World Cancer Research Fund International Systematic Literature Review

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

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List of Abbreviations used in the CUP Report

CUP	Continuous Update Project
WCRF/AICR	World Cancer Research Fund/American Institute for Cancer Research
SLR	Search 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 report

40-y	The 40-year cohort
AHS	Agricultural Health Study
BEACON	The International Barrett's and Esophageal Adenocarcinoma Consortium
BRHS	British Regional Heart Study
CCPPS	Copenhagen Centre for Prospective Population Studies
CECS	Chinese Elderly Cohort Study
CGRECSS	The Coordinating Group for the Research of Esophageal Carcinoma Screening Study, China 1974
CNRPCS	China Nationally Representative Prospective Cohort Study
CONOR	The Cohort of Norway
CPS I/II	Cancer Prevention Study I/II
DOS	Danish Obesity Study
DSDA	Danish Seventh-Day Adventists
ERFC	Emerging Risk Factors Collaboration
EPIC	European Prospective Investigation into Cancer and Nutrition
GPRDC	General Practitioners Research Database Cohort
HEC2000	Health Examinee Cohort in 2000
HHP	Honolulu Heart Program
IWHS	Iowa Women's Health Study Cohort
JACC	Japan Collaborative Cohort study
JAMS	Japanese Alcoholic Men Study
JPC	Japanese Physicians Cohort
JPHC	Japan Public Health Centre-based Prospective Study
KCPS	Korean Cancer Prevention Study
KCS	Kangwha Cohort Study
KNHIC	Korean National Health Insurance Corporation Study
KPMCP	Kaiser Permanente Medical Care Program
MCCS	Melbourne Collaborative Cohort Study
MCS	Miyagi Cohort Study

Me-Can	The Metabolic syndrome and Cancer project
MPP	The Malmo Preventive Project
MWS	Million Women's Study
NCS	The Norwegian Counties Study
NCVSC	Norwegian Cardiovascular Screening Cohort
NIH-AARP	NIH-AARP Diet and Health Study
NIT Cohort	Linxian Nutrition Intervention Trials - General Population Trial Follow-up
NLCS	The Netherlands Cohort Study
NSPT	Norwegian Screening Programme for Tuberculosis
OCS	Ohsaki Cohort Study
Oslo	The Oslo Study I
SBES	Seattle Barrett's Esophagus Study
SCWC	Swedish Construction Workers Cohort
SCStudy	Shanghai Cohort Study
SPCJ	Six Prefecture Cohort, Japan
VHM&PP	The Vorarlverg Health Monitoring and Prevention Programme
VIP	The Västerbotten Intervention Project

Background

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

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

The methods of the SLR are described in details in the protocol for the CUP review on oesophageal cancer (version 2, March 2013 in Appendix 2).

Summary of judgements of the WCRF-AICR Second Expert Report, 2007

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

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

	DECREASES RISK	INCREASES RISK
Convincing		**Alcoholic drinks** **Body fatness**[1]
Probable	**Non-starchy vegetables**[2] **Fruits**[2] **Foods containing beta-carotene**[3] **Foods containing vitamin C**[3]	**Maté**[4]
Limited — suggestive	Foods containing dietary fibre[3] Foods containing folate[3] Foods containing pyridoxine[3 5] Foods containing vitamin E[3]	Red meat[6] Processed meat[7] High-temperature drinks
Limited — no conclusion	Cereals (grains) and their products; starchy roots, tubers, and plantains; pulses (legumes); soya and soya products; herbs, spices, and condiments; poultry; fish; eggs; milk and dairy products; total fat; saturated fatty acids; monounsaturated fatty acids; polyunsaturated fatty acids; sugary foods and drinks; salt; salting; fermenting; pickling; smoked and cured foods; nitrates and nitrites; frying; grilling (broiling) and barbecuing (charbroiling); protein; vitamin A; retinol; thiamin; riboflavin; calcium; iron; zinc; pro-vitamin A carotenoids; beta-cryptoxanthin; Seventh-day Adventist diets; adult attained height; energy intake	
Substantial effect on risk unlikely	None identified	

1 For oesophageal adenocarcinomas only.
2 Judgements on vegetables and fruits do not include those preserved by salting and/or pickling.
3 Includes both foods naturally containing the constituent and foods which have the constituent added (see chapter 3.5.3). Dietary fibre is contained in plant foods (see box 4.1.2 and chapter 4.2).
4 As drunk traditionally in parts of South America, scalding hot through a metal straw. Any increased risk of cancer is judged to be caused by epithelial damage resulting from the heat, and not by the herb itself.
5 Vitamin B6.
6 The term 'red meat' refers to beef, pork, lamb, and goat from domesticated animals.
7 The term 'processed meat' refers to meats preserved by smoking, curing, or salting, or addition of chemical preservatives.

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.

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Modifications to the existing protocol

The protocol on oesophageal cancer was prepared in March 2013 (see Appendix 2). The following modifications had been introduced:

Review team: Christophe Stevens join the team as database manager.

Timeline: The current review includes publications included in Medline up to February 28th 2014.

Methods:

Meta-analysis was performed for the exposures whose relationship with oesophageal cancer was judged convincing, probable or limited suggestive in the 2005 SLR even when the number of studies did not amount to five or more – a criteria for updating the dose-response meta-analysis in the protocol.

In the CUP review, there were not enough data to do dose-response meta-analyses on specific alcoholic drinks. To complement the information on total alcoholic drinks (evidence graded as convincing in the Second Expert Report), meta-analyses for the highest compared to the lowest categories of alcohol drinks intakes were conducted in the CUP. The results are showed in forest plots and tables in the corresponding sections.

Non-linear dose response curves were plotted using restricted cubic splines for each study, with knots fixed at percentiles 10%, 50%, and 90% through the distribution. These were combined using multivariate meta-analysis. When the number of studies with three or more categories of exposure – a requirement of the method- was low or there was no suggestion of non-linear dose response association from the studies, non-linear meta-analysis was not conducted. The analyses were performed in Stata 12.0.

Notes on methods

- The search and WCRF database update for the Second Expert Report ended in December 30th 2005. The CUP team at IC updated the search from January 1st 2006 up to February 28th 2014 (See Flowchart).
- Oesophageal squamous cell carcinoma (SCC) and adenocarcinoma (AC) have different geographic distributions and risk factors including tobacco smoking, alcoholic drinks and BMI. In analyses on oesophageal cancer (all cancer types combined) the RRs in the studies depend on the proportion of cases with squamous cell carcinoma and adenocarcinoma in the study populations. However, the summary RRs are shown for oesophageal cancer (all types combined) because many studies reported for oesophageal cancer. When the data allowed it, the results are shown for squamous cell carcinomas and adenocarcinomas separately, following the analyses on oesophageal cancer (all types).
- Where results were only presented separately for specific cancer types (e.g. oesophageal adenocarcinoma and squamous cell carcinoma), these were first combined before inclusion in the analysis on total oesophageal cancer.

- The first dose-response forest plot is the analysis of all studies combined. This is followed by stratified analysis by oesophageal cancer type whenever possible.
- Linear dose-response meta-analysis were updated when at least two new publications with enough data for dose-response meta-analysis were identified during the CUP and if there were in total five cohort studies or five randomised controlled trials. The meta-analyses include studies identified during the 2005 SLR and studies identified during the CUP SLR. Studies may not have presented sufficient data for use in a meta-analysis. As such, a meta-analysis was not conducted even though the number of studies met the criteria for analysis.
- Exposures for which the evidence was judged as convincing, probable or limited-suggestive in the Second Expert Report were reviewed even if the number of studies was below the previous figures; in some exposures, the new data did not justify conducting meta-analysis and the data are tabulated.
- Evidence on upper aerodigestive tract cancers and/or combined cancers of the oesophagus and stomach were reviewed separately. Meta-analysis was conducted when possible.
- The increment units used in the linear dose-response analyses were chosen to be consistent with other CUP SLRs, which may not be comparable with those used in the meta-analyses in the previous SLR. However, if most of the identified studies reported servings, times, these were used as increment unit, as indicated in the Protocol.
- The statistical methods to derive missing data are described in the protocol.
- The method of Hamling (Hamling, 2008) was used to recalculate relative risks (RRs) and confidence intervals (CIs) for a categorical comparison alternative to that reported by the study. The method was also used to derive an overall result on oesophageal cancer when only results by its subtype were reported
- 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, 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.
- Only summary relative risks estimated with random effect models are shown.
- Highest vs lowest forest plots show the relative risk estimates for the highest vs the reference category in each study. The overall summary estimate was not calculated (except for physical activity and alcohol type domains).
- The dose-response forest plots show the relative risk per unit of increase for each study (most often derived by the CUP review team from categorical data). The relative risk is denoted by a box (larger boxes indicate that the study has higher precision, and greater weight). Horizontal lines denote 95% confidence intervals (CIs). Arrowheads indicate truncations. The diamond at the bottom shows the

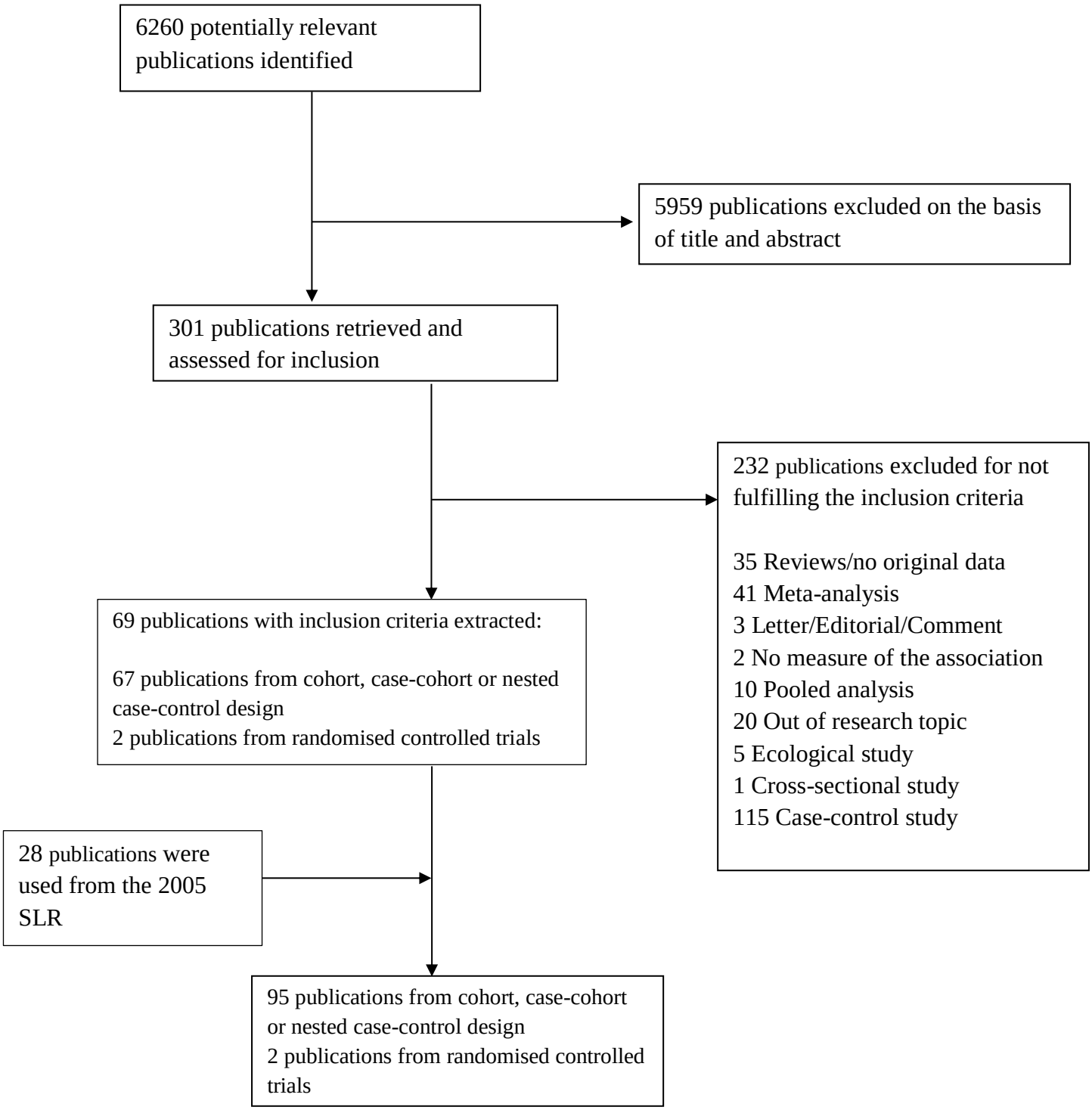
summary relative risk estimate and corresponding 95% CI. The unit of increase is indicated in each figure and in the summary table for each exposure.

- When the 95% CI of a RR spanned 1.00, the association was considered as statistically not significant. When the upper or lower CI was 1.00, the association was considered of borderline significance.
- Dose-response plots showing the RR estimates for each exposure level in the studies are also presented for each exposure in the review. The relative risks estimates were plotted in the mid-point of each category level (x-axis) and connected through lines.
- Exploratory non-linear dose-response meta-analyses were conducted only when there were five or more studies with three or more categories of exposure – a requirement of the method. Non-linear meta-analyses are not included in the sections for the other exposures when not conducted.
- The non-linear dose-response curve and the bubble graph were presented when a significant non-linear association was observed.
- The interpretation of the non-linear dose-response analyses should be based on the shape of the curve and not only on the p-value because the number of observations tended to be low. Bubble graphs are also presented.
- Loss to follow up was defined as low when <10% was reported by the study.

Continuous Update Project: Results of the search

Flow chart of the search for oesophageal cancer

Search period January 1st 2006-February 28th 2014



Results by exposure

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

The exposure code is the exposure identification in the database. Only exposures identified during the CUP are shown.

Exposure Code	Exposure Name	Number of publications		Total number of publications
		2005 SLR	CUP	
1	Patterns of diet	5	5	10
2.1.1	Corn	1	1	2
2.1.1.2.3	Rice	2	1	3
2.1.2	Root vegetables	0	1	1
2.1.2.1	Sweet potatoes	1	1	2
2.1.2.1	Potatoes	1	1	2
2.2	Total fruits and vegetables	0	2	2
2.2.1	Vegetables	3	7	10
2.2.1.1.1	Carrots	1	3	4
2.2.1.1.6	Beetroot	0	1	1
2.2.1.2	Cruciferous vegetables	0	4	4
2.2.1.2.2	Cabbage	1	1	2
2.2.1.2.5	Cauliflower	1	1	2
2.2.1.2.6	Brussels sprouts	0	1	1
2.2.1.2.7	Sauerkraut	0	1	1
2.2.1.2.8	Kale	0	1	1
2.2.1.3	Allium vegetables	1	2	3
2.2.1.3.5	Onion	0	1	1
2.2.1.4	Green leafy vegetables	1	5	6
2.2.1.4.4	Seaweed	1	1	2
2.2.1.4.5	Cooked endive	0	1	1
2.2.1.5	Yellow vegetables	2	1	3
2.2.1.5	Tomatoes	1	3	4
2.2.1.5	Raw leafy vegetables	0	1	1
2.2.1.5	Wild plants	0	1	1
2.2.1.5	Mushrooms	0	1	1
2.2.1.6	Raw vegetables	0	1	1
2.2.1.12	Pickled vegetables	5	2	7
2.2.2	Fruits	4	8	12
2.2.2.1	Citrus fruits	1	7	8
2.2.2.2	Apple, pears	1	1	2
2.2.2.2	Other fruits	1	2	3

2.2.2.2.1	Banana	1	1	2
2.2.2.2.4	Strawberries	0	1	1
2.2.2.2.7	Melon	0	1	1
2.2.2.2.11	Grape	0	1	1
2.3	Pulses (legumes)	0	3	3
2.3.1.1	Miso soup	3	1	4
2.3.2	Beans	1	2	3
2.3.2.2	Tofu	1	1	2
2.5.1	White meat	0	1	1
2.5.1	Meat	2	2	4
2.5.1.2	Processed meat	3	6	9
2.5.1.3	Red and processed meat	0	6	6
2.5.1.3.1	Beef	1	1	2
2.5.1.3.3	Pork	2	1	3
2.5.1.4	Poultry	0	4	4
2.5.1.5	Liver	0	1	1
2.5.2	Fish	4	4	8
2.5.2	Fish paste	0	1	1
2.5.2.3	Dried and salted fish	1	1	2
2.5.4	Eggs	5	2	7
2.6.1.1	Butter	0	1	1
2.6.1.4	Cod liver oil	0	1	1
2.6.3	Margarine	0	1	1
2.6.4	Sugars	0	1	1
2.6.4	Fructose	0	1	1
2.7	Dairy foods	0	1	1
2.7.1	Milk	3	3	6
2.7.2	Cheese	0	1	1
2.7.3	Yoghurt	0	1	1
2.9.13	Sweets	0	1	1
3.4.2	Carbonated beverages	0	1	1
3.5	Fruit juices	1	2	3
3.6.1	Coffee	1	5	6
3.6.1	Caffeinated coffee	0	1	1
3.6.1	Decaffeinated coffee	0	1	1
3.6.2	Black tea	1	1	2
3.6.2	Tea	1	4	5
3.6.2.2	Green tea	1	3	4
3.6.3	Maté	0	0	0
3.7.1	Age start alcohol consumption	0	1	1
3.7.1	Total alcohol (as ethanol)	15	18	33
3.7.1	Alcoholic drinks - years since stopping	0	1	1

3.7.1	Alcoholism	2	2	4
3.7.1	Drinking duration	0	1	1
3.7.1	Drinking frequency	0	1	1
3.7.1	Lifetime alcohol consumption	0	1	1
3.7.1.1	Beers	4	6	10
3.7.1.2	Rice wine	0	1	1
3.7.1.2	Wines	2	5	7
3.7.1.3	Spirits	0	3	3
3.7.1.4	Liquor	3	3	6
4.1.2.9	Nitrate	0	2	2
4.2	Preserved foods	0	2	2
4.2.5.3	Salted/salty foods	2	2	4
4.3.5.4.1	NDMA (n-nitrosodimethylamine)	0	2	2
4.3.5.4.1	Nitrite	0	3	3
4.4.2	Acrylamide	0	2	2
4.4.2.5	Frying/fried foods	3	1	4
4.4.2.5	MeIQx	0	1	1
4.4.2.7	Bap	0	1	1
4.4.2.8	DiMeIQx	0	1	1
4.4.2.8	PhiP	0	1	1
4.4.2.9	Mutagen index	0	1	1
5.1	Carbohydrate	1	1	2
5.1.2	Dietary fibre	1	0	1
5.1.4	Mono/disaccharides	0	1	1
5.1.4	Sucrose	0	1	1
5.1.4	Sugars (as nutrients)	1	1	2
5.1.5	Glycaemic index	0	1	1
5.1.5	Glycaemic load	0	1	1
5.2	Total fat (as nutrients)	1	3	4
5.3	Protein	1	1	2
5.3.1	Methionine	0	1	1
5.4	Alcohol (as ethanol)	4	3	7
5.4	Lifetime ethanol intake	0	1	1
5.5.1	Vitamin A, supplements	0	1	1
5.5.1.2	Beta-carotene	2	3	5
5.5.3	Folic acid, supplements	0	1	1
5.5.3	Dietary folate	0	1	1
5.5.5	Thiamin (vitamin B1), supplement	0	1	1
5.5.7	Dietary pyridoxine (vitamin B6)	0	1	1
5.5.8	Dietary vitamin B12 intake	0	1	1
5.5.9	Vitamin C	1	3	4
5.5.10	Serum 25-hydroxyvitamin D	0	1	1

5.5.11	Vitamin E	2	1	3
5.5.11	Alpha-tocopherol from food	0	1	1
5.5.11	Alpha-tocopherol supplement	0	3	3
5.5.11	Gamma-tocopherol	0	1	1
5.5.13	Multivitamin supplement	1	2	3
5.6	Calcium and vitamin D, supplement	0	1	1
5.6.2	Haem iron	0	3	3
5.6.3	Calcium from food and supplements	0	1	1
5.6.3	Calcium, supplements	0	2	2
5.6.3	Dietary calcium	0	1	1
5.6.4	Selenium, supplements	0	1	1
5.6.4	Selenium, toenail	0	1	1
5.6.6	Serum phosphate	0	1	1
5.6.7	Zinc supplements	0	1	1
5.6.7	Dietary zinc intake	0	1	1
5.7.5	Lignans	0	1	1
5.7.7	Total nitroso compounds	0	1	1
5.8	Flavonoids	0	1	1
5.8	Flavan-3-ols	0	1	1
5.8	Anthocyanidins	0	1	1
5.8	Flavonols	0	1	1
5.8	Flavanones	0	1	1
5.8	Flavones	0	1	1
5.8	Isoflavones	0	1	1
6.1	Physical activity index	0	1	1
6.1.1.1	Occupational physical activity	0	2	2
6.1.1.2	Recreational activity	1	5	6
6.1.1.2	Bicycling	0	1	1
6.1.1.2	Walking	2	1	3
6.1.1.3	Gardening	0	1	1
6.1.3	Vigorous physical activity	1	3	4
6.2	Sitting	0	1	1
6.2	Television watching	0	2	2
7.1	Energy intake	2	1	3
7.1.0.1	Percent of energy from fat	0	1	1
7.1.0.1	Percent of energy from saturated fat	0	1	1
7.1.0.1	Energy from monounsaturated fat	0	1	1
7.1.0.1	Percent of energy from polyunsaturated fat	0	1	1
7.1.0.1	Energy from trans fatty acids	0	1	1
7.1.0.1	Percent of energy from long-chain n-3 fatty acids	0	1	1
8.1.1	BMI	7	18	25
8.1.1	BMI at younger age	0	3	3

8.1.3	Weight	3	4	7
8.1.3	Weight at 20 years	0	1	1
8.1.5	Fat free mass	0	1	1
8.1.5	Fat mass	0	1	1
8.1.5	Body fat	1	1	2
8.1.6	BMI change	0	2	2
8.2.1	Waist circumference	0	4	4
8.2.2	Hips circumference	0	2	2
8.2.3	Waist to hip ratio	0	4	4
8.2.5	Other marker for fat distribution e.g., CT, ultrasound	0	1	1
8.3.1	Height	4	8	12
8.4.1	Birth weight	0	1	1

1 Patterns of diet

Eleven publications from ten cohorts (from which five publications identified in the 2005 SLR) have investigated dietary patterns in relation to oesophageal cancer. No meta-analysis was conducted because of the differences across the patterns investigated in the studies. The study results are described and tabulated.

Table 2 Dietary patterns and oesophageal cancer risk. Number of studies and number reporting significant associations by dietary pattern

Dietary patterns by study design	Number of studies	Number of studies showing significant association
Randomized controlled trial	0	0
Cohort studies		
Health scores	1	Inverse with AC and SCC
Diet diversity scores	1	Inverse association of fruit diversity, and fruit and vegetable (combined) diversity with SCC
Diet and smoking pattern	1	Positive association for smoking, drinking, eating meat every day and less leafy vegetables vs less drinking, smoking, meat intake and more vegetables
Diet preferences (vegetables, salt, type of breakfast)	2	0
Mediterranean diet	1	Inverse association for SCC only
Seventh-day's Adventists	1	0
High temperature food	4*	1 (Increased risk)

*One study is on upper aerodigestive tract cancers.

Cohort studies

Health Scores

No studies were identified in the 2005 SLR. One study on "a priori" heath indices scores was identified in the CUP (Li, 2013). Lower risk of squamous cell carcinoma and adenocarcinoma with related with higher concordance with the 2005 Dietary Guidelines for Americans (the score included grains, vegetables, fruits, meat, dairy, pulses, fats, oils, sodium, alcohol, and added sugar). Adjustments factors included smoking, BMI, education, physical activity, total energy and alcohol intake.

Diet diversity scores

No studies were identified in the 2005 SLR. One study was identified in the CUP. The study (EPIC) examined the association of a score of vegetable and fruits diversity and SCC. Higher

variety of fruits and vegetables consumed was significantly related to lower risk of oesophageal SCC (Jeurnink, 2012). In analysis of diversity of fruits and vegetables separately, significantly lower SCC cancer risk was reported for increasing the variety of fruits but not vegetables. Study adjustment included BMI, smoking, energy intake, red and processed meat consumption, alcohol intake and mutual adjustment of fruits and vegetables.

Diet preferences

No study was identified in the 2005 SLR. Two Asian studies identified in the CUP investigated diet preferences. In a Korean study in men, preference for vegetables or a mixture of vegetables and meat compared to preference for meat was non-significantly inversely related to oesophageal cancer risk (Yung, 2008). In a Japanese study on oesophageal cancer mortality (Iso, 2007), preference for salty food (like compared to dislike), preference for fatty food and Japanese or Western breakfast were unrelated to oesophageal cancer mortality. The study was only adjusted for age and study area.

Mediterranean Diet

One study was identified in the CUP and no studies were identified in the 2005 SLR. Li, 2013 (NIH-AARP) reported strong inverse association with increasing alternative Mediterranean Diet (aMED) score for squamous cell carcinoma and non-significant inverse association for adenocarcinoma. The score included vegetables, legumes, fruit, nuts, whole grains, fish, meat, alcohol, and ratio of monounsaturated to saturated fat.

No new studies were identified in the CUP. In a Japanese study identified in the 2005 SLR, men who smoked, consumed alcohol and meat, and did not consume green and yellow vegetables daily were at an increased risk for oesophageal cancer incidence (Hirayama, 1985). No adjustments were made for other confounders.

Adventists Diet

In a historical cohort study of males in Denmark, a Seventh Day Adventist diet was not associated with risk of oesophageal cancer compared to diet of members of other temperance societies (Jensen, 1983).

High temperature food

One study was identified in the CUP and three studies in the 2005 SLR. The results of the four studies were discordant. Ren, 2010 (NIH-AARP, USA) and Tran, 2005 (China) reported non-significant inverse associations with hot tea and hot liquid consumption, respectively. A Japanese study found a significant positive association for hot tea consumption and oesophageal cancer risk (Kinjo, 1998). In a cohort study conducted among Japanese-American men, Chyou, 1995 reported that very hot food (compared to cool/warm) was positively, but not significantly, associated with risk of squamous cell cancers of the upper aerodigestive tract, (35 were cases of oesophageal cancer out of 92 cases in the analysis) after controlling for age, alcohol use and smoking.

1 Patterns of diet

Table 3 Dietary patterns and oesophageal cancer risk. Number of studies in the CUP SLR

Cohort studies

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors
Health index scores								
Li, 2013 STM80193 USA	NIH- AARP, Prospective Cohort, Age: 50-71 years, M/W	215/ 494 968 9.7 years	Record linkage to state cancer registry databases.	Validated 124- item FFQ	Incidence, SCC	Dietary Guidelines for Americans (grains, vegetables, legumes, fruits, milk, meat, fish, oils, saturated fat, sodium, alcohol, added sugar) Score quintile 5 vs quintile 1	0.51 (0.31-0.86) Ptrend:0.001	Age, sex, BMI, race, education, smoking, total energy intake, usual physical activity, vigorous physical activity
		633/			AC		0.75 (0.57-0.98) Ptrend:0.1	
Diet diversity scores								
Jeurnink, 2012 oes008211 0 European countries	EPIC, Prospective Cohort, Age: 35-70 years, M/W	98/ 452 269 8.4 years	Cancer registries, health insurance records, pathology records, active follow-up, death certificate	FFQ, dietary questionnaires and food record	Incidence, SCC	Diet Diversity Score –total number of individual vegetable and fruit products eaten at least once in two weeks (range 0–40) Per increment of 2 types of fruits and vegetables	0.88 (0.79-0.97)	Stratified by age, gender, centre; adjusted for smoking, energy intake, red and processed meat, BMI, alcohol, fruit and vegetable consumption
						Vegetable diversity score (range 0–26)		Additionally adjusted

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors
						Per increment of 2 of types of vegetables	0.89 (0.77-1.03)	for fruit consumption
						Fruits diversity score (range 0–14) Per increment of 2 types of fruits	0.76 (0.62-0.94)	Additionally adjusted for vegetable consumption
Diet preference								
Yung, 2008 LUN20276 Korea	KNHIC, Prospective Cohort, Age: 40- years, M	293/ 444 963 6 years	Cancer registry	FFQ	Incidence, oesophageal cancer	Dietary preference: Vegetables or mixture of vegetables and meat vs meat	All men: 0.79 (0.53-1.20)	Age, BMI, employment, fasting blood sugar, leisure - physical activity, smoking status, alcohol drinking
Iso, 2007 LUN20294 Japan	JACC, Prospective Cohort, Age: 40-79 years, M/W	121 men, 22 women/ 105 500 15 years	Date and cause of death annually or biannually confirmed with authorities authorization	Validated FFQ	Mortality, oesophageal cancer Men Women	Preference for salty food (like vs dislike)	0.89 (0.45-1.76) 0.48 (0.16-1.40)	Age, area of study
					Men Women	Preference for fatty food (like vs dislike)	0.76 (0.49-1.17) 1.38 (0.54-3.55)	
					Type of breakfast (Usually vs not usually)			
					Men	Japanese style	1.33 (0.74-2.40)	

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors
					Women		1.54 (0.46-5.15)	
					Men Women	Western style	0.77 (0.41-1.46) 1.07 (0.33-3.46)	
Dietary and smoking pattern								
Hirayama, 1985 oes00054 Japan	Six Prefecture Cohort, Japan, Prospective Cohort, M/W	26 889 16 years	Area residency lists	Questionnaire	Risk, oesophageal cancer	Smoking, drinking, consuming meat daily; green leafy vegetables non-daily vs smoking, drinking, consuming meat not daily; green leafy vegetables daily	5.76 (p<0.001)	
Mediterranean Diet								
Li, 2013 STM80193 USA	NIH- AARP, Prospective Cohort, Age: 50-71 years, M/W	215/ 494 968 9.7 years	Record linkage to state cancer registry databases.	Validated 124- item FFQ	Incidence, SCC	Alternative Mediterranean Diet (aMED) score components: vegetables, legumes, fruit, nuts, whole grains, fish, ratio of monounsaturated to saturated fat, meat, alcohol 7-9 vs 0-2	0.44 (0.22-0.88) Ptrend:0.03	Age, sex, BMI, race, education, smoking, total energy intake, usual physical activity, vigorous physical activity
		633/			AC		0.91 (0.66-1.25) Ptrend:0.25	
Adventists Diets								
Jensen, 1983 oes00138 Denmark	DSDA, Historical Cohort, M, Temperance	6/ 1 589 34 years		Unknown	Incidence, oesophageal cancer	Seventh Day Adventists vs members of other temperance societies	1.60 (0.60-3.50)	

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors
	Society members							
Food temperature								
Ren, 2010 oes00814 USA	NIH- AARP, Prospective Cohort, Age: 50-71 years, M/W	123/ 481 563 6 years	Record linkage to state cancer registry databases.	FFQ Hot tea	Incidence, SCC	≥1 cup/day vs none	0.57 (0.30-1.07) Ptrend:0.10	Age, sex, tobacco smoking, alcohol drinking, BMI, education, ethnicity, usual physical activity, vigorous physical activity, intake of fruits, vegetables, red meat, white meat, and calories
		305/			AC		0.97 (0.67-1.41) Ptrend:0.98	
Tran, 2005 oes00804 China	NIT Cohort, Prospective Cohort, Age: 40-69 years, M/W	1 958/ 29 584 15 years	Monthly contact by either village health workers or interviewers, and cancer diagnoses verified by senior diagnosticians	FFQ Hot liquid in summer	Incidence, SCC	≥1 vs 0 times/year	0.96 (0.87-1.07)	Age, sex
				Hot liquid in winter			0.95 (0.87-1.04)	
Kinjo, 1998 oes00350 Japan	Six Prefecture Cohort, Japan, Prospective Cohort, Age: 40- years, M/W	328 men, 112 women/ 220 272 15 years	Area residency lists	Questionnaire Hot tea	Mortality, oesophageal cancer	Hot vs not hot	1.50 (1.10-1.90)	Age, sex, alcohol consumption, area of residence, occupation, other nutrients, foods or supplements, smoking habits
					Men		1.50 (1.10-2.00)	Age, area of residence,

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors
					Women		1.80 (1.10-2.90)	occupation
Chyou, 1995 oes00128 USA	HHP, Prospective Cohort, M, Japanese residents of Hawaii	92/ 7 995 25 years	Selective service roll	FFQ and 24 hour recall Temperature of foods	Incidence, upper aerodigestive tract, squamous cell carcinoma	Hot/boiling hot vs cool/warm	1.44 (0.91-2.26)	Age, alcohol consumption, smoking habits

2 Foods

2.2 Total fruit and vegetables

No cohort studies were identified in the 2005 SLR. Two studies were identified in the CUP. Meta-analyses were not conducted.

In the NIH-AARP study (Freedman, 2007a), total fruit and vegetable intake was inversely associated with SCC risk (HR for the highest compared to lowest intake: 0.78, 95% CI: 0.67–0.91; Ptrend: 0.02), but not adenocarcinoma risk (HR: 0.98, 95% CI: 0.90–1.08; Ptrend: 0.68). In a Japanese study in men (Yamaji, 2008), an increase in consumption of total fruit and vegetables by 100 grams per day (g/day) was associated with a decreased risk of oesophageal SCC (HR: 0.89; 95% CI: 0.79–0.99; Ptrend: 0.01).

A significant inverse association for the risk of oesophageal adenocarcinoma (summary RR for highest compared to lowest intake: 0.68, 95 CI: 0.49-0.93; I^2: 38.9%, p: 0.16) was reported in a published meta-analysis (Li, 2014) of four case-control studies and the NIH-AARP study as identified above.

The sections below are on fruits and vegetables as separate exposures. All the studies that reported results on fruit intake and oesophageal cancer also reported on vegetable intake (see Appendix 1).

2.2.1 Vegetables

Randomised controlled trial

No randomised controlled trial was identified

Cohort studies

Summary

Main results:

Five out of seven identified studies (2925 cases) were included in the dose-response meta-analysis. No significant association of vegetables intake with oesophageal cancer risk was observed. The results were similar in men (high heterogeneity, three studies) and women (no heterogeneity, two studies).

In analysis by cancer type, a significant inverse association was observed for adenocarcinomas (three studies, no heterogeneity). A non-significant (inverse) association was observed for squamous cell carcinomas (SCC) (four studies, moderate heterogeneity). All studies on SCC reported inverse associations (significant only in the Japanese study) except a study on Chinese population that reported no significant association of vegetables in take with SCC risk (Tran, 2005). This is a study in Linxian, an area in China with high rate of oesophageal cancer characterized by poor nutritional status. When this study was excluded from the sensitivity analysis, the summary RR remained statistically non-significant.

Only one study reported results by smoking status (Steevens, 2011). Vegetables intake was significantly associated to oesophageal AC and SCC among current smokers but no significant association was observed in former and never smokers.

Two studies were excluded from the dose-response analysis. Non-significant (inverse) association for oesophageal cancer risk was observed in one study (Fan, 2008) and a significant inverse dose-response trend with oesophageal and gastric cardia carcinomas (combined) was observed in the other study (Yu, 1993).

Moderate heterogeneity was observed; the number of studies was too small to allow full investigation. There was no significant evidence of publication or small study bias (p=0.15) but visual inspection of funnel plot suggested small studies with a positive association are missing.

Sensitivity analyses:

The summary RR remained non-significant in influence analysis, ranging from 0.92 (95% CI=0.80-1.06) and 0.92 (0.79-1.08) when George, 2009 (36% weight) and Tran, 2005 (42% weight) to 1.01 (0.95-1.08) when Yamaji, 2008 (14% weight) were omitted, respectively.

Non-linear dose-response meta-analysis:

Non-linear dose-response analysis was not conducted due to small number of studies.

Study quality:

The NIT cohort was on people who participated in vitamin/mineral trials (Tran, 2005). The exposure investigated was fresh vegetable intake and the intake range was lower than vegetable intake in other cohorts included in the dose-response analysis.

All studies included in the analysis used FFQ to assess vegetables intake. The EPIC study (Gonzalez, 2006a) also used diet history and food record. Tran, 2005 interviewed participants for nine dietary items only and measured fresh vegetables intake in times/year. The NIH-AARP Study measured in cup-equivalent/1000 kcal/day (George, 2009) or servings/1000 kcal/day (Freedman, 2007a). The units were converted to grams/day using standard methods.

Loss to follow-up was low in most studies. All studies examined cancer incidence, which was ascertained by pathology records and/or records linkage to cancer registries.

All studies included in the dose-response analysis were adjusted for age and sex and all studies except Tran, 2005 were adjusted for smoking status, frequency and duration of smoking and alcohol consumption. George, 2009 and Gonzalez, 2006a were further adjusted for socioeconomic status, body fatness, total energy intake, and physical activity. In Steevens, 2011, BMI was considered for adjustment but not included in the final model.

No studies were adjusted for Helicobacter pylori status. In one study (Gonzalez, 2006a) that reported non-significant inverse associations of vegetable intake and risk of oesophageal adenocarcinoma, the association did not differ among Helicobacter pylori infected and non-infected subjects.

Table 4 Vegetables intake and oesophageal cancer risk. Number of studies in the CUP SLR

	Number
Studies identified	7* (10 publications)
Studies included in forest plot of highest compared with lowest exposure	6
Studies included in linear dose-response meta-analysis	5
Studies included in non-linear dose-response meta-analysis	Not enough studies

Note: Include cohort, nested case-control and case-cohort designs
*Included one study reported results on oesophageal/gastric cardia carcinoma

Table 5 Vegetables intake and oesophageal cancer risk. Summary of the linear dose-response meta-analysis in the 2005 SLR and CUP

	2005 SLR		CUP
Increment unit used	No meta-analysis		100g/day
All studies			
Studies (n)	-		5
Cases (total number)	-		2925
RR (95%CI)	-		0.98 (0.90-1.06)
Heterogeneity (I^2, p-value)	-		30.5%, 0.22
P value Egger test	-		0.15
Stratified and sensitivity analysis			
Sex	**Men**		**Women**
Studies (n)	3		2
RR (95%CI)	0.91 (0.77-1.08)		0.97 (0.80-1.16)
Heterogeneity (I^2, p-value)	64.1 %, 0.06		0%, 0.59
Histological type	**Adenocarcinoma (AC)**		**Squamous cell carcinoma (SCC)**
Studies (n)	3		4
Cases (total number)	415		2273
RR (95%CI)	0.89 (0.80-0.99)		0.91 (0.81-1.03)
Heterogeneity (I^2, p-value)	0%, 0.67		49.2%, 0.12
Geographic location	**Asia**	**Europe**	**North America**
Studies (n)	2	2	1
RR (95%CI)	0.92 (0.74-1.14)	0.88 (0.66-1.17)	1.03 (0.93-1.14)
Heterogeneity (I^2, p-value)	75.8%, 0.04	0%, 0.61	-

Other stratified analysis

Duration of follow-up	**5-<10 years**	**≥10 years**
Studies (n)	3	2
RR (95%CI)	0.92 (0.74-1.13)	1.00 (0.93-1.09)
Heterogeneity (I^2, p- value)	60.9%, 0.08	0%, 0.49
Number of cases	**<500 cases**	**≥500 cases**
Studies (n)	3	2
RR (95%CI)	0.83 (0.71-0.98)	1.02 (0.96-1.08)
Heterogeneity (I^2, p-value)	0%, 0.79	0%, 0.78
Adjustment for:		
Socioeconomic status/body fatness/energy intake/physical activity*	**Not adjusted**	**Adjusted**
Studies (n)	3	2
RR (95%CI)	0.93 (0.80-1.08)	1.02 (0.93-1.13)
Heterogeneity (I^2, p-value)	54.2%, 0.11	0%, 0.39

*The same adjustments were made in the studies.

Table 6 Vegetable intake and oesophageal cancer risk. Results of meta-analyses and pooled analyses published after the 2005 SLR

Author, Year	Number of studies	Total number of cases	Studies country, area	Outcome	Comparison	RR (95%CI)	P trend	Heterogeneity (I^2, p value)
Meta-analyses								
Li, 2014	9 studies (3 cohorts[1], 6 case-control)	1572 cases	Australia, 10 European countries, Sweden, The Netherlands, UK, USA,	Oesophageal AC	Per 100 g/day (6 studies)	0.91 (0.83-0.99)	-	22.9%, 0.26
					High vs low			
					Cohorts	0.76 (0.54-1.05)	-	0%, 0.51
					Case-control	0.75 (0.53-1.06)	-	58.5%, 0.03
					All studies	0.76 (0.54-0.96)	-	40.4%, 0.10
Liu, 2013	24 studies (5 cohorts[2], 19 case-control)	10 037 cases	China, Europe, France, Iran Italy, Japan, Paraguay, Taiwan, The Netherlands, South America, Turkey, Uruguay, USA	Oesophageal SCC	Per 100 g/day (15 studies)	0.84 (0.78-0.92)	-	82.0%, <0.001
					High vs low			
					Cohorts	0.80 (0.60-1.06)	-	36.2%, 0.18
					Case-control	0.52 (0.41-0.65)	-	64.6%, <0.001
					All studies	0.56 (0.45-0.69)	-	75.8%, <0.001

[1]All cohorts were identified and included in the present review

[2] One of the cohorts (Fan, 2008) was identified in the CUP but not included in the dose-response analysis

Table 7 Vegetables intake and oesophageal cancer risk. Main characteristics of studies included in the linear dose-response meta-analysis

Note: Zheng, 1995 (yellow/orange vegetables) and Hirayama, 1990 (green-yellow vegetables) included in the 2005 SLR were excluded from the present review on total vegetable intake.

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Missing data derived for analyses
Steevens, 2011 oes00817 The Netherlands	NLCS, Case Cohort, Age: 55-69 years, M/F	137/ 48223 16.3 years	Record linkage to cancer registries	Validated FFQ, 157-item	Incidence AC	297 vs 104 g/day For 25 g/day	0.59 (0.33-1.06) Ptrend:0.18 0.95 (0.89-1.02)	Age, sex, smoking status and duration, cigarettes/day, alcohol, red meat, fish, fruits (BMI considered but not included in the final model)	Rescaled the RR for the increment unit used, Hamling's method was used to calculate RRs for EAC and ESCC combined
		43 26 68			Current smoker Never smoker Former smoker	For 25 g/day	0.85 (0.75-0.97) 0.97 (0.84-1.13) 1.02 (0.93-1.11)		
		106/1977 31/2303			Men Women	For 25 g/day	0.99 (0.91-1.06) 0.86 (0.75-0.97)		
		96/4280			SCC	297 vs. 104 g/day For 25 g/day	0.61 (0.29-1.32) Ptrend:0.67 0.96 (0.89-1.04)		
		46 22 28			Current smoker Never smoker Former smoker	For 25 g/day	0.90 (0.81-0.99) 1.08 (0.98-1.19) 0.96 (0.83-1.11)		
		54/1977 42/2303			Men Women	For 25 g/day	0.90 (0.80-1.00) 1.03 (0.95-1.12)		
George, 2009 oes000811 USA	NIH-AARP, Prospective Cohort, Age: 50-71 years, M/F	463/ 288,109 (M) 78/ 195,229 (F)	Record linkage to state cancer registry databases.	FFQ, 124-item	Incidence, oesophageal cancer Men	1.1-3.25 vs. 0-0.44 cups/1000 kcal/day	1.04 (0.78-1.39) Ptrend:0.85	Age, smoking status, time since quitting, dose, energy intake, BMI, alcohol, physical activity, education, race, marital status,	Distribution of cases and person-years, and mid-points per exposure quintile, exposure values using mean energy intake,
					Women	1.44-4.38 vs 0-0.56 cups/1000 kcal/day	1.21 (0.54-2.71) Ptrend:0.58		

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Missing data derived for analyses
								family history of cancer, fruits, menopausal hormone therapy (in women)	RRs for men and women combined with fixed effect model
Yamaji, 2008 oes00859 Japan	JPHC, Prospective Cohort, Age: 40-69 years, M	116/ 38,790 7.7 years	Active follow-up, cancer registries, death certificate	FFQ, 138-item	Incidence, SCC	286 vs 88 g/day Per 100g/day	0.68 (0.42-1.10) Ptrend:0.10 0.81 (0.66-0.98)	Age, residence area, cigarette smoking, alcohol drinking	
Freedman, 2007a oes00858 USA	NIH-AARP, Prospective Cohort, Age: 50- years, M/F	213/ 490,802 5 years	Record linkage to state cancer registry databases.	FFQ, 124-item (Vegetables, dried beans, sweet potatoes, yam combined)	Incidence AC	3.18 vs 0.7 servings/1000 kcal Per 1 serving/ 1000 kcal	0.92 (0.57-1.50) Ptrend:0.52 0.88 (0.75-1.04)	Sex, age, BMI, education, alcohol, smoking (and quit, dose), vigorous physical activity, usual daily activity total energy intake, fruits	Included in analysis by cancer type (George 2009 used for oesophageal cancer) Intake estimated using mean energy intake and standard portion size
		103/ 490,802			SCC	3.18 vs 0.7 servings/1000 kcal Per 1 serving/ 1000 kcal	0.57 (0.28-1.18) Ptrend:0.10 0.84 (0.66-1.07)		
González, 2006a oes00841 10 European countries	EPIC, Prospective Cohort, Age: 35-70 years, M/F	65/ 481,518 6.5 years	Cancer registry, death registry, active follow up (health insurance, pathology records)	FFQ, diet history, food record	Incidence AC	≥207.15(M)/ 257.45(W) vs ≤111.53(M)/ 145.53 (W) g/day Per 100 g/day	0.71 (0.34-1.48) Ptrend:0.36 0.72 (0.32-1.64)	Centre, age, sex, height, weight, education level, smoking status, cigarette dose, physical activity, alcohol, energy intake, red meat, processed meat	
		19			H.pylori infected	Per 100 g/day	0.59 (0.12-2.99) 0.69 (0.13-3.66)		

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Missing data derived for analyses
		28			H.pylori non infected				
Tran, 2005 oes00804 China	NIT Cohort, Prospective Cohort, Age: 40-69 years, M/F	1958/ 29,584 15 years	Monthly contact by either village health workers or interviewers, and cancer diagnoses verified by senior diagnosticians	Questionnaire, 9 items Fresh vegetables	Incidence, SCC	>915 vs ≤549 times/year	1.02 (0.88-1.19) Ptrend:0.70	Age, sex	Distribution of cases and person-years, and mid-points per exposure quantile, exposure values using standard portion size

Table 8 Vegetables intake and oesophageal cancer risk. Main characteristics of studies excluded from the linear dose-response meta-analysis

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Inclusion/exclusion
Li, 2013 oes00902 USA	NIH- AARP, Prospective Cohort, Age: 50-71 years, M/W, Retired	848/ 494 968 9.7 years	Record linkage to state cancer registry databases.	Validated FFQ, 124-item	Incidence, SCC	HEI-2005 scoring criteria ≥1.1 vs <1.1cups/1000kcal aMED Diet scoring criteria ≥1.86 vs <1.86 cups	1.07 (0.95-1.21) 1.05 (0.78-1.40)	Age, sex, BMI, race, education, smoking, total energy intake, usual activity throughout the day, vigorous physical activity, other components in dietary index, and alcohol intake in SCC analysis only	Excluded, exposure was meeting dietary index criteria or not (same study as George, 2009, OES000811; Freedman, 2007a, OES00858)
		215/ 633/			 AC		 1.03 (0.96-1.11) 1.00 (0.85-1.17)		
Fan, 2008 oes00871 China	SCStudy, Prospective Cohort, Age: 45-64 years, M	68 SCC, 8AC 282,679 person- years	Cancer registry, Shanghai vital statistics office, medical history	Questionnaire, interview	Incidence, oesophageal cancer	Quantile 3 vs Quantile 1	Fresh vegetables 0.71 (0.26-1.95) Ptrend:0.34	Age, year of interview, area, education, BMI, years of smoking, years of drinking, drinking amount	Excluded, exposure not quantified
Guo, 1994 oes00103 China	Linxian Nutrition Intervention Trial, Nested Case Control, Age: 40-69 years, M/F	639/ 3195 controls 6 years	Monthly contact by either village health workers or interviewers, and cancer diagnoses verified by senior diagnosticians	Questionnaire	Incidence, SCC	≥60 vs ≤30 times/month	0.80 (0.60-1.00) Ptrend:0.08	Sex, age, smoking habits, family history of specific cancer, vitamins	Superseded by Tran, 2005 oes00804

Yu, 1993 oes00758 China	CGRECSS, Historical Cohort, Age: 30- years, M/W	1162/ 12 693 15 years	Area residency lists	Interview	Incidence/ Mortality, oesophageal/ gastric cardia carcinoma	Regular vs occasional/never	0.66 (0.44-0.99) Ptrend:<0.05	Age, sex	Excluded, oesophageal and cardia gastric cancer combined

Figure 1 RR estimates of oesophageal cancer by levels of vegetables intake

Note: George, 2009 (NIH-AARP) is not included in this figure. A previous publication of the same study (Freedman, 2007; NIH-AARP) is included because provided data for adenocarcinoma and SCC.

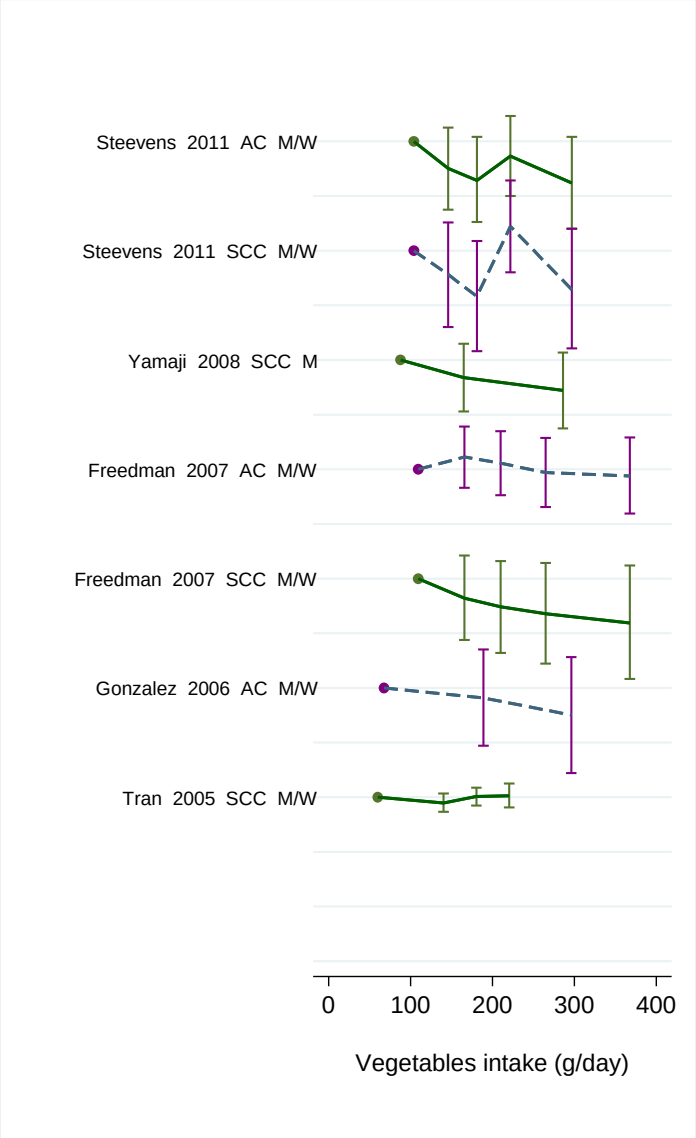
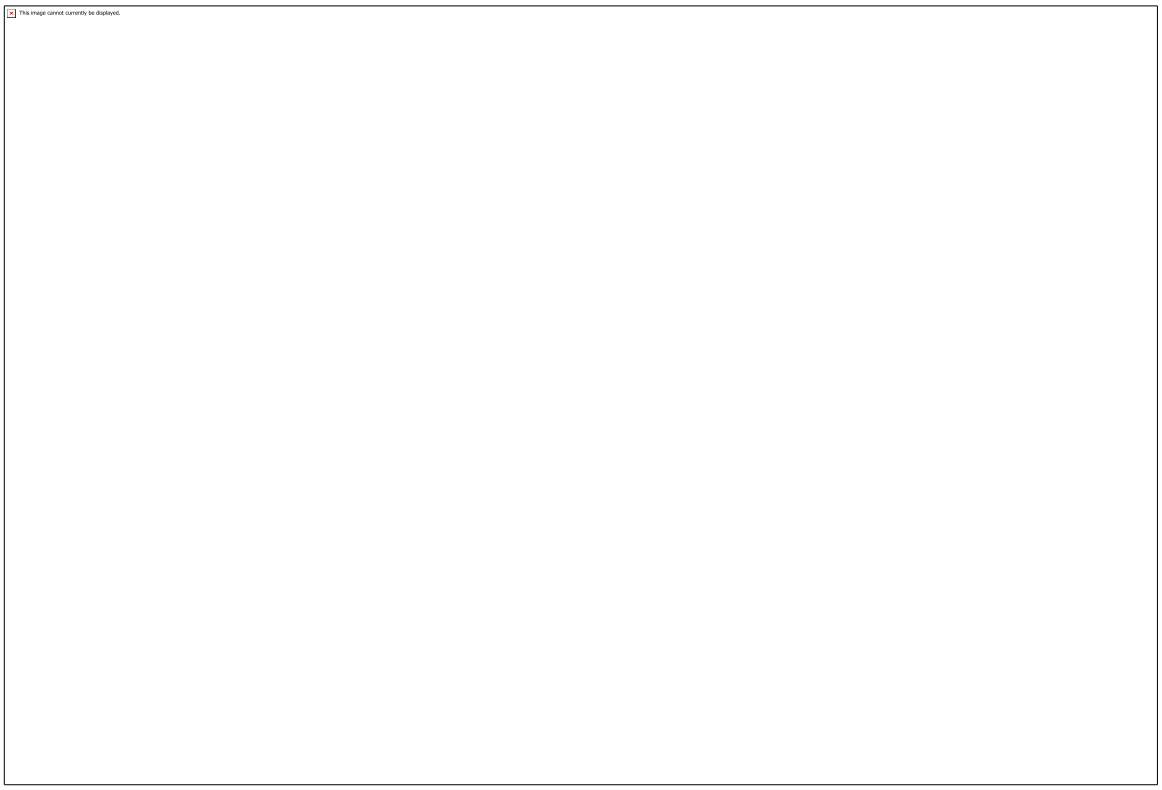


Figure 2 RR (95% CI) of oesophageal cancer for the highest compared with the lowest level of vegetables intake



Note: The intake comparison in Gonzalez, 2006 was ≥207.15 vs ≤111.53 g/day in men and ≥257.45 vs ≤145.53 g/day in women

Figure 3 Relative risk of oesophageal cancer for 100g/day increase of vegetables intake
Note: Only oesophageal adenocarcinomas in Gonzalez, 2006

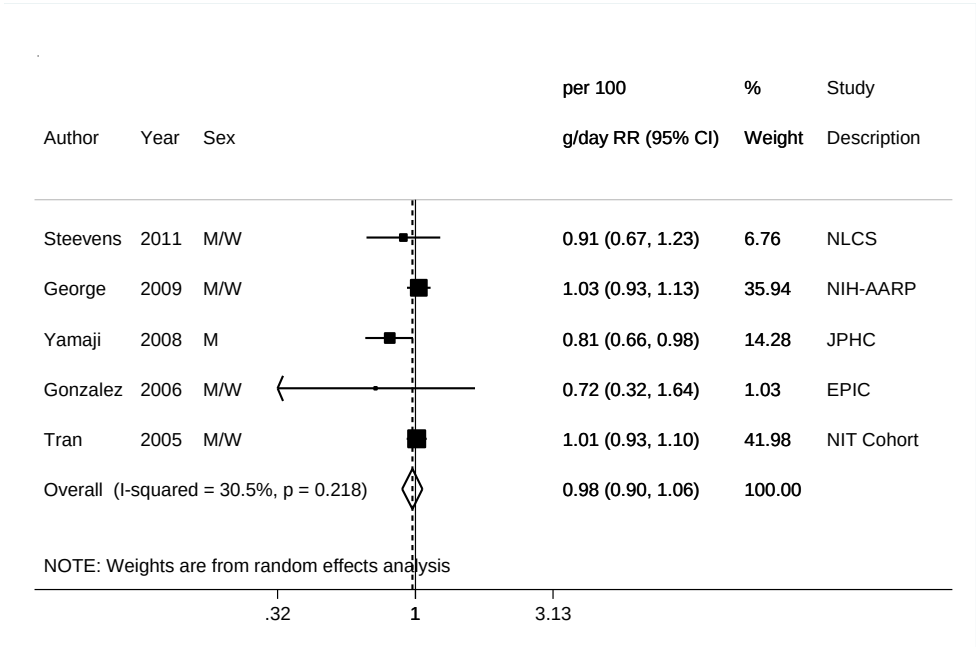
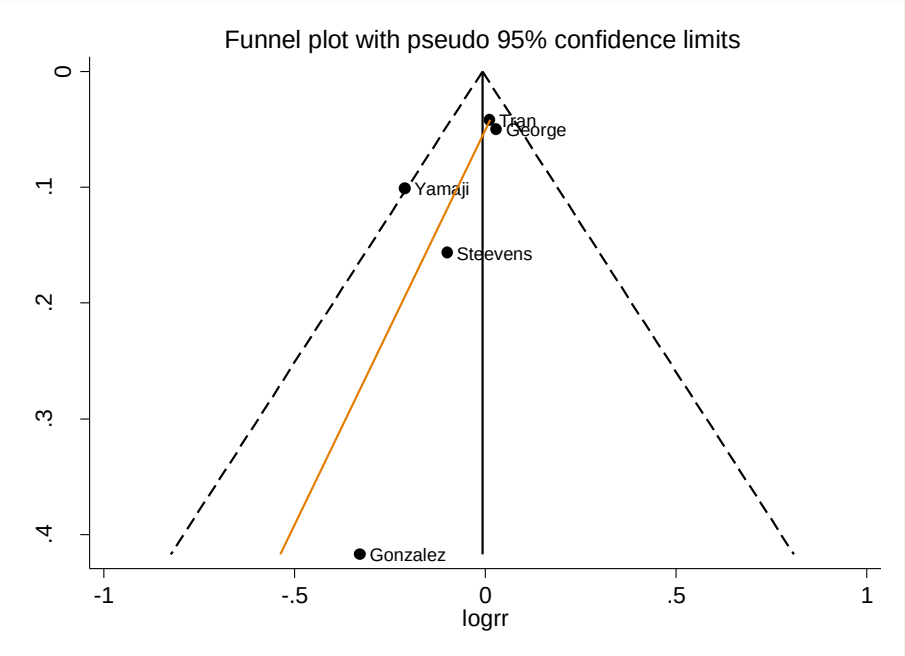


Figure 4 Funnel plot of studies included in the dose response meta-analysis of vegetables intake and oesophageal cancer



Egger's test P=0.15

Figure 5 Relative risk of oesophageal cancer for 100g/day increase of vegetables intake by sex

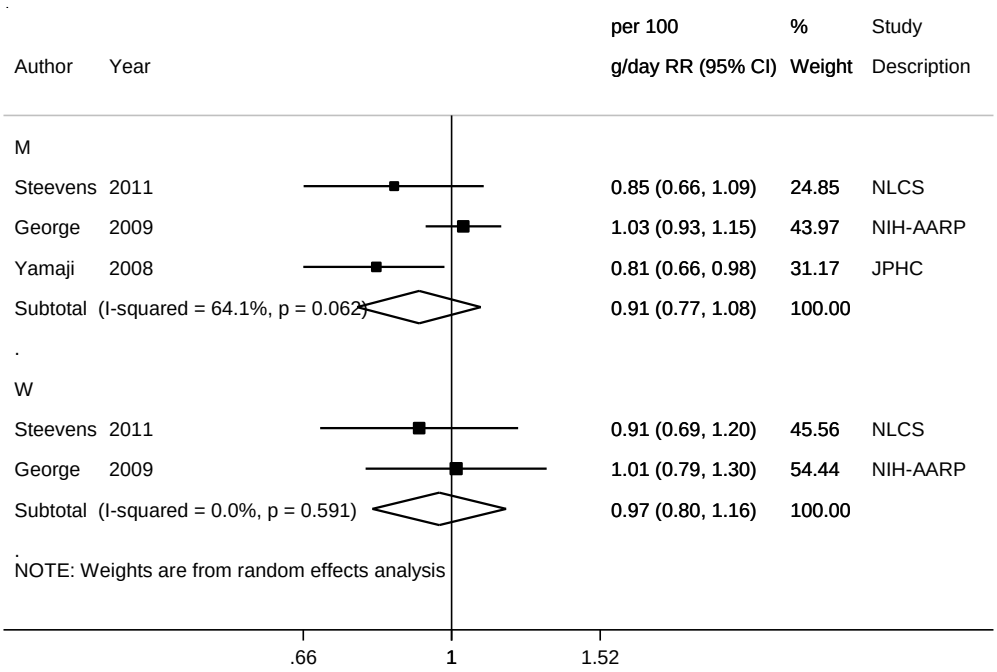


Figure 6 Relative risk of oesophageal cancer for 100g/day increase of vegetables intake by cancer type

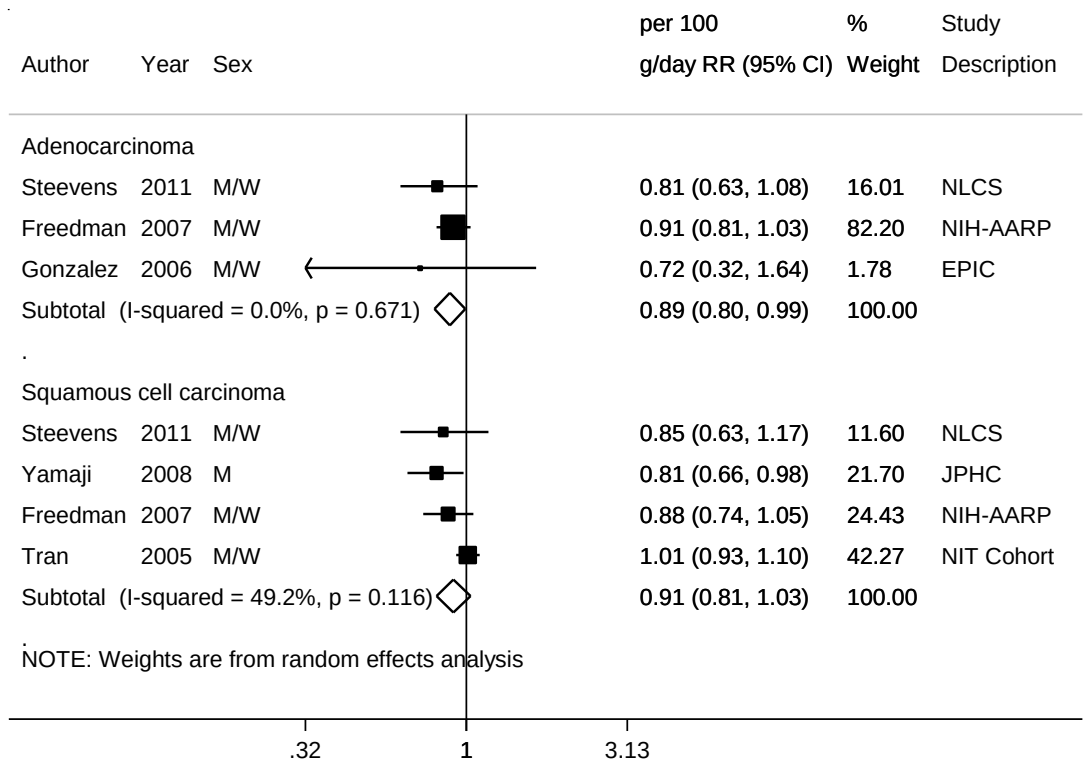
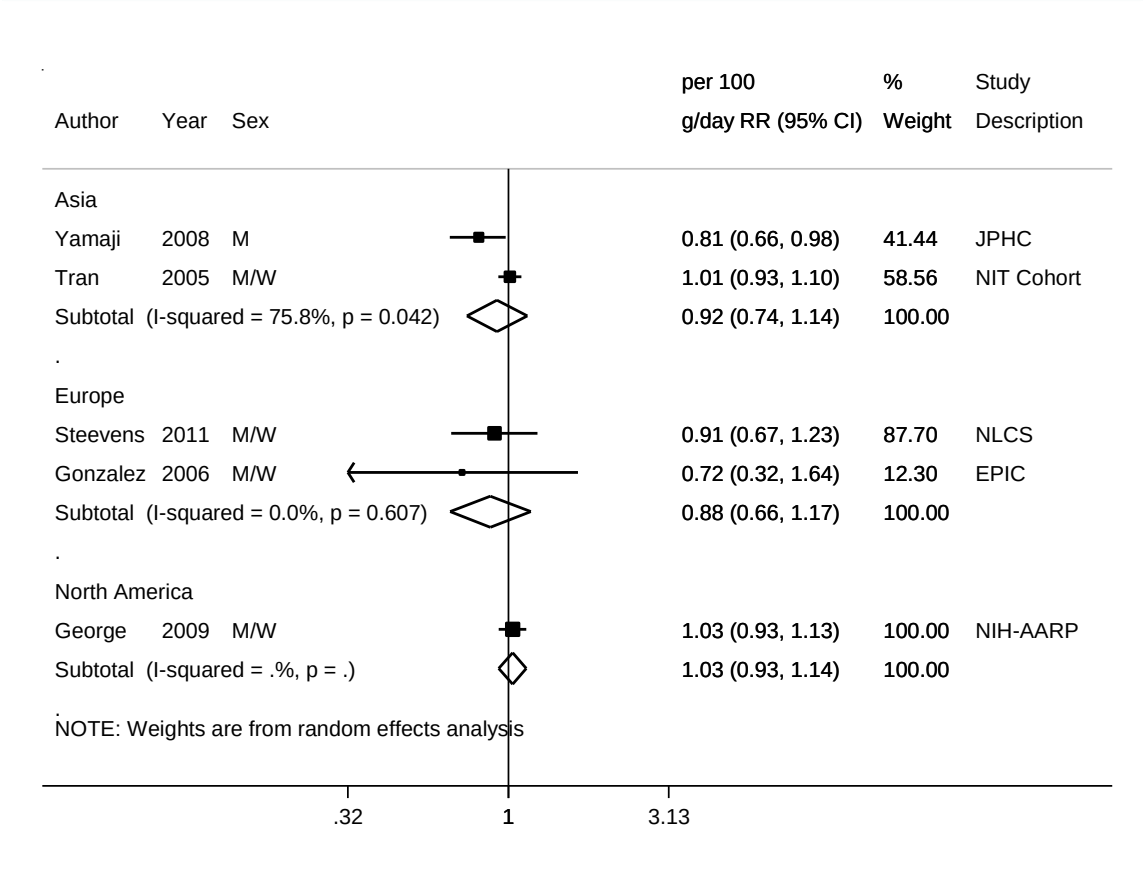


Figure 7 Relative risk of oesophageal cancer for 100g/day increase of vegetables intake by geographic location



2.2.1.4 Green leafy vegetables

Randomised controlled trial

No randomised controlled trial was identified

Cohort studies

Summary

Main results:

Five studies (915 cases) were included in the dose-response meta-analysis. A significant inverse association of green leafy vegetable intake with oesophageal cancer was observed. In analysis by cancer type, the association was significant for oesophageal adenocarcinoma (three studies, no heterogeneity) but not significant for oesophageal squamous cell carcinoma. The NIH-AARP study (Freedman, 2007a) contributed 82% weight in the analysis on oesophageal cancer (see Sensitivity analysis)

No heterogeneity was observed. There was no significant evidence of publication or small study bias (p=0.23) but the number of studies was too small to allow full investigation. Visual inspection of the funnel plot suggested small studies with a positive association are missing.

One study was excluded from the dose-response analysis (Kjaerheim, 1998). The study investigated lettuce intake and risk of upper aerodigestive tract cancer and no significant association was observed.

Sensitivity analyses:

When the NIH-AARP study (Freedman, 2007a) that contributed 82% weight to the analysis was omitted, the summary RR became non-significant (RR=0.80, 95% CI=0.61-1.06). In this study the significant inverse association was observed for adenocarcinomas (213 cases). The association was inverse but not significant for SCC (103 cases).

Non-linear dose-response meta-analysis:

Non-linear dose-response analysis was not conducted due to small number of studies.

Study quality:

All studies included in the analysis assessed dietary intake using FFQ or a combination of methods (FFQ, diet history, or food records, Gonzalez, 2006a). The definition of green leafy vegetables varied between the studies, including leafy vegetables (endives and spinach) (Steevens, 2011), Chenopodiacea (raw spinach and cooked spinach) (Freedman, 2007a), spinach and garland chrysanthemum (Iso, 2007), and leafy vegetables except cabbages (borage, chard, endive, lettuce, spinach, thistle) (Gonzalez, 2006a). Freedman, 2007a also reported results on Compositae (lettuce) but this was not included as results on spinach (more commonly included by other studies) were used. No heterogeneity was observed between the studies.

Iso, 2007 measured intake in times/week and Freedman, 2007a (NIH-AARP) measured in servings/1000 kcal/day. The units were converted to grams/day using standard methods.

Loss to follow-up was low in most studies and cancer incidence was confirmed by cancer registries. The only mortality study (Iso, 2007) ascertained the cases by death certification. When this study was omitted, the summary RR remained the same.

All studies included in the analysis were adjusted for age and sex, alcohol intake and smoking, except Iso, 2007. Gonzalez, 2006a and Freedman, 2007a were also adjusted for socioeconomic status, body fatness, total energy intake, and physical activity.

Table 9 Green leafy vegetables intake and oesophageal cancer risk. Number of studies in the CUP SLR

	Number
Studies identified	6*
Studies included in forest plot of highest compared with lowest exposure	5
Studies included in linear dose-response meta-analysis	5
Studies included in non-linear dose-response meta-analysis	Not enough studies

Note: Include cohort, nested case-control and case-cohort designs
*Included one study reported results on upper aerodigestive tract cancer

Table 10 Green leafy vegetables intake and oesophageal cancer risk. Summary of the linear dose-response meta-analysis in the 2005 SLR and CUP

	2005 SLR	**CUP**
Increment unit used	No meta-analysis	50g/day
All studies		
Studies (n)	-	5
Cases (total number)	-	915
RR (95%CI)	-	0.86 (0.77-0.97)
Heterogeneity (I^2, p-value)	-	0%, 0.81
P value Egger test	-	0.23
Stratified and sensitivity analysis		
Sex	**Men**	**Women**
Studies (n)	2	1
RR (95%CI)	0.84 (0.52-1.36)	0.63 (0.25-1.62)
Heterogeneity (I^2, p-value)	38.8%, 0.20	-
Histological type	**Adenocarcinoma (AC)**	**Squamous cell carcinoma (SCC)**
Studies (n)	3	3
Cases (total number)	415	315

RR (95%CI)	0.85 (0.74-0.96)		0.89 (0.75-1.06)
Heterogeneity (I^2, p-value)	0%, 0.89		0%, 0.50
Geographic location	**Asia**	**Europe**	**North America**
Studies (n)	2	2	1
RR (95%CI)	0.82 (0.56-1.20)	0.75 (0.47-1.21)	0.88 (0.77-1.00)
Heterogeneity (I^2, p-value)	14.5%, 0.28	0%, 1.00	-

Other stratified analysis

Duration of follow-up	**5-<10 years**	**≥10 years**
Studies (n)	3	2
RR (95%CI)	0.86 (0.76-0.97)	0.90 (0.63-1.30)
Heterogeneity (I^2, p- value)	0%, 0.51	0%, 0.63
Number of cases	**<200 cases**	**≥200 cases**
Studies (n)	3	2
RR (95%CI)	0.81 (0.61-1.09)	0.88 (0.77-1.00)
Heterogeneity (I^2, p-value)	0%, 0.53	0%, 0.71
Adjustment for:		
Socioeconomic status/body fatness/energy intake/physical activity*	**Not adjusted**	**Adjusted**
Studies (n)	3	2
RR (95%CI)	0.82 (0.60-1.12)	0.87 (0.77-0.99)
Heterogeneity (I^2, p-value)	0%, 0.54	0%, 0.60

*The same adjustments were made in the studies.

Table 11 Green leafy vegetables intake and oesophageal cancer risk. Main characteristics of studies included in the linear dose-response meta-analysis

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Missing data derived for analyses
Steevens, 2011 oes00817 The Netherlands	NLCS, Case Cohort, Age: 55-69 years, M/W	233/ 4280 16.3 years	Record linkage to cancer registries)	Validated FFQ, 157-item,	Incidence	Leafy vegetables (endives and spinach), cooked		Age, sex, smoking status, cigarettes/day, smoking duration, alcohol, red meat, fish, fruits, all other vegetables	Rescaled the RR for the increment unit used, Hamling's method was used to calculate RRs for EAC and ESCC combined
		137/4280			AC	42 vs 4 g/day Per 25 g/day	0.83 (0.47-1.46) Ptrend:0.4 0.89 (0.65-1.22)		
		96/4280			SCC		0.75 (0.35-1.60) Ptrend:0.66 0.94 (0.66-1.33)		
Yamaji, 2008 oes00859 Japan	JPHC, Prospective Cohort, Age: 40-69 years, M	116/ 38 790 7.7 years	Active patient notification, cancer registries, and death certificate	Validated FFQ, 16 fruit and 30 vegetable items	Incidence, SCC	Green leafy vegetables 34 vs 6 g/day Per 100 g/day	0.69 (0.43-1.09) Ptrend:0.1 0.39 (0.11-1.33)	Age, cigarette smoking, study area, alcohol drinking	
Freedman, 2007a oes00858 USA	NIH- AARP, Prospective Cohort, Age: 50- years, M/W	316/ 490 802 5 years	Record linkage to state cancer registry databases.	Validated FFQ, 124-item	Incidence	Chenopodiacea: raw spinach and cooked spinach		Age, sex, BMI, alcohol, education, smoking dose, total energy intake, usual activity throughout the day, vigorous physical activity	Distrubution of person-years per tertile, exposure values using mean energy intake, Hamling's method was used to calculate RRs for EAC and ESCC combined
		213/490 802			AC	0.96 vs 0 servings/1000 kcal	0.66 (0.46-0.95) Ptrend:0.02		
		103/490 802			SCC		0.87 (0.52-1.45)		
Iso, 2007	JACC,	173/	Date and cause	Validated FFQ,	Mortality,	Spinach, garland		Age, area of	Exposure values

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Missing data derived for analyses
oes00847 Japan	Prospective Cohort, Age: 40-79 years, M/W	105 500 15 years 147/43 850 26/60 169	of death annually or biannually confirmed with authorities authorization	39-item	oesophageal cancer Men Women	chrysanthemumm ≥5 vs <3 times/week	 1.03 (0.68-1.56) 0.71 (0.30-1.70)	study	using standard portion size, mid-points of exposure categories, RRs for men and women combined using fixed effect model
González, 2006a oes00841 10 European countries	EPIC, Prospective Cohort, Age: 35-70 years, M/W	65/ 481 518 6.5 years	Cancer Cancer registry, death registry, active follow up (health insurance, pathology records)	FFQ, diet history, food record	Incidence, AC	Leafy vegetables except cabbages Quantile 3 vs Quantile 1 Per 50 g/day	 0.35 (0.12-1.04) Ptrend:0.07 0.75 (0.42-1.34)	Centre, age, sex, height, weight, education level, smoking, physical activity, alcohol, energy intake, red meat, processed meat	Rescaled the RR for the increment unit used

Table 12 Green leafy vegetables intake and oesophageal cancer risk. Main characteristics of studies excluded from the linear dose-response meta-analysis

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Inclusion/exclusion
Freedman, 2007a oes00858 USA	NIH-AARP, Prospective Cohort, Age: 50- years, M/W	316/ 490 802 5 years	Record linkage to state cancer registry databases	Validated FFQ, 124-item,	Incidence AC	Compositae: lettuce 0.54 vs 0.03 servings/1000 kcal	1.11 (0.78-1.58)	Age, sex, BMI, alcohol, education, smoking dose, total energy intake, usual activity throughout the day, vigorous physical activity	Excluded, results on Chenopodiacea :raw spinach and cooked spinach was included
		213/490 802							
		103/490 802			SCC		0.62 (0.36-1.06)		
Kjaerheim, 1998 oes00130 Norway	Norwegian Men UADT, Prospective Cohort, M	62/ 10 900 25 years	Population survey	FFQ, 32-item,	Incidence, upper aerodigestive tract cancer	Lettuce ≥6 vs <1 times/month	1.00 (0.40-2.40) Ptrend: >0.5	Age, alcohol consumption, smoking habits	Excluded, UADT cancer, lettuce only

Figure 8 RR estimates of oesophageal cancer by levels of green leafy vegetables intake

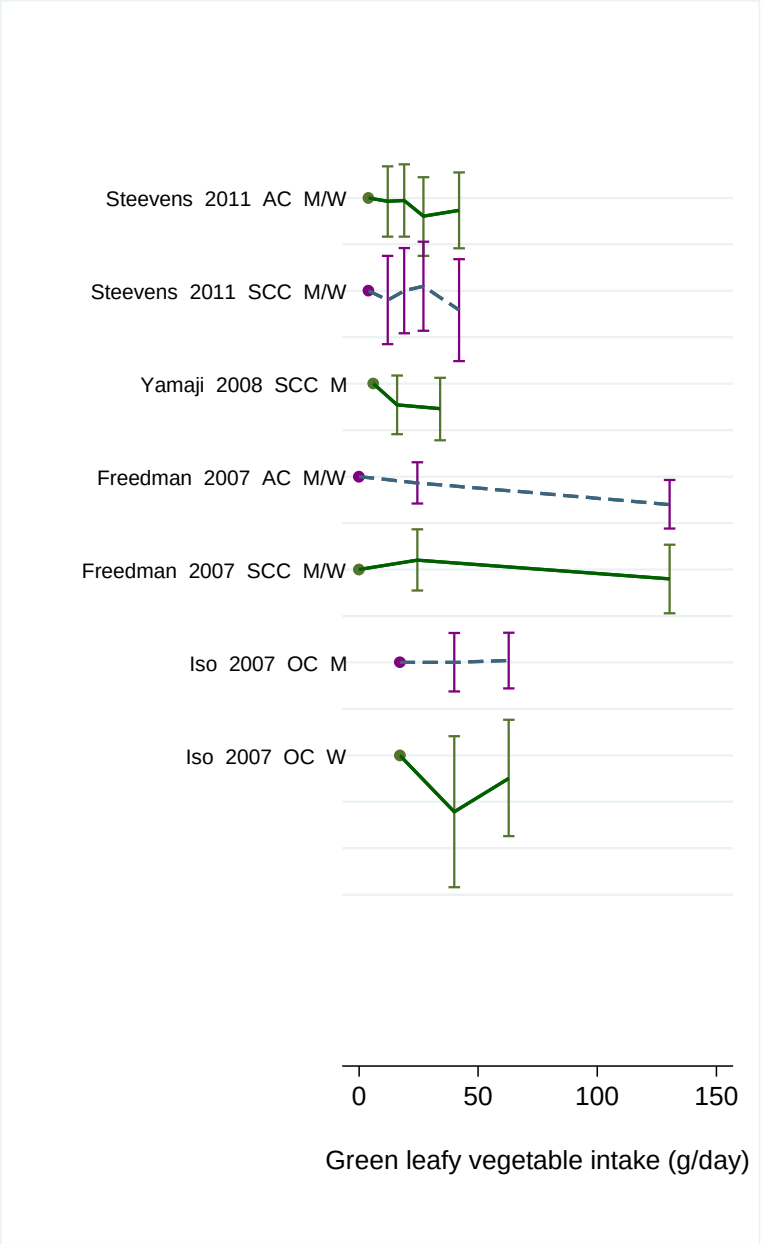


Figure 9 RR (95% CI) of oesophageal cancer for the highest compared with the lowest level of green leafy vegetables intake

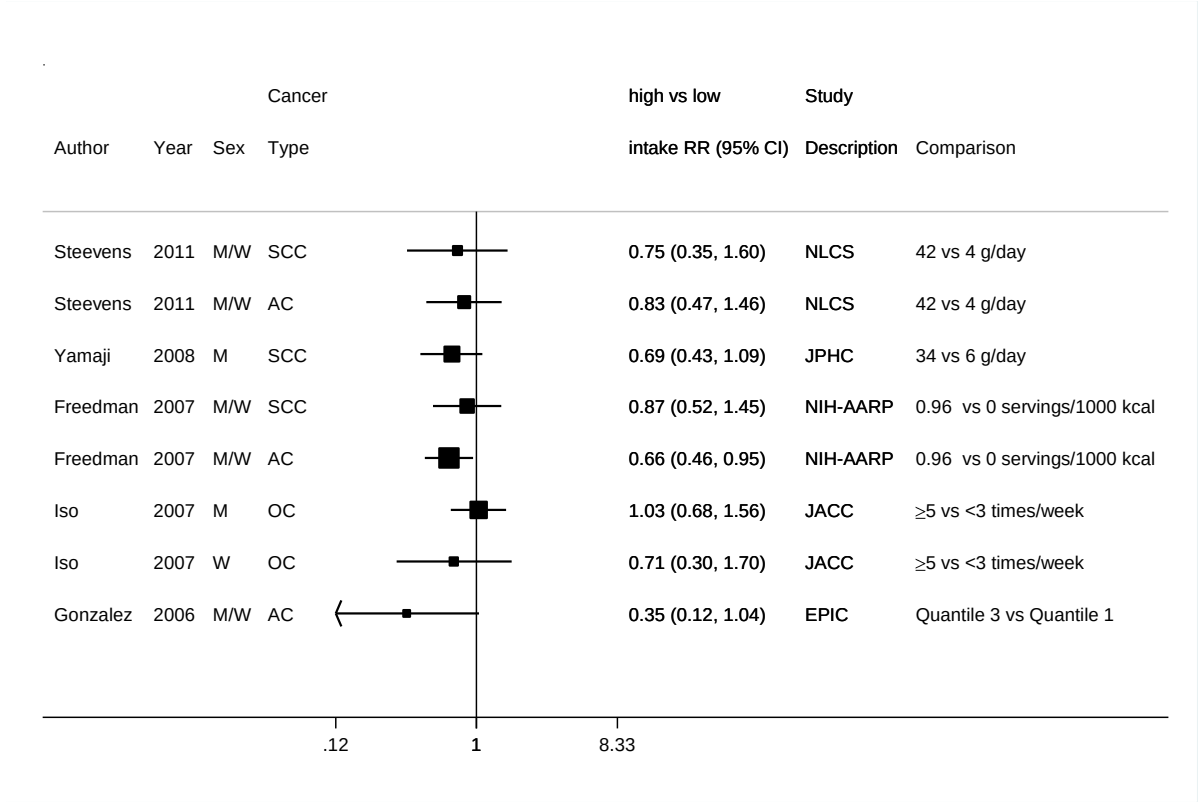


Figure 10 Relative risk of oesophageal cancer for 50g/day increase of green leafy vegetable intake

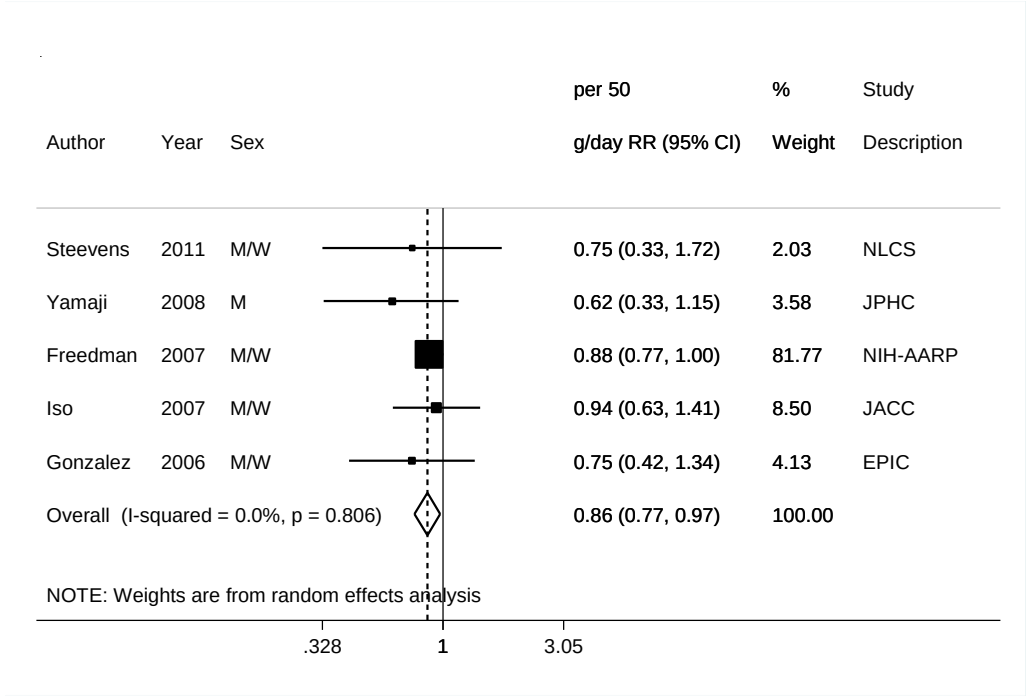
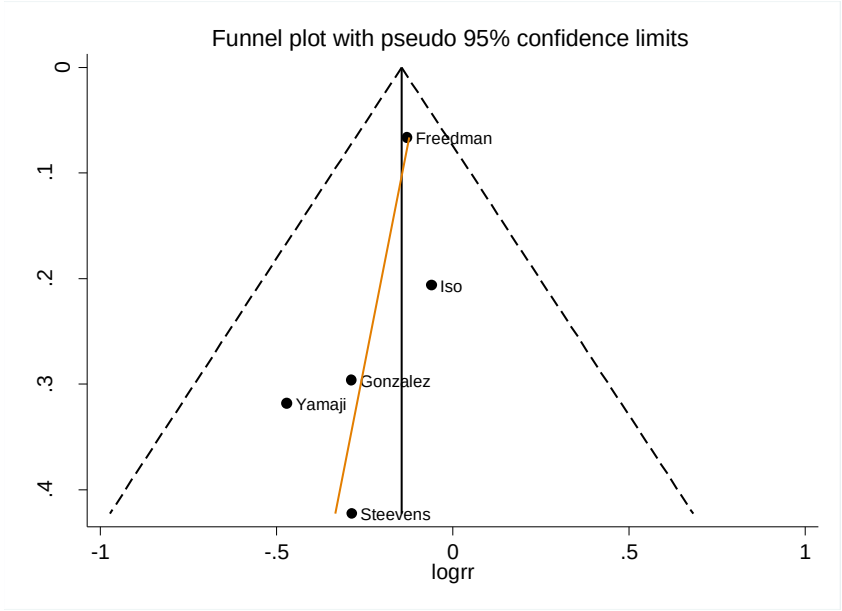


Figure 11 Funnel plot of studies included in the dose response meta-analysis of green leafy vegetables intake and oesophageal cancer



Egger's test P=0.23

Figure 12 Relative risk of oesophageal cancer for 50g/day increase of green leafy vegetables intake by sex

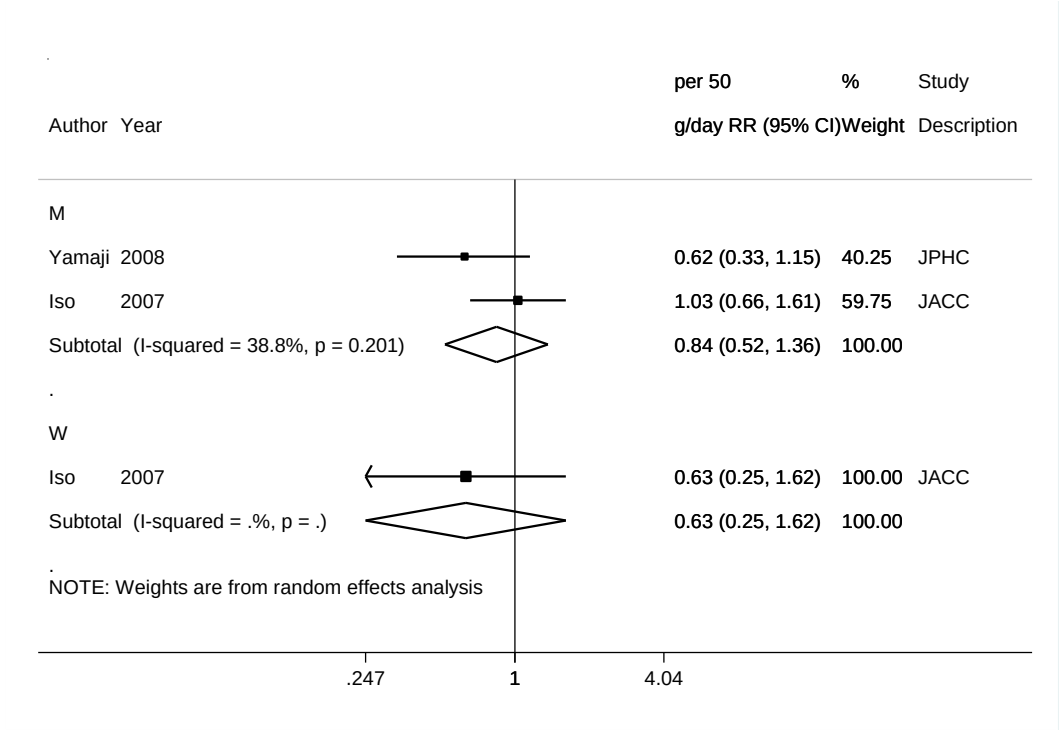


Figure 13 Relative risk of oesophageal cancer for 50g/day increase of green leafy vegetables intake by cancer type

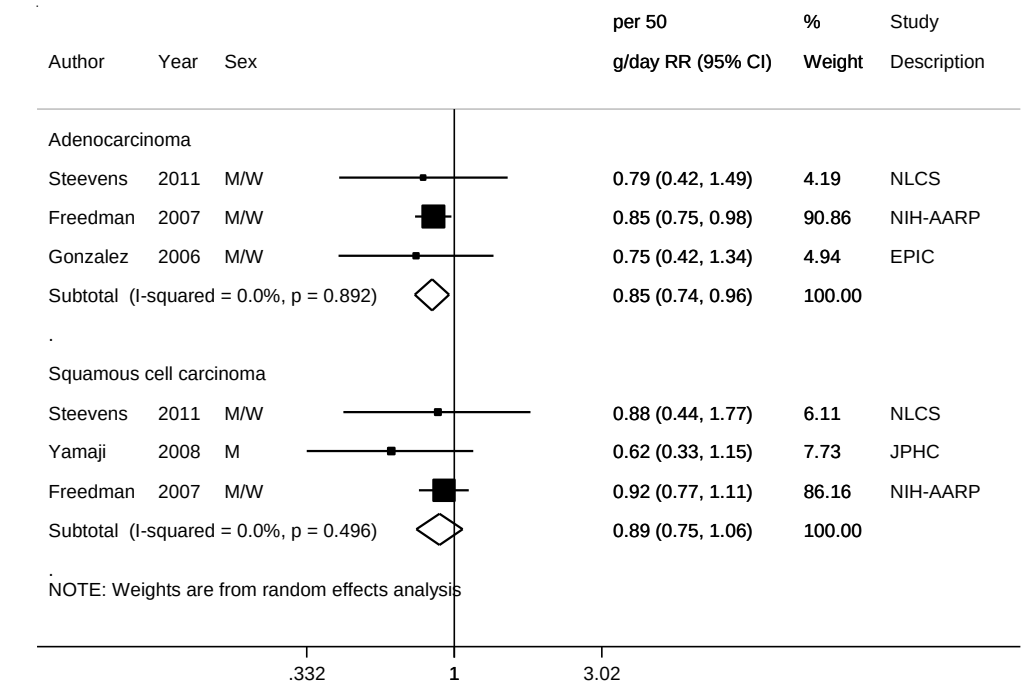
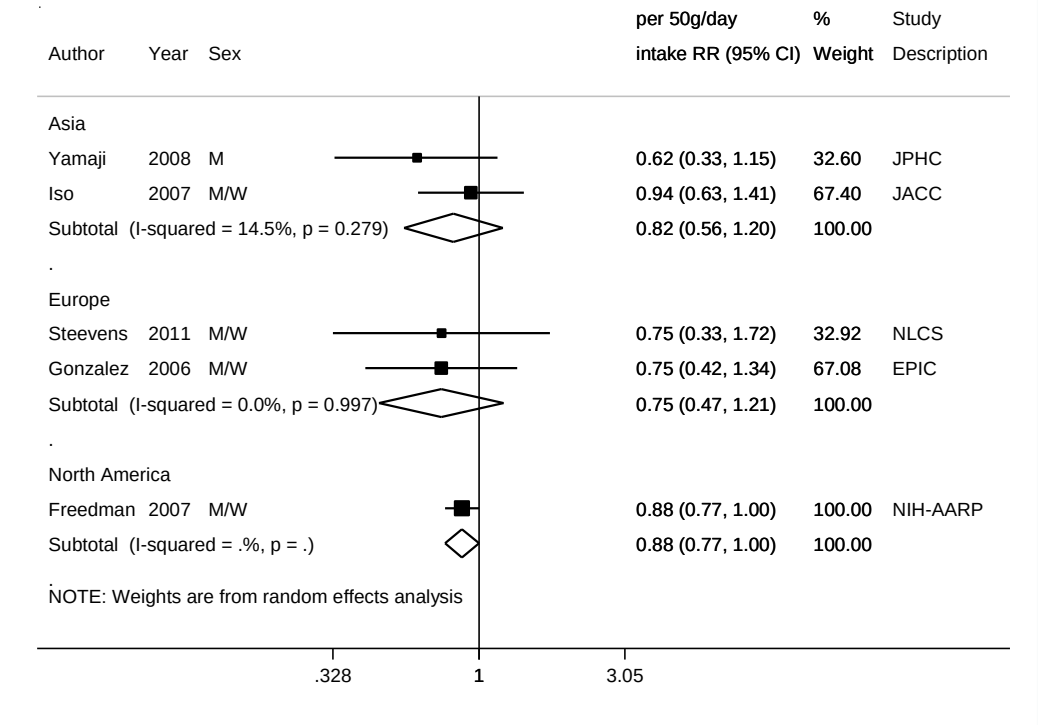


Figure 14 Relative risk of oesophageal cancer for 50g/day increase of green leafy vegetables intake by geographic location



2.2.1.2 Cruciferous vegetables and other vegetables

Four studies reported on cruciferous vegetables intake (Steevens, 2011; Gonzalez, 2006a; Freedman, 2007a; Yamaji, 2008). No significant association was observed in all studies except in the Japanese study (Yamaji, 2008) in which cruciferous vegetables intake was significantly inversely associated with SCC risk.

For other vegetables (carrots, allium vegetables and others) the limited number of studies did not allow any analyses.

2.2.2 Fruits

Randomised controlled trial

No randomised controlled trial was identified

Cohort studies

Summary

Main results:

Four studies (967 cases) were included in the dose-response meta-analysis.

A borderline significant inverse association with oesophageal cancer risk was observed. No heterogeneity was observed. The number of studies to examine publication or small study bias was too small. Non-significant association was observed for adenocarcinomas (three studies, no heterogeneity); a significant inverse association was observed for squamous cell carcinomas (three studies, no heterogeneity).

A significant inverse association was observed in men (three studies, no heterogeneity) and no significant association was observed in women (two studies, low heterogeneity). Borderline or non-significant (inverse) associations were observed in other subgroups.

One study stratified the analyses by smoking status. Non-significant associations with fruit intake were reported in current, never, or former smokers (Steevens, 2011), and no heterogeneity across groups was observed.

Five studies were excluded from the dose-response analysis. None of the studies reported significant associations with oesophageal cancer risk (Fan, 2008), oesophageal SCC (Guo, 1994), oesophageal cancer mortality (Iso, 2007), SCC of the upper aerodigestive tract (Chyou, 1995) or oesophageal and gastric cardia carcinomas (Yu, 1993).

Sensitivity analyses:

The summary RR did not change materially when studies were omitted in turn in influence analysis. When the NIH-AARP (George, 2009) that contributed 76% weight was omitted, the summary RR was 0.90 (95% CI=0.80-1.02).

Non-linear dose-response meta-analysis:

Non-linear dose-response analysis was not conducted due to small number of studies.

Study quality:

All studies included in the analysis used FFQ to assess fruit intake and one assessed fruit and fruit juice intake (Freedman, 2007a). The EPIC study (Gonzalez, 2006a) also used diet history and food records. The NIH-AARP Study measured in servings/1000 kcal/day (Freedman, 2007a) or cup-equivalent/1000 kcal/day (George, 2009). The units were converted to grams/day using standard methods.

Loss to follow-up was low in most studies and cancer incidence was confirmed by records in cancer registries.

All studies included in the analysis were adjusted for age, sex, alcohol, and smoking. Gonzalez, 2006a and George, 2009 were further adjusted for socioeconomic status, body fatness, total energy intake, and physical activity. No studies were adjusted for Helicobacter pylori status.

In a nested case-control study in EPIC, the analyses were stratified by Helicobacter pylori status. No significant association was observed across infected or non-infected subjects (Gonzalez, 2006a).

Table 13 Fruit intake and oesophageal cancer risk. Number of studies in the CUP SLR

	Number
Studies identified	9* (12 publications)
Studies included in forest plot of highest compared with lowest exposure	6
Studies included in linear dose-response meta-analysis	4
Studies included in non-linear dose-response meta-analysis	Not enough studies

Note: Include cohort, nested case-control and case-cohort designs. * Included one study reported results on upper aerodigestive tract cancers and one on oesophageal/gastric cardia carcinoma.

Table 14 Fruit intake and oesophageal cancer risk. Summary of the linear dose-response meta-analysis in the 2005 SLR and CUP

	2005 SLR	**CUP**
Increment unit used	No meta-analysis	100g/day
All studies		
Studies (n)	-	4
Cases (total number)	-	967

RR (95%CI)	-	0.94 (0.89-1.00)
Heterogeneity (I^2, p-value)	-	0%, 0.83
P value Egger test	-	-
Stratified and sensitivity analysis		
Sex	**Men**	**Women**
Studies (n)	3	2
RR (95%CI)	0.93 (0.88-0.99)	1.00 (0.87-1.14)
Heterogeneity (I^2, p-value)	0%, 0.91	0.5%, 0.32
Histological type	**Adenocarcinoma (AC)**	**Squamous cell carcinoma (SCC)**
Studies (n)	3	3
Cases (total number)	422	320
RR (95%CI)	1.03 (0.95-1.11)	0.84 (0.75-0.94)
Heterogeneity (I^2, p-value)	0%, 0.42	0%, 0.58

Geographic location	**Asia**	**Europe**	**North America**
Studies (n)	1	2	1
RR (95%CI)	0.90 (0.76-1.07)	0.91 (0.77-1.07)	0.95 (0.89-1.02)
Heterogeneity (I^2, p-value)	-	0%, 0.60	-

Other stratified analysis

Duration of follow-up	**5-<10 years**	**≥10 years**
Studies (n)	3	1
RR (95%CI)	0.94 (0.89-1.00)	0.93 (0.77-1.13)
Heterogeneity (I^2, p- value)	0%, 0.65	-
Number of cases	**<200 cases**	**≥200 cases**
Studies (n)	2	2
RR (95%CI)	0.89 (0.76-1.03)	0.95 (0.89-1.01)
Heterogeneity (I^2, p-value)	0%, 0.72	0%, 0.81
Adjustment for:		
Socioeconomic status/body fatness/energy intake/physical activity*	**Not adjusted**	**Adjusted**
Studies (n)	2	2
RR (95%CI)	0.91 (0.80-1.04)	0.95 (0.89-1.01)
Heterogeneity (I^2, p-value)	0%, 0.80	0%, 0.46

*The same adjustments were made in the studies.

Table 15 Fruit intake and oesophageal cancer risk. Results of meta-analyses and pooled analyses published after the 2005 SLR.

Author, Year	Number of studies	Total number of cases	Studies country, area	Outcome	Comparison	RR (95%CI)	P trend	Heterogeneity (I^2, p value)
Meta-analyses								
Li, 2014	9 studies (3 cohorts[1], 6 case-control)	1572 cases	Australia, 10 European countries, German, Sweden, The Netherlands, UK, USA,	Oesophageal AC	Per 100 g/day (6 studies)	0.87 (0.76-0.99)	-	71.0%, 0.004
					High vs low			
					Cohorts	0.99 (0.72-1.36)	-	0%, 0.97
					Case-control	0.59 (0.38-0.90)	-	62.6%, 0.02
					All studies	0.73 (0.55-0.98)	-	52.9%, 0.03
Liu, 2013	29 studies (5 cohorts[2], 24 case-control)	10 037 cases	China, Europe, France, Germany, Iran, India, Italy, Japan, Taiwan, The Netherlands, South America, Turkey, Uruguay, UK, USA	Oesophageal SCC	Per 100 g/day (19 studies)	0.61 (0.52-0.72)	-	89.7%, <0.001
					High vs low			
					Cohorts	0.68 (0.55-0.86)	-	25.1%, 0.25
					Case-control	0.51 (0.41-0.63)	-	71.5%, <0.001
					All studies	0.53 (0.44-0.64)	-	73.7%, <0.001

[1]All cohorts were identified and included in the present review

[2] One of the cohorts (Fan, 2008) was identified in the CUP but not included in the dose-response analysis

Table 16 Fruit intake and oesophageal cancer risk. Main characteristics of studies included in the linear dose-response meta-analysis

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Missing data derived for analyses
Steevens, 2011 oes00817 The Netherlands	NLCS, Case Cohort, Age: 55-69 years, M/W	245/4280 16.3 years	Record linkage to cancer registries	Validated FFQ, 157-item	Incidence			Age, sex, smoking status, cigarettes/day, smoking duration, alcohol, red meat, fish, vegetables	Rescaled the RR for the increment unit used, Hamling's method was used to calculate RRs for EAC and ESCC combined
		144/4280			AC	326 vs 43 g/day	0.97 (0.57-1.67) Ptrend:0.77		
						Per 25 g/day	1.00 (0.96-1.05)		
		46/ 28/ 70/			Current smoker Never smoker Former smoker	Per 25 g/day	0.93 (0.86-1.01) 0.99 (0.92-1.07) 1.03 (0.97-1.08)		
		112/1977 32/2303			Men Women		1.00 (0.96-1.05) 0.98 (0.91-1.06)		
		101/4280			SCC	326 vs 43 g/day	0.62 (0.32-1.22) Ptrend:0.11		
						Per 25 g/day	0.95 (0.90-1.01)		
		48/ 23/ 30/			Current smoker Never smoker Former smoker	Per 25 g/day	0.91 (0.82-1.01) 1.01 (0.94-1.08) 0.94 (0.85-1.03)		
		55/1977 46/2303			Men Women		0.91 (0.83-1.00) 0.98 (0.91-1.05)		
George, 2009 oes00811 USA	NIH-AARP, Prospective Cohort, Age: 50-71 years, M/W,	541/ 483 338 6.9 years	Record linkage to state cancer registry databases.	FFQ, 124-item	Incidence, oesophageal cancer	1.6-5.13 vs 0-0.44 cup/1000 kcal/day		Age, smoking, energy intake, BMI, alcohol, physical activity, education, race, marital status, family history of	Distribution of cases and person-years, and mid-points per exposure quintile, exposure values using mean
		463/288 109			Men		0.74 (0.53-1.02) Ptrend:0.08		
		78/195 229			Women	1.91-5.58 vs 0-0.6 cup/1000	1.09 (0.54-2.20) Ptrend: 0.71		

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Missing data derived for analyses
						kcal/day		cancer, fruits, menopausal hormone therapy (in women)	energy intake, RRs for men and women combined with fixed effect model
Yamaji, 2008 oes00859 Japan	JPHC, Prospective Cohort, Age: 40-69 years, M	116/ 38 790 7.7 years	Active patient notification, cancer registries, and death certificate	Validated FFQ, 16 fruit and 30 vegetable items	Incidence, SCC	280 vs 47 g/day Per 100 g/day	0.65 (0.39-1.08) Ptrend:0.09 0.90 (0.76-1.07)	Age, cigarette smoking, study area, alcohol drinking	
Freedman, 2007a oes00858 USA	NIH-AARP, Prospective Cohort, Age: 50- years, M/W	316/ 490 802 5 years	Record linkage to state cancer registry databases	Validated FFQ, 124-item	Incidence	3.25 vs 0.4 servings/1000 kcal Per 1 serving/1000 kcal		Age, sex, BMI, vegetable intake, alcohol, education, smoking dose, total energy intake, usual activity throughout the day, vigorous physical activity	Exposure values using mean energy intake, rescaled the RR for the increment unit used
		213/490 802			AC		1.04 (0.64-1.69) Ptrend:0.57 1.07 (0.94-1.21)		
		103/490 802			SCC		0.46 (0.21-1.00) Ptrend:0.03 0.73 (0.57-0.93)		
González, 2006a oes00841 10 European countries	EPIC, Prospective Cohort, Age: 35-70 years, M/W	65/ 481 518 6.5 years	Cancer registry, death registry, active follow up (health insurance, pathology records)	FFQ, diet history, food record	Incidence AC	≥234.29 (M)/ 292.36 (W) vs ≤102.09(M)/ 157.22(W) g/day Per 100 g/day	0.94 (0.49-1.80) Ptrend:0.75	Centre, age, sex, height, weight, education level, smoking, physical activity, alcohol, energy intake, red meat, processed meat	
							0.84 (0.60-1.17)		
		19/ 28/			H.pylori infected H.pylori non infected	Per 100 g/day	0.79 (0.39-1.61) 0.61 (0.25-1.48)		

Table 17 Fruit intake and oesophageal cancer risk. Main characteristics of studies excluded from the linear dose-response meta-analysis

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Inclusion/exclusion
Li, 2013 oes00902 USA	NIH- AARP Diet and Health Study, Prospective Cohort, Age: 50-71 years, M/W, Retired	848/ 494 968 9.7 years	Cancer registry, death master file, national death index plus, postal service database	Validated FFQ, 124-item	Incidence, oesophageal cancer	HEI-2005 scoring criteria ≥0.8 vs <0.8 cups/1000kcal	0.92 (0.84-1.02)	Age, sex, BMI, race, education, smoking, total energy intake, usual activity throughout the day, vigorous physical activity, other components in dietary index, and alcohol intake in SCC analysis only	Excluded, exposure was meeting dietary index criteria or not (same study as George, 2009, OES000811; Freedman, 2007a, OES00858)
		215/			SCC	aMED Diet scoring criteria ≥2.30 vs <2.30 cups	0.65 (0.48-0.88)		
		633/			AC		1.00 (0.94-1.06)		
							0.94 (0.79-1.10)		
Fan, 2008 oes00871 China	SCStudy, Prospective Cohort, Age: 45-64 years, M	101/ 18 244 282 679 person-years	Cancer registry, shanghai vital statistics office, medical history	Questionnaire and interview	Incidence, oesophageal cancer	Quantile 3 vs quantile 1	0.46 (0.25-0.88)	Age at interview, BMI, number of years of smoking, year of interview, drinking amount, education, neighbourhood of residence at recruitment, years of drinking	Excluded, exposure not quantified
Iso, 2007 oes00847 Japan	JACC, Prospective Cohort,	157/ 105 500 15 years	Date and cause of death annually or	Validated FFQ Fruits other than citrus fruits, 39-	Mortality, oesophageal cancer	Other fruits excluding citrus		Age, area of study	Excluded, other fruits excluding citrus fruits

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Inclusion/exclusion
	Age: 40-79 years, M/W	134/41 395 23/56 195	biannually confirmed with authorities authorization	item	Men Women	fruits ≥5 vs <3 times/week	0.77 (0.49-1.20) 1.53 (0.60-3.94)		
Tran, 2005 oes00804 China	NIT Cohort, Prospective Cohort, Age: 40-69 years, M/W	1958/ 29 584 15 years	Monthly contact by either village health workers or interviewers, and cancer diagnoses verified by senior diagnosticians	Questionnaire	Incidence, SCC	>13 vs 0-1 times/year	0.80 (0.70-0.91)	Age, sex	Same as Guo, 1994, OES00103, extremely low fruit intake, not comparable with other studies
Chyou, 1995 oes00128 USA	HHP, Prospective Cohort, M	92/ 7995 25 years	Selective service roll	FFQ and 24 hour recall	Incidence, SCC UADT cancer	≥5 vs 0-1 servings/week	0.65 (0.39-1.07)	Age, alcohol consumption, smoking habits	Excluded, UADT cancer
Guo, 1994 oes00103 China	NIT Cohort, Nested Case Control, Age: 40-69 years, M/W	639/ 29 584 6 years	Monthly contact by either village health workers or interviewers, and cancer diagnoses verified by senior diagnosticians	Questionnaire	Incidence, SCC	≥1 vs <0 times/month	0.90 (0.80-1.10)	Family history of specific cancer, smoking habits, vitamins	Excluded, extremely low fruit intake, not comparable with other studies
Yu, 1993 oes00758 China	CGRECSS, Historical Cohort,	1162/ 12 693 15 years	Area residency lists	Interview	Mortality/incidence, oesophageal/gas	Regular/occasional vs never	0.99 (0.85-1.15)	Age, sex	Excluded, oesophageal and gastric cancer,

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Inclusion/exclusion
	Age: 30- years, M/W				tric cardia carcinoma				only two exposure categories

Figure 15 RR estimates of oesophageal cancer by levels of fruit intake
Note: George, 2009 was excluded from the figure as another publication of the same study (Freedman, 2007; NIH-AARP) was shown.

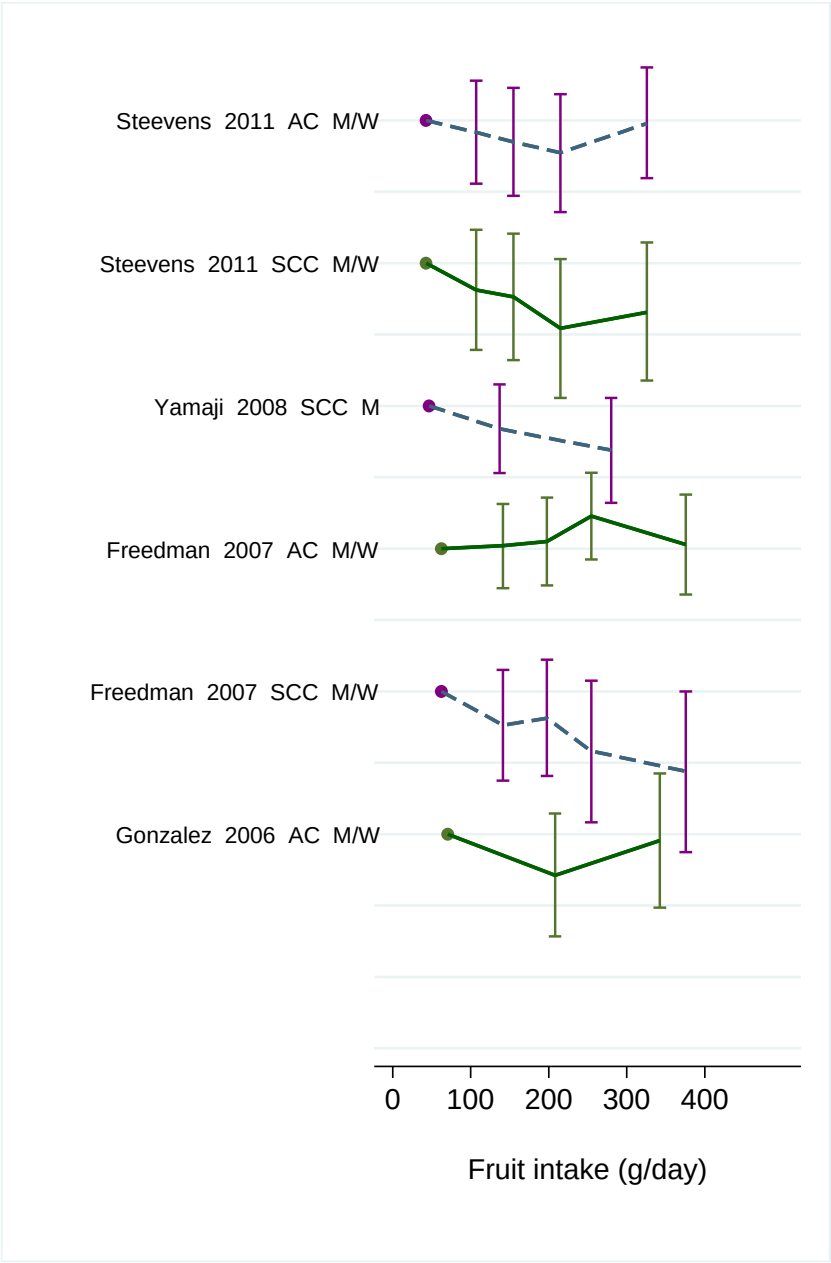


Figure 16 RR (95% CI) of oesophageal cancer for the highest compared with the lowest level of fruit intake

Note: The intake comparison in Gonzalez, 2006 was ≥234.29 vs ≤102.09 g/day in men and ≥292.36 vs ≤157.22 g/day in women

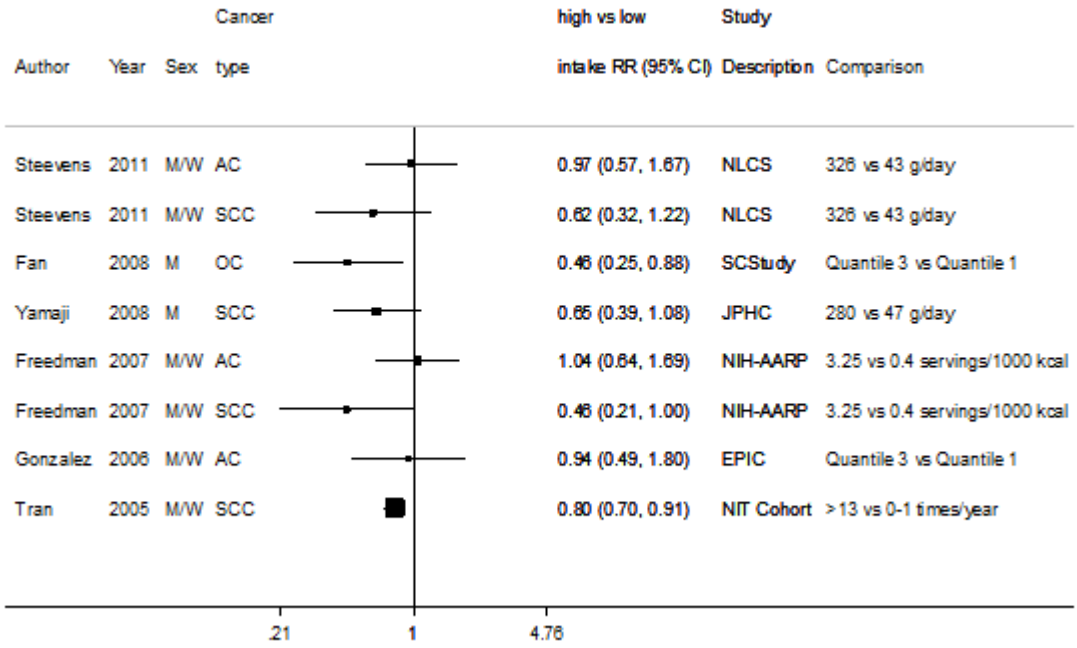


Figure 17 Relative risk of oesophageal cancer for 100g/day increase of fruit intake

Note: George, 2009 (NIH-AARP) is included in the analysis on oesophageal cancer but did not report by cancer type. A previous publication (Freedman, 2007, NIH-AARP) is included in the analysis by cancer type.

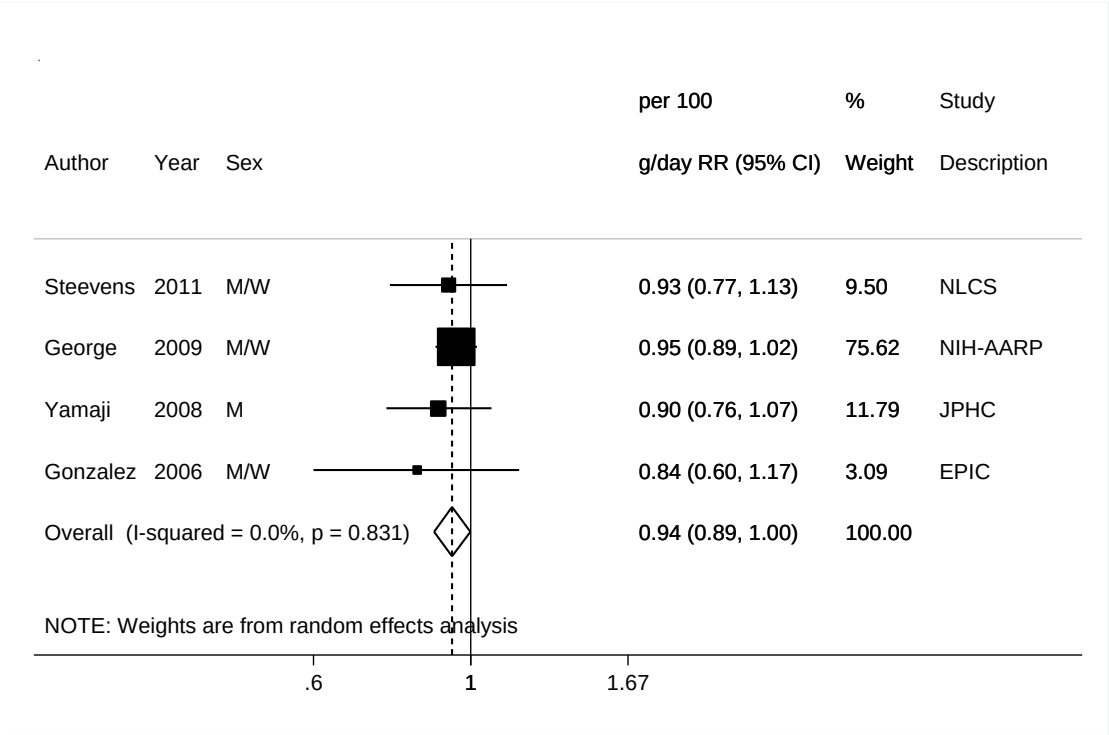


Figure 18 Relative risk of oesophageal cancer for 100g/day increase of fruit intake by sex

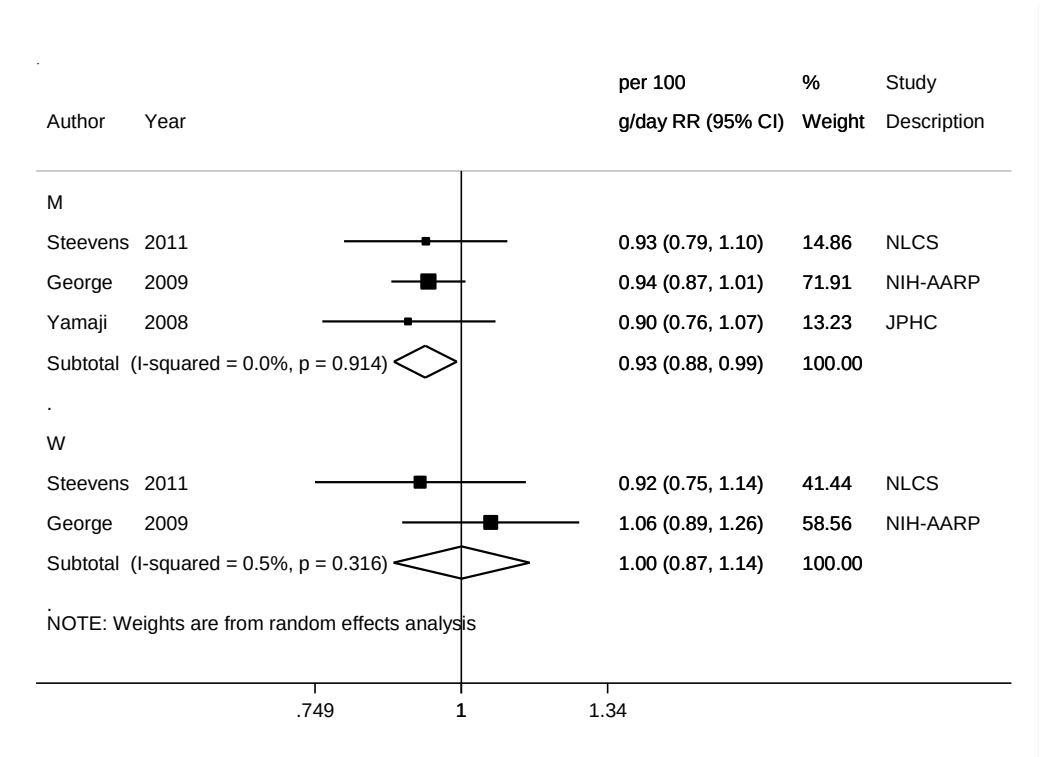


Figure 19 Relative risk of oesophageal cancer for 100g/day increase of fruit intake by cancer type

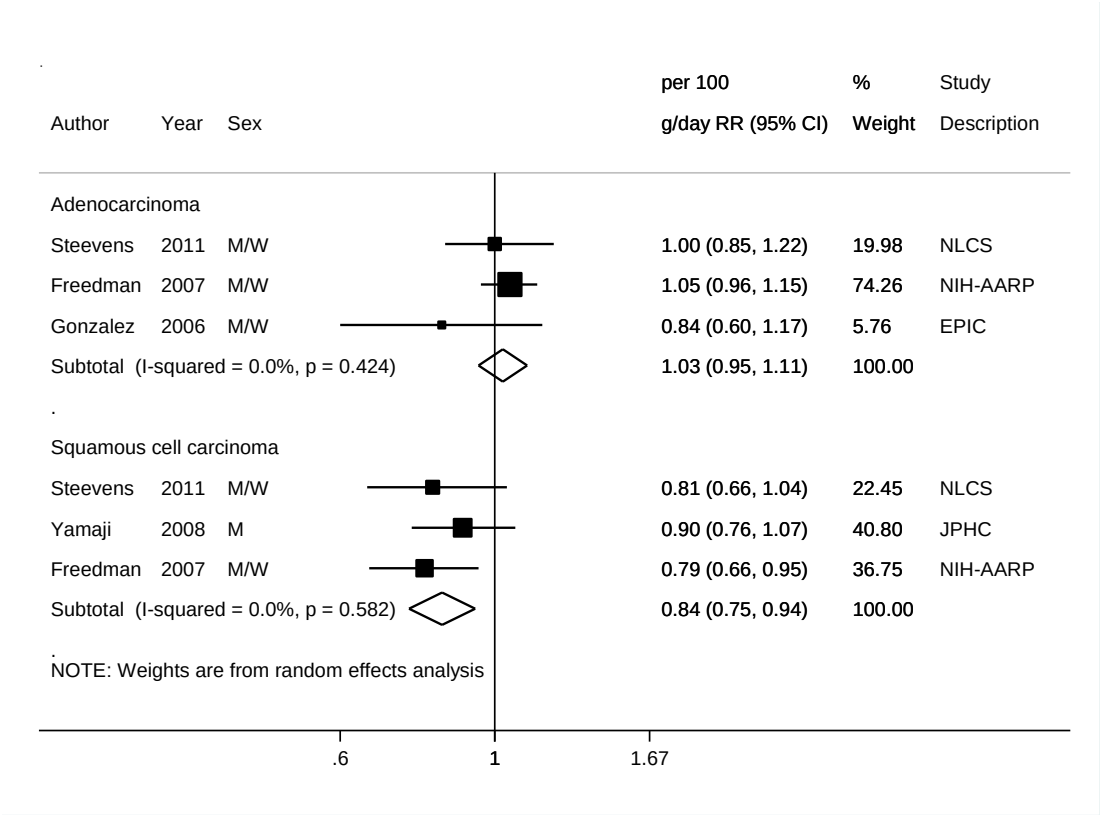
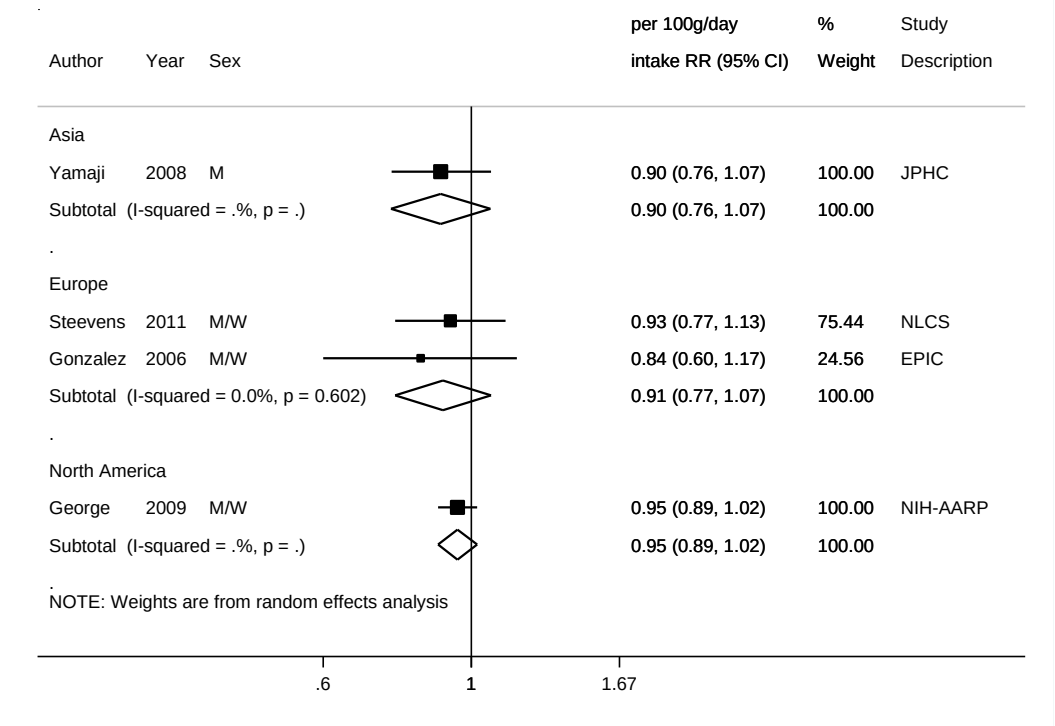


Figure 20 Relative risk of oesophageal cancer for 100g/day increase of fruit intake by geographic location



2.2.2.1 Citrus fruit

Randomised controlled trial

No randomised controlled trial was identified

Cohort studies

Summary

Main results:

Six studies (1057 cases) were included in the dose-response meta-analysis. A borderline significant inverse association of citrus fruit intake with oesophageal cancer risk was observed (RR for 100 g increase: 0.86; 95% CI: 0.74-1.00). Non-significant inverse associations were observed for adenocarcinomas (three studies, no heterogeneity) and squamous cell carcinomas (three studies, low heterogeneity), and in other subgroup analyses.

Two studies were excluded from the dose-response analysis. Fan, 2008 reported a non-significant inverse association for oesophageal cancer. Kjaerheim, 1998 reported a significant dose-response trend for upper aerodigestive cancer risk.

No heterogeneity was observed. There was no evidence of publication or small study bias (p=0.55).

Sensitivity analyses:

When a Japanese study on oesophageal cancer mortality (Iso, 2007, 3% weight) was omitted in influence analysis, the summary RR became significant (RR per 100 g: 0.85; 95% CI=0.73-0.99). When the NIH-AARP study (Freedman, 2007a; 45% weight) was omitted, the summary RR was 0.84 (95% CI=0.69-1.04).

In the Ohsaki Cohort Study, Japan (Li, 2010) citrus fruit but not fruits or vegetable intake was investigated (see Appendix 1). In this study there was a non-significant inverse association of citrus fruits with oesophageal cancer. The summary RR remained unchanged when this study was omitted.

Non-linear dose-response meta-analysis:

Non-linear dose-response analysis was not conducted due to small number of studies.

Study quality:

All studies included in the dose-response analysis used FFQ to assess citrus fruit intake. The EPIC study (Gonzalez, 2006a) also used diet history and food records. Two studies measured intake in times/week (Li, 2010; Iso, 2007) and the NIH-AARP Study (Freedman, 2007a) measured in servings/1000 kcal/day. The units were converted to grams/day using standard methods.

Loss to follow-up was low in most studies and cancer incidence was confirmed by records linkage to cancer registries.

All studies were adjusted for age and sex and all studies except one (Iso, 2007) were adjusted for smoking and alcohol consumption. When the less adjusted study (Iso, 2007), the only

mortality study in the analysis, was excluded from the sensitivity analysis, a significant inverse association was observed. This study was only adjusted for age and study area.

No studies were adjusted for ethnicity or Helicobacter pylori status. One study (Gonzalez, 2006a) that reported non-significant inverse associations of citrus fruits with risk of oesophageal adenocarcinoma also reported similar results in Helicobacter pylori infected and non-infected study participants.

Table 18 Citrus fruit intake and oesophageal cancer risk. Number of studies in the CUP SLR

	Number
Studies identified	8*
Studies included in forest plot of highest compared with lowest exposure	7
Studies included in linear dose-response meta-analysis	6
Studies included in non-linear dose-response meta-analysis	Not enough studies

Note: Include cohort, nested case-control and case-cohort designs. *Seven studies on oesophageal cancer and one study on upper aerodigestive tract cancers.

Table 19 Citrus fruit intake and oesophageal cancer risk. Summary of the linear dose-response meta-analysis in the 2005 SLR and CUP

	2005 SLR	**CUP**
Increment unit used	No meta-analysis	100g/day
All studies		
Studies (n)	-	6
Cases (total number)	-	1057
RR (95%CI)	-	0.86 (0.74-1.00)
Heterogeneity (I^2, p-value)	-	0%, 0.83
P value Egger test	-	0.55
Stratified and sensitivity analysis		
Sex	**Men**	**Women**
Studies (n)	2	1
RR (95%CI)	0.93 (0.70-1.24)	0.63 (0.08-5.23)
Heterogeneity (I^2, p-value)	0%, 0.34	-

Histological type	**Adenocarcinoma (AC)**		**Squamous cell carcinoma (SCC)**
	3		3
Cases (total number)	422		320
RR (95%CI)	0.93 (0.78-1.11)		0.87 (0.69-1.08)
Heterogeneity (I^2, p-value)	0%, 0.58		22.9%, 0.27
	Asia	**Europe**	**North America**
Studies (n)	3	2	1
RR (95%CI)	0.87 (0.67-1.13)	0.80 (0.57-1.13)	0.88 (0.70-1.11)
Heterogeneity (I^2, p-value)	0%, 0.45	0%, 0.54	-

Other stratified analysis

Duration of follow-up	**5-<10 years**	**10-<15 years**	**≥15 years**
Studies (n)	4	-	2
RR (95%CI)	0.85 (0.72-1.02)	-	0.88 (0.63-1.24)
Heterogeneity (I^2, p- value)	0%, 0.70	-	0%, 0.40
Number of cases	**<100 cases**	**100-200 cases**	**≥200 cases**
Studies (n)	1	3	2
RR (95%CI)	0.59 (0.21-1.65)	0.87 (0.67-1.13)	0.87 (0.71-1.05)
Heterogeneity (I^2, p-value)	-	0%, 0.45	0%, 0.81
Adjustment for:			
Socioeconomic status/body fatness/energy intake/physical activity*	**Not adjusted**	**Adjusted**	
Studies (n)	3	3	
RR (95%CI)	0.89 (0.71-1.11)	0.84 (0.68-1.04)	
Heterogeneity (I^2, p-value)	0%, 0.70	0%, 0.52	

*The same adjustments were made in the studies.

Table 20 Citrus fruit intake and oesophageal cancer risk. Main characteristics of studies included in the linear dose-response meta-analysis

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Missing data derived for analyses
Steevens, 2011 oes00817 The Netherlands	NLCS, Case Cohort, Age: 55-69 years, M/W	245/4280 16.3 years	Record linkage to cancer registries)	Validated FFQ, 157-item	Incidence	156 vs non-users g/day Per 25 g/day	0.55 (0.31-0.98) Ptrend:0.37 0.97 (0.90-1.04)	Age, sex, smoking status, cigarettes/day, smoking duration, alcohol, red meat, fish, vegetable, all other fruits	Rescaled the RR for the increment unit used, Hamling's method was used to calculate RRs for EAC and ESCC combined
		144/4280			AC				
		101/4280			SCC		0.54 (0.27-1.07) Ptrend:0.38 1.01 (0.92-1.10)		
Li, 2010 oes00899 Japan	OCS, Prospective Cohort, Age: 40-79 years, M/W	151/ 42 470 9 years (max) 323 204 person-years	Miyagi prefectural cancer registry	Validated FFQ, 40-item	Incidence, oesophageal cancer	≥7 vs ≤2 times/week	0.71 (0.43-1.16) Ptrend:0.18	Age, sex, BMI, smoking, alcohol, employment, education, walking, exercise or sports, diabetes, gastric ulcer, hypertension, family history of cancer, energy intake, intake of tea, coffee, miso soup, rice, soybean, dairy products, fish, meat, vegetables, and	Exposure values using standard portion size, mid-points of exposure categories

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Missing data derived for analyses
								other fruits	
Yamaji, 2008 oes00859 Japan	JPHC, Prospective Cohort, Age: 40-69 years, M	116/ 38 790 7.7 years	Active patient notification, cancer registries, and death certificate	Validated FFQ, 16 fruit and 30 vegetable items	Incidence, SCC	127 vs 10 g/day Per 100 g/day	0.78 (0.48-1.25) Ptrend:0.21 0.89 (0.66-1.20)	Age, cigarette smoking, study area, alcohol drinking	
Freedman, 2007a oes00858 USA	NIH-AARP, Prospective Cohort, Age: 50- years, M/W	316/ 490 802 5 years	Record linkage to state cancer registry databases.	Validated FFQ, 124-item	Incidence	1.12 vs 0.08 servings/1000 kcal	0.96 (0.69-1.35)	Age, sex, BMI, alcohol, education, smoking dose, total energy intake, usual activity throughout the day, vigorous physical activity	Distrubution of person-years per tertile, exposure values using mean energy intake, Hamling's method was used to calculate RRs for EAC and ESCC combined
		213/490 802			AC				
		103/490 802			SCC		0.58 (0.34-0. 99) Ptrend:0.05		
Iso, 2007 oes00847 Japan	JACC, Prospective Cohort, Age: 40-79 years, M/W	164/105 500 15 years	Date and cause of death annually or biannually confirmed with authorities authorization	Validated FFQ, 39-item	Mortality, oesophageal cancer	≥5 vs <3 times/week	1.18 (0.73-1.89)	Age, area of study	Exposure values using standard portion size, mid-points of exposure categories, RRs for men and women combined using fixed effect model
		139/43 011			Men				
		25/59 504			Women		0.80 (0.30-2.11)		

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Missing data derived for analyses
González, 2006a oes00841 10 European countries	EPIC, Prospective Cohort, Age: 35-70 years, M/W	65/ 481 518 6.5 years	Cancer registry, death registry, active follow up (health insurance, pathology records)	FFQ, diet history, food record	Incidence, AC	≥43.40(M)/ 60.71(W) vs ≤10.68(M)/ 17.43(W) g/day Per 50 g/day	0.73 (0.39-1.37) Ptrend:0.22 0.77 (0.46-1.28)	Centre, age, sex, height, weight, education level, smoking, physical activity, alcohol, energy intake, red meat, processed meat	Rescaled the RR for the increment unit used
		19/ 28/			H.pylori infected H.pylori non infected	Per 50 g/day	0.86 (0.40-1.86) 0.71 (0.17-3.00)		

Table 21 Citrus fruit intake and oesophageal cancer risk. Main characteristics of studies excluded from the linear dose-response meta-analysis

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Inclusion/exclusion
Fan, 2008 oes00871 China	SCStudy, Prospective Cohort, Age: 45-64 years, M	101/ 18 244 282 679 person-years	Cancer registry, Shanghai vital statistics office, medical history	Questionnaire and interview	Incidence, oesophageal cancer	Orange or tangerine, Quantile 3 vs Quantile 1	0.56 (0.30-1.05) Ptrend:0.06	Age at interview, BMI, number of years of smoking, year of interview, drinking amount, education, neighbourhood of residence at recruitment, years of drinking	Excluded, exposure not quantified
Kjaerheim, 1998 oes00130 Norway	Norwegian Men UADT, Prospective Cohort, M	60/ 10 900 25 years	Population survey	FFQ, 32-item	Incidence, upper aerodigestive tract cancer	Oranges ≥6 vs <1 times/month	0.50 (0.30-1.00) Ptrend:0.03	Age, alcohol consumption, smoking habits, bread	Excluded, UADT cancer, oranges only

Figure 21 RR estimates of oesophageal cancer by levels of citrus fruit intake

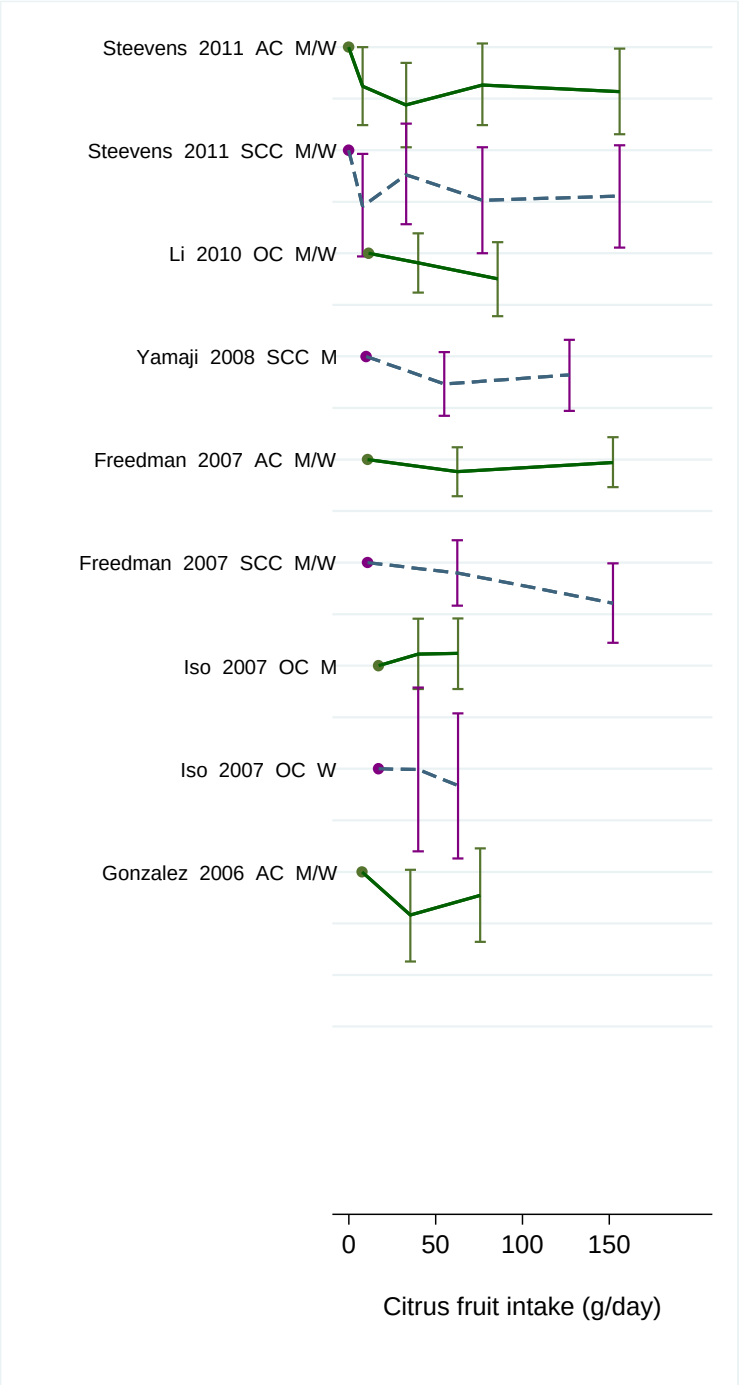
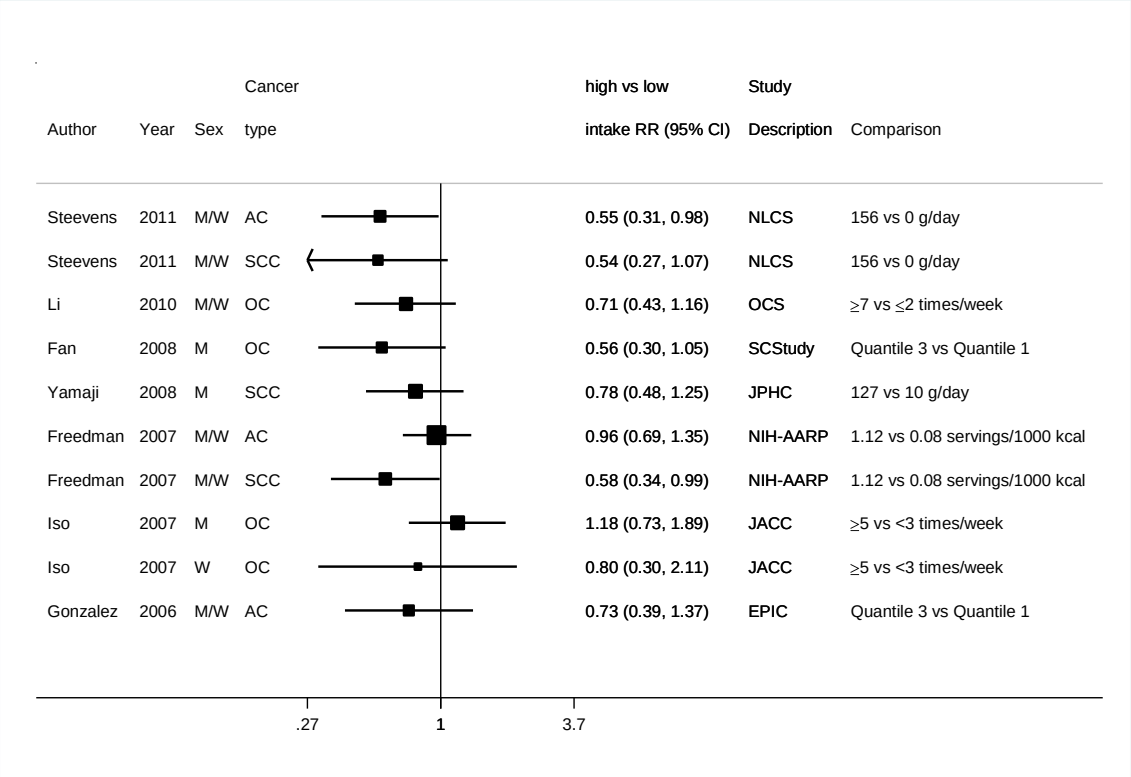


Figure 22 RR (95% CI) of oesophageal cancer for the highest compared to the lowest level of citrus fruit intake



Note: The intake comparison in Gonzalez, 2006 was ≥43.40 vs ≤10.68 g/day in men and ≥60.71 vs ≤17.43 g/day in women

Figure 23 Relative risk of oesophageal cancer for 100g/day increase of citrus fruit intake

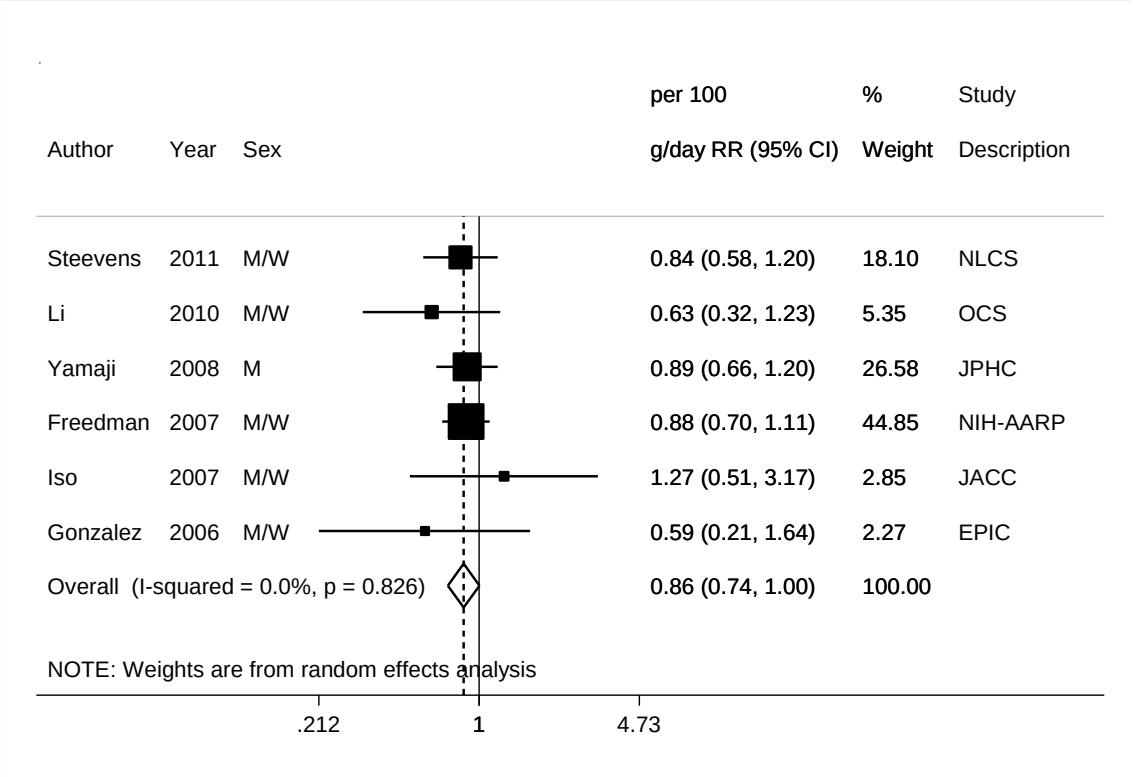
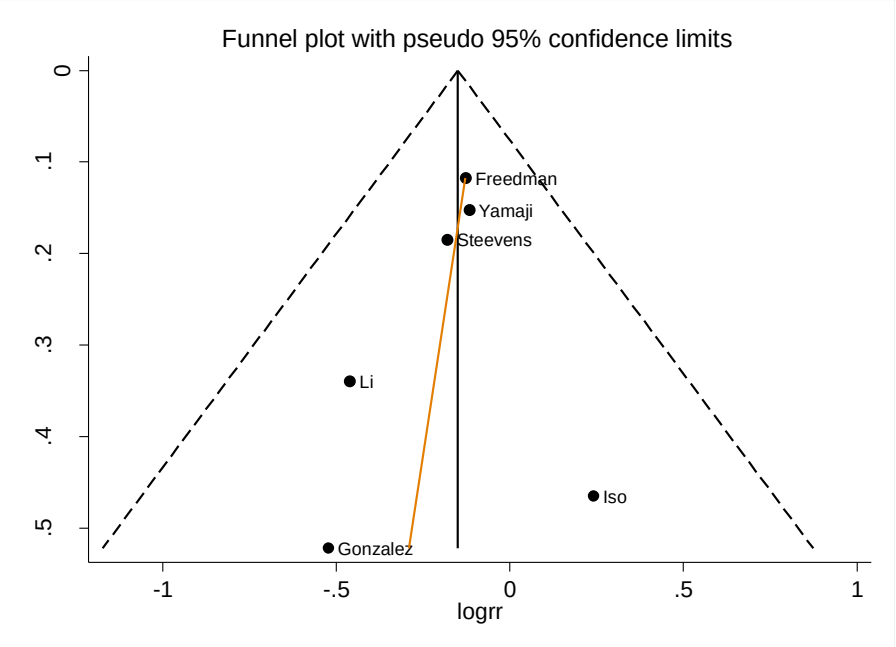


Figure 24 Funnel plot of studies included in the dose response meta-analysis of citrus fruit intake and oesophageal cancer



Egger's test P=0.55

Figure 25 Relative risk of oesophageal cancer for 100g/day increase of citrus fruit intake by sex

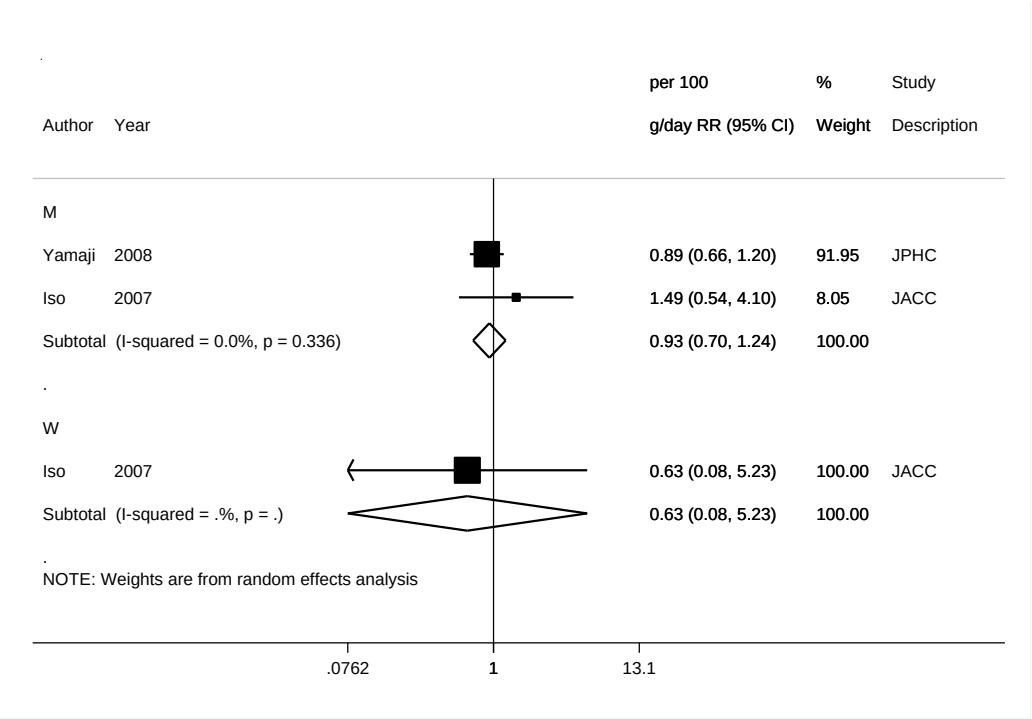


Figure 26 Relative risk of oesophageal cancer for 100g/day increase of citrus fruit intake by cancer type

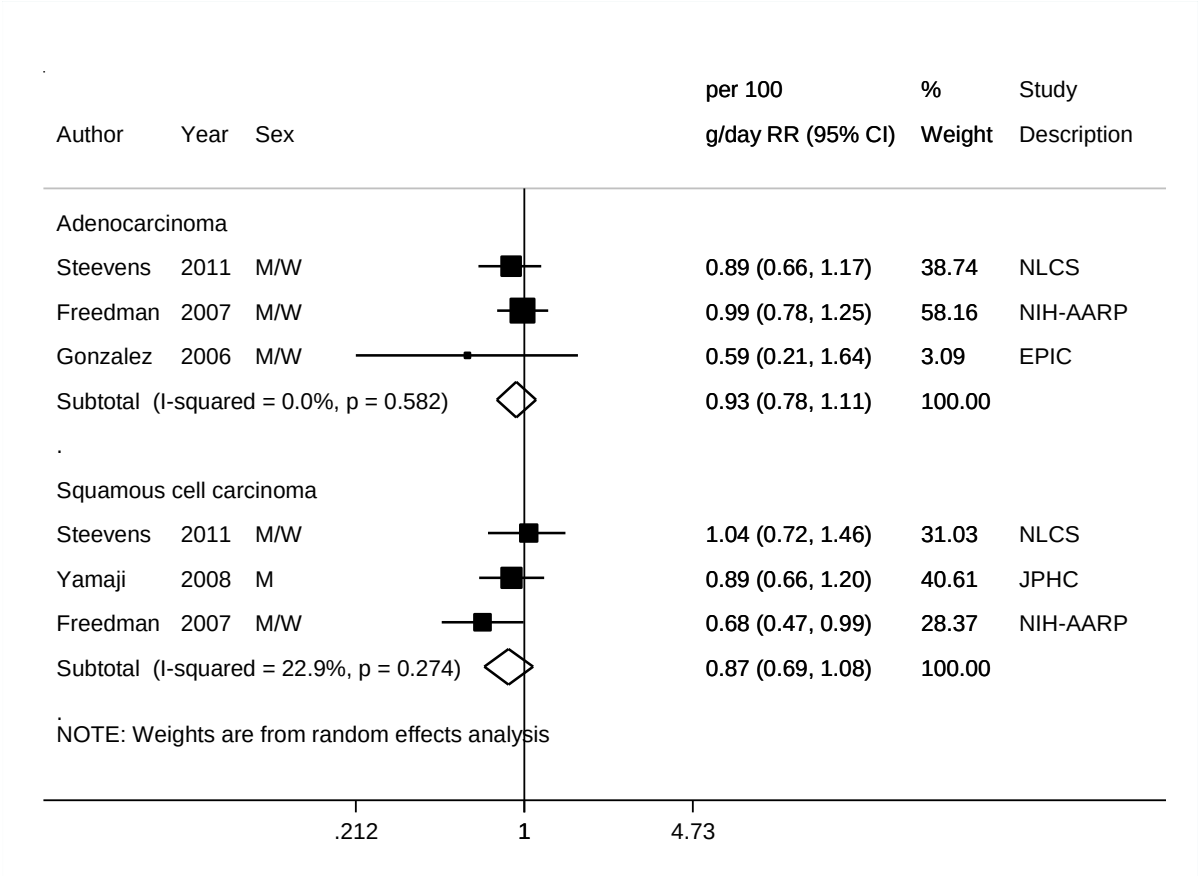
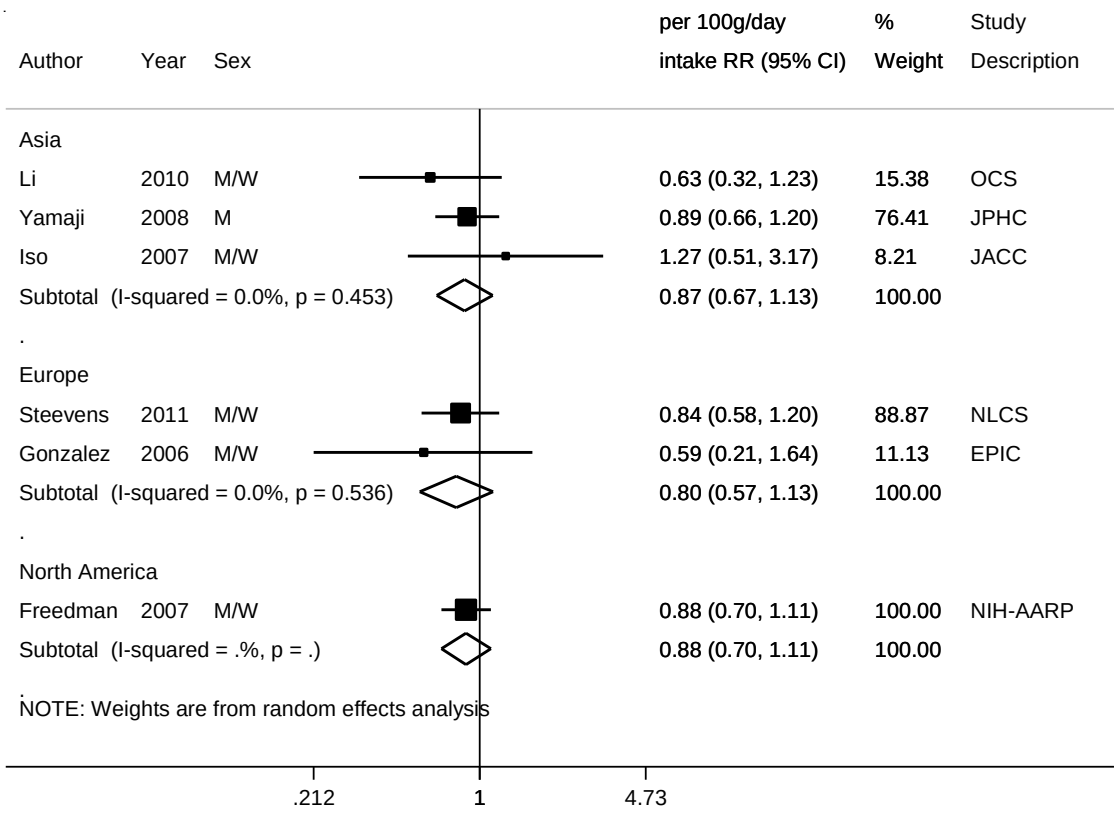


Figure 27 Relative risk of oesophageal cancer for 100g/day increase of citrus fruit intake by geographic location



2.5 Meat, poultry, fish and eggs

2.5.1 Meat

Four studies reported on meat intake and oesophageal cancer risk (Fan, 2008; Gonzalez, 2006b; Guo, 1994; Hirayama, 1990). All studies reported non-significant associations.

There was not enough information to do linear dose-response meta-analysis.

2.5.1.2 Processed meat

Cohort studies

Summary

Main results:

Although meta-analysis are updated in the CUP when there are at least five studies with the required data, this section has been included because the evidence that processed meat is causally related to oesophageal cancer risk was judged as limited suggestive in the Second Expert report.

There were three publications on aerodigestive tract cancer and six publications on oesophageal cancer. Four studies (1388 cases) could be included in the dose-response meta-analysis of oesophageal cancer. A significant positive association with oesophageal cancer was observed. Non- significant (positive) association was observed for adenocarcinomas (three studies, high heterogeneity) and borderline significant positive association was observed for squamous cell carcinomas (two studies, no heterogeneity).

There was no evidence of heterogeneity. Test of publication or small study bias was not conducted due to small number of studies.

Sensitivity analyses:

The summary RRs ranged from 1.19 (95% CI=0.86-1.64) when Jakszyn, 2013 (44% weight) was omitted to 1.47 (95% CI=1.08-2.00) when Cross, 2011 (38% weight) was omitted.

Non-linear dose-response meta-analysis:

Non-linear dose-response meta-analysis was not conducted due to small number of studies.

Study quality:

All studies included in the analyses assessed dietary intake using FFQ; in one study (Jakszyn, 2013) a combination of methods (FFQ, diet history, or food records) was used. The definition of processed meat varied between the studies, including processed red meat (Jakszyn, 2013), ham and sausages (Iso, 2007), ham, bacon, and sausages (Chyou, 1995), and processed meat and fish (Zheng, 1995).

In four studies (Iso, 2007, Kjaerheim, 1998, Chyou, 1995, and Zheng, 1995) intake was expressed in times or servings/week or /month; two studies expressed intake in grams per kcals (Jakszyn, 2013 (EPIC); Cross, 2011 (NIH-AARP). Intakes were all rescaled to grams per day using standard portion sizes and mean energy intakes described in the publications.

Loss to follow-up was low in most studies and cancer incidence was confirmed by records linkage to the cancer registries. The only mortality study (Iso 2007) ascertained the cases by death certification.

All studies included in the analysis were adjusted for age and sex.

Studies on upper aerodigestive tract cancers (UADT):

Three other studies on upper aerodigestive tract cancers and processed meat were identified in the CUP. The study results for the highest compared to the lowest intake are shown in the forest plot together with the studies on oesophageal cancer. When a dose-response meta-analysis was conducted separately for studies on UADT, non-significant positive association was observed (no heterogeneity).

Table 22 Processed meat intake and oesophageal cancer risk. Number of studies in the CUP SLR

	Number
Studies identified Oesophageal cancer Upper aero-digestive tract	 4 (6 publications) 3 (3 publications)
Studies included in forest plot of highest compared with lowest exposure	7*
Studies included in linear dose-response meta-analyses Oesophageal cancer Upper aero-digestive tract	 4 3
Studies included in non-linear dose-response meta-analysis	Not enough studies

Note: Include cohort, nested case-control and case-cohort designs.
*Include three studies on upper aerodigestive tract cancers.

Table 23 Processed meat intake and oesophageal cancer risk. Summary of the linear dose-response meta-analysis in the CUP*

	CUP	
Increment unit used	Per 50 g/day	
	Oesophageal cancer	**Upper aerodigestive cancers**
Studies (n)	4	3
Cases (total number)	1388	193
RR (95%CI)	1.39 (1.09-1.77)	1.38 (0.75-2.54)
Heterogeneity (I^2, p-value)	0%, 0.53	0%, 0.89
P value Egger test	-	-

Stratified and sensitivity analysis of oesophageal cancer			
Sex	**Men**	**Women**	
Studies (n)	2	2	
RR (95%CI)	1.15 (0.59-2.25)	1.13 (0.07-19.62)	
Heterogeneity (I^2, p-value)	9.5%, 0.29	72.8%, 0.06	
Histological type	**Adenocarcinoma (AC)**	**Squamous cell carcinoma (SCC)**	
Studies (n)	3	2	
Cases	912	322	
RR (95%CI)	1.19 (0.85-1.68)	1.34 (1.00-1.81)	
Heterogeneity (I^2, p-value)	63.4%, 0.07	0%, 0.49	
Geographic location	**Asia**	**Europe**	**North America**
Studies (n)	1	2	1
RR (95%CI)	1.00 (0.36-2.75)	1.50 (1.02-2.20)	1.26 (0.85-1.87)
Heterogeneity (I^2, p-value)	-	17.9%, 0.27	-
Other stratified analyses			
Duration of follow-up	**10-<15 years**	**≥15 years**	
Studies (n)	2	2	
RR (95%CI)	1.47 (1.10-1.96)	1.06 (0.60-1.87)	
Heterogeneity (I^2, p- value)	12.7%, 0.29	0%, 0.88	
Number of cases	**<200 cases**	**≥200 cases**	
Studies (n)	2	2	
RR (95%CI)	1.59 (1.12-2.25)	1.21 (0.86-1.71)	
Heterogeneity (I^2, p-value)	0%, 0.34	0%, 0.73	
Adjustment for:			
Socioeconomic status	**Not adjusted**	**Adjusted**	
Studies (n)	2	2	
RR (95%CI)	1.22 (0.84-1.76)	1.50 (1.02-2.20)	
Heterogeneity (I^2, p-value)	0%, 0.68	17.9%, 0.27	
Alcohol and physical activity**	**Not adjusted**	**Adjusted**	
Studies (n)	2	2	
RR (95%CI)	1.59 (1.12-2.25)	1.21 (0.86-1.71)	
Heterogeneity (I^2, p-value)	0%, 0.34	0%, 0.73	

*No meta-analysis of cohort studies was conducted in the 2005 SLR
**The same adjustments were made in the studies

Table 24 Processed meat intake and oesophageal cancer risk. Results of meta-analyses and pooled analyses published after the 2005 SLR

Author, Year	Number of studies	Total number of cases	Studies country, area	Outcome	Comparison	RR (95%CI)	P trend	Heterogeneity (I^2, p value)
Meta-analyses								
Zhu, 2014	15 studies (3 cohorts*, 12 case-control)	3274 (1737 SCC, 1537 AC)	China, Italy, Iran, Ireland, The Netherlands, Paraguay, Switzerland, United States, Uruguay, Europe	Incidence, Oesophageal cancer	High vs low Cohorts Case-control All studies	 1.25 (0.83-1.86) 1.39 (1.00-1.93) 1.33 (1.04-1.69)	 - - -	 63.4%, 0.01 63.4%, 0.002 61.5%, <0.001
	10 studies (2 cohorts, 8 case-control)			SCC	Cohorts Case-control All studies	1.34 (0.62-2.92) 1.37 (0.84-2.24) 1.35 (0.92-2.00)	- - -	68.5%, 0.042 75.4%, <0.001 71.3%, <0.001
	7 studies (3cohorts, 4 case-control)			AC	Cohorts Case-control All studies	1.21 (0.67-2.16) 1.45 (1.04-2.03) 1.23 (1.01-1.50)	- - -	69.3%, 0.02 0%, 0.87 40.9%, 0.11
Choi, 2013	18 studies (3 cohorts*, 15 case-control)	5013	Asia, Europe, South America, United States	Incidence, Oesophageal cancer Cohorts Case-control All studies	Per 100 g/day Cohorts High vs low 	 1.37 (0.88-2.13) 1.25 (0.83-1.86) 1.36 (1.07-1.74) 1.32 (1.08-1.62)	 - - - -	 33.5%, 0.17 63.4%, 0.01 57.1%, <0.01 58.4%, <0.01
	7 case-control and cohort			SCC		1.08 (0.80-1.44)	-	
	8 case-control and cohort			AC		1.38 (1.07-1.78)	-	-

Huang, 2013	9 studies (3 cohorts*, 6 case-control,)	2358	Europe, United States	Incidence, Oesophageal AC	Per 50 g/day All studies (7 studies) High vs low Cohorts Case-control All studies	 1.37 (1.03-1.81) 1.35 (0.78-2.33) 1.54 (1.15-2.07) 1.41 (1.09-1.83)	 - - - -	 71.0%, 0.002 75.9%, 0.02 0%, 0.78 39.4%, 0.11
Qu, 2013	15 studies (2 cohorts*, 13 case-control)	6499	Argentina, China, Italy, Iran, The Netherlands, Switzerland, United States, Uruguay, Europe	Incidence, Oesophageal (all types) or SCC	Per 50 g/day Cohorts Case-control All studies High vs low Cohorts Case-control All studies	 1.42 (0.98-2.05) 1.96 (1.31-2.93) 1.81 (1.32-2.48) 1.28 (0.88-1.86) 1.62 (1.22-2.16) 1.55 (1.22-1.97)	 - - - - - -	 0%, 0.60 62.2%, 0.003 56.5%, 0.01 0%, 0.81 51.0%, 0.02 45.3%, 0.03
	8 studies			SCC	High vs low	1.41 (1.11-1.78)	-	0%, 0.57
Salehi, 2013	17 studies (2 cohorts*, 15 case-control)	2630 (1947 SCC, 1339 AC)	Argentina , China, Ireland, Europe, Paraguay, Switzerland, Uruguay, USA,	Incidence, Oesophageal cancer (8 studies) SCC AC	High vs low Per 50g All studies (6 studies) All studies (6 studies)	1.41 (1.13-1.76) 1.57 (1.22-2.01) 1.17 (0.90-1.51) 1.37 (1.05-1.78)	- - - -	62.0%, <0.001 0.35 0.20

*All cohorts were identified and included in the present review

Table 25 Processed meat intake and oesophageal cancer risk. Main characteristics of studies included in the linear dose-response meta-analysis

Note: Zheng, 1995 was included in meat, poultry, fish and eggs in the 2005 SLR and is included in the present review on processed meat; three studies (Kjaerheim, 1998; Chyou, 1995; Zheng, 1995) reported results on processed meat intake and upper aerodigestive tract cancers and were included in a separate meta-analysis

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Inclusion/ exclusion
Jakszyn, 2013 oes00864 Denmark,France,Germany,Greece,Italy,Netherlands,Norway,Spain,Sweden,UK	EPIC, Prospective Cohort, Age: 35-70 years, M/W	137/ 481 419 11 years	Cancer registry, health insurance records, active follow up and mortality registry	Questionnaire + recall	Incidence, AC	Processed red meat Per 25 g/2000 kcal	1.31 (1.08-1.58)	Age, sex, BMI, educational level, fresh fruits and vegetables intake, smoking status, number of cigarettes smoked, time since quitting smoking, total energy intake, unprocessed red meat, white meat	Exposure units rescaled, using mean energy intake estimated from the tertiles values in the publication
						58.62 vs 6.32 g/2000 kcal	2.27 (1.33-3.89) Ptrend: 0.004		
Keszei, 2012 oes00822 The Netherlands	NLCS, Case Cohort, Age: 55-69 years, M/W	252/4827 16.3 years 59/1928	Annual linkage to the Netherlands cancer registry and the nationwide network of histopathology and cytopathology in	Validated FFQ, 150-item	Incidence, SCC, men	45.5 vs 3.7 g/day	3.47 (1.21-9.94) Ptrend: 0.04	Age, BMI, education level, intakes of fruit, vegetable, alcohol, non-occupational physical activity, smoking status cigarettes/day,	Results by cancer types were combined using the method of Hamling, results by sex were combined using a fixed effect model
						Per 50 g/day	2.15 (1.14-4.08)		
		114/1928			AC, men	45.5 vs 3.7 g/day	0.94 (0.46-1.89) Ptrend: 0.84		
						Per 50 g/day	0.88 (0.50-1.53)		
		48/1995			SCC, women	26.0 vs 3.5	0.63 (0.28-1.44)		

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Inclusion/ exclusion
			The Netherlands (PALGA)			g/day	Ptrend: 0.31	smoking years, total energy intake, lower oesophageal sphincter relaxing medication	
						Per 50 g/day	0.37 (0.09-1.52)		
		31/1995			AC, women	26.0 vs 3.5 g/day	0.58 (0.22-1.50) Ptrend: 0.20		
						Per 50 g/day	0.71 (0.14-3.45)		
Cross, 2011 oes00827 USA	NIH- AARP, Prospective Cohort, Age: 50-71 years, M/W	845/494 979 10 years 215/	Record linkage to state cancer registry databases.	Validated FFQ, 124-item	Incidence SCC	Per 10 g/1000kcal	1.08 (0.96-1.21) 1.32 (0.83-2.10) Ptrend: 0.09	Age, sex, BMI, calories intake, ethnicity, work - physical activity, alcohol drinking, fruit and vegetable intake, saturated fat intake, tobacco use, vigorous physical activity	Exposure units rescaled using mean energy intake by quintile in the publication, distribution of person-years by quantiles, results by cancer types combined using Hamling method
		630/			Incidence, AC	23.2 vs 1.7 g/1000 kcal	1.03 (0.96-1.11) 1.08 (0.81-1.43) Ptrend: 0.26		
Iso, 2007 oes00847 Japan	JACC, Prospective Cohort, Age: 40-79 years, M/W	154/ 105 500 15 years 133/ 40 153	Date and cause of death annually or biannually confirmed with authorities authorization	Validated FFQ, 39-item	Mortality, oesophageal cancer Men	Ham and sausages ≥3-4 vs <1 times/week	0.90 (0.56-1.46)	Age, area of study	Mid-points of exposure categories, times converted to grams using 50 g as standard conversion, results by sex combined using fixed effect model
		21/ 46 986			Women		2.10 (0.70-6.32)		
Kjaerheim, 1998 oes00130	Norwegian Men UADT,	68/ 10 900	Population survey	FFQ, 32-item	Incidence, mouth, tongue, pharynx,	High vs low times/month	1.60 (0.40-6.90) Ptrend: >0.5	Age, alcohol consumption,	Separate analysis on UADTC - mid-

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Inclusion/ exclusion
Norway	Prospective Cohort, M	25 years			larynx, oesophagus,			smoking habits	points of exposure categories, times converted to grams using 50 g as standard conversion
Chyou, 1995 oes00128 USA	HHP, Prospective Cohort, M	92/ 7 995 25 years	Selective service roll	FFQ and 24 hour recall	Incidence, upper aerodigestive tract, squamous cell,	Ham, bacon, and sausages >5 vs 0-1 servings/week	1.24 (0.73-2.10) Ptrend: 0.44	Age, alcohol consumption, smoking habits	Separate analysis on UADTC - mid-points of exposure categories, servings converted to grams using a standard conversion of 50g
Zheng, 1995 oes00047 USA	IWHS, Prospective Cohort, Age: 55-669 years, W, Postmenopausal	33/ 34 691 7 years	Driving license/private health care list	Semi-quantitative FFQ, 127-item	Incidence, upper aerodigestive cancer	Processed meat and fish >13 vs <4.4 times/month	1.30 (0.60-3.20)	Age, educational level, smoking habits	Separate analysis on UADTC - distribution of person-years, mid-points of exposure categories, intake in times converted to grams using a standard conversion of 50g

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

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Inclusion/exclusion
Cross, 2007 oes00840 USA	NIH- AARP, Prospective Cohort, Age: 50-71 years, M/W	548/ 494 036 6.8 years	Linkage of the cohort with database to state cancer registries	Validated FFQ	Incidence, oesophageal cancer	22.6 vs 1.6 g/1000kcal	0.94 (0.70-1.25) Ptrend:0.69	Age, sex, education, marital status, family history of cancer, race, BMI, smoking, frequency of vigorous physical activity, total energy intake, alcohol intake, fruit and vegetable consumption	Superseded by Cross, 2011, OES00827
González, 2006a oes00830 Denmark,France,Germany,Greece,Italy,Netherlands,Norway,Spain,Sweden,UK	EPIC, Prospective Cohort, Age: 35-70 years, M/W	65/ 465 586 6.5 years	Cancer registries, health insurance records, pathology rec & active follow up	FFQ, dietary questionnaires, food record	Incidence, AC	Per 50 g	1.16 (0.82-1.65)	Age, sex, centre, citrus fruit intake, education level, energy intake, height, leisure - physical activity, poultry, vegetable intake, weight, work - physical activity, alcohol intake, other fruits intake, red meat, smoking intensity, tobacco use	Superseded by Jakszyn, 2013, OES00864
						Quantile 3 vs quantile 1	3.54 (1.57-7.99) Ptrend: 0.002		

Figure 28 RR estimates of oesophageal cancer by levels of processed meat intake
Note: Kjaerheim, 1998, Chyou, 1995, and Zheng, 1995 reported results on upper aerodigestive tract cancers and were analysed in a separate meta-analysis.

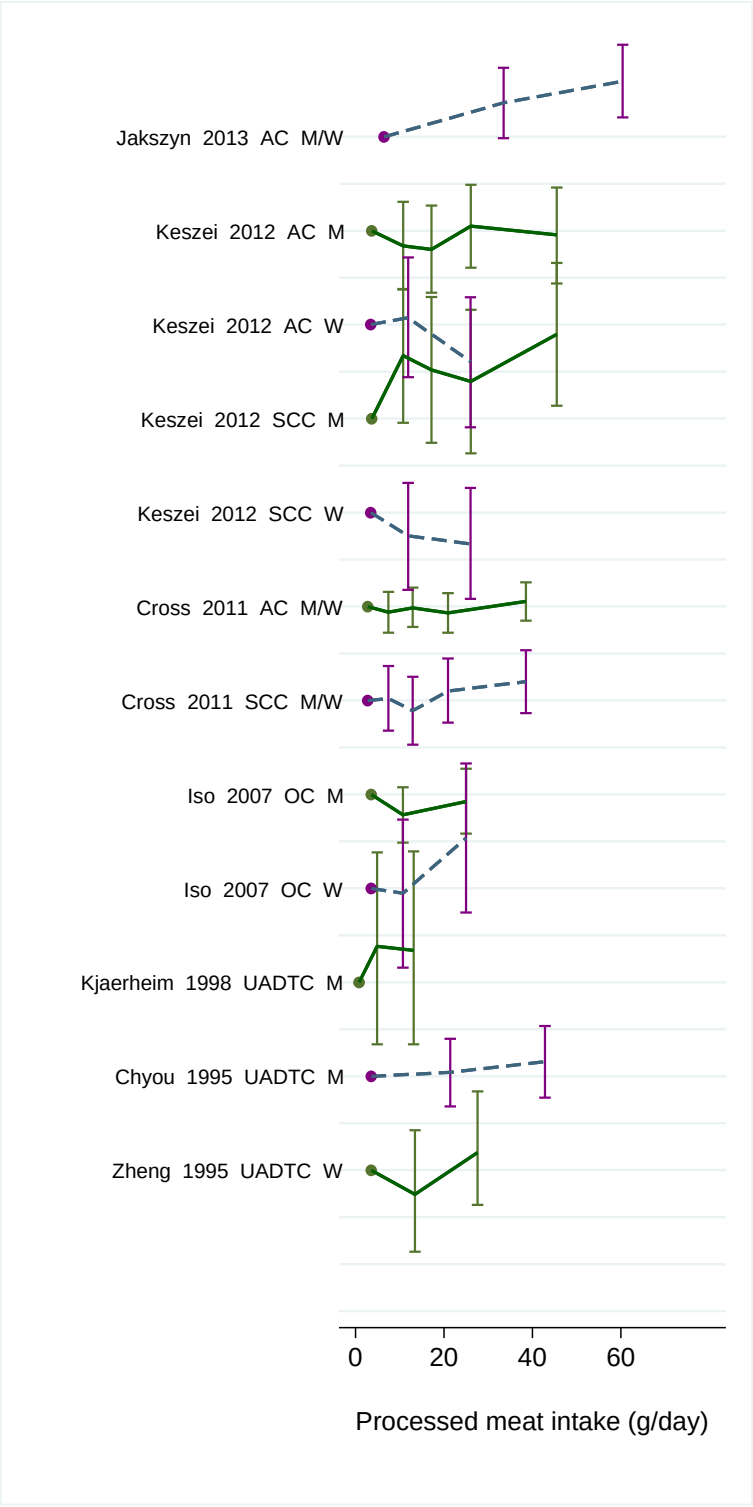


Figure 29 RR (95% CI) of oesophageal cancer for the highest compared with the lowest level of processed meat intake

Note: Kjaerheim, 1998, Chyou, 1995, and Zheng, 1995 reported results on upper aerodigestive tract cancers and were analysed in a separate meta-analysis.

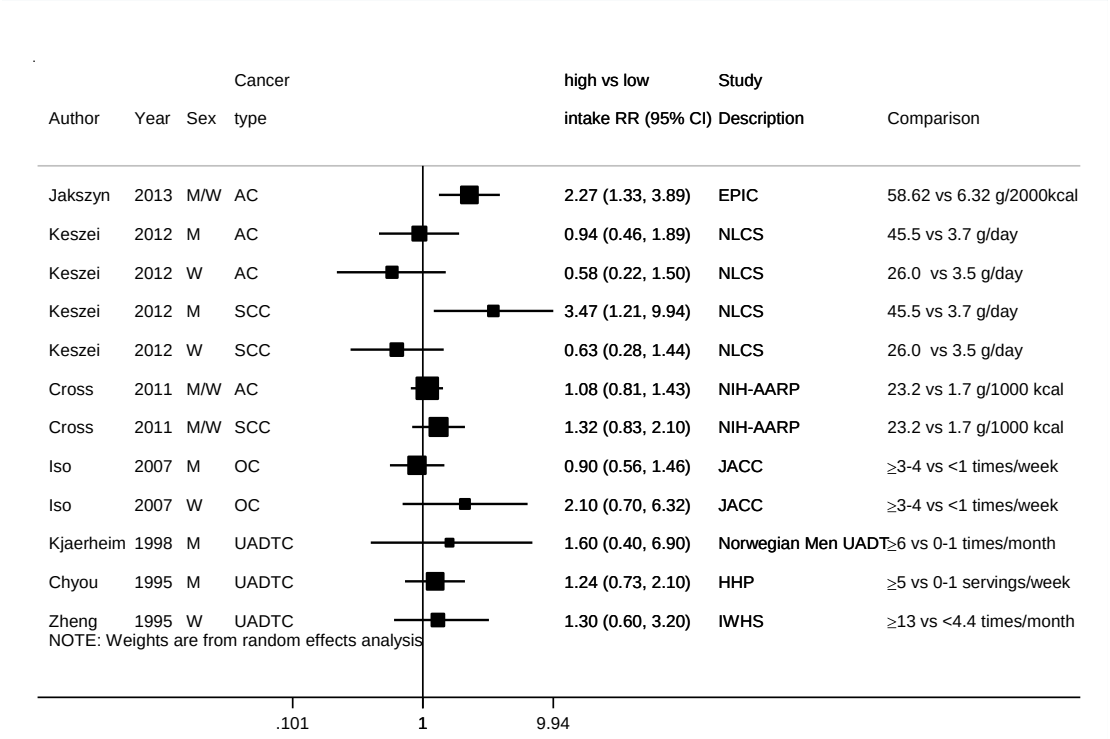


Figure 30 Relative risk of oesophageal cancer for 50 g/day increase of processed meat intake

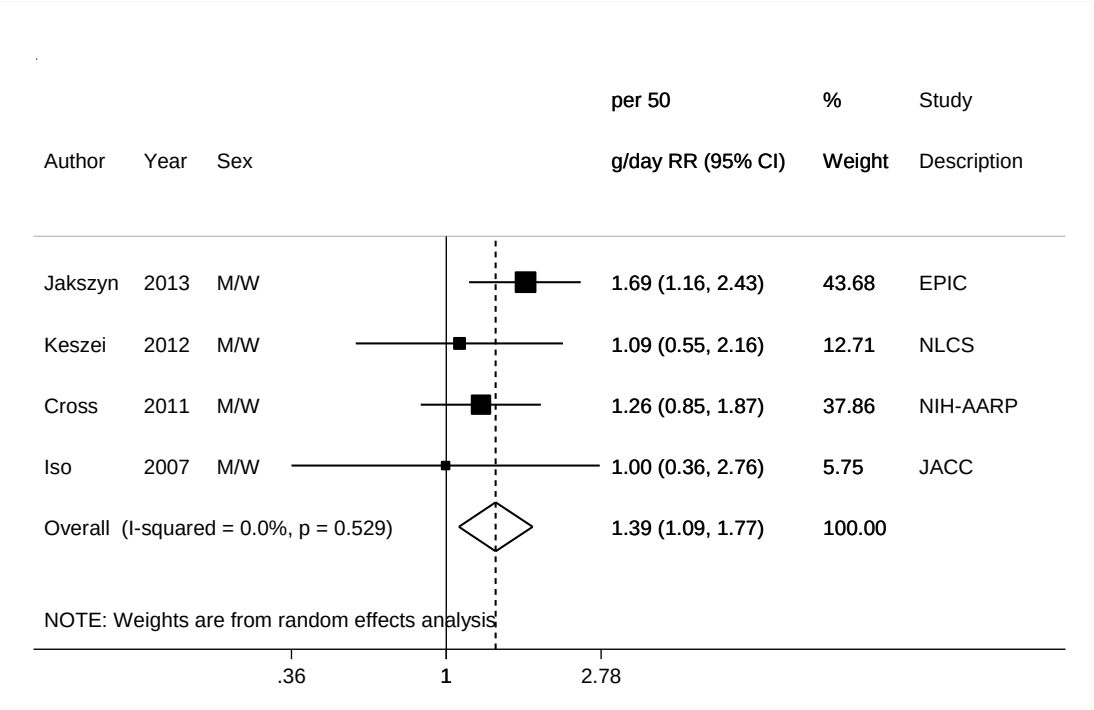


Figure 31 Relative risk of oesophageal cancer for 50g/day increase of processed meat intake by sex

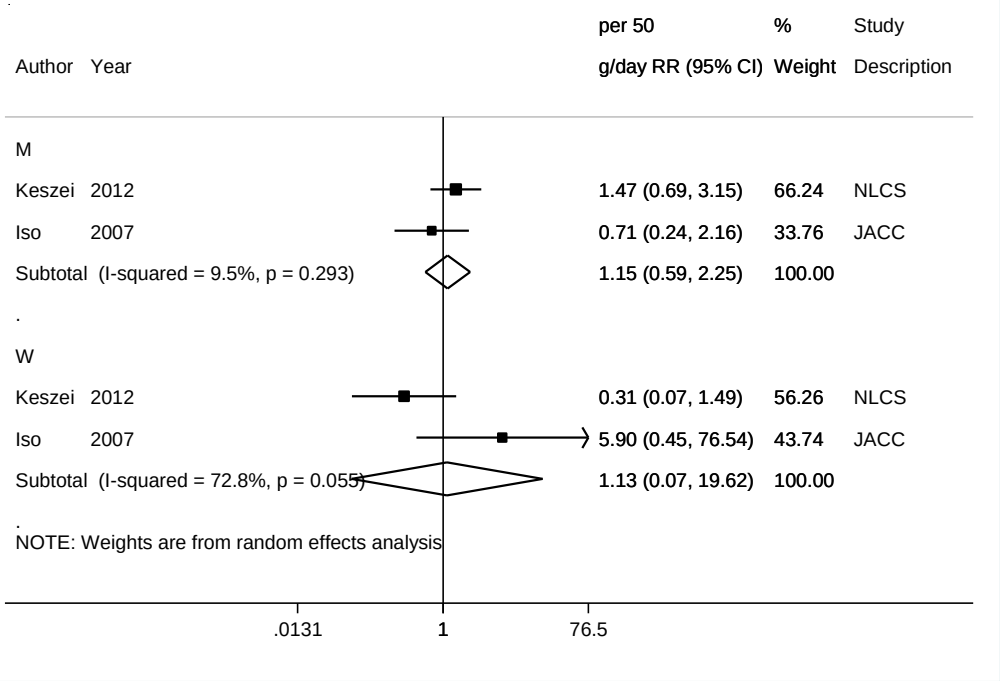


Figure 32 Relative risk of oesophageal cancer for 50g/day increase of processed meat intake by geographic location

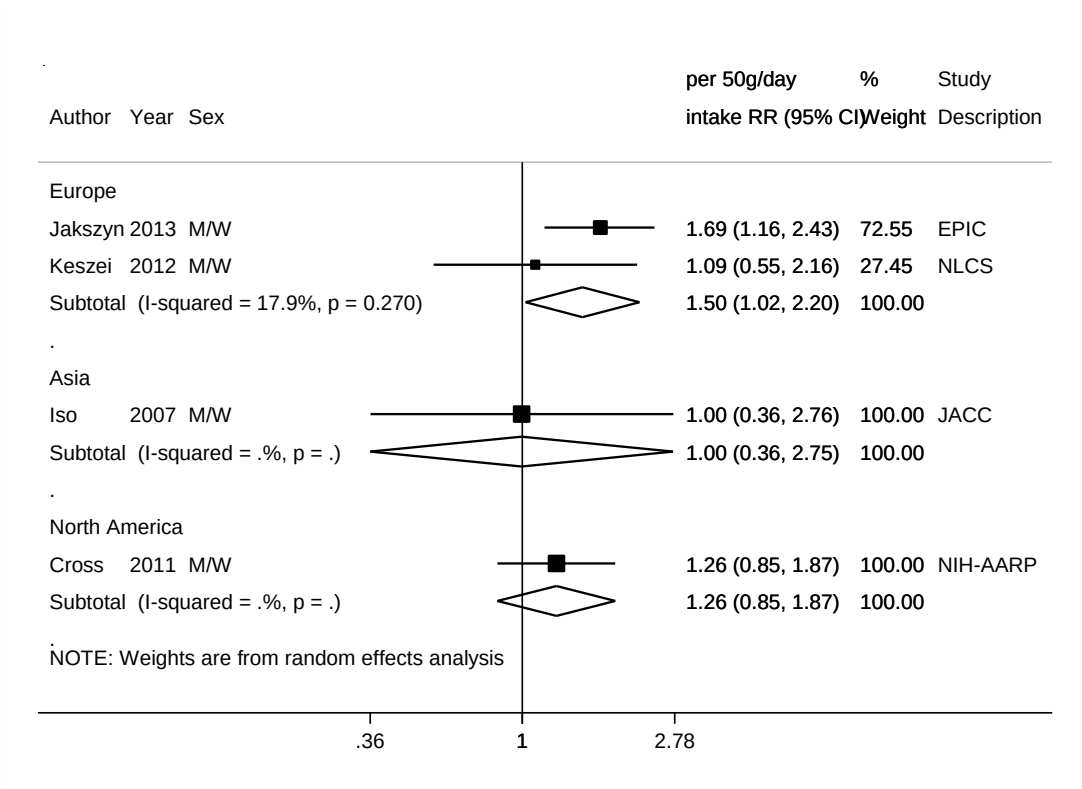


Figure 33 Relative risk of oesophageal cancer for 50g/day increase of processed meat intake by cancer type

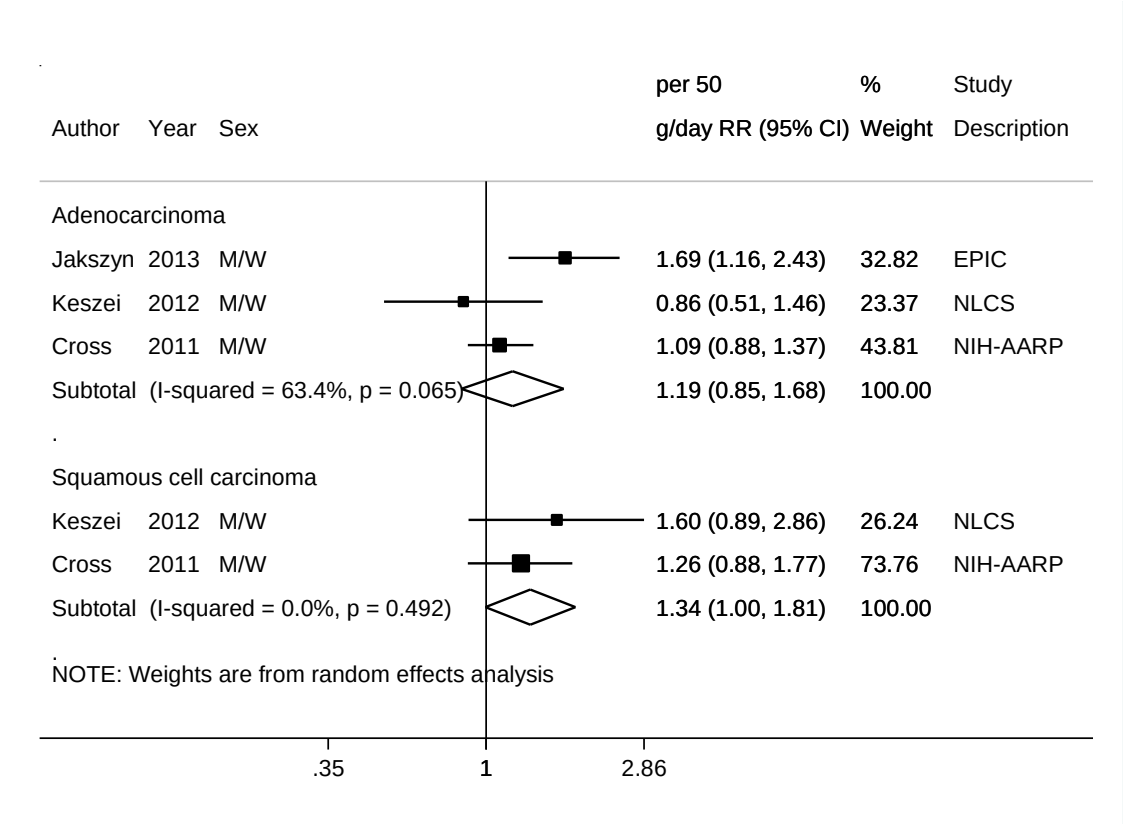
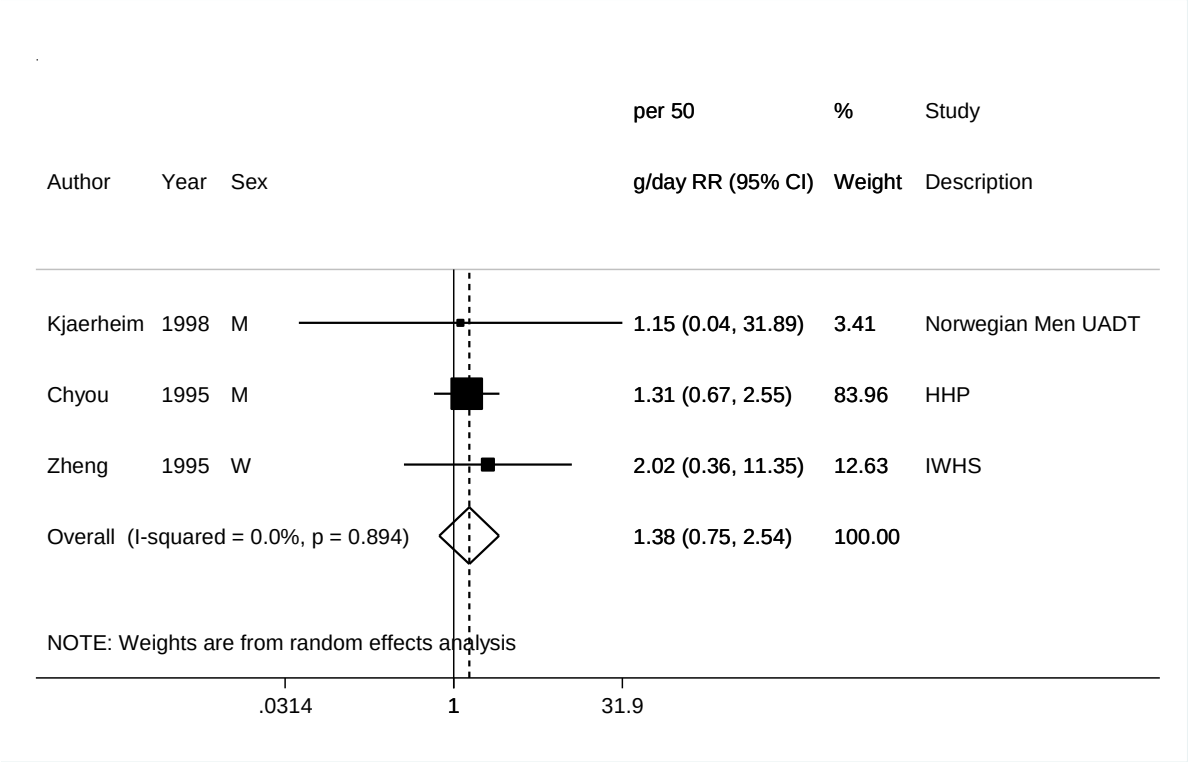


Figure 34 Relative risk of upper aerodigestive cancers for 50g/day increase of processed meat intake



2.5.1.3 Red and processed meat

Cohort studies

Summary

Main results:

Meta-analyses are updated in the CUP when there are at least five studies with the required data. This section has been included because the evidence that red meat is causally related to oesophageal cancer risk was judged as limited suggestive in the Second Expert report.

Three studies, two on red meat (Jakszyn, 2013; Keszei, 2012) and one on red and processed meat combined (Cross, 2011) were identified in the CUP. There were no cohort studies in the 2005 SLR.

All three studies (1234 cases) could be included in the dose-response meta-analysis. A non-significant positive association was observed for oesophageal cancer risk. No significant association was observed for adenocarcinomas (three studies, low heterogeneity) and significant positive association was observed for squamous cell carcinomas (two studies, no heterogeneity).

No heterogeneity was observed. Test of publication or small study bias was not conducted due to small number of studies.

Sensitivity analyses:

The summary RR remained non-significant in influence analysis, ranging from 1.16 (95% CI=0.81-1.68) when Cross, 2011 (on red and processed meat combined) (54% weight) was omitted to 1.26 (95% CI=0.96-1.65) when Jakszyn, 2013 (15% weight) was omitted.

In analysis by cancer subtype, the summary relative risk estimate for oesophageal AC after excluding Cross, 2011 was RR=0.81, 95% CI=0.57-1.16 (two studies: Jakszyn, 2013; Keszei, 2012); the only remaining study on SCC reported a RR of 1.37, 95% CI=0.82- 2.30) (Keszei, 2012).

Non-linear dose-response meta-analysis:

Non-linear dose-response meta-analysis was not conducted due to small number of studies.

Study quality:

All studies included in the analysis assessed dietary intake using FFQ; a combination of methods was used in one study (FFQ, diet history, or food records) (Jakszyn, 2013). In two studies (EPIC; Jakszyn, 2013 and the NIH-AARP; Cross, 2011) the exposure was expressed in grams/1000 kcal/day and grams/2000 kcal/day and these were rescaled to grams/day using mean energy intakes reported in the publications.

Cancer incidence was confirmed by records linkage to the cancer registries in the studies.

All studies included in the analysis were adjusted for age, sex, smoking, energy intake, and BMI.

Table 27 Red and processed meat intake and oesophageal cancer risk. Number of studies in the CUP SLR

	Number
Studies identified	3 (6 publications)
Studies included in forest plot of highest compared with lowest exposure	3
Studies included in linear dose-response meta-analysis	3
Studies included in non-linear dose-response meta-analysis	Not enough studies

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

Table 28 Red and processed meat intake and oesophageal cancer risk. Summary of the highest versus the lowest meta-analysis in the CUP

	2005 SLR	**CUP**
Increment unit used	No meta-analysis	100g/day
All studies		
Studies (n)	-	3
Cases (total number)	-	1234
RR (95%CI)	-	1.22 (0.95-1.56)
Heterogeneity (I^2, p-value)	-	0%, 0.81
P value Egger test	-	-
Stratified analysis		
Histological type	**Adenocarcinoma (AC)**	**Squamous cell carcinoma (SCC)**
Studies (n)	3	2
Cases (total number)	912	322
RR (95%CI)	0.97 (0.79-1.20)	1.40 (1.04-1.89)
Heterogeneity (I^2, p-value)	6.4%, 0.34	0%, 0.92

Table 29 Red and processed meat intake and oesophageal cancer risk. Results of meta-analyses and pooled analyses published after the 2005 SLR

Author, Year	Number of studies	Total number of cases	Studies country, area	Outcome	Comparison	RR (95%CI)	P trend	Heterogeneity (I^2, p value)
Meta-analyses								
Zhu, 2014	15 studies (3 cohorts*, 12 case-control)	3545 (2008 SCC 1537 AC)	China, Italy, Iran, Ireland, The Netherlands, Paraguay, Switzerland, United States, Uruguay, Europe	Incidence, oesophageal cancer	High vs low Cohorts Case-control All studies	 1.22 (0.89-1.68) 1.78 (1.30-2.44) 1.55 (1.22-1.96)	 - - -	 40.9%, 0.12 68.3%, <0.001 63.6%, <0.001
	10 studies (2 cohorts, 8 case-control)			SCC	Cohorts Case-control All studies	1.54 (1.04-2.27) 2.01 (1.28-3.16) 1.86 (1.31-2.66)	-	47%, 0.15 78.5%, <0.001 72.6%, <0.001
	7 studies (3 cohorts, 4 case-control)			AC	Cohorts Case-control All studies	1.09 (0.84-1.41) 1.42 (1.02-1.98) 1.20 (0.98-1.48)		30.0%, 0.23 0%, 0.73 1.9%, 0.42
Choi, 2013	27 studies (4 cohorts**, 18 case-control)	7489	Asia, Europe, South America, United States	Incidence, Oesophageal cancer	Per 100 g/day Cohorts (3 studies) High vs low Cohorts Case-control All studies	1.05 (0.91-1.21) 1.26 (1.00-1.59) 1.44 (1.16-1.80) 1.38 (1.17-1.64)	-	0.2%, 0.42 35.3%, 0.15 72.8%, <0.01 67.1%, <0.01
	9 studies			SCC AC	High vs low	1.55 (1.10-2.17) 1.42 (1.02-1.98)	-	-

Huang, 2013	9 studies (3 cohorts*, 6 case-control)	2358	Ireland, Europe, The Netherlands, United States	Incidence, Oesophageal AC	Per 100 g/day Cohorts Case-control All studies High vs low Cohorts Case-control All studies	 1.14, no 95% CI 1.79, no 95% CI 1.45 (1.09-1.93) 1.11 (0.88-1.41) 1.56 (1.14-2.14) 1.31 (1.05-1.64)		 - - 61.8%, 0.02 0%, 0.45 8.1%, 0.36 18.9%, 0.27
Qu, 2013	16 studies (2 cohorts*, 14 case-control)	6499	Argentina, China, Italy, Iran, Japan, The Netherlands, Paraguay, Switzerland, United States, Uruguay, Europe	Incidence, Oesophageal or SCC	High vs low Cohorts Case-control All studies	 1.52 (1.03-2.25) 1.59 (1.24-2.04) 1.57 (1.26-1.95)		 0%, 0.35 60.6%, 0.002 56.0%, 0.003
	11 studies (2 cohorts, 9 case-control)			Incidence, Oesophageal or SCC	Per 100 g/day Cohorts Case-control All studies	 1.31 (0.97-1.77) 1.43 (1.12-1.83) 1.40 (1.16-1.70)	-	 45.3%, 0.18 55.4%, 0.02 51.7%, 0.02
	7 studies			SCC	High vs low	1.42 (1.14-1.75)		6.6%, 0.38
Salehi, 2013	14 studies (2 cohorts*, 12 case-control)	2630 (1947 SCC 1339 AC)	Argentina , China, Ireland, Europe, Paraguay, Switzerland, Uruguay, USA,	Incidence, Oesophageal cancer	High vs low Dose-response (2 studies) Null association	1.40 (1.09-1.81)	-	0.001
	7 studies 6 studies			SCC AC	High vs low)	1.63 (1.00-2.63) 1.19 (0.98-1.44)		0.001 0.90

*All cohorts were identified and included in the present review. **One cohort (Yu, 1993) reported results on pork only and was reviewed in a separate section of the present report.

Table 30 Red and processed meat intake and oesophageal cancer risk. Main characteristics of studies included in the linear dose-response meta-analysis

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Inclusion/exclusion
Jakszyn, 2013 oes00864 Denmark,France,Germany,Greece,Italy,Netherlands,Norway,Spain,Sweden,UK	EPIC, Prospective Cohort, Age: 35-70 years, M/W	137/ 481 419 11 years	Cancer registry, health insurance records, active follow up and mortality registry	Questionnaire + recall	Incidence, AC	Unprocessed red meat Per 25 g/2000 kcal	1.00 (0.85-1.18)	Age, sex, BMI, educational level, fresh fruits and vegetables intake, smoking status, number of cigarettes smoked, processed red meat, time since quitting smoking, total energy intake, white meat	Exposure units rescaled, using mean energy intake estimated from the tertiles values in the publication
						75.93 vs 10.38 g/2000 kcal	1.00 (0.60-1.66) Ptrend: 0.91		
Keszei, 2012 oes00822 The Netherlands	NLCS, Case Cohort, Age: 55-69 years, M/W	252/ 4827 16.3 years 59/1928	Annual linkage to Netherlands cancer registry and network of histopathology and cytopathology (PALGA)	Validated FFQ	Incidence SCC, men	Red meat (beef, pork, minced meat, liver and other non-poultry meat)(raw weight) 145.9 vs 45.8 g/day Per 50 g/day	2.66 (0.94-7.48) Ptrend: 0.06 1.32 (0.95-1.84)	Age, BMI, education level, smoking status, intakes of fruit, vegetable, alcohol, non-occupational physical activity, cigarettes/day, smoking years, total energy intake, use of lower oesophageal sphincter	Exposure units rescaled, results by cancer types were combined using the method of Hamling, results by sex were combined using a fixed effect model
		114/1928			AC, men	145.9 vs 45.8 g/day Per 50 g/day	0.57 (0.28-1.19) Ptrend: 0.20 0.84 (0.67-1.07)		
		48/1995			SCC, women	115.9 vs 46.9	0.87 (0.42-1.79)		

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Inclusion/exclusion
						g/day	Ptrend: 0.73	relaxing medication	
						Per 50 g/day	0.97 (0.64-1.47)		
		31/1995			AC, women	115.9 vs 46.9 g/day	1.09 (0.44-2.75) Ptrend: 0.76		
						Per 50 g/day	0.96 (0.58-1.60)		
Cross, 2011 oes00827 USA	NIH- AARP, Prospective Cohort, Age: 50-71 years, M/W	845/ 494 979 10 years	Record linkage to state cancer registry databases.	Validated FFQ	Incidence SCC	Red meat and processed meat combined Per 10 g/1000kcal	1.06 (1.00-1.13) 1.79 (1.07-3.01) Ptrend: 0.02	Age, sex, BMI, calories intake, ethnicity, work - physical activity, alcohol drinking, fruit and vegetable intake, saturated fat intake, tobacco use, vigorous physical activity	Exposure units rescaled using mean energy estimated from quintile values in publication, distribution of person-years by quantiles, results by cancer types were combined using Hamling method
		215/							
		630/			AC	64.8 vs 10 g/1000 kcal	1.01 (0.98-1.06) 1.15 (0.84-1.57) Ptrend: 0.49		

Table 31 Red and processed meat intake and oesophageal cancer risk. Main characteristics of studies excluded from the linear dose-response meta-analysis

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Inclusion/exclusion
Li, 2013 oes00902 USA	NIH- AARP, Prospective Cohort, Age: 50-71 years, M/W, Retired	848/ 494 968 9.7 years	Cancer registry, death master file, national death index plus, postal service database	Validated FFQ, 124-item	Incidence, oesophageal cancer	aMED Diet scoring criteria <2.45 vs ≥2.45 oz	0.91 (0.68-1.21)	Age, sex, BMI, race, education, smoking, total energy intake, usual activity throughout the day, vigorous physical activity, other components in dietary index, and alcohol intake in SCC analysis only	Excluded, exposure was meeting dietary index criteria or not
		215/			SCC				
		633/			AC		0.96 (0.81-1.13)		(same study as Cross, 2011, OES00827)
Cross, 2007 oes00840 USA	NIH- AARP, Prospective Cohort, Age: 50-71 years, M/W	548/ 494 036 6.8 years	Record linkage to state cancer registry databases.	Validated FFQ	Incidence, oesophageal cancer	Red meat and processed meat 62.7 vs 9.8 g/1000kcal	1.51 (1.09-2.08) Ptrend:0.13	Age, sex, education, marital status, family history of cancer, race, BMI, smoking, vigorous physical activity, total energy intake, alcohol intake, fruit and vegetable consumption	Superseded by Cross, 2011 OES00827
González, 2006b oes00830 Denmark,France,Germany,Greece,Italy,Netherlands,Norway,Spain,Sweden,UK	EPIC, Prospective Cohort, Age: 35-70 years, M/W	65/ 465 586 6.5 years	Cancer registries, health insurance records, pathology rec & active follow up	FFQ, dietary questionnaires, food record	Incidence, AC	Red meat Per 50 g	1.13 (0.84-1.51)	Age, sex, centre, citrus fruit intake, education level, energy intake, height, leisure - physical activity, poultry, processed meat, vegetable intakes, weight, work - physical activity, alcohol intake, other fruits e, smoking intensity, tobacco use	Superseded by Jakszyn, 2013, OES00864
						Quantile 3 vs quantile 1	1.67 (0.75-3.72)		

Figure 35 RR estimates of oesophageal cancer by levels of red and processed meat intake

Figure 36 RR (95% CI) of oesophageal cancer for the highest compared with the lowest level of red and processed meat intake

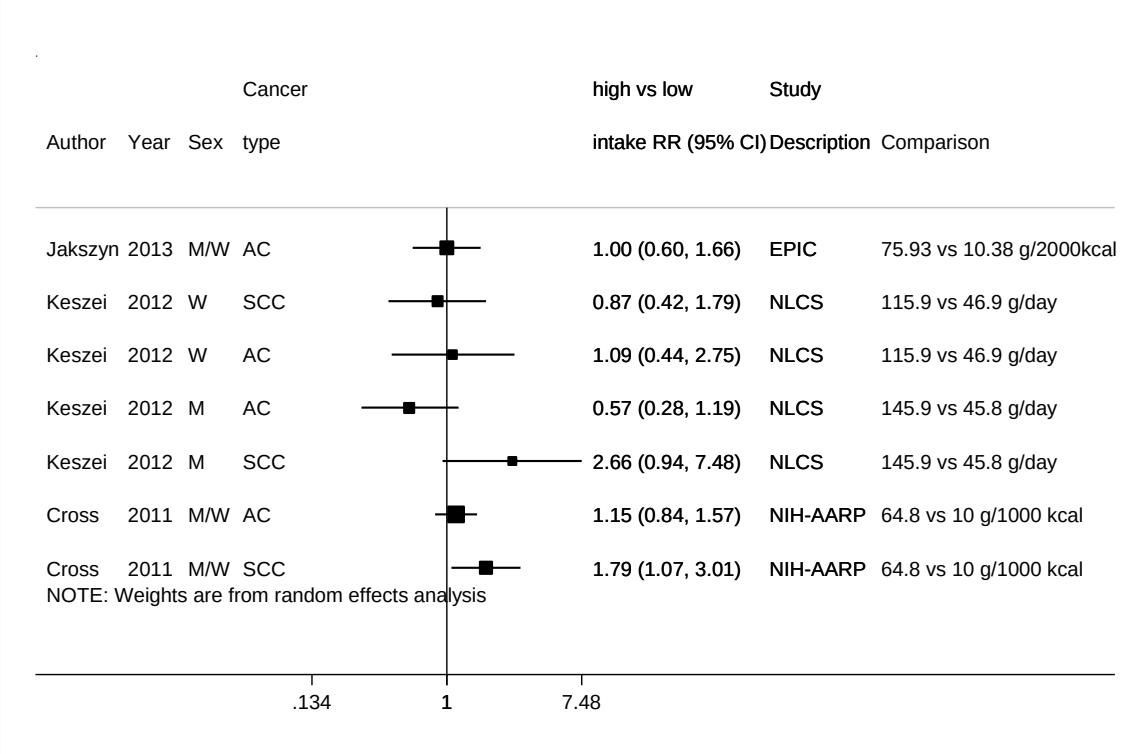


Figure 37 Relative risk of oesophageal cancer for 100 g/day increase of red and processed meat intake

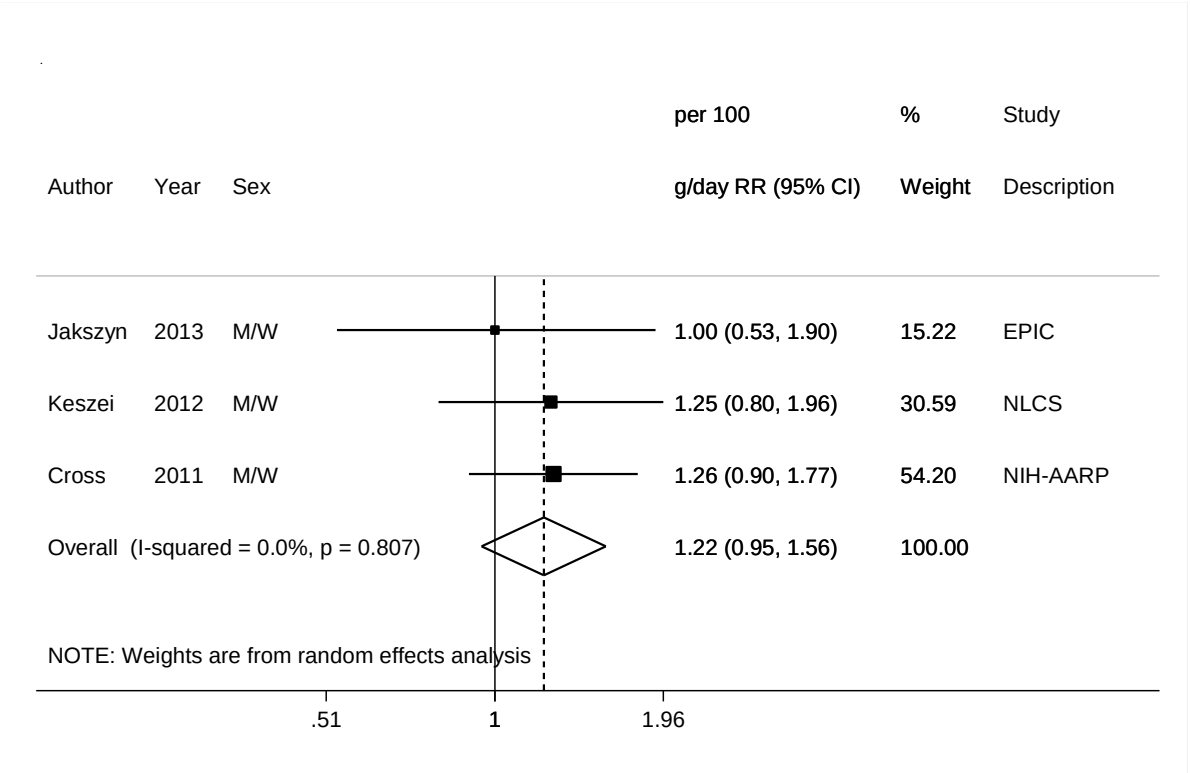
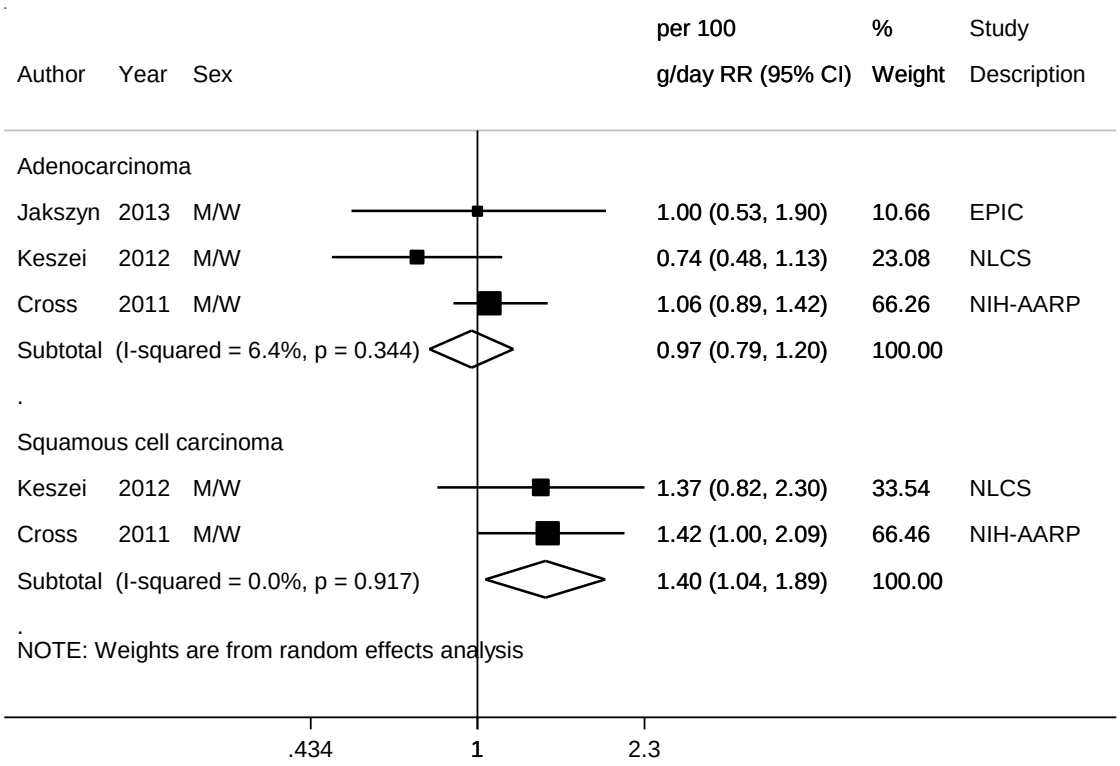


Figure 38 Relative risk of oesophageal cancer for 100g/day increase of red and processed meat intake by cancer type



2.5.1.3 Beef, pork, lamb

No dose-response meta-analysis was possible on specific red meat types. Three studies were identified (one study in the CUP).

In a Japanese study on cancer mortality (Iso, 2007) beef intake was not related to oesophageal cancer mortality in men and women. There was a borderline significant positive association with pork intake in men but not in women.

Kjaerheim, 1998 reported a non-significant positive association of pork or lamb intake with upper aerodigestive tract cancer risk, and a borderline significant positive association with beef.

Yu, 1993 reported a significant positive association of pork intake with oesophageal or cardia gastric cancer risk.

2.5.1.4 Poultry

Three studies (four publications) reported on poultry and oesophageal cancer risk (Jakszyn, 2013; Daniel, 2011; Iso, 2007; Gonzalez, 2006).

When comparing the highest versus the lowest intake, no significant associations were observed in one study that reported on chicken intake and oesophageal cancer in men and women (Iso, 2007), and in two studies on poultry intake and oesophageal adenocarcinoma

(Jakszyn, 2013; Daniel, 2011) (P trend: 0.24 and 0.92, respectively). One study reported a significant inverse trend for poultry intake and squamous cell carcinoma (Daniel, 2011) (P trend: 0.04).

2.5.2 Fish

Five studies (six publications) on fish and oesophageal cancer risk were identified (Li, 2013; Daniel, 2011; Fan, 2008; Iso, 2007; Kinjo, 1998; Hirayama, 1990). When comparing the highest versus the lowest intake, one study reported a significant inverse association (Fan, 2008) (P trend: 0.04), one reported a significant positive association (Hirayama, 1990) and two studies reported non-significant associations (Iso, 2007; Kinjo, 1998) with oesophageal cancer. One study reported non-significant associations with oesophageal adenocarcinoma (P trend: 0.06) and squamous cell carcinoma (Daniel, 2011) (P trend: 0.84).

Two other studies reported non-significant associations of fish intake with risk of upper aerodigestive tract cancers (Kjaerheim, 1998; Chyou, 1995; P trend: >0.5 and 0.47, respectively).

3 Beverages

3.6 Hot drinks

3.6.1 Coffee

Randomised controlled trials

No randomised controlled trials were identified.

Cohort studies

Summary

Main results:

Five studies (1 144 cases) were included in the dose-response meta-analysis. Coffee consumption was not significantly associated with oesophageal cancer risk. No significant associations were observed in the limited number of studies on oesophageal SCC and adenocarcinomas.

Moderate heterogeneity was observed. There were not enough studies to explore sources of heterogeneity. Visual inspection of the forest plots shows that the earlier studies, both in Japanese populations, reported inverse associations. More recent studies in North American and European populations reported no significant associations. There was no evidence of a significant publication or small study bias (p=0.48).

A study in Japanese American men (Chyou, 1995) reported non-significant (positive) relationship between coffee intake and the risk of squamous cell carcinoma of the upper aerodigestive tract (study not included in the dose-response analysis).

Sensitivity analyses:

The summary RRs ranged from 0.91 (95% CI=0.80-1.05) when EPIC (Zamora-Ros, 2014) was omitted to 0.98 (95% CI=0.92-1.04) when the JACC (Iso, 2007), the only study reporting on cancer mortality, was omitted.

Study quality:

Loss to follow-up was low in most studies. Cancer outcome was confirmed using death certificates (Iso, 2007), a combination of methods (Zamora-Ros, 2014) or cancer registries in all remaining studies.

All studies used FFQ or a combination of methods (Zamora-Ros, 2014) to assess coffee intake. Intake was assessed in ml/day (Zamora-Ros, 2014), times or occasions per day/week/month (Iso, 2007), cups/day or as “never”, “occasionally”, and ≥1 cup/day (≥150ml) (Naganuma, 2008). All were expressed as cups/day in order for the dose-response meta-analysis. In one Norwegian study (Tverdal, 2011) the highest category of coffee intake was nine or more cups/day of coffee, much higher than the top intake in the other studies.

All studies included in the dose-response analysis were adjusted for age, sex, BMI and smoking habits except the study on mortality (Iso, 2007) that was only adjusted for age and study area.

Table 32 Coffee intake and oesophageal cancer risk. Number of studies in the CUP SLR

	Number
Studies identified	6*
Studies included in forest plot of highest compared with lowest exposure	5
Studies included in linear dose-response meta-analysis	5
Studies included in non-linear dose-response meta-analysis	Not enough studies

Note: Include cohort, nested case-control and case-cohort designs. * Include one study that reported on upper aerodigestive tract cancers.

Table 33 Coffee and oesophageal cancer risk. Summary of the linear dose-response meta-analysis in the 2005 SLR and CUP

	2005 SLR	**CUP**
Increment unit used	No meta-analysis	1 cup/day
All studies		
Studies (n)	-	5
Cases (total number)	-	1144
RR (95%CI)	-	0.93 (0.85-1.02)
Heterogeneity (I^2, p-value)	-	49.2%, 0.10
P value Egger test	-	0.48
Stratified analysis		
Histological type	**Adenocarcinoma (AC)**	**Squamous cell carcinoma (SCC)**
Studies (n)	2	3
Cases	447	393
RR (95%CI)	0.96 (0.90-1.04)	1.02 (0.89-1.15)
Heterogeneity (I^2, p-value)	3.5%, 0.31	49.8%, 0.14

Table 34 Coffee and oesophageal cancer risk. Results of meta-analyses and pooled analyses published after the 2005 SLR

Author, Year	Number of studies	Total number of cases	Studies country, area	Outcome	Comparison	RR (95%CI)	P trend	Heterogeneity (I^2, p value)
Meta-analyses								
Zheng, 2013	17 studies (5 cohorts, 12 case-control)		Asia, Europe, United States, South America	Incidence OC All	Highest vs. non/lowest	0.88(0.76-1.01)		38.4%, 0.06
					Per 2 cups/day	1.00 (0.89-1.12		
				Case-control studies	Highest vs. non/lowest	0.88 (0.74-1.04)		44.8%, 0.05
				Cohort studies		0.88 (0.65-1.19)		31.3%, 0.21
Turati, 2011	7 studies (1 cohort - MCS II, 6 case-control)	2117 ESCC cases	Asia, Europe, United States, South America	Incidence SCC	Highest vs. lowest drinking	0.87 (0.65-1.17)		74.6%, 0.001
				SCC Case-control studies		0.92 (0.67-1.27)		
		415 EAC cases		AC Case-control studies		1.18 (0.81-1.71)		43.7%, 0.17
Yu, 2011	Not specified			Incidence OC	Highest vs. lowest	0.55 (0.37-0.74)		

Table 35 Coffee intake and oesophageal cancer risk. Main characteristics of studies included in the linear dose-response meta-analysis

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Missing data derived for analyses
Zamora-Ros, 2014 oes00893 Denmark,France, Germany,Greece, Italy,Netherlands, Norway,Spain, Sweden,UK	EPIC, Prospective Cohort, Age: 35-70 years, M/W	339/ 442 143 11.1 years	Cancer and pathology registry, active follow up, health insurance record, mortality registry, and contact of participants or next-of-kin	Country-specific validated dietary questionnaires	Incidence, oesophageal cancer All	>477 vs. <150 ml/day Per 100 ml/day	0.84 (0.59-1.20) Ptrend: 0.46 0.99 (0.95-1.02)	Age, sex, centre, education, BMI, energy intake, fruit & vegetables, tea, red and processed meat, smoking status, physical activity, all cancer and SCC adjusted for alcohol	RR rescaled to cups/day using 200ml cup as standard size
		211/ 128/			Men Women	Per 100 ml/day	0.97 (0.93-1.01) 1.01 (0.96-1.07)		
		142/			AC	>477 vs. <150 ml/day Per 100 ml/day	1.15 (0.66-1.98) Ptrend: 0.57 1.00 (0.95-1.05)		
		174/			SCC	>477 vs. <150 ml/day Per 100 ml/day	0.66 (0.40-1.07) Ptrend: 0.13 0.97 (0.93-1.01)		
Tverdal, 2011 oes00867 Norway	NCVSC, Prospective Cohort, Age: 40-45 years, M/W	96/ 389 624 14.4 years	Cancer registry	Questionnaire	Incidence, SCC	9+ vs. 1-4 cups/day Per 1 cup/day	0.97 (0.50-1.88) 1.06 (0.82-1.36)	Sex, BMI, education, smoking	For highest vs lowest plot Hamling's method was used to calculate RRs using the lowermost category as reference
Ren, 2010 oes00814 USA	NIH- AARP, Prospective Cohort, Age: 50-71 years,	305/ 481 563 6 years	Linkage of the cohort with database to state cancer registries	124-item FFQ	Incidence, AC	>3 vs. <1 cup/day	0.81 (0.57-1.16) Ptrend: 0.14	Age, sex, BMI, ethnicity, tobacco use, alcohol intake, education,	Hamling's method was used to combine RRs for EAC and ESCC
		123/			Incidence, SCC		1.53 (0.83-2.82) Ptrend: 0.13		

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Missing data derived for analyses
	M/W							physical activity, vigorous physical activity, intakes of fruit, vegetable, white meat, red meat, total energy	cancer, distribution of person-years by exposure categories, mid-points of exposure categories
Naganuma, 2008 oes00866 Japan	MCS II, Prospective Cohort, Age: 40-64 years, M/W	112/ 38 679 12.8 years	Cancer registry	FFQ	Incidence, oesophageal cancer (>80% SCC)	≥1 cup/day vs. never	0.60 (0.37-0.97) Ptrend: 0.05	Age, sex, BMI, cigarette smoking, green tea intake, alcohol intake, fruit and vegetable intake	Mid-points of exposure categories
Iso, 2007 oes00847 Japan	JACC, Prospective Cohort, Age: 40-79 years, M/W	143/ 105 500 15 years 26/	Date and cause of death annually or biannually confirmed with authorities authorization	Validated FFQ, 39-item	Mortality, oesophageal cancer	≥2 times/day vs. ≤2 times/month	Men: 0.52 (0.33-0.83) Women: 0.17 (0.02-1.30)	Age, area of study	Mid-points per exposure category, RRs for men and women were combined using fixed effect model

Table 36 Coffee intake and oesophageal cancer risk. Main characteristics of studies excluded from the linear dose-response meta-analysis

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Reasons for exclusion
Chyou, 1995 oes00128 USA	HHP, Prospective Cohort, M, Japanese residents of Hawaii	92/ 7 995 24 years	Cancer registry/hospital records	FFQ, 24-hour diet recall history	Incidence, upper aerodigestive tract, SCC	≥5 vs. ≤1 servings/week	1.44 (0.63-3.32) Ptrend: 0.44	Age, alcohol consumption, smoking habits	Excluded, combined cancer sites

Figure 39 RR estimates of oesophageal cancer by levels of coffee intake

Figure 40 RR (95% CI) of oesophageal cancer for the highest compared with the lowest level of coffee intake

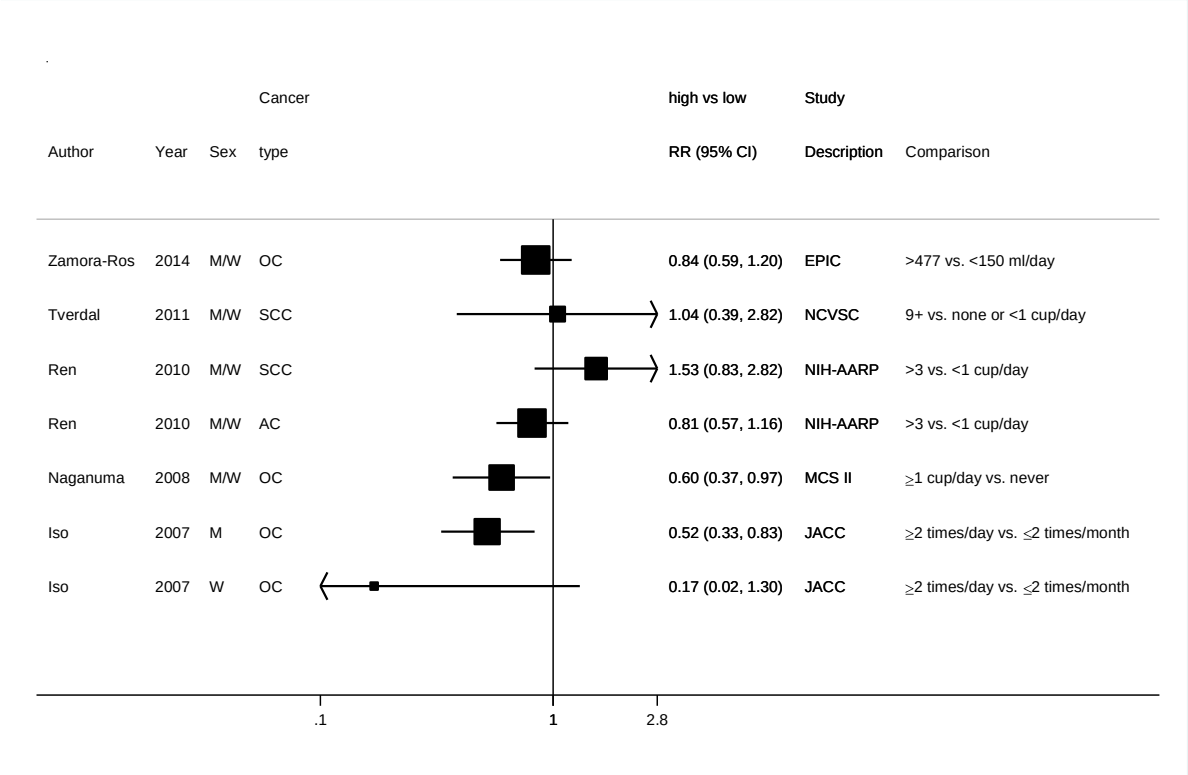


Figure 41 Relative risk of oesophageal cancer for 1 cup/day increase of coffee intake

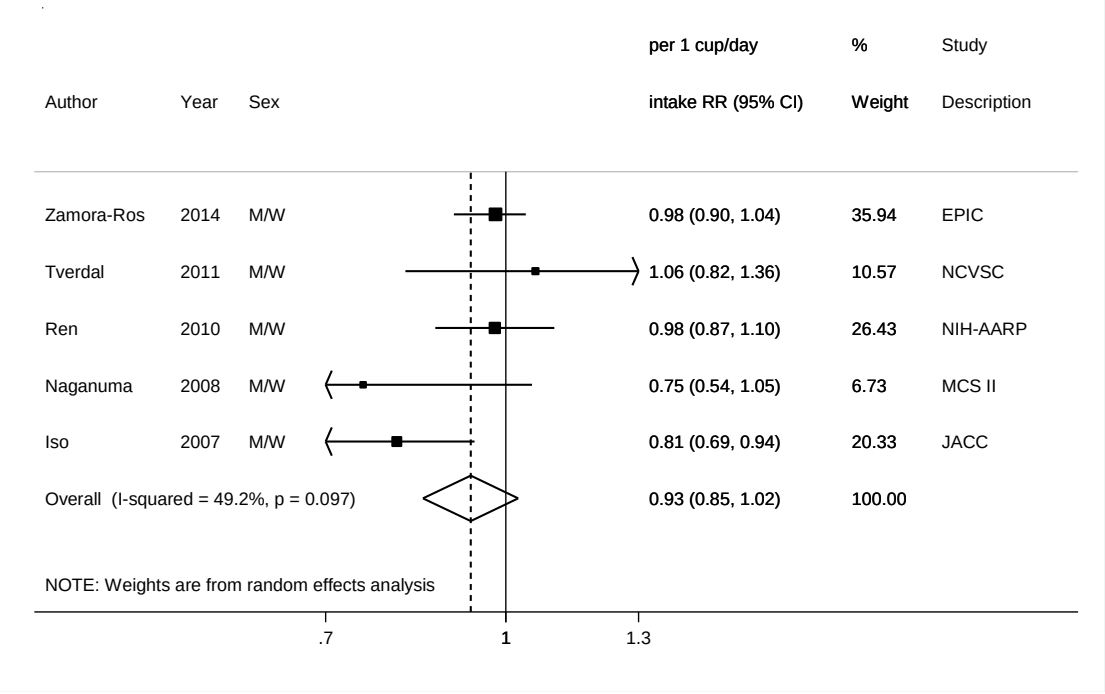
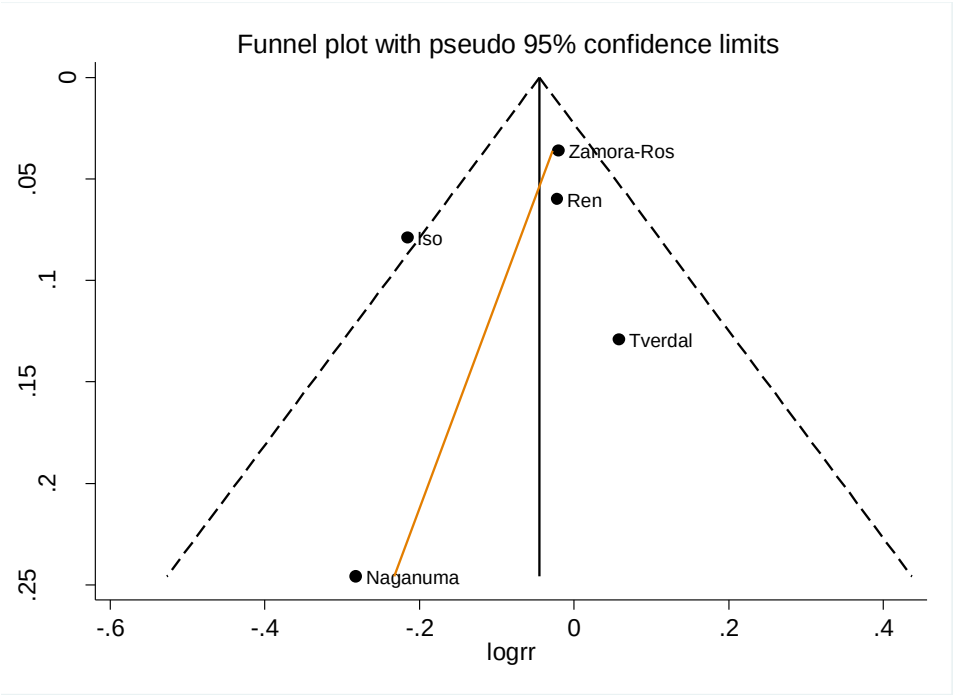
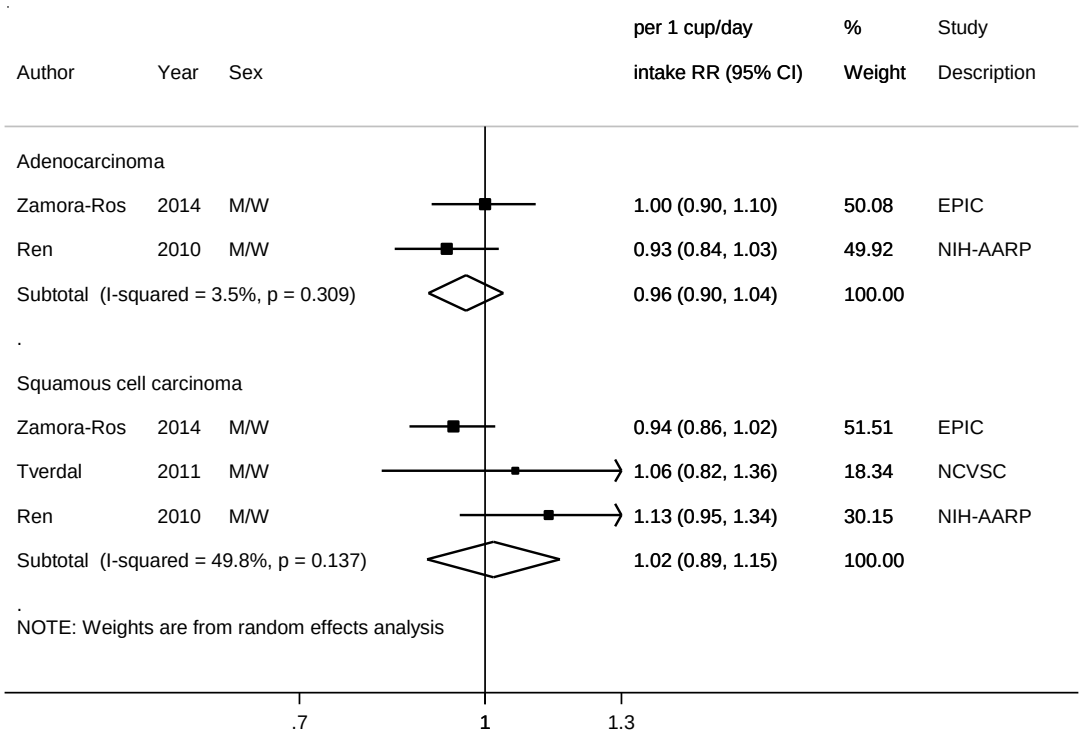


Figure 42 Funnel plot of studies included in the dose response meta-analysis of coffee intake and oesophageal cancer



Egger's test p=0.48

Figure 43 Relative risk of oesophageal cancer for 1 cup/day increase of coffee intake by cancer type



3.6.3 Mate

No cohort studies were identified in the CUP. A meta-analysis of five case-control studies in the Second Expert Report showed an summary RR estimate of 1.16 (95% CI=1.07-1.25) for one cup/day increase.

In 1991, the International Agency for Research of Cancer classified drinking hot mate as "probably carcinogenic to humans (Group 2A)" and mate as "not classifiable as to its carcinogenicity to humans (Group 3) (IARC Working Group, 1991). There was "limited evidence for carcinogenicity of hot mate drinking in humans;" "no data available on the drinking of cold mate;" and "no data on its carcinogenicity in experimental animals".

A published meta-analysis (end date of search April 5 2012) of nine case-control studies reported a RR estimate for ever vs never drinking mate of 2.57 (95% CI=1.66–3.98) (Andrici, 2013).

A published pooled analysis of two case-control studies, a 1988 to 2005 Uruguay study and a 1986 to 1992 multinational study in Argentina, Brazil, Paraguay, and Uruguay, including 1,400 cases and 3,229 controls -and included in the published meta-analysis (Andrici, 2013) - reported an adjusted RR estimate for SCC by ever compared with never use of mate of 1.60 (95% CI=1.2-2.2) (Lubin, 2014). The ORs increased linearly with the cumulative mate consumption. The strength of association increased with higher mate temperatures. The RR estimates for warm, hot and very hot mate consumption, compared to no consumption were 1.20 (95%: 0.8–1.7), 1.61 (95% CI: 1.2–2.2) and 2.15 (95%: 1.5–3.1) respectively (Ptrend<0.01)

3.6.4 High-temperature drinks

Summary of evidence from cohort studies relating to high-temperature drinks and oesophageal cancer.

One cohort study was identified in the CUP and three studies in the 2005 SLR. Only one study in China showed a significant increased risk of oesophageal cancer (mortality) with drinking tea hot compared with not hot.

Study	Cases	Outcome	Comparison	RR (95% CI)	Exposure
NIH-AARP Ren, 2010 USA	123	Incidence: SCC	≥ 1 cup/day vs. none	0.57 (0.30-1.07)	Hot tea
	305	Incidence AC		0.97 (0.67-1.41)	
NIT cohort Tran, 2005 China	1958	Incidence SCC	≥ 1 vs. 0 times/year	0.96 (0.87-1.07)	Hot liquid in summer
				0.95 (0.87-1.04)	Hot liquid in winter
Six Prefecture Cohort Kinjo, 1998 Japan	440	Mortality OC	Hot vs. not hot	1.50 (1.10-1.90)	Tea

HHP Chyou, 1995 Japanese in Hawaii, USA	92 35 cases were OC	Incidence UADT, SCC	Hot/boiling vs. cool/warm	1.44 (0.91-2.26)	24 hr recall of temperature of foods

One study did not adjust for smoking or alcohol (Tran 2005).

5 Dietary constituents

5.1.2 Dietary fibre

One cohort study reported on fibre intake and oesophageal cancer risk (IWHS; Kasum, 2002). Inverse association was observed for total fibre, total grain fibre, whole-grain fibre, and refined-grain fibre but no confidence intervals were given. The study was adjusted for age, smoking habits, alcohol consumption, and energy intake.

A published meta-analysis reported a significant inverse association with oesophageal adenocarcinoma (summary RR for highest vs lowest fibre intake: 0.66, 95% CI: 0.44-0.98, 8 studies) and a non-significant inverse association with oesophageal squamous cell carcinoma (RR: 0.61, 95% CI: 0.31-1.20, 5 studies) (Coleman, 2013). All studies included were case-control studies and there were evidence of high heterogeneity (I^2:83% and 87%, respectively, both $p<0.001$).

5.4.1 Total Alcohol (as ethanol)

Cohort studies

Summary

Main results:

Seventeen studies (6618 cases) were included in the dose-response meta-analysis. Significantly positive association was found between alcohol (as ethanol) consumption and oesophageal cancer risk. The association was observed for oesophageal squamous cell carcinomas and not for adenocarcinomas.

Six studies were excluded from the dose-response analyses, two of which reported risk estimates for combined sites of upper aerodigestive tract. Most of the excluded studies reported significant positive associations (Khaerheim, 1998; Chyou, 1995; Kono, 1987), two studies reported non-significant inverse associations of alcohol intake and oesophageal cancer (consumers vs. non-consumers in Tran, 2005 and daily vs. less than daily consumption in Yu, 1993) and a cohort of alcoholics people reported non-significant positive associations with oesophageal squamous cell carcinoma (Yokoyama, 2006).

Substantial heterogeneity was observed in analyses on oesophageal cancer but also in the meta-analyses on adenocarcinoma and SCC. Heterogeneity remained unexplained in stratified analysis. Visual inspection of the forest plot indicates that a substantial part of heterogeneity on the analysis on SCC is due to one study (Lindbland, 2005 see Study quality).

Sensitivity and stratified analyses:

High heterogeneity persisted in analysis on oesophageal cancer stratified by geographic location, years of follow-up, study size, year of publication, adjustment factors. No heterogeneity was observed in studies on women (four studies, overall positive association).

It was not possible to do stratified meta-analyses of studies on SCC due to low number of studies. After exclusion of one study identified as outlier in the funnel plot (Lindbland, 2005) the significant positive association with squamous cell carcinoma persisted and the heterogeneity was reduced (I^2: 39.3%; see *Study quality* below for comment on alcohol consumption assessment in this study) and the lack of association remained with adenocarcinomas (I^2:20.3%) (see Figure 54).

In a sensitivity analysis, the studies on squamous cell carcinomas were combined with the Asian studies on oesophageal cancer incidence (because SCC is the most frequent type in that geographic region). The combined RR (1.28 (95% CI=1.16-1.41; I^2=94.4%, p<0.001) was similar to the associations observed in studies that reported on SCC. There was evidence of substantial unexplained heterogeneity.

Non-linear dose-response meta-analysis:

There was significant evidence of non-linear dose-response association (p for non-linearity =0.03) for oesophageal cancer and ethanol intake. However, the curve looks linear in most of the intake range. The bubbles are highly dispersed in the plot. This is consistent with the high

heterogeneity observed in the linear dose response meta-analysis on oesophageal cancer (I^2:95.3%) that was mainly driven by the difference of association of alcohol intake with adenocarcinomas and squamous cell carcinomas.

A non-linear dose-response analysis was conducted combining the studies on oesophageal squamous cell carcinoma and the Asian studies on oesophageal cancer incidence. There was significant evidence of non-linearity (p=0.04). The increase is linear in most of the intake range and only at low intakes the dose-response slope is steeper. Most of the observations in the analysis were for intakes below 80 g/day. There were not enough studies on oesophageal adenocarcinoma with the data needed for non-linear dose-response meta-analyses.

Study quality:

Loss to follow-up was low in most studies. Cancer outcome was confirmed using cancer, death and pathology registries in most studies. Several studies did not differentiate oesophageal SCC from adenocarcinomas.

Alcohol intake was assessed by questionnaires or FFQ in most studies. However, in Lindblad, 2005, alcohol intake was obtained from a computerized database of patient records (GPRD) that was not specifically designed for dietary or alcohol intake assessment and could have provided less accurate information compared to dietary questionnaires. The reference category in this study included consumption of up to 2 units of alcohol per day and most of the study participants were in the two lowest categories of alcohol intake. Moreover, alcohol intake was unknown for 42% of the participants (and the histological type was unknown in 44% of the cases).

Alcohol consumption was converted to ethanol intake (g) using conversion units given in the publications. A standard conversion unit was applied in eight studies (Yaegashi, 2014; Hardikar, 2013; Kimm, 2010; Freedman, 2007b; Lindblad, 2005; Kasum, 2002; Kinjo, 1998; Boffetta, 1990).

In several studies, it was unclear if the category of non-drinkers included former drinkers; three studies did not include former drinkers in the reference category (Yaegashi, 2014, Weikert, 2009, Nakaya, 2005); the reference category included low alcohol consumers in two studies (Ishiguro, 2009 and Lindblad, 2005). Analyses were restricted to alcohol drinkers in Allen, 2009.

All studies included in the dose-response analysis were adjusted for age and sex. All studies on squamous cell carcinoma were adjusted for smoking and all studies on oesophageal adenocarcinoma were adjusted for BMI or WHR, apart from Yates, 2014 (70 cases). Only one study adjusted for history of gastro-oesophageal reflux (Lindbland, 2005). No studies were adjusted for ethnicity.

Table 37 Total alcohol intake and oesophageal cancer risk. Number of studies in the CUP SLR

	Number
Studies identified	24 (33 publications)*
Studies included in forest plot of highest compared with lowest exposure	21
Studies included in linear dose-response meta-analysis	17
Studies included in non-linear dose-response meta-analysis	15

*****Included two studies and another two publications reported results on upper aerodigestive tract cancers.

Table 38 Total alcohol (as ethanol) intake and oesophageal cancer risk. Summary of the linear dose-response meta-analysis in the 2005 SLR and CUP

	2005 SLR	**CUP**
Increment unit used	1 drink/week	10g/day
All studies		
Studies (n)	1*	17
Cases (total number)	71	6618
RR (95%CI)	1.26 (1.10-1.44)	1.24 (1.16-1.33)
Heterogeneity (I^2, p-value)	-	95.3%, <0.001
P value Egger test	-	0.001
Stratified analysis		
Sex	**Men**	**Women**
Studies (n)	11	4
RR (95%CI)	1.34 (1.22-1.47)	1.25 (1.14-1.37)
Heterogeneity (I^2, p-value)	94.8%, <0.001	0%, 0.72
Histological type	**Adenocarcinoma (AC)**	**Squamous cell carcinoma (SCC)****
Studies (n)	6	6
RR (95%CI)	1.00 (0.98-1.02)	1.25 (1.12-1.41)
Heterogeneity (I^2, p-value)	0.7%, 0.41	95.0%, <0.001
Outcome	**Incidence**	**Mortality**
Studies (n)	11	7
RR (95%CI)	1.22 (1.10-1.34)	1.35 (1.18-1.53)
Heterogeneity (I^2, p-value)	95.3%, <0.001	95.2%, <0.001

*Outcome in Kjaerheim, 1998 study was upper aerogastric tract cancer.
**RR estimates of "non adenocarcinoma oesophageal cancers" in Allen, 2009 were included in the analysis on SCC.

Other stratified analyses

Geographic area	**Asia**	**Europe**	**North America**
Studies (n)	9	4	4
RR (95%CI)	1.34 (1.19-1.49)	1.16 (1.01-1.33)	1.17 (1.07-1.28)
Heterogeneity (I^2, p-value)	94.5%, <0.001	95.1%, <0.001	51.4%, 0.10
Duration of follow-up	**5-<10 years**	**10-<15 years**	**≥15 years**
Studies (n)	4	6	6
RR (95%CI)	1.15 (0.99-1.34)	1.43 (1.29-1.58)	1.17 (1.08-1.27)
Heterogeneity (I^2, p- value)	84.0%, 0.01	81.6%, <0.001	90.8%, <0.001
Number of cases	**<500 cases**	**500-<1000 cases**	**≥1000 cases**
Studies (n)	14	1	2
RR (95%CI)	1.26 (1.19-1.32)	1.04 (1.01-1.07)	1.22 (0.84-1.75)
Heterogeneity (I^2, p-value)	70.1%, <0.001	-	98.7%, <0.001
Publication year	**<2000**	**2000-<2010**	**≥2010**
Studies (n)	2	8	7
RR (95%CI)	1.70 (0.91-3.16)	1.20 (1.08-1.33)	1.24 (1.09-1.41)
Heterogeneity (I^2, p-value)	93.7%, <0.001	95.1 %, <0.001	93.8%, <0.001
Adjustment for:			
Socioeconomic status	**Not adjusted**	**Adjusted**	
Studies (n)	8	9	
RR (95%CI)	1.20 (1.10-1.30)	1.28 (1.18-1.38)	
Heterogeneity (I^2, p-value)	96.7%, <0.001	76.7%, 0.001	
Smoking			
Studies (n)	3	14	
RR (95%CI)	1.24 (1.00-1.53)	1.25 (1.15-1.36)	
Heterogeneity (I^2, p-value)	97.4%, <0.001	94.8%, <0.001	
Body fatness			
Studies (n)	7	10	
RR (95%CI)	1.34 (1.17-1.54)	1.20 (1.09-1.31)	
Heterogeneity (I^2, p-value)	95.3%, <0.001	94.6%, <0.001	
Total energy intake			
Studies (n)	14	3	
RR (95%CI)	1.26 (1.17-1.35)	1.15 (1.06-1.25)	
Heterogeneity (I^2, p-value)	96.1%, <0.001	0%, 0.66	
Physical activity			

Studies (n)	14	3	
RR (95%CI)	1.24 (1.15-1.32)	1.27 (1.06-1.52)	
Heterogeneity (I^2, p-value)	95.8%, <0.001	82 %, 0.004	
Comorbidities			
Studies (n)	15	2***	
RR (95%CI)	1.27 (1.18-1.37)	1.08 (0.93-1.26)	
Heterogeneity (I^2, p-value)	91.9%, <0.001	87.1%, 0.005	

****Lindblad, 2005 adjusted for reflux, Yi, 2010 adjusted for history of chronic disease

Table 39 Total alcohol intake and oesophageal cancer risk. Results of meta-analyses and pooled analyses published after the 2005 SLR

Author, Year	Number of studies	Total number of cases	Studies country, area	Outcome	Comparison	RR (95%CI)	P trend	Heterogeneity (I^2, p value)
Meta-analyses								
Bagnardi, 2013	9 cohorts, 18 case-control studies	3322	Europe, North America, Asia	SCC	Light drinkers (up to 1 drink/day) vs. non-drinkers	1.30 (1.09-1.56)		>50%
	9 cohorts					1.34 (0.96-1.87)		
Prabhu, 2013	18 cohort and population-based case-control studies	-	China, Korea, Japan, Europe	SCC	>200 g alcohol/week vs. never	4.65 (3.61-5.99)		71%, <0.001
	5 cohorts					3.51 (3.09-4.00)		0%, 0.55
Pooled-analysis								
Freedman, 2011* (BEACON Consortium)	9 case-control, 2 cohort studies	2064	Europe, North America, Australia	AC	≥7 drinks/day vs. none	0.97 (0.68-1.36)	0.21	
(Cohorts: Kaiser Permanente Multiphasic Health Checkup Study, NIH-AARP)	5 case-control, 2 cohort studies	1016		SCC		9.62 (4.26-21.71)	<0.0001	

***** Kaiser-Permanente Multiphasic Health and National Institutes of Health AARP Diet and Health (NIH-AARP) study are included in the CUP analyses

Table 40 Total alcohol intake and oesophageal cancer risk. Main characteristics of studies included in the linear dose-response meta-analysis

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Missing data derived for analyses
Yaegashi, 2014 oes00892 Japan	JACC study, Prospective Cohort, Age: 40-79 years, M	196/ 42 408 20 years	Date and cause of death annually or biannually confirmed with authorities authorization	Self-administered questionnaire	Mortality, oesophageal cancer	3 + units/day vs. non-drinkers	4.62 (2.46-8.68), Ptrend: 0.02	Age, centre, fruit & vegetable consumption	Units converted to ethanol (g) using 22g ethanol per unit, mid-points of exposure categories
Yates, 2014 oes00894 UK	EPIC-Norfolk, Prospective Cohort, Age: 39-74 years, M/W	66/ 24 066 15 years	Cancer and pathology registries	FFQ	Incidence, AC	>28 units/week vs. no alcohol	0.83 (0.22-3.18), Ptrend: 0.09	Age, gender	Superseded by Weikert, 2009 Used in analysis on adenocarcinoma: calculated distribution of person-years and mid-points by exposure categories, units converted to ethanol (g) using 7.9g ethanol per unit
Hardikar, 2013 oes00875 USA	SBES, Prospective Cohort, Age: 30- years, M/W, Barretts's oesophagus patients	45/ 411 6.2 years	Biopsy	Structured personal interview	Incidence, AC	>3 vs. 0 drinks/day	1.00 (0.37-2.69)	Age, cigarette smoking, NSAID use, gender, waist to hip ratio	Distribution of person-years mid-points by exposure categories. Drinks converted to ethanol (g) using a standard conversion of 12.5g ethanol per drink
Shen, 2013 oes00881 China	CECS, Prospective Cohort, Age: 65- years, M/W	115/ 66 820 10.5 years	Hospital records and death register	Questionnaire	Mortality, oesophageal cancer	>3 units/day vs. never	6.63 (2.92-15.02)	Age, sex, BMI, health status, smoking status, education, exercise, housing, monthly expenditure	Distribution of person-years and mid-points by exposure categories. Units converted to ethanol (g) using 10g/unit.
		69/			Men		5.49 (2.23-13.48)		

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Missing data derived for analyses
Yang, 2012 oes00807 China	CNRPCS, Prospective Cohort, Age: 40-79 years, M	848/ 218 189 15 years	Annual follow up by trained staff, death certificate and symptoms described by family members	Interview	Mortality, oesophageal cancer	≥700 g/week vs. non-drinkers	1.63 (1.12-2.39)	5-yr age-group, geographic area, education, smoking	Distribution of person-years by exposure categories, mid-points of exposure categories, ethanol intake in g/week converted to g/day
Kimm, 2010 oes00868 Korea	KCPS, Prospective Cohort, Age: 30-93 years, M	1 383/ 782 632 14 years	Cancer registry, hospital admission and death certificate	Questionnaire	Incidence, oesophageal cancer	≥100 g/day vs. non-drinker	4.10 (2.90-5.80)	Age, BMI, aspartate aminotransferase, exercise	Distribution of person-years by exposure categories, mid-points of exposure categories. Soju equivalents converted to ethanol (g)
		996/			Mortality, oesophageal cancer		3.40 (2.20-5.30)		
Steevens, 2010 oes00816 Netherlands	NLCS, Case Cohort, Age: 55-70 years, M/W	107/ 4 214 16.3 years	Annual record linkage to the Netherlands cancer and pathology registers	Validated FFQ	Incidence, SCC	≥30 g/day vs. abstainer	4.61 (2.24-9.50) Ptrend:0.001	Age, sex, BMI, education level, energy intake, smoking status, fish intake, fruit and vegetable intake, smoking dose and duration	-
						Per 10 g/day	1.32 (1.19-1.45)		
		59/			Men		1.28 (1.15-1.43)		
		48/			Women		1.62 (1.31-2.00)		
		145/			Incidence, AC	≥30 g/day vs. abstainer	1.04 (0.54-2.02) Ptrend: 0.93		
						Per 10 g/day	1.01 (0.90-1.14)		
		114/			Men		0.99 (0.88-1.12)		
		31/			Women		1.23 (0.93-1.64)		
Yi, 2010 oes00818 Korea	KCS, Prospective Cohort,	19/ 6 291 20.8 years	Death records/calls or follow up	Interview and questionnaire	Mortality, oesophageal cancer	High ≥540 g/week vs. none	5.62 (1.45-21.77) Ptrend:0.09	Age, BMI, education level, smoking habits,	Distribution of person-years by exposure categories, mid-points of

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Missing data derived for analyses
	Age: 55- years, M/W		visits/death certificates		Men			ginseng intake, history of chronic disease, exposure to pesticide	exposure categories
Allen, 2009 oes00848 UK	MWS, Prospective Cohort, Age: 55 years, W	534/ 1 280 296 7.2 years	National health service central registers	Questionnaire	Incidence, oesophageal cancer, drinkers only	Per 10 g/day	1.22 (1.08-1.38)	Age, BMI, physical activity, socio-economic status, region of residence, smoking, use of HRT, use of oral contraception	Drinks converted to ethanol (g) using 10 g for one drink in analysis on adenocarcinomas
		395/			Non-adenocarcinoma (RRs used in SCC analysis)	≥15 vs. ≤2 drinks/week	2.99 (2.24-4.00)		
		226/			AC		0.79 (0.39-1.59)		
Ishiguro, 2009 oes00870 Japan	JPHC, Prospective Cohort, M	215/ 44 970 14 years maximum	Cancer registry, death certificate and active patients notification of local hospital	Self-administered questionnaire	Incidence, SCC	≥300+ g/week vs. nondrinkers	4.64 (2.88-7.48) Ptrend: 0.001	BMI, flushing response, preference for hot foods and drinks, smoking status, study area, age at baseline	Mid-points of exposure categories
Weikert, 2009 oes00869 Denmark, France, Germany, Italy, Netherlands, Spain, Sweden, UK	EPIC, Prospective Cohort, Age: 35-70 years, M/W	52/ 98 505 8.6 years	Cancer registry, health insurance records, active follow up and mortality registry	Mainly FFQs (88-266 food items)	Incidence, SCC Men	Per 10 g	1.22 (1.15-1.29)	BMI, smoking, education, fruit and vegetable intake	RRs for men and women combined using fixed effect model
		35/ 172748			Women	Per 10 g	1.31 (1.12-1.53)		

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Missing data derived for analyses
Fan, 2008 oes00871 China	SCStudy, Prospective Cohort, Age: 45-64 years, M	101/ 18 244 15.5 years	Cancer registry, Shanghai vital statistics office, medical history	Face-to-face interview using a structured questionnaire	Incidence, oesophageal cancer	80+ g/day vs. non-drinkers	4.65 (2.31-9.36)	Age at interview, BMI, fresh fruit, number of years of smoking, year of interview, education, fresh vegetables, neighbourhood of residence at recruitment, preserved food intake	Mid-points of exposure categories
Freedman, 2007b oes00820 USA	NIH- AARP, Prospective Cohort, Age: 50- years, M/W	97/ 474 606 4.6 years	Record linkage to state cancer registry databases.	Validated FFQ	Incidence, SCC	>3 vs. >0-1 drinks/day	4.93 (2.69-9.03) Ptrend:<0.0001	Age sex, BMI, education level, fruit and vegetable consumption, smoking status, total energy, usual physical activity, vigorous physical activity	Drinks converted to ethanol (g) using 13g of ethanol per drink, distribution and mid-points of person-years. Hamling's method used to calculate RRs using the lowermost category as reference, and to combine RRs for SCC and AC cancers
		205/			AC		1.10 (0.69-1.74) Ptrend: 0.68		
Lindblad, 2005 oes00796 UK	GPRDC, Nested Case Control, M/W	534/	GPs records	Interviewed by GP	Incidence, oesophageal cancer	>34 vs. 0-2 units/day	1.76 (1.16-2.66)	Age, sex, BMI, smoking habits, calendar year, reflux symptoms	Units converted to ethanol (g) using 7.9g of ethanol per unit mid-points of exposure categories
		87/			AC		1.25 (0.61-2.55)		
		178/			SCC		3.39 (1.28-8.99)		
Nakaya, 2005 oes00900 Japan	MCS II, Prospective Cohort,	52/ 21 201 7.6 years	Miyagi prefectural cancer registry	Self-administered questionnaire	Incidence, oesophageal cancer	≥22.8 g/day vs. never-drinkers	3.2 (1.1-8.9) Ptrend: 0.004	Age, smoking, education, consumption of	Mid-points of exposure categories

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Missing data derived for analyses
	Age: 40-64 years, M							juice, spinach, carrot or pumpkin, tomato	
Kasum, 2002 oes00033 USA	IWHS, Prospective Cohort, Age: 55-69 years, Post-menopausal women	21/ 34 351 14 years	Health Registry of Iowa	127-item FFQ	Incidence, oesophageal cancer	≥2 vs. 0 drinks/day	1.90	Age, energy intake, smoking, intake of grains, vegetables	Mid-points of exposure categories, confidence intervals, drinks converted to ethanol (g) using a standard conversion of 12.5g ethanol per drink
Kinjo, 1998 oes00350 Japan	SPCJ, Prospective Cohort, Age: 40- years, M/W	440/ 220 272 14 years	Annually by vital statistics kept at each public health centre	Questionnaire	Mortality, oesophageal cancer	>4 times/week or more vs. none	2.10 (1.60-2.80) Ptrend: <0.001	Age, sex, area of residence, occupation, green-yellow vegetables, tea intake, smoking	Distribution of person-years by exposure categories, mid-points of exposure categories, intake in times converted to ethanol (g) using a standard conversion of 12.5g ethanol per time
		328/			Men		2.40 (1.80-3.30) Ptrend: <0.001	Age, area of residence, occupation	
		112/			Women		2.00 (0.60-6.20) Ptrend: 0.57		
Boffetta, 1990 oes00888 USA	CPS I, Prospective Cohort, Age: 40-59 years, M	185/ 276 802 12 years	Death certificate and medical records	Questionnaire	Mortality, oesophageal cancer	6+ drinks/day vs. non-drinkers	5.79 (3.44-9.74)	Age, education, smoking	Mid-point of highest exposure category, drinks converted to ethanol (g) using a standard conversion of 12.5g ethanol per drink

Table 41 Total alcohol intake and oesophageal cancer risk. Main characteristics of studies excluded from the linear dose-response meta-analysis

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Reasons for exclusion
Li, 2013 STM80193 USA	NIH- AARP, Prospective Cohort, Age: 50-71 years, M/W	215/ 494 968 9.7 years	Cancer registry, death master file, national death index plus, postal service database	Validated FFQ	Incidence, SCC	<5 or >25 vs. 5-25g/day	0.79 (0.56-1.11)	Age, sex, BMI, race, education, modified total score, smoking, total energy intake, usual activity throughout the day, vigorous physical activity	Only two levels of exposure, Freedman, 2007b used instead
		633/			AC		0.99 (0.83-1.19)		
Kim, 2010 oes00810 Korea	HEC 2000, Prospective Cohort, Age: 40-69 years, M	213/ 1 341 393 5 years	National death certificate	Interview during health examinations	Mortality, oesophageal cancer Men	≥90 g/day vs. non-drinkers	3.33 (2.17-5.12), Ptrend: <0.0001	Age, regular exercise, >=3 times/week, BMI, diastolic and systolic blood pressure, fasting blood sugar, residential (urban/rural), smoking status	Superseded by Kimm, 2010 (different cohort name but study population overlaps)
Ozasa, 2007 oes00836 Japan	JACC, Prospective Cohort, M/W	117/ 12 years	Date and cause of death annually or biannually confirmed with authorities authorization	Interview	Mortality, oesophageal cancer Men	81+ ml/day vs. rare/none	4.63 (2.28-9.37)	Age, study area	Superseded by Yaegashi, 2014
		23/			Women	<54 ml/day vs. rare/none	2.06 (0.74-5.73)		Only two categories, used in HvL analysis only
Ishikawa, 2006 oes00861	MCS I & II, Prospective Cohort,	78/ 26 723 9 years	Miyagi prefectural cancer registry	Self-administered questionnaire	Incidence, oesophageal cancer	Daily vs. never or occasionally	2.73 (1.55-4.81) Ptrend: <0.001	Age, cigarette smoking, intake of black tea, green tea	Included in HvL analysis, only two categories; Nakaya,

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Reasons for exclusion
Japan	Age: 40- years, M	(cohort I), 7.6 years (cohort II)						and coffee	2005 used in dose-response meta-analysis
Yokoyama, 2006 oes00860 Japan	JAMS, Prospective Cohort, Age: 40-79 years, M, Alcoholics	33/ 805 31 months	Endoscopic diagnosis	Questionnaire	Incidence, SCC	≥100 vs. ≤99 g/day	1.52 (0.75-3.09)	Age	Included in HvL analysis, only two categories
Sakata, 2005 oes00802 Japan	JACC, Prospective Cohort, Age: 40-79 years, M	76/ 42 578 11 years	Date and cause of death annually or biannually confirmed with government authorization	Questionnaire	Mortality, oesophageal cancer	>3 units/day vs. non-drinkers	6.39 (2.54-16.12) Ptrend: 0.03	Age, clinic site	Superseded by Yaegashi, 2014
Tran, 2005 oes00804 China	NIT Cohort, Prospective Cohort, Age: 40-69 years, M/W	1958/ 29 584 15 years	Monthly contact by either village health workers or interviewers, and cancer diagnoses verified by senior diagnosticians	Interviewed using not validated questionnaire	Incidence, SCC	Any in previous 12 months vs. no consumption	0.92 (0.82-1.03)	Age, sex	Included in HvL analysis, only two categories
Kjaerheim, 1998 oes00130 Norway	Norwegian Men UADT, Prospective Cohort,	71/ 10 960 25 years	Cancer registry	Questionnaire	Incidence, upper aerogastric tract cancer	4-7 vs. never or 1 time/week	3.2 (1.6-6.1) Ptrend: 0.01	Age, tobacco use, consumption of bread, oranges	Excluded, cancer is not only oesophageal cancer

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Reasons for exclusion
	Age: average 59 years, M								
Chyou, 1995 oes00128 USA	HHP, Prospective Cohort, Age: 45- years, M, Japanese residents in Hawaii	92/ 7 995 24 years	Cancer registry/hospital records	FFQ, 24-hour diet recall history	Incidence, upper aerodigestive tract cancer	25+ oz/month vs. non-drinker	4.67 (2.62-8.32), Ptrend:<0.001	Age, number of cigarettes/day, number of years smoked	Excluded, combined cancer sites
Zheng, 1995 oes00047 USA	IWHS, Prospective Cohort, Age: 55-69 years, Post-menopausal women	59/ 34 691 7 years	State Health Registry of Iowa	Semi-quantitative FFQ, 127-item	Incidence, upper digestive tract cancers (mouth, pharynx, oesophagus)	Median or more (≥3.4 g/day) vs. nondrinkers	1.4 (0.6-3.1)	Age, education, smoking status, pack-years of smoking	Superseded by Kasum, 2002, combined cancer sites
Yu, 1993 oes00758 China	CGRECSS, Historical Cohort, Age: 30- years, M/W	1162/ 12 693 15 years	Area residency lists	Interview	Incidence, oesophageal cancer	Daily vs. less than daily	0.50 (0.21-1.20)	Age, sex	Excluded, only two exposure categories, used in HvL analysis only
Kato, 1992 oes00334 USA	HHP, Prospective Cohort, Age: 45- years, M, Japanese residents of Hawaii	75/6701 19 years	Cancer registry/hospital records	FFQ, 24-hour diet recall history	Incidence, oral-pharynx, oesophagus, larynx	≥30 vs. 0 ml/day	5.4 (2.8-10.4), Prend:<0.01	Age, smoking	Superseded by Chyou, 1995, combined cancer sites

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Reasons for exclusion
Hirayama, 1990 oes00294 Japan	SPCJ, Nested Case Control, M/W	17 years	Unknown	Questionnaire	Mortality, oesophageal cancer	Every day vs. not daily	2.28 (1.96-2.65)	Age, sex standardised	Superseded by Kinjo, 1998, standardised mortality ratio
Hirayama, 1989 oes00295 Japan	SPCJ, Prospective Cohort, Age: 40- years, M/W	265 118 17 years	Checking against vital statistics at participating public health centres. Causes of death coded by author	Questionnaire	Mortality, oesophageal cancer, Men	Daily drinkers vs. non-drinkers	2.28	Age	Superseded by Kinjo, 1998, standardised mortality ratio
Kono, 1987 oes00364 Japan	JPC, Prospective Cohort, Age: 27-89 years, M, Japanese physicians	5 130 19 years	Vital status checked in membership lists of medical associations or the city or town office. Death certificates obtained	Self-administered questionnaire	Mortality, oesophageal cancer	≥2 go/day vs. never/past/occasional drinkers	14.46 (3.00-69.71)	Age, smoking habits	No cases and person-years per category, used in HvL analysis

Figure 44 RR estimates of oesophageal cancer by levels of total alcohol (as ethanol) intake

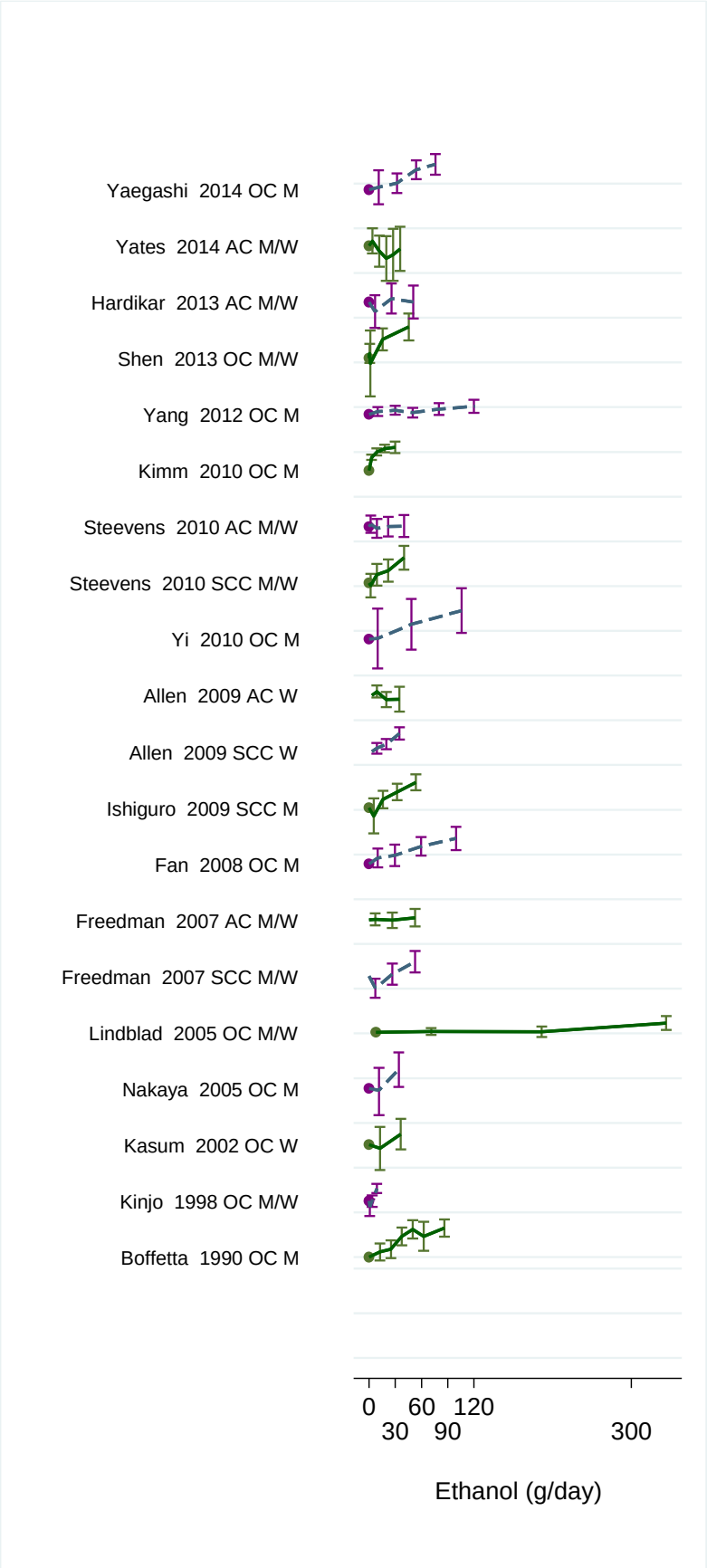


Figure 45 RR (95% CI) of oesophageal cancer for the highest compared with the lowest level of total alcohol intake

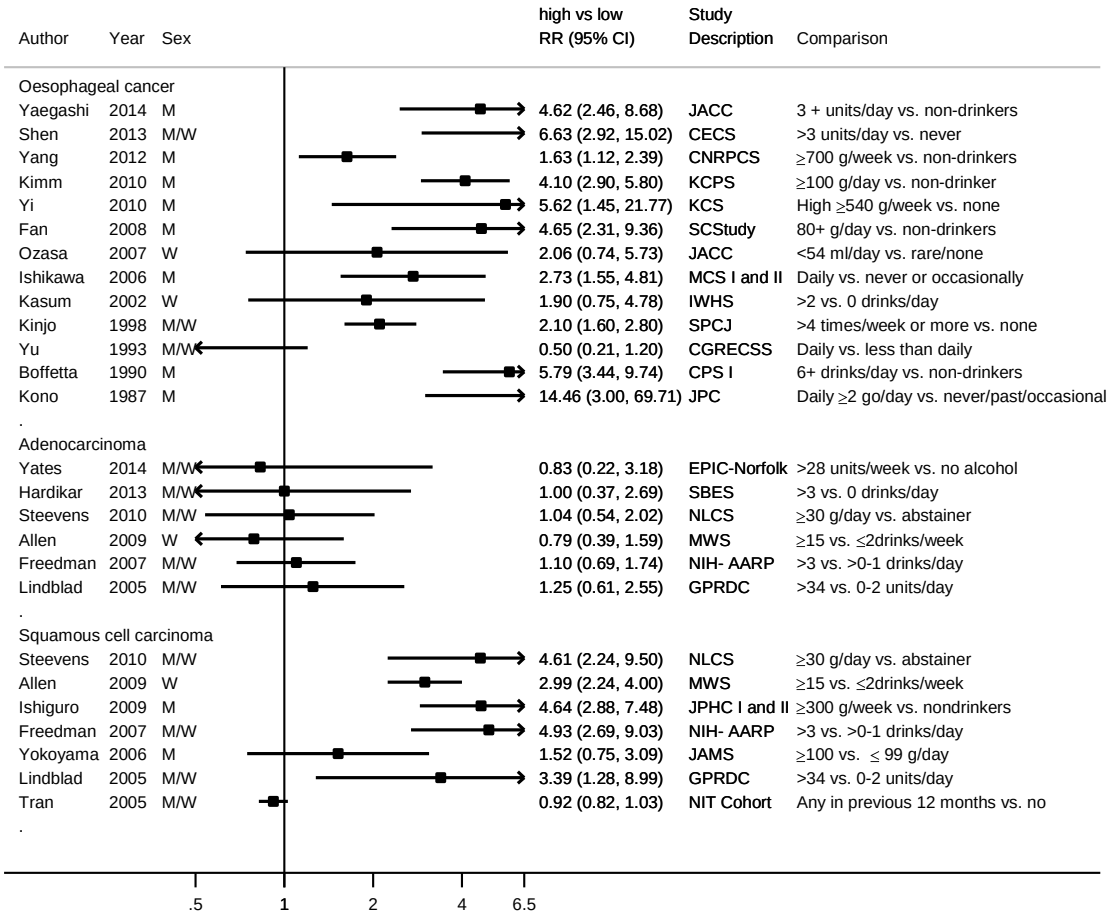
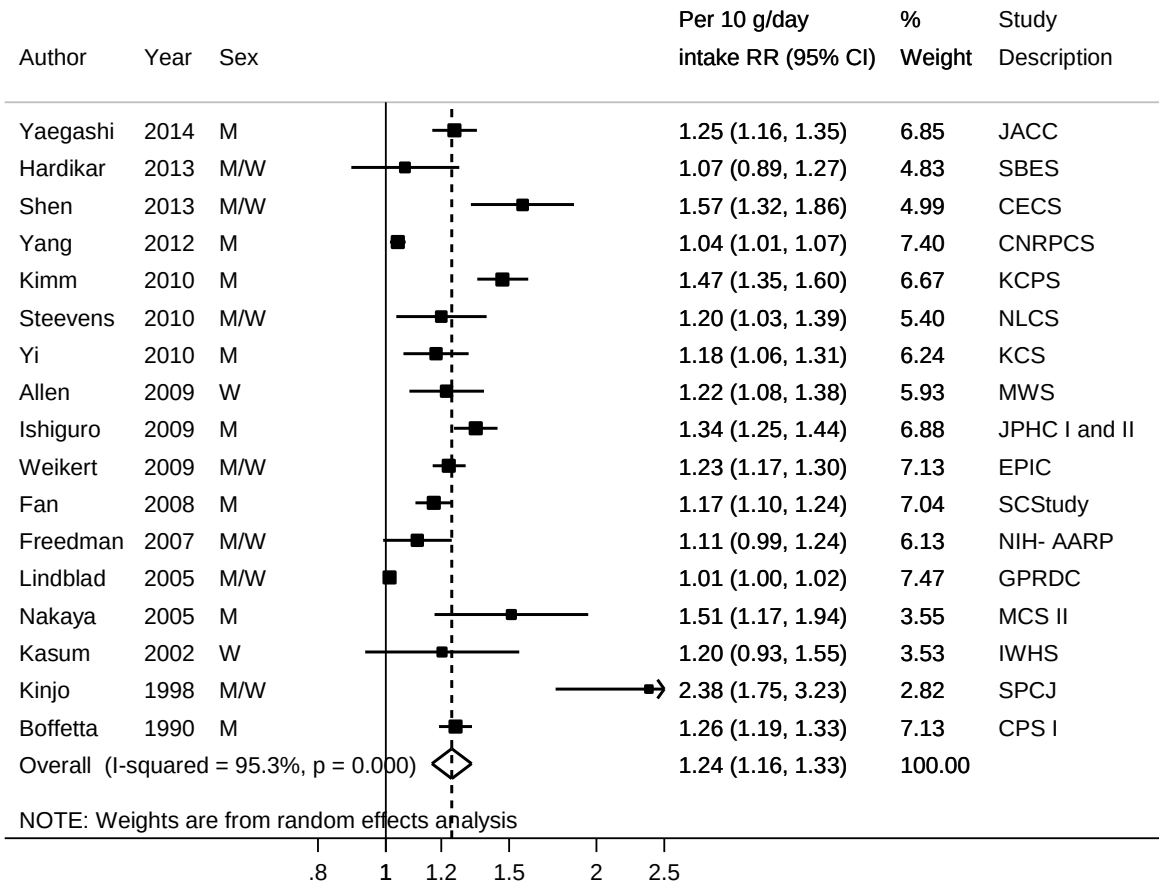
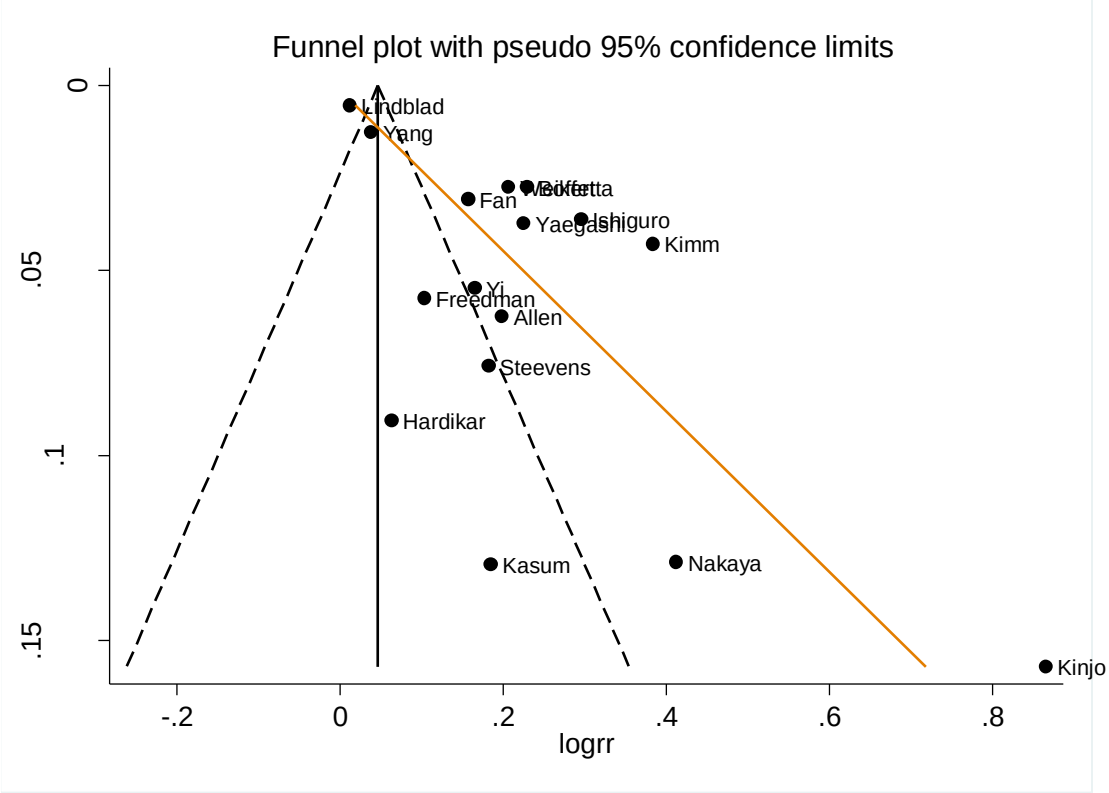


Figure 46 Relative risk of oesophageal cancer for 10 g/day increase of total alcohol (as ethanol) intake



Note: All studies (any type of oesophageal cancer) are included

Figure 47 Funnel plot of studies included in the dose response meta-analysis of total alcohol intake and oesophageal cancer



P=0.001

Figure 48 Relative risk of oesophageal cancer for 10 g/day increase of total alcohol (as ethanol) intake by sex

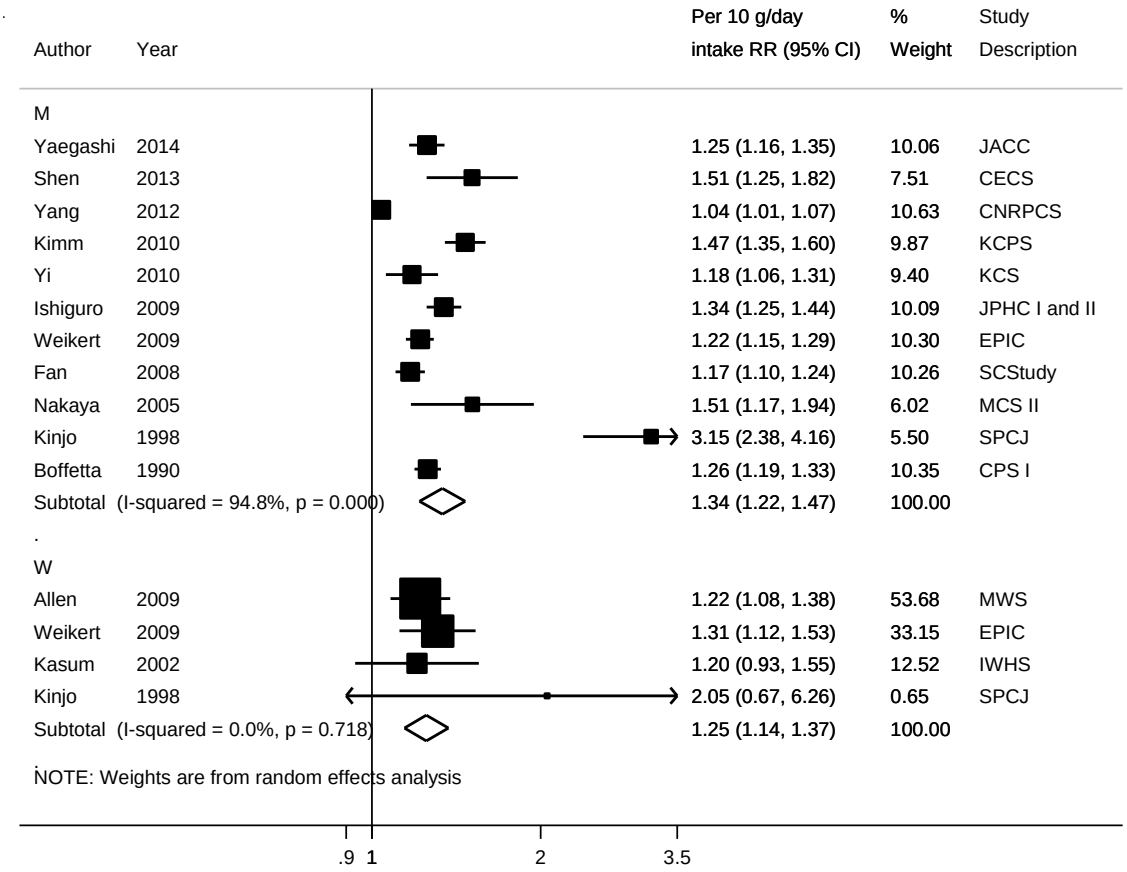


Figure 49 Relative risk of oesophageal cancer for 10 g/day increase of total alcohol (as ethanol) intake by cancer outcome

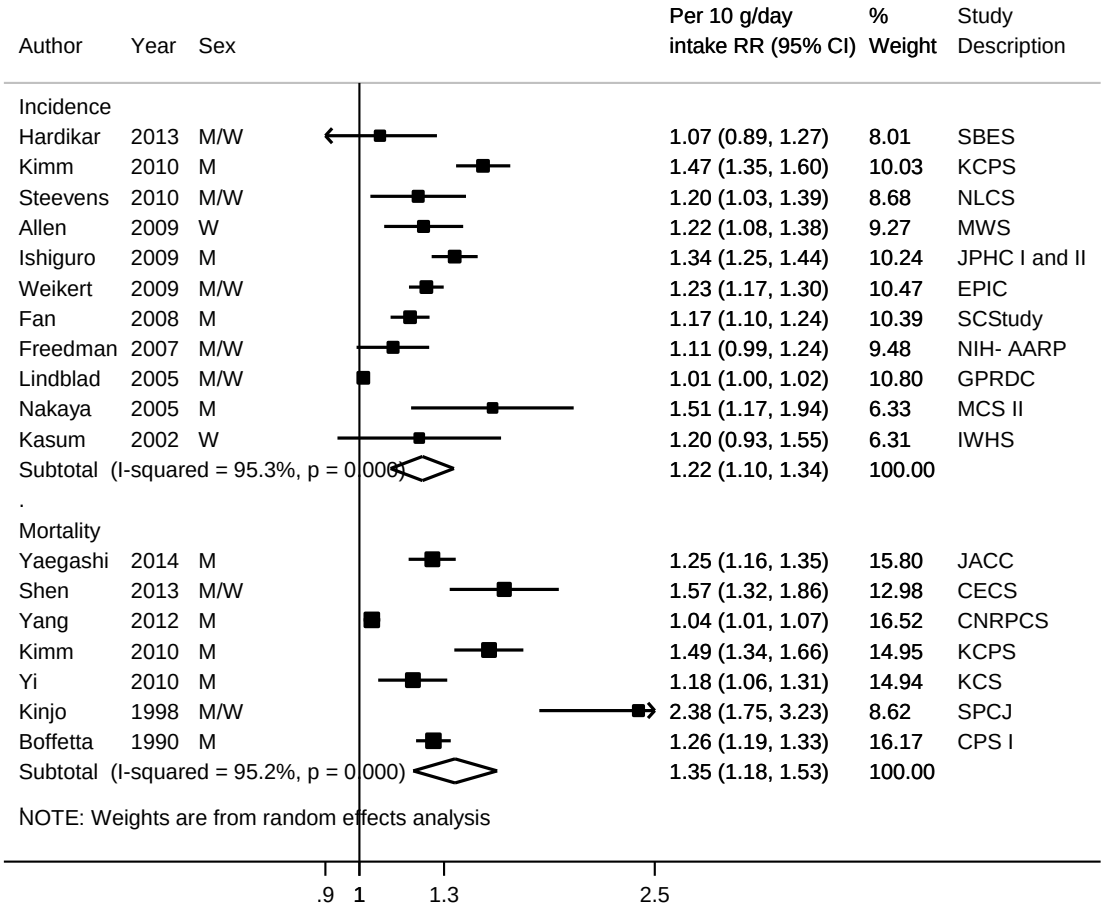


Figure 50 Relative risk of oesophageal cancer for 10 g/day increase of total alcohol (as ethanol) intake by geographic location

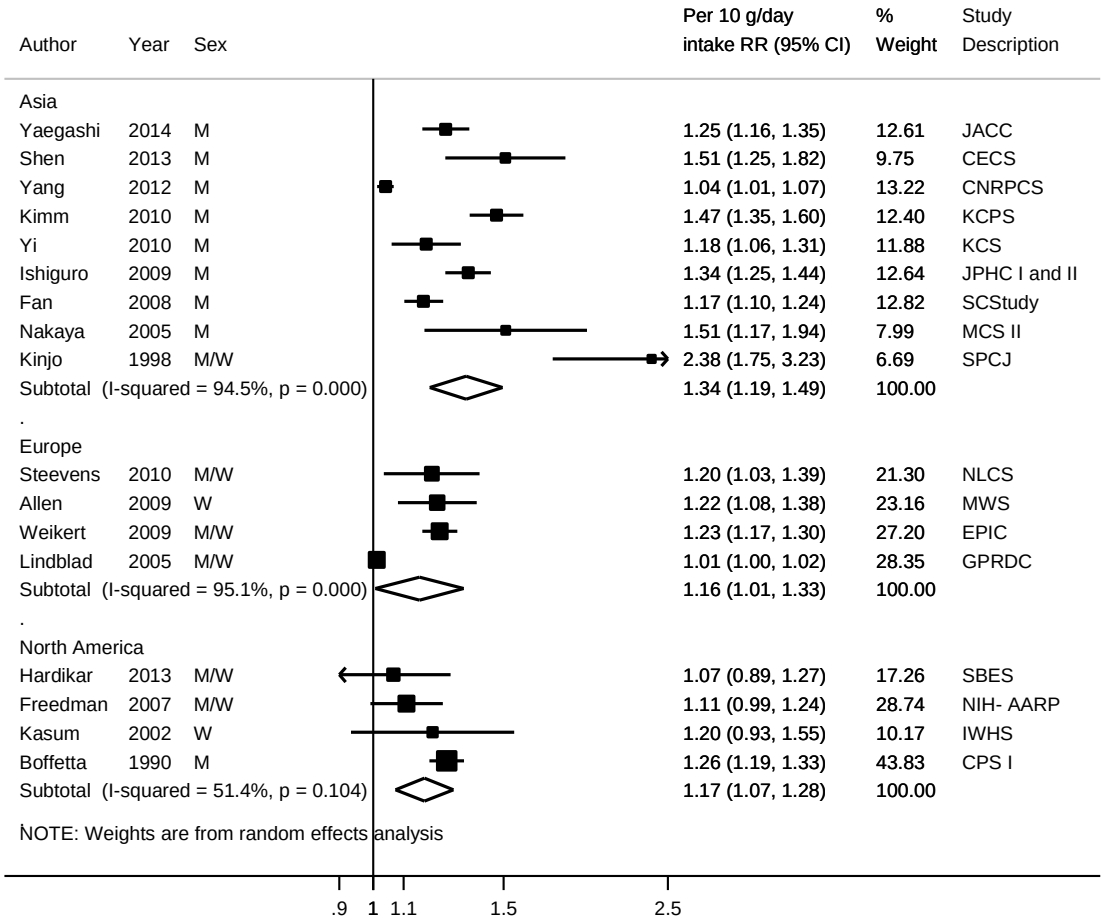


Figure 51 Relative risk of oesophageal cancer for 10g/day increase of total alcohol (as ethanol) intake by cancer type

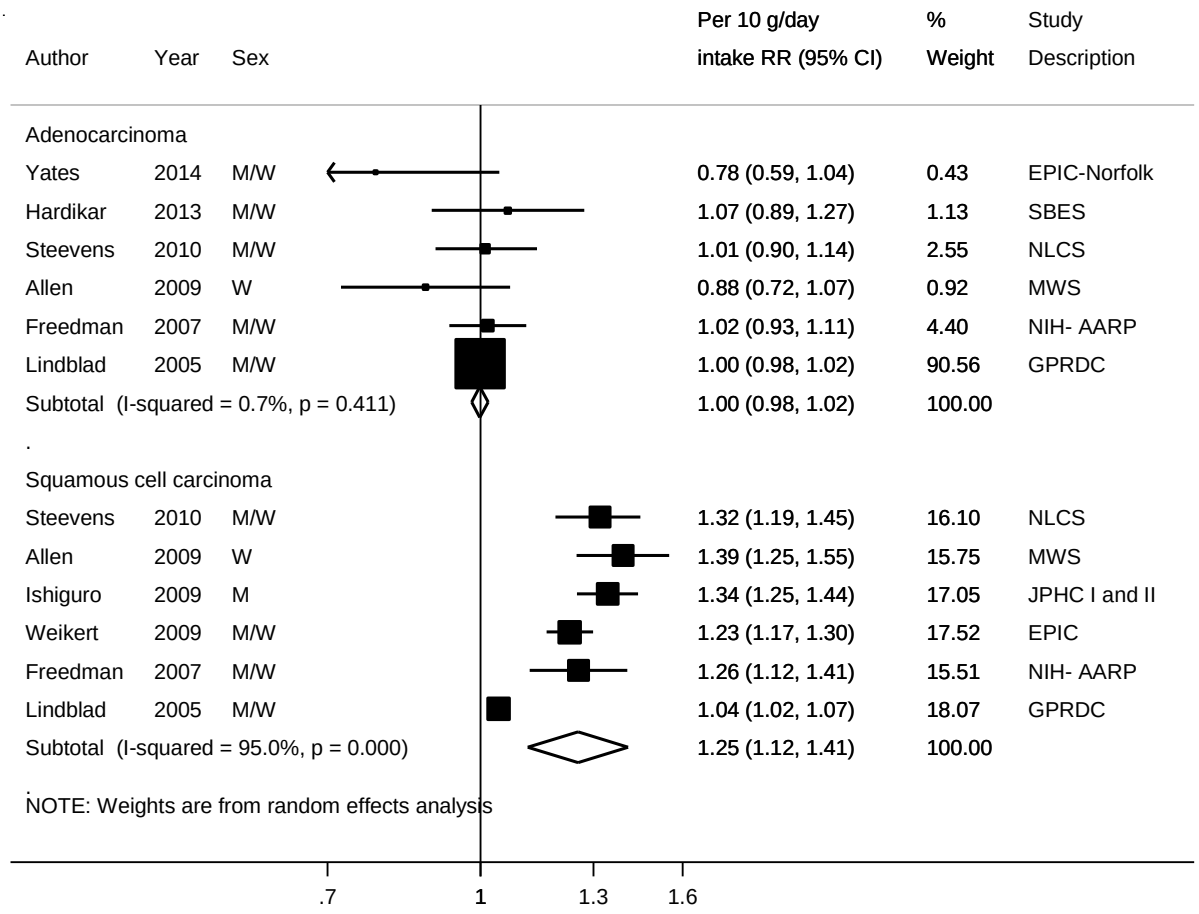
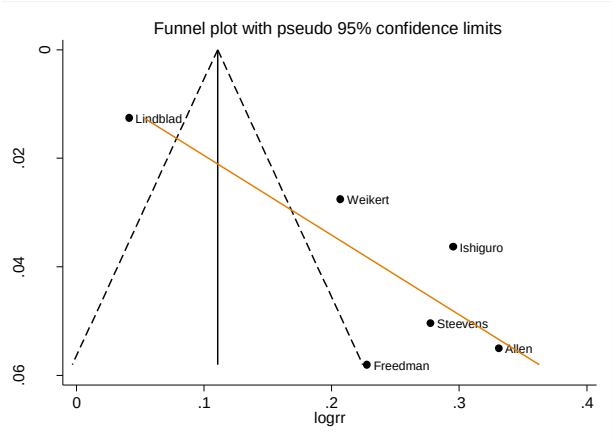
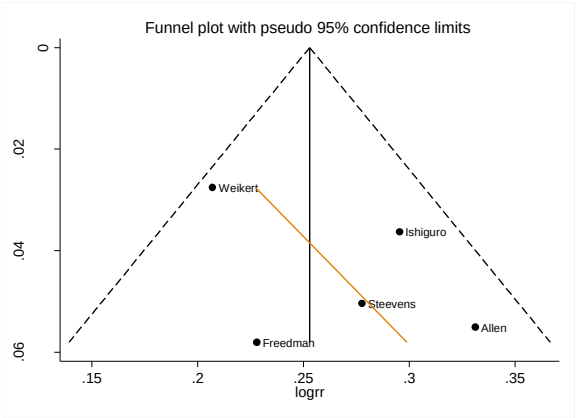


Figure 52 Funnel plot of studies included in the dose response meta-analysis of total alcohol intake and oesophageal squamous cell carcinoma

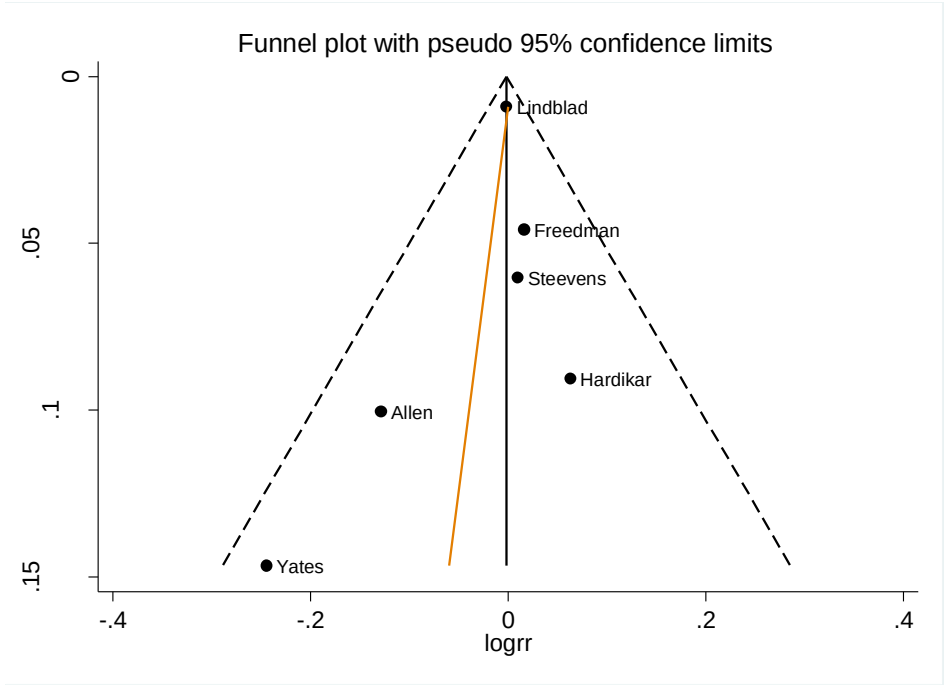




All studies P=0.009 (all studies)

P=0.29(excluding Lindbland, 2005)

Figure 53 Funnel plot of studies included in the dose response meta-analysis of total alcohol intake and oesophageal adenocarcinoma



P=0.47

Figure 54 Relative risk of oesophageal cancer for 10g/day increase of total alcohol (as ethanol) intake by cancer type, excluding Lindblad, 2005

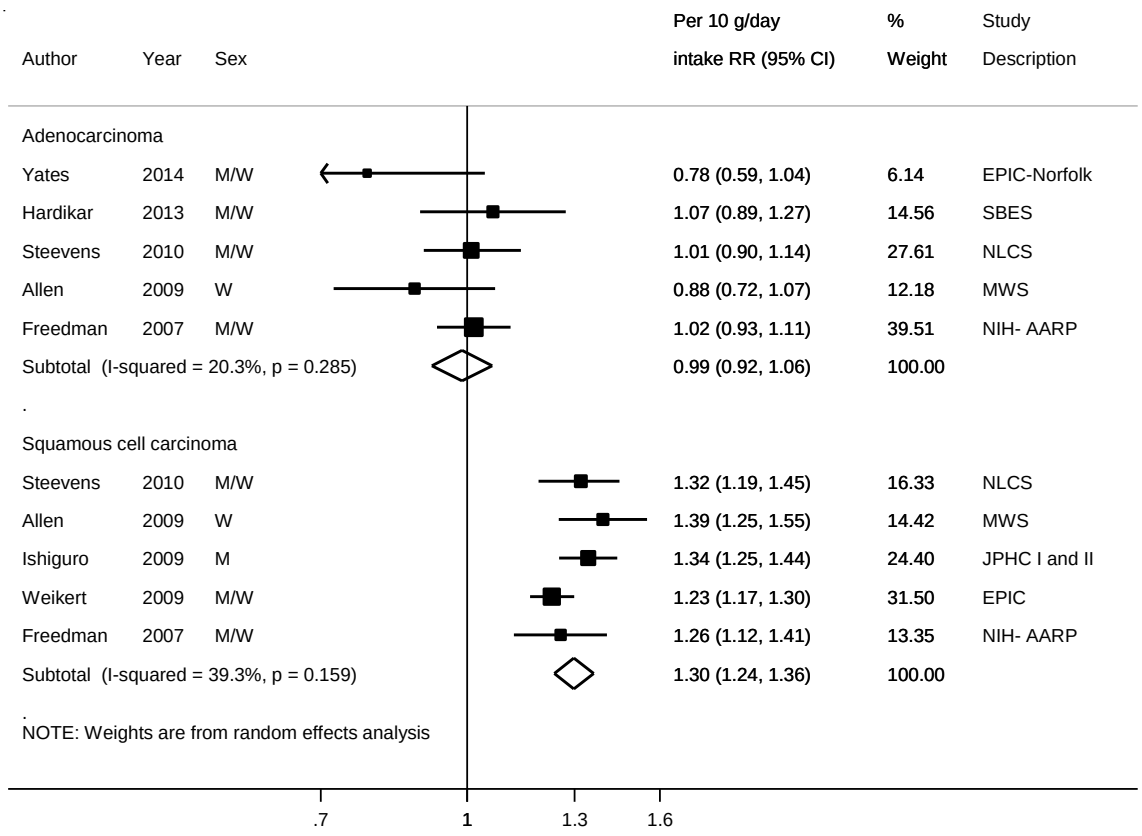


Figure 55 Relative risk of SCC (European and North American studies) and oesophageal cancer incidence (Asian studies) for 10g/day increase of total alcohol (as ethanol) intake

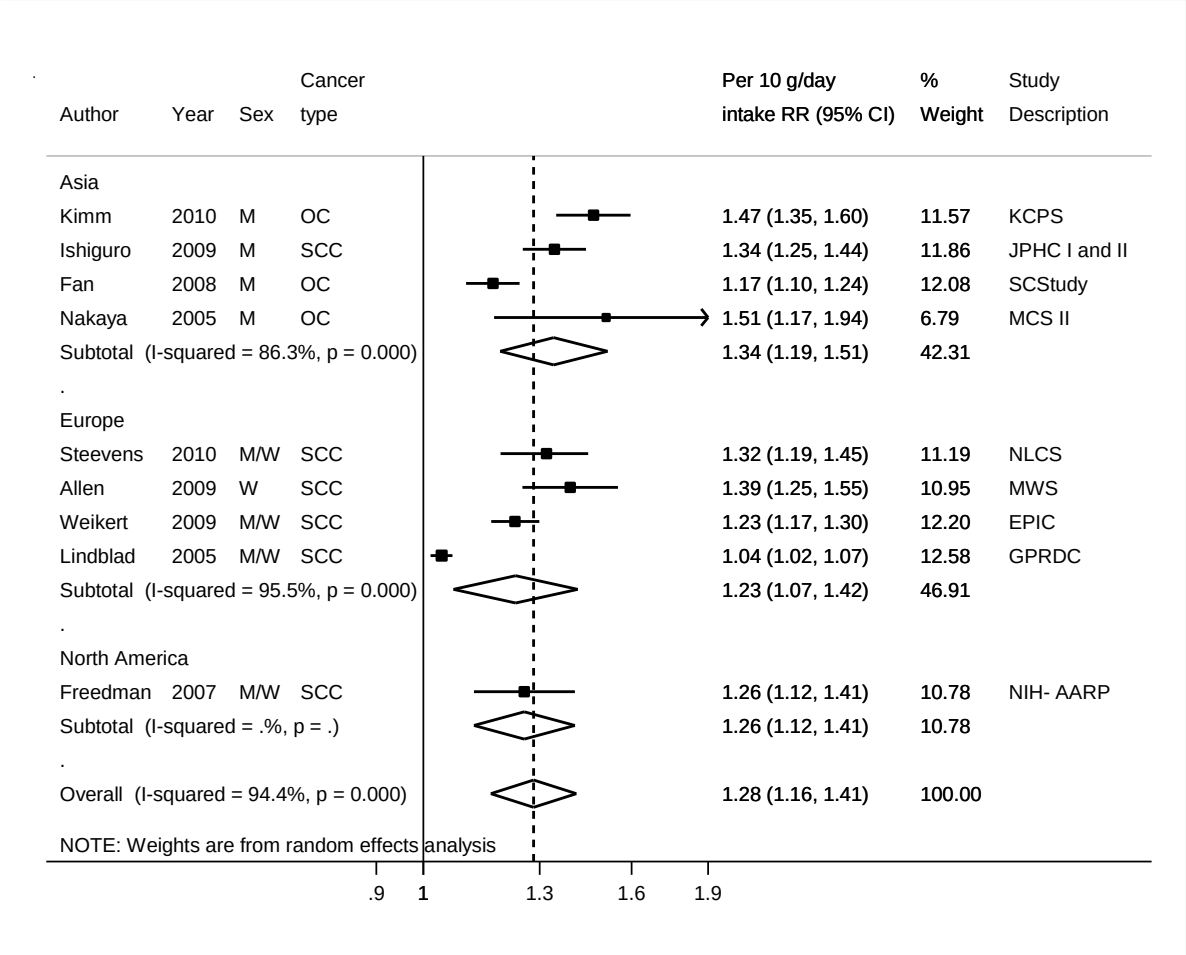
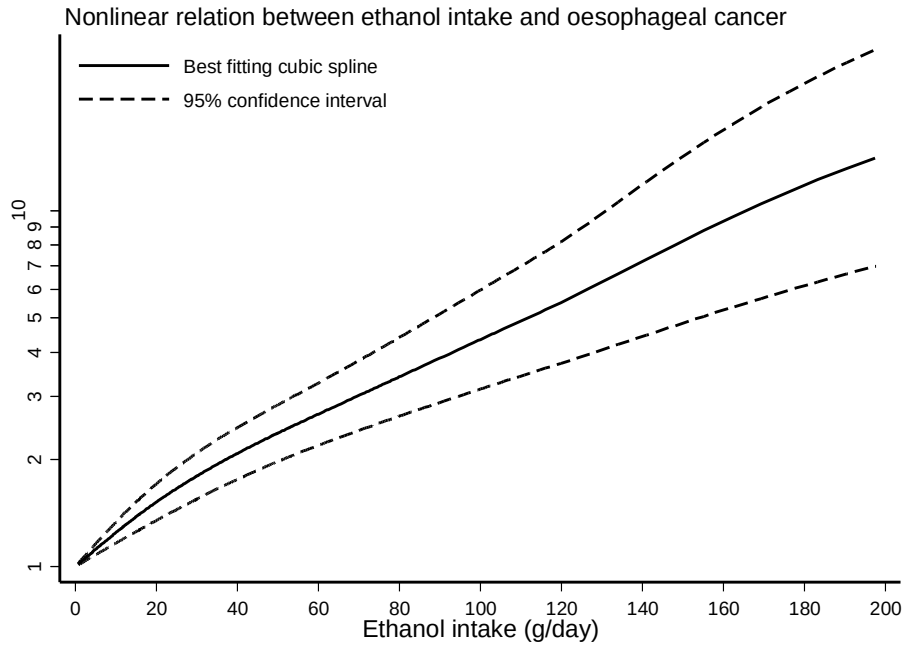


Figure 56 Non-linear dose-response meta-analysis of total alcohol (as ethanol) intake and oesophageal cancer

Note: The highest intake category of >34 units/day (>268.6 ethanol g/day) in Lindblad, 2005 study was excluded from non-linear analysis.



P for non-linearity =0.03

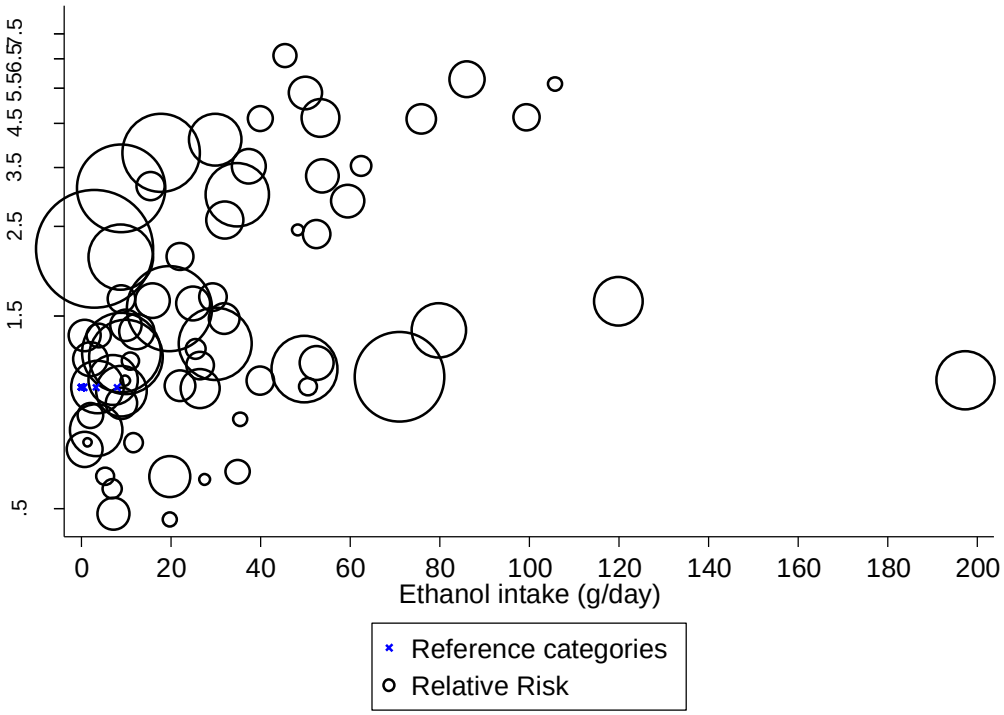
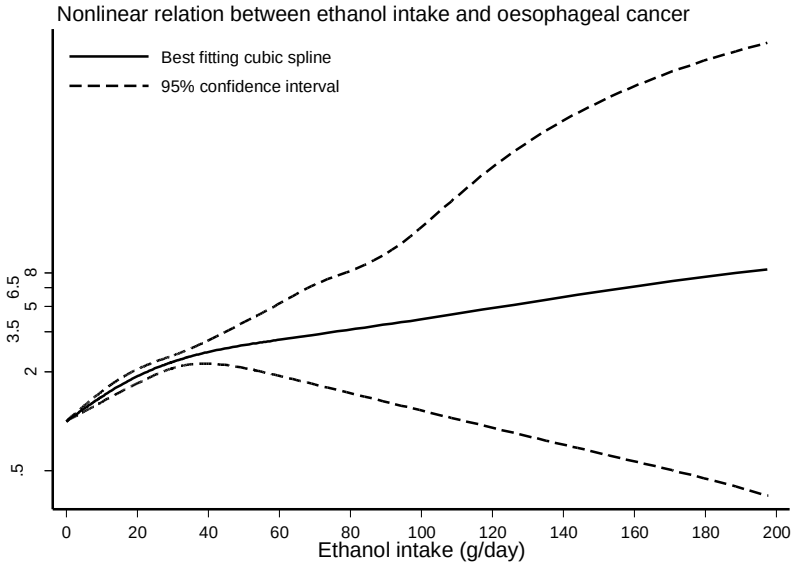


Table 42 Relative risk of oesophageal cancer and total alcohol (as ethanol) intake estimated using non-linear models

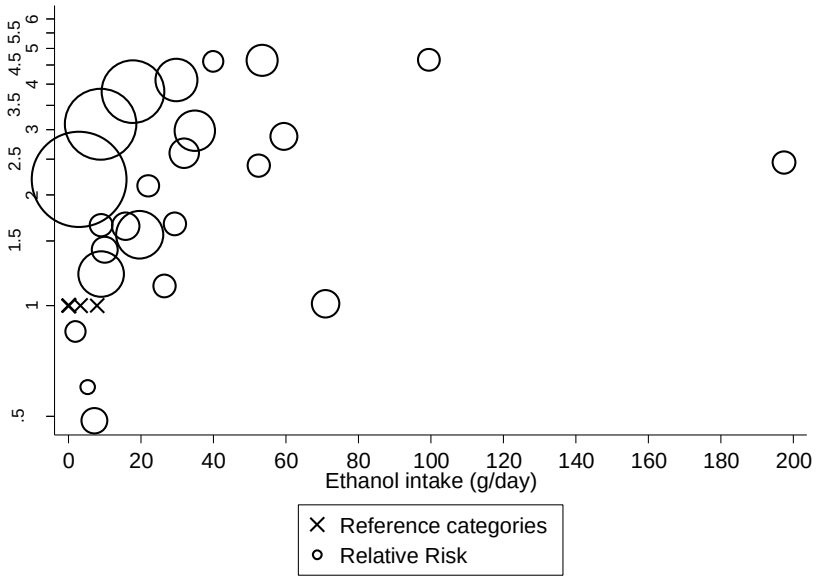
Ethanol (g/day)	RR (95%CI)
0	1.00
5.4	1.13 (1.09-1.17)
10	1.25 (1.16-1.33)
15.5	1.39 (1.26--1.54)
19.7	1.51 (1.34-1.70)
25	1.66 (1.45-1.90)
35.5	1.95 (1.66-2.29)
40	2.08 (1.76-2.46)
50	2.37 (1.91-2.85)
62.5	2.76 (2.25-3.40)
79.9	3.41 (2.64-4.39)
105.8	4.65 (3.31-6.54)
197.5	14.03 (6.97-28.26)

Figure 57 Non-linear dose-response meta-analysis of total alcohol (as ethanol) intake and squamous cell carcinomas combined with the Asian studies (on oesophageal cancer incidence as endpoint)

Note: The highest intake category of >34 units/day (>268.6 ethanol g/day) in Lindblad, 2005 study was excluded from non-linear analysis.



P for non-linearity = 0.04



Note: There were not enough studies on oesophageal adenocarcinoma with the data needed for non-linear dose-response meta-analyses.

Table 43 Relative risk of squamous cell carcinomas combined with the Asian studies (on oesophageal cancer incidence as endpoint) and alcohol (ethanol) intake estimated using non-linear models

Ethanol (g/day)	RR (95%CI)
0	1.00
5.4	1.21 (1.16-1.26)
10	1.41 (1.31-1.52)
16	1.69 (1.53--1.86)
22	1.97 (1.79-2.17)
34.9	2.47 (2.22-2.76)
40	2.64 (2.24-3.11)
59.5	3.12 (1.90-5.12)
71.1	3.39 (1.65-6.95)
99.5	4.16 (1.17-14.77)
197.5	8.41 (0.35-200.46)

5.4.1 Beers

Cohort studies

Summary

Main results:

There were not enough studies to conduct dose-response meta-analysis. Oesophageal cancer was significantly positively associated with beer intake when comparing the highest versus lowest beer intake category. The association was significant for squamous cell carcinoma (only two studies) and positive but not significant for oesophageal adenocarcinoma (four studies).

When the two studies reporting on squamous cell carcinomas (NIH-AARP, Freedman, 2007 and NLCS, Stevens, 2010) were combined with the Asian studies (Fan, 2008 and Yaegashi, 2008), the RR was 2.08 (95% CI=1.42-3.05; I^2=3.8%, p=0.37). In the Shanghai Cohort study (Fan, 2008) , 68 of the oesophageal cancer cases had squamous cell carcinoma, six has adenocarcinomas, one another histology and 24 cases had unknown histology. The number of cases by histological type was not given in the Japanese study (Yaegashi, 2008).

The study on oesophageal cancer in Chinese men (Fan, 2008) adjusted by intake of other alcoholic beverages and the observed association with oesophageal cancer was similar to the association reported in the Japanese study (Yaegashi, 2014) that did not adjust by other types of alcoholic drinks. The two studies on SCC adjusted the analysis on beer intake by intake of other alcoholic drinks (Steevens, 2010; Freedman, 2007). In the EPIC-Norfolk study (Yates, 2014) the RR shown in the table and figure was not adjusted for other types of alcoholic beverages; the authors indicated in the paper that the magnitude of the association was similar when alcohol intake was included in the model.

Table 44 Beer intake and oesophageal cancer risk. Number of studies in the CUP SLR

	Number
Studies identified	9 (10 Publications)*
Studies included in forest plot of highest compared with lowest exposure	6
Studies included in linear dose-response meta-analysis	Not enough studies
Studies included in non-linear dose-response meta-analysis	Not enough studies

*Included three studies (four publications) that reported results on upper aerodigestive tract cancers.

Table 45 Beer intake and oesophageal cancer risk. Summary of the highest versus lowest meta-analysis in the 2005 SLR and CUP

	2005 SLR	CUP
Increment unit used	No meta-analysis	Highest vs lowest
All studies		
Studies (n)	-	6
Cases (total number)	-	835
RR (95%CI)	-	1.62 (1.16-2.26)
Heterogeneity (I^2, p-value)	-	21.4%, 0.26
P value Egger test	-	-
Stratified analysis		
Histological type	**Adenocarcinoma (AC)**	**Squamous cell carcinoma (SCC)**
Studies (n)	4	2
RR (95%CI)	1.14 (0.72-1.79)	2.56 (1.18-5.57)
Heterogeneity (I^2, p-value)	0 %, 0.63	44.3%, 0.18
	Squamous cell carcinoma and Asian studies	
Studies (n)		4
RR (95%CI)		2.08 (1.42-3.05)
Heterogeneity (I2, p-value)		3.8%, 0.37

Table 46 Beer intake and oesophageal cancer risk. Results of meta-analyses and pooled analyses published after the 2005 SLR

Author, Year	Number of studies	Total number of cases	Studies country, area	Outcome	Comparison	RR (95%CI)	P trend	Heterogeneity (I^2, p value)
Pooled-analysis								
Freedman, 2011* (BEACON Consortium) (Cohorts: Kaiser Permanente Multiphasic Health Checkup Study, NIH-AARP)	9 case-control, 1 cohort study	1379	Europe, North America, Australia	AC	≥5 drinks/day vs. none	0.63 (0.40-0.99)	0.12	0%

***** National Institutes of Health AARP Diet and Health (NIH-AARP) study is included in the CUP analyses

Note: mainly case-control studies. Individuals with undetected tumours or their precursor conditions, such as gastro-oesophageal reflux, might avoid alcohol because it provokes symptoms.

Table 47 Beer intake and oesophageal cancer risk. Main characteristics of studies included in the highest compared to the lowest meta-analysis

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Inclusion/ exclusion
Yaegashi, 2014 oes00892 Japan	JACC study, Prospective Cohort, Age: 40-79 years, M	65/ 42 408 20 years	Date and cause of death annually or biannually confirmed with government authorization	Self-administered questionnaire	Mortality, oesophageal cancer	Beer drinkers vs. non-drinkers	1.72 (0.96-3.08)	Age, centres, fruit & vegetable consumption	Included
Yates, 2014 oes00894 UK	EPIC-Norfolk, Prospective Cohort, Age: 39-74 years, M/W	66 24 066 15 years	Cancer and pathology registries	FFQ	Incidence, AC and gastro-oesophageal junction	Drinkers vs. non-drinkers	1.91 (0.70-5.18)	Age, gender	Included
Hardikar, 2013 oes00875 USA	SBES, Prospective Cohort, Age: 30- years, M/W	45/ 411 6.2 years	Biopsy and follow up	Structured personal interview	Incidence, AC	>3 vs. 0 drinks/day	1.34 (0.39-4.57) Ptrend: 0.94	Age, cigarette smoking, NSAID use, gender, waist to hip ratio	Included
Steevens, 2010 oes00816 Netherlands	NLCS, Case Cohort, Age: 55-70 years, M/W	107/ 4 214 16.3 years	Annual record linkage to the Netherlands cancer and pathology registers	Validated FFQ	Incidence, SCC	>2 glasses/day vs. no beer	1.62 (0.64-4.09) Ptrend: 0.23	Age, sex, BMI, education level, energy intake, smoking status, ethanol intake, fish intake, fruit and vegetable intake, smoking dose and duration	Included
						Per 1 glass/day	1.10 (0.92-1.32)		
		145/			Incidence, AC	>2 glasses/day vs. no beer	1.07 (0.44-2.62)		
						Per 1 glass/day	0.98 (0.82-1.17)		
Fan, 2008	SCStudy,	54/	Cancer registry,	Face-to-face	Incidence,	1+ drink/day	1.71 (0.66-4.42)	Age at interview, BMI, fresh	Included

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Inclusion/ exclusion
oes00871 China	Prospective Cohort, Age: 45-64 years, M	~18 244 15.5 years (Men who consumed rice wine and/or spirits only were excluded)	Shanghai vital statistics office, medical history	interview using a structured questionnaire	oesophageal cancer	vs. non-drinkers		fruit, number of years of smoking, spirits, year of interview, education, fresh vegetables, neighbourhood of residence at recruitment, preserved food intake, rice wine, spirits	
Freedman, 2007b oes00820 USA	NIH- AARP, Prospective Cohort, Age: 50- years, M/W	97/ 474 606 4.6 years	Record linkage to state cancer registry databases.	Validated FFQ	Incidence, SCC	>3 vs. >0-1 drink/day	3.61 (1.76-7.39) Ptrend: 0.0002	Age, sex, BMI, education level, fruit and vegetable consumption, liquor consumption, smoking status, wine consumption, total energy, usual physical activity, vigorous physical activity	Included
		205/			Incidence, AC		0.85 (0.41-1.75) Ptrend: 0.46		Included

Table 48 Beer intake and oesophageal cancer risk. Main characteristics of studies excluded from the highest compared to the lowest meta-analysis

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Reasons for exclusion
Grønbaek, 1998 oes00053 Denmark	CCPPS, Prospective Cohort, Age: 20-98 years, M/W	156/ 28 180 13.5 years	Cancer register	Questionnaire	Incidence, oropharyngeal and oesophageal cancer	≥7 vs. <0 drinks/week	2.90 (1.80-4.80)	Age, sex, educational level, smoking habits	Excluded, combined cancer sites
Kjaerheim, 1998 oes00130 Norway	Norwegian Men UADT, Prospective Cohort, M	71/ 10 900 25 years	Cancer registry	Questionnaire	Incidence, upper aerogastric tract cancer	4-7 vs. <1 time/week or never	4.40 (2.40-8.30) Ptrend:<0.001	Age, smoking habits	Excluded, combined cancer sites
Chyou, 1995 oes00128 USA	HHP, Prospective Cohort, M, Japanese residents of Hawaii	92/ 7 995 24 years	Cancer registry/hospital records	FFQ, 24-hour diet recall history	Incidence, upper aerodigestive tract cancer	>361+ oz/month vs. non-drinker	3.66 (2.01-6.69) Ptrend:<0.0001	Age, smoking habits	Excluded, combined cancer sites
Kato, 1992 oes00334 USA	HHP, Prospective Cohort, M, Japanese residents of Hawaii	71/ 6 701 25 years	Cancer registry/hospital records	FFQ, 24-hour diet recall history	Incidence, oral-pharyngeal, laryngeal, and oesophageal cancer	≥500 vs. 0 ml/day	2.60 (1.50-4.60) Ptrend: <0.01	Age, smoking habits	Excluded, combined cancer sites, same study as Chyou, 1995

Figure 58 RR estimates of oesophageal cancer by levels of beer intake

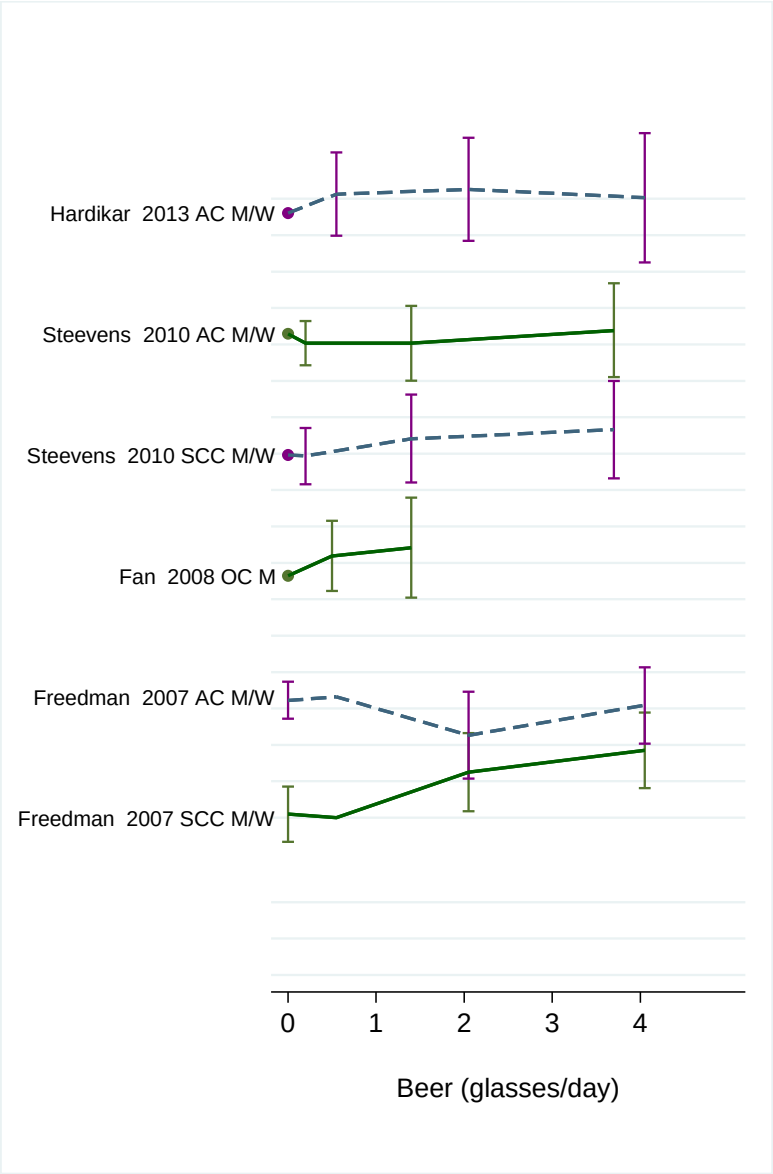
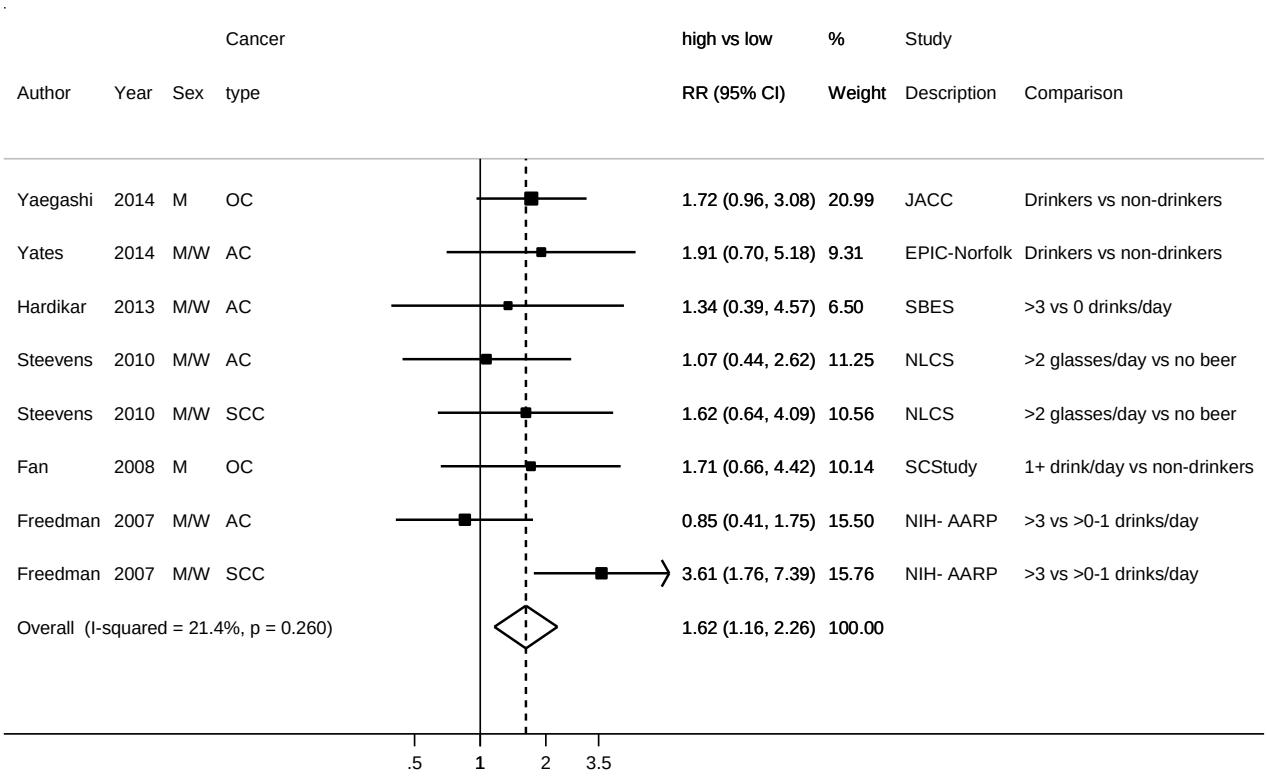
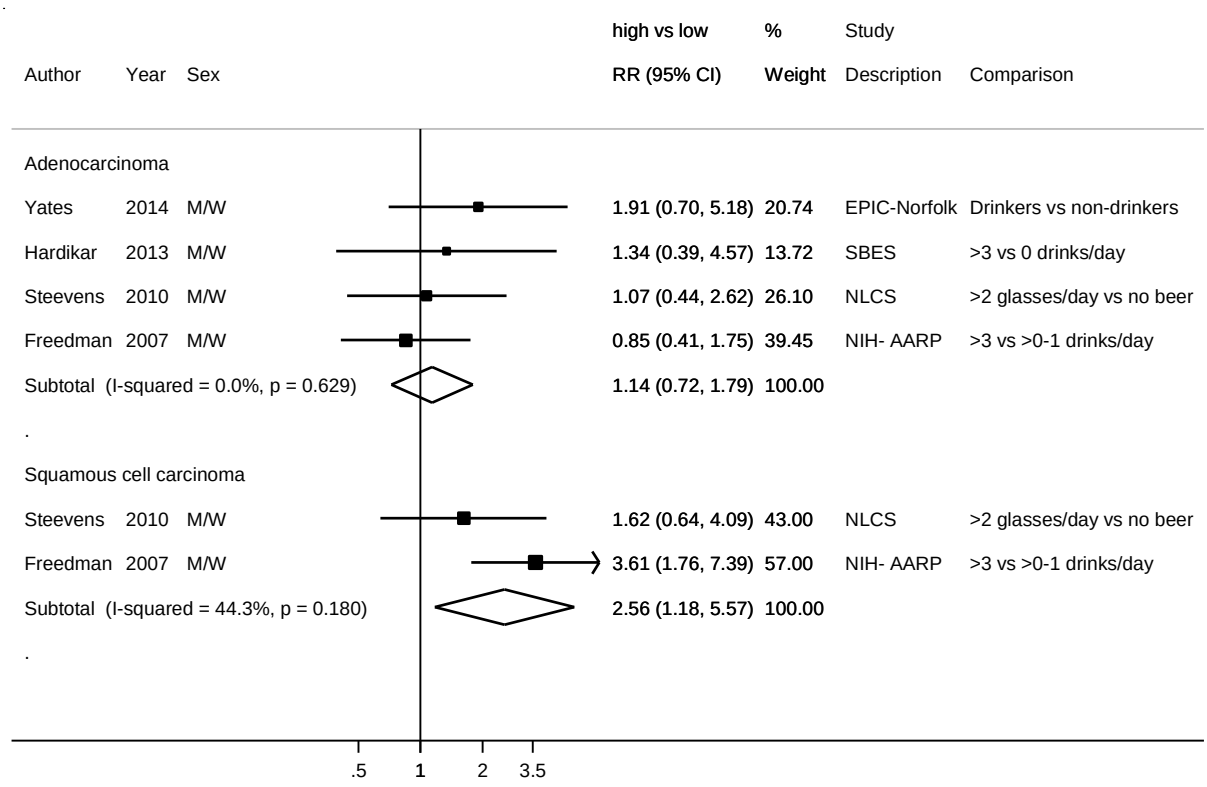


Figure 59 RR (95% CI) of oesophageal cancer for the highest compared with the lowest level of beer intake



Note: Yates, 2004 included cases of cancers of oesophageal and gastro-oesophageal junction adenocarcinomas

Figure 60 RR (95% CI) of oesophageal cancer for the highest compared with the lowest level of beer intake by cancer type



Note: Yates, 2014 included cases of cancers of oesophageal and gastro-oesophageal junction adenocarcinomas

5.4.2 Wine

Cohort studies

Summary

Main results:

Five studies were identified but there was not enough data to do dose-response meta-analysis. No significant association was observed comparing the highest versus lowest wine intake and oesophageal cancer risk. The number of cases in the highest intake category was seven or less in all studies and for that reason, confidence intervals are wide. Only one study (Yates, 2014) did not provide case numbers by intake levels. This study included cases of cancers of oesophageal and gastro-oesophageal junction adenocarcinomas.
The two studies on SCC adjusted the analysis by intake of other alcoholic drinks (Steevens, 2010; Freedman, 2007). In the EPIC-Norfolk study (Yates, 2014) the RR shown in the table and figure was not adjusted for other types of alcoholic beverages but the authors indicated that the magnitude of the association was similar when alcohol intake was included in the

model. No adjustment for other alcoholic beverages was made in the other two studies. None of the included studies reported significant associations.

In two studies (Hardikar, 2013; Freedman, 2007), participants with low wine intake (1-2 drinks) had lower oesophageal cancer risk (although not statistically significant) than those that reported not drinking wine. In one study (Yates, 2014), a borderline inverse association was observed when comparing wine drinkers with non-drinkers of wine. The suggestion of a risk decrease associated with low wine intake was not observed for other alcoholic beverages in the same studies.

Table 49 Wine intake and oesophageal cancer risk. Number of studies in the CUP SLR

	Number
Studies identified	7*
Studies included in forest plot of highest compared with lowest exposure	5
Studies included in linear dose-response meta-analysis	Not enough studies
Studies included in non-linear dose-response meta-analysis	Not enough studies

*Two studies reported results on upper aerodigestive tract cancers.

Table 50 Wine intake and oesophageal cancer risk. Summary of the highest versus lowest meta-analysis in the 2005 SLR and CUP

	2005 SLR	**CUP**
Increment unit used	No meta-analysis	Highest vs lowest
All studies		
Studies (n)	-	5
Cases (total number)	-	694
RR (95%CI)	-	1.06 (0.55-2.07)
Heterogeneity (I^2, p-value)	-	51.5%, 0.05
P value Egger test	-	-
Stratified and sensitivity analysis in the CUP		
Histological type	**Adenocarcinoma (AC)**	**Squamous cell carcinoma (SCC)**
Studies (n)	4	2
RR (95%CI)	0.93 (0.45-1.92)	0.81 (0.09-7.01)
Heterogeneity (I^2, p-value)	42.6 %, 0.16	67.8%, 0.08

Table 51 Wine intake and oesophageal cancer risk. Results of meta-analyses and pooled analyses published after the 2005 SLR

Author, Year	Number of studies	Total number of cases	Studies country, area	Outcome	Comparison	RR (95%CI)	P trend	Heterogeneity (I^2, p value)
Pooled-analysis								
Freedman, 2011* (BEACON Consortium) (Cohorts: Kaiser Permanente Multiphasic Health Checkup Study, NIH-AARP)	9 case-control, 1 cohort study	969	Europe, North America, Australia	AC	≥3 drinks/day vs. none	1.49 (0.80-2.78)	0.40	0%

***** National Institutes of Health AARP Diet and Health (NIH-AARP) study is included in the CUP analyses

Table 52 Wine intake and oesophageal cancer risk. Main study characteristics of studies included in the highest vs lowest meta-analysis

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Inclusion/ exclusion
Yaegashi, 2014 oes00892 Japan	JACC study, Prospective Cohort, Age: 40-79 years, M	25/ 42 408 20 years	Date and cause of death annually or biannually confirmed with government authorization	Self-administered questionnaire	Mortality, oesophageal cancer	Wine drinkers vs. non-drinkers	2.61 (0.86-7.94)	Age, centres, fruit & vegetable consumption	Included
Yates, 2014 oes00894 UK	EPIC-Norfolk, Prospective Cohort, Age: 39-74 years, M/W	66 24 066 15 years	Cancer and pathology registries	FFQ	Incidence, oesophageal AC and gastro-oesophageal junction	Drinkers vs. non-drinkers	0.49 (0.23-1.04)	Age, gender	Included
Hardikar, 2013 oes00875 USA	SBES, Prospective Cohort, Age: 30- years, M/W	45/ 411 6.2 years	Biopsy and follow up	Structured personal interview	Incidence, AC	>1-3 vs. 0 drinks/day	1.35 (0.32-5.74) Ptrend: 0.10	Age, sex, cigarette smoking, NSAID use, WHR	Included
Steevens, 2010 oes00816 Netherlands	NLCS, Case Cohort, Age: 55-70 years, M/W	107/ 4 214 16.3 years	Annual record linkage to the Netherlands cancer and pathology registers	Validated FFQ	Incidence, SCC	>2 glasses/day vs. no wine	0.30 (0.07-1.23) Ptrend: 0.05	Age, sex, BMI, education level, energy intake, smoking status, ethanol intake, fish intake, fruit and vegetable intake, smoking dose and duration	Included
						Per 1 glass/day	0.67 (0.50-0.90)		
		145/			Incidence, AC	>2 glasses/day vs. no wine	0.79 (0.28-2.20) Ptrend: 0.64		
						Per 1 glass/day	0.89 (0.67-1.19)		
Freedman, 2007b oes00820 USA	NIH- AARP, Prospective Cohort, Age: 50- years,	97/ 474 606 4.6 years	Record linkage to state cancer registry databases.	Validated FFQ	Incidence, SCC	>3 vs >0-1 drinks/day	2.75 (0.37-20.41) Ptrend: 0.81	Age, sex, BMI, beer consumption, education level, fruit and vegetable	Included
		205/			Incidence,	>3 vs >0-1	2.84 (0.69-		

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Inclusion/ exclusion
	M/W,				AC	drinks/day	11.58) Ptrend: 0.23	consumption, liquor consumption, smoking status, total energy, usual physical activity, vigorous physical activity	

Table 53 Wine intake and oesophageal cancer risk. Main characteristics of studies excluded from the highest compared to the lowest meta-analysis

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Reasons for exclusion
Grønbaek, 1998 oes00053 Denmark	CCPPS, Prospective Cohort, Age: 20-98 years, M/W	156 28 180 14 years	Cancer register	Questionnaire	Incidence, oropharyngeal and oesophageal cancer	≥7 vs. <0 drinks/week	0.40 (0.20-0.80)	Age, sex, educational level, smoking habits	Excluded, combined cancer sites
Chyou, 1995 oes00128 USA	HHP, Prospective Cohort, M	92/ 7 995 24 years	Cancer registry/hospital records	FFQ, 24-hour diet recall history	Incidence, upper aerodigestive tract cancer	>4 oz/month vs. non-drinker	3.80 (1.76-8.18) Ptrend:<0.0001	Age, smoking habits	Excluded, combined cancer sites

Figure 61 RR estimates of oesophageal cancer by levels of wine intake

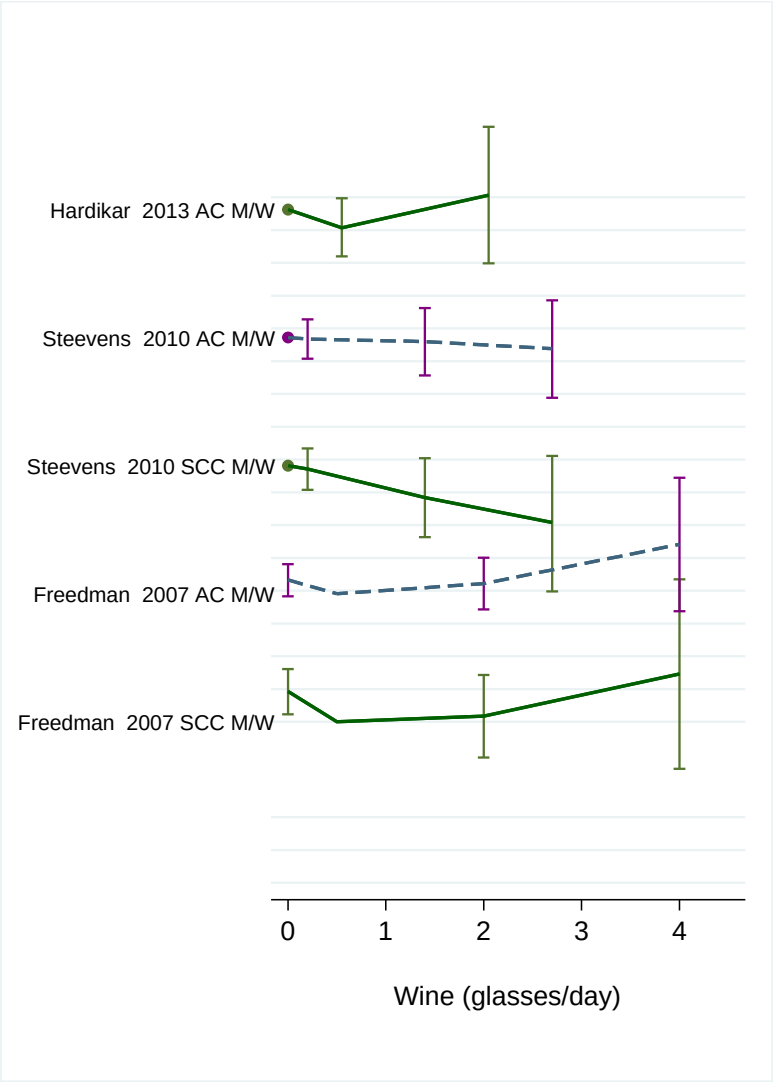


Figure 62 RR (95% CI) of oesophageal cancer for the highest compared with the lowest level of wine intake

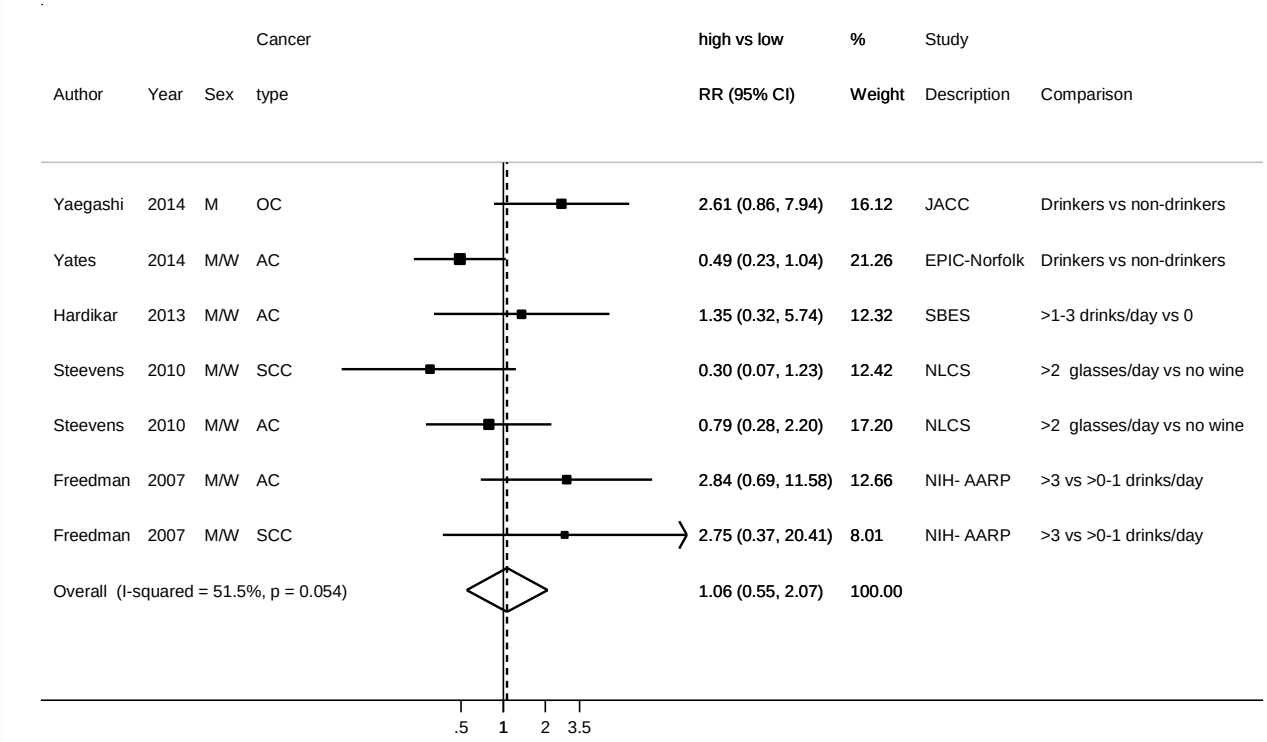
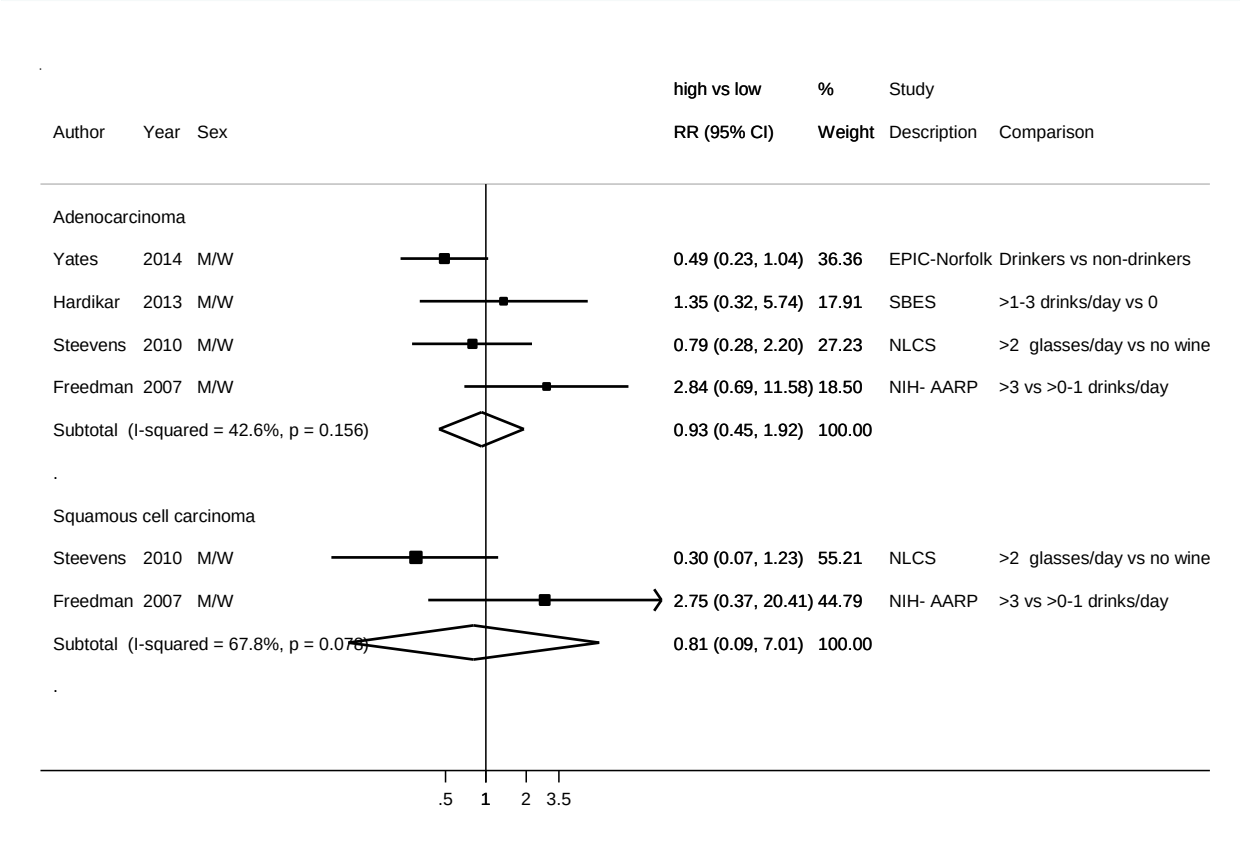


Figure 63 RR (95% CI) of oesophageal cancer for the highest compared with the lowest level of wine intake by cancer type



5.4.3 Spirits

Cohort studies

Summary

Main results:

There were not enough studies with enough data to conduct dose-response meta-analysis. Significant positive association with oesophageal cancer risk was observed when comparing the highest versus lowest intake of spirits (six studies). No significant association was observed when studies were stratified by cancer subtype (four studies for AC and two studies for SCC).

When the two studies reporting on squamous cell carcinomas (NIH-AARP, Freedman, 2007 and NLCS, Stevens, 2010) were combined with the Asian studies (SC Study, Fan, 2008 and JACC, Yaegashi, 2008), the RR was 3.41 (95% CI=2.16-5.38; I^2=41.7%, p=0.16). In the Shanghai Cohort study, 68 of the oesophageal cancer cases had squamous cell carcinoma, 6 cases has adenocarcinomas, 1 another histology and 24 cases had unknown histology. No data on histological type was given in the Japanese study (Yaegashi, 2008).

The two studies on SCC adjusted the analysis on spirits intake by intake of other alcoholic drinks (Steevens, 2010; Freedman, 2007). The study on oesophageal cancer in Chinese men (Fan, 2008) also adjusted by intake of other alcoholic beverages. In the EPIC-Norfolk study (Yates, 2014) the RR shown in the table and figure was not adjusted for other types of alcoholic beverages but the authors indicated that the magnitude of the association was similar when alcohol intake was included in the model.

Table 54 Spirits intake and oesophageal cancer risk. Number of studies in the CUP SLR

	Number
Studies identified	9*
Studies included in forest plot of highest compared with lowest exposure	6
Studies included in linear dose-response meta-analysis	Not enough studies
Studies included in non-linear dose-response meta-analysis	Not enough studies

*Three studies reported results on upper aerodigestive tract cancers.

Table 55 Spirits intake and oesophageal cancer risk. Summary of the highest versus lowest meta-analysis in the 2005 SLR and CUP

	2005 SLR*	**CUP**
Increment unit used	Highest vs lowest	Highest vs lowest
All studies		
Studies (n)	1	6
Cases (total number)	156*	813
RR (95%CI)	1.50 (1.19-1.89)	1.85 (1.05-3.26)
Heterogeneity (I^2, p-value)	-	78.1%, <0.001
P value Egger test	-	-
Stratified analysis in the CUP		
Histological type	**Adenocarcinoma (AC)**	**Squamous cell carcinoma (SCC)**
Studies (n)	4	2
RR (95%CI)	0.94 (0.63-1.40)	2.77 (0.98-7.84)
Heterogeneity (I^2, p-value)	0 %, 0.47	72.7%, 0.06
	Squamous cell carcinoma and Asian studies	
Studies (n)		4
RR (95%CI)		3.41 (2.16-5.38)
Heterogeneity (I2, p-value)		41.7%, 0.16

*Upper digestive tract cancer cases.

Table 56 Spirits intake and oesophageal cancer risk. Results of meta-analyses and pooled analyses published after the 2005 SLR

Author, Year	Number of studies	Total number of cases	Studies country, area	Outcome	Comparison	RR (95%CI)	P trend	Heterogeneity (I^2, p value)
Meta-analysis								
Pooled-analysis								
Freedman, 2011* (BEACON Consortium) (Cohorts: Kaiser Permanente Multiphasic Health Checkup Study, NIH-AARP)	9 case-control, 1 cohort study	1188	Europe, North America, Australia	AC	≥5 drinks/day (liquor) vs. none	1.52 (0.82-2.80)	0.10	0%

***** National Institutes of Health AARP Diet and Health (NIH-AARP) study is included in the CUP analyses

Table 57 Spirits intake and oesophageal cancer risk. Main characteristics of studies included in the highest compared to the lowest meta-analysis

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Inclusion/ exclusion
Yaegashi, 2014 oes00892 Japan	JACC study, Prospective Cohort, Age: 40-79 years, M	43/ 42 408 20 years	Date and cause of death annually or biannually confirmed with government authorization	Self-administered questionnaire, whisky	Mortality, Oesophageal cancer	Whisky drinkers vs. non-drinkers	2.99 (1.53-5.84)	Age, centres, fruit & vegetable consumption	Included
Yates, 2014 oes00894 UK	EPIC-Norfolk, Prospective Cohort, Age: 39-74 years, M/W	66 24 066 15 years	Cancer and pathology registries	FFQ, spirits	Incidence, AC and gastro-oesophageal junction	Drinkers vs. non-drinkers	0.68 (0.33-1.39)	Age, gender	Included
Hardikar, 2013 oes00875 USA	SBES, Prospective Cohort, Age: 30- years, M/W	45/ 411 6.2 years	Biopsy and follow-up	Structured personal interview, liquor	Incidence, AC	>3 vs. 0 drinks/day	1.27 (0.38-4.27) Ptrend: 0.42	Age, cigarette smoking, NSAID use, gender, waist to hip ratio	Included
Steevens, 2010 oes00816 Netherlands	NLCS, Case Cohort, Age: 55-70 years, M/W	107/ 4 214 16.3 years	Annual record linkage to the Netherlands cancer and pathology registers	Validated FFQ, liquor	Incidence, SCC	>2 glasses/day vs. no liquor	1.55 (0.64-3.78) Ptrend: 0.11	Age, sex, BMI, education level, energy intake, smoking status, ethanol intake, fish intake, fruit and vegetable intake, smoking dose and duration	Included
						Per 1 glass/day	1.21 (0.92-1.60)		
		145/			Incidence, AC	>2 glasses/day vs. no liquor	1.53 (0.68-3.48) Ptrend: 0.36		
						Per 1 glass/day	1.12 (0.87-1.43)		
Fan, 2008 oes00871 China	SCStudy, Prospective Cohort, Age: 45-64	101/ 18 244 15.5 years	Cancer registry, shanghai vital statistics office, medical history	Face-to-face interview using a structured questionnaire,	Incidence, oesophageal cancer	4+ drinks/day vs. non-drinkers	4.93 (2.60-9.36) Ptrend: <0.0001	Age at interview, BMI, fresh fruit, years of smoking, year of interview, beer, education, fresh	Included

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Inclusion/ exclusion
	years, M			spirits				vegetables, residence place at recruitment, preserved food intake, rice wine	
Freedman, 2007b oes00820 USA	NIH- AARP, Prospective Cohort, Age: 50- years, M/W	97/ 474 606 4.6 years	Record linkage to state cancer registry databases.	Validated FFQ, liquor	Incidence, SCC	>3 vs. >0-1 drink/day	4.50 (2.39-8.49) Ptrend: <0.0001	Age, sex, BMI, beer, wine consumption, education level, fruit and vegetable consumption, smoking status total energy, physical activity, vigorous activity	Included
		205/			Incidence, AC		0.82 (0.42-1.61) Ptrend: 0.93		

Table 58 Spirits intake and oesophageal cancer risk. Main characteristics of studies excluded from the highest compared to the lowest meta-analysis

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Reasons for exclusion
Grønbaek, 1998 oes00053 Denmark	CCPPS, Prospective Cohort, Age: 20-98 years, M/W	156/ 28 180 13.5 years	Cancer register	Questionnaire, spirits	Incidence, oropharyngeal and oesophageal cancer	≥7 vs. <0 drinks/week	1.50 (1.20-1.90)	Age, sex, educational level, smoking habits	Excluded, combined cancer sites
Kjaerheim, 1998 oes00130 Norway	Norwegian Men UADT, Prospective Cohort, M	71/ 10 900 25 years	Cancer registry	Questionnaire, spirits	Incidence, upper aerogastric tract cancer	4-7 vs. <1 time/week or never	2.70 (1.10-7.00) Ptrend: 0.06	Age, smoking habits	Excluded, combined cancer sites
Chyou, 1995 oes00128 USA	HHP, Prospective Cohort, M, Japanese residents of Hawaii	92/ 7 995 24 years	Cancer registry/hospital records	FFQ, 24-hour diet recall history, spirits	Incidence, upper aerodigestive tract cancer	>4 oz/month vs. non-drinker	3.61 (1.98-6.58) Ptrend: <0.0001	Age, smoking habits	Excluded, combined cancer sites

Figure 64 RR estimates of oesophageal cancer by levels of spirits intake

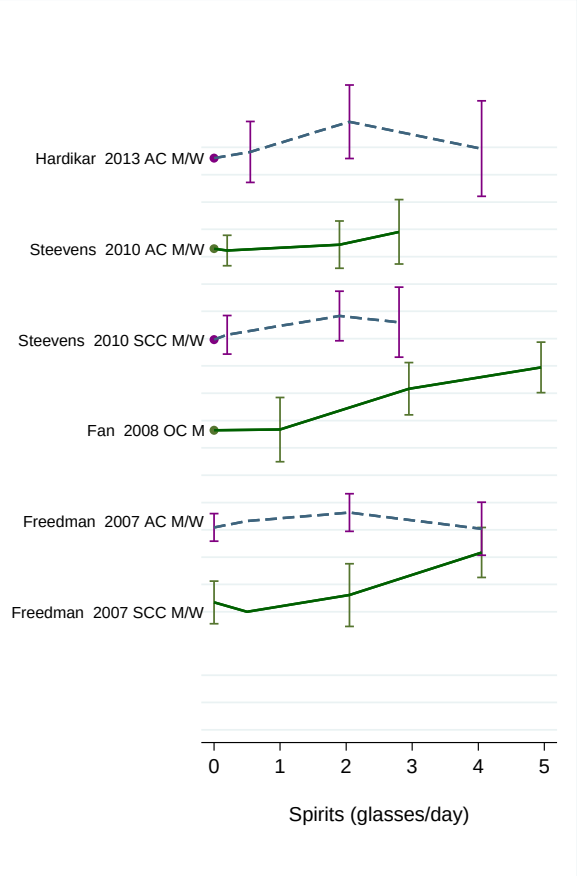


Figure 65 RR (95% CI) of oesophageal cancer for the highest compared with the lowest level of spirits intake

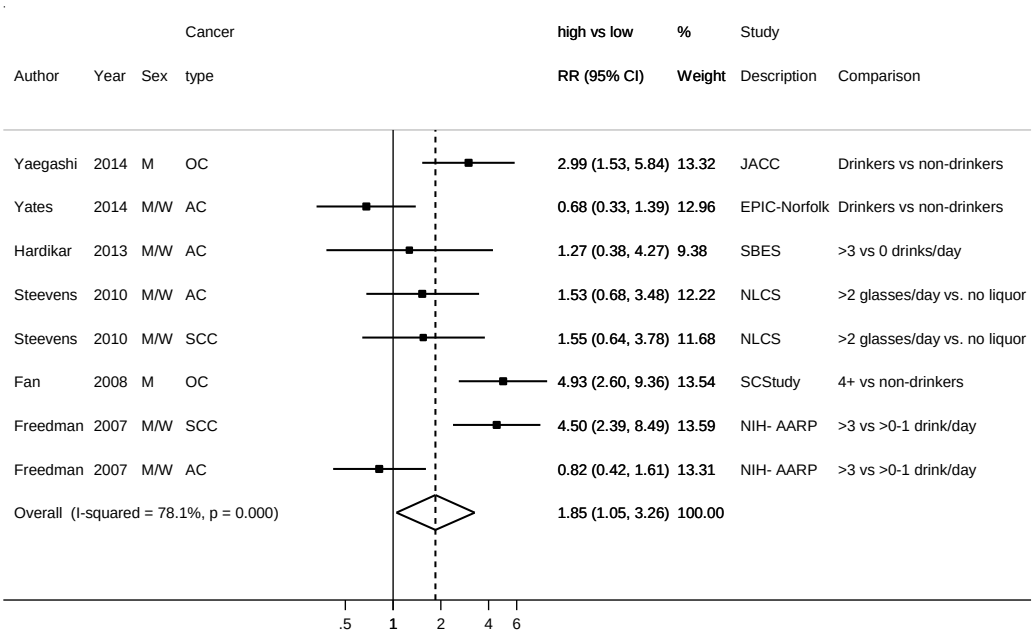
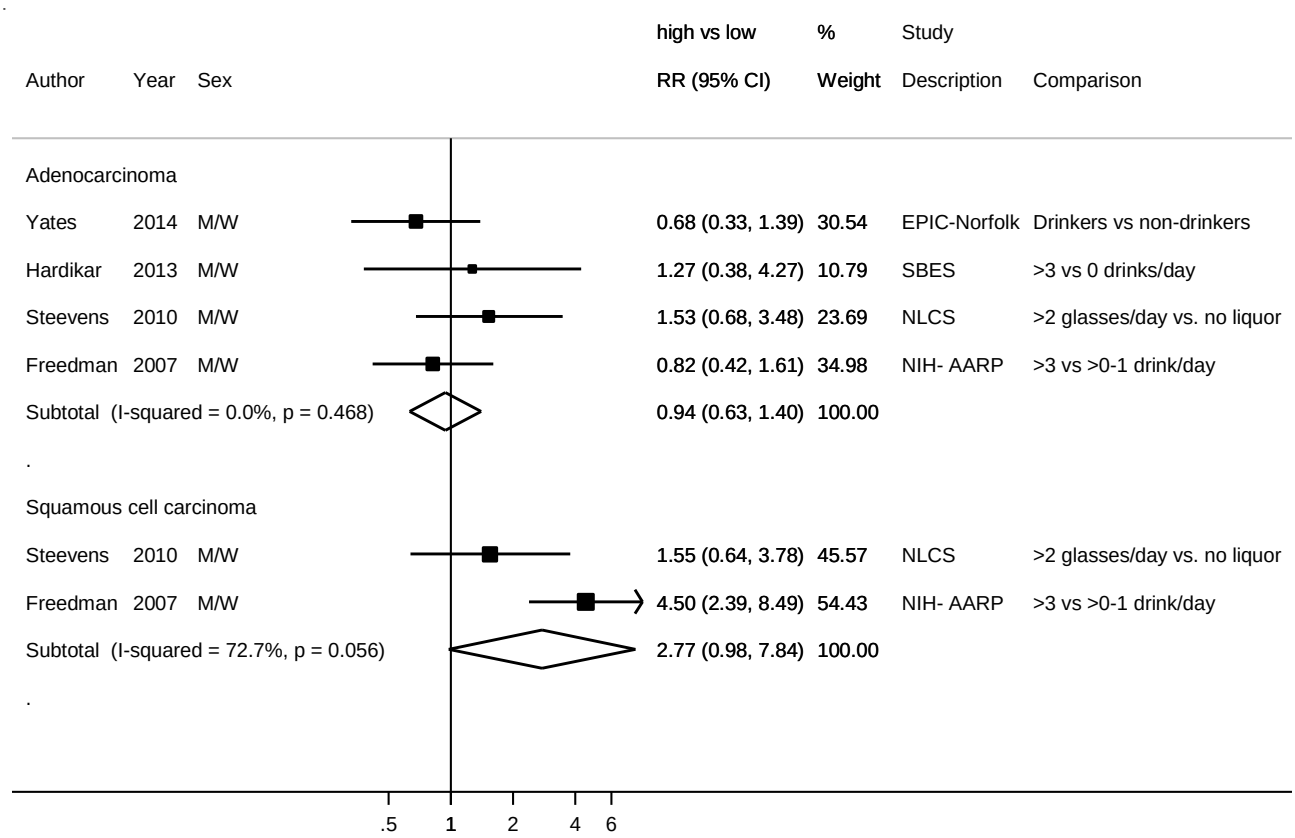


Figure 66 RR (95% CI) of oesophageal cancer for the highest compared with the lowest level of spirits intake by cancer type



5.5.1.2 Beta-carotene

There were not enough studies to update linear dose-response meta-analysis. The section is included because foods containing beta-carotene were judged as probable related to a decreased oesophageal cancer risk in the Second Expert Report. Study results are tabulated.

Randomised controlled trial

One double-blind randomised placebo controlled trial of beta-carotene supplement and alpha-tocopherol (2x2 factorial design) in male smokers in Finland reported that neither alpha-tocopherol, nor beta-carotene supplementation reduced the incidence or mortality for oesophageal cancer (Wright, 2007).

Cohort studies

Summary

Main results:

One cohort study on supplement use and four studies on blood beta-carotene levels were identified (one of this is the study on baseline blood beta-carotene levels in the ATBC trial (Wright, 2007). Dose-response meta-analysis was not conducted as the number of studies was small. No meta-analysis was conducted in the 2005 SLR.

The only significant association was the inverse relationship with baseline blood levels of beta-carotene and subsequent oesophageal cancer risk in the ATBC trial (2x2 double blind placebo controlled trial on alpha-tocopherol and beta-carotene) (Wright, 2007, 39 cases).

One meta-analysis on dietary beta-carotene reported RR of 0.46; 95% CI: 0.36-0.58 (4 studies) and 0.69; 95% CI: 0.45- 1.07 (6 studies) for adenocarcinoma and squamous cell carcinomas respectively for the highest compared to the lowest intake. The RR was 0.58 (95% CI 0.44- 0.77, 1 prospective cohort and 12 case-control studies) for oesophageal cancer (Ge, 2013).

Table 59 Beta-carotene and oesophageal cancer risk. Main characteristics of studies.
Randomised controlled trials

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors
Wright, 2007 oes00872 Finland	ATBC, 2x2 factorial double-blind placebo controlled randomised trial on alpha-tocopherol and beta-carotene supplementation Age: 50-69 years, Male smokers	24/ 29 133 6.1 years	Finnish cancer registry and death certificates	Intervention: 20 mg beta-carotene supplementation Control: no supplementation	Incidence, oesophageal cancer	Supplementation vs no supplementation with beta-carotene	0.85 (0.38-1.90)	Age at randomization, alcohol consumption, BMI, education level, energy intake, intervention assignment, smoking dose and duration
		15/			Mortality		0.67 (0.24-1.88)	
		13/		Intervention: 20 mg beta-carotene supplementation Control: placebo	Incidence	Supplementation vs placebo	0.86 (0.29-2.56)	
		10/			Mortality		0.67 (0.19-2.37)	

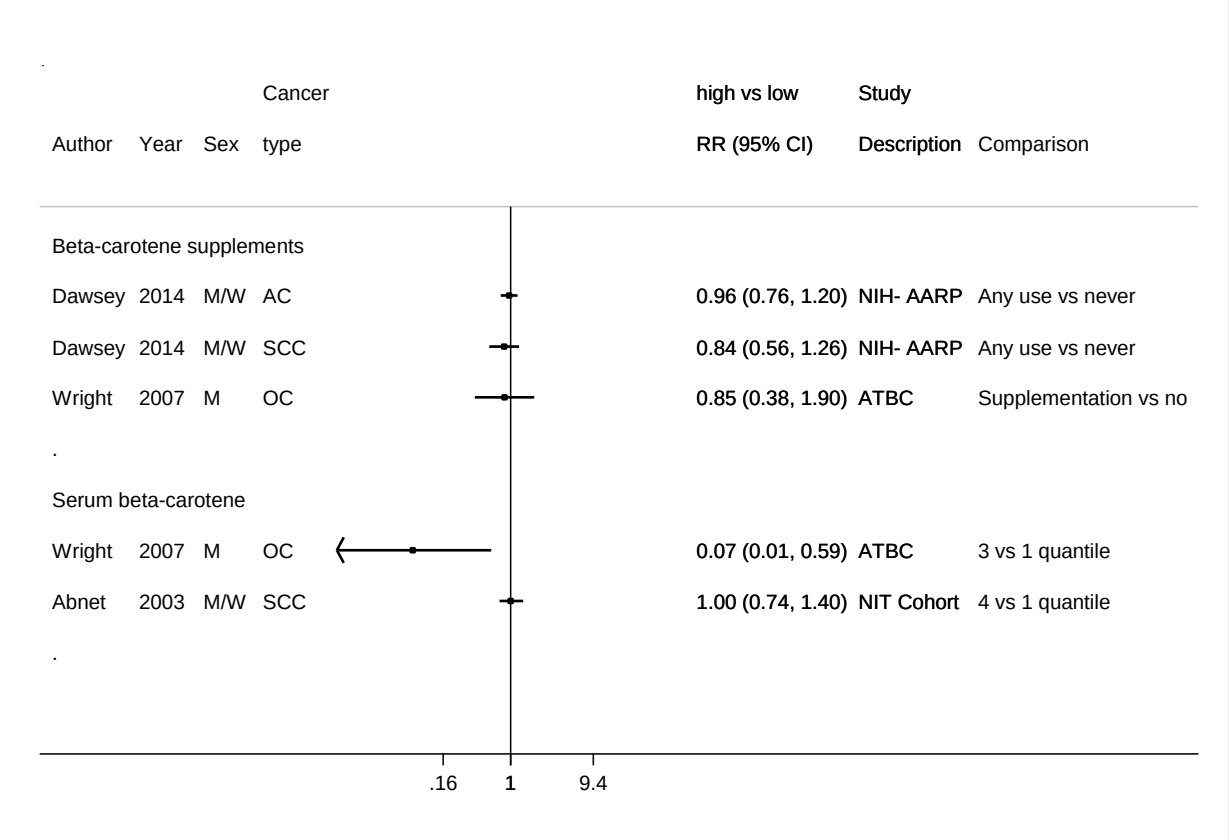
Observational studies

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors
Beta-carotene, supplements								
Dawsey, 2014 oes00890	NIH- AARP, Prospective Cohort, Age: 50-71 years,	625/ 490 593 11 years	Record linkage to state cancer registry	FFQ Beta-carotene supplement use	Incidence, AC	Any use vs never	0.96 (0.76-1.20)	Age, sex, BMI, fruit & veg consumption, smoking status,

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors
USA	M/W	212/	databases.		SCC		0.84 (0.56-1.26)	alcohol intake, education, smoking intensity, total energy intake, usual physical activity, vigorous activity
Beta-carotene, blood								
Wright, 2007 oes00872 Finland	ATBC, 2x2 factorial double-blind placebo controlled randomised trial on alpha-tocopherol and beta-carotene supplementation Age: 50-69 years, Male smokers	39/ 29 133 6.1 years		HPLC method Serum beta-carotene at trial baseline	Incidence and mortality, oesophageal cancer	Highest vs lowest tertile	0.07 (0.01-0.59) Ptrend:0.008	
Abnet, 2003 oes00056 China	NIT Cohort, Case Cohort, Age: 40-69 years, M/W, Intervention trial participants	590 6.25 years	Monthly contact by either village health workers or interviewers, and cancer diagnoses verified by senior diagnosticians	HPLC method Serum beta-carotene	Incidence, SCC	Quartile 4 vs quartile 1	1.00 (0.74-1.40) Ptrend:0.72	Age, sex, alcohol consumption, BMI, smoking habits, cholesterol
						Per 2.5 µg/dL	1.00 (0.95-1.10)	
Knekt, 1991 oes00357 Finland	FMCHES, Nested Case Control, Age: 15- years, M/W	9 cases, 16 controls 9 years	Cancer registry	HPLC, samples stored at -20C	Incidence, oesophageal cancer,	RR:1.64 Ptrend:0.33		
Oesophageal and other cancers, beta-carotene, blood								

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors
Nomura, 1997 oes00139 USA	HHP, Nested Case Control, Men Japanese residents of Hawaii	69 total, 28 oesophageal cancers 20 years	Hospital records, linkage with the Hawaii Tumour Registry	HPLC method Serum beta-carotene	Incidence, upper aerodigestive tract SCC	3 vs 1 quantile	0.11 (0.04-0.31) Ptrend:<0.01	Age, alcohol consumption, smoking habits

Figure 67 RR (95% CI) of oesophageal cancer for the highest compared with the lowest level of beta-carotene supplements and serum levels



Note: Wright, 2007 is a RCT

5.5.3 Folate

There were not enough studies to update linear dose-response meta-analysis. This section is included because the evidence that foods containing folate are related to decreased oesophageal cancer risk was judged as limited suggestive in the Second Expert Report.

Folic acid supplements and dietary folate were investigated in the NIH-AARP study. The authors reported an elevated risk of oesophageal squamous cell carcinoma with low intake of folate (RR Q1 vs Q3: 1.91; 95% CI: 1.17-3.10), but no significant association with high intake (RR Q5 vs Q3: 1.07; 95% CI: 0.59, 1.94). Folate intake was not associated with oesophageal adenocarcinoma (RR Q1 vs Q3: 1.23; 95% CI: 0.95-1.57, RR Q5 vs Q3: 1.00; 95% CI: 0.76- 1.31) (Xiao, 2014).

In the same study, acid folic supplement use was not related to risk of oesophageal adenocarcinomas (HR: 1.05; 95% CI: 0.65–1.71) and SCC (HR: 0.82; 95% CI: 0.60–1.13) compared with no use (Dawsey, 2014).

A high dietary folate intake was inversely associated with the risk of oesophageal cancer in a recent published meta-analysis of nine case-control studies (Tio, 2013). The summary RR was 0.59 (95% CI=0.51-0.69, I^2=21.1%, p=0.24). Significant inverse associations were also

observed by oesophageal cancer types (for SCC: RR=0.63, 95% CI=0.44-0.89; I^2=47.7%, p=0.13, 4 studies; for AC: RR=0.57, 95% CI=0.43-0.76, I^2=44.9%, p=0.16, 3 studies).

5.5.7 Pyridoxine (vitamin B6)

There were not enough studies to update linear dose-response meta-analysis. This section is included because the evidence that foods containing pyridoxine are related to decreased oesophageal cancer risk was judged as limited suggestive in the Second Expert Report.

One study reported on Dietary vitamin B6 and oesophageal cancer was investigated in the NIH-AARP (Xiao, 2014). Dietary vitamin B6 was not related with the risk of oesophageal adenocarcinoma (RR Q1 vs Q3: 1.20; 95% CI: 0.93-1.55, RR Q5 vs Q3:1.00; 95% CI: 0.76-1.32) or squamous cell carcinoma (RR Q1 vs Q3: 1.38; 95% CI: 0.91-2.12, RR Q5 vs Q3: 0.86; 95% CI: 0.51, 1.45).

5.5.9 Vitamin C

The evidence that foods containing vitamin C are causally linked to oesophageal cancer was judged as "Probable" in the Second expert report. For that reason, the results of cohort studies on vitamin C and oesophageal cancer have been tabulated in this section although no dose-response meta-analysis could be conducted. No meta-analysis of cohort studies was conducted in the 2005 SLR. Study results and main characteristics are tabulated.

Randomised controlled trial

No randomised controlled trial was identified.

Cohort studies

Summary

Two cohort studies reported no significant association of vitamin C supplement use with oesophageal cancer incidence (Dawsey, 2014) or mortality (Iso, 2007).

One study in a Chinese population with poor nutritional status reported no significant association of oesophageal SCC with plasma Vitamin C levels (Lam, 2013).

One study reported no significant association of dietary vitamin C with risk of mouth, pharynx and oesophageal cancers (all combined in the analysis) (Zheng, 1995).

One meta-analysis on dietary vitamin C reported RR of oesophageal adenocarcinoma and cardia cancer of 0.65; 95% CI: 0.54-0.78, P for heterogeneity<0.02 (7 case-control studies) and 0.49; 95% CI: 0.39- 0.62 (4 studies), P for heterogeneity: 0.10 (4 case-control studies) for oesophageal adenocarcinomas (Kubo, 2007).

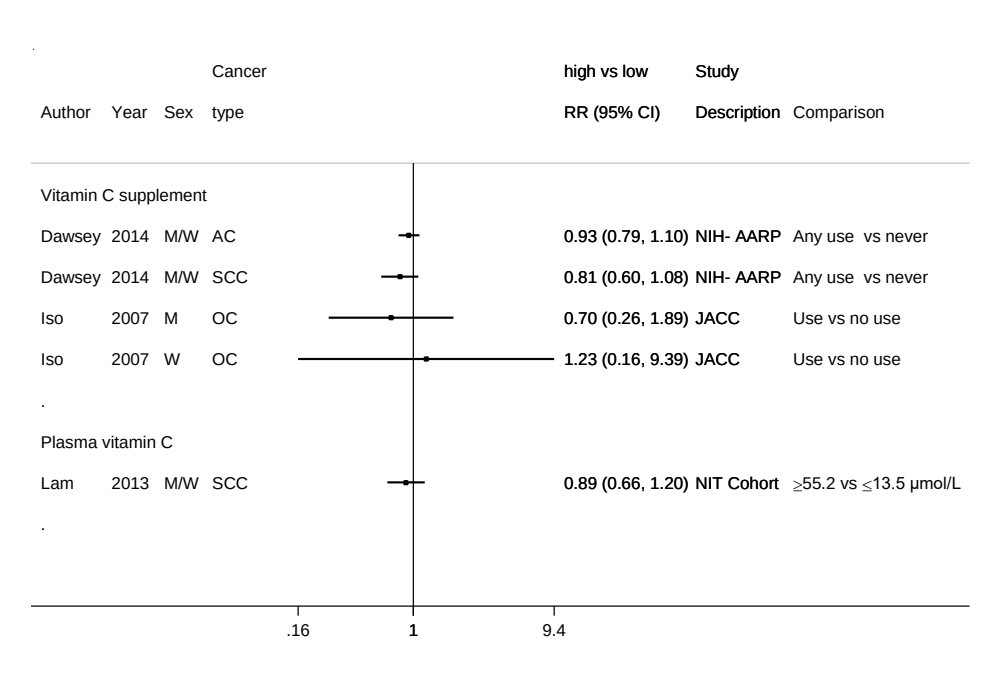
Table 60 Vitamin C and oesophageal cancer risk. Main characteristics of identified studies.

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors
Vitamin C, supplements								
Dawsey, 2014 oes00890 USA	NIH- AARP, Prospective Cohort, Age: 50-71 years, M/W	625/ 490 593 11 years	Record linkage to state cancer registry databases.	FFQ, Vitamin C supplement	Incidence, AC	Any use* vs never	0.93 (0.79-1.10)	Age, sex, BMI, smoking status and intensity, education, fruits and vegetables intakes, alcohol, total energy intake, physical activity, vigorous activity
		212/			Incidence, SCC		0.81 (0.60-1.08)	
Iso, 2007 oes00847 Japan	JACC, Prospective Cohort, Age: 40-79 years, M/W	151/ 105 500 15 years	Date and cause of death annually or biannually confirmed with government authorization	Validated FFQ Vitamin C supplement	Mortality, oesophageal cancer Men	Use vs no use	0.70 (0.26-1.89)	Age, area of study
		24/			Women		1.23 (0.16-9.39)	
Vitamin C, blood								
Lam, 2013 oes00880 China	NIT Cohort, Case Cohort, Age: 40-69 years, M/W	618/ 16 000 7 years	Monthly checks of village doctors' records and quarterly checks of the Linxian Cancer Registry	Plasma vitamin C (HPLC)	Incidence, SCC	≥55.2 vs ≤13.5 µmol/L	0.89 (0.66-1.20) Ptrend:0.35	Age, sex, BMI, H. Pylori infection, season of blood draw, smoking
						Per 20 µmol/L	0.97 (0.86-1.09)	
Vitamin C, from foods								

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors
Zheng, 1995 oes00141 USA	IWHS, Prospective Cohort, Age: 55-69 years, Post-menopausal women	33/ 34 691 7 years	Iowa Health Registry and Death Registry	FFQ Dietary vitamin C	Incidence, mouth, pharynx, oesophagus	>5.56 vs <4.97 mg/day	0.70 (0.30-1.70) Ptrend:0.45	Age, energy intake, smoking habits

* Any use defined as taking supplements more than once per month.

Figure 68 RR (95% CI) of oesophageal cancer for the highest compared with the lowest level of vitamin C (plasma or supplement use)



5.5.11 Vitamin E

The evidence on food containing Vitamin E and oesophageal cancer was judged as limited suggestive (decreases risk) in the Second Expert Report.

Two studies and one randomised controlled trial were identified in the CUP. The study characteristics and results are tabulated.

In the NIH-AARP (Carman, 2009) there was some evidence of association of dietary alfa-tocopherol, with significant decreased risk of oesophageal squamous cell carcinoma (158 cases) and borderline significant increased oesophageal adenocarcinoma (382 cases) risk in the continuous analyses but no trend was observed in categorical analyses. There was no significant association with Vitamin E supplements. One study reported no significant association of dietary vitamin E with oral, pharyngeal, and oesophageal cancer risk (all cancers combined) (Zheng, 1995). The ATBC trial of male smokers reported non-significant inverse associations in those who took alfa-tocopherol supplementation compared with those with no supplementation or placebo (Wright, 2007).

One published meta-analysis of observational studies reported a non-significant inverse association with oesophageal adenocarcinoma (summary RR for highest vs lowest=0.80, 95% CI=0.63-1.03, p heterogeneity=0.59, 3 case-control studies) (Kubo, 2007). Another published meta-analysis of RCTs reported no significant association with vitamin E supplements alone or with other supplements compared to the control (RR=1.00, 95% CI=0.88-1.14) (Alkhenizan, 2007).

Table 61 Vitamin E and oesophageal cancer risk. Main characteristics of identified studies.

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors
Alfa-tocopherol, diet								
CARMAN, 2009 oes00824 USA	NIH- AARP, Prospective Cohort, Age: 50-71 years, M/W	382 AC, 158 SCC/ 490 593 ~ 7years	Record linkage to state cancer registry databases.	FFQ, Alfa-tocopherol	Incidence, AC	Continuous per 1.17 mg increased intake	1.05 (1.00–1.11)	Age, sex, supplementary vitamin E, smoking, education, physical activity, alcohol consumption, BMI and total calorie intake.
					Incidence, SCC		0.90 (0.81–0.99)	
					Incidence, AC	Q4 vs Q1	1.27 (0.94–1.72) Ptrend: 0.64	
					Incidence, SCC		0.90 (0.58–1.40) Ptrend: 0.12	
Zheng, 1995 oes00141 USA	IWHS, Prospective cohort	33 mouth, pharynx and oesophagus cancers /34 691 women ~6 years	State Health Registry and Death Index	FFQ, Vitamin E	Incidence, mouth, pharynx and oesophageal	>2.93 mg vs <2.01 mg	0.8 (0.3-2.0) P trend: 0.67	Age, smoking, total energy intakes
Supplement Vitamin E								
Carman, 2009 oes00824 USA	NIH- AARP, Prospective Cohort, Age: 50-71 years, M/W	158 AC, 288 SCC/ 490 593 ~ 7years	Record linkage to state cancer registry databases.	FFQ, Alfa-tocopherol	Incidence, AC	Continuous per 71 mg increased intake	1.00 (0.93–1.08)	Age, sex, dietary alfa-tocopherol, smoking, education, physical activity, alcohol consumption, BMI and total calorie intake.
					Incidence, SCC		0.92 (0.82–1.04)	
					Incidence, AC	>360 g vs none vs Q1	0.91 (0.56-1.48) Ptrend: 0.83	
					Incidence, SCC		1.03(0.49-2.19) Ptrend: 0.23	

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors
Supplement alpha-tocopherol								
Wright, 2007 oes00872 Finland	ATBC, 2x2 factorial double-blind placebo controlled randomised trial on alpha-tocopherol and beta-carotene supplementation Age: 50-69 years, Male smokers	24/ 29 133 6.1 years	Finnish cancer registry and death certificates	Intervention: 50 mg dl α-tocopheryl acetate supplementation Control: no supplementation	Incidence, oesophageal cancer	Supplementation vs no supplementation with dl α-tocopheryl acetate	0.85 (0.38-1.89)	Age at randomization, alcohol consumption, BMI, education level, energy intake, intervention assignment, smoking dose and duration
		15/			Mortality		0.50 (0.17-1.47)	
		13/		Intervention: 50 mg dl α-tocopheryl acetate supplementation Control: placebo	Incidence	Supplementation vs placebo	0.86 (0.29-2.56)	
		9/			Mortality		0.50 (0.13-2.00)	

6 Physical activity

Five studies (seven publications) assessed physical activity using different instruments and for a variety of physical activities. One study (Wannamethee, 2001) investigated incidence of upper aerodigestive tract and stomach cancers (combined) and these results are also displayed in the tables.

Dose-response meta-analyses were not possible. Four studies reported results on recreational physical activity (leisure time physical activity, recreational and household activities, sports) and a meta-analysis of the highest compared to the lowest activity level was conducted.

A few studies reported on total physical activity using an index, occupational physical activity, vigorous physical activity, walking, sitting, and television viewing and these results are shown in tables. Details of the physical activity assessment in each cohort included in the review are tabulated below. Study characteristics and main results are shown in tables.

Table 62 Main characteristics of physical activity assessment in studies include in the review

Study	Domains	Description of assessment	Validation
British Regional Heart Study (BRHS) (Wannamethee, 2001)	Leisure time	Frequency of regular walking, cycling (including to work); recreational activities (gardening, pleasure walk, do-it-yourself), sports (vigorous: running, golf, swimming, tennis, sailing, digging)	Not indicated
European Prospective Investigation into Nutrition and Cancer (EPIC) (Huerta, 2010)	Occupational Leisure time	Interview in part of the cohort or self-administered. Occupational activity (unemployed, sedentary, standing, manual, heavy manual and unknown), non-occupational physical activity (housework, home repair, gardening, stair climbing), recreational activities (walking, cycling and all other sports combined), vigorous nonoccupational activity (recreational and household activities causing sweating or faster heartbeat).	Relative validity and reproducibility undertaken; the questionnaire was found to be satisfactory for the ranking of subjects, less suitable for estimation of energy expenditure. Construct validity by correlation with BMI
Japan Collaborative Cohort Study for Evaluation of Cancer (JACC) (Suzuki, 2007)	Leisure time	Questionnaire. Frequency of sport or physical exercise, time walking, time watching TV	Not indicated
Korean National Health Insurance Corporation Study 2002 (KNHIC)	Leisure time	Frequency and duration of vigorous, sweat-producing leisure physical activity	Not indicated

(Yun, 2008)			
National Institutes of Health – AARP Diet and Healthy Study (NIH-AARP) (Arem, 2014; Cook, 2013; Leitzmann, 2009)	Occupational Leisure time	Questionnaires. Routine at work (sitting, walking, lifting light loads or climbing stairs or hills, heavy work or carry heavy loads); frequency of activities of any type that lasted 20 minutes or more and caused either increases in breathing or heart rate or working up a sweat; recreational moderate-vigorous physical activity; sitting; TV watching	Not validated with reference instruments; a similar questionnaire showed good reliability and reasonable validity

6.1 Physical activity index

One cohort study assessed physical activity using an index that combined occupational activity and time spent in sport and cycling (Huerta, 2010). No significant association with oesophageal adenocarcinoma was observed when comparing the highest with the lowest activity level. The analysis was adjusted for weight, height and other potential confounders.

6.1.1.1 Occupational physical activity

Two cohort studies investigated physical activity (Cook, 2013; Huerta, 2010). Non-significant (inverse) associations were observed when comparing manual/heavy work compared with sedentary work. The analyses were adjusted by BMI, or weight and height, and other potential confounders.

Table 63 Physical activity and oesophageal cancer risk. Results of meta-analyses and pooled analyses published after the 2005 SLR

Author, Year	Number of studies	Total number of cases	Studies country, area	Outcome	Physical activity/ Subgroup	RR (95%CI) High vs low	P trend	Heterogeneity (I^2, p value)
Meta-analyses								
Chen, 2014	3 cohorts** 4 case-control 7 studies	984	Canada, China, Europe, Japan, Korea, Norway, Turkey, UK, USA	Incidence, Oesophageal cancer	Any physical activity Cohorts Case-control All studies	 0.78 (0.66-0.92) 0.55 (0.28-1.10) 0.73 (0.56-0.97)		 0%, 0.51 73.4%, 0.01 58.4%, 0.02
	3 case-control, 1 cohort 1 case-control				Men Women	0.81 (0.64-1.02) 0.35 (0.04-3.15)		26.8%, 0.25 -
	2 cohorts 1 case-control, 1 cohort			SCC AC		0.25 (0.01-4.97)* 0.79 (0.58-1.08)		92.0%, <0.0001 0%, 0.51
	3 case-control			Oesophageal cancer	Occupational activity	0.49 (0.17-1.38)*		78.7%, 0.003
	1 case-control, 2 cohorts				Recreational activity	0.80 (0.63-1.01)		8.8%, 0.33

*Results from supplementary figure S4 of publication **The three cohort studies were included in the CUP review

Table 64 Physical activity index and oesophageal cancer risk. Main characteristics of studies identified

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Inclusion/exclusion
Huerta, 2010 oes00846 Denmark, France,Germany Greece,Italy, Netherlands, Spain,Sweden, UK	EPIC, Prospective Cohort, Age: 25-75 years	80/ 420 449 8.8 years	Cancer registries, health insurance records, pathology rec, active follow up, death certificate	Questionnaire	Incidence, AC	Physical activity index (occupational activity and sports and cycling) Active vs inactive	0.98 (0.48-2.01) Ptrend: 0.95	Age, sex, alcohol consumption, centre, education level, fruit intake, height, smoking status, weight, red and processed meat, total energy intake	No analysis

Table 65 Occupational physical activity and oesophageal cancer risk. Main characteristics of studies identified

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Inclusion/exclusion
Cook, 2013 oes00877 USA	NIH- AARP Diet and Health Study, Prospective Cohort, Age: 50-71 years, M/W	846/ 493 802 215/	Record linkage to state cancer registry databases.	Baseline questionnaire	Incidence SCC	Heavy work vs all day sitting	0.73 (0.27-2.01)	Age, sex, alcohol consumption, BMI, cigarette smoking, ethnicity, fruit consumption, perceived health, education, vegetable consumption	No analysis
		631/			AC		0.60 (0.34-1.07)		
		215/			SCC	Lift light loads, climb vs all day sitting	0.73 (0.40-1.35)		
		631			AC		0.90 (0.65-1.26)		
		215/			SCC	Walking, minimal lifting vs all day sitting	0.91 (0.53-1.55)		
		631			AC		0.83 (0.61-1.12)		
		215/			SCC	Mostly sitting vs all day sitting	1.08 (0.63-1.84)		
		631			AC		0.89 (0.65-1.20)		
Huerta, 2010 oes00846 Denmark,France, Germany,Greece, Italy,Netherlands, Spain,Sweden, UK	EPIC, Prospective Cohort, Age: 25-75 years	39/ 420 449 8.8 years	Cancer registries, health insurance records, pathology rec, active follow up, death certificate	Questionnaire	Incidence, AC	Manual work vs sedentary occupation	0.95 (0.41-2.20)	Age, sex, alcohol consumption, centre, education level, fruit intake, height, smoking status, weight, red and processed meat, total energy intake	No analysis
						Manual work vs standing occupation	1.61 (0.77-3.41)		

6.1.1.2 Recreational physical activity

Randomised controlled trial

No randomised controlled trial was identified

Cohort studies

Summary

Main results:

Five cohort studies (seven publications) reported results on leisure time physical activity, recreational and household activities, or sports. One study (Wannamethee, 2001) was on combined upper aerodigestive tract and stomach cancers only, and was excluded from the meta-analysis of oesophageal cancer risk. Non-significant (inverse) association (no heterogeneity, four studies) was observed for the highest compared with the lowest recreational physical activity level. All studies adjusted for BMI or weight and height, except the study on mortality (Suzuki, 2007).

For upper aerodigestive tract cancer (Leitzmann, 2009) and combined upper aerodigestive tract and stomach cancers (Wannamethee, 2001), significant inverse associations were reported.

Table 66 Recreational physical activity and oesophageal cancer risk. Number of studies in the CUP SLR

	Number
Studies identified	5 (7 publications)*
Studies included in forest plot of highest compared with lowest exposure	4
Studies included in linear dose-response meta-analysis	Not enough studies

Note: *****Included one study (Wannamethee, 2001) reported results on upper aerodigestive tract and stomach cancers combined only.

Table 67 Recreational physical activity and oesophageal cancer risk. Summary of the highest versus lowest meta-analysis in the and CUP

	2005 SLR	**CUP**
Comparison	No meta-analysis	High vs low
All studies		
Studies (n)	-	4
Cases (total number)	-	1366
RR (95%CI)	-	0.85 (0.72-1.01)
Heterogeneity (I^2, p-value)	-	0%, 0.72
P value Egger test	-	-

Table 68 Recreational physical activity and oesophageal cancer risk. Main characteristics of studies identified

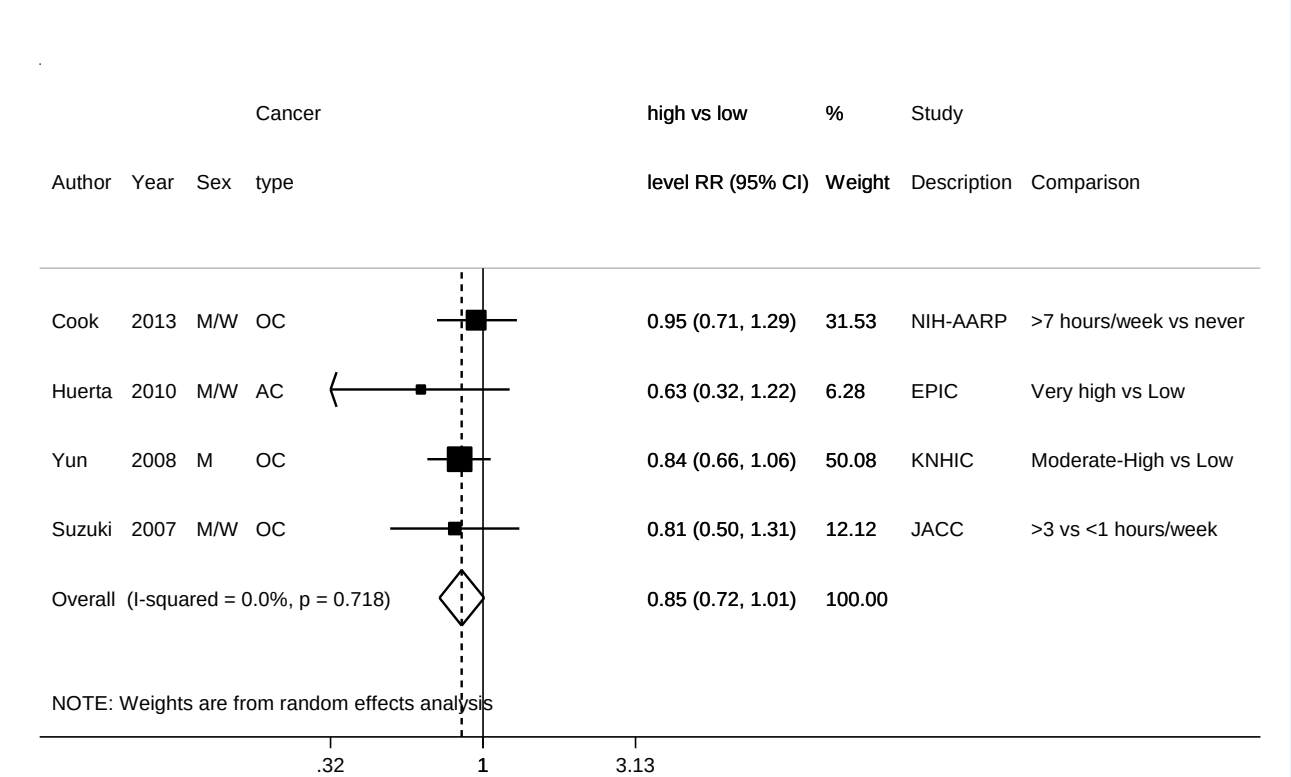
Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Inclusion/ exclusion
Arem, 2014 oes00879 USA	NIH-AARP, Prospective Cohort, Age: 50-71 years, M/W	491/ 293 511 12.1 years	Record linkage to state cancer registry databases.	Questionnaire Moderate to vigorous physical activity during the last 10 years	Mortality, oesophageal cancer	>7 hrs/week vs never/rare	0.80 (0.60-1.08) Ptrend: 0.25	Sex, BMI, calories, diabetes, healthy eating index 2010 score, marital status, race, alcohol intake, education, smoking status and dose	Excluded, analysis included incident data from Cook, 2013, OES00877, NIH-AARP
						Per 1 hour increase	0.98 (0.96-1.01)		
		62/			Never smokers	Per 1 hour increase	0.96 (0.89-1.05)		
		429/			Ever smokers		0.99 (0.96-1.02)		
		25/ 297			Inactive obese vs active non-obese		1.28 (0.85-1.94)		
		106/297			Active obese vs active non-obese		1.63 (1.30-2.04)		
		63/297			Inactive obese vs active non-obese		1.30 (0.99-1.72)		
Cook, 2013 oes00877 USA	NIH- AARP, Prospective Cohort, Age: 50-71 years, M/W	846/ 493 802 4 795 319 person-years 128/	Record linkage to state cancer registry databases.	Risk factor questionnaire	Incidence SCC	Typical recreational moderate-vigorous physical activity in the last 10 years	0.88 (0.49-1.58) Ptrend:0.50	Age, sex, alcohol consumption, BMI, cigarette smoking, ethnicity, fruit consumption, perceived health, education, vegetable consumption	Included, results by cancer types were combined using a fixed effect model
		377/			AC	>7 hours/week vs never	0.98 (0.69-1.39) Ptrend:0.84		
		215/		Baseline questionnaire	SCC	Typical physical activity and sports during ages 15-18 years >5 times/week vs never	0.53 (0.23-1.23) Ptrend:0.75		Not analysed
		631/			AC		0.57 (0.30-1.07) Ptrend:0.07		
		215/			SCC	Strenuous physical activity during last 12 months >5 times/week vs	0.84 (0.47-1.52) Ptrend:1.00		Not analysed

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Inclusion/ exclusion
		631/			AC	never	0.74 (0.49-1.12) Ptrend:0.47		
Huerta, 2010 oes00846 Denmark,France,Germany, Greece,Italy, Netherlands, Spain,Sweden, UK	EPIC, Prospective Cohort, Age: 25-75 years M/W	80/ 420 449 8.8 years	Cancer registries, health insurance records, pathology rec, active follow up, death certificate	Questionnaire	Incidence, AC	Recreational and household physical activity Very high vs low	0.63 (0.32-1.22) Ptrend:0.18	Age, sex, centre, weight, height, alcohol consumption, education levels, smoking status, intakes of fruit, red and processed meat, total energy	Included
						Gardening Active vs never	0.74 (0.44–1.23) Ptrend: 0.43		Not analysed
						Cycling Active vs never	1.30 (0.79–2.15) Ptrend: 0.96		
						Vigorous >2 h/week vs none	0.72 (0.36-1.42) Ptrend:0.31		
						Sport Active vs never	0.68 (0.41–1.12) Ptrend:0.09		
Leitzmann, 2009 oes00813 USA	NIH- AARP, Prospective Cohort, Age: 50-71 years, M/W	523/ 487 732 8 years	Record linkage to state cancer registry databases.	Baseline questionnaire	Incidence	Physical activity lasting ≥20 min. and caused increase in breathing, heart rate or sweating ≥5 vs 0 times/week	1.05 (0.64-1.74) Ptrend:0.76	Age, BMI, sex, family history of cancer, smoking status, intensity and time since quitting smoking, alcohol intake, marital status, race/ethnicity, education intakes of fruit and vegetables,	Superseded by Cook, 2013, OES00877
		149/			SCC				
		374/			AC		0.75 (0.53-1.06) Ptrend: 0.24		
		1016			Upper gastrointestinal tract		0.73 (0.59-0.89) Ptrend:0.007		

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Inclusion/ exclusion
								red meat	
Yun, 2008 oes00833 Korea	KNHIC, Prospective Cohort, Age: 40- years, M	293/ 444 963 6 years	Cancer registry	Self-report	Incidence, oesophageal cancer	Vigorous, sweat producing leisure time physical activity	0.84 (0.66-1.06)	Age, BMI, dietary preference, employment, fasting blood sugar, smoking status, alcohol drinking	Included
		63/			Never smokers/ex-smokers	Moderate-high vs low	0.89 (0.54-1.47)		
		230/			Current smoker		0.82 (0.62-1.08)		
Suzuki, 2007 oes00837 Japan	JACC, Prospective Cohort, M/W	147/ 109 778 124/ 456 405 person-years	Date and cause of death annually or biannually confirmed with government authorization	Questionnaire	Mortality, oesophageal cancer Men	Sports	0.79 (0.47-1.33)	Age, study area	Included, results by sex were combined using a fixed effect model
		23/ 638 490 person-years			Women	>3 vs <1 hours/week	0.93 (0.26-3.24)		
		110/ 405 988 person-years			Men	Duration of sports in the school times Yes vs little	0.96 (0.60-1.53)		Not analysed
		20/ 580 648 person-years			Women		1.74 (0.56-5.38)		
Wannamethee, 2001 oes00712 England,	BRHS, Prospective Cohort, Age: 40-59	124/ 7588 18.8 years	Health care registries	Questionnaire	Incidence, combined upper aerodigestive tract and	Vigorous sports Yes vs no	0.56 (0.32-0.96)	Age, alcohol consumption, smoking habits, socio-economic	Combined UADTC and stomach cancers, not
						≥2 times/week vs <1 time/month	0.38 Ptrend: 0.01		

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Inclusion/ exclusion
Wales, Scotland	years, M				stomach cancers	Vigorous vs none-moderate	0.46 (0.11-1.90) Ptrend:0.05	status	analysed

Figure 69 RR (95% CI) of oesophageal cancer for the highest compared with the lowest level of recreational physical activity



Note: Moderate-vigorous activity (Cook, 2013); recreational and household activity (Huerta, 2010); vigorous, sweat-producing leisure time activity (Yun, 2008); Sports (Suzuki, 2007). Suzuki investigated mortality for oesophageal cancer.

6.1.1.4 Walking

Three cohort studies reported results on walking, one (Suzuki, 2007) on oesophageal mortality, one (Huerta, 2010) on oesophageal adenocarcinoma risk, and one on the risk of combined upper aerodigestive tract and stomach cancers (Wannamethee, 2001). Non-significant inverse associations were observed in the studies.

6.1.3 Vigorous physical activity

Four cohort studies (five publications) reported results on vigorous physical activity (Cook, 2013; Huerta, 2010; Leitzmann, 2009; Yun, 2008; Wannamethee, 2001). Non-significant inverse associations were observed in the studies of oesophageal cancer (AC &/SCC) (Cook, 2013; Huerta, 2010; Leitzmann, 2009; Yun, 2008). Significant inverse associations were observed in the studies of upper aerodigestive tract cancer (Leitzmann, 2009) and combined upper aerodigestive tract and stomach cancers (Wannamethee, 2001). Study details and results are in the Table together with recreational physical activity.

6.2 Physical inactivity

Only one study (Cook, 2013) reported results on sitting and two studies (Cook, 2013; Suzuki, 2007) reported results on TV watching. Non-significant associations were observed in the studies.

Table 69 Walking and oesophageal cancer risk. Main characteristics of studies identified.

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors
Huerta, 2010 oes00846 Denmark,France ,Germany, Greece,Italy, Netherlands, Spain,Sweden, UK	EPIC, Prospective Cohort, Age: 25-75 years	80/ 420 449 8.8 years	Cancer registries, health insurance records, pathology rec, active follow up, death certificate	Questionnaire	Incidence, oesophageal adenocarcinoma	Walking T3 vs never	0.73 (0.32-1.67) Ptrend:0.59	Age, sex, alcohol consumption, centre, education level, fruit intake, height, smoking status, weight, red and processed meat, total energy intake
Suzuki, 2007 oes00837 Japan	JACC, Prospective Cohort, M/W	137/ 109 778 116/ 430 341 person-years	Date and cause of death annually or biannually confirmed with government authorization	Questionnaire	Mortality, oesophageal cancer Men	Walking > 1 vs <0.5 hours/day	0.97 (0.63-1.50)	Age, study area
		21/ 602 515 person-years			Women		0.57 (0.23-1.47)	
Wannamethee, 2001 oes00712 England, Wales, Scotland	BRHS, Prospective Cohort, Age: 40-59 years, M	124/ 7588 18.8 years	Health care registries	Questionnaire	Incidence, combined upper aerodigestive tract and stomach cancers	Walking back and to work >60 vs <20 minutes/day	0.97 (0.39-2.42)	Age, alcohol consumption, smoking habits, socio-economic status

Table 70 Physical inactivity and oesophageal cancer risk. Main characteristics of studies identified

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Inclusion/exclusion
Cook, 2013 oes00877 USA	NIH- AARP, Prospective Cohort, Age: 50-71 years, M/W	505/ 493 802 4 795 319 person-years	Record linkage to state cancer registry databases.	Risk factors questionnaire	Incidence SCC	Sitting >9 vs <3 hours/day	0.87 (0.40-1.90) Ptrend: 0.78	Age, sex, alcohol consumption, BMI, cigarette smoking, ethnicity, fruit consumption, perceived health, education, vegetable consumption	Not analysed
		377/			AC		0.69 (0.41-1.15) Ptrend: 0.36		
		128/			SCC	TV watching >7 vs <1 hours/day	0.78 (0.26-2.32) Ptrend: 0.88		
		377/			AC		0.55 (0.29-1.01) Ptrend: 0.09		
Suzuki, 2007 oes00837 Japan	JACC, Prospective Cohort, M/W	137/ 109 778	Date and cause of death annually or biannually confirmed with government authorization	Questionnaire	Mortality, oesophageal cancer Men	TV watching ≥4 vs <2 hours/day	1.17 (0.69-1.98)	Age, study area	Not analysed
		150/ 564 310 person-years							
		27/ 493 675 person-years			Women		0.75 (0.23-2.46)		

8 Anthropometry

8.1.1 Body Mass Index (BMI)

Cohort studies

Summary

Main results:

The analyses were conducted for oesophageal cancer (any type), adenocarcinomas and squamous cell carcinomas.

Sixteen studies (10 342 cases) were included in the dose-response meta-analysis. No significant association of BMI with oesophageal cancer was observed (high heterogeneity).

In analysis by cancer type, a significant positive association with adenocarcinomas (nine studies, moderate heterogeneity) and a significant inverse association with squamous cell carcinomas (eight studies, high heterogeneity) were observed. When combined with the published results of a non-overlapping pooled analysis of seven cohorts (Lindkvist, 2014), the significant positive association with oesophageal adenocarcinomas (1839 cases) and the significant inverse association with squamous cell carcinomas (4532 cases) remained similar (see Table).

There was no evidence of a significant publication or small study bias (p=0.9).

Three studies were excluded from the dose-response analysis. One study reported a significant inverse association with oesophageal cancer (Samanic, 2004), one reported a significant increased incidence in obese patients compared with the general public (Moller, 1994) and in a cohort of alcoholics (Yokoyama, 2006), significant inverse associations with oesophageal SCC were observed.

One additional study (MacInnis, 2006) that found a significant positive association of BMI with distal oesophageal and cardia stomach cancers (30 cases) was not included in the analysis. Three studies included in the dose-response analysis of oesophageal cancer also reported for some cancer sites combined, showing significant inverse associations with SCC of the upper and middle oesophagus, and distal oesophagus (Oh, 2005), significant positive associations with oesophageal AC (Yates, 2014; 87% of the 65 cancers involved the gastro-oesophageal junction), and non-significant (inverse) association with upper aerodigestive cancer mortality (140 cases) (Chen, 2012)

Sensitivity and stratified analyses:

The high heterogeneity observed in analysis for oesophageal cancer (81.7%) was not explained in stratified analyses. It should be attributable to the proportion of cases of SSC and adenocarcinomas in each study.

Although in several Asian studies the analyses were not conducted by cancer type, a higher proportion of cases should have been SCC cancer cases. BMI was inversely associated with oesophageal cancer in Asian studies (five studies, no heterogeneity) but not in European studies (six studies, high heterogeneity) and North American studies (five studies, low heterogeneity). Other stratified analyses on oesophageal cancers are tabulated, but the

interpretation of the results is hampered by the differential association of BMI with oesophageal adenocarcinomas and SCC.

Stratified analyses within each type of oesophageal cancer were limited by the low number of studies. Within each cancer type, the associations were similar in men and women, in studies with self-reported or measured weight and height, in studies adjusted and not adjusted by smoking, and in in European and North-American studies.

There were not enough studies to do meta-analysis by smoking status. In the EPIC study (Steffen, 2009) and the NIH-AARP (Abnet, 2008), BMI seemed to be more strongly associated with oesophageal adenocarcinoma risk in smokers than in non-smokers, but the interaction tests were not significant. In EPIC (Steffen, 2009) BMI was significantly inversely associated with SCC risk among smokers but not among non-smokers (P for interaction = 0.004). In the Million Women Study (Reeves, 2007) the association of BMI was similar in never smokers and the entire cohort for oesophageal adenocarcinomas (53 and 150 cases respectively) and squamous cell carcinomas (83 and 263 cases respectively).

In the pooled study – Me-Can (Lindkvist, 2014) there was no interaction between smoking status and BMI for oesophageal adenocarcinomas and SCC. The associations were of similar trend inside each cancer type but significant only in former and current smokers for adenocarcinomas and in current smokers for SCC.

Non-linear dose-response meta-analysis:

A non-linear association was observed in analysis on oesophageal cancer; the interpretation is difficult as oesophageal adenocarcinomas and SSC have an opposite relationship with BMI. The increased risk of AC with increasing BMI seems linear. There was significant evidence of non-linearity for SCC ($p<0.001$) mainly because the curve starts to flatten above 30 kg/m^2 of BMI

Study quality:

Some studies recruited specific populations: the Seattle Barrett's Oesophagus Study (SBES, Hardikar, 2013) was a high-risk cohort of Barrett's Oesophagus patients; the NIT cohort is a follow-up of participants in a randomized trial of vitamin/minerals in China where poor nutritional status was common (Tran, 2005). BMI was from <20 to ≥ 23 kg/m^2 in this study. One American study was on pesticides applicators and their spouses (Andreotti, 2010). Influence analysis showed that none of these studies had a strong influence in the summary RR.

Loss to follow-up was low when reported and cancer outcome was confirmed using medical notes or cancer registries in most studies. However, several studies did not differentiate oesophageal SCC from AC.

In studies on oesophageal cancer with measured weight and height, inverse associations with BMI were observed on average, while in studies with self-reported height and weight (and in one study from medical records) the association was positive. However, among studies on AC and SCC the associations did not differ by weight and height assessment method.

All studies included in the dose-response analysis were adjusted at least for age and sex. The overall positive association with AC and the inverse association with SCC were observed independently of the adjustment for smoking.

Table 71 BMI and oesophageal cancer risk. Number of studies in the CUP SLR

	Number
Studies identified	20 (25 publications)*
Studies included in forest plot of highest compared with lowest BMI	16
Studies included in linear dose-response meta-analysis	16
Studies included in non-linear dose-response meta-analysis	13

*****Includes four studies on distal oesophageal and gastric cardia cancer, upper aerodigestive cancers, upper, middle, and distal oesophageal and gastric cardia cancers, or cancers that involved gastro-oesophageal junction.

Table 72 BMI and oesophageal cancer. Summary of the linear dose-response meta-analysis in the 2005 SLR and CUP

	2005 SLR	**CUP**
Increment unit used	1 kg/m2	5 kg/m2
All studies		
Studies (n)	1	16
Cases (total number)	1065	10342
RR (95%CI)	1.07 (1.00-1.14)	0.99 (0.89-1.09)
Heterogeneity (I^2, p-value)	-	81.7%, <0.001
P value Egger test	-	0.90
Stratified and sensitivity analysis (all studies)		
	Men	**Women**
Studies (n)	9	6
RR (95%CI)	0.94 (0.82-1.08)	1.21 (0.90-1.61)
Heterogeneity (I^2, p-value)	78.6%, <0.001	84.6%, <0.001
	Incidence	**Mortality**
Studies (n)	13	4
RR (95%CI)	1.00 (0.90-1.12)	0.95 (0.73-1.23)
Heterogeneity (I^2, p-value)	79.3%, <0.001	85.3%, <0.001
Stratified and sensitivity analysis (by cancer type)		
Histological type	**Adenocarcinoma (AC)**	**Squamous cell carcinoma (SCC)**
Studies (n)	9	8

Cases	1725	4348
RR (95%CI)	1.48 (1.35-1.62)	0.64 (0.56-0.73)
Heterogeneity (I^2, p-value)	36.7%, 0.13	71.4%, 0.001
P value Egger test	0.69	0.18
Men		
Studies (n)	3	2
RR (95%CI)	1.56 (1.39-1.74)	0.77 (0.71-0.84)
Heterogeneity (I^2, p-value)	0%, 0.63	0%, 0.42
Women		
Studies (n)	3	2
RR (95%CI)	1.48 (1.29-1.71)	0.58 (0.46-0.72)
Heterogeneity (I^2, p-value)	0%, 0.87	73.7%, 0.05
Asia		
Studies (n)	-	1
RR (95%CI)	-	0.76 (0.67-0.87)
Heterogeneity (I2, p-value)	-	-
Europe		
Studies (n)	6	6
RR (95%CI)	1.56 (1.44-1.69)	0.63 (0.53-0.74)
Heterogeneity (I2, p-value)	0%, 0.71	74.5%, 0.001
North America		
Studies (n)	3	1
RR (95%CI)	1.32 (1.10-1.57)	0.56 (0.42-0.74)
Heterogeneity (I2, p-value)	37.2%, 0.20	-
BMI self-reported		
Studies (n)	3	2
RR (95%CI)	1.52 (1.22-1.89)	0.52 (0.44-0.62)
Heterogeneity (I^2, p-value)	73.4%, 0.02	0%, 0.55
BMI measured		
Studies (n)	5	5
RR (95%CI)	1.53 (1.39-1.67)	0.67 (0.59-0.76)
Heterogeneity (I^2, p-value)	0%, 0.45	67.7%, 0.02
BMI from medical records		
Studies (n)	1	1
RR (95%CI)	1.41 (1.13-1.76)	0.81 (0.55-1.20)
Heterogeneity (I^2, p-value)	-	-
Non-smokers		
Studies (n)	2	2
RR (95%CI)	1.62 (1.23-2.13)	0.59 (0.44-0.79)
Heterogeneity (I^2, p-value)	0%, 0.53	0%, 0.57

Not adjusted for smoking		
Studies (n)	2	3
RR (95%CI)	1.56 (1.40-1.74)	0.71 (0.64-0.80)
Heterogeneity (I^2, p-value)	0%, 0.83	49.8%, 0.14
Adjusted for smoking		
Studies (n)	7	5
RR (95%CI)	1.45 (1.29-1.63)	0.60 (0.49-0.73)
Heterogeneity (I^2, p-value)	42.3%, 0.11	63.5%, 0.03
All studies and Pooling Project		
Studies (n)	16	15
Cases (total number)	1839	4532
RR (95%CI)	1.51 (1.38-1.65)	0.64 (0.57-0.72)
Heterogeneity (I2, p-value)	43.3%, 0.07	68.3%, 0.001
P value test publication bias	0.62	0.13

Other stratified analyses on oesophageal cancers (not enough studies to do analysis by cancer type)

Geographic area	**Asia**	**Europe**	**North America**
Studies (n)	5	6	5
RR (95%CI)	0.78 (0.71-0.85)	1.02 (0.89-1.17)	1.15 (1.06-1.25)
Heterogeneity (I^2, p-value)	0%, 0.78	77.6%, <0.001	22.3%, 0.27
BMI assessment	**Self-reported**	**Measured**	**Medical records**
Studies (n)	7	8	1
RR (95%CI)	1.17 (1.08-1.27)	0.86 (0.80-0.93)	1.17 (1.03-1.34)
Heterogeneity (I^2, p-value)	17.6%, 0.30	43.9%, 0.09	-
Duration of follow-up	**5-<10 years**	**10-<15 years**	**≥15 years**
Studies (n)	6	5	5
RR (95%CI)	1.11 (0.98-1.26)	0.94 (0.73-1.22)	0.94 (0.82-1.08)
Heterogeneity (I^2, p- value)	45.6%, 0.10	78.0%, 0.001	87.9%, <0.001
Number of cases	**<500 cases**	**500-<1000 cases**	**≥1000 cases**
Studies (n)	10	2	4
RR (95%CI)	1.06 (0.94-1.19)	0.94 (0.61-1.46)	0.91 (0.76-1.08)
Heterogeneity (I^2, p-value)	53.5%, 0.02	94.2%, <0.001	91.2%, <0.001
Publication year	**≤2005**	**>2005**	
Studies (n)	5	11	
RR (95%CI)	0.98 (0.83-1.16)	0.99 (0.86-1.13)	
Heterogeneity (I^2, p-value)	90.4%, <0.001	74.4%, <0.001	
Adjustment for:			
Socioeconomic status	**Not adjusted**	**Adjusted**	

Studies (n)	12	4	
RR (95%CI)	0.95 (0.85-1.05)	1.11 (0.97-1.27)	
Heterogeneity (I^2, p-value)	73.0%, <0.001	66.2%, 0.03	
Smoking			
Studies (n)	4	12	
RR (95%CI)	0.88 (0.78-0.98)	1.03 (0.92-1.15)	
Heterogeneity (I^2, p-value)	57.1%, 0.07	75.2%, <0.001	
Alcohol intake			
Studies (n)	9	7	
RR (95%CI)	0.94 (0.85-1.04)	1.04 (0.89-1.20)	
Heterogeneity (I^2, p-value)	62.9%, 0.01	81.5%, <0.001	
Physical activity			
Studies (n)	12	4	
RR (95%CI)	0.95 (0.85-1.05)	1.11 (0.97-1.27)	
Heterogeneity (I^2, p-value)	73.0%, <0.001	66.2%, 0.03	

Table 73 BMI and oesophageal cancer risk. Results of meta-analyses and pooled analyses published after the 2005 SLR

Author, Year	Number of studies	Total number of cases	Studies country, area	Outcome	Comparison	RR (95%CI)	P trend	Heterogeneity (I^2, p value)
Meta-analyses								
Turati, 2013	22 studies (10 cohorts, 12 case-control)	7945 Oesophageal and gastric cardia adenocarcinoma	Australia, Canada, China, European countries, Germany, Ireland, Norway, Sweden, Taiwan, The Netherlands, UK, USA	Oesophageal gastric cardia adenocarcinoma Men Women Case-control studies Cohort studies Oesophageal adenocarcinoma Gastric cardia adenocarcinoma	≥30 kg/m^2 vs normal weight Per 5 kg/m^2 Per 5 kg/m^2 ≥30 kg/m^2 vs normal weight ≥30 kg/m^2 vs normal weight Per 5 kg/m^2	2.34 (1.95-2.81) 1.11 (1.09-1.14) 1.13 (1.09-1.17) 1.08 (0.97-1.20) 3.23 (1.59-6.56) 2.18 (1.85-2.58) 2.73 (2.16-3.46) 1.13 (1.11-1.16) 1.93 (1.52-2.45) 1.07 (1.04-1.10)		 76.9%, 0.01 33.8%, 0.15
Renehan, 2008	6 cohorts	3186 cases (817 (M),319(W) AC cases; 1315(M), 735(W) SCC cases)	Australia, Korea, Norway, Sweden UK	Incidence AC Men Women SCC Men Women	Per 5 kg/m^2	 1.52 (1.33-1.74) 1.51 (1.31-1.74) 0.71 (0.59-0.84) 0.57 (0.47-0.68)		 23.9%, 0.26 0%, 0.95 49.3%, 0.14 59.9%, 0.11

Smith, 2008	14 studies (5 cohorts, 9 case-control)	8842 (1676 AC, 6047 SCC, 1119 unspecified)	China, Japan, Ireland, Italy, Korea, Norway, UK, USA, Switzerland	Incidence/mortality AC Cohort (1 study, 575 cases) Case-control (6 studies, 1101 cases) SCC Cohort (3 studies, 3691 cases) Case-control (7 studies, 1469 cases)	Per 5 kg/m^2	 1.53 (1.30-1.79) 1.54 (1.39-1.71) 0.69 (0.63-0.75) 0.49 (0.44-0.55)		 - 0.01 - <0.001
Kubo, 2006	11 studies (1 cohorts, 10 case-control)	2488 (oesophageal adenocarcinoma ±cardia gastric carcinomas)	China, Europe, United States	Incidence, oesophageal and gastric cardia adenocarcinoma Men Women Oesophageal AC Men Women	Overweight or obese vs normal weight Obese vs normal weight	1.7 (1.6-1.9) 2.2 (1.7-2.7) 2.0 (1.4-2.9) 2.4 (2.0-2.8) 2.4 (1.9-3.2) 2.1 (1.4-3.2)	- - - - - -	<0.01 0.01 0.20 <0.01 0.35 0.94

Pooled-analyses								
Lindkvist, 2014 (Me-Can) (Oslo, NCS, CONOR, 40-y, VHM&PP, VIP, MPP)	7 cohorts	324 (114 AC, 184 SCC, 26 others)	Austria, Sweden, Norway	Incidence, AC	31.3 vs 20.7 kg/m^2	7.34 (2.88-18.68)	-	<0.0001
					Per 5 kg/m^2	1.78 (1.45-2.17)	-	
				Never smoker (25 cases)	Per 1 unit *z*-score	1.22 (0.83-1.77)	-	
				Former smoker (36 cases)		1.87 (1.49-2.35)	-	
				Current smoker (52 cases)		1.54 (1.22-1.94)	-	
				SCC	31.3 vs 20.7 kg/m^2	0.38 (0.23-0.62)	-	<0.0001
					Per 5 kg/m^2	0.62 (0.50-0.79)	-	
				Never smoker (29 cases)	Per 1 unit *z*-score	0.72 (0.47-1.09)	-	
				Former smoker (25 cases)		0.91 (0.59-1.40)	-	
				Current smoker (129 cases)		0.63 (0.52-0.77)	-	

Hoyo, 2012 (BEACON Consortium) (Cohorts: Kaiser Permanente Multiphasic Health Check-up Study, NIH-AARP)	2 cohorts and 10 case-control studies	3719 (1897 oesophageal adenocarcinoma 1822 oesophagogastric junction adenocarcinoma)	Cohorts: Kaiser Permanente Multiphasic Health Check-up Study and NIH-AARP Study, North America, Europe, Australia	Incidence, All AC Oesophageal AC Oesophagogastric junction adenocarcinoma	Per 1 kg/m^2	1.08 (1.06-1.10) 1.09 (1.06-1.12) 1.07 (1.05-1.09)		75% 76% 54%
				All AC Oesophageal AC Oesophagogastric junction adenocarcinoma	≥40 vs <25 kg/m^2	3.65 (2.50-5.34) 4.76 (2.96-7.66) 3.07 (1.89-4.99)		0% 0% 0%
				Men All AC Oesophageal AC Oesophagogastric junction adenocarcinoma	Per 1 kg/m^2	 1.09 (1.06-1.11) 1.09 (1.06-1.13) 1.08 (1.06-1.11)		 75% 76% 51%
				Women All AC Oesophageal AC Oesophagogastric junction adenocarcinoma		 1.05 (1.03-1.07) 1.07 (1.04-1.10) 1.04 (1.01-1.07)		 0% 13% 0%

Note: All cohort studies identified in the published meta-analyses were included in the CUP review. The seven component cohorts in the Me-Can study (Lindkvist, 2014) and the Kaiser Permanente Cohort in the BEACON Consortium (Hoyo, 2012) did not publish results previously. Sensitivity analysis was conducted by including the pooled results from the Me-Can study.

Table 74 BMI and oesophageal cancer risk. Main characteristics of studies included in the linear dose-response meta-analysis

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Missing data derived for analyses
Hardikar, 2013 oes00875 USA	SBES, Prospective Cohort, Age: 30- years, M/W Barrett's Oesophagus patients	45/ 411 6.2 years	Biopsy and follow up	Measured height and weight	Incidence, AC	>35 vs 25 kg/m^2	1.21 (0.32-4.48) Ptrend:0.73	Age, cigarette smoking, NSAID, gender	Rescaled the RR to 5 kg/m^2 increase in BMI
						Per 1 kg/m^2	1.01 (0.94-1.10)		
Andreotti, 2010 oes00845 USA	AHS, Prospective Cohort, M, Pesticide applicators	33/ 67 947 10 years	Cancer registry	Self-reported height and weight	Incidence, oesophageal cancer, men	25.0-29.9 vs 18.5-24.9 kg/m^2	2.09 (0.84-5.15)	Age, smoking status	Rescaled the RR to 5 kg/m^2 increase in BMI
						Per 1 kg/m^2	1.01 (0.94-1.10)		
Steffen, 2009 oes00865 Denmark,France,Germany,Greece,Italy,Netherlands,Norway,Spain,Sweden,UK	EPIC, Prospective Cohort, Age: 25-70 years, M/W	198/ 346 554 8.9 years	Cancer and mortality registries, active follow up	Measured height and weight	Incidence			Age, study centre, sex, education, smoking status and duration, baseline and lifelong alcohol consumption, physical activity, intake of fruits, vegetables, meat and meat products	Average BMI per category in men and women and distribution of persons per category, Hamling's method was used to calculate RRs for AC and SCC combined
		88/			AC	31.0(M)/31.4(W) vs 22.2(M)/20.5(W) kg/m^2	2.60 (1.23-5.51) Ptrend:0.01		
		40/			Non-smokers		2.26 (0.77-6.62) Ptrend:0.11		
		47/			Smokers		3.72 (1.20-11.50) Ptrend:0.01		
		110/			SCC		0.26 (0.14-0.51) Ptrend:<0.0001		
		31/					0.81 (0.24-2.67) Ptrend:0.89		
		79/			Non-smokers		0.18 (0.08-0.40) Ptrend:<0.0001		

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Missing data derived for analyses
					Smokers				
Abnet, 2008 oes00829 USA	NIH-AARP, Prospective Cohort, Age: 50-71 years, M/W	371/ 480 475 8 years	Record linkage to state cancer registry databases.	Self-reported weight and height	Incidence, AC	≥35 vs 18.5-<25 kg/m^2	2.27 (1.44-3.59)	Age, sex, alcohol consumption, (cigarette smoking), physical activity, education	Distributions of persons and mid-points per exposure category, for the non-linear analysis, RRs with the lowermost category as reference was calculated using the Hamling's method
		293/ 70/			Nonsmokers Smokers		2.33 (1.39-3.93) 4.37 (1.65-11.57)		
Corley, 2008 oes00826 USA	KPMCP, Nested Case Control, M/W	230/ 1797 controls 42 years 94/	Cancer registry, individual record review	Measured height and weight	Incidence AC	≥30 vs 18.5-24.9 kg/m^2 Per 1 kg/m^2	3.17 (1.43-7.04) 1.10 (1.04-1.17)	Matched for age, sex , year of examination, adjusted for ethnicity	Rescaled the RRs to 5 kg/m2 increment, mid-points of BMI categories, Hamling's method was used to calculate RRs for AC and SCC combined
		136/			SCC		0.30 (0.13-0.72) 0.89 (0.84-0.94)		
Jee, 2008 oes00839 Korea	KCPS, Prospective Cohort, Age: 30-95 years, M/W (overlapped with KNHIC)	1594/ 1 213 829 10.8 years 1 501/770 556	Cancer registry and hospital records	Measured height and weight	Incidence, oesophageal cancer Men	>30 vs 23-24.9 kg/m^2	0.53 (0.17-1.66) Ptrend:<0.0001	Age, smoking	Distributions of persons and mid-points per BMI category, RRs for men and women were combined using fixed effect model, for the non-linear analysis, RRs
		93/443 273			Women		2.44 (0.51-11.70) Ptrend:0.84		

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Missing data derived for analyses
									with the lowermost category as reference was calculated using the Hamling's method
Smith, 2008 oes00874 China	CNRPCS, Prospective Cohort, Age: 40-79 years, M	1082/ 221 156 10 years	Death register/ death certificates	Measured height and weight	Mortality, oesophageal cancer	Per 5 kg/m^2	0.75 (0.64-0.89)	Age, (alcohol consumption), area, (smoking)	-
		887/			Men, BMI >=18.5, good health				
		243/			Regular alcohol consumer		0.69 (0.51-0.92)		
		225/			Never smokers		0.62 (0.45-0.85)		
Fujino, 2007 oes00834 Japan	JACC, Prospective Cohort, M/W	169/1 314 653 person-years 12 years	Date and cause of death annually or biannually confirmed with government authorization	Self-reported in survey	Mortality, oesophageal cancer	>30 vs 18.5-24 kg/m^2	0.64 (0.09-4.63)	Age, study area	Mid-points of BMI categories, RRs for men and women were combined using fixed effect model, for the non-linear analysis, RRs with the lowermost category as reference was calculated using the Hamling's method
		146/			Men				
		23/			Women		5.95 (1.27-27.87)		
Merry, 2007 oes00832	NLCS, Case-cohort,	225/ 4782	Cancer registry and pathology	Self-reported height and	Incidence	≥30.0 vs 20.0-24.9 kg/m^2			Mid-points of BMI categories,

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Missing data derived for analyses
Netherlands	Age: 55-69 years, M/W	13.3 years 133/	database	weight	AC	Per 1 kg/m^2	3.96 (2.27-6.88) Ptrend:0.001 1.14 (1.08-1.21)	Age, sex	Hamling's method was used to calculate RRs for AC and SCC combined and for the non-linear analysis, RRs using the lowermost category as reference
		92/			SCC		0.93 (0.38-2.26) Ptrend:0.04 0.90 (0.82-0.98)	Age, sex, number of years of smoking, current smoking, number of cigarettes smoked per day	
Reeves, 2007 oes00850 UK	MWS, Prospective Cohort, Age: 50-64 years, W	413/ 1 222 630 5 years 150/ 53/	National health records	Self-reported height and weight	Incidence AC Never smokers	≥30 vs 22.5-24.9 kg/m^2 Per 10 kg/m^2 Per 10 kg/m^2	Floated absolute risk: 2.54 (1.89-3.41) RR and conventional 95% CI: 2.54 (1.57-4.12) 2.38 (1.59-3.56) 2.99 (1.51-5.90)	Age, geographic region, reproductive history, (smoking status), socio-economic status, alcohol intake, physical activity	Conventional 95% CIs using Orsini's method, rescaled the RRs to 5 kg/m^2, distribution of persons and mid-points per BMI category, Hamling's method was used to calculate RRs for AC and SCC combined and for the non-linear analysis, RRs using the lowermost category as reference
		263/ 83/			SCC Never smokers	≥30 vs 22.5-24.9 kg/m^2 Per 10 kg/m^2 Per 10 kg/m^2	Floated absolute risk: 0.47 (0.31-0.73) RR and conventional 95% CI: 0.47 (0.29-0.77) 0.26 (0.18-0.38) 0.32 (0.17-0.63)		

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Missing data derived for analyses
		293/ 1 222 630 7 years			Mortality	≥30 vs 22.5-24.9 kg/m^2	Floated absolute risk:2.75 (1.97-3.85)		
		111/			AC		RR and conventional 95% CI: 2.75 (1.57-4.81)		
						Per 10 kg/m^2	2.24 (1.40-3.58)		
		182/			SCC	≥30 vs 22.5-24.9 kg/m^2	Floated absolute risk: 0.42 (0.24-0.73)		
							RR and conventional 95% CI: 0.42 (0.22-0.79)		
						Per 10 kg/m^2	0.22 (0.14-0.35)		
Samanic, 2006 oes00851 Sweden	SCWC, Prospective Cohort, Age: 18-67 years, M	320/ 362 552 19 years	Linkage with the National Swedish cancer register	Measured height and weight	Incidence, oesophageal cancer	>30 vs 18.5-24.9 kg/m^2	1.14 (0.76-1.73) Ptrend:0.37	Age, calendar year, smoking	Distribution of persons and mid-points per BMI category, for the non-linear analysis of SCC, Hamling's method was used to calculate RRs using the lowermost category as reference
		82/			AC		2.72 (1.33-5.55) Ptrend:0.01		
		208/			SCC		0.77 (0.43-1.36) Ptrend:0.01		
Kuriyama, 2005 oes00856 Japan	MCS I, Prospective Cohort,	61/ 27 539 9 years	Cancer registry	Self-reported height and weight	Incidence, oesophageal cancer	≥27.5 vs 18.5-24.9 kg/ m^2	1.13 (0.40-3.18) Ptrend:0.90	Age, smoking status, alcohol drinking status,	Mid-points of exposure categories

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Missing data derived for analyses
	Age: 40- years, M/W	54/12 485			Men			consumption of meat, fish, fruits, green or yellow vegetables, and bean-paste soup, type of health insurance	
		7/15 054			Women	≥25 vs 18.5-24.9 kg/m^2	0.21 (0.02-2.75) Ptrend:0.21	Further adjusted for menopausal status, parity, age at menarche, age at end of first pregnancy	Results excluded from dose-response analysis, only two BMI categories
Lindblad, 2005 oes00796 UK	GPRDC, Nested Case Control, Age: 40-84 years M/W	526/ 5790 controls 4 340 207 person-years 7 years (max)	GP records	Extracted from GP notes in database	Incidence, oesophageal cancer	>30 vs 20-24 kg/m^2	1.35 (1.02-1.77) Ptrend:0.31	Age, (sex), alcohol consumption, smoking habits, calendar year, reflux symptoms	Mid-points of exposure categories, for the non-linear analysis, Hamling's method was used to calculate RRs using the lowermost category as reference
		187/5790			AC		1.93 (1.24-3.01) Ptrend:0.005		
		145/3918			Men		1.76 (1.03-3.02)		
		42/1872			Women		2.13 (0.97-4.71)		
		86/5790			SCC		0.28 (0.10-0.79) Ptrend:0.01		
Tran, 2005 oes00804 China	NIT Cohort, Prospective Cohort, Age: 40-69	1958/ 29 584 15 years	Monthly contact by either village health workers or	Measured height and weight	Incidence, SCC	≥23 vs <20 kg/m^2	0.81 (0.72-0.92) Ptrend:<0.001	Age, gender	Distributions of cases, person-years, and mid-points per exposure quantile

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Missing data derived for analyses
	years, M/W		interviewers, and cancer diagnoses verified by senior diagnosticians						
Engeland, 2004 oes00795 Norway	Norwegian BMI/Height Prospective Cohort 1963-1989, Prospective Cohort, M/W	2245/ 2 001 697 23 years 1597/963 696 648/1 038 001	Population survey	Measured height and weight	Incidence, oesophageal cancer Men Women	>30 vs 18.5-24.9 kg/m^2	1.05 (0.84-1.31) Ptrend:0.01 0.64 (0.50-0.82) Ptrend:<0.001	Height, age at entry, birth cohort	Distribution of cases and mid-points per BMI category, RRs for men and women were combined using fixed effect model, for the non-linear analysis, Hamling's method was used to calculate RRs using the lowermost category as reference
		448/963 696 127/1 038 001			AC Men Women		2.58 (1.81-3.68) Ptrend:<0.001 2.06 (1.25-3.39) Ptrend:0.002		
		1023/963 696 472/1 038 001			SCC Men Women		0.68 (0.50-0.93) Ptrend:<0.001 0.43 (0.32-0.59) Ptrend:<0.001		
Calle, 2003 oes00070 USA, Columbia, Puerto Rico	CPS II, Prospective Cohort, Age: 30- years, M/W	1065/ 900 053 16 years 876/107 030		Self-reported height and weight	Mortality, oesophageal cancer Men	35-39.9 vs 18.5-24.9 kg/m^2	1.63 (0.95-2.80) Ptrend:0.13	Age, education, race, marital status, physical activity, smoking status and number of	Distributions of persons and mid-points per BMI category, RRs for men and women were combined

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Missing data derived for analyses
								cigarette smoked, vegetable intake, fat intake, aspirin use, alcohol use	using fixed effect model
		189/276 564			Women	30-34.9 vs 18.5-24.9 kg/m^2	1.39 (0.86-2.25)	Further adjusted for oestrogen replacement therapy	

Table 75 BMI and oesophageal cancer risk. Main characteristics of studies excluded from the linear dose-response meta-analysis

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Inclusion/exclusion
Yates, 2014 oes00894 UK	EPIC-Norfolk, Prospective Cohort, Age: 39-74 years, M/W	65/ 24 066 15 years (max)	Cancer and pathology registries	Measured height and weight	Incidence, oesophageal adenocarcinoma, gastroesophageal junction	≥35 vs 18.5-<23 kg/m^2	4.95 (1.11-22.17) Ptrend: 0.51	Age, gender	Superseded by Steffen, 2009, OES00865.; 54 cases had tumour s in gastro-oesophageal junction
Chen, 2012 oes00843 China	CNRPCS, Prospective Cohort, Age: 40-79 years, M	846/ 142 214 15 years 706/ 140/	Review of medical records and death certificates	Measured height and weight	Mortality Upper aerodigestive cancer BMI 15 to <23.5kg/m² BMI 23.5 to <35kg/m²	Per 5 kg/m^2	1.06 (0.83-1.37) 0.87 (0.51-1.50)	Age, alcohol consumption, smoking habits, area, education	Excluded, UADT cancer (Results on oesophageal cancer from another publication was included in the analysis)
O'Doherty, 2012 oes00844 USA	NIH-AARP, Prospective Cohort, Age: 50-71 years, M/W,	253/ 218 854 9 years	Record linkage to state cancer registry databases.	Self-reported height and weight in baseline questionnaire	Incidence, AC	≥35 vs <18.5 kg/m^2	2.11 (1.09-4.09) Ptrend: <0.01	Age, sex, alcohol consumption, antacid use, aspirin use, cigarette smoking, diabetes, ethnicity, marital status, physical activity, red meat intake,	Superseded by Abnet, 2008, OES00829

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Inclusion/exclusion
								education, fruit and vegetable intake, non-steroidal anti-inflammatory drug use, total energy, white meat intake	
MacInnis, 2006 oes00895 Australia	MCCS, Prospective Cohort, Age: 27-75 years, M/W	30/ 41 295 11.3 years	Cancer registry	Measured height and weight	Incidence, distal oesophageal and gastric cardia cancer	≥30 vs <25 kg/m^2 Per 5 kg/m^2	3.70 (1.10-12.40) 1.63 (1.08-2.47)	Sex, age-underlying cox models, county of birth, educational level, physical activity	Excluded, distal oesophageal and gastric cardia cancer
Yokoyama, 2006 oes00860 Japan	JAMS, Prospective Cohort, Age: 40-79 years, M, Alcoholics	33/ 805 31 months	Endoscopic diagnosis	Measured height and weight	Incidence SCC UADT cancer	≥23.2 vs ≤18.9 kg/m^2	0.12 (0.02-0.97) 0.28 (0.09-0.85)	Age	Excluded, alcoholics, BMI lower than other cohorts
Oh, 2005 oes00883 Korea	KNHIC, Prospective Cohort, Age: 20- years, M (overlapped with KCPS)	781 283 10 years 159/ 150/	Cancer registry	Measured height and weight	Incidence Upper and middle oesophageal cancer SCC of upper and middle oesophageal	27.0-29.9 vs 18.5-22.9 kg/m^2	0.38 (0.17-0.87) Ptrend:0.001 0.40 (0.17-0.92) Prend:0.002	Age, alcohol consumption, area of residence, family history of cancer, smoking status, exercise	Excluded, specific cancers (Results on oesophageal cancer from another publication was included in the

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Inclusion/exclusion
					cancer				analysis)
		254/			Distal oesophageal and gastric cardia cancer		0.59 (0.34-1.05) Ptrend:0.03		
		88/			SCC of distal oesophagus and gastric cardia		0.11 (0.01-0.76) Ptrend:<0.001		
Samanic, 2004 oes00571 USA	Veterans Obesity and Cancer Study, Prospective Cohort, Age: 18-100 years, M	10 321 4 500 700 12 years 6 318/3 668 486 4 003/832 214	Hospital records	Patients with obesity as diagnosis in hospitals	Incidence, oesophageal cancer White males Black males	Obese vs non-obese	0.87 (0.77-0.97) 0.34 (0.27-0.44)	Age, calendar year	Excluded, only two BMI categories
Guo, 1994 oes00103 China	NIT Cohort, Nested Case Control, Age: 40-69 years, M/W, Intervention trial participants	639/ 29 584 5 years	Monthly contact by either village health workers or interviewers, and cancer diagnoses verified by senior diagnosticians	Measured height and weight at physical examinations	Incidence, SCC	>23 vs <20 kg/m^2	0.70 (0.60-0.90) Ptrend: <0.01	Matched for age and sex, adjusted for family history of cancer in first degree relatives, years of smoking, intervention group	Superseded by Tran, 2005, OES00804

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Inclusion/exclusion
Møller, 1994 oes00471 Denmark	DOS, Prospective Cohort, M/W	26/ 37 957 4.8 years	Death register and cancer registry	Patients with obesity as diagnosis in hospitals	Mortality/ incidence, oesophageal cancer	Obese vs general populations	1.90 (1.20-2.80)	Age, calendar period	Excluded, standardised incidence ratio
		13/12 331			Men		1.90 (1.00-3.30)		
		13/25 626			Women		1.90 (1.00-3.20)		

Figure 70 RR estimates of oesophageal cancer by levels of BMI

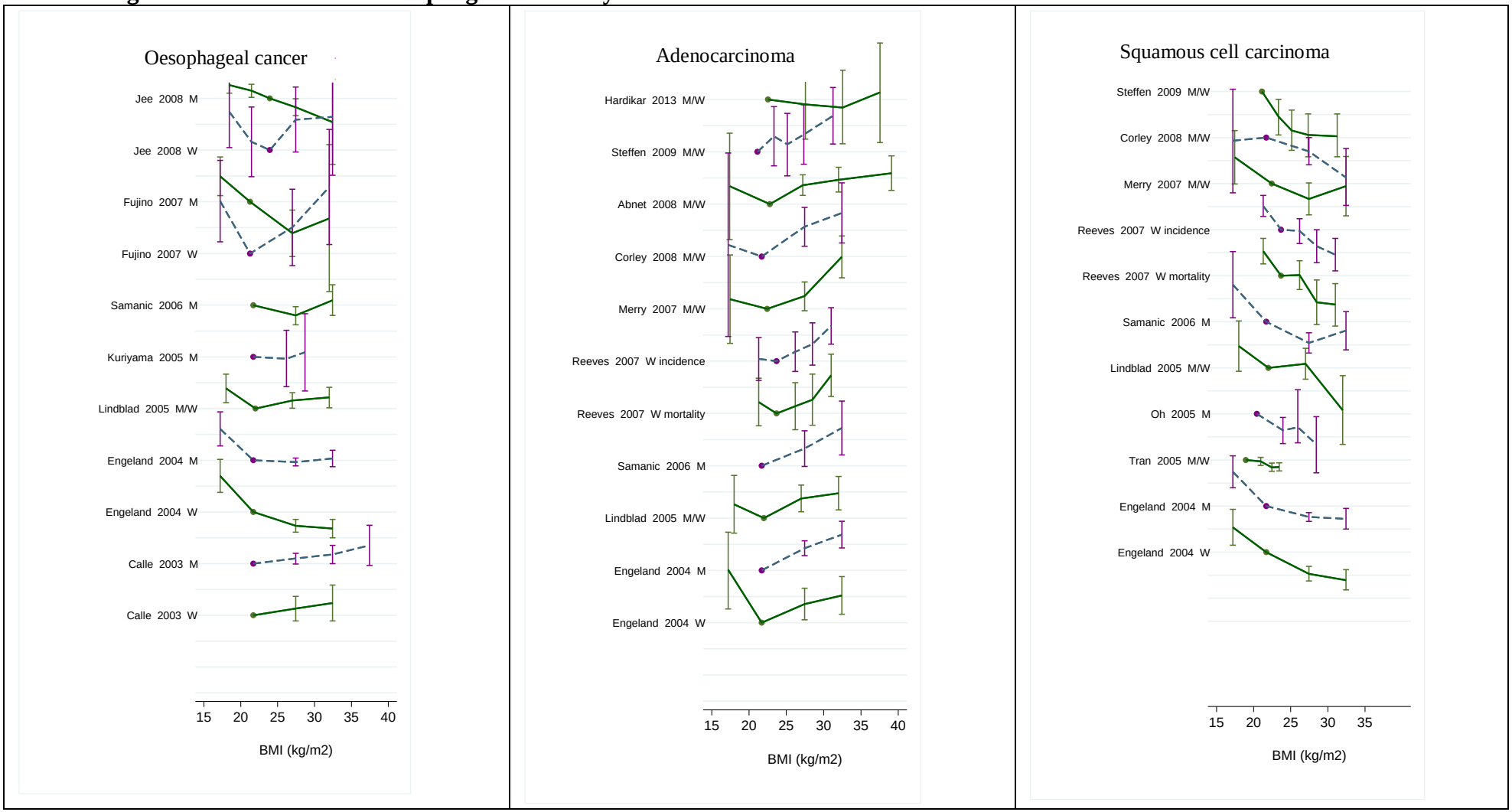
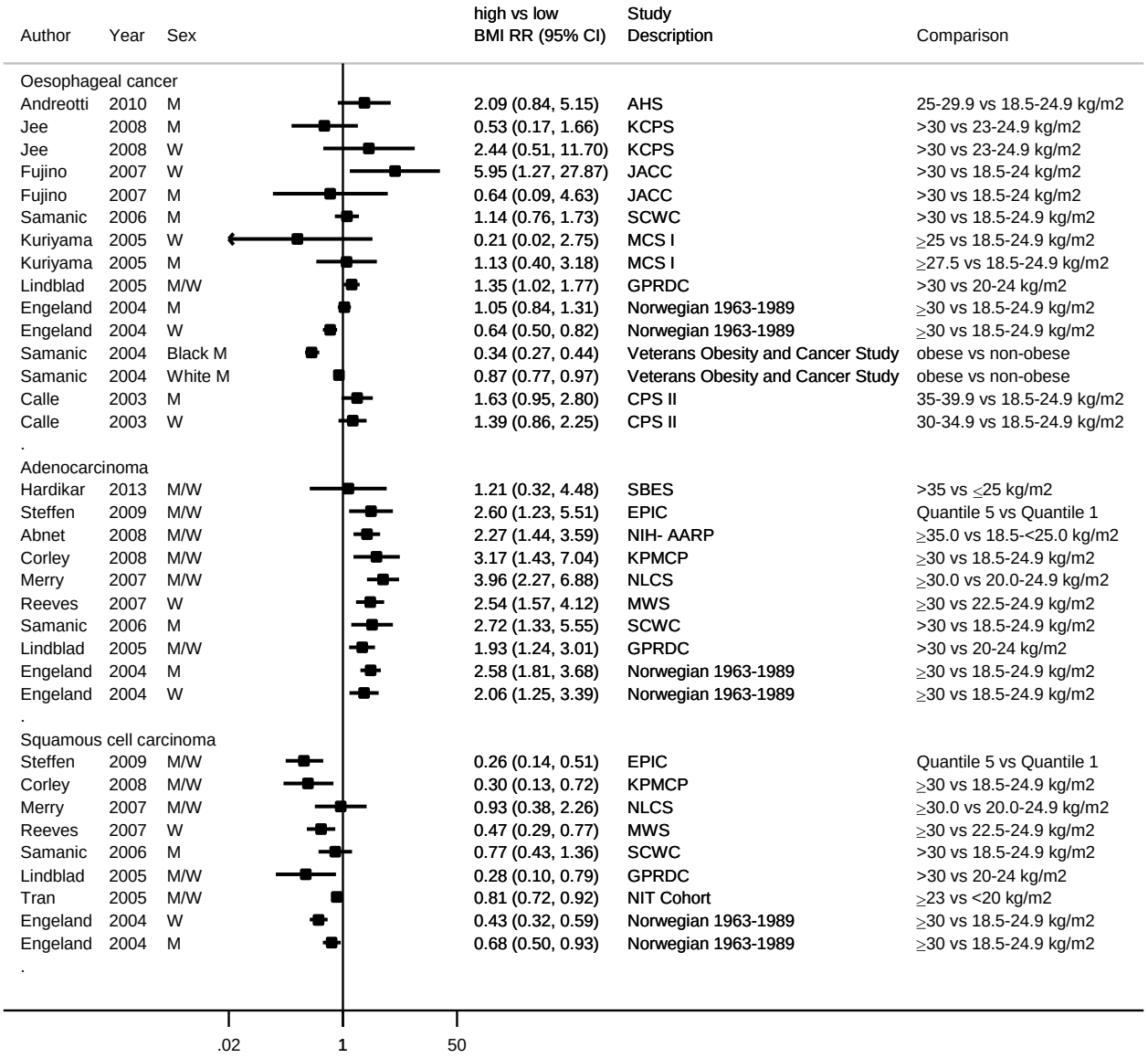
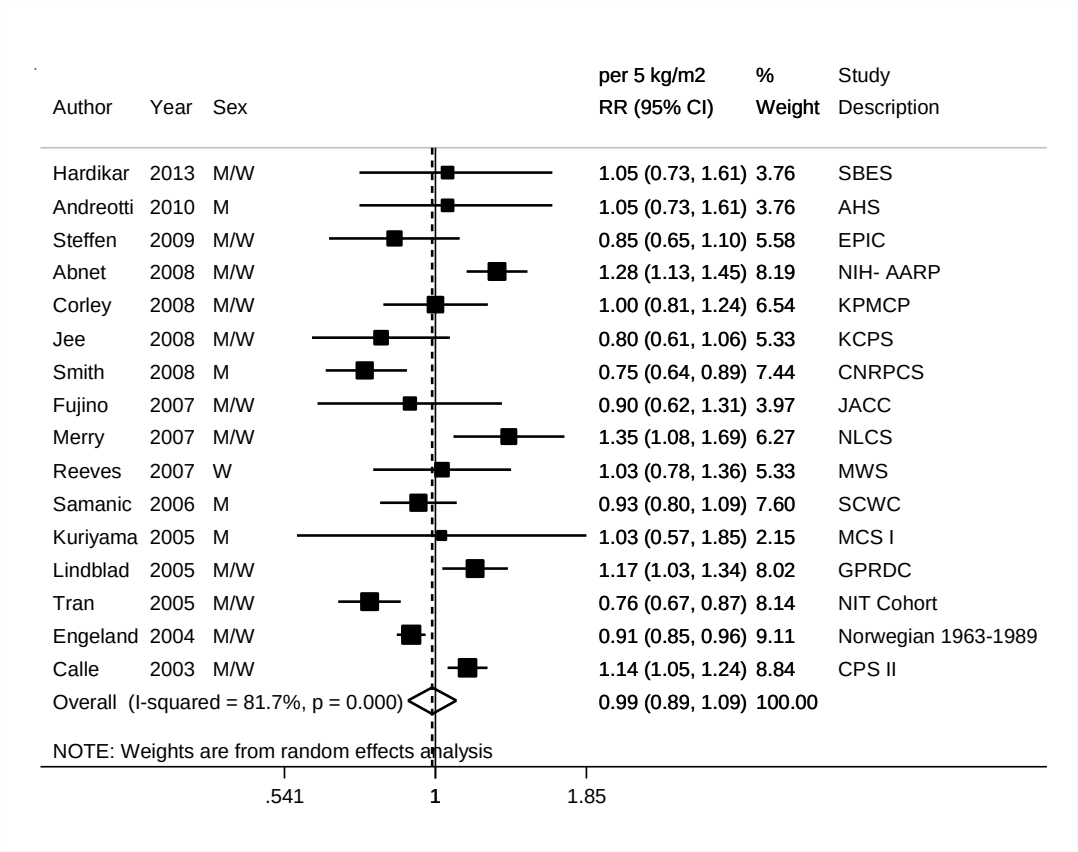


Figure 71 RR (95% CI) of oesophageal cancer for the highest compared with the lowest level of BMI



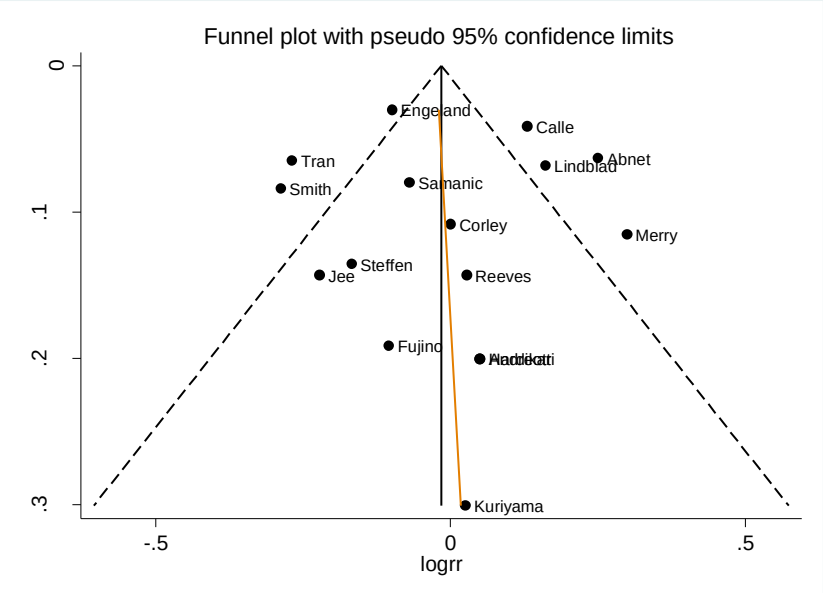
Note: The BMI comparison was 31.0 vs 22.2 kg/m^2 for men and 31.4 vs 20.5 kg/m^2 for women in EPIC (Steffen, 2009); RRs and conventional CIs for adenocarcinoma and squamous cell carcinoma incidence were shown in MWS (Reeves, 2007).

Figure 72 Relative risk of oesophageal cancer for 5 kg/m^2 increase of BMI



Note: RR for adenocarcinoma and squamous cell carcinomas were combined before inclusion in the meta-analysis

Figure 73 Funnel plot of studies included in the dose response meta-analysis of BMI and oesophageal cancer



Egger's test p=0.90

Figure 74 Relative risk of oesophageal cancer for 5 kg/m^2 increase of BMI by sex

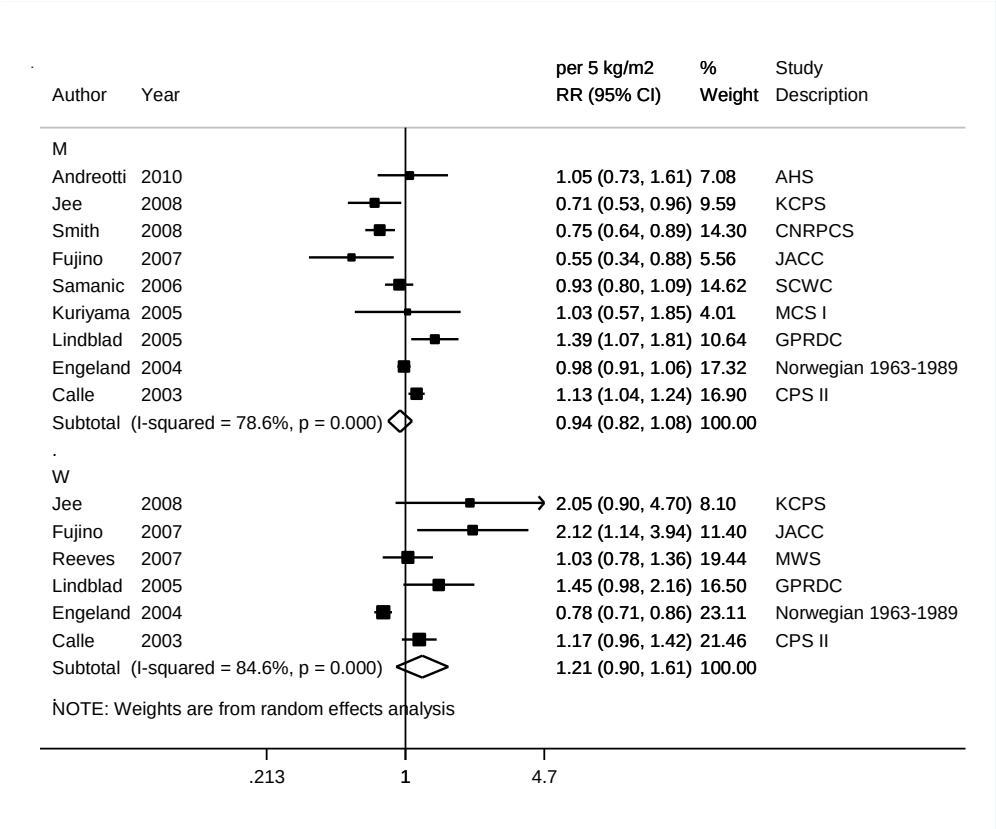


Figure 75 Relative risk of oesophageal cancer for 5 kg/m^2 increase of BMI by cancer outcome

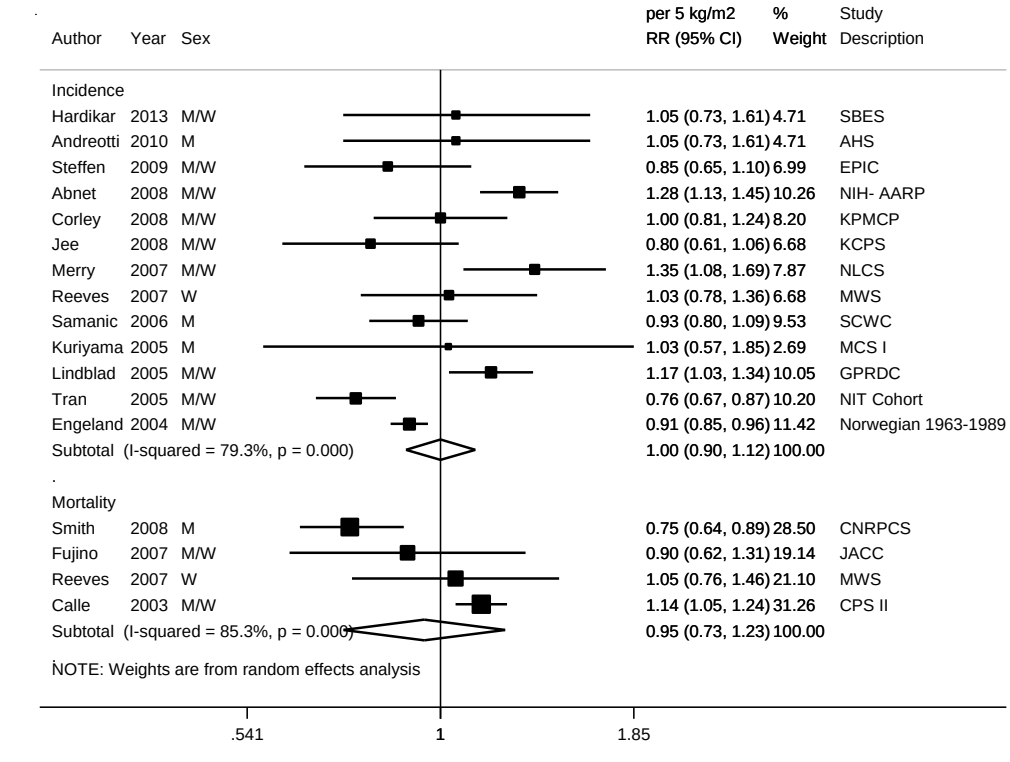


Figure 76 Relative risk of oesophageal cancer for 5 kg/m^2 increase of BMI by geographic location

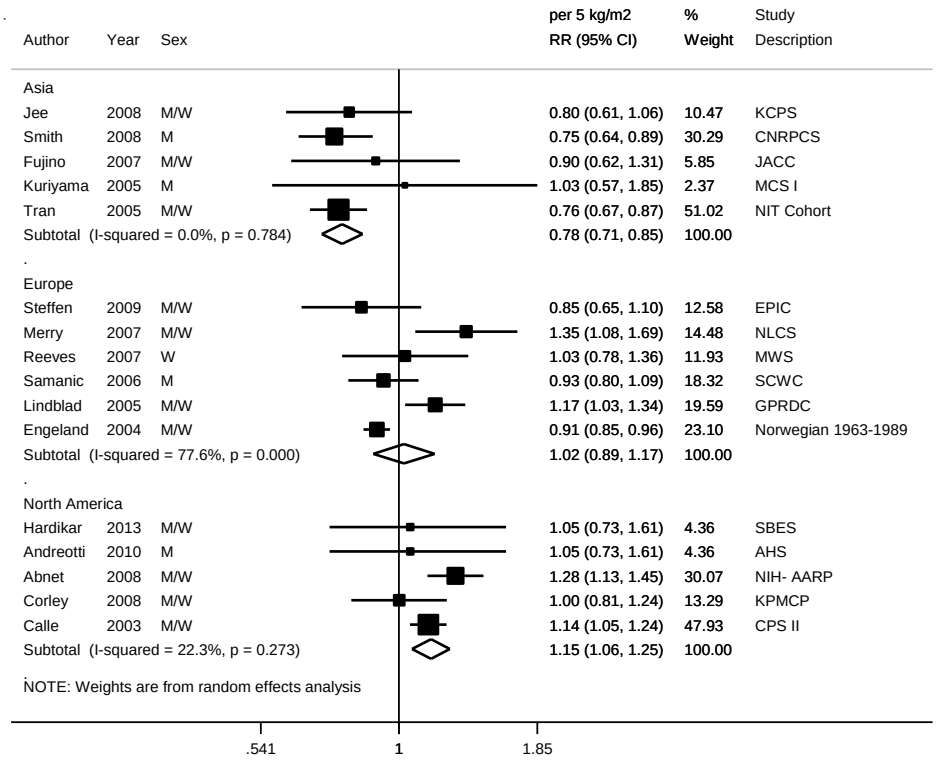


Figure 77 Relative risk of oesophageal cancer for 5 kg/m^2 increase of BMI by exposure assessment methods

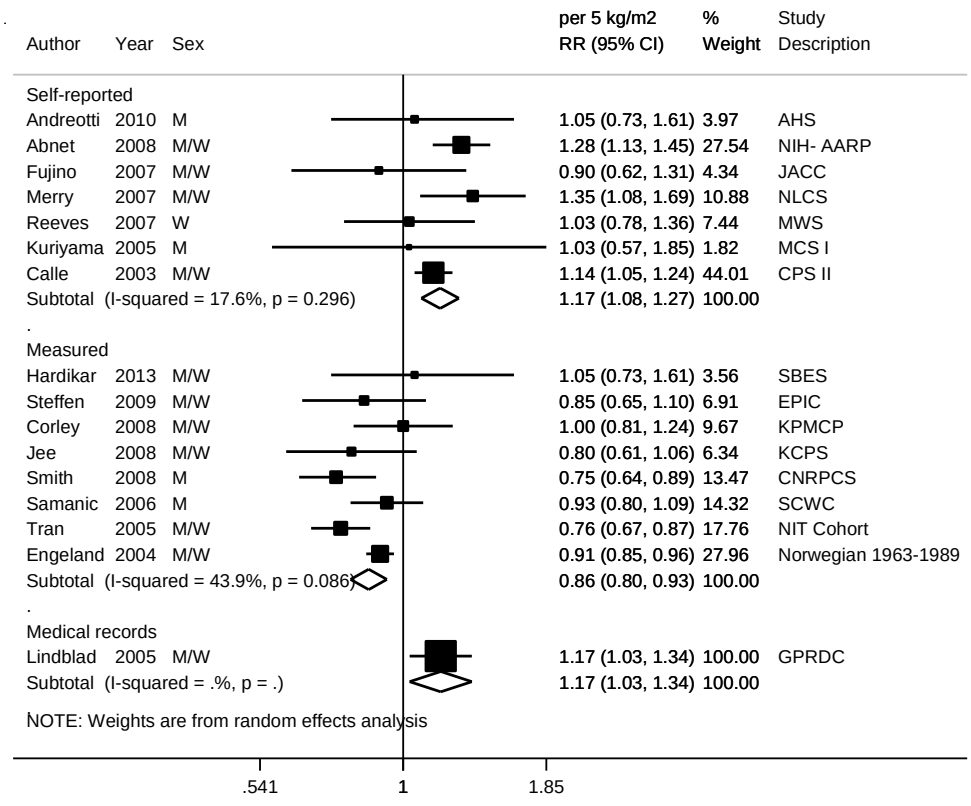


Figure 78 Relative risk of oesophageal cancer for 5 kg/m^2 increase of BMI by cancer type

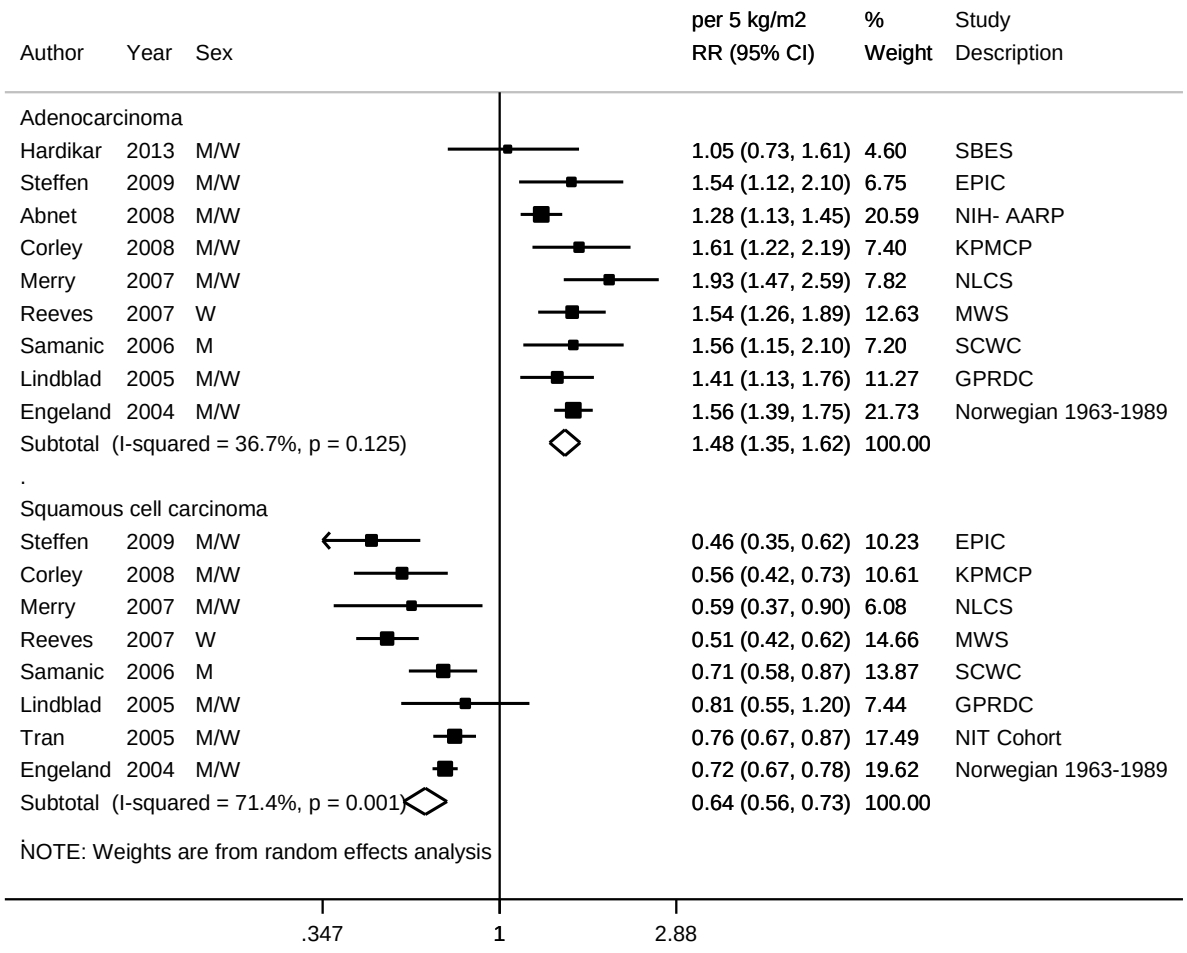
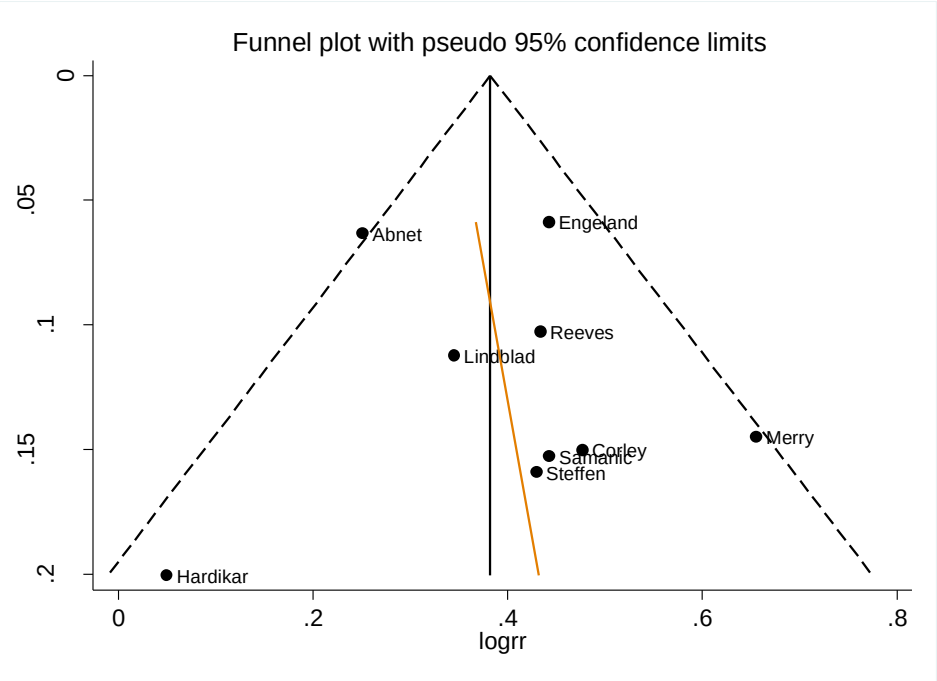
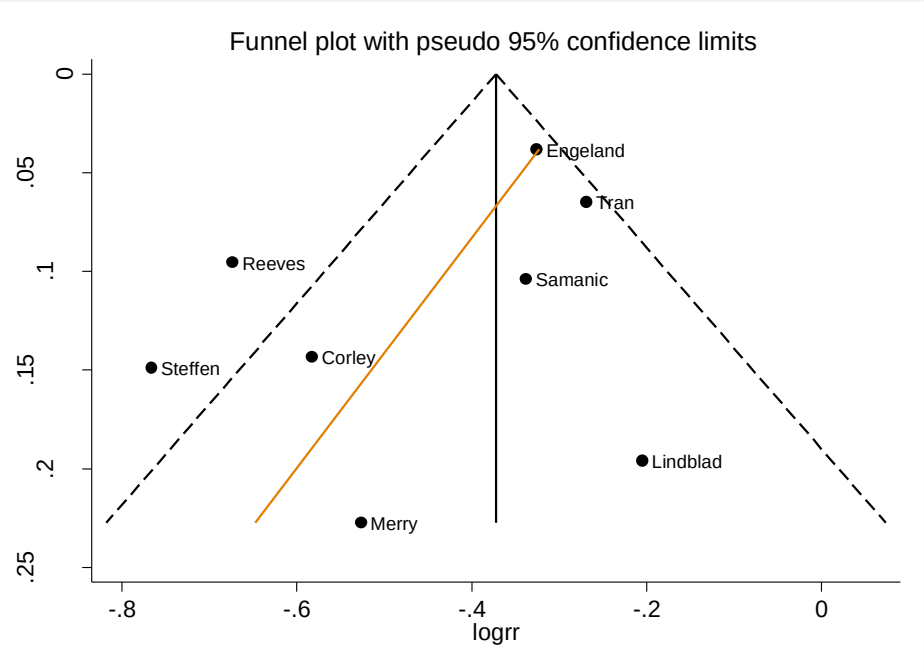


Figure 79 Funnel plot of studies included in the dose response meta-analysis of BMI and oesophageal adenocarcinoma



Egger's test p=0.69

Figure 80 Funnel plot of studies included in the dose response meta-analysis of BMI and oesophageal squamous cell carcinoma



Egger's test p=0.18

Figure 81 Relative risk of oesophageal adenocarcinoma for 5 kg/m^2 increase of BMI by sex

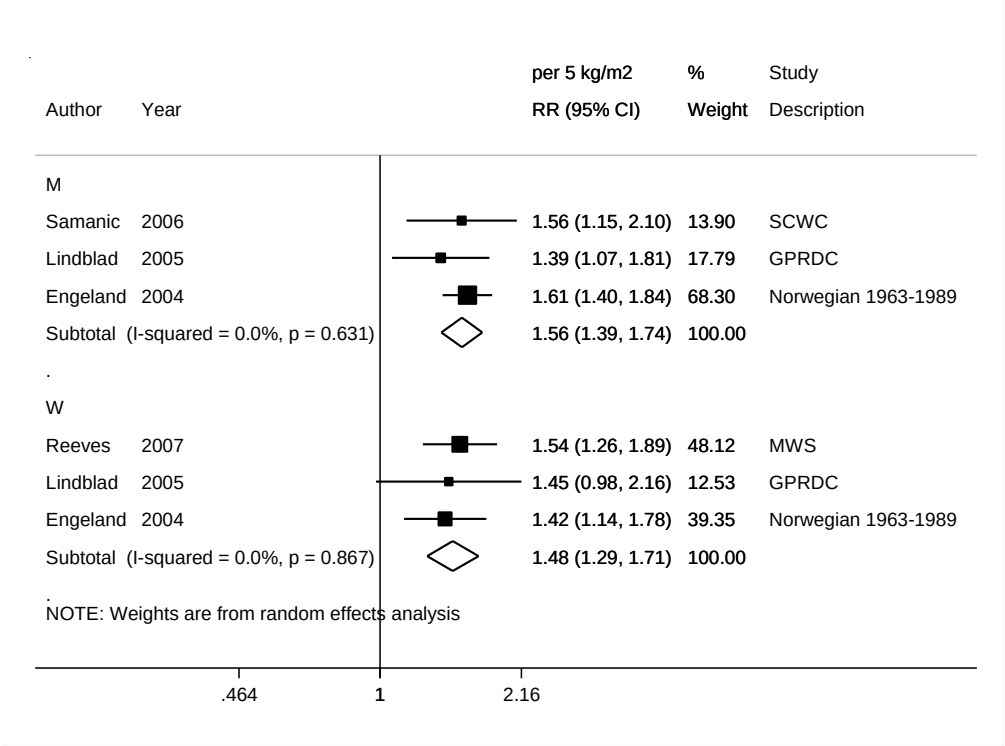


Figure 82 Relative risk of oesophageal squamous cell carcinoma for 5 kg/m^2 increase of BMI by sex

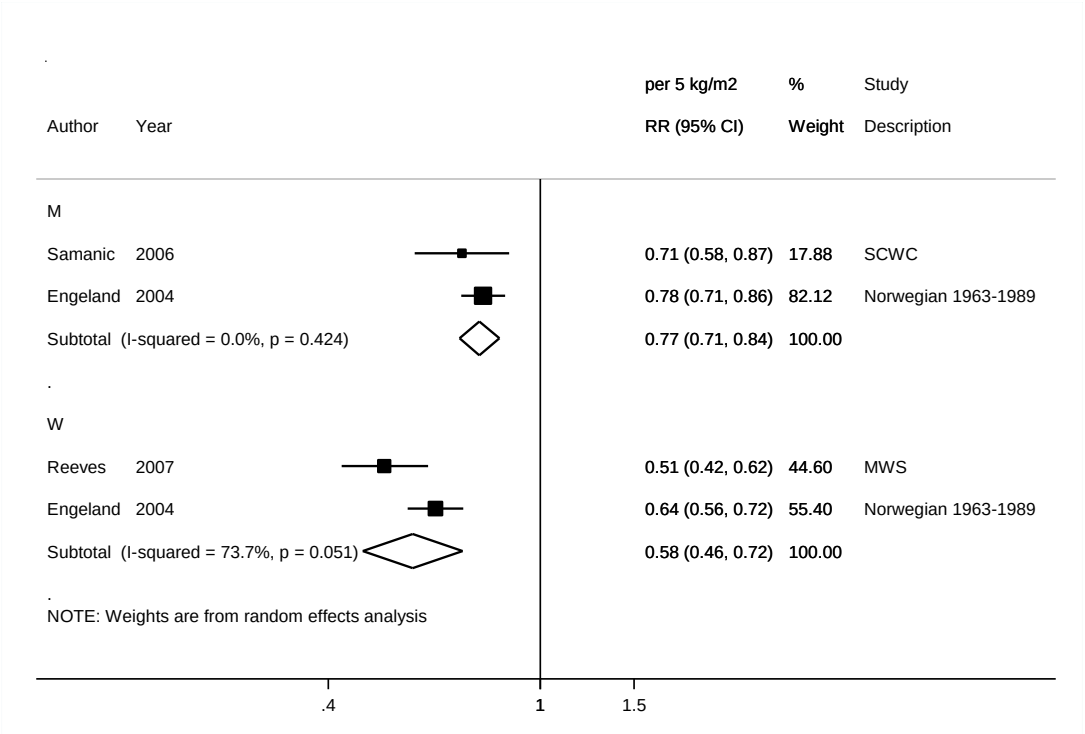
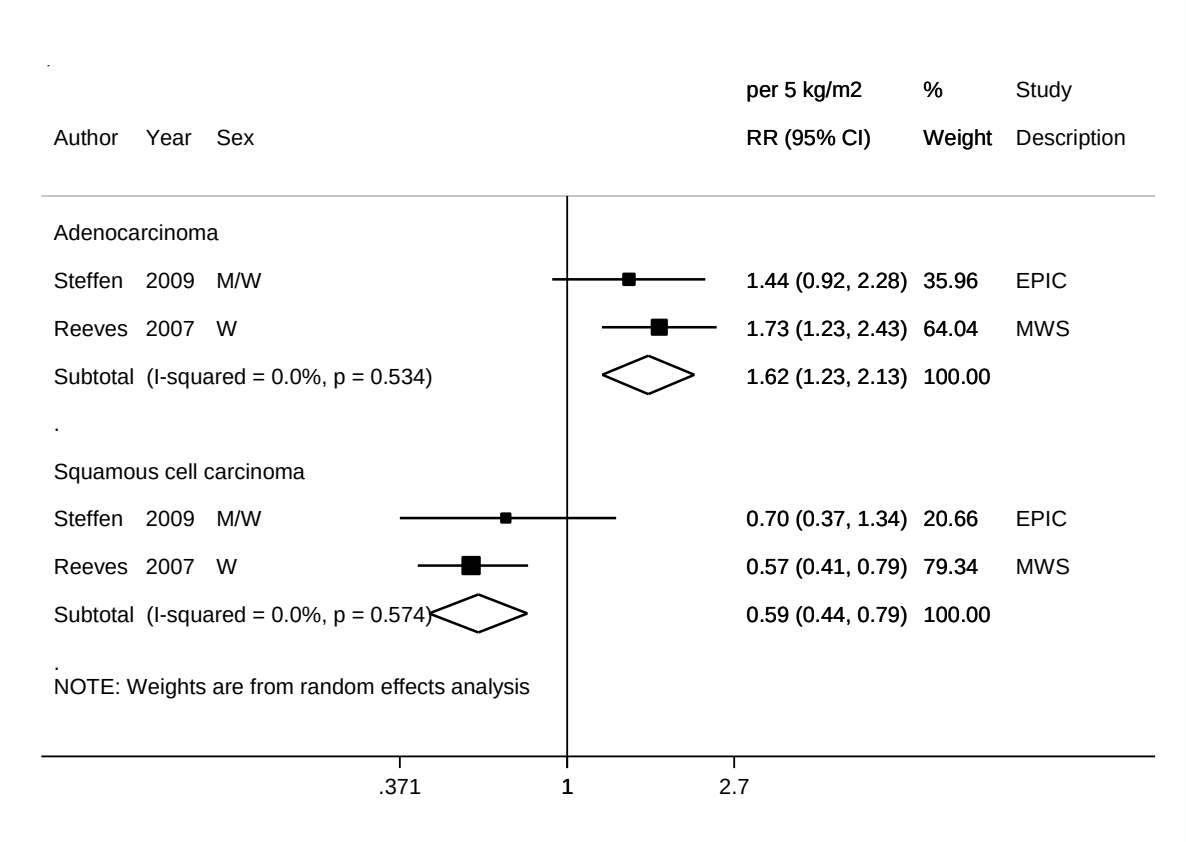


Figure 83 Relative risk of oesophageal cancer for 5 kg/m^2 increase of BMI by cancer type among non-smokers



Note: In Smith, 2008 (see Table of excluded studies for reasons of exclusion) the RR of oesophageal cancer (mainly SCC in Chinese men) per 5 kg/m2 BMI increase was 0.62 (0.45-0.85) in never smokers and 0.81 (0.67-0.97) in ever smokers.

Figure 84 Relative risk of oesophageal adenocarcinoma for 5 kg/m^2 increase of BMI by geographic location

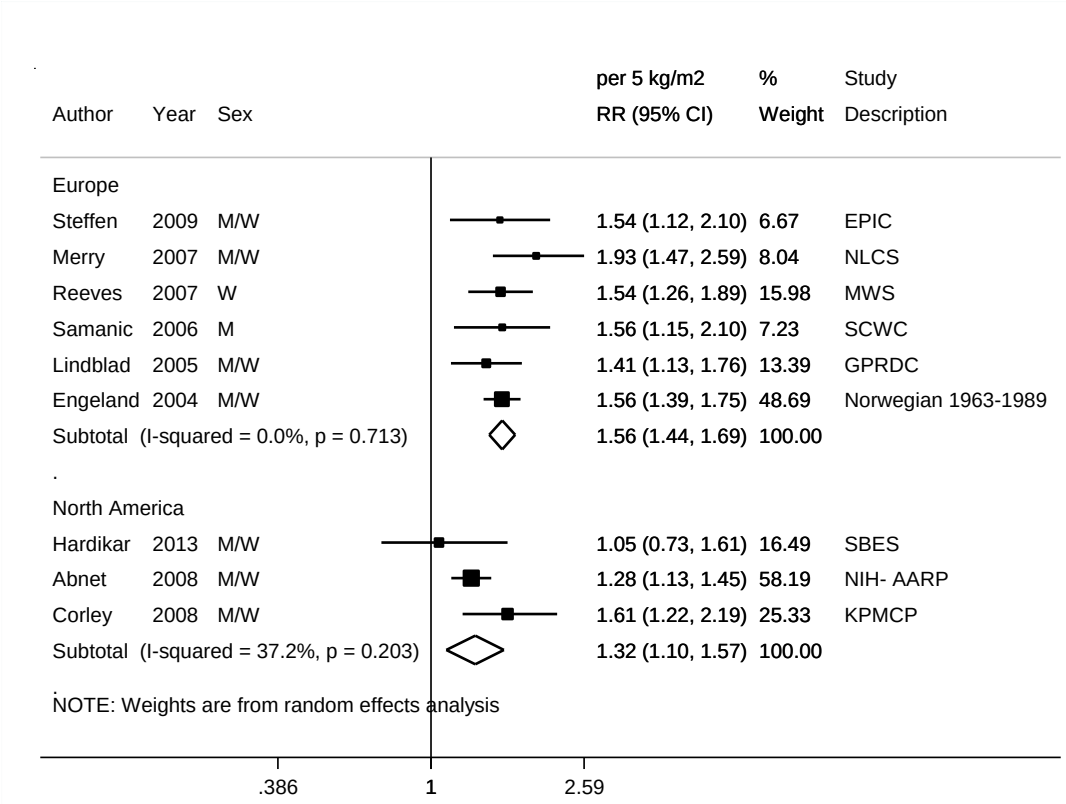


Figure 85 Relative risk of oesophageal squamous cell carcinoma for 5 kg/m^2 increase of BMI by geographic location

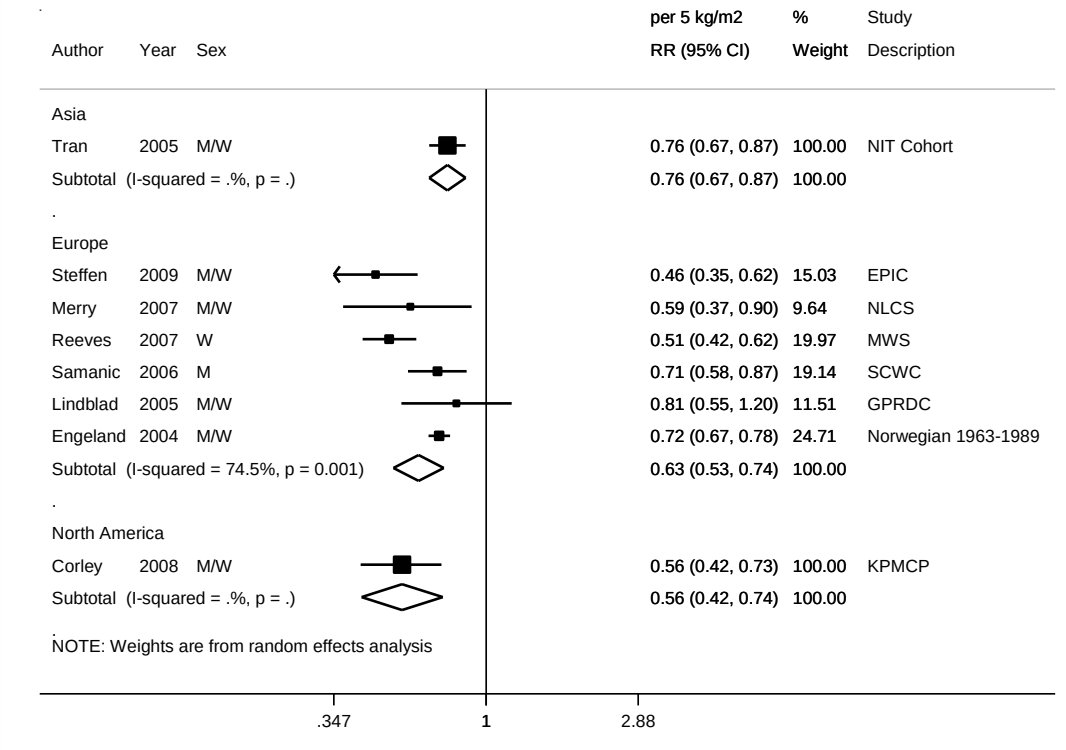


Figure 86 Relative risk of oesophageal adenocarcinoma for 5 kg/m^2 increase of BMI by exposure assessment methods

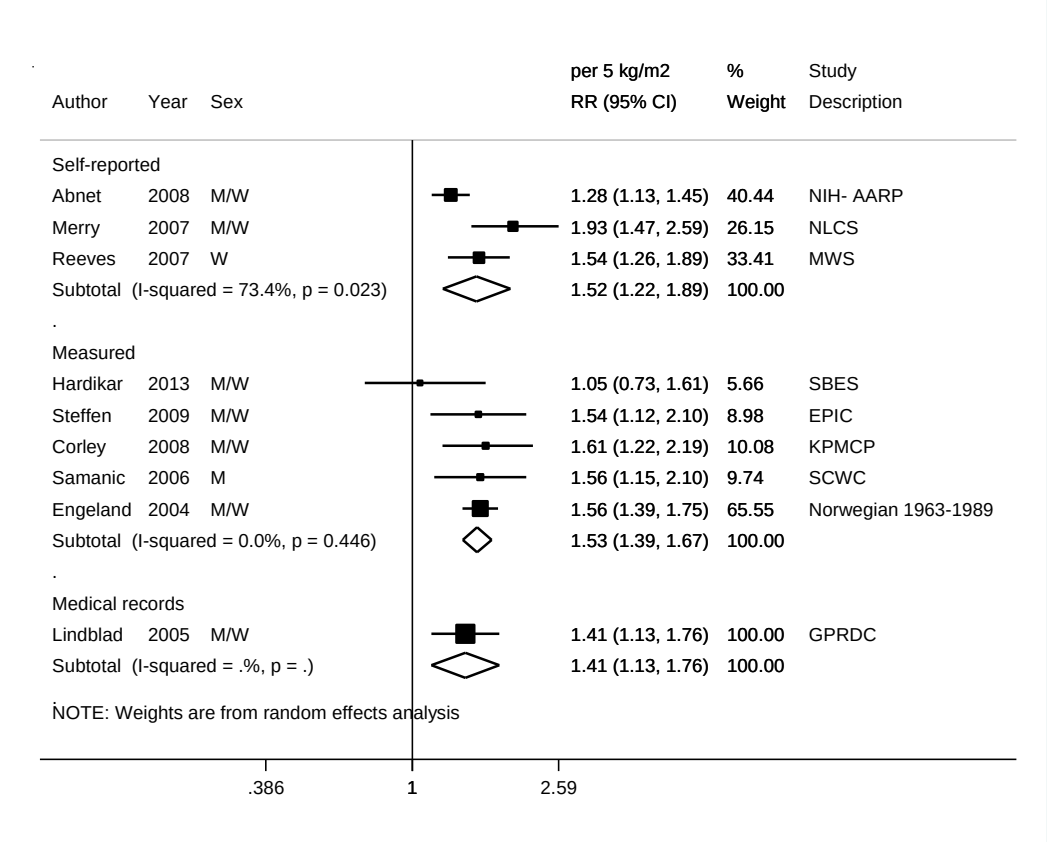


Figure 87 Relative risk of oesophageal squamous cell carcinoma for 5 kg/m^2 increase of BMI by exposure assessment methods

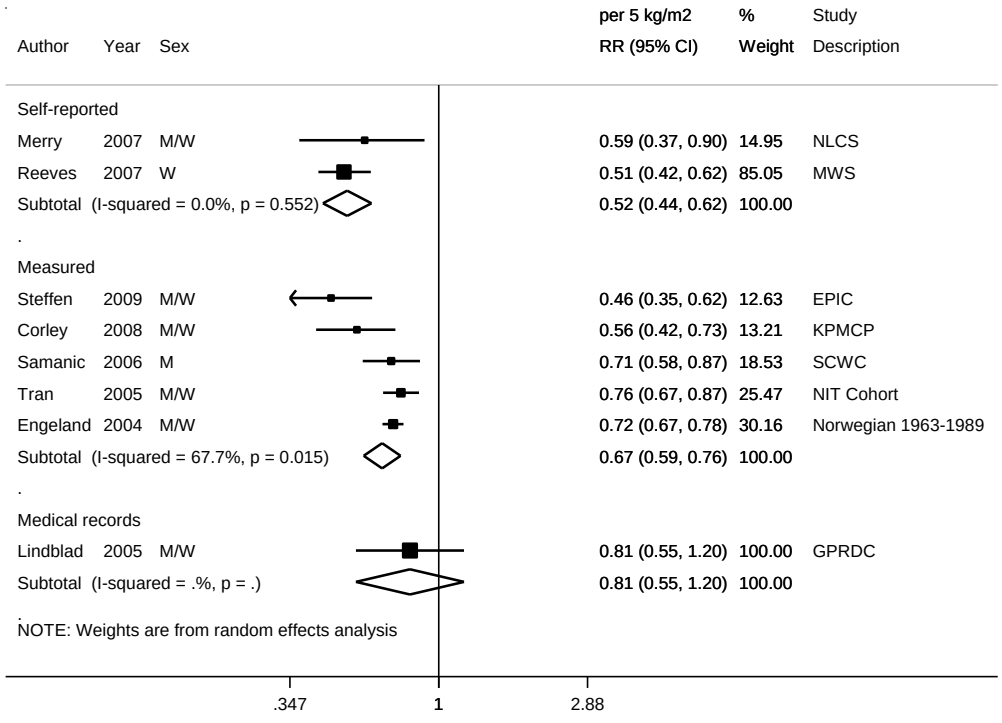


Figure 88 Relative risk of oesophageal adenocarcinoma for 5 kg/m^2 increase of BMI by adjustment for smoking

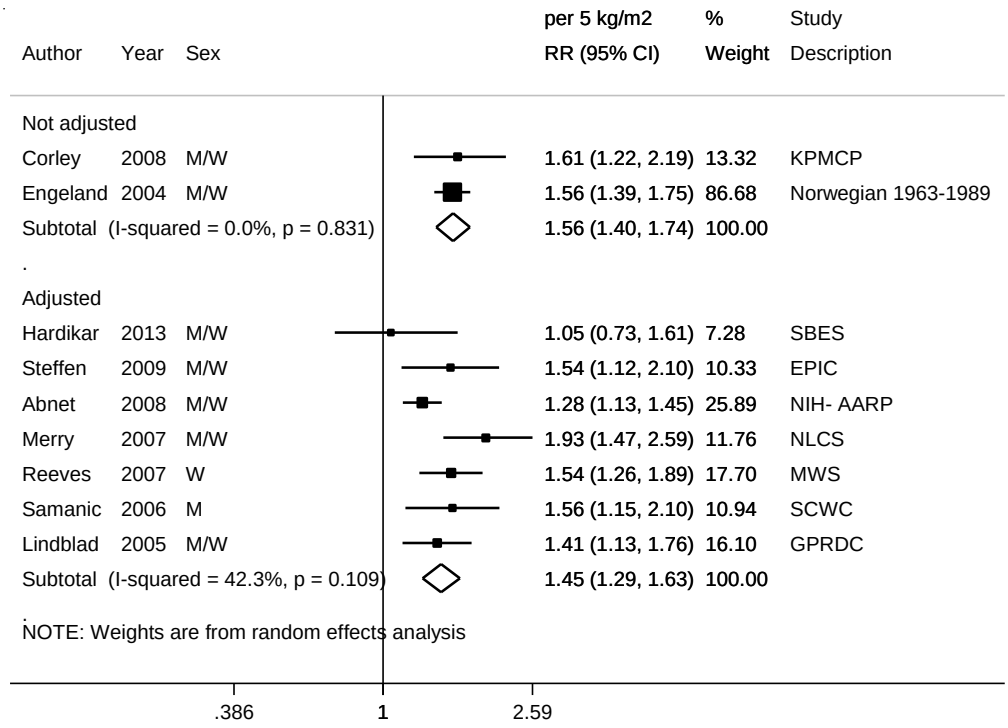


Figure 89 Relative risk of oesophageal squamous cell carcinoma for 5 kg/m^2 increase of BMI by adjustment for smoking

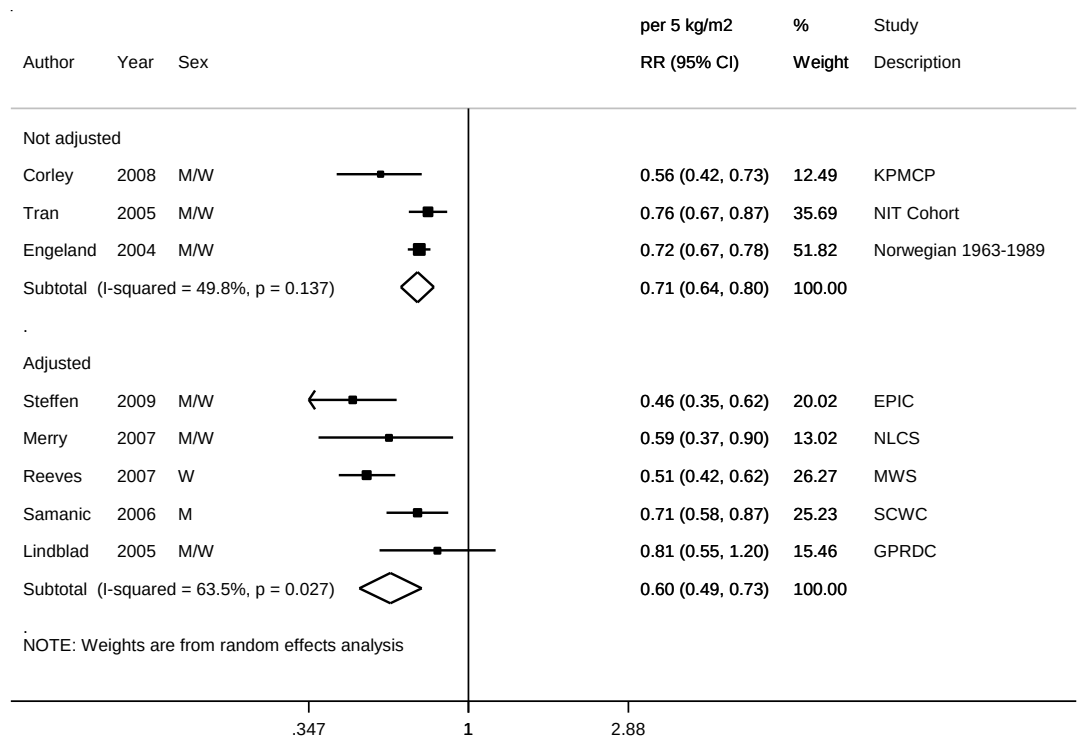


Figure 90 Relative risk of oesophageal adenocarcinoma for 5 kg/m^2 increase of BMI: Me-Can project (7 cohorts) and 9 studies identified in the CUP

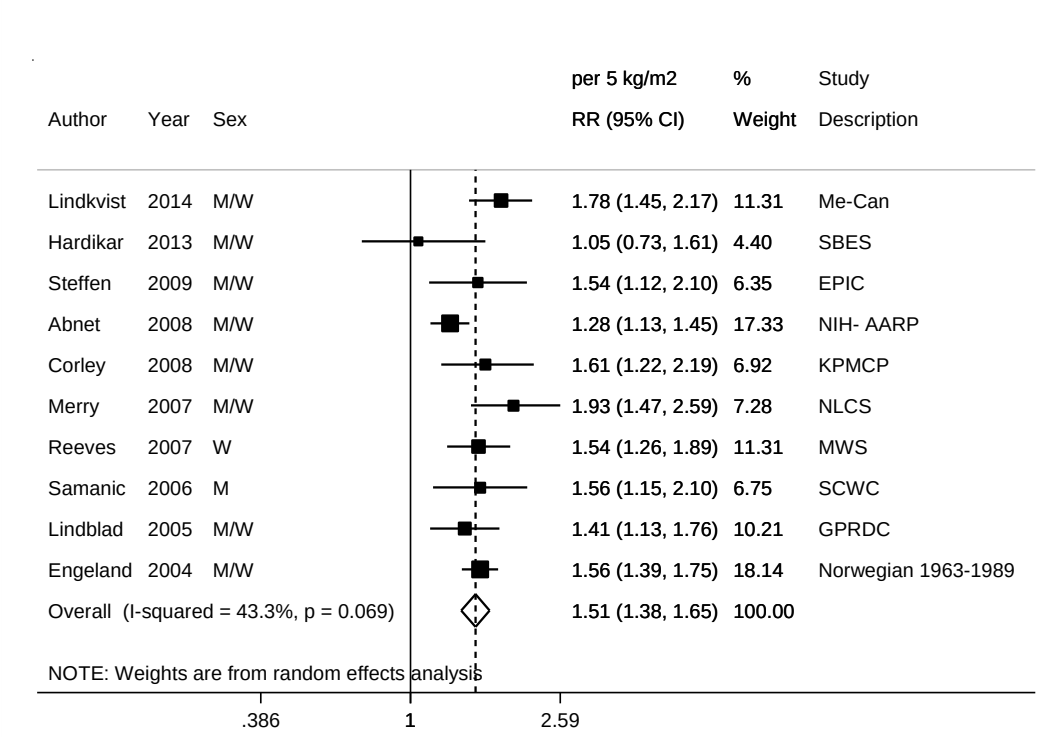


Figure 91 Relative risk of squamous cell carcinoma for 5 kg/m^2 increase of BMI: Me-Can project (7 cohorts) and 8 studies identified in the CUP

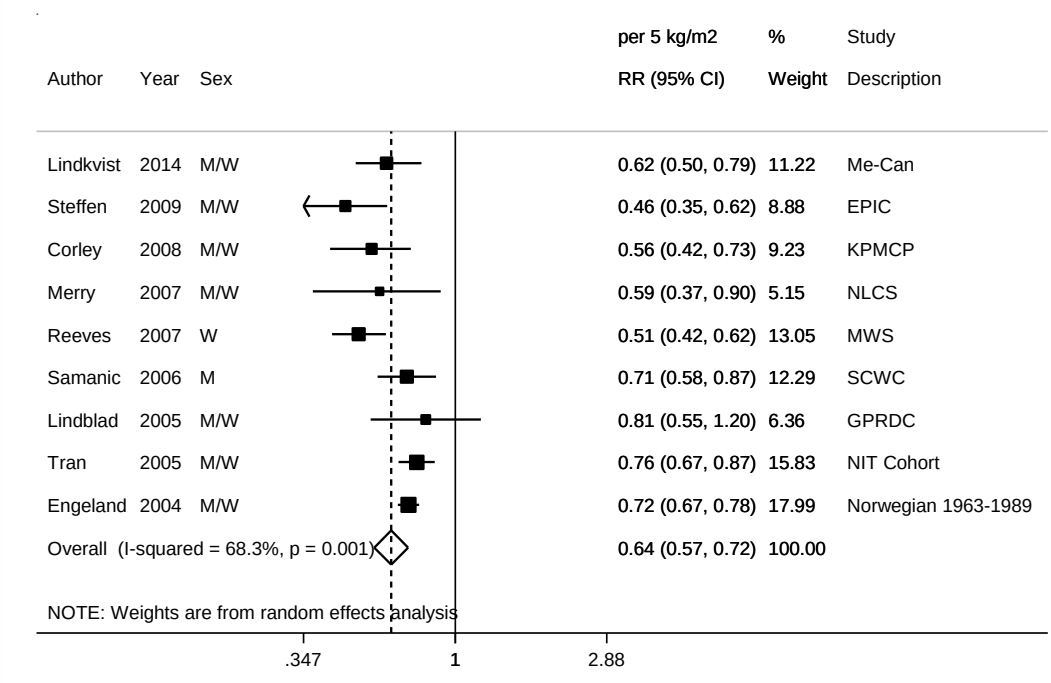
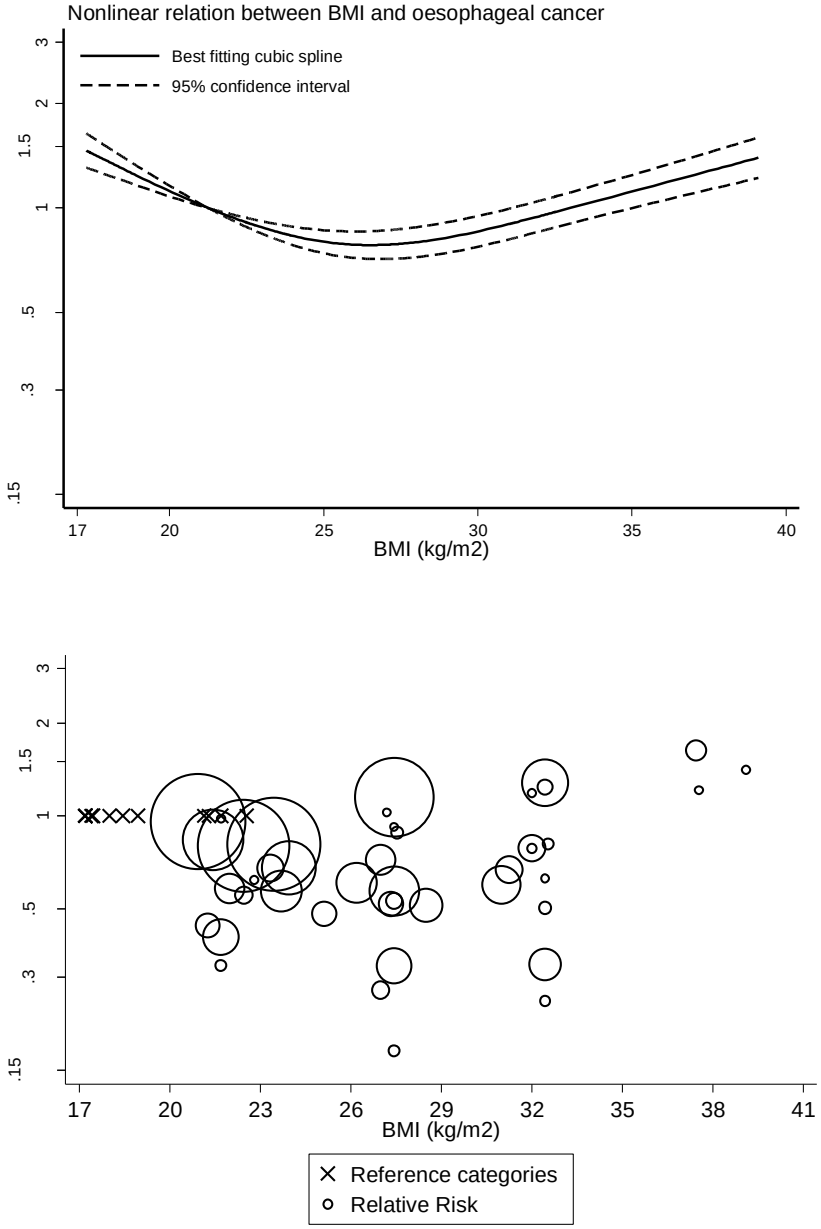


Figure 92 Non-linear dose-response meta-analysis of BMI and oesophageal cancer

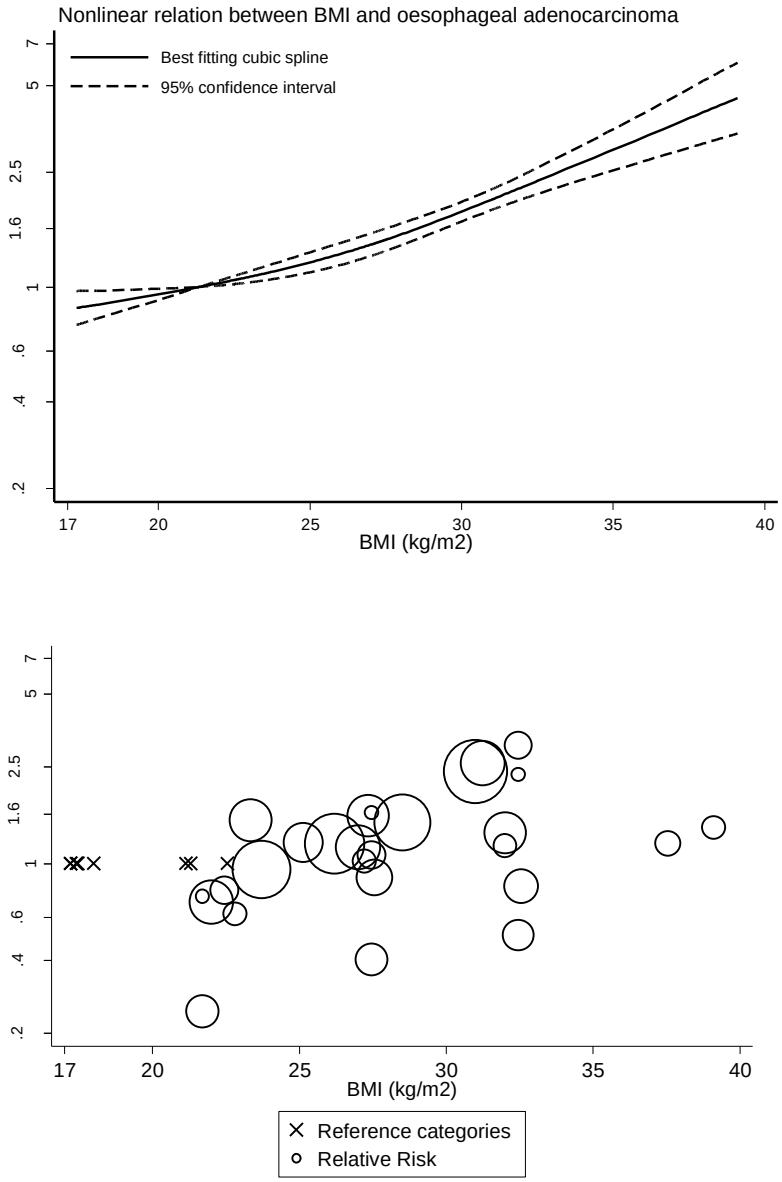


P non-linear <0.001

Table 76 Relative risk of oesophageal cancer and BMI estimated using non-linear models

BMI (kg/m^2)	RR (95%CI)
17.20	1.48 (1.31-1.66)
18.00	1.36 (1.24-1.49)
21.25	1.00
23.34	0.86 (0.82-0.90)
25.13	0.80 (0.74-0.86)
27.34	0.79 (0.71-0.87)
31.00	0.90 (0.81-0.99)

Figure 93 Non-linear dose-response meta-analysis of BMI and oesophageal adenocarcinoma

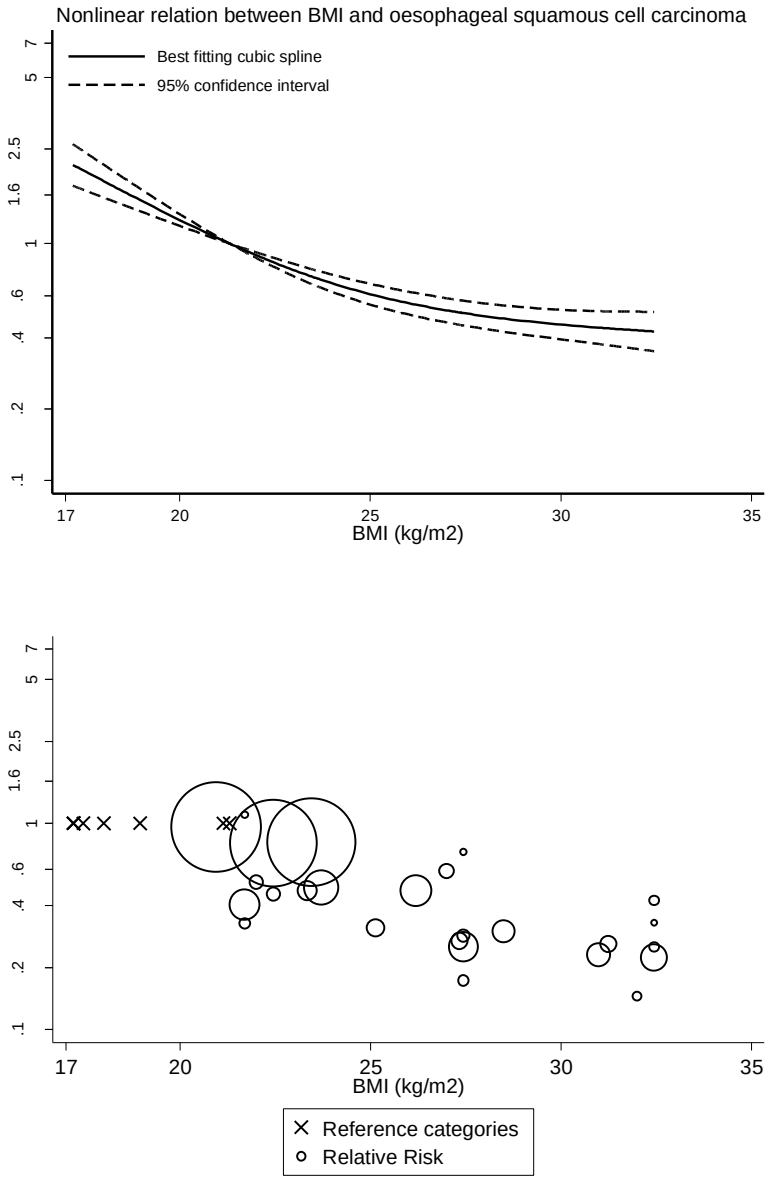


P non-linear =0.07

Table 77 Relative risk of oesophageal adenocarcinoma and BMI estimated using non-linear models

BMI (kg/m^2)	RR (95%CI)
17.20	0.84 (0.73-0.97)
18.00	0.87 (0.78-0.97)
21.30	1.00
23.34	1.11 (1.05-1.17)
25.13	1.23 (1.13-1.33)
27.34	1.44 (1.32-1.58)
31.00	2.01 (1.86-2.19)

Figure 94 Non-linear dose-response meta-analysis of BMI and oesophageal squamous cell carcinoma



P non-linear <0.001

Table 78 Relative risk of oesophageal squamous cell carcinoma and BMI estimated using non-linear models

BMI (kg/m^2)	RR (95%CI)
17.20	2.14 (1.75-2.62)
18.00	1.83 (1.56-2.15)
21.30	1.00
23.34	0.74 (0.69-0.79)
25.13	0.60 (0.54-0.67)
27.34	0.51 (0.45-0.58)
31.00	0.44 (0.38-0.52)

8.1.3 Weight

Cohort studies

Summary

Main results:

Five studies (1797 cases) were included in the dose-response meta-analysis. Weight was not associated with oesophageal cancer risk. In analysis by cancer type, a significant positive association with adenocarcinomas (two studies, low heterogeneity) and a non-significant inverse association with squamous cell carcinomas (two studies, high heterogeneity) were observed.

There was no evidence of publication or small study bias (p=0.51), but the analysis had low power due to small number of studies. Visual inspection of the funnel plot showed asymmetry, with missing studies showing positive association.

One study not included from the dose response meta-analysis (MacInnis, 2006) reported a significant positive association with combined distal oesophageal and cardia stomach cancer (30 cases).

Sensitivity and stratified analyses:

In influence analysis, the summary RRs ranged from 0.91 (95% CI=0.84-0.98) when O'Doherty, 2012 that contributed 23% weight was omitted to 0.98 (95% CI=0.86-1.11) when Tulinius, 1997 that contributed 12% weight was omitted.

Stratified analyses were not conducted due to low number of studies.

Non-linear dose-response meta-analysis:

Non-linear dose-response analysis was not conducted due to small number of studies.

Study quality:

Apart from Tran, 2005 (1958 cases), all other studies were small sized. In three studies weight and height were measured and in two studies they were self-reported.

Only two (O'Doherty, 2012; Steffen, 2009) out of the five studies adjusted for multiple confounders. Fujino, 2007 was adjusted for age and study area, and analyses were grouped by sex; Tran, 2005 was adjusted for age and sex only; and Tulinius 1997 was adjusted for age only.

Table 79 Weight and oesophageal cancer risk. Number of studies in the CUP SLR

	Number
Studies identified	6 (7 publications)*
Studies included in forest plot of highest compared with lowest exposure	4
Studies included in linear dose-response meta-analysis	5
Studies included in non-linear dose-response meta-analysis	Not enough studies

* Included one study reported results on distal oesophageal and gastric cardia cancer.

Table 80 Weight and oesophageal cancer risk. Summary of the linear dose-response meta-analysis in the 2005 SLR and CUP

	2005 SLR	**CUP**
Increment unit used	No meta-analysis	5 kg
All studies		
Studies (n)	-	5
Cases (total number)	-	1797
RR (95% CI)	-	0.94 (0.83-1.07)
Heterogeneity (I^2, p-value)	-	90.0%, <0.001
p value Egger test	-	0.51
Histological type	**Adenocarcinoma (AC)**	**Squamous cell carcinoma (SCC)**
Studies (n)	2	2
Cases (total number)	341	2068
RR (95%CI)	1.15 (1.09-1.22)	0.87 (0.72-1.06)
Heterogeneity (I^2, p-value)	0.1%, 0.32	92.1%, <0.001

Table 81 Weight and oesophageal cancer risk. Main characteristics of studies included in the linear dose-response meta-analysis

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Missing data derived for analyses
O'Doherty, 2012 oes00844 USA	NIH- AARP, Prospective Cohort, Age: 50-71 years, M/W	253/ 218 854 12 years maximum	Record linkage to state cancer registry databases.	Self-reported in baseline questionnaire	Incidence, AC	4 vs 1 quartile	2.66 (1.76-4.02) Ptrend:<0.01	Age, sex, alcohol consumption, antacid use, aspirin use, cigarette smoking, diabetes, ethnicity, height, marital status, physical activity, red meat intake, education, fruit and vegetable intake, non-steroidal anti-inflammatory drug use, total energy, white meat intake	Average weight per category, distribution of person-years by exposure category
Steffen, 2009 oes00865 Denmark,France,Germany,Greece,Italy,Netherlands,Norway,Spain,Sweden,UK	EPIC, Prospective Cohort, Age: 25-70 years, M/W	198/ 346 554 8.9 years	Cancer and mortality registries, active follow up	Measured	Incidence, AC	5 vs 1 quantile	1.85 (0.92-3.70) Ptrend:0.11	Age, sex, education, smoking status, smoking duration, baseline alcohol consumption, and lifelong alcohol consumption, physical activity, intake of fruits, vegetables, and meat and meat products	Average weight per category, distribution of person-years by exposure quintiles, RRs by cancer subtype were combined using the method of Hamling
		88/							
		110/			SCC		0.33 (0.18-0.60) Ptrend:<0.001		
Fujino, 2007 oes00834 Japan	JACC, Prospective Cohort, M/W	173/1 335 366 person-years 12 years	Date and cause of death annually or biannually	Self-reported in survey	Mortality, oesophageal cancer				Mid-points of exposure categories, RRs for men and

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Missing data derived for analyses
		148/ 549 584 person-years	confirmed with government authorization		Men	≥63 vs <55 kg	0.50 (0.32-0.78)	Age, study area	women were combined using fixed effect model
		25/ 785 782 person-years			Women	≥55 vs <49 kg	1.94 (0.77-4.85)		
Tran, 2005 oes00804 China	NIT Cohort, Prospective Cohort, Age: 40-69 years, M/W	1 958 29 584 15 years	Monthly contact by either village health workers or interviewers, and cancer diagnoses verified by senior diagnosticians	Measured at physical examinations	Incidence, SCC	≥60 vs <50 kg	0.86 (0.75-0.98) Ptrend:.0.06	Age, sex	Mid-points of exposure, distribution of person-years by exposure quantiles
Tulinius, 1997 oes00898 Iceland	Reykjavik Study, Historical Cohort, Age: 50 years, W	15/ 22 946 27 years (max)	Cancer registry	Measured at study clinic	Incidence, oesophageal cancer Women	Per 1 kg	0.94 (0.89-0.99)	Age	Dose-response results only, exposure units rescaled

Table 82 Weight and oesophageal cancer risk. Main characteristics of studies excluded from the linear dose-response meta-analysis

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Reasons for exclusion
MacInnis, 2006 oes00895 Australia	MCCS, Prospective Cohort, Age: 27-75 years, M/W	30/ 41 295 11.3 years	Cancer registry	Measured at baseline by trained nurses	Incidence, distal oesophageal and gastric cardia cancer	3 tertile vs 1 tertile	2.30 (1.00-5.20)	Sex, age-underlying cox models, county of birth, educational level, physical activity	Excluded, distal oesophageal and gastric cardia cancer
						Per 10 kg	1.40 (1.07-1.84)		
Guo, 1994 oes00103 China	NIT Cohort, Nested Case Control, Age: 40-69 years, M/W	640/ 29 584 5 years	Monthly contact by either village health workers or interviewers, and cancer diagnoses verified by senior diagnosticians	Measured at physical examinations	Incidence, oesophageal cancer (nearly all SCC)	≥61 vs ≤50 kg	0.70 (0.50-0.90) Ptrend:0.01	Body weight, family history of specific cancer, smoking habits, vitamins	Excluded, superseded by Tran, 2005, OES00804

Figure 95 RR estimates of oesophageal cancer by levels of weight
Note: Tulinius, 1997 did not report RRs (95% CI) for quantitative levels of weight and was excluded from the figure

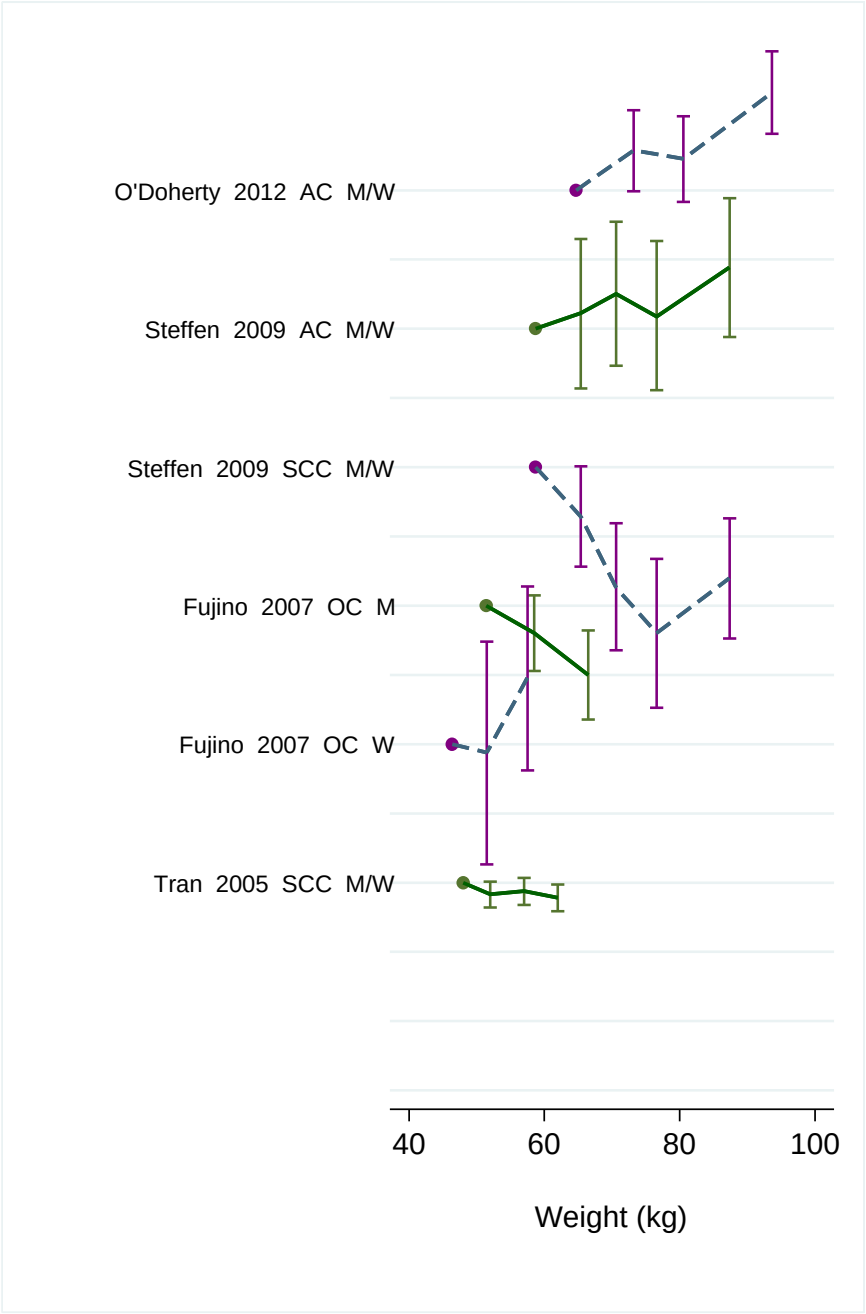


Figure 96 RR (95% CI) of oesophageal cancer for the highest compared with the lowest level of weight

Note: Only studies reporting RRs (95% CI) for the highest compared with the lowest level of weight are shown

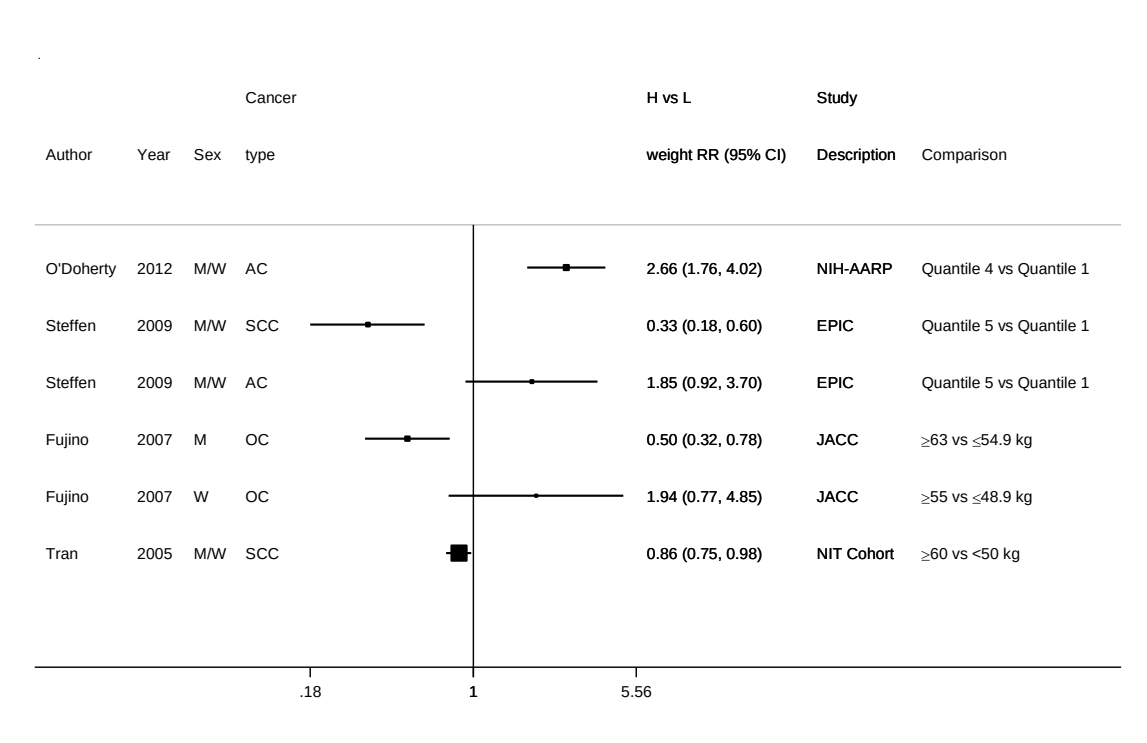


Figure 97 Relative risk of oesophageal cancer for 5 kg increase of weight

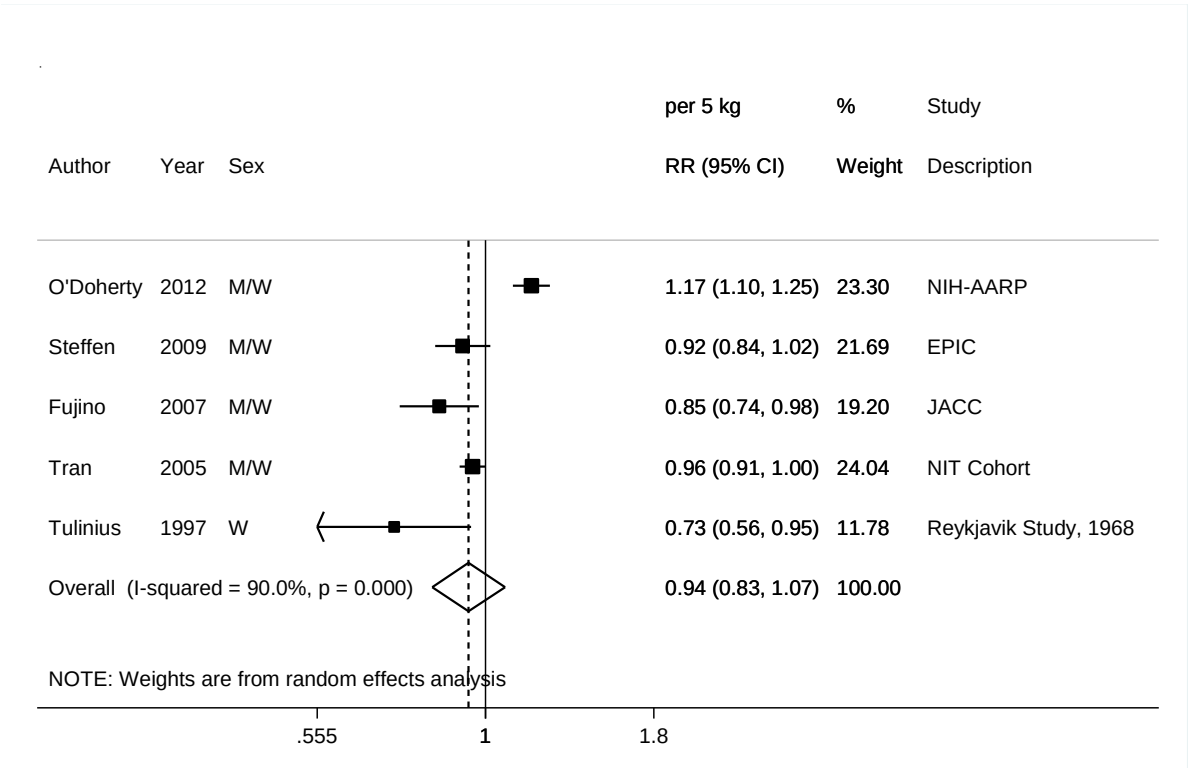
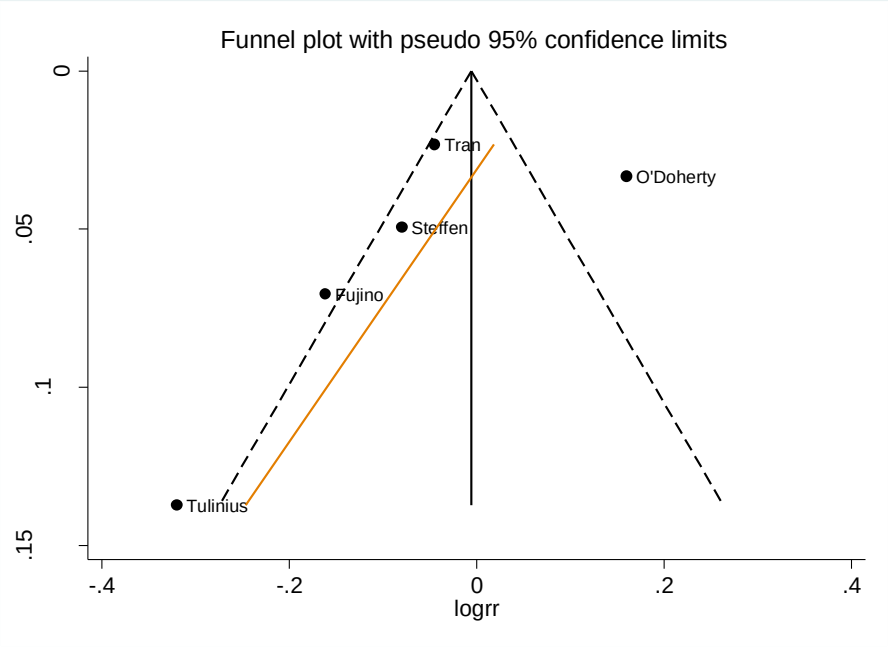
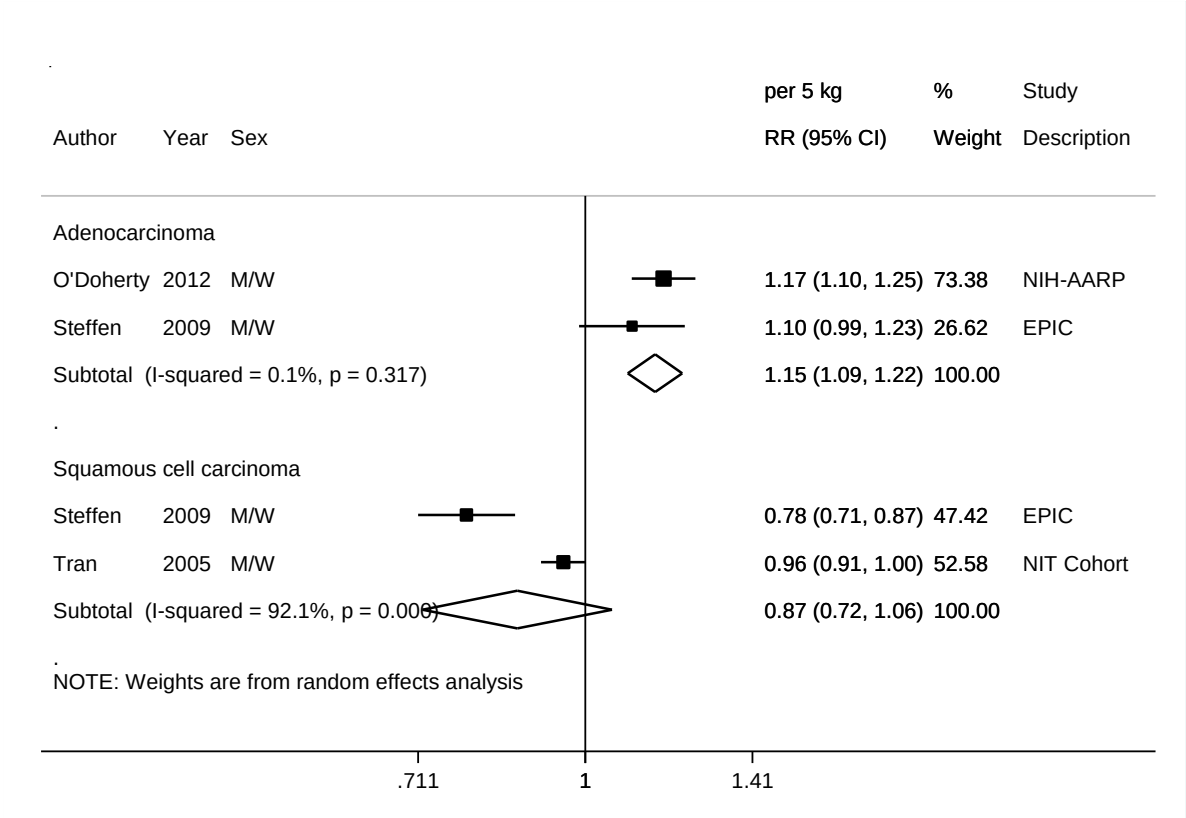


Figure 98 Funnel plot of studies included in the dose response meta-analysis of weight and oesophageal cancer



Egger's test p=0.51

Figure 99 Relative risk of oesophageal cancer for 5 kg increase of weight by cancer type



8.2.1 Waist circumference

Cohort studies

Summary

Main results:

Although the number of studies to conduct a dose-response meta-analysis is low this section has been included as supplementary evidence on body fatness.

The identified studies reported results by cancer subtype. Two studies (335 cases) were included in the dose-response meta-analysis of oesophageal AC. Significant positive association with low heterogeneity between studies was observed. The only study on SCC (103 cases) reported non-significant (inverse) association.

The test of publication or small study bias was not conducted due to small number of studies.

In the NIH-AARP study (O'Doherty, 2012) the significant positive association of weight with oesophageal adenocarcinoma remained similar after further adjustment for hip circumference. Adjustment for BMI in the EPIC study (Steffen, 2009), attenuated the association of waist circumference with adenocarcinoma that became non-significant (Ptrend = 0.05). The inverse association with SCC became a positive association BMI whereas the inverse association with BMI was even strengthened.

When stratified by smoking status, the EPIC study (Steffen, 2009) observed non-significant positive associations with AC and SCC among non-smokers. Among smokers, a significant positive association with AC and a significant inverse association with SCC were observed.

Two other studies were not included in the dose-response meta-analysis. One study (MacInnis, 2006) reported a significant positive association of waist circumference with lower oesophageal and cardia stomach cancer risk. The other study (Corley, 2008) assessed the standing thigh anterior-posterior diameter and reported observed a significant positive association with AC that was strengthened in the model adjusted for BMI, and a non-significant inverse association with SCC that became a non-significant positive association with SCC in the model adjusted for BMI.

Sensitivity and stratified analysis was not conducted due to small number of studies.

Non-linear dose-response analysis was not conducted due to small number of studies.

Study quality:

All studies were small sized. In one study, weight and height were measured and in the other study, they were self-reported. Both studies adjusted for multiple confounders.

Table 83 Waist circumference and oesophageal cancer risk. Number of studies in the CUP SLR

	Number
Studies identified	4*
Studies included in forest plot of highest compared with lowest exposure	2
Studies included in linear dose-response meta-analysis	2
Studies included in non-linear dose-response meta-analysis	Not enough studies

Note: Include cohort, nested case-control and case-cohort designs *Included one study reported results on anterior-posterior diameter and one study on combined lower oesophageal and cardia stomach cancer.

Table 84 Waist circumference and oesophageal cancer risk. Summary of the linear dose-response meta-analysis in the 2005 SLR and CUP*

	CUP	
Comparison	Per 10 cm	
Histological type	**Adenocarcinoma (AC)**	**Squamous cell carcinoma (SCC)**
Studies (n)	2	1
Cases (total number)	335	103
RR (95%CI)	1.34 (1.17-1.52)	0.83 (0.66-1.03)
Heterogeneity (I^2, p-value)	9.6%, 0.29	-
P value Egger test	-	-

* No meta-analysis was conducted in the 2005 SLR

Table 85 Central adiposity* and oesophageal cancer risk. Results of meta-analyses and pooled analyses published after the 2005 SLR

Author, Year	Number of studies	Total number of cases	Studies country, area	Outcome	Comparison	RR (95%CI)	P trend	Heterogeneity (I^2, p value)
Meta-analyses								
Singh, 2013	6 studies (3** cohorts, 1 nested case-control, 2 case-control)	841	Australia, Europe, Ireland, USA	Incidence, AC	Central adiposity vs normal body fat distribution (5 studies)	2.51 (1.56-4.04)	-	62%, 0.03

*Central adiposity included abdominal fat accessed by computed tomography, WC, or WHR

**The three cohorts and the nested case-control study were included in the present review

Table 86 Waist circumference and oesophageal cancer risk. Main characteristics of studies included in the linear dose-response meta-analysis

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Missing data derived for analyses
O'Doherty, 2012 oes00844 USA	NIH-AARP, Prospective Cohort, Age: 50-71 years, M/W	253/ 218 854 9 years	Record linkage to state cancer registry databases.	Self-reported waist and hip measurements	Incidence, AC	Quantile 4 vs quantile 1	2.01 (1.35-3.00) Ptrend: <0.01	Age, sex, alcohol consumption, antacid use, aspirin or , non-steroidal anti-inflammatory drug use, cigarette smoking, diabetes, ethnicity, education, marital status, physical activity, red meat intake, white meat intake, fruit and vegetable intake, total energy	Weighted average exposure values and distribution of persons per category
							2.03 (1.21-3.39) Ptrend: 0.01	Further adjusted for hip circumference	
Steffen, 2009 oes00865 Denmark,France ,Germany,Greec e,Italy,Netherlan ds,Norway,Spai	EPIC, Prospective Cohort, Age: 25-70 years, M/W	185/ 346 554 8.9 years 82/	Cancer and mortality registries, active follow up	Measured waist and hip	Incidence AC	Quantile 5 vs quantile 1	3.07 (1.35-6.98) Ptrend: 0.003 0.62 (0.32-1.20)	Age, study centre (stratification), sex, education, smoking status and duration,	Weighted average exposure values and distribution of persons per category

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Missing data derived for analyses
n,Sweden,UK		103/			SCC		Ptrend: 0.08	baseline alcohol consumption, lifelong alcohol consumption, physical activity, intake of fruits, vegetables, meat and meat products	
					AC SCC		2.73 (0.91-8.19) Ptrend: 0.10 6.91 (2.54-18.80) Ptrend: 0.0002	Further adjusted for BMI	
		38/ 30/			Nonsmokers AC SCC		2.30 (0.79-6.73) Ptrend: 0.04 1.58 (0.42-5.85) Ptrend: 0.33	Age, study centre (stratification), sex, education, current alcohol consumption, lifelong alcohol consumption, physical activity, intake of fruits, vegetables, meat and meat products	
		44/ 73/			Smokers AC SCC		4.14 (1.14-15.10) Ptrend: 0.02 0.41 (0.19-0.91) Ptrend: 0.01		

Table 87 Waist circumference and oesophageal cancer risk. Main characteristics of studies excluded from the linear dose-response meta-analysis

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Inclusion/exclusion
Corley, 2008 oes00826 USA	KPMCP, Nested Case Control, M/W	127/ 2800 controls	Cancer registry, individual record review	Measured abdominal diameter	Incidence	Anterior-posterior diameter		Age, sex, year of examination	Excluded, exposure was anterior-posterior diameter
		55/			AC	Per 1 cm	1.10 (1.03-1.17)		
						≥25 vs <20 cm	3.47 (1.29-9.33)		
		72/			SCC	Per 1 cm	1.00 (0.94-1.06)		
						≥25 vs <20 cm	0.78 (0.32-1.92)		
		55/			AC	≥25 vs <20 cm	4.78 (1.14-20.11)	Further adjusted for BMI	
		72/			SCC		1.29 (0.32-5.20)		
		55/			AC		3.91 (1.26-12.02)	Age, sex, year of examination, GERD-type symptoms	
MacInnis, 2006 oes00895 Australia	MCCS, Prospective Cohort, Age: 27-75 years, M/W	30/ 41 295 11.3 years	Cancer registry	Measured waist and hip	Incidence, lower oesophageal and gastric cardia cancer	Per 10 cm	1.46 (1.05-2.04)	Sex, age-underlying cox models, county of birth, educational level, physical activity	Excluded, lower oesophageal and gastric cardia cancer
						Quantile 3 vs quantile 1	2.90 (1.20-6.90)		

Figure 100 RR estimates of oesophageal cancer by levels of waist circumference

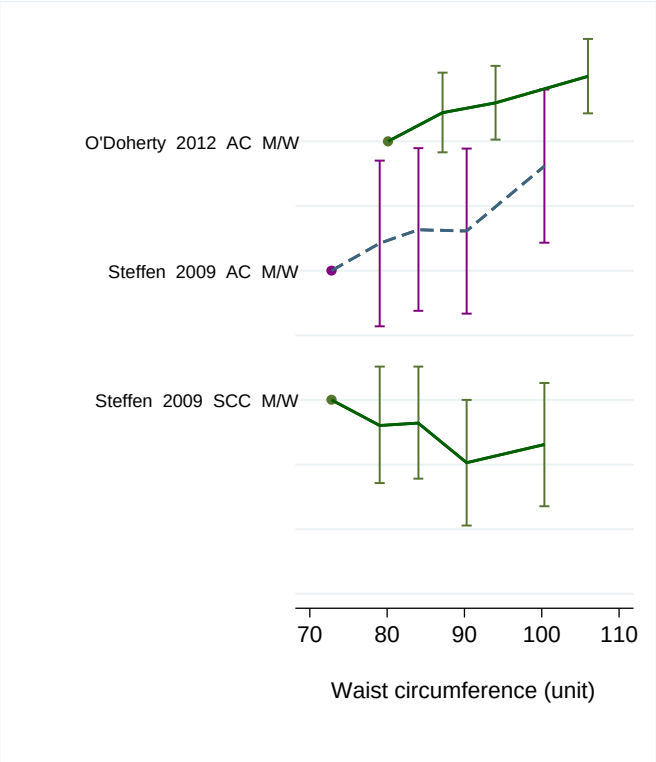


Figure 101 RR (95% CI) of oesophageal cancer for the highest compared with the lowest level of waist circumference

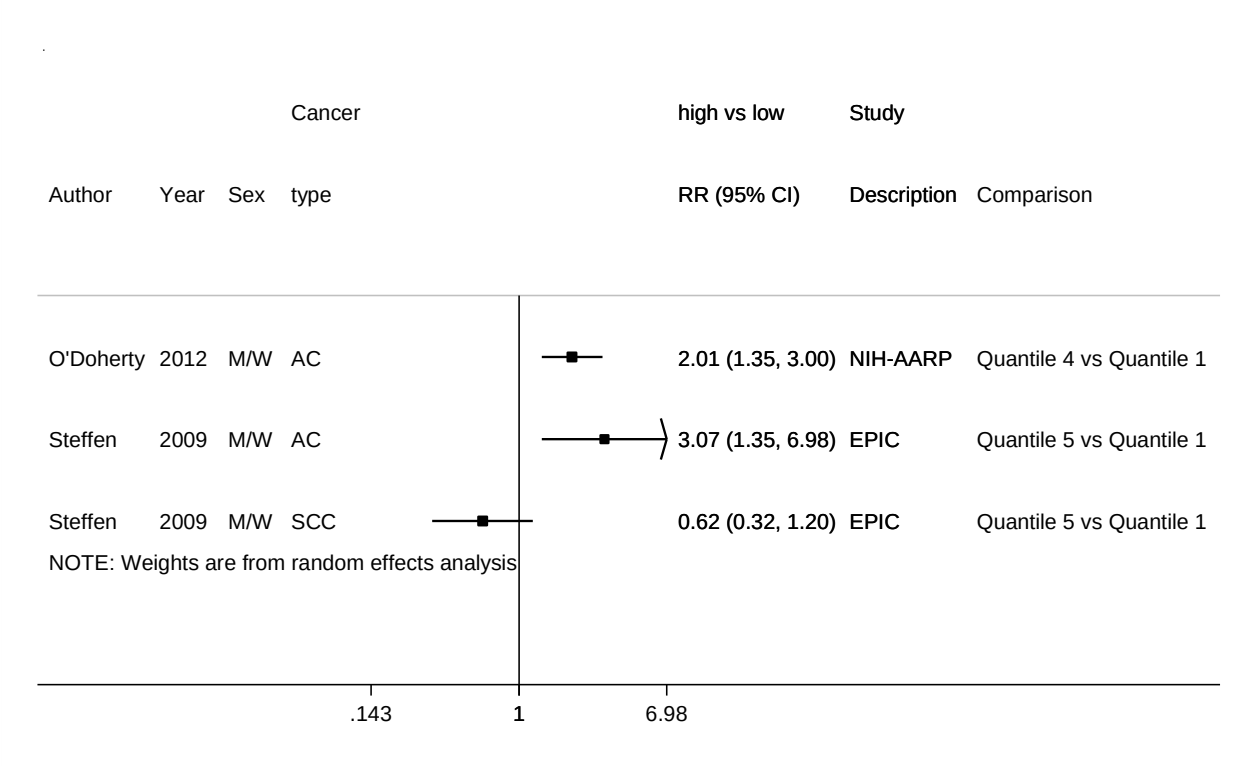
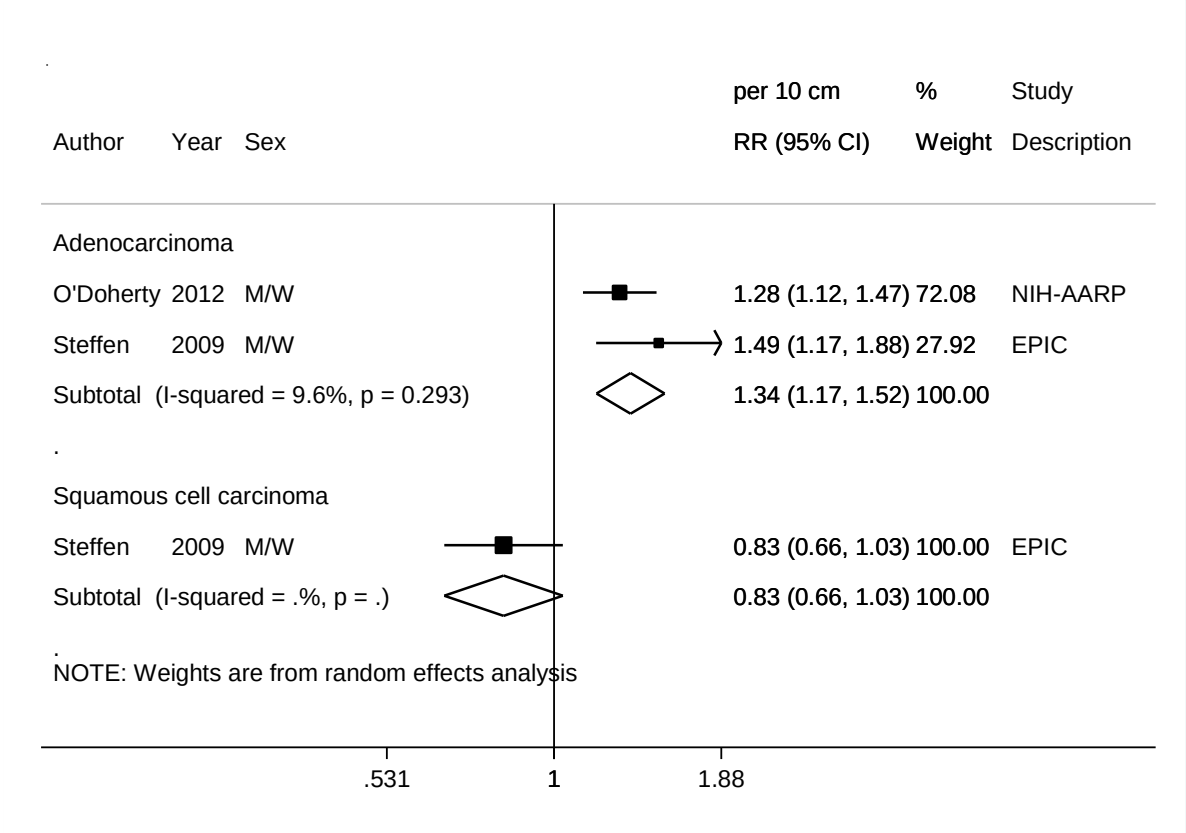


Figure 102 Relative risk of oesophageal cancer for 10 cm increase of waist circumference by cancer type



8.2.3 Waist to hip ratio

Cohort studies

Summary

Main results:

Although the number of studies to conduct a dose-response meta-analysis is limited, this section has been included as supplementary evidence on body fatness.

An overall dose-response meta-analysis of oesophageal cancer was not conducted as studies only reported results by cancer subtype.Three studies (380 cases) were included in the dose-response meta-analysis of oesophageal AC. Significant positive association with low heterogeneity between studies was observed. One study on SCC (103 cases) reported a non-significant positive association.

Test of publication or small study bias was not conducted due to small number of studies.

Adjustment for BMI attenuated the positive associations of WHR with AC (O'Doherty, 2012; Steffen, 2009). The positive association with SCC became stronger with a significant dose-response trend (Steffen, 2009).

Another study reported non-significant positive association of waist-hip ratio with lower oesophageal and cardia stomach cancer risk MacInnis, 2006).

Sensitivity and stratified analyses:

In influence analysis, the summary RRs ranged from 1.27 (95% CI=1.06-1.51) when Steffen, 2009 (23% weight) to 1.56 (95% CI=1.05-2.33) when O'Doherty, 2012 (61% weight) were omitted.

Stratified analysis was not conducted due to small number of studies.

Non-linear dose-response analysis was not conducted due to small number of studies.

Study quality:

Hardikar, 2013 was a cohort of Barrett's oesophagus patients. All studies were small sized. In two studies weight and height were measured and in one study they were self-reported.

Two studies adjusted for multiple confounders. Hardikar, 2013 was adjusted for age, sex, smoking, and NSAID use only.

Significant positive association remained when each study was omitted in turn in influence analysis.

Table 88 Waist to hip ratio and oesophageal cancer risk. Number of studies in the CUP SLR

	Number
Studies identified	4*
Studies included in forest plot of highest compared with lowest exposure	3
Studies included in linear dose-response meta-analysis	3
Studies included in non-linear dose-response meta-analysis	Not enough studies

Note: Include cohort, nested case-control and case-cohort designs *Included one study reported results on combined lower oesophageal and cardia stomach cancer.

Table 89 Waist to hip ratio and oesophageal cancer risk. Summary of the linear dose-response meta-analysis in the 2005 SLR and CUP*

	CUP	
Increment unit used	Per 0.1 unit	
Histological type	**Adenocarcinoma (AC)**	**Squamous cell carcinoma (SCC)**
Studies (n)	3	1
Cases (total number)	380	103
RR (95%CI)	1.38 (1.10-1.73)	1.21 (0.83-1.77)
Heterogeneity (I^2, p-value)	26.9%, 0.25	-
P value Egger test	-	-

*No meta-analysis was conducted in the 2005 SLR

Table 90 Central adiposity* and oesophageal cancer risk. Results of meta-analyses and pooled analyses published after the 2005 SLR

Author, Year	Number of studies	Total number of cases	Studies country, area	Outcome	Comparison	RR (95%CI)	P trend	Heterogeneity (I^2, p value)
Meta-analyses								
Singh, 2013	6 studies (3** cohorts, 1 nested case-control, 2 case-control)	841	Australia, Europe, Ireland, USA	Incidence, AC	Central adiposity vs normal body fat distribution (5 studies)	2.51 (1.56-4.04)	-	62%, 0.03

*Central adiposity included abdominal fat accessed by computed tomography, WC, or WHR

**The three cohorts and the nested case-control study were included in the present review

Table 91 Waist to hip ratio and oesophageal cancer risk. Main characteristics of studies included in the linear dose-response meta-analysis

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Missing data derived for analyses
Hardikar, 2013 oes00875 USA	SBES, Prospective Cohort, Age: 30- years, M/W Barrett's oesophagus patients	45/ 411 33 635 person-months	Biopsy and follow up	Measured waist and hip	Incidence, AC	1.02 vs 0.86	1.48 (0.60-3.61)	Age, (sex) cigarette smoking, NSAID	Mid-points per exposure category
		41/			Men	1.03 vs 0.9	1.53 (0.59-3.96)		
		4/			Women	0.96 vs 0.78	0.95 (0.05-18.92)		
O'Doherty, 2012 oes00844 USA	NIH-AARP, Prospective Cohort, Age: 50-71 years, M/W	253/ 218 854 9 years	Record linkage to state cancer registry databases.	Self-reported waist and hip measurements	Incidence, AC	Per 0.1 units	1.27 (1.05-1.53)	Age, sex, alcohol consumption, antacid use, aspirin use, cigarette smoking, diabetes, ethnicity , marital status, physical activity, red meat intake, education, fruit and vegetable intake, non-steroidal anti-inflammatory drug use, total energy, white meat intake	
						Quantile 4 vs quantile 1	1.81 (1.24-2.64) Ptrend: <0.01		

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Missing data derived for analyses
						Quantile 4 vs quantile 1	1.47 (0.99-2.18) Ptrend: 0.02	Further adjusted for BMI	
Steffen, 2009 oes00865 Denmark,France,Germany,Greece,Italy,Netherlands,Norway,Spain,Sweden,UK	EPIC, Prospective Cohort, Age: 25-70 years, M/W	185/ 346 554 8.9 years	Cancer and mortality registries, active follow up	Measured waist and hip	Incidence			Age, study centre (stratification), sex, education, smoking status, smoking duration, baseline alcohol consumption, lifelong alcohol consumption, physical activity, intake of fruits, vegetables, meat and meat products	Weighted average exposure values and distribution of persons per category
		82/			AC		2.12 (0.98-4.57) Ptrend: 0.004		
		103/			SCC		1.11 (0.57-2.18) Ptrend: 0.24		
		82/			AC	Quantile 5 vs quantile 1	1.66 (0.71-3.84) Ptrend: 0.05	Further adjusted for BMI	
		103/			SCC		3.12 (1.48-6.54) Ptrend: 0.0001		
					Nonsmokers			Age, study centre (stratification), sex, education, current alcohol consumption, lifelong alcohol consumption, physical activity, intake of fruits, vegetables, meat and meat products	
		38/			AC		1.67 (0.52-5.43) Ptrend: 0.28		
		30/			SCC		1.91 (0.53-6.80) Ptrend: 0.1		
					Smokers		1.89 (0.57-6.20) Ptrend: 0.06		
		44/			AC		3.72 (1.46-9.51) Ptrend: 0.001		
		73/			SCC				

Table 92 Waist to hip ratio and oesophageal cancer risk. Main characteristics of studies excluded from the linear dose-response meta-analysis

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Inclusion/exclusion
MacInnis, 2006 oes00895 Australia	MCCS, Prospective Cohort, Age: 27-75 years, M/W	30/ 41 295 11.3 years	Cancer registry	Measured waist and hip	Incidence, lower oesophageal and gastric cardia cancer	Per 0.1	1.59 (0.93-2.69)	Sex, age-underlying cox models, county of birth, educational level, physical activity	Excluded, lower oesophageal and gastric cardia cancer
						Quantile 3 vs quantile 1	2.10 (0.80-5.50)		

Figure 103 RR estimates of oesophageal cancer by levels of waist to hip ratio

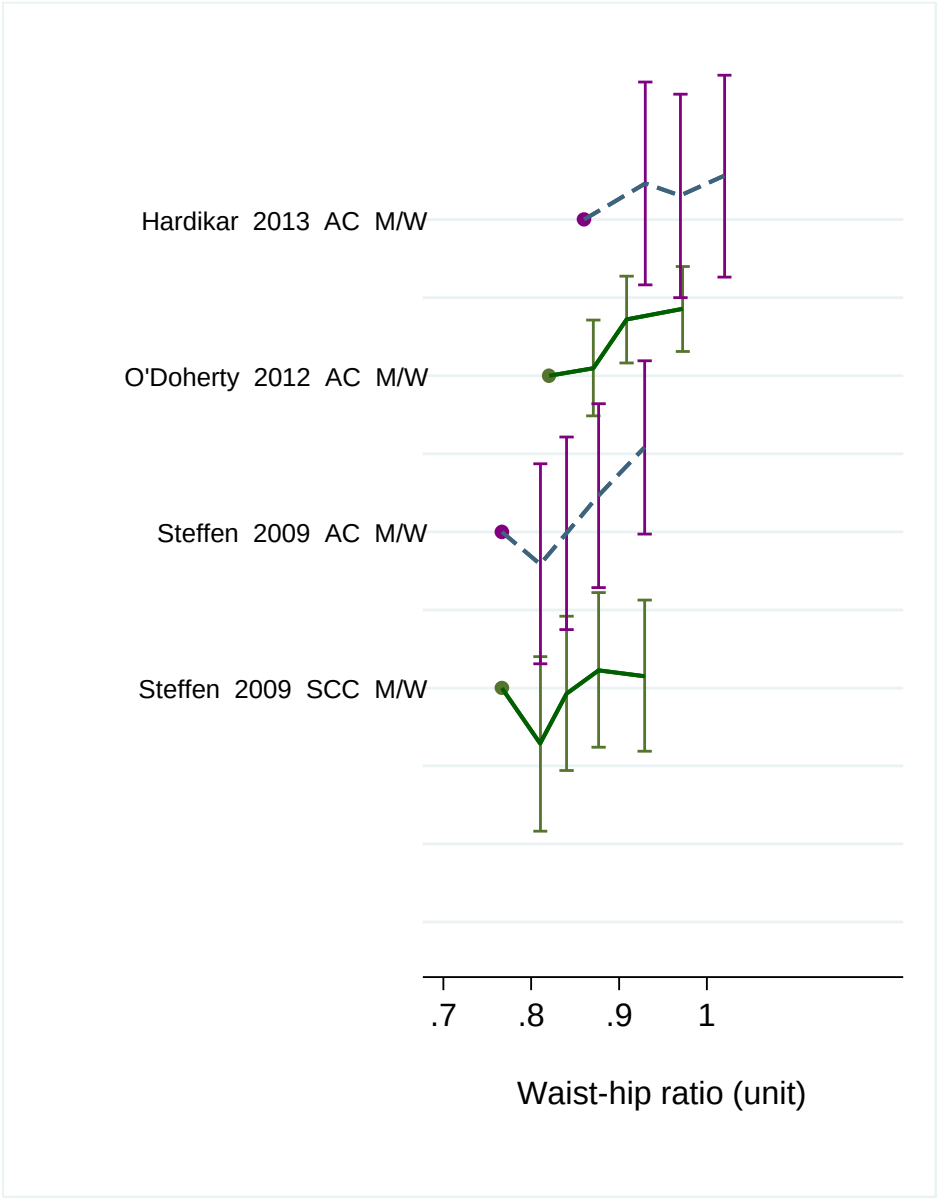


Figure 104 RR (95% CI) of oesophageal cancer for the highest compared with the lowest level of waist to hip ratio

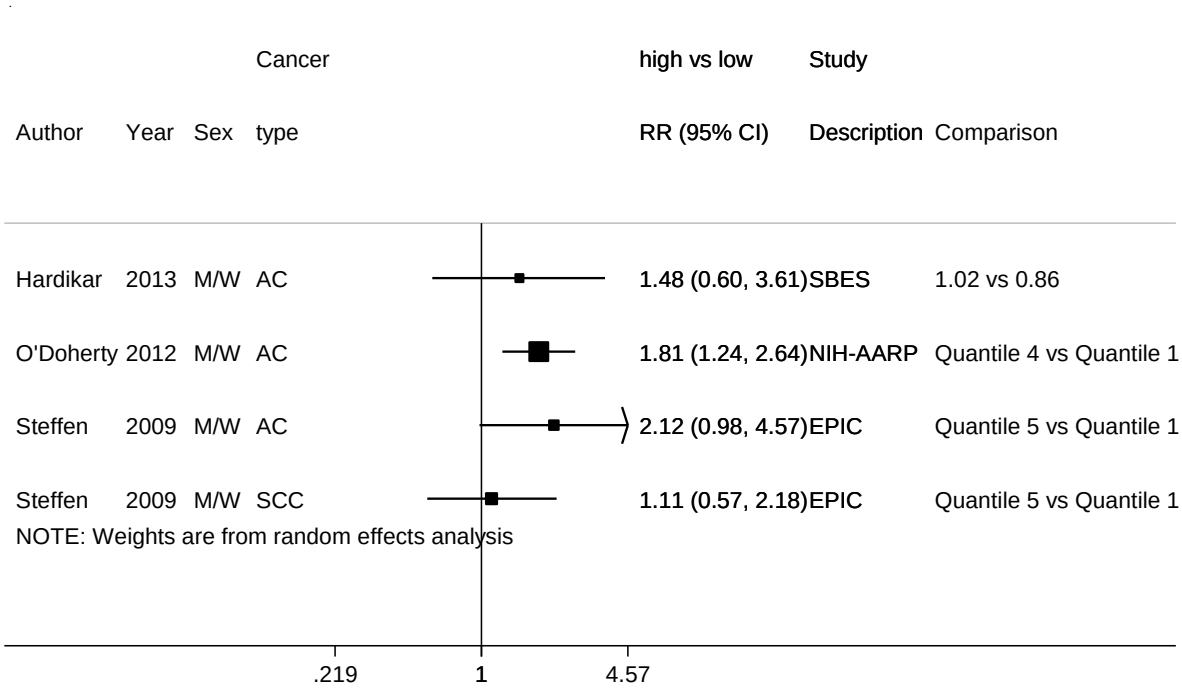
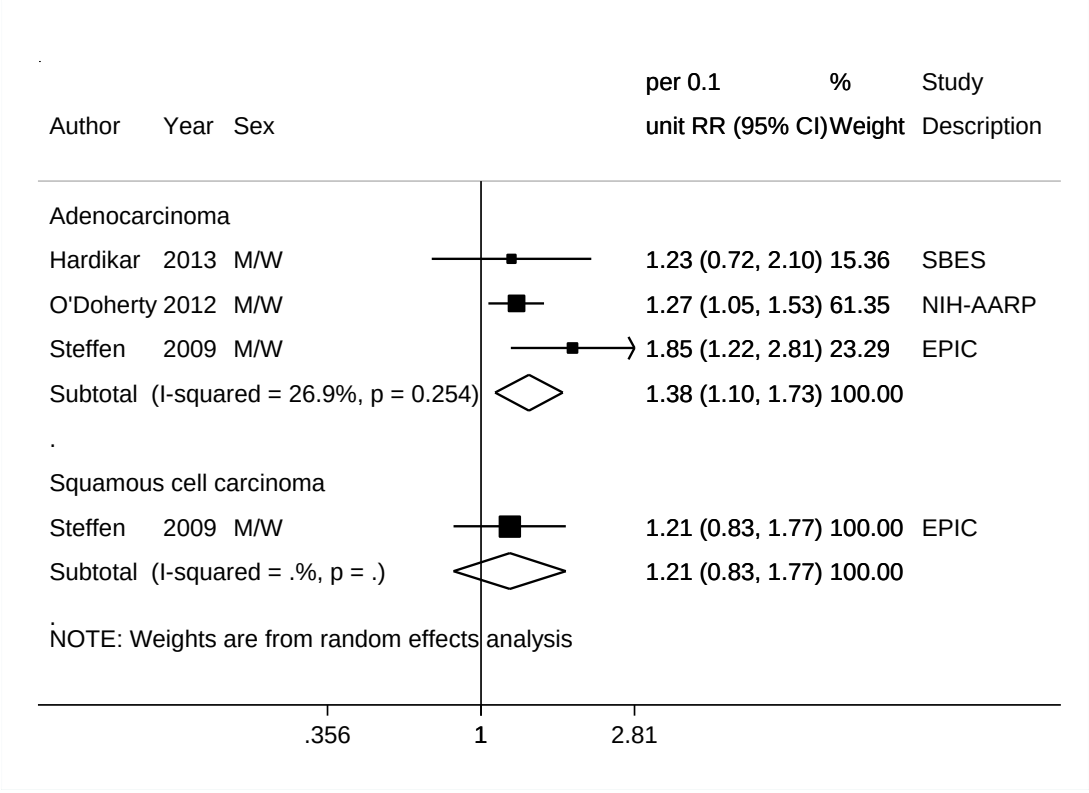


Figure 105 Relative risk of oesophageal cancer for 0.1 unit increase of waist to hip ratio by cancer type



8.3.1 Height (and proxy measures)

Cohort studies

Summary

Main results:

Nine studies (7222 cases) were included in the dose-response meta-analysis. Height was not significantly associated with oesophageal cancer risk. No significant associations were observed in meta-analyses stratified by sex, for adenocarcinomas or squamous cell carcinomas.

A study (McInnis, 2006) that reported a no significant association of height with distal oesophageal and cardia stomach cancer combined (30 cases) was not included in the dose-response analysis.

There was no evidence of publication or small study bias (p=0.44). However, twenty studies were identified in the CUP SLR on BMI and only nine studies have published on height and oesophageal cancer (see Appendix 1).

Sensitivity analyses:

In influence analysis, the RRs ranged from 0.99 (95% CI=0.94-1.04) when Tran, 2005 (NIT Cohort) was omitted to 1.02 (95% CI=0.98-1.07) when Engeland, 2004 (NSPT) was omitted.

In the stratified meta-analyses, the only significant association (positive) was in Asian studies, mainly influenced by one study (Tran, 2005).

Non-linear dose-response meta-analysis:

There was no evidence of non-linear relationship between height and oesophageal cancer (p=0.22).

Study quality:

Height was measured in five studies and self-reported in four studies. The observed associations were similar in analyses stratified by self-reported or measured height. Loss to follow-up was low in all studies. Cancer was assessed by record linkage to cancer and death registers or medical records in all studies.

Most studies adjusted for main risk factors but the two studies that reported significant associations (in opposite directions) adjusted only by age and sex.

Table 93 Height and oesophageal cancer risk. Number of studies in the CUP SLR

	Number
Studies identified	10 (12 publications)*
Studies included in forest plot of highest compared with lowest exposure	8
Studies included in linear dose-response meta-analysis	9

Studies included in non-linear dose-response meta-analysis	7

* Included one study reported results on distal oesophageal and gastric cardia cancer.

Table 94 Height and oesophageal cancer risk. Summary of the linear dose-response meta-analysis in the 2005 SLR and CUP

	2005 SLR	**CUP**
Increment unit used	No meta-analysis	Per 5 cm
All studies		
Studies (n)	-	9
Cases (total number)	-	7222
RR (95%CI)	-	1.00 (0.95-1.06)
Heterogeneity (I^2, p-value)	-	72.3%, <0.001
P value Egger test	-	0.44
Studies pooled with ERFC		
Studies (n)	-	127
Cases (total number)	-	5639
RR (95%CI)	-	1.02 (0.97-1.06)
Heterogeneity (I^2, p-value)	-	49.2%, 0.07
P value Egger test	-	0.41
Stratified and sensitivity analysis		
Sex	**Men**	**Women**
Studies (n)	4	3
RR (95%CI)	1.01 (0.93-1.09)	0.98 (0.92-1.05)
Heterogeneity (I^2, p-value)	72.9 %, 0.01	45.8%, 0.16
Outcome	**Incidence**	**Mortality**
Studies (n)	7	2
RR (95%CI)	0.99 (0.94-1.05)	1.06 (0.94-1.18)
Heterogeneity (I^2, p-value)	77.3%, <0.001	0%, 0.36
Histological type	**Adenocarcinoma (AC)**	**Squamous cell carcinoma (SCC)**
Studies (n)	3	3
Cases	474	2165
RR (95%CI)	0.93 (0.85-1.00)	1.01 (0.91-1.12)
Heterogeneity (I^2, p-value)	0%, 0.76	41.9%, 0.18

Geographic location	**Asia**	**Europe**	**North America**
Studies (n)	3	5	1
RR (95%CI)	1.06 (1.02-1.10)	0.97 (0.93-1.01)	0.89 (0.79-1.01)
Heterogeneity (I^2, p-value)	0%, 0.72	20.9%, 0.28	-

Other stratified and sensitivity analyses

Duration of follow-up	**5-<10 years**	**10-<15 years**	**≥15 years**
Studies (n)	4	2	3
RR (95%CI)	1.00 (0.96-1.05)	1.02 (0.83-1.27)	0.99 (0.93-1.05)
Heterogeneity (I^2, p- value)	43.7%, 0.15	55.8%, 0.13	90.8%, <0.001
Number of cases	**<500 cases**	**500-<1000**	**≥1000 cases**
Studies (n)	5	1	3
RR (95%CI)	0.98 (0.96-1.00)	1.05 (0.99-1.12)	0.99 (0.94-1.04)
Heterogeneity (I^2, p-value)	0%, 0.55	-	90.9%, <0.001
Publication year		**≥2004 - <2010**	**≥2010**
Studies (n)		7	2
RR (95%CI)		1.00 (0.96-1.05)	0.99 (0.95-1.02)
Heterogeneity (I^2, p-value)		77.2%, <0.001	24.9%, 0.25

Adjustment for:			
Socioeconomic status	**Not adjusted**	**Adjusted**	
Studies (n)	4	5	
RR (95%CI)	0.99 (0.93-1.05)	1.00 (0.97-1.04)	
Heterogeneity (I^2, p-value)	87.6%, <0.001	27.3%, 0.24	
Smoking			
Studies (n)	3	6	
RR (95%CI)	0.99 (0.93-1.06)	1.00 (0.97-1.03)	
Heterogeneity (I^2, p-value)	91.4%, <0.001	17.3%, 0.30	
Alcohol intake			
Studies (n)	5	4	
RR (95%CI)	0.99 (0.94-1.05)	1.00 (0.96-1.05)	
Heterogeneity (I^2, p-value)	83.5%, <0.001	43.7%, 0.15	
Physical activity			
Studies (n)	5	4	

RR (95%CI)	1.00 (0.97-1.04)	0.99 (0.93-1.05)	
Heterogeneity (I^2, p-value)	27.3%, 0.24	87.6%, <0.001	
BMI			
Studies (n)	4	5	
RR (95%CI)	1.01 (1.00-1.02)	0.99 (0.95-1.03)	
Heterogeneity (I^2, p-value)	0%, 0.46	67.7%, 0.02	
Comorbidities (diabetes)			
Studies (n)	7	2	
RR (95%CI)	1.00 (0.96-1.04)	0.98 (0.96-1.00)	
Heterogeneity (I^2, p-value)	77.3%, <0.001	0%, 0.55	

Table 95 Height and oesophageal cancer risk. Results of meta-analyses and pooled analyses of prospective studies published after the 2005 SLR

Author, Year	Number of studies	Total number of cases	Studies country, area	Outcome	Comparison	RR (95%CI)	P trend	Heterogeneity (I^2, p value)
Pooled analysis								
Emerging Risk Factors Collaboration (ERFC), 2012	121	984 oesophageal cancer cases	Most participants in Europe (60%) and North America (33%)	Mortality, oesophageal cancer	Per 6.5 cm	0.98 (0.91-1.06)		20%

Note: All cohort studies identified in the published pooled analysis (EPIC, Whitehall study and NSPT) were included in the present review. Sensitivity analysis was conducted by including the pooled results from the ERFC study.

Table 96 Height and oesophageal cancer risk. Main characteristics of studies included in the linear dose-response meta-analysis

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Missing data derived for analyses
O'Doherty, 2012 oes00844 USA	NIH- AARP, Prospective Cohort, Age: 50-71 years, M/W	253/ 218 854 9 years	Record linkage to state cancer registry databases.	Questionnaire	Incidence, AC	4th vs. 1st quartile	0.69 (0.47-1.01) Ptrend: 0.09	Age, sex, alcohol consumption, education, antacid use, aspirin use, non-steroidal anti-inflammatory drug use, cigarette smoking, diabetes, ethnicity, marital status, physical activity, red meat and white meat intake, weight, fruit and vegetable intake, total energy,	Distribution of person-years by exposure categories, weighted average of exposure quartiles in cm
Green, 2011 oes00896 UK	MWS, Prospective Cohort, Age: 56.1years, W	1 167/ 1 297 124 9.4 years	Cancer registry	Questionnaire	Incidence, oesophageal cancer	Per 10 cm	1.04 (0.91-1.19)	Age, age at first birth, age at menarche, BMI, parity, smoking status, socio-economic status, alcohol, region, strenuous exercise	Continuous RR rescaled for 5 cm increment
Steffen, 2009 oes00865 Denmark,France,Germany, Greece,Italy, Netherlands, Norway,Spain,Sweden,UK	EPIC, Prospective Cohort, Age: 25-70 years, M/W	88/ 346 554 8.9 years	Cancer and mortality registries, active follow up	Measured	Incidence, AC	5th vs. 1st quantile	0.86 (0.41-1.80) Ptrend: 0.62	Age, centre, age at recruitment, sex, education, smoking habits, alcohol consumption, physical activity, intake of fruits, vegetables, and meat and meat products	Distribution of person-years by exposure quantiles, weighted average of exposure quantiles, Hamling's method was used to calculate RRs for EA and ESCC cancer combined
		110/			SCC		1.04 (0.50-2.19) Ptrend: 0.62		

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Missing data derived for analyses
Sung, 2009 oes00808 Korea	KNHIC, Prospective Cohort, Age: 40-64 years, middle-class men	877/ 412 494 8.7 years	Linkage with cancer registry, national health insurance and death report	Measured	Incidence, oesophageal cancer Men	>171.1 vs. ≤164.5 cm	1.15 (0.95-1.40)	Age, alcohol consumption, area of residence, BMI, cigarette smoking, level of monthly salary, occupation, regular exercise	Distribution of cases per category for non-linear analysis
						Per 5 cm	1.05 (0.99-1.12)		
Fujino, 2007 oes00834 Japan	JACC, Prospective Cohort, M/W	146 men/ 549 584 person-years 12 years	Date and cause of death annually or biannually confirmed with government authorization	Self-reported in survey	Mortality, oesophageal cancer Men	>165 vs 159.9 cm	1.34 (0.86-2.08)	Age, study area	Mid-points of exposure categories, RRs for men and women were combined using fixed effect model
		24/			Women	>154 vs 148.9 cm	1.64 (0.55-4.88)		
Merry, 2007 oes00832 Netherlands	NLCS, Case Cohort, Age: 55-69 years, M/W	86/ 4 782 13.3 years	Cancer registry and pathology database	Questionnaire	Incidence, SCC	M ≥185, W≥175 vs. M<170 W<160 cm	0.37 (0.13-1.08) Ptrend: 0.22	Age, sex, fruit consumption, number of years of smoking, alcohol intake, current smoking, number of cigarettes smoked per day	Weighted average of quantiles, RRs for EAC and ESCC cancer combined with Hamling's method
						Per 5 cm	0.90 (0.74-1.11)		
		124/			AC	M ≥185, W≥175 vs. M <170 W<160 cm	0.86 (0.40-1.85) Ptrend: 0.40		
						Per 5 cm	0.95 (0.83-1.08)		

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Missing data derived for analyses
Batty, 2006 oes00876 UK	Whitehall Study, Prospective Cohort, Age: 40-64 years, M	124/ 17 353 maximum 35 years	Death certificates	Measured	Mortality, oesophageal cancer	≥181 vs. <171 cm	0.99 (0.58-1.70)	Age, BMI, cholesterol, diabetes, employment grade, glucose intolerance, marital status, physical activity, smoking habits, systolic blood pressure, triceps skinfold thickness, disease at baseline	Distributions of cases, person-years and mid-points per exposure category, for the non-linear analysis
						Per 5 cm	1.02 (0.89-1.17)		
Tran, 2005 oes00804 China	NIT Cohort, Prospective Cohort (Post-trial Linxian), Age: 40-69 years, M/W	1 958/ 29 584 15 years	Monthly contact by either village health workers or interviewers, and cancer diagnoses verified by senior diagnosticians	Measured	Incidence, SCC	≥1.64 vs. <1.53 m	1.28 (1.08-1.52) Ptrend: 0.009	Age, sex	Distributions of cases, person-years and mid-points per exposure quantile in cm
Engeland, 2004 oes00795 Norway	NSPT, Prospective Cohort, Age: 20-74 years, M/W	1 597/ 2 001 617 23 years	Cancer and death registries	Measured	Incidence, oesophageal Men	<160 vs. 170-179 cm	0.99 (0.87-1.12) Ptrend: <0.001	BMI, age at entry, birth cohort	Mid-points per exposure category, Slopes for men and women were combined using fixed effect model, Hamling's method was used to calculate RRs using the lowest category as reference
		648/			Women	<150 vs. 160-169 cm	0.76 (0.54-1.06) Ptrend: 0.09		
		1 023/			SCC Men	<160 vs. 170-179 cm	1.02 (0.87-1.20) Ptrend: 0.001		
		472/			Women	<150 vs. 160-169 cm	0.69 (0.46-1.03) Ptrend: 0.5		
		448/			AC Men	<160 vs. 170-179 cm	0.95 (0.75-1.21) Ptrend: 0.1		

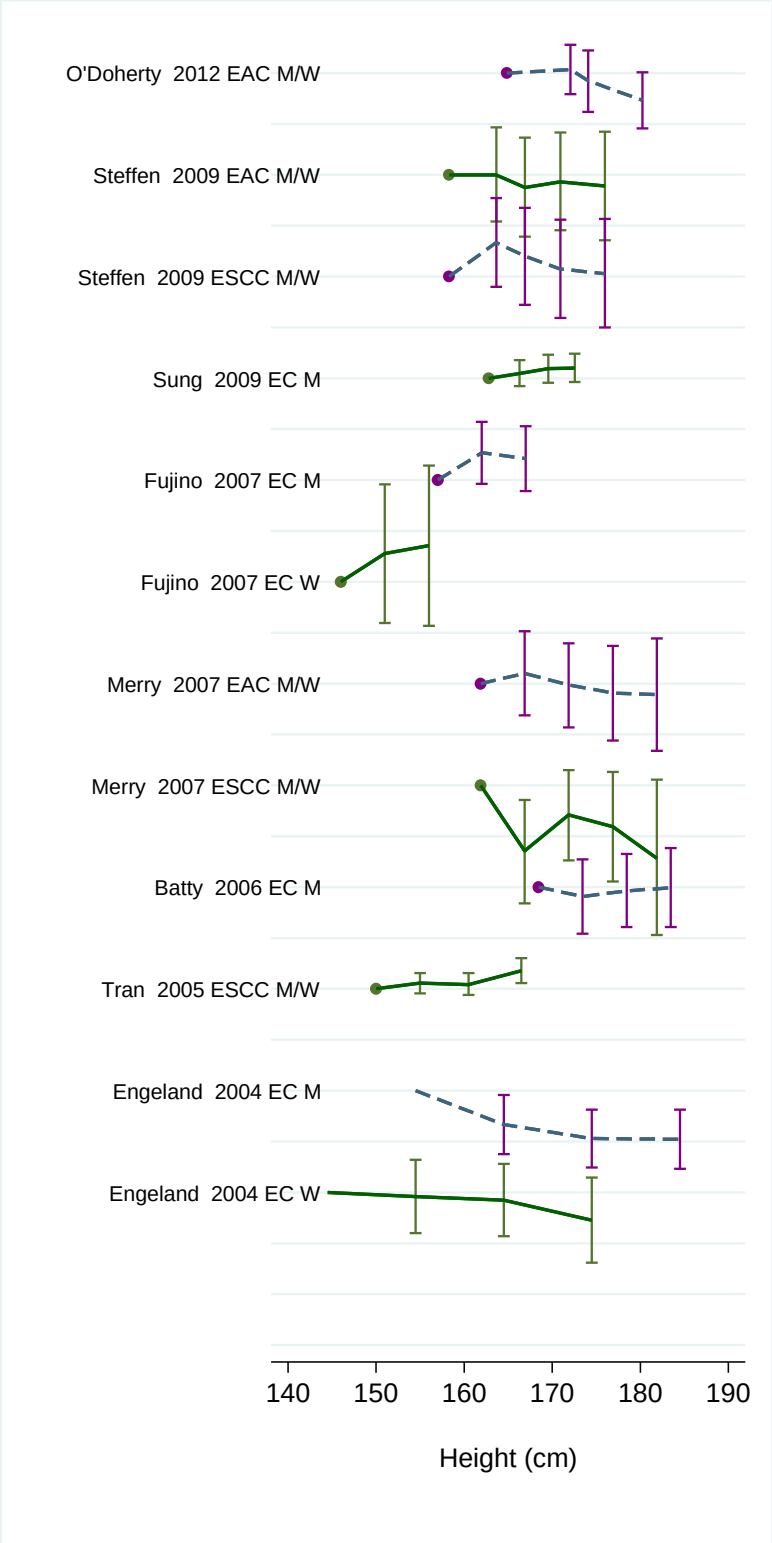
Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Missing data derived for analyses
		127/			Women	<150 vs. 160-169 cm	0.73 (0.33-1.61) Ptrend: 0.06		

Table 97 Height and oesophageal cancer risk. Main characteristics of studies excluded from the linear dose-response meta-analysis

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Reasons for exclusion
MacInnis, 2006 oes00895 Australia	MCCS, Prospective Cohort, Age: 27-75 years, M/W	30/ 41 295 11.3 years	Cancer registry	Measured	Incidence, distal oesophageal and gastric cardia cancer	3rd vs. 1st quantile	1.60 (0.60-4.10)	Sex, age-underlying cox models, country of birth, educational level, physical activity	Excluded, combined cancer sites
						Per 10 cm	1.22 (0.69-2.15)		
Tretli, 1999 oes00905 Norway	NSPT, Prospective Cohort, Age: 30-69 years, M/W	742/ 1 122 852 20 years	Linkage with Cancer Registry and Statistics Norway	Measured	Incidence oesophageal cancer Men	5th vs. 1st quantile	0.64 (0.51-0.80)	Attained age, age at entry, birth cohort, and county of residence	Superseded by Engeland, 2004
		274/			Women		0.65 (0.44-0.96)		
		509/			SCC Men		0.70 (0.53-0.92)		
		197/			Women		0.64 (0.41-1.01)		
		94/			AC Men		0.43 (0.21-0.90)		

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Reasons for exclusion
Guo, 1994 oes00103 China	NIT Cohort, Nested Case Control, Age: 40-69 years, M/W	640/ 29 584 6 years	Monthly contact by either village health workers or interviewers, and cancer diagnoses verified by senior diagnosticians	Measured	Incidence/mortality, SCC	≥165 vs. <154 cm	0.90 (0.60-1.20) Ptrend: 0.40	Family history of specific cancer, height, smoking habits, vitamins	Superseded by Tran, 2005

Figure 106 RR estimates of oesophageal cancer by levels of height



Note: the RR showed for Engeland, 2004 had been recalculated using the lowest height category as reference.

Figure 107 RR (95% CI) of oesophageal cancer for the highest compared with the lowest level of height

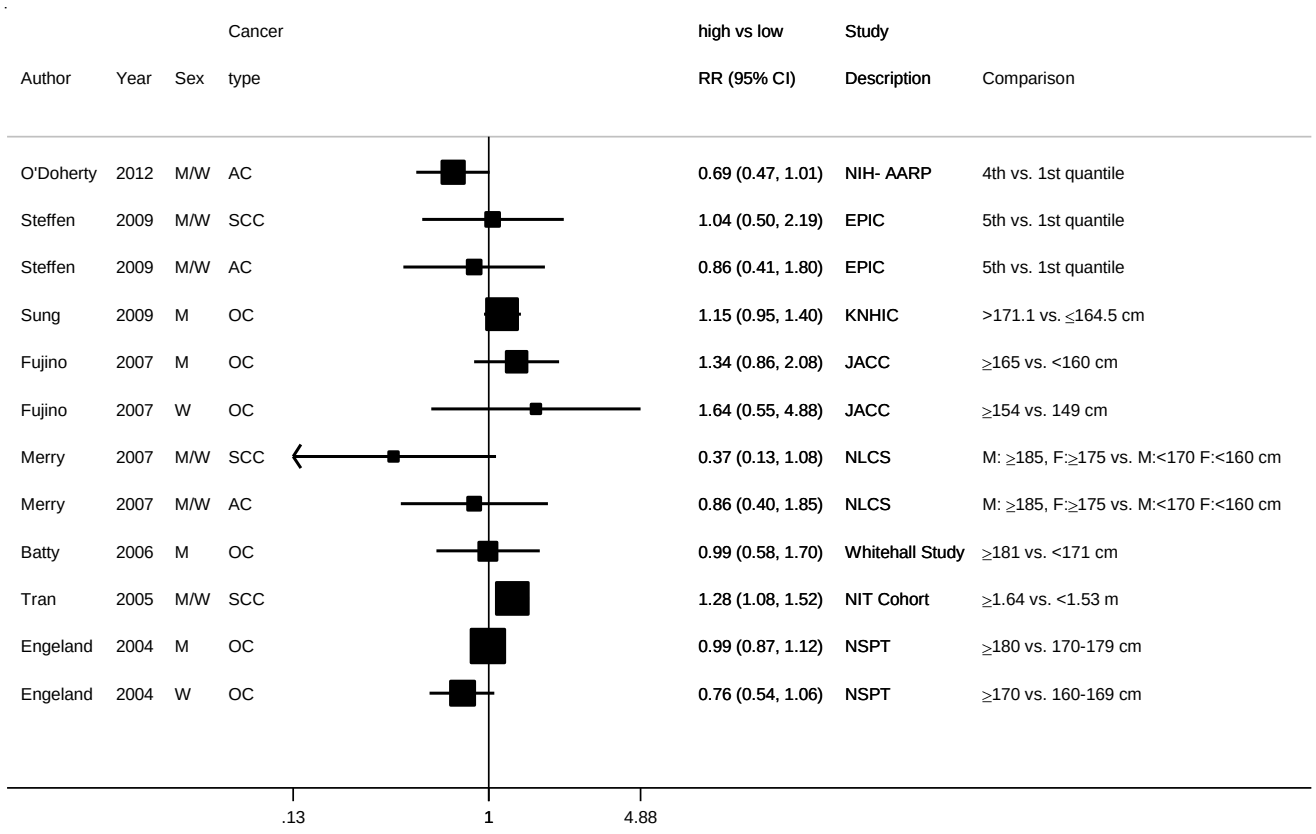


Figure 108 Relative risk of oesophageal cancer for 5 cm increase of height

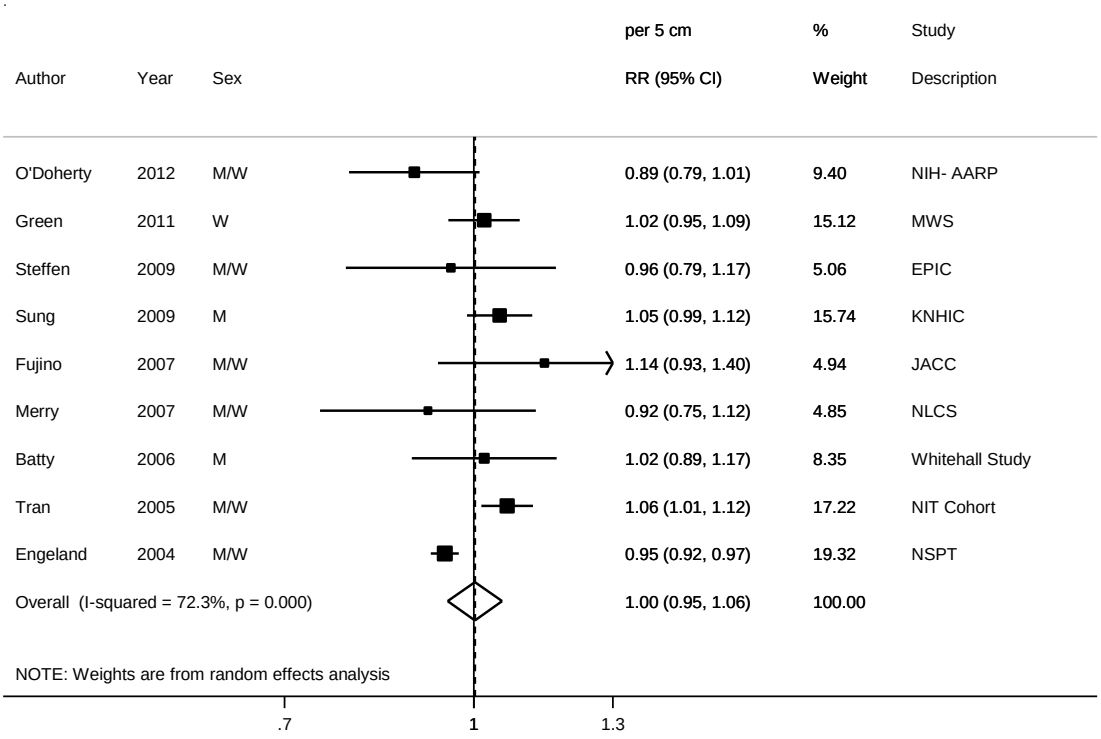
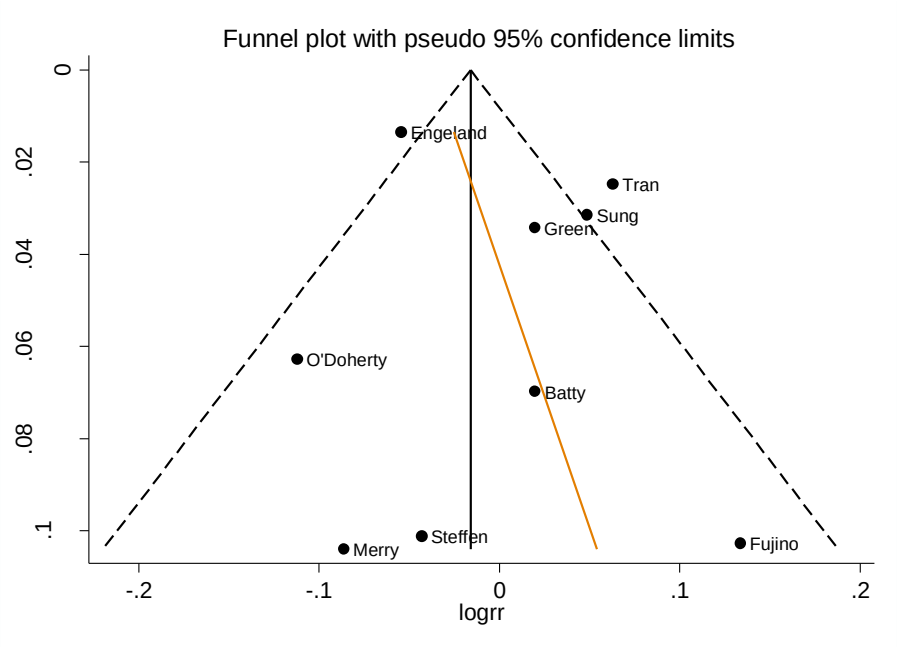


Figure 109 Funnel plot of studies included in the dose response meta-analysis of height and oesophageal cancer



Egger's test p=0.44

Figure 110 Relative risk of oesophageal cancer for 5 cm increase of height pooled with ERFC

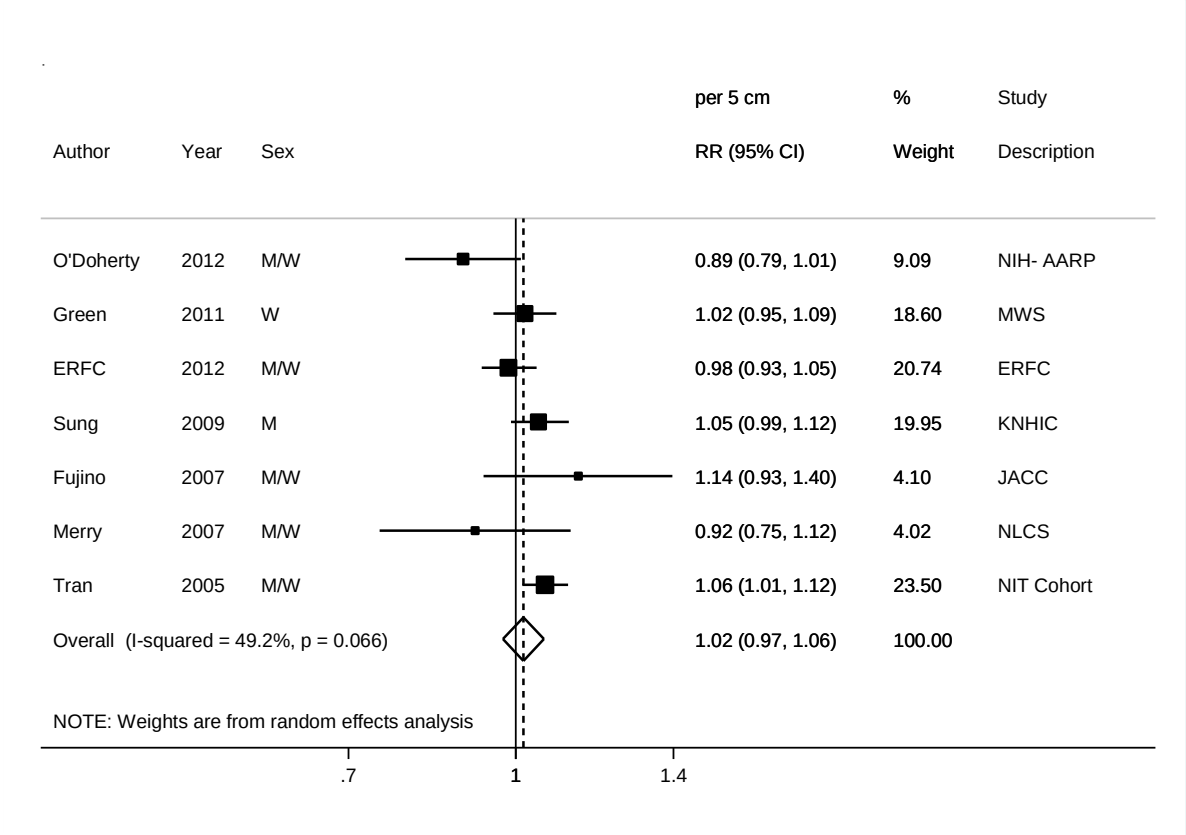


Figure 111 Relative risk of oesophageal cancer for 5 cm increase of height by sex

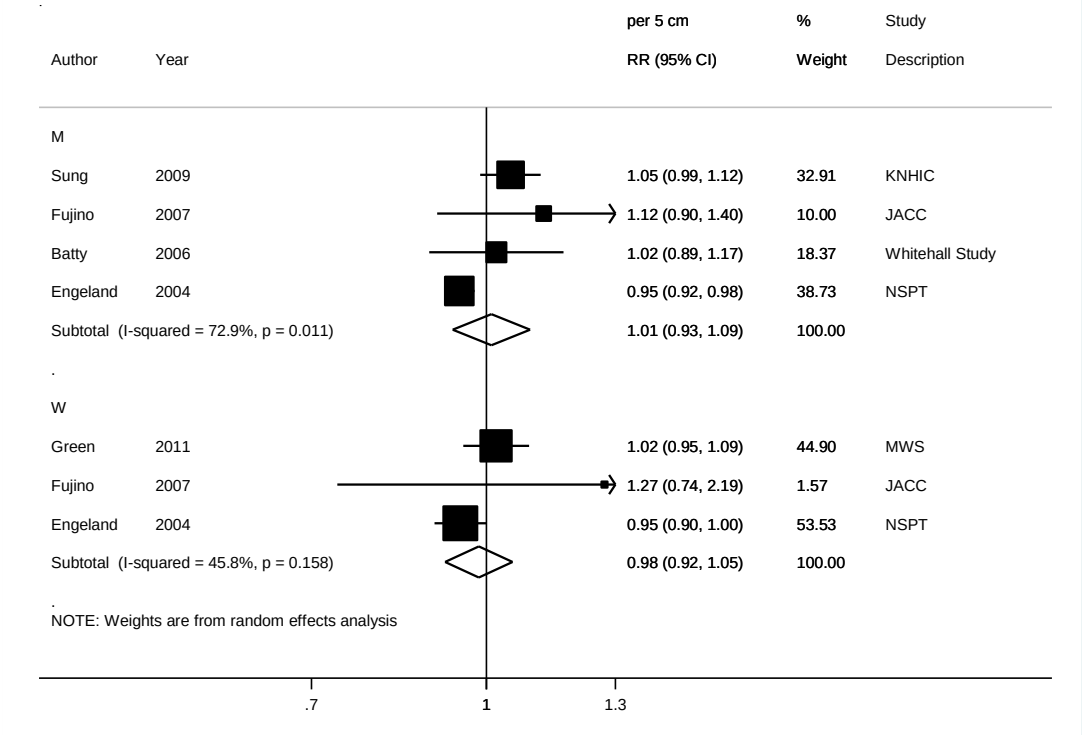


Figure 112 Relative risk of oesophageal cancer for 5 cm increase of height by cancer outcome

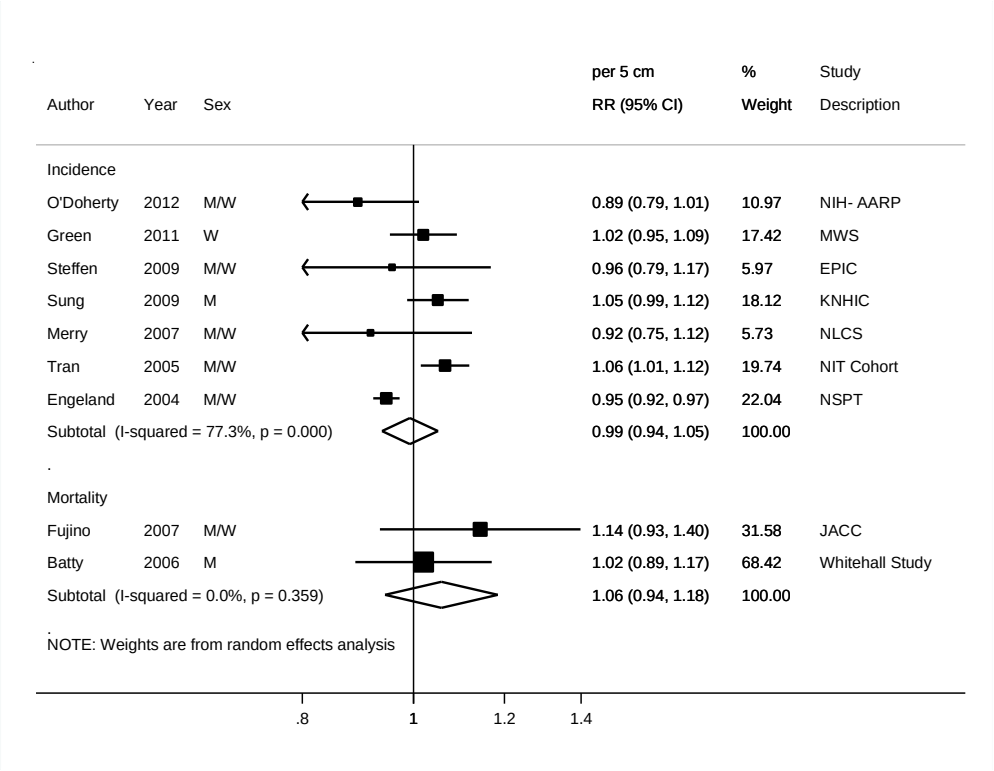


Figure 113 Relative risk of oesophageal cancer for 5 cm increase of height by cancer type

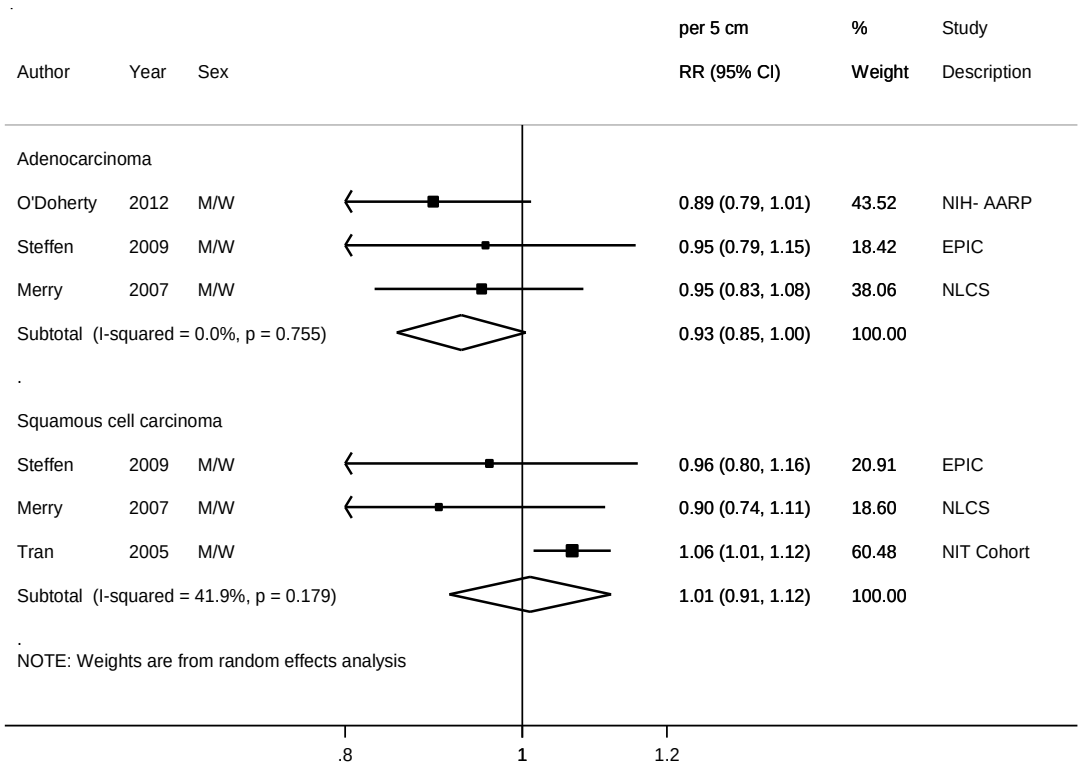
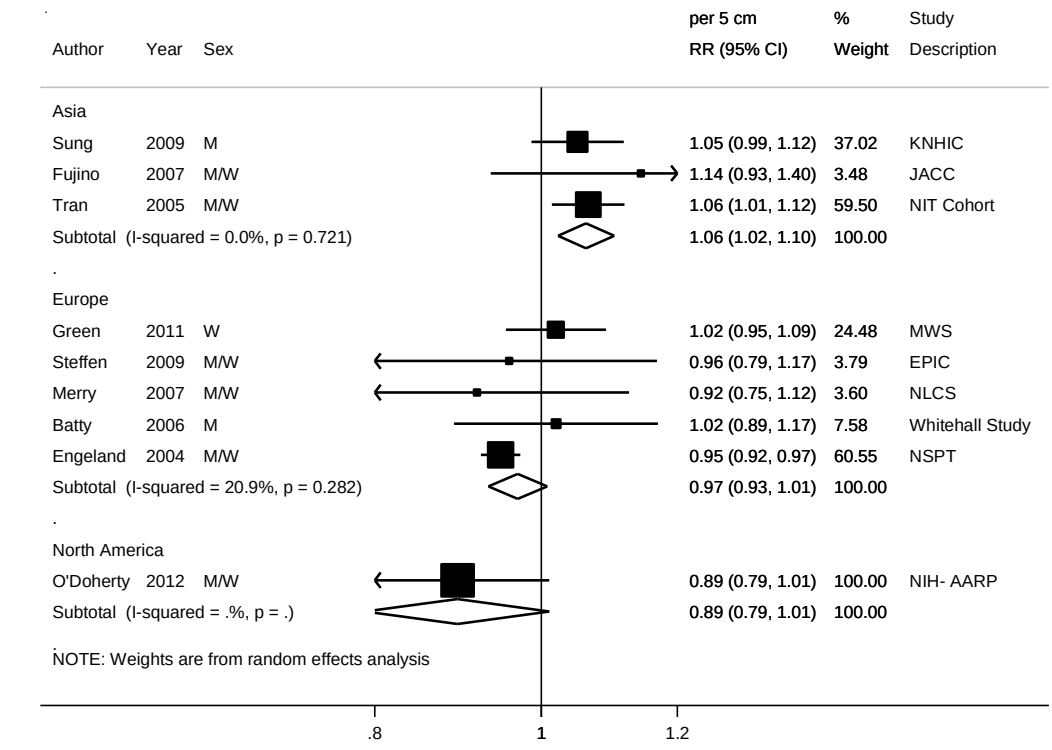


Figure 114 Relative risk of oesophageal cancer for 5 cm increase of height by geographic location



Reference list

1. Coffee, tea, mate, methylxanthines and methylglyoxal. IARC Working Group on the Evaluation of Carcinogenic Risks to Humans. Lyon, 27 February to 6 March 1990. IARC Monogr Eval Carcinog Risks Hum 1991;51:1-513.

2. Adult height and the risk of cause-specific death and vascular morbidity in 1 million people: individual participant meta-analysis. Int J Epidemiol 2012;41:1419-33.

3. Abnet CC, Qiao YL, Dawsey SM, et al. Prospective study of serum retinol, beta-carotene, beta-cryptoxanthin, and lutein/zeaxanthin and esophageal and gastric cancers in China. Cancer Causes Control 2003;14:645-55.

4. Abnet CC, Freedman ND, Hollenbeck AR, et al. A prospective study of BMI and risk of oesophageal and gastric adenocarcinoma. Eur J Cancer 2008;44:465-71.

5. Alkhenizan A, Hafez K. The role of vitamin E in the prevention of cancer: a meta-analysis of randomized controlled trials. Ann Saudi Med 2007;27:409-14.

6. Allen NE, Beral V, Casabonne D, et al. Moderate alcohol intake and cancer incidence in women. J Natl Cancer Inst 2009;101:296-305.

7. Andreotti G, Hou L, Beane Freeman LE, et al. Body mass index, agricultural pesticide use, and cancer incidence in the Agricultural Health Study cohort. Cancer Causes Control 2010;21:1759-75.

8. Andrici J, Eslick GD. Mate consumption and the risk of esophageal squamous cell carcinoma: a meta-analysis. Dis Esophagus 2013;26:807-16.

9. Arem H, Moore SC, Park Y, et al. Physical activity and cancer-specific mortality in the NIH-AARP Diet and Health Study cohort. Int J Cancer 2014;135:423-31.

10. Bagnardi V, Rota M, Botteri E, et al. Light alcohol drinking and cancer: a meta-analysis. Ann Oncol 2013;24:301-8.

11. Batty GD, Shipley MJ, Langenberg C, et al. Adult height in relation to mortality from 14 cancer sites in men in London (UK): evidence from the original Whitehall study. Ann Oncol 2006;17:157-66.

12. Boffetta P, Garfinkel L. Alcohol drinking and mortality among men enrolled in an American Cancer Society prospective study. Epidemiology 1990;1:342-8.

13. Calle EE, Rodriguez C, Walker-Thurmond K, et al. Overweight, obesity, and mortality from cancer in a prospectively studied cohort of U.S. adults. N Engl J Med 2003;348:1625-38.

14. Carman S, Kamangar F, Freedman ND, et al. Vitamin E intake and risk of esophageal and gastric cancers in the NIH-AARP Diet and Health Study. Int J Cancer 2009;125:165-70.

15. Chen Y, Yu C, Li Y. Physical activity and risks of esophageal and gastric cancers: a meta-analysis. PLoS One 2014;9:e88082.

16. Chen Z, Yang G, Offer A, et al. Body mass index and mortality in China: a 15-year prospective study of 220 000 men. Int J Epidemiol 2012;41:472-81.

17. Choi Y, Song S, Song Y, et al. Consumption of red and processed meat and esophageal cancer risk: meta-analysis. World J Gastroenterol 2013;19:1020-9.

18. Chyou PH, Nomura AM, Stemmermann GN. Diet, alcohol, smoking and cancer of the upper aerodigestive tract: a prospective study among Hawaii Japanese men. Int J Cancer 1995;60:616-21.

19. Coleman HG, Murray LJ, Hicks B, et al. Dietary fiber and the risk of precancerous lesions and cancer of the esophagus: a systematic review and meta-analysis. Nutr Rev 2013;71:474-82.

20. Cook MB, Matthews CE, Gunja MZ, et al. Physical Activity and Sedentary Behavior in Relation to Esophageal and Gastric Cancers in the NIH-AARP Cohort. PLoS One 2013;8:e84805.

21. Corley DA, Kubo A, Zhao W. Abdominal obesity and the risk of esophageal and gastric cardia carcinomas. Cancer Epidemiol Biomarkers Prev 2008;17:352-8.

22. Cross AJ, Leitzmann MF, Gail MH, et al. A prospective study of red and processed meat intake in relation to cancer risk. PLoS Med 2007;4:e325.

23. Cross AJ, Freedman ND, Ren J, et al. Meat consumption and risk of esophageal and gastric cancer in a large prospective study. Am J Gastroenterol 2011;106:432-42.

24. Daniel CR, Cross AJ, Graubard BI, et al. Prospective investigation of poultry and fish intake in relation to cancer risk. Cancer Prev Res (Phila) 2011;4:1903-11.

25. Dawsey SP, Hollenbeck A, Schatzkin A, et al. A prospective study of vitamin and mineral supplement use and the risk of upper gastrointestinal cancers. PLoS One 2014;9:e88774.

26. Engeland A, Tretli S, Bjorge T. Height and body mass index in relation to esophageal cancer; 23-year follow-up of two million Norwegian men and women. Cancer Causes Control 2004;15:837-43.

27. Fan Y, Yuan JM, Wang R, et al. Alcohol, tobacco, and diet in relation to esophageal cancer: the Shanghai Cohort Study. Nutr Cancer 2008;60:354-63.

28. Freedman ND, Abnet CC, Leitzmann MF, et al. A prospective study of tobacco, alcohol, and the risk of esophageal and gastric cancer subtypes. Am J Epidemiol 2007;165:1424-33 b.

29. Freedman ND, Park Y, Subar AF, et al. Fruit and vegetable intake and esophageal cancer in a large prospective cohort study. Int J Cancer 2007;121:2753-60 a.

30. Freedman ND, Murray LJ, Kamangar F, et al. Alcohol intake and risk of oesophageal adenocarcinoma: a pooled analysis from the BEACON Consortium. Gut 2011;60:1029-37.

31. Fujino Y. Anthropometry, development history and mortality in the Japan Collaborative Cohort Study for Evaluation of Cancer (JACC). Asian Pac J Cancer Prev 2007;8 Suppl:105-12.

32. Ge XX, Xing MY, Yu LF, et al. Carotenoid intake and esophageal cancer risk: a meta-analysis. Asian Pac J Cancer Prev 2013;14:1911-8.

33. George SM, Park Y, Leitzmann MF, et al. Fruit and vegetable intake and risk of cancer: a prospective cohort study. Am J Clin Nutr 2009;89:347-53.

34. Gonzalez CA, Jakszyn P, Pera G, et al. Meat intake and risk of stomach and esophageal adenocarcinoma within the European Prospective Investigation Into Cancer and Nutrition (EPIC). J Natl Cancer Inst 2006;98:345-54 b.

35. Gonzalez CA, Pera G, Agudo A, et al. Fruit and vegetable intake and the risk of stomach and oesophagus adenocarcinoma in the European Prospective Investigation into Cancer and Nutrition (EPIC-EURGAST). Int J Cancer 2006;118:2559-66 a.

36. Green J, Cairns BJ, Casabonne D, et al. Height and cancer incidence in the Million Women Study: prospective cohort, and meta-analysis of prospective studies of height and total cancer risk. Lancet Oncol 2011;12:785-94.

37. Gronbaek M, Becker U, Johansen D, et al. Population based cohort study of the association between alcohol intake and cancer of the upper digestive tract. BMJ 1998;317:844-7.

38. Guo W, Blot WJ, Li JY, et al. A nested case-control study of oesophageal and stomach cancers in the Linxian nutrition intervention trial. Int J Epidemiol 1994;23:444-50.

39. Hamling J, Lee P, Weitkunat R, et al. Facilitating meta-analyses by deriving relative effect and precision estimates for alternative comparisons from a set of estimates presented by exposure level or disease category. Stat Med 2008;27:954-70.

40. Hardikar S, Onstad L, Blount PL, et al. The role of tobacco, alcohol, and obesity in neoplastic progression to esophageal adenocarcinoma: a prospective study of Barrett's esophagus. PLoS One 2013;8:e52192.

41. Higgins JP, Thompson SG. Quantifying heterogeneity in a meta-analysis. Stat Med 2002;21:1539-58.

42. Hirayama T. Mortality in Japanese with life-styles similar to Seventh-Day Adventists: strategy for risk reduction by life-style modification. Natl Cancer Inst Monogr 1985;69:143-53.

43. Hirayama T. Association between alcohol consumption and cancer of the sigmoid colon: observations from a Japanese cohort study. Lancet 1989;2:725-7.

44. Hirayama T. [A large scale cohort study on the effect of life styles on the risk of cancer by each site]. Gan No Rinsho 1990;Spec No:233-42.

45. Hoyo C, Cook MB, Kamangar F, et al. Body mass index in relation to oesophageal and oesophagogastric junction adenocarcinomas: a pooled analysis from the International BEACON Consortium. Int J Epidemiol 2012;41:1706-18.

46. Huang W, Han Y, Xu J, et al. Red and processed meat intake and risk of esophageal adenocarcinoma: a meta-analysis of observational studies. Cancer Causes Control 2013;24:193-201.

47. Huerta JM, Navarro C, Chirlaque MD, et al. Prospective study of physical activity and risk of primary adenocarcinomas of the oesophagus and stomach in the EPIC (European

Prospective Investigation into Cancer and nutrition) cohort. Cancer Causes Control 2010;21:657-69.

48. Ishiguro S, Sasazuki S, Inoue M, et al. Effect of alcohol consumption, cigarette smoking and flushing response on esophageal cancer risk: a population-based cohort study (JPHC study). Cancer Lett 2009;275:240-6.

49. Ishikawa A, Kuriyama S, Tsubono Y, et al. Smoking, alcohol drinking, green tea consumption and the risk of esophageal cancer in Japanese men. J Epidemiol 2006;16:185-92.

50. Iso H, Kubota Y. Nutrition and disease in the Japan Collaborative Cohort Study for Evaluation of Cancer (JACC). Asian Pac J Cancer Prev 2007;8 Suppl:35-80.:35-80.

51. Jakszyn P, Lujan-Barroso L, Agudo A, et al. Meat and heme iron intake and esophageal adenocarcinoma in the European Prospective Investigation into Cancer and Nutrition study. Int J Cancer 2013;133:2744-50.

52. Jee SH, Yun JE, Park EJ, et al. Body mass index and cancer risk in Korean men and women. Int J Cancer 2008;123:1892-6.

53. Jensen OM. Cancer risk among Danish male Seventh-Day Adventists and other temperance society members. J Natl Cancer Inst 1983;70:1011-4.

54. Jeurnink SM, Buchner FL, Bueno-de-Mesquita HB, et al. Variety in vegetable and fruit consumption and the risk of gastric and esophageal cancer in the European Prospective Investigation into Cancer and Nutrition. Int J Cancer 2012;131:E963-E973.

55. Kasum CM, Jacobs DR, Jr., Nicodemus K, et al. Dietary risk factors for upper aerodigestive tract cancers. Int J Cancer 2002;99:267-72.

56. Kato I, Nomura AM, Stemmermann GN, et al. Prospective study of the association of alcohol with cancer of the upper aerodigestive tract and other sites. Cancer Causes Control 1992;3:145-51.

57. Keszei AP, Schouten LJ, Goldbohm RA, et al. Red and processed meat consumption and the risk of esophageal and gastric cancer subtypes in The Netherlands Cohort Study. Ann Oncol 2012;23:2319-26.

58. Kim MK, Ko MJ, Han JT. Alcohol consumption and mortality from all-cause and cancers among 1.34 million Koreans: the results from the Korea national health

insurance corporation's health examinee cohort in 2000. Cancer Causes Control 2010;21:2295-302.

59. Kimm H, Kim S, Jee SH. The independent effects of cigarette smoking, alcohol consumption, and serum aspartate aminotransferase on the alanine aminotransferase ratio in korean men for the risk for esophageal cancer. Yonsei Med J 2010;51:310-7.

60. Kinjo Y, Cui Y, Akiba S, et al. Mortality risks of oesophageal cancer associated with hot tea, alcohol, tobacco and diet in Japan. J Epidemiol 1998;8:235-43.

61. Kjaerheim K, Gaard M, Andersen A. The role of alcohol, tobacco, and dietary factors in upper aerogastric tract cancers: a prospective study of 10,900 Norwegian men. Cancer Causes Control 1998;9:99-108.

62. Knekt P, Aromaa A, Maatela J, et al. Serum micronutrients and risk of cancers of low incidence in Finland. Am J Epidemiol 1991;134:356-61.

63. Kono S, Ikeda M, Tokudome S, et al. Cigarette smoking, alcohol and cancer mortality: a cohort study of male Japanese physicians. Jpn J Cancer Res 1987;78:1323-8.

64. Kubo A, Corley DA. Body mass index and adenocarcinomas of the esophagus or gastric cardia: a systematic review and meta-analysis. Cancer Epidemiol Biomarkers Prev 2006;15:872-8.

65. Kubo A, Corley DA. Meta-analysis of antioxidant intake and the risk of esophageal and gastric cardia adenocarcinoma. Am J Gastroenterol 2007;102:2323-30.

66. Kuriyama S, Tsubono Y, Hozawa A, et al. Obesity and risk of cancer in Japan. Int J Cancer 2005;113:148-57.

67. Lam TK, Freedman ND, Fan JH, et al. Prediagnostic plasma vitamin C and risk of gastric adenocarcinoma and esophageal squamous cell carcinoma in a Chinese population. Am J Clin Nutr 2013;98:1289-97.

68. Leitzmann MF, Koebnick C, Freedman ND, et al. Physical activity and esophageal and gastric carcinoma in a large prospective study. Am J Prev Med 2009;36:112-9.

69. Li B, Jiang G, Zhang G, et al. Intake of vegetables and fruit and risk of esophageal adenocarcinoma: a meta-analysis of observational studies. Eur J Nutr 2014;53:1511-21.

70. Li WQ, Kuriyama S, Li Q, et al. Citrus consumption and cancer incidence: the Ohsaki cohort study. Int J Cancer 2010;127:1913-22.

71. Li WQ, Park Y, Wu JW, et al. Index-based dietary patterns and risk of esophageal and gastric cancer in a large cohort study. Clin Gastroenterol Hepatol 2013;11:1130-6.

72. Lindblad M, Rodriguez LA, Lagergren J. Body mass, tobacco and alcohol and risk of esophageal, gastric cardia, and gastric non-cardia adenocarcinoma among men and women in a nested case-control study. Cancer Causes Control 2005;16:285-94.

73. Lindkvist B, Johansen D, Stocks T, et al. Metabolic risk factors for esophageal squamous cell carcinoma and adenocarcinoma: a prospective study of 580 000 subjects within the Me-Can project. BMC Cancer 2014;14:103.

74. Liu J, Wang J, Leng Y, et al. Intake of fruit and vegetables and risk of esophageal squamous cell carcinoma: a meta-analysis of observational studies. Int J Cancer 2013;133:473-85.

75. Lubin JH, De SE, Abnet CC, et al. Mate drinking and esophageal squamous cell carcinoma in South america: pooled results from two large multicenter case-control studies. Cancer Epidemiol Biomarkers Prev 2014;23:107-16.

76. MacInnis RJ, English DR, Hopper JL, et al. Body size and composition and the risk of gastric and oesophageal adenocarcinoma. Int J Cancer 2006;118:2628-31.

77. Merry AH, Schouten LJ, Goldbohm RA, et al. Body mass index, height and risk of adenocarcinoma of the oesophagus and gastric cardia: a prospective cohort study. Gut 2007;56:1503-11.

78. Moller H, Mellemgaard A, Lindvig K, et al. Obesity and cancer risk: a Danish record-linkage study. Eur J Cancer 1994;30A:344-50.

79. Naganuma T, Kuriyama S, Kakizaki M, et al. Coffee consumption and the risk of oral, pharyngeal, and esophageal cancers in Japan: the Miyagi Cohort Study. Am J Epidemiol 2008;168:1425-32.

80. Nakaya N, Tsubono Y, Kuriyama S, et al. Alcohol consumption and the risk of cancer in Japanese men: the Miyagi cohort study. Eur J Cancer Prev 2005;14:169-74.

81. Nomura AM, Ziegler RG, Stemmermann GN, et al. Serum micronutrients and upper aerodigestive tract cancer. Cancer Epidemiol Biomarkers Prev 1997;6:407-12.

82. O'Doherty MG, Freedman ND, Hollenbeck AR, et al. A prospective cohort study of obesity and risk of oesophageal and gastric adenocarcinoma in the NIH-AARP Diet and Health Study. Gut 2012;61:1261-8.

83. Oh SW, Yoon YS, Shin SA. Effects of excess weight on cancer incidences depending on cancer sites and histologic findings among men: Korea National Health Insurance Corporation Study. J Clin Oncol 2005;23:4742-54.

84. Ozasa K. Alcohol use and mortality in the Japan Collaborative Cohort Study for Evaluation of Cancer (JACC). Asian Pac J Cancer Prev 2007;8 Suppl:81-8.

85. Prabhu A, Obi KO, Rubenstein JH. Systematic review with meta-analysis: race-specific effects of alcohol and tobacco on the risk of oesophageal squamous cell carcinoma. Aliment Pharmacol Ther 2013;38:1145-55.

86. Qu X, Ben Q, Jiang Y. Consumption of red and processed meat and risk for esophageal squamous cell carcinoma based on a meta-analysis. Ann Epidemiol 2013;23:762-70.

87. Reeves GK, Pirie K, Beral V, et al. Cancer incidence and mortality in relation to body mass index in the Million Women Study: cohort study. BMJ 2007;335:1134.

88. Ren JS, Freedman ND, Kamangar F, et al. Tea, coffee, carbonated soft drinks and upper gastrointestinal tract cancer risk in a large United States prospective cohort study. Eur J Cancer 2010;46:1873-81.

89. Renehan AG, Tyson M, Egger M, et al. Body-mass index and incidence of cancer: a systematic review and meta-analysis of prospective observational studies. Lancet 2008;371:569-78.

90. Sakata K, Hoshiyama Y, Morioka S, et al. Smoking, alcohol drinking and esophageal cancer: findings from the JACC Study. J Epidemiol 2005;15 Suppl 2:S212-S219.

91. Salehi M, Moradi-Lakeh M, Salehi MH, et al. Meat, fish, and esophageal cancer risk: a systematic review and dose-response meta-analysis. Nutr Rev 2013;71:257-67.

92. Samanic C, Gridley G, Chow WH, et al. Obesity and cancer risk among white and black United States veterans. Cancer Causes Control 2004;15:35-43.

93. Samanic C, Chow WH, Gridley G, et al. Relation of body mass index to cancer risk in 362,552 Swedish men. Cancer Causes Control 2006;17:901-9.

94. Shen C, Schooling CM, Chan WM, et al. Alcohol intake and death from cancer in a prospective Chinese elderly cohort study in Hong Kong. J Epidemiol Community Health 2013;67:813-20.

95. Singh S, Sharma AN, Murad MH, et al. Central adiposity is associated with increased risk of esophageal inflammation, metaplasia, and adenocarcinoma: a systematic review and meta-analysis. Clin Gastroenterol Hepatol 2013;11:1399-412.

96. Smith M, Zhou M, Whitlock G, et al. Esophageal cancer and body mass index: results from a prospective study of 220,000 men in China and a meta-analysis of published studies. Int J Cancer 2008;122:1604-10.

97. Steevens J, Schouten LJ, Goldbohm RA, et al. Alcohol consumption, cigarette smoking and risk of subtypes of oesophageal and gastric cancer: a prospective cohort study. Gut 2010;59:39-48.

98. Steevens J, Schouten LJ, Goldbohm RA, et al. Vegetables and fruits consumption and risk of esophageal and gastric cancer subtypes in the Netherlands Cohort Study. Int J Cancer 2011;129:2681-93.

99. Steffen A, Schulze MB, Pischon T, et al. Anthropometry and esophageal cancer risk in the European prospective investigation into cancer and nutrition. Cancer Epidemiol Biomarkers Prev 2009;18:2079-89.

100. Sung J, Song YM, Lawlor DA, et al. Height and site-specific cancer risk: A cohort study of a korean adult population. Am J Epidemiol 2009;170:53-64.

101. Suzuki K. Health conditions and mortality in the Japan Collaborative Cohort Study for Evaluation of Cancer (JACC). Asian Pac J Cancer Prev 2007;8 Suppl:25-34.

102. Tio M, Andrici J, Cox MR, et al. Folate intake and the risk of upper gastrointestinal cancers: a systematic review and meta-analysis. J Gastroenterol Hepatol 2014;29:250-8.

103. Tran GD, Sun XD, Abnet CC, et al. Prospective study of risk factors for esophageal and gastric cancers in the Linxian general population trial cohort in China. Int J Cancer 2005;113:456-63.

104. Tretli S, Robsahm TE. Height, weight and cancer of the oesophagus and stomach: a follow-up study in Norway. Eur J Cancer Prev 1999;8:115-22.

105. Tulinius H, Sigfusson N, Sigvaldason H, et al. Risk factors for malignant diseases: a cohort study on a population of 22,946 Icelanders. Cancer Epidemiol Biomarkers Prev 1997;6:863-73.

106. Turati F, Galeone C, La VC, et al. Coffee and cancers of the upper digestive and respiratory tracts: meta-analyses of observational studies. Ann Oncol 2011;22:536-44.

107. Turati F, Tramacere I, La VC, et al. A meta-analysis of body mass index and esophageal and gastric cardia adenocarcinoma. Ann Oncol 2013;24:609-17.

108. Tverdal A, Hjellvik V, Selmer R. Coffee intake and oral-oesophageal cancer: follow-up of 389,624 Norwegian men and women 40-45 years. Br J Cancer 2011;105:157-61.

109. Wannamethee SG, Shaper AG, Walker M. Physical activity and risk of cancer in middle-aged men. Br J Cancer 2001;85:1311-6.

110. Weikert C, Dietrich T, Boeing H, et al. Lifetime and baseline alcohol intake and risk of cancer of the upper aero-digestive tract in the European Prospective Investigation into Cancer and Nutrition (EPIC) study. Int J Cancer 2009;125:406-12.

111. Wright ME, Virtamo J, Hartman AM, et al. Effects of alpha-tocopherol and beta-carotene supplementation on upper aerodigestive tract cancers in a large, randomized controlled trial. Cancer 2007;109:891-8.

112. Xiao Q, Freedman ND, Ren J, et al. Intakes of folate, methionine, vitamin B6, and vitamin B12 with risk of esophageal and gastric cancer in a large cohort study. Br J Cancer 2014;110:1328-33.

113. Yaegashi Y, Onoda T, Morioka S, et al. Joint effects of smoking and alcohol drinking on esophageal cancer mortality in Japanese men: findings from the Japan collaborative cohort study. Asian Pac J Cancer Prev 2014;15:1023-9.

114. Yamaji T, Inoue M, Sasazuki S, et al. Fruit and vegetable consumption and squamous cell carcinoma of the esophagus in Japan: the JPHC study. Int J Cancer 2008;123:1935-40.

115. Yang L, Zhou M, Sherliker P, et al. Alcohol drinking and overall and cause-specific mortality in China: nationally representative prospective study of 220,000 men with 15 years of follow-up. Int J Epidemiol 2012;41:1101-13.

116. Yates M, Cheong E, Luben R, et al. Body mass index, smoking, and alcohol and risks of Barrett's esophagus and esophageal adenocarcinoma: a UK prospective cohort study. Dig Dis Sci 2014;59:1552-9.

117. Yi SW, Sull JW, Linton JA, et al. Alcohol consumption and digestive cancer mortality in Koreans: the Kangwha Cohort Study. J Epidemiol 2010;20:204-11.

118. Yokoyama A, Omori T, Yokoyama T, et al. Risk of squamous cell carcinoma of the upper aerodigestive tract in cancer-free alcoholic Japanese men: an endoscopic follow-up study. Cancer Epidemiol Biomarkers Prev 2006;15:2209-15.

119. Yu X, Bao Z, Zou J, et al. Coffee consumption and risk of cancers: a meta-analysis of cohort studies. BMC Cancer 2011;11:96.

120. Yu Y, Taylor PR, Li JY, et al. Retrospective cohort study of risk-factors for esophageal cancer in Linxian, People's Republic of China. Cancer Causes Control 1993;4:195-202.

121. Yun YH, Lim MK, Won YJ, et al. Dietary preference, physical activity, and cancer risk in men: national health insurance corporation study. BMC Cancer 2008;8:366.

122. Zamora-Ros R, Lujan-Barroso L, Bueno-de-Mesquita HB, et al. Tea and coffee consumption and risk of esophageal cancer: the European prospective investigation into cancer and nutrition study. Int J Cancer 2014;135:1470-9.

123. Zheng JS, Yang J, Fu YQ, et al. Effects of green tea, black tea, and coffee consumption on the risk of esophageal cancer: a systematic review and meta-analysis of observational studies. Nutr Cancer 2013;65:1-16.

124. Zheng W, Sellers TA, Doyle TJ, et al. Retinol, antioxidant vitamins, and cancers of the upper digestive tract in a prospective cohort study of postmenopausal women. Am J Epidemiol 1995;142:955-60.

125. Zhu HC, Yang X, Xu LP, et al. Meat consumption is associated with esophageal cancer risk in a meat- and cancer-histological-type dependent manner. Dig Dis Sci 2014;59:664-73.

Appendix 1

a) Fruit or vegetable items investigated by each study

Several studies investigated vegetables, green leafy vegetables, fruits, and citrus fruits and oesophageal cancer risk. The fruit or vegetable items investigated by each study are indicated with a cross in the list below:

				Fruit or vegetable items			
Author	**Year**	**Country**	**Study name**	**Vegetables**	**Green leafy vegetables**	**Fruits**	**Citrus fruits**
Steevens	2011	The Netherlands	NLCS	x	x	x	x
Li	2010	Japan	OCS				x
George	2009	USA	NIH-AARP	x		x	
Freedman	2007			x	x	x	x
Fan	2008	China	SCStudy	x		x	x
Yamaji	2008	Japan	JPHC	x	x	x	x
Iso	2007	Japan	JACC		x		x
Gonzalez	2006	Europe	EPIC	x	x	x	x
Tran	2005	China	NIT Cohort	x			
Guo	1994					x	

b) Meat items investigated by each study

Several studies investigated red and processed meat, and processed meat and oesophageal cancer risk. The meat items investigated by each study are indicated with a cross in the list below:

				Meat	
Author	**Year**	**Country**	**Study name**	**Red and processed meat**	**Processed meat**
Jakszyn	2013	Europe	EPIC	x	x
Keszei	2012	The Netherlands	NLCS	x	x
Cross	2011	USA	NIH-AARP	x	x
Iso	2007	Japan	JACC		x
Kjaerheim	1998	Norway	Norwegian Men UADT		x
Chyou	1995	USA	HHP		x
Zheng	1995	USA	IWHS		x

c) Anthropometric characteristics investigated by each study

Several studies investigated BMI, height, waist circumference, and waist-to-hip ratio and oesophageal cancer risk. The anthropometric characteristics investigated by each study are indicated with a cross in the list below:

				Anthropometric characteristic			
Author	**Year**	**Country**	**Study name**	**BMI**	**Height**	**Waist circumference**	**Waist-hip ratio**
Hardikar	2013	USA	SBES	x			x
Andreotti	2010	USA	AHS	x			
Steffen	2009	Europe	EPIC	x	x	x	x
Abnet	2008	USA	NIH- AARP	x			
O'Doherty	2012				x	x	x
Corley	2008	USA	KPMCP	x		x	
Jee	2008	Korea	KCPS/KNHIC	x			
Sung	2009				x		
Smith	2008	China	CNRPCS	x			
Fujino	2007	Japan	JACC	x	x		
Merry	2007	The Netherlands	NLCS	x	x		
Reeves	2007	UK	MWS	x			
Green	2011				x		
MacInnis	2006	Australia	MCCS	x		x	x
Samanic	2006	Sweden	SCWC	x			
Yokoyama	2006	Japan	JAMS	x			
Batty	2006	UK	WS		x		
Kuriyama	2005	Japan	MCS I	x			
Lindblad	2005	UK	GPRDC	x			
Tran	2005	China	NIT Cohort	x	x		
Engeland	2004	Norway	Norwegian BMI/Height Prospective Cohort 1963-1989	x	x		
Samanic	2004	USA	Veterans Obesity and Cancer Study	x			
Calle	2003	USA, Puerto Rico	CPS II	x			
Moller	1994	Denmark	DOS	x			

Appendix 2

Protocol *Version 2*

Continuous Update and Systematic Literature Review of Randomised Controlled Trials and Prospective Studies on Food, Nutrition, Physical Activity and the Risk of Oesophageal Cancer.

Prepared by: CUP Team, Imperial College London, March 2013

INTRODUCTION

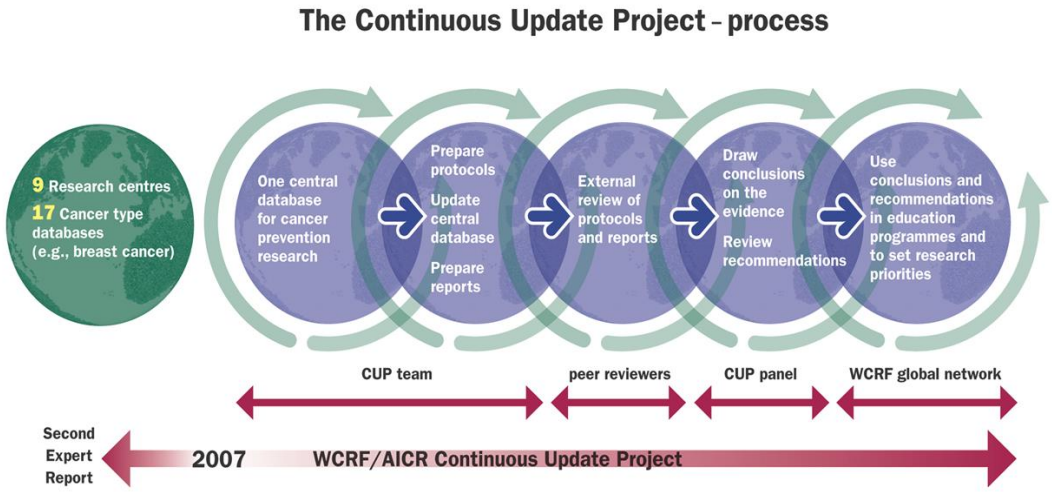
The World Cancer Research Fund/ American Institute for Cancer Research: (WCRF/AICR) has been a global leader in elucidating the relationship between food, nutrition, physical activity and cancer. The First and Second Expert Reports (1;2) represent the most extensive analyses of the existing science on the subject to date.

The Second Expert Report features eight general and two special recommendations based on solid evidence which, when followed, will be expected to reduce the incidence of cancer. More recently, empirical evidence from a large European cohort study showed that people with lifestyle in agreement with the WCRF/AICR recommendations experienced decreased risk of cancer after an average follow-up time of ten years (3). The main risk reductions were for cancers of the colon and rectum, and oesophageal cancer, and significant associations were observed for cancers of the breast, endometrium, lung, kidney, upper aerodigestive tract, liver, and oesophagus.

The Second Expert Report was informed by a process of seventeen systematic literature reviews (SLRs) all of the evidence published. To keep the evidence current and updated into the future, WCRF/AICR is undertaking the Continuous Update Project (CUP) in collaboration with Imperial College London (ICL). The CUP [http://www.wcrf.org/cancer_research/cup/index.php] is an on-going systematic literature review on food, nutrition, physical activity and body fatness, and cancer risk. The project ensures that the evidence, on which the WCRF/AICR recommendations are based, continues to be the most-up-to-date and comprehensive available.

WCRF/AICR has convened a panel of experts for the CUP consisting of leading scientists in the field of diet, physical activity, obesity and cancer, who will consider the evidence produced by the systematic literature reviews conducted by the research team at ICL. The CUP Panel will judge the evidence, draw conclusions and make recommendations for cancer prevention. The entire CUP process will provide an impartial analysis and interpretation of the data as a basis for reviewing and where necessary revising the 2007 WCRF/AICR's cancer prevention recommendations (**Figure 1**).

Figure 1. The Continuous Update Process



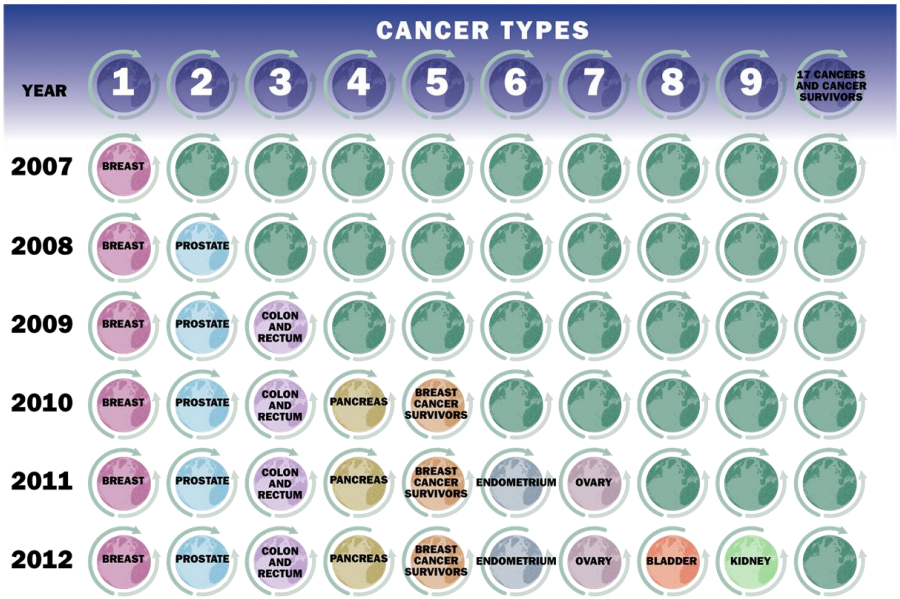
The CUP builds on the foundations of the Second Expert Report to ensure a consistent approach to reviewing the evidence (4). A team at ICL conducts the CUP SLRs, where a central database has been created by merging the cancer-specific databases generated in the 2007 SLR's. A key step of the CUP is the update of the central database with the results of randomised controlled trials and prospective studies. The CUP Expert Panel advised that these are the study designs that should be prioritized for update because the 2007 WCRF recommendations had been mainly based on the results of randomised controlled trials and prospective cohort studies.

The WCRF database is being updated at ICL in a rolling programme. The CUP started in 2007 and breast cancer was the first cancer to be updated, followed by prostate and colorectal cancers. When a cancer site is included in the CUP, the team at ICL keeps updating the database for that cancer and all the other cancers already included in the CUP (**Figure 2**). Currently, the central database is being updated for cancers of the breast, prostate, colon and rectum, pancreas, ovary, endometrium, bladder, kidney, gallbladder, liver and stomach.

Periodically, the CUP team at ICL prepares SLR reports with updated meta-analyses by request of the CUP Panel and Secretariat. The protocols and reports of systematic literature reviews by the IC team are available at http://www.dietandcancerreport.org/cancer_resource_center/continuous_update_project.php).

The present document is the protocol for the continuous update and the SLR on food, nutrition, physical activity and the risk of oesophageal cancer. The peer-reviewed protocol will represent the agreed plan. Should departure from the agreed plan be considered necessary at a later stage, the CUP Expert Panel must agree this and the reasons be documented.

Figure 2. The Continuous Update Project- rolling programme

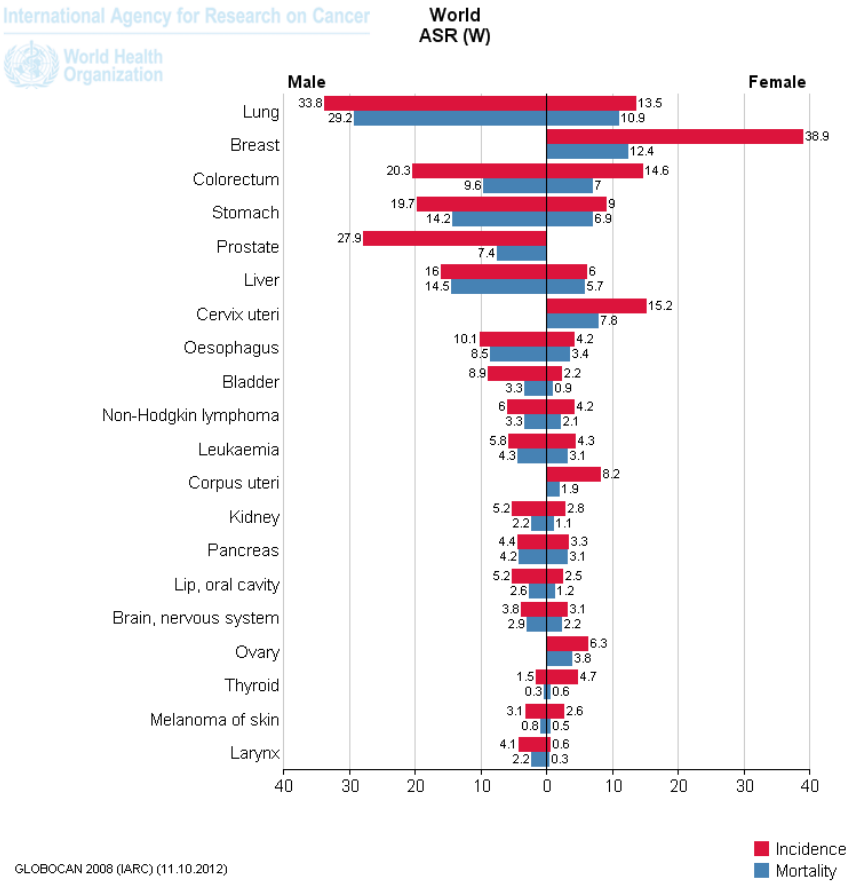


OESOPHAGEAL CANCER: EPIDEMIOLOGY AND RISK FACTORS.

Oesophageal cancer is the eight most common incident cancer worldwide and the sixth most common cause of death from cancer (**Figure 3**). There is a substantial racial and gender disparity in the incidence of oesophageal cancer. In general, rates in men exceed those of women. Data from Cancer Incidence in Five Continents Vol. X (CI5X) and GLOBOCAN 2012 showed that the male to female ratio of oesophageal adenocarcinoma is about 4-fold, ranging from 1.7 in sub-Saharan Africa to 8.5 in Northern America. The global male to female ratio of oesophageal squamous cell carcinoma is 2.7, and it is highest in Eastern Europe (7.8) and lowest in Northern Africa and Western Asia (1.2).

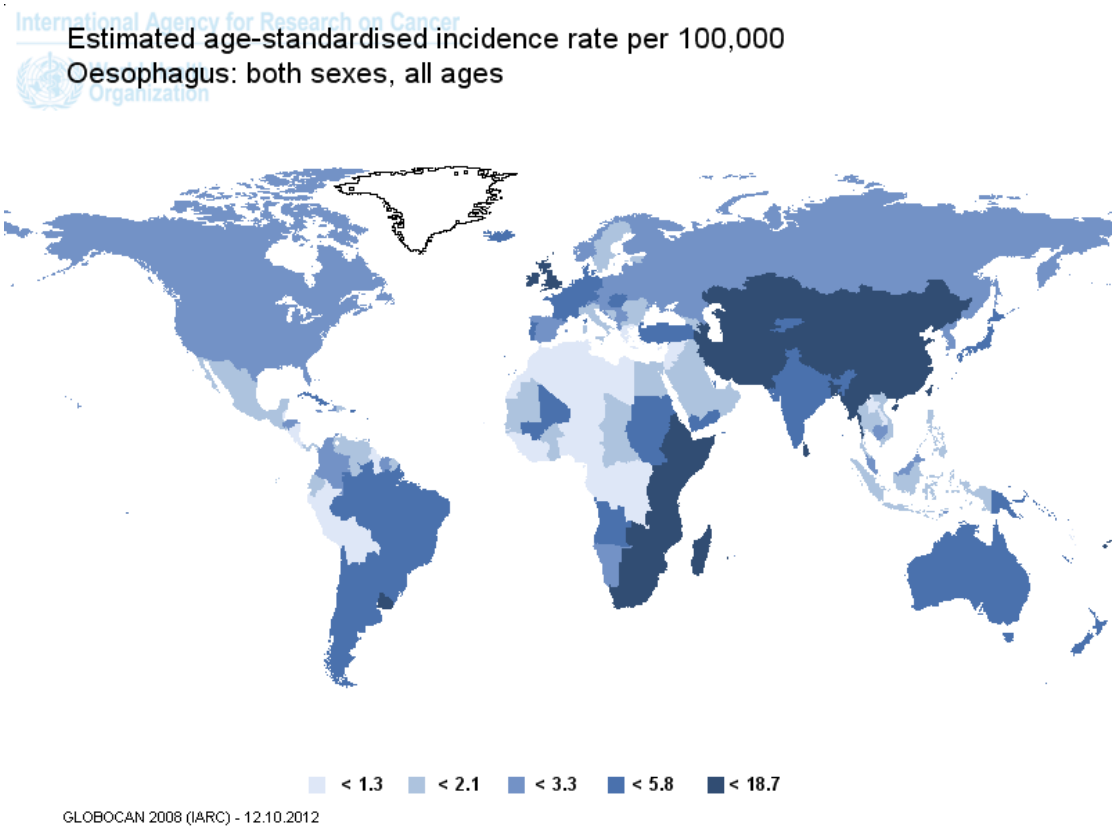
; the incidence is approximately two to four fold greater in men than in women, and in United States, it is four times higher in whites than in African Americans (5).

Figure 3. Estimated age (world)-standardized incidence and mortality rates by sex of selected cancers (per 100 000). World. 2008



The incidence of oesophageal cancer and the distribution of cases according to the main histological types - squamous cell carcinoma (SCC) and adenocarcinoma- vary throughout regions of the world. Before the 1970s, SCC constituted over 90% of all oesophageal cancer cases worldwide. However, the incidence rates of oesophageal adenocarcinoma have sharply increased among white population of high income countries. A rapid increase in the prevalence of Barrett's oesophagus, a condition that confers about a 100-fold increased risk of developing oesophageal adenocarcinoma (EAC), has also been documented (6). SCC continue to be the most frequent histological type found in people living in the area from northeast China to north central Asia, Afghanistan and northern Iran (the 'Asian Oesophageal Cancer Belt'). Other high-risk areas are Eastern Sub-Saharan Africa and some areas of Finland, Iceland, and France (**Figure 4**) (5).

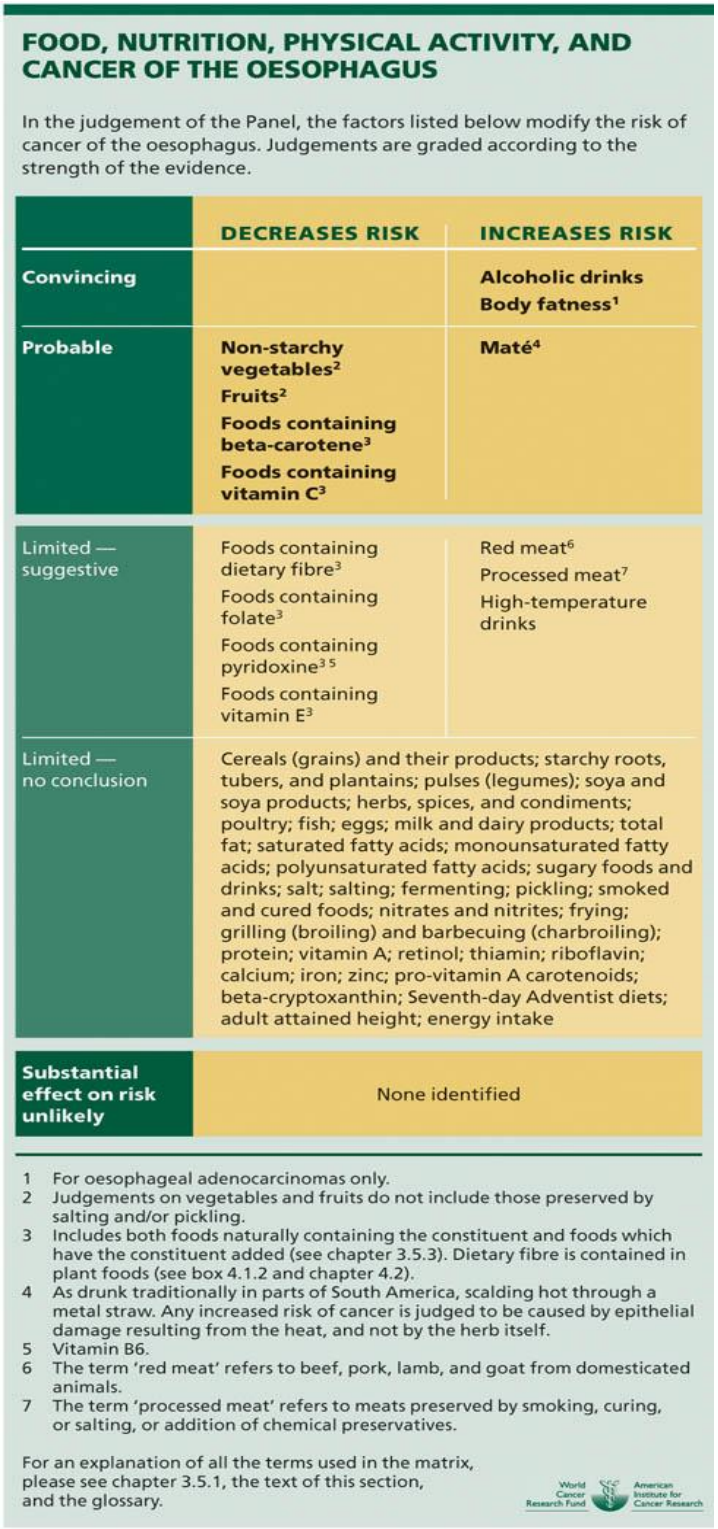
Figure 4. Estimated age-standardized incidence of oesophageal cancer (per 100 000). World 2008



The role of genetic factors in oesophageal cancer is not clear. Given the changes in the incidence rate in different geographic areas, it is likely that lifestyle and other environmental factors play important roles along with genetic factors. A number of studies have demonstrated a positive dose-response relationship of squamous cell oesophageal cancer risk with alcohol consumption and cigarette smoking (7-9) whereas tobacco smoking and, probably, absence of H pylori in the stomach may increase the risk of oesophageal adenocarcinoma (10).

The expert panel of the WCRF/AICR Second Report (1) concluded that the evidence that body fatness increases the risk of adenocarcinoma of the oesophagus and that alcohol drinking increases the risk of oesophageal cancer was convincing. There was no other "convincing" evidence of an association of food, nutrition and physical activity with oesophageal cancer risk. The panel considered that the evidence supported that fruits, non-starchy vegetables, foods containing β-carotene, and vitamins C were "probably" protective against the risk of oesophageal cancer, while the evidence on a role of foods containing fibre, folate, pyridoxine and vitamin E was judged as "limited evidence" of a protective effect. The panel also concluded that drinking maté probably increases oesophageal cancer risk, while the evidence on a role of red meat and processed meat was judged as "limited evidence" of an increased risk (Figure 5). Since the number of studies was limited, the Panel could not evaluate risk factors separately for squamous cell carcinoma and adenocarcinoma of the oesophagus.

Figure 5. Summary of judgements of the 2007 Second Expert Report on oesophageal cancer 2007 (1)



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

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

	DECREASES RISK	INCREASES RISK
Convincing		**Alcoholic drinks** **Body fatness[1]**
Probable	**Non-starchy vegetables[2]** **Fruits[2]** **Foods containing beta-carotene[3]** **Foods containing vitamin C[3]**	**Maté[4]**
Limited — suggestive	Foods containing dietary fibre[3] Foods containing folate[3] Foods containing pyridoxine[3 5] Foods containing vitamin E[3]	Red meat[6] Processed meat[7] High-temperature drinks
Limited — no conclusion	Cereals (grains) and their products; starchy roots, tubers, and plantains; pulses (legumes); soya and soya products; herbs, spices, and condiments; poultry; fish; eggs; milk and dairy products; total fat; saturated fatty acids; monounsaturated fatty acids; polyunsaturated fatty acids; sugary foods and drinks; salt; salting; fermenting; pickling; smoked and cured foods; nitrates and nitrites; frying; grilling (broiling) and barbecuing (charbroiling); protein; vitamin A; retinol; thiamin; riboflavin; calcium; iron; zinc; pro-vitamin A carotenoids; beta-cryptoxanthin; Seventh-day Adventist diets; adult attained height; energy intake	
Substantial effect on risk unlikely	None identified	

1 For oesophageal adenocarcinomas only.
2 Judgements on vegetables and fruits do not include those preserved by salting and/or pickling.
3 Includes both foods naturally containing the constituent and foods which have the constituent added (see chapter 3.5.3). Dietary fibre is contained in plant foods (see box 4.1.2 and chapter 4.2).
4 As drunk traditionally in parts of South America, scalding hot through a metal straw. Any increased risk of cancer is judged to be caused by epithelial damage resulting from the heat, and not by the herb itself.
5 Vitamin B6.
6 The term 'red meat' refers to beef, pork, lamb, and goat from domesticated animals.
7 The term 'processed meat' refers to meats preserved by smoking, curing, or salting, or addition of chemical preservatives.

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

*Note**:** The number of studies was limited and the Panel could not evaluate risk factors separately for squamous cell carcinoma and adenocarcinoma of the oesophagus*

CUP UPDATE OF THE SYSTEMATIC LITERATURE REVIEW ON OESOPHAGEAL CANCER

1. RESEARCH QUESTION

The research topic is:

The associations between food, nutrition and physical activity and the risk of oesophageal squamous cell carcinomas and oesophageal adenocarcinomas.

The main objective is:

To summarize the evidence from prospective studies and randomised controlled trials on the association between foods, nutrients, physical activity, body adiposity and the risk of oesophageal squamous cell carcinomas and oesophageal adenocarcinomas in men and women.

2. REVIEW TEAM

Name	Current position at IC	Role within team
Teresa Norat	Principal Research Fellow	Principal investigator
Doris Chan	Research Assistant	Supervisor of data extraction. Data analyst, SLR report preparation
Ana Rita Vieira	Research Assistant	Data analyst, SLR report preparation
Leila Abar	Research Assistant	Systematic search, article selection, data extraction
Deborah Navarro	Research Assistant	Systematic search, article selection, data extraction
Snieguole Vingeliene	Research Assistant	Systematic search, article selection, data extraction

Review coordinator, WCRF: Rachel Thompson

Statistical advisor: Darren Greenwood, senior Research Lecturer, University of Leeds

All the reviewers are trained in the procedures for literature search, data selection and extraction for systematic literature reviews. The reviewers that will conduct the data analyses have experience in meta-analyses. Selected SLRs published by members of the ICL team are in the References Section (11-23).

3. TIMELINE

The SLRs for the Second Expert Report ended in December 30th 2005. The SLR centre extracted all the data from relevant articles published up to this date for the Second Expert Report.

The CUP team at IC will search and extract data of the articles from prospective studies and randomised controlled trials published from January 1st 2006. The reviewers will verify that there are not duplicities in the database using a module for article search implemented in the interface for data entry.

List of tasks and deadlines for the continuous update on oesophageal cancer:

Task	Deadline
Start Medline search of relevant articles published from January 1st 2006	March 1, 2013
Start review of title and abstracts of articles identified in electronic search and select papers for complete review	March 15, 2013
Download papers and select relevant papers for data extraction	March 28, 2013
Start data extraction	April 15, 2013
Start hand search of references	April 15, 2013
Start quantitative analysis of articles included in PubMed up to 30th May 2014*	July 1, 2014
Start writing SLR report	July 1, 2014
Send SLR report for review to CUP secretariat	October 30, 2014
Review and modify SLR report according to reviewer's comments	January 2015
Send reviewed SLR report to CUP secretariat	January 31, 2015
Transfer Endnote files to SLR CUP Secretariat	February 28, 2015
Panel meeting	June 2015

*End date of the intermediate systematic literature review to the CUP Panel

4. SEARCH STRATEGY

4.1. Search database

The Medline database (includes coverage from 70 countries) will be searched using PubMed as platform. The rationale for searching only in Medline is that the results of the SLR's for the Second Expert Report indicated that searching reports of prospective studies in databases other than Medline was not cost effective (24). Central and ClinialTrials.gov will be searched for evidence of trials relevant to this review.

4.2. Hand searching for cited references

The review team will also hand search the references of reviews and meta-analyses identified during the search.

4.3 Search strategy for PubMed

The CUP review team will use the search strategy established in the SLR Guidelines for the WCRF-AICR Second Expert Report (24). A first search will be conducted using as date limits January 1st 2006 to February 28th 2013 and subsequent searches will be conducted every month.

The search will be conducted in three steps:

1) Searching for studies relating to food, nutrition and physical activity

2) Searching for studies relating to oesophageal cancer

3) Searching for studies relating food, nutrition and physical activity, and oesophageal cancers

The full search strategy is in **Annex** 1.

5. STUDY SELECTION CRITERIA FOR THE UPDATE

5.1 Inclusion criteria

The articles to be included in the review:

- Must have as exposure/intervention: dietary patterns, foods, nutrients –dietary, supplemental or both-, diet biomarkers, indicators of body adiposity in early life, adolescence or adulthood, changes in body adiposity, height, and breastfeeding.
- Must have as outcome of interest incidence or mortality of oesophageal cancer¥
- Included in Medline from January 1st 2006¶
- Have to present results from an epidemiologic study in men and/or women of one of the following types:
    - Randomized controlled trial
    - Group randomized controlled trial (Community trial)
    - Prospective cohort study

- Nested case-control study
- Case-cohort study
- Historical cohort study

- In individuals free of cancer at the moment of exposure assessment or intervention (except non melanoma skin cancer)

¥ *Articles identified in the search with the following outcomes: "gastro-oesophageal" cancer, "upper aero-digestive cancers" and other cancers groups that explicitly includes oesophageal cancer will also be extracted. The cancers group name will be indicated in the database under "cancer type" and the description of the cancers included in the identified groups will be indicated under "cancer type description".*

¶ *January 1st 2006 is the closure date of the database for the Second Expert Report.*

5.2 Exclusion criteria

- Cohort studies in which the only measure of the relationship between the relevant exposure and outcome is the mean difference of exposure (this is because the difference is not adjusted for main confounders).
- Articles in foreign language that cannot be translated (members in the review team can read Chinese, French, Italian, Spanish and Portuguese).

6. ARTICLE SELECTION

First, all references obtained with the searches in PubMed will be imported in a Reference Manager Database using the filter Medline.

The article selection will follow three steps:

1. An electronic search will first be undertaken within Reference Manager to facilitate the identification of irrelevant records by using the terms indicated below. Relevance will be assessed upon reading of the titles and abstracts of the articles identified by the electronic search.

List of terms for use within Reference Manager Database

Radiotherapy

Chemotherapy

Cisplatinum

Docetaxel

Cell

Inhibitor

Novel

Model

Receptor

Antibody

Transgenic

Mice

Hamster

Rat

Dog

Cat

In vitro

2. In a second step, two reviewers will assess the titles and abstracts of the remaining articles.

3. In a third step, the reviewers will assess the full manuscripts of all papers for which eligibility could not be determined by reading the title and abstract.

The reviewers will solve any disagreements about the study or exposure relevance by discussion with the principal investigator.

6.1 Reference Manager Files

Five user-defined fields (**Table 1**) will be created in the Reference Manager database where the reviewers will indicate:

1) if the study was selected upon reading of title and abstract, or entire article
2) the study design of articles on exposures/interventions and outcome relevant to the review
3) the status of data extraction of included articles
4) the WCRF code assigned to included studies during data extraction
5) reasons for exclusion of articles on exposures/interventions and outcome relevant to the review

Table 1. User-defined fields and terms to be used in the Reference Manager database for identification of the status of articles identified in the searches

Field	**Use**	**Terms**	**Notes**
User Def 1	Indicate result of assessment for inclusion	Excludedabti	Excludedabti: paper exclusion based on abstract and title
		Excluded	Excluded: paper exclusion based on full paper text
		Included	Included: reports of case-control studies, cohort studies, pooled analysis and trials relevant to the review.
User Def 2	Reasons for exclusion	No measure of association No original data Commentary, no original data Foreign article in [*language*] No adequate study design Meta-analysis Already extracted Cancer survivors	No original data uses data from others No adequate study design includes non-controlled trials, cross-sectional analysis, ecological studies. Already extracted refers to studies identified by another search Cancer survivors for studies that are not in people free of cancer at baseline
User Def 3	Study design	Randomized controlled trial (RCT) Prospective cohort study Retrospective cohort study	Case-control study-other: when the comparison populations are neighbors, friends, and any other case in which the controls are not population- or

		Nested case-control study Case cohort study Population-based case-control study Hospital-based case-control study Case-control study- other Pooled analysis of cohort studies Pooled analysis of case-control studies	hospital- based. Case-control studies and pooled analyses are identified as included but the data are not extracted to the database.
User Def 4	WCRF code	OES+ consecutive digits	WCRF codes are assigned automatically by the data extraction software when performing the data extraction.
User Def 5	Cancer group	Indicates if the study report aggregative cancer types such as gastro-oesophageal cancer, upper aero-digestive or other	The data should be extracted in the article has inclusion criteria

7. DATA EXTRACTION

The IC team will update the WCRF-AICR central database using an interface created or this purpose **(Figure 6)**. The application will automatically check that the paper has not already been extracted to the database using author name, publication year and journal references. The data extracted will be double-checked by a second reviewer.

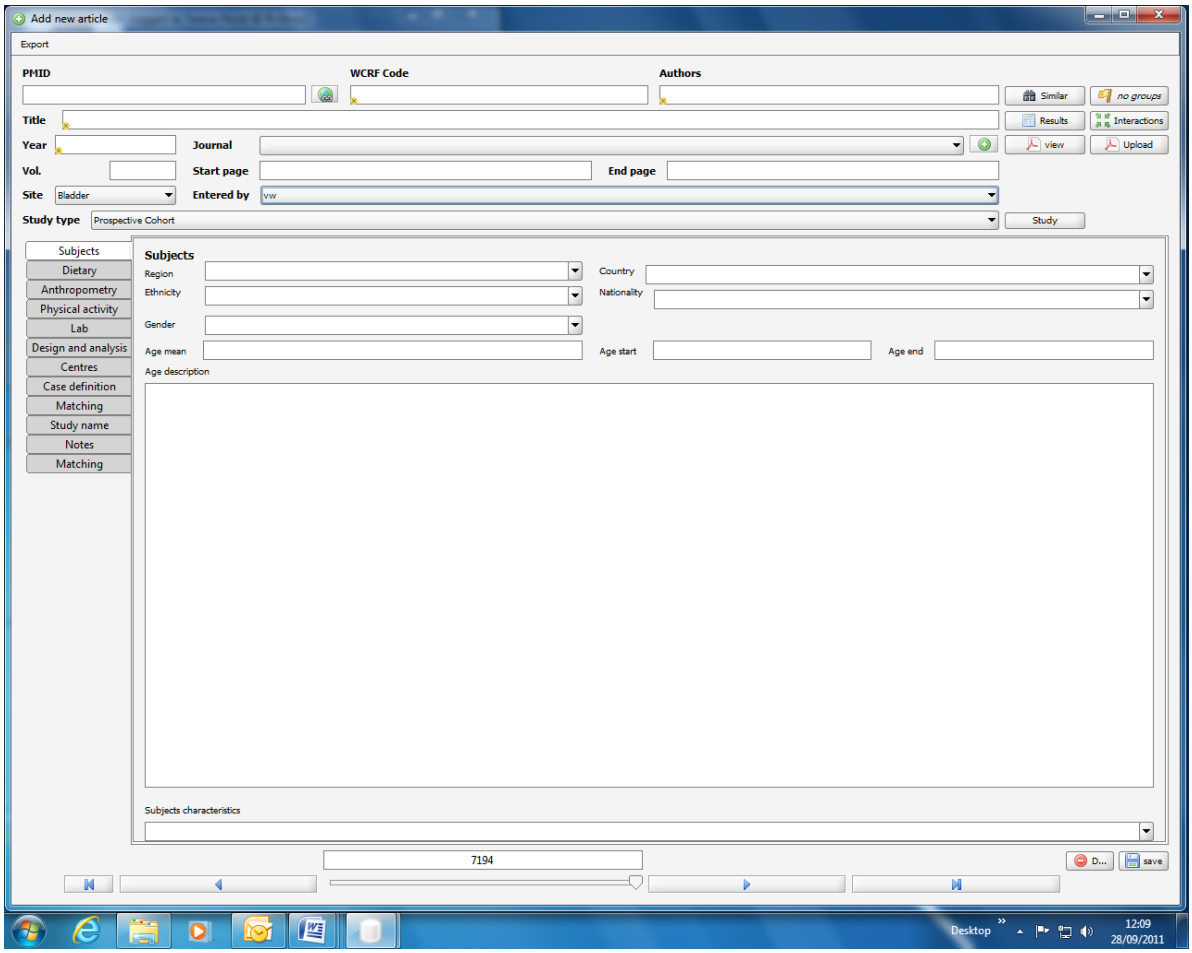
The data to be extracted include study design, name, characteristics of study population, mean age, distribution by sex, country, recruitment year, methods of exposure assessment, definition of exposure, definition of outcome, method of outcome assessment, study size, length of follow up, lost to follow-up, analytical methods and whether methods for correction of measurement error were used.

The ranges, means or median values for each level of the exposure will be extracted as reported in the paper. For each result, the reviewers will extract the covariates included in the analytical models and the matching variables. Measures of association, number of cases and number of comparison individuals or person years for each category of exposure will be extracted for each model used in the analyses as reported in the papers. The reviewer will not do any calculation during this phase. Stratified and subgroup analyses, and results of interaction analyses will be extracted (e.g. by sex, age group, smoking status, BMI category, alcohol intake level, etc.)

The reviewer should extract the results for each histological type of cancer (SCC or adenocarcinoma). Results on "oesophageal cancer" without indication of histological type will be extracted as a separate category, as well as the results for any other cancer group that includes oesophageal cancer (e.g.. gastro-oesophageal cancer, upper aero-digestive tract, other).

The reviewer will also extract all the associations observed in stratified or interaction analyses in the paper,

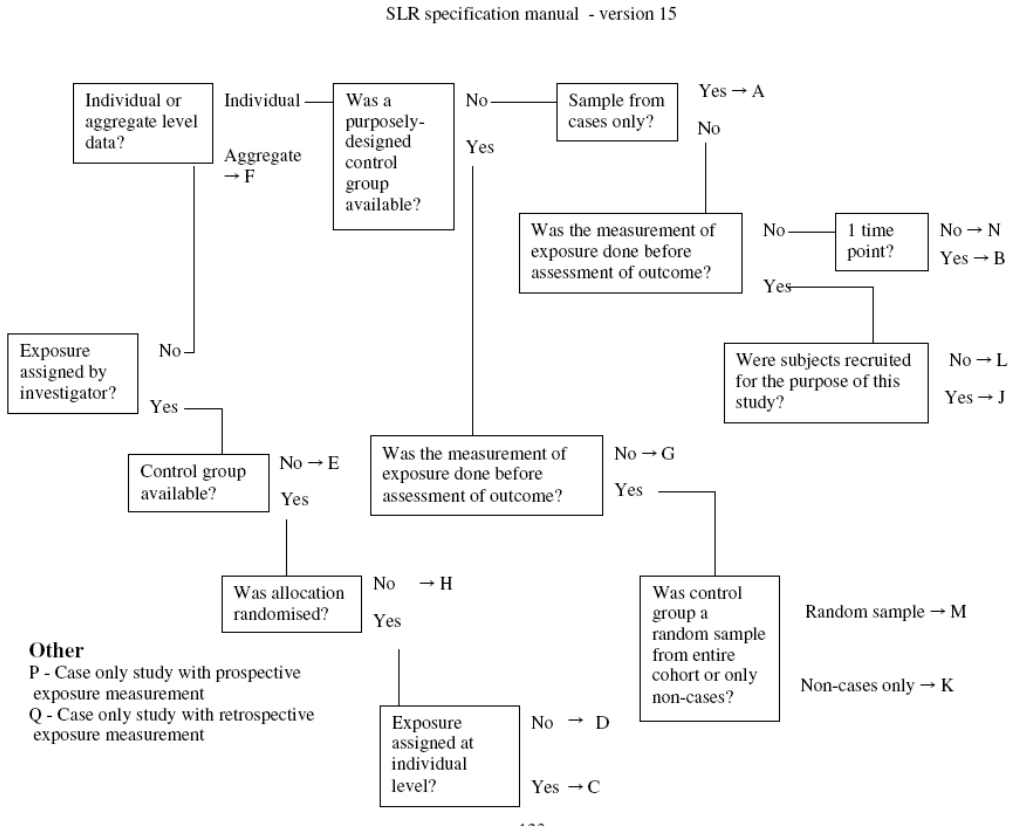
Figure 6. CUP interface. Example of screen for data entry.



7.1 Allocation of study design

The study design algorithm devised for use of the SLR centres for the Second Expert Report will be used to allocate study designs to papers. In some cases, it will be appropriate to assign more than one design to a particular paper (e.g. analyses in the entire cohort and nested case-control). The algorithm is in **Figure 7**.

Figure 7. Study design algorithm (From: SLR specification manual)



Key to study design algorithm

Study design A Case-study / case series

Study design B Cross-sectional study

Study design C Randomised controlled trial

Study design D Group randomized control trial

Study design E Uncontrolled trial

Study design F Ecologic study

Study design G Case-control study

Study design H Non-randomized control trial

Study design J Prospective cohort study

Study design K Nested case-control study

Study design L Historical cohort study

Study design M Case-cohort study

Study design N Time series with multiple measurements

Study design P Case only study with prospective exposure measurement

Study design Q Case only study with retrospective exposure measurement

7.2 Study identifier

The CUP team will use the same labelling of articles used in the SLR process for the Second Expert Report: the unique identifier for an article will be constructed using a 3-letter code to represent the cancer site: OES (oesophageal cancer), followed by a 5-digit number that will be generated sequentially by the software during data extraction.

7.3 Codification of exposures/interventions.

The exposures/interventions will be codified during data extraction as in the Second Expert Report. The main headings and sub-headings codes are in **Annex 2**. Wherever possible, the reviewer will use the sub-heading codes. Additional codes have been programmed in the database to facilitate the data entry.

The reviewer should also extract the description of the exposure/intervention definition in the free text box provided for that purpose in the data entry screen. The definition will be extracted as it appears in the paper.

The main headings for codification of the exposure groups are:

1. **Patterns of diet**, includes regionally defined diets, socio-economically defined diets, culturally defined diets, individual level dietary patterns, other dietary patterns, breastfeeding and other issues

2. **Foods**, including starchy foods; fruit and (non-starchy) vegetables; pulses (legumes); nuts and seeds; meat, poultry, fish and eggs; fats, oils and sugars; milk and dairy products; and herbs, spices, and condiments, and composite foods.

3. **Beverages**, including total fluid intake, water, milk, soft drinks, fruit juices, hot drinks and alcoholic drinks.

4. **Food production** including traditional methods and chemical contaminants, food preservation, processing and preparation.

5. **Dietary constituents**, including carbohydrate, lipids, protein, alcohol, vitamins, minerals, phytochemicals, nutrient supplements and other bioactive compounds

6. **Physical activity**, including total physical activity, physical inactivity and surrogate markers for physical activity.

7. **Energy balance**, including energy intake, energy density and energy expenditure.

8. **Anthropometry**, including markers of body composition, markers of body fat distribution, height and other skeletal measures, and growth in foetal life, infancy or childhood.

7.3.1 Codification of biomarkers of exposure

Biomarkers of exposure will be included under the heading and with the code of the corresponding exposure.

During the SLR for the Second Expert Report, some review centres opted for including in the review only biomarkers for which there was strong evidence on reliability or validity whereas other centres opted for including results on all the biomarkers retrieved in the search, independently of their validity. For the evaluation of the evidence, the Panel of Experts took in consideration the validity of the reported biomarkers.

However, since the identification and validation of other biomarkers is an expanding are in nutritional epidemiology (25), the CUP team will extract the data for all biomarkers of intake reported in the studies, independently of whether validity and reliability had been or not fully documented.

7. 4 Codification of outcomes.

The reviewer will indicate in the field: outcome type, whether the outcome is incidence or mortality and in outcome subtype, if the results are on oesophageal adenocarcinoma, squamous cell carcinoma or oesophageal cancer not specified.

7.5 Extraction and labelling of study results

The reviewer will extract the measures of association (RR estimates and confidence intervals) for the relevant exposures from all the statistical models shown in the paper, including subgroups, stratified analyses, interactions and sensitivity analyses. These results are shown in the paper in tables, in the text or as supplemental information.

The reviewer should label the results as unadjusted, intermediately adjusted, or most adjusted model, depending of the models:

- The results of univariate models will be labelled “unadjusted”.
- The results obtained with the model including the higher number of covariables in the article will be labelled “most adjusted”.
- The results obtained using any multivariable model that is not the most adjusted model will be labelled “intermediately” adjusted.

In addition, the reviewer will indicate the “best model “for meta-analyses.

The “best” model will be selected using two criteria: level of control for confounding and completeness of the data for dose-response meta-analysis. The best model will be the most adjusted model in the article.

Sometimes, the researchers use models that include variables likely to be in the causal pathway with the purpose of exploring hypothetical mechanisms. When “mechanistic” models are reported by the authors, the “intermediately” adjusted result with the highest number of covariables will be indicated as “best model”. The mechanistic” models will be extracted and labelled as most adjusted model, but not as best model for meta-analysis. If there are enough results with these models, they can be used in separate analysis.

In addition to adjustment, other criteria to consider for identifying the ‘best model’ for meta-analysis are the completeness of the data (e.g. the most adjusted does not provide all the data needed or the information to compute missing values but the data of the less adjusted model is more complete). In such situations, a model that is not the most adjusted model will be identified as “best model” for meta-analyses.

8. QUALITY CONTROL OF THE ARTICLE SELECTION AND DATA EXTRACTION.

A second reviewer at ICL will check the article selection and the data extraction. If there are discrepancies between the reviewers, the discrepancy will be discussed with the Principal Investigator.

9. DATA ANALYSIS

9.1 Meta-analysis

The CUP team at IC will update the meta-analyses conducted for the Second Report. The CUP SLR will not conduct meta-analysis using as contrast the highest vs. the lowest category of exposure/intervention except when most of the papers identified have categorised participants in two groups (e.g. breastfeeding categorised as yes vs. no, use of multivitamins categorised as yes vs. no) and for physical activity because usually quantitative levels are not provided.

Meta-analyses will be conducted for oesophageal squamous cell carcinoma and for adenocarcinomas Studies on oesophageal cancer with histology not specified will be analysed separately.

The meta-analyses will be conducted for studies on incidence and mortality as outcome separately and combined.

Studies on cancers with different anatomical localisations (for example, gastro-oesophageal cancers) will not be pooled together with those of oesophageal cancer.

Where results from two or three cohort studies are reported in the same paper, the results of each cohort will be included separately in the CUP meta-analysis instead of using the pooled result reported in the paper. The purpose is to look at heterogeneity across study results. The same will be done for the results of pooling projects or consortia.

Sensitivity analyses will be conducted including the overall results of pooling projects or cohort consortia identified. The same study will not be included twice in one meta-analysis.

The results of the individual studies will be displayed graphically in forests plots of the highest vs. the lowest comparison for each study, but a summary estimate will not be calculated, to avoid pooling different exposure levels. In all forest plots, the studies will be ordered by publication year, with the most recent on the top.

Linear dose-response meta-analysis will be conducted to express the results of each study in the same increment unit for a given exposure and the results will be shown in a dose-response forest plot. For comparability, the increment units for the linear dose-response analyses will be those used in the meta-analyses in the previous SLRs (**Table 2**) but another increment may have to be used in the range of exposure in the identified papers is smaller than the recommended increment unit. If most of the identified studies report servings, times, units these will be used as increment unit.

Non-linear dose-response meta-analyses will be conducted as exploratory analysis.

Table 2.Recommended increment units for meta-analyses.

Exposure	Increment unit
Total fruits and vegetables	100 g
Non starchy vegetables	100 g
Fruits	100 g
Citrus fruits	50 g
Red meat	100 g
Processed meat	50 g
Poultry	100 g
Fish	50 g
Eggs	25 g
Salt	1 g
Coffee	1 cup
Tea	1 cup
Alcoholic drinks	1 drink/day
Alcohol (as ethanol)	10 g
Dietary calcium	200 mg
Dietary fibre	10 g
Folate	100 µg
Blood selenium	10 µg/L
Beer	10 g/day (approx. one drink)
Wine	10 g/day (approx. one drink)
BMI	5 kg/m^2
Waist	2.5 cm (1 inch)
Waist-to-hip	0.1 unit
Height	5 cm

Physical activity	5 MET-h per week

9.2 Selection of exposures for a dose-response meta-analysis

The meta-analysis will include studies identified during the SLR and studies identified during the CUP.

A dose-response meta-analysis will be conducted when at least two new reports of trials or two news reports or cohort studies with enough data for dose-response meta-analysis are identified during the CUP and if the total number of studies to be included is at least of 5 in each study design, or if there is a pooling project or consortium of studies published. The minimum number of two studies was not derived statistically but it is a number of studies that can be reasonable expected to have been published after the Second Expert Report.

Where a particular study has published more than one paper on the same exposure, the analysis using the larger number of cases will be selected but if the most recent paper does not provide enough information for the dose-response meta-analysis, the previous publication with the required information will be used. The results section will indicate whether the reports of the same study are similar or not.

9.3 Selection of results for meta-analyses

The results based on "best" adjusted models will be used in the dose-response meta-analyses. When the linear dose-response estimate is reported in an article, this will be used in the CUP dose-response meta-analysis. If the results are presented only for categorical exposures/intervention (quantiles or pre-defined categories), the slope of the dose-response relationship for each study will be derived from the categorical data.

9.4 Derivation of data required for meta-analyses.

The data required to derive the dose-response slope from categorical data are:

1. number of cases for each exposure category
2. person-years -or number of comparison individuals nested case-control analyses- for each exposure category
3. median, mean or cut-offs of exposure categories.

The information provided in the articles is often incomplete and this may result in exclusions of results from meta-analyses. In the SLR on oesophageal and prostate cancers for the Second Expert Report, only 64% of the cohort studies provided enough data to be included in dose-response meta-analysis, and there was empirical evidence that studies that showed an association were more likely to be usable in dose-response meta-analysis than studies that did not show any evidence (26).

The failure to include all available evidence will reduce precision of summary estimates and may also lead to bias if propensity to report results in sufficient detail is associated with the magnitude and/or direction of associations. To address the data incompleteness, a number of

approaches will be undertaken to derive the missing data from the available data where possible (26). The approaches are summarized in **Table 3.**

Table 3. Approaches to derive missing information for meta-analyses in the CUP

Type of data	Problem	Approach
Dose-response data	Serving size is not quantified or ranges are missing, but group descriptions are given	Use serving size recommended in SLR
	Standard error missing	The p value (either exact or the upper bound) is used to estimate the standard error
Quantile-based data	Numbers of controls (or the denominator in cohort studies) are missing	Group sizes are assumed to be approximately equal
	Confidence interval is missing	Use raw numbers of cases and person years (or controls in nested case-control studies) to calculate confidence interval (although doing so may result in a somewhat smaller standard error than would be obtained in an adjusted analysis)
	Group mean are missing	This information may be estimated by using the method of Chêne and Thompson (27) with a normal or lognormal distribution, as appropriate, or by taking midpoints (scaled in unbounded groups according to group numbers) if the number of groups is too small to calculate a distribution (3-4 groups)
Category data	Numbers of controls (or the denominator in cohort studies) is missing	Derive these numbers from the numbers of cases and the reported odds ratios (proportions will be correct unless adjustment for confounding factors considerably alter the crude odds ratios)

For estimating the "dose-response" for each study, means or medians of the exposure categories will be assigned as "dose" if reported in the articles; if not reported, the midpoints of the exposure range will be assigned to the relative risk of the corresponding category. For lowest or highest open-ended categories the amplitude of the nearest category will be used for the calculation of the midpoint. In cases where the units of measurement differed between

results, the units would be converted, where possible. Where assumptions had to be made on portion or serving sizes the assumptions used in the WCRF/AICR Second Expert Report will be applied (4) (**Table 4**). For studies reporting intakes in grams/1000 kcal/day, the intake in grams/day will be estimated using the average energy intake reported in the article.

Table 4. List of conversion units

Item	Conversion of one unit
Beer	400ml serving
Cereals	60g serving
Cheese	35g serving
Dried fish	10g serving
Eggs	55g serving (1 egg)
Fats	10g serving
Fruit & Vegetables	80g serving
Fruit Juice	125ml serving
General drinks inc. soft & hot drinks	200ml serving
Meat & Fish	120g serving
Milk	50ml serving
Milk as beverage	200ml serving
Processed cheese slice	10g serving
Processed meat	50g serving
Shellfish	60g serving
Spirits	25ml serving
Staple foods (rice, pasta, potatoes, beans & lentils, foods boiled in soy sauce)	150g serving
Water & Fluid intake	8oz cup
Wine	125ml serving

9.5 Statistical Methods

The slopes of the dose-response relationships will be derived from categorical data using generalized least-squares for trend estimation (command GLST in Stata) (28). This method

accounts for the correlation between relative risks estimates with respect to the same reference category (29). The dose-response model is forcing the fitted line to go through the origin and whenever the assigned dose corresponding to the reference group (RR=1) is different from zero, this will be rescaled to zero and the assigned doses to the other exposure categories will be rescaled accordingly.

The study specific log odds ratios per unit increase in exposure will be combined in a random effect model using the method of DerSimonian and Laird (30), with the estimate of heterogeneity being taken from the inverse-variance fixed-effect model.

Publication and related bias (e.g. small study bias) will be explored through visual examination of funnel plots and Egger's test (31). Funnel plots will be shown when there are at least four studies included in the analysis.

Heterogeneity between studies will be quantified with the I^2 statistic - where cut points I^2 values of 30%, and 50% correspond to low, moderate, and high degrees of heterogeneity (32). Heterogeneity will be assessed visually from forest plots and with statistical tests (P value <0.05 will be considered statistically significant) but the interpretation will rely mainly in the I^2 values as the test has low power and the number of studies will probably be limited.

Potential sources of heterogeneity will be explored by stratified analyses when the number of studies allows it (at least two studies in each stratum). The variables that will be explored as sources of heterogeneity are oesophageal cancer histology, outcome (incidence or mortality), gender, geographic area, level of control for confounder, publication year, length of follow-up. Meta-regression will be conducted when the number of studies allows it.

The interpretation of stratified analysis should be cautious. If a considerable number of study characteristics are investigated in a meta-analysis containing only a small number of studies, then there is a high probability that one or more study characteristics will be found to explain heterogeneity, even in the absence of real associations.

Potential non-linear dose-response relationships will be explored using fractional polynomial models (33). The best fitting second order fractional polynomial regression model defined as the one with the lowest deviance will be determined. Non-linearity will be tested using the likelihood ratio test (34). These analyses will be conducted using a program in Stata prepared by D. Greenwood, statistical advisor of the project.

All analyses will be conducted in Stata/SE 12.1.

9.7 Sensitivity analyses

Sensitivity analyses will be carried out to investigate how robust the overall findings of the CUP are relative to key decisions and assumptions that were made in the process of conducting the update. The purpose of doing sensitivity analyses is to strengthen the confidence that can be placed in the results.

Sensitivity analysis will be done as a minimum in the following cases:

- Including and excluding studies where there is some ambiguity as to whether they meet the inclusion criteria, for example it may be unclear what histological types are considered in a study (e.g. it is unclear if part of the cases are not of the same histology as the others)
- Including and excluding studies where exposure level was inferred by the authors (for example assigning a standard portion size when this is not provided) or other missing information was derived from the data.
- Influence-analyses where each individual study will be omitted in turn in order to investigate the sensitivity of the pooled estimates to inclusion or exclusion of particular studies (35).
- Including the results of pooling projects of cohort studies. In these analyses, the reviewer will check that studies in the pooled analyses are not included also as individual studies.

10. SYSTEMATIC LITERATURE REVIEW

An updated SLR will be sent to the CUP Secretariat on January 30, 2015 for discussion in the Expert Panel.

The SLR report will include the following elements:

1. Modifications of the approved protocol

    Any modification required during the review will be described

2. Results of the search

    Flowchart with number of records downloaded, number of papers thought potentially relevant after reading titles and abstracts and number of papers included. The reasons for excluding papers should also be described.

3. Summary tables of studies identified in the continuous update

    Number of studies by study design and publication year.

    Number of studies by exposure (main heading and selected subheadings) and publication year

    Number of studies by exposure and outcome subtype

4. Tabulation of study characteristics

The tables will include study characteristics (e.g. population, exposure, outcome, study design) and main study results.

The tables will include the information required by the Panel to judge the quality of the studies included in the analyses (Newcastle –Ottawa quality assessment scale (36) for cohort studies and the Cochrane Collaboration's tool for assessing risk of bias (37)).

Example of table of study characteristics for cohort studies (in two parts below):

Author, Year, country, WCRF Code	Study design	Country, Ethnicity, other characteristics	Age (mean)	Cases (n)	Non cases (n/person-years)	Case ascertainment	Follow-up (years)

Assessment details	Category of exposure	Subgroup	No cat	RR	(95% CI)	p trend	Adjustment factors						
							A	B	C	D	E	F	G

10. 6 Graphic presentation

Tabular presentation will be complemented with graphic displays when two or more new studies have been published during the CUP. Study results will be displayed in forest plots showing relative risk estimates and 95% confidence interval of ‘‘high versus low’’ comparisons for each study. Dose-response graphs will be given for individual studies for which the information is available. Funnel plots will be shown when there are at least four studies.

10.7 Results of the dose-response meta-analysis

Main characteristics of included and excluded studies in dose-response meta-analysis will be tabulated, and reasons for exclusions will be detailed.

The results of meta-analysis will be presented in tables and forest plots. The tables will include a comparison with the results of the meta-analyses undertaken during the SLR for the Second Expert Report.

All forest plots in the report will have the same format. Footnotes will provide quantified information (statistical tests and I^2 statistics) on the degree of heterogeneity between the displayed studies.

Meta-regression, stratified analyses and sensitivity analyses results will be presented in tables and, if the number of studies justifies it, in forest plots.

Reference List

1. World Cancer Research Fund/ American Institute for Cancer Research: Food, Nutrition, Physical Activity, and the Prevention of Cancer: a global perspective. Washington DC: 2007.

2. World Cancer Research Fund/ American Institute for Cancer Research. Food, Nutrition and the Prevention of Cancer: a global perspective. Washington DC : 1997.

3. Romaguera D, Vergnaud AC, Peeters PH et al. Is concordance with World Cancer Research Fund/American Institute for Cancer Research guidelines for cancer prevention related to subsequent risk of cancer? Results from the EPIC study. Am J Clin Nutr 2012;96:150-63.

4. World Cancer Research Fund/ American Institute for Cancer Research. Systematic Literature Review. The SLR Specification Manual In . In: AICR, ed. Food, Nutrition, Physical Activity and the Prevention of Cancer: A Global Perspective (Support Resource) . Washington DC: 2007.

5. Ferlay J, Shin HR, Bray F, Forman D, Mathers C and Parkin DM. GLOBOCAN 2008 v1.2, Cancer Incidence and Mortality Worldwide: IARC CancerBase No. 10 [Internet]. Lyon, France: International Agency for Research on Cancer; 2010. http://globocan.

6. Phillips WA, Lord RV, Nancarrow DJ, Watson DI, Whiteman DC. Barrett's esophagus. J Gastroenterol Hepatol 2011;26:639-48.

7. Islami F, Fedirko V, Tramacere I, Bagnardi V, Jenab M, Scotti L, et al. Alcohol drinking and esophageal squamous cell carcinoma with focus on light-drinkers and never-smokers: a systematic review and meta-analysis. Int J Cancer. 2011; 129(10): 2473-84

8. Li Y, Yang H, Cao J. Association between alcohol consumption and cancers in the Chinese population--a systematic review and meta-analysis. PLoS One 2011;6:e18776.

9. Oze I, Matsuo K, Wakai K et al. Alcohol drinking and esophageal cancer risk: an evaluation based on a systematic review of epidemiologic evidence among the Japanese population. Jpn J Clin Oncol 2011;41:677-92.

10. Kamangar F, Chow WH, Abnet CC, Dawsey SM. Environmental causes of esophageal cancer. Gastroenterol Clin North Am 2009;38:27-57, vii.

11. Moskal A, Norat T, Ferrari P, Riboli E. Alcohol intake and colorectal cancer risk: a dose-response meta-analysis of published cohort studies. Int J Cancer 2007;120:664-71.

12. Druesne-Pecollo N, Latino-Martel P, Norat T et al. Beta-carotene supplementation and cancer risk: a systematic review and metaanalysis of randomized controlled trials. Int J Cancer 2010;127:172-84.

13. Saadatian-Elahi M, Norat T, Goudable J, Riboli E. Biomarkers of dietary fatty acid intake and the risk of breast cancer: a meta-analysis. Int J Cancer 2004;111:584-91.

14. Aune D, Greenwood DC, Chan DS et al. Body mass index, abdominal fatness and pancreatic cancer risk: a systematic review and non-linear dose-response meta-analysis of prospective studies. Ann Oncol 2012;23:843-52.

15. Aune D, Chan DS, Lau R et al. Carbohydrates, glycemic index, glycemic load, and colorectal cancer risk: a systematic review and meta-analysis of cohort studies. Cancer Causes Control 2012;23:521-35.

16. Aune D, Lau R, Chan DS et al. Dairy products and colorectal cancer risk: a systematic review and meta-analysis of cohort studies. Ann Oncol 2012;23:37-45.

17. Aune D, Chan DS, Vieira AR et al. Dietary compared with blood concentrations of carotenoids and breast cancer risk: a systematic review and meta-analysis of prospective studies. Am J Clin Nutr 2012;96:356-73.

18. Aune D, Chan DS, Greenwood DC et al. Dietary fiber and breast cancer risk: a systematic review and meta-analysis of prospective studies. Ann Oncol 2012;23:1394-402.

19. Aune D, Chan DS, Lau R et al. Dietary fibre, whole grains, and risk of colorectal cancer: systematic review and dose-response meta-analysis of prospective studies. BMJ 2011;343:d6617. doi: 10.1136/bmj.d6617.:d6617.

20. Aune D, Chan DS, Vieira AR et al. Dietary fructose, carbohydrates, glycemic indices and pancreatic cancer risk: a systematic review and meta-analysis of cohort studies. Ann Oncol 2012;23:2536-46.

21. Riboli E, Norat T. Epidemiologic evidence of the protective effect of fruit and vegetables on cancer risk. Am J Clin Nutr 2003;78:559S-69S.

22. Druesne-Pecollo N, Touvier M, Barrandon E et al. Excess body weight and second primary cancer risk after breast cancer: a systematic review and meta-analysis of prospective studies. Breast Cancer Res Treat 2012;135:647-54.

23. Chan DS, Lau R, Aune D et al. Red and processed meat and colorectal cancer incidence: meta-analysis of prospective studies. PLoS One 2011;6:e20456.

24. Kaiser Permanente SLR Team. Systematic Literature Review. The associations between food, nutrition and physical activity and the risk of endometrial cancer and underlying mechanisms. 2012. Food, Nutrition, Physical Activity and the Prevention of Cancer: A Global Perspective (Support Resource).Washington DC: AICR , 2007 .

25. Jenab M, Slimani N, Bictash M, Ferrari P, Bingham SA. Biomarkers in nutritional epidemiology: applications, needs and new horizons. Hum Genet 2009;125:507-25.

26. Bekkering GE, Harris RJ, Thomas S et al. How much of the data published in observational studies of the association between diet and prostate or bladder cancer is usable for meta-analysis? Am J Epidemiol 2008;167:1017-26.

27. Chene G, Thompson SG. Methods for summarizing the risk associations of quantitative variables in epidemiologic studies in a consistent form. Am J Epidemiol 1996;144:610-21.

28. Orsini N, Bellocco R, Greenland S. Generalized least squares for trend estimation of summarized dose-response data . Stata J 2006;6:40-57.

29. Greenland S, Longnecker MP. Methods for trend estimation from summarized dose-response data, with applications to meta-analysis. Am J Epidemiol 1992;135:1301-9.

30. DerSimonian R, Laird N. Meta-analysis in clinical trials. Control Clin Trials 1986;7:177-88.

31. Egger M, Davey SG, Schneider M, Minder C. Bias in meta-analysis detected by a simple, graphical test. BMJ 1997;315:629-34.

32. Higgins JP, Thompson SG. Quantifying heterogeneity in a meta-analysis. Stat Med 2002;21:1539-58.

33. Royston P, Ambler G, Sauerbrei W. The use of fractional polynomials to model continuous risk variables in epidemiology. Int J Epidemiol 1999;28:964–974.

34. Rota M, Bellocco R, Scotti L, Tramacere I, Jenab M, Corrao G et al. Random-effects meta-regression models for studying nonlinear dose-response relationship, with an application to alcohol and esophageal squamous cell carcinoma. Stat Med. 2010;29 :2679-87.

35. Tobias A. Assessing the influence of a single study in meta-analysis. Stata Tech Bull 1999;47:15-7.

36. Stang A. Critical evaluation of the Newcastle-Ottawa scale for the assessment of the quality of nonrandomized studies in meta-analyses. Eur J Epidemiol 2010;25:603-5.

37. Cochrane Handbook for Systematic Reviews of Interventions . http://www.cochrane.org/training/cochrane-handbook . 2012.

Annex 1. WCRF - PUBMED SEARCH STRATEGY

1) Searching for all studies relating to food, nutrition and physical activity:

1 diet therapy[MeSH Terms] OR nutrition[MeSH Terms]

#2 diet[tiab] OR diets[tiab] OR dietetic[tiab] OR dietary[tiab] OR eating[tiab] OR

intake[tiab] OR nutrient*[tiab] OR nutrition[tiab] OR vegetarian*[tiab] OR vegan*[tiab] OR "seventh day adventist"[tiab] OR macrobiotic[tiab]

#3 food and beverages[MeSH Terms]

#4 food*[tiab] OR cereal*[tiab] OR grain*[tiab] OR granary[tiab] OR

wholegrain[tiab] OR wholewheat[tiab] OR roots[tiab] OR plantain*[tiab] OR tuber[tiab] OR tubers[tiab] OR vegetable*[tiab] OR fruit*[tiab] OR pulses[tiab] OR beans[tiab] OR lentils[tiab] OR chickpeas[tiab] OR legume*[tiab] OR soy[tiab] OR soya[tiab] OR nut[tiab] OR nuts[tiab] OR peanut*[tiab] OR groundnut*[tiab] OR (seeds[tiab] and (diet*[tiab] OR food*[tiab])) OR meat[tiab] OR beef[tiab] OR pork[tiab] OR lamb[tiab] OR poultry[tiab] OR chicken[tiab] OR turkey[tiab] OR duck[tiab] OR fish[tiab] OR ((fat[tiab] OR fats[tiab] OR fatty[tiab]) AND (diet*[tiab] or food*[tiab] or adipose[tiab] or blood[tiab] or serum[tiab] or plasma[tiab])) OR egg[tiab] OR eggs[tiab] OR bread[tiab] OR (oils[tiab] AND and (diet*[tiab] or food*[tiab] or adipose[tiab] or blood[tiab]or serum[tiab] or plasma[tiab])) OR shellfish[tiab] OR seafood[tiab] OR sugar[tiab] OR syrup[tiab] OR dairy[tiab] OR milk[tiab] OR herbs[tiab] OR spices[tiab] OR chilli[tiab] OR chillis[tiab] OR pepper*[tiab] OR condiments[tiab] OR tomato*[tiab]

#5 fluid intake[tiab] OR water[tiab] OR drinks[tiab] OR drinking[tiab] OR tea[tiab]

OR coffee[tiab] OR caffeine[tiab] OR juice[tiab] OR beer[tiab] OR spirits[tiab] OR

liquor[tiab] OR wine[tiab] OR alcohol[tiab] OR alcoholic[tiab] OR beverage*[tiab] OR (ethanol[tiab] and (drink*[tiab] or intake[tiab] or consumption[tiab])) OR yerba mate[tiab] OR ilex paraguariensis[tiab]

#6 pesticides[MeSH Terms] OR fertilizers[MeSH Terms] OR "veterinary

drugs"[MeSH Terms]

#7 pesticide*[tiab] OR herbicide*[tiab] OR DDT[tiab] OR fertiliser*[tiab] OR

fertilizer*[tiab] OR organic[tiab] OR contaminants[tiab] OR contaminate*[tiab] OR

veterinary drug*[tiab] OR polychlorinated dibenzofuran*[tiab] OR PCDF*[tiab] OR

polychlorinated dibenzodioxin*[tiab] OR PCDD*[tiab] OR polychlorinated

biphenyl*[tiab] OR PCB*[tiab] OR cadmium[tiab] OR arsenic[tiab] OR chlorinated

hydrocarbon*[tiab] OR microbial contamination*[tiab]

#8 food preservation[MeSH Terms]

#9 mycotoxin*[tiab] OR aflatoxin*[tiab] OR pickled[tiab] OR bottled[tiab] OR

bottling[tiab] OR canned[tiab] OR canning[tiab] OR vacuum pack*[tiab] OR

refrigerate*[tiab] OR refrigeration[tiab] OR cured[tiab] OR smoked[tiab] OR

preserved[tiab] OR preservatives[tiab] OR nitrosamine[tiab] OR hydrogenation[tiab] OR fortified[tiab] OR additive*[tiab] OR colouring*[tiab] OR coloring*[tiab] OR

flavouring*[tiab] OR flavoring*[tiab] OR nitrates[tiab] OR nitrites[tiab] OR solvent[tiab] OR solvents[tiab] OR ferment*[tiab] OR processed[tiab] OR antioxidant*[tiab] OR genetic modif*[tiab] OR genetically modif*[tiab] OR vinyl chloride[tiab] OR packaging[tiab] OR labelling[tiab] OR phthalates[tiab]

#10 cookery[MeSH Terms]

#11 cooking[tiab] OR cooked[tiab] OR grill[tiab] OR grilled[tiab] OR fried[tiab] OR

fry[tiab] OR roast[tiab] OR bake[tiab] OR baked[tiab] OR stewing[tiab] OR stewed[tiab] OR casserol*[tiab] OR broil[tiab] OR broiled[tiab] OR boiled[tiab] OR (microwave[tiab] and (diet*[tiab] or food*[tiab])) OR microwaved[tiab] OR re-heating[tiab] OR reheating[tiab] OR heating[tiab] OR re-heated[tiab] OR heated[tiab] OR poach[tiab] OR poached[tiab] OR steamed[tiab] OR barbecue*[tiab] OR chargrill*[tiab] OR heterocyclic amines[tiab] OR polycyclic aromatic hydrocarbons[tiab] OR dietary acrylamide[tiab]

#12 ((carbohydrates[MeSH Terms] OR proteins[MeSH Terms]) and (diet*[tiab] or food*[tiab])) OR sweetening agents[MeSH Terms]

#13 salt[tiab] OR salting[tiab] OR salted[tiab] OR fiber[tiab] OR fibre[tiab] OR

polysaccharide*[tiab] OR starch[tiab] OR starchy[tiab] OR carbohydrate*[tiab] OR

lipid*[tiab] OR ((linoleic acid*[tiab] OR sterols[tiab] OR stanols[tiab]) AND (diet*[tiab] or food*[tiab] or adipose [tiab] or blood[tiab] or serum[tiab] or plasma[tiab])) OR sugar*[tiab] OR sweetener*[tiab] OR saccharin*[tiab] OR aspartame[tiab] OR acesulfame[tiab] OR cyclamates[tiab] OR maltose[tiab] OR mannitol[tiab] OR sorbitol[tiab] OR sucrose[tiab] OR xylitol[tiab] OR cholesterol[tiab] OR protein[tiab] OR proteins[tiab] OR hydrogenated dietary oils[tiab] OR hydrogenated lard[tiab] OR hydrogenated oils[tiab]

#14 vitamins[MeSH Terms]

#15 supplements[tiab] OR supplement[tiab] OR vitamin*[tiab] OR retinol[tiab] OR

carotenoid*[tiab] OR tocopherol[tiab] OR folate*[tiab] OR folic acid[tiab] OR methionine[tiab] OR riboflavin[tiab] OR thiamine[tiab] OR niacin[tiab] OR pyridoxine[tiab] OR cobalamin[tiab] OR mineral*[tiab] OR (sodium[tiab] AND (diet*[tiab] or food*[tiab])) OR iron[tiab] OR ((calcium[tiab] AND (diet*[tiab] or food*[tiab] or supplement*[tiab])) OR selenium[tiab] OR (iodine[tiab] AND and (diet*[tiab] or food*[tiab] or supplement*[tiab] or deficiency)) OR magnesium[tiab] OR potassium[tiab] OR zinc[tiab] OR copper[tiab] OR phosphorus[tiab] OR manganese[tiab] OR chromium[tiab] OR phytochemical[tiab] OR allium[tiab] OR isothiocyanate*[tiab] OR glucosinolate*[tiab] OR indoles[tiab] OR polyphenol*[tiab] OR phytoestrogen*[tiab] OR genistein[tiab] OR saponin*[tiab] OR coumarin*[tiab] OR lycopene[tiab]

#16 physical fitness[MeSH Terms] OR exertion[MeSH Terms] OR physical endurance[MeSH Terms] or walking[MeSH Terms]

#17 recreational activit*[tiab] OR household activit*[tiab] OR occupational

activit*[tiab] OR physical activit*[tiab] OR physical inactivit*[tiab] OR exercise[tiab]

OR exercising[tiab] OR energy intake[tiab] OR energy expenditure[tiab] OR energy

balance[tiab] OR energy density[tiab]

#18 body weight [MeSH Terms] OR anthropometry[MeSH Terms] OR body composition[MeSH Terms] OR body constitution[MeSH Terms] OR obesity [MeSH Terms] OR obesity [MeSH Terms]

#19 weight loss[tiab] or weight gain[tiab] OR anthropometry[tiab] OR birth weight[tiab] OR birthweight[tiab] OR birth-weight[tiab] OR child development[tiab] OR height[tiab] OR body composition[tiab] OR body mass[tiab] OR BMI[tiab] OR

obesity[tiab] OR obese[tiab] OR overweight[tiab] OR over-weight[tiab] OR over

weight[tiab] OR skinfold measurement*[tiab] OR skinfold thickness[tiab] OR

DEXA[tiab] OR bio-impedence[tiab] OR waist circumference[tiab] OR hip circumference[tiab] OR waist hip ratio*[tiab] OR weight change [tiab] OR adiposity [tiab] OR abdominal fat [tiab] OR body fat distribution [tiab] OR body size [tiab] OR waist-to-hip ratio [tiab]

#20 #1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR

#12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19

#21 animal[MeSH Terms] NOT human[MeSH Terms]

#22 #20 NOT #21

2) Searching for all studies relating to oesophageal cancer:

#23 Esophageal Neoplasms [MeSH]

#24 Esophag*[tiab] OR oesophag*[tiab] OR upper aero digestive tract[tiab]

#25 malign*[tiab] OR cancer*[tiab] OR carcinoma*[tiab] OR tumor*[tiab] OR tumour*[tiab] OR adenocarcinoma*[tiab] OR carcinoma, squamous cell*[tiab] OR carcinoma, small cell*[tiab] OR high grade dysplasia[tiab]

#26 #24 AND #25

#27 Esophagogastric neoplasm*[tiab] OR esophagogastric cancer*[tiab] OR esophagogastric carcino* OR esophagogastric tumo*[tiab] OR esophagogastric metasta* [tiab] OR esophagogastric malign*[tiab] OR esophagogastric adenocarcinoma* [tiab] OR esophagogastric neoplasm*[tiab]

#28 Esophago gastric cancer*[tiab] OR esophago gastric carcino* OR esophago gastric tumo*[tiab] OR esophago gastric metasta* [tiab] OR esophago gastric malign*[tiab] OR esophago gastric adenocarcinoma* [tiab] OR Barrett's adenocarcinoma [tiab]

#29 Oesophagogastric neoplasm*[tiab] OR oesophagogastric cancer*[tiab] OR oesophagogastric carcino* OR oesophagogastric tumo*[tiab] OR oesophagogastric metasta* [tiab] OR oesophagogastric malign*[tiab] OR oesophagogastric adenocarcinoma* [tiab]

#30 Oesophago gastric neoplasm*[tiab] OR oesophago gastric cancer*[tiab] OR oesophagogastric carcino* OR oesophago gastric tumo*[tiab] OR oesophagogastric metasta* [tiab] OR oesophago gastric malign*[tiab] OR oesophagogastric adenocarcinoma* [tiab]

#31 #27 OR #28 OR #29 OR #30

#32 #23 OR #26 OR #31

3) Searching for all studies relating oesophageal cancer, and food, nutrition and physical activity:

#32 #22 AND #32

Annex 2. LIST OF HEADINGS AND EXPOSURE CODES (minimum list)
**Indicates codes added during the CUP*

1 Patterns of diet

1.1 Regionally defined diets

*1.1.1 Mediterranean diet

Include all regionally defined diets, evident in the literature. These are likely to include Mediterranean, Mesoamerican, oriental, including Japanese and Chinese, and "western type".

1.2 Socio-economically defined diets

To include diets of low-income, middle-income and high-income countries (presented, when available in this order). Rich and poor populations within low-income, middle-income and high-income countries should also be considered. This section should also include the concept of poverty diets (monotonous diets consumed by impoverished populations in the economically-developing world mostly made up of one starchy staple, and may be lacking in micronutrients).

1.3 Culturally defined diets

To include dietary patterns such as vegetarianism, vegan diets, macrobiotic diets and diets of Seventh-day Adventists.

1.4 Individual level dietary patterns

To include work on factor and cluster analysis, and various scores and indexes (e.g. diet diversity indexes) that do not fit into the headings above.

1.5 Other dietary patterns

Include under this heading any other dietary patterns present in the literature, that are not regionally, socio-economically, culturally or individually defined.

1.6 Breastfeeding

1.6.1 Mother

Include here also age at first lactation, duration of breastfeeding, number of children breast-fed

1.6.2 Child

Results concerning the effects of breastfeeding on the development of cancer should be disaggregated into effects on the mother and effects on the child. Wherever possible detailed information on duration of total and exclusive breastfeeding, and of complementary feeding should be included.

1.7 Other issues

For example results related to diet diversity, meal frequency, frequency of snacking, dessert-eating and breakfast-eating should be reported here. Eating out of home should be reported here.

2 Foods

*2.0.1 Plant foods

2.1 Starchy foods

2.1.1 Cereals (grains)

* 2.1.1.0.1 Rice, pasta, noodles

* 2.1.1.0.2 Bread

* 2.1.1.0.3 Cereal

** Report under this subheading the cereals when it is not specified if they are wholegrain or refined cereals (e.g. fortified cereals)*

2.1.1.1 Wholegrain cereals and cereal products

* 2.1.1.1.1 Wholegrain rice, pasta, noodles

* 2.1.1.1.2 Wholegrain bread

* 2.1.1.1.3 Wholegrain cereal

2.1.1.2 Refined cereals and cereal products

* 2.1.1.2.1 Refined rice, pasta, noodles

* 2.1.1.2.2 Refined bread

* 2.1.1.2.3 Refined cereal

2.1.2 Starchy roots, tubers and plantains

* 2.1.2.1 Potatoes

2.1.3 Other starchy foods

**Report polenta under this heading*

2.2 Fruit and (non-starchy) vegetables

Results for "fruit and vegetables" and "fruits, vegetables and fruit juices" should be reported here. If the definition of vegetables used here is different from that used in the first report, this should be highlighted.

2.2.1 Non-starchy vegetables

This heading should be used to report total non-starchy vegetables. If results about specific vegetables are reported they should be recorded under one of the sub-headings below or if not covered, they should be recorded under '2.2.1.5 other'.

2.2.1.1 Non-starchy root vegetables and tubers

*2.2.1.1.1 Carrots

2.2.1.2 Cruciferous vegetables
2.2.1.3 Allium vegetables
2.2.1.4 Green leafy vegetables (not including cruciferous vegetables)
2.2.1.5 Other non-starchy vegetables

*2.2.1.5.13 Tomatoes
*2.2.1.5.1 Fresh beans (e.g. string beans, French beans) and peas

Other non-starchy vegetables' should include foods that are botanically fruits but are eaten as vegetables, e.g. courgettes. In addition vegetables such as French beans that do not fit into the other categories, above.

If there is another sub-category of vegetables that does not easily fit into a category above eg salted root vegetables (ie you do not know if it is starchy or not) then report under 2.2.1.5. and note the precise definition used by the study. If in doubt, enter the exposure more than once in this way.

2.2.1.6 Raw vegetables

This section should include any vegetables specified as eaten raw. Results concerning specific groups and type of raw vegetable should be reported twice i.e. also under the relevant headings 2.2.1.1 –2.2.1.5.

2.2.2 Fruits

*2.2.2.0.1 Fruit, dried

*2.2.2.0.2 Fruit, canned

*2.2.2.0.3 Fruit, cooked

2.2.2.1 Citrus fruit

2.2.2.1.1 Oranges
2.2.2.1.2 Other citrus fruits (e.g. grapefruits)

2.2.2.2 Other fruits

*2.2.2.2.1 Bananas

*2.2.2.2.4 Melon

*2.2.2.2.5 Papaya

*2.2.2.2.7 Blueberries, strawberries and other berries

*2.2.2.2.8 Apples, pears

*2.2.2.2.10 Peaches, apricots, plums

*2.2.2.2.11 Grapes

If results are available that consider other groups of fruit or a particular fruit please report under 'other', specifying the grouping/fruit used in the literature.

2.3 Pulses (legumes)

*2.3.1 Soya, soya products

*2.3.1.1 Miso, soya paste soup

*2.3.1.2 Soya juice

*2.3.1.4 Soya milk

*2.3.1.5 Tofu

*2.3.2 Dried beans, chickpeas, lentiles

*2.3.4 Peanuts, peanut products

Where results are available for a specific pulse/legume, please report under a separate heading.

2.4 Nuts and Seeds

To include all tree nuts and seeds, but not peanuts (groundnuts). Where results are available for a specific nut/seed, e.g. brazil nuts, please report under a separate heading.

2.5 Meat, poultry, fish and eggs

Wherever possible please differentiate between farmed and wild meat, poultry and fish.

2.5.1 Meat

This heading refers only to red meat: essentially beef, lamb, pork from farmed domesticated animals either fresh or frozen, or dried without any other form of preservation. It does not refer to poultry or fish.

Where there are data for offal (organs and other non-flesh parts of meat) and also when there are data for wild and non-domesticated animals, please show these separately under this general heading as a subcategory.

2.5.1.1 Fresh Meat
2.5.1.2 Processed meat

*2.5.1.2.1 Ham

*2.5.1.2.1.7 Burgers

*2.5.1.2.8 Bacon

*2.5.1.2.9 Hot dogs

*2.5.1.2.10 Sausages

Repeat results concerning processed meat here and under the relevant section under 4. Food Production and Processing. Please record the definition of 'processed meat' used by each study.

2.5.1.3 Red meat

*2.5.1.3.1 Beef

*2.5.1.3.2 Lamb

*2.5.1.3.3 Pork

*2.5.1.3.6 Horse, rabbit, wild meat (game)

Where results are available for a particular type of meat, e.g. beef, pork or lamb, please report under a separate heading.

Show any data on wild meat (game) under this heading as a separate sub-category.

2.5.1.4 Poultry

Show any data on wild birds under this heading as a separate sub-category.

*2.5.1.5 Offals, offal products (organ meats)

2.5.2 Fish

*2.5.2.3 Fish, processed (dried, salted, smoked)

*2.5.2.5 Fatty Fish

*2.5.2.7 Dried Fish

*2.5.2.9 White fish, lean fish

2.5.3 Shellfish and other seafood

2.5.4 Eggs

2.6 Fats, oils and sugars

2.6.1 Animal fats

*2.6.1.1 Butter
*2.6.1.2 Lard
*2.6.1.3 Gravy
*2.6.1.4 Fish oil

2.6.2 Plant oils
2.6.3 Hydrogenated fats and oils

*2.6.3.1 Margarine

Results concerning hydrogenated fats and oils should be reported twice, here and under 4.3.2 Hydrogenation

2.6.4 Sugars

This heading refers to added (extrinsic) sugars and syrups as a food, that is refined sugars, such as table sugar, or sugar used in bakery products.

2.7 Milk and dairy products

Results concerning milk should be reported twice, here and under 3.3 Milk

*2.7.1 Milk, fresh milk, dried milk

*2.7.1.1 Whole milk, full-fat milks

*2.7.1.2 Semi skimmed milk, skimmed milk, low fat milk, 2% Milk

*2.7.2 Cheese

*2.7.2.1 Cottage cheese

*2.7.2.2 Cheese, low fat

*2.7.3 Yoghurt, buttermilk, sour milk, fermented milk drinks

*2.7.3.1 Fermented whole milk

*2.7.3.2 Fermented skimmed milk

*2.7.7 Ice cream

2.8 Herbs, spices, condiments

*2.8.1 Ginseng

*2.8.2 Chili pepper, green chili pepper, red chili pepper

2.9 Composite foods

Eg, snacks, crisps, desserts, pizza. Also report any mixed food exposures here ie if an exposure is reported as a combination of 2 or more foods that cross categories (eg bacon and eggs). Label each mixed food exposure.

*2.9.1 Cakes, biscuits and pastry

*2.9.2 Cookies

*2.9.3 Confectionery

*2.9.4 Soups

*2.9.5 Pizza

*2.9.6 Chocolate, candy bars

*2.9.7 Snacks

3 Beverages

3.1 Total fluid intake

3.2 Water

3.3 Milk

For results concerning milk please report twice, here and under 2.7 Milk and Dairy Products.

3.4 Soft drinks

Soft drinks that are both carbonated and sugary should be reported under this general heading. Drinks that contain artificial sweeteners should be reported separately and labelled as such.

3.4.1 Sugary (not carbonated)
3.4.2 Carbonated (not sugary)

The precise definition used by the studies should be highlighted, as definitions used for various soft drinks vary greatly.

*3.5 Fruit and vegetable juices

*3.5.1 Citrus fruit juice

*3.5.2 Fruit juice

*3.5.3 Vegetable juice

*3.5.4 Tomato juice

3.6 Hot drinks

3.6.1 Coffee
3.6.2 Tea

Report herbal tea as a sub-category under tea.

3.6.2.1 Black tea
3.6.2.2 Green tea
3.6.3 Maté
3.6.4 Other hot drinks

3.7 Alcoholic drinks

3.7.1 Total

3.7.1.1 Beers
3.7.1.2 Wines
3.7.1.3 Spirits
3.7.1.4 Other alcoholic drinks

4 Food production, preservation, processing and preparation

4.1 Production

4.1.1 Traditional methods (*to include 'organic')*
4.1.2 Chemical contaminants

Only results based on human evidence should be reported here (see instructions for dealing with mechanistic studies). Please be comprehensive and cover the exposures listed below:

4.1.2.1 Pesticides
4.1.2.2 DDT
4.1.2.3 Herbicides
4.1.2.4 Fertilisers
4.1.2.5 Veterinary drugs
4.1.2.6 Other chemicals

4.1.2.6.1 Polychlorinated dibenzofurans (PCDFs)
4.1.2.6.2 Polychlorinated dibenzodioxins (PCDDs)
4.1.2.6.3 Polychlorinated biphenyls (PCBs)

4.1.2.7 Heavy metals

4.1.2.7.1 Cadmium
4.1.2.7.2 Arsenic

4.1.2.8 Waterborne residues

4.1.2.8.1 Chlorinated hydrocarbons

4.1.2.9 Other contaminants

Please also report any results that cover the cumulative effect of low doses of contaminants in this section.

4.2 Preservation

4.2.1 Drying

4.2.2 Storage

4.2.2.1 Mycotoxins

4.2.2.1.1 Aflatoxins
4.2.2.1.2 Others

4.2.3 Bottling, canning, vacuum packing
4.2.4 Refrigeration
4.2.5 Salt, salting

4.2.5.1 Salt
4.2.5.2 Salting
4.2.5.3 Salted foods

4.2.5.3.1 Salted animal food
4.2.5.3.2 Salted plant food

4.2.6 Pickling
4.2.7 Curing and smoking

4.2.7.1 Cured foods

4.2.7.1.1 Cured meats
4.2.7.1.2 Smoked foods

For some cancers e.g. colon, rectum, oOesophageal and pancreas, it may be important to report results about specific cured foods, cured meats and smoked meats. N-*nitrososamines should also be covered here.*

4.3 Processing

4.3.1 Refining

Results concerning refined cereals and cereal products should be reported twice, here and under 2.1.1.2 refined cereals and cereal products.

4.3.2 Hydrogenation

Results concerning hydrogenated fats and oils should be reported twice, here and under 2.6.3 Hydrogenated fats and oils

4.3.3 Fermenting
4.3.4 Compositional manipulation

4.3.4.1 Fortification
4.3.4.2 Genetic modification
4.3.4.3 Other methods

4.3.5 Food additives

4.3.5.1 Flavours

Report results for monosodium glutamate as a separate category under 4.3.5.1 Flavours.

4.3.5.2 Sweeteners (non-caloric)
4.3.5.3 Colours
4.3.5.4 Preservatives

4.3.5.4.1 Nitrites and nitrates

4.3.5.5 Solvents
4.3.5.6 Fat substitutes
4.3.5.7 Other food additives

Please also report any results that cover the cumulative effect of low doses of additives.
Please also report any results that cover synthetic antioxidants

4.3.6 Packaging

4.3.6.1 Vinyl chloride
4.3.6.2 Phthalates

4.4 Preparation

4.4.1 Fresh food

4.4.1.1 Raw

Report results regarding all raw food other than fruit and vegetables here. There is a separate heading for raw fruit and vegetables (2.2.1.6).

4.4.1.2 Juiced

4.4.2 Cooked food

4.4.2.1 Steaming, boiling, poaching
4.4.2.2 Stewing, casseroling
4.4.2.3 Baking, roasting
4.4.2.4 Microwaving
4.4.2.5 Frying
4.4.2.6 Grilling (broiling) and barbecuing
4.4.2.7 Heating, re-heating

Some studies may have reported methods of cooking in terms of temperature or cooking medium, and also some studies may have indicated whether the food was cooked in a direct or indirect flame. When this information is available, it should be included in the SLR report.

Results linked to mechanisms e.g. heterocyclic amines, acrylamides and polycyclic aromatic hydrocarbons should also be reported here. There may also be some literature on burned food that should be reported in this section.

5 Dietary constituents

Food constituents' relationship to outcome needs to be considered in relation to dose and form including use in fortified foods, food supplements, nutrient supplements and specially formulated foods. Where relevant and possible these should be disaggregated.

5.1 Carbohydrate

5.1.1 Total carbohydrate
5.1.2 Non-starch polysaccharides/dietary fibre

5.1.2.1 Cereal fibre
5.1.2.2 Vegetable fibre
5.1.2.3 Fruit fibre

5.1.3 Starch

5.1.3.1 Resistant starch

5.1.4 Sugars
*5.1.5 Glycemic index, glycemic load

This heading refers to intrinsic sugars that are naturally incorporated into the cellular structure of foods, and also extrinsic sugars not incorporated into the cellular structure of foods. Results for intrinsic and extrinsic sugars should be presented separately. Count honey and sugars in fruit juices as extrinsic. They can be natural and unprocessed, such as honey, or refined such as table sugar. Any results related to specific sugars e.g. fructose should be reported here.

5.2 Lipids

5.2.1 Total fat
5.2.2 Saturated fatty acids
5.2.3 Monounsaturated fatty acids
5.2.4 Polyunsaturated fatty acids

5.2.4.1 n-3 fatty acids

Where available, results concerning alpha linolenic acid and long chain n-3 PUFA should be reported here, and if possible separately.

5.2.4.2 n-6 fatty acids
5.2.4.3 Conjugated linoleic acid

5.2.5 Trans fatty acids
5.2.6 Other dietary lipids, cholesterol, plant sterols and stanols.

For certain cancers, e.g. endometrium, lung, and pancreas, results concerning dietary cholesterol may be available. These results should be reported under this section.

5.3 Protein

5.3.1 Total protein

5.3.2 Plant protein
5.3.3 Animal protein

5.4 Alcohol

This section refers to ethanol the chemical. Results related to specific alcoholic drinks should be reported under 3.7 Alcoholic drinks. Past alcohol refers, for example, to intake at age 18, during adolescence, etc.

*5.4.1 Total Alcohol (as ethanol)

*5.4.1.1Alcohol (as ethanol) from beer
*5.4.1.2Alcohol (as ethanol) from wine
*5.4.1.3Alcohol (as ethanol) from spirits
*5.4.1.4Alcohol (as ethanol) from other alcoholic drinks
* 5.4.1.5 Total alcohol (as ethanol), lifetime exposure

* 5.4.1.6 Total alcohol (as ethanol), past

5.5 Vitamins

*5.5.0 Vitamin supplements
*5.5.0.1 Vitamin and mineral supplements
*5.5.0.2 Vitamin B supplement

5.5.1 Vitamin A

5.5.1.1 Retinol
5.5.1.2 Provitamin A carotenoids

5.5.2 Non-provitamin A carotenoids

Record total carotenoids under 5.5.2 as a separate category marked Total Carotenoids.

5.5.3 Folates and associated compounds

*5.5.3.1 Total folate

*5.5.3.2 Dietary folate

*5.5.3.3 Folate from supplements

Examples of the associated compounds are lipotropes, methionine and other methyl donors.

5.5.4 Riboflavin
5.5.5 Thiamin (vitamin B1)
5.5.6 Niacin
5.5.7 Pyridoxine (vitamin B6)
5.5.8 Cobalamin (vitamin B12)
5.5.9 Vitamin C

5.5.10 Vitamin D (and calcium)
5.5.11 Vitamin E
5.5.12 Vitamin K
5.5.13 Other

If results are available concerning any other vitamins not listed here, then these should be reported at the end of this section. In addition, where information is available concerning multiple vitamin deficiencies, these should be reported at the end of this section under 'other'.

5.6 Minerals

5.6.1 Sodium
5.6.2 Iron
5.6.3 Calcium (and Vitamin D)
5.6.4 Selenium
5.6.5 Iodine
5.6.6 Other

Results are likely to be available on other minerals e.g. magnesium, potassium, zinc, copper, phosphorus, manganese and chromium for certain cancers. These should be reported at the end of this section when appropriate under 'other'.

5.7 Phytochemicals

5.7.1 Allium compounds
5.7.2 Isothiocyanates
5.7.3 Glucosinolates and indoles
5.7.4 Polyphenols
5.7.5 Phytoestrogens eg genistein
5.7.6 Caffeine
5.7.7 Other

Where available report results relating to other phytochemicals such as saponins and coumarins. Results concerning any other bioactive compounds, which are not phytochemicals should be reported under the separate heading 'other bioactive compounds'. Eg flavonoids, isoflavonoids, glycoalkaloids, cyanogens, oligosaccharides and anthocyanins should be reported separately under this heading.

5.8 Other bioactive compounds

6 Physical activity

6.1 Total physical activity (overall summary measures)

6.1.1 Type of activity

6.1.1.1 Occupational
6.1.1.2 Recreational

6.1.1.3 Household
6.1.1.4 Transportation

6.1.2 Frequency of physical activity

*6.1.2.1 Frequency of occupational physical activity

*6.1.2.2 Frequency of recreational physical activity

6.1.3 Intensity of physical activity

*6.1.3.1 Intensity of occupational physical activity

*6.1.3.2 Intensity of recreational physical activity

6.1.4 Duration of physical activity

*6.1.4.1Duration of occupational physical activity
*6.1.4.2Duration of recreational physical activity

6.2 Physical inactivity
6.3 Surrogate markers for physical activity e.g. occupation

7 Energy balance

7.1 Energy intake

*7.1.0.1 Energy from fats

*7.1.0.2 Energy from protein

*7.1.0.3 Energy from carbohydrates

*7.1.0.4 Energy from alcohol

*7.1.0.5 Energy from all other sources

7.1.1 Energy density of diet

7.2 Energy expenditure

8 Anthropometry

8.1 Markers of body composition

8.1.1 BMI

8.1.2 Other weight adjusted for height measures
8.1.3 Weight
8.1.4 Skinfold measurements
8.1.5 Other (e.g. DEXA, bio- impedance, etc)
8.1.6 Change in body composition (including weight gain)

8.2 Markers of distribution of fat

8.2.1 Waist circumference
8.2.2 Hips circumference
8.2.3 Waist to hip ratio
8.2.4 Skinfolds ratio
8.2.5 Other e.g. CT, ultrasound

8.3 Skeletal size

8.3.1 Height (and proxy measures)
8.3.2 Other (e.g. leg length)

8.4 Growth in fetal life, infancy or childhood

8.4.1 Birthweight
8.4.2 Weight at one year