLR	CUP
Studies (n)	2	7
Cases (n)	202	3821
Increment unit	Per 1 serving/week	Per 100g/day
RR (95% CI)	0.92 (0.62-1.37)	0.91 (0.81-1.03)
Heterogeneity (I^2, p-value)	I^2=75.6%, p=0.04	I^2=0%, p=0.60

Table 43 Inclusion/exclusion table for meta-analysis of poultry/chicken intake and bladder cancer

WCRF code	Author	Year	Study design	Study name	Sex	Cancer outcome	2005 SLR	CUP dose-response	CUP H vs. L forest plot	Estimated values	Exclusion reason
BLA97205	Daniel C	2011	Prospective cohort study	NIH-AARP Diet and Health Study	M/F	Incidence	No	Yes	Yes	Midpoints. Person-years. Conversion to g/d	
BLA97160	Larsson SC	2009	Prospective cohort study	Swedish Mammography Cohort and Cohort of Swedish men	M/F	Incidence	No	Yes	Yes	Midpoints. Conversion to g/day	
BLA97203	Iso H	2007	Prospective cohort study	Japan Collaborative Cohort Study (JACC Study)	M/F	Mortality	No	Yes	Yes	Midpoints. Conversion to g/day	
BLA97213	Michaud D	2006	Prospective cohort study	Health Professionals Follow-up Study and Nurses' Health Study	M/F	Incidence	No	Yes	Yes	Midpoints. Conversion to g/day	Reported results on chicken with and without skin separately
BLA10545	Sakauchi F	2004	Prospective cohort study	Japan Collaborative Cohort Study (JACC)	M/F	Mortality	Yes	No	No		Superseded by Iso, 2007
BLA02708	Nagano J	2000	Prospective cohort study	Life Span Study, atomic bomb survivors, Japan	M/F	Incidence/Mortality	Yes	Yes	Yes	Midpoints. Conversion to g/day	

Figure 41 Highest versus lowest forest plot of poultry/chicken and bladder cancer



Note: For Michaud 2006 only results of chicken with skin are shown (for comparability with other studies)

Figure 42 Dose-response meta-analysis of poultry/chicken and bladder cancer, per 100g/day

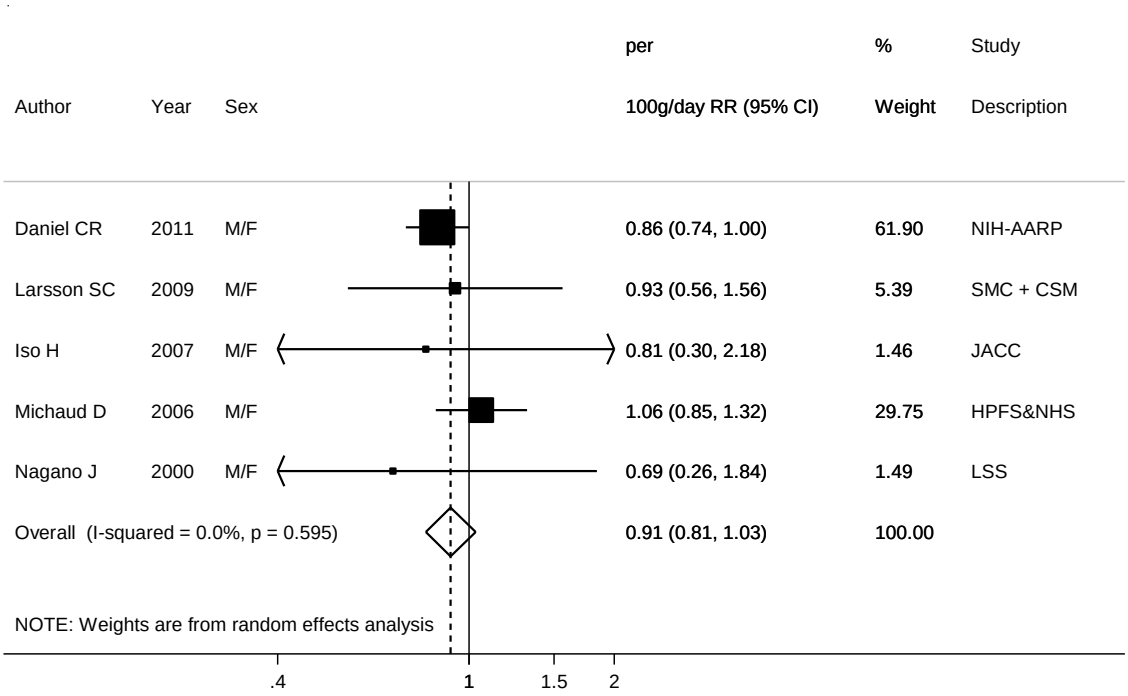
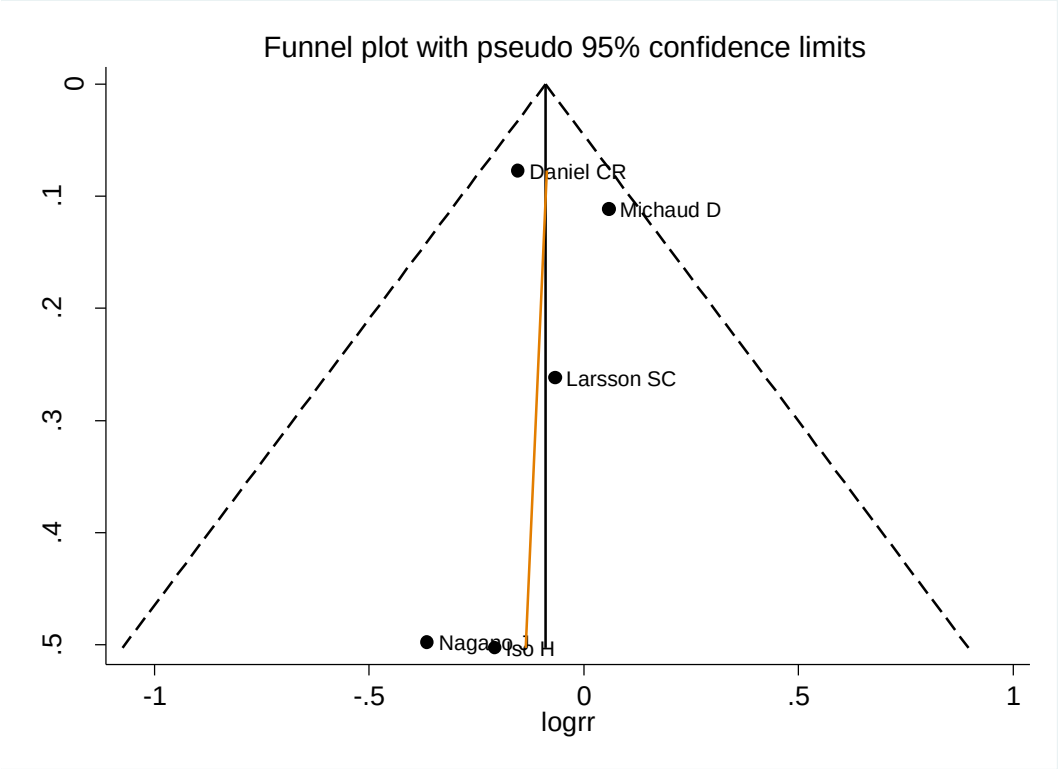
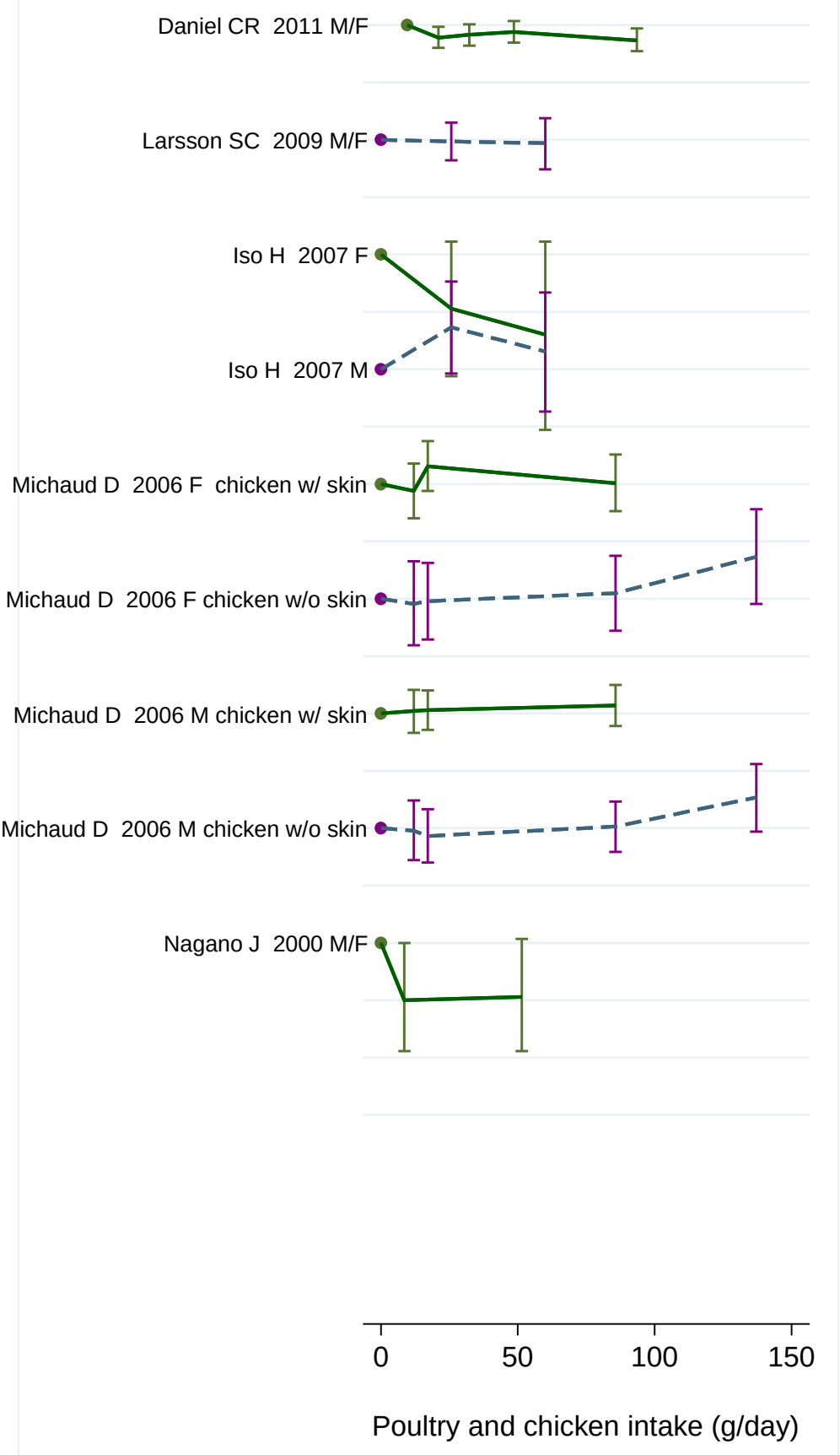


Figure 43 Funnel plot of poultry intake and bladder cancer



Egger's test p=0.32

Figure 44 Dose-response graph of poultry/chicken and bladder cancer



2.5.2 Fish

Methods

Seven studies in total, three studies from two articles identified in the CUP. One updated publication of the JACC study was also identified in the CUP. The unit used in the dose-response analysis was 50g/day; 1 serving of fish was considered equivalent to 120g of fish. Fish intake definition included intake of any fish, shellfish of canned tuna (Holick, 2006; Daniel, 2011) or fish –without specification- (Chyou, 1993; Steineck, 1988). In two Japanese studies, fish intake excluded processed or preserved fish, e.g. salted or dried fish, or fish paste (Nagano, 2000; Sakauchi, 2004).

Outcome was incidence of bladder cancer in all studies except one study that investigated urothelial cancer death -including cancers of the bladder, renal pelvis or urethers- (Sakauchi, 2004) and one study on cancers of the lower urinary tract (70 bladder cancer cases out of 83 cases, Chyou, 1993). All results were adjusted for smoking status and dose except one that showed only age-adjusted results (Iso, 2007).

Main results

The summary RR per 50g of fish per day was 1.02 (95% CI: 0.91-1.15, I^2=47.5%, pheterogeneity=0.11, n=5). It was not possible to stratify the analysis by smoking status. There is no evidence of publication bias (p=0.26). There was no evidence of non-linearity (p=0.71).

Heterogeneity

There was evidence of moderate heterogeneity, I^2=47.5%, pheterogeneity=0.11.

Comparison with the Second Expert Report

In the 2005 SLR the evidence relating fish to bladder cancer was considered limited-no conclusion.

Published meta-analyses or pooled analyses

A meta-analysis of five cohort and nine case-control studies was found. For the cohort studies the overall estimate of the highest versus lowest analysis was 0.84 95% CI: 0.42-1.26, I^2=64.8%, pheterogeneity=0.02 (Li Z, 2011).

Table 44 Studies on fish intake identified during the CUP

Author/year	Country	Study name	Number of cases	Years of follow-up	Sex	RR	LCI	UCI	Contrast
Daniel C, 2011	USA	NIH-AARP	2296	9 years	M/F	1.13	0.99	1.29	21.4 vs. 3.6 g/1000kcal/day

		Diet and Health Study							
Holick CN, 2006	USA	NHS	235	18 years	F	1.33	0.74	2.40	≥1 serving/d vs. ≤1-3 servings/month
		HPFS	501	16 years	M	0.71	0.48	1.04	
Iso H, 2007	Japan	JACC study	118	12 years	M	0.9	0.5	1.63	≥5 vs. <3 times/w
					F	0.28	0.08	0.96	

Table 45 Overall evidence on fish and bladder cancer

SLR	Summary of evidence
2005 SLR	4 studies were identified and 2 studies were included in the meta analysis and found a non-significant association between fish and bladder cancer.
CUP	Four new cohort studies reported on fish and bladder cancer and showed a non-significant association.

Table 46 Summary of results of the dose-response meta-analysis of fish and bladder cancer

Bladder cancer		
	2005 SLR	CUP
Studies (n)	2	5
Cases (n)	184	3246
Increment unit	Per 1 serving/week	Per 50g/day
RR (95% CI)	0.96 (0.87-1.05)	1.02 (0.91-1.15)
Heterogeneity (I^2, p-value)	I^2=0%, p=0.65	I^2=47.5%, p=0.11

Table 47 Inclusion/exclusion table for meta-analysis of fish intake and bladder cancer

WCRF code	Author	Year	Study design	Study name	Sex	Cancer outcome	2005 SLR	CUP dose-response	CUP H vs. L forest plot	Estimated values	Exclusion reason
BLA97205	Daniel C	2011	Prospective cohort study	NIH-AARP Diet and Health Study	M/F	Incidence	No	Yes	Yes	Midpoints. Person-years. Conversion to g/d	
BLA97151	Holick CN	2006	Prospective cohort study	Health Professionals Follow-up Study and Nurses' Health Study	M/F	Incidence	No	Yes	Yes	Midpoints. Conversion to g/day	
BLA97203	Iso H	2007	Prospective cohort study	Japan Collaborative Cohort Study (JACC Study)	M/F	Mortality	No	Yes	Yes	Midpoints. Conversion to g/day	
BLA10545	Sakauchi F	2004	Prospective cohort study	Japan Collaborative Cohort Study (JACC)	M/F	Mortality	Yes	No	No		Superseded by Iso, 2007
BLA02708	Nagano J	2000	Prospective cohort study	Life Span Study, atomic bomb survivors, Japan	M/F	Incidence/Mortality	Yes	No	Yes		Identified in the 2005 SLR, not used because of insufficient data
BLA00777	Chyou PH	1993	Prospective cohort study	Honolulu Heart Program	M	Incidence/ Mortality	Yes	Yes	Yes	Person-years. Midpoints. Conversion to g/day	
BLA01325	Steineck	1988	Prospective cohort study	Swedish Twins Cohort	M/F	Incidence/ Mortality	Yes	No	Yes		Only high versus low results

Figure 45 Highest versus lowest forest plot of fish and bladder cancer

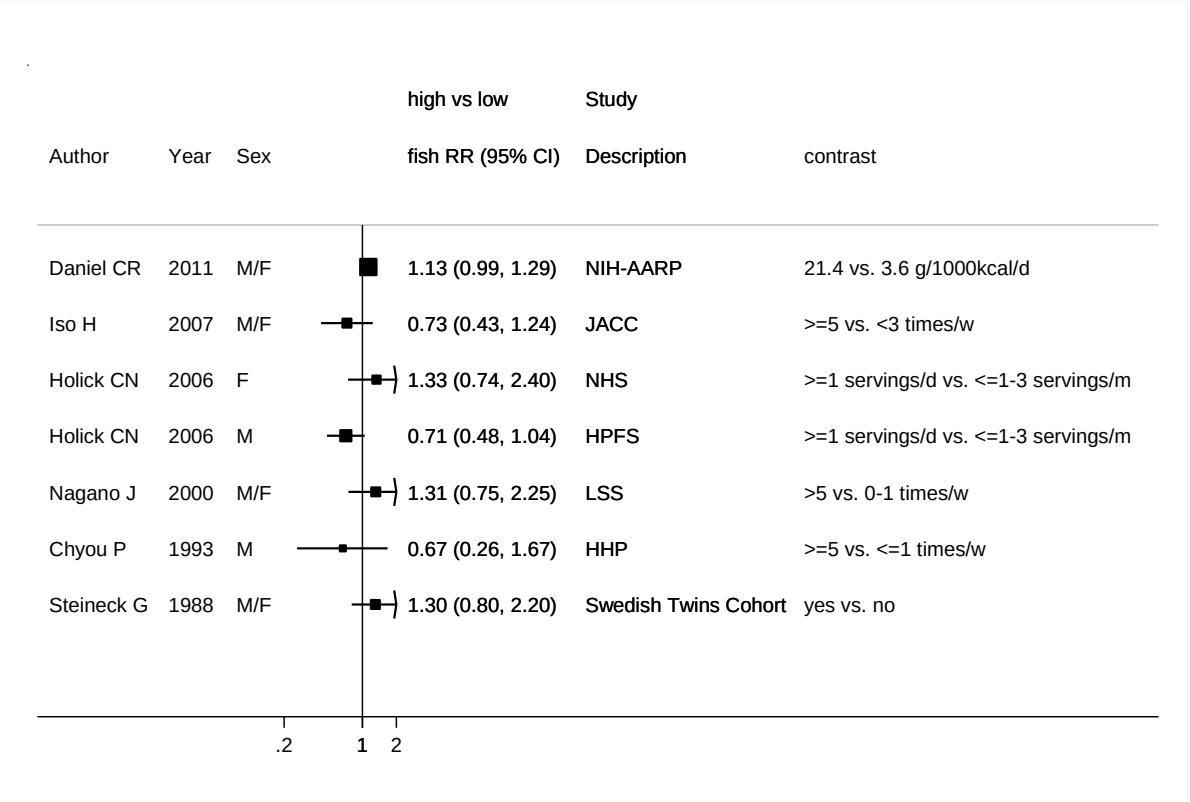


Figure 46 Dose-response meta-analysis of fish and bladder cancer, per 50g/day

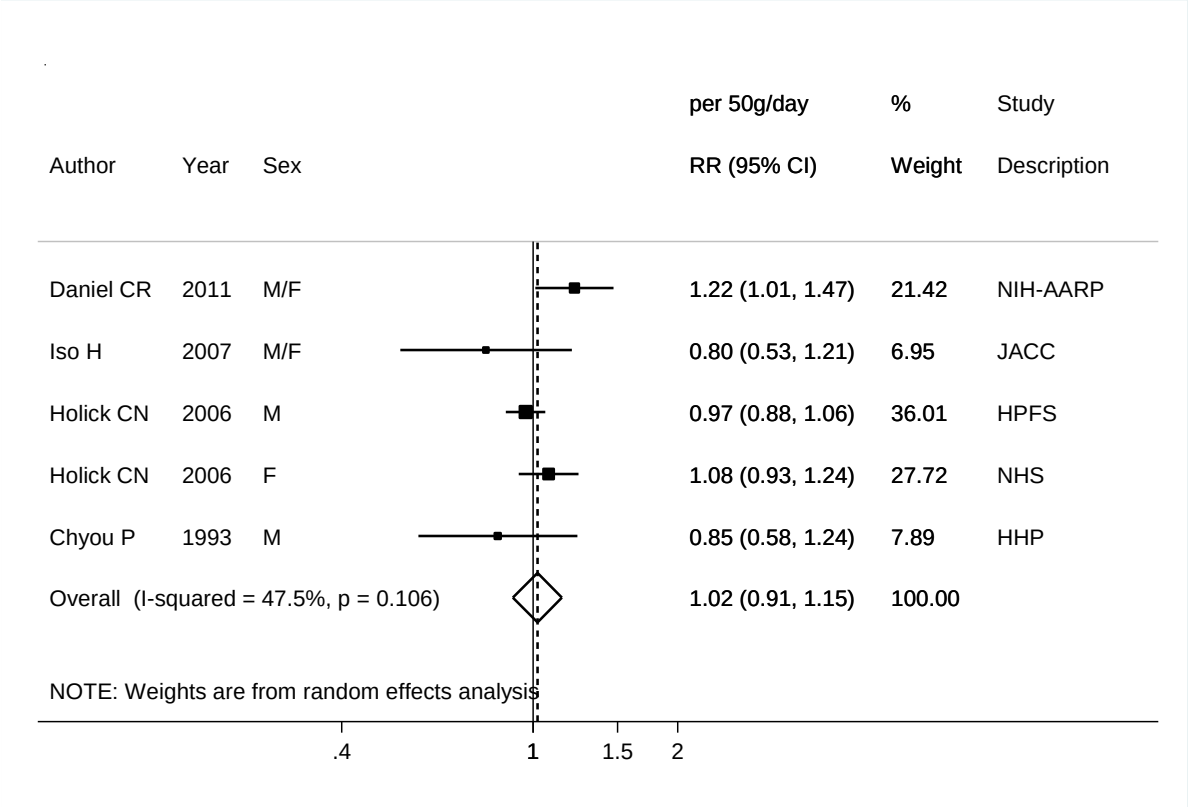
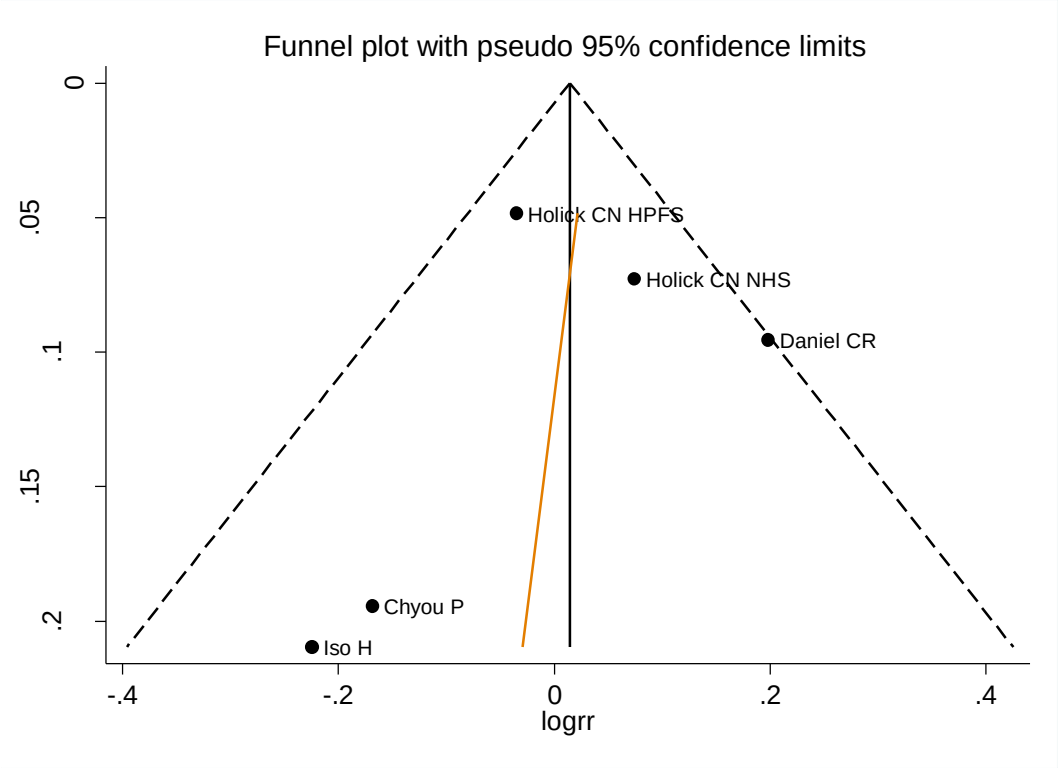


Figure 47 Funnel plot of processed fish intake and bladder cancer



Egger's test p= 0.26

Figure 48 Dose-response graph of fish and bladder cancer

2.7 Milk and dairy products

A total of eleven studies have investigated milk and dairy products in relation to bladder cancer. From these, ten studies reported on milk intake and one study reported on milk and dairy products combined, but not on milk intake (NIH-AARP; Park, 2009). Five out of the eleven studies reported on cheese intake, one study on yoghurt and three on cultured milk or fermented milk products.

The outcome is bladder cancer in all studies except two studies on milk intake that included also cases of cancers of the renal pelvis and urethers (JACC, Sakauchi, 2004; Honolulu Heart Program, Chyou, 1993).

Dairy products

Methods
Four new studies on dairy products that include milk, yogurt and cheese and bladder cancer were identified in the CUP.
The unit used in the dose-response analysis was 400g/day. One study (Park, 2009) reported the intake of dairy foods in servings/1000kcal/day, which were converted to g/day using the average between the median of the fifth and first quintile of dairy products intake for men and women respectively.

Main results
The summary RR per 400g/day of dairy products per day was 0.94 (95% CI: 0.87-1.01, I^2=0%, pheterogeneity=0.45, n=3).

Heterogeneity
There was no evidence of heterogeneity, I^2=0%, pheterogeneity=0.45.

Comparison with the Second Expert Report
In the 2005 SLR there was no analysis on dairy products and bladder cancer.

Published meta-analyses or pooled analyses
No published meta-analyses or pooled analyses were identified.

Table 48 Studies on dairy products intake identified during the CUP

Author/year	Country	Study name	Number of cases	Years of follow-up	Sex	RR	LCI	UCI	Contrast
Park Y, 2009	USA	NIH-ARRP	1417 men 264 women	7 years	M	0.86	0.72	1.02	1.4 vs. 0.2 servings/1000kcal/d
					F	1.45	0.97	2.18	1.6 vs. 0.2 servings/1000kcal/d
Keszei AP, 2009	Netherlands	Netherlands Cohort Study	1549	16.3 years	M/F	1.01	0.81	1.27	556 vs. 73 g/d

Larsson, 2008 (a)	Sweden	Swedish Mammography Cohort and Cohort of Swedish men	485	9.4 years	M/F	0.87	0.66	1.15	8.9 vs. 2.6 servings/d

Table 49 Overall evidence on dairy products intake and bladder cancer

SLR	Summary of evidence
2005 SLR	No study was identified.
CUP	Four new cohort studies reported on dairy intake and bladder cancer and showed no significant association.

Table 50 Summary of results of the dose-response meta-analysis of dairy products intake and bladder cancer

Bladder cancer		
	2005 SLR*	CUP
Studies (n)		3
Cases (n)		3451
Increment unit		Per 400g/day
RR (95% CI)		0.94 (0.87-1.01)
Heterogeneity (I^2, p-value)		I^2=0%, p=0.45

* No meta-analysis was conducted in the SLR.

Table 51 Inclusion/exclusion table for meta-analysis of dairy products intake and bladder cancer

WCRF code	Author	Year	Study design	Study name	Sex	Cancer outcome	2005 SLR	CUP dose-response	CUP H vs. L forest plot	Estimated values	Exclusion reason
BLA97216	Park Y	2009	Prospective cohort study	NIH-ARRP	M/F	Incidence	No	Yes	Yes	Person-years and number of cases per quintile. Weighted average intake men and women. Conversion to servings/d	
BLA97172	Keszei AP	2009	Prospective cohort study	Netherlands Cohort Study	M/F	Incidence	No	Yes	Yes	Conversion to servings/d	
BLA97157	SC	2008 (a)	Prospective cohort study	Swedish Mammography Cohort and Cohort of Swedish men	M/F	Incidence	No	Yes	Yes		

Figure 49 Highest versus lowest forest plot of dairy products intake and bladder cancer

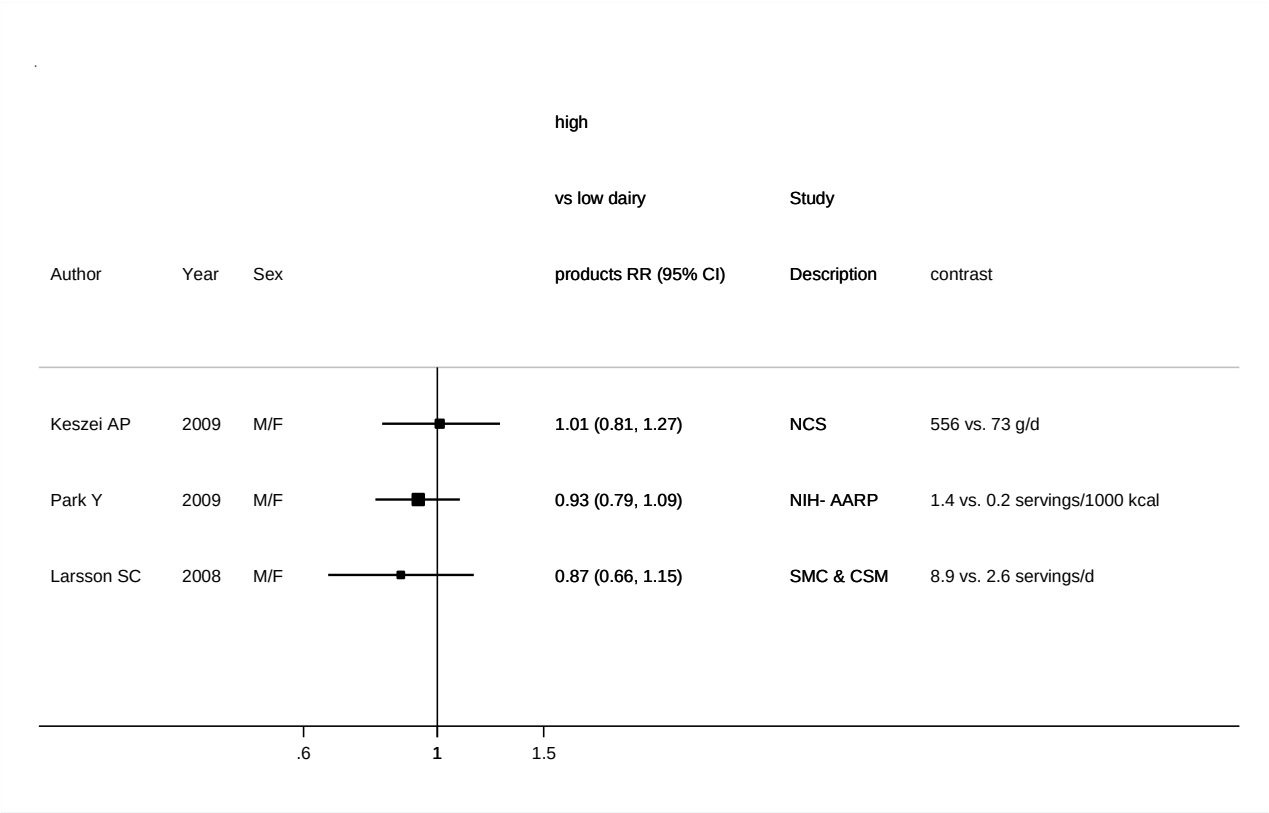


Figure 50 Dose-response meta-analysis of dairy products intake and bladder cancer, per 400g/day

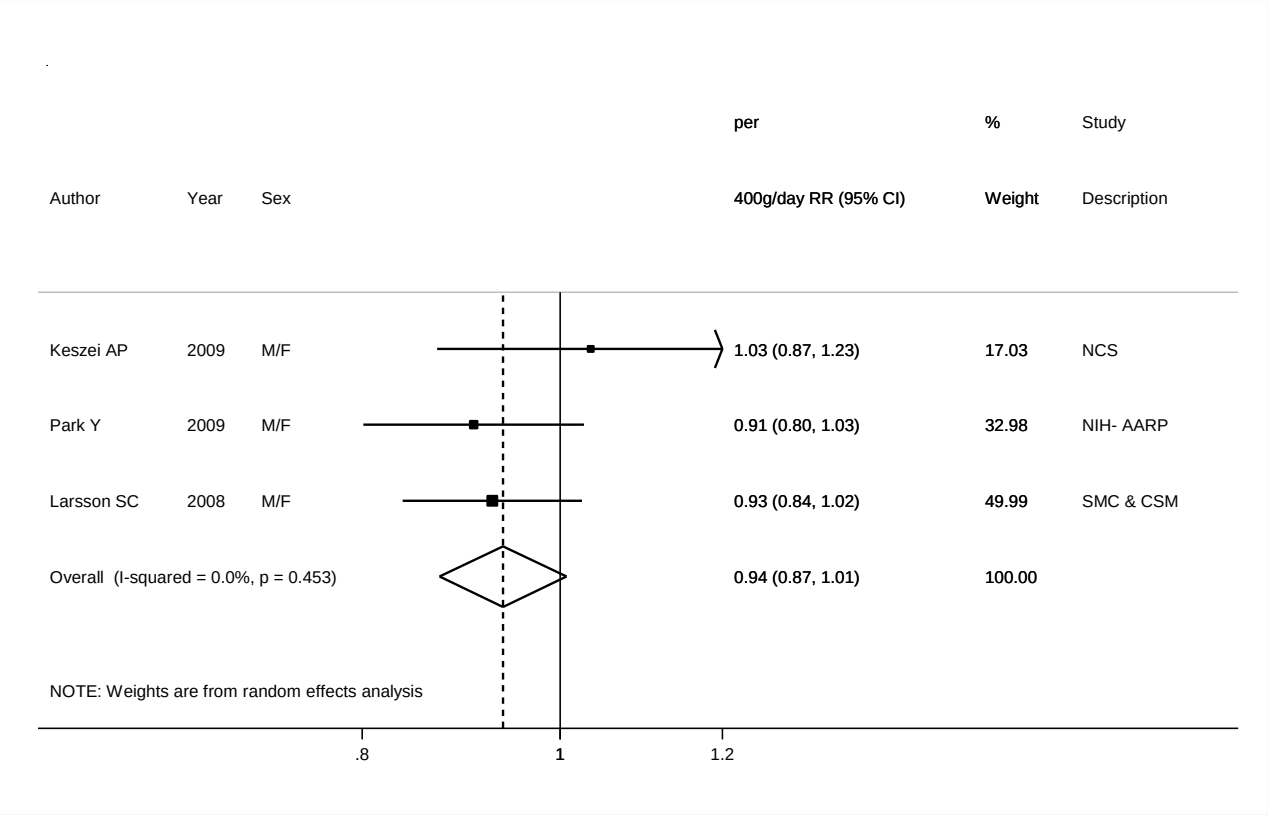
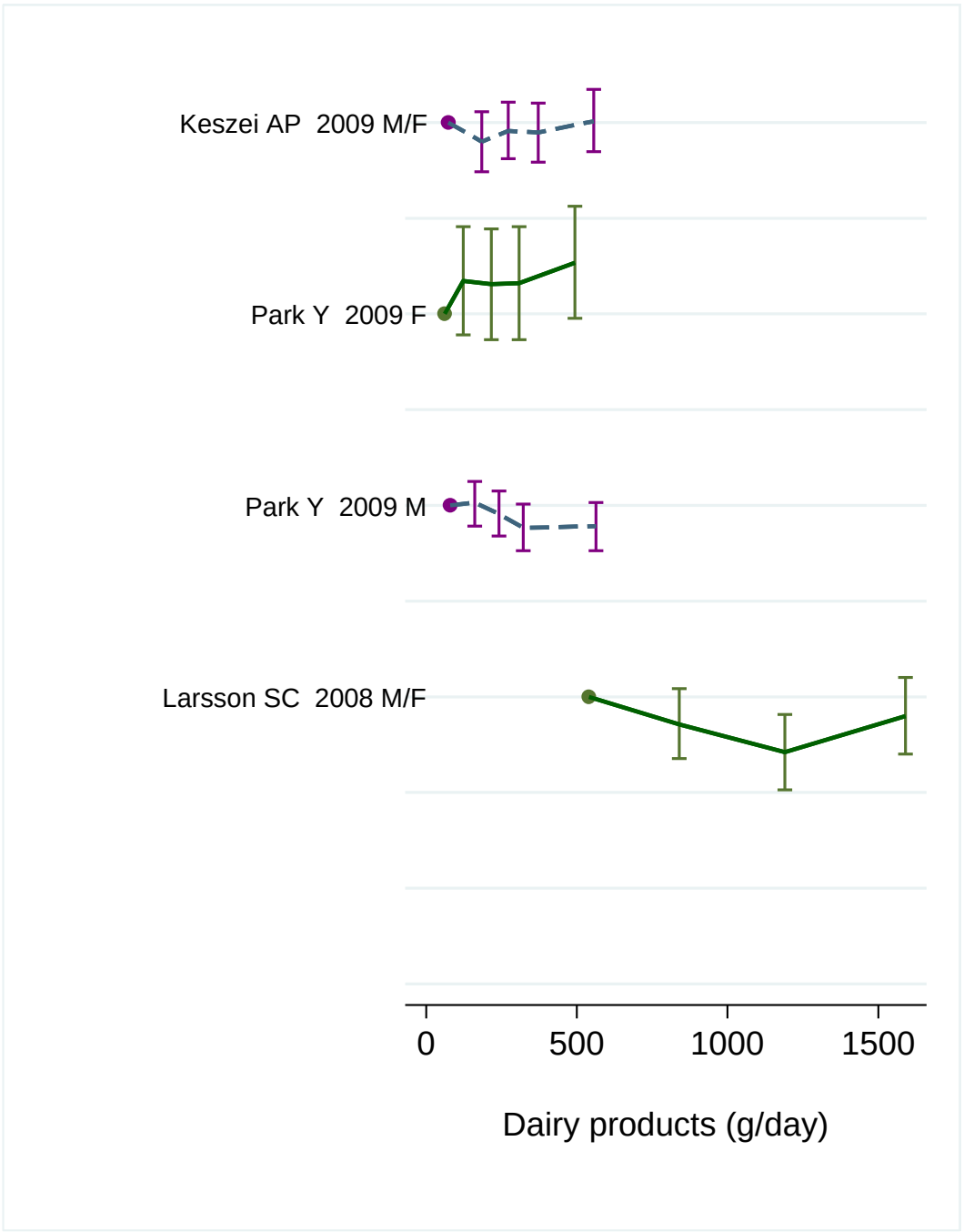


Figure 51 Dose-response graph of dairy intake and bladder cancer



2.7.1 Milk

Methods

Ten studies were identified from which five studies were identified during the CUP. One updated publication of the JACC study was also identified in the CUP. The unit used in the dose-response analysis was one serving/day. Studies reporting in millilitres of milk were converted to servings, using as conversion unit 200ml equivalent to one serving of milk. One study (Keszei AP, 2009) reported the intake of non-fermented milk products; the other studies reported the intake of milk and milk beverages.

Main results

The summary RR per 1 serving of milk per day (200ml) was 0.98 (95% CI: 0.90-1.05, I^2=38.8%, pheterogeneity=0.15, n=7). Egger's test of publication bias was not significant (p=0.14) but the funnel plot shows that the two smallest studies (in Asian populations) found stronger inverse relationships than the other studies. The summary RR per 100ml/day of milk was 0.99 (95% CI: 0.95-1.02, I^2=38.8%, pheterogeneity=0.15, n=7). There was no evidence of non-linearity (p=0.46).

Heterogeneity

There was evidence of moderate heterogeneity, I^2=38.8%, pheterogeneity=0.15.

Comparison with the Second Expert Report

In the 2005 SLR the evidence relating milk to bladder cancer was considered limited suggestive of a decrease risk.

Published meta-analyses or pooled analyses

A meta-analysis of 19 published case-control and cohort studies reported decreased risk of bladder cancer (OR= 0.84; 95% CI: 0.71-0.97) when comparing the highest with the lowest category of milk intake (Mao, 2011). When the analysis was restricted to the cohort studies the overall RR was 0.88 (0.76-1.0). A significant inverse association was observed in Asian (OR=0.60; 95% CI: 0.40-0.81) but not in North American (OR=0.89; 95% CI: 0.76-1.03), and European studies (OR=1.05; 95% CI: 0.85-1.26). Another meta-analysis including 14 cohort and case-control studies on milk (involving 4879 cases) and 6 studies on dairy products (3087 cases) found no significant association of bladder cancer with milk intake (RR= 0.89, 95% CI 0.77-1.02) and dairy products (RR= 0.95, 95% CI 0.71-1.27) (Li, 2011). An inverse association was detected in Japanese populations (RR= 0.56, 95% CI 0.40-0.80).

Table 52 Studies on milk intake identified during the CUP

Author/year	Country	Study name	Number of cases	Years of follow-up	Sex	RR	LCI	UCI	Contrast
Ros MM, 2011	Europe	EPIC	513	9.3 years	M/F	1.04	0.83	1.31	Men ≥226 vs. <45 ml/d

									Women ≥203 vs. 27 ml/d
Keszei AP, 2009	Netherlands	NCS	1549	16.3 years	M/F	1.08	0.86	1.39	436 vs. 27 g/d
Iso H, 2007	Japan	JACC study	118	12 years	M	0.67	0.40	1.11	≥5 vs. <3 servings/w
					F	0.63	0.28	1.41	
Larsson, 2008 (a)	Sweden	Swedish Mammography Cohort and Cohort of Swedish men	485	9.4 years	M/F	0.97	0.75	1.26	≥3.2 vs. <0.2 servings/d

Table 53 Overall evidence on milk intake and bladder cancer

SLR	Summary of evidence
2005 SLR	4 studies were included in the meta analysis. One study reported a protective effect of milk on bladder cancer mortality.
CUP	Five new cohort studies reported on milk intake and bladder cancer and showed no significant association.

Table 54 Summary of results of the dose-response meta-analysis of milk intake and bladder cancer

Bladder cancer		
	2005 SLR	CUP
Studies (n)	4	7
Cases (n)	527	3013
Increment unit	Per 1 serving/day	Per 1 serving/day
RR (95% CI)	0.82 (0.67-0.99)	0.98 (0.90-1.05)
Heterogeneity (I^2, p-value)	I^2=57%, p=0.07	I^2=38.8%, p=0.15
Stratified analysis		
Men		0.93 (0.81-1.08)
Heterogeneity (I^2, p-value)		I^2=49.3%, p=0.12, n=4
Women		0.90 (0.39-2.10)
Heterogeneity (I^2, p-value)		I^2=31.5%, p=0.23, n=2

Table 55 Inclusion/exclusion table for meta-analysis of milk intake and bladder cancer

WCRF code	Author	Year	Study design	Study name	Sex	Cancer outcome	2005 SLR	CUP dose-response	CUP H vs. L forest plot	Estimated values	Exclusion reason
BLA97177	Ros MM	2011	Prospective cohort study	EPIC	M/F	Incidence	No	Yes	Yes	Person-years. Weighted average intake men and women. Conversion to servings/d	
BLA97172	Keszei AP	2009	Prospective cohort study	Netherlands Cohort Study	M/F	Incidence	No	Yes	Yes	Conversion to servings/d	
BLA97203	Iso H	2007	Prospective cohort study	Japan Collaborative Cohort Study (JACC Study)	M/F	Mortality	No	Yes	Yes	Midpoints.	
BLA97157	Larsson SC	2008(a)	Prospective cohort study	Swedish Mammography Cohort and Cohort of Swedish men	M/F	Incidence	No	Yes	Yes		
BLA10545	Sakauchi F	2004	Prospective cohort study	Japan Collaborative Cohort Study (JACC)	M/F	Mortality	Yes	No	No		Superseded by Iso H, 2007
BLA02708	Nagano J	2000	Prospective cohort study	Life Span Study, atomic bomb survivors, Japan	M/F	Incidence/Mortality	No	No	Yes		Insufficient data
BLA02841	Michaud D	1999	Prospective cohort study	Health Professionals Follow-up Study	M	Incidence/Mortality	Yes	Yes	No		Only reported continuous results

BLA00777	Chyou PH	1993	Prospective cohort study	Honolulu Heart Program	M	Incidence/ Mortality	Yes	Yes	Yes	Person-years. Midpoints.	
BLA01090	Mills P	1991	Prospective cohort study	Adventists Health Study	M/F	Incidence	Yes	No	No		Insufficient data. Only data on whole milk.
BLA01190	Ursin G	1990	Prospective cohort study	Norwegian Cohort Study	M/F	Incidence/Mortality	Yes	No	Yes		Insufficient data. Adjusted RR and confidence intervals available for male and included in the HvL forest plot

Figure 52 Highest versus lowest forest plot of milk intake and bladder cancer

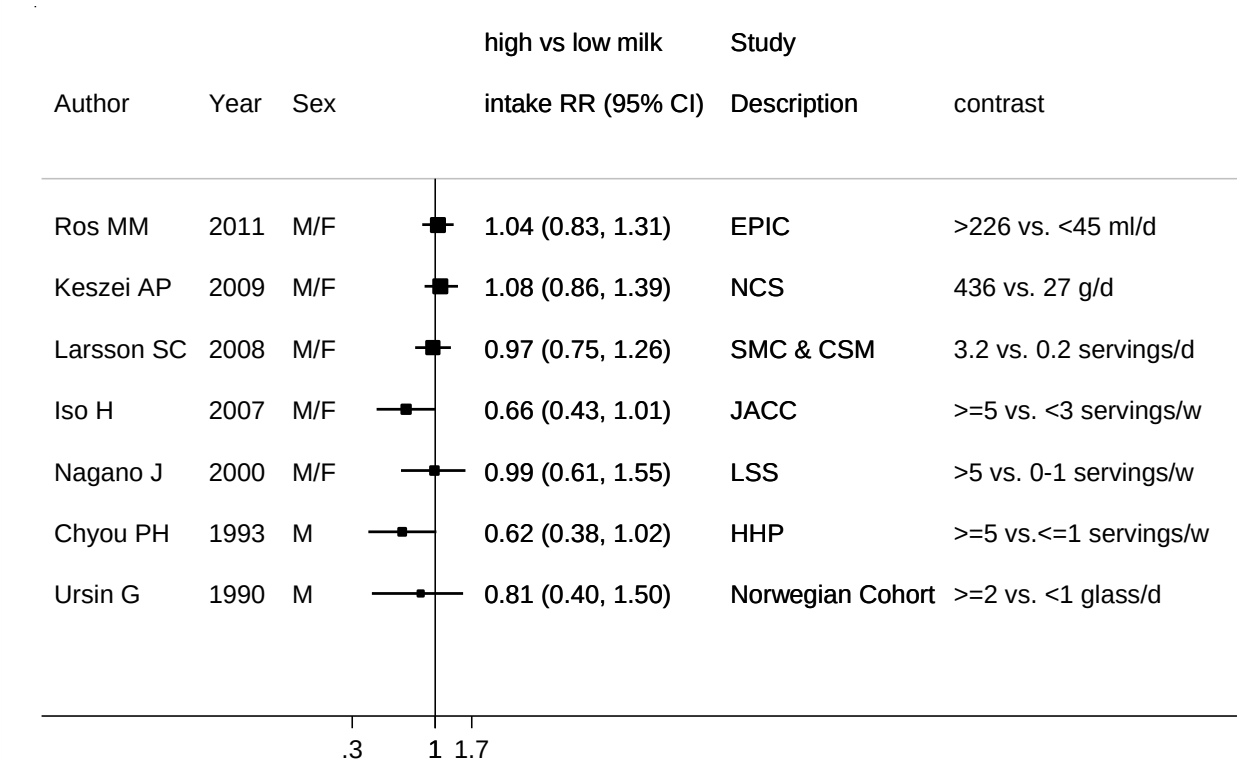


Figure 53 Dose-response meta-analysis of milk intake and bladder cancer, per 1serving/day

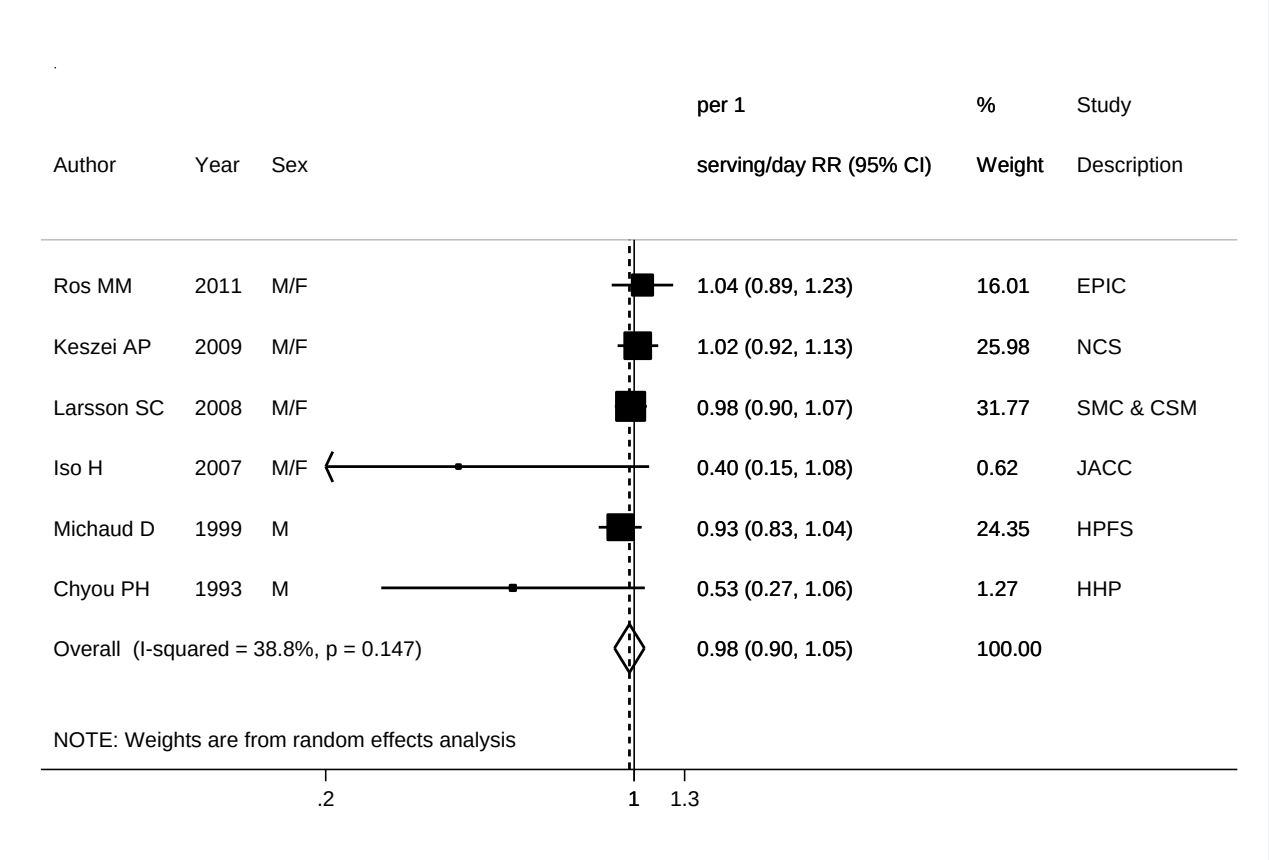
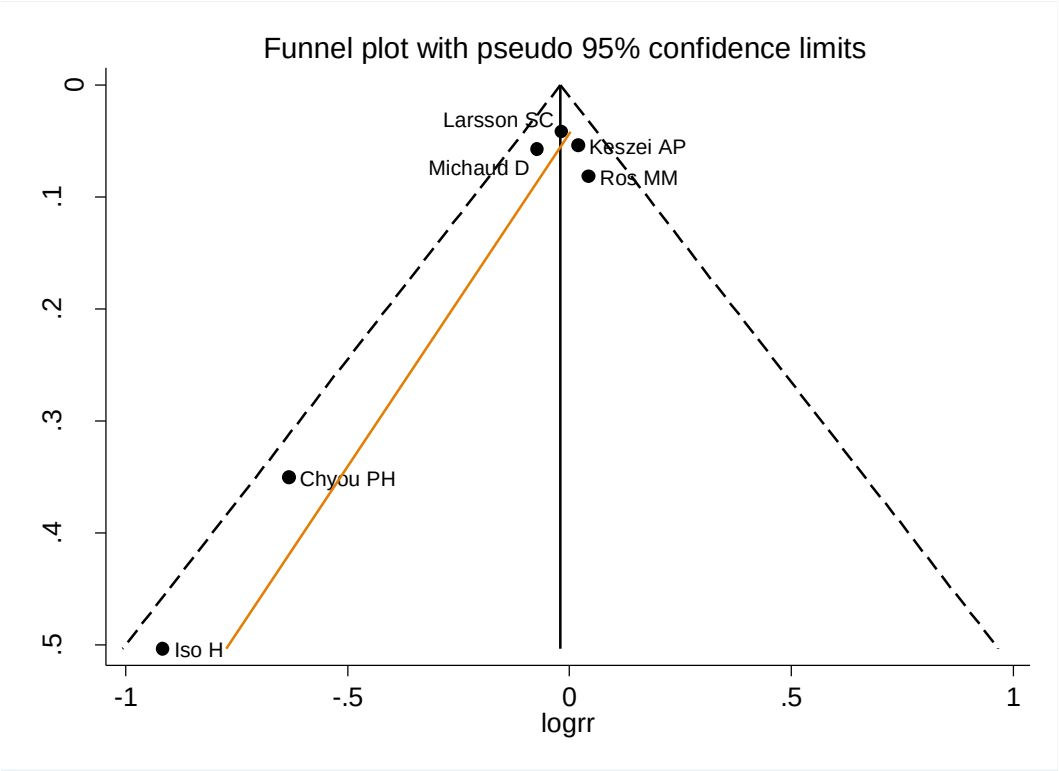


Figure 54 Funnel plot of milk intake and bladder cancer



Egger's test p=0.14

Figure 55 Dose-response graph of milk intake and bladder cancer

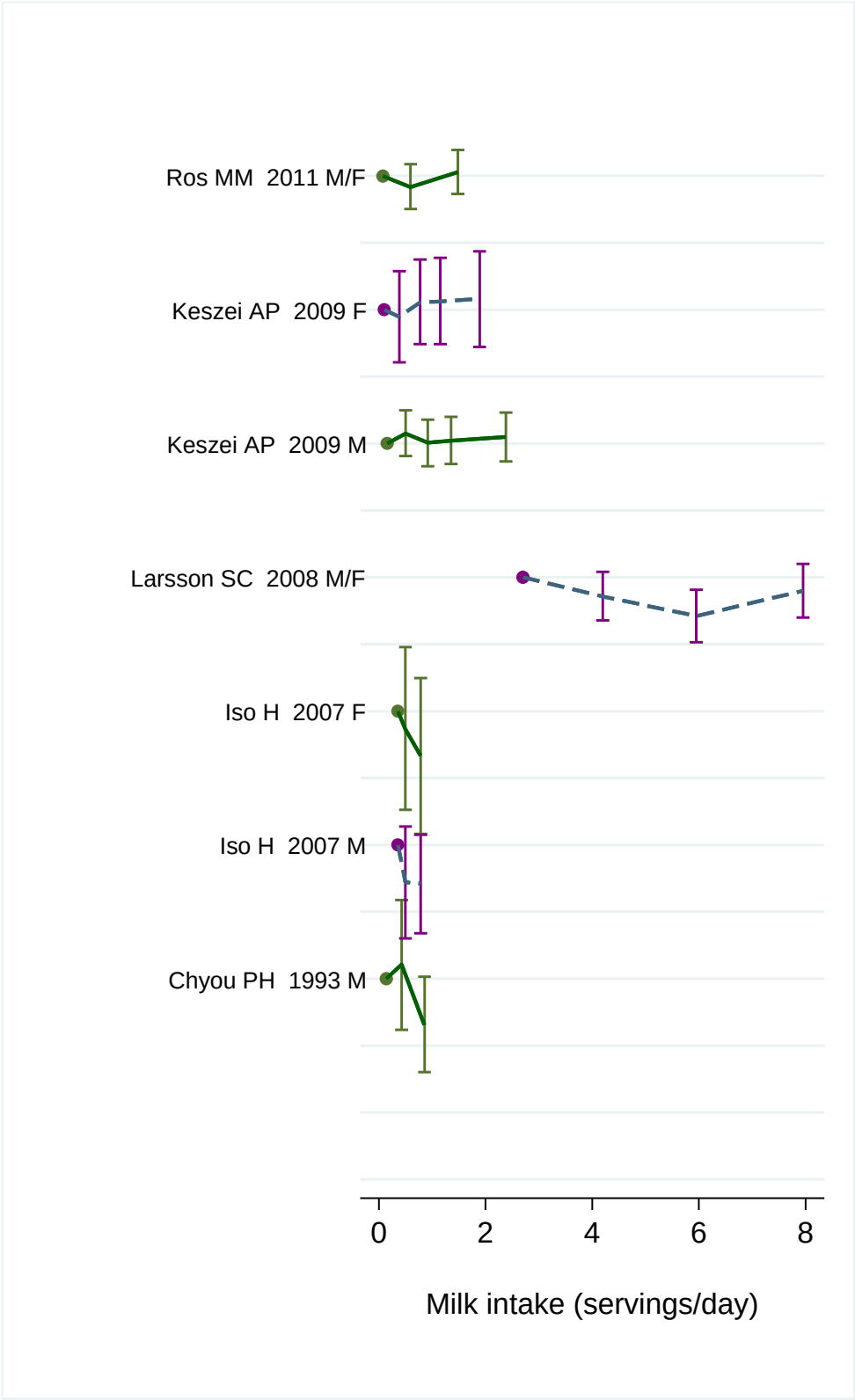
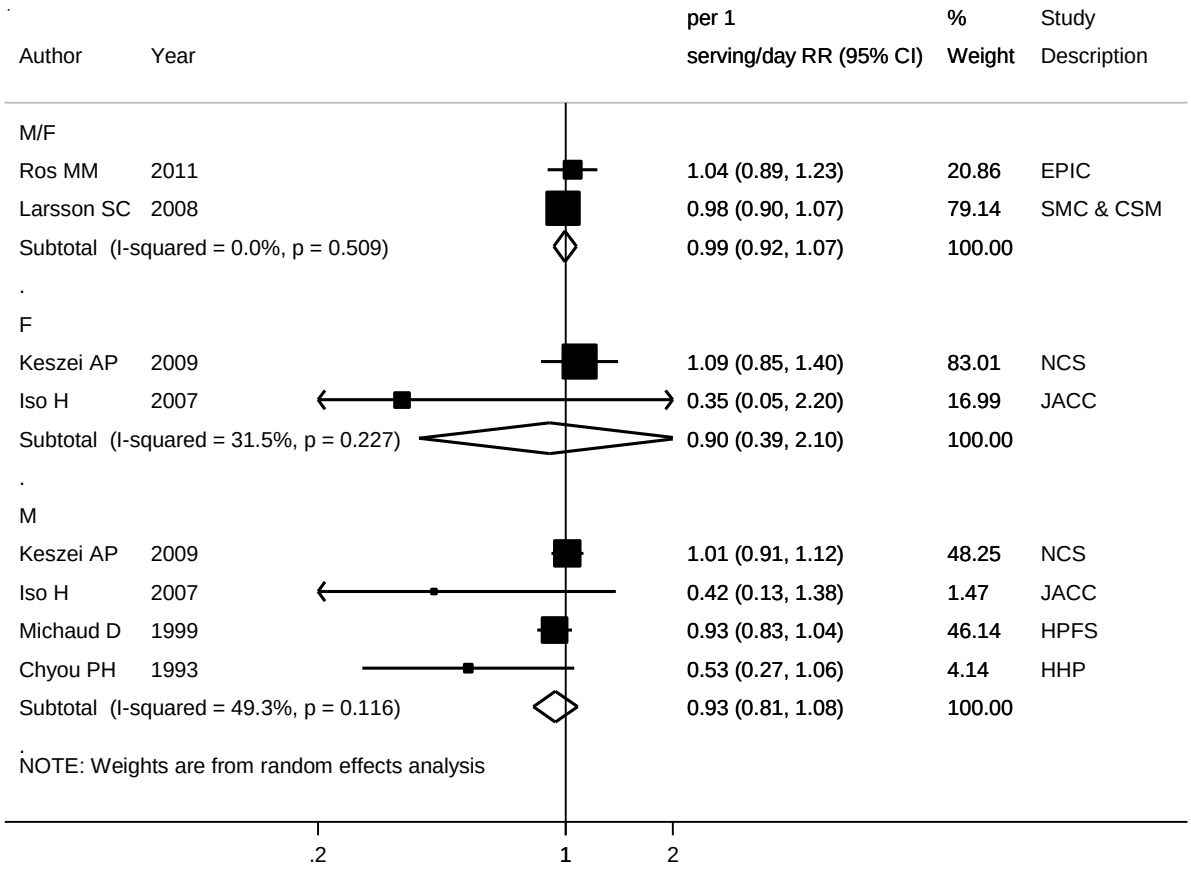


Figure 56 Dose-response meta-analysis of milk intake and bladder cancer, per 1serving/day, stratified by sex



2.7.2 Cheese

Methods

Five studies reported on cheese and bladder cancer (Keszei, 2009; Larsson, 2008a; Iso 2007; Mills, 1991). Four studies were identified in the CUP. One updated publication of the JACC study was also identified in the CUP. The unit used in the dose-response analysis was one serving/day. Studies reporting in grams per day were converted to servings, using as conversion unit 35g equivalent to one serving of cheese.

Main results

The summary RR per 1 serving of cheese per day was 1.02 (95% CI: 0.88-1.18, I^2=60.6%, pheterogeneity=0.08, n=4).

Heterogeneity

There was evidence of high heterogeneity (I^2=60.6%, pheterogeneity=0.08).

Comparison with the Second Expert Report

In the SLR two studies (Sakauchi, 2004; Mills, 1991) found a non-significant association between cheese and bladder cancer.

Published meta-analyses or pooled analyses

No published meta-analyses or pooled analyses were identified.

Table 56 Studies on cheese intake identified during the CUP

Author/year	Country	Study name	Number of cases	Years of follow-up	Sex	RR	LCI	UCI	Contrast
Keszei AP, 2010	Netherlands	Netherlands Cohort Study	1549	16.3 years	M/F	1.19	0.93	1.52	56 vs. 1 g/d
Iso H, 2007	Japan	JACC study	118	12 years	M	0.26	0.04	1.88	>3-4 vs. <1 servings/w
					F	0.44	0.06	3.32	
Larsson, 2008(a)	Sweden	Swedish Mammography Cohort and Cohort of Swedish men	485	9.4 years	M/F	0.78	0.58	1.07	6 vs. 1 servings/d

Table 57 Overall evidence on cheese intake and bladder cancer

SLR	Summary of evidence
2005 SLR	2 studies were identified, only one study quantified the results.
CUP	Three new cohort studies reported on milk intake and bladder cancer and showed no significant association.

Table 58 Summary of results of the dose-response meta-analysis of cheese intake and bladder cancer

Bladder cancer		
	2005 SLR*	CUP
Studies (n)		4
Cases (n)		2152
Increment unit		Per 1 serving/day
RR (95% CI)		1.02 (0.88-1.18)
Heterogeneity (I^2, p-value)		I^2=60.6%, p=0.08

*No meta-analysis was conducted in the SLR.

Table 59 Inclusion/exclusion table for meta-analysis of cheese intake and bladder cancer

WCRF code	Author	Year	Study design	Study name	Sex	Cancer outcome	2005 SLR	CUP dose-response	CUP H vs. L forest plot	Estimated values	Exclusion reason
BLA97172	Keszei AP	2009	Prospective cohort study	Netherlands Cohort Study	M/F	Incidence	No	Yes	Yes	Conversion to servings/d	
BLA97203	Iso H	2007	Prospective cohort study	Japan Collaborative Cohort Study (JACC Study)	M/F	Mortality	No	Yes	Yes	Midpoints. Conversion to servings/d	
BLA97157	Larsson SC	2008(a)	Prospective cohort study	Swedish Mammography Cohort and Cohort of Swedish men	M/F	Incidence	No	Yes	Yes	-	
BLA10545	Sakauchi F	2004	Prospective cohort study	Japan Collaborative Cohort Study (JACC)	M/F	Mortality	Yes	No	No		Superseded by Iso H, 2007
BLA01090	Mills P	1991	Prospective cohort study	Adventists Health Study	M/F	Incidence	Yes	No	No		Insufficient data

Figure 57 Highest versus lowest forest plot of cheese intake and bladder cancer

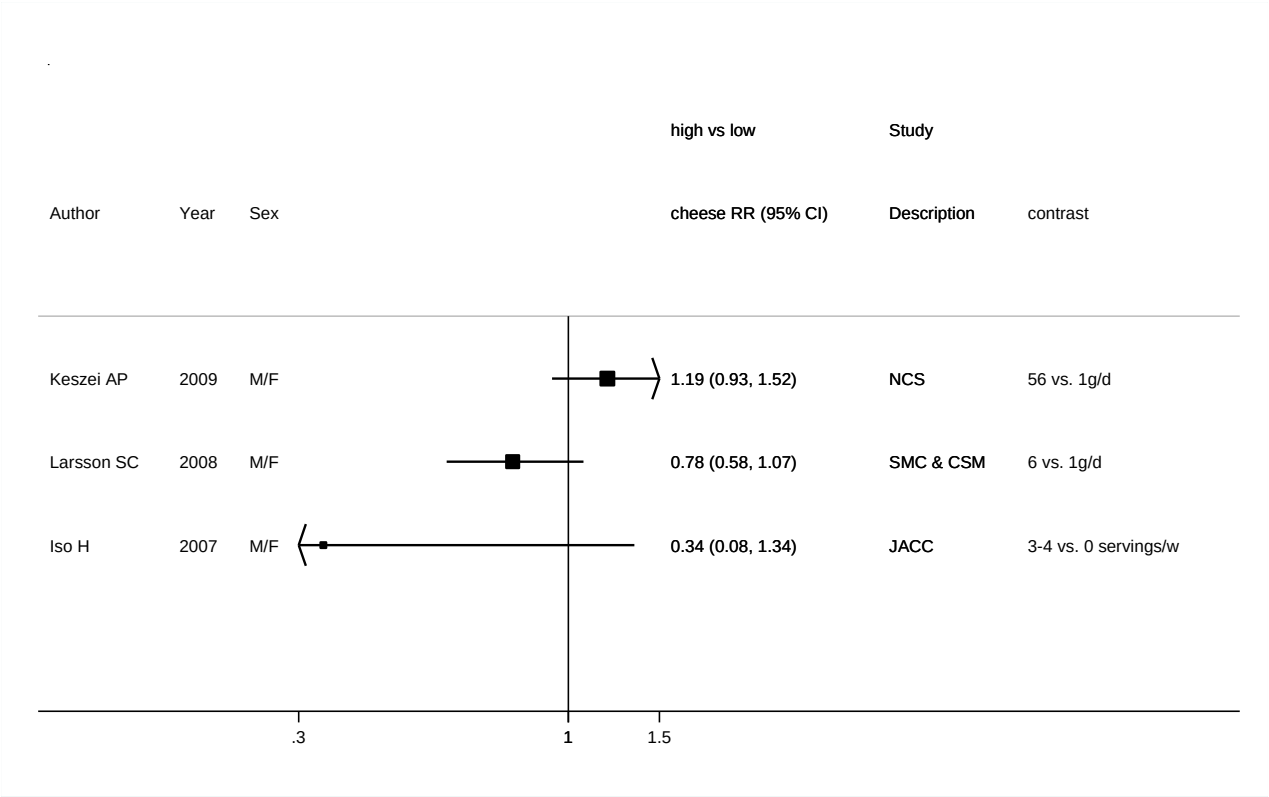


Figure 58 Dose-response meta-analysis of cheese intake and bladder cancer, per 1serving/day

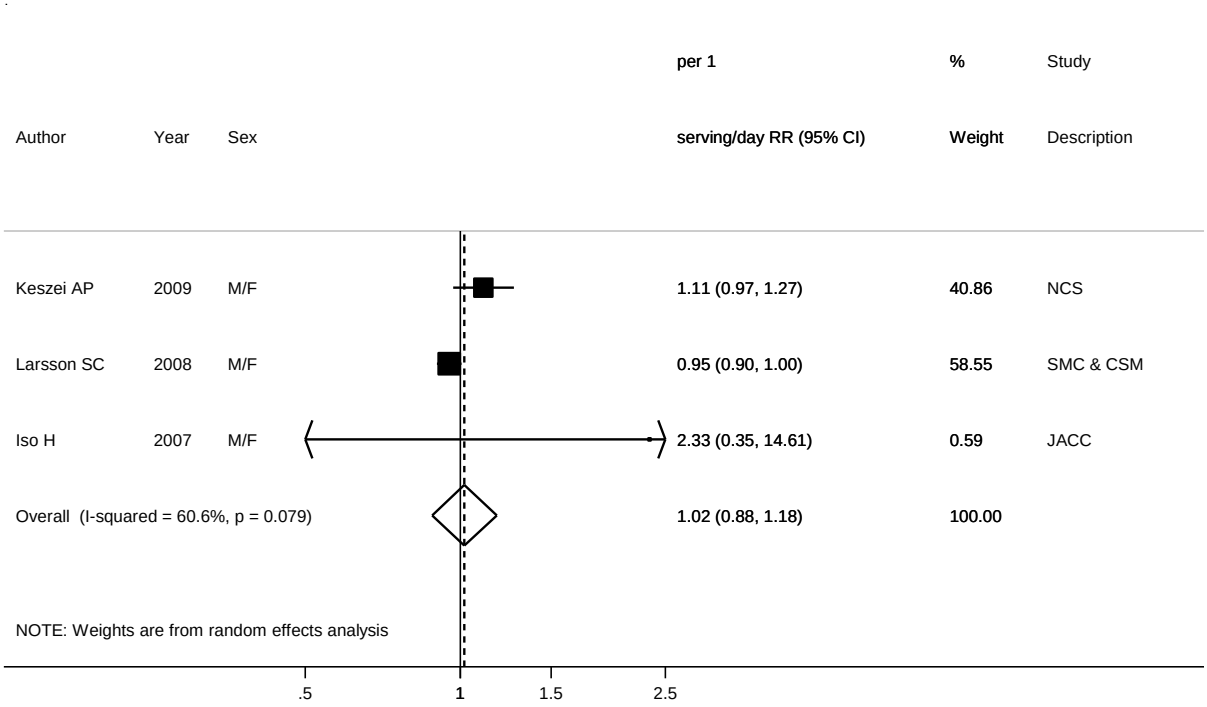
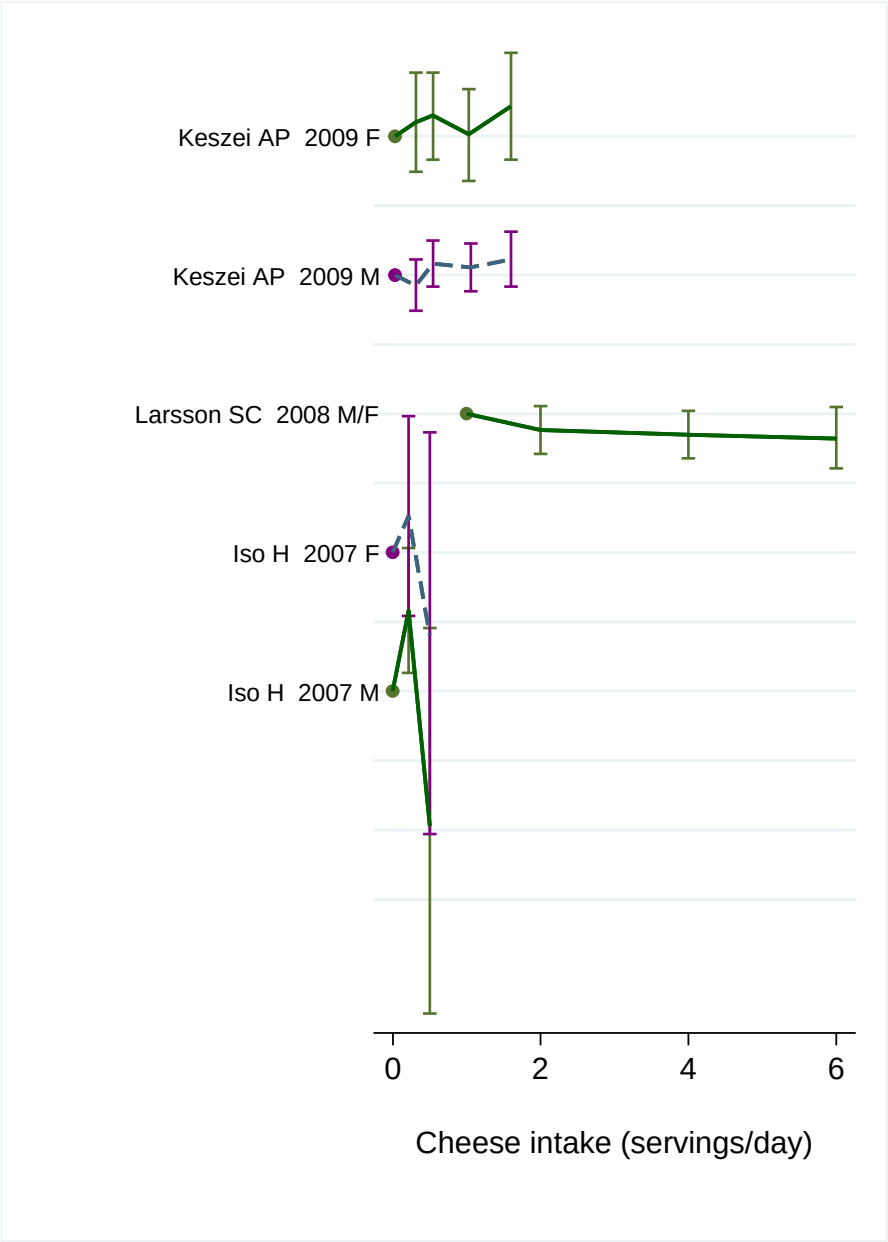


Figure 59 Dose-response graph of cheese intake and bladder cancer



2.7.3 Yoghurt and fermented milk products

Methods

Four studies (three articles) were on yoghurt and fermented milk products and bladder cancer (Keszei, 2009; Larsson, 2008a; Iso 2007). The three studies were identified during the CUP. One updated publication of the JACC study was also identified in the CUP. In this section were included studies that reported results on yoghurt, fermented milk products or cultured milk and bladder cancer risk. The unit used in the dose-response analysis was one serving/day. Studies reporting in grams per day were converted to servings, using as conversion unit 200g equivalent to one serving of yoghurt.

Main results

The summary RR per 1 serving of yoghurt and fermented milk products per day was 0.93 (95% CI: 0.75-1.17, I^2=66.0%, pheterogeneity=0.05, n=4).

Heterogeneity

There was evidence of high heterogeneity (I^2=61.5%, pheterogeneity=0.07).

Comparison with the Second Expert Report

In the 2005 SLR there was only one cohort study (Sakauchi, 2004) on yoghurt and bladder cancer.

Published meta-analyses or pooled analyses

No published meta-analyses or pooled analyses were identified.

Table 60 Studies on yoghurt and fermented milk products intake identified during the CUP

Author/year	Country	Study name	Number of cases	Years of follow-up	Sex	RR	LCI	UCI	Contrast
Keszei AP, 2009	Netherlands	Netherlands Cohort Study	1549	16.3 years	M/F	0.97	0.79	1.19	248 vs. 0 g/d
Iso H, 2007	Japan	JACC study	118	12 years	M	0.36	0.05	2.65	≥5 vs. <3 servings/w
					F	0.60	0.08	4.49	
Larsson, 2008(a)	Sweden	Swedish Mammography Cohort and Cohort of Swedish men	485	9.4 years	M/F	0.62	0.46	0.85	2 vs. 0 servings/d

Table 61 Overall evidence on yoghurt and fermented milk products and bladder cancer

SLR	Summary of evidence
2005 SLR	One study was identified and found non-significant association between yoghurt and bladder cancer.

CUP	Four new cohort studies reported on yoghurt and fermented products and bladder cancer, three showed a non-significant association and one showed a protective effect.

Table 62 Summary of results of the dose-response meta-analysis of yoghurt and fermented milk products and bladder cancer

Bladder cancer		
	2005 SLR*	CUP
Studies (n)		4
Cases (n)		2152
Increment unit		Per 1 serving/day
RR (95% CI)		0.93 (0.75-1.17)
Heterogeneity (I^2, p-value)		I^2=66.0%, p=0.05

* No meta-analysis was conducted in the SLR.

Table 63 Inclusion/exclusion table for meta-analysis of yoghurt and fermented milk products and bladder cancer

WCRF code	Author	Year	Study design	Study name	Sex	Cancer outcome	2005 SLR	CUP dose-response	CUP H vs. L forest plot	Estimated values	Exclusion reason
BLA97172	Keszei AP	2009	Prospective cohort study	Netherlands Cohort Study	M/F	Incidence	No	Yes	Yes	Conversion to servings/d	
BLA97203	Iso H	2007	Prospective cohort study	Japan Collaborative Cohort Study (JACC Study)	M/F	Mortality	No	Yes	Yes	Midpoints. Conversion to servings/d	
BLA97157	Larsson SC	2008(a)	Prospective cohort study	Swedish Mammography Cohort and Cohort of Swedish men	M/F	Incidence	No	Yes	Yes		
BLA10545	Sakauchi F	2004	Prospective cohort study	Japan Collaborative Cohort Study (JACC)	M/F	Mortality	Yes	No	No		Superseded by Iso H, 2007

Figure 60 Highest versus lowest forest plot of yoghurt and fermented milk products and bladder cancer

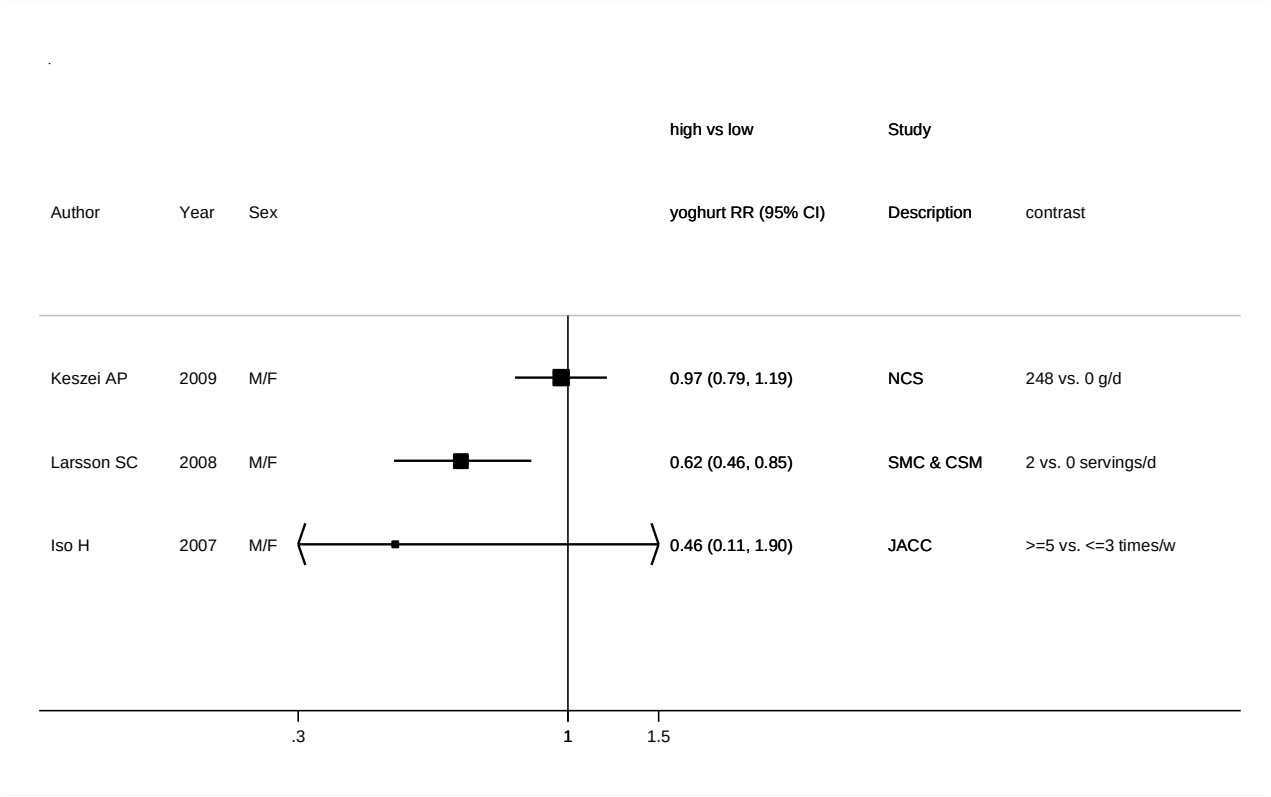


Figure 61 Dose-response meta-analysis of yoghurt and fermented milk products and bladder cancer, per 1serving/day

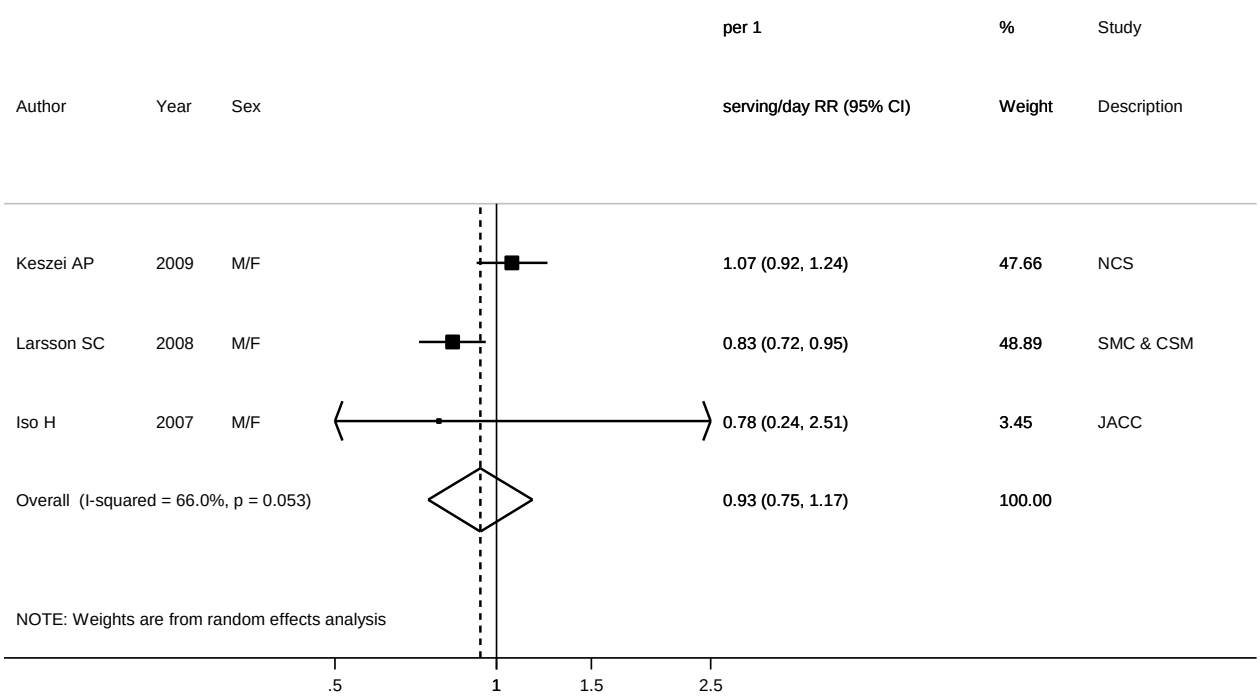
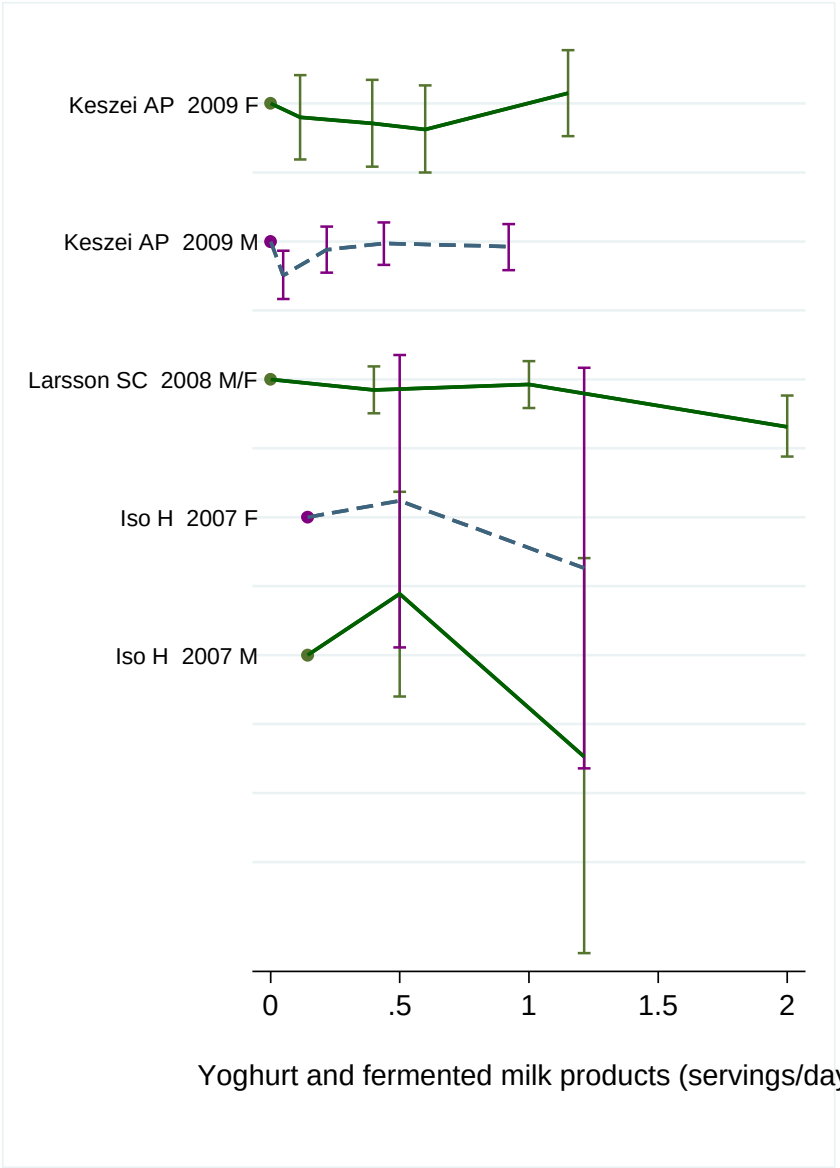


Figure 62 Dose-response graph of yoghurt and fermented milk products and bladder cancer



3 Beverages

3.1 Total fluid intake

Methods
Five studies from six articles were identified. Two studies were identified during the CUP, one was new and another was an updated publication of the HPFS.

Main results
The summary RR per 1000 ml per day was 1.04 (95% CI: 0.96-1.12, I^2=52.3%, pheterogeneity=0.12, n=3).
There was not enough data to do analyses stratified by smoking status. Two studies stratified by smoking status (Ros, 2011; Zhou, 2012) and found a non-significant association.

Heterogeneity
There was evidence of moderate heterogeneity, I^2=52.3%, pheterogeneity=0.12.

Comparison with the Second Expert Report
In the 2005 SLR the overall result of the meta-analysis showed a non-significant association between fluid intake and bladder cancer, the conclusion was limited- no conclusion.

Published meta-analyses or pooled analyses
No published meta-analyses or pooled analyses were identified.

Table 64 Studies on total fluid intake identified during the CUP

Author/year	Country	Study name	Number of cases	Years of follow-up	Sex	RR	LCI	UCI	Contrast
Ros MM, 2011	Europe	EPIC	513	9.3 years	M/F	1.12	0.86	1.45	Men ≥2425 vs. <1735 ml/d Women ≥ 2046 vs. <1438ml/d
						1.01	1.0	1.02	Per 100ml
Zhou J, 2012	USA	HPFS	823	22 years	M	1.02	0.79	1.32	>2531 vs. <1290 ml/d

Table 65 Overall evidence on fluid intake and bladder cancer

SLR	Summary of evidence
2005 SLR	3 cohort studies were included in the meta analysis and found a non-

	significant association between fluid intake and bladder cancer.
CUP	Two studies reported on fluid intake and bladder cancer and showed no significant association.

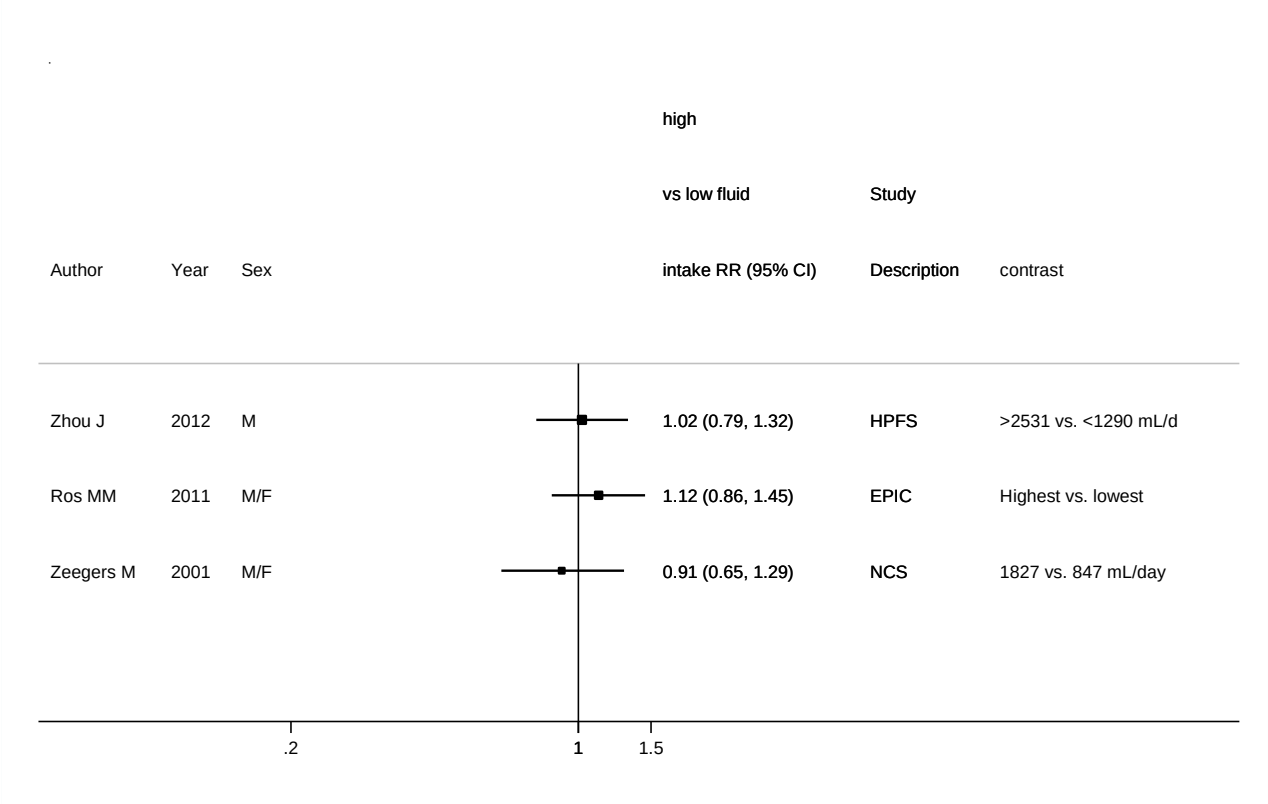
Table 66 Summary of results of the dose-response meta-analysis of fluid intake and bladder cancer

Bladder cancer		
	2005 SLR	CUP
Studies (n)	3	3
Cases (n)	1101	1905
Increment unit	Per litre/day	Per 1000ml/d
RR (95% CI)	0.86 (0.68-1.08)	1.04 (0.96-1.12)
Heterogeneity (I^2, p-value)	I^2=49.9%, p=0.14	52.3%, p=0.12

Table 67 Inclusion/exclusion table for meta-analysis of fluid intake and bladder cancer

WCRF code	Author	Year	Study design	Study name	Sex	Cancer outcome	2005 SLR	CUP dose-response	CUP H vs. L forest plot	Estimated values	Exclusion reason
BLA97184	Zhou J,	2012	Prospective cohort study	Health Professionals Follow-up Study	M	Incidence	No	Yes	Yes	Midpoints	
BLA97177	Ros MM	2011		EPIC	M/F	Incidence	No	Yes	Yes	Person-years. Weighted average intake range for men and women.	
BLA00367	Zeegers M	2001	Prospective cohort study	Netherlands Cohort Study	M/F	Incidence	Yes	Yes	Yes	Person-years	
BLA10670	Michaud D	2004	Prospective cohort study	ATBC Study	M	Incidence	Yes	No	No		Only results stratified by toenail arsenic level
BLA02841	Michaud D	1999(b)	Prospective cohort study	Health Professionals Follow-up Study	M	Incidence/Mortality	Yes	No	No		Superseded by Zhou 2012
BLA01090	Mills P	1991	Prospective cohort study	California Seventh-Day Adventists 1976-1982	M/F	Incidence	Yes	No	No		Insufficient data.

Figure 63 Highest versus lowest forest plot of fluid intake and bladder cancer



For Ros MM, 2011 the contrast was ≥2425vs. <1735 ml/d for men and ≥2046 vs. <1438 ml/d for women.

Figure 64 Dose-response meta-analysis of fluid intake and bladder cancer, per 1000ml/day

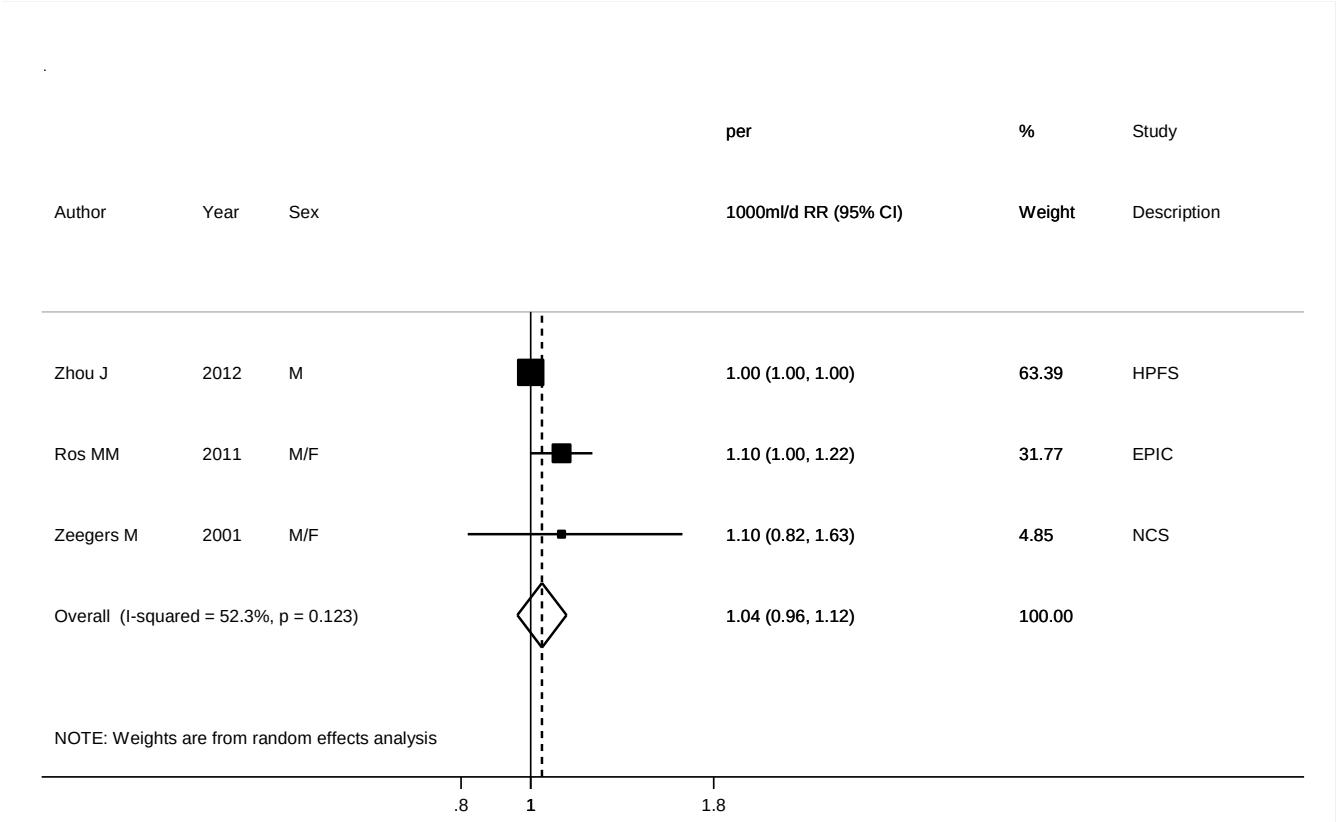
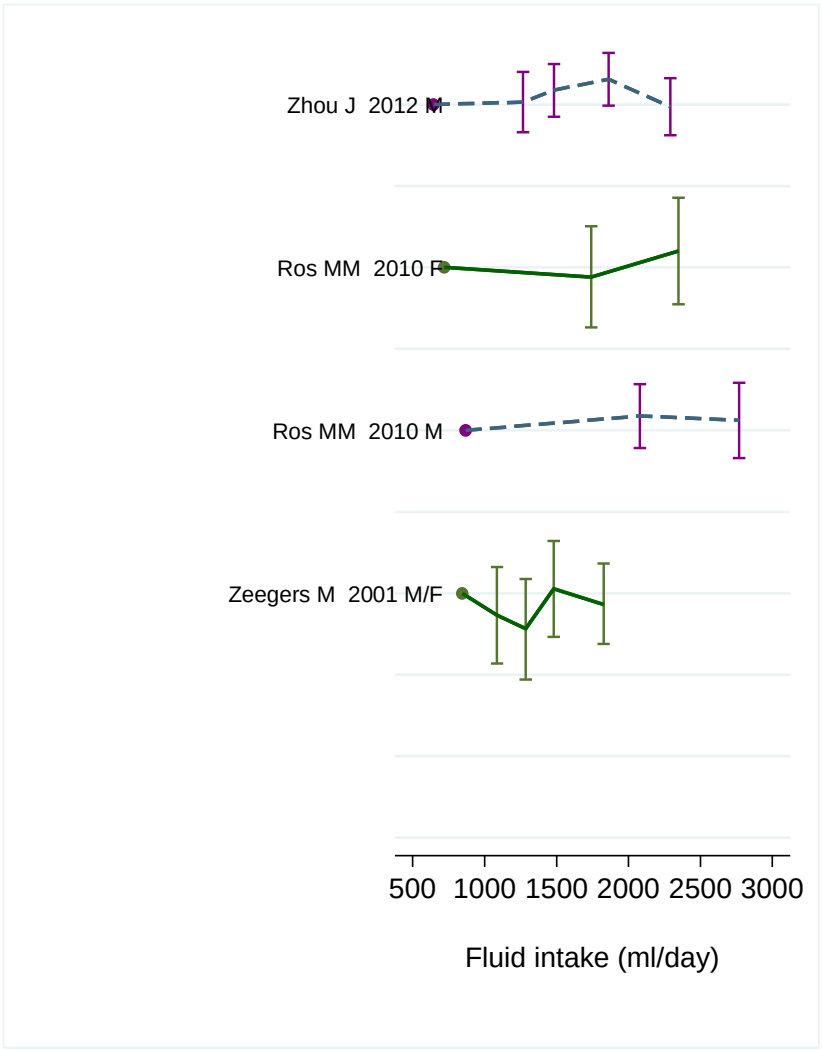


Figure 65 Dose-response graph of fluid intake and bladder cancer



3.6.1 Coffee

Methods

15 articles from 14 studies were identified; three were identified in the CUP. One updated publication of the JACC study was also identified in the CUP. The unit used in the dose-response analysis was one cup/day. Studies reporting in ml of coffee were converted to cups of coffee, using as conversion unit 200ml equivalent to 1 cup of coffee.

One study was on cancers of the lower urinary tract -70 bladder cancer cases out of 83 cases- (Chyou, 1993). All except four studies (Iso, 2007; Tripathi, 2002; Stenvold, 1994; Snowdon, 1984) adjusted the results by smoking status or smoking duration and dose.

Main results

The summary RR per 1 cup of coffee per day was 1.02 (95% CI: 0.97-1.06, I^2=34.1%, pheterogeneity=0.13, n=11).

There was no significant evidence of publication bias with Egger's test, p=0.09. Visual inspection of the funnel plot shows that the three smaller studies reported positive associations and that no small study showing negative association was identified. After excluding the two studies with mortality as outcome, the RR was 1.02 (95% CI: 0.98-1.06, I^2=16.4%, pheterogeneity=0.30, n=9).

There was not enough data to do analyses stratified by smoking status. Three studies stratified the analyses by smoking status (Ros, 2010; Kurahashi, 2009; Mills, 1991). In two studies a non-significant association was observed in all strata of smoking status (Ros, 2010; Mills, 1991). In the Japan Public Health Center-based Prospective Study (JPHC, Kurahashi, 2009), coffee consumption was associated with an increased risk of bladder cancer in never- or former-smoking men, with hazard ratios in the highest categories of coffee (one or more cups per day) compared to almost none of 2.24 (95% CI: 1.21–4.16). A non-significant association was observed in smokers.

After stratification by sex, the RR per 1 cup of coffee per day was 1.02 (95% CI: 0.98-1.06, I^2=0%, pheterogeneity=0.57, n=5) for men and 0.95 (95% CI: 0.82-1.11, I^2=76.2%, pheterogeneity=0.006, n=4) for women. There was no evidence of non-linearity (p=0.90).

Heterogeneity

There was a moderate heterogeneity, I^2=34.1%, pheterogeneity=0.13.

Comparison with the Second Expert Report

In the 2005 SLR the evidence relating coffee to bladder cancer was considered limited- no conclusion.

Published meta-analyses or pooled analyses

A meta-analysis of 23 case–control studies with 7690 cases and 13,507 controls, and 5 cohort studies with 700 cases and 229,099 participants showed a non-significant association between coffee consumption and bladder cancer in cohort studies. The highest versus lowest RR for cohort studies was 1.01(95%CI: 0.69–1.48, 4 vs. 1 cup/day) (Zhou, 2012).

In a meta-analysis of 4 cohort studies the RRs for an increment of 1 cup/day of coffee were 1.04 (95% CI: 1.00–1.09) in men and 0.83 (95% CI: 0.72–0.96) in women (Pelucchi, 2009).

Table 68 Studies on coffee identified during the CUP

Author/year	Country	Study name	Number of cases	Years of follow-up	Sex	RR	LCI	UCI	Contrast
Ros MM, 2011	Europe	EPIC	513	9.3 years	M/F	1.11	0.85	1.43	Men ≥875 vs. <429 ml/d Women ≥ 500 vs. <250 ml/d
Kurahashi N, 2009	Japan	JPHC study	206	12.6 years	M	1.37	0.75	2.51	≥3 cups/day vs. almost none
					F	0.55	0.23	1.33	≥1 cups/day vs. almost none
Iso H, 2007	Japan	JACC study	127	12 years	M	1.02	0.59	1.76	≥2/day vs. ≤1-2/m
					F	0.56	0.21	1.50	

Table 69 Overall evidence on coffee and bladder cancer

SLR	Summary of evidence
2005 SLR	8 cohort studies were included in the meta analysis and found a non-significant association between coffee and bladder cancer.
CUP	Three cohort studies reported on coffee and bladder cancer and showed no significant association.

Table 70 Summary of results of the dose-response meta-analysis of coffee and bladder cancer

Bladder cancer		
	2005 SLR	CUP
Studies (n)	8	11
Cases (n)	1225	2098
Increment unit	Per 1 cup/day	Per 1 cup/day
RR (95% CI)	1.01 (0.96-1.07)	1.02 (0.97-1.06)
Heterogeneity (I^2, p-value)	I^2=27.1%, p=0.21	I^2=34.1%, p=0.13, n=11
Stratified analysis		
Men		1.02 (0.98-1.06)
Heterogeneity (I^2, p-value)		I^2=0%, p=0.57, n=5
Women		0.95 (0.82-1.11)
Heterogeneity (I^2, p-value)		I^2=76.2%, p<0.01, n=4

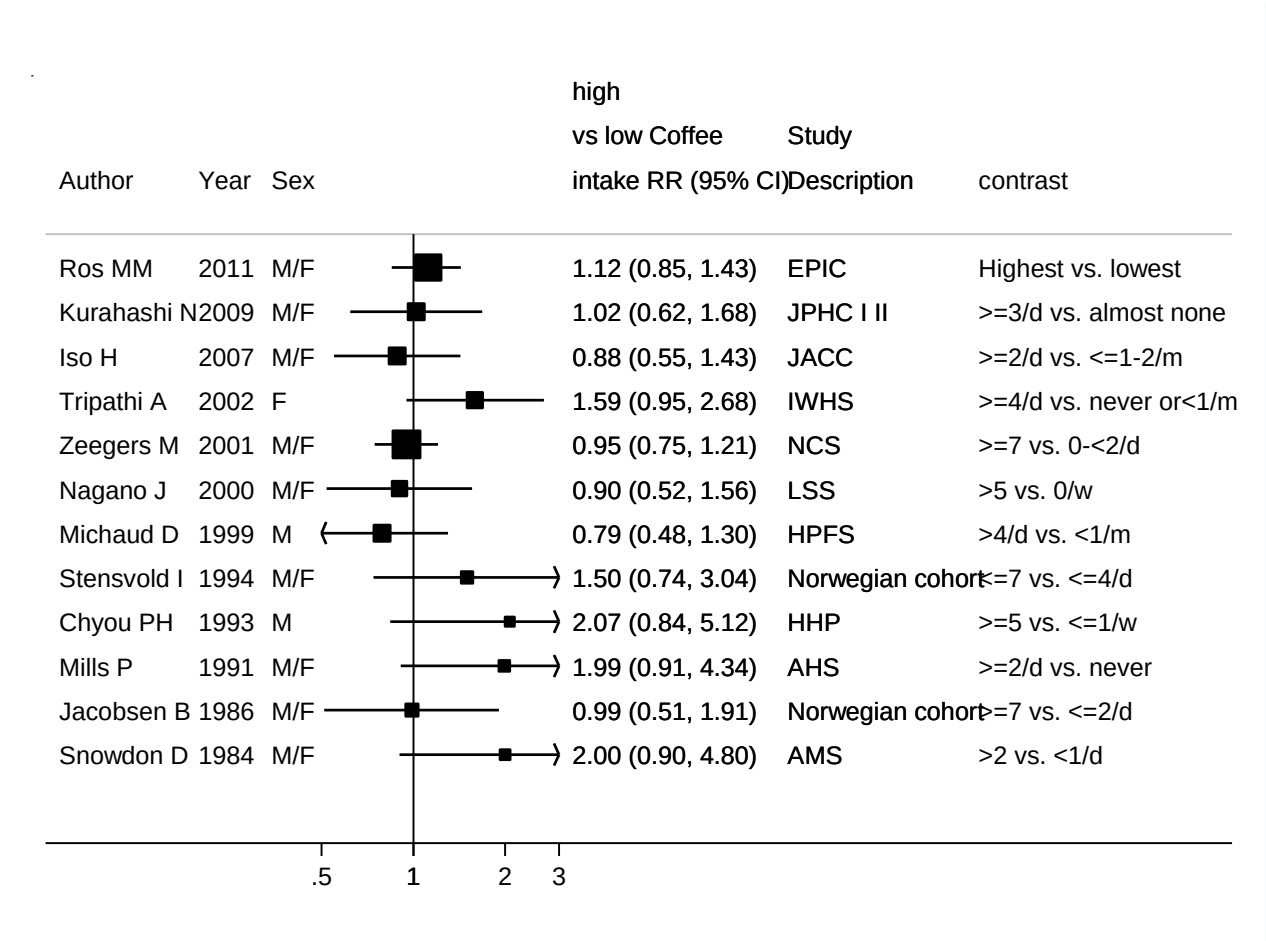
Table 71 Inclusion/exclusion table for meta-analysis of coffee and bladder cancer

WCRF code	Author	Year	Study design	Study name	Sex	Cancer outcome	2005 SLR	CUP dose-response	CUP H vs. L forest plot	Estimated values	Exclusion reason
BLA97177	Ros MM	2011	Prospective cohort study	EPIC	M/F	Incidence	No	Yes	Yes	Person-years. Weighted average intake range for men and women. Conversion ml to cups/d	
BLA97171	Kurahashi N	2009	Prospective cohort study	The Japan Public Health Center-based Prospective Study (JPHC study)	M/F	Incidence	No	Yes	Yes	Midpoints. Conversion cups/week to cups/day	
BLA97203	Iso H	2007	Prospective cohort study	Japan Collaborative Cohort Study (JACC Study)	M/F	Mortality	No	Yes	Yes	Midpoints. Conversion cups/week to cups/day	
BLA00182	Tripathi A	2002	Prospective cohort study	Iowa Women's Health Study	F	Incidence	Yes	Yes	Yes	Midpoints. Convert to cups/day	
BLA00367	Zeegers M	2001 (a)	Prospective cohort study	Netherlands Cohort Study	M/F	Incidence	Yes	Yes	Yes	Midpoints	
BLA02708	Nagano J	2000	Prospective cohort study	Life Span Study, atomic bomb survivors, Japan	M/F	Incidence/Mortality	Yes	Yes	Yes	Midpoints. Conversion to cups/day	
BLA02841	Michaud D	1999(b)	Prospective cohort study	Health Professionals Follow-up Study	M	Incidence/Mortality	Yes	Yes	Yes	Midpoints. Conversion to cups/day	
BLA03167	Zheng W	1996	Prospective	Iowa Women's	F	Incidence	Yes	No	No		Superseded

			cohort study	Health Study							by Tripathi A, 2002
BLA00671	Stensvold I	1994	Prospective cohort study	Cardiovascular Screening Programme Norway	M/F	Incidence/ Mortality	Yes	Yes	Yes	Confidence intervals. Midpoints	
BLA00777	Chyou PH	1993	Prospective cohort study	Honolulu Heart Program	M	Incidence/ Mortality	Yes	Yes	Yes	Person-years. Midpoints. Conversion to cups/day	
BLA01090	Mills P	1991	Prospective cohort study	California Seventh-Day Adventists 1976-1982	M/F	Incidence	Yes	Yes	Yes	Midpoints. Conversion to cups/day	
BLA01525	Jacobsen B	1986	Prospective cohort study	2cohorts of Norwegian men + spouses/siblings participants in CC study	M/F	Incidence/ Mortality	Yes	No	Yes	Confidence intervals	
BLA01645	Whittemore A	1985	Prospective cohort study	Follow up of male students from Harvard and female students from Pennsylvania University	M/F	Incidence	No	No	No		Referred in the text that coffee was not associated with bladder cancer before or after adjusting for smoking
BLA10322	Snowdon D	1984	Prospective cohort study	Adventists Mortality study 1960-1980	M/F	Mortality	Yes	Yes	Yes		
BLA01645	Whittemore A	1984	Prospective cohort study	Follow up of male students from Harvard	M/F	Incidence	No	No	No		Insufficient data. Referred in

				and female students from Pennsylvania							the text that coffee was not associated with bladder cancer before or after adjusting for smoking

Figure 66 Highest versus lowest forest plot of coffee and bladder cancer



For Ros MM, 2011 the contrast was ≥875 vs. <429 ml/d for men and ≥500 vs. <250 ml/d for women.

Figure 67 Dose-response meta-analysis of coffee and bladder cancer, per 1cup/day

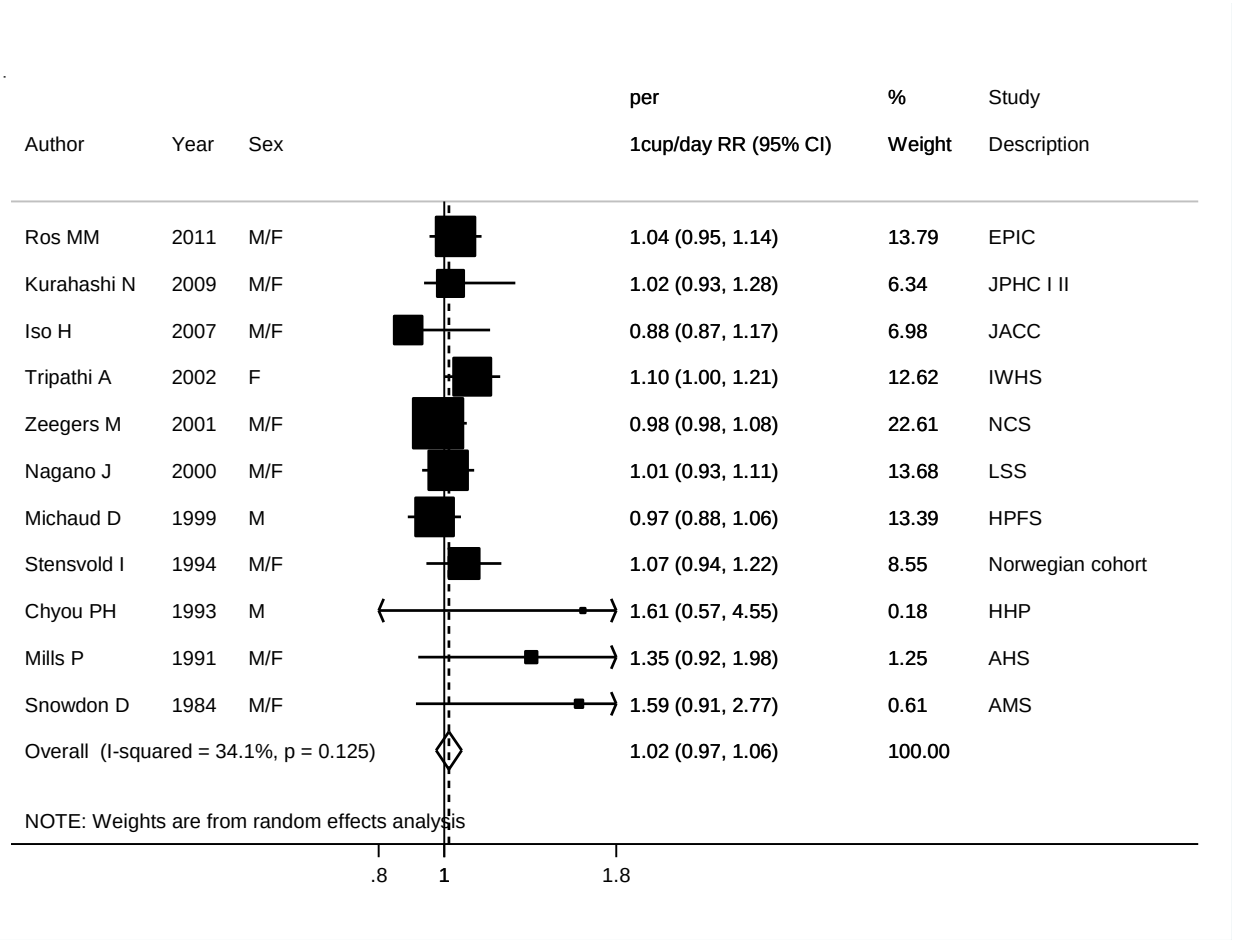
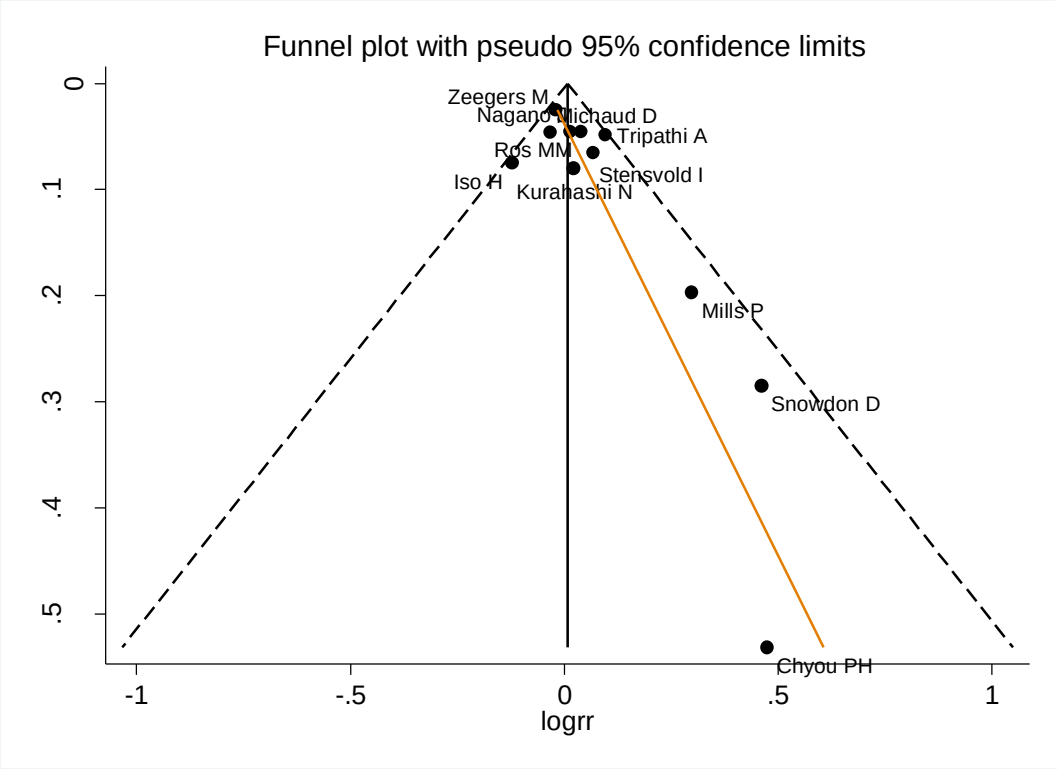


Figure 68 Funnel plot of coffee intake and bladder cancer



Egger's test p=0.09

Figure 69 Dose-response graph of coffee and bladder cancer

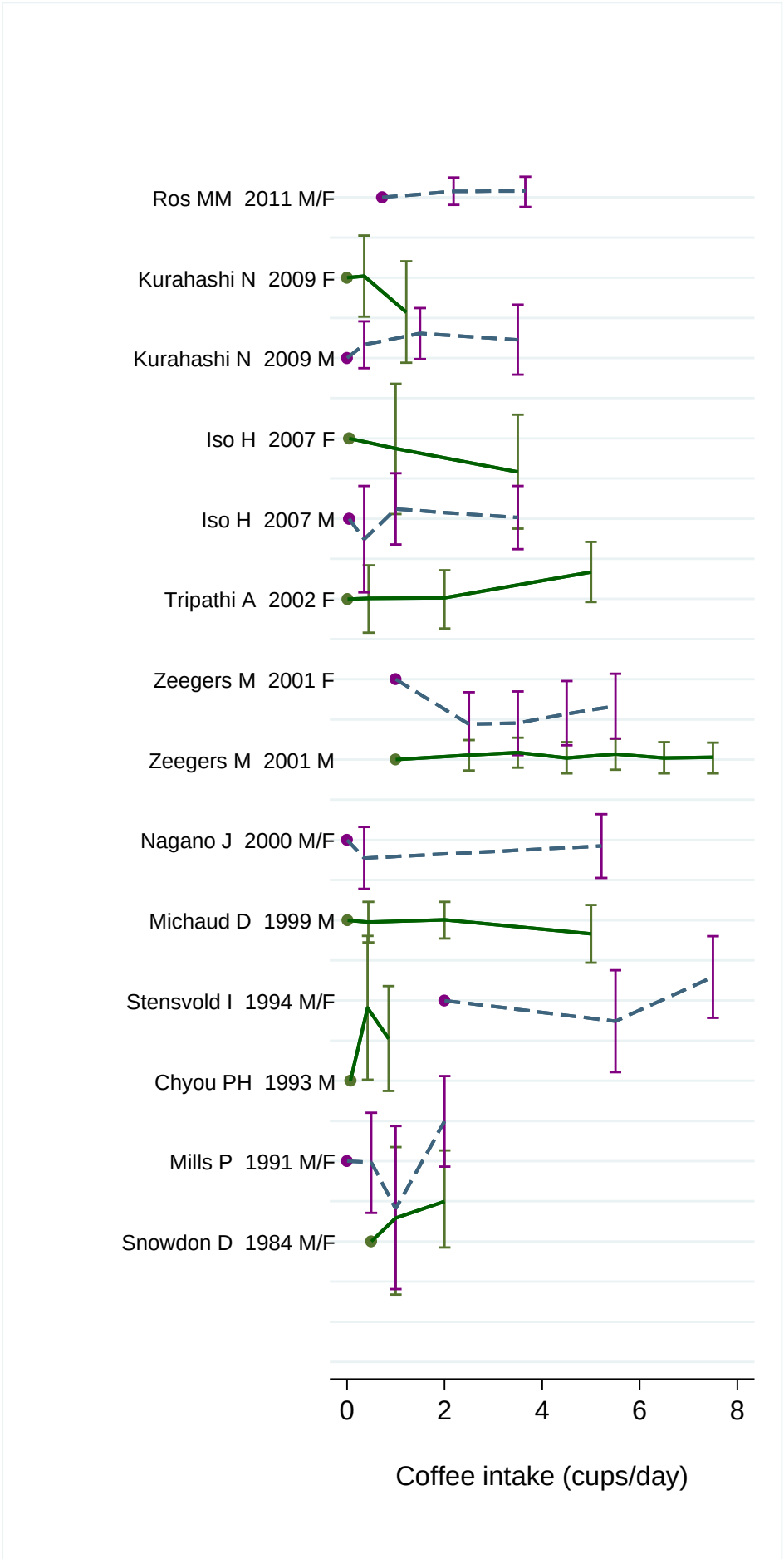
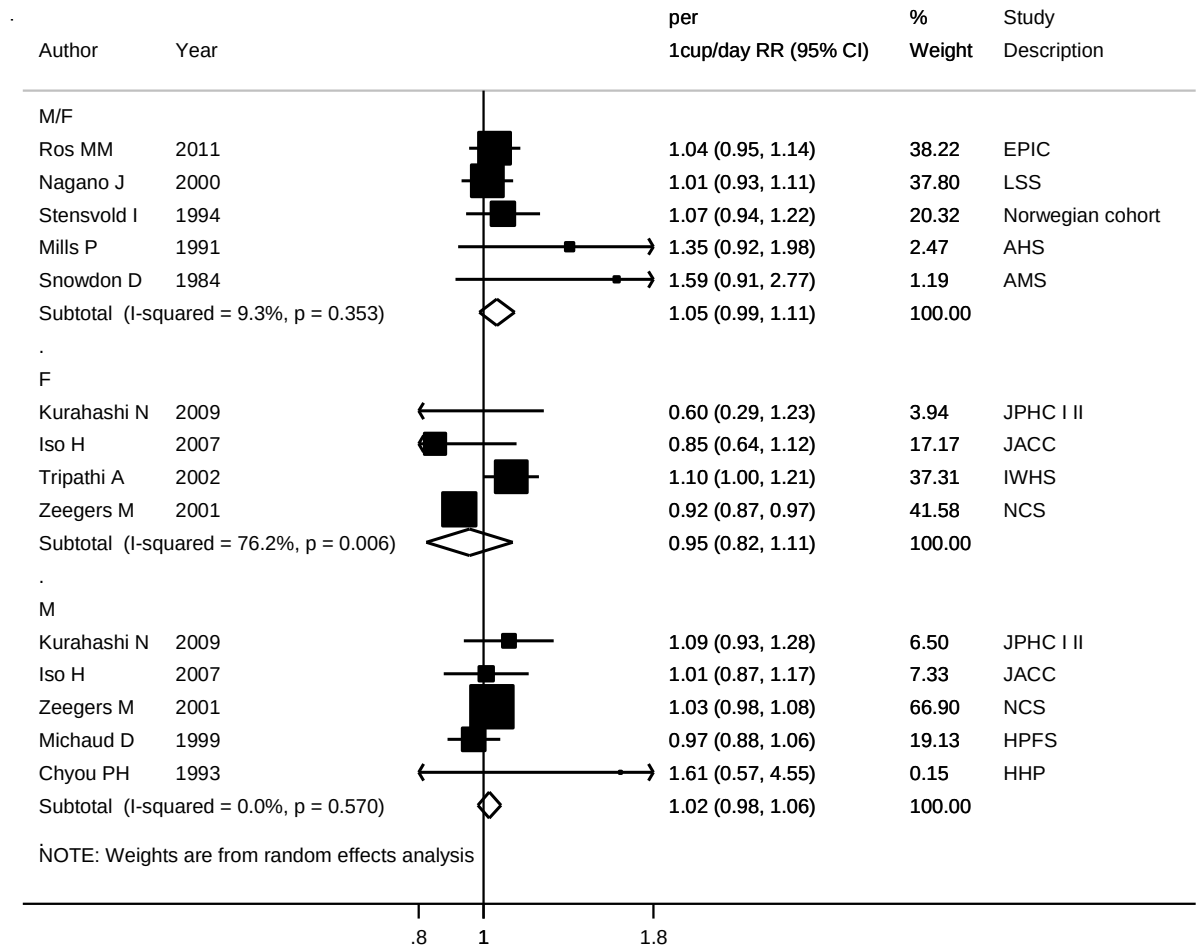


Figure 70 Dose-response meta-analysis of coffee and bladder cancer, per 1cup/day, stratified by sex



3.6.2 Tea

Methods

Four articles from four studies were identified, from which one was identified in the CUP. The unit used in the dose-response analysis was one cup/day. Studies reporting in ml of tea were converted to cups of tea, using as conversion unit 200ml equivalent to 1 cup of tea.

All except one study (Tripathi, 2002) adjusted the results by smoking status or smoking duration and dose.

Main results

The summary RR per 1 cup of tea per day was 0.94 (95% CI: 0.89-0.98, I^2=0%, pheterogeneity=0.41, n=4). There was not enough data to stratify the analysis by smoking status.

Heterogeneity

There was no evidence of heterogeneity, I^2=0%, pheterogeneity=0.41.

Comparison with the Second Expert Report

In the 2005 SLR the evidence relating tea to bladder cancer was considered limited- no conclusion.

Published meta-analyses or pooled analyses

A meta-analysis of 23 cohort and case control studies was published on tea and bladder cancer risk. The overall estimate for the cohort studies was (0.94 95% CI:0.78-1.09, I^2=0%, pheterogeneity=0.47, n=6, consumption of tea vs. no consumption of tea) (Qin, 2012).

Table 72 Studies on tea identified during the CUP

Author/year	Country	Study name	Number of cases	Years of follow-up	Sex	RR	LCI	UCI	Contrast
Ros MM, 2011	Europe	EPIC	513	9.3 years	M/F	0.91	0.72	1.14	Men ≥200 vs. <12 ml/d Women ≥ 264 vs. <16 ml/d

Table 73 Overall evidence on tea and bladder cancer

SLR	Summary of evidence
2005 SLR	3 cohort studies were included in the meta analysis and found a non-significant association between tea and bladder cancer.
CUP	One new cohort study reported on tea and bladder cancer and showed no significant association. The meta-analysis shows a significant inverse association

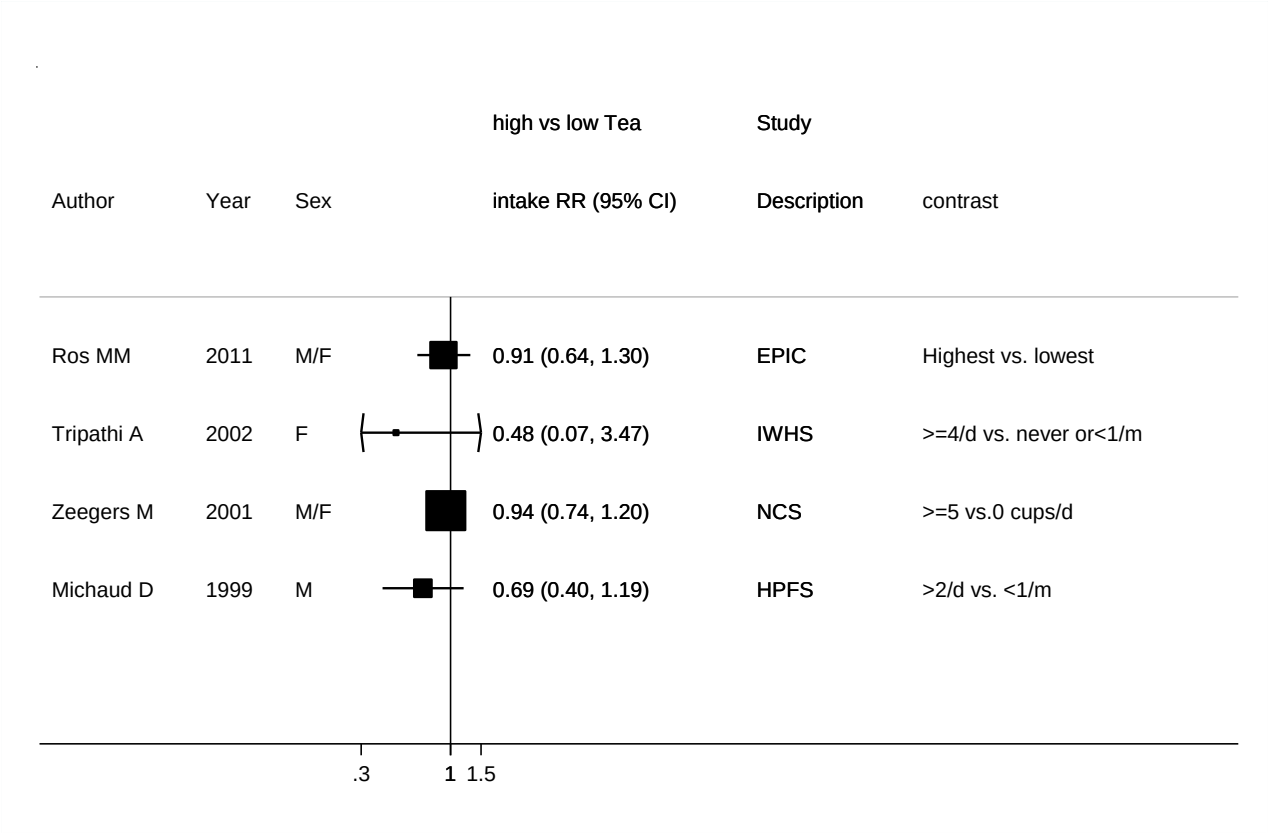
Table 74 Summary of results of the dose-response meta-analysis of tea and bladder cancer

Bladder cancer		
	2005 SLR	CUP
Studies (n)	3	4
Cases (n)	933	1446
Increment unit	Per 1 cup/day	Per 1 cup/day
RR (95% CI)	0.95 (0.90-0.99)	0.94 (0.89-0.98)
Heterogeneity (I^2, p-value)	I^2=0%, p=0.56	I^2=0%, p=0.41

Table 75 Inclusion/exclusion table for meta-analysis of tea and bladder cancer

WCRF code	Author	Year	Study design	Study name	Sex	Cancer outcome	2005 SLR	CUP dose-response	CUP H vs. L forest plot	Estimated values	Exclusion reason
BLA97177	Ros MM	2011	Prospective cohort study	EPIC	M/F	Incidence	No	Yes	Yes	Person-years. Weighted average intake range men and women. Conversion ml to cups/d	
BLA00182	Tripathi A	2002	Prospective cohort study	Iowa Women's Health Study	F	Incidence	Yes	Yes	Yes	Midpoints. Convert to cups/day	
BLA00367	Zeegers M	2001(a)	Prospective cohort study	Netherlands Cohort Study	M/F	Incidence	Yes	Yes	Yes	Midpoints	
BLA02841	Michaud D	1999(b)	Prospective cohort study	Health Professionals Follow-up Study	M	Incidence/Mortality	Yes	Yes	Yes	Midpoints. Conversion to cups/day	

Figure 71 Highest versus lowest forest plot of tea and bladder cancer



For Ros MM, 2011 the contrast was ≥200 vs. <12 ml/d for men and ≥ 264 vs. <16 ml/d for women.

Figure 72 Dose-response meta-analysis of tea and bladder cancer, per 1cup/day

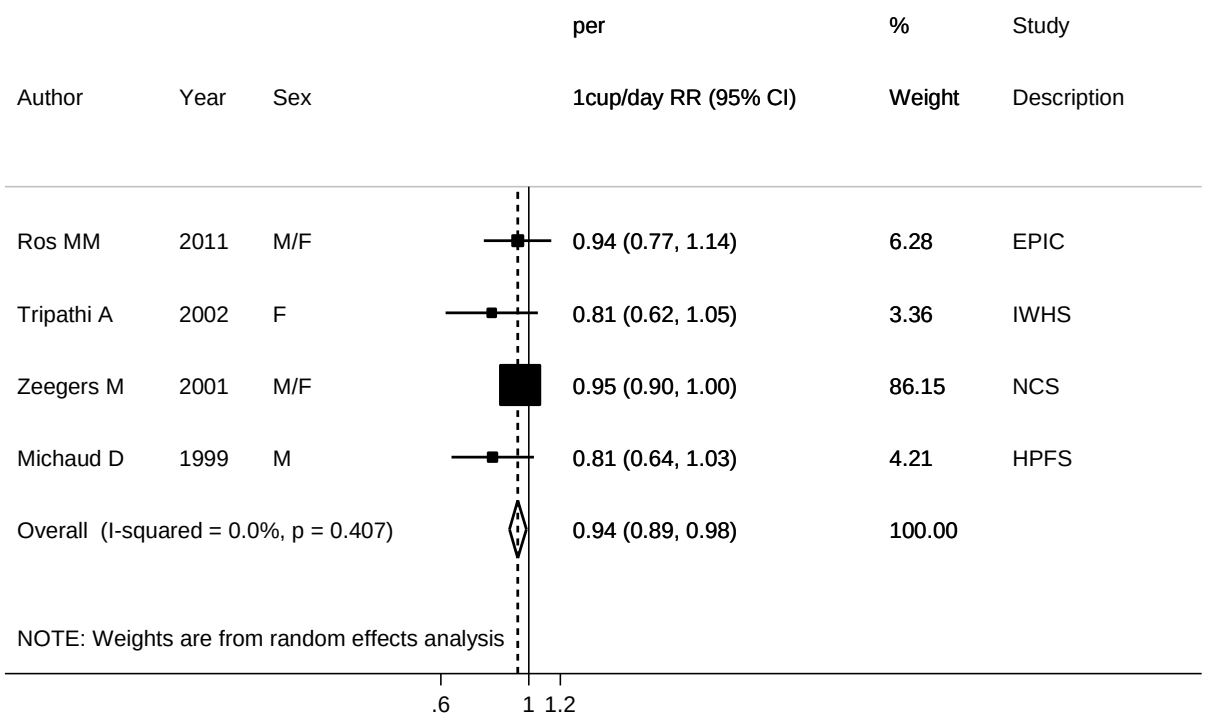
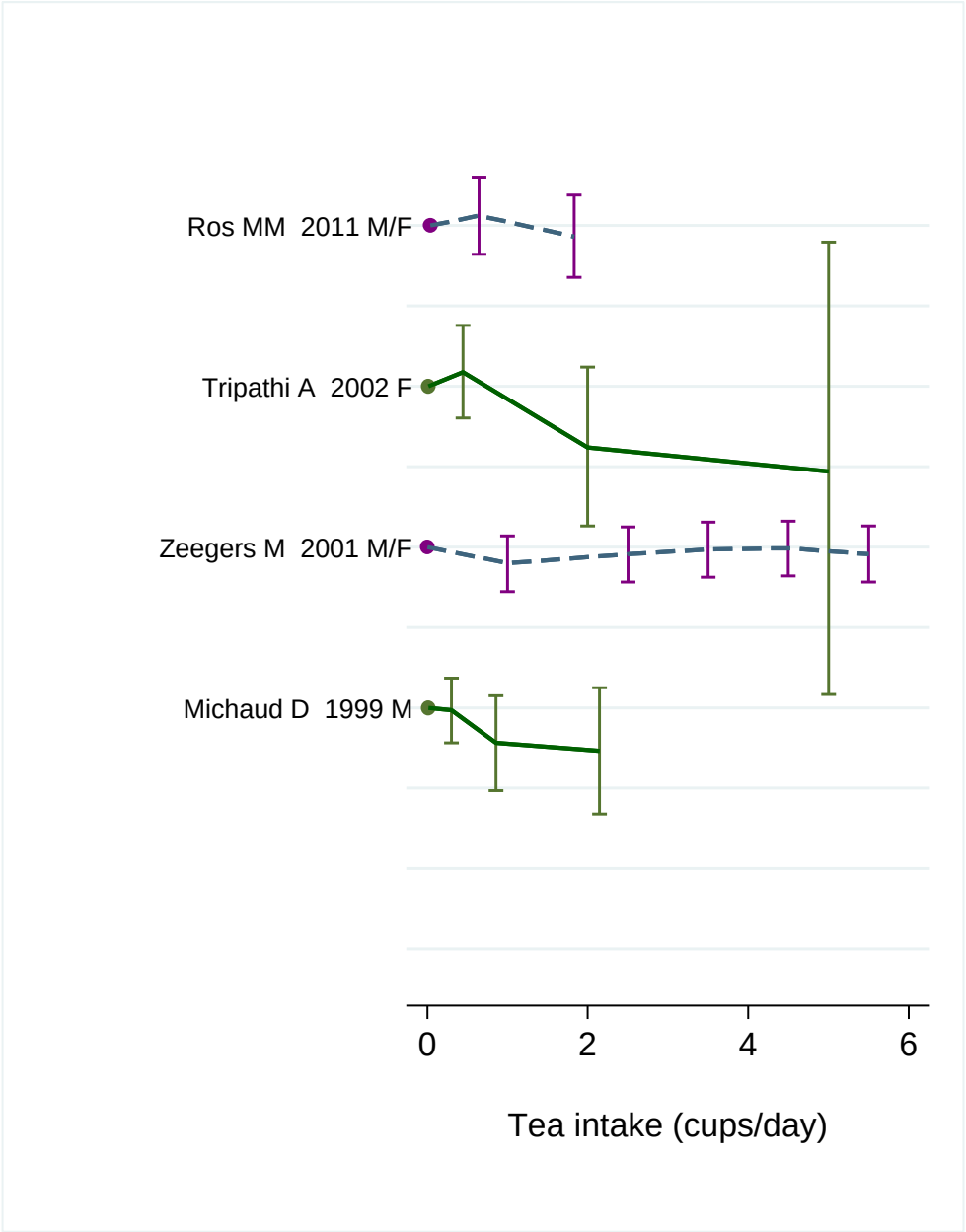


Figure 73 Dose-response graph of tea and bladder cancer



3.6.2.2 Green Tea

Methods
Four articles from four studies, of which two were identified in the CUP. The unit used in the dose-response analysis was one cup/day. Studies reporting in ml of tea were converted to cups of tea, using as conversion unit 200ml equivalent to 1 cup of tea.

Main results
The summary RR per 1 cup of tea per day was 1.01 (95% CI: 0.73-1.40, I^2=0%, pheterogeneity=0.82, n=3). It was not possible to stratify the analysis by smoking status.

Heterogeneity
There was no evidence of heterogeneity, I^2=0%, pheterogeneity=0.82.

Comparison with the Second Expert Report
In the 2005 SLR the evidence relating green tea to bladder cancer was considered limited- no conclusion.

Published meta-analyses or pooled analyses
No published meta-analyses or pooled analyses were identified.

Table 76 Studies on green tea identified during the CUP

Author/year	Country	Study name	Number of cases	Years of follow-up	Sex	RR	LCI	UCI	Contrast
Kurahashi N, 2009	Japan	JPHC study	206	12.6 years	M	0.90	0.56	1.45	≥5 vs. <1 cups/day
					F	2.29	1.06	4.92	≥5 vs. <3 cups/day
Iso H, 2007	Japan	JACC Study	127	12 years	M	1.13	0.58	1.19	≥4/day vs. ≤3-4/w
					F	0.86	0.35	2.10	

Table 77 Overall evidence on green tea and bladder cancer

SLR	Summary of evidence
2005 SLR	2 cohort studies were identified; one was on green tea frequency of consumption. Both found a non-significant association between green tea and bladder cancer.
CUP	Two new cohort studies reported on green tea and bladder cancer and showed no significant association.

Table 78 Summary of results of the dose-response meta-analysis of green tea and bladder cancer

Bladder cancer		
	2005 SLR*	CUP
Studies (n)		3
Cases (n)		447
Increment unit		Per 1 cup/day
RR (95% CI)		1.01 (0.73-1.40)
Heterogeneity (I^2, p-value)		0%, p=0.82

* No meta-analysis was conducted in the SLR.

Table 79 Inclusion/exclusion table for meta-analysis of green tea and bladder cancer

WCRF code	Author	Year	Study design	Study name	Sex	Cancer outcome	2005 SLR	CUP dose-response	CUP H vs. L forest plot	Estimated values	Exclusion reason
BLA97171	Kurahashi N	2009	Prospective cohort study	The Japan Public Health Center-based Prospective Study (JPHC study)	M/F	Incidence	No	Yes	Yes	Midpoints. Conversion cups/week to cups/day	
BLA97203	Iso H	2007	Prospective cohort study	Japan Collaborative Cohort Study (JACC Study)	M/F	Mortality	No	Yes	Yes	Midpoints. Conversion cups/week to cups/day	
BLA02708	Nagano J	2001	Prospective cohort study	Life Span Study, atomic bomb survivors, Japan	M/F	Incidence/Mortality	Yes	Yes	Yes	Midpoints. Conversion to cups/day	
BLA00777	Chyou PH	1993	Prospective cohort study	Honolulu Heart Program	M	Incidence/ Mortality	Yes	No	Yes	Person-years. Midpoints. Conversion to cups/day	Only high vs. low results

Figure 74 Highest versus lowest forest plot of green tea and bladder cancer

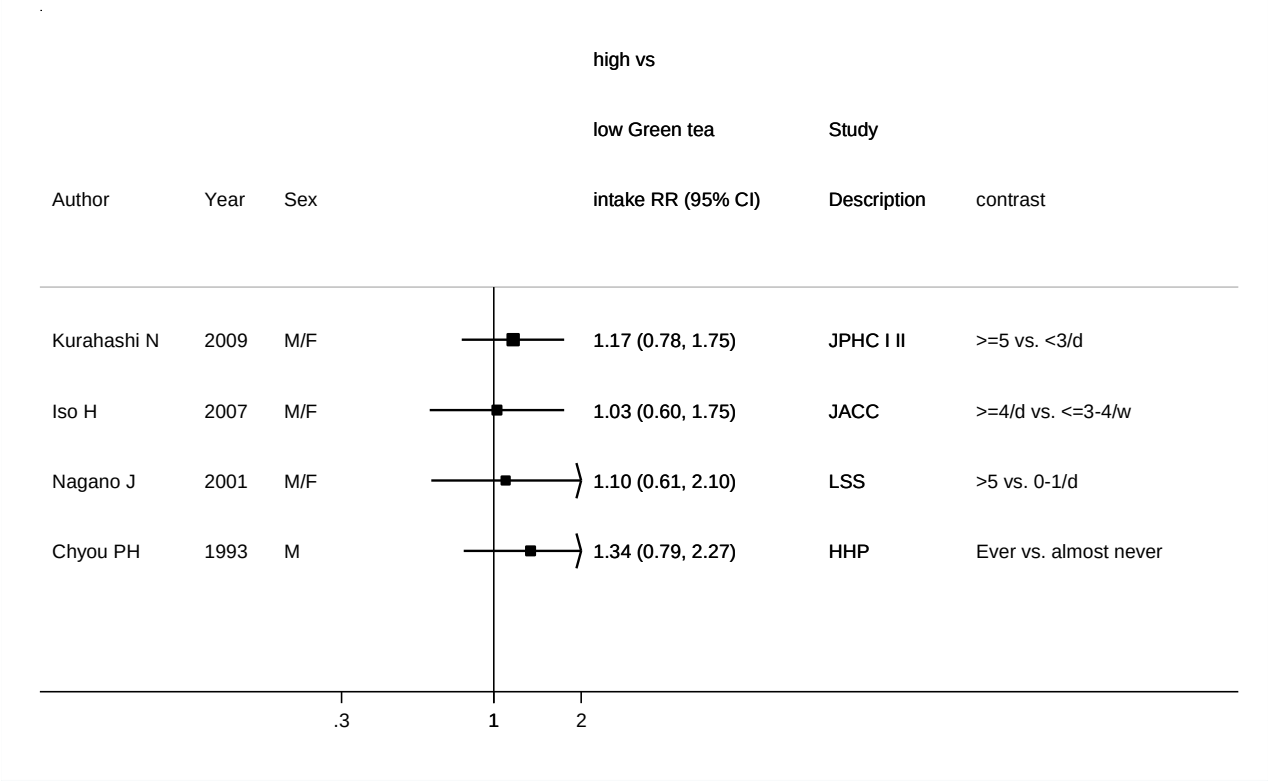


Figure 75 Dose-response meta-analysis of green tea and bladder cancer, per 1cup/day

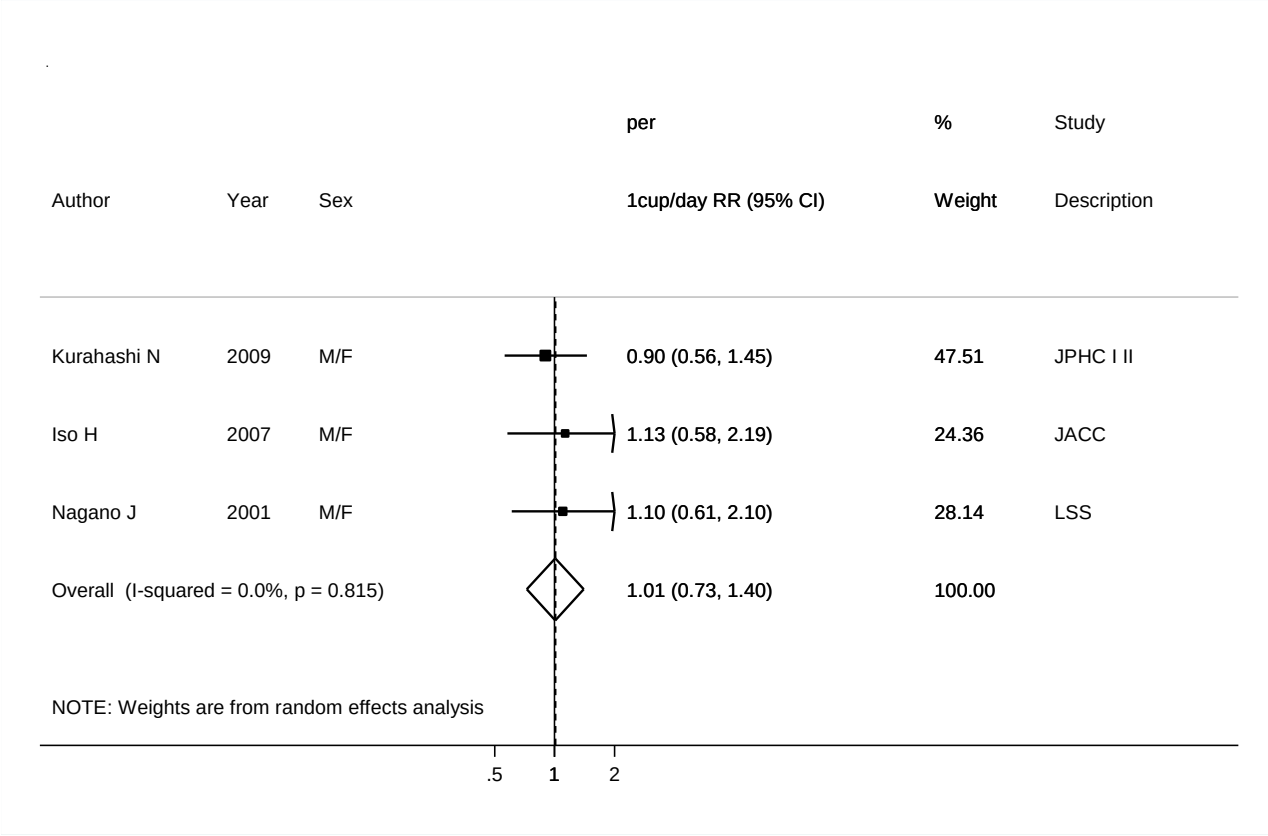
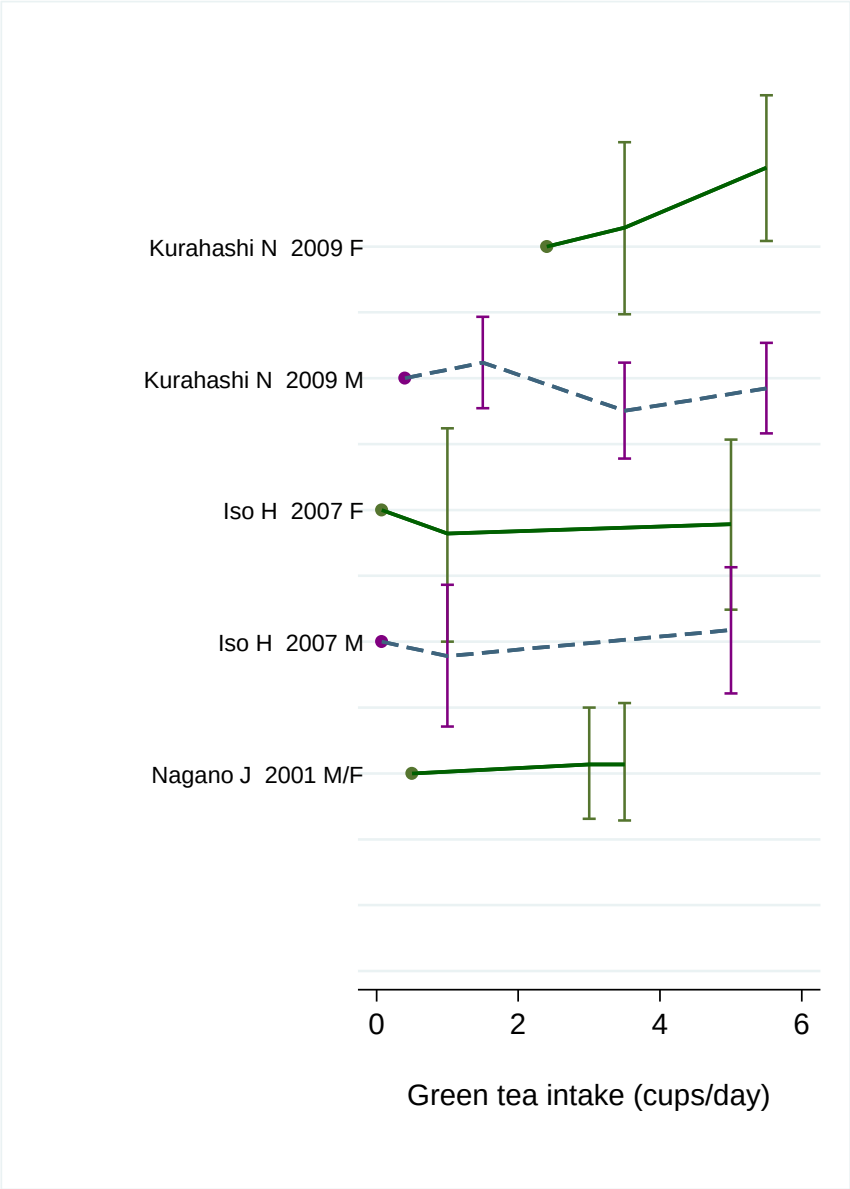


Figure 76 Dose-response graph of green tea and bladder cancer



3.6.2.1 Black Tea

Methods
3 studies, 1 identified in the CUP. The unit used in the dose-response analysis was one cup/day. Studies reporting in ml of tea were converted to cups of tea, using as conversion unit 200ml equivalent to 1 cup of tea. From the 3 studies identified, one was of frequency of black tea consumption (use vs. no use), therefore was only possible to conduct a highest versus lowest analysis for black and bladder cancer.

Main results
The summary RR for the highest vs. lowest analysis was 0.98 (95% CI: 0.63-1.50, I^2=37.3%, pheterogeneity=0.20, n=3).

Heterogeneity
There was evidence of moderate heterogeneity, I^2=37.3%, pheterogeneity=0.20.

Comparison with the Second Expert Report
In the 2005 SLR the evidence relating black tea to bladder cancer was considered limited- no conclusion.

Published meta-analyses or pooled analyses
No published meta-analyses or pooled analyses were identified.

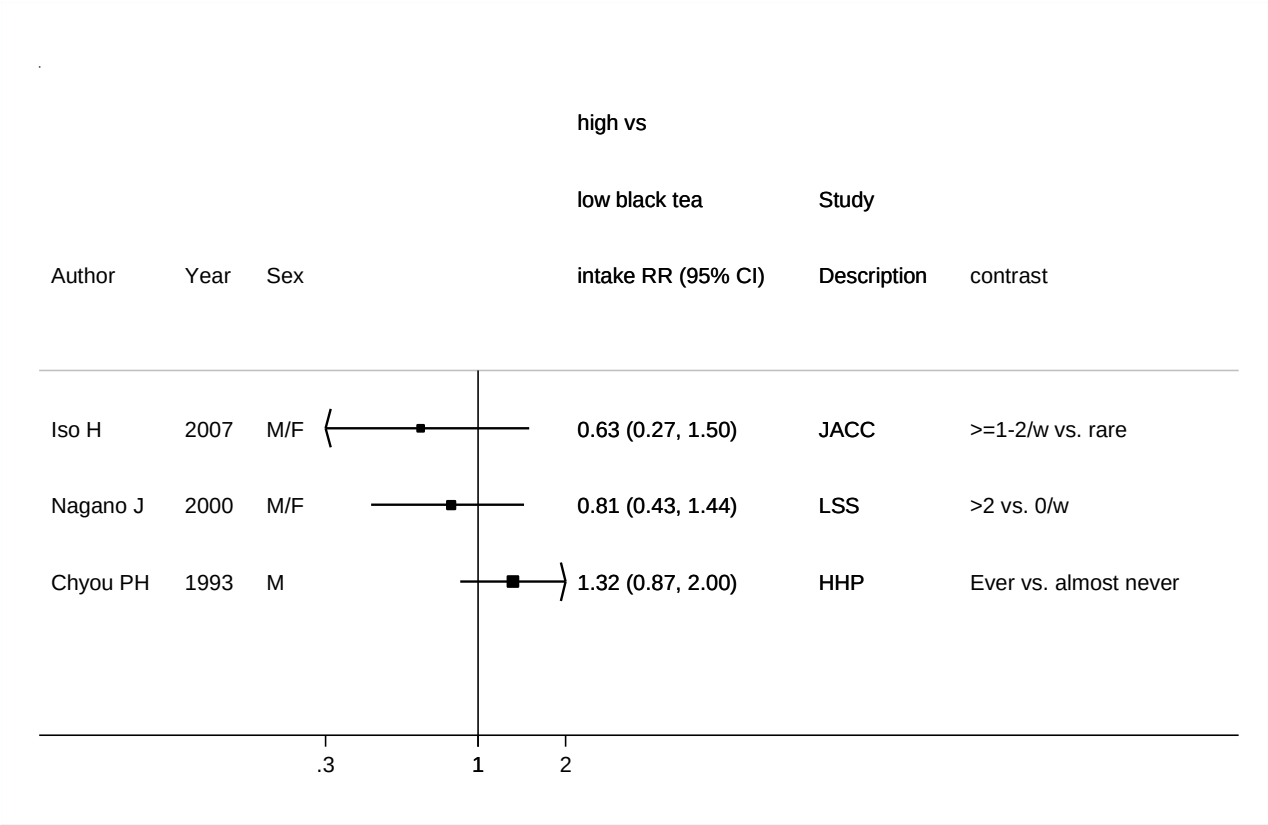
Table 80 Studies on black tea identified during the CUP

Author/year	Country	Study name	Number of cases	Years of follow-up	Sex	RR	LCI	UCI	Contrast
Iso H, 2007	Japan	JACC Study	127	12 years	M	0.23	0.06	0.95	≥1-2/w vs. rare
					F	1.20	0.40	3.56	

Table 81 Inclusion/exclusion table for meta-analysis of black tea and bladder cancer

WCRF code	Author	Year	Study design	Study name	Sex	Cancer outcome	2005 SLR	CUP dose-response	CUP H vs. L forest plot	Estimated values	Exclusion reason
BLA97203	Iso H	2007	Prospective cohort study	Japan Collaborative Cohort Study (JACC Study)	M/F	Mortality	No	No	Yes	Midpoints. Conversion cups/week to cups/day	Insufficient data to conduct dose-response analysis of black tea and bladder cancer
BLA02708	Nagano J	2000	Prospective cohort study	Life Span Study, atomic bomb survivors, Japan	M/F	Incidence/Mortality	Yes	No	Yes	Midpoints. Conversion to cups/day	Insufficient data to conduct dose-response analysis of black tea and bladder cancer
BLA00777	Chyou PH	1993	Prospective cohort study	Honolulu Heart Program	M	Incidence/ Mortality	Yes	No	Yes	Person-years. Midpoints. Conversion to cups/day	Only high vs. low results

Figure 77 Highest versus lowest forest plot of black tea and bladder cancer



4.1.2.7.1 Arsenic

Methods
Eleven articles from eight studies on arsenic in drinking water and bladder cancer or urinary cancer were identified. Five articles from 3 studies were identified in the CUP. From the eight studies, three studies were on populations from low-risk areas (Europe and United States: Baastrup et al, 2008; Michaud et al, 2004-toenail arsenic, Kurttio et al, 1999), one study was in Mormons in US (Lewis et al, 1999) and the remaining studies were from areas with high exposure to arsenic in Taiwan and Japan. The exposure arsenic in drinking water was based on the measurement of arsenic levels in well water and cumulative exposure was calculated from the duration and amount of water consumed. The study in Mormons (Lewis et al, 1999) and the study in Japan (Tsuda et al, 1995) quantified the risk increase as SMR (expected numbers derived from rates of the general population). Due to the variability in arsenic exposure assessment across studies, it was not possible to conduct meta-analyses.

Main results
The studies in high-risk areas (Chung et al, 2013; Hsu et al, 2011; Chen et al, 2010; Tsuda et al, 1995) reported a significant increased risk of cancers of the bladder or urothelial carcinomas with increasing levels of cumulative exposure to arsenic from drinking water:

No association with risk of bladder cancer was observed in three of the studies in populations with low levels of exposure, arsenic in drinking water (Baastrup et al, 2008; Michaud et al, 2004) or toenail arsenic (Lewis et al, 1990). In the Finnish study (Kurttio et al, 1999), a significant increased risk of bladder cancer was observed in participants with exposure >0.5 μg/L relative to <0.1 μg/L of arsenic in water during the third to nine years prior to diagnosis. Bladder cancer was not related to the daily or the cumulative doses of arsenic, and no association was observed with exposure to arsenic 10 years or more prior to diagnosis.

Relevant information and the highest versus lowest RR (or SMR) for each study are included in the table.

Comparison with the Second Expert Report
In the 2005 SLR the evidence that in drinking water modifies the risk of bladder cancer was judged as limited suggestive. Arsenic and arsenic compounds are graded Class 1 carcinogens (IARC).

Published meta-analyses or pooled analyses
A meta-analysis of 6 case-control and 2 cohort studies in populations with low-levels of exposure to arsenic in drinking water (<100-200 microg/L) showed no significant relationship with bladder cancer when comparing highest vs. lowest levels of arsenic exposure in never (RR: 0.81; 95% CI: 0.60–1.08) and ever smokers (RR: 1.24; 95% CI: 0.99–1.56), and for all individuals combined (RR=1.11; 95% CI: 0.95–1.30) (Mink P, 2008)*. A previous meta-analysis including 2 cohort and

5 case-control studies from high and low-level arsenic areas found a non-significant dose-response association (slope= 0.004 (in units of per μg/L) (95% CI: -0.03, 0.01) (Chu HA, 2006).

*Study funded by the Wood Preservative Science Council (WPSC), Manakin-Sabot, Virginia, a trade association of manufacturers of wood preservatives; some preservatives may contain arsenic.

Table 82 Summary table of results on arsenic and bladder cancer

Author	Year	Study design	Study name	Sex	Cancer outcome	Information	RR	LCI	UCI	Contrast/ Adjustment*
Chung	2013	Prospective cohort study 43 deaths	South-western Taiwan cohort 1989-1996	M/F	Mortality Bladder cancer	High risk area Average arsenic concentration in well water, assessed in 1960	7.22	0.95	55.04	>.071 vs. <0.05 mg/l
						Duration of well water drinking (years)	6.22	1.32	29.37	>=28 vs. <16 years
						Cumulative arsenic exposure (µg/l/years)	7.74	0.97	61.51	>=19.5 vs. <9.1
		*Adjusted for age, sex, education and smoking				Urinary profile InAs%	3.53	1.16	10.77	>=7.86 vs. <4.22 5
						MMA%	1.77	0.72	4.36	>=15.31 VS. <8.34
						DMA%	3.05	1.11	8.37	<76.13 vs. >=85.8
						PMI	0.56	0.24	1.32	>=2.75 VS. <1.32
						SMI	2.85	1.04	7.83	<4.90 vs. >=9.82
Hsu LI	2011	Prospective cohort study 41 cases urothelial carcinoma	South-western Taiwan cohort 1989-1996	M/F	Incidence Urothelial carcinoma	High risk area (mean >100µg/L) Exposure: Cumulative arsenic exposure from well water (mg/L*yr)	19.31	2.46	151.24	20 vs. 0-9.9 mg/L*yr Adjusted for sex and age
Chen CL	2010	Prospective cohort study 45 cases urothelial carcinoma	North-eastern Taiwan cohort 1991/1994 - 2006	M/F	Incidence Urothelial carcinoma	High risk area (mean >100 µg/L) Exposure: Arsenic concentration in well water collected at enrolment (µg/L)	7.80	2.64	23.1	≥300 vs. <10 µg/L Adjusted for sex and age
						Exposure: Cumulative arsenic exposure from well water	12.6	3.40	46.8	≥10000 vs. <400 µg/L Adjusted for

						(µg/L*yr)				sex and age
Huang YK	2008	Prospective cohort study 37 cases urothelial carcinoma	South-western Taiwan cohort 1989-2001	M/F	Incidence Urothelial carcinoma	High risk area mean >100 µg/L Exposure: Average concentration of arsenic in artesian well water consumed (mg/l)	6.5	0.8	53.1	≥0.9 vs. 0-0.4 mg/l Adjusted for smoking status
						Exposure: Cumulative arsenic exposure from well water (mg/L*yr)	7.9	1.7	37.9	>=20 mg/L*y vs. none Adjusted for smoking status
Baastrup R	2008	Prospective cohort study 214 bladder cancers	Danish cohort Diet, Cancer and Health	M/F	Incidence Bladder cancer	Low risk area (median 0.7 µg/L /) Exposure: Time-weighted average exposure (µg/L) in drinking water	1.00	0.91	1.11	Per µg/L Adjusted for smoking status, duration, intensity and other covariates
Michaud D	2004	Nested case-control study 280 cases	ATBC study	M	Incidence Bladder cancer	Exposure: toenail arsenic level (µg/g)	1.13	0.70	1.81	>0.161 vs. <0.05 µg/g Adjusted for smoking duration, intensity and other covariates
Chiou H	2001	Prospective cohort study 11 cases	North-eastern Taiwan cohort 1991/1994 - 1996	M/F	Incidence Transitional cell carcinoma	High risk area (mean >100 µg/L) Exposure: Arsenic concentration in well water collected at enrolment (µg/L)	15.1	1.7	138.5	>100 vs. 0-10 µg/L Adjusted for smoking and other covariates
Lewis D	1999	Retrospective cohort study	Cohort of Mormons, Utah, USA	M/F	Mortality for cancer of bladder and other urinary	Low risk area Exposure: Arsenic in water in ppb	SMR* F 1.18 1.10 M			Low and high Exposure: <1000 ppb-y >=5000 ppb-y

					organs		0.36 0.95			<1000 ppb-y >=5000 ppb-y
Kurttio P	1999	Case-cohort study 61 cases	Finland 1981-1995	M/F	Incidence Bladder cancer	Low risk area (median 0.1 µg /L) Exposure: Concentration of arsenic in water µg /L	2.44	1.11	5.37	≥0.5 vs. <0.1 µg/L Adjusted for age, sex and smoking status
						Cumulative arsenic exposure from well water 10 years of more before cancer diagnosis	1.50	0.71	3.15	>=2 vs. <0.5 mg
						Cumulative arsenic exposure from well water 10 years of more before cancer diagnosis	0.53	0.25	1.10	>=2 vs. <0.5 mg
Tsuda T	1995	Retrospective cohort study 3 cases	Japan 1959-1992	M/F	Mortality from cancer of bladder and renal pelvis	High risk area Exposure: Arsenic in water in ppm	SMR* 31.18	8.62	91.75	≥1 ppm
Chiou H	1995	Prospective cohort study 29 cases	South-western Taiwan cohort 1988-1993	M/F	Incidence Bladder cancer	High risk area (mean >100 µg/L) Exposure: Average arsenic concentration in well water	3.3	1.00	11.1	≥0.71 vs. ≤0.05 mg/L Adjusted for age, sex, smoking status
						Cumulative arsenic exposure from well water (mg/L*yr)	5.1	1.5	17.3	≥20 mg/L*yr vs. none

*SMR: Standardized mortality ratio.

5 Dietary constituents

5.4 Alcohol (as ethanol)

Methods

Ten studies were identified, from which two were identified in the CUP. The unit used in the dose-response analysis was 10g/day. One study (Ros, 2011) reported alcohol intake in millilitres per day, which was converted to grams/day using ethanol density as 0.7g/ml and considering an average percentage of ethanol of 12.5%. Another study (Michaud, 1999b) reported the relative risk of bladder cancer per 240 ml of alcohol, which was converted to grams per day considering that one alcoholic drink is equivalent to 200 ml and contains 12.5 g of alcohol. Three studies could not be included in the dose-response meta-analysis.
All included studies were on bladder cancer except one study (Chyou, 1993) on cancers of the lower urinary tract cancer (70 bladder cancer cases out of 83 cases in the study). All studies adjusted by smoking status and pack-years or duration and smoking dose.

Main results

The summary RR per 10g of ethanol per day was 0.97 (95% CI: 0.91-1.04, I^2=44.6%, pheterogeneity=0.09, n=7) with evidence of publication bias (p Egger's test =0.02. The smaller study reported a stronger positive association compared to the other studies. It was not possible to stratify the analysis by smoking status. After stratification by sex, the RR was 1.01 (95% CI: 0.94-1.08, I^2=30.2%, pheterogeneity=0.24, n=3) for men and 1.02 (95% CI: 0.74-1.41, I^2=63.1%, pheterogeneity=0.07, n=3) for women. There was no evidence of non-linearity (p=0.99).

Heterogeneity

There was evidence of moderate heterogeneity, I^2=44.6%, pheterogeneity=0.09.

Comparison with the Second Expert Report

In the 2005 SLR the evidence relating alcohol to bladder cancer was considered limited- no conclusion.

Published meta-analyses or pooled analyses

A meta-analysis of 19 cohort and case-control studies was published and showed a non-significant association between alcohol intake and bladder cancer, the overall estimate for cohort studies was (OR = 0.99, 95% CI 0.85–1.14, I^2=17.1%, pheterogeneity=0.30, n=6) (Mao, 2010). Another meta-analysis of 16 case–control and 3 cohort studies, including a total of 11 219 cases of bladder compared moderate alcohol drinkers (<3 drinks per/day) with non-drinkers and the overall estimate was 1.07 (95% CI 0.85–1.36) among cohort studies and 0.99 (95% CI 0.89–1.09) among case–control studies. All the data on heavy drinkers were from case–control studies (RR = 1.02, 95% CI 0.78–1.33, ≥3 drinks/day vs. non-drinkers) (Pelucchi 2012).

Table 83 Studies on alcohol intake identified during the CUP

Author/year	Country	Study name	Number of cases	Years of follow-up	Sex	RR	LCI	UCI	Contrast
Ros MM, 2011	Europe	EPIC	513	9.3 years	M/F	0.93	0.73	1.17	Men ≥437 vs. <171 ml/d Women ≥131 vs. 30 ml/d
Allen, 2009	United Kingdom	Million Women Study	928	7.2 years	F	0.93	0.82	1.05	Per 10g/d
						1.02	0.92	1.14	≥15 vs. ≤ 2 drinks/w

Table 84 Overall evidence on alcohol intake and bladder cancer

SLR	Summary of evidence
2005 SLR	4 studies were included in the meta analysis. Overall, no significant association between alcohol and bladder cancer was observed.
CUP	Two new cohort studies reported on alcohol intake and bladder cancer and showed no significant association.

Table 85 Summary of results of the dose-response meta-analysis of alcohol intake and bladder cancer

Bladder cancer		
	2005 SLR	CUP
Studies (n)	4	7
Cases (n)	980	2673
Increment unit	Per 1 serving/day	Per 10g/day
RR (95% CI)	1.00 (0.94-1.06)	0.97 (0.91-1.04)
Heterogeneity (I^2, p-value)	I^2=21.3%, p=0.28	I^2=44.6%, p=0.09
Stratified analysis		
Men		1.01 (0.94-1.08)
Heterogeneity (I^2, p-value)		I^2=30.2%, p=0.24, n=3
Women		1.02 (0.74-1.41)
Heterogeneity (I^2, p-value)		I^2=63.1%, p=0.07, n=3

Table 86 Inclusion/exclusion table for meta-analysis of alcohol intake and bladder cancer

WCRF code	Author	Year	Study design	Study name	Sex	Cancer outcome	2005 SLR	CUP dose-response	CUP H vs. L forest plot	Estimated values	Exclusion reason
BLA97177	Ros MM	2011	Prospective cohort study	EPIC	M/F	Incidence	No	Yes	Yes	Person-years. Weighted average intake range men and women. Conversion to g/d	
BLA97195	Allen N	2009	Prospective cohort study	Million Women Study	F	Incidence/ Mortality	No	Yes	Yes		
BLA10680	Djoussé L	2004	Retrospective cohort study	Framingham Heart Study	M/F	Incidence/ Mortality	Yes	Yes	Yes	Person-years. Midpoints	
BLA00182	Tripathi A	2002	Prospective cohort study	IWHS	F	Incidence	Yes	Yes	Yes	Midpoints	
BLA00409	Zeegers M	2001(d)	Prospective cohort study	Netherlands Cohort Study	M/F	Incidence	Yes	Yes	Yes	Midpoints	
BLA02841	Michaud D	1999	Prospective cohort study	Health Professionals Follow-up Study	M	Incidence/Mortality	Yes	Yes	No		Only reported continuous results.
BLA05236	Murata M	1996	Nested case-control study	Chiba Study Centre Japan	M	Incidence	Yes	No	No	.	Unadjusted results only (matched by age and sex)
BLA00777	Chyou PH	1993	Prospective cohort study	Honolulu Heart Program	M	Incidence/ Mortality	Yes	Yes	Yes	Person-years. Midpoints	
BLA01090	Mills P	1991	Prospective	California	M/F	Incidence	Yes	No	Yes		Only high

			cohort study	Seventh-Day Adventists 1976-1982							vs. low results
BLA10422	Hirayama	1979	Prospective cohort study	Japan 1995	M	Mortality	Yes	No	No		Drinking frequency, not enough information available

Figure 78 Highest versus lowest forest plot of alcohol and bladder cancer

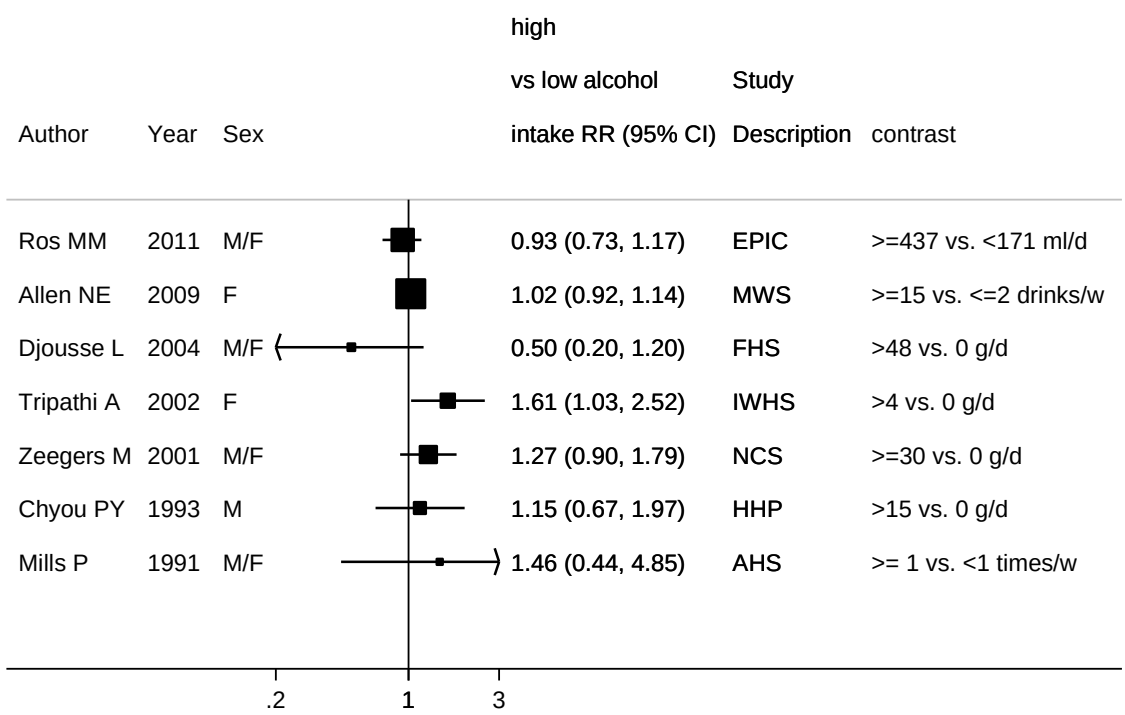


Figure 79 Dose-response meta-analysis of alcohol and bladder cancer, per 10g/day

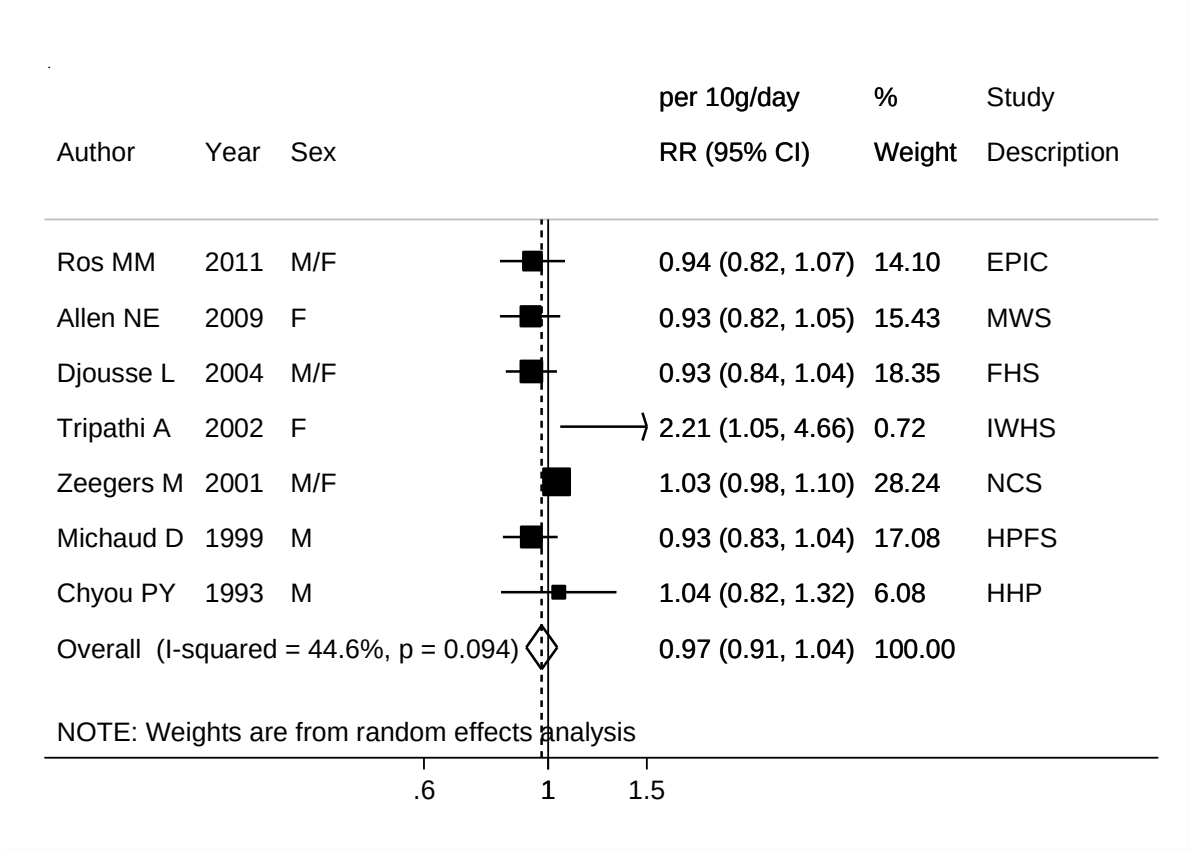
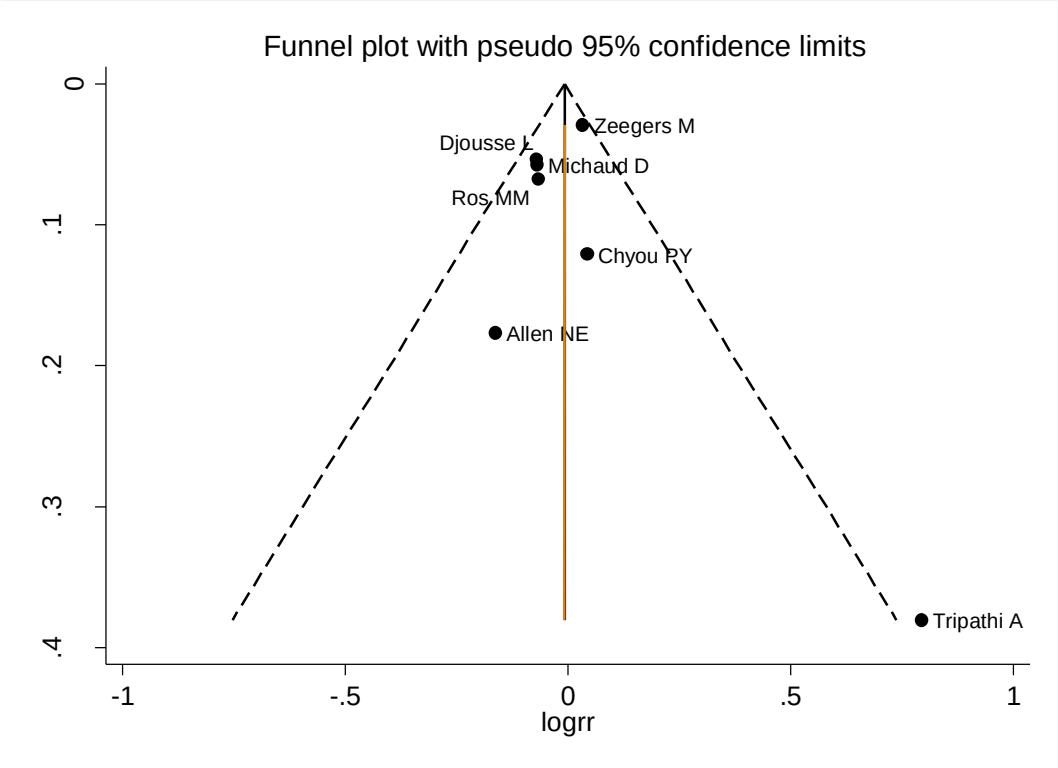


Figure 80 Funnel plot of alcohol intake and bladder cancer



Egger's test p=0.02

Figure 81 Dose-response graph of alcohol and bladder cancer

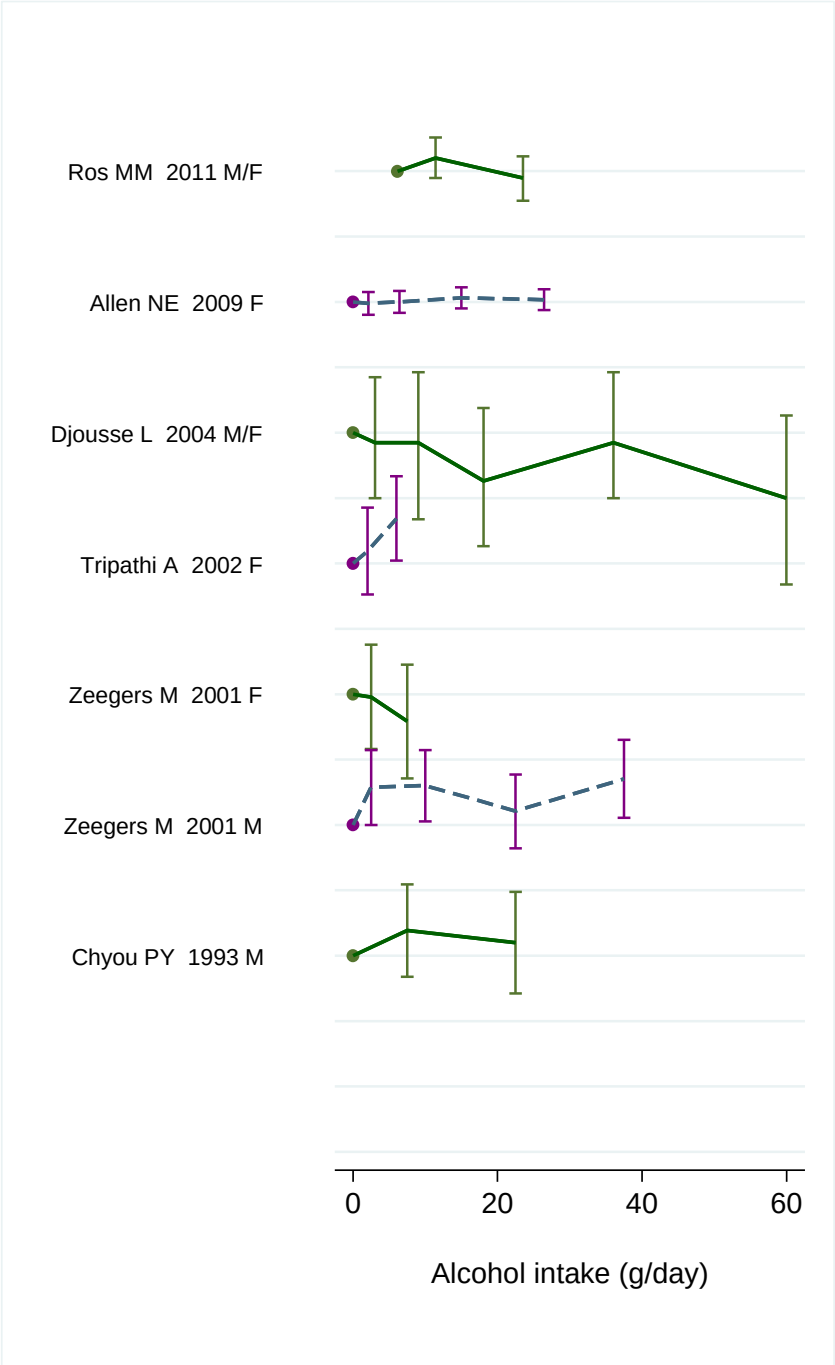
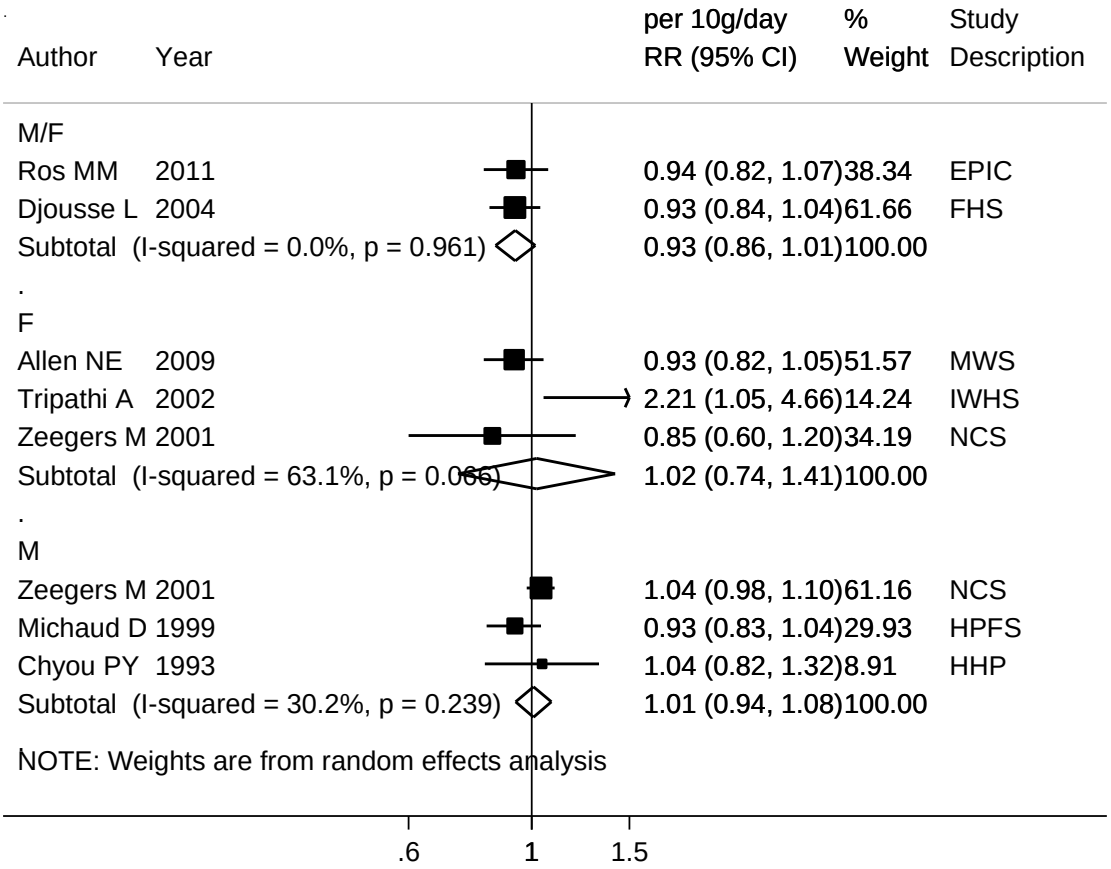


Figure 82 Dose-response meta-analysis of alcohol and bladder cancer, per 10g/day, stratified by sex



5.5.3 Folic acid supplements

Methods
2 studies both identified during the CUP.

Main results
The summary RR per 100 μg/day of folic acid supplements was 0.99 (95% CI: 0.95-1.02, I^2=0%, pheterogeneity=0.49, n=2).

Heterogeneity
There was no evidence of heterogeneity, I^2=0%, pheterogeneity=0.49.

Comparison with the Second Expert Report
No studies on folic acid supplements and bladder cancer were identified during the 2005 SLR.

Published meta-analyses or pooled analyses

An individual-patient-data meta-analysis of randomized controlled trials that compared folic acid versus placebo reported that folic acid is not related to bladder cancer risk (Vollsett, 2013). The studies included in the analysis were completed before 2011, had scheduled treatment duration of at least 1 year, included at least 500 participants, and recorded data on cancer incidence during the first 5 years of treatment. The summary RR of bladder cancer in the intervention group with folic acid (102 bladder cancer cases, 24 799 participants) compared to placebo (105 bladder cancer cases, 24 8220 participants) was 0.97 (95% CI: 0.68–1.39). The daily doses of folic acid used in the trials ranged from 0.5 mg to 5 mg, except in one trial of a 40 mg daily dose.

Table 87 Studies on folic acid supplements identified during the CUP

Author/year	Country	Study name	Number of cases	Years of follow-up	Sex	RR	LCI	UCI	Contrast
Hotaling J, 2011	USA	VITamins And Lifestyle cohort	330	6 years	M/F	0.73	0.44	1.22	>400.1-1400 μg/d vs. no supplement
Roswall N, 2009	Denmark	Danish Diet, Cancer and Health study	322	10.6 years	M/F	1.36	0.97	1.91	>83.2-≥150 μg/d vs. no supplement

Table 88 Overall evidence on folic acid supplements and bladder cancer

SLR	Summary of evidence
2005 SLR	No study was identified.
CUP	Two studies were identified, both studies showed non-significant results.

Table 89 Summary of results of the dose-response meta-analysis of folic acid supplements and bladder cancer

Bladder cancer		
	2005 SLR*	CUP
Studies (n)		2
Cases (n)		652
Increment unit		Per 100 μg/day
RR (95% CI)		0.99 (0.95-1.02)
Heterogeneity (I^2, p-value)		I^2=0%, p=0.49

* No meta-analysis was conducted in the SLR.

Table 90 Inclusion/exclusion table for meta-analysis of folic acid supplements and bladder cancer

WCRF code	Author	Year	Study design	Study name	Sex	Cancer outcome	2005 SLR	CUP dose-response	CUP H vs. L forest plot	Estimated values	Exclusion reason
BLA97180	Hotaling J	2011	Prospective cohort study	VITamins And Lifestyle cohort	M/F	Incidence	No	Yes	Yes	Midpoints. Person-years.	
BLA97168	Roswall N	2009	Prospective cohort study	Danish Diet, Cancer and Health study	M/F	Incidence	No	Yes	Yes	Midpoints. Person-years.	

Figure 83 Highest versus lowest forest plot of folic acid supplements and bladder cancer

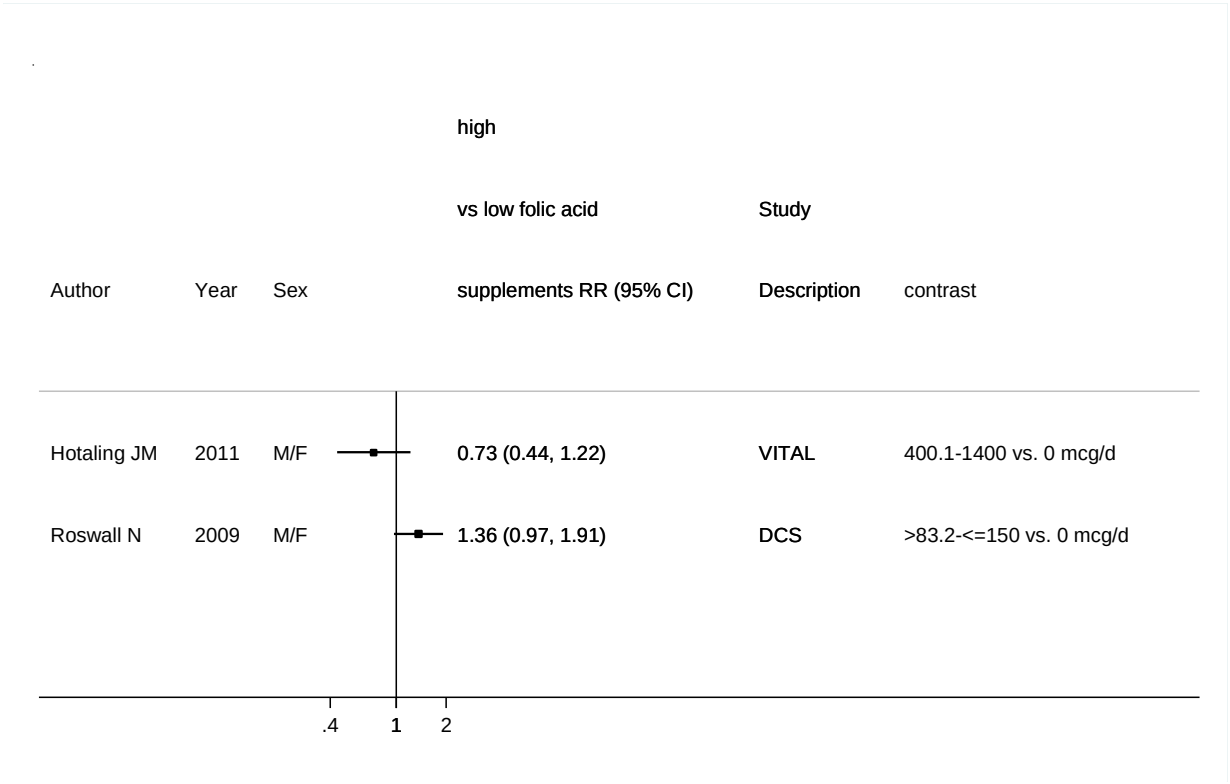


Figure 84 Dose-response meta-analysis of folic acid supplements and bladder cancer, per 100 µg/day

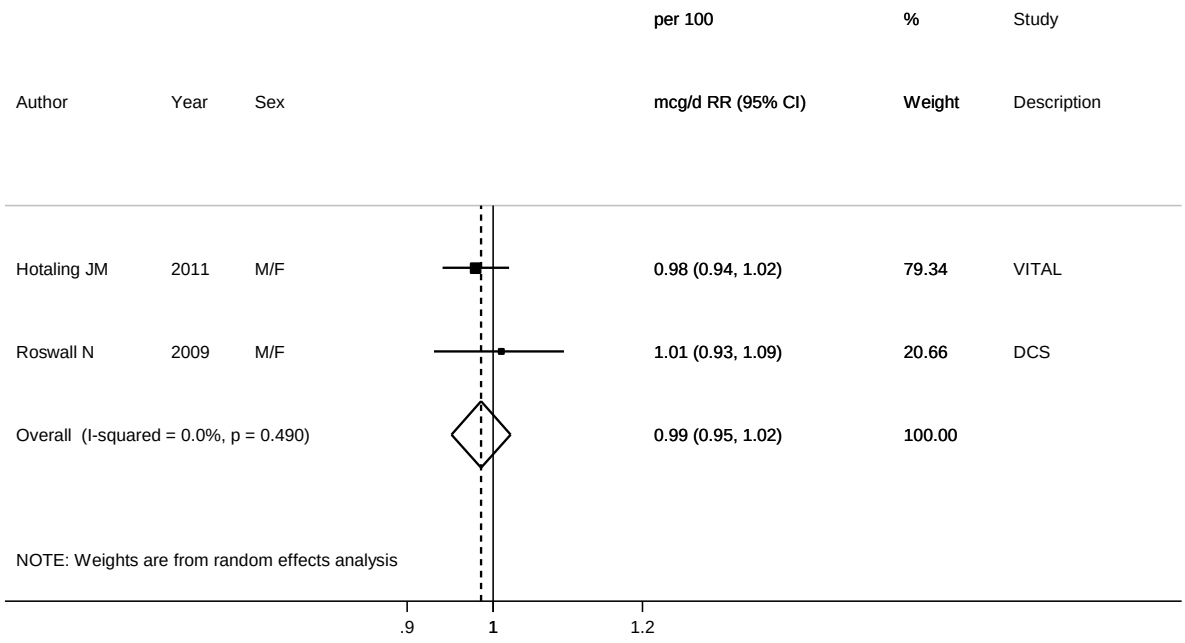
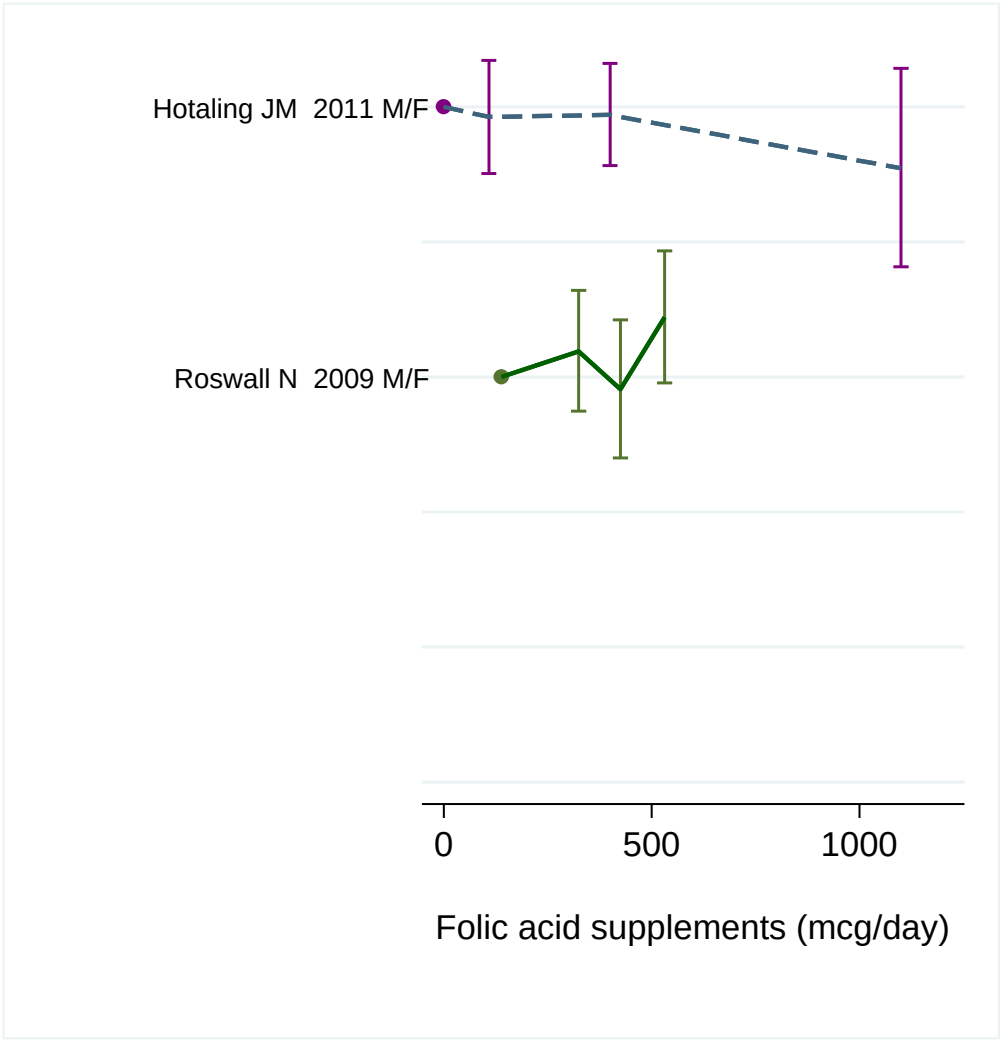


Figure 85 Dose-response graph of folic acid supplements and bladder cancer



5.5.8 Total vitamin C

Methods

Four studies were published; one study was identified during the CUP. The dose response results are presented for an increment of 40 mg/day.

Main results

The summary RR per 40 mg/day of total vitamin C was 1.00 (95% CI: 0.99-1.01, I^2=21%, pheterogeneity=0.28, n=3).

Heterogeneity

There was evidence of moderate heterogeneity, I^2=21%, pheterogeneity=0.28.

Comparison with the Second Expert Report

There were three studies in total, with two studies on total vitamin C and bladder cancer included in the meta-analysis, which showed a non-significant relationship. The evidence for vitamin C and bladder cancer was considered limited-no conclusion.

Published meta-analyses or pooled analyses

No published meta-analyses or pooled analyses were identified.

Table 91 Studies on total vitamin C identified during the CUP

Author/year	Country	Study name	Number of cases	Years of follow-up	Sex	RR	LCI	UCI	Contrast
Roswall N, 2009	Denmark	Danish Diet, Cancer and Health study	322	10.6 years	M/F	1.23	0.87	1.75	>181.5 ≤80.2 mg/d

Table 92 Overall evidence on total vitamin C and bladder cancer

SLR	Summary of evidence
2005 SLR	Three studies were identified and two studies were included in the meta-analysis, which was non-significant.
CUP	One new study was identified and showed non-significant result.

Table 93 Summary of results of the dose-response meta-analysis of total vitamin C and bladder cancer

Bladder cancer		
	2005 SLR	CUP
Studies (n)	2	3
Cases (n)	557	879
Increment unit	Per 40mg/day	Per 40mg/day
RR (95% CI)	1.00 (0.99-1.00)	1.00 (0.99-1.01)
Heterogeneity (I^2, p-value)	I^2=0%, p=0.72	I^2=21%, p=0.28

Table 94 Inclusion/exclusion table for meta-analysis of total vitamin C and bladder cancer

WCRF code	Author	Year	Study design	Study name	Sex	Cancer outcome	2005 SLR	CUP dose-response	CUP H vs. L forest plot	Estimated values	Exclusion reason
BLA97168	Roswall N	2009	Prospective cohort study	Danish Diet, Cancer and Health study	M/F	Incidence	No	Yes	Yes	Midpoints. Person-years	
BLA11803	Holick C	2005	Prospective cohort study	Nurses' Health Study	F	Incidence	Yes	Yes	Yes		
BLA00432	Michaud D	2000	Prospective cohort study	Health Professionals Follow-up study	M	Incidence	Yes	Yes	Yes		
BLA00922	Shibata A	1992	Prospective cohort study	Laguna Hills Study USA	M	Incidence	Yes	No	Yes		Insufficient data

Figure 86 Highest versus lowest forest plot of total vitamin C and bladder cancer

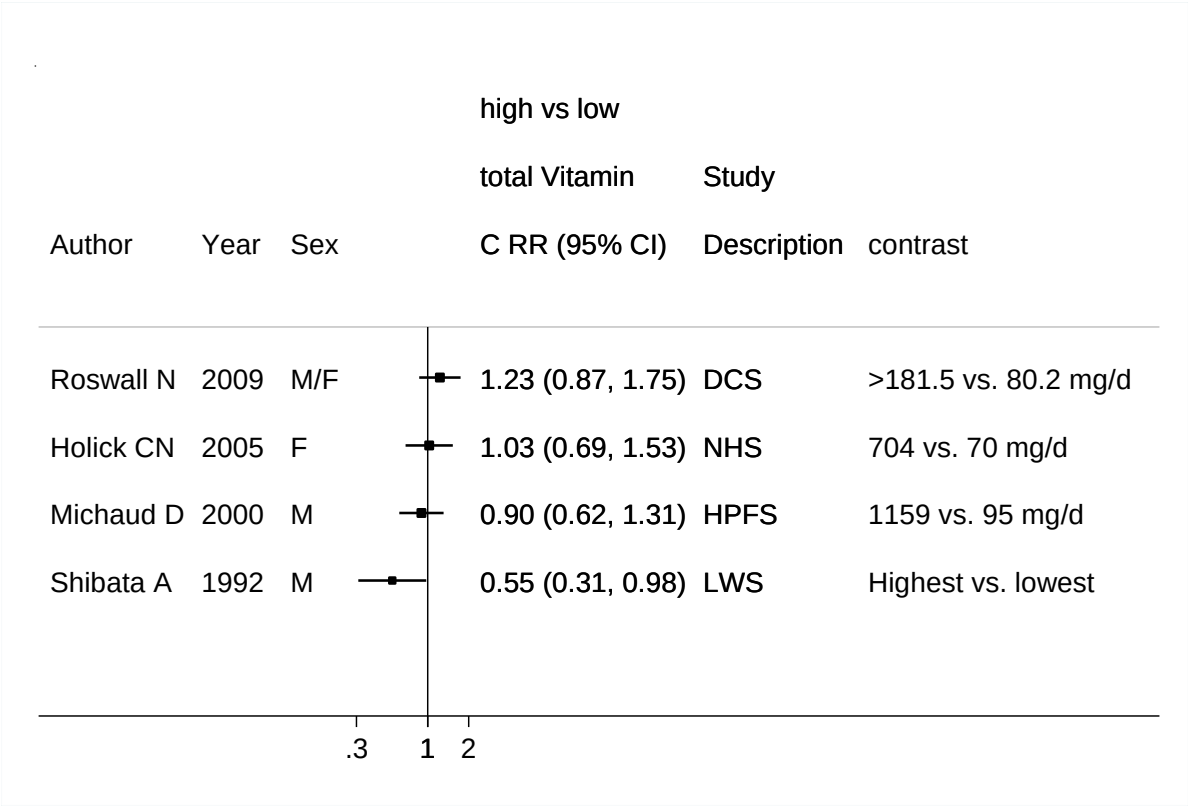


Figure 87 Dose-response meta-analysis of total vitamin C and bladder cancer, per 40mg/day

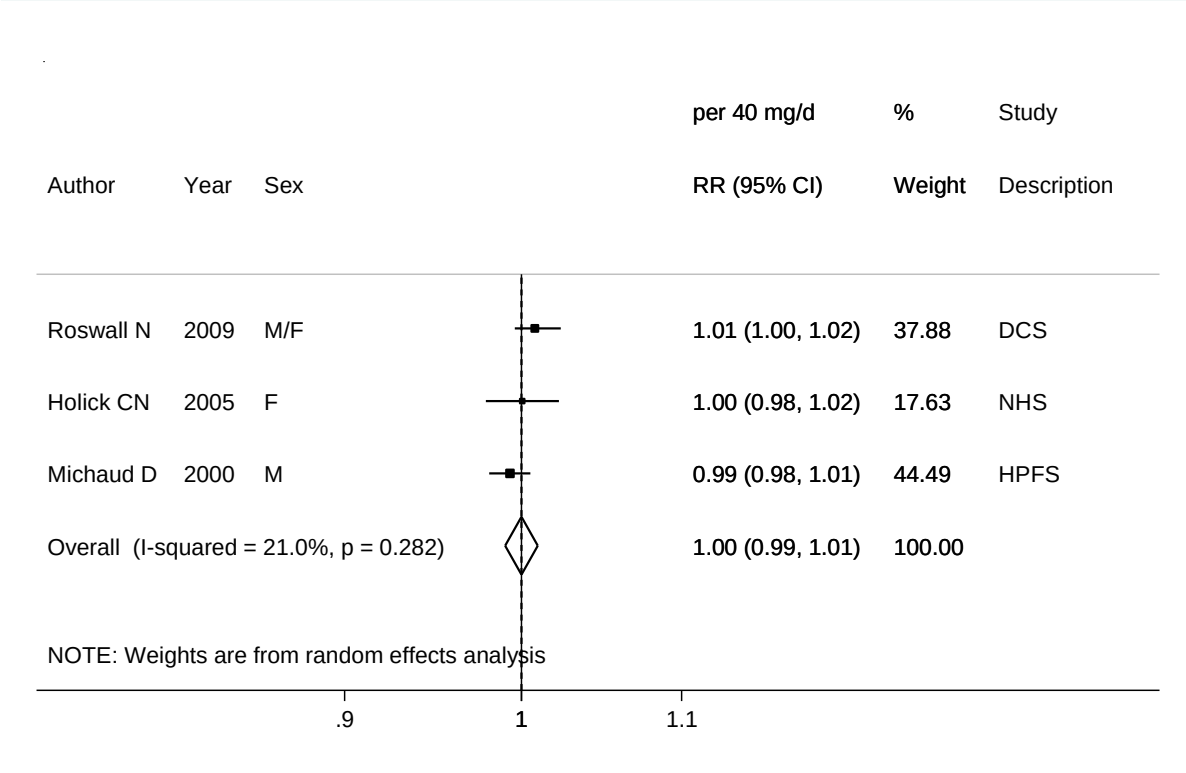
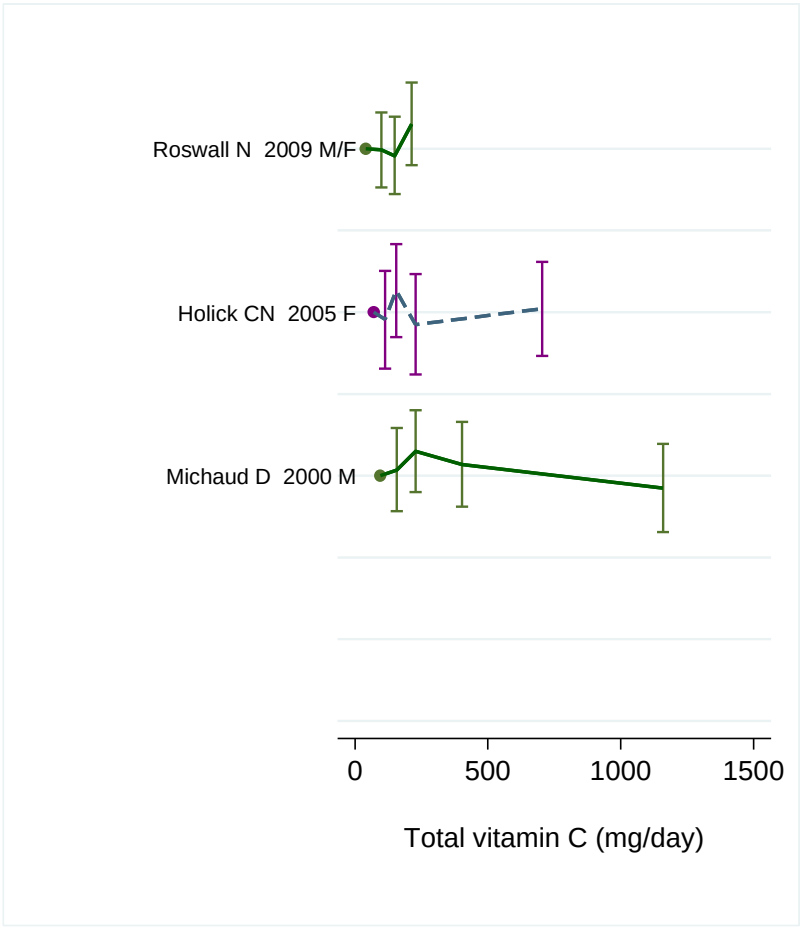


Figure 88 Dose-response graph of total vitamin C and bladder cancer



5.5.9 Dietary vitamin C

Methods
Six studies were published, from which two were identified during the CUP. The dose response results are presented for an increment of 40 mg/day.

Main results
The summary RR per 40 mg/day of dietary vitamin C was 1.02 (95% CI: 0.95-1.10, I^2=31.8%, pheterogeneity=0.21, n=5).

Heterogeneity
There was evidence of moderate heterogeneity, I^2=31.8%, pheterogeneity=0.21.

Comparison with the Second Expert Report
The summary of three studies on dietary vitamin C and bladder cancer identified in the 2005 SLR showed a non-significant relationship.

Published meta-analyses or pooled analyses
No published meta-analyses or pooled analyses were identified.

Table 95 Studies on dietary vitamin C identified during the CUP

Author/year	Country	Study name	Number of cases	Years of follow-up	Sex	RR	LCI	UCI	Contrast
Ros MM, 2012	Europe	EPIC	856	8.9 years	M/F	1.11	0.82	1.51	≥143.77 vs. ≤73.11 mg/d
Roswall N, 2009	Denmark	Danish Diet, Cancer and Health study	322	10.6 years	M/F	0.99	0.70	1.39	>120.5vs. ≤62.8 mg/d

Table 96 Overall evidence on dietary vitamin C and bladder cancer

SLR	Summary of evidence
2005 SLR	Four studies were identified and three studies were included in the meta-analysis which showed a non-significant association overall
CUP	Two new studies were identified, both showed non-significant results.

Table 97 Summary of results of the dose-response meta-analysis of dietary vitamin C and bladder cancer

Bladder cancer		
	2005 SLR	CUP
Studies (n)	3	5
Cases (n)	984	2162
Increment unit	Per 40mg/day	Per 40mg/day
RR (95% CI)	1.07 (0.97-1.18)	1.02 (0.95-1.10)
Heterogeneity (I^2, p-value)	I^2=19.6%, p=0.29	I^2=31.8%, p=0.21

Table 98 Inclusion/exclusion table for meta-analysis of dietary vitamin C and bladder cancer

WCRF code	Author	Year	Study design	Study name	Sex	Cancer outcome	2005 SLR	CUP dose-response	CUP H vs. L forest plot	Estimated values	Exclusion reason
BLA97211	Ros MM	2012	Prospective cohort study	EPIC study	M/F	Incidence	No	Yes	Yes	Midpoints	
BLA97168	Roswall N	2009	Prospective cohort study	Danish Diet, Cancer and Health study	M/F	Incidence	No	Yes	Yes	Midpoints. Person-years	
BLA00335	Zeegers M	2001(c)	Prospective cohort study	Netherlands Cohort Study	M/F	Incidence	Yes	Yes	Yes	Estimated RR	
BLA00185	Michaud D	2002	Prospective cohort study	ATBC study	M	Incidence/Mortality	Yes	Yes	Yes	Person-years	
BLA00432	Michaud D	2000	Prospective cohort study	Health Professionals Follow-up study	M	Incidence	Yes	No	Yes		Insufficient data
BLA00922	Shibata A	1992	Prospective cohort study	Laguna Hills Study USA	M	Incidence	Yes	Yes	Yes	Person-years	

Figure 89 Highest versus lowest forest plot of dietary vitamin C and bladder cancer

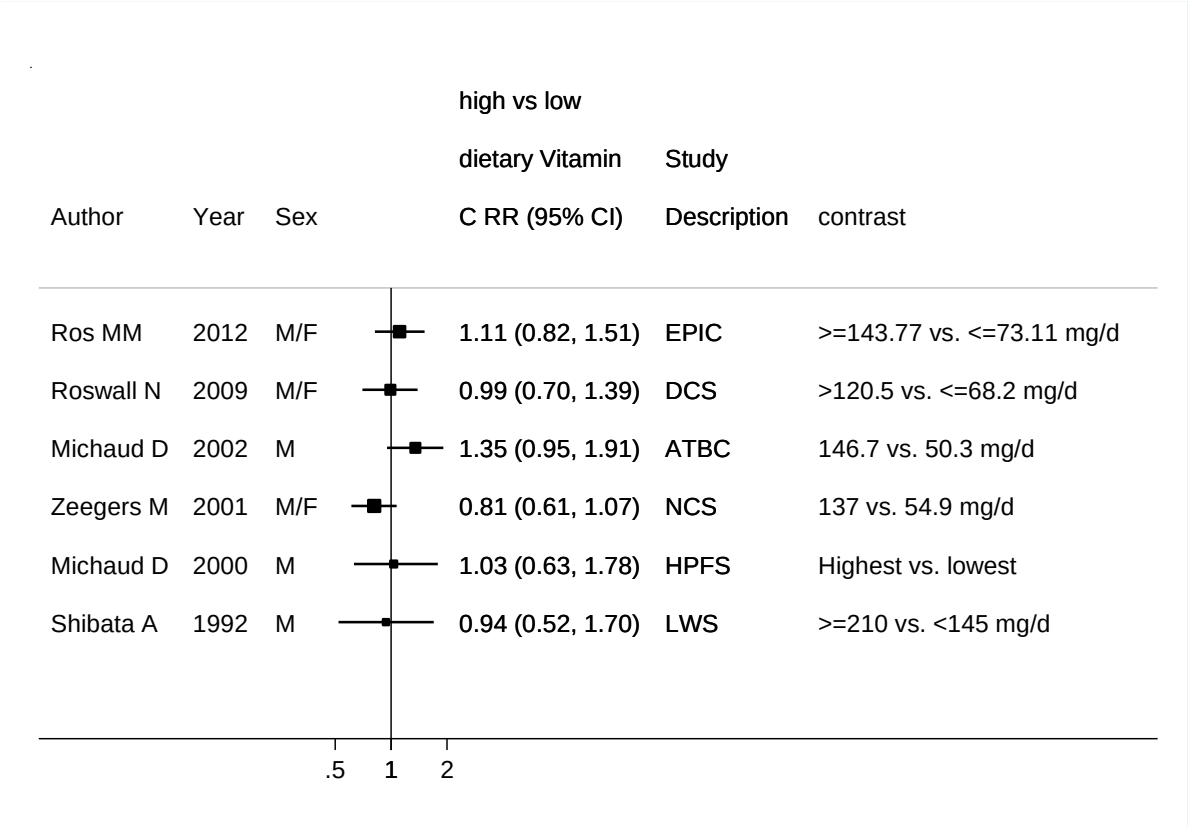


Figure 90 Dose-response meta-analysis of dietary vitamin C and bladder cancer, per 40mg/day

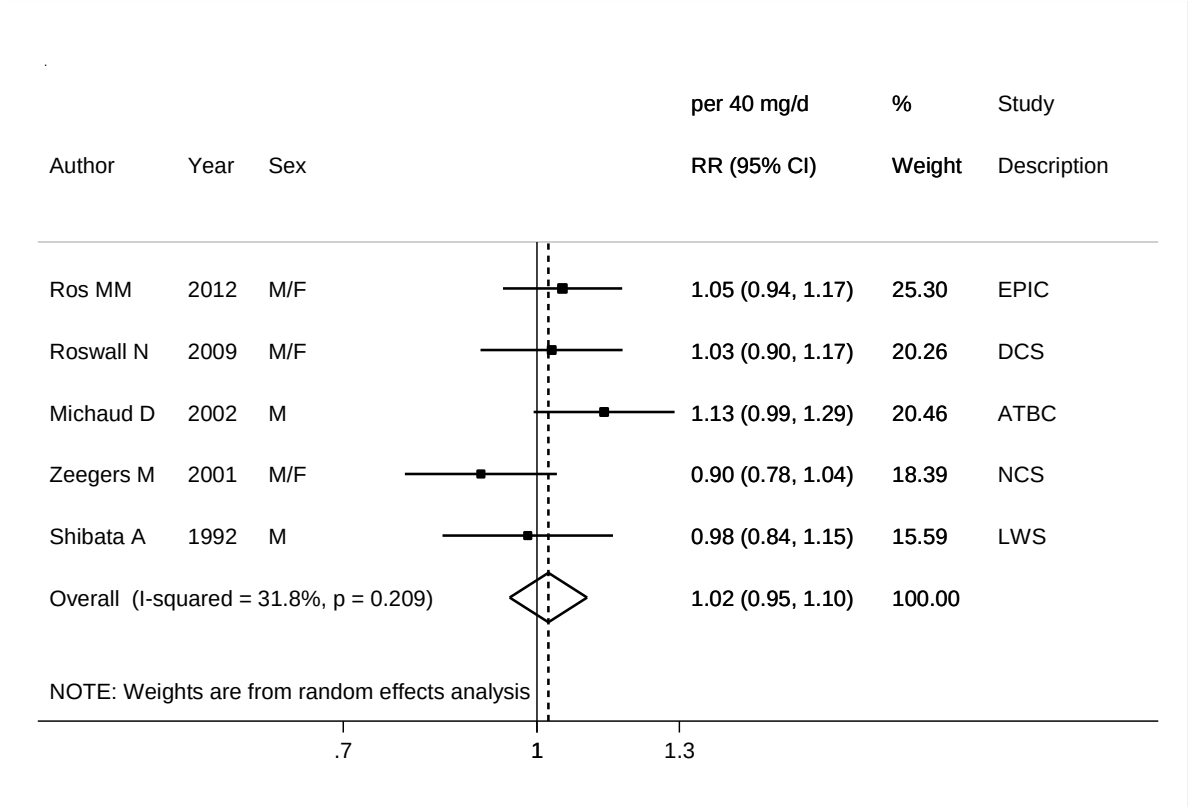
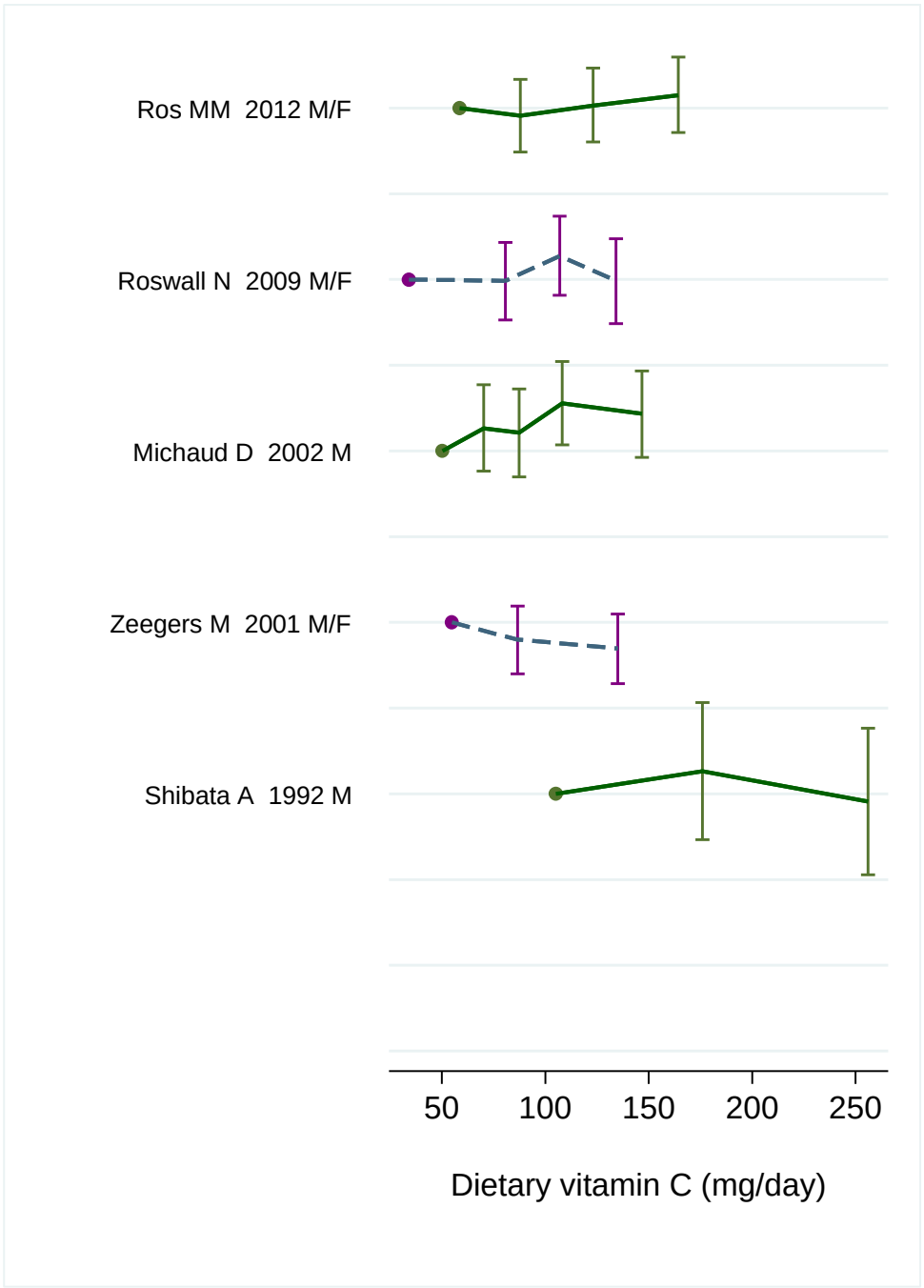


Figure 91 Dose-response graph of dietary vitamin C and bladder cancer



5.5.9 Vitamin C supplements

Methods

Eight studies were identified, three of them during the CUP. Four studies were included in the meta-analysis. The dose response results are presented for an increment of 40 mg/day.

Main results

The summary RR per 40 mg/day of vitamin C supplements was 0.99 (95% CI: 0.98-1.00, I^2=26.9%, pheterogeneity=0.25, n=4).

Heterogeneity

There was evidence of low heterogeneity, I^2=26.9%, pheterogeneity=0.25.

Comparison with the Second Expert Report

Two studies from the five studies identified on vitamin C supplements and bladder cancer were included in the meta-analysis and showed a non-significant relationship.

Published meta-analyses or pooled analyses

No published meta-analyses or pooled analyses were identified.

Table 99 Studies on vitamin C supplements identified during the CUP

Author/year	Country	Study name	Number of cases	Years of follow-up	Sex	RR	LCI	UCI	Contrast
Hotaling J, 2011	USA	VITamins And Lifestyle cohort	330	6 years	M/F	0.90	0.67	1.23	>322.06-1600 vs. 0 mg/d
Roswall N, 2009	Denmark	Danish Diet, Cancer and Health study	322	10.6 years	M/F	1.19	0.86	1.66	>34.1-≥60 vs. 0 mg/d
Iso H, 2007	Japan	JACC Study	91	12 years	M	1.98	0.85	4.59	Use vs. no use

Table 100 Overall evidence on vitamin C supplements and bladder cancer

SLR	Summary of evidence
2005 SLR	Five studies were identified and two studies were included in the meta-analysis, which showed a non-significant relationship.
CUP	Three new studies were identified, all studies showed non-significant results.

Table 101 Summary of results of the dose-response meta-analysis of vitamin C supplements and bladder cancer

Bladder cancer		
	2005 SLR	CUP
Studies (n)	2	4
Cases (n)	389	1041
Increment unit	Per 40mg/day	Per 40mg/day
RR (95% CI)	0.98 (0.95-1.01)	0.99 (0.98-1.00)
Heterogeneity (I^2, p-value)	I^2=67.9%, p=0.08	I^2=26.9%, p=0.25

Table 102 Inclusion/exclusion table for meta-analysis of vitamin C supplements and bladder cancer

WCRF code	Author	Year	Study design	Study name	Sex	Cancer outcome	2005 SLR	CUP dose-response	CUP H vs. L forest plot	Estimated values	Exclusion reason
BLA97180	Hotaling J	2011	Prospective cohort study	VITamins And Lifestyle cohort	M/F	Incidence	No	Yes	Yes	Midpoints. Person-years	
BLA97168	Roswall N	2009	Prospective cohort study	Danish Diet, Cancer and Health study	M/F	Incidence	No	Yes	Yes	Midpoints. Person-years	
BLA97203	Iso H	2007	Prospective cohort study	Japan Collaborative Cohort Study (JACC Study)	M	Mortality	No	No	Yes		Only high versus low results
BLA11803	Holick C	2005	Prospective cohort study	Nurses' Health Study	F	Incidence	Yes	No	No		No RRs. Reported in the text that vitamin C supplements were not related to bladder cancer risk
BLA00179	Jacobs E	2002	Prospective cohort study	Cancer Prevention Study II	M/F	Incidence	Yes	No	Yes		Only results on the duration of vitamin C supplementation
BLA00335	Zeegers M	2001(c)	Prospective cohort study	Netherlands Cohort Study	M/F	Incidence	Yes	No	Yes	Estimated RR	
BLA00432	Michaud D	2000	Prospective cohort study	Health Professionals Follow-up study	M	Incidence	Yes	Yes	Yes	Midpoints	
BLA00922	Shibata A	1992	Prospective cohort study	Laguna Hills Study USA	M	Incidence	Yes	Yes	Yes		

Figure 92 Highest versus lowest forest plot of vitamin C supplements and bladder cancer

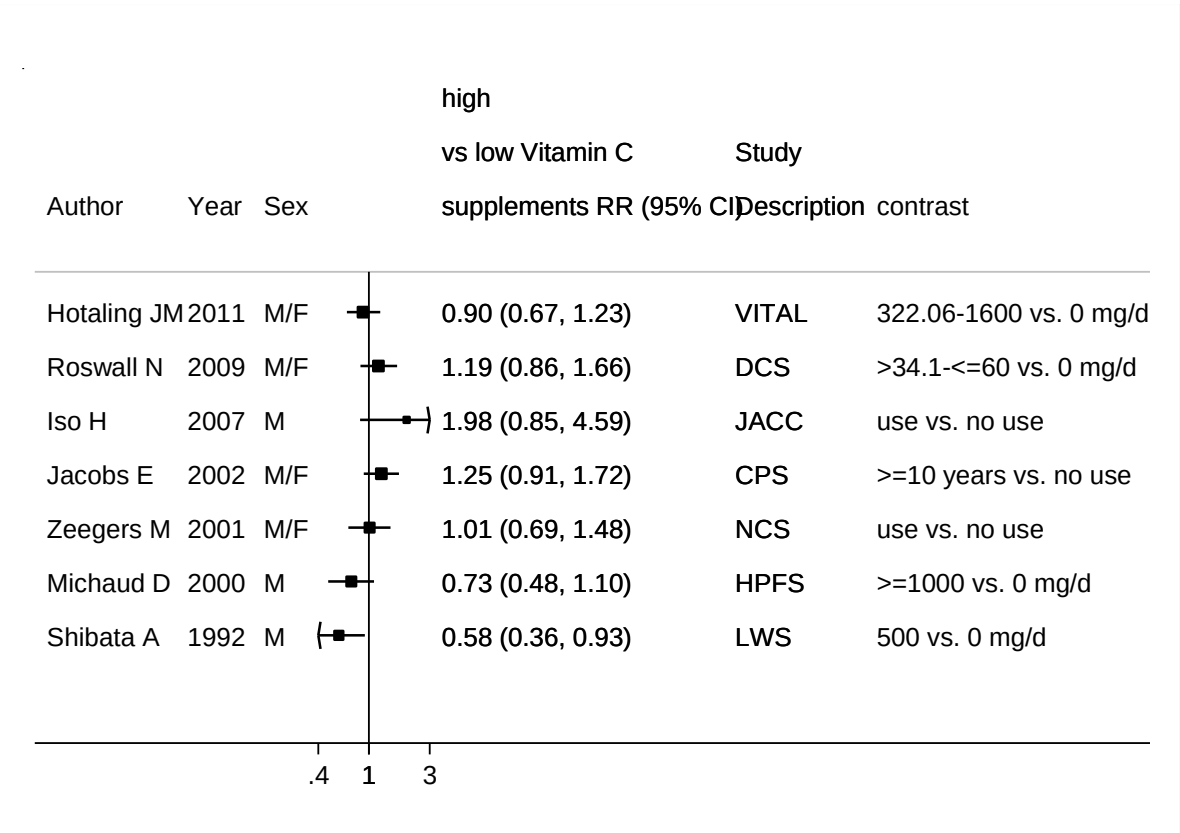


Figure 93 Dose-response meta-analysis of vitamin C supplements and bladder cancer, per 40mg/day

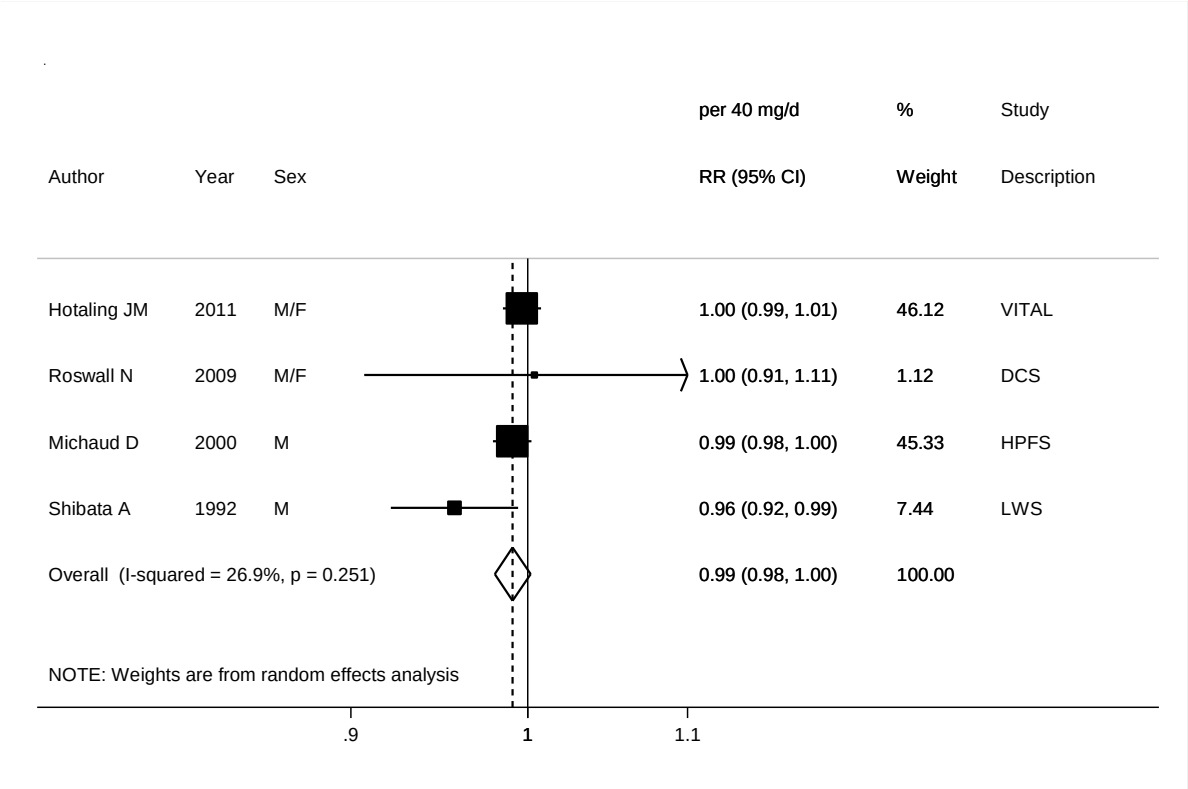
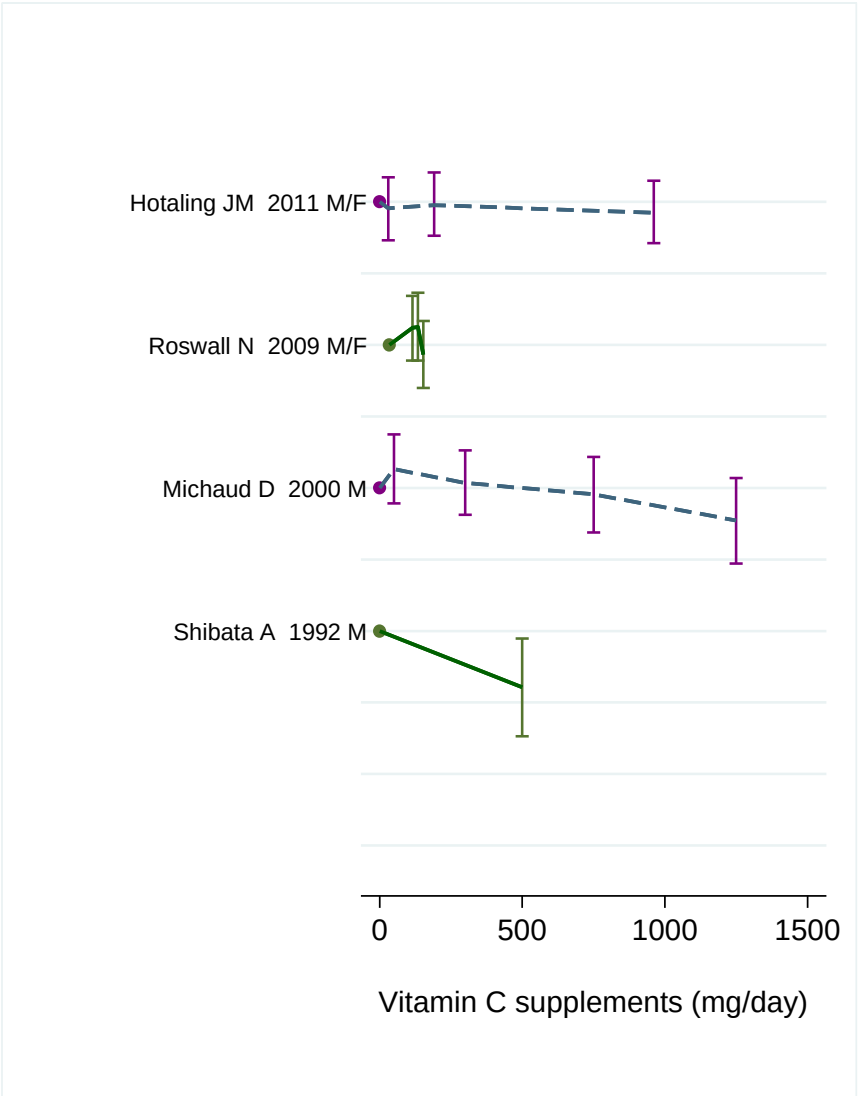


Figure 94 Dose-response graph of vitamin C supplements and bladder cancer



5.5.10 Blood25-hydroxy vitamin D

Methods

Three studies were identified, all during the CUP. One was on plasma 25-hydroxy vitamin D (Afzal, 2013) and the two others were on serum levels.

All studies were on bladder cancer and all results were adjusted by smoking status, pack-years, and other covariates.

Main results

The summary RR 10nmol/L of blood 25-hydroxy vitamin D was 1.11 (95% CI: 0.92-1.34, I^2=83%, pheterogeneity=0.003, n=3). It was not possible to stratify the analysis by smoking status.

Heterogeneity

There was evidence of high heterogeneity, I^2=83%, pheterogeneity=0.003.

Comparison with the Second Expert Report

In the 2005 SLR no studies on blood 25-hydroxy vitamin D and bladder cancer were identified.

Published meta-analyses or pooled analyses

No published meta-analyses or pooled analyses were identified.

Table 103 Studies on blood 25-hydroxy vitamin D identified during the CUP

Author/year	Country	Study name	Number of cases	Years of follow-up	Sex	RR	LCI	UCI	Contrast
Afzal S, 2013	Denmark	Copenhagen City Heart Study	112	28 years	M/F	1.28	1.06	1.54	Per 50% reduction in plasma 25(OH)D
Mondul AM, 2012	USA	PLCO study	375	-	M/F	0.74 0.85	0.29 0.53	1.87 1.38	<25 vs. 50-<75 nmol/L ≥75 vs. 50-<75 nmol/L
Mondul AM, 2010	Finland	ATBC study	250	-	M	1.73	1.03	2.91	<25 vs. ≥50 nmol/L

Table 104 Overall evidence on blood 25-hydroxy vitamin D and bladder cancer

SLR	Summary of evidence
2005 SLR	No study was identified.
CUP	Three new studies reported on blood 25-hydroxy vitamin D and bladder cancer. Two studies showed that lower 25(OH) D was associated with a statistically significantly increased risk of bladder cancer.

Table 105 Summary of results of the dose-response meta-analysis of blood 25-hydroxy vitamin D and bladder cancer

Bladder cancer		
	2005 SLR*	CUP
Studies (n)		3
Cases (n)		737
Increment unit		Per 10 nmol/L
RR (95% CI)		1.11 (0.92-1.34)
Heterogeneity (I^2, p-value)		I^2=83%, p<0.01

* No meta-analysis was conducted in the SLR.

Table 106 Inclusion/exclusion table for meta-analysis of blood 25-hydroxy vitamin D and bladder cancer

WCRF code	Author	Year	Study design	Study name	Sex	Cancer outcome	2005 SLR	CUP dose-response	CUP H vs. L forest plot	Estimated values	Exclusion reason
BLA97214	Afzal S	2013	Prospective Cohort Study	Copenhagen City Heart Study	M/F	Incidence	No	Yes	No		Only continuous results provided
BLA97207	Mondul AM	2012	Nested case-control study	Prostate, Lung, Colorectal, and Ovarian (PLCO) Cancer Screening Study	M/F	Incidence	No	Yes	Yes		
BLA97178	Mondul AM	2010	Nested case-control study	Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study	M	Incidence	No	Yes	Yes		

Figure 95 Lowest versus highest forest plot of blood 25-hydroxy vitamin D and bladder cancer

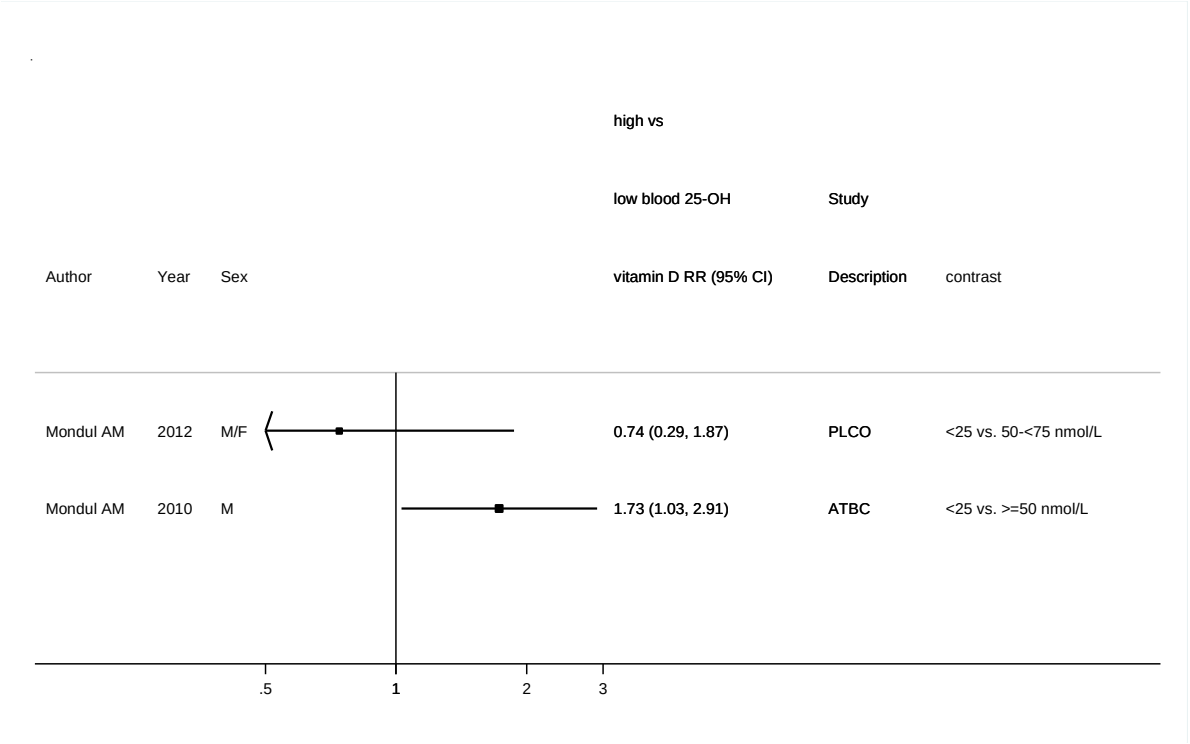
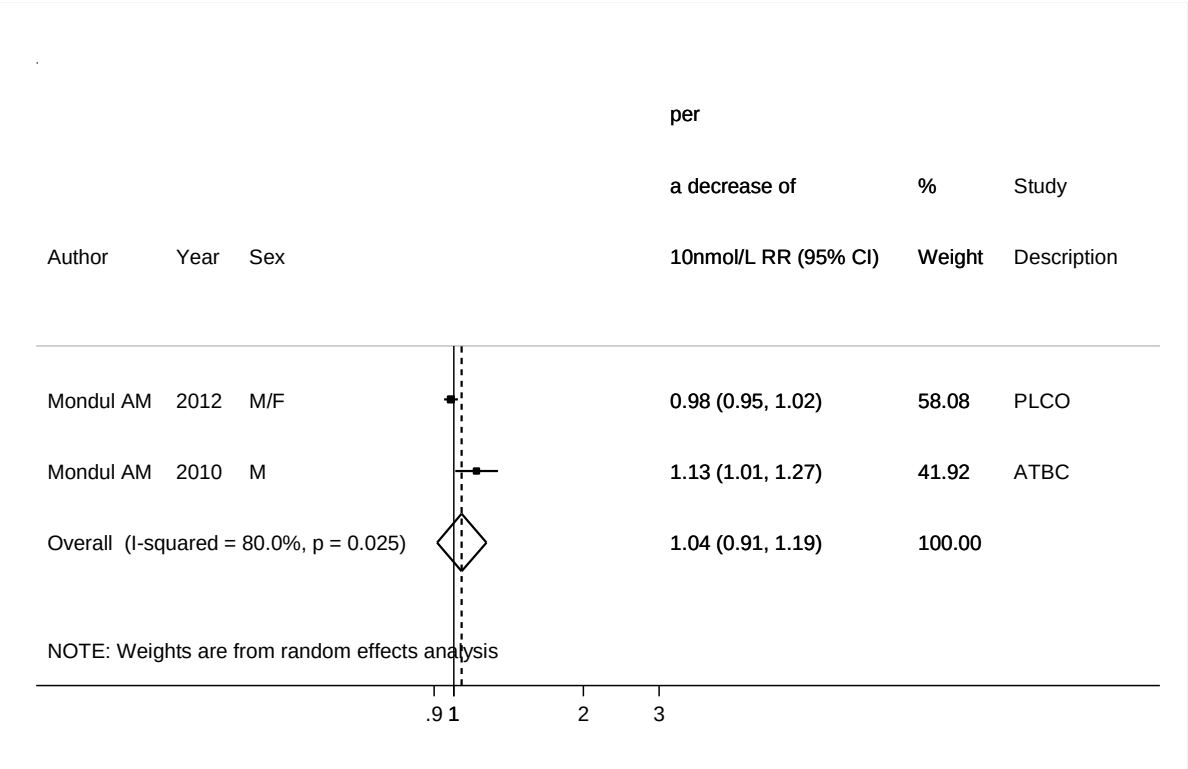


Figure 96 Dose-response meta-analysis of blood 25-hydroxy vitamin D and bladder cancer, per a decrease of 10nmol/L



5.5.11 Vitamin E supplements

Methods

8 studies, 3 were identified during the CUP. Due to the high variability of the units used to assess the vitamin E supplementation only 4 studies could be included in the dose-response meta-analysis. 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.

Main results

The summary RR per 100 IU/day of vitamin E supplement was 0.99 (95% CI: 0.97-1.01, I^2=12.1%, pheterogeneity=0.33, n=4). It was not possible to stratify the analysis by smoking status.

Heterogeneity

There was evidence of low heterogeneity, I^2=12.1%, pheterogeneity=0.33.

Comparison with the Second Expert Report

In the 2005 SLR the evidence relating vitamin E supplements use to bladder cancer was considered limited- no conclusion.

Published meta-analyses or pooled analyses

No published meta-analyses or pooled analyses were identified.

Table 107 Studies on vitamin E supplements identified during the CUP

Author/year	Country	Study name	Number of cases	Years of follow-up	Sex	RR	LCI	UCI	Contrast
Hotaling J, 2011	USA	VITamins And Lifestyle cohort	330	6 years	M/F	0.95	0.70	1.29	215.1-1000 vs. 0 mg/d
Roswall N, 2009	Denmark	Danish Diet, Cancer and Health study	322	10.6 years	M/F	0.97	0.66	1.44	>10 vs. 0 mg/d
Iso H, 2007	Japan	JACC Study	91	12 years	M	0.75	0.18	3.06	Use vs. no use
			39		F	0.39	0.05	2.87	

Table 108 Overall evidence on vitamin E supplements and bladder cancer

SLR	Summary of evidence
2005 SLR	Two studies were included in the meta-analysis, which showed a non-significant relationship between vitamin E supplements and bladder cancer.
CUP	Two new studies could be included in the dose-response meta-analysis; both showed a non-significant relationship between vitamin E supplements and bladder cancer.

Table 109 Summary of results of the dose-response meta-analysis of vitamin E supplements and bladder cancer

Bladder cancer		
	2005 SLR	CUP
Studies (n)	2	4
Cases (n)	389	1041
Increment unit	100 IU/day	Per 100 IU/day
RR (95% CI)	0.95(0.91-1.00)	0.99 (0.97-1.01)
Heterogeneity (I^2, p-value)	I^2=0%, p=0.39	I^2=12.1%, p=0.33

Table 110 Inclusion/exclusion table for meta-analysis of vitamin E supplements and bladder cancer

WCRF code	Author	Year	Study design	Study name	Sex	Cancer outcome	2005 SLR	CUP dose-response	CU H vs. L forest plot	Estimated values	Exclusion reason
BLA97180	Hotaling J	2011	Prospective cohort study	VITamins And Lifestyle cohort	M/F	Incidence	No	Yes	Yes	Midpoints. Person-years. Conversion to IU/day	
BLA97168	Roswall N	2009	Prospective cohort study	Danish Diet, Cancer and Health study	M/F	Incidence	No	Yes	Yes	Midpoints. Person-years. Conversion to IU/day	
BLA97203	Iso H	2007	Prospective cohort study	Japan Collaborative Cohort Study (JACC Study)	M/F	Mortality	No	No	Yes		Only high versus low results
BLA11803	Holick C	2005	Prospective cohort study	Nurses' Health Study	F	Incidence	Yes	No	No		Identified in the 2005 SLR, relationship not quantified, only reported in the text that vitamin E supplements were not related to bladder cancer risk
BLA00179	Jacobs E	2002	Prospective cohort study	Cancer Prevention Study II	M/F	Incidence	Yes	No	Yes		Only results on the duration of vitamin E supplementation
BLA00335	Zeegers M	2001(c)	Prospective cohort study	Netherlands Cohort Study	M/F	Incidence	Yes	No	Yes	Estimated RR	

BLA00432	Michaud D	2000	Prospective cohort study	Health Professionals Follow-up study	M	Incidence	Yes	Yes	Yes	Midpoints. Conversion to IU/day	
BLA00922	Shibata A	1992	Prospective cohort study	Laguna Hills Study USA	M	Incidence	Yes	Yes	Yes	Conversion to IU/day	

Figure 97 Highest versus lowest forest plot of vitamin E supplements and bladder cancer

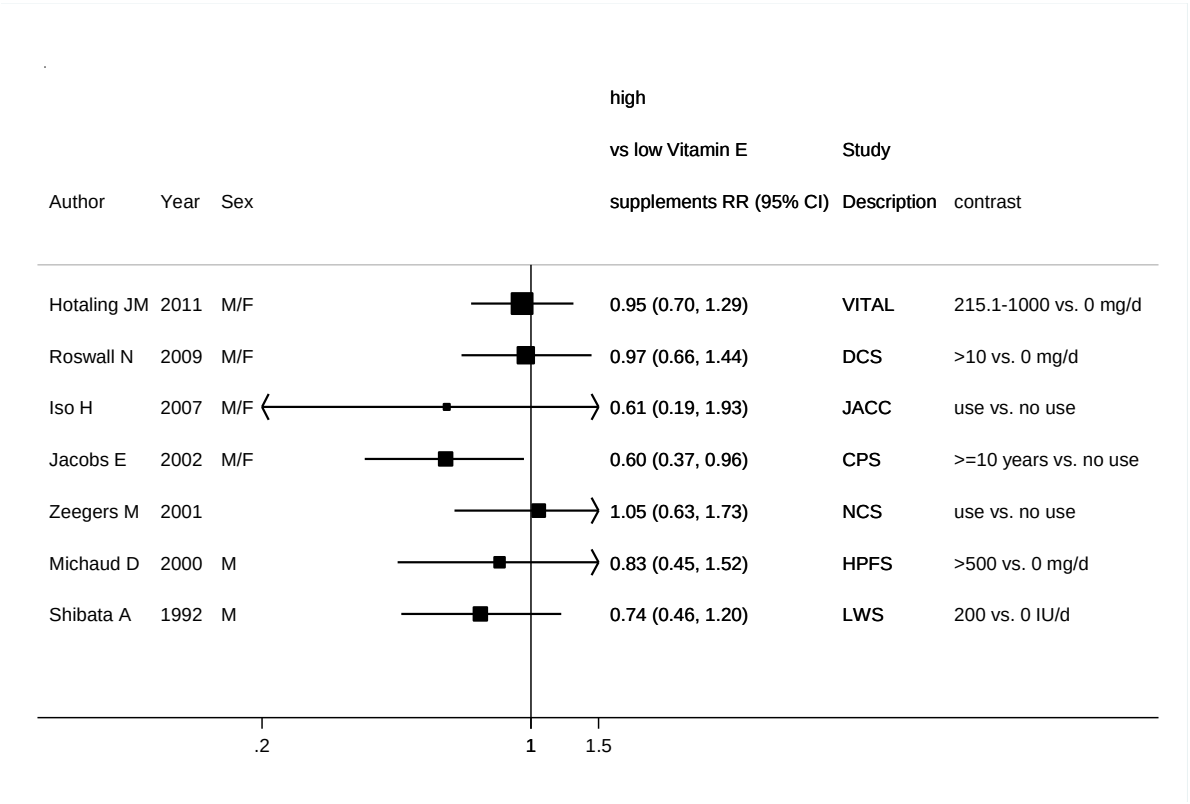


Figure 98 Dose-response meta-analysis of vitamin E supplements and bladder cancer, per 100 IU/day

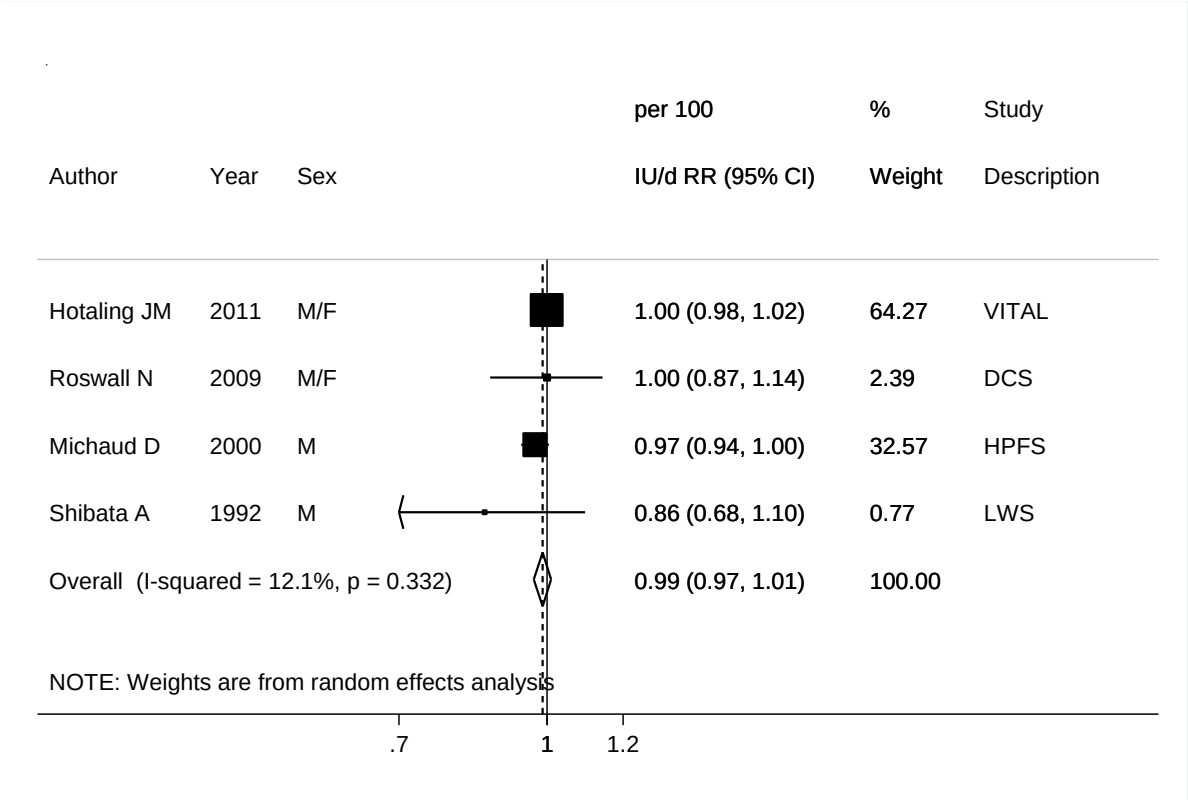
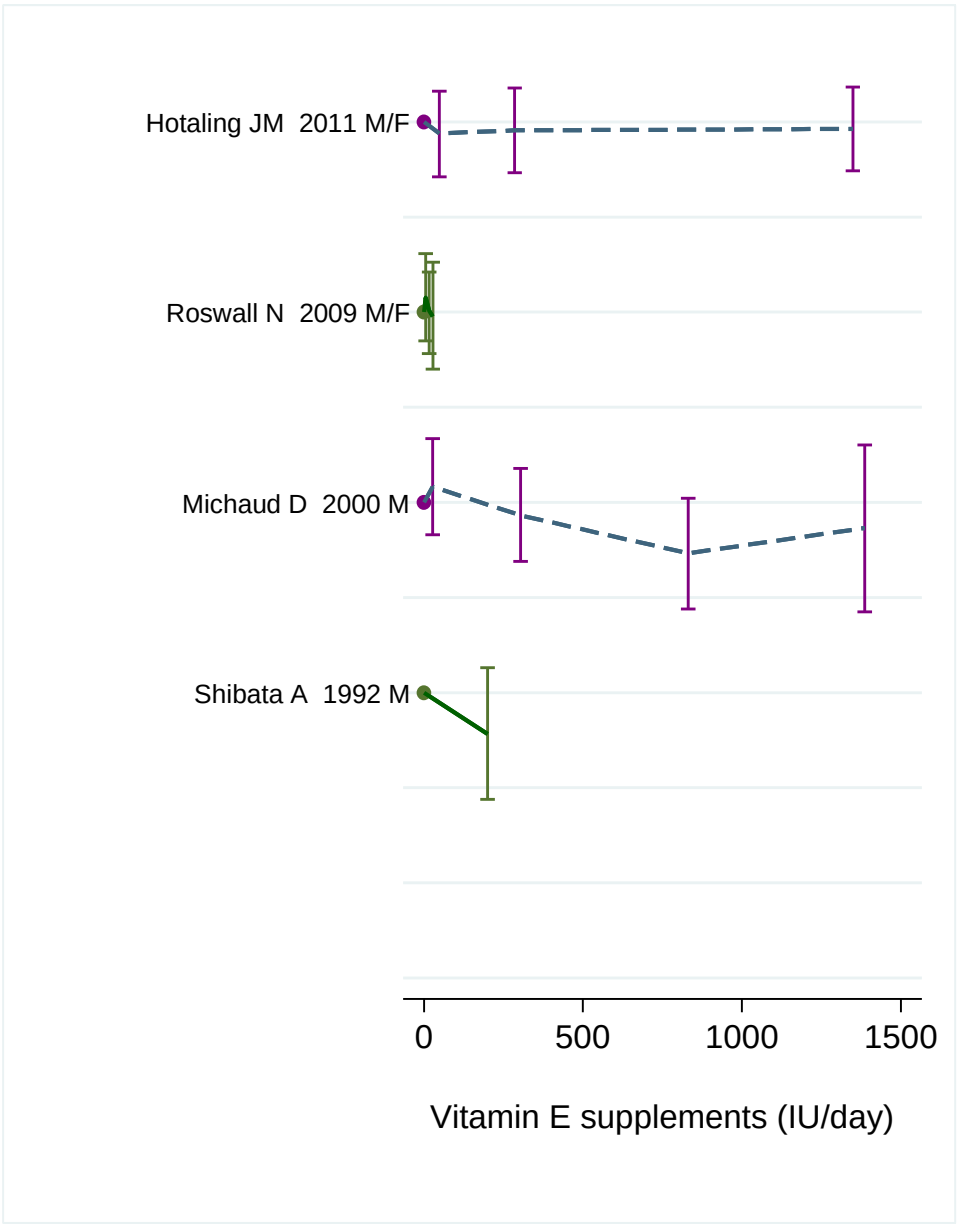


Figure 99 Dose-response graph of vitamin E supplements and bladder cancer



5.5.13 Multivitamins

Methods

Five studies were identified, three of which during the CUP. Due to the high variability of units used to assess multivitamin use, only high versus low analysis could be conducted.

Main results

The overall result of the highest versus lowest analysis was 1.05 (95% CI: 0.78-1.41, I^2=62.4%, pheterogeneity=0.05, n=4).

Comparison with the Second Expert Report

In the 2005 SLR the evidence relating multivitamin use to bladder cancer was considered limited- no conclusion.

Published meta-analyses or pooled analyses

No published meta-analyses or pooled analyses were identified.

Table 111 Studies on multivitamins identified during the CUP

Author/year	Country	Study name	Number of cases	Years of follow-up	Sex	RR	LCI	UCI	Contrast
Hotaling J, 2011	USA	VITamins And Lifestyle cohort	330	6 years	M/F	0.98	0.76	1.28	>8-10 vs. 0 pills-yrs
Neuhouser M, 2009	USA	Women's Health Initiative	379	8 years	F	0.83	0.65	1.06	Yes vs. no
Iso H, 2007	Japan	JACC Study	91	12 years	M	2.08	1.15	3.75	Use vs. no use
			40		F	1.25	0.36	4.28	

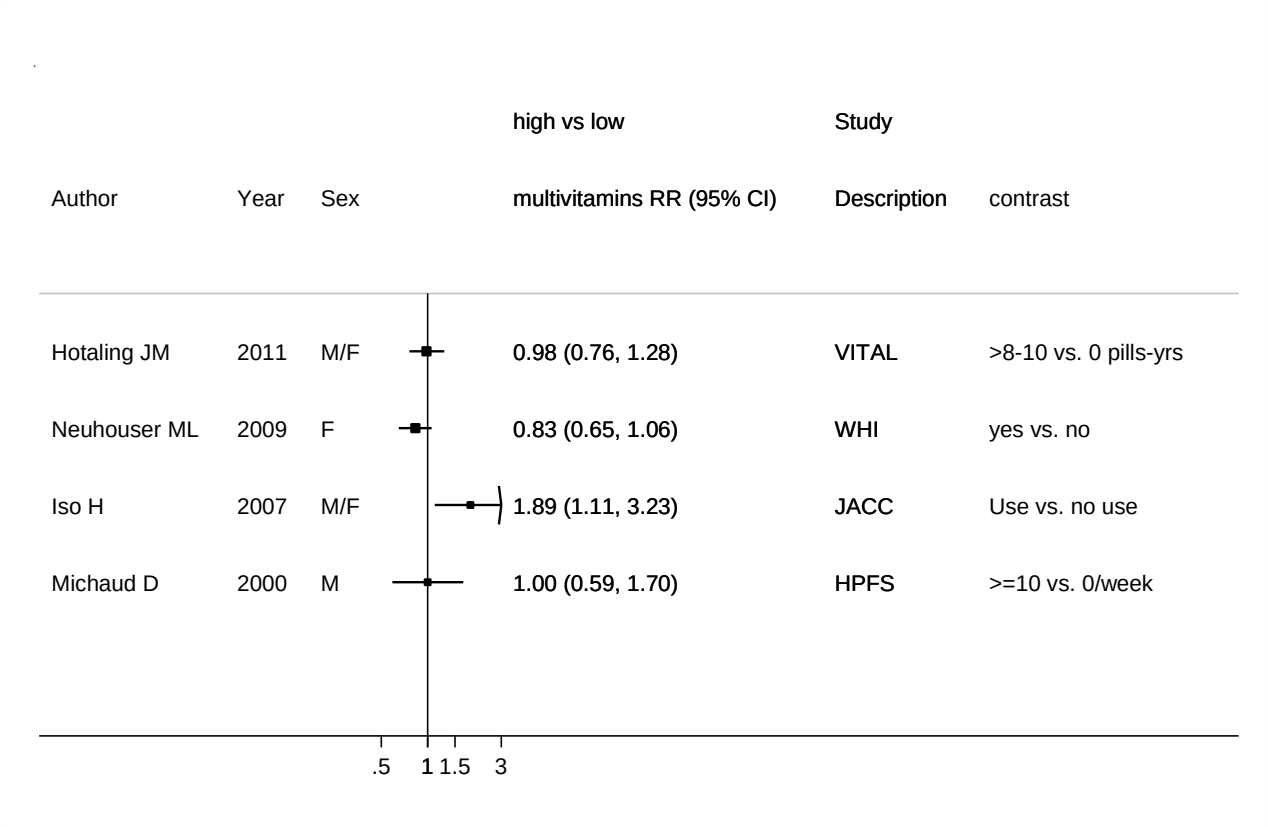
Table 112 Overall evidence on multivitamins and bladder cancer

SLR	Summary of evidence
2005 SLR	Two studies were identified. One mentioned in the text that supplement intake of multivitamins was not related to bladder cancer risk and the other showed a non-significant relationship between multivitamins and bladder cancer. No meta-analysis was conducted in the 2005 SLR.
CUP	Three new studies were identified. Only one showed a significant increase risk of bladder cancer for men taking multivitamins. All the other studies showed non-significant results.

Table 113 Inclusion/exclusion table for meta-analysis of multivitamins and bladder cancer

WCRF code	Author	Year	Study design	Study name	Sex	Cancer outcome	2005 SLR	CUP dose-response	CUP H vs. L forest plot	Estimated values	Exclusion reason
BLA97180	Hotaling J	2011	Prospective cohort study	VITamins And Lifestyle cohort	M/F	Incidence	No	No	Yes		
BLA97170	Neuhouser M	2009	Prospective cohort study	Women's Health Initiative	F	Incidence	No	No	Yes		
BLA97203	Iso H	2007	Prospective cohort study	Japan Collaborative Cohort Study (JACC Study)	M/F	Mortality	No	No	Yes		
BLA11803	Holick C	2005	Prospective cohort study	Nurses' Health Study	F	Incidence	Yes	No	No		Identified in the 2005 SLR, relationship not quantified, only reported in the text that multivitamin use was not related to bladder cancer risk
BLA00432	Michaud D	2000	Prospective cohort study	Health Professionals Follow-up study	M	Incidence	Yes	No	Yes		

Figure 100 Highest versus lowest forest plot of multivitamins and bladder cancer



5.6.3 Dietary calcium

Methods
Four studies were identified, 3 of them during the CUP. The dose response results are presented for an increment of 200 mg/day.

Main results
The summary RR per 200 mg/day of dietary calcium was 1.00 (95% CI: 0.97-1.03, I^2=59.6%, pheterogeneity=0.06, n=4).

Heterogeneity
There was evidence of high heterogeneity, I^2=59.6%, pheterogeneity=0.06.

Comparison with the Second Expert Report
One study on dietary calcium and bladder cancer was identified in the 2005 SLR and showed non-significant relationship.

Published meta-analyses or pooled analyses
No published meta-analyses or pooled analyses were identified.

Table 114 Studies on dietary calcium identified during the CUP

Author/year	Country	Study name	Number of cases	Years of follow-up	Sex	RR	LCI	UCI	Contrast
Allen NE, 2012	Europe	EPIC study	1416	11.3 years	M/F	1.24	1.01	1.52	1,197 vs. 732 mg/d
						1.03	0.98	1.07	Per 300mg/day
Park Y, 2009	USA	NIH-AARP	1417	7 years	M	0.94	0.78	1.12	1247 vs. 478 mg/d
			264		F	1.23	0.82	1.84	1101 vs. 409 mg/d
Keszei AP, 2010	Netherlands	The Netherlands Cohort Study	1549	16.3 years	M/F	0.97	0.76	1.24	1353 vs. 545 mg/d

Table 115 Overall evidence on dietary calcium and bladder cancer

SLR	Summary of evidence
2005 SLR	One study was identified and showed a non-significant relationship.
CUP	Three new studies were identified; one study showed a significant increase risk of bladder cancer with higher consumption of dietary calcium. A non-significant association was observed in the other studies.

Table 116 Summary of results of the dose-response meta-analysis of dietary calcium and bladder cancer

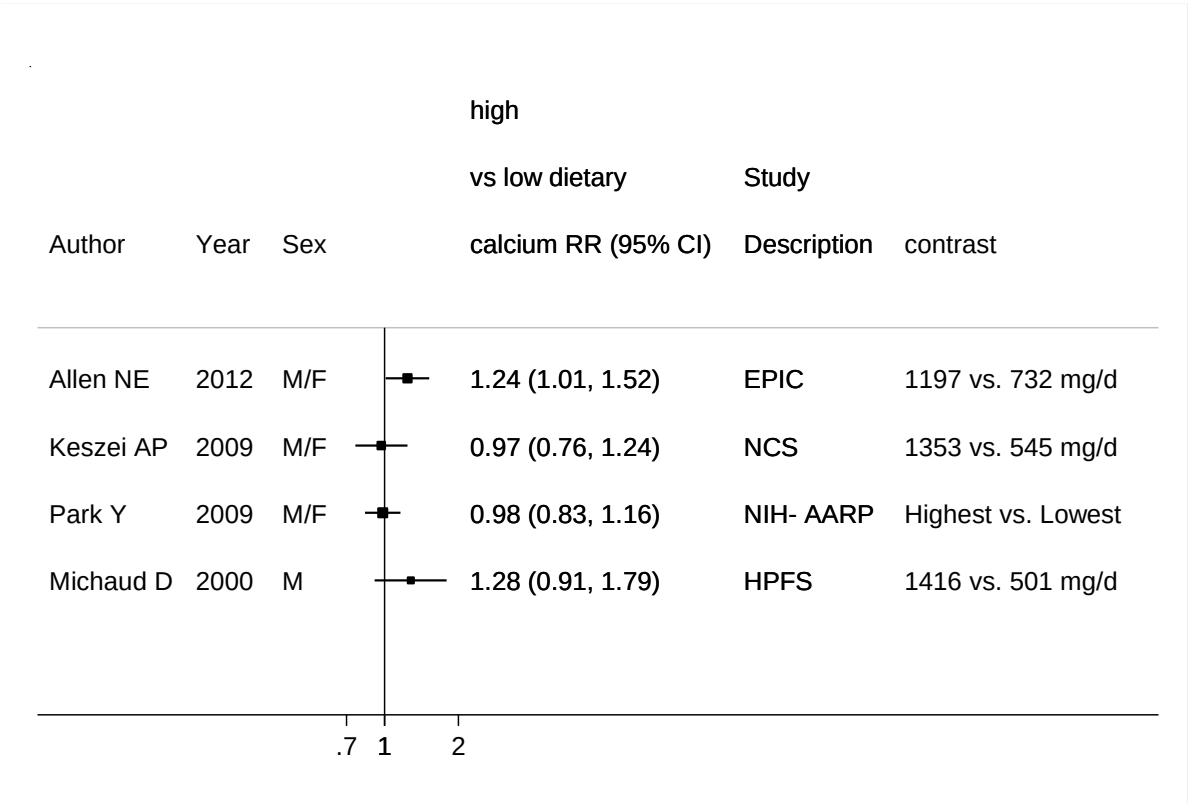
Bladder cancer		
	2005 SLR*	CUP
Studies (n)		4
Cases (n)		4966
Increment unit		Per 200mg/day
RR (95% CI)		1.00 (0.97-1.03)
Heterogeneity (I^2, p-value)		I^2=59.6%, p=0.06

* No meta-analysis was conducted in the SLR.

Table 117 Inclusion/exclusion table for meta-analysis of dietary calcium and bladder cancer

WCRF code	Author	Year	Study design	Study name	Sex	Cancer outcome	2005 SLR	CUP dose-response	CUP H vs. L forest plot	Estimated values	Exclusion reason
BLA97199	Allen NE	2012	Prospective cohort study	EPIC study	M/F	Incidence	No	Yes	Yes		
BLA97216	Park Y	2009	Prospective cohort study	NIH-AARP	M/F	Incidence	No	Yes	Yes	Person-years	
BLA97172	Keszei AP	2009	Prospective cohort study	The Netherlands Cohort Study	M/F	Incidence	No	Yes	Yes		
BLA00432	Michaud D	2000	Prospective cohort study	Health Professionals Follow-up study	M	Incidence	Yes	Yes	Yes	Person-years	

Figure 101 Highest versus lowest forest plot of dietary calcium and bladder cancer



For Park Y, 2009 the contrast was 1247 vs. 478 mg/d for men and 1101 vs. 409 mg/d for women.

Figure 102 Dose-response meta-analysis of dietary calcium and bladder cancer, per 200mg/day

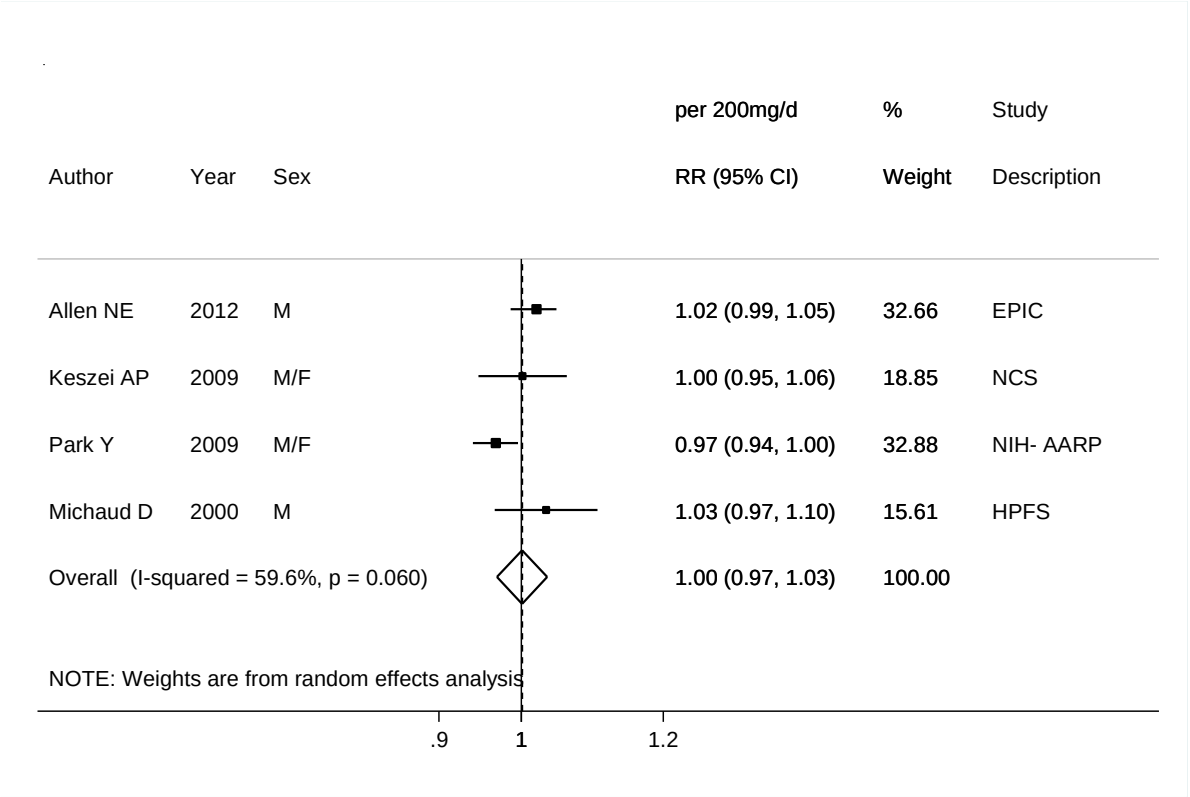
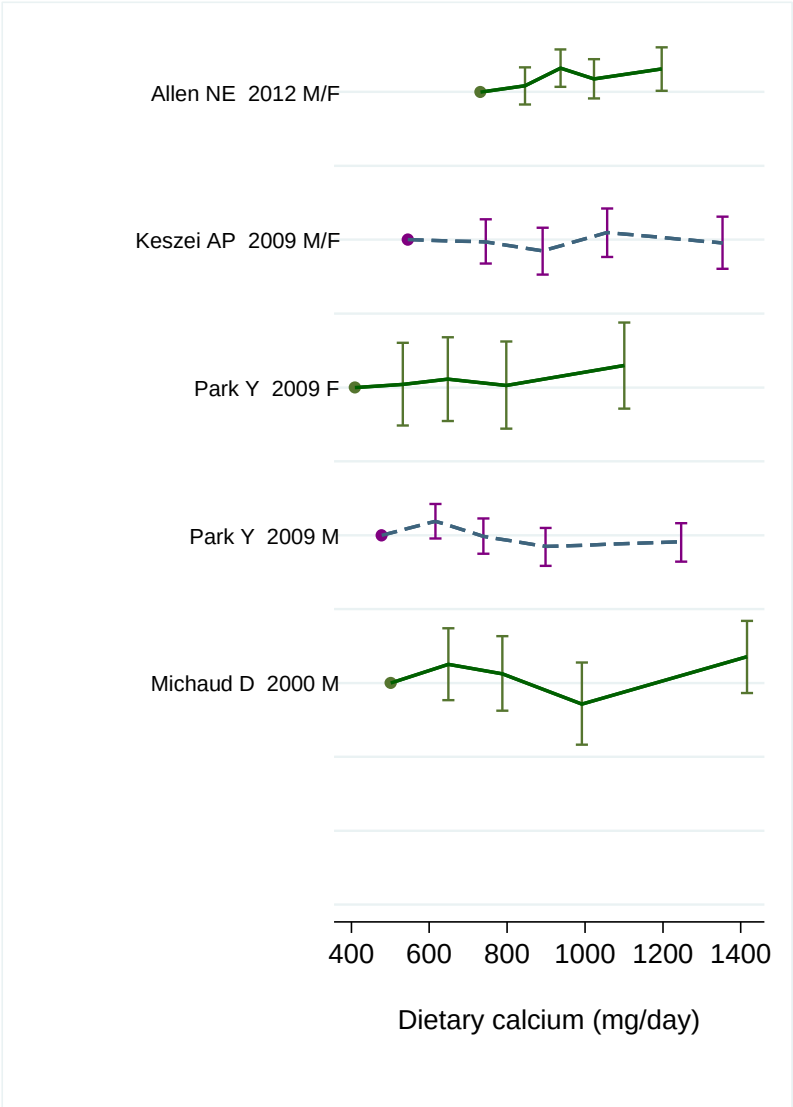


Figure 103 Dose-response graph of dietary calcium and bladder cancer



5.6.3 Calcium supplements

Methods

Only two cohort studies have been identified, both in the CUP. Analyses were conducted to complement the analyses on dietary calcium. Because in one study supplemental calcium was categorized in two levels, it was only possible to conduct high versus low analysis.
One randomised controlled trial was identified. The Women's Health Initiative (WHI) trial of calcium plus vitamin D (Brunner R. 2011).

Main results

The overall result of the highest versus lowest analysis was 0.92 (95% CI: 0.72-1.17, I^2=0%, pheterogeneity=0.48, n=2).

Comparison with the Second Expert Report

No studies on supplemental calcium and bladder cancer were found in the 2005 SLR.

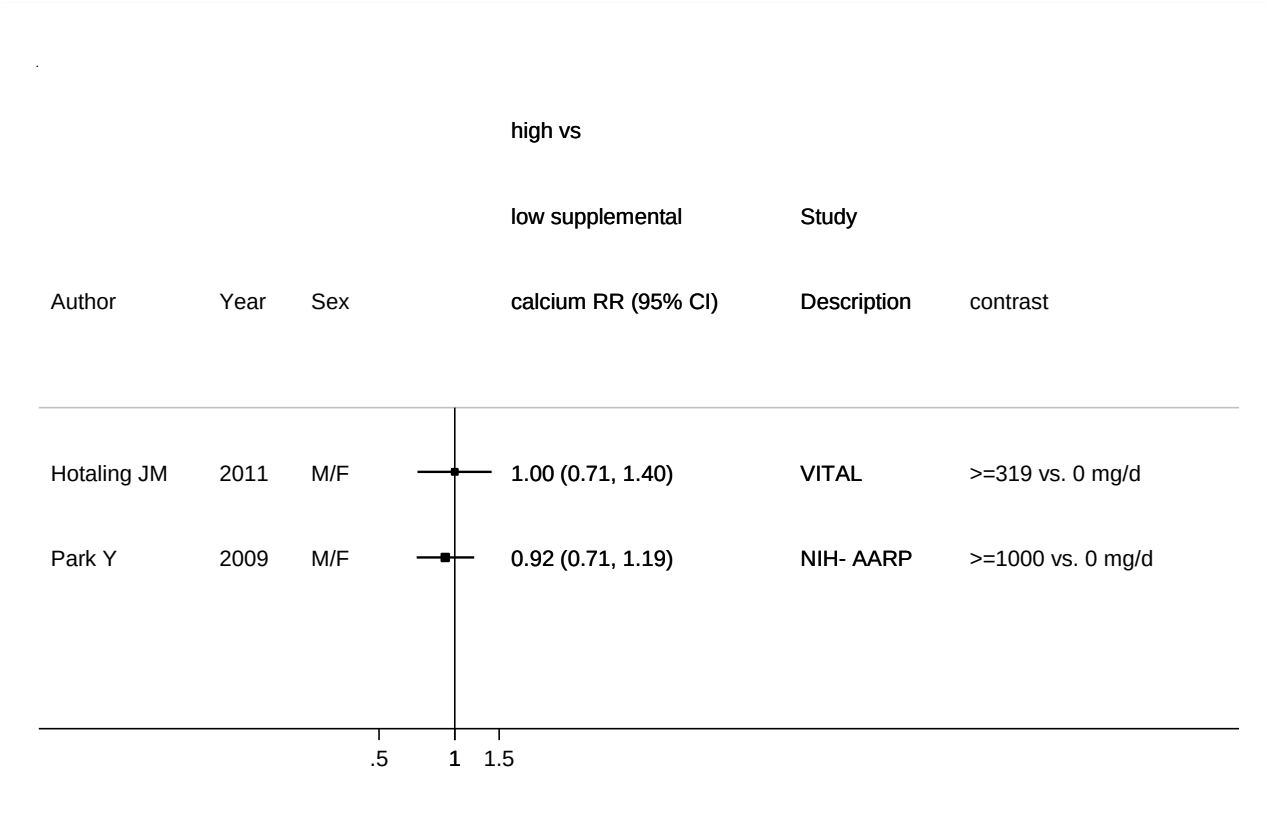
Published meta-analyses or pooled analyses

No published meta-analyses or pooled analyses were identified.

Table 118 Studies on supplemental calcium identified during the CUP

Author/year	Country	Study name	Number of cases	Years of follow-up	Sex	RR	LCI	UCI	Contrast
Hotaling J, 2011	USA	VITamins And Lifestyle cohort	330	6 years	M/F	1.00	0.71	1.40	≥319 vs. 0 mg/d
Park Y, 2009	USA	NIH-AARP	1417	7 years	M	0.84	0.59	1.18	≥1000 vs. 0mg/d
			264		F	1.03	0.69	1.53	

Figure 104 Highest versus lowest forest plot of supplemental calcium and bladder cancer



6 Physical activity

Methods

Twelve studies from 9 articles on physical activity bladder cancer, were identified, from which 8 studies in the CUP. All studies were on recreational physical activity except one on total physical activity (Severson, 1989).

Main results

The wide variability in the methods of assessment of physical activity used did not allow dose-response analyses to be conducted. The highest versus lowest overall RR was 0.94 (95% CI=0.83-1.06, 12 studies).

Comparison with the Second Expert Report

In the 2005 SLR the evidence relating physical activity to bladder cancer was considered limited-no conclusion.

Published meta-analyses or pooled analyses

No published meta-analyses or pooled analyses were identified.

Table 119 Studies on physical activity identified during the CUP

Author/year	Country	Study name	Number of cases	Years of follow-up	Sex	RR	LCI	UCI	Contrast
Batty GD, 2010 (a)	United Kingdom	Whitehall study, London	78	40 years	M	1.47	0.77	2.80	Inactive vs. active
Koebnick C, 2008	USA	NIH- AARP	1719	8 years	M/F	0.87	0.74	1.02	≥5 vs. 0 times/w
Yun YH, 2008	Korea	Korea National Health Insurance Study	414	6 years	M	0.94	0.77	1.15	Moderate-high vs. low
Holick CN, 2007	USA	NHS + HPFS	502 men	16 years	M	1.01	0.76	1.34	> 34 vs. ≤2 MET-h/w
			204 women	26 years	F	0.91	0.58	1.41	>21.7 vs. ≤2 MET-h/w
Schnohr P, 2005	Denmark	The Copenhagen Centre for Prospective Population	247	14 years	M	0.83	0.57	1.21	Vigorous vs. low activity

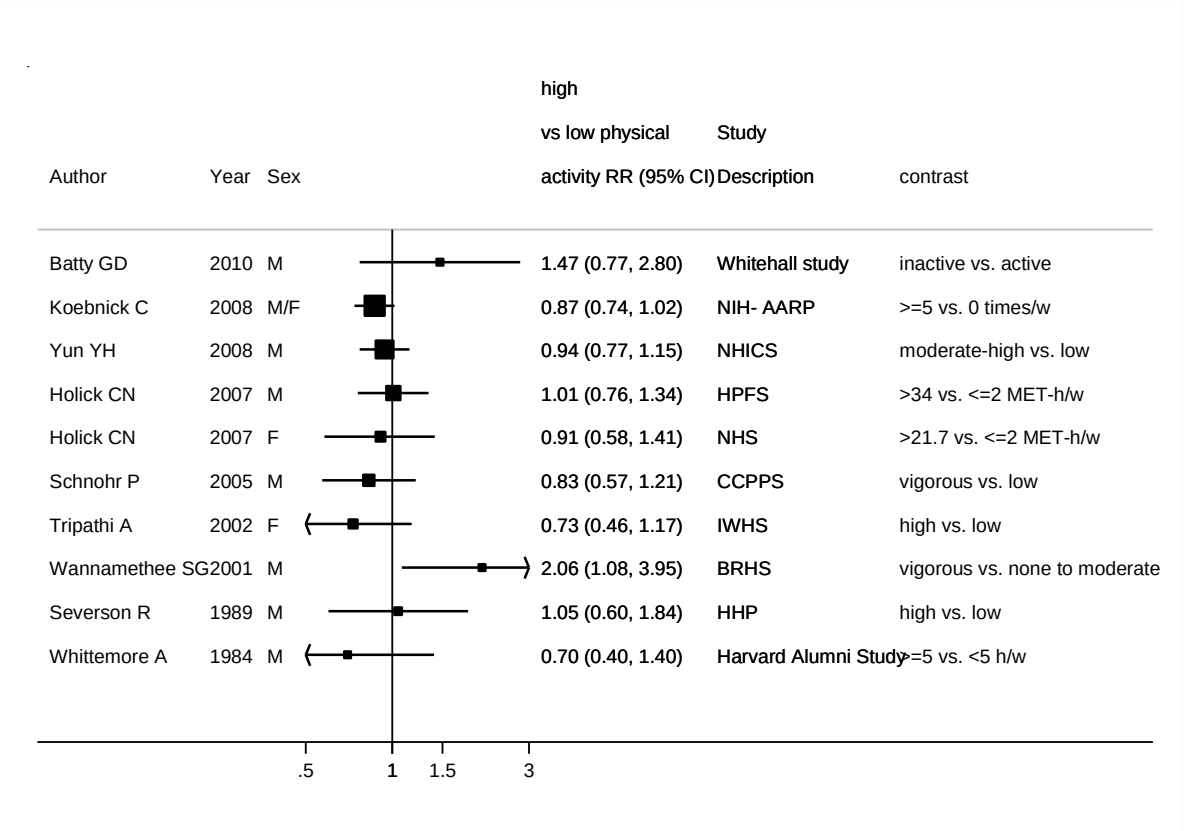
		Studies: Copenhagen City Heart Study, the Copenhagen County Centre of Preventive Medicine and the Copenhagen Male Study							

Table 120 Inclusion/exclusion table for meta-analysis of physical activity and bladder cancer

WCRF code	Author	Year	Study design	Study name	Sex	Cancer outcome	2005 SLR	CUP dose-response	CUP H vs. L forest plot	Estimated values	Exclusion reason
BLA97197	Batty GD	2010(a)	Prospective cohort study	Whitehall study, London	M	Mortality	No		Yes		
BLA97161	Koebnick C	2008	Prospective cohort study	NIH- AARP	M/F	Incidence	No		Yes		
BLA97209	Yun YH	2008	Prospective cohort study	Korea National Health Insurance Study	M	Incidence	No		Yes		
BLA97156	Holick CN	2007	Prospective cohort study	NHS + HPFS	M/F	Incidence	No		Yes		
BLA97223	Schnohr P	2005	Prospective cohort study	Copenhagen City Heart Study, the Copenhagen County Centre of Preventive Medicine and the Copenhagen Male Study	M	Incidence	No		Yes		
BLA00182	Tripathi A	2002	Prospective cohort study	Iowa Women's Health Study	F	Incidence	Yes		Yes		
BLA00319	Wannamethee SG	2001	Prospective cohort study	British Regional Heart Study	M	Incidence/ Mortality	Yes		Yes		

BLA03541	Severson R	1989	Prospective cohort study	Honolulu Heart Program	M	Incidence/ Mortality	Yes		Yes		
BLA01670	Whittemore A	1985	Prospective cohort study	Follow up of male students from Harvard and Pennsylvania University	M	Incidence/ Mortality	Yes		Yes		

Figure 105 Highest versus lowest forest plot of physical activity and bladder cancer



7 Energy intake

Methods

Five studies identified three of them during the CUP. The dose response results are presented for an increment of 500kcal/day.

Main results

The summary RR per 500 kcal/day of energy intake was 0.99 (95% CI: 0.96-1.04, I^2=0%, pheterogeneity=0.91, n=3).

Heterogeneity

There was no evidence of heterogeneity, I^2=0%, pheterogeneity=0.91.

Comparison with the Second Expert Report

In the 2005 SLR the evidence relating energy intake to bladder cancer was considered limited- no conclusion.

Published meta-analyses or pooled analyses

No published meta-analyses or pooled analyses were identified.

Table 121 Studies on energy intake identified during the CUP

Author/year		Study name	Number of cases	Years of follow-up	Sex	RR	LCI	UCI	Contrast
Allen NE, 2012	Europe	EPIC study	1416	11.3 years	M/F	1.01	0.85	1.20	2442 vs. 1798 kcal/d
						0.99	0.95	1.04	Per 500 kcal increase
Prentice RL, 2009	USA	WHI	99	12 years	F	1.05	0.47	2.39	Q4 vs. Q1
Iso H, 2007	Japan	JACC Study	89	12 years	M	0.44	0.14	1.41	Modified vs. no change
			39		F	1.45	0.50	424	

Table 122 Overall evidence on energy intake and bladder cancer

SLR	Summary of evidence
2005 SLR	Two studies were included in the meta-analysis, which showed a non-significant relationship between energy intake and bladder cancer.
CUP	Three new studies were identified, all of them showed a non-significant relationship between energy intake and bladder cancer.

Table 123 Summary of results of the dose-response meta-analysis of energy intake and bladder cancer

Bladder cancer		
	2005 SLR	CUP
Studies (n)	2	3
Cases (n)	416	1832
Increment unit	Per 500kcal/day	Per 500kcal/day
RR (95% CI)	1.02 (0.93-1.11)	1.010.99(0.96-1.04)
Heterogeneity (I^2, p-value)	I^2=0%, p=0.96	I^2=0%, p=0.91

Table 124 Inclusion/exclusion table for meta-analysis of energy intake and bladder cancer

WCRF code	Author	Year	Study design	Study name	Sex	Cancer outcome	2005 SLR	CUP dose-response	CUP H vs. L forest plot	Estimated values	Exclusion reason
BLA97199	Allen NE	2012	Prospective cohort study	EPIC study	M/F	Incidence	No	Yes	Yes	Person-years	
BLA97194	Prentice RL	2009	Prospective cohort study	Women's Health Initiative Dietary Modification and Observational study	F	Incidence	No	No	Yes		
BLA97203	Iso H	2007	Prospective cohort study	Japan Collaborative Cohort Study (JACC Study)	M/F	Mortality	No	No	Yes		Only high versus low results
BLA00432	Michaud D	2000	Prospective cohort study	Health Professionals Follow-up study	M	Incidence	Yes	Yes	Yes	Person-years	
BLA00777	Chyou PH	1993	Prospective cohort study	Honolulu Heart Program	M	Incidence/ Mortality	Yes	Yes	Yes	Person-years. Midpoints	

Figure 106 Highest versus lowest forest plot of energy intake and bladder cancer

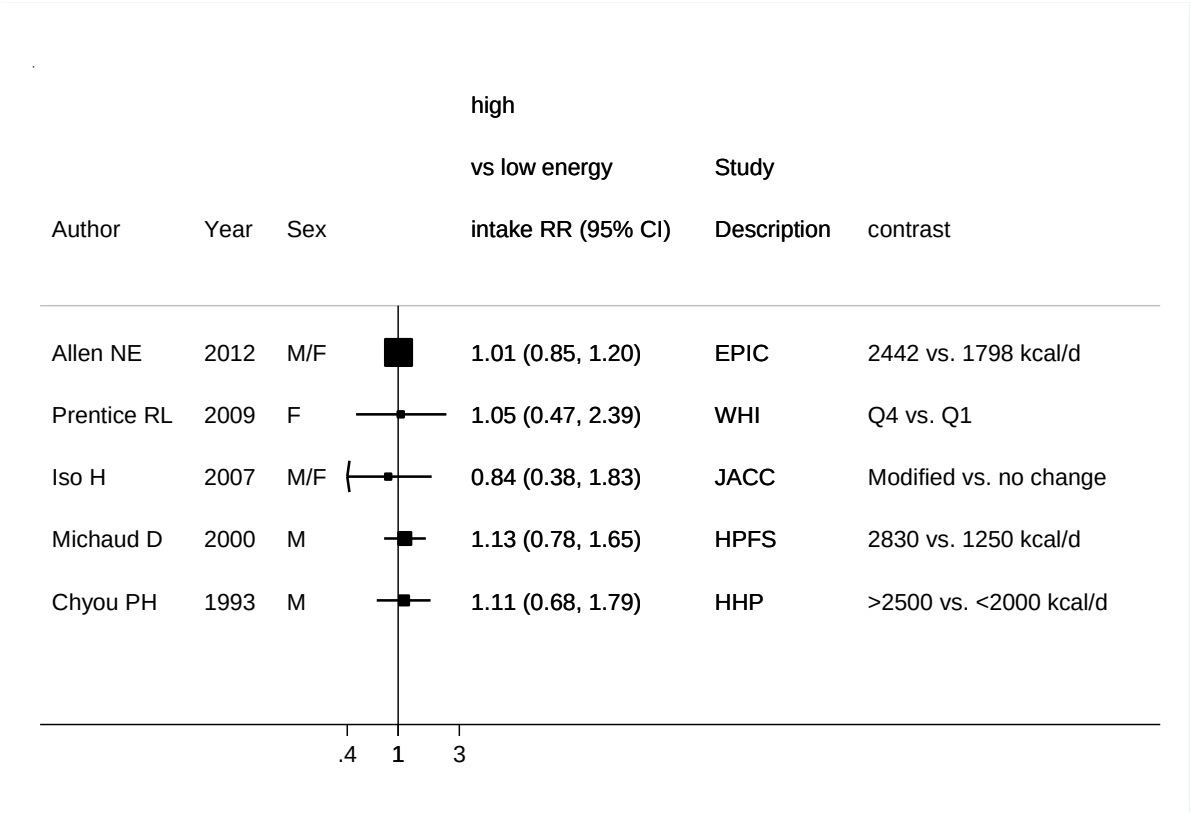


Figure 107 Dose-response meta-analysis of energy intake and bladder cancer, per 500kcal/day

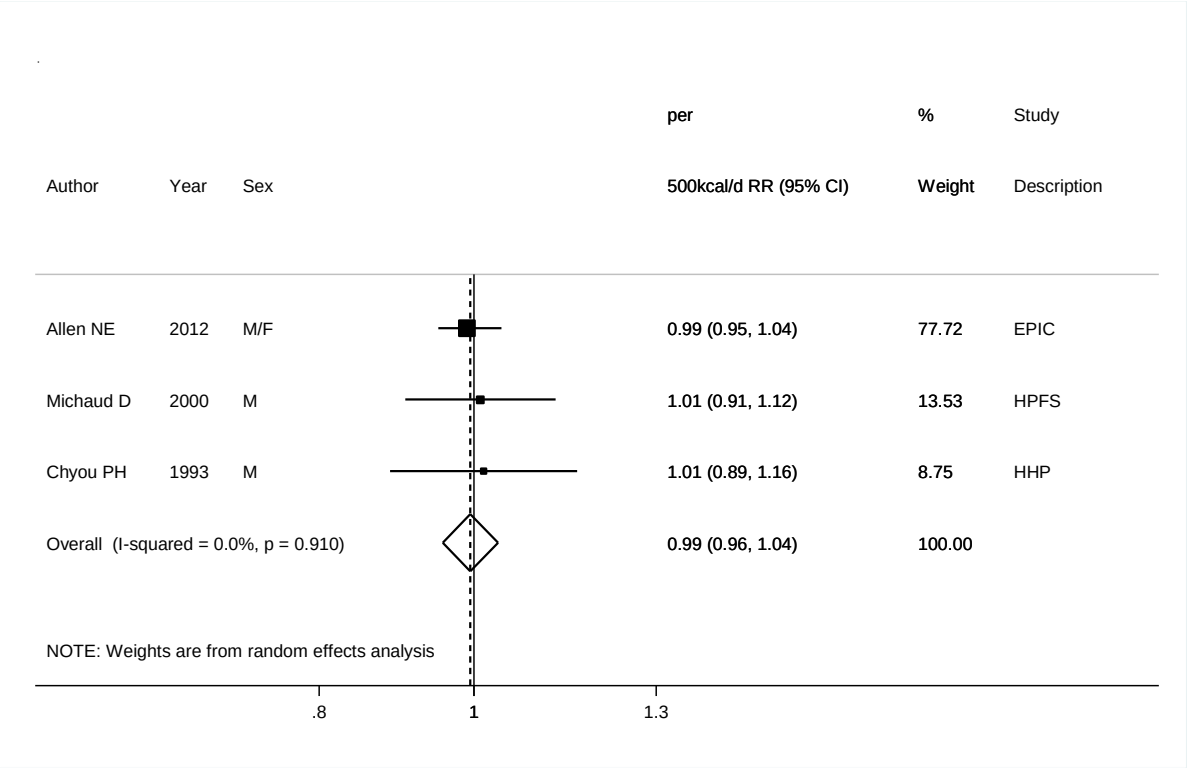
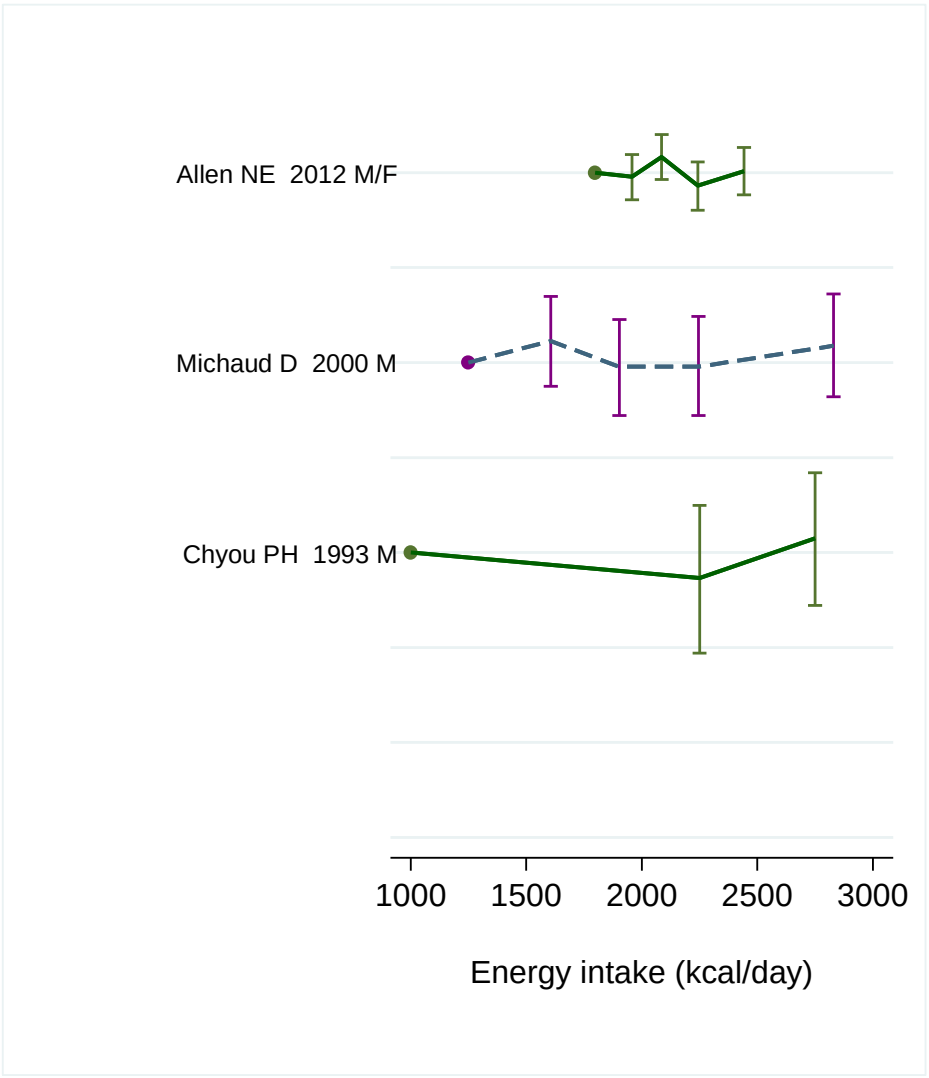


Figure 108 Dose-response graph of energy intake and bladder cancer



8 Anthropometry

8.1.1 BMI

Methods

A total of 22 studies (25 articles) of BMI and bladder cancer were identified, twelve of which in the CUP.

Dose-response analyses and stratified analyses of BMI and bladder cancer risk were conducted per 5 BMI units. The method by Hamling et al, 2008 was used to convert risk estimates when the reference category was not the lowest category. Nonlinear dose-response analyses were conducted using restricted cubic splines (Hamling, 2008).

Main results

The summary RR per 5 BMI units was 1.03 (95% CI: 0.97-1.09, I2=55.1%, pheterogeneity=0<0.01, n=17). The results were similar by sex with summary RRs of 1.01 (95% CI: 0.93-1.10, I2=50%, pheterogeneity=0.04, n=9) and 1.03 (95% CI: 0.94-1.14, I2=50%, pheterogeneity=0.04, n=10), in men and women, respectively.

When stratified by geographic location, the summary RR was 0.97 (95% CI: 0.89-1.05, I2=36%, pheterogeneity=0.16, n=6) for European studies, 1.06 (95% CI: 1.00-1.11, I2=20%, pheterogeneity=0.27, n=8) for the American studies and 1.20 (95% CI: 1.01-1.42, I2=24%, pheterogeneity=0.24, n=3) for the Asian studies. In a sensitivity analysis, including the Asian Pacific Cohort Studies Collaboration in addition to the CUP data the overall summary RR was 1.03 (95% CI: 0.98-1.09, I2=52%, pheterogeneity=0<0.01), while the subgroup analysis of Asian studies showed a summary RR of 1.21 (95% CI: 1.08-1.35, I2=1%, pheterogeneity=0.39).

There was a suggestion of a nonlinear association between BMI and bladder cancer, pnonlinearity=0.08. Compared with 20 kg/m^2 as reference, there was a decreased risk for lower BMI and a weak increased risk for higher BMI up to 28 kg/m^2 (visual inspection of the spline model), but not further increase in risk at higher levels of BMI.

Heterogeneity

There was high heterogeneity in the analyses at least partially explained by geographic location of the studies. Asian studies tended to report stronger positive associations. There was indication of publication bias with Egger's test, p<0.01.

Comparison with the Second Expert Report

In the 2005 SLR the evidence relating body fatness to bladder cancer was considered limited and no conclusion was possible.

Published meta-analyses or pooled analyses

A pooled analysis within the Me-Can project (7 cohorts) reported a RR of 1.13 (95% CI: 0.94-1.35) in men and 0.87 (95% CI: 0.58-1.32) in women when comparing the groups of individuals with mean BMI 30.8 with 21.5 (Haggstrom et al, 2011). A pooled analysis of 39

cohort studies within the Asian Pacific Cohort Studies Collaboration found a non-significant association between BMI and bladder cancer mortality and reported a hazard ratio of 0.72 (95% CI: 0.29-1.79) for BMI 30-60 vs. 18.5-24.9 and 1.09 (95% CI: 0.78-1.54) per 5 kg/m^2 (Parr, 2010).

Table 125 Studies on BMI identified during the CUP

Author/ year	Country	Study name	Number of cases	Years of Follow-up	Sex	RR	LCI	UCI	Contrast (kg/m^2)
Andreotti, 2010	USA	Agricultural Health Study	148	10 years	M	1.41 1.01	0.82 0.96	2.41 1.05	30-34.9 vs. 18.5-24.9 Per 1 unit
					F	0.97 0.93	0.32 0.83	2.89 1.05	30-34.9 vs. 18.5-24.9 Per 1 unit
Prentice, 2009,	USA	Women's Health Initiative	99	12 years	F	0.74	0.34	1.6	Per 10 units
Jee, 2008	Korea	National Health Insurance Corporation Study	2439	10.8 years	M/F	1.02 0.74	0.52 0.27	1.97 2.06	≥30 vs. 23-24.9 ≥30 vs. 23-24.9
Koebnick, 2008	USA	NIH-AARP Diet and Health Study	1719	~7.2 years	M/F	1.28	1.02	1.61	≥35 vs. 18.5-24.9
Larsson, 2008 (c)	Sweden	Cohort of Swedish Men	388	~8.8 years	M	0.79	0.29	2.14	>=35 vs. 18.5-24.9
Fujino, 2007	Japan	Japan Collaborative Cohort Study	117	~14 years	M/F	1.31 1.23	0.18 0.16	9.53 9.16	>=30 vs. 18.5-24 >=30 vs. 18.5-24
Reeves, 2007	UK	Million Women's Study	615	5.4 years	F	1.07 1.09	0.88 0.89	1.30 1.34	>=30 vs. 22.5-24.9 Per 10 units
Holick, 2007	USA	Health Professional's Follow-up Study	507	16 years	M	1.01 1.00	0.68 0.97	1.50 1.03	≥30 vs. 18-22.9 Per 1 unit
Holick,	USA	Nurses'	359	26	F	1.31	0.91	1.89	≥30 vs.

2007		Health Study		years		1.02	0.99	1.04	18-22.9 Per 1 unit
Samanic, 2006	Sweden	Swedish Construction Workers Cohort Study	2030	19 years	M	0.91	0.76	1.09	≥30 vs. <25
Cantwell, 2006	USA	Breast Cancer Detection and Demonstration Project	167	15.3 years	F	0.83	0.26	2.63	≥35 vs. 18.5-<25
Rapp, 2005	Austria	The Vorarlberg Health Monitoring and Promotion Program	229	9.9 years	M/F	0.74 1.60	0.45 0.76	1.22 3.36	≥30 vs. 18-24.9 ≥30 vs. 18-24.9

Table 126 Overall evidence on BMI and bladder cancer

SLR	Summary of evidence
2005 SLR	Four nested case-control studies and six cohort studies were identified. One nested case-control study reported an inverse association, and the remaining studies reported no significant association.
Continuous Update Project	Of the twelve additional cohort studies identified in the CUP, one reported a significant positive association, while the remaining studies reported no significant association.

Table 127 Summary of results of the dose-response meta-analysis of BMI and bladder cancer

Bladder cancer		
	2005 SLR	CUP
Studies (n)	5	17
Cases (n)	2149	10571
RR (95% CI)	1.00 (0.98-1.03)	1.03 (0.97-1.09)
Quantity	5 kg/m^2	5 kg/m^2
Heterogeneity (I^2, p-value)	43.5, p=0.13	I^2=55.1%, p<0.01
By sex		
Men	-	1.01 (0.93-1.10)
Heterogeneity (I^2, p-value)	-	I^2=50%, p=0.04, n=9
Women	-	1.03 (0.94-1.14)
Heterogeneity (I^2, p-value)	-	I^2=50%, p=0.04, n=10
By geographic area		

Europe	-	0.97 (0.89-1.05)
Heterogeneity (I^2, p-value)	-	I^2=36%, p=0.16, n=6
North-America	-	1.06 (1.00-1.11)

Heterogeneity (I^2, p-value)	-	I^2=20%, p=0.27, n=8
Asia	-	1.20 (1.01-1.42)
Heterogeneity (I2, p-value)	-	I^2=24%, p=0.27, n=3

Table 128 Inclusion/exclusion table for meta-analysis of BMI and bladder cancer

WCRF code	Author	Year	Study design	Study name	Sex	Cancer outcome	2005 SLR	CUP dose-response	CUP H vs. L forest plot	Estimated values	Exclusion reason
BLA97196	Andreotti	2010	Prospective cohort	Agricultural Health Study	M/F	Incidence	No	Yes	Yes	Person-years, midpoints	
BLA97194	Prentice	2009	Prospective cohort	Women's Health Initiative	F	Incidence	No	Yes	No		Only continuous estimate
BLA97189	Jee	2008	Prospective cohort	National Health Insurance Corporation Study, Korea	M/F	Incidence	No	Yes	Yes	Person-years, midpoints, converted RRs	
BLA97161	Koebnick	2008	Prospective cohort	NIH-AARP Diet and Health Study	M/F	Incidence	No	Yes	Yes	Midpoints	
BLA97159	Larsson	2008(c)	Prospective cohort	Cohort of Swedish Men	M	Incidence	No	Yes	Yes		
BLA97212	Fujino	2007	Prospective cohort	Japan Collaborative Cohort Study	M/F	Mortality	No	Yes	Yes	Midpoints, converted RRs	
BLA97192	Reeves	2007	Prospective cohort	Million Women's Study	F	Incidence/ Mortality	No	Yes	Yes	Midpoints, converted RRs	
BLA97155	Holick	2007	Prospective cohort	Health Professional's Follow-up Study	M	Incidence	No	Yes	Yes	Midpoints	
BLA97155	Holick	2007	Prospective cohort	Nurses' Health Study	F	Incidence	No	Yes	Yes	Midpoints	
BLA97186	Samanic	2006	Prospective cohort	Swedish Construction Workers Cohort	M	Incidence	No	Yes	Yes	Midpoints, person-years	
BLA97152	Cantwell	2006	Prospective cohort	Breast Cancer Detection Demonstration	F	Incidence	No	Yes	Yes	Midpoints, converted RRs	

				Project follow-up cohort							
BLA97220	Rapp	2005	Prospective cohort	The Vorarlberg Health Monitoring and Promotion Program	M/F	Incidence	No	Yes	Yes		
BLA11288	Batty	2005	Prospective cohort	The Whitehall Study	M	Mortality	Yes	Yes	Yes	Midpoints	
BLA97149	Oh	2005	Prospective cohort	Korea National Health Insurance Corporation Study	M	Incidence	Yes	No	No		Overlap with Jee et al, 2008
BLA06932	Calle	2003	Prospective cohort	Cancer Prevention Study 2	M/F	Mortality	Yes	Yes	Yes	Midpoints, person-years	
BLA00083	Nomura	2003	Nested case-control study	Honolulu Heart Program	M	Incidence	Yes	No	No		No risk estimates
BLA00182	Tripathi	2002	Prospective cohort	Iowa Women's Health Study	F	Incidence	Yes	Yes	Yes	Midpoints	
BLA00183	Michaud	2002(b)	Nested case-control study	Alpha-Tocopherol Beta-Carotene Cancer Prevention Study	M	Incidence	Yes	No	No		No risk estimates
BLA03990	Hirvonen	2001	Prospective cohort	Alpha-Tocopherol Beta-Carotene Cancer Prevention Study	M	Incidence	Yes	No	No		No risk estimates
BLA08832	Persson-Moschos	2000	Nested case-control study	Sweden 1974-1982	M	Incidence	Yes	No	No		No risk estimates
BLA02708	Nagano	2000	Prospective cohort	Life Span Study	M/F	Incidence	Yes	Yes	Yes	Midpoints	

BLA02765	Kurrtio	1999	Nested case-control study	Finland 1981-1995	M/F	Incidence	Yes	No	No		No risk estimates, outcome was kidney cancer
BLA10320	Tulinius	1997	Prospective cohort	Icelandic Cardiovascular Risk Factors Study	F	Incidence	Yes	Yes	No		Continuous estimate, no result for men
BLA01645	Whittemore	1985	Nested case-control study	Harvard Pennsylvania Alumni Study	M	Incidence	Yes	No	No		No risk estimates
BLA01670	Whittemore	1984	Nested case-control study	Harvard Pennsylvania Alumni Study	M	Incidence	Yes	No	No		No risk estimates

Figure 109 Highest versus lowest forest plot of BMI and bladder cancer

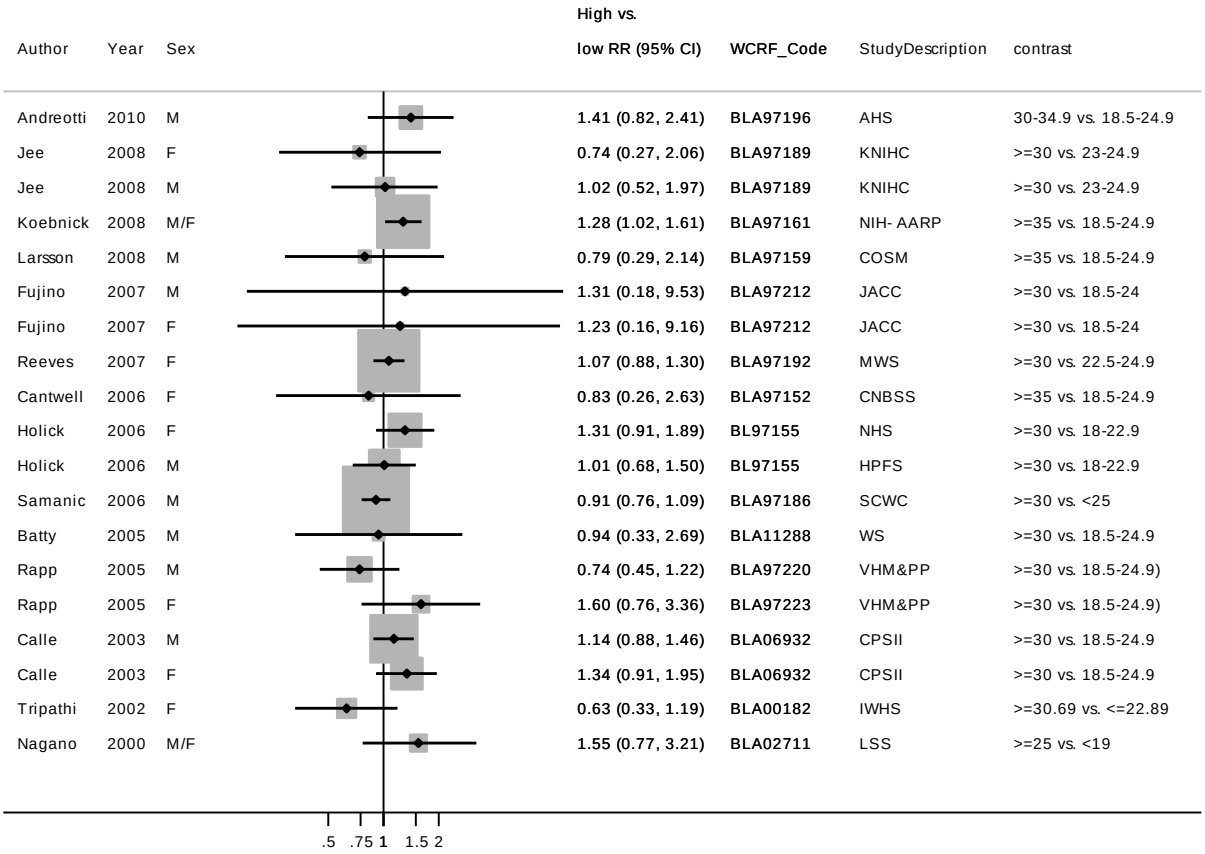


Figure 110 Dose-response meta-analysis of BMI and bladder cancer, per 5 units increase

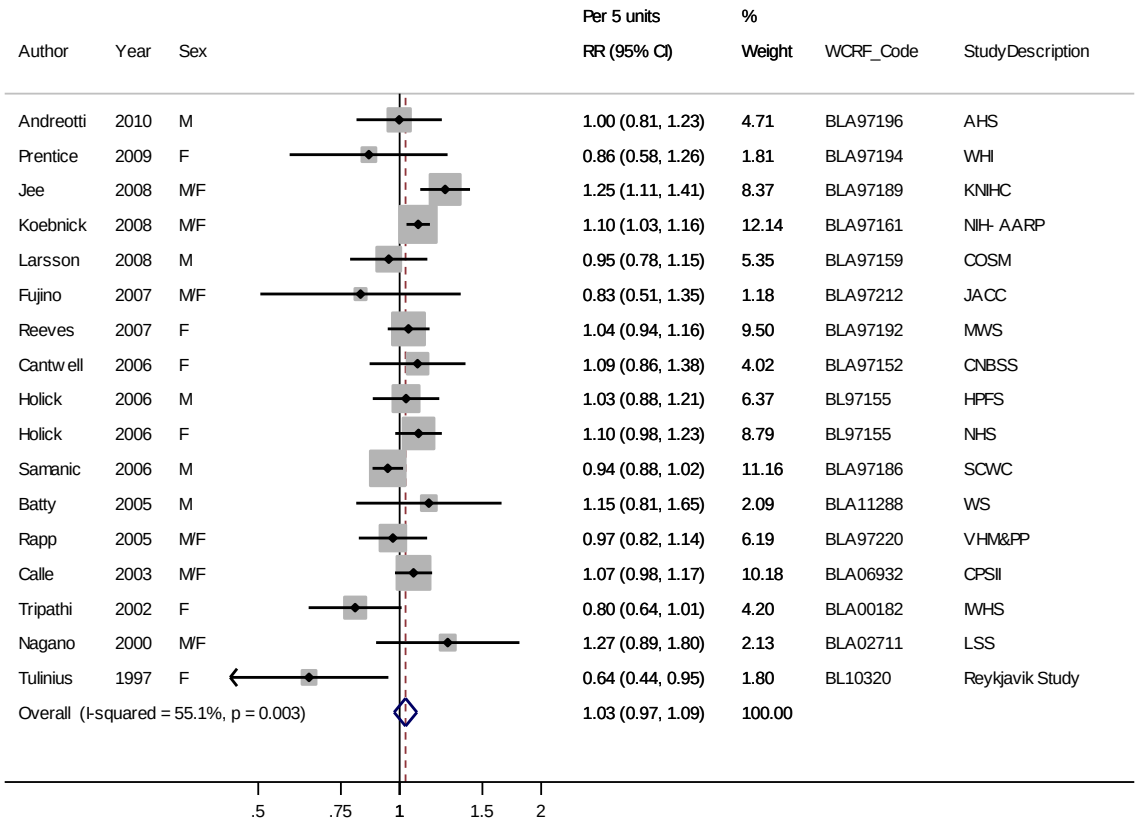


Figure 111 Dose-response meta-analysis of BMI and bladder cancer stratified by sex, per 5 units increase

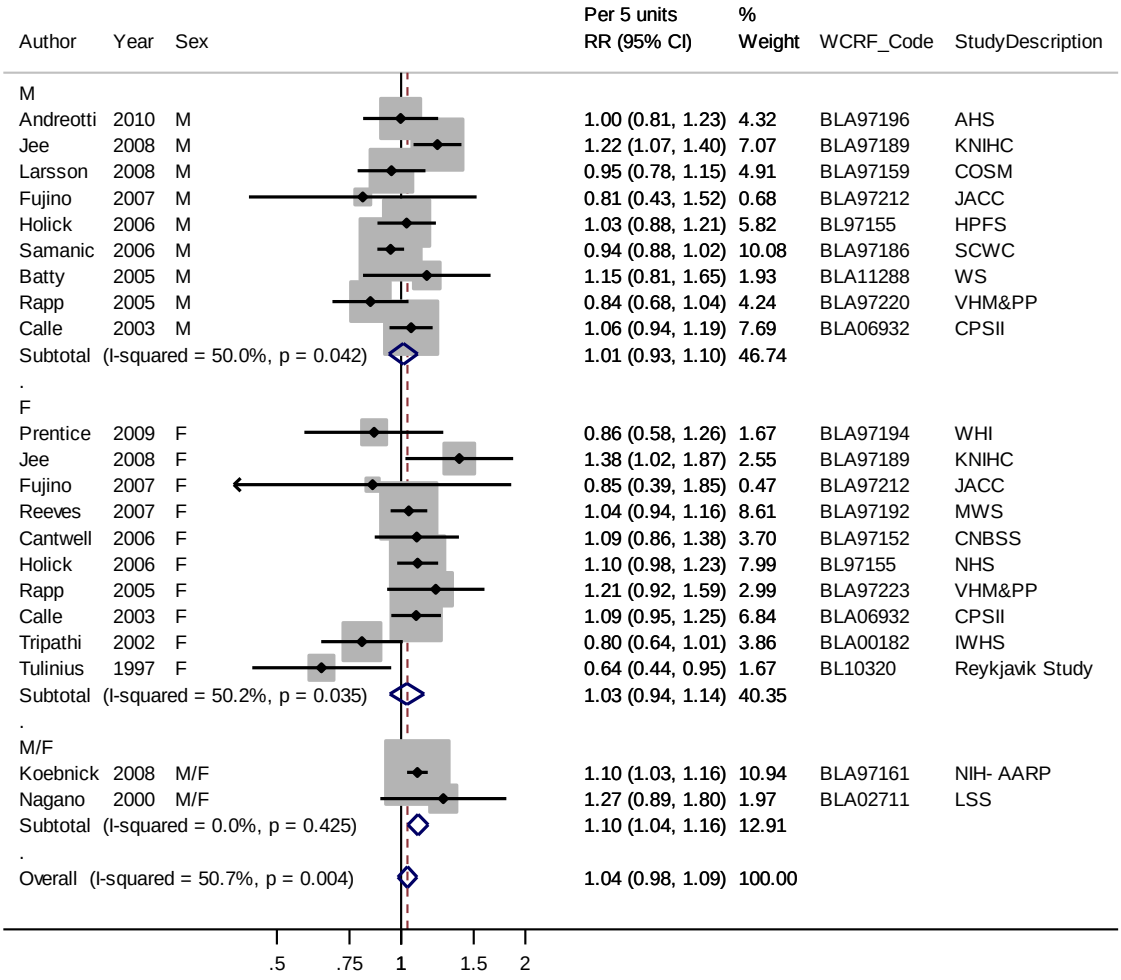


Figure 112 Dose-response meta-analysis of BMI and bladder cancer stratified by outcome, per 5 units increase

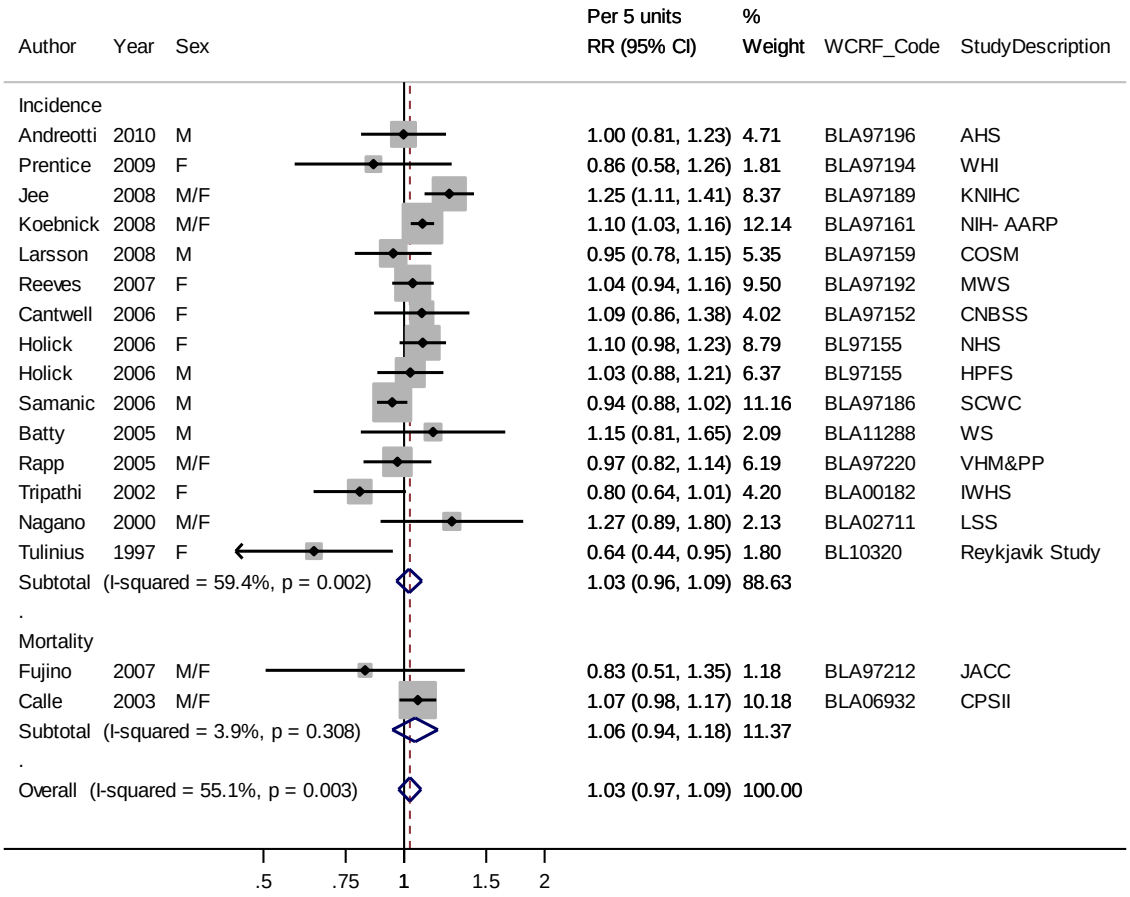


Figure 113 Dose-response meta-analysis of BMI and bladder cancer, stratified by location, per 5 units increase

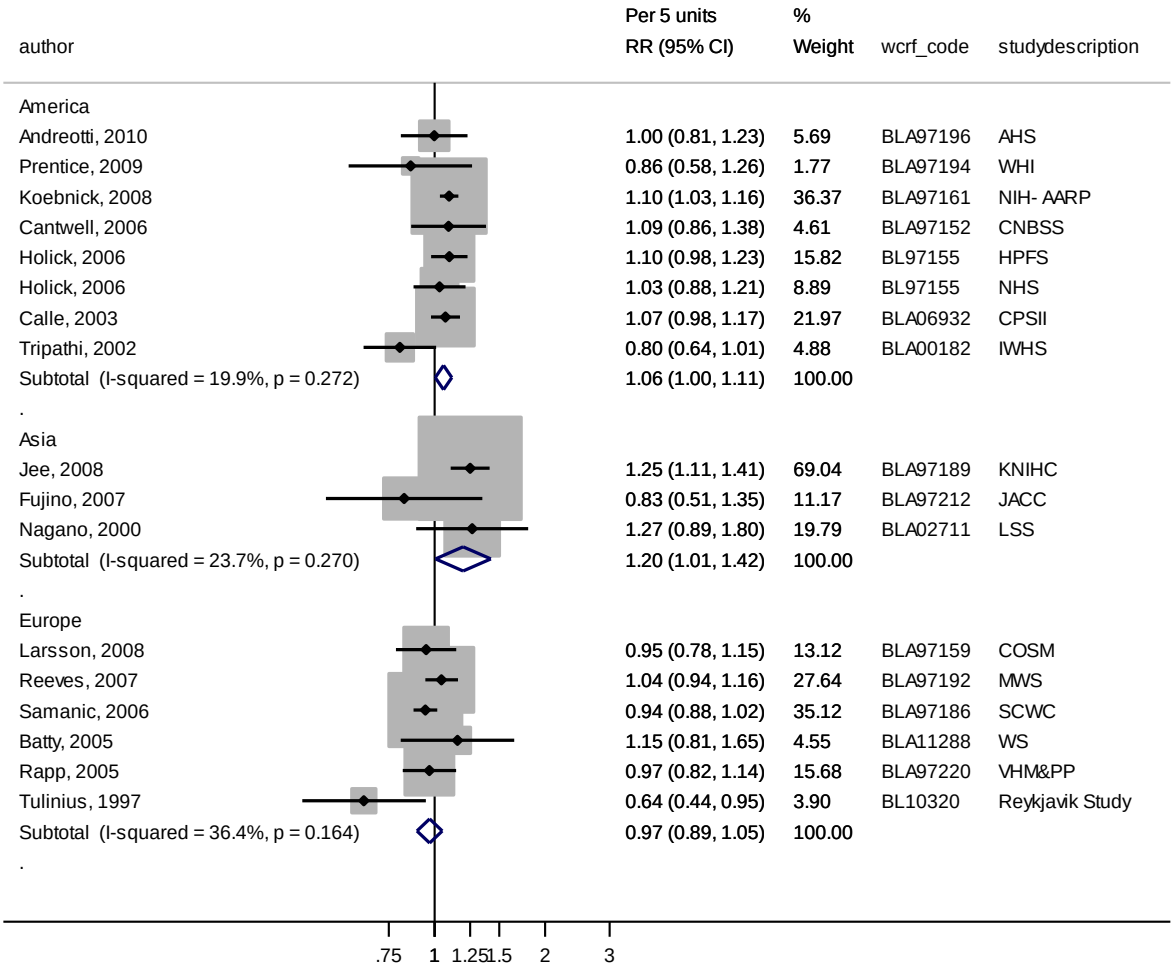
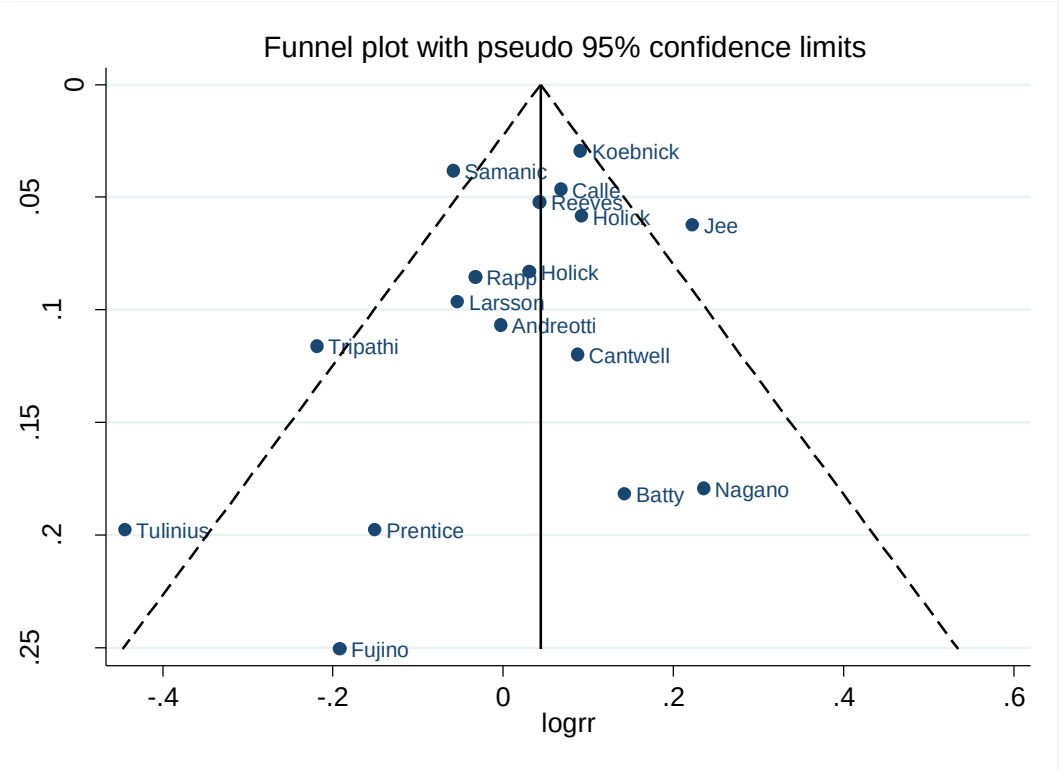


Figure 114 Funnel plot of BMI and bladder cancer



Egger's test, p<0.01

Figure 115 Dose-response graph of BMI and bladder cancer

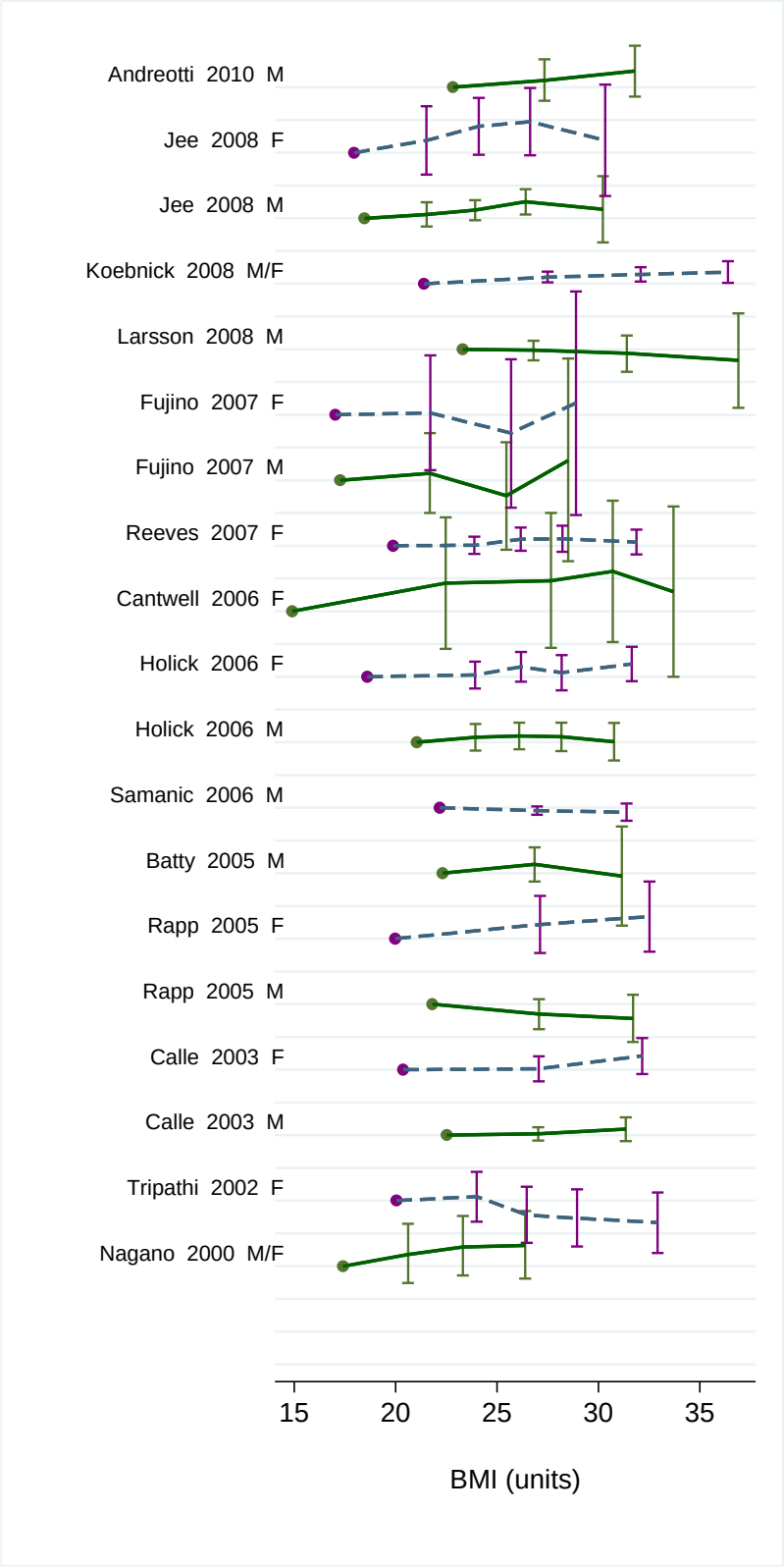


Figure 116 BMI and bladder cancer with the Asian Cohort Collaboration

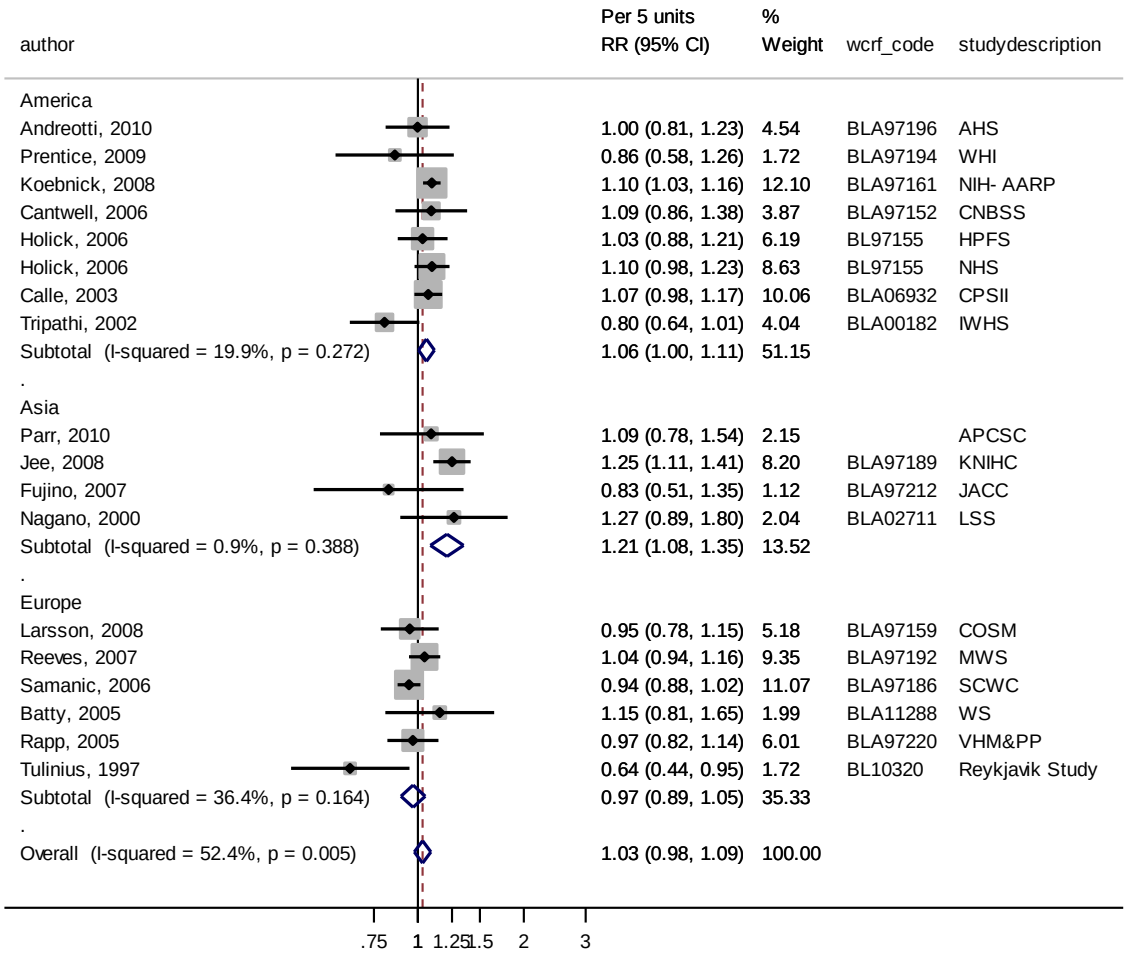
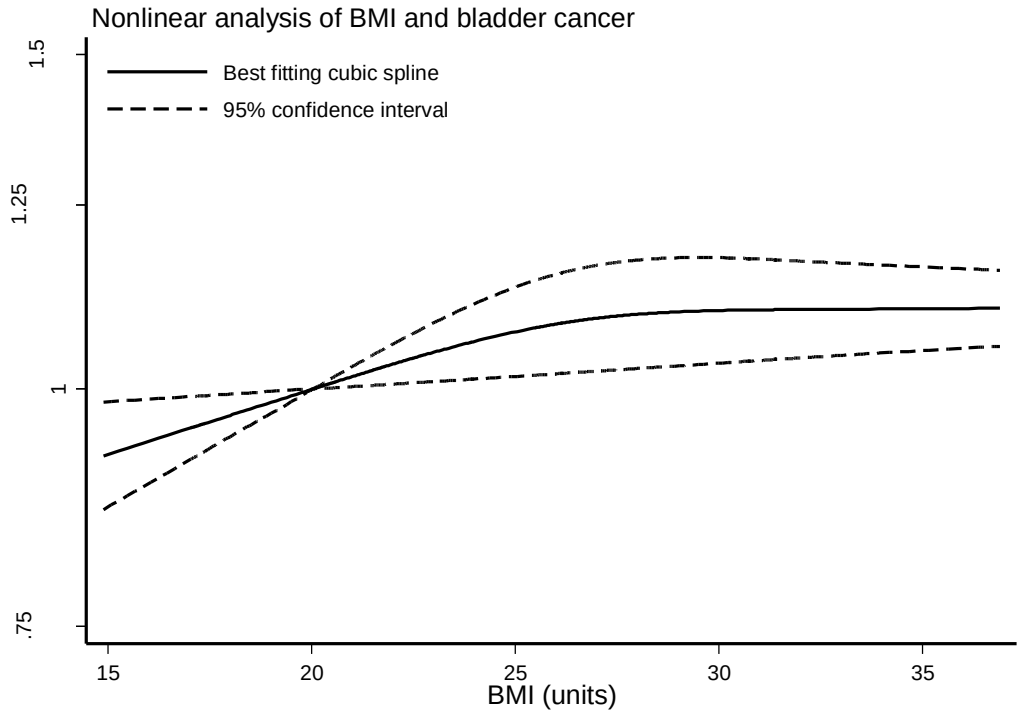


Figure 117 Nonlinear dose-response analysis for BMI and bladder cancer



p for nonlinearity=0.08

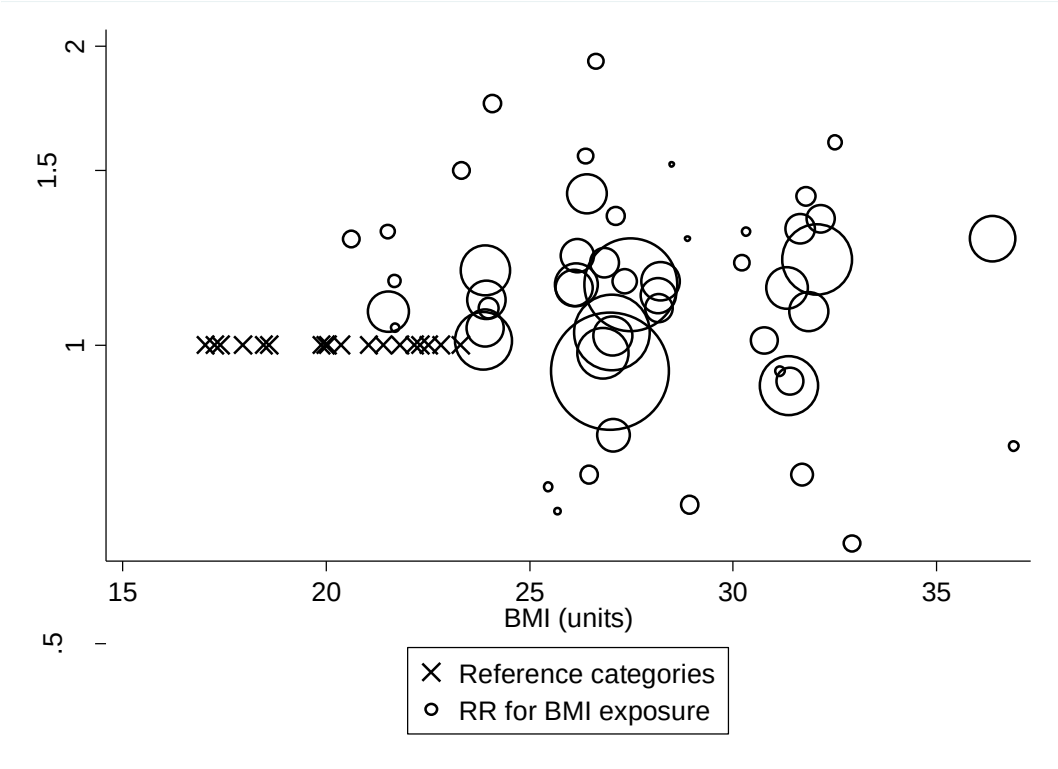


Table 129 Table with BMI values and corresponding RRs (95% CIs) for nonlinear analysis of BMI and bladder cancer

BMI (Kg/m^2)	RR (95% CI)
17.4	0.96 (0.93-0.99)
20	1.00
22.5	1.04 (1.01-1.07)
25.5	1.08 (1.02-1.14)
27.5	1.09 (1.02-1.17)
30.2	1.10 (1.03-1.17)
32.5	1.10 (1.04-1.17)
36.4	1.10 (1.05-1.16)

8.2.1 Waist circumference

Methods

A total of 2 cohort studies of waist circumference and bladder cancer were included in the analysis and one of these was identified in the CUP.

Dose-response analyses of waist circumference and bladder cancer risk were conducted per 10 cm.

Main results

The summary RR per 10 cm was 0.89 (95% CI: 0.79-0.99, I2=0%, pheterogeneity=0.88).

Heterogeneity

There was no heterogeneity in the analyses, I2=0%, pheterogeneity=0.88.

Comparison with the Second Expert Report

In the 2005 SLR the evidence relating waist circumference to bladder cancer was considered limited and no conclusion was possible.

Published meta-analyses or pooled analyses

No published meta-analyses or pooled analyses were identified.

Table 130 Table of studies on waist circumference identified during the CUP

Author/ year/	Country	Study name	Number of cases	Follow-up	Sex	RR	LCI	UCI	Contrast
Larsson, 2008 (c)	Sweden	Cohort of Swedish Men	388	~8.8 years	M	1.00	0.72	1.39	107 vs. 85 cm

Table 131 Overall evidence on waist circumference and bladder cancer

SLR	Summary of evidence
2005 SLR	One study was identified and reported no significant association.
Continuous update	One additional study was identified and reported no significant association. The meta-analysis shows a significant inverse association

Table 132 Summary of results of the dose-response meta-analysis of waist circumference and bladder cancer

Bladder cancer		
	2005 SLR	CUP
Studies (n)	-	2
Cases (n)	-	500
RR (95% CI)	-	0.89 (0.79-0.99)
Quantity	-	Per 10 cm
Heterogeneity (I^2, p-value)	-	I^2=0%, p=0.88

Table 133 Inclusion/exclusion table of waist circumference and bladder cancer

WCRF code	Author	Year	Study design	Study name	Subgroup	Cancer outcome	2005 SLR	CUP dose-response	CUP H vs. L forest plot	Estimated values	Exclusion reason
BLA97159	Larsson	2008(c)	Prospective cohort	Cohort of Swedish Men	M	Incidence	No	Yes	Yes		
BLA00182	Tripathi	2002	Prospective cohort	Iowa Women's Health Study	F	Incidence	Yes	Yes	Yes	Midpoints	

Figure 118 Highest versus lowest fore plot of waist circumference and bladder cancer

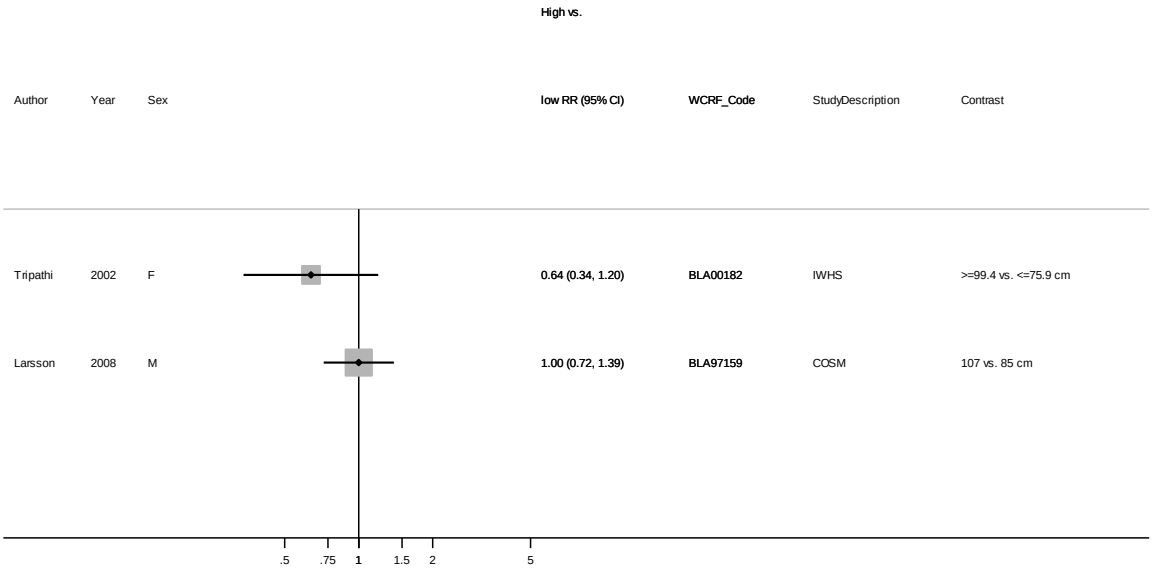


Figure 119 Dose-response meta-analysis of waist circumference and bladder cancer, per 10 cm

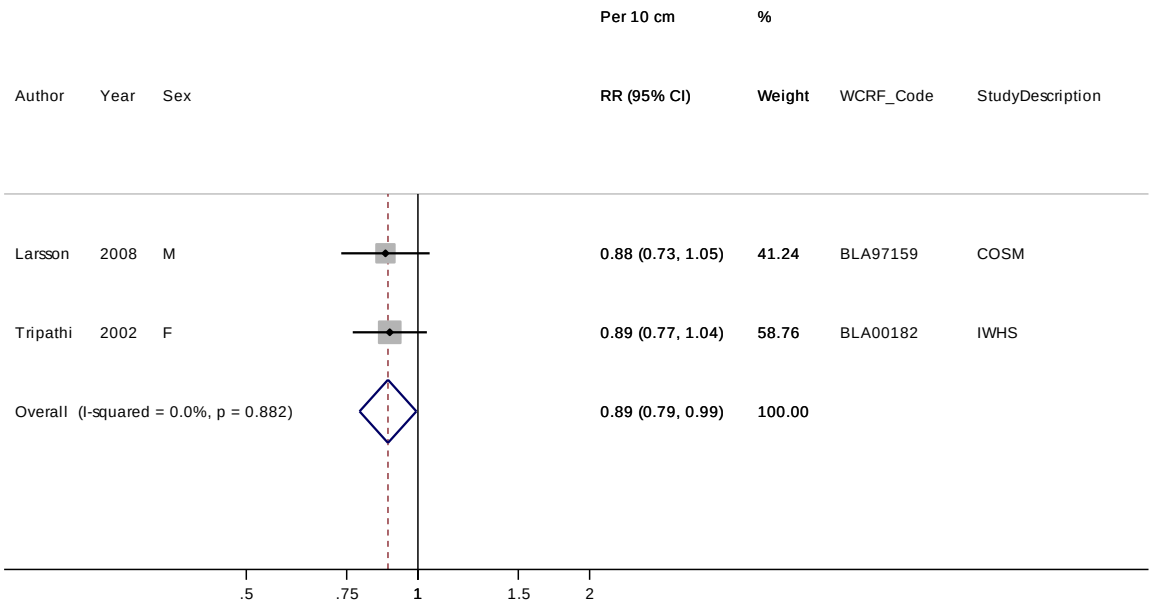
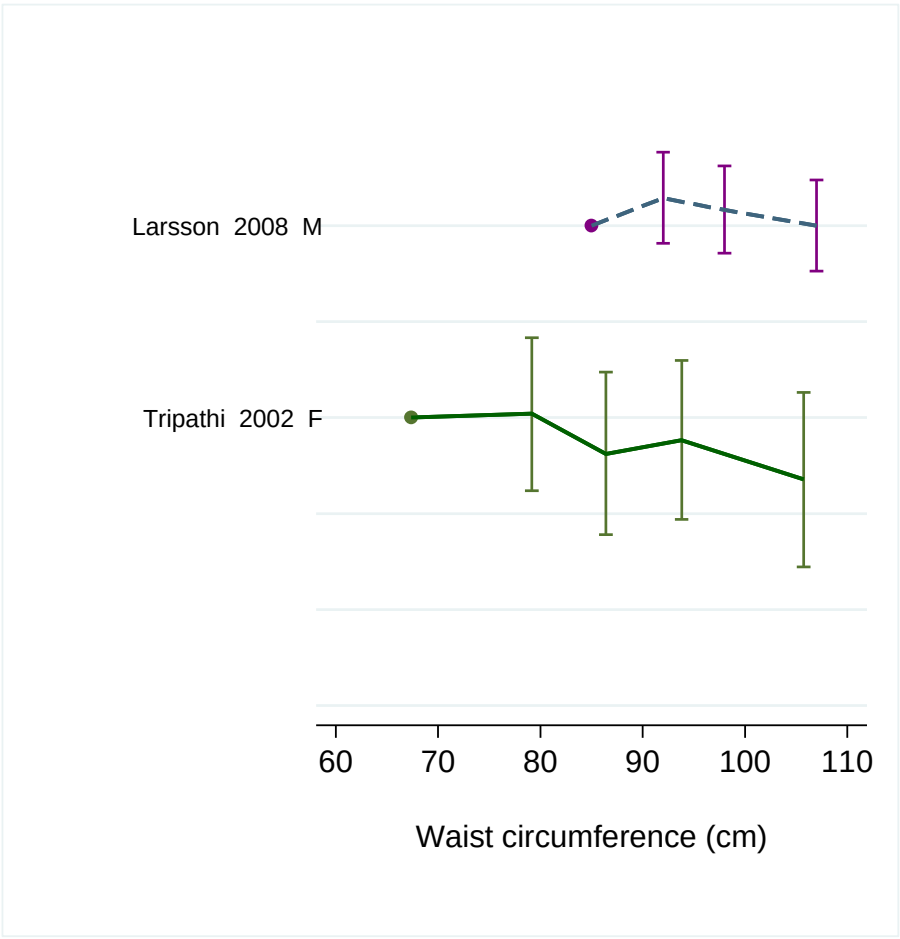


Figure 120 Dose-response graphs of waist circumference and bladder cancer



8.3.1 Height

Methods
A total of 11 studies (10 articles) of height and bladder cancer were identified. Seven studies (6 articles) were identified in the CUP. Dose-response analyses and stratified analyses of height and bladder cancer risk were conducted per 5 cm. Nonlinear dose-response analyses were conducted using restricted cubic splines.

Main results
The summary RR per 5 cm was 0.99 (95% CI: 0.95-1.02, I2=6.8%, pheterogeneity=0.38). The results were similar when stratified by sex, summary RR = 0.98 (95% CI: 0.92-1.05, I2=27%, pheterogeneity=0.24) in men and 1.00 (95% CI: 0.95-1.05, I2=0%, pheterogeneity=0.70) in women, respectively.
There was evidence of nonlinearity, $p<0.0001$, mainly driven by the results of an Asian study with reference category lower than the other studies. The relative risks estimates from the nonlinear model were not statistically significant.
When the results of the Asian Pacific Cohort Studies Collaboration was included together with the CUP data the summary RR per 5 cm increase in height was 1.02 (95% CI: 0.96-1.08, I2=59%, pheterogeneity=0.01). A significant positive association emerged in the subgroup of Asian studies, summary RR=1.25 (95% CI: 1.11-1.40, I2=0%, pheterogeneity=0.62).

Heterogeneity
There was little heterogeneity in the analyses. There was no indication of publication bias with Egger's test, p=0.10.

Comparison with the Second Expert Report
In the 2005 SLR the evidence relating height to bladder cancer was considered limited and no conclusion was possible.

Published meta-analyses or pooled analyses
A pooled analysis of 38 Asian cohort studies on height and bladder cancer mortality reported a hazard ratio of 1.31 (95% CI: 1.09-1.58) for men and 1.43 (95% CI: 0.97-2.13) for women for a 6 cm increase in height (Batty, 2010b).

Table 134 Studies on height identified during the CUP

Author/year	Country	Study name	Number of cases	Years of Follow-up	Sex	RR	LCI	UCI	Contrast
Kabat, 2013	USA	Canadian National Breast Screening Study	158	16.2 years	F	1.05	0.81	1.36	Per 10 cm
Green, 2011	UK	Million Women's Study	1354	9.4 years	F	1.00	0.88	1.14	Per 10 cm
Larsson, 2008 (c)	Sweden	Cohort of Swedish Men	388	~8.8 years	M	0.83	0.62	1.12	185 vs. 170 cm
Fujino, 2007	Japan	Japan Collaborative Cohort Study	117	~14 years	M/F	1.33 1.99	0.77 0.74	2.30 5.38	≥165 vs. <160 cm ≥154 vs. <149 cm
Holick, 2007	USA	Health Professional's Follow-up Study	507	16 years	M	0.69 0.68	0.50 0.45	0.95 1.01	>6.00 vs. ≤5.60 feet Per 1 foot
Holick, 2007	USA	Nurses' Health Study	359	26 years	F	0.98 0.91	0.70 0.54	1.37 1.55	>5.50 vs. ≤5.10 feet Per 1 foot
Batty, 2006	UK	Whitehall Study	146	Up to 35 years	M	1.38 1.06	0.78 0.93	2.44 1.20	≥181.0 vs. <171.0 cm Per 5 cm

Table 135 Overall evidence on height and bladder cancer

SLR	Summary of evidence
2005 SLR	Five studies were identified, of which three reported risk estimates and all found no significant association.[1]
Continuous Update Project	Of the seven additional cohort studies identified in the CUP, one reported a significant negative association, and the remaining studies reported no significant association.

[1] One of these studies (BLA11601, Song et al, 2003) reported on urinary tract cancers (which includes kidney cancer) and is excluded in the current report.

Table 136 Summary of results of the dose-response meta-analysis of height and bladder

Bladder cancer		
	2005 SLR	CUP
Studies (n)	-	8
Cases (n)	-	3056
RR (95% CI)	-	0.99 (0.95-1.02)
Quantity	-	5 cm
Heterogeneity (I^2, p-value)	-	I^2=6.8%, p=0.38
By sex		
Men	-	0.98 (0.92-1.05)
Heterogeneity (I^2, p-value)	-	I^2=27%, p=0.24
Women	-	1.00 (0.95-1.05)
Heterogeneity (I^2, p-value)	-	I^2=0%, p=0.70

Table 137 Inclusion/exclusion table of height and bladder cancer

WCRF code	Author	Year	Study design	Study name	Subgroup	Cancer outcome	2005 SLR	CUP dose-response	CUP H vs. L forest plot	Estimated values	Exclusion reason
BLA97208	Kabat	2013	Prospective cohort	Canadian National Breast Screening Study	F	Incidence	No	Yes	No		Only continuous estimate
BLA97227	Green	2011	Prospective cohort	Million Women's Study	F	Incidence	No	Yes	No		Only continuous estimate
BLA97159	Larsson	2008(c)	Prospective cohort	Cohort of Swedish Men	M	Incidence	No	Yes	Yes		
BLA97212	Fujino	2007	Prospective cohort	Japan Collaborative Cohort Study	M/F	Mortality	No	Yes	Yes	Midpoints	
BLA97155	Holick	2007	Prospective cohort	Health Professional's Follow-up Study	M	Incidence	No	Yes	Yes	Midpoints	
BLA97155	Holick	2007	Prospective cohort	Nurses' Health Study	F	Incidence	No	Yes	Yes	Midpoints	
BLA97226	Batty	2006	Prospective cohort	The Whitehall Study	M	Mortality	Yes	Yes	Yes	Midpoints	
BLA10320	Tulinius	1997	Prospective cohort	Icelandic Cardiovascular Risk Factor Study	M/F	Incidence	Yes	No	No		No risk estimates
BLA10347	Leon	1995	Prospective cohort	The Whitehall Study	M	Mortality	Yes	No	No		Overlap with Batty et al, 2006 BLA
BLA13608	Albanes	1988	Prospective cohort	National Health And Nutrition Examination Survey I	M	Incidence	Yes	Yes	Yes		No risk estimates
BLA01645	Whittemore	1985	Nested case-control study	Harvard Pennsylvania Alumni Study	M	Incidence	Yes	No	No		No risk estimates

Figure 121 Highest versus lowest forest plot of height and bladder cancer

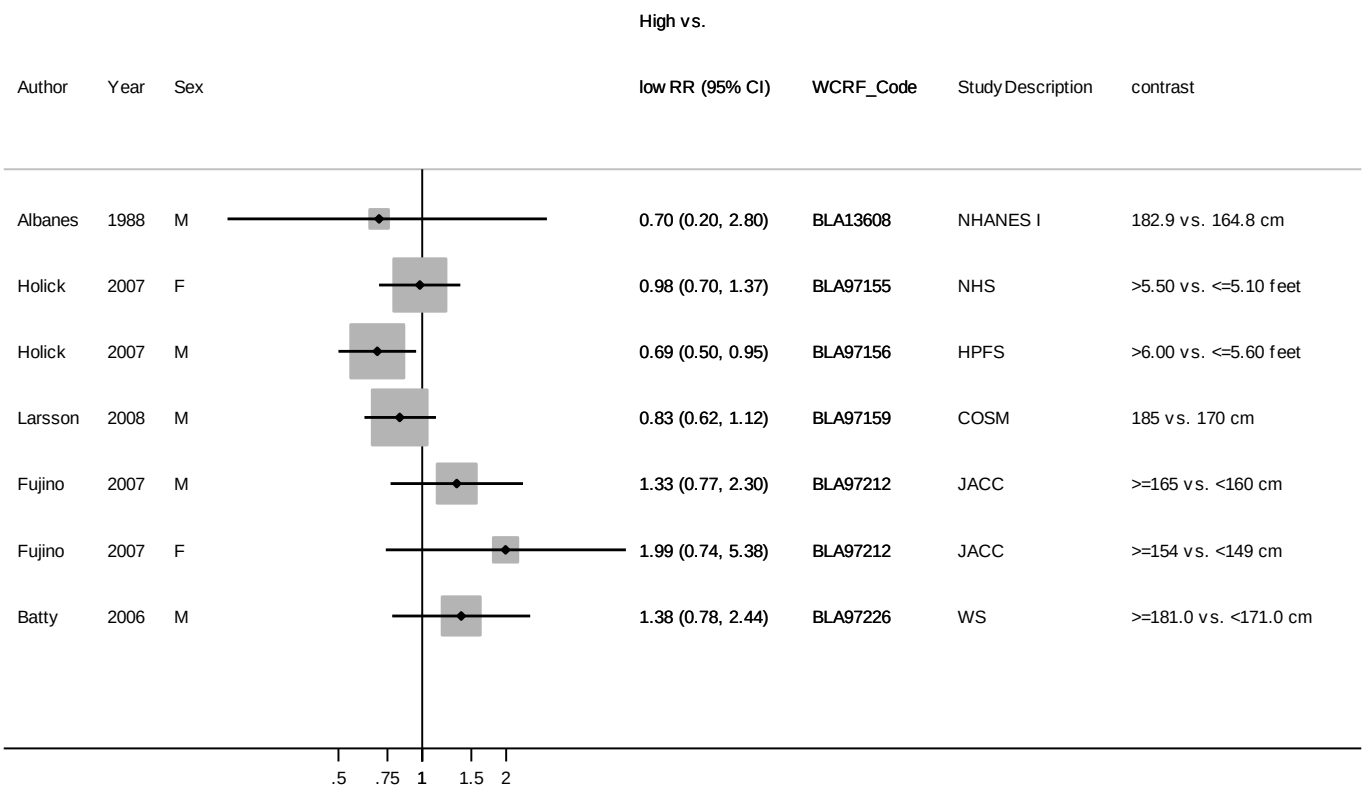


Figure 122 Dose-response meta-analysis of height and bladder cancer, per 5 cm

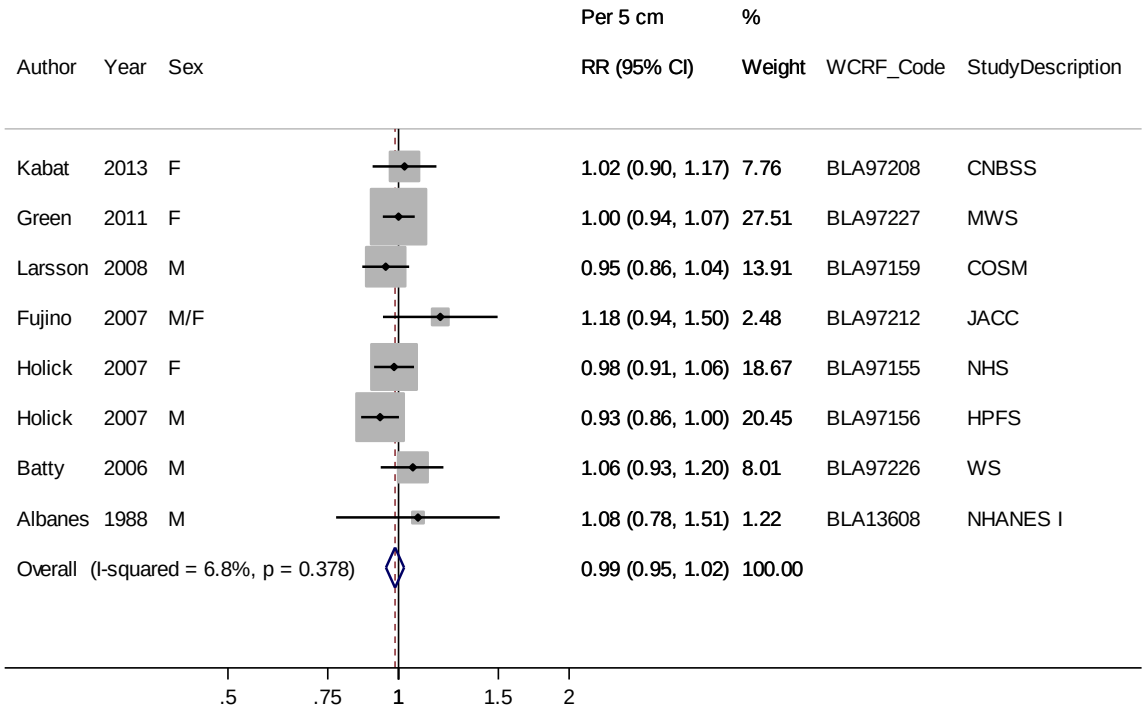


Figure 123 Dose-response meta-analysis of height and bladder cancer stratified by sex, per 5 cm

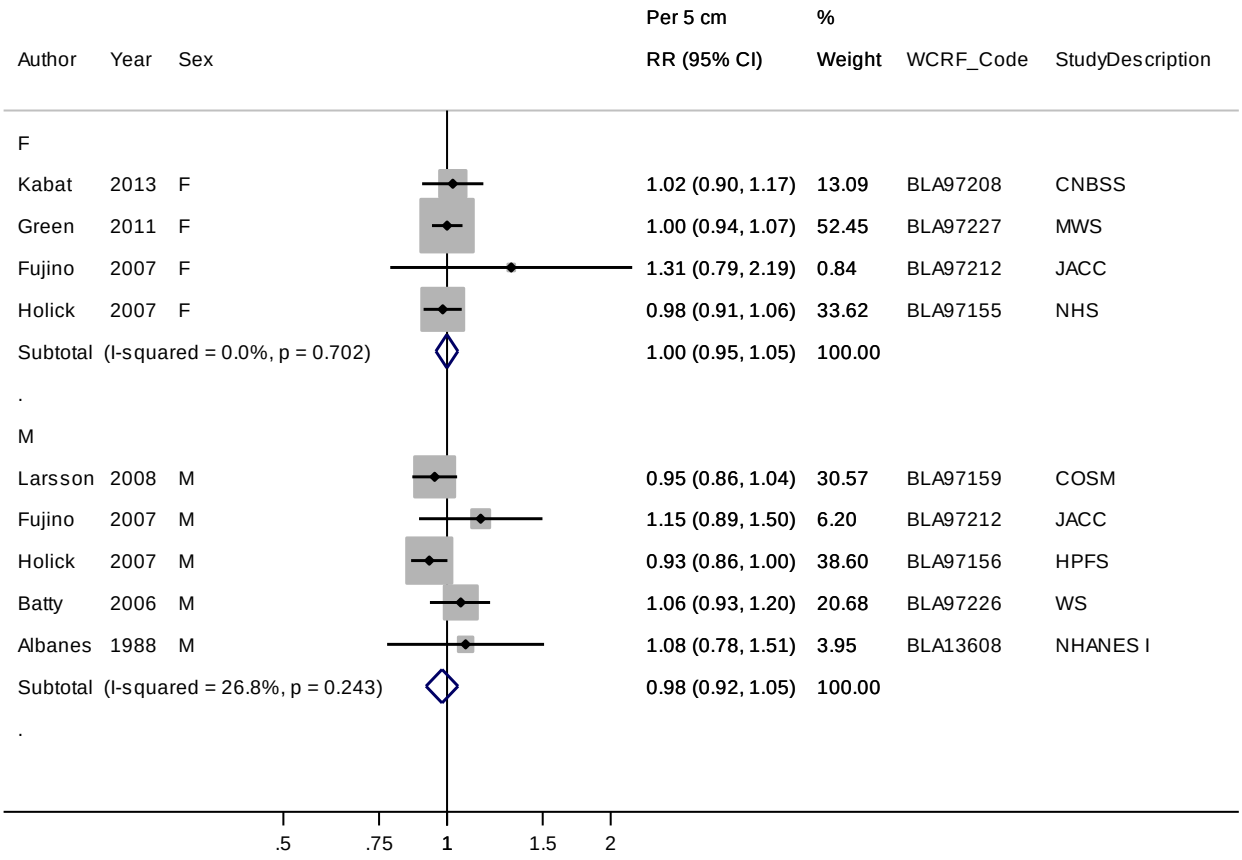
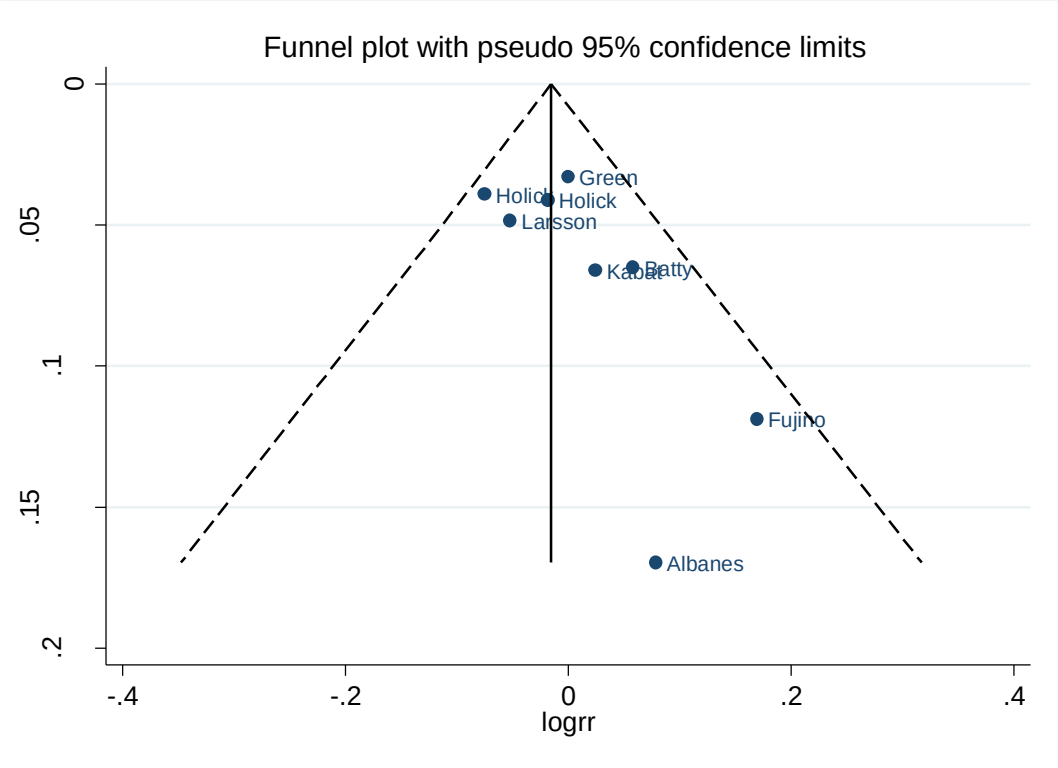


Figure 124 Funnel plot of height and bladder cancer



Egger's test p=0.10

Figure 125 Dose-response graphs for height and bladder cancer

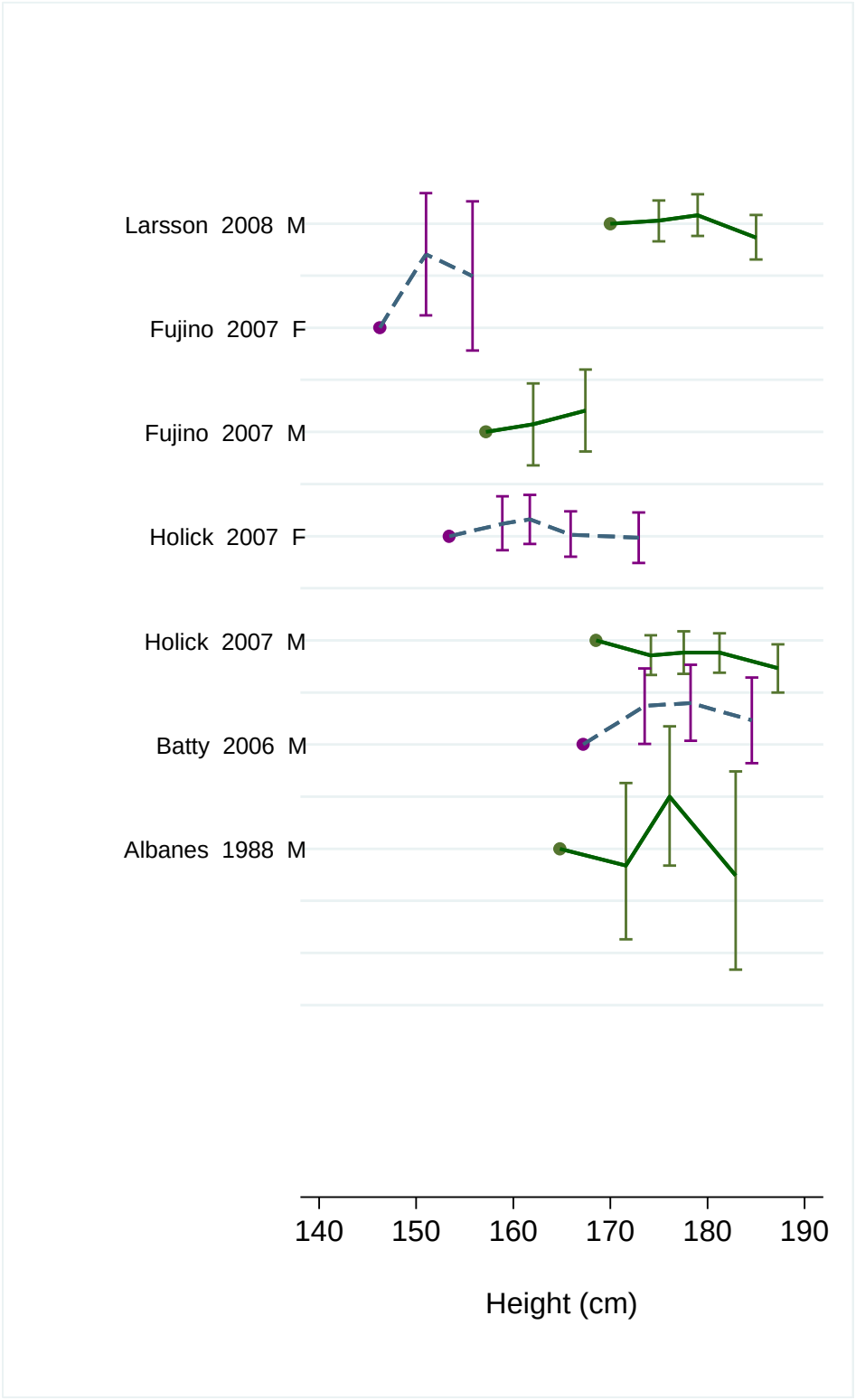


Figure 126 Height and bladder cancer including Asia Pacific Cohort Studies Collaboration

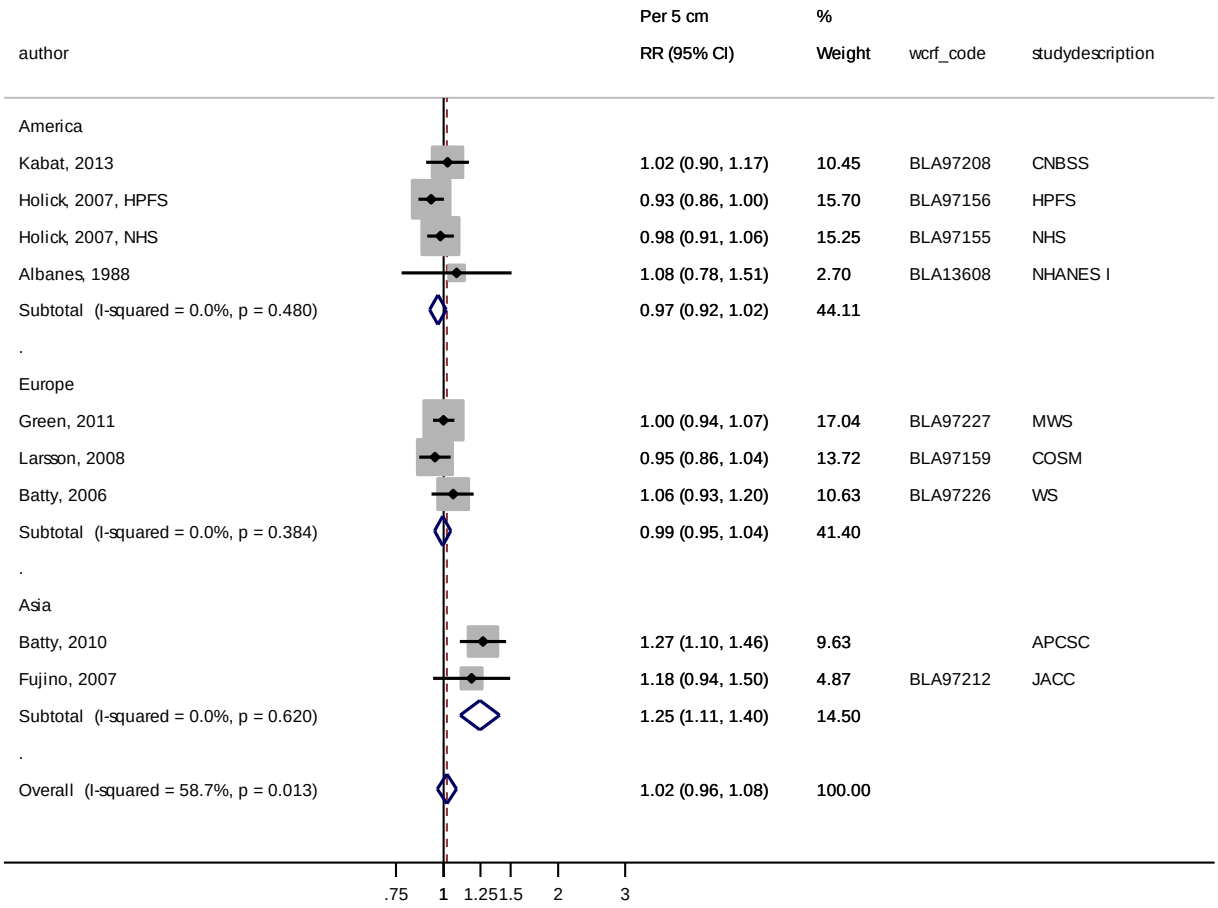
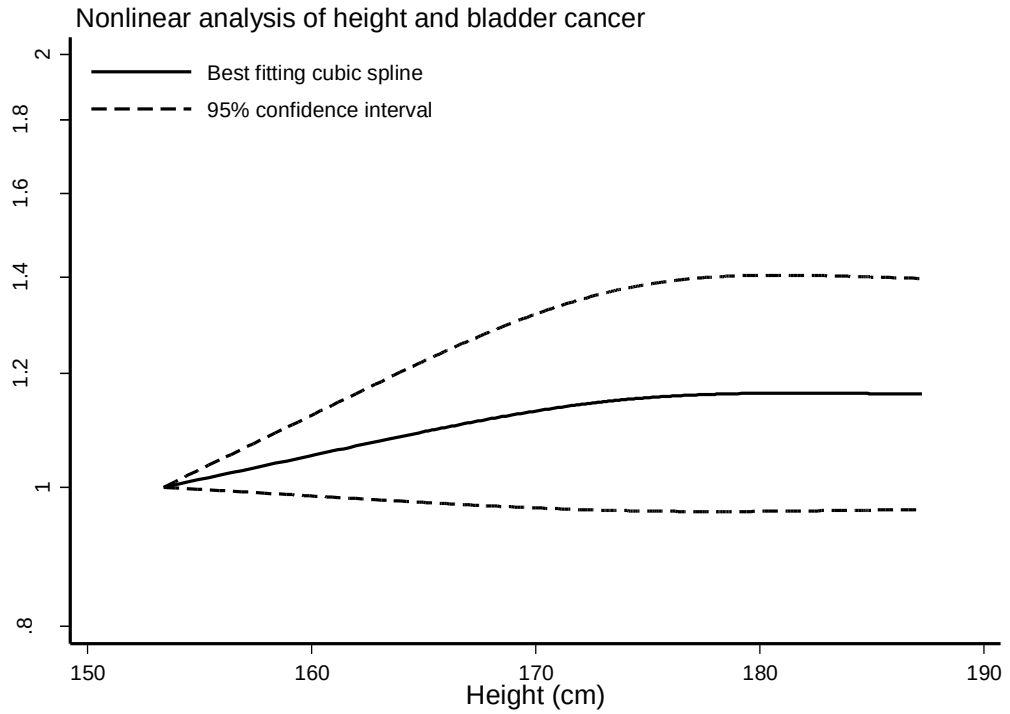


Figure 127 Nonlinear dose-response analysis of height and bladder cancer



$p_{nonlinearity}<0.0001$

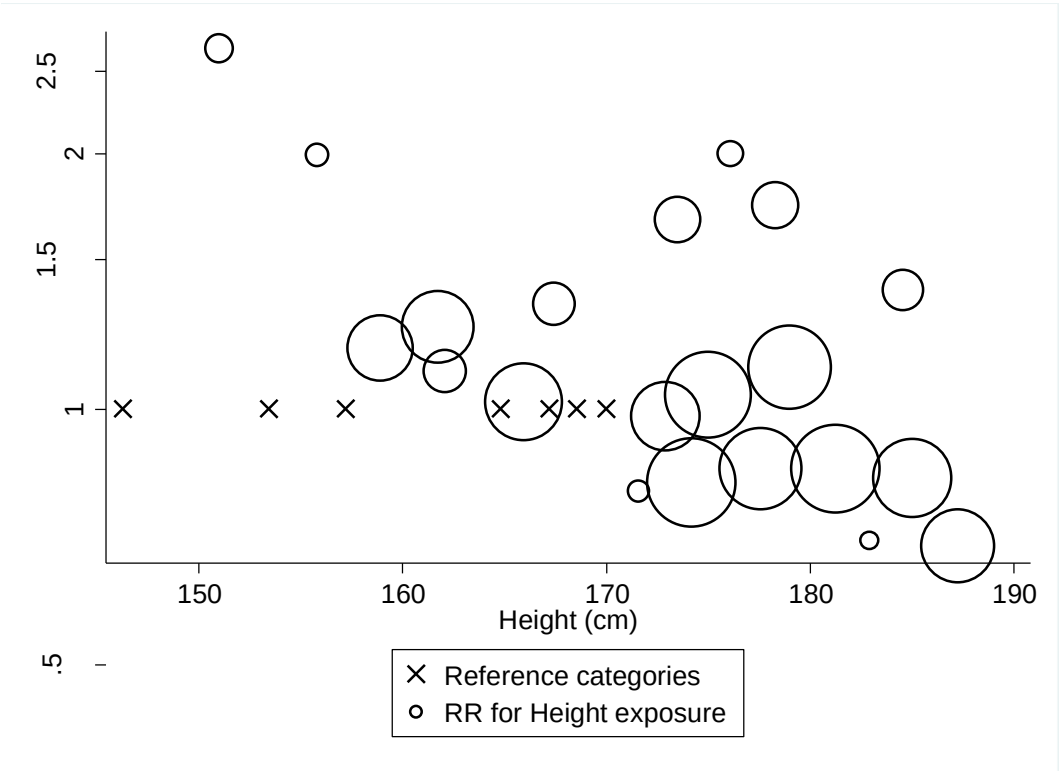


Table 138 Table with height values and corresponding RRs (95% CIs) for nonlinear analysis of height and bladder cancer

Height (cm)	RR (95% CI)
153.4	1.00
162	1.07 (0.98-1.16)
170	1.13 (0.97-1.32)
175	1.15 (0.96-1.38)
181	1.16 (0.96-1.40)
185	1.16 (0.96-1.40)

Annex. Anthropometric characteristics investigated by each study

Several studies investigated BMI, height and waist circumference. The anthropometric characteristics investigated by each study are indicated with a cross in the list below:

First author	Year	Study name	BMI	Height	Waist
Kabat	2013	Canadian National Breast Screening Study		x	
Andreotti	2010	Agricultural Health Study	x		
Prentice	2009	Women's Health Initiative	x		
Jee	2008	National Health Insurance Corporation Study, Korea	x		
Koebnick	2008	NIH-AARP Diet and Health Study	x		
Larsson	2008(c)	Cohort of Swedish Men	x	x	x
Fujino	2007	Japan Collaborative Cohort Study	x	x	
Green Reeves	2011 2007	Million Women's Study	x	x	
Holick	2007	Health Professional's Follow-up Study Nurses' Health Study	x	x	
Samanic	2006	Swedish Construction Workers Cohort	x		
Cantwell	2006	Breast Cancer Detection Demonstration Project follow-up cohort	x		
Rapp	2005	The Vorarlberg Health Monitoring and Promotion Program	x		
Batty	2005	The Whitehall Study	x	x	
Oh	2005	Korea National Health Insurance Corporation Study	x		
Calle	2003	Cancer Prevention Study 2	x		
Nomura	2003	Honolulu Heart Program	x		
Tripathi	2002	Iowa Women's Health Study	x		x
Michaud	2002(b)	Alpha-Tocopherol Beta-Carotene Cancer Prevention Study	x		
Hirvonen	2001	Alpha-Tocopherol Beta-Carotene Cancer Prevention Study	x		
Persson-Moschos	2000	Sweden 1974-1982	x		
Nagano	2000	Life Span Study	x		
Kurrtio	1999	Finland 1981-1995	x		
Tulinius	1997	Icelandic Cardiovascular Risk Factors Study	x	x	
Albanes	1988	National Health And Nutrition Examination Survey I		x	
Whittemore	1985	Harvard Pennsylvania Alumni Study	x	x	

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