World Cancer Research Fund International Systematic Literature Review

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

Analysing research on cancer prevention and survival

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List of Abbreviations used in the CUP Report

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

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

AHS[1]	Adventist Health Study
AHS[2]	Agricultural Health Study
ATBC	Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study
B[a]P	Benzo[a]pyrene
BASEL	B-type Natriuretic Peptide for Acute Shortness of Breath EvaLuation Study
BOCS	Boyd Orr Cohort Study
BRHS	British Regional Heart Study
CAHS	College Alumni Health Study
CCCJ	Chiba Cancer Registry, Japan
CCHT	Changle County Helicobacter Trial
CCPPS	Copenhagen Centre for Prospective Population Studies
CECS	Chinese Elderly Cohort Study
CNC	Combined Norwegian Cohorts
CNRPCS	China Nationally Representative Prospective Cohort Study
COSM	Cohort of Swedish Men
CPS	Cancer Prevention Study
DiMeIQx	2-amino-3,4,8-trimethylimidazo[4,5-f]quinoxaline
DOS	Danish Obesity Study
DSDA	Danish Seventh-Day Adventists
EPIC	European Prospective Investigation into Cancer and Nutrition
FMCHES	Finnish Mobile Clinic Health Examination Survey
FPC	Fukuoka Prefecture Cohort
GPRDC	General Practitioners Research Database Cohort
HAHS	Harvard Alumni Health Study

Hawaii-Japan DOH Survey	Hawaii-Japan Department of Health Survey
HERPACC	Hospital-based Epidemiologic Research Program at Aichi Cancer Center
HEC	Health Examinee Cohort
HFSS	Health Food Shoppers Study
HGCS	Hokkaido Government Cohort Study
HKC	Higashi-Kamo Cohort
HHP	Honolulu Health Program
HUNT	Nord-Trøndelag Health Study
IWHS	Iowa Women's Health Study Cohort
JACC	Japan Collaborative Cohort study
JPC	Japanese Physicians Cohort
JPHC	Japan Public Health Centre-based Prospective Study
JSDA	Japanese Seventh-Day Adventists
KCPS	Korean Cancer Prevention Study
KCS	Kangwha Cohort Study
KMCC	Korean Multi-Center Cancer Cohort
KNHIC	Korean National Health Insurance Corporation Study
KPMCP	Kaiser Permanente Medical Care Program
KRIS	Kaunas Rotterdam Intervention Study
LBS	Lutheran Brotherhood Insurance Society Cohort Study
MCCS	Melbourne Collaborative Cohort Study
MCS	Miyagi Cohort Study
MeIQx	2-amino-3,8-dimethylimidazo[4,5-f]quinoxaline
MIHDPS	Multifactorial Ischemic Heart Disease Prevention Study
MRC/BHS HPS	Medical Research Council/British Heart Foundation Heart Protection Study
MWS	Million Women's Study
NCS	The Norwegian Counties Study
NCVSC	Norwegian Cardiovascular Screening Cohort
NHI	Ohsaki National Health Insurance Cohort Study
NIT cohort	Linxian Nutrition Intervention Trials - General Population Trial Follow-up
NLCS	The Netherlands Cohort Study
NIH-AARP	NIH-AARP Diet and Health Study
NSHDC	Northern Sweden Health and Disease Cohort
NSPT	Norwegian Screening Programme for Tuberculosis
OCS	Ohaski Cohort Study
PhIP	2-amino-1-methyl-6-phenylimidazo[4,5-b]pyridine
QCSTC	Qixia County Selenium Trial, China
RERFCJ	Radiation Effects Research Foundation Cohort, Japan
RPS	The Renfrew/Paisley Study
SECS	Shizuoka Elderly Cohort Study

SCStudy	Shanghai Cohort Study
SCWC	Swedish Construction Workers Cohort
SKCS	South Korean Civil Servants
SMC	Swedish Mammography Cohort
SMHS	Shanghai Men's Health Study
STR	Swedish Twin Registry
SUVIMAX	Supplémentation en Vitamines et Minéraux Antioxydants Study (The)
SWHS	Shanghai Women's Health Study
TCCJ	Takayama City Cohort, Japan
VHM&PP	The Vorarlverg Health Monitoring and Prevention Programme
VIP	The Västerbotten Intervention Project
WHI-DM	Women's Health Initiative-Dietary Modification Study
WHI-OS	Women's Health Initiative-Observational Study

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 stomach 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 stomach cancer (version 2, February 2013 in Appendix 2).

Persistent colonization of the human stomach with Helicobacter pylori is a strong risk factor for non-cardia gastric cancer but has been found inversely associated with the risk of gastric cardia cancer. Most of the studies included in this SLR could not control for H. Pylori infection. The meta-analysis for blood carotenoids show similar results in studies adjusted or not adjusted for H Pylori status. Similar stratified analyses were not possible for other exposures. Evidence for an interaction of dietary factors and H Pylori infection was provided by at least two studies. In a Chinese study (Epplein, 2014) higher intakes of red meat, haeme iron and sodium intake were associated to an increased risk of gastric cancer, and higher fruit intake with a decreased risk in individuals with high-risk H Pylori infection (defined as sero-positivity to 5–6 virulent *H. pylori* proteins; 140 high-risk cases). Weaker and not significant associations were observed in the low-risk individuals, but the number of cases were low (86 low-risk cases). In EPIC (Gonzalez, 2006b) the positive association of total, red, and processed meat intakes with an increased risk of gastric non-cardia cancer was more evident in H. pylori antibody-positive subjects.

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

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

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

	DECREASES RISK	INCREASES RISK
Convincing		
Probable	**Non-starchy vegetables[1]** **Allium vegetables[1]** **Fruits[1]**	**Salt[2]** **Salted and salty foods**
Limited — suggestive	Pulses (legumes)[3] Foods containing selenium[4]	Chilli[1] Processed meat[5] Smoked foods[6] Grilled (broiled) or barbecued (charbroiled) animal foods[6]
Limited — no conclusion	Cereals (grains) and their products; dietary fibre; potatoes; starchy roots, tubers, and plantains; nuts and seeds; herbs, spices, and condiments; meat (unprocessed); poultry; eggs; milk and dairy products; fats and oils; total fat; fatty acid composition; cholesterol; sugars; sugar (sucrose); fruit juices; coffee; tea; alcohol; dietary nitrate and nitrite, *N*-nitrosodimethylamine; drying or dried food; protein; thiamin; riboflavin; vitamin C; vitamin D; multivitamin/mineral supplements; calcium; iron; selenium supplements; carotenoids; culturally defined diets; meal frequency; eating speed; body fatness; energy intake	
Substantial effect on risk unlikely	None identified	

1 Judgements on vegetables and fruits do not include those preserved by salting and/or pickling.
2 'Salt' here means total salt consumption, from processed foods, including salty and salted foods, and also salt added in cooking and at the table.
3 Including soya and soya products.
4 Includes both foods naturally containing the constituent and foods which have the constituent added (see chapter 3.5.3).
5 The term 'processed meat' refers to meats preserved by smoking, curing, or salting, or addition of chemical preservatives.
6 The evidence is mostly from meats preserved or cooked in these ways.

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

World Cancer Research Fund — American Institute for Cancer Research

Modifications to the existing protocol

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

Review team: Christophe Stevens joined 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 stomach cancer was judged 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 (see Notes on Methods below).

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 ICL updated the search from January 1st 2006 up to February 28th 2014 (see Flowchart).
- 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.
- 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.
- 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 stomach cancer when only results by its subsite were reported.

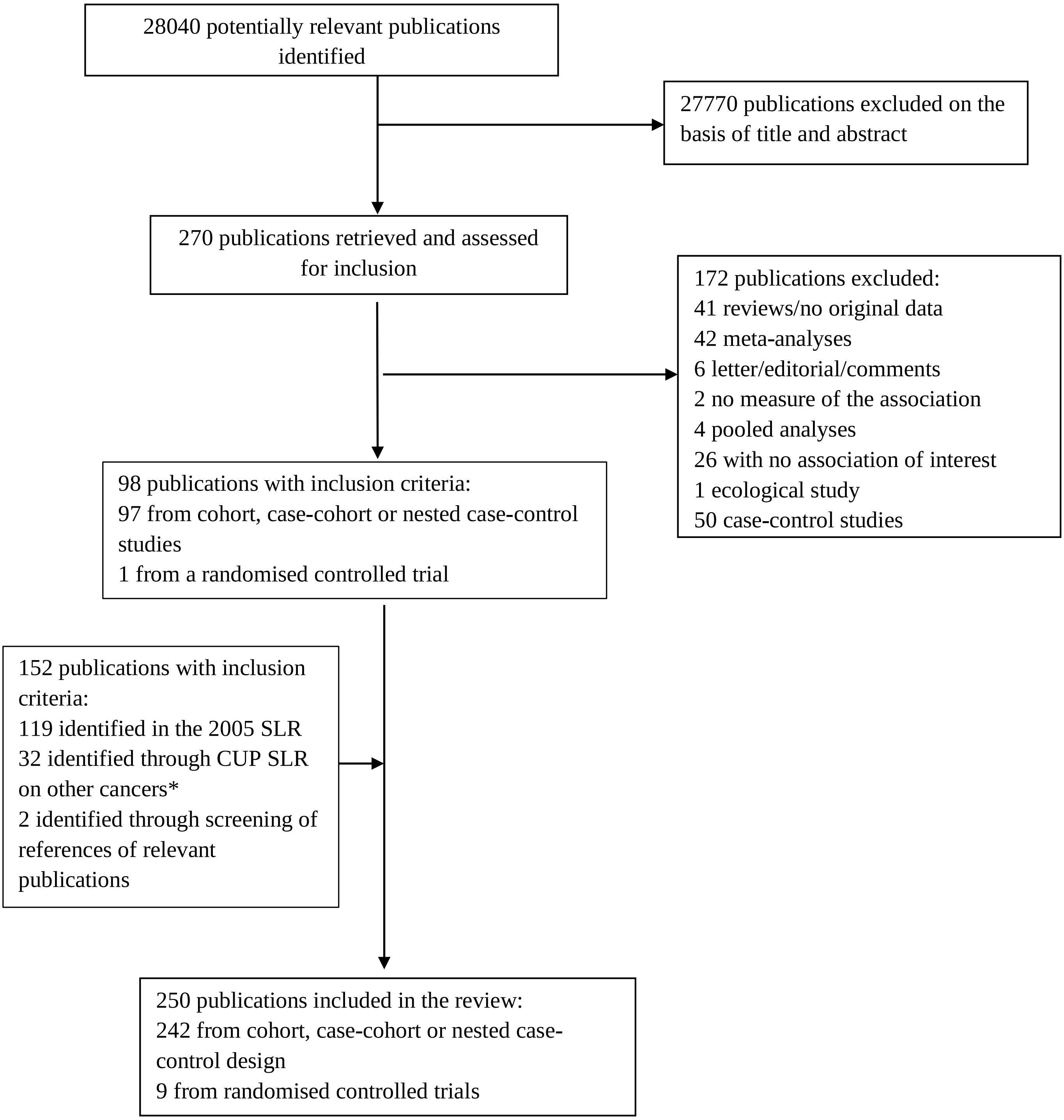
- The interpretation of heterogeneity tests should be cautious when the number of studies is low. Visual inspection of the forest plots and funnel plots is recommended.
- The I^2 statistic describes the proportion of total variation in study estimates that is due to heterogeneity (Higgins, 2002). Low 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 the summary relative risks estimated using 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 only calculated when linear dose-response meta-analysis was not possible, e.g. physical activity; salt.
- 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.
- Where results were only presented separately for specific cancer sites (e.g. gastric cardia cancer, non-cardia gastric cancer), these were first combined before inclusion for the analysis on total stomach cancer.
- When a study investigated distal gastric cancers, these were included only in the meta-analysis with non-cardia gastric cancers.
- When a study reported results on a specific stomach cancer site only, this is included in the analysis of the respective stomach cancer site whenever possible.
- The first dose-response forest plot is the analysis of all studies on total stomach cancer combined. This is followed by stratified analysis by stomach cancer sites whenever possible.
- 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 restricted cubic splines method. Non-linear meta-analyses are not included in the sections for the other exposures when there were not enough studies with the required data. One exception was for processed meat intake where data reported by

the studies were not sufficient to use in the restricted cubic spline analysis. A second family fractional polynomial regression model was used.

- 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 to support the interpretation.
- 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 stomach cancer – Continuous update project
Search period January 1st 2006-February 28th 2014



*Publications on total and cancer-specific associations in which stomach cancer was not mentioned in the title or abstract but were identified during CUP SLR searches in PubMed for other cancers

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 (RCT/cohorts)		Total number of publications
		2005 SLR	CUP	
1.1.1	Mediterranean diet	0	3	3
1.1.1	Regional diet	1	2	3
1.3	Vegetarian diet	5	1	6
1.4	Low fat diet	0	1	1
1.4	Health index scores	1	2	3
1.4	Diet diversity scores	0	1	1
1.4	A posteriori nutrient patterns	0	1	1
1.4	Diet preference	1	2	3
1.6.1	Breastfeeding - mother	1	2	3
1.6.1	Total duration of breastfeeding	0	1	1
2.1.1	Corn	0	1	1
2.1.1.2.3	Rice	7	1	8
2.1.2.1	Sweet potatoes	0	1	1
2.1.2.1	Potatoes	2	1	3
2.2	Fruit and vegetables	5	4	9
2.2.1	Total vegetables	15	8	23
2.2.1	Cooked vegetables	0	1	1
2.2.1	Fried vegetables	0	1	1
2.2.1	Fruiting vegetables	0	2	2
2.2.1.1	Non-starchy root vegetables and tubers	1	2	3
2.2.1.1.1	Carrots	4	4	8
2.2.1.1.6	Beetroot	1	1	2
2.2.1.2	Cruciferous vegetables	5	5	10
2.2.1.2.1	Chinese cabbage	1	1	2
2.2.1.2.2	Cabbage	3	1	4
2.2.1.2.5	Cauliflower	0	1	1
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/onion	3	4	7
2.2.1.4	Green leafy vegetables/spinach	7	6	13
2.2.1.4.4	Seaweed	5	2	7

Exposure Code	Exposure Name	Number of publications (RCT/cohorts)		Total number of publications
		2005 SLR	CUP	
2.2.1.4.5	Cooked endive	0	1	1
2.2.1.5	Pickled vegetables	18	3	21
2.2.1.5	Green-yellow vegetables	19	1	20
2.2.1.5	Leafy vegetables, cooked	0	1	1
2.2.1.5	Lettuce, cabbage	0	1	1
2.2.1.5	Mushrooms	3	2	5
2.2.1.5	Raw leafy vegetables	0	1	1
2.2.1.5	Solanaceae	0	1	1
2.2.1.5	Umbelliferae	0	1	1
2.2.1.5	White vegetables	2	1	3
2.2.1.5	Wild plants	0	1	1
2.2.1.5	Tomatoes	4	2	6
2.2.1.6	Raw vegetables	7	1	8
2.2.2	Fruits	26	8	34
2.2.2	Non citrus fruit	0	1	1
2.2.2.1	Citrus fruits	7	7	14
2.2.2.1.1	Oranges and fresh orange juice	0	1	1
2.2.2.2	Apple, pears	2	1	3
2.2.2.2	Berries	2	1	3
2.2.2.2	Rosaceae	0	1	1
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)	3	5	8
2.3.1	Soy beans	1	1	2
2.3.1	Soya, soya products	3	3	6
2.3.1.1	Miso soup	13	3	16
2.3.1.3	Foods boiled in soy sauce	1	1	2
2.3.1.4	Soya milk	2	1	3
2.3.1.5	Tofu or tofu/soy bean	6	3	9
2.5.1	White meat	0	1	1
2.5.1	Meat	12	1	13
2.5.1.2	Processed meat	10	6	16
2.5.1.2.8	Bacon	2	1	3
2.5.1.2.10	Sausages and hot dogs	1	1	2
2.5.1.3	Red meat	4	3	7
2.5.1.3	Red and processed meat	0	2	2

Exposure Code	Exposure Name	Number of publications (RCT/cohorts)		Total number of publications
		2005 SLR	CUP	
2.5.1.3.1	Beef	1	1	2
2.5.1.3.3	Pork	1	1	2
2.5.1.4	Poultry/chicken	4	3	7
2.5.1.5	Offal/Liver	4	2	6
2.5.2	Fish	11	5	16
2.5.2	Fish paste	0	1	1
2.5.2.3	Dried and salted fish (processed fish)	10	3	13
2.5.4	Eggs	6	2	8
2.6.1.1	Butter	2	1	3
2.6.1.4	Cod liver oil	0	1	1
2.6.3	Margarine	4	1	5
2.6.4	Sugars (as foods)	0	1	1
2.6.4	Fructose	0	1	1
2.7	Dairy foods	2	3	5
2.7.1	Milk	12	1	13
2.7.2	Cheese	3	1	4
2.7.3	Yoghurt	3	1	4
2.8	Chilli	0	0	0
2.8	Herbs	0	1	1
2.8.1	Ginseng	3	1	4
2.9	Restaurant, fast foods	0	1	1
2.9.13	Sweets	0	1	1
3.4.2	Carbonated beverages	1	1	2
3.5	Fruit juices	3	2	5
3.6.1	Coffee	11	7	18
3.6.2	Tea, black tea	8	2	10
3.6.2.2	Green tea	13	4	17
3.6.2.2	Green tea duration of consumption	0	1	1
3.7.1	Age start alcohol consumption	0	2	2
3.7.1	Alcoholic drinks - years since stopping	0	1	1
3.7.1	Alcoholism	7	2	9
3.7.1	Drinking duration	0	2	2
3.7.1	Drinking frequency	14	3	17
3.7.1	Lifetime alcohol consumption	0	1	1
3.7.1.1	Beer	5	5	10
3.7.1.1	Light beer	0	1	1
3.7.1.2	Rice wine	0	1	1
3.7.1.2	Wine	4	5	9

Exposure Code	Exposure Name	Number of publications (RCT/cohorts)		Total number of publications
		2005 SLR	CUP	
3.7.1.3	Spirits	5	6	11
3.7.1.4	Soju	0	1	1
4.1.2.9	Dietary nitrate	6	2	8
4.2	Preserved foods	0	1	1
4.2.5.1	Total salt	3	4	7
4.2.5.1	Added salt	2	2	4
4.2.5.1	Preference for salty food	5	2	7
4.2.5.3	Salted food	4	3	7
4.3.5.4.1	NDMA (n-nitrosodimethylamine)	2	4	6
4.3.5.4.1	Dietary nitrite	4	3	7
4.4.2	Acrylamide	0	2	2
4.4.2.5	Frying	5	2	7
4.4.2.6	Grilling (broiling) and barbecuing	3	0	3
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	5	1	6
5.1.2	Dietary fibre	3	1	4
5.1.2.1	Cereal fibre	1	1	2
5.1.2.2	Vegetable fibre	1	1	2
5.1.2.3	Fruit fibre	1	1	2
5.1.4	Mono/disaccharides	0	1	1
5.1.4	Sucrose	1	1	2
5.1.4	Sugars (as nutrients)	0	1	1
5.1.5	Glycaemic index	0	2	2
5.1.5	Glycaemic load	0	2	2
5.2	Total fat (as nutrients)	4	2	6
5.2.2	Saturated fatty acids	1	1	2
5.2.4.1.1	Serum DHA	0	1	1
5.2.4.1.2	Serum DPA	0	1	1
5.2.4.1.3	Serum EPA	0	1	1
5.2.5	Trans fatty acids	0	1	1
5.3.1	Methionine	0	1	1
5.4	Total alcohol (as ethanol)	23	17	40
5.5.0.1	Multivitamin supplement	7	4	11
5.5.0.1	Duration of multivitamin use	1	1	2

Exposure Code	Exposure Name	Number of publications (RCT/cohorts)		Total number of publications
		2005 SLR	CUP	
5.5.1	Vitamin A from food and supplements	0	1	1
5.5.1	Dietary vitamin A	1	3	4
5.5.1	Vitamin A supplement	1	1	2
5.5.1.1	Blood retinol	11	3	14
5.5.1.1	Dietary retinol	4	3	7
5.5.1.1	Retinol from food and supplements	0	1	1
5.5.1.2	Dietary beta-carotene	5	2	7
5.5.1.2	Beta-carotene supplement	6	1	7
5.5.1.2	Dietary alpha-carotene	1	1	2
5.5.1.2	Serum alpha-carotene	2	3	5
5.5.1.2	Serum beta-carotene	8	3	11
5.5.1.2	Dietary beta-cryptoxanthin	0	1	1
5.5.1.2	Serum beta-cryptoxanthin	0	3	3
5.5.1.2	Dietary provitamin A carotenoids	1	1	2
5.5.1.2	Serum provitamin A	0	1	1
5.5.2	Blood total carotenoids	3	1	4
5.5.2	Dietary lutein and zeaxanthin	1	1	2
5.5.2	Blood lutein and zeaxanthin	2	3	5
5.5.2	Blood lutein	0	1	1
5.5.2	Blood zeaxanthin	0	1	1
5.5.2	Blood canthaxanthin	0	2	2
5.5.2	Dietary lycopene	2	1	3
5.5.2	Blood lycopene	2	3	5
5.5.2	Blood xanthophylls	0	1	1
5.5.3	Total folate	2	1	3
5.5.3	Dietary folate	0	3	3
5.5.3	Folic acid supplements	1	1	2
5.5.3	Plasma folate	0	1	1
5.5.3	Plasma homocysteine	0	1	1
5.5.4	Riboflavin	0	1	1
5.5.7	Dietary pyridoxine (vitamin B6)	0	1	1
5.5.7	Blood pyridoxine (vitamin B6)	1	1	2
5.5.8	Dietary vitamin B12 intake	0	1	1
5.5.8	Plasma vitamin B12 intake	0	1	1
5.5.9	Dietary vitamin C	5	3	8
5.5.9	Vitamin C supplement	4	2	6
5.5.9	Blood vitamin C	5	3	8
5.5.10	Blood 25-hydroxyvitamin d	0	2	2

Exposure Code	Exposure Name	Number of publications (RCT/cohorts)		Total number of publications
		2005 SLR	CUP	
5.5.11	Dietary vitamin E	4	2	6
5.5.11	Vitamin E supplement	4	3	7
5.5.11	Dietary alpha-tocopherol	1	1	2
5.5.11	Blood alpha-tocopherol	1	3	4
5.5.11	Dietary gamma-tocopherol	1	1	2
5.5.11	Blood gamma-tocopherol	2	2	4
5.5.13	Antioxidant indices	0	1	1
5.6.2	Iron from food and supplements	0	1	1
5.6.2	Dietary iron	2	1	3
5.6.2	Dietary haem iron	1	4	5
5.6.2	Iron supplements	0	1	1
5.6.2	Serum iron	2	2	4
5.6.2	Serum ferritin	2	1	3
5.6.3	Calcium from food and supplements	0	1	1
5.6.3	Dietary calcium	2	1	3
5.6.3	Calcium supplements	0	3	3
5.6.4	Dietary selenium	0	1	1
5.6.4	Selenium supplement	2	1	3
5.6.4	Selenium, toenail	1	1	2
5.6.6	Serum phosphate	0	1	1
5.6.7	Zinc supplements	0	1	1
5.7.2	Urine isothiocyanates	0	1	1
5.7.4	Polyphenols	1	1	2
5.7.5	Genistein	0	1	1
5.7.5	Plasma genistein	0	2	2
5.7.5	Lignans	0	2	2
5.7.5	Plasma daidzein	0	2	2
5.7.5	Plasma enterolactone	0	1	1
5.7.5	Plasma equol	0	1	1
5.7.5	Plasma isoflavones	0	1	1
5.7.7	Total nitroso compounds	0	2	2
5.8	Anthocyanidins	0	1	1
5.8	Flavan-3-ols	0	1	1
5.8	Flavanones	0	1	1
5.8	Flavones	0	1	1
5.8	Flavonoids	2	1	3
5.8	Flavonols	0	1	1
5.8	Isoflavones	0	2	2

Exposure Code	Exposure Name	Number of publications (RCT/cohorts)		Total number of publications
		2005 SLR	CUP	
6.1	Physical activity	0	2	2
6.1	Physical activity index	0	1	1
6.1	Physical activity level	0	1	1
6.1	Physical activity score	0	1	1
6.1.1.1	Activity during working hours	1	2	3
6.1.1.2	Recreational activity	4	3	7
6.1.1.2	Leisure time physical activity score	0	1	1
6.1.1.2	Bicycling	0	1	1
6.1.1.2	Sports	0	1	1
6.1.1.2	Sports activity	0	1	1
6.1.1.2	Walking	0	1	1
6.1.1.3	Gardening	0	1	1
6.1.2	Frequency of physical activity	0	1	1
6.1.3	Vigorous physical activity	0	2	2
6.1.3.2	Intensity of recreational physical activity	0	1	1
6.1.3.2	Moderate and strenuous recreational activity	0	1	1
6.1.3.2	Moderate and strenuous recreational activity in late adulthood	0	1	1
6.1.3.2	Walking pace	1	1	2
6.1.4	Duration of physical activity	0	2	2
6.1.4.2	Duration of walking	0	1	1
6.2	Sitting	0	1	1
6.2	Television watching	0	2	2
7.1	Energy intake	7	1	8
7.1.0.1	Percent of energy from fat	2	1	3
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	2	2
7.1.0.1	Percent of energy from long-chain n-3 fatty acids	0	1	1
8.1.1	BMI	20	18	38
8.1.1	BMI at younger age (16 – 25 years)	4	4	8
8.1.1	BMI at 40 years	0	1	1
8.1.3	Weight	4	2	6
8.1.3	Weight at 20 years	0	1	1
8.1.5	Fat free mass	1	1	2
8.1.5	Fat mass	0	1	1
8.1.5	Body fat	1	1	2

Exposure Code	Exposure Name	Number of publications (RCT/cohorts)		Total number of publications
		2005 SLR	CUP	
8.1.6	BMI change	1	1	2
8.1.6	Weight change	0	1	1
8.2.1	Waist circumference	0	2	2
8.2.2	Hips circumference	0	1	1
8.2.3	Waist to hip ratio	0	1	1
8.2.5	Other marker for fat distribution e.g. CT, ultrasound	0	1	1
8.3.1	Height	9	10	19
8.4.1	Birth weight	2	2	4

1 Patterns of diet

No meta-analysis was conducted because of the differences across the patterns investigated in the studies. Study results are summarized in tables.

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

Dietary patterns by study design	Number of studies	Number of studies showing significant association
Randomised controlled trial		
Low fat diet	1	0 (stomach cancer was not primary or secondary outcome)
Cohort studies		
Health scores	3	1 (inverse association with healthier diet in women but not in men)
Diet diversity scores	1	0
Dietary patterns defined by factor analysis	1	1 (inverse association for dairy product pattern in men but not in women)
Diet preferences (vegetables, salt*, spicy food)	3	1 (inverse association for liking easily digested food, positive association for liking spicy food)
Vegetarians	8	2 (inverse association)
Mediterranean diet	3	1 (inverse association for all adenocarcinomas and gastric cardia, inverse but not significant for non-cardia)
Regional diet	3	3 (Inverse association of Western style breakfast in men but not in women, no association with Japanese breakfast (1 study); positive for traditional Japanese diet and no association with Western diet (1 study); positive for Western and traditional Japanese diet vs. Western diet only (1 study)
Seventh-day Adventists	3	1 (lower incidence) 2 lower mortality)
Breastfeeding - Mother	3	0
Breastfeeding - Child	1	0

*See section '4.2.5.1 Preference for salty food'.

Randomised controlled trials

One randomised controlled trial was identified: the Women's Health Initiative Dietary Modification Randomised Controlled Trial (Prentice, 2007). The intervention aimed to reduce total fat intake to 20% of energy and to increase consumption of vegetables, fruits, and grains. At 1 year, 3 years, and 6 years, the percentage of energy from fat were 10.7%, 9.5%, and 8.1% lower in the intervention group versus the comparison group, respectively. For the same comparison and time periods, consumption of vegetables and fruits was higher in the intervention group by 1.2, 1.3, and 1.1 servings, and grain consumption was higher by 0.9, 0.7, and 0.4 servings, respectively. The intervention group was lower in weight by an average of 1.9 kg at 1 year and 0.4 kg at 7.5 years versus the comparison group.

The intervention diet did not modify the incidence of stomach cancer compared with the usual diet (RR=1.10, 95% CI=0.55-2.19) Stomach cancer was not a primary or secondary cancer outcome in the trial. The trial was also negative for the primary cancer endpoints (breast and endometrial cancer) and the only effect was a reduction of ovarian cancer incidence.

Cohort studies

Health Scores

Three studies on “a priori” heath indices/diet scores were identified. A Swedish study reported that a score of low carbohydrate- high protein (LCHP) diets was largely unrelated to stomach cancer risk (Nilsson, 2013).

In the NIH-AARP cohort, a non-significant (inverse) association with higher concordance with the 2005 Dietary Guidelines for Americans was observed (Li, 2013). The study was adjusted for age, sex, race, BMI, smoking status, education, physical activity, and total energy intake.

One study identified in the 2005 SLR reported significant inverse association with higher concordance with a “healthy dietary pattern” in women after adjusting for BMI, energy intake, education, family history of stomach cancer, (Kim, 2004). Non-significant positive association was reported in men after additionally adjusting for alcohol drinking. A “healthy dietary pattern” was defined as high intakes of vegetables, fruits, soy products, seaweeds, mushroom, milk, beans and yogurt.

Diet diversity scores

Only one study on diet diversity scores was identified (EPIC cohort, Jeurnink, 2012). Non-significant (positive) association with stomach cancer were observed per each increment of two types of fruits, vegetables, or fruits and vegetables combined. Study adjustments included BMI, smoking, energy intake, red and processed meat consumption, and alcohol intake.

Dietary patterns defined by factor analysis

One study was identified. In this Japanese study (Pham, 2010), the “vegetables” and “animal foods” patterns were not significantly (positively) related to stomach cancer in men and women. A “dairy product pattern” was significantly inversely related to stomach cancer in men. The association was inverse but not significant in women. The study was adjusted for age, smoking status, history of gastric ulcer, BMI, education, and total energy intake. The “Vegetable” pattern did not include pickled vegetables.

Diet preferences

Three Asian studies investigated diet preferences. In a Korean study, meal irregularity and preference for animal products was non-significantly associated with higher risk of stomach cancer (Kim, 2010). In Japanese study (Iso, 2007), preference for fatty food (like compared to dislike) was associated with non-significant lower stomach cancer mortality. A Japanese study identified in the 2005 SLR (Inoue, 1996) reported significant inverse associations of stomach cancer risk for liking “easily digested food” (not defined in the publication) and positive association with liking “spicy food”. Positive but non-significant association was reported for liking greasy food. The comparisons were with not liking each food type. The analyses were only adjusted for age and sex.

Mediterranean Diet

The results of the three identified studies were discordant. The risk of gastric cardia adenocarcinoma risk was inversely associated with a Mediterranean Diet Score in the EPIC cohort (Buckland, 2010). A non-significantly (positive) associated with the Alternative Mediterranean Diet Score in the NIH-AARP cohort (Li, 2013). Both studies reported non-significant (inverse) associations of the scores with non-cardia adenocarcinoma. The analyses were adjusted for BMI, smoking, education, and total energy intake and in the NIH-AARP, also for physical activity and race. In the North Sweden cohort (VIP, Tognon, 2012), stomach cancer mortality was non-significantly (positive) associated with a Mediterranean Diet Score in men and women, and both combined.

Vegetarian Diet

In the study identified during the CUP, the EPIC-Oxford study, the incidence of stomach cancer was significantly lower in vegetarians than in meat eaters (Key, 2009). In the 2005 SLR the summary relative risk estimate of stomach cancer from seven additional cohort studies (five publications) was 0.88 (0.60-1.28) for vegetarians compared to non-vegetarians (p=0.4). Only one publication (two cohorts) reported lower stomach cancer risk in vegetarians compared to general population (Appleby, 2002a).

Regional Diet

One study was identified in the CUP and two studies were identified in the 2005 SLR. In a Japanese study (Iso, 2007), stomach cancer mortality was significantly inversely related with consumption of Western-style breakfast (usually versus not usually) in men but not in women and it was not related (non-significant positive association) to Japanese-style breakfast. In a Japanese study identified in 2005 SLR, individuals with a diet composed of a mixture of Oriental foods with a majority of Western foods had higher risk of stomach cancer compared to those who ate mostly Western foods (Nomura, 1990). Using a dietary pattern derived from factor analysis, Kim, 2004 found that the traditional Japanese dietary pattern, which was closely correlated with the intake of salted food such as salted fish roe, salted fish preserves, pickled vegetables, dried fish, and miso soup, was significantly associated with an increased risk of stomach cancer in both sexes.

Seventh-day Adventists

No new studies were identified in the CUP. Three cohort studies (five publications) were included in the 2005 SLR meta-analysis. One cohort reported lower mortality and incidence, one cohort reported lower morality and one cohort reported lower morality but not lower incidence of stomach cancer in Seventh-day Adventists compared to non Adventists. The summary relative risk was 0.60 (0.44-0.80) when comparing Seventh-day Adventists with Non Seventh-day Adventists (p=0.001).

Breastfeeding – Mother

Two studies were identified in the CUP and one study was identified in the 2005 SLR. None of the studies reported significant associations of stomach cancer with breastfeeding (Kvale, 1988; Persson, 2008a; Duell, 2010).

Breastfeeding – Child

No new studies were identified in the CUP. In a historical cohort, having been breast-fed compared with never having been breast-fed, was not associated with the incidence of gastric cancer (Martin, 2005).

Table 3 Dietary patterns and stomach cancer risk. Results of meta-analyses of prospective studies published after the 2005 SLR

Author, Year	Number of studies	Total number of cases	Studies country, area	Outcome	Comparison	RR (95%CI)	P trend	Heterogeneity (I^2, p value)
Meta-analysis								
Bertuccio, 2013	3 cohort, 5 case-control studies	2437	Europe, North America, South America, Asia	Incidence Gastric cancer	'Prudent/healthy' dietary pattern, highest vs. lowest intake level	0.75 (0.63-0.90)		58.9%, p=0.009
	3 cohorts					0.71 (0.58-0.88)		
	3 case-control studies	645		Cardia cancer		0.76 (0.61-0.94)		0%, p=0.67
	3 cohort, 4 case-control studies	1792		Distal/NOS cancer		0.75 (0.58-0.97)		71.5%, p=0.002
	3 cohort, 5 case-control studies	2440		Incidence Gastric cancer	'Western/unhealthy' dietary pattern, highest vs. lowest intake level	1.51 (1.21-1.89)		58.6%, p=0.01
	3 cohorts					1.67(1.32-2.10)		
	3 case-control studies	645		Cardia cancer		2.05 (1.51-2.87)		0%, p=0.63
	3 cohort, 4 case-control studies	1795		Distal/NOS cancer		1.36 (1.07-1.73)		56.4%, p=0.03

Table 4 Dietary patterns and stomach cancer risk. Number of studies in the CUP SLR

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
Prentice, 2007 STM80158 USA	WHI-DM, Randomised Control Trial, Age: 50-79 years, Post-menopausal women	33/ 48 835 8 years	Self -report, medical record and pathology report reviewed by centrally trained physician	Intervention: reduce total fat intake to 20% energy intake, increase consumption of vegetables, fruits, and grains Control: usual diet Baseline diet measured by FFQ	Incidence, stomach cancer	Low fat (intervention) vs. usual diet	1.10 (0.55-2.19)	Stratified by age, randomisation status in the WHI hormone therapy trial

Patterns of diet (cont.)

Cohort studies

NOTE: Preference for salty food is discussed in a section about salt 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
Health index scores								
Li, 2013 STM80193 USA	NIH- AARP, Prospective Cohort, Age: 50-71 years, M/W, Retired	453/ 494 968 9.7 years	Cancer registry, death master file, national death index plus, postal service database	Dietary Guidelines for Americans (grains, vegetables, legumes, fruits, milk, meat, fish, oils, saturated fat, sodium, alcohol, added sugar) Validated 124- item FFQ	Incidence, cardia adenocarcinoma	5 vs. 1 quintile	0.92 (0.67-1.27) Ptrend:0.56	Age, sex, BMI, race, education, smoking, total energy intake, usual physical activity, vigorous physical activity
		501/			Non-cardia adenocarcinoma		0.88 (0.65-1.20) Ptrend:0.15	
Nilsson, 2013 STM80169 Sweden	VIP, Prospective Cohort, Age: 30- years, M/W	69/ 62 582 9.7 years	Cancer registry	Low Protein- High Carbohydrate (LPHC) score; descending deciles of energy-adjusted carbohydrate and ascending deciles of energy-adjusted protein assigned to1 to 10 points FFQ & 24-hr dietary recall	Incidence, stomach cancer	High vs. low points	0.84 (0.40-1.79) Ptrend:0.53	Age, sex, energy intake, obesity, alcohol, education, saturated fat, sedentary behaviour, smoking

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors
Kim, 2004 STM24497 Japan	JPHC I, Prospective Cohort, Age: 40-59 years, M/W	285 men, 115 women/ 42 112 10 years	Hospital records, population-based cancer registries and death certificates, histologically confirmed	Healthy dietary pattern (vegetables, fruits, soy products, seaweeds, mushroom, milk, beans and yogurt) FFQ	Incidence, stomach cancer Men Women	4 vs. 1quantile	1.13 (0.78-1.63) Ptrend:0.39 0.56 (0.32-0.96) Ptrend:0.03	Age, alcohol consumption, BMI, educational level, energy intake, family history of stomach cancer, smoking habits
Diet diversity scores								
Jeurnink, 2012 STM80067 10 European countries	EPIC, Prospective Cohort, Age: 35-70 years, M/W	180/ 452 269 8.4 years	Cancer registries, health insurance records, pathology records, active follow-up, death certificate	Diet Diversity Score (DDS) –number of different vegetables and fruits eaten at least once in two weeks. FFQ, dietary questionnaires and food record	Incidence, Non-cardia adenocarcinoma	DDS vegetables and fruits (range 0–40) Per increment of 2 types fruits and vegetables	1.06 (0.98-1.14)	Stratified by age, gender, centre; adjusted for smoking, BMI, energy intake, red and processed meat, alcohol
						DDS vegetables (range 0–26) Per increment of 2 types of vegetables	1.07 (0.97-1.19)	Additionally adjusted for fruit consumption
						DDS fruits (range 0–14) Per increment of 2 types of fruits	1.33 (0.76-2.33)	Additionally adjusted for vegetable consumption
***A posteriori* dietary patterns**								

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors
Pham, 2010 STM80104 Japan	JACC, Prospective Cohort, Age: 40-79 years, M/W	320 men, 157 women/ 63 403 327 630 person-years	Death certificate	Dietary patterns defined by factor analysis Validated 38 food item FFQ	Mortality, stomach cancer Men Women	Vegetable pattern 4 vs. 1 quartile	1.15 (0.83-1.59) Ptrend:0.47 0.99 (0.63-1.57) Ptrend:0.83	Age, BMI, education level, stomach disorders, history of gastric ulcer, stomach cancer screening, tobacco use, total energy intake
					Men Women	Animal food pattern 4 vs. 1 quartile	1.02 (0.73-1.45) Ptrend:0.90 1.31 (0.78-2.21) Ptrend:0.41	
					Men Women	Dairy product pattern 4 vs. 1 quartile	0.72 (0.52-0.99) Ptrend:0.03 0.77 (0.48-1.23) Ptrend:0.17	
Diet preference								
Kim, 2010 STM80099 Korea	KNHIC, Prospective Cohort, Age: 30-80 years, M/W	12 393 total, 9620 men, 2773 women/ 2 248 129 7 years	Cancer registry	Self-administered questionnaire	Incidence, stomach cancer All Men Women	Meal regularity: irregular vs. regular	1.04 (0.97-1.11) 1.05 (0.97-1.13) 1.00 (0.89-1.13)	Age, sex, alcohol consumption, BMI, family history of cancer, physical activity, smoking habits
					All Men Women	Preference for animal products vs. mostly vegetables	1.01 (0.94-1.09) 1.00 (0.92-1.08) 1.04 (0.86-1.26)	

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors
Iso, 2007 STM80144 Japan	JACC, Prospective Cohort, Age: 40-79 years, M/W	763 men, 373 women/ 105 500 15 years	Municipal resident registration records, death certificates	Validated FFQ	Mortality, stomach cancer Men Women	Preference for fatty food (like vs. dislike)	0.83 (0.68-1.02) Ptrend:<0.10 0.98 (0.76-1.26)	Age, area of study
Inoue, 1996 STM06116 Japan	HERPACC, Prospective Cohort, M/W, Endoscopy patients	69/ 5 373 6 years	Hospital records, cancer registry, death certificates	FFQ	Incidence, stomach cancer	Greasy food liked vs. not liked	1.70 (0.88-3.29)	Age, sex
						Easily digested food liked vs. not liked	0.45 (0.26-0.77)	
						Spicy food liked vs. not liked	1.86 (1.03-3.34)	
Mediterranean Diet								
Li, 2013 STM80193 USA	NIH- AARP, Prospective Cohort, Age: 50-71 years, M/W, Retired	453/ 494 968 9.7 years	Cancer registry, death master file, national death index plus, postal service database	Alternative Mediterranean Diet (aMED) score components: vegetables, legumes, fruit, nuts, whole grains, fish, ratio of monounsaturated to saturated fat, meat, alcohol Validated 124- item FFQ	Incidence, cardia adeno-carcinoma	7-9 vs. 0-2 (score)	1.10 (0.76-1.61) Ptrend:0.90	Age, sex, BMI, race, education, smoking, total energy intake, usual physical activity, vigorous physical activity
		501/			Non-cardia adenocarcinoma		0.75 (0.52-1.09) Ptrend:0.11	

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
Tognon, 2012 STM80190 Sweden	VIP, Prospective Cohort, Age: 30-60 years, M/W	52 total, 31 men and 21 women/ 77 151 9 years	VIP database with the Swedish national cause-of-death registry	Modified Mediterranean Diet score components: vegetables and potatoes, fruit and juices, whole-grain cereals, fish and fish products, ratio of polyunsaturated to saturated fat, alcohol, meat, dairy products 84-item validated FFQ	Mortality, stomach cancer All	Per 1 point score increase	1.14 (0.96-1.35)	Age, sex, obesity, physical activity, smoking status, education
					Men		1.07 (0.85-1.34)	
					Women		1.24 (0.95-1.64)	
Buckland, 2010 STM80128 10 European countries	EPIC, Prospective Cohort, Age: 35-70 years, M/W	449/ 485 044 8.9 years	Pathology review	Mediterranean Diet (rMED) score components: vegetables, legumes, fruit, cereal, fish and seafood, olive oil, alcohol, meat, dairy products FFQ, dietary questionnaires and food record	Incidence, gastric adeno-carcinoma	11-18 vs. 0-6	0.67 (0.47-0.94) Ptrend:0.02	Stratified by centre and age, adjusted for sex, BMI, education level, smoking status, smoking intensity, total energy intake
		132/			Cardia adeno-carcinoma		0.45 (0.21-0.91) Ptrend:0.04	
		206/			Non-cardia adenocarcinoma		0.71 (0.44-1.17) Ptrend:0.15	
Vegetarian Diet								
Key, 2009 STM80125 UK	EPIC-Oxford Cohort and Oxford Vegetarian Study,	49/ 61 566 12.2 years	United Kingdom's National Health Service Central Register	Semi-quantitative FFQ	Incidence, stomach cancer	Vegetarian vs. meat eater	0.36 (0.16-0.78)	Age, sex, alcohol consumption, BMI, study/method of recruitment, physical activity level, smoking

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors
	Prospective Cohort, Age: 20-89 years, M/W							
Chang-Claude, 2005 STM44318 Germany	German Vegetarian Study, Prospective Cohort, Age: 10- years, M/W Vegetarians and healthy-eaters	11/ 1 904 21 years	Family, GP, death certificate	FFQ	Mortality, stomach cancer	SMR of vegetarians vs. general population	91.00 (51.00-163.00)	Age, sex
Appleby, 2002a STM44257 UK	Oxford Vegetarian Study, Prospective Cohort, M/W	10/ 11 045 17.6 years	Health registers	FFQ	Mortality, stomach cancer	SMR of vegetarians vs. general population	26 (7-67)	Age
	Health Food Shoppers Study, Prospective Cohort , Age: 16-89 years, M/W,	16/ 10 736 18.7 years					59.00 (34.00-95.00)	

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors
	Health Conscious							
Key, 1999	Adventist Health study	26/28 952	Record linkage with death certificate file, the National Death Index and church records		Mortality, stomach cancer	Death rate ratios of vegetarians vs. non-vegetarians	1.58 (0.68-3.70)	Age, sex, smoking
	Adventist Mortality study	30/24 538	Record linkage and personal contact				0.64 (0.30-1.36)	
Kinlen, 1983 STM09066 England	Vegetarian Society, Manchester and London, UK, Historical Cohort, M/W	25/ 759 35 years	NHS central registry	Lifestyle grouping	Mortality, stomach cancer	SMR of vegetarians vs. general population	1.33 (0.62-2.54)	Age, sex
Kinlen, 1982 STM44288 UK	Oxford Nuns, UK, Historical Cohort, W	31/ 2 334 68 years	NHS central registry	Lifestyle grouping	Mortality, stomach cancer	SMR of no meat group vs. general population	0.95	Age
Regional Diets								
Iso, 2007 STM80144	JACC, Prospective	763 men, 373	Municipal resident registration	Validated FFQ	Mortality, stomach cancer	Type of breakfast Japanese style	Men: 1.19 (0.93-1.53)	Age, area of study

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors
Japan	Cohort, Age: 40-79 years, M/W	women/ 105 500 15 years	records, death certificates			Usually vs. not usually	Women: 1.23(0.83-1.73)	
						Western style Usually vs. not usually	Men: 0.66 (0.50-0.89) Ptrend:<0.01 Women: 0.88 (0.63-1.24)	
Kim, 2004 STM24497 Japan	JPHC I, Prospective Cohort, Age: 40-59 years, M/W	285 men, 115 women/ 42 112 10 years	Hospital records, population-based cancer registries and death certificates, histologically confirmed	Traditional dietary pattern (pickled vegetables, salted fish, roe, fish, rice, miso soup with a negative loading for bread and butter; sake, shochu, beer for men) FFQ	Incidence, stomach cancer	Traditional dietary pattern 4 vs. 1quantile	Men: 2.88 (1.76-4.72) Ptrend:<0.001 Women: 2.40 (1.32-4.35) Ptrend:<0.01	Age, alcohol consumption (in men), BMI, educational level, energy intake, family history of stomach cancer, smoking habits
				Western dietary pattern (meat, poultry, cheese, bread, butter, soft drinks, tea, coffee, alcohol (for men) FFQ	Incidence, stomach cancer	Western dietary pattern 4 vs. 1quantile	Men: 0.85 (0.60-1.38) Ptrend:0.45 Women: 1.13 (0.66-1.93) Ptrend:0.42	
Nomura, 1990 STM14814 USA	HHP, Prospective Cohort, Age: 45- years, M, Japanese residents of	150/ 7 990 10.6 years	Cancer registry/ hospital records	17-item FFQ	Mortality, stomach cancer	Mixed diet (oriental and western) vs. western diet	2.10 (1.10-4.10)	Age

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors
	Hawaii							
Seventh-day Adventists								
Mills, 1994 STM44313 USA	AHS, Prospective Cohort, M/W, Seventh Day Adventists	15 men, 4 women/ 31 208 6 years	Cancer registry	FFQ	Incidence, stomach cancer Men	SMR (with general population)	0.50 (0.23-0.95)	Age
					Women		0.16 (0.03-0.52)	
Kuratsune, 1986 STM14021 Japan	JSDA, Prospective Cohort, M/W, Seventh Day Adventists	3 men, 4 women/ 6 742 6 years	Population registry/church records	Lifestyle grouping	Mortality, stomach cancer Men	SMR (with general population)	0.32 (p<0.05)	Age
					Mortality, stomach cancer Women		0.26 (p<0.05)	
Berkel, 1983 STM44283 Netherlands	DSDA, Prospective Cohort, Age: 10-100 years, M/W, Seventh Day Adventists	16/ 3 217 10 years	Population registry	Lifestyle grouping	Mortality, stomach cancer	SMR (with general population)	0.59 (0.34-0.96)	Age
Jensen, 1983 STM44286 Denmark	DSDA, Prospective Cohort, M, Temperance	10/ 1 589 24 years	Cancer registry	Lifestyle grouping	Incidence, stomach cancer	SMR (with Copenhagen men)	1.10 (0.50-2.00)	Age, sex

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors
	Society members							
Lemon, 1964 STM44312 USA	AHS, Prospective Cohort, Age: 11- years, M/W, Seventh Day Adventists	25 men, 22 women/ 47 866 5 years	Membership records, follow-up mailing, confirmed by death certificates	Lifestyle grouping	Mortality, stomach cancer Men	SMR (with general population)	75.76	Age
					Women		66.67	
Breastfeeding - Mother								
Duell, 2010 STM80076 10 European studies	EPIC, Prospective Cohort, Age: 51 years, W	181/ 335 216 8.7 years	Cancer registries, health insurance records, pathology records and active follow-up	Questionnaire	Incidence, gastric adeno-carcinoma	Yes vs. no	0.83 (0.59-1.17)	Age, BMI, centre, red meat intake, smoking status, vegetable and fruit intake, calorie adjusted, education
Persson, 2008a STM80187 Japan	JPHC, Prospective Cohort, Age: 40-69 years, W	324/ 44 453 12 years	Active patient notification from hospitals, cancer registries and death certificates	Questionnaire	Incidence, stomach cancer (72% non-cardia)	Ever vs. never	Premenopausal women 1.00 (0.72-1.39)	Age, study area, family history of gastric cancer
		290/					Post-menopausal women 1.29 (0.95-1.77)	
Kvåle, 1988 STM07360 Norway	NCS, Prospective Cohort, Age: 27-69	372/ 48 607 19 years	Cancer registry	Questionnaire	Incidence, stomach cancer	Per 2 months increase in lactation duration	1.03 Ptrend:0.40	Age, parity, urban/rural

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors
	years, W							
Breastfeeding - Child								
Martin, 2005 STM80005 UK	BOCS, Historical Cohort, Age: 0-19 years, M/W	25/ 4 379 55 years	Cancer registry	Interview	Incidence, stomach cancer	Ever having been breastfed vs. never	1.22 (0.47-3.15)	Sex, area of residence, birth order, childhood socio-economic status, household expenditure on food
		23/			Mortality		1.43 (0.51-4.01)	

2 Foods

2.2 Total fruit and vegetables

Randomised controlled trials

See section on Dietary patterns. A diet low in fat and with increased consumption of fruits, vegetables and grains did not modify stomach cancer risk when compared to usual diet (Prentice, 2007).

Cohort studies

Summary

Main results:

Five studies (1588 cases) out of eight studies were included in the dose-response meta-analysis. No significant associations of fruit and vegetable consumption were observed for stomach cancer, gastric cardia cancer – 2 studies, no heterogeneity and non-cardia gastric cancer – 2 studies, low heterogeneity.

Three studies could not be included in the meta-analysis. One study reported significant inverse associations for all participants combined (Terry, 1998) and one study for men but not women (McCullough, 2001). No significant association was observed in the third study (Chyou, 1990).

High heterogeneity was observed. Earlier studies tended to show stronger inverse associations (visual inspection of forest plot). There was significant evidence of publication or small study bias (p=0.02). Visual inspection of funnel plots suggests smaller studies with a positive association were missing. A small study on Japanese in Hawaii reported an inverse association stronger of what could be expected by random variation (see funnel plot).

Two studies reported results by smoking status (Gonzalez, 2012; Larsson, 2006c). Among never smokers, one study (Gonzalez, 2012) reported a non-significant association and one study (Larsson, 2006c) reported a significant inverse association. Among current/ever smokers, both studies reported non-significant inverse associations.

Sensitivity analyses:

The summary RRs ranged from 0.90 (95% CI=0.81-1.00) when Freedman, 2008 (31.4% weight) to 0.97 (95% CI=0.93-1.02) when Galanis, 1998 (3.6% weight) were omitted in influence analysis.

Non-significant associations were observed in most stratified analyses, apart from the analyses with studies of 5 – 10 years follow-up, not adjusted for BMI/physical activity, or adjusted for comorbidities. The significant inverse association observed in these analyses could be explained by Larsson, 2006c which contributed 37.7% - 39.3% weights (graphs not shown).

Non-linear dose-response meta-analysis:

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

Study quality:

The study showing the strongest inverse association (Galanis, 1998) examined fresh fruit and raw vegetables intake in Japanese residents of Hawaii. Loss to follow-up due to migration was estimated to be 10.7% in this study. Only 108 cases were included in the analysis.

Cancer outcome was confirmed using medical notes or records in cancer registries in most studies.

All studies used FFQ to assess fruit and vegetable intake. Other methods were used in addition to the country-specific questionnaires in EPIC (Gonzalez, 2012). Gonzalez, 2012 was the only study that corrected for measurement error of diet. A borderline significant inverse association was observed with the calibrated intake.

All studies included in the dose-response analysis were adjusted for age, sex, and socioeconomic status. None of the studies were adjusted for Helicobacter pylori status.

Table 5 Fruit and vegetable intake and stomach cancer risk. Number of studies in the CUP SLR

	Number
Studies identified	8
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

Table 6 Fruit and vegetable intake and stomach cancer risk. Summary of the linear dose-response meta-analysis in the 2005 SLR and CUP

	2005 SLR	**CUP**
Increment unit used	100g/day	100g/day
All studies		
Studies (n)	2	5
Cases (total number)	372	1588
RR (95%CI)	0.81 (0.58-1.14)	0.95 (0.89-1.01)
Heterogeneity (I^2, p-value)	81.5%, 0.02	67.0%, 0.02
P value Egger test	-	0.02
Stratified and sensitivity analysis*		
Sex	**Men**	**Women**
Studies (n)	2	2
RR (95%CI)	0.76 (0.41-1.41)	0.96 (0.74-1.25)

Heterogeneity (I^2, p-value)	85.6%, 0.01	32.2%, 0.23
Cancer subsite	**Gastric cardia cancer**	**Non-cardia gastric cancer**
Studies (n)	2 (n=399)	2 (n=519)
RR (95%CI)	0.97 (0.91-1.02)	1.01 (0.97-1.06)
Heterogeneity (I^2, p-value)	0%, 0.85	18.8%, 0.27
Geographic location	**Europe**	**North America****
Studies (n)	3	2
RR (95%CI)	0.95 (0.88-1.01)	0.82 (0.52-1.29)
Heterogeneity (I^2, p-value)	41.7%, 0.18	86.7%, 0.01

* No stratified analysis in the 2005 SLR **One study in North America was in Japanese residents in Hawaii

Other stratified analysis

Duration of follow-up	**<5 years**	**5-<10 years**	**≥10 years**
Studies (n)	1	2	2
RR (95%CI)	1.01 (0.96-1.06)	0.90 (0.83-0.98)	0.81 (0.53-1.24)
Heterogeneity (I^2, p-value)	-	0%, 0.43	85%, 0.01
Number of cases	**<200 cases**	**200-<400 cases**	**≥400 cases**
Studies (n)	2	2	1
RR (95%CI)	0.77 (0.57-1.03)	0.98 (0.91-1.06)	0.98 (0.94-1.02)
Heterogeneity (I^2, p-value)	65.7%, 0.09	45.8%, 0.17	-
Adjustment for:			
Ethnicity	**Not adjusted**	**Adjusted**	
Studies (n)	3	2	
RR (95%CI)	0.95 (0.88-1.01)	0.82 (0.52-1.29)	
Heterogeneity (I^2, p-value)	41.7%, 0.18	86.7%, 0.01	
Alcohol/energy intake*			
Studies (n)	2	3	
RR (95%CI)	0.79 (0.55-1.15)	0.98 (0.93-1.03)	
Heterogeneity (I^2, p-value)	78.6%, 0.03	53.2%, 0.12	
BMI/physical activity**			
Studies (n)	3	2	
RR (95%CI)	0.85 (0.73-0.99)	0.99 (0.96-1.02)	
Heterogeneity (I^2, p-value)	58.5%, 0.09	0%, 0.39	
Comorbidities***			

Studies (n)	3	2	
RR (95%CI)	0.97 (0.90-1.05)	0.90 (0.83-0.98)	
Heterogeneity (I^2, p-value)	74.5%, 0.02	0%, 0.43	

*and** The same adjustments were made in the studies

***Larsson, 2006c adjusted for diabetes; Botterweck, 1998 adjusted for stomach disorders

Table 7 Fruit and vegetable intake and stomach 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
Gonzalez, 2012 STM80139 Denmark,France ,Germany,Greec e,Italy,Netherlan ds,Norway,Spai n,Sweden,U.K.	EPIC, Prospective Cohort, Age: 35-70 years, M/W	683/ 477 312 11.02 years	Cancer registries, health insurance records, pathology rec, active follow up, death certificate	FFQ, dietary questionnaires, food record	Incidence, gastric adenocarcinoma	≥610.7 (M)/547.1(W) vs. ≤187.4 (M)/233.4 (W) g/day	0.77 (0.57-1.04) Ptrend: 0.02	Age, sex, BMI, centre, educational level, energy intake, physical activity, alcohol intake, red and processed meat, smoking	
					All	Per 100 g/day	0.98 (0.94-1.02)		
		240/			Never smokers		1.00 (0.94-1.07)		
		206/			Former smokers		0.99 (0.92-1.06)		
		225/			Current smokers		0.93 (0.86-1.00)		
		201/			Gastric cardia adenocarcinoma	≥610.7 (M)/547.1(W) vs. ≤187.4 (M)/233.4 (W	0.90 (0.51-1.58) Ptrend: 0.17		
						Per 100 g/day	0.96 (0.88-1.04)		
		323/			Non-cardia gastric adenocarcinoma	≥610.7 (M)/547.1(W) vs. ≤187.4 (M)/233.4 (W	0.70 (0.45-1.08) Ptrend: 0.12		
						Per 100 g/day	0.99 (0.94-1.05)		
		203/			Intestinal gastric cancer	≥610.7 (M)/547.1(W) vs. ≤187.4 (M)/233.4 (W	0.71 (0.42-1.22) Ptrend: 0.16		

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Missing data derived for analyses
						Per 100 g/day	0.99 (0.92-1.06)		
		217/			Diffuse gastric cancer	≥610.7 (M)/547.1(W) vs. ≤187.4 (M)/233.4 (W	0.73 (0.42-1.28) Ptrend: 0.20		
						Per 100 g/day	0.96 (0.89-1.03)		
Freedman, 2008 STM80097 USA	NIH-AARP, Prospective Cohort, Age: 50-71 years, M/W, Retired	394/ 490 802 4.5 years	Linkage with 11 state cancer registry databases	Validated 124-item FFQ	Incidence, stomach cancer All	5.81 vs. 1.51 serving/ 1000kcal	0.91 (0.64-1.30) Ptrend: 0.78	Age, sex, BMI, ethnicity, alcohol intake, cigarette-smoke-dose, education, total energy, usual activity throughout the day, vigorous physical activity	Intake values using mean energy intake
						Per 1 serving/ 1000 kcal	1.01 (0.95-1.08)		
		313/ 292 898			Men	Per 1 serving/ 1000 kcal	1.00 (0.93-1.08)		
						5.81 vs. 1.51 serving/ 1000kcal	0.86 (0.58-1.29) Ptrend: 0.65		
		81/ 197 904			Women	5.81 vs. 1.51 serving/ 1000kcal	1.19 (0.52-2.70) Ptrend: 0.86		
						Per 1 serving/ 1000 kcal	1.03 (0.92-1.16)		
		198/			Gastric cardia cancer	5.81 vs. 1.51 serving/000kcal	0.77 (0.44-1.33) Ptrend: 0.33		
						Per 1 serving/ 1000 kcal	0.96 (0.87-1.06)		
		196/			Non-cardia	5.81 vs. 1.51	0.97 (0.61-1.54)		

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Missing data derived for analyses
					gastric cancer	serving/ 1000kcal	Ptrend: 0.60		
						Per 1 serving/ 1000 kcal	1.05 (0.97-1.14)		
Larsson, 2006c STM80086 Sweden	SMC and COSM, Prospective Cohort, Age: 45-83 years, M/W	139/ 82 002 7.2 years	Cancer registry/ mortality registry	96-item validated FFQ	Incidence, stomach cancer All	≥5.0 vs. <2.0 servings/day	0.54 (0.32-0.91) Ptrend: 0.06	Age, sex, diabetes, smoking status, alcohol intake, education, pack years of smoking, processed meat intake, total energy intake	Exposure values using standard portion size, mid-points of exposure categories
		60/			Never smokers		0.38 (0.17-0.88)		
		79/			Ever smokers		0.66 (0.33-1.32)		
		84/ 45 338			Men		0.50 (0.25-0.97)		
		55/ 36 664			Women		0.53 (0.21-1.31)		
Botterweck, 1998 STM04445 Netherlands	NLCS, Case Cohort, Age: 55-69 years, M/W	264/ 120 852 6.3 years	Cancer registry	Validated 150-item self-administered semi-quantitative FFQ	Incidence, stomach cancer	544 vs. 190 g/day	0.72 (0.48-1.1) Ptrend: 0.14	Age, sex, educational level, family history of stomach cancer, smoking habits, stomach disorders	-
Galanis, 1998 STM04769 USA	Hawaii-Japan DOH Survey, Prospective Cohort,	108/ 11 907 14.8 years	Cancer registry	19-item FFQ	Incidence, stomach cancer All	≥14 vs. 0-7 times/week	0.50 (0.30-0.80) Ptrend: 0.02	Age, sex , educational level, place of birth; smoking	Exposure values using standard portion size, mid-points of
		44/			Women		0.70 (0.30-1.70)		

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Missing data derived for analyses
	Age: 18- years, M/W, Japanese residents of Hawaii	6297					Ptrend: 0.22	and alcohol consumption (in men only)	exposure categories
		64/ 5610			Men		0.40 (0.20-0.80) Ptrend: 0.04		

Table 8 Fruit and vegetable intake and stomach 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
McCullough, 2001 STM02243 USA	CPS II, Prospective Cohort, Age: 30- years, M/W	1349970 045 14 years 910/ 436 654	Death register/ subject or family	32-item FFQ	Mortality, stomach cancer Men	>21.5 vs. 0-13.4 days/week	0.79 (0.67-0.93) Ptrend: 0.003	Age, aspirin use, BMI, smoking habits, educational level, ethnicity/ race, family history of stomach cancer, multivitamin supplement, vitamin c supplement	Exposure is sum of plant food score
		439/ 533 391			Women	>23.5 vs. 0-15.4 days/week	1.18 (0.93-1.5) Ptrend: 0.16		
Terry, 1998 STM04864 Sweden	Swedish Twin Registry, Prospective Cohort, Age: 67years, M/W,	116/ 11 546 21 years	Cancer registry	23-item FFQ	Incidence, stomach cancer	None/very little vs. high	5.53 (1.67-18.31) Ptrend <0.05	Age, sex, BMI, alcohol consumption, childhood socio-economic status, smoking habits	Exposure levels not quantified, no number of cases or comparison subjects per

Author, Year, 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
									exposure level
Chyou, 1990 STM12425 USA	HHP, Case Cohort, Age: 58years, M, Japanese residents of Hawaii	111/ 8006 18 years	Cancer registry/ hospital records	24-hour dietary recall	Mortality, stomach cancer	Vegetables and fruits Higher vs. < median intake	0.7	Age, smoking habits	No confidence intervals

Figure 1 RR estimates of stomach cancer by levels of fruit and vegetable intake

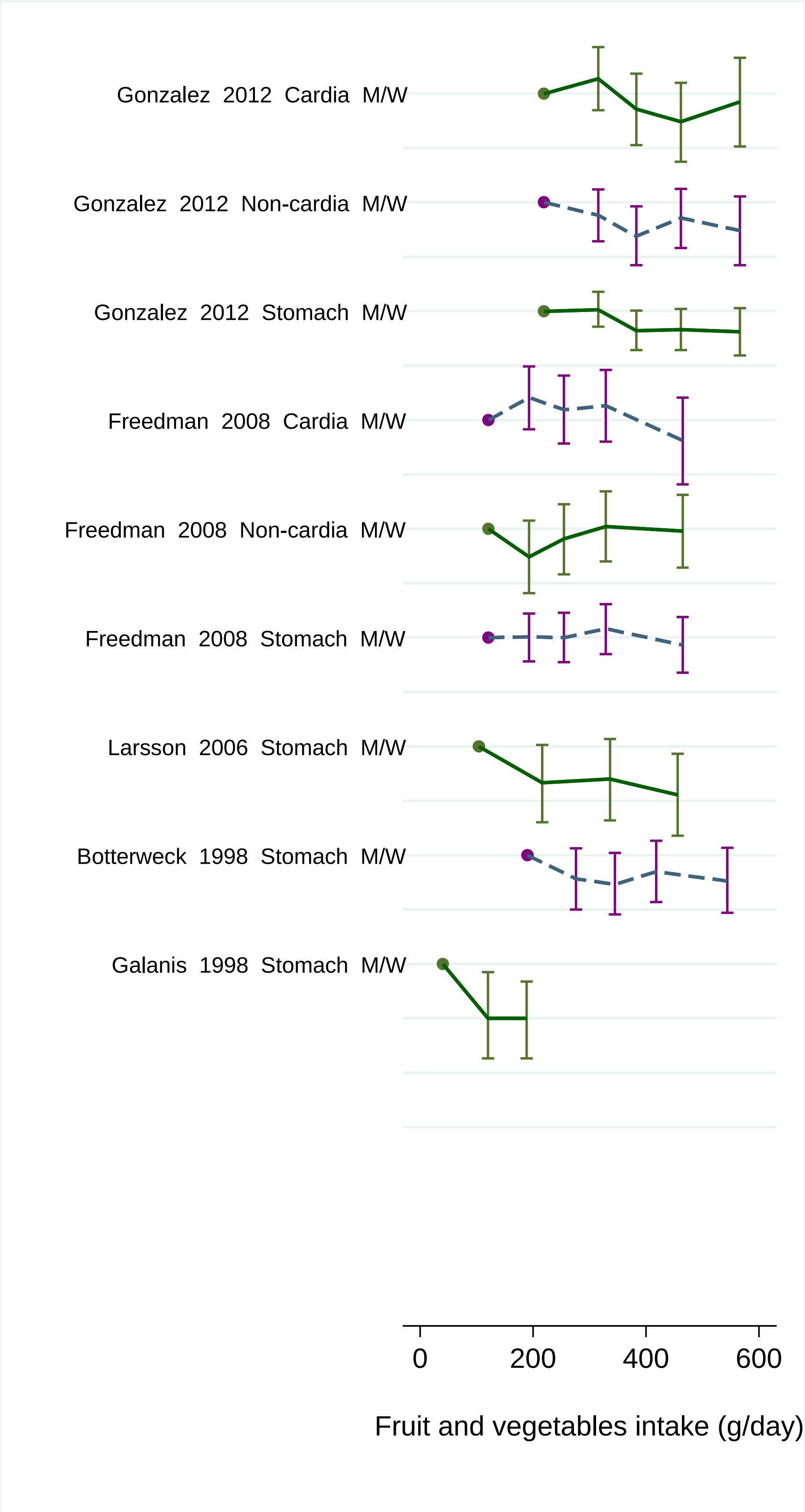


Figure 2 RR (95% CI) of stomach cancer for the highest compared to the lowest level of fruit and vegetable intake

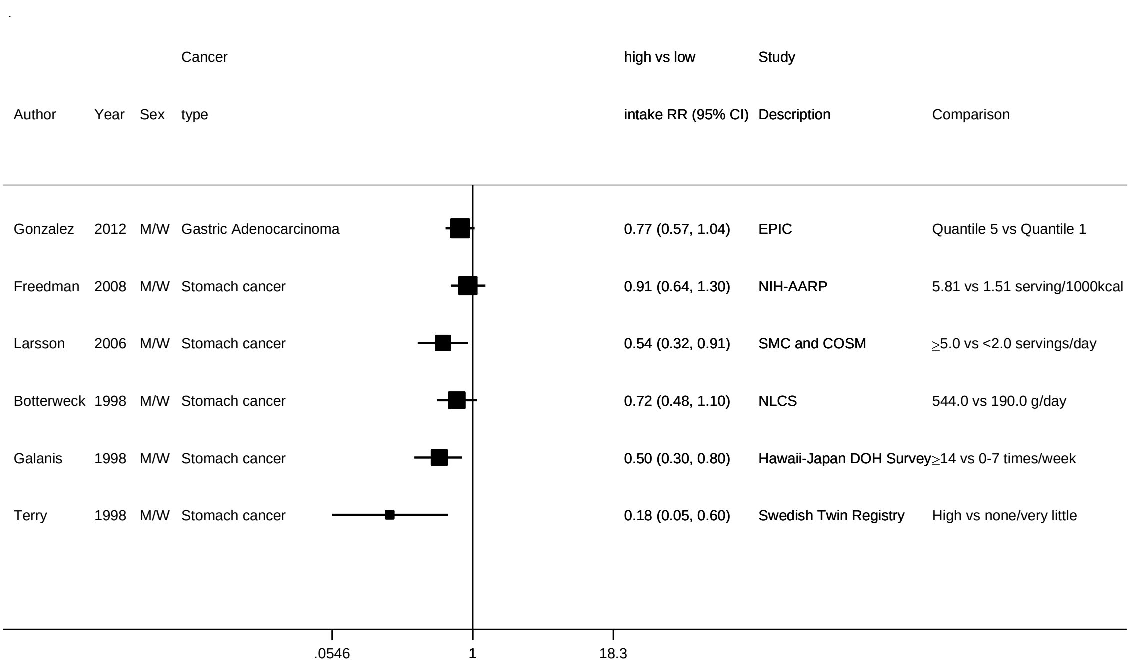


Figure 3 Relative risk of stomach cancer for 100g/day increase of fruit and vegetable intake

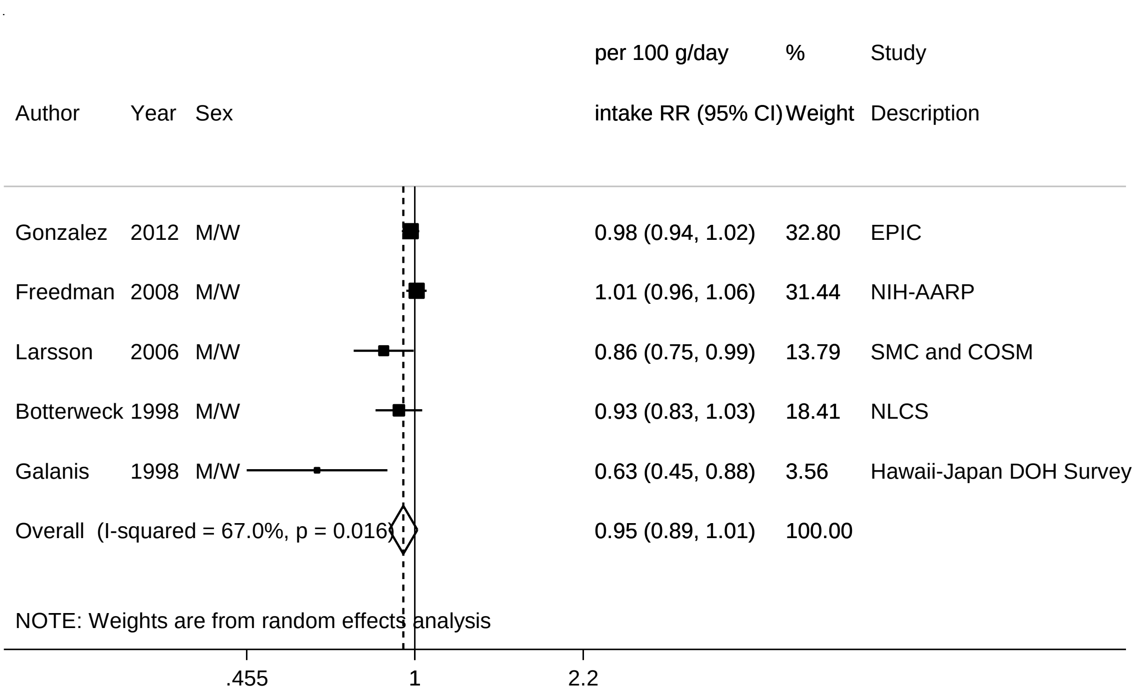
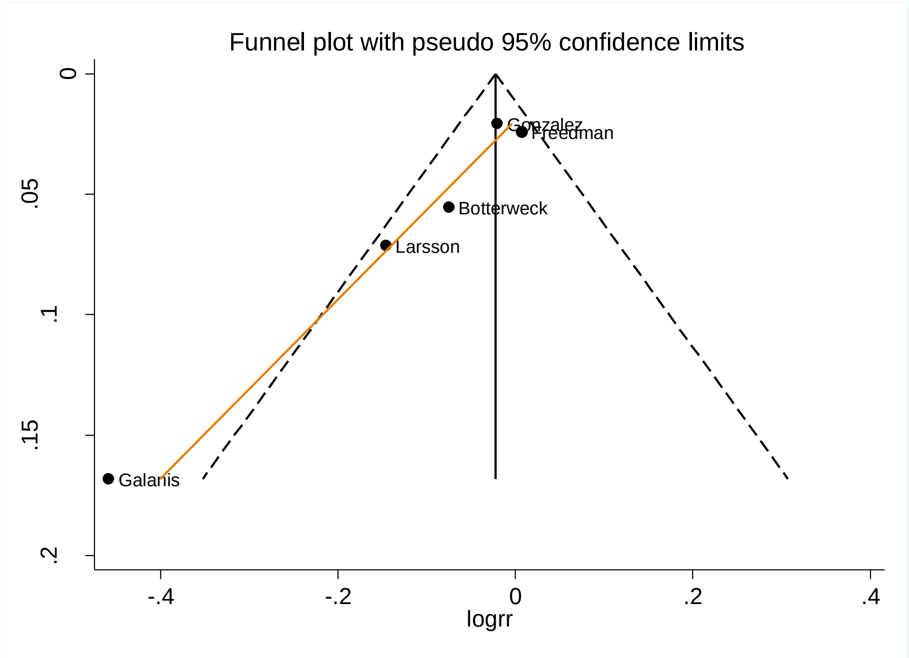


Figure 4 Funnel plot of studies included in the dose response meta-analysis of fruit and vegetable intake and stomach cancer



Egger's test p=0.02

Figure 5 Relative risk of stomach cancer for 100g/day increase of fruit and vegetable by sex

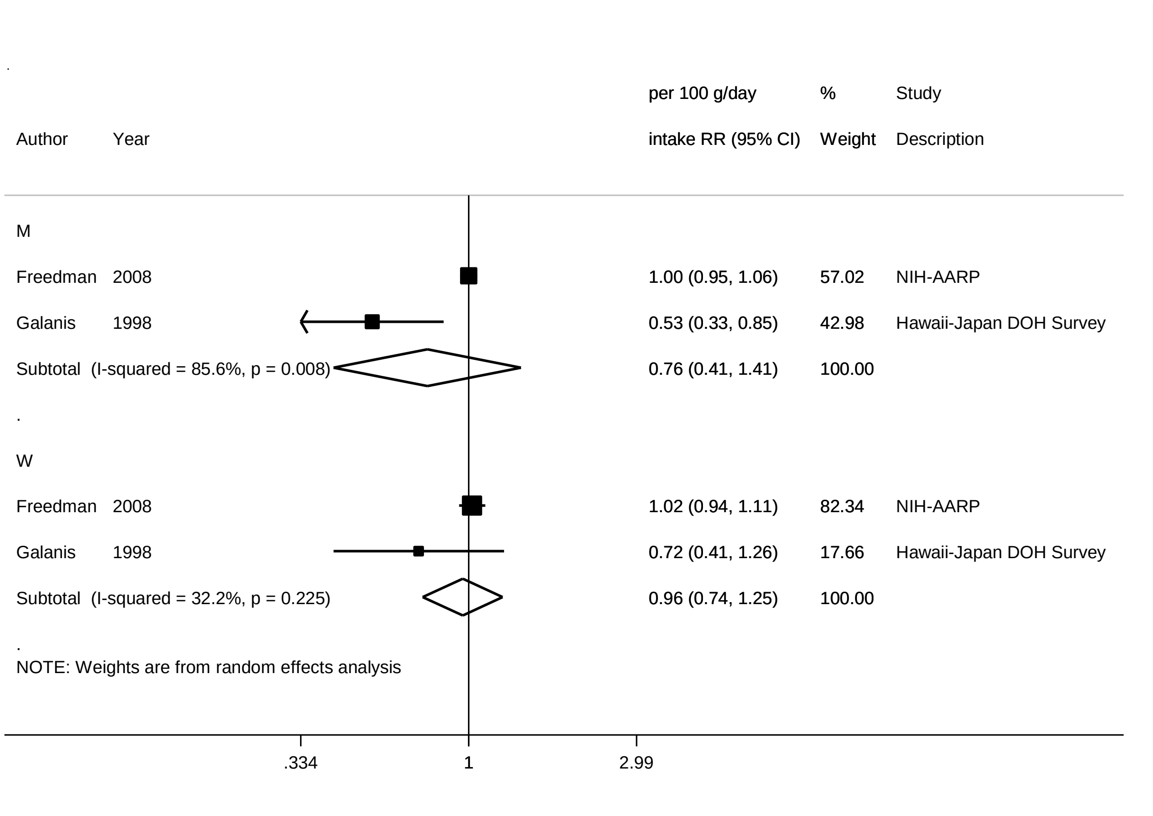


Figure 6 Relative risk of stomach cancer for 100g/day increase of fruit and vegetable by cancer site

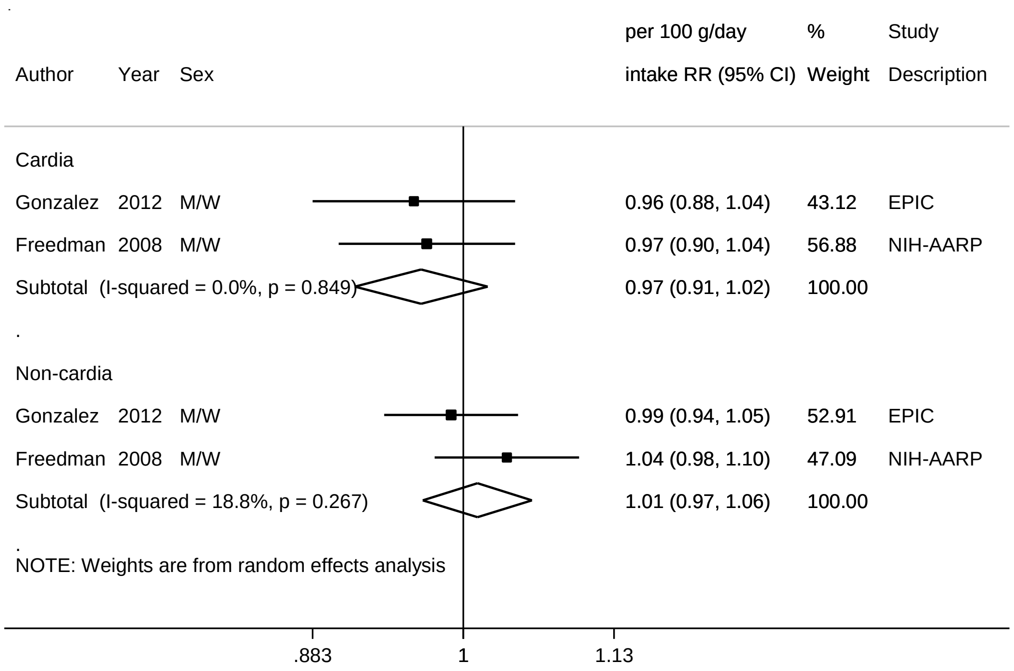
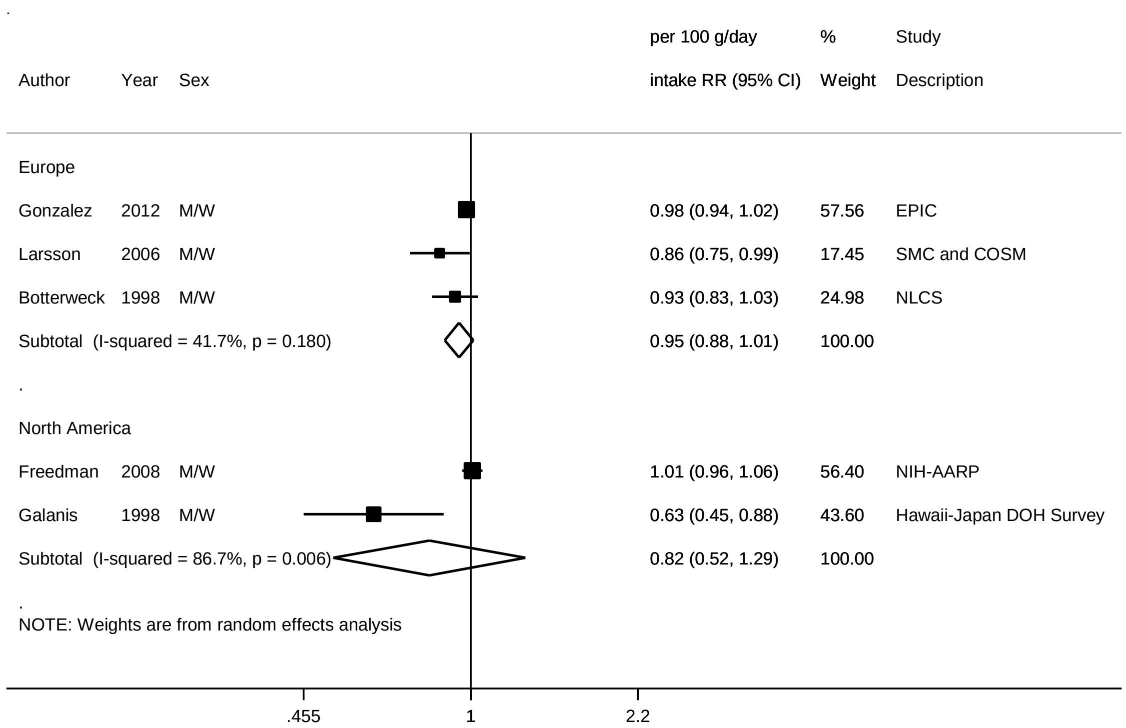


Figure 7 Relative risk of stomach cancer for 100g/day increase of fruit and vegetable by geographic location



2.2.1 Total vegetables

Randomised controlled trials

The WHI-DM trial reported on low-fat dietary pattern (Prentice, 2007). See section on dietary patterns.

Cohort studies

Summary

Main results:

Eleven studies (6062 cases) out of sixteen studies were included in the dose-response meta-analysis. No significant association of vegetable consumption and stomach cancer risk was observed in the overall analysis, and for gastric cardia and non-cardia gastric cancer.

Three studies were excluded from the dose-response analyses. All studies found non-significant results, on stomach cancer (Kasum, 2002; Kneller, 1991) and gastric non-cardia cancer (Wong, 2004). In addition, two studies (in one publication) on distal gastric cancer only, reported non-significant inverse association in women and no significant association in men (Epplein, 2010).

Moderate heterogeneity was observed. There was no significant evidence of publication or small study bias. There was a suggestion of selective reporting; less studies reported on vegetables than on fruits (see Appendix 1).

Sensitivity analyses:

The summary RRs ranged from 0.94 (95% CI=0.90-0.99) when Tran, 2005 was omitted to 0.97 (95% CI=0.92-1.03) when Larsson, 2006c was omitted in influence analysis. The first study (Trans, 2005) is a follow-up of the participants in a randomized controlled trial of five years supplementation with 1 to 8 vitamin/mineral combinations, in Linxian, China, a region with high prevalence of poor overall nutritional status and high rates of oesophageal and gastric cardia cancers. The analysis was adjusted for sex and age.

Three studies reported results stratified by smoking status (Ko, 2013; Gonzalez, 2012; Steevens, 2011), one additional study included smokers only (Nouraie, 2005). Three of these studies could be included in the stratified meta-analyses of stomach cancer and its subtype. Non-significant positive associations were observed in never smokers; inverse although no significant associations were observed in current and former smokers. Similar associations were reported in the study that was excluded from the analysis (Ko, 2013).

In subgroup meta-analyses, no significant associations were observed in men and women. Significant inverse associations were observed in smaller studies (<500 cases), in studies that adjusted for smoking or total energy intake but not in other subgroups.

Non-linear dose-response meta-analysis:

There was no evidence of non-linear dose-response for stomach cancer and vegetable intake (p=0.81).

Study quality:

Population characteristics varied across studies. The ATBC study is a follow-up of participants in an intervention trial of supplements in smokers (Nouraie, 2005). The NIT cohort (Linxian, China) is a follow-up of participants in a 5 years intervention trial of vitamin/mineral (Tran, 2005). No significant associations were observed in these studies.

Loss to follow-up was low in most studies. Cancer outcome was confirmed using medical notes or records in cancer registries in most studies.

Chyou, 1990 used a 24-hour dietary recall questionnaire to assess vegetable intake. All other studies used FFQ. Other methods were used in addition to the country-specific questionnaires in EPIC (Gonzalez, 2012). Gonzalez (2012) reported dose-response results for calibrated intake of vegetables. The inverse association was slightly stronger after calibration, but remained non-significant. In one publication (Tran, 2005) it was indicated that the food questionnaire was not validated.

All studies included in the dose-response analysis were adjusted for age and sex. None of the studies were adjusted for Helicobacter pylori status. In one study (Gonzalez, 2006a), stomach cancer was not associated with vegetable intake in H. pylori positive or negative participants.

Table 9 Vegetable intake and stomach cancer risk. Number of studies in the CUP SLR

	Number
Studies identified	16* (23 publications)
Studies included in forest plot of highest compared with lowest exposure	12
Studies included in linear dose-response meta-analysis	11
Studies included in non-linear dose-response meta-analysis	9

Note: Include cohort, nested case-control and case-cohort designs *Included two cohort studies in one publication (Epplein, 2010) reported results on distal gastric cancer only.

Table 10 Vegetable intake and stomach cancer risk. Summary of the linear dose-response meta-analysis in the 2005 SLR and CUP

	2005 SLR	**CUP**
Increment unit used	100g/day	100g/day
All studies		
Studies (n)	7	11
Cases (total number)	3394	6062
RR (95%CI)	0.98 (0.91-1.06)	0.96 (0.91-1.02)
Heterogeneity (I^2, p-value)	44.0%, 0.07	34.1%, 0.13
P value Egger test	0.70	0.16
Stratified and sensitivity analysis		
Men		
Studies (n)	3	5
RR (95%CI)	0.96 (0.81-1.14)	0.94 (0.87-1.01)

Heterogeneity (I^2, p-value)	-	1.9%, 0.40
Women		
Studies (n)	2	3
RR (95%CI)	1.13 (0.89-1.16)	1.01 (0.82-1.24)
Heterogeneity (I^2, p-value)	-	63.9%, 0.06
Incidence and mortality		
Studies (n)	-	2
RR (95%CI)	-	0.78 (0.56-1.08)
Heterogeneity (I^2, p-value)	-	0%, 0.36
Incidence		
Studies (n)	-	7
RR (95%CI)	-	0.96 (0.90-1.03)
Heterogeneity (I^2, p-value)	-	51.1%, 0.06
Mortality		
Studies (n)	-	2
RR (95%CI)	-	1.03 (0.85-1.24)
Heterogeneity (I^2, p-value)	-	0%, 0.98
Cancer subsite	Proximal stomach cancer	Gastric cardia cancer
Studies (n)	4	6
RR (95%CI)	1.05 (0.95-1.16)	1.00 (0.94-1.06)
Heterogeneity (I^2, p-value)	-	0%, 0.63
	Distal stomach cancer	Non-cardia gastric cancer
Studies (n)	4	8
RR (95%CI)	1.02 (0.87-1.20)	0.98 (0.94-1.03)
Heterogeneity (I^2, p-value)	-	0%, 0.66

Other stratified analyses

Geographic area	**Asia**	**Europe**	**North America**
Studies (n)	4	4	3
RR (95%CI)	1.00 (0.89-1.14)	0.94 (0.86-1.01)	0.94 (0.83-1.07)
Heterogeneity (I^2, p-value)	34.7%, 0.20	17.1%, 0.31	22.2%, 0.28
Duration of follow-up	**5-<10 years**	**10-<15 years**	**≥15 years**
Studies (n)	3	5	3
RR (95%CI)	0.91 (0.81-1.02)	0.95 (0.89-1.02)	0.99 (0.85-1.16)
Heterogeneity (I^2, p-value)	19.7%, 0.29	0%, 0.73	61.9%, 0.07
Number of cases	**<500 cases**	**500-<1000 cases**	**≥1000 cases**
Studies (n)	6	3	2
RR (95%CI)	0.86 (0.76-0.96)	0.96 (0.91-1.00)	1.08 (1.00-1.17)
Heterogeneity (I^2, p-value)	0%, 0.63	0%, 0.93	0%, 0.69
Publication year	**<2000**	**2000-<2010**	**>=2010**
Studies (n)	1	7	3
RR (95%CI)	0.66 (0.41-1.07)	0.96 (0.87-1.05)	0.96 (0.90-1.03)
Heterogeneity (I^2, p-value)	-	51.6%, 0.05	0%, 0.93
Adjustment for confounders:			
Socioeconomic status	**Not adjusted**	**Adjusted**	
Studies (n)	5	6	
RR (95%CI)	0.95 (0.82-1.10)	0.95 (0.90-1.00)	
Heterogeneity (I^2, p-value)	62.2%, 0.03	0%, 0.87	

Smoking	Not adjusted	Adjusted	
Studies (n)	3	8	
RR (95%CI)	0.97 (0.78-1.20)	0.95 (0.90-0.99)	
Heterogeneity (I^2, p-value)	70.3%, 0.03	0%, 0.76	
Ethnicity	**Not adjusted**	**Adjusted**	
Studies (n)	9	2	
RR (95%CI)	0.95 (0.87-1.03)	0.95 (0.89-1.02)	
Heterogeneity (I^2, p-value)	44.5%, 0.07	0%, 0.53	
Alcohol intake	**Not adjusted**	**Adjusted**	
Studies (n)	6	5	
RR (95%CI)	0.93 (0.80-1.09)	0.95 (0.91-1.00)	
Heterogeneity (I^2, p-value)	56.9%, 0.04	0%, 0.92	
BMI	**Not adjusted**	**Adjusted**	
Studies (n)	6	5	
RR (95%CI)	0.94 (0.82-1.07)	0.95 (0.90-1.00)	
Heterogeneity (I^2, p-value)	58.2%, 0.04	0%, 0.88	
Total energy intake	**Not adjusted**	**Adjusted**	
Studies (n)	7	4	
RR (95%CI)	0.97 (0.87-1.08)	0.94 (0.90-0.99)	
Heterogeneity (I^2, p-value)	45.1%, 0.09	0%, 0.72	
Physical activity	**Not adjusted**	**Adjusted**	
Studies (n)	9	2	
RR (95%CI)	0.95 (0.86-1.04)	0.95 (0.90-1.01)	
Heterogeneity (I^2, p-value)	43.3%, 0.08	0%, 0.80	

Stratified analysis by smoking status

Smoking status	Never smokers	Former smokers	Current smokers
Stomach cancer			
Studies (n)	2	2	3
RR (95%CI)	1.05 (0.94-1.18)	0.90 (0.80-1.02)	0.91 (0.81-1.01)
Heterogeneity (I^2, p-value)	0%, 0.41	0%, 0.87	0%, 0.70
Gastric cardia cancer			
Studies (n)	1	1	2
RR (95%CI)	1.52 (0.95-2.42)	0.81 (0.55-1.21)	0.89 (0.62-1.27)
Heterogeneity (I^2, p-value)	-	-	0%, 0.42
Non-cardia gastric cancer			
Studies (n)	1	1	2
RR (95%CI)	1.04 (0.77-1.40)	0.92 (0.72-1.18)	0.85 (0.70-1.05)
Heterogeneity (I^2, p-value)	-	-	0%, 0.94

Table 11 Vegetable intake and stomach cancer risk. Results of meta-analyses and pooled analyses of prospective studies published after the 2005 SLR

Author, Year	Number of studies	Total number of cases	Studies country, area	Outcome	Comparison	RR (95%CI)	P trend	Heterogeneity (I^2, p value)
Meta-analyses								
Wang Q, 2014	13 cohorts (11 cohorts in dose-response analysis)	6632	USA, Japan, China, Korea, Finland, Denmark, France, Germany, Greece, Italy, the Netherlands, Norway Spain, Sweden, UK	Incidence/mortality, Gastric cancer	High vs. low	0.96 (0.88-1.06)		21.1%, 0.20
					Per 100 g/day	0.96 (0.91-1.01)		49.7%, 0.01
				Men	High vs. low	0.94 (0.84-1.05)		0%, 0.63
				Women		1.07 (0.91-1.25)		0%, 0.48
				Gastric cardia cancer		1.06 (0.90-1.25)		0%, 0.50
				Gastric non-cardia cancer		0.94 (0.81-1.09)		0%, 1.00

Table 12 Vegetable intake and stomach 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
Ko, 2013 STM80184 Korea	KMCC, Prospective Cohort, Age: 30-90 years, M/W	152/ 9724 8.5 years	Cancer registry and death certificates	14-item self-administered FFQ	Incidence, stomach cancer All	≥1 time/day vs. almost never	0.68 (0.27-1.68)	Age, sex, area of residence, BMI, cigarette smoking, alcohol drinking	Exposure values using standard portion size, mid-points of exposure categories
		107/3714 45/6010 64/ 43/			Men Women Men, current smokers Men, non-smokers	High vs. low	0.91 (0.60-1.49) 1.08 (0.55-2.13) 0.83 (0.48-1.45) 1.02 (0.52-1.99)		
Gonzalez, 2012 STM80139 Denmark,France,Germany,Greece,Italy,Netherlands,Norway,Spain,Sweden,U.K.	EPIC, Prospective Cohort, Age: 35-70 years, M/W	683/ 477 312 11.02 years	Cancer registries, health insurance records, pathology rec, active follow up, death certificate	FFQ, dietary questionnaires, food record	Incidence, gastric adenocarcinoma	262.9 (M)/238.2 (W) vs. 104.3 (M)/111.3 (W) g/day Per 100 g/day	0.90 (0.66-1.21) 0.96 (0.89-1.04)	Age, sex, BMI, centre, educational level, energy intake, physical activity, total fruits consumption, alcohol intake, red and processed meat, smoking	
		240			Never smokers	Quintile 5 vs. quantile 1 Per 100 g/day	1.16 (0.70-1.94) 1.03 (0.91-1.17)		
		206			Former smokers	Quintile 5 vs. quintile 1 Per 100 g/day	0.57 (0.32-1.01) 0.91 (0.79-1.05)		
		225			Current smokers	Quintile 5 vs. quintile 1 Per 100 g/day	1.16 (0.68-1.98) 0.94 (0.81-1.08)		

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
		201/			Gastric cardia adenocarcinoma	Quintile 5 vs. quintile 1 Per 100 g/day	0.80 (0.47-1.38) 0.93 (0.80-1.08)		
		323/			Gastric non-cardia adenocarcinoma	Quintile 5 vs. quintile 1 Per 100 g/day	1.02 (0.65-1.60) 0.97 (0.87-1.09)		
		203/			Intestinal gastric cancer	Quintile 5 vs. quintile 1 Per 100 g/day	0.95 (0.55-1.64) 0.99 (0.87-1.14)		
		217/			Diffuse gastric cancer	Quintile 5 vs. quintile 1 Per 100 g/day	1.24 (0.72-2.13) 1.02 (0.89-1.17)		
Steevens, 2011 STM80062 Netherlands	NLCS, Case Cohort, Age: 55-69 years, M/W	148/ 4651 16.3 years	Annual linkage to national cancer registry and network of histopathology and cytopathology	150-item self-administered validated FFQ	Incidence, gastric cardia adenocarcinoma	297 vs. 104 g/day Per 25 g/day	0.87 (0.50-1.52) 1.00 (0.94-1.07)	Age, sex, alcohol consumption, duration of smoking, fruit intake, red meat intake, current smoking, fish intake, number of cigarettes smoked per day	RRs for gastric cardia adenocarcinoma and gastric non-cardia adenocarcinoma combined using Hamling's method.
		125/ 23/ 24/ 72/ 52			Men Women Never smokers Former smokers Current smokers	Per 25 g/day	0.99 (0.92-1.07) 1.04 (0.93-1.16) 1.11 (0.99-1.25) 0.95 (0.86-1.05) 0.99 (0.90-1.10)		
		443/			Non-cardia gastric adenocarcinoma	297 vs. 104 g/day Per 25 g/day	0.90 (0.64-1.26) 0.98 (0.94-1.02)		
		294/ 149/ 105/			Men Women Never smokers	Per 25 g/day	0.99 (0.92-1.07) 1.01 (0.95-1.07) 1.01 (0.94-1.09)		

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Missing data derived for analyses
		180/158			Former smokers Current smokers		0.98 (0.92-1.04) 0.96 (0.90-1.01)		
Epplein, 2010 STM80129 China	SWHS and SMHS, Prospective Cohort, Age: 40-74 years, M/W	206/ 73 064	Review of medical records	Validated 81-item (SMHS) and 77-item (SWHS) FFQs	Incidence, distal stomach cancer Women	>353.7 vs. ≤179.5 g/day	0.89 (0.60-1.31)	Age, education level, smoking, total energy intake	Distribution of person-years by exposure quintiles, mid-points of exposure categories (Included in analysis of non-cardia stomach cancer only)
		132/ 59 247			Incidence, distal stomach cancer Men	>429.3 vs. ≤212.9 g/day	1.00 (0.59-1.68)		
George, 2009 STM80057 USA	NIH-AARP, Prospective Cohort, Age: 50-71 years, M/W, Retired	137/ 195 229	Linkage to 11 state cancer registries and SEERS	Validated 124-item self-administered FFQ	Incidence, stomach cancer Women	1.44-4.38 vs. 0-0.56 cup/1000 kcal/day	0.86 (0.47-1.58)	Age, BMI, energy intake, family history of stomach cancer, fruit intake, marital status, physical activity, race, alcohol, education, menopausal hormone therapy use, smoking	Distribution of cases and person-years by intake quintiles, exposure values using mean energy intake, mid-points of intake categories, RRs for men and women combined
		507/ 288 109			Incidence, stomach cancer Men	1.11-3.25 vs. 0-0.44 cup/1000 kcal/day	0.93 (0.69-1.25)		
Freedman, 2008 STM80097 USA	NIH-AARP, Prospective Cohort, Age: 50-71	198/ 490 802 4.5 years	Linkage with 11 state cancer registry databases	Validated 124-item FFQ	Incidence, cardia cancer	3.15 vs. 0.71 serving/ 1000kcal	1.03 (0.61-1.72)	Age, sex, BMI, ethnicity, fruit intake, alcohol intake, cigarette-	Exposure values using mean energy intake
						Per 1	0.98 (0.84-1.14)		

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Missing data derived for analyses
	years, M/W, Retired					serving/1000 kcal		smoke-dose, education, total energy, usual activity throughout the day, vigorous physical activity	(Same study as George, 2009, STM80057, included in analysis by cancer subsite)
		196/			Incidence, non-cardia cancer	3.15 vs. 0.71 serving/ 1000kcal	0.90 (0.58-1.47)		
						Per 1 serving/1000 kcal	0.97 (0.85-1.12)		
Larsson, 2006c STM80086 Sweden	SMC and COSM, Prospective Cohort, Age: 45-83 years, M/W	139/ 82 002 7.2 years	Cancer registry/ mortality registry	96-item validated FFQ	Incidence, stomach cancer	≥2.5 vs. <1.0 servings/day	0.56 (0.34-0.93)	Age, sex, diabetes, smoking status, alcohol intake, education, pack years of smoking, processed meat intake, total energy intake	Exposure values using standard portion size, mid-points of exposure categories
		84/ 45 338			Men		0.54 (0.29-0.98)		
		55/ 36 664			Women		0.56 (0.22-1.40)		
Nouraie, 2005 STM44426 Finland	ATBC, Prospective Cohort, Age: 50-69 years, M, Smokers	22027 110 12 years 57/	Cancer registry	Validated 276-item self-administered FFQ	Incidence, stomach cancer Cardia cancer	>148 vs. <66 g/day	0.81 (0.27-2.48)	Age, dietary nitrate, educational level, energy intake, smoking habits	RRs for cardia and non-cardia gastric cancers combined using Hamling's method, distribution of cases and person-years by intake quartiles, mid-points of intake quartiles
		163/			Non-cardia cancer	>148 vs. <66 g/day	0.85 (0.43-1.68)		

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Missing data derived for analyses
Tran, 2005 STM44270 Linxin, China	NIT Cohort, Prospective Cohort, Age: 40-69 years, M/W, Intervention trial participants	1452/ 29 584 15 years	Follow-up visits, contacts with local commune, hospitals, and study medical team	Non-validated 8-item FFQ	Incidence, stomach cancer	>2.5 vs. ≤1.5 times/day		Age, sex	RRs for gastric cardia cancer and distal gastric cancer combined using Hamling's method, intake values using standard portion size, mid-points of intake categories
		1089/			Cardia cancer		1.17 (0.96-1.42)		
		363/			Non-cardia cancer	>2.5 vs. <=1.5 times/day	1.04 (0.71-1.53)		
Fujino, 2002 STM01512 Japan	JACC, Prospective Cohort, Age: 40-79 years, M/W	379/ 44 930 10 years	Population registry	FFQ	Mortality, stomach cancer			Age	Hamling's method was used to calculate the RRs for alternative vegetable intake comparisons. Intake values using standard portion size, mid-points of intake categories, RRs for men and women combined
		261/ 18 746			Men	Every day vs. >3 times/week	1.19 (0.90-1.58)		
		118/ 26 184			Women	Every day vs. >3 times/week	1.02 (0.66-1.57)		
Kobayashi, 2002 STM01446 Japan	JPHC I, Prospective Cohort, Age: 40-59 years,	404/ 39 993 10 years	Hospital records, population-based cancer registries and	Validated 44-item self-administered FFQ	Incidence, stomach cancer	214.5 vs. 55.8 g/day	0.75 (0.54-1.04)	Age, sex, BMI, alcohol intake, educational level, energy intake, family	
		47/			Cardia cancer	214.5 vs. 55.8 g/day	0.65 (0.24-1.79)		

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Missing data derived for analyses
	M/W	289/	death certificates, histologically confirmed		Non-cardia cancer	214.5 vs. 55.8 g/day	0.84 (0.57-1.23)	history of stomach cancer, highly salted food intake, history of peptic ulcer, smoking habits, study area, vitamin a supplement, vitamin c supplement, vitamin e supplement	
		112/			Undifferentiated non-cardia cancer	214.5 vs. 55.8 g/day	1.22 (0.68-2.19)		
		164/			Differentiated non-cardia cancer	214.5 vs. 55.8 g/day	0.53 (0.31-0.91)		
McCullough, 2001 STM02243 USA	CPS II, Prospective Cohort, Age: 30- years, M/W	1349/ 970 045 14 years	Death registry/ subject or family	32- item FFQ	Mortality, stomach cancer			Age, aspirin use, BMI, educational level, ethnicity/race, family history of stomach cancer, multivitamin supplement, smoking habits, vitamin c supplement	Distribution of person-years by intake category, intake values using standard portion size, RRs for men and women combined, mid-points of intake categories
		910/ 436 654			Men	≥13 vs. 0-7.9 days/week	0.89 (0.76-1.05)		
		439/ 533 391			Women	≥14 vs. 0-8.9 days/week	1.25 (0.99-1.58)		
Chyou, 1990 STM12425 USA	HHP, Case Cohort, Age: 58years, M, Japanese residents of Hawaii	111/ 8006 18 years	Cancer registry/ hospital records	24-h dietary recall questionnaire	Mortality, stomach cancer	≥80 vs. 0 g/day	0.70 (0.4-1.10)	Age, smoking habits	Mid-points of intake categories
		83/			Intestinal gastric cancer		0.8		

Table 13 Vegetable intake and stomach 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, Retired	954/ 494 968 9.7 years 453/	Cancer registry, death master file, national death index plus, postal service database	Validated FFQ, 124-item	Incidence, stomach Gastric cardia adenocarcinoma	HEI-2005 scoring criteria for total vegetables ≥1.1 vs. <1.1 cups/1000kcal	1.06 (0.97-1.16)	Age, sex, BMI, race, education, modified total score, smoking, total energy intake, usual activity throughout the day, vigorous physical activity	Excluded, exposure was meeting dietary index criteria or not (same study as George, 2009, STM80057; Freedman, 2008, STM80097)
		501/			Non-cardia adenocarcinoma		1.06 (0.97-1.15)		
		453/			Cardia adenocarcinoma	aMED scoring criteria for vegetables (no white potatoes) ≥1.86 vs. < 1.86 cups	1.01 (0.83-1.22)		
		501/			Non-cardia adenocarcinoma		0.97 (0.80-1.16)		
Gonzalez, 2006a STM44425 France, Italy, Spain, U.K., Netherlands, Greece, Germany, Sweden, Denmark	EPIC, Prospective Cohort, Age: 35-70 years, M/W	330/ 481 518 6.5 years	Cancer registry	FFQ, dietary questionnaires, food record	Incidence, stomach cancer	Per 100 g/day	0.91 (0.65-1.28)	Age, sex, alcohol consumption, educational level, energy intake, height, physical activity, processed meat,	Superseded by Gonzalez, 2012, STM80139
		94/			Cardia		0.99 (0.50-1.97)		
		159/			Non-cardia		0.96 (0.60-1.52)		
		109/			Intestinal		0.66 (0.35-1.22)		
		116/			Diffuse		1.18 (0.69-2.03)		

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Reasons for exclusion
		40/ 22/ 12/ 16/ 9			H. pylori -ve Stomach cancer Cardia Non-cardia Intestinal Diffuse	Per 100 g/day	1.53 (0.49-4.78) 2.42 (0.54-10.80) 0.70 (0.03-16.7) 1.17 (0.19-7.10) 0.43 (0.001-392.0)	red meat intake, smoking habits, weight, date of blood collection, H. pylori infection, study area	
		201/ 47/ 113/ 77/ 82			H. pylori +ve Stomach cancer Cardia Non-cardia Intestinal Diffuse	Per 100 g/day	1.11 (0.71-1.74) 1.42 (0.58-3.45) 1.25 (0.71-2.20) 0.88 (0.44-1.80) 1.22 (0.64-2.34)		
Wong, 2004 STM00527 China	CCHT, Prospective Cohort, Age: 42years, M/W, H. pylori eradication trial participants	18/ 1630 7.5 years	Clinical trial follow up records	FFQ	Incidence, lower third gastric cancer	≥2 vs. <2 times/week	1.62 (0.64-4.10)		Only two intake categories, outcome was lower third gastric cancer
Kasum, 2002 STM01746 USA	IWHS, Prospective Cohort, Age: 55-69 years, post-menopausal women	56/ 34 651 14 years	Cancer registry	127-item FFQ	Incidence, stomach cancer	Quantile 3 vs. quantile 1	No significant association	Age, alcohol consumption, energy intake, smoking habits	Excluded, no measure of association (same study as Zheng, 1995 STM06417)
Hirvonen, 2001 STM02213 Finland	ATBC, Prospective Cohort,	111/ 27 110 6.1 years	Cancer registry	Validated 276-item self-administered	Incidence, stomach cancer	Means intake		Age	Superseded by Nouraie, 2005, STM44426

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Reasons for exclusion
	Age: 50-69 years, Men smokers			FFQ					
Botterweck, 1998 STM04445 Netherlands	NLCS, Case Cohort, Age: 55-69 years, M/W	265/ 120 852 6.3 years	Cancer registry	Validated 150-item self-administered semi-quantitative FFQ	Incidence, stomach cancer	Per 25 g/day	0.98 (0.94-1.02)	Age, sex, educational level, family history of stomach cancer, fruit, smoking habits, stomach disorders	Superseded by Steevens, 2011, STM80062
Nomura, 1995 STM11198 USA	HHP, Case Cohort, Japanese men, residents of Hawaii	111/ 6860 23 years	Cancer registry/ hospital records	Dietary recall	Mortality, gastric adenocarcinoma	≥80 g/day vs. none	0.60 (0.30-0.90)	Age	Superseded by Chyou, 1990, STM12425
Zheng, 1995 STM06417 USA	IWHS, Prospective Cohort, Age: 55-69 years, post-menopausal women	26/ 34 691 7 years	Cancer registry	127-item self-administered semi-quantitative FFQ	Incidence, stomach cancer	Quantile 3 vs. quantile 1	No significant association	Age, educational level, pack-years of smoking, smoking habits	Excluded, no measure of association (same study as Kasum, 2002, STM01746)
Guo, 1994 STM10900 Linxin, China	NIT Cohort, Nested Case Control, Age: 40-69 years, M/W, Intervention trial participants	538/ 29 584 5 years	Follow-up visits, contacts with local commune, hospitals, and study medical team	FFQ	Incidence, stomach cancer	>60 vs. <30 times/month	1.10 (0.80-1.40)	Family history of cancer, intervention group, smoking habits	Superseded by Tran, 2005, STM44270

Author, Year, 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
Kneller, 1991 STM07350 USA	LBS, Prospective Cohort, Age: 35- years, M, mainly of Scandinavian descent	75/ 17 633 20 years	Health insurance company records	FFQ	Mortality, stomach cancer	Quantile 4 vs. quantile 1	0.90 (0.48-1.78)	Age, smoking habits	Excluded, exposure not quantified

Figure 8 RR estimates of stomach cancer by levels of vegetable intake

Note: Epplein, 2010 was included in the analysis of non-cardia gastric cancer only.

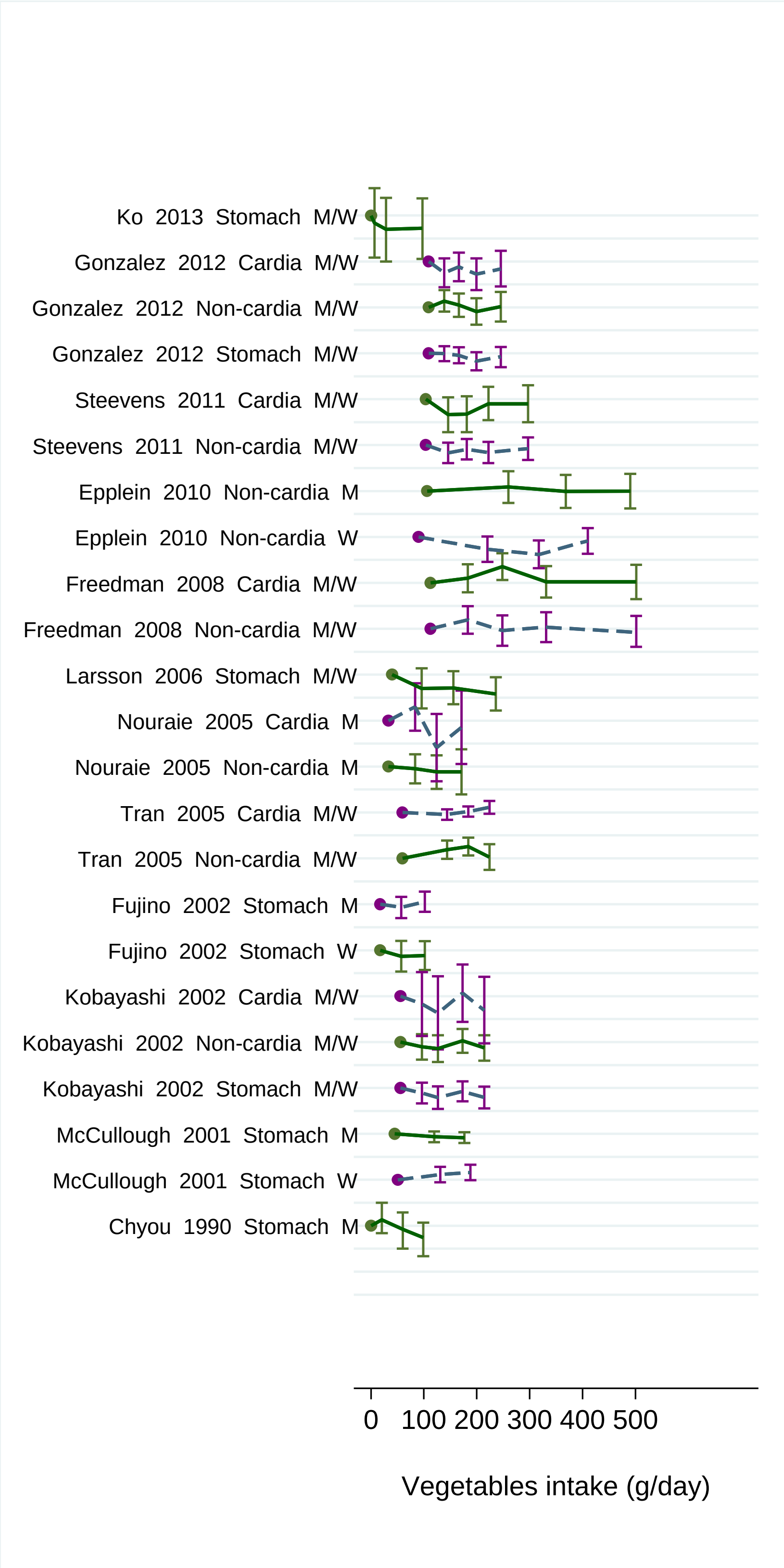


Figure 9 RR (95% CI) of stomach cancer for the highest compared with the lowest level of vegetable intake

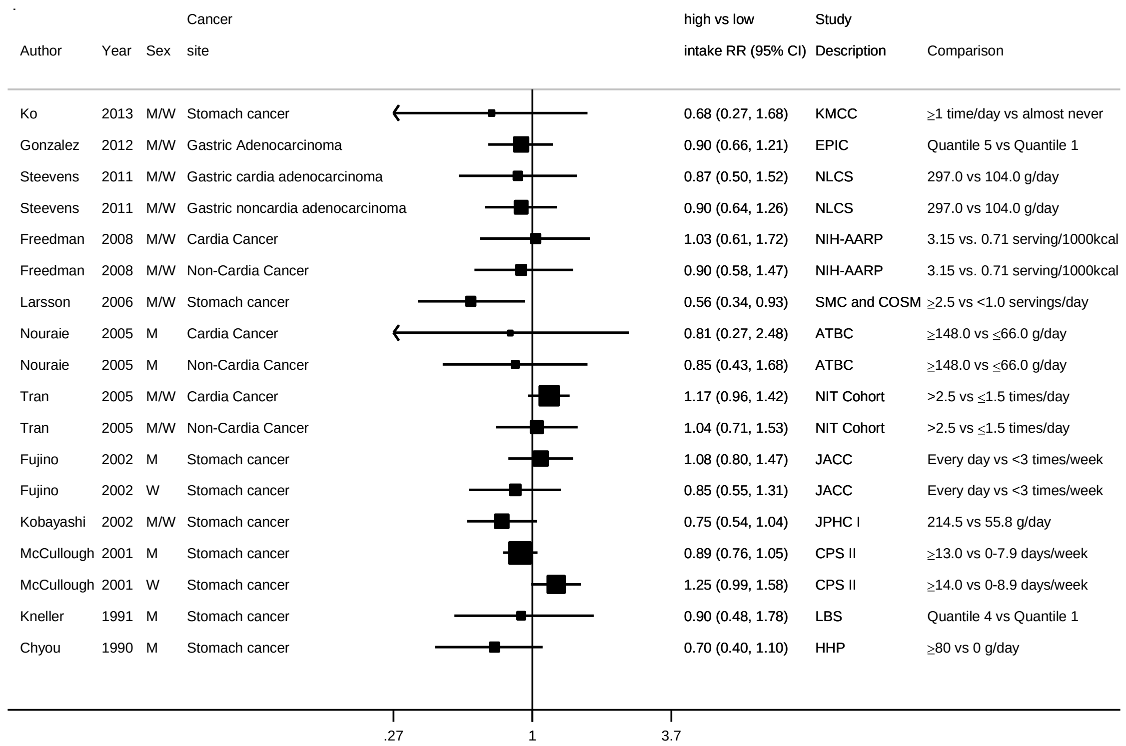


Figure 10 Relative risk of stomach cancer for 100g/day increase of vegetable intake

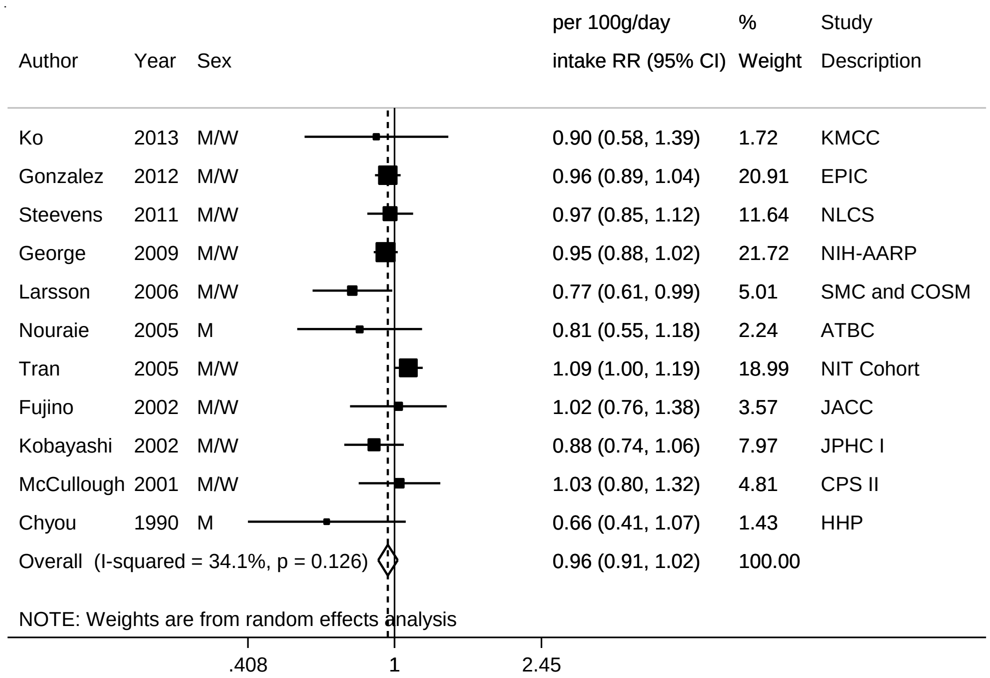
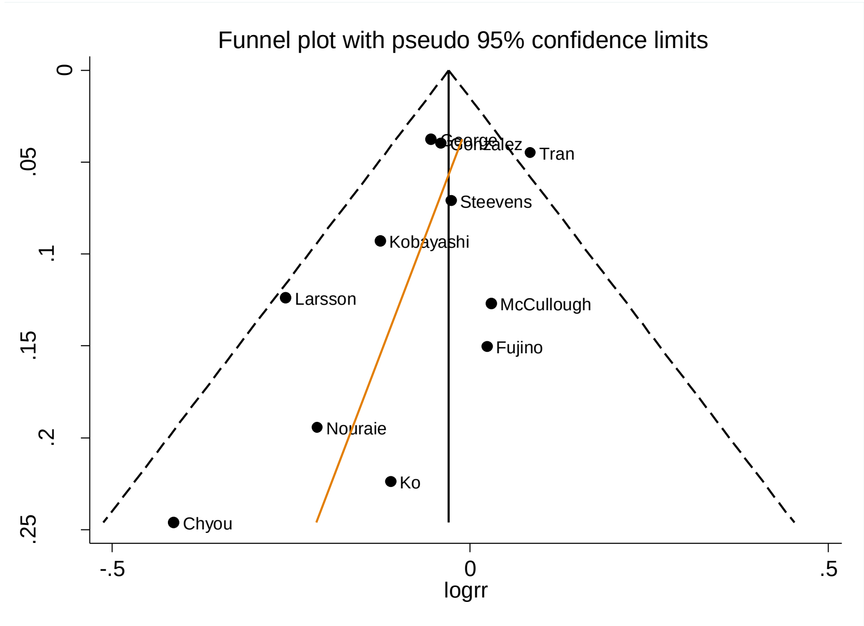


Figure 11 Funnel plot of studies included in the dose response meta-analysis of vegetable intake and stomach cancer



Egger's test p=0.16

Figure 12 Relative risk of stomach cancer for 100g/day increase of vegetable intake by sex

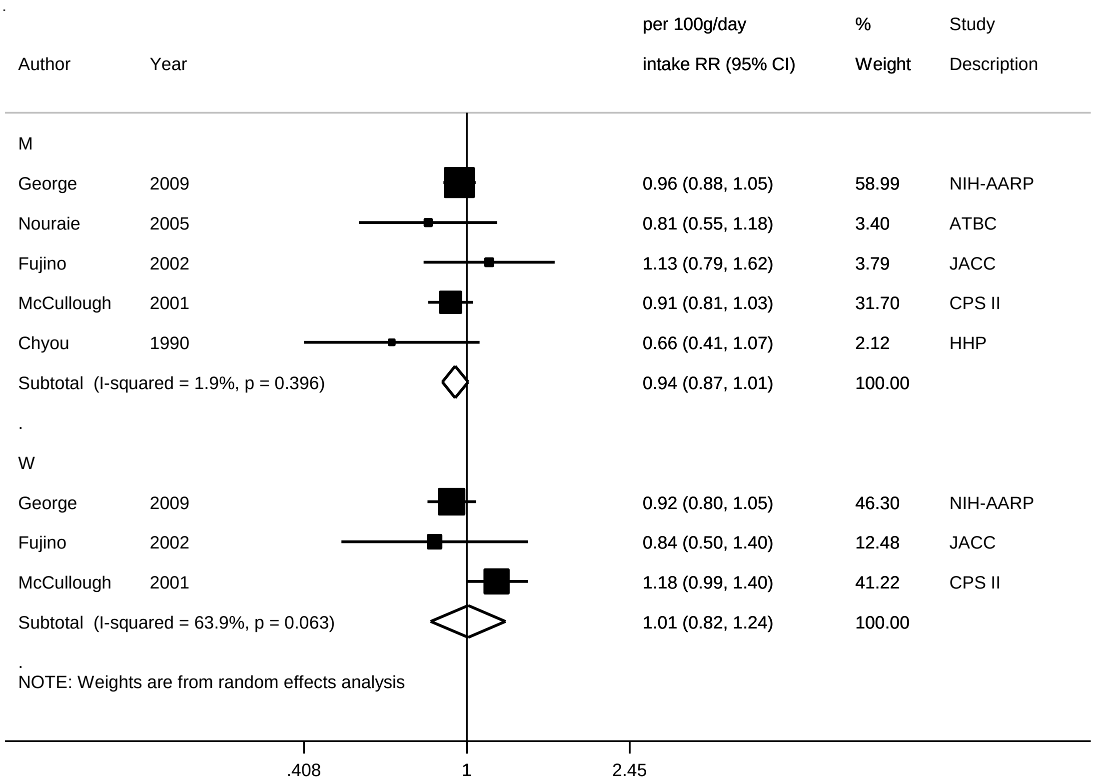


Figure 13 Relative risk of stomach cancer for 100g/day increase of vegetable intake by cancer outcome

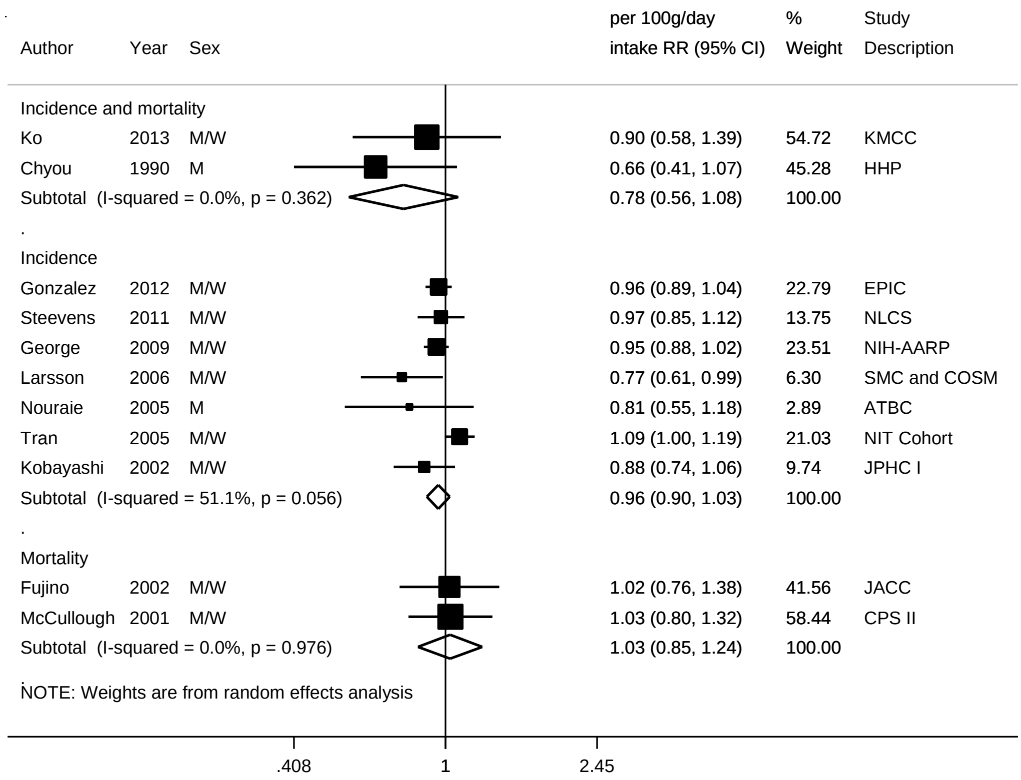


Figure 14 Relative risk of stomach cancer for 100g/day increase of vegetable intake by cancer site

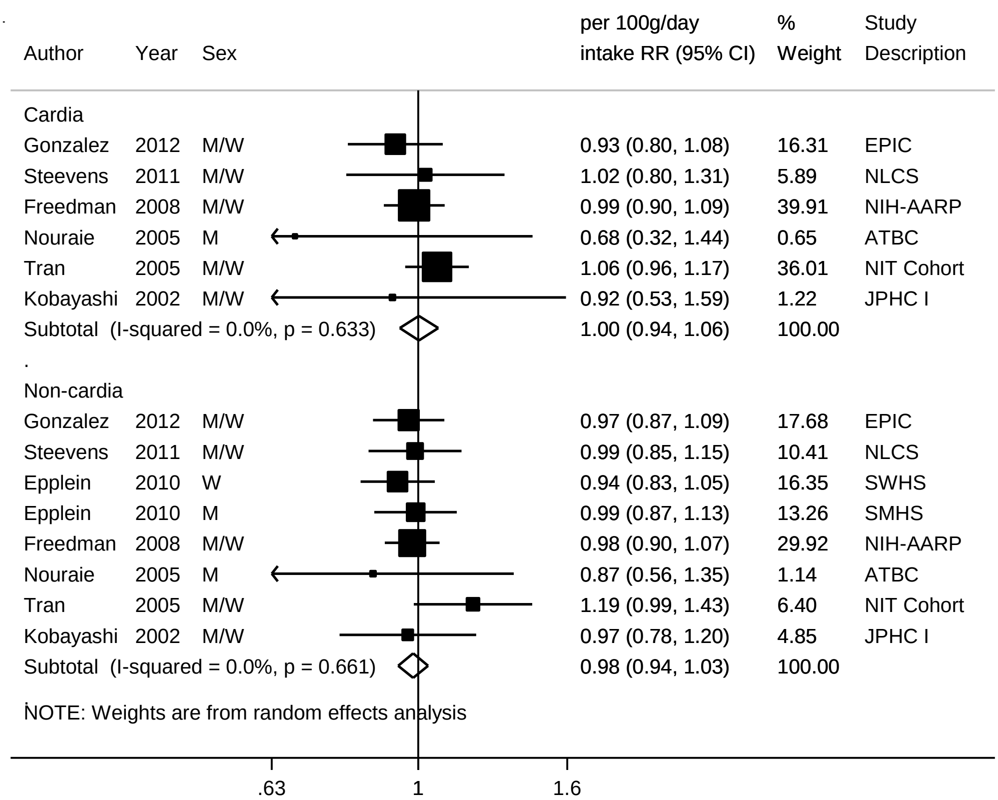


Figure 15 Relative risk of stomach cancer for 100g/day increase of vegetable intake by cancer site geographic location

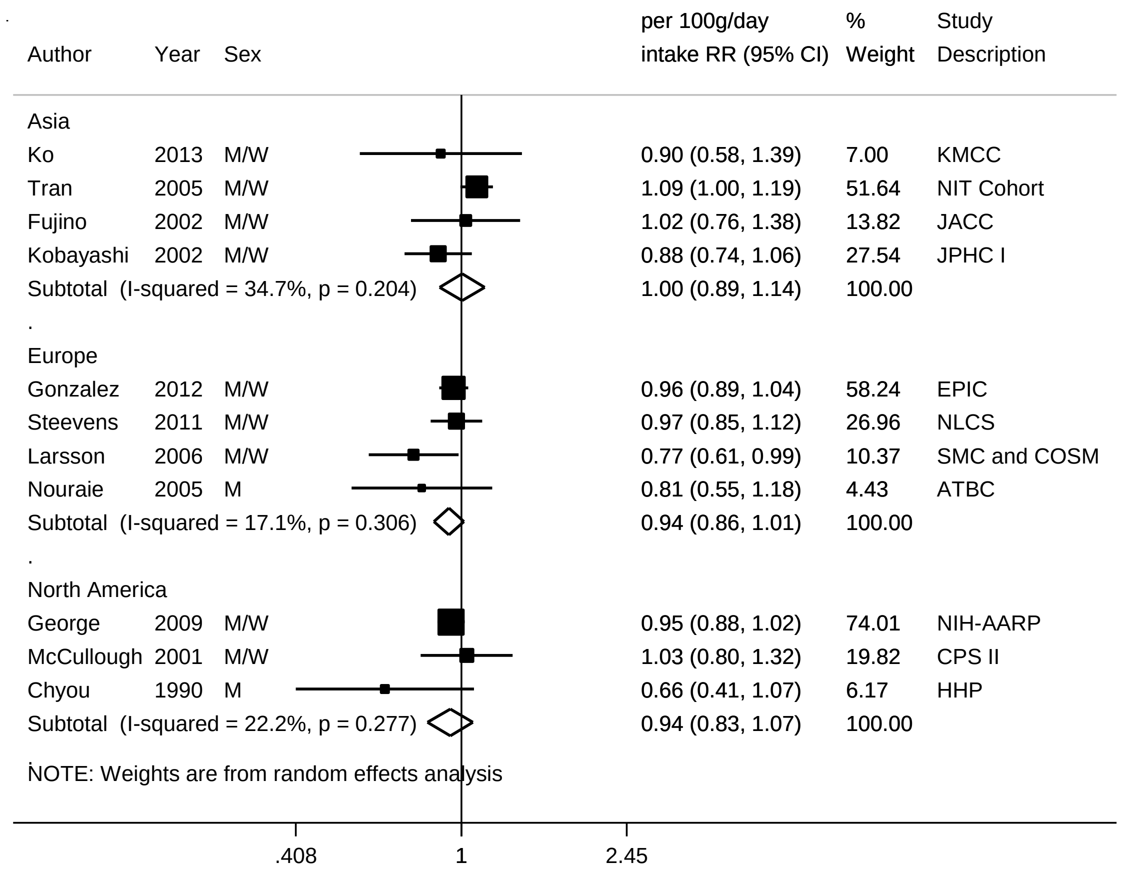


Figure 16 Relative risk of stomach cancer for 100g/day increase of vegetable intake by cancer site among never smokers

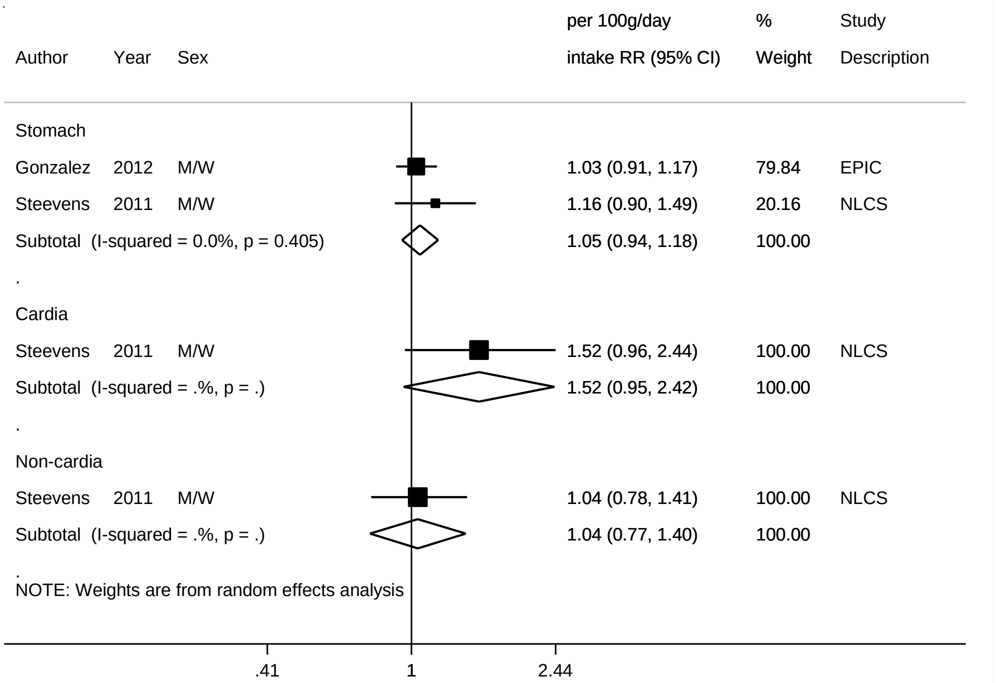


Figure 17 Relative risk of stomach cancer for 100g/day increase of vegetable intake by cancer site among former smokers

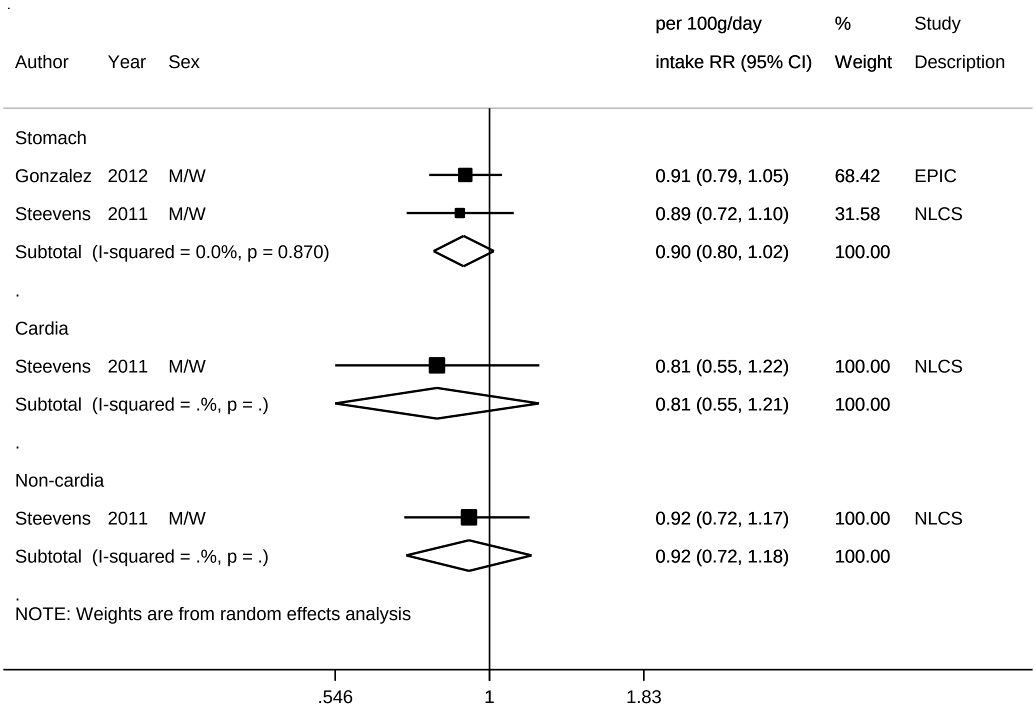
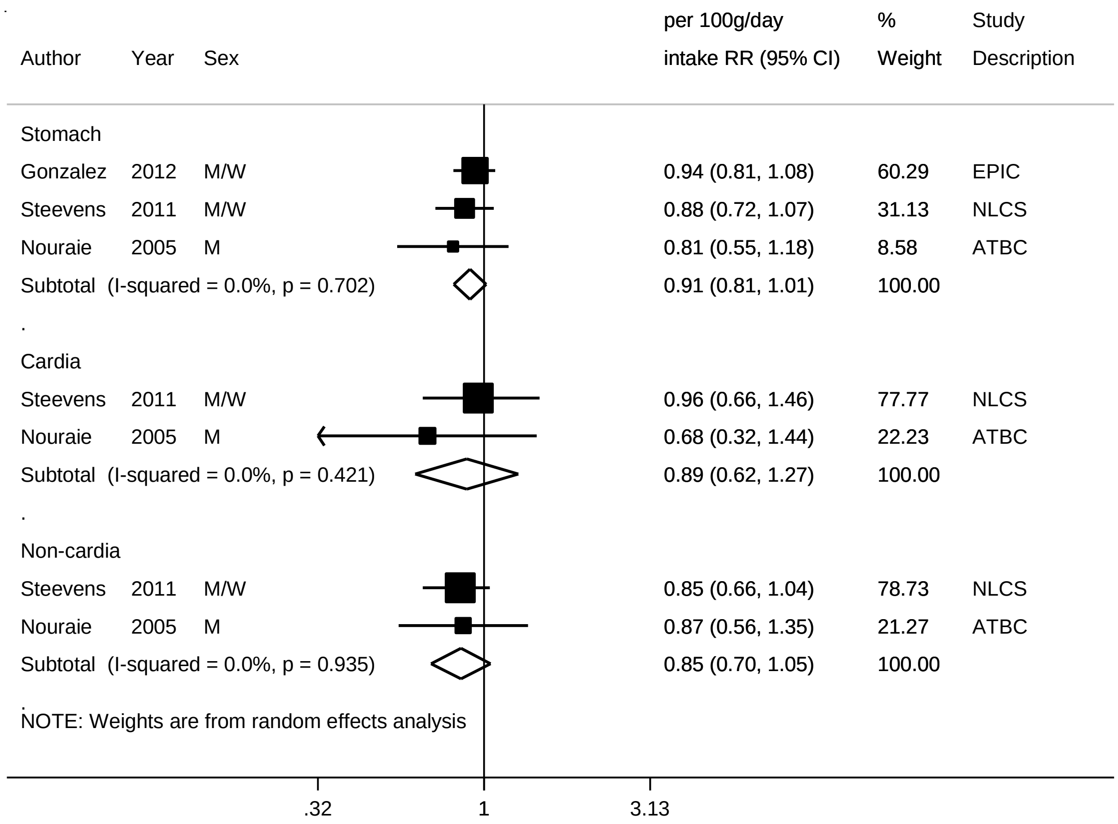


Figure 18 Relative risk of stomach cancer for 100g/day increase of vegetable intake by cancer site among current smokers



2.2.1.2 Cruciferous vegetables

Randomised controlled trials

No randomised controlled trial was identified.

Cohort studies

Summary

Main results:

Four studies (1807 cases) out of nine were included in the dose-response meta-analysis. No significant associations were observed for stomach cancer, for gastric cardia cancer (three studies, high heterogeneity) and non-cardia gastric cancer (five studies, no heterogeneity).

Three studies (Zheng, 1995; Kneller, 1991; Chyou, 1990) were excluded from the dose-response analysis. No significant associations were reported. In addition, two studies (in one publication) on distal gastric cancer only, reported non-significant associations (Epplein, 2010).

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

Sensitivity analyses:

The summary RRs ranged from 0.86 (95% CI=0.64-1.14) when Freedman, 2008 (62.2% weight) was omitted to 0.98 (95% CI=0.81-1.18) when Larsson, 2006c (10.9% weight) was omitted in influence analysis.

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 used FFQ to assess cruciferous vegetables intake. The definition of cruciferous vegetables varied between studies, but mainly included cabbages, broccoli, and cauliflower (details in Footnote in figure). The summary estimate remained non-significant when each study was omitted in turn in influence analysis.

Loss to follow-up was low. Cancer outcome was confirmed using record linkages to the cancer registries.

All studies included in the dose-response analysis were adjusted for several risk factors. None of the studies were adjusted for Helicobacter pylori status.

Table 14 Cruciferous vegetables intake and stomach 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	8*
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 two cohorts in one publication (Epplein, 2010) that reported results on distal gastric cancer only.

Table 15 Cruciferous vegetables intake and stomach cancer risk. Summary of the linear dose-response meta-analysis in the 2005 SLR and the CUP

	2005 SLR	**CUP**
Increment unit used	100 g/day	50 g/day
All studies		
Studies (n)	2	4
Cases (total number)	596	1807
RR (95%CI)	0.85 (0.40-1.79)	0.94 (0.79-1.13)
Heterogeneity (I^2, p-value)	0%, 0.9	0%, 0.58
P value Egger test	-	-
Stratified analysis		
Gastric cardia cancer		
Studies (n)	-	3 (n=547)
RR (95%CI)	-	0.78 (0.48-1.26)
Heterogeneity (I^2, p-value)	-	51.6%, 0.13
Non-cardia gastric cancer		
Studies (n)	-	5 (n=1300)
RR (95%CI)	-	1.01 (0.92-1.10)
Heterogeneity (I^2, p-value)	-	0%, 0.63

Table 16 Cruciferous vegetables intake and stomach cancer risk. Results of meta-analyses and pooled analyses of prospective studies published after the 2005 SLR

Author, Year	Number of studies	Total number of cases	Studies country, area	Outcome	Comparison	RR (95%CI)	P trend	Heterogeneity (I^2, p value)
Meta-analyses								
Wu 2013	22 studies (16 case-control, 6 cohorts)	7594	China, Europe, Italy, Japan, Korea, Poland, Spain, Sweden, Uruguay, USA,	Incidence, Gastric cancer	Cruciferous vegetables High vs. low			
					Prospective studies	0.89 (0.77-1.02)	-	0%, 0.76
					Case-control studies	0.78 (0.71-0.86)	-	21.8%, 0.20
					All studies (n=22)	0.81 (0.75-0.88)	-	12%, 0.29
				Gastric cardia cancer	All studies (n=4)	0.84 (0.65-1.09)	-	33.5%, 0.21
				Gastric non-cardia cancer	All studies (n=6)	0.86 (0.74-0.99)	-	2.3%, 0.41

The six cohorts identified were included in the present review.

Table 17 Cruciferous vegetables intake and stomach 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
Gonzalez, 2012 STM80139 Denmark,France ,Germany,Greec e,Italy,Netherlan ds,Norway,Spai n,Sweden,U.K.	EPIC, Prospective Cohort, Age: 35-70 years, M/W	683/ 477 312 11 years	Cancer registries, health insurance records, pathology rec, active follow up, death certificate	FFQ (88 – 266-item), dietary questionnaires, food record Broccoli, Brussels sprout, cabbage, cauliflower, kale	Incidence, gastric adenocarcinoma	26.7 (M)/26.9 (W) vs. 10.3 (M)/11.1(W) g/day	1.13 (0.85-1.51) Ptrend: 0.45	Age, sex, BMI, centre, educational level, energy intake, other vegetables intake, physical activity, total fruits consumption, alcohol intake, red and processed meat, smoking	Distribution of cases and person-years by intake quintiles, weighted average of exposure values
		201/			Gastric cardia adenocarcinoma		0.93 (0.57-1.52) Ptrend: 0.80		
		323/			Gastric non-cardia adenocarcinoma		1.61 (1.01-2.58) Ptrend: 0.25		
		203/			Intestinal gastric cancer		0.74 (0.44-1.24) Ptrend: 0.31		
		217/			Diffuse gastric cancer		1.03 (0.62-1.73) Ptrend: 0.36		
Steevens, 2011 STM80062 The Netherlands	NLCS, Case Cohort, Age: 55-69 years, M/W	591/ 4651 16.3 years 148/	Annual linkage to The Netherlands cancer registry and the nationwide network of histopathology and cytopathology (PALGA)	Validated FFQ Brassica vegetables	Incidence, gastric cardia adenocarcinoma	59 vs. 11 g/day Per 25 g/day	0.51 (0.28-0.92) 0.72 (0.54-0.95)	Age, sex, alcohol consumption, duration of smoking, fruit intake, red meat intake, all other vegetables, current smoking, fish intake, number of cigarettes smoked per day	RRs for gastric cardia adenocarcinoma and gastric non-cardia adenocarcinoma combined using Hamling's method, rescaled the RR for the increment unit used
		443/			Gastric non-cardia adenocarcinoma		0.95 (0.66-1.35) 1.05 (0.90-1.21)		
Epplein, 2010 STM80129	SWHS and SMHS,	206/ 73 064	Review of medical records	Validated FFQ Bok choy,	Incidence, Distal stomach	>129.6 vs. ≤51.2	0.95 (0.65-1.37)	Age, education level, smoking,	Distribution of person-years by

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Missing data derived for analyses
China	Prospective Cohort, Age: 40-74 years, M/W			cabbage, Napa cabbage, cauliflower, white turnip, garland chrysanthemum, shepherd's purse, clover, and amaranth	cancer Women	g/day		total energy intake	exposure quintiles, mid-points of exposure categories (Included in analysis of gastric non-cardia cancer)
		132/ 59 247			Men	>164.9 vs. ≤71.4 g/day	1.05 (0.66-1.66)		
Freedman, 2008 STM80097 USA	NIH-AARP, Prospective Cohort, Age: 50-71 years, M/W, Retired	394/ 490 802 4.5 years 198/	Linkage with 11 state cancer registry databases	Validated FFQ Cruciferae: broccoli, cauliflower, Brussels sprouts, turnip, cabbage, coleslaw, collard, mustard, and kale	Incidence, cardia cancer	0.46 vs. 0.06 serving/1000kca l	0.95 (0.67-1.35)	Age, sex, BMI, ethnicity, alcohol intake, cigarette-smoke-dose, education, total energy, usual activity throughout the day, vigorous physical activity	Distribution of person-years by intake tertiles, exposure values using mean energy intake (1990 kcal/day) and standard portion size of 80 g/day, RRs for cardia and non-cardia gastric cancers combined using Hamling's method
		196/			Non-cardia cancer		1.03 (0.72-1.48)		
Larsson, 2006c STM80086 Sweden	SMC and COSM, Prospective Cohort, Age: 45-83 years,	139/ 82 002 7.2 years	Cancer registry/mortalit y register/populati on registry	Validated FFQ White cabbage, red cabbage, Chinese cabbage, cauliflower,	Incidence, stomach cancer	≥3.0 vs. <0.5 servings/week	0.70 (0.43-1.15) Ptrend: 0.30	Age, sex, diabetes, smoking status, alcohol intake, education, pack years of	Servings converted to grams using the conversion of 80 g per serving, mid-points of

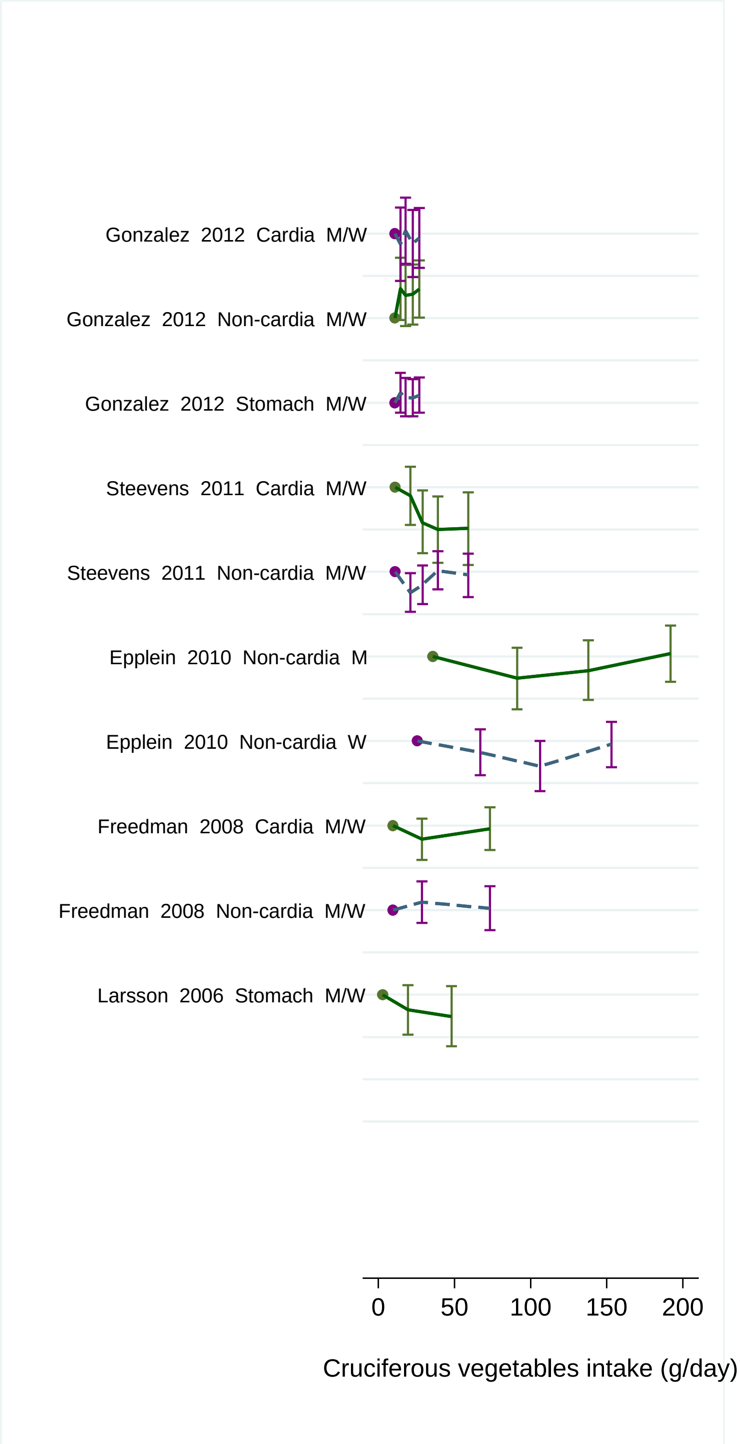
Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Missing data derived for analyses
	M/W			broccoli, and Brussels sprouts				smoking, processed meat intake, total energy intake	exposure categories

Table 18 Cruciferous vegetables intake and stomach 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
Gonzalez, 2006a STM44425 France, Italy, Spain, U.K., Netherlands, Greece, Germany, Sweden, Denmark	EPIC, Prospective Cohort, Age: 35-70 years, M/F	311/ 481 518 6.5 years	Cancer registries, health insurance records, pathology rec, active follow up, death certificate	FFQ (88 – 266-item), dietary questionnaires, food record	Incidence, gastric adenocarcinoma	Q4 vs. Q1 Per 100 g/day	0.83 (0.55-1.28) Ptrend: 0.46 1.00 (0.83-1.20)	Age, sex, alcohol consumption, educational level, energy intake, height, physical activity, processed meat, red meat intake, smoking habits, weight	Superseded by Gonzalez, 2012, STM80139
		89/			Gastric cardia adenocarcinoma		1.25 (0.60-2.62) Ptrend: 0.46 1.19 (0.94-1.50)		
		150/			Gastric non-cardia adenocarcinoma		0.59 (0.30-1.16) Ptrend: 0.20 1.00 (0.78-1.29)		
		102/			Intestinal gastric cancer		1.27 (0.63-2.53) Ptrend: 0.55 1.33 (1.09-1.63)		
		109/			Diffuse gastric cancer		0.82 (0.40-1.70) Ptrend: 0.68 0.73 (0.50-1.07)		
Botterweck, 1998 STM04445 Netherlands	NLCS, Case Cohort, Age: 55-69 years, M/F	265/ 120 852 6.3 years	Cancer registry	FFQ	Incidence, stomach cancer	58 vs. 10 g/day	Brassicas - Brussels sprouts, cauliflower, kale 0.93 (0.61-1.43) Ptrend: 0.29	Age, sex, educational level, family history of stomach cancer, fruit, smoking habits, stomach disorders	Superseded by Steevens, 2011 STM80062
Zheng, 1995 STM06417 USA	IWHS, Prospective Cohort,	26/ 34 691 7 years	Cancer registry	FFQ	Incidence, stomach cancer	Quantile 3 vs. quantile 1	No significant association	Age, educational level, pack-years	Excluded, no measure of association

Author, Year, 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: 55-69 years, F, Post-menopausal women							of smoking, smoking habits	
Kneller, 1991 STM07350 USA	LBS, Prospective Cohort, Age: 35- years, M, Mainly of Scandinavian descent	75/ 17 633 20 years	Health insurance company records	FFQ	Mortality, stomach cancer	Quantile 4 vs. quantile 1	1.30 (0.67-2.68)	Age, smoking habits	Excluded, exposure levels not quantified
Chyou, 1990 STM12425 USA	HHP, Case Cohort, Age: 58.00years, M, Japanese residents of Hawaii	111/ 8006 18 years	Cancer registry/ hospital records	FFQ + recall	Incidence/mortality, stomach cancer	Consumer vs. none	Cruciferous vegetables, cabbage accounted for 77% 0.70 (0.40-1.20)	Age, smoking habits	Excluded, exposure levels not quantified

Figure 19 RR estimates of stomach cancer by levels of cruciferous vegetables intake



Note: Cruciferous vegetables varied between studies. Gonzalez, 2012: Cabbages (broccoli, Brussels sprout, cabbage, cauliflower, kale); Steevens, 2011: Brassica vegetables; Epplein, 2010: bok choy, cabbage, Napa cabbage, cauliflower, white turnip, garland chrysanthemum, shepherd's purse, clover, and amaranth; Freedman, 2008: Cruciferae: broccoli, cauliflower, Brussels sprouts, turnip, cabbage, coleslaw, collard, mustard, and kale; Larsson, 2006c: white cabbage, red cabbage, Chinese cabbage, cauliflower, broccoli, and Brussels sprouts

Figure 20 2 RR (95% CI) of stomach cancer for the highest compared with the lowest level of cruciferous vegetables intake

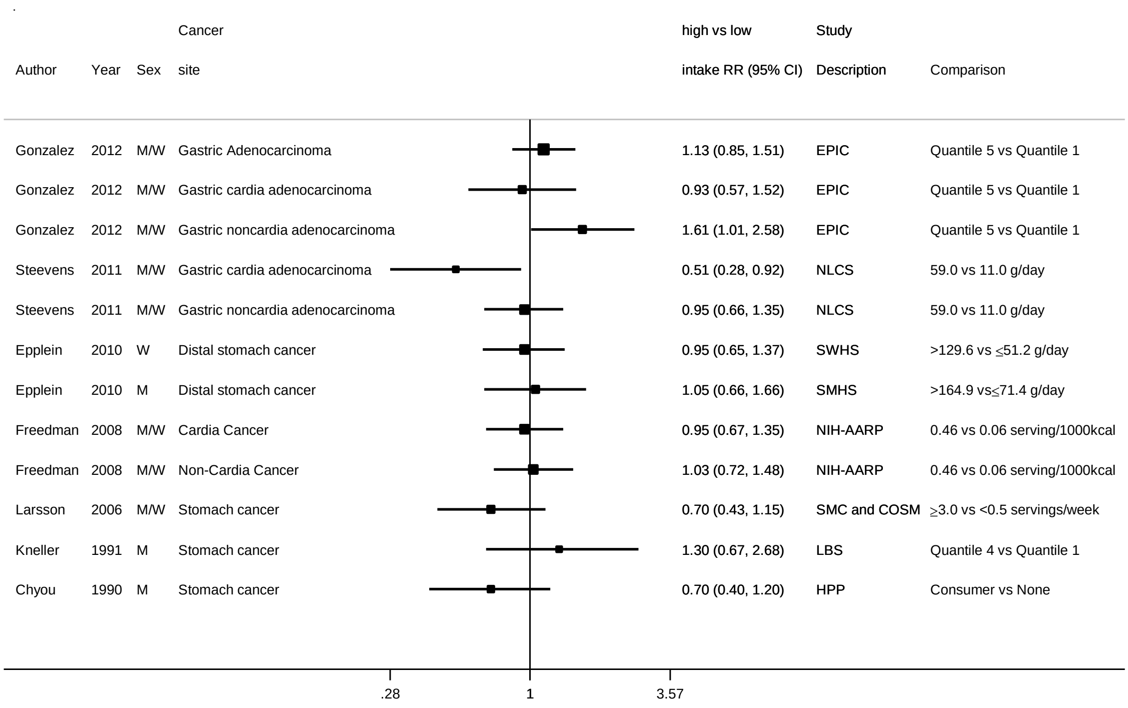


Figure 21 Relative risk of stomach cancer for 50 g/day increase of cruciferous vegetables intake

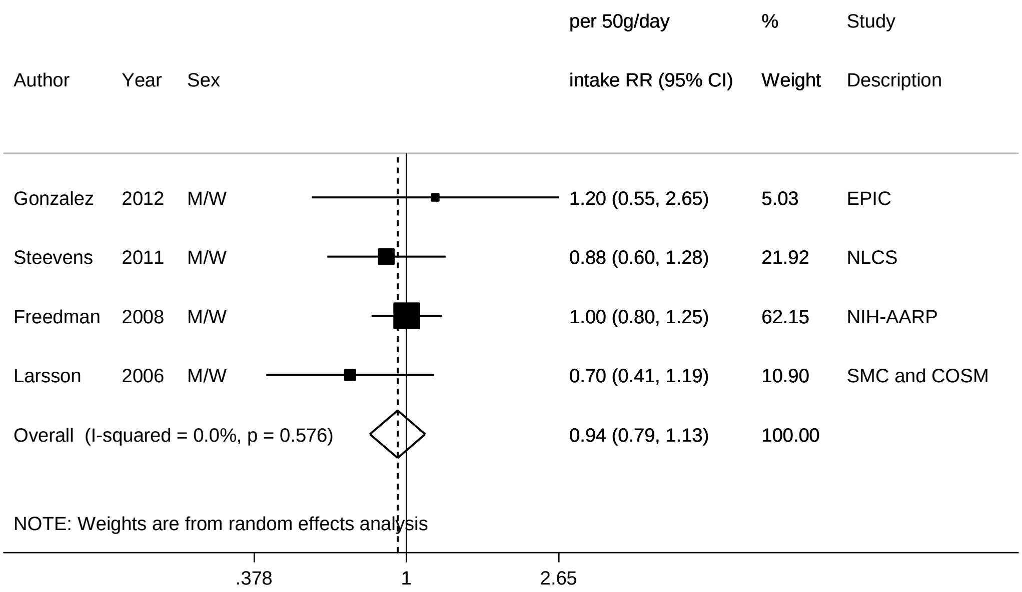
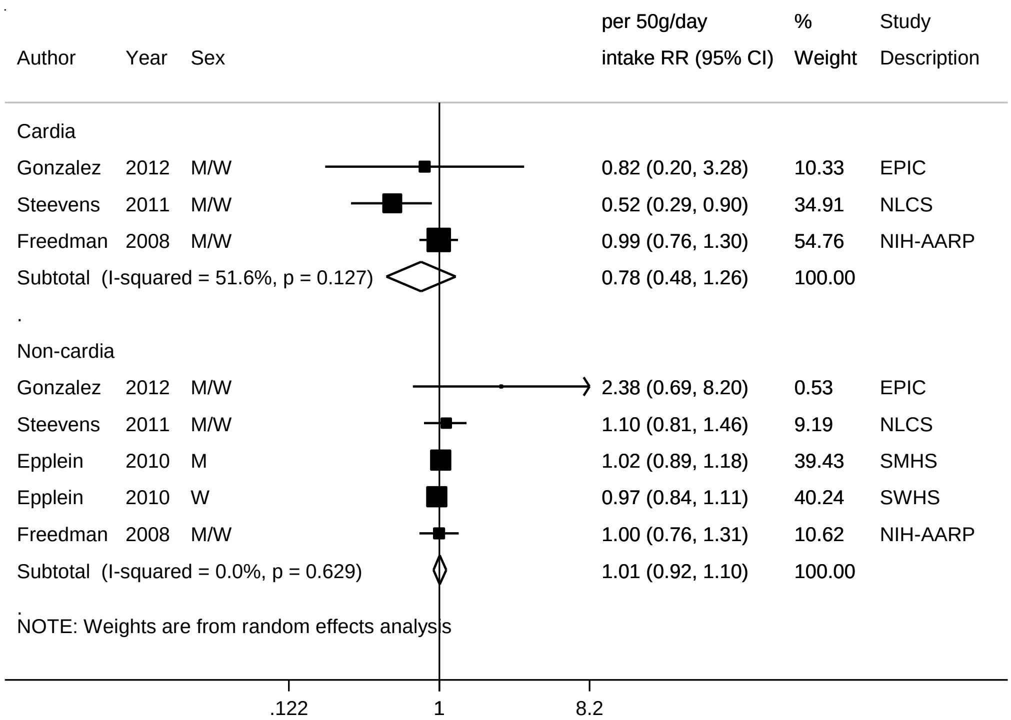


Figure 22 Relative risk of stomach cancer for 50 g/day increase of cruciferous vegetables intake by cancer site



2.2.1.3 Allium vegetables

Randomised controlled trials

One randomised placebo-controlled trial in China reported no significant effect of garlic supplement use on stomach cancer incidence, mortality, or oesophageal and stomach cancer mortality combined (Ma, 2012).

Table 19 Allium vegetables intake and stomach cancer risk. Main characteristics of randomised controlled trials included in the CUP SLR

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Intervention	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors
Ma, 2012 STM80100 China	Shandong Intervention Trial, Randomised Control Trial, Age: 35-64 years, M/W	103/ 3365 14.7 years	Endoscopy, biopsy, cancer registry, medical records	7 years of supplementation with a mixture of garlic extract and steam-distilled garlic oil; 95% compliance to garlic treatment	Incidence, stomach cancer	Garlic treatment vs. Placebo	0.80 (0.53-1.20)	Age, sex, alcohol consumption, baseline histopathology, smoking history
		43/			Mortality, stomach cancer		0.65 (0.35-1.20)	
		60/			Mortality, stomach and oesophageal cancer		0.62 (0.37-1.05)	

Cohort studies

Summary

Main results:

Although meta-analysis are updated in the CUP when there are at least five studies with the data required for analysis, this section has been included because the evidence that allium vegetables are causally related to stomach cancer risk was judged as probable in the Second Expert report.

Three studies (1413 cases) were included in the dose-response meta-analysis. No significant associations were observed for stomach cancer, gastric cardia (two studies, low heterogeneity) and non-cardia gastric cancer (four studies, no heterogeneity).

Two studies from one publication that reported results on distal gastric cancer only were excluded from the analysis of stomach cancer (Epplein, 2010). Non-significant association was observed.

Two publications (Steevens, 2011; Dorant, 1996) of the same cohort from the Netherlands (NLCS) investigated specific allium items. No significant associations of onion or leeks with stomach cancer were observed and a non-significant positive association was observed for garlic supplement use (only supplement) compared with no supplements use.

No heterogeneity was observed in the dose-response meta-analysis. Test of publication or small study bias was not conducted due to small number of studies.

Sensitivity analyses:

The summary RR did not change materially when each study was omitted in turn in influence analysis.

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 used FFQ to assess allium vegetables intake. The definition of allium vegetables varied between studies. There was one European study (Gonzalez, 2012 - onion and garlic), one Dutch study (Steevens, 2011 - onion and leek), one Swedish study (Larsson, 2006 - onion, leek, and garlic), and two Chinese studies (Epplein, 2010 - onion, garlic, chives). Loss to follow-up was low. Cancer outcome was confirmed using medical notes or record linkages to the cancer registries.

All studies included in the dose-response analysis were adjusted for several risk factors. The less adjusted was the study by Epplein, 2010 that was adjusted for age, education level, smoking, and total energy intake.

Table 20 Allium vegetables intake and stomach cancer risk. Number of studies in the CUP SLR

	Number
Studies identified	5* (6 publications)
Studies included in forest plot of highest compared with lowest exposure	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 two cohorts in one publication (Epplein, 2010) that reported results on distal gastric cancer only.

Table 21 Allium vegetables intake and stomach cancer risk. Summary of the linear dose-response meta-analysis in the 2005 SLR and the CUP

	2005 SLR	**CUP**
Increment unit used	100 g/day	10 g/day
All studies		
Studies (n)	2	3
Cases (total number)	439	1413
RR (95%CI)	0.55 (0.35-0.87)	1.01 (0.96-1.07)
Heterogeneity (I^2, p-value)	0%, 0.8	0%, 0.85
P value Egger test	-	-
Stratified analysis		
Gastric cardia cancer		
Studies (n)	-	2 (n=349)
RR (95%CI)	-	1.04 (0.96-1.13)
Heterogeneity (I^2, p-value)	-	6.8%, 0.30
Non-cardia gastric cancer		
Studies (n)	-	4 (n=1104)
RR (95%CI)	-	0.99 (0.95-1.04)
Heterogeneity (I^2, p-value)	-	0%, 0.76

Table 22 Allium vegetables intake and stomach cancer risk. Results of meta-analyses and pooled analyses of prospective studies published after the 2005 SLR

Author, Year	Number of studies	Total number of cases	Studies country, area	Outcome	Comparison	RR (95%CI)	P trend	Heterogeneity (I^2, p value)
Meta-analyses								
Zhou 2011	21 studies (8 hospital-based case-control, 11 population-based case-control, 2 cohorts*)	7644	China, Denmark, France, Germany, Greece, Iran, Italy, Japan, Korea, Lithuania, Norway, Poland, Serbia, Spain, Sweden, The Netherlands, Uruguay, UK, Venezuela	Incidence, Gastric cancer	Allium High vs. low			
					Cohorts	0.66 (0.46-0.86)	-	0%, 0.46
					Hospital-based case-control	0.49 (0.29-0.70)	-	76%, <0.0001
					Population-based case-control	0.55 (0.41-0.69)	-	88.4%, <0.0001
					All studies	0.54 (0.43-0.65)	-	83.6%, <0.0001
				Proximal gastric cancer	All studies (n=4)	0.65 0.35-0.94	-	-, 0.59
				Distal gastric cancer	All studies (n=4)	0.70 0.58 0.82	-	-, 0.19

*The two publications of cohort studies in Zhou, 2011 were superseded by more recent publications (EPIC, Gonzalez, 2012 and NLCS, Steveens, 2011) that were included in the present CUP SLR.

Table 23 Allium vegetables intake and stomach 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
Gonzalez, 2012 STM80139 Denmark,France,Germany,Greece,Italy,Netherlands,Norway,Spain,Sweden,UK	EPIC, Prospective Cohort, Age: 35-70 years, M/W	683/ 477 312 11 years	Cancer registries, health insurance records, pathology rec, active follow up, death certificate	FFQ (88 – 266-item), dietary questionnaires, food record Onion, garlic	Incidence, gastric adenocarcinoma	26.6 (M)/17.1 (W) vs. 7.6 (M)/ 6.2 (W) g/day	0.97 (0.76-1.25) Ptrend: 0.94	Age, sex, BMI, centre, educational level, energy intake, other vegetables intake, physical activity, total fruits consumption, alcohol intake, red and processed meat, smoking	Distribution of cases and person-years by intake quintiles, weighted average of exposure values
		201/			Gastric cardia adenocarcinoma		0.87 (0.56-1.36) Ptrend: 0.84		
		323/			Gastric non-cardia adenocarcinoma		1.08 (0.74-1.57) Ptrend: 0.32		
		203/			Intestinal gastric cancer		1.31 (0.83-2.08) Ptrend: 0.14		
		217/			Diffuse gastric cancer		0.84 (0.53-1.34) Ptrend: 0.09		
Steevens, 2011 STM80062 The Netherlands	NLCS, Case Cohort, Age: 55-69 years, M/W	591/ 4651 16.3 years 148/	Annual linkage to the Netherlands cancer registry and the nationwide network of histopathology and cytopathology (PALGA)	Validated FFQ, 150-item Leeks and onion	Incidence Gastric cardia adenocarcinoma	Leeks and onion 62 vs. 5 g/day Per 25 g/day	1.55 (0.94-2.56) 1.14 (0.97-1.35)	Age, sex, alcohol consumption, duration of smoking, fruit intake, red meat intake, all other vegetables, current smoking, fish intake, number of cigarette smoked per day	RRs for gastric cardia adenocarcinoma and gastric non-cardia adenocarcinoma combined using Hamling's method, rescaled the RR for the increment unit used
		443/			Gastric non-cardia adenocarcinoma		0.97 (0.69-1.35) 0.98 (0.87-1.11)		
		148/			Gastric cardia adenocarcinoma	Onion	1.21 (0.95-1.53)		

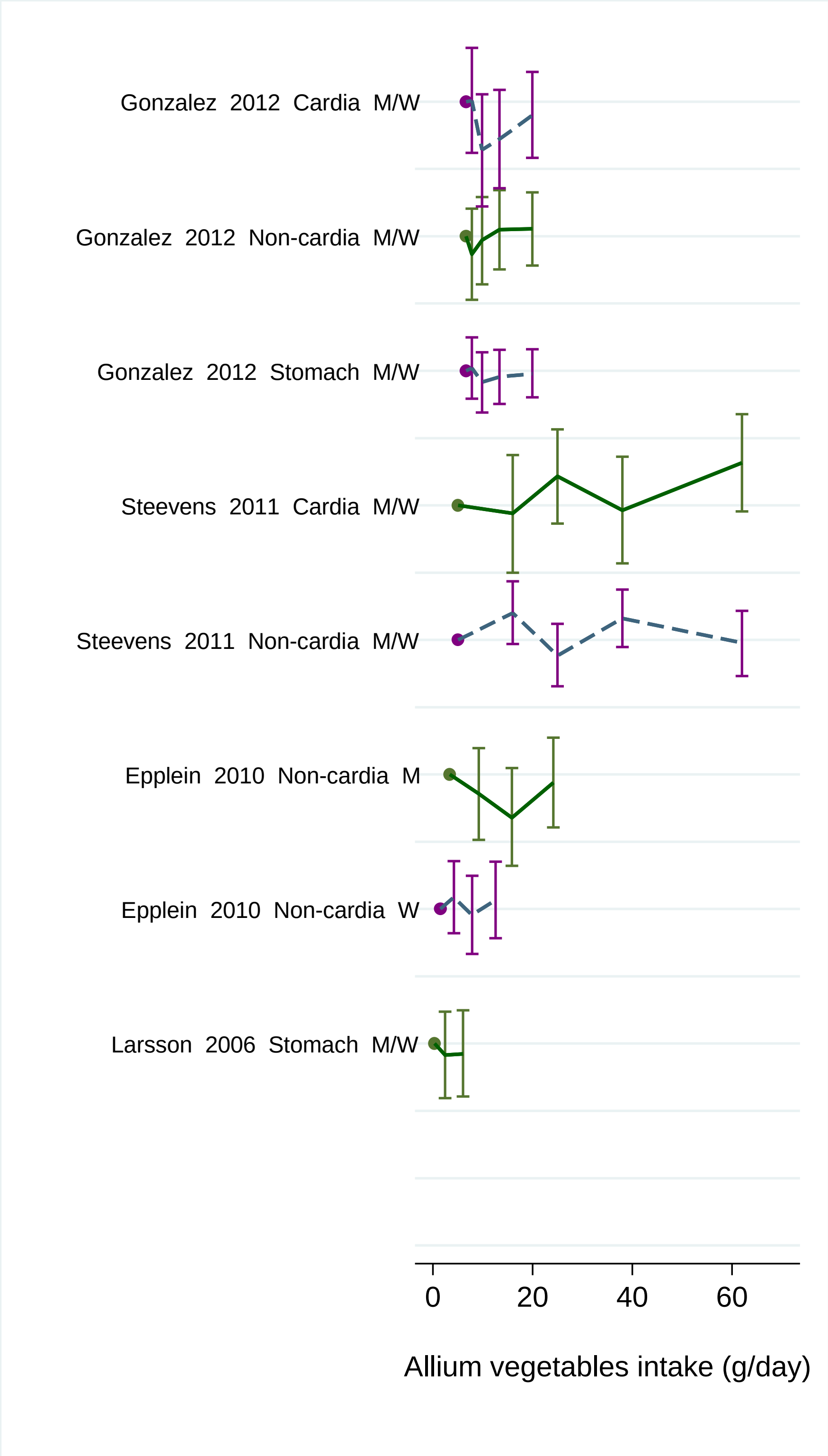
Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Missing data derived for analyses
		443/			Gastric non-cardia adenocarcinoma	Per 25 g/day	0.91 (0.78-1.06)		
Epplein, 2010 STM80129 China	SWHS, SMHS, Prospective Cohort, Age: 40-74 years, M/W	338/ 132 311 206/ 73 064	Review of medical records	Validated FFQ, 77-item in SWHS, 81-item in SMHS Garlic, garlic shoots, heads of garlic, onions, green onions, and Chinese chives	Incidence, distal stomach cancer Women	>10.2 vs. ≤2.9 g/day	1.10 (0.74-1.63) Ptrend: 0.88	Age, education level, smoking, total energy intake	Distribution of person-years by exposure quintiles, mid-points of exposure categories (Included in analysis of non-cardia gastric cancer)
		132/ 59 247			Men	>20.0 vs. ≤6.7 g/day	0.92 (0.58-1.46) Ptrend: 0.51		
Larsson, 2006c STM80086 Sweden	SMC and COSM, Prospective Cohort, Age: 45-83 years, M/W	139/ 82 002 7.2 years	Cancer/ mortality/ population registries	Validated FFQ, 96-item Onion, leek, garlic	Incidence, stomach cancer	≥3.0 vs. <0.5 servings/week	0.90 (0.58-1.41) Ptrend: 0.78	Age, sex, diabetes, smoking status, alcohol intake, education, pack years of smoking, processed meat intake, total energy intake	Servings converted to grams using the conversion of 10 g per serving, mid-points of exposure categories

Table 24 Allium vegetables intake and stomach 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
Gonzalez, 2006a STM44425 France, Italy, Spain, UK, Netherlands, Greece, Germany, Sweden, Denmark	EPIC, Prospective Cohort, Age: 35-70 years, M/W	300/ 481 518 6.5 years	Cancer registries, health insurance records, pathology rec, active follow up, death certificate	FFQ (88 – 266-item), dietary questionnaires, food record Onion, garlic	Incidence, gastric adenocarcinoma	Quantile 4 vs. quantile 1 Per 10 g/day	0.77 (0.50-1.20) 0.89 (0.62-1.28)	Age, sex, alcohol consumption, educational level, energy intake, height, physical activity, processed meat, red meat intake, smoking habits, weight	Superseded by Gonzalez, 2012, STM80139
		85/			Gastric cardia adenocarcinoma		0.88 (0.40-1.95) 0.84 (0.39-1.82)		
		146/			Gastric non-cardia adenocarcinoma		1.02 (0.54-1.92) 1.04 (0.67-1.63)		
		99/			Intestinal gastric cancer		0.47 (0.21-1.05) 0.70 (0.38-1.29)		
		106/			Diffuse gastric cancer		1.64 (0.77-3.47) 1.30 (0.75-2.23)		
Dorant, 1996 STM10788 The Netherlands	NLCS, Case Cohort, Age: 55-69 years, M/W	139/ 120 852 3.3 years	Cancer registry	FFQ, 150-item Onion, leeks	Incidence, stomach cancer	Onion ≥76 g/day vs. none	0.50 (0.26-0.96)	Age, sex, alcohol consumption, beta-carotene intake, educational level, family history of stomach cancer, smoking habits, stomach disorders, vitamin c	Excluded, specific type of allium vegetable (Steevens, 2011 STM80062 of the same study was included in the dose response analysis)
		30/			Cardia cancer	Onion ≥0.5 vs. 0 number/day	2.12 (0.60-7.48)		
		84/			Non-cardia cancer		0.35 (0.15-0.86)		
Dorant, 1996 STM10788 Netherlands	NLCS, Case Cohort, Age: 55-69 years, M/W	139/	Cancer registry	FFQ	Stomach cancer	Leeks ≥2 times/month vs. none	0.69 (0.42-1.15)		
		30/			Cardia cancer		0.86 (0.37-1.98)		
		84/			Non-cardia cancer		0.59 (0.32-1.09)		

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Reasons for exclusion
Dorant, 1996 STM10788 Netherlands	NLCS, Case Cohort, Age: 55-69 years, M/W	127/	Cancer registry	FFQ	Stomach cancer	Exclusively garlic supplement vs. no supplements	1.29 (0.62-2.67)	Age, sex, alcohol consumption, beta-carotene intake, educational level, family history of stomach cancer, leek consumption, onion consumption, smoking habits, stomach disorders, vitamin c	

Figure 23 RR estimates of stomach cancer by levels of allium vegetables intake



Note: Allium vegetables varied between studies. Gonzalez, 2012: onion and garlic; Steevens, 2011: onion and leek; Epplein, 2010: onion, garlic, chives; Larsson, 2006c: onion, leek, and garlic. Epplein, 2010 was included in the analysis on distal gastric cancer only.

Figure 24 RR (95% CI) of stomach cancer for the highest compared with the lowest level of allium vegetables intake

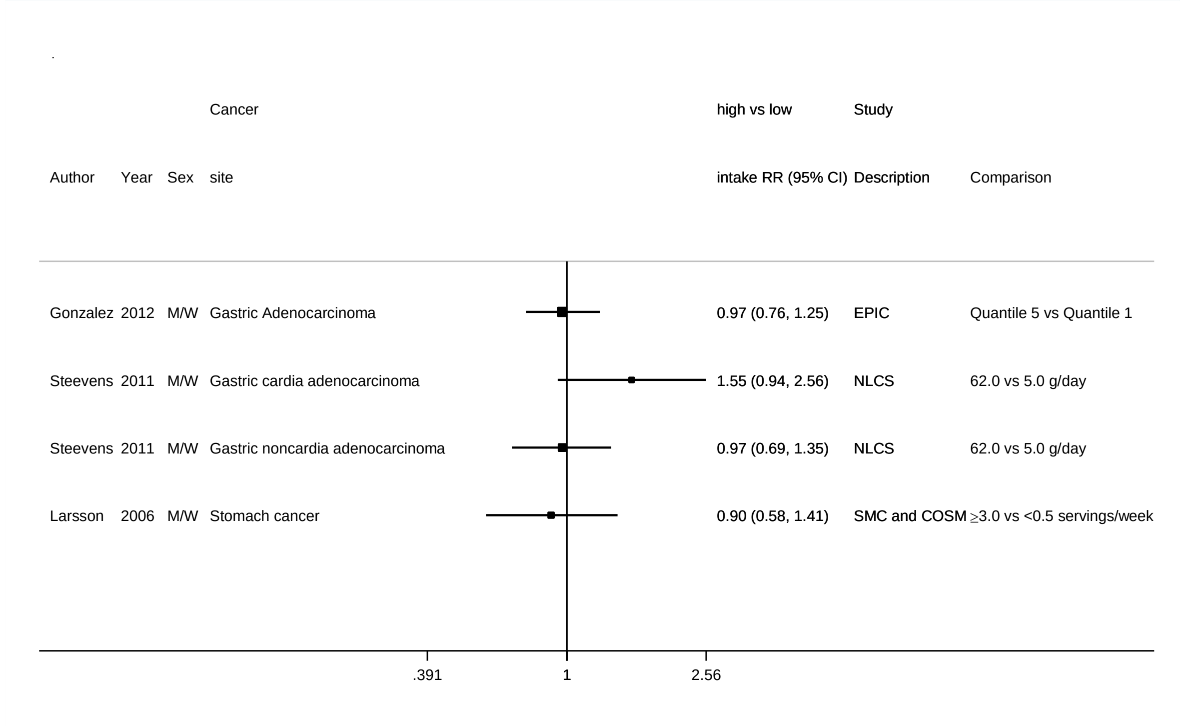


Figure 25 Relative risk of stomach cancer for 10 g/day increase of allium vegetables intake

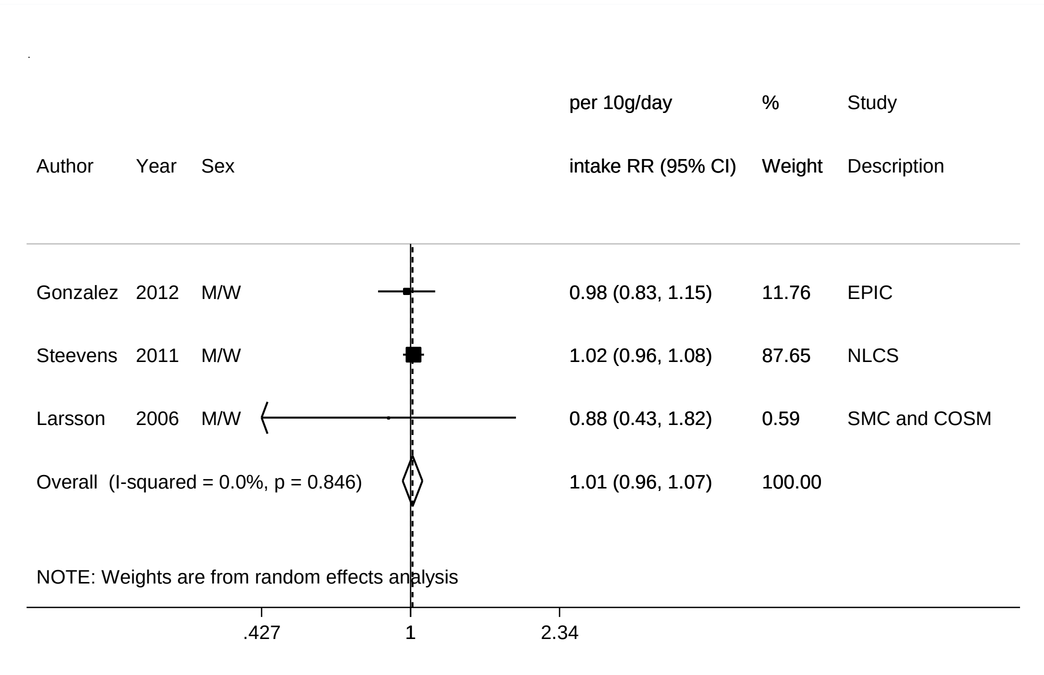
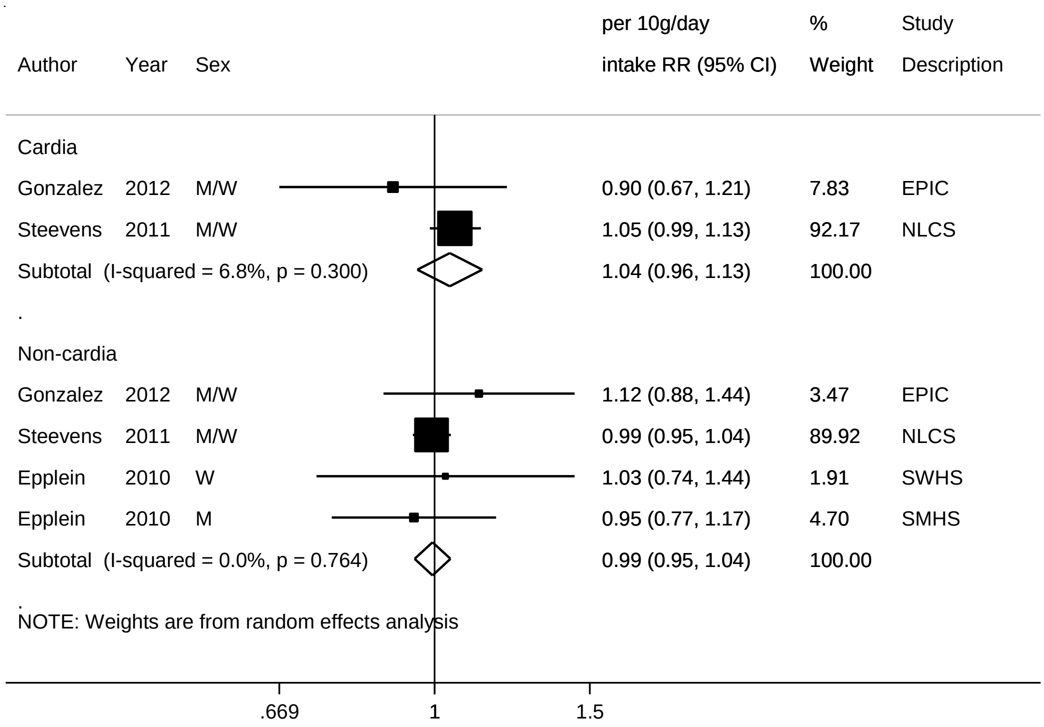


Figure 26 Relative risk of stomach cancer for 10 g/day increase of allium vegetables intake by cancer site



2.2.1.4 Green leafy vegetables

Randomised controlled trials

No randomised controlled trial was identified.

Cohort studies

Summary

Main results:

Seven studies (3398 cases) out of ten studies were included in the dose-response meta-analysis. Green leafy vegetables consumption was not associated with stomach cancer risk; a borderline significant positive association was observed for gastric cardia cancer and a non-significant (inverse) association was observed for non-cardia gastric cancer.

Non-significant associations were reported in the studies excluded from the dose-response analysis (Zheng, 1995 on stomach cancer and two studies in one publication -Epplein, 2010- on distal gastric cancer only.

Moderate heterogeneity was observed. There was no significant evidence of publication or small study bias. Visual inspection of the funnel plot suggested small studies with a positive association were missing.

Sensitivity analyses:

The summary RRs ranged from 0.96 (95% CI=0.83-1.12) when Freedman, 2008 (35.0% weight) was omitted to 1.05 (95% CI=0.97-1.13) when Larsson, 2006 (4.7% weight) was omitted in influence analysis.

Non-linear dose-response meta-analysis:

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

Study quality:

Loss to follow-up was low in most studies. Cancer outcome was confirmed using medical notes, death certificates, or records in cancer registries.

All studies used FFQ to assess green leafy vegetables intake. The definition of green leafy vegetables varied between studies. One study (Freedman, 2008) was on raw and cooked spinach. All studies included in the dose-response analysis were adjusted for multiple risk factors except one study that was adjusted only for age and smoking habits (Chyou, 1990). None of the studies were adjusted for Helicobacter pylori status.

Table 25 Green leafy vegetables intake and stomach cancer risk. Number of studies in the CUP SLR

	Number
Studies identified	10* (13 publications)

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

Note: Include cohort, nested case-control and case-cohort designs *Included two studies in one publication (Epplein, 2010) on distal gastric cancer only.

Table 26 Green leafy vegetables intake and stomach cancer risk. Summary of the linear dose-response meta-analysis in the 2005 SLR and CUP

	2005 SLR		**CUP**
Increment unit used	100g/day		50g/day
All studies			
Studies (n)	4		7
Cases (total number)	1110		3398
RR (95%CI)	0.85 (0.58-1.25)		1.01 (0.91-1.12)
Heterogeneity (I^2, p-value)	0%, 0.96		37.0%, 0.15
P value Egger test	0.3		0.07
Stratified and sensitivity analysis*			
Sex	**Men**		**Women**
Studies (n)	2		1
RR (95%CI)	1.15 (0.61-2.18)		1.21 (0.65-2.25)
Heterogeneity (I^2, p-value)	62.1%, 0.10		-
Cancer site	**Gastric cardia cancer**		**Non-cardia gastric cancer**
Studies (n)	3		5
RR (95%CI)	1.11 (1.00-1.22)		0.99 (0.92-1.07)
Heterogeneity (I^2, p-value)	0%, 0.40		0%, 0.42
Geographic location	**Asia**	**Europe**	**North America**
Studies (n)	2	3	2
RR (95%CI)	1.07 (0.87-1.32)	0.82 (0.65-1.04)	1.05 (0.92-1.19)
Heterogeneity (I^2, p-value)	63.0%, 0.10	0%, 0.57	17.7%, 0.27

*No stratified analysis in the 2005 SLR

Other stratified analyses

Duration of follow-up	**<10 years**	**10-<15 years**	**≥15 years**
Studies (n)	2	2	3
RR (95%CI)	0.90 (0.57-1.41)	0.94 (0.80-1.10)	1.06 (0.86-1.30)

Heterogeneity (I^2, p-value)	75.2%, 0.04	0%, 0.60	29.7%, 0.24
Number of cases	**<500 cases**	**≥500 cases**	
Studies (n)	4	3	
RR (95%CI)	0.97 (0.84-1.13)	1.04 (0.83-1.30)	
Heterogeneity (I^2, p-value)	48.6%, 0.12	40%, 0.19	
Publication year	**<2000**	**2000-2010**	**≥2010**
Studies (n)	1	4	2
RR (95%CI)	0.88 (0.63-1.24)	1.04 (0.91-1.19)	0.89 (0.68-1.16)
Heterogeneity (I^2, p-value)	-	55.6%, 0.08	0%, 0.86
Adjustment for confounders:			

Socioeconomic status/total energy intake*	**Not adjusted**	**Adjusted**
Studies (n)	3	4
RR (95%CI)	1.06 (0.86-1.30)	0.96 (0.83-1.12)
Heterogeneity (I^2, p-value)	29.7%, 0.24	51.3%, 0.10
Alcohol intake		
Studies (n)	2	5
RR (95%CI)	1.06 (0.80-1.41)	0.97 (0.85-1.11)
Heterogeneity (I^2, p-value)	56.7%, 0.13	37.1%, 0.17
BMI		
Studies (n)	4	3
RR (95%CI)	0.95 (0.73-1.23)	1.03 (0.93-1.14)
Heterogeneity (I^2, p-value)	56.8%, 0.07	22.2%, 0.28
Physical activity		
Studies (n)	5	2
RR (95%CI)	0.97 (0.82-1.15)	1.03 (0.86-1.22)
Heterogeneity (I^2, p-value)	46.7%, 0.11	38.0%, 0.20
Comorbidities**		
Studies (n)	5	2
RR (95%CI)	1.06 (0.97-1.16)	0.85 (0.61-1.19)
Heterogeneity (I^2, p-value)	13.4%, 0.33	51.9%, 0.15

***** The same adjustments were made in the studies
******Larsson, 2006c adjusted for diabetes; Kobayashi, 2002 adjusted for stomach disorder

Table 27 Green leafy vegetables intake and stomach 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
Gonzalez, 2012 STM80139 Denmark, France, Germany, Greece, Italy, Netherlands, Norway, Spain, Sweden, UK	EPIC, Prospective Cohort, Age: 35-70 years, M/W	683/ 477 312 11 years	Cancer registries, health insurance records, pathology records, active follow up, death certificate	FFQ, dietary questionnaires, food record Leafy vegetables: borage, chard, endive, lettuce, spinach, thistle	Incidence, gastric adenocarcinoma	46.3 (M)/ 47.0 (W) vs. 8.0 (M/W) g/day	0.96 (0.72-1.27)	Age, sex, BMI, centre, physical activity educational level, intake of energy, other vegetables, fruits, alcohol, red and processed meat, smoking	Distribution of cases and person-years by intake quintiles, weighted average of exposure values
		201/			Gastric cardia		1.29 (0.70-2.39)		
		323/			Gastric non-cardia		0.87 (0.59-1.28)		
		203/			Intestinal gastric cancer		0.91 (0.56-1.46)		
		217/			Diffuse gastric cancer		0.91 (0.57-1.46)		
Steevens, 2011 STM80062 The Netherlands	NLCS, Case Cohort, Age: 55-69 years, M/W	616/ 4651 16.3 years	Annual linkage to national cancer registry and network of histopathology and cytopathology	Validated FFQ Cooked endive and spinach	Incidence, gastric adenocarcinoma	42 vs. 4 g/day Per 25 g/day		Age, sex, alcohol consumption, duration of smoking, fruit intake, red meat intake, all other vegetables, current smoking, fish intake, number of cigarettes smoked per day	RRs for gastric cardia adenocarcinoma and gastric non-cardia adenocarcinoma combined using Hamling's method.
		148/			Gastric cardia adenocarcinoma		1.18 (0.66-2.09) 1.29 (0.96-1.74)		
		443/			Gastric non-cardia adenocarcinoma		0.87 (0.61-1.23) 0.92 (0.76-1.10)		
Epplein, 2010 STM80129 China	SWHS and SMHS, Prospective Cohort, Age: 40-74 years, M/W	373/ 132 311	Review of medical records	Validated FFQ	Incidence, distal stomach cancer			Age, education level, smoking, total energy intake	Distribution of person-years by quintiles, mid-points of exposure categories
		132/59 247			Men	>117.1 vs. ≤38.3 g/day	0.90 (0.57-1.42)		
		206/73 064			Women	>108.2 vs. ≤37.2 g/day	0.76 (0.52-1.10)		

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Missing data derived for analyses
									(included in the analysis of non-cardia stomach cancer only)
Freedman, 2008 STM80097 USA	NIH-AARP, Prospective Cohort, Age: 50-71 years, M/W, Retired	394/ 490 802 4.5 years 198/	Linkage with 11 state cancer registry databases	Validated 124-item FFQ Chenopodiaceae: raw and cooked spinach	Incidence, stomach cancer Cardia cancer	0.96 vs. 0 servings/ 1000 kcal	1.12 (0.81-1.55)	Age, sex, BMI, ethnicity, vegetable intake, alcohol intake, cigarette-dose, education, total energy, usual activity throughout the day, vigorous physical activity	Distribution of person-years by intake tertiles, exposure values using mean energy intake (1990 kcal/day) and standard portion size of 80 g/day, RRs for cardia and non-cardia gastric cancers were combined using the method of Hamling
		196/			Non-cardia cancer		1.13 (0.80-1.60)		
Iso, 2007 STM80144 Japan	JACC, Prospective Cohort, Age: 40-79 years, M/W	1076/ 105 500 15 years 728/43 850 348/60 169	Municipal resident registration records, death certificates	Validated FFQ Spinach and garland chrysanthemum	Mortality, stomach cancer Men Women	≥5 vs. <3 times/week	1.21 (1.00-1.47) 1.08 (0.81-1.43)	Age, area of study	Exposure values using standard portion size, mid-points of exposure categories, RRs for men and women combined
Larsson, 2006c STM80086	SMC and COSM,	139/ 82 002	Cancer registry/ mortality	Validated FFQ	Incidence, stomach cancer	≥3.0 vs. <0.5 servings/week	0.64 (0.42-0.99)	Age, sex, diabetes, smoking status,	Exposure values using standard

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Missing data derived for analyses
Sweden	Prospective Cohort, Age: 45-83 years, M/W	7.2 years	registry/ population registry					alcohol intake, education, pack years of smoking, processed meat intake, total energy intake	portion size, mid-points of exposure categories
Kobayashi, 2002 STM01446 Japan	JPHC I, Prospective Cohort, Age: 40-59 years, M/W	404/ 39 993 10 years	Hospital records, population-based cancer registries and death certificates, histologically confirmed	FFQ	Incidence, stomach cancer	Almost daily vs. <1 days/week	0.77 (0.40-1.46)	Age, sex, alcohol consumption, BMI, educational level, energy intake, family history of stomach cancer, highly salted food intake, history of peptic ulcer, smoking habits, study area, supplements of vitamin a, c, e	Exposure values using standard portion size, mid-points of exposure categories
Chyou, 1990 STM12425 USA	HHP, Case Cohort, Age: 58 years, M, Japanese residents of Hawaii	111/ 8006 18 years	Cancer registry/ hospital records	FFQ + recall	Incidence, stomach cancer	≥60 vs. 0 g/day	0.70 (0.40-1.20)	Age, smoking habits	Mid-points of exposure categories

Table 28 Green leafy vegetables intake and stomach 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
Iso, 2007 STM80144 Japan	JACC, Prospective Cohort, Age: 40-79 years, M/W	1076/ 105 500 15years 650/40 209 318/56 330	Municipal resident registration records, death certificates	Validated FFQ Lettuce and cabbage	Mortality, stomach cancer Men Women	≥5 vs. <3 times/week	 1.23 (0.99-1.51) 1.25 (0.93-1.66)	Age, area of study	Results on spinach and garland chrysanthemum was included from the same study
Gonzalez, 2006a STM44425 France, Italy, Spain, U.K., Netherlands, Greece, Germany, Sweden, Denmark	EPIC, Prospective Cohort, Age: 35-70 years, M/W	330/ 481 518 6.5 years	Cancer registry	FFQ	Incidence, stomach cancer	Quantile 4 vs. quantile 1 Per 100 g/day	1.19 (0.79-1.81) 1.01 (0.88-1.16)	Age, sex, centre, weight, education level, height, physical activity (leisure and work), intake of red meat, alcohol, processed meat, energy, tobacco use smoking intensity	Superseded by Gonzalez, 2012, STM80139
		94/			Gastric cardia adenocarcinoma		1.50 (0.69-3.26) 0.94 (0.68-1.31)		
		159/			Gastric non-cardia adenocarcinoma		1.15 (0.64-2.08) 0.99 (0.82-1.19)		
		109/			Intestinal gastric cancer		0.69 (0.33-1.46) 0.88 (0.68-1.14)		
		116/			Diffuse gastric cancer		1.50 (0.75-2.98) 1.10 (0.88-1.36)		
Tokui, 2005 STM80105 Japan	JACC, Prospective Cohort, Age: 40-79 years, M/W	859/ 44 930 12 years 436/ 206/	Population registry	FFQ	Mortality, stomach cancer Men Women	≥1/day vs. 1-2 times/month or less	 1.29 (0.89-1.87) 1.40 (0.72-2.70)	Age	Superseded by Iso 2007, STM80144

Author, Year, 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
Yatsuya, 2004 STM00003 Japan	JACC, Prospective Cohort, Age: 40-79 years, M/W	94/ 65 184 10years	Population registry	FFQ	Incidence, stomach cancer	≥ 3-4 vs. ≤1-2 times/week	Pvalue: 0.55		Superseded by Iso 2007, STM80144, no measure of association
Botterweck, 1998 STM04445 Netherlands	NLCS, Case Cohort, Age: 55-69 years, M/W	265/ 120 852 6.3 years	Cancer registry	FFQ	Incidence, stomach cancer	41 vs. 4 g/day	0.96 (0.63-1.44)	Age, sex, educational level, family history of stomach cancer, fruit, smoking habits, stomach disorders	Superseded by Steevens 2011, STM80062
Zheng, 1995 STM06417 USA	IWHS, Prospective Cohort, Age: 55-69 years, post-menopausal women	26/ 34 691 7 years	Cancer registry	FFQ	Incidence, stomach cancer	Quantile 3 vs. quantile 1	Non-significant association	Age, educational level, pack-years of smoking, smoking habits	Excluded, no measure of association

Figure 27 RR estimates of stomach cancer by levels of green leafy vegetables

Note: Epplein, 2010 was included in the analysis of distal gastric cancer only.

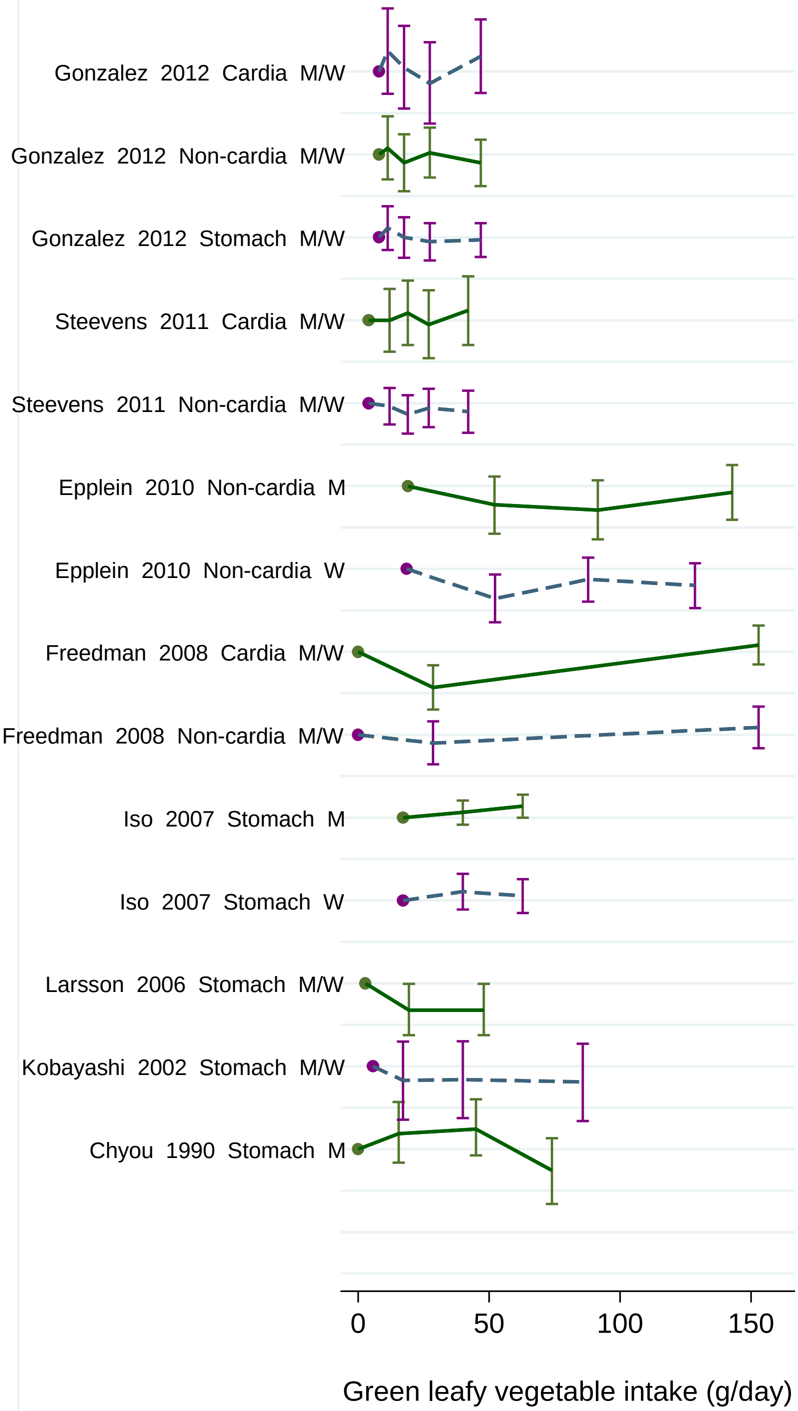


Figure 28 RR (95% CI) of stomach cancer for the highest compared with the lowest level of green leafy vegetables intake

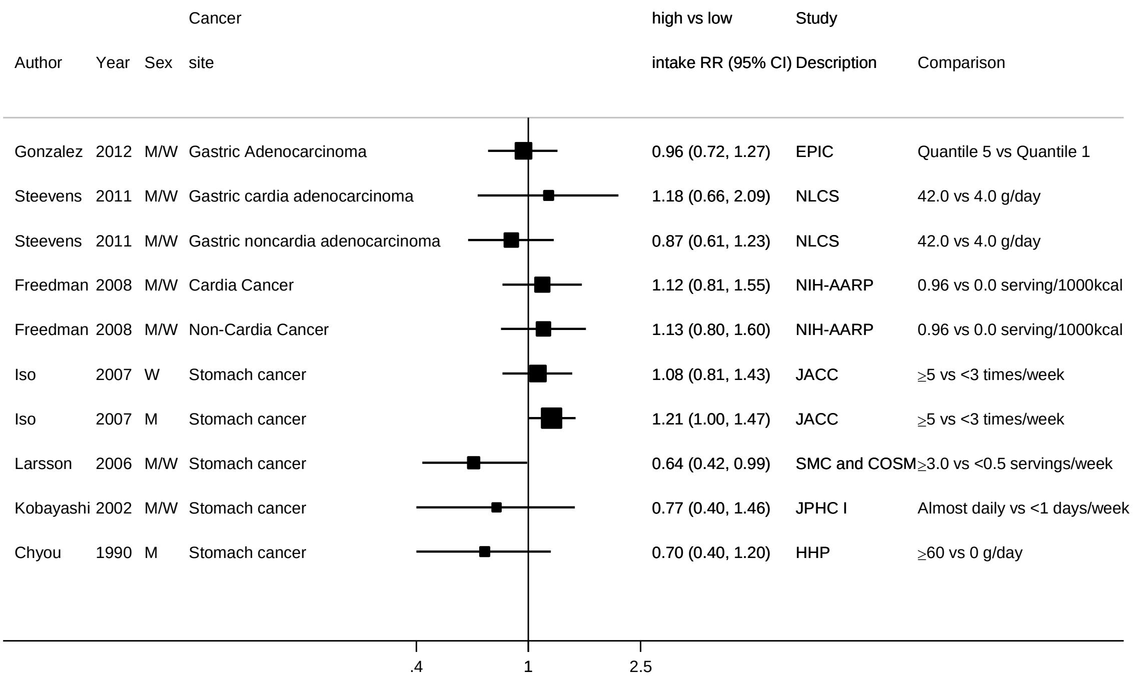


Figure 29 Relative risk of stomach cancer for 50g/day increase of green leafy vegetables intake

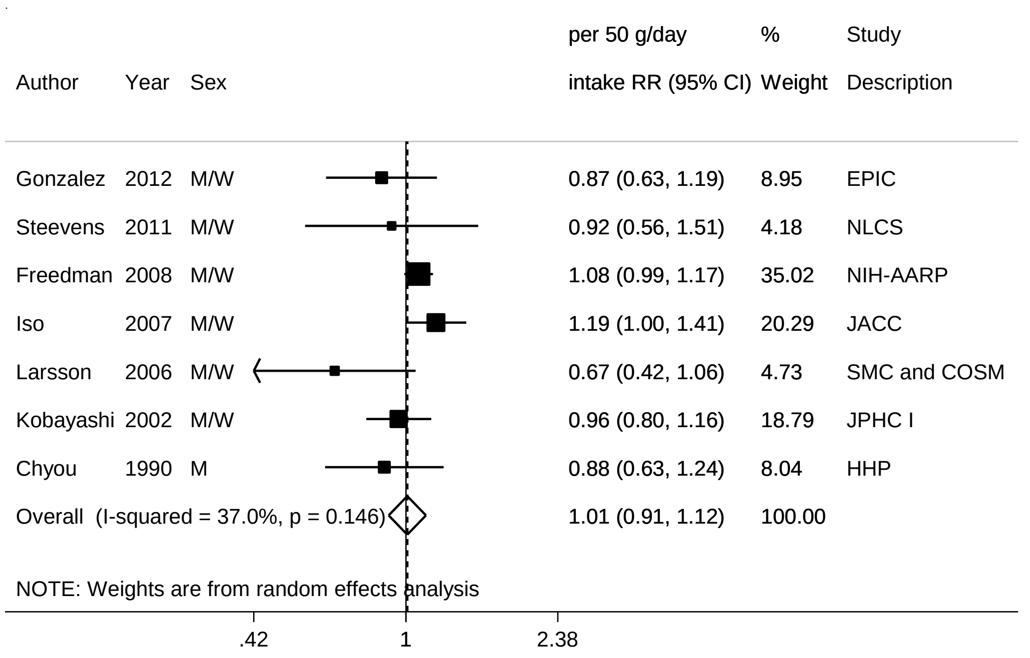
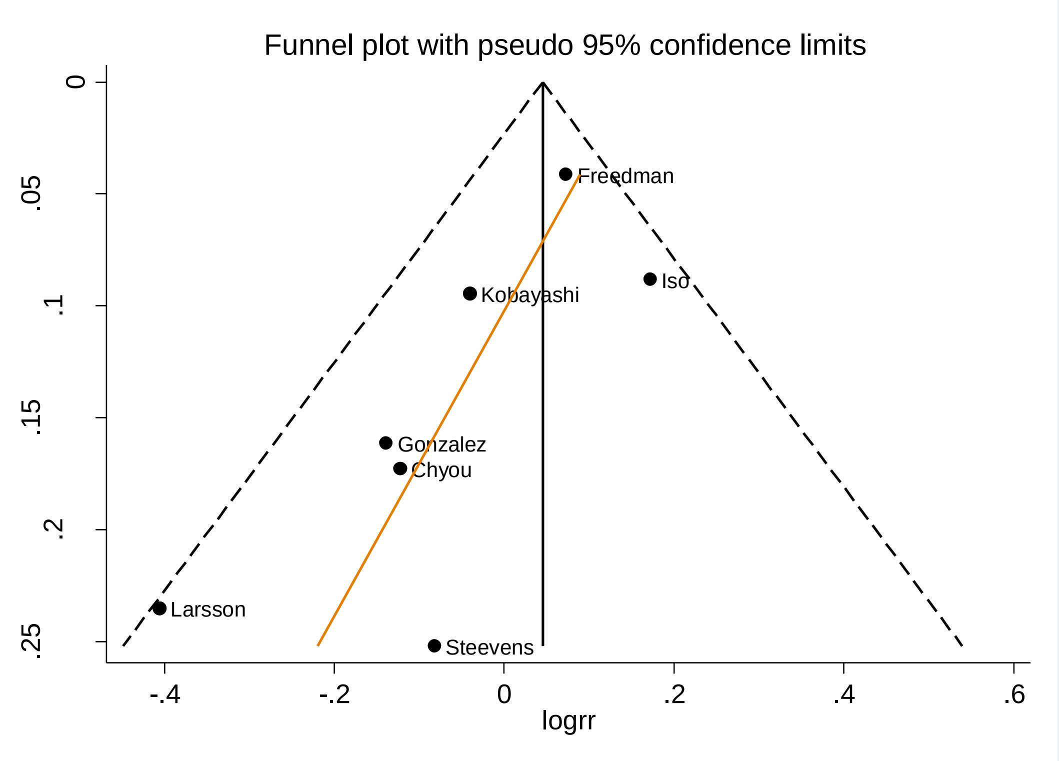


Figure 30 Funnel plot of studies included in the dose response meta-analysis of green leafy vegetables and stomach cancer



Egger's test p=0.07

Figure 31 Relative risk of stomach cancer for 50g/day increase of green leafy vegetables by sex

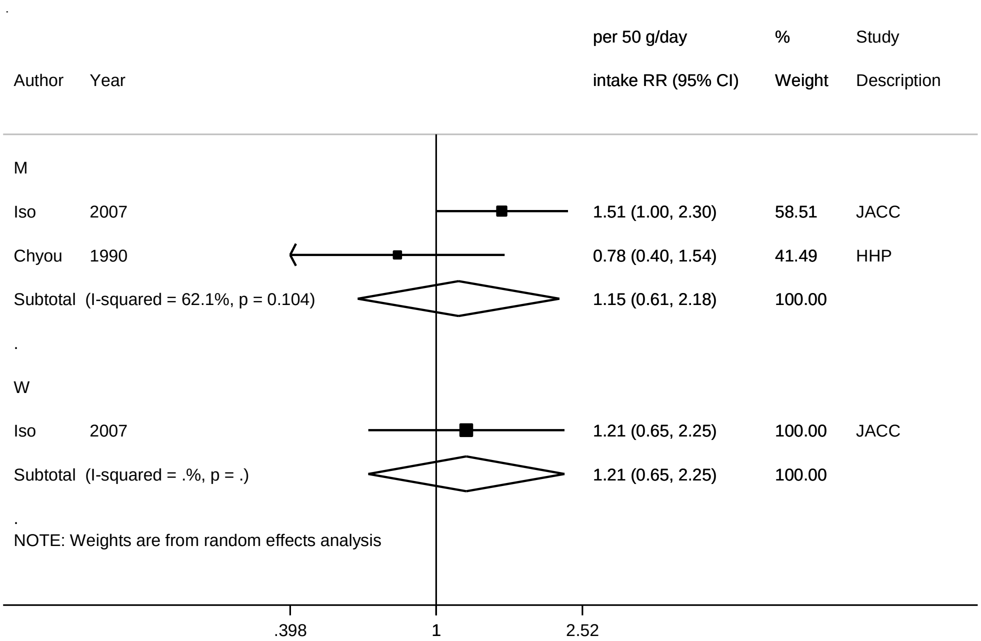


Figure 32 Relative risk of stomach cancer for 50g/day increase of green leafy vegetables by cancer site

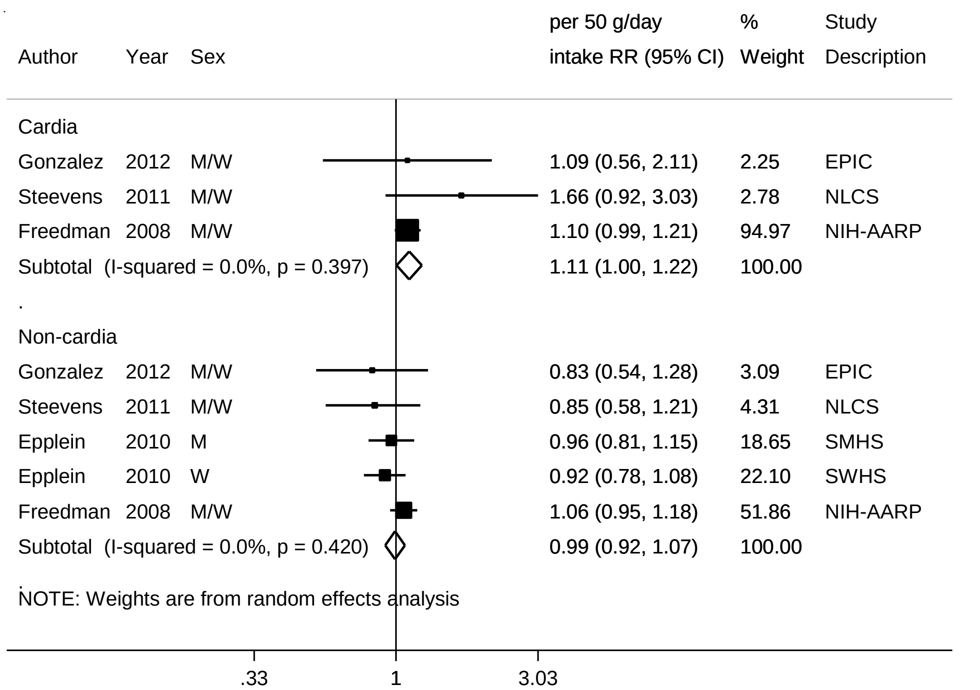
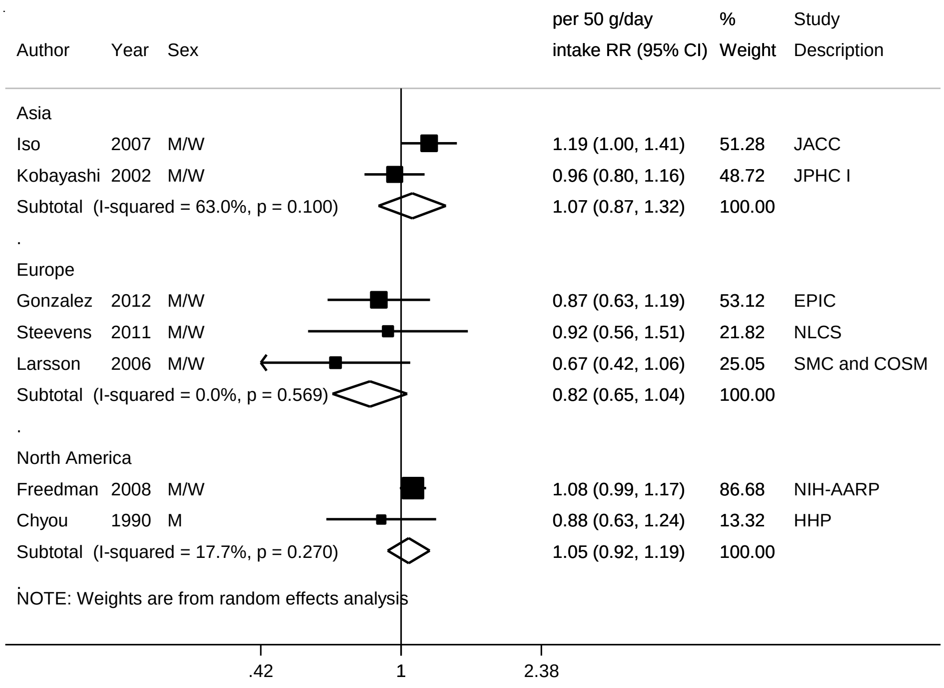


Figure 33 Relative risk of stomach cancer for 50g/day increase of green leafy vegetables by geographic location



2.2.1.5 Pickled vegetables

Randomised controlled trials

No randomised controlled trial was identified.

Cohort studies

Summary

Main results:

Nine studies (3932 cases) out of fourteen studies were included in the dose-response meta-analysis. Pickled vegetable consumption was significantly positively associated with stomach cancer risk.

Five studies were excluded from the dose-response meta-analysis. No significant associations were observed in three excluded studies. Two publications did not provide measures of association.

No heterogeneity was observed. There was no significant evidence of publication or small study bias.

Sensitivity and stratified analyses:

The summary RR did not change materially when studies were omitted in turn in influence analysis.

Significant associations were observed in stratified analysis of three or more studies in which incidence was an outcome, in studies with a follow-up of 10 years or longer, and in studies published after year 2000.

Study quality:

Loss to follow-up was low in most studies. Cancer outcome was confirmed using medical notes or records in cancer registries, hospitals, and death certificates in most studies.

One study was conducted in Europe (Botterweck, 1998), two studies in Japanese residents of Hawaii -Hawaii-Japan DOH Survey (Galanis, 1998) and HHP cohort (Nomura, 1990). The remaining studies were conducted in Japan.

The exposure investigated was pickled vegetables (Takachi, 2010; Iso 2007; Galanis, 1998) pickled food (Ngoan, 2002), pickles (Sauvaget 2005, Kato 1992a, b; Nomura, 1990), and gherkins (Botterweck, 1998).

Pickled vegetable consumption was assessed in grams in two studies (Takachi, 2010 and Botterweck, 1998) while all remaining studies reported intake as times/day/week/month. One time was considered as one serving for the meta-analysis in this review. All studies included in the dose-response analysis were adjusted for age and sex (or stratified). Takachi, 2010 was the only study adjusting for BMI, energy, alcohol, and physical activity. None of the studies were adjusted for H. pylori status.

Significant associations were observed in studies that adjusted for smoking but not in those that adjusted for socioeconomic status (educational level).

Table 29 Pickled vegetable intake and stomach cancer risk. Number of studies in the CUP SLR

	Number
Studies identified	14 (21 publications)
Studies included in forest plot of highest compared with lowest exposure	11
Studies included in linear dose-response meta-analysis	9
Studies included in non-linear dose-response meta-analysis	Not enough studies

Table 30 Pickled vegetable intake and stomach cancer risk. Summary of the linear dose-response meta-analysis in the 2005 SLR and CUP

	2005 SLR	**CUP**
Increment unit used	20 g/day	0.5 serving/day (20g/day)
	All studies	
Studies (n)	6	9
Cases (total number)	1305	3932
RR (95%CI)	0.98 (0.90-1.05)	1.09 (1.05-1.13)
Heterogeneity (I^2, p-value)	0%, 0.5	0%, 0.44
P value Egger test	0.4	0.14
	Stratified and sensitivity analysis*	
Outcome	**Incidence**	**Mortality**
Studies (n)	6	3
RR (95%CI)	1.09 (1.02-1.16)	1.07 (0.97-1.18)
Heterogeneity (I^2, p-value)	28%, 0.23	0%, 0.65

***No stratified analysis in the 2005 SLR

Other stratified analyses

Duration of follow-up	**5-<10 years**	**10-<15 years**	**≥15 years**
Studies (n)	1	4	2
RR (95%CI)	0.63 (0.30-1.32)	1.10 (1.05-1.15)	1.08 (1.01-1.15)
Heterogeneity (I^2, p- value)	-	0%, 0.77	0%, 0.89
Number of cases	**<500 cases**	**500-<1000 cases**	**≥1000 cases**
Studies (n)	6	1	2
RR (95%CI)	1.05 (0.93-1.20)	1.11 (1.05-1.17)	1.08 (1.01-1.15)
Heterogeneity (I^2, p-value)	27.6%, 0.23	-	0%, 0.89

Publication year	**<2000**	**2000-<2010**	**>=2010**
Studies (n)	5	3	1
RR (95%CI)	1.03 (0.85-1.25)	1.08 (1.01-1.14)	1.11 (1.05-1.17)
Heterogeneity (I^2, p-value)	-	0%, 0.99	-
Adjustment for confounders:			
Socioeconomic status	Not adjusted	Adjusted	
Studies (n)	6	3	
RR (95%CI)	1.11 (1.06-1.15)	1.02 (0.85-1.21)	
Heterogeneity (I^2, p-value)	0%, 0.85	58.9%, 0.09	
Smoking			
Studies (n)	5	4	
RR (95%CI)	1.07 (0.98-1.18)	1.08 (1.01-1.16)	
Heterogeneity (I^2, p-value)	0%, 0.66	44.8%, 0.14	

Table 31 Pickled vegetable intake and stomach cancer risk. Results of meta-analyses and pooled analyses of prospective studies published after the 2005 SLR

Author, Year	Number of studies	Total number of cases	Studies country, area	Outcome	Comparison	RR (95%CI)	P trend	Heterogeneity (I^2, p value)
Meta-analyses								
D'Elia, 2012	7 cohorts		Asia, USA	Incidence/mortality, gastric cancer	High vs. low	1.27 (1.09-1.49)		25%, 0.20
Ren, 2012	10 cohort and 50 case-control studies	16 448	Asia, Europe, USA, South America	Incidence/mortality, gastric cancer	High vs. low	1.52 (1.37-1.68)		80%, <0.001
	10 cohorts	3 692	Asia, Europe, USA			1.32 (1.10-1.59)		69.9%, <0.001
	50 case-control studies		Asia, Europe, USA, South America			1.56 (1.39-1.75)		80.8%, <0.001

Table 32 Pickled vegetable intake and stomach 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
Takachi, 2010 STM80133 Japan	JPHC I and II, Prospective Cohort, Age: 45-74 years, M/W	867/ 77 500 10 years maximum	Active patient notification from hospitals, cancer registries and death certificate	Validated 138- item FFQ Pickled vegetables (Chinese radishes, cabbage, green leafy vegetables, plums, cucumbers, eggplant; 1.5-7.6% salt content)	Incidence, stomach cancer	85 vs. 3.3 g	2.24 (1.71-2.93) Ptrend:<0.01	Age, sex, BMI, calcium intake, energy intake, physical activity, smoking status, alcohol, potassium	Distribution of person-years by exposure categories. Grams converted to times/day using 40g as a standard portion size
Iso, 2007 STM80144 Japan	JACC, Prospective Cohort, Age: 40-79 years, M/W	579/ 105 500 15 years	Municipal resident registration records, death certificates	FFQ Pickled vegetables	Mortality, stomach cancer Men	≥5 vs. <3 times/week	1.07 (0.89-1.30)	Age, area of study	Mid-points of exposure categories
		275/			Women		1.08 (0.82-1.42)		
Sauvaget, 2005 STM44428 Japan	LSS, Prospective Cohort, Age: 34-98 years, M/W, Atomic bomb survivors	1 270/ 38 540 19 years	Cancer registry	22- item FFQ Pickles	Incidence, stomach cancer	5+ vs. <2 times/week	1.11 (0.98-1.26) Ptrend:0.025	Age, sex, area of residence, educational level, radiation exposure, smoking habits	
Ngoan, 2002 STM01668 Japan	FPC, Prospective Cohort, Age: 15-96 years, M/W	62/ 13 250 13 years	Resident registry	Self-administered FFQ Pickled food	Mortality, stomach cancer	≥2 times/day ≤2-4 times/week	1.50 (0.70-3.20)	Age, sex, fat intake, Japanese soup, liver, pickled foods, processed meat, smoking habits	Distribution of person-years by exposure categories, mid-points of exposure

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Missing data derived for analyses
									categories
Botterweck, 1998 STM04445 Netherlands	NLCS, Case Cohort, Age: 55-69 years, M/W	265/ 120 852 6.3 years	Cancer registry	150-item semi-quantitative FFQ Gherkins	Incidence, stomach cancer	Per 25 g/day	0.30 (0.09-0.95)	Age, sex, educational level, family history of stomach cancer, fruit, smoking habits, stomach disorders, vegetable intake	RR rescaled to an increment used
Galanis, 1998 STM04769 USA	Hawaii-Japan DOH Survey, Prospective Cohort, Age: 18- years, M/W, Japanese residents of Hawaii	108/ 11 907 14.8 years	Cancer registry	13-food item, 6-beverage item FFQ Pickled vegetables	Incidence, stomach cancer	7 or more times/week vs. none	1.10 (0.70-1.80) Ptrend:0.75	Age, sex, educational level, place of birth	Distribution of person-years by exposure categories, mid-points of exposure categories
Kato, 1992b STM06734 Japan	Higashi-Kamo Cohort, Prospective Cohort, Age: 30-80 years, M/W	57/ 9 753 6 years	Death certificates	25-item questionnaire Pickles	Mortality, stomach cancer	Daily vs. ≤1-2 times/week	0.75 (0.38-1.49) Ptrend:0.59	Age, sex	Mid-points of exposure categories
Kato, 1992a STM13746 Japan	HERPACC, Prospective Cohort, M/W, Endoscopy patients	41/ 3 914 4.4 years	Hospital records, cancer registry, death certificates	10-item self-administered questionnaire Pickles	Incidence, stomach cancer	Daily vs. ≤ 1-2 times/month	1.77 (0.67-4.70) Ptrend:0.186	Age, sex, area of residence	Mid-points of exposure categories
Nomura, 1990	HHP,	150/	Cancer registry/	20-item FFQ, 24-	Incidence,	≥5 vs. ≤1	1.20 (0.80-1.70)	Age	

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Missing data derived for analyses
STM14814 USA	Prospective Cohort, Age: 45- years, M, Japanese residents of Hawaii	7 990 10.6 years	hospital records	hour diet recall, Pickles	stomach cancer	times/week			

Table 33 Pickled vegetable intake and stomach 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
Kurosawa, 2006 STM80085 Japan	Higashi-Yamanashi County, Japan, Prospective Cohort, Age: 30- years, M/W	76/ 8 035 11 years	Death certificate	FFQ Pickled vegetables	Mortality, stomach cancer	High vs. low and intermediate	4.28 (1.70-10.77) Ptrend:<0.01	Age, sex	Superseded by Iso, 2007
Tokui, 2005 STM80105 Japan	JACC, Prospective Cohort, Age: 40-79 years, M/W	516/ 44 930 12 years	Municipal resident registration records, death certificates	FFQ Pickles	Mortality, stomach cancer Men	1+ times/day vs. 1-2 times/month	1.09 (0.82-1.47) Ptrend:0.48	Age	Superseded by Iso, 2007
		255/			Women		1.47 (0.90-2.39) Ptrend:0.26		
Tran, 2005 STM44270 Linxin, China	NIT Cohort, Prospective Cohort, Age: 40-69 years, M/W, Intervention trial participants	1089/ 29 584 15 years	Follow-up visits, contacts with local commune, hospitals, and study medical team	FFQ Pickled vegetables	Incidence, cardia cancer	≥1 time/year vs. never	1.04 (0.85-1.29)	Age, sex	Excluded, two levels of exposure, used in HvL analysis only
		363/			Non-cardia cancer		1.09 (0.76-1.56)		
Khan, 2004 STM20239 Japan	HGCS, Prospective Cohort, Age: 40- years, M/W	36/ 1 524 14 years	Follow-up surveys	FFQ Japanese pickle	Mortality, stomach cancer Men	2-7 times/week vs. never-several times/month/year	0.90 (0.30-3.10)	Age, smoking habits	Excluded, two levels of exposure, used in HvL analysis only
Tsugane, 2004	JPHC I, Prospective	358/ 39 065	Hospital records,	FFQ Pickled	Incidence, stomach cancer	Almost every day vs. almost none	1.17 (0.74-1.84) Ptrend:0.69	Age, fruit, non-green-yellow	Superseded by Takachi, 2010

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Reasons for exclusion
STM00441 Japan	Cohort, Age: 40-59 years, M/W	12 years maximum	population-based cancer registries and death certificates, histologically confirmed	vegetables	Men			vegetable intake, smoking habits, PHC area	
					Women		1.32 (0.60-2.91) Ptrend:0.46		
Wong, 2004 STM00527 China	CCHT, Prospective Cohort, Age: 42.00years, M/W, H. pylori eradication trial participants	18/ 1 630 7.8 years	Clinical trial follow-up records	FFQ Preserved vegetables	Incidence, lower third gastric cancer	≥2 vs. <2 times/week	0.28 (0.04-2.10)		Excluded, two levels of exposure, used in HvL analysis only
Fujino, 2002 STM01512 Japan	JACC, Prospective Cohort, Age: 40-79 years, M/W	236/ 44 930 10 years	Population registry	FFQ Pickles	Mortality, stomach cancer Men	Every day vs. <3 times/week	0.92 (0.69-1.24)	Age	Superseded by Iso, 2007
		106/			Women		0.89 (0.39-1.41)		
Kobayashi, 2002 STM01446 Japan	JPHC I, Prospective Cohort, Age: 40-59 years, M/W	404/ 39 993 10 years	Hospital records, population-based cancer registries and death certificates, histologically confirmed	FFQ Pickled vegetables	Incidence, stomach cancer	Almost daily vs. <1 day/week	0.86 (0.57-1.28) Ptrend:0.57	Age, sex, alcohol consumption, BMI, educational level, energy intake, family history of stomach cancer, highly salted food intake, history of peptic ulcer, smoking habits, study area, vitamin a supplement,	Superseded by Takachi, 2010

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Reasons for exclusion
								vitamin c supplement, vitamin e supplement	
Inoue, 1996 STM06116 Japan	HERPACC, Prospective Cohort, M/W, Endoscopy patients	69/ 5 373 6 years	Hospital records, cancer registry, death certificates	FFQ Salt preference	Incidence, stomach cancer	Daily vs. occasionally	0.92 (0.75-1.13)	Age, sex	Excluded, two levels of exposure, used in HvL analysis only, superseded by Kato 1992a
Guo, 1994 STM10900 Linxin, China	NIT Cohort, Nested Case Control, Age: 40-69 years, M/W, Intervention trial participants	538/ 29 584 5 years	Follow-up visits, contacts with local commune, hospitals, and study medical team	FFQ Pickled vegetables	Incidence, stomach cancer	1+ times/month vs. none	0.90 (0.70-1.30)	Family history of cancer, intervention group, smoking habits	Superseded by Tran, 2005
Chyou, 1990 STM12425 USA	HHP, Case Cohort, Age: 58.00years, M, Japanese residents of Hawaii	111/ 8 006 18 years	Cancer registry/ hospital records	FFQ + recall Pickles	Incidence, Stomach cancer	(mean exposure)		Age	Superseded by Nomura, 1990, no risk estimate
Ikeda, 1983 STM09004 Japan	RERFCJ, Prospective Cohort, Age: 50.00years, M/W, Atomic bomb survivors	79/ 7 553 11 years	Cancer registry/ population register	Questionnaire (general) Salted pickle	Mortality, stomach cancer	(correlation)		Sex, age at interview, broiled fish, educational level, fruit, milk consumption, radiation exposure, rice intake, smoking habits	Excluded, no risk estimate

Figure 34 RR estimates of stomach cancer by levels of pickled vegetable intake

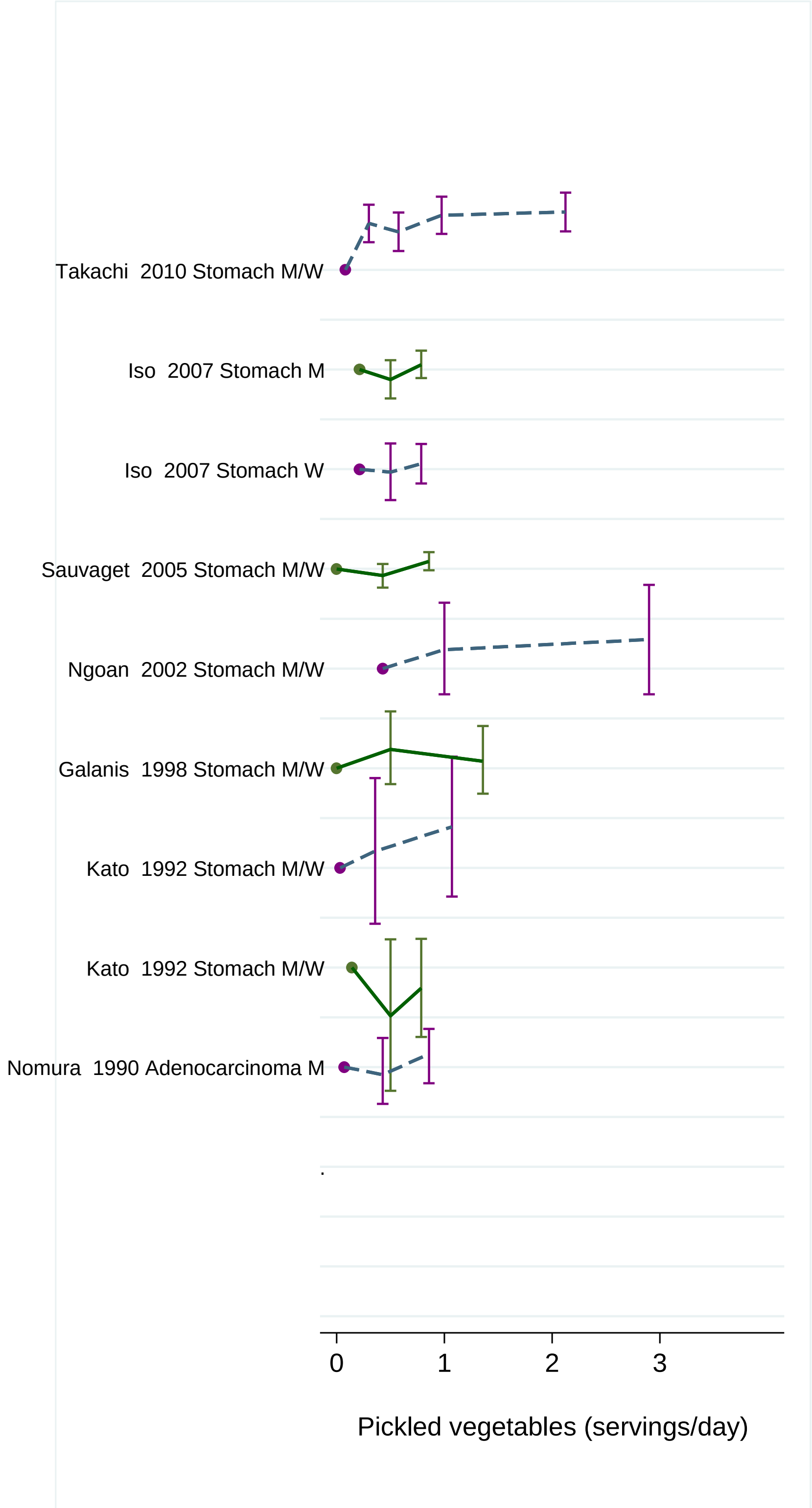


Figure 35 RR (95% CI) of stomach cancer for the highest compared with the lowest level of pickled vegetable intake

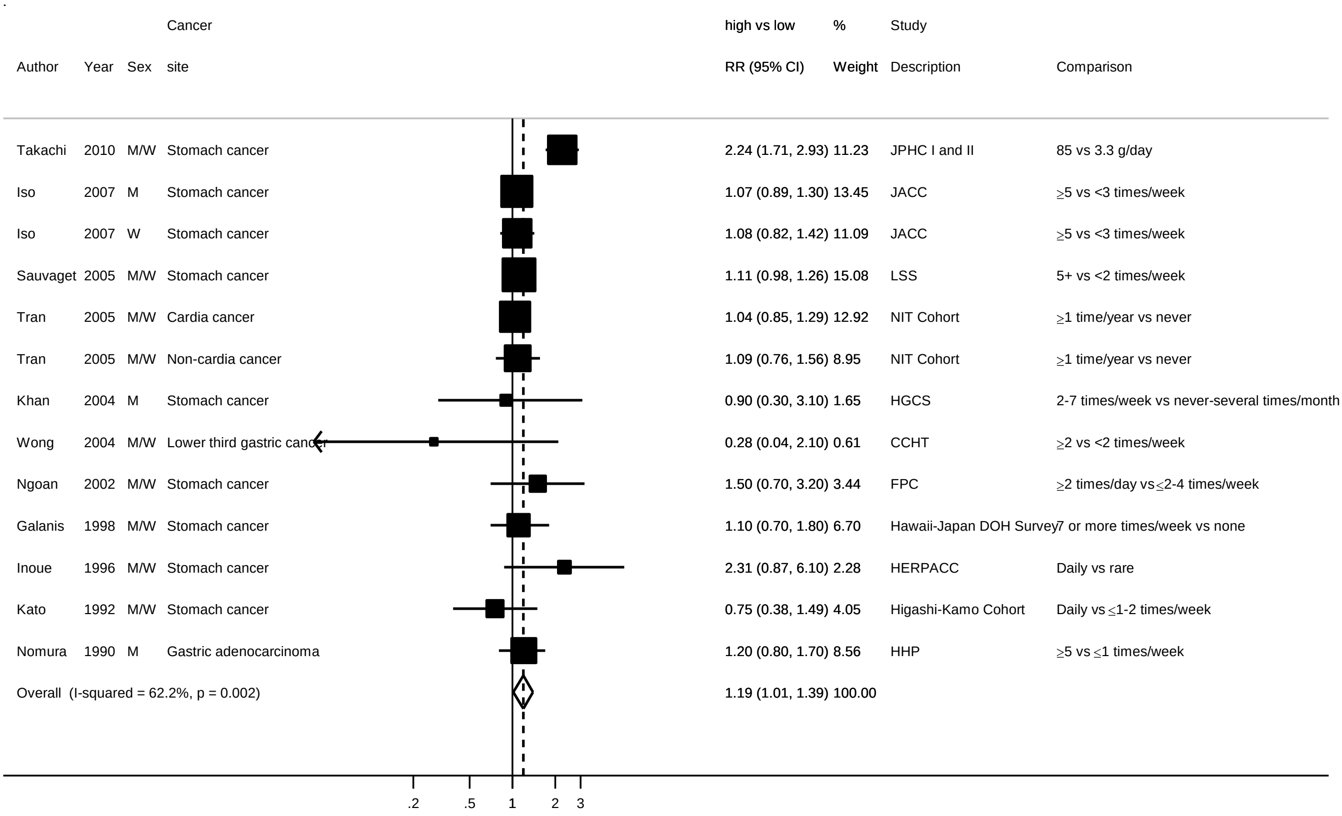


Figure 36 Relative risk of stomach cancer incidence for 0.5 serving/day increase of pickled vegetable intake

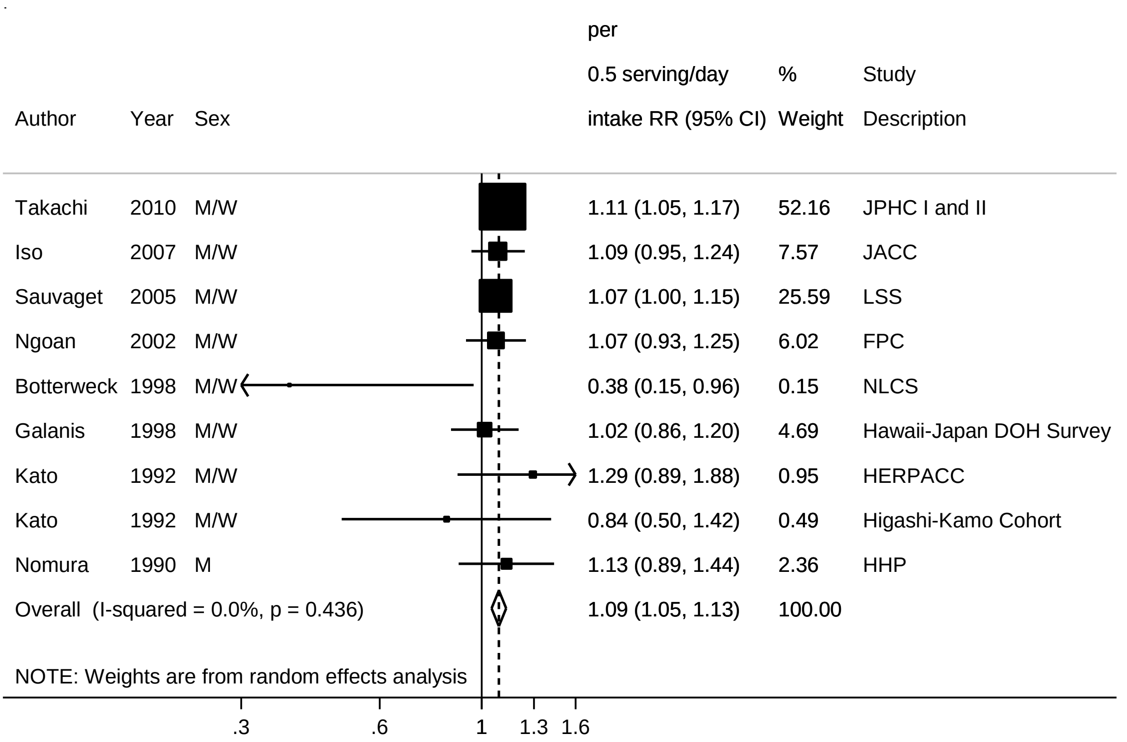
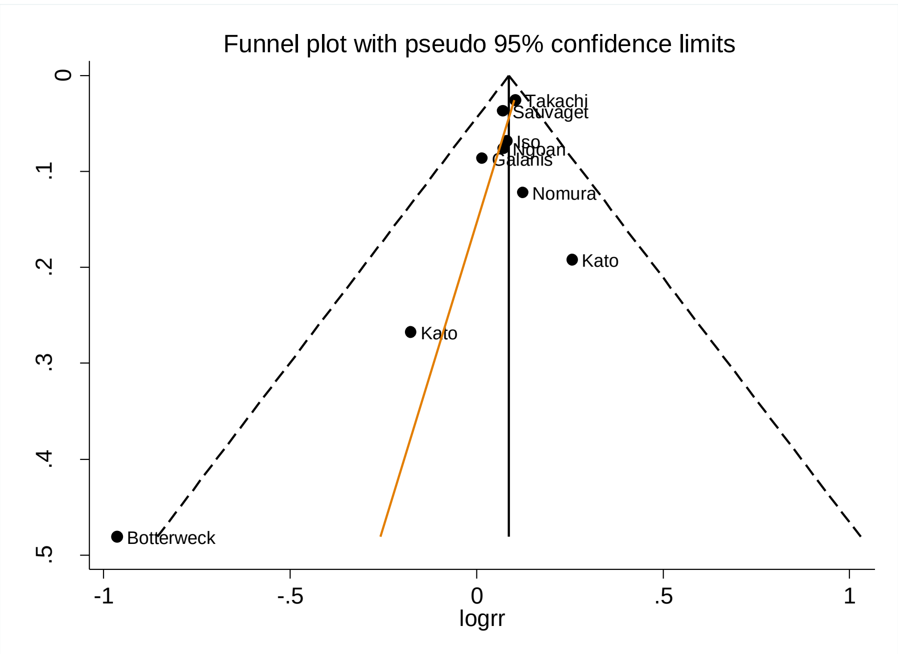
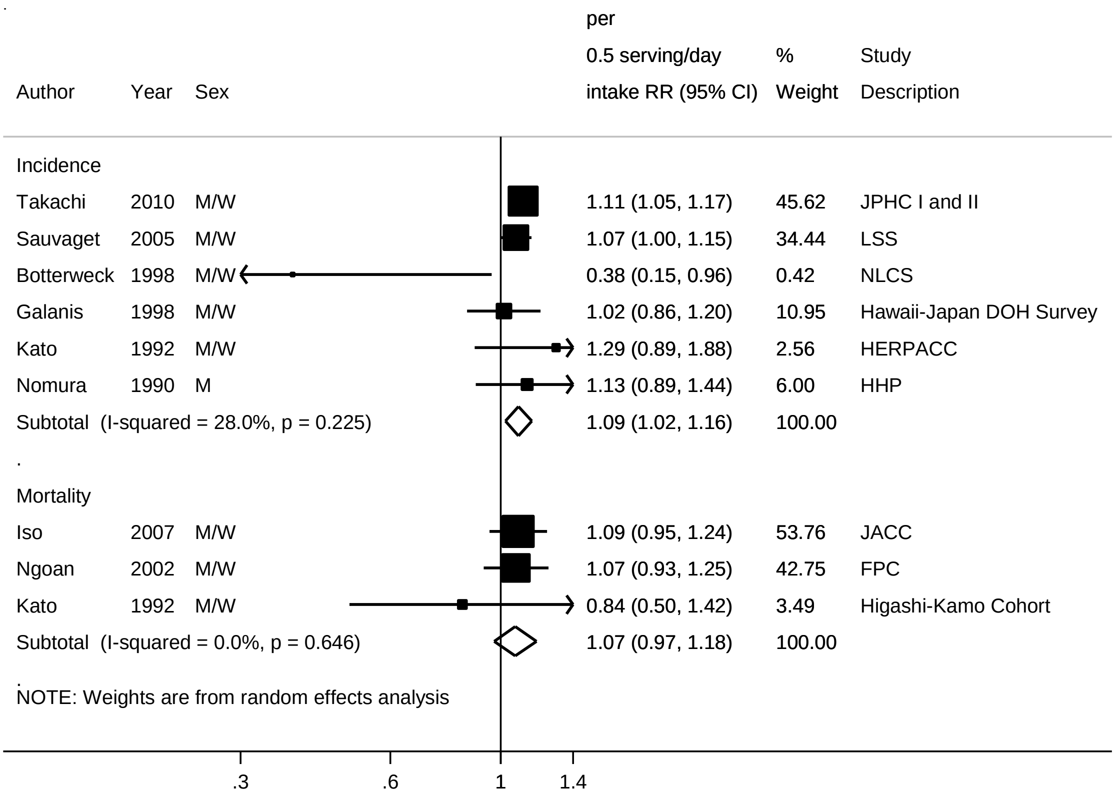


Figure 37 Funnel plot of studies included in the dose response meta-analysis of pickled vegetable intake and stomach cancer



Egger's test p=0.14

Figure 38 Relative risk of stomach cancer for 0.5 serving/day increase of pickled vegetable intake by cancer outcome



2.2.2 Fruits

Randomised controlled trials

The WHI-DM trial had reported results on low fat and high plant food dietary pattern (Prentice, 2007). See section on dietary pattern.

Cohort studies

Summary

Main results:

Thirteen studies (4905 cases) out of twenty-four studies were included in the dose-response meta-analysis. No significant associations of fruit consumption were observed for stomach cancer, for gastric cardia cancer (four studies, no heterogeneity) and non-cardia gastric cancer (six studies, moderate heterogeneity).

Nine studies were excluded from the dose-response analyses. One study observed a significant inverse association (Galanis, 1998). The remaining studies reported non-significant associations. No heterogeneity was observed. There was no significant evidence of publication or small study bias.

Sensitivity analyses:

The summary RRs remained non-significant is influence analysis, ranging from 0.96 (95% CI=0.90-1.02) when George, 2009 (41.2% weight) was omitted to 0.99 (95% CI=0.95-1.02) when Nouraie, 2005 (2.4% weight) was omitted.

Five studies reported results stratified by smoking status (Gonzalez, 2012; Steevens, 2011; SMHS, SWHS - Epplein, 2010; Appleby, 2002), one additional study included smokers only (Nouraie, 2005). Five of these studies could be included in the stratified meta-analyses of stomach cancer and its subtypes. No significant associations were observed in never smokers and former smokers. Inverse associations were observed in current smokers; and were significant for stomach cancer and borderline significant for non-cardia gastric cancer. A non-significant positive association of fruit intake (daily versus non-daily intake) and stomach cancer mortality was observed among non-smokers in the study that could not be included in the meta-analysis (Appleby, 2002).

The results were similar in studies that adjusted or not adjusted for socioeconomic status, smoking, ethnicity, alcohol intake, anthropometric measures, total energy intake, physical activity, and comorbidities and in subgroup analyses by duration of follow-up, number of cases, and publication year.

Non-linear dose-response meta-analysis:

There was evidence of non-linear dose-response for stomach cancer and fruit intake ($p<0.001$). The curve approaches a linear relationship in most of the intake range but shows an increased risk for decreasing levels of fruits intake in a range below approximately 80 grams/day and a very light protection with increasing intakes above this level. The increase risk at low levels remained in influence analysis.

Study quality:

Some studies recruited specific populations: The ATBC study was originated from an intervention trial of supplements in smokers (Nouraie, 2005). The HERPACC study included patients who underwent gastroscopy (Inoue, 1996).

Loss to follow-up was low in most studies, with the exception of the study of atomic-bomb survivors (LSS) (Sauvaget, 2005), in which 17% participants were lost due to migration.

Cancer outcome was confirmed using medical notes or records in cancer registries in most studies.

All studies used FFQ to assess fruit intake. Nomura, 1990 also used a 24-hour dietary recall questionnaire. Other methods were used in addition to the country-specific questionnaires in EPIC (Gonzalez, 2012). Gonzalez, 2012 reported dose-response associations for calibrated intake of fruits. The inverse association was slightly stronger than the association with observed fruit intake, but remained non-significant.

All studies included in the dose-response analysis were adjusted for age and sex. None of the studies were adjusted for Helicobacter pylori status.

Table 34 Fruit intake and stomach cancer risk. Number of studies in the CUP SLR

	Number
Studies identified	24* (34 publications)
Studies included in forest plot of highest compared with lowest exposure	18
Studies included in linear dose-response meta-analysis	13
Studies included in non-linear dose-response meta-analysis	7

Note: Include cohort, nested case-control and case-cohort designs *Included two cohort studies in one publication (Epplein, 2010) on distal gastric cancer only.

Table 35 Fruit intake and stomach cancer risk. Summary of the linear dose-response meta-analysis in the 2005 SLR and CUP

	2005 SLR	**CUP**
Increment unit used	100g/day	100g/day
All studies		
Studies (n)	8	13
Cases (total number)	1 689	4905
RR (95%CI)	0.95 (0.89-1.02)	0.98 (0.94-1.02)
Heterogeneity (I^2, p-value)	30%, 0.2	8.3%, 0.36
P value Egger test	0.5	0.49

Stratified and sensitivity analysis		
Men	**2005 SLR**	**CUP**
Studies (n)	5	5
RR (95%CI)	0.98 (0.91-1.06)	0.99 (0.90-1.10)
Heterogeneity (I^2, p-value)	-	14.9%, 0.32
Women	**2005 SLR**	**CUP**
Studies (n)	3	3
RR (95%CI)	0.99 (0.93-1.06)	0.98 (0.89-1.07)
Heterogeneity (I^2, p-value)	-	0%, 0.47
Cancer site	Proximal stomach cancer	Gastric cardia cancer
Studies (n)	3	4
RR (95%CI)	0.95 (0.68-1.32)	0.96 (0.90-1.02)
Heterogeneity (I^2, p-value)	-	0%, 1.00
	Distal stomach cancer	Non-cardia gastric cancer
Studies (n)	3	6
RR (95%CI)	0.87 (0.64-1.18)	0.99 (0.93-1.05)
Heterogeneity (I^2, p-value)	-	36.4%, 0.16

	CUP (other stratified analysis)		
Increment unit used	100g/day		
Outcome	**Incidence**	**Mortality**	**Incidence and mortality**
Studies (n)	8	4	2
RR (95%CI)	0.98 (0.95-1.01)	1.08 (0.72-1.61)	0.84 (0.57-1.24)
Heterogeneity (I^2, p-value)	0%, 0.73	74.5%, 0.01	0%, 0.46
Geographic area	**Asia**	**Europe**	**North America**
Studies (n)	7	4	2
RR (95%CI)	0.99 (0.81-1.21)	0.97 (0.93-1.02)	0.96 (0.77-1.21)
Heterogeneity (I^2, p-value)	33.9%, 0.17	0%, 0.57	16.9%, 0.27
Duration of follow-up	**5-<10 years**	**10-<15 years**	**≥15 years**
Studies (n)	5	5	3
RR (95%CI)	1.00 (0.82-1.21)	0.97 (0.93-1.02)	0.94 (0.85-1.05)
Heterogeneity (I^2, p- value)	46.1%, 0.12	0%, 0.47	0%, 0.60
Number of cases	**<500 cases**	**500-<1000**	**≥1000 cases**
Studies (n)	9	3	1

RR (95%CI)	0.94 (0.80-1.10)	0.99 (0.96-1.02)	0.91 (0.71-1.18)
Heterogeneity (I^2, p-value)	29.0%, 0.19	0%, 0.77	-
Publication year	**<2000**	**2000-<2010**	**≥2010**
Studies (n)	3	7	3
RR (95%CI)	1.06 (0.43-2.61)	0.99 (0.95-1.03)	0.98 (0.93-1.02)
Heterogeneity (I^2, p-value)	75.1%, 0.02	0%, 0.58	0%, 0.93
Adjustment for: confounders			
Socioeconomic status	**Not adjusted**	**Adjusted**	
Studies (n)	5	8	
RR (95%CI)	0.96 (0.86-1.08)	0.98 (0.92-1.03)	
Heterogeneity (I^2, p-value)	0%, 0.50	26.9%, 0.21	
Smoking			
Studies (n)	4	9	
RR (95%CI)	1.10 (0.64-1.87	0.98 (0.95-1.01)	
Heterogeneity (I^2, p-value)	63.7%, 0.04	0 %, 0.87	
Alcohol intake			
Studies (n)	7	6	
RR (95%CI)	0.96 (0.77-1.19)	0.99 (0.95-1.02)	
Heterogeneity (I^2, p-value)	46.4%, 0.08	0%, 0.93	
BMI			
Studies (n)	9	4	
RR (95%CI)	0.94 (0.83-1.07)	0.99 (0.96-1.02)	
Heterogeneity (I^2, p-value)	29.5%, 0.18	0%, 0.85	
Total energy intake			
Studies (n)	8	5	
RR (95%CI)	0.98 (0.84-1.14)	0.99 (0.95-1.02)	
Heterogeneity (I^2, p-value)	29.1%, 0.20	0%, 0.54	
Physical activity			
Studies (n)	11	2	
RR (95%CI)	0.94 (0.85-1.04)	0.99 (0.96-1.03)	
Heterogeneity (I^2, p-value)	13.0%, 0.32	0%, 0.57	
Comorbidities			
Studies (n)	11	2*	
RR (95%CI)	0.98 (0.93-1.03)	0.91 (0.74-1.11)	
Heterogeneity (I^2, p-value)	19.4%, 0.26	0%, 0.87	

*Larsson, 2006c adjusted for diabetes, Kobayashi, 2002 adjusted for stomach disorder

Analysis stratified by smoking status

Increment unit used	100g/day		
Smoking status	**Never smokers**	**Former smokers**	**Current smokers**
Stomach cancer			
Studies (n)	2	2	3
RR (95%CI)	0.99 (0.92-1.06)	1.02 (0.95-1.09)	0.89 (0.81-0.97)
Heterogeneity (I^2, p-value)	0%, 0.98	0%, 0.89	0%, 0.80
Gastric cardia cancer			
Studies (n)	1	1	2
RR (95%CI)	1.08 (0.81-1.45)	0.96 (0.80-1.15)	0.88 (0.66-1.16)
Heterogeneity (I^2, p-value)	-	-	0%, 0.52
Distal gastric cancer			
Studies (n)	2	1	3
RR (95%CI)	0.96 (0.82-1.12)	1.04 (0.91-1.20)	0.73 (0.53-1.00)
Heterogeneity (I^2, p-value)	0%, 0.77	-	72%, 0.03

Table 36 Fruit intake and stomach cancer risk. Results of meta-analyses and pooled analyses of prospective studies published after the 2005 SLR

Author, Year	Number of studies	Total number of cases	Studies country, area	Outcome	Comparison	RR (95%CI)	P trend	Heterogeneity (I^2, p value)
Meta-analyses								
Wang Q, 2014	16 cohorts (11 cohorts in dose-response analysis)	6632	USA, Japan, China, Korea, Finland, Denmark, France, Germany, Greece, Italy, the Netherlands, Norway Spain, Sweden, UK	Incidence/mortality, Gastric cancer	High vs. low	0.90 (0.83-0.98)		0.7%, 0.45
					Per 100 g/day	0.95 (0.91-0.99)		38%, 0.06
				Men	High vs. low	0.94 (0.83-1.07)		20.1%, 0.25
				Women		0.97 (0.76-1.24)		54.2%, 0.04
				Gastric cardia cancer		0.88 (0.76-1.02)		0%, 0.99
				Gastric non-cardia cancer		0.89 (0.77-1.02)		0%, 0.59

Comparison of CUP and Wang, 2014:

Additional studies included in the CUP meta-analysis that are not in Wang, 2014: Ngoan, 2002 (stomach cancer mortality); Inoue, 1996; Kato, 1992 (stomach cancer mortality)

Studies included in Wang, 2014 but not included in CUP: Epplein, 2010 because it is only on distal gastric cancer only; Tran, 2005 because highest intake was very low (≥13 times/year) and not comparable to other cohort studies. When Epplein, 2010 was included with the studies of incident cancer in a sensitivity analysis, the summary RR was 0.98 (95% CI=0.95-1.01, I^2=0%, p=0.76, 10 studies)

Other differences: George, 2009; Nomura, 1990 included in CUP because higher number of cases than the reports of the same cohorts by Freedman, 2008 and Chyou, 1990 respectively that were included in Wang, 2014.

Table 37 Fruit intake and stomach 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
Ko, 2013 STM80184 Korea	KMCC, Prospective Cohort, Age: 30-90 years, M/W	166/ 9724 8.5 years	Cancer registry and death certificates	14-item self-administered FFQ	Incidence, stomach cancer	≥1 time/day vs. almost never	1.10 (0.55-2.22) Ptrend: 0.59	Age, sex, area of residence, BMI, cigarette smoking, alcohol drinking	Exposure values using standard portion size, mid-points of exposure categories
		116/ 3714			Men	High vs. low	1.04 (0.92-1.19)		
		50/ 6010			Women		1.11 (0.90-1.36)		
Gonzalez, 2012 STM80139 Denmark,France ,Germany,Greec e,Italy,Netherlan ds,Norway,Spai n,Sweden,U.K.	EPIC, Prospective Cohort, Age: 35-70 years, M/W	683/ 477 312 11.02 years	Cancer registries, health insurance records, pathology records, active follow up, death certificate	FFQ, dietary questionnaires, food record	Incidence, gastric adenocarcinoma	≥386.4 (M)/346.2 (W) vs. 63.8 (M)/ 106.9 (W) g/day Per 100 g/day	0.84 (0.63-1.11) 0.98 (0.93-1.03)	Age, sex, BMI, centre, educational level, energy intake, physical activity, total vegetable consumption, alcohol intake, red and processed meat, smoking	
		201/			Gastric cardia adenocarcinoma		0.86 (0.51-1.45) 0.96 (0.86-1.06)		
		323/			Non-cardia gastric adenocarcinoma		0.80 (0.54-1.20) 1.00 (0.93-1.07)		
		203/			Intestinal gastric cancer		0.92 (0.55-1.54) 0.99 (0.90-1.08)		
		217/			Diffuse gastric cancer		0.59 (0.36-0.97) 0.92 (0.83-1.02)		
Steevens, 2011 STM80062 Netherlands	NLCS, Case Cohort, Age: 55-69 years, M/W	616/4651 16.3 years	Annual linkage to the national cancer registry and the network of	150-item self-administered validated FFQ	Incidence,			Age, sex, alcohol consumption, smoking status and duration,	RRs for gastric cardia adenocarcinoma and gastric non-cardia
		156/			Gastric cardia	326 vs. 43 g/day	0.85 (0.50-1.42)		

Author, Year, 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
			histopathology and cytopathology		adenocarcinoma All	Per 25 g/day	0.99 (0.95-1.03)	cigarettes per day, intake of red meat, fish, total vegetable	adenocarcinoma combined using Hamling's method.
		132/			Men	Per 25 g/day	0.96 (0.92-1.01)		
		24/			Women		1.08 (1.02-1.14)		
		27/			Smokers		1.02 (0.95-1.10)		
		110/			Never smokers		0.99 (0.95-1.03)		
		74/			Former smokers		0.99 (0.95-1.04)		
		460/			Non-cardia All	326 vs. 43 g/day	0.86 (0.62-1.18) 1.00 (0.97-1.02)		
		304/			Men	Per 25 g/day	0.99 (0.96-1.02)		
		156/			Women		1.00 (0.97-1.04)		
		186/			Smokers		1.01 (0.97-1.04)		
		55/			Never smokers		0.95 (0.87-1.04)		
		164/			Former smokers		0.98 (0.93-1.03)		
Epplein, 2010 STM80129 China	SWHS and SMHS, Prospective Cohort, Age: 40-74 years, M/W	338/132 311 206/	Review of medical records	Validated 81-item (SMHS) and 77-item (SWHS) FFQs	Incidence, distal stomach cancer Women	>357.8 vs. ≤134.2 g/day	0.98 (0.65-1.49)	Age, education level, smoking, total energy intake	Distribution of person-years by exposure quintiles, mid-points of exposure categories (Included in analysis of non-cardia stomach cancer only)
		132/			, Men	>215.7 vs. <=56.5 g/day	0.79 (0.48-1.30)		

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Missing data derived for analyses
George, 2009 STM80057 USA	NIH-AARP, Prospective Cohort, Age: 50-71 years, M/W, Retired	137/ 483,338	Linkage to 11 state cancer registries and seers	Validated 124-item self-administered FFQ	Incidence, stomach cancer Women	1.91-5.58 vs. 0-0.6 cup/1000 kcal/day	0.75 (0.43-1.31)	Age, BMI, energy intake, family history of stomach cancer, marital status, physical activity, race, vegetable intake, alcohol, education, menopausal hormone therapy use, smoking	Distribution of cases and person-years by exposure quintiles, exposure values using mean energy intake, mid-points of exposure categories, RRs for men and women combined
		507/			Men	1.6-5.13 vs. 0-0.44 cup/1000 kcal/day	1.15 (0.85-1.55)		
Freedman, 2008 STM80097 USA	NIH-AARP, Prospective Cohort, Age: 50-71 years, M/W, Retired	394/ 490, 802 4.5 years 198/	Linkage with 11 state cancer registry databases	Validated 124-item FFQ	Incidence, stomach cancer Cardia cancer	Per 1 serving/1000 kcal 3.2 vs. 0.45 serving/ 1000kcal	0.94 (0.82-1.09) 0.80 (0.48-1.32)	Age, sex, BMI, ethnicity, vegetable intake, alcohol intake, cigarette- dose, education, total energy, usual activity throughout the day, vigorous physical activity	Exposure values using mean energy intake (Included in analysis by cancer subsite)
		196/			Non-cardia cancer		1.12 (1.00-1.26) 1.22 (0.78-1.91)		
Larsson, 2006c STM80086 Sweden	SMC and COSM, Prospective Cohort, Age: 45-83 years, M/W	139/ 82 002 7.2 years	Cancer registry/ mortality registry	96-item validated FFQ	Incidence, stomach cancer	≥2.5 vs. <1.0 servings/day	0.86 (0.52-1.43)	Age, sex, diabetes, smoking status, alcohol intake, education, pack years of smoking,	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
								processed meat intake, total energy intake	
Nouraie, 2005 STM44426 Finland	ATBC, Prospective Cohort, Age: 50-69 years, Men Smokers	220/ 27 110 12 years	Cancer registry	Validated 276-item self-administered FFQ	Incidence, stomach cancer	>167 vs. <61 g/day		Age, dietary nitrate, educational level, energy intake, smoking habits	RRs for cardia and non-cardia gastric cancers combined using Hamling's method, distribution of cases and person-years , and mid-points of exposure categories
		57/			Cardia cancer		1.00 (0.47-2.18)		
		163/			Non-cardia cancer		0.66 (0.43-1.02)		
Sauvaget, 2005 STM44428 Japan	LSS, Prospective Cohort, Age: 34-98 years, M/W, Atomic bomb survivors	1270/ 38 540 19 years	Cancer registry	22-item FFQ	Incidence, stomach cancer	≥5 vs. <2 times/week	0.97 (0.84-1.13)	Age, sex, area of residence, educational level, radiation exposure, smoking habits	Exposure values using standard portion size, mid-points of exposure categories
Sauvaget, 2003 STM01065 Japan	LSS, Prospective Cohort, Age: 34-103 years, M/W, Atomic bomb survivors	617/ 38 540 16 years	Cancer registry	Validated 22-item FFQ	Mortality, stomach cancer All	Daily/ almost daily vs. ≤1 times/week	0.80 (0.65-0.98) Ptrend:0.03	Age, sex, alcohol consumption, BMI, city/town, educational level, radiation exposure, smoking habits, vegetable intake	Exposure values using standard portion size, mid-points of exposure categories (Included in analysis of
		(data not shown)			Women	Daily/ almost daily vs. ≤1 times/week	0.65 (p<0.05)		

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Missing data derived for analyses
									cancer mortality)
Fujino, 2002 STM01512 Japan	JACC, Prospective Cohort, Age: 40-79 years, M/W	379/ 44930 10 years	Population registry	FFQ	Mortality, stomach cancer	Every day vs. >3 times/week		Age	Hamling's method was used to calculate the RRs for alternative fruit intake comparisons, exposure values using standard portion size, mid-points of exposure categories, RRs for men and women combined
		261/ 18 746			Men		1.03 (0.78-1.35)		
		118/ 26 184			Women		1.22 (0.79-1.87)		
Kobayashi, 2002 STM01446 Japan	JPHC I, Prospective Cohort, Age: 40-59 years, M/W	404/ 39 993 10 years	Hospital records, population-based cancer registries and death certificates, histologically confirmed	Validated 44-item self-administered FFQ	Incidence, stomach cancer	Almost daily vs. <1 days/week	0.70 (0.48-1.01)	Age, sex, BMI, alcohol consumption, educational level, energy intake, family history of stomach cancer, highly salted food intake, history of peptic ulcer, smoking habits, study area, supplement	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
								use of vitamin a, vitamin c , or vitamin e	
Ngoan, 2002 STM01668 Japan	FPC, Prospective Cohort, Age: 15-96 years, M/W	113/ 13 250 13 years	Resident registry	Self-administered FFQ	Mortality, stomach cancer All	≥2 times/day vs. ≤2-4 times/week	0.80 (0.30-2.10)	Age, sex, fat intake, Japanese soup, liver, pickled foods, processed meat, smoking habits	Distribution of person-years by exposure category, exposure values using standard portion size, mid-points of exposure categories
		38/			Women		1.50 (0.60-3.80)	Age	
		75/			Men		1.60 (0.80-3.30)		
Inoue, 1996 STM06116 Japan	HERPACC, Prospective Cohort, M/W, Endoscopy patients	64/ 5373 6 years	Hospital records, cancer registry, death certificates	Self-administered FFQ	Incidence, stomach cancer	Daily vs. ≤1-2 times/month	0.58 (0.25-1.31)	Age, sex	Missing exposure values, used from Kato 1992a STM13746
Kato, 1992b STM06734 Japan	Higashi-Kamo Cohort, Prospective Cohort, Age: 30-80 years, M/W	57/ 9753 6 years	Cancer registry/ hospital records	25-item questionnaire	Mortality, stomach cancer	Daily vs. ≤1-2 times/week	1.92 (1.03-3.59)	Age, sex	Exposure values using standard portion size, mid-points of exposure
Nomura, 1990 STM14814 USA	HHP, Prospective Cohort, Age: 45- years, M, Japanese	150/ 7990 19 years	Cancer registry/ hospital records	20-item FFQ, 24-hour diet recall	Incidence/ mortality, stomach cancer	≥5 vs. ≤1 times/week	0.80 (0.50-1.30)	Age	Distribution of person-years by exposure category, exposure values using standard

Author, Year, 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
	residents of Hawaii								portion size, mid-points of exposure categories

Table 38 Fruit intake and stomach 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, Retired	954/ 494 968 9.7 years	Cancer registry, death master file, national death index plus, postal service database	Validated FFQ, 124-item	Incidence, stomach cancer	HEI-2005 scoring criteria for total fruit ≥0.8 vs. <0.8 cups/1000kcal		Age, sex, BMI, race, education, modified total score, smoking, total energy intake, usual activity throughout the day, vigorous physical activity	Excluded, exposure was meeting dietary index criteria or not (same study as George, 2009, STM80057; Freedman, 2008, STM80097)
		453/			Gastric cardia adenocarcinoma		0.92 (0.86-1.00)		
		501/			Non-cardia adenocarcinoma		0.98 (0.91-1.05)		
		453/			Cardia adenocarcinoma	aMED scoring criteria for fruit ≥2.3 vs. <2.3cups	0.81 (0.66-0.98)		
		501/			Non-cardia adenocarcinoma		0.94 (0.79-1.14)		
Gonzalez, 2006a STM44425 France, Italy, Spain, U.K.,	EPIC, Prospective Cohort, Age: 35-70	330/ 481 518 6.5 years	Cancer registry	FFQ, dietary questionnaires, food record	Incidence, stomach cancer	Per 100 g/day	1.04 (0.91-1.20)	Age, sex, alcohol consumption, educational	Superseded by Gonzalez , 2012, STM80139
		94/			Cardia		1.02 (0.80-1.30)		

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Reasons for exclusion
Netherlands, Greece, Germany, Sweden, Denmark	years, M/W	159/			Non-cardia		1.03 (0.85-1.26)	level, energy intake, height, physical activity, processed meat, red meat intake, smoking habits, weight, date of blood collection, H. pylori infection, study area	
		109/			Intestinal		1.02 (0.82-1.28)		
		116/			Diffuse		0.97 (0.74-1.29)		
		40/			H. pylori -ve Stomach cancer	Per 100 g/day	0.72 (0.39-1.33)		
		22/			Cardia		0.61 (0.25-1.47		
		12/			Non-cardia		0.64 (0.14-2.89)		
		16/			Intestinal		0.81 (0.33-1.95)		
		9/			Diffuse		0.0 (0.001-3.09)		
		201/			H. pylori +ve Stomach cancer	Per 100 g/day	0.98 (0.81-1.20)		
		47/			Cardia		0.76 (0.48-1.22)		
		113/			Non-cardia		1.10 (0.87-1.39)		
		77/			Intestinal		0.90 (0.65-1.25)		
		82/			Diffuse		0.90 (0.64-1.24)		
Kurosawa, 2006 STM80085 Japan	Higashi-Yamanashi County, Japan, Prospective Cohort, Age: 30- years, M/W	73/ 8035 11 years	Death certificate	29-item FFQ	Mortality, stomach cancer	High vs. low	0.93 (0.37-2.33)	Age, sex	Excluded, exposure not quantified
Tran, 2005 STM44270 Linxin, China	NIT Cohort, Prospective Cohort, Age: 40-69	1452/ 29 584 15 years	Follow-up visits, contacts with local commune, hospitals, and	Non-validated 8-item FFQ	Incidence, stomach cancer	>13 vs. ≤1 times/year	0.89 (0.75-1.05)	Age, sex	Excluded, extremely low fruit intake, not comparable with

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Reasons for exclusion
	years, M/W, Intervention trial participants	1089/	study medical team		Cardia cancer				other studies; when estimated a dose-response slope, 95% CI ranged from 0 – 1067
		363/			Non-cardia cancer		0.95 (0.71-1.28)		
Khan, 2004 STM20239 Japan	HGCS, Prospective Cohort, Age: 40- years, M/W	36/ 3158 14 years	Follow-up surveys	37-item FFQ	Mortality, stomach cancer Men	2-7 times/week vs. never-several times/month	1.10 (0.40-3.00)	Age, smoking habits	Excluded, two exposure categories only
Wong, 2004 STM00527 China	CCHT, Prospective Cohort, Age: 42years, M/W, H. pylori eradication trial participants	18/ 1630 7.5 years	Clinical trial follow up records	FFQ	Incidence, lower third gastric cancer	≥2 vs. <2 times/week	0.90 (0.21-3.93)		Excluded, two exposure categories only, study of lower third gastric cancer only
Appleby, 2002b STM00026 England	HFSS, Prospective Cohort, Age: 16-89 years, M/W, Health Conscious	40/ 10 741 25 years	NHS central registry	FFQ	Mortality, stomach cancer	Daily vs. <daily times/week	0.88 (0.41-1.88)	Age, sex, smoking habits	Excluded, two exposure categories only
		17/			Men		1.73 (0.49-6.16)	Age, smoking habits	
		23/			Women		0.52 (0.20-1.34)	Age, smoking habits	
		32/			Non-smokers		1.12 (0.43-2.93)	Age, sex	
Kasum, 2002 STM01746 USA	IWHS, Prospective Cohort,	56/ 34 651 14 years	Cancer registry	127-item FFQ	Incidence, stomach cancer	Quantile 3 vs. quantile 1	No significant association	Age, alcohol consumption, energy intake,	Excluded, no measure of association

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Reasons for exclusion
	Age: 55-69 years, post-menopausal women							smoking habits	
Hirvonen, 2001 STM02213 Finland	ATBC, Prospective Cohort, Age: 50-69 years, Men Smokers	111/ 27 110 6.1 years	Cancer registry	Validated 276-item self-administered FFQ	Incidence, stomach cancer	mean exposure comparison	-	Age	Superseded by Nouraie , 2005, STM44426
Botterweck, 1998 STM04445 Netherlands	NLCS, Case Cohort, Age: 55-69 years, M/W	282/ 120 852 6.3 years	Cancer registry	Validated 150-item self-administered semi-quantitative FFQ	Incidence, stomach cancer	Per 25 g/day	0.98 (0.96-1.01)	Age, sex, educational level, family history of stomach cancer, smoking habits, stomach disorders, vegetable intake	Superseded by Steevens , 2011, STM80062
						325 vs. 46 g/day	0.97 (0.64-1.48)		
Galanis, 1998 STM04769 USA	Hawaii-Japan DOH Survey, Prospective Cohort, Age: 18- years, M/W, Japanese residents of Hawaii	108/ 11 907 14.8 years	Cancer registry	19-item FFQ	Incidence, stomach cancer	≥7 vs. 0-6 times/week	0.60 (0.40-0.90)	Age, education, place of birth, (sex), and in men only alcohol intake status, smoking	Excluded, two exposure categories only
		64/5610			Men		0.60 (0.30-1.00)		
		44/6297			Women		0.70 (0.40-1.40)		

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Reasons for exclusion
Nomura, 1995 STM11198 USA	HHP, Case Cohort, M, Japanese residents of Hawaii	111/ 6860 23 years	Cancer registry/ hospital records	Dietary recall	Mortality, gastric adenocarcinoma	≥301 g/day vs. none	0.60 (0.40-1.00)	Age	Superseded by Nomura et a l., 1990, STM14814
Zheng, 1995 STM06417 USA	IWHS, Prospective Cohort, Age: 55-69 years, Post-menopausal women	26/ 34 691 7 years	Cancer registry	127-item self-administered semi-quantitative FFQ	Incidence, stomach cancer	Quantile 3 vs. quantile 1	No significant association	Age, educational level, pack-years of smoking, smoking habits	Excluded, no measure of association (same study as Kasum , 2002, STM01746)
Guo, 1994 STM10900 Linxin, China	NIT Cohort, Nested Case Control, Age: 40-69 years, M/W, Intervention trial participants	538/ 29 584 5 years	Follow-up visits, contacts with local commune, hospitals, and study medical team	FFQ	Incidence, stomach cancer	≥1 times/month vs. never	0.90 (0.80-1.10)	Family history of cancer, intervention group, smoking habits	Excluded, extremely low fruit intake, not comparable with other studies (same study as Tran , 2005, STM44270)
Kato, 1992a STM13746 Japan	HERPACC, Prospective Cohort, M/W, Endoscopy patients	44/ 3914 4.4 years	Hospital records, cancer registry, death certificates	10-item FFQ	Incidence, stomach cancer	Daily vs. ≤1-2 times/month	0.55 (0.20-1.52)	Age, sex, area of residence	Superseded by Inoue , 1996, STM06116
Kneller, 1991 STM07350	LBS, Prospective	75/ 17633	Health insurance company	FFQ	Mortality, stomach cancer	Quantile 4 vs. quantile 1	1.50 (0.75-2.93)	Age, smoking habits	Excluded, exposure not

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Reasons for exclusion
USA	Cohort, Age: 35- years, Men, mainly of Scandinavian descent	20 years	records						quantified
Chyou, 1990 STM12425 USA	HHP, Case Cohort, Age: 58years, Men, Japanese residents of Hawaii	111/ 8006 18 years	Cancer registry/ hospital records	24-hour dietary recall	Mortality, stomach cancer	High vs. none	0.80 (0.40-1.30)	Age, smoking habits	Superseded by Nomura, 1990, STM14814
		83/			intestinal gastric cancer	High vs. none	0.6		
Ikeda, 1983 STM09004 Japan	RERFCJ, Prospective Cohort, Age: 50years, M/W, Atomic bomb survivors	79/ 7 553 11 years	Cancer registry/ population register	Questionnaire (general)	Mortality, stomach cancer		No significant association		Excluded, no measure of association

Figure 39 RR estimates of stomach cancer by levels of fruit intake

Note: Epplein, 2010 was included in the analysis of non-cardia gastric cancer only. The mortality study of Sauvaget, 2003 was included in the analysis of stomach cancer mortality only.

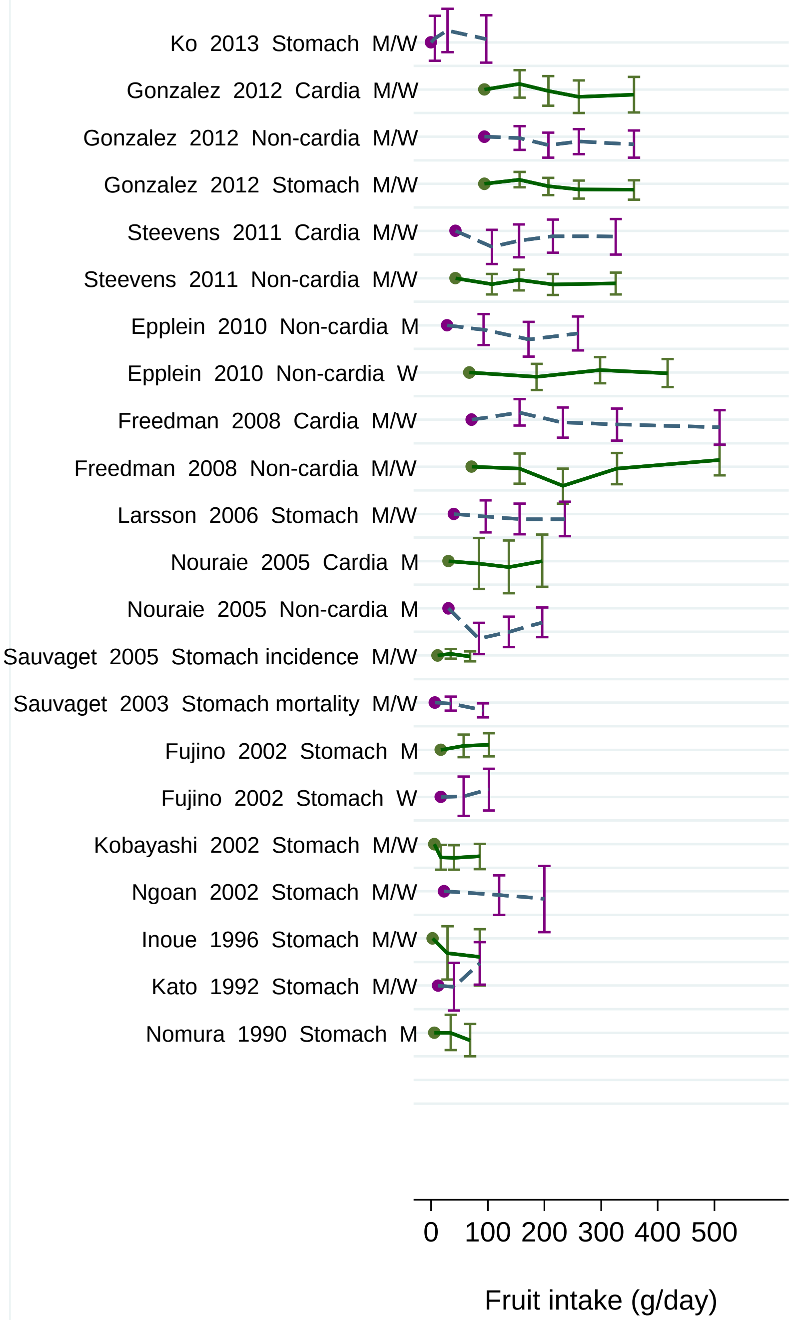


Figure 40 RR (95% CI) of stomach cancer for the highest compared to the lowest level of fruit intake

Author	Year	Sex	Cancer site	high vs low intake RR (95% CI)	Study Description	Comparison
Ko	2013	M/W	Stomach cancer	1.10 (0.55, 2.22)	KMCC	≥1 time/day vs almost never
Gonzalez	2012	M/W	Gastric adenocarcinoma	0.84 (0.63, 1.11)	EPIC	Quantile 5 vs Quantile 1
Steevens	2011	M/W	Gastric cardia adenocarcinoma	0.85 (0.50, 1.42)	NLCS	326.0 vs 43.0 g/day
Steevens	2011	M/W	Gastric noncardia adenocarcinoma	0.86 (0.62, 1.18)	NLCS	326.0 vs 43.0 g/day
Freedman	2008	M/W	Cardia Cancer	0.80 (0.48, 1.32)	NIH-AARP	3.2 vs. 0.45 serving/1000kcal
Freedman	2008	M/W	Non-Cardia Cancer	1.22 (0.78, 1.91)	NIH-AARP	3.2 vs. 0.45 serving/1000kcal
Kurosawa	2006	M/W	Stomach cancer	0.93 (0.37, 2.33)	Higashi-Yamanashi County, Japan	High vs Low
Larsson	2006	M/W	Stomach cancer	0.86 (0.52, 1.43)	SMC and COSM	≥2.5 vs <1.0 servings/day
Nouraie	2005	M	Cardia Cancer	1.00 (0.47, 2.18)	ATBC	≥167.0 vs ≤61.0 g/day
Nouraie	2005	M	Non-Cardia Cancer	0.66 (0.43, 1.02)	ATBC	≥167.0 vs ≤61.0 g/day
Sauvaget	2005	M/W	Stomach cancer	0.97 (0.84, 1.13)	LSS	>5 vs <2 times/week
Khan	2004	M	Stomach cancer	1.10 (0.40, 3.00)	HGCS	2-7 times/week vs never-several times/month
Appleby	2002	M/W	Stomach cancer	0.88 (0.41, 1.88)	HFSS	Daily vs <Daily
Fujino	2002	M	Stomach cancer	1.16 (0.82, 1.63)	JACC	Every day vs ≤3 times/week
Fujino	2002	W	Stomach cancer	1.24 (0.67, 2.30)	JACC	Every day vs ≤3 times/week
Kobayashi	2002	M/W	Stomach cancer	0.70 (0.48, 1.01)	JPHC I	Almost daily vs <1 days/week
Ngoan	2002	M/W	Stomach cancer	0.80 (0.30, 2.10)	FPC	≥2 times/day vs ≤ 2-4 times/week
Galanis	1998	M/W	Stomach cancer	0.60 (0.40, 0.90)	Hawaii-Japan DOH Survey	≥7 vs 0-6 times/week
Inoue	1996	M/W	Stomach cancer	0.58 (0.25, 1.31)	HERPACC	Daily vs ≤1-2 times/month
Kato	1992	M/W	Stomach cancer	1.92 (1.03, 3.59)	Higashi-Kamo Cohort	Daily vs ≤1-2 times/week
Kneller	1991	M	Stomach cancer	1.50 (0.75, 2.93)	LBS	Quantile 4 vs Quantile 1
Nomura	1990	M	Gastric adenocarcinoma	0.80 (0.50, 1.30)	HHP	≥5 vs ≤1 times/week

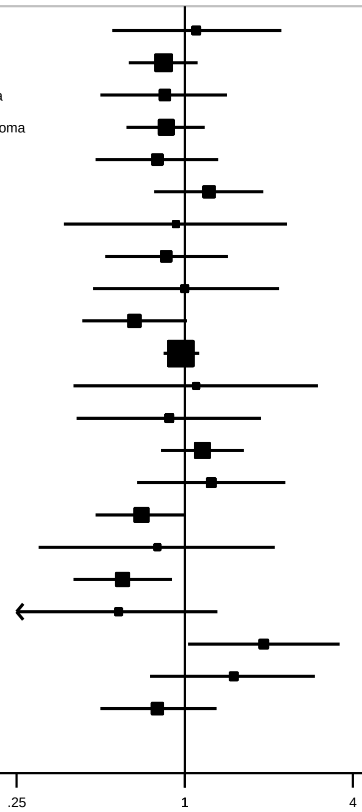


Figure 41 Relative risk of stomach cancer for 100g/day increase of fruit intake

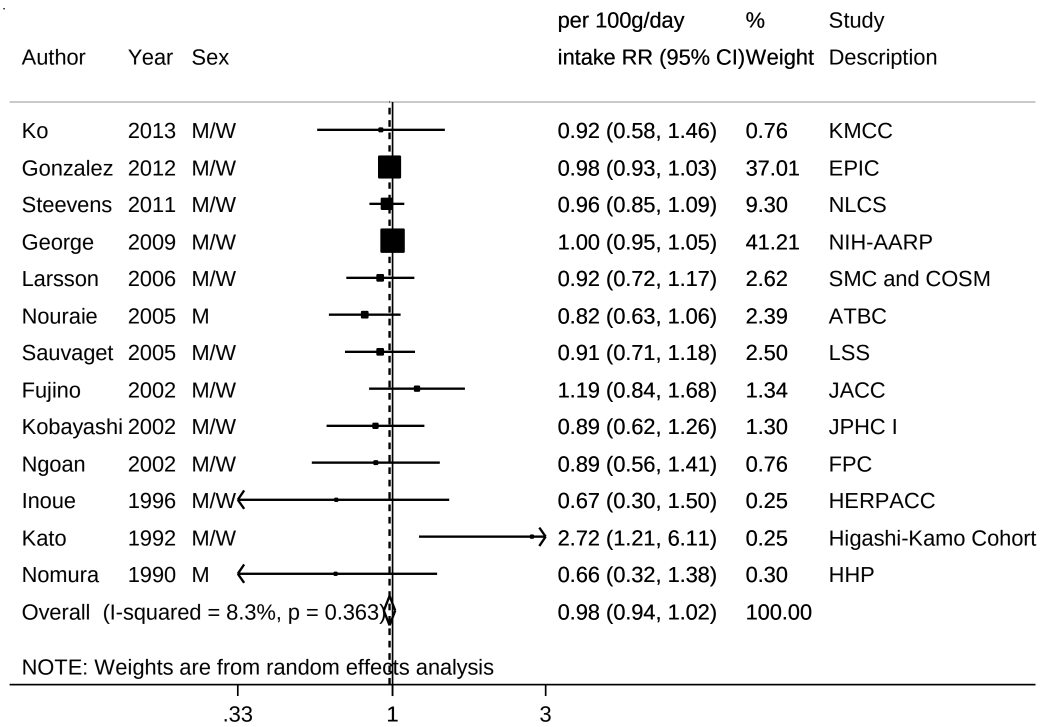
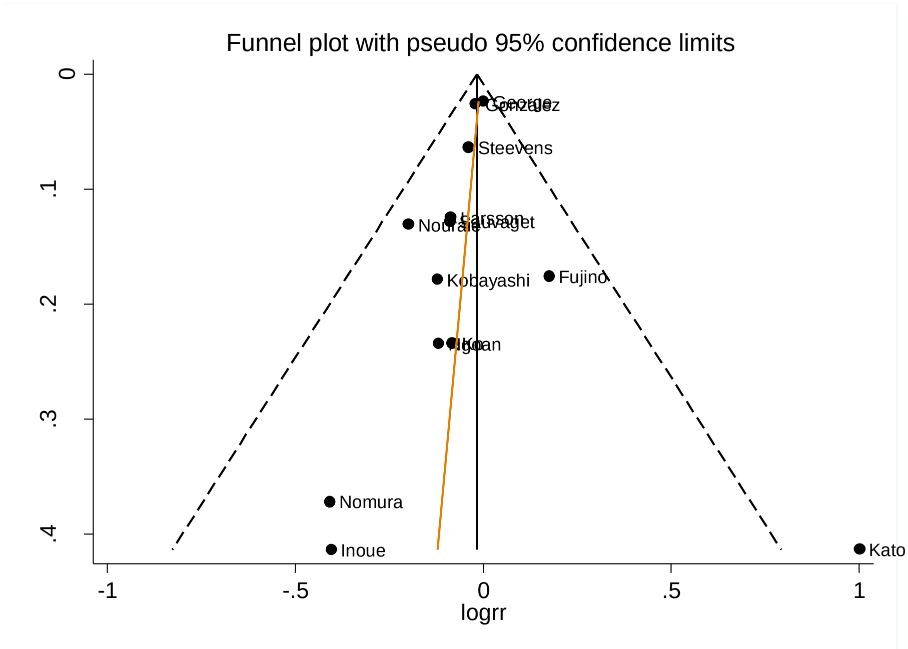


Figure 42 Funnel plot of studies included in the dose response meta-analysis of fruit intake and stomach cancer



Egger's test p=0.49

Figure 43 Relative risk of stomach cancer for 100g/day increase of fruit intake by sex

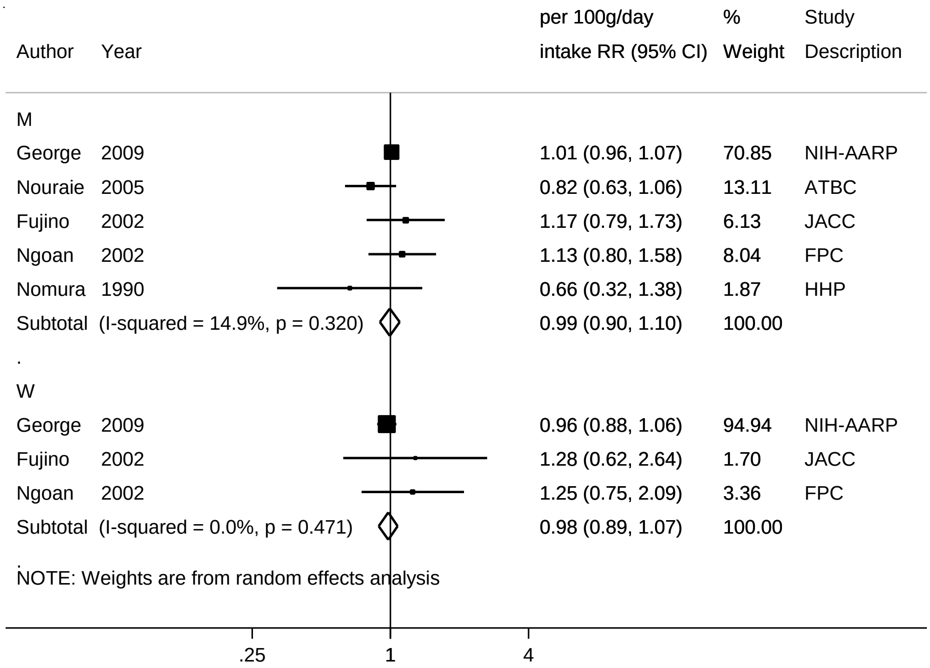


Figure 44 Relative risk of stomach cancer for 100g/day increase of fruit intake by cancer outcome

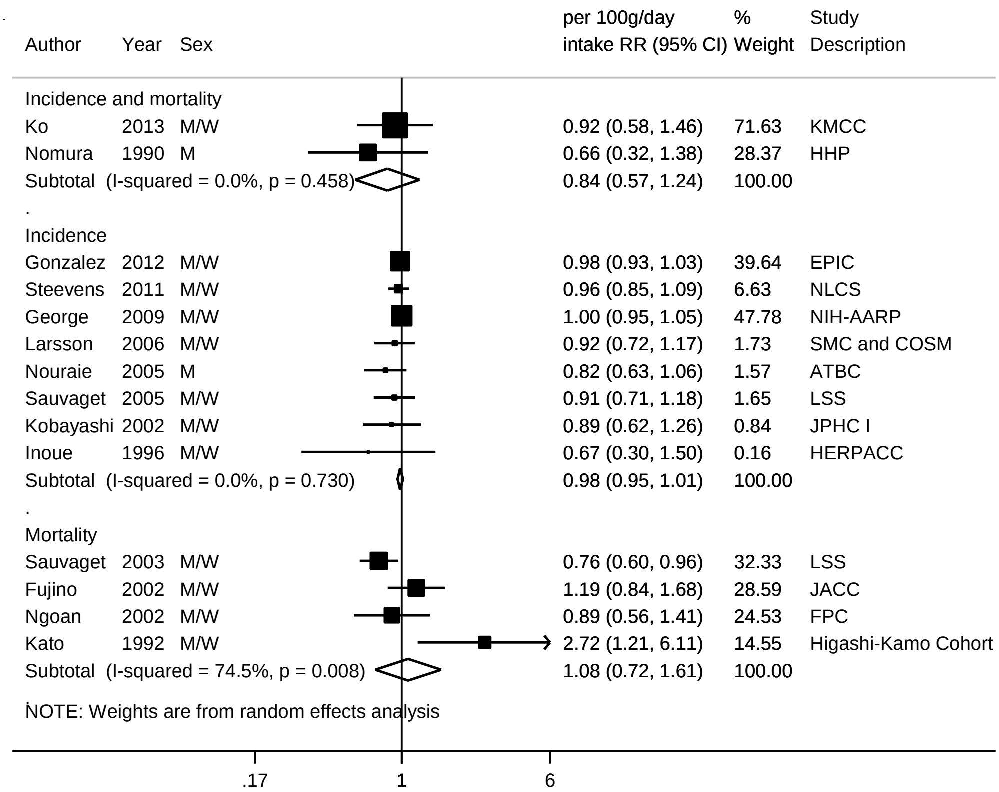


Figure 45 Relative risk of stomach cancer for 100g/day increase of fruit intake by cancer site

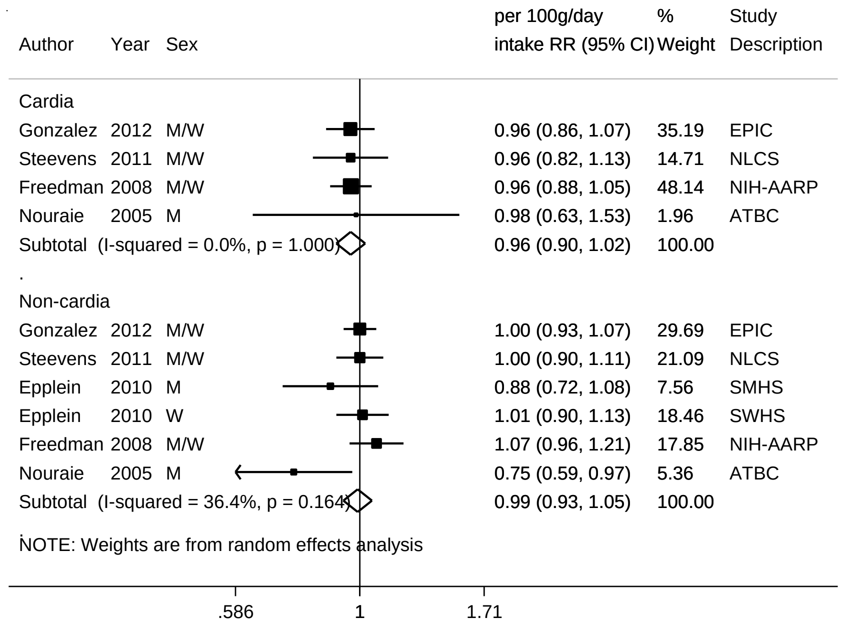


Figure 46 Relative risk of stomach cancer for 100g/day increase of fruit intake by geographic location

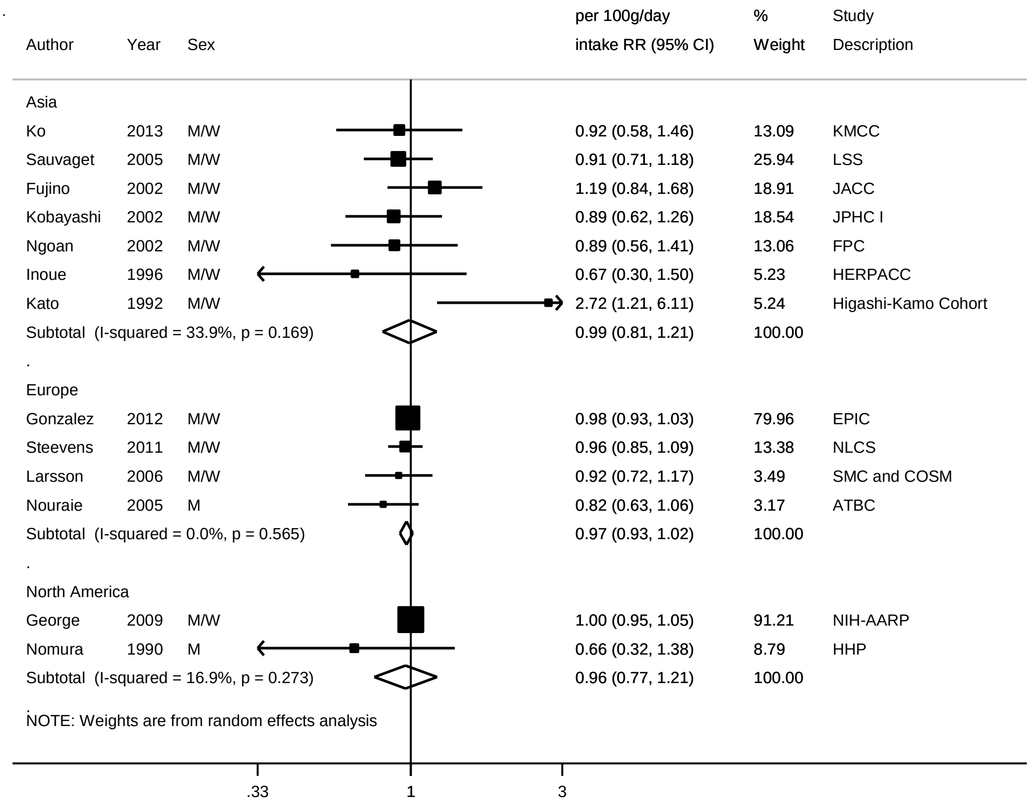


Figure 47 Relative risk of stomach cancer for 100g/day increase of fruit intake by cancer site among never smokers

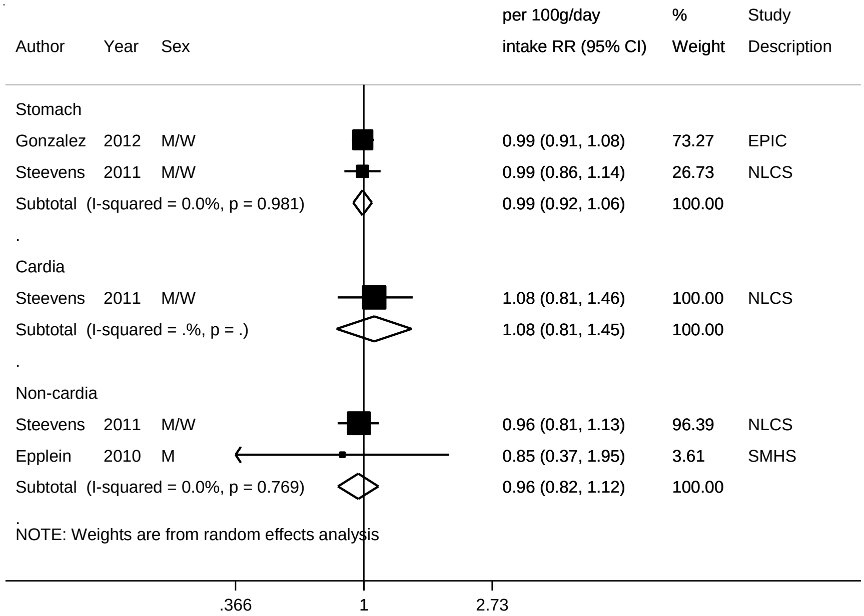


Figure 48 Relative risk of stomach cancer for 100g/day increase of fruit intake by cancer site among former smokers

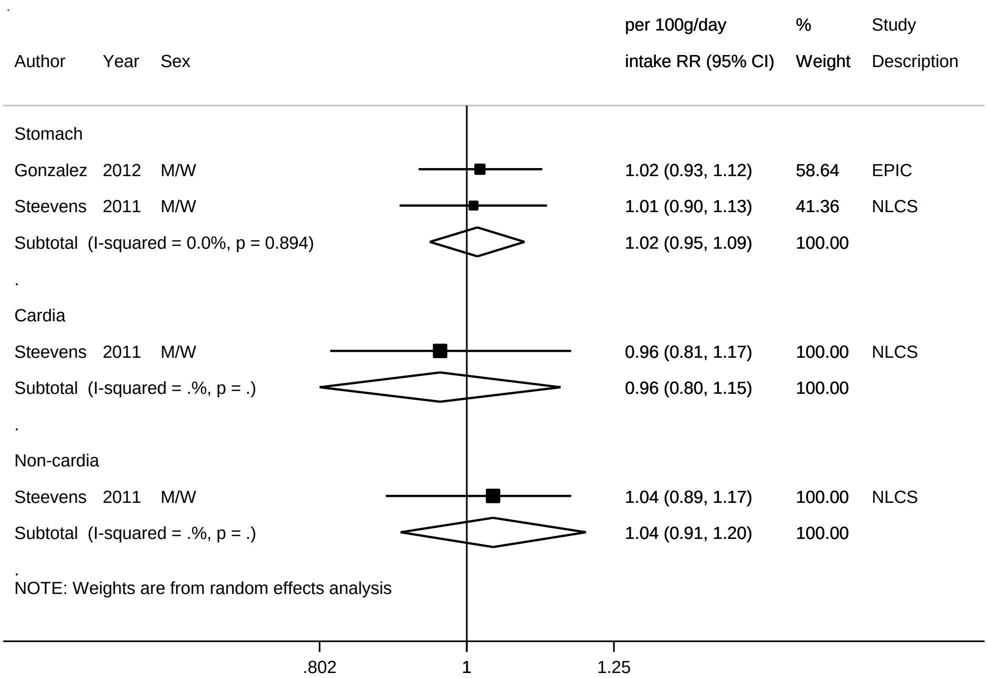


Figure 49 Relative risk of stomach cancer for 100g/day increase of fruit intake by cancer site among current smokers

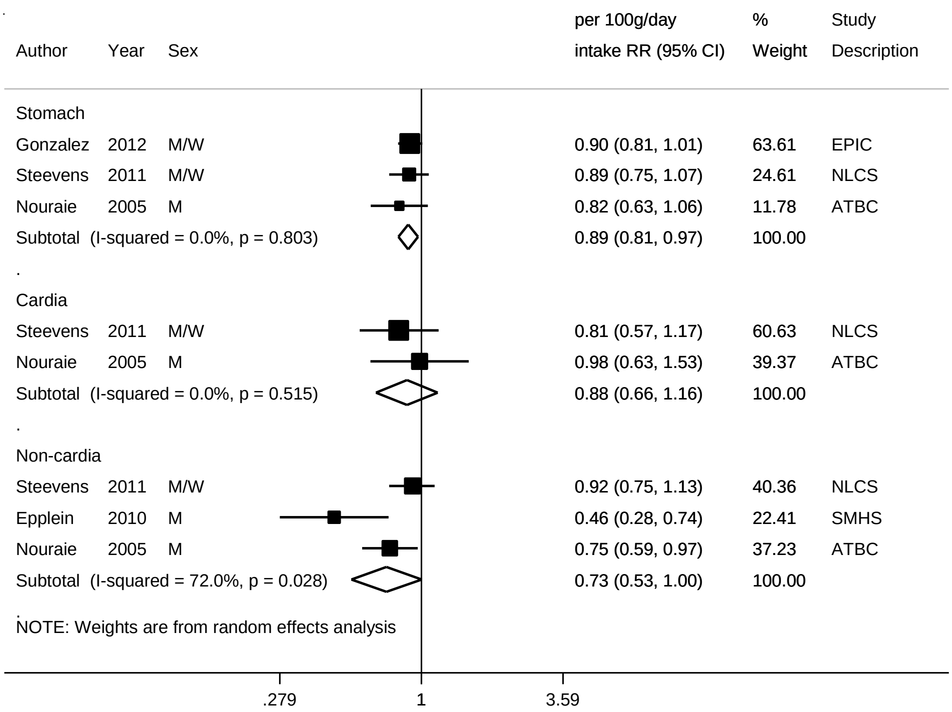
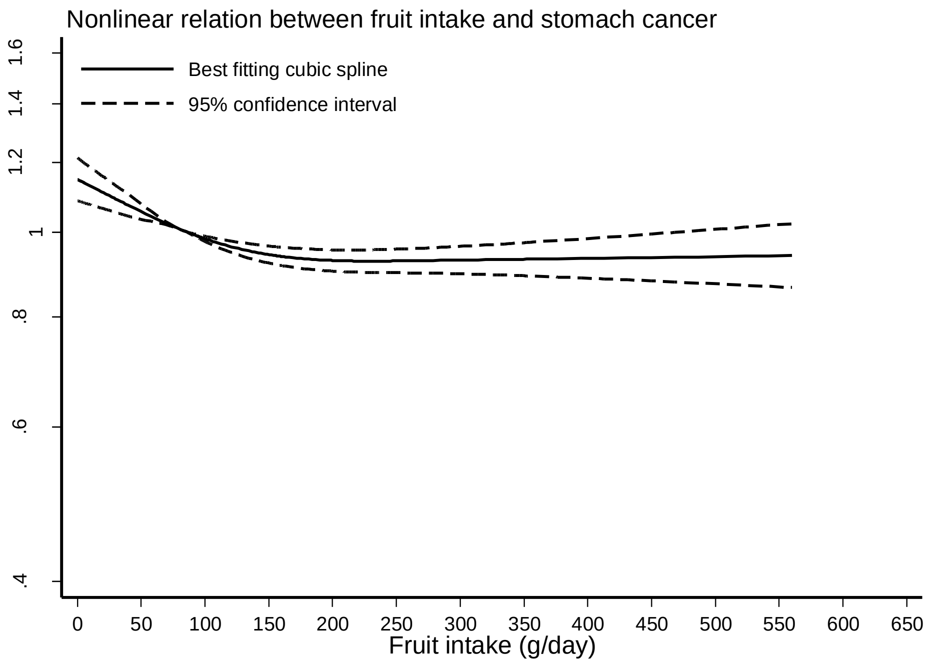


Figure 50 Non-linear dose-response meta-analysis of fruit intake and stomach cancer



P for non-linearity <0.001

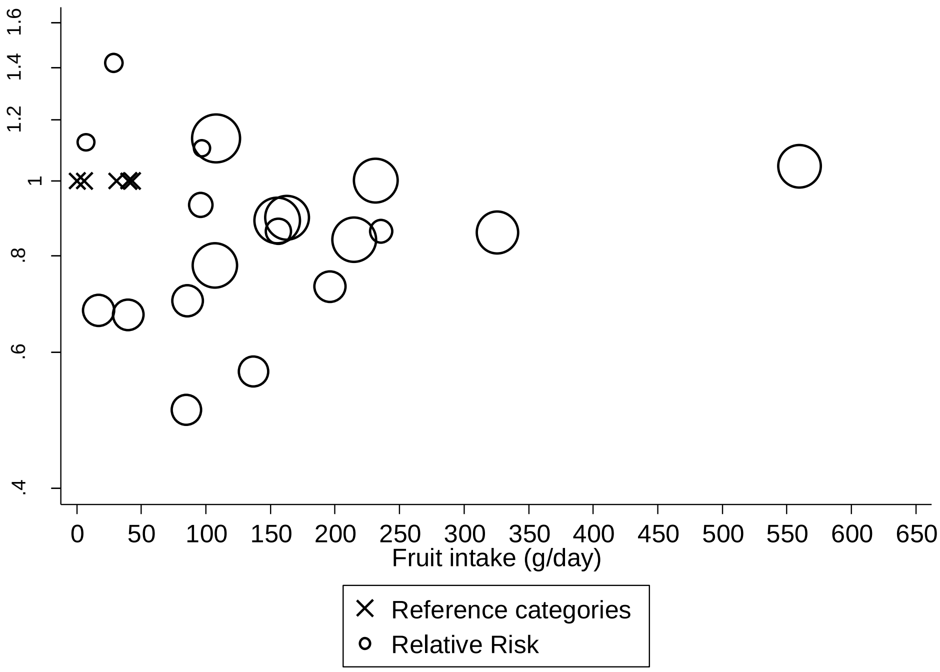


Table 39 Relative risk of stomach cancer and fruit intake estimated using non-linear models

Fruit (g/day)	RR (95%CI)
0	1.18 (1.11-1.26)
43	1.08 (1.05-1.11)
86	1.00
137	0.95 (0.93-0.97)
196	0.94 (0.92-0.97)
236	0.95 (0.92-0.98)

2.2.2.1 Citrus fruits

Randomised controlled trials

No randomised controlled trial was identified.

Cohort studies

Summary

Main results:

Six studies (4907 cases) out of eleven were included in the dose-response meta-analysis. Citrus fruit intake was not related to stomach cancer. A significant inverse association was observed for gastric cardia cancer (three studies and high heterogeneity) but not for non-cardia gastric cancer (five studies, low heterogeneity).

Of the studies excluded from the dose-response analysis, two studies reported no significant difference in mean intake of citrus fruits between cases and non-cases in the cohorts (Chyou, 1990; Stahelin, 1986) and the remaining studies reported no significant association.

Low heterogeneity was observed in the analysis. There was no significant evidence of publication or small study bias.

Sensitivity analyses:

The summary RRs ranged from 0.93 (95% CI=0.86-1.02) when Freedman, 2008 to 0.99 (95% CI=0.89-1.09) when McCullough, 2001 was omitted in influence analysis.

Non-linear dose-response meta-analysis:

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

Study quality:

Loss to follow-up was low in most studies. Cancer outcome was confirmed using medical notes, death certificates, or records in cancer registries.

All studies used FFQ to assess citrus fruit intake. Two studies (Steevens, 2011; McCullough, 2001) included citrus fruit juice in this group. Results were similar in these two studies and other studies included in the analysis. Gonzalez, 2012 also reported dose-response results for calibrated intake of citrus fruits. The inverse association was slightly stronger than the association with observed citrus fruit intake, but remained non-significant.

All studies included in the dose-response analysis were adjusted for age, sex, smoking and other confounders, except a Japanese study (Iso, 2007) that only adjusted for age and geographic area. None of the studies were adjusted for Helicobacter pylori status. No clear pattern emerged in an analysis in a subset of participants with known H. Pylori infection status in EPIC (Gonzalez, 2006a).

Table 40 Citrus fruit intake and stomach cancer risk. Number of studies in the CUP SLR

	Number
Studies identified	11* (14 publications)
Studies included in forest plot of highest compared with lowest exposure	6
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. *Included two studies in one publication (Epplein, 2010) on distal gastric cancer only and were included only in the subgroup analysis.

Table 41 Citrus fruit intake and stomach cancer risk. Summary of the linear dose-response meta-analysis in the 2005 SLR and CUP

	2005 SLR	**CUP**
Increment unit used	100g/day	100g/day
All studies		
Studies (n)	4	6
Cases (total number)	2072	4907
RR (95%CI)	0.95 (0.90-1.00)	0.96 (0.88-1.05)
Heterogeneity (I^2, p-value)	0%, 0.9	11.2%, 0.34
P value Egger test	0.7	0.25
Stratified and sensitivity analysis		
Men		
Studies (n)	2	2
RR (95%CI)	0.95 (0.89-1.01)	0.91 (0.76-1.09)
Heterogeneity (I^2, p-value)	-	7.7%, 0.30
Women		
Studies (n)	1	2
RR (95%CI)	0.99 (0.87-1.12)	1.20 (0.67-2.15)
Heterogeneity (I^2, p-value)	-	65.2%, 0.09
Other stratified analysis in the CUP		
Outcome type*	**Incidence**	**Mortality**
Studies (n)	4	2

RR (95%CI)	0.96 (0.87-1.07)	1.03 (0.73-1.46)	
Heterogeneity (I^2, p-value)	0%, 0.53	69.7%, 0.07	
Cancer site*	**Gastric cardia cancer**	**Non-cardia gastric cancer**	
Studies (n)	3	5	
RR (95%CI)	0.76 (0.58-0.99)	1.04 (0.94-1.16)	
Heterogeneity (I^2, p-value)	52.8%, 0.12	1.0%, 0.40	
Geographic location*	**Asia**	**Europe**	**North America**
Studies (n)	2	2	2
RR (95%CI)	1.10 (0.85-1.41)	0.92 (0.81-1.04)	0.97 (0.81-1.16)
Heterogeneity (I^2, p-value)	21.4%, 0.26	0%, 0.51	55.4%, 0.13
Number of cases	**<500 cases**	**500-<1000 cases**	**≥1000 cases**
Studies (n)	1	2	2
RR (95%CI)	1.08 (0.88-1.31)	0.92 (0.81-1.04)	1.03 (0.73-1.46)
Heterogeneity (I^2, p-value)	-	0%, 0.51	69.7%, 0.07
Duration of follow-up	**<10 years**	**≥10 years**	
Studies (n)	2	4	
RR (95%CI)	1.05 (0.89-1.23)	0.93 (0.84-1.04)	
Heterogeneity (I^2, p-value)	0%, 0.62	20.6%, 0.29	
Publication year	**<2010**	**≥2010**	
Studies (n)	3	3	
RR (95%CI)	1.02 (0.85-1.24)	0.93 (0.83-1.04)	
Heterogeneity (I^2, p-value)	56.3%, 0.10	0%, 0.73	
Adjustment for confounders:			
Ethnicity	**Not adjusted**	**Adjusted**	
Studies (n)	4	2	
RR (95%CI)	0.96 (0.85-1.09)	0.97 (0.81-1.16)	
Heterogeneity (I^2, p-value)	11.3%, 0.34	55.4%, 0.13	
Socioeconomic status/BMI**			
Studies (n)	2	4	
RR (95%CI)	1.02 (0.69-1.53)	0.95 (0.87-1.04)	
Heterogeneity (I^2, p-value)	69.2%, 0.07	0%, 0.51	
Alcohol intake			
Studies (n)	2	4	
RR (95%CI)	1.03 (0.73-1.46)	0.96 (0.87-1.07)	

Heterogeneity (I^2, p-value)	69.7%, 0.07	0%, 0.53
Total energy intake/physical activity**		
Studies (n)	3	3
RR (95%CI)	0.94 (078-1.14)	0.99 (0.89-1.10)
Heterogeneity (I^2, p-value)	46.2%, 0.16	0%, 0.56

* No stratified analysis in the 2005 SLR

** The two adjustment factor were included or not in the studies

Table 42 Citrus fruit intake and stomach cancer risk. Results of meta-analyses and pooled analyses of prospective studies published after the 2005 SLR

Author, Year	Number of studies	Total number of cases	Studies country, area	Outcome	Comparison	RR (95%CI)	P trend	Heterogeneity (I^2, p value)
Meta-analyses								
Wang Q, 2014	5 cohorts*	3415	USA; China; The Netherlands; Germany; Italy; Sweden; Denmark; France; Greece; Norway; Spain; UK	Incidence/mortality, Gastric cancer	High vs. low	0.88 (0.76-1.02)		47.6%, 0.05

*All studies identified were included in the present review.

Table 43 Citrus fruit intake and stomach 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
Gonzalez, 2012 STM80139 Denmark,France ,Germany,Greec e,Italy,Netherlan ds,Norway,Spai n,Sweden,U.K.	EPIC, Prospective Cohort, Age: 35-70 years, M/W	683/ 477 312 11.02 years	Cancer registries, health insurance records, pathology records, active follow up, death certificate	FFQ, dietary questionnaires, food record	Incidence, gastric adenocarcinoma	103.6 (M)/84.2 (W) vs. 10.8 (M)/22.7 (W) g/day) Per 50 g/day	0.87 (0.68-1.12) Ptrend: 0.07 0.97 (0.90-1.04)	Age, sex, BMI, centre, educational level, energy intake, physical activity, total vegetable consumption, alcohol intake, other fruits, red and processed meat, smoking, other fresh fruits	
		201/			Cardia		0.61 (0.38-1.00) Ptrend: 0.01 0.85 (0.71-1.02)		
		323/			Non-cardia		1.25 (0.86-1.80) Ptrend: 0.46 1.03 (0.95-1.13)		
		203/			Intestinal		0.86 (0.55-1.35) Ptrend: 0.29 0.98 (0.86-1.11)		
		217/			Diffuse		0.87 (0.56-1.37) Ptrend: 0.40 0.95 (0.83-1.07)		
Steevens, 2011 STM80062 Netherlands	NLCS, Case Cohort, Age: 55-69 years, M/W	156/ 4651 16.3 years	Annual linkage to The Netherlands cancer registry and network of histopathology and cytopathology	150-item self-administered validated FFQ	Incidence, gastric cardia adenocarcinoma	156 vs. 0 g/day Per 25 g/day	0.38 (0.21-0.69) Ptrend:0.003 0.88 (0.81-0.97)	Age, sex, alcohol consumption, smoking status, duration and cigarettes per day, intake of red meat , other fruits, fish and	RRs for cardia and non-cardia gastric cancers combined using Hamling's method
		460/			Non-cardia		0.80 (0.56-1.15) Ptrend: 0.46 0.99 (0.95-1.03)		

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Missing data derived for analyses
								vegetables	
Epplein, 2010 STM80129 China	SWHS and SMHS, Prospective Cohort, Age: 40-74 years, M/W	206/ 132 311	Review of medical records	Validated 81-item (SMHS) and 77-item (SWHS) FFQs	Incidence, distal stomach cancer Women	>31.9 vs. ≤6.1 g/day	0.94 (0.62-1.42) Ptrend: 0.86	Age, education level, smoking, total energy intake	Distribution of person-years by intake quintiles, mid-points of intake categories (Included in the analysis of distal gastric cancer only)
		132/			Men	>18.0 vs. ≤1.6 g/day	0.70 (0.41-1.18) Ptrend: 0.34		
Li, 2010 STM89939 Japan	OCS, Prospective Cohort, Age: 40-79 years, M/W	806/ 42 470 9 years	Miyagi prefectural cancer registry	FFQ	Incidence, stomach cancer	≥7 vs. <2 times/week	0.99 (0.80-1.21)	Age, sex, BMI, cigarette smoking, alcohol intake, exercise and walking time, educational years, job status, diabetes, gastric ulcer, hypertension, family history cancer, energy intake, intakes of meat, fish, miso soup, soybean, fruits, vegetables, tea, coffee, dairy products, and rice	Intake values using standard portion size, mid-points of intake 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
Freedman, 2008 STM80097 USA	NIH-AARP, Prospective Cohort, Age: 50-71 years, M/W, Retired	198/ 490 802 4.5 years	Linkage with 11 state cancer registry databases	Validated 124-item FFQ	Incidence, cardia cancer	1.12 vs. 0.08 serving/ 1000kcal	0.88 (0.62-1.23)	Age, sex, BMI, ethnicity, alcohol intake, cigarette- dose, education, total energy, usual activity throughout the day, vigorous physical activity	Distribution of person-years by intake tertiles, intake using mean energy intake, RRs for cardia and non-cardia gastric cancers combined using Hamling's method.
		196/			Non-cardia		1.36 (0.96-1.94)		
Iso, 2007 STM80144 Japan	JACC, Prospective Cohort, Age: 40-79 years, M/W	715/ 105 500/ 15 years	Municipal resident registration records, death certificates	Validated FFQ	Mortality, stomach cancer Men	≥5 vs. <3 times/week	1.06 (0.86-1.30)	Age, area of study	Intake values using standard portion size, mid-points of intake categories, RR for men and women combined
		344/			Women	≥5 vs. <3 times/week	1.29 (0.95-1.74)		
McCullough, 2001 STM02243 USA	CPS II, Prospective Cohort, Age: 30- years, M/W	910/ 970 045 14years	Death registry/ subject or family	32-item FFQ	Mortality, stomach cancer Men	>7 vs. 0-1.9 times/week	0.88 (0.75-1.03)	Age, BMI, educational level, family history of stomach cancer, multivitamin supplement, smoking habits, aspirin use, ethnicity/race, vitamin c supplement	Distribution of person-years by intake tertiles, intake values using standard portion size, mid-points of intake categories, RRs for men and women combined
		439/			Women	>7 vs. 0-2.9 times/week	0.97 (0.78-1.21)		

Table 44 Citrus fruit intake and stomach 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
Gonzalez, 2006a STM44425 France, Italy, Spain, U.K., Netherlands, Greece, Germany, Sweden, Denmark	EPIC, Prospective Cohort, Age: 35-70 years, M/W	330/ 481 518/ 6.5 years	Cancer registry	FFQ, dietary questionnaires, food record	Incidence, gastric adenocarcinoma	Quantile 4 vs. quantile 1 Per 50 g/day	0.88 (0.63-1.24) Ptrend: 0.21 0.96 (0.77-1.22)	Age, sex, centre, education level, energy intake, height, leisure - physical activity, red meat intake, weight, work - physical activity, alcohol intake, processed meat intake, smoking	Superseded by Gonzalez, 2012, STM80139
		94/			Cardia		0.62 (0.32-1.19) Ptrend: 0.08 0.77 (0.47-1.22)		
		159/			Non-cardia		1.10 (0.68-1.78) Ptrend: 0.96 1.08 (0.82-1.40)		
		109/			Intestinal		0.95 (0.53-1.69) Ptrend: 0.60 1.01 (0.73-1.40)		
		116/			Diffuse		0.95 (0.53-1.68) Ptrend: 0.46 0.79 (0.50-1.28)		
		40/			H. pylori -ve gastric adenocarcinoma	Per 50 g/day	0.49 (0.18-1.33)	Additionally adjusted by date of blood collection	
		22/			Cardia		0.61 (0.17-2.15)		
		12/			Non-cardia		0.47 (0.05-4.39)		
		16/			Intestinal		0.54 (0.11-2.54)		
		9/			Diffuse		0 (0-20.90)		
		201/			H. pylori +ve gastric adenocarcinoma		0.89 (0.64-1.22)		

Author, Year, 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
		47/			Cardia		0.46 (0.20-1.04)		
		113/			Non-cardia		1.20 (0.82-1.75)		
		77/			Intestinal		0.95 (0.59-1.53)		
		82/			Diffuse		0.64 (0.36-1.14)		
Tokui, 2005 STM80105 Japan	JACC, Prospective Cohort, Age: 40-79 years, M/W	389/ 44 930 12years	Population registry	33-item FFQ	Mortality, stomach cancer Men	More than once/day vs. 1-2 times/month or less	0.92 (0.71-1.21) Ptrend: 0.80	Age	Superseded by Iso, 2007, STM80144
		192/			Women		1.03 (0.65-1.63) Ptrend: 0.65		
Yatsuya, 2004 STM00003 Japan	JACC, Prospective Cohort, Age: 40-79 years, M/W	92 men 85 women/ 65 184 10 years	Population registry	FFQ	Incidence, stomach cancer	≥3-4 vs. ≤1-2 times/week	No significant difference in consumption between cases and non-cases (Men p=0.49 Women p=0.78)		Superseded by Iso, 2007, STM80144
Botterweck, 1998 STM04445 Netherlands	NLCS, Case Cohort, Age: 55-69 years, M/W	282/ 120 852 6.3 years	Cancer registry	Validated 150-item self-administered semi-quantitative FFQ	Incidence, stomach cancer	175 vs. 3 g/day	0.86 (0.57-1.29) Ptrend: 0.20	Age, sex, educational level, family history of stomach cancer, smoking habits, stomach disorders, vegetable intake	Superseded by Steevens, 2011, STM80062
Zheng, 1995 STM06417 USA	IWHS, Prospective Cohort, Age: 55-69	26/ 34 691 7 years	Cancer registry	127-item self-administered semi-quantitative FFQ	Incidence, stomach cancer	Quantile 3 vs. quantile 1	Non-significant inverse association	Age, educational level, pack-years of smoking, smoking habits	Excluded, no measure of association

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Reasons for exclusion
	years, post-menopausal women								
Chyou, 1990 STM12425 USA	HHP, Case Cohort, Age: 58years, M, Japanese residents of Hawaii	111/ 8006 18 years	Cancer registry/ hospital records	24-hour dietary recall	Mortality, stomach cancer	mean exposure comparison		Age	Excluded, no measure of association
Stahelin, 1986 STM15664 Switzerland	BASEL II and III, Nested Case Control, M Age: 18-65 years	19/ 4224 7 years	Cancer registry/ death certificate	Questionnaire (general)	Mortality, stomach cancer	≥3 vs. <3 times/week	No significant difference in consumption between cases and non-cases (p=0.07)		Excluded, no measure of association

Figure 51 RR estimates of stomach cancer by levels of citrus fruit intake

Note: Epplein, 2010 was included in the analysis of distal gastric cancer only.

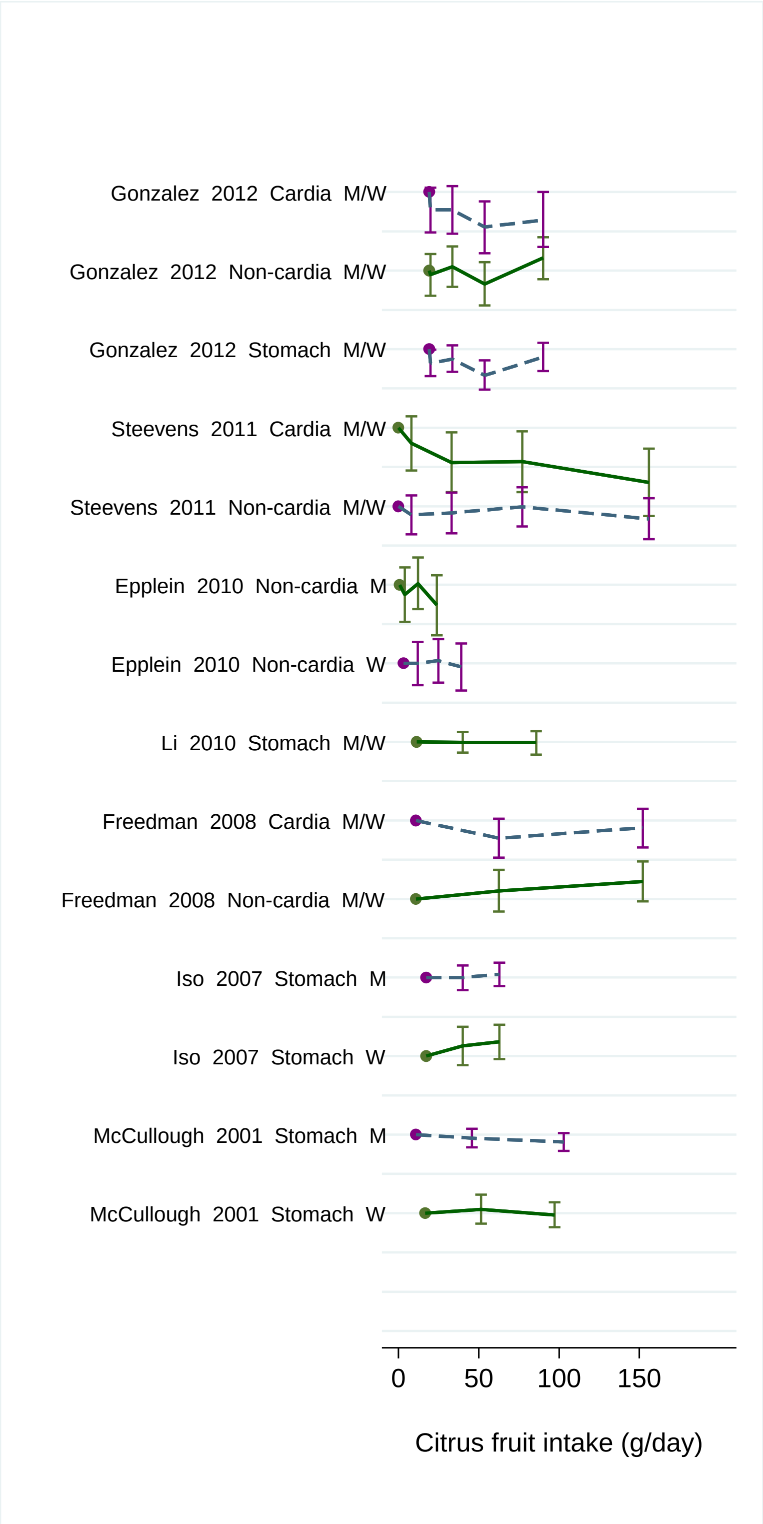


Figure 52 RR (95% CI) of stomach cancer for the highest compared with the lowest level of citrus fruit intake

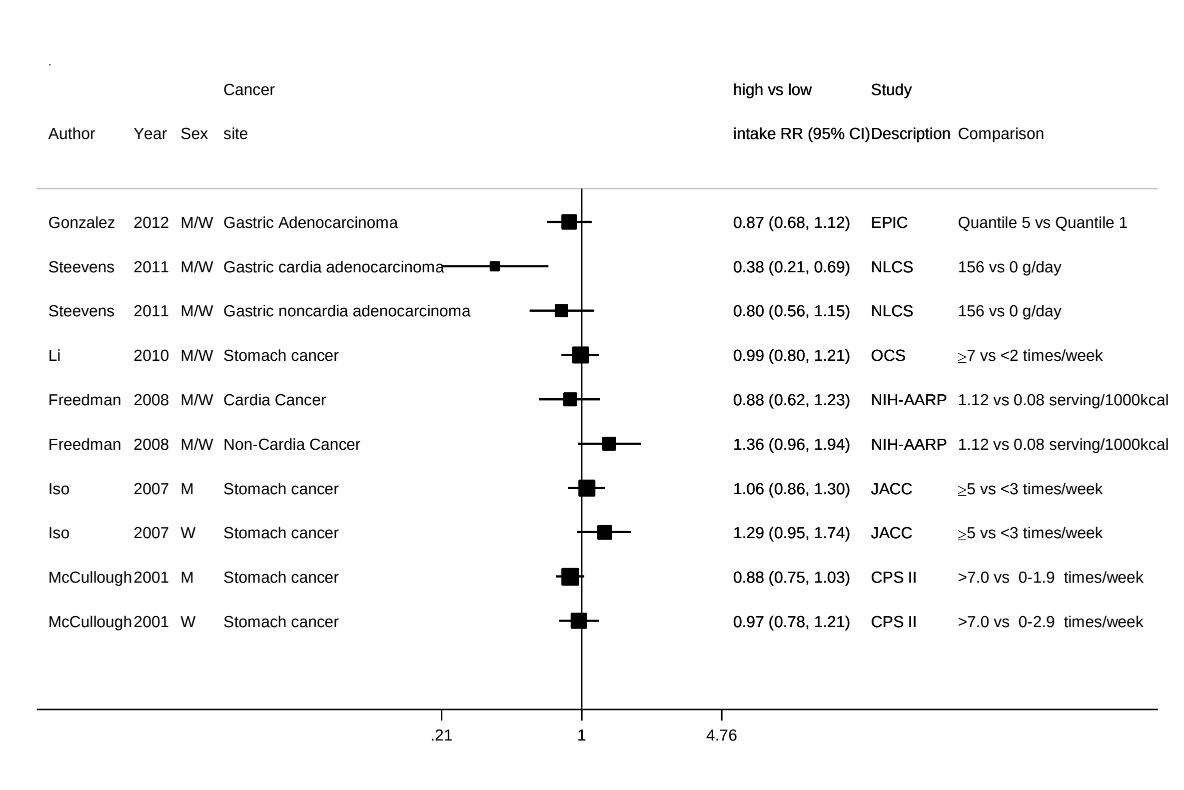


Figure 53 Relative risk of stomach cancer for 100g/day increase of citrus fruit intake

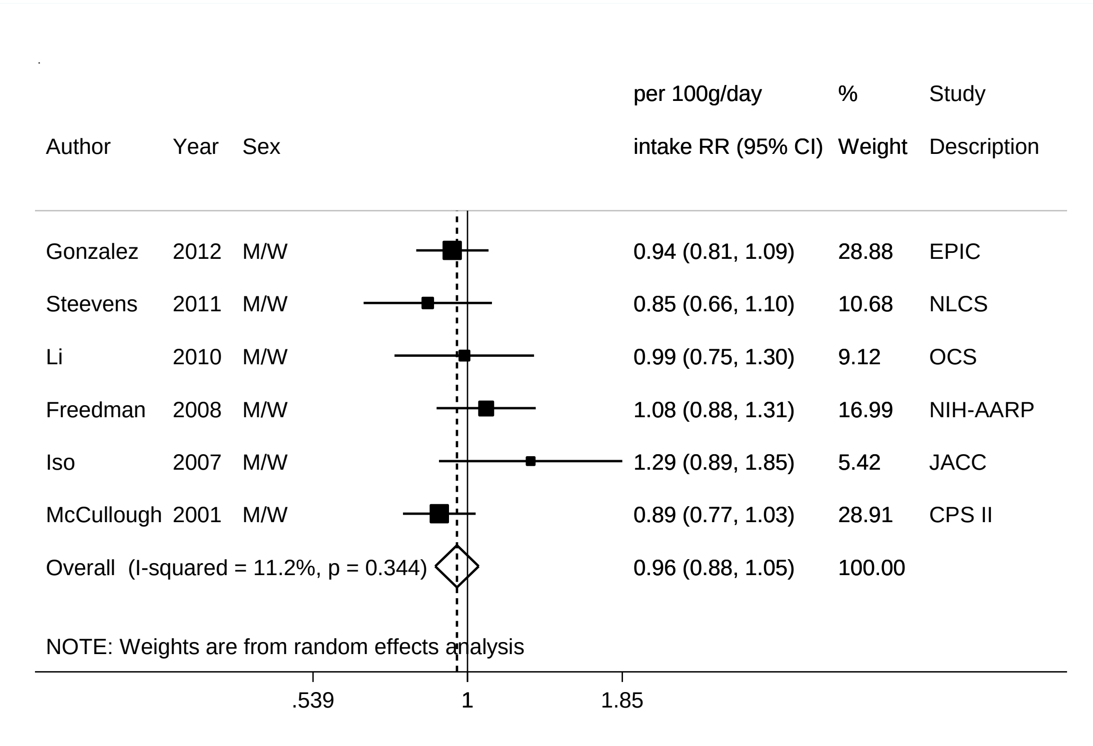
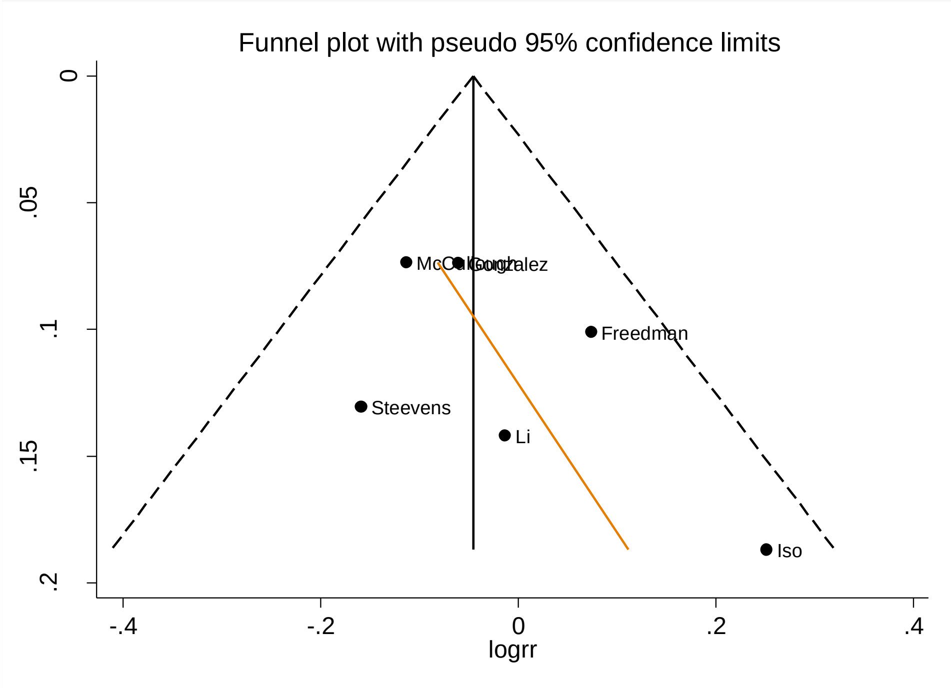


Figure 54 Funnel plot of studies included in the dose response meta-analysis of citrus fruit intake and stomach cancer



Egger's test p=0.25

Figure 55 Relative risk of stomach cancer for 100g/day increase of citrus fruit intake by cancer site by sex

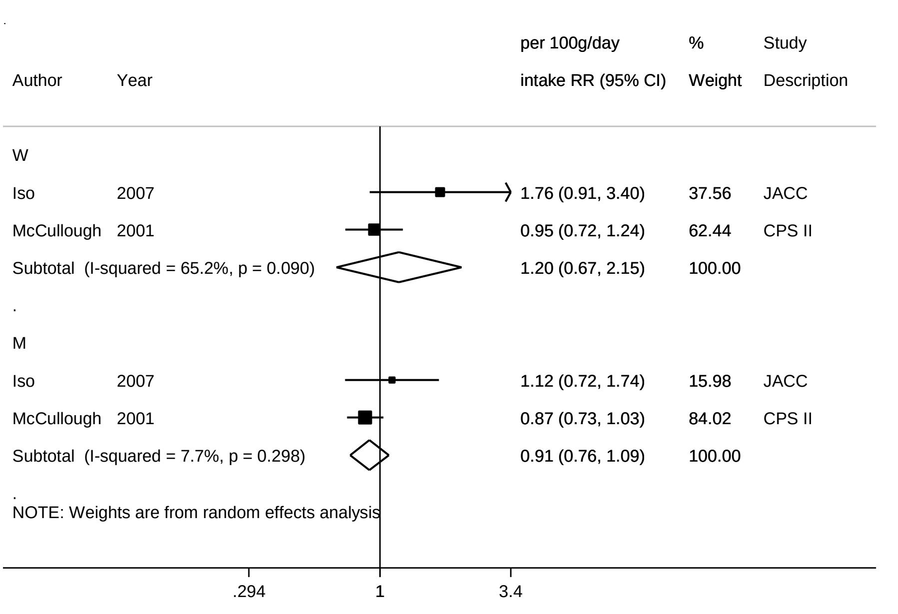


Figure 56 Relative risk of stomach cancer for 100g/day increase of citrus fruit intake by cancer site by outcome type

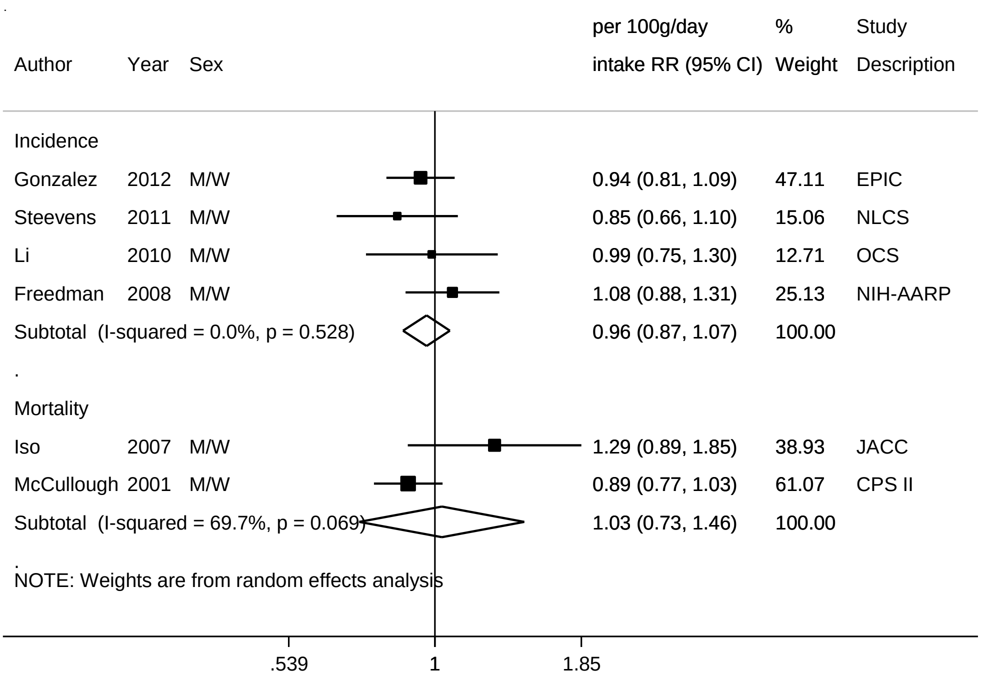


Figure 57 Relative risk of stomach cancer for 100g/day increase of citrus fruit intake by cancer site

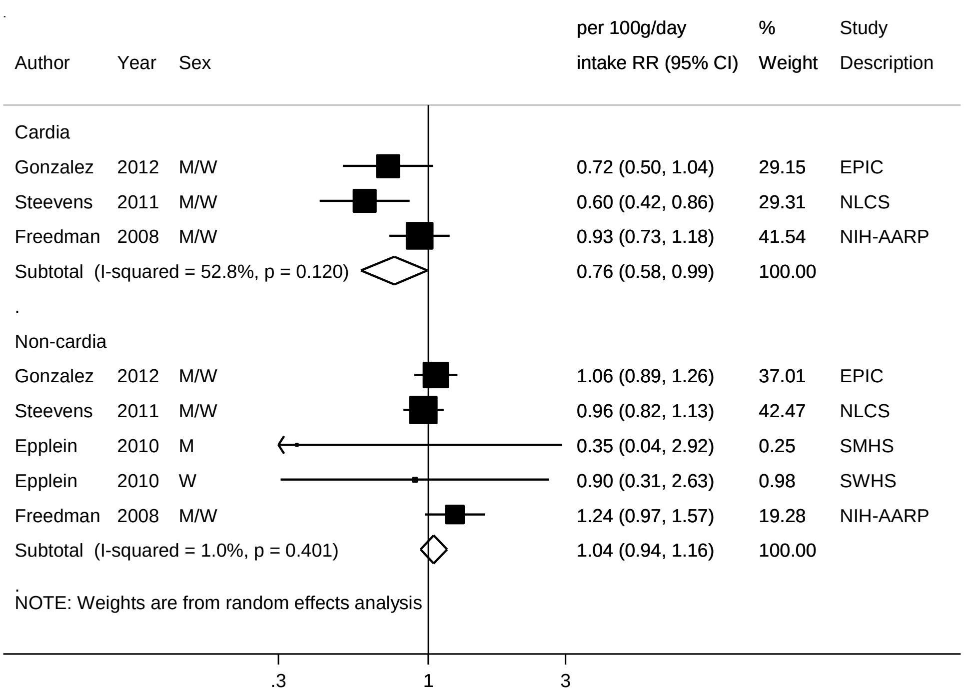
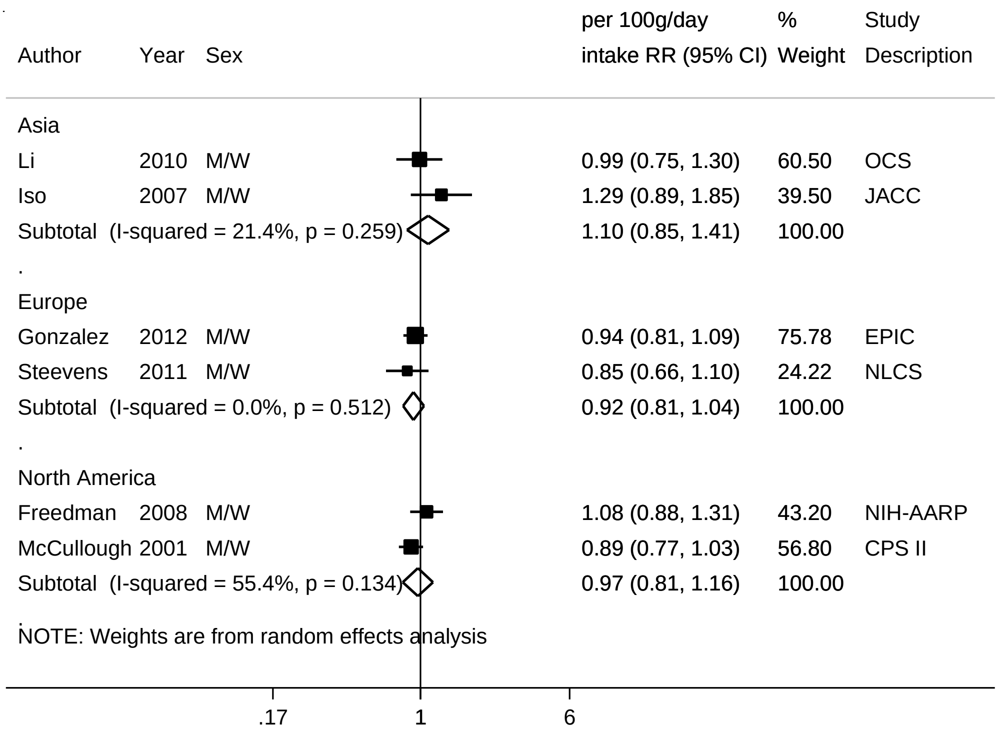


Figure 58 Relative risk of stomach cancer for 100g/day increase of citrus fruit intake by geographic location



2.3 Pulses (legumes)

Randomised controlled trials

No randomised controlled trial was identified.

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 pulses (legumes) are causally related to stomach cancer risk was judged as limited suggestive in the Second Expert report.

Four (three publications) out of six studies identified could be included in the dose-response meta-analysis. Two studies (Steevens, 2011; Freedman, 2008) reported results by stomach cancer subsites and two studies in one publication (Epplein, 2010) reported results on distal gastric cancer only.

No significant associations were observed in the analyses of stomach cancer (two studies, 985 cases, low heterogeneity), gastric cardia cancer (two studies, 346 cases, no heterogeneity), and non-cardia gastric cancer (four studies, 977 cases, low heterogeneity).

Test of publication or small study bias, sensitivity analysis, and non-linear dose-response meta-analysis were not conducted due to small number of studies.

No published meta-analysis or pooled analysis was identified.

Two studies were excluded from the dose-response analysis. One study reported no significant difference between the intakes of legumes, seeds, and nuts in cases and non-cases (Chyou, 1990). One study reported a significant positive association of boiled beans intake with stomach cancer mortality in men and non-significant (inverse) association in women (Iso, 2007). The NLCS study was included in the analysis on pulses but also reported non-significant inverse associations of string beans and French green beans intakes with the risk of stomach cancer (Botterweck, 1998) and its subsites (Steevens, 2011).

Study quality:

There were one American, one Dutch, and two Chinese studies included in the dose-response analyses. All studies examined stomach cancer risk as outcomes, which were confirmed using medical notes or record linkage to the cancer registries. Loss to follow-up was low.

All studies used FFQ to assess pulses/legumes intake**.** Two studies included in the dose-response analyses were adjusted for age, sex, smoking, alcohol intake and other confounders. One study (Epplein, 2010) was adjusted for age, education level, smoking and total energy intake.

Table 45 Pulses (legumes) intake and stomach cancer risk. Number of studies in the CUP SLR

	Number
Studies identified	6* (8 publications)
Studies included in forest plot of highest compared with lowest exposure	4*
Studies included in linear dose-response meta-analysis	2 stomach 2 cardia 4 non-cardia
Studies included in non-linear dose-response meta-analysis	Not enough studies

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

*Include two cohort studies in one publication (Epplein, 2010) on distal gastric cancer only.

Table 46 Pulses (legumes) intake and stomach cancer risk. Summary of the linear dose-response meta-analysis in the 2005 SLR and the CUP

	2005 SLR	**CUP**
Increment unit used	20g/day	50g/day
All studies		
Studies (n)	2	2
Cases (total number)	375	985
RR (95%CI)	0.93 (0.82-1.05)	0.98 (0.79-1.21)
Heterogeneity (I^2, p-value)	60.0%, 0.1	23.0%, 0.25
P value Egger test	-	
Stratified analysis		
Gastric cardia cancer		
Studies (n)	-	2 (n=346)
RR (95%CI)	-	1.03 (0.84-1.27)
Heterogeneity (I^2, p-value)	-	0%, 0.58
Non-cardia gastric cancer		
Studies (n)	-	4 (n=977)
RR (95%CI)	-	0.97 (0.83-1.14)
Heterogeneity (I^2, p-value)	-	5.6%, 0.37

Table 47 Pulses (legumes) intake and stomach 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 STM80062 The Netherlands	NLCS, Case Cohort, Age: 55-69 years, M/W	591/ 4035 16.3 years 148/	Record linkage to cancer registries	Validated FFQ, 157-item Legumes and pulses	Incidence Gastric cardia adenocarcinoma	Per 25 g/day 62 vs. 11 g/day	0.96 (0.76-1.20) 0.60 (0.34-1.06)	Age, sex, alcohol consumption, duration of smoking, fruit intake, red meat intake, all other vegetables, current smoking, fish intake, number of cigarettes smoked per day	Rescaled the RR for the increment unit used, Hamling's method was used to calculate RRs for cardia and non-cardia gastric cancers combined
		443/			Gastric non-cardia adenocarcinoma		0.90 (0.78-1.03) 0.83 (0.59-1.18)		
Epplein, 2010 STM80129 China	SWHS and SMHS, Prospective Cohort, Age: 40-74 years, M/W	338/ 132 311 206/ 73 064	Review of medical records	Validated FFQ Legumes	Incidence, distal stomach cancer Women	>39.5 vs. ≤13.8 g/day	1.14 (0.77-1.69)	Age, education level, smoking, total energy intake	Distribution of person-years and mid-points of exposure categories (results included in the analysis of non-cardia stomach cancer only)
		132/ 59 247			Men	>52.0 vs. ≤19.7 g/day	0.94 (0.57-1.51)		
Freedman, 2008 STM80097 USA	NIH- AARP, Prospective Cohort, Age: 50-71 years,	394/ 490 802 4.5 years	Linkage with 11 state cancer registry databases	Validated FFQ Leguminosae: dried beans, string beans, and peas	Incidence Cardia cancer	0.59 vs. 0.12 serving/1000kcal	1.08 (0.76-1.52)	Age, sex, BMI, ethnicity, alcohol intake, cigarette-smoke-dose, education,	Distribution of person-years by exposure category, 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
	M/W, Retired	198/						total energy, usual activity throughout the day, vigorous physical activity	using mean energy intake and standard portion size of 80 g/day, Hamling's method was used to calculate RRs for cardia and non-cardia stomach cancer combined
		196/			Non-cardia cancer	0.59 vs. 0.12 serving/1000kcal	1.03 (0.73-1.45)		

Table 48 Pulses (legumes) intake and stomach 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, Retired	954/ 494 968 9.7 years	Cancer registry, death master file, national death index plus, postal service database	Validated FFQ, 124-item	Incidence, stomach cancer	aMED scoring criteria for legumes ≥0.08 vs. <0.08 cups		Age, sex, BMI, race, education, modified total score, smoking, total energy intake, usual activity throughout the day, vigorous physical activity	Excluded, exposure was meeting dietary index criteria or not (same study as Freedman, 2008, STM80097)
		453/			Gastric cardia adenocarcinoma		1.16 (0.95-1.40)		
		501/			Incidence, gastric non-cardia adenocarcinoma		0.86 (0.71-1.03)		
Steevens, 2011 STM80062 The Netherlands	NLCS, Case Cohort, Age: 55-69 years, M/W	591/ 4035 16.3 years	Record linkage to cancer registries	Validated FFQ, 157-item String beans/French beans	Incidence	Per 25 g/day		Age, sex, alcohol consumption, duration of smoking, fruit intake, red meat intake, all other vegetables, current smoking, fish intake, number of cigarettes smoked per day	Excluded, specific pulses item (results on total pulses/legume intake included in analysis)
		148/			Gastric cardia adenocarcinoma		0.91 (0.64-1.31)		
		443/			Non-cardia adenocarcinoma		0.86 (0.68-1.08)		
Iso, 2007 STM80144 Japan	JACC, Prospective Cohort, Age: 40-79 years,	1024/ 105 500 15 years 690/	Municipal resident registration records, death certificates	Validated FFQ Boiled beans	Mortality, stomach cancer Men	≥3 vs. <1 times/week	1.30 (1.05-1.60)	Age, area of study	Excluded, specific pulses item (same study as

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Reasons for exclusion
	M/W								Tokui, 2005, STM80105)
		334/			Women		0.98 (0.72-1.32)		
Tokui, 2005 STM80105 Japan	JACC, Prospective Cohort, Age: 40-79 years, M/W	611/ 44 930 12 years 414/	Population registry	FFQ Boiled beans	Mortality, stomach cancer Men	≥1 times/week vs. none	0.93 (0.60-1.44)	Age	Excluded, specific pulses item (same study as Iso, 2007, STM80144)
		197/			Women		0.84 (0.46-1.56)		
Botterweck, 1998 STM04445 The Netherlands	NLCS, Case Cohort, Age: 55-69 years, M/W	264/ 120 852 6.3 years	Cancer registry	FFQ Pulses/legumes	Incidence, stomach cancer	Total pulses/legumes 60 vs. 10 g/day	0.70 (0.47-1.06)	Age, sex, educational level, family history of stomach cancer, fruit, smoking habits, stomach disorders	Superseded by Steevens, 2011, STM80062
						String/French beans Per 25 g/day	0.86 (0.66-1.12)		Excluded, specific pulses item
						Broad beans Per 25 g/day	1.07 (0.67-1.73)		
Chyou, 1990 STM12425 USA	HHP, Case Cohort, Age: 58.00years, M, Japanese residents of Hawaii	111/ 8006 18 years	Cancer registry/ hospital records	FFQ + recall Legumes, seeds, nuts	Incidence/mortality, stomach cancer	(mean exposure)		Age	Excluded, no measure of association

Figure 59 RR estimates of stomach cancer by levels of pulses (legumes) intake

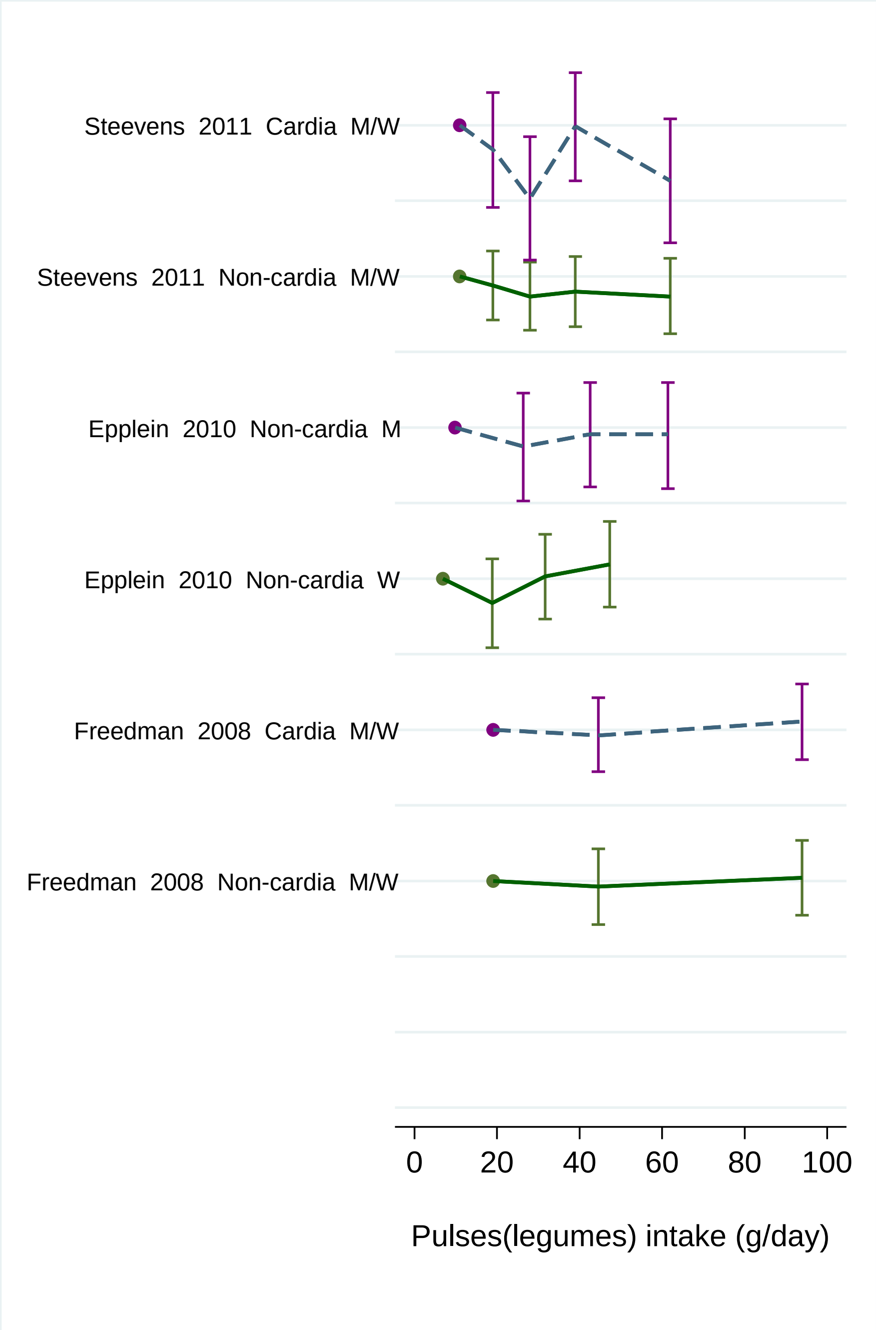


Figure 60 RR (95% CI) of stomach cancer for the highest compared with the lowest level of pulses (legumes) intake

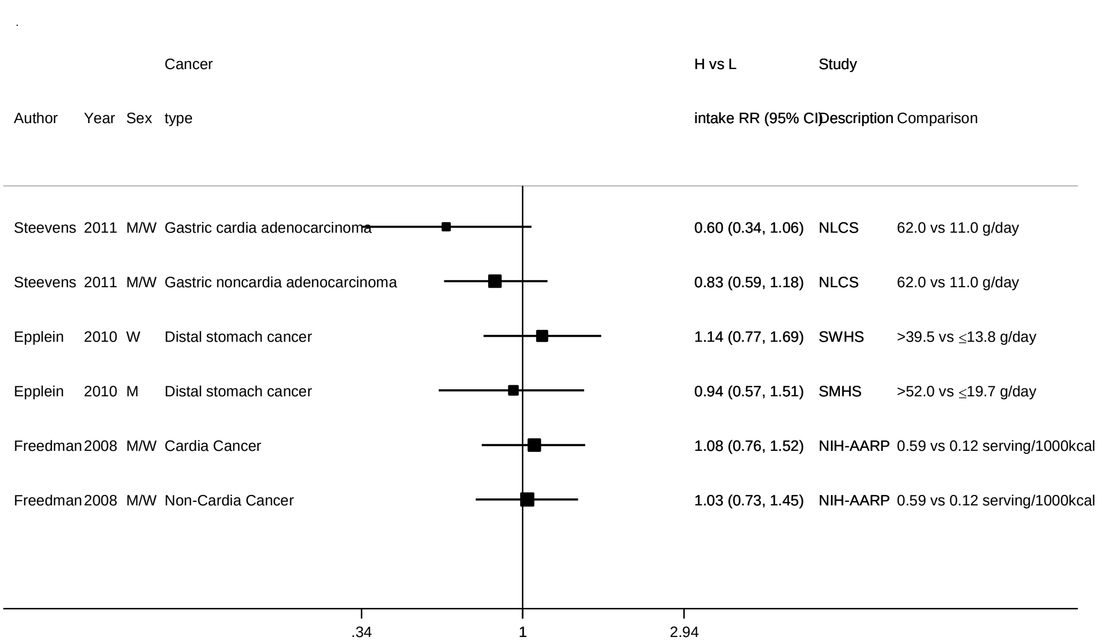
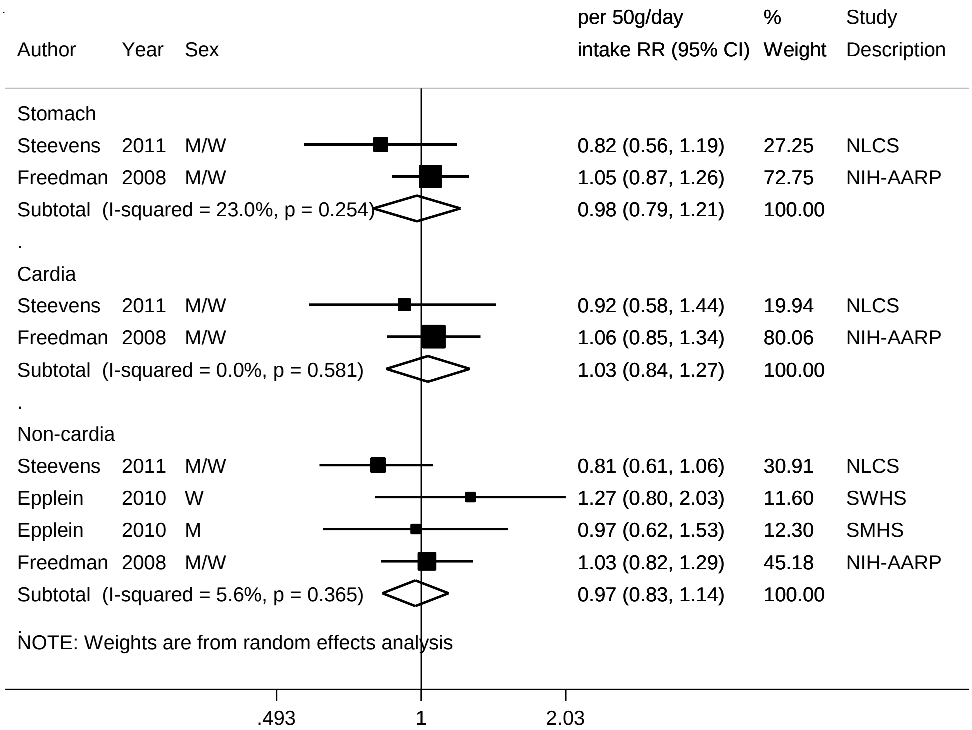


Figure 61 Relative risk of stomach cancer for 50 g/day increase of pulses (legumes) intake



2.3.1 Soy products

The evidence that pulses (legumes) are causally related to stomach cancer risk was judged as limited suggestive in the Second Expert report. For that reason, the results and main characteristics of cohort studies on soy products and stomach cancer have been tabulated in this section although no dose-response meta-analysis could be conducted. In the 2005 SLR, two cohort studies were identified (Ahn, 1997; Nagata, 2002). Only one of the studies (two estimates) (Nagata, 2002) could be included in a meta-analysis (summary RR=0.86, 95% CI=0.77-0.96).

Randomised controlled trials

No randomised controlled trial was identified.

Cohort studies

Summary

Seven studies (six publications) were identified: non-fermented soy foods intake in four studies and fermented soy foods intake in two studies. The relative risks estimates for the highest compared with the lowest intake of the soy products are shown in a forest plot below.

Total soy foods intake was investigated in four studies (Hara, 2012, Kurosawa, 2006; Nagata, 2002; Ahn, 1997). Overall, all associations were not significant (inverse except in men in Hara, 2012) apart from a significant inverse association observed in men in one study (Nagata, 2002).

Three (Ko, 2013; Kweon, 2013, SMHS; Nagata, 2002) out of the four studies reported results on non-fermented soy foods observed an inverse association with stomach cancer (one was statistically significant). The remaining study observed a non-significant positive association (Kweon, 2013, SWHS).

Non-significant associations with fermented soy foods intake were observed in two studies (positive in Ko, 2013; positive in men and an inverse in women in Nagata, 2002).

Table 49 Soy products intake and stomach cancer risk. Number of studies in the CUP SLR

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

Note: *One publication included two prospective cohorts (Kweon, 2013)

Table 50 Soy foods intake and stomach cancer risk. Main characteristics of studies identified

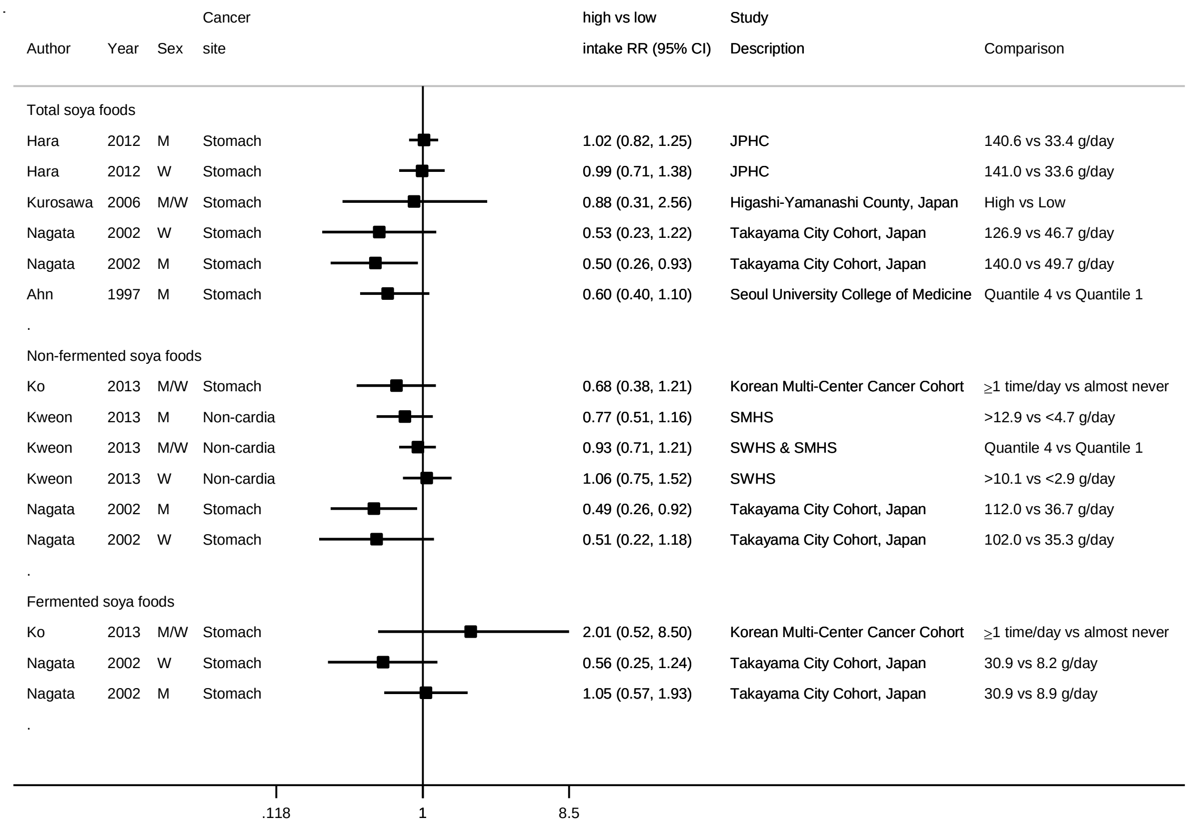
Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Reasons for exclusion
Ko, 2013 STM80184 Korea	KMCC, Prospective Cohort, Age: 30-90 years, M/W	165/ 9724 8.5 years	Cancer registry and death certificates	Fermented soy bean paste FFQ	Incidence, stomach cancer All	≥1 time/day vs. almost never	2.01 (0.52-8.50) Ptrend: 0.18	Age, sex, area of residence, BMI, cigarette smoking, alcohol drinking	
		115/			Men	High vs. low	1.06 (0.93-1.21)		
		50/			Women		1.10 (0.90-1.34)		
		66/			Men, current smokers		0.99 (0.58-1.68)		
		49/			Men, non smokers		1.31 (0.69-2.48)		
		165/ 9724 8.5 years		Soy beans and non-fermented soy food FFQ	Incidence, stomach cancer All	≥1 time/day vs. almost never	0.68 (0.38-1.21) Ptrend: 0.04		
		115/			Men	High vs. low	0.77 (0.52-1.13)		
		50/			Women		0.41 (0.22-0.78)		
		66/			Men, current smokers		0.63 (0.36-1.09)		
		49/			Men, non smokers		0.82 (0.43-1.57)		
Kweon, 2013 STM80182 China	SWHS and SMHS, Prospective	493/ 128 194	Cancer registry, by post	Excluded fermented products - non-	Incidence, distal stomach cancer	Quantile 4 vs. quantile 1	0.93 (0.71-1.21)	Age, sex, BMI, ever smoked, fruit intake, met-	(studies also reported separate results

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Reasons for exclusion
	Cohort, M/W	211/		fresh soy bean curd - fried tofu, vegetarian chicken, and bean curd cake Validated FFQ	Men	>12.9 vs. <4.7 g/day	0.77 (0.51-1.16)	hours per week, red meat intake, sodium intake, total caloric intake, vegetable intake, born in urban shanghai, chronic gastritis history, drinking history, family history of gastric cancer, family income, smoking dose	combining soymilk, tofu, fresh bean, dry bean, and soy bean sprout)
		282/			Women	>10.1 vs. <2.9 g/day	1.06 (0.75-1.52)		
Hara, 2012 STM80121 Japan	JPHC, Prospective Cohort, Age: 45-74 years, M/W	899/39 569 350/45 312	Active patient notification, hospital registries and linkage with population-based cancer registries	Fermented and non-fermented soy foods Validated FFQ, 138-item, 8 soy food items	Incidence, stomach cancer Men Women	140.6 vs. 33.4 g/day 141.0 vs. 33.6 g/day	1.02 (0.82-1.25) Ptrend: 0.99 0.99 (0.71-1.38) Ptrend: 0.80	Age, BMI, centre, energy intake, fruit intake, salt intake, smoking status, vegetable intake, ethanol intake, family history of gastric cancer, fish intake	
		899/39 569 350/45 312			Cardia and upper-third gastric cancer Men Women	140.6 vs. 33.4 g/day 141.0 vs. 33.6 g/day	1.82 (0.92-3.60) Ptrend: 0.20 1.10 (0.39-3.08) Ptrend: 0.60		
		899/39 569			Distal stomach cancer Men	140.6 vs. 33.4 g/day	0.95 (0.73-1.22) Ptrend: 0.80		

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Reasons for exclusion
		350/45 312			Women	141.0 vs. 33.6 g/day	1.02 (0.68-1.53) Ptrend: 0.80		
Kurosawa, 2006 STM80085 Japan	Higashi-Yamanashi County, Japan, Prospective Cohort, Age: 30- years, M/W	65/ 8 035 11 years	Death certificate	Total beans and soy foods FFQ	Mortality, stomach cancer	High vs. low score	0.88 (0.31-2.56) Ptrend: 0.66	Age, sex, fruits intake, green yellow vegetable intake, salted foods, smoking habits, beans and bean products, mountain herbs	
Nagata, 2002 STM01669 Japan	TCCJ, Prospective Cohort, Age: 35- years, M/W	121/ 30 304 7 years 81/13 880 40/ 16 424	Population registry	Total soy products FFQ	Mortality, stomach cancer Men Women	140 vs. 49.7 g/day 126.9 vs. 46.7 g/day	0.50 (0.26-0.93) Ptrend: 0.03 0.53 (0.23-1.22) Ptrend: 0.15	Age, BMI, energy intake; in addition, for men – rice and salt intakes, smoking; for women – age at menarche, marital status, coffee consumption	
		81/13 880 40/ 16 424		Fermented soy products	Men Women	30.9 vs. 8.9 g/day 30.9 vs. 8.2 g/day	1.05 (0.57-1.93) Ptrend: 0.84 0.56 (0.25-1.24) Ptrend: 0.16		
		81/13 880 40/ 16 424		Non-fermented soy products	Men Women	112.0 vs. 36.7 g/day 102.0 vs. 35.3 g/day	0.49 (0.26-0.92) Ptrend: 0.03 0.51 (0.22-1.18) Ptrend: 0.13		
Ahn, 1997 STM05373 Korea	Seoul University College of Medicine,	44/ 14 533 3 years	Unknown / not reported	Total soybean foods including tofu	Incidence, stomach cancer	Quantile 4 vs. quantile 1	0.60 (0.40-1.10) Ptrend: 0.09		(Exposure categories not quantified)

Author, Year, 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
	Korea, Prospective Cohort, Age: 40- years, M								

Figure 62 RR (95% CI) of stomach cancer for the highest compared with the lowest level of soy foods intake



2.3.1.1 Miso soup

Randomised controlled trials

No randomised controlled trial was identified.

Cohort studies

Summary

Main results:

Six studies (3911 cases) out of ten were included in the dose-response meta-analysis. Miso soup consumption was not related to stomach cancer risk.

Four studies were excluded from the dose-response analysis. Two studies found significant inverse associations (Khan, 2004; Hirayama, 1984) and two studies found non-significant positive associations (Galanis, 1998; Inoue, 1996).

No heterogeneity was observed. There was no significant evidence of publication or small study bias.

Sensitivity analyses:

Two studies had high weight in the analysis (Hara, 2012 contributed 40% and Iso, 2007, 44% weight). The summary RR did not change materially when studies were omitted in turn in influence analysis. All studies reported non-significant association.

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 dose-response analysis were on Japan or in Japanese residents in Hawaii (Nomura, 1990). Loss to follow-up was low in most studies, with the exception of the study of atomic-bomb survivors (LSS) (Sauvaget, 2005), in which 17% participants were lost due to migration. Cancer outcome was confirmed using medical notes, death certificates, or records in resident or cancer registries.

All studies used FFQ to assess miso soup intake. Nomura, 1990 also used a 24-hr dietary questionnaire. All studies included in the dose-response analysis adjusted or stratified for age and sex, which were the only factors in three (Iso, 2007; Kato, 1992b; Nomura, 1990) studies. Ngoan, 2002 was further adjusted for smoking. Sauvaget, 2005 was further adjusted for smoking and socioeconomic status. Hara, 2012 was the only study adjusted for total energy intake and other confounding factors. None of the studies was adjusted for Helicobacter pylori status. The summary RR did not change materially in influence analysis when each study was omitted in turn.

Table 51 Miso soup intake and stomach cancer risk. Number of studies in the CUP SLR

	Number
Studies identified	10 studies (16 publications)
Studies included in forest plot of highest compared with lowest exposure	10
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

Table 52 Miso soup intake and stomach cancer risk. Summary of the linear dose-response meta-analysis in the 2005 SLR and CUP

	2005 SLR	**CUP**
Increment unit used	1 serving/day	1 serving/day
All studies		
Studies (n)	4	6
Cases (total number)	771	3911
RR (95%CI)	1.03 (0.81-1.32)	1.01 (0.95-1.08)
Heterogeneity (I^2, p-value)	70.4%, 0.009	0%, 0.99
P value Egger test	0.06	0.86
Stratified analysis		
Men		
Studies (n)	4	4
RR (95%CI)	0.97 (0.66-1.41)	1.03 (0.95-1.11)
Heterogeneity (I^2, p-value)	-	0%, 0.45
Women		
Studies (n)	2	3
RR (95%CI)	1.02 (0.86-1.22)	0.95 (0.77-1.18)
Heterogeneity (I^2, p-value)	-	58.5%, 0.09

	Other stratified analysis CUP	
Outcome	**Incidence**	**Mortality**
Studies (n)	2	3
RR (95%CI)	1.02 (0.93-1.11)	1.01 (0.93-1.11)

Heterogeneity (I^2, p-value)	0%, 0.95	0%, 0.87
Duration of follow-up	**<15 years**	**≥15 years**
Studies (n)	3	3
RR (95%CI)	1.03 (0.94-1.12)	1.01 (0.93-1.09)
Heterogeneity (I^2, p-value)	0%, 0.90	0%, 0.92
Number of cases	**<150 cases**	**≥1000 cases**
Studies (n)	3	3
RR (95%CI)	1.04 (0.81-1.34)	1.01 (0.95-1.08)
Heterogeneity (I^2, p-value)	0%, 0.81	0%, 0.99
Publication year	**<2005**	**≥2005**
Studies (n)	3	3
RR (95%CI)	1.04 (0.81-1.34)	1.01 (0.95-1.08)
Heterogeneity (I^2, p-value)	0%, 0.81	0%, 0.99
Adjustment for confounders:		
Smoking	Not adjusted	Adjusted
Studies (n)	3	3
RR (95%CI)	1.01 (0.92-1.10)	1.02 (0.94-1.11)
Heterogeneity (I^2, p-value)	0%, 0.91	0%, 0.90

Table 53 Miso soup intake and stomach cancer risk. Results of meta-analyses and pooled analyses of prospective studies published after the 2005 SLR

Author, Year	Number of studies	Total number of cases	Studies country, area	Outcome	Comparison	RR (95%CI)	P trend	Heterogeneity (I^2, p value)
Meta-analyses								
D'Elia, 2012	8 cohorts	3022	Japan and USA (Japanese residence in Hawaii)	Incidence/mortality, gastric cancer	High vs. low	1.05 (0.88-1.25)		27.0%, 0.18
Kim, 2011	9 cohorts 13 case-control studies		Japan, Korea	Gastric cancer risk	High vs. low	1.11 (0.88-1.41) 1.34 (1.04-1.73)		

The eight cohort studies in D'Elia, 2012 were included in the highest compared to lowest forest plot in the present CUP review.

In eight out of the nine cohorts in Kim, 2011, the exposure was miso soup. The cohort studies on miso soup were included in the highest compared to lowest forest plot in in the CUP review on miso soup and not in this section. One study on total fermented soy food included in Kim, 2011 is shown in the corresponding section in the CUP SLR.

Table 54 Miso soup intake and stomach 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
Hara, 2012 STM80121 Japan	JPHC, Prospective Cohort, Age: 45-74 years, M/W	1249/ 91 246 806 550 person years	Active patient notification, hospital registries and linkage with population-based cancer registries	Validated FFQ	Incidence, stomach cancer				Exposure values using standard portion size, RRs for men and women combined using fixed model
		899/39 569			Men	449 vs. 63 ml/day	1.17 (0.94-1.47)	Age, BMI, centre, energy intake, fruit intake, salt intake, smoking status, vegetable intake, ethanol intake, family history of gastric cancer, fish intake	
		350/45 312			Women	384 vs. 47 ml/day	0.71 (0.50-1.01)		
		104/			Men Cardia and upper-third gastric cancer	449 vs. 63 ml/day	1.18 (0.61-2.27)		
		609/			Distal stomach cancer		1.22 (0.92-1.61)		
		33/			Women Cardia and upper-third gastric cancer	384 vs. 47 ml/day	0.83 (0.25-2.76)		
		237/			Distal stomach cancer		0.69 (0.45-1.05)		
		287/			Stomach cancer Never users of exogenous female hormones	384 vs. 47 ml/day	0.65 (0.45-0.96)	Age, BMI, centre, energy intake, fruit intake, salt intake, smoking status, vegetable intake, ethanol	
		40/			Ever users of		1.01 (0.33-3.05)		

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Missing data derived for analyses
					exogenous female hormones			intake, family history of gastric cancer, fish intake, menopausal status	
Iso, 2007 STM80144 Japan	JACC, Prospective Cohort, Age: 40-79 years, M/W	1064/ 105 500 15 years	Municipal resident registration records, death certificates	Validated FFQ	Mortality, stomach cancer	≥2 vs. ≤1 bowls/day		Age, area of study	Mid-points of exposure categories, RRs for men and women combined using fixed model
		702/42696			Men		0.96 (0.77-1.20)		
		362/58494			Women		1.18 (0.89-1.58)		
Sauvaget, 2005 STM44428 Japan	LSS, Prospective Cohort, Age: 34-98 years, M/W, Atomic bomb survivors	1270/ 38 540 19 years	Cancer registry	22-item FFQ	Incidence, stomach cancer	≥5 vs. <2 times/week	1.01 (0.88-1.16)	Age, sex, area of residence, educational level, radiation exposure, smoking habits	Mid-points of exposure categories
Ngoan, 2002 STM01668 Japan	FPC, Prospective Cohort, Age: 15-96 years, M/W	112/ 13 250 13 years	Resident registry	Self-administered FFQ	Mortality, stomach cancer	>2 times/day vs. <4 times/week	1.70 (0.60-4.50)	Age, sex, fat intake, Japanese soup, liver, pickled foods, processed meat, smoking habits	Mid-points of exposure categories
		75/			Men		1.40 (0.70-3.20)	Age	
		37/			Women		0.70 (0.20-3.40)		
Kato, 1992b	Higashi-Kamo	54/	Cancer registry/	FFQ	Mortality,	≥2 vs. <1	1.04 (0.48-2.25)	Age, sex	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
STM06734 Japan	Cohort, Prospective Cohort, Age: 30-80 years, M/W	9753 6 years	hospital records		stomach cancer	cups/day			exposure categories
Nomura, 1990 STM14814 USA	HHP, Prospective Cohort, Age: 45- years, M, Japanese residents of Hawaii	150/ 7990 19 years	Cancer registry/ hospital records	FFQ + recall	Incidence, stomach cancer	≥5 vs. ≤1 times/week	0.90 (0.50-1.30)	Age	Mid-points of exposure categories

Table 55 Miso soup intake and stomach 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
Takachi, 2010 STM80133 Japan	JPHC, Prospective Cohort, Age: 45-74 years, M/W	867/ 77 500 593 620 person years	Active patient notification from hospitals, cancer registries and death certificate	FFQ	Mortality, stomach cancer	458 vs. 42 g	1.10 (0.87-1.39)	Age, sex, BMI, calcium intake, energy intake, physical activity, smoking status, alcohol, potassium	Superseded by Hara, 2012, STM80121
Tokui, 2005 STM80105 Japan	JACC, Prospective Cohort, Age: 40-79 years, M/W	796/ 44 930 12 years 530/ 266/	Population registry	FFQ	Mortality, stomach cancer Men Women	Every day vs. none	 1.44 (0.86-2.42) 1.46 (0.81-2.61)	Age	Superseded by Iso, 2007, STM80144
Khan, 2004 STM20239 Japan	HGCS, Prospective Cohort, Age: 40- years, M/W	51/ 3158 14 years 36/1524	Follow-up surveys	FFQ	Mortality, stomach cancer Men	2-7 times/week vs. never-several times/month	 0.20 (0.10-0.80)	Age, smoking habits	Excluded, only two intake categories
Tsugane, 2004 STM00441 Japan	JPHC I, Prospective Cohort, Age: 40-59 years, M/W	473/ 39 065 12 years 358/ 115/	Hospital records, population-based cancer registries and death certificates, histologically confirmed	FFQ	Incidence, stomach cancer Men Women	≥3 vs. <1 cups/day	 1.75 (1.22-2.51) 1.11 (0.67-1.84)	Age, fruit, non green-yellow vegetable intake, smoking habits	Superseded by Hara, 2012, STM80121

Author, Year, 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
Galanis, 1998 STM04769 USA	Hawaii-Japan DOH Survey, Prospective Cohort, Age: 18- years, M/W, Japanese residents of Hawaii	108/ 11 907 15 years 64/5610 44/6297	Cancer registry	FFQ	Incidence, stomach cancer Men Women	≥1 time/week vs. none	1.20 (0.80-1.80) 1.20 (0.70-2.00) 1.30 (0.70-2.40)	Age, sex, educational level, place of birth Analysis among men also adjusted for alcohol consumption and smoking	Excluded, only two intake categories
Inoue, 1996 STM06116 Japan	HERPACC, Prospective Cohort, M/W, Endoscopy patients	64/ 5 373 6 years	Hospital records, cancer registry, death certificates	FFQ	Incidence, stomach cancer	Daily vs. rarely	2.49 (0.60-10.30)	Age, sex	Excluded, exposure not quantified
Hirayama, 1990 STM00028 Japan	Six Prefecture Cohort, Japan, Prospective Cohort, Age: 40- years, M/W	/ 265 118 17 years	Annual residence survey/death certificate	Questionnaire (general)	Mortality, stomach cancer	Daily vs. <daily	0.86 (0.82-0.90)	Age, sex	Excluded, only two intake categories
Hirayama, 1989 STM00027 Japan	Six Prefecture Cohort, Japan, Prospective Cohort, Age: 40- years, M/W	/ 265 118 17 years	Annual residence survey/death certificate	Questionnaire (general)	Mortality, stomach cancer	Daily vs. <daily	0.85	Age, sex	Superseded by Hirayama, 1990, STM00028
Hirayama, 1984 STM08768	Six Prefecture Cohort, Japan,	/ 265 118	Annual residence	Questionnaire (general)	Mortality, stomach cancer	Daily vs. <daily	0.86 (0.82-0.91)		Superseded by Hirayama, 1990,

Author, Year, 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	Prospective Cohort, Age: 40- years, M/W	16 years	survey/death certificate						STM00028
Hirayama, 1982 STM09358 Japan	Six Prefecture Cohort, Japan, Prospective Cohort, Age: 40- years, M/W	3888/ 265 118 13 years	Annual residence survey/death certificate	Questionnaire (general)	Mortality, stomach cancer	Daily vs. none times/year	0.59	Age	Superseded by Hirayama, 1990, STM00028

Figure 63 RR estimates of stomach cancer by levels of miso soup intake

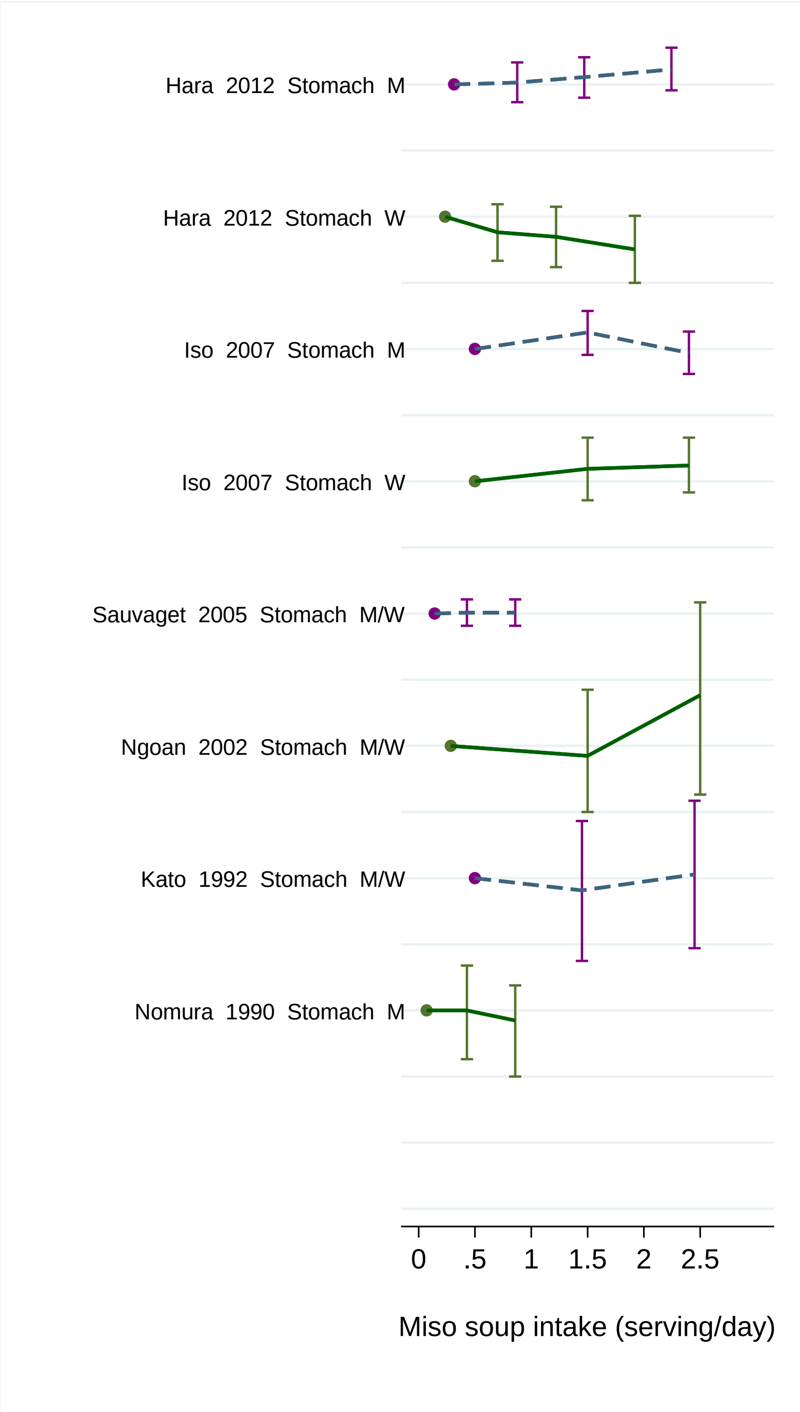


Figure 64 RR (95% CI) of stomach cancer for the highest compared with the lowest level of miso soup intake

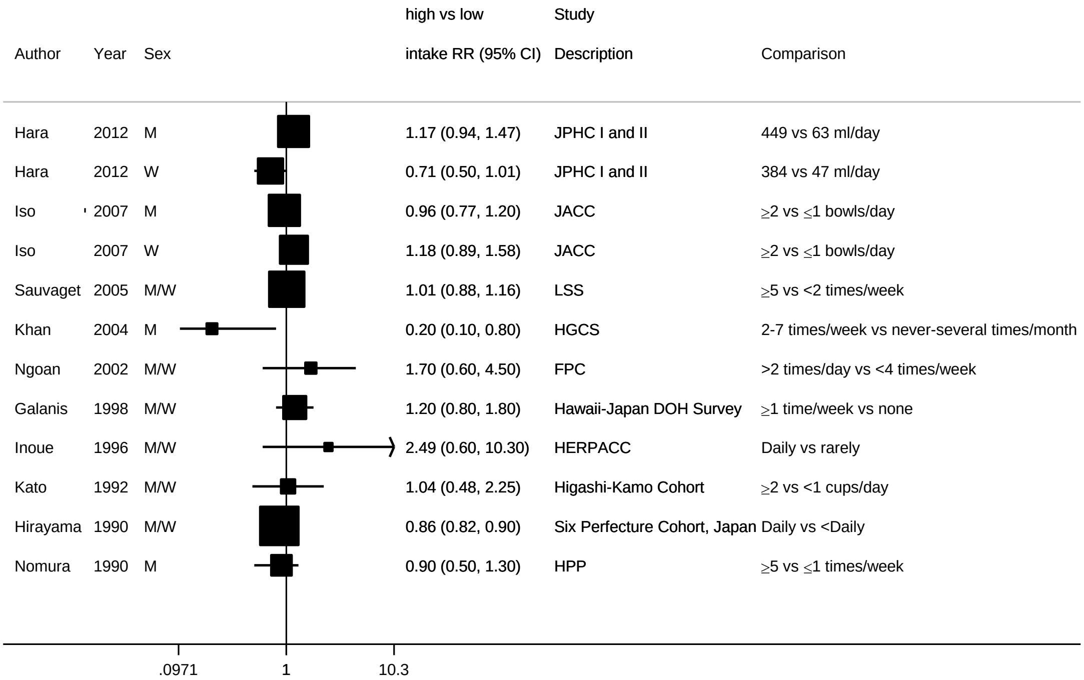


Figure 65 Relative risk of stomach cancer for 1 serving/day increase of miso soup intake

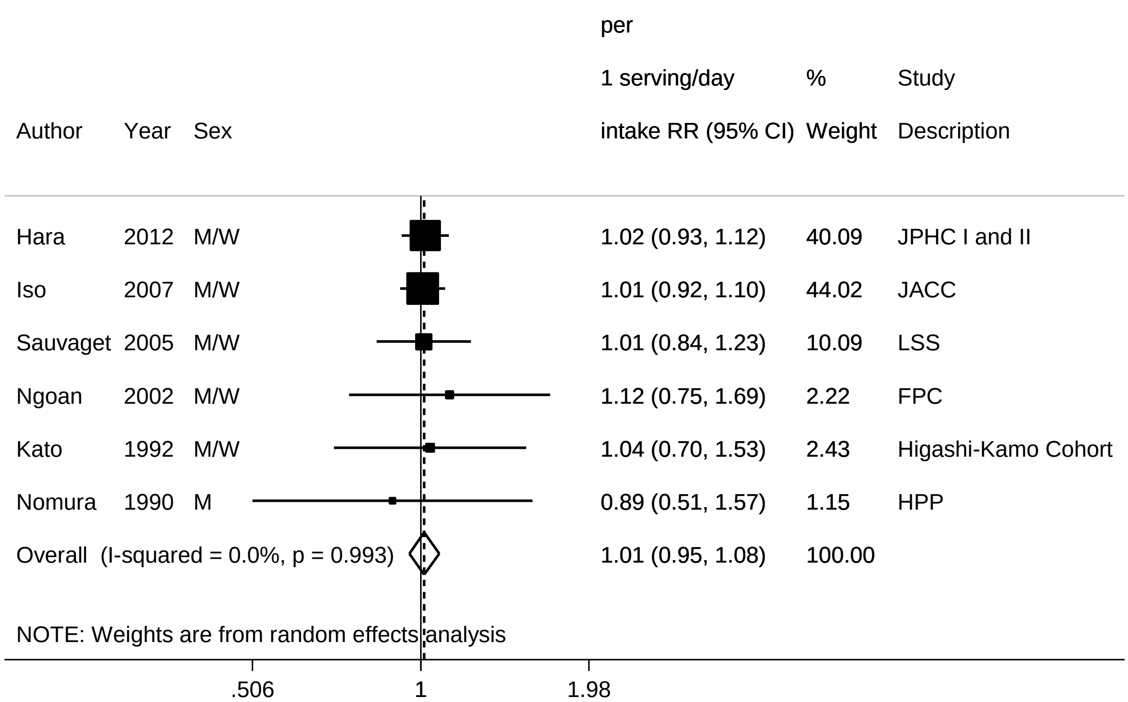
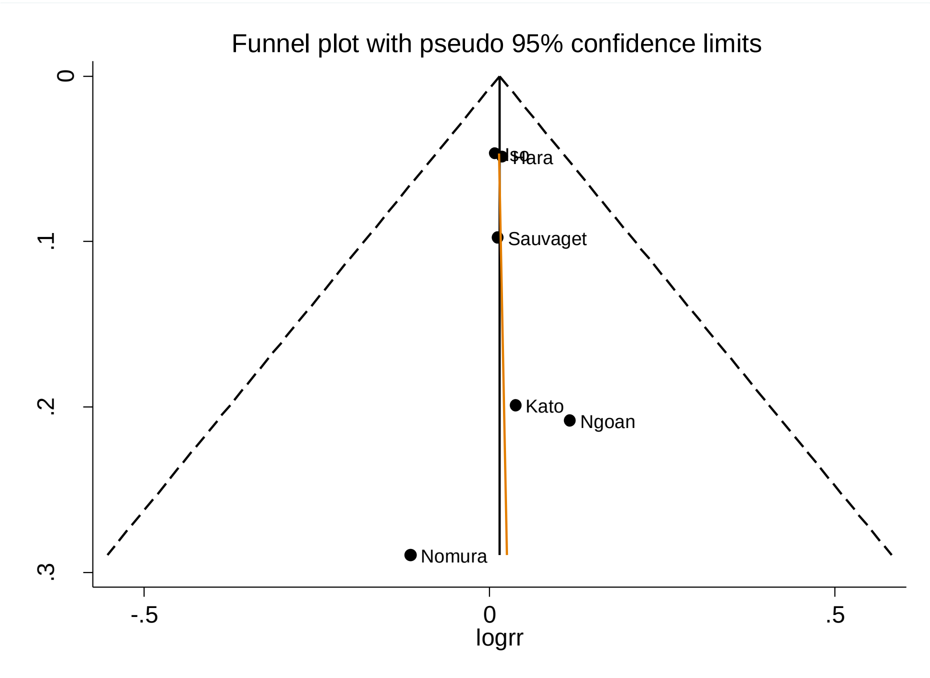


Figure 66 Funnel plot of studies included in the dose response meta-analysis of miso soup intake and stomach cancer



Egger’s test p=0.86

Figure 67 Relative risk of stomach cancer for 1 serving/day increase of miso soup intake by sex

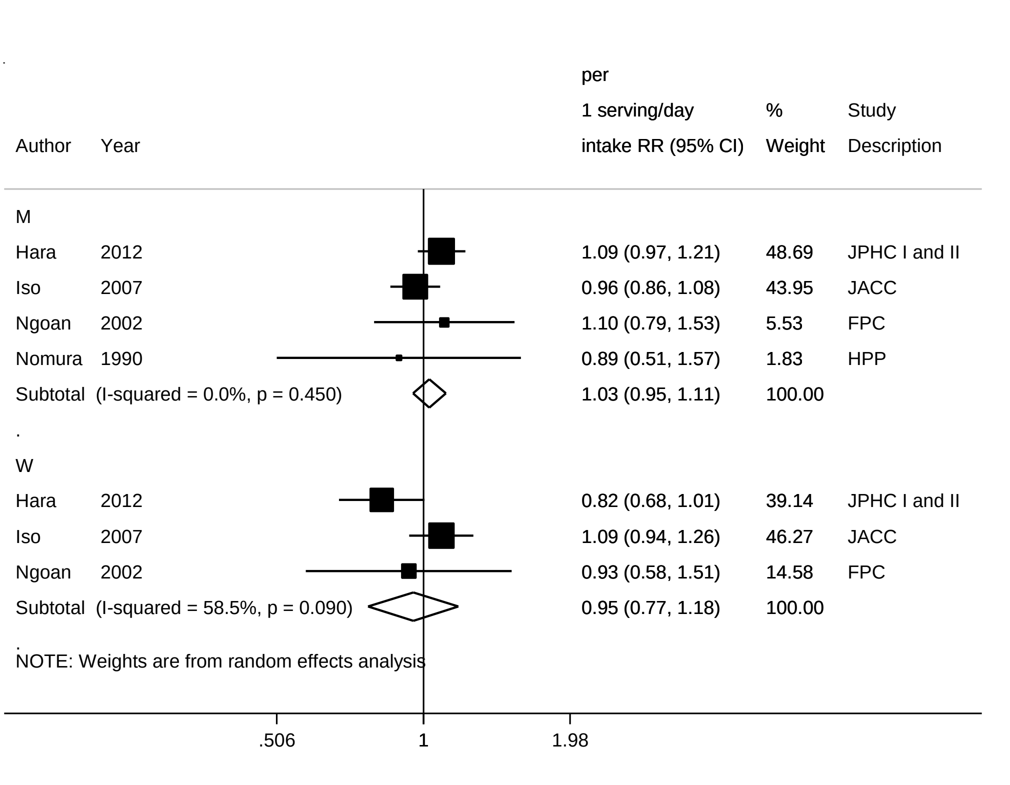
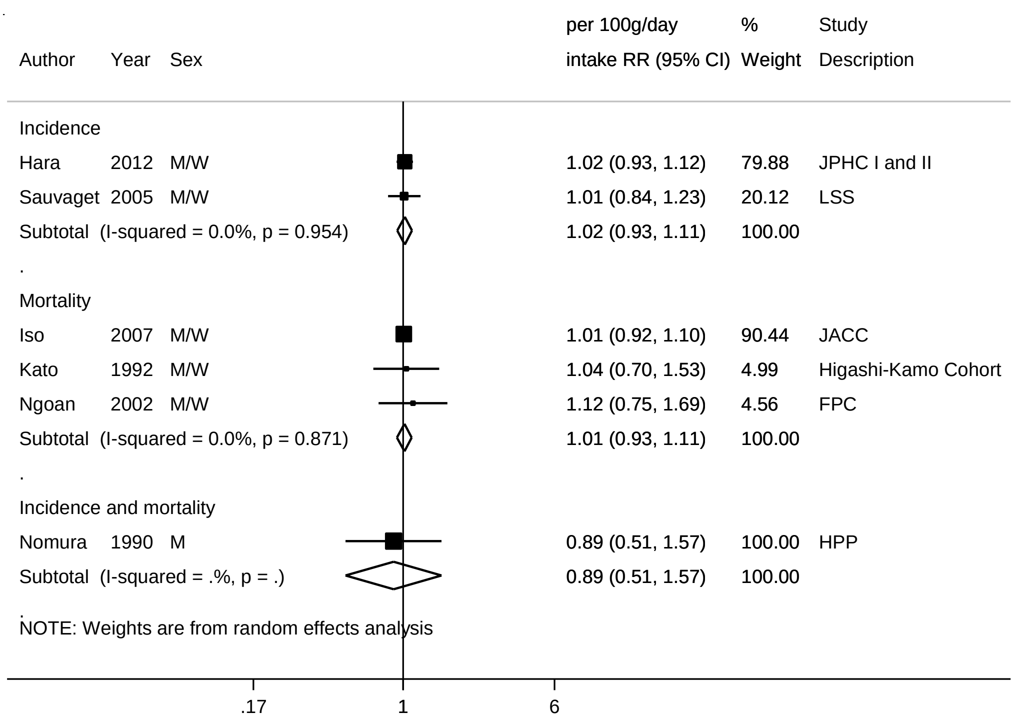


Figure 68 Relative risk of stomach cancer for 1 serving/day increase of miso soup intake by cancer outcome



2.3.1.5 Tofu

Randomised controlled trials

No randomised controlled trial was identified.

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 pulses (legumes) is causally related to stomach cancer risk was judged as limited suggestive in the Second Expert report.

Four studies (2614 cases) were included in the dose-response meta-analysis. A non-significant inverse association was observed for stomach cancer risk. In the subgroup analysis, an inverse association in men (three studies, no heterogeneity) and a positive association in women (two studies, moderate heterogeneity) that were both statistically non-significant were observed.

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

Five studies were excluded from the dose-response analysis. One study reported a significant inverse dose-response trend in tofu and soy beans intake and stomach cancer risk in women but not in men (Ko, 2013). One study reported non-significant positive associations of tofu intake and stomach cancer mortality by sex (Khan, 2004). Two cohorts in one publication reported results on tofu and distal gastric cancer risk only (Kweon, 2013). Inverse associations were observed that were significant in men but not in women. One study did not report a measure of association of tofu intake (Nagata, 2002).

Sensitivity analysis:

The summary RRs ranged from 0.72 (95% CI=0.42-1.26) when Iso, 2007 was omitted to 1.03 (95% CI=0.86-1.23) when Ngoan, 2002 was omitted in influence analysis.

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 were Asian studies or was a cohort of Japanese residents in Hawaii (Nomura, 1990). LSS was a study of atomic bomb survivors (Sauvaget, 2005). 17% participants were lost due to migration in this study. Loss to follow-up was low in other studies. Cancer outcome was confirmed using hospital records, records in cancer registries or resident registries. Two were mortality studies (Iso, 2007; Ngoan, 2002). All studies used FFQ to assess tofu intake. Two studies (Iso, 2007; Nomura, 1990) included in the dose-response analysis adjusted or stratified for minimal confounding factors only (age, sex). The other two studies (Sauvaget, 2008; Ngoan, 2002) were also adjusted for smoking. None of the studies were adjusted for total energy intake or Helicobacter pylori status. The summary estimate remained non-significant when each study was omitted in turn in influence analysis.

Table 56 Tofu intake and stomach cancer risk. Number of studies in the CUP SLR

	Number
Studies identified	9* (9 publications)
Studies included in forest plot of highest compared with lowest exposure	5
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 two studies from one publication (Kweon, 2013) on distal gastric cancer only.

Table 57 Tofu intake and stomach cancer risk. Summary of the linear dose-response meta-analysis in the 2005 SLR and the CUP

	2005 SLR	**CUP**
Increment unit used	1 serving/day	1 serving/day
All studies		
Studies (n)	3	4
Cases (total number)	308	2614
RR (95%CI)	0.68 (0.33-1.39)	0.89 (0.65-1.22)
Heterogeneity (I^2, p-value)	38.3%, 0.2	55.3%, 0.08
P value Egger test	-	-
Stratified analysis		
Men		
Studies (n)	-	3
RR (95%CI)	-	0.90 (0.68-1.21)
Heterogeneity (I^2, p-value)	-	0%, 0.87
Women		
Studies (n)	-	2
RR (95%CI)	-	1.38 (0.78-2.43)
Heterogeneity (I^2, p-value)	-	31.8%, 0.23

Table 58 Tofu intake and stomach 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
Iso, 2007 STM80144 Japan	JACC, Prospective Cohort, Age: 40-79 years, M/W	1087/ 105 500 15 years	Municipal resident registration records, death certificates	Validated FFQ	Mortality, stomach cancer	≥5 vs. <3 times/week		Age, area of study	Mid-points of exposure categories, RRs for men and women were combined using fixed effect model
		731/			Men		0.96 (0.79-1.17)		
		356/			Women		1.34 (1.02-1.76)		
Sauvaget, 2005 STM44428 Japan	LSS, Prospective Cohort, Age: 34-98 years, M/W, Atomic bomb survivors	1270/ 38 540 19 years	Cancer registry	FFQ	Incidence, stomach cancer	≥5 vs. <2 times/week	1.01 (0.85-1.20) Ptrend: 0.49	Age, sex, area of residence, educational level, radiation exposure, smoking habits	Mid-points of exposure categories
Ngoan, 2002 STM01668 Japan	FPC, Prospective Cohort, Age: 15-96 years, M/W	107/ 13 250 13 years	Resident registry	25-item FFQ	Mortality, stomach cancer	≥1 time/day vs. 2-4 times/month	0.40 (0.20-0.90)	Age, sex, fat intake, Japanese soup, liver, pickled foods, processed meat, smoking habits	Mid-points of exposure categories
		73/ 5917			Men		0.90 (0.40-1.80)	Age	
		34/ 7333			Women		0.80 (0.30-2.20)		
Nomura, 1990	HHP,	150/	Cancer registry/	20-item FFQ,	Incidence/mortal	≥5 vs. 0-1	0.70 (0.20-2.30)	Age	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
STM14814 USA	Prospective Cohort, Age: 45- years, M, Japanese residents of Hawaii	7990 19 years	hospital records	24-hr dietary recall	ity, stomach cancer	times/week			exposure categories

Table 59 Tofu intake and stomach 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
Ko, 2013 STM80184 Korea	KMCC, Prospective Cohort, Age: 30-90 years, M/W	165/ 9724 8.5 years	Cancer registry and death certificates	FFQ Tofu and soybeans	Incidence, stomach cancer	≥1 time/day vs. almost never times	0.68 (0.38-1.21) Ptrend: 0.04	Age, sex, area of residence, BMI, cigarette smoking, alcohol drinking	Excluded, soybeans combined with tofu
		115/ 3714			Men	High vs. low	0.77 (0.52-1.13)		
		50/ 6010			Women		0.41 (0.22-0.78)		
		66/ 23 922 person-years			Men, current smokers		0.63 (0.36-1.09)		
		49/ 6453 Person-years			Men, non smokers		0.82 (0.43-1.57)		
Kweon, 2013 STM80182 China	SWHS and SMHS, Prospective Cohort, M/W	493/ 128 687	Cancer registry, by post	Validated FFQ, 81-item (SMHS), 77-items (SWHS)	Incidence, distal stomach cancer	Quantile 4 vs. quantile 1	0.72 (0.55-0.95) Ptrend: 0.08	Age, sex, BMI, ever smoked, fruit intake, met-hours per week, red meat intake, sodium intake, total caloric intake, vegetable intake, born in urban shanghai, chronic gastritis history, drinking history, family history of gastric	Excluded, distal stomach cancer only
		211/ 58 241			Men	>8.5 vs. <3.1 g/day	0.64 (0.42-0.99) Ptrend: 0.02		
		282/ 70 446			Women	>6.9 vs. <2.4 g/day	0.82 (0.57-1.17) Ptrend: 0.73		

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Reasons for exclusion
								cancer, family income, smoking dose	
Tokui, 2005 STM80105 Japan	JACC, Prospective Cohort, Age: 40-79 years, M/W	716/ 44 930 12 years	Population registry	FFQ	Mortality, stomach cancer	≥1/day vs. 1-2/month or less times/week		Age	Superseded by Iso, 2007, STM80144
		472/			Men		1.07 (0.73-1.58) Ptrend: 0.97		
		244/			Women		1.41 (0.75-2.64) Ptrend: 0.25		
Khan, 2004 STM20239 Japan	HGCS, Prospective Cohort, Age: 40- years, M/W	51/ 3158 14 years	Follow-up surveys	FFQ	Mortality, stomach cancer	2-7 times/week vs. never-several times times/month			Excluded, only two intake categories
		36/ 1524			Men		3.60 (0.50-26.00)	Age, smoking habits	
		15/ 1634			Women		1.10 (0.10-8.50)	Age, health education, health screening, health status, smoking habits	
Nagata, 2002 STM01669 Japan	TCCJ, Prospective Cohort, Age: 35- years, M/W	121/ 30 304 7 years	Population registry	FFQ	Mortality, stomach cancer	(mean exposure)			Excluded, no measure of association

Table 60 Tofu intake and stomach cancer risk. Results of meta-analyses and pooled analyses of prospective studies published after the 2005 SLR

Author, Year	Number of studies	Total number of cases	Studies country, area	Outcome	Comparison	RR (95%CI)	P trend	Heterogeneity (I^2, p value)
Meta-analyses Non-fermented soy foods								
Kim 2011	18 (6 cohorts*, 12 case-controls)			Incidence/mortality, gastric cancer Cohort studies (n=6) Case-control studies (n=12) All studies (n=18)	High vs. low	 0.83 (0.60-1.13) 0.57 (0.46-0.71) 0.64 (0.54-0.77)		55.7% 56.8% 64.3%

* Four cohorts Kim, 2011 were on tofu intake (Ngoan, 2002; Khan, 2004; Sauvaget, 2005; Tokui, 2005) and were included in this section of the present review. Two cohorts on total non-fermented soy foods intake in Kim, 2011 (Nagata, 2002; Kurosawa, 2006) were included in the corresponding section in the CUP review.

Figure 69 RR estimates of stomach cancer by levels of tofu intake

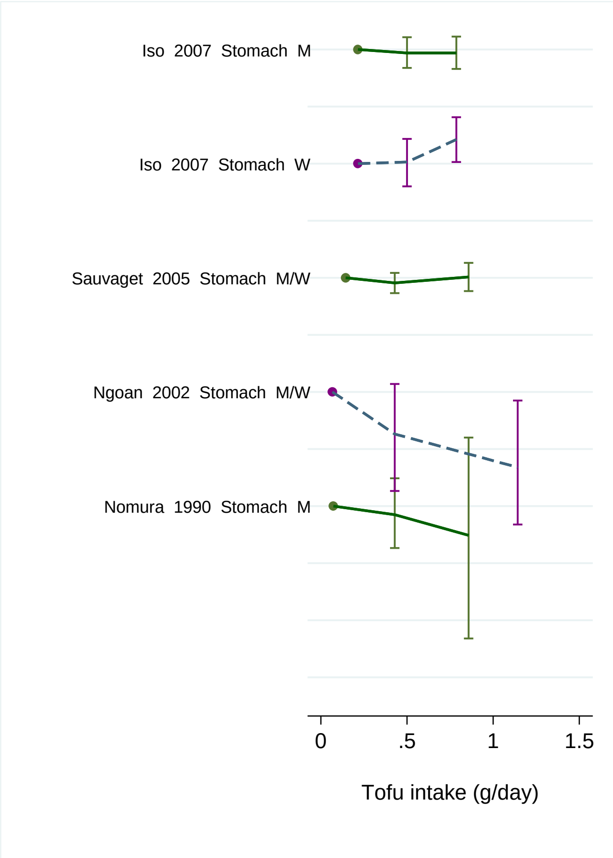


Figure 70 RR (95% CI) of stomach cancer for the highest compared with the lowest level of tofu intake

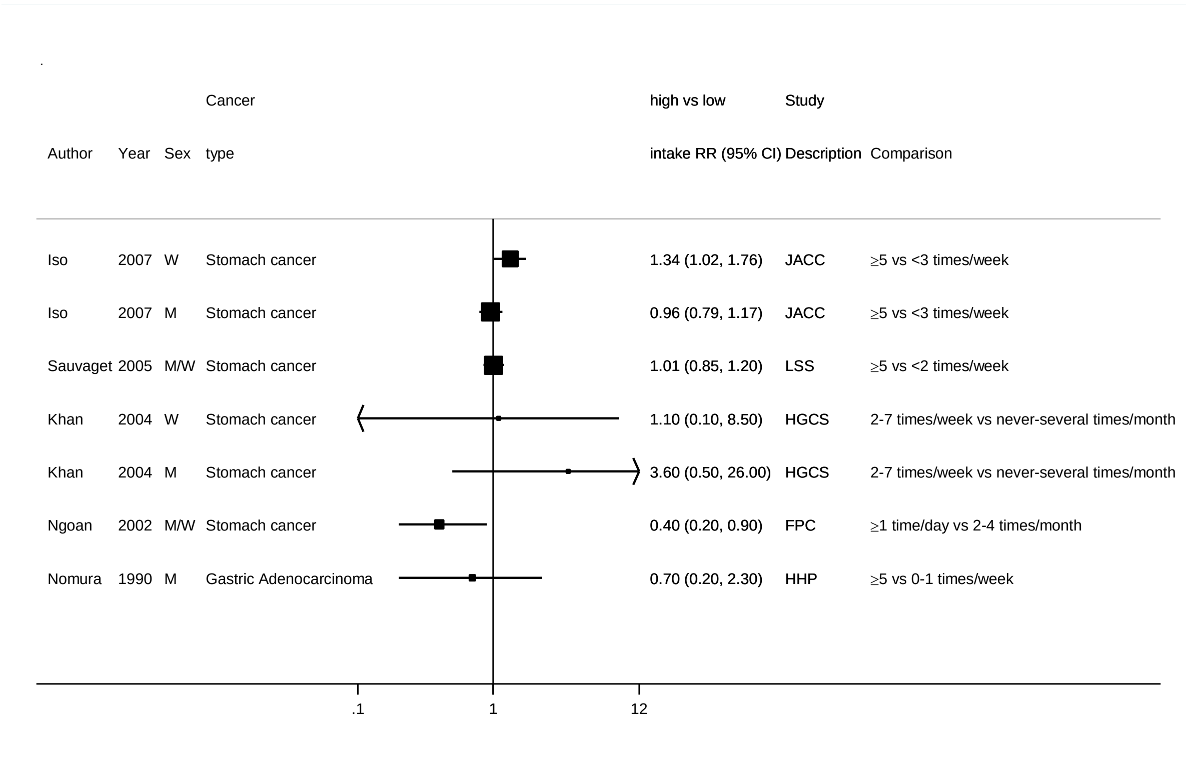


Figure 71 Relative risk of stomach cancer for 1 serving/day increase of tofu intake

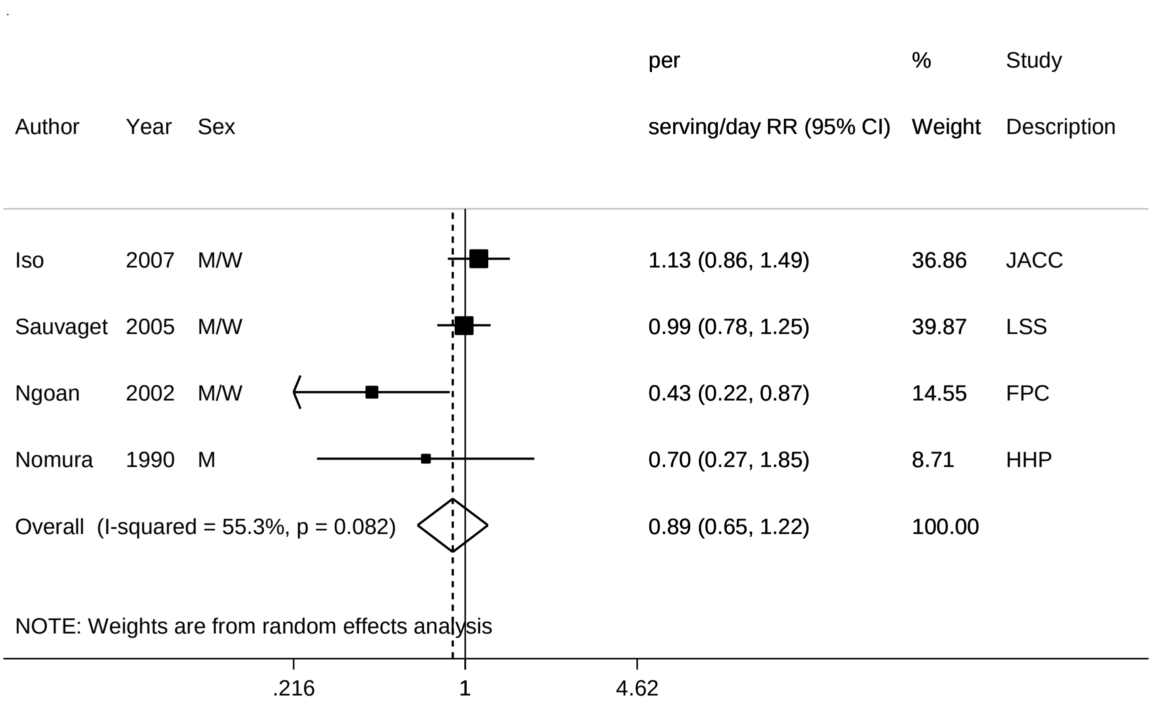
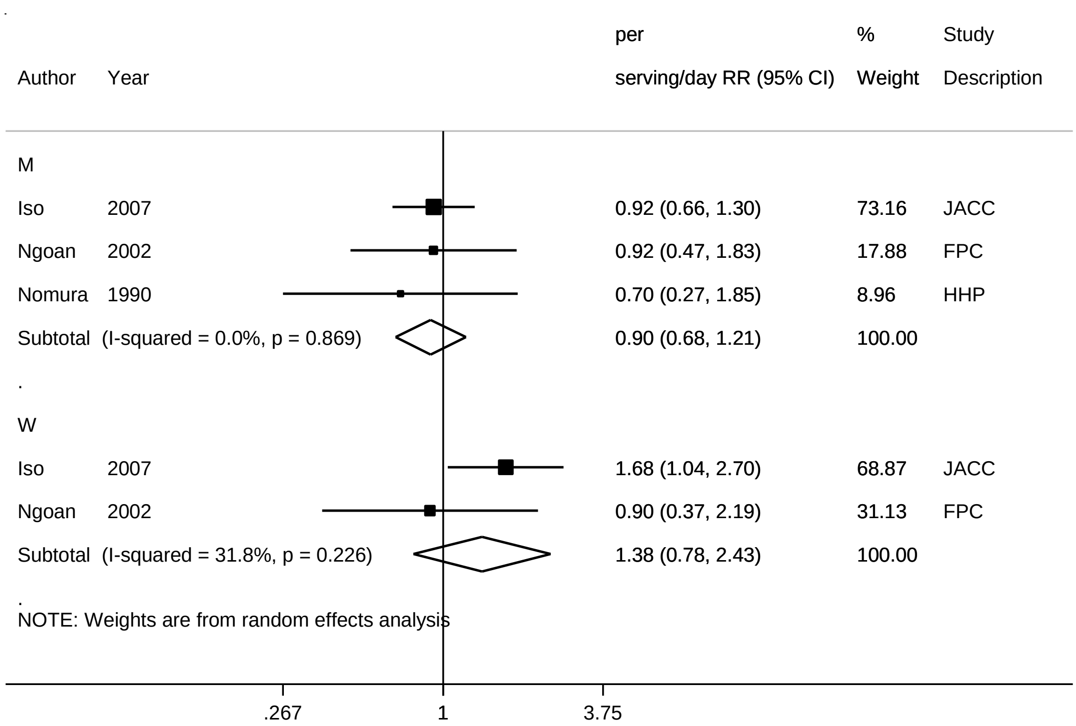


Figure 72 Relative risk of stomach cancer for 1 serving/day increase of tofu intake, by sex



2.5 Meat, poultry, fish and eggs

2.5.1 Meat

The only study on total meat intake and stomach cancer risk identified in the CUP, reported non-significant association (Ko, 2013). In the 2005 SLR, non-significant association of stomach cancer with total meat intake was observed in the meta-analysis of five cohort studies and in other five studies excluded from the meta-analysis.

2.5.1.2 Processed meat

Randomised controlled trials

No randomised controlled trial was identified.

Cohort studies

Summary

Main results:

Ten studies (4728 cases) out of twelve identified were included in the dose-response meta-analysis. Processed meat intake was significantly positively associated with risk of stomach cancer and non-cardia gastric cancer (three studies and low heterogeneity), but not with gastric cardia cancer (three studies, no heterogeneity). Positive associations were observed in other subgroup analyses.

Two studies were excluded from the dose-response analysis. One study reported a non-significant inverse association (Knekt, 1999) and the other study, a non-significant inverse association in women and no significant association (RR=1.0) in men (Khan, 2004).

No heterogeneity was observed. There was some evidence of publication or small study bias (p=0.05). Visual inspection of funnel plot suggests the asymmetry is mainly driven by the smallest study (Zheng, 1995) that reported a very strong positive association.

Sensitivity analyses:

The summary RR for stomach cancer did not change materially when studies were omitted in turn in influence analysis with the exception of influence analysis of studies on non-cardiac gastric cancer, in which the summary significant positive association disappeared when EPIC (Gonzalez, 2006b) was excluded from the analysis (summary RR:1.08; 95% CI:0.90-1.31, two studies).

The results of subgroup analyses by adjustment for confounders, including socioeconomic factors, smoking, alcohol intake, BMI, and total energy intake, showed in general similar results in adjusted and unadjusted studies, although statistical significance was lost in some analyses probably due to lack of statistical power.

Non-linear dose-response meta-analysis:

A restricted cubic spline model was not conducted due to insufficient data in the studies. Alternatively, non-linear associations were explored using fractional polynomial models as the data was suggestive of nonlinear relationships. There was no significance evidence of non-linear dose-response between processed meat intake and stomach cancer (p=0.09), although the curve shows the dose-response starts from intakes above approximately 25 g/day.

Study quality:

The population in Galanis, 1998 was Japanese residents of Hawaii. Loss to follow-up due to migration was 10.7% in this study. Only 108 cases were included in the analysis. Other studies reported only small loss to follow-up.

Cancer outcome was confirmed using medical notes or records in cancer registries in most incidence studies.

All studies used FFQ to assess processed meat intake, apart from Nomura, 1990 that used a 24-hour dietary recall questionnaire. Gonzalez, 2006b also reported dose-response results for calibrated intake of processed meat that showed a slightly stronger positive association with stomach cancer after partially correcting for measurement error.

Most studies included in the meta-analysis were adjusted for age, sex and other potential confounders including smoking and alcohol. Two studies (Iso, 2007; Nomura, 1990) controlled only for age. No studies were adjusted for Helicobacter pylori status. Gonzalez, 2006b reported a significant positive association between processed meat intake and stomach cancer risk in subjects with positive H. pylori status (201 cases) but not in those with negative status (40 cases).

Note:

Dietary nitrate and nitrite intake from processed meats were assessed in several prospective studies (Keszei, 2013; Cross, 2011; Knekt, 1999). No significant associations with gastric cancer or its subtypes were reported. RRs for the highest vs. the lowest level of dietary nitrate from processed meats were 0.81 (95% CI = 0.52-1.25) for gastric cardia cancer and 1.04 (95% CI = 0.69-1.55) for non-cardia cancer (Cross, 2011, NIH-AARP). For dietary nitrite intake, RRs were 0.71 (95% CI = 0.47-1.08) and 0.93 (95% CI = 0.63-1.37) for gastric cardia and non-cardia cancer in Cross, 2011; and 1.18 (95% CI = 0.75-1.86) and 1.23 (95% CI = 0.89-1.70) among men and 0.62 (95% CI=0.20-1.90) and 1.08 (95% CI = 0.71-1.63) among women, respectively in Keszei, 2013 (NLCS); and for gastric cancer 0.71 (95% CI = 0.28-1.78) in Knekt, 1999 (Finnish Mobile Health Clinic study).

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

	Number
Studies identified	12 (16 publications)
Studies included in forest plot of highest compared with lowest exposure	12
Studies included in linear dose-response meta-analysis	10
Studies included in non-linear dose-response meta-analysis	10

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

Table 62 Processed meat intake and stomach cancer risk. Summary of the linear dose-response meta-analysis in the 2005 SLR and CUP

	2005 SLR	**CUP**
Increment unit used	20 g/day	50 g/day
	All studies	
Studies (n)	8	10
Cases (total number)	2404	4728
RR (95%CI)	1.02 (1.00-1.05)	1.19 (1.06-1.34)
Heterogeneity (I^2, p-value)	0%, 0.60	0%, 0.66
P value Egger test	0.40	0.05
	Stratified analysis	
Men		
Studies (n)	5	6
Cases	1207	2278
RR (95%CI)	1.02 (0.99-1.05)	1.25 (1.02-1.53)
Heterogeneity (I^2, p-value)	-	7.3%, 0.37
Women		
Studies (n)	5	6
Cases	536	1150
RR (95%CI)	1.05 (0.97-1.13)	1.40 (1.00-1.96)
Heterogeneity (I^2, p-value)	-	0%, 0.42
Incidence		
Studies (n)	-	7
Cases	-	2377
RR (95%CI)	-	1.21 (1.04-1.41)
Heterogeneity (I^2, p-value)	-	0%, 0.42
Mortality		
Studies (n)	-	3
Cases	-	2351
RR (95%CI)	-	1.15 (0.95-1.41)
Heterogeneity (I^2, p-value)	-	0%, 0.71
Cancer site	Proximal stomach cancer	Gastric cardia cancer
Studies (n)	-	3

Cases	-	711
RR (95%CI)	-	0.99 (0.81-1.21)
Heterogeneity (I^2, p-value)	-	0%, 0.79
	Distal stomach cancer	Non-cardia gastric cancer
Studies (n)	-	3
Cases	-	1149
RR (95%CI)	-	1.18 (1.01-1.38)
Heterogeneity (I^2, p-value)	-	3.2%, 0.36
Asia		
Studies (n)	-	2
Cases	-	1002
RR (95%CI)	-	1.22 (0.83-1.79)
Heterogeneity (I^2, p-value)	-	0%, 0.45
Europe		
Studies (n)	-	3
Cases	-	1138
RR (95%CI)	-	1.24 (1.02-1.50)
Heterogeneity (I^2, p-value)	-	6.7%, 0.34
North America*		
Studies (n)	-	5
Cases	-	2588
RR (95%CI)	-	1.14 (0.95-1.37)
Heterogeneity (I^2, p-value)	-	0%, 0.44

* Two studies in North America were in Japanese residents in Hawaii (Galanis, 1998; Nomura, 1990)

Other stratified analyses

Duration of follow-up	**5-<10 years**	**10-<15 years**	**≥15 years**
Studies (n)	2	4	4
RR (95%CI)	2.02 (0.43-9.59)	1.11 (0.92-1.35)	1.31 (1.03-1.68)
Heterogeneity (I^2, p- value)	62.6%, 0.10	0%, 0.78	0%, 0.57
Number of cases	**<500 cases**	**500-<1000 cases**	**≥1000 cases**
Studies (n)	6	3	1
RR (95%CI)	1.29 (1.06-1.58)	1.12 (0.88-1.42)	1.13 (0.90-1.43)
Heterogeneity (I^2, p-value)	5.7%, 0.38	0%, 0.73	-
Publication year	**<2000**	**2000-<2010**	**≥2010**

Studies (n)	3	5	2
RR (95%CI)	1.43 (0.80-2.58)	1.19 (1.04-1.36)	1.11 (0.83-1.49)
Heterogeneity (I^2, p-value)	20.3%, 0.29	0%, 0.56	0%, 0.43
Adjustment for:			
Socioeconomic status	**Not adjusted**	**Adjusted**	
Studies (n)	4	6	
RR (95%CI)	1.16 (0.91-1.48)	1.20 (1.04-1.39)	
Heterogeneity (I^2, p-value)	0%, 0.66	3.7%, 0.39	
Smoking			
Studies (n)	4	6	
RR (95%CI)	1.31 (0.98-1.74)	1.17 (1.02-1.33)	
Heterogeneity (I^2, p-value)	0%, 0.54	0%, 0.53	
Alcohol intake			
Studies (n)	6	4	
RR (95%CI)	1.19 (0.99-1.43)	1.19 (1.01-1.40)	
Heterogeneity (I^2, p-value)	0%, 0.58	1.7%, 0.38	
BMI			
Studies (n)	5	5	
RR (95%CI)	1.29 (0.97-1.73)	1.17 (1.03-1.33)	
Heterogeneity (I^2, p-value)	0%, 0.51	0%, 0.53	
Total energy intake			
Studies (n)	6	4	
RR (95%CI)	1.19 (0.99-1.43)	1.19 (1.01-1.40)	
Heterogeneity (I^2, p-value)	0%, 0.58	1.7%, 0.38	
Physical activity			
Studies (n)	7	3	
RR (95%CI)	1.23 (1.03-1.47)	1.16 (0.99-1.36)	
Heterogeneity (I^2, p-value)	0%, 0.44	0%, 0.69	

Table 63 Processed meat intake and stomach cancer risk. Results of meta-analyses and pooled analyses of prospective studies published after the 2005 SLR

Author, Year	Number of studies	Total number of cases	Studies country, area	Outcome	Comparison	RR (95%CI)	P trend	Heterogeneity (I^2, p value)
Meta-analyses								
Zhu, 2013	26 studies overall	9917	Canada, China, Japan, Finland, Denmark, France, Germany, Greece, India, Iran, Italy, Lithuania, the Netherlands, Mexico, Norway Spain, Sweden, Taiwan, UK, USA Uruguay	Incidence/mortality, Gastric cancer	High vs. low intake	1.45 (1.26-1.65)		61.0%, <0.001
	9 cohorts*	3902				1.18 (1.00-1.38)		49.3%, 0.05
	8 population-based case-control	2395				1.42 (1.19-1.70)		15.6%, 0.31
	10 hospital-based case-control studies	3914				1.79 (1.55-2.10)		37.4%, 0.11
	7 studies	2021		Men		1.26 (1.09-1.46)		37.3%, 0.14
	7 studies	1517		Women		1.16 (0.99-1.36)		41.4%, 0.12
	4 studies	968		Gastric cardia cancer		0.95 (0.76-1.19)		2.7%, 0.38
	4 studies	1515		Gastric non-cardia cancer		1.27 (1.07-1.52)		41.9%, 0.16

*The nine cohort studies identified were included in the present review.

Table 64 Processed meat intake and stomach 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
Keszei, 2012 STM80068 The Netherlands	NLCS, Case Cohort, Age: 55-69 years, M/W	652/ 4 827 16.3 years 139/ 329/	Annual linkage to the Netherlands cancer registry and the nationwide network of histopathology and cytopathology in the NDLS (Palga)	Validated 150-item FFQ All meat items undergone nitrite treatment, smoking, or fermentation, including sausages, bacon, ham, cold cuts, croquettes, and frankfurters	Incidence Men Gastric cardia adenocarcinoma Non-cardia adenocarcinoma	45.5 vs. 3.7 g/day Per 50 g/day	1.49 (0.81-2.75) 1.19 (0.78-1.79) 1.15 (0.71-1.86) 1.15 (0.83-1.59)	Age, BMI, education level, fruit intake, smoking status, vegetable intake, alcohol intake, non-occupational physical activity, number of cigarettes smoked per day, total energy intake, years of smoking	RRs for gastric cardia adenocarcinoma and gastric non-cardia adenocarcinoma combined using Hamling's method, RRs for men and women combined using fixed model
		24/ 160/			Women Gastric cardia adenocarcinoma Gastric non-cardia adenocarcinoma	26 vs. 3.5 g/day Per 50 g/day	1.12 (0.36-3.47) 1.11 (0.73-1.70) 0.70 (0.14-3.47) 1.02 (0.54-1.93)		
Cross, 2011 STM80074 USA	NIH-AARP, Prospective Cohort, Age: 50-71 years, M/W, Retired	955/ 494 979 10 years 454/	Linkage of the cohort with database to state cancer registries	Validated 124-item self-administered FFQ Bacon, red meat sausage, poultry sausage, luncheon meats, cold cuts, ham, regular hotdogs and low-fat	Incidence Gastric cardia adenocarcinoma	23.2 vs 1.7 g/1000 kcal Per 10 g/1000 kcal	0.82 (0.59-1.14) 1.00 (0.92-1.09)	Age, sex, BMI, calories intake, ethnicity, work - physical activity, alcohol drinking, fruit and vegetable intake, saturated fat intake, tobacco use, vigorous	Distribution of person-years by exposure quintiles, exposure values using mean energy intake

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Missing data derived for analyses
				hotdogs made from poultry				physical activity	
		501/			Gastric non-cardia adenocarcinoma	23.2 vs 1.7 g/1000 kcal Per 10 g/1000 kcal	1.09 (0.81-1.48) 1.02 (0.94-1.11)		
Iso, 2007 STM80144 Japan	JACC, Prospective Cohort, Age: 40-79 years, M/W	940/ 105 500 15 years 639/40 153	Municipal resident registration records, death certificates	Validated FFQ Ham and sausages	Mortality, stomach cancer Men	≥3-4 vs. <1 times/week	1.11 (0.89-1.38)	Age, area of study	Exposure values using standard portion size, mid-points of exposure categories, RRs for men and women combined using fixed model
		301/54 783			Women	≥3-4 vs. <1 times/week	0.96 (0.68-1.35)		
Gonzalez, 2006b STM44432 France, Italy, Spain, UK, The Netherlands, Germany, Sweden, Denmark	EPIC, Prospective Cohort, Age: 35-70 years, M/W	330/ 465 586 6.5 years	Cancer registry	FFQ, dietary questionnaires, food record Ham, bacon, sausages, processed meat cuts, hamburgers, meatballs, and pates	Incidence, gastric adenocarcinoma	85.6 (M)/45.4 (W) vs. 19.1(M)/13.1 (W) Per 50 g	1.62 (1.08-2.41) 1.18 (0.97-1.43)	Age, sex, centre, cigarette smoking, citrus fruit intake, energy intake, height, leisure - physical activity, red meat intake, vegetable intake, weight, work - physical activity, alcohol intake, education, other fruits intake,	
		94/ 159/ 109/ 116/			Gastric cardia adenocarcinoma Non-cardia adenocarcinoma Intestinal gastric cancer Diffuse gastric cancer		1.14 (0.52-2.49) 0.89 (0.59-1.34) 1.92 (1.11-3.33) 1.36 (1.06-1.74) 1.78 (0.84-3.77) 1.27 (0.93-1.75) 1.47 (0.76-2.82) 1.04 (0.75-1.43)		

Author, Year, 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
								poultry intake, tobacco use	
	Nested Case Control	241/ 481 518 6.5 years 201/ 47/ 113/			H. pylori +ve Stomach cancer Cardia cancer Non-cardia cancer	Per 50 g/day	2.00 (1.06-3.79) 1.62 (0.47-5.55) 2.67 (1.20-5.93)	Age, sex, alcohol consumption, area of residence, cigarette use, date of blood collection, educational level, energy intake, fruit, height, Helicobacter pylori infection, leisure-time physical activity, occupational physical activity, smoking habits, vegetable intake, weight	
		40/ 22/ 12/			H. pylori -ve Stomach cancer Cardia cancer Non-cardia cancer	Per 50 g/day	0.45 (0.05-4.01) 0.86 (0.03-27.00) 0.002 (<0.001-62.600)		
Larsson, 2006b STM80079 Sweden	SMC, Prospective Cohort, W	156/ 61 433 18 years	Linkage of the cohort with National Swedish cancer registry and regional cancer registry	Validated 67-item FFQ Bacon or side pork, sausage or hotdogs, and ham or salami	Incidence, stomach cancer	≥3.0 vs. <1.5 servings/week Per 10 g/day	1.66 (1.13-2.45) 1.16 (1.00-1.35)	Age, BMI, education level, alcohol intake, fruit and vegetable intake, total energy intake	

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Missing data derived for analyses
Ngoan, 2002 STM01668 Japan (result on women was excluded)	FPC, Prospective Cohort, Age: 15-96 years, M/W	62/ 13 250 13 years	Resident registry	Self-administered FFQ	Mortality, stomach cancer	≥ 1 time/day vs. 2-4 times/month	2.00 (0.80-5.40)	Age, sex, fat intake, Japanese soup, liver, pickled foods, processed meat, smoking habits	Exposure values using standard portion size, mid-points of exposure categories
		47/3448			Men	≥ 1 time/day vs. 2-4 times/month	3.40 (1.40-8.10)	Age	
McCullough, 2001 STM02243 USA	CPS II, Prospective Cohort, Age: 30- years, M/W	1349/ 970 045 14 years 910/	Death register/ subject or family	32-item FFQ Processed meat, smoked meats, frankfurters/ sausage, fried bacon, ham	Mortality, stomach cancer Men	≥4.5 vs. 0-0.9 days/week	1.08 (0.87-1.33)	Age, aspirin use, BMI, educational level, ethnicity/race, family history of stomach cancer, multivitamin supplement, smoking habits, vitamin c supplement	Distribution of person-years by exposure tertiles, exposure values using standard portion size, mid-points of exposure categories
		439/			Women	≥3 vs. 0-1.4 days/week	1.11 (0.88-1.39)		
Galanis, 1998 STM04769 USA	Hawaii-Japan DOH Survey, Prospective Cohort, Age: 18- years, M/W, Japanese residents of Hawaii	108/ 11 907 14.8 years	Cancer registry	19-item FFQ	Incidence, stomach cancer	≥3 or more vs. none times/week	1.00 (0.60-1.70)	Age, sex, educational level, place of birth	Exposure values using standard portion size, mid-points of exposure categories
		64/			Men		1.00 (0.50-1.90)	Age, alcohol consumption, educational	

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Missing data derived for analyses
								level, place of birth, smoking habits	
		44/			Women		1.20 (0.60-2.40)	Age, educational level, place of birth	
Zheng, 1995 STM06417 USA	IWHS, Prospective Cohort, Age: 55-69 years, Post-menopausal women	26/ 34 691 7 years	Cancer registry	127-item self-administered semi-quantitative FFQ Processed meat and fish intake	Incidence, stomach cancer	≥13 vs. <4.4 times/month	2.20 (0.80-6.00)	Age, educational level, pack-years of smoking, smoking habits	Distribution of person-years by exposure tertiles, exposure values using standard portion size, mid-points of exposure categories
Nomura, 1990 STM14814 USA	HHP, Prospective Cohort, Age: 45- years, M, Japanese residents of Hawaii	150/ 7 990 19 years	Cancer registry/ hospital records	20-item FFQ, 24- hour diet recall Ham, bacon, or sausage	Incidence, stomach cancer	≥5 vs. ≤1 times/week	1.30 (0.90-2.00)	Age	Exposure values using standard portion size, mid-points of exposure categories

Table 65 Processed meat intake and stomach 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
Duell, 2013 STM80172 Denmark,France ,Germany, Greece,Italy,The Netherlands, Norway,Spain, Sweden,UK	EPIC, Nested Case Control, Age: 58 years, M/W	365/ 1649 14 years (max)	Linkage with regional cancer registries, health insurance records, cancer and pathology registries and active follow-up of study subjects	FFQ, diet history, 7-day food diary	Incidence, stomach cancer	≥39.58 vs. ≤16.88 g/day	1.58 (1.12-2.23)	Age at recruitment, sex, country	Superseded by Gonzalez, 2006b, STM44432 – processed meat was not the main focus in the publication and the model was less adjusted
Cross, 2007 STM80109 USA	NIH-AARP, Prospective Cohort, Age: 50-71 years, M/W, Retired	658/ 494 036 6.8 years	Cancer registry and national death index	Validated 124-item FFQ Bacon, red meat sausage, poultry sausage, luncheon meats, cold cuts, ham, regular hot dogs and low-fat hot dogs made from poultry	Incidence, stomach cancer	22.6 vs. 1.6 g/1000 kcal	1.00 (0.78-1.30)	Age, sex, BMI, educational level, family history of cancer, fruit and vegetable consumption, marital status, race, smoking status, alcohol intake, frequency of vigorous physical activity, total energy intake	Superseded by Cross, 2011, STM80074
Khan, 2004	HGCS,	51/	Follow-up	37-item FFQ	Mortality,				Excluded, only

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Reasons for exclusion
STM20239 Japan	Prospective Cohort, Age: 40- years, M/W	3158 14 years	surveys	Ham and sausage	stomach cancer	2-7 times/week vs. never-several times/month			two intake categories
		36/			Men		1.00 (0.50-2.10)	Age, smoking habits	
		15/			Women		0.70 (0.20-2.60)	Age, health education, health screening, health status, smoking habits	
van den Brandt, 2003 STM00622 The Netherlands	NLCS, Case Cohort, Age: 55-69 years, M/W	282/ 120 852 6.3 years	Cancer registry	Validated 150-item semi-quantitative FFQ Bacon, smoked sausage, sliced cold meats, boiled ham, rashers, bacon, smoked beef, pork loin roll, other cold meat	Incidence, stomach cancer	Bacon as component of the hot meal ≥0.1 g/day vs none	1.33 (1.03-1.71)	Age, sex, educational level, family history of cancer, smoking habits, stomach disorders	Specific processed meat items, superseded by Keszei, 2012, STM80068
						Smoked sausage as component of the hot meal >3 g/day vs none	0.95 (0.67-1.35)		
						Total sliced cold meats >20 g/day vs none	1.33 (0.85-2.09)		
						Boiled ham >5 g/day vs none	0.77 (0.56-1.07)		
						Rashers, bacon ≥0.1 g/day vs	0.94 (0.72-1.23)		

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Reasons for exclusion
						none			
						Smokers beef, pork loin roll ≥0.1 g/day vs none Other sliced cold meat >4 g/day vs none	0.92 (0.71-1.19) 1.29 (0.96-1.72)		
Ngoan, 2002 STM01668 Japan	FPC, Prospective Cohort, Age: 15-96 years, M/W	62/ 13 250 13 years 12/4094	Resident registry	Self-administered FFQ	Mortality, stomach cancer Women	2-4 times/week vs 2-4 times/month	1.90 (0.60-6.30)	Age	Excluded, only two intake categories (overall result and result on men were included)
Knekt, 1999 STM03959 Finland	FMCHES, Prospective Cohort, Age: 15-99 years, M/W	68/ 9985 21 years	Cancer registry	Dietary history Cured meat and meat products	Incidence, stomach cancer	Quantile 4 vs quantile 1	0.49 (0.22-1.06)	Age, sex, energy intake, geographical area, smoking habits	Excluded, exposure not quantified
Chyou, 1990 STM12425 USA	HHP, Case Cohort, Age: 58 years, M, Japanese residents of Hawaii	111/ 8006 18 years	Cancer registry/ hospital records	24-hour dietary recall	Mortality, stomach cancer	Mean intakes		Age	Superseded by Nomura, 1990, STM14814

Figure 73 RR estimates of stomach cancer by levels of processed meat intake

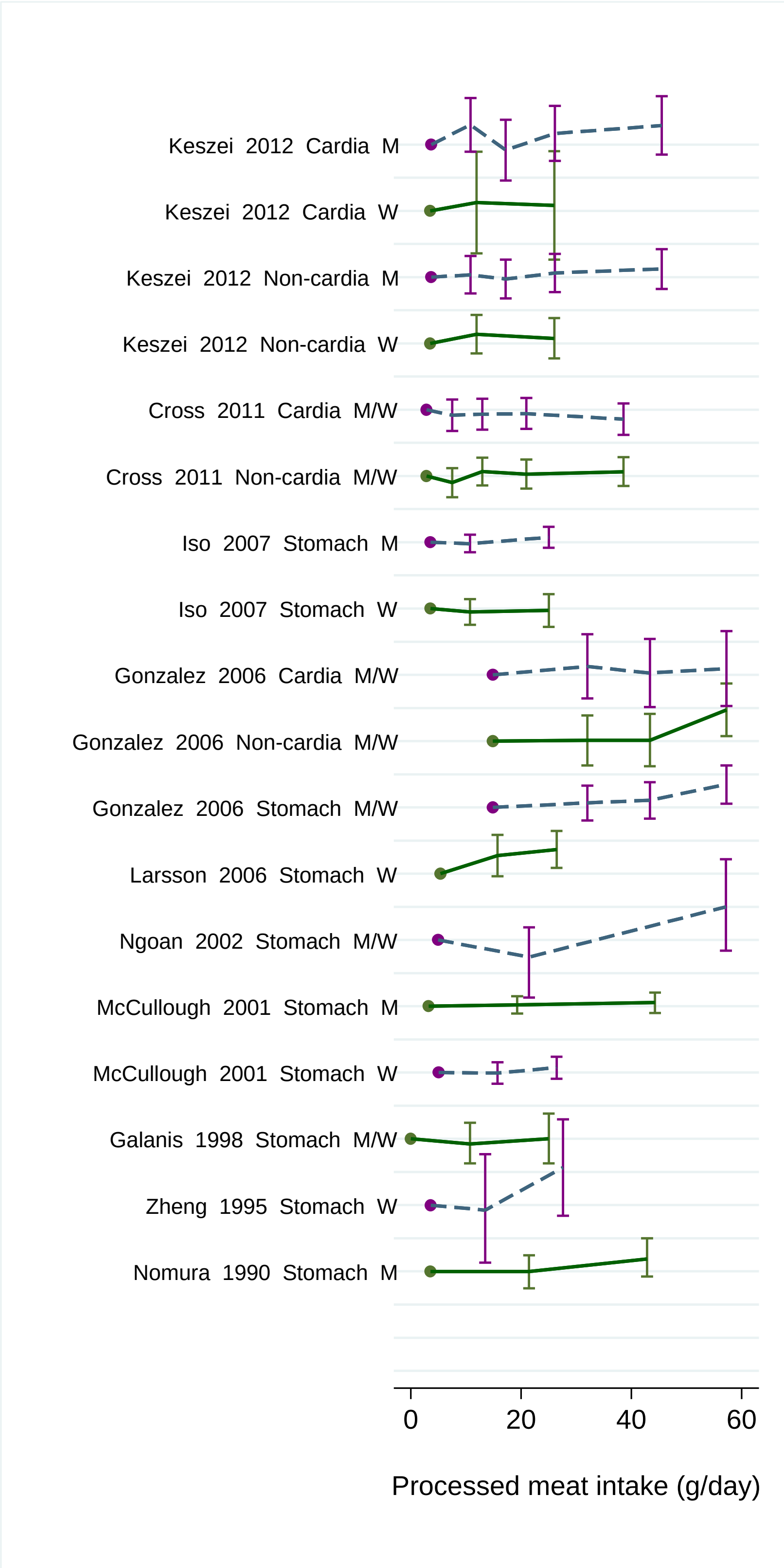


Figure 74 RR (95% CI) of stomach cancer for the highest compared with the lowest level of processed meat intake

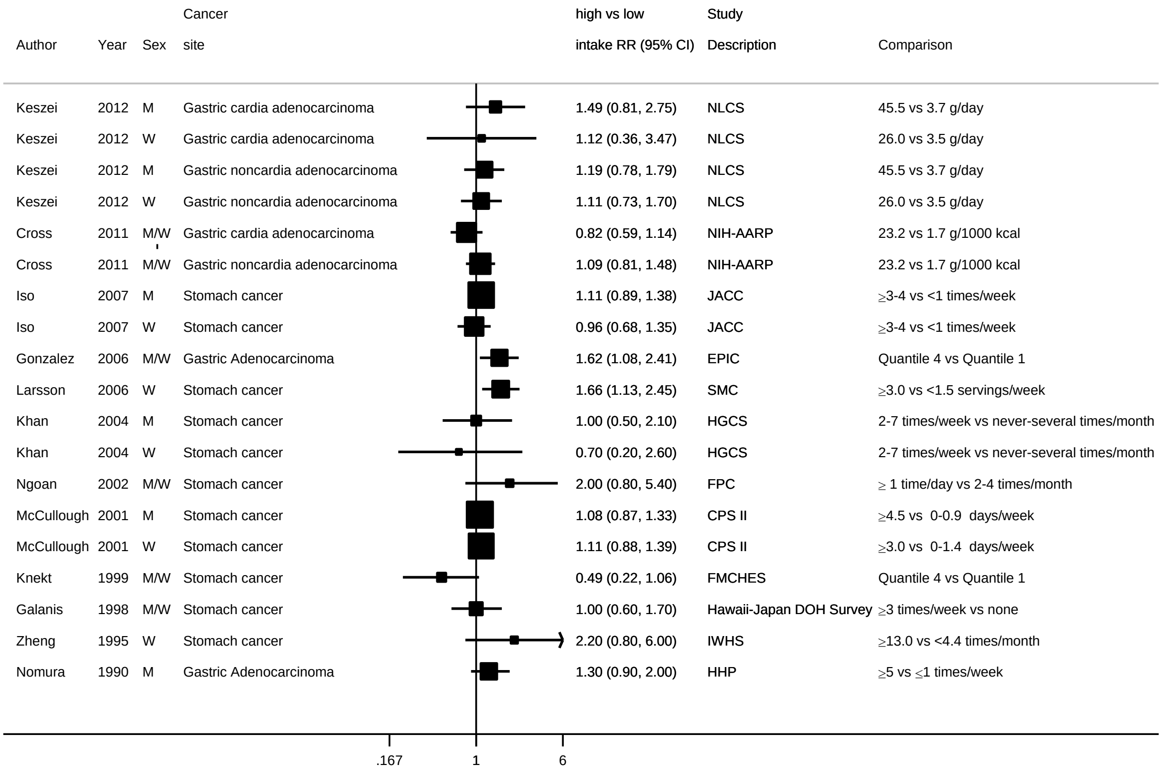


Figure 75 Relative risk of stomach cancer for 50 g/day increase of processed meat intake

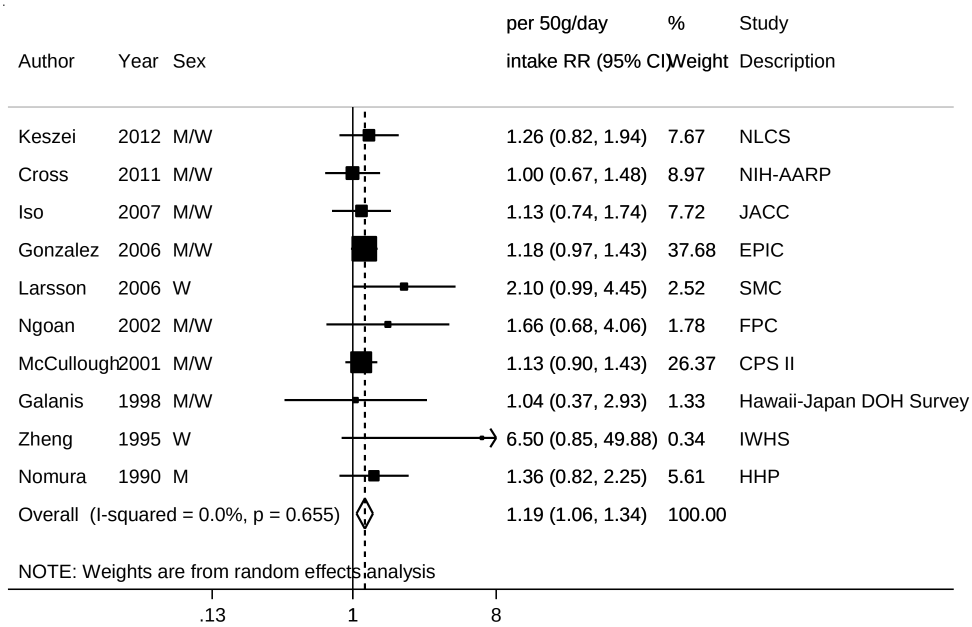
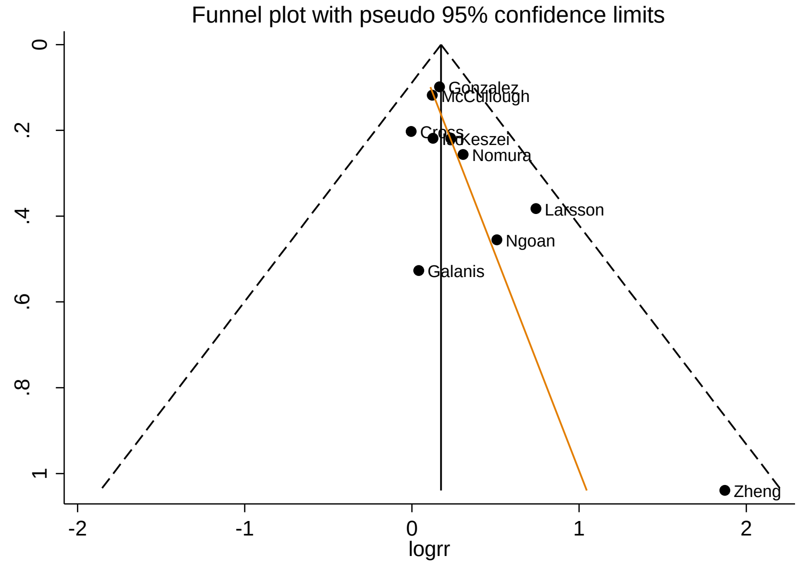


Figure 76 Funnel plot of studies included in the dose response meta-analysis of processed meat intake and stomach cancer



Egger's test p=0.05

Figure 77 Relative risk of stomach cancer for 50 g/day increase of processed meat intake by sex

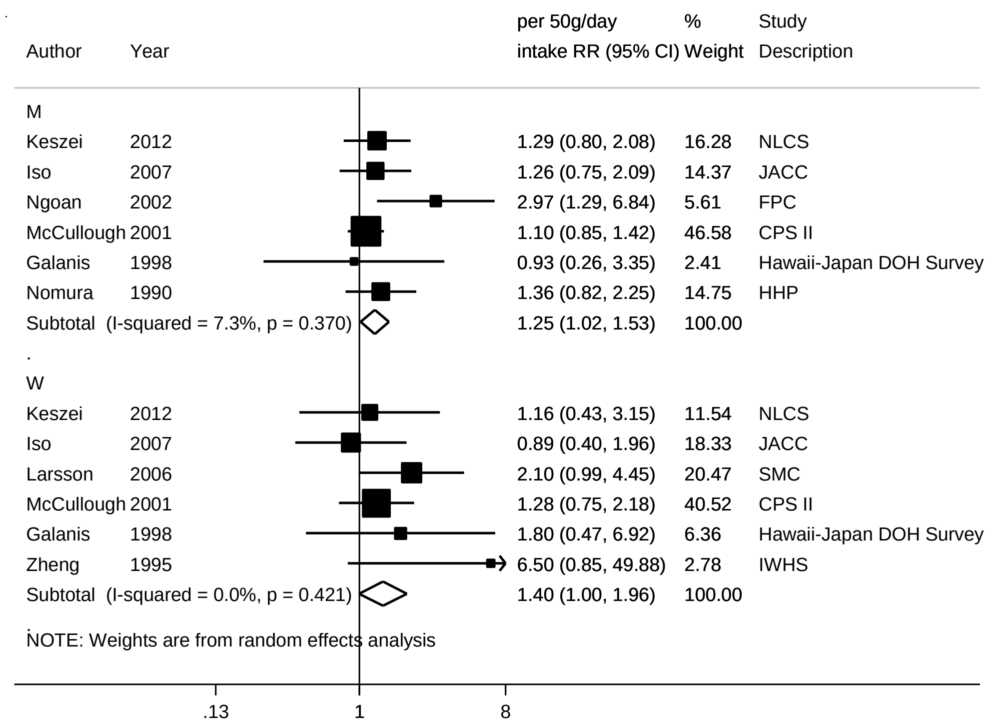


Figure 78 Relative risk of stomach cancer for 50 g/day increase of processed meat intake by cancer outcome

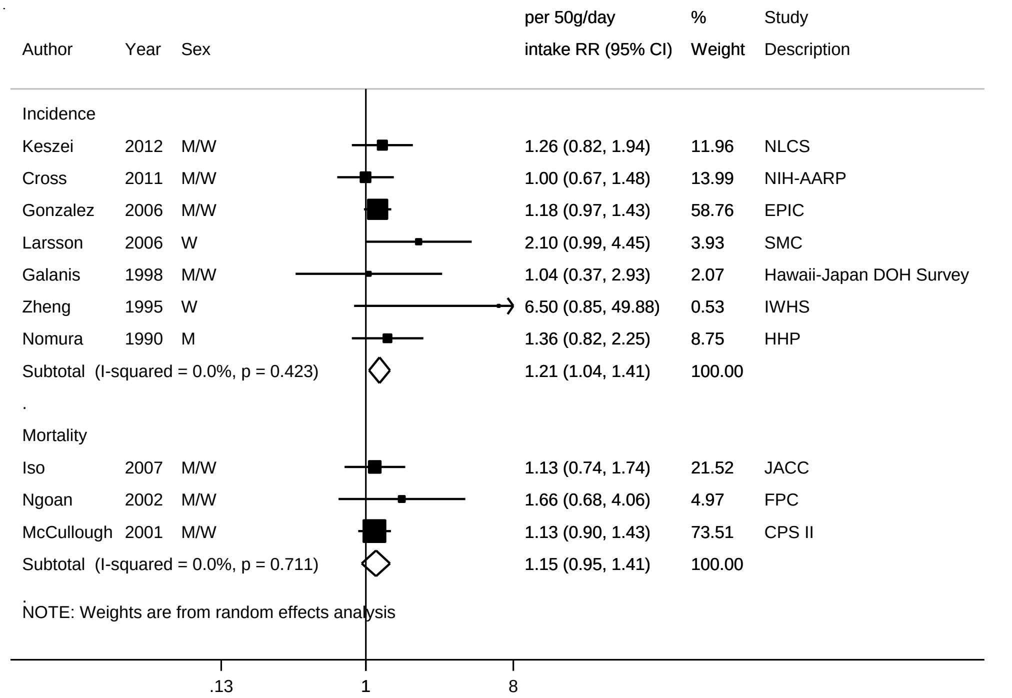


Figure 79 Relative risk of stomach cancer for 50 g/day increase of processed meat intake by cancer site

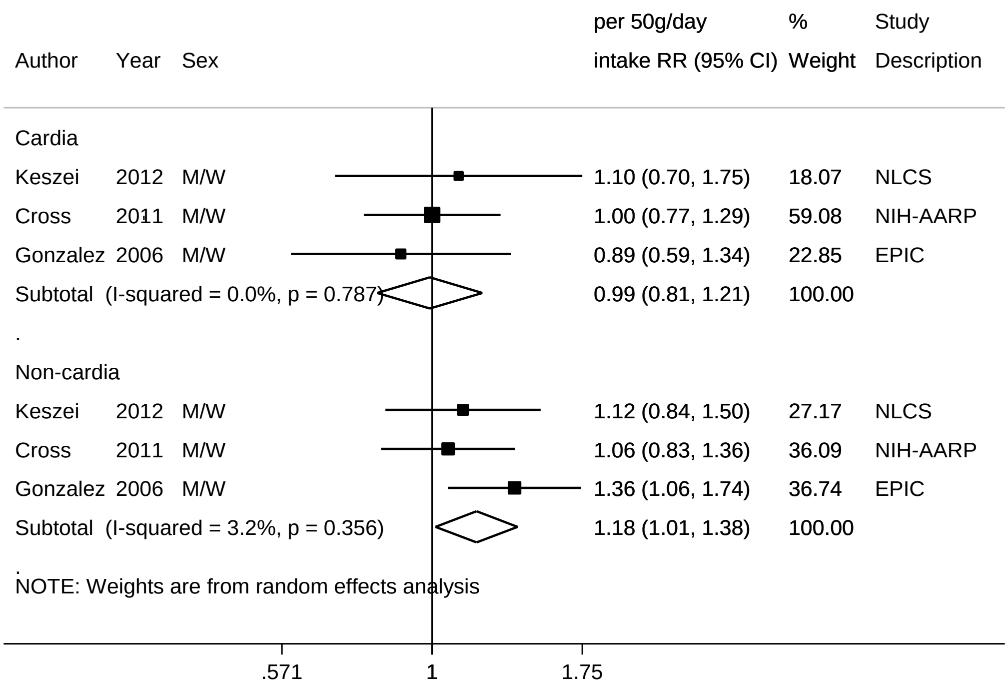


Figure 80 Relative risk of stomach cancer for 50 g/day increase of processed meat intake by geographic location

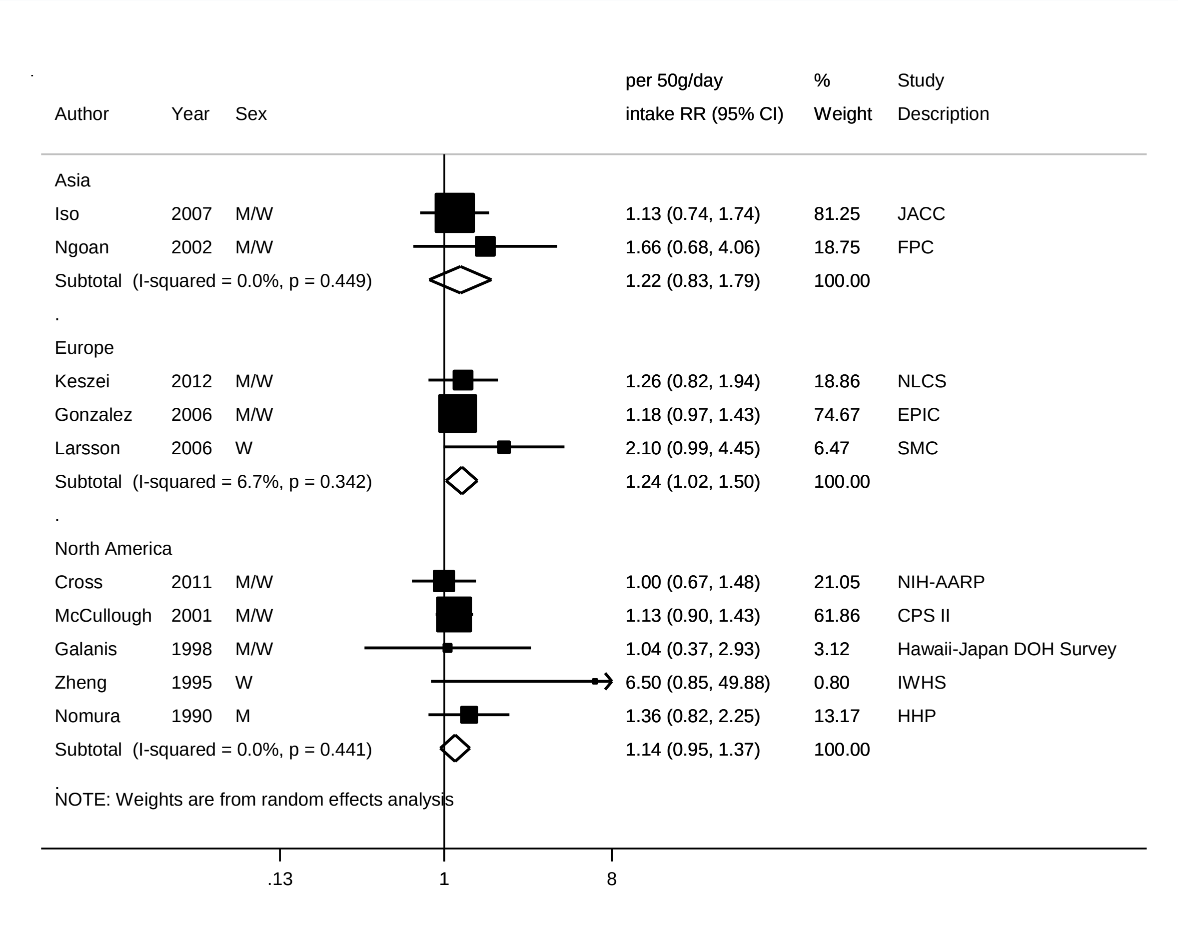
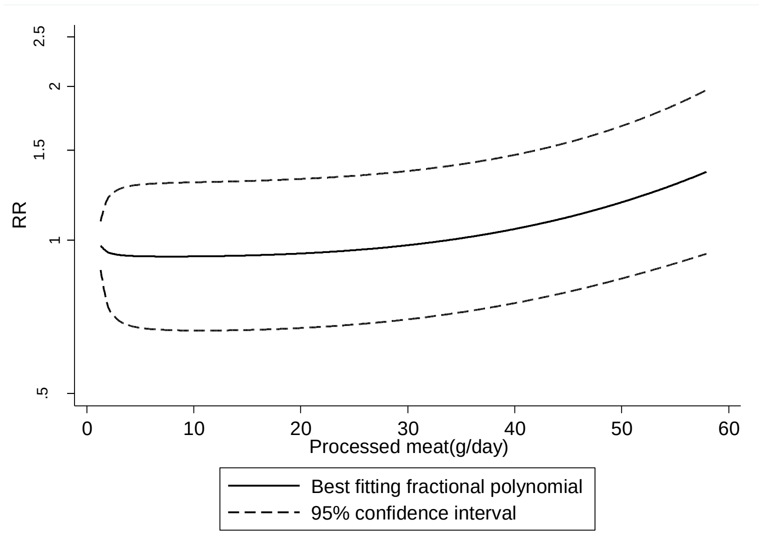


Figure 81 Non-linear dose-response meta-analysis of processed meat intake and stomach cancer



P for non-linearity = 0.09

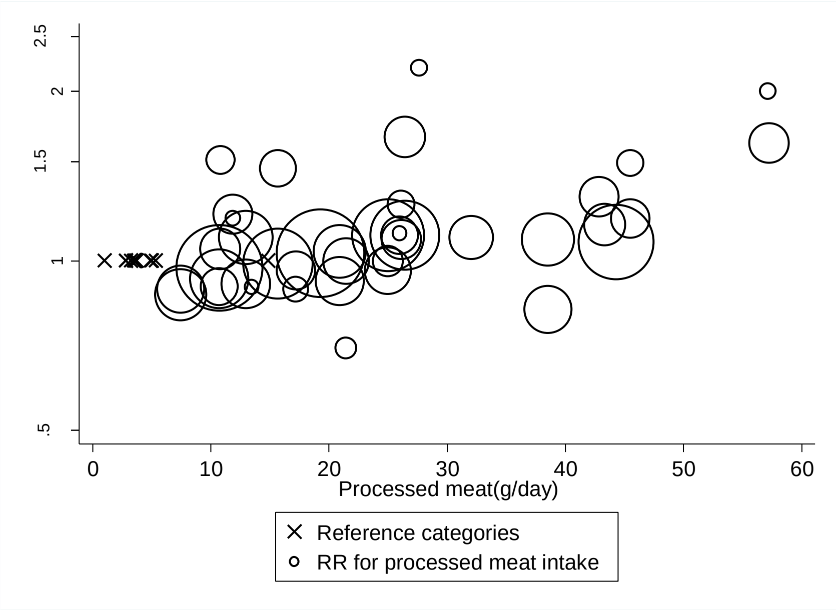


Table 66 Relative risk of stomach cancer and processed meat intake estimated using non-linear models

Processed meat (g/day)	RR
1	1
10	0.93 (0.66-1.30)
20	0.94 (0.67-1.32)
40	1.05 (0.75-1.47)
50	1.19 (0.84-1.67)

2.5.1.3 Red meat

Randomised controlled trials

No randomised controlled trial was identified.

Cohort studies

Summary

Main results:

Meta-analysis is updated in the CUP when there are at least five studies with the required data. This section on (unprocessed) red meat has been included to complement the results on processed meat because the evidence that processed meat is causally related to stomach cancer risk was judged as limited suggestive in the Second Expert report.

Four studies (2408 cases) out of five identified studies were included in the dose-response meta-analysis. Red meat intake was non-significantly positively associated with stomach cancer. No heterogeneity was observed. Test of publication or small study bias was not conducted due to small number of studies.

Non-significant associations were observed for non-cardia gastric cancer (positive association, two studies, high heterogeneity) and gastric cardia cancer (inverse association, two studies, no heterogeneity).

One study excluded from the dose-response analysis reported non-significant association in men (positive) and women (inverse) (Khan, 2004).

Sensitivity analyses:

The summary RRs ranged from 1.07 (95% CI=0.88-1.29) when Gonzalez, 2006b was omitted to 1.17 (95% CI=0.98-1.41) when Keszei, 2012 was omitted in influence analysis.

Non-linear dose-response meta-analysis:

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

Study quality:

All studies used FFQ to assess red meat intake. Larsson, 2006b reported specifically on unprocessed red meat. Other studies examined red meats including beef and pork. Other methods were used in addition to country-specific questionnaires in EPIC (Gonzalez, 2006b). Gonzalez, 2006b reported dose-response results for calibrated intake of red meat. The positive association was stronger after calibration, but remained non-significant. Omitting this study in the analysis slightly increased the strength of the association but it remained non-significant.

Sauvaget, 2005 was a cohort of atomic bomb survivors (LSS). Sensitivity analysis showed that this study did not have a strong influence in the summary RR.

Smoking was not adjusted for in Larsson, 2006. Alcohol intake, total energy intake, and BMI were not adjusted for in Sauvaget, 2005. Gonzalez, 2006b adjusted for height but not BMI. No studies adjusted for Helicobacter Pylori status. One study conducted analyses by H. pylori status in a case-control nested within a cohort and showed non-significant positive associations in both positive and negative status participants (Gonzalez, 2006b).

Table 67 Red meat intake and stomach 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	5
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

Table 68 Red meat intake and stomach cancer risk. Summary of the linear dose-response meta-analysis in the 2005 SLR and CUP

	2005 SLR	**CUP**
Increment unit used	20 g/day	100 g/day
All studies		
Studies (n)	3	4
Cases (total number)	663	2408
RR (95%CI)	1.05 (0.90-1.22)	1.12 (0.95-1.32)
Heterogeneity (I^2, p-value)	23.0%, 0.30	0%, 0.65
P value Egger test	0.20	-
Stratified and sensitive analysis*		
Sex	**Men**	**Women**
Studies (n)	1	2
RR (95%CI)	1.13 (0.74-1.72)	0.93 (0.55-1.59)
Heterogeneity (I^2, p-value)	-	38.2%, 0.20
Cancer site	**Gastric cardia cancer**	**Non-cardia gastric cancer**
Studies (n)	2 (n=257)	2 (n=648)
RR (95%CI)	0.97 (0.68-1.39)	1.28 (0.81-2.03)
Heterogeneity (I^2, p-value)	0%, 0.63	69.3%, 0.07

*No stratified analysis in the 2005 SLR

Other stratified analyses

Number of cases	**<500 cases**	**≥500 cases**
Studies (n)	2	2
RR (95%CI)	1.28 (0.97-1.69)	1.05 (0.86-1.28)
Heterogeneity (I^2, p-value)	0%, 0.85	0%, 0.57
Adjustment for confounders:		
Physical activity	**Not adjusted**	**Adjusted**
Studies (n)	2	2
RR (95%CI)	1.11 (0.89-1.39)	1.13 (0.85-1.51)
Heterogeneity (I^2, p-value)	0%, 0.74	34.9%, 0.22

Table 69 Red meat intake and stomach 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
Keszei, 2012 STM80068 The Netherlands	NLCS, Case Cohort, Age: 55-69 years, M/W	652/ 4827 16.3 years 139/ 329/ 24/ 160/	Annual linkage to The Netherlands cancer registry and the nationwide network of histopathology and cytopathology (PALGA)	Validated 150-item FFQ Beef, pork, minced meat, liver, and other non-poultry meat	Incidence, stomach cancer Men Gastric cardia adenocarcinoma Gastric non-cardia adenocarcinoma Women Gastric cardia adenocarcinoma Gastric non-cardia adenocarcinoma	145.9 vs 45.8 g/day Per 50 g/day 115.9 vs 46.9 g/day Per 50 g/day 115.9 vs 46.9 g/day Per 50 g/day 115.9 vs 46.9 g/day Per 50 g/day	1.00 (0.56-1.78) 0.98 (0.77-1.25) 1.15 (0.77-1.71) 1.05 (0.91-1.22) 0.45 (0.17-1.19) 0.77 (0.39-1.49) 0.85 (0.57-1.26) 0.96 (0.75-1.23)	Age, BMI, education level, smoking status, intake of vegetables, fruits, alcohol, total energy, non occupational physical activity, cigarettes smoked per day, years of smoking	RRs for gastric cardia adenocarcinoma and gastric non-cardia adenocarcinoma combined using Hamling's method, RRs for men and women combined using fixed model
Gonzalez, 2006b STM44432 Denmark, France, Germany, Greece, Italy,The Netherlands, Norway, Spain, Sweden,UK	EPIC, Prospective Cohort, Age: 35-70 years, M/W	330/ 465 586 6.5 years 94/ 159/	Cancer registries, health insurance records, pathology rec, active follow up, death certificate	FFQ, dietary questionnaires, food record Pork, beef, veal, and lamb	Incidence, gastric adenocarcinoma Gastric cardia adenocarcinoma Gastric non-cardia adenocarcinoma	84.6 (M)/52.9 (W) vs 34.3 (M)/22.6 (W) Per 50 g	1.50 (1.02-2.22) 1.14 (0.97-1.33) 1.17 (0.53-2.60) 1.04 (0.79-1.38) 1.65 (0.97-2.82) 1.30 (1.04-1.63)	Age, sex, centre, cigarette smoking, citrus fruit intake, energy intake, height, leisure - physical activity, vegetable intake, weight, work -	

Author, Year, 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
		109/ 116/			Intestinal gastric cancer Diffuse gastric cancer		1.23 (0.61-2.51) 1.03 (0.76-1.40) 1.74 (0.93-3.24) 1.13 (0.84-1.51)	physical activity, alcohol intake, education, other fruits intake, poultry intake, processed meat intake, tobacco use	
	Nested Case Control	241/ 481 518 6.5 years 201/ 47/ 113/			H pylori +ve Incidence Stomach cancer Cardia cancer Non-cardia cancer	Per 50 g/day	1.26 (0.69-2.32) 0.56 (0.16-2.00) 1.93 (0.90-4.12)	Age, sex, alcohol consumption, area of residence, cigarette use, date of blood collection, educational level, energy intake, fruit, height, Helicobacter pylori infection, leisure-time physical activity, occupational physical activity, smoking habits, vegetable intake, weight	
		40/ 22/ 12/			H pylori -ve Incidence Stomach cancer Cardia cancer Non-cardia cancer	Per 50 g/day	1.78 (0.27-11.70) 1.55 (0.10-24.50) 1.22 (0.01-237.00)		

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Missing data derived for analyses
Larsson, 2006b STM80079 Sweden	SMC, Prospective Cohort, W	156/ 61 433 18 years	Linkage of the cohort with national Swedish cancer registry and regional cancer registry	Validated 67-item FFQ Unprocessed red meat	Incidence, stomach cancer	≥3.5 vs <2 servings/week Per 10 g/day	1.07 (0.69-1.66) 1.02 (0.96-1.08)	Age, BMI, education level, alcohol intake, fruit and vegetable intake, total energy intake	
Sauvaget, 2005 STM44428 Japan	LSS, Prospective Cohort, Age: 34-98 years, M/W, Atomic bomb survivors	1270/ 38 540 19 years	Cancer registry	22-item FFQ Beef/pork	Incidence, stomach cancer	≥5 vs <2 times/week	1.06 (0.85-1.34)	Age, sex, area of residence, educational level, radiation exposure, smoking habits	Exposure values using standard portion size, mid-points of exposure categories

Table 70 Red meat intake and stomach 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, Retired	954/ 494 968 9.7 years	Cancer registry, death master file, national death index plus, postal service database	Validated FFQ, 124-item	Incidence, stomach cancer	aMED scoring criteria for red and processed meat combined <2.45 vs ≥2.45oz		Age, sex, BMI, race, education, modified total score, smoking, total energy intake, usual activity throughout the day, vigorous physical activity	Excluded, exposure was meeting dietary index criteria or not (same study as Cross, 2011, STM80074)
		453/			Gastric cardia adenocarcinoma		0.95 (0.78-1.16)		
		501/			Gastric non-cardia adenocarcinoma		1.08 (0.90-1.31)		
Khan, 2004 STM20239 Japan	HGCS, Prospective Cohort, Age: 40- years, M/W	51/ 3158 14 years	Follow-up surveys	37-item FFQ Meat except chicken	Mortality, stomach cancer	2-7 times/week vs never-several times/month		Age, smoking habits	Excluded, two exposure levels only
		36/1524			Men		1.40 (0.70-2.80)	Age, health education, health screening, health status, smoking habits	
		15/1634			Women		0.90 (0.30-2.50)		
van den Brandt, 2003 STM00622 The Netherlands	NLCS, Case Cohort, Age: 55-69 years, M/W	282/ 120 852 6.3 years	Cancer registry	Validated 150-item semi-quantitative FFQ Smoked beef and pork roll	Incidence, stomach cancer	Some vs none	0.92 (0.71-1.19)	Age, sex, educational level, family history of cancer, smoking habits, stomach disorders	Superseded by Keszei, 2012, STM80068

Figure 82 RR estimates of stomach cancer by levels of red meat intake

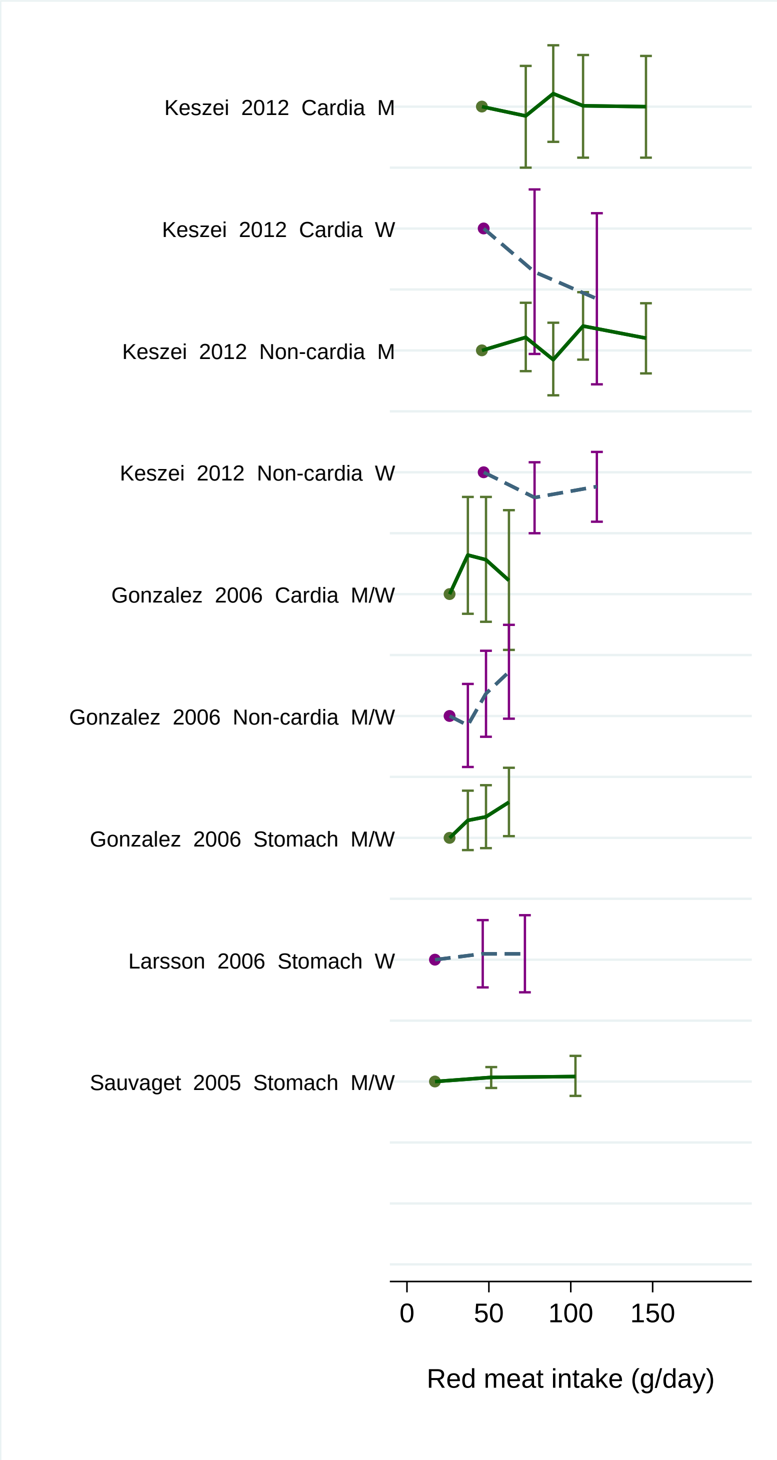


Figure 83 RR (95% CI) of stomach cancer for the highest compared with the lowest level of red meat intake

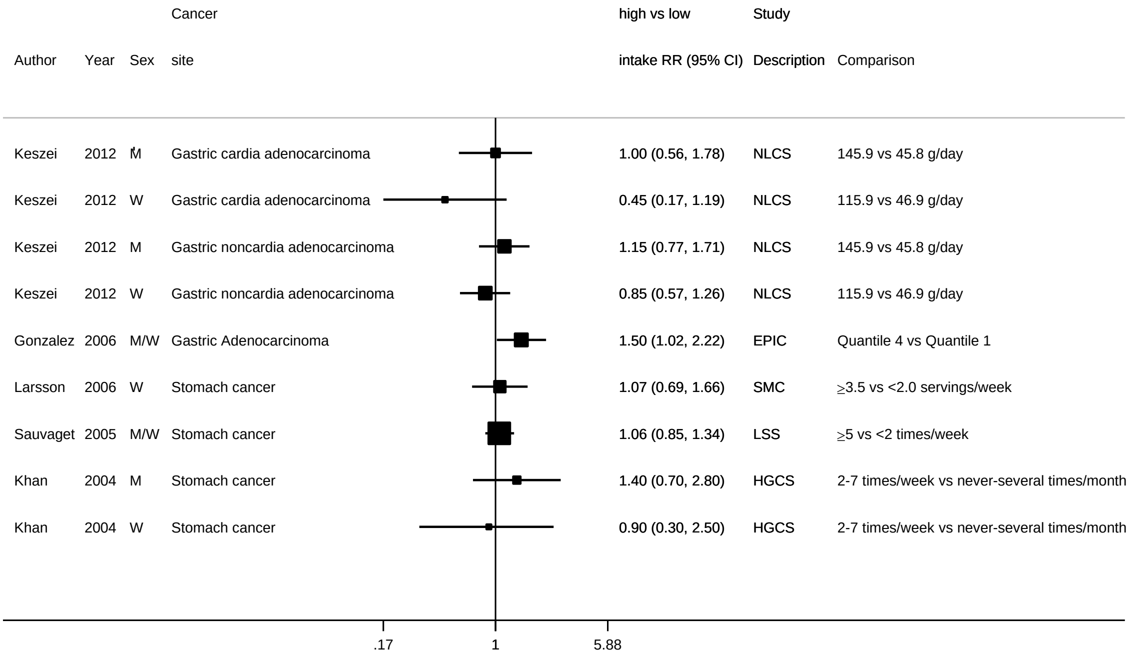


Figure 84 Relative risk of stomach cancer for 100 g/day increase of red meat intake

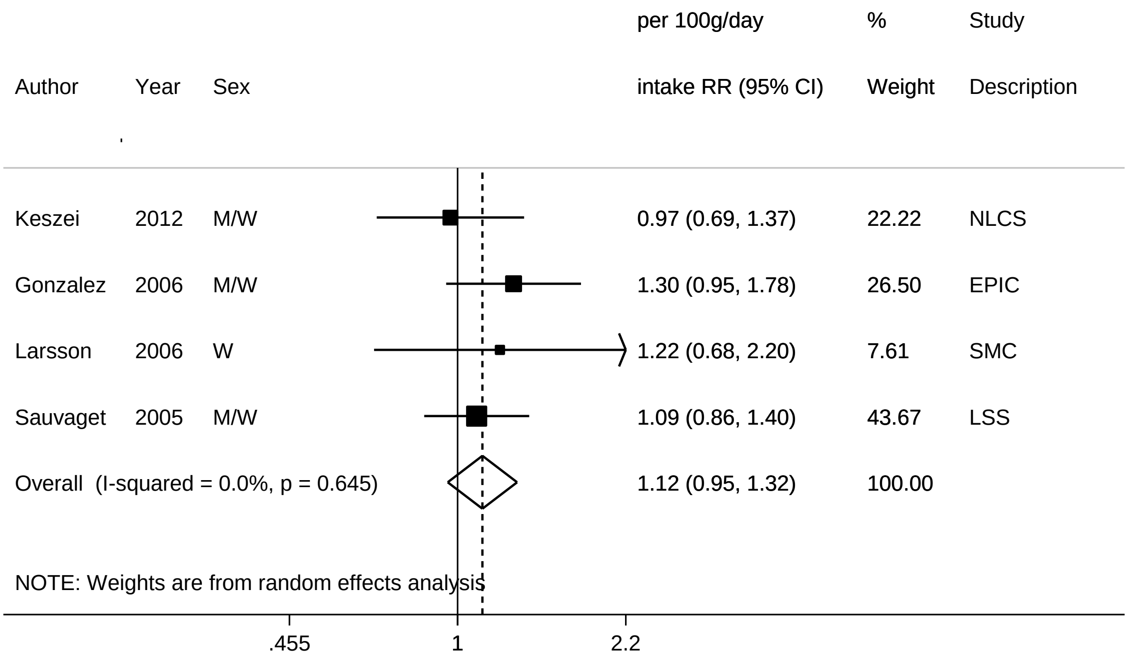


Figure 85 Relative risk of stomach cancer for 100 g/day increase of red meat intake by sex

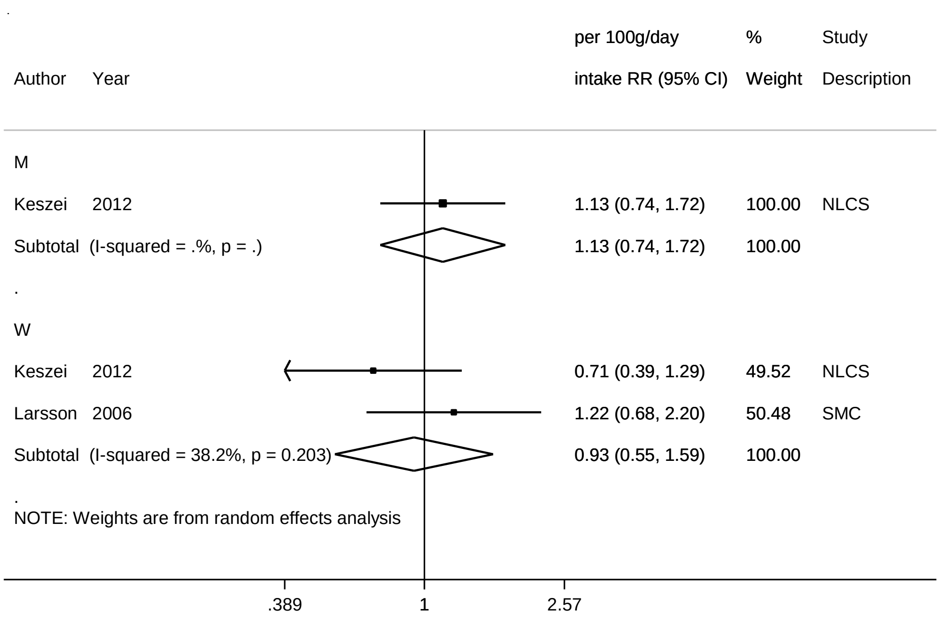
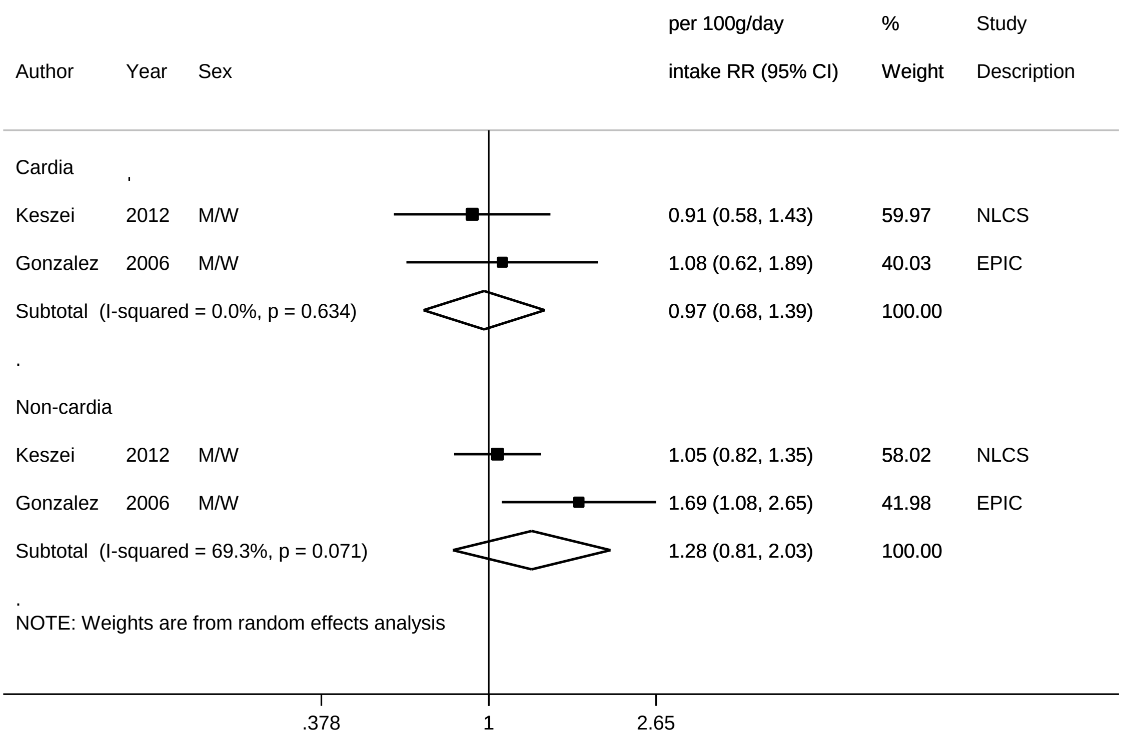


Figure 86 Relative risk of stomach cancer for 100 g/day increase of red meat intake by cancer site



2.5.1.3 Red and processed meat

One cohort study (two publications) (Cross, 2011; Cross, 2007) was identified in the CUP. The study found no association of red and processed meat with cardia and non-cardia gastric cancer.No studies were identified in the 2005 SLR.

A sensitivity analysis was conducted by combining the study on red and processed meat (Cross, 2011, 955 cases) with the studies included in the section 2.5.1.3. Red Meat (unprocessed) (Keszei, 2012; Gonzalez, 2006b; Larsson, 2006; Sauvaget, 2005).

Main results:

Red and processed meat intake was not significantly associated with stomach cancer overall (summary RR per 100g/day=1.07, 95% CI=0.92-1.23) (no heterogeneity, five studies, 3363 cases), and in other subgroups. Non-significant inverse association with gastric cardia cancer and non-significant positive association with non-cardia gastric cancer were observed.

There was no significant evidence of publication or small study bias in the limited number of studies in the analysis.

Sensitivity analyses:

The summary RRs ranged from 1.01 (95% CI=0.86-1.19) when Gonzalez, 2006b (on pork, beef, veal, and lamb) was omitted to 1.12 (95% CI=0.95-1.32) when Cross, 2011 (on red and processed meat combined) was omitted in influence analysis.

Non-linear dose-response meta-analysis:

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

Study quality:

Cross, 2011 used FFQ to assess red meat and processed meat intake. Multiple factors, except Helicobacter Pylori status, were adjusted for in the study.

Table 71 Red and processed meat intake and stomach cancer risk. Number of studies in the CUP SLR

	Number
Studies identified	1
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

*Keszei, 2012; Gonzalez, 2006b; Larsson, 2006; Sauvaget, 2005; Khan, 2004 (forest plot of highest compared with lowest exposure only) on unprocessed red meat, as reported in section 2.5.1.3 red meat, were included as a sensitivity analysis.

Table 72 Red and processed meat intake and stomach cancer risk. Summary of the linear dose-response meta-analysis in the 2005 SLR and CUP

	2005 SLR		CUP
Increment unit used	-		100 g/day
All studies			
Studies (n)	-		5
Cases (total number)	-		3363
RR (95%CI)	-		1.07 (0.92-1.23)
Heterogeneity (I^2, p-value)	-		0%, 0.47
P value Egger test	-		0.91
Stratified and sensitive analysis*			
Cancer site	**Gastric cardia cancer**		**Non-cardia gastric cancer**
Studies (n)	3 (n=711)		3 (n=1149)
RR (95%CI)	0.99 (0.80-1.23)		1.13 (0.85-1.51)
Heterogeneity (I^2, p-value)	0%, 0.89		56.8%, 0.10
Geographic location	**Asia**	**Europe**	**North America**
Studies (n)	1	3	1
RR (95%CI)	1.09 (0.86-1.40)	1.15 (0.92-1.42)	0.87 (0.63-1.20)
Heterogeneity (I^2, p-value)	-	0%, 0.45	-

Other stratified analyses*

Number of cases	**<500 cases**	**≥500 cases**
Studies (n)	2	3
RR (95%CI)	1.28 (0.97-1.69)	1.00 (0.84-1.18)
Heterogeneity (I^2, p-value)	0%, 0.85	0%, 0.54
Publication year	**<2010**	**≥2010**
Studies (n)	3	2
RR (95%CI)	1.17 (0.98-1.41)	0.91 (0.72-1.16)
Heterogeneity (I^2, p-value)	0%, 0.69	0%, 0.66
Adjustment for confounders:		
Physical activity	**Not adjusted**	**Adjusted**
Studies (n)	2	3
RR (95%CI)	1.11 (0.89-1.39)	1.03 (0.81-1.32)
Heterogeneity (I^2, p-value)	0%, 0.74	38.5%, 0.20

*All studies identified in the CUP

Table 73 Red and processed meat intake and stomach cancer risk. Results of meta-analyses and pooled analyses of prospective studies published after the 2005 SLR

Author, Year	Number of studies	Total number of cases	Studies country, area	Outcome	Comparison	RR (95%CI)	P trend	Heterogeneity (I^2, p value)
Meta-analyses								
Zhu, 2013	17 studies overall	8484	Canada, China, Denmark, France, Korea, Germany, Greece, Iran, Italy, Poland, the Netherlands, Norway Spain, Sweden, UK, USA, Uruguay	Incidence/mortality, gastric cancer	High vs low intake	1.45 (1.22-1.73)		76.4%, <0.001
	4 cohorts*	2111				1.02 (0.90-1.17)		43.4%, 0.15
	7 population-based case-control	3974				1.64 (1.17-2.28)		82.1%, <0.001
	6 hospital-based case-control	2399				1.61 (1.41-1.85)		29.5%, 0.21
	3 studies	1406		Men		1.06 (0.89-1.26)		0%, 0.56
	4 studies	765		Women		0.88 (0.71-1.08)		0%, 0.48
	5 studies	1567		Gastric cardia cancer		1.26 (1.05-1.52)		39.4%, 0.16
	5 studies	1831		Distal gastric cancer		1.26 (0.92-1.71)		74.0%, 0.004

*The four cohort studies identified, including Cross, 2011, were included in the present review.

Table 74 Red and processed meat intake and stomach cancer risk. Main characteristics of studies included in the linear dose-response meta-analysis (For other studies on unprocessed red meat, see section 2.5.1.3 red meat)

Author, Year, 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
Cross, 2011 STM80074 USA	NIH-AARP, Prospective Cohort, Age: 50-71 years, M/W, Retired	955/ 494 979 10 years	Linkage of the cohort with database to state cancer registries	Validated 124-item self-administered FFQ Red and processed meat combined	Incidence			Age, sex, tobacco smoking, BMI, ethnicity, intakes of total energy, alcohol, fruit and vegetables, and saturated fat, vigorous and physical activity at work	Distribution of person-years by exposure quintiles, exposure values using mean energy intake
		454/			Gastric cardia adenocarcinoma	64.8 vs 10 g/1000 kcal Per 10 g/1000 kcal	1.04 (0.72-1.51) 1.00 (0.95-1.04)		
		501/			Gastric non-cardia adenocarcinoma	64.8 vs 10 g/1000 kcal Per 10 g/1000 kcal	0.77 (0.56-1.06) 0.99 (0.94-1.04)		

Table 75 Red and processed meat intake and stomach 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
Cross, 2007 STM80109 USA	NIH-AARP, Prospective Cohort, Age: 50-71 years, M/W, Retired	658/ 494 036 6.8 years	Cancer registry and national death index	Validated 124-item FFQ Red and processed meat combined	Incidence, stomach cancer	62.7 vs 9.8 g/1000 kcal	1.05 (0.81-1.38)	Age, sex, smoking, BMI, educational level, marital status, race, family history of cancer, intakes of total energy, fruit and vegetables, and alcohol, vigorous physical activity	Superseded by Cross, 2011, STM80074

Figure 87 RR estimates of stomach cancer by levels of red and processed meat intake

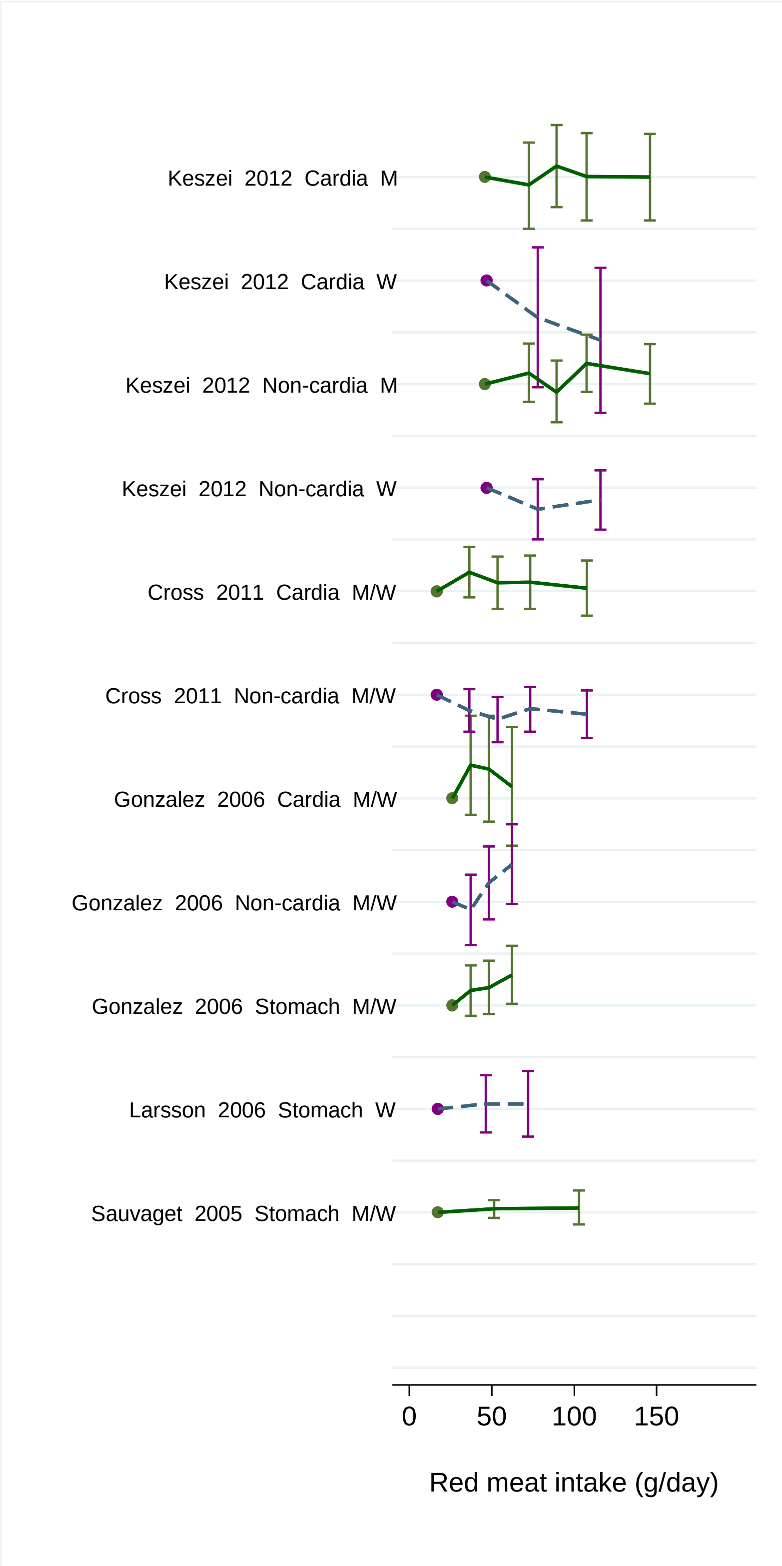


Figure 88 RR (95% CI) of stomach cancer for the highest compared with the lowest level of red and processed meat intake

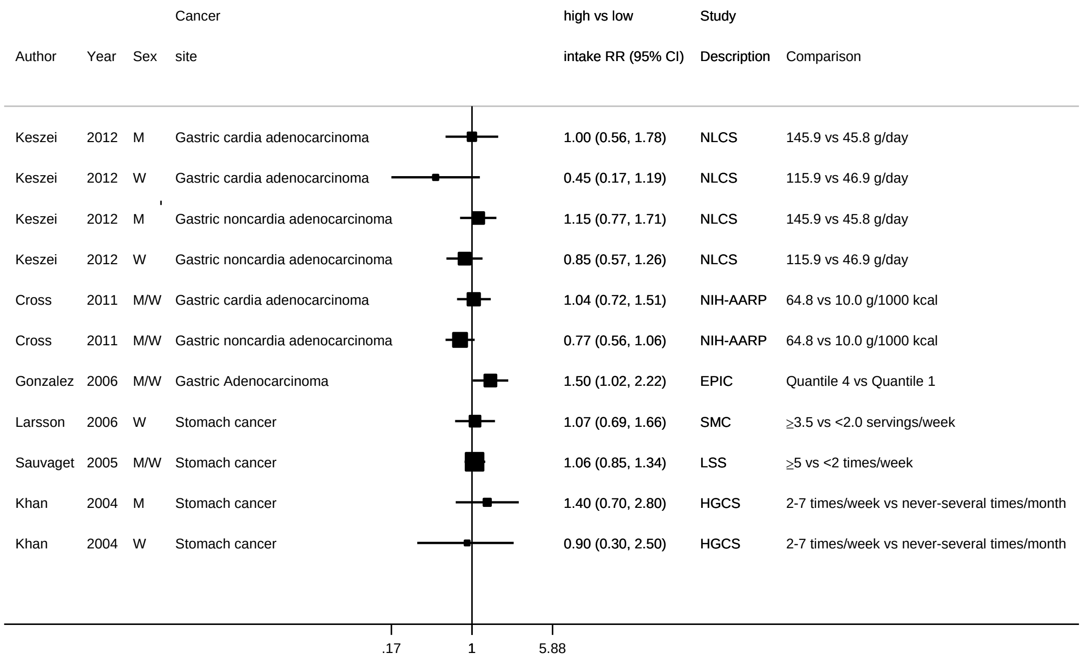


Figure 89 Relative risk of stomach cancer for 100 g/day increase of red and processed meat intake

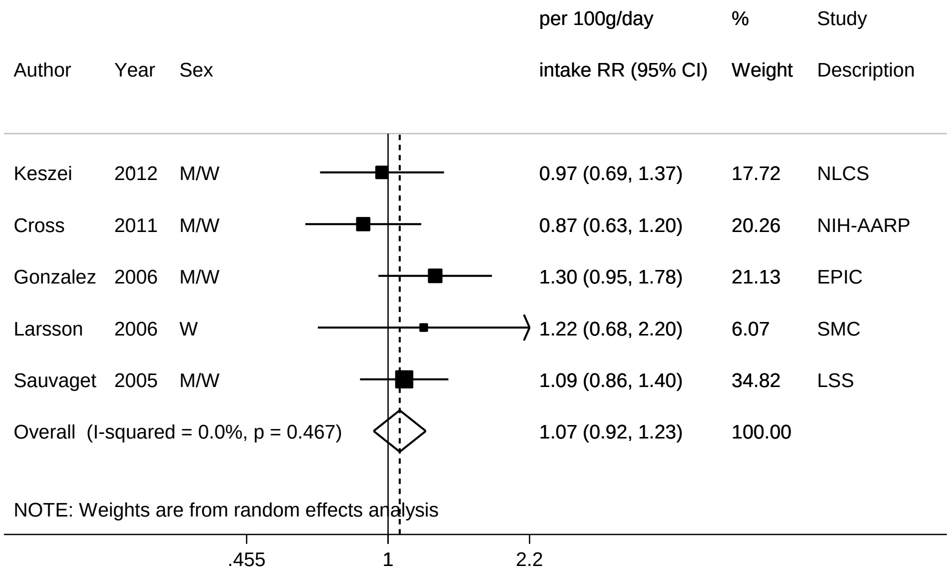
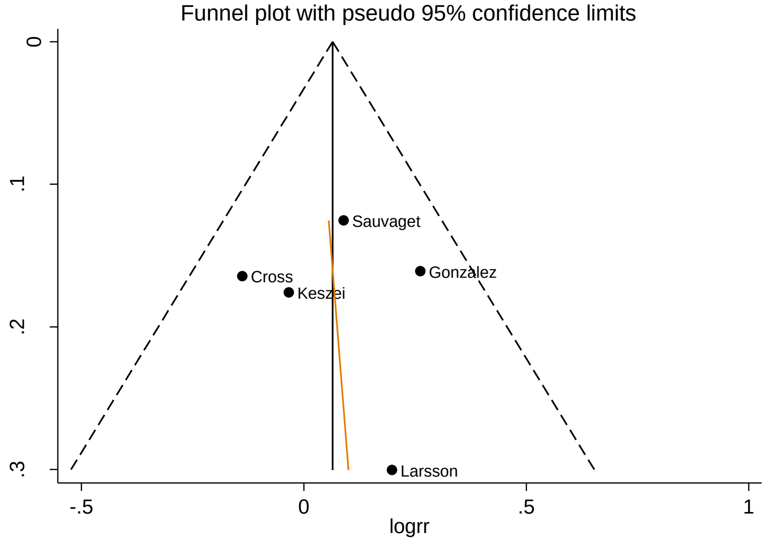


Figure 90 Funnel plot of studies included in the dose response meta-analysis of red and processed meat intake and stomach cancer



Egger's test p=0.91

Figure 91 Relative risk of stomach cancer for 100 g/day increase of red and processed meat intake by cancer site

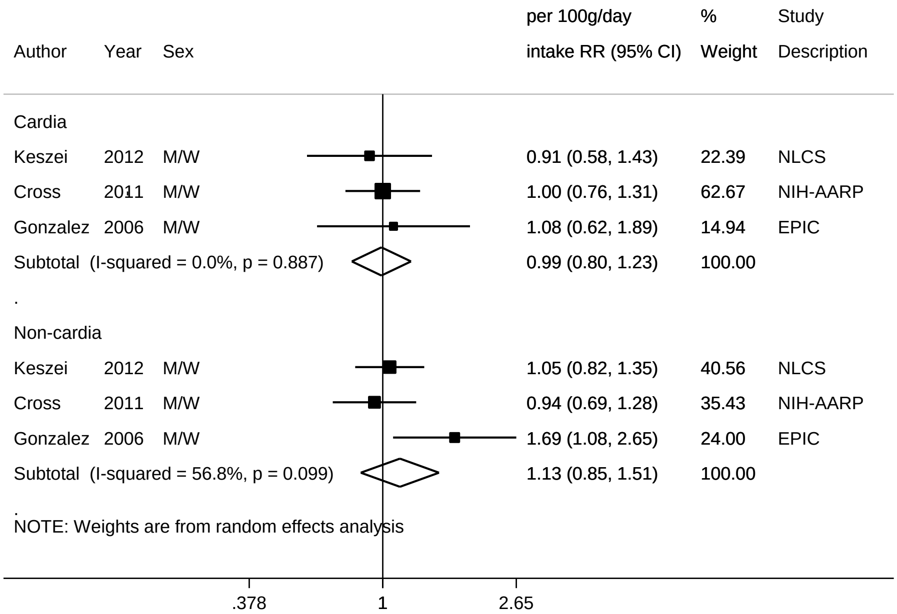
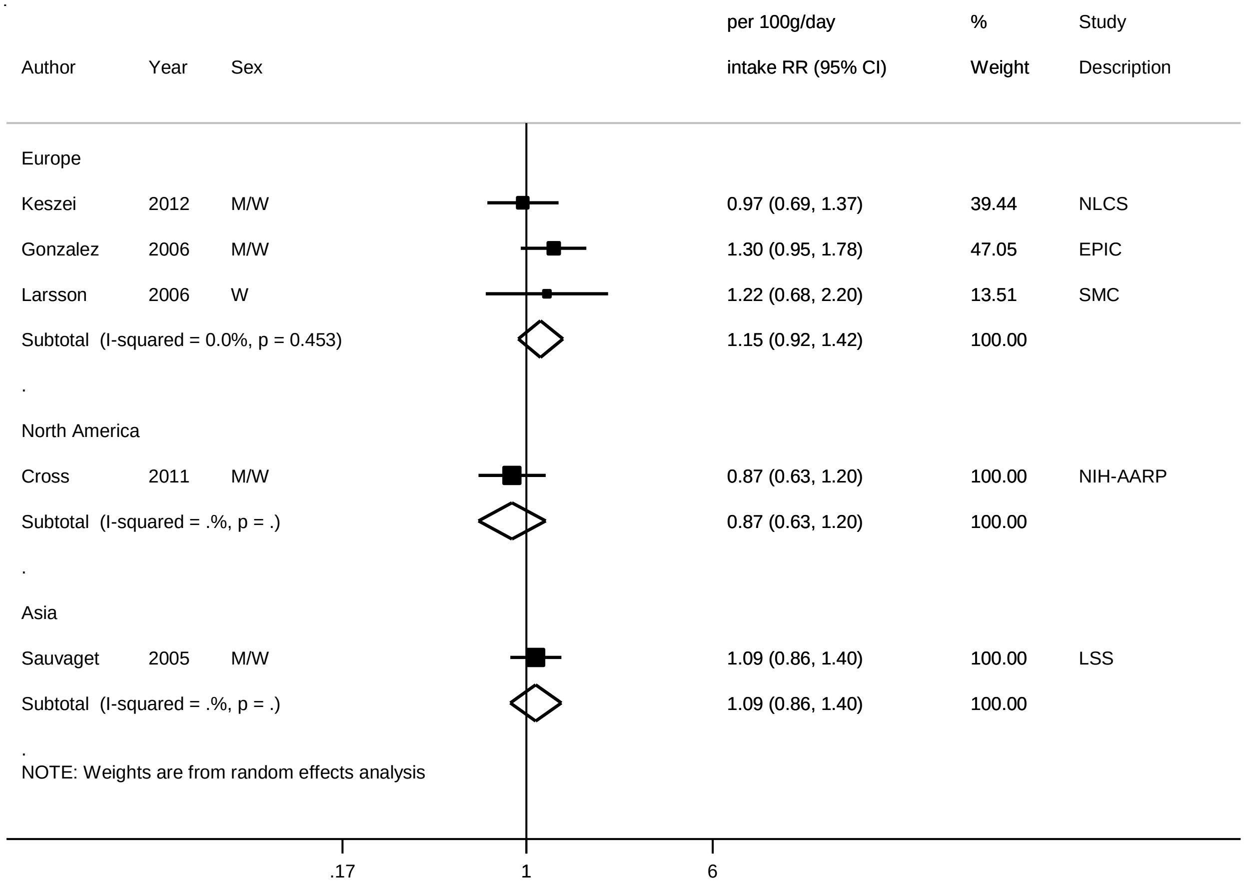


Figure 92 Relative risk of stomach cancer for 100 g/day increase of red and processed meat intake by geographic location



2.5.1.4 Poultry

Randomised controlled trials

No randomised controlled trial was identified.

Cohort studies

Summary

Main results:

Five out of six studies identified were included in the dose-response meta-analysis (3708 cases). Poultry intake was not associated with the risk of stomach cancer, gastric cardia cancer (two studies, no heterogeneity) and non-cardia gastric cancer (two studies, high heterogeneity).

The study excluded from the dose-response analysis reported non-significant inverse association (Khan, 2004).

Low heterogeneity was observed. There was no evidence of publication or small study bias.

No published meta-analysis or pooled study was identified

Sensitivity analyses:

The summary RRs ranged from 0.93 (95% CI=0.75-1.17) when Sauvaget, 2005 was omitted to 1.07 (95% CI=0.87-1.31) when Daniel, 2011 was omitted in influence analysis.

Non-linear dose-response meta-analysis:

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

Study quality:

Sauvaget, 2005 was a cohort of atomic bomb survivors (LSS). Iso, 2007 was a mortality study. All studies used FFQ to assess poultry intake. Three studies (Iso, 2007; Sauvaget, 2005; Khan, 2004) assessed chicken only.

Studies included in the dose-response analysis were adjusted for multiple confounders, apart from Iso, 2007 in which only age, sex, and study centre were adjusted. Daniel, 2011 and Gonzalez, 2006b further mutually adjusted for other types of meat. Non-significant associations with stomach cancer in analyses stratified by Helicobacter pylori status were observed in Gonzalez, 2006b.

Table 76 Poultry intake and stomach 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	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

Table 77 Poultry intake and stomach cancer risk. Summary of the linear dose-response meta-analysis in the 2005 SLR and CUP

	2005 SLR	**CUP**
Increment unit used	10 g/day	100 g/day
All studies		
Studies (n)	2	5
Cases (total number)	381	3708
RR (95%CI)	0.97 (0.90-1.06)	0.98 (0.82-1.17)
Heterogeneity (I^2, p-value)	0%, 0.9	13.8%, 0.33
P value Egger test	0.7	0.46
Stratified analysis*		
	Gastric cardia cancer	**Non-cardia gastric cancer**
Studies (n)	2	2
Cases	512	669
RR (95%CI)	1.09 (0.79 -1.51)	0.88 (0.47-1.68)
Heterogeneity (I^2, p-value)	0%, 0.38	63.9%, 0.10

*No stratified analysis in the 2005 SLR

Table 78 Poultry intake and stomach 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
Daniel, 2011 STM80058 USA	NIH-AARP, Prospective Cohort, Age: 50-71 years, M/W, Retired	928/ 492 186 9.1 years 418/	Linkage of the cohort with database to state cancer registries	Validated FFQ	Incidence, cardia cancer	51.2 vs 5.3 g/1000kcal	1.00 (0.73-1.36) Ptrend: 0.37	Age, sex, BMI, family history of cancer, marital status, race, red meat intake, smoking status, alcohol intake, education, fish intake, frequency of vigorous physical activity, fruit and vegetable intake, menopausal hormone therapy use, total energy intake	Exposure values using mean energy intake, distributions of cases and person-years by exposure quintiles, Hamling's method was used to calculate RRs for cardia and non-cardia gastric cancers combined
		510/			Non-cardia cancer		0.80 (0.59-1.07) Ptrend: 0.10		
Iso, 2007 STM80144 Japan	JACC, Prospective Cohort, Age: 40-79 years, M/W	1023/ 105 500 15 years 686/	Municipal resident registration records, death certificates	Validated FFQ Chicken	Mortality, stomach cancer Men	≥3-4 vs <1 times/week	1.06 (0.84-1.33)	Age, area of study	Exposure values using standard portion size of 120 g, mid-points of exposure categories, RRs for men and women combined using fixed model
		337/			Women		0.94 (0.68-1.30)		
González, 2006 STM44432	EPIC, Prospective Cohort,	330/ 465 586 6.5 years	Cancer registries, health insurance records,	FFQ, dietary questionnaires, food record	Incidence, gastric adenocarcinoma	Per 10 g/day Quantile 4 (Men: 29-690	1.01 (0.96-1.07) 1.47 (1.04-2.10) Ptrend: 0.04	Age, sex, centre, cigarette smoking, citrus	Rescaled the RR for the increment unit used

Author, Year, 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
Denmark,France,Germany,Greece,Italy,Netherlands,Norway,Spain,Sweden,UK	Age: 35-70 years, M/W	94/	pathology rec, active follow up, death certificate		Gastric cardia adenocarcinoma	g/day; Women: 26-690 g/day) vs quantile 1 (Men: 0-7 g/day; Women: 0-5 g/day)	0.96 (0.86-1.08) 1.57 (0.80-3.09) Ptrend: 0.16	fruit intake, energy intake, height, leisure - physical activity, red meat intake, vegetable intake, weight, work - physical activity, alcohol intake, education, other fruits intake, processed meat intake, tobacco use	
		159/			Gastric non-cardia adenocarcinoma		1.03 (0.96-1.11) 1.65 (1.00-2.74) Ptrend: 0.03		
		109/			Intestinal gastric cancer		1.03 (0.93-1.13) 1.46 (0.81-2.62) Ptrend: 0.21		
		116/			Diffuse gastric cancer		1.05 (0.97-1.14) 1.87 (1.05-3.33) Ptrend: 0.03		
		201/			H. pylori positive Gastric adenocarcinoma	Per 10 g/day	1.07 (0.84-1.36)		
		47/			H. pylori positive Gastric cardia adenocarcinoma		0.75 (0.46-1.22)		
		113/			H. pylori positive Non-cardia gastric adenocarcinoma		1.13 (0.80-1.60)		
		40/			H. pylori negative Gastric adenocarcinoma	Per 10 g/day	1.05 (0.56-1.98)		

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Missing data derived for analyses
		22/			H.pylori negative Gastric cardia adenocarcinoma		1.22 (0.55-2.70)		
		12/			H. pylori negative Non-cardia gastric adenocarcinoma		1.76 (0.34-9.19)		
Larsson, 2006b STM80079 Sweden	SMC, Prospective Cohort, W	156/ 61 433 18 years	Linkage of the cohort with national Swedish cancer registry and regional cancer registry	Validated FFQ	Incidence, stomach cancer	Per 10 g/day ≥0.5 vs <0.2 servings/week	0.79 (0.60-1.05) 0.58 (0.31-1.09) Ptrend: 0.12	Age, BMI, education level, alcohol intake, fruit and vegetable intake, total energy intake	
Sauvaget, 2005 STM44428 Japan	LSS, Prospective Cohort, Age: 34-98 years, M/W, Atomic bomb survivors	1 270/ 38 540 19 years	Cancer registry	FFQ Chicken	Incidence, stomach cancer	≥5 vs <2 times/week	1.37 (0.95-1.97) Ptrend: 0.24	Age, sex, area of residence, educational level, radiation exposure, smoking habits	Exposure values using standard portion size, mid-points of exposure categories

Table 79 Poultry intake and stomach 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
Tokui, 2005 STM80105 Japan	JACC, Prospective Cohort, Age: 40-79 years, M/W	859/ 110 792 12 years	Population registry	FFQ Chicken	Mortality, stomach cancer	≥1 times/day vs none		Age	Superseded by Iso, 2007, STM80144
		425/			Men		0.73 (0.39-1.37) Ptrend: 0.98		
		213/			Women		1.33 (0.55-3.17) Ptrend: 0.33		
Khan, 2004 STM20239 Japan	HGCS, Prospective Cohort, Age: 40- years, M/W	51/ 3158 14 years	Follow-up surveys	FFQ Chicken	Mortality, stomach cancer	2-7 times/week vs never-several times/month			Excluded, only two intake categories
		36/ 1524			Men		0.90 (0.50-1.90)	Age, smoking habits	
		15/ 1634			Women		0.90 (0.30-2.70)	Age, health education, health screening, health status, smoking habits	

Figure 93 RR estimates of stomach cancer by levels of poultry intake

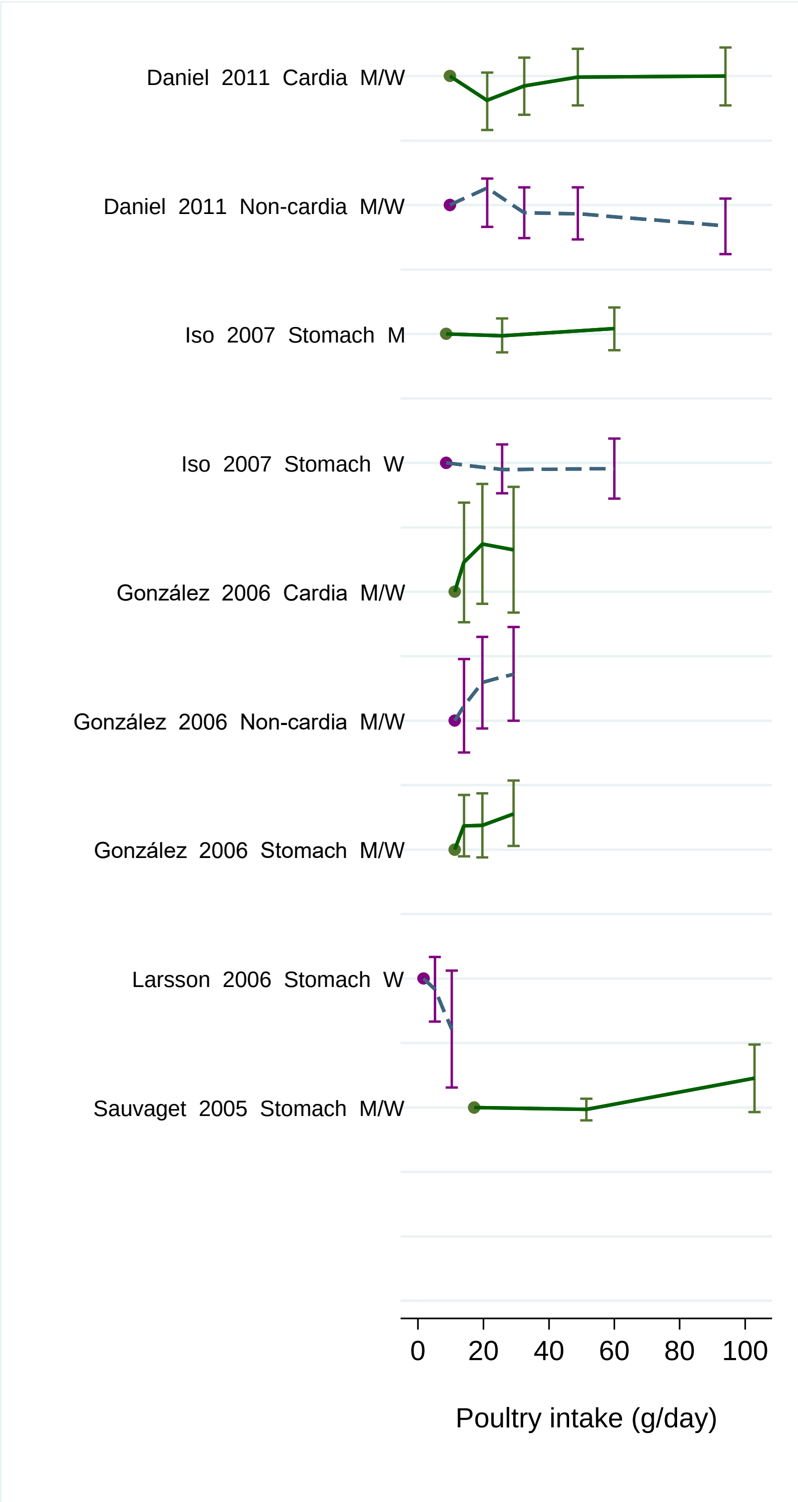


Figure 94 RR (95% CI) of stomach cancer for the highest compared with the lowest level of poultry intake

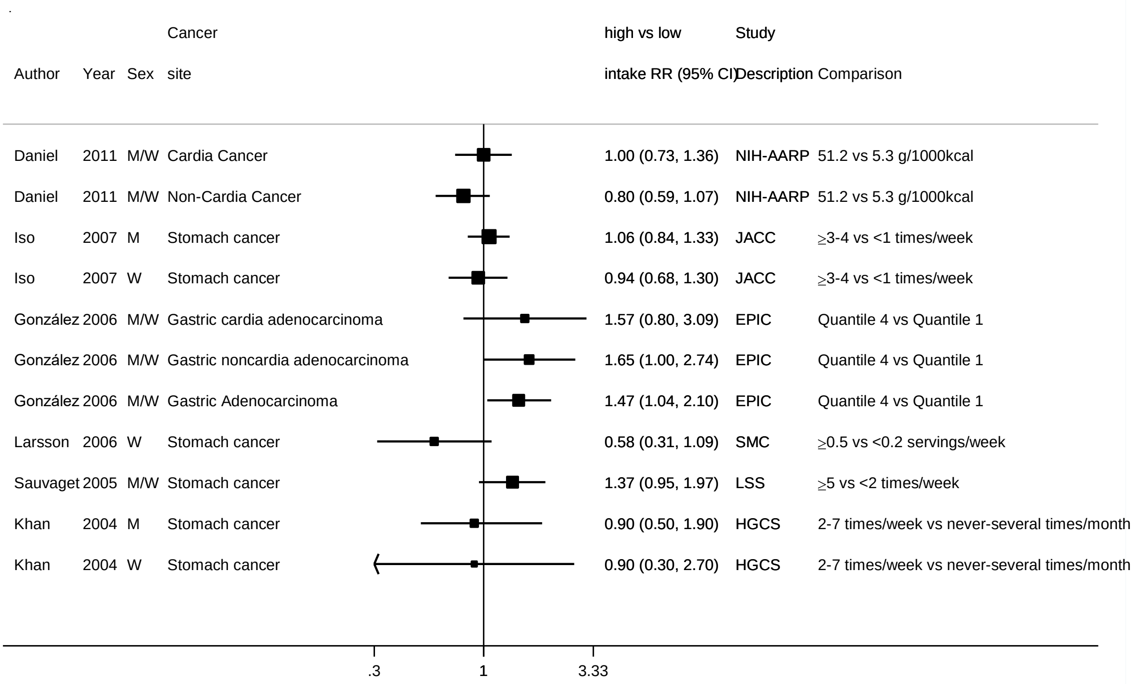


Figure 95 Relative risk of stomach cancer for 100 g/day increase of poultry intake

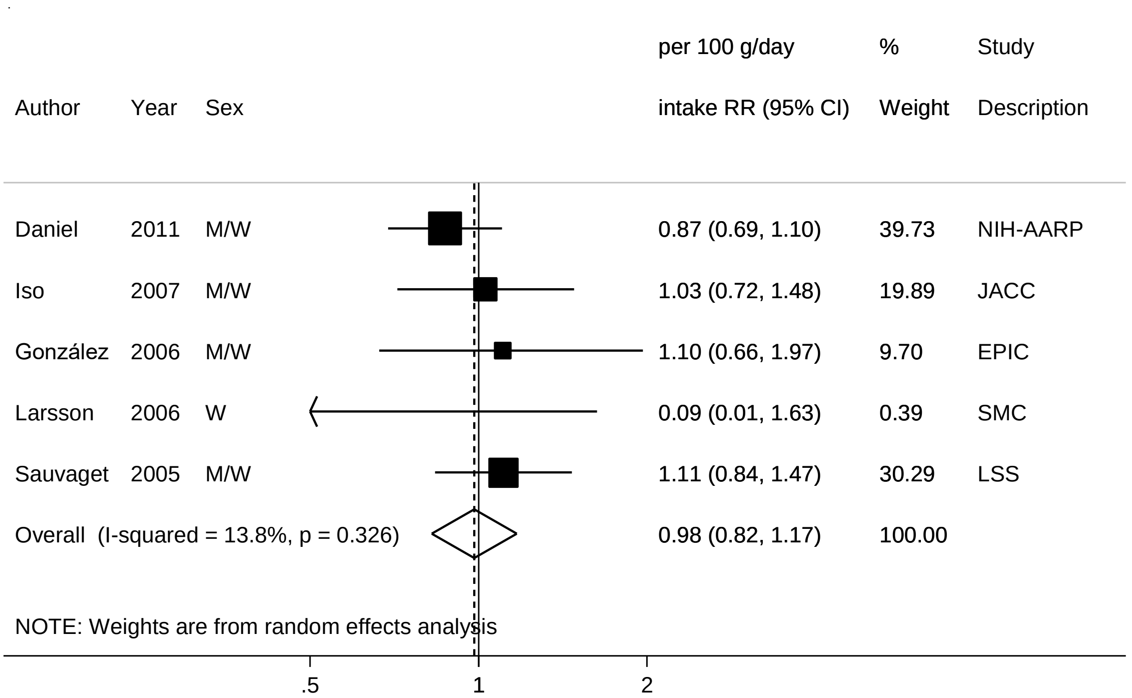
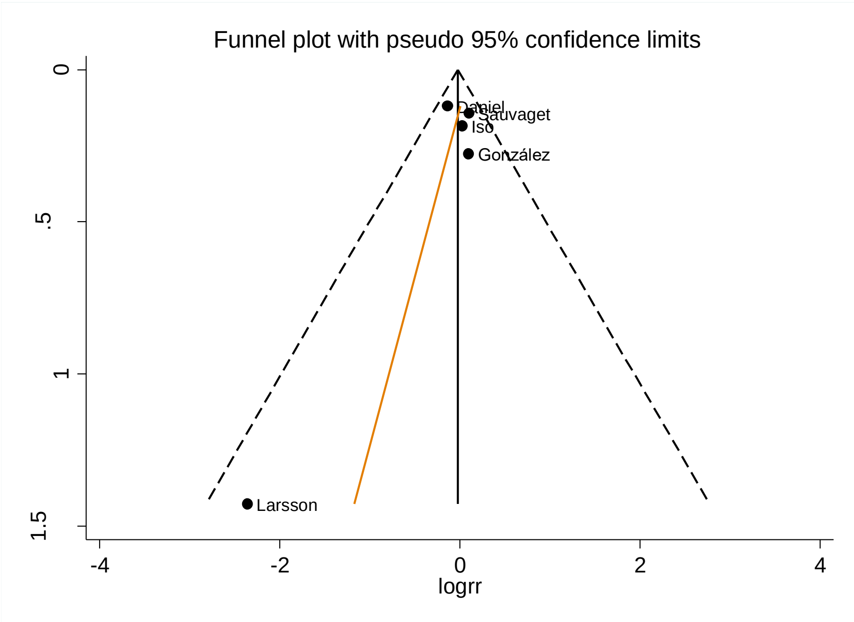
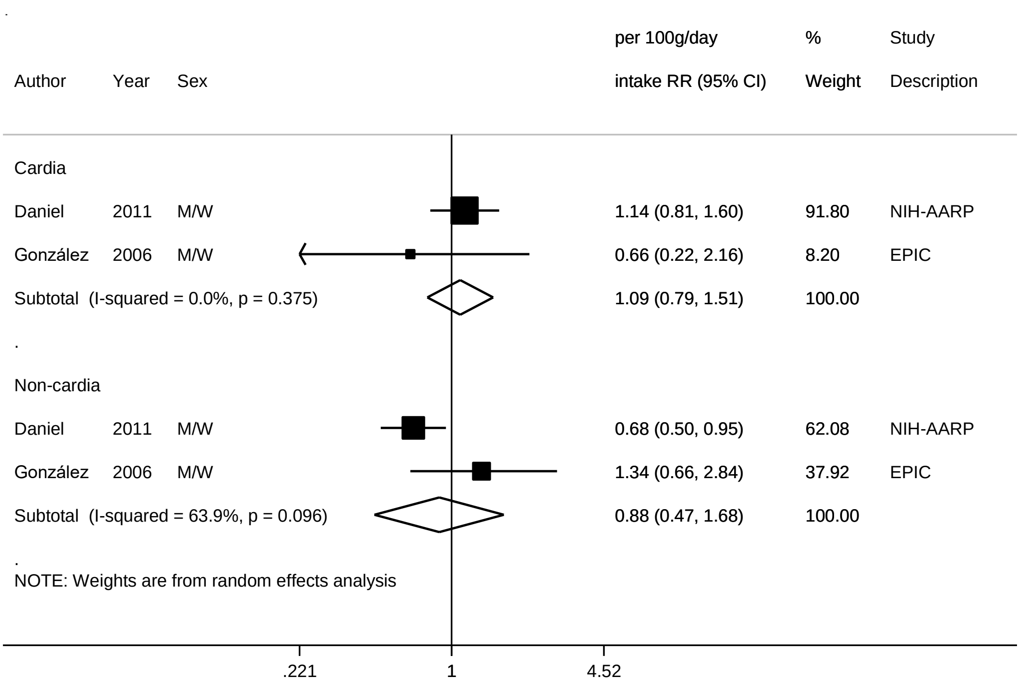


Figure 96 Funnel plot of studies included in the dose response meta-analysis of poultry intake and stomach cancer



Egger's test p=0.46

Figure 97 Relative risk of stomach cancer for 100 g/day increase of poultry intake, by cancer site



2.5.2 Fish

Randomised controlled trials

No randomised controlled trial was identified.

Cohort studies

Summary

Main results:

Eight studies (2700 cases) were included in the dose-response meta-analysis out of twelve identified studies. No significant association of fish consumption was observed for stomach cancer and in subgroup analyses.

Four studies were excluded from the dose-response analysis. Three studies observed non-significant associations (Sauvaget, 2005; Khan, 2004; Knekt, 1999); two were studies on fish cooked in specific ways (Sauvaget, 2005; Khan, 2004). The remaining study observed a borderline significant inverse association (Hirayama, 1990).

No heterogeneity was observed. There was no significant evidence of publication or small study bias.

Sensitivity analyses:

The summary RR did not change materially when studies were omitted in turn in influence analysis.

Non-linear dose-response meta-analysis:

Non-linear dose-response analysis was not conducted due to not enough studies with sufficient data.

Study quality:

The study on cancer mortality by Kneller, 1991 on American people of mainly Scandinavian descent had 23% participants lost after 20 years of follow-up. There were 74 deaths for stomach cancer identified among 17 633 subjects. Ko, 2013 included both incidence and mortality cases, but only eight cases were identified from the death certificates.

All studies used FFQ to assess fish intake, apart from Nomura, 1990 that used a 24-hour dietary recall questionnaire. In Kneller, 1991 the uppermost category of fish intake (fresh or frozen) was lower (≥3 times/month) than in the other studies. The studies by Nomura, 1990 and Kneller, 1991 had little influence in the summary RR as shown in the sensitivity analysis. Studies included in the meta-analysis were adjusted or stratified for age and sex. Only one study (Daniel, 2011) was adjusted for ethnicity or physical activity, and two (Daniel, 2011; Larsson, 2006) for total energy intake. Results were similar between studies. No studies were adjusted for Helicobacter pylori status. The summary RRs were similar in the stratified meta-analyses by other adjustments.

Table 80 Fish intake and stomach cancer risk. Number of studies in the CUP SLR

	Number
Studies identified	12 (16 publications)
Studies included in forest plot of highest compared with lowest exposure	10
Studies included in linear dose-response meta-analysis	8
Studies included in non-linear dose-response meta-analysis	Not enough studies

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

Table 81 Fish intake and stomach cancer risk. Summary of the linear dose-response meta-analysis in the 2005 SLR and CUP

	2005 SLR	**CUP**	
Increment unit used	20 g/day	25 g/day	
All studies			
Studies (n)	5	8	
Cases (total number)	382	2700	
RR (95%CI)	0.99 (0.97-1.00)	1.03 (0.98-1.07)	
Heterogeneity (I^2, p-value)	0%, 0.5	0%, 0.98	
P value Egger test	0.06	0.17	
Men			
Studies (n)	4	4	
Cases	332	1027	
RR (95%CI)	1.06 (0.99-1.13)	1.02 (0.96-1.07)	
Heterogeneity (I^2, p-value)	-	0%, 0.70	
Women			
Studies (n)	2	3	
Cases	50	541	
RR (95%CI)	0.96 (0.82-1.12)	1.03 (0.94-1.14)	
Heterogeneity (I^2, p-value)	-	14.5%, 0.31	
Stratified and sensitivity analyses. CUP			
Outcome	**Incidence**	**Mortality**	**Incidence and mortality**
Studies (n)	3	4	1
Cases	1234	1301	165

RR (95%CI)	1.07 (0.97-1.19)	1.02 (0.96-1.07)	1.03 (0.91-1.17)
Heterogeneity (I^2, p-value)	0 %, 1.00	0%, 0.86	-
Geographic area	**North America***	**Europe**	**Asia**
Studies (n)	3	1	4
Cases	1152	156	1392
RR (95%CI)	1.07 (0.95-1.20)	1.08 (0.89-1.31)	1.02 (0.97-1.07)
Heterogeneity (I^2, p-value)	0%, 0.99	-	0%, 0.85
Duration of follow-up	5-<10 years	10-<15 years	≥15 years
Studies (n)	3	1	4
RR (95%CI)	1.05 (0.95-1.16)	0.99 (0.85-1.16)	1.03 (0.97-1.08)
Heterogeneity (I^2, p- value)	0%, 0.82	-	0%, 0.85
Publication year	**<2000**	**2000-<2010**	**≥2010**
Studies (n)	3	3	2
RR (95%CI)	1.08 (0.96-1.22)	1.02 (0.96-1.07)	1.04 (0.93-1.16)
Heterogeneity (I^2, p-value)	0%, 0.93	0%, 0.80	0%, 0.82
Adjustment for: confounders			
Socioeconomic status	**Not adjusted**	**Adjusted**	
Studies (n)	5	3	
RR (95%CI)	1.02 (0.97-1.07)	1.05 (0.95-1.15)	
Heterogeneity (I^2, p-value)	0%, 0.87	0%, 0.92	
Smoking			
Studies (n)	4	4	
RR (95%CI)	1.03 (0.98-1.08)	1.02 (0.93-1.12)	
Heterogeneity (I^2, p-value)	0%, 0.73	0%, 0.96	
Alcohol intake			
Studies (n)	5	3	
RR (95%CI)	1.02 (0.97-1.07)	1.05 (0.95-1.15)	
Heterogeneity (I^2, p-value)	0%, 0.87	0%, 0.92	
BMI			
Studies (n)	5	3	
RR (95%CI)	1.02 (0.97-1.07)	1.05 (0.95-1.15)	
Heterogeneity (I^2, p-value)	0%, 0.87	0%, 0.92	

* One study in North America was in Japanese residents in Hawaii (Nomura, 1990).

Table 82 Fish intake and stomach cancer risk. Results of meta-analyses and pooled analyses of prospective studies published after the 2005 SLR

Author, Year	Number of studies	Total number of cases	Studies country, area	Outcome	Comparison	RR (95%CI)	P trend	Heterogeneity (I^2, p value)
Meta-analyses								
Wu, 2011	17 studies overall	5323	Brazil, Canada, China, France, India, Italy, Iran, Japan, Mexico, Sweden, Uruguay	Incidence/mortality, Gastric cancer	High vs low	0.87 (0.71-1.07)		73.3%, <0.001
	2 cohorts*					1.11 (0.77-1.62)		0%, 0.79
	8 population-based case-control studies					0.87 (0.60-1.27)		82.1%, <0.001
	7 hospital-based case-control studies					0.82 (0.63-1.05)		56.3%, 0.033

*Both cohort studies identified were included in the present review

Table 83 Fish intake and stomach 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
Ko, 2013 STM80184 Korea	KMCC, Prospective Cohort, Age: 30-90 years, M/W	165/ 9724 8.5 years	Cancer registry and death certificates	14-item self-administered FFQ	Incidence and mortality, stomach cancer	≥1 time/day vs almost never	1.46 (0.65-3.28)	Age, sex, area of residence, BMI, cigarette smoking, alcohol drinking	Exposure values using standard portion size, mid-points of exposure categories
		115/			Men	High vs low	0.96 (0.84-1.09)		
		50/			Women		1.02 (0.82-1.26)		
Daniel, 2011 STM80058 USA	NIH-AARP, Prospective Cohort, Age: 50-71 years, M/W, Retired	928/ 492 186 9.1 years 418/ 510/	Linkage of the cohort with database to state cancer registries	Validated 124-item FFQ	Incidence Cardia cancer Non-cardia cancer	21.4 vs 3.6 g/1000kcal	0.98 (0.71-1.35) 1.11 (0.84-1.48)	Age, sex, BMI, family history of cancer, marital status, race, red meat intake, smoking status, alcohol intake, education, frequency of vigorous physical activity, fruit and vegetable intake, menopausal hormone therapy use, poultry intake, total energy intake	Exposure values using mean energy intake, distributions of cases and person-years by exposure quintiles, RRs for gastric cardia cancer and gastric non-cardia cancer combined using Hamling's method
Iso, 2007 STM80144 Japan	JACC, Prospective Cohort, Age: 40-79 years,	1081/ 105 500 15 years 731/	Municipal resident registration records, death certificates	Validated FFQ	Mortality, stomach cancer Men	≥5 vs <3 times/week	0.97 (0.80-1.18)	Age, area of study	Exposure values using standard portion size, mid-points of exposure

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Missing data derived for analyses
	M/W	43 918 350/ 59 796			 Women		1.17 (0.88-1.55)		categories, RRs for men and women combined using fixed model
Larsson, 2006b STM80079 Sweden	SMC, Prospective Cohort, W	156/ 61 433 18 years	Linkage of the cohort with national Swedish cancer registry and regional cancer registry	Validated 67-item FFQ	Incidence, stomach cancer	≥2.0 vs <1.2 servings/week Per 10 g/day	1.14 (0.75-1.72) 1.03 (0.95-1.11)	Age, BMI, education level, alcohol intake, fruit and vegetable intake, total energy intake	
Ngoan, 2002 STM01668 Japan	FPC, Prospective Cohort, Age: 15-96 years, M/W	107/ 13 250 13 years	Resident registry	Self-administered FFQ	Mortality, stomach cancer	≥1 time/day vs 2-4 times/month	1.00 (0.40-2.20)	Age, sex, fat intake, Japanese soup, liver, pickled foods, processed meat, smoking habits	Exposure values using standard portion size, mid-points of exposure categories
		72/ 5631 35/ 6841			Men Women		1.50 (0.70-3.10) 0.60 (0.20-1.70)	Age	
Kato, 1992b STM06734 Japan	Higashi-Kamo Cohort, Prospective Cohort, Age: 30-80 years, M/W	39/ 9753 6 years	Cancer registry/ hospital records	25-item FFQ	Mortality, stomach cancer	Daily vs ≤1-2 times/week	1.21 (0.36-4.11)	Age, sex	Exposure values using standard portion size, mid-points of exposure categories
Kneller, 1991	LBS,	74/	Health insurance	35-item FFQ	Mortality,	≥3 vs <1	1.10 (0.55-2.08)	Age, smoking	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
STM07350 USA	Prospective Cohort, Age: 35- years, M, Mainly of Scandinavian descent	17 633 20 years	company records		stomach cancer	times/month		habits	using standard portion size, mid-points of exposure categories
Nomura, 1990 STM14814 USA	HHP, Prospective Cohort, Age: 45- years, M, Japanese residents of Hawaii	150/ 7990 19 years	Cancer registry/ hospital records	20-item FFQ, 24- hour dietary recall	Incidence, stomach cancer	≥5 vs ≤1 times/week	0.90 (0.50-1.80)	Age	Exposure values using standard portion size, mid-points of exposure categories

Table 84 Fish intake and stomach 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, Retired	954/ 494 968 9.7 years	Cancer registry, death master file, national death index plus, postal service database	Validated FFQ, 124-item	Incidence, stomach cancer	aMED scoring criteria ≥0.60 vs <0.60oz		Age, sex, BMI, race, education, modified total score, smoking, total energy intake, usual activity throughout the day, vigorous physical activity	Excluded, exposure was meeting dietary index criteria or not (same study as Daniel, 2011, STM80058)
		453/			Gastric cardia adenocarcinoma		1.03 (0.85-1.24)		
		501/			Gastric non-cardia		1.15 (0.96-1.38)		

Author, Year, 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
					adenocarcinoma				
Sauvaget, 2005 STM44428 Japan	LSS, Prospective Cohort, Age: 34-98 years, M/W, Atomic bomb survivors	1270/ 38 540 19 years	Cancer registry	22-item FFQ	Incidence, stomach cancer	Broiled fish Fish except broiled ≥5 vs <2 times/week	0.84 (0.55-1.29) 1.16 (0.97-1.39)	Age, sex, area of residence, educational level, radiation exposure, smoking habits	Excluded, specific results on fish cooked in different ways
Tokui, 2005 STM80105 Japan	JACC, Prospective Cohort, Age: 40-79 years, M/W	859/ 44 930 12 years 479/ 238/	Population registry	33-item FFQ	Mortality, stomach cancer Men Women	≥1 time/day vs 1-2 times/month or less	 0.95 (0.68-1.33) 1.41 (0.82-2.45)	Age	Superseded by Iso, 2007, STM80144
Khan, 2004 STM20239 Japan	HGCS, Prospective Cohort, Age: 40- years, M/W	51/ 3158 14 years 36/1524 15/1634	Follow-up surveys	37-item FFQ	Mortality, stomach cancer Men Women	Baked fish Raw fish Boiled fish 2-7 times/week vs never-several times/month	1.00 (0.50-2.40) 1.60 (0.80-3.14) 1.40 (0.70-2.80) 1.60 (0.40-7.00) 2.00 (0.70-5.80) 3.00 (0.80-10.50)	Age, smoking habits Age, health education, health screening, health status, smoking habits	Excluded, specific results on fish cooked in different ways
Knekt, 1999 STM03959	FMCHES, Prospective	68/ 9985	Cancer registry	Dietary history interview	Incidence, stomach cancer	Quantile 4 vs quantile 1	0.93 (0.43-2.00)	Age, sex, energy intake,	Excluded, exposure not

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Reasons for exclusion
Finland	Cohort, Age: 15-99 years, M/W	21 years						geographical area, smoking habits	quantified
Hirayama, 1990 STM00028 Japan	Six Prefecture Cohort, Japan, Prospective Cohort, Age: 40- years, M/W	/ 265 118 17 years	Annual residence survey/death certificate	Questionnaire (general)	Mortality, stomach cancer	Daily vs <daily	0.95 (0.91-1.00)	Age, sex	Excluded, only two intake categories
Hirayama, 1989 STM00027 Japan	Six Prefecture Cohort, Japan, Prospective Cohort, Age: 40- years, M/W	/ 265 118 17 years	Annual residence survey/death certificate	Questionnaire (general)	Mortality, stomach cancer	Daily vs <daily	0.95	Age, sex	Superseded by Hirayama, 1990, STM00028
Hirayama, 1984 STM08768 Japan	Six Prefecture Cohort, Japan, Prospective Cohort, Age: 40- years, M/W	/ 265 118 16 years	Annual residence survey/death certificate	Questionnaire (general)	Mortality, stomach cancer	Daily vs <daily	0.98		Superseded by Hirayama, 1990, STM00028

Figure 98 RR estimates of stomach cancer by levels of fish intake

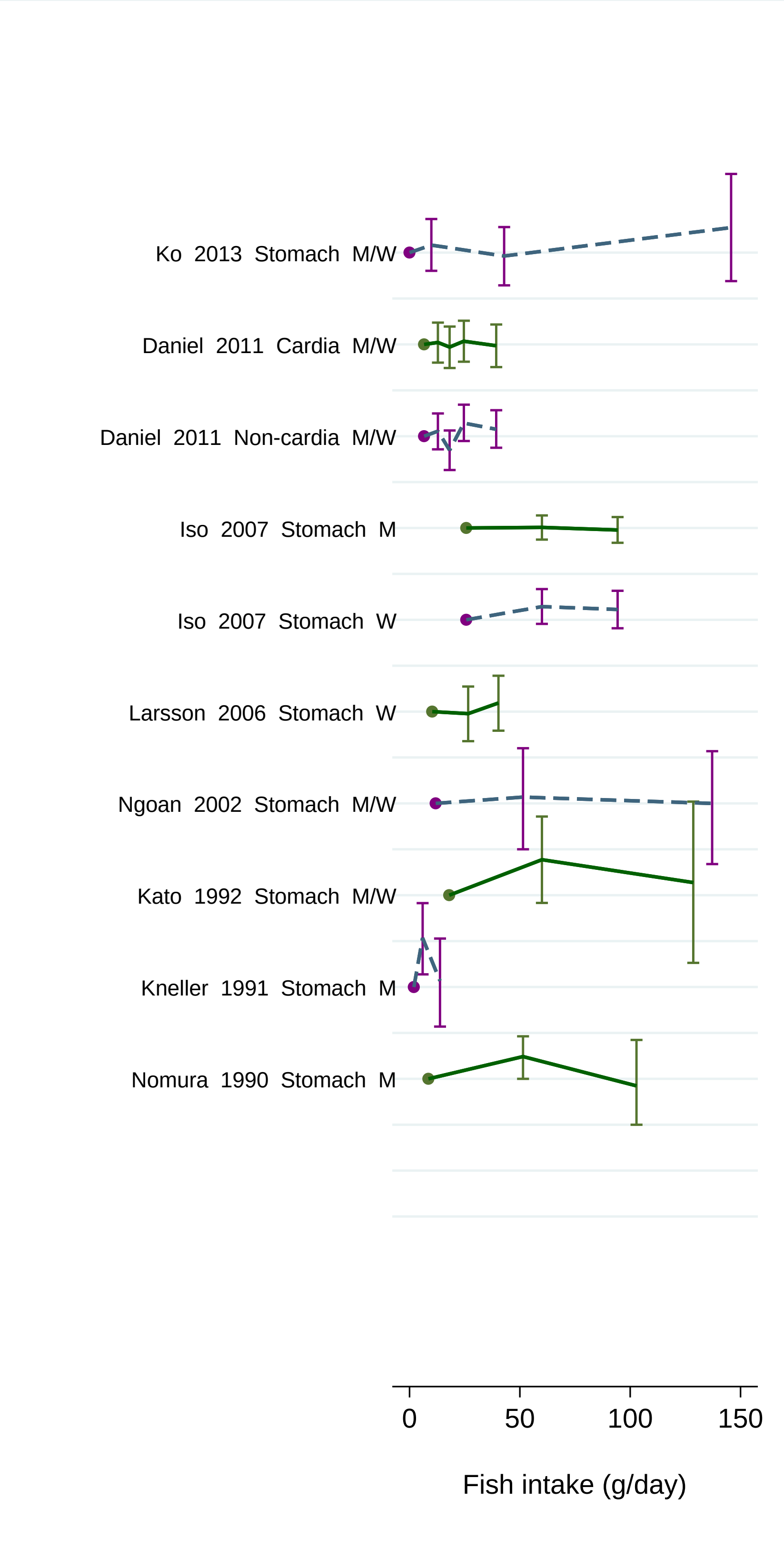


Figure 99 RR (95% CI) of stomach cancer for the highest compared with the lowest level of fish intake

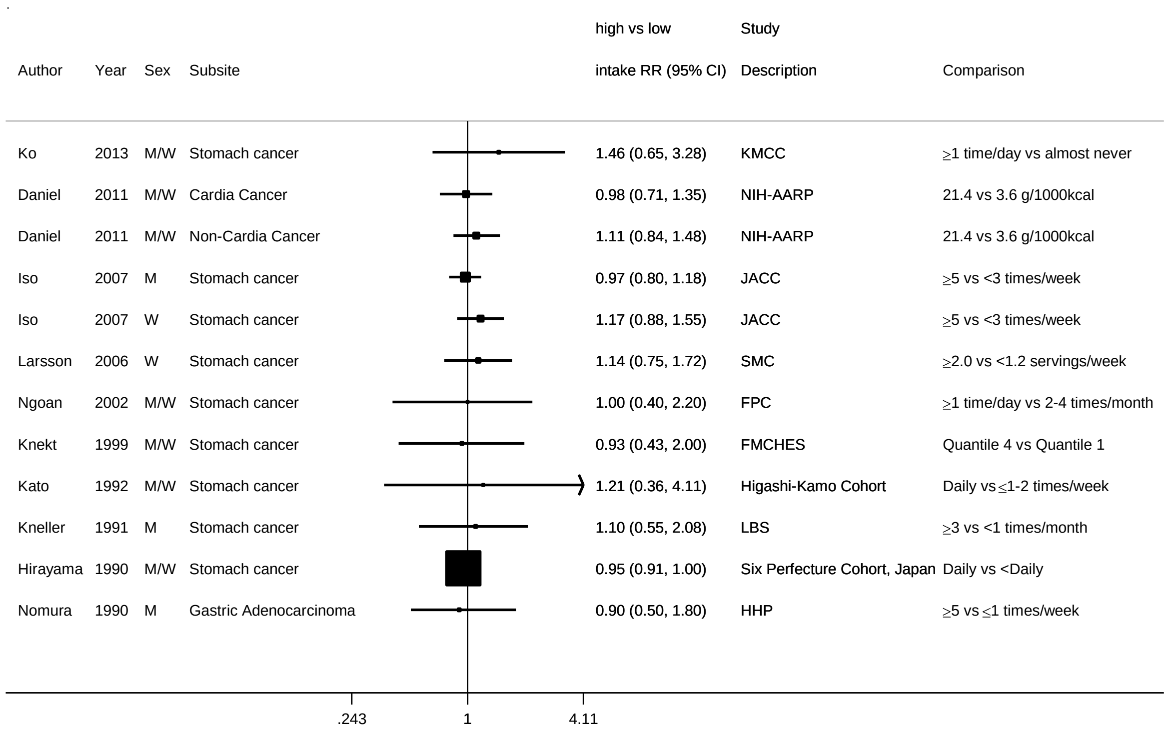


Figure 100 Relative risk of stomach cancer for 25 g/day increase of fish intake

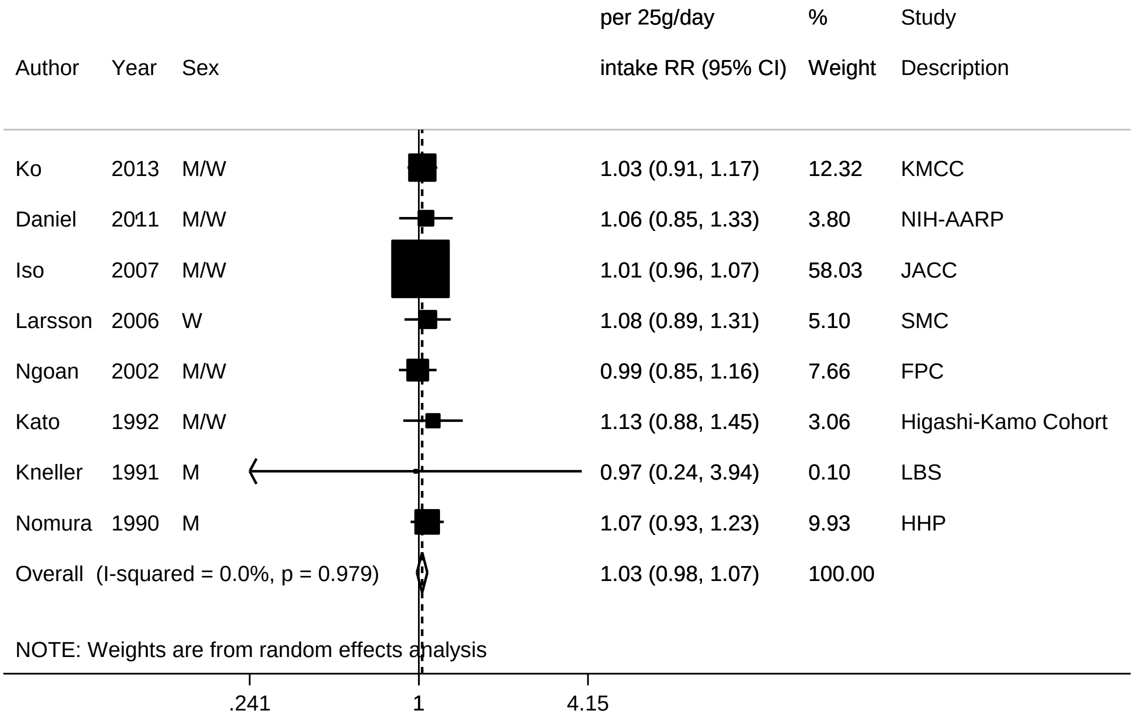
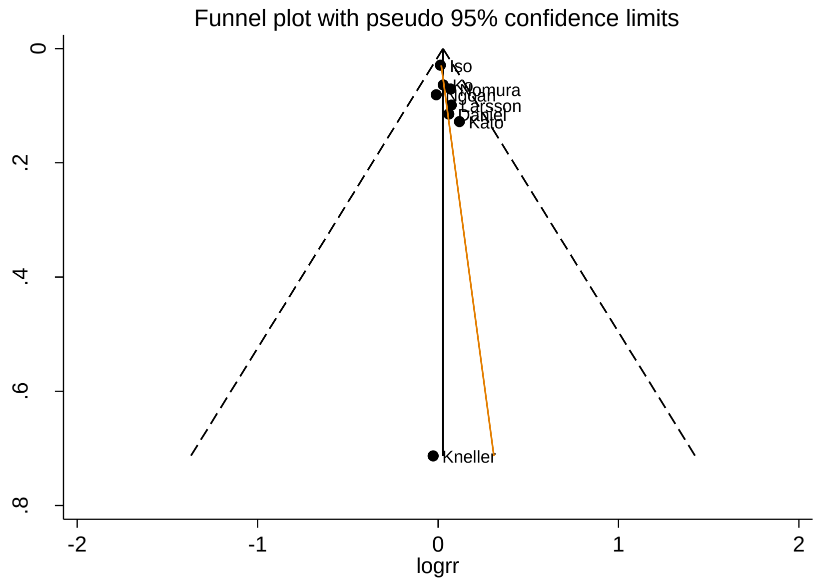


Figure 101 Funnel plot of studies included in the dose response meta-analysis of fish intake and stomach cancer



Egger's test p=0.17

Figure 102 Relative risk of stomach cancer for 25 g/day increase of fish intake by sex

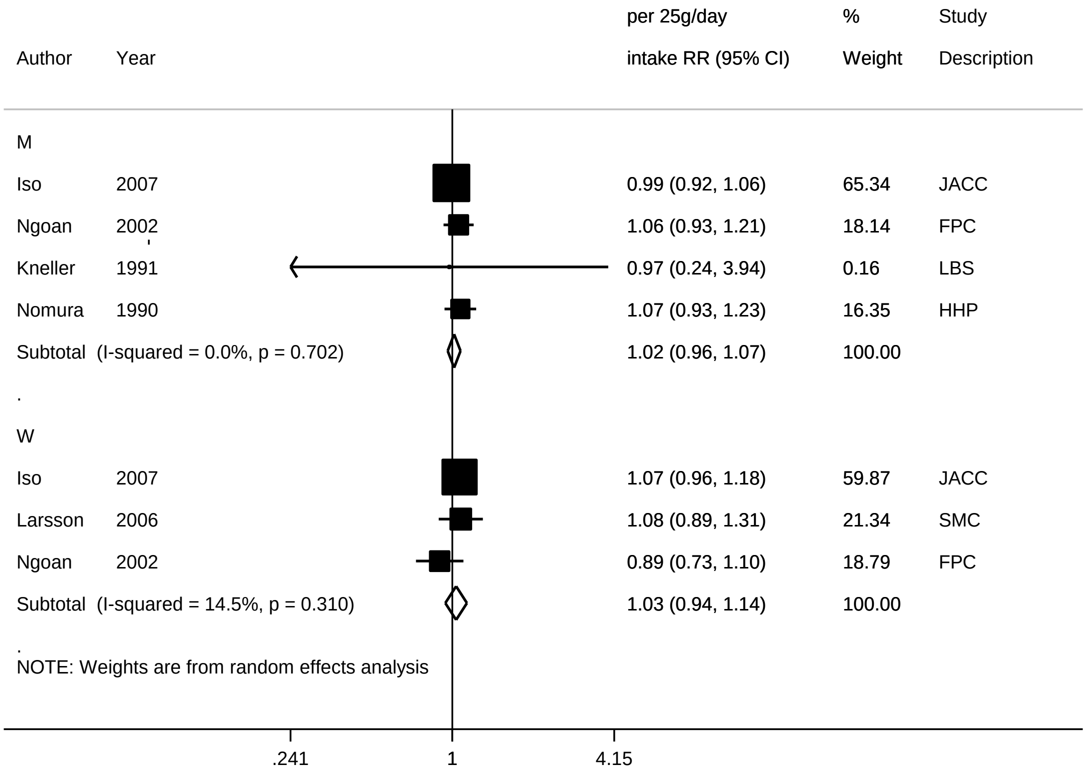


Figure 103 Relative risk of stomach cancer for 25 g/day increase of fish intake by cancer outcome

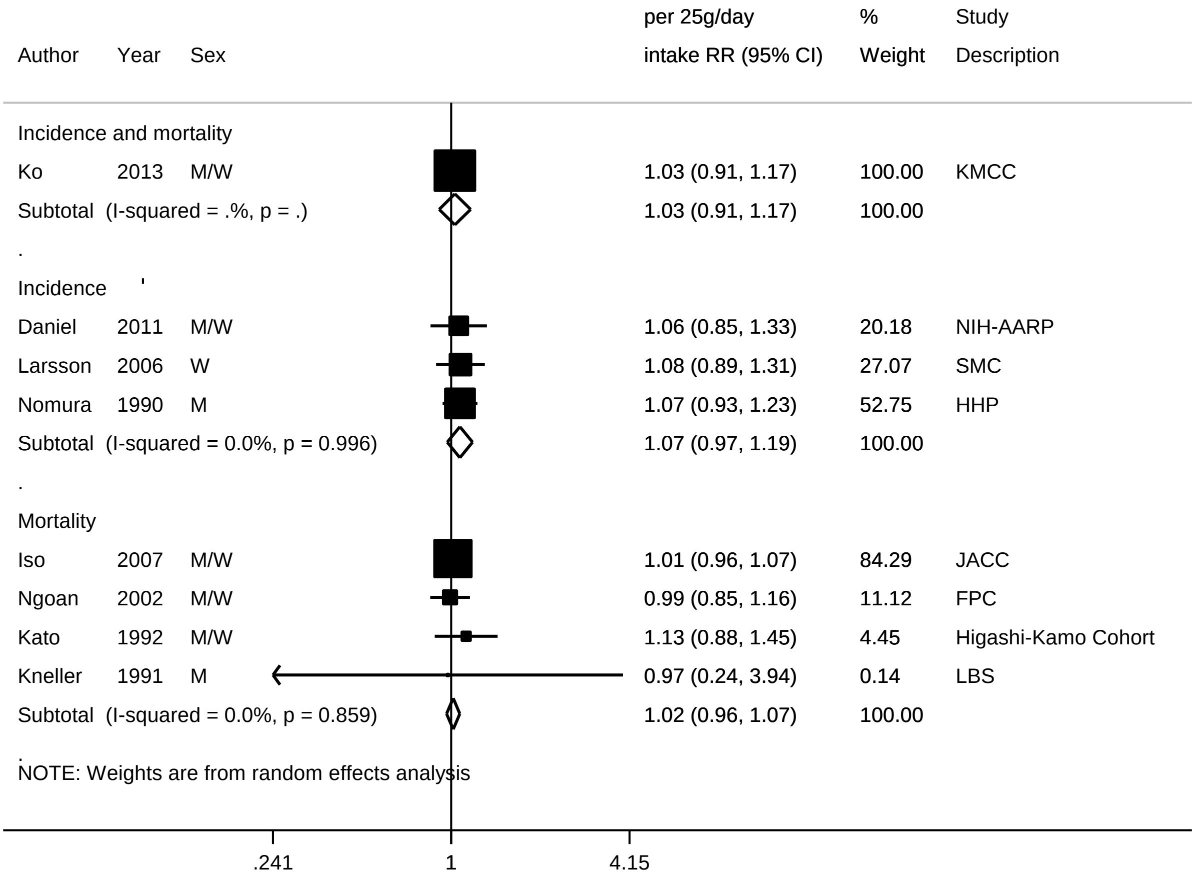
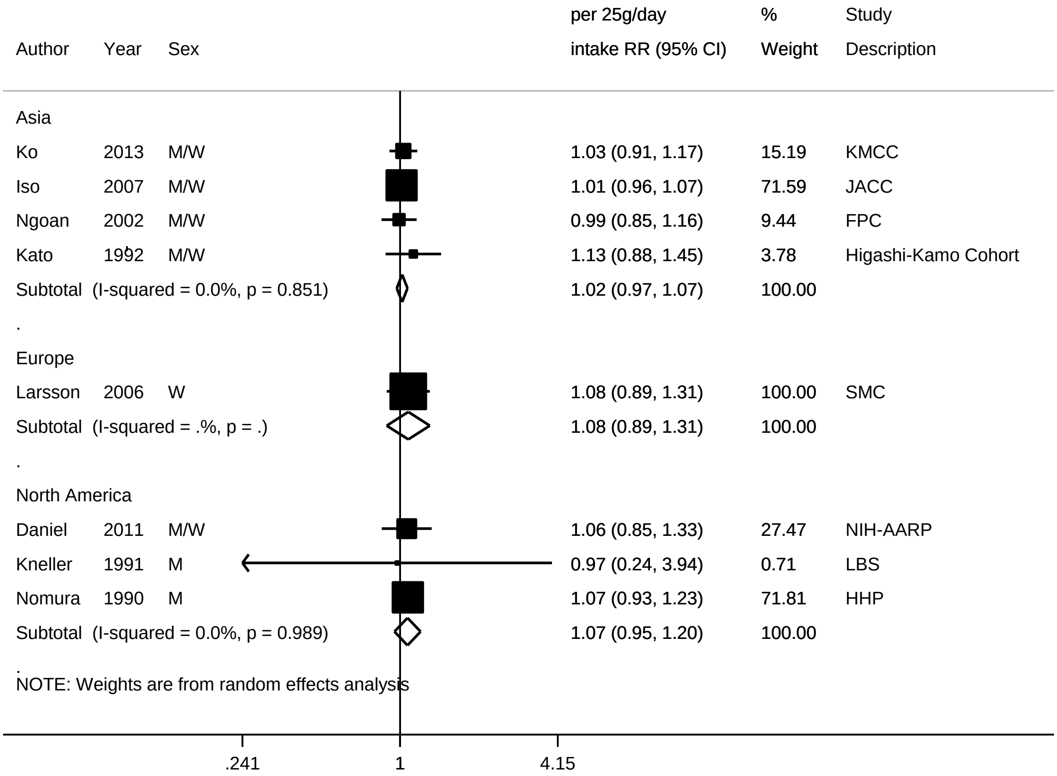


Figure 104 Relative risk of stomach cancer for 25 g/day increase of fish intake by geographic location



2.5.2 Processed fish

Randomised controlled trials

No randomised controlled trial was identified.

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 salted and salty foods are causally related to stomach cancer risk was judged as probable in the Second Expert report.

Four studies (2110 cases) out of eleven identified studies were included in the dose-response meta-analysis. No significant association of processed fish consumption (salted or dried fish) and stomach cancer risk was observed.

No significant association with stomach cancer was observed in six studies excluded from the meta-analysis (Khan, 2004; Knekt, 1999; Galanis, 1998; Inoue, 1996; Kneller, 1991; Ikeda, 1983) and in another study on risk of lower-third stomach cancer (Wong, 2004).

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 did not change materially when studies were omitted in turn in influence analysis.

A highest versus lowest meta-analysis was conducted as a sensitivity analysis as many studies could not be included in the dose-response meta-analysis. The summary RR was 1.15 (95% CI=1.01 – 1.31, I^2=0%, p=0.64, 8 studies), which became non-significant when Takachi, 2010 was removed in influence analysis (summary not shown in the forest plot).

Non-linear dose-response meta-analysis:

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

Study quality:

All studies included in the dose-response analysis were from Japan (Takachi, 2010; Iso, 2007; Ngoan, 2002) or Korea (Ko, 2013).

All studies used FFQ to assess processed fish intake. Processed fish was dried or salted fish in most studies, and smoked or salted fish in one study.

Both incidence and mortality cases were included in Ko, 2013, but only eight cases were identified from the death certificates in this study. All other studies included in the dose-response analysis examined the risk of stomach cancer mortality.

Studies included in the dose-response analysis were adjusted for multiple confounders, apart from Iso, 2007 that only adjusted for age and participant residence area.

Table 85 Processed fish intake and stomach cancer risk. Number of studies in the CUP SLR

	Number
Studies identified	11 (13 publications)
Studies included in forest plot of highest compared with lowest exposure	8
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

Table 86 Processed fish intake and stomach cancer risk. Summary of the linear dose-response meta-analysis in the 2005 SLR and CUP

	2005 SLR	**CUP**
Increment unit used	20 g/day	20 g/day
All studies		
Studies (n)*	4	4
Cases (total number)	698	2110
RR (95%CI)	1.43 (1.09-1.89)	1.06 (0.98-1.15)
Heterogeneity (I^2, p-value)	31.0%, 0.20	0%, 1.00
P value Egger test	0.90	-

Note: The publications included in the 2005 SLR and the CUP SLR are different. The 2005 SLR included the studies by Ikeda, 1983; Kneller, 1991; Inoue, 1996; and Tsugane, 2004. In the CUP, Ikeda, 1983 and Inoue, 1996 were excluded because only reported results on two categories (as per protocol); Kneller, 1991 was excluded because the consumption level was too low and not comparable to other studies; Tsugane, 2004 was superseded by Takachi, 2010. The CUP included Ngoan, 2002 that was included under 2.5.2 fish products and dishes in the 2005 SLR and three studies published after 2006

Table 87 Processed fish intake and stomach cancer risk. Results of meta-analyses and pooled analyses of prospective studies published after the 2005 SLR

Author, Year	Number of studies	Total number of cases	Studies country, area	Outcome	Comparison	RR (95%CI)	P trend	Heterogeneity (I^2, p value)
Meta-analyses								
D'Elia, 2012	8 cohorts*	1447	Japan, USA	Incidence/mortality, gastric cancer	High vs low salted fish intake	1.24 (1.03-1.50)		0%, 0.75

*All studies apart from Kato, 1992a was included in the present review. Kato, 1992a examined specific salted fish products only (salted fish gut and cod roe). The RR for ≥2-3 times/week vs ≤1-2 times/month was 1.35 (95% CI = 0.66-2.77) in this Japanese cohort in subjects who had undergone gastroscopic examination.

Table 88 Processed fish intake and stomach 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
Ko, 2013 STM80184 Korea	KMCC, Prospective Cohort, Age: 30-90 years, M/W	166/ 9724 8.5 years	Cancer registry and death certificates	14-item self-administered FFQ Salted fish	Incidence and mortality, stomach cancer	≥1 time/day vs almost never	1.24 (0.58-2.64)	Age, sex, area of residence, BMI, cigarette smoking, alcohol drinking	Exposure values using standard portion size, mid-points of exposure categories
		116/3714			Men	High vs low	1.02 (0.90-1.16)		
		50/6010			Women		0.97 (0.78-1.21)		
Takachi, 2010 STM80133 Japan	JPHC, Prospective Cohort, Age: 45-74 years, M/W	867/ 77 500 593 620 person years	Active patient notification from hospitals, cancer registries and death cert.	Validated 138-item FFQ Dried or salted fish	Mortality, stomach cancer	43.0 vs 0.5 g	1.46 (1.14-1.88)	Age, sex, BMI, calcium intake, energy intake, physical activity, smoking status, alcohol, potassium	Distributions of person-years by exposure quintiles
Iso, 2007 STM80144 Japan	JACC, Prospective Cohort, Age: 40-79 years, M/W	1019/ 105 500 15 years 686/42416 333/57735	Municipal resident registration records, death certificates	Validated FFQ Dried or salted fish	Mortality, stomach cancer Men Women	>3-4 vs <1 times/week	1.12 (0.89-1.40) 0.92 (0.67-1.26)	Age, area of study	Exposure values using standard portion size, mid-points of exposure categories, RRs for men and women combined using fixed model
Ngoan, 2002 STM01668 Japan	FPC, Prospective Cohort, Age: 15-96	58/ 13 250 13 years	Resident registry	Self-administered FFQ Processed fish	Mortality, stomach cancer	≥ 1 time/day vs 2-4 times/month	1.10 (0.50-2.80)	Age, sex, fat intake, Japanese soup, liver, pickled foods,	Exposure values using standard portion size, 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
	years, M/W							processed meat, smoking habits	exposure categories
		47/3483			Men		2.10 (0.90-4.90)	Age	
		11/4337			Women		1.40 (0.30-7.30)	Age	

Table 89 Processed fish intake and stomach 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
Tokui, 2005 STM80105 Japan	JACC, Prospective Cohort, Age: 40-79 years, M/W	859/ 110 792 12 years	Population registry	33-item FFQ Dried or salted fish, processed fish product	Mortality, stomach cancer	Dried or salted fish		Age	Superseded by Iso, 2007, STM80144
		374/ 188/			Men Women	≥1 time/day vs none	1.14 (0.74-1.76) 0.92 (0.53-1.58)		
		356/ 175/			Men Women	Boiled fish paste 3-4 times/week or more vs none	1.21 (0.86-1.71) 1.25 (0.76-2.06)		
Khan, 2004 STM20239 Japan	HGCS, Prospective Cohort, Age: 40- years, M/W	51/ 3158 14 years	Follow-up surveys	37-item FFQ Salty fish	Mortality, stomach cancer	2-7 times/week vs never-several times/month			Excluded, only two intake categories
		36/1524			Men		0.90 (0.50-1.80)	Age, smoking habits	
		15/1634			Women		1.50 (0.50-4.20)	Age, health education, health screening, health status, smoking habits	
Tsugane, 2004 STM00441 Japan	JPHC I, Prospective Cohort, Age: 40-59 years,	486/ 39 065 12 years	Hospital records, population-based cancer registries and	Validated 27-item FFQ Dried or salted fish	Incidence, stomach cancer	Almost daily vs almost none		Age, fruit, non green-yellow vegetable intake, smoking habits	Superseded by Takachi, 2010, STM80133
		358/			Men		2.23 (1.37-3.63)		

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	Reasons for exclusion
	M/W	128/	death certificates, histologically confirmed		Women		1.22 (0.53-2.82)		
Wong, 2004 STM00527 China	CCHT, Prospective Cohort, Age: 42 years, M/W, H. pylori eradication trial participants	18/ 1630 7.5 years	Clinical trial follow up records	FFQ Salty fish	Incidence, lower third gastric cancer	≥2 vs <2 times/week	1.22 (0.49-3.08)		Excluded, only two intake categories
Knekt, 1999 STM03959 Finland	FMCHES, Prospective Cohort, Age: 15-99 years, M/W	68/ 9985 21 years	Cancer registry	Dietary history Smoked and salty fish	Incidence, stomach cancer	Quantile 4 vs quantile 1	0.98 (0.49-1.96)	Age, sex, energy intake, geographical area, smoking habits	Excluded, exposure not quantified
Galanis, 1998 STM04769 USA	Hawaii-Japan DOH Survey, Prospective Cohort, Age: 18- years, M/W, Japanese residents of Hawaii	108/ 11 907 14.8 years	Cancer registry	19-item FFQ Dried or salted fish	Incidence, stomach cancer	≥1 time/week vs none	1.00 (0.60-1.70)	Age, years of education, place of birth and gender (combined analysis). Analysis in men also adjusted for cigarette smoking and alcohol intake status	Excluded, only two intake categories
		64/			Men		1.00 (0.50-1.90)		
		44/			Women		1.10 (0.50-2.60)		
Inoue, 1996	HERPACC,	61/	Hospital	Self-	Incidence,		1.17 (0.68-2.01)	Age, sex	Excluded, only

Author, Year, WCRF Code, Country	Study name, Characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Reasons for exclusion
STM06116 Japan	Prospective Cohort, M/W, Endoscopy patients	5373 6 years	records, cancer registry, death certificates	administered FFQ Salted or dried fish	stomach cancer	≥2-3 times/week vs rarely			two intake categories
Kneller, 1991 STM07350 USA	LBS, Prospective Cohort, Age: 35- years, M, Mainly of Scandinavian descent	72/ 17 633 20 years	Health insurance company records	35-item FFQ Salted fish	Mortality, stomach cancer	≥1 times/month vs never	1.90 (0.98-3.59)	Age, smoking habits	Excluded, extremely low salted fish intake, not comparable with other studies
Ikeda, 1983 STM09004 Japan	RERFCJ, Prospective Cohort, Age: 50 years, M/W, Atomic bomb survivors	79/ 7553 11 years	Cancer registry/ population register	Questionnaire (general) Dried fish	Mortality, stomach cancer	≥2 vs <2 times/week	0.95		Excluded, only two intake categories, no 95 CI

Figure 105 RR estimates of stomach cancer by levels of processed fish intake

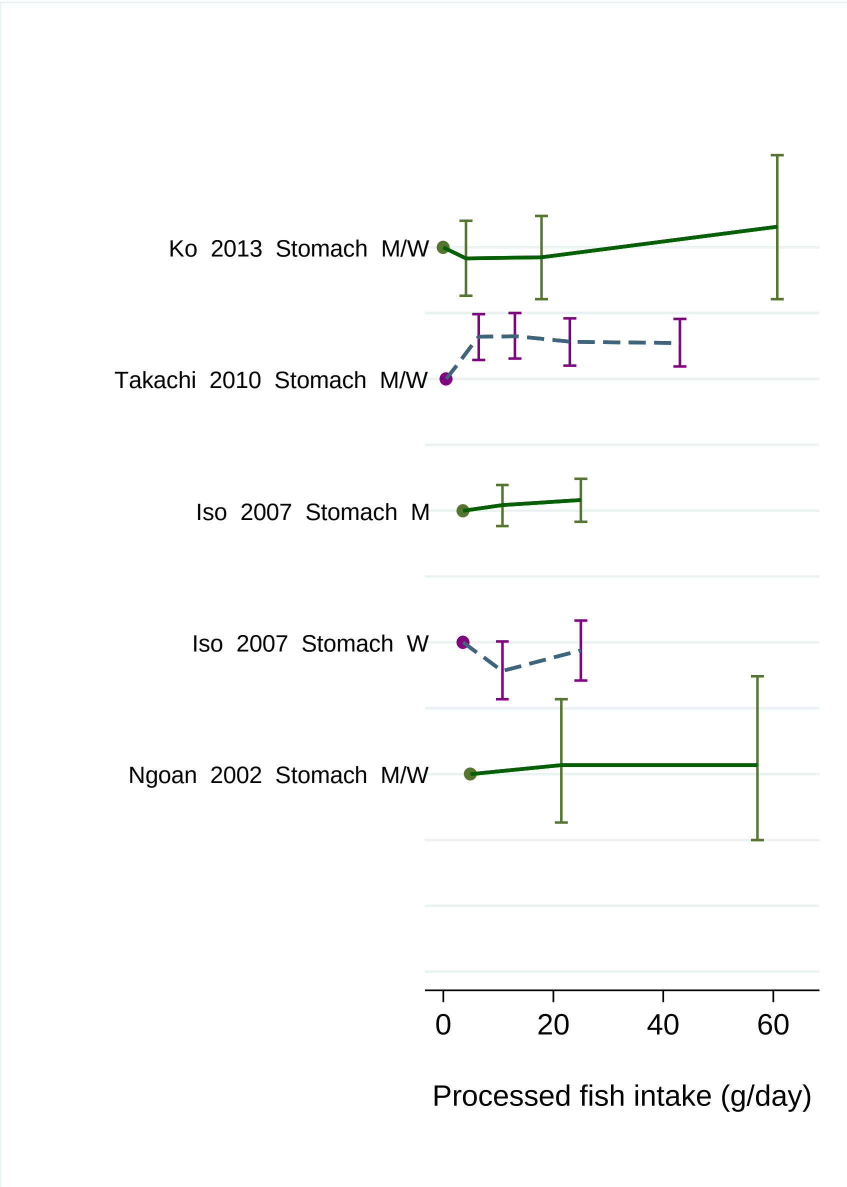
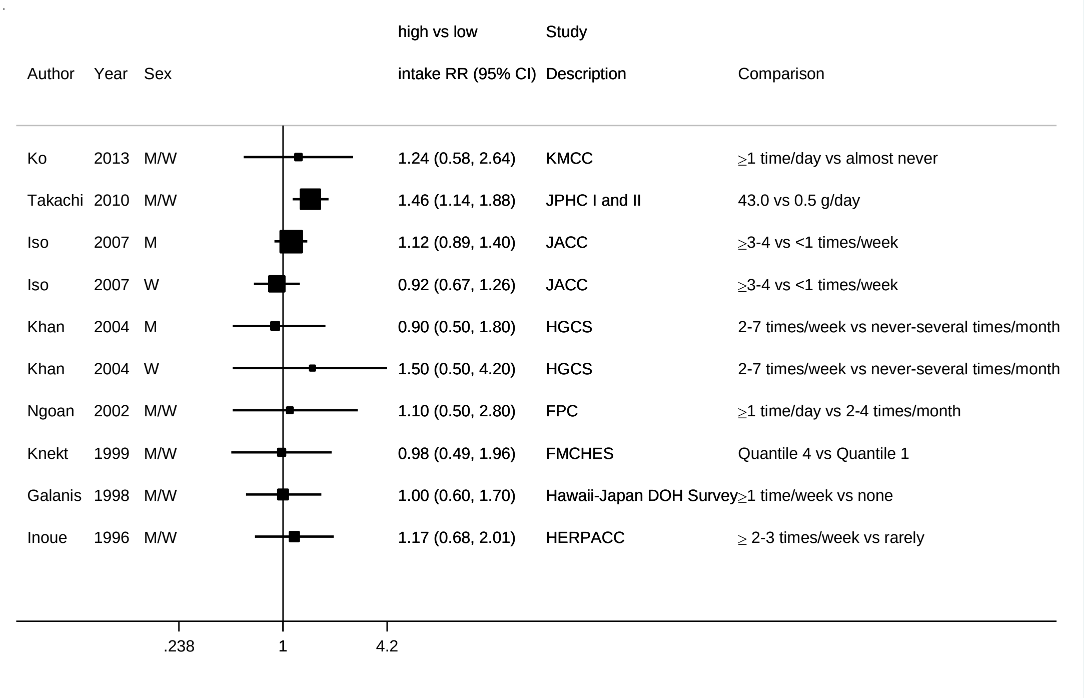
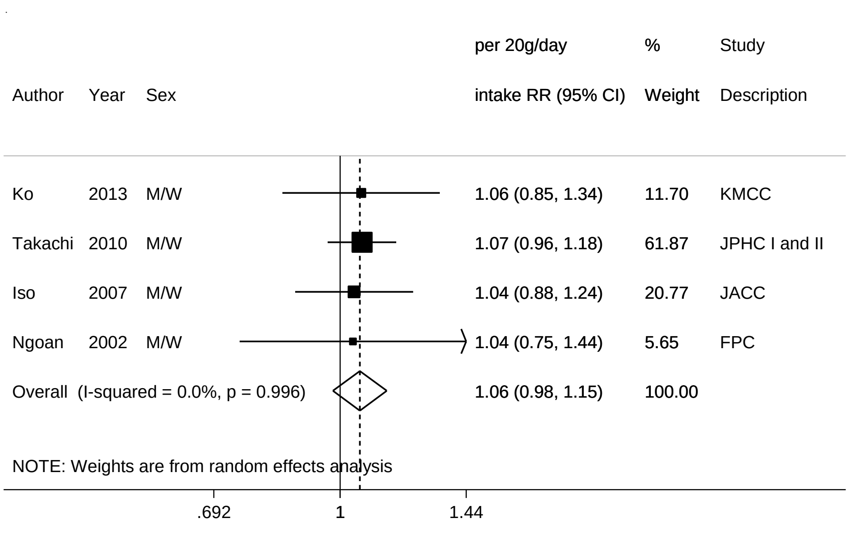


Figure 106 RR (95% CI) of stomach cancer for the highest compared with the lowest level of processed fish intake



Note: All studies were on stomach cancer. Wong, 2004 was on lower third gastric cancer only and was excluded. Two additional studies (Kneller, 1991; Ikeda, 1983) were excluded due to insufficient data. The summary RR for the highest versus lowest intake was 1.15 (95% CI=1.01 – 1.31, I^2=0%, p=0.64). When Takachi, 2010 was removed in influence analysis, the summary RR became non-significant.

Figure 107 Relative risk of stomach cancer for 20 g/day increase of processed fish intake



2.5.4 Eggs

Randomised controlled trials

No randomised controlled trial was identified.

Cohort studies

Summary

Main results:

Five studies (2965 cases) were included in the dose-response meta-analysis. No significant association of egg consumption and stomach cancer risk was observed for stomach cancer.

One study by Khan, 2004 was excluded from the dose-response analyses which reported no significant association.

No meta-analyses and pooled analyses of prospective studies were identified.

No heterogeneity was observed.

There was no significant evidence of publication bias or small study bias.

Sensitivity analyses:

The summary RR did not change materially when studies were omitted in turn in influence analysis. All studies were conducted in Asia apart one study on Japanese residents in Hawaii (Nomura, 1990). After excluding this study, the RR remained the same.

Study quality:

Loss to follow-up was low in most studies.

Cancer outcome was confirmed reviewing cancer registry, resident registry, hospital records or using death certificates in most studies.

FFQ was the main method used to estimate consumption of eggs. Intake was reported as times/day/week/month/year in all studies.

Three studies were adjusted for age and sex (Tran, 2005; Ngoan, 2002; Nomura, 1990). Iso, 2007 was additionally adjusted for study area. Ko, 2013 adjusted for multiple factors including BMI, smoking, and alcohol consumption. None of the studies adjusted for Helicobacter Pylori status, socioeconomic status, comorbidities, physical activity, and total energy intake.

Subgroup analysis by cancer site was not conducted. Tran, 2005 was the only study reporting stratified results by cancer site. Significant inverse association was reported only for gastric cardia cancer comparing the highest with the lowest intake category (1089 cases, RR= 0.76; 95% CI=0.64-0.90).

Table 90 Egg intake and stomach cancer risk. Number of studies in the CUP SLR

	Number
Studies identified	6 (8 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

Table 91 Egg intake and stomach cancer risk. Summary of the linear dose-response meta-analysis in the 2005 SLR and CUP

	2005 SLR	**CUP**
Increment unit used	20g/day	1 time/week
All studies		
Studies (n)	4	5
Cases (total number)	855	2965
RR (95%CI)	0.99 (0.93-1.05)	1.02 (0.99-1.05)
Heterogeneity (I^2, p-value)	8.5%, 0.4	0%, 0.46
P value Egger test	0.3	0.22

Table 92 Egg intake and stomach 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 analysis
Ko, 2013 STM80184 Korea	KMCC, Prospective Cohort, Age: 30-90 years, M/W	166/ 9 724 8.5 years	Cancer registry and death certificates	FFQ	Incidence, stomach cancer	≥1 time/day vs almost never	1.23 (0.65-2.31) Ptrend:0.92	Age, sex, area of residence, BMI, cigarette smoking, alcohol drinking	Mid-points of exposure categories
Iso, 2007 STM80144 Japan	JACC, Prospective Cohort, Age: 40-79 years, M/W	724/ 105 500 15 years	Municipal resident registration records, death certificates	Validated FFQ	Mortality, stomach cancer Men	≥5 vs <3 times/week	1.02 (0.86-1.22)	Age, area of study	Mid-points of exposure categories, RRs for men and women combined
		357/			Women		1.29 (1.00-1.68)		
Tran, 2005 STM44270 Linxin, China	NIT Cohort, Prospective Cohort, Age: 40-69 years, M/W, Intervention trial participants	1 089/ 29 584 15 years	Follow-up visits, contacts with local commune, hospitals, and study medical team	FFQ	Incidence, cardia cancer	>36 vs ≤2 times/year	0.76 (0.64-0.90) Ptrend:0.008	Age, sex	Distribution of cases by exposure categories, RRs for cardia stomach cancer and non-cardia stomach cancer combined using Hamling's method, mid-points of intake categories
		363/			non-cardia cancer		0.99 (0.73-1.33) Ptrend:0.56		
Ngoan, 2002 STM01668 Japan	FPC, Prospective Cohort, Age: 15-96 years, M/W	108/ 13 250 13 years	Resident registry	FFQ	Mortality, stomach cancer	≥1 time/day vs ≤2-4 times/week	0.90 (0.80-1.10)	Age, sex, fat intake, Japanese soup, liver, pickled foods, processed meat, smoking habits	Only two exposure categories, used in HvL only
		77/			Men		0.80 (0.40-1.60)	Age	Mid-points of exposure categories, RRs
Nomura,	HHP,	150/	Cancer registry/	FFQ +	Incidence,	≥5 vs ≤1	1.30 (0.80-2.00)	Age	

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Missing data derived for analysis
1990 STM14814 USA	Prospective Cohort, Age: 45- years, M, Japanese residents of Hawaii	7 990 19 years	hospital records	recall	stomach cancer	time/week			

Table 93 Egg intake and stomach 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
Tokui, 2005 STM80105 Japan	JACC, Prospective Cohort, Age: 40-79 years, M/W	574/ 44 930 12 years	Population registry	FFQ	Mortality, stomach cancer Men	1+/day vs 1-2/month or less	1.13 (0.79-1.62) Ptrend:0.64	Age	Superseded by Iso, 2007
		285/			Women		2.32 (1.22-4.42) Ptrend:0.01		
Khan, 2004 STM20239 Japan	HGCS, Prospective Cohort, Age: 40- years, M/W	36/ 3 158 14 years	Follow-up surveys	FFQ	Mortality, stomach cancer Men	2-7 times/week vs never, several times/month/year	2.50 (0.60-10.30)	Age, smoking habits	Excluded, two exposure categories only, used in HvL
		15/			Women		1.20 (0.30-5.20)	Age, health education, health screening, health status, smoking habits	
Guo, 1994 STM10900 Linxin, China	NIT Cohort, Nested Case Control, Age: 40-69 years, M/W, Intervention trial participants	538/ 29 584 5 years	Follow-up visits, contacts with local commune, hospitals, and study medical team	FFQ	Incidence, stomach cancer	>6 times/month vs 0	0.90 (0.70-1.20)	Family history of cancer, intervention group, smoking habits	Superseded by Tran, 2005

Figure 108 RR estimates of stomach cancer by levels of egg intake

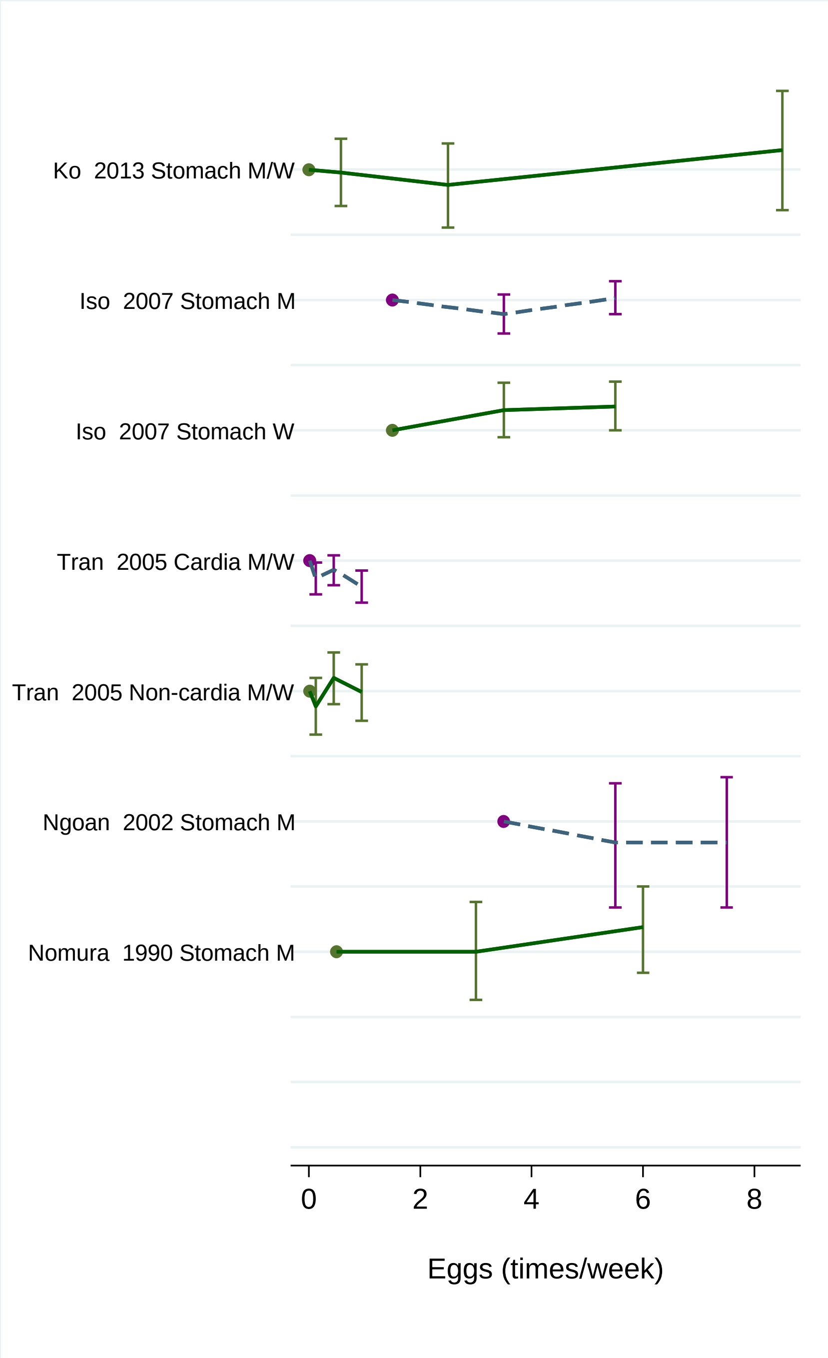


Figure 109 RR (95% CI) of stomach cancer for the highest compared with the lowest level of egg intake

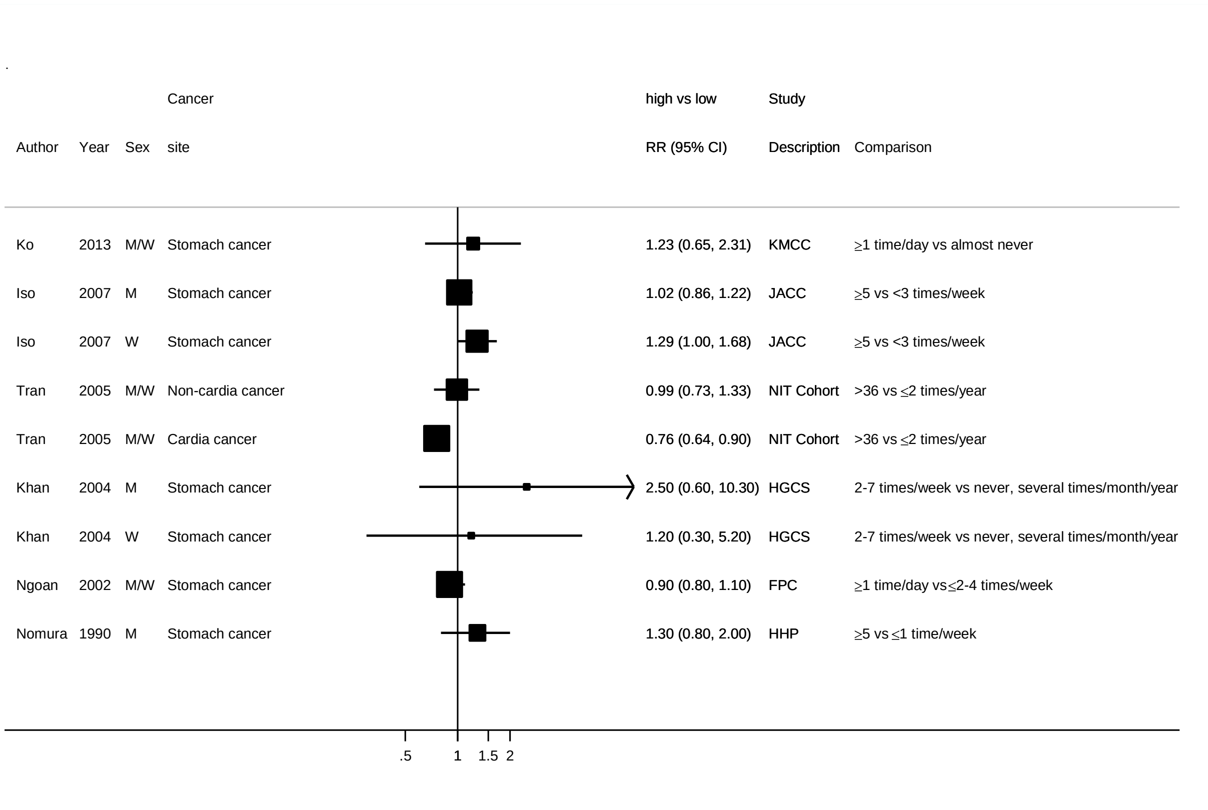


Figure 110 Relative risk of stomach cancer incidence for 1 time/week increase of egg intake

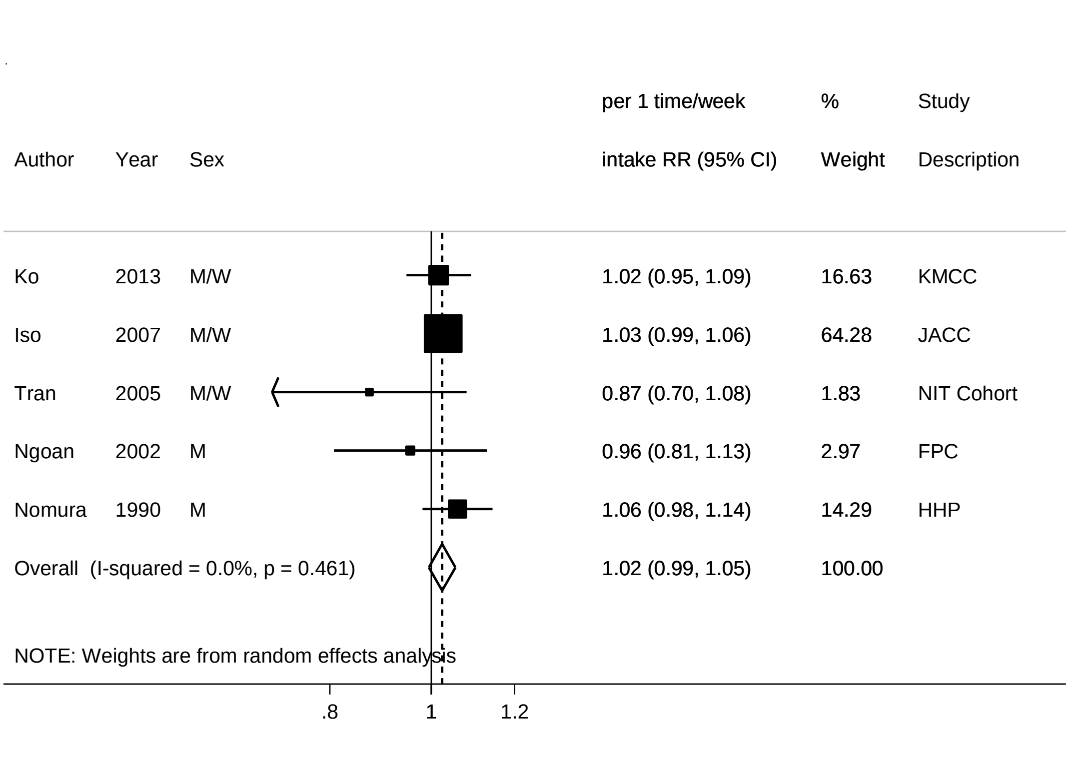
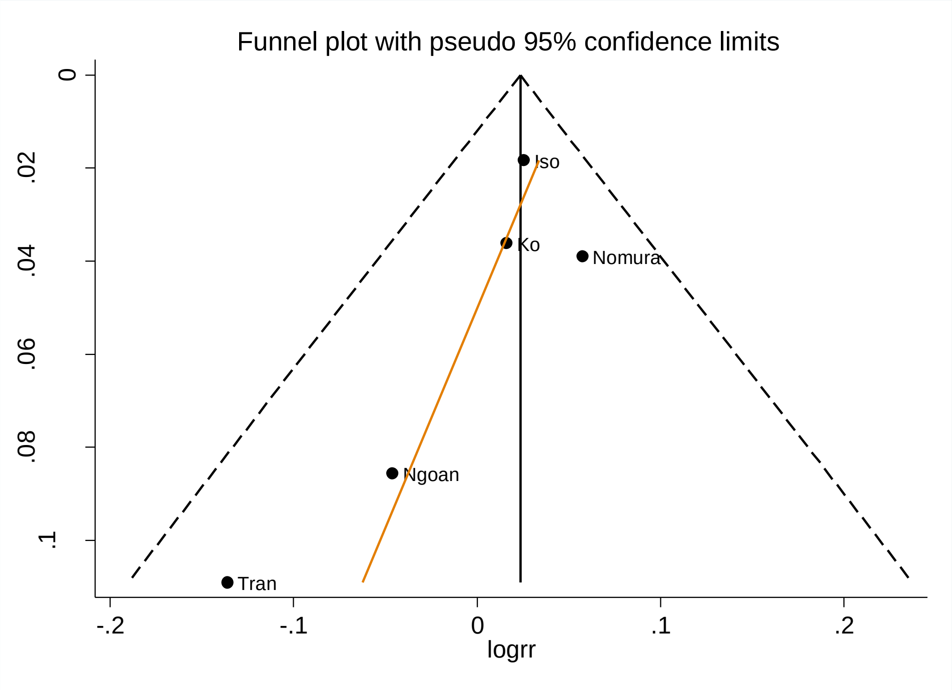


Figure 111 Funnel plot of studies included in the dose response meta-analysis of egg and stomach cancer



Egger's test p=0.22

2.8 Chilli

No cohort study was identified in both the 2005 SLR and the CUP. Fourteen case-control studies were identified in the 2005 SLR. Six studies reported significant positive associations between chilli consumption and risk of stomach cancer. Three studies found significant inverse associations. The remaining studies reported non-significant results. No meta-analysis was conducted.

3 Beverages

3.6.1 Coffee

Randomised controlled trials

No randomised controlled trial was identified.

Cohort studies

Summary

Main results:

Ten studies (6 941 cases) were included in the dose-response meta-analysis. Coffee consumption was not significantly associated with stomach cancer risk.

Six studies were excluded from the dose-response analyses. No significant association was observed in the excluded studies with the exception of a study in Japanese men and women in which coffee intake was positively associated with mortality for stomach cancer (40 deaths) (Nagata, 2002).

Moderate heterogeneity was observed. There was no significant evidence of publication or small study bias.

In the only study that reported associations by cancer site (Ren, 2010, NIH-AARP cohort), the risk of cancer of the gastric cardia was significantly positively associated with higher coffee intake. No significant association was observed for non cardia gastric cancer.

Sensitivity analyses:

The summary RR did not change materially when studies were omitted in turn in the influence analysis. The summary RRs ranged from 0.99 (95% CI=0.97-1.01) when Larsson, 2006a was omitted to 1.01 (95% CI=0.96-1.06) when Klatsky, 1993 was omitted.

Non-linear dose-response meta-analysis:

There was no evidence of non-linear dose-response association (p for non-linearity = 0.67).

Study quality:

Loss to follow-up was low in most studies. Cancer outcome was confirmed using medical notes or records in cancer registries in most studies.

All studies used FFQ to assess coffee intake. Coffee intake was assessed as times or occasions per day/week/month in three studies (Ko, 2013; Nilsson, 2010; Iso, 2007); Nilsson, 2010 specified that more than one cup per occasion may have been consumed but the amount could not be considered in the analysis. All remaining studies expressed intake in cups. Cup volume was defined in Bidel, 2012 and Sugiyama, 2010 studies as 100ml and 150ml, respectively. Only one study (Nilsson, 2010) investigated the consumption of filtered, boiled and total coffee; none of the remaining studies specified coffee type.

All studies included in the dose-response analysis were adjusted for age, sex, smoking and other potential confounders except one study (Iso, 2007) that only accounted for age in the analyses. No studies were adjusted for Helicobacter pylori infection or socioeconomic status.

Similar results were also observed in analyses stratified by sex, duration of follow-up, number of cases, publication year, geographic location, and adjustment for confounders. The heterogeneity was lower in the studies that controlled for smoking (eight studies) although the results were similar to those of the group of studies that did not adjust for smoking.

Table 94 Coffee intake and stomach cancer risk. Number of studies in the CUP SLR

	Number
Studies identified	16 (18 publications)
Studies included in forest plot of highest compared with lowest exposure	13
Studies included in linear dose-response meta-analysis	10
Studies included in non-linear dose-response meta-analysis	-

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

Table 95 Coffee intake and stomach cancer risk. Summary of the linear dose-response meta-analysis in the 2005 SLR and CUP

	2005 SLR	**CUP**
Increment unit used	1 cup/day	1 cup/day
All studies		
Studies (n)	3	10
Cases (total number)	237	6941
RR (95%CI)	0.97 (0.77-1.22)	1.00 (0.97-1.03)
Heterogeneity (I^2, p-value)	62.2%, 0.03	37.1%, 0.11
P value Egger test	0.9	0.31
Stratified and sensitivity analysis		
Men		
Studies (n)	3	5
RR (95%CI)	1.09 (0.73-1.63)	0.97 (0.93-1.00)
Heterogeneity (I^2, p-value)	-	0%, 0.45
Women		
Studies (n)	3	5
RR (95%CI)	0.93 (0.57-1.50)	1.04 (0.98-1.10)
Heterogeneity (I^2, p-value)	-	8.5%, 0.36
Other stratified analyses. CUP		

Outcome	**Incidence**	**Mortality**	
Studies (n)	7	3	
RR (95%CI)	1.02 (0.95-1.10)	0.99 (0.97-1.00)	
Heterogeneity (I^2, p-value)	55.4%, 0.04	0%, 0.68	
Geographic location	**Asia**	**Europe**	**North America***
Studies (n)	3	4	3
RR (95%CI)	1.00 (0.95-1.06)	1.01 (0.93-1.09)	1.04 (0.95-1.13)
Heterogeneity (I^2, p-value)	0%, 0.46	60.6%, 0.06	57.4%, 0.10
Duration of follow-up	**5-<10 years**	**10-<15 years**	**≥15 years**
Studies (n)	3	3	4
RR (95%CI)	1.00 (0.92-1.08)	1.00 (0.86-1.17)	1.02 (0.96-1.08)
Heterogeneity (I^2, p-value)	42.2%, 0.18	45.6%, 0.16	55.1%, 0.08
Publication year	**<2000**	**2000-<2010**	**≥2010**
Studies (n)	3	2	5
RR (95%CI)	0.99 (0.92-1.05)	1.07 (0.93-1.22)	1.00 (0.94-1.06)
Heterogeneity (I^2, p-value)	46.3%, 0.16	69.4%, 0.07	17.7%, 0.30
Number of cases	**<500 cases**	**≥1000 cases**	
Studies (n)	8	2	
RR (95%CI)	1.02 (0.95-1.09)	0.99 (0.97-1.00)	
Heterogeneity (I^2, p-value)	48.2%, 0.06	0%, 0.40	
Adjustment for			
Smoking	**Not adjusted**	**Adjusted**	
Studies (n)	2	8	
RR (95%CI)	1.07 (0.93-1.22)	0.99 (0.96-1.01)	
Heterogeneity (I^2, p-value)	69.4%, 0.07	18.4 %, 0.28	
Ethnicity	**Not adjusted**	**Adjusted**	
Studies (n)	8	2	
RR (95%CI)	1.00 (0.95-1.06)	1.01 (0.93-1.10)	
Heterogeneity (I^2, p-value)	41.3%, 0.10	56.3%, 0.13	
Alcohol intake	**Not adjusted**	**Adjusted**	
Studies (n)	3	7	
RR (95%CI)	0.99 (0.94-1.05)	1.01 (0.96-1.05)	
Heterogeneity (I^2, p-value)	24.2%, 0.27	47.9%, 0.07	
BMI	**Not adjusted**	**Adjusted**	

Studies (n)	4	6	
RR (95%CI)	1.03 (0.95-1.13)	0.98 (0.97-1.00)	
Heterogeneity (I^2, p-value)	62.7%, 0.05	0%, 0.43	
Total energy intake	**Not adjusted**	**Adjusted**	
Studies (n)	8	2	
RR (95%CI)	0.99 (0.96-1.03)	1.07 (0.95-1.20)	
Heterogeneity (I^2, p-value)	41.8%, 0.10	0%, 0.57	
Physical activity	**Not adjusted**	**Adjusted**	
Studies (n)	6	4	
RR (95%CI)	1.00 (0.95-1.05)	1.00 (0.94-1.06)	
Heterogeneity (I^2, p-value)	52.8%, 0.06	19.0%, 0.30	
Comorbidities	**Not adjusted**	**Adjusted**	
Studies (n)	8	2	
RR (95%CI)	1.01 (0.97-1.06)	0.97 (0.93-1.01)	
Heterogeneity (I^2, p-value)	48.1%, 0.06	0%, 0.88	

* One study in North America was in Japanese residents in Hawaii.

Table 96 Coffee intake and stomach cancer risk. Results of meta-analyses and pooled analyses of prospective studies published after the 2005 SLR

Author, Year	Number of studies	Total number of cases	Studies country, area	Outcome	Comparison	RR (95%CI)	P trend	Heterogeneity (I^2, p value)
Meta-analyses								
Botelho F, 2006	7 cohorts	2691	USA, Japan, the Netherlands, Norway	Incidence/mortality, gastric cancer	High vs low	1.02 (0.76-1.37)		0.12
	23 cohort and case control studies combined		USA, Japan, the Netherlands, Norway, Italy, Taiwan, Turkey, Spain, Sweden, China, Poland, Venezuela, India, Uruguay			0.97 (0.86-1.09)		0.08
	5 population-based case-control studies		Japan, Sweden, China, Poland, Venezuela			0.90 (0.70-1.15)		0.19

*All cohort studies were included in the present review.

Table 97 Coffee intake and stomach 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
Ko, 2013 STM80184 Korea	KMCC, Prospective Cohort, Age: 30-90 years, M/W	165/ 9,724 8.5 years	Cancer registry and death certificates	FFQ	Incidence, stomach cancer All	≥1 time/day vs almost never times	0.94 (0.63-1.41)	Age, sex, area of residence, BMI, cigarette smoking, alcohol drinking	Exposure measurement unit of times/day used as cups/day, intake per week, month converted to intake per day, mid-points of exposure categories
		115/			Men	High vs low	1.0 (0.88-1.13)		
		50/			Women	High vs low	0.92 (0.75-1.13)		
Bidel, 2012 STM80119 Finland	Finland 1972-2006, Prospective Cohort, Age: 26-74 years, M/W	299/ 60,041 18 years	Finnish cancer registry	Self-administered questionnaire	Incidence, stomach cancer All	≥10 vs 0 cups/day	0.75 (0.4-1.41)	Age, alcohol consumption, BMI, cigarette smoking, history of diabetes, leisure - physical activity, study year, tea consumption, education	Distribution of person-years by exposure categories, mid-points of exposure categories
		181/			Men		0.53 (0.26-1.09)		
		118/			Women		2.07 (0.53-8.15)		
Nilsson, 2010 STM80157 Sweden	VIP, Prospective Cohort, Age: 30-60 years, M/W	70/ 64,603 15 years	Cancer registry	Validated FFQ	Incidence, stomach cancer	≥4 vs <1 times/day	0.99 (0.44-2.21)	Age, sex, BMI, recreational physical activity, education, smoking	Exposure measurement unit of occasions/day used as cups/day. Distribution of person-years by exposure categories, mid-points of exposure categories.
Ren, 2010 STM80059 USA	NIH-AARP, Prospective Cohort, Age: 50-71 years, M/W,	231/ 481,563 6 years	Linkage of the cohort with database to state cancer registries	FFQ	Incidence, cardia cancer	>3 vs <1 cups/day	1.57 (1.03-2.39)	Age, sex, BMI, caloric intake, ethnicity, red meat intake, tobacco use, alcohol intake,	RRs for cardia and non-cardia gastric cancers combined using
		223/			Incidence,		1.06 (0.68-		

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Missing data derived for analyses
	Retired				non-cardia cancer		1.64)	education, fruit and vegetable intake, usual physical activity, vigorous physical activity, white meat intake	Hamling's method, distribution of person-years by exposure categories, mid-points of exposure categories
Sugiyama, 2010 STM80132 Japan	MCS II, Prospective Cohort, Age: 40-64 years, M/W	88/ 37,742 10.3 years	Death certificate	Questionnaire	Mortality, stomach cancer Men	1 vs never cup	0.97 (0.54-1.74)	Age, consumption of alcohol,, black tea, dairy products, fruit and vegetables, miso soup, rice, tea, fish, green tea, meat, energy intake, cigarette smoking, education level, , , history of diabetes, hypertension, walking time	Mid-points of exposure categories, distribution of person-years by exposure categories, RRs for men and women combined
		35/			Mortality, stomach cancer Women		0.71 (0.27-1.88)		
Iso, 2007 STM80144 Japan	JACC, Prospective Cohort, Age: 40-79 years, M/W	720/ 105,500 15 years	Municipal resident registration records, death certificates	Validated FFQ	Mortality, stomach cancer Men	≥2 times/day vs ≤2 times/month	0.97 (0.79-1.18)	Age, area of study	Intake per week/month converted to intake per day, exposure measurement unit of times/day used as cups/day, mid-points of exposure categories, RRs for men and women combined
		353/			Mortality, stomach cancer Women		1.09 (0.82-1.46)		
Larsson, 2006a STM80111 Sweden	SMC, Prospective Cohort, W	160/ 61,433 15.7 years	Linkage to Swedish cancer registry	Validated FFQ	Incidence, stomach cancer	≥4 cups/day vs ≤1 cup/day cups/day	1.86 (1.04-3.34)	Age, education level, tea consumption, time period, alcohol intake	Mid-points of exposure categories
Galanis, 1998 STM04769 USA	Hawaii-Japan DOH Survey, Prospective Cohort,	108/ 11,907 14.8 years	Cancer registry	FFQ	Incidence, stomach cancer All	2 or more vs none cups/day	1.8 (1.0-3.3)	Age, sex, educational level, place of birth	Distribution of person-years by exposure categories, mid-point of exposure in the third

Author, Year, 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: 18- years, M/W, Japanese residents of Hawaii	64/			Incidence, stomach cancer Men		2.2 (0.9-5.3)	Age, alcohol consumption, educational level, place of birth, smoking habits	category
		44/ 11,907 14.8 years			Incidence, stomach cancer Women		1.6 (0.7-3.8)	Age, educational level, place of birth	
Stensvold, 1994 STM03186 Norway	NCVSC, Prospective Cohort, Age: 35-54 years, M/W	46/ 42,973 10.1 years	Cancer registry	FFQ	Incidence, stomach cancer Men	≥7 vs ≤2 cups/day	0.5	Age, area of residence, smoking habits	RRs calculated using regression coefficients, exposure units rescaled, RRs for men and women combined. Confidence intervals of RRs for men and women, mid-points of exposure categories for non-linear analysis.
		32/			Incidence, stomach cancer Women		0.5		
Klatsky, 1993 STM00025 USA	KPMCP, Prospective Cohort, Age: 20-84 years, M/W	78/ 128,934 8 years	Death register	Questionnaire (general)	Mortality, stomach cancer	>6 vs 0 cups/day	0.88 (0.76-1.02)	Age, sex, race, BMI, smoking, alcohol, education, marital status	Distribution of person-years by exposure categories

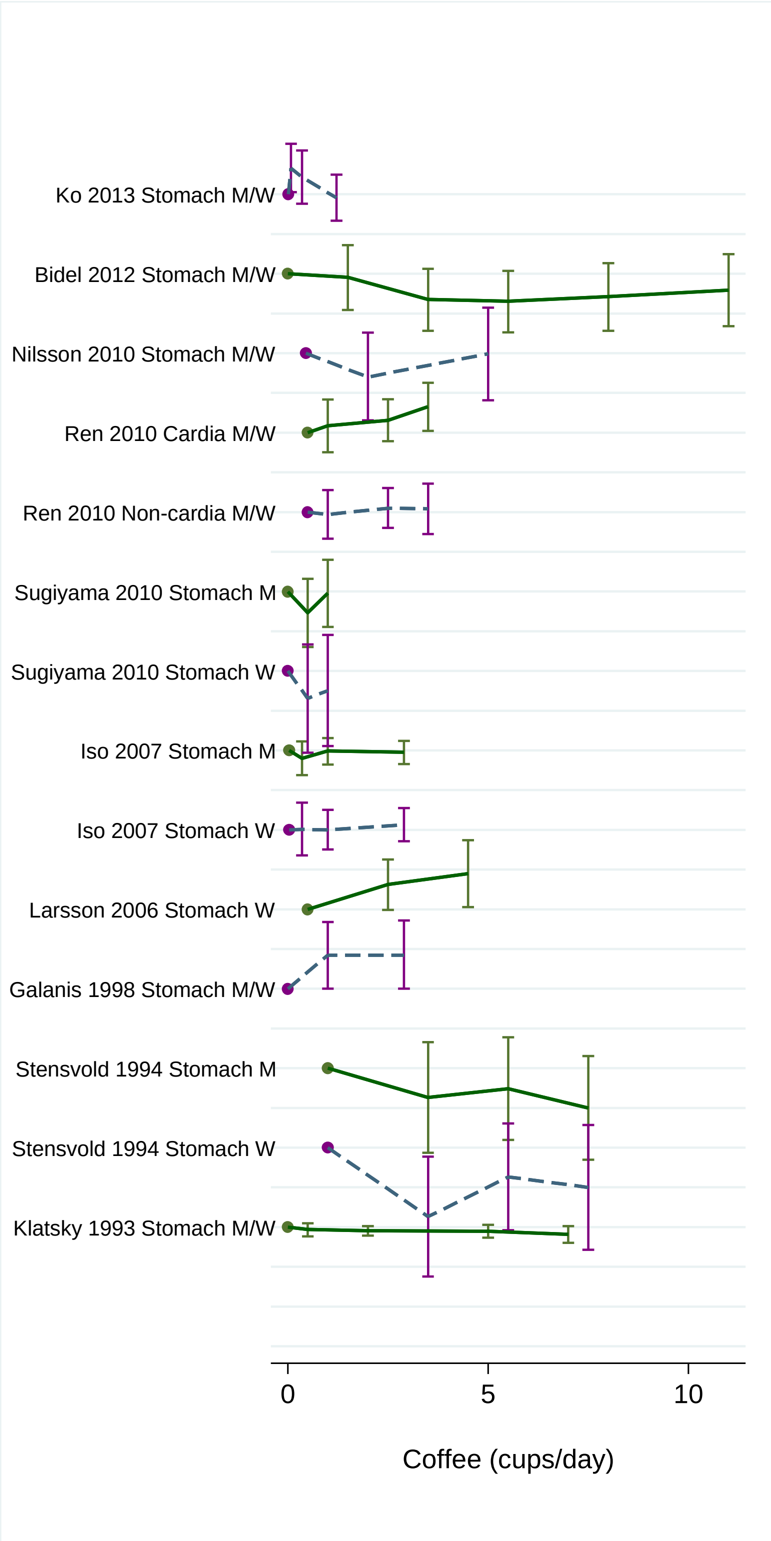
Table 98 Coffee intake and stomach cancer risk. Main characteristics of studies excluded from the linear dose-response meta-analysis

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
Tokui, 2005 STM80105 Japan	JACC, Prospective Cohort, Age: 40-79 years, M/W	536/ 44,930 12 years	Population registry	FFQ	Mortality, stomach cancer Men	1+/day vs none cups/week	0.81 (0.65-0.99)	Age	Superseded by Iso, 2007 STM80144
		115/ 9,724 8.5 years			Women		1.0 (0.74-1.35)		
Khan, 2004 STM20239 Japan	HGCS, Prospective Cohort, Age: 40- years, M/W	36/ 3,158 14 years	Follow-up surveys	FFQ	Mortality, stomach cancer Men	2-7x/week vs never-several/month times/month	1.0 (0.5-2.0)	Age, smoking habits	Excluded, two exposure categories only
		15/			Women		0.3 (0.1-1.4)	Age, health education, health screening, health status, smoking habits	
Nagata, 2002 STM01669 Japan	TCCJ, Prospective Cohort, Age: 35- years, M/W	40/ 30,304 7 years	Population registry	FFQ	Mortality, stomach cancer	Daily vs rare/never ml/day	2.54	Age, total energy intake	Excluded, two exposure categories only, missing confidence intervals
Ngoan, 2002 STM01668 Japan	FPC, Prospective Cohort, Age: 15-96 years, M/W	116/ 13,250 13 years	Resident registry	FFQ	Mortality, stomach cancer	Daily drinking vs not daily times/day	1.0 (0.9-1.1)		Excluded, two exposure categories only
Tsubono, 2001 STM02797 Japan	MCS I, Prospective Cohort, Age: 40- years, M/W	419/26,311 9 years	Histology	FFQ	Incidence, stomach adenocarcinoma	≥3 cups/day vs never	1.0 (0.6-1.6)	Sex, age, green-tea consumption, type of health insurance, history of peptic ulcer, smoking, consumption of	Superseded by Sugiyama, 2010 STM80132

Author, Year, 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
								alcohol, rice, black tea, meat, green or yellow vegetables, pickled vegetables, other vegetables, fruits, and bean-paste soup	
Jacobsen, 1986 STM09619 Norway	CNC, Prospective Cohort, Age: 35- years, M/W	147/ 16,555 11.5 years	Cancer registry	Questionnaire (general)	Mortality, stomach cancer	≥7 vs ≤2 cups/day	1.46	Age, sex, area of residence	Excluded, two exposure categories only, missing confidence intervals
Nomura, 1986 STM14813 USA	HHP, Prospective Cohort, Japanese residents of Hawaii	106/ 7,355 15 years	Cancer registry/ hospital records	Dietary recall	Mortality, stomach cancer	5+ vs 0 cups/day	1.2	Age	Excluded, only incidence rate
Whittemore, 1985 STM00030 USA	CAHS, Nested Case Control, Age: 17- years, M/W	64/ 51,477 50 years	Population registry/ death certificates	Questionnaire (general)	Incidence, stomach cancer	Drinker vs non-drinker	No association (data not shown)		Excluded, no measure of association

Figure 112 RR estimates of stomach cancer by levels of coffee intake

Note: Only studies reporting RRs (95% CI) for quantitative levels of coffee intake are shown.



Bidel, 2012 is a study in Finnish men and women. Intake was reported in cups/day

Figure 113 RR (95% CI) of stomach cancer for the highest compared with the lowest level of coffee intake

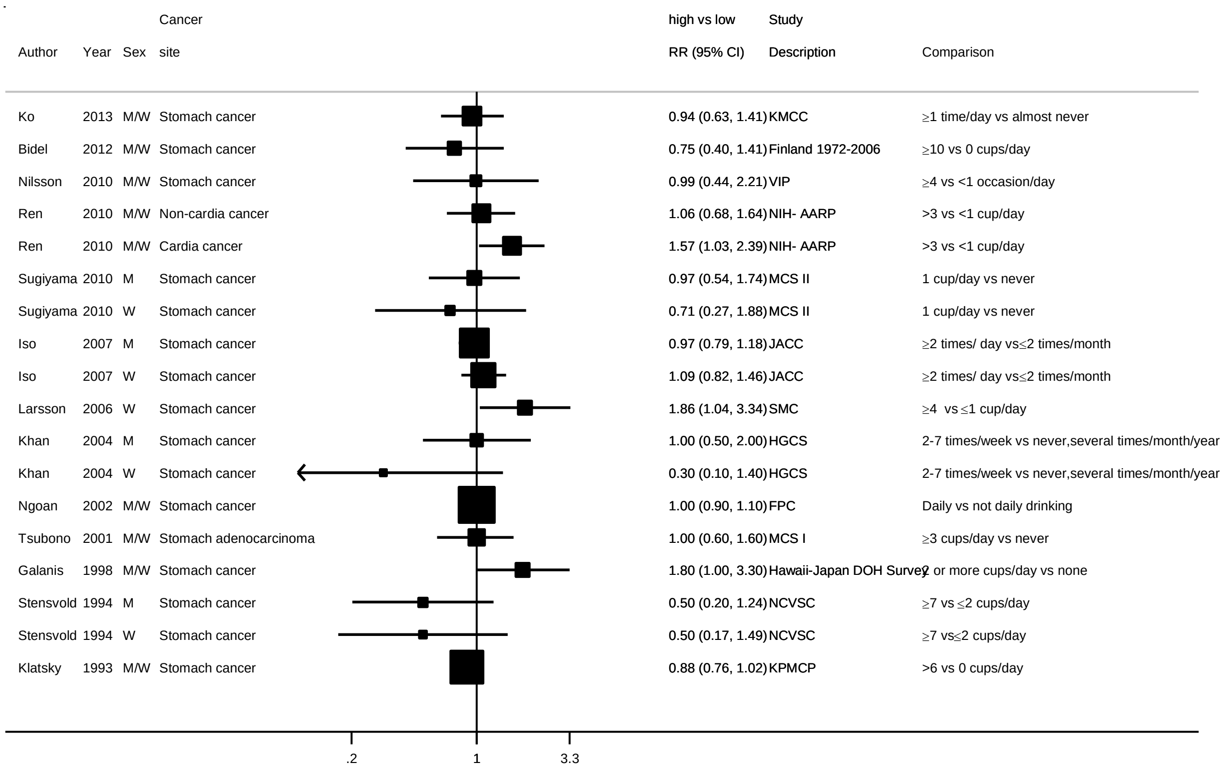


Figure 114 Relative risk of stomach cancer for 1 cup/day increase of coffee intake

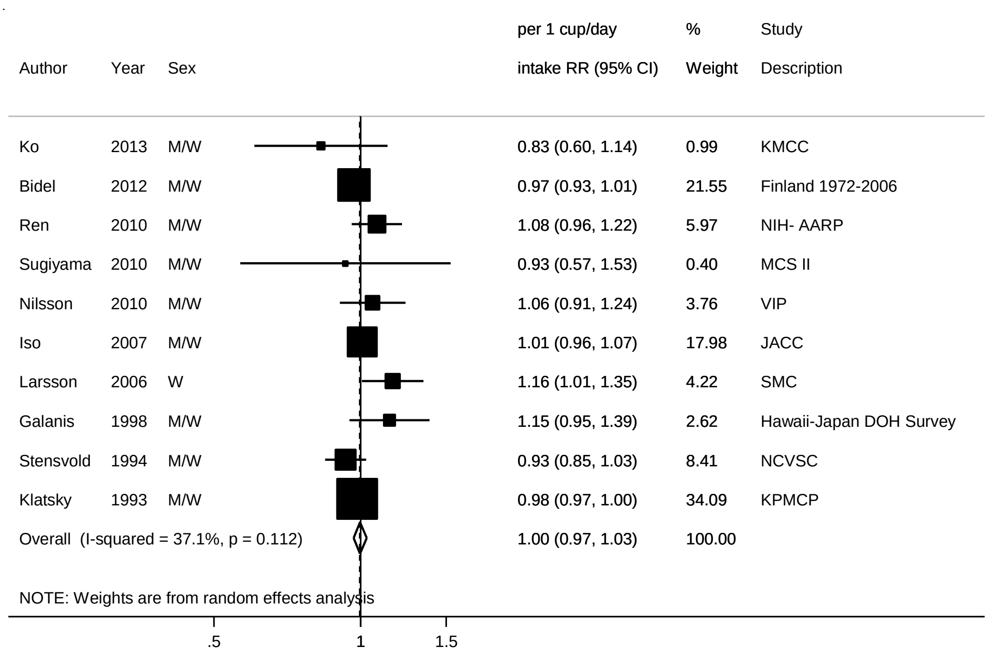
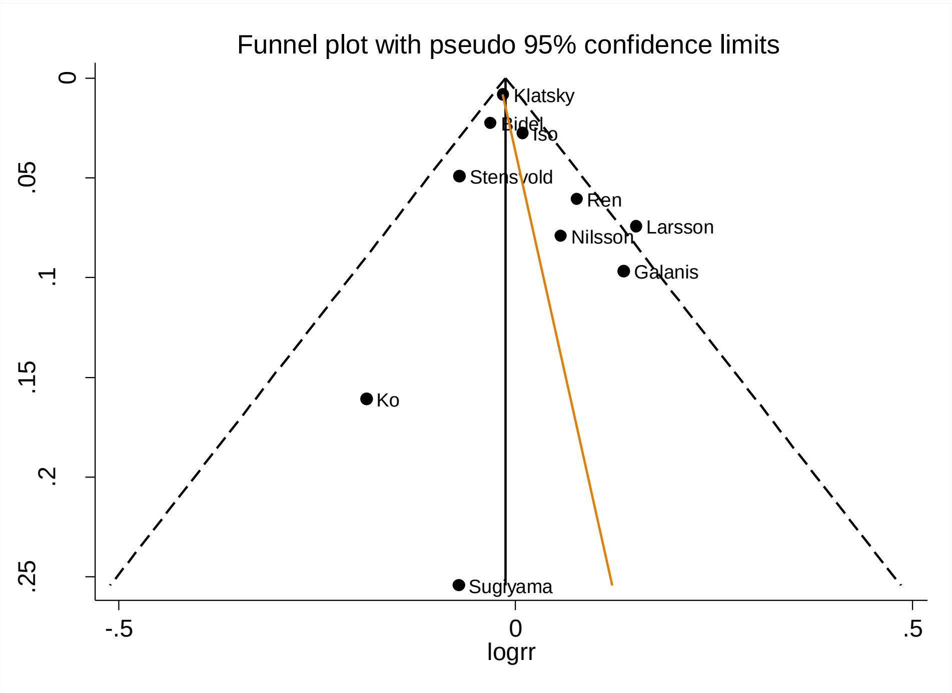


Figure 115 Funnel plot of studies included in the dose response meta-analysis of coffee intake and stomach cancer



Egger's test p=0.31

Figure 116 Relative risk of stomach cancer for 1 cup/day increase of coffee intake by sex

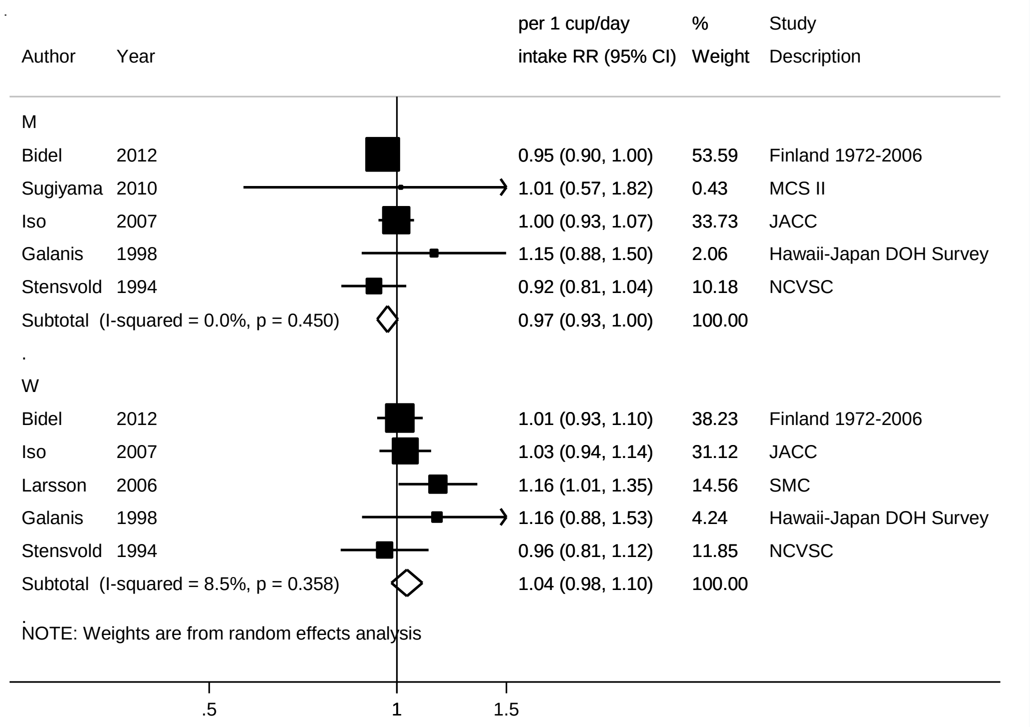


Figure 117 Relative risk of stomach cancer for 1 cup/day increase of coffee intake by cancer outcome

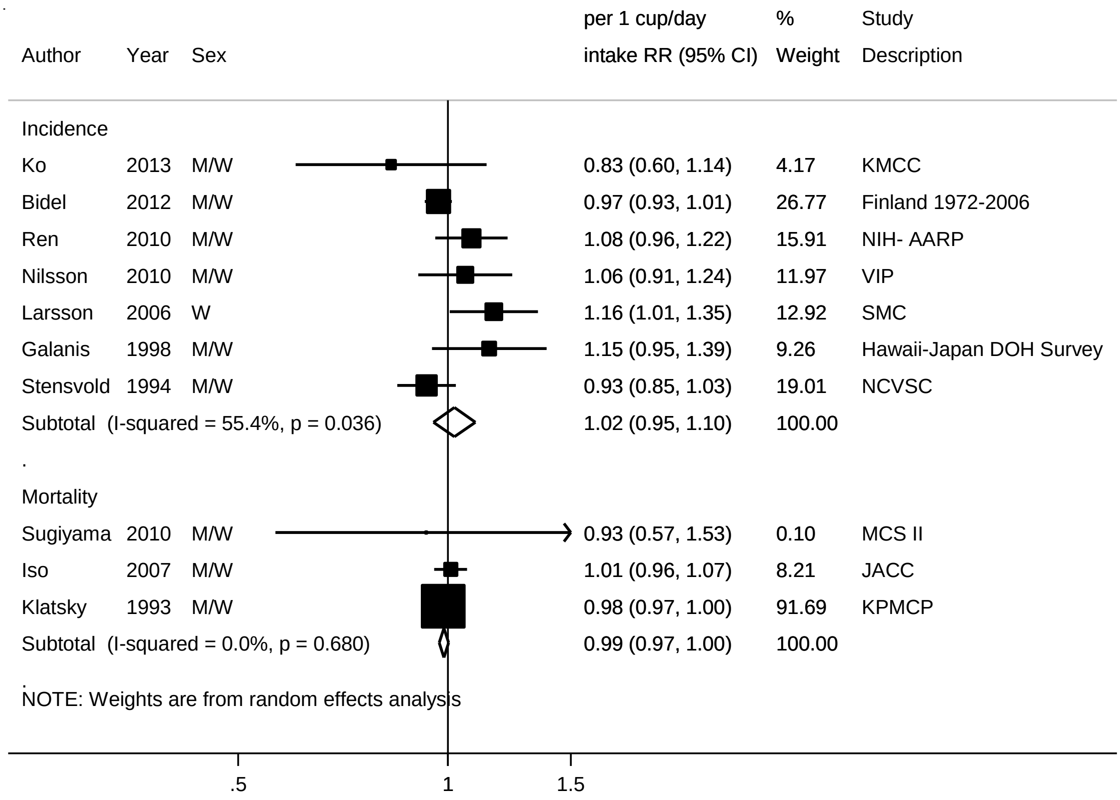
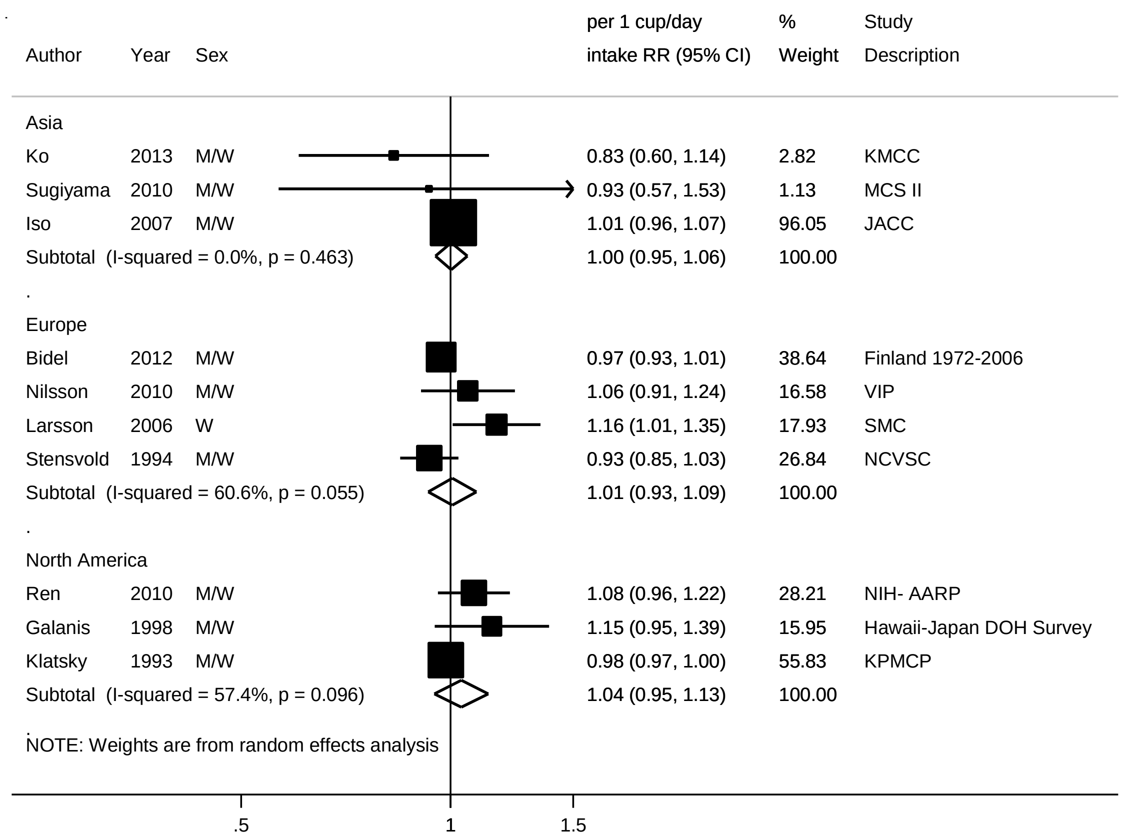


Figure 118 Relative risk of stomach cancer for 1 cup/day increase of coffee intake by geographic location



3.6.2 Tea, black tea

Randomised controlled trials

No randomised controlled trial was identified.

Cohort studies

Summary

Main results:

There were not enough studies with the required data to conduct a dose-response meta-analysis. Study characteristics and results of all studies are tabulated; the relative risk estimates for the highest compared to the lowest tea intake of four studies are shown in a forest plot.

Nine studies were identified. Results were discordant across studies. The only significant result was a higher observed compared to expected mortality for stomach cancer in men in UK. The analyses were adjusted only by age. No published meta-analyses or pooled prospective studies were identified.

Table 99 Tea, black tea intake and stomach 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	4
Studies included in linear dose-response meta-analysis	Not enough studies

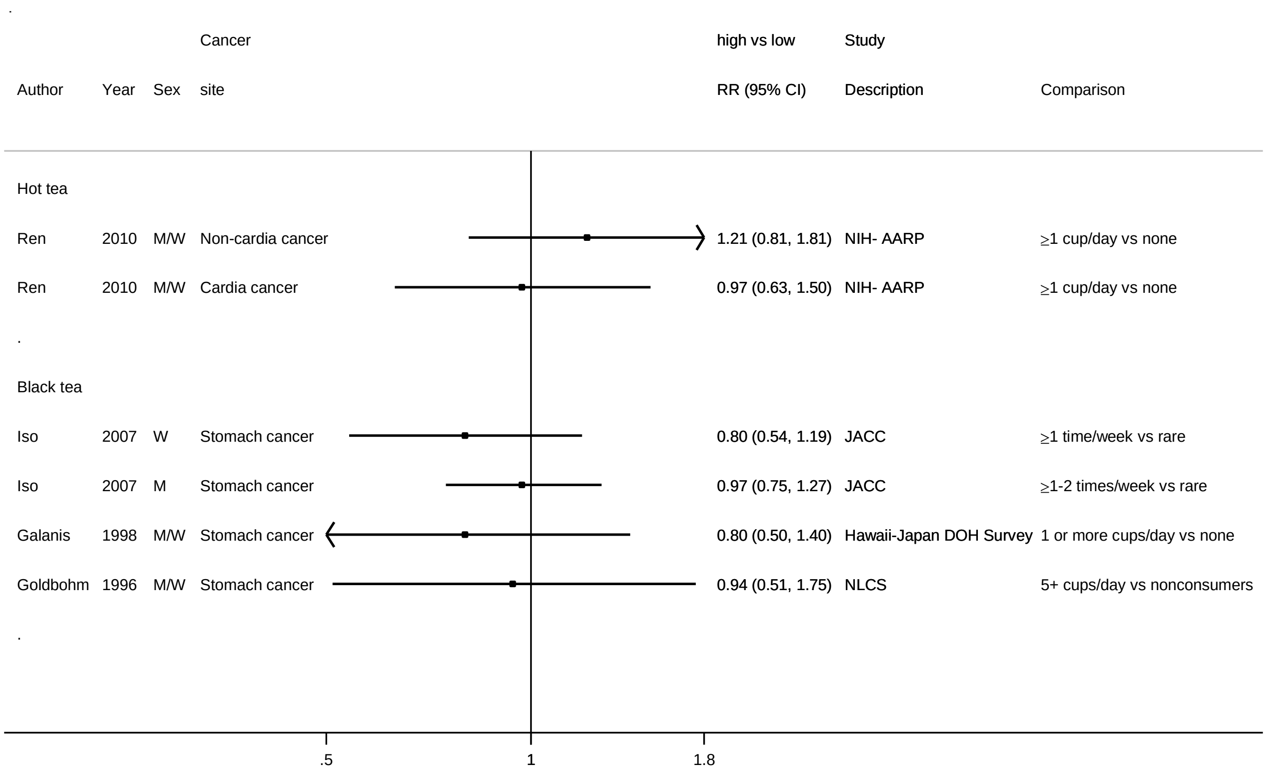
Table 100 Tea, black tea intake and stomach cancer risk. Main characteristics of studies identified

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	Notes
Ren, 2010 STM80059 USA	NIH- AARP, Prospective Cohort, Age: 50-71 years, M/W, Retired	231/ 481 563 6 years	Linkage of the cohort with database to state cancer registries	124-item FFQ Hot tea	Incidence, cardia cancer	≥1 cup/ day vs none	0.97 (0.63-1.50) Ptrend:0.85	Age, sex, BMI, caloric intake, ethnicity, red meat intake, tobacco use, alcohol intake, education, fruit and vegetable intake, usual physical activity, vigorous physical activity, white meat intake	
		224/			Non-cardia cancer		1.21 (0.81-1.81) Ptrend:0.52		
Iso, 2007 STM80144 Japan	JACC, Prospective Cohort, Age: 40-79 years, M/W	563/ 105,500.00 15.00 years	Municipal resident registration records, death certificates	Validated FFQ Black tea	Mortality, stomach cancer Men	≥1-2 times/week vs. rare	0.97 (0.75-1.27)	Age, area of study	
		276/			Women	≥1 time/week vs. rare	0.80 (0.54-1.19)		
Tokui, 2005 STM80105 Japan	JACC, Prospective Cohort, Age: 40-79 years, M/W	408/ 110,792 11 years	Municipal resident registration records, death certificates	Validated FFQ Black tea	Mortality, stomach cancer Men	1+ vs. less than 1 cup/day	1.41 (0.98-2.03)	Age	Superseded by Iso, 2007
		201/			Women		1.03 (0.60-1.79)		
Hirvonen, 2001 STM02213 Finland	ATBC, Prospective Cohort, Age: 50-69 years, M, Smokers	111/ 27 110 6.1 years	Cancer registry	FFQ Tea	Incidence, stomach cancer	(mean exposure)	Age		Excluded, no risk estimate
Galanis, 1998 STM04769 USA	Hawaii-Japan DOH Survey, Prospective	108/ 11 907 14.8 years	Cancer registry	13-food item, 6-beverage item FFQ	Incidence, stomach cancer	1 or more cups/day vs none	0.80 (0.50-1.40)	Age, sex, education, place of birth	Only two intake categories, used in HvL 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	Notes
	Cohort, Age: 18- years, M/W, Japanese residents of Hawaii			Black tea					
Goldbohm, 1996 STM10879 Netherlands	NLCS, Case Cohort, Age: 55-69 years, M/W	183/ 120 852 4 years	Cancer registry	150-item self-administered semi-quantitative FFQ Black tea	Incidence, stomach cancer	≥5 cups/day vs non-consumers	0.94 (0.51-1.75) Ptrend:0.73	Age, sex, coffee consumption, educational level, family history of stomach cancer, smoking habits, vitamin c	
Klatsky, 1993 STM00025 USA	KPMCP, Prospective Cohort, Age: 20-84 years, M/W	78/ 128 934 8 years	Death register	Questionnaire (general) Tea	Mortality, stomach cancer	≥4 cups/day or ≥1 cups/day vs none	Not reported Tea intake not related to any of the causes of death investigated	Age, sex, race, BMI, smoking, alcohol, education, marital status	No relative risk estimate (no increased risk)
Kinlen, 1988 STM07810 England	General Register Office London Cohort, Prospective Cohort, Age: 45-60 years, M	172/ 14 085 17 years	NHS central registry	Questionnaire (general) Tea	Mortality, stomach cancer	10+ vs 0-3 cups/day	Observed/ expected ratio: 1.44 Ptrend:<0.0005	Age	Expected deaths for men of England and Wales
Heilbrun, 1986 STM13311 USA	HHP, Prospective Cohort, Age: 45-68 years,	136/ 7 833 16 years	Cancer registry/ hospital records	Questionnaire (general)	Mortality, stomach cancer		No association	Age	No relative risk estimate reported

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Notes
	M, Japanese residents of Hawaii								
Whittemore, 1985 STM00030 USA	CAHS, Nested Case Control, Age: 17- years, M/W	64/ 51 477 50 years	Population registry/death certificates	Questionnaire (general)	Incidence and mortality, stomach cancer		No association		No relative risk estimate reported

Figure 119 RR (95% CI) of stomach cancer for the highest compared with the lowest level of tea, black tea intake



3.6.2 Green tea

Randomised controlled trials

No randomised controlled trial was identified.

Cohort studies

Summary

Main results:

Nine studies (4379 cases) out of twelve were included in the dose-response meta-analysis. No significant association of green tea with stomach cancer was observed.

Three studies were excluded from the dose-response analyses. All studies found non-significant associations (Khan, 2004; Wong, 2004; Nakachi, 2000).

All studies were conducted in Asia except one study on Japanese living in Hawaii.

Low heterogeneity was observed.

There was no significant evidence of publication bias or small study bias.

Sensitivity analyses:

The summary RR did not change materially when studies were omitted in turn in influence analysis. Non-linear dose-response meta-analysis:

There was statistical evidence of non-linear dose-response for stomach cancer and green tea intake. There is a risk decrease approximately in the range 1.5 to 3.5 cups/day with respect to no consumption or very high intakes. However, this pattern is not observed in the studies (see Figure RR estimates of stomach cancer by levels of green tea consumption).Study quality:

Loss to follow-up was low in most studies.

Cancer outcome was confirmed histologically or using death certificate in most studies.

Green tea intake was assessed using FFQ. In a subset of a Chinese cohort in women (Nechuta, 2012), the validity of the questionnaire for green tea was examined using urinary excretion of a specific tea polyphenol. A statistically significant trend between increasing green tea leaves consumed (g/d) and urinary excretion of EGC was observed.

The intake units used varied between the studies. Nechuta, 2012 reported consumption of green tea leaves (g/day). Iso, 2007, Sauvaget, 2005, and Ngoan, 2002 used times or occasions per day/week/month. The remaining studies used cups. Times or occasions were used in the meta-analysis as equivalent of cup. Cup volume was described as 60-90ml in Suzuki, 2009 and 100 ml in Kuriyama, 2006 and Tsubono, 2001.

All studies included in the dose-response analysis were adjusted for age, sex, smoking status, alcohol intake and other potential confounders except Iso, 2007 which was stratified by sex and adjusted for age only. Only Kuriyama, 2006 was adjusted for total energy intake.

None of the studies were adjusted for Helicobacter pylori status.

Subgroup analysis by cancer subsite was not conducted. Sasazuki, 2004 was the only study reporting stratified results by cancer subsite. Significant inverse association was reported for distal gastric cancer in the highest category (five cups or more) among women, RR 0.51 (95% CI=0.30-0.86).

Table 101 Green tea intake and stomach cancer risk. Number of studies in the CUP SLR

	Number
Studies identified	12 (17 publications)
Studies included in forest plot of highest compared with lowest exposure	12
Studies included in linear dose-response meta-analysis	9
Studies included in non-linear dose-response meta-analysis	6

Table 102 Green tea intake and stomach cancer risk. Summary of the linear dose-response meta-analysis in the 2005 SLR and CUP

	2005 SLR	**CUP**
Increment unit used	1 cup/day	1 cup/day
Studies (n)	5	9
Cases (total number)	1053	4379
RR (95%CI)	1.02 (0.99-1.05)	1.01 (0.99-1.03)
Heterogeneity (I^2, p-value)	0%, 0.5	11.2%, 0.34
P value Egger test	0.4	0.37
Men		
Studies (n)	5	6
RR (95%CI)	1.03 (0.99-1.08)	1.02 (0.99-1.05)
Heterogeneity (I^2, p-value)	-	14.0%, 0.33
Women		
Studies (n)	5	7
RR (95%CI)	0.97 (0.93-1.02)	0.98 (0.94-1.01)
Heterogeneity (I^2, p-value)	-	0%, 0.70
Studies in the CUP and Pooling Analysis of Asian cohorts*		
	Women	**Men**
Studies (n)	9	8
Cases (total number)	1159	2632

RR (95%CI)	0.96 (0.93-0.99)	1.06 (0.93-1.21)	
Heterogeneity (I^2, p-value)	0%, 0.54	31.4%, 0.23	
P value test publication bias	-	-	
Other stratified and sensitivity analysis. CUP meta-analysis			
Outcome	**Mortality**	**Incidence**	
Studies (n)	4	5	
RR (95%CI)	1.02 (0.99-1.04)	1.00 (0.97-1.04)	
Heterogeneity (I^2, p-value)	0%, 0.93	49.7%, 0.09	
Duration of follow-up	**5-<10 years**	**10-<15 years**	**≥15 years**
Studies (n)	3	4	2
RR (95%CI)	1.03 (0.99-1.07)	0.99 (0.93-1.04)	1.01 (0.99-1.04)
Heterogeneity (I^2, p-value)	0%, 0.81	35.5%, 0.20	0%, 0.90
Number of cases	**<500 cases**	**500-<1000 cases**	**≥1000 cases**
Studies (n)	6	1	2
RR (95%CI)	1.02 (0.97-1.06)	0.98 (0.95-1.02)	1.01 (0.99-1.04)
Heterogeneity (I^2, p-value)	26.1%, 0.24	-	0%, 0.90
Adjustment for:			
Anthropometric measures	**Not adjusted**	**Adjusted**	
Studies (n)	6	3	
RR (95%CI)	1.01 (0.99-1.03)	0.99 (0.95-1.04)	
Heterogeneity (I^2, p-value)	16.4%, 0.31	21.1%, 0.28	
Socioeconomic status			
Studies (n)	5	4	
RR (95%CI)	1.01 (0.99-1.03)	1.00 (0.96-1.05)	
Heterogeneity (I^2, p-value)	0%, 0.47	44.2 %, 0.15	
Alcohol intake**			
Studies (n)	4	4	
RR (95%CI)	1.00 (0.99-1.02)	1.03 (1.00-1.07)	
Heterogeneity (I^2, p-value)	0%, 0.56	0%, 0.46	
Physical activity			
Studies (n)	6	3	
RR (95%CI)	1.01 (0.99-1.03)	0.99 (0.95-1.04)	
Heterogeneity (I^2, p-value)	16.4%, 0.31	21.1%, 0.28	
Comorbidities			
Studies (n)	6	3	

RR (95%CI)	1.01 (0.99-1.03)	1.00 (0.96-1.05)	
Heterogeneity (I^2, p-value)	10.7%, 0.35	41.0%, 0.18	

*Pooled study by Inoue, 2009a counted JPHC I and JPHC II as two cohorts.

**Nechuta, 2012 study among non-smoking and non-alcohol drinking women was excluded.

Table 103 Green tea intake and stomach cancer risk. Results of meta-analyses and pooled analyses of prospective studies published after the 2005 SLR

Author, Year	Number of studies	Total number of cases	Studies country, area	Outcome	Comparison	RR (95%CI)	P trend	Heterogeneity (I^2, p value)
Meta-analysis								
Kang, 2010	7 cohorts	2774	Japan, North America, China	Incidence Gastric cancer	High vs low	1.03 (0.92-1.16)		
	11 case-control studies	4040				0.74 (0.63-0.86)		
	All	6814				0.86 (0.74-1.00)		
Pooled-analysis								
Inoue, 2009a	6 cohorts	2495	Japan: JPHC I and II, JACC, MIYAGI, 3-prefectures MIYAGI, 3 prefectures-AICHI	Incidence Gastric cancer Men	≥5 vs <1 cup/day	1.06 (0.86-1.30)	0.74	0.10
		217		Women		0.79 (0.65-0.96)	0.04	0.28
		947		Proximal (upper third) Men	≥1 vs <1 cup/day	1.43 (0.96-2.14)	0.08	0.74
		1082		Women		1.17 (0.52-2.60)	0.87	0.85
		53		Distal (lower two thirds) Men		0.96 (0.79-1.17)	0.86	0.48
		370		Women		0.70 (0.50-0.96)	0.04	0.36

Note: The total number of cases in Kang, 2010 meta-analysis was estimated from study characteristics' table.

Table 104 Green tea intake and stomach 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
Nechuta, 2012 STM80064 China	SWHS, Prospective Cohort, Age: 40-70 years, Women Nonsmokers, non-alcohol drinkers	293/ 69 310 11 years	Medical records and cancer registries	Interview Regular tea (88.2% green tea drinkers only)	Incidence, stomach cancer, non-smoker/ drinker	≥150 g/month vs never	0.82 (0.52-1.29)	Age, BMI, diabetes, family history of cancer, marital status, occupation, education, exercise, fruit and vegetable, meat	Distribution of person-years by exposure categories, mid-points of exposure categories
Suzuki, 2009 STM80124 Japan	SECS, Prospective Cohort, Age: 65-84 years, M/W	68/ 12 251 6 years	National statistics office	Baseline questionnaire	Mortality, stomach cancer	Per 1 cup/day	1.04 (0.95-1.13)	Age, sex, alcohol consumption, BMI, smoking status, frequency of physical activity	
						≥7 vs <1 cups/day	0.81 (0.18-3.54)		
Iso, 2007 STM80144 Japan	JACC, Prospective Cohort, Age: 40-79 years, M/W	690/ 105 500 15 years	Municipal resident registration records, death certificates	Validated FFQ	Mortality, stomach cancer Men	≥4 times/day vs ≤4 times/week	1.21 (0.95-1.54)	Age, area of study	Intake per week converted to intake per day, exposure measurement unit of times/day used as cups/day, mid-points of exposure categories, RRs for men and women combined
		330/			Women	≥4 times/day vs ≤3 times/week	1.02 (0.74-1.40)		
Kuriyama, STM89948 2006 Japan	NHI, Prospective Cohort, Age: 40-79,	193/ 40 530 Up to 7 years	Death certificates	Validated FFQ	Mortality, stomach cancer All	≥5 vs <1 cup/day	1.17 (0.78-1.76)	Age, job status, education, BMI, exercise, walking duration, history of hypertension, diabetes	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
	M/W	138/			Men		1.20 (0.74-1.95)	mellitus, gastric ulcer, smoking, alcohol, energy intake, consumption of miso, soybean products, meat, fish, dairy, fruits, vegetables, oolong tea, black tea, coffee	
		55/			Women		1.08 (0.50-2.33)		
Sauvaget, 2005 STM44428 Japan	LSS, Prospective Cohort, Age: 34-98 years, M/W, Atomic bomb survivors	1,270/ 38 540 19 years	Cancer registry	22- item FFQ	Incidence, stomach cancer	5+ vs <2 times/week	1.06 (0.89-1.25)	Age, sex, area of residence, educational level, radiation exposure, smoking habits	Times/day used as cups/day, mid-points of exposure categories
Sasazuki, 2004 STM24538 Japan	JPHC I and II, Prospective Cohort, Age: 40-69 years, M/W	665/ 34 832 11 years - cohort I; 6 years – cohort II	Hospital records, population-based cancer registries and death certificates, histologically confirmed	27-item (cohort I), 33-item (cohort II) questionnaires	Incidence, gastric cancer Men	5+ vs <1 cups/day	0.97 (0.77-1.22)	Age, area of residence , smoking habits	Distribution of person-years and cases by exposure categories, mid-points of exposure categories, RRs for men and women combined
		227/ 38 111			Women		0.70 (0.47-1.05)		
Ngoan, 2002 STM01668 Japan	FPC, Prospective Cohort, Age: 15-96 years, M/W	106/ 13 250 13 years		Self-administered questionnaire	Mortality, stomach cancer All	≥ 1 time/day vs ≤ 2-4 times/month	1.90 (0.60-6.20)	Age, sex, smoking status processed meat, liver, cooking or salad oil, suimono, and pickled food	Intake per week/month converted to intake per day, exposure measurement unit of times/day used as cups/day, person-years
		73/			Men		1.30 (0.70-2.50)		

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	Missing data derived for analyses
		33/			Women		2.20 (0.70-6.70)		per category and mid-points of exposure categories
Tsubono, 2001 STM02797 Japan	MCS I, Prospective Cohort, Age: 40- years, M/W	419/ 26 311 9 years	Miyagi prefectural cancer registry	Validated 14-item FFQ	Incidence, gastric cancer All	≥5 vs <1 cup/day	1.20 (0.90-1.60)	Age, sex (combined analysis), alcohol consumption, bean-paste soup intake, black tea consumption, coffee consumption, fruit, health insurance, history of peptic ulcer, meat intake, pickles, rice intake, smoking habits, vegetable intake	Mid-points of exposure categories
		296/			Men		1.50 (1.00-2.10)		
		123/			Women		0.80 (0.50-1.30)		
Galanis, 1998 STM04769 USA	Hawaii-Japan DOH Survey, Prospective Cohort, Age: 18- years, M/W, Japanese residents of Hawaii	108/ 11 907 14.8 years	Cancer registry	13-food item, 6-beverage item FFQ	Incidence, stomach cancer All	2 or more vs none cups/day	1.50 (0.90-2.30)	Age, sex (combined analysis), educational level, place of birth and in men, smoking status and alcohol	Person-years per category and mid-points of exposure categories
		64/			Men		1.60 (0.90-2.90)		
		44/			Women		1.30 (0.60-2.60)		

Table 105 Green tea intake and stomach 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
Hoshiyama, 2004 STM00440 Japan	JACC, Nested Case Control, Age: 40-79 years, M/W	151/ 65 184 10 years	Population registry	FFQ	Incidence, stomach cancer	≥10 vs <1 cups/day	1.20 (0.60-2.50)	Age, sex, bean-paste soup intake, educational level, family history of stomach cancer, fruit, H. pylori infection, history of peptic ulcer, rice intake, salt preference, smoking habits, vegetable intake	Superseded by Iso, 2007; used in non-linear with more exposure categories
Khan, 2004 STM20239 Japan	HGCS, Prospective Cohort, Age: 40- years, M/W	36/ 3158 14 years	Follow-up surveys	FFQ	Mortality, stomach cancer Men	2-7x/week vs never-several/month times/month	1.10 (0.40-2.50)	Age, smoking habits	Excluded, only two intake categories
		15/			Women		0.70 (0.20-1.90)	Age, health education, health screening, health status, smoking habits	
Wong, 2004 STM00527 China	CCHT, Prospective Cohort, Age: 42.00years, M/W, M/W, H. pylori eradication trial participants	18/ 1630 7.5 years	Clinical trial follow up records	FFQ	Incidence, lower third gastric cancer	2+ vs <2 times/week	1.55 (0.58-4.14)		Excluded, only two intake categories
Yatsuya, 2004 STM00003 Japan	JACC, Prospective Cohort, Age: 40-79 years, M/W	105/307 10 years	Population registry	FFQ	Mortality, stomach cancer Men	≥ 3-4 vs ≤ 1-2 times/week	0.89 (0.40-1.97)	H. pylori infection, the number of siblings, smoking status, drinking habit, preference of salty foods, consumption of	Excluded, only two intake categories, superseded by Iso, 2007
		97/192			Women		1.73 (0.82-3.65)		

Author, Year, 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
								green – yellow vegetables, citrus fruits and green tea, and education	
Fujino, 2002 STM01512 Japan	JACC, Prospective Cohort, Age: 40-79 years, M/W	237/ 44 930 10 years	Population registry	FFQ	Mortality, stomach cancer Men	Every day vs <3 times/week	1.11 (0.75-1.63)	Age	Superseded by Iso, 2007
		108/			Women		1.43 (0.78-2.62)		
Hoshiyama, 2002 STM01545 Japan	JACC, Prospective Cohort, Age: 40-79 years, M/W	240/ 72 851 8.1 years	Population registry	FFQ	Mortality, stomach cancer Men	≥10 vs <1 cups/day	1.00 (0.50-2.00)	Age, bean-paste soup intake, family history of stomach cancer, fruit, history of peptic ulcer, rice intake, salt preference, smoking habits, vegetable intake	Superseded by Iso, 2007
		119/			Women		0.70 (0.30-2.00)		
Nagano, 2001 STM02392 Japan	LSS, Prospective Cohort, Age: 34-103 years, M/W, Atomic bomb survivors	836/ 38 540 16 years	Cancer registry	FFQ	Incidence, stomach cancer	5+ vs 0-1 times/day	0.95 (0.76-1.20)	Age, sex, alcohol consumption, BMI, calendar year, city/town, educational level, radiation exposure, smoking habits	Superseded by Sauvaget, 2005
Nakachi, 2000 STM00012 Japan	SPC, Prospective Cohort, Age: 53.00years, M/W	140/ 8552 11 years	Death certificates	Questionnaire (general)	Mortality, stomach cancer	10+ vs >3 cups/day	0.69 (0.23-1.88)	Age, sex, alcohol consumption, cereals, smoking habits, vegetable intake	Excluded, only two levels of intake

Figure 120 RR estimates of stomach cancer by levels of green tea consumption

Note: All RRs are for total stomach cancer.

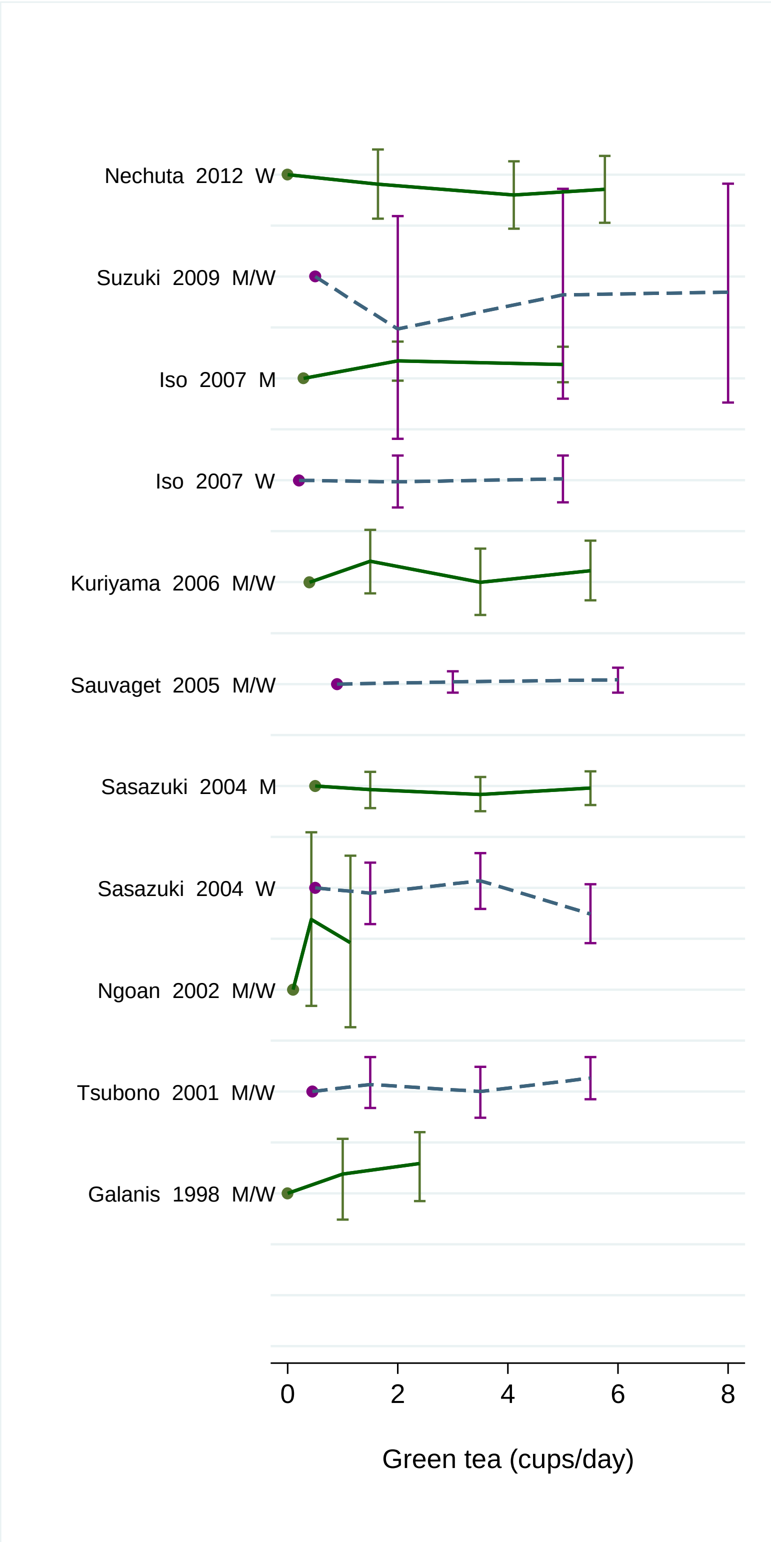


Figure 121 RR (95% CI) of stomach cancer for the highest compared with the lowest level of green tea intake

Note: All RRs are for total stomach cancer.

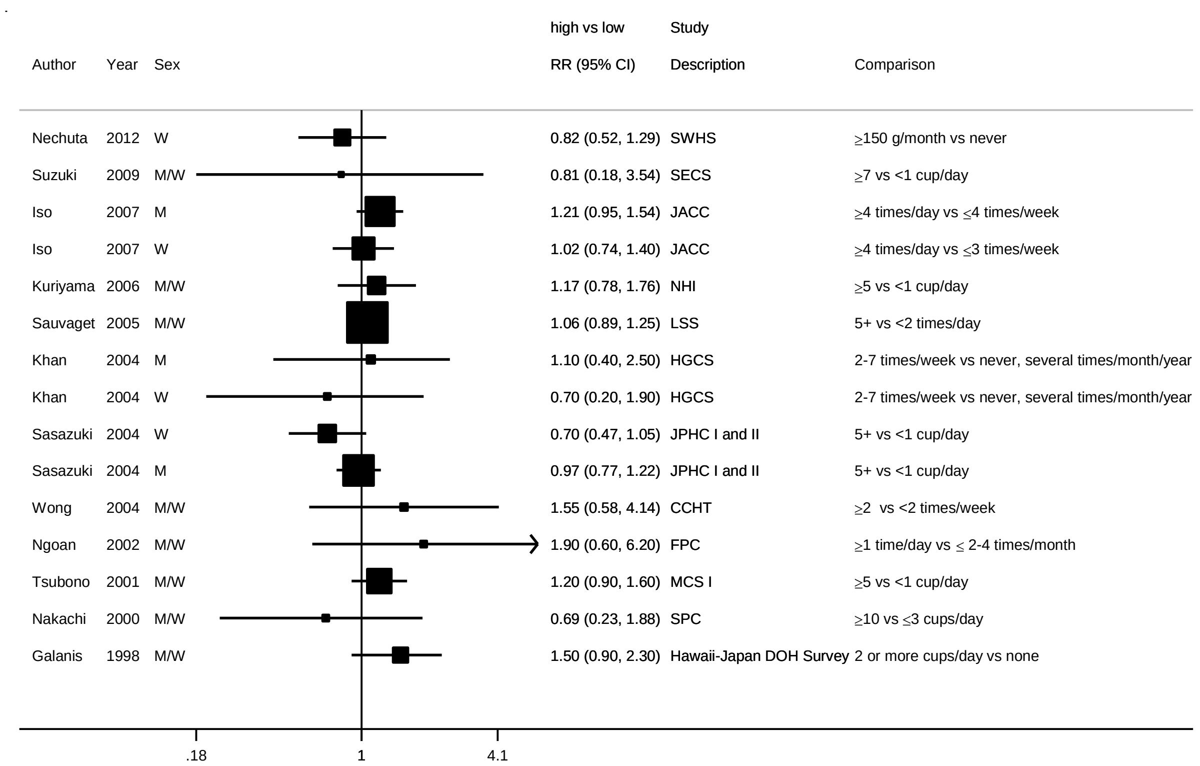


Figure 122 Relative risk of stomach cancer for 1 cup/day increase of green tea intake

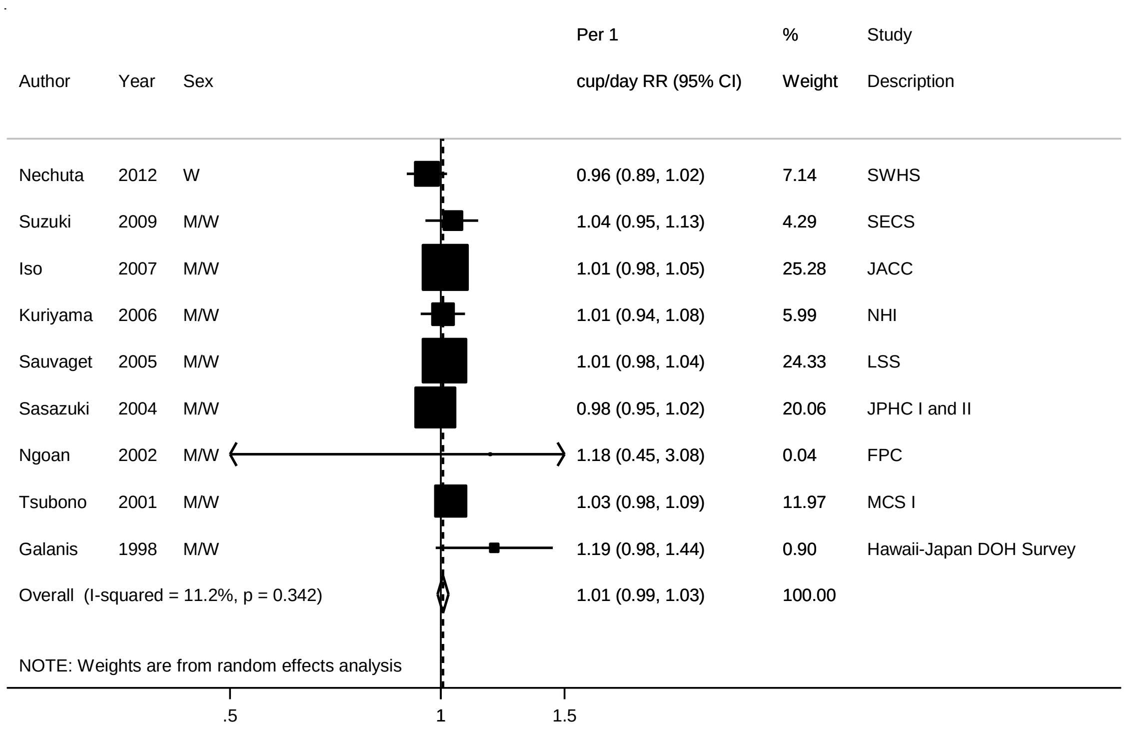
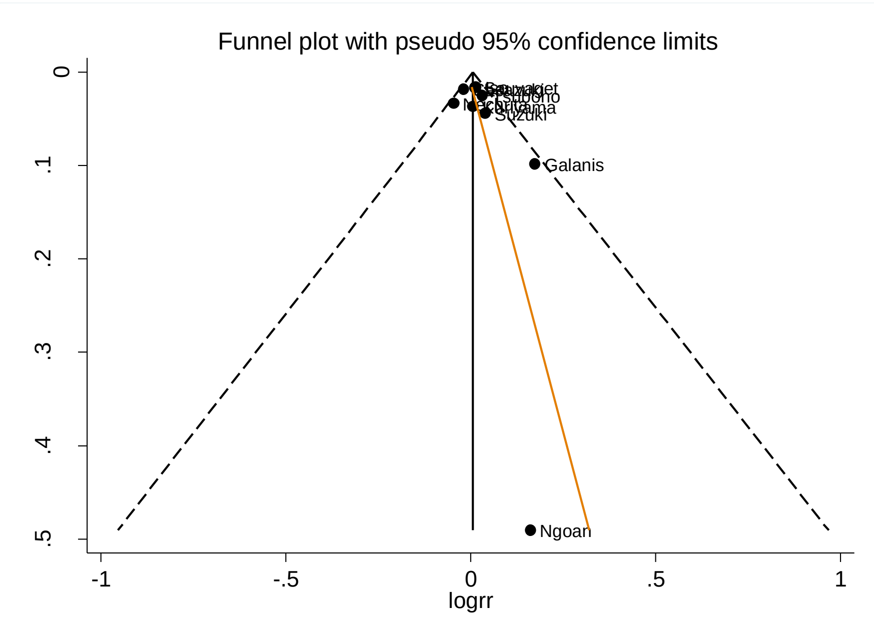


Figure 123 Funnel plot of studies included in the dose response meta-analysis of green tea intake and stomach cancer



Egger's test p=0.37

Figure 124 Relative risk of stomach cancer for 1 cup/day increase of green tea intake by sex

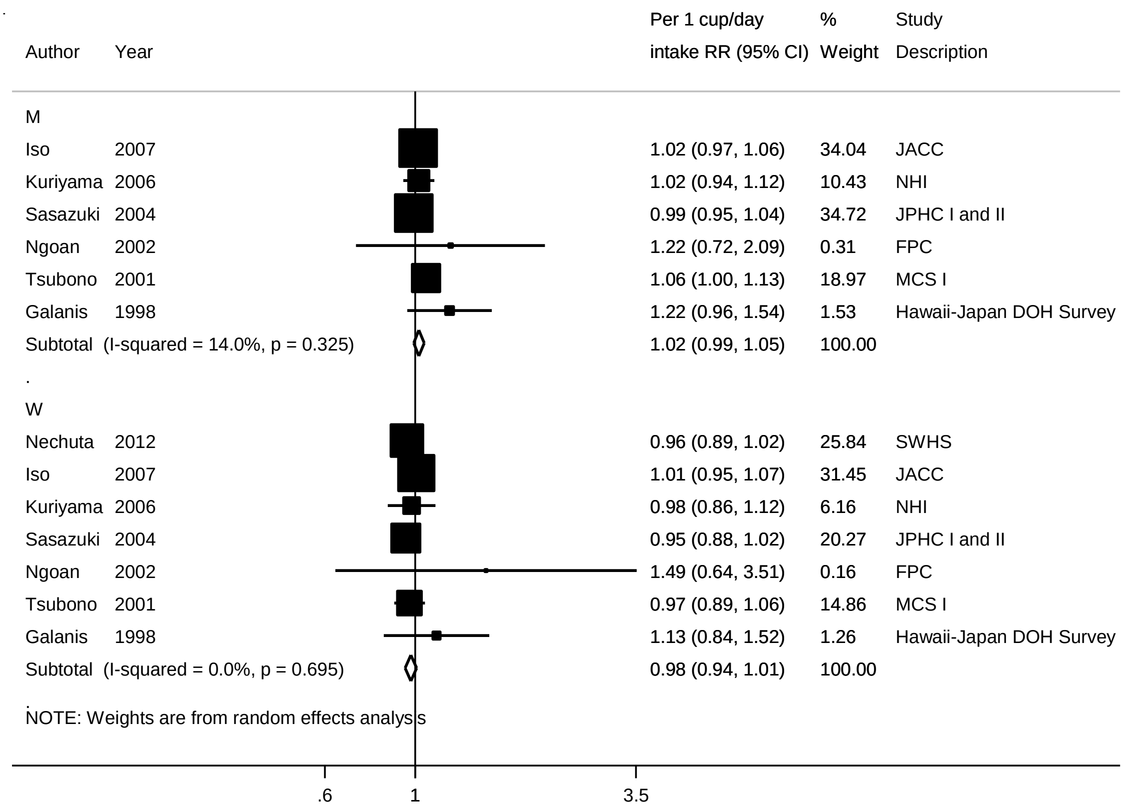


Figure 125 Relative risk of stomach cancer for 1 cup/day increase of green tea intake by cancer outcome

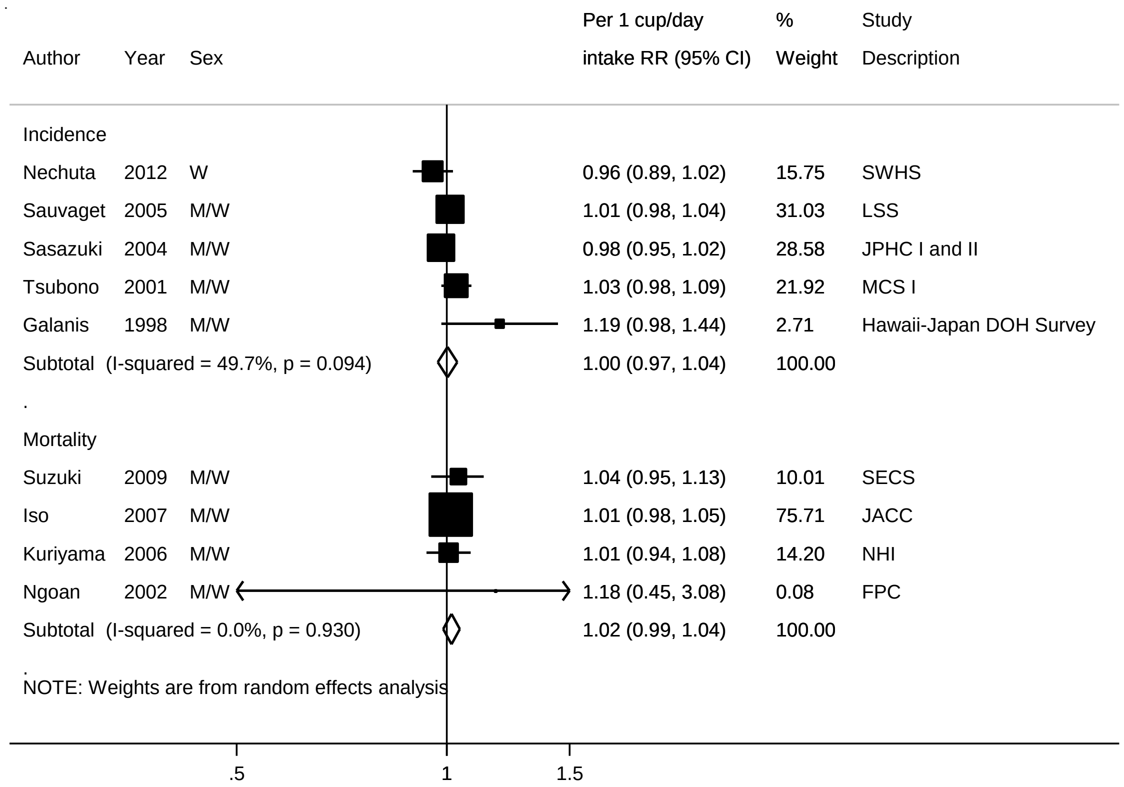
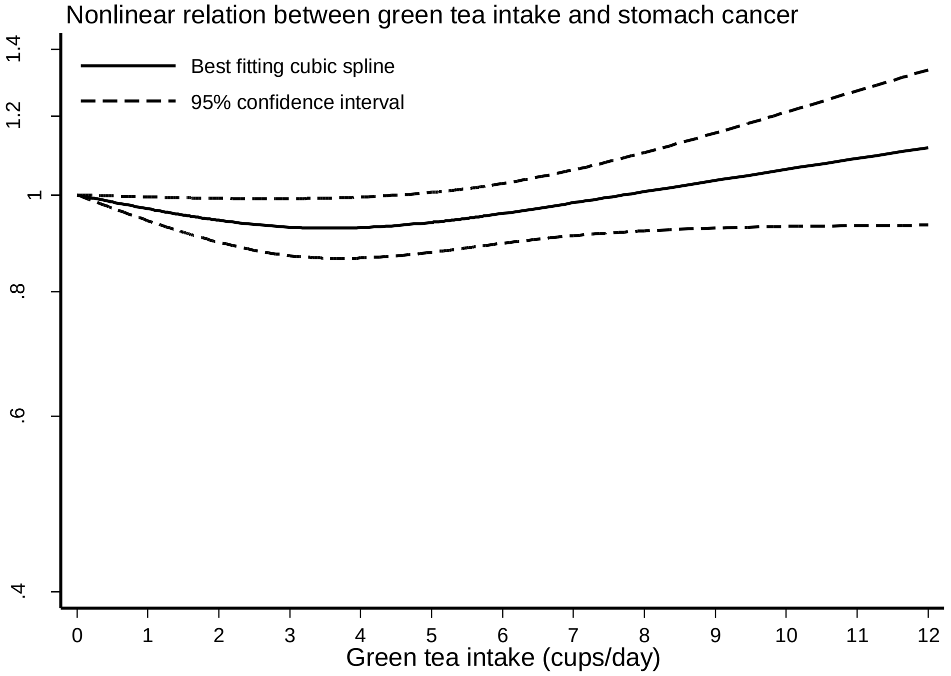


Figure 126 Non-linear dose-response meta-analysis of green tea intake and stomach cancer



P for non-linearity =0.02

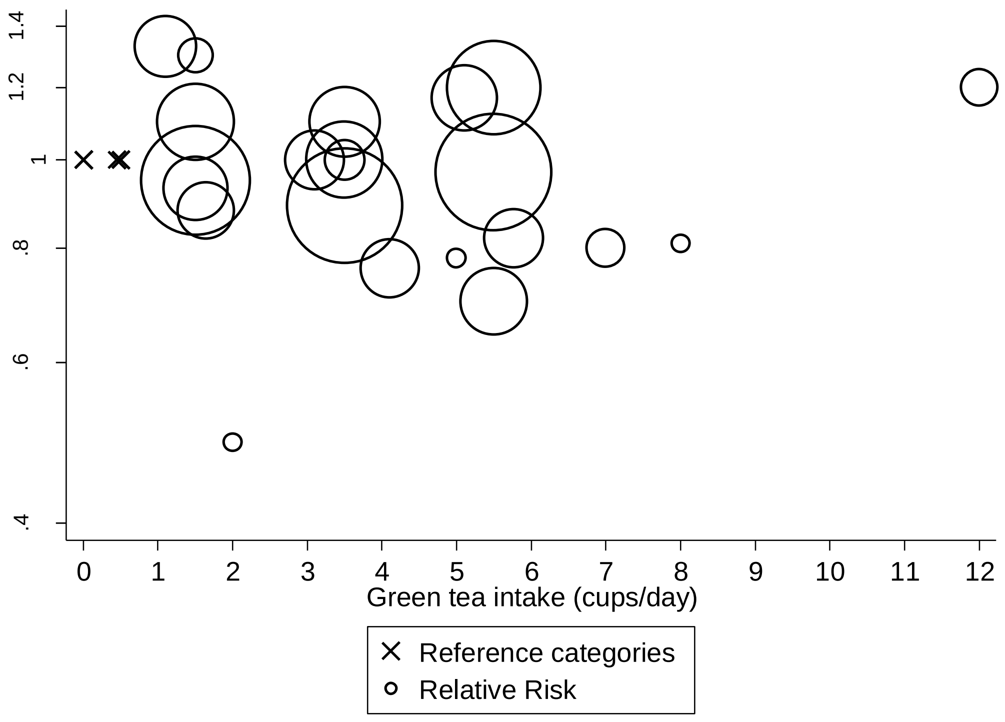


Table 106 Relative risk of stomach cancer and green tea intake estimated using non-linear models

Green tea (cups/day)	RR (95%CI)
0	1.00
0.5	0.98 (0.97-1.00)
1.5	0.95 (0.92-0.99)
2	0.94 (0.90-0.99)
3.5	0.93 (0.86-0.99)
5	0.94 (0.88-1.01)
8	1.01 (0.92-1.10)
12	1.12 (0.93-1.33)

5.4.1 Total Alcohol (as ethanol)

Randomised controlled trials

No randomised controlled trial was identified.

Cohort studies

Summary

Main results:

Twenty three studies (11 926 cases) out of 30 studies were included in the dose-response meta-analysis. A marginally significant positive association was found between alcohol (as ethanol) consumption and stomach cancer risk.

Seven studies were excluded from the dose-response analyses. No significant associations were observed in the excluded studies.

Significant and moderate heterogeneity (38.6%) was observed. Stratified and sensitivity analyses did not indicate a source of heterogeneity. The relationships were of similar magnitude in men and women, statistically significant in men (13 studies, I^2=37.4%) but not in women (5 studies, I^2=19.2%). No significant associations were observed for cardia or non-cardia gastric cancers. Similar estimates were observed on average in studies on mortality or incidence as endpoint. Most associations were not significant in analyses stratified by geographic area, study size, duration of follow-up and adjustment for potential risk factors.

In a meta-analysis comparing the highest with the lowest category of alcohol intake in six studies that reported results by smoking status, the association of stomach cancer with alcohol intake was stronger and more heterogeneous across studies in smokers than in non-smokers.

There was significant evidence of small study bias. Small studies with estimates below the average are missing.

Sensitivity analyses:

In influence analysis, the summary RRs ranged from 1.01 (95% CI=1.00-1.03) when Sung, 2007 (KNHIC, Korea) was omitted to 1.03 (95% CI=1.01-1.04) when Lindblad, 2005 (GPRDC, UK) was omitted.

Non-linear dose-response meta-analysis:

There was no evidence of non-linear dose-response association (p for non-linearity = 0.32).

Study quality:

Most studies reported alcohol intake in grams/day. Some studies reported intake in drinks (Allen, 2009; Freedman, 2007; Galanis, 1998), ml (Ozasa, 2007; Kato, 1992b), times (Sjödahl, 2007), and ounces (Nomura, 1995), per day/week/14 days or a month and in these studies, intake was approximated to grams/day.

In one study (Lindblad, 2005), the highest category of alcohol intake was much higher than in the other studies (> than 34 units per day in men and women combined). Alcohol intake was obtained from a computerized database of patient records not specifically designed for dietary assessment and might have provided less accurate information compared to the dietary questionnaires used in other studies. The estimate for the highest category (>34 units/day) was excluded from non-linear dose-response analysis in this systematic literature review.

The reference category (non-drinkers) was defined differently across studies. Former drinkers were excluded from "non-drinkers" in three studies (Jung, 2012; Nakaya, 2005; Kono, 1986). Non-drinkers in Yang, 2012 and Sjödahl, 2007 were people who did not drink over the past 12 months and the last 14 days, respectively. The dose response estimates in three studies (Everatt, 2012; Duell, 2011 and Allen, 2009) were restricted to alcohol drinkers at baseline. One study (Freedman, 2007) had no data on past alcohol use. The remaining studies did not specify if former drinkers at baseline were considered as "non-drinkers".

All studies included in the dose-response analysis were adjusted for age, sex, smoking and other confounders. No studies were adjusted for Helicobacter pylori infection or ethnicity.

Loss to follow-up was low in most studies. Cancer cases were identified by record linkage to cancer registries and death registries in most studies, general practitioners or hospital records in a few studies.

Table 107 Total alcohol intake and stomach cancer risk. Number of studies in the CUP SLR

	Number
Studies identified	30 (39 publications)
Studies included in forest plot of highest compared with lowest exposure	26
Studies included in linear dose-response meta-analysis	23
Studies included in non-linear dose-response meta-analysis	19

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

Table 108 Total alcohol (as ethanol) intake and stomach 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)	7	23
Cases (total number)	752	11926
RR (95%CI)	1.01 (0.99-1.02)	1.02 (1.00-1.04)
Heterogeneity (I^2, p-value)	12%, 0.3	38.6%, 0.03
P value Egger test	0.9	0.03
Stratified and sensitivity analysis		
Men		
Studies (n)	5	13
RR (95%CI)	1.00 (0.98-1.03)	1.03 (1.01-1.05)
Heterogeneity (I^2, p-value)	-	37.4%, 0.09
Women		
Studies (n)	1	5*
RR (95%CI)	1.01 (0.98-1.04)	1.02 (0.90-1.15)
Heterogeneity (I^2, p-value)	-	19.2%, 0.29

*Yi, 2010 and Kato, 1992b were excluded due to very low number of cases in categories.

Other stratified analyses

Cancer site	**Gastric cardia cancer**	**Non-cardia gastric cancer**	
Studies (n)	6	7	
RR (95%CI)	1.01 (0.99-1.03)	1.03 (0.97-1.09)	
Heterogeneity (I^2, p-value)	0%, 0.49	83.2%, <0.001	
Outcome	**Incidence, all**	**Incidence, men**	**Incidence, women**
Studies (n)	16	8	3
RR (95%CI)	1.01 (0.98-1.04)	1.04 (1.02-1.07)	1.07 (0.69-1.65)
Heterogeneity (I^2, p-value)	60.7%, 0.001	4.7%, 0.39	36.8%, 0.21
	Mortality, all	**Mortality, men**	**Mortality, women**
Studies (n)	7	5	2
RR (95%CI)	1.02 (1.00-1.04)	1.02 (0.99-1.05)	1.06 (0.94-1.20)
Heterogeneity (I^2, p-value)	17.4%, 0.30	46.1%, 0.12	0%, 0.58

Geographic area	Asia**	Europe	North America
Studies (n)	14	7	2
RR (95%CI)	1.03 (1.01-1.04)	1.02 (0.98-1.06)	0.98 (0.87-1.11)
Heterogeneity (I^2, p- value)	20.9%, 0.23	45.9%, 0.09	0%, 0.64
	Asia, all	**Asia, men**	**Asia, women**
Studies (n)	3	7	2
RR (95%CI)	1.04 (0.97-1.11)	1.04 (1.01-1.06)	1.06 (0.94-1.20)
Heterogeneity (I^2, p-value)	55.1%, 0.11	3.1%, 0.40	0%, 0.58
	Europe, all	**Europe, men**	**Europe, women**
Studies (n)	4	1	2
RR (95%CI)	1.00 (0.98-1.02)	1.09 (1.00-1.19)	1.15 (0.65-2.03)
Heterogeneity (I^2, p-value)	10.5%, 0.34		66.4%, 0.09
Duration of follow-up	**5-<10 years**	**10-<15 years**	**≥15 years**
Studies (n)	9	3	9
RR (95%CI)	1.03 (1.00-1.07)	1.03 (1.00-1.07)	1.01 (0.99-1.03)
Heterogeneity (I^2, p- value)	26.8%, 0.21	0%, 0.93	5.6%, 0.39
Number of cases	**<500 cases**	**500-<1000 cases**	**≥1000 cases**
Studies (n)	17	2	4
RR (95%CI)	1.03 (1.01-1.05)	0.97 (0.89-1.05)	1.02 (0.99-1.05)
Heterogeneity (I^2, p-value)	0%, 0.61	0%, 0.48	81.6%, 0.001
Publication year	**<2000**	**2000-<2010**	**≥2010**
Studies (n)	6	9	8
RR (95%CI)	1.02 (0.97-1.08)	1.02 (0.99-1.05)	1.01 (1.00-1.03)
Heterogeneity (I^2, p-value)	8.7%, 0.36	63.1 %, 0.006	0%, 0.43
Adjustment for:	**Not adjusted**	**Adjusted**	
Socioeconomic status			
Studies (n)	4	19	
RR (95%CI)	1.02 (0.98-1.07)	1.02 (1.01-1.04)	
Heterogeneity (I^2, p-value)	51.4%, 0.10	17.2%, 0.24	
Smoking			
Studies (n)	3	20	
RR (95%CI)	1.02 (0.97-1.07)	1.02 (1.00-1.04)	
Heterogeneity (I^2, p-value)	34.3 %, 0.22	38.7%, 0.04	
BMI			
Studies (n)	11	12	

RR (95%CI)	1.02 (1.00-1.04)	1.02 (1.00-1.05)	
Heterogeneity (I^2, p-value)	7.2%, 0.38	52.6%, 0.02	
Total energy intake			
Studies (n)	20	3	
RR (95%CI)	1.02 (1.00-1.04)	1.02 (0.98-1.06)	
Heterogeneity (I^2, p-value)	44.8%, 0.02	0%, 0.65	
Physical activity			
Studies (n)	20	3	
RR (95%CI)	1.02 (1.01-1.04)	0.96 (0.88-1.06)	
Heterogeneity (I^2, p-value)	44.2%, 0.02	0%, 0.63	
Comorbidities			
Studies (n)	21	2	
RR (95%CI)	1.03 (1.01-1.05)	0.99 (0.98-1.00)	
Heterogeneity (I^2, p-value)	13.6%, 0.28	0%, 0.97	

**Two studies of Japanese residents in Hawaii (Hawaii-Japan DOH Survey and HHP) were included in the subgroup of Asian cohorts.

Table 109 Total alcohol intake and stomach cancer risk. Results of meta-analyses of prospective studies published after the 2005 SLR

Author, Year	Number of studies	Total number of cases	Studies country, area	Outcome	Comparison	RR (95%CI)	P trend	Heterogeneity (I^2, p value)
Meta-analysis								
Tramacere, 2012	15 cohorts	13343	Japan, North America, Europe, Korea, China	Incidence/mortality Gastric cancer	Drinkers vs non-drinkers	1.04 (0.97-1.11)		31.2%, p=0.11
	15 cohort, 44 case-control studies	34557				1.07 (1.01-1.13)		52%, p<0.001

Table 110 Total alcohol intake and stomach 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
Yang, 2012 STM80052 China	CNRPCS, Prospective Cohort, Age: 40-79 years, M	1 137/ 218 189 15 years	Annual follow up by trained staff, death certificate and symptoms described by family members	Questionnaire	Mortality, stomach cancer	>=700 g/week vs non-drinkers	1.15 (0.85-1.57), p=0.02	5-yr age group, geographic area, education, smoking	Distribution of person-years by exposure categories, mid-points of exposure categories, intake per week converted to intake per day
Everatt, 2012 STM80096 Lithuania	KRIS and MIHDPS, Prospective Cohort, Age: 40-59 years, M	185/ 7 150 30 years	Cancer registry	Questionnaire	Incidence, stomach cancer	≥100 vs 0.1- 9.9 g/week	1.90 (1.13-3.18)	Age, BMI, study, education, smoking	
						Per 90 g/week	1.12 (1.00-1.25)		Exposure units rescaled
Jung, 2012 STM80098 Korea	KMCC, Prospective Cohort, Age: 20- years, M/W	90/ 16 320 9.3 years	Death certificate	Questionnaire	Mortality, stomach cancer	>504.01 vs 0.01-90g/week	2.93 (1.18-7.31)	Age, sex, BMI, geographic area, smoking habits, educational attainment	Distribution of person-years by exposure categories, mid-points of exposure categories, intake per week converted to intake per day, reference 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
									changed using Hamling's method.
Duell, 2011 STM80134 Denmark,France ,Germany,Greec e,Italy,Netherlan ds,Norway,Spai n,Sweden,UK	EPIC, Prospective Cohort, Age: 35-70 years, M/W	444/ 478 459 8.8 years	Cancer registries, health insurance records, pathology records & active follow up	FFQ, dietary questionnaires, food record	Incidence, gastric adenocarcinoma	Per 15 g	1.05 (0.98-1.13)	Age, sex, centre, education level, vegetable intake, intake of fruits, nuts, seeds, processed and red meat, smoking, total energy intake	Exposure units rescaled
						≥60 vs 0.1-4.9 g/day	1.65 (1.06-2.58)		
		130/			Incidence, gastric cardia adenocarcinoma	≥60 vs 0.1-4.9 g/day	1.19 (0.56-2.52)		Distribution of person-years by exposure categories, mid-points of exposure categories, reference category changed using Hamling's method.
		205/			Incidence, gastric non-cardia adenocarcinoma	≥60 vs 0.1-4.9 g/day	2.90 (1.53-5.48)		
Kim, 2010 STM80056 Korea	HEC 2000, Prospective Cohort, Age: 40-69, M/W	282/ 5 years Women	Korea National Statistical Office	Interview during health examinations	Mortality, stomach cancer Women (Sung 2007 on incidence used for men)	≥90 g/day of suju equivalents vs non-drinkers	1.48 (0.85-2.57)	Age, residential (urban, rural), smoking, regular exercise, BMI, systolic and diastolic blood pressure, fasting blood sugar, and total cholesterol	Soju equivalents converted to g/day of ethanol, distribution of person-years and cases by exposure categories, mid-points of exposure categories
Steevens, 2010b	NLCS,	164/	Annual record	Validated FFQ	Incidence,	Per 10 g/day	0.98 (0.88-1.08)	Age, sex, BMI,	

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Missing data derived for analyses
STM80061 Netherlands	Case Cohort, Age: 55-70 years, M/W	4 617 16 years	linkage to The Netherlands cancer registry and pathology registry		gastric cardia adenocarcinoma	≥30 g/day vs abstainer	0.90 (0.50-1.64)	education level, energy intake, current smoking status, fish intake, fruit and vegetable intake, smoking dose and duration	RRs for cardia and non-cardia gastric cancers combined using Hamling's method
		491/			Incidence, gastric non-cardia adenocarcinoma	Per 10 g/day	1.02 (0.95-1.09)		
						≥30 g/day vs abstainer	1.00 (0.68-1.47)		RRs for cardia and non-cardia gastric cancers combined using Hamling's method
		140/			Incidence, gastric cardia adenocarcinoma Men	Per 10 g/day	0.98 (0.89-1.09)	Age, BMI, education level, energy intake, current smoking status, fish intake, fruit and vegetable intake, smoking dose and duration	
		331/			Incidence, gastric non-cardia adenocarcinoma Men	Per 10 g/day	1.03 (0.95-1.11)		
		24/			Incidence, gastric cardia adenocarcinoma Women	Per 10 g/day	0.84 (0.41-1.75)		
		160/			Incidence, gastric non-cardia adenocarcinoma	Per 10 g/day	0.96 (0.78-1.18)		

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Missing data derived for analyses
					Women				
Moy, 2010 STM80101 China	SCStudy, Prospective Cohort, Age: 45-64 years, M	391/ 18 244 up to 20 years	Biennial home visits/linkage cancer registry/vital stats	FFQ	Incidence, stomach cancer	40+ g/day vs non-drinkers	1.15 (0.85-1.55)	Age at interview, BMI, education level, fruit intake, vegetable intake, year of interview, neighbourhood of residence at recruitment, preserved food intake, years of smoking	Mid-points of exposure categories
Yi, 2010 STM80108 Korea	KCS, Prospective Cohort, Age: 55- years, M/W	100/ 6 291 20.8 years	Death records/calls or follow up visits/death certificates	Questionnaire and interview	Mortality, stomach cancer Men	≥540 g/week vs none	1.01 (0.57-1.77)	Age, BMI, education level, smoking habits, ginseng intake, history of chronic disease, pesticide use	Distribution of person-years by exposure categories, intakes in g/week converted to g/day, mid-points of exposure categories, RRs for men and women combined
		53/			Women	≥12 g/week vs none	2.59 (1.06-6.33)		
Allen, 2009 STM80146 UK	MWS, Prospective Cohort,	545/ 1 280 296 7 years	National health service central registers	Questionnaire	Incidence, stomach cancer Drinkers only	Per 10 g/day	0.93 (0.81-1.07)	Age, BMI, physical activity, socio-	

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Missing data derived for analyses
	Age: 55 years, W	821			Incidence, stomach cancer	≥15 vs ≤2 drinks/week	1.02 (0.73-1.43)	economic status, region of residence, smoking, use of HRT, use of oral contraception	Converted floating CIs to conventional for HvL analysis
Freedman, 2007 STM80065 USA	NIH- AARP, Prospective Cohort, Age: 50- years, M/W, Retired	188/ 474 606 4.6 years	Linkage of the cohort with database to state cancer registries	Validated FFQ	Incidence, gastric cardia adenocarcinoma	>3 vs >0-1 drinks/day	1.57 (0.98-2.52)	Age, sex, BMI, fruit & veg consumption, smoking status, education, total energy intake, usual physical activity, vigorous physical activity and for non-cardia, race/ethnicity	Drinks/day converted to g/day, distribution of person-years by exposure categories, mid-points of exposure categories, reference category changed using Hamling's method, RRs for cardia and non-cardia adenocarcinomas combined using Hamling's method
		187/			Incidence, gastric non-cardia adenocarcinoma	>3 vs >0-1 drinks/day	0.62 (0.30-1.27)		
Larsson, 2007a STM80088 Sweden	SMC, Prospective Cohort, W	160/ 61 433 18 years	Linkage of the cohort with national Swedish cancer registry and	Validated FFQ	Incidence, stomach cancer, follow-up from 1987-2005	≥40.0 g/week vs non-drinkers	1.33 (0.79-2.25)	Age, coffee intake, education, fruit and vegetable intake,	Intakes in g/week converted to g/day, 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
			regional cancer registry					processed meat intake, smoking	exposure categories
Ozasa, 2007 STM80148 Japan	JACC, Prospective Cohort, M/W	550/ 12 years			Mortality, stomach cancer Men	81+ ml/day vs rare/none	1.11 (0.79-1.54)	Age, study area	Intakes in ml/day converted to g/day, mid-points of exposure categories
		295/			Women	81+ ml/day vs rare/none	3.23 (0.80-13.10)		
Sjödahl, 2007 STM80092 Norway	HUNT-I, Prospective Cohort, Age: 20- years, M/W	251/ 69 962 16 years 224/	Cancer registry	Questionnaire	Incidence, stomach cancer	≥5 times/14 days vs never drinking	1.49 (0.78-2.83)	Sex, attained age, BMI, education, tobacco use	Intake in times converted to g/day using 12.5g standard conversion per drink/time, mid-points of exposure categories, distribution of person-years by exposure categories
Sung, 2007 STM80118 Korea	KNHIC, Prospective cohort Age: 30- years, M	3452/ 12 242 6.5 years	Cancer registry	Questionnaire	Incidence/mortality Stomach cancer	≥25 vs 0 g/day	1.2 (1.1-1.4), p<0.001	age, BMI, smoking and preference for saltiness in food	Distribution of person-years by exposure categories, mid-points of exposure categories
					Cardia and upper third		1.3 (0.8-2.2)		
					Distal stomach cancer		1.3 (1.2-1.5), p<0.001		

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Missing data derived for analyses
Lindblad, 2005 STM44427 UK	GPRDC, Nested Case-control, Age: 40-84 years, M/W	1023/ 3 000 000 2 years	GPs records		Incidence, gastric adenocarcinoma	>34 vs 0-2 units/day	0.75 (0.44-1.27)	Age, sex, BMI, reflux, smoking habits, year of recruitment	Intakes in units/day converted to g/day, mid-points of exposure categories
		195/			Cardia adenocarcinoma	>34 vs 0-2 units/day	1.04 (0.37-2.93)		
		327/			Non-cardia adenocarcinoma	>34 vs 0-2 units/day	0.29 (0.07-1.18)		
Nakaya, 2005 STM82465 Japan	MCS II, Prospective Cohort, Age: 40-64 years, M	247/ 21 201 7 years	Cancer registry	Questionnaire (general)	Incidence, stomach cancer	≥22.8 g/day vs never-drinkers	1.00 (0.70-1.50)	Age, educational level, fruit juice, smoking habits, vegetable intake	Mid-points of exposure categories
Sasazuki, 2002 STM01464 Japan	JPHC I, Prospective Cohort, Age: 40-59 years, M	273/ 19 657 10 years	Hospital records, population-based cancer registries and death certificates, histologically confirmed	Questionnaire (general)	Incidence, stomach cancer	322.5+ g/week vs 0-3 days/month	1.10 (0.80-1.60)	Age, BMI, fruit, salted cod roe or fish gut, smoking habits, study area, vegetable intake	Intakes in g/week converted to g/day, mid-points of exposure categories, distribution of person-years by exposure categories, types of lower third gastric cancer combined using Hamling's method
		35/			Incidence, cardia and upper third gastric cancer		3.00 (0.80-11.10)		
		124/			Incidence, distal/lower third gastric cancer, differentiated type		0.90 (0.50-1.50)		
		63/			Incidence, distal/lower third gastric		1.30 (0.70-2.60)		

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Missing data derived for analyses
					cancer, undifferentiated type				
Galanis, 1998 STM04769 USA	Hawaii-Japan DOH Survey, Prospective Cohort, Japanese residents of Hawaii M/W	108/ 11907 14.8 years	Cancer registry/ hospital records	FFQ	Incidence, stomach cancer Men	3 or more drinks/day vs non-drinkers	1.20 (0.50-2.60)	Age, years of education, Japanese place of birth, smoking, drinking status	Intake in drinks/day converted to ethanol g/day using 12.5g ethanol per drink, distribution of person-years by exposure categories, mid-points of exposure categories
Murata, 1996 STM05764 Japan	CCCJ, Nested Case-control, M	246/ 17 200 9 years	Cancer registry	Questionnaire (general)	Incidence, stomach cancer	2.1+ vs 0 cups/day	0.50	Matched on sex, birth year, and first digit of the address code	Intake in cups/day converted to g/day, mid-points of exposure categories, confidence intervals
Nomura, 1995 STM11198 USA	HHP, Prospective Cohort, Age: 45- years, M, Japanese	245/ 7 972 26 years	Cancer registry/ hospital records	FFQ + recall	Incidence, gastric adenocarcinoma	40+ oz/month + vs non-drinkers	1.20 (0.80-1.80)	Age, smoking habits	Intake in oz/month of ethanol converted to g/day, distribution of

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Missing data derived for analyses
	residents of Hawaii								person-years by exposure categories, mid-points of exposure categories
Zheng, 1995 STM06417 USA	IWHS, Prospective Cohort, Age: 55-69 years, W, Post-menopausal women	26/ 34 691 7 years	Cancer registry	FFQ	Incidence, stomach cancer	Median or more, ≥3.4 g/day vs non-drinkers	0.80 (0.30-2.20)	Age, educational level, smoking habits	Mid-points of exposure categories, distribution of person-years by exposure categories
Kato, 1992b STM06734 Japan	HKC, Prospective Cohort, Age: 30-80 years, M/W	57/ 9 753 6 years	Cancer registry/ hospital records	FFQ	Mortality, stomach cancer	Daily ≥50 ml/day vs none	2.75 (1.20-6.29)	Age, sex, cooking methods, family history of stomach cancer, smoking habits	Intakes in ml/day converted to g/day, mid-points of exposure categories, distribution of person-years by exposure categories
		35/			Men	Daily ≥50 ml/day vs none	3.63 (1.44-9.11)	Age	
		22/			Women	Daily vs none	1.29 (0.17-9.69)	Age	
Kono, 1986 STM08535 Japan	JPC, Prospective Cohort, Age: 27- years,	116/ 5 135 19 years	Employer records and population register	Questionnaire (general)	Mortality, stomach cancer	Daily, ≥2 go vs non-drinker	1.10 (0.60-2.10)	Age, smoking habits	Distribution of person-years by exposure categories, mid-

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Missing data derived for analyses
	M, Physicians								points of exposure categories, intake in go/day converted to g/day

Table 111 Total alcohol intake and stomach 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, Retired	453/ 494 968 9.7 years	Cancer registry, death master file, national death index plus, postal service database	Validated FFQ	Incidence, cardia adenocarcinoma	<5 or >25 vs. 5-25g/day	0.84 (0.67-1.06)	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, 2007 used instead
		501/			Non-cardia adenocarcinoma		0.87 (0.70-1.08)		
Shen, 2013 STM80186 China	CECS, Prospective Cohort, Age: 65- years, M/W, Elderly	335/ 66 820 10 years	Hospital records and death register	Questionnaire	Mortality, stomach cancer	High vs never	0.53 (0.13-2.15)	Age, sex, BMI, health status, smoking status, education, exercise, housing, monthly	No quantifiable exposure groups, only used in HvL 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
								expenditure	
Kim, 2010 STM80056 Korea	HEC 2000, Prospective Cohort, Age: 40-69, M/W (results for women were included in analysis)	1326/ 5 years/ M	Korea National Statistical Office	Interview during health examinations	Mortality, stomach cancer	≥90 g/day of suju equivalents vs non-drinkers	1.23 (1.00-1.51), p= 0.03	age, residential (urban, rural), smoking, regular exercise, BMI, systolic and diastolic blood pressure, fasting blood sugar	Superseded by Sung, 2007 study (study population overlap)
Barstad, 2005 STM80131 Denmark	CCPPS, Pooled analysis of three cohorts, Age: 21-93 years, M/W	122/ 28 463 389 051 person-years	Cancer registry	Questionnaire (general)	Incidence, stomach cancer	28+ vs <1 drink/week	1.13 (0.41-1.86)	Age, sex, smoking habits	Missing cases and person-years per category, only used in HvL analysis
Yuan, 2004 STM44236 China	SCStudy, Nested Case-control, Age: 45-64 years, M	191/ 18 244 12 years	Home visits/linkage cancer registry/vital stats	Questionnaire (general)	Mortality, stomach cancer	Heavy drinkers vs non-drinkers	1.63 (1.02-2.60)	Smoking habits	Superseded by Moy, 2010, missing CIs, person-years per category
Yatsuya, 2004 STM00003 Japan	JACC, Prospective Cohort, Age: 40-79 years, M/W	88/ 65 184 10 years	Population registry	FFQ	Mortality, stomach cancer	Heavy drinkers vs none			No risk estimate, superseded by Ozasa, 2007
Kasum, 2002 STM01746 USA	IWHS, Prospective Cohort, Age: 55-69	56/ 34 691 14 years	Cancer registry	FFQ	Incidence, stomach cancer	≥2 vs 0 drinks/day	1.15	Smoking, intake of whole grains, refined grains, yellow/orange	No confidence intervals, superseded by Zheng, 1995

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Reasons for exclusion
	years, W, Post-menopausal women							vegetables, total energy intake	
Sun, 2002 STM01531 China	SCStudy, Nested Case-control, Age: 45-64 years, M	190/ 18 244 12 years	Home visits/linkage cancer registry/vital stats	Questionnaire (general)	Incidence, stomach cancer	29+ drinks/week vs none			No risk estimate, superseded by Moy, 2010
Hirvonen, 2001 STM02213 Finland	ATBC, Prospective Cohort, Age: 50-69 years, M, Smokers	111/ 27 110 6.1 years	Cancer registry	FFQ	Incidence, stomach cancer	(mean exposure)		Age	Mean exposure only
Terry, 1998 STM04864 Sweden	STR, Prospective Cohort, Age: 67.00years, M/W, Twins	116/ 11 546 21 years	Cancer registry	FFQ	Incidence, stomach cancer	Moderate vs none times/week	1.36 (0.83-2.24)	Age, sex, BMI, childhood socio-economic status, fruit, smoking habits, vegetable intake	No quantifiable exposure categories (none, light, moderate), used in HvL analysis only
Kneller, 1991 STM07350 USA	LBS, Prospective Cohort, Age: 35- years, M, Mainly of	75/ 17 633 20 years	Health insurance company records	FFQ	Mortality, stomach cancer	Highest quartile vs lowest quartile	1.10	Age, smoking habits	Only two exposure categories, no confidence intervals or a p value

Author, Year, 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
	Scandinavian descent								
Nomura, 1990 STM14814 USA	HHP, Prospective Cohort, Age: 45- years, M, Japanese residents of Hawaii	150/ 7 990 10.6 years	Cancer registry/ hospital records	FFQ	Incidence, stomach cancer	≥40 oz/month vs non-drinker	1.10 (0.70-1.90)	Age, smoking habits	Superseded by Nomura, 1995
Stemmermann, 1990 STM15699 USA	HHP, Prospective Cohort, M, Japanese residents of Hawaii	174/ 7 572 24 years	Cancer registry/ hospital records	FFQ	Incidence, stomach cancer	40+ oz/month vs non-drinker	1.17 (0.73-1.90)	Age, smoking habits	Superseded by Nomura, 1995
Kono, 1987 STM08119 Japan	JPC, Prospective Cohort, Age: 27-89 years, M, Physicians	116/ 5 130 19 years	Employer records and population register	Questionnaire (general)	Mortality, stomach cancer	Daily, ≥2 go vs never/past	1.17 (0.66-2.07)	Age, smoking habits	No cases and person-years per category, superseded by Kono 1986
Pollack, 1984 STM08890 USA	HHP, Prospective Cohort, Age: 45-68 years, M, Japanese	99/ 7 837 14 years	Hospital records, death certificates, cancer registry	Dietary recall	Incidence, stomach cancer	40+ oz/month vs none		Age, smoking habits	No risk estimates, superseded by Nomura, 1995

Author, Year, 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
	residents of Hawaii								
Gordon, 1984 STM08750 USA	FHS, Prospective Cohort, Age: 29-62 years, M/W	13/ 5 209 22 years	Hospital visitors	Questionnaire (general)	Mortality, stomach cancer	(correlation)		Age, lipoproteins density, smoking habits, systolic blood pressure, weight	No risk estimates
Klatsky, 1981 STM00014 USA	KPMCP and Oakland, Prospective Cohort, Age: 20-84 years, M/W	13/ 8 060 10 years	Death register	Questionnaire (general)	Mortality, stomach cancer	6+ vs 0 drinks/day		Age, sex, ethnicity/race, smoking habits	No risk estimates

Figure 127 RR estimates of stomach cancer by levels of total alcohol (as ethanol) intake

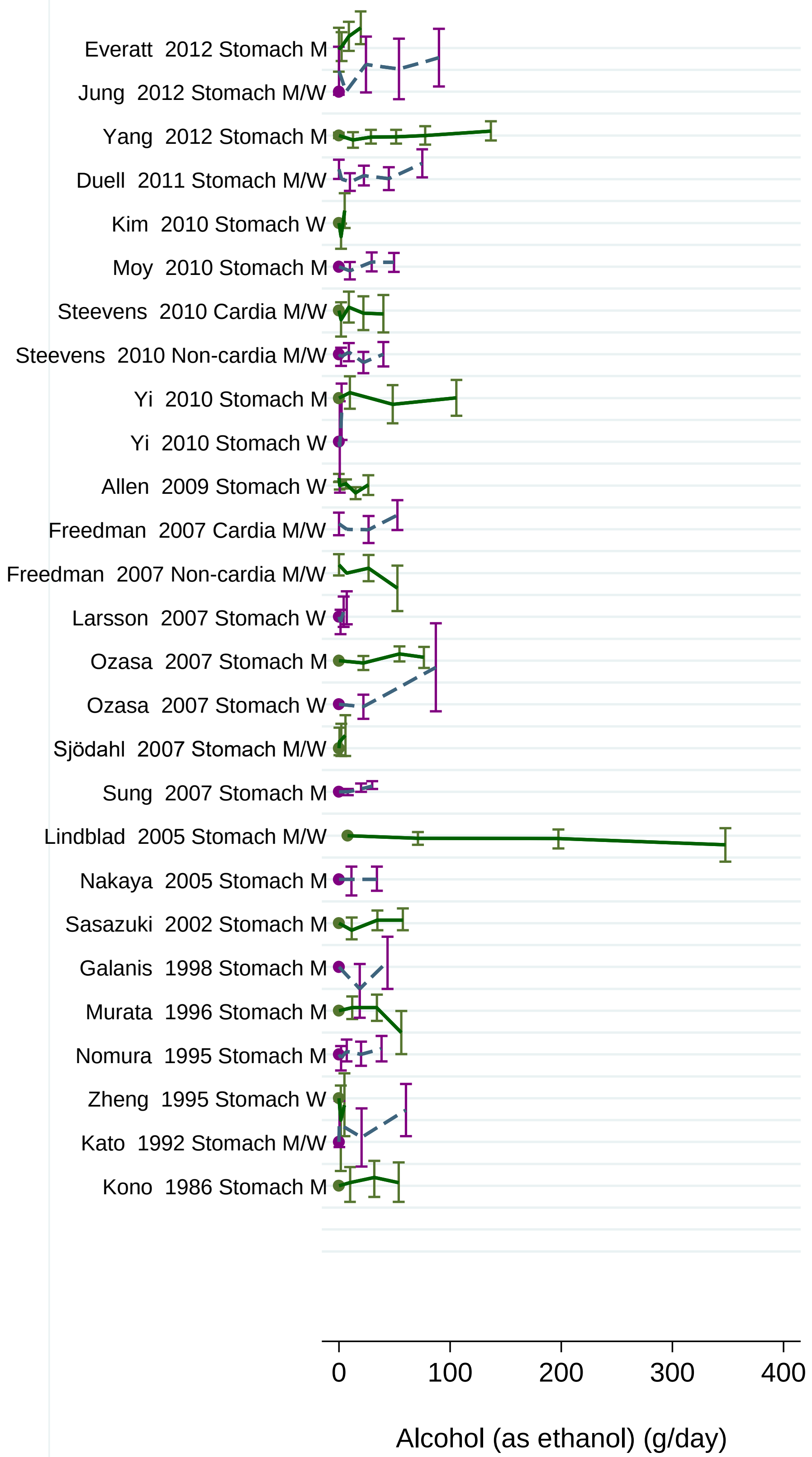


Figure 128 RR (95% CI) of stomach cancer for the highest compared with the lowest level of total alcohol intake

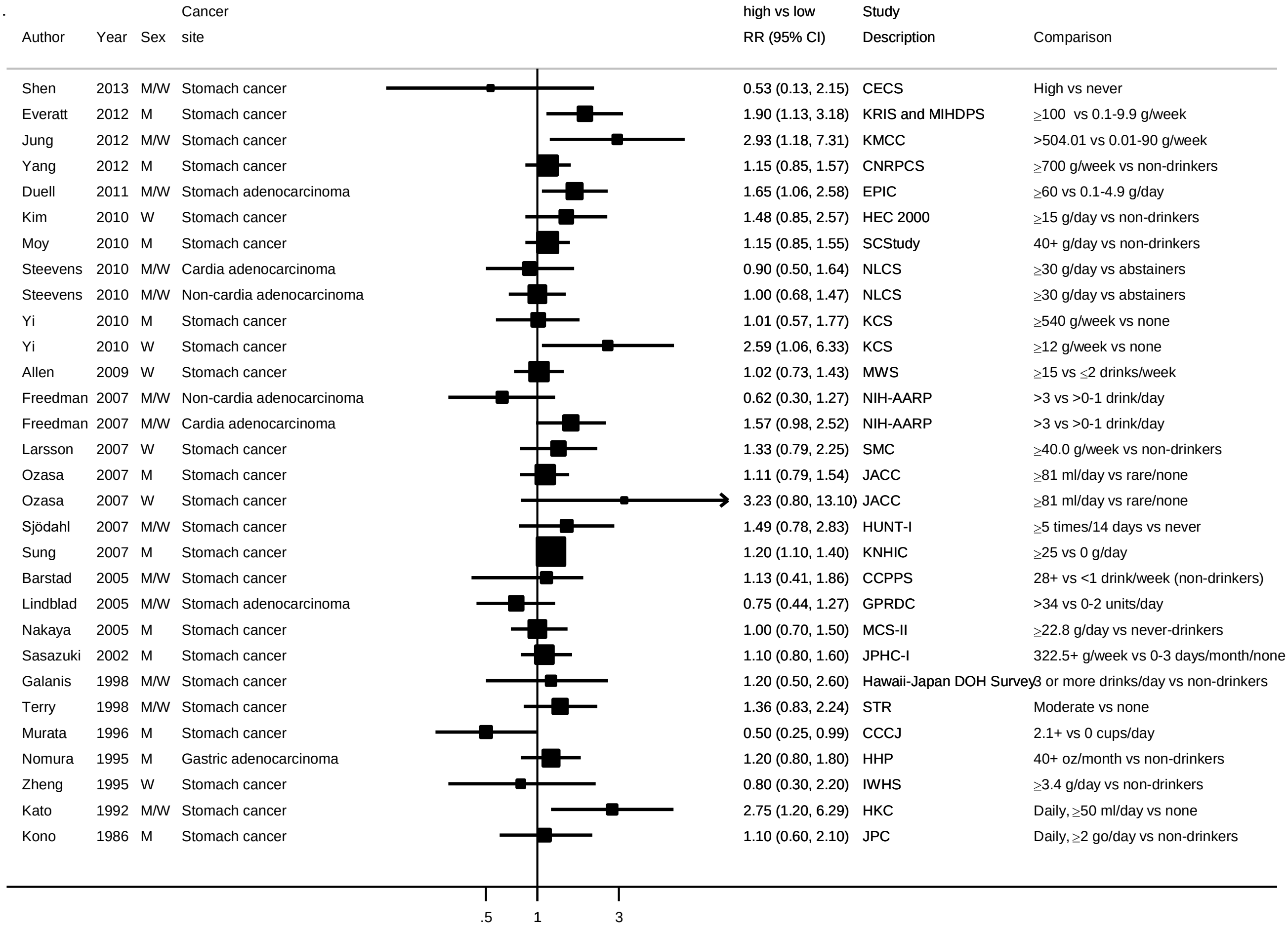


Figure 129 Relative risk of stomach cancer for 10 g/day increase of total alcohol (as ethanol) intake

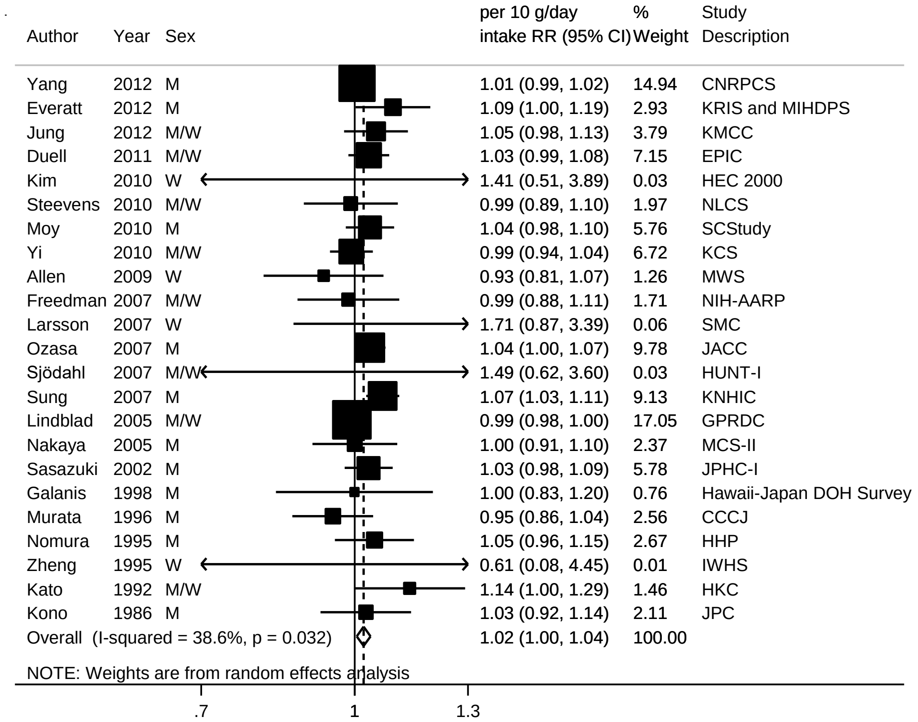
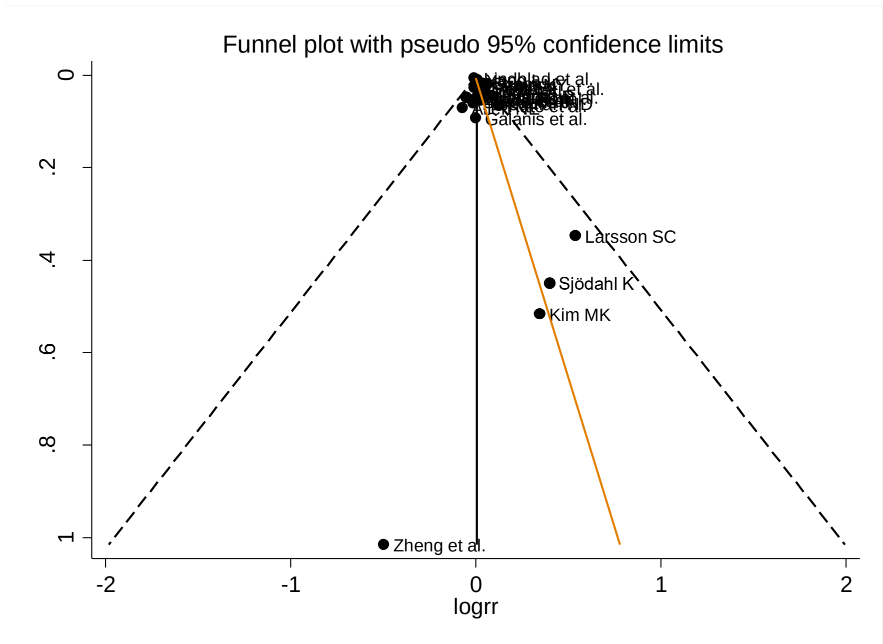


Figure 130 Funnel plot of studies included in the dose response meta-analysis of total alcohol intake and stomach cancer



Egger's test p=0.03

Figure 131 Relative risk of stomach cancer for 10 g/day increase of total alcohol (as ethanol) intake by sex

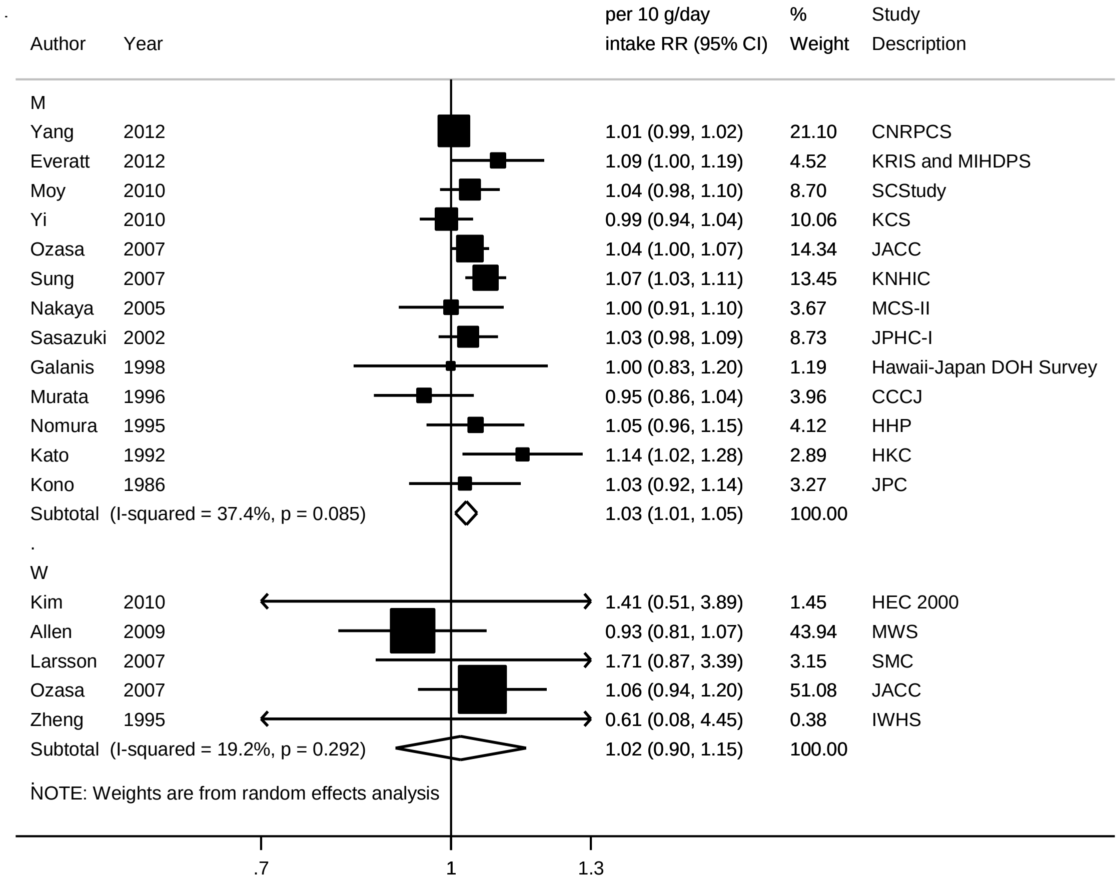


Figure 132 Relative risk of stomach cancer for 10 g/day increase of total alcohol (as ethanol) intake by cancer outcome

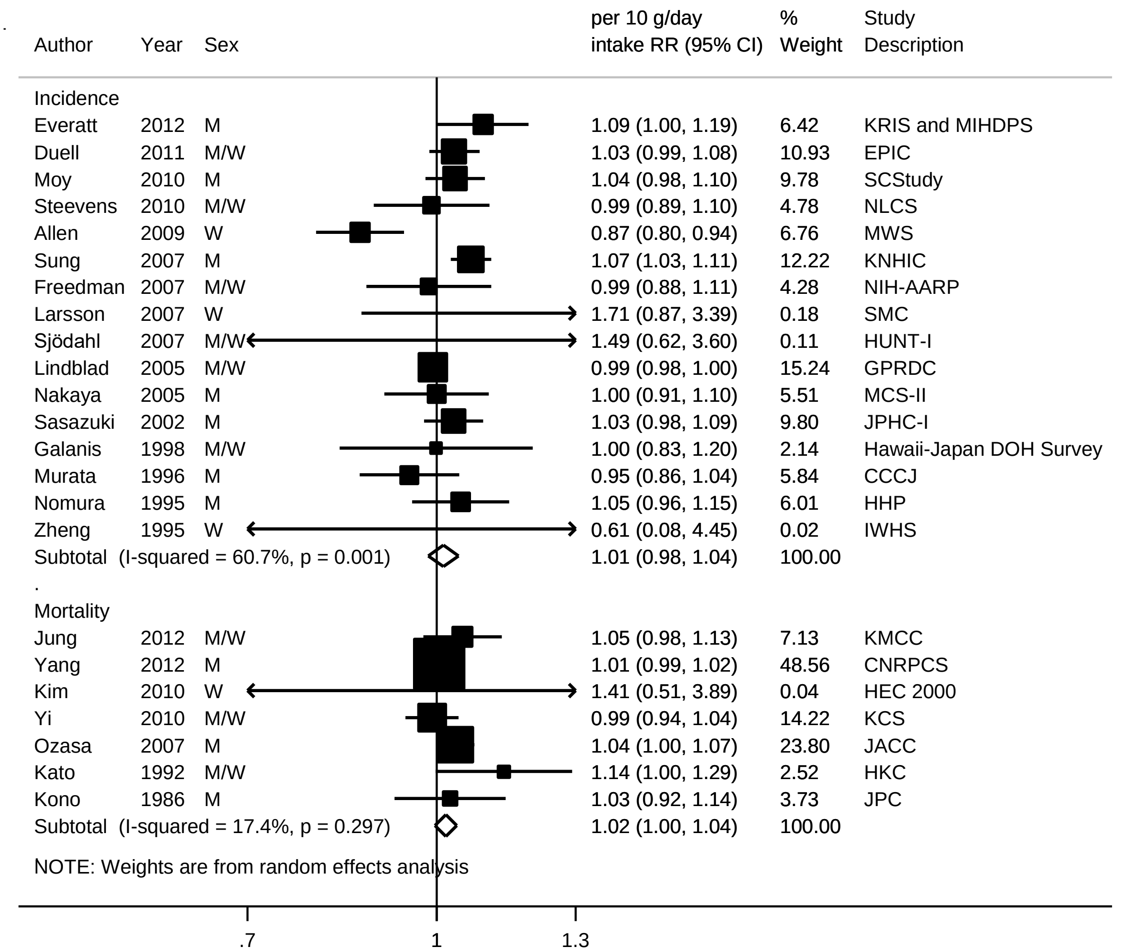


Figure 133 Relative risk of stomach cancer for 10 g/day increase of total alcohol (as ethanol) intake by cancer outcome and sex

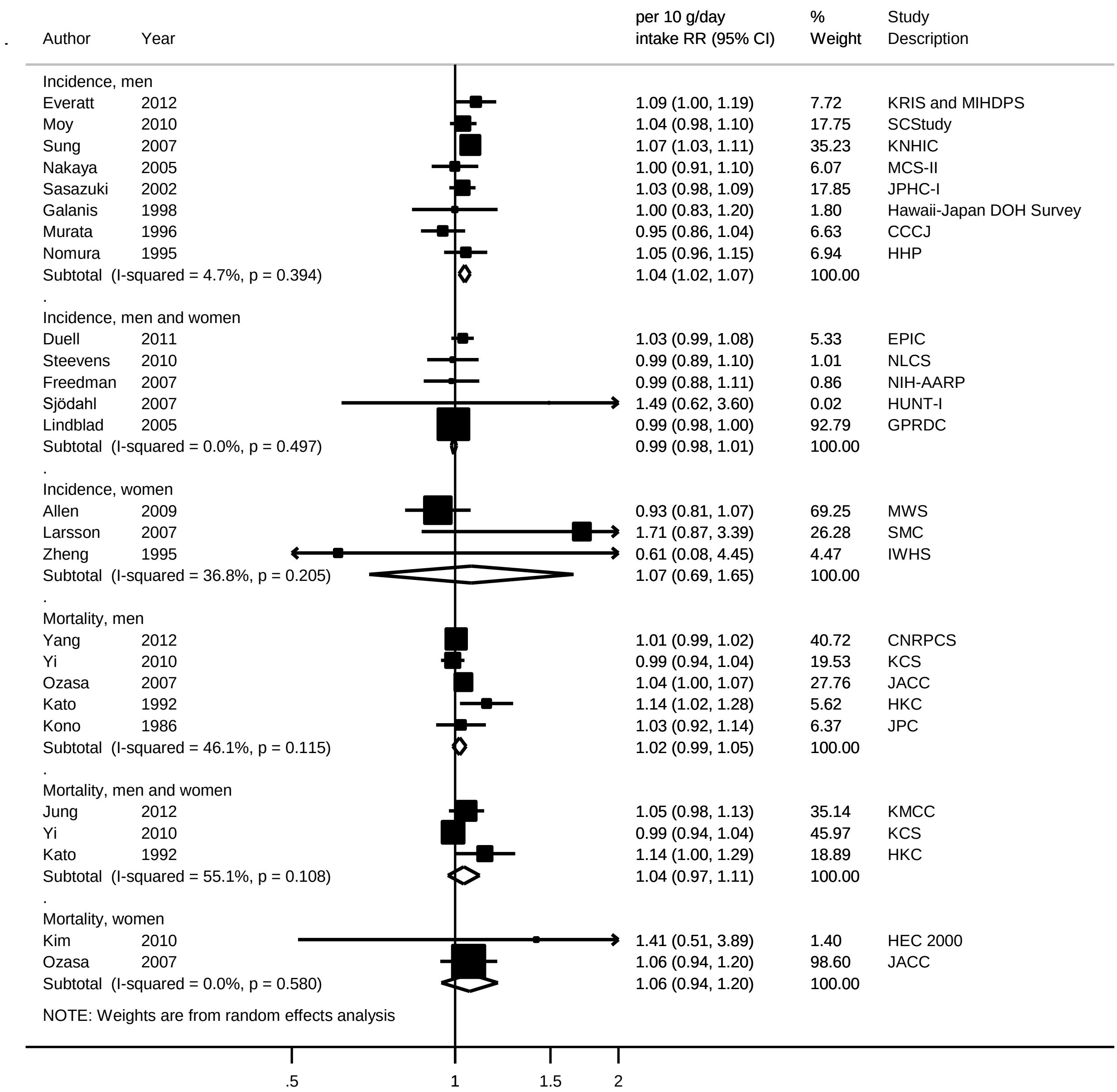


Figure 134 Relative risk of stomach cancer for 10g/day increase of total alcohol (as ethanol) intake by cancer site

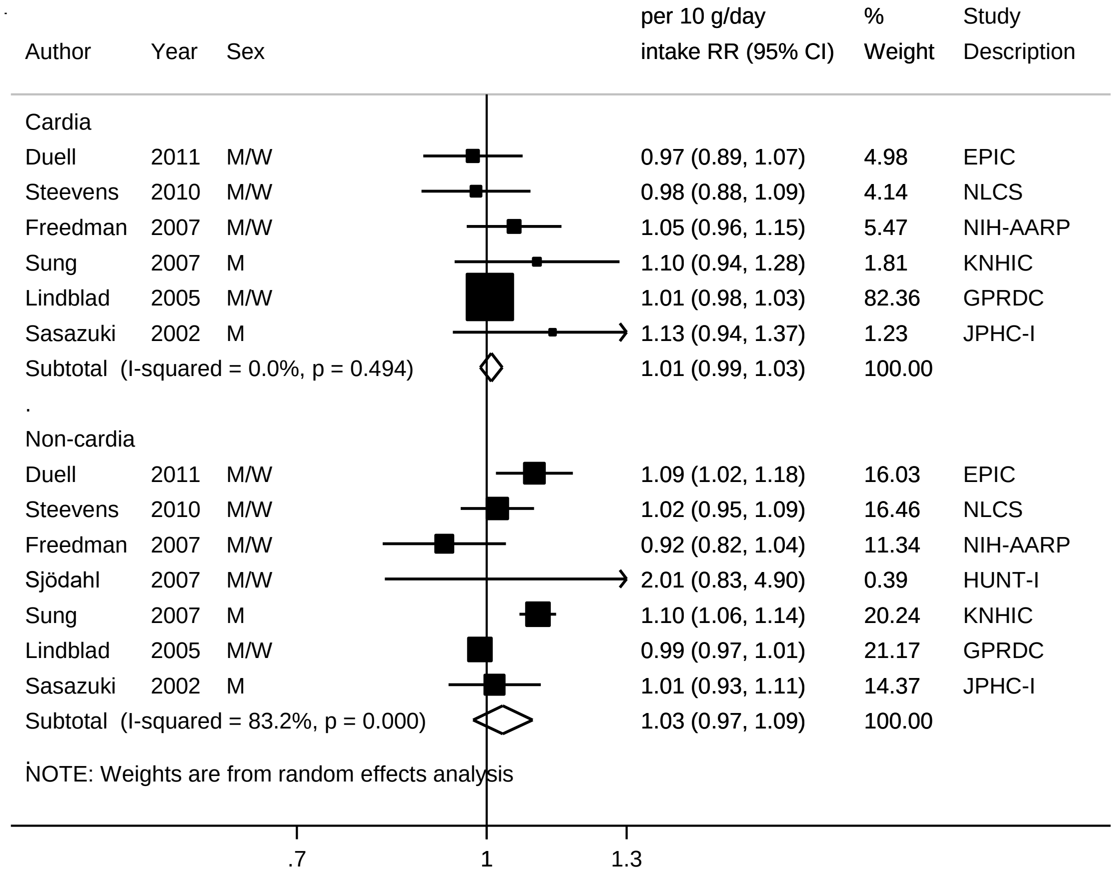


Figure 135 Relative risk of stomach cancer for 10 g/day increase of total alcohol (as ethanol) intake by geographic location

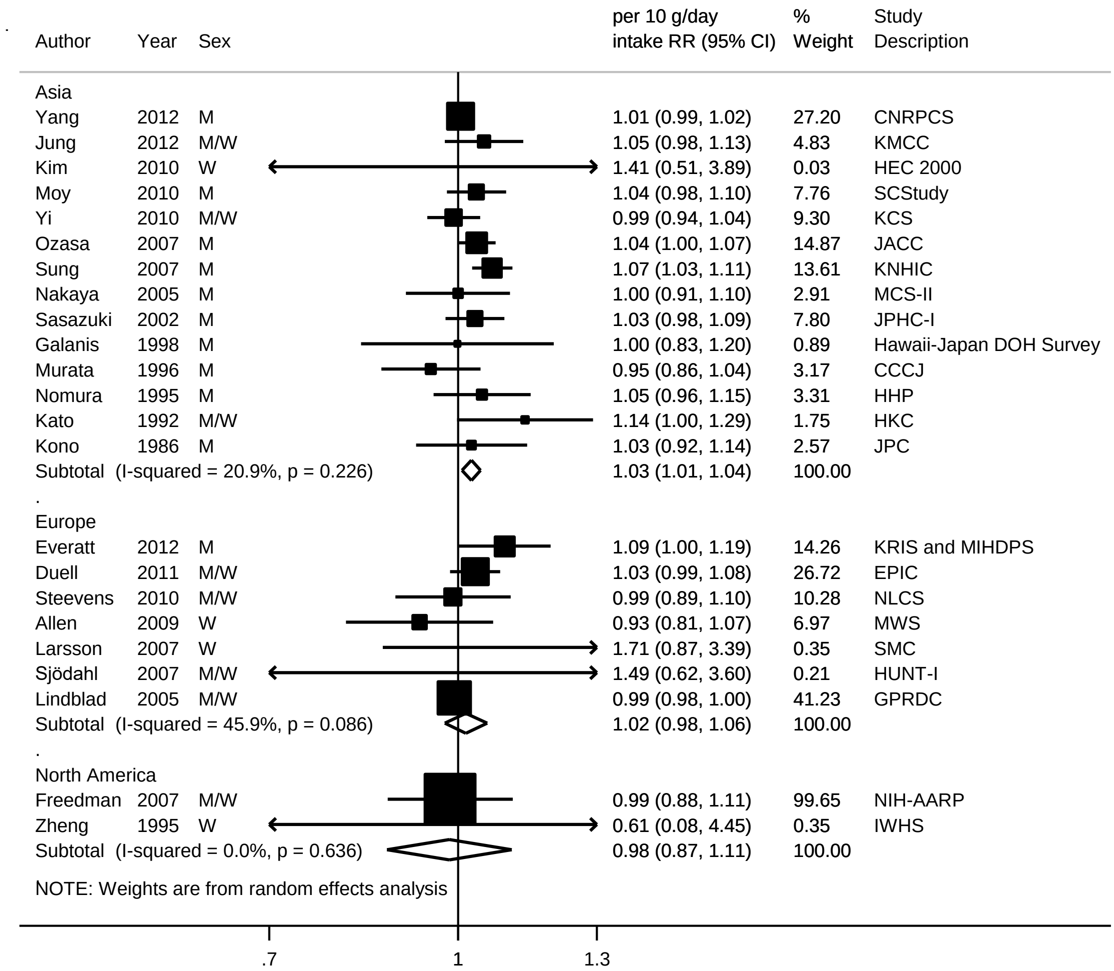


Figure 136 Relative risk of stomach cancer incidence for 10 g/day increase of total alcohol (as ethanol) intake by geographic location and sex

Author	Year	Sex	per 10 g/day intake RR (95% CI)	% Weight	Study Description
Asia, men					
Moy	2010	M	1.04 (0.98, 1.10)	19.11	SCStudy
Sung	2007	M	1.07 (1.03, 1.11)	39.03	KNHIC
Nakaya	2005	M	1.00 (0.91, 1.10)	6.41	MCS-II
Sasazuki	2002	M	1.03 (0.98, 1.09)	19.22	JPHC-I
Galanis	1998	M	1.00 (0.83, 1.20)	1.88	Hawaii-Japan DOH Survey
Murata	1996	M	0.95 (0.86, 1.04)	7.01	CCCJ
Nomura	1995	M	1.05 (0.96, 1.15)	7.34	HHP
Subtotal (I-squared = 3.1%, p = 0.402)			1.04 (1.01, 1.06)	100.00	
.					
Europe, men					
Everatt	2012	M	1.09 (1.00, 1.19)	100.00	KRIS and MIHDPS
Subtotal (I-squared = .%, p = .)			1.09 (1.00, 1.19)	100.00	
.					
Europe, men and women					
Duell	2011	M/W	1.03 (0.99, 1.08)	15.08	EPIC
Steevens	2010	M/W	0.99 (0.89, 1.10)	3.20	NLCS
Sjödahl	2007	M/W	1.49 (0.62, 3.60)	0.05	HUNT-I
Lindblad	2005	M/W	0.99 (0.98, 1.00)	81.67	GPRDC
Subtotal (I-squared = 10.5%, p = 0.341)			1.00 (0.98, 1.02)	100.00	
.					
Europe, women					
Allen	2009	W	0.93 (0.81, 1.07)	65.47	MWS
Larsson	2007	W	1.71 (0.87, 3.39)	34.53	SMC
Subtotal (I-squared = 66.4%, p = 0.085)			1.15 (0.65, 2.03)	100.00	
.					
North America, men and women					
Freedman	2007	M/W	0.99 (0.88, 1.11)	100.00	NIH-AARP
Subtotal (I-squared = .%, p = .)			0.99 (0.88, 1.11)	100.00	
.					
North America, women					
Zheng	1995	W	0.61 (0.08, 4.45)	100.00	IWHS
Subtotal (I-squared = .%, p = .)			0.61 (0.08, 4.45)	100.00	

NOTE: Weights are from random effects analysis

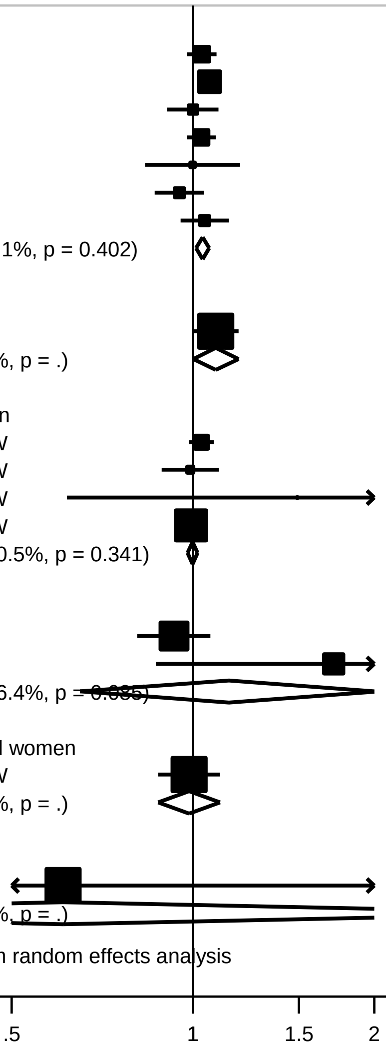


Figure 137 Relative risk of stomach cancer mortality for 10 g/day increase of total alcohol (as ethanol) intake by geographic location and sex

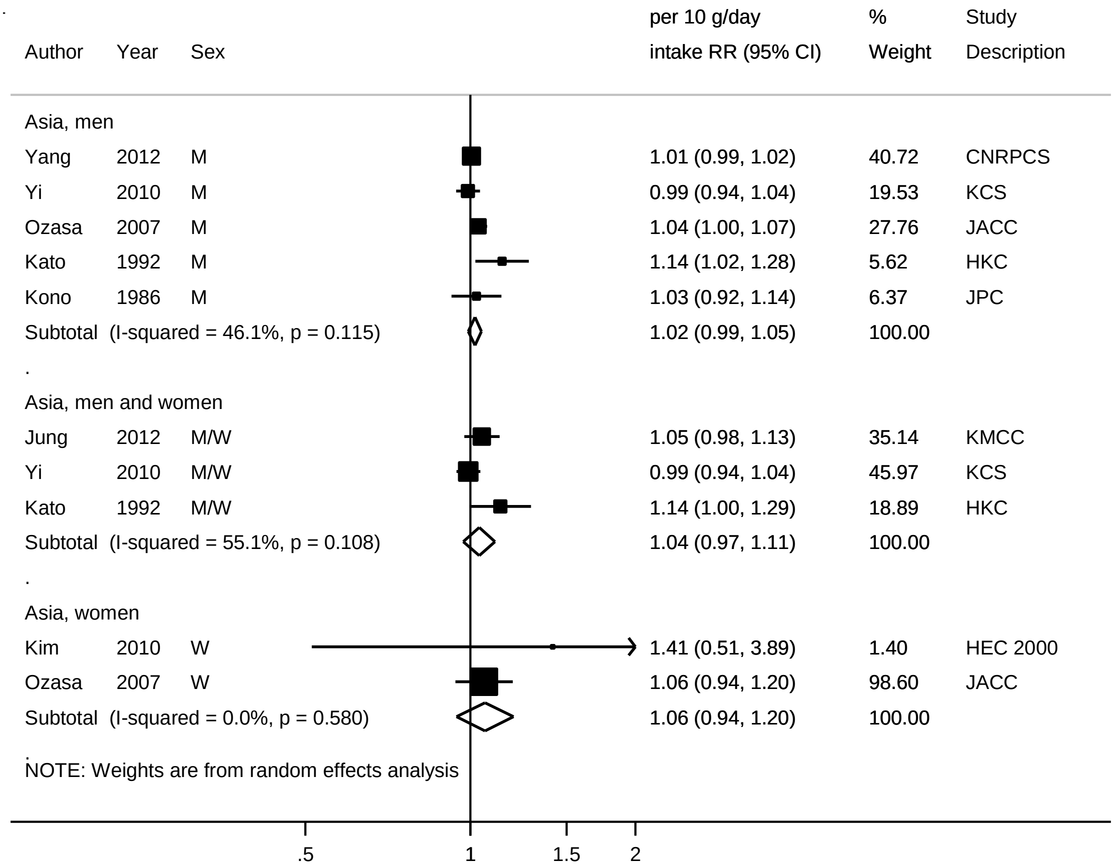
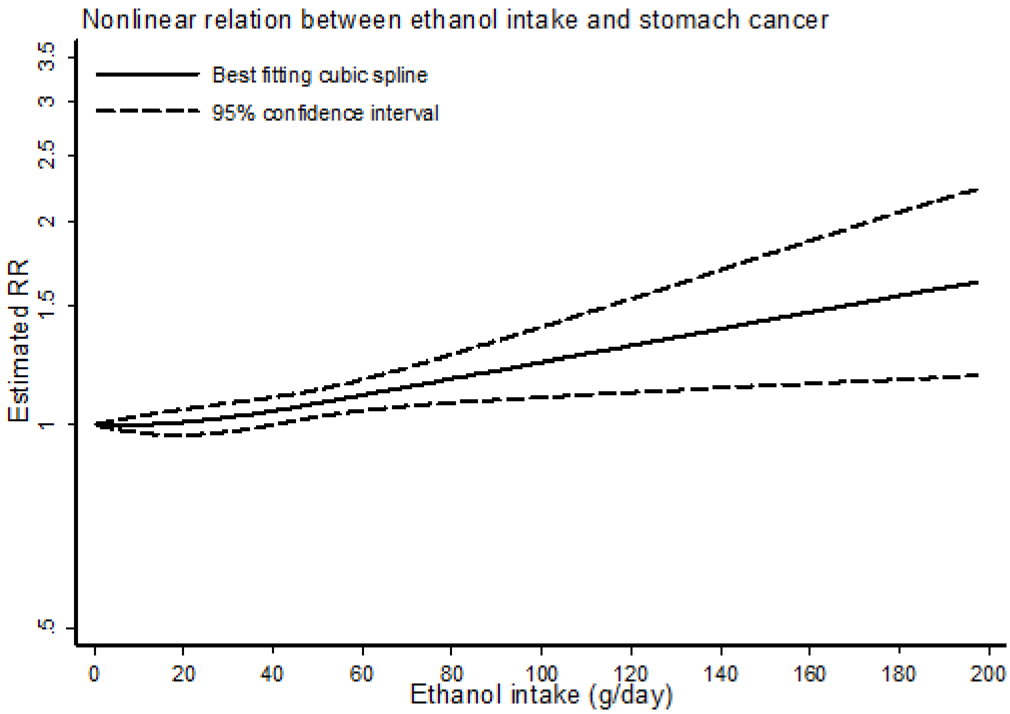


Figure 138 Non-linear dose-response meta-analysis of total alcohol (as ethanol) intake and stomach cancer



P for non-linearity =0.32

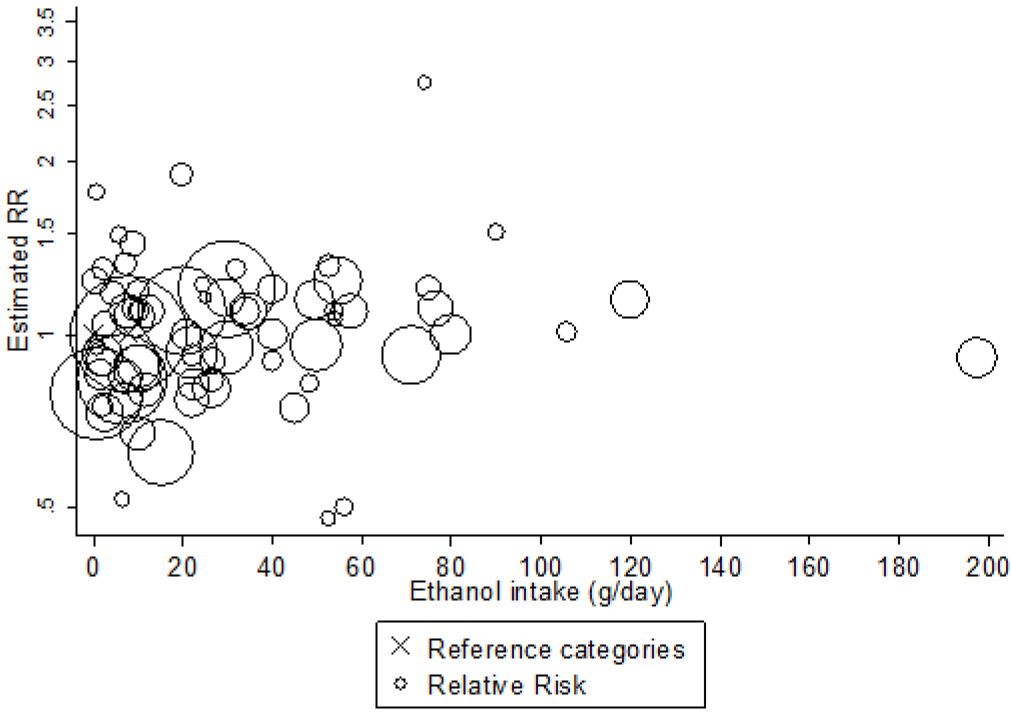
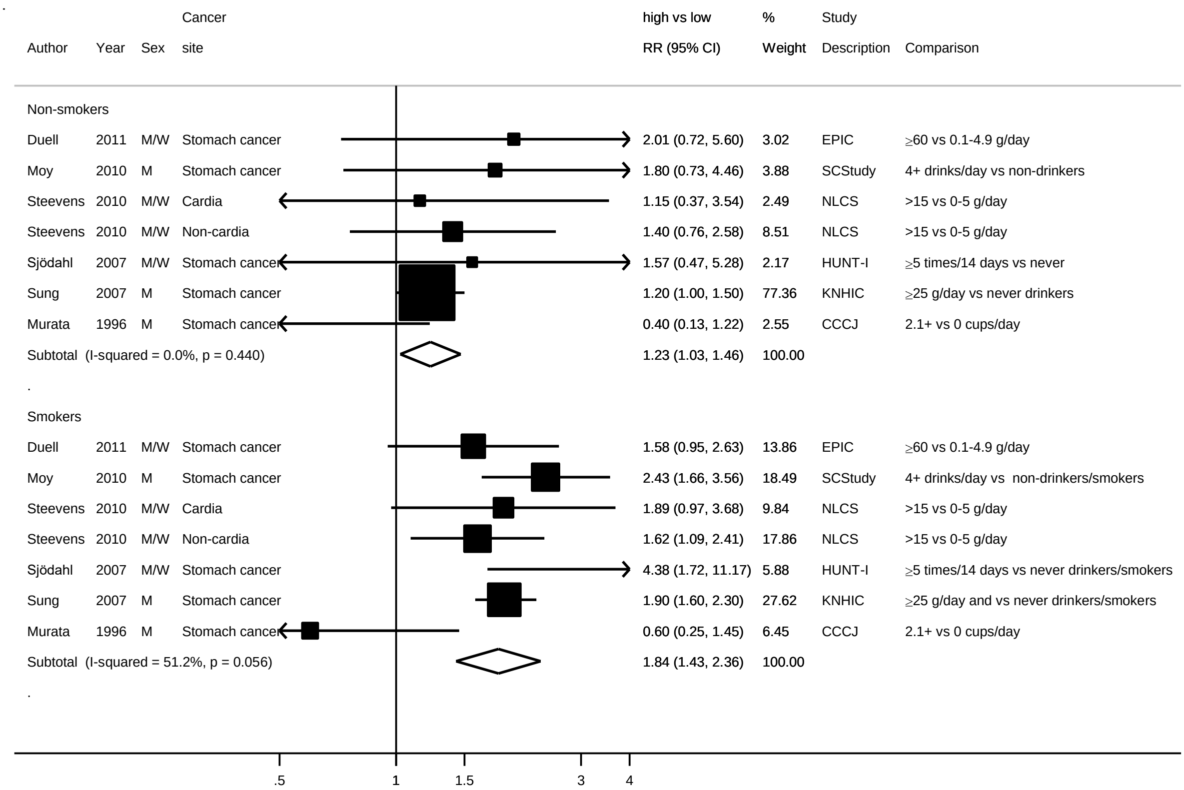


Table 112 Relative risk of stomach cancer and total alcohol (as ethanol) intake estimated using non-linear models

Ethanol (g/day)	RR (95%CI)
0	1.00
10	1.00 (0.98-1.03)
22	1.01 (0.97-1.06)
32	1.03 (0.98-1.08)
45	1.06 (1.01-1.11)
53	1.08 (1.03-1.13)
58	1.09 (1.04-1.14)
71	1.13 (1.05-1.21)
80	1.15 (1.06-1.26)
90	1.19 (1.07-1.32)
106	1.24 (1.08-1.42)
120	1.28 (1.08-1.52)

Figure 139 RR (95% CI) of stomach cancer for the highest compared with the lowest level of total alcohol intake by smoking status



Note: "Smokers' definition includes current smokers, ever smokers. There was not enough data to do dose-response meta-analysis

3.7.1.1 Beer

Randomised controlled trials

No randomised controlled trial was identified.

Cohort studies

Summary

Main results:

Six studies (2137 cases) out of nine were included in the dose-response meta-analysis. The increment unit used was 1 drink/day. Beer consumption was significantly positively associated with stomach cancer risk. The significance did not persist after the exclusion of one American study (Freedman, 2007) and in most stratified analyses.

Three studies were excluded from the dose-response meta-analysis. No significant associations were observed in all three excluded studies. In one study (Larsson, 2007a) the multivariate RR was 2.09 (95% CI=1.11-3.93), p-trend=0.02 and 0.91 (95%CI=0.57-1.46), p-trend=0.75 when comparing the highest with the lowest category of medium/strong - strong beer and light beer intake, respectively.

Low heterogeneity was observed. There was no significant evidence of publication or small study bias. However, the number of studies on beer intake is lower than in the dose-response meta-analysis on alcohol intake (23 studies).

No meta-analyses or pooled prospective studies were identified.

Sensitivity analyses:

The summary RRs ranged from 1.05 (95% CI=0.97-1.13) when Freedman, 2007 was omitted to 1.10 (95% CI=1.03-1.19) when Steevens, 2010b was omitted.

Moy, 2010, Freedman, 2007, and Barstad, 2005 reported beer intake in drinks/day containing 12.6g, 13g, and 12 g of ethanol, respectively. Beer intake was assessed in glasses/day and oz/month in Steevens, 2011 and Nomura, 1990, respectively.

All studies included in the dose-response analysis were adjusted for age, sex, and smoking. None of the studies were adjusted for Helicobacter pylori infection, socioeconomic status, ethnicity, and comorbidities.

Table 113 Beer intake and stomach 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	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 and case-cohort designs

Table 114 Beer intake and stomach 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	1 drink/day
All studies		
Studies (n)	2	6
Cases (total number)	272	2137
RR (95%CI)	1.00 (0.99-1.02)	1.08 (1.01-1.16)
Heterogeneity (I^2, p-value)	0%, 0.7	0.6%, 0.41
P value Egger test	-	0.45

Other stratified analyses

<table>
<tr><td>Geographic area</td><td colspan="2">Asia</td><td colspan="2">Europe</td><td>North America</td></tr>
<tr><td>Studies (n)</td><td colspan="2">1</td><td colspan="2">3</td><td>2</td></tr>
<tr><td>RR (95%CI)</td><td colspan="2">1.06 (0.80-1.41)</td><td colspan="2">1.04 (0.94-1.14)</td><td>1.16 (1.03-1.30)</td></tr>
<tr><td>Heterogeneity (I^2, p-value)</td><td colspan="2">-</td><td colspan="2">18.8%, 0.29</td><td>0%, 0.51</td></tr>
<tr><td>Number of cases</td><td colspan="2"><500 cases</td><td colspan="2">500-<1000 cases</td><td>≥1000 cases</td></tr>
<tr><td>Studies (n)</td><td colspan="2">5</td><td colspan="2">1</td><td>-</td></tr>
<tr><td>RR (95%CI)</td><td colspan="2">1.11 (1.03-1.19)</td><td colspan="2">0.94 (0.79-1.13)</td><td></td></tr>
<tr><td>Heterogeneity (I^2, p-value)</td><td colspan="2">0%, 0.66</td><td colspan="2">-</td><td></td></tr>
<tr><td>Publication year</td><td colspan="2"><2000</td><td colspan="2">2000-<2010</td><td>>=2010</td></tr>
<tr><td>Studies (n)</td><td colspan="2">1</td><td colspan="2">2</td><td>3</td></tr>
<tr><td>RR (95%CI)</td><td colspan="2">1.07 (0.84-1.38)</td><td colspan="2">1.10 (0.95-1.27)</td><td>1.05 (0.94-1.18)</td></tr>
<tr><td>Heterogeneity (I^2, p-value)</td><td colspan="2">-</td><td colspan="2">55.3%, 0.14</td><td>14.6%, 0.31</td></tr>
<tr><td colspan="6">Adjustment for confounders:</td></tr>
<tr><td>BMI</td><td colspan="3">Not adjusted</td><td colspan="2">Adjusted</td></tr>
<tr><td>Studies (n)</td><td colspan="3">3</td><td colspan="2">3</td></tr>
<tr><td>RR (95%CI)</td><td colspan="3">1.07 (0.98-1.18)</td><td colspan="2">1.07 (0.92-1.25)</td></tr>
<tr><td>Heterogeneity (I^2, p-value)</td><td colspan="3">0%, 0.62</td><td colspan="2">50.2%, 0.13</td></tr>
<tr><td>Total energy intake</td><td colspan="3">Not adjusted</td><td colspan="2">Adjusted</td></tr>
<tr><td>Studies (n)</td><td colspan="3">3</td><td colspan="2">3</td></tr>
<tr><td>RR (95%CI)</td><td colspan="3">1.04 (0.93-1.16)</td><td colspan="2">1.09 (0.97-1.23)</td></tr>
<tr><td>Heterogeneity (I^2, p-value)</td><td colspan="3">0%, 0.92</td><td colspan="2">50.9%, 0.13</td></tr>
<tr><td>Physical activity</td><td colspan="3">Not adjusted</td><td colspan="2">Adjusted</td></tr>
<tr><td>Studies (n)</td><td colspan="3">5</td><td colspan="2">1</td></tr>
<tr><td>RR (95%CI)</td><td colspan="3">1.05 (0.97-1.13)</td><td colspan="2">1.18 (1.04-1.34)</td></tr>
<tr><td>Heterogeneity (I^2, p-value)</td><td colspan="3">0%, 0.64</td><td colspan="2">-</td></tr>
</table>

Table 115 Beer intake and stomach 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
Duell, 2011 STM80134 Denmark, France, Germany, Greece,Italy, Netherlands, Norway,Spain ,Sweden,UK	EPIC, Prospective Cohort, Age: 35-70 years, M/W	444/ 478 459 4 160 578 person years	Cancer registries, health insurance records, pathology records & active follow up	FFQ, dietary questionnaires, food record	Incidence, gastric adenocarcinoma	≥30 vs 0.1-4.9 g/day	1.75 (1.13-2.73)	Age, sex, centre, education level, vegetable intake, ethanol from liquor, ethanol from wine, intake of fruits, nuts, seeds, processed and red meat, smoking, total energy intake	Ethanol converted to drinks using 13.5g standardised measurement per drink, mid-points of exposure categories, reference category changed using Hamling's method.
Moy, 2010 STM80101 China	SCStudy, Prospective Cohort, Age: 45-64 years, M	391/ 18 244 19 years	Biennial home visits/linkage/ cancer registry/vital stats	FFQ	Incidence, stomach cancer	1+ drinks vs non-drinkers	1.21 (0.79-1.84)	Age at interview, BMI, education level, fruit intake, spirits consumption, vegetable intake, wine consumption, year of interview, neighbourhood of residence at recruitment, preserved food intake, years of smoking	Mid-points of exposure categories
Steevens, 2010b STM80061 Netherlands	NLCS, Case Cohort, Age: 55-70 years, M/W	164/ 56806 16 years	Annual record linkage to the Netherlands cancer and pathology registry	Validated FFQ	Incidence, gastric cardia adenocarcinoma	Per 1 glass/day	1.03 (0.86-1.24)	Age, sex, BMI, education level, energy intake, current smoking status, fish intake, fruit and vegetable intake, smoking dose and duration	RRs for cardia and non-cardia gastric cancers combined using Hamling's method
						>2 glasses/day vs no beer	0.90 (0.39-2.07)		
		491/			Incidence, gastric non-cardia adenocarcinoma	Per 1 glass/day	1.15 (1.03-1.29)		
						>2	1.58 (0.95-		

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Missing data derived for analyses
						glasses/day vs no beer	2.63)		
Freedman, 2007 STM80065 USA	NIH- AARP, Prospective Cohort, Age: 50- years, M/W, Retired	188/ 474 606 4.6 years	Linkage of the cohort with database to state cancer registries	Validated FFQ	Incidence, gastric cardia adenocarcinoma	>3 vs >0-1 drinks/day	1.17 (0.55-2.52)	Age, sex, BMI, fruit & veg consumption, liquor consumption, smoking status, wine consumption, education, total energy intake, usual physical activity, vigorous physical activity	Distribution of person-years by exposure categories, mid-points of exposure categories, reference category changed using Hamling's method, RRs for cardia and non-cardia gastric cancers combined using Hamling's method
		187/			Incidence, gastric non-cardia adenocarcinoma	>3 vs >0-1 drinks/day	1.02 (0.40-2.61)	Additionally adjusted for race/ethnicity	
Barstad, 2005 STM80131 Denmark	CCPPS, Prospective Cohort, Age: 21-93 years, M/W	122/ 28 463 33 years	Cancer registry	Questionnaire (general)	Incidence, stomach cancer	Per 1 drink/day	1.02 (0.88-1.17)	Age, sex, smoking habits	
Nomura, 1990 STM14814 USA	HHP, Prospective Cohort, Age: 45- years, M, Japanese residents of Hawaii	150/ 7 990 19 years	Cancer registry/ hospital records	FFQ + recall	Incidence, stomach cancer	≥500 oz/month vs non-drinker	1.10 (0.70-1.70)	Age, smoking habits	Distribution of person-years by exposure categories, mid-points of exposure categories, 400ml serving was used as a standard serving/drink

Table 116 Beer intake and stomach 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
Everatt, 2012 STM80096 Lithuania	KRIS and MIHDPS, Prospective Cohort, Age: 40-59 years, M	16/ 7 150 30 years	Cancer registry	Questionnaire	Incidence, stomach cancer	Highest vs lowest	1.52 (0.66-3.51)	BMI, education, smoking, vodka, wine	Excluded, only two exposure categories, used in HvL analysis only
		185/				≥1 vs <1 litres/time	0.79 (0.39-1.62)	Age, BMI, study, education, smoking, vodka, wine	Excluded, intake per one occasion
Larsson, 2007a STM80088 Sweden	SMC, Prospective Cohort, W	160/ 61 433 18 years	Linkage of the cohort with national and regional Swedish cancer registry	Validated FFQ, light beer	Incidence, stomach cancer, follow-up from 1987-2005	>2 vs 0 servings/week	0.91 (0.57-1.46)	Age, coffee intake, education, fruit and vegetable intake, processed meat intake, intake of other alcoholic drinks	Excluded, exposures are types of beer
				Medium-strong/strong beer		>1 vs 0 servings/week	2.09 (1.11-3.93) Ptrend:0.02		
Knekt, 1999 STM03959 Finland	FMCHES, Prospective Cohort, Age: 15-99 years, M/W	45/ 9 985 21 years	Cancer registry	Dietary history	Incidence, stomach cancer	>median vs no	0.57 (0.23-1.42)	Age, sex, geographical area, smoking habits	Exposure not quantified, used in HvL analysis only
Kneller, 1991 STM07350 USA	LBS, Prospective Cohort, Age: 35- years, M, Mainly of Scandinavian descent	75/ 17 633 20 years	Health insurance company records	FFQ	Mortality, stomach cancer	Highest intake vs never	1.10	Age, smoking habits	Excluded, no confidence intervals or a p value
Pollack, 1984 STM08890 USA	HHP, Prospective Cohort, Age: 45-68 years, M, Japanese residents of Hawaii	99/ 7 837 14 years	Hospital records, death certificates, cancer registry	Dietary recall	Incidence, stomach cancer	(mean exposure)			Excluded, no measure of association, superseded by Nomura, 1990

Figure 140 RR estimates of stomach cancer by levels of beer intake

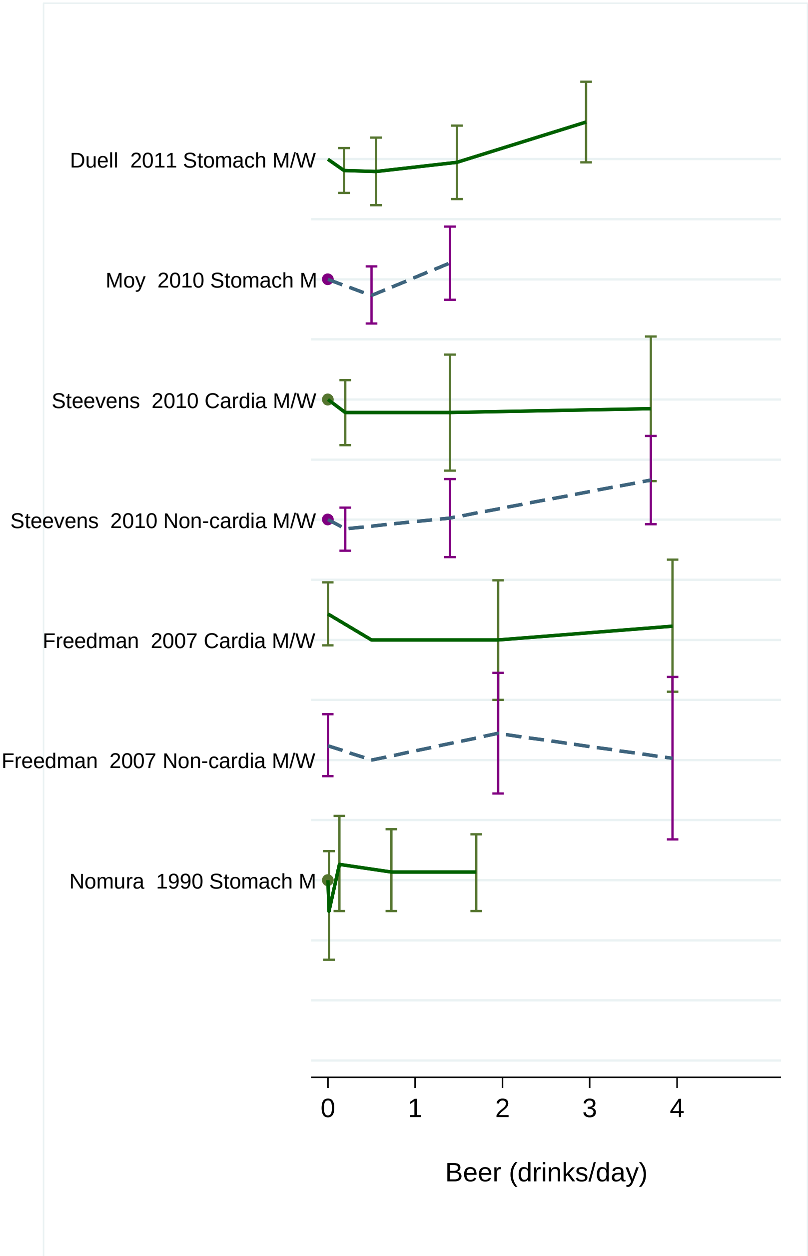


Figure 141 RR (95% CI) of stomach cancer for the highest compared with the lowest level beer intake

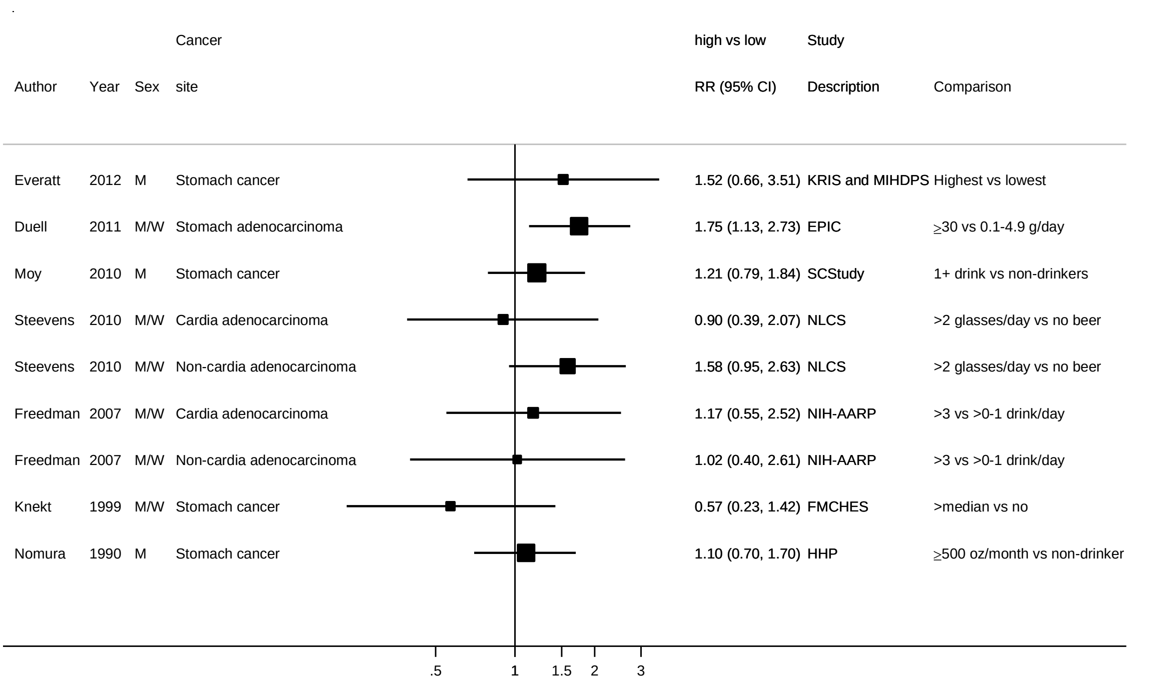


Figure 142 Relative risk of stomach cancer incidence for 1 drink/day increase of beer intake

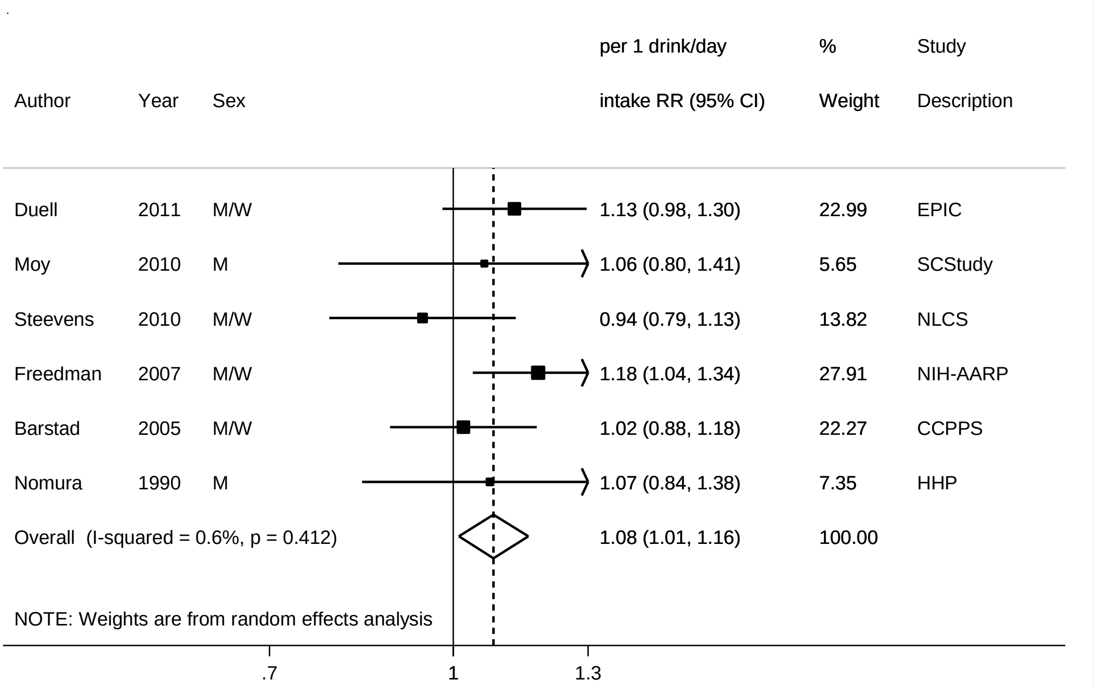
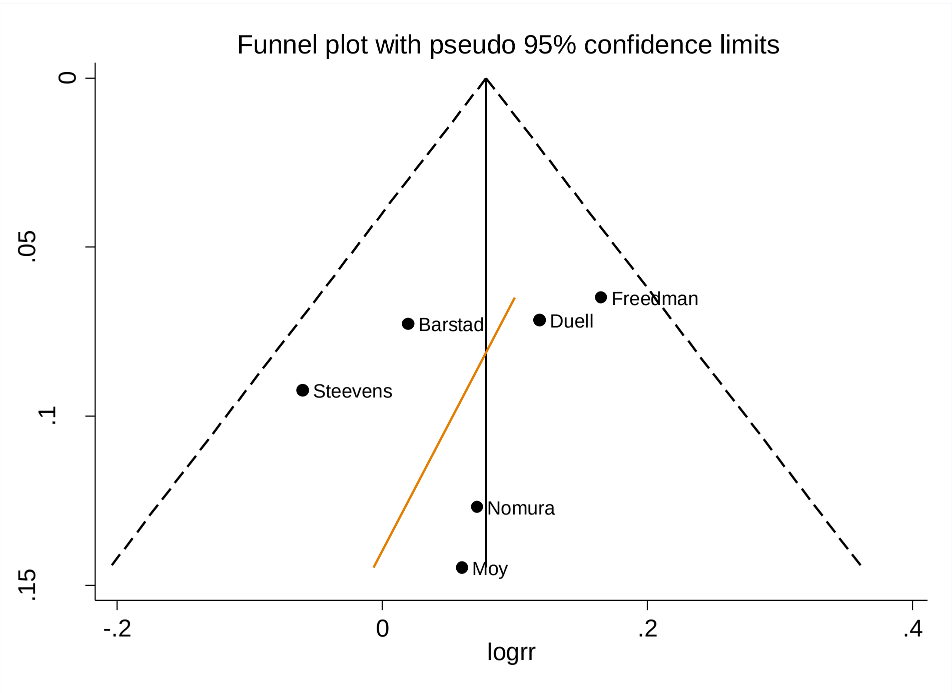
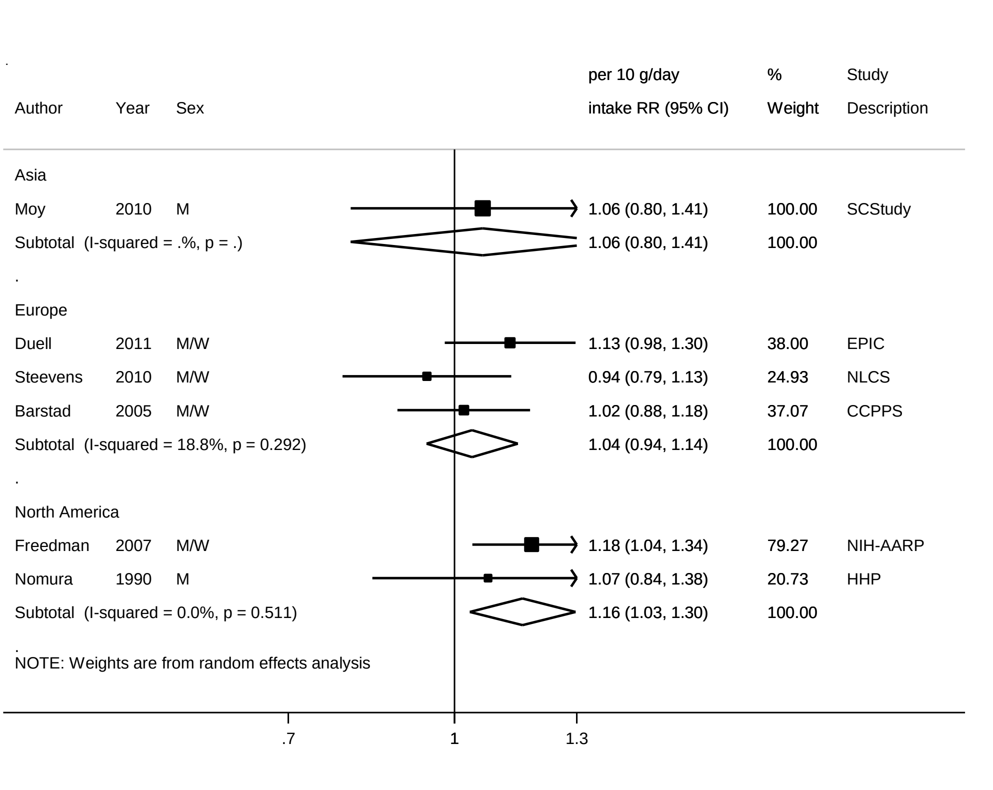


Figure 143 Funnel plot of studies included in the dose response meta-analysis of beer and stomach cancer



Egger's test p=0.45

Figure 144 Relative risk of stomach cancer for 1 drink/day increase of beer intake by geographic location



3.7.1.2 Wine

Randomised controlled trials

No randomised controlled trial was identified.

Cohort studies

Summary

Main results:

Five studies (1756 cases) were included in the dose-response meta-analysis. Wine consumption was not associated with stomach cancer risk.

No meta-analyses or pooled prospective studies were identified.

Three studies were excluded from the dose-response meta-analysis. No significant associations were observed in the excluded studies. Nomura, 1990 study was excluded due to low exposure of ≥2oz/month (0.016 glasses/day) in the highest category with a RR of 0.7 (95% CI=0.4-1.3) compared to the lowest.

Moderate heterogeneity was observed. There was no significant evidence of publication or small study bias. However, the number of studies on wine intake is lower than in the dose-response meta-analysis on alcohol intake (23 studies).

Sensitivity analyses:

The summary RRs ranged from 0.92 (95% CI=0.79-1.08) when Freedman, 2007 was omitted to 1.01 (95% CI=0.92-1.11) when Barstad, 2005 was omitted.

Study quality.

Steevens, 2010b; Freedman, 2007, and Barstad, 2005 reported wine intake in glasses or drinks/day. Larsson, 2007a estimated wine intake in servings/week. In Duell, 2011 study ethanol from wine was reported, using 13.5g/drink standardized measurement across all types of alcoholic beverages.

Duell, 2011 study accounted for 35.9% of the weight. More than half of the non-drinkers at baseline were former drinkers (based on their lifetime alcohol consumption history. The reference category in the analysis was light drinkers. The definition of non-drinkers in Larsson, 2007a study was not provided; Freedman, 2007 study had no data on past alcohol use.

All studies included in the dose-response analysis were adjusted for age, sex and other confounders. None of the studies were adjusted for Helicobacter pylori infection or comorbidities.

Table 117 Wine intake and stomach cancer risk. Number of studies in the CUP SLR

	Number
Studies identified	8 (9 publications)

Studies included in forest plot of highest compared with lowest exposure	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 and case-cohort designs

Table 118 Wine intake and stomach cancer risk. Summary of the linear dose-response meta-analysis in the 2005 SLR and CUP

	2005 SLR	**CUP**
Increment unit used	1 glass/week	1 glass/day
All studies		
Studies (n)	2	5
Cases (total number)	272	1756
RR (95%CI)	0.93 (0.87-0.99)	0.97 (0.83-1.14)
Heterogeneity (I^2, p-value)	0%, 0.4	51.3%, 0.08
P value Egger test	-	0.56

Other stratified analyses

Geographic area	**Asia**	**Europe**	**North America**
Studies (n)		4	1
RR (95%CI)		0.92 (0.79-1.08)	1.20 (0.96-1.50)
Heterogeneity (I^2, p-value)		38%, 0.18	-
Number of cases	**<500 cases**	**500-<1000 cases**	**≥1000 cases**
Studies (n)	4	1	
RR (95%CI)	0.96 (0.75-1.23)	0.95 (0.80-1.12)	
Heterogeneity (I^2, p-value)	81.9%, 0.05	-	
Publication year	**<2000**	**2000-<2010**	**>=2010**
Studies (n)		3	2
RR (95%CI)		0.86 (0.46-1.61)	0.98 (0.88-1.08)
Heterogeneity (I^2, p-value)		74.2%, 0.02	0%, 0.65
Adjustment for confounders:			

Socioeconomic status	**Not adjusted**	**Adjusted**
Studies (n)	1	4
RR (95%CI)	0.60 (0.39-0.93)	1.01 (0.92-1.11)
Heterogeneity (I^2, p-value)	-	0%, 0.40

Smoking		
Studies (n)	1	4
RR (95%CI)	0.61 (0.02-21.44)	0.97 (0.82-1.15)
Heterogeneity (I^2, p-value)	-	63.1 %, 0.04
BMI		
Studies (n)	3	2
RR (95%CI)	0.81 (0.53-1.24)	1.05 (0.83-1.33)
Heterogeneity (I^2, p-value)	58.6%, 0.09	62.9%, 0.10
Total energy intake		
Studies (n)	2	3
RR (95%CI)	0.60 (0.39-0.92)	1.02 (0.91-1.14)
Heterogeneity (I^2, p-value)	0%, 0.99	30%, 0.24
Physical activity		
Studies (n)	4	1
RR (95%CI)	0.92 (0.79-1.08)	1.20 (0.96-1.50)
Heterogeneity (I^2, p-value)	38%, 0.18	-

Table 119 Wine intake and stomach 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	Reasons for exclusion
Duell, 2011 STM80134 Denmark,France,Germany,Greece,Italy,Netherlands,Norway,Spain,Sweden,UK	EPIC, Prospective Cohort, Age: 35-70 years, M/W	444/ 478 459 8.8 years	Cancer registries, health insurance records, pathology records & active follow up	FFQ, dietary questionnaires, food record	Incidence, gastric adenocarcinoma	≥30 vs 0.1-4.9 g/day	0.89 (0.60-1.30)	Age, sex, centre, education level, vegetable intake, ethanol from beer, ethanol from liquor, intake of fruits, nuts, seeds, processed and red meat, smoking, total energy intake	Ethanol converted to drinks using 13.5g standardised measurement per drink, mid-points of exposure categories, reference category changed using Hamling's method.
Steevens, 2010b STM80061 Netherlands	NLCS, Case Cohort, Age: 55-70 years, M/W	164/ 4 617 16 years	Annual record linkage to The Netherlands cancer registry and pathology records	Validated FFQ	Incidence, gastric cardia adenocarcinoma	Per 1 glass/day	0.87 (0.62-1.21)	Age, sex, BMI, education level, energy intake, current smoking status, ethanol intake, fish intake, fruit and vegetable intake, smoking dose and duration	RRs for cardia and non-cardia gastric cancers combined using Hamling's method
						>2 glasses/day vs no wine	1.04 (0.40-2.70)		
		491/			Incidence, gastric non-cardia adenocarcinoma	Per 1 glass/day	0.93 (0.77-1.13)		
						>2 glasses/day vs no wine	0.88 (0.48-1.63)		
Freedman, 2007 STM80065 USA	NIH- AARP, Prospective Cohort, Age: 50- years, M/W, Retired	188/ 474 606 5 years	Linkage of the cohort with database to state cancer registries	Validated FFQ	Incidence, gastric cardia adenocarcinoma	>3 vs >0-1 drink/day	3.01 (0.73-12.31), p=0.09	Age, sex, BMI, fruit & veg consumption, liquor consumption, smoking status, beer intake, education, total energy intake, usual physical activity, vigorous physical activity	Distribution of person-years by exposure categories, mid-points of exposure categories, reference category changed using Hamling's method, RRs for
		187/			Incidence, gastric		4.29 (1.05-17.61)	Additionally	

Author, Year, 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
					non-cardia adenocarcinoma			adjusted for race/ethnicity	cardia and non-cardia gastric cancers combined using Hamling's method
Larsson, 2007a STM80088 Sweden	SMC, Prospective Cohort, W	160/ 61 433 18 years	Linkage of the cohort with national and regional Swedish cancer registry	Validated FFQ	Incidence, stomach cancer, follow-up from 1987-2005	>0.5 vs 0 servings/week	0.98 (0.58-1.66)	Age, coffee intake, education, fruit and vegetable intake, processed meat intake, intake of other alcoholic drinks	Servings per week converted to glasses per day
Barstad, 2005 STM80131 Denmark	CCPPS, Prospective Cohort, Age: 21-93 years, M/W	122/ 28 463 33 years	Cancer registry	Questionnaire (general)	Incidence, stomach cancer	Per 1 drink/day	0.60 (0.39-0.93), p=0.02	Age, sex, smoking habits	

Table 120 Wine intake and stomach 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
Everatt, 2012 STM80096 Lithuania	KRIS and MIHDPS, Prospective Cohort, Age: 40-59 years, M	17/ 7 150 30 years	Cancer registry	Questionnaire	Incidence, stomach cancer	Highest vs lowest	1.72 (0.67-4.40)	BMI, beer, vodka intake, education, smoking	Only two exposure categories, used in HvL analysis only
		185/				≥0.5 vs <0.5 litres/time	2.95 (1.30-6.68)	Age, BMI, study, beer, vodka intake, education, smoking	Excluded, intake per one occasion
Hirvonen, 2001 STM02213 Finland	ATBC, Prospective Cohort, Age: 50-69 years, M, Smokers	111/ 27 110 6.1 years	Cancer registry	FFQ	Incidence, stomach cancer		(mean exposure)	Age	Excluded, mean exposure only
Nomura, 1990 STM14814 USA	HHP, Prospective Cohort, Age: 45- years, M, Japanese residents of Hawaii	150/ 7 990 10.6 years	Cancer registry/ hospital records	FFQ + recall	Incidence, stomach cancer	≥2 oz/month vs non-drinker	0.70 (0.40-1.30)	Age, smoking habits	Excluded, very low intake of ≥2oz/month (0.016 glasses/day) in the highest category
Pollack, 1984 STM08890 USA	HHP, Prospective Cohort, Age: 45-68 years, M, Japanese residents of Hawaii	99/ 7 837 14 years	Hospital records, death certificates, cancer registry	Dietary recall	Incidence, stomach cancer		(mean exposure)		Excluded, mean exposure only, superseded by Nomura, 1990

Figure 145 RR estimates of stomach cancer by levels of wine intake

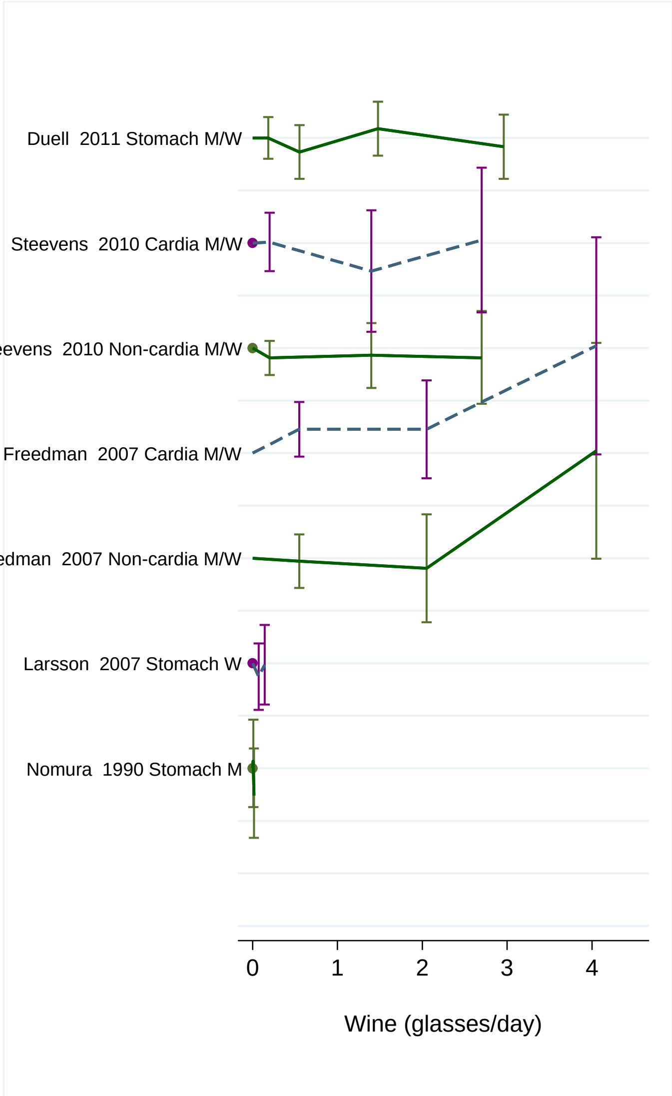


Figure 146 RR (95% CI) of stomach cancer for the highest compared with the lowest level wine intake

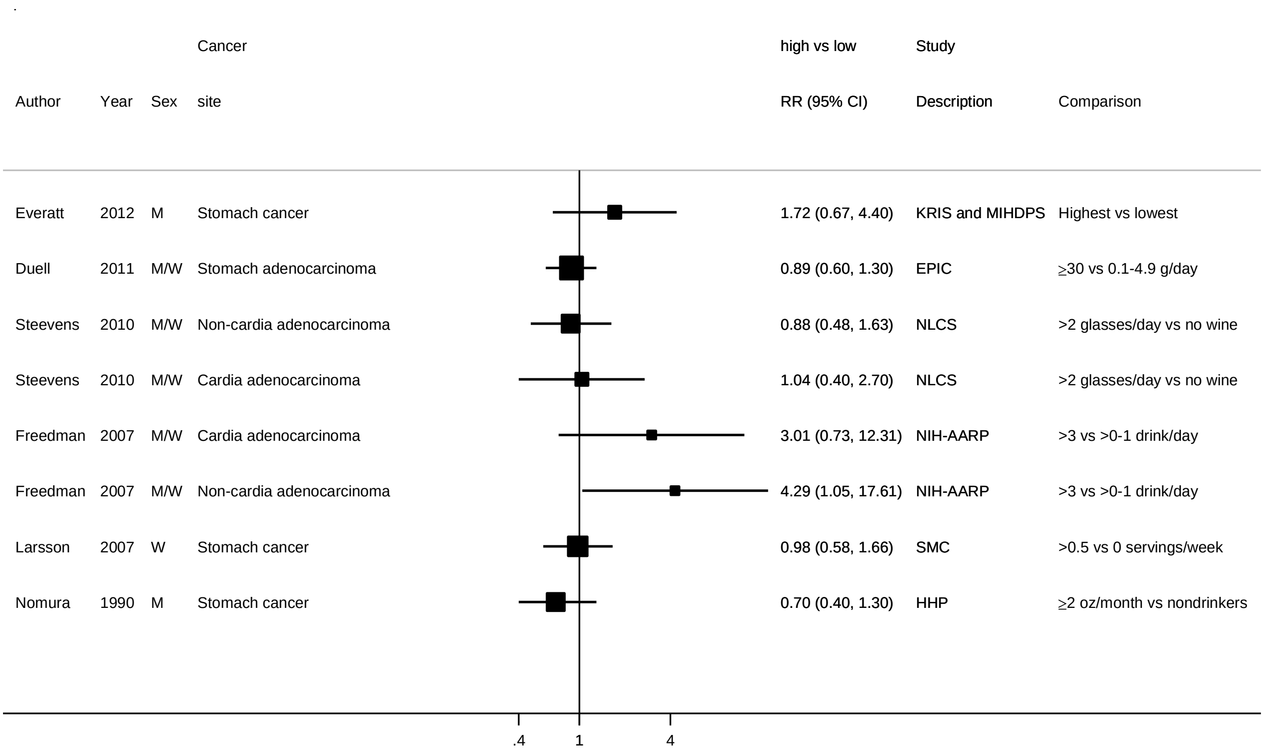


Figure 147 Relative risk of stomach cancer incidence for 1 glass/day increase of wine intake

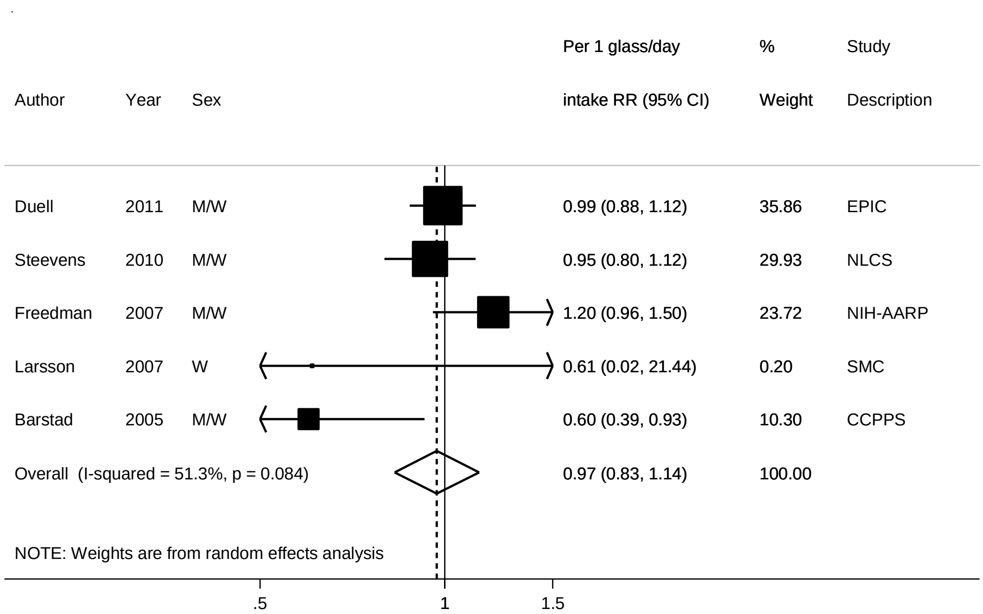
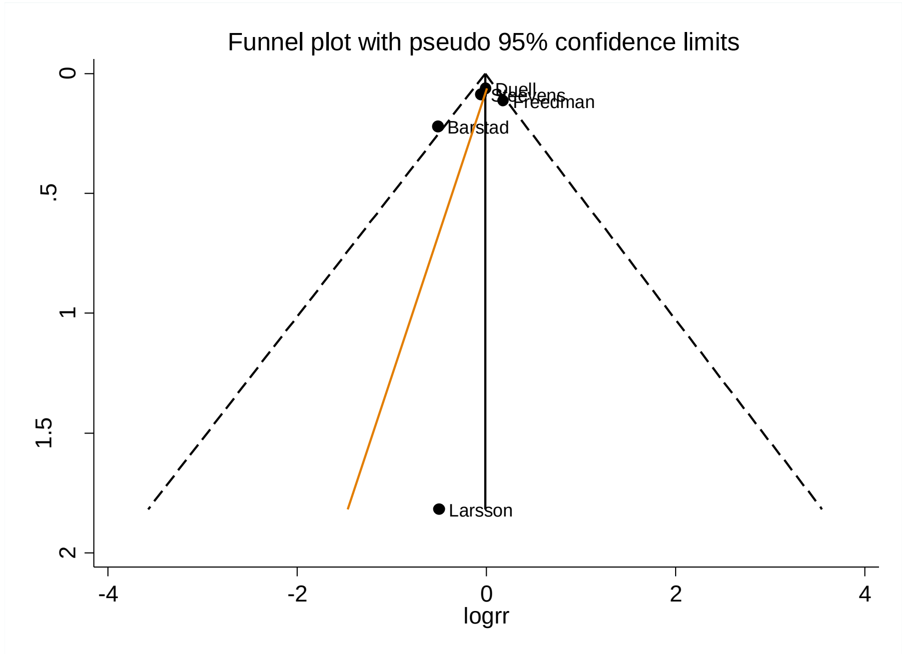
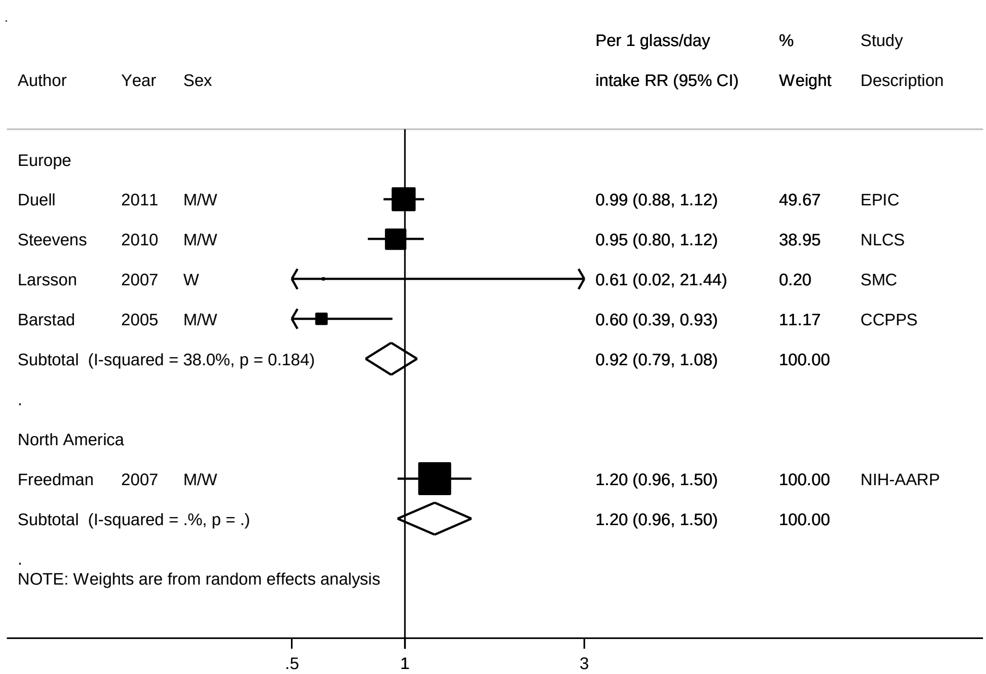


Figure 148 Funnel plot of studies included in the dose response meta-analysis of wine and stomach cancer



Egger's test p=0.56

Figure 149 Relative risk of stomach cancer for 1 drink/day increase of wine intake by geographic location



3.7.1.3 Spirits

Randomised controlled trials

No randomised controlled trial was identified.

Cohort studies

Summary

Main results:

Seven studies (2288 cases) were included in the dose-response meta-analysis. Spirits and liquors consumption was not significantly associated with stomach cancer risk.

Three studies were excluded from the dose-response meta-analysis. No significant associations were observed in the excluded studies. Larsson, 2007a study was excluded due to low intakes and resulting wide confidence interval, RR of 9.04(95% CI=0.16-510.06) per 1 drink/day increase.

Low heterogeneity was observed. There was no significant evidence of publication or small study bias. However, the number of studies on beer intake is lower than in the dose-response meta-analysis on alcohol intake (23 studies).

Sensitivity analyses:

The summary RRs ranged from 1.01 (95% CI=0.95-1.06) when Moy, 2010 was omitted to 1.04 (95% CI=0.99-1.09) when Steevens, 2010b was omitted.

Non-linear dose-response meta-analysis:

There was no evidence of non-linear dose-response association (p for non-linearity = 0.86).

No meta-analyses or pooled prospective studies were identified.

Study quality:

All studies included in the dose-response analysis were adjusted for age, sex, and smoking. None of the studies were adjusted for Helicobacter pylori infection or ethnicity.

Moy, 2010; Steevens, 2010; Freedman, 2007, and Barstad, 2005 reported spirits or liquor intake in glasses or drinks/day. Duell, 2011 study used a 13.5g ethanol/drink standardized measurement across all drink types to report intake of ethanol from liquor and spirits. Nomura, 1990 estimated intake of spirits in oz/month.

Duell, 2011 study included more than half former drinkers in the category of non-drinkers. Freedman, 2007 study had no data on past alcohol use. All remaining studies did not specify if non-drinkers category included former drinkers.

Table 121 Spirits intake and stomach cancer risk. Number of studies in the CUP SLR

	Number
Studies identified	10 (11 publications)

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

Note: Include cohort and case-cohort designs

Table 122 Spirits intake and stomach 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	1 drink/day
	All studies	
Studies (n)	2	7
Cases (total number)	272	2288
RR (95%CI)	1.03 (1.00-1.05)	1.03 (0.98-1.08)
Heterogeneity (I^2, p-value)	0%, 0.8	6.6%, 0.38
P value Egger test	-	0.86
	Stratified and sensitivity analysis*	
Outcome	**Incidence**	**Mortality**
Studies (n)	6	1
RR (95%CI)	1.04 (0.98-1.11)	1.00 (0.93-1.08)
Heterogeneity (I^2, p-value)	10.4%, 0.35	-
Geographic area	**Asia****	**Europe**
Studies (n)	3	2
RR (95%CI)	1.04 (0.99-1.10)	0.94 (0.80-1.09)
Heterogeneity (I^2, p-value)	9.6%, 0.33	0%, 0.82
	North America	
Studies (n)	1	
RR (95%CI)	0.97 (0.84-1.12)	
Heterogeneity (I2, p-value)	-	

*No stratified analysis in the 2005 SLR. **Nomura, 1990 study of Japanese residents in Hawaii (HHP) was included in the subgroup of Asian cohorts.

Other stratified analyses

Duration of follow-up	**5-<10 years**	**10-<15 years**	**≥15 years**
Studies (n)	1	1	4
RR (95%CI)	1.07 (0.99-1.15)	1.14 (0.91-1.42)	1.00 (0.93-1.08)
Heterogeneity (I^2, p- value)	-	-	8.5%, 0.35
Number of cases	**<500 cases**	**500-<1000 cases**	**≥1000 cases**
Studies (n)	6	1	
RR (95%CI)	1.04 (0.99-1.09)	0.93 (0.79-1.09)	-
Heterogeneity (I^2, p-value)	0%, 0.45	-	
Publication year	**<2000**	**2000-<2010**	**>=2010**
Studies (n)	1	2	4
RR (95%CI)	1.14 (0.91-1.42)	1.06 (0.85-1.33)	1.02 (0.97-1.08)
Heterogeneity (I^2, p-value)	-	59.2%, 0.12	4.4%, 0.37

Adjustment for confounders:		
Socioeconomic status	**Not adjusted**	**Adjusted**
Studies (n)	2	4
RR (95%CI)	1.17 (1.00-1.38)	1.02 (0.97-1.07)
Heterogeneity (I^2, p-value)	-	0%, 0.46
BMI		
Studies (n)	3	4
RR (95%CI)	1.15 (0.98-1.34)	1.02 (0.96-1.07)
Heterogeneity (I^2, p-value)	0%, 0.70	16.6%, 0.31
Total energy intake		
Studies (n)	4	3
RR (95%CI)	1.05 (0.99-1.12)	0.95 (0.86-1.06)
Heterogeneity (I^2, p-value)	19.8%, 0.29	0%, 0.92
Physical activity		
Studies (n)	6	1
RR (95%CI)	1.04 (0.98-1.09)	0.97 (0.84-1.12)
Heterogeneity (I^2, p-value)	12.6%, 0.33	-
Comorbidities		
Studies (n)	6	1
RR (95%CI)	1.04 (0.98-1.11)	1.00 (0.93-1.08)
Heterogeneity (I^2, p-value)	10.4%, 0.35	-

Table 123 Spirits intake and stomach 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	Reasons for exclusion
Duell, 2011 STM80134 Denmark,France, Germany,Greece, Italy,Netherlands, Norway,Spain,Sweden,UK	EPIC, Prospective Cohort, Age: 35-70 years, M/W	444/ 478 459 8.8 years	Cancer registries, health insurance records, pathology records & active follow up	FFQ, dietary questionnaires, food record	Incidence, gastric adenocarcinoma	≥10 vs 0.1-4.9 g/day	1.08 (0.71-1.63)	Age, sex, centre, education level, vegetable intake, ethanol from beer, ethanol from wine, intake of fruits, nuts, seeds, processed and red meat, smoking, total energy intake	Ethanol converted to drinks using 13.5g standardised measurement per drink, mid-points of exposure categories, reference category changed using Hamling's method.
Steevens, 2010b STM80061 Netherlands	NLCS, Case Cohort, Age: 55-70 years, M/W	164/ 4 617 16 years	Annual record linkage to the Netherlands cancer and pathology registers	Validated FFQ	Incidence, gastric cardia adenocarcinoma	Per 1 glass/day	1.07 (0.79-1.45)	Age, sex, BMI, education level, energy intake, current smoking status, ethanol intake, fish intake, fruit and vegetable intake, smoking dose and duration	RRs for cardia and non-cardia gastric cancers combined using Hamling's method
						>2 glasses/day vs no liquor	0.72 (0.24-2.18)		
		491/			Incidence, gastric non-cardia adenocarcinoma	Per 1 glass/day	0.90 (0.76-1.07)		
						>2 glasses/day vs no liquor	0.58 (0.33-1.03)		
Moy, 2010 STM80101 China	SCStudy, Prospective Cohort, Age: 45-64 years,	391/ 18 244 9.2 years	Biennial home visits/linkage/cancer registry/vital stats	FFQ	Incidence, stomach cancer	4+ drinks/day vs non-drinkers	1.40 (0.92-2.14), p=0.08	Age at interview, BMI, education level, fruit intake, vegetable intake, year of interview,	Mid-points of exposure categories

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Reasons for exclusion
	M							neighbourhood of residence at recruitment, preserved food intake, years of smoking	
Yi, 2010 STM80108 Korea	KCS, Prospective Cohort, Age: 55- years, M/W	71/ 6 291 20.8 years	Death records/calls or follow up visits/death certificates	Questionnaire and interview	Mortality, stomach cancer Male	High ≥540 g/week vs none	1.15 (0.60-2.19)	Age, BMI, education level, smoking habits, ginseng intake, history of chronic disease, pesticide use	Distribution of person-years by exposure categories, intakes in g/week converted to g/day, mid-points of exposure categories
Freedman, 2007 STM80065 USA	NIH- AARP, Prospective Cohort, Age: 50- years, M/W, Retired	188/ 474 606 4.6 years	Linkage of the cohort with database to state cancer registries	Validated FFQ	Incidence, gastric cardia adenocarcinoma	>3 vs >0-1 drinks/day, p=0.02	2.15 (1.20-3.87)	Age, sex, BMI, beer consumption, fruit & veg consumption, smoking status, wine consumption, education, total energy intake, usual physical activity, vigorous physical activity	Distribution of person-years by exposure categories, mid-points of exposure categories, reference category changed using Hamling's method, RRs for cardia and non-cardia gastric cancers
		187/			Gastric non-cardia	>3 vs >0-1 drinks/day,	0.27 (0.07-1.10)	Additionally adjusted for	

Author, Year, 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
					adenocarcinoma	p=0.05		race/ethnicity	combined using Hamling's method
Barstad, 2005 STM80131 Denmark	CCPPS, Prospective Cohort, Age: 21-93 years, M/W	122/ 28 463 33 years	Cancer registry	Questionnaire (general)	Incidence, stomach cancer	Per 1 drink/day	1.22 (0.95-1.56), p=0.12	Age, sex, smoking habits	
Nomura, 1990 STM14814 USA	HHP, Prospective Cohort, Age: 45- years, M, Japanese residents of Hawaii	150/ 7 990 19 years	Cancer registry/ hospital records	FFQ	Incidence, stomach cancer	≥50 oz/month vs non-drinker	1.00 (0.50-2.1)	Age, smoking habits	Distribution of person-years by exposure categories, mid-points of exposure categories, oz/month converted to drink/day using 25ml as a standard serving size

Table 124 Spirits intake and stomach 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
Everatt, 2012 STM80096 Lithuania	KRIS and MIHDPS, Prospective Cohort, Age: 40-59 years, M	13/ 7 150 30 years	Cancer registry	Questionnaire	Incidence, stomach cancer	Highest vs lowest	1.50 (0.66-3.42)	BMI, beer, education, smoking, vodka	Excluded, only two exposure categories, used in HvL analysis only
Larsson, 2007a STM80088 Sweden	SMC, Prospective Cohort, W	160/ 61 433 18 years	Linkage of the cohort with national Swedish cancer registry and regional cancer registry	Validated FFQ	Incidence, stomach cancer, follow-up from 1987-2005	1 vs 0 servings/week	1.38 (0.72-2.65)	Age, coffee intake, education, fruit and vegetable intake, processed meat intake, beer, wine consumption	Excluded, low exposure
Kneller, 1991 STM07350 USA	LBS, Prospective Cohort, Age: 35- years, M, Mainly of Scandinavian descent	75/ 17 633 20 years	Health insurance company records	FFQ	Mortality, stomach cancer	Highest quartile vs lowest quartile	1.10	Age, smoking habits	Excluded, only two exposure categories, no confidence intervals or a p value
Pollack, 1984 STM08890 USA	HHP, Prospective Cohort, Age: 45-68 years, M, Japanese residents of Hawaii	99/ 7 837 14 years	Hospital records, death certificates, cancer registry	Dietary recall	Mortality, stomach cancer		(mean exposure)		Excluded, mean exposure only, superseded by Nomura, 1990

Figure 150 RR estimates of stomach cancer by levels of spirits intake

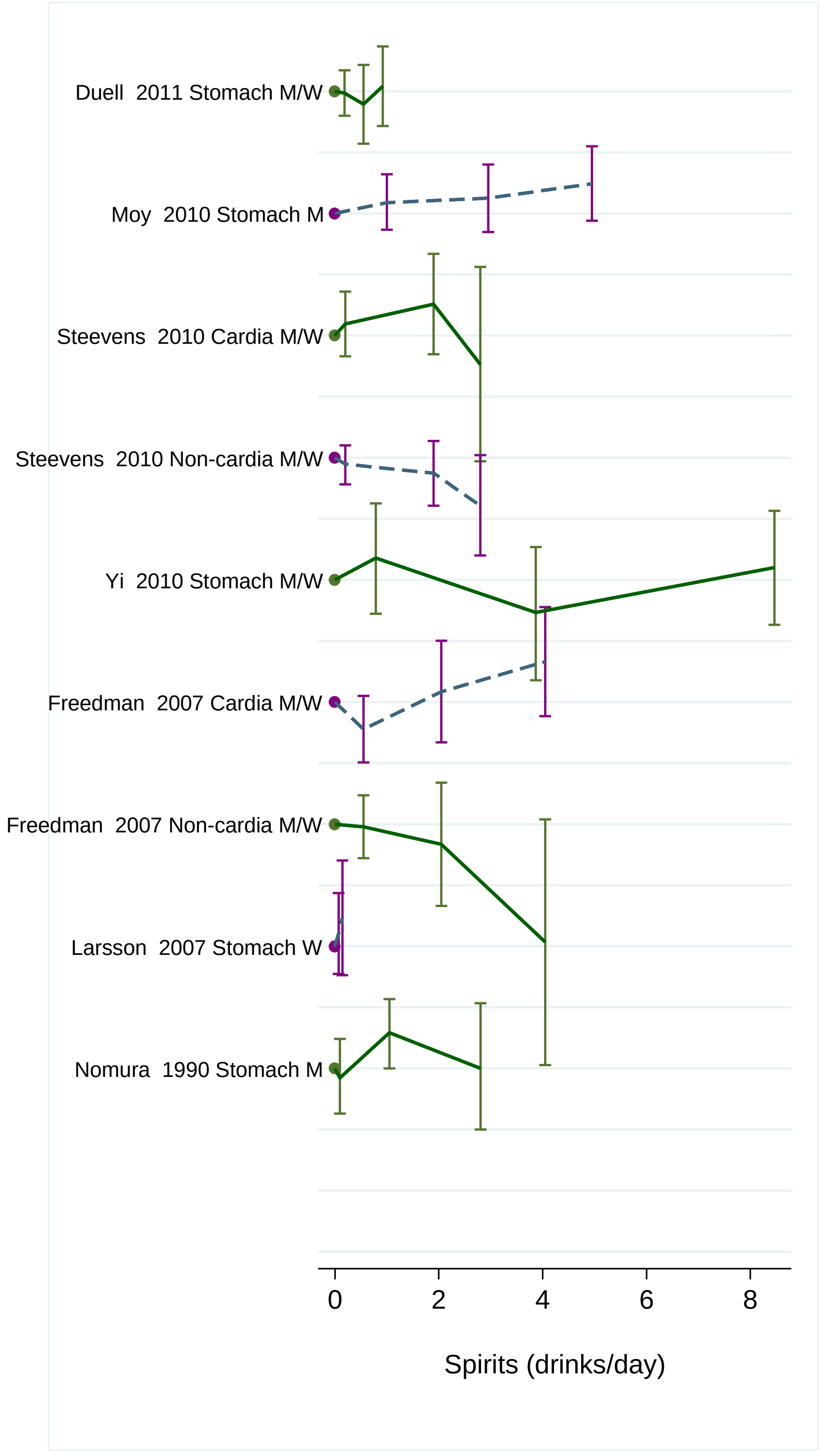


Figure 151 RR (95% CI) of stomach cancer for the highest compared with the lowest level of spirits intake

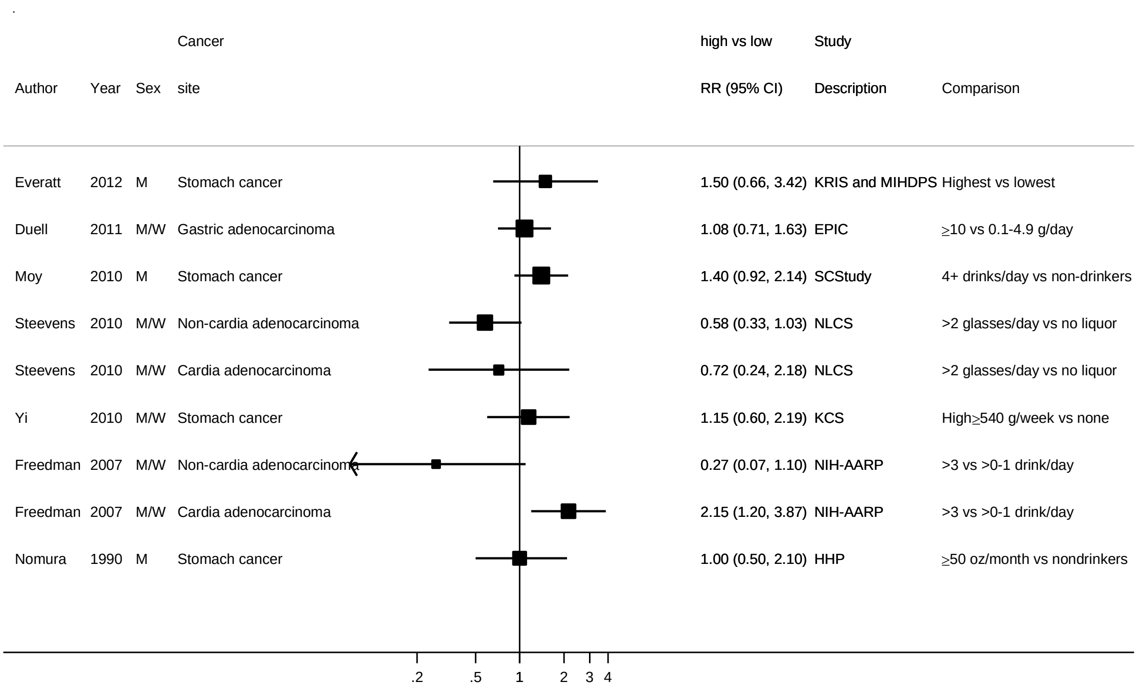


Figure 152 Relative risk of stomach cancer incidence for 1 drink/day increase of spirits intake

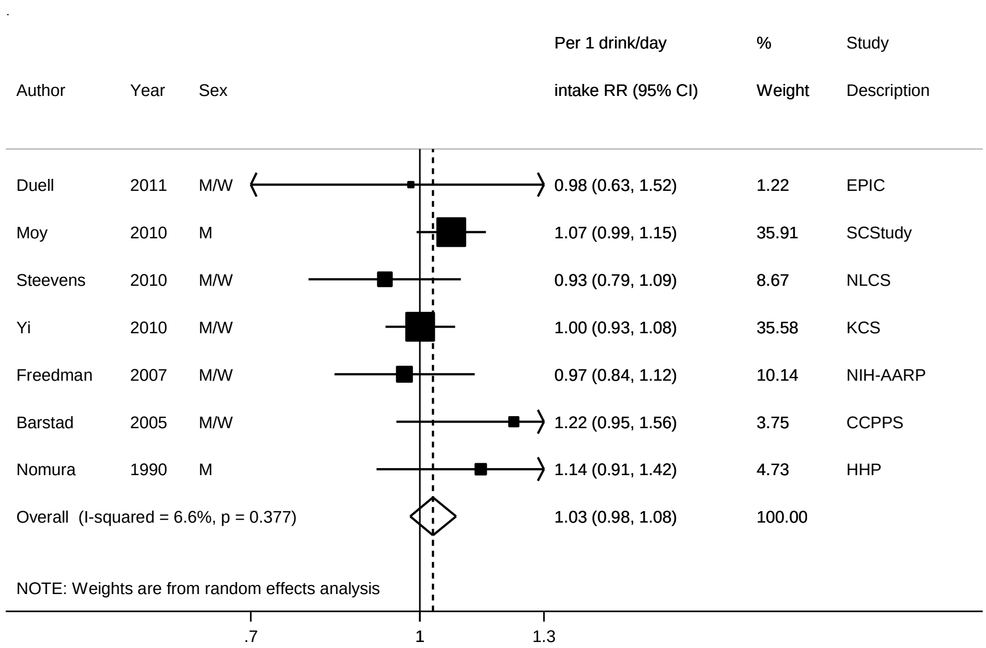
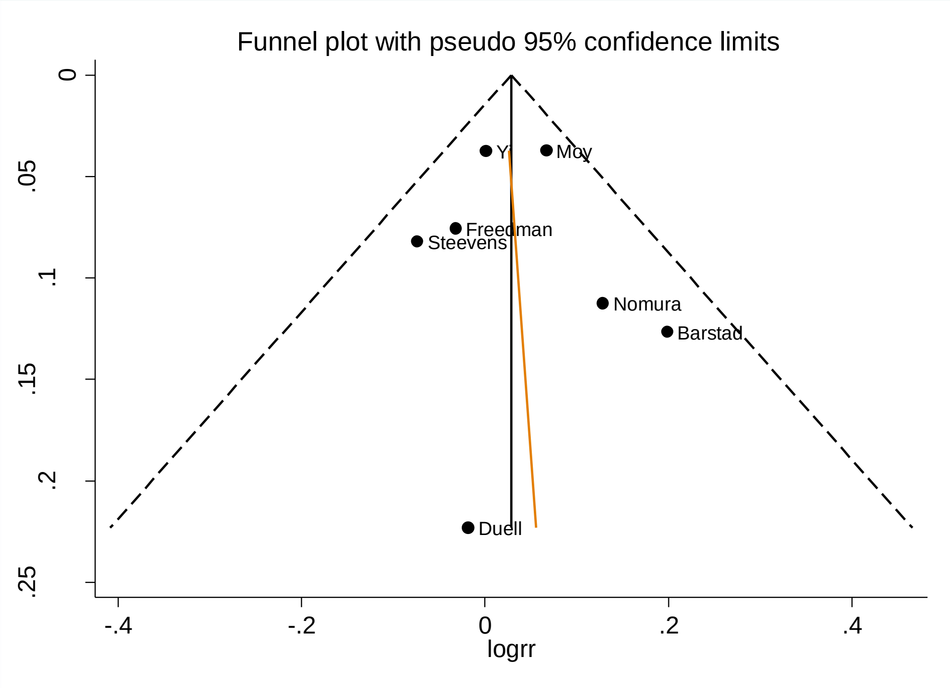


Figure 153 Funnel plot of studies included in the dose response meta-analysis of spirits and stomach cancer



Egger’s test p=0.86

Figure 154 Relative risk of stomach cancer for 1 drink/day increase of spirits intake by cancer outcome

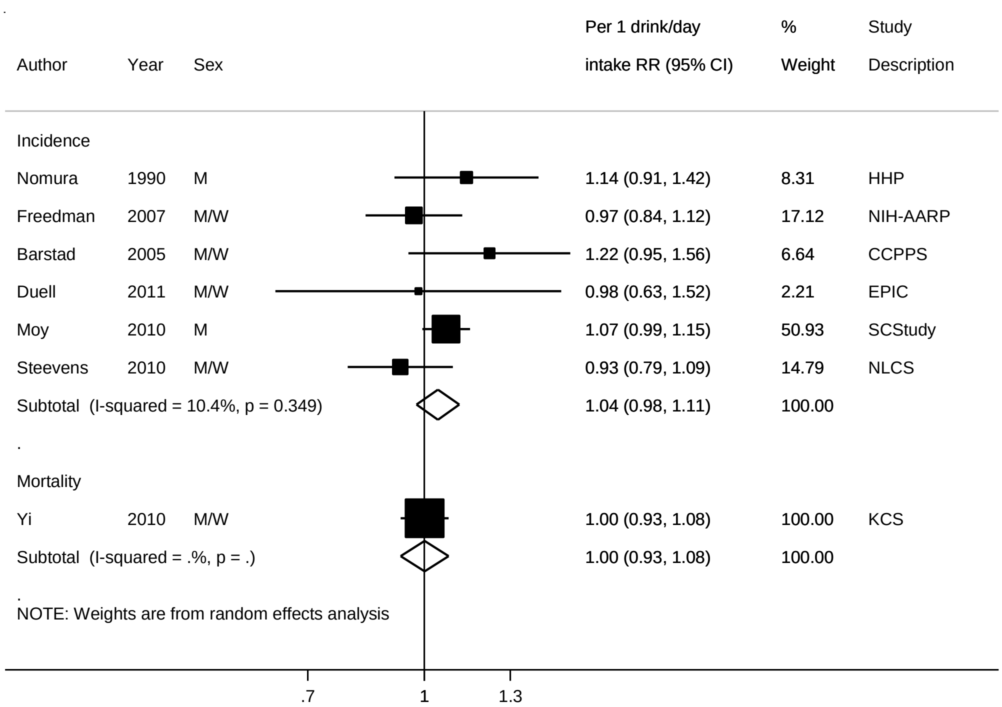


Figure 155 Relative risk of stomach cancer for 1 drink/day increase of spirits intake by geographic location

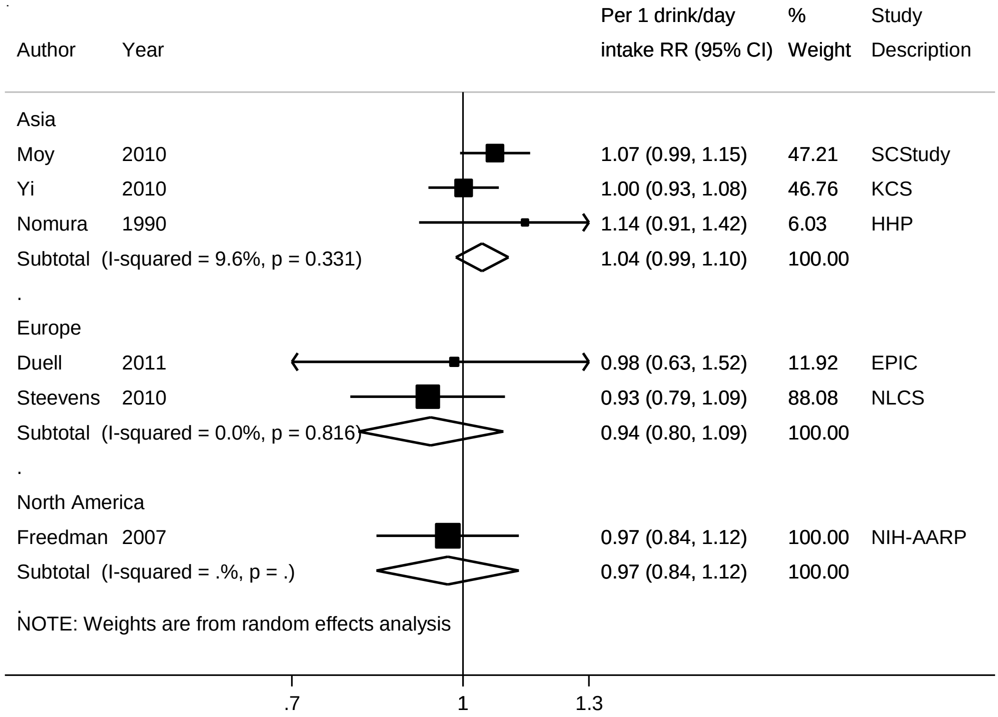
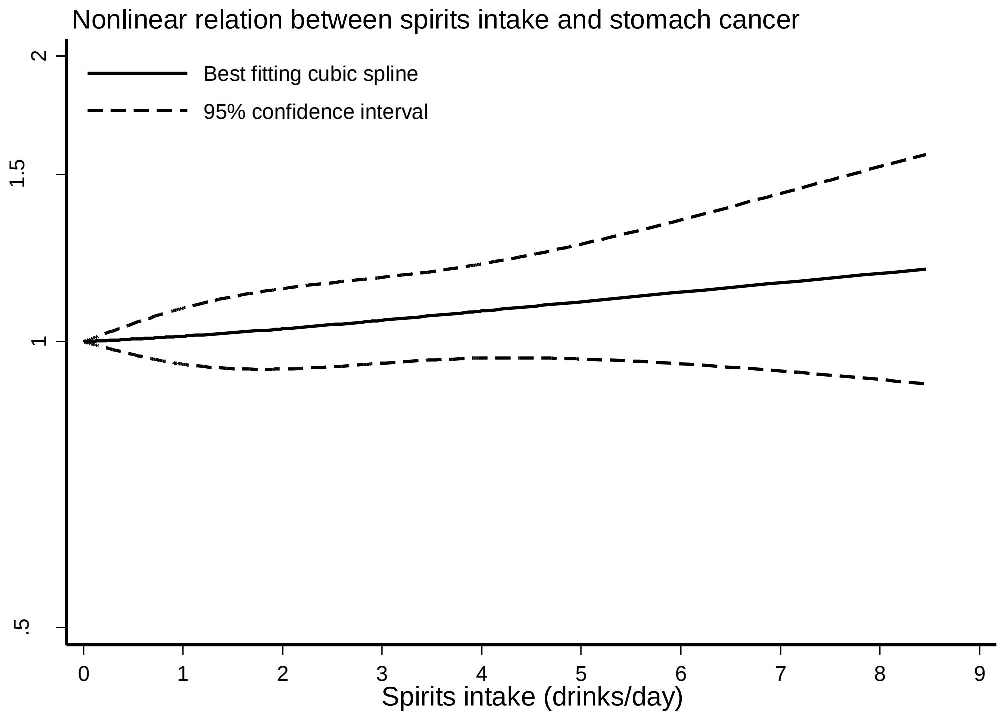


Figure 156 Non-linear dose-response meta-analysis of spirits intake and stomach cancer



P for non-linearity =0.86

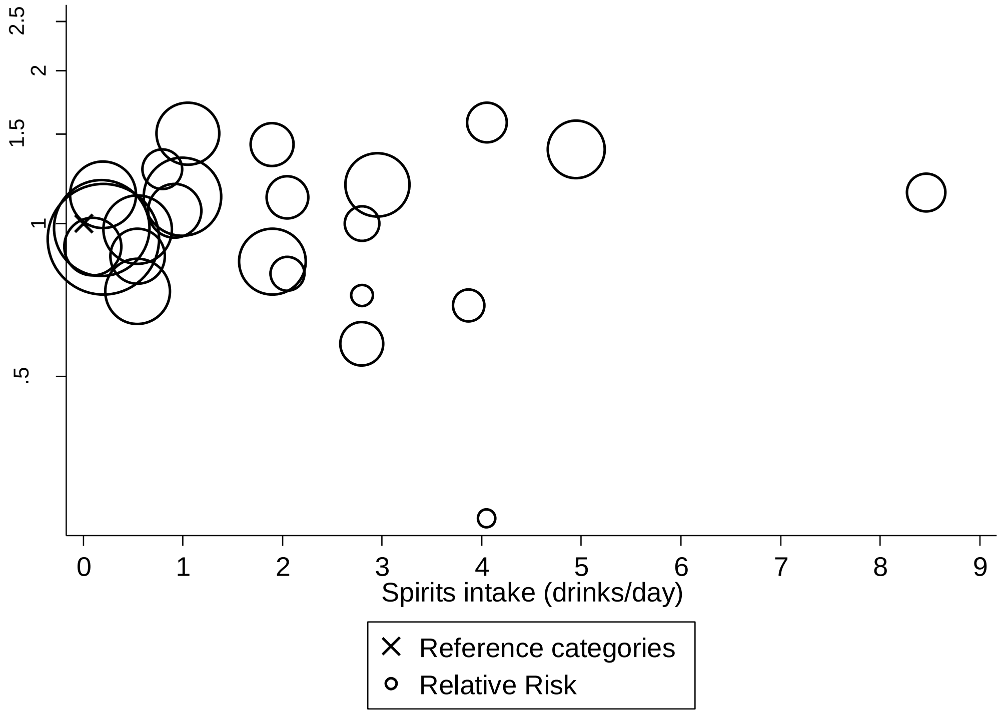


Table 125 Relative risk of stomach cancer and spirits intake estimated using non-linear models

Spirits (drinks/day)	RR (95%CI)
0	1.00
0.55	1.01 (0.97-1.05)
1	1.01 (0.95-1.09)
1.9	1.03 (0.94-1.13)
2.8	1.05 (0.95-1.16)
3.87	1.07 (0.96-1.20)
4.05	1.08 (0.96-1.21)
4.95	1.10 (0.96-1.26)
8.46	1.19 (0.90-1.57)

4.2 Preservation

4.2.5.1 Total salt

Randomised controlled trials

No randomised controlled trial was identified.

Cohort studies

Summary

Main results:

There were not enough data to conduct dose-response meta-analysis. No significant association was observed comparing the highest versus lowest salt intake (six studies, 2658 cases).

The studies investigated dietary sodium or dietary salt intake using food frequency questionnaires. The analyses were adjusted for several confounders including age, sex, smoking, and alcohol intake and in one study, H. Pylori status. Only one study adjusted only for age and energy intake (Nagata, 2002).

Table 126 Total salt intake and stomach 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	6
Studies included in linear dose-response meta-analysis	Not enough studies

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

Table 127 Total salt intake and stomach cancer risk. Summary of the linear dose-response meta-analysis in the 2005 SLR and CUP

	2005 SLR	**CUP**
Increment unit used	Per 1 g/day	Highest vs lowest
All studies		
Salt, total salt use		
Studies (n)	2	6
Cases (total number)	796	2658
RR (95%CI)	1.12 (1.05-1.19)	1.02 (0.94-1.12)
Heterogeneity (I^2, p-value)	65%, 0.06	57.8%, 0.03
P value Egger test	0.3, <0.001	-

Table 128 Total salt intake and stomach cancer risk. Results of meta-analyses and pooled analyses of prospective studies published after the 2005 SLR

Author, Year	Number of studies	Total number of cases	Studies country, area	Outcome	Comparison	RR (95%CI)	P trend	Heterogeneity (I^2, p value)
Meta-analysis								
D'Elia, 2012	7 cohort studies	1474	Japan, Netherlands, Norway	Incidence and/or mortality, Gastric cancer	High vs low Salted food (3 studies) Galanis, 1998; Ngoan, 2002; Kurosawa, 2006), total salt intake (4 studies)	1.68 (1.17-2.41)		71%, <0.01
Ge, 2012	4 cohort and 7 case-control studies	12039	Korea, China, Japan, Spain, Portugal, Colombia, Iran, Mexico	Incidence and/or mortality, Gastric cancer	High vs low Sodium intake (4 studies), salted food (6 studies), salt preference (1 study)	2.05 (1.60-2.62)		92%, <0.01
	2 cohort and 2 case-control studies	10827			High vs low Salt intake	1.20 (1.15-1.26)		67%, 0.03

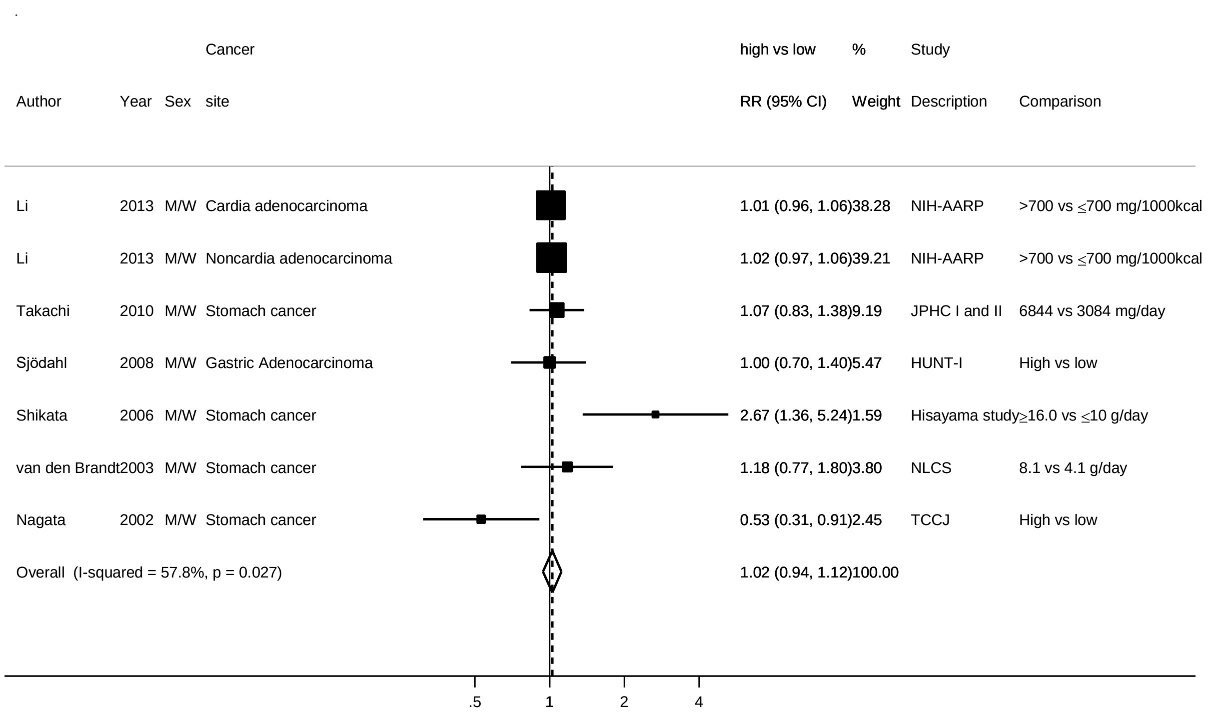
Cohorts identified in reviews were included in the present meta-analysis. The meta-analyses combined studies on salt intake and on salty food intake (D'Elia, 2012) or on sodium intake, salted food and salt preference (Ge, 2012). For comparison with D'Elia, 2012, the RR (highest vs lowest) =1.12 (95% CI; 1.00-1.26) I^2:68.5%, 10 studies including salt and salted foods in the CUP meta-analysis. For comparison with Ge, 2012, if the CUP meta-analysis is done including studies on salt, salted food and salt preference, the RR (highest vs lowest) =1.09 (95% CI; 1.01-1.19) I^2:62.8%, 13 studies

Table 129 Total salt intake and stomach 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	Missing data for dose-response meta-analysis
Li, 2013 STM80193 USA	NIH- AARP, Prospective Cohort, Age: 50-71 years, M/W	453/ 494 968 9.7 years	Cancer registry, death master file, national death index plus, postal service database	124-item validated FFQ Sodium	Incidence, cardia adenocarcinoma	≤700 vs >700 mg/1000kcal	0.99 (0.94-1.04)	Age, sex, BMI, race, education, modified total score, smoking, total energy intake, usual activity throughout the day, vigorous physical activity	RRs for two exposure categories only, RR recalculated for high vs low comparison
		501/			Non-cardia adenocarcinoma		0.98 (0.94-1.03)		
Takachi, 2010 STM80133 Japan	JPHC I and II, Prospective Cohort, Age: 45-74 years, M/W	867/ 77 500 593 620 person-years	Active patient notification from hospitals, cancer registries and death cert.	Validated 138-item FFQ Sodium	Incidence, stomach cancer	6844 vs 3084 mg/day	1.07 (0.83-1.38) Ptrend:0.64	Age, sex, BMI, calcium intake, energy intake, physical activity, smoking status, alcohol, potassium	
Sjödahl, 2008b STM80093 Norway	HUNT-I, Prospective Cohort, Age: 49.00years, M/W	313/ 73 133 15.4 years	Cancer registry	Questionnaire Summary score of salt intake	Incidence, gastric adenocarcinoma	High vs low	1.00 (0.70-1.40) Ptrend:0.55	Age, occupation, physical activity, smoking, alcohol drinking	No values of salt intake
Shikata, 2006 STM80113 Japan	Hisayama Study, Prospective Cohort, Age: 40- years, M/W	93/ 2 467 14 years	Hospital, pathology and autopsy records	70- item semi-quantitative FFQ Salt	Incidence, stomach cancer	≥16.0 vs ≤10 g/day	2.67 (1.36-5.24) Ptrend:<0.01	Age, sex, BMI, dietary factors, family history of cancer, gastritis, H. pylori infection, history of peptic ulcer, physical activity,	

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Missing data for dose-response meta-analysis
								smoking habits, total cholesterol, alcohol intake, diabetes mellitus	
Tsugane, 2004 STM00441 Japan	JPHC I, Prospective Cohort, Age: 40-59 years, M/W	358/ 39 065 12 years maximum	Hospital records, population-based cancer registries and death certificates, histologically confirmed	FFQ Salt intake	Incidence, stomach cancer Men	9.9 vs 2.9 g/day	1.5 (0.98-2.29) Ptrend:0.08	Age, fruit, non-green-yellow vegetable intake, smoking habits, PHC area	Superseded by Takachi, 2010
		128/			Women	8.2 vs 2.6 g/day	1.09 (0.61-1.94) Ptrend:0.85		
van den Brandt, 2003 STM00622 Netherlands	NLCS, Case Cohort, Age: 55-69 years, M/W	282/ 120 852 6.3 years	Cancer registry	150-item semi-quantitative FFQ Dietary salt	Incidence, stomach cancer	8.1 vs 4.1 g/day	1.18 (0.77-1.80) Ptrend:0.43	Age, sex, educational level, family history of cancer, smoking habits, stomach disorders	
Nagata, 2002 STM01669 Japan	TCCJ, Prospective Cohort, Age: 35- years, M/W	81/ 30 304 7 years	Population registry	169-item semi-quantitative FFQ Salt	Mortality, stomach cancer Men	Highest vs lowest	0.53 (0.31-0.91)	Age, energy intake	RRs for two exposure categories only

Figure 157 RR (95% CI) of stomach cancer for the highest compared with the lowest level of total salt intake



4.2.5.1 Added salt

Randomised controlled trials

No randomised controlled trial was identified.

Cohort studies

Summary

Main results:

There were not enough data to conduct dose-response meta-analysis. No significant association was observed comparing the highest versus lowest added salt intake (four studies, 1704 cases) and stomach cancer risk.

Table 130 Added salt intake and stomach cancer risk. Number of studies in the CUP SLR

	Number
Studies identified	4 (4 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: Include cohort, nested case-control and case-cohort designs

Table 131 Added salt intake and stomach cancer risk. Summary of the linear dose-response and highest versus lowest meta-analysis in the 2005 SLR and CUP

	2005 SLR*	CUP
Increment unit used		High vs low
Studies (n)	-	4
Cases (total number)	-	1612
RR (95%CI)	-	1.03 (0.85-1.25)
Heterogeneity (I^2, p-value)	-	0%, 0.76
P value Egger test	-	-

*No meta-analysis was performed for table salt and salt added in food preparation or cooking in 2005 SLR.

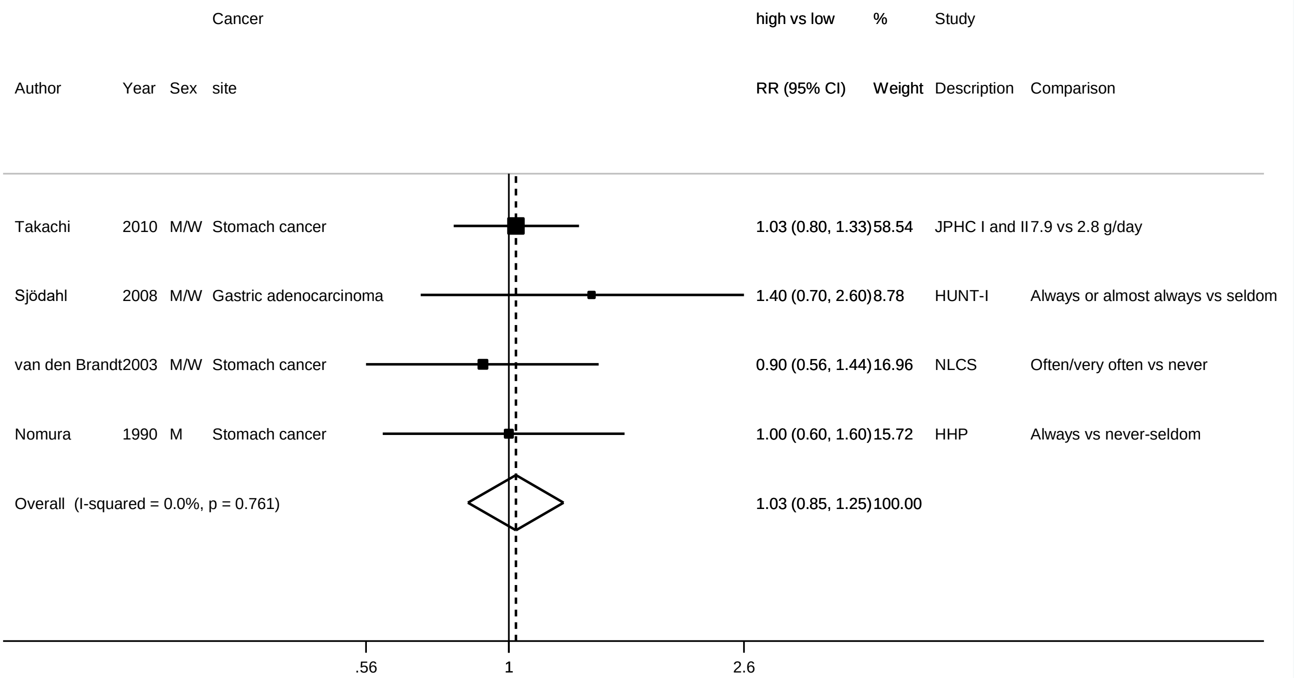
Table 132 Added salt intake and stomach cancer risk. Results of meta-analyses and pooled analyses of prospective studies published after the 2005 SLR

Author, Year	Number of studies	Total number of cases	Studies country, area	Outcome	Comparison	RR (95%CI)	P trend	Heterogeneity (I^2, p value)
Meta-analysis								
Bonequi, 2013	7 case-control studies		Colombia, Mexico, Venezuela	Incidence and/or mortality, Gastric cancer	Table salt use, yes vs. no	2.24 (1.53-3.29)		57.2%, 0.03

Table 133 Added salt intake and stomach 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	Missing data for dose-response meta-analysis
Takachi, 2010 STM80133 Japan	JPHC I and II, Prospective Cohort, Age: 45-74 years, M/W	867/ 77 500 593 620 person-years	Active patient notification from hospitals, cancer registries and death cert.	Validated 138-item FFQ Cooking and table salt	Incidence, stomach cancer	7.9 vs. 2.8 g/day	1.03 (0.80-1.33) Ptrend:1.00	Age, sex, BMI, calcium intake, energy intake, physical activity, smoking status, alcohol, potassium	
Sjödahl, 2008b STM80093 Norway	HUNT-I, Prospective Cohort, Age: 49.00years, M/W	313/ 73 133 15.4 years	Cancer registry	Questionnaire Frequency of sprinkling extra salt on food	Incidence, Gastric adenocarcinoma	Always or almost always vs. seldom	1.40 (0.70-2.60) Ptrend:0.11	Age, occupation, physical activity, smoking habits, alcohol drinking	Added salt as categorical variable
van den Brandt, 2003 STM00622 Netherlands	NLCS, Case Cohort, Age: 55-69 years, M/W	282/ 120 852 6.3 years	Cancer registry	150-item semi-quantitative FFQ Use of salt at the table	Incidence, stomach cancer	Often/very often vs. never	0.90 (0.56-1.44) Ptrend:0.13	Age, sex, educational level, family history of cancer, smoking habits, stomach disorders	Added salt as categorical variable
Nomura, 1990 STM14814 USA	HHP, Prospective Cohort, Age: 45- years, M, Japanese residents of Hawaii	150/ 7 990 10.3 years	Cancer registry/ hospital records	20-item FFQ, 24- hour diet recall Table salt/shoyu	Incidence, stomach cancer	Always vs. never-seldom	1.00 (0.60-1.60)	Age	Added salt as categorical variable

Figure 158 RR (95% CI) of stomach cancer for the highest compared with the lowest level of added salt intake



4.2.5.1 Preference for salty food

Randomised controlled trials

No randomised controlled trial was identified.

Cohort studies

Summary

Main results:

There were not enough data to conduct dose-response meta-analysis. Significant positive association was observed comparing preference for salty food versus no preference (four studies, 13 626 cases).

No published meta-analyses and pooled analyses of prospective studies published after the 2005 SLR were identified.

Table 134 Preference for salty food and stomach cancer risk. Number of studies in the CUP SLR

	Number
Studies identified	4 (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: Include cohort, nested case-control and case-cohort designs

Table 135 Preference for salty food and stomach cancer risk. Summary of the linear dose-response meta-analysis in the 2005 SLR and CUP

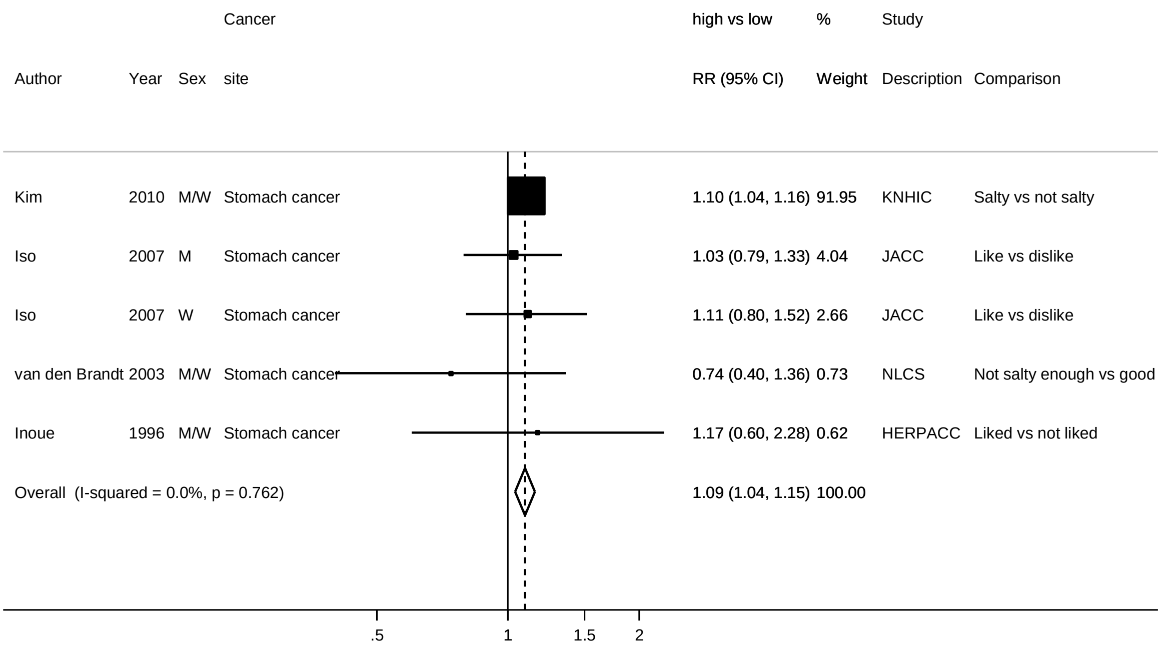
	2005 SLR	**CUP**
Increment unit used	Preference vs not	Preference vs not
Studies (n)	4	4
Cases (total number)	1440	13626
RR (95%CI)	1.07 (0.76-1.51)	1.09 (1.04-1.15)
Heterogeneity (I^2, p-value)	38%, 0.2	0%, 0.76
P value Egger test	0.03	-

Table 136 Preference for salty food and stomach 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	Missing data for dose-response meta-analysis
Kim, 2010 STM80099 Korea	KNHIC, Prospective Cohort, Age: 30-80 years, M/W	12 393/ 2 248 129 7 years	Cancer registry	Self-administered questionnaire Salt preference	Incidence, stomach cancer	Salty vs. not salty	1.10 (1.04-1.16)	Age, sex, alcohol consumption, BMI, family history of cancer, physical activity, smoking habits	Salt preference is categorical
Iso, 2007 STM80144 Japan	JACC, Prospective Cohort, Age: 40-79 years, M/W	579/ 105 500 15 years	Municipal resident registration records, death certificates	Validated FFQ Preference for salty foods	Mortality, stomach cancer Men	Like vs. dislike	1.03 (0.79-1.33)	Age, area of study	Salt preference is categorical
		275/			Women		1.11 (0.80-1.52)		
Tokui, 2005 STM80105 Japan	JACC, Prospective Cohort, Age: 40-79 years, M/W	428/ 44 930 12 years	Municipal resident registration records, death certificates	FFQ Preference for salty foods	Mortality, stomach cancer Men	Very much vs. no	1.36 (0.67-2.78) Ptrend:0.12	Age	Superseded by Iso, 2007
		197/			Women		1.89 (0.62-5.79) Ptrend:0.57		
Yatsuya, 2004 STM00003 Japan	JACC, Prospective Cohort, Age: 40-79 years, M/W	202/ 65 184 10 years	Municipal resident registration records, death certificates	FFQ Salty food preference	Mortality, stomach cancer	Like vs. dislike			Superseded by Iso, 2007, no risk estimate
van den Brandt,	NLCS,	282/	Cancer registry	FFQ	Incidence,	Not salty	0.74 (0.40-1.36)	Age, sex,	Salt preference

Author, Year, 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 for dose-response meta-analysis
2003 STM00622 Netherlands	Case Cohort, Age: 55-69 years, M/W	120 852 6.3 years		Taste of restaurant food	stomach cancer	enough vs. good	Ptrend:0.05	educational level, family history of cancer, smoking habits, stomach disorders	is categorical
Fujino, 2002 STM01512 Japan	JACC, Prospective Cohort, Age: 40-79 years, M/W	261/ 18 746	Municipal resident registration records, death certificates	Validated FFQ Preference of salty foods	Mortality, stomach cancer Men	Like vs. dislike (%)	1.25 (0.81-1.94)	Age	Superseded by Iso, 2007
		118/26184			Women		1.31 (0.76-2.25)		
Inoue, 1996 STM06116 Japan	HERPACC, Prospective Cohort, M/W, Endoscopy patients	69/ 5 373 6 years	Hospital records, cancer registry, death certificates	Self-administered FFQ Salt preference	Incidence, stomach cancer	Liked vs. not liked	1.17 (0.60-2.28)	Age, sex	Salt preference is categorical

Figure 159 RR (95% CI) of stomach cancer for the highest compared with the lowest level of preference for salty foods



4.2.5.3 Salted food

Randomised controlled trials

No randomised controlled trial was identified.

Cohort studies

Summary

Main results:

There were not enough data to conduct dose-response meta-analysis. Significant positive association was observed for stomach cancer and salted food intake (five studies, 635 cases). The type of salted food was not specified in one study, salted plant food in some studies, salted animal foods in other studies or both combined.

Table 137 Salted food intake and stomach 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	5
Studies included in linear dose-response meta-analysis	Not enough studies

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

Table 138 Salted food intake and stomach cancer risk. Summary of the linear dose-response meta-analysis in the 2005 SLR and CUP

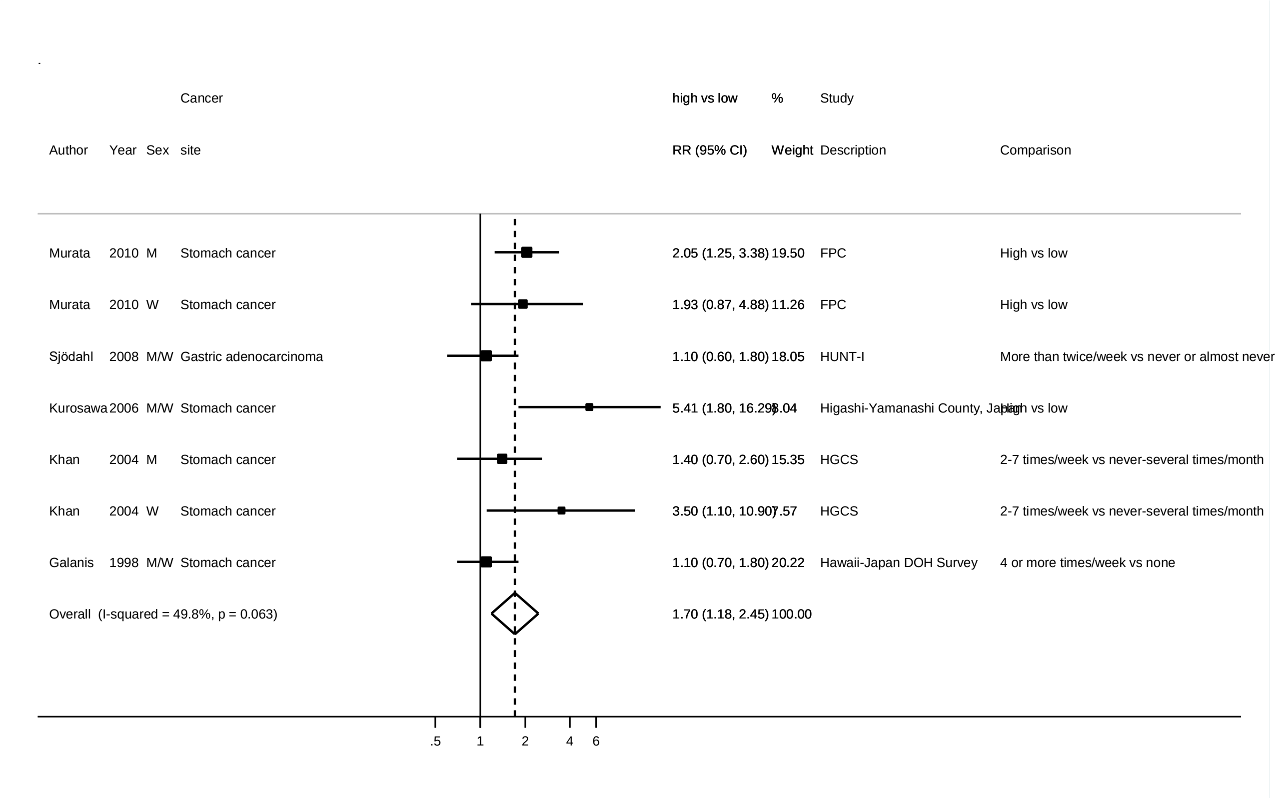
	2005 SLR	**CUP**
Increment unit used	Per 1 serving/day	High vs low
Studies (n)	3	5
Cases (total number)	275	635
RR (95%CI)	1.32 (0.90-1.95)	1.70 (1.18-2.45)
Heterogeneity (I^2, p-value)	0%, 0.4	49.8%, 0.06
P value Egger test	<0.05	-

Table 139 Salted food intake and stomach cancer risk. Main characteristics of studies included in 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	Missing data for dose-response meta-analysis
Murata, 2010 STM80103 Japan	FPC, Prospective Cohort, Age: 40-79 years, M/W	67/ 6 830 13.9 years	Death certificate	Self-administered questionnaire Salted food (type not specified)	Mortality, stomach cancer Men	High vs low	2.05 (1.25-3.38)	Age, alcohol habits, BMI, fruit intake, history of diabetes, physical activity, smoking habits, tea consumption, vegetable intake, red and processed meat	Only two categories
		20/			Women		1.93 (0.87-4.88)		
Sjödahl, 2008b STM80093 Norway	HUNT-I, Prospective Cohort, Age: 49.00years, M/W	313/ 73 133 15.4 years	Cancer registry	Questionnaire Salted meat, fish	Incidence, gastric adenocarcinoma	More than twice/week vs never or almost never	1.10 (0.60-1.80) Ptrend:0.39	Age, occupation, physical activity, smoking, alcohol drinking	
Kurosawa, 2006 STM80085 Japan	Higashi-Yamanashi County, Japan, Prospective Cohort, Age: 30- years, M/W	76/ 8 035 11 years	Death certificate	29-item FFQ Highly salted foods: pickled vegetables, foods boiled in soy sauce	Mortality, stomach cancer	High vs low	5.41 (1.80-16.29) Ptrend:<0.01	Age, sex, fruits, green yellow vegetable intake, smoking habits, beans and bean products, mountain herbs	Only two categories
Khan, 2004 STM20239 Japan	HGCS, Prospective Cohort, Age: 40- years, M/W	36/ 1 524 14 years	Follow-up surveys	Baseline survey of 37 dietary factors Salty confectionary	Mortality, stomach cancer Men	2-7 times/week vs never-several times/year/month	1.40 (0.70-2.60)	Age, smoking habits	
		15/ 1 634 14 years			Women		3.50 (1.10-10.90) Ptrend:<0.05		

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Missing data for dose-response meta-analysis
Ngoan, 2002 STM01668 Japan	FPC, Prospective Cohort, Age: 15-96 years, M/W	116/ 13 250 13 years	Resident registry	Self-administered FFQ Salted foods	Mortality, stomach cancer	High vs low	1.40 (0.60-3.20)	Age, sex, fat intake, Japanese soup, liver, pickled foods, processed meat, smoking habits	Superseded by Murata, 2010
Galanis, 1998 STM04769 USA	Hawaii-Japan DOH Survey, Prospective Cohort, Age: 18- years, M/W, Japanese residents of Hawaii	108/ 11 907 14.8 years	Cancer registry	13-food item, 6-beverage item FFQ High-salt foods (miso soup, pickled vegetables, dried fish)	Incidence, stomach cancer	4 or more times/week vs none	1.10 (0.70-1.80) Ptrend:0.65	Age, sex, educational level, place of birth	
Kato, 1992b STM06734 Japan	Higashi-Kamo Cohort, Prospective Cohort, Age: 30-80 years, M/W	57/ 9 753 6 years	Death certificates	25-item questionnaire Salted food	Mortality, stomach cancer	Daily vs ≤1-2 times/day		Age, sex	Excluded, no risk estimate

Figure 160 RR (95% CI) of stomach cancer for the highest compared with the lowest level of salted food intake



Note: Salted foods were salted foods not specified (Murata, 2010), salted meat and fish (Sjödahl, 2008), pickled vegetables (Kurosawa, 2006), salty confectionary (Khan, 2004), miso soup and vegetables (Galanis, 1998).

4.4.2.5 Frying

Five cohort studies were identified, of which only one (Iso, 2007) was from the CUP. Studies examined frying as cooking method (Kato, 1992b), or the intakes of fried foods (Ko, 2013; Iso, 2007), pan-fried animal foods (Knekt, 1994) or fried vegetables (Nomura, 1990). No significant associations were reported.

4.4.2.6 Grilling (broiling) and barbecuing

Three cohort studies were identified in the 2005 SLR. There were no additional studies from the CUP. Consumption of broiled fish was significantly positively associated with mortality for stomach cancer in a Japanese cohort (RR for twice or more weekly compared with less frequent consumption=1.7 P<0.05; Ikeda, 1983) but not in another Japanese cohort of atomic bomb survivors (RR for five or more times compared to less than twice weekly = 0.84; 95% CI: 0.55-1.29; Sauvaget, 2005). Consumption of broiled meats three to four times per week compared with less frequent consumption was associated with increased mortality for stomach cancer in another cohort (RR: 2.27; 95% CI:1.06-4.85) (Kato, 1992b).

4.4.2.6.7 Polycyclic aromatic hydrocarbons

There were no studies from the 2005 SLR. One cohort study identified in the CUP (Cross, 2011) estimated intake of B[a]P, a marker of polycyclic aromatic hydrocarbons, using the information collected on meat cooking methods (grilled/barbecued, panfried, microwaved, and broiled) and doneness levels (well-done and medium / rare) with the database (CHARRED) derived with that purpose. B[a]P was not significantly associated with gastric cardia cancer (RR for Q5 vs Q1=1.09, 95% CI = 0.73-1.61, p-trend = 0.547 and RR for an increase of 10 ng = 1.00 (95% CI= 0.97 - 1.04)) and non-cardia gastric cancer (RR for Q5 vs Q1=0.99, 95% CI = 0.67-1.46, p-trend= 0.925 and RR for an increase of 10 ng = 0.99 (0.94 – 1.03).

4.4.2.6.8 Heterocyclic amines

There were no studies from the 2005 SLR. One cohort study identified in the CUP (Cross, 2011) estimated different heterocyclic amines' intake using the information collected on meat cooking methods (grilled/barbecued, panfried, microwaved, and broiled) and doneness levels (well-done and medium / rare) with the database (CHARRED) derived with that purpose. A significant positive association between DiMeIQx and gastric cardia cancer was observed for the highest compared to the lowest quintile of intake (RR=1.44, 95% CI = 1.01-2.07, p-trend = 0.104) and in continuous analysis, the RR for 0.5 ng increase was 1.01 (95% CI=1.00 – 1.02). DiMeIQx intake was not associated with non-cardia gastric cancer risk (RR for Q5 vs Q1= 0.97, 95% CI = 0.68-1.39, p-trend = 0.934). No significant associations were observed for other heterocyclic amines when comparing the highest to the lowest quintile intake or in continuous analysis. The RR for 5 ng increase of MelQx were 1.01 (95% CI = 0.99-1.03) for gastric cardia cancer and 0.98 (95% CI = 0.94-1.02) for non-cardia cancer. The RR for 25 ng increase of PhlP were 1.01 (95% CI=0.98- 1.04) and 1.01 (95% CI = 0.98-1.04), respectively.

5 Dietary constituents

5.5.0.1 Multivitamins

Randomised controlled trials

Five randomised controlled trials were identified, one of which was identified during the CUP. One trial provided no measure of association and was excluded (4 cases).

In the Shandong randomised placebo controlled trial in a Chinese population with high risk of stomach cancer, seven years supplementation with a mixture of vitamin C, vitamin E, and selenium did not reduce gastric cancer incidence or mortality during the intervention and 7.3 years after the intervention ended (RR= 0.81; 95% CI:0.54-1.22, 102 cases) (Ma, 2012). Of three other studies identified in the 2005 SLR, only in one study a reduction of stomach cancer mortality was observed in the group supplemented with vitamin E, selenium and beta-carotene (Blot, 1993).

Table 140 Vitamin and mineral supplement intake and stomach cancer risk. Main characteristics of randomised controlled trials included in the CUP SLR

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Inclusion/ exclusion
Ma, 2012 STM80100 China	Shandong Intervention Trial, Randomised Control Trial, Age: 35-64 years, M/W	103/ 3365 14.7 years	Endoscopy, biopsy, cancer registry, medical records	Active follow-up, 95% compliance to vitamin treatment	Incidence, stomach cancer	Vitamin treatment (vitamin C, E, and selenium) vs placebo	0.81 (0.54-1.22)	Age, sex, alcohol consumption, baseline histopathology, smoking history	
		43/			Mortality, stomach cancer		0.55 (0.29-1.03)		
		60/			Mortality, stomach and oesophageal cancer		0.51 (0.30-0.87)		
Hercberg, 2004 STM44322 France	SU.VI.MAX, Randomised Control Trial, Age: 35-60 years, M/W	4/ 12 741 7.5 years	Histologic reports, causes of death were confirmed by information from relatives or physicians	74% compliance to vitamin or placebo treatment	Incidence, stomach cancer	Supplement (120 mg ascorbic acid, 30 mg vitamin E, 6 mg beta carotene, 100 of selenium, 20 mg zinc) vs placebo			No measure of association, only 4 cases
Heart Protection Study Collaborative Group, 2002 STM00018 UK	MRC/BHS HPS, Randomised Control Trial, Age: 40-80 years, M/W Adults with coronary disease, other occlusive arterial disease, or diabetes	116/	UK national registries, general practitioners' or hospital records	80% compliance to vitamin or placebo treatment	Incidence, stomach cancer	Supplement (600 mg vitamin E, 250 mg vitamin C, and 20 mg beta carotene daily) vs placebo	P=0.1 (no effect)		
Blot, 1993 STM01215	NIT-General Population Trial,	539 total	Follow-up by village doctors,	93% overall	Incidence, stomach cancer	5000 IU retinol, 22.5 mg zinc vs placebo	0.96 (0.81-1.14)	Adjusted for matching variables,	

Author, Year, 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
China	Randomised Control Trial, Age: 40-69 years, M/W	incident cases and 331 total deaths / 29 584 5.3 years	hospital records, medical team review	pill disappearanc e rate for all participants	Morality		1.03 (0.83-1.28)	cigarette smoking parental history of cancer	
					Incidence	3.2 mg riboflavin, 40 mg niacin vs placebo	1.04 (0.88-1.23)		
					Mortality		1.00 (0.81-1.24)		
					Incidence	120 mg ascorbic acid, 30 µg molybdenum vs placebo	1.10 (0.92-1.30)		
					Mortality		1.09 (0.88-1.36)		
					Incidence	15 mg beta carotene, 50 µg selenium, 30 µg alpha-tocopherol vs placebo	0.84 (0.71-1.00)		
					Mortality		0.79 (0.64-0.99)		
Li, 1993 STM14152 China	NIT-Dysplasia Trial, Randomised Control Trial, Age: 40-69 years, M/W Adults with oesophageal dysplasia	177/ 3318 6 years	Routine surveillance, cytologic and endoscopic screenings	Compliance rate of 87% in the placebo group and 89% in the supplement group	Incidence, stomach cancer	Supplement (14 vitamins and 12 minerals) vs placebo	1.17 (0.87-1.58)	Age, sex, area of residence, baseline histopathology	
		159/			Cardia cancer		1.05 (0.77-1.43)		
		18/			Non-cardia cancer		3.54 (1.17-10.76)		
		77/			Mortality, stomach cancer		1.18 (0.76-1.85)		
		66/			cardia cancer		1.04 (0.64-1.69)		
		11/			Mortality, non-cardia cancer		2.68 (0.71-10.11)		

Cohort studies

Summary

Main results:

Dose-response meta-analysis was not conducted. Only one out of five studies had the information required to do it. Five studies (3485 cases) were included in a meta-analysis comparing use of multivitamin supplement with no use. No significant association was observed for use/regular use versus no use and stomach cancer risk in men, women, and all combined.

Study quality:

Most studies used self-administered questionnaires to collect data on supplement use. In the WHI follow-up women brought in bottles of supplements to the baseline clinic visit and interviewers directly transcribed ingredients for each supplement (Neuhouser, 2009).

All studies were adjusted for age, sex, smoking and other confounders except Iso, 2007 that adjusted only for age and area. No studies were adjusted for Helicobacter pylori infection.

Loss to follow-up was low in most studies. Cancer cases were identified by record linkage to cancer registries and death registries or using records from death certificates in most studies. In the WHI cancer cases were ascertained by self-report using semi-annual or annual questionnaire and confirmed by medical records (Neuhouser, 2009).

Table 141 Multivitamin supplement intake and stomach cancer risk. Number of studies in the CUP SLR

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

Table 142 Multivitamin supplement intake and stomach cancer risk. Summary of the dose-response and highest versus lowest meta-analysis in the 2005 SLR and CUP

	2005 SLR*	**CUP**
Increment unit used	-	Use vs no use
All studies		
Studies (n)	-	5
Cases (total number)	-	3485

RR (95%CI)	-	0.95 (0.87-1.03)
Heterogeneity (I^2, p-value)	-	0%, 0.82
P value Egger test	-	0.95
Stratified and sensitivity analysis		
Men	Men	Women
Studies (n)	3	5
RR (95%CI)	0.97 (0.88-1.08)	0.90 (0.77-1.05)
Heterogeneity (I^2, p-value)	0%, 0.63	0%, 0.92

* No meta-analysis was performed in 2005 SLR.

Table 143 Vitamin and mineral supplement intake and stomach cancer risk. Main study characteristics.

Author, Year, 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
Dawsey, 2014 STM80189 USA	NIH-AARP, Prospective Cohort, Age: 50-71 years, M/W, Retired	450 men and women/ 490 593 11 years	Postal service, Social Security Administration Death Master File, cancer registry databases	FFQ, any multivitamin supplements	Incidence, gastric cardia adenocarcinoma	>7 times/week vs never	1.16 (0.74-1.80)	Age, sex, education, smoking status and intensity, alcohol intake, fruit and vegetable intake, BMI, vigorous physical activity, usual physical activity, total energy intake	RRs for cardia and non-cardia combined using fixed model
						Any use vs never	1.12 (0.93-1.35)		
					Men		1.12 (0.92-1.36)		
					Women		1.13 (0.65-1.96)		
		493 men and women			Incidence, gastric non-cardia adenocarcinoma	>7 times/week vs never	0.65 (0.39-1.08)		
						Any use vs never	0.90 (0.76-1.08)		
					Men		0.91 (0.74-1.13)		
					Women		0.89 (0.63-1.24)		
Neuhouser, 2009 STM80156 USA	WHI-DM and OS, Prospective Cohort, Age: 50-79 years, W, Post-menopausal women	101/ 161 806 8 years	Self-report verified by medical record	A standardised interviewer-administered questionnaire, any multivitamins	Incidence, stomach cancer	Yes vs no	0.96 (0.60-1.53)	Age, race, years since menopause, BMI, education, alcohol, smoking, health status, history of bilateral oophorectomy, region, physical activity, duration of prior E alone use, fruit and vegetable intake, percent energy from fat, use of vitamin C/vitamin E/Calcium, history of cancer, HT trial randomisation	
		97/		Multi-vitamins with minerals			1.00 (0.61-1.62)		

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	Inclusion/ exclusion
								assignment, DM randomisation or OS enrolment	
Iso, 2007 STM80144 Japan	JACC, Prospective Cohort, Age: 40-79 years, M/W	750/ 105 500 15 years	Municipal resident registration records, death certificates	Validated FFQ, multivitamin supplements	Mortality, stomach cancer Men	Use vs no use	0.96 (0.74-1.26)	Age, area of study	
		368/			Women		0.81 (0.54-1.23)		
Jacobs, 2002 STM01980 USA	CPS II, Prospective Cohort, Age: 30- years, M/W	1 297 total: 854 men, 443 women/ 1 045 923 16 years	Death register/ subject or family	Questionnaire (general), multivitamins	Mortality, stomach cancer All	Regular user vs nonuser	0.89 (0.77-1.03)	Age, sex, aspirin use, citrus fruits/juices intake, educational level, ethnicity/race, high-fibre grains intake, smoking habits, vegetable intake, vitamin C supplement, vitamin E supplement	
					Men		0.91 (0.76-1.09)		
					Women		0.87 (0.69-1.10)		
Zheng, 1995 STM06417 USA	IWHS, Prospective Cohort, Age: 55-69 years, Post-menopausal women	26/ 34 691 7 years	Cancer registry	FFQ, multivitamin supplements	Incidence, stomach cancer	Use vs not use mg/day	1.20 (0.50-2.90)	Age, smoking, total energy intake	

Figure 161 RR (95% CI) of stomach cancer for the highest compared with the lowest level of multivitamin supplement intake

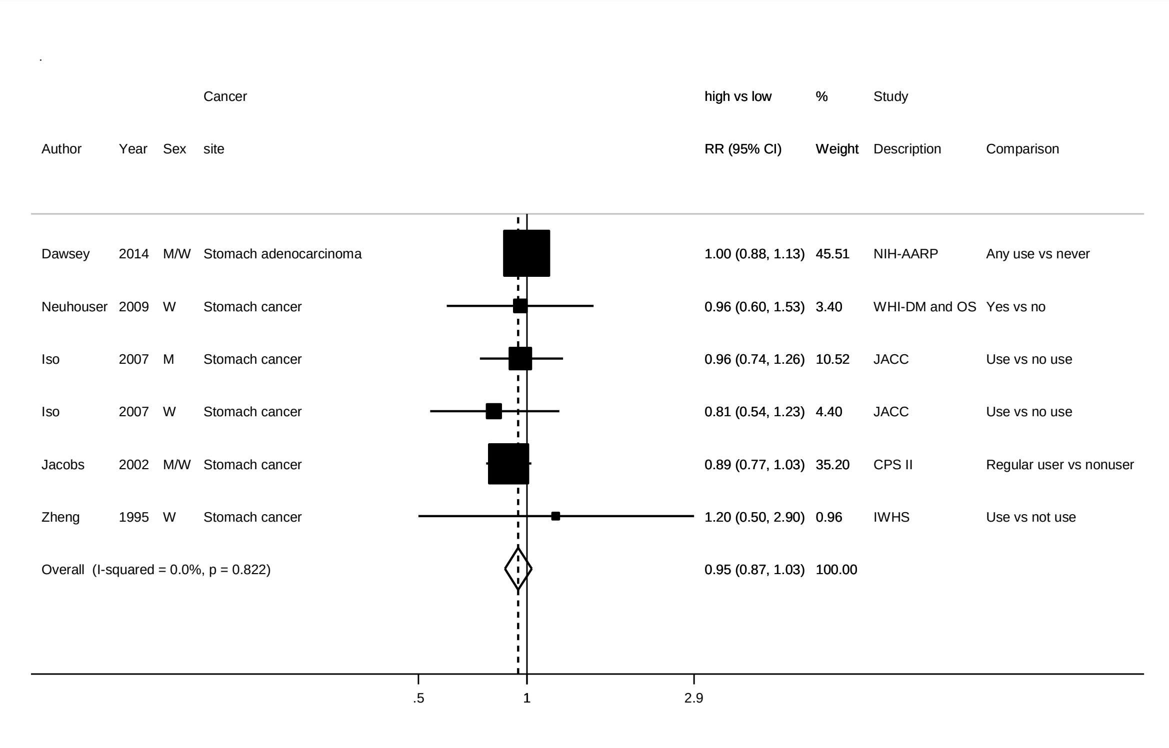


Figure 162 RR (95% CI) of stomach cancer for the highest compared with the lowest level of multivitamin supplement intake by sex

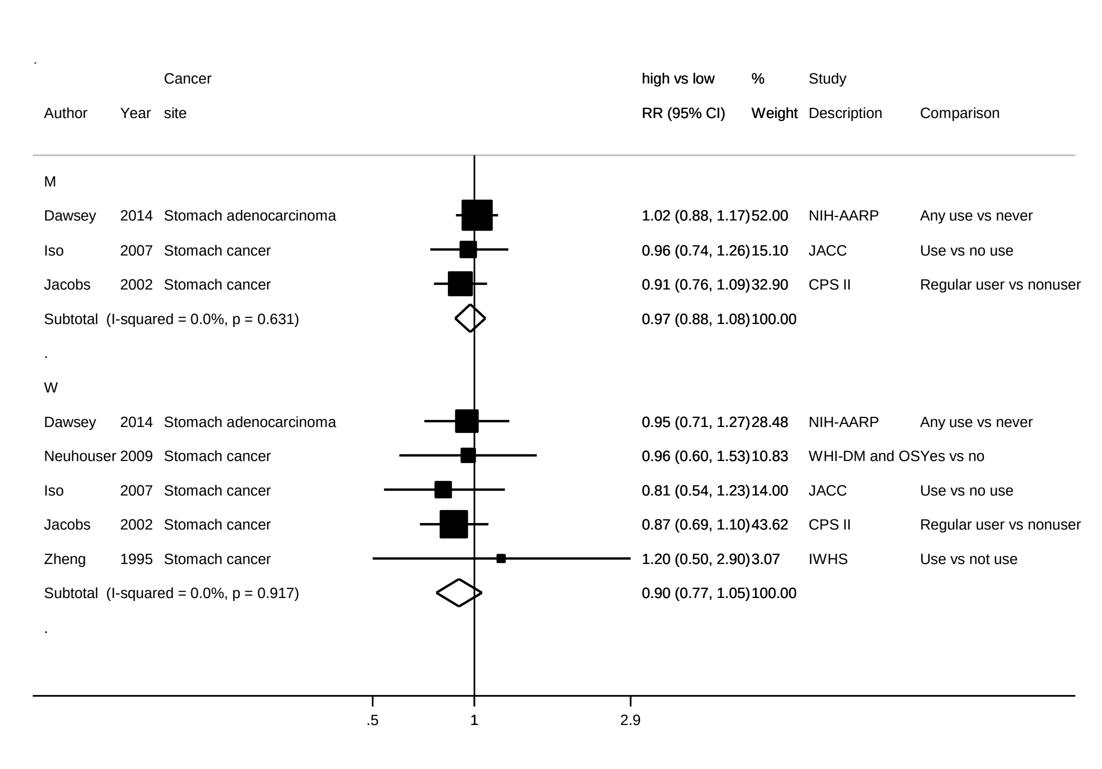
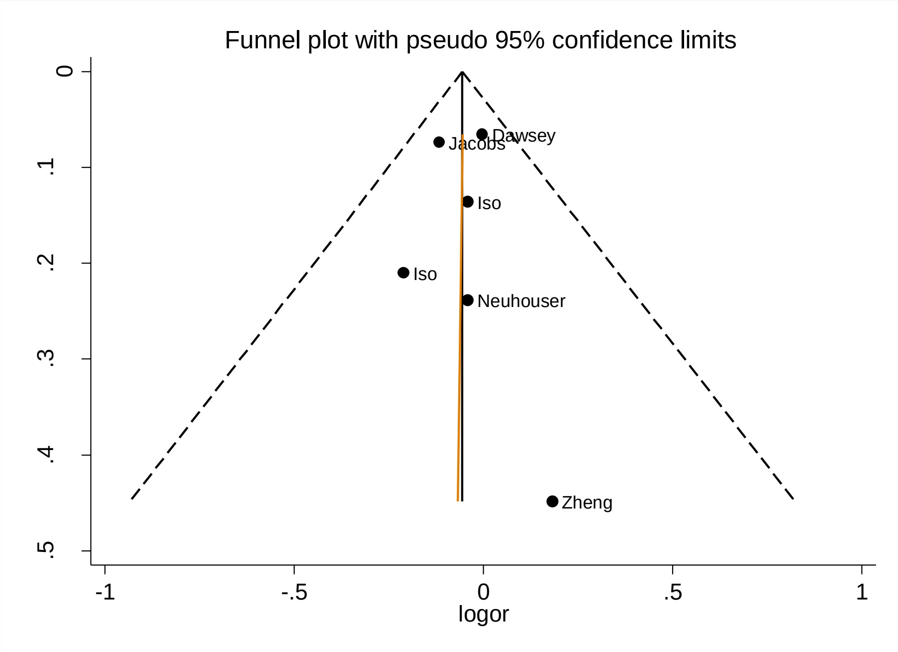


Figure 163 Funnel plot of studies included in the analysis of multivitamin use and stomach cancer



Egger's test p=0.95

5.5.1.1 Dietary retinol

Randomised controlled trials

No randomised controlled trial was identified.

Summary

Main results:

There were not enough studies to conduct dose-response meta-analysis. No significant association with stomach cancer was observed comparing the highest versus lowest dietary retinol intake (seven studies, 1040 cases).

Table 144 Dietary retinol intake and stomach cancer risk. Number of studies in the CUP SLR

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

Note: Include cohort, nested case-control and case-cohort designs. *Included two cohort studies in one publication (Epplein, 2010) reporting results on distal gastric cancer only.

Table 145 Dietary retinol intake and stomach cancer risk. Summary of the linear dose-response and highest versus lowest meta-analysis in the 2005 SLR and CUP

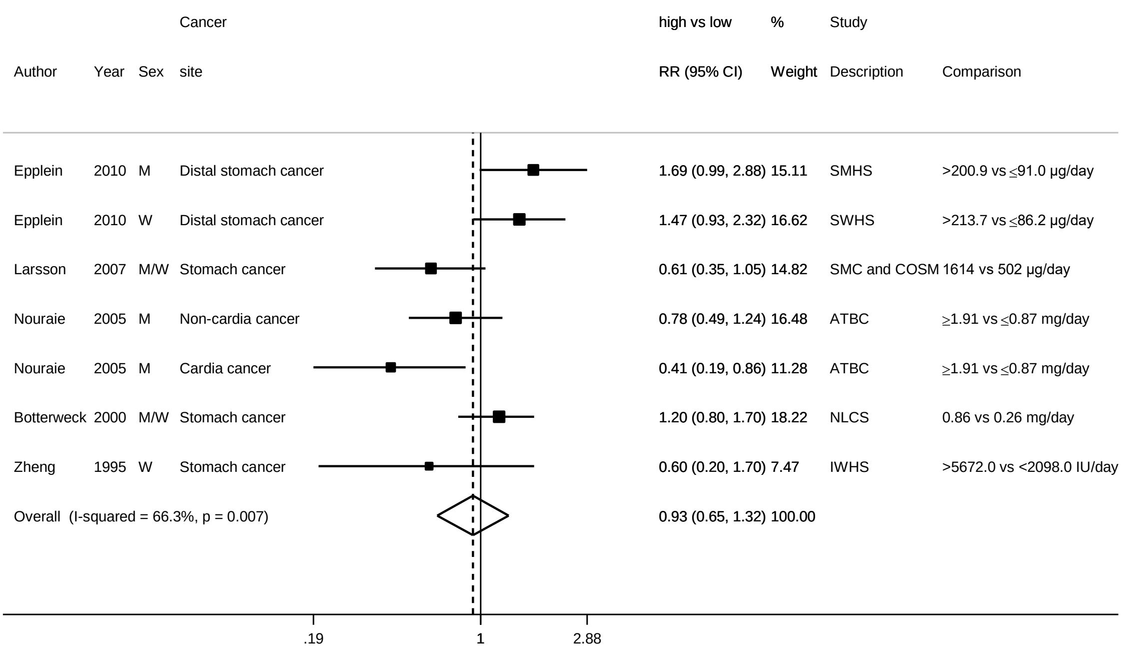
	2005 SLR	**CUP**
Increment unit used	100µg/day	High vs low
All studies		
Studies (n)	3	6
Cases (total number)	419	1040
RR (95%CI)	1.07 (0.96-1.18)	0.93 (0.65-1.32)
Heterogeneity (I^2, p-value)	88.3%, <0.001	66.3%, 0.01
P value Egger test	0.2	-

Table 146 Dietary retinol intake and stomach 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	Reasons for exclusion
Epplein, 2010 STM80129 China	SWHS and SMHS, Prospective Cohort, Age: 40-74 years, M/W	132/59 247	Cancer registry, vital statistics database, biennial in-home interviews	Validated 81-item (SMHS) and 77-item (SWHS) FFQs	Incidence, distal stomach cancer Men	>200.9 vs ≤91.0 µg/day	1.69 (0.99-2.88) Ptrend:0.05	Age, education level, smoking, total energy intake	
		206/73 064			Women	>213.7 vs ≤86.2 µg/day	1.47 (0.93-2.32) Ptrend:0.30		
Larsson, 2007b STM80069 Sweden	SMC and COSM, Prospective Cohort, Age: 45-83 years, M/W	139/ 82 002 7.2 years	Cancer registry	Validated FFQ	Incidence, stomach cancer	1614 vs 502 µg/day	0.61 (0.35-1.05) Ptrend:0.03	Age, sex, diabetes, pack-years cigarette smoking, smoking status, education, total energy intake	
Jenab, 2006 STM80084 Denmark,France, Germany, Greece,Italy, Netherlands, Norway,Spain, Sweden,UK	EPIC, Nested Case Control, Age: 35-70 years, M/W	244/ 889 3.2 years	Cancer registries, health insurance records, pathology records & active follow up	FFQ, dietary questionnaires, food record	Incidence, stomach cancer	Per 0.89 mg/day	1.10 (0.93-1.29) Ptrend:0.45	BMI, H. pylori infection, smoking status, smoking duration, smoking intensity, total energy intake	Only dose-response RR for continuous increase
Nouraie, 2005 STM44426 Finland	ATBC, Prospective Cohort, Age: 50-69 years,	57/ 27 110 12 years	Cancer registry	Validated 276-item self-administered FFQ	Incidence, cardia cancer	≥1.91 vs ≤0.87 mg/day	0.41 (0.19-0.86) Ptrend:0.04	Age, dietary nitrate, educational level, energy intake, smoking habits	
		163/			Non-cardia cancer		0.78 (0.49-1.24) Ptrend:0.24		

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Reasons for exclusion
	M, Smokers								
Botterweck, 2000 STM03522 Netherlands	NLCS, Case Cohort, Age: 55-69 years, M/W	208/ 120 852 6.3 years	Cancer registry, pathology register	Validated 150-item self-administered semi-quantitative FFQ	Incidence, stomach cancer	0.86 vs 0.26 mg/day	1.20 (0.80-1.70)	Age, sex, educational level, family history of stomach cancer, smoking habits, stomach disorders	
Zheng, 1995 STM06417 USA	IWHS, Prospective Cohort, Age: 55-69 years, W, Post-menopausal women	26/ 34 691 7 years	Cancer registry	127-item self-administered semi-quantitative FFQ	Incidence, stomach cancer	>5672 vs <2098 IU/day	0.60 (0.20-1.70) Ptrend:0.36	Age, energy intake, pack-years of smoking, smoking habits	
Chyou, 1990 STM12425 USA	HHP, Case Cohort, Age: 58.00years, M, Japanese residents of Hawaii	111/ 8 006 18 years	Cancer registry/ hospital records	24-hour dietary recall	Mortality, stomach cancer	(mean exposure)		Age	Excluded, no measure of association

Figure 164 RR (95% CI) of stomach cancer for the highest compared with the lowest level of dietary retinol intake



5.5.1.1 Blood retinol

Randomised controlled trials

No randomised controlled trial was identified.

Summary

Main results:

Six studies (1718 cases) out of nine were included in the dose-response meta-analysis. No significant association of blood retinol with stomach cancer risk was observed. Significant inverse association was observed for cardia adenocarcinoma (three studies, no heterogeneity) and non-significant inverse association was observed for non-cardia adenocarcinoma (three studies, low heterogeneity).

Three studies were excluded from the dose-response analyses (Ito, 2006; Knekt, 1990b; Eichholzer, 1996). Ito, 2006 reported non-significant inverse association and Eichholzer, 1996 non-significant positive association between blood retinol and stomach cancer risk. Knekt, 1990b reported significant positive association among men and non-significant inverse association in women, comparing highest with lowest blood retinol concentrations.

Moderate heterogeneity (46.7%) was observed.

There was no evidence of a significant publication or small study bias (p=0.53).

No meta-analyses or pooled prospective studies were identified.

Sensitivity analyses:

In influence analysis, the summary RRs ranged from 0.93 (95% CI=0.88-0.99) when Persson, 2008b (JPHC I and II) was omitted to 0.99 (95% CI=0.93-1.04) when Jenab, 2006 (EPIC) was omitted.

Non-linear dose-response meta-analysis:

There was strong evidence of non-linear dose-response association (p for non-linearity <0.001). The risk of stomach cancer decreases with increasing levels of blood beta-carotene from the lowest level of 13.2 µg/dL up to approximately 60 µg/dL. The risk is slightly increasing up to the highest concentration of 113.1 µg/dL but the significant inverse association remains with all levels of intake.

Study quality:

Identification and ascertainment of cancer cases was completed using multiple methods in most studies. Blood samples were analysed using a reverse-phase high-performance liquid chromatography method (HPLC) in all studies. The values of blood retinol levels are not overlapping in the studies. The range from the highest to the lowest category is wider in one study (Persson, 2008b) that reported a non-significant positive association.

All studies were adjusted for smoking apart from Nomura, 1995 that was adjusted for age only.

Table 147 Blood retinol and stomach cancer risk. Number of studies in the CUP SLR

	Number
Studies identified	9 (14 publications)
Studies included in forest plot of highest compared with lowest exposure	9
Studies included in linear dose-response meta-analysis	6
Studies included in non-linear dose-response meta-analysis	5

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

Table 148 Blood retinol and stomach cancer risk. Summary of the linear dose-response meta-analysis in the 2005 SLR and CUP

	2005 SLR	**CUP**
Increment unit used	1 µmol/L	10µg/dL
All studies		
Studies (n)	3	7
Cases (total number)	330	1718
RR (95%CI)	0.82 (0.52-1.30)	0.96 (0.90-1.03)
Heterogeneity (I^2, p-value)	43%, 0.2	46.7%, 0.10
P value Egger test	0.8	0.53
Stratified and sensitivity analysis. CUP		
Sex	**Men**	**Women**
Studies (n)	3	-
Cases	522	-
RR (95%CI)	0.98 (0.89-1.06)	-
Heterogeneity (I^2, p-value)	0%, 0.70	-
Cancer site	**Gastric cardia cancer**	**Non- cardia gastric cancer**
Studies (n)	3	3
Cases	522	377
RR (95%CI)	0.88 (0.79-0.98)	0.95 (0.84-1.08)
Heterogeneity (I^2, p-value)	0%, 0.97	4.6%, 0.35

Other stratified analyses

Geographic location	**Asia**	**Europe**	**North America**
Studies (n)	3	2	1

RR (95%CI)	0.98 (0.89-1.07)	0.91 (0.78-1.06)	1.08 (0.81-1.46)
Heterogeneity (I^2, p-	55.8%, 0.10	42%, 0.18	-
Adjustment for	**Not adjusted**	**Adjusted**	
BMI			
Studies (n)	3	3	
RR (95%CI)	0.98 (0.89-1.06)	0.94 (0.83-1.06)	
Heterogeneity (I^2, p-	0%, 0.70	76.9%, 0.01	
H. pylori status			
Studies (n)	3	3	
RR (95%CI)	0.95 (0.89-1.02)	0.94 (0.82-1.09)	
Heterogeneity (I^2, p-	0%, 0.49	72.7%, 0.03	

Table 149 Blood retinol and stomach 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	Reasons for exclusion
Persson, 2008b STM80091 Japan	JPHC I and II, Nested Case Control, Age: 40-69 years, M/W	511/ 1 022 14 years maximum	Active patient notification from hospitals, cancer registries and death certificates	Measured in plasma using HPLC method	Incidence, stomach cancer	113.1 vs 57 µg/dL	1.39 (0.90-2.16) Ptrend:0.25	Matched by age, sex, study area, blood donation date, time since last meal at blood donation; adjusted for BMI, H. pylori infection, salt intake, family history of gastric cancer, salty foods, smoking	
Jenab, 2006 STM80084 Denmark, France, Germany, Greece,Italy, Netherlands, Norway,Spain, Sweden,UK	EPIC, Nested Case Control, Age: 35-70 years, M/W	244/ 889 3.2 years	Cancer registries, health insurance records, pathology records and active follow-up	Measured in plasma using HPLC method	Incidence, gastric adenocarcinoma	≥63.8 vs <42.4 µg/dL	0.55 (0.33-0.93) Ptrend:0.005	Matched by age, sex, study centre, date of blood sample collection; adjusted for BMI, H. pylori infection, smoking status, smoking duration, smoking intensity, total energy intake	
						Per 12.5 µg/dL	0.80 (0.67-0.97)		Rescaled RR for the increment unit used
		70/			gastric cardia adenocarcinoma		0.88 (0.63-1.25)		
		127/			gastric non-cardia adenocarcinoma		0.79 (0.59-1.04)		
Nouraie, 2005 STM44426 Finland	ATBC, Prospective Cohort,	57/ 27 110 12 years	Cancer registry	Measured in serum using HPLC method	Incidence, gastric cardia adenocarcinoma	≥662 vs ≤501 µg/L	0.75 (0.37-1.54) Ptrend:0.17	Age, dietary nitrate, educational level, smoking	Distribution of person-years and cases by exposure

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Reasons for exclusion
	Age: 50-69 years, M, Smokers	163/			gastric non-cardia adenocarcinoma		0.94 (0.60-1.48) Ptrend:0.66	habits	quantiles, mid-points of exposure categories, RRs for cardia and non-cardia gastric cancers combined using Hamling's method
Yuan, 2004 STM44236 China	SCStudy, Nested Case Control, Age: 45-64 years, M	191/ 18 244 12 years	Home visits/linkage cancer registry/vital stats	Measured in serum using HPLC method	Incidence, stomach cancer	>57 vs <38.9 µg/dL	0.86 (0.52-1.43) Ptrend:0.45	Matched by age, time of blood collection, neighbourhood of residence; adjusted for alcohol consumption, H. pylori infection, smoking habits, urinary epigallocatechin	Mid-points of exposure categories
Abnet, 2003 STM00424 Linxin, China	NIT Cohort, Case Cohort, Age: 40-69 years, M/W, Intervention trial participants	395/ 29 484 6.25 years	Follow-up visits, contacts with local commune, hospitals, and study medical team	Measured in serum using HPLC method	Incidence, gastric cardia adenocarcinoma	≥42.2 vs ≤25.3 µg/dL	0.82 (0.59-1.2) Ptrend:0.07	Age, sex, alcohol, BMI, cholesterol, foods or supplements, smoking habits, continuous results additionally adjusted for other vitamins	Distribution of cases and non-cases by exposure quantiles, mid-points of exposure categories, RRs for cardia and non-cardia gastric cancers combined using Hamling's method
						Per 8.4 µg/dL	0.90 (0.83-0.99)		
		87/			Gastric non-cardia adenocarcinoma	≥42.2 vs ≤25.3 µg/dL	0.79 (0.39-1.6) Ptrend:0.94		
						Per 8.4 µg/dL	1.00 (0.85-1.20)		
Nomura, 1995 STM11198 USA	HHP, Case Cohort, M,	70/ 7 972 26 years	Cancer registry, hospital records	Measured in serum using HPLC method	Incidence, stomach cancer	67+ vs ≤55 µg/dL	1.20 (0.60-2.20) Ptrend:1	Age	Mid-points of exposure categories

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

Table 150 Blood retinol and stomach 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
Ito, 2006 STM80153 Japan	HRCS, Prospective Cohort, Age: 39-85 years, M/W	17/ 3 204 11.7 years	Death certificate	Measured in serum using HPLC method	Mortality, stomach cancer	Per 1 log unit	0.88 (0.19-3.76) Ptrend:0.87	Age, sex, alcohol consumption, biomarkers, smoking status	Excluded, increment is not reported
Ito, 2005 STM44299 Japan	HRCS, Prospective Cohort, Age: 39-79 years, M/W	20/ 3 182 10.5 years	Death certificate	Measured in serum using HPLC method	Mortality, stomach cancer	High vs low	1.16 (0.26-4.79) Ptrend:0.97	Age, sex, ALT activity, serum cholesterol, smoking habits	Not quantified exposure levels, used in HvL analysis only, superseded by Ito, 2006
Eichholzer, 1996 STM10799 Switzerland	BASEL III, Prospective Cohort, Age: 20-79 years, M, Pharmaceutical Co. Employees	28/ 2 974 17 years	Death certificates	Measured fluorimetrically in plasma	Mortality, stomach cancer	<2.45 vs ≥2.45 vs µmol/L	1.53 (0.69-3.41)	Age, plasma lipids (cholesterol plus triglycerides), smoking habits	Only LvH results, RR inverted for HvL comparison, used in HvL analysis only
Knekt, 1990b STM44247 Finland	FMCHES, Nested Case Control,	32/ 36 265	Cancer registry	Measured in serum using HPLC method	Incidence, stomach cancer Men	≤550 vs >770 µg/L	0.30 (0.10-1.00)	Matched by sex, age, place of residence;	Only LvH results, RR inv erted for HvL

Author, Year, 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: 15-99 years, M/W	22/			Women	≤490 vs >710 µg/L	1.6 (0.40-6.60)	adjusted for smoking habits	comparison, used in HvL analysis only
Stähelin, 1991 STM07438 Switzerland	BASEL III, Prospective Cohort, Age: 20-79 years, M, Pharmaceutical Co. employees	20/ 2 974 12 years	Death certificates	Measured fluorimetrically in plasma	Mortality, stomach cancer	<2.45 vs. ≥2.45 vs µmol/L			Superseded by Eichholzer, 1996, no risk estimate
Stähelin, 1987 STM08301 Switzerland	BASEL III, Prospective Cohort, Age: 20-79 years, M, Pharmaceutical Co. employees	17/ 2 975 9 years	Death certificates	Measured fluorimetrically in plasma	Mortality, stomach cancer	Mean values			Superseded by Eichholzer, 1996, no risk estimate
Stähelin, 1986 STM15664 Switzerland	BASEL II and III, Prospective Cohort, Age: 18-65 years, M, Pharmaceutical Co. employees	19/ 4 224 7 years	Death certificates	Measured fluorimetrically in plasma	Mortality, stomach cancer	Mean values			Superseded by Eichholzer, 1996, no risk estimate
Nomura, 1985b STM14815 USA	HHP, Case Cohort, M, Japanese residents of Hawaii	70/ 6 800 10 years	Cancer registry/ hospital records	Measured in serum using HPLC method	Incidence, stomach cancer	Median values			Superseded by Nomura, 1995, no risk estimates

Figure 165 RR estimates of stomach cancer by levels of blood retinol

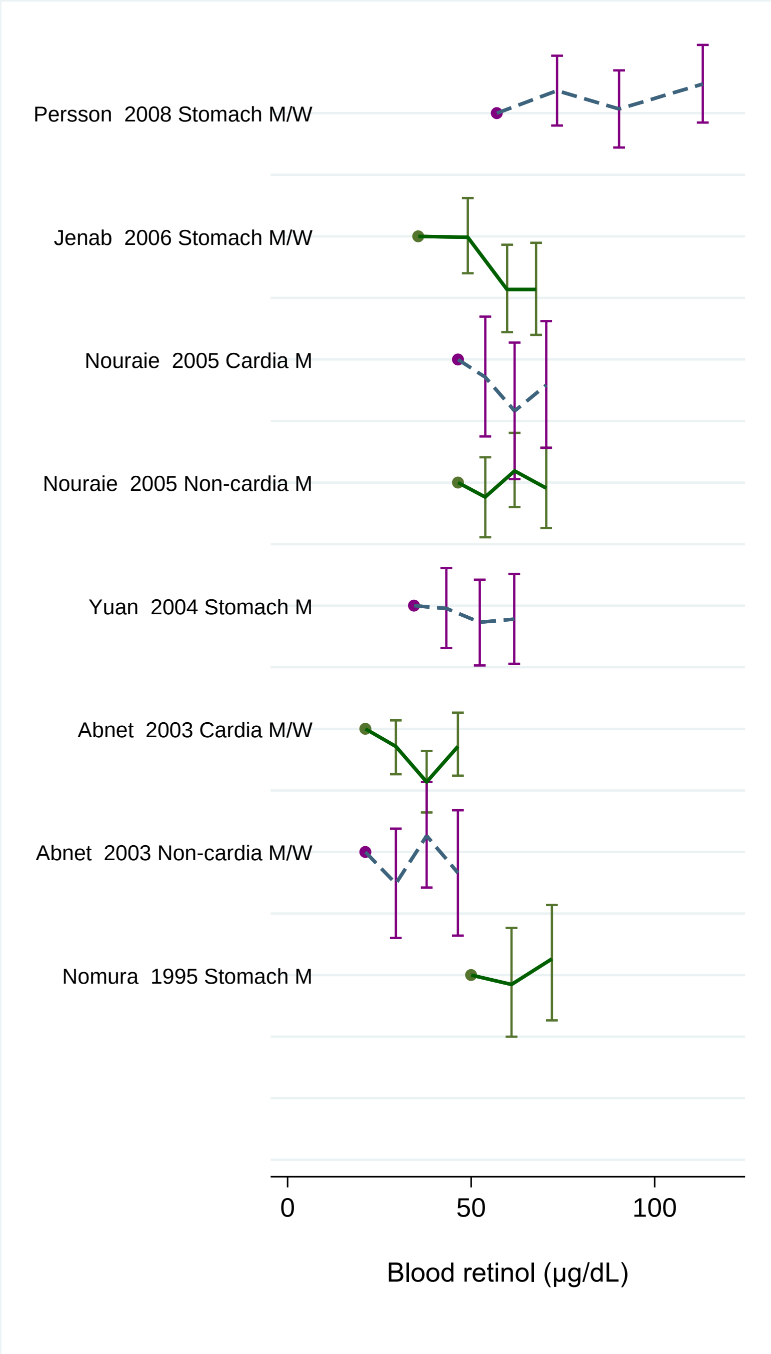
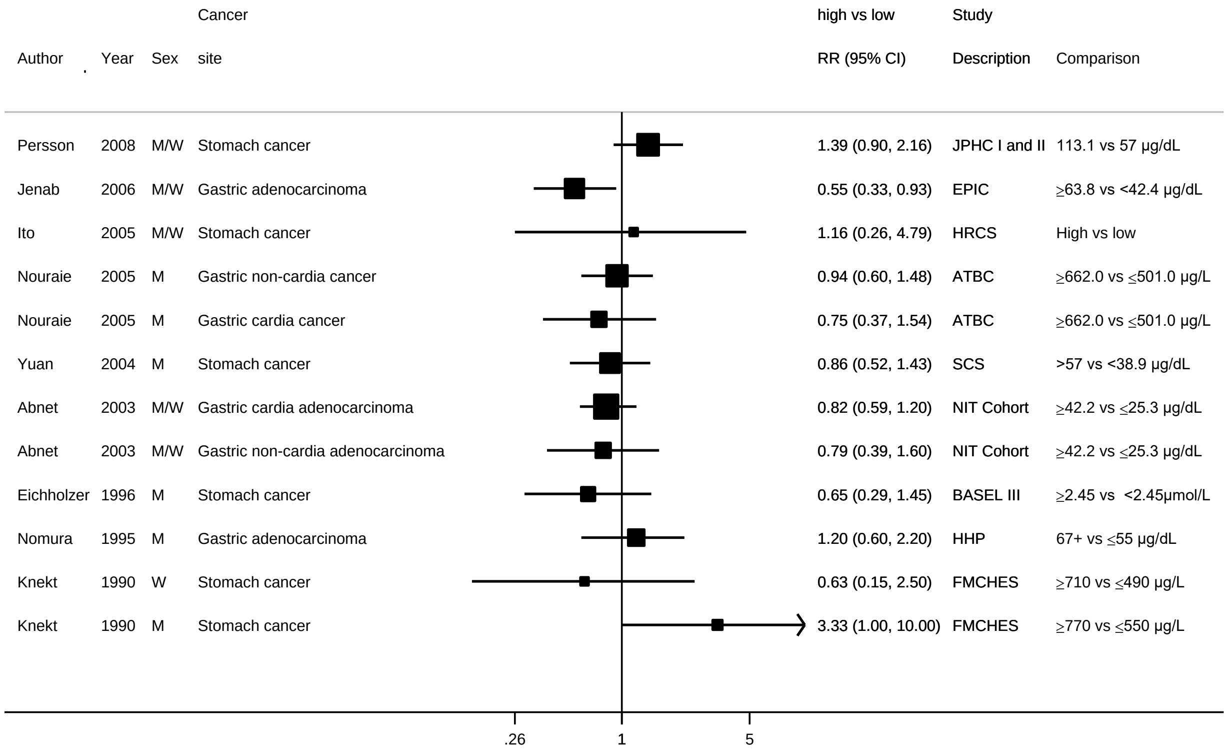


Figure 166 RR (95% CI) of stomach cancer for the highest compared with the lowest level of blood retinol



167 Figure 168 Relative risk of stomach cancer for 10 µg/dL increase of blood retinol

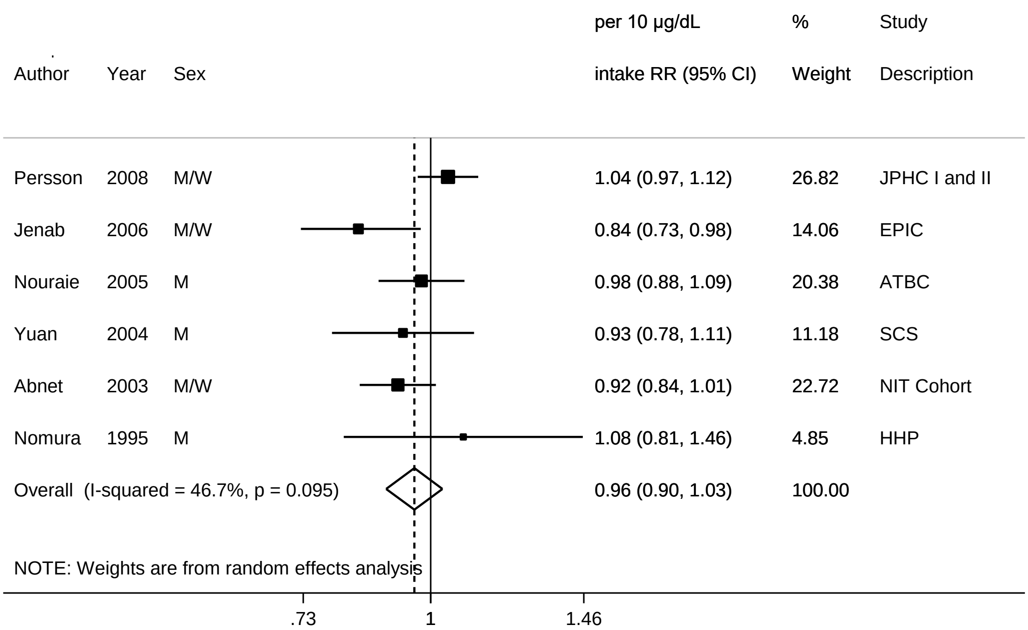
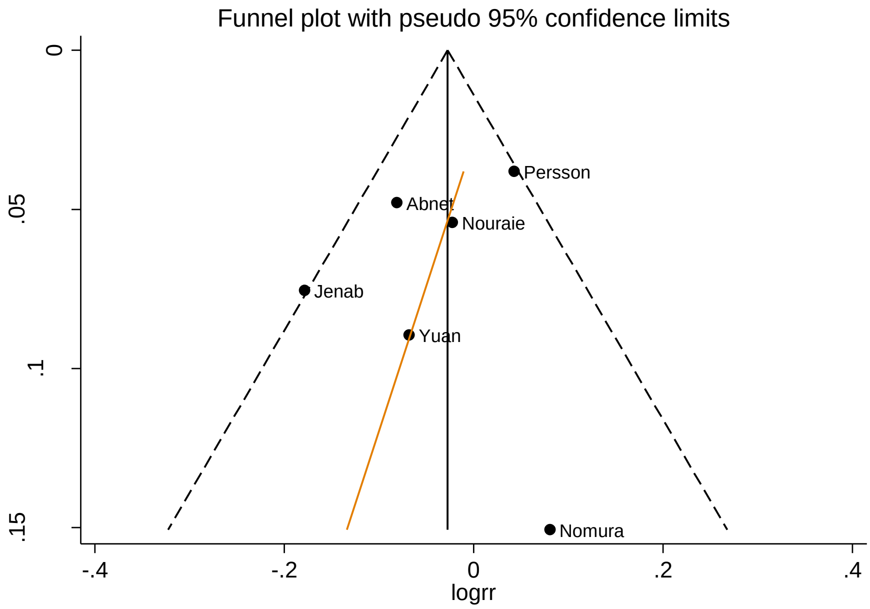


Figure 169 Funnel plot of studies included in the dose response meta-analysis of blood retinol and stomach cancer



Egger's test P=0.53

Figure 170 Relative risk of stomach cancer for 10µg/dL increase of blood retinol by sex

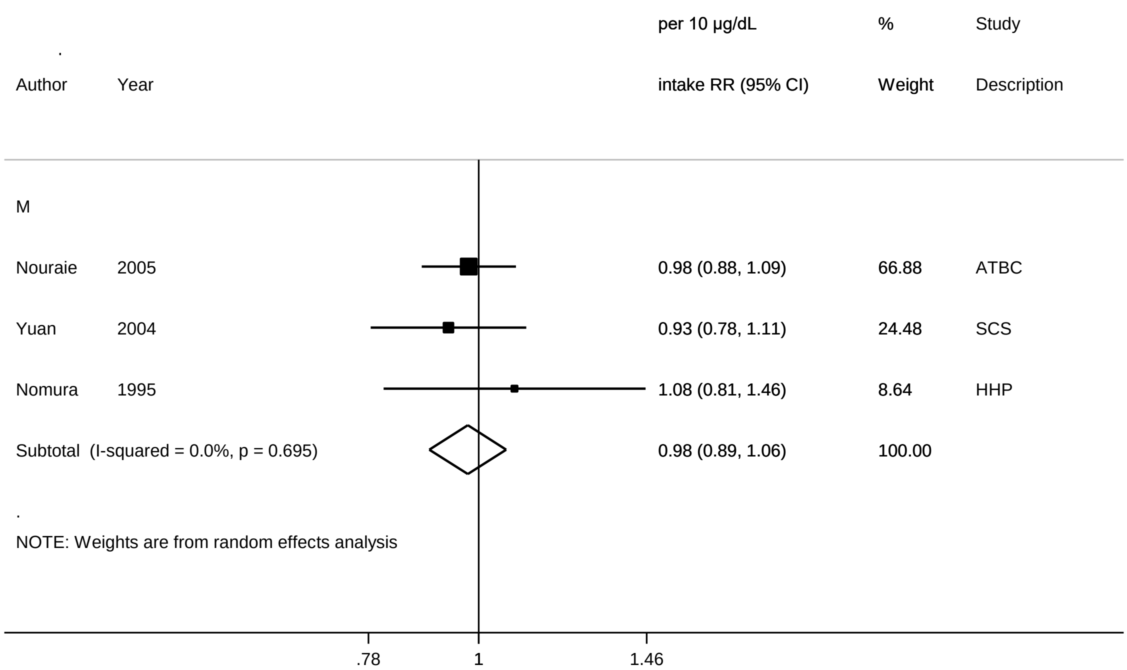


Figure 171 Relative risk of stomach cancer for 10µg/dL increase of blood retinol by cancer site

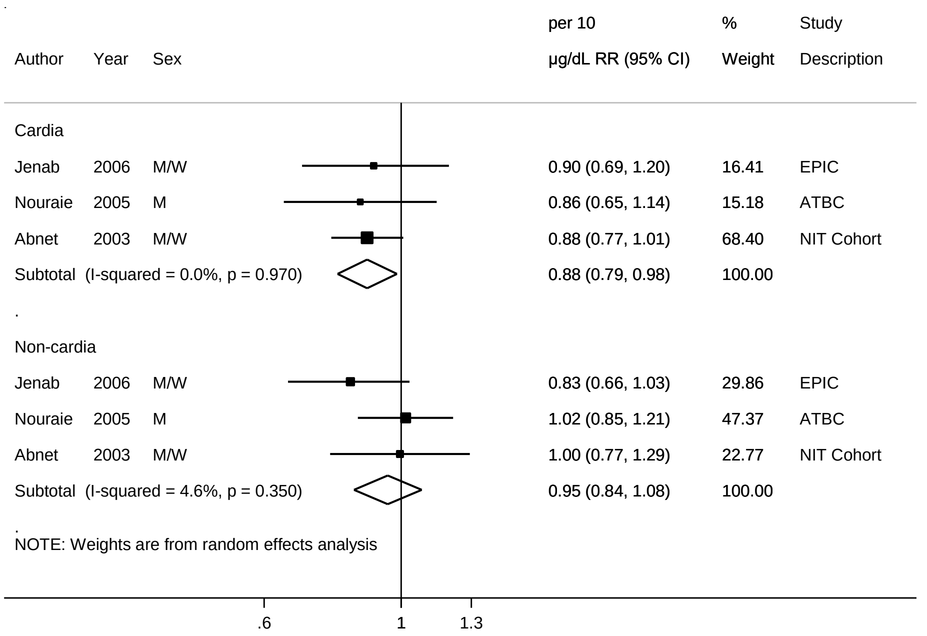


Figure 172 Relative risk of stomach cancer for 10µg/dL increase of blood retinol by geographic location

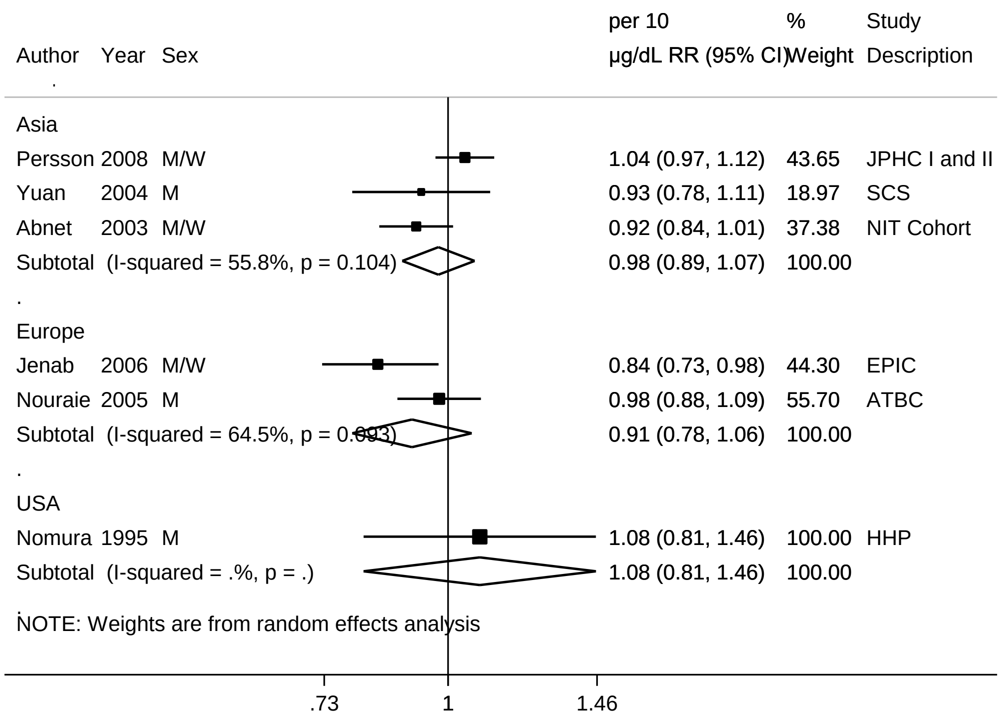
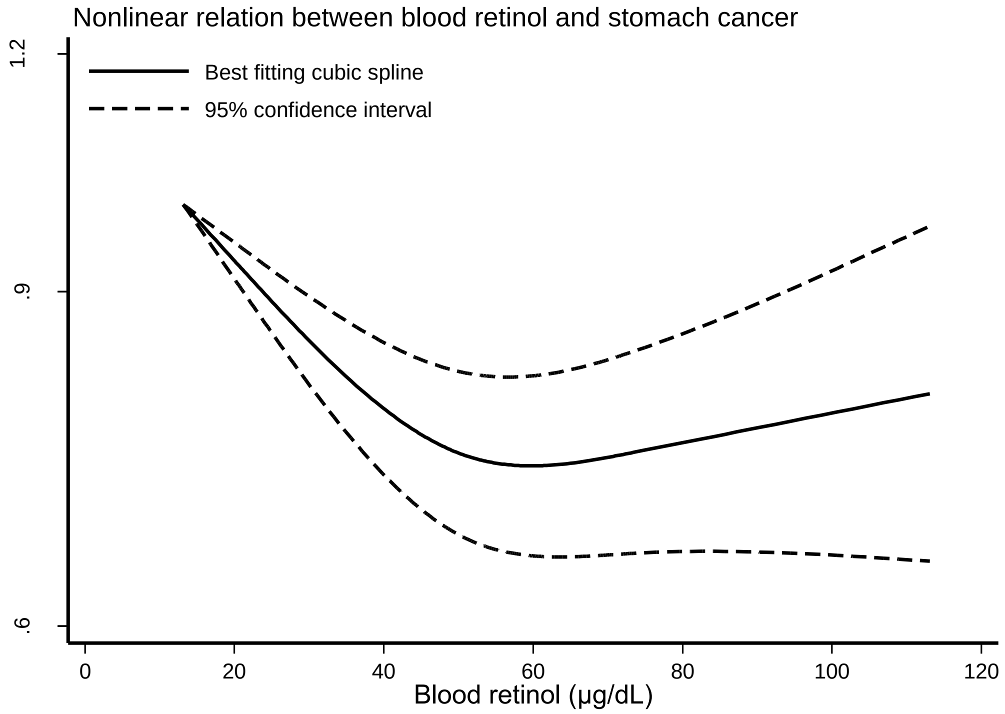


Figure 173 Non-linear dose-response meta-analysis of blood retinol and stomach cancer



P non-linear <0.001

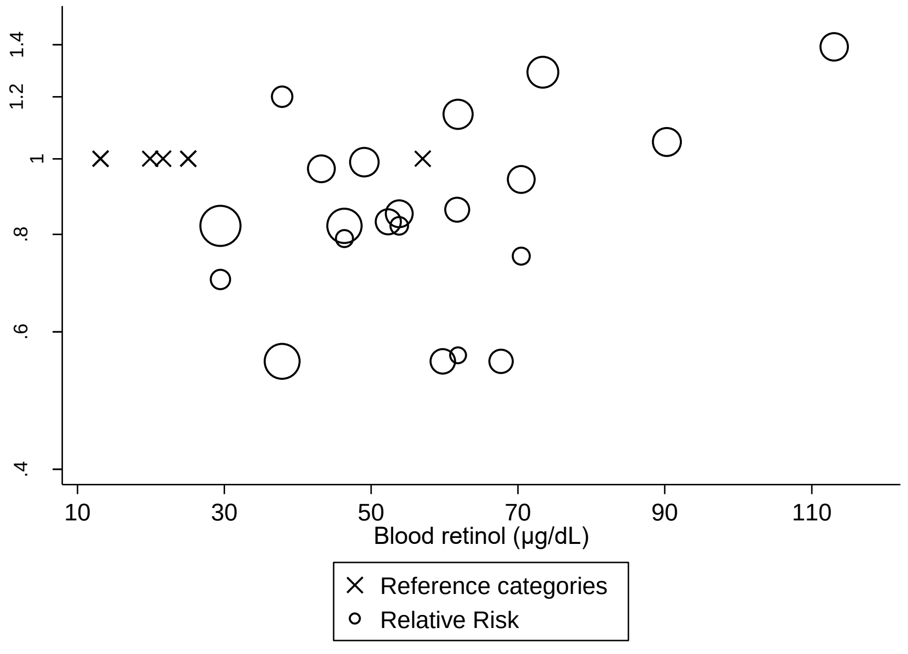


Table 151 Relative risk of stomach cancer and blood retinol estimated using non-linear models

Blood retinol (µg/dL)	RR (95%CI)
13.15	1.00
21.7	0.92 (0.89-0.94)
29.5	0.85 (0.81-0.90)
46.4	0.75 (0.68-0.82)
52.3	0.73 (0.66-0.81)
61.8	0.73 (0.65-0.81)
70.4	0.74 (0.65-0.83)
73.4	0.74 (0.66-0.84)
90.3	0.76 (0.66-0.89)
113.1	0.80 (0.65-0.97)

5.5.1.2 Dietary beta-carotene

Cohort studies

Summary

Main results:

Five cohort studies (6 publications) reported on dietary beta-carotene. Dose-response meta-analysis was not conducted as the number of studies was small.

Two studies were identified in the CUP. Larsson, 2007b found significant inverse association in the highest versus lowest analysis and non-significant inverse association per increment of 1000 µg RE/day. Jenab, 2006 reported non-significant positive association per increment of 2.4 mg/day. The pooled estimate of relative risk from two cohort studies (Botterweck, 2000; Chyou, 1990) included in the 2005SLR meta-analysis was 0.87 (95% CI=0.51-1.49) per 1000 µg/day.

Table 152 Dietary beta-carotene and stomach 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
Larsson, 2007b STM80069 Sweden	SMC and COSM, Prospective Cohort, Age: 45-83 years, M/W	139/ 82 002 7.2 years	Cancer registry	Validated FFQ	Incidence, stomach cancer	5210 vs 1107 µg/day	0.55 (0.32-0.94) Ptrend:0.07	Age, sex, diabetes, pack-years cigarette smoking, smoking status, education, total energy intake	
						Per 1,000 µg RE/day	0.57 (0.31-1.03)		
Jenab, 2006 STM80084 Denmark,France, Germany, Greece,Italy, Netherlands, Norway,Spain, Sweden,UK	EPIC, Nested Case Control, Age: 35-70 years, M/W	244/ 889 3.2 years	Cancer registries, health insurance records, pathology records & active follow up	FFQ, dietary questionnaires, food record	Incidence, stomach cancer	Per 2.4 mg/day	1.04 (0.88-1.24)	BMI, H.pylori infection, smoking status, smoking duration, smoking intensity, total energy intake	
Nouraie, 2005 STM44426 Finland	ATBC, Prospective Cohort, Age: 50-69 years, M, Smokers	57/ 27 110 12 years	Cancer registry	Validated 276-item self-administered FFQ	Incidence, cardia cancer	≥2.66 vs ≤1.14 mg/day	0.85 (0.35-2.05)	Age, dietary nitrate, educational level, energy intake, smoking habits	
		163/			Incidence, Non-cardia		1.33 (0.80-2.22)		
Hirvonen, 2001 STM02213 Finland	ATBC, Prospective Cohort, Age: 50-69 years, M, Smokers	111/ 27 110 6.1 years	Cancer registry	FFQ	Incidence, stomach cancer		(mean exposure)	Age	Superseded by Nouraie, 2005, mean exposure only

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Inclusion/ exclusion
Botterweck, 2000 STM03522 Netherlands	NLCS, Case Cohort, Age: 55-69 years, M/W	208/ 120 852 6.3 years	Cancer registry, pathology register	Validated 150-item self-administered semi-quantitative FFQ	Incidence, stomach cancer	4.77 vs 1.43 mg/day	1.20 (0.80-1.80)	Age, sex, educational level, family history of stomach cancer, smoking habits, stomach disorders	
Chyou, 1990 STM12425 USA	HHP, Case Cohort, Age: 58 years, M, Japanese residents of Hawaii	111/ 8 006 18 years	Cancer registry/ hospital records	24-hour dietary recall	Mortality, stomach cancer		(mean exposure)	Age	Excluded, mean exposure only

5.5.1.2 Blood beta-carotene

Cohort studies

Summary

Main results:

Six studies (1718 cases) were included in the dose-response meta-analysis. No significant association of blood beta-carotene with stomach cancer risk was observed. Significant inverse association was observed for men (five studies, moderate heterogeneity) and non-significant inverse association was observed for women (two studies, no heterogeneity).

Three studies were excluded from the dose-response analysis. Ito, 2006 reported non-significant inverse association between blood beta-carotene and stomach cancer risk. Knekt, 1990 reported non-significant positive association in the highest vs lowest comparison. Wald, 1988 reported no risk estimates.

High heterogeneity (80.1%) was observed. There was no evidence of a significant publication or small study bias (p=0.34).

Sensitivity analyses:

In influence analysis, the summary RRs ranged from 0.91(95% CI=0.84-0.98) when Jenab, 2006 (EPIC) was omitted to 0.96 (95% CI=0.88-1.04) when Nomura, 1995 (HHP) was omitted.

To test the influence of very low blood beta-carotene levels in some studies in the analysis, we excluded a study with very low range of blood beta-carotene levels (Abnet, 2003, highest category: >7.3 µg/dL) and in two other studies (Persson, 2008b; Yuan, 2004), we excluded the referent categories (around 2.3 µg/dL) and recalculated the RRs using the second category as referent. The results were materially the same as in the initial analysis. The summary RR for an increase of 5 µg/dL was 0.95 (95% CI: 0.87-1.04; 5 studies, I^2:76.4%).

Significant inverse association was observed in Asian studies (three studies, low heterogeneity) but not in European studies.

Non-linear dose-response meta-analysis:
There was no evidence of non-linear dose-response association (p for non-linearity = 0.10).

Study quality:

Loss to follow-up was low in most studies and cancer outcome was confirmed using medical notes or record linkage in the cancer registries in most studies.

Blood samples were analysed using a reverse-phase high-performance liquid chromatography method (HPLC) in all studies but the range of blood levels vary and don’t overlap across studies.

Significant inverse association was observed in studies that did not adjust for BMI but non-significant inverse association was observed in BMI adjusted studies.

Table 153 Blood beta-carotene and stomach cancer risk. Number of studies in the CUP SLR

	Number
Studies identified	9 (11 publications)
Studies included in forest plot of highest compared with lowest exposure	8
Studies included in linear dose-response meta-analysis	6
Studies included in non-linear dose-response meta-analysis	5

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

Table 154 Blood beta-carotene and stomach cancer risk. Summary of the linear dose-response meta-analysis in the 2005 SLR and CUP

	2005 SLR	**CUP**
Increment unit used	0.1 µmol/L	5µg/dL
All studies		
Studies (n)	2	6
Cases (total number)	261	1718
RR (95%CI)	0.87 (0.82-0.93)	0.94 (0.86-1.02)
Heterogeneity (I^2, p-value)	0%, 0.9	80.1%, <0.001
P value Egger test	-	0.34
Stratified and sensitivity analysis		
Sex	**Men**	**Women**
Studies (n)	4	2
Cases	823	169
RR (95%CI)	0.88 (0.80-0.97)	0.97 (0.87-1.07)
Heterogeneity (I^2, p-value)	62.2%, 0.05	-
Cancer site	**Gastric cardia**	**Non cardia gastric**
Studies (n)	2	2
Cases	452	250
RR (95%CI)	0.99 (0.89-1.10)	1.01 (0.93-1.11)
Heterogeneity (I^2, p-value)	0%, 0.85	0%, 0.65

Other stratified analyses

Geographic location	**Asia**	**Europe**	**North America**
Studies (n)	3	2	1
RR (95%CI)	0.90 (0.83-0.96)	1.02 (0.98-1.06)	0.85 (0.78-0.92)
Heterogeneity (I^2, p-value)	8.5%, 0.34	0%, 0.88	-
Adjustment for	**Not adjusted**	**Adjusted**	
BMI			
Studies (n)	3	3	
RR (95%CI)	0.90 (0.79-1.02)	0.97 (0.87-1.08)	
Heterogeneity (I^2, p-value)	70.6%, 0.03	81.5%, 0.004	
Alcohol intake			
Studies (n)	4	2	
RR (95%CI)	0.94 (0.85-1.04)	0.91 (0.74-1.13)	
Heterogeneity (I^2, p-value)	86.4%, <0.001	53.9%, 0.14	
H. pylori status			
Studies (n)	3	3	
RR (95%CI)	0.94 (0.82-1.09)	0.93 (0.82-1.05)	
Heterogeneity (I^2, p-value)	71.9%, 0.03	86.0%, 0.001	

Table 155 Blood beta-carotene and stomach cancer risk. Results of meta-analyses and pooled analyses of prospective studies published after the 2005 SLR

Author, Year	Number of studies	Total number of cases	Studies country, area	Outcome	Comparison	RR (95%CI)	P trend	Heterogeneity (I^2, p value)
Meta-analyses								
Li, 2014*	5 prospective cohort studies	1648	China, Europe, Japan	Incidence/mortality, gastric cancer	High vs low	0.83 (0.57-1.19)		62.2%, 0.03

*All studies identified in this meta-analysis were included in the present review

Table 156 Blood beta-carotene and stomach 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
Persson, 2008b STM80091 Japan	JPHC I and II, Nested Case Control, Age: 40-69 years, M/W	511/ 1 022 14 years maximum	Active patient notification from hospitals, cancer registries and death certificates	Measured in plasma using HPLC method	Incidence, stomach cancer	38.4 vs 4.5 µg/dL	0.46 (0.28-0.75) Ptrend:<0.01	Matched by age, sex, study area, blood donation date, time since last meal at blood donation; adjusted for BMI, H. pylori infection, salt intake, family history of gastric cancer, salty foods, smoking	
		342/			Men	28.5 vs 3.3 µg/dL	0.47 (0.27-0.81) Ptrend:<0.01		
		169/			Women	48.5 vs 11.7 µg/dL	0.76 (0.35-1.70) Ptrend:0.59		
		181/			Men, smokers	29 vs 3.3 µg/dL	0.29 (0.06-1.55) Ptrend:<0.01		
		161/			Men, non-smokers	28.4 vs 3.3 µg/dL	0.19 (0.06-0.66) Ptrend:<0.01		
Jenab, 2006 STM80084 Denmark, France, Germany, Greece,Italy, Netherlands, Norway,Spain, Sweden,UK	EPIC, Nested Case Control, Age: 35-70 years, M/W	244/ 889 3.2 years	Cancer registries, health insurance records, pathology records and active follow-up	Measured in plasma using HPLC method	Incidence, gastric adenocarcinoma	Per 18.9 µg/dL	1.09 (0.94-1.27)	Matched by age, sex, study centre, date of blood sample collection; adjusted for BMI, H. pylori infection, smoking status, smoking duration, smoking intensity, total energy intake	RR rescaled for an increment used
						≥26.5 vs <12.0 µg/dL	1.13 (0.69-1.86) Ptrend:0.539		
Nouraie, 2005	ATBC,	57/	Cancer registry	Measured in	Incidence,	≥262 vs ≤110	0.92 (0.44-1.95)	Age, dietary	Distributions 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	Inclusion/exclusion
STM44426 Finland	Prospective Cohort, Age: 50-69 years, M, Smokers	27 110 12 years		serum using HPLC method	gastric cardia adenocarcinoma	µg/L	Ptrend:0.92	nitrate, educational level, smoking habits	person-years and mid-points of exposure quantiles, RRs for cardia and non-cardia cancer combined using Hamling's method
		163/			gastric non-cardia adenocarcinoma		1.05 (0.67-1.67) Ptrend:0.57		
Yuan, 2004 STM44236 China	SCStudy, Nested Case Control, Age: 45-64 years, M	191/ 18 244 12 years	Cancer registry, Shanghai Municipal Vital Statistics Office, annual in-person re-interviews	Measured in serum using HPLC method	Incidence, stomach cancer	>14.8 vs <6 µg/dL	0.62 (0.37-1.06) Ptrend:0.05	Matched by age, time of blood collection, neighbourhood of residence; adjusted for alcohol consumption, H. pylori infection, smoking habits, urinary epigallocatechin	Mid-points of exposure quantiles
Abnet, 2003 STM00424 China	NIT Cohort, Case Cohort, Age: 40-69 years, M/W, Intervention trial	395/ 29 484 6.25 years	Follow-up visits, contacts with local commune, hospitals, and study medical	Measured in serum using HPLC method	Incidence, gastric cardia adenocarcinoma	Per 2.5 µg/dL	1.00 (0.96-1.10)	Age, sex, alcohol, BMI, cholesterol, foods or supplements,	Distribution of cases and non-cases by exposure

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Inclusion/exclusion
	participants		team			≥7.4 vs ≤2.4 µg/dL	0.95 (0.67-1.40)	smoking habits, continuous results additionally adjusted for other vitamins	quantiles, mid-points of exposure categories, RRs for stomach cardia and non-cardia cancer combined using Hamling's method
		87/			Gastric non-cardia adenocarcinoma	Per 2.5 µg/dL	1.00 (0.91-1.10)		
						≥7.3 vs ≤2.4 µg/dL	1.90 (0.89-3.90)		
Nomura, 1995 STM11198 USA	HHP, Case Cohort, M, Japanese residents of Hawaii	70/ 7 972 26 years	Cancer registry, hospital records	Measured in serum using HPLC method	Incidence, gastric adenocarcinoma	41+ vs ≤22 µg/dL	0.30 (0.20-0.70) Ptrend:0.08	Age	Mid-points of exposure categories

Table 157 Blood beta-carotene and stomach 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
Ito, 2006 STM80153 Japan	HRCS, Prospective Cohort, Age: 39-85 years, M/W	17/ 3 204 11.7 years	Death certificate	Measured in serum using HPLC method	Mortality, stomach cancer	Per 1 log unit	0.81 (0.41-1.60)	Age, sex, alcohol consumption, biomarkers, smoking status	Excluded, increment is not reported

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Inclusion/exclu sion
Ito, 2005 STM44299 Japan	HRCS, Prospective Cohort, Age: 39-79 years, M/W	20/ 3 182 10.5 years	Death certificate	Measured in serum using HPLC method	Mortality, stomach cancer	High vs low	0.62 (0.17-2.31) Ptrend:0.50	Age, sex, ALT activity, serum cholesterol, smoking habits	Superseded by Ito, 2006, not quantified exposure levels, used in HvL analysis only
Knekt, 1990b STM44247 Finland	FMCHES, Nested Case Control, Age: 15-99 years, M/W	32/ 36 265 8 years	Cancer registry	Measured in serum using HPLC method	Incidence, stomach cancer Men	Lowest vs highest quantile	0.80 (0.20-2.80)	Matched by sex, age, place of residence; adjusted for smoking habits	Only LvH results, RRs inverted for HvL comparison, used in HvL analysis only
		22			Women		0.90 (0.20-3.80)		
Wald, 1988 STM00079 England	BUPA, Nested Case Control, Age: 35-64 years, M	13/ 22 000 10 years	Cancer registry	Measured in serum using HPLC method	Incidence, stomach cancer	Mean values			Excluded, no risk estimate
Nomura, 1985b STM14815 USA	HHP, Case Cohort, Age: 64.00years, M, Japanese residents of Hawaii	70/ 6 860 10 years	Cancer registry, hospital records	Measured in serum using HPLC method	Mortality, stomach cancer	Mean values			Superseded by Nomura, 1995, no risk estimate

Figure 174 RR estimates of stomach cancer by levels of blood beta-carotene

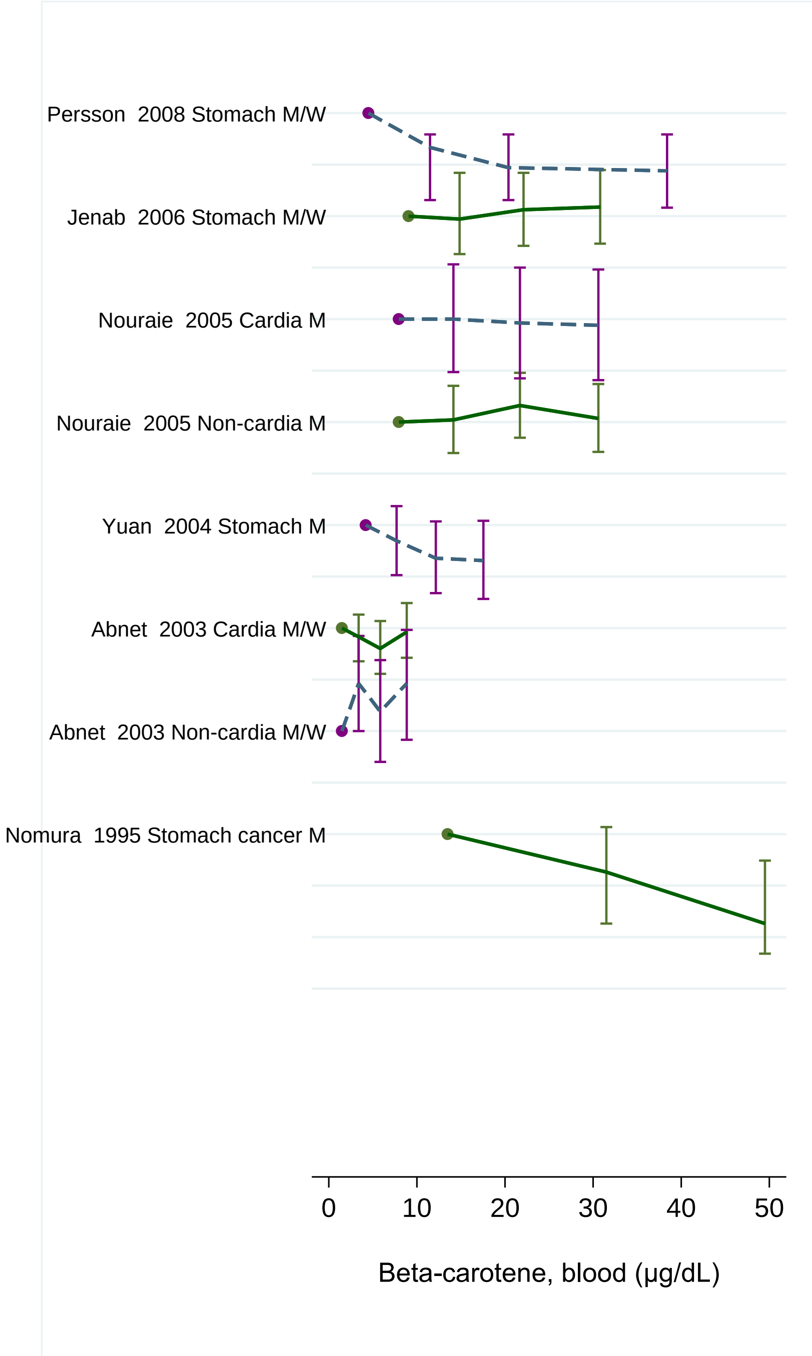


Figure 175 RR (95% CI) of stomach cancer for the highest compared with the lowest level of blood beta-carotene

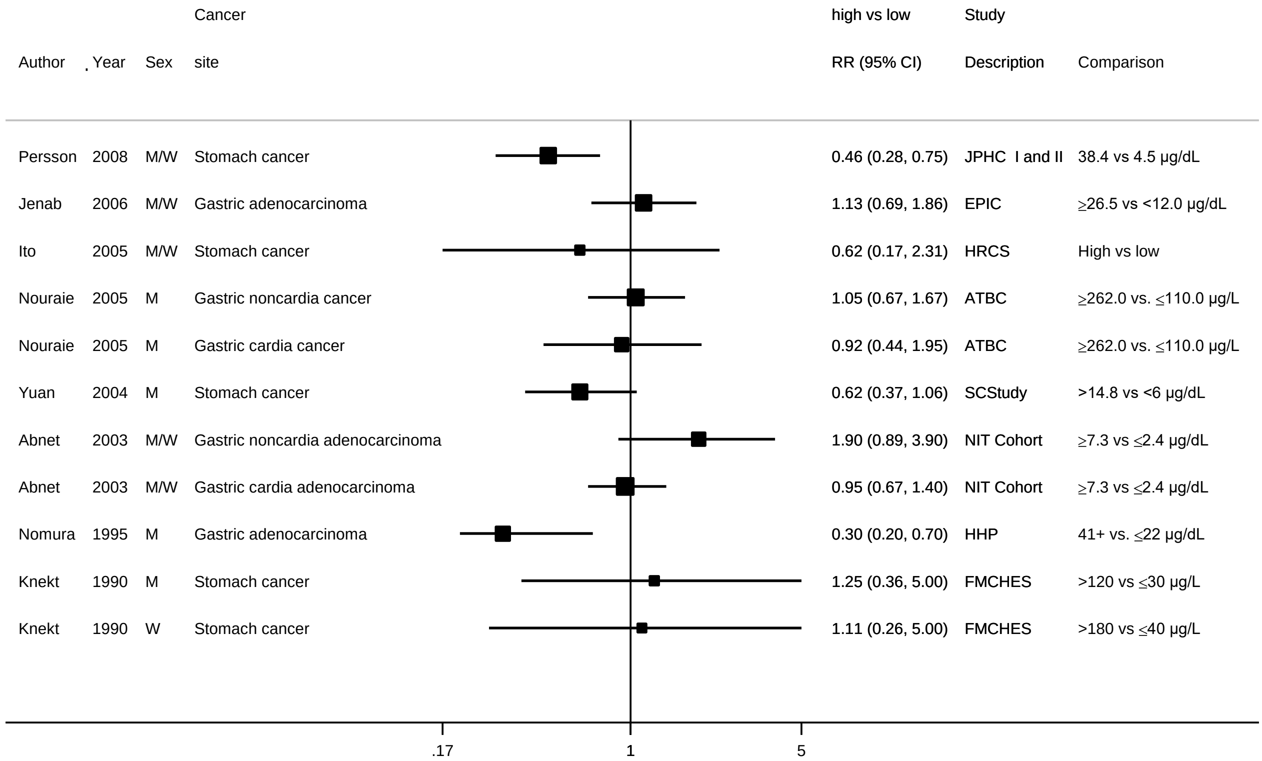


Figure 176 Relative risk of stomach cancer for 5 µg/dL increase of blood beta-carotene

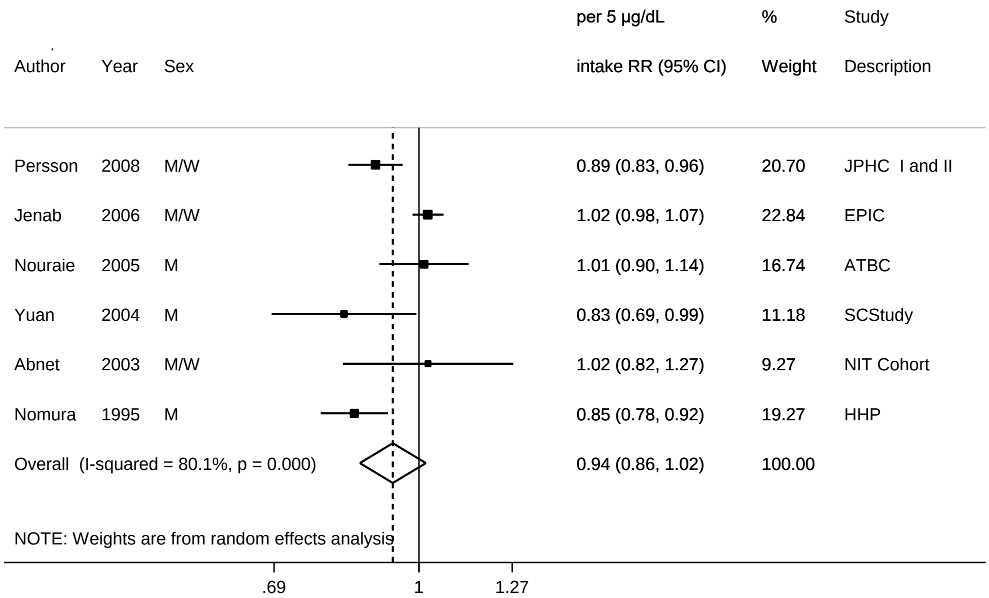
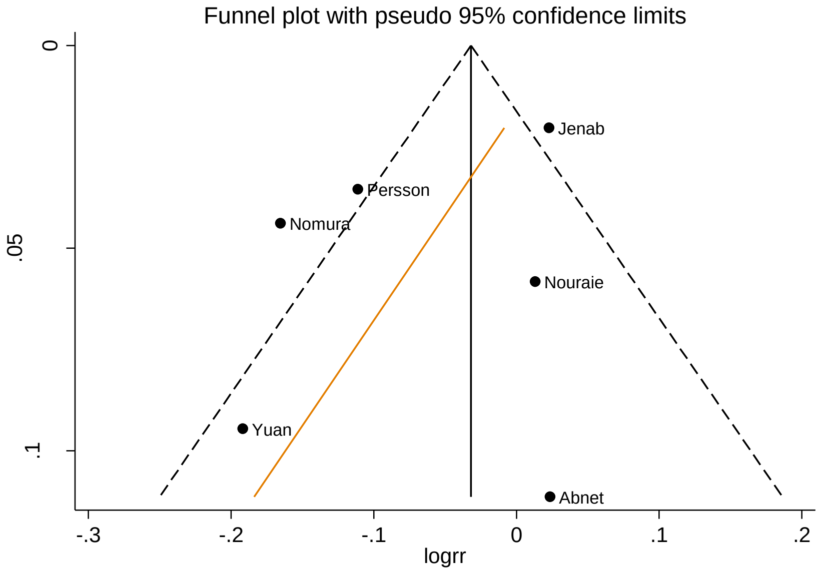


Figure 177 Funnel plot of studies included in the dose response meta-analysis of blood beta-carotene and stomach cancer



Egger's test p=0.34

Figure 178 Relative risk of stomach cancer for 5 µg/dL increase of blood beta-carotene by sex

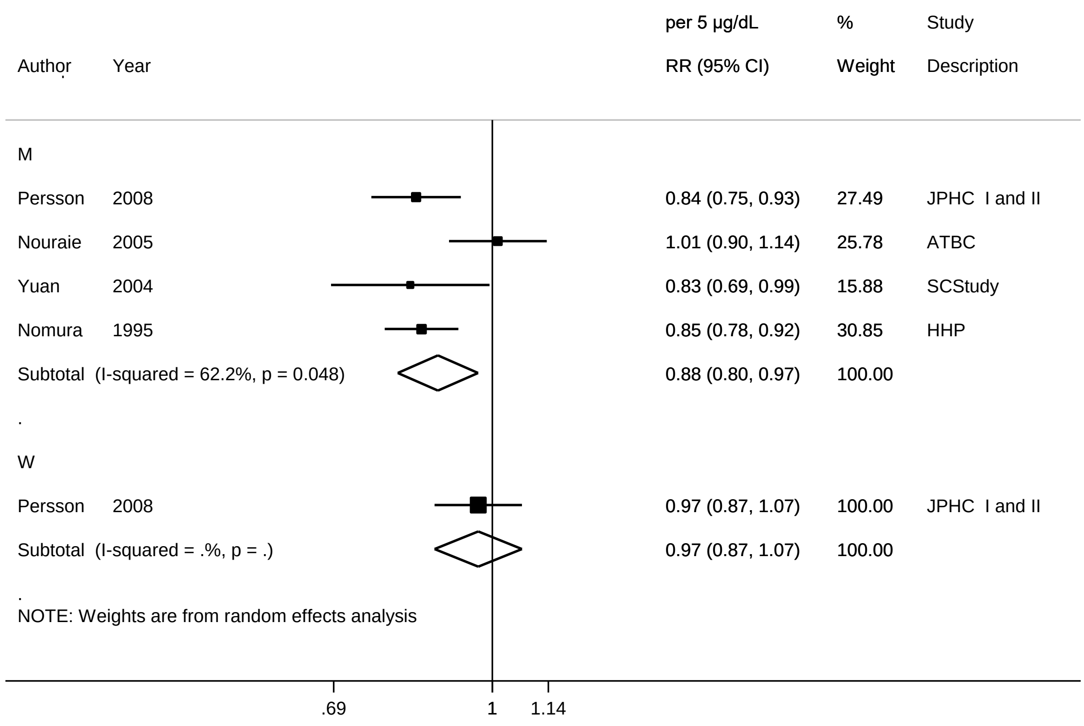


Figure 179 Relative risk of stomach cancer for 5 µg/dL increase of blood beta-carotene by cancer site

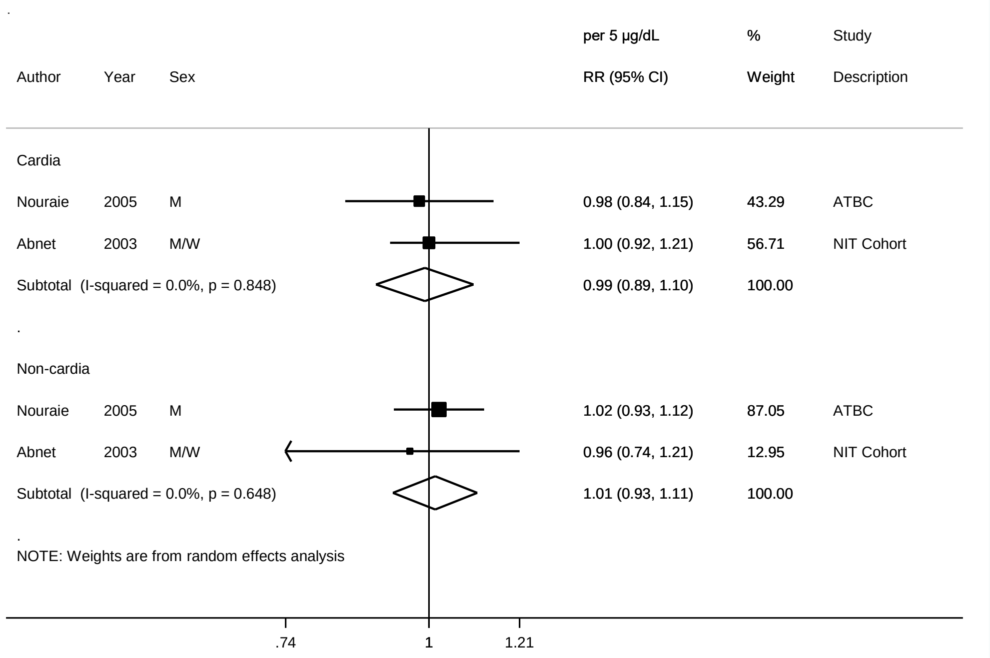


Figure 180 Relative risk of stomach cancer for 5 µg/dL increase of blood beta-carotene by geographic location

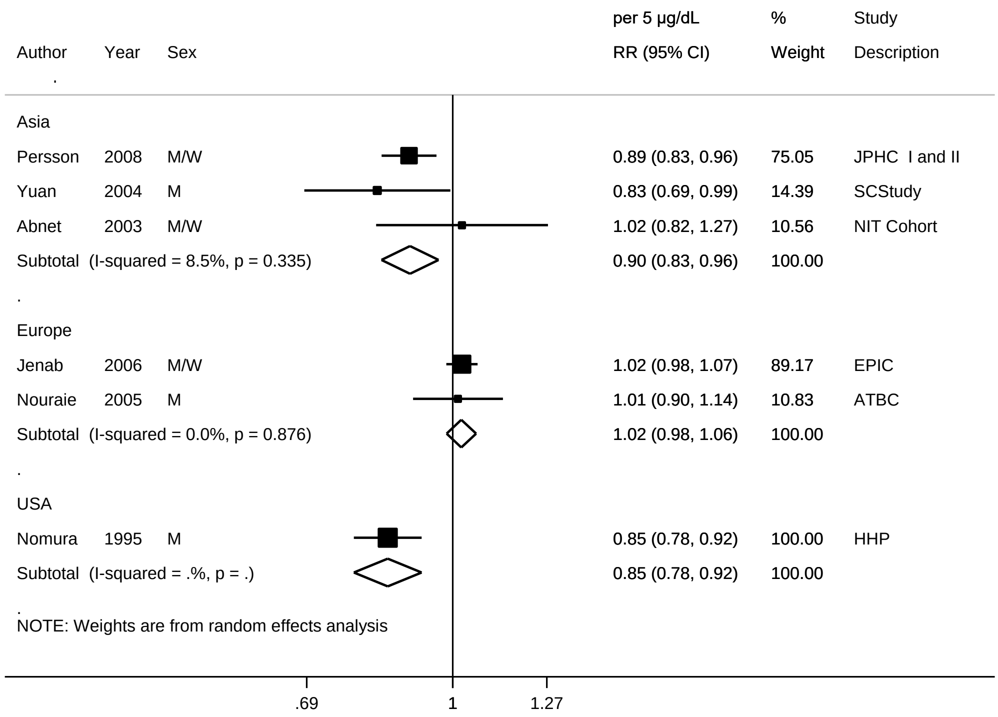


Figure 181 Relative risk of stomach cancer for 5 µg/dL increase of blood beta-carotene in sensitivity analysis after excluding a study with very low range of blood beta-carotene levels (Abnet, 2003) and the referent category of two other studies (around 2.3 µg/dL)

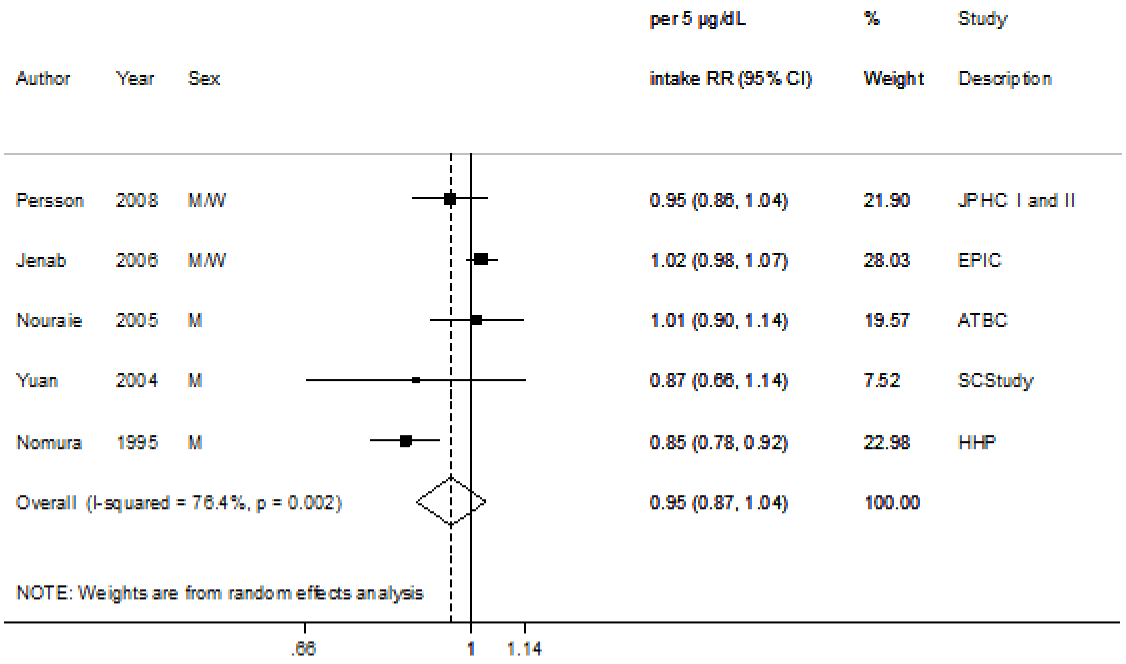
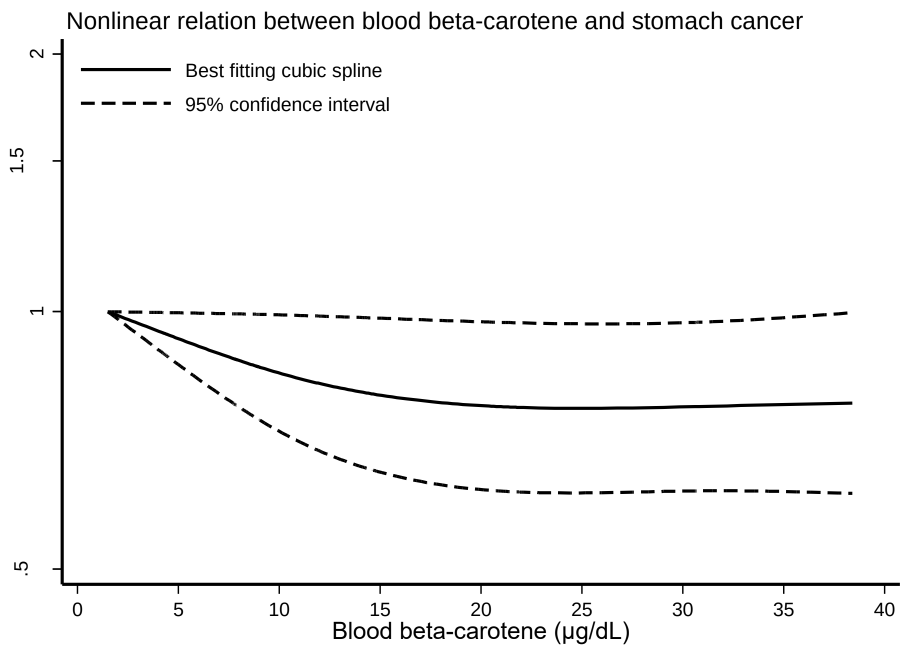


Figure 182 Non-linear dose-response meta-analysis of blood beta-carotene and stomach cancer



P non-linear =0.10

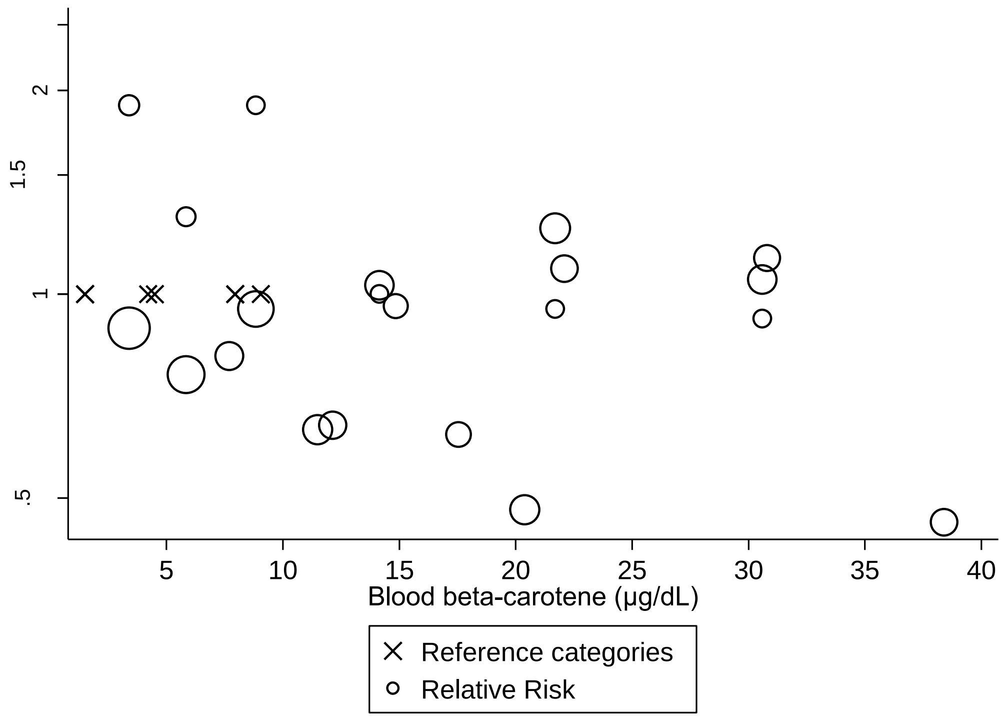


Table 158 Relative risk of stomach cancer and blood beta-carotene estimated using non-linear models

Blood beta-carotene (µg/dL)	RR (95%CI)
1.5	1.00
3.4	0.95 (0.93-1.00)
4.5	0.94 (0.89-1.00)
8.9	0.86 (0.75-0.99)
14.9	0.80 (0.65-0.98)
20.4	0.78 (0.62-0.97)
30.6	0.77 (0.62-0.97)
38.4	0.78 (0.61-01.00)

5.6.4 Selenium

Randomised controlled trial

One randomised controlled trial of selenium and allitridum supplement in China reported significant lower stomach cancer incidence and mortality among men but not women or all participants combined in the intervention group compared with placebo group (Zheng, 2005; Li, 2004).

Table 159 Selenium supplement intake and stomach cancer risk. Main characteristics of 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	Reasons for exclusion
Zheng, 2005 STM44430 China	QCSTC, Randomised Controlled Trial, Age: 34-74 years, M/W	5 years after 3-year intervention	Unknown / not reported	Intervention: 200 mg allitridum daily and 100 µg sodium selenite every other day for 1 month in 3 successive years Control: placebo	Mortality, stomach cancer Men	Supplementation vs placebo	0.30 (0.12-0.77)	Age, drinking, smoking, family history of gastric cancer and history of gastric disease	Incidence and mortality results used from Li, 2004 study
					Women		0.63 (0.10-3.92)		
Li, 2004 STM24583 China	QCSTC, Randomised Controlled Trial, Age: 34-74 years, M/W	/5033 5 years after 3-year intervention	Unknown / not reported	Intervention: 200 mg allitridum daily and 100 µg sodium selenite every other day for 1 month in 3 successive years Control: placebo	Incidence/ mortality, stomach cancer All	Supplementation vs placebo	0.48 (0.21-1.06)	Age, family history of cancer, smoking, alcohol consumption, history of stomach illness	
					Men		0.36 (0.14-0.92)		
					Women		1.14 (0.22-5.76)		

Cohort studies

Summary

Main results:

Nine cohort studies (10 publications) reported on selenium; two on selenium from diet, one from supplements, five on blood levels, and one on toenail selenium. Dose-response meta-analysis was not conducted as the number of studies was small. No meta-analysis was conducted in the 2005 SLR.

Two studies on dietary selenium and distal gastric cancer (one publication, Epplein, 2010) showed a non-significant positive association of dietary selenium and stomach cancer among men (SMHS) and non-significant inverse association among women (SWHS).

One study comparing use with no use of selenium supplement showed non-significant inverse association for cardia cancer and non-significant positive association for distal gastric cancer (Dawsey, 2014).

One study on toenail selenium and gastric cardia adenocarcinoma was identified (Steevens, 2010a). A significant inverse association was observed among women but not men or all participants combined.

No new study on blood selenium and stomach cancer risk was identified. Of the five published studies identified in the 2005 SLR, two showed significant inverse association with gastric cardia but not with non-cardia gastric cancer mortality. No significant association was observed in the remaining studies.

No published meta-analyses or pooled analyses were identified.

Table 160 Selenium and stomach 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	7
Studies included in linear dose-response meta-analysis	Not enough studies

Note: Include cohort, nested case-control and case-cohort designs. *Included two cohort studies in one publication (Epplein, 2010) reporting results on distal gastric cancer only.

Table 161 Selenium and stomach 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	Reasons for exclusion
Selenium, from foods									
Epplein, 2010 STM80129 China	SWHS and SMHS, Prospective Cohort, Age: 40-74 years, M/W	132/ 59247 3.6 years	Review of medical records	Validated 81-item (SMHS) and 77-item (SWHS) FFQs	Incidence, distal stomach cancer Men	>61.4 vs ≤35.8 µg/day	1.38 (0.76-2.50) Ptrend:0.34	Age, education level, smoking, total energy intake	
		206/ 73064 9.2 years			Women	>55.0 vs ≤30.9 µg/day	0.92 (0.56-1.52) Ptrend:0.67		
Selenium, from supplements									
Dawsey, 2014 STM80189 USA	NIH- AARP, Prospective Cohort, Age: 50-71 years, M/W, Retired	450/ 490 593 11 years	Postal service, social security administration death master file, national death index	FFQ	Incidence, gastric cardia adenocarcinoma	Any* use of supplements vs none	0.87 (0.59-1.28)	Age, sex, alcohol consumption, BMI, smoking status, education, fruit and vegetable intake, smoking intensity, total energy intake, usual activity throughout the day, vigorous physical activity	
		493/			Gastric non-cardia adenocarcinoma		1.25 (0.91-1.70)		
					Women		0.63 (0.10-3.92)		
					Men		0.36 (0.14-0.92)		
					Women		1.14 (0.22-5.76)		
Selenium, serum									

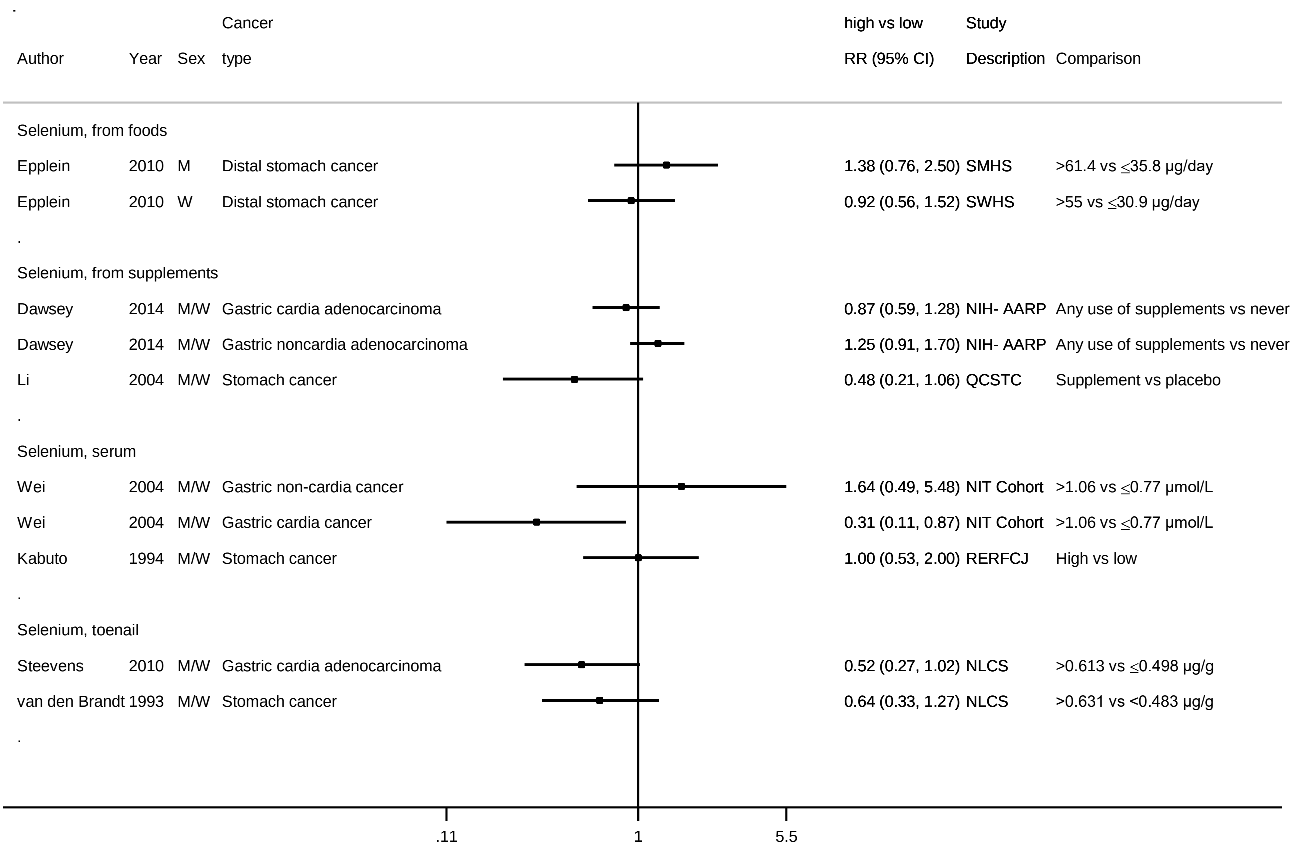
Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Reasons for exclusion
Wei, 2004 STM00543 Linxin, China	NIT Cohort, Case Cohort, Age: 40-69 years, M/W, Intervention trial participants	36/ 1 103 15 years	Follow-up visits, contacts with local commune, hospitals, and study medical team	Serum selenium	Mortality, gastric cardia cancer	Per 0.15 µmol/L	0.75 (0.59-0.95)	Age, sex, alcohol consumption, BMI, cholesterol, smoking habits	
						>1.06 vs ≤0.77 µmol/L	0.31 (0.11-0.87)		
		24/ 1 103 15 years			Gastric non-cardia cancer	Per 0.15 µmol/L	0.99 (0.75-1.32)		
						>1.06 vs ≤0.77 µmol/L	1.64 (0.49-5.48)		
Mark, 2000 STM03024 Linxin, China	NIT Cohort, Case Cohort, Age: 40-69 years, M/W, Intervention trial participants	402/ 29 584 5 years	Follow-up visits, contacts with local commune, hospitals, and study medical team	Graphite furnace atomic absorption spectrophotometry, serum selenium	Incidence, gastric cardia cancer	92 vs 52 µg/L	0.47 (0.33-0.65)	Age, sex stratified	Superseded by Wei, 2004
		87/			Gastric non-cardia cancer		1.07 (0.55-2.08)		
		232/			Mortality, gastric cardia cancer		0.59 (0.39-0.90) Ptrend:0.01		
		/68			Non-cardia gastric cancer		1.03 (0.85-2.02) Ptrend:0.98		
You, 2000 STM03076 China	Linqu County Study, China, Prospective Cohort, Age: 35-64 years, M/W, Endoscopy subjects	66/ 2 628 4.5 years	Unknown / not reported	High performance liquid chromatography (HPLC), serum selenium	Incidence, dysplasia of the stomach and gastric cancer	>3.29 vs. 2.48 µg/dL	1.70 (0.80-3.40)		Excluded, dysplasia of the stomach and gastric cancer combined
Kabuto,	RERFCJ,	201/	Cancer registry/	Neutron activation	Mortality,	Low vs high	1.00 (0.59-1.90)	Age, sex, date	Converted to

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Reasons for exclusion
1994 STM10979 Japan	Nested Case Control, Age: 59.00years, M/W, Atomic bomb survivors	20 000 10 years	population register	analysis, serum selenium	stomach cancer			of blood collection, radiation exposure, smoking habits, study area	high versus low
Knekt, 1990a STM13874 Finland	FMCHES, Nested Case Control, Age: 15-99 years, M/W	58/ 39 268 10 years	Cancer registry	Serum selenium	Incidence, stomach cancer Men	≥78 vs <49 µg/L	0.09 Ptrend:<0.01	Smoking habits	Excluded, no confidence intervals
		37/			Women		0.27 Ptrend:0.15		
Nomura, 1987 STM08353 USA	HHP, Case Cohort, Age: 51-75 years, M, Japanese residents of Hawaii	66/ 6 860 11 years	Cancer registry/ hospital records	Neutron activation analysis, serum selenium	Mortality, stomach cancer	<10.31 vs ≥13.31 mcg/dl	0.90 Ptrend:0.88	Age	Excluded, no confidence interval
Selenium, toenail									
Steevens, 2010a STM80060 Netherlands	NLCS, Case Cohort, Age: 55-69 years, M/W	114/ 2 186 16.3 years	Annual record linkage to the Netherlands cancer and pathology registries	Instrumental neutron activation analysis	Incidence, gastric cardia adenocarcinoma	Per 0.06 µg/g	0.91 (0.80-1.02)	Age, sex, alcohol consumption, BMI, smoking status, number of cigarettes smoked per day, smoking duration	The same study as van den Brandt, 1993
						>0.613 vs ≤0.498 µg/g	0.52 (0.27-1.02) Ptrend:0.14		
		40/			Men	Per 0.06 µg /g	0.94 (0.84-1.06)		
		24/			Women		0.73 (0.56-0.95)		
van den Brandt,	NLCS, Case Cohort,	92 total, 72 men, 20	Cancer registry	Instrumental neutron activation analysis	Incidence, stomach cancer	>0.63 vs <0.48 µg /g	0.64 (0.33-1.27) Ptrend:0.47	Age, sex, beta-carotene and	The same study as

Author, Year, 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
1993 STM16077 Netherlands	Age: 55-69 years, M/W	women/ 120 852 3.3 years			All			vitamin C intake, educational level, smoking habits	Steevens, 2010a
					Men		0.40 (0.17-0.96)		
					Women	≤0.63 vs ≤0.48 µg /g	1.68 (0.43-6.54)		

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

Figure 183 RR (95% CI) of stomach cancer for the highest compared with the lowest level of selenium



6 Physical activity

6.1 Total physical activity

Randomised controlled trials

No randomised controlled trial was identified.

Cohort studies:

Summary

Three studies reported on measures of total physical activity (a combination of occupational and non-occupational activities). Study characteristics and results are tabulated.

One study (EPIC, Huerta, 2010) reported a significant inverse association of a score of physical activity and risk of gastric adenocarcinoma. The significant inverse association was observed in non-cardia gastric adenocarcinomas but not in adenocarcinomas of the gastric cardia. In a Japanese study (Inoue, 2008) a significant inverse association was observed in women but not in men. No significant association was observed in a study on Japanese men living in Hawaii (Severson, 1989).

Table 162 Total physical activity and stomach cancer risk. Main study characteristics

Author, Year, 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 STM80131 Denmark,France ,Germany, Greece,Italy, Netherlands, Spain,Sweden, UK	EPIC, Prospective Cohort, Age: 25-75 years, M/W	410/ 420 449 9 years	Combination of methods: cancer registries, health insurance records, pathology records, active follow up, death certificate	Questionnaire Cambridge physical activity index (combination of occupational activity and time spent in sport and cycling)	Incidence, gastric adenocarcinoma	Active versus inactive	0.69 (0.50–0.94) Ptrend=0.006	Age, sex, alcohol consumption, education level, fruit intake, height, smoking status, weight, centre, red and processed meat, total energy intake
		188/			Gastric non-cardia adenocarcinoma		0.44 (0.26–0.74) P trend=0.001	
		123/			Gastric cardia adenocarcinoma		1.05 (0.59–1.86)	
		163/			Stomach cancer, H. pylori -ve		0.22 (0.04–1.27) P trend=0.07	
		33			Stomach cancer, H. pylori +ve		0.70 (0.39–1.27) P trend=0.02	
		148/			Intestinal gastric cancer		0.67 (0.39–1.16)	
		139/			Diffuse gastric cancer		0.69 (0.40–1.20)	
Inoue, 2008 Japan STM80151	JPHC Prospective Cohort general-population Age: 45–74 years, M/W	621 men /79,771 5 years	Notification from major hospitals in study area, population-based cancer registries and death certificates	Questionnaire (average time/day in heavy physical work or strenuous exercise, sitting and standing or walking ; expressed in METs	Stomach cancer	Highest vs lowest	Men 1.04 (0.84-1.29) Women 0.63 (0.42- 0.94) Ptrend : 0.02	Age, area, total energy intake, history of diabetes, smoking status and cigarettes/day in smokers alcohol intake status and amount, BMI

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors
Severson, 1989 Hawaii, US STM15466	Japan Hawaii cancer study, Prospective cohort Japanese men living in Hawaii	172/7686	Hawaii tumour registry	Questionnaire Semi-quantitative estimate of the activity at home and recreational	Mortality stomach cancer	Tertile 3 vs tertile 1	1.34 (0.95-1.95) P trend=0.10	Age, BMI, cigarette smoking

6.1.1.1 Occupational activity

Randomised controlled trials

No randomised controlled trial was identified.

Cohort studies:

Summary

Three studies reported inconsistent results on physical activity at work and stomach cancer risk. Study characteristics and results are tabulated.

One study (NIH-AARP, Cook, 2013) reported a significant increased risk of gastric cardia adenocarcinomas in participants doing heavy work compared to sitting most of the time at work. A significant positive association with moderate/ heavy work activity compared with mainly sitting was also observed in a cohort of Japanese men in Hawaii (Severson, 1989). Work activity was not significantly related with cardia and non-cardia gastric cancer in EPIC (Huerta, 2010).

Table 163 Physical activity at work and stomach cancer risk. Main characteristics of 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
Cook, 2013 STM80180 USA	NIH- AARP, Prospective Cohort, Age: 50-71 years, M/W, Retired	453 cardia and 501 non-cardia gastric adenocarcinoma / 487 732 8 years	Linkage of the cohort with database to state cancer registries	Questionnaire	Incidence, gastric cardia adenocarcinoma	Heavy work vs all day sitting	1.77 (1.01-3.09) Ptrend=0.43	Age,sex, BMI, education, ethnicity, perceived health status, alcohol consumption, smoking, time since quitting, cigarettes/day in current smokers, fruit and vegetable consumption
					Non-cardia gastric adenocarcinoma		0.98 (0.54-1.78)	
Huerta, 2010 STM80131 Denmark,France ,Germany, Greece,Italy, Netherlands, Spain,Sweden, UK	EPIC, Prospective Cohort, Age: 25-75 years, M/W	410/ 420 449 9 years	Combination of methods: cancer registries, health insurance records, pathology records, active follow up, death certificate	Questionnaire Cambridge physical activity index (combination of occupational activity and time spent in sport and cycling)	Incidence, gastric adenocarcinoma	Active versus inactive	0.92 (0.62–1.37)	Age, sex, alcohol consumption, education level, fruit intake, height, smoking status, weight, centre, red and processed meat, total energy intake
		188/			Gastric non-cardia adenocarcinoma		0.82 (0.44–1.52)	
		123/			Gastric cardia adenocarcinoma		0.70 (0.33–1.48)	
		163/			Stomach cancer, H. pylori -ve		1.03 (0.16–6.46)	
		33			Stomach cancer, H. pylori +ve		0.83 (0.40–1.74)	
		148/			Intestinal gastric cancer		0.84 (0.43–1.63)	
		139/			Diffuse gastric		1.07 (0.54–2.11)	

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
					cancer			
Severson, 1989 Hawaii, US STM15466	Japan Hawaii cancer study, Prospective cohort Japanese men living in Hawaii	172/7686	Hawaii tumour registry	Questionnaire Semi-quantitative estimate of the activity at home and recreational	Mortality stomach cancer	Moderate/heavy vs mainly sitting	1.74 (1.08-2.71)	Age, BMI, cigarette smoking

6.1.1.2 Leisure-time physical activity

Randomised controlled trials

No randomised controlled trial was identified.

Cohort studies

Summary

Main results:

Included in leisure-time physical activity were studies that reported on non-occupational activity as an overall score, frequency or duration. Included are also studies that reported on sports activities. Because of differences between studies in the way leisure time physical activity was reported, it was not possible to conduct dose-response meta-analysis. Study results were summarised for the highest compared with the lowest physical activity category. Details of the physical activity assessment in each cohort included in the review are tabulated below.

When comparing the highest versus the lowest leisure-time physical activity, no significant association (inverse) was observed for stomach cancer (9 studies, high heterogeneity). The association was statistically significant for stomach cancer mortality. Non-significant inverse associations were observed for gastric cardia cancer (two studies, no heterogeneity) and for non-cardia gastric cancer (three studies, high heterogeneity). One study (Whittemore, 1985) could not be included in the analysis because of insufficient data. No significant association between exercise habits at college and stomach cancer risk was reported.

Table 164 Main characteristics of physical activity assessment in studies include in the review

Study	Domains	Description of assessment	Validation
Harvard Alumni Health Study (HAHS)	Leisure time	Participation in sports assessed by questionnaire	Not indicated
Whitehall Study	Leisure time	Questionnaire: Walking pace, hobbies/sports (inactive: no physical exertion, moderately active: gardening, home maintenance and woodwork, active: swimming, cycling, and athletics)	Not indicated
British Regional Heart Study (BRHS)	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)	Leisure time Occupational Total	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	Relative validity and reproducibility undertaken; the questionnaire was found to be satisfactory for the ranking of subjects,

		all other sports combined), vigorous non-occupational activity (recreational and household activities causing sweating or faster heartbeat). Recreational and household activities included in the SLR as leisure time activity	less suitable for estimation of energy expenditure. Construct validity by correlation with BMI
Japan Collaborative Cohort Study for Evaluation of Cancer (JACC)	Leisure time	Questionnaire. Sports time, walking time, duration of sports in the school	Not indicated
Nord-Trøndelag Health Study (HUNT)	Leisure time	Questionnaire. Frequency of recreational physical exercise during a week (walking, skiing, swimming, other sports), duration per occasion, and intensity of activity.	Not indicated
Korean National Health Insurance Corporation Study 2002 (KNHIC)	Leisure time	Frequency and duration of vigorous, sweat-producing leisure physical activity	Not indicated
National Institutes of Health – American Association of Retired Persons Diet and Healthy Study (NIH-AARP)	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

Table 165 Leisure-time physical activity and stomach cancer risk. Number of studies in the CUP SLR

	Number
Studies identified	10 (13 publications)
Studies included in forest plot of highest compared with lowest exposure	9
Studies included in linear dose-response meta-analysis	Not enough studies

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

Table 166 Leisure-time physical activity and stomach cancer risk. Summary of the highest versus lowest meta-analysis in the CUP

Note: No meta-analysis of cohort studies was conducted in the 2005 SLR

	CUP		
By outcome	**All studies**	**Incidence**	**Mortality**
Studies (n)	9	6	3
Cases (total number)	6123	5210	1014
RR (95%CI)	0.88 (0.76-1.04)	0.92 (0.74-1.15)	0.81 (0.68-0.97)
Heterogeneity (I^2, p-value)	61.9%, 0.007	73.1%, 0.002	0%, 0.63
By cancer site	**Gastric cardia cancer**	**Non-cardia gastric cancer**	
Studies (n)	2	3	
Cases (total number)	436	696	
RR (95%CI)	0.87 (0.64-1.17)	0.72 (0.45-1.15)	
Heterogeneity (I^2, p-value)	0%, 0.64	72.2%, 0.03	

Table 167 Physical activity and stomach cancer risk. Results of meta-analyses and pooled analyses of prospective studies published after the 2005 SLR

Author, Year	Number of studies	Total number of cases	Studies country, area	Outcome	Comparison	RR (95%CI)	P trend	Heterogeneity (I^2, p value)
Meta-analyses								
Behrens, 2014	9 cohort and 12 case-control studies		North-America, Europe, Australia, Asia	Gastric adenocarcinoma	Highest vs. lowest physical activity (included both recreational, total physical activity)	0.82 (0.76-0.90)	-	NA
				Gastric cardia		0.83 (0.69-0.99)		
				Gastric non-cardia		0.72 (0.62-0.84)		
				Gastric adenocarcinoma subsite unspecified		0.86 (0.76-0.96)		
Abioye, 2014	7 cohort and 4 case-control studies	7944 cases	North-America, Europe, Asia	Gastric cancer	Highest vs. lowest Includes studies on recreational and total physical activity	Cohorts 0.81 (0.68-0.96) Case-control studies 0.78 (0.66-0.91)	-	68.5%, p=0.001 0%, p=0.55
Singh, 2013	7 cohort studies and9 case-control studies	11111 cases	North-America, Europe, Asia	Gastric cancer		Cohorts 0.83 (0.71-0.97) Case-control studies 0.75 (0.69-0.82)	- -	59%, p=0.02 0%, p=0.66

Table 168 Leisure-time physical activity and stomach cancer risk. Main characteristics of studies included in the highest compared to 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
Batty, 2010 STM80095 UK	Whitehall Study, Prospective Cohort, Age: 40-69 years, Men, Civil Servants	101/ 6729 40 years	National health service central registers	Questionnaire	Mortality, stomach cancer	Inactive vs active	1.53 (0.88-2.64) Ptrend=0.04	Age, BMI, employment grade, forced expiratory volume in 1 second, smoking
Huerta, 2010 STM80131 Denmark,France ,Germany, Greece,Italy, Netherlands, Spain,Sweden, UK	EPIC, Prospective Cohort, Age: 25-75 years, M/W	410/ 420 449 9 years	Combination of methods: cancer registries, health insurance records, pathology records, active follow up, death certificate	Questionnaire (Recreational and household activity)	Incidence, stomach cancer	W: 153.7 vs 36.0 MET-hrs/wk M: 114.1 vs 22.0 MET-hrs/wk	1.07 (0.80-1.43)	Age, sex, alcohol consumption, education level, fruit intake, height, smoking status, weight, centre, red and processed meat, total energy intake
		188/			Gastric non-cardia adenocarcinoma		1.15 (0.76-1.76)	
		123/			Gastric cardia adenocarcinoma		0.97 (0.56-1.69)	
		163/			Stomach cancer, H. pylori -ve		0.50 (0.09-2.62)	
		33			Stomach cancer, H. pylori +ve		0.90 (0.53-1.53)	
		148/			Intestinal gastric cancer		0.97 (0.61-1.54)	
		139/			Diffuse gastric cancer		1.42 (0.83-2.43)	
Leitzmann, 2009 STM80055 USA	NIH- AARP, Prospective Cohort,	1016/ 487 732 8 years	Linkage of the cohort with database to state	Questionnaire	Incidence, adenocarcinoma of the upper	≥5 vs 0 times/week	0.73 (0.59-0.89)	Age, BMI, family history of cancer, intakes

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors
	Age: 50-71 years, M/W, Retired		cancer registries		gastrointestinal tract			of fruit and vegetables, marital status, race/ethnicity, red meat intake, smoking status, smoking intensity, time since quitting smoking, alcohol intake, education, gender,
		865/			Men		0.63 (0.51-0.78)	
		151/			Women		0.72 (0.44-1.19)	
		313			Gastric cardia		0.83 (0.58, 1.19)	
		329			Non-cardia gastric		0.62 (0.44, 0.87)	
Yun, 2008 STM80094 Korea	Prospective Cohort, Age: 40- years, MKNHIC,	3633/ 4 449 637 6 years	Cancer registry	Questionnaire	Incidence, stomach cancer	Moderate-high vs low	0.91 (0.86-0.98)	Age, BMI, dietary preference, employment, fasting blood sugar, smoking status, alcohol intake
Sjödahl, 2008a STM80107 Norway	HUNT-I, Prospective Cohort, Age: 20- years, M/W	215/ 73 133 15 years	Histology	Questionnaire	Incidence, gastric adenocarcinoma	High vs no activity	0.5 (0.3-0.9)	Age, BMI, occupation, salt intake, smoking habits, alcohol intake
		179/			Incidence, gastric non-cardia adenocarcinoma		0.5 (0.3-0.9)	

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors
Suzuki, 2007 STM80147 Japan	JACC Prospective Cohort, Age: 40-79 years, M/W	577/ 109 778	Death certificate	Questionnaire	Mortality, stomach cancer, men	<1 hr vs >3 hrs hours/week	1.26 (1.00-1.59)	Age, study area
		277/			Women	<1 hr vs >3 hrs hours/week	1.03 (0.72-1.46)	
Wannamethee, 2001 STM02206 UK	BRHS, Prospective Cohort, Age: 40-59 years, M	59/ 7588 19 years	Cancer registry/ death certificate	Questionnaire/interview	Mortality, stomach cancer	Vigorous vs none/occasional/ light/moderate (times/week)	0.60 (0.14-2.47)	Age, alcohol consumption, BMI, smoking habits, socio-economic status
Severson, 1989 Hawaii, US STM15466	Japan Hawaii cancer study, Prospective cohort Japanese men living in Hawaii	172/7686	Hawaii tumour registry	Questionnaire Semi-quantitative estimate of the activity at home and recreational	Mortality stomach cancer	Moderate or heavy vs mostly sitting	1.45 (1.07-1.97)	Age, BMI, cigarette smoking
Paffenbarger, 1987 STM89950 USA	HAHS & University of Pennsylvania, Cohort, Age: 35-70 years, M/W	41/ 56 683 32 years	Population registry/ death certificates	Questionnaire	Incidence, stomach cancer	≥5 vs <5 hours/week	1.05, p=0.898	Age, sex, birth year

Table 169 Leisure-time physical activity and stomach cancer risk. Main characteristics of studies excluded

Author, Year, 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 STM80183 USA	NIH-AARP, Prospective Cohort, Age: 50-71 years, M/W, Retired	230/ 293 511 12 years	Linkage to the social security administration death master file and the national death index	Questionnaire	Mortality, stomach cancer, ever smokers	Per 1 hours/week	0.99 (0.95-1.04)	Sex, BMI, calories, diabetes, healthy eating index 2010 score, marital status, race, alcohol intake, education	Overlap with Leitzmann, 2009 STM80055
Cook, 2013 STM80180 USA	NIH- AARP, Prospective Cohort, Age: 50-71 years, M/W, Retired	501/ 303 033	Postal service, social security administration death master file, national death index	Questionnaire	Incidence, gastric non-cardia adenocarcinoma	5 times/week vs never times	0.62 (0.34-1.15)	Age, sex, alcohol consumption, BMI, cigarette smoking, ethnicity, fruit consumption, perceived health, education, vegetable consumption	Overlap with Leitzmann, 2009 STM80055
		453/			Incidence, gastric cardia adenocarcinoma	5 times/week vs never times	0.67 (0.33-1.37)		
Smith, 2000b STM00029 England	Whitehall Study, Prospective Civil Servants Cohort, Age: 40-64 years, M,	72/ 6 702 25 years	Cancer registry	Self-completed questionnaire	Mortality, stomach cancer	Inactive vs active	1.07 (0.50-2.10)	Age, BMI, employment grade, lung capacity, smoking habits	Overlap with Batty, 2010 STM80095
Whittemore, 1985 STM00030 USA	CAHS, Nested Case Control, Age: 17- years, M/W	64/ 51 477 50 years	Population registry/ death certificates		Incidence, stomach cancer	≥5 vs <5 hours/week	No association		Data not shown

Figure 184 RR (95% CI) of stomach cancer incidence and mortality for the highest compared with the lowest level of leisure-time physical activity

Author	Year	sex	Cancer	High vs. low (95% CI)	% Weight	WCRF_Code	StudyDescription	contrast
Batty	2010	M	Stomach cancer	0.65 (0.38, 1.13)	6.25	STM80095	Whitehall study	Active vs. Inactive
Huerta	2010	M/W	Gastric adenocarcinoma	1.07 (0.80, 1.43)	13.36	STM80131	EPIC	153.7/114.1 vs. 36.0/22.0 MET-hrs/wk W/M
Leitzmann	2009	M/W	Stomach cancer	0.71 (0.56, 0.91)	15.26	STM80055	NIH-AARP	>=5 vs. 0 times/wk
Sjödahl	2008	M/W	Stomach cancer	0.50 (0.30, 0.90)	6.18	STM80107	HUNT-I	High vs. no activity
Yun	2008	M	Stomach cancer	0.91 (0.86, 0.98)	23.40	STM80094	KNHIC	Moderate/high vs. low
Suzuki	2007	M/W	Stomach cancer	0.84 (0.69, 1.02)	17.85	STM80147	JACC	>3 vs. <1 hr/wk
Wannamethee	2001	M	Stomach cancer	0.60 (0.14, 2.47)	1.15	STM02206	BRHS	Vigorous vs. none/moderate
Severson	1989	M	Stomach cancer	1.45 (1.07, 1.97)	12.76	STM15466	HHP	Moderate/heavy vs. mostly sitting
Paffenbarger	1987	M	Stomach cancer	1.05 (0.50, 2.21)	3.79	STM89950	HAHS	>=5 vs. <5 h/wk
Overall (I-squared = 61.9%, p = 0.007)				0.88 (0.76, 1.04)	100.00			

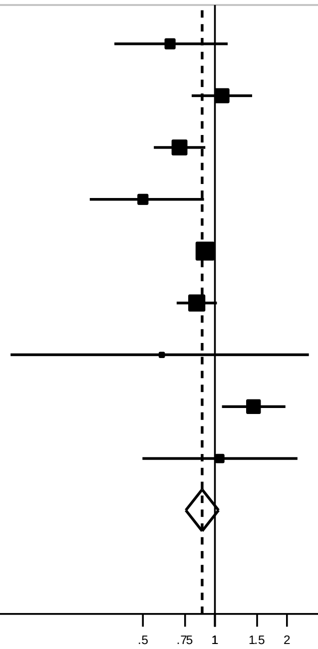


Figure 185 RR (95% CI) of stomach cancer for the highest compared with the lowest level of leisure-time physical activity, stratified by outcome

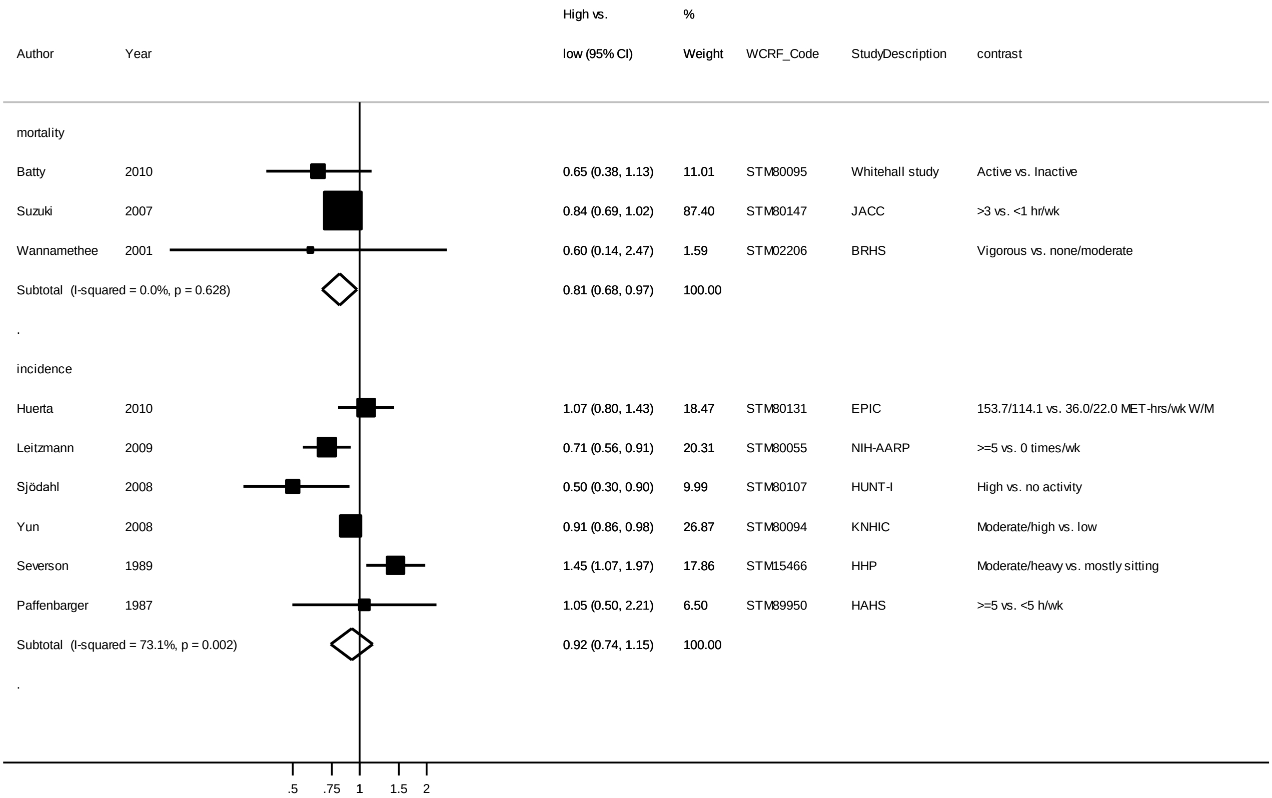
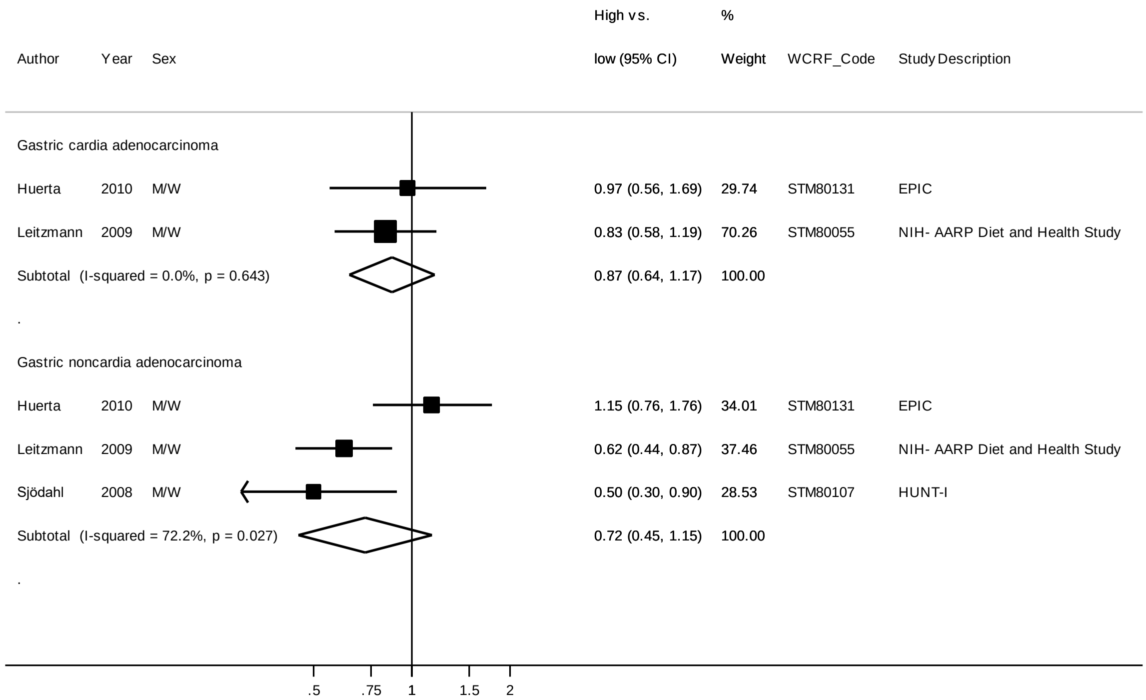


Figure 186 RR (95% CI) of stomach cancer for the highest compared with the lowest level of leisure-time physical activity by cancer site



6.1.1.4 Transportation (walking)

Randomised controlled trials

No randomised controlled trial was identified.

Cohort studies:

Summary

None of the three identified studies reported a significant association between walking or walking pace and incidence or mortality for stomach cancer.

Table 170 Walking and stomach cancer risk. Main study characteristics.

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors
Batty, 2010 STM80095 UK	Whitehall Study, Prospective Cohort, Age: 40-69 years, Men, Civil Servants	101/ 6729 40 years	National health service central registers	Questionnaire	Mortality, stomach cancer	Walking pace Slower vs faster	1.03 (0.43-2.50)	Age, BMI, employment grade, forced expiratory volume in 1 second, smoking
Huerta, 2010 STM80131 Denmark,France ,Germany, Greece,Italy, Netherlands, Spain,Sweden, UK	EPIC, Prospective Cohort, Age: 25-75 years, M/W	410/ 420 449 9 years	Combination of methods: cancer registries, health insurance records, pathology records, active follow up, death certificate	Questionnaire	Incidence, gastric adenocarcinoma	T3 (METs/hour) vs never	1.57 (0.98–2.52)	Age, sex, alcohol consumption, education level, fruit intake, height, smoking status, weight, centre, red and processed meat, total energy intake
		188/			Gastric non-cardia adenocarcinoma		1.45 (0.74–2.84)	
		123/			Gastric cardia adenocarcinoma		1.38 (0.62–3.10)	
		148/			Intestinal gastric cancer		1.34 (0.69–2.62)	
		139/			Diffuse gastric cancer		1.70 (0.76–3.79)	
Suzuki, 2007 STM80147 Japan	JACC Prospective Cohort, Age: 40-79 years, M/W	577/ 109 778	Death certificate	Questionnaire	Mortality, stomach cancer, men	<0.5 1 hr vs >1 hour/week	1.14 (0.94-1.38)	Age, study area
		277/			Women	<0.5 1 hr vs >1 hour/week	1.24 (0.94-1.64)	

6.1.3 Vigorous physical activity

Randomised controlled trials

No randomised controlled trial was identified.

Cohort studies:

Summary

Three studies reported on vigorous physical activity and stomach cancer risk. Study characteristics and results are tabulated.

One study (NIH-AARP, Cook, 2013) reported a significant inverse association of higher strenuous physical activity compared with lower for non-cardia but not for cardia gastric adenocarcinomas. A study in Japan (Inoue, 2008) reported a significant inverse association of higher compared with lower heavy work or strenuous exercise and stomach cancer in men but not in women. Vigorous physical activity was not significantly related to gastric adenocarcinoma risk in EPIC (Huerta, 2010).

6.2 Physical inactivity

Randomised controlled trials

No randomised controlled trial was identified.

Cohort studies:

Summary

None of the two studies identified reported a significant association between time spent sitting or watching TV and risk of stomach cancer.

Table 171 Moderate/vigorous physical activity and stomach cancer risk. Main study characteristics

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors
Cook, 2013 STM80180 USA	NIH- AARP, Prospective Cohort, Age: 50-71 years, M/W, Retired	453 cardia and 501 non-cardia gastric adenocarcinoma / 487 732 8 years	Linkage of the cohort with database to state cancer registries	Questionnaire	Incidence, gastric cardia adenocarcinoma	Strenuous activity >5 times/week vs rarely	0.71 (0.46-1.10) Ptrend=0.41	Age,sex, BMI, education, ethnicity, perceived health status, alcohol consumption, smoking, time since quitting, cigarettes/day in current smokers, fruit and vegetable consumption
					Non-cardia gastric adenocarcinoma		0.58 (0.39-088) Ptrend:0.01	
Huerta, 2010 STM80131 Denmark,France ,Germany, Greece,Italy, Netherlands, Spain,Sweden, UK	EPIC, Prospective Cohort, Age: 25-75 years, M/W	410/ 420 449 9 years	Combination of methods: cancer registries, health insurance records, pathology records, active follow up, death certificate	Questionnaire	Incidence, gastric adenocarcinoma	Vigorous activity >2 hours/week vs none	0.92 (0.67–1.23)	Age, sex, alcohol consumption, education level, fruit intake, height, smoking status, weight, centre, red and processed meat, total energy intake
		188/			Gastric non-cardia adenocarcinoma		0.98 (0.60–1.60)	
		123/			Gastric cardia adenocarcinoma		1.14 (0.68–1.91)	
		163/			Stomach cancer, H. pylori -ve		0.74 (0.14–3.95)	
		33			Stomach cancer, H. pylori +ve		1.15 (0.62–2.11)	
		148/			Intestinal gastric cancer		1.10 (0.66–1.81)	
		139/			Diffuse gastric		0.69 (0.40–1.20)	

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors
					cancer			
Inoue, 2008 Japan STM80151	JPHC Prospective Cohort general-population Age: 45–74 years, M/W	621 men /79,771 5 years	Notification from major hospitals in study area, population-based cancer registries and death certificates	Questionnaire	Stomach cancer	Heavy physical work or strenuous exercise ≥1 hour/day vs none	Men 0.89 (0.81- 0.98) Ptrend:0.01 Women 0.84 (0.70- 1.01) Ptrend : 0.04	Age, area, total energy intake, history of diabetes, smoking status and cigarettes/day in smokers alcohol intake status and amount, BMI

Table 172 Physical inactivity and stomach cancer risk. Main study characteristics

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors
Cook, 2013 STM80180 USA	NIH- AARP, Prospective Cohort, Age: 50-71 years, M/W, Retired	453 gastric cardia and 501 non-cardia gastric cancer/ 303 033	Postal service, social security administration death master file, national death index	Questionnaire	Incidence, gastric non-cardia adenocarcinoma	Time watching TV >7 hours/day vs <1 hour/day	Gastric cardia 1.36 (0.60- 3.06)	Age, sex, alcohol consumption, BMI, cigarette smoking, ethnicity, fruit consumption, perceived health, education, vegetable consumption
							Non-cardia gastric cancer 0.94 (0.42- 2.11)	
						Time sitting >9 hours/day vs <3 hours/day	Gastric cardia 1.00 (0.62-1.61)	
							Non-cardia gastric cancer 0.82 (0.46- 1.47)	
Suzuki, 2007 STM80147 Japan	JACC Prospective Cohort, Age: 40-79 years, M/W	577/ 109 778	Death certificate	Questionnaire	Mortality, stomach cancer, men	Time watching TV >2 vs <2 hours/week	1.13 (0.87- 1.45)	Age, study area
		277/			Women	>2 vs <2 hours/week	1.08 (0.77- 1.50)	

8 Anthropometry

8.1.1 Body Mass Index (BMI)

Randomised controlled trials

No randomised controlled trial was identified.

Cohort studies

Summary

Main results:

Nineteen studies (28 916 cases) were included in the dose-response meta-analysis. No significant association of BMI with stomach cancer risk was observed in all studies combined and in studies in men and women. Significant positive association was observed for gastric cardia cancer (seven studies, high heterogeneity) and non-significant inverse association was observed for non-cardia gastric cancer (seven studies, moderate heterogeneity). The difference of associations between cardia and non-cardia gastric cancers was observed in studies in which weight and height was measured (Samanic, 2006; Tran, 2005; medical notes – Lindblad, 2005) or self-reported (Abnet, 2008; Merry, 2007). When the non-overlapping studies (17 studies) were combined with the results of the published pooled analysis of seven cohorts (Lindkvist, 2013), no significant association with stomach cancer was observed (29770 cases).

Nine studies were excluded from the dose-response analysis. One study reported significant inverse associations in men and women (Tretli, 1999). There was a significant trend in incident rates across BMI categories in another cohort (Nomura, 1985a). Non-significant associations were observed in three studies (Tanaka, 2007; Samanic, 2004; Hara, 2000) and in another three studies that reported standardised incidence ratio of obese patients compared with non-obese patients or the general population (Hemminki, 2011; Wolk, 2001; Moller, 1994). There was no significant difference in mean BMI between cases and non-cases in one cohort (Stahelin, 1986).

Two studies that reported results on combined distal oesophageal and cardia stomach cancers were not included in the analysis – MacInnis, 2006 reported significant positive association (98 cases) and Oh, 2005 reported non-significant inverse association (254 cases).

High heterogeneity was observed between studies, which could partly be explained by cancer types (cardia and non-cardia gastric cancer). There was no evidence of a significant publication or small study bias (p=0.29).

No significant association was observed in the dose-response analysis of stomach cancer among non-smokers (three studies, low heterogeneity). Meta-analysis restricted to smokers was not possible. One study (Chen, 2012) reported a non-significant positive association among ever smokers and another study (Abnet, 2008) reported a significant positive association with gastric cardia cancer and a non-significant positive association with gastric non-cardia cancer among smokers.

Sensitivity and stratified analyses:

The summary RR did not change materially when studies were omitted in turn in influence analysis.

Non-significant associations with stomach cancer were observed in analyses stratified by study size, publication year, years of follow-up, in studies in which weight and height were self-assessed and in those in which they were measured. Significant positive association was observed in North American studies (three studies, no heterogeneity) but not in European and Asian studies.

Among the subgroups by sex, geographic location, and BMI assessment method, positive associations with gastric cardia cancer and inverse associations with non-cardia gastric cancer were observed. For gastric cardia cancer, the positive associations were significant in European studies (three studies, high heterogeneity), North American studies (two studies, no heterogeneity), and in the studies of self-assessed weight and height (three studies, no heterogeneity). For non-cardia gastric cancer, the inverse associations were significant in the only study reported results in men (Samanic, 2006) or in Asians (Tran, 2005). Other associations among the subgroups were not significant.

Non-linear dose-response meta-analysis:

There was evidence of non-linear relationships between BMI and stomach cancer (13 studies) and its subsites (all $p<0.001$). For stomach cancer, a significant risk increase was observed for BMI above 31 kg/m^2. For gastric cardia cancer, a steeper curve was observed, with significant increased risk from 26 kg/m^2 (five studies). For gastric non-cardia cancer, significant decreased risk was observed with an increase of BMI, which leveled off at 27 kg/m^2 (five studies).

Study quality:

Some studies recruited specific populations: participants of the Linxin NIT cohort were randomly assigned to 1 of 8 vitamin/mineral trials (Tran, 2005). BMI was from <20 to ≥23 kg/m^2 in this study. Andreotti, 2010 recruited pesticides applicators and their spouses in America. The study of atomic-bomb survivors (LSS) (Sauvaget, 2005) estimated 17% participants were lost due to migration. BMI was from <19 to >24 kg/m^2 in this study. Sensitivity analysis showed that none of these studies had a strong influence in the summary RR.

Loss to follow-up was low in most studies and cancer outcome was confirmed using medical notes or record linkage in the cancer registries in most studies.

About half of the studies included in the dose-response analysis measured height and weight of the study participants, another half used self-reported measurements, and one study used medical records. Sensitivity analysis showed that studies with self-reported height and weight showed overall positive although non-significant association while studies in which height and weight were measured showed no significant association on average. A significant positive association was observed on average on studies that adjusted for some indicators on socioeconomic status but no significant association was observed in studies that did not control for it. All studies included in the dose-response analysis were adjusted for age and sex. None of the studies were adjusted for Helicobacter pylori status.

Table 173 BMI and stomach cancer risk. Number of studies in the CUP SLR

	Number
Studies identified	30 (38 publications)
Studies included in forest plot of highest compared with lowest exposure	23 (24 publications)
Studies included in linear dose-response meta-analysis	19
Studies included in non-linear dose-response meta-analysis	13

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

Table 174 BMI and stomach cancer risk. Summary of the linear dose-response meta-analysis in the 2005 SLR and CUP

	2005 SLR	**CUP**
Increment unit used	5 kg/m^2	5 kg/m^2
Studies (n)	8	19
Cases (total number)	2817	28 916
RR (95%CI)	0.99 (0.90-1.09)	1.01 (0.96-1.06)
Heterogeneity (I^2, p-value)	44.0%, 0.06	57.5%, 0.001
P value Egger test	0.7	0.29
Sex:		
Men		
Studies (n)	6	11
Cases	965	18 619
RR (95%CI)	0.95 (0.82-1.10)	1.00 (0.90-1.10)
Heterogeneity (I^2, p-value)	-	73.4%, <0.001
Women		
Studies (n)	3	9
Cases	270	6137
RR (95%CI)	1.10 (0.95-1.27)	0.98 (0.92-1.05)
Heterogeneity (I^2, p-value)	-	25.1%, 0.22
Cancer site	Proximal stomach cancer	Gastric cardia cancer

Studies (n)	3	7
Cases	1367	2050
RR (95%CI)	1.32 (0.86-2.01)	1.23 (1.07-1.40)
Heterogeneity (I^2, p-value)	-	55.6%, 0.04
	Distal stomach cancer	Non-cardia gastric cancer
Studies (n)	2	7
Cases	555	2432
RR (95%CI)	0.79 (0.61-1.02)	0.93 (0.85-1.02)
Heterogeneity (I^2, p-value)	-	35.4%, 0.16
Stratified analyses in the CUP		
Outcome*	Incidence	Mortality
Studies (n)	15	5
Cases	26 501	2818
RR (95%CI)	1.00 (0.95-1.07)	1.04 (0.98-1.09)
Heterogeneity (I^2, p-value)	63.4%, <0.001	0%, 0.41
Other subgroups	Non-smokers	Men, Gastric cardia cancer**
Studies (n)	3	3
Cases	1271	360
RR (95%CI)	1.00 (0.87-1.16)	1.13 (0.98-1.30)
Heterogeneity (I^2, p-value)	28.9%, 0.25	0%, 0.65
	All CUP studies and Pooling Projects	
Studies (n)	-	24
Cases (total number)	-	29 770
RR (95%CI)	-	1.01 (0.96-1.06)
Heterogeneity (I^2, p-value)	-	60.0%, 0.001
P value test publication bias	-	0.26

*Only incident studies reported results by cancer site. **In addition, one study (Samanic, 2006) reported results on cancers other than gastric cardia in men and one study (Lindblad, 2005) on gastric cardia cancer in women. None of the studies reported on non-cardia gastric cancer in women (see figure below).

Other stratified analyses of stomach cancer and its subsites in the CUP

Geographic area:	**Stomach**	**Gastric cardia cancer**	**Non-cardia gastric cancer**
Asia			
Studies (n)	7	2	1

RR (95%CI)	0.99 (0.92-1.07)	1.08 (0.73-1.59)	0.63 (0.42-0.94)
Heterogeneity (I^2, p- value)	40.0%, 0.13	54.4%, 0.14	-
Europe			
Studies (n)	9	3	4
RR (95%CI)	0.98 (0.91-1.05)	1.27 (1.01-1.60)	0.93 (0.83-1.04)
Heterogeneity (I^2, p- value)	51.3%, 0.04	61.9%, 0.07	32.3%, 0.22
North-America			
Studies (n)	3	2	1
RR (95%CI)	1.11 (1.05-1.06)	1.32 (1.18-1.48)	0.99 (0.87-1.12)_
Heterogeneity (I^2, p- value)	0%, 0.38	0%, 0.50	-
Weight and height:	**Stomach**	**Gastric cardia cancer**	**Non-cardia gastric cancer**
Self-reported			
Studies (n)	8	3	2
RR (95%CI)	1.05 (0.99-1.11)	1.39 (1.25-1.55)	0.98 (0.87-1.10)
Heterogeneity (I^2, p- value)	41.9%, 0.10	0%, 0.50	0%, 0.80
Measured			
Studies (n)	10	3	4
RR (95%CI)	0.95 (0.87-1.03)	1.06 (0.92-1.23)	0.89 (0.75-1.06)
Heterogeneity (I^2, p- value)	60.0%, 0.01	16.9%, 0.30	53.4%, 0.09
Medical records			
Studies (n)	1	1	1
RR (95%CI)	1.10 (0.97-1.24)	1.23 (0.94-1.62)	0.98 (0.78-1.22)
Heterogeneity (I^2, p- value)	-	-	-
Other stratified analyses of stomach cancer in the CUP			
Duration of follow-up	**5-<10 years**	**10-<15 years**	**≥15 years**
Studies (n)	5	6	8
RR (95%CI)	1.07 (0.99-1.17)	1.01 (0.94-1.09)	0.96 (0.87-1.05)
Heterogeneity (I^2, p- value)	45.1%, 0.12	41.8%, 0.13	66.5%, <0.01
Number of cases	**<500 cases**	**500-<1000 cases**	**≥1000 cases**
Studies (n)	9	5	5
RR (95%CI)	0.98 (0.89-1.09)	1.07 (1.00-1.14)	0.97 (0.89-1.06)
Heterogeneity (I^2, p-value)	41.6%, 0.09	45.7%, 0.12	68.7%, 0.01
Publication year	**≤2005**	**>2005**	
Studies (n)	8	11	

RR (95%CI)	1.01 (0.94-1.09)	1.00 (0.94-1.08)	
Heterogeneity (I^2, p-value)	52.3%, 0.04	62.7%, <0.01	
Adjustment for:			
Socioeconomic status	**Not adjusted**	**Adjusted**	
Studies (n)	10	9	
RR (95%CI)	0.97 (0.89-1.06)	1.05 (1.01-1.10)	
Heterogeneity (I^2, p-value)	68.4%, 0.001	7.1%, 0.38	
Smoking			
Studies (n)	5	14	
RR (95%CI)	0.90 (0.81-1.00)	1.04 (1.00-1.09)	
Heterogeneity (I^2, p-value)	50.2%, 0.09	46.2%, 0.03	
Alcohol intake			
Studies (n)	12	7	
RR (95%CI)	0.97 (0.91-1.04)	1.07 (1.02-1.13)	
Heterogeneity (I^2, p-value)	56.9%, 0.01	22.3%, 0.26	
Physical activity			
Studies (n)	14	5	
RR (95%CI)	0.99 (0.93-1.05)	1.06 (0.99-1.14)	
Heterogeneity (I^2, p-value)	55.5%, 0.01	44.9%, 0.12	
Previous or existing illness* **			
Studies (n)	16	3	
RR (95%CI)	1.00 (0.94-1.05)	1.07 (0.99-1.17)	
Heterogeneity (I^2, p-value)	63.2%, <0.001	0%, 0.88	

*** History of gastric ulcer and bleeding, disease at entry (glucose intolerance and diabetes status), reflux

Table 175 BMI and stomach cancer risk. Results of meta-analyses and pooled analyses of prospective studies published after the 2005 SLR

Author, Year	Number of studies	Total number of cases	Studies country, area	Outcome	Comparison	RR (95%CI)	P trend	Heterogeneity (I^2, p value)
Meta-analyses								
Chen, 2013	24 cohorts* (13 cohorts in dose-response analysis)	41 791	Asia, USA, Europe, Australia	Incidence/mortality, Gastric cancer	Per 5 kg/m^2	1.00 (0.94-1.05)		58.8%, <0.001
					≥30.0 vs reference kg/m^2	1.06 (0.99-1.12)		0%, 0.49
					25.0-29.9 vs reference kg/m^2	1.01 (0.96-1.07)		22.2%, 0.24
				Men	Per 5 kg/m^2	1.03 (0.95-1.12)		-
				Women		0.97 (0.90-1.05)		-
				Gastric cardia cancer		1.32 (1.07-1.64)		81.9%, <0.001
				Gastric non-cardia cancer		0.92 (0.85-1.01)		51.0%, 0.05
Pooled-analyses								
Lindkvist, 2013 Me-Can (Oslo, NCS, CONOR, 40-y, VHM&PP, VIP, MPP)	7 cohorts	1210	Austria, Norway, Sweden	Incidence, gastric adenocarcinoma Men Women	Per 5 kg/m^2 High vs low	1.01 (0.91-1.13) 1.00 (0.80-1.24) 0.99 (0.88-1.12) 0.85 (0.61-1.20)		

*23 out of 24 cohort studies identified in this most recent published meta-analysis were included in the present review. The remaining study was a pooling project (Lindkvist, 2013, Me-Can) and was included in the sensitivity analysis in the present review.

Table 176 BMI and stomach 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
Chen, 2012 STM80120 China	CNRPCS, Prospective Cohort, Age: 40-79 years, M	955/ 142 214 15 years	Review of medical records and death certificates	Measured at study baseline	Mortality, stomach cancer			Age, alcohol intake, area, education, smoking	
		757/		BMI 15 to <23.5 kg/m²	All Ever smokers Never smokers Current smokers	Per 5 kg/m²	0.74 (0.59-0.94) 0.74 (0.56-0.96) 0.77 (0.47-1.29) 0.65 (0.45-0.94)		
		198/		BMI 23.5 to <35 kg/m²	All Ever smokers Never smokers	Per 5 kg/m²	0.96 (0.61-1.49) 1.16 (0.71-1.91) 0.51 (0.19-1.35)		Included in the dose-response meta-analysis
Andreotti, 2010 STM80127 USA	AHS[2], Prospective Cohort, M/W, Pesticide applicators and their spouses	54/ 67 947 10 years 41/39 628	Cancer registry	Self-reported height and weight in questionnaire	Incidence, stomach cancer Men	30.0-34.9 vs 18.5-24.9 kg/m² Per 1 kg/m²	1.61 (0.66-3.91) 1.07 (0.99-1.14)	Age, smoking status	Rescaled the RR for the increment unit used
		13/28 319			Women	25.0-29.9 vs 18.5-24.9 kg/m² Per 1 kg/m²	1.38 (0.42-4.53) 0.95 (0.83-1.07)	Age	
Abnet, 2008 STM80081 USA	NIH- AARP, Prospective Cohort, Age: 50-71 years, M/W,	622/ 480 475 8 years 307/	Linkage of the cohort with database to state cancer registries	Self-reported height and weight in baseline questionnaire	Incidence, gastric adenocarcinoma Gastric cardia	≥35 vs 18.5-<25 kg/m²	2.46 (1.60-3.80)	Age, sex, alcohol consumption, cigarette smoking, education, physical activity	Hamling's method was used to calculate RRs for gastric cardia cancer and gastric non-cardia cancer combined and for the non-linear analysis, RRs using the lowermost category as reference
		315/			Gastric non-cardia		0.84 (0.50-1.42)		
		245/			Non-smokers: Gastric cardia	≥35 vs 18.5-<25 kg/m²	2.54 (1.58-4.10)		
					Gastric non-		0.93 (0.52-1.67)	Also adjusted for	

Author, Year, 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
		252/			cardia			ethnicity	
		58/			Smokers: Gastric cardia		3.39 (1.21-9.50)		
		54/			Gastric non-cardia		1.06 (0.31-3.59)	Also adjusted for ethnicity	
Corley, 2008 STM80073 USA	KPMCP, Nested Case Control, M/W	99/206 974 42 years (max)	Cancer registry, individual record review	Measured at physical examination	Incidence, gastric cardia adenocarcinoma	≥30 vs 18.5-24.9 kg/m^2 Per 1 kg/m^2	2.04 (0.99-4.21) 1.04 (0.98-1.09)	Age, sex, ethnicity, year of examination	Rescaled the RR for the increment unit used (Included in the analysis of gastric cardia cancer only)
Jee, 2008 STM80154 Korea	KCPS, Prospective Cohort, Age: 30-95 years, M/W (overlapped with KNHIC)	18 684/ 1 213 829 10.8 years 14 568/770 556 4 116/443 273	Cancer registry and hospital records	Measured at health examination	Incidence, stomach cancer Men Women	≥30 vs 23-24.9 kg/m^2	 1.31 (1.05-1.64) 0.84 (0.64-1.11)	Age, smoking	Distributions of person-years and mid-points of exposure categories, RRs for men and women combined using fixed model, and for the non-linear analysis, RRs with the lowermost category as reference using the Hamling's method
Persson, 2008a STM80187 Japan	JPHC, Prospective Cohort, Age: 40-69 years, W	368/ 44 453 12 years	Active patient notification from hospitals, cancer registries and	Measured height and weight	Incidence, stomach cancer	≥25 vs ≤19.9 kg/m^2	0.74 (0.53-1.04)	Age, family history of gastric cancer, study area	Mid-points of exposure categories
		97/			Differentiated gastric cancer		1.12 (0.57-2.21)		

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Missing data derived for analyses
		242/	death cert.		Undifferentiated gastric cancer		0.60 (0.39-0.91)		
Sjödahl, 2008a STM80107 Norway	HUNT-I, Prospective Cohort, Age: 20- years, M/W	249/ 73 133 15.4 years	Histology	Measured at clinical examination	Incidence, gastric adenocarcinoma	≥30.0 vs 18.5-24.9 kg/m^2	1.10 (0.70-1.80)	Age, alcohol consumption, occupation, recreational physical activity level, salt intake, smoking	Mid-points of exposure categories, and for the non-linear analysis, RRs with the lowermost category as reference using the Hamling's method
		207/			Gastric non-cardia adenocarcinoma		1.20 (0.70-2.10)		
Fujino, 2007 STM80145 Japan	JACC, Prospective Cohort, M/W	1060/1 314 653 person-years 12 years 719/ 341/		Self-reported in survey	Mortality, stomach cancer Men Women	≥30 vs 18.5-24.0 kg/m^2	1.04 (0.49-2.20) 1.52 (0.82-2.80)	Age, study area	Mid-points of exposure categories, RRs for men and women combined using fixed model, and for the non-linear analysis, RRs with the lowermost category as reference using the Hamling's method
Merry, 2007 STM80089 The Netherlands	NLCS, Case Cohort, Age: 55-69 years, M/W	603/ 5155 13.3 years 163/	Cancer registry and pathology database	Self-reported height and weight at baseline	Incidence, gastric cardia adenocarcinoma	≥30.0 vs 20.0-24.9 kg/m^2 Per 1 kg/m^2	2.73 (1.56-4.79) 1.10 (1.04-1.16)	Age, sex	Rescaled the RR for the increment unit used, mid-points of exposure categories, Hamling's method was used to combine RRs for cardia, distal, and
		235/			Distal gastric adenocarcinoma		0.68 (0.34-1.35)	Age, sex, education level,	

Author, Year, 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
							0.99 (0.94-1.04)	current smoking, number of cigarettes smoked per day, smoking years	NOS gastric cancers and for the non-linear analysis, RRs using the lowermost category as reference
		173/			Not otherwise specified (NOS) gastric adenocarcinoma		0.77 (0.35-1.68) 0.98 (0.93-1.04)	Age, sex, education level, current smoking, history of gastric ulcer and bleeding, number of cigarettes smoked per day, smoking years	
Reeves, 2007 STM80162 UK	MWS, Prospective Cohort, Age: 50-64 years, W	521/ 1 222 630 5.4 years 170/	National health service central registers	Self-reported weight and height	Incidence, stomach cancer	≥30 vs 22.5-24.9 kg/m^2 Per 10 kg/m^2	Floating absolute risks: 1.04 (0.84-1.27) Conventional RR: 1.04 (0.79-1.37) 0.90 (0.72-1.13)	Age, geographic region, physical activity, reproductive history, (smoking status), socio-economic status, alcohol intake	Conventional 95% CIs using Orsini's method, for the non-linear analysis RRs with the lowermost category as reference using the Hamling's method, rescaled the RR for the increment unit used
					Never smokers	Per 10 kg/m^2	0.89 (0.59-1.34)		
		403/1 222 630 7.0 years			Mortality, stomach cancer	≥30 vs 22.5-24.9 kg/m^2 Per 10 kg/m^2	Floating absolute risks: 1.24 (0.99-1.55) Conventional RR: 1.24 (0.91-1.70) 0.98 (0.76-1.26)		
Lukanova, 2006 STM89932 Sweden	NSHDC, Prospective Cohort, Age: 29-61 years, M/W	72/ 68 786 8 years 46/33 424	Cancer registry	Measured at medical examination	Incidence, stomach cancer Men	>27.7 vs 18.5-	1.22 (0.54-2.83)	Age, smoking, calendar year	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
		26/35 362			Women	23.4 kg/m^2 >26 vs 18.5-22.8 kg/m^2	0.57 (0.18-1.74)		
MacInnis, 2006 STM89937 Australia	MCCS, Prospective Cohort, Age: 27-75 years, M/W	98/41 295 11.3 years	Cancer registry	Height and weight measured at baseline	Incidence Gastric non-cardia adenocarcinoma	≥30 vs <25 kg/m^2 Per 5 kg/m^2	1.00 (0.50-1.80) 0.95 (0.70-1.30)	Age, sex, education level, physical activity	Included in the analysis of gastric non-cardia cancer only (identified through reference list of published review)
Samanic, 2006 STM80163 Sweden	SCWC, Prospective Cohort, Age: 18-67 years, M	1281/ 362 552 19 years	Linkage with the National Swedish cancer register	Height and weight measured at baseline	Incidence, stomach cancer	≥30 vs 18.5-24.9 kg/m^2	0.83 (0.66-1.05)	Age, smoking status, calendar year	Distributions of person-years and mid-points of exposure categories
		229/			Gastric cardia cancer		1.09 (0.64-1.85)		
		1052/			Other than cardia stomach cancer		0.78 (0.61-1.01)		
Batty, 2005 STM89936 UK	Whitehall Study, Prospective Cohort, Age: 40-64 years, M	190/ 17 347 38 years	NHS central registry	Measured	Mortality, stomach cancer	≥30.0 vs 18.5-24.9 kg/m^2	1.23 (0.59-2.58)	Age, employment grade, physical activity, smoking habit, marital status, disease at entry, weight loss in the last year, blood pressure-lowering medication, height adjusted forced expiratory volume in one second, triceps skinfold thickness,	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
								systolic blood pressure, plasma cholesterol, glucose intolerance and diabetes status	
Kuriyama, 2005 STM00006 Japan	MCS I, Prospective Cohort, Age: 40- years, M/W	440/ 27 539 9 years 314/12 485	Cancer registry	Self-reported height and weight at baseline	Incidence, gastric adenocarcinoma Men	≥30.0 vs 18.5-24.9 kg/m^2	1.13 (0.53-2.41)	Age, smoking status, alcohol consumption, intake of bean-paste soup, fish, meat, fruits, and green or yellow vegetables, type of health insurance	Mid-points of exposure categories
		126/15 054			Women		0.79 (0.29-2.17)	Also adjusted for menopausal status, age at menarche, age at end of first pregnancy, parity	
		50/			Cardia cancer, men		2.16 (0.51-9.09)		
Lindblad, 2005 STM44427 UK	GPRDC, Nested case-control, Age: 40-84 years, M/W	598/ 4 340 207 person-years 7 years (max) 113/ 192/	GP records	Extracted from GP notes in database	Incidence, gastric adenocarcinoma Cardia Non-cardia	≥30 vs 20-24 kg/m^2	1.21 (0.94-1.56) 1.46 (0.84-2.54) 0.87 (0.54-1.41)	Age, (sex), calendar year, alcohol consumption, reflux, smoking	Mid-points of exposure categories , for the non-linear analysis RRs with the lowermost category as reference using the Hamling's method
		81/			Gastric cardia		1.18 (0.58-2.42)		

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Missing data derived for analyses
					cancer Men				
		32/			Women		1.91 (0.76-4.84)		
Rapp, 2005 STM81020 Austria	VHM&PP, Prospective Cohort, Age: 35-54 years, M/W	264/ 145 931 9.9 years 146/67 447 118/78 484	Cancer registry/ death certificate	Collected at physical examination	Incidence, stomach cancer Men Women	≥30 vs 18.5-24.9 kg/m2 ≥35 vs 18.5-24.9 kg/m2	0.72 (0.40-1.33) 1.34 (0.57-3.13)	Age, occupation, smoking status	Mid-points of exposure categories
Sauvaget, 2005 STM44428 Japan	LSS, Prospective Cohort, Age: 34-98 years, M/W, Atomic bomb survivors	1162/ 38 540 19 years	Cancer registry	Self-reported height and weight	Incidence, stomach cancer	>24 vs <19 kg/m^2	1.05 (0.85-1.29)	Age, sex, area of residence, educational level	Mid-points of exposure categories
Tran, 2005 STM44270 Linxin, China	NIT Cohort, Prospective Cohort, Age: 40-69 years, M/W, Intervention trial participants	1452/ 29 584 15 years 1 089/ 363/	Follow-up visits, contacts with local commune, hospitals, and study medical team	Measured height and weight at physical examinations	Incidence, stomach cancer Cardia Non-cardia	≥23 vs <20 kg/m^2	0.95 (0.80-1.13) 0.68 (0.49-0.93)	Age, sex	Hamling's method was used to calculate RRs for gastric cardia cancer and gastric non-cardia cancer combined, distributions of cases and person-years and mid-points of exposure quartiles
Calle, 2003 STM00970 USA	CPS II, Prospective Cohort, Age: 30- years, M/W	1453/ 900 053 16 years	Death register/ subject or family	Self-reported height and weight a year prior to study baseline	Mortality, stomach cancer	≥35.0 vs 18.5-24.9 kg/m^2		Age, education, smoking status and number of cigarettes smoked, physical	Mid-points of exposure categories, RRs for men and women 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
		945/404 576			Men		1.94 (1.21-3.13)	activity, alcohol use, marital status, race, aspirin use, fat consumption and vegetable consumption	using fixed model
		508/495 477			Women		1.08 (0.61-1.89)	Also adjusted for oestrogen-replacement therapy	
Tulinius, 1997 STM00697 Iceland	Reykjavik Study, Historical Cohort, Age: 50 years, M/W	246/ 22 946 27 years (max) 171/11 366	Cancer registry	Measured at study clinic	Incidence, stomach cancer Men	Per 1 kg/m^2	0.94 (0.89-0.98)	Age	Rescaled the RR for the increment unit used

Table 177 BMI and stomach 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
O'Doherty, 2012 STM80123 USA	NIH- AARP, Prospective Cohort, Age: 50-71 years, M/W	316/ 218 854 9 years 191/ 125/	Linkage of the cohort with database to state cancer registries	Self-reported in baseline questionnaire	Incidence, gastric adenocarcinoma Cardia adenocarcinoma Non-cardia adenocarcinoma	≥35 vs <18.5 kg/m2	3.67 (2.00-6.71) 0.99 (0.34-2.84)	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	Superseded by Abnet, 2008, STM80123
Hemminki, 2011 STM80150 Sweden	Sweden 1964-2006, Historical Cohort, M/W	38/ 30 020 14.8 years	Cancer registry	Patients with obesity diagnosis in hospitals	Incidence, stomach cancer	Obese vs non-obese	1.02 (0.72-1.41)	Age, sex, socio-economic status, period, region	Excluded, standardised incidence ratio
Inoue, 2009b STM80152 Japan	JPHC, Prospective Cohort, Age: 40-69 years, M/W	371/ 27 724 10.2 years 233/ 138/	Cancer registry, hospital admission and death certificate	Measured height and weight	Incidence, stomach cancer Men Women	>25 vs 24.9 kg/m^2	0.78 (0.56-1.08) 0.85 (0.58-1.25)	Age, cholesterol, smoking status, study area, alcohol intake	Superseded by Persson, 2008a, only two BMI categories (results on men were included in high vs low analysis)
Song, 2008	KNHIC,	1251/	Cancer registry,	Measured at	Incidence,	≥30 vs 21-22.9	1.02 (0.75-1.39)	Age, height,	Superseded by Jee,

Author, Year, 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
STM80161 Korea	Prospective Cohort, Age: 40-64 years, W, Post-menopausal (overlapped with KCPS)	170 481 8.75 years	death report and Korea National Health Insurance Corporation	health examination	stomach cancer	kg/m^2 Per 1 kg/m^2	 1.00 (0.98-1.02)	smoking status, alcohol intake, pay level at study entry, physical exercise	2008, STM80154
Tanaka, 2007 STM80137 Japan	TCCJ, Prospective Cohort, Age: 35- years, M/W	129/ 28 443 7 years 65/ 36/	National statistics office	Self-reported height and weight	Mortality, stomach cancer Men Women	High vs low	0.71 (0.43-1.18) 0.53 (0.24-1.20) 0.50 (0.19-1.32)	Age, marital status, alcohol intake, education, physical activity score, smoking history	Excluded, exposure not quantified
MacInnis, 2006 STM89937 Australia	MCCS, Prospective Cohort, Age: 27-75 years, M/W	98/41 295 11.3 years	Cancer registry	Height and weight measured at baseline	Incidence, Lower oesophageal and gastric cardia adenocarcinoma	≥30 vs <25 kg/m^2 Per 5 kg/m^2	3.70 (1.10-12.40) 1.63 (1.08-2.47)	Age, sex, education level, physical activity	Excluded, outcome combined distal oesophageal and gastric cardia cancers (results on non-cardia gastric cancer was included in the analysis)
Jansson, 2005 STM44429 Sweden					Incidence, cardia stomach cancer	≥30 vs ≤21.9 kg/m^2			Superseded by Samanic, 2006, STM80163, no measure of association, reported incidence rates across BMI categories only
Oh, 2005	KNHIC,	5293/	Cancer registry	Measured at	Incidence,	≥30 vs 18.5-		Age, alcohol	Superseded by Jee,

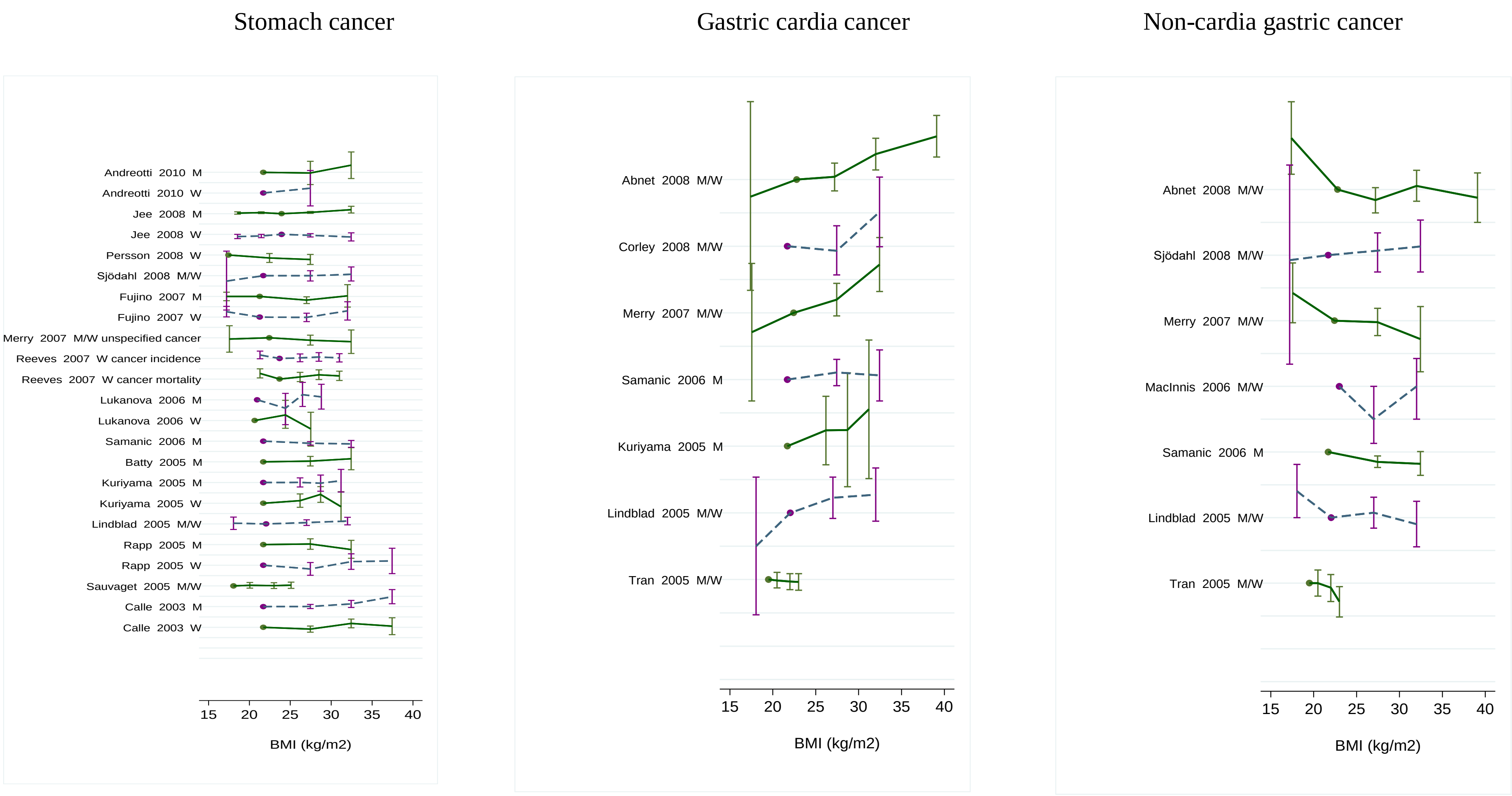
Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Reasons for exclusion
STM80415 Korea	Prospective Cohort, Age: 20- years, M (overlapped with KCPS)	781 283 10 years 1054/		health examination	stomach cancer Never smokers	22.9 kg/m^2	1.25 (0.96-1.63) 2.05 (1.32-3.19)	consumption, area of residence, family history of cancer, physical activity, (smoking habits)	2008, STM80154 (Included in the analysis of non-smokers)
		254/			Distal oesophageal and gastric cardia cancer	27-29.9 vs 18.5-22.9 kg/m^2	0.59 (0.34-1.05)		
		88/			Squamous cell carcinoma in distal oesophagus and gastric cardia		0.11 (0.01-0.76)		
Samanic, 2004 STM22631 USA	Veterans Obesity and Cancer Study, Prospective Cohort, Age: 51 years, M	7486/ 4 500 700 12 years 5298/3 668 486 913/ 4385/	Hospital records	Patients with obesity as diagnosis in hospitals	Incidence White, stomach cancer Cardia Non-cardia	Obese vs non-obese	1.07 (0.95-1.20) 1.38 (1.09-1.77) 1.00 (0.88-1.14)	Age, calendar year	Excluded, only two BMI categories
		2188/832 214 136/ 2052/			Black, stomach cancer Cardia Non-cardia		0.98 (0.79-1.20) 0.78 (0.32-1.91) 0.99 (0.80-1.22)		
Wolk, 2001 STM44273 Sweden	Obesity Cohort, Sweden, Prospective Cohort, Age: 46 years,	59/ 28 129 10.3 years 19/8165	Cancer registry	Patients with obesity as diagnosis in hospitals	Incidence, stomach cancer Men	Obese vs general population	1.00 (0.70-1.30) 0.80 (0.50-1.30)	Age	Excluded, standardised incidence ratio

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Reasons for exclusion
	M/W	40/19 964			Women		1.10 (0.80-1.40)		
Hara, 2000 STM19583 Japan	Saga Prefecture Cohort, Prospective Cohort, Age: 40-69 years, M/W	49/ 2073 14 years 39/1065 10/1008	Cancer registry	Self-reported in questionnaire	Incidence, stomach cancer Men Women	≥24.2 vs 19.8-24.2 kg/m^2	 1.10 (0.47-2.53) 0.58 (0.07-5.21)	Age, alcohol consumption, physical activity, smoking habits	Excluded, two exposure category comparisons only
Tretli, 1999 STM03853 Norway	NSPT, Prospective Cohort, Age: 30-69 years, M/W	9814/ 1 122 852 20 years 6077/ 980/ 586/ 1676/ 3737/ 395/ 418/ 1253/	Cancer registry	Measured	Mortality/incidence Men Stomach cancer Cardia Corpus Pyloric Women Stomach cancer Cardia Corpus Pyloric	Quantile 5 vs Quantile 1	0.65 (0.60-0.70) 1.04 (0.86-1.24) 0.90 (0.72-1.13) 0.77 (0.67-0.88) 0.76 (0.69-0.84) 0.84 (0.62-1.13) 0.84 (0.63-1.12) 0.80 (0.67-0.95)	Age, area of residence, calendar year, year of recruitment	Excluded, exposure not quantified
Nomura, 1995 STM11198 USA	HHP, Prospective Cohort, Age: 45- years, M, Japanese residents of Hawaii	250/ 7972 26 years	Cancer registry/ hospital records	Measured	Incidence, gastric adenocarcinoma	Mean exposure comparison		Age	Excluded, no measure of association (same study as Nomura, 1985a, STM14812; Chyou, 1994, STM12426) which were also excluded)
Chyou, 1994	HHP,	229/	Cancer registry/	Measured	Incidence, gastric	Mean exposure		Age	Excluded, no

Author, Year, 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
STM12426 USA	Prospective Cohort, Age: 46-68 years, M, Japanese residents of Hawaii	7840 23 years	hospital records		adenocarcinoma	comparison			measure of association (same study as Nomura, 1995, STM11198; Nomura, 1985a, STM14812 which were also excluded)
Guo, 1994 STM10900 Linxin, China	NIT Cohort, Nested Case Control, Age: 40-69 years, M/W, Intervention trial participants	538/ 29 584 5 years	Follow-up visits, contacts with local commune, hospitals, and study medical team	Measured height and weight at physical examinations	Incidence, stomach cancer	>23 vs <20 kg/m^2	0.80 (0.60-1.00)	Matched for age and sex, adjusted for family history of cancer in first degree relatives, years of smoking, intervention group	Superseded by Tran, 2005, STM44270
Moller, 1994 STM00004 Denmark	DOS, Prospective Cohort, Age: 9-90 years, M/W	73/ 37 957 4.8 years	Death register and cancer registry	Patients with obesity as diagnosis in hospitals	Mortality/incidence, stomach cancer	Obese vs general populations	1.10 (0.90-1.40)	Age, calendar period	Excluded, standardised incidence ratio
		30/12 331			Men		1.10 (0.70-1.50)		
		43/25 626			Women		1.10 (0.80-1.50)		
Stahelin, 1986 STM15664 Switzerland	BASEL II and III, Nested Case Control, Age: 18-65 years, M	23/ 4224 7 years	Cancer registry/ death certificate		Mortality, stomach cancer	Mean exposure comparison			Excluded, no measure of association
Nomura, 1985a STM14812 USA	HHP, Prospective Cohort, M,	104/ 7868 15 years	Cancer registry/ hospital records	Measured	Incidence, stomach cancer	26.32-44.59 vs 14.31-21.25 kg/m^2	P for trend <0.001	Age	Excluded, no measure of association

Author, Year, 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
	Japanese residents of Hawaii								(same study as Chyou, 1994, STM12426; Nomura, 1995, STM11198, which were also excluded)

Figure 187 RR estimates of stomach cancer by levels of BMI



Note: Corley, 2008 was included in the analysis of gastric cardia cancer only and MacInnis, 2006 in non-cardia gastric cancer only.

Figure 188 RR (95% CI) of stomach cancer for the highest compared with the lowest level of BMI

Author	Year	Sex	high vs low BMI RR (95% CI)	Study Description	Comparison kg/m2
Stomach					
Andreotti	2010	M	1.61 (0.66, 3.91)	AHS	30.0-34.9 vs 18.5-24.9
Andreotti	2010	W	1.38 (0.42, 4.53)	AHS	25.0-29.9 vs 18.5-24.9
Inoue	2009	M	0.78 (0.56, 1.08)	JPHC	>25 vs 24.9
Jee	2008	M	1.31 (1.05, 1.64)	KCPS	≥30 vs 23-24.9
Jee	2008	W	0.84 (0.64, 1.11)	KCPS	≥30 vs 23-24.9
Persson	2008	W	0.74 (0.53, 1.04)	JPHC	≥25 vs ≤19.9
Sjödahl	2008	M/W	1.10 (0.70, 1.80)	HUNT-I	≥30.0 vs 18.5-24.9
Fujino	2007	M	1.04 (0.49, 2.20)	JACC	≥30.0 vs 18.5-24.0
Fujino	2007	W	1.52 (0.82, 2.80)	JACC	≥30.0 vs 18.5-24.0
Reeves	2007	W	1.04 (0.79, 1.37)	MWS	≥30 vs 22.5-24.9
Tanaka	2007	M/W	0.71 (0.43, 1.18)	TCCJ	High vs Low
Lukanova	2006	M	1.22 (0.54, 2.83)	NSHDC	>27.7 vs 18.5-23.4
Lukanova	2006	W	0.57 (0.18, 1.74)	NSHDC	>26 vs 18.5-22.8
Samanic	2006	M	0.83 (0.66, 1.05)	SCWC	≥30 vs 18.5-24.9
Batty	2005	M	1.23 (0.59, 2.58)	Whitehall study	≥30 vs 18.5-24.9
Kuriyama	2005	M	1.13 (0.53, 2.41)	MCS I	≥30.0 vs 18.5-24.9
Kuriyama	2005	W	0.79 (0.29, 2.17)	MCS I	≥30.0 vs 18.5-24.9
Lindblad	2005	M/W	1.21 (0.94, 1.56)	GPRDC	≥30 vs 20-24
Rapp	2005	M	0.72 (0.40, 1.33)	VHM&PP	≥30 vs 18.5-24.9
Rapp	2005	W	1.34 (0.57, 3.13)	VHM&PP	≥35 vs 18.5-24.9
Sauvaget	2005	M/W	1.05 (0.85, 1.29)	LSS	>24 vs <19
Samanic	2004	M Black	0.98 (0.79, 1.20)	United States Veterans	Obese vs Non obese
Samanic	2004	M White	1.07 (0.95, 1.20)	United States Veterans	Obese vs Non-obese
Calle	2003	M	1.94 (1.21, 3.13)	CPS II	≥35.0 vs 18.5-24.9
Calle	2003	W	1.08 (0.61, 1.89)	CPS II	≥35.0 vs 18.5-24.9
Hara	1999	M	1.10 (0.47, 2.53)	Saga Prefecture Cohort	≥24.2 vs 19.8-24.2
Hara	1999	W	0.58 (0.07, 5.21)	Saga Prefecture Cohort	≥24.2 vs 19.8-24.2
Tretli	1999	M	0.65 (0.60, 0.70)	NSPT	Quantile 5 vs Quantile 1
Tretli	1999	W	0.76 (0.69, 0.84)	NSPT	Quantile 5 vs Quantile 1
Cardia					
Abnet	2008	M/W	2.46 (1.60, 3.80)	NIH-AARP	≥35 vs 18.5-<25
Corley	2008	M/W	2.04 (0.99, 4.21)	KPMCP	≥30 vs 18.5-24.9
Merry	2007	M/W	2.73 (1.56, 4.79)	NLCS	≥30.0 vs 20.0-24.9
Samanic	2006	M	1.09 (0.64, 1.85)	SCWC	≥30 vs 18.5-24.9
Kuriyama	2005	M	2.16 (0.51, 9.09)	MCS I	≥30.0 vs 18.5-24.9
Lindblad	2005	M/W	1.46 (0.84, 2.54)	GPRDC	≥30 vs 20-24
Tran	2005	M/W	0.95 (0.80, 1.13)	NIT Cohort	≥23 vs <20
Non-cardia					
Abnet	2008	M/W	0.84 (0.50, 1.42)	NIH-AARP	≥35 vs 18.5-<25
Sjödahl	2008	M/W	1.20 (0.70, 2.10)	HUNT-I	≥30.0 vs 18.5-24.9
Merry	2007	M/W	0.68 (0.34, 1.35)	NLCS	≥30.0 vs 20.0-24.9
MacInnis	2006	M/W	1.00 (0.50, 1.80)	MCCS	≥30 vs <25
Samanic	2006	M	0.78 (0.61, 1.01)	SCWC	≥30 vs 18.5-24.9
Lindblad	2005	M/W	0.87 (0.54, 1.41)	GPRDC	≥30 vs 20-24
Tran	2005	M/W	0.68 (0.49, 0.93)	NIT Cohort	≥23 vs <20
Unspecified					
Merry	2007	M/W	0.77 (0.35, 1.68)	NLCS	≥30.0 vs 20.0-24.9

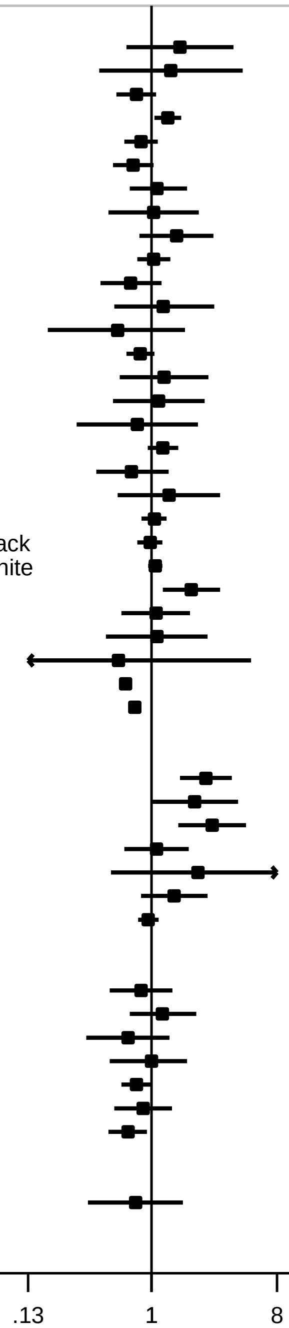


Figure 189 Relative risk of stomach cancer for 5 kg/m^2 increase of BMI

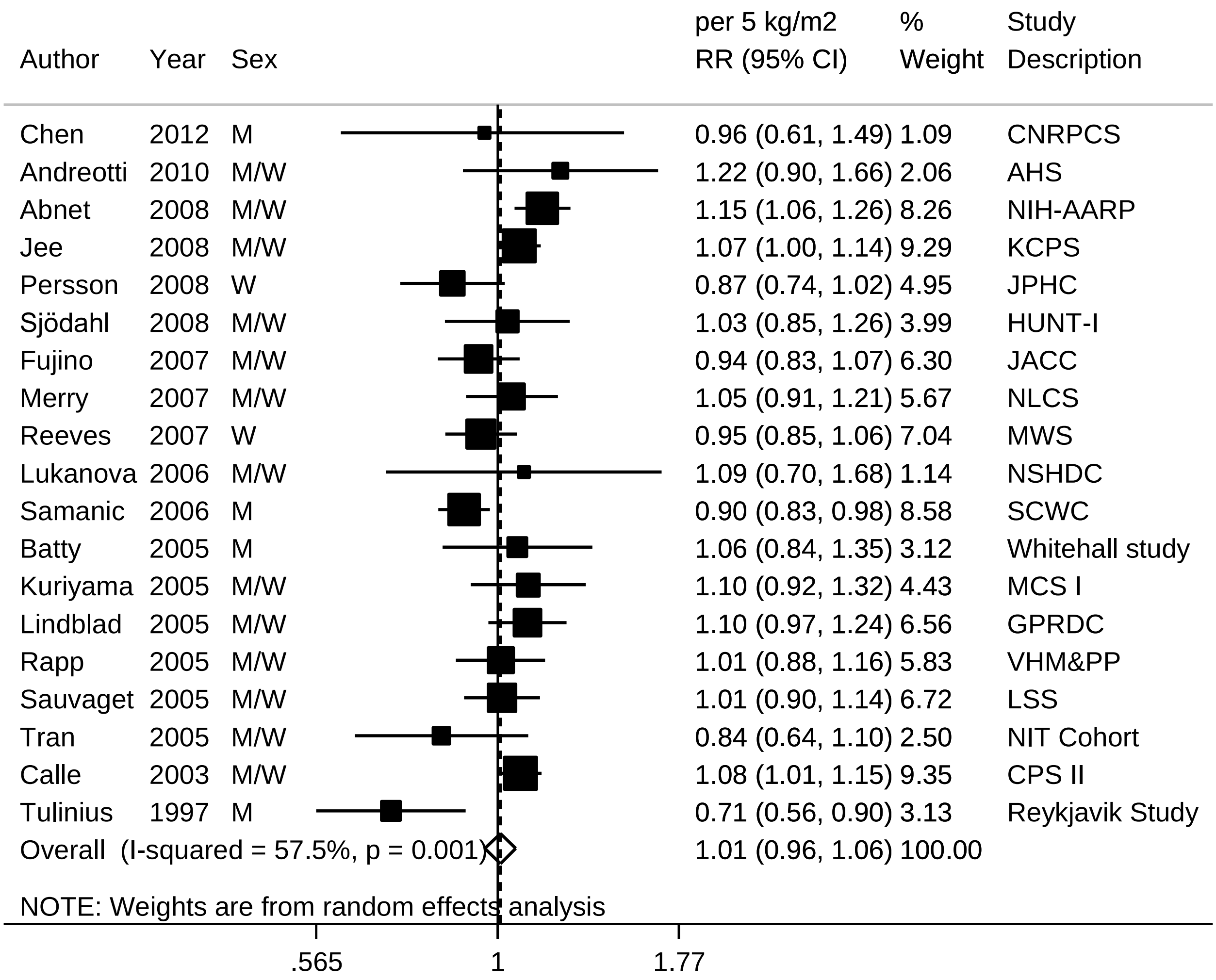
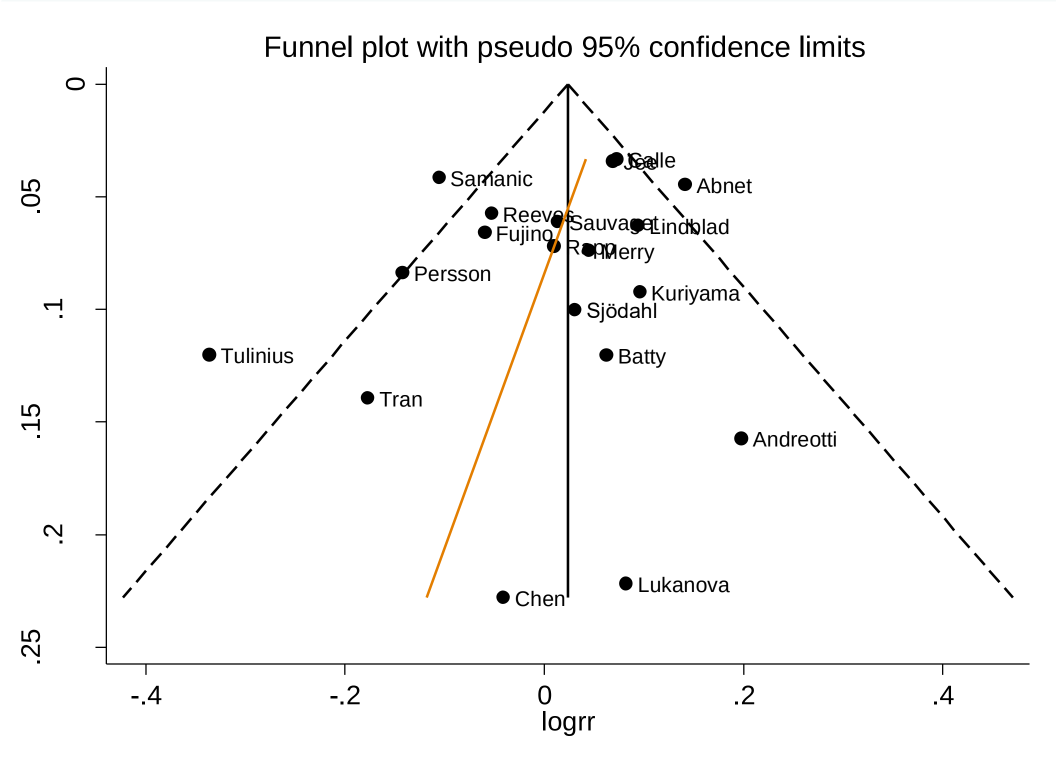


Figure 190 Funnel plot of studies included in the dose response meta-analysis of BMI and stomach cancer



Egger’s test p=0.29

Figure 191 Relative risk of stomach cancer for 5 kg/m² increase of BMI by sex

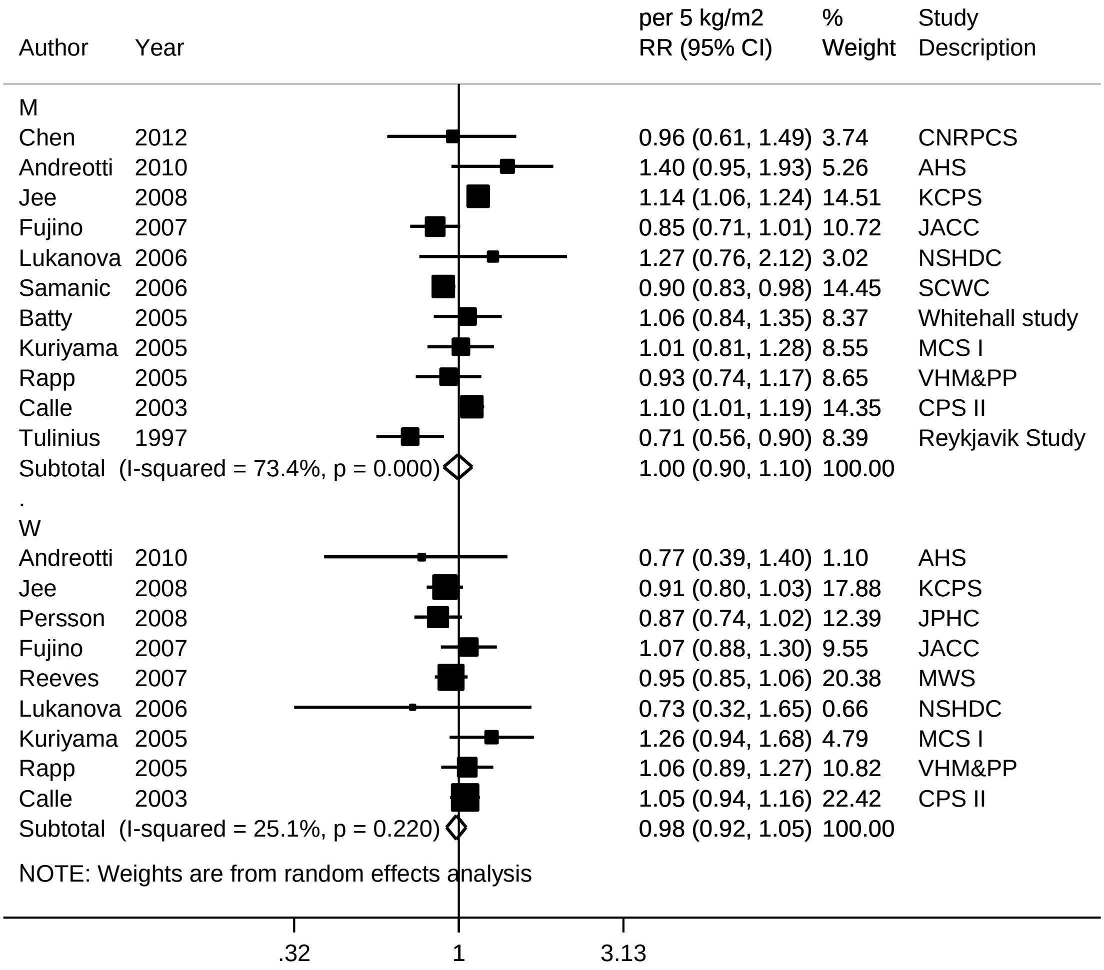


Figure 192 Relative risk of stomach cancer for 5 kg/m^2 increase of BMI by sex and cancer site

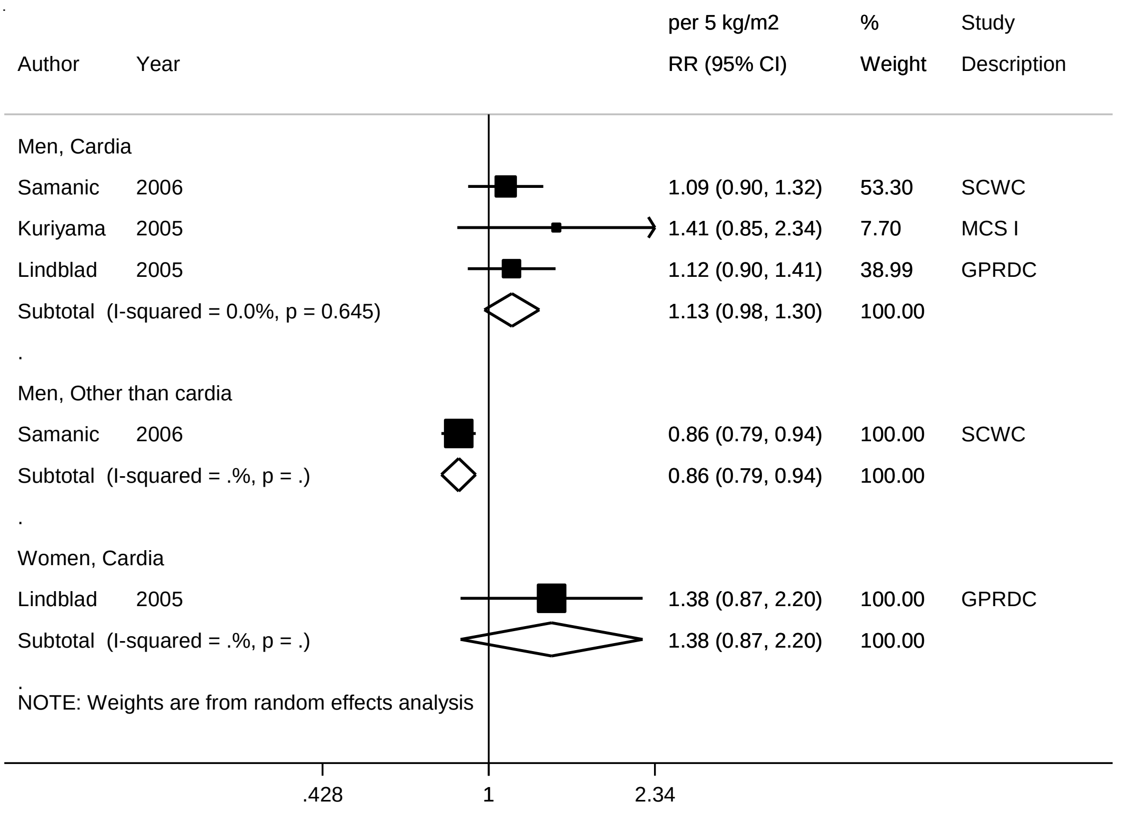


Figure 193 Relative risk of stomach cancer for 5 kg/m² increase of BMI by cancer outcome

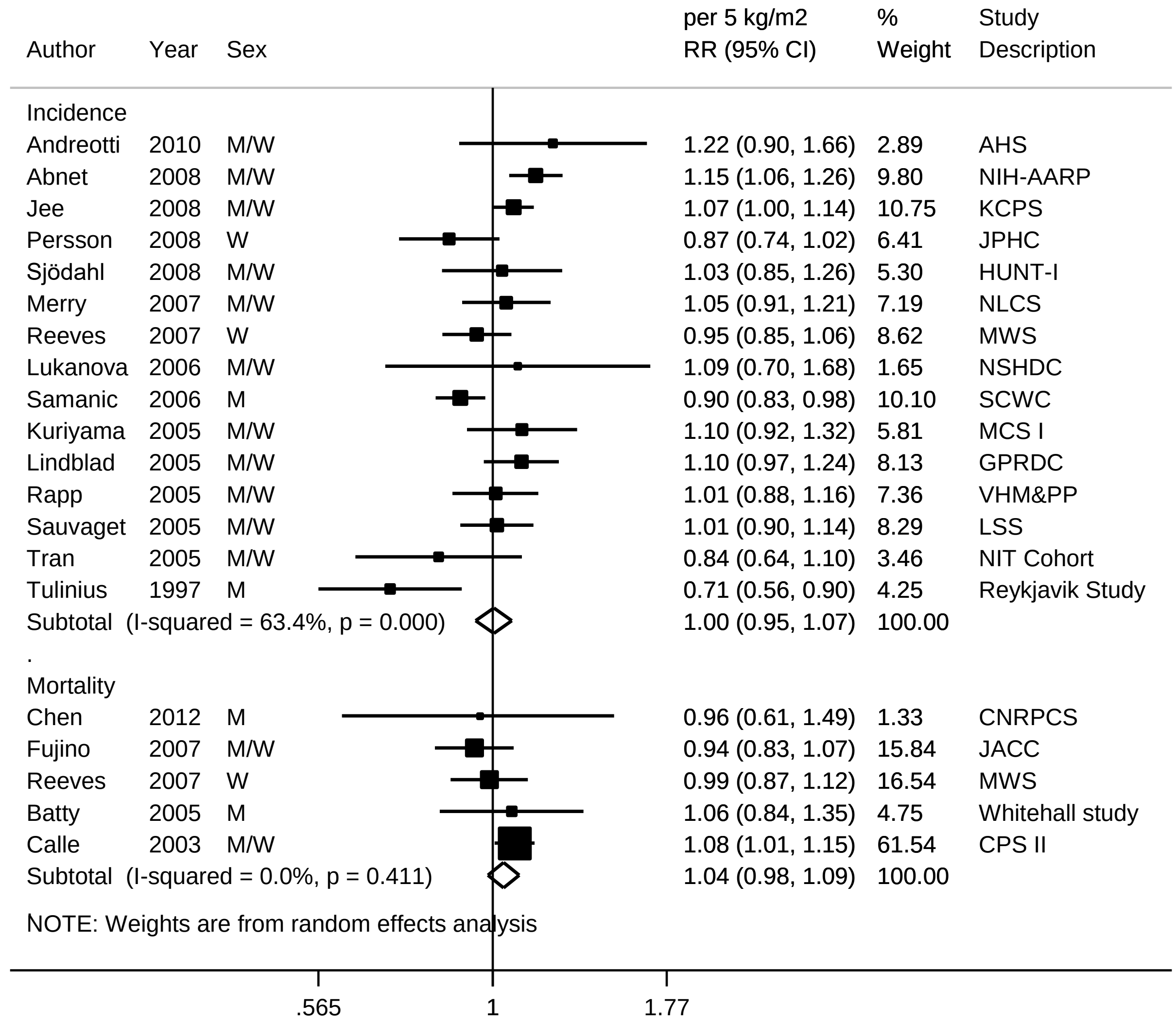


Figure 194 Relative risk of stomach cancer for 5 kg/m^2 increase of BMI by cancer site

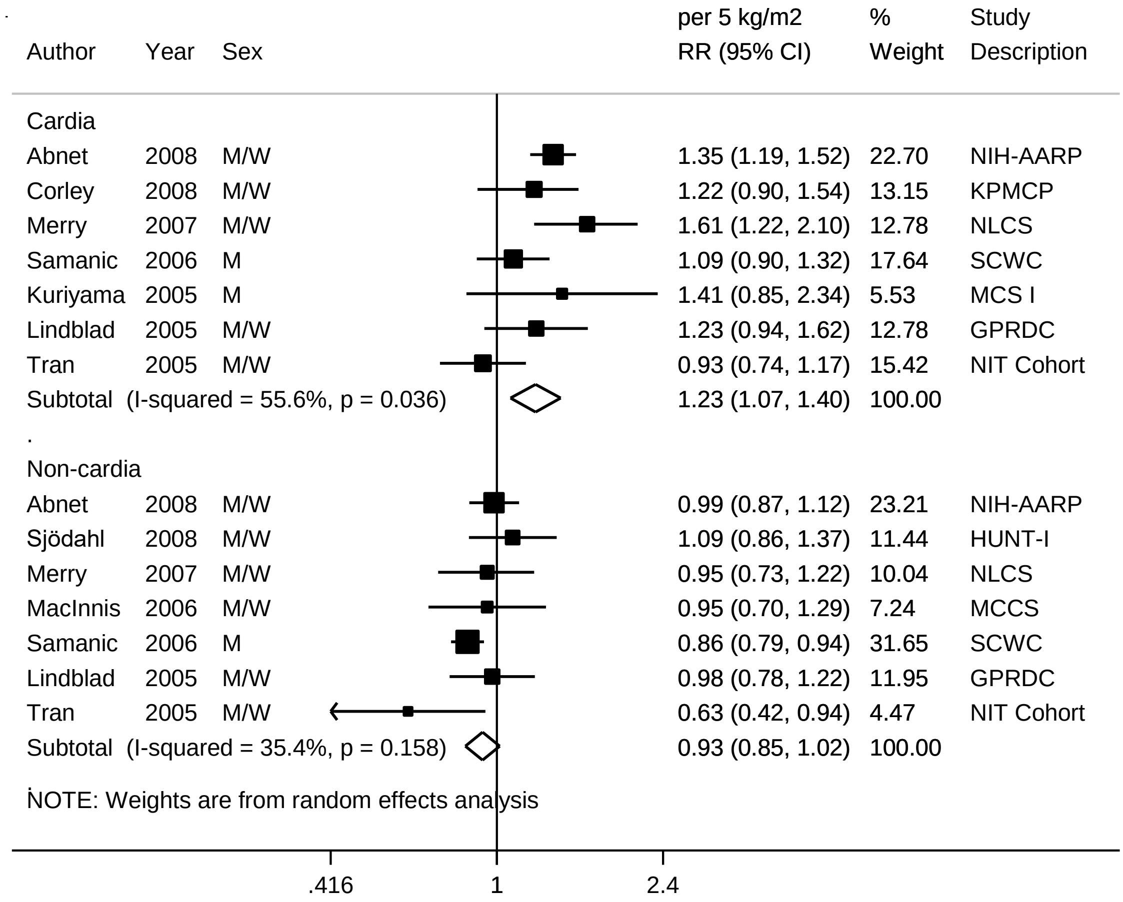


Figure 195 Relative risk of stomach cancer for 5 kg/m^2 increase of BMI by geographic location

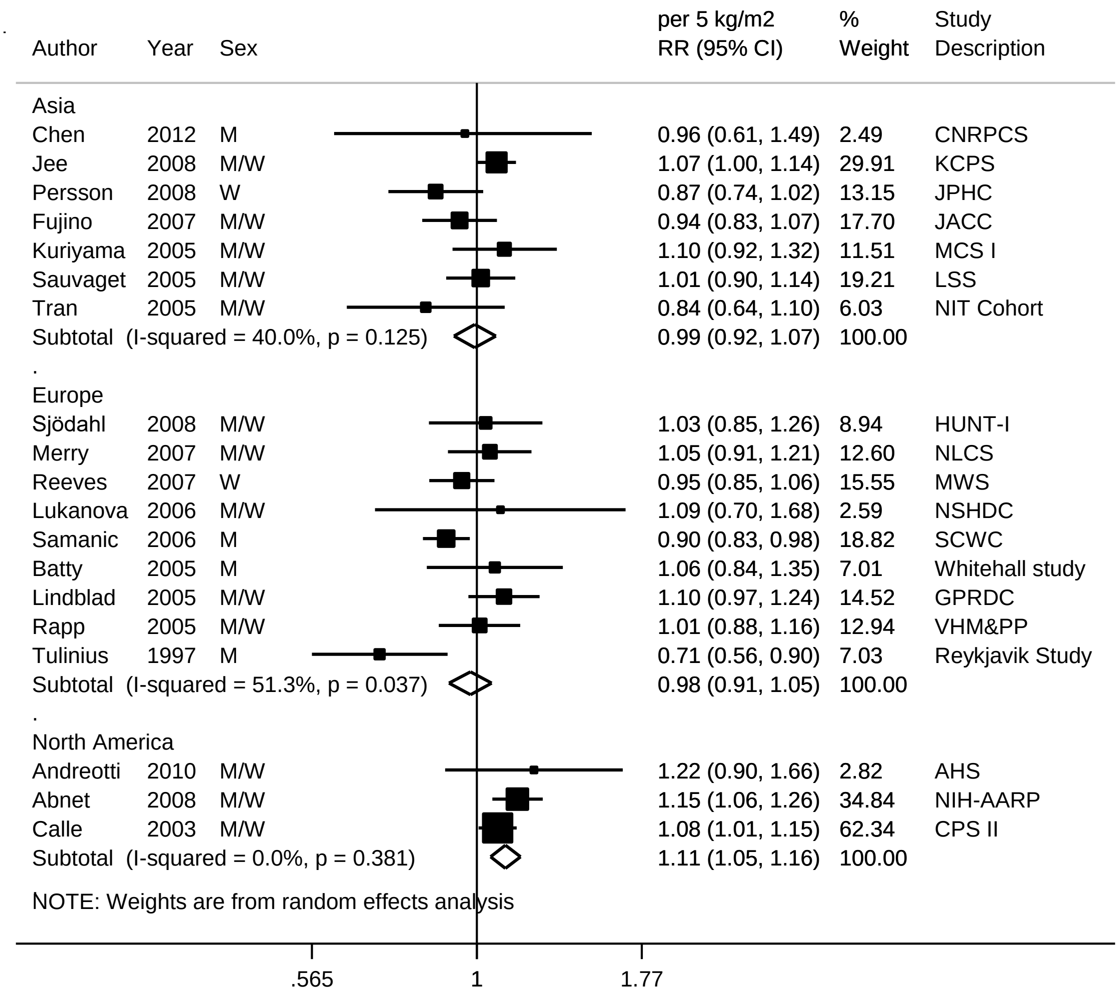


Figure 196 Relative risk of stomach cancer for 5 kg/m^2 increase of BMI by geographic location and cancer site

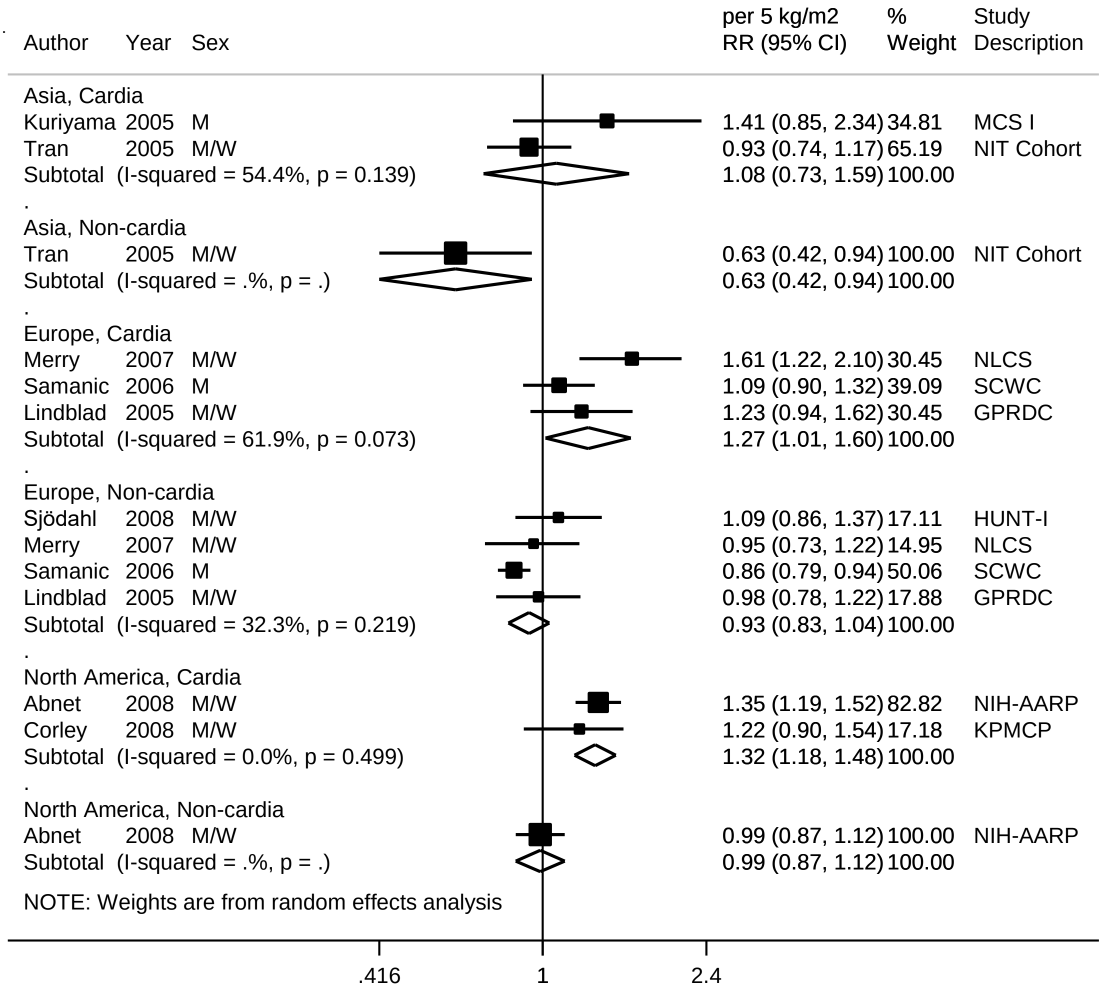


Figure 197 Relative risk of stomach cancer for 5 kg/m^2 increase of BMI by exposure assessment methods

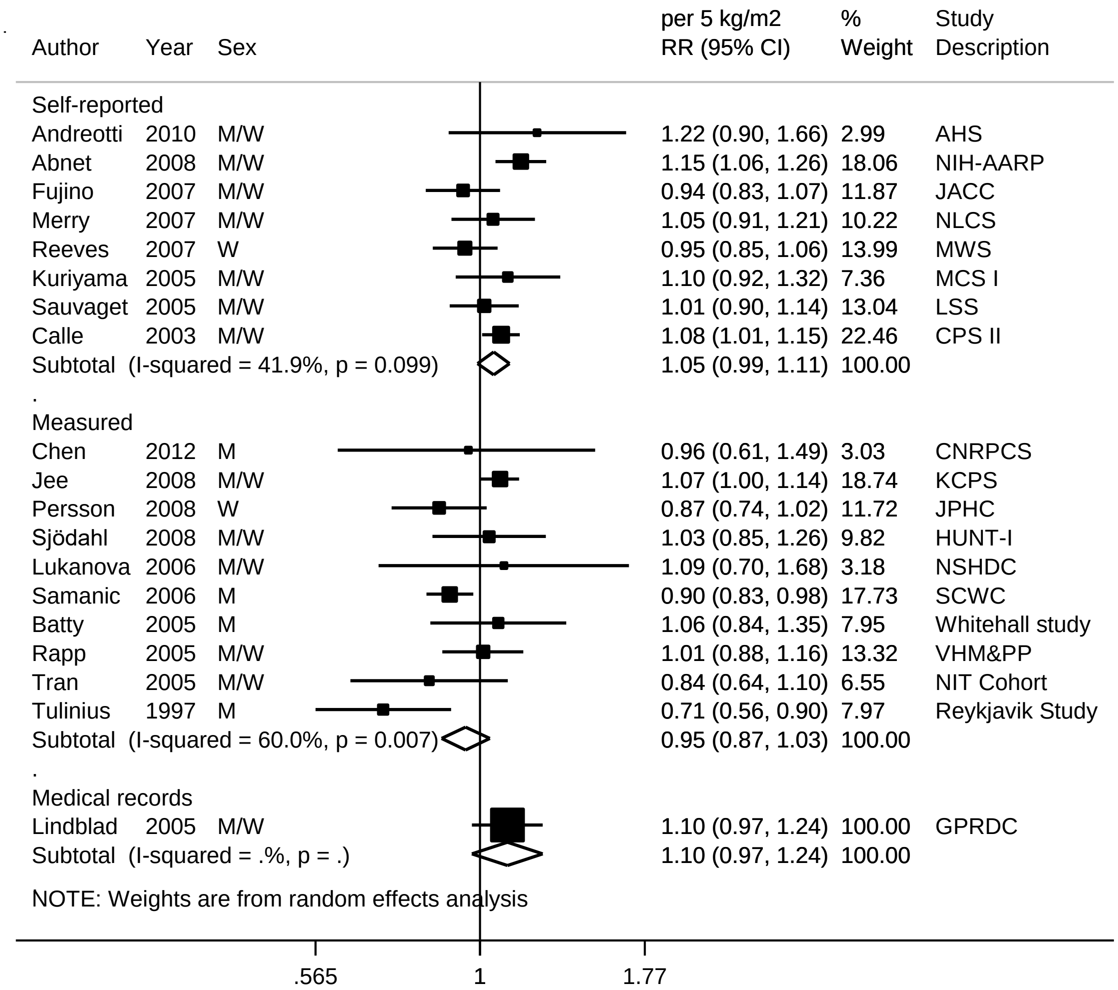


Figure 198 Relative risk of stomach cancer for 5 kg/m^2 increase of BMI by exposure assessment methods and cancer site

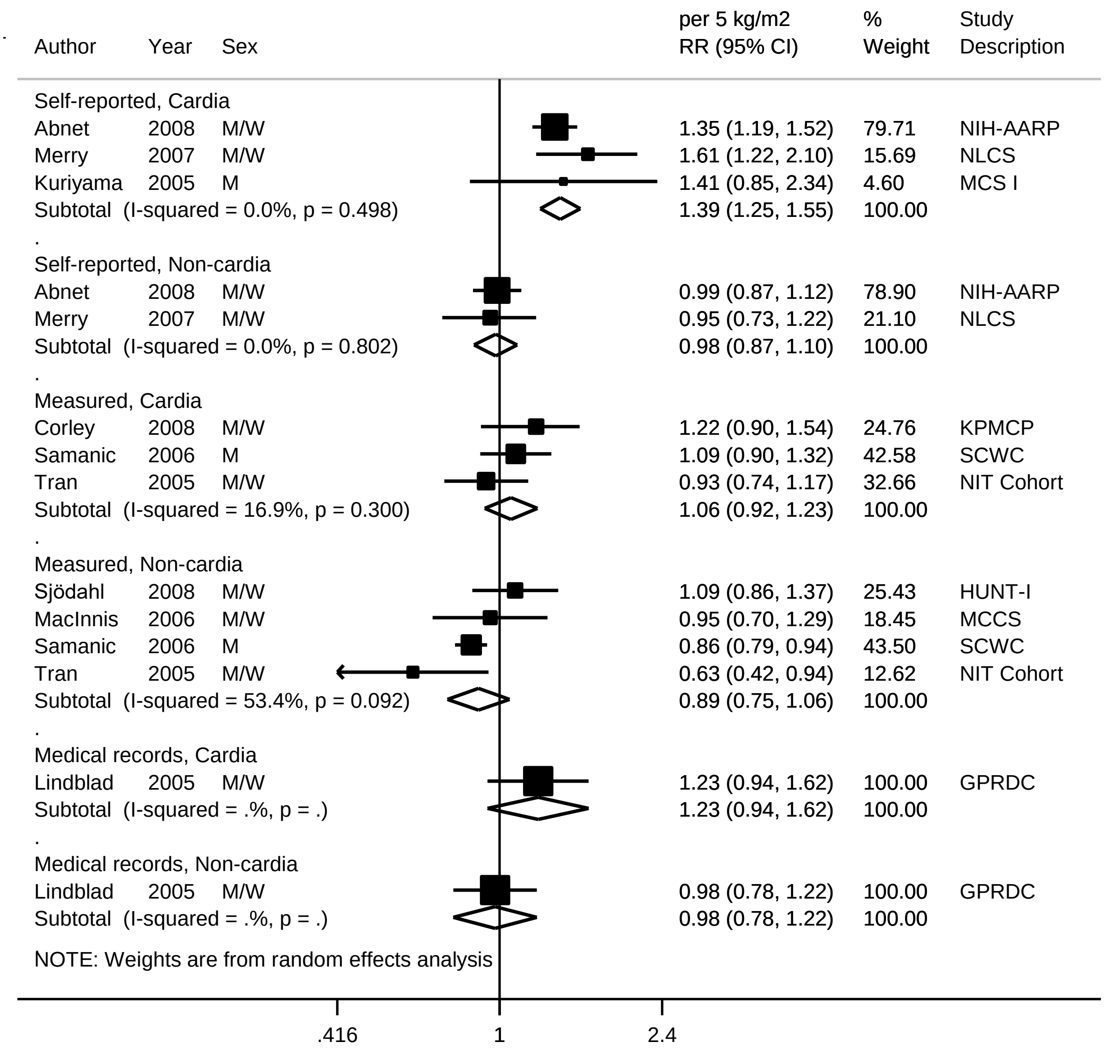


Figure 199 Relative risk of stomach cancer for 5 kg/m² increase of BMI among non-smokers

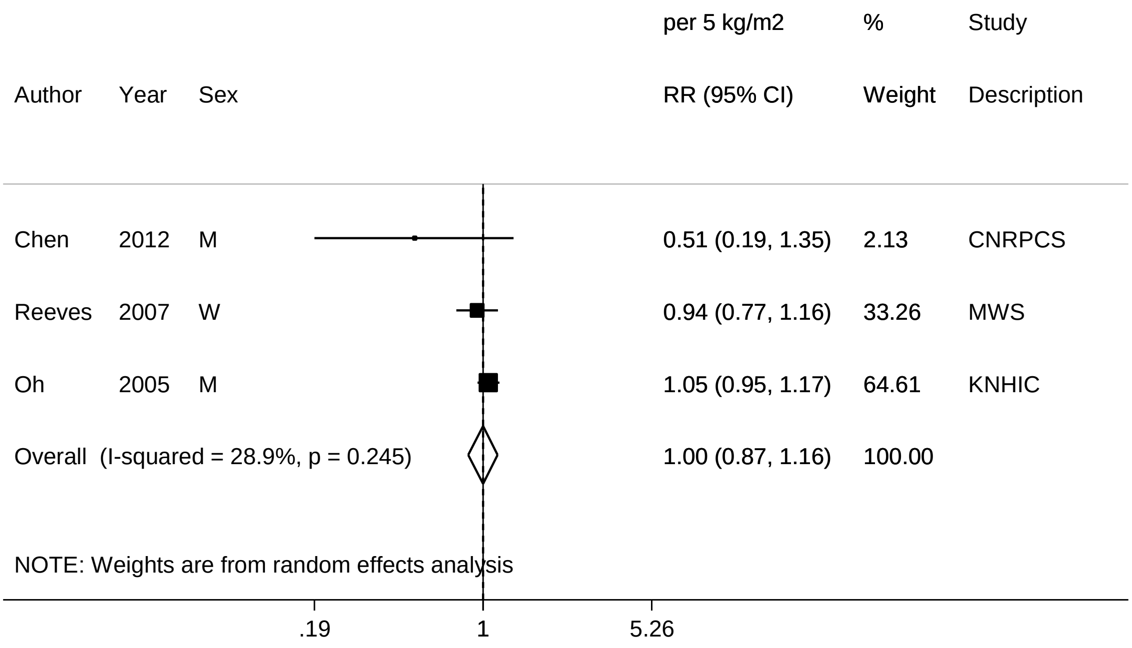
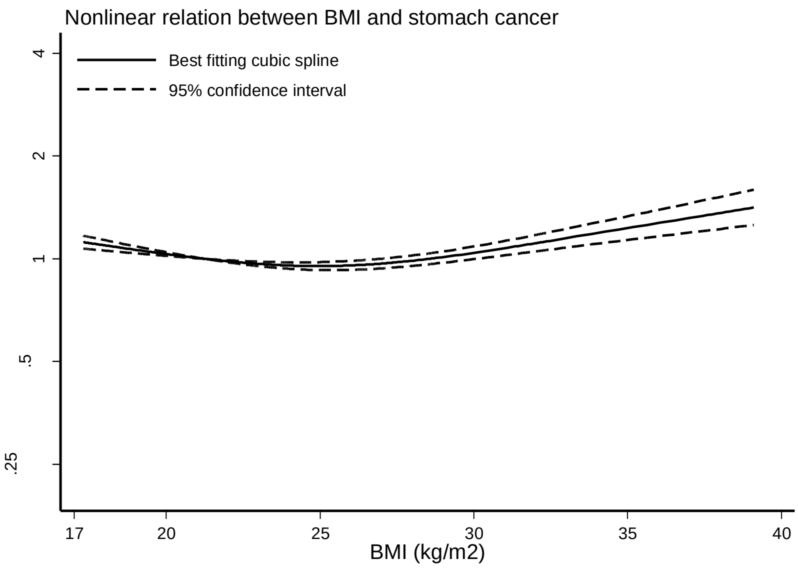


Figure 200 Non-linear dose-response meta-analysis of BMI and stomach cancer



P non-linear <0.001

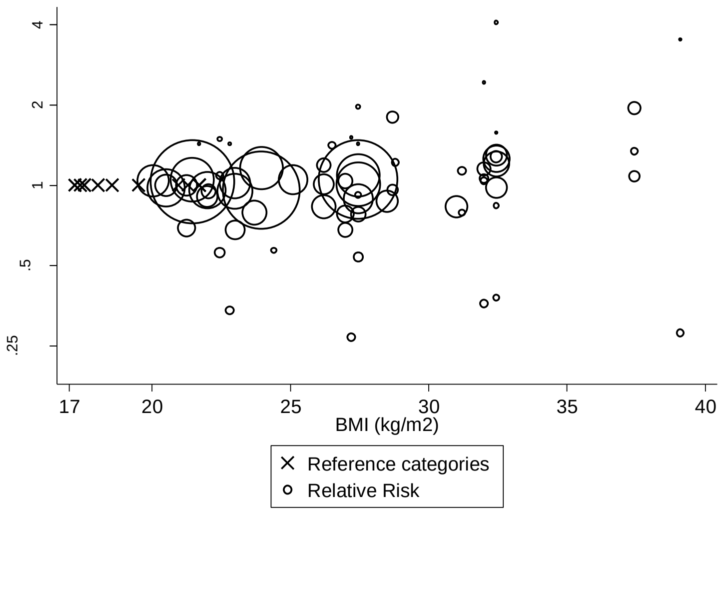
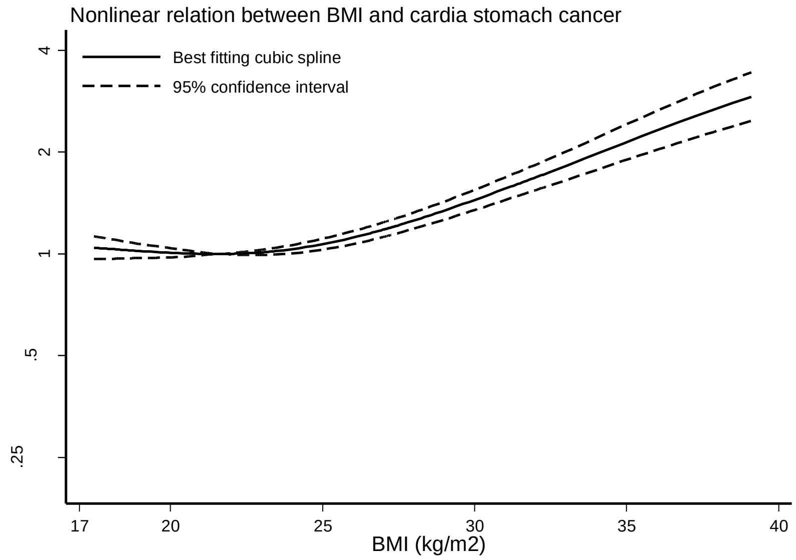


Table 178 Relative risk of stomach cancer and BMI estimated using non-linear models

BMI (kg/m²)	RR (95%CI)
17.20	1.12 (1.07-1.17)
19.50	1.05 (1.03-1.07)
21.30	1.00
23.70	0.96 (0.94-0.98)
25.10	0.95 (0.93-0.98)
27.45	0.98 (0.94-1.01)
31.00	1.07 (1.02-1.13)
37.45	1.34 (1.21-1.48)

Figure 201 Non-linear dose-response meta-analysis of BMI and gastric cardia cancer



P non-linear <0.001

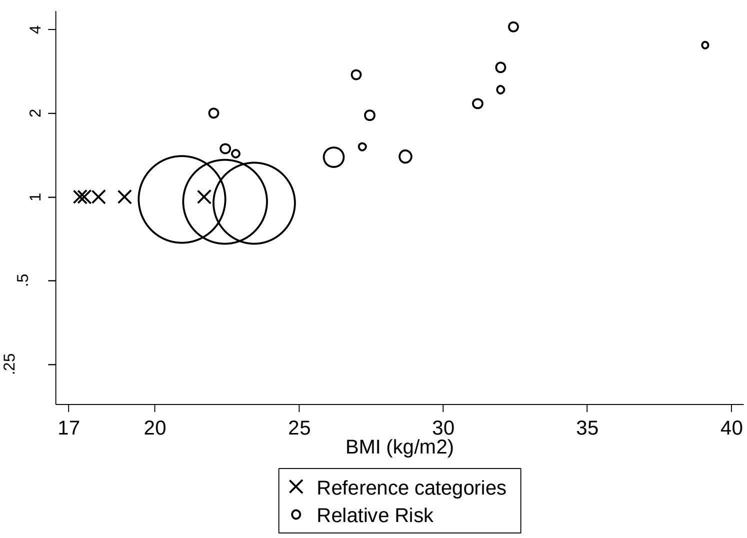
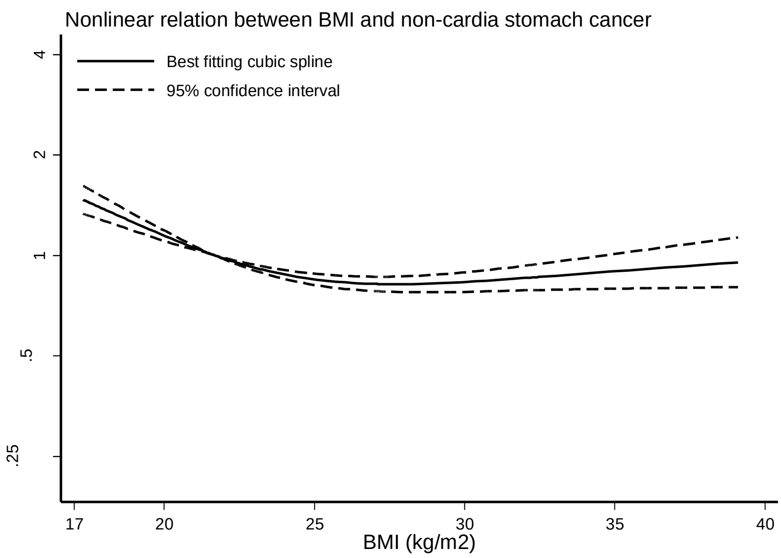


Table 179 Relative risk of gastric cardia cancer and BMI estimated using non-linear models

BMI (kg/m2)	RR (95%CI)
17.40	1.04 (0.96-1.13)
18.95	1.02 (0.97-1.07)
21.70	1.00
23.45	1.02 (1.00-1.04)
26.20	1.13 (1.08-1.18)
28.70	1.32 (1.24-1.40)
32.00	1.68 (1.54-1.84)

Figure 202 Non-linear dose-response meta-analysis of BMI and non-cardia gastric cancer



P non-linear <0.001

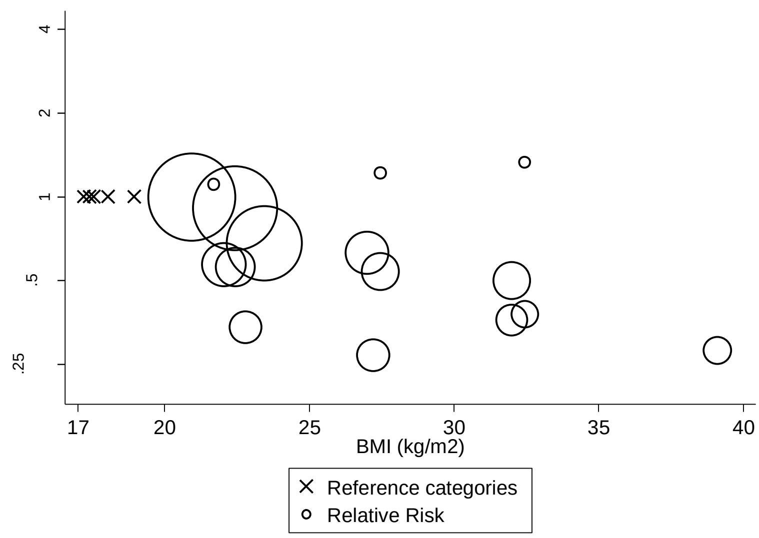


Table 180 Relative risk of non-cardia gastric cancer and BMI estimated using non-linear models

BMI (kg/m^2)	RR (95%CI)
17.20	1.48 (1.34-1.64)
18.95	1.26 (1.19-1.33)
21.70	1.00
23.45	0.90 (0.88-0.92)
27.00	0.82 (0.78-0.86)
32.00	0.86 (0.79-0.93)

8.1.1 BMI at early adulthood

Cohort studies

Six studies (eight publications) were identified. Four publications were from the 2005 SLR and four were from the CUP. Dose-response analysis was not conducted as only four studies reported results on stomach cancer could be included.

The definition of BMI at early adulthood varied between studies – 16-19 years (Levi, 2013), average 18.4 years (Gray, 2012), at 20 years (Merry, 2007; Tanaka, 2007), and at 25 years (Terry, 1998; Nomura, 1985a).

Two cohorts observed significant positive associations, with stomach cancer risk (Terry, 1998) and mortality in women, but not in men (Tanaka, 2007). Three cohorts reported non-significant positive associations with stomach cancer mortality (Gray, 2012), gastric cardia cancer risk (Merry, 2007), and gastric non-cardia cancer risk (Levi, 2013; Merry, 2007). One study reported no significant association (data not shown) (Nomura, 1985a).

8.1.3 Weight

Cohort studies

Five studies (six publications) were identified. Dose-response meta-analysis was not conducted as only three studies reported results on stomach cancer could be included in the analysis.

JACC (Fujino, 2007) and the Linxian General Population Trial (Guo, 1994) observed no significant association between weight and stomach cancer risk. One study (Tulinius, 1997) reported significant inverse association in men, but not in women.

The Linxian General Population Trial further reported results by stomach cancer sites (Tran, 2005), which observed no significant association with gastric cardia cancer and a significant inverse association with gastric non-cardia cancer. One study (O'Doherty, 2012) reported significant positive associations in cardia and non-cardia gastric cancers. One study reported no significant difference in mean weight between cases and non-cases (Chyou, 1994).

8.2.1 Waist circumference

Two studies were identified in the CUP only.

Positive associations of waist circumference were reported in one study (O'Doherty, 2012), and a significant trend was observed for cardia stomach adenocarcinoma (P trend <0.01), but not for non-cardia adenocarcinoma (P trend=0.19). When further adjusted for hip circumference in the models, the associations were attenuated but remained significant with cardia adenocarcinoma and remained similar with non-cardia adenocarcinoma.

No significant association of anterior-posterior diameter with cardia adenocarcinoma risk was observed in the other study (Corley, 2008).

8.2.2 Hip circumference

One study was identified in the CUP only.

Positive associations of hip circumference, in which a significant dose-response trend were reported with cardia stomach adenocarcinoma (P trend=0.01), but not with non-cardia adenocarcinoma (P trend=0.37) (O'Doherty, 2012). When further adjusted for waist circumference in the models, the association with cardia adenocarcinoma became inversely associated with a non-significant trend (P trend=0.54), and the positive association with non-cardia adenocarcinoma was attenuated and remained non-significant (P trend=1.00).

8.2.3 Waist to hip ratio

One study was identified in the CUP only.

Non-significant positive associations of waist to hip ratio with cardia stomach adenocarcinoma (P trend=0.08) and non-cardia adenocarcinoma (P trend=0.05) were reported (O'Doherty, 2012). The associations were attenuated when further adjusted for BMI in the models.

8.3.1 Height

Cohort studies

Summary

Main results:

Ten studies were included in the dose-response meta-analysis. No significant association was observed between height and stomach cancer risk, overall or in men and women. No significant association was observed for gastric cardia cancer, non-cardia cancer, stomach cancer incidence, or mortality.

Seven studies were excluded from the dose-response analysis. Two studies did not report cut-off points for height (Tretli, 1999; Tanaka, 2007). Non-significant associations by sex were reported in these two studies, which included a strong but non-signficant inverse association among men in Tanaka, 2007. No risk estimates were reported in three studies (Whittemore, 1985; Chyou, 1994; Tulinius, 1997) and two publications were duplicates (Lyon, 1995; Song, 2003).

Results on combined distal oesophageal and gastric cardia cancers were not included in the analysis – MacInnis, 2006 reported no significant association.

Moderate heterogeneity was observed between studies, but this appeared to be driven by one slightly outlying study (Persson, 2008a), and when excluded I^2=13.9%, $p_{heterogeneity}$=0.32, and the summary RR remained similar, RR=1.00 (95% CI: 0.98-1.02). There was no evidence of a significant publication or small study bias (p=0.09).

Sensitivity and stratified analyses:

The summary RR did not change materially when studies were omitted in turn in influence analysis. No significant association was observed when stratified by geographic location.

Non-linear dose-response meta-analysis:

There was no evidence of a non-linear relationship between height and stomach cancer (5 studies) (p=0.08).

Study quality:

Some studies recruited specific populations: participants of the Linxin NIT cohort were randomly assigned to 1 of 8 vitamin/mineral trials (Tran, 2005). The WHI has a trial component and an observational study component. The clinical trial component consisted of three randomised controlled interventions: hormone therapy, low-fat diet modification and calcium-vitamin D supplementation. Sensitivity analysis showed that none of these studies had a strong influence in the summary RR.

Loss to follow-up was low in most studies reported data and cancer outcome was confirmed using medical notes or records in cancer registries in most studies.

All studies included in the dose-response analysis were adjusted for age and sex. No studies were adjusted for Helicobacter pylori status.

Table 181 Height and stomach cancer risk. Number of studies in the CUP SLR

	Number
Studies identified	17 (19 publications)
Studies included in forest plot of highest compared with lowest exposure	9
Studies included in linear dose-response meta-analysis	10
Studies included in non-linear dose-response meta-analysis	5

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

Table 182 Height and stomach cancer risk. Summary of the linear dose-response meta-analysis in the 2005 SLR and CUP

	2005 SLR	CUP
Increment unit used	5 cm	5 cm
All studies		
Studies (n)	4	10
Cases (total number)	>1840	16381
RR (95%CI)	0.97 (0.93-1.01)	0.98 (0.95-1.02)
Heterogeneity (I^2, p-value)	0%, p=0.40	56.4%, 0.01
P value Egger test	-	0.09
Stratified and sensitivity analysis		
Men		
Studies (n)	-	4
Cases	-	9695
RR (95%CI)	-	1.01 (0.94-1.09)
Heterogeneity (I^2, p-value)	-	60.0%, p=0.06
Women		
Studies (n)	-	6
Cases	-	4315
RR (95%CI)	-	0.98 (0.91-1.05)
Heterogeneity (I^2, p-value)	-	66.9%, p=0.01
Cancer site	Gastric cardia cancer	Non-cardia gastric cancer
Studies (n)	3	3
Cases	1425	556
RR (95%CI)	1.02 (0.91-1.16)	1.01 (0.88-1.15)
Heterogeneity (I^2, p-value)	70.6%, p=0.03	35.1%, p=0.21
Outcome		
Incidence		
Studies (n)	-	7
Cases	-	14661
RR (95%CI)	-	0.99 (0.95-1.03)
Heterogeneity (I^2, p-value)	-	68.4%, p=0.004
Mortality		
Studies (n)	-	3
Cases	-	1069

RR (95%CI)	-	0.96 (0.87-1.05)
Heterogeneity (I^2, p-value)	-	71.8%, p=0.03

Other stratified analyses

Geographic area	**Asia**	**Europe**	**North America**
Studies (n)	4	4	2
RR (95%CI)	0.98 (0.92-1.04)	0.99 (0.93-1.04)	0.96 (0.86-1.08)
Heterogeneity (I^2, p-value)	77.4%, 0.004	23.9%, 0.27	48.2%, 0.17

Table 183 Height and stomach 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-analyses								
The Emerging Risk Factor Collaboration	121 prospective studies	2154 deaths	International	Mortality, stomach cancer	Per 6.5 cm	0.95 (0.91-1.00)	-	14%

Table 184 Height and stomach 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 the analysis
Kabat, 2013 STM80175 USA	WHI, Prospective Cohort, Age: 50-79 years, W	152/ 144 701 12 years	Self-report verified by medical record and pathology report	All participants had their height measured by trained staff at baseline. Height was measured to the nearest 0.1 cm.	Incidence, stomach cancer	Per 10 cm	1.05 (0.82-1.35)	Age, ethnicity, pack-years cigarette smoking, randomisation, alcohol, education	Converted to 5 cm
O'Doherty, 2012 STM80123 USA	NIH- AARP, Prospective Cohort, Age: 50-71 years, M/W, Retired	191/ 218 854 9 years	Linkage of the cohort with database to state cancer registries	Height was derived from information provided in the baseline questionnaire. sex-specific quartiles were used for height	Incidence, gastric cardia adenocarcinoma Incidence, gastric non-cardia adenocarcinoma	Quantile 4 vs quantile 1 Quantile 4 vs quantile 1	0.70 (0.46-1.07) Ptrend:0.09 0.84 (0.50-1.42) Ptrend: 0.25	Age, sex, alcohol consumption, antacid use, aspirin use, cigarette smoking, diabetes, ethnicity, marital status, physical activity, red meat intake, weight, education, fruit and vegetable intake, non-	Weighted average height estimated for men and women 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 the analysis
								steroidal anti-inflammatory drug use, total energy, white meat intake	
		125/			Incidence, gastric non-cardia adenocarcinoma	Quantile 4 vs quantile 1	0.84 (0.50-1.42) Ptrend:0.25		
Green, 2011 STM89938 UK	MWS, Prospective Cohort, Age: 56.00years, W	1 177/ 1 297 124 9 years	Cancer registry	Women who answered a study questionnaire in 2006–07, a sample selected at random (on the basis of day of birth) were asked in 2006–09 to have their height measured by their family doctor	Incidence, stomach cancer	Per 10 cm	1.03 (0.90-1.18)	Age, age at first birth, age at menarche, BMI, parity, socio-economic status, alcohol, region, smoking, strenuous exercise	Converted to 5 cm
		407/			Never smoker	Per 10 cm	1.03 (0.74-1.19)		
		345/			Current smoker	Per 10 cm	1.20 (0.94-1.17)		
Sung, 2009 STM80053 Korea	KNHIC, Prospective Cohort, Age: 40-64	8 777/ 788 789 9 years	Linkage with cancer registry, national health insurance and	Measured by trained a nurse in light clothing.	Incidence, stomach cancer Men	>171.1 vs 164.5 cm	1.03 (0.97-1.09)	Age, alcohol consumption, area of residence, BMI,	Distribution of cases and midpoints estimated

Author, Year, 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 the analysis
	years, M/W, middle-class adults		death report					cigarette smoking, level of monthly salary, occupation, regular exercise	
						Per 5 cm	1.01 (0.99-1.03)		
		2 274/			Women	>158.1 vs 151.0 cm	1.01 (0.89-1.14)		
						Per 5 cm	1.00 (0.95-1.04)		
Persson, 2008a STM80187 Japan	JPHC, Prospective Cohort, Age: 40-69 years, W	368/ 44 453 12 years	Active patient notification from hospitals, cancer registries and death cert.	Self-administered questionnaire.	Incidence, stomach cancer	≥156 vs ≤146.9 cm	0.57 (0.41-0.80) Ptrend:0.01	Age, family history of cancer, study area	Midpoints estimated
		333/			Postmenopausal women	≥156 vs ≤146.9 cm	0.63 (0.44-0.90) Ptrend:0.01		
		242/			Incidence, undifferentiated gastric cancer	≥156 vs ≤146.9 cm	0.56 (0.37-0.85) Ptrend:0.01		
		217/			Postmenopausal women	≥156 vs ≤146.9 cm	0.59 (0.38-0.92) Ptrend:0.02		
		97/			Incidence, differentiated gastric cancer	≥156 vs ≤146.9 cm	0.51 (0.27-0.98) Ptrend:0.05		
		89/			Postmenopausal	≥156 vs ≤146.9	0.62 (0.32-1.23)		

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Missing data derived for the analysis
					women	cm	Ptrend:0.17		
Fujino, 2007 STM80145 Japan	JACC, Prospective Cohort, M/W	725/		Obtained from survey, no further details provided.	Mortality, stomach cancer Men	≥165 vs <160 cm	1.18 (0.98-1.41)	Age, study area	Midpoints estimated
		344/			Women	≥154 vs <149 cm	1.16 (0.87-1.54)		
Merry, 2007 STM80089 Netherlands	NLCS, Case Cohort, Age: 55-69 years, M/W	235/ 5 155 13 years	Cancer registry and pathology database	Self-reported height at baseline.	Incidence, distal stomach cancer	M: ≥185, f:≥175 vs m:<170 f:<160 cm	0.54 (0.27-1.08) Ptrend:0.07	Age, sex, BMI at baseline, current smoking, education, number of cigarettes smoked per day, smoking years	Weighted average height for men and women combined was estimated
						Per 5 cm	0.92 (0.83-1.01) Ptrend:0.06		
		173/			Incidence, not otherwise specified gastric adenocarcinoma	M: ≥185, f:≥175 vs m:<170 f:<160 cm	1.30 (0.71-2.39) Ptrend:0.52	History of gastric ulcer and bleeding	
						Per 5 cm	1.03 (0.90-1.18) Ptrend:0.06		
		145/			Incidence, gastric cardia adenocarcinoma	M: ≥185, f:≥175 vs m:<170 f:<160 cm	1.85 (0.88-3.92) Ptrend:0.06		
						Per 5 cm	1.07 (0.95-1.21) Ptrend:0.06		
Batty, 2006	Whitehall Study,	193/	UK national	Measured	Mortality,	>181 vs 170.9	0.84 (0.53-1.31)	Age, BMI,	Distribution of

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Missing data derived for the analysis
STM80179 UK	Prospective Cohort, Age: 40-64 years, M, civil servants	17 353 35	health service central register	height.	stomach cancer	cm	Ptrend:0.2	cholesterol, diabetes, disease at entry, glucose intolerance, marital status, physical activity, smoking habits, systolic blood pressure, triceps skinfold thickness, grade	cases estimated
						Per 5 cm	0.96 (0.86-1.07)		
MacInnis, 2006 STM89937 Australia	MCCS, Prospective Cohort, Age: 27-75 years, M/W	68/ 41 295 11 years	Cancer registry	Height was measured at baseline by trained nurses	Incidence, gastric non-cardia adenocarcinoma	Quantile 3 vs quantile 1	1.80 (0.90-3.50)	Sex, age-underlying cox models, county of birth, educational level, physical activity	(Identified through reference list of published review)
						Per 10 cm	1.37 (0.94-1.99)		Converted to 5 cm (Included in the non-cardia gastric cancer analysis only)
		30/			Incidence, distal oesophageal and gastric cardia	Quantile 3 vs quantile 1	1.60 (0.60-4.10)		
						Per 10 cm	1.22 (0.69-2.15)		

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Missing data derived for the analysis
					cancer				
Tran, 2005 STM44270 Linxin, China	NIT Cohort, Prospective Cohort, Age: 40-69 years, M/W, Intervention trial participants	1 089/ 29 584 15 years	Follow-up visits, contacts with local commune, hospitals, and study medical team		Incidence, cardia cancer	≥164 vs <153 cm	1.19 (0.94-1.50) Ptrend:0.132	Age, sex	Midpoints and distribution of cases and person-years estimated
		363/			Incidence, non-cardia cancer	≥164 vs <153 cm	1.06 (0.70-1.60) Ptrend:0.821		
Smith, 2000b STM03480 Scotland	RPS, Prospective Cohort, Age: 45-64 years, M/W	15 393 20 years	Cancer registry		Mortality, stomach cancer	Per 10 cm	0.75 (0.56-1.03)	Age, deprivation index, socio-economic status	Converted to 5 cm

Table 185 Height and stomach 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
Tanaka, 2007 STM80137 Japan	TCCJ, Prospective Cohort,	89/ 28 443 7 years	National statistics office	Self-reported height at baseline	Mortality, stomach cancer Men	High vs low	0.30 (0.09-1.02) Ptrend:0.66	Age, BMI at age 20 years, marital status, alcohol	No quantification of height

Author, Year, 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: 35- years, M/W	46/		The correlation coefficients, comparing the self-reported values in the questionnaire and the values actually measured, was 0.93 for height in both sexes.	Women		1.34 (0.35-5.11) Ptrend:0.77	intake, education, physical activity, smoking history	
Song, 2003 STM00747 Korea	SKCS, Prospective Cohort, Age: 40-64 years, M, Civil Servants	1 198/ 386 627 6 years	Population registry		Mortality, stomach cancer	Per 5 cm	0.98 (0.93-1.04)	Age, alcohol consumption, area of residence, BMI, blood glucose levels, cholesterol, hypertension, income, occupation, physical activity, smoking habits	Duplicate, overlaps with Sung, 2009 STM80053

Author, Year, 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
Tretli, 1999, STM03853, Norway	NSPT, Prospective Cohort Age: 30-69 years, M/W	9814/ 1 122 852 20 years	Cancer registry	Measured	Incidence, stomach cancer	Highest vs. lowest quintile	0.99 (0.91-1.07), Men 0.99 (0.90-1.10), Women	Age, age at entry, birth cohort, county of residence	No cut-off values for quintiles
Tulinius, 1997 STM00697, Iceland	Reykjavik Study/Icelandic Cancer Registry	246/ 22 946 27 years	Cancer registry	Measured	Mortality, stomach cancer			Age	No risk estimates
Leon, 1995 STM44435 England	Whitehall Study, Prospective Cohort, Age: 40-64 years, M, Civil Servants	18 403 18 years	Cancer registry		Mortality, stomach cancer	Per 6 inches	1.07 (0.69-1.65)	Age, employment grade	Duplicate, overlaps with Batty, 2006 STM80179
Chyou, 1994 STM12426 USA	HHP, Prospective Cohort, Age: 46-68 years, M, Japanese residents of Hawaii	229/ 7 840 23 years	Cancer registry/ hospital records		Mortality, gastric adenocarcinoma	(mean exposure)		Age	No risk estimates, only mean height
Guo, 1994 STM10900	NIT Cohort, Nested Case	538/ 29 584	Follow-up visits, contacts with		Incidence, stomach cancer	>165 vs <154 cm	0.90 (0.60-1.30) Ptrend:0.52	Family history of cancer,	Duplicate, overlaps with

Author, Year, 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
Linxin, China	Control, Age: 40-69 years, M/W, Intervention trial participants	5 years	local commune, hospitals, and study medical team					intervention group, smoking habits	Tran, 2005 STM44270
Whittemore, 1985 STM00030 USA	CAHS, Nested Case Control, Age: 17- years, M/W	64/ 51 477 50 years	Population registry/ death certificates		Incidence, stomach cancer	(mean exposure)			No risk estimates, only mean height

Figure 203 RR estimates of stomach cancer by levels of height

Note: MacInnis, 2006 was included in the analysis of non-cardia gastric cancer only

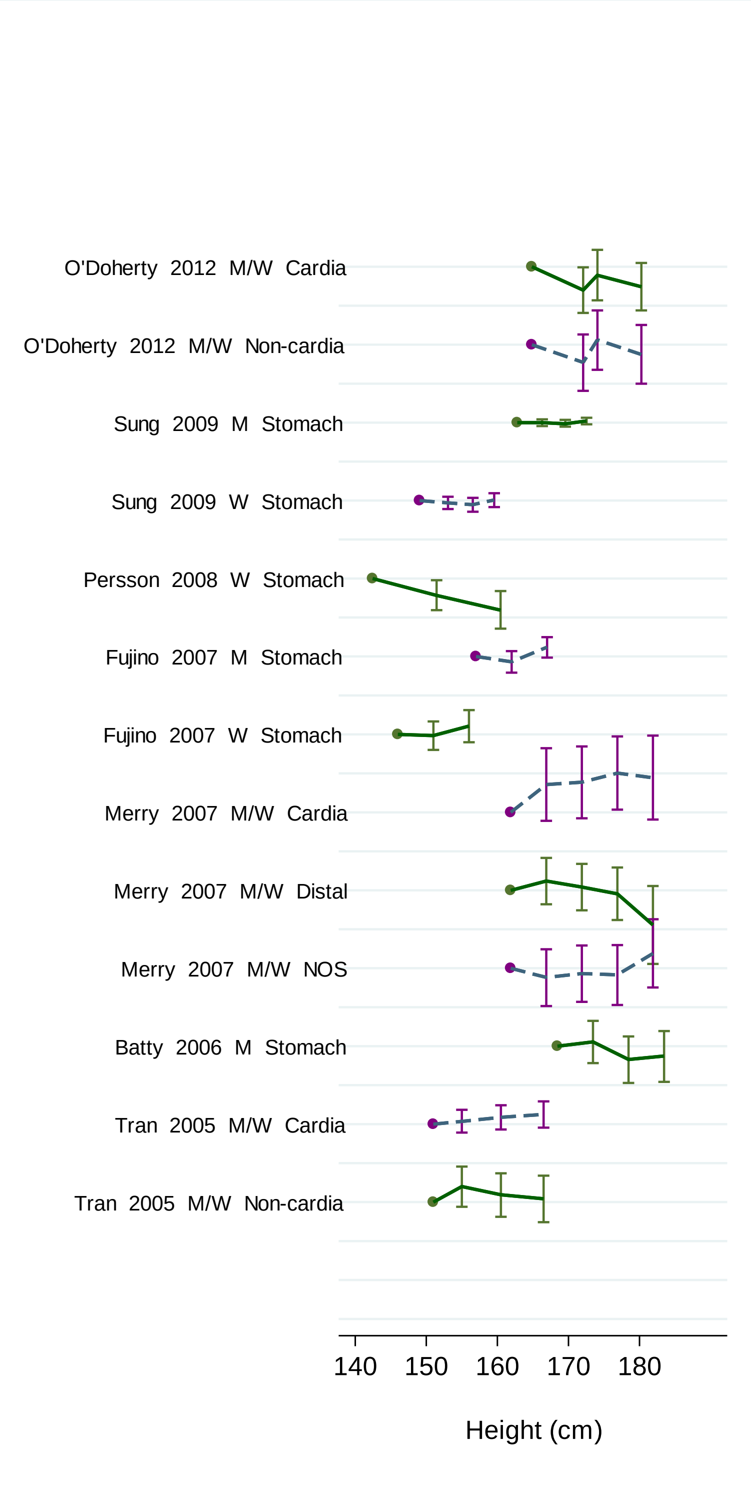


Figure 204 RR (95% CI) of stomach cancer for the highest compared with the lowest level of height

Author	Year	Sex	OutcomeSubType	High vs. low RR (95% CI)	StudyDescription	Comparison
O'Doherty	2012	M/W	Gastric cardia adenocarcinoma	0.70 (0.46, 1.07)	NIH- AARP	Quantile 4 vs Quantile 1
O'Doherty	2012	M/W	Gastric noncardia adenocarcinoma	0.84 (0.50, 1.42)	NIH- AARP	Quantile 4 vs Quantile 1
Sung	2009	M	Stomach cancer	1.03 (0.97, 1.09)	KNHIC	>171.1 vs ≤164.5 cm
Sung	2009	W	Stomach cancer	1.01 (0.89, 1.14)	KNHIC	>158.1 vs ≤151 cm
Persson	2008	W	Stomach cancer	0.57 (0.41, 0.80)	JPHC	≥156 vs ≤146.9 cm
Merry	2007	M/W	Gastric cardia adenocarcinoma	1.85 (0.88, 3.92)	NLCS	M: ≥185, F: ≥175 vs M:<170 F:<160 cm
Merry	2007	M/W	Distal stomach cancer	0.54 (0.27, 1.08)	NLCS	M: ≥185, F: ≥175 vs M:<170 F:<160 cm
Merry	2007	M/W	not otherwise specified gastric adenocarcinoma	1.30 (0.71, 2.39)	NLCS	M: ≥185, F: ≥175 vs M:<170 F:<160 cm
Tanaka	2007	M	Stomach cancer	0.30 (0.09, 1.02)	TCCJ	High vs Low
Tanaka	2007	W	Stomach cancer	1.34 (0.35, 5.11)	TCCJ	High vs Low
Fujino	2007	M	Stomach cancer	1.18 (0.98, 1.41)	JACC	≥165 vs <160 cm
Fujino	2007	W	Stomach cancer	1.16 (0.87, 1.54)	JACC	≥154 vs <149 cm
Batty	2006	M	Stomach cancer	0.84 (0.53, 1.31)	Whitehall study	>181 vs <184
MacInnis	2006	M/W	Gastric noncardia adenocarcinoma	1.80 (0.90, 3.50)	MCCS	Quantile 3 vs Quantile 1
Tran	2005	M/W	Cardia Cancer	1.19 (0.94, 1.50)	NIT Cohort	≥164 vs <153 cm
Tran	2005	M/W	Non-Cardia Cancer	1.06 (0.70, 1.60)	NIT Cohort	≥164 vs <153 cm
Tretli	1999	M	Stomach cancer	0.99 (0.91, 1.07)	NSPT	Quantile 5 vs Quantile 1 cm
Tretli	1999	W	Stomach cancer	0.99 (0.90, 1.10)	NSPT	Quantile 5 vs Quantile 1 cm

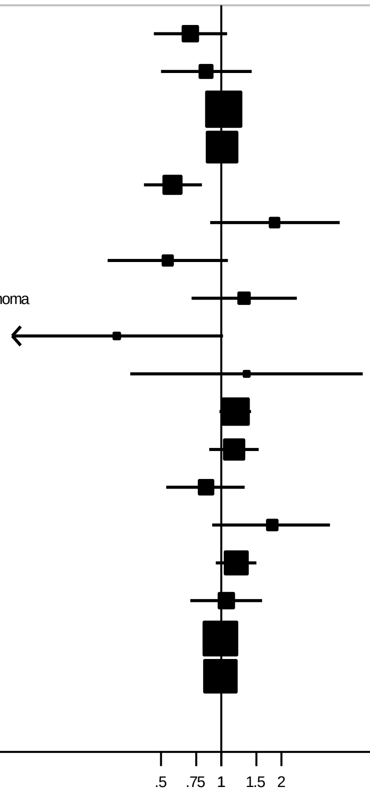


Figure 205 Relative risk of stomach cancer for 5 cm increase in height

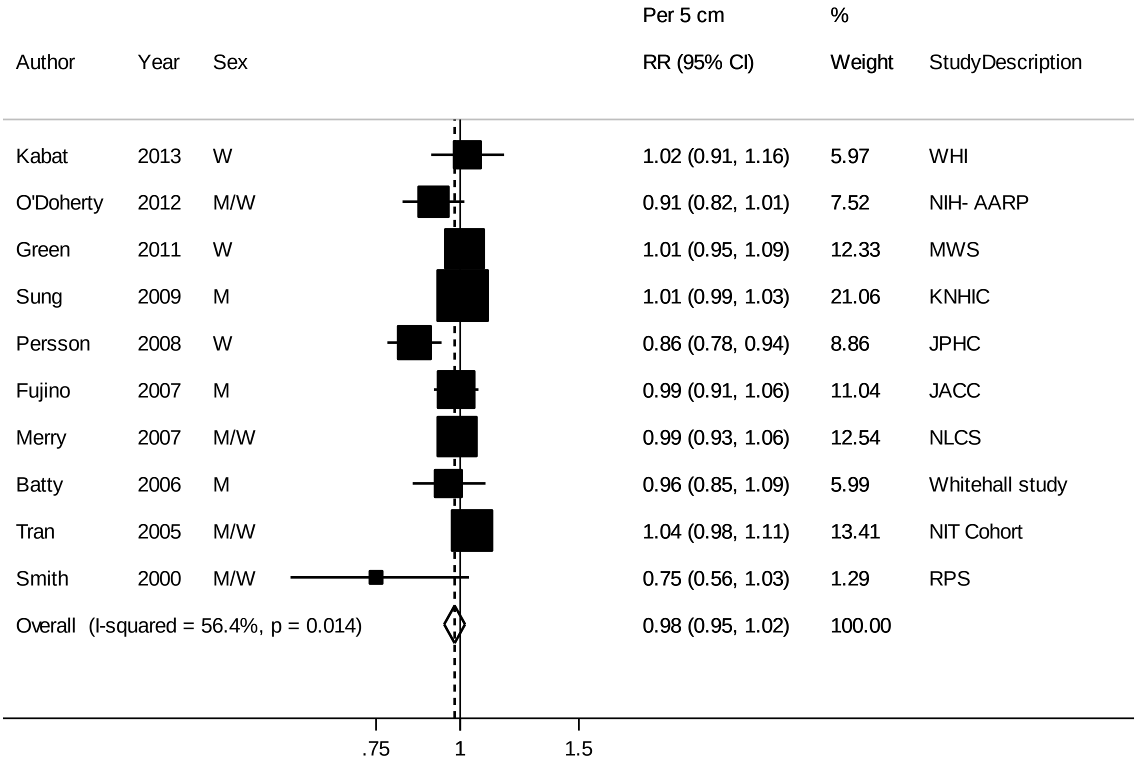
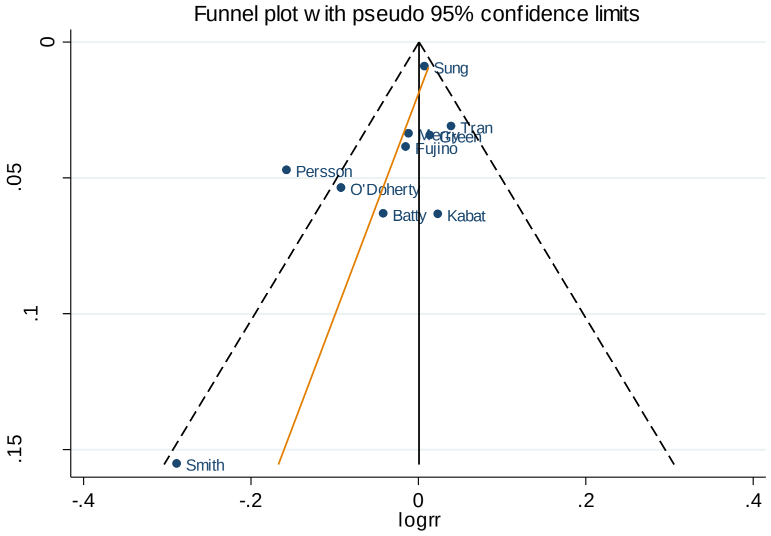


Figure 206 Funnel plot of studies included in the dose response meta-analysis of height and stomach cancer



Egger’s test p=0.09

Figure 207 Relative risk of stomach cancer for 5 cm increase of height by sex

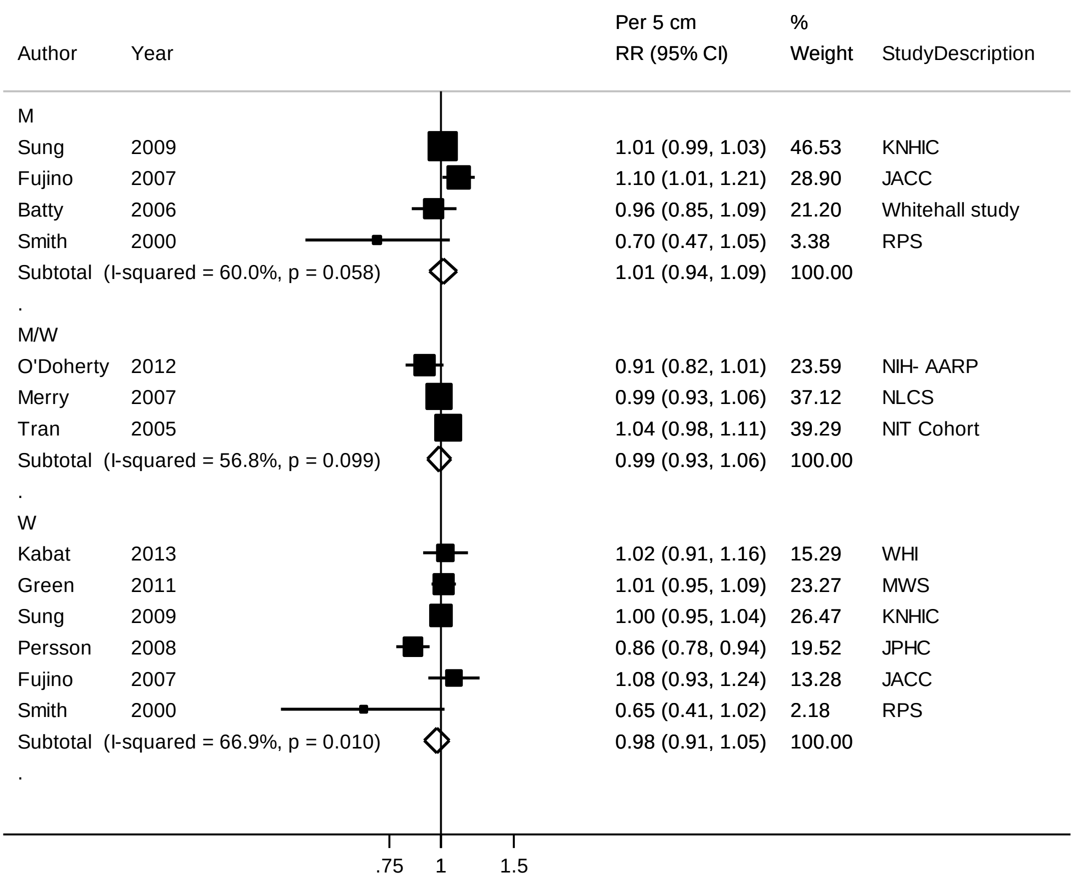


Figure 208 Relative risk of stomach cancer for 5 cm increase of height by cancer outcome

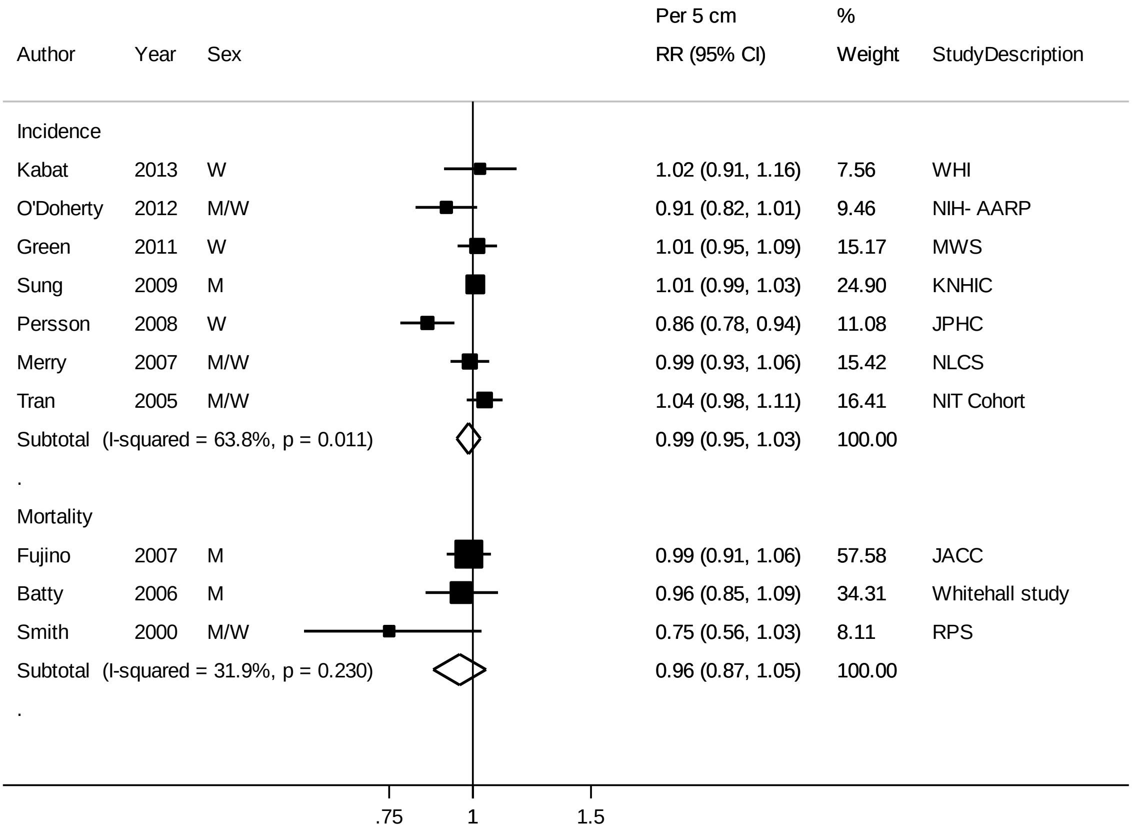


Figure 209 Relative risk of stomach cancer for 5 cm increase of height by cancer site

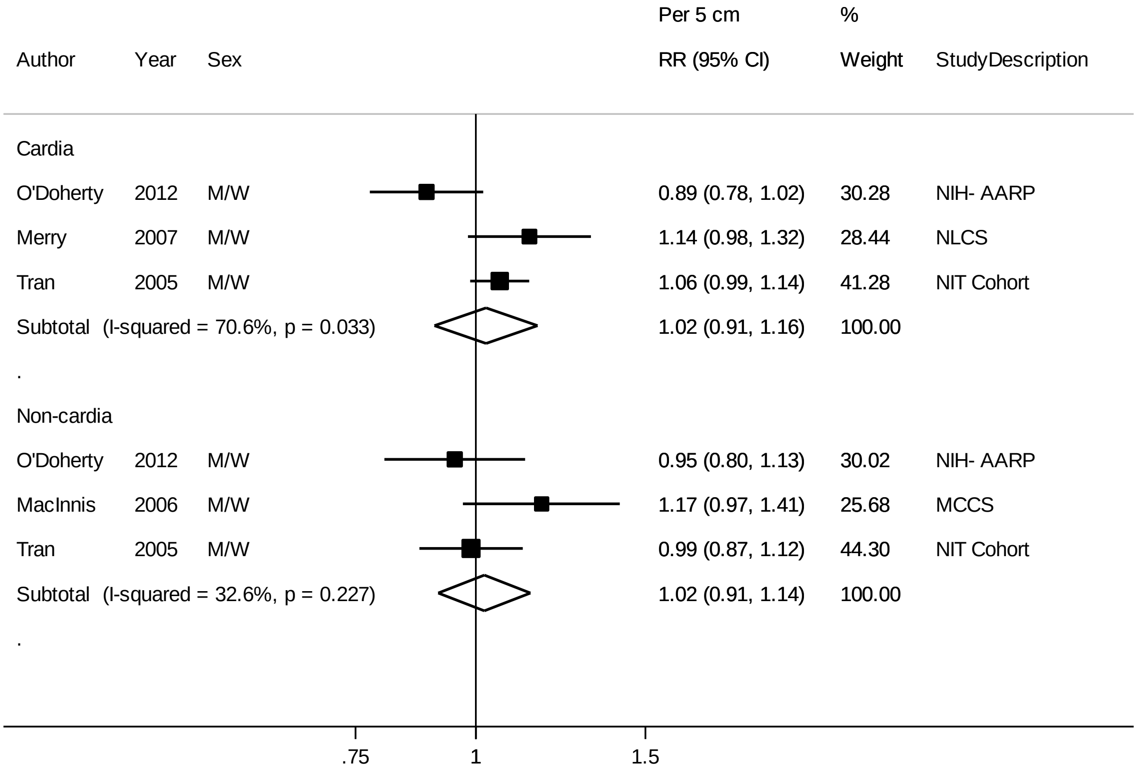


Figure 210 Relative risk of stomach cancer for 5 cm increase of height by geographic location

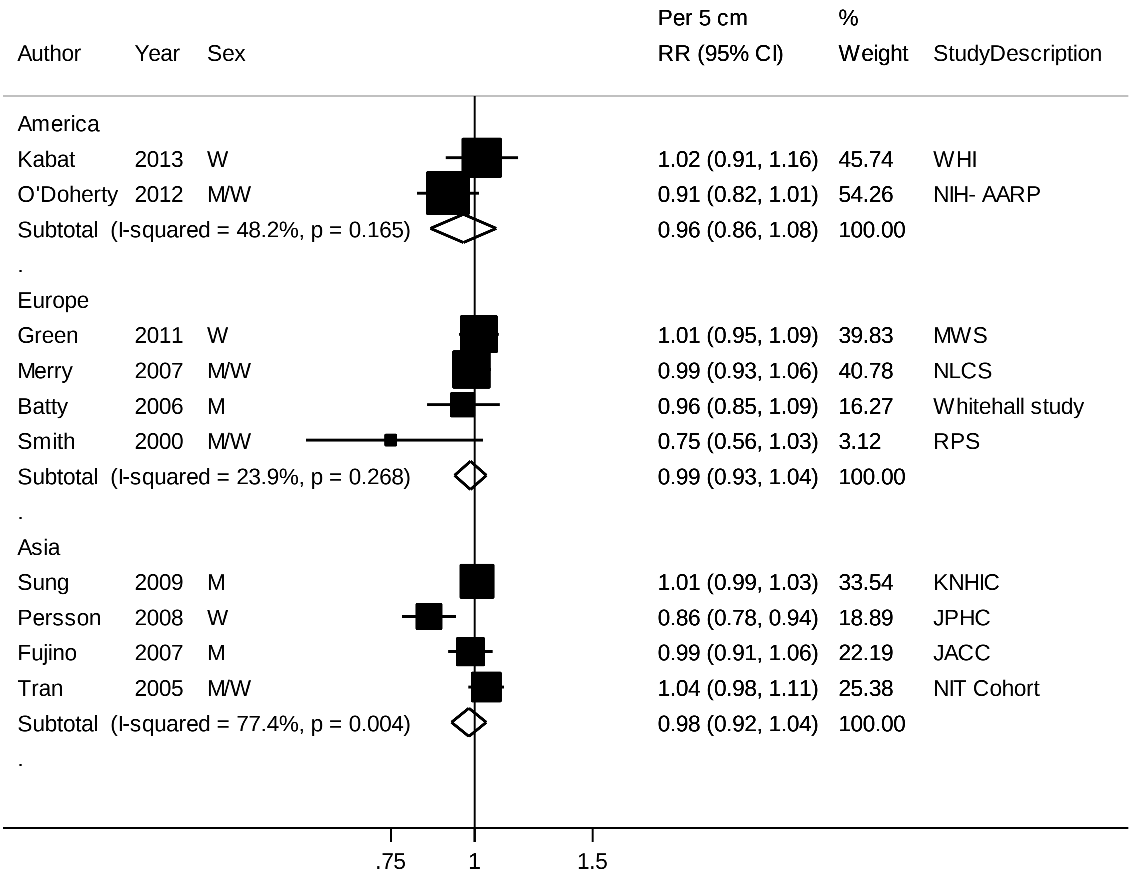
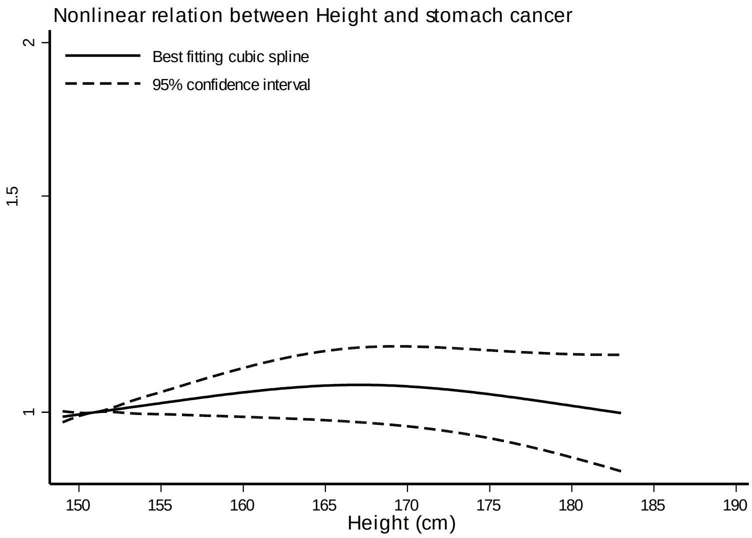


Figure 211 Non-linear dose-response meta-analysis of height and stomach cancer



P non-linear =0.08

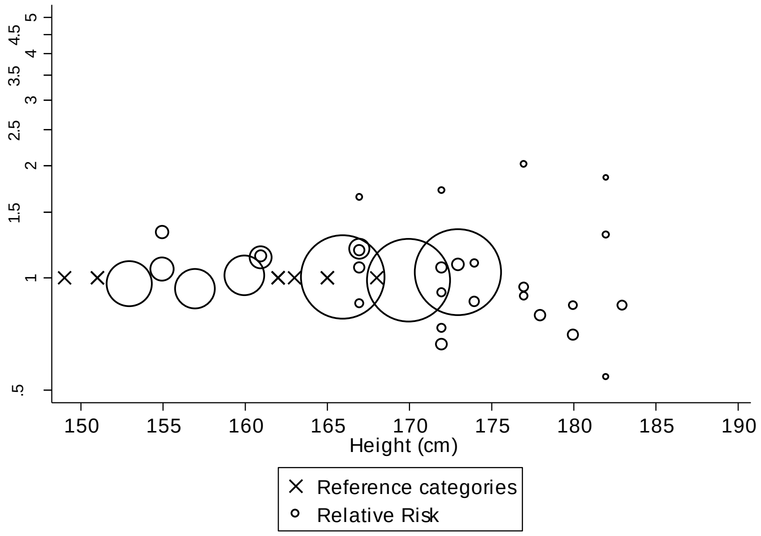


Table 186 Relative risk of stomach cancer and height estimated using non-linear models

Height (cm)	RR (95%CI)
151	1.00
155	1.02 (1.00-1.04)
160	1.04 (0.99-1.06)
165	1.05 (0.99-1.12)
170	1.05 (0.97-1.13)
174	1.04 (0.96-1.13)
180	1.01 (0.92-1.11)

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Appendix 1

Several studies investigated related dietary exposures or anthropometric characteristics and stomach cancer risk. The items or characteristics investigated by each study are indicated with a cross in the list below:

a) Fruit or vegetable items investigated by each study

				Fruit or vegetable items						
Author	**Year**	**Country**	**Study name**	**Total fruit and vegetables**	**Vegetables**	**Cruciferous vegetables**	**Allium vegetables**	**Green leafy vegetables**	**Fruits**	**Citrus fruit**
Ko	2013	Korea	KMCC		x				x	
Gonzalez	2012	Europe	EPIC	x	x	x	x	x	x	x
Steevens	2011	The Netherlands	NLCS		x	x	x	x	x	x
Botterweck	1998			x						
Epplein	2010	China	SMHS and SWHS		x	x	x	x	x	x
Li	2010	Japan	OCS							x
George	2009	USA	NIH-AARP		x				x	
Freedman	2008			x	x	x		x		x
Kurosawa	2006	Japan	Higashi-Yamanashi County, Japan						x	
Larsson	2006c	Sweden	SMC and COSM	x	x	x	x	x	x	
Nouraie	2005	Finland	ATBC		x				x	
Tran	2005	China	NIT Cohort		x				x	
Sauvaget	2005	Japan	LSS						x	
Khan	2004	Japan	HGCS						x	
Wong	2004	China	CCHT		x				x	
Appleby	2002	UK	HFSS						x	
Iso	2007	Japan	JACC					x		x
Fujino	2002				x				x	

Kasum	2002	USA	IWHS		x			x	
Zheng	1995					x	x		x
Kobayashi	2002	Japan	JPHC I		x		x	x	
Ngoan	2002	Japan	FPC					x	
McCullough	2001	USA	CPS II	x	x				x
Galanis	1998	Hawaii, USA	Hawaii-Japan DOH Survey	x				x	
Terry	1998	Sweden	Swedish Twin Registry	x					
Inoue	1996	Japan	HERPACC					x	
Kato	1992b	Japan	Higashi-Kamo Cohort					x	
Kneller	1991	USA	LBS		x	x		x	
Nomura	1990	Hawaii, USA	HHP					x	
Chyou	1990			x	x	x	x		x
Stahelin	1986	Switzerland	BASEL II and III						x
Ikeda	1983	Japan	RERFCJ					x	

b) Meat items investigated by each study

				Meat items			
Author	Year	Country	Study name	Processed meat	Red and processed meat	Poultry	Fish
Ko	2013	Korea	KMCC				x
Keszei	2012	The Netherlands	NLCS	x	x		
Daniel	2011	USA	NIH-AARP			x	x
Cross	2011	USA	NIH-AARP	x	x		
Iso	2007	Japan	JACC	x		x	x
Gonzalez	2006	Europe	EPIC	x	x	x	
Larsson	2006b	Sweden	SMC	x	x	x	x
Sauvaget	2005	Japan	LSS		x	x	x
Khan	2004	Japan	HGCS	x	x	x	x
Ngoan	2002	Japan	FPC	x			x
McCullough	2001	USA	CPS II	x			
Knekt	1999	Finland	FMCHES	x			x
Galanis	1998	USA	Hawaii-Japan DOH Survey	x			
Zheng	1995	USA	IWHS	x			
Kato	1992b	Japan	Higashi-Kamo Cohort				x
Kneller	1991	USA	LBS				x
Hirayama	1990	Japan	Six Prefecture Cohort				x
Nomura	1990	USA	HHP	x			x

c) Alcoholic items investigated by each study

				Alcohol			
Author	**Year**	**Country**	**Study name**	**Total alcohol (as ethanol)**	**Beer**	**Wine**	**Spirits**
Shen	2013	China	CECS	x			
Yang	2012	China	CNRPCS	x			
Everatt	2012	Lithuania	KRIS and MIHDPS	x	x	x	x
Jung	2012	Korea	KMCC	x			
Duell	2011	10 European countries	EPIC	x	x	x	x
Kim	2010	Korea	HEC 2000	x			
Steevens	2010	The Netherlands	NLCS	x	x	x	x
Moy	2010	China	SCStudy	x	x		x
Yi	2010	Korea	KCS	x			x
Allen	2009	UK	MWS	x			
Freedman	2007	USA	NIH-AARP	x	x	x	x
Larsson	2007	Sweden	SMC	x		x	x
Ozasa	2007	Japan	JACC	x			
Sjödahl	2007	Norway	HUNT-I	x			
Sung	2007	Korea	KNHIC	x			
Barstad	2005	Denmark	CCPPS	x	x	x	x
Lindblad	2005	UK	GPRDC	x			
Nakaya	2005	Japan	MCS-II	x			
Sasazuki	2002	Japan	JPHC-I	x			
Hirvonen	2001	Finland	ATBC			x	
Knekt	1999	Finland	FMCHES		x		
Galanis	1998	USA	Hawaii-Japan DOH Survey	x			
Terry	1998	Sweden	STR	x			
Murata	1996	Japan	CCCJ	x			
Nomura	1995	USA	HHP	x			

Nomura	1990				x	x	x
Zheng	1995	USA	IWHS	x			
Kato	1992b	Japan	HKC	x			
Kneller	1991	USA	LBS		x		x
Kono	1986	Japan	JPC	x			

d) Anthropometric characteristics investigated by each study

				Anthropometric characteristics				
Author	**Year**	**Country**	**Study name**	**BMI**	**Height**	**Waist circumference**	**Hip circumference**	**Waist-hip ratio**
Kabat	2013	USA	WHI		x			
Chen	2012	China	CNRPCS	x				
Green	2011	UK	MWS		x			
Reeves	2007			x				
Hemminki	2011	Sweden	Sweden 1964-2006	x				
Andreotti	2010	USA	AHS[2]	x				
Abnet	2008	USA	NIH- AARP	x				
O'Doherty	2012				x	x	x	x
Sung	2009	Korea	KNHIC		x			
Jee	2008		KCPS	x				
Song	2003		SKCS		x			
Corley	2008	USA	KPMCP	x		x		
Persson	2008	Japan	JPHC	x	x			
Sjödahl	2008	Norway	HUNT-I	x				
Fujino	2007	Japan	JACC	x	x			
Merry	2007	The Netherlands	NLCS	x	x			
Tanaka	2007	Japan	TCCJ	x	x			
Lukanova	2006	Sweden	NSHDC	x				

MacInnis	2006	Australia	MCCS	x	x
Samanic	2006	Sweden	SCWC	x	
Baty	2006	UK	Whitehall study, London		x
Batty	2005			x	
Kuriyama	2005	Japan	MCS I	x	
Lindblad	2005	UK	GPRDC	x	
Rapp	2005	Austria	VHM&PP	x	
Sauvaget	2005	Japan	LSS	x	
Tran	2005	China	NIT Cohort	x	x
Samanic	2004	USA	United States Veterans	x	
Calle	2003	USA	CPS II	x	
Wolk	2001	Sweden	Obese Cohort, Sweden	x	
Smith	2000	UK, Scotland	RPS		x
Hara	2000	Japan	Saga Prefecture Cohort	x	
Tretli	1999	Norway	NSPT	x	x
Tulinius	1997	Iceland	Reykjavik Study/Icelandic Cancer Registry	x	x
Chyou	1994	USA	HHP		x
Nomura	1985			x	
Whittemore	1985	USA	CAHS		x
Moller	1994	Denmark	Obese Danish Cohort	x	
Stahelin	1986	Switzerland	BASEL II and III	x	

Appendix 2

Protocol *Version 2*

Continuous update of the epidemiological evidence on food, nutrition, physical activity and the risk of gastric cancer.

Prepared by: CUP team, Imperial College London, October 2012
Revised in February 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 was informed by a process of systematic literature reviews (SLRs) all of the evidence published. Seventeen SLRs were carried out in different centres and the information collected was stored in one database for each of the cancer sites that were reviewed.

The second report features eight general and two special recommendations based on solid evidence which, when followed, will be expected to reduce the incidence of cancer. A recent study in a large European cohort study showed that people with lifestyle in agreement with the WCRF/AICR recommendations experienced a decreased risk of cancer after an average follow-up time of ten years. The main risk reductions were observed for cancers of the colon and rectum, and stomach cancer, and significant associations were observed for cancers of the breast, endometrium, lung, kidney, upper aerodigestive tract, liver, and oesophagus but not for prostate, ovarian, pancreatic, and bladder cancers (3).

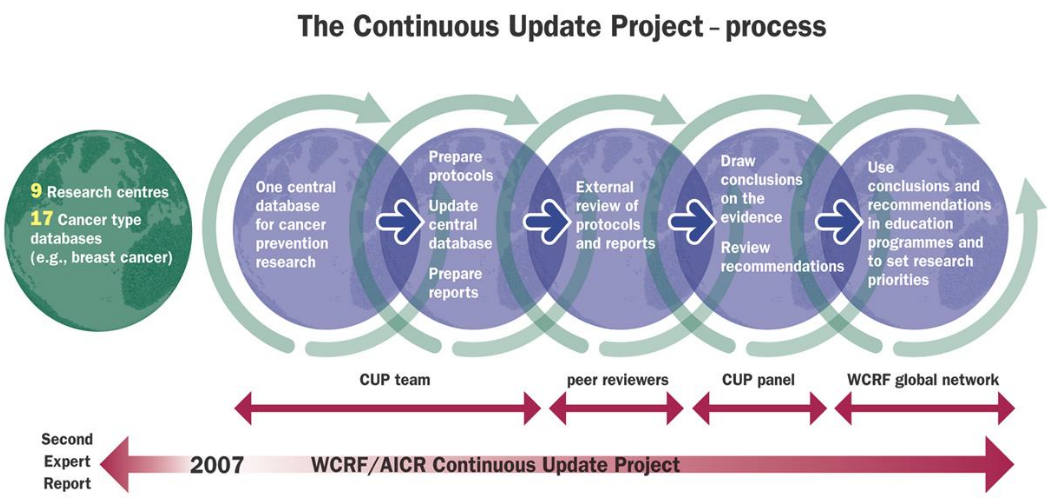
To keep the evidence current and updated into the future, WCRF/AICR is undertaking the Continuous Update Project (CUP) in collaboration with Imperial College London (ICL). The CUP [http://www.wcrf.org/cancer_research/cup/index.php] is an ongoing review of nutrition and cancer research on food, nutrition, physical activity and body fatness, and cancer risk that captures and reviews the evidence as it accumulates. 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.

The CUP builds on the foundations of the second expert report to ensure a consistent approach to reviewing the evidence and it follows the methods developed specifically for the Second Expert Report. The methods are detailed in the SLR Specification Manual (4).

The CUP is conducted by a team at ICL, where a central database has been created by merging the cancer-specific databases generated during the SLR's in the participating centres. A key step of the CUP is to update the central database with evidence published since the Second Expert Report. The meta-analyses conducted for the Second Expert Report will be updated by adding the new evidence identified during the CUP to the evidence collected in the 2007 SLRs.

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 and meta-analyses, and draw conclusions before making recommendations. 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 evidence of the different cancers is being updated progressively in a rolling programme. The CUP started in 2007 and breast cancer was the first cancer to be updated, followed by prostate cancer, colorectal cancer and other cancer sites. When a cancer site is included in the review, the CUP 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 up-to-date for cancers of the breast, prostate, colon and rectum, pancreas, ovary, endometrium, bladder, kidney, gallbladder and liver.

Periodically, the CUP team at ICL prepares reports on the relationship of foods, nutrition, physical activity and body weight by request of the CUP Panel and the Secretariat of the project. The CUP team at ICL has completed updated reports on cancers of the breast, colon and rectum, and pancreas.

The protocols and reports of the CUP are available at http://www.dietandcancerreport.org/cancer_resource_center/continuous_update_project.php).

The present document is the protocol for the continuous update of the epidemiological evidence on food, nutrition, physical activity and the risk of stomach cancer. The peer-reviewed protocol will represent the agreed plan for the continuous update. Should departure from the agreed plan be considered necessary at a later stage, the CUP Expert Panel must agree this and the reasons documented.

Figure 2. The Continuous Update Project- rolling programme

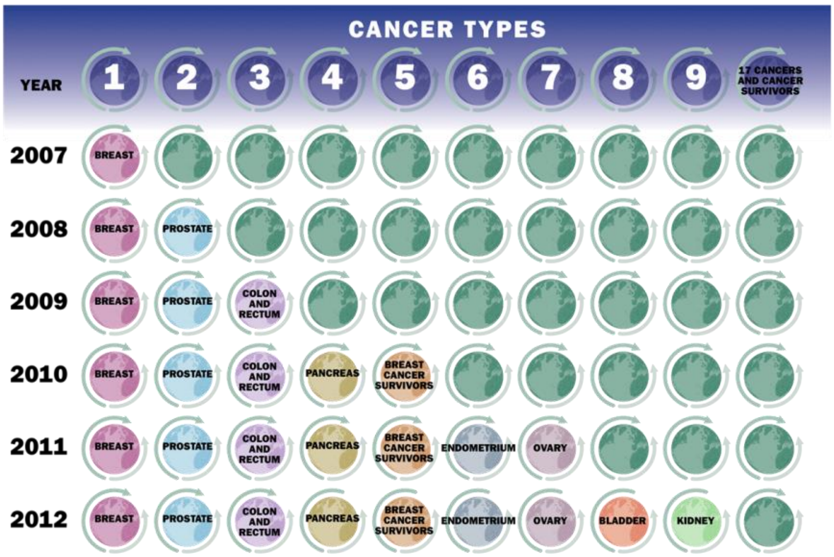
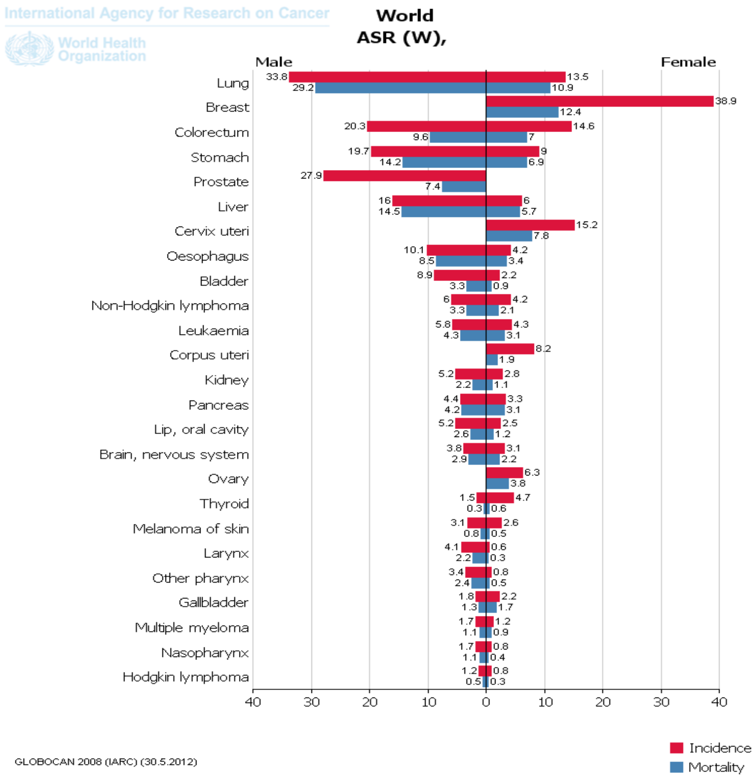


Figure 3. Estimated age (world)-standardized incidence and mortality rates of most frequent cancers (per 100 000) by sex. World. 2008



- **Gastric cancer: Epidemiology and clinical aspects**

Gastric cancers, also called stomach cancer, are cancer that forms in tissues lining the stomach. Gastric cancer is the fourth most common malignancy and the second leading cause of death due to cancer worldwide. In 2008, more than 990,000 cases were recorded (7.8% of new cancers) with 738,000 deaths (5) **(Figure 3).** Gastric cancer has a poor prognosis as it is usually diagnosed at an advanced stage. In many populations, age-standardized incidence rates are about twice as high in men as in women.

Gastric cancer has two main anatomical localizations in the stomach: tumours arising in the cardia – upper portion of the stomach that adjoins the opening of the oesophagus into the stomach- and those from distal stomach (non-cardia).

The vast majority of gastric malignancies are adenocarcinomas, which are commonly divided into intestinal type and diffuse (undifferentiated) type carcinomas (6). Most gastric carcinomas are of the intestinal type. Both histologic types are strongly associated with *H. pylori* infection (7).

Premalignant gastric lesions are risk factors for the development of intestinal-type gastric adenocarcinomas. A multistep sequence of the precursor lesions generally precedes these tumours, in a cascade in which *H. pylori* causes chronic inflammation of the gastric mucosa, followed by a slowly progression through the premalignant stages of atrophic gastritis, intestinal metaplasia and dysplasia to gastric adenocarcinoma. The risk for progression of *H. pylori*-induced gastritis toward premalignant lesions and gastric cancer depends on the duration, distribution, and severity of chronic active *H. pylori* gastritis. [reviewed by de Vries and Kuipers (8)].

The highest incidence rates of gastric cancer are observed in some countries from Eastern Asia, South America and Eastern Europe **(Figure 4).** The highest age-standardised incidence rates for both sex combined are in the Republic of Korea (41.4 per 100, 000), Mongolia (34.0 per 100,000), Japan (31.1 per 100,000) and China (29.8 per 100,000) (5).

The incidence of gastric cancer has declined over the past 50 years in most Western countries. However, while the incidence of non-cardia gastric cancer has declined in most countries, the rates of cardia cancer has remained stable, or rose in several European countries, Japan and North America (9)

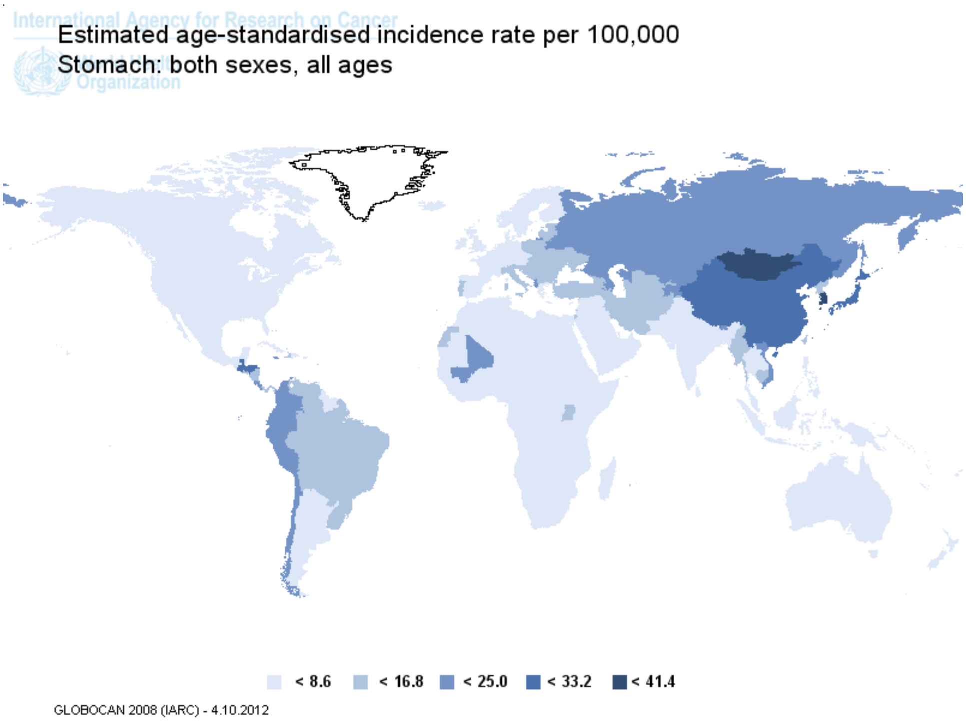
- **Gastric cancer: Risk factors**

H. pylori has been classified as carcinogenic to humans Group 1 by the International Agency for Research on Cancer (10) and it is considered the single most common cause of gastric cancer. *H.pylori* infection is strongly associated with cancers located in the distal stomach (non-cardia), whereas no association has been observed for tumours located in the cardia (7)

Tobacco smoking is considered a risk factor of gastric cancer. Between 11 and 18% of gastric cancer cases are estimated to be attributable to smoking (11).

There is evidence showing that fruits and vegetables probably decrease the risk of stomach cancer and that high salt intake probably increases it (1;12;13). Other nutritional factors that have been found related to gastric cancer are processed meat intake and grilled, broiled and barbecued meats but the evidence is not convincing (1).

Figure 4. Estimated age (world)-standardized incidence and mortality rate of stomach cancer per 100 000. World. 2008



- **Judgement of the WCRF-AICR second export report on stomach cancer**

In the judgement of the Panel of the WCRF-AICR second expert report, non-starchy vegetables, including specifically allium vegetables, as well as fruits probably protect against stomach cancer. Salt and salt-preserved foods are probably causes of this cancer. There was limited evidence suggesting that pulses (legumes), including soya and soya products, and foods containing selenium protect against stomach cancer. The evidence suggesting that chilli, processed meat, smoked foods, and grilled (broiled) and barbecued (charbroiled) animal foods are causes of stomach cancer was judged as limited (**Figure 5**).

Figure 5. Summary of judgements of the 2007 Second Expert Report on stomach cancer (1)

FOOD, NUTRITION, PHYSICAL ACTIVITY AND CANCER OF THE STOMACH		
In the judgment of the Panel, the factors listed below modify the risk of cancer of the stomach. Judgement are graded according to the strength of the evidence		
	DECREASE RISK	INCREASE RISK
CONVINCING		
PROBABLE	Non-starchy vegetables[1] Allium vegetables[1] Fruits[1]	Salt[2] Salted and salty foods
POSSIBLY	Pulses (legumes)[3] Foods containing selenium4	Chilli[1] Processed meat[5] Smoked foods[6] Grilled (broiled) or barbecued (charbroiled) animal foods[6]
LIMITED- SUGGESTIVE	Cereals (grains) and their products; dietary fibre; potatoes; starchy roots, tubers, and plantains; nuts and seeds; herbs, spices, and condiments; meat (unprocessed); poultry; eggs; milk and dairy products; fats and oils; total fat; fatty acid composition; cholesterol; sugars; sugar (sucrose); fruit juices; coffee; tea; alcohol; dietary nitrate and nitrite, ***N***-nitrosodimethylamine; drying or dried food; protein; thiamin; riboflavin; vitamin C; vitamin D; multivitamin/mineral supplements; calcium; iron; selenium supplements; carotenoids; culturally defined diets; meal frequency; eating speed; body fatness; energy intake	
SUBSTANTIAL EFFECT ON RISK UNLIKELY	None identified	

[1] Judgements on vegetables and fruits do not include those preserved by salting and/or pickling.
[2] 'Salt' here means total salt consumption, from processed foods, including salty and salted foods, and also salt added in cooking and at the table.
[3] Including soya and soya products.
[4] Includes both foods naturally containing the constituent and foods, which have the constituent added (see chapter 3.5.3).
[5] The term 'processed meat' refers to meats preserved by smoking, curing, or salting, or addition of chemical preservatives.
[6] The evidence is mostly from meats preserved or cooked in these ways.

1. Research question

The research topic is:

The associations between food, nutrition and physical activity and the risk of stomach cancer.

The main objective is:

To summarize the evidence from prospective studies and randomised controlled trials on the association between foods, nutrients, vitamin, minerals, physical activity, overweight and obesity with the risk of stomach cancers 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, report preparation
Ana Rita Vieira	Research Assistant	Data analyst, report preparation
Deborah Navarro	Research Assistant	Systematic search, article selection, data extraction
Leila Abar	Research Assistant	Systematic search, article selection, data extraction
Snieguole Vingeliene	Research Assistant	Systematic search, article selection, data extraction

Review coordinator, WCRF: Rachel Thomson
Statistical advisor: Darren Greenwood, senior Research Lecturer, University of Leeds

All the reviewers have been trained in the procedures for literature search, data selection and data extraction. The reviewers that will conduct the data analyses are trained in statistical methods for meta-analyses and have conducted several systematic reviews in the CUP that have been published in peer reviewed journals (14-25).

3. Timeline

The SLR's for the Second Expert Report ended in December 30th 2005. All the data from relevant articles published up to this date was extracted by the SLR centre for the Second Expert Report. The continuous update 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 that has been implemented in the interface for data entry.

List of tasks and deadlines for the continuous update on stomach cancer:

Task	Deadline
Start Medline search of relevant articles published from January 1st 2006	1st December 2012
Review title and abstracts of articles identified in initial electronic search (initial search will include articles added in Medline up to 31st December 2012). Select papers for complete review	15th January 2013
Review relevant papers. Select papers for data extraction	30th January 2013
Start data extraction	1st February 2013
Hand search of references	Monthly
Continuous Medline search of relevant articles included in Medline after 31st December 2012	Monthly
Continuous selection of relevant papers based on title, abstract or complete review.	Monthly
Start quantitative analysis of articles published up to 30th March 2014*	1st May 2014
Start report writing	1st September 2014
Send report for review to CUP secretariat	30th October 2014
Review and modify report according to reviewer's comments	31th January 2015
Send reviewed report to CUP secretariat	31th January 2015
Transfer Endnote files to CUP Secretariat	31th January 2015

*For the intermediate report to the CUP Panel, end date of search will be March 30th 2014

4. Search strategy

4.1. Search database

The search aims to identify all types of evidence relevant to the research question. The Medline database (includes coverage from 70 countries) will be searched using PubMed as platform. The rationale fo searching only in Medline is that the results of the SLR's for the Second Expert Report indicated that searching in databases other than Medline was not cost effective (26). 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(4). The full search strategy is in **Annex** 1.

The search will be conducted in three steps:

1) Searching for studies relating to food, nutrition and physical activity

2) Searching for all studies relating to stomach cancer:
3) Searching for all studies relating food, nutrition and physical activity, and stomach cancer

The detailed search strategy is in Appendix 1.

5. Study selection criteria for the update

5.1 Inclusion criteria

The articles to be included in the review:

- Have to present results on an exposure/intervention relevant to the review. The detailed list of exposures/interventions is in **Annex** 2.
- Must have as outcome of interest incidence or mortality of gastric (stomach) cancer, cardia or non-cardia gastric cancers
- Have to present results from an epidemiologic study in men and 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
- Have any publication date¶

† The references of case-control studies will be stored in a Reference Manager database, but the study results will not be extracted in the central database (see Section 6).

¶ The review team will search and extract data from articles included in Medline from January 1st 2006, closure date of the database for the Second Expert Report. Any articles missing in the 2007 SLR that may be identified by screening articles references will be included independently of publication date.

5.2 Exclusion criteria

- Studies with cases of different anatomical localisations in addition to gastric cancer. For instance, gastrointestinal cancer, gastro-oesophageal cancers, etc.
- 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 if cannot be translated (excluding articles in Chinese, French, Italian, Spanish, Portuguese and Iranian because at members in the review team can read these languages).

6. Article selection

All references obtained with the search in PubMed will be imported in a Reference Manager Database using the filter Medline.

Additionally, customized fields will be implemented in the RefMan database (see Section 6.1).

The article selection will follow three steps:

1. An electronic search will be undertaken within Reference Manager to facilitate the identification of irrelevant records. The titles and abstracts of the articles identified by the search in Reference Manager will be the first assessed for inclusion/exclusion. This will be achieved by applying a list of terms developed and tested during the preparation of the WCRF-AICR Second Expert Report:

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. The relevance of articles in language other than English will be assessed by inspection of the title and if available in English, the abstract. If the same study is published in English and in another language, only the article in English will be kept.
3. Full papers will then be obtained for all papers for which eligibility could not be assessed by reading the title and abstract and two reviewers will then assess these papers.
4. Disagreements between the reviewers will be solved by discussion with the principal investigator.
5. If a paper reports outcomes for more than one cancer site, the reviewer will extract the data for the other cancer sites in the database, using the WCRF code of the cancers in question

6.1 Reference Manager Files

Five customized fields will be created in the reference manager database. They will be used to indicate if the study was selected upon reading of title, abstract, or entire article, the study design of included articles, the status of data extraction of the included article, the WCRF code assigned and for excluded articles, the reason for exclusion (**Table 1**)

Table 1. User-defined fields to be created in Reference Manager during article selection and data extraction.

Field	**Use**	**Terms used**	**Notes**
User Def 1	Indicate if article is relevant to the CUP review	Excludedabti; Included; excluded;	Excludedabti means excluded basing on abstract and title of the article. Without "abti" means full text is reviewed.
User Def 2	If excluded, reasons	No associations of interest; No original data/duplicates; Commentary; Foreign article in [*language*] Not adequate study design Pooled studies/meta-analyses	No associations of interest include situations such as "out of the research topic", "no measure of relationship", "no specific outcome"
User Def 3	Study design	Randomized controlled trial (RCT) Prospective cohort study Retrospective cohort study Nested case-control study Case cohort study Population-based case-control study Hospital-based case-control study Case-control study- other type of controls or control type unclear	The CUP only extract data from RCT, cohort/cohort based studies. Case-control studies are identified but the data is not extracted to the database.
User Def 4	WCRF code of the article	This is done during the data extraction	WCRF codes are assigned automatically in the application when performing extraction.
User Def 5	Other notes, name of study	Indicate if includes more than one anatomical localization e.g. stomach and esophagus, gastro-	

		oesophageal cancer, gastrointestinal cancers	

7. Data extraction

The IC team will update the WCRF-AICR central database using the interface created at Imperial College for this purpose **(Figure 6)**.

Data extracted will include study design, 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 categories will be extracted as reported in the paper.

For each result, the reviewer will extract the covariates included in the analytical model and the matching variables. The reviewer will extract the information provided about *H.pylori* infection in the population even if this was not used as covariate in the main analysis. 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. Stratified and subgroup analyses, and results of interaction analyses will also be extracted.

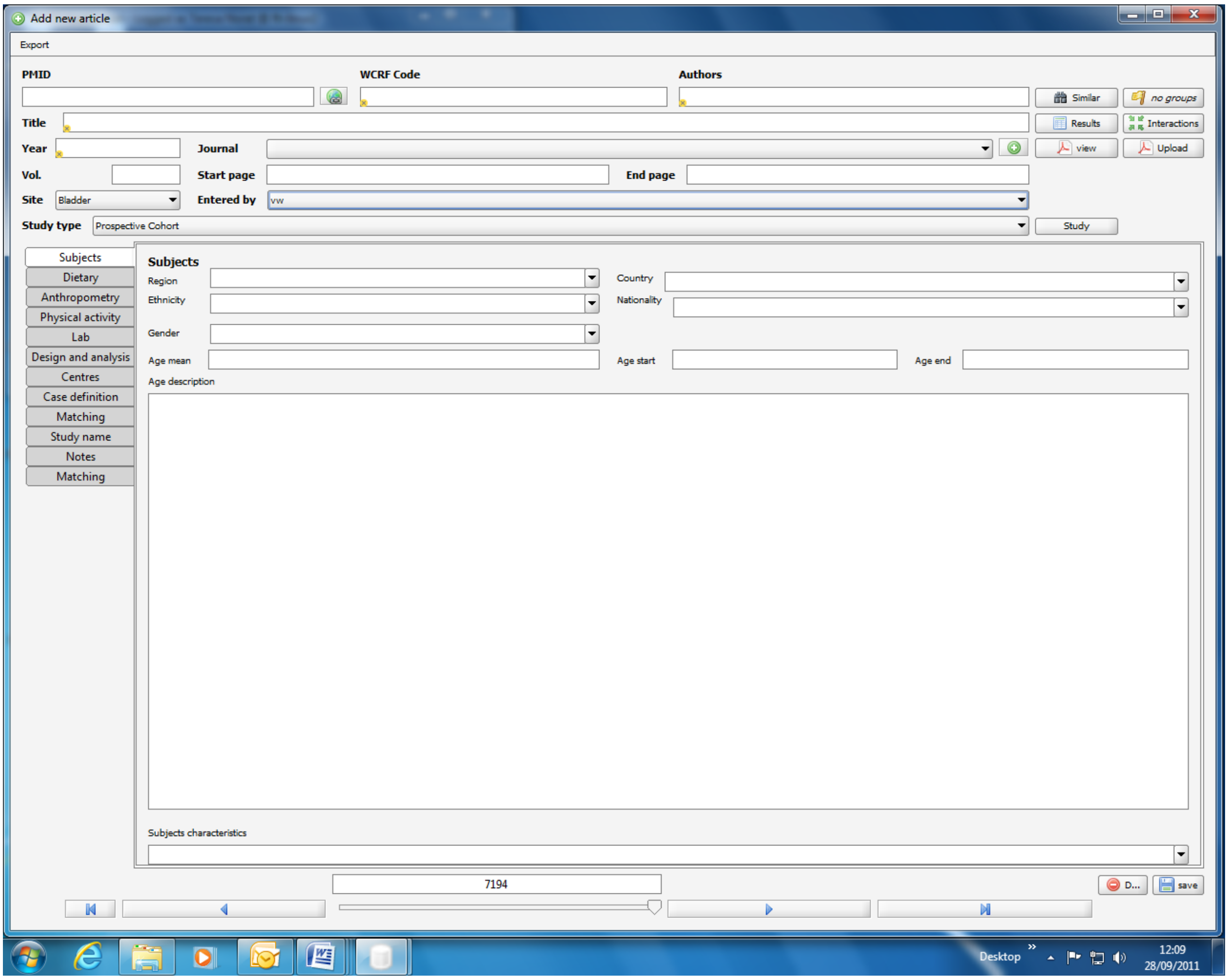
When indicated, the reviewer should also extract for each result:

- Anatomical localisation within the stomach (cardia, non-cardia)

- Histological type (adenocarcinoma, intestinal, diffuse)

- If for a subgroup or stratified analysis, the description of the subgroup or stratum

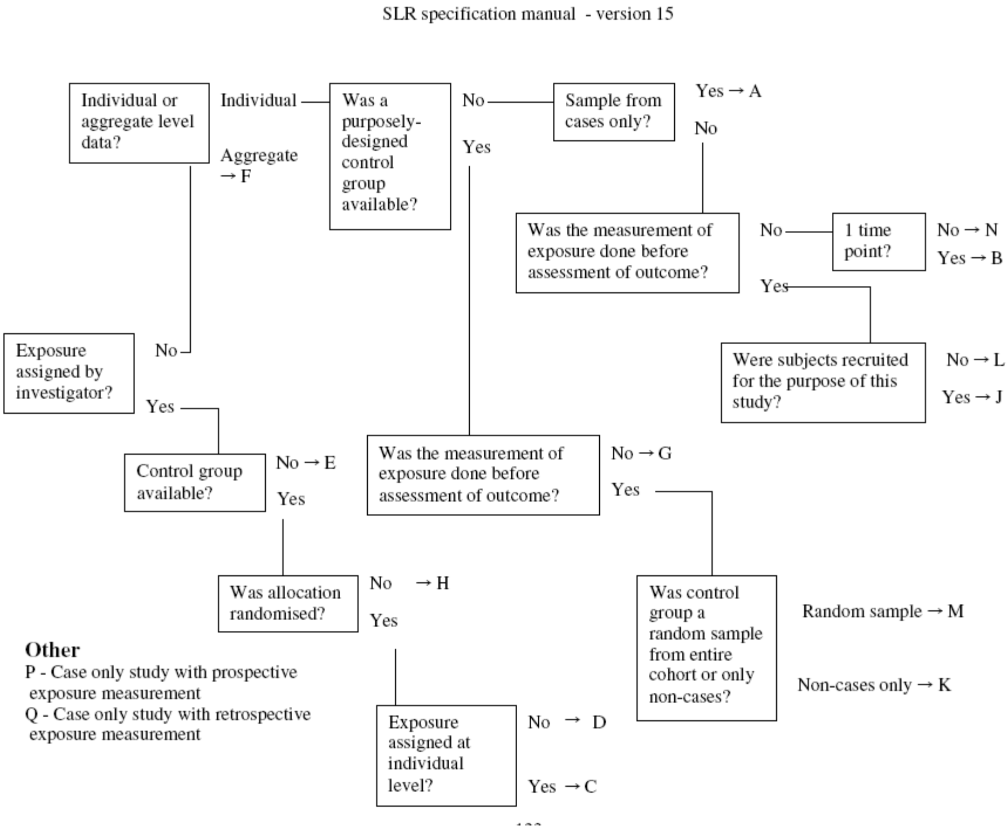
Figure 6. Example of screen for data entry. CUP



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
Other (see definitions in Appendix K)
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: STM (stomach cancer), followed by a 5-digit number that will be allocated in sequence automatically by the interface during data extraction.

7.3 Codification of exposures/interventions.

Exposures/interventions will be codified as in the Second Expert Report for consistency. An abbreviated list of codes is in Annex 2. Additional codes for sub-exposures have been added and are programmed in the database to facilitate and standardise the data entry.

The exposures are coded by main headings and sub-headings. Wherever possible, the reviewer will use sub-heading codes. The reviewer should also extract the details of the exposure definition in the free text box in the data entry screen.

The 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 fetal 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.

The CUP will conduct meta-analysis for the biomarkers for which the evidence on validity and reliability was considered strong for the purpose of the Second Expert Report (full list in Annex 3). However, since the identification and validation of biomarkers is an area of research in nutritional epidemiology (27), 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 Extraction and labelling of study results

The reviewer will extract the associations (RR estimates and confidence intervals) with the relevant exposures from all the statistical models shown in the paper, including subgroup, stratified analyses and sensitivity analyses. These results can be presented in the paper in tables, in the text or as supplemental information.

The reviewer should label the results as unadjusted, intermediately adjusted, most adjusted model, depending of the models that are shown in the paper:

- The results for an exposure obtained with univariate models will be labelled "unadjusted".
- The results for an exposure obtained with a multivariable model including only as covariates age, sex, and in dietary analyses energy intake, will be labelled "less adjusted".
- The results for an exposure 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 less or the most adjusted model, will be labelled "intermediately" adjusted.

In addition, the reviewer will indicate the "best model "for use in meta-analyses.

The "best" model will be the most adjusted model in the article that is a not a "mechanistic" model, which is a model that include variables likely to be in the causal pathway (e.g. milk intake as main exposure in a model adjusted for dietary calcium). When such models are reported, the "intermediately" adjusted result with the highest number of covariates will be indicated as "best model" (e.g. the most adjusted model for milk that does not include calcium).

Sometimes, potential risk factors are not kept in the final model because their inclusion in the model does not substantially modify the risk estimates. If this is indicated in the article text, this model should be considered the "best model".

In addition to adjustment, other subsidiary criteria to consider for identifying the 'best model' for meta-analysis are the completeness of the data (e.g. where number of cases is provided over where missing).

8. Quality control of the article selection and data extraction.

The article selection and the data extracted will be checked by a second reviewer at ICL. If there are discrepancies between the reviewers, the PI will decide and if there is still any doubt about the relevance of a study, the CUP Secretariat will be consulted.

9. Data analysis

9.1 Dose-response meta-analysis

Forest plots showing the study specific results for the highest versus lowest comparison exposure levels will be presented, but a meta-analytical estimate for the highest versus lowest comparison will not be calculated, to avoid pooling different exposure levels. Such as in the Second Expert Report, only linear dose-response meta-analysis will be conducted. This will allow expressing the results of each study in the same increment unit for a given exposure. In addition, non-linear dose-response meta-analyses will be conducted as exploratory analysis. In all forest plots, the studies will be ordered by publication year.

The analyses will be conducted separately for 1) cardia gastric cancer, 2) non-cardia gastric cancer and 3) studies that report on "stomach cancer" or "gastric cancer" without specifying the cancer site. Studies on cases with cancers from combined anatomical localisations will not be included (for instance, gastro-oesophageal cancers). Studies with incidence as outcome will be analysed separately from those with mortality as outcome.

Separate analyses by gender and for both gender combined will be conducted. For the analysis on both gender combined, the results for men and women in the study will be pooled first using fixed effect models and then included in the meta-analysis of "Both genders". This is essentially equivalent to including the estimate for each gender and will provide a better estimate of heterogeneity across studies.

When enough number of studies are identified, separate meta-analyses will be conducted for the subgroups reported in the papers, such as in smokers and non-smokers, with antecedents of H Pylori infection or not, and others.

Where results from two or more cohort studies are reported in the same paper, the results of each cohort will be included separately if they are provided and the pooled result will not be included. The purpose is to maintain the independence of observations included and to look at heterogeneity across study results.

The statistical methods are described in section 9.5

9.2 Selection of exposures for a dose-response meta-analysis

A dose-response meta-analysis will be conducted when at least two new reports of trials or of two cohort studies are identified during the CUP. This refers to studies providing enough information to conduct dose-response meta-analysis. 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.

The meta-analysis will include studies identified during the SLR and studies identified during the CUP. Special care will be taken to avoid including more than once the same study. 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 does not provide enough information for the dose-response meta-analysis, the publication with the required information will be selected.

If the results of the same study are not consistent across time and the most recent publication of a study cannot be included in the meta-analysis, the CUP team will conduct influence analysis of this study.

9.3 Selection of results data for meta-analyses

The results based on "best" adjusted models (full multivariable model in the articles) will be used in the dose-response meta-analyses.

When the relative risk estimate per unit of increase is reported in an article, this will be used in the CUP dose-response meta-analysis.

If the results are presented only in categorical variables (quantiles or pre-defined categories), the slope of the dose-response relationship will be derived from the categorical data.

The data required to derive the dose-response slope in each study are:

1. number of individuals with the disease for each exposure category
2. person-years -or number of individuals without the disease in nested case-control analyses- for each exposure category
3. exact cut-offs of exposure categories, or mean or median of each category.

9.4 Derivation of data required for meta-analyses.

The information provided in the articles is often incomplete and this may result in exclusions of results from meta-analyses. For instance, only 64% of the results of cohort studies on stomach and prostate cancer provided enough data to be included in dose-response meta-analysis in the SLR for the Second Expert Report. There is also empirical evidence that studies that showed evidence of an association were more likely to be usable in dose-response meta-analysis than results that did not show any evidence (28).

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, missing data will be derived when possible during the phase of statistical analyses using other information provided in the paper (**Table 2**).

A number of approaches will be taken to derive the number of controls (or person-years) and mean exposure value for each exposure category from the available data where possible (28). When intake was expressed in "times" or "servings of intake", we will convert it into grams (g) using standard portion sizes used in the WCRF/AICR report (4) .

Means or medians of the intake categories will be assigned as "dose" when reported in the articles; if not reported, midpoints will be assigned to the relative risk of the corresponding category. If the upper boundary for the highest category was not reported, we will assume that the boundary had the same amplitude as the nearest category. 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. The approaches are summarized in **Table 2**.

9.5 Statistical Methods

For the linear dose-response meta-analyses, we will pool the slopes of the dose-response relationships reported in the studies. When only relative risk estimates for categorical data are reported in the paper, we will derive the slope of the "dose"-response association from the categorical data using generalized least-squares for trend estimation (29). This method accounts for the correlation between relative risks estimates with respect to the same reference category (30). The dose-response model is forcing the fitted line to go through the origin (logRR=0, dose=0). Therefore, whenever the assigned dose corresponding to the reference group (RR=1) is different from zero, all the assigned doses will be rescaled.

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 (31), with the estimate of heterogeneity being taken from the inverse-variance fixed-effect model.

Table 2. 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	Standard error and hence confidence interval were calculated from raw numbers (although doing so may result in a somewhat smaller standard error than would be obtained in an adjusted analysis)
	Group mean are missing	This information may be estimated by using the method of Chêne and Thompson(4;32) 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	These numbers may be inferred based on numbers of cases and the reported odds ratio (proportions will be correct unless adjustment for confounding factors considerably alter the crude odds ratios)

Publication and related bias (e.g. small study bias) will be explored through visual examination of funnel plots and Egger's test (33).

Heterogeneity between studies will be assessed visually from forest plots and with statistical tests (P value <0.05 will be considered statistically significant). Heterogeneity will be quantified with the I^2 statistic - where I^2 values of 25%, 50%, and 75% correspond to cut-off points for low, moderate, and high degrees of heterogeneity (34).

Stratified analyses will be performed to investigate potential sources of heterogeneity even if the initial overall test for heterogeneity is non-significant as these tests often have low power. The variables that will be explored as sources of heterogeneity are outcome definition, method of exposure assessment, gender, geographic area/country, level of adjustment (for instance, adjustment for dietary factors likely to be related to the risk of the investigated cancer), and in particular adjustment for *H.pylori* infection (for nongastric cardia and gastric cancer, site non-specified), publication year, study size, length of follow-up. These variables will be explored if there are at least two studies in each of the categories of the variable. Meta-regression will be conducted when the number of studies allows it.

The interpretation should be cautious. If a considerable number of study characteristics are considered as possible explanations for heterogeneity in a meta-analysis containing only a small number of studies, then there is a high probability that one or more will be found to explain heterogeneity, even in the absence of real associations between the study characteristics and the size of associations.

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 types of cancers are considered in a study (e.g. it is unclear if part of the cases might be of oesophageal cancer)
- Including and excluding studies where exposure 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.

All analyses will be conducted in Stata/SE 12.1.

10. Reports

An updated report will be sent to the CUP Secretariat in 2014. The report will include the following elements:

10.1 Modifications of the approved protocol

Any modification required during the review will be described

10.2 Results of the search

Information on 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.
This information will be summarised in a flowchart.

10. 3 Description of studies identified in the continuous update

Number of studies by study design and publication year.
Number of studies by population characteristics (gender, geographic area, others)

Number of studies by exposure (main heading and selected subheadings) and publication year
Number of studies by exposure and outcome subtype

10.4 Summary of number of studies by exposure and study type in the database, separated on studies identified in the continuous update and studies identified during the CUP.

10.5 Tabulation of study characteristics

The tables will include study characteristics (e.g. population, exposure, outcome, study design) and results of the study (e.g. direction and magnitude).

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 (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	OR	(95% CI)	p trend	Adjustment factors						
							A	B	C	D	E	F	G

Where
A: Age
B: Ethnicity, race
C: Smoking
D: Anthropometric factors
E: Alcohol intake
F: Family history
G: Others, e.g. dietary factors, socioeconomic status, *H.pylori* infection

10.6 Graphic presentation

Tabular presentation will be complemented with graphic displays when the number of studies justifies it. 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 five studies.

10.7 Results of 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.

The results of meta-regression, stratified analyses and sensitivity analysis will be presented in tables and, when the number of studies justifies it, in forest plots.

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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 physical 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 stomach cancer:

#23 Stomach neoplasms[MeSH Terms]

#24 Stomach neoplasm*[tiab] OR stomach cancer*[tiab] OR stomach carcino* OR stomach tumo*[tiab] OR stomach metasta* [tiab] OR stomach malign*[tiab] OR stomach adenocarcinoma* [tiab]

#25 Gastric neoplasm* [tiab] OR gastric cancer*[tiab] OR gastric carcino* [tiab] or gastric tumo*[tiab] OR gastric metasta*[tiab] OR gastric malign*[tiab] OR gastric adenocarcinoma* [tiab]

#26 Gastrointestinal neoplasms[mesh terms] OR gastrointestinal neoplas*[tiab] OR gastrointestinal cancer*[tiab] OR gastrointestinal carcino*[tiab] OR gastrointestinal tumo*[tiab] OR gastrointestinal metasta*[tiab] OR gastrointestinal malign*[tiab] OR gastrointestinal adenocarcinoma*[tiab]

#27 Digestive tract neoplasm*[tiab] OR digestive tract cancer*[tiab] OR digestive tract carcino*[tiab] OR digestive tract tumo*[tiab] OR digestive tract metasta*[tiab] OR digestive tract malign*[tiab] OR digestive tract adenocarcinoma*[tiab]

#28 Alimentary tract neoplasm*[tiab] OR alimentary tract cancer*[tiab] OR alimentary tract carcino*[tiab] OR alimentary tract tumo*[tiab] OR alimentary tract metasta*[tiab] OR alimentary tract malign* OR alimentary tract adenocarcinoma*[tiab]

#29 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]

#30 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]

#31 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]

#32 Oesophago gastric neoplasm*[tiab] OR oesophago gastric cancer*[tiab] OR oesophago gastric carcino* OR oesophago gastric tumo*[tiab] OR oesophago gastric metasta* [tiab] OR oesophago gastric malign*[tiab] OR oesophago gastric adenocarcinoma* [tiab]

#33 Stomach adenoma*[tiab] OR gastric adenoma*[tiab] OR gastrointestinal adenoma*[tiab] OR digestive tract adenoma*[tiab] OR alimentary tract adenoma*[tiab] OR esophagogastric adenoma*[tiab] OR esophagogastric adenoma*[tiab] OR oesophagogastric adenoma*[tiab] OR oesophagogastric adenoma*[tiab]

#**34** #23 OR #24 OR #25 OR #26 OR #27 OR #28 OR #29 OR #30 OR #31 OR #32 OR #33

3) Searching for all studies relating stomach cancer, and food, nutrition and physical activity:

#35 #22 AND #34

Annex 2. List of headings and exposure codes (minimum list)
**Indicated 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, lentils
*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 Offal, 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

E.g. snacks, crisps, desserts, pizza. Also report any mixed food exposures here i.e. if an exposure is reported as a combination of 2 or more foods that cross categories (e.g. 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, stomach 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)

*5.4.1.1 Alcohol (as ethanol) from beer
*5.4.1.2 Alcohol (as ethanol) from wine
*5.4.1.3 Alcohol (as ethanol) from spirits
*5.4.1.4 Alcohol (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 componds, which are not phytochemicals should be reported under the separate heading 'other bioactive compounds'. E.g. 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