World Cancer Research Fund International Systematic Literature Review

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

CUP Continuous Update Project

Analysing research on cancer prevention and survival

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Date completed:
28/11/2014
Date revised:
20/12/2016

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List of Abbreviations used in the CUP SLR

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

Other abbreviations used in Tables

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

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

AHS	Californian Seventh Day Adventists
Aichi	Aichi Cancer Registry Study
APC	Anderson Plan Cohort
ATBC	Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study
Basel Study	Basel Switzerland Study
BIRNH	Belgian Interuniversity Research on Nutrition and Health
BOCS	Boyd Orr Cohort Study
BRHS	British Regional Heart Study
BUPA	BUPA Study
BWHS	Black Women’s Health Study
CARET	Carotene and Retinol Efficacy Trial
Caerphilly	Caerphilly, South Wales, Cohort
CCCJ	Chiba Cancer Cohort, Japan
CCPS	Copenhagen Centre for Prospective Population Studies
CECS	Chinese Elderly Cohort Study
CLUE	Campaign Against Cancer and Stroke, Washington County, Maryland
CMHS	California Men's Health Study
CMS	Copenhagen Male Study

CNBSS	Canadian National Breast Screening Study
CNRPCS	China Nationally Representative Prospective Cohort Study
COSMOS	Continuous Observation of Smoking Subjects
CPS	Cancer Prevention Study
CPRD	Clinical Practice Research Datalink
DCH	Danish Diet, Cancer and Health study
Dutch Cohort	Dutch Male Birth Cohort
E3N	*Étude Épidémiologique auprès des femmes de la Mutuelle Générale de l'Éducation Nationale*
EPIC	European Prospective Investigation into Cancer and Nutrition
ESTHER	Epidemiologische Studie zu Chancen der Verhütung, Früherkennung und optimierten Therapie chronischer Erkrankungen in der älteren Bevölkerung
Finnish Athletes	Cohort of Finnish Male Athletes
FinDrink	FinDrink Study
FMCHS	Finnish Mobile Clinic Health Examination Survey
FHS	Framingham Heart Study
FinRisk	The FinRisk Study
French WWII	French Second World War Cohort
HAHS	Harvard Alumni Health Study
HES/ MFHS	Mini-Finland Health Survey
HFSS	Health Food Shoppers Study
HGSC/ Hokkaido	Hokkaido Government Cohort Study
HHP	Honolulu Heart Program
Hiroshima Nagasaki	Hiroshima Nagasaki Study
HPFS	Health Professionals Follow-up Study
ICSS	Israel Civil Servant Study
IWHS	Iowa Women's Health Study
JACC	Japan Collaborative Cohort Study
Japan-Hawaii	Japan-Hawaii Cancer Study
JPHC	The Japan Public Health Centre-based Prospective Study
KCP	Kaiser Permanente Medical Care Program
KRIS	Kaunas Rotterdam Intervention Study and Multifactorial Ischemic Heart Disease Prevention Study
KIHD	Kuopio Ischaemic Heart Disease Risk Factor Study
KMICS/ KMIC	Korea Medical Insurance Corporation
KMCC	Korean Multi-Centre Cancer Cohort
KNHIC	Korea National Health Insurance Corporation Study
Korea 2004-2013	Korea Cohort 2004-2013
LBS	Lutheran Brotherhood Cohort Study
LSS	Life Span Study, atomic bomb survivors, Japan
LWS	Leisure World Study, Laguna Hills Study USA
MCCS	The Melbourne Collaborative Cohort Study

MCS	Miyagi Cohort Study
MEC	Multiethnic Cohort Study
MRFIT	The Multiple Risk Factor Intervention Trial
Monica10, Inter99, Health2006	MONICA 10 & Inter99 & Health 2006 Cohort Study
MWS	Million Women Study
Nagoya 1983-2000	Nagoya 1983-2003 Cohort Study
NHANES	National Health and Nutrition Examination Survey
NHEFS	Nutrition Examination Survey Epidemiology Follow-up Study
NHIS	National Health Interview Survey
NIH-AARP	NIH-AARP Diet and Health Study
NHS	Nurses' Health Study
NKP	North Karella Project
NLCS	The Netherlands Cohort Study on Diet and Cancer
Norway 1967-78	Norway 1967-1978 Cohort Study
NSC	Norway Study Cohort
NYSC	New York State Cohort Study
Oahu	Oahu Cohort Study
Ohsaki/OCS	Ohsaki Cohort Study
PHS	Physicians Health Study
PLCO	Prostate, Lung, Colorectal, and Ovarian (PLCO) Cancer Screening Study
Reykjavik Study	Reykjavik Study Cohort
SCHS	Singapore Chinese Health Study
SECS	Shizuoka Elderly Cohort Study
Shanghai China	Shanghai Study Cohort
SHOW	Smoking Health Study of Wisconsin
Shell Study	Shell Oil Company's Study
SMHS	Shanghai Men's Health Study
SMART	Second Manifestations of ARTerial disease (SMART) study
SWHS	Shanghai Women's Health Study
TAC	Taiwan Arsenic Cohort, 1985-2000
VHM&PP	The Vorarlberg Health Monitoring and Prevention Program
VITAL	Vitamins And Lifestyle cohort
WES	Western Electric Company Study
WHI-DI & OS	Women's Health Initiative - Dietary Modification Trial and Observational Study
WS	Whitehall Study
YTC/Chinese Miners	Chinese Miners, High Risk Population Study
Zutphen Study	Zutphen Study Cohort

Background

The main objective of the present systematic literature review is to update the evidence from prospective studies and randomised controlled trials on the association between foods, nutrients, physical activity, body adiposity and the risk of lung 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 lung cancer (version 2, July 2013 in Annex).

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

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

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

	DECREASES RISK	INCREASES RISK
Convincing		**Arsenic in drinking water**[1] **Beta-carotene supplements**[2]
Probable	**Fruits**[3] **Foods containing carotenoids**[4]	
Limited — suggestive	Non-starchy vegetables[3] Foods containing selenium[4] Foods containing quercetin[4] Selenium[5] Physical activity[6]	Red meat[7] Processed meat[8] Total fat Butter Retinol supplements[2] Low body fatness
Limited — no conclusion	Cereals (grains) and their products; starchy tubers; dietary fibre; pulses (legumes); poultry; fish; eggs; milk and dairy products; total fat; animal fats; plant oils; soft drinks; coffee; tea; alcohol; preservation, processing, and preparation; carbohydrate; protein vitamin A; thiamin; riboflavin; niacin; vitamin B6; folate; vitamin C; vitamin E; multivitamins; calcium; copper; iron; zinc; pro-vitamin A carotenoids; lycopene; flavonoids; culturally-defined diets; body size, shape, and composition (except low body fatness); energy intake	
Substantial effect on risk unlikely	None identified	

1 The International Agency for Research on Cancer has graded arsenic and arsenic compounds as Class 1 carcinogens. The grading for this entry applies specifically to inorganic arsenic in drinking water.
2 The evidence is derived from studies using high-dose supplements (20 mg/day for beta-carotene; 25 000 international units/day for retinol) in smokers.
3 Judgements on vegetables and fruits do not include those preserved by salting and/or pickling.
4 Includes both foods naturally containing the constituent and foods which have the constituent added (see chapter 3.5.3).
5 The evidence is derived from studies using supplements at a dose of 200 μg/day.
6 Physical activity of all types: occupational, household, transport, and recreational.
7 The term 'red meat' refers to beef, pork, lamb, and goat from domesticated animals.
8 The term 'processed meat' refers to meats preserved by smoking, curing, or salting, or addition of chemical preservatives.

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

World Cancer Research Fund American Institute for Cancer Research

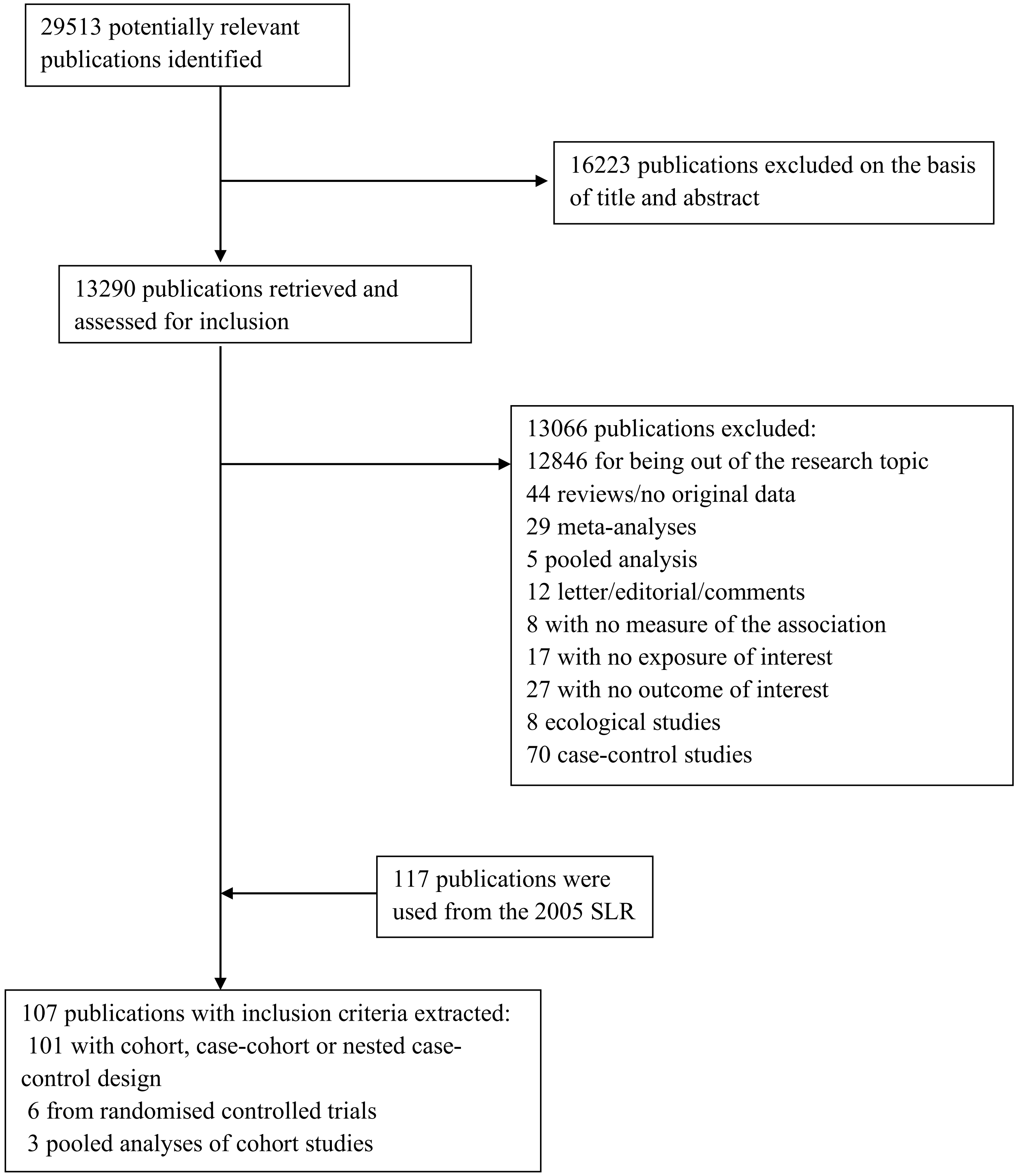
Notes on methods

- The article search and WCRF database update for the Second Expert Report ended in December 30th 2005. The CUP team at IC updated the search from January 1st 2006 up to September 30th 2014 (See Flowchart).
- 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.
- The term "dose-response meta-analysis" refers to meta-analysis conducted using log-linear dose-response models. Non-linear meta-analysis refers to meta-analysis using log-non-linear models.
- Exposures for which the evidence was judged as convincing, probable or limited-suggestive in the Second Expert Report were reviewed even if the number of publications was below the previous figures; in most cases, the new data on these exposures are tabulated and no meta-analyses were conducted.
- For comparability, the increment units for the dose-response analyses were those used in the meta-analyses in the CUP- SLR conducted for other cancers . However, if most of the identified studies reported in a different unit (servings or times/day instead of g/day) these were used as increment unit, as indicated in the Protocol. The units used may differ from those used in the 2005 SLR.
- The statistical methods to derive missing data are described in the protocol.
- The interpretation of heterogeneity tests should be cautious when the number of studies is low. Visual inspection of the forest plots and funnel plots is recommended.
- The I^2 statistic describes the proportion of total variation in study estimates that is due to heterogeneity. Low heterogeneity might account for less than 30 per cent of the variability in point estimates, and high heterogeneity for substantially more than 50 per cent. These values are tentative, because the practical impact of heterogeneity in a meta-analysis also depends on the size and direction of effects.
- Only summary relative risks estimated with random effect models are shown.
- Highest vs lowest forest plots show the relative risk estimates for the highest vs the reference category in each study. The overall summary estimate was not calculated except for exposures such as physical activity, supplement use our total fat where dose-response analysis could not be conducted or when the pooling project results could be included in a highest compared to lowest analysis, but not in a dose-response analysis.
- The dose-response forest plots show the relative risk per unit of increase for each study (most often derived by the CUP review team from categorical data). The relative risk is denoted by a box (larger boxes indicate that the study has higher precision, and greater weight). Horizontal lines denote 95% confidence intervals (CIs). Arrowheads indicate truncations. The diamond at the bottom shows the summary relative risk estimate and corresponding 95% CI. The unit of increase is indicated in each figure and in the summary table for each exposure.

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

Continuous Update Project: Results of the search

Flow chart of the search for lung cancer – Continuous Update Project
Search period January 1st 2006-September 30th 2014



Cohort studies. Results by exposure

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

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

Exposure Code	Exposure Name	Number of publications		Total number of publications
		2005 SLR	CUP	
1.3	Vegetarian diets	2	1	3
1.3	Seventh-day Adventist diet	-	1	
1.4	Health Index Score	2	2	4
1.4	Dietary pattern derived by factor analysis	1	1	2
1.4	Diet preferences	-	2	2
1.1.1	Mediterranean diet	0	1	1
1.6.1	Total duration of breastfeeding	0	1	1
2.1.1	Cereals (grains)	7	1	8
2.1.1.0.3	Bread	0	1	1
2.1.1.1.3	Pasta	0	1	1
2.1.1.2.3	Rice	0	2	2
2.1.2	Root vegetables	0	3	3
2.1.2.1	Potatoes	0	3	3
2.1.2.1	Sweet potatoes	0	1	1
2.2	Fruit and (non-starchy) vegetables	10	9	19
2.2	Vegetables and fruits high in lutein	0	1	1
2.2.1	Fried vegetables	0	1	1
2.2.1	Fruiting vegetables	0	2	2
2.2.1	Total vegetables	22	10	32
2.2.1	Vegetables rich in carotenoids	0	1	1
2.2.1.1	Garlic and onion	0	2	2
2.2.1.1.1	Carrots and carrots juice	0	2	2
2.2.1.2	Cruciferous vegetables	13	4	17
2.2.1.2.11	Radishes	0	1	1
2.2.1.2.2	Chinese cabbage	0	2	2
2.2.1.2.3	Cabbage	0	3	3
2.2.1.2.3	Green cabbage	0	1	1
2.2.1.2.5	Cauliflower	0	1	1
2.2.1.3	Allium vegetables	2	2	4
2.2.1.3.1	Garlic supplement or extract	0	1	1

Exposure Code	Exposure Name	Number of publications		Total number of publications
		2005 SLR	CUP	
2.2.1.4	Green leafy vegetables	8	4	12
2.2.1.4	Spinach/other greens	0	1	1
2.2.1.4.2	Spinach	0	2	2
2.2.1.4.4	Seaweed	0	1	1
2.2.1.5	Artichokes	0	1	1
2.2.1.5	Cucumbers, melons, squash	0	1	1
2.2.1.5	Lettuce, cabbage	0	1	1
2.2.1.5	Mixed salad	0	1	1
2.2.1.5	Mushrooms	0	2	2
2.2.1.5	Pickles	0	1	1
2.2.1.5	Pumpkin	0	1	1
2.2.1.5.13	Tomatoes	0	3	3
2.2.2	Total fruits	34	10	44
2.2.2.1	Citrus fruits	9	8	17
2.2.2.2	Apples, pears	0	1	1
2.2.2.2	Berries	0	1	1
2.2.2.2	Rosaceae	0	2	2
2.2.2.2	Stone fruit	0	2	2
2.2.2.2.1	Bananas	0	1	1
2.2.2.2.11	Grape	0	2	2
2.2.2.2.4	Watermelon	0	1	1
2.3	Pulses (legumes)	6	4	10
2.3.1	Soya foods	0	1	1
2.3.1.1	Miso soup	0	1	1
2.3.1.5	Tofu, soybeans	0	2	2
2.3.2	Beans	0	1	1
2.4	Nuts and seeds	1	2	3
2.5	Meat, poultry, fish and eggs	1	0	1
2.5	Panfried red and processed meat	0	1	1
2.5.1	Broiled meat	0	1	1
2.5.1	Processed and organ meat	0	2	2
2.5.1	Red and processed meat	0	1	1
2.5.1	Total meat	11	1	12
2.5.1	Well-/very well done meat	0	1	1
2.5.1	White meat	0	2	2
2.5.1.2	Ham and sausages	0	1	1
2.5.1.2	Microwaved red meat	0	1	1
2.5.1.2	Processed meat	4	7	11
2.5.1.2.2	Fried meat	0	1	1

Exposure Code	Exposure Name	Number of publications		Total number of publications
		2005 SLR	CUP	
2.5.1.3	Red meat	2	6	8
2.5.1.3	Veal	0	1	1
2.5.1.3.1	Beef	1	2	3
2.5.1.3.3	Pork	3	3	6
2.5.1.4	Poultry	4	4	8
2.5.1.5	Liver	0	1	1
2.5.1.5	Offals	0	1	1
2.5.2	Fish	8	5	13
2.5.2	Fish paste	0	1	1
2.5.2.3	Dried and salted fish	0	1	1
2.5.2.4	Fried fish	0	1	1
2.5.3	Shellfish and other seafood	2	1	3
2.5.4	Eggs	8	3	11
2.6	Fat preference	0	1	1
2.6.1.1	Butter	2	2	4
2.6.1.4	Cod liver oil	0	1	1
2.6.1.4	Fish oil	0	1	1
2.6.2	Olive oil	0	1	1
2.6.2	Vegetable oil	0	1	1
2.6.3	Margarine	0	2	2
2.6.4	Fructose	0	1	1
2.6.4	Sugars (as foods)	0	1	1
2.7	Dairy products	0	4	4
2.7	Milk and dairy products	9	0	9
2.7.1	Milk	6	2	8
2.7.2	Cheese	0	2	2
2.7.3	Yoghurt	0	2	2
2.7.7	Ice cream	0	1	1
2.8	Herbs	0	1	1
2.8.1.3	Ginseng	0	1	1
2.9	Honey and jam	0	1	1
2.9	Pie	0	1	1
2.9	Salted cracker	0	1	1
2.9.1	Cakes, biscuits and pastry	0	1	1
2.9.11	Soups	0	1	1
2.9.13	Sweets	0	2	2
2.9.14	Pizza	0	1	1
3.2	Well or spring water (public water supply)	0	1	1
3.4	Soft drinks	3	1	4

Exposure Code	Exposure Name	Number of publications		Total number of publications
		2005 SLR	CUP	
3.5	Fruit and vegetable juices	4	1	5
3.5.1	Citrus fruit juice	0	1	1
3.6.1	Coffee	6	4	10
3.6.2	Black tea	2	1	3
3.6.2	Tea	5	1	6
3.6.2.2	Green tea	5	4	9
3.7	Binge drinking habits	0	1	1
3.7.1	Alcohol consumption	0	12	12
3.7.1	Alcoholic drinks	12	2	14
3.7.1	Alcoholic drinks - precocity of use (age at first use)	0	1	1
3.7.1	Alcoholic drinks - years since stopping	0	1	1
3.7.1	Alcoholism	2	2	4
3.7.1	Drinking duration	0	1	1
3.7.1	Drinking frequency	0	1	1
3.7.1	Total alcoholic drinks	32	2	34
3.7.1.1	Beers	6	3	9
3.7.1.2	Red wines	0	2	2
3.7.1.2	White wines	0	2	2
3.7.1.2	Wines	4	3	7
3.7.1.4	Liquor/Spirits	5	3	8
4.1.2.7.2	Arsenic	6	4	10
4.2	Preserved foods	0	1	1
4.2.5.1	Salt	0	1	1
4.3.5.4.1	Ndma (n-nitrosodimethylamine)	0	1	1
4.3.5.4.1	Nitrite	0	1	1
4.3.5.4.1	Nitrosamines	0	1	1
4.4.2	Acrylamide	0	2	2
4.4.2	Rare/medium done red meat	0	2	2
4.4.2	Well/very well done red meat	0	1	1
4.4.2.3	Baked meat	0	1	1
4.4.2.5	Fried foods	0	1	1
4.4.2.5	Pan-fried	0	1	1
4.4.2.6	Grilled meat	0	1	1
4.4.2.6	Grilled/barbecued red meat	0	1	1
4.4.2.6	Oven-broiled red meat	0	1	1
4.4.2.6	Rare/medium	0	1	1

Exposure Code	Exposure Name	Number of publications		Total number of publications
		2005 SLR	CUP	
	grilled/barbecued red meat			
4.4.2.7	Bap	0	2	2
4.4.2.8	Dimelqx	0	3	3
4.4.2.8	Melqx	0	1	1
4.4.2.8	Phip	0	2	2
4.4.2.9	Mutagen index, meat	0	2	2
5.1	Total carbohydrate	3	0	3
5.1.1	Preference diet low in carbohydrates	0	1	1
5.1.2	Crude fibre	1	0	1
5.1.2	Dietary fibre	1	0	1
5.1.2	Insoluble fibre	1	0	1
5.1.3	Starch	1	0	1
5.1.4	Mono/disaccharides	0	1	1
5.1.4	Sucrose	0	1	1
5.1.4	Sugars (as nutrients)	0	1	1
5.1.5	Glycemic index	0	1	1
5.1.5	Glycemic load	0	1	1
5.2	Total fat (as nutrients)	5	2	7
5.2.2	Saturated fatty acids	4	0	4
5.2.3	Monounsaturated fatty acids	4	0	4
5.2.4	Polyunsaturated fatty acids	4	1	5
5.2.4.2	N-6 fatty acids	1	0	1
5.2.5	Trans fatty acids	0	1	1
5.3	Protein	2	1	3
5.3.1	Methionine	0	3	3
5.3.1	Serum methionine	0	1	1
5.3.2	Plant protein	1	0	1
5.3.3	Animal protein	1	0	1
5.4	Alcohol (as ethanol)	29	20	49
5.5	Vitamins	12	0	12
5.5	Vitamins supplement	0	1	1
5.5.1	Dietary vitamin A	4	1	5
5.5.1	Total vitamin A	5	0	5
5.5.1	Preformed vitamin A	1	0	1
5.5.1	Vitamin a supplement	2	1	3
5.5.1.1	Retinol supplement	1	2	3
5.5.1.1	Retinol, dietary	6	1	7
5.5.1.1	Serum retinol	17	3	20
5.5.1.2	Beta-carotene supplements	1	2	3

Exposure Code	Exposure Name	Number of publications		Total number of publications
		2005 SLR	CUP	
5.5.1.2	Beta-carotene, dietary	18	1	19
5.5.1.2	Serum beta-carotene	17	3	20
5.5.1.2	Beta-cryptoxanthin, dietary	7	1	8
5.5.1.2	Provitamin A carotenoids	6	0	6
5.5.1.2	Alpha-carotene, dietary	8	0	8
5.5.1.2	alpha-carotene, blood	7	3	10
5.5.1.2	Beta-cryptoxanthin, dietary	6	1	7
5.5.1.2	Serum beta-cryptoxanthin	7	3	10
5.5.1.2	Serum provitamin A	0	1	1
5.5.1.2	Serum total carotenes	0	1	1
5.5.10	25-hydroxy vitamin D	0	1	1
5.5.10	Blood 25-hydroxyvitamin D	0	7	7
5.5.10	Total vitamin D	0	1	1
5.5.10	Vitamin D and calcium	1	0	1
5.5.10	Vitamin D supplement	0	1	1
5.5.11	Alpha-tocopherol	12	0	12
5.5.11	Alpha-tocopherol from food	0	1	1
5.5.11	Gamma-tocopherol	3	0	3
5.5.11	Plasma alpha-tocopherol	0	1	1
5.5.11	Plasma tocopherol (vitamin E)	0	1	1
5.5.11	Serum alpha-tocopherol	0	1	1
5.5.11	Serum tocopherol (vitamin E)	0	1	1
5.5.11	Total alpha-tocopherol intake	0	1	1
5.5.11	Total tocopherol serum levels	0	1	1
5.5.11	Vitamin beta-E + gamma-E	0	1	1
5.5.11	Vitamin delta-E	0	1	1
5.5.11	Vitamin E	17	1	18
5.5.11	Vitamin E from foods	0	1	1
5.5.11	Vitamin E from supplements	2	4	6
5.5.12	Vitamin K	0	1	1
5.5.13	B complex vitamin supplement	0	1	1
5.5.13	Duration of multivitamin use	0	1	1
5.5.13	Multivitamin supplement	0	6	6
5.5.13	Multivitamins/minerals	0	1	1

Exposure Code	Exposure Name	Number of publications		Total number of publications
		2005 SLR	CUP	
5.5.13	Other vitamins (including multivitamins)	2	1	3
5.5.13	Supplement containing vitamin C and E	0	1	1
5.5.2	Carotenoids, dietary	9	1	10
	Carotenoids, blood	5	2	7
5.5.2	Lutein	0	1	1
5.5.2	Lutein and zeaxanthin, dietary	5	0	5
5.5.2	Lutein and zeaxanthin, blood	6	3	9
5.5.2	Lycopene, dietary	9	0	9
5.5.2	Lycopene, blood	6	3	9
5.5.2	Serum canthaxanthin	0	1	1
5.5.2	Serum total xanthophylls	0	1	1
5.5.3	Dietary folate	5	6	11
5.5.3	Folate supplement	0	2	2
5.5.3	Folates and associated compounds	9	1	10
5.5.3	Folic acid from supplements	0	1	1
5.5.3	Plasma folate	3	1	4
5.5.3	Plasma homocysteine	0	1	1
5.5.4	Riboflavin	2	3	5
5.5.4	Riboflavin, biomarker	0	1	1
5.5.5	Thiamin (vitamin B1)	2	1	3
5.5.5	Thiamin (vitamin B1) supplement	0	1	1
5.5.6	Niacin	2	2	4
5.5.7	Plasma pyridoxine (vitamin B6)	0	1	1
5.5.7	Pyridoxine (vitamin B6)	3	2	5
5.5.8	Cobalamin (vitamin B12)	2	1	3
5.5.8	Dietary vitamin B12 intake	0	1	1
5.5.8	Plasma cobalamin (vitamin B12)	0	1	1
5.5.9	Dietary vitamin c	14	3	17
5.5.9	Supplemental vitamin C	3	3	6
5.5.9	Total vitamin C	0	1	1
5.6.1	Sodium	1	1	2
5.6.2	Heme iron	0	2	2

Exposure Code	Exposure Name	Number of publications		Total number of publications
		2005 SLR	CUP	
5.6.2	Iron	5	1	6
5.6.2	Iron, serum	0	1	1
5.6.3	Calcium	0	1	1
5.6.3	Calcium from supplements	0	1	1
5.6.3	Dietary calcium	0	4	4
5.6.3	Supplemental calcium	0	1	1
5.6.3	Total calcium	0	2	2
5.6.4	Toenail selenium	3	0	3
5.6.4	Dietary selenium	2	0	2
5.6.4	Selenium, serum	11	2	13
5.6.6	Cadmium	0	2	2
5.6.6	Magnesium	0	3	3
5.6.6	Other minerals	4	0	4
5.6.6	Phosphate	0	1	1
5.6.6	Phosphorus	0	1	1
5.6.7	Zinc	0	1	1
5.7.2	Isothiocyanates	1	1	2
5.7.2	Urine isothiocyanates	0	1	1
5.7.5	Plasma daidzein	0	1	1
5.7.5	Plasma genistein	0	1	1
5.7.5	Plasma glycitein	0	1	1
5.7.5	Total isoflavones	0	1	1
5.7.7	Total nitroso compounds	0	1	1
5.7.7	Quercetin	0	2	2
5.8	Anthocyanidins	0	2	2
5.8	Flavan-3-ols	0	2	2
5.8	Flavanones	0	2	2
5.8	Flavones	0	2	2
5.8	Flavonoids	0	3	3
5.8	Flavonols	0	2	2
5.8	Isoflavones	0	5	5
6.1	Physical activity	4	1	5
6.1	Physical activity index	0	1	1
6.1	Physical activity level	0	1	1
6.1	Total physical activity (overall summary measures)	13	0	13
6.1.1.1	Occupational physical activity	4	3	7
6.1.1.2	Bicycling	0	1	1
6.1.1.2	Leisure time physical	0	1	1

Exposure Code	Exposure Name	Number of publications		Total number of publications
		2005 SLR	CUP	
	activity score			
6.1.1.2	Recreational activity	13	9	22
6.1.1.2	Recreational physical activity index	0	1	1
6.1.1.2	Sports	0	3	3
6.1.1.2	Stair climbing	0	2	2
6.1.1.2	Walking	0	2	2
6.1.1.3	Gardening	0	1	1
6.1.1.3	Household activity	2	2	4
6.1.2	Frequency of physical activity	0	2	2
6.1.3	Moderate and vigorous physical activity	0	1	1
6.1.3	Total light physical activity	0	1	1
6.1.3	Vigorous physical activity	0	2	2
6.1.3.2	Moderate and strenuous recreational activity in late adulthood	0	1	1
6.1.3.2	Moderate leisure time activity	0	1	1
6.1.3.2	Vigorous recreational activity	0	2	2
6.1.3.2	Walking pace	0	1	1
6.1.4	Duration of physical activity	0	1	1
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	3	10
7.1.0.2	Energy from protein	0	1	1
8.1.1	BMI	24	23	47
8.1.1	BMI (after menopause)	0	1	1
8.1.1	BMI at 18 yrs	0	2	2
8.1.1	BMI at 20 yrs	0	1	1
8.1.1	BMI at 40 yrs	0	1	1
8.1.1	BMI at age 50	0	1	1
8.1.1	BMI at certain age	0	1	1
8.1.3	Weight	4	2	6
8.1.3	Weight at 18 yrs	0	1	1
8.1.3	Weight at 20 yrs	0	1	1
8.1.3	Weight at certain age	0	1	1

Exposure Code	Exposure Name	Number of publications		Total number of publications
		2005 SLR	CUP	
8.1.6	Weight change	0	1	1
8.1.6	Weight change since 18 yrs	0	1	1
8.1.6	Weight change, from age 20	0	1	1
8.2.1	Waist circumference	1	5	6
8.2.2	Hips circumference	0	1	1
8.2.3	Waist to hip ratio	1	4	5
8.2.5	Other marker for fat distribution eg ct, ultrasound	1	1	2
8.3.1	Height	1	8	9
8.3.2	Biacromial diameter	0	1	1
8.3.2	Leg length	1	1	2
8.3.2	Other skeletal size (e.g. leg length)	2	1	3
8.3.2	Trunk length	0	1	1
8.4.1	Birthweight	0	3	3

1. Patterns of diet

No meta-analysis was conducted because of the differences across the patterns investigated in the studies. A narrative review follows.

Table 2 Dietary patterns and lung 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
Cohort studies		
Health scores	4	3*
Dietary patterns defined by factor analysis	2	Inverse associations for some but not all factors
Diet preferences (vegetables, salt, type of breakfast)	2	Inverse associations for preference for vegetables only in current smokers or low salt in men
Vegetarians	3	1
Seventh-day's Adventists	1	0
Mediterranean diet	1	1

*In one study, the score included smoking

Randomised controlled trials

One randomised controlled trial was identified: the Women's Health Initiative Dietary Modification Randomised Controlled Trial (Prentice, 2007). Lung cancer was not the primary or secondary outcome. Compared to usual diet, the intervention (to reduce total fat intake to 20% of energy and to increase consumption of vegetables, fruits, and grains) did not had an effect on lung cancer risk. The trial did not show an effect for the primary cancer endpoints (breast and endometrial cancer) and the only effect was a reduction of ovarian cancer incidence.

Cohort studies

Health Index Scores

Two studies in women on “a priori” heath indices scores were identified in the CUP and two studies were identified in the 2005 SLR. All scores included fruits and vegetables as component.
The results of the two studies identified in the CUP were discordant. In the E3N French cohort in women (Dartois, 2014), a strong inverse association with higher concordance with the French lifestyle recommendations was observed (the score included smoking, alcohol, fruits and vegetables consumption, BMI and physical activity), It is unclear if the association was mainly driven by the component on smoking. In the Women Health Initiative observational study, lung cancer was not associated with the American Cancer Society score including BMI, physical activity, fruit and vegetables, carotenoids, whole grains, red and processed meats, and alcohol (Thomson, 2014). The study was adjusted for smoking status and cigarettes pack-years.
The two studies identified in the 2005 SLR reported significant inverse associations with higher concordance with dietary recommendations. In the Breast Cancer Detection Demonstration Project (Mai, 2005), lung cancer risk was inversely associated with higher concordance with the Recommended Food Score after adjusting for smoking and energy intake (the score components were fruits, vegetables, whole grains, lean meats or meat alternatives, and low-fat dairy). In one large cohort of post-menopausal women, lung cancer risk was inversely related to a score based on the Dietary Guidelines for Americans (Harnack, 2002)(the score included fruits, vegetables, whole grains, saturated fats, milk, sweets, sodium, alcohol). The study was adjusted for smoking status and pack-years.

Dietary patterns defined by factor analysis

One study was identified in the CUP and one study in the 2005 SLR. A study in heavy male smokers derived nutrient patterns using principal component analysis (Gnagnarella, 2013b). The only component significantly related to lung cancer risk, after adjustment for other nutrient factors was the factor “Vitamins and fibre” (higher loads for fibre, potassium, vitamin C, vitamin E and folate). The three other factors (“Animal products”, “Starch” and “Other PUFAs”) were unrelated to lung cancer risk (this study also found an inverse risk of lung cancer with higher Mediterranean Diet score- see below). In the Netherlands Cohort Study on Diet and Cancer, (Balder, 2005) statistically significant trend associations were observed for “Salad vegetables pattern” (high factor loadings on several fruits and vegetables, pasta, rice, poultry, fish, and oil) and with “Sweet foods pattern” (high factor loadings on cakes and cookies, sweet sandwich spread, sweets and candies, and strawberries). No evidence of association was observed for “Cooked vegetables pattern”, “Pork, processed meat, and potatoes pattern or “Brown/white bread substitution pattern”. The analysis was adjusted for smoking status, cigarettes/day and years of smoking.

Diet preferences

Two Asian studies identified in the CUP investigated diet preferences. In a Korean study in men, preference for vegetables or a mixture of vegetables and meat compared to preference for meat was inversely significantly related to lung cancer risk in current smokers. No significant association was observed in never and former smokers (Yung, 2008). In the Japanese study on lung cancer mortality (Iso, 2007), preference for salty food (like compared to dislike) was related to significant increased risk of lung cancer mortality in men but not in women. Preference for fatty food, Japanese or Western breakfast was unrelated to lung cancer mortality. The study was not adjusted by smoking.

Vegetarians and vegans diets

Three studies were identified, from which one was identified in the CUP.
In the largest study, the EPIC-Oxford cohort, lung cancer risk was not related to vegetarianism compared to being meat eater (Key, 2009). From the studies identified in the 2005 SLR, one small study found lower risk of lung cancer in vegetarians and vegans compared to general population (Chang-Claude, 1992) and the other study did not find any difference on lung cancer risk between vegetarians and non-vegetarians (Key, 1999).

Seventh Day Adventists diet

One study reported no significant association (Fraser, 1999).

Mediterranean Diet

In a small study in Italian male heavy smokers, low adherence to a Mediterranean diet was associated with increased risk of lung cancer (Gnagnarella, 2013b- see Dietary patterns defined by factor analysis above).

1 Patterns of diet

Table 3 Dietary patterns and lung 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	Intervention	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors
Prentice, 2007 LUN20298 USA	WHI-DM, Randomised Control Trial, Age: 50-79 years, W	357/ 48 835 8 years	Self -report, medical record and pathology report reviewed by centrally trained physician	Intervention: reduce total fat intake to 20% of energy and to increase consumption of vegetables, fruits, and grains Control: usual diet	Incidence, lung cancer	Intervention vs usual diet	0.92 (0.75-1.14)	Age, randomised treatment (participants randomly allocated)

Patterns of diet (cont.)

Cohort studies

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors
Health index scores								
Dartois, 2014 LUN26850 France	E3N,1990, Prospective Cohort, Age: 43-68 years, W	213/ 64 732 8 years	Self-report verified by medical and pathological records reviewed by physicians	Self-administered questionnaire	Incidence, lung cancer	French Index Score components: smoking, alcohol, fruits and vegetables, BMI, physical activity Score 4.5-5 vs 0-2	0.19 (0.11-0.30) Ptrend:0.01	Age at first full term pregnancy, age at menarche, menopausal status, number of children, residence, education, first-degree relative with cancer, menopausal hormone therapy use, professional activity, use of oral contraception
Thomson, 2014 LUN20380 USA	WHI-OS, Prospective Cohort, Age: 50-79 years, postmenopausal	833/ 65 838 13 years	Mailed annual questionnaire, cancer registries, national death index and medical records	FFQ	Incidence, lung cancer	American Cancer Society score components: BMI, physical activity, fruit	1.14 (0.81-1.60) Ptrend:0.16	Age, aspirin use, oestrogen plus progesterone use, family history of cancer, NSAID

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors
	women					and vegetables, carotenoids, whole grains, red and processed meats, alcohol Score 7-8 vs 0-2 score		use, parous/ nulliparous, race/ethnicity, unopposed oestrogen use, education, having a healthcare provider, smoking, pack-years, total energy intake
		285/ 65 838 13 years			Mortality, lung cancer	Score 4 vs 0-2	1.07 (0.75-1.52) Ptrend:0.50	
Mai, 2005 LUN17484 USA	Breast Cancer Detection Demonstration Project	353 incident cases, 279 deaths/ 37 135 women 9.5 years	Self-reports (confirmed by medical records), death certificates, state cancer registries	62-item Block-NCI FFQ	Lung cancer incidence	RFS (fruits, vegetables, whole grains, lean meats or meat alternatives, and low-fat dairy)	Quartile 4 vs 1 0.62 (0.46-0.84) Ptrend <0.01	Energy intake, smoking (ever/never), NSAID use, BMI, colonoscopies
					Lung cancer mortality		0.54 (0.38-0.76) P trend < 0.01	
Harnack, 2002 LUN00499 USA	Iowa Women's Health Study	528/ 34 708 postmenopausal women	State Health Registry and death certificates	FFQ 127 items	Incidence of cancers of lung and bronchus	Dietary guidelines for Americans (fruits, vegetables, whole grains, saturated fats, milk, sweets,	Quintile 5 vs 1 0.73 (0.54-0.97) Ptrend:0.05	Age, energy intake, physical activity, BMI, smoking status and pack-years, physical activity, HRT, reproductive

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors
						sodium, alcohol)		factors, co-morbidities,
Dietary patterns derived by factor analysis								
Gnagnarella, 2013b LUN26863 Italy	COSMOS (Continuous Observation of Smoking Subjects), Prospective Cohort, Age: 50-84 years, M/W, Smokers	178 cases/ 4336/ 5.7 years	Screening examinations, telephone contact	FFQ	Incidence, lung cancer	Quintile 4 vs quintile 1 Factor: Animal products	1.23 (0.80-1.89) Ptrend:0.18	Age, sex, BMI, supplement use, current smoking status, education, pack years of smoking, total energy intake, mutually adjusted for each pattern
						Factor: Other PUFA	0.88 (0.58-1.34) Ptrend:0.59	
						Factor: Starch rich	1.00 (0.66-1.51) Ptrend:0.94	
						Factor: Vitamins and fibre	0.57 (0.36-0.90) Ptrend:0.01	
Balder, 2005 LUN17448 The Netherlands	The Netherlands (Case-)Cohort Study Age: 55- 69 years Men	1426 cases/ 58 279 men/ 9.3 years	Record linkage to Netherlands Cancer and Pathology Registries	Semi-quantitative FFQ 150 items	Incidence, lung cancer	Factor: Salad vegetables	Per 1 SD 0.87 (0.78-0.96) In never smokers (52 cases) 1.21 (0.94-1.56)	All other dietary patterns, age at baseline, total energy intake, smoking status , cigarettes/day, years smoking cigarettes, education, family history of lung cancer,
						Cooked vegetables	0.95 (0.86-1.05)	
						Pork, processed meats, potatoes	1.10 (0.98-1.25)	

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors
						Sweet foods	0.80 (0.70-0.90)	physical activity
						Brown/white bread substitution	0.99 (0.89-1.09)	
Diet preference								
Iso, 2007 LUN20294 Japan	JACC, Prospective Cohort, Age: 40-79 years, M/W	707 men, 186 women/ 105 500 15 years	Municipal resident registration records, death certificates	Validated FFQ	Mortality, lung cancer Men Women	Preference for salty food (like vs dislike)	1.36(1.06-1.76) 1.02(0.69-1.52)	Age, area of study
					Men Women	Preference for fatty food (like vs dislike)	1.09(0.90-1.32) 1.00(0.73-1.37)	
						Type of breakfast (Usually vs not usually)		
					Men Women	Japanese style	0.92(0.75-1.14) 1.13(0.77-1.67)	
					Men Women	Western style	0.96(0.76-1.21) 0.84(0.57-1.24)	
Yun, 2008 LUN20276 Korea	KNHIC, Prospective Cohort,	1 591/ 444 963 6 years	Linkage with cancer registry, national health	FFQ	Incidence, lung cancer	Dietary preference: Vegetables or	All men: 0.81 (0.68-0.98)	Age, BMI, employment, fasting blood

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors
	Age: 40- years, M	364 cases	insurance and death report			mixture of vegetables and meat vs meat	Never/former smokers 0.95 (0.61-1.48)	sugar, leisure - physical activity, smoking status, alcohol drinking
		1215 cases					Current smokers 0.76(0.63- 0.93)	
Mediterranean Diet								
Gnagnarella, 2013a LUN26858 Italy	COSMOS (Continuous Observation of Smoking Subjects), Prospective Cohort, Age: 50-84 years, M/W, Heavy smokers	178/ 4336 6 years	Screening examinations, telephone contact	FFQ	Incidence, lung cancer	8-9 vs 0-1 score	0.10 (0.01-0.77) Ptrend:0.04	Age, sex, asbestos occupation, fish, olive oil, energy, fruit and vegetable, smoking status and dose, tea, wine
Vegetarian Diet								
Key, 2009 LUN20290 UK	EPIC-Oxford, Prospective Cohort, Age: 20-89 years, M/W	165/ 61 566 12 years	Record linkage with the United Kingdom's National Health Service Central Register	Semi-quantitative FFQ	Incidence, lung cancer	Vegetarian vs meat eater	1.11 (0.75-1.65)	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
Chang-Claude, 1992 LUN08681 Germany	Vegetarians and healthy-eaters	1 male case, 2 female cases/ 1904/ 11 years	Registrar's office and death certificates	Self-reported vegetarianism	Lung cancer mortality	SMR (with general population)	SMR Men 0.08 (0.0-0.39) Women 0.89 (0.11-3.22)	Age
Adventist Diets								
Fraser, 1990 LUN12836 USA	Non-Hispanic white Californian Seventh-day's Adventists	45 cases/ 34 918/ 6 years	Population-based cancer registries and death registry	Vegetarian, fish-poultry eaters, and non vegetarians (self-reported)	Lung cancer incidence	Vegetarians vs no vegetarians	1.16 (0.56- 2.38) p=0.69	Age, sex, current and past smoking

2 Foods
2.2 Fruit and vegetables

Randomised controlled trial
No randomised controlled trial was identified (see section on Dietary Patterns).

Cohort studies

Summary

Main results:
Fourteen studies (9609 cases) out of 16 studies (19 publications) were included in the dose-response meta-analysis. A significant inverse association of fruit and vegetable consumption with lung cancer was observed (RR per 100 g: 0.96; 95% CI= 0.94-0.98). Two studies were excluded from the dose-response analyses; both reported non-significant associations.
High heterogeneity was observed. The heterogeneity persisted in analysis stratified by sex, geographic location, smoking status and level of adjustment for smoking. The associations in stratified analyses were of similar magnitude, but in some analyses with lower number of studies the statistical significance was lost. Only three studies could be included in stratified analysis by smoking; no significant associations were observed in smokers and never smokers (not enough data on former smokers). There were no data to do analyses by cancer type.
There was significant evidence of publication or small study bias in the CUP review ($p < 0.01$). Visual inspection of the funnel plot suggests that small studies showing positive or null associations may be missing. All the studies included in the analysis on fruit and vegetables except one (Slatore, 2008) also reported on fruits and vegetables separately and lung cancer risk(see appendix 1).

Sensitivity analysis:
The overall association remained statistically significant in influence analysis. The summary RRs ranged from 0.95 (95% CI=0.92-0.98) when Wright, 2008 was omitted to 0.97 (95% CI=0.95-0.99) when Voorrips, 2000 was omitted.

There was evidence of non-linear dose-response of lung cancer and fruit and vegetable intake ($p < 0.01$). The risk decreases with increasing intakes up to approximately 400 g/day. No further benefit is apparent for increasing intakes above this value.

Study quality:
All studies identified in the CUP used FFQ to assess fruit and vegetable intake. The types of fruit and vegetables may vary between studies. In one study (Büchner, 2010) the association was corrected for dietary measurement error using regression calibration and similar inverse association was observed using the observed and calibrated intake values. Repeated dietary

measurements were used in the NHS and the HPFS (Feskanich, 2000). Cancer outcome was confirmed using records in cancer registries in most studies and loss of follow-up was small. The fourteen studies included in the dose-response analysis were at least adjusted for age, sex. Twelve studies adjusted for smoking status, duration and intensity, and two studies adjusted for smoking status.

Pooling project of cohort studies:
Lung cancer was significantly inversely related to fruit and vegetables intake in the Pooling Project of Cohort Studies (Smith-Warner, 2003; seven cohorts). The association was significant in current smokers (1915 cases) but not in never smokers (259 cases) and former smokers (981 cases), and for adenocarcinomas and squamous cell carcinomas, but not for small cell carcinomas.
The Pooling Project used cohort-specific cutpoints and could not be included in the CUP dose-response meta-analysis. A meta-analysis of the highest compared to the lowest intake category including the Pooling Project (18% weight in the analysis) and the non overlapping studies identified in the CUP was then conducted. A significant inverse association was observed (18 studies). In analysis stratified by smoking status (eight studies) a borderline significant association was observed in smokers and no significant association was observed in never and former smokers

Table 4 Fruit and vegetable intake and lung cancer risk. Number of studies in the CUP SLR

	Number
Studies identified	16 (19 publications)
Studies included in forest plot of highest compared with lowest exposure	14
Studies included in dose-response meta-analysis	14
Studies included in nonlinear dose-response meta-analysis	11

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

Table 5 Fruit and vegetable intake and lung cancer risk. Summary of the dose-response meta-analysis in the 2005 SLR and CUP.

	2005 SLR	**CUP**
Increment unit used	80 g/day	100 g/day
Studies (n)	6	14
Cases (total number)	3419	9609
RR (95%CI)	0.96 (0.92-1.00)	0.96 (0.94-0.98)
Heterogeneity (I^2, p-value)	72%	63.6%, < 0.01
P value Egger test		< 0.01

Table 5 (cont.)

Stratified and sensitivity analysis (no analyses conducted in the 2005 SLR)			
Smoking status	**Never smokers**	**Current smokers**	**Former smokers**
Studies (n)	3	3	1
Cases (total number)	604	2680	
RR (95%CI)	1.00 (0.94-1.07)	0.98 (0.95-1.02)	0.99 (0.97-1.01)
Heterogeneity (I^2, p-value)	32.1%, 0.23	58.5%, 0.09	
Adjustment for smoking	**Smoking status only**	**Intensity and duration of smoking**	
Studies (n)	2	12	
RR (95%CI)	0.74 (0.56-0.97)	0.96 (0.94-0.99)	
Heterogeneity (I^2, p-value)	0%, 0.39	64.3%, <0.01	
Sex	**Men**	**Women**	
Studies (n)	5	4	
RR (95%CI)	0.99 (0.94-1.04)	0.94 (0.87-1.01)	
Heterogeneity (I^2, p-value)	56.6% , 0.06	75.6%, <0.01	
Geographic location	**Asia**	**Europe**	**North America**
Studies (n)	3	4	7
RR (95%CI)	0.96 (0.90- 1.03)	0.90 (0.82-0.99)	0.98 (0.95-1.01)
Heterogeneity (I^2, p-value)	13.6% , 0.31	83.7% , <0.001	39.6%, 0.25

Table 6 Fruit and vegetables and lung cancer risk. Highest versus lowest meta-analyses of the Pooling Project and non overlapping studies in the CUP.

Pooling project of cohort studies and non-overlapping studies identified in the CUP			
Comparison	Highest vs lowest intake		
Studies (n)	18		
Cases (total number)	11941		
RR (95%CI)	0.86(0.78-0.94)		
Heterogeneity (I^2, p-value)	36.5%, 0.08		
Stratified highest versus lowest analysis			
Smoking status	**Never smokers**	**Current smokers**	**Former smokers**
Studies (n)	8	8	7
Cases (total number)	863	6178	4393
RR (95%CI)	0.94 (0.70-1.27)	0.90 (0.81-1.00)	0.95(0.83-1.10)
Heterogeneity (I^2, p-value)	19.1%, 0.29	0%, 0.69	36.1%, 0.19

Table 7 Fruit and vegetable intake and lung cancer risk. Results of pooled analyses of prospective studies published after the 2005 SLR.

Author, Year	Number of cohort studies	Total number of cases	Studies country, area	Outcome	Comparison	RR (95%CI)	P trend	Heterogeneity (p value)
Smith-Warner, 2003 Pooling Project of Cohort Studies AHS, ATBC, CNBSS, HPFS, IWHS, NYSC, NHS	7	3206	USA, Europe	Lung cancer All	Q5 vs Q1	0.79(0.69-0.90)	<0.01	0.70
	7	3206			≥600 vs <200g/day	0.76(0.63-0.91)		0.38
	5	259		Never smokers	Q4 vs Q1	0.67(0.38-1.19)	0.29	0.17
		981		Past smokers		0.85(0.69-1.06)	0.29	0.84
		1915		Current smokers		0.84(0.71-0.98)	0.03	0.58
	6	956		Adenocarcinoma	Q4 vs Q1	0.80 (0.67-0.94)	0.02	0.73
		538		Small cell carcinoma	Q4 vs Q1	0.90(0.73-1.11)	0.52	0.42
		901		Squamous cell carcinoma	Q4 vs Q1	0.76(0.63-0.91)	0.01	0.50

Table 8 Fruit and vegetable intake and lung cancer risk. Main characteristics of studies 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	Missing data derived for analyses
Wie, 2014 LUN26882 Korea	Korea 2004-2013, Prospective Cohort, M/W	36/ 8024 7 years	Cancer registry and medical records	3-day food record	Incidence, lung cancer	≥600 vs <600 g/day	0.37 (0.07-1.93)	Age, sex, BMI, income, marital status, physical activity, alcohol, education, energy, smoking	
						Per 100 g/day	0.82 (0.57-1.17)		
Gnagnarella, 2013a LUN26858 Italy	COSMOS, Cohort of heavy smokers enrolled in lung cancer screening trial, Age: 50-84 years M/W heavy smokers	178/ 4336 5.7 years	Screening examinations, telephone contact	FFQ 188 food items	Incidence, lung cancer	554.4 vs 110.9 g /day	0.56 (0.36-0.87) Ptrend:0.03	Age, sex, asbestos occupation, energy, smoking	Distribution of person-years by exposure category
Takata, 2013 LUN26860 China	Shanghai Men's Health Study, Prospective Cohort, Age: 40-74 years, M	359/ 61 092 5.5 years	Biennial home visits (diagnosis verified by medical chart review), record linkage to Cancer Registry	Validated FFQ	Incidence, lung cancer	779.7 vs 233.4 g/day	0.76 (0.55-1.07) Ptrend:0.07	Age, BMI smoking status, education, family history of lung cancer, history of chronic	Distribution of person-years by exposure category

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Missing data derived for analyses
			and Vital Statistics Registry					bronchitis, cigarettes/day, years smoking, , intake of tea, vegetables, total caloric intake	
Büchner, 2010b LUN20360 Denmark,France ,Germany,Greec e,Italy,Netherlan ds,Norway,Spai n,Sweden,U.K.	EPIC, Prospective Cohort, Age: 25-70 years, M/W	1830/ 478 535 8.7 years	Cancer registries, health insurance records, active follow up confirmed with pathology records, death registries	FFQ, dietary questionnaires, food record	Incidence, lung cancer	Per 100 g/day	0.94 (0.89-0.99)	Age, alcohol consumption, centre, duration of smoking, education level, energy intake, height, physical activity, smoking status, weight, gender, lifetime and baseline intensity of smoking, time since quitting smoking, vegetable consumption	Distribution of person-years by exposure category, mid-points of exposure categories
		1167			Incidence, lung cancer, current smokers	Per 100 g/day	0.93 (0.90-0.97)		
		467			Incidence, lung cancer, former smokers	Per 100 g/day	0.97 (0.83-1.15)		
		187			Incidence, lung cancer, never smokers	Per 100 g/day	1.02 (0.86-1.21)		
		964			Incidence, lung cancer, men	Per 100 g/day	0.91 (0.85-0.98)		
		866			Incidence, lung cancer, women	Per 100 g/day	0.91 (0.83-0.99)		
		574			Incidence, adeno-	Per 100 g/day	0.96 (0.88-1.05)		

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Missing data derived for analyses
					carcinoma				
		363			Incidence, squamous cell carcinoma	Per 100 g/day	0.96(0.90-1.02)		
		286			Incidence, small cell carcinoma	Per 100 g/day	0.95 (0.83-1.09)		
		137			Incidence, large cell carcinoma	Per 100 g/day	1.03 (0.94-1.13)		
Slatore, 2008 LUN20344 USA	VITAL, Prospective Cohort, Age: 50-76 years, M/W	448/ 77 126 4.05 years	SEER registry/hospital records/ pathology	Self-administered questionnaire	Incidence, lung cancer	>5.1 vs 0-2 servings/day	0.90 (0.68-1.19)	Age, sex, pack years squared, pack-years, years of smoking	
Wright, 2008 LUN20306 USA	NIH-AARP, Prospective Cohort, Age: 50-71 years, M/W, Retired	3834/ 472 081 8 years	Annual linkage to state cancer registries and national death index plus	Validated FFQ	Incidence, lung cancer, men	>4.29 vs <1.82 servings/1000 kcal/day	0.93 (0.83-1.04) Ptrend:0.17	Age, BMI, energy intake, family history of cancer, race, smoking status, alcohol intake, education, physical activity, smoking dose, time since quitting	Distribution of person-years by exposure category, mid-points of exposure categories. Intake values estimated using mean energy intake
		2201			Incidence, lung cancer,women	>5.37 vs <2.39 servings/1000 kcal/day	0.98 (0.85-1.13) Ptrend:0.56		
		1196			Incidence, lung cancer, women current smokers	>5.37 vs <2.39 servings/1000 kcal/day	0.93 (0.76-1.15) Ptrend:0.73		
		835			Incidence, lung cancer, women	>5.37 vs <2.39 servings/1000	1.03 (0.82-1.29) Ptrend:0.55		

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Missing data derived for analyses
					former smokers	kcal/day		smoking	
		170			Incidence, lung cancer,women never smokers	>5.37 vs <2.39 servings/1000 kcal/day	0.99 (0.58-1.69) Ptrend:0.86		
		141			Incidence, lung cancer, men never smokers	>4.29 vs <1.82 servings/1000 kcal/day	0.77 (0.44-1.35) Ptrend:0.56		
		2110			Incidence, lung cancer, men former smokers	>4.29 vs <1.82 servings/1000 kcal/day	0.91 (0.79-1.05) Ptrend:0.22		
		1583			Incidence, lung cancer, men current smokers	>4.29 vs <1.82 servings/1000 kcal/day	1.0 (0.77-1.29) Ptrend:0.69		
Liu, 2004 LUN10203 Japan	JPHC study-cohort I and II, Prospective Cohort, Age: 40-69 years, M/W	317/ 93 338 10 years	Hospital records, population-based cancer registries and death certificates	FFQ - study-specific	Incidence, lung cancer, current smokers	Highest vs lowest	1.01 (0.72-1.40)	Age, sex, areas, sports, alcohol intake, BMI, vitamin supplement use, salted fish and meat, pickled vegetables, smoking status, smoking duration, cigarettes/ day	Mid-points of exposure categories.
		198			Incidence, adenocarcinoma	Highest vs lowest	1.02 (0.56-1.87)		
		176			Incidence, other tumour types	Highest vs lowest	0.85 (0.57-1.25)		
		106			Incidence, lung cancer, non-smokers	Highest vs lowest	1.95 (0.84-4.52)		

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Missing data derived for analyses
Neuhouser, 2003 LUN00354 USA	CARET, Prospective Cohort Age: 45-69 years, M/W	742 12 years	Lung cancer is primary endpoint of the trial. Active follow-up confirmed in medical and pathology records	FFQ - study-specific	Incidence, lung cancer	≥11.1 vs <1.9 servings/week	Intervention group 0.76 (0.55-1.06)	Age, sex, smoking status, total pack-years of smoking, asbestos exposure, race/ethnicity, and enrollment center	Distribution of person-years and cases by exposure category, mid-points of exposure categories. Exposure values using standard portion size. RRs for intervention and placebo combined
							Placebo 0.73 (0.51-1.04)		
Feskanich, 2000 LUN00986 USA	Nurses' Health Study (NHS) + Health Professionals Follow-up Study (HPFS), Prospective Cohort, Age: 30-75 years, M/W	519/ 125 061 12 years	Verbal or written self-report, if possible confirmed by medical records, and death certificates	FFQ - study-specific	Incidence, lung cancer, women	>7.3 vs 2.8 servings/day	0.79 (0.59-1.06)	Age, , follow-up cycle, smoking status, years since quitting - past smokers-, cigarettes /day - current smokers-, age start smoking, total energy intake, availability of	Distribution of person-years by exposure category, mid-points of exposure categories. Exposure values using standard portion size.
		269			Incidence, lung cancer, women, current smokers	Quintile 5 vs quintile 1	0.74 (0.27-2.07)		
		54			Incidence, lung cancer, women non-smokers	Quintile 5 vs quintile 1	0.58 (0..28-1.18)		
		193			Incidence, lung cancer, women former smokers	Quintile 5 vs quintile 1	1.03 (0.63-1.71)		

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Missing data derived for analyses
		232			Incidence, adenocarcinoma, women	Quintile 5 vs quintile 1	0.95 (0.62-1.48)	diet data after baseline	
		179			Incidence, women, non-small cell (SCC, adenocarcinoma, large cell), women	Quintile 5 vs quintile 1	0.74 (0.46-1.21)		
		274			Incidence, lung cancer, men	>3.3 vs 1.1-1.7 servings/day	1.12 (0.74-1.69)		
		86			Incidence, men, current smokers	Quintile 5 vs quintile 1	1.14 (0.54-2.41)		
		24			Incidence, men, non-smokers	Quintile 5 vs quintile 1	0.74 (0.27-2.04)		
		148			Incidence, men, former smokers	Quintile 5 vs quintile 1	1.27 (0.72-2.22)		
		93			Incidence, adenocarcinoma, men	Quintile 5 vs quintile 1	1.49 (0.75-2.98)		
		120			Incidence, Non-small cell (SCC, adenocarcinoma, large cell), men	Quintile 5 vs quintile 1	0.86(0.48-1.64)		

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Missing data derived for analyses
Voorrips, 2000b LUN01162 Netherlands	Netherlands Cohort Study on Diet and Cancer (NLCS), Case Cohort, Age: 55-69 years, M/W	963/ 120 852 3.2 years	Regional cancer registries and computerized national database of pathology report (PALGA)	FFQ - study-specific	Incidence, lung cancer, men, non-smokers	554 vs 191 g/day	0.70 (0.50-1.00)	Age, sex, educational level, family history of specific cancer, smoking habits	
Knekt, 1999 LUN01416 Finland	Finnish Mobile Clinic Health Examination Survey, Prospective Cohort, Age: 20-69 years, M	138/4545 25 years	National cancer registry	FFQ - study-specific	Incidence, lung cancer	225 vs 116 g/day	0.60 (0.38-0.96)	Age, smoking status	Distribution of person-years and cases by exposure category
Steinmetz, 1993 LUN02740 USA	IWHS, Nested Case Control, Age: 55-69 years, W, Post-menopausal	81/ 41 837 4 years	Iowa Health registry (part of SEER)	FFQ - study-specific	Incidence, lung cancer, current smokers	>48 vs <24 servings/week	0.49 (0.28-0.86)	Age, energy intake, smoking habits	Used only in stratified analysis by cancer type (Superseded by Olson, 2002 LUN00502) 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. Exposure values using standard portion size.
Shibata, 1992 LUN08664 USA	LWS, Prospective Cohort, Age: 74years, M/W	70/ 11 580 6 years	Death by reports of friends or relatives, National Death Index; incidence through hospital records	FFQ - study-specific	Incidence, lung cancer, women	≥8.3 vs <5.9 servings/day	0.58(0.32-1.04)	Age, smoking habits	Distribution of person-years by exposure category, mid-points of exposure categories. Exposure values using standard portion size.
		94			Incidence, lung cancer, men	≥7.9 vs <5.5 servings/day	1.22 (0.72-2.07)		

Table 9 Fruit and vegetable intake and lung cancer risk. Main characteristics of studies excluded 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	Reasons for exclusion
Büchner, 2010a LUN20322 Denmark,France,Germany,Greece,Italy,Netherlands,Norway,Spain,Sweden,UK	EPIC, Prospective Cohort, Age: 25-70 years, M/W	1607/ 452 187 8.7 years	Cancer registry, health insurance records, active follow up and mortality registry	Validated FFQ	Incidence, lung cancer	23-40 vs 0-10 servings/every 2 weeks	0.96 (0.75-1.21) Ptrend:0.65	Age, sex, centre, BMI, smoking status, years smoking, lifetime number of cigarettes, energy intake from fat and nonfat sources, fruit and vegetables consumption	Used only in highest versus lowest analysis. Superseded by Büchner, 2010b LUN20360
Tasevska, 2009 LUN20353 USA	NIH-AARP, Prospective Cohort, Age: 50-71 years, M/W, Retired	467 976 8 years	Annual linkage to state cancer registries and national death index plus	Validated FFQ	Incidence, lung cancer, women	High intake vs low intake	0.75 (0.48-1.18)	Age, BMI, energy intake, physical activity, race, alcohol intake, education, saturated fat intake, smoking	Superseded by Wright, 2008 LUN20306
					Incidence, lung cancer, men	High intake vs low intake	1.68 (1.03-2.75)		
Linseisen, 2007 LUN20323 France, Italy, Spain, U.K., Netherlands,	EPIC, Prospective Cohort, Age: 25-70 years,	1126/ 478 590 6.4 years	Cancer registries, health insurance records, pathology rec,	FFQ, dietary questionnaires, food record	Incidence, lung cancer	Q5 vs Q1	0.88 (0.68-1.14)	Education level, energy intake from fat and nonfat sources, height, smoking	Superseded by Büchner, 2010b LUN20360
		1126			Incidence, lung cancer	Per 100 g	0.97 (0.94-1.01)		

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Reasons for exclusion
Greece, Germany, Sweden, Denmark, Norway	M/W	731	active follow up, death certificate		Incidence, lung cancer, current smokers	Q5 vs Q1	0.68 (0.47-0.99)	status, weight, work - physical activity, ethanol intake, processed and red meat, smoking duration	
		731			Incidence, lung cancer, current smokers	Per 100 g	0.94 (0.90-0.98)		
		291			Incidence, lung cancer, former smokers	Q5 vs Q1	1.20 (0.75-1.94)		
		291			Incidence, lung cancer, former smokers	Per 100 g	1.00 (0.95-1.06)		
		98			Incidence, lung cancer, never smokers	Q5 vs Q1	0.80 (0.37-1.74)		
		98			Incidence, lung cancer, never smokers	Per 100 g	1.01 (0.92-1.11)		
Skuladottir, 2004 LUN05185 Denmark	Danish Diet Cancer and Health Study, Prospective Cohort, Age: 50-64 years,	247/ 54 158 8 years	Cancer Registry	FFQ - study-specific	Incidence, lung cancer	567-1394 vs 78-291 g/d	0.65 (0.46-0.94)	Age, other, smoking habits	Superseded by Büchner, 2010b LUN20360
		70			Incidence, adenocarcinoma	Per 100 g	0.92 (0.82-1.02)		
		49			Incidence, squamous cell	Per 100 g	0.91 (0.79-1.04)		

Author, Year, WCRF Code, Country	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	43			Incidence, small cell	Per 100 g	0.89 (0.77-1.04)		
Yong, 1997 LUN01778 USA	Nagoya 1985-2000Prospective Cohort, Age: 25-74 years, M/W	248/ 10 068 19 years	Follow-up interviews confirmed with hospital records and death certificates	FFQ - study-specific					Article in Chinese (translated) with insufficient data
Wang, 1985 LUN04098 USA	USA 1959-1970, Prospective Cohort, Age: 45-79 years, M/W	2952/ 750 000 12 years	Active follow-up, data from medical doctors, death certificates	FFQ - study-specific	Mortality, lung cancer	0-2 days/week vs 5-7 days/week day/month	1.79		Unadjusted results, no confidence interval

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

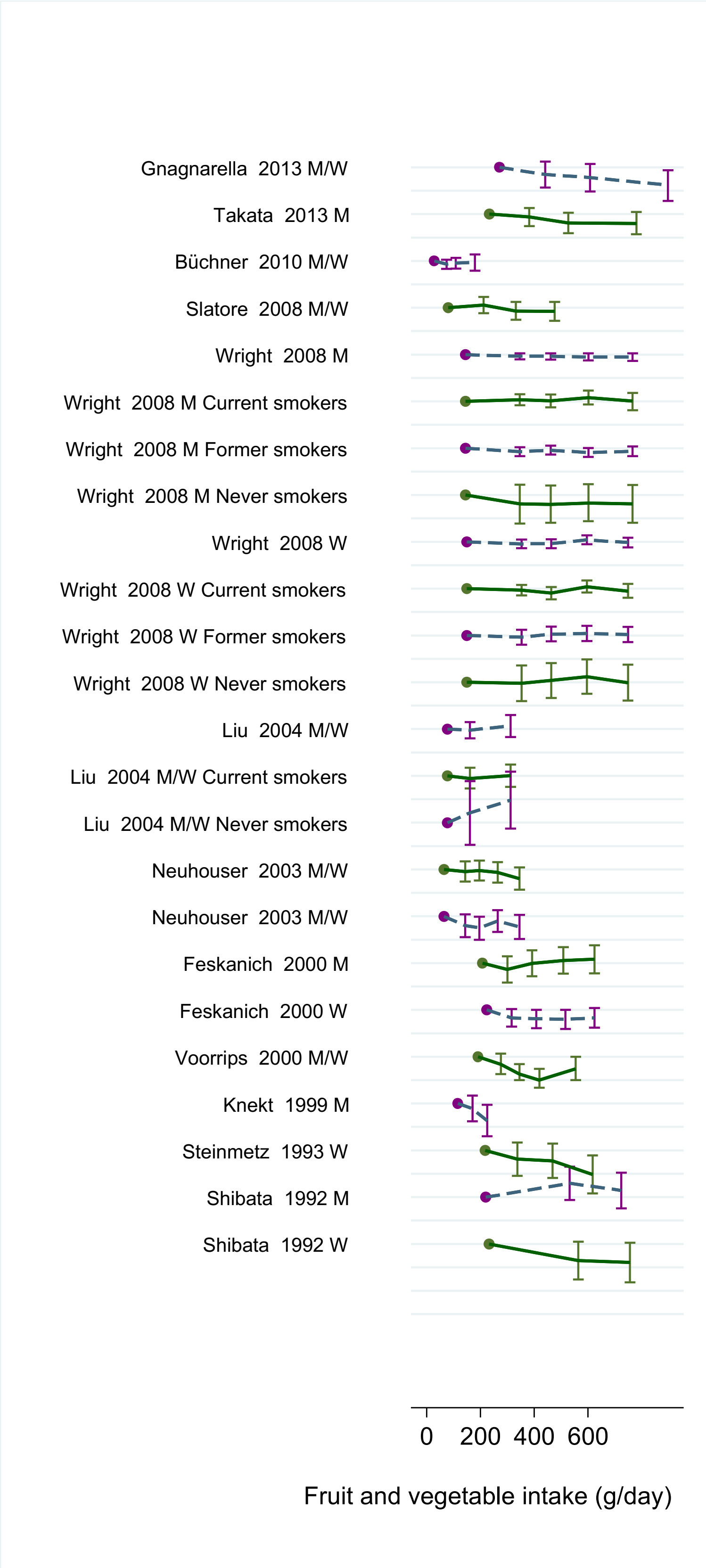
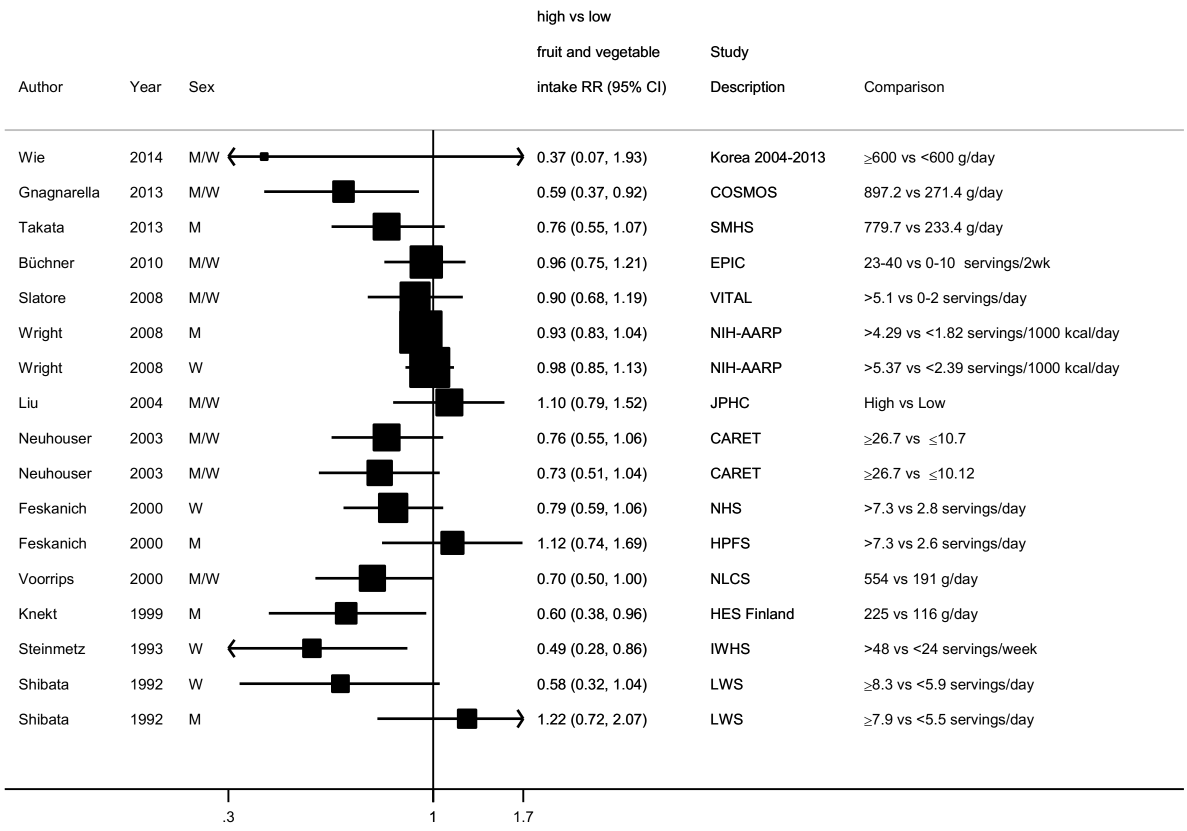


Figure 2 RR (95% CI) of lung cancer for the highest compared with the lowest level of fruit and vegetable intake.



CARET study (Neuhouser, 2003) is a follow-up of a RCT, both the intervention and placebo arms of the trial are represented in the graph.

Figure 3 RR (95% CI) of lung cancer for the highest compared with the lowest level of fruit and vegetable intake (CUP combined with Pooling Project)

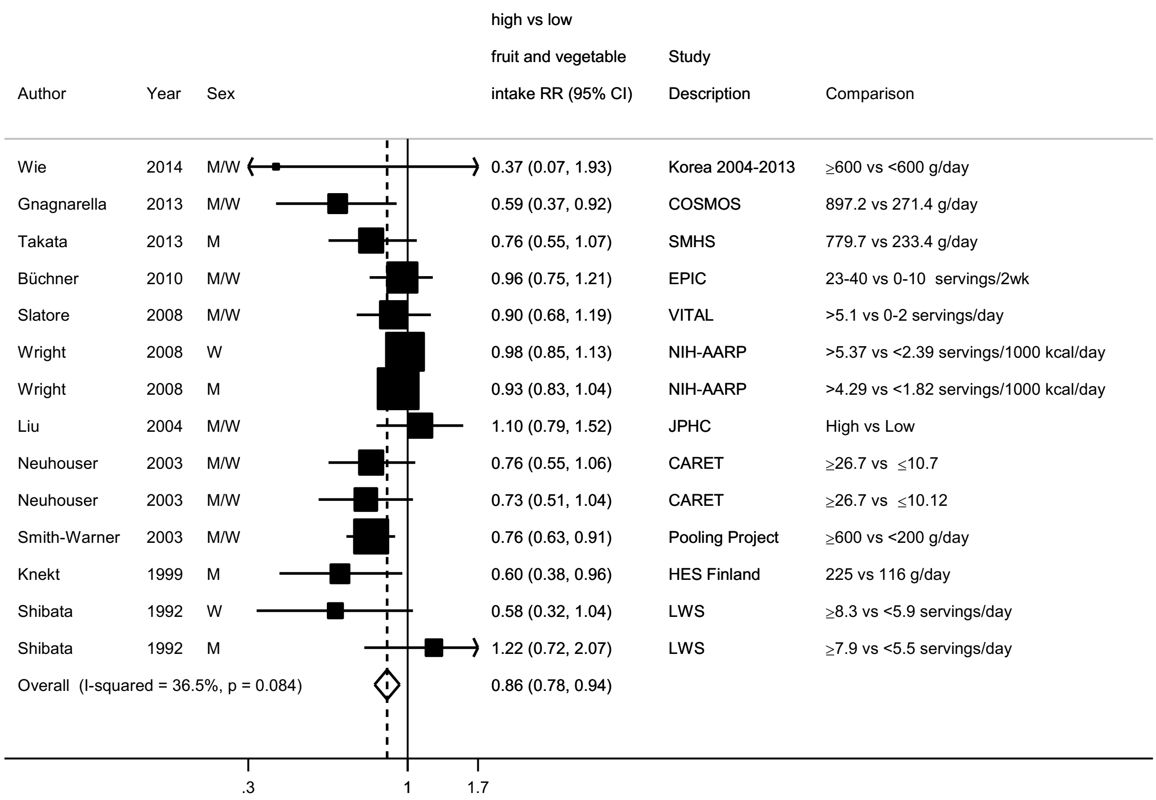


Figure 4 RR (95% CI) of lung cancer for 100g/day increase of fruit and vegetable intake

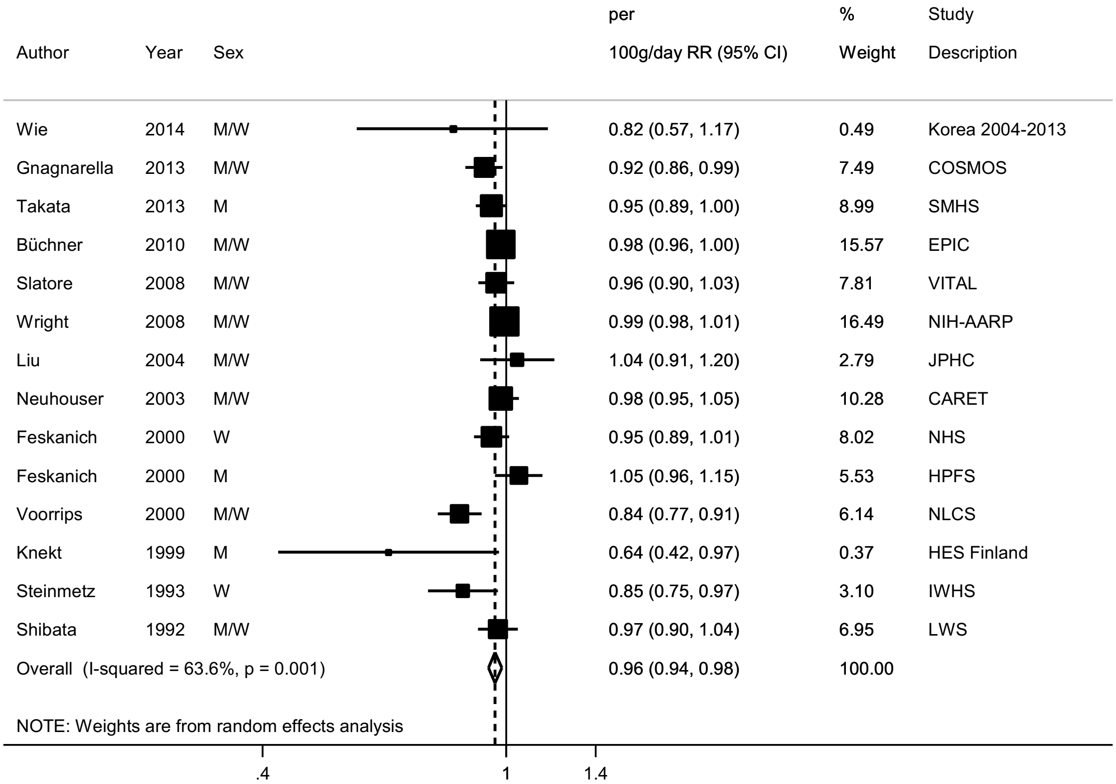
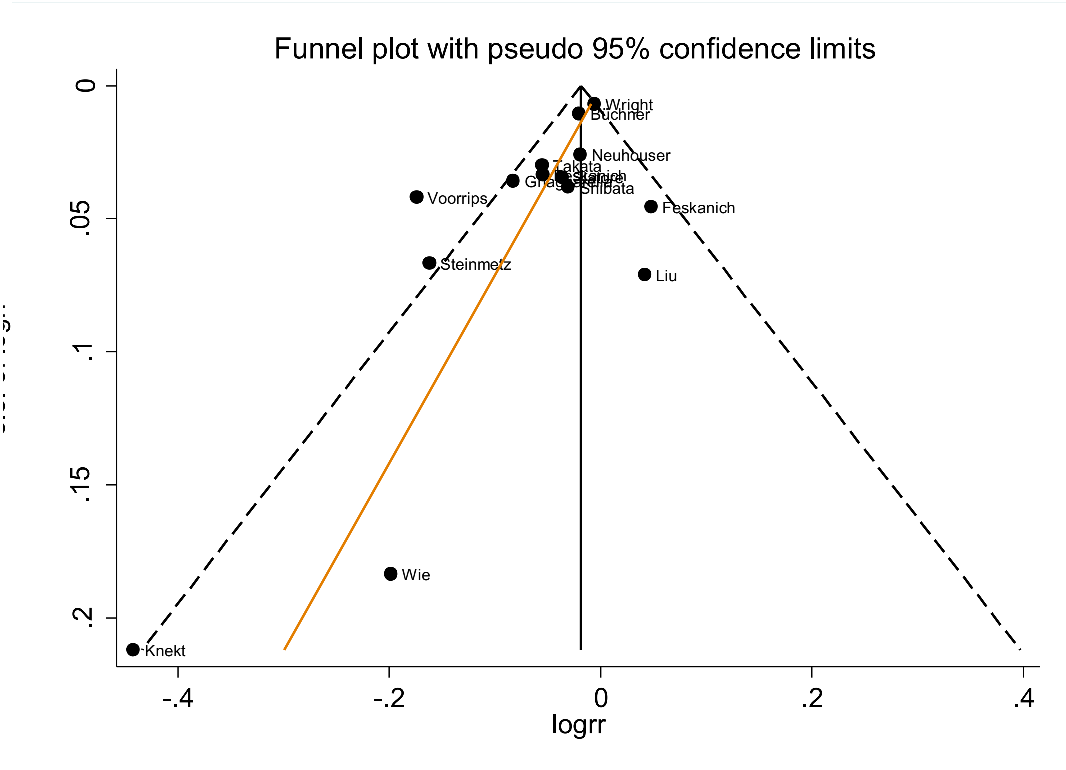


Figure 5 Funnel plot of studies included in the dose response meta-analysis of fruit and vegetable intake and lung cancer



Egger's test $p < 0.01$

Figure 6 RR (95% CI) of lung cancer for 100g/day increase of fruit and vegetable intake by sex

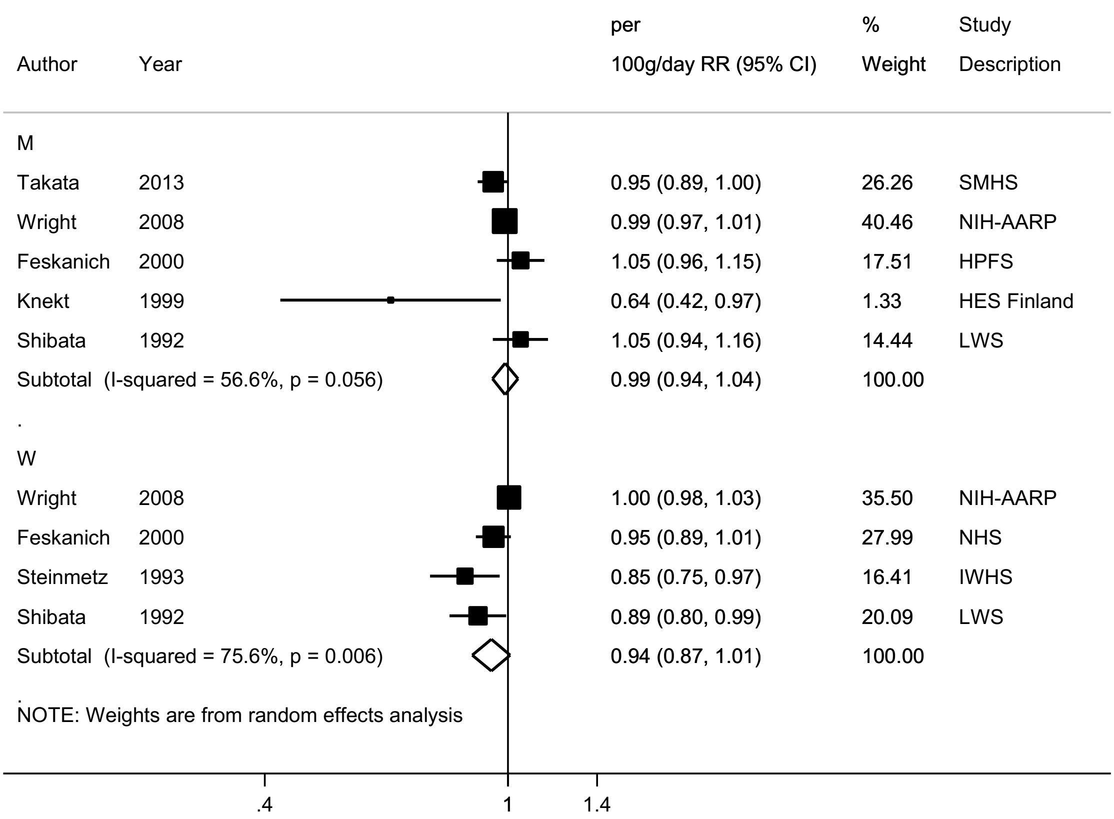


Figure 7 RR (95% CI) of lung cancer for 100g/day increase of fruit and vegetable intake by smoking status

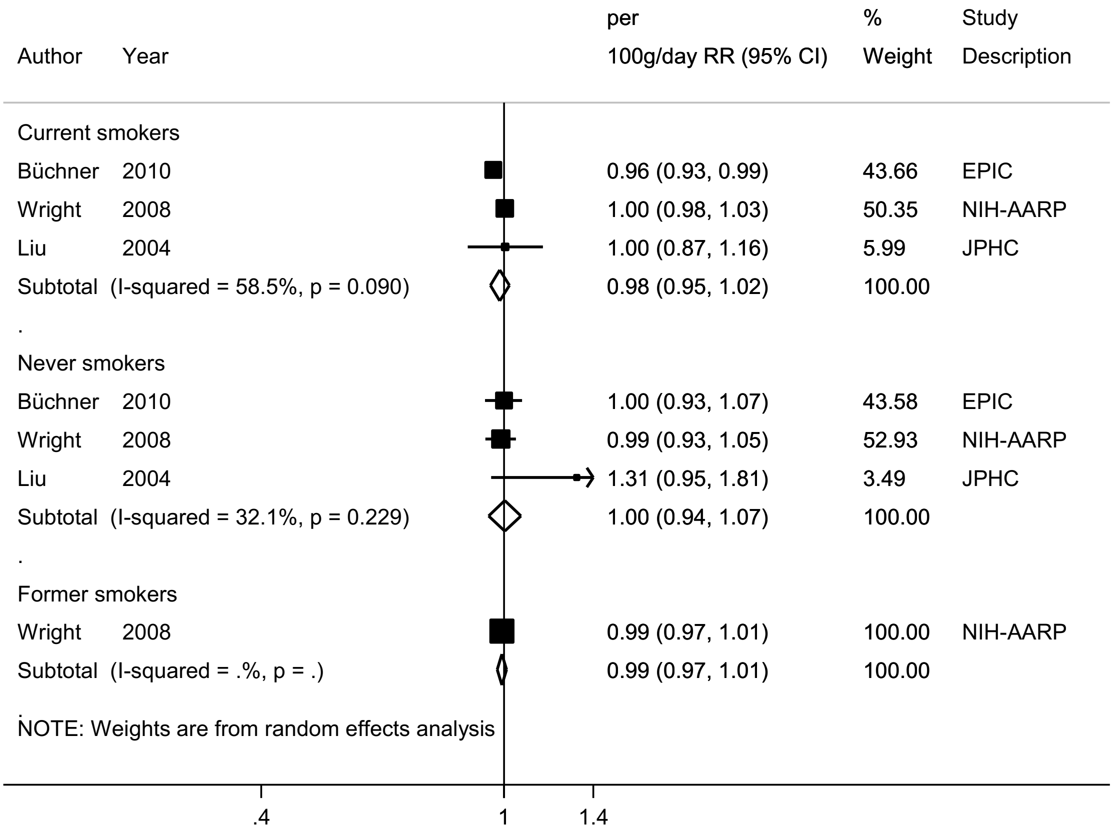


Figure 8 RR (95% CI) of lung cancer for 100g/day increase of fruit and vegetable intake by geographic location

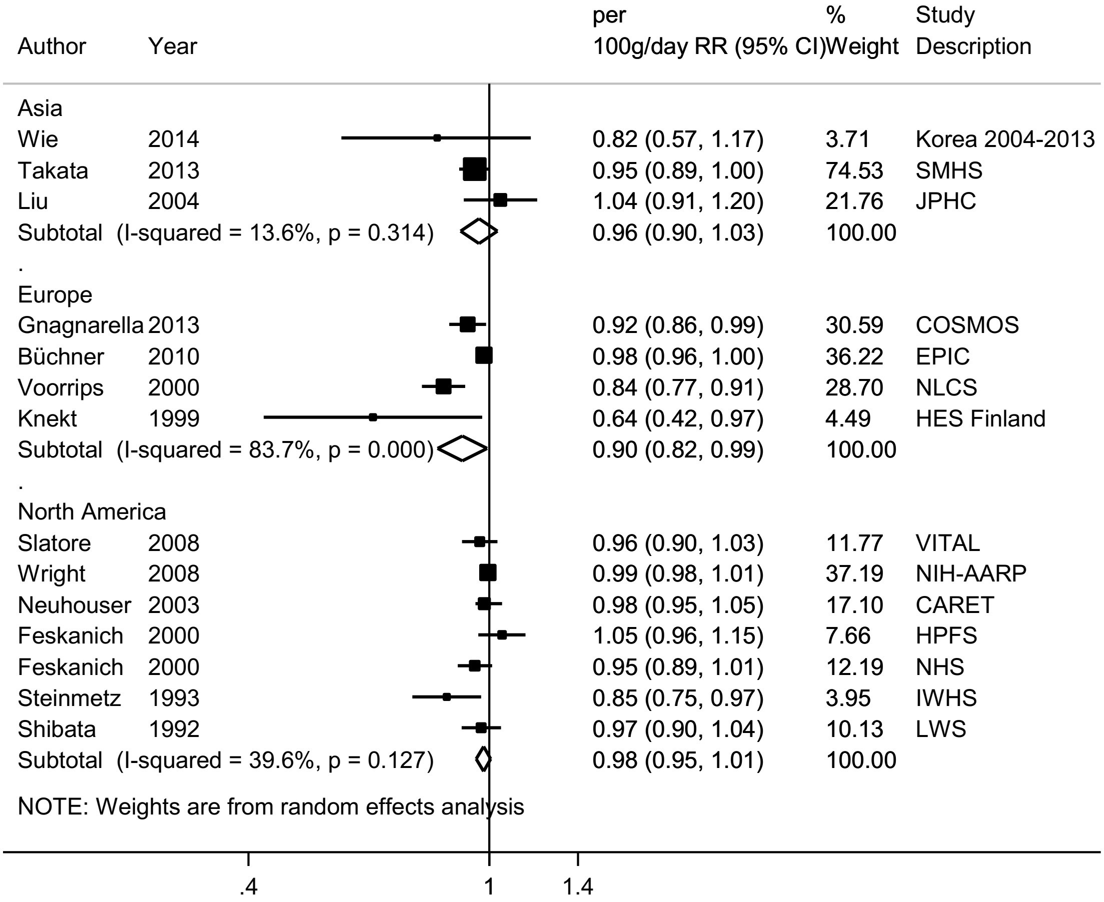
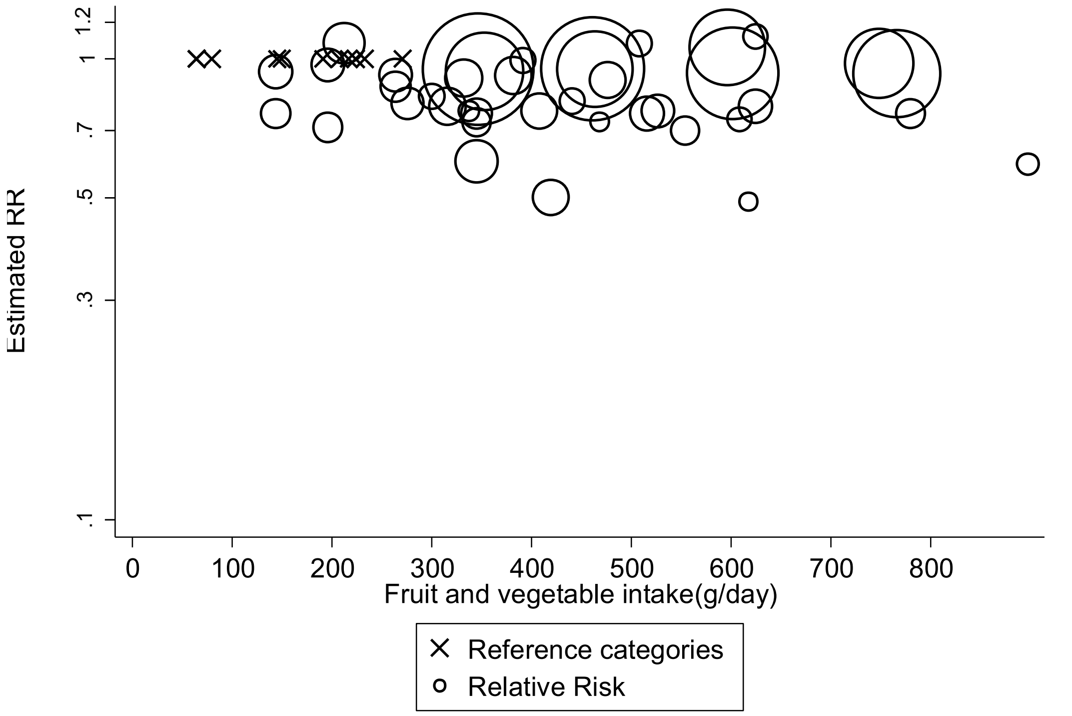
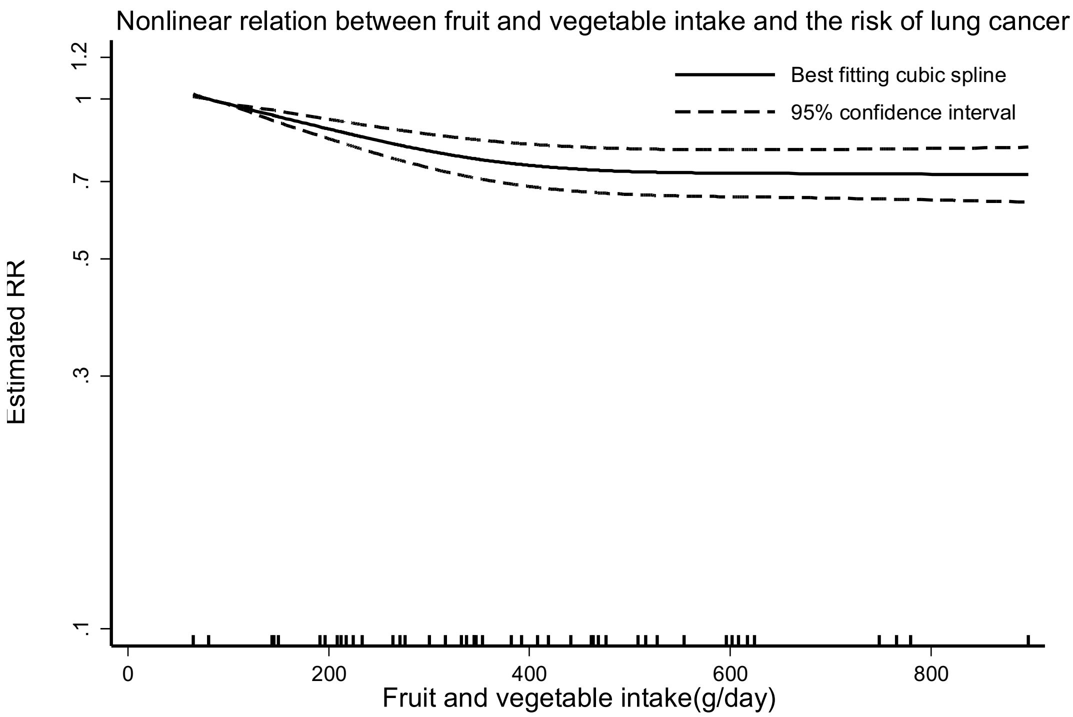


Figure 9 Relative risk of lung cancer and fruit and vegetable intake estimated using non-linear models





$p < 0.01$

Table 10 Table with fruit and vegetable intake values and corresponding RRs (95% CIs) for non-linear analysis of fruit and vegetable intake and lung cancer

Fruit and vegetable intake (g/day)	RR (95%CI)
80	1
200	0.87(0.83-0.91)
300	0.79(0.74-0.86)
500	0.73 (0.66-0.81)
780	0.72 (0.65-0.81)

2.2.1 Vegetables

Cohort studies

Summary

Twenty studies (12 563 cases) out of 24 studies (32 publications) were included in the dose-response meta-analysis. A significant inverse association was observed (RR per 100 g: 0.94; 95% CI= 0.89-0.98). Four studies were excluded from the dose-response analyses; all reported non significant associations. In analysis stratified by smoking status (six studies) the significant inverse association was restricted to current smokers. No significant associations were observed in former and never smokers. The inverse association was observed in men but not in women.
Moderate heterogeneity was observed that was not explained in analyses stratified by sex, smoking, geographic location. The meta-analyses by cancer type were not significant, but only two to four studies were included in the analyses.
There was significant evidence of publication or small study bias ($p < 0.01$). The asymmetry is driven by a small study showing an inverse association.

Sensitivity analysis:
The overall association remained statistically significant in influence analysis. The summary RRs ranged from 0.93 (95% CI=0.88-0.97) when George, 2009 was omitted to 0.97 (95% CI=0.94-0.99) when Holick, 2002 was omitted.
There was evidence of a non-linear dose-response of lung cancer and vegetable intake ($p < 0.01$) with decreasing risks for increasing intakes up to 300-400 g and no further decrease for higher intake levels.

Study quality:
Cancer outcome was confirmed using record linkage with cancer registries in most studies. All studies used FFQ to assess vegetable intake. Büchner, 2010 was the only study that corrected for measurement error of diet. Similar results were observed with the observed and calibrated intakes. Repeated dietary measurements were used in the NHS and the HPFS (Feskanich, 2000).
All studies included in the dose-response analysis were adjusted at least for age, sex, and smoking status. Most studies (18 out of 19 studies) adjusted for smoking status, duration and intensity.

Pooling project of cohort studies:
In the Pooling Project of Cohort Studies (Smith-Warner, 2003) lung cancer risk was not significantly associated with vegetable intake (seven cohorts). No significant association was observed in analyses stratified by smoking status or cancer type.
A dose-response analysis including the Pooling Project was not possible because cohort-specific cutpoints were used in this study. A meta-analysis of the highest compared to the lowest intake category including the Pooling Project (5.8% weight in the analysis) and the non overlapping studies identified in the CUP was then conducted. A significant inverse association was observed (24 studies). In analysis stratified by smoking status, the significant association was restricted to smokers and no significant association was observed in never and former smokers (eight and nine studies respectively).

Table 11 Vegetable intake and lung cancer risk. Number of studies in the CUP SLR

	Number
Studies identified	24 (32 publications)
Studies included in forest plot of highest compared with lowest intake	21
Studies included in dose-response meta-analysis	20
Studies included in non-linear dose-response meta-analysis	15

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

Table 12 Vegetable intake and lung cancer risk. Summary of the dose-response meta-analysis in the 2005 SLR and CUP.

	2005 SLR	CUP
Increment unit used	80 g/day	100 g/day
All studies		
Studies (n)	10	20
Cases (total number)	6667	12 563
RR (95%CI)	0.95(0.92-0.98)	0.94 (0.89-0.98)
Heterogeneity (I^2, p-value)	0%	47.9%, <0.01
P value Egger test		<0.01

Stratified and sensitivity analysis (no analyses conducted in the 2005 SLR)			
Smoking status	**Never smokers**	**Current smokers**	**Former smokers**
Studies (n)	5	6	4
Cases (total number)	680	6520	3771
RR (95%CI)	1.00 (0.91-1.10)	0.88 (0.79-0.99)	0.97 (0.91-1.05)
Heterogeneity (I^2, p-value)	0%, 0.44	81.0%, <0.001	24.8%, 0.26
Sex	**Men**	**Women**	
Studies (n)	9	6	
RR (95%CI)	0.94 (0.88-1.00)	1.02 (0.98-1.06)	
Heterogeneity (I^2, p-value)	44.9% , 0.07	0%, 0.56	
Outcome	**Incidence**	**Mortality**	
Studies (n)	16	4	
RR (95%CI)	0.94 (0.89-0.90)	0.97 (0.85- 1.11)	
Heterogeneity (I^2, p-value)	56.4%, < 0.01	0%, 0.67	
Cancer type	**Small cell carcinoma**	**Squamous cell carcinoma**	**Adenocarcinoma**
Studies (n)	2	2	4
RR (95%CI)	0.94 (0.66-1.32)	1.00 (0.90-1.12)	0.98 (0.91-1.07)
Heterogeneity (I^2, p-value)	48.2%, 0.17	0%, 0.61	0%, 0.84
Geographic location	**Asia**	**Europe**	**North America**
Studies (n)	5	6	9
RR (95%CI)	0.98 (0.93- 1.04)	0.88 (0.78-0.99)	0.95 (0.90-1.02)
Heterogeneity (I^2, p-value)	0% , 0.97	64.4% , 0.02	30.2%, 0.18
Adjustment on smoking	**Smoking status**	**Intensity and duration of smoking**	
Studies (n)	2	18	
RR (95%CI)	1.01(0.87-1.17)	0.93(0.88-0.98)	
Heterogeneity (I^2, p-value)	0%, 0.90	53.3%, < 0.01	

Table 13 Vegetable intake and lung cancer risk. Highest versus lowest meta-analyses of the Pooling Project and non overlapping studies in the CUP.

Pooling project of cohort studies and non overlapping studies identified in the CUP SLR			
Comparison	Highest vs lowest		
Studies (n)	24		
Cases (total number)	18927		
RR (95%CI)	0.93(0.88-0.98)		
Heterogeneity (I^2, p-value)	0%, 0.69		
Stratified highest versus lowest analysis with Pooling Project			
Smoking status	**Never smokers**	**Current smokers**	**Former smokers**
Studies (n)	9	10	8
Cases (total number)	939	8435	4752
RR (95%CI)	0.96(0.76-1.20)	0.88(0.80-0.97)	0.98(0.83-1.16)
Heterogeneity (I^2, p-value)	0%, 0.44	32.2%, 0.18	55.3%, 0.06

Table 14 Vegetable intake and lung cancer risk. Results of pooled analyses of prospective studies published after the 2005 SLR.

Author, Year	Number of cohort studies	Total number of cases	Studies country, area	Outcome	Comparison	RR (95%CI)	P trend	Heterogeneity (I^2, p value)
Smith-Warner, 2003 AHS, ATBC, CNBSS, HPFS, IWHS, NYSC, NHS Pooling Project of cohort studies	7	3206	USA, Europe	Lung cancer All	Q5 vs Q1	0.88(0.78-1.00)	0.12	0.76
					≥400 vs <100 g/day	0.90(0.71-1.12)		
	5	259		Never smokers	Q4 vs Q1	0.90(0.58-1.40)	0.75	0.35
		981		Past smokers		0.97(0.76-1.24)	0.83	0.30
		1915		Current smokers		0.86(0.74-1.00)	0.14	0.85
	6	956		Adenocarcinoma	Q4 vs Q1	0.91 (0.75-1.11)	0.53	0.25
		538		Small cell carcinoma		0.98(0.77-1.26)	0.92	0.26
		901		Squamous cell carcinoma		0.94(0.78-1.12)	0.84	0.53

Table 15 Vegetable intake and lung cancer risk. Main characteristics of studies 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	Missing data derived for analysis
Bradbury, 2014 LUN26881 Europe	EPIC, Prospective Cohort	1830/ 470 000	Cancer registries, health insurance records, active follow up with cases confirmed by pathology records	Questionnaire	Incidence, lung cancer	Per 100 g/day	0.94 (0.88-1.01)	Age, sex, centre, smoking status, duration, lifetime and baseline cigarettes/day, time since quitting smoking education, energy intake, weight, height, physical activity, vegetable consumption alcohol	Estimation of confidence intervals. Used only in highest versus lowest and dose-response analysis. Büchner, 2010b LUN20360 was used in stratified analysis
						≥305 vs ≤99 g/day	0.58		
Gnagnarella, 2013a LUN26858 Italy	COSMOS (Continuous Observation of Smoking Subjects), Prospective Cohort, Age: 50-84 years heavy smokers	178/ 4336 5.70 years	Screening examinations	FFQ	Incidence, lung cancer	185.07 vs 46.99 g/1000 kcal/day	0.63 (0.40-0.97) Ptrend:0.02	Age, sex, energy intake, smoking duration, average daily cigarettes consumption, years of cessation, asbestos exposure, fruits	Distribution of person-years by exposure category

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Missing data derived for analysis
								and vegetables, fish, red meat, olive oil, tea and wine intake	
Takata, 2013 LUN26860 China	Shanghai Men's Health Study, Prospective Cohort, Age: 40-74 years, M	359/ 61 092 5.50 years	Biennial home visits (diagnosis verified by medical chart review), record linkage to Cancer Registry and Vital Statistics Registry	Validated FFQ	Incidence, lung cancer	545.5 vs 158 g/day	0.88 (0.64-1.22) Ptrend:0.49	Age, BMI, fruit intake, tea consumption, total caloric intake, current smoking status, education, family history of lung cancer, history of chronic bronchitis, number of cigarettes smoked per day, years of smoking	Distribution of person-years by exposure category
Takata, 2012 LUN26859 China	SWHS, Prospective Cohort, Age: 40-70 years, W, never smokers	428/ 71 267 11.2	Shanghai cancer registry & the shanghai vital statistics registry	FFQ	Incidence, lung cancer	475 vs 136 g/d	0.93 (0.70-1.23) Ptrend:0.69	Age, BMI, income, occupation, total caloric intake, history of asthma, passive smoking	Distribution of person-years by exposure category

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Missing data derived for analysis
Büchner, 2010 LUN20360b Denmark,France ,Germany,Greec e,Italy,Netherlan ds,Norway,Spai n,Sweden,U.K.	EPIC, Prospective Cohort, Age: 25-70 years, M/W	1830/ 478 535 8.7 years	Cancer registries, health insurance records, active follow up with cases confirmed by pathology records	FFQ, dietary questionnaires, food record	Incidence, lung cancer	>307 vs <97 g/day	0.96 (0.79-1.17) Ptrend:0.58	Fruit consumption, age, alcohol consumption, centre, duration of smoking, education level, energy intake, height, physical activity, smoking status, weight, gender, lifetime and baseline intensity of smoking, time since quitting smoking	Distribution of person-years by exposure category, mid-points of exposure categories
		1167			Incidence, lung cancer, current smokers	>307 vs <97 g/day	0.87 (0.66-1.13) Ptrend:0.15		
		964			Incidence, lung cancer, men	>307 vs <97 g/day	1.04 (0.79-1.37) Ptrend:0.89		
		866			Incidence, lung cancer, women	>307 vs <97 g/day	0.89 (0.68-1.17) Ptrend:0.60		
		578			Incidence, adenocarcinoma	>307 vs <97 g/day	1.10 (0.78-1.55) Ptrend:0.66		
		467			Incidence, lung cancer, former smokers	>307 vs <97 g/day	1.04 (0.73-1.49) Ptrend:0.62		
		363			Incidence, squamous cell carcinoma	>307 vs <97 g/day	0.96 (0.62-1.50) Ptrend:0.75		
		286			Incidence, small cell carcinoma	>307 vs <97 g/day	1.17 (0.67-2.02) Ptrend:0.57		
		187			Incidence, lung cancer, never smokers	>307 vs <97 g/day	0.81 (0.46-1.45) Ptrend:0.90		

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Missing data derived for analysis
		137			Incidence, large cell carcinoma	>307 vs <97 g/day	0.81 (0.38-1.72) Ptrend:0.55		
George, 2009 LUN20265 USA	NIH-AARP Diet and Health, Prospective Cohort, Age: 50-71 years, M/W, Retired	4092/ 483 338	Annual linkage to state cancer registries and national death index plus	FFQ	Incidence, lung cancer, men	1.1-3.25 vs 0-0.44 cup1000 kcal/day	0.87 (0.78-0.96) Ptrend:0.02	Age, BMI, family history of cancer, fruit, marital status, physical activity, race, alcohol, education, smoking menopausal hormone therapy use energy intake,	Distribution of person-years by exposure category, mid-points of exposure categories Exposure values using mean energy intake RRs for men and women combined
		2347			Incidence, lung cancer, women	1.44-4.38 vs 0-0.56 cup/1000 kcal/day	1.08 (0.94-1.23) Ptrend:0.22		
Wright, 2008 LUN20306 USA	NIH-AARP Diet and Health, Prospective Cohort, Age: 50-71 years, M/W, Retired	2110/ 472 081 8.0 years	Annual linkage to state cancer registries and national death index plus	Validated FFQ	Incidence, lung cancer, male former smokers	>2.20 vs <0.87 servings/1000 kcal/day	0.88 (0.77-1.01) Ptrend:0.01	Age, BMI, energy intake, family history of cancer, race, smoking status, alcohol intake, education, physical activity, smoking dose, time since quitting	Used in stratified analysis by smoking. Distribution of person-years by exposure category, mid-points of exposure categories. Exposure values
		1583			Incidence, lung cancer, male current smokers	>2.20 vs <0.87 servings/1000 kcal/day	0.97 (0.81-1.16) Ptrend:0.90		
		1196			Incidence, lung cancer, women current smokers	>2.86 vs <1.11 servings/1000 kcal/day	1.01 (0.84-1.22) Ptrend:0.75		
		835			Incidence, lung cancer, women	>2.86 vs <1.11 servings/1000	1.26 (1.01-1.58) Ptrend:0.07		

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Missing data derived for analysis
					former smokers	kcal/day		smoking, past smoking dose	using Exposure values using mean energy intake
		170			Incidence, lung cancer, women never smokers	>2.86 vs <1.11 servings/1000 kcal/day	0.72 (0.42-1.22) Ptrend:0.27		
		141			Incidence, lung cancer, male never smokers	>2.20 vs <0.87 servings/1000 kcal/day	0.94 (0.56-1.59) Ptrend:0.99		
Liu, 2004 LUN10203 Japan	JPHC study-cohort I and II, Prospective Cohort, Age: 40-69 years, M/W	317/ 93 338 10.0 years	Hospital records, population-based cancer registries and death certificates	FFQ - study-specific	Incidence, lung cancer, current smokers	Highest vs Lowest	0.97 (0.71-1.34)	Age, sex, areas, sports, alcohol intake, BMI, vitamin supplement use, salted fish and meat, pickled vegetables, smoking status, smoking duration, cigarettes/ day	Mid-points of exposure categories.
		198			Incidence, adenocarcinoma	Highest vs Lowest	1.13 (0.66-1.94)		
		176			Incidence, other tumour types	Highest vs Lowest	0.79 (0.55-1.16)		
		106			Incidence, lung cancer, non-smokers	Highest vs Lowest	1.37 (0.79-2.37)		
Alavanja, 2004 LUN16965 USA	AHS, Prospective Cohort, M/W, No specific group	206/ 89 658 6.20 years	Iowa and North Carolina cancer registries; state death registries and National Death Index	FFQ - study-specific	Mortality, lung cancer, men	≥7 times/wk vs <4 times/wk	0.80 (0.50-1.20)	Age, sex, clinic site, educational level, ethnicity/race, family history of specific cancer, presence of other diseases,	Distribution of person-years by exposure category, mid-points of exposure categories. Exposure values
		48			Mortality, lung cancer, women	≥7times/wk vs <4 times/wk servings/week	0.60 (0.20-1.70)		

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 analysis
								smoking status, pack-years, physical activity	using standard portion size. RRs for men and women combined
Jansen, 2004 LUN19603 Netherlands	Zutphen Study, Prospective Cohort, Age: 65-84 years, M	42/ 730 00 10.0 years	Data from Central Bureau of Statistics, diagnosis verified through cancer registry, hospital discharge or general practitioner	FFQ - study-specific	Incidence, lung cancer	200+ vs 0-150 g/day	0.95 (0.44-2.07)	age, alcohol consumption, BMI, energy intake, physical activity, smoking habits, vegetable intake	Distribution of person-years by exposure category, mid-points of exposure categories.
Neuhouser, 2003 LUN00354 USA	CARET, Prospective Cohort, Age: 45-69 years, M/W	742 12 years	Lung cancer is primary endpoint of the trial. Active follow-up confirmed in medical and pathology records	FFQ - study-specific	Incidence, lung cancer, intervention	>66.8 vs 1-26 servings/month	0.81 (0.65-1.21)	Age, sex, smoking status, total pack-years of smoking, asbestos exposure, race/ethnicity, and enrollment center	Distribution of person-years and cases by exposure category Mid-points of exposure categories. Exposure values using standard portion size. RRs for intervention and
					Incidence, lung cancer, control	>66.8 vs 1-26 servings/month	0.82 (0.59-1.14)		

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 analysis
									placebo combined
Sauvaget, 2003 LUN05721 Japan	Life Span Study, Prospective Cohort, Age: 34-103 years, M/W	563/ 38 540 16.0 years	Japanese nation-wide family registration system (Koseki) that provides complete mortality ascertainment	FFQ - study-specific	Mortality, Lung cancer	Daily vs 0-4 times/month	0.95 (0.76-1.19)	Age, sex, alcohol consumption, area of residence, BMI, educational level, other, smoking status	Distribution of person-years by exposure category, mid-points of exposure categories. Exposure values using standard portion size.
Takezaki, 2003 LUN00268 Japan	Aichi Cancer Registry Study, Prospective Cohort, Age: 30- years, M/W	51/ 5885 14.0 years	Cancer registry	FFQ - study-specific	Incidence, Lung cancer	High vs low times/week	1.06 (0.52-2.16)	Age sex, smoking status, cigarettes/day -2 categories- , occupation.	Mid-points of exposure categories. Exposure values using standard portion size.
Holick, 2002 LUN00515 Finland	ATBC, Prospective Cohort, Age: 50-69 years, M, Smokers only	1644/ 29 133 11.0 years	Finnish Cancer Registry and the Register of Causes of Death	FFQ - study-specific	Incidence, lung cancer	>156 vs <52 g/day	0.75(0.63-0.88)	Age, years smoked, cigarettes/day, trial group, supplement use , energy intake, cholesterol, and fat	Distribution of person-years by exposure category
Breslow, 2000	National Health	158/	Record linkage	FFQ - block	Mortality, lung	>13.6 vs 0-5.2	0.90 (0.50-1.50)	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 analysis
LUN01082 USA	Interview Survey (NHIS), Prospective Cohort, Age: 18-87 years, M/W	20 195 8.5 years	to National Death Index		cancer	servings/week		smoking duration, packs/day	exposure categories. Exposure values using standard portion size
Feskanich, 2000 LUN00986 USA	Nurses' Health Study + Health Professionals Follow-up Study, Prospective Cohort, Age: 30-75 years, M/W	519/ 125 061 12.0 years	Verbal or written self-report, if possible confirmed by medical records, and death certificates	FFQ - study-specific	Women Incidence, lung cancer	4.7 vs 1.85 servings/day	0.68 (0.51-0.90)	Age, follow-up cycle, smoking status, years since quitting -past smokers-, cigarettes /day -current smokers-, age start smoking, total energy intake, availability of diet data after baseline	Distribution of person-years by exposure category, mid-points of exposure categories. Exposure values using standard portion size.
		269			Women, current smokers	Quintile 5 vs quintile 1	0.59 (0.39-0.89)		
		193			Women , former smokers	Quintile 5 vs quintile 1	0.85 (0.53-1.36)		
		148			Women , non-smokers	Quintile 5 vs quintile 1	1.12 (0.65-1.94)		
		54			Women, non-smokers	Quintile 3 vs quintile 1	0.94 (0.46-1.91)		
		232			Women, adenocarcinoma	Quintile 5 v. quintile 1	0.76 (0.50-1.17)		
		179			Women, non-small cell cancer (SCC, adeno-carcinoma, large	Quintile 5 vs quintile 1	0.63 (0.39-1.02)		

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Missing data derived for analysis
					cell)				
		274			Incidence, lung cancer, men	4.5 vs 1.3 servings/day	1.04 (0.69-1.57)		
		86			Incidence, lung cancer, men, current smokers	Quintile 5 vs quintile 1	0.95 (0.45-2.03)		
		24			Incidence, lung cancer, men, non-smokers	Tertile 3 vs Tertile 1	0.57 (0.21-1.57)		
		148			Incidence, lung cancer, men, former smokers	Quintile 5 vs quintile 1	1.12 (0.65-1.94)		
		120			Incidence, non-small cell (SCC, adenocarcinoma, large cell), men	Quintile 5 vs quintile 1	0.86 (0.47-1.58)		
		93			Incidence, adenocarcinoma men	Quintile 5 vs quintile 1	2.08 (1.00-4.36)		
Voorrips, 2000b LUN01162 Netherlands	Netherlands Cohort Study on Diet and Cancer (NLCS), Case Cohort,	910/ 120 852 3.20 years	Regional cancer registries and computerized national database of	FFQ - study-specific	Incidence, lung cancer	286 vs 103 g/day	0.70 (0.50-1.00)	Age, sex, educational level, family history of lung cancer, current	
		575			Incidence, men, squamous cell	Quintile 5 vs quintile 1	0.60 (0.40-0.90)		

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Missing data derived for analysis
	Age: 55-69 years, M/W	532	pathology report (PALGA)		Incidence, lung cancer, current smokers	286 vs 103 g/day	0.70 (0.50-1.00)	smoker, years of smoking, cigarettes/day	
		321			Incidence, lung cancer, former smokers	286 vs 103 g/day	0.70 (0.40-1.10)		
		146			Incidence, men, adenocarcinoma	Quintile 5 vs quantile 1	0.80 (0.40-1.40)		
		68			Incidence, women, squamous cell	Tertile 3 vs Tertile 1	1.40 (0.80-2.70)		
		57			Incidence, lung cancer, non-smokers	286 vs 103 g/day	1.80 (0.70-4.70)		
		44			Incidence, women, adenocarcinoma	Tertile 3 vs Tertile 1	1.00 (0.50-2.30)		
Knekt, 1999 LUN01416 Finland	Finnish Mobile Clinic Health Examination Survey, Prospective Cohort, Age: 20-69 years, M,	138/4545 25 years	National cancer registry	FFQ - study-specific	Incidence, lung cancer	118 vs 61 g/day	0.83 (0.54-1.26)	Age, smoking status	Distribution of person-years and cases by exposure category

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Missing data derived for analysis
Steinmetz, 1993 LUN02740 USA	IWHS, Nested Case Control, Age: 55-69 years, W, Post menopausal	81/ 41 837 4.0 years	Iowa Health Registry (part of SEER registry)	FFQ - study-specific	Incidence, lung cancer, current smokers	>31 vs <14 servings/week	0.63 (0.30-1.33)	Age, energy intake, pack-years of smoking	Distribution of person-years by exposure category, mid-points of exposure categories.
		45			Incidence, adenocarcinoma	>31 vs <14 servings/week	0.47 (0.18-1.21)		
		38			Incidence, lung cancer, former smokers	>31 vs <14 servings/week	0.31 (0.11-0.88)		
		37			Incidence, small cell	>31 vs <14 servings/week	0.44 (0.14-1.37)		
		25			Incidence, squamous cell (SCC)	>31 vs <14 servings/week	0.64 (0.21-1.91)		
		19			Incidence, lung cancer, non-smokers	>31 vs <14 servings/week	1.08 (0.27-4.39)		
		12			Incidence, Large cell	>48 vs <24 servings/week	0.06 (0.01-0.67)		
Chow, 1992 LUN02888 USA	LBS, Prospective Cohort, Age: 35- years, M,	219/ 17 633 20.0 years	Death certificates	FFQ - study-specific	Mortality, lung cancer	>160 vs <46 times/month	1.20 (0.60-2.30)	Age, other, smoking status	Mid-points of exposure categories. Exposure values using standard portion size.

Author, Year, WCRF Code, Country	Study 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
Shibata, 1992 LUN08664 USA	LWS, Prospective Cohort, Age: 74.00years, M/W,	70/ 11 580 6.0 years	Death by reports of friends or relatives, National Death Index; incidence through hospital records	FFQ - study-specific	Incidence, lung cancer, women	>4.8 vs 0-3.1servings/day	0.58 (0.32-1.05)	Age, smoking habits	Distribution of person-years by exposure category, mid-points of exposure categories. Exposure values using standard portion size
		97			Incidence, lung cancer, men	>4.8 vs 0-3.1servings/day	1.37 (0.74-2.25)		

Table 16 Vegetable intake and lung cancer risk. Main characteristics of studies excluded 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	Reasons for exclusion
Pavanello, 2012 LUN20332 Denmark	DCH, Nested Case Control, Age: 50-64 years, M/W	425/ 160 725	Danish cancer registry	FFQ	Incidence, lung cancer	>188 vs <109 g/day	0.42 (0.31-0.58)	Alcohol consumption, cyp1a2 polymorphism, occupational exposure, gender, pack yrs of smoking, passive smoking	Component of EPIC (Büchner, 2010b LUN20360)
Sakoda, 2011 LUN20351 USA	CARET, Nested Case Control, Age: 45-69 years, M/W	365/ 18 314	Lung cancer is primary endpoint of the trial. Active follow-up confirmed in medical and pathology records	FFQ	Incidence, lung cancer	>13.4 vs ≤8.4 serving/week	ORGA 1.37 (0.98-1.90) ORAA 1.84 (1.11–3.06)	Age, sex, enrolment year, smoking status, occupational asbestos exposure	Only has gene interactions results, Neuhouser, 2003 LUN00354 was used
Linseisen, 2007 LUN20323 France, Italy, Spain, U.K., Netherlands, Greece,	EPIC, Prospective Cohort, Age: 25-70 years, M/W	1126/ 478 590 6.4 years	Cancer registries, health insurance records, active follow up confirmed with	FFQ, dietary questionnaires, food record	Incidence, lung cancer	247.9 vs 109.1 g/day	1.06 (0.83-1.36)	Education level, energy intake from fat and nonfat sources, height, smoking status, weight,	Superseded by Büchner, 2010b LUN20360
		1126			Incidence, lung cancer	Per 100 g	1.01 (0.95-1.07)		
		731			Incidence, lung	247.9 vs 109.1	0.78 (0.54-1.13)		

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Reasons for exclusion
Germany, Sweden, Denmark, Norway			pathology records, death registries		cancer, current smokers	g/day		work - physical activity, ethanol intake, processed and red meat, smoking duration	
		731			Incidence, lung cancer, current smokers	Per 100 g	0.78 (0.62-0.98)		
		291			Incidence, lung cancer, former smokers	247.9 vs 109.1 g/day	1.33 (0.85-2.08)		
		291			Incidence, lung cancer, former smokers	Per 100 g	1.30 (0.95-1.76)		
		98			Incidence, lung cancer, never smokers	247.9 vs 109.1 g/day	0.97 (0.46-2.04)		
		98			Incidence, lung cancer, never smokers	Per 100 g	1.42 (0.85-2.39)		
Skuladottir, 2004 LUN05185 Denmark	Danish Diet Cancer and Health Study, Prospective Cohort, Age: 50-64 years,	247/ 54 158 8.0 years	Cancer registry	FFQ - study-specific	Incidence, lung cancer	171-479 vs 17-68 g/month	0.67 (0.46-0.97)	Age, other, smoking habits	Component of EPIC (Büchner, 2010b LUN20360)
		79			Incidence, adenocarcinoma	Per 100 g/day	0.94 (0.72-1.23)		
		49			Incidence, squamous cell	Per 100 g/day	0.91 (0.63-1.30)		

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
	M/W	43			Incidence, small cell	Per 100 g/day	0.61 (0.39-0.97)		
Khan, 2004 LUN00068 Japan	Japan, Hokkaido Cohort Study, Prospective Cohort, Age: 40- years, M/W	3158 14.8 years	Annual follow-up survey, cause of death classified by researchers	Dietary history questionnaire	Mortality, lung cancer, men	Several times/week or everyday vs never or several times/year or several times/month	0.70 (0.40-1.30)	Age, smoking	Used only in highest versus lowest analysis. Only 2 categories
					Mortality, lung cancer, women		1.9 (0.40-8.9)		
Miller, 2002 LUN00442 Europe	EPIC, Prospective Cohort, Age: 25-70 years, M/W	482 924 4.00 years	Cancer registries, health insurance records, active follow up with cases confirmed by pathology records	FFQ - study-specific	Incidence, lung cancer	Quartile 4 vs quartile 1 g/day	0.96 (0.72-1.28)	Smoking habits	Superseded by Büchner, 2010b LUN20360
Fu, 1997 LUN01468 Japan	Nagoya, 1983-2000, Prospective Cohort, Age: 40- years, M/W	24 489 10.0 years	Follow-up based on data from Aichi local council	Dietary history questionnaire	Incidence, lung cancer, men		0.80 (0.54-1.20)		Article in Chinese (translated) with insufficient data
					Incidence, lung cancer, women		0.47 (0.23-0.94)		
Ocke, 1997 LUN01851 Netherlands	Zutphen Study, Prospective Cohort,	54/ 561 12.5 years	Data from Central Bureau of Statistics,	Dietary history questionnaire	Incidence, lung cancer	>33rd percentile vs ≤33rd percentile	0.84 (0.50-1.42)		Superseded by Jansen, 2004 LUN19603

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Reasons for exclusion
	Age: 40-59 years, M,		diagnosis verified through cancer registry, hospital discharge or general practitioner						
Knekt, 1991b LUN03018 Finland	Finnish Mobile Clinic Health Examination Survey, Prospective Cohort, Age: 20-69 years, M	4583 20.0 years	Cancer registry	FFQ - study-specific	Incidence, lung cancer, current smokers	Lowest vs highest tertile	0.98	Age, smoking habits	Superseded by Knekt, 1999 LUN01416
					Incidence, lung cancer , non-smokers	Lowest vs highest tertile	1.44		
Wang, 1985 LUN04098 USA	USA 1959-1970, Prospective Cohort, Age: 45-79 years, M/W	750 000 12.0 years	Active follow-up, data from medical doctors, death certificates	FFQ - study-specific	Mortality, lung cancer	0-2 days/week vs 5-7 days/week day/week	1.30	Not available	No confidence intervals, unadjusted results
Kvåle, 1983 LUN04322 Norway	Norway, 1967-1978, Prospective Cohort, M/W	68/ 16 713 11.5 years	Cancer Registry of Norway and death registry	Dietary history questionnaire	Incidence, lung cancer	Highest indices vs lowest indices times/month	0.74	Age, area of residence, smoking habits, urban/rural status	No confidence interval

Figure 10 Relative risk estimates of lung cancer by levels of vegetable intake

Note: *Squamous cell, large cell and small cell carcinoma combined (Kreyberg I).
The graph is presented in two panels because of the high number of studies.

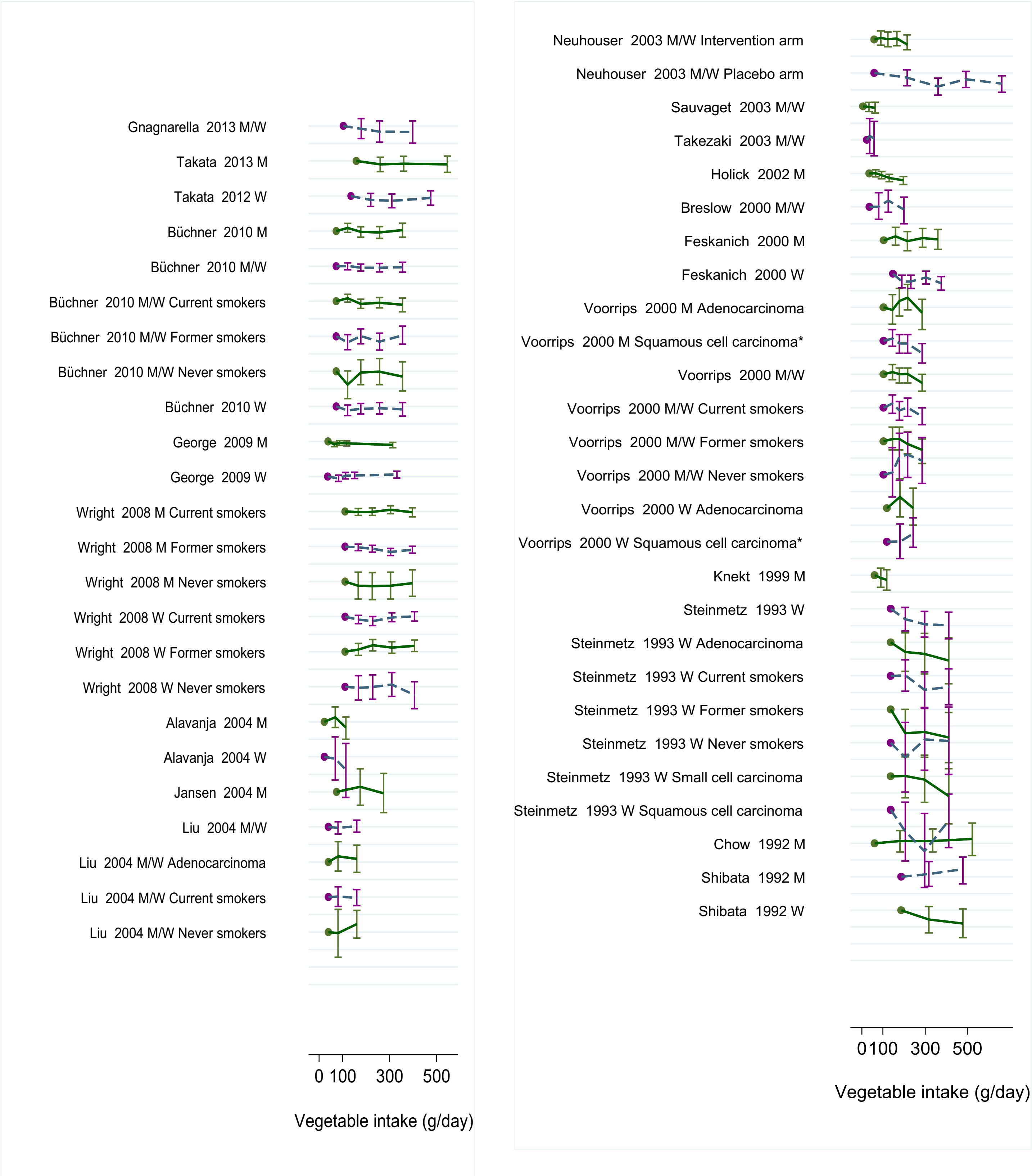
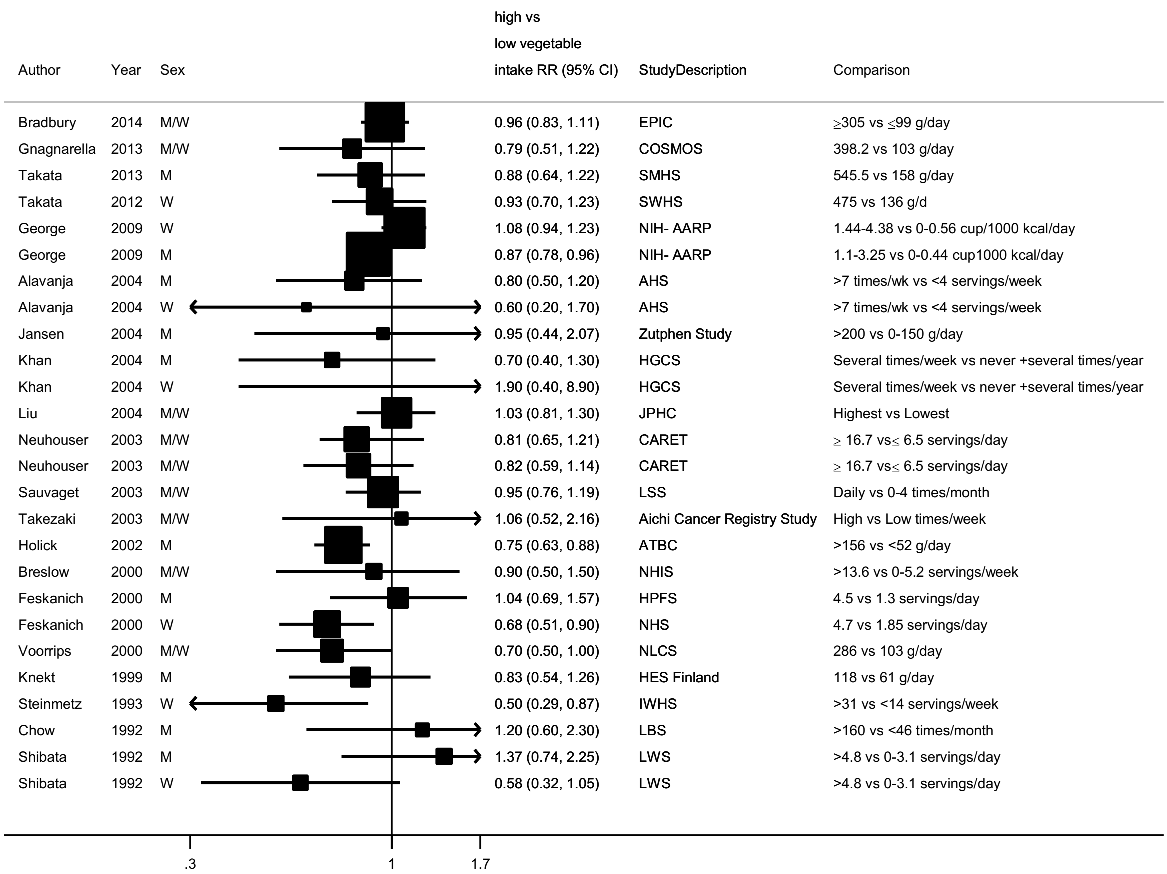


Figure 11 RR (95% CI) of lung cancer for the highest compared with the lowest level of vegetable intake



CARET study (Neuhouser, 2003) is a follow-up of a RCT, both the intervention and placebo arms of the trial are represented in the graph.

Figure 12 RR (95% CI) of lung cancer for the highest compared with the lowest level of vegetable intake combined with Pooling Project

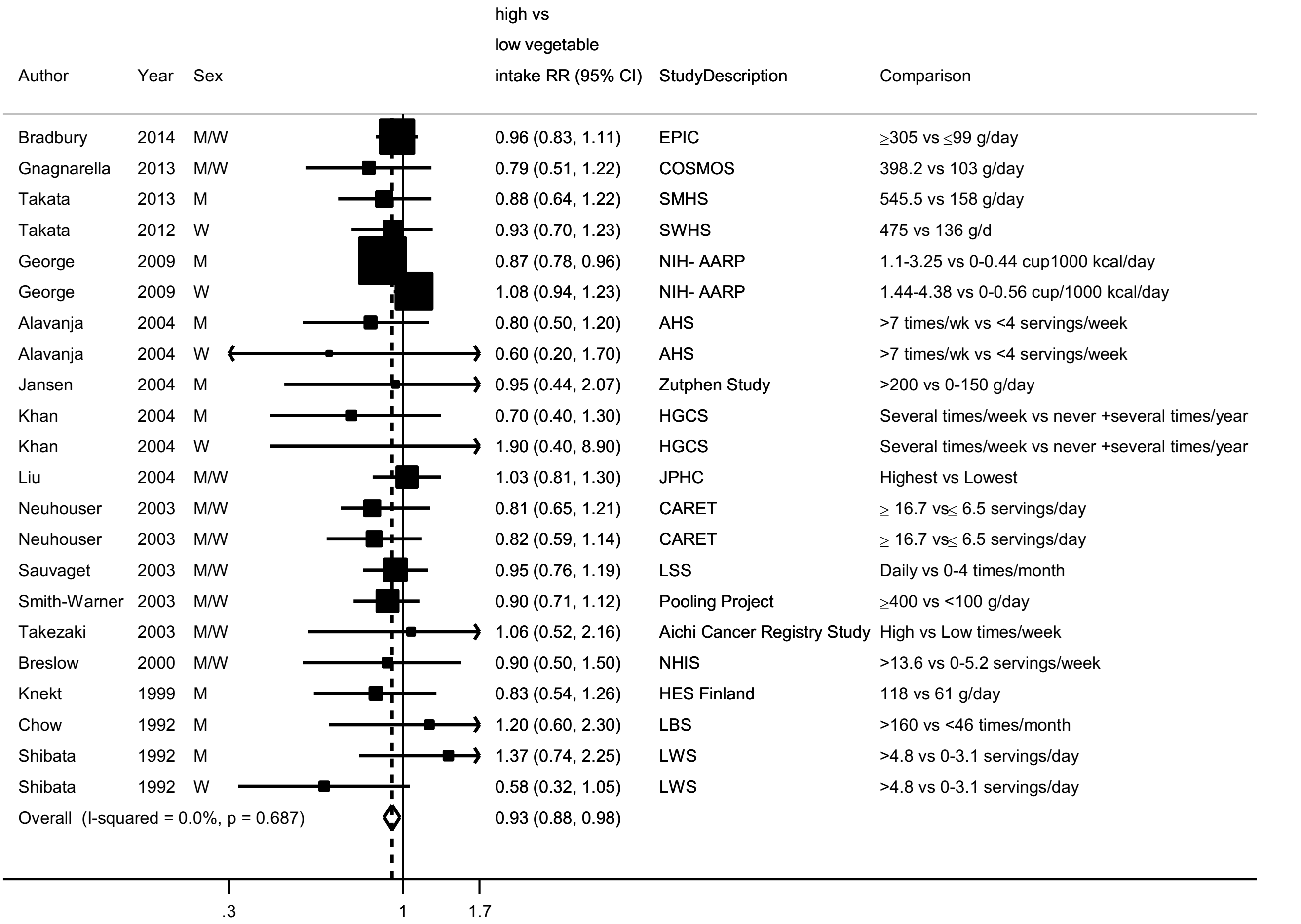


Figure 13 RR (95% CI) of lung cancer for 100g/day increase of vegetable intake

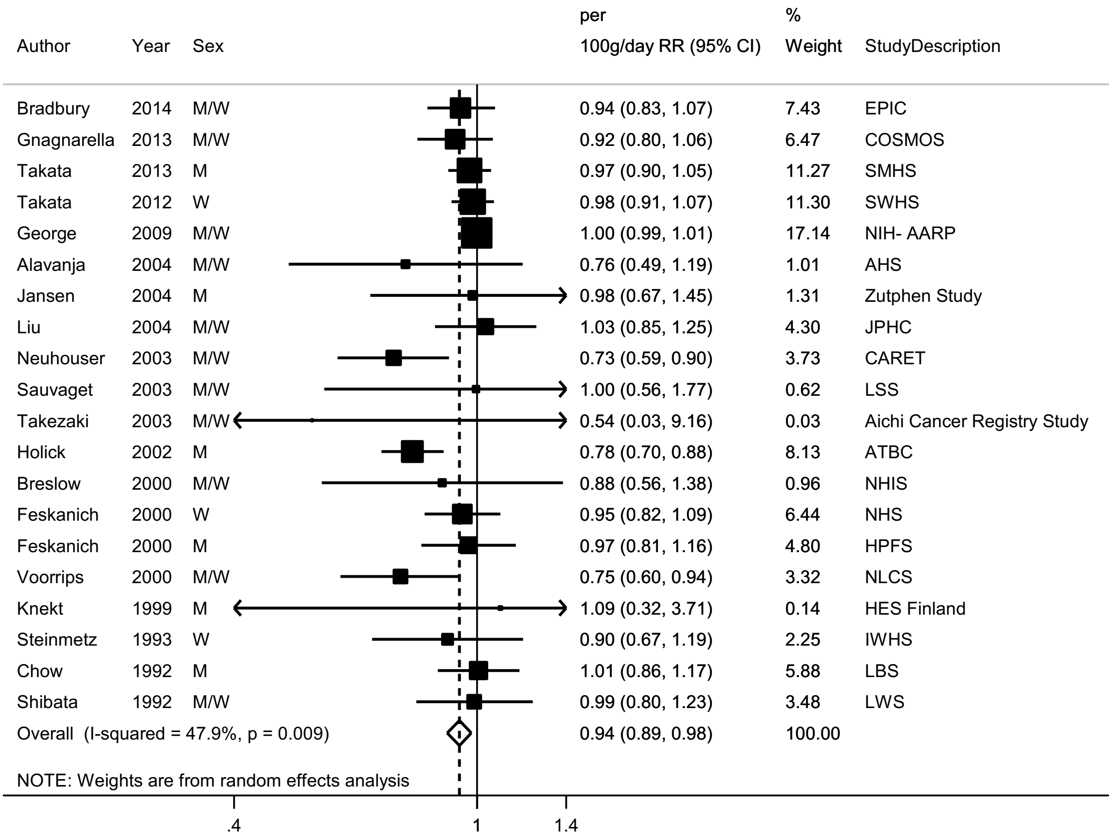
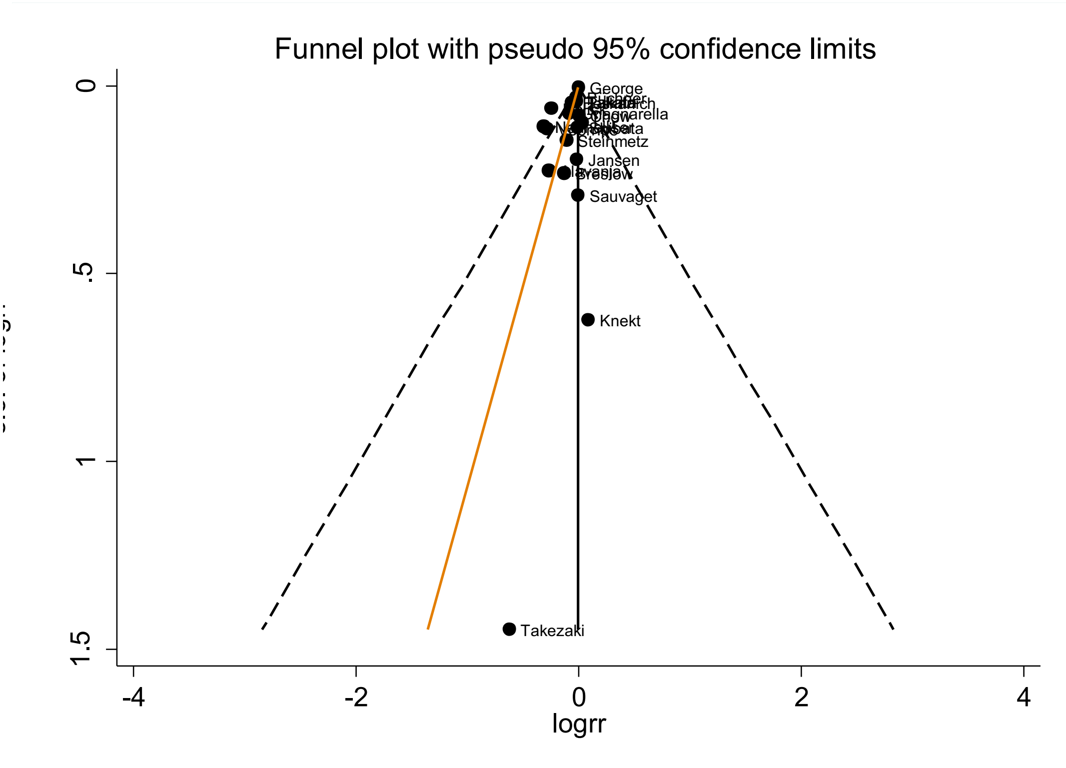


Figure 14 Funnel plot of studies included in the dose response meta-analysis of vegetable intake and lung cancer



Egger's test p < 0.01

Figure 15 RR (95% CI) of lung cancer for 100g/day increase of vegetable intake by sex

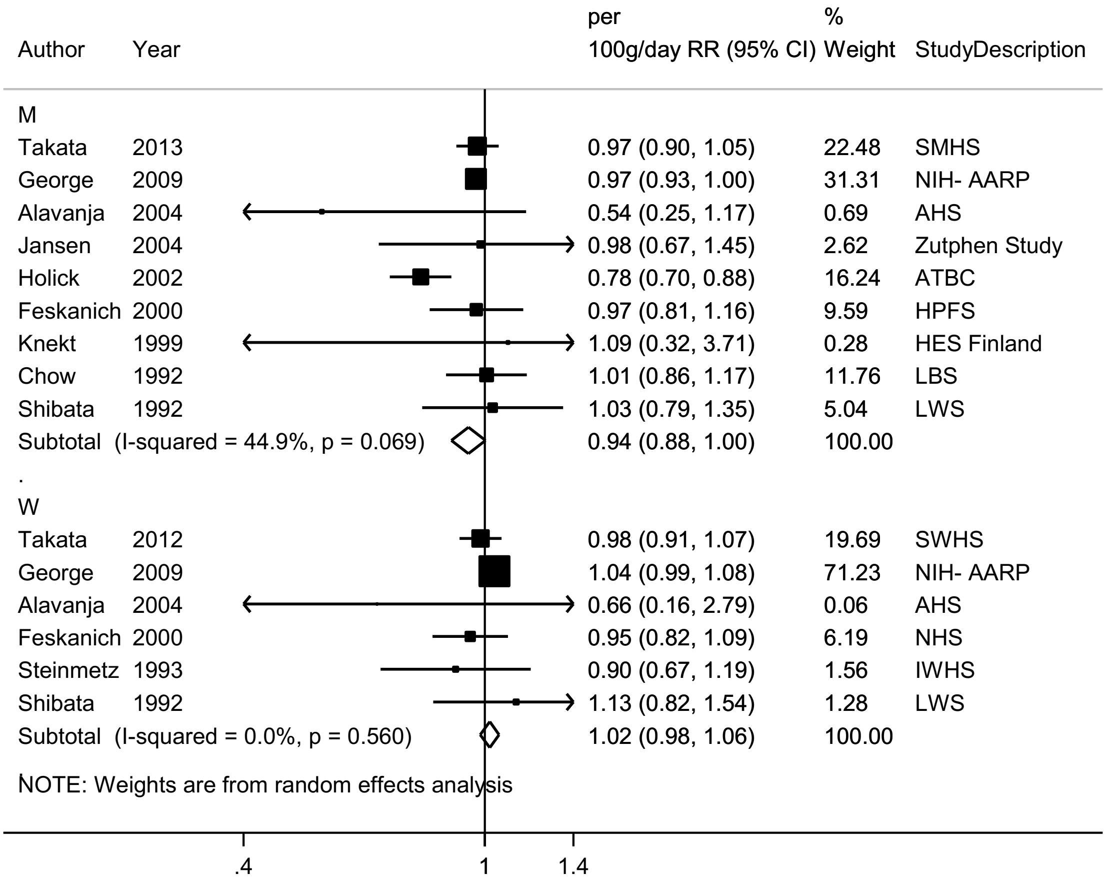


Figure 16 RR (95% CI) of lung cancer for 100g/day increase of vegetable intake by cancer outcome

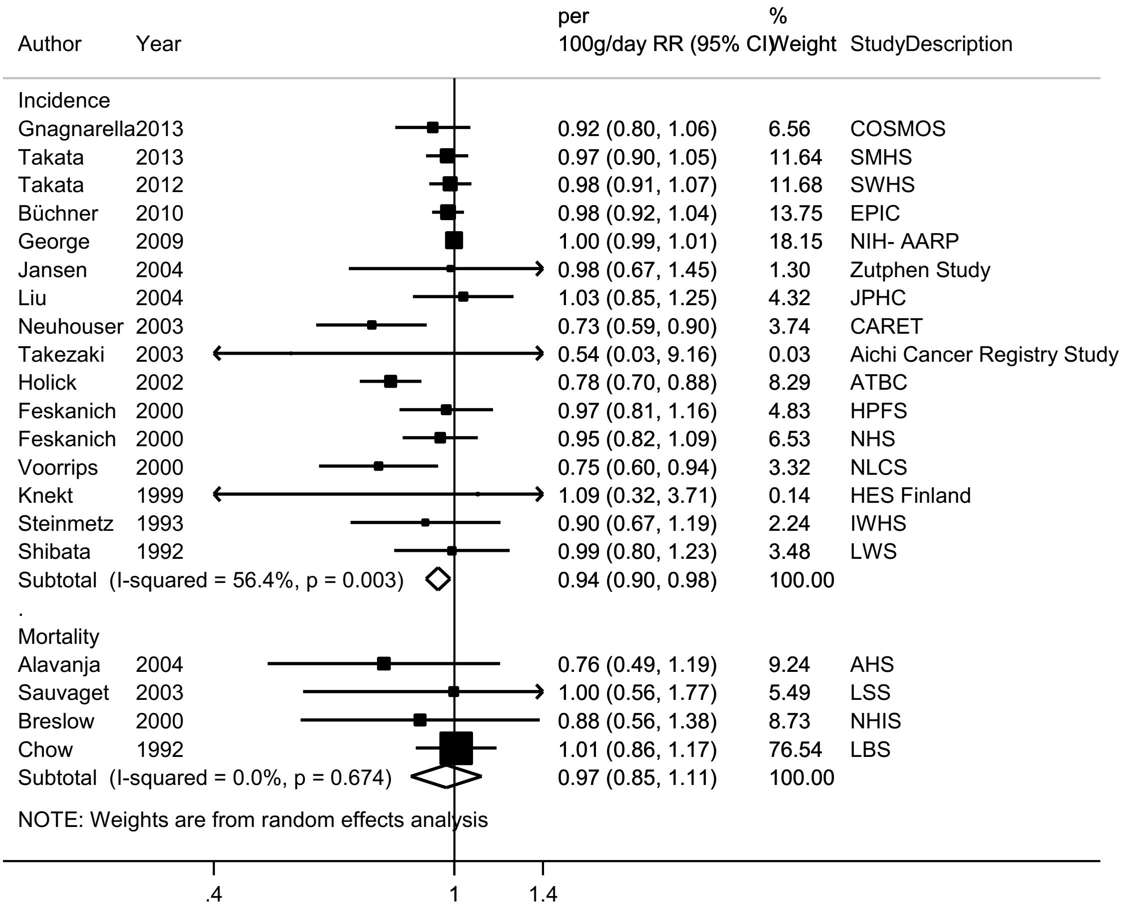


Figure 17 RR (95% CI) of lung cancer for 100g/day increase of vegetable intake by cancer site

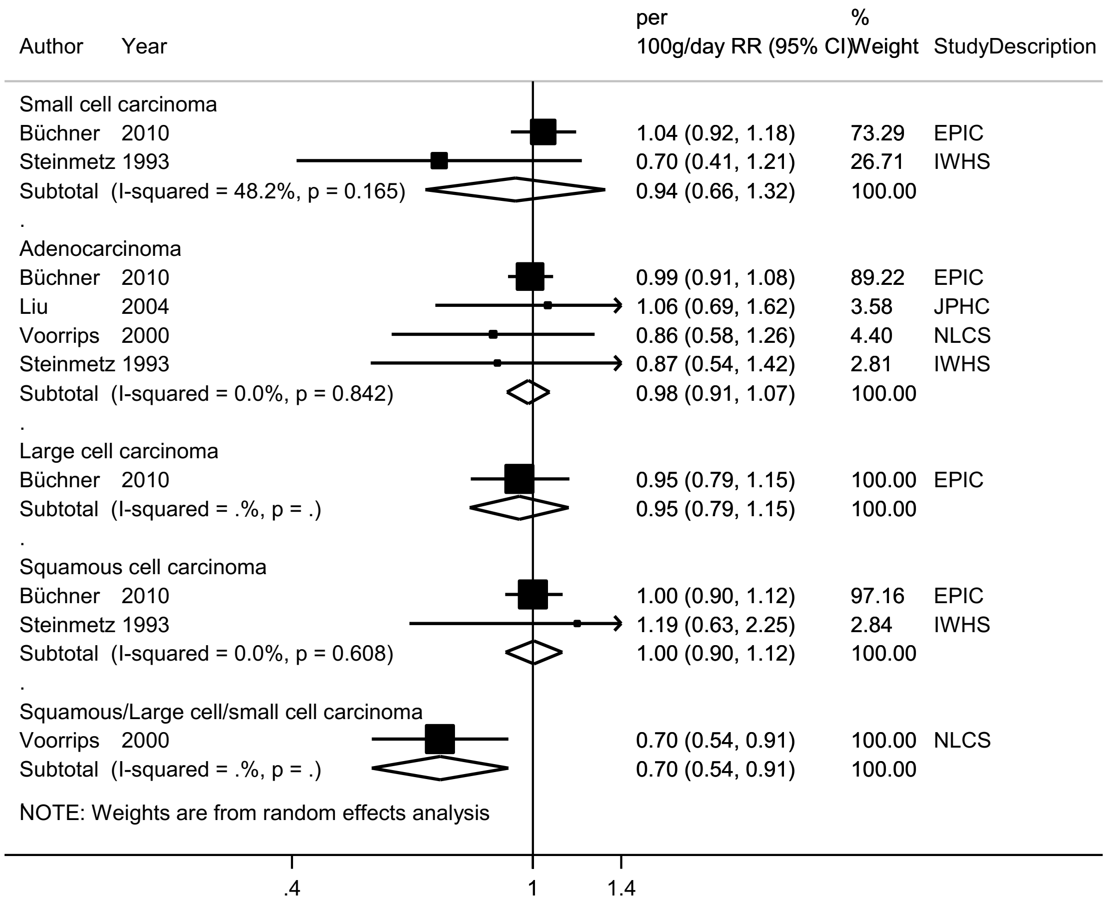


Figure 18 RR (95% CI) of lung cancer for 100g/day increase of vegetable intake by smoking status

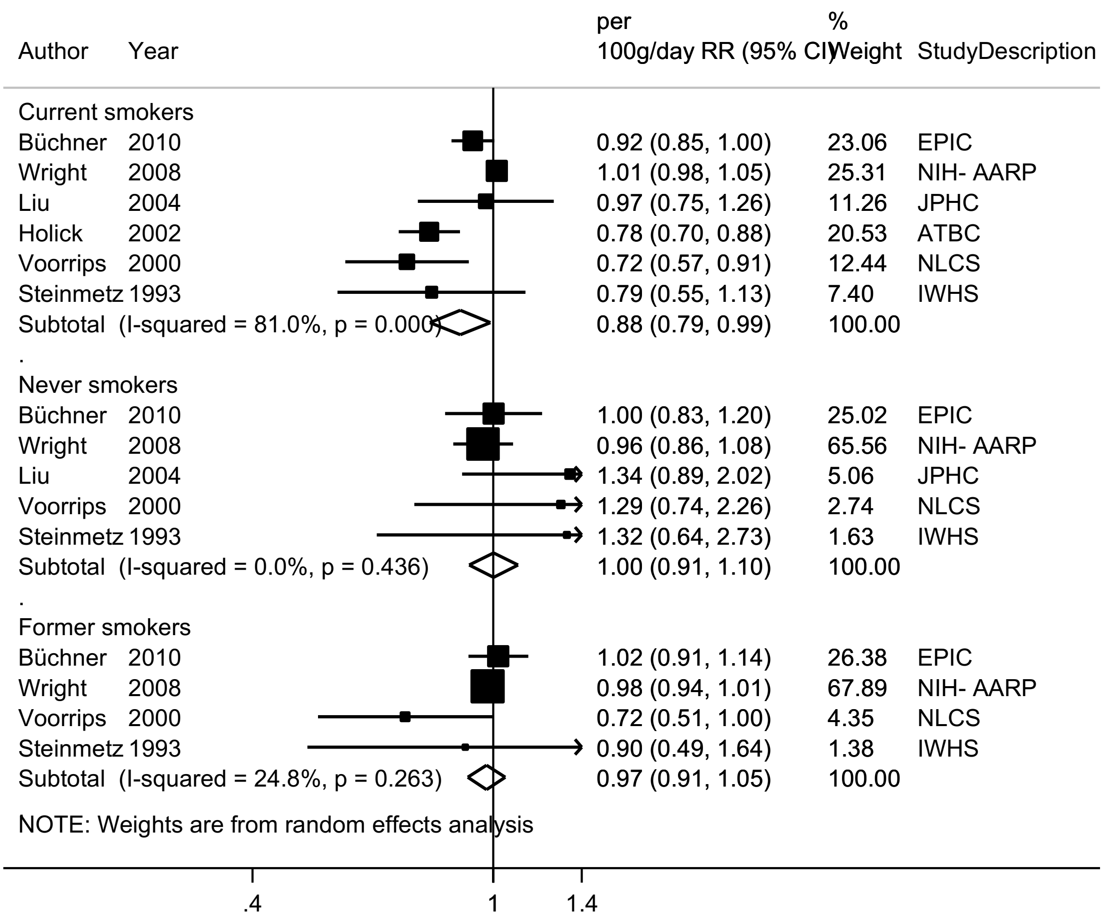


Figure 19 RR (95% CI) of lung cancer for 100g/day increase of vegetable intake by geographic location

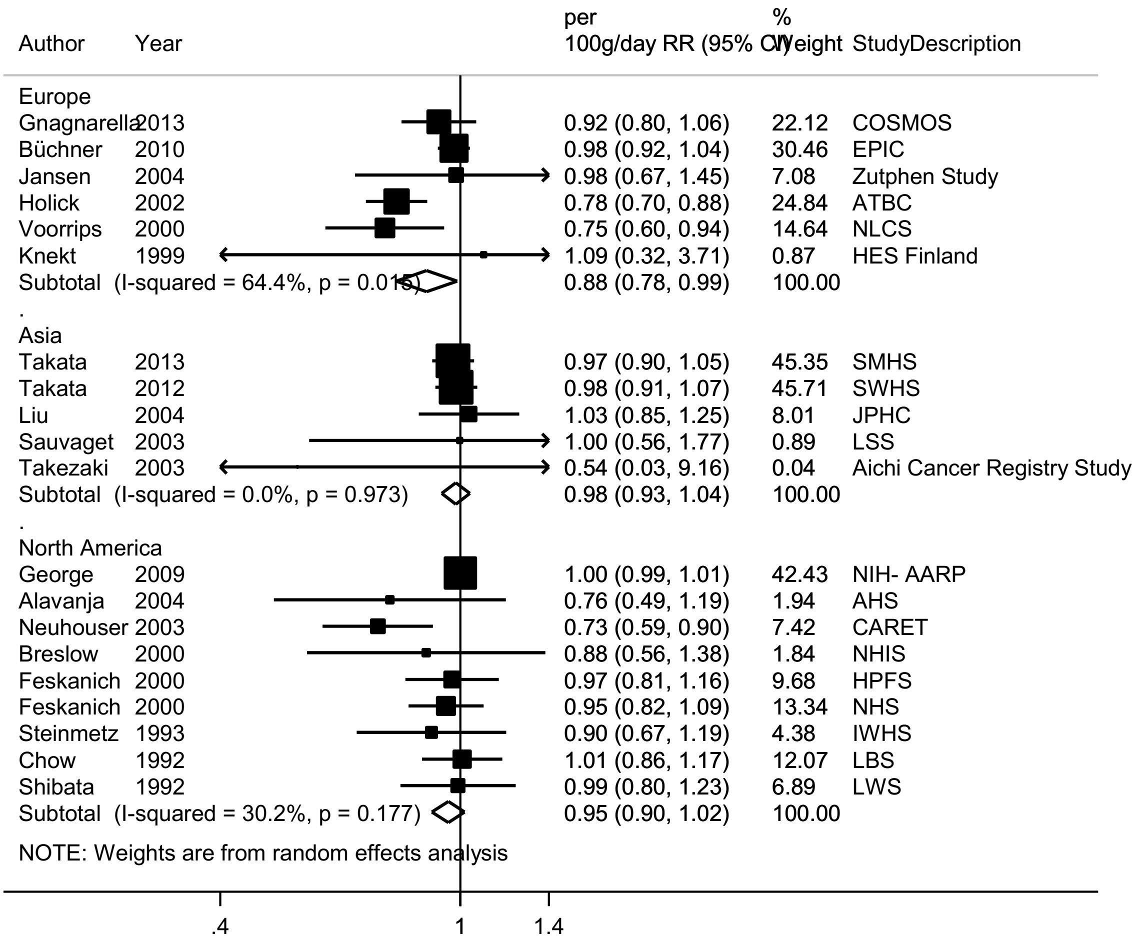
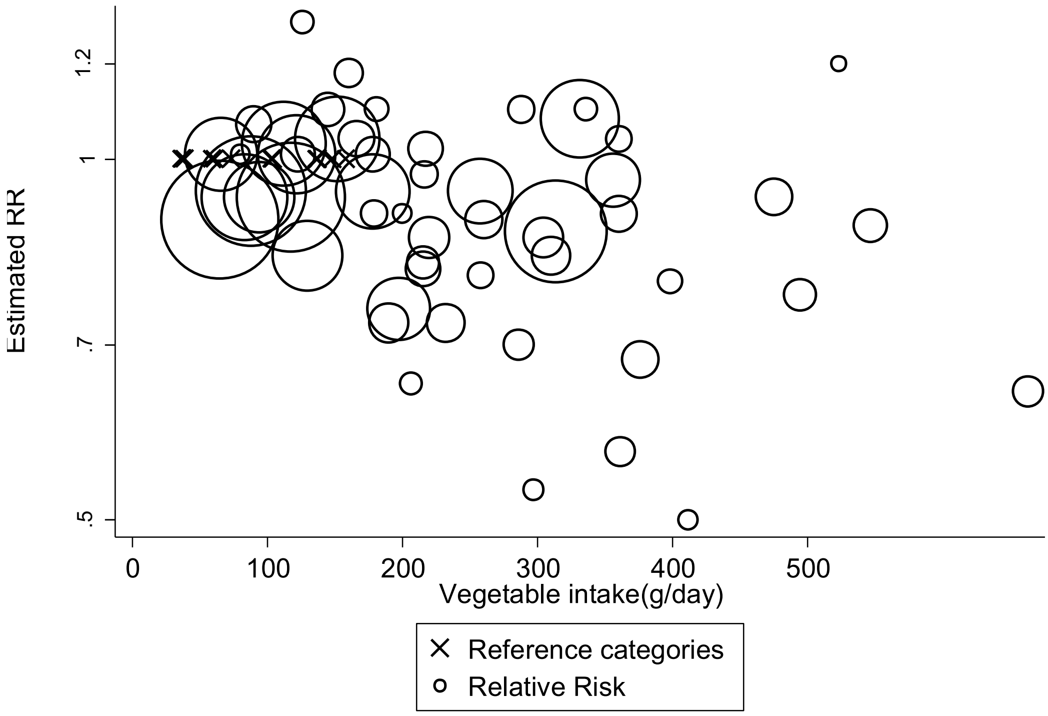
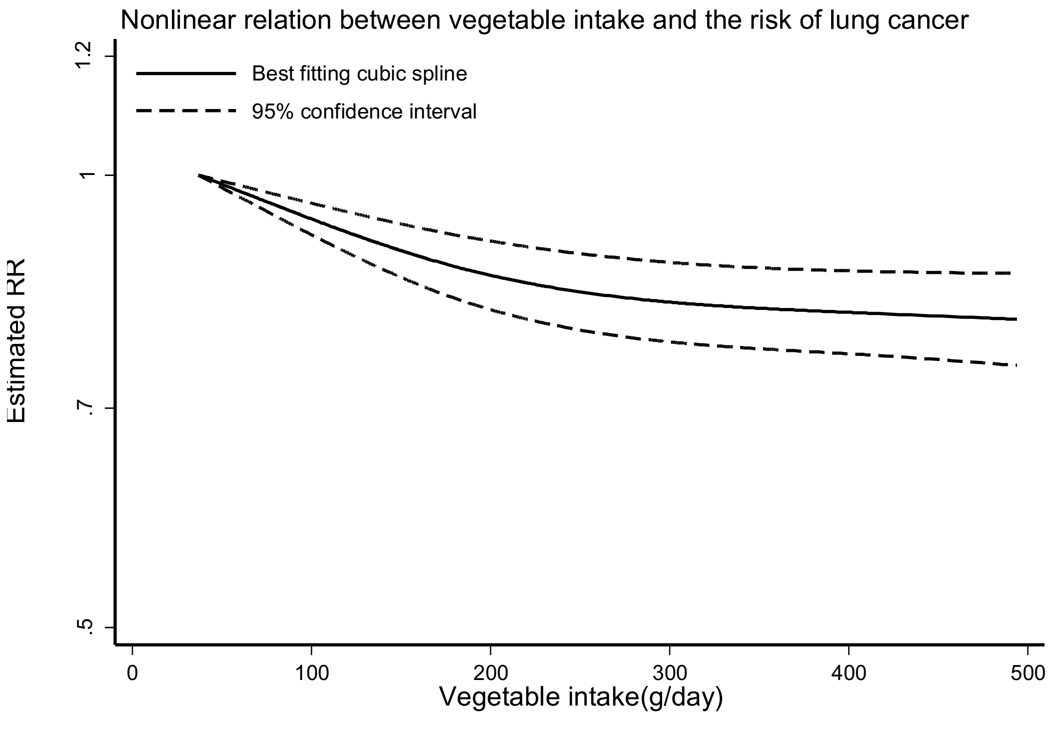


Figure 20 Relative risk of lung cancer and vegetable intake estimated using non-linear models





$p < 0.01$

Table 17 Table with vegetable intake values and corresponding RRs (95% CIs) for non-linear analysis of vegetable intake and lung cancer

Vegetable intake (g/day)	RR (95%CI)
37	1
100	0.93(0.91-0.95)
200	0.86(0.81-0.90)
300	0.82 (0.77-0.87)

2.2.1.2 Cruciferous vegetables

Cohort studies

Summary

Main results:
Eleven studies (11 467 cases) out of twelve studies (17 publications) were included in the dose-response meta-analysis. A significant inverse association was observed. The only study (Kvåle, 1983) excluded from the dose-response analyses reported non significant inverse association.
Moderate heterogeneity was observed that wasreduced after stratification by sex or geographic location.
It was not possible to conduct meta-analyses stratified by smoking status. Six studies reported associations according to smoking status with inconsistent results:
-one North-American study in women did not find association in never, former and current smokers (Steinmetz, 1993 in USA women); one study in European populations (Buchner, 2010) did not find association in the entire cohort (1830 cases) and in smokers (1167 cases)
- one study in USA men and women did not find association in never, former or current smokers among women, but in men there was a significant inverse association in former smokers and no significant association in never and current smokers (Wright, 2008)
- one study in North-American men and women find significant inverse association in former and current smokers and no association innever smokers (although low number of cases, Lam, 2010)
- one study (Wu, 2013) in never smokers Chinese women reported a significant inverse association
-onestudy in smokers and people exposed to asbestos (CARET, Neuhouser, 2003) reported no significant association.
There was significant evidence of publication or small study bias ($p < 0.01$). The asymmetry was driven by smaller studies showing inverse associations.

Sensitivity analysis:
The summary RRs ranged from 0.91 (95% CI=0.85-0.97) when Wright, 2008 was omitted to 0.95 (95% CI=0.92-0.99) when Lam, 2010 was omitted. The overall result remained the same (RR=0.91, 95%CI=0.85-0.97, 38.2%, p=0.10) when the EPIC study, in which only cabbageintake was investigated, was excluded.
There was evidence of a non-linear dose-response (p < 0.01). The risk decrease was observed for increasing intakes in the lower range of intake of the curve and the curve appears flat at higher intake levels.

Study quality:
Cancer outcome was confirmed using records in cancer registries or active follow-up with verification in medical records.
All studies used FFQ to assess intake. Two studies were in Chinese men and women, two studies in European populations and the remaining were North-American studies. The type of cruciferous vegetables differed across studies (see Table of study characteristics). In EPIC (Büchner, 2010) the analyses were only for "cabbages" and it was the only study that corrected for measurement error of diet. Similar results were observed with the calibrated intake. Repeated dietary measurements were used in the NHS and the HPFS (Feskanich, 2000). The range of intake was wider in the Asian studies compared to the other studies.
All studies included in the dose-response analysis were adjusted at least for age, sex, and smoking status.

Pooling project of cohort studies:
In the Pooling Project of Cohort study, intake of broccoli or cabbage was not related to lung cancer risk (five cohorts, Smith-Warner, 2003).

Table 18 Cruciferous vegetables intake and lung 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	11
Studies included in dose-response meta-analysis	11
Studies included in non-linear dose-response meta-analysis	9

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

Table 19 Cruciferous vegetables intake and lung cancer risk. Summary of the dose-response meta-analysis in the 2005 SLR and CUP.

	2005 SLR	CUP
Increment unit used	1 serving/day	50 g/day
All studies		
Studies (n)	2	11
Cases (total number)	543	11 467
RR (95%CI)	0.96(0.63-1.47)	0.92 (0.87-0.98)
Heterogeneity (I^2, p-value)	0%	33.3%, 0.13
P value Egger test		< 0.01

Stratified and sensitivity analysis (no analyses conducted in the 2005 SLR)			
Sex	**Men**	**Women**	
Studies (n)	4	4	
RR (95%CI)	0.95 (0.90-1.00)	0.94 (0.85-1.05)	
Heterogeneity (I^2, p-value)	0% , 0.97	57.1%, 0.07	
Geographic location	**Asia**	**Europe**	**North America**
Studies (n)	2	2	7
RR (95%CI)	0.94 (0.88- 1.00)	0.98 (0.85-1.12)	0.84 (0.72-0.98)
Heterogeneity (I^2, p-value)	0% , 0.83	0% , 0.46	56.7%, 0.03

Table 20 Cruciferous vegetables intake and lung cancer risk. Results of meta-analyses and pooled analyses of prospective studies published after the 2005 SLR.

Author, Year	Number of cohort studies	Total number of cases	Studies country, area	Outcome	Comparison	RR (95%CI)	P trend	Heterogeneity (I^2, p value)
Smith-Warner, 2003 CNBSS, HPFS, IWHS, NYSC, NHS Pooling Project of Cohort Studies	5	2172	USA, Europe	Lung cancer incidence and mortality	Broccoli ≥1 vs 0 serving/week	1.05(0.89-1.24)	0.33	0.68
	5	2848	USA, Europe		Cabbage ≥1 vs 0 serving/week	1.01 (0.88-1.17)	0.62	0.79

Table 21 Cruciferous vegetable intake and lung cancer risk. Main characteristics of studies 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	Missing data derived for analyses
Takata, 2013 LUN26860 China	Shanghai Men's Health Study, Prospective Cohort, Age: 40-74 years, M	359/ 61 092 5.50 years	Biennial home visits (diagnosis verified by medical chart review), record linkage to Cancer Registry and Vital Statistics Registry	Validated FFQ Include Chinese greens, cabbage, Napa cabbage, cauliflower, white turnip, garland chrysanthemum, shepherd's purse, watercress, and amaranth	Incidence, lung cancer	216.7 vs 48.1 g/day	0.80 (0.59-1.10) Ptrend:0.20	Age, smoking status, number of cigarettes/ day, years of smoking, education, family history of lung cancer, history of chronic bronchitis, BMI, intake of fruits, tea, total calorie,	Distribution of person-years by exposure category
Wu, 2013 LUN26862 China	SWHS, Prospective Cohort, Age: 40-70 years, W	417/ 72 695 11.1	Shanghai cancer registry & the shanghai vital statistics registry	FFQ Include Chinese greens, green cabbage, Chinese cabbage, cauliflower, white turnip, cauliflower	Incidence, lung cancer	>122.82 vs <58.58 g/d	0.73 (0.54-1.00) Ptrend:0.16	Age, smoking status, pack years, BMI, physical activity, education, family income, intake of other vegetables, total energy intake	Distribution of person-years by exposure category, mid-points of exposure categories
					Incidence, lung cancer, never smokers	>122.82 vs <58.58 g/d	0.59 (0.40-0.87) Ptrend:0.05		
Büchner, 2010 LUN20360b	EPIC, Prospective	1830/ 478 535	Cancer registries,	FFQ, dietary questionnaires,	Incidence, lung cancer	Per 100g/day	1.00 (0.96–1.05)	Age, sex, centre, smoking	Used in the dose response

Author, Year, WCRF Code, Country	Study 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,Norway, Spain,Sweden, U.K. Netherlands	Cohort, Age: 25-70 years, M/W	8.7 years	health insurance records, active follow up confirmed with pathology records, death registries	food records Included cabbages				status,duration, lifetime and baseline smoking intensity, time since quitting, education level, intake of fruits, alcohol, energy intake, height, weight, physical activity	analysis. Miller, 2004 used in highest versus lowest analysis
		574			Incidence, adeno-carcinoma		1.03 (0.94–1.12)		
		286			Incidence, small cell carcinoma		1.01 (0.87–1.14)		
		137			Incidence, large cell carcinoma		0.97 (0.79–1.20)		
		363			Incidence, squamous cell carcinoma		0.98 (0.89–1.09)		
		1167			Incidence, lung cancer, current smokers		1.00 (0.93–1.08)		
Lam, 2010 LUN20328 USA	CLUE II, Nested Case Control, Age: 18- years, M/W	274/ 22 631 15 years	Cancer registry and mortality registry	Validated FFQ Included broccoli, coleslaw, cabbage, sauerkraut, and mustard greens, turnip greens and collards	Incidence, lung cancer	0.6-0.68 vs 0.08 serving/1000 kcal/day	0.57 (0.38-0.85) Ptrend:0.01	Age, BMI, energy intake, total fruit and non-cruciferous vegetable intake, smoking status, number of cigarettes smoked	Distribution of person-years by exposure category, mid-points of exposure categories Exposure values using mean
		150			Incidence, lung cancer, men		0.72 (0.37-1.37) Ptrend:0.18		
		124			Incidence, lung cancer, women		0.52 (0.29-0.92) Ptrend:0.07		
		144			Incidence, lung		0.52 (0.29-0.95)		

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
					cancer, current smokers		Ptrend:0.02		energy intake
		110			Incidence, lung cancer, former smokers		0.49 (0.27-0.92) Ptrend:0.05		
		20			Incidence, lung cancer, never smokers		4.52 (0.40-50.82) Ptrend:0.28		
Wright, 2008 LUN20306 USA	NIH-AARP Diet and Health, Prospective Cohort, Age: 50-71 years, M/W, Retired	3834 472 081 8.0 years	Annual linkage to state cancer registries and national death index plus	Validated FFQ Included broccoli, cauliflower, Brussels sprouts, turnips,cabbage, coleslaw, collard greens, mustard greens, and kale	Incidence, lung cancer, men	0.5 vs 0.03 servings/1000 kcal/day	0.92 (0.83-1.02) Ptrend:0.09	Age, BMI, energy intake, family history of cancer, race, smoking status, alcohol intake, education, physical activity, smoking dose, time since quitting smoking, past smoking dose	Used in stratified analysis by smoking. Distribution of person-years by exposure category, mid-points of exposure categories. Exposure values using Exposure values using mean energy intake
		899			Incidence, lung cancer, men former smokers		0.85 (0.74-0.97) Ptrend:0.03		
		680			Incidence, lung cancer, men current smokers		0.99 (0.84-1.17) Ptrend:0.83		
		56			Incidence, lung cancer, men never smokers		1.10 (0.64-1.87) Ptrend:0.61		
		2201			Incidence, lung cancer, women	0.77 vs 0.06 servings/1000 kcal/day	1.00 (0.87-1.14) Ptrend:0.65		

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	Missing data derived for analyses
		535			Incidence, lung cancer, women Current smokers		1.01 (0.84-1.20) Ptrend:0.46		
		367			Incidence, lung cancer, women former smokers		1.13 (0.90-1.42) Ptrend:0.53		
		67			Incidence, lung cancer, women never smokers		0.66 (0.39-1.12) Ptrend:0.06		
Neuhouser, 2003 LUN00354 USA	CARET, Prospective Cohort, Age: 45-69 years, M/W	742 12 years	Lung cancer is primary endpoint of the trial. Active follow-up confirmed in medical and pathology records	FFQ Include broccoli, cauliflower or Brussels sprouts, coleslaw, cabbage, sauerkraut, and mustard greens, turnip greens, collards	Incidence, lung cancer, intervention group	≥3.5 vs ≤0.5 servings/week	0.91 (0.65-1.28)	Age, sex, smoking status, total pack-years of smoking, asbestos exposure, race/ethnicity, and enrollment center	Distribution of person-years and cases by exposure category Mid-points of exposure categories. Exposure values using standard portion size. RRs for intervention and placebo combined
					Incidence, lung cancer, control group	≥3.5 vs ≤0.5 servings/week	0.68 (0.45-1.04)		

Author, Year, WCRF Code, Country	Study 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
Feskanich, 2000 LUN00986 USA	Nurse's Health Study (NHS) + Health Professionals Follow-up Study (HPFS), Prospective Cohort, Age: 30-75 years, M/W	274/ 125 061 12.0 years	Verbal or written self-report, if possible confirmed by medical records, and death certificates	FFQ - study-specific Include broccoli, cabbage/cole-slaw/sauerkraut, cauliflower, Brussels sprouts, kale/mustard or chard greens	Incidence, lung cancer, women	>4.8 vs <1.3 servings/week	0.74 (0.55-0.99)	Age, follow-up cycle, smoking status, years since quitting -past smokers-, cigarettes /day -current smokers-, age start smoking, total energy intake, availability of diet data after baseline	Distribution of person-years by exposure category, mid-points of exposure categories. Exposure values using standard portion size
		269			Incidence, lung cancer, men	>5 vs <1.3 servings/week	1.11 (0.76-1.64)		
Voorrips, 2000b LUN01162 Netherlands	Netherlands Cohort Study on Diet and Cancer (NLCS), Case Cohort, Age: 55-69 years, M/W	910/ 120 852 3.20 years	Regional cancer registries and computerized national database of pathology report (PALGA)	FFQ - study-specific	Incidence, lung cancer	58 vs 10 g/day	0.80 (0.60-1.20)	Age, sex, educational level, family history of lung cancer, current smoker, years of smoking, cigarettes/day	
Steinmetz, 1993 LUN02740 USA	IWHS, Nested Case Control, Age: 55-69 years, Post menopausal women	138/ 41 837 4.0 years	Iowa Health Registry (part of SEER registry)	FFQ - study-specific Brassicas, including Brussels sprouts, cauliflower, cabbage (white,	Incidence, lung cancer	>3 vs >0 servings/week	0.72 (0.40-1.29)	Age, energy intake, pack-years of smoking	Distribution of person-years by exposure category, mid-points of exposure categories.
		81			Incidence, lung cancer, current smokers		0.95 (0.43-2.12)		
		38			Incidence, lung		0.37 (0.13-1.08)		

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
				green) , kale	cancer, former smokers				
		19			Incidence, lung cancer, never smokers		2.01 (0.36-11.20)		
		45			Incidence, adeno-carcinoma		0.46 (0.15-1.42)		
		37			Incidence, small cell carcinoma		1.52 (0.44-5.19)		
		25			Incidence, squamous cell carcinoma		1.05 (0.28-3.95)		
		12			Incidence, large cell carcinoma		0.09 (0.01-0.77)		
Chow, 1992 LUN02888 USA	LBS, Prospective Cohort, Age: 35- years, M	219/ 17 633 20.0 years	Death certificates	FFQ - study-specific Cruciferous vegetables	Mortality, lung cancer	>8 vs <2 times/month	0.80 (0.50-1.40)	Age, other, smoking status	Mid-points of exposure categories. Exposure values using standard portion size.

Table 22 Cruciferous vegetables intake and lung cancer risk. Main characteristics of studies excluded 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	Reasons for exclusion
Takata, 2012 LUN26859 China	SWHS, Prospective Cohort, Age: 40-70 years, W, never smokers	428/ 71 267 11.2	Shanghai cancer registry & the shanghai vital statistics registry	FFQ	Incidence, lung cancer	475 vs 136 g/d	0.93 (0.70-1.23) Ptrend:0.69	Age, BMI, income, occupation, total caloric intake, history of asthma, passive smoking	Superseded by Wu, 2013 LUN26862
Sakoda, 2011 LUN20351 USA	CARET, Nested Case Control, Age: 45-69 years, M/W	365/ 18 314	Lung cancer is primary endpoint of the trial. Active follow-up confirmed in medical and pathology records	FFQ	Incidence, lung cancer	>2-3 vs ≤1serving/week	ORGA 1.23 (0.88–1.72) ORAA 1.36 (0.84–2.20)	Age, sex, enrolment year, smoking status, occupational asbestos exposure	Only has gene interactions results, Neuhouser, 2003 LUN00354 was used
Fowke, 2011 LUN20324 China	SWHS, Nested Case Control, Age: 40-70 years, W, Non smokers	209/ 65 754	Cancer registry and death certificates and medical records	Validated FFQ	Incidence, lung cancer	Quartile 4 vs quartile 1	0.94 (0.58-1.53)	age, asthma, fat intake, gstm1, gstt1, number of births, soy intake, alcohol intake, education	Superseded by Wu, 2013 LUN26862
Miller, 2004 LUN00169	EPIC, Prospective	860/ 519 978	Cancer and Death registries,	FFQ - study-specific	Incidence, lung cancer	Quintile 5 vs quintile 1	1.21 (0.92-1.60)	Age, sex, anthropometry,	Used only in highest versus

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Reasons for exclusion
Europe	Cohort, Age: 25-70 years, M/W	10 years	Health insurance records, active follow, cases confirmed by pathology records or death certificate					smoking habits	lowest analysis. Büchner, 2010b LUN20360 used in dose-response analysis
Miller, 2002 LUN00442 Europe	EPIC, Prospective Cohort, Age: 25-70 years, M/W	482 924 4 years	Cancer and Death registries, Health insurance records, active follow, cases confirmed by pathology records or death certificate	FFQ - study-specific	Incidence, lung cancer	Quartile 4 vs quartile 1 g/day	0.96 (0.72-1.28)	Age, sex, anthropometry,, smoking habits	Superseded by Büchner, 2010b LUN20360
Speizer, 1999 LUN01255 USA	NHS, Prospective Cohort, Age: 30-55 years, W	399/ 118 351 12 years	Active follow-up, cases confirmed with medical and pathology records	FFQ - study-specific	Incidence, lung cancer	>5 vs 0 times/week	0.20	Age, smoking habits	Superseded by Feskanich, 2000 LUN00986
Kvåle, 1983 LUN04322	Norway, 1967-1978,	68/ 16 713	Cancer Registry of Norway and	Dietary history questionnaire	Incidence, lung cancer	Highest indices vs lowest	0.79	Age, area of residence,	No confidence interval

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Reasons for exclusion
Norway	Prospective Cohort, M/W	11.5 years	death registry			indices times/month		smoking habits, urban/rural status	

Figure 21 RR estimates of lung cancer by levels of cruciferous vegetables intake

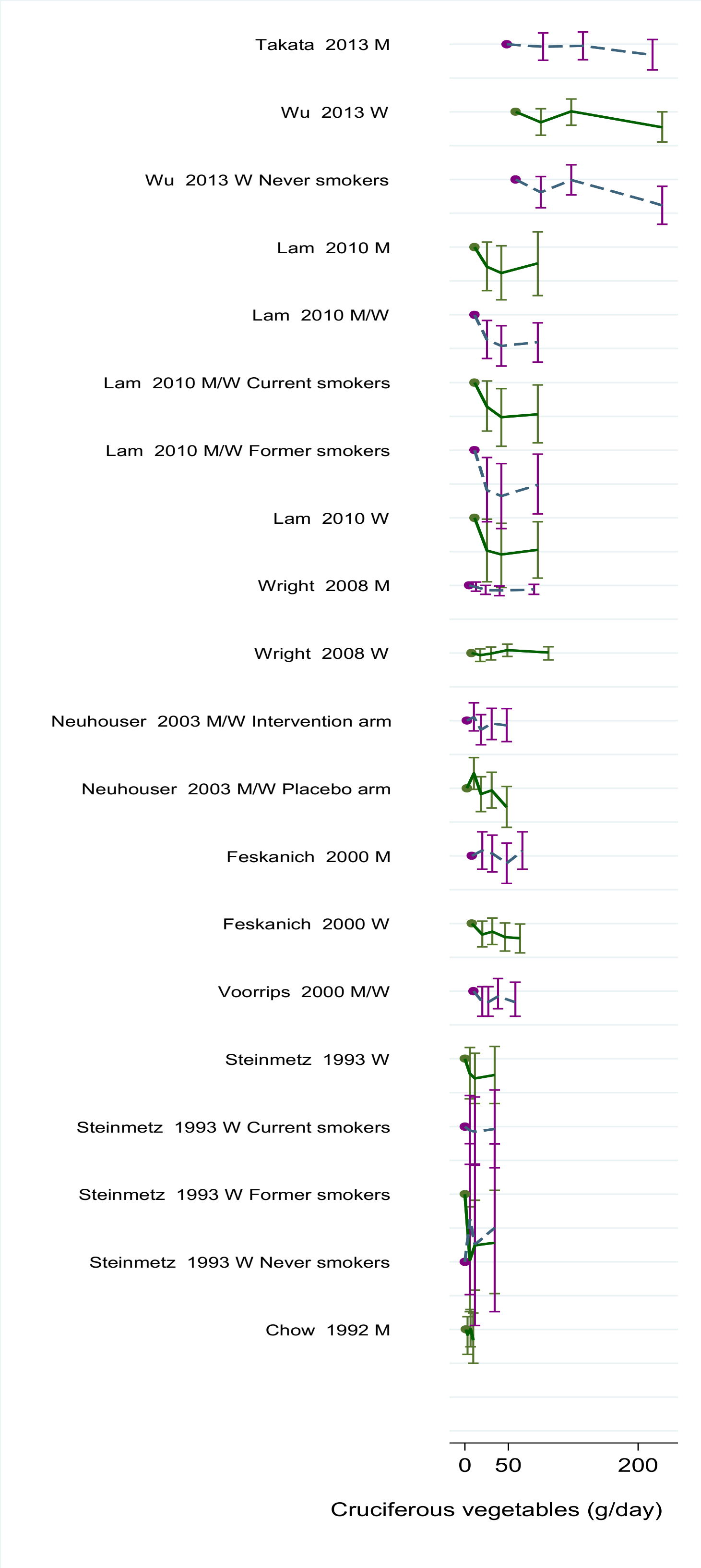
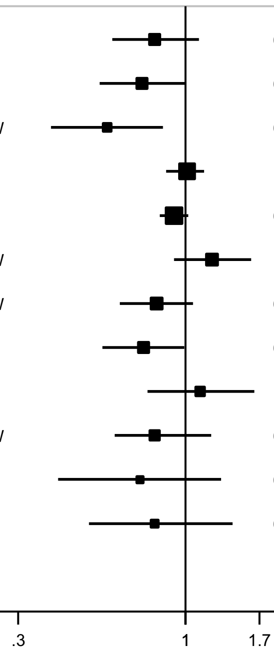


Figure 22 RR (95% CI) of lung cancer for the highest compared with the lowest level of cruciferous vegetables intake



Author	Year	Sex	high vs low cruciferous vegetable intake RR (95% CI)	Study Description	Comparison
Takata	2013	M	0.80 (0.59, 1.10)	SMHS	216.7 vs 48.1 g/day
Wu	2013	W	0.73 (0.54, 1.00)	SWHS	>122.82 vs <58.58 g/d
Lam	2010	M/W	0.57 (0.38, 0.85)	CLUE II	0.6-0.68 vs 0.08 serving/1000 kcal/day
Wright	2008	W	1.01 (0.87, 1.14)	NIH-AARP	0.77 vs 0.06 servings/1000 kcal/day
Wright	2008	M	0.92 (0.83, 1.02)	NIH-AARP	0.5 vs 0.03 servings/1000 kcal/day
Miller	2004	M/W	1.21 (0.92, 1.60)	EPIC	Q5 vs Q1
Neuhouser	2003	M/W	0.81 (0.62, 1.05)	CARET	≥3.5 vs ≤0.5 servings/week
Feskanich	2000	W	0.74 (0.55, 0.99)	NHS	>4.8 vs <1.3 servings/week
Feskanich	2000	M	1.11 (0.76, 1.64)	HPFS	>5 vs <1.3 servings/week
Voorrips	2000	M/W	0.80 (0.60, 1.20)	NLCS	58 vs 10 g/day
Steinmetz	1993	W	0.72 (0.40, 1.29)	IWHS	>3 vs >0 servings/week
Chow	1992	M	0.80 (0.50, 1.40)	LBS	>8 vs <2 times/month

Figure 23 RR (95% CI) of lung cancer for 50 g/day increase of cruciferous vegetable intake

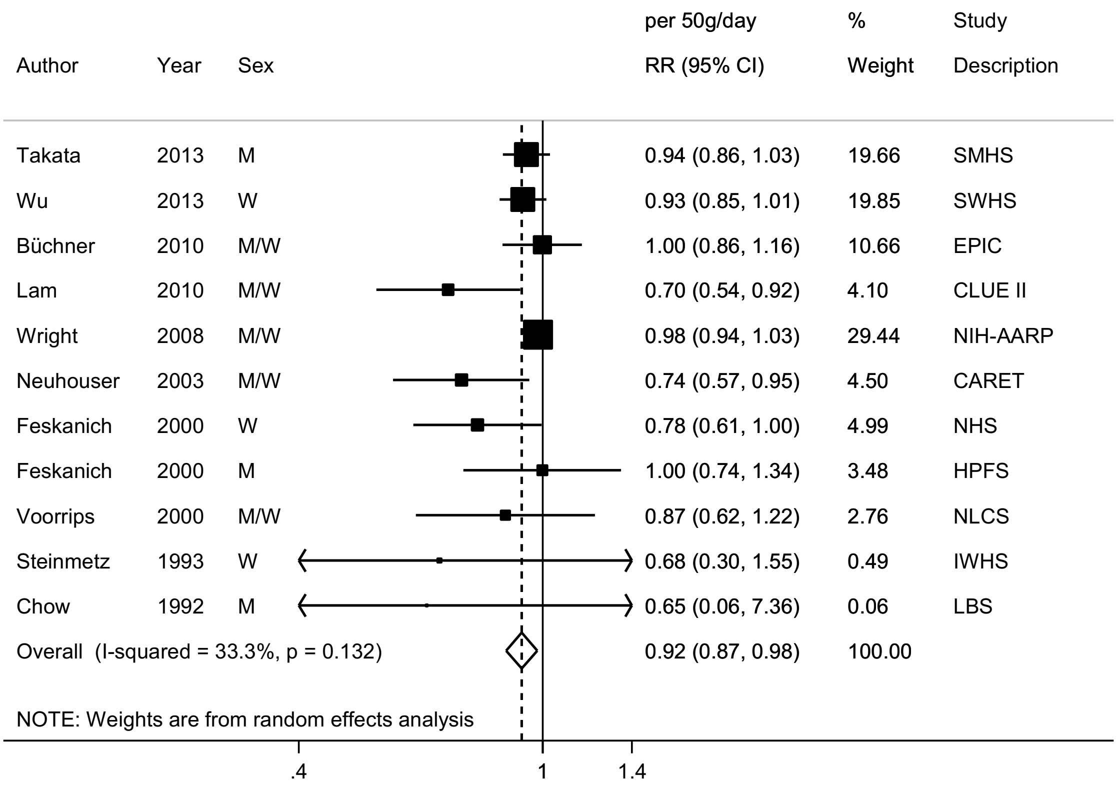
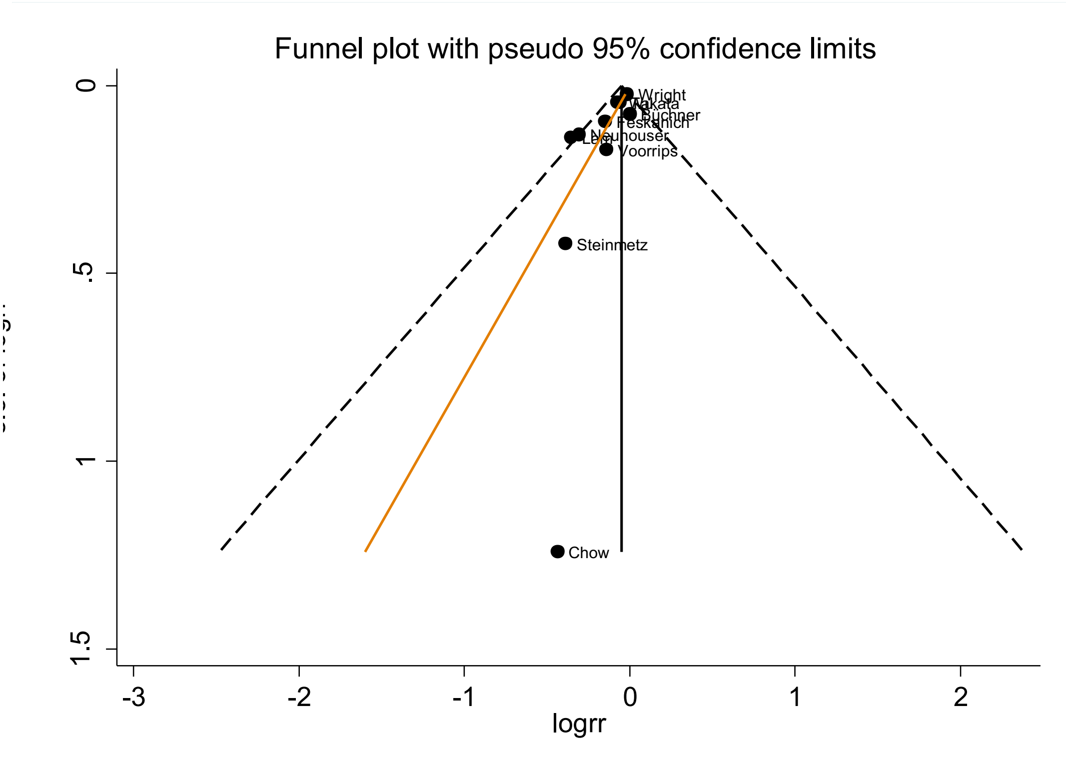


Figure 24 Funnel plot of studies included in the dose response meta-analysis of cruciferous vegetables intake and lung cancer



Egger's test p < 0.01

Figure 25 RR (95% CI) of lung cancer for 50g/day increase of cruciferous vegetable intake by sex

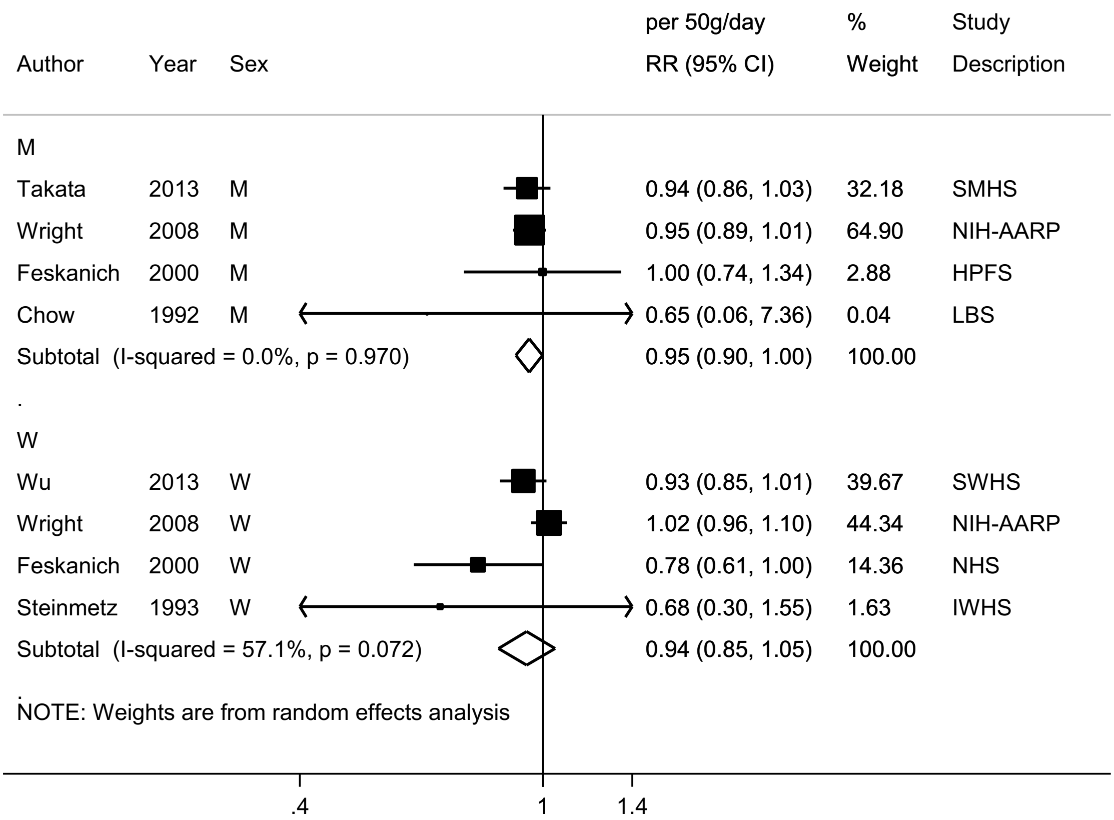


Figure 26 RR (95% CI) of lung cancer for 50g/day increase of cruciferous vegetable intake by geographic location

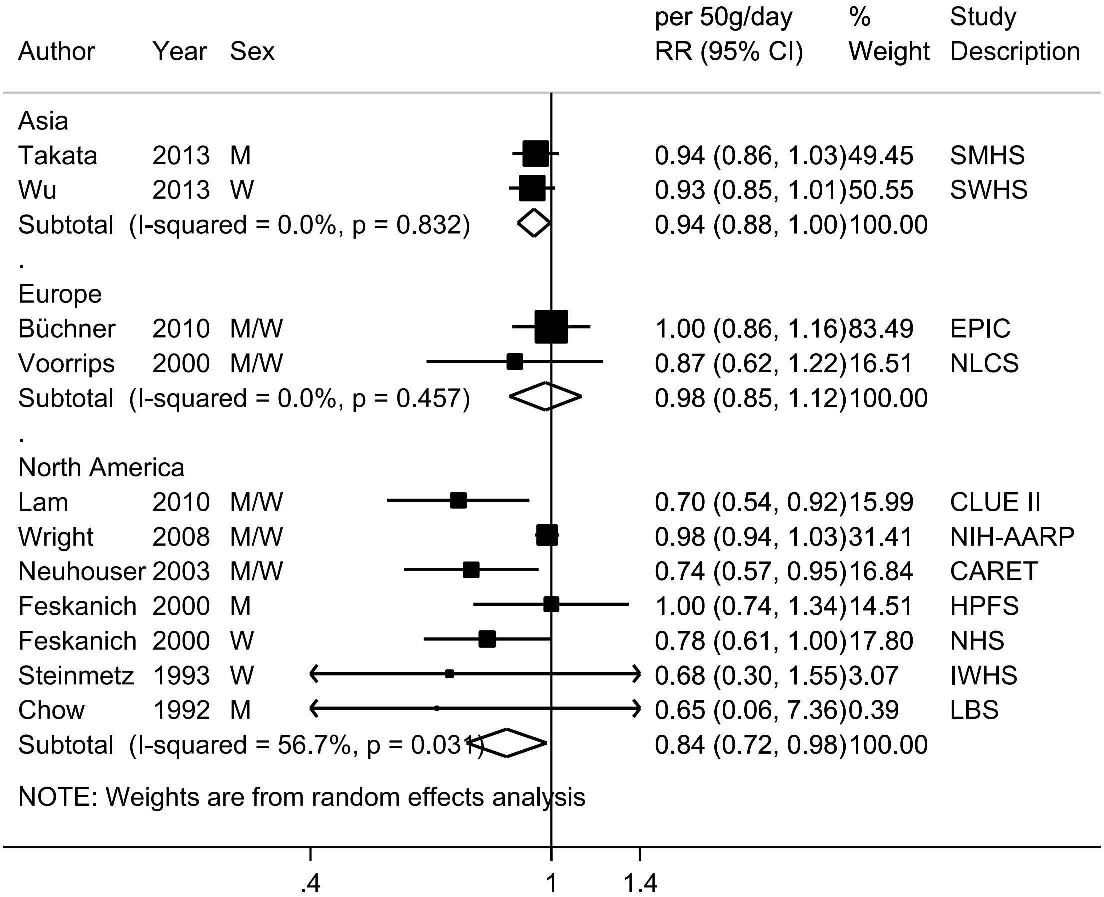
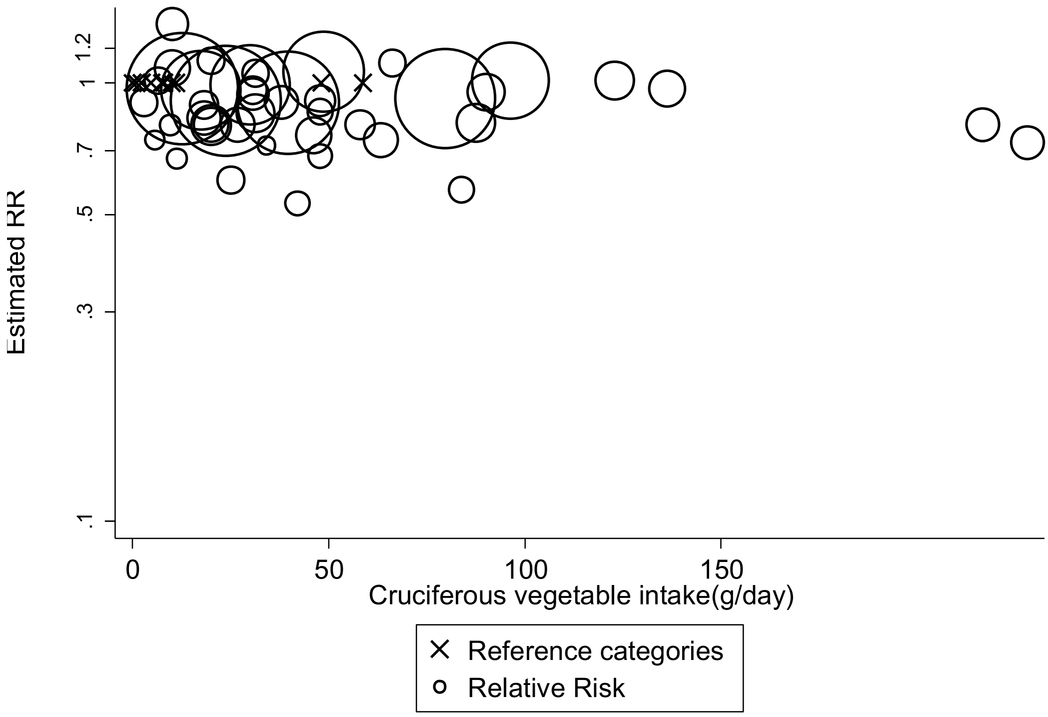
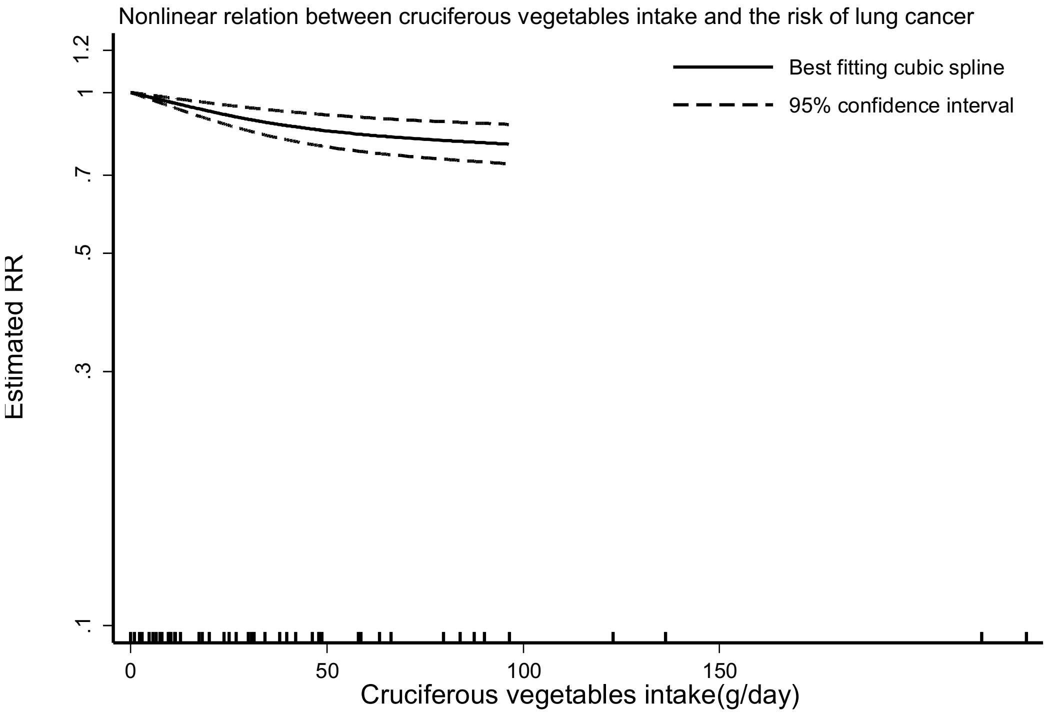


Figure 27 Relative risk of lung cancer and cruciferous vegetables intake estimated using non-linear models





$p < 0.01$

Table 23 Table with cruciferous vegetables intake values and corresponding RRs (95% CIs) for non-linear analysis of cruciferous vegetables intake and lung cancer

Cruciferous vegetables intake (g/day)	RR (95%CI)
0	1
50	0.88(0.82-0.93)
100	0.81(0.74-0.88)
150	0.75(0.68-0.83)

2.2.1.4 Green leafy vegetables

Cohort studies

Summary

Main results:
Eight studies (5732 cases) out of 10 studies (12 publications) were included in the dose-response meta-analysis. An inverse association of borderline statistical significance was observed. In meta-analysis stratified by smoking status (3 studies), an inverse association was observed only in former smokers, non-significant inverse associations were s observed in current smokers and in never smokers.
One study was excluded from the dose-response analyses; it reported non-significant association.
Moderate heterogeneity was observed that was more important within North-American studies (see Table of summary results of meta-analysis).
There was no evidence of publication or small study bias (p=0.22).

Sensitivity analysis:
The summary RRs ranged from 0.83 (95% CI=0.71-0.99) when Büchner, 2010b was omitted to 0.94 (95% CI=0.88-1.00) when Steinmetz, 1993 was omitted in influence analysis.
There was evidence of non-linear dose-response relationship ($p < 0.01$). This was mainly driven by one study (IWHS, Steinmtez, 1993-see bubble plot).

Study quality:
Cancer outcome was confirmed using records in cancer registries in most studies.
All studies used FFQ to assess leafy vegetable intake. Büchner, 2010b was the only study that corrected for measurement error of diet. Similar results were observed with the observed and

calibrated intake. Repeated dietary measurements were used in the NHS and the HPFS (Feskanich, 2000).

All studies included in the dose-response analysis were adjusted at least for age, sex, and smoking status. All except one study adjusted for smoking intensity and duration.

Table 24 Green leafy vegetables intake and lung cancer risk. Number of studies in the CUP SLR

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

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

Table 25 Green leafy vegetables intake and lung cancer risk. Summary of the dose-response meta-analysis in the 2005 SLR and CUP.

	2005 SLR	**CUP**
Increment unit used	1 serving/day	50 g/day
	All studies	
Studies (n)	3	8
Cases (total number)	931	5732
RR (95%CI)	0.91(0.89-0.93)	0.89 (0.79-1.00)
Heterogeneity (I^2, p-value)	0%	49.8%, 0.05
P value Egger test		0.23

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

Stratified and sensitivity analysis (no analyses conducted in the 2005 SLR)			
Smoking status	**Never smokers**	**Current smokers**	**Former smokers**
Studies (n)	4	4	3
RR (95%CI)	0.96(0.76-1.22)	0.83 (0.66-1.06)	0.63(0.41-0.95)
Heterogeneity (I^2, p-value)	0%, 0.94	43.7%, 0.15	28.4%, 0.25
Sex	**Men**	**Women**	
Studies (n)	3	4	
RR (95%CI)	0.89 (0.81-0.99)	0.83 (0.54-1.28)	
Heterogeneity (I^2, p-value)	1.4% , 0.36	74.5%, <0.01	
Geographic location	**Asia**	**Europe**	**North America**
Studies (n)	3	2	3
RR (95%CI)	0.90 (0.82- 0.99)	0.97 (0.89-1.06)	0.76 (0.48-1.22)
Heterogeneity (I^2, p-value)	0% , 0.76	0% , 0.52	80.3%, <0.01

Table 26 Green leafy vegetables intake and lung cancer risk. Main characteristics of studies 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	Missing data derived for analyses
Takata, 2013 LUN26860 China	Shanghai Men's Health Study, Prospective Cohort, Age: 40-74 years, M	359/ 61 092 5.50 years	Biennial home visits (diagnosis verified by medical chart review), record linkage to Cancer Registry and Vital Statistics Registry	Validated FFQ	Incidence, lung cancer	216.7 vs 48.1 g/day	0.72 (0.53-0.98) Ptrend:0.08	Age, BMI, fruit intake, tea consumption, total caloric intake, current smoking status, education, family history of lung cancer, history of chronic bronchitis, number of cigarettes smoked per day, years of smoking	Distribution of person-years by exposure category
Takata, 2012 LUN26859 China	SWHS, Prospective Cohort, Age: 40-70 years, W, never smokers	428/ 71 267 11.2	Shanghai cancer registry & the shanghai vital statistics registry	FFQ	Incidence, lung cancer	23 vs 2 g/d	1.00 (0.76-1.31) Ptrend:0.85	Age, BMI, income, occupation, total caloric intake, history of asthma, passive smoking	

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Missing data derived for analyses
Büchner, 2010b LUN20360 Denmark,France ,Germany,Greec e,Italy,Netherlan ds,Norway,Spai n,Sweden,U.K.	EPIC, Prospective Cohort, Age: 25-70 years, M/W	1830/ 478 535 8.7 years	Cancer registries, health insurance records, active follow up confirmed with pathology records, death registries	FFQ, dietary questionnaires, food record	Incidence, lung cancer	Per 100g/day	1.00 (0.96–1.05)	Fruit consumption, age, alcohol consumption, centre, duration of smoking, education level, energy intake, height, physical activity, smoking status, weight, gender, lifetime and baseline intensity of smoking, time since quitting smoking	Used only in the dose response analysis. Linseisen, 2007 used in highest versus lowest analysis
Linseisen, 2007 LUN20323 France, Italy, Spain, UK, Netherlands, Greece, Germany, Sweden, Denmark,	EPIC, Prospective Cohort, Age: 25-70 years, M/W	1136/ 478 590 6.4 years	Cancer registries, health insurance records, pathology rec, active follow up, death certificate	FFQ, dietary questionnaires, food record	Incidence, lung cancer	47.4 vs 7.3 g/day	0.83 (0.60-1.15)	Education level, energy intake from fat and nonfat sources, height, smoking status, weight, work - physical activity, ethanol intake,	Distribution of person-years by exposure category
		731			Incidence, lung cancer, current smokers	47.4 vs 7.3 g/day	0.80 (0.52-1.24)		
		291			Incidence, lung cancer , former smokers	47.4 vs 7.3 g/day	0.68 (0.35-1.30)		

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
Norway		98			Incidence, lung cancer, never smokers	47.4 vs 7.3 g/day	1.05 (0.38-2.93)	processed and red meat, smoking duration	
Ozasa, 2001 LUN00725 Japan	JACC study, Prospective Cohort, Age: 40-70 years, M/W	388/ 98 248 7.7 years	Population death registries	FFQ - study-specific	Mortality, lung cancer	Almost every day vs 1-2 times/w	0.76 (0.59-0.98)	Age, family history of cancer, smoking status, cigarettes/day and smoking duration	Exposure values using standard portion size
		386			Mortality, lung cancer, men		0.78 (0.60-1.00)		
		263			Mortality, lung cancer, current smokers		0.80 (0.59-1.09)		
		108			Mortality, lung cancer, women		1.19 (0.75-1.90)		
					Mortality, lung cancer, former smokers		0.65 (0.39-1.07)		
Feskanich, 2000 LUN00986 USA	Nurses' Health Study (NHS) + Health Professionals Follow-up Study (HPFS), Prospective Cohort, Age: 30-75	274/ 125 061 12.0 years	Verbal or written self-report, if possible confirmed by medical records, and death certificates	FFQ - study-specific	Incidence, lung cancer, women	>3.5 vs <0.49 servings/week	0.90 (0.68-1.20)	Age, follow-up cycle, smoking status, years since quitting - past smokers-, cigarettes /day - current smokers-, age start smoking, total	Distribution of person-years by exposure category, mid-points of exposure categories. Exposure values using standard
		269			Incidence, lung cancer, men	>3.5 vs <0.49 servings/week	0.99 (0.65-1.49)		

Author, Year, WCRF Code, Country	**Study name, characteristics**	**Cases/ Study size Follow-up (years)**	**Case ascertainment**	**Exposure assessment**	**Outcome**	**Comparison**	**RR (95%CI) Ptrend**	**Adjustment factors**	**Missing data derived for analyses**
	years, M/W							energy intake, availability of diet data after baseline	portion size.
Voorrips, 2000b LUN01162 Netherlands	Netherlands Cohort Study on Diet and Cancer (NLCS), Case Cohort, Age: 55-69 years, M/W	910/ 120 852 3.20 years	Regional cancer registries and computerized national database of pathology report (PALGA)	FFQ - study-specific	Incidence, lung cancer	41vs 4 g/day	0.80 (0.60-1.10)	Age, sex, educational level, family history of lung cancer, current smoker, years of smoking, cigarettes/day	
Steinmetz, 1993 LUN02740 USA	IWHS, Nested Case Control, Age: 55-69 years, W, Post menopausal	138/ 41 837 4.0 years	Iowa Health Registry (part of SEER registry)	FFQ - study-specific	Incidence, lung cancer	>6 vs 0-1 servings/week	0.45 (0.26-0.79)	Age, energy intake, pack-years of smoking	Distribution of person-years by exposure category, mid-points of exposure categories.
		81			Incidence, lung cancer, current smokers		0.54 (0.27-1.10)		
		38			Incidence, lung cancer, former smokers		0.25 (0.08-0.78)		
		19			Incidence, lung cancer, non-smokers		0.84 (0.25-2.76)		
		45			Incidence, adenocarcinoma		0.69 (0.30-1.57)		

Author, Year, WCRF Code, Country	Study 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
		37			Incidence, small cell		0.26 (0.08-0.87)		
		25			Incidence, squamous cell		0.43 (0.14-1.39)		
		12			Incidence, large cell		0.08 (0.01-0.73)		

Table 27 Green leafy vegetables intake and lung cancer risk. Main characteristics of studies excluded 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	Reasons for exclusion
Khan, 2004 LUN00068 Japan	Japan, Hokkaido Cohort Study, Prospective Cohort, Age: 40- years, M/W	3 158 14.8 years	Annual follow-up survey, cause of death classified by researchers	Dietary history questionnaire	Mortality, lung cancer, men	Several times/week vs never or several times/year	1.10 (0.60-2.20)	Age, smoking status	Used only in highest versus, only two categories
Miller, 2004 LUN00169 Europe	EPIC, Prospective Cohort, Age: 25-70 years, M/W	860/ 519 978 10 years	Cancer and Death registries, Health insurance records, active follow, cases confirmed by pathology records or death certificate	FFQ - study-specific	Incidence, lung cancer	Quintile 5 vs Quintile 1	1.21 (0.92-1.60)	Age, anthropometry, body weight, smoking status, cigarettes/day, years of smoking	Superseded by Büchner, 2010b LUN20360
Speizer, 1999 LUN01255 USA	NHS, Prospective Cohort, Age: 30-55 years, W	399/ 118 351 12 years	Active follow-up, cases confirmed with medical and pathology records	FFQ - study-specific	Incidence, lung cancer	>5 vs 0 times/week	1.10	Age, smoking habits	Superseded by Feskanich, 2000 LUN00986
Kvåle, 1983	Norway, 1967-	68/	Cancer registry	Dietary history	Incidence, lung	Highest indices	0.96	Age, area of	No measure of

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Reasons for exclusion
LUN04322 Norway	1978, Prospective Cohort, M/W	16 713 11.5 years		questionnaire	cancer	vs lowest indices times/month		residence, smoking habits, urban/rural status	association

Figure 28 RR estimates of lung cancer by levels of green leafy vegetables intake

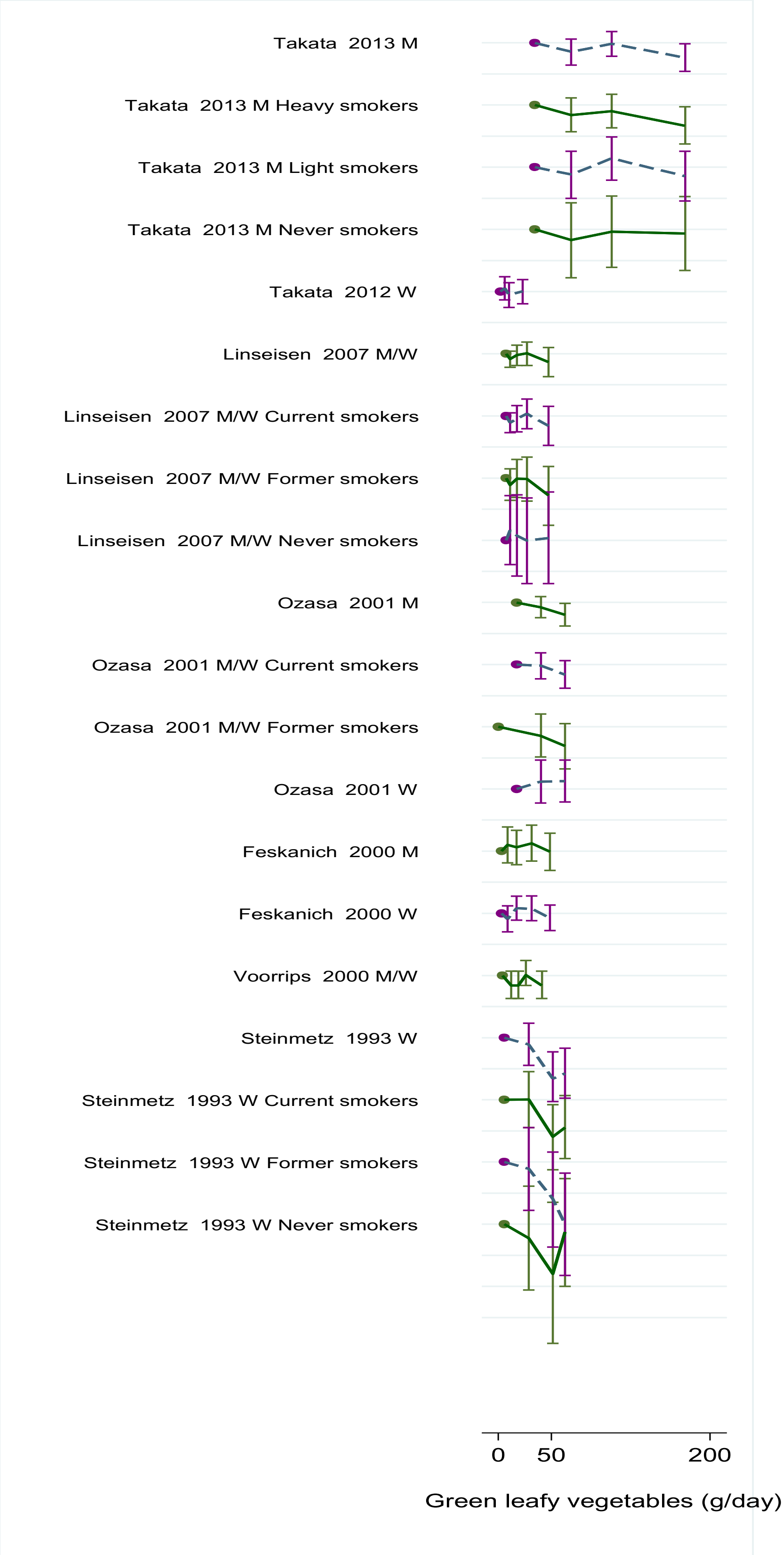


Figure 29 RR (95% CI) of lung cancer for the highest compared with the lowest level of green leafy vegetables intake

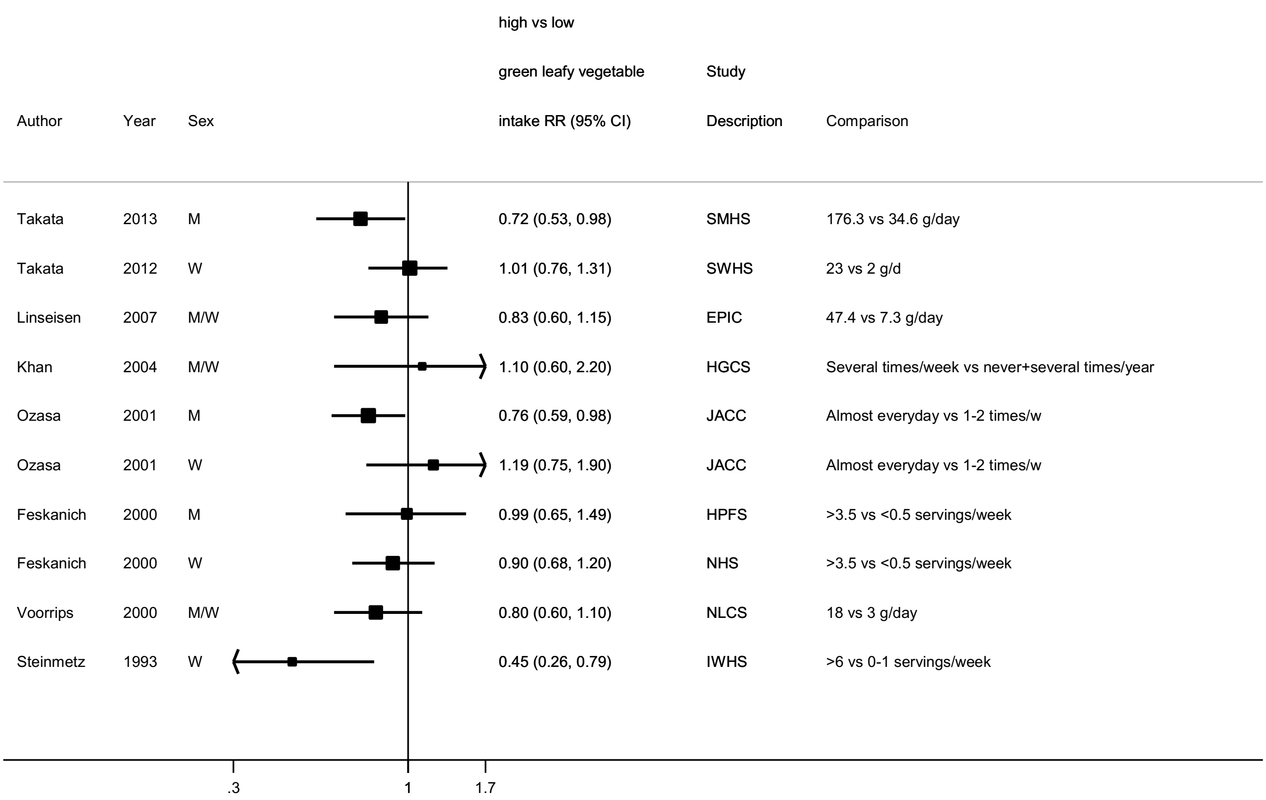


Figure 30 RR (95% CI) of lung cancer for 50 g/day increase of green leafy vegetables intake

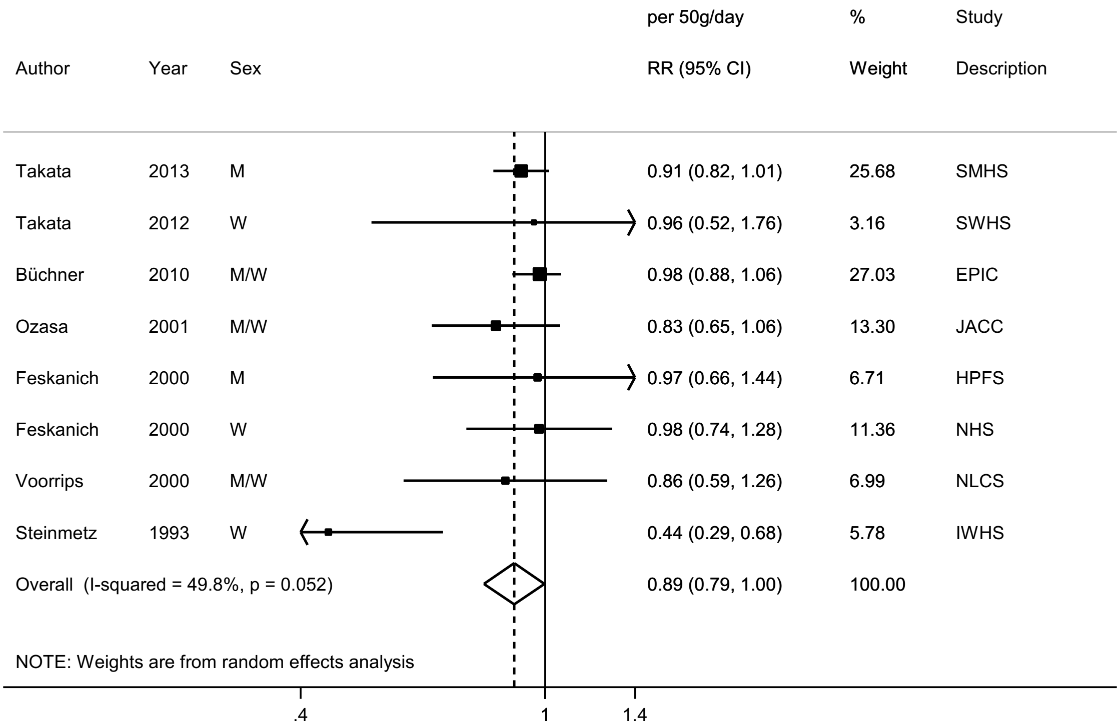
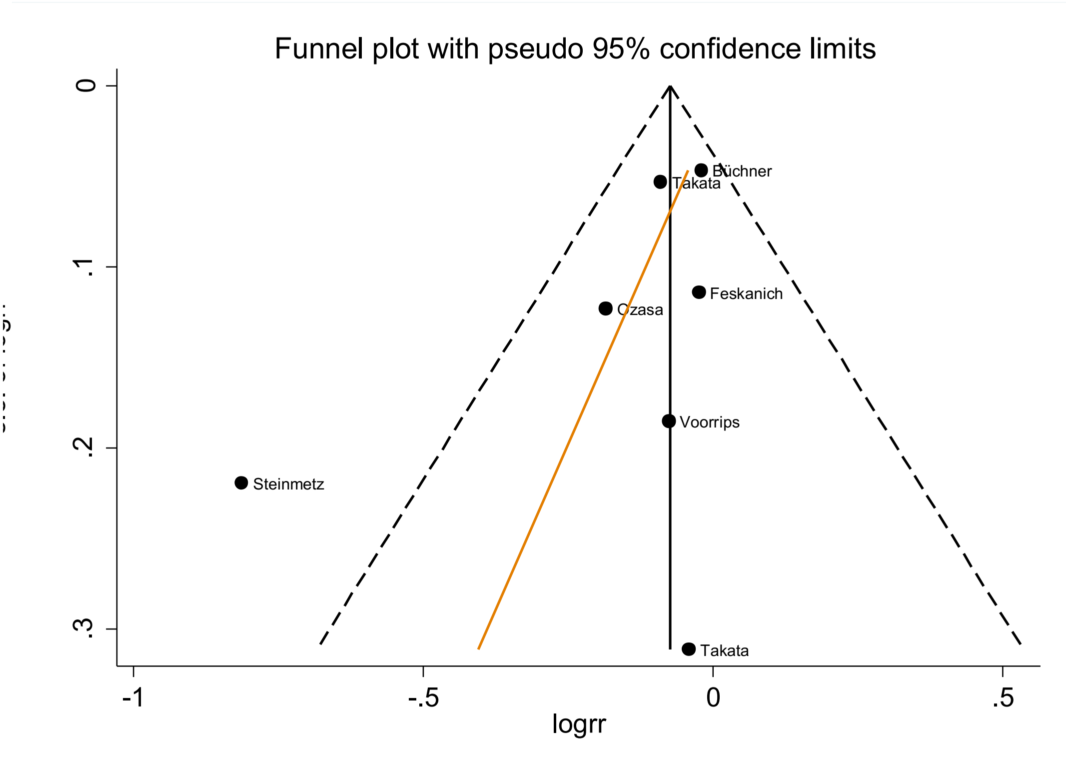


Figure 31 Funnel plot of studies included in the dose response meta-analysis of green leafy vegetables intake and lung cancer



Egger’s test p=0.23

Figure 32 RR (95% CI) of lung cancer for 50g/day increase of green leafy vegetables intake by sex

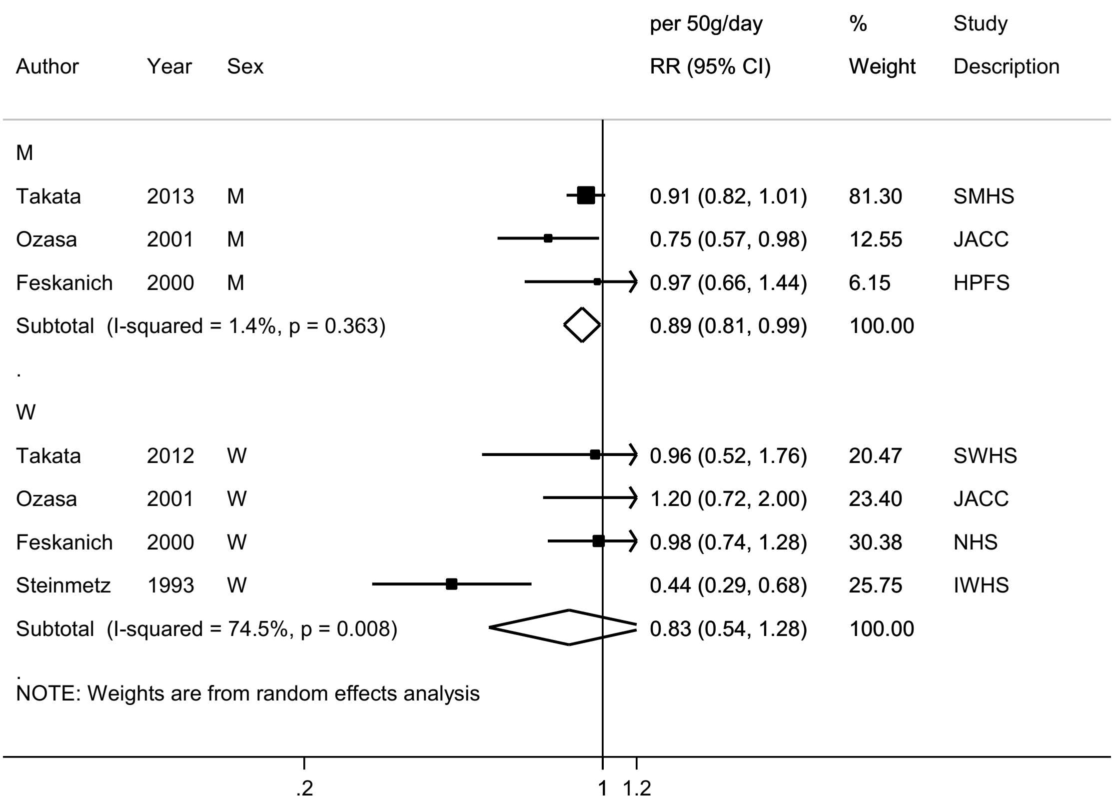


Figure 33 RR (95% CI) of lung cancer for 50g/day increase of green leafy vegetables intake by smoking status

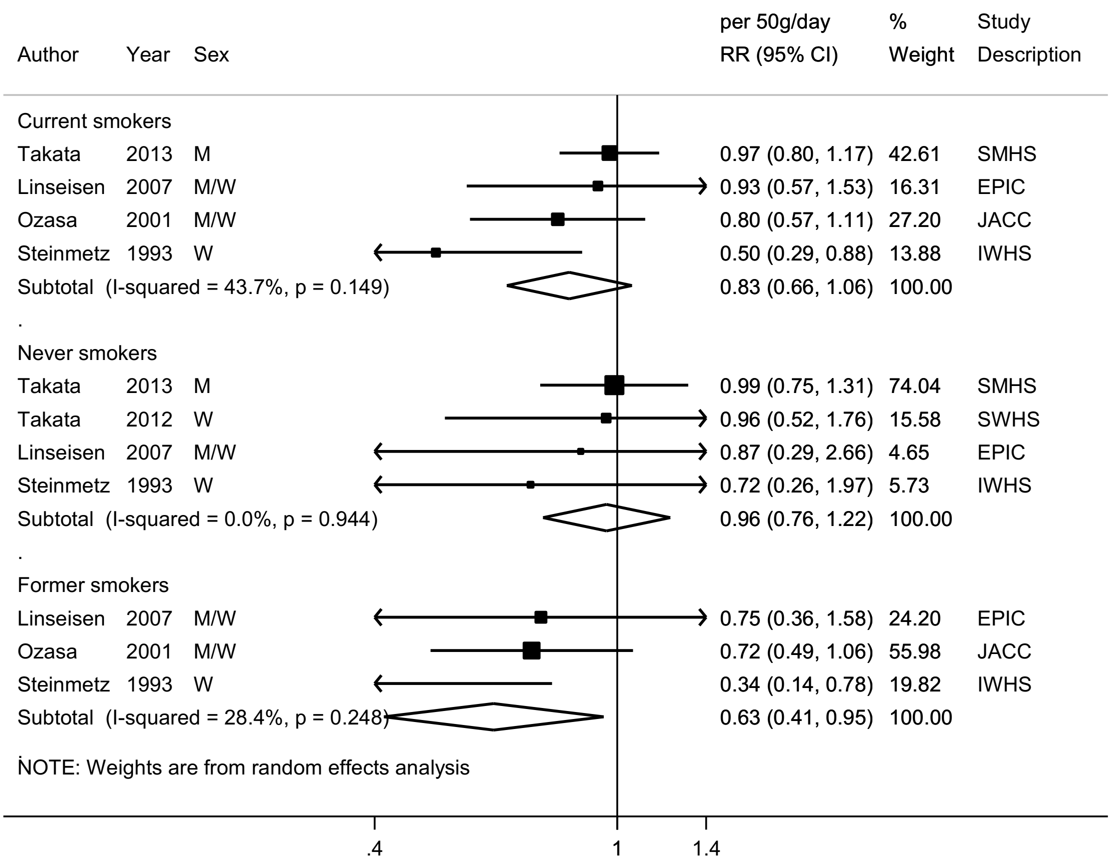


Figure 34 RR (95% CI) of lung cancer for 50g/day increase of green leafy vegetables intake by geographic location

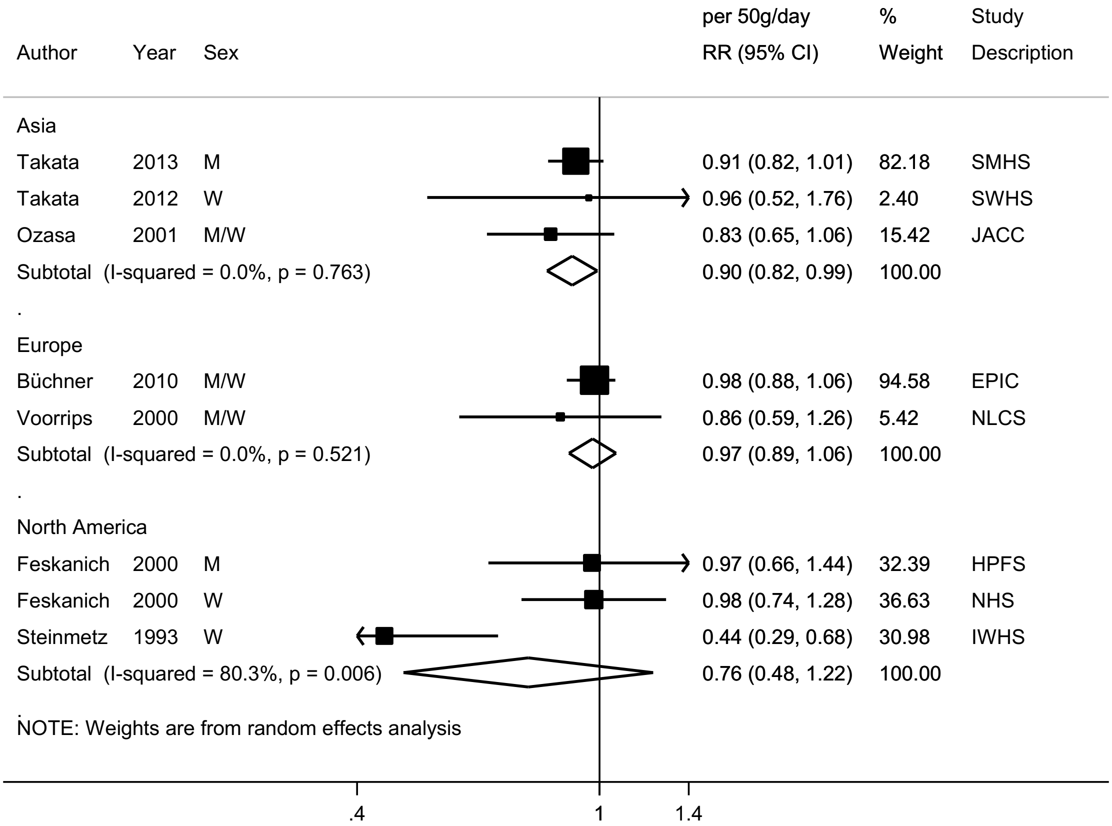
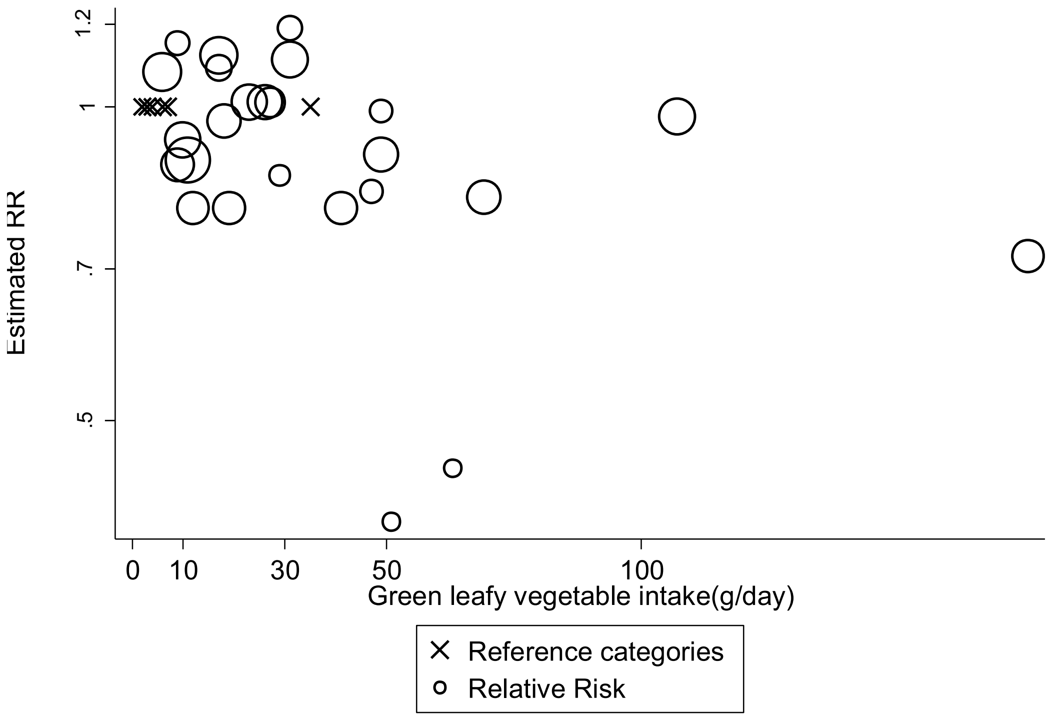
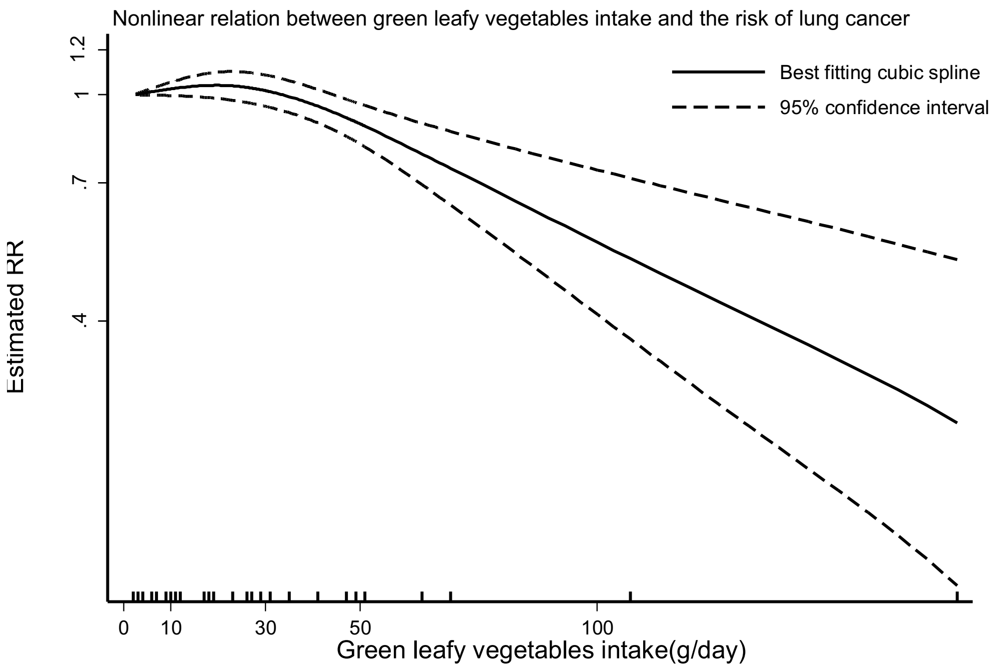


Figure 35 Relative risk of lung cancer and green leafy vegetables intake estimated using non-linear models





$p < 0.01$

Table 28Table with green leafy vegetables intake values and corresponding RRs (95% CIs) for non-linear analysis of green leafy vegetables intake and lung cancer

Green leafy vegetables intake (g/day)	RR (95%CI)
0	1
25	1.03(0.97-1.09)
50	0.91(0.85-0.98)
100	0.52 (0.37-0.71)

2.2.2 Fruits

Cohort studies

Summary

Main results:
Twenty three studies (14 506 cases) out of 30 studies (44 publications) were included in the dose-response meta-analysis. A significant inverse association was observed. Five studies were excluded from the dose-response analyses; all reported nonsignificant associations. High heterogeneity was observed. In stratified analysis, the results were similar and significant in men and women and in studies with incidence and mortality as outcome. In analysis stratified by smoking status (nine studies) a significant inverse association was found for current smokers, but not for former or never smokers. There was high heterogeneity across studies in current smokers.
There was significant evidence of publication or small study bias ($p < 0.01$). The funnel plot shows that the smaller studies identified reported stronger inverse associations than the average and there were no small studies reporting positive associations.

Sensitivity analysis:
The overall association remained statistically significant in influence analysis. The summary RRs ranged from 0.91 (95% CI=0.87-0.95) when Takata, 2012 was omitted to 0.93 (95% CI=0.89-0.96) when Neuhouser, 2003 was omitted.
There was evidence of a non-linear dose-response relationship of lung cancer and fruit intake ($p < 0.01$). There was a decrease in lung cancer risk for increasing levels of fruit intake up to 200-300 g/day and no further risk decrease for increasing intake above this level.

Study quality:
All studies used FFQ to assess fruit intake. Büchner, 2010b was the only study that corrected for measurement error of diet using regression calibration. Similar results were observed

with the calibrated intake. Repeated dietary measurements were used in the NHS and the HPFS (Feskanich, 2000). Cancer outcome was confirmed using records in cancer registries in most studies.
All studies included in the dose-response analysis were at least adjusted for age, sex, and smoking status. Most studies (21 studies) adjusted for intensity, duration of smoking and other smoking variables in addition to smoking status. The overall association remained the same when the analysis was restricted to these studies (see Table of summary results).

Pooling project of cohort studies:
An inverse association was observed in the Pooling Project of Cohort Studies (Smith-Warner, 2003, seven studies)
The association was significant in current smokers (1915 cases) but not in never smokers (259 cases) and former smokers (981 cases), and for adenocarcinomas and squamous cell carcinomas, but not for small cell carcinomas.
A dose-response analysis including the Pooling Project was not possible because cohort-specific cutpoints were used in the analyses. A meta-analysis of the highest compared to the lowest intake category including the Pooling Project (11% weight in the analysis) and the nonoverlapping studies identified in the CUP was then conducted. A significant inverse association was observed (18 studies). In highest vs lowest meta-analysis stratified by smoking status (12 studies), the significant association was restricted to smokers and former smokers; no significant association was observed in never smokers.

Table 29 Fruit intake and lung cancer risk. Number of studies in the CUP SLR

	Number
Studies <u>identified</u>	30 (44 publications)
Studies included in forest plot of highest compared with lowest exposure	26
Studies included in dose-response meta-analysis	23
Studies included in non-linear dose-response meta-analysis	14

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

Table 30 Fruit intake and lung cancer risk. Summary of the dose-response meta-analysis in the 2005 SLR and CUP.

	2005 SLR	CUP
Increment unit used	80 g/day	100 g/day
All studies		
Studies (n)	14	23
Cases (total number)	7649	14506
RR (95%CI)	0.94 (0.90-0.97)	0.92 (0.88-0.95)
Heterogeneity (I^2, p-value)	34%	56.8%, <0.01
P value Egger test		<0.01

Stratified and sensitivity analysis (no analyses conducted in the 2005 SLR)			
Smoking status	**Never smokers**	**Current smokers**	**Former smokers**
Studies (n)	8	9	5
RR (95%CI)	1.03 (0.97-1.09)	0.91 (0.85-0.98)	0.97 (0.92-1.02)
Heterogeneity (I^2, p-value)	0%, 0.71	56.6%, <0.02	0%, 0.69
Sex	**Men**	**Women**	
Studies (n)	11	9	
RR (95%CI)	0.94 (0.89-0.99)	0.95 (0.92-0.99)	
Heterogeneity (I^2, p-value)	45.5% , 0.05	24.2%, 0.23	
Outcome	**Incidence**	**Mortality**	
Studies (n)	18	5	
RR (95%CI)	0.93 (0.89-0.97)	0.82 (0.72- 0.94)	
Heterogeneity (I^2, p-value)	61.8%, < 0.001	0%, 0.74	
Cancer type	**Small cell carcinoma**	**Squamous cell carcinoma**	**Adenocarcinoma**
Studies (n)	2	2	5
RR (95%CI)	0.84 (0.62-1.15)	0.88 (0.70-1.11)	0.94 (0.83-1.07)
Heterogeneity (I^2, p-value)	37.8%, 0.21	14.8%, 0.28	34.4%, 0.19
Geographic location	**Asia**	**Europe**	**North America**
Studies (n)	6	6	11
RR (95%CI)	0.94 (0.83- 1.06)	0.91 (0.88-0.96)	0.91 (0.86-0.97)
Heterogeneity (I^2, p-value)	60.0% , 0.03	19.9% , 0.28	61.2%, <0.01
Adjustment on smoking	**Smoking status**	**Intensity and duration of smoking**	
Studies (n)	2	21	
RR (95%CI)	0.69(0.38-1.24)	0.92 (0.89-0.96)	
Heterogeneity (I^2, p-value)	66.3%, 0.09	56.9%, <0.01	

Table 31 Fruit intake and lung cancer risk. Highest versus lowest meta-analyses of the Pooling Project and non overlapping studies in the CUP.

Pooling project of cohort studies and non-overlapping studies identified in the CUP SLR	
Comparison	Highest vs lowest
Studies (n)	28
Cases (total number)	14 783
RR (95%CI)	0.81(0.75-0.87)
Heterogeneity (I^2, p-value)	22.6%, 0.17

Stratified highest versus lowest analysis with Pooling Project			
Smoking status	**Never smokers**	**Current smokers**	**Former smokers**
Studies (n)	12	13	9
Cases (total number)	2184	6280	3790
RR (95%CI)	0.91(0.71-1.17)	0.83(0.75-0.92)	0.89(0.81-0.99)
Heterogeneity (I^2, p-value)	33.1%, 0.14	16.4%, 0.29	0%, 0.96

Table 32 Fruit intake and lung cancer risk. Results of meta-analyses and pooled analyses of prospective studies published after the 2005 SLR.

Author, Year	Number of cohort studies	Total number of cases	Studies country, area	Outcome	Comparison	RR (95%CI)	P trend	Heterogeneity (I^2, p value)
Meta-analyses								
Wakai, 2011	4	1093	All Japanese	Lung cancer Incidence and Mortality	Highest vs lowest	0.87(0.74-1.03)		Q statistic p ≥0.05
					Per 1 serving/day	0.88(0.66-1.16)		Q statistic p <0.05
Pooled-analyses								
Smith-Warner, 2003 AHS, ATBC, CNBSS, HPFS, IWHS, NYSC, NHS	7	3206	USA, Europe	Lung cancer All	Q5 vs Q1	0.77(0.67-0.87)	<0.01	0.56
					≥400 vs <100 g/day	0.82(0.68-0.98)		
	5	259		Never smokers	Q4 vs Q1	0.59(0.34-1.04)	0.16	0.09
	5	981		Past smokers		0.85(0.69-1.05)	0.43	0.49
	5	1915		Current smokers		0.82(0.68-0.99)	0.23	0.13
	6	956		Adenocarcinoma	Q4 vs Q1	0.84 (0.71-0.99)	0.10	0.48
	6	538		Small cell carcinoma		0.93(0.71-1.23)	0.71	0.14
	6	901		Squamous cell carcinoma		0.75(0.59-0.96)	0.17	0.12

Table 33 Fruit intake and lung cancer risk. Main characteristics of studies 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	Missing data derived for analyses
Bradbury, 2014 LUN26881 Europe	EPIC, Prospective Cohort	1830/ 470 000	Cancer and Death registries, Health insurance records, active follow, cases confirmed by pathology records or death certificate	Questionnaire	Incidence, lung cancer	Per 100 g/day	0.94 (0.88-1.01)	Age, alcohol consumption, centre, duration of smoking, education level, energy intake, height, physical activity, smoking status, weight, gender, lifetime and baseline intensity of smoking, time since quitting smoking, vegetable consumption	Estimation of confidence intervals. Used only in highest versus lowest and dose-response analysis. Büchner, 2010b LUN20360 was used in stratified analysis
						≥356 vs ≤89 g/day	0.80		
Gnagnarella, 2013a LUN26858 Italy	COSMOS, Cohort of heavy smokers enrolled in lung cancer screening trial, Age: 50-84 years	178/ 4336 5.7 years	Screening examinations	FFQ	Incidence, lung cancer	554.4 vs 110.9 g /day	0.56 (0.36-0.87) Ptrend:0.02	Age, sex, energy intake, smoking duration, average daily cigarettes consumption, years of	Distribution of person-years by exposure category

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Missing data derived for analyses
	M/W heavy smokers							cessation, asbestos exposure, fruits and vegetables, fish, red meat, olive oil, tea and wine intake	
Takata, 2013 LUN26860 China	Shanghai Men's Health Study, Prospective Cohort, Age: 40-74 years, M	359/ 61 092 5.5 years	Biennial home visits (diagnosis verified by medical chart review), record linkage to Cancer Registry and Vital Statistics Registry	Validated FFQ	Incidence, lung cancer	286.3 vs 21.1 g/day	0.75 (0.54-1.04) Ptrend:0.09	Age, BMI, tea consumption, total caloric intake, vegetable intake, current smoking status, education, family history of lung cancer, history of chronic bronchitis, number of cigarettes smoked per day, years of smoking	Distribution of person-years by exposure category
Takata, 2012 LUN26859 China	SWHS, Prospective Cohort,	428/ 71 267 11.2	Shanghai cancer registry & the shanghai vital	FFQ	Incidence, lung cancer	460 vs 78 g/d	1.11 (0.83-1.48) Ptrend:0.50	Age, BMI, income, occupation,	Distribution of person-years by exposure

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Missing data derived for analyses
	Age: 40-70 years, W, never smokers		statistics registry					total caloric intake, history of asthma, passive smoking	category
Büchner, 2010b LUN20360 Denmark,France,Germany,Greece,Italy,Netherlands,Norway,Spain,Sweden,U.K.	EPIC, Prospective Cohort, Age: 25-70 years, M/W	1830/ 478 535 8.7 years	Cancer and Death registries, Health insurance records, active follow, cases confirmed by pathology records or death certificate	FFQ, dietary questionnaires, food record	Incidence, lung cancer	>357 vs <90 g/day	0.8 (0.66-0.96) Ptrend:0.01	Age, alcohol consumption, centre, duration of smoking, education level, energy intake, height, physical activity, smoking status, weight, gender, lifetime and baseline intensity of smoking, time since quitting smoking, vegetable consumption	Distribution of person-years by exposure category, mid-points of exposure categories
		1167			Incidence, lung cancer, current smokers	>357 vs <90 g/day	0.79 (0.62-1.02) Ptrend:0.04		
		964			Incidence, lung cancer, men	>357 vs <90 g/day	0.82 (0.63-1.08) Ptrend:0.12		
		866			Incidence, lung cancer, women	>357 vs <90 g/day	0.77 (0.59-1.00) Ptrend:0.06		
		574			Incidence, adenocarcinoma	>357 vs <90 g/day	0.85 (0.60-1.19) Ptrend:0.20		
		467			Incidence, lung cancer, former smokers	>357 vs <90 g/day	0.84 (0.59-1.21) Ptrend:0.24		
		363			Incidence, squamous cell carcinoma	>357 vs <90 g/day	0.77 (0.50-1.19) Ptrend:0.16		
		286			Incidence, small cell carcinoma	>357 vs <90 g/day	0.77 (0.46-1.27) Ptrend:0.21		

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
		187			Incidence, lung cancer, never smokers	>357 vs <90 g/day	0.94 (0.50-1.77) Ptrend:0.63		
		137			Incidence, large cell carcinoma	>357 vs <90 g/day	1.07 (0.54-2.14) Ptrend:0.39		
George, 2009 LUN20265 USA	NIH-AARP Diet and Health, Prospective Cohort, Age: 50-71 years, M/W	4092/ 483 338	Linkage with 11 state cancer registry databases	FFQ	Incidence, lung cancer, men	1.6-5.13 vs 0-0.44 cup/1000kcal/day	0.91 (0.81-1.01) Ptrend:0.05	Age, BMI, energy intake, family history of cancer, marital status, physical activity, race, vegetable intake, alcohol, education, smoking menopausal hormone therapy use	Distribution of person-years by exposure category, mid-points of exposure categories Exposure values using mean energy intake RRs for men and women combined
		2347			Incidence, lung cancer, women	1.91-5.58 vs 0-0.6 cup1000 kcal/day	0.89 (0.77-1.02) Ptrend:0.163		
Kabat, 2008 LUN20341 USA	WHI-DM and OS, Prospective Cohort, Age: 50-79 years, postmenopausal women	1304/ 159 659 7.8 years	Lung cancer was not the primary outcome of the trial. Follow-up by mail or phone. Self-reported lung cancers verified by local		Incidence, lung cancer	≥3.0 vs <0.82 servings/day	0.85 (0.68-1.05) Ptrend:0.04	Age, ethnicity, physical activity, smoking status, study, total caloric intake, intake of vegetables,	Mid-points of exposure categories. Exposure values using standard portion size

Author, Year, WCRF Code, Country	Study 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
			review of pathology reports					fruits, fat, alcohol intake, education, pack years of smoking, HRT use	
Wright, 2008 LUN20306 USA	NIH-AARP Diet and Health, Prospective Cohort, Age: 50-71 years, M/W	2110/ 472 081 8 years	Annual linkage to state cancer registries and national death index plus	Validated FFQ	Incidence, lung cancer, men former smokers	>2.27 vs <0.65 servings/1000 kcal/day	0.91 (0.79-1.05) Ptrend:0.36	Age, BMI, energy intake, family history of cancer, race, smoking status, alcohol intake, education, physical activity, smoking dose, time since quitting smoking	Used only in stratified analysis by smoking (Superseded by George, 2009 LUN20265). Distribution of person-years by exposure category, mid-points of exposure categories. Exposure values using mean energy intake
		1583			Incidence, lung cancer, men current smokers	>2.27 vs <0.65 servings/1000 kcal/day	0.84 (0.69-1.04) Ptrend:0.12		
		1196			Incidence, lung cancer, women current smokers	>2.76 vs <0.89 servings/1000 kcal/day	0.95 (0.78-1.17) Ptrend:0.58		
		835			Incidence, lung cancer, women former smokers	>2.76 vs <0.89 servings/1000 kcal/day	0.94 (0.75-1.17) Ptrend:0.85		
		170			Incidence, lung cancer, women never smokers	>2.76 vs <0.89 servings/1000 kcal/day	1.08 (0.64-1.84) Ptrend:0.99		
		141			Incidence, lung cancer, men never smokers	>2.27 vs <0.65 servings/1000 kcal/day	0.81 (0.46-1.41) Ptrend:0.35		
Alavanja, 2004	AHS,	213/	Iowa and North	FFQ - study-	Mortality, lung	≥7 vs ≤2	0.90 (0.50-1.40)	Age, sex, clinic	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
LUN16965 USA	Prospective Cohort, M/W	89 658 6.2 years	Carolina cancer registries; state death registries and National Death Index	specific	cancer , men	servings/week		site, educational level, ethnicity/race, family history of specific cancer, presence of other diseases, smoking status, pack-years	person-years by exposure category, mid-points of exposure categories. Exposure values using standard portion size. RRs for men and women combined
					Mortality, lung cancer, women	≥7 vs ≤2 servings/week	0.60 (0.20-1.60)		
Jansen, 2004 LUN19603 Netherlands	Zutphen Study, Prospective Cohort, Age: 65-84 years, M	42/ 730 10 years	Data from Central Bureau of Statistics, diagnosis verified through cancer registry, hospital discharge or general practitioner	FFQ - study-specific	Incidence, lung cancer	>200 vs 0-100 g/day	0.58 (0.26-1.29)	Age, alcohol consumption, BMI, energy intake, physical activity, smoking habits	Distribution of person-years by exposure category, mid-points of exposure categories.
Liu, 2004 LUN10203 Japan	JPHC study-cohort I and II, Prospective Cohort, Age: 40-69	317/ 93 338 10 years	Hospital records, population-based cancer registries and death certificates	FFQ - study-specific	Incidence, lung cancer, current smokers	Highest vs lowest	1.16 (0.84-1.58)	Age, sex, areas, sports, alcohol intake, BMI, vitamin supplement use,	Mid-points of exposure categories.
		198			Incidence, adenocarcinoma	Highest vs lowest	1.40 (0.79-2.48)		

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Missing data derived for analyses
	years, M/W	176			Incidence, other tumour types	Highest vs lowest	0.96 (0.62-1.49)	salted fish and meat, pickled vegetables, smoking status, smoking duration, cigarettes/ day	
		106			Incidence, lung cancer, non-smokers	Highest vs lowest	2.09 (0.56-7.83)		
Sauvaget, 2003 LUN05721 Japan	Life Span Study, Prospective Cohort, Age: 34-103 years, M/W	563/ 38 540 16 years	Japanese nation-wide family registration system (Koseki) that provides complete mortality ascertainment	FFQ - study-specific	Mortality, lung cancer	Daily vs 0-1 times/week	0.80 (0.65-0.98)	Age, sex, alcohol consumption, area of residence, BMI, educational level, other, smoking status	Distribution of person-years by exposure category, mid-points of exposure categories. Exposure values using standard portion size.
		15			Mortality, lung cancer, men non-smokers	Daily vs 0-1 times/week	0.19(0.05-0.79)		
		47			Mortality, lung cancer, men former smokers	Daily vs 0-1 times/week	1.06 (0.50-2.26)		
		189			Mortality, lung cancer, men current smokers ≤20/day	Daily vs 0-1 times/week	0.67(0.46-0..98)		
		94			Mortality, lung cancer, men current smokers >20/day	Daily vs 0-1 times/week	0.57(0.32-1.00)		
		112			Mortality, lung cancer, women	Daily vs 0-1 times/week	0.97(0.57-1.65)		

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	Missing data derived for analyses
					non-smokers				
		63			Mortality, lung cancer, women current smokers	Daily vs 0-1 times/week	1.06(0.56-2.00)		
Takezaki, 2003 LUN00268 Japan	Aichi Cancer Registry Study, Prospective Cohort, Age: 30- years, M/W	51/ 5885 14 years	Cancer registry	FFQ - study-specific	Incidence, lung cancer	≥5 vs <3 times/week	0.61 (0.29-1.3)	Age sex, smoking status, cigarettes/day - 2 categories- , occupation.	Mid-points of exposure categories. Exposure values using standard portion size.
Neuhouser, 2003 LUN00354 USA	CARET, Prospective Cohort Age: 45-69 years, M/W	742 12 years	Lung cancer is primary endpoint of the trial. Active follow-up confirmed in medical and pathology records	FFQ - study-specific	Incidence, lung cancer	≥11.1 vs <1.9 servings/week	0.56 (0.39-0.81) intervention	Age, sex, smoking status, total pack-years of smoking, asbestos exposure, race/ethnicity, and enrollment center	Distribution of person-years and cases by exposure category Mid-points of exposure categories. Exposure values using standard portion size. RRs for intervention and placebo combined
							0.79 (0.57-1.11) placebo		
Holick, 2002 LUN00515	ATBC, Prospective	1644/ 29 133	Finnish Cancer Registry and the	FFQ - study-specific	Incidence, lung cancer	>188 vs <45 g/day	0.87 (0.74-1.02)	Age, years smoked,	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
Finland	Cohort, Age: 50-69 years, M, Smokers only	11 years	Register of Causes of Death					cigarettes/day, trial group, supplement use , energy intake, cholesterol, and fat	exposure category
Olson, 2002 LUN00502 USA	IWHS, Prospective Cohort, Age: 55-69 years, W, Post-menopausal	553/ 38 006 12 years	Iowa Health Registry (part of SEER registry)	FFQ - study-specific	Incidence, lung cancer	≥25 vs ≤10 servings/week	0.8 (0.61-1.06)	Smoking habits, smoking habits	Mid-points of exposure categories. Exposure values using standard portion size.
Ozasa, 2001 LUN00725 Japan	JACC study, Prospective Cohort, Age: 40-70 years, M/W, No specific group	84/ 98 248 7.7 years	Population death registries	FFQ - study-specific	Mortality, lung cancer, women	>3-4/week vs ≤1-2/month	0.80 (0.42-1.5)	Age, family history of cancer, smoking habits	Mid-points of exposure categories. Exposure values using standard portion size. RRs for men and women combined
		300			Mortality, lung cancer, men	>3-4/week vs ≤1-2/month	0.73 (0.55-0.97)		
Breslow, 2000 LUN01082 USA	NHIS, Prospective Cohort, Age: 18-87 years,	154/ 20 195 8.5 years	Record linkage to National Death Index	FFQ - block	Mortality, lung cancer	>11.6 vs 0-3 servings/week	0.90 (0.50-1.60)	Age, sex, smoking duration, packs/day	Mid-points of exposure categories. 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
	M/W								portion size.
Feskanich, 2000 LUN00986 USA	Nurses' Health Study (NHS) + Health Professionals Follow-up Study (HPFS), Prospective Cohort, Age: 30-75 years, M/W	519/ 125 061 12 years	Verbal or written self-report, if possible confirmed by medical records, and death certificates	FFQ - study-specific	Incidence, lung cancer, women	>3.3 vs 1.1-1.7 servings/day	0.76 (0.56-1.02)	Age, follow-up cycle, smoking status, years since quitting - past smokers-, cigarettes /day - current smokers-, age start smoking, total energy intake, availability of diet data after baseline	Distribution of person-years by exposure category, mid-points of exposure categories. Exposure values using standard portion size.
		274			Incidence, lung cancer, men	>3.3 vs 1.1-1.7 servings/day	1.22 (0.8-1.87)		
		269			Incidence, lung cancer, women, current smokers	Quintile 5 vs quintile 1 servings/day	0.89 (0.59-1.35)		
		54			Incidence, lung cancer, women , non-smokers	tertile 3 vs tertile 1 servings/day	0.34 (0.16-0.72)		
		193			Incidence, lung cancer, women , former smokers	Quintile 5 vs quintile 1 servings/day	0.78 (0.47-1.29)		
		86			Incidence, lung cancer, men, current smokers	Quintile 5 vs quintile 1 servings/day	0.95 (0.45-2.03)		
		24			Incidence, lung cancer, men, non-smokers	Tertile 3 vs tertile 1 servings/day	0.59 (0.21-1.67)		
		148			Incidence, lung cancer, men, former smokers	Quintile 5 vs quintile 1 servings/day	1.34 (0.71-2.52)		

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Missing data derived for analyses
		232			Incidence, adenocarcinoma, women	Quintile 5 vs quintile 1 servings/day	0.79 (0.49-1.25)		
		179			Incidence, non-small cell (SCC, adenocarcinoma, large cell), women	Quintile 5 vs quintile 1 servings/day	0.78 (0.48-1.26)		
		93			Incidence, adenocarcinoma, men	Quintile 5 vs quintile 1 servings/day	1.30 (0.65-2.58)		
		120			Incidence, non-small cell (SCC, adenocarcinoma, large cell), men	Quintile 5 vs quintile 1 servings/day	0.90 (0.47-1.73)		
Voorrips, 2000b LUN01162 Netherlands	Netherlands Cohort Study on Diet and Cancer (NLCS), Case Cohort, Age: 55-69 years, M/W	963/ 120 852 3.2 years	Regional cancer registries and computerized national database of pathology report (PALGA)	FFQ - study-specific	Incidence, lung cancer, men, non-smokers	325 vs 46 g/day	0.80 (0.60-1.10)	Age, sex, educational level, family history of lung cancer, current smoker, years of smoking, cigarettes/day	
		611			Incidence , Squamous cell carcinoma, men	Quintile 5 vs quintile 1	0.70 (0.50-1.10)		
		568			Incidence, lung cancer, Current smokers	325 vs 46 g/day	0.70 (0.40-1.00)		
		331			Incidence, lung	325 vs 46 g/day	0.80 (0.50-1.30)		

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
					cancer, Former smokers				
		150			Incidence, adenocarcinoma, men	Quintile 5 vs quintile 1	0.80 (0.40-1.30)		
		77			Incidence , Squamous cell carcinoma, women	Tertile 3 vs tertile 1	0.60 (0.30-1.10)		
		62			Incidence, lung cancer, Non-smokers	325 vs 46 g/day	1.40 (0.60-3.20)		
		44			Incidence , Adenocarcinoma, women	Tertile3 vs tertile 1	0.90 (0.40-1.90)		
Knekt, 1999 LUN01416 Finland	Finnish Mobile Clinic Health Examination Survey, Prospective Cohort, Age: 20-69 years, M	138/4545 25 years	Cancer registry	FFQ - study-specific	Incidence, lung cancer	3180 vs 1170 g/month	0.58 (0.37-0.93)	Age, smoking habits	Distribution of person-years and cases by exposure category
Steinmetz, 1993 LUN02740	IWHS, Nested Case	81/ 41 837	Iowa Health Registry (part of	FFQ - study-specific	Incidence, lung cancer, current	>18 vs <7 servings/week	0.95 (0.46-1.96)	Age, energy intake, pack-	Used only in stratified

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Missing data derived for analyses
USA	Control, Age: 55-69 years, W, post menopausal	4 years	SEER registry)		smokers			years of smoking	analysis by cancer type (Superseded by Olson, 2002 LUN00502) Mid-points of exposure categories. Exposure values using standard portion size.
Chow, 1992 LUN02888 USA	LBS, Prospective Cohort, Age: 35- years, M	209/ 17 633 20 years	Death certificates	FFQ - study-specific	Mortality, lung cancer	>90 vs <31 times/month	0.70 (0.40-1.30)	Age, other, smoking habits	Mid-points of exposure categories. Exposure values using standard portion size.
Shibata, 1992 LUN08664 USA	LWS, Prospective Cohort, Age: 74years, M/W	70/ 11 580 6 years	Death by reports of friends or relatives, National Death Index; incidence through hospital records	FFQ - study-specific	Incidence, lung cancer, women	>3.7 vs 0-2.3 servings/day	0.68 (0.37-1.24)	Age, smoking habits	Distribution of person-years by exposure category, mid-points of exposure categories. Exposure values using standard portion size.
		94			Incidence, lung cancer, men	≥3.5 vs <2.2 servings/day	0.99 (0.59-1.56)		

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Missing data derived for analyses
Fraser, 1991 LUN03076 USA	Adventist Health Study, Prospective Cohort, Age: 25- years, M/W, Vegetarians/Healthy Diet	52/ 34 198 6 years	Active follow-up by mail with confirmation through medical records and SEER registry where available	FFQ - study-specific	Incidence, lung cancer	≥2 times/day vs <3 times/week	0.26 (0.10-0.70)	Age, sex, smoking habits	Mid-points of exposure categories. Exposure values using standard portion size.
		32			Incidence, lung cancer, current smokers	≥2 times/day vs <3 times/week	0.22 (0.08-0.97)		
		20			Incidence, lung cancer , non-smokers	≥2 times/day vs <3 times/week	0.28 (0.06-2.68)		

Table 34 Fruit intake and lung cancer risk. Main characteristics of studies excluded 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	Reasons for exclusion
Pavanello, 2012 LUN20332 Denmark	DCH, Nested Case Control, Age: 50-64 years, M/W	425/ 160 725	Danish cancer registry	FFQ	Incidence, lung cancer	>186.1 vs 86 g/day	0.32 (0.23-0.44)	Alcohol consumption, cyp1a2 polymorphism, occupational exposure, gender, pack years of smoking, passive smoking	Superseded by Büchner, 2010b LUN20360

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Reasons for exclusion
Sakoda, 2011 LUN20351 USA	CARET, Nested Case Control, Age: 45-69 years, M/W	365/ 18 314	Lung cancer is primary endpoint of the trial. Active follow-up confirmed in medical and pathology records	FFQ	Incidence, lung cancer	>8.5 vs ≤3.5 serving/week	ORGA 1.22 (0.86-1.73) ORAA 1.64 (0.97–2.76)	Age, sex, enrolment year, smoking status, occupational asbestos exposure	Only has gene interactions results, Neuhouser, 2003 LUN00354 was used
Linseisen, 2007 LUN20323 France, Italy, Spain, U.K., Netherlands, Greece, Germany, Sweden, Denmark, Norway	EPIC, Prospective Cohort, Age: 25-70 years, M/W	1126/ 478 590 6.4 years	Cancer registries, health insurance records, pathology rec, active follow up, death certificate	FFQ, dietary questionnaires, food record	Incidence, lung cancer	345.7 vs 85.4 g/day	0.75 (0.59-0.96)	Education level, energy intake from fat and nonfat sources, height, smoking status, weight, work - physical activity, ethanol intake, processed and red meat, smoking duration	Superseded by Büchner, 2010b LUN20360
		1126			Incidence, lung cancer	Per 100 g	0.95 (0.91-0.99)		
		731			Incidence, lung cancer, current smokers	345.7 vs 85.4 g/day	0.72 (0.52-0.99)		
		731			Incidence, lung cancer, current smokers	Per 100 g	0.94 (0.88-1.00)		
		291			Incidence, lung cancer, former smokers	345.7 vs 85.4 g/day	0.93 (0.59-1.48)		
		291			Incidence, lung cancer, former smokers	Per 100 g	0.95 (0.87-1.04)		

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Reasons for exclusion
		98			Incidence, lung cancer, never smokers	345.7 vs 85.4 g/day	0.59 (0.25-1.38)		
		98			Incidence, lung cancer, never smokers	Per 100 g	0.96 (0.84-1.10)		
Skuladottir, 2004 LUN05185 Denmark	Danish Diet Cancer and Health Study, Prospective Cohort, Age: 50-64 years, M/W	247/ 54 158 8 years	Cancer registry	FFQ - study-specific	Incidence, lung cancer	165-643 vs 5-40 g/day	0.86 (0.59-1.26)	Age, other, smoking habits	Superseded by Büchner, 2010b LUN20360
		79			Incidence, adenocarcinoma	Per 100 g/day	0.96 (0.80-1.15)		
		49			Incidence, squamous cell	Per 100 g/day	0.82 (0.62-1.09)		
		43			Incidence, small cell	Per 100 g/day	1.00 (0.77-1.30)		
Khan, 2004 LUN00068 Japan	Japan, Hokkaido Cohort Study, Prospective Cohort, Age: 40- years, M	3158 14.80 years	Annual follow-up survey, cause of death classified by researchers	Dietary history questionnaire	Mortality, lung cancer, men	Several times/week + everyday vs never + several times/year + several times/month times	0.80 (0.30-2.20)	Age, smoking habits	Used only in highest versus lowest analysis. Only 2 categories
Miller, 2004 LUN00169	EPIC, Prospective	860/ 519 978	Cancer and Death registries,	FFQ - study-specific	Incidence, lung cancer, men	Quintile 5 vs >0 g/day	0.56 (0.43-0.73)	Age, anthropometry,	Superseded by Büchner, 2010b

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Reasons for exclusion
Europe	Cohort, Age: 25-70 years, M/W	10 years	Health insurance records, active follow, cases confirmed by pathology records or death certificate					smoking habits	LUN20360
Miller, 2002 LUN00442 Europe	EPIC, Prospective Cohort, Age: 25-70 years, M/W	482 924 4 years	Cancer and Death registries, Health insurance records, active follow, cases confirmed by pathology records or death certificate	FFQ - study-specific	Incidence, lung cancer	Quartile 4 vs quantile 1 g/day	0.78 (0.58-1.04)	Smoking habits	Superseded by Büchner, 2010b LUN20360
Jansen, 2001 LUN00857 Europe	Seven Countries Study, Prospective Cohort, Age: 40-59 years, M, Smokers	149/ 1578 12.5 years	Active follow-up, death coded by researchers based on death certificate medical and hospital records	Dietary history questionnaire	Mortality	Tertile 3 vs tertile 1	0.69 (0.46-1.02)	Age, area of residence, energy intake, other nutrients, foods or supplements, smoking habits	Used only in highest versus lowest analysis. No quantile range
Hirvonen, 2001 LUN00745	ATBC, Prospective	791/ 27 110	Finnish Cancer Registry and Register of	FFQ - study-specific	Incidence, lung cancer	>1470 vs 1359 mg/month	0.83 (0.68-1.0)	Age, energy intake, other	Superseded by Holick, 2002

Author, Year, WCRF Code, Country	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: 50-69 years, M, Smokers only	6.1 years	causes of Death					nutrients, foods or supplements, smoking habits	LUN00515
Speizer, 1999 LUN01255 USA	NHS, Prospective Cohort, Age: 30-55 years, W	399/ 118 351 12 years	Active follow-up, cases confirmed with medical and pathology records	FFQ - study-specific	Incidence, lung cancer	>30 vs never times/month		Age, smoking habits	Superseded by Feskanich, 2000 LUN00986
Knekt, 1997 LUN01779 Finland	Finnish Mobile Clinic Health Examination Survey, Prospective Cohort, Age: 15-99 years, M/W	9959 24 years	Finnish Cancer Registry	FFQ - study-specific	Incidence, lung cancer	Quartile 4 vs quartile 1 g/month	0.42 (0.23-0.76)	Age, sex, anthropometry, area of residence, energy intake, other, other nutrients, foods or supplements, smoking habits	Superseded by Knekt, 1999 LUN01416
Fu, 1997 LUN01468, Japan	Nagoya,1983-2000 M/W	161/24 489	Follow-up based on data from Aichi local council	Questionnaire			M 0.86(0.58-1.28) W 1.28 (0.63-2.60)		Article in Chinese (translated) with insufficient data
Ocke, 1997 LUN01851 Netherlands	Zutphen Study, Prospective Cohort,	54/ 561 12.5 years	Data from Central Bureau of Statistics,	Dietary history questionnaire	Incidence, lung cancer	>33rd percentile vs ≤33rd percentile	0.73 (0.44-1.22)	Age, smoking, energy intake	Used only in highest versus lowest analysis.

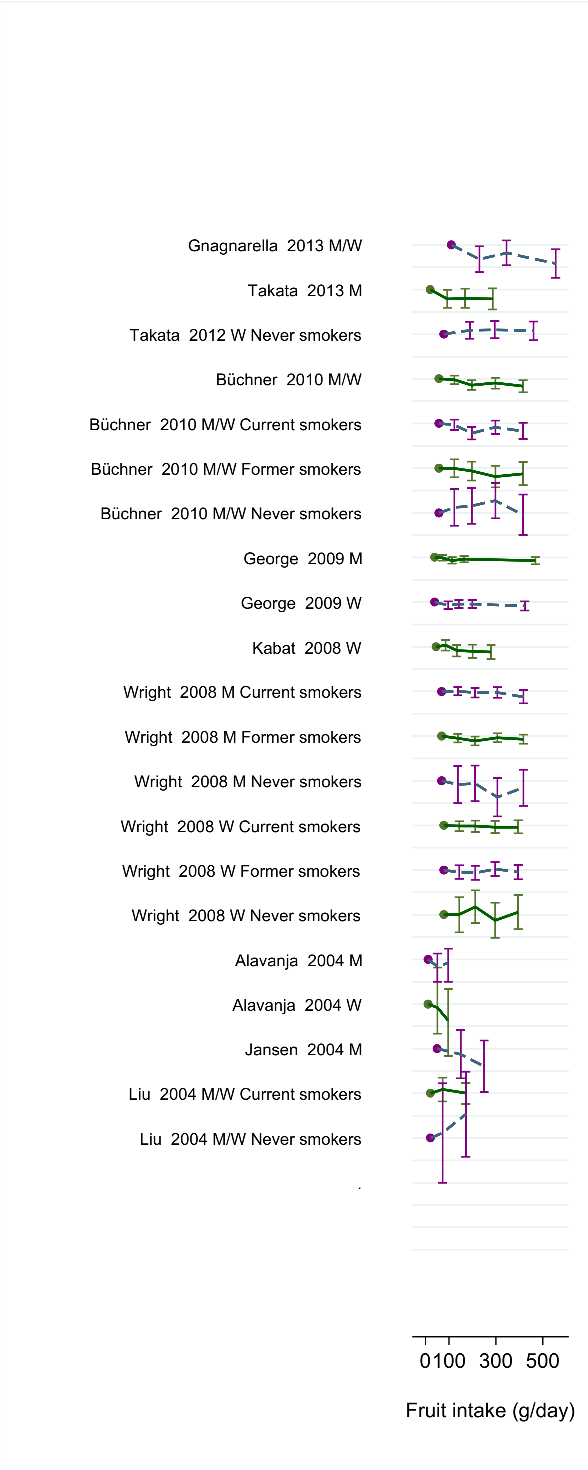
Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Reasons for exclusion
	Age: 40-59 years, M		diagnosis verified through cancer registry, hospital discharge or general practitioner						Exposure not quantified
Key, 1996 LUN01947 U.K.	HFSS, Prospective Cohort, Age: 16-80 years, M/W, Vegetarians/ Healthy Diet	10 771 16.8 years	Death certificate	FFQ - study-specific	Mortality, lung cancer	Daily vs less than daily	0.59 (0.34-1.02)	Age, sex, smoking habits	Used only in highest versus lowest analysis. Only 2 categories
Knekt, 1993 LUN02684 Finland	Finnish Mobile Clinic Health Examination Survey, Nested Case Control, Age: 15- years, M	21 172 9 years	Cancer registry	FFQ - study-specific	Incidence, lung cancer, current smokers	Lowest tertile vs highest tertile g/month	0.9 (0.6-1.5)	Age	Superseded by Knekt, 1999 LUN01416
Knekt, 1991b LUN03018 Finland	Finnish Mobile Clinic Health Examination Survey,	4583 20 years	Cancer registry	FFQ - study-specific	Incidence, lung cancer, current smokers	Lowest tertile vs highest tertile	0.98	Age, smoking habits	Superseded by Knekt, 1999 LUN01416

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Reasons for exclusion
	Prospective Cohort, Age: 20-69 years, M								
Kromhout, 1987 LUN03765 Netherlands	Zutphen Study, Prospective Cohort, Age: 40-59 years, M	878 12.5 years	Data from Central Bureau of Statistics, diagnosis verified through cancer registry, hospital discharge or general practitioner	Dietary history questionnaire	Mortality, lung cancer	Quartile 4 vs quartile 1	0.31 (0.15-0.65)	Age	Superseded by Ocke, 1997 LUN01851
Wang, 1985 LUN04098 USA	USA 1959-1970, Prospective Cohort, Age: 45-79 years, M/W	2952/ 750 000 12 years	Active follow-up, data from medical doctors, death certificates	FFQ - study-specific	Mortality, lung cancer	5-7 times/wk 3-4 times/wk 0-2 times/wk	Mortality ratio: 1 1.23 1.75		No confidence interval or SE, no measure of association
Kvale, 1983 LUN04322 Norway	Norway, 1967-1978, Prospective Cohort, M/W	70/ 16 713 11.5 years	Cancer Registry of Norway and death registry	Dietary history questionnaire	Incidence, lung cancer, men	Highest indices vs lowest indices times/month	1.1	Age, area of residence, smoking habits, urban/rural status	No confidence interval or SE

Figure 36 RR estimates of lung cancer by levels of fruit intake

*Squamous cell, large cell and small cell carcinoma combined Kreyberg I

The graph is presented in two panels because of the high number of studies.



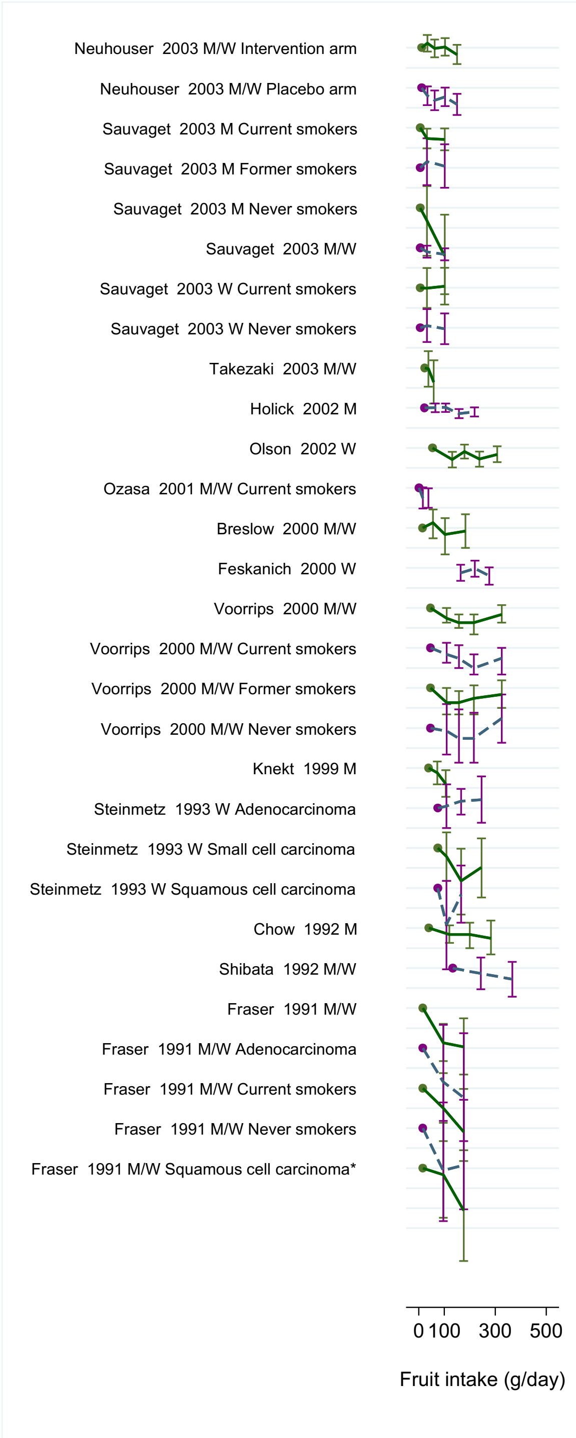
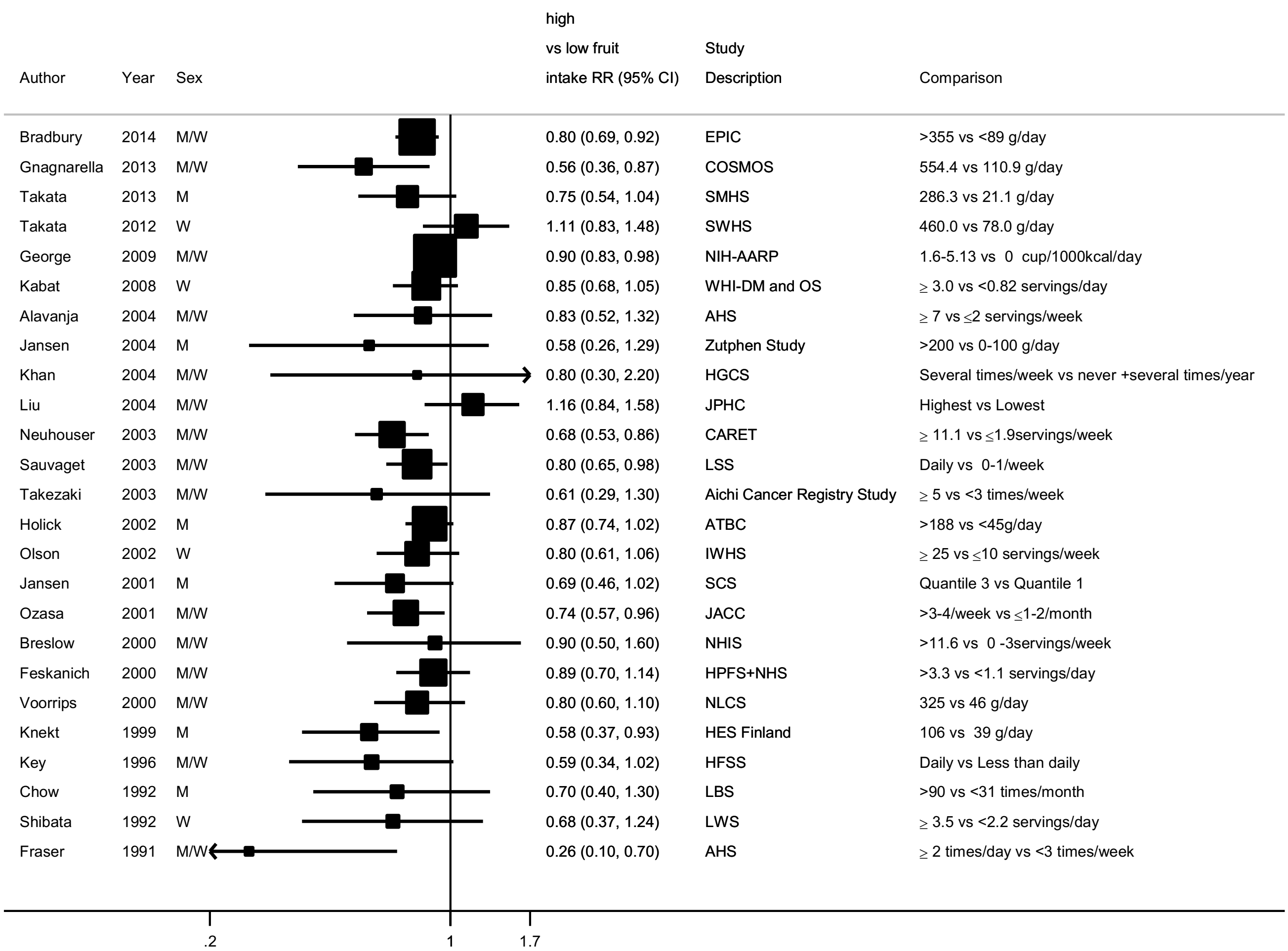
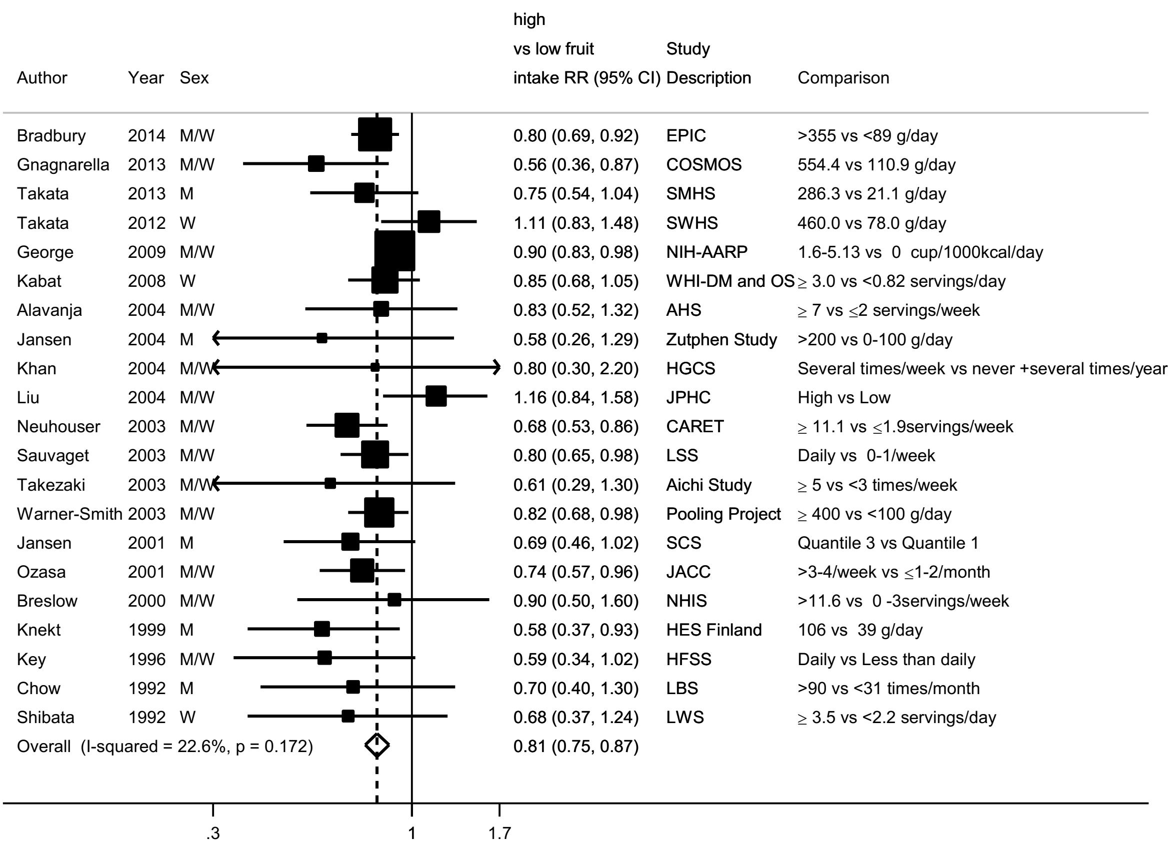


Figure 37 RR (95% CI) of lung cancer for the highest compared with the lowest level of fruit intake



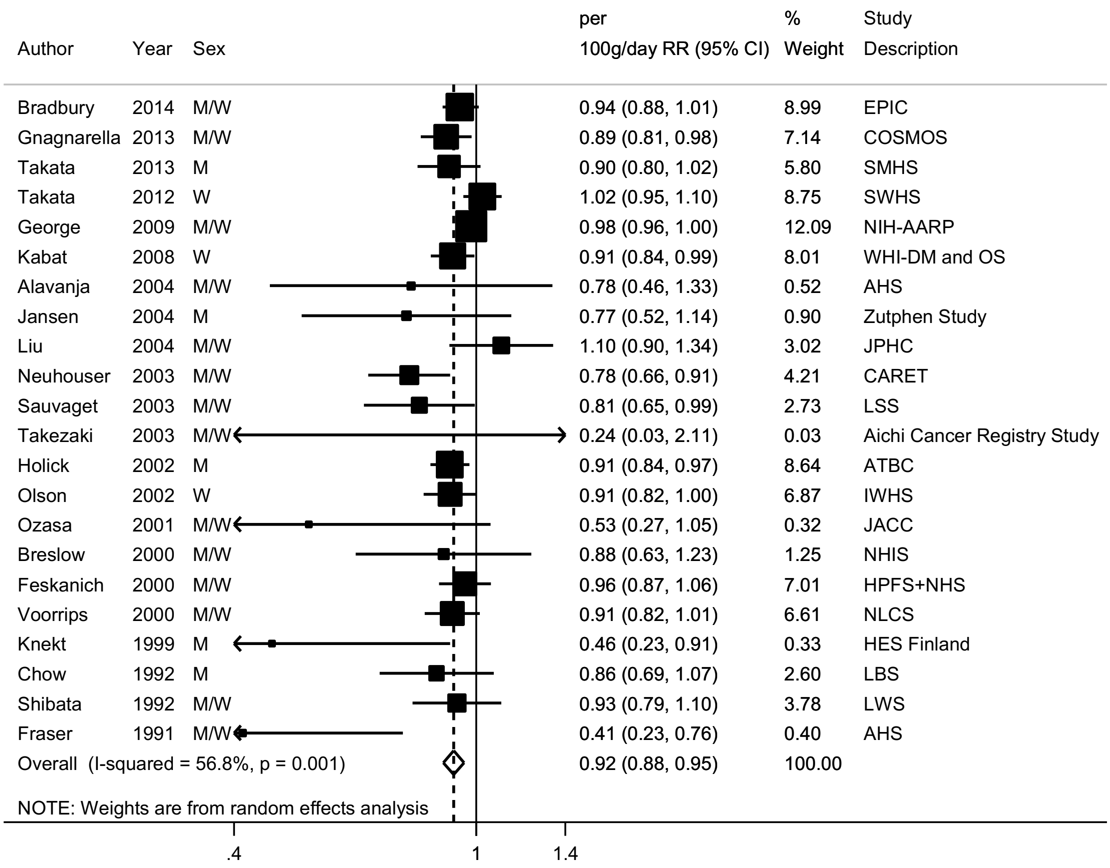
For Alavanja, 2004 AHS refers to the Agricultural Health Study and for Fraser, 1991 AHS refers to the Adventist Health Study

Figure 38 RR (95% CI) of lung cancer for the highest compared with the lowest level of fruit intake combined with Pooling Project



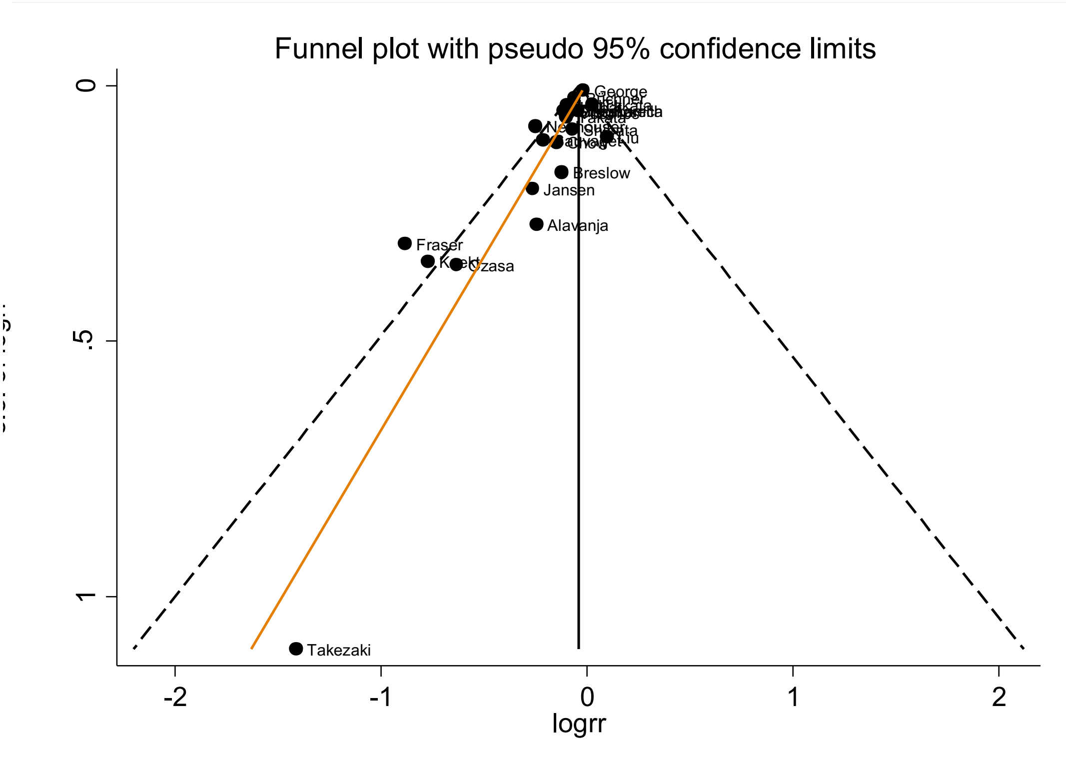
CARET study (Neuhouser, 2003) is a follow-up of a RCT, both the intervention and placebo arms of the trial are represented in the graph.

Figure 39 RR (95% CI) of lung cancer for 100g/day increase of fruit intake



For Alavanja, 2004 AHS refers to the Agricultural Health Study and for Fraser, 1991 AHS refers to the Adventist Health Study

Figure 40 Funnel plot of studies included in the dose response meta-analysis of fruit intake and lung cancer



Egger's test p < 0.01

Figure 41 RR (95% CI) of lung cancer for 100g/day increase of fruit intake by sex

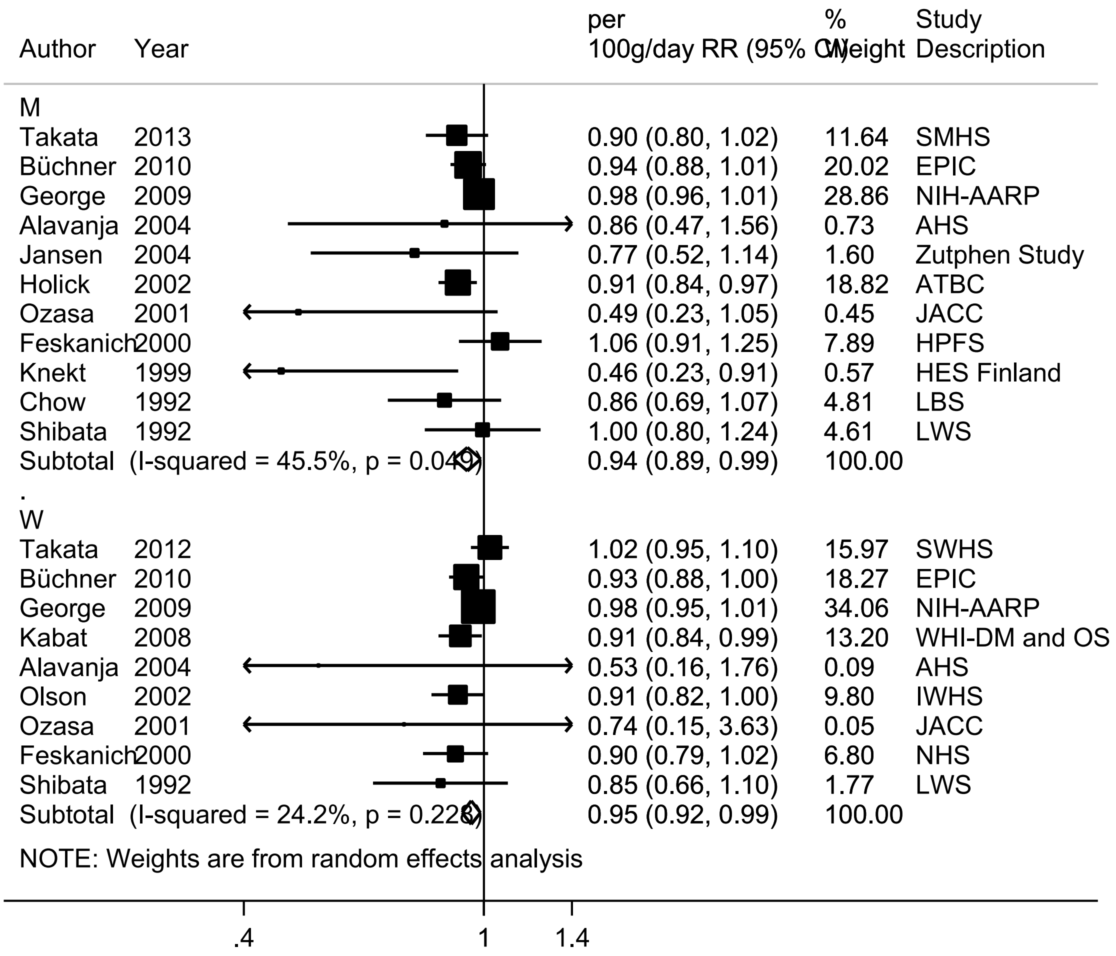


Figure 42 RR (95% CI) of lung cancer for 100g/day increase of fruit intake by cancer outcome

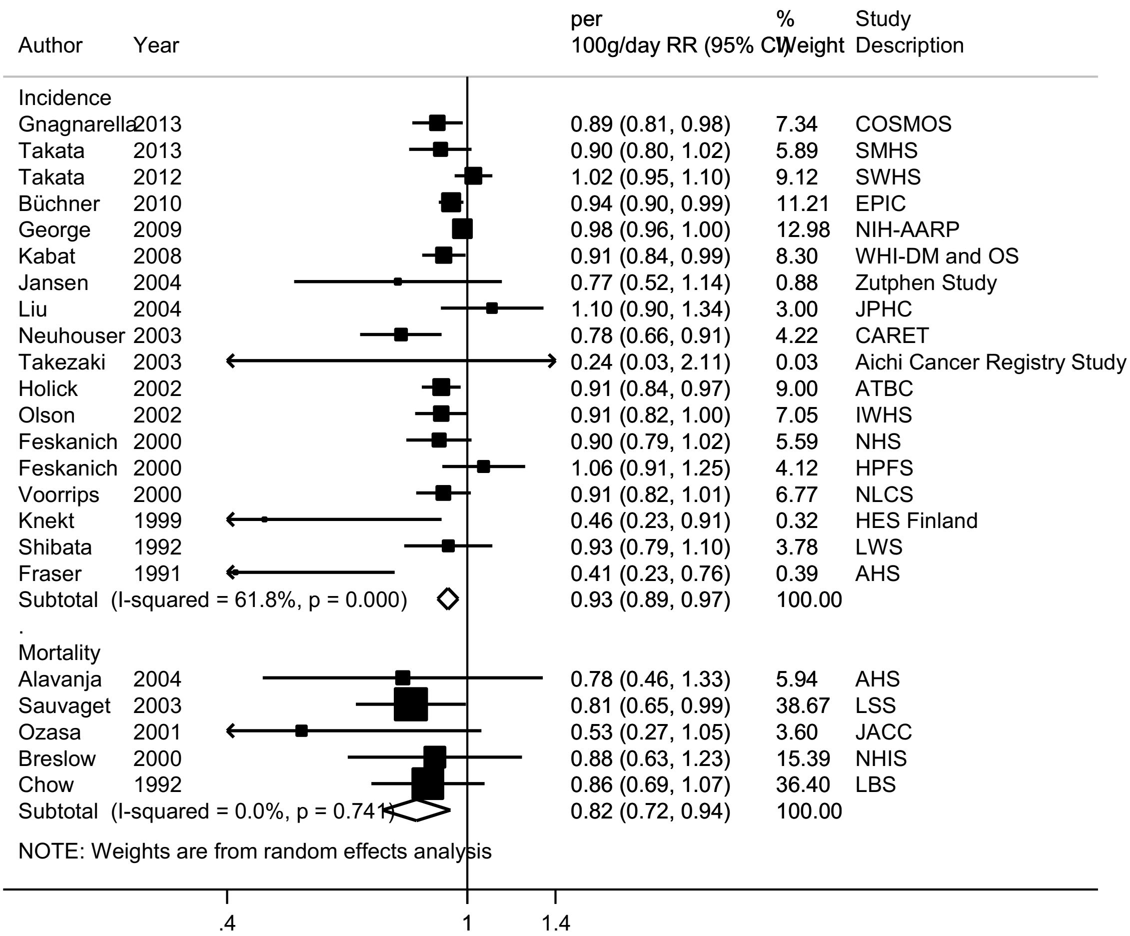


Figure 43 RR (95% CI) of lung cancer for 100g/day increase of fruit intake by cancer site

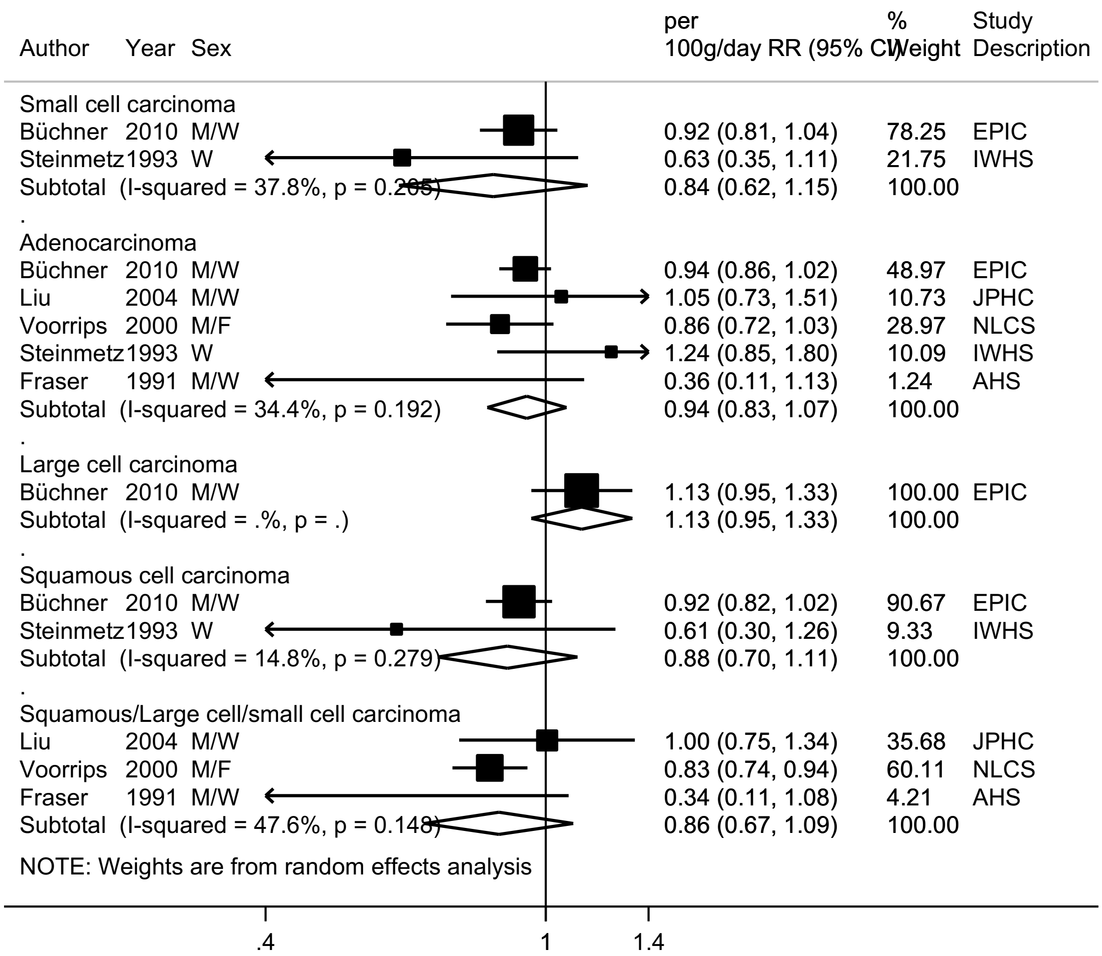


Figure 44 RR (95% CI) of lung cancer for 100g/day increase of fruit intake by smoking status

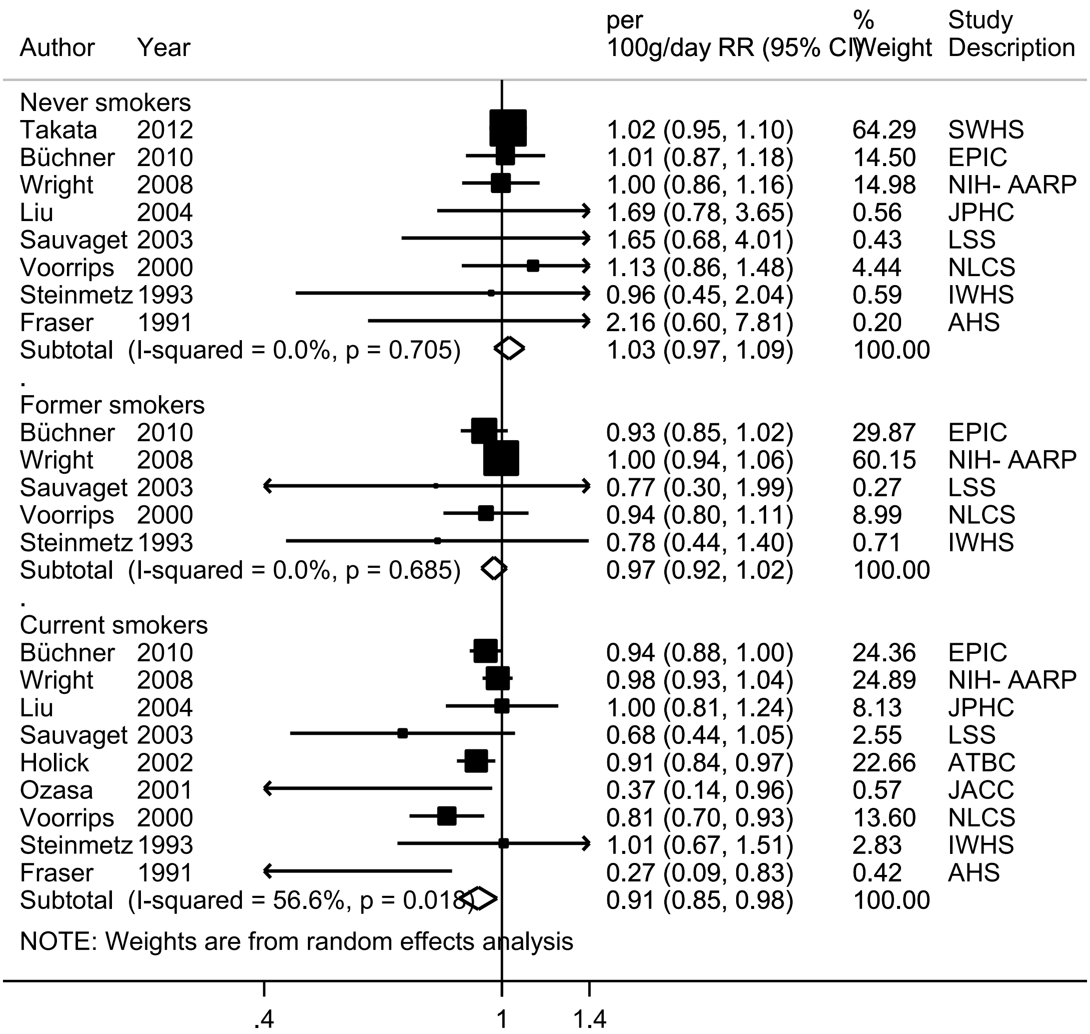


Figure 45 RR (95% CI) of lung cancer for 100g/day increase of fruit intake by geographic location

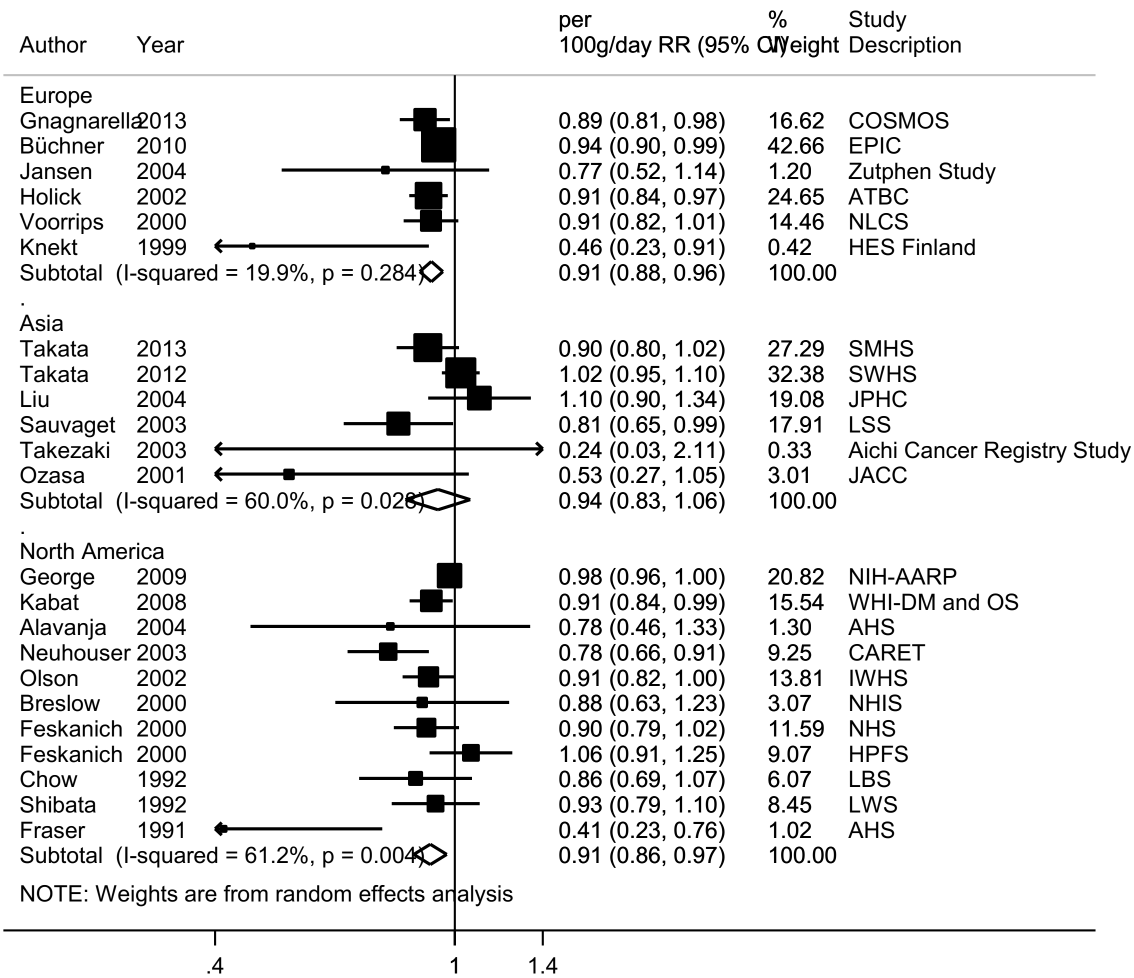
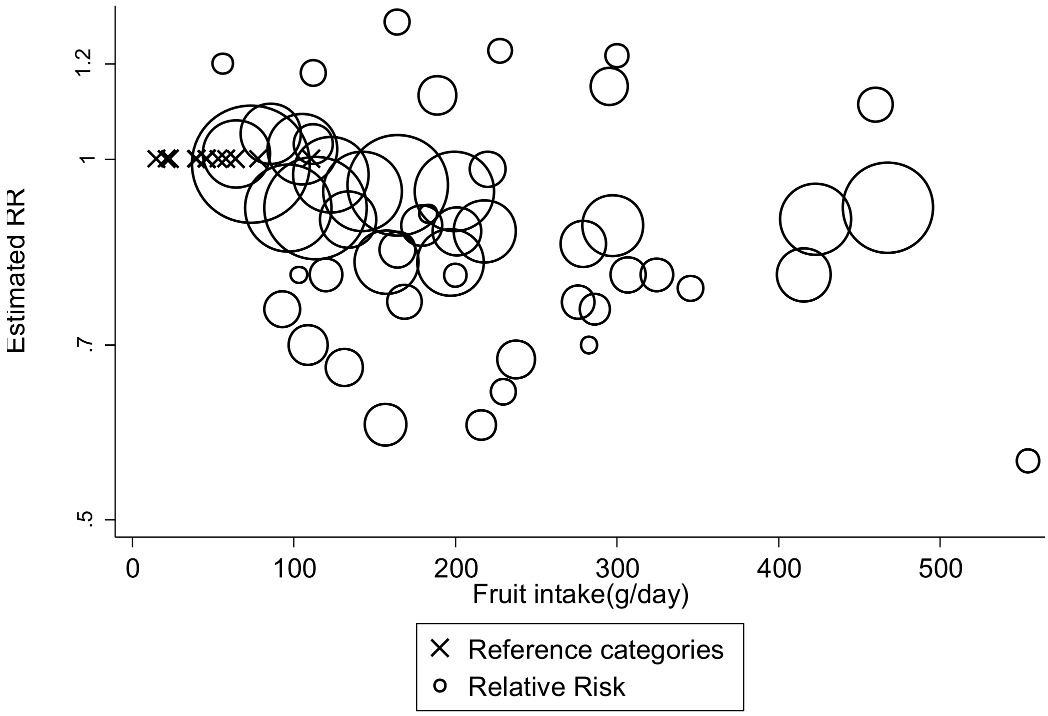
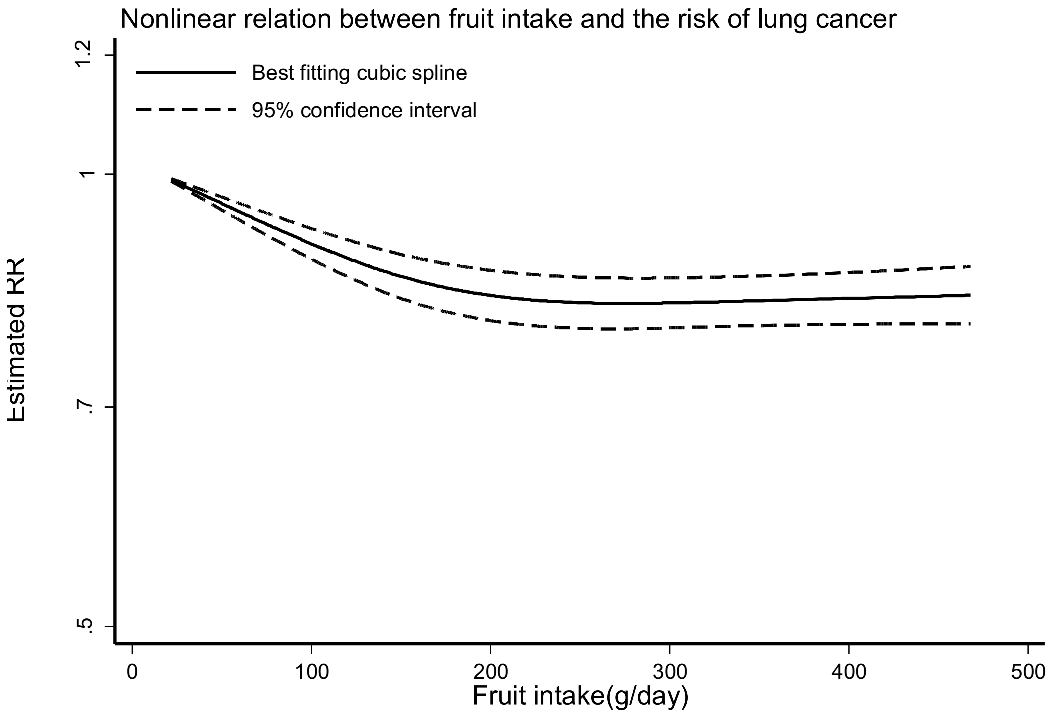


Figure 46 Relative risk of lung cancer and fruit intake estimated using non-linear models





$p < 0.01$

Table 35 Table with fruit intake values and corresponding RRs (95% CIs) for non-linear analysis of fruit intake and lung cancer

Fruit intake (g/day)	RR (95%CI)
15	1
100	0.88(0.87-0.91)
200	0.83(0.79-0.86)
300	0.82 (0.79-0.85)

2.2.2.1 Citrus fruits

Cohort studies

Summary

Main results:
Eleven studies (6382 cases) out of 14 studies (17 publications) –one publication reported on two cohorts- were included in the dose-response meta-analysis. A significant inverse association but with high heterogeneity was observed. The three studies that could not be included in the dose-response meta-analyses reported non-significant inverse associations. Heterogeneity was explored in stratified analyses. The heterogeneity was more evident in North-American studies, but the number of studies in Europe and Asia were low. Stronger associations were observed in Asian studies (two studies). Similar associations were observed in men and women (four studies).
Only three studies could be included in dose-response meta-analysis stratified by smoking status. Inverse non-significant association was observed for smokers and former smokers, and positive non-significant association was observed in non-smokers. In meta-analyses of the highest compared to the lowest intakes, the association was inverse and significant in current smokers, inverse but not significant in former smokers, but there was no significant association in non-smokers (four studies).
There was significant evidence of publication or small study bias ($p < 0.01$). The asymmetry is driven by small studies on the left side of the funnel plot and there are no small studies on the right side.

Sensitivity analysis:
The inverse association persisted in influence analysis. The summary RRs ranged from 0.88 (95% CI=0.81-0.96) when Wright, 2008 was omitted to 0.92 (95% CI=0.86-0.99) when Iso, 2007 was omitted. After excluding the only study not adjusted for smoking (Iso, 2007) the RR was 0.92(0.86-0.99).

There was evidence of non-linear dose-response relationship ($p < 0.01$). Lung cancer risk decreases with increasing levels of citrus fruit intake up to around 70 g/day and no further risk reduction is observed for increasing intakes above this value.

Study quality:
All studies used FFQ to assess citrus fruit intake. Büchner, 2010b was the only study that corrected for measurement error of diet. Similar results were observed with the calibrated intake. Repeated dietary measurements were used in the NHS and the HPFS (Feskanich, 2000).
Cancer outcome was confirmed by record linkage to cancer registries in most studies.
Nine studies in the CUP SLR adjusted for smoking dose, duration and other smoking-related variables. When the dose-response meta-analysis was restricted to the studies with better adjustment for confounding by smoking, a statistically inverse association was observed.

Pooling project of cohort studies:
The Pooling Project of Cohort studies reported a significant association of citrus fruits (oranges and tangerines) with lung cancer when comparing the highest to the lowest intake (Smith-Warner, 2003). Significant heterogeneity was detected (p=0.01).
Exploratory analysis conducted by the authors in the Pooling Project of cohort studies (Smith-Warner, 2003) showed that control for confounding by smoking was better in models that adjusted for smoking status, duration and dose compared to models adjusting for smoking status.
When the Pooling Project of Cohort Studies was combined with the non overlapping studies identified in the CUP (15 studies), the association was inverse, but of borderline statistical significance (RR for the highest compared to the lowest intake: 0.93; 95% CI= 0.88-1.00).

Table 36 Citrus fruit intake and lung cancer risk. Number of studies in the CUP SLR

	Number
Studies identified	14 (17 publications)
Studies included in forest plot of highest compared with lowest exposure	13
Studies included in dose-response meta-analysis	11
Studies included in non-linear dose-response meta-analysis	8

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

Table 37 Citrus fruit intake and lung cancer risk. Summary of the dose-response meta-analysis in the 2005 SLR and CUP.

	2005 SLR	**CUP**
Increment unit used	80 g/day	100 g/day
All studies		

Studies (n)	4	11
Cases (total number)	1794	6382
RR (95%CI)	0.93 (0.84-1.04)	0.91 (0.85-0.98)
Heterogeneity (I^2, p-value)	34%, 0.21	52.7%, 0.02
P value Egger test		<0.01
All studies and Pooling Projects (Highest vs lowest intake)		
Studies (n)		15
Cases (total number)		12 021
RR (95%CI)		0.93 (0.88-1.00)
Heterogeneity (I^2, p-value)		49.4%, 0.05

Stratified and sensitivity analysis (no analyses were conducted in the 2005 SLR) Relative risks for 100 grams increase			
Smoking status	**Never smokers**	**Current smokers**	**Former smokers**
Studies (n)	3	3	2
RR (95%CI)	1.27 (0.83-1.94)	0.74 (0.51-1.06)	0.68(0.42-1.11)
Heterogeneity (I^2, p-value)	0%, 0.64	81%, <0.01	0%, 0.46
Sex	**Men**	**Women**	
Studies (n)	4	4	
RR (95%CI)	0.83 (0.61-1.12)	0.86 (0.71-1.05)	
Heterogeneity (I^2, p-value)	68.6% , 0.02	70.0%, 0.02	
Outcome	**Incidence**	**Mortality**	
Studies (n)	10	1	
RR (95%CI)	0.92(0.86-0.99)	0.58(0.35-0.96)	
Heterogeneity (I^2, p-value)	47.5%, 0.05		
Geographic location	**Asia**	**Europe**	**North America**
Studies (n)	3	3	5
RR (95%CI)	0.66 (0.41- 1.04)	0.94 (0.85-1.03)	0.92 (0.84-1.00)
Heterogeneity (I^2, p-value)	36.8% , 0.21	0% , 0.60	67.7%, 0.02
Adjustment for smoking	**Smoking status**	**Smoking intensity and duration**	**No adjustment**
Studies (n)	1	9	1
RR (95%CI)	0.35(0.11-1.05)	0.93(0.87-0.99)	0.58(0.35-0.96)
Heterogeneity (I^2, p-value)		42.4% ,0.09	

Table 38 Citrus fruit intake and lung cancer risk. Results of pooled analyses of prospective studies published after the 2005 SLR.

Author, Year	Number of cohort studies	Total number of cases	Studies country, area	Outcome	Comparison	RR (95%CI)	P trend	Heterogeneity (I^2, p value)
Pooled analyses								
Smith-Warner, 2003	5	2552	HPFS, IWHS, NYSC, NHS, NLCS USA, Europe	Lung cancer incidence and mortality	Oranges and tangerines ≥1/2 vs 0 servings/day	0.74 (0.58–0.95)	< 0.01	0.01
	6	2701	CNBSS, HPFS, IWHS, NYSC, NHS, NLCS USA, Europe		Orange and grapefruit juice ≥1/2 vs 0 servings/day	0.82 (0.71–0.94)	0.01	0.27

Table 39 Citrus fruit intake and lung cancer risk. Main characteristics of studies 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	Missing data derived for analyses
Gnagnarella, 2013a LUN26858 Italy	COSMOS (Continuous Observation of Smoking Subjects), Prospective Cohort, Age: 50-84 years M/W heavy smokers	178/ 4336 5.7 years	Screening examinations	FFQ	Incidence, lung cancer	59.82 vs 1.68 g/1000 kcal/day	0.71 (0.46-1.11) Ptrend:0.06	Age, sex, energy intake, smoking duration, average daily cigarettes consumption, years of cessation, asbestos exposure, fruits and vegetables, fish, red meat, olive oil, tea and wine intake	Distribution of person-years by exposure category; g/1000 kcal was rescaled
Takata, 2013 LUN26860 China	Shanghai Men's Health Study, Prospective Cohort, Age: 40-74 years, M	359/ 61 092 5.5 years	Biennial home visits (diagnosis verified by medical chart review), record linkage to Cancer Registry and Vital Statistics Registry	Validated FFQ	Incidence, lung cancer	27 vs 0 g/day	0.72 (0.53-1.00) Ptrend:0.07	Age, BMI, tea consumption, total caloric intake, vegetable intake, current smoking status, education, family history of lung cancer, history of chronic bronchitis, number of cigarettes	Distribution of person-years by exposure category

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Missing data derived for analyses
								smoked per day, years of smoking	
Büchner, 2010b LUN20360 Denmark,France ,Germany,Greec e,Italy,Netherlan ds,Norway,Spai n,Sweden,U.K.	EPIC, Prospective Cohort, Age: 25-70 years, M/W	1830/ 478 535 8.7 years	Cancer registries, health insurance records, pathology rec & active follow up	FFQ, dietary questionnaires, food record	Incidence, lung cancer	Per 25 g/day	0.99 (0.96-1.02)	Age, centre, sex, smoking status, smoking duration, lifetime and baseline smoking intensity, time since quitting, energy intake, vegetable intake, weight, height, alcohol consumption, physical activity, school level	.
					Incidence, lung cancer, current smokers	Per 25 g/day	1.01 (0.98-1.03)		
Li, 2010 LUN26872 Japan	OCS, Prospective Cohort, Age: 40-75 years, M/W	445/ 42 470 9 years	Miyagi prefecture cancer registry	FFQ	Incidence, lung cancer, excluded 1st 3yrs of follow-up	Daily vs <2 times/week	0.95 (0.68-1.32)	Age, sex, BMI, black tea consumption, diabetes, energy intake, fish total, gastric ulcer, hypertension, job status, miso soup, alcohol, coffee, dairy products,	Exposure values using standard portion size

Author, Year, WCRF Code, Country	Study 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
								education years, family history cancer, green tea, other fruits, rice, smoking habits, soybean products, tea, time engaging in sports or exercise, total meat, vegetable (total), walking time	
Cutler, 2008 LUN20338 USA	IWHS, Prospective Cohort, Age: 55-69 years, W, postmenopausal women	113/ 34 708 18 years	Linkage to the State Health Registry of Iowa, part of SEER registry	Validated FFQ	Incidence, lung cancer, never smokers	>8 vs <4 servings/week	1.12(0.70-1.76)	Age, BMI, education level, energy intake, multivitamin use, race, level of physical activity, pack years of smoking	Exposure values using standard portion size
		647			Incidence, lung cancer, current smokers		0.73(0.60-0.89)		
Wright, 2008 LUN20306 USA	NIH-AARP Diet and Health, Prospective Cohort, Age: 50-71 years, M/W, Retired	281 288 participants 8 years follow-up 3834 1583 892 141	Annual linkage to state cancer registries and national death index plus	Validated FFQ	Incidence, lung cancer All men Men current smokers Men former smokers Men never smokers	1.35 vs 0.04 servings/1000 kcal/day	0.99 (0.89-1.10) Ptrend:0.68 0.99 (0.84-1.18) Ptrend:0.68 1.00 (0.88-1.15) Ptrend:0.92 0.63 (0.36-1.10) Ptrend:0.09	Age, BMI, energy intake, family history of cancer, race, smoking status, alcohol intake, education, physical activity,	Distribution of person-years by exposure category, mid-points of exposure categories. Exposure values rescales using

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Missing data derived for analyses
		190 793 participants 2201/ 1196 835 170			Incidence, lung cancer All women Women current smokers Women former smokers Women never smokers	1.51 vs 0.05 servings/1000 kcal/day	0.91 (0.79-1.04) Ptrend:0.55 0.84 (0.70-1.02) Ptrend:0.18 1.00 (0.81-1.24) Ptrend:0.57 0.82 (0.50-1.36) Ptrend:0.81	smoking dose, time since quitting smoking	mean energy intake
Iso, 2007 LUN20294 Japan	JACC, Prospective Cohort, Age: 40-79 years, M/W	82 cases men/243 cases women/ 105 500 / 15 years	Population death registries	Validated FFQ	Mortality, lung cancer Men Women	≥5 vs <3 times/week	0.78 (0.64-0.95) 1.02 (0.72-1.44)	Age, area of study	Exposure values using standard portion size
Neuhouser, 2003 LUN00354 USA	CARET, Prospective Cohort, Age: 45-69 years, M/W, Heavy smokers and exposed to asbestos	742 12 years	Primary outcome of the trial. Active follow-up with confirmation by clinical records and pathology reports	FFQ - study-specific	Incidence, lung cancer Intervention arm Placebo arm	≥6.9 vs ≤ 0.4 servings/week	0.84 (0.58-1.21) 0.72 (0.46-1.10)	Age, sex, smoking status, total pack-years of smoking, asbestos exposure, race/ethnicity, and enrollment center	Distribution of person-years and cases by exposure category. Exposure values using standard portion size and midpoints of exposure categories. RRs for intervention and placebo arms were combined
Ozasa, 2001 LUN00725	JACC study, Prospective	98 248 participants	Population death registries	FFQ - study-specific	Mortality, lung cancer	>3-4/week vs ≤1-2/month	1.22 (0.64-2.33)	Age, family history of	Used only in stratified

Author, Year, WCRF Code, Country	Study 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
Japan	Cohort, Age: 40-70 years, M/W	7.7 years/ 77 221			Men former smoker Men current smoker		0.66 (0.47-0.91)	cancer, smoking habits	analysis by smoking (for total Iso, 2007 LUN20294 was used). Exposure values using standard portion size and midpoints. RRs for men and women combined
		73			Mortality, lung cancer, women never smoker	>3-4/week vs ≤1-2/month	1.18 (0.54-2.57)		
Feskanich, 2000 LUN00986 USA	Nurses' Health Study (NHS) Prospective Cohort, Age: 30-55 years, W	519/ 77 283 ~12 years	Confirmation searched by medical records and death certificates	FFQ - study-specific	Incidence, lung cancer, women	>9.0 vs 2.0-3.9 servings/day	0.72 (0.54-0.97)	Age, follow-up cycle, smoking status, years since quitting -past smokers-, cigarettes /day -current smokers-, age start smoking, total energy intake, availability of diet data after baseline	Distribution of person-years by exposure category, mid-points of exposure categories. Exposure values using standard portion size.
	Health Professionals Follow-up Study (HPFS) Prospective Cohort Age: 40-75 years, M	274/ 47 778 ~10 years			Incidence, lung cancer, men	>9.8 vs 2.0-4.4 servings/day	1.12 (0.77-1.61)		
Voorrips, 2000b LUN01162 Netherlands	Netherlands Cohort Study on Diet and Cancer (NLCS), Case Cohort, Age: 55-69	963/ 120 852 3.2 years	Computerized record linkage with all regional cancer registries and with national	FFQ - study-specific	Incidence, lung cancer, men, non-smokers	175 vs 3 g/day	0.80 (0.60-1.10)	Age, sex, educational level, family history of lung cancer, current	

Author, Year, WCRF Code, Country	Study 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		database of pathology reports					smoker, years of smoking, cigarettes/day	

Table 40 Citrus fruit intake and lung cancer risk. Main characteristics of studies excluded 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	Reasons for exclusion
Sakoda, 2011 LUN20351 USA	CARET, Nested Case Control, Age: 45-69 years, M/W	365/ 18 314	Lung cancer is primary endpoint of the trial. Active follow-up confirmed in medical and pathology records	FFQ	Incidence, lung cancer by CHRNA5 SNP rs16969968	>8.5 vs ≤3.5 serving/week	ORGA 1.39 (0.99-1.94) ORAA 1.75 (1.70-2.86)	Age, sex, enrolment year, smoking status, occupational asbestos exposure	Only has gene interactions results, Neuhouser, 2003 LUN00354 was used
Linseisen, 2007 LUN20323 France, Italy, Spain, U.K., Netherlands, Greece, Germany, Sweden, Denmark, Norway	EPIC, Prospective Cohort, Age: 25-70 years, M/W	1126/ 478 590 6.4 years	Cancer registries, health insurance records, pathology rec, active follow up, death certificate	FFQ, dietary questionnaires, food record	Incidence, lung cancer	87.2 vs 24.6 g/day Per 10 g	0.87 (0.70-1.07) 0.99 (0.98-1.00)	Education level, energy intake from fat and nonfat sources, height, smoking status, weight, work - physical activity, ethanol intake, processed and	Use in stratified analysis by smoking. Superseded by Büchner, 2010b LUN20360
		731			Incidence, lung cancer, current smokers	87.2 vs 24.6 g/day Per 10 g	0.76 (0.57-1.01) 0.99 (0.98-1.01)		
		291			Incidence, lung cancer, former smokers	87.2 vs 24.6 g/day Per 10 g	0.97 (0.64-1.47) 0.97 (0.94-1.00)		

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Reasons for exclusion
		98			Incidence, lung cancer, never smokers	87.2 vs 24.6 g/day Per 10 g	1.06 (0.56-2.00) 1.01 (0.97-1.05)	red meat, smoking duration	
Speizer, 1999 LUN01255 USA	NHS, Prospective Cohort, Age: 30-55 years, W, No specific group	399/ 118 351 12 years	Active follow-up, cases confirmed with medical and pathology records	FFQ - study-specific	Incidence, lung cancer	>1 vs never times/day	0.70	Age, smoking habits	Superseded by Feskanich, 2000 LUN00986
Fraser, 1991 LUN03076 USA	Adventist Health Study, Prospective Cohort, Age: 25- years, M/W, Vegetarians/Healthy Diet	55/ 34 198 6 years	Annual mail, confirmation through medical records, SEER registry where available	FFQ - study-specific	Incidence, lung cancer	≥3times/week vs <3 times/week times/week	0.64 (0.35-1.17)	Age, sex, smoking habits	Only 2 categories Used only in highest versus lowest analysis.
Kromhout, 1987 LUN03765 Netherlands	Zutphen Study, Prospective Cohort, Age: 40-59 years, M	878 12.5 years	Data from Central Bureau of Statistics, diagnosis verified through cancer registry, hospital discharge or general practitioner	Dietary history questionnaire	Mortality, lung cancer	Quartile 4 vs quartile 1	0.50 (0.24-1.02)	Age	Exposure not quantified Used only in highest versus lowest analysis.
Stahelin, 1986 LUN03946	Basel Study , Nested Case	38/ 4 224	Active follow-up, cause of	Not available	Mortality, lung cancer	3 times weekly vs <3	0.63 (0.30-1.33)	Age	Only 2 categories 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	Reasons for exclusion
Switzerland	Control, Age: 20-79 years, M	13 years	death coded by researchers			times/week			only in highest versus lowest analysis.

Figure 47 RR estimates of lung cancer by levels of citrus fruit intake

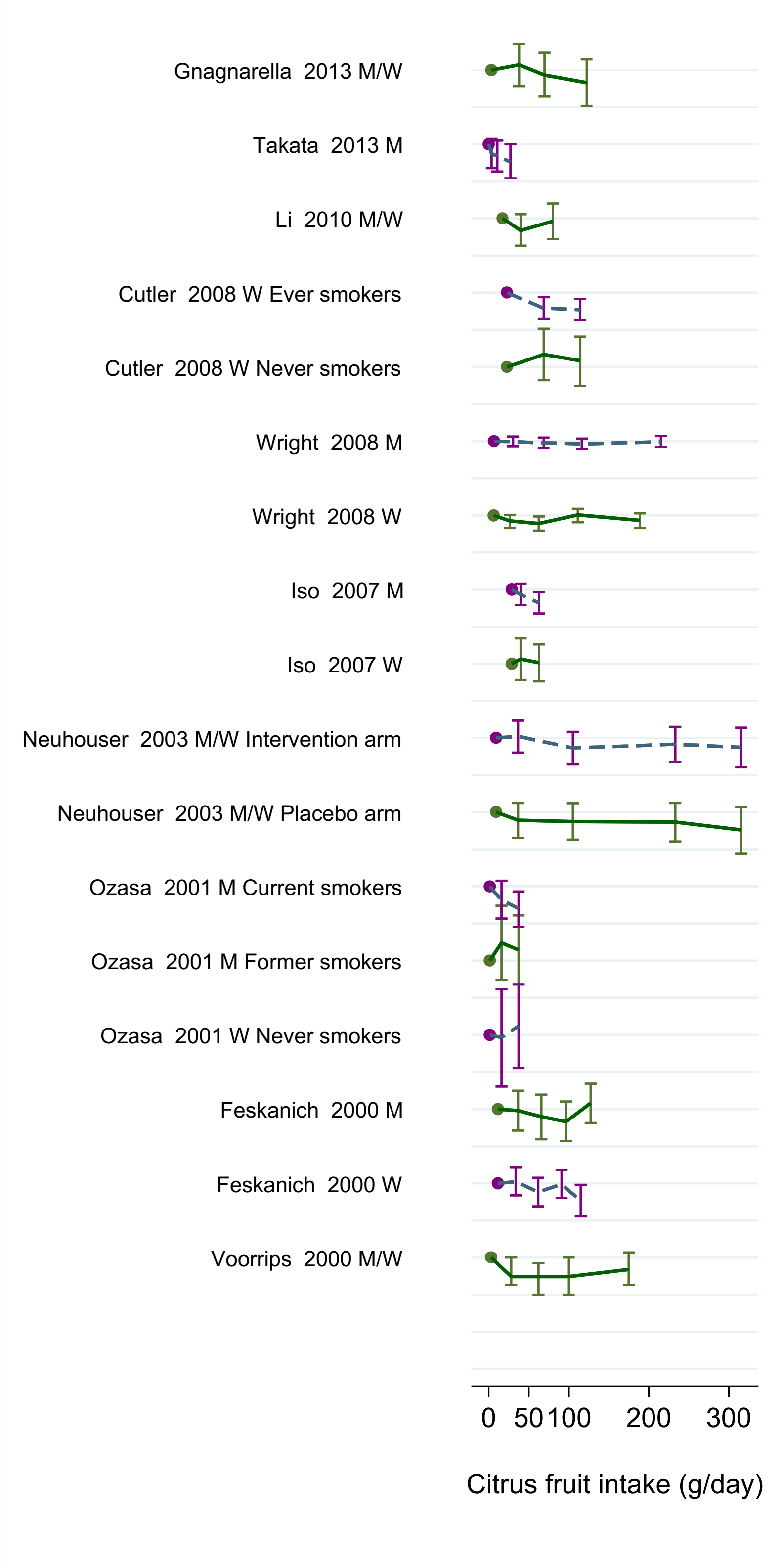


Figure 48 RR (95% CI) of lung cancer for the highest compared to the lowest level of citrus fruit intake

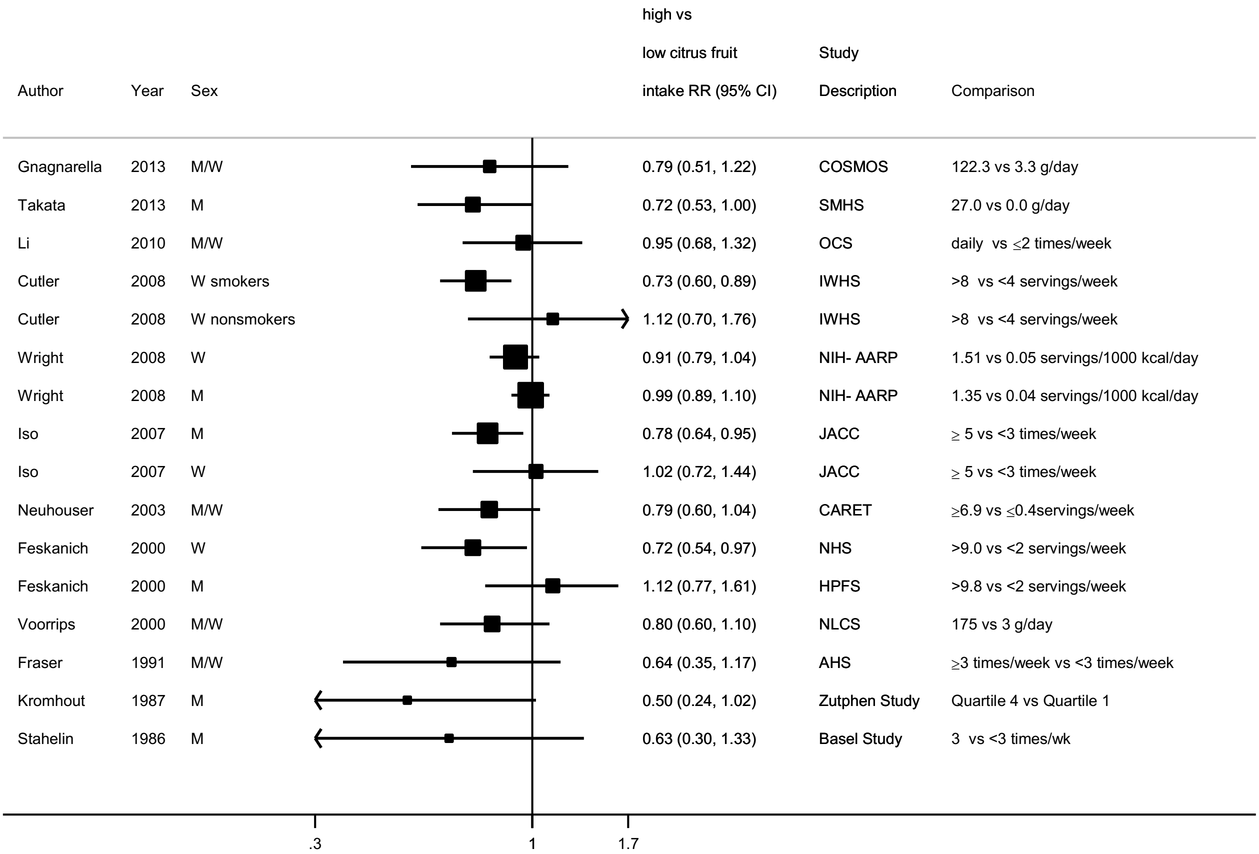


Figure 49 RR (95% CI) of lung cancer for 100g/day increase of citrus fruit intake

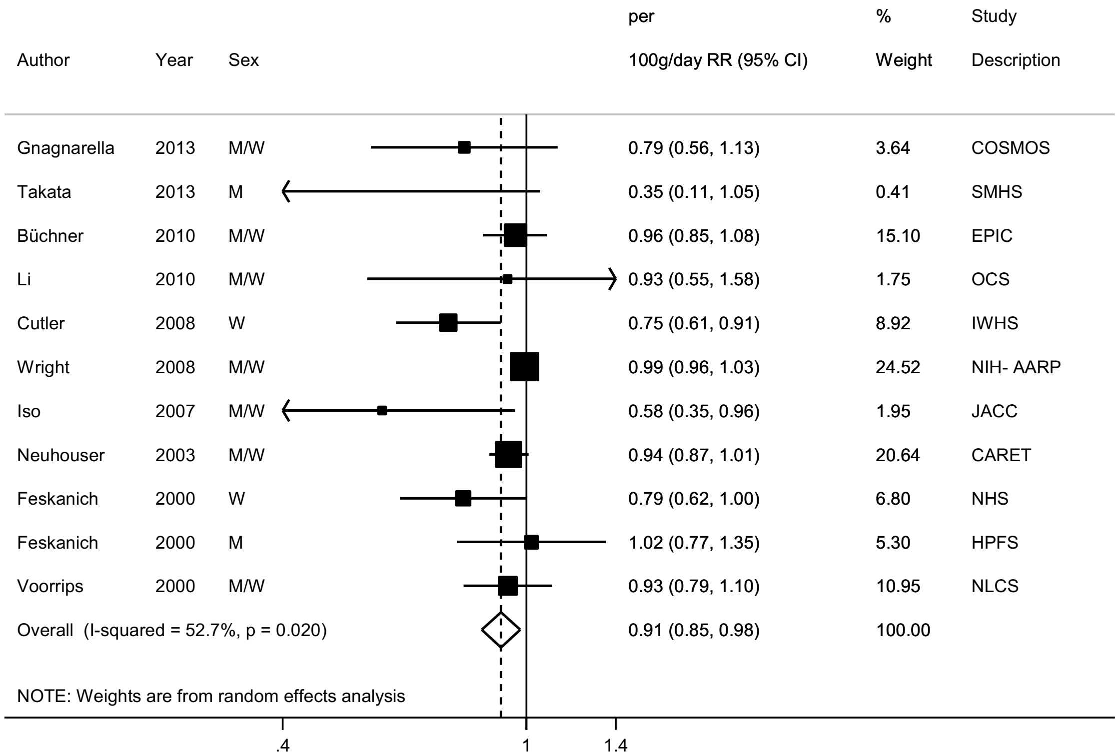


Figure 50 RR (95% CI) of lung cancer for 100g/day increase of citrus fruit intake, excluding study not adjusted for smoking status

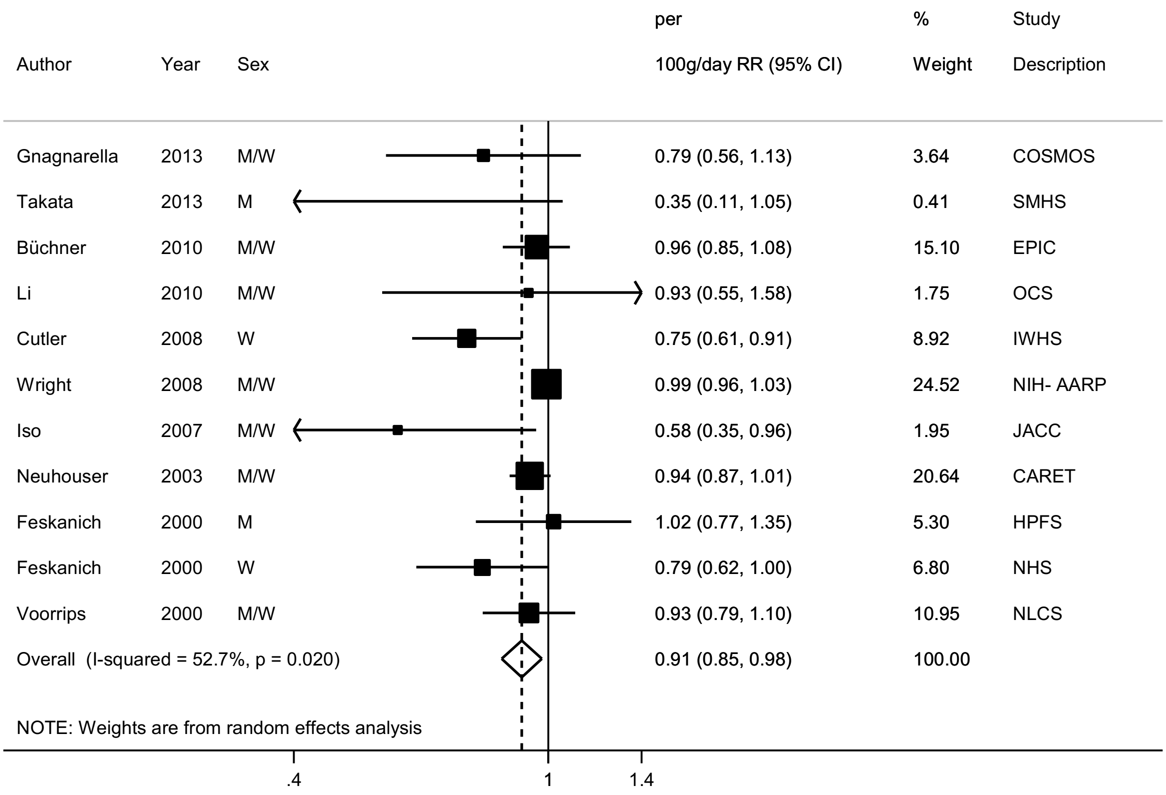
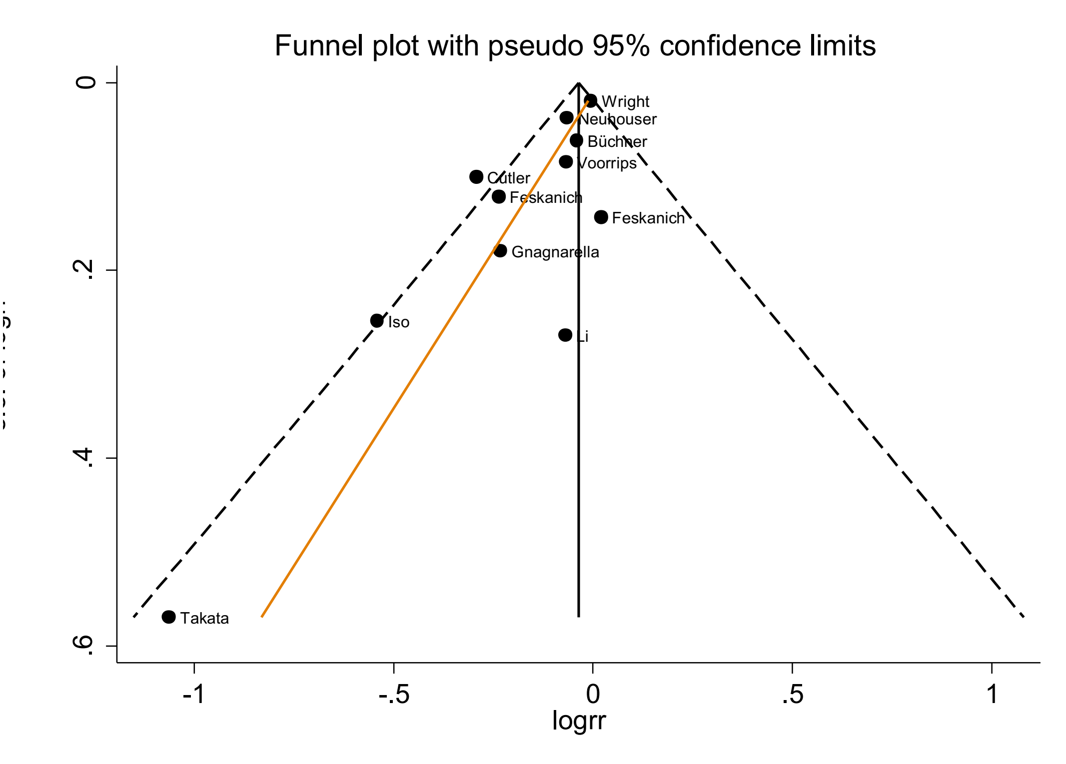


Figure 51 Funnel plot of studies included in the dose response meta-analysis of citrus fruit intake and lung cancer



Egger's test $p < 0.01$

Figure 52 RR (95% CI) of lung cancer for 100g/day increase of citrus fruit intake by sex

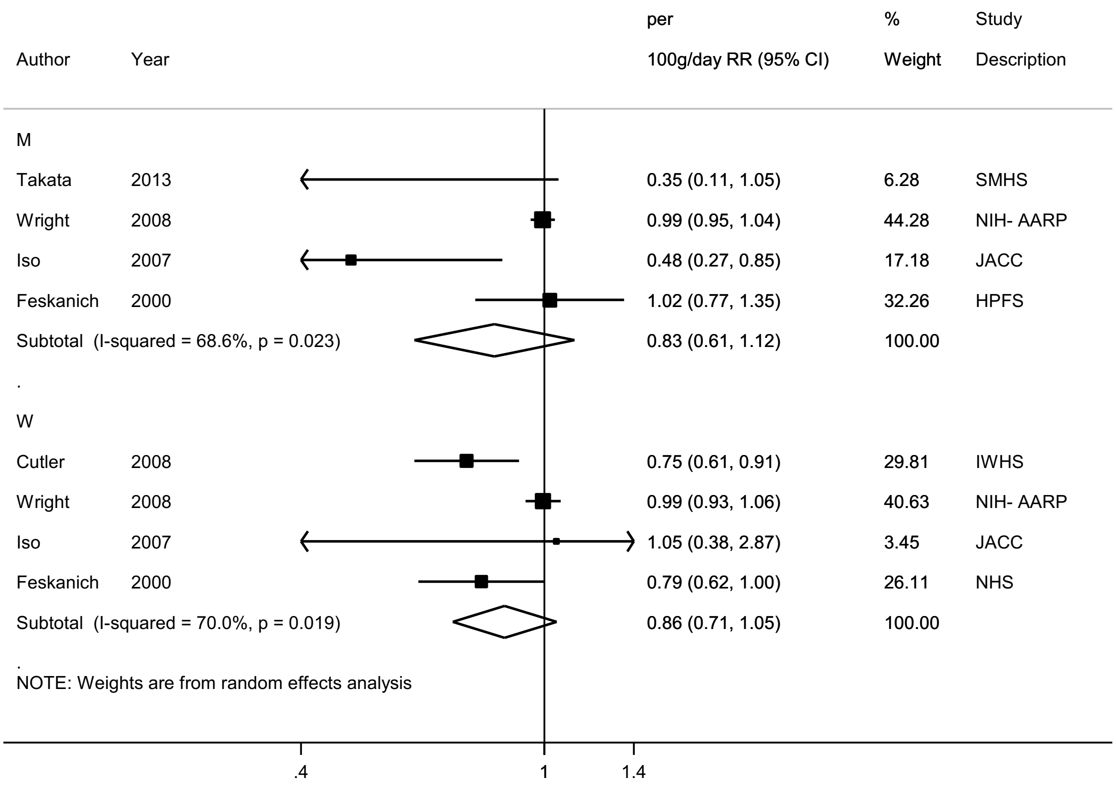


Figure 53 RR (95% CI) of lung cancer for 100g/day increase of citrus fruit intake by cancer outcome

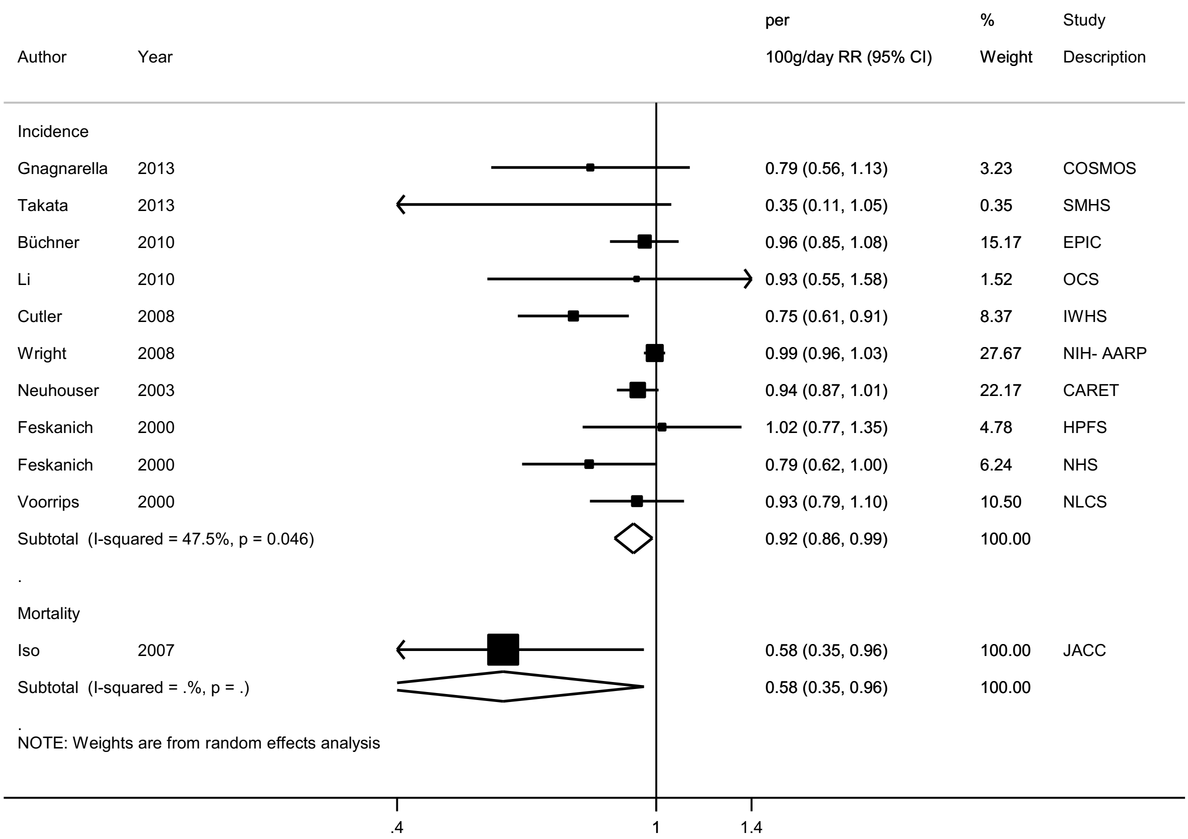


Figure 54 RR (95% CI) of lung cancer for 100g/day increase of citrus fruit intake by smoking status

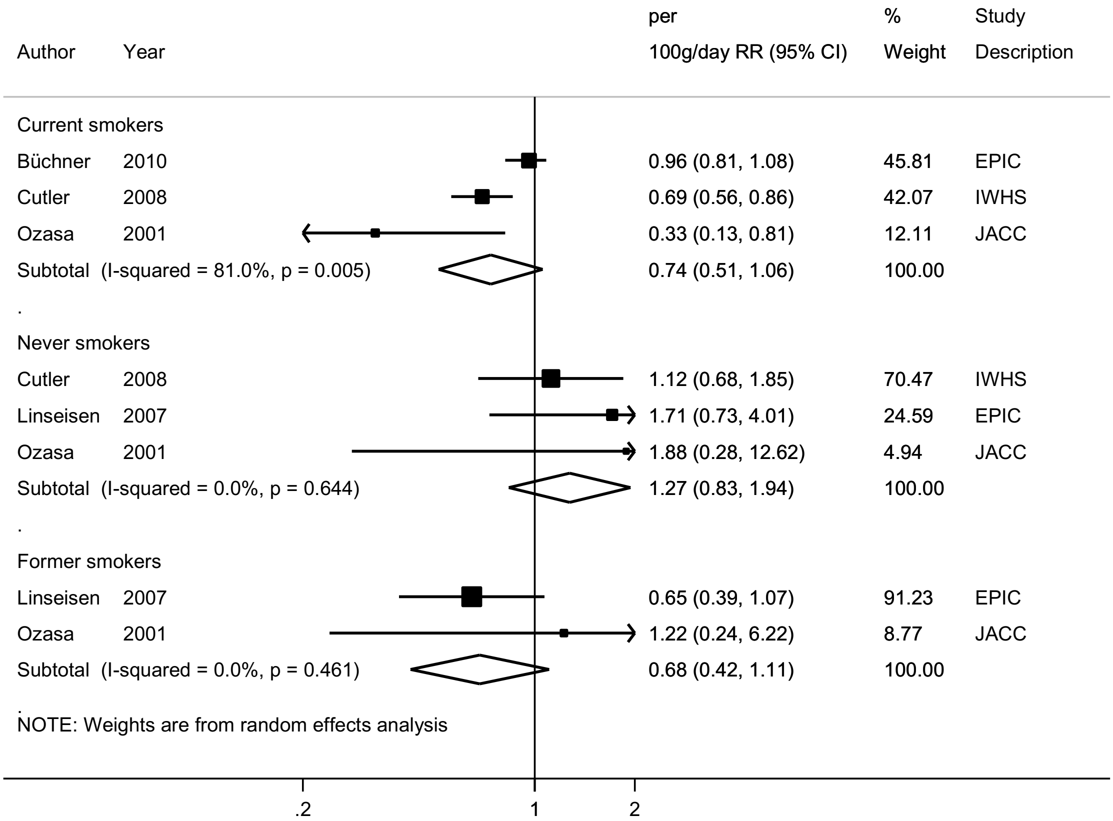


Figure 55 RR (95% CI) of lung cancer for the highest compared to the lowest level of citrus fruit intake by smoking status

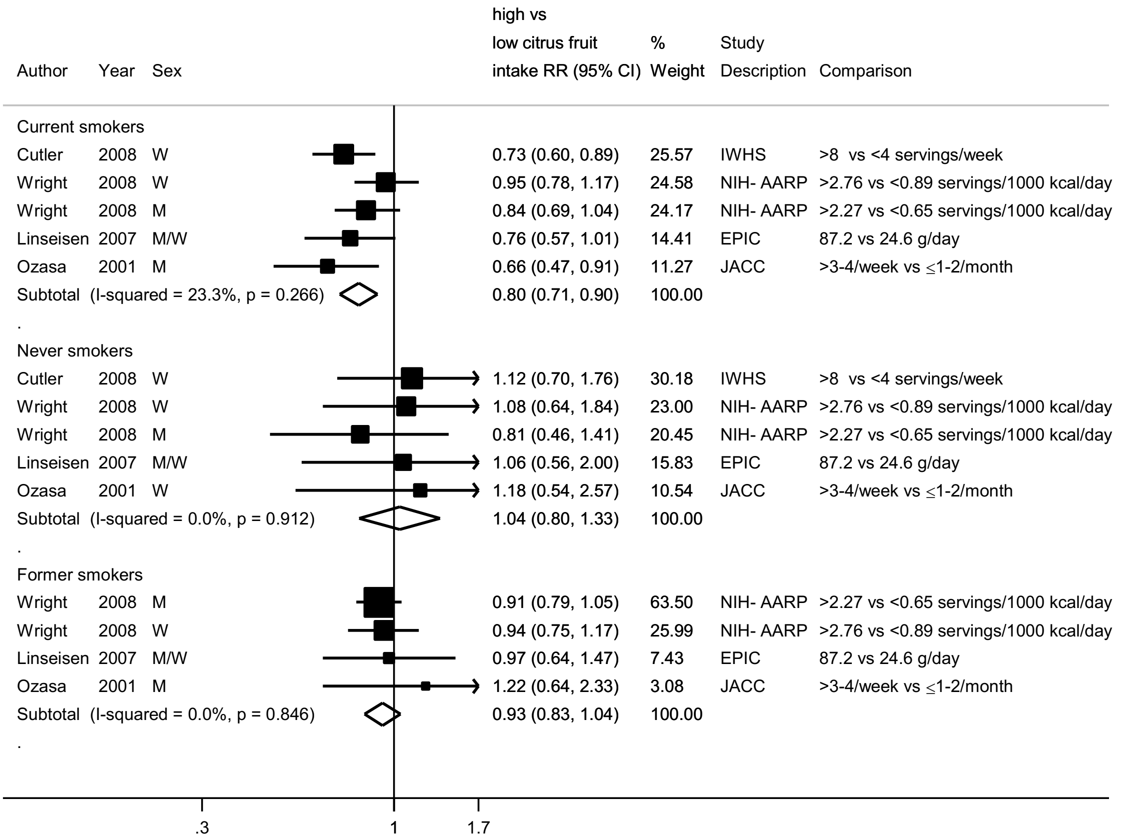


Figure 56 RR (95% CI) of lung cancer for 100g/day increase of citrus fruit intake by geographic location

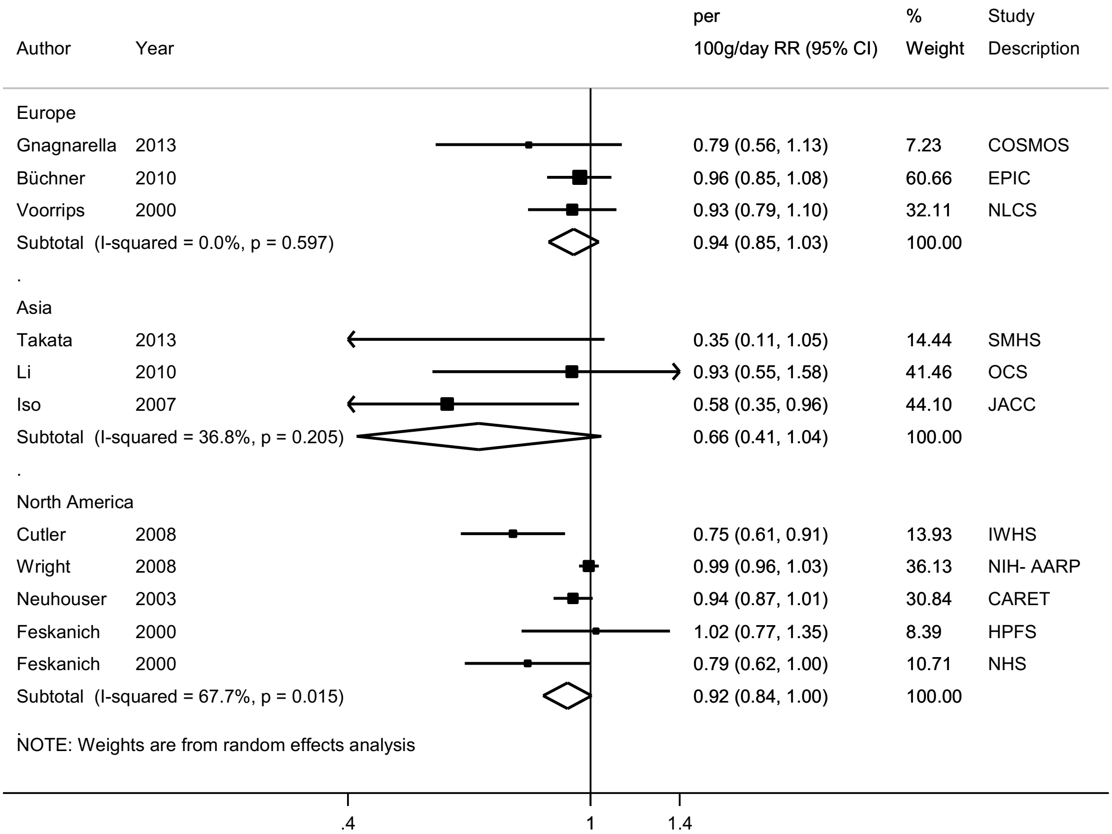
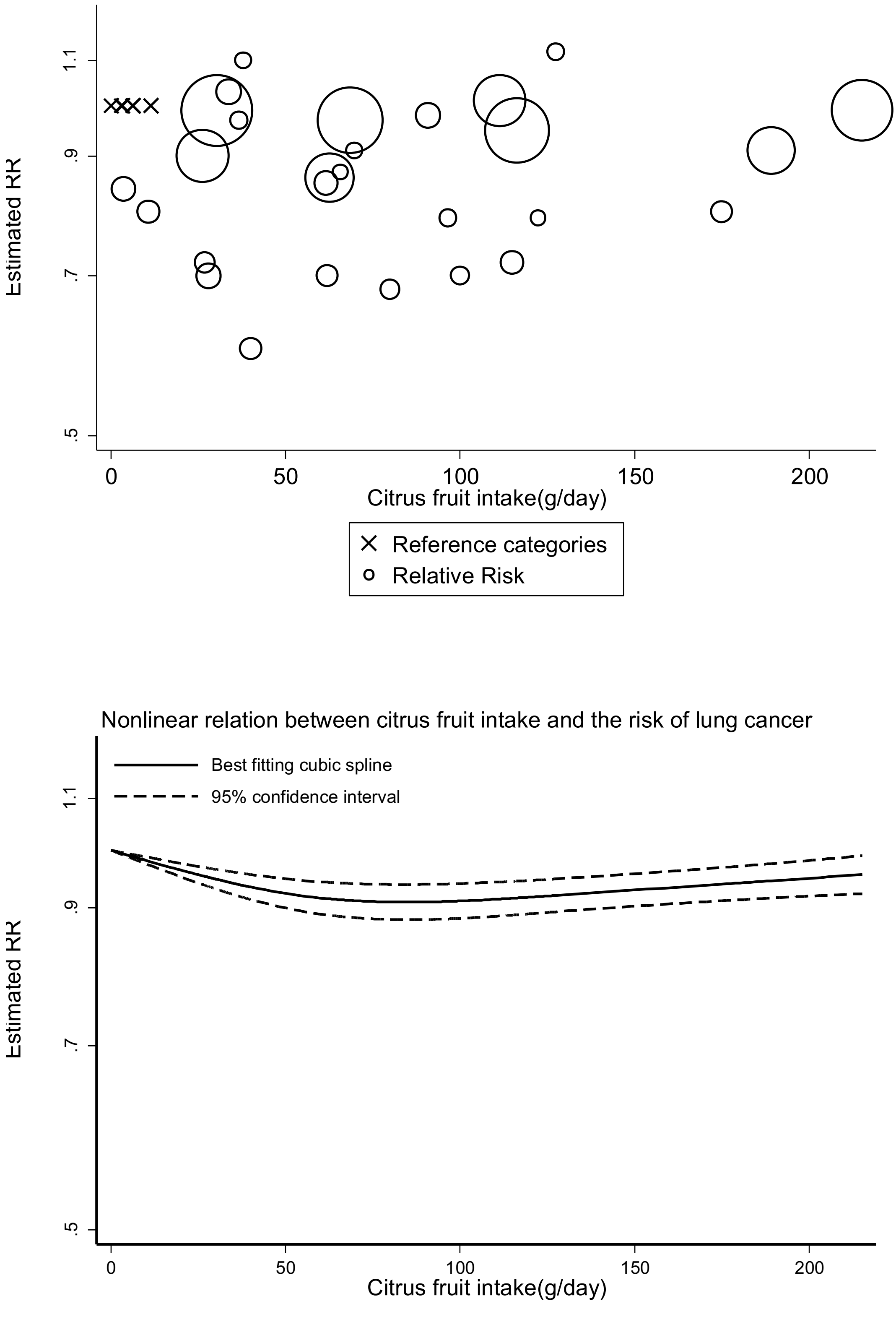


Figure 57 Relative risk of lung cancer and citrus fruit intake estimated using non-linear models

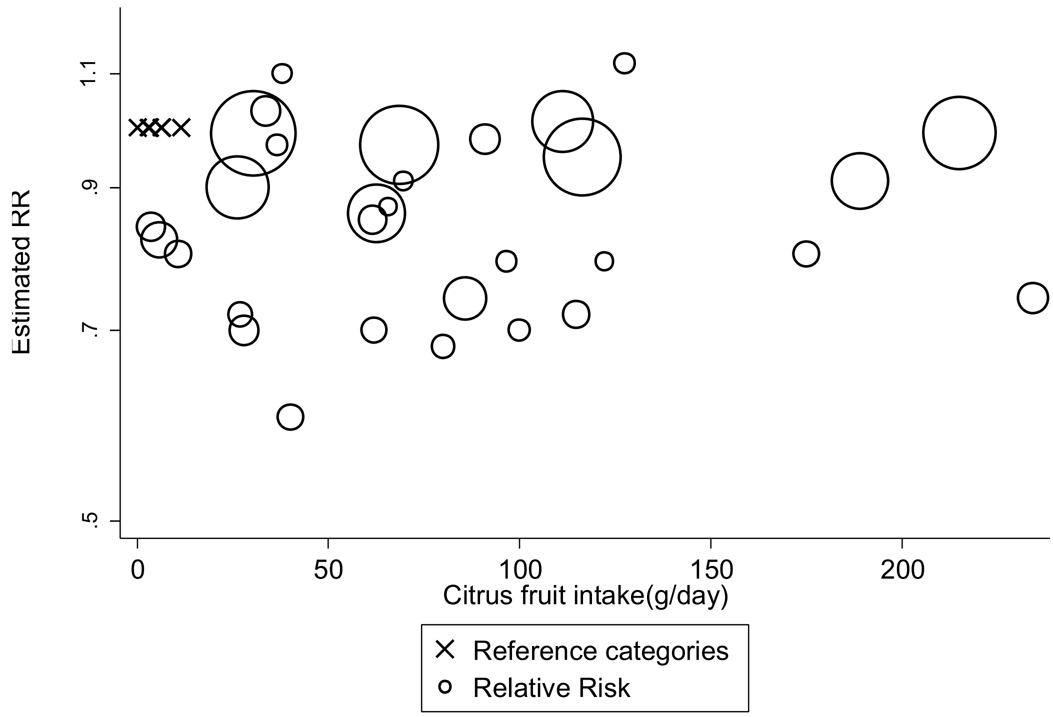


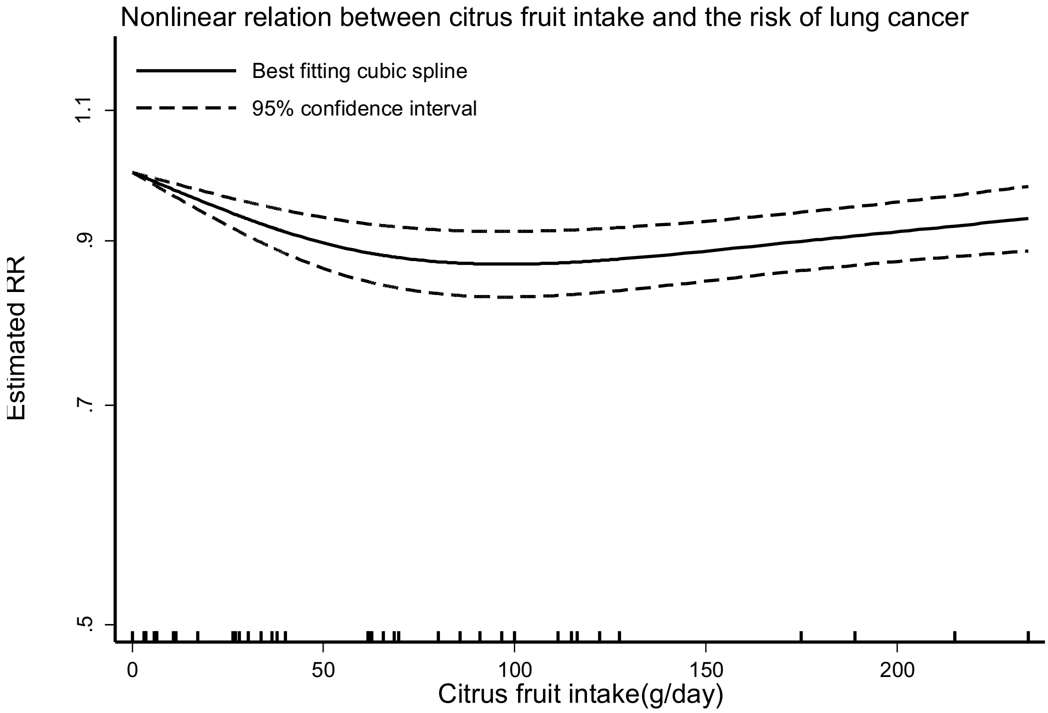
$p < 0.01$

Table 41 Table with citrus fruit intake values and corresponding RRs (95% CIs) for non-linear analysis of citrus fruit intake and lung cancer

Citrus fruit intake (g/day)	RR (95%CI)
0	1
30	0.95 (0.94-0.96)
70	0.92(0.88-0.94)
175	0.94 (0.91-0.97)
215	0.96(0.93-0.99)

Figure 58 Relative risk of lung cancer and citrus fruit intake estimated using non-linear models including the Pooling Project





p < 0.01

Table 42 Table with citrus fruit intake values and corresponding RRs (95% CIs) for non-linear analysis of citrus fruit intake and lung cancer

Citrus fruit intake (g/day)	RR (95%CI)
0	1
30	0.93 (0.91-0.96)
70	0.88(0.84-0.92)
175	0.89 (0.86-0.94)
215	0.94(0.89-0.98)

2.3 Legumes

Cohort studies

Summary

Main results:
Eight studies (8926 cases) out of 11 studies (10 publications) were included in the dose-response meta-analysis. No significant association and no heterogeneity were observed.
Only one study (Wright, 2008) explored the association of legumes intake and lung cancer by smoking status. A borderline significant (inverse) association was observed in former smokers, but there was no significant association in current and never smokers. All studies had incidence as outcome.
There was evidence of publication or small study bias (p=0.04) and the funnel plots indicates that small studies on the right side of the funnel plot are missing.

Sensitivity analysis:
The summary RRs ranged from 0.99(95% CI=0.97-1.01) when Neuhouser, 2003 was omitted to 1.03 (95% CI=0.97-1.11) when Wright, 2008 was omitted.
There was evidence of non-linear dose-response for lung cancer and legumes intake, (p < 0.01). However, the curve is flat in most of the intake range. Only two studies (Wright, 2008; Neuhouser, 2003) reported intakes higher than 80g/day.

Study quality:
Cancer outcome was confirmed using cancer registries in most studies.
All studies used FFQ. Only studies that reported on total legumes intake were included.
Repeated dietary measurements were used in the NHS and the HPFS (Feskanich, 2000).
All studies included in the dose-response analysis were adjusted at least for age, sex, and smoking status, intensity and duration of smoking.

Pooling project of cohort studies:
The Pooling Project showed a not significant association between beans inake and lung cancer risk.

Table 43 Legumes intake and lung cancer risk. Number of studies in the CUP SLR

	Number
Studies identified	11 (10 publications)
Studies included in forest plot of highest compared with lowest exposure	11
Studies included in dose-response meta-analysis	8
Studies included in non-linear dose-response meta-analysis	7

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

Table 44 Legumes intake and lung cancer risk. Summary of the dose-response meta-analysis in the 2005 SLR and CUP.

	2005 SLR	CUP
Increment unit used	1 serving/day	50 g/day
All studies		
Studies (n)	2	8
Cases (total number)	543	8926
RR (95%CI)	1.15(0.79-1.69)	1.00 (0.98-1.02)
Heterogeneity (I^2, p-value)	0%	0%, 0.64
P value Egger test		0.04

Stratified and sensitivity analysis (no analyses conducted in the 2005 SLR)			
Sex	**Men**	**Women**	
Studies (n)	3	3	
RR (95%CI)	0.98 (0.96-1.01)	1.01 (0.98-1.05)	
Heterogeneity (I^2, p-value)	0% , 0.92	0%, 0.52	
Geographic location	**Asia**	**Europe**	**North America**
Studies (n)	2	2	4
RR (95%CI)	0.97 (0.80- 1.17)	0.85 (0.63-1.14)	1.01 (0.97-1.05)
Heterogeneity (I^2, p-value)	0% , 0.71	0% , 0.57	13.7%, 0.32

Table 45 Legumes intake and lung cancer risk. Results of meta-analyses and pooled analyses of prospective studies published after the 2005 SLR.

Author, Year	Number of cohort studies	Total number of cases	Studies country, area	Outcome	Comparison	RR (95%CI)	P trend	Heterogeneity (I^2, p value)
Pooled-analyses								
Smith-Warner, 2003	6	2630	ATBC, CNBSS, HPFS, IWHS, NLCS, NHS USA, Europe	Lung cancer incidence and mortality	Beans ≥1 vs 0 serving/week	1.11 (0.87-1.43)	0.67	0.25
	6	2173	ATBC, CNBSS, HPFS, IWHS, NYCS, NHS USA, Europe		Peas, lima beans ≥1 vs 0 serving/week	1.03 (0.89-1.18)	0.74	0.42
	7	2867	AHS, CNBSS, HPFS, IWHS, NYCS, NLCS, NHS USA, Europe		Mature beans or lentils	1.01 (0.85-1.19)	0.89	0.54

Table 46 Legumes intake and lung cancer risk. Main characteristics of studies 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	Missing data derived for analyses
Gnagnarella, 2013a LUN26858 Italy	COSMOS (Continuous Observation of Smoking Subjects), Prospective Cohort, Age: 50-84 years, M/W heavy smokers	178/ 4336 5.7 years	Screening examinations	FFQ	Incidence, lung cancer	13.65 vs 1.23 g/1000 kcal/day	0.98 (0.66-1.45) Ptrend:0.96	Age, sex, energy intake, smoking duration, average daily cigarettes consumption, years of cessation, asbestos exposure, fruits and vegetables, fish, red meat, olive oil, tea and wine intake	Distribution of person-years by exposure category
Takata, 2013 LUN26860 China	Shanghai Men's Health Study, Prospective Cohort, Age: 40-74 years, M	359/ 61 092 5.50 years	Biennial home visits, linkage to cancer registry and death registry	Validated FFQ	Incidence, lung cancer	72.3 vs 12.5 g/day	0.97 (0.71-1.33) Ptrend:0.98	Age, BMI, fruit intake, tea consumption, total caloric intake, current smoking status, education, family history of lung cancer, history of chronic	Distribution of person-years by exposure category

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Missing data derived for analyses
								bronchitis, number of cigarettes smoked per day, years of smoking	
Takata, 2012 LUN26859 China	SWHS, Prospective Cohort, Age: 40-70 years, W, never smokers	428/ 71 267 11.2	Shanghai cancer registry and the Shanghai vital statistics registry	FFQ	Incidence, lung cancer	56 vs 9 g/d	0.98 (0.74-1.30) Ptrend:0.65	Age, BMI, income, occupation, total caloric intake, history of asthma, passive smoking	Distribution of person-years by exposure category
Wright, 2008 LUN20306 USA	NIH-AARP Diet and Health, Prospective Cohort, Age: 50-71 years, M/W, Retired	3834/ 472 081 8.0 years	Annual linkage to state cancer registries and national death index plus	Validated FFQ	Incidence, lung cancer, men	0.69 vs 0.08 servings/1000 kcal/day	0.92 (0.83-1.02) Ptrend:0.16	Age, BMI, energy intake, family history of cancer, race, alcohol intake, education, past smoking dose, physical activity, time since quitting smoking	Distribution of person-years by exposure category, mid-points of exposure categories. Exposure values using Exposure values using mean energy intake
		2201			Incidence, lung cancer, women	0.81 vs 0.09 servings/1000 kcal/day	1.07 (0.94-1.22) Ptrend:0.65		
		856			Incidence, lung cancer, men former smokers	0.69 vs 0.08 servings/1000 kcal/day	0.86 (0.75-0.99) Ptrend:0.03		
		657			Incidence, lung cancer, men current smokers	0.69 vs 0.08 servings/1000 kcal/day	1.00 (0.85-1.17) Ptrend:0.79		

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
		350			Incidence, lung cancer, women former smokers	0.81 vs 0.09 servings/1000 kcal/day	1.14 (0.93-1.41) Ptrend:0.26		
		67			Incidence, lung cancer, women never smokers	0.81 vs 0.09 servings/1000 kcal/day	0.83 (0.51-1.35) Ptrend:0.59		
		64			Incidence, lung cancer, men never smokers	0.69 vs 0.08 servings/1000 kcal/day	0.87 (0.53-1.43) Ptrend:0.85		
		507			Incidence, lung cancer, women current smokers	0.81 vs 0.09 servings/1000 kcal/day	1.05 (0.88-1.26) Ptrend:0.87		
Neuhouser, 2003 LUN00354 USA	CARET, Prospective Cohort, Age: 45-69 years, M/W	742 12 years	Primary outcome of the trial. Active follow-up with confirmation by clinical records and pathology reports	FFQ - study-specific	Incidence, lung cancer, intervention	≥6.2 vs ≤1.8 servings/week	1.10 (0.81-1.50)	Age, sex, smoking status, total pack-years of smoking, asbestos exposure, race/ethnicity, and enrollment center	Distribution of person-years and cases by exposure category Mid-points of exposure categories. Exposure values using standard portion size. RRs for intervention and placebo
					Incidence, lung cancer, placebo		1.00 (0.70-1.41)		

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Missing data derived for analyses
									combined
Feskanich, 2000 LUN00986 USA	Nurses' Health Study and Health Professionals Follow-up Study Prospective Cohorts, Age: 30-75 years, M/W	274/ 125 061 12.0 years	Active follow-up, cases confirmed with medical and pathology records	FFQ - study-specific	Incidence, lung cancer, women	>2 vs <0.49 servings/week	1.07 (0.77-1.49)	Age, follow-up cycle, smoking status, years since quitting - past smokers-, cigarettes /day - current smokers-, age start smoking, total energy intake, availability of diet data after baseline	Distribution of person-years by exposure category, mid-points of exposure categories. Exposure values using standard portion size.
		269			Incidence, lung cancer, men	>3.1 vs <0.69 servings/week	1.21 (0.81-1.81)		
Voorrips, 2000b LUN01162 Netherlands	Netherlands Cohort Study on Diet and Cancer (NLCS), Case Cohort, Age: 55-69 years, M/W	910/ 120 852 3.20 years	Regional cancer registries and computerized national database of pathology report (PALGA)	FFQ - study-specific	Incidence, lung cancer	60 vs 10 g/day	0.80 (0.60-1.20)	Age, sex, educational level, family history of lung cancer, current smoker, years of smoking, cigarettes/day	

Table 47 Legumes intake and lung cancer risk. Main characteristics of studies excluded 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	Reasons for exclusion
Khan, 2004 LUN00068 Japan	Japan, Hokkaido Cohort Study, Prospective Cohort, Age: 40- years, M/W	3158 14.8 years	Annual follow-up survey, cause of death classified by researchers	Dietary history questionnaire	Mortality, lung cancer, men	Several times/week vs never or several times/year	0.60 (0.30-1.30)	Age, smoking habits	Used only in highest versus lowest, only two categories
Miller, 2002 LUN00442 Europe	EPIC, Prospective Cohort, Age: 25-70 years, M/W	482 924 4 years	Cancer registries, Health insurance records, active follow confirmation by pathology records or death certificate	FFQ - study-specific	Incidence, lung cancer	Quintile 5 vs Quintile 1	0.71 (0.51-1.00)	Age, anthropometry, body weight, smoking habits	Used only in highest versus lowest No quantile range
Knekt, 1999 LUN01416 Finland	Finnish Mobile Clinic Health Examination Survey, Prospective Cohort, Age: 20-69 years, M	138/4545 25 years	Cancer registry	FFQ - study-specific	Incidence, lung cancer	8 vs 4 g/day	0.88 (0.58-1.34)	Age, smoking habits	Used only in highest versus lowest

Figure 59 RR estimates of lung cancer by levels of legumes intake

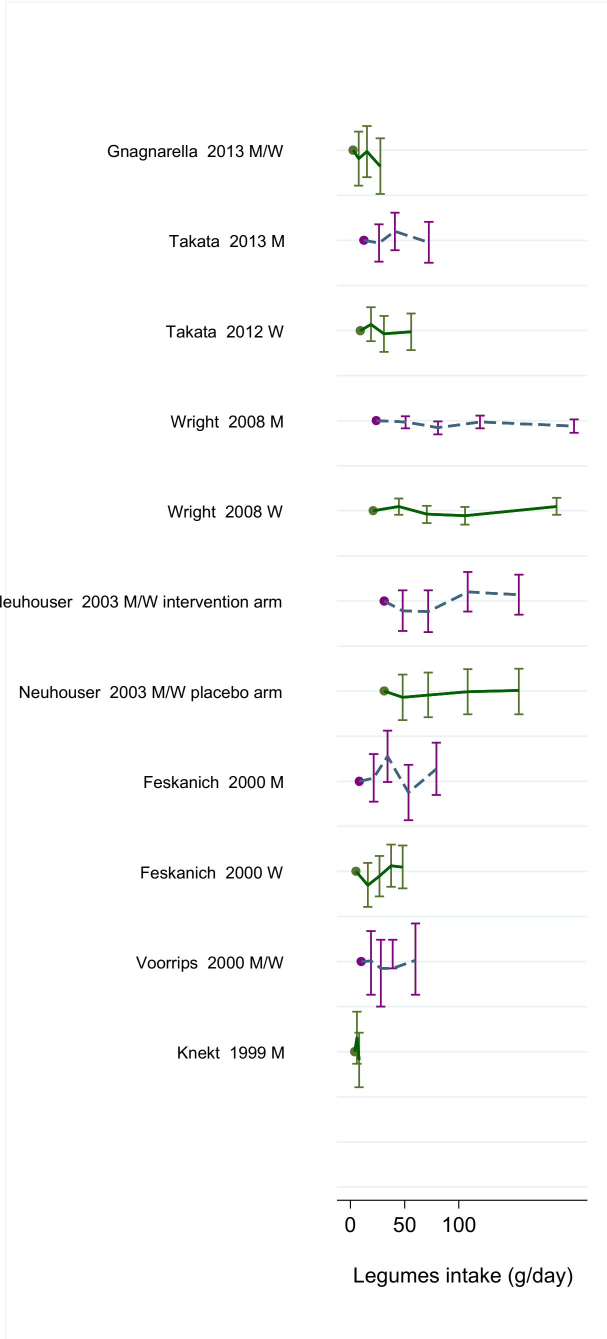


Figure 60 RR (95% CI) of lung cancer for the highest compared with the lowest level of legumes intake

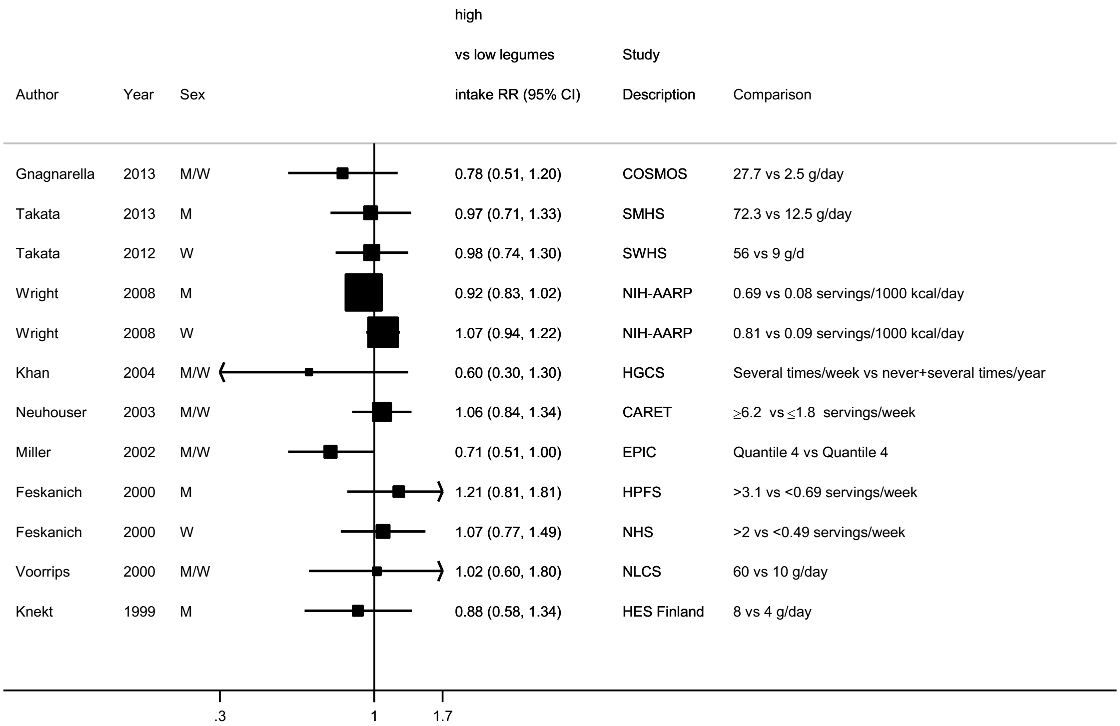


Figure 61 RR (95% CI) of lung cancer for 50 g/day increase of legumes intake

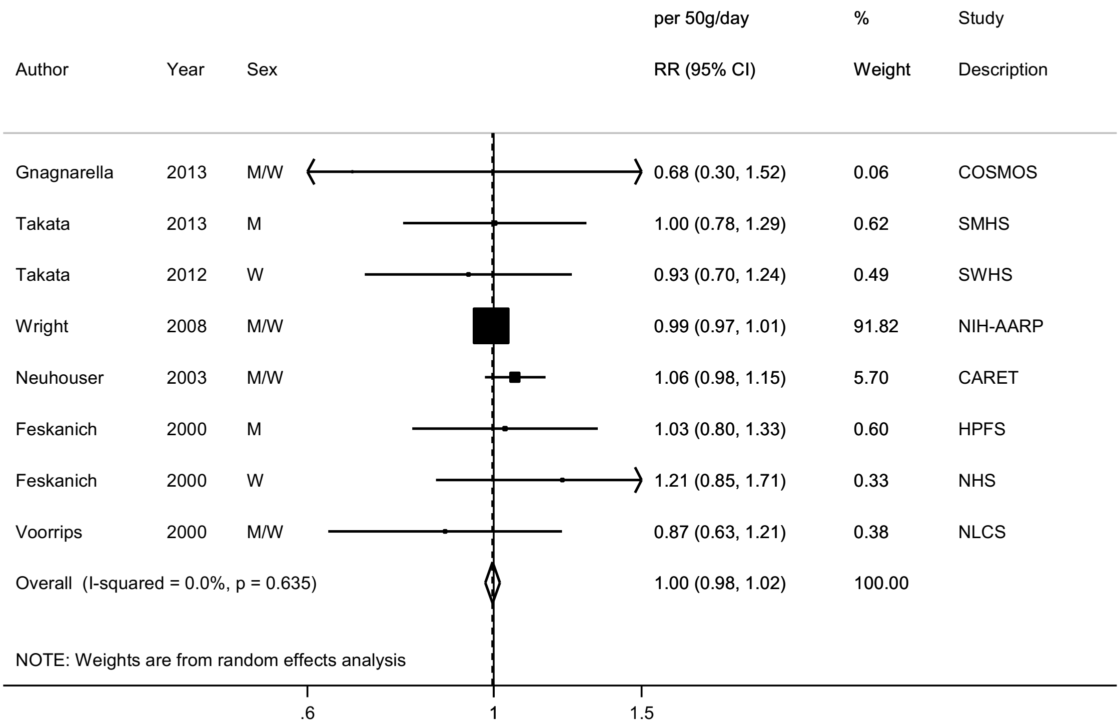
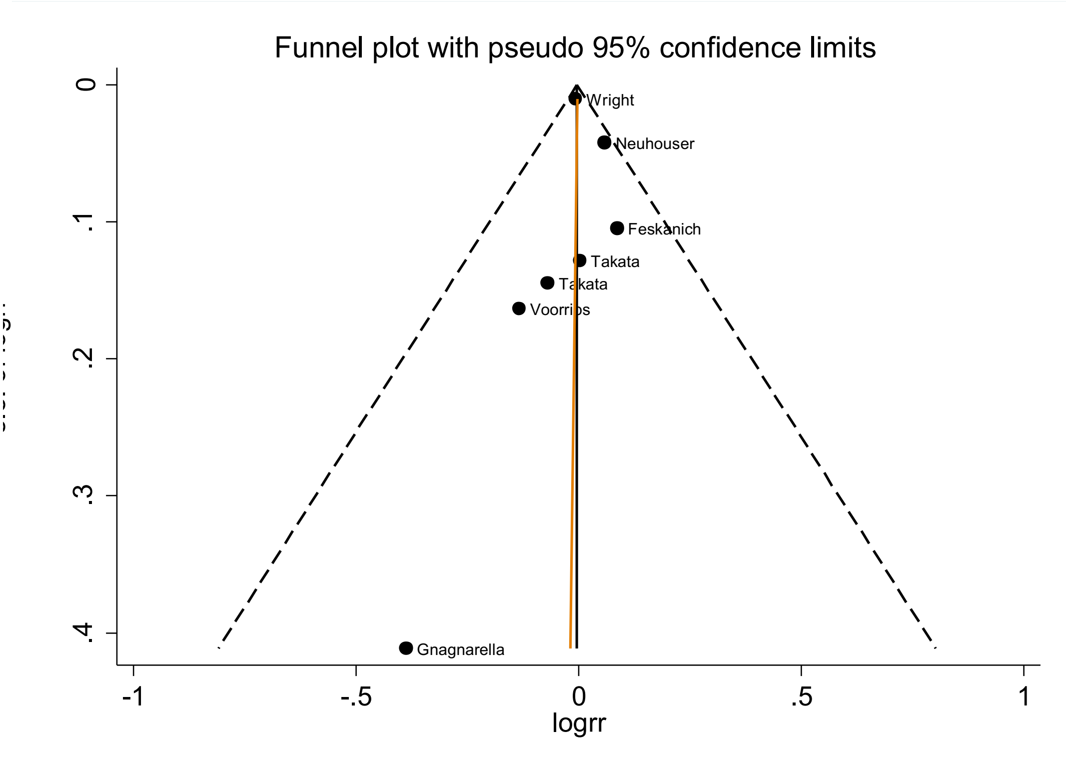


Figure 62 Funnel plot of studies included in the dose response meta-analysis of legumes intake and lung cancer



Egger's test p=0.04

Figure 63 RR (95% CI) of lung cancer for 50g/day increase of legumes intake by sex

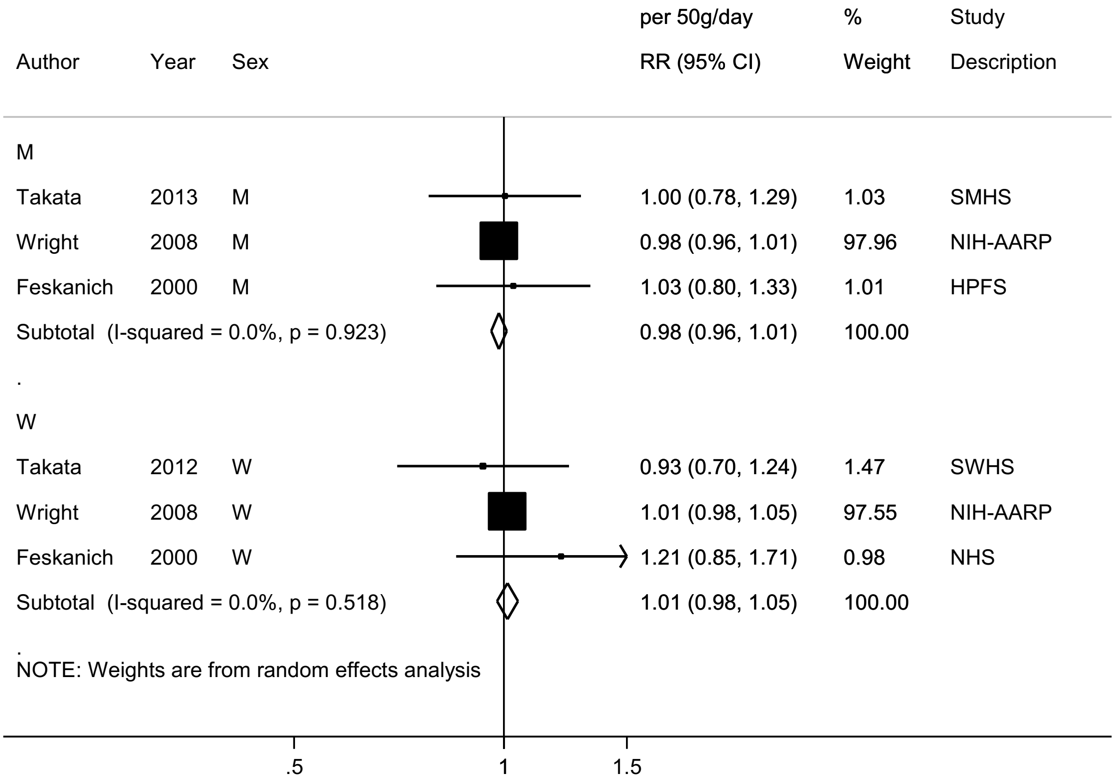


Figure 64 RR (95% CI) of lung cancer for 50g/day increase of legumes intake by geographic location

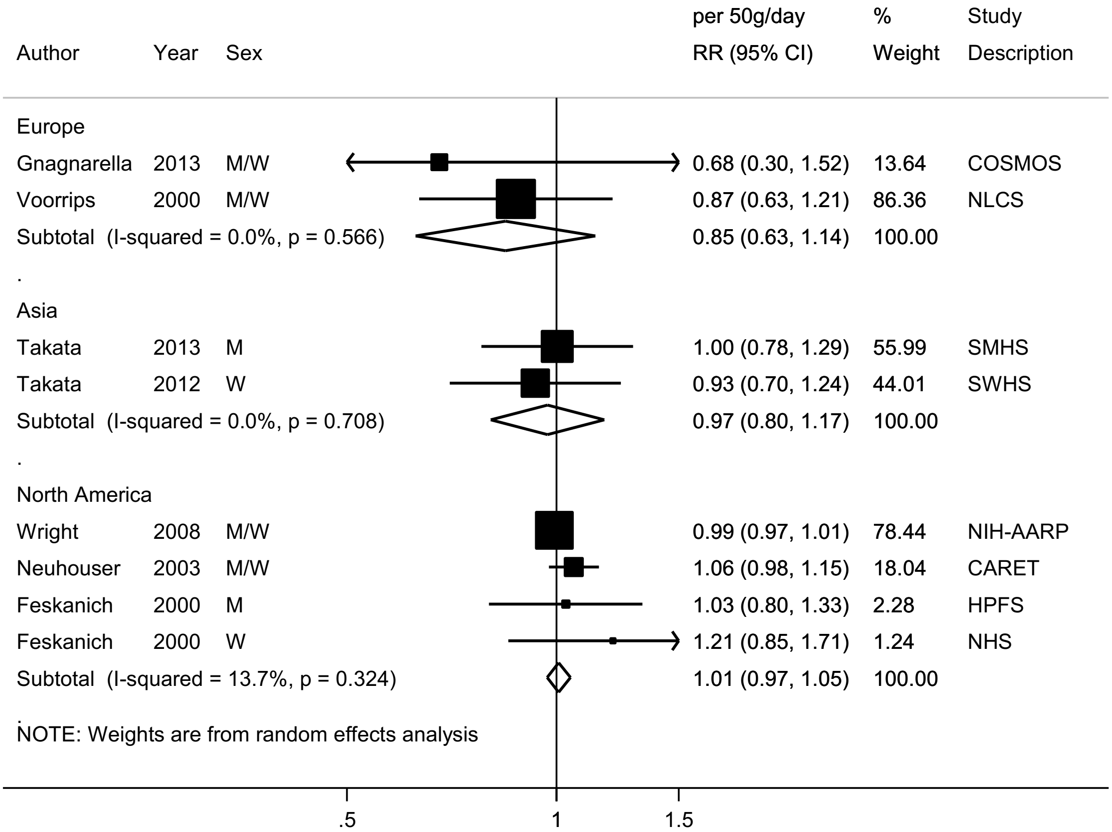
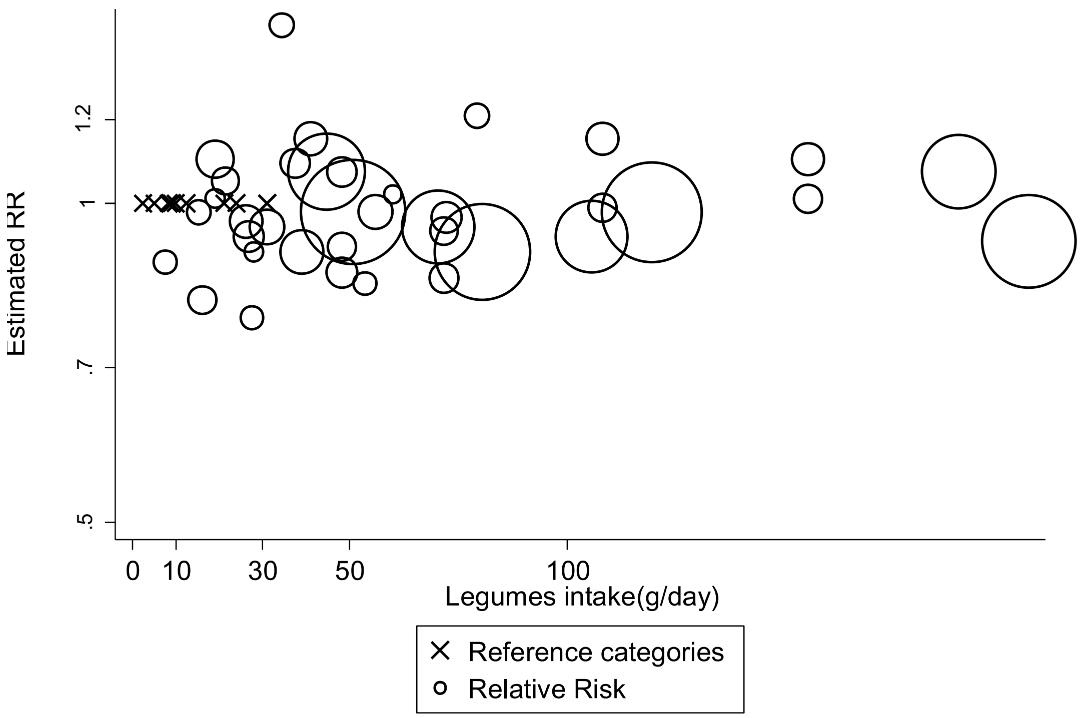
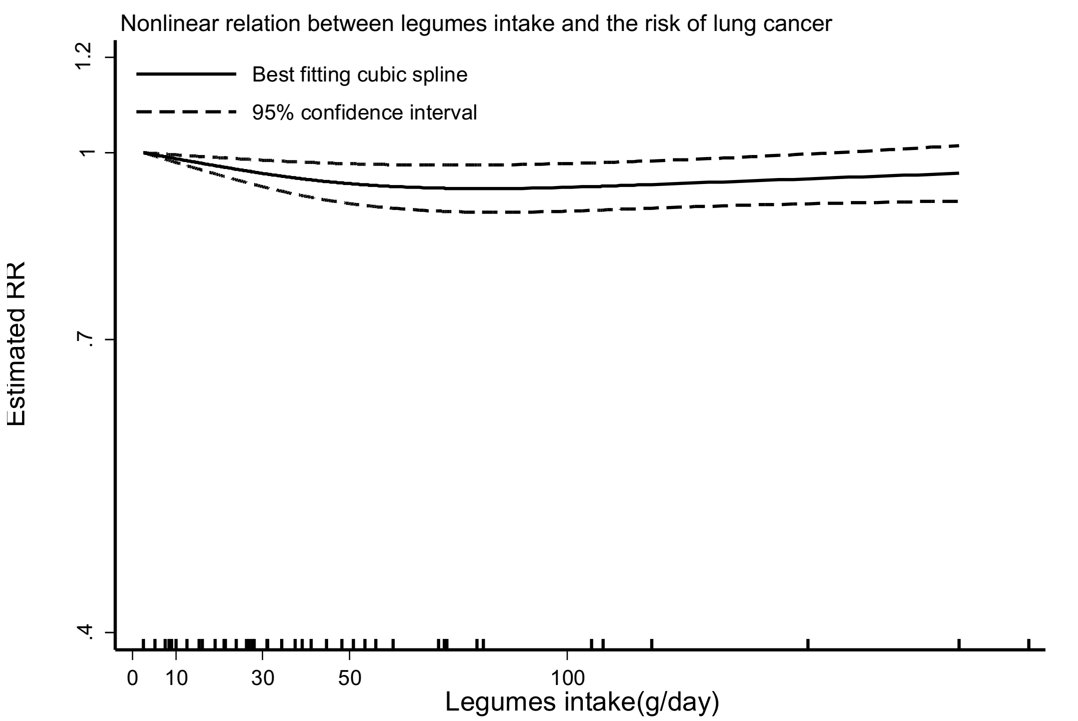


Figure 65 Relative risk of lung cancer and legumes intake estimated using non-linear models





$p < 0.01$

Table 48 Table with legumes intake values and corresponding RRs (95% CIs) for non-linear analysis of legumes intake and lung cancer

Legumes intake (g/day)	RR (95%CI)
2.5	1
20	0.97(0.95-0.99)
50	0.94(0.91-0.98)
100	0.94 (0.89-0.98)

2.5.1 Total meat

Cohort studies

Summary

Main results:

Six studies (964 cases) out of ten identified studies were included in the dose-response meta-analysis. There was a significant positive association between total meat consumption and lung cancer risk. The four excluded studies (one each from Japan, tin miners in China, Finland and Norway) with sample size below 170 cases did not report significant associations. No heterogeneity was observed.
There was no significant evidence of publication or small study bias (p=0.22). EPIC (Linsensein, 2011), the NIH-AARP and the PLCO studies (Tasevska, 2009, 2011) are large studies that reported on red meat and processed meat and lung cancer risk but did not published results on total meat intake and are not included in this section of the review.

Sensitivity analyses:
The summary RR remained borderline or significant when studies were omitted in turn in the influence analysis, ranging from 1.13 (95% CI=1.0-1.27) when Breslow, 2000 was omitted to 1.24 (95% CI=1.04-1.47) when Chow, 1992 was omitted. The study by Chow, 1992 had 51% of weight in the dose-response meta-analysis.

Study quality:
Cancer outcome was confirmed using cancer registries in most studies.
All studies included in the dose-response analysis were adjusted at least for age, sex, and smoking status. Five studies adjusted for smoking duration and intensity.

Table 49 Total meat intake and lung cancer risk. Number of studies in the CUP SLR

	Number
Studies identified	10 (12 publications)
Studies included in forest plot of highest compared with lowest exposure	8
Studies included in 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 50 Total meat intake and lung cancer risk. Summary of the dose-response meta-analysis in the 2005 SLR and CUP

	2005 SLR	CUP
Increment unit used	Per serving per week	100 g/day
All studies		
Studies (n)	2	6
Cases (total number)	204	964
RR (95%CI)	0.97 (0.86-1.10)	1.16 (1.04-1.30)
Heterogeneity (I^2, p-value)		0%, 0.55
P value Egger test		0.22

Table 51 Total meat intake and lung 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								
Yang, 2012b	6 cohorts	679	USA, Japan, Norway, Denmark, France, Germany, Greece, Italy, Netherlands, Norway, Spain, Sweden, UK	Incidence/mortality	High vs low	1.30 (1.05-1.60)		0%, 0.53

Table 52 Total meat intake and lung cancer risk. Main characteristics of studies included in the 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
Gnagnarella, 2013a LUN26858 Italy	COSMOS, Cohort of heavy smokers enrolled in lung cancer screening trial, Age: 50-84 years, M/W heavy smokers	178/ 4336 5.7 years	Screening examinations	FFQ	Incidence, lung cancer	207.3 vs 52.85 g/day	1.72 (1.05-2.82) Ptrend:0.09	Age, sex, energy intake, smoking duration, cigarettes/day, years of cessation, asbestos exposure, fruits and vegetables, fish, red meat, olive oil, tea and wine intake	Distribution of person-years by exposure quartiles
Takezaki, 2003 LUN00268 Japan	Aichi Prefecture Study, Prospective Cohort, Age: 30- years, M/W	51/ 5885 14 years	Follow-up based on data from Aichi local council	FFQ - study-specific	Incidence, lung cancer	≥ 5 times/week vs < 3 times/week	1.18 (0.41-3.41)	Age sex, smoking status, cigarettes/day -2 categories- , occupation.	Times/week converted to g/day
Breslow, 2000 LUN01082 USA	NHIS, Prospective Cohort, Age: 18-87 years, M/W	158/ 20 195 8.5 years	National Death Index	FFQ	Mortality, lung cancer	Meat, fish, poultry > 7.6 vs 0-3.7 servings/week	2.0 (1.2-3.5) Ptrend: < 0.03	Age, sex, smoking duration, packs/day	Servings/week converted to g/day

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Missing data derived for analyses
Veierød, 1997 LUN01643 Norway	NHSS, Prospective Cohort, Age: 16-56 years, M/W	151/ 51 452 11.2 years	Cancer registry	FFQ - study-specific	Incidence, lung cancer	≥ 5 vs ≤ 2 times/week	0.9 (0.5-1.6)	Age, sex, smoking status	Times/month converted to g/day
Chow, 1992 LUN02888 USA	LBS, Prospective Cohort, Age: 35- years, M	219/ 17 633 20 years	Death certificate	FFQ - study-specific	Mortality, lung cancer	> 75 vs < 16 times/month	1.3 (0.7-2.3)	Age, smoking habits, industry/ occupation	Times/months converted to g/day, mid-point exposure
Fraser, 1991 LUN03076 USA	AHS, Prospective Cohort, Age: 25- years, M/W, Vegetarians/Healthy Diet	59/ 34 198 6 years	Active follow-up by mail with confirmation through medical records and SEER registry where available	FFQ - study-specific	Incidence, lung cancer	Meat, fish or poultry > 2 time/week vs never	1.31 (0.52-3.28) Ptrend: 0.33	Age, sex, smoking habits	Times/week converted to g/day

Table 53 Total meat intake and lung cancer risk. Main characteristics of studies excluded in the 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
Khan, 2004 LUN00068 Japan	HGCS, Prospective cohort study, Age: ≥ 40 years, M/W	41/ 3158 14.8 years	Annual follow-up survey, cause of death classified by researchers		Mortality, lung cancer, men	Highest vs lowest	1.1 (0.6-2.0)	Age, health status, health education, health screening & smoking	Used only in highest versus lowest analysis. Only 2 categories
		10/			Mortality, lung cancer, women		1.3 (0.4-4.5)		
Ratnasinghe, 2000 LUN01072 China	Yunnan Tin, 1992-1999, Nested Case Control study, Age: 41-79 years, M/W tin miners	108 cases/216 controls 6 years	Cancer Registry of YTC or annual screens	Dietary history questionnaire	Incidence, lung cancer		p for mean differences =0.37		No RR available
Knekt, 1993 LUN02684 Finland	FMCHES, Nested Case Control, Age: ≥ 15 years, M	144/ 5 303 9 years	Finnish Cancer Registry	Dietary history	Incidence, lung cancer, current smokers	Lowest vs highest	0.8 (0.5-1.3)	Age	Used only in highest versus lowest analysis. Only 2 categories, lowest vs highest tertiles recalculated to high vs low for the forest plot
					Incidence, lung cancer, non-smokers		0.9 (0.4-2.4)		
Knekt, 1991b LUN03018 Finland	FMCHES, Age: 20-69 years,	117/ 4583 20 years	Finnish Cancer Registry	Dietary history	Incidence, lung cancer, non-smokers	Lowest vs highest	0.88 p=0.74	Age, smoking habits	No confidence intervals same as Knekt,

Author, Year, WCRF Code, Country	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				Incidence, lung cancer, smokers		0.75 p=0.47		1993 LUN02684
Knekt, 1991a LUN03143 Finland	FMCHES, Age: 20-69 years, M	117/ 4583 20 years	Finnish Cancer Registry	FFQ - study-specific	Incidence, lung cancer	Highest vs lowest	1.2 (0.8-1.9)	Age, smoking	Only two categories Same as Knekt, 1993 LUN02684
Kvåle, 1983 LUN04322 Norway	Norway, 1967-1978, Prospective Cohort, M/W	168/ 16 713 11.5 years	Cancer Registry of Norway	Dietary history questionnaire	Incidence, primary tumour of lung cancer	Highest vs lowest	1.33	Age, cigarette smoking, urban/rural place of residency	No measure of association

Figure 66 RR estimates of lung cancer by levels of total meat intake

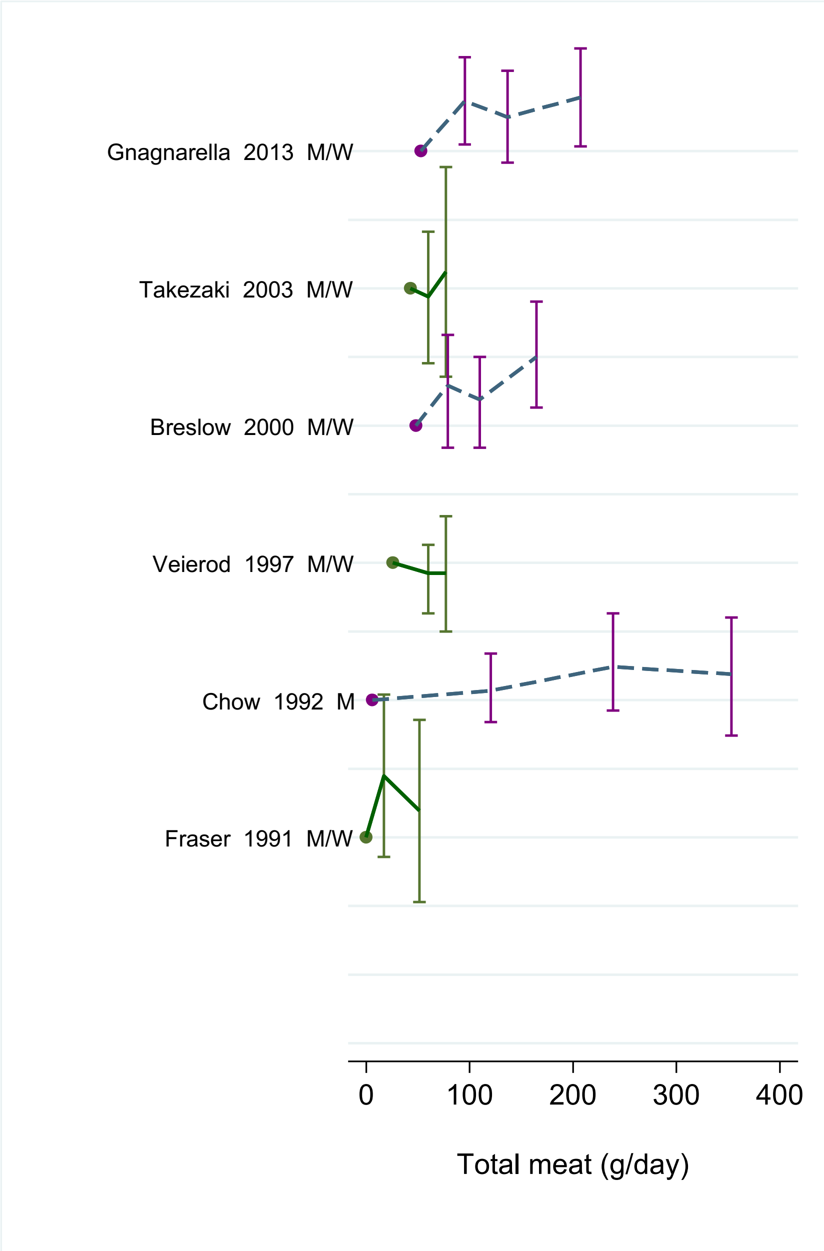
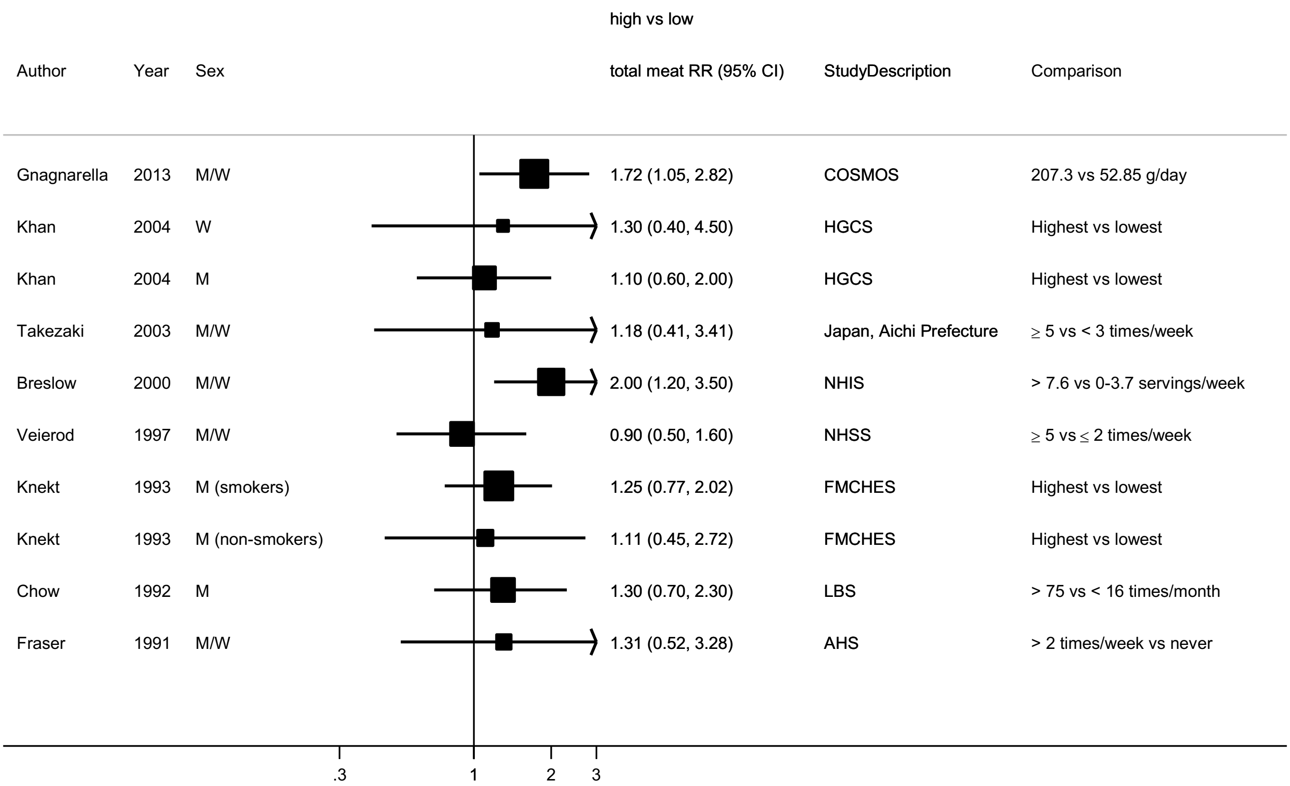


Figure 67 RR (95% CI) of lung cancer for the highest compared with the lowest level of total meat intake



* In study of Khan, 2004, the comparison is several times per week or every day vs never, several times per year or several times per month.

Figure 68 RR (95% CI) of lung cancer for 100 g/day increase of total meat intake

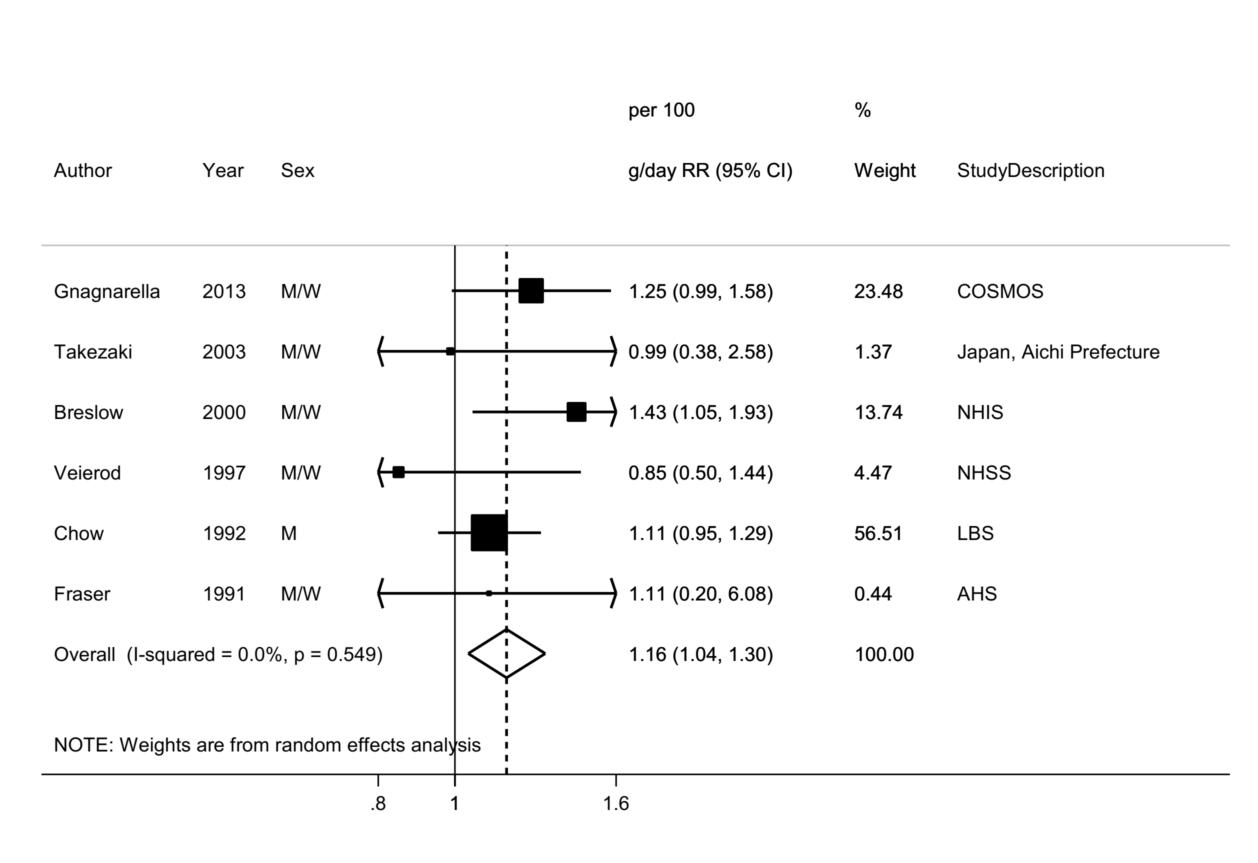
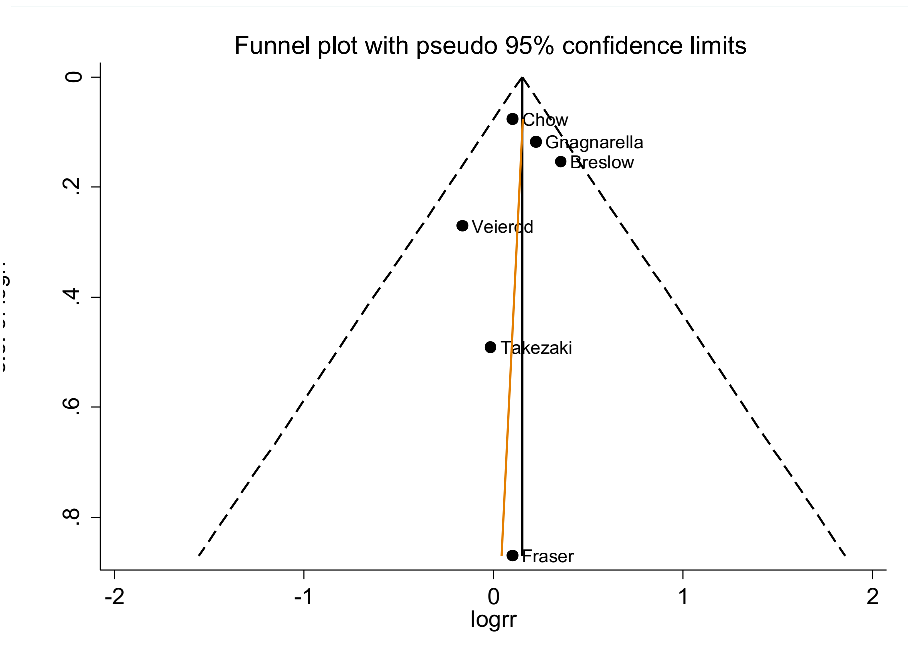


Figure 69 Funnel plot of studies included in the dose response meta-analysis of total meat intake and lung cancer



Egger's test p=0.22

2.5.1.2 Processed meat

Cohort studies

Main results:
Seven studies (10 292 cases) out of 9 studies (11 publications) were included in the dose-response meta-analysis. A significant positive association was observed. One cohort study excluded from the analysis showed no significant association (Khan 2004, 51 cases, Japanese men and women).
Three studies explored interaction with smoking (see Table). No effect modification was observed in two studies (Breslow, 2000; Linseisen, 2011) and in one study, a positive association was observed only in current and former smokers men (less than 10 years of quitting) but not in women and in men never smoker or who quit smoking more than 10 years before study baseline (Tasevska, 2011).)
The three studies that investigated the association of processed meats with lung cancer types provided inconsistent results (see Table). In the EPIC study (Linseisen, 2011), a non-significant inverse association was observed for small cell carcinoma and non-significant association were observed for other lung cancer type. In the NIH-AARP (Tasevska, 2009), a positive significant association with processed meat (in men only) was observed for squamous cell carcinoma, and positive non-significant association were observed for small cell carcinoma and adenocarcinoma. No significant association was observed with large cell carcinoma. In the PLCO study (Tasevska, 2011), there was no significant association for any of the histological subtypes in neither men nor women.
There was low heterogeneity in the analyses. The funnel plot suggests that small studies showing positive associations are missing (p value test of publication or small study bias =0.04).

Sensitivity analyses:
The observed overall positive association was influenced by one large study. The summary RR was 1.07 (95% CI=0.94-1.22) when the NIH-AARP (Tasevska, 2009) with 58% weight was omitted. There was evidence of non-linear dose-response ($p < 0.01$). However, the association is linear in most of the intake range. After excluding the only study not adjusted for smoking (Iso, 2007) the RR was 1.16(1.07-1.27).

Study quality:
All studies except one used FFQ to assess the intake of processed meat. One study assessed diet with 3-days food records. No association was observed in this study (Wei, 2014). Cases were assessed by periodic screening or record linkage to cancer registries.
One study calibrated for diet measurement error (Linseisen, 2011). The relative risk estimates were strengthened after correction (RR, 95% CI were 1.06; 0.97-1.15 and 1.13; 0.95-1.34 before and after calibration respectively).
All studies were adjusted by main confounders. All studies were adjusted for smoking status, duration, dose or time since quitting except one study on mortality that reported no

significant inverse association (Iso, 2007) and one study that adjust only for smoking status and did not report significant association (the same study that used food records- (Wie, 2014).

Two studies were in screening trials. One study (Gnagnarella, 2013a) was in heavy smokers participating in a trial of screening of lung cancer. The other study (Tasevska, 2011) was on participants in a screening trial of lung and other cancers (PLCO study).

Table 54 Processed meat consumption and lung 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	7
Studies included in dose-response meta-analysis	7
Studies included in non-linear dose-response meta-analysis	5

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

Table 55 Processed meat consumption and lung cancer risk. Summary of the dose-response meta-analysis in the 2005 SLR and CUP

	2005 SLR	**CUP**
Increment unit used	Serving per week	50 g/day
All studies		
Studies (n)	2	7
Cases (total number)	830	10 292
RR (95%CI)	1.03 (0.92-1.16)	1.14 (1.05-1.24)
Heterogeneity (I^2, p-value)	0%	0%, 0.53
P value Egger test		0.04
Stratified and sensitivity analysis		
	Men	**Women**
Studies (n)	3	3
RR (95%CI)	1.01 (0.73-1.41)	1.04 (0.81-1.35)
Heterogeneity (I^2, p-value)	74.9%, 0.02	4.7%, 0.35
	Incidence	**Mortality**
Studies (n)	5	2
RR (95%CI)	1.17 (1.07-1.27)	0.79 (0.56-1.12)
Heterogeneity (I^2, p-value)	0%, 0.98	0%, 0.97

Table 56 Processed meat consumption and lung cancer risk by lung cancer type.

Author, year, country	Study, sex	Subgroup	Comparison	RR (95%CI)
Linseisen, 2011 LUN20342 Europe	EPIC, M/W 574 cases 137 cases 286cases 363cases	Adenocarcinoma Large cell carcinoma Small cell carcinoma Squamous cell carcinoma	Continuous models per 50 g/day	1.03 (0.87–1.21) 1.17 (0.89–1.55) 0.99 (0.81–1.22) 1.12 (0.94–1.34
Tasevska, 2011 LUN20339 USA	PLCO, M/W			No statistically significant increase in risk for any of the histological subtypes (data not shown)
Tasevska, 2009, LUN20353, USA	NIH-AARP, M/W	Adenocarcinoma Small cell carcinoma Squamous cell carcinoma Large cell carcinoma	Highest vs lowest	M; 1.15 (0.97-1.36) W: 0.89 (0.72-1.09) M: 1.31 (0.98-1.76) W: 1.24 (0.86-1.78) M: 1.39 (1.10-1.75) W: 1.09 (0.74-1.61) M: 1.05 (0.67-1.65) W: 1.64 (0.87-3.06)

Table 57 Processed meat consumption and lung cancer risk by smoking status.

Author, Year, country	Study, country	Subgroup	Comparison	RR (95%CI)	P trend
Linseisen, 2011 LUN20342 Europe	EPIC, M/W			Not modified by smoking p-interaction = 0.07	
Tasevska, 2009, LUN20353, USA	NIH-AARP, M/W	Never smokers Former smokers (>10 years) Former smokers 1-10 years Current smokers	Percentile 90 vs Percentile 10	M;1.06 (0.69-1.64) W:0.89 (0.62-1.29) M:1.07 (0.93-1.24) W: 1.04 (0.82-1.32) M;1.31 (1.11-1.55) W: 1.09 (0.87-1.36) M:1.18 (1.04-1.33) W:1.10 (0.96-1.26)	0.79 0.55 0.33 0.74 < 0.01 0.46 < 0.01 0.17
Breslow, 2000 LUN01082 USA	NHIS, M/W			No significant interactions with smoking duration	

Table 58 Processed meat consumption and lung 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								
Xue, 2014	5	7070	China, Denmark, France, Germany, Greece, Japan, Italy, Netherlands, Norway, Spain, Sweden, UK, USA	Incidence and mortality	Per 50 g	1.09 (0.99-1.19)		0.09
Yang, 2012b	4	9174	China, Denmark, France, Germany, Greece, Japan, Italy, Netherlands, Norway, Spain, Sweden, UK, USA	Incidence and mortality	Highest vs lowest	1.05 (0.92-1.19)		49.2%, 0.08

Table 59 Processed meat consumption and lung cancer risk. Main characteristics of studies included in the 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
Wie, 2014 LUN26882 Korea	Korea 2004-2013, Prospective cohort study, M/W	36/ 8024 7 years	Cancer registry and medical records	3 days food record	Incidence, lung cancer	Per 10 g/day	1.02 (0.82-1.27)	Age, sex, energy, BMI, smoking, alcohol use, physical activity, income, education, marital status	RR recalculated for an increment of 50 g/day
Gnagnarella, 2013a LUN26858 Italy	COSMOS, Cohort of screening trial, Age: 50-84 years, M/W, Current and former heavy smokers	178/ 4336 5.7 years	Screening examinations	FFQ	Incidence, lung cancer	54.55 vs 6.9 g/day	1.27 (0.79-2.05) Ptrend: 0.47	Age, sex, energy intake, smoking duration, average daily cigarettes consumption, years of cessation, asbestos exposure, fruits and vegetables, fish, red meat, olive oil, tea and wine intake	Distribution of person-years by exposure quartiles
Linseisen, 2011 LUN20342 Denmark, France, Germany, Greece, Italy, Netherlands,	EPIC, Prospective Cohort, Age: 25-70 years, M/W	1822/ 47 /8021 8.7 years	Cancer and mortality registries, health insurance & pathology records, active follow up	FFQ and diet history	Incidence, lung cancer	Per 50 g ≥ 80 vs 0-9 g/day	All cases 1.13 (0.95-1.34) 0.92 (0.73-1.17)	Age, sex, centre, weight and height, smoking status and duration, cigarettes/day, time since smoking cessation,	Total person years

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Missing data derived for analyses
Norway, Spain, Sweden, UK								physical activity, alcohol consumption, education, energy from fat and energy from carbohydrates and protein, fruits and vegetable intake	
Tasevska, 2011 LUN20339 USA	PLCO, Prospective Cohort, Age: 55-74 years, M/W	454/ 99 579 8years	Cancer registry, death certificates, screening, physicians or next of kin reports	Semi-quantitative FFQ	Incidence, lung cancer, men	> 16.9 vs ≤ 4.2 g/1000 kcal	1.12 (0.83-1.53) Ptrend: 0.22	Age, race, BMI, education, cigar or pipe smoking, age started smoking, smoking years, smoking dose, years since smoking stopped fruits and vegetables, total fat, alcohol, energy intakes	Distribution of cases and person-years by exposure quintiles, exposure values using mean energy consumption
		328/ 99 579 8years			Incidence, lung cancer, women	> 11.6 vs ≤ 2.4 g/1000 kcal	0.98 (0.68-1.41) Ptrend: 0.32		
Tasevska, 2009, LUN20353, USA	NIH-AARP, Prospective Cohort, Age: 50-71 years, M/W	4089/ 467 9768 8 years	Annual linkage to state cancer registries and national death index plus	Validated FFQ	Incidence, lung cancer, men	> 18.2 vs ≤ 4.0 g/1000 kcal	1.23 (1.10-1.37) Ptrend:<0.01	Age, BMI, physical activity, race, education, smoking status, cigarettes/day, time since	Distribution of cases and person-years by exposure quintiles, 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
	Retired	2272/ 467 9768 8 years			Incidence, lung cancer, women	> 12.5 vs ≤ 2.3 g/1000 kcal	1.00 (0.87-1.15) Ptrend: 0.58	quitting, intakes of red meat, , alcohol, energy, fruit and vegetables, saturated fat	using mean energy consumption
Iso, 2007, LUN20294, Japan	JACC, Prospective cohort study, Age: 40-79 years, M/W	734/ 105 500 15 years	Population death registries	Validated FFQ	Mortality, lung cancer, men	≥ 3-4 times/week vs < 1time/week	0.78 (0.62-0.98)	Age, area of study	Exposure unit conversion
		221/ 105 500 15 years			Mortality, lung cancer, women		1.29 (0.89-1.85)		
Breslow, 2000 LUN01082 USA	NHIS, Prospective Cohort, Age: 18-87 years, M/W	158/ 20 195 8.5 years	National Death Index	FFQ	Mortality, lung cancer	> 3 vs 0-0.5 servings/week	0.80 (0.50-1.40) Ptrend: <0.72	Age, sex, smoking duration (years), and packs per day smoked	Servings/week converted to g/day

Table 60 Processed meat consumption and lung cancer risk. Main characteristics of studies excluded from the 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
Pavanello, 2012 LUN20332 Denmark	DCH, Nested Case Control, Age: 50-64 years, M/W	425/ 57 053	Danish cancer registry	FFQ	Incidence, lung cancer	> 36.2 vs ≤ 19.6 g/day	1.56 (1.13-2.16) Ptrend: < 0.01	Sex	Cohort included in EPIC study by Linseisen, 2011
Cross, 2007 LUN20285 USA	NIH-AARP, Prospective Cohort, Age: 50-71 years, M/W Retired	6769/ 494 036 6.8 years	Cancer registry and national death index	FFQ	Incidence, lung cancer	22.6 vs 1.6 g/1000 kcal	1.16 (1.06-1.26) Ptrend: < 0.01	Age, sex, BMI, family history of cancer, marital status, race, smoking status, alcohol consumption, education, frequency of vigorous physical activity, fruit and vegetable consumption, total energy consumption	Superseded by Tasevska, 2009 LUN20353
Khan, 2004, LUN00068, Japan	HGCS, Prospective cohort study,	41/ 3158 14.8 years	Annual follow-up survey, cause of death	Survey	Mortality, lung cancer, Men	Highest vs lowest	1.1 (0.5-2.3)	Age, health status, health	Used only in highest versus lowest analysis.

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Reasons for exclusion
	Age: ≥ 40 years, M/W	10/	classified by researchers		Mortality, lung cancer, Women		0.4 (0.1-3.1)	education, health screening & smoking	Only 2 categories
Ozasa, 2001 LUN00725 Japan	JACC, Prospective Cohort, Age: 40-70 years, M/W	362/ 98 248 7.7 years	Population death registries	FFQ - study-specific	Mortality, lung cancer, men	≥ 3-4 times/week vs ≤ 1-2 times/month	0.72 (0.52-0.99) Ptrend: 0.05	Age, family history of cancer, smoking habits	Superseded by Iso, 2007 LUN20294
		104/ 98 248 7.7 years			Mortality, lung cancer, women		1.79 (1.07-3.01) Ptrend: 0.03		

Figure 70 RR estimates of lung cancer by levels of processed meat consumption

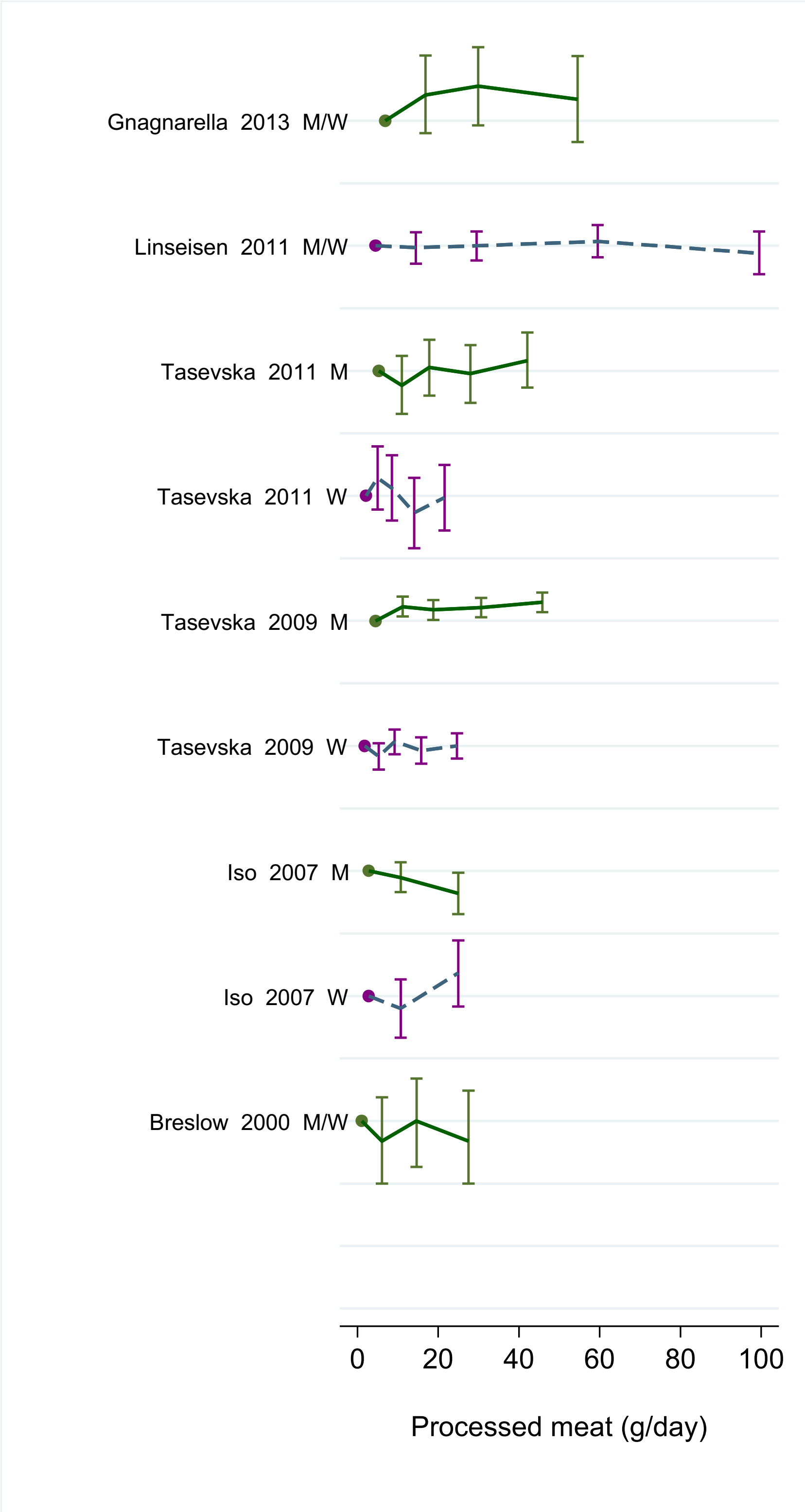
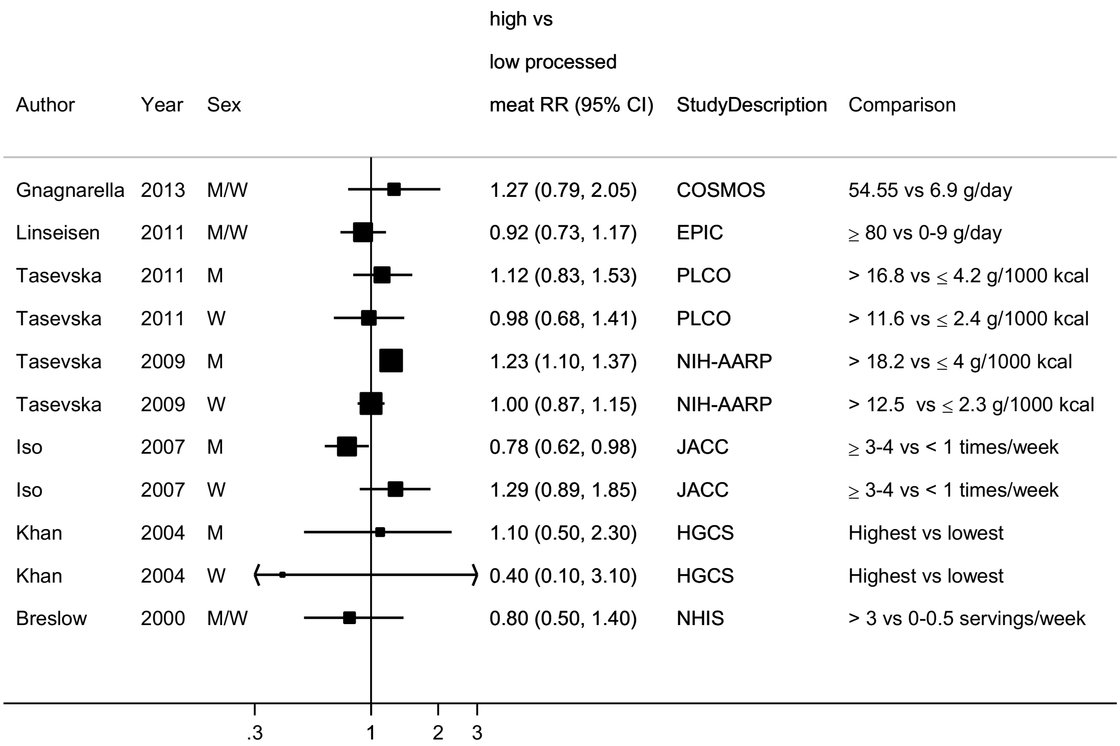


Figure 71 RR (95% CI) of lung cancer for the highest compared with the lowest level of processed meat consumption



* In study of Khan, 2004, the comparison is several times per week or every day vs never, several times per year or several times per month.

Figure 72 RR (95% CI) of lung cancer for 50 g/day increase of processed meat consumption

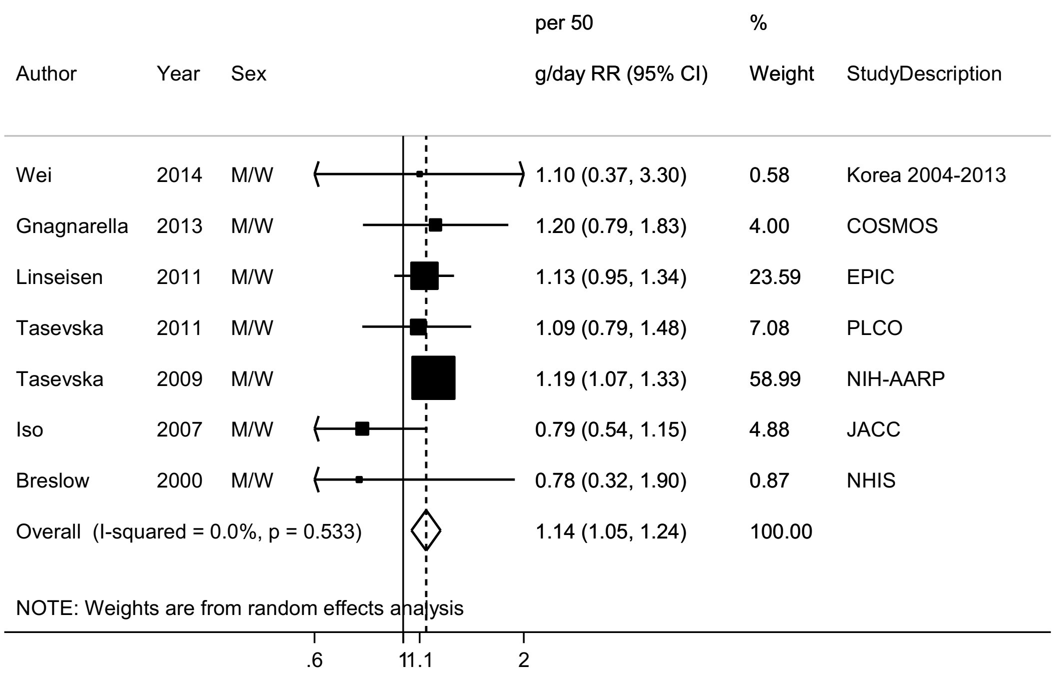


Figure 73 RR (95% CI) of lung cancer for 50 g/day increase of processed meat consumption, excluding study not adjusted for smoking status

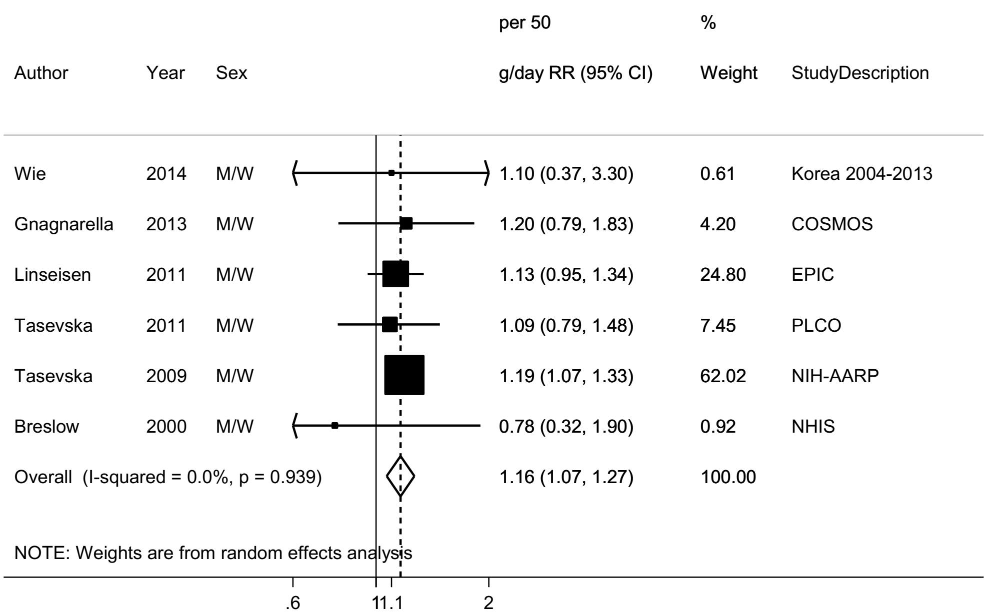
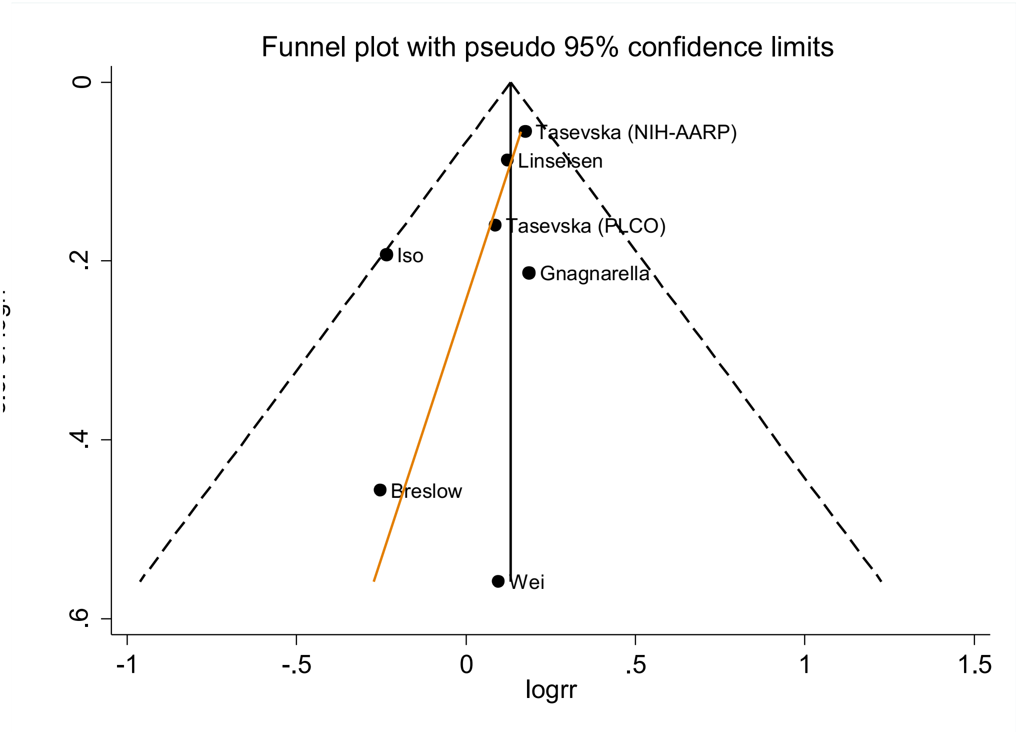


Figure 74 Funnel plot of studies included in the dose response meta-analysis of processed meat consumption and lung cancer



Egger's test p=0.04

Figure 75 RR (95% CI) of lung cancer for 50 g/day increase of processed meat by sex

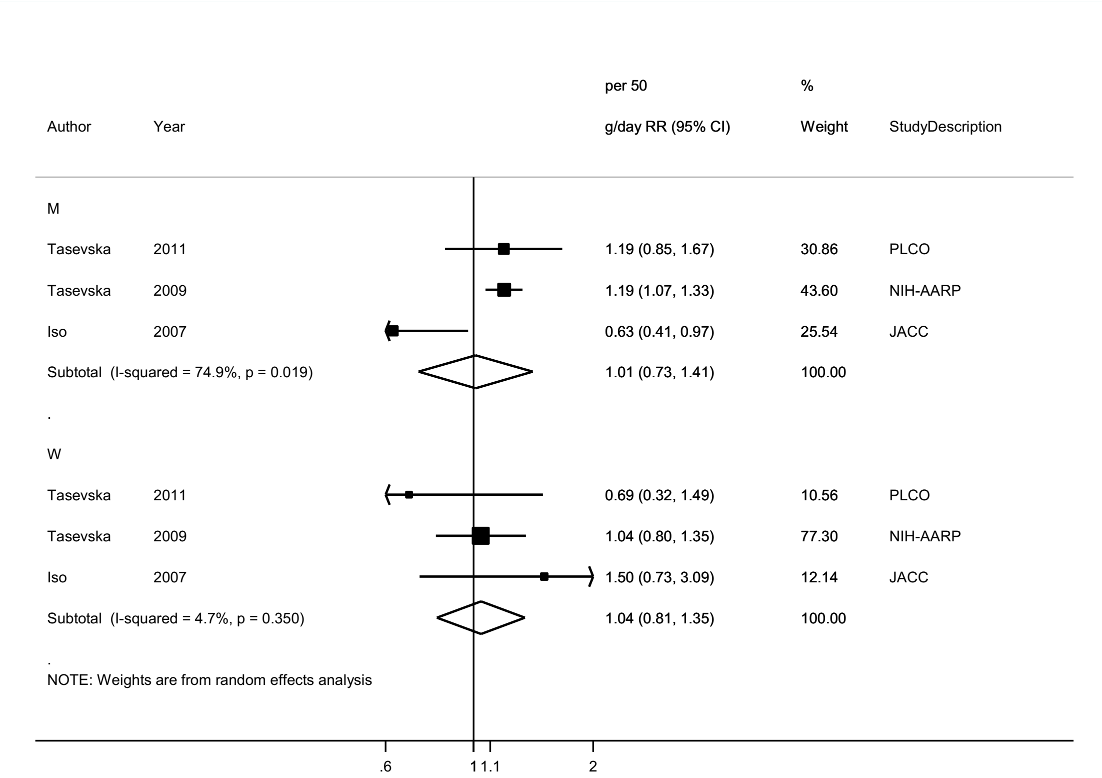


Figure 76 RR (95% CI) of lung cancer for 50 g/day increase of processed meat by cancer outcome

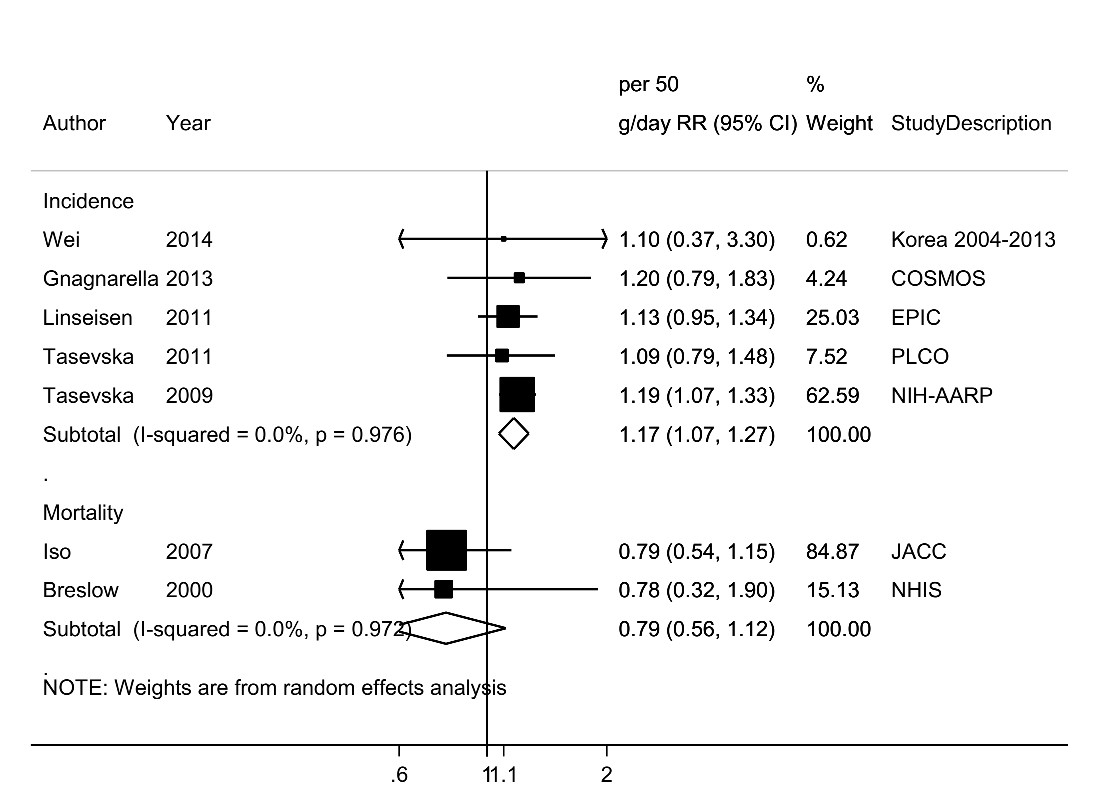
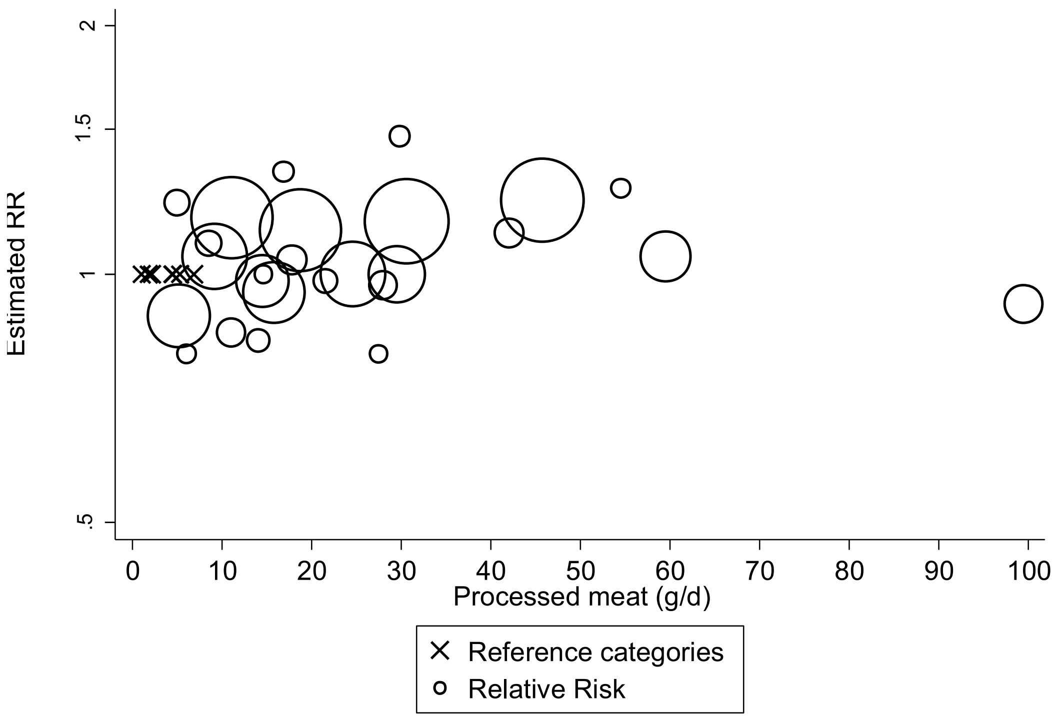
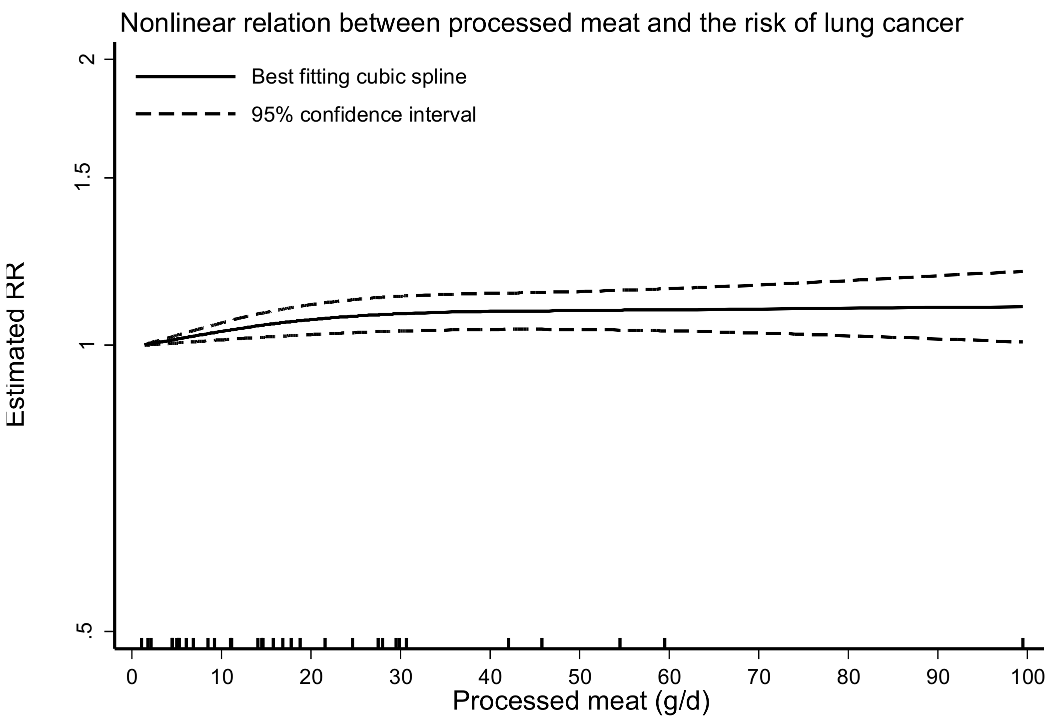


Figure 77 Relative risk of lung cancer and processed meat intake estimated using non-linear models





$p < 0.01$

Table 61 Table with processed meat intake values and corresponding RRs (95% CIs) for non-linear analysis of processed meat and lung cancer

Processed meat intake (g/day)	RR (95%CI)
1.0	1.00
15.8	1.05 (1.02-1.09)
29.9	1.08 (1.04-1.13)
54.5	1.09 (1.04-1.14)
99.5	1.10 (1.01-1.20)

2.5.1.3 Red meat

Cohort studies

Main results:
All the cohort studies identified in the review (seven studies (9765 cases), eight publications) were included in the dose-response meta-analysis. Lung cancer risk was significantly positively associated with red meat intake.
One study on cancer mortality on Japanese men and women reported on beef and pork intake separately and was not included in the analysis (Iso, 2007). In this study, beef intake was significantly associated with higher mortality from lung cancer in women, but not in men, and lung cancer risk was not related to pork intake.
High heterogeneity was observed. Visual inspection of the forest plot suggests it is explained by two studies that reported stronger associations than the average: one Italian study in high risk people participating in a screening of lung cancer (Gnagnarella, 2013a) and the follow-up of the 1987 National Health Interview Survey with lung cancer mortality as endpoint. Both studies were adjusted for smoking duration and intensity.
There was no evidence of publication or small study bias (p=0.57).

Four studies investigated red meat and lung cancer by smoking status (see Table 65). In the study on current and former smokers (Gnagnarella, 2013a), the association was significant in both but stronger in former than in current smokers. In the NIH-AARP study (Tasevska, 2009), there was no significant interaction with smoking; the association was significant only in former smokers men who stop smoking less than ten years before baseline. In two other studies (Linseisen, 2011, in which lung cancer risk was nto related to red meat intake and Breslow 2000 showing a borderline statistical positive association with lung cancer mortality), smoking did not modify the association of lung cancer with red meat intake.

Results by histological types were not consistent (see Table 64). The only significant associations were for adenocarcinomas in a study on current and former smokers (Gnagnarella, 2013a) and in the NIH-AARP (Tasevska, 2009) for squamous cell carcinomas in men and small cell carcinomas in women. No significant associations with any lung cancer types were observed in the other two studies (Linseisen, 2011; Tasevska, 2011).

Sensitivity analysis:
In influence analysis, statistical significance was lost when the Italian study of lung cancer screening was excluded (Gnagnarella, 2013a). The summary RRs ranged from 1.17 (95% CI=0.97-1.40) when Gnagnarella, 2013a was omitted to 1.29 (95% CI=1.07-1.55) when Takata, 2012 was omitted.
There was no evidence of non-linear dose-response of lung cancer and red meat intake (p > 0.05) (Figures not shown).

Study quality:
Most studies used FFQ to assess the intake of red meat. One study corrected relative risk estimates for measurement error of diet (Linseisen, 2011) and this slightly strengthened the association with red meat but it remained not significant.
All studies adjusted for smoking status, intensity, duration except one study (Wei, 2014) that adjusted smoking in two categories (yes and no). A positive association was observed but the overall association in the meta-analysis is still significant when this study is excluded. One study on non-smoker Chinese women (Takata, 2012) was adjusted for passive smoking. One study was on heavy smokers participating in a screening trial of lung cancer (Gnagnarella, 2013a) and one study was in participants in screening of lung and other cancers (PLCO, Tasevska, 2011).

Table 62 Red meat consumption and lung cancer risk. Number of studies in the CUP SLR

	Number
Studies identified	7 (8 publications)
Studies included in forest plot of highest compared with lowest exposure	6
Studies included in dose-response meta-analysis	7
Studies included in non-linear dose-response meta-analysis	6

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

Table 63 Red meat consumption and lung cancer risk. Summary of the dose-response meta-analysis in the 2005 SLR and CUP

	2005 SLR	CUP
Increment unit used		100 g/day
All studies		
Studies (n)		7
Cases (total number)		9765
RR (95%CI)		1.22 (1.02-1.46)
Heterogeneity (I^2, p-value)		65.8%, < 0.01
p value Egger test		0.57
Stratified and sensitivity analysis		
	Men	**Women**
Studies (n)	2	3
RR (95%CI)	1.14 (1.05-1.24)	1.08 (0.90-1.29)
Heterogeneity (I^2, p-value)	0%, 0.64	18.1%, 0.30

Table 64 Red meat consumption and lung cancer risk relationship by histological type.

Author, year, country	Study, sex	Subgroup	Comparison	RR (95%CI)
Gnagnarella, 2013a LUN26858 Italy	COSMOS, M/W Current and former smokers	Adenocarcinomas Other subtypes	Highest vs lowest	1.88 (1.16-3.04) 1.57 (0.76-3.36)
Linseisen, 2011 LUN20342 Europe	EPIC, M/W	Adenocarcinoma Large cell carcinoma Small cell carcinoma Squamous cell carcinoma	Continuous models per 50 g/day	1.21 (0.89–1.65) 1.25 (0.73–2.14) 1.13 (0.67–1.89) 0.88 (0.54–1.45)
Tasevska, 2011 LUN20339 USA	PLCO, M/W			No statistically significant increase in risk for any of the histological subtypes (data not shown)
Tasevska, 2009, LUN20353, USA	NIH-AARP, M/W	Adenocarcinoma Large cell carcinoma Small cell carcinoma Squamous cell carcinoma	Highest vs lowest	M: 1.16 (0.96- 1.39) W: 0.98 (0.79- 1.23) M: 1.57 (0.95- 2.58) W: 1.28 (0.69- 2.35) M: 1.13 (0.82- 1.57) W: 1.74 (1.14- 2.66) M: 1.34 (1.04- 1.73) W: 1.05 (0.71- 1.57)

Table 65 Red meat consumption and lung cancer risk relationship by smoking status.

Author, Year, country	Study, country	Subgroup	Comparison	RR (95%CI)	P trend
Gnagnarella, 2013a LUN26858 Italy	COSMOS, M/W Current and former smokers	Former smoker Current smoker	Highest vs lowest	3.72 (1.13-12.2) 1.58 (1.02-2.44)	
Linseisen, 2011 LUN20342 Europe	EPIC, M/W			Not modified by smoking p-interaction = 0.72	
Tasevska, 2009, LUN20353, USA	NIH-AARP, M/W	Never smoker Former smokers, quit <10 y ago Former smokers, quit 1-10 y ago Current smoker	Highest vs lowest	M: 1.19 (0.69- 2.06) W: 1.21 (0.76- 1.94) M: 1.29 (1.09- 1.54) W: 1.31 (0.96- 1.79) M: 1.12 (0.92- 1.36) W: 1.14 (0.87- 1.50) M: 1.13 (0.98- 1.29) W: 1.10 (0.94- 1.28)	0.52 0.44 <0.01 0.09 0.24 0.32 0.09 0.26
Breslow, 2000 LUN01082 USA	NHIS, M/W			No significant interactions with smoking duration	

Table 66 Red meat consumption and lung 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								
Xue, 2014	6	7070	China, Denmark, France, Germany, Greece, Japan, Italy, Netherlands, Norway, Spain, Sweden, UK, USA	Incidence and mortality	Per 120 g	1.21 (1.14-1.28)		0.71
Yang, 2012b	5	9174	China, Denmark, France, Germany, Greece, Japan, Italy, Netherlands, Norway, Spain, Sweden, UK, USA	Incidence and mortality	Highest vs lowest	1.20 (1.10-1.30)		0%, 0.92

Table 67 Red meat consumption and lung cancer risk. Main characteristics of studies included in the 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
Wie, 2014 LUN26882 Korea	Korea 2004-2013, Prospective cohort study, M/W	36/ 8024 7 years	Cancer registry and medical records	3 days food record	Incidence, lung cancer	Per 10 g/day	1.27 (1.09-1.47)	Age, sex, energy, BMI, smoking (yes or no), alcohol use, physical activity, income, education, marital status	RR recalculated for an increment of 100 g/day
Gnagnarella, 2013a LUN26858 Italy	COSMOS, Cohort of screening trial, Age: 50-84 years M/W Current and former smokers	178/ 4336 5.7 years	Screening examinations	FFQ	Incidence, lung cancer	127.75 vs 21.95 g/day	1.76 (1.12-2.78) Ptrend: < 0.01	Age, sex, energy intake, smoking duration, cigarettes/day, years of cessation, asbestos exposure, fruits and vegetables, fish, red meat, olive oil, tea and wine intake	Distribution of person-years by exposure quartiles
Takata, 2012 LUN26859 China	SWHS, Prospective Cohort, Age: 40-70	428/ 71 267 11.2 years	Shanghai cancer registry & the shanghai vital statistics registry	FFQ (77 items)	Incidence, lung cancer	87 vs 17 g/d	0.85 (0.63-1.16) Ptrend: 0.47	Age, BMI, income, occupation, total caloric	Distribution of person-years by exposure quartile

Author, Year, WCRF Code, Country	Study 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, W never smokers							consumption, history of asthma, passive smoking	
Linseisen, 2011 LUN20342 Denmark, France, Germany, Greece, Italy, Netherlands, Norway, Spain, Sweden, UK	EPIC, Prospective Cohort, Age: 25-70 years, M/W	1822/ 478 021 8.7 years	Cancer and mortality registries, health insurance & pathology records, active follow up	FFQ, diet history	Incidence, lung cancer	Per 50 g	1.06 (0.89-1.27)	Age, sex, body weight and height, smoking status and duration, cigarettes /day physical activity, time since smoking cessation, alcohol consumption, centre,, education, energy intake from fat and from carbohydrates and protein, fruits and vegetables	Total person-years
						≥ 80 vs 0-9 g/day	1.19 (0.94-1.50)		

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Missing data derived for analyses
Tasevska, 2011 LUN20339 USA	PLCO, Prospective Cohort, Age: 55-74 years, M/W	454/ 99 579 8 years	Cancer registry, death certificates, screening, physicians or next of kin reports	Semi-quantitative FFQ	Incidence, lung cancer, men	> 54.8 vs ≤ 20.9 g/1000 kcal	1.11 (0.79-1.56) Ptrend: 0.42	Age, BMI, cigar or pipe smoking, age started smoking, years smoking maximum amount, smoking dose, years since quitted smoking, energy adjusted vegetable and fruit servings and total fat, race,, alcohol consumption, education, caloric intake	Distribution of cases and person-years by exposure quintiles, exposure values using mean energy consumption
		328/			Incidence, lung cancer, women	> 42.5 vs ≤ 14.6	1.30 (0.87-1.95) Ptrend: 0.65		
Tasevska, 2009, LUN20353, USA	NIH-AARP, Prospective Cohort, Age: 50-71 years, M/W	4089/ 467 976 8 years	Annual linkage to state cancer registries and national death index plus	FFQ	Incidence, lung cancer, men	> 54.7 vs ≤ 19.2 g/1000 kcal	1.22 (1.09-1.38) Ptrend: < 0.01	Age, BMI, smoking status (including time since quitting, cigarettes/day) physical activity, race, education, consumption of red meat,	Distribution of cases and person-years by exposure quintiles, exposure values using mean energy consumption
		2272/			Incidence, lung cancer, women	> 43.8 vs ≤ 13.3	1.13 (0.97-1.32) Ptrend: 0.05		

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Missing data derived for analyses
								unprocessed meat, alcohol, energy, fruits and vegetables, saturated fat, total meat, white meat	
Breslow, 2000 LUN01082 USA	NHIS, Prospective Cohort, Age: 18-87 years, M/W	158/ 20 195 8.5 years	National Death Index	FFQ	Mortality, lung cancer	> 6.6 vs 0-2.3 servings/week	1.60 (1.00-2.60) Ptrend: < 0.01	Age, sex, smoking status, duration and packs/day	Servings/week converted to g/day

Table 68 Red meat consumption and lung cancer risk. Main characteristics of studies excluded in the 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 LUN20285 USA	NIH-AARP, Prospective Cohort, Age: 50-71 years, M/W	6769/ 494 036 6.8 years	Cancer registry and National Death Index	FFQ	Incidence, lung cancer	62.7 vs 9.8 g/1000 kcal	1.20 (1.10-1.31) Ptrend: < 0.01	Age, sex, BMI, family history of cancer, marital status, race, smoking status, education, frequency of vigorous physical activity, consumption of fruits and vegetables, and total energy	Superseded by Tasevska, 2009 LUN20353

Figure 78 RR estimates of lung cancer by levels of red meat consumption

Figure 79 RR (95% CI) of lung cancer for the highest compared with the lowest level of red meat consumption

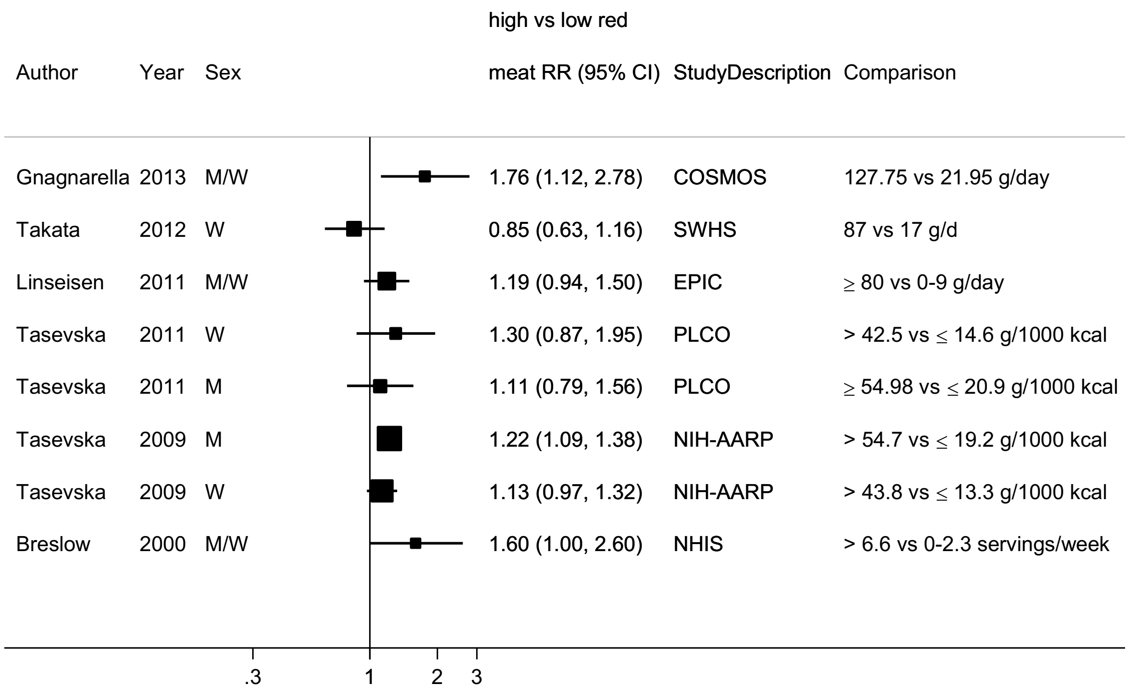


Figure 80 RR (95% CI) of lung cancer for 100 g/day increase of red meat consumption

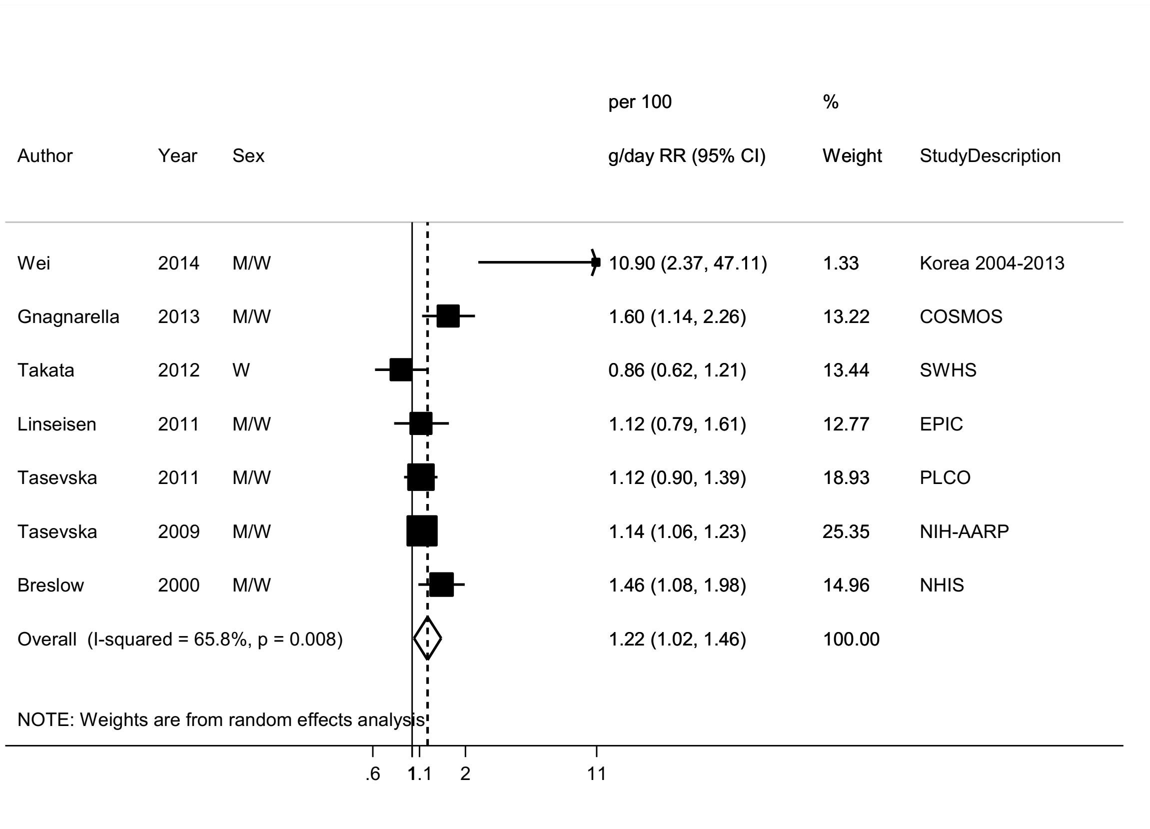
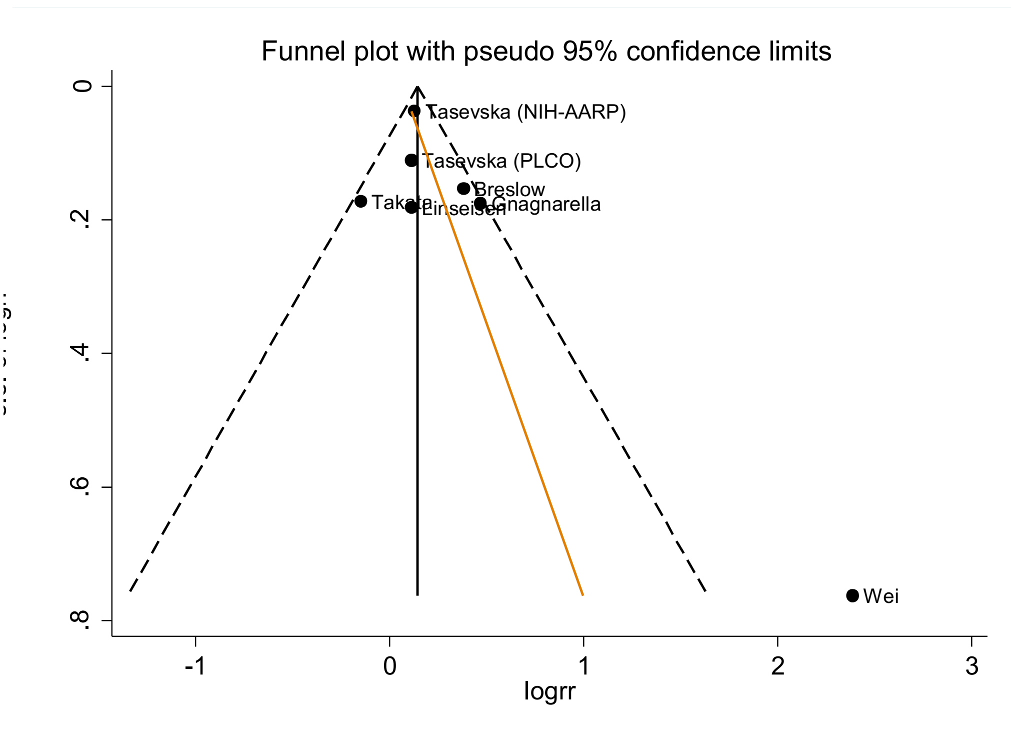
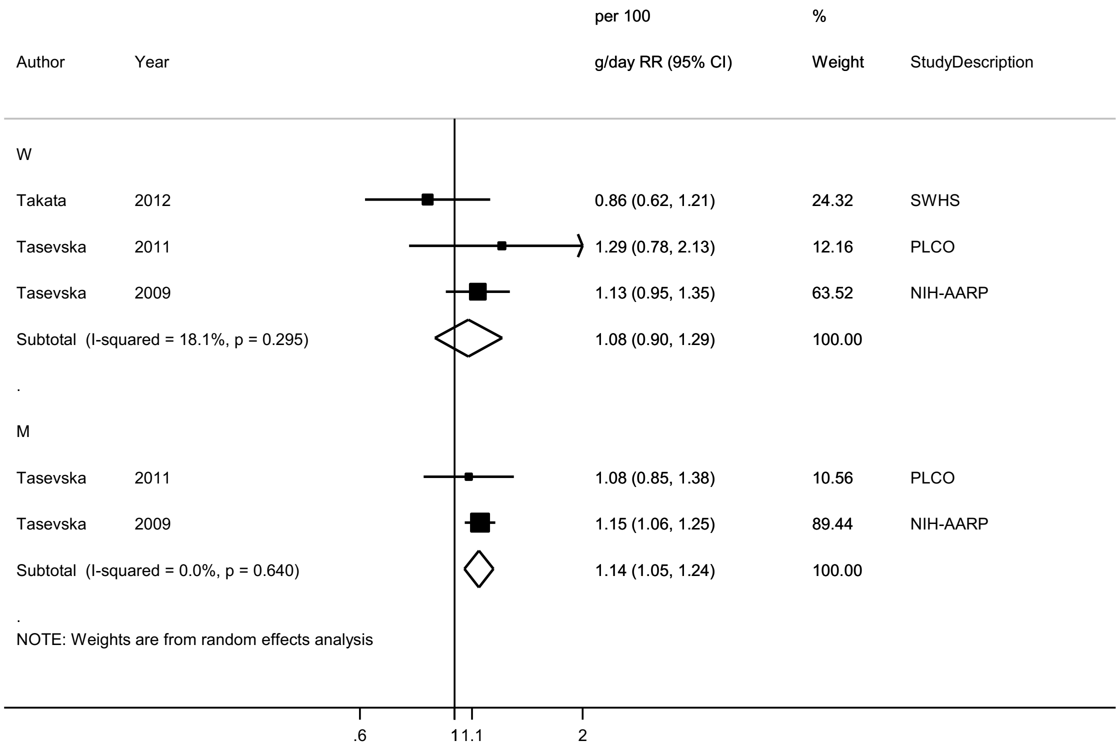


Figure 81Funnel plot of studies included in the dose response meta-analysis of red meat consumption and lung cancer



Egger's test p=0.57

Figure 82 RR (95% CI) of lung cancer for 100 g/day increase of red meat by sex



2.5.1.4 Poultry

Cohort studies

Summary

Main results:
Six studies (11 707 cases) out of eight cohort studies were included in the dose-response meta-analysis. A significantinverse association was found that was driven by one study with 9751 cases (NIH-AARP, Daniel 2011) (95% weight in the analysis) that was the only study showing a significant inverse association. In this study, white meat (poultry and fish) was not related to lung cancer in substitution models with red meat intake and lung cancer was not related to fish intake.
Two studies were excluded from the dose-response analyses, one with only two categories of exposure and the other on fried chicken. None of the studies reported significant associations. There was no evidence of heterogeneity. There was no statistical evidence of publication or small study bias (p=0.70) .The funnel plot shows
one small study in vegetarians and healthy diet people that reported a positive association (Fraser, 1991).

Sensitivity analyses:
In influence analysis, the statistical significance was lost when the large NIH-AARP study (Daniel, 2011) was omitted (RRs: 0.89; 95% CI=0.65-1.22; 95% weight in the meta-analysis). After excluding the only study not adjusted for smoking (Iso, 2007) the RR was 0.90(0.84-0.97).

Study quality:
All studies used FFQ to assess the intake of poultry. All studies were adjusted at least for age and smoking status and cigarettes/day at study enrolment, except the JACC study (Iso, 2007) that did not adjust for smoking and a small study that adjusted for smoking status only (Fraser, 1991). No study stratified by smoking status. One study in nonsmoker women (428 cases, Takata, 2013) that reported an inverse but no significant association was adjusted for passive smoking.

Table 69 Poultry consumption and lung cancer risk. Number of studies in the CUP SLR

	Number
Studies identified	8 (8 publications)
Studies included in forest plot of highest compared with lowest exposure	7
Studies included in 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 70 Poultry consumption and lung cancer risk. Summary of the dose-response meta-analysis in the 2005 SLR and CUP

	2005 SLR	CUP
Increment unit used		100 g/day
All studies		
Studies (n)		6
Cases (total number)		11 707
RR (95%CI)		0.91 (0.85-0.97)
Heterogeneity (I^2, p-value)		0%, 0.57
P value Egger test		0.70
Stratified and sensitivity analysis		
	Incidence	**Mortality**
Studies (n)	3	3
RR (95%CI)	0.89 (0.49-1.59)	0.92 (0.67-1.26)
Heterogeneity (I^2, p-value)	33.4%, 0.22	0%, 0.64

Table 71 Poultry consumption and lung cancer risk. Results of meta-analyses and pooled analyses of prospective studies published after the 2005 SLR

Author, Year	Number of cohort studies	Total number of cases	Studies country, area	Outcome	Comparison	RR (95%CI)	P trend	Heterogeneity (I^2, p value)
Meta-analyses								
Yang, 2012b	3	10029	China, Denmark, France, Germany, Greece, Japan, Italy, Netherlands, Norway, Spain, Sweden, UK, USA	Incidence and mortality	Highest vs lowest	0.95(0.64–1.39)		51.2%, 0.12

Table 72 Poultry consumption and lung cancer risk. Main characteristics of studies included in the 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
Takata, 2012 LUN26859 China	SWHS, Prospective Cohort, Age: 40-70 years, W, never smokers	428/ 71 267 11.2 years	Shanghai cancer registry and Shanghai vital statistics registry	Validated FFQ	Incidence, lung cancer	29 vs 2 g/day	0.90 (0.67-1.21) Ptrend: 0.34	Age, BMI, income, total caloric intake, occupation, history of asthma, passive smoking	Distribution of person-years by exposure quartile
Daniel, 2011 LUN20266 USA	NIH-AARP, Prospective Cohort, Age: 50-71 years, M/W	9751/ 492 186 9.1 years	Cancer registry	Validated FFQ	Incidence, lung cancer	51.2 vs 5.3 g/1000 kcal	0.91 (0.85-0.97) Ptrend: 0.01	Age, sex, education, marital status, family history of cancer, race, BMI, smoking status(including time and intensity), vigorous physical activity, MHT in women, and intake of alcohol, fruit, vegetables, fish, red meat and total energy	Distribution of person-years and cases by exposure quintiles, exposure values using mean energy consumption, g/1000 kcal converted to g/day
Iso, 2007	JACC,	806/	Population death	Validated FFQ	Mortality, lung	≥ 3-4 vs < 1	0.99 (0.80-1.21)	Age, area of	Times/week

Author, Year, WCRF Code, Country	Study 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
LUN20294 Japan	Prospective Cohort, Age: 40-79 years, M/W	105 500 15 years	registries		cancer, men	times/week		study	converted to g/day
		233/ 105 500 15 years			Mortality, lung cancer, women	≥ 3-4 vs < 1 times/week	0.99 (0.65-1.50)		
Breslow, 2000 LUN01082 USA	NHIS, Prospective Cohort, Age: 18-87 years, M/W	158/ 20 195 8.5 years	National Death Index	FFQ	Mortality, lung cancer	> 1.1 vs 0-0.2 servings/week	1.10 (0.60-2.00) Ptrend: < 0.65	Age, sex, smoking duration, packs/day	Servings/week converted to g/day
Chow, 1992 LUN02888 USA	LBS, Prospective Cohort, Age: 35- years, M	219/ 17 633 20 years	Death certificates	FFQ - study-specific	Mortality, lung cancer	> 13 vs < 4 times/month	0.7 (0.4-1.2)	Age, smoking status, cigarettes/day, industry/ occupation	Times/month converted to g/day
Fraser, 1991 LUN03076 USA	AHS, Prospective Cohort, Age: 25- years, M/W, Vegetarians/ Healthy Diet	59/ 34 198 6 years	Active follow-up by mail with confirmation through medical records and SEER registry where available	FFQ - study-specific	Incidence, lung cancer	≥ 1 time/week vs never	2.20 (0.84-5.77) Ptrend: 0.20	Age, sex, smoking status	Times/week converted to g/day

Table 73 Poultry consumption and lung cancer risk. Main characteristics of studies excluded from the 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
Khan, 2004, LUN00068, Japan	HGCS, Prospective cohort study, Age: ≥ 40 years, M/W	41/ 3158 14.8 years	Annual follow-up survey, cause of death classified by researchers		Mortality, lung cancer, men	Several times per week + every day vs never + several times per year + several times per month	1.2 (0.6-2.2)	Age, health status, health education, health screening & smoking	Used only in highest versus lowest analysis. Only 2 categories
		10/ 3158 14.8 years			Mortality, lung cancer, women		0.5 (0.1-2.5)		
Butler, 2013 LUN26852, China	SCHS, Prospective Cohort, Age: 45-74 years, M/W	1130/ 61 321 11.5 years	Singapore cancer registry database	Validated FFQ	Incidence, lung cancer	≥ median, 42 Vs < media, 42 times/year	0.93 (0.80-1.08)	Age, sex, BMI, dialect group, education, interview year, cigarettes/day, smoking status, years since quit smoking, years of smoking , total energy intake	Exposure is fried chicken

Figure 83 RR estimates of lung cancer by levels of poultry consumption

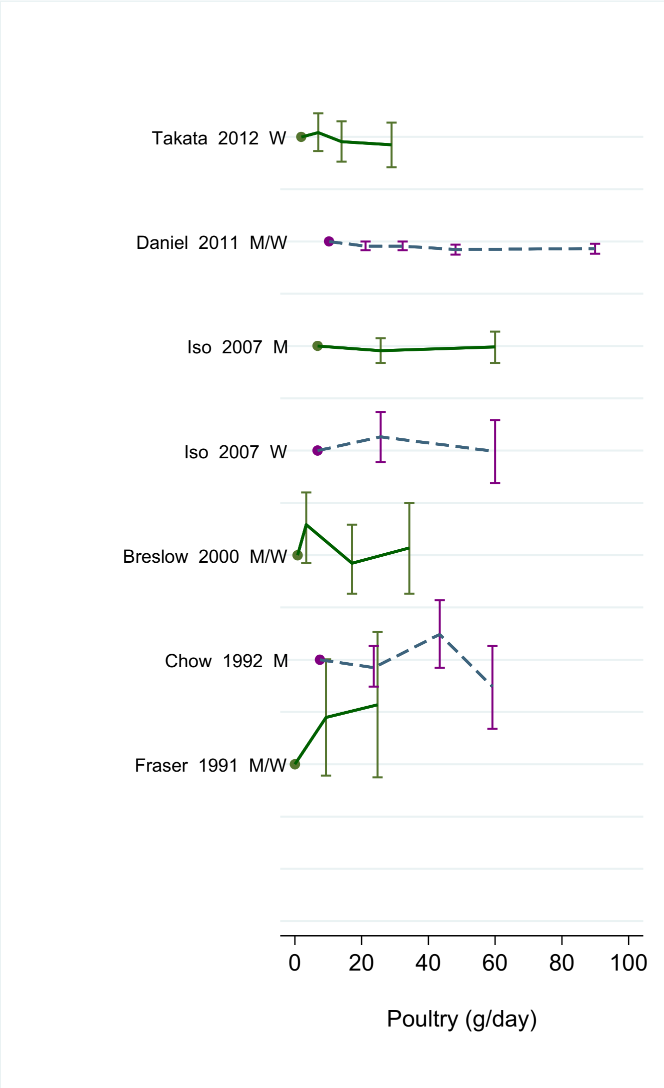
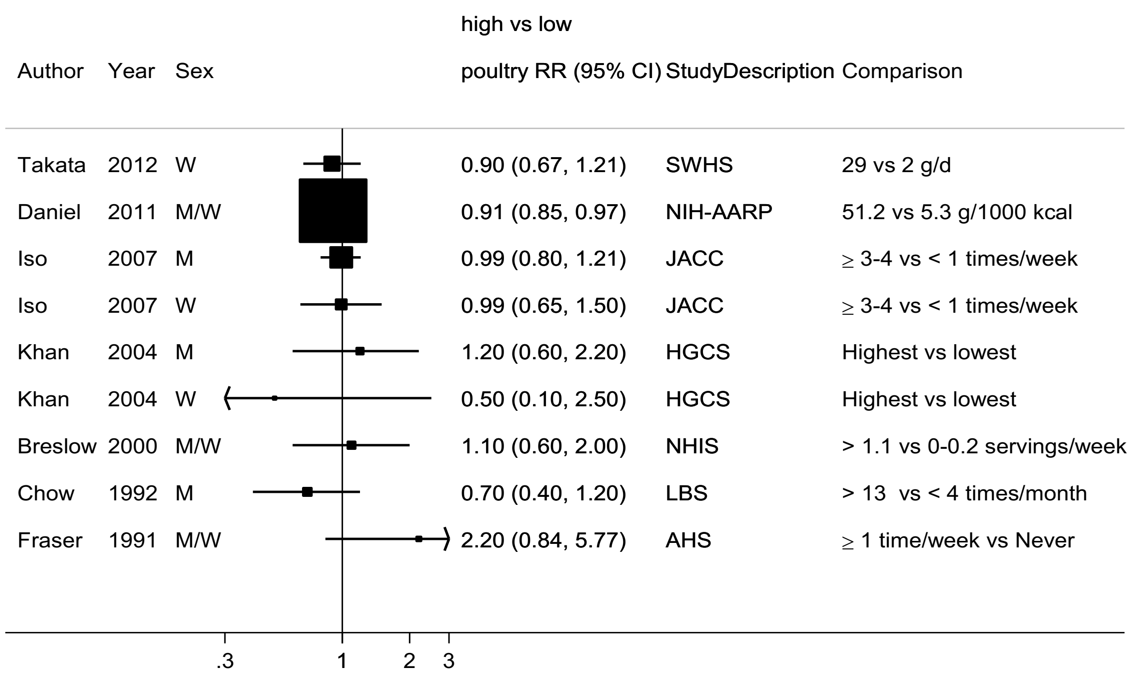


Figure 84 RR (95% CI) of lung cancer for the highest compared with the lowest level of poultry consumption



* In study of Khan, 2004, the comparison is several times per week + every day vs never + several times per year + several times per month.

Figure 85 RR (95% CI) of lung cancer for 100 g/day increase of poultry consumption

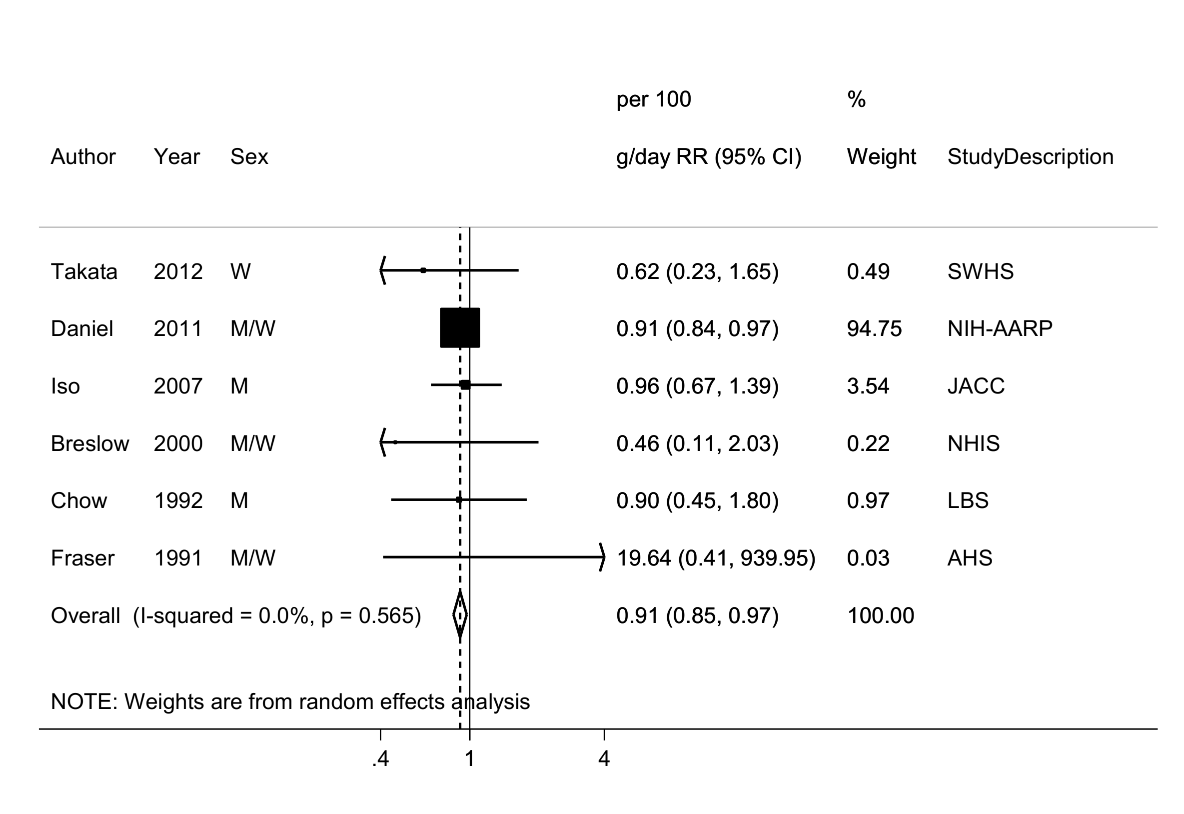


Figure 86 RR (95% CI) of lung cancer for 100 g/day increase of poultry consumption, after excluding study not adjusted for smoking status

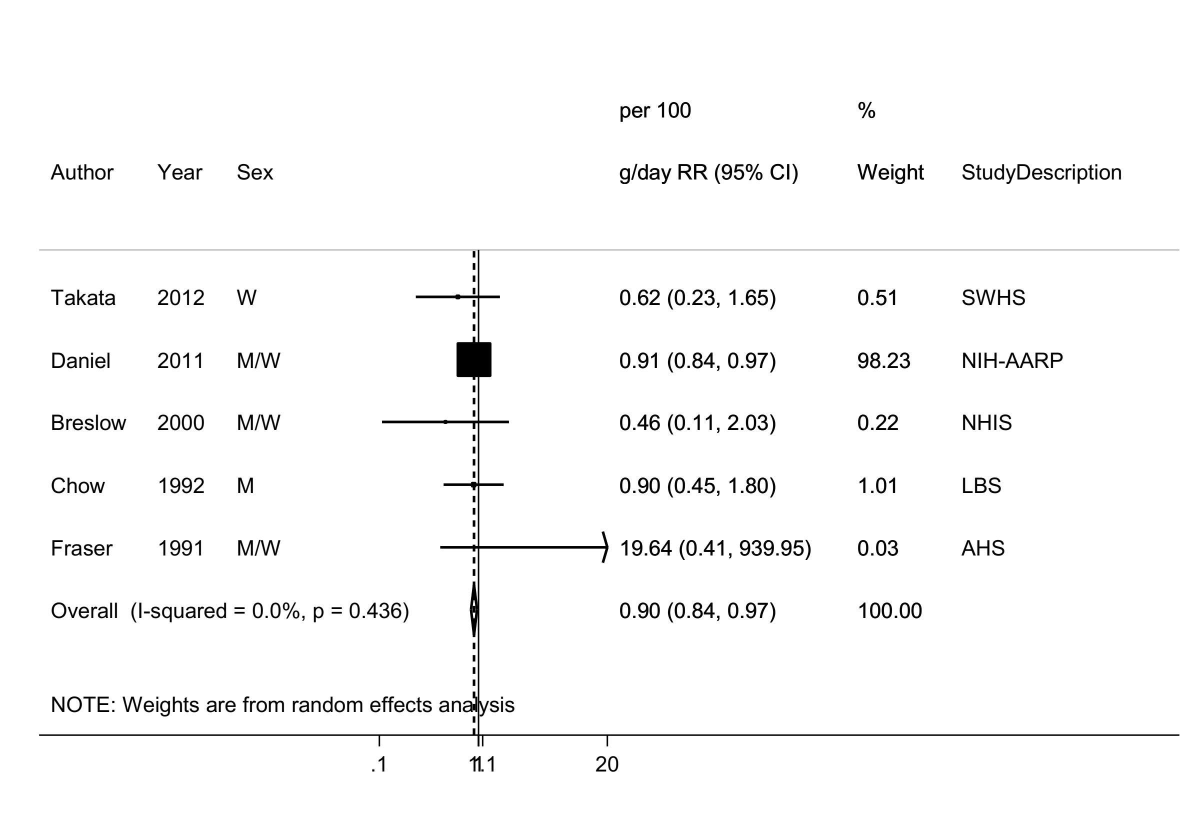
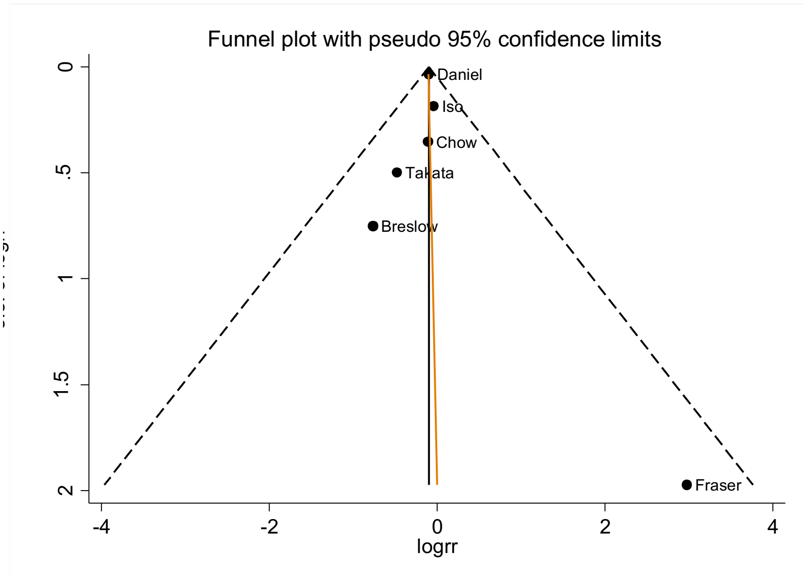
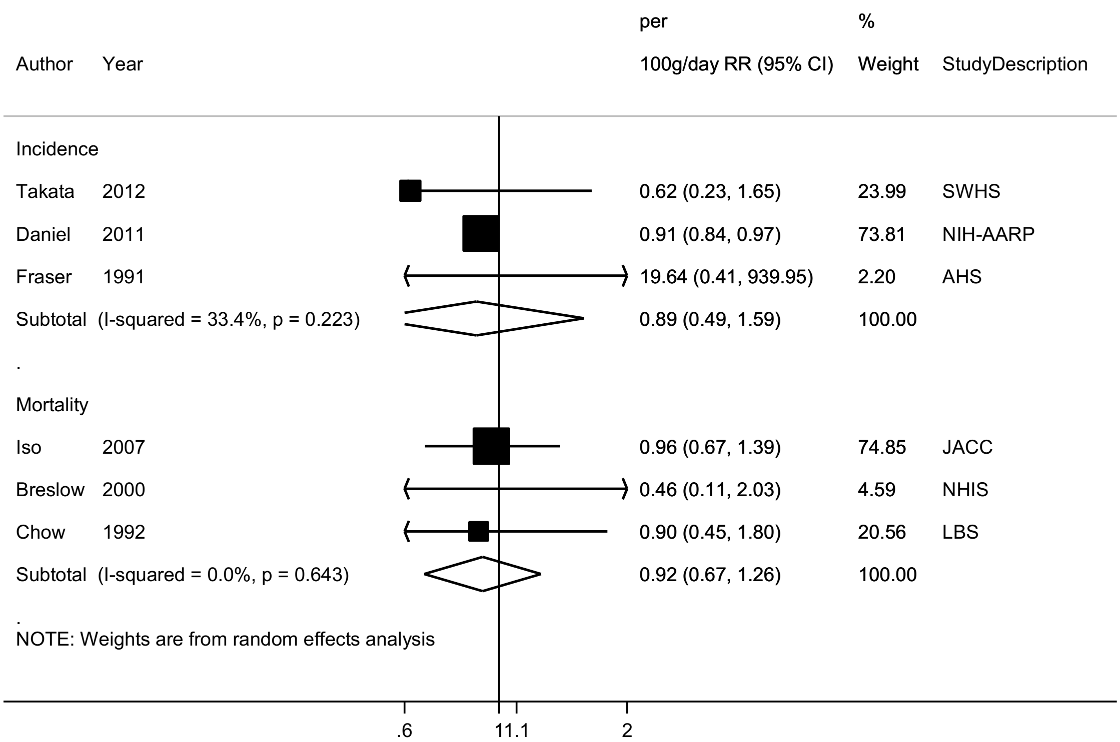


Figure 87 Funnel plot of studies included in the dose response meta-analysis of poultry consumption and lung cancer



Egger's test= 0.70

Figure 88 RR (95% CI) of lung cancer for 100 g/day increase of poultry by cancer outcome



2.5.2 Fish

Cohort studies

Summary

Main results:
Eight studies (13 695 cases) out of 11 cohort studies (13 publications) identified in the search were included in the dose-response meta-analysis. There was no association between lung cancer risk and fish intake. Two excluded studies did not report association (Khan, 2004; Kvale, 1983). In the third excluded study (Knekt, 1993) inverse associations were observed that were significant in current smokers but not in never smokers.

High heterogeneity was observed. Visual inspection of the forest plot shows that two smaller and olders studies that adjusted for smoking status but not for more smoking variables (Veierod, 1997; Khan, 2004) and the study on lung cancer screening in high risk population (Gnagnarella, 2013a) are inconsistent with larger, more recent studies.
There was no evidence of publication or small study bias (p=0.85) but the funnel plot indicates that a small study in Japanese men and women (Takezaki, 2003) reported a significant inverse association that was stronger than expected.

Sensitivity analyses:
The summary remained not significant but changed direction when studies were omitted in turn in the influence analysis. The summary RRs ranged from 0.97 (95% CI=0.90-1.05) when Daniel, 2011 was omitted to 1.0 (95% CI=0.94-1.05) when Gnagnarella, 2013a was omitted.
There was no evidence of non-linear dose-response association (Figure not shown). After excluding the only study not adjusted for smoking (Iso, 2007) the RR was 0.98(0.90-1.06).

Study quality:
All studies used FFQ to assess the intake of fish. One study reported on fresh fish (Iso, 2007, Japan). One study corrected relative risk estimates for measurement error of diet (Linseisen, 2011) and the relationship remained non-significant after calibration.
Three studies were on special populations: one study was on heavy smokers participating in a screening trial of lung cancer (Gnagnarella, 2013a), one on Chinese women who had never smoked (Takata, 2012) and one was in participants in screening for lung and other cancers (PLCO, Tasevska, 2011)
One study was on lung cancer mortality that did not adjust for smoking (Iso, 2007) and two studies adjusted for smoking status ((Veierod, 1997; Khan, 2004). The study in women never smokers controlled for passive smoking (Takata, 2012). The other studies adjusted for smoking status, duration and intensity.

Table 74 Fish consumption and lung 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	10
Studies included in dose-response meta-analysis	8
Studies included in non-linear dose-response meta-analysis	6

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

Table 75 Fish consumption and lung cancer risk. Summary of the dose-response meta-analysis in the 2005 SLR and CUP

	2005 SLR	**CUP**
Increment unit used	Serving per week	25 g/day
All studies		
Studies (n)	3	8
Cases (total number)	876	13 695
RR (95%CI)	0.93 (0.77-1.12)	0.99 (0.93-1.05)
Heterogeneity (I^2, p-value)	87%	66%, < 0.01
P value Egger test		0.85
Stratified and sensitivity analysis		
Sex	**Men**	**Women**
Studies (n)	2	2
RR (95%CI)	1.00 (0.96-1.05)	0.98 (0.93-1.04)
Heterogeneity (I^2, p-value)	0%, 0.88	0%, 0.62
	Incidence	**Mortality**
Studies (n)	6	2
RR (95%CI)	0.97 (0.89-1.06)	0.99 (0.95-1.03)
Heterogeneity (I^2, p-value)	75.4%, < 0.01	0%, 0.78

Table 76 Fish consumption and lung 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								
Song, 2014a	3	11624	Europe, North America, Japan	Lung cancer		0.95 (0.73-1.24)		
Yang, 2012b	7	12486	China, Denmark, France, Germany, Greece, Japan, Italy, Netherlands, Norway, Spain, Sweden, UK, USA	Incidence and mortality	Highest vs lowest	1.02 (0.96-1.08)		23.7%, 0.24

Table 77 Fish consumption and lung cancer risk. Main characteristics of studies included in the 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
Gnagnarella, 2013a LUN26858 Italy	COSMOS, Cohort of heavy smokers enrolled in lung cancer screening trial, Age: 50-84 years, M/W heavy smokers	178/ 4336 5.7 years	Screening examinations	FFQ	Incidence, lung cancer	63.55 vs 8 g/day	0.69 (0.45-1.06) Ptrend:0.05	Age, sex, energy intake, smoking duration, average daily cigarettes consumption, years of cessation, asbestos exposure, fruits and vegetables, fish, red meat, olive oil, tea and wine intake	
Takata, 2012 LUN26859 China	SWHS, Prospective Cohort, Age: 40-70 years, W, never smokers	428/ 71 267 11.2	Shanghai cancer registry and Shanghai vital statistics registry	FFQ	Incidence, lung cancer	96 vs 13 g/day	1.02 (0.76-1.38) Ptrend:0.79	Age, BMI, income, occupation, total caloric intake, history of asthma, passive smoking	Distribution of person-years by exposure quartiles
Daniel, 2011 LUN20266 USA	NIH-AARP, Prospective Cohort, Age: 50-71	9751/ 492 186 9.1 years	Cancer registry	Validated FFQ	Incidence, lung cancer	21.4 vs 3.6 g/1000 kcal	1.01 (0.94-1.08) Ptrend:0.65	Age, BMI, family history of cancer, HRT use, marital	Distribution of person-years and number of 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	Missing data derived for analyses
	years, M/W							status, race, intake of fruits, red meat, alcohol, poultry, vegetables, total calorie, smoking status, education, vigorous physical activity	quintiles, g/1000 kcal converted to g/day
Linseisen, 2011 LUN20342 Denmark, France, Germany, Greece, Italy, Netherlands, Norway, Spain, Sweden, UK	EPIC, Prospective Cohort, Age: 25-70 years, M/W	1822/ 478 021 8.70 years	Cancer and mortality registries, health insurance and pathology records, active follow up	FFQ	Incidence, lung cancer	≥ 80 vs 0-9 g/day Per 50 g	1.08 (0.86-1.36) 1.10 (0.91-1.35)	Age, sex, body weight and height, smoking status, duration of smoking, time since smoking cessation, cigarettes/day, physical activity, alcohol intake, centre, education, energy from fat and energy from carbohydrates and protein, fruits and vegetable intake	Total person-years and its distribution by 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
Iso, 2007 LUN20294 Japan	JACC, Prospective Cohort, Age: 40-79 years, M/W	855/ 105 500 15 years	Population death registries	Validated FFQ	Mortality, lung cancer, men	≥ 5 vs < 3 times/week	1.02 (0.86-1.22)	Age, area of study	Mid-point exposure, servings/week converted to g/day
		238/			Mortality, lung cancer, women		0.88 (0.63-1.24)		
Takezaki, 2003 LUN00268 Japan	Aichi Prefecture Study, Prospective Cohort, Age: 30- years, M/W	51/ 5885 14 years	Follow-up based on data from Aichi local council	FFQ - study-specific	Incidence, lung cancer	≥ 3 times/week vs < 1 time/week	0.19 (0.08-0.46)	Age sex, smoking status, cigarettes/day -2 categories- , occupation.	Servings/week converted to g/day
Veierød, 1997 LUN01643 Norway	NHSS, Prospective Cohort, Age: 16-56 years, M/W	151/ 51 452 11.2 years	Cancer registry	FFQ - study-specific	Incidence, lung cancer	≥ 5 vs < 1 times/week	3.00 (1.20-7.30)	Age, sex, smoking status	Servings/month converted to g/day
Chow, 1992 LUN02888 USA	LBS, Prospective Cohort, Age: 35- years, M	219 17 633 20 years	Death certificate	FFQ - study-specific	Mortality, lung cancer	> 15 vs < 2 times/month	1.0 (0.5-2.1)	Age, smoking status, industry/ occupation	Servings/months converted to g/day, mid-point exposure

Table 78 Fish consumption and lung cancer risk. Main characteristics of studies excluded from the 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
Khan, 2004, LUN00068, Japan	HGCS, Prospective cohort study, Age: ≥ 40 years, M/W	41/ 3158 14.8 years	Questionnaire (37 food items)	Survey	Mortality, lung cancer, men	Highest vs lowest	0.60 (0.30-1.10)	Age, health status, health education, health screening & smoking	Included in highest versus lowest analysis. Only 2 categories
		10/			Mortality, lung cancer, women		1.1 (0.2-5.3)		
Ozasa, 2001 LUN00725 Japan	JACC, Prospective Cohort, Age: 40-70 years, M/W	387/ 98 248 7.7 years	Population death registries	FFQ - study-specific	Mortality, lung cancer, men	Almost every day vs ≤ 1-2/week	1.03 (0.79-1.34) Ptrend: 0.72	Age, family history of cancer, smoking habits	Superseded by Iso, 2007 LUN20294
		105/ 98 248 7.7 years			Mortality, lung cancer, women		0.88 (0.52-1.49) Ptrend: 0.50		
Knekt, 1993 LUN02684 Finland	FMCHE, Nested Case Control, Age: ≥ 15 years, M	21 172 9 years	Cancer registry	FFQ - study-specific	Incidence, lung cancer, current smokers	Lowest vs highest	0.5 (0.3-0.8)	Age	Included in highest versus lowest analysis. Only 2 categories, lowest vs highest tertiles recalculated to high vs low
					Incidence, lung cancer, non-smokers		0.6 (0.3-1.6)		
Knekt, 1991b LUN03018 Finland	FMCHE, Age: 20-69 years,	4583 20 years	Finnish cancer registry	FFQ - study-specific	Incidence, lung cancer, non-smokers	Lowest vs highest	0.50	Age, smoking habits	No confidence intervals Same as Knekt,

Author, Year, WCRF Code, Country	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				Incidence, lung cancer, smokers		0.50		1993 LUN02684
Kvåle, 1983 LUN04322 Norway	Norway, 1967-1978, Prospective Cohort, M/W	168/ 16 713 11.5 years	Cancer Registry of Norway	Dietary history questionnaire	Incidence, primary tumour of lung cancer	Highest vs lowest	0.82 Ptrend: 0.63	Age, cigarette smoking, urban/rural place of residency	Intake is a score of frequency

Figure 89 RR estimates of lung cancer by levels of fish consumption

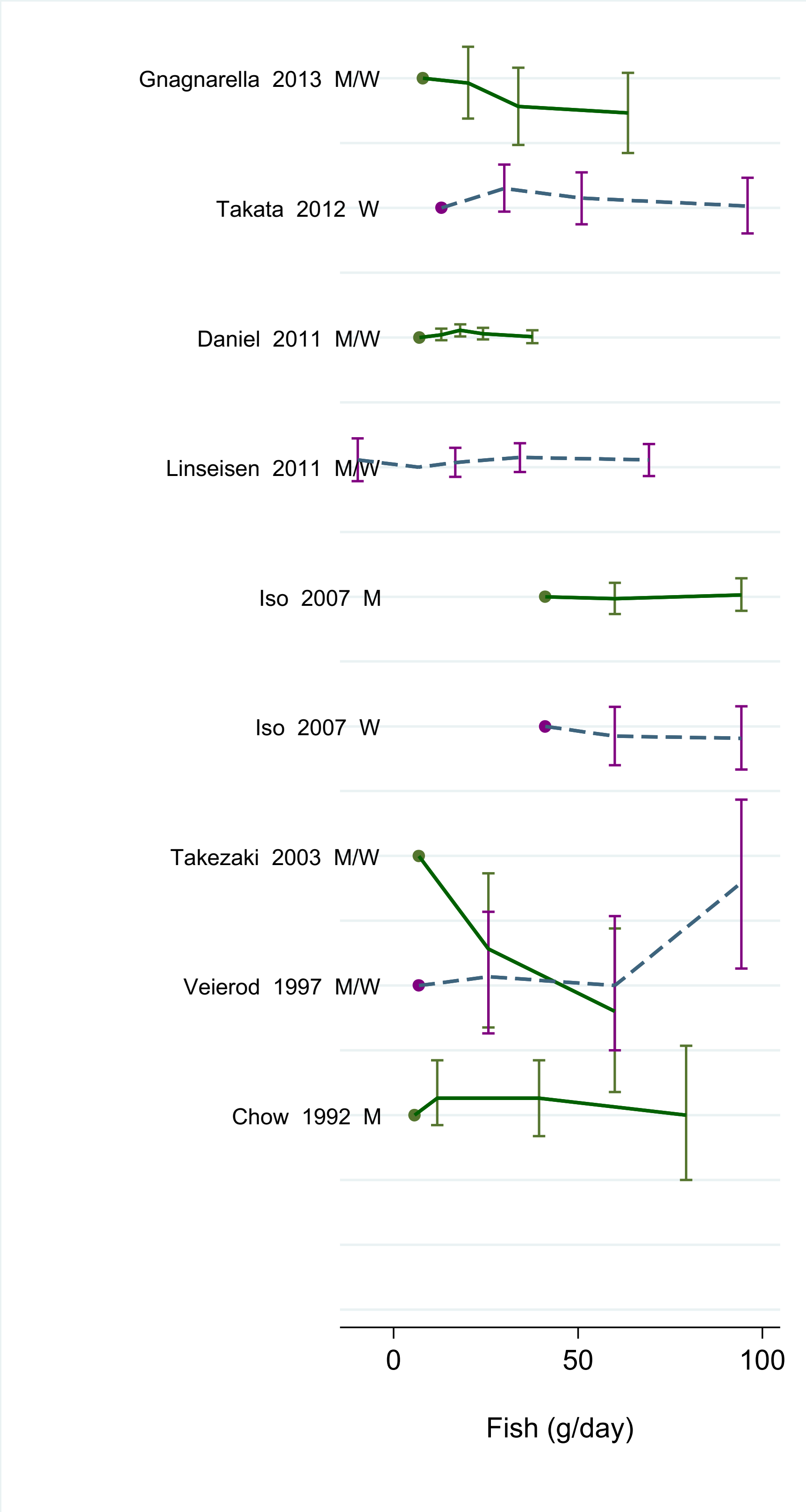
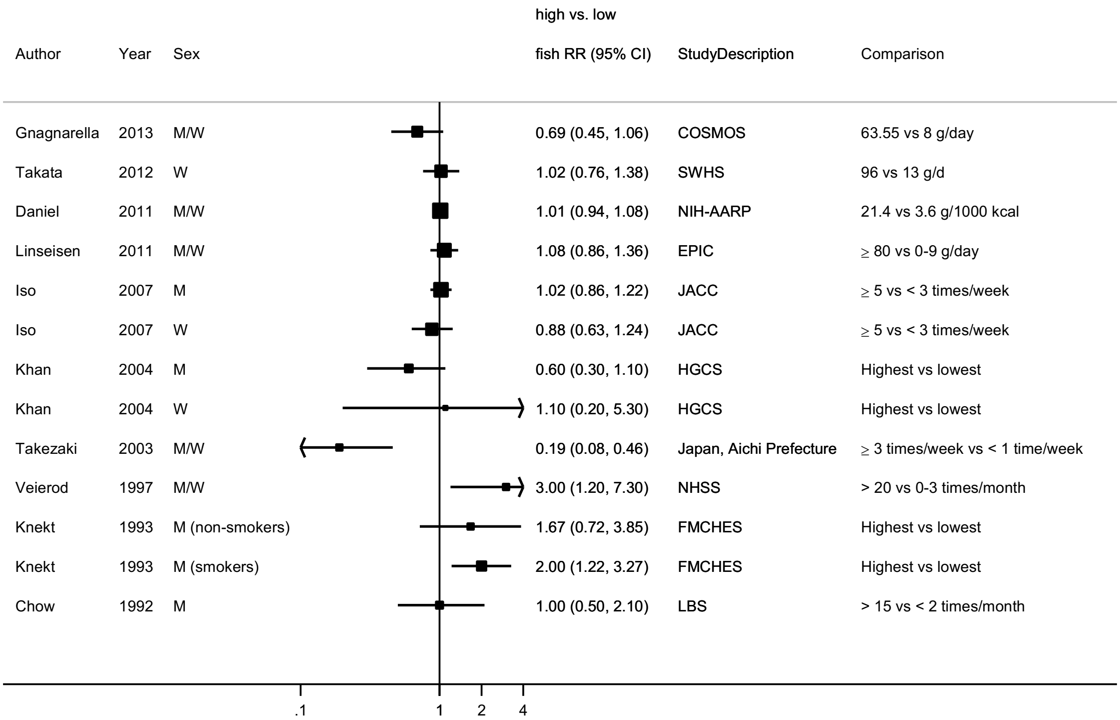


Figure 90 RR (95% CI) of lung cancer for the highest compared with the lowest level of fish consumption



* In study of Khan, 2004, the comparison is several times per week or every day vs never, several times per year or several times per month.

Figure 91 RR (95% CI) of lung cancer for 25 g/day increase of fish consumption

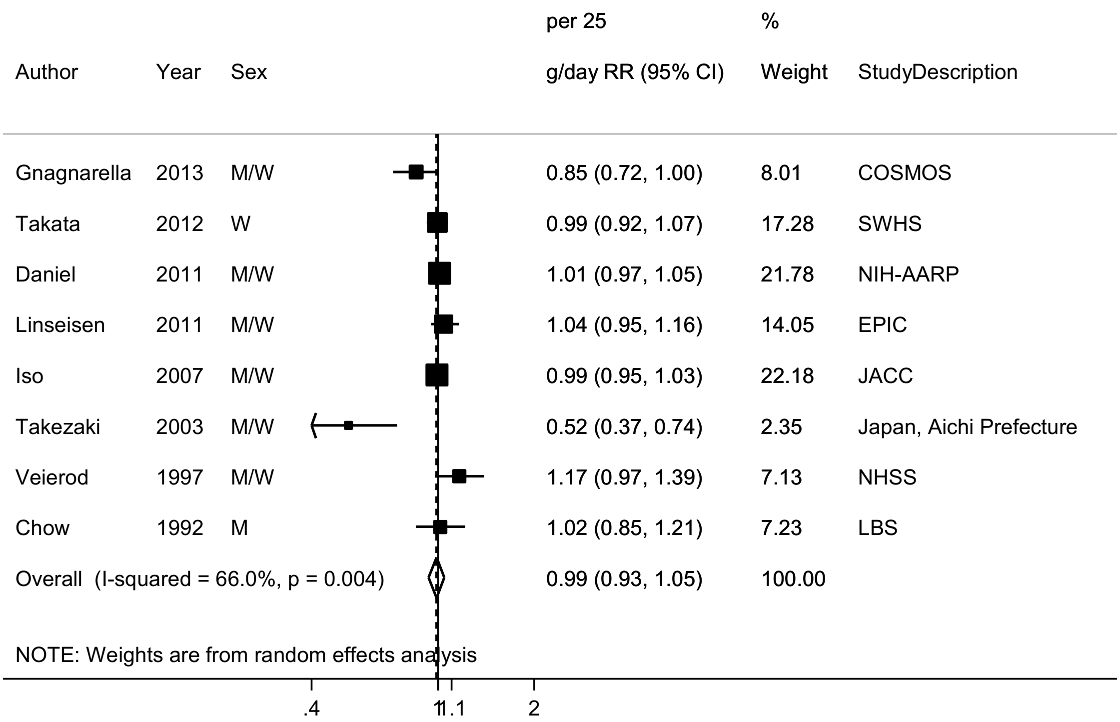


Figure 92 RR (95% CI) of lung cancer for 25 g/day increase of fish consumption, after excluding study not adjusted by smoking status

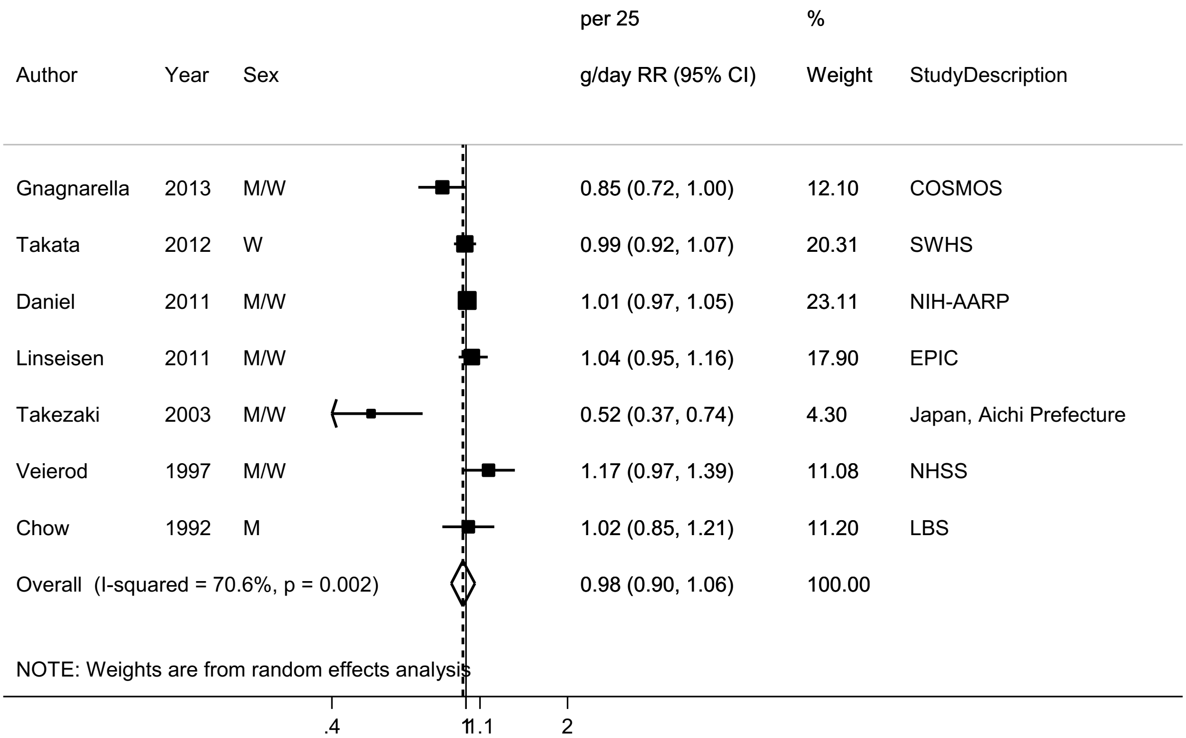
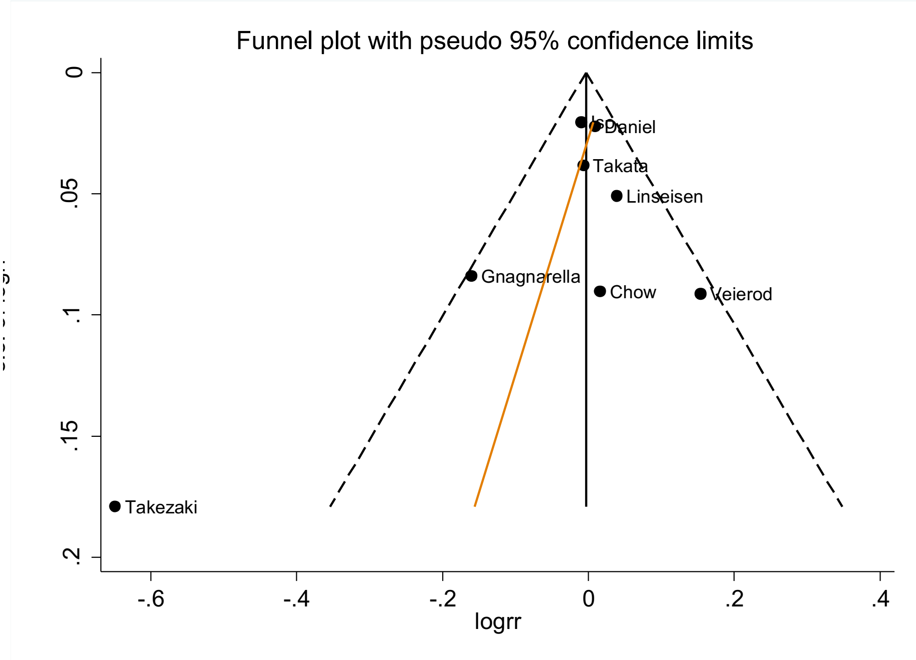


Figure 93 Funnel plot of studies included in the dose response meta-analysis of fish consumption and lung cancer



Egger's test p=0.85

Figure 94 RR (95% CI) of lung cancer for 25 g/day increase of fish by sex

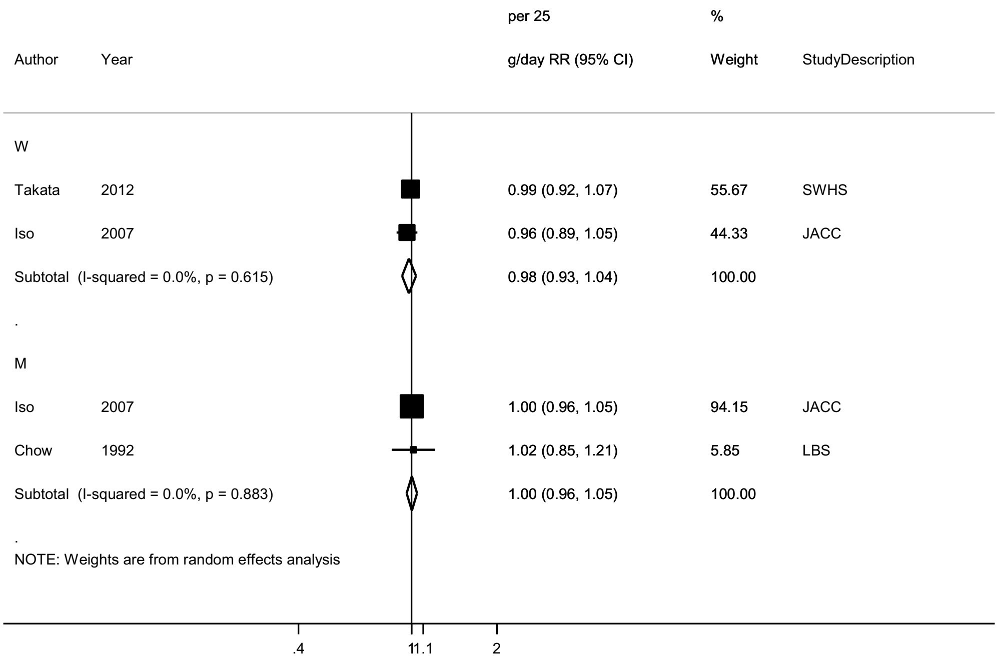
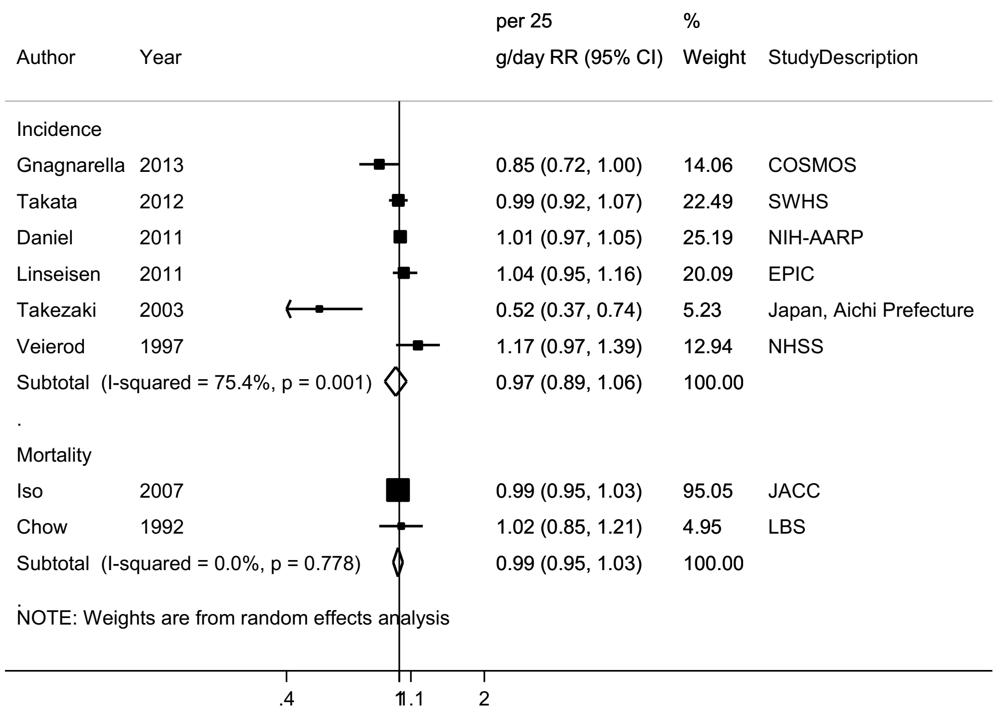


Figure 95 RR (95% CI) of lung cancer for 25 g/day increase of fish by cancer outcome



2.5.4 Eggs

Cohort studies

Summary

Five studies (2075 cases) out of 9 cohort studies identified in the search (11 publications) were included in the dose-response meta-analysis. No significant association between eggs intake and lung cancer risk was observed.

No heterogeneity was observed. There was no evidence of publication or small study bias (p=0.23) but only five studies are included in the analysis. The forest plot suggests that small studies showing inverse associations are missing.

Sensitivity analyses:
The summary RR did not change materially when studies were omitted in turn in the influence analysis. The summary RRs ranged from 0.95 (95% CI=0.91-1.00) when Veierod, 1997 was omitted to 0.97 (95% CI=0.91-1.04) when Iso, 2007 was omitted.

Study quality:
All studies used FFQ to assess the intake of eggs. All studies included in the dose-response analysis were adjusted for age and smoking status except the JACC study (Iso, 2007) on lung cancer mortality that did not adjust for smoking. The study in women never smokers was controlled for passive smoking (Takata, 2012). Only one study adjusted for smoking intensity (Gnagnarella, 2013a).

One study was on heavy smokers participating in a screening trial of lung cancer (Gnagnarella, 2013a); one study was on Chinese women who had never smoked (Takata, 2012).

Table 79 Eggs consumption and lung 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 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 80 Eggs consumption and lung cancer risk. Summary of the dose-response meta-analysis in the 2005 SLR and CUP

	2005 SLR	**CUP**
Increment unit used		20 g/day
All studies		
Studies (n)		5
Cases (total number)		2075
RR (95%CI)		0.96 (0.92-1.00)
Heterogeneity (I^2, p-value)		0%, 0.48
P value Egger test		0.23
Stratified and sensitivity analysis		
	Incidence	**Mortality**
Studies (n)	3	2
RR (95%CI)	1.00(0.87-1.15)	0.96 (0.91-1.01)
Heterogeneity (I^2, p-value)	35.2%, 0.21	0%, 0.58

Table 81 Eggs consumption and lung cancer risk. Main characteristics of studies included in the 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
Gnagnarella, 2013a LUN26858 Italy	COSMOS, Cohort of heavy smokers enrolled in lung cancer screening trial, Age: 50-84 years, M/W heavy smokers	178/ 4 336 5.7 years	Screening examinations	FFQ	Incidence, lung cancer	28.90 vs 3.50 g/day	0.93 (0.62-1.14) Ptrend:0.79	Age, sex, energy intake, smoking duration, average daily cigarettes consumption, years of cessation, asbestos exposure, fruits and vegetables, fish, red meat, olive oil, tea and wine intake	Distribution of person-years by exposure quartiles
Takata, 2012 LUN26859 China	SWHS, Prospective Cohort, Age: 40-70 years, W, never smokers	428/ 71 267 11.2	Shanghai cancer registry and Shanghai vital statistics registry	FFQ	Incidence, lung cancer	87 vs 6 g/day	0.87 (0.52-1.44) Ptrend:0.26	Age, BMI, income, occupation, total caloric intake, history of asthma, passive smoking	Distribution of person-years by exposure quartiles
Iso, 2007 LUN20294 Japan	JACC, Prospective Cohort,	855/ 105 500 15 years	Population death registries	Validated FFQ	Mortality, lung cancer, men	≥ 5 vs < 3 /week	0.89 (0.76-1.05)	Age, area of study	Mid-point exposure, servings/week

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Missing data derived for analyses
	Age: 40-79 years, M/W	238			Mortality, lung cancer, women		0.93 (0.68-1.26)		converted to g/day
Veierød, 1997 LUN01643 Norway	NHSS, Prospective Cohort, Age: 16-56 years, M/W	151/ 51 452 11.2 years	Cancer registry	FFQ - study-specific	Incidence, lung cancer	≥ 5 vs < 1 number/week	1.6 (0.8-3.5)	Age, sex, smoking status	Number/week converted to g/day
Chow, 1992 LUN02888 USA	LBS, Prospective Cohort, Age: 35- years, M	219/ 17 633 20 years	Death certificate	FFQ - study-specific	Mortality, lung cancer	> 31 vs < 10 times/month	0.9 (0.6-1.3)	Age, smoking status, industry/ occupation	Servings/months converted to g/day, mid-point exposure

Table 82 Eggs consumption and lung cancer risk. Main characteristics of studies excluded from the 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
Khan, 2004, LUN00068, Japan	HGCS, Prospective cohort study, Age: ≥ 40 years, M/W	41/ 3158 14.8 years	Annual follow-up survey, cause of death classified by researchers	Survey	Mortality, lung cancer, men	Highest vs lowest	1.0 (0.4-2.5)	Age, health status, health education, health screening & smoking	Used only in highest versus lowest analysis. Only 2 categories
		10/ 3158 14.8 years			Mortality, lung cancer, women				
Knekt, 1993 LUN02684 Finland	FMCHES, Nested Case Control, Age: ≥ 15 years, M	21 172 9 years	Finnish cancer Registry	FFQ - study-specific	Incidence, lung cancer, current smokers	Lowest vs highest	1.0 (0.6-1.6)	Age	Used only in highest versus lowest analysis. Only 2 categories, lowest vs highest tertiles recalculated to high vs low
					Incidence, lung cancer, non-smokers		1.4 (0.6-3.4)		
Knekt, 1991b LUN03018 Finland	FMCHES, Age: 20-69 years, M	4583 20 years	Finnish cancer Registry	FFQ - study-specific	Incidence, lung cancer, non-smokers	Lowest vs highest	1.37	Age, smoking habits	Superseded by Knekt, 1993 LUN02684
					Incidence, lung cancer, smokers		0.95		
Knekt, 1991a LUN03143 Finland	FMCHES, Age: 20-69 years,	4583 20 years	Finnish cancer Registry	FFQ - study-specific	Incidence, lung cancer	Highest vs lowest	0.9 (0.6-1.4)	Age, smoking	Superseded by Knekt, 1993 LUN02684

Author, Year, WCRF Code, Country	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								
Shekelle, 1991 LUN03021 USA	US, Western Electric Prospective cohort study Age: 41-57 years, M	57/ 1878 24 years	Annual self-reported, confirmed through medical records. Death certificates	FFQ - study-specific	Incidence, lung cancer	Highest vs lowest	1.40 (0.70-2.70)	Age, smoking habits, intake of dietary beta-carotene, % of calories from fat	Used only in highest versus lowest analysis. Only 2 categories
Kvåle, 1983 LUN04322 Norway	Norway, 1967-1978, Prospective Cohort, M/W	168/ 16 713 11.5 years	Cancer Registry of Norway	Dietary history questionnaire	Incidence, lung cancer	Highest vs lowest	0.90 Ptrend: 0.59	Age, cigarette smoking, urban/rural place of residency	Intake is a score of frequency

Figure 96 RR estimates of lung cancer by levels of eggs consumption

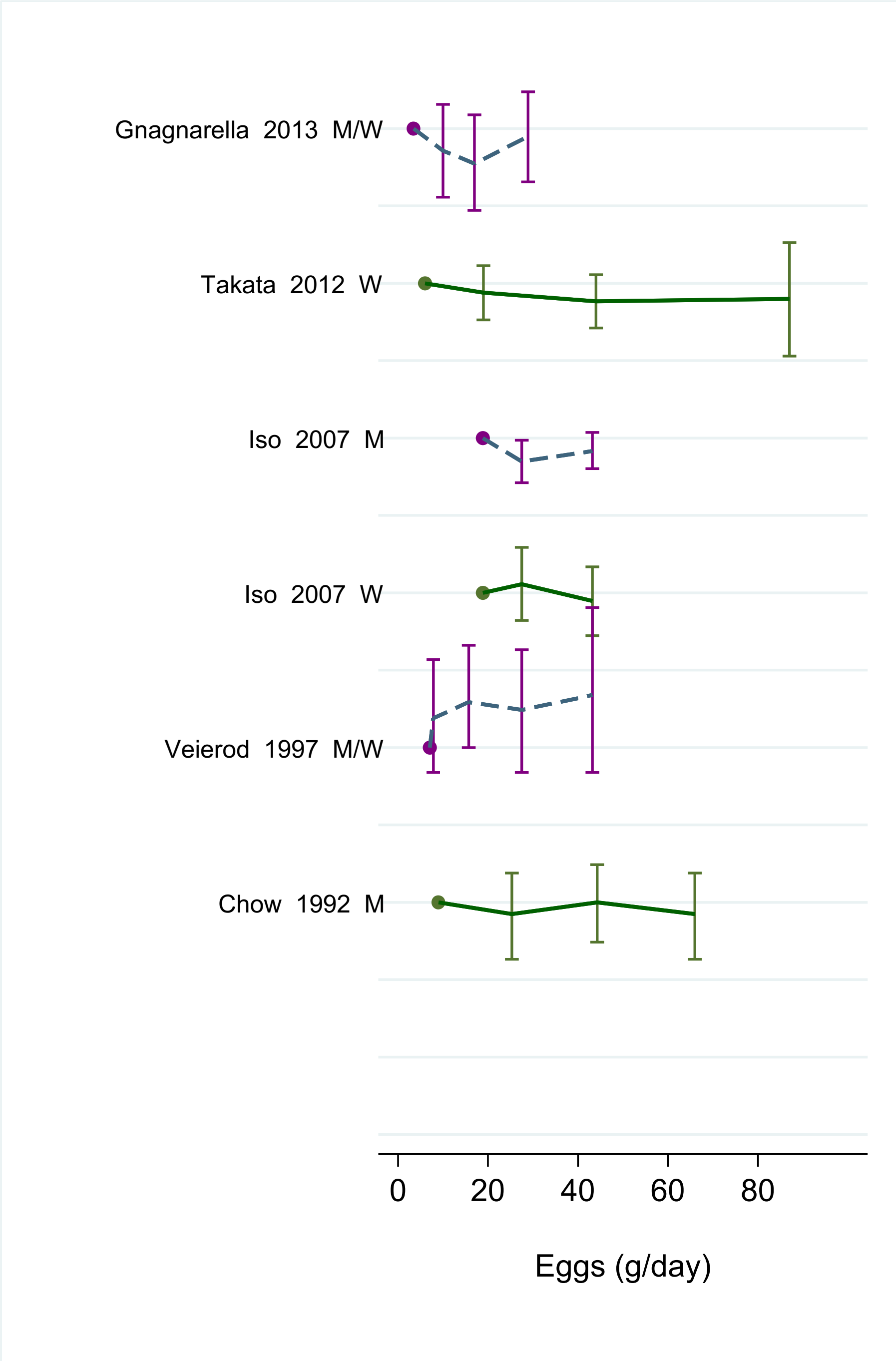
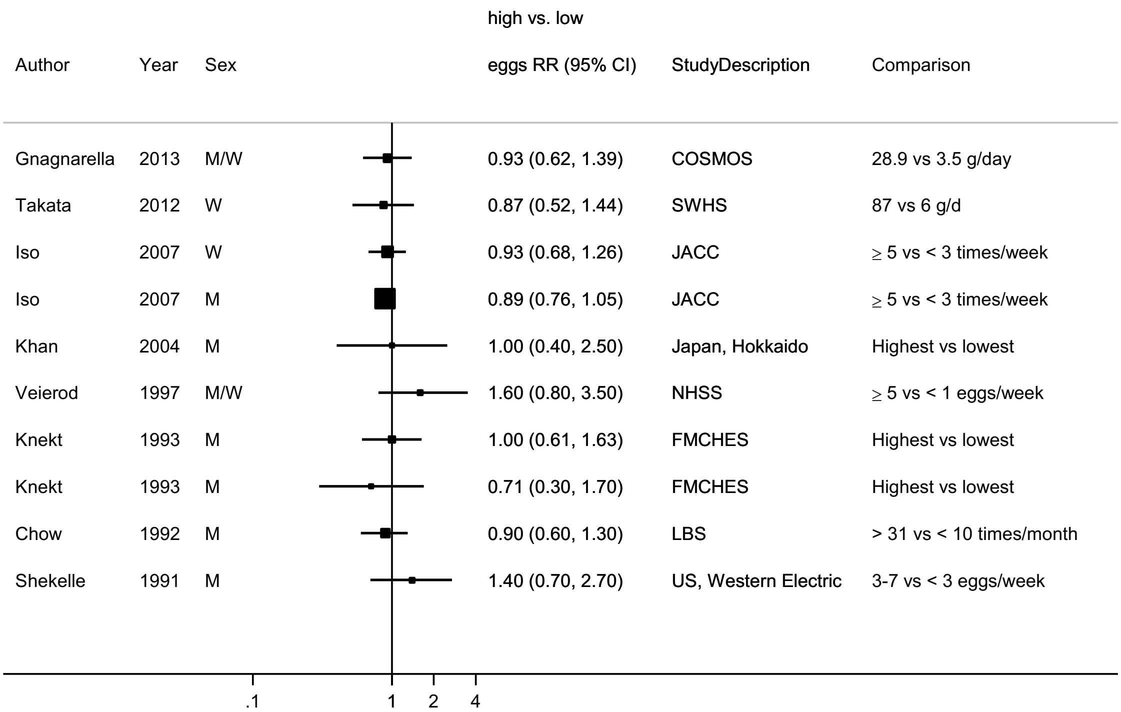


Figure 97 RR (95% CI) of lung cancer for the highest compared with the lowest level of eggs consumption



* In study of Khan, 2004, the comparison is several times per week or every day vs never, several times per year or several times per month.

Figure 98 RR (95% CI) of lung cancer for 20 g/day increase of eggs consumption

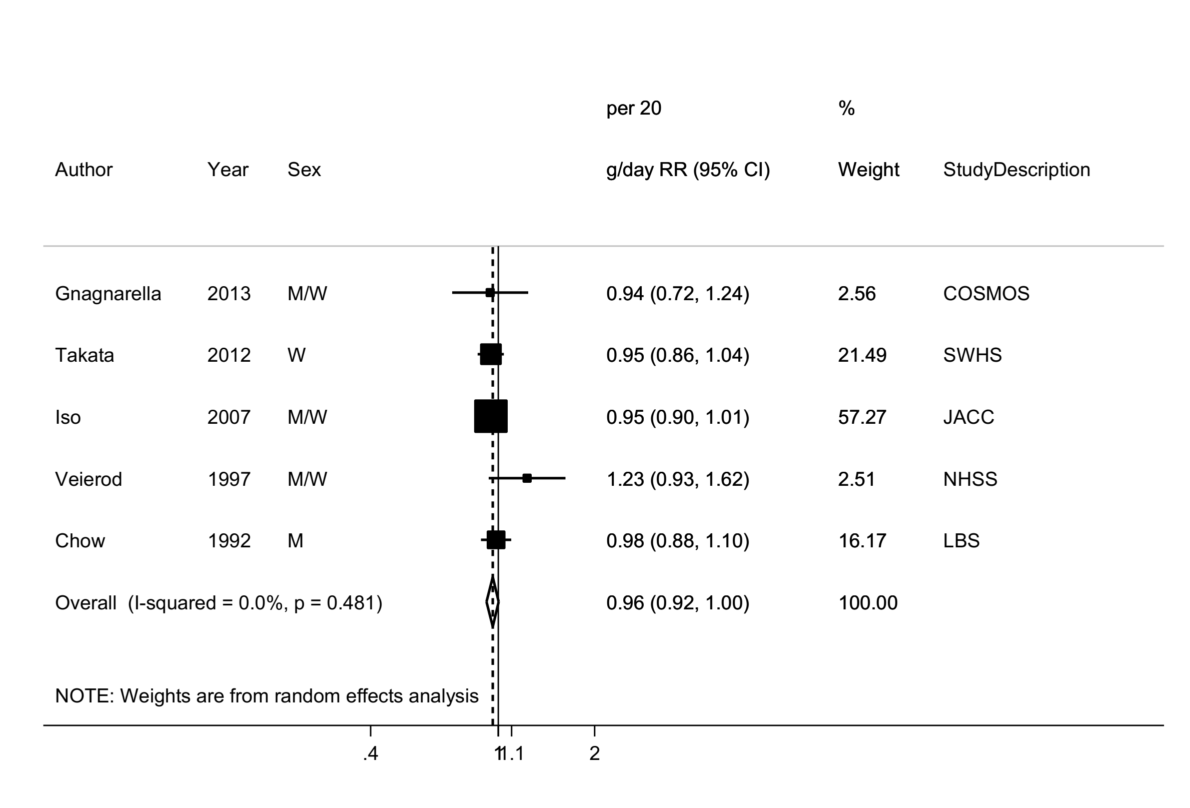
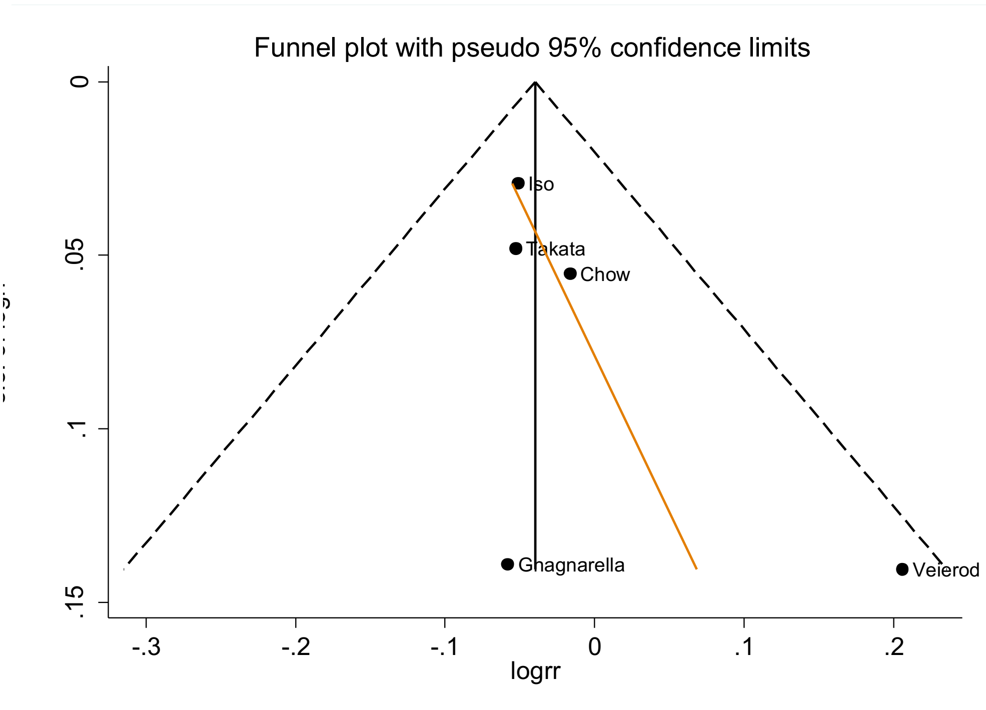
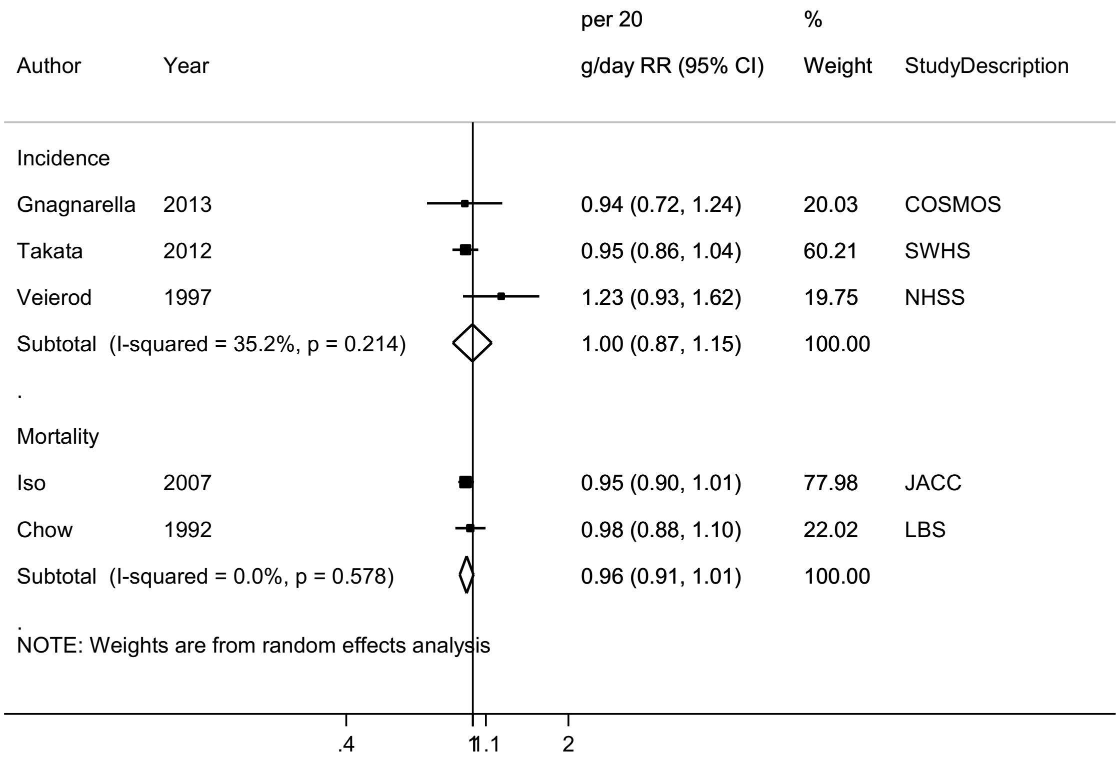


Figure 99 Funnel plot of studies included in the dose response meta-analysis of eggs consumption and lung cancer



Egger's test p=0.23

Figure 100 RR (95% CI) of lung cancer for 20 g/day increase of eggs by cancer outcome



2.6.1.1 Butter

Two cohort studies were identified in the CUP, one was an update from a study previously identified in the 2005SLR. In total three cohort studies on butter intake and lung cancer have been published. Two reported no association and one reported a borderline significant positive association. No meta-analysis was conducted.

The section is included in the CUP SLR because the evidence that butter intake increases lung cancer risk was judged as limited suggestive in the Second Expert Report. The evidence in the 2005SLR was based on a highest compared to lowest analysis of eight case-control studies (no overall was provided). Seven of the eight studies reported butter consumption to be associated with lung cancer in the direction of increased risk, reporting odds ratios ranging from 1.27 to 2.02, only two of these studies had significant results.

Table 83 Butter and lung cancer risk. Main characteristics of studies identified in CUP and 2005 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
Gnagnarella, 2013 LUN26858 Italy	COSMOS (Continuous Observation of Smoking Subjects), Prospective Cohort, Age: 50-84 years	178/ 4 336 6 years	Screening examinations	FFQ	Incidence, lung cancer	1.24 vs 0 g/1000 kcal/day	1.04 (0.69-1.56) Ptrend:0.55	Age, sex, asbestos occupation, energy, smoking history (duration, average daily cigarettes consumption, years of cessation)
Iso, 2007 LUN20294 Japan	JACC, Prospective Cohort, Age: 40-79	717/ 105 500 15 years	Municipal resident registration records, death	Validated FFQ	Mortality, lung cancer, men	≥3-4 vs <1 times/week	1.10 (0.84-1.44)	Age, area of study
		217			Women	≥3-4 vs <1	1.51 (0.97-2.34)	

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors
	years, M/W		certificates			times/week		
Ozasa, 2001 LUN00725 Japan	JACC study, Prospective Cohort, Age: 40-70 years, M/W, No specific group	317/ 98 248 8 years		FFQ - study-specific	Mortality, lung cancer, men	12-16 times/month vs scarcely an times/month	0.92 (0.65-1.30)	Age, family history of cancer, smoking habits
					Mortality, lung cancer, women		0.90 (0.46-1.77)	
					Mortality, lung cancer, current smokers		0.94 (0.62-1.42)	
Knekt, 1991 LUN03143 Finland	Finland, 1966, Prospective Cohort, Age: 20-69 years, M	4 538 20 years	Cancer registry	FFQ - study-specific	Incidence, lung cancer	Tertile 3 vs tertile 1 g/month	1.80 (1.00-3.00)	Age, energy intake, other nutrients, foods or supplements, smoking habits

2.7.1 Milk

Cohort studies

Summary

Main results:
Seven studies (1578 cases) were included in the dose-response meta-analysis. No significant (inverse) association was observed.
There was low heterogeneity and no significant evidence of publication or small study bias (p=0.55).

Sensitivity analysis:
The summary RRs ranged from 0.76 (95% CI=0.60-0.97) when Gnagnarella, 2013a was omitted (the study had 43% of weight in the analysis) to 0.99 (95% CI=0.82-1.20) when Iso, 2007 was omitted in the influence analysis.
There were a limited number of studies on lung cancer subtypes and by smoking status and no stratified analyses could be conducted.

Study quality:
Cancer outcome was identified through cancer registry in most studies and milk intake was assessed using FFQ in all studies. One study on lung cancer mortality (Iso, 2007) did not adjust by smoking. After excluding the only study not adjusted for smoking (Iso, 2007) the RR was 1.00(0.83-1.21).

One study was in heavy smokers or people exposed to asbestos participating in a screening trial on early lung cancer diagnosis (Gnagnarella, 2013a). One study was in Adventists (Fraser, 1991).

Table 84 Milk intake and lung cancer risk. Number of studies in the CUP SLR

	Number
Studies identified	7 (8 publications)
Studies included in forest plot of highest compared with lowest exposure	6
Studies included in dose-response meta-analysis	5
Studies included in non-linear dose-response meta-analysis	Not enough studies

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

Table 85 Milk intake and lung cancer risk. Summary of the dose-response meta-analysis in the 2005 SLR and CUP.

	2005 SLR	**CUP**
Increment unit used	No meta-analysis	1 cup/day
All studies		
Studies (n)		5
Cases (total number)		1578
RR (95%CI)		0.89 (0.73-1.08)
Heterogeneity (I^2, p-value)		19.4 %, 0.29
P value Egger test		0.55

Table 86 Milk intake and lung cancer risk. Main characteristics of studies 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	Missing data derived for analyses
Gnagnarella, 2013a LUN26858 Italy	COSMOS, Prospective Cohort, Age: 50-84 years M/W heavy smokers	178/ 4336 6 years	Screening examinations	FFQ	Incidence, lung cancer	280 g/d vs none	0.99 (0.70-1.41)	Age, sex, smoking status and dose, exposure to asbestos, total energy	Mid-points of exposure
Iso, 2007 LUN20294 Japan	JACC, Prospective Cohort, Age: 40-79 years, M/W	791/ 105 500 15 years	Population death registries	Validated FFQ	Mortality, lung cancer, men	≥5 times/week vs <3 times/week	0.81 (0.68-0.95)	Age, area of study	Mid-points of exposure
		232			Mortality, lung cancer, women		0.84 (0.61-1.15)		
Takezaki, 2003 LUN00268 Japan	Aichi Cancer Registry Study, Prospective Cohort, Age: 30- years, M/W	51/ 5885 14 years	Cancer Registry	FFQ - study-specific	Incidence, lung cancer	Everyday vs almost never	0.68 (0.28-1.64)	Age sex, smoking status, cigarettes/day - 2 categories- occupation.	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
Breslow, 2000 LUN01082 USA	National Health Interview Survey (NHIS), Prospective Cohort, Age: 18-87 years, M/W	157/ 20 195 8 years	Mortality records	FFQ	Mortality, lung cancer	> 8 servings/week vs 0 serving/week	0.70 (0.30-1.70)	Age, sex, smoking habits, packs per day smoked	Mid-points of exposure
Fraser, 1991 LUN03076 USA	Adventist Health Study, Prospective Cohort, Age: 25- years, M/W Vegetarians/ Healthy Diet	54/ 34 198 6 years	Active follow-up by mail with confirmation through medical records and SEER registry where available	FFQ - study-specific	Incidence, lung cancer	≥7 times/week vs <1 time/week	0.88 (0.37-2.12)	Age, sex, smoking habits	Mid-points of exposure

Table 87 Milk consumption and lung cancer risk. Main characteristics of studies excluded 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) P trend	Adjustment factors	Reasons for exclusion
Khan, 2004 LUN00068 Japan	Japan, Hokkaido Cohort Study, Prospective Cohort, Age: 40- years, M/W	3 158 15 years	Annual follow-up survey, cause of death classified by researchers	Dietary history questionnaire	Mortality, lung cancer	Several times/week or everyday vs never or several times/year or several times/month	1.10 (0.60-2.10)	Age, smoking habits	Used only in highest versus lowest analysis. Only 2 categories
Ozasa, 2001 LUN00725 Japan	JACC study, Prospective Cohort, Age: 40-70 years, M/W	387/ 98 248 8 years	Population death registries	FFQ - study-specific	Mortality, lung cancer, men	6-7 times/week vs scarcely any times	0.87 (0.67-1.14)	Age, family history of cancer, smoking habits	Superseded by Iso, 2007 (LUN20294)
		109			Mortality, lung cancer , women		0.89 (0.50-1.59)		
Kvåle, 1983 LUN04322 Norway	Norway, 1967-1978, Prospective Cohort, M/W	81/ 16 713 12 years	Cancer registry	Dietary history	Incidence, lung cancer, men	Highest intake vs lowest intake drinks/day	0.64	Age, area of residence, smoking habits, urban/rural status	No confidence intervals and only 2 categories

Figure 101 RR estimates of lung cancer by levels of milk intake

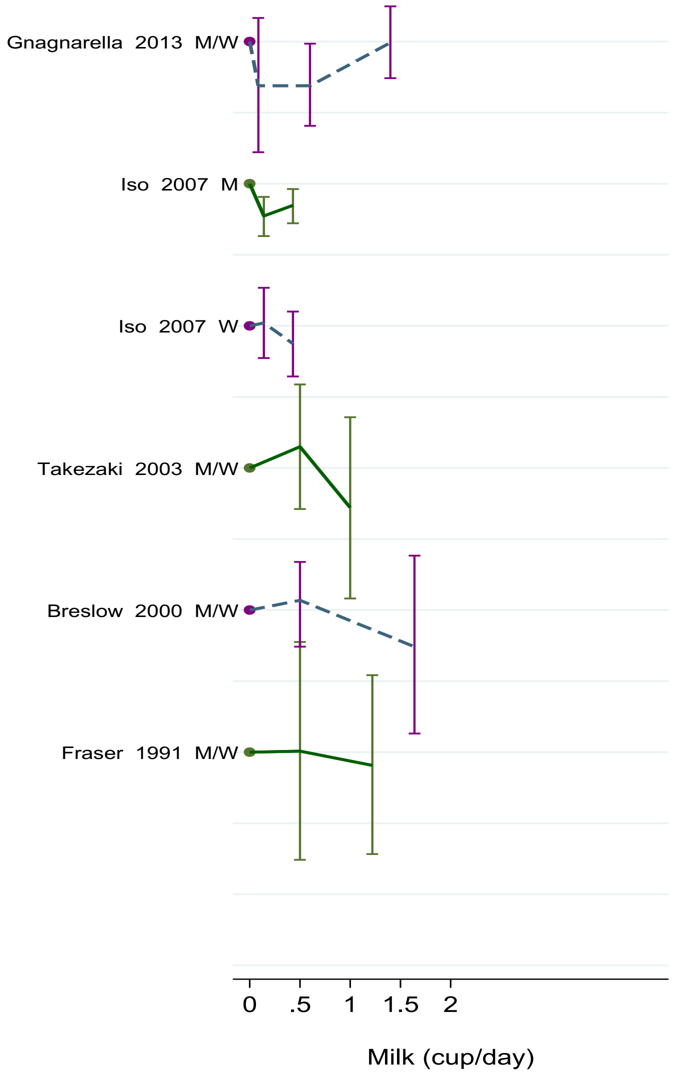


Figure 102 RR (95% CI) of lung cancer for the highest compared with the lowest level of milk intake

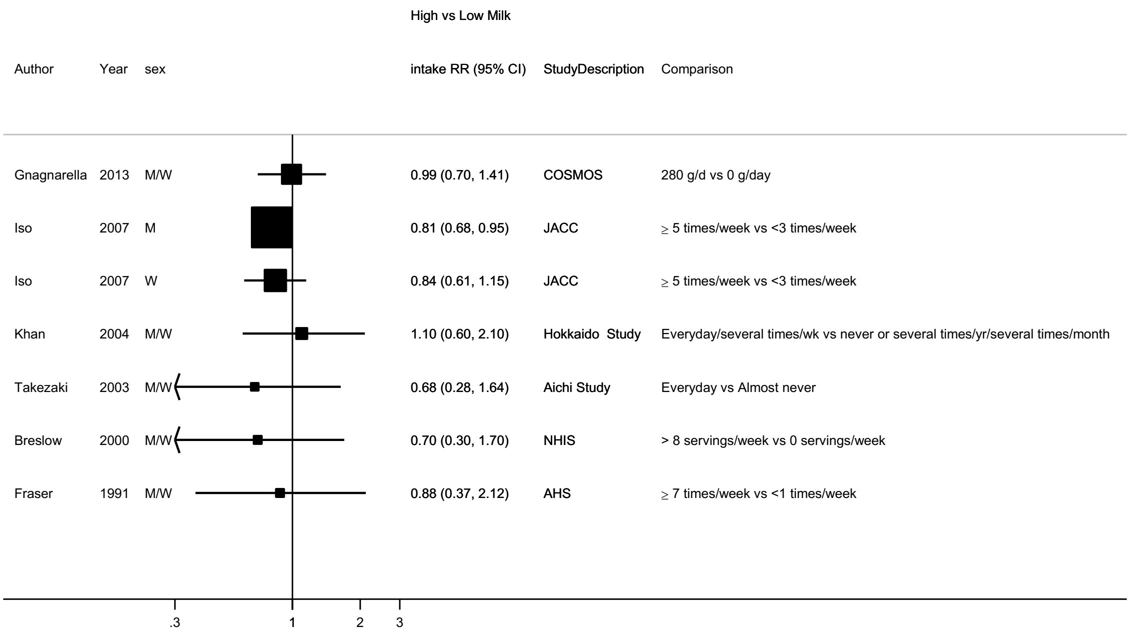


Figure 103 RR (95% CI) of lung cancer for 1 cup/day increase of milk intake

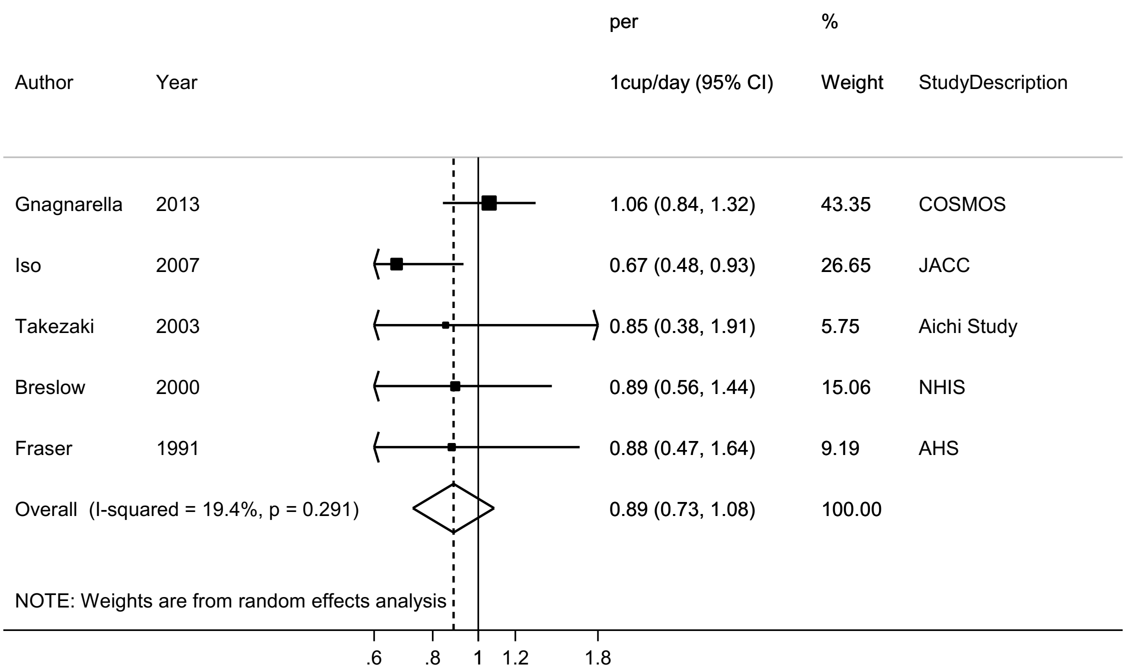


Figure 104 RR (95% CI) of lung cancer for 1 cup/day increase of milk intake, after excluding study not adjusted for smoking status

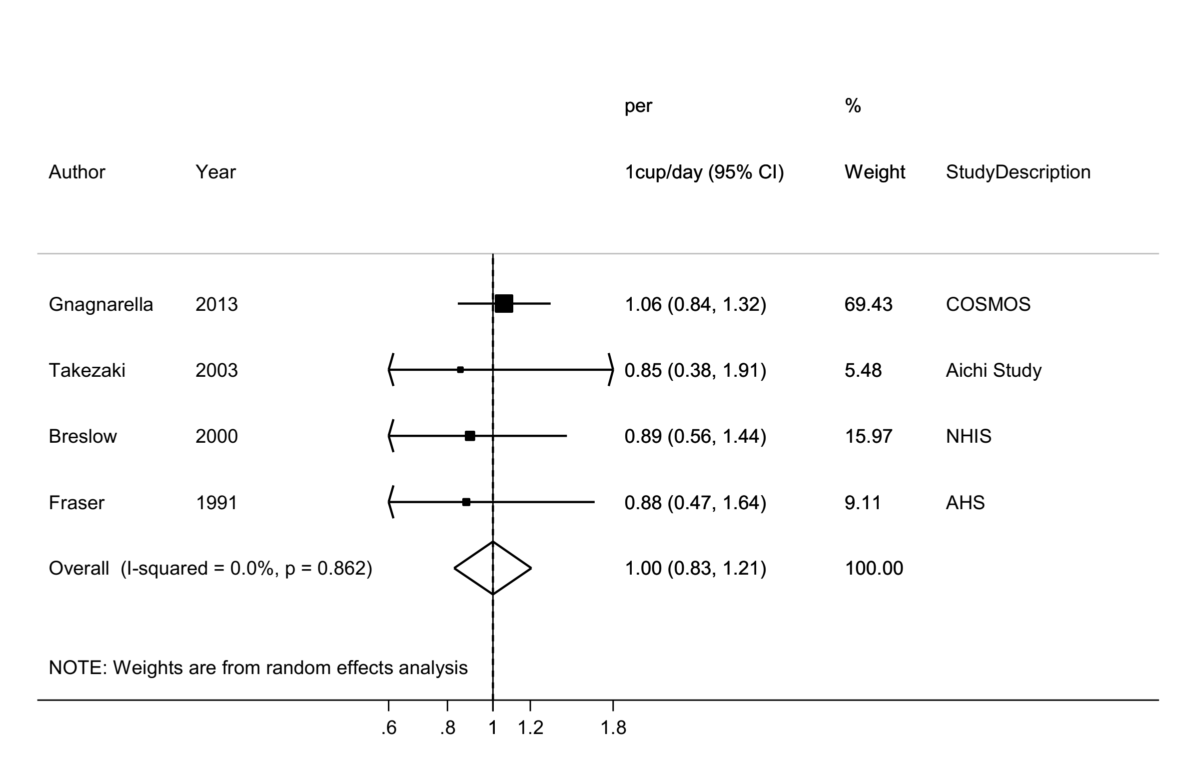
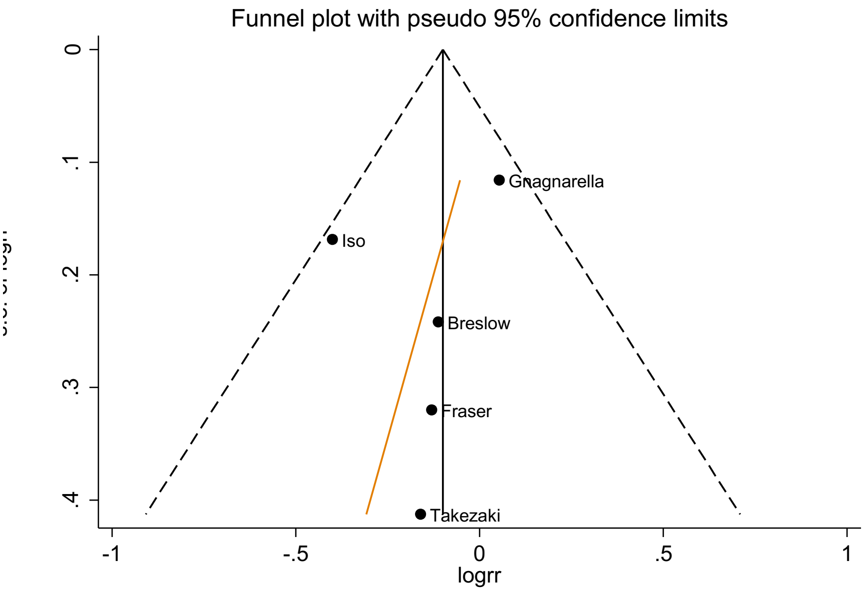


Figure 105 Funnel plot of studies included in the dose response meta-analysis of milk intake and lung cancer



Egger's test p=0.55

3 Beverages

3.6.1 Coffee

Cohort studies

Summary

Main results:
Seven studies (1904 cases) out of ten were included in the dose-response meta-analysis. A significant positive association was observed. Heterogeneity was moderate.
There was no significant evidence of publication or small study bias (p=0.63).

Sensitivity analysis:
The summary RRs ranged from 1.04 (95% CI=0.98-1.10) when Chow, 1992 was omitted to 1.10 (95% CI=1.05-1.15) when Iso, 2007 was omitted in the influence analysis.
In Chow, 1992 (in Lutheran white men) the excess risk with high coffee intake was observed almost entirely among current cigarette smokers; no increased risk was observed among nonsmokers or former smokers (data not shown in the article).

Study quality:
Cancer outcome was confirmed using cancer registry records in most studies and coffee intake was assessed using FFQ or questionnaire in all studies.
One study (Iso, 2007) did not adjusted by smoking status. When this study was omitted from the analysis the summary RR was 1.10 (95% CI=1.05-1.15)

Table 88 Coffee intake and lung cancer risk. Number of studies in the CUP SLR

	Number
Studies identified	10 (10 publications)
Studies included in forest plot of highest compared with lowest exposure	9
Studies included in 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

Table 89 Coffee intake and lung cancer risk. Summary of the dose-response meta-analysis in the 2005 SLR and CUP.

	2005 SLR	CUP
Increment unit used	1 cup/week	1 cup/day

All studies		
Studies (n)	3	7
Cases (total number)	337	1904
RR (95%CI)	1.06 (0.61-1.86)	1.07 (1.01-1.13)
Heterogeneity (I^2, p-value)	0%	51.7 %, 0.05
P value Egger test		0.63
Sex	**Men**	**Women**
Studies (n)	4	3
RR (95%CI)	1.08 (0.99-1.18)	1.05 (0.88-1.26)
Heterogeneity (I^2, p-value)	74.3%, <0.01	52.7%, 0.12

Table 90 Coffee intake and lung 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								
Tang, 2010	5 Cohort 8 Case-control	624 4750	Europe, USA, Canada, Uruguay, Japan	Incidence, lung cancer	Highest versus lowest coffee intake	1.27 (1.04-1.54) (total) 1.13 (0.90-1.41) (case-control) 1.57 (1.15-2.14) (cohort)		58.6%, < 0.01 53.5%, 0.04 45.1%, 0.12
					Per 2 cups/day	1.14 (1.04-1.26)		41.2%, 0.09
Wang, 2012	3 cohorts 6 case-control	3008		Incidence, lung cancer	Per 1 cup/day	1.04 (0.85–1.26)	p non-linearity = 0.63	< 0.01
					Per 2 cups/day	1.11 (0.92–1.34)		
					Per 3/cups/day	1.23 (1.05–1.44)		
					Per 4 cups/day	1.36 (1.17–1.59)		
					Per 5 cups/day	1.53 (1.30–1.79)		
					Per 6 cups/day	1.72 (1.39–2.11)		
					Per 7 cups/day	1.95 (1.45–2.61)		

Table 91 Coffee intake and lung cancer risk. Main characteristics of studies 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	Missing data derived for analyses
Gnagnarella, 2013a LUN26858 Italy	COSMOS Prospective Cohort, Age: 50-84 years M/W heavy smokers	178/ 4336 6 years	Screening examinations	FFQ	Incidence, lung cancer	≥5 cups/d vs never	1.11 (0.47-2.56)	Age, sex, energy intake, smoking duration, average daily cigarettes consumption, years of cessation, asbestos exposure, fruits and vegetables, fish, red meat, olive oil, tea and wine intake	Mid-points of exposure categories Exposure values using standard portion size
Sugiyama, 2010 LUN20292 Japan	MCS, Prospective Cohort, Age: 40-64 years, M/W	82/ 37 742 10 years	Death certificate	Question-naire	Mortality, lung cancer	1 cup/day vs never	1.72 (0.85-3.47)	Age, sex, education, alcohol consumption, BMI, black tea, oolong tea, green tea, smoking status and cigarettes/day, dairy products, energy intake, fruit & veg consumption, history of diabetes, history of hypertension, miso soup, rice intake, tea consumption, fish intake, green tea intake, total meat, walking time	Mid-points of exposure
		82			Mortality, lung cancer , men		1.72 (0.85-3.47)		
		33			Mortality, lung cancer, women		0.38 (0.13-1.16)		

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Missing data derived for analyses
Iso, 2007 LUN20294 Japan	JACC, Prospective Cohort, Age: 40-79 years, M/W	845 (men) 105 500 15 years	Population death registries	Validated FFQ	Mortality, lung cancer, men	≥2 times/day vs ≤1-2 times/month	0.94 (0.78-1.14)	Age, area of study	Mid-points of exposure
		253 (women)			Mortality, lung cancer, women		1.23 (0.88-1.73)		
Takezaki, 2003 LUN00268 Japan	Aichi Cancer Registry Study, Prospective Cohort, Age: 30- years, M/W	51 5 885 14 years	Cancer registry	FFQ - study-specific	Incidence, lung cancer	Every day vs almost never	1.20 (0.60-2.40)	Age, sex, occupation, smoking status and cigarettes/day (two categories only)	Mid-points of exposure Exposure values using standard portion size
Stensvold, 1994 LUN02421 Norway	Norway Cohort study Prospective Cohort, Age: 35-54 years, M/W	93 (men) 42 973 10 years	Cancer Registry of Norway	FFQ - study-specific	Incidence, lung cancer, men	≥7 vs ≤2 cups/day Per 1 unit increase	2.4 p < 0.01 Coeff trend: 0.28 (0.07-0.45)	Age, area of residence, smoking status, cigarettes/day	Rescale reference category Recalculate RR from exponent coefficient
		32 (women)			Incidence, lung cancer, women	≥7 vs ≤2 cups/day Per 1 unit increase	2 (ns) Coeff trend 0.25 (-0.08, 0.58)		
Chow, 1992 LUN02888 USA	LBS, Prospective Cohort,	218/ 17 633 20 year	Death Certificate	FFQ - study-specific	Mortality lung cancer	> 6 cups/day vs <3 cups/day	2.40 (1.40-4.20)	Age, industry occupation, smoking status	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
	Age: 35- years, M								
Nomura, 1986 LUN03914 USA	Oahu Cohort Study Prospective Cohort, Age: 45-79 years, M	110/ 7925 18 years	Continuous surveillance in local hospitals and record linkage with cancer registry	FFQ - study-specific	Incidence lung cancer	≥5 cups/day vs 0	1.44 (0.76-2.72)	Age, smoking habits, years of smoking , number of cigarette smoked,	Estimated missing confidence intervals Mid-points of exposure

Table 92 Coffee consumption and lung cancer risk. Main characteristics of studies excluded 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) P trend	Adjustment factors	Reasons for exclusion
Hirvonen, 2010 LUN20270 Finland	ATBC, Prospective Cohort, Age: 50-69 years, M, Smokers	27 111 10 years	Finnish Cancer Registry and the Register of Causes of Death	Diet history method	Incidence lung cancer	880 g/day vs 300 g/day	1.17 (0.99-1.37)	Age, alcohol consumption, BMI, physical activity, supplementation group, number of cigarettes smoked per day	Used only in highest versus lowest analysis. Only 2 categories
Khan, 2004 LUN00068 Japan	Japan, Hokkaido Cohort Study, Prospective Cohort, Age: 40- years, M/W	3158 15 years	Annual follow-up survey, cause of death classified by researchers	Dietary history questionnaire	Mortality, lung cancer	Several times/week or everyday vs never or several times/year or several times/month	0.70 (0.40-1.40)	Age, smoking habits	Used only in highest versus lowest analysis. Only 2 categories
Fu, 1997 LUN01468	Nagoya, 1983-2000 Prospective Cohort, M		Follow-up based on data from Aichi local council				M 2.02 (1.34-3.05) W 0.94 (0.44-1.93)		Article in Chinese

Figure 106 RR estimates of lung cancer by levels of coffee intake

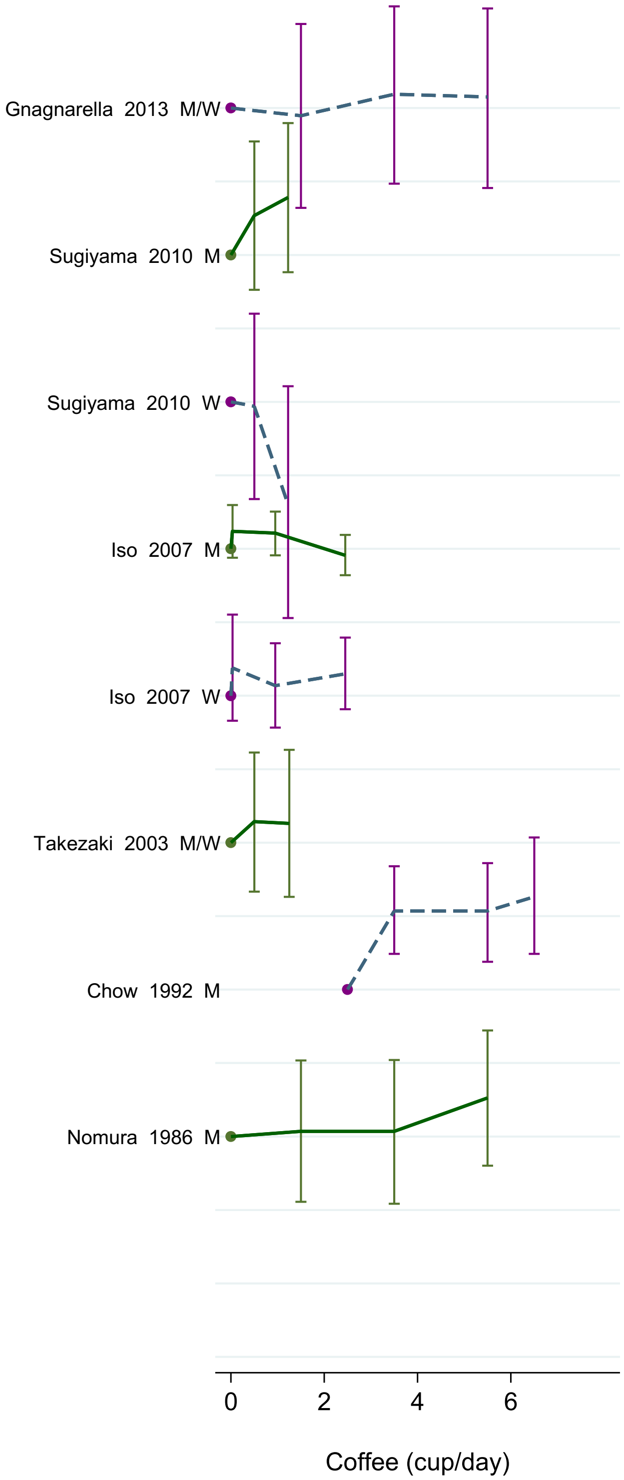


Figure 107 RR (95% CI) of lung cancer for the highest compared with the lowest level of coffee intake

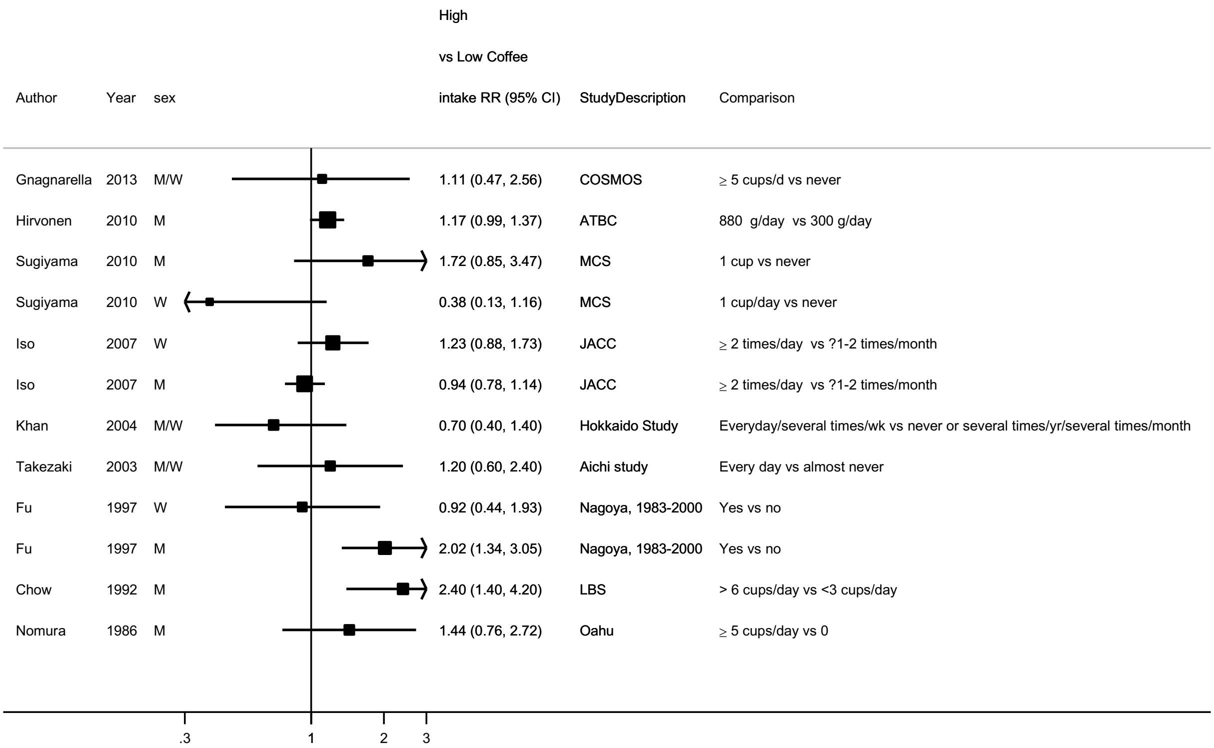


Figure 108 RR (95% CI) of lung cancer for 1 cup/day increase of coffee intake

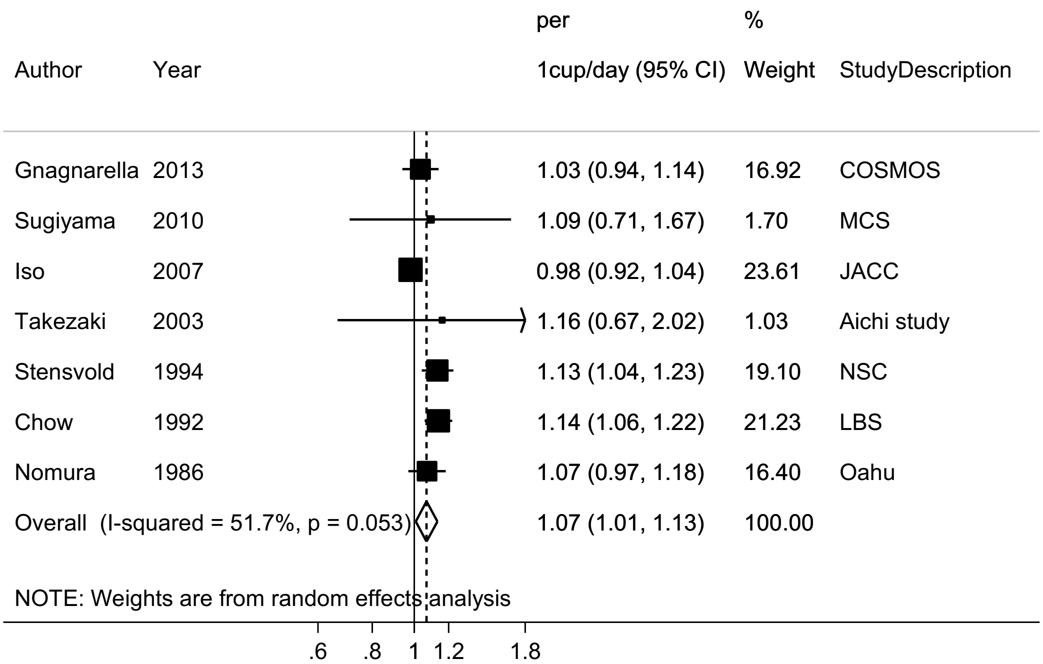


Figure 109 RR (95% CI) of lung cancer for 1 cup/day increase of coffee intake, after excluding study not adjusted for smoking status

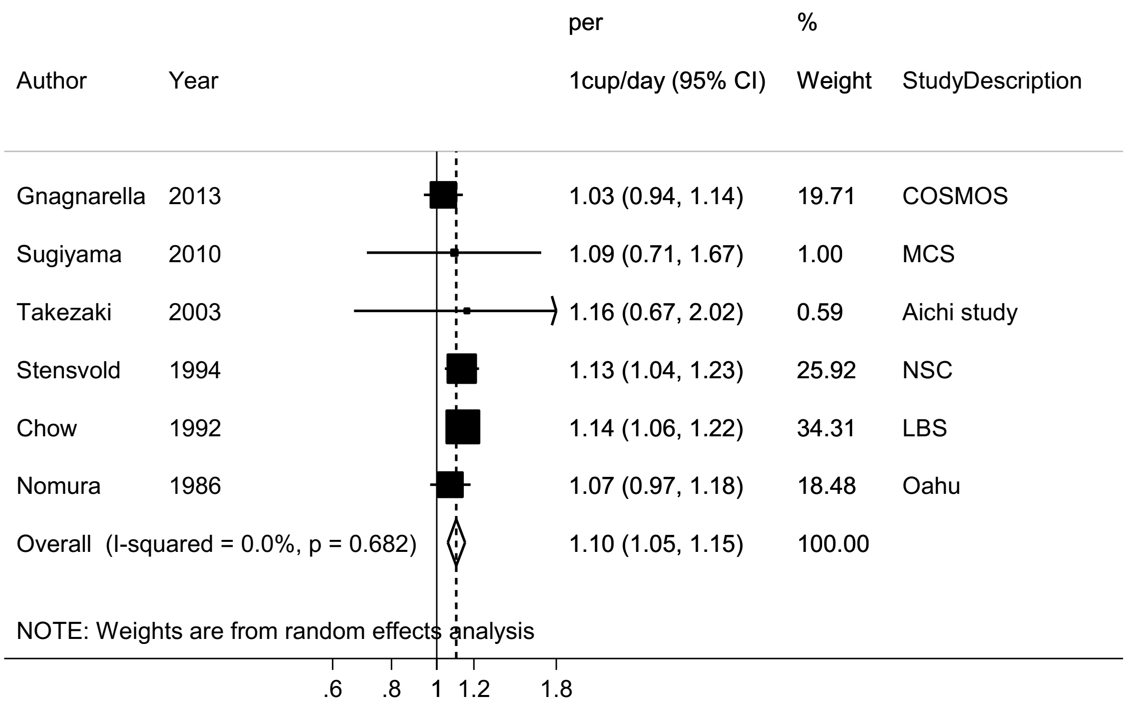
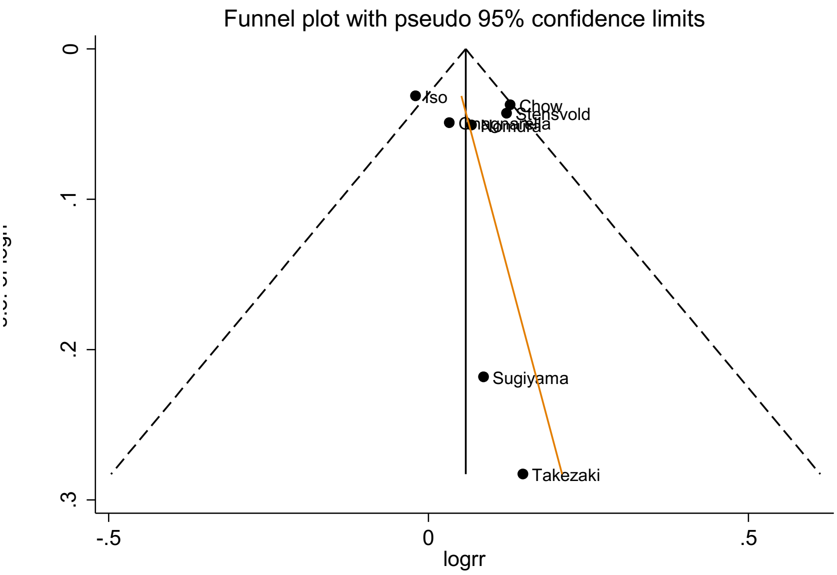
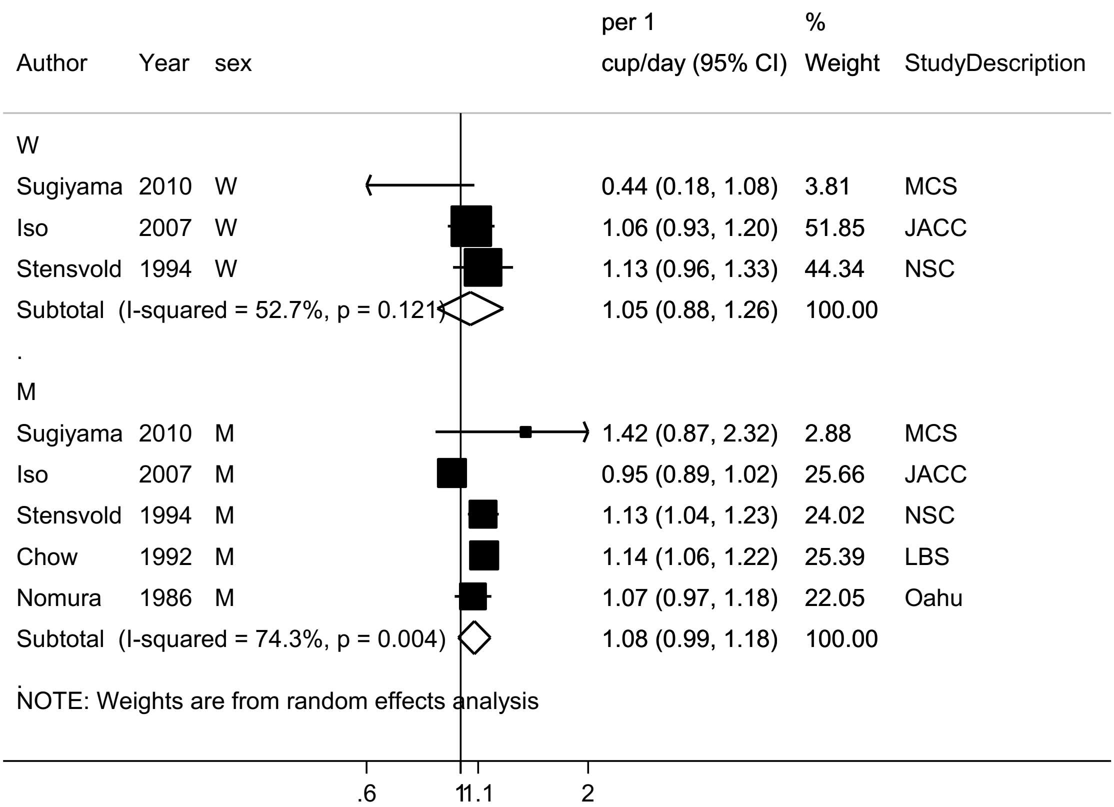


Figure 110 Funnel plot of studies included in the dose response meta-analysis of coffee intake and lung cancer



Egger's test p=0.63

Figure 111 RR (95% CI) of lung cancer for 1 cup/day increase of coffee intake by sex



3.6.2.2 Green tea

Cohort studies

Summary

Main results:
Five out of eight identified studies (1934 cases) were included in the dose-response meta-analysis. Green tea intake was not associated with lung cancer. Moderate heterogeneity was observed. There was no significant evidence of publication or small study bias (p=0.42).

Sensitivity analysis:
The summary RRs ranged from 1.00 (95% CI=0.96-1.04) when Iso, 2007 was omitted to 1.03 (95% CI=1.00-1.06) when Nagano, 2001 was omitted in the influence analysis.
There were not studies to do meta-analysis on lung cancer subtypes and by smoking status

Study quality:
Cancer outcome was confirmed using cancer registry records in most studies and green tea intake was assessed using FFQ in all studies.
One study (Iso, 2007) did not adjusted by smoking status. After excluding this study (Iso, 2007) the RR was 1.00(0.96-1.04).

Table 93 Green tea intake and lung cancer risk. Number of studies in the CUP SLR

	Number
Studies identified	8 (9 publications)
Studies included in forest plot of highest compared with lowest exposure	8
Studies included in dose-response meta-analysis	5
Studies included in non-linear dose-response meta-analysis	Not enough studies

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

Table 94 Green tea intake and lung cancer risk. Summary of the dose-response meta-analysis in the 2005 SLR and CUP.

	2005 SLR	**CUP**
Increment unit used	1 cup/week	1 cup/day
	All studies	
Studies (n)	2	5
Cases (total number)	212	1934
RR (95%CI)	1.11 (0.83, 1.47)	1.01 (0.98-1.05)

Heterogeneity (I^2, p-value)		31.0 %, 0.21
P value Egger test		0.42

Table 95 Green tea intake and lung 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, 2014	6 cohorts, 10 case-control studies	9881	Japan, China, Czech Republic, USA	Incidence	Highest vs lowest	0.75 (0.62-0.91)		73.4%, <0.01
Wang, 2012	3 cohorts 3 case-control studies	2381	China, Japan	Incidence	Per 1 cup/day	0.81 (0.73–0.89)	p non-linearity =0.001	< 0.01
					Per 3/cups/day	0.73(0.62–0.85)		
					Per 5 cups/day	0.81 (0.68–0.95)		
					Per 10 cups/day	0.67 (0.48–0.79)		
Tang, 2009	5 cohorts 7 case-control studies	1468 2931	China, Japan, USA, Czech Republic	Incidence	Highest vs lowest green tea intake			
				All studies		0.78 (0.61–1.00)		78.5%, < 0.01
				Case-control studies		0.87 (0.65–1.17)		63.9%, 0.01
				Cohort studies		0.68 (0.45–1.02)		82.2%, < 0.01
				All studies	Per 2 cups/day	0.82 (0.71–0.96)		

Note: In Wang, 2014, the RR for the highest vs the lowest intake of tea (green or black) were 0.91 (0.77-1.08) for 12 cohort studies and 0.72 (0.63-0.83) for 26 case-control studies

Table 96 Green tea intake and lung cancer risk. Main characteristics of studies 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	Missing data derived for analyses
Suzuki, 2009 LUN20289 Japan	SECS, Prospective Cohort, Age: 65-84 years, M/W	88/ 12 251 6 years	National statistics office	FFQ	Mortality lung cancer,	≥7 vs <1 cups/day Per 1 cup/day	1.24 (0.29-5.25) 1.04 (0.95-1.13)	Age, sex, alcohol consumption, BMI, smoking status, physical activity	Mid-points of exposure
Li, 2008 LUN20335 Japan	OCS, Prospective Cohort, Age: 40-79 years, M/W	302/ 41 440 7 years	Record linkage with cancer registries	Validated FFQ	Incidence lung cancer,	≥5 vs <1 cups/day	1.17 (0.85-1.61)	Age, sex, BMI, education level, family history of cancer, marital status, smoking status, duration, cigarettes per day, passive smoking, walking, alcohol intake, intake of meat, coffee, fish, fruit and vegetables, soybean products, energy intake	Mid-points of exposure
Iso, 2007 LUN20294 Japan	JACC, Prospective Cohort, Age: 40-79 years, M/W	845 (men) 105 500 15 years	Population death registries	Validated FFQ	Mortality lung cancer, men	≥2 times/day vs ≤1-2 times/month	1.41 (1.12-1.77)	Age, area of study	Mid-points of exposure
		253 (women)			Mortality lung cancer, women		1.14 (0.79-1.66)		

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Missing data derived for analyses
Takezaki, 2003 LUN00268 Japan	Aichi Cancer Registry Study, Prospective Cohort, Age: 30- years, M/W	51 5 885 14 years	Cancer Registry	FFQ - study-specific	Incidence, lung cancer	≥ 7 cups/day vs < 3 cups/day	0.78 (0.31-1.97)	Age sex, smoking status, cigarettes/day - 2 categories- , occupation.	Mid-points of exposure
Nagano, 2001 LUN00798 Japan	LSS Prospective Cohort, M/W	395/ 38 540 14 years	Cancer registry, death certificate	Dietary history questionnaire	Incidence, lung cancer	>5 times/day vs 1-0 times/day	0.79 (0.59-1.10)	Age, sex, radiation exposure, alcohol consumption, BMI, calendar year, educational level, other, smoking habits	Distribution of person-years/non-cases by exposure category Mid-points of exposure

Table 97 Green tea consumption and lung cancer risk. Main characteristics of studies excluded 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) P trend	Adjustment factors	Reasons for exclusion
Kuriyama, 2006 LUN26883 Japan	OCS Prospective Cohort, Age: 40-79 years, M/W	218/ 40 530 7 years	Death certificate	Self-reported FFQ	Mortality, lung cancer	≥ 5 cups/day vs < 1 cups/day	1.18 (0.81-1.72)	Age, sex, job status, education, BMI, physical activity, history of hypertension, diabetes mellitus, and gastric ulcer, smoking status, alcohol drinking, energy intake, consumption of rice, miso soup, soybean products, l meat fish, dairy products, fruits, and vegetables, oolong tea, black tea, and coffee	Superseded by Li, 2008 (LUN20335)
Khan, 2004 LUN00068 Japan	Japan, Hokkaido Cohort Study, Prospective	3158 15 years	Annual follow-up survey, cause of death	Dietary history questionnair	Mortality, lung cancer	Several times/week or everyday vs never or several times/year	0.60 (0.30-1.20)	Age, smoking habits	Used only in highest versus lowest analysis.

	Cohort, Age: 40- years, M/W		classified by researchers	e		or several times/month			Only 2 categories
Nakachi, 2000 LUN26884 Japan	Saitama Prefecture Cohort, Prospective Cohort, M/W	69/ 8552 11 years	Death certificate	Self-reported FFQ	Mortality, lung cancer	≥ 10 cups/day vs < 10 cups/day	0.33 (0.11-0.94)	Age, sex, lifestyle factors	Two categories (included in HvL graph)
Fu, 1997 LUN01468	Nagoya, 1983-2000 Prospective Cohort		Follow-up based on data from Aichi local council				M 1.29 (0.88-1.90) W 1.54 (0.79-2.98)		Article in Chinese (included in HvL graph)

Figure 112 RR estimates of lung cancer by levels of green tea intake

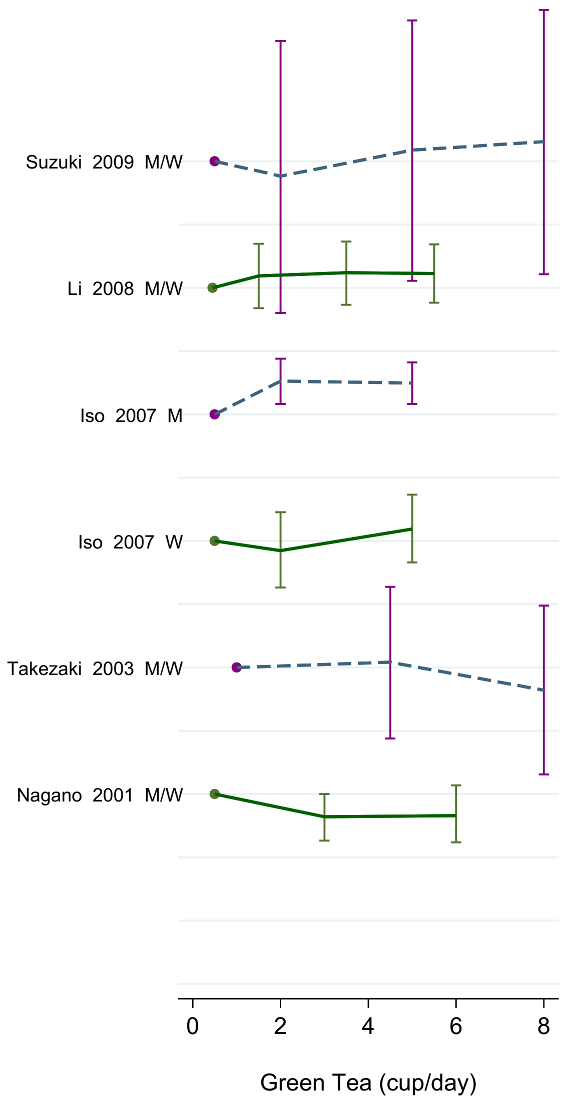


Figure 113 RR (95% CI) of lung cancer for the highest compared with the lowest level of green tea intake

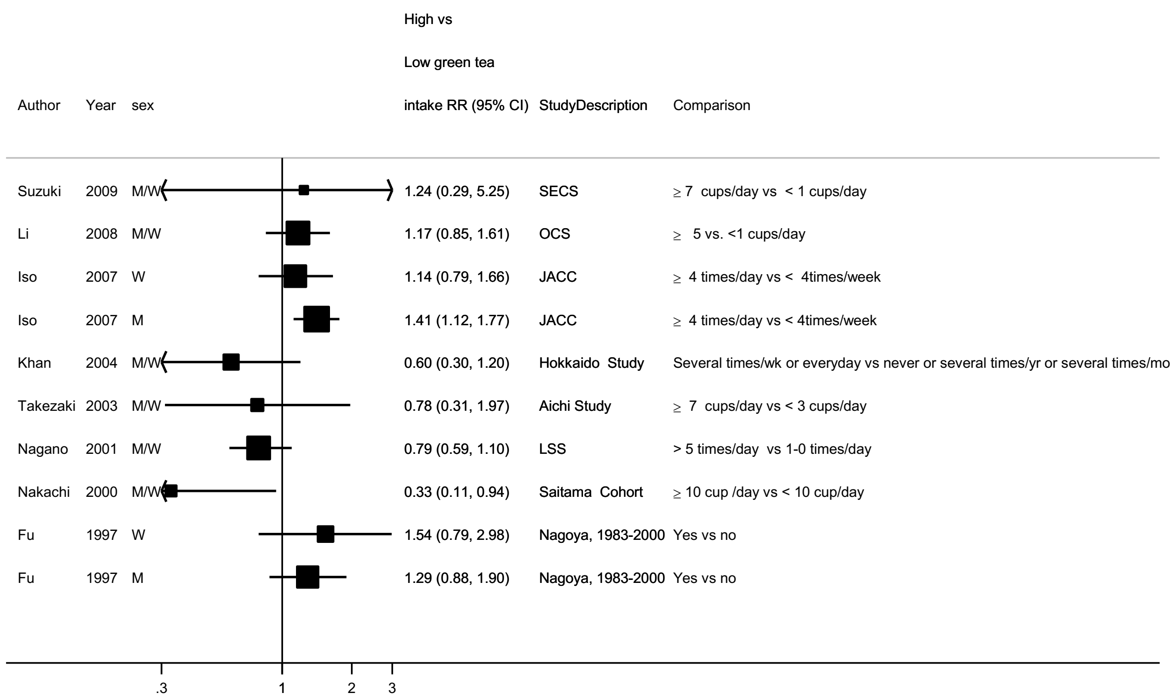


Figure 114 RR (95% CI) of lung cancer for 1 cup/day increase of green tea intake

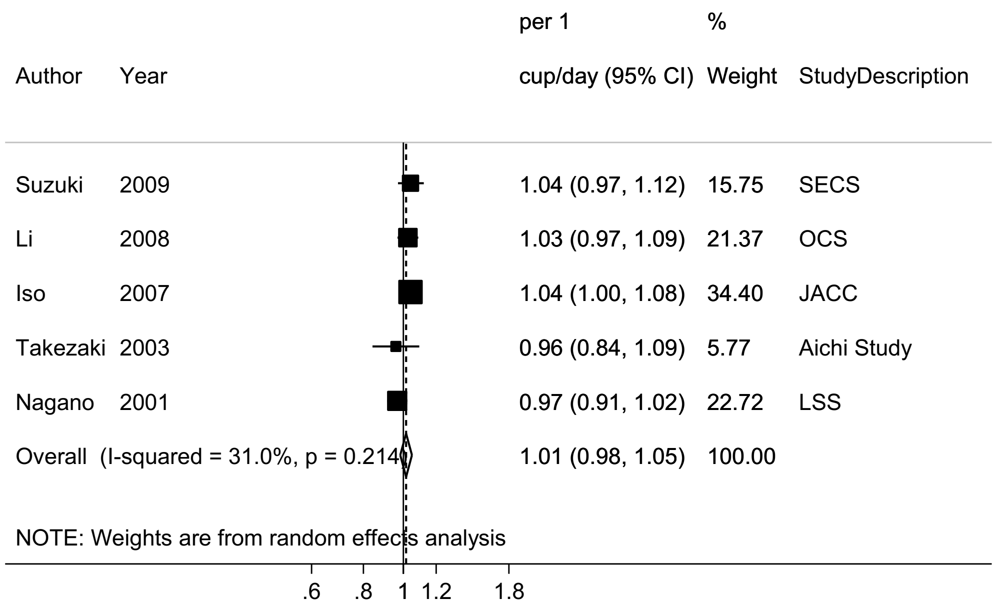


Figure 115 RR (95% CI) of lung cancer for 1 cup/day increase of green tea intake, after excluding study not adjusted for smoking status

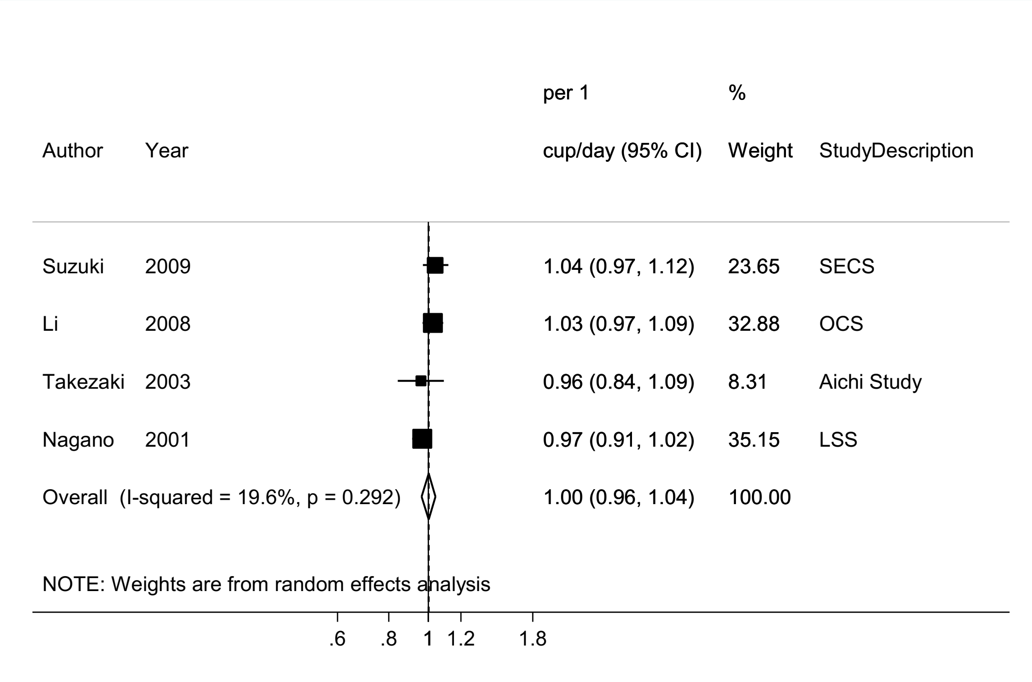
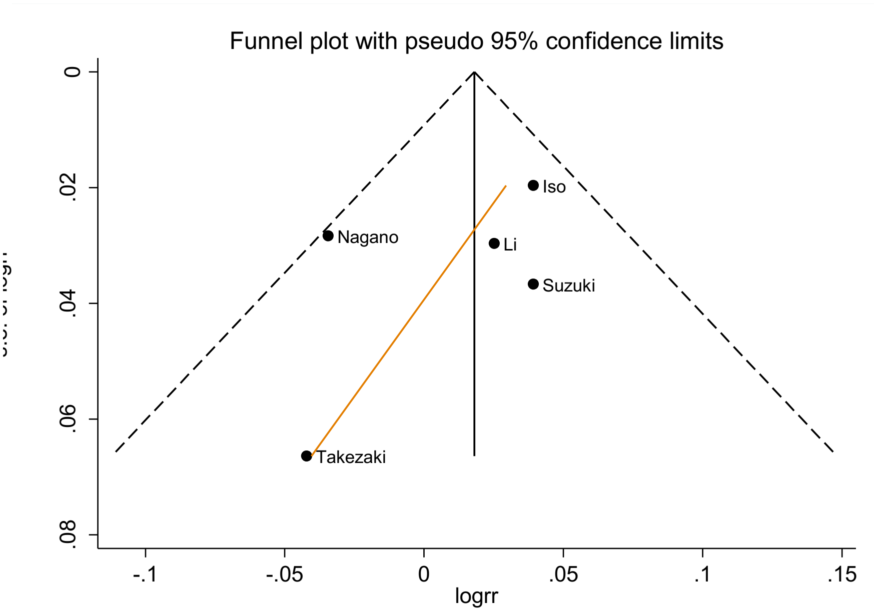


Figure 116 Funnel plot of studies included in the dose response meta-analysis of green tea intake and lung cancer



Egger's test p=0.42

4.1.2.7.2 Arsenic

Note: IARC has classified arsenic and inorganic arsenic compounds as carcinogenic to humans (Group 1) (IARC Monographs On The Evaluation Of Carcinogenic Risks To Humans Volume 100C (2012): Arsenic, Metals, Fibres and Dusts**)**

Cohort studies

Main results:
Ten publications from four studies on arsenic and lung cancer were identified. Four new publications were identified during the CUP.
From the four recent publications, three were on arsenic in drinking water (Chung, 2013; Chen, 2010; Basstrup, 2008) and one was on dietary arsenic intake from foods (Sawada, 2013).
Two studies on arsenic in drinking water were on populations from high-risk areas (Chung, 2013; Chen, 2010) and one study was in a low-risk area (Baastrup, 2008).
The measurement of exposure arsenic in drinking water was based on arsenic levels in well water. Cumulative exposure was calculated from the amount of water consumed and the years of residence in the area.
Due to the variability in median arsenic exposure and outcomes across studies, it was not possible to conduct meta-analyses.
The studies in high risk areas (Chung, 2013; Chen, 2010) showed a significant increased risk of the lung cancer with increasing levels of cumulative exposure to arsenic from drinking water.
No association with risk of lung cancer was observed in the Danish Cohort Study which is in a population with low levels of exposure to arsenic in drinking water (Baastrup, 2008).
One study on arsenic from foods (the Japan Public Health Center-based (JPHC) study) reported a significant dose-response association of total arsenic and inorganic arsenic intake and risk of lung cancer but this only in men and current men smokers (Sawada, 2013).

Table 98 Studies on arsenic identified in the CUP and 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	Missing data derived for analyses
Chung, 2013 LUN26871 Taiwan	Taiwan Arsenic Study, Prospective Cohort, Age: 30- years, M/W	71/ 1563 20 years	Death register	High risk area; Cumulative arsenic exposure from well water (µg/L*year) by interview	Mortality, lung cancer	≥ 19.5 vs < 9.1 (µg/L*year)	1.47 (0.66-3.31)	Age, sex, education, smoking	
		43			Mortality, lung cancer, men		*SMR 6.05 (4.38–8.15)	Age	
		28			Mortality, lung cancer , women		*SMR 7.18 (4.77–10.38)		
Sawada, 2013 LUN26867 Japan	JPHC, Prospective Cohort, Age: 45-74 years, M/W	685/ 90 378 11 years	Hospital records, population-based cancer registries and death certificates	Dietary arsenic intake by validated FFQ	Incidence, lung cancer, men	247.5 vs 88.8 µg /day (Organic arsenic)	1.23 (0.96-1.57) Ptrend:0.07	Age, BMI, leisure time physical activity, smoking status, alcohol intake, area	
						102.2 vs 36.5 µg/day (Inorganic arsenic)	1.28 (1.00-1.62) Ptrend:0.05		
		522			Incidence, lung cancer, men, ever smokers	Highest vs lowest (Arsenic)	1.29 (1.03-1.61) Ptrend:0.03		
						Highest vs lowest	1.36 (1.09-1.70) Ptrend:0.01		

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Missing data derived for analyses
						(Inorganic arsenic)			
		418			Incidence, lung cancer, men, current smoker	Highest vs lowest (Arsenic)	1.37 (1.06-1.77) Ptrend:0.03		
						Highest vs lowest (Inorganic arsenic)	1.38 (1.07-1.77) Ptrend:0.01		
		104			Incidence, lung cancer, men, past smokers	Highest vs lowest (Arsenic)	1.16 (0.71-1.87) Ptrend:0.54		
						Highest vs lowest (Inorganic arsenic)	1.22 (0.77-1.94) Ptrend:0.26		
		77			Incidence, lung cancer, men, never smokers	Highest vs lowest (Arsenic)	0.49 (0.27-0.86) Ptrend:0.01		
						Highest vs lowest (Inorganic arsenic)	0.72 (0.41-1.29) Ptrend:0.27		
		254			Incidence, lung cancer, women	25.3 vs 93.7 µg/day	1.16 (0.81-1.65) Ptrend:0.28	Age, BMI, leisure time	

Author, Year, WCRF Code, Country	Study 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
						(Organic arsenic)		physical activity, menopausal status, smoking status, alcohol intake, area, use of hormone replacement therapy, use of oral contraception	
						107.6 vs 37.1 µg/day (Inorganic arsenic)	1.37 (0.95-1.98) Ptrend:0.08		
		30			Incidence, lung cancer, women, ever smokers	Highest vs lowest (Arsenic)	0.67 (0.26-1.76) Ptrend:0.42		
						Highest vs lowest (Inorganic arsenic)	0.67 (0.27-1.72) Ptrend:0.40		
		26			Incidence, lung cancer, women, current smokers	Highest vs lowest (Arsenic)	0.40 (0.13-1.20) Ptrend:0.10		
						Highest vs lowest (Inorganic arsenic)	0.45 (0.16-1.29) Ptrend:0.13		
		224			Incidence, lung cancer, women, never smokers	Highest vs lowest (Arsenic)	1.25 (0.90-1.75) Ptrend:0.17		
						Highest vs lowest	1.57 (1.12-2.20) Ptrend:0.01		

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Missing data derived for analyses
						(Inorganic arsenic)			
Chen, 2010 LUN20361 Taiwan	North-eastern Taiwan cohort, Prospective Cohort, Age: 40- years, M/W	178/ 6888 11 years	Cancer registry	High risk area (mean >100μg/L); Cumulative arsenic exposure from well water (μg/L*year)	Incidence, lung cancer	≥ 10 000 vs < 400 (μg/L*year)	2.08 (1.33-3.27) Ptrend:<0.01	Age, educational level, cigarette smoking status, sex, habitual alcohol consumption	
				High risk area (mean > 100μg/L); Arsenic concentration in well water collected at enrolment (μg/L) by standardized questionnaire		≥ 300 vs < 10 μg/L	2.25 (1.43-3.55) Ptrend:<0.01		
		75			Incidence, lung cancer, Incidence, lung cancer, squamous cell carcinoma	≥ 300 vs < 10 μg/L	2.13 (1.09-4.17) Ptrend:<0.01		
		51			Incidence, lung cancer, adenocarcinoma		1.63 (0.65-4.05) Ptrend:0.66		
		30			Incidence, lung cancer,, other		2.25 (0.65-7.71) Ptrend:0.19		

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Missing data derived for analyses
					histological types				
		22			Incidence, lung cancer, small cell carcinoma		5.15 (1.44-18.40) Ptrend:0.02		
Baastrup, 2008 LUN20303 Denmark	DCH, Prospective Cohort, Age: 50-64 years, M/W	402/ 56 378 10 years	Danish cancer registry	Low risk area (median 0.7 µg/L); Time-weighted average exposure (µg/L) in drinking water by questionnaire	Incidence, lung cancer	Per 1 µg/L	IRR** 0.99 (0.90-1.08)	Area of enrolment, occupation, smoking status, education, fruit and vegetable intake, smoking duration, smoking intensity	
						Per 5 mg/L	IRR** 1.00 (0.98-1.03)		
Chen, 2004 LUN17199 Taiwan	Taiwan study in south-western and north-eastern, Prospective Cohort, Age: 58.00years, M/W, Blackfoot population	139/ 10 591 8 years	National cancer registry	High risk areas; Average arsenic levels in well water, µg/L by questionnaire	Incidence, lung cancer	≥ 700 vs < 10 µg/L	3.29 (1.60-6.78)	Age, sex, alcohol consumption, area of residence, educational level, smoking habits	
Nakadaira, 2002 LUN00653	Nakajo Town Study,	7/ 86	Death certificate		Mortality, lung cancer, men	Observed deaths vs expected	11.01		

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Missing data derived for analyses
Japan	Prospective Cohort, M/W,	34 years			Mortality, lung cancer, women	Observed deaths vs expected	5.34		
Chiou, 1995 LUN02284 Taiwan	South-western Taiwan cohort, Prospective Cohort, M/W, Blackfoot population	17/ 2 256 5 years	Health examination, home visit personal interview, household registration data check, national death certification and cancer registry	High risk area; Average arsenic concentration in well water by questionnaire	Incidence, lung cancer	High vs unexposed mg/L	4.01 (1.00-16.12)	Age, sex, presence of other diseases, smoking habits	
Tsuda, 1995 LUN08192 Japan	Japan 1959-1992, Historical Cohort, M/W	9/ 454 33 years	Death certificate	High risk area ; Arsenic in water in ppm	Mortality, lung cancer		*SMR 3.66 (1.81-7.03)		
		9/			Mortality, lung cancer	≥ 1ppm	*SMR 15.69 (7.38-31.02)		
Tsuda, 1989 LUN03479 Japan	Nakajo Japan, Prospective Cohort, M/W	6/ 281 28 years	Death certificate	Arsenic concentration in well water (34 wells) recorded	Mortality, lung cancer	≥ 0.5 ppm	*SMR 1641 (715-3634)		
		5			Mortality, lung cancer, current smokers		*SMR 1873 (738-4419)		

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Missing data derived for analyses
		1			Mortality, lung cancer, non-smokers		*SMR 1014 (52-5838)		
Chen, 1988 LUN03572 Taiwan	Taiwan study, Prospective Cohort, M/W, Blackfoot population	27/ 1008 16 years		Questionnaire	Mortality, lung cancer	BFD patients vs general population	*SMR 1049	Age, sex	
						BFD patients vs residents in BFD-endemic area	*SMR 284		

*SMR: Standardized mortality ratio.
** IRR: Incident Rate Ratio.

5 Dietary constituents

5.2 Total Fat

The section is included in the CUP SLR because the evidence that total fat intake increases lung cancer risk was judged as limited suggestive in the Second Expert Report. The evidence in the 2005 SLR was based on five cohort studies and nine case-control studies (in highest vs lowest forest plots). The results of dose-response meta-analysis (n=2 cohort studies included) was RR= 1.01 (95% CI= 0.94-1.09) per 10 grams of fat per day.
Two studies were identified in the CUP (Gnagnarella, 2013 and Iso, 2007) and no meta-analysis was conducted. The 2005 SLR found a RR 1.01 (95% CI 0.94-1.09 per 10 g/day, 2 studies).
One Pooling Project (Warner-Smith, 2002) was identified and showed a non-significant association (RR per 5% increase total energy from fat= 1.01(0.98–1.05, for 9 studies). In the 2005SLR there was no meta-analyis in percentage of energy from fat because the studies identified reported in different units of intake.We could not conduct a dose-response meta-analysis including the studies from the Pooling Project and the three studies not included in the Pooling Project (Gnagnarella, 2013; Iso 2007 and Veierød, 1997) because the studies used different units to measure fat intake. It was possible to conduct a highest compared to lowest analysis with the overall result of RR=0.98 (95%CI=0.85-1-13, 13 studies). After excluding the only study not adjusted for smoking (Iso, 2007) the RR was 1.08(0.89-1.30).

Table 99 Total fat and lung cancer risk. Main characteristics of studies identified in CUP and 2005 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
Gnagnarella, 2013 LUN26858 Italy	COSMOS (Continuous Observation of Smoking Subjects), Prospective Cohort, Age: 50-84 years	178/ 4 336 6 years	Screening examinations	FFQ	Incidence, lung cancer	47.2 vs 15.2 g/day	0.81 (0.50-1.31) Ptrend:0.14	Age, sex, asbestos occupation, energy, smoking
						20.59 vs 7.8 g/1000kcal/d	0.62 (0.40-0.96) Ptrend:0.02	
Iso, 2007 LUN20294 Japan	JACC, Prospective Cohort, Age: 40-79 years, M/W	855/ 105 500 15 years	Municipal resident registration records, death certificates	Questionnaire	Mortality, lung cancer, men	Modified vs no change fat intake (medical advise)	0.87(0.72-1.05)	Age, area of study
		246			women		0.84(0.61-1.17)	
		57			Men	Preference for fatty foods (yes vs no)	1.00 (0.73-1.37)	
		246			Women		1.09 90.90-1.32)	
Speizer, 1999 LUN01255 USA	NHS, Prospective Cohort, Age: 30-55 years, W	399/ 118 351 12 years	Hospital records and pathology reports	FFQ - study-specific	Incidence, lung cancer	Quintile 5 vs quintile 1	1.10 (0.80-1.40)	Age, energy intake, smoking habits
Bandera, 1997 LUN01693 USA	New York State Cohort, 1980, Prospective Cohort,	395/ 48 000 7 years	New York State Department of Health's Vital Statistics	FFQ - study-specific	Mortality, lung cancer	Tertile 3 vs tertile 1	1.44 (1.11-1.87)	Age, educational level, energy intake, smoking habits
		200			Current smokers		1.26 (0.88-1.80)	

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
	Age: 40-80 years, M/W,	176	Section and Cancer Registry,		Current smokers		1.38 (0.92-2.06)	
		130			Women		1.07 (0.70-1.63)	
		122			Squamous cell		2.01 (1.22-3.31)	
		100			Adeno-carcinoma		1.03 (0.63-1.68)	
Veierød, 1997 LUN01643 Norway	Norwegian Health Screening Service (NHSS), Prospective Cohort, Age: 16-56 years, M/W,	149/ 51 452 11 years	Cancer registry	FFQ - study-specific	Incidence, lung cancer	>2340 vs <1947 g/month	1.40 (0.90-2.30)	Age, sex, energy intake, smoking habits
Wu, 1994 LUN02422 USA	IWHS, Prospective Cohort, Age: 55-69 years, W, Post menopausal	212/ 34 708 8 years	SEER	FFQ - study-specific	Incidence, lung cancer	>83 vs <49.4 g/day	0.80 (0.50-1.20)	Age, energy intake, other, physical activity, smoking habits,
		84			Current smokers	>83 vs <49.4 g/day	0.70 (0.40-1.10)	
		77			Incidence, adenocarcinoma	>83 vs <49.4 g/day	0.90 (0.50-1.80)	
		57			Incidence, adenocarcinoma, current smokers	>83 vs <49.4 g/day	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
		3			Incidence, lung cancer, non-smokers	>2490 vs <1482	1.80 (0.70-4.30)	
Knekt, 1991 LUN03143 Finland	Finland, 1966, Prospective Cohort, Age: 20-69 years, M	4 538 20 years	Cancer registry	FFQ - study-specific	Incidence, lung cancer	>4200 vs <3141 g/month	1.55 (0.78-3.10)	Age, energy intake, smoking habits

Table 100 Total fat intake and lung cancer risk. Results of meta-analyses and pooled analyses of prospective studies

Author, Year	Number of cohort studies	Total number of cases	Studies country, area	Outcome	Comparison	RR (95%CI)	P trend	Heterogeneity (I^2, p value)
Smith-Warner, 2002 AHS, ATBC, CNBSS, HPFS, IWHS, NYSC, NHS, NLCS Pooling Project of cohort studies	9	3188	USA, Europe	Lung cancer All	5% of energy increase in total fat intake	1.01(0.98–1.05)		
					Q4 vs Q1	1.04 (0.92–1.17)	0.67	0.66
		1907		Current smokers	5% of energy increase in total fat intake	1.01 (0.96–1.06)		0.87
		973		Former smokers		1.01 (0.93–1.10)		
		257		Never smokers		1.03 (0.91–1.17)		

Figure 117 RR (95% CI) of lung cancer for the highest compared with the lowest level of total fat intake combined with Pooling Project.

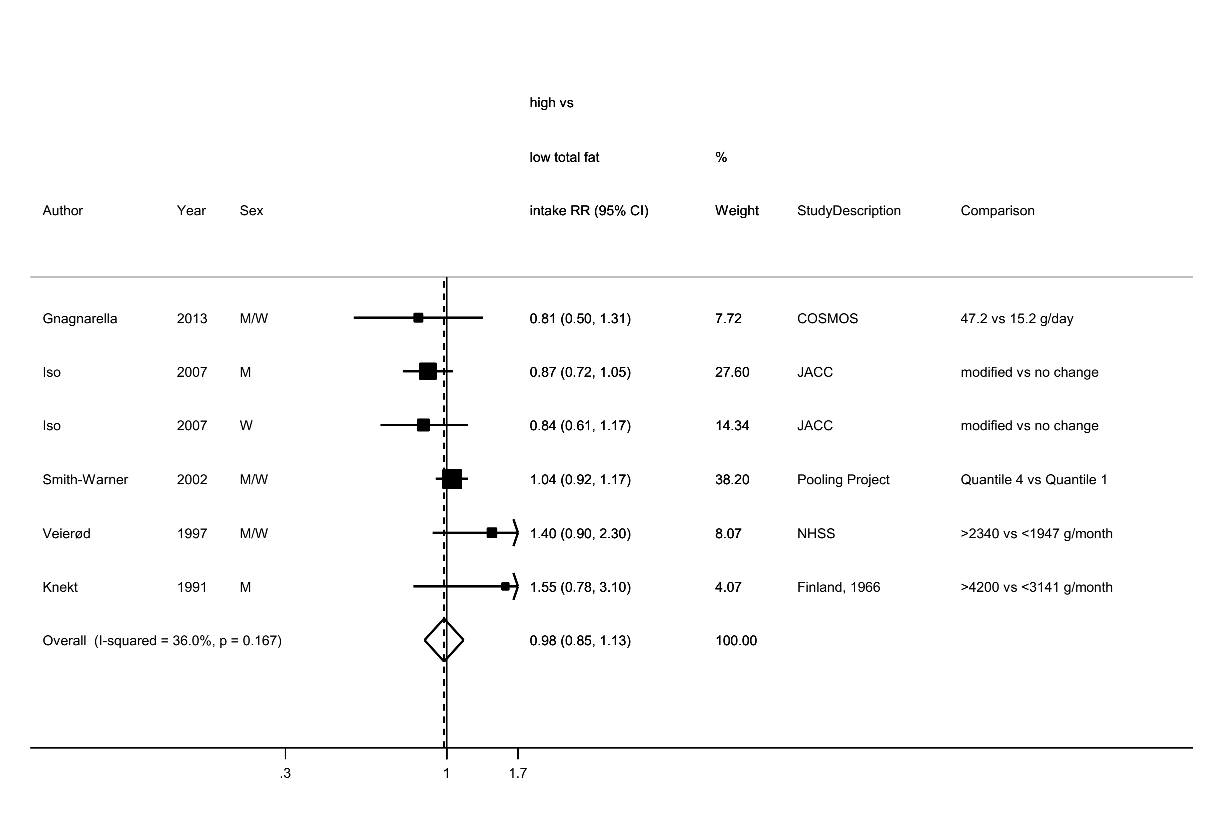
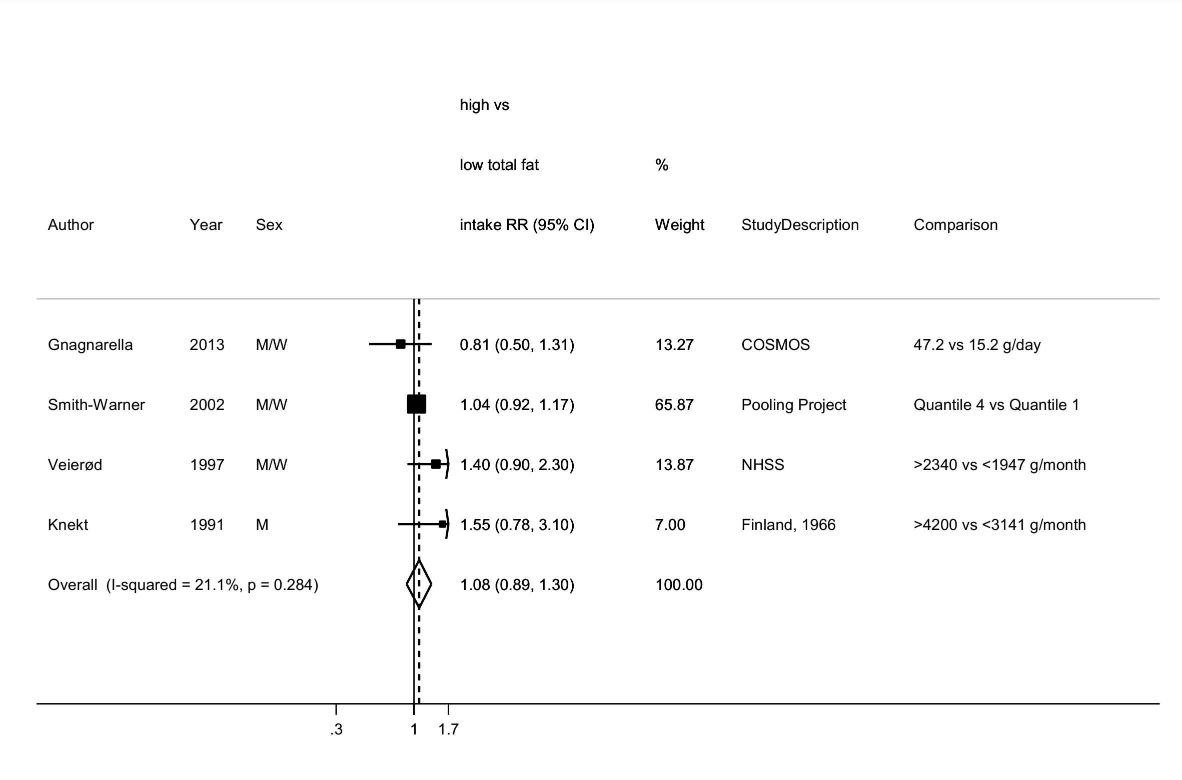


Figure 118 RR (95% CI) of lung cancer for the highest compared with the lowest level of total fat intake, after excluding study not adjusted for smoking status



5.4 Ethanol

Cohort studies

Summary

Main results:
Fourty five studies from fifty publications were identified. Thirty two cohort studies (24 156 cases) were included in the dose-response meta-analysis. Alcoholic drinks intake (as ethanol) was significantly positively associated with lung cancer.

One study (Sorensen, 1998) was not included in the analysis because reported on cirrhotic individuals.

High heterogeneity was observed (66.6%). In stratified analyses, the results were similar for incidence and mortality. A weak significant positive association but heterogeneous was observed in men and no association was observed in women, with lower heterogeneity. No significant associations were observed in analyses stratified by smoking status or by lung cancer subtype (limited number of studies available). In meta-regression analysis, year of publication and adjustment for smoking significantly explained heterogeneity, but not geographic location, unit of intake (servings or g/day), sex, outcome or study size. Most recent studies and more adjustment for smoking reported lower RR estimates (p=0.012) if published after 2006 compared with published before 2002; p=0.017 for more adjusted compared with unadjusted in metaregression models with both variables).

There was significant evidence of publication or small study bias (p=0.02). The asymmetry suggests missing small studies on the left sied of the plot.

There was evidence of a non-linear dose-response for lung cancer and ethanol intake ($p < 0.01$). No increase was evident at low levels and the risk becomes significant at approximately 40 grams per day of ethanol intake.

Sensitivity analysis:

The overall association was similar in influence analysis. The summary RRs ranged from 1.02 (95% CI=1.01-1.04) when Lee, 2002 was omitted to 1.04 (95% CI=1.02-1.06) when Thun, 2009 was omitted.

The summary estimate for an increase of 10 g/day of ethanol after exclusion of studies that did not adjust for smking was 1.03 (95% CI=1.01-1.04).

Study quality:

Cancer outcome was confirmed in most studies using cancer registries or medical records. Nine studies were on mortality, but the overall result was similar to that of studies on lung cancer incidence.
All studies used questionnaire to assess alcohol intake. Kim, 2010 reported on ethanol from *soju* drink only. Twenty three studies (including the Pooling Project studies) reported results in grams per day, or grams per week or ounce per day or miligrams per day of ethanol and nine studies provided results by drinks per day or cups per day or servings per day. Measurement unit did not explain heterogeneity in meta-regression models.
Four studies did not adjusted for smoking; five studies adjusted for smoking status only, 10 studies adjusted for smoking status and intensity (cigarettes/day, pack-years) smoked and 11 studies adjusted for smoking status, intensity and duration (years smoking /time since quitting). The studies included in the Pooling Project adjusted for smoking status, smoking duration for past and current smokers and cigarettes smoked daily for current smoker.

Pooling Project of cohort studies

Lung cancer was significantly positively associated to alcohol intake in the Pooling Project of Cohort Studies (Freudenheim, 2005; seven cohorts) (See Table of Pooling Project results)
The Pooling Project was combined with the nonoverlapping studies identified in the CUP (see Summary Table).

Table 101 Ethanol and lung cancer risk. Number of studies in the CUP SLR

	Number
Studies identified	45 (50 publications)
Studies in forest plot of highest compared with lowest exposure	36
Studies in dose-response meta-analysis	32
Studies in non-linear dose-response meta-analysis	28

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

Table 102 Ethanol intake and lung cancer risk. Summary of the dose-response meta-analysis in the 2005 SLR and CUP.

	2005 SLR	**CUP**
Increment unit used	10 grams/week	10 grams/day
All studies		
Studies (n)	9	26
Cases (total number)	3088	21940

RR (95%CI)	1.02 (1.00-1.05)	1.03 (1.01-1.05)
Heterogeneity (I^2, p-value)	86%	67.3%, < 0.001
P value Egger test		0.08
CUP & Pooling Project (Freudenheim, 2005)		
Studies (n)		32
Cases (total number)		24 630
RR (95%CI)		1.03 (1.02-1.05)
Heterogeneity (I^2, p-value)		66.6%, < 0.001
P value Egger test		0.02

Stratified and sensitivity analysis (no analyses conducted in the 2005 SLR)			
Smoking status	**Never smokers**	**Current smokers**	**Non-smokers**
	CUP		
Studies (n)	4	5	5
Cases	1350	4255	2151
RR (95%CI)	0.96(0.92-1.00)	1.01 (0.97-1.02)	0.99 (0.88-1.11)
Heterogeneity (I^2, p-value)	0%, 0.41	0%, 0.49	69.8%, 0.03
	CUP and Pooling Project		
		Current smokers*	**Non-smokers***
Studies (n)		4	4
Cases		4179	888
RR (95%CI)		1.01(0.97-1.05)	1.18 (0.97-1.43)
Heterogeneity (I^2, p-value)		57.8%, 0.05	87.4%, <0.001
Sex	**Men***	**Women***	**Men and Women**
Cases	11727	12102	1882
Studies (n)	21	16	6
RR (95%CI)	1.04 (1.02-1.06)	1.01 (0.98-1.05)	0.99 (0.96-1.02)
Heterogeneity (I^2, p-value)	72.9%, <0.001	38.5%, 0.06	0%, 0.49
Outcome	**Incidence***	**Mortality**	
Studies (n)	23	9	
Cases	15081	9549	
RR (95%CI)	1.04 (1.01-1.06)	1.03 (1.00-1.06)	
Heterogeneity (I^2, p-value)	49.1%, <0.01	81.9% <0.001	
Cancer type	**Small cell carcinoma***	**Squamous cell carcinoma***	**Adenocarcinoma***
Studies (n)	3	4	6
Cases	808	1477	1827

RR (95%CI)	1.03 (0.97-1.10)	1.00 (0.93-1.09)	1.06 (1.02-1.09)	
Heterogeneity (I^2, p-value)	53.1%, 0.09	66.2%, 0.01	16.6%, 0.30	
Geographic location	**Asia**	**Europe***	**North America***	
Studies (n)	11	7	14	
RR (95%CI)	1.04 (1.01-1.06)	1.04 (0.99-1.07)	1.03 (1.00-1.07)	
Heterogeneity (I^2, p-value)	73.2%, <0.001	73.4%, 0.001	55.7%, 0.006	
Adjustment by smoking	**No adjustment**	**Smoking status only**	**Smoking status, intensity**	**Smoking status, intensity, duration**
Studies (n)	4	5	10	11 *
RR (95%CI)	1.15 (1.02-1.31)	1.03 (0.99-1.03)	1.02 (0.99-1.05)	1.04 (1.01-1.08)
Heterogeneity (I^2, p-value)	83.8%, <0.001	76.7%, 0.002	0%, 0.76	61.2%, 0.004
Excluding studies that did not adjust for smoking *				
Studies (n)	28			
RR (95%CI)	1.03 (1.01-1.04)			
Heterogeneity (I^2, p-value)	59.7%, <0.001			

*Indicates when the Pooling Project (Freudenheim, 2005) was included in the analyses

Table 103 Alcohol intake and lung 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								
Bagnardi, 2011 (never smokers)	4 Cohort 6 Case-control	1913	Europe, North America, Japan, China	Incidence	Drinkers vs non-drinkers	1.02 (0.92-1.28) 1.25 (0.68-2.31) Total: 1.21 (0.95-1.55)		31% 86% 77%
Li, 2011	2 Cohort 4 Case-control	1104	China	Incidence	Drinkers vs non-drinkers	1.27 (0.85-1.91) 1.59 (0.86-2.94) Total: 1.39 (0.93-2.07)	0.25 0.14 0.03	69%, 0.07 79%, <0.01 71%, <0.01
Pooled analyses								
Freudenheim, 2005	7 cohorts	3137	Europe and North America	Incidence	≥ 30 g/d vs none	1.21 (0.91-1.61) Men	0.03	0.09
						1.16 (0.94-1.43) Women	0.03	0.35

Two other meta-analyses were identified, one including Japanese studies (Uehara 2010) and the other Chinese study (Fan 2009)

Table 104 Alcohol consumption (ethanol) and lung cancer risk. Main characteristics of studies 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	Missing data derived for analyses
Shen, 2013 LUN20376 China	CECS, Prospective Cohort, Age: 65- years, M/W Elderly	428 men, 841 women/ 66 820 10.5 years	Hospital records and death register	Questionnaire	Mortality, lung cancer, men	≥ 3 units (30 g/d) vs never	1.45 (1.05-1.99)	Age, sex, education, housing, monthly expenditure, BMI, exercise, health status, smoking status	Mid-points of exposure categories Exposure values using standard portion size Distribution of person-years/non-cases by exposure category
					Mortality, lung cancer, women	≥ 2 units (20 g/d) vs never	0.98 (0.55-1.75)		
Breslow, 2011 LUN20286 USA	NHIS, Prospective Cohort, Age: 18- years, M/W	1299/ 323 354 2 716 472 person years	Medical records	Questionnaire	Mortality, lung cancer, men	Heavier drinker (≥ 14 drinks/week) vs never drinker	All men 1.21 (0.93-1.57) Never smokers 0.52 (0.14-1.92)	Marital status, region, education, race, smoking status, BMI	Mid-points of exposure categories Exposure values using standard portion size Mid-points of exposure categories
		1101			Mortality, lung cancer, women	Heavier drinker (≥ 7 drinks/week) vs never drinker	All women 1.37 (1.04-1.8) Never smokers 1.48 (0.41- 5.30)		
Jung, 2012 LUN20279 Korea	KMCC, Prospective Cohort,	123/ 16 320 9.3 years	Death certificate	Questionnaire	Mortality, cancers of the lung and	> 504.01 g/week vs 0.01-90 g/ week	2.09 (0.87-5.03)	Age, sex, BMI, smoking status, geographic area,	Rescale 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
	Age: 20- years, M/W				bronchus			educational attainment	Distribution of person-years/non-cases by exposure category Mid-points of exposure categories
Yang, 2012a LUN20260 China	CNRPCS, Prospective Cohort, Age: 40-79 years, M	1082/ 218 189 15 years	Death certificate, medical attention, described by family members	Questionnaire	Mortality, lung cancer	≥ 700 g/week vs nondrinkers	1.25 (0.97-1.62)	Geographic area, 5-yr age-group, education, smoking	Rescale floating confidence intervals Mid-points of exposure categories
Chao, 2011 LUN20355 USA	VITAL, Prospective Cohort, Age: 50-76 years, M/W	580/ 66 186 390 284 person years	Cancer registry	FFQ	Incidence, lung cancer	At baseline ≥ 3 drinks/d vs nondrinkers	1.00 (0.72-1.39)	Sex, race, education, household income, BMI, history of COPD/emphysema, duration, of cigarette smoking (duration smoked, pack-years), family	Mid-points of exposure categories Distribution of person-years/non-cases by exposure category Exposure values using standard portion size
		310			Incidence, lung cancer men		0.99 (0.68-1.46)		
		246			Incidence, lung cancer, women		0.98 (0.47-2.01)		
		206			Incidence,		1.36 (0.81-2.27)		

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Missing data derived for analyses
					lung cancer, adeno-carcinoma			history of lung cancer, high intensity physical activity, intakes of fruit and vegetables, and fat	
		99			Incidence, lung cancer, squamous cell		2.54 (1.36-4.73)		
Kim, 2010 LUN20264 Korea	KNHIC, Prospective Cohort, Age: 40-69 years, M/W	1700/ 1 341 393 5 years	National death certificate	Questionnaire	Mortality, lung cancer, men	≥ 90.0 g/day vs nondrinkers	0.90 (0.74-1.08)	Age, residential (urban/rural), smoking status, ≥3 times/week regular exercise, BMI, systolic blood pressure, diastolic blood pressure, fasting blood sugar	Distribution of cases and person-years by exposure category Mid-points of exposure categories
		222			Mortality, lung cancer, women	≥ 15.0 g/day vs nondrinkers	0.94 (0.45-1.94)		
Laukkanen, 2010 LUN26864 Finland	KIHD, Prospective Cohort, Age: 42-60 years, M	52/ 2268 16.7	Finnish cancer registry	Questionnaire	Incidence, lung cancer	10g/week (continuous)	1.01 (1.0-1.02)	Age, years spent smoking and number of cigarettes, BMI, physical activity, fat intake, fibre intake, energy intake	Rescaled continuous 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
Allen, 2009 LUN20275 U.K.	MWS, Prospective Cohort, Age: 55years, W	5,203/ 1 280 296 7.2 years	National health service central registers	Questionnaire	Incidence, lung cancer	≥ 15 drinks/week vs nondrinkers	1.01 (0.9-1.12)	Age, area of residence, socio-economic status, BMI, smoking (never, past, or current smokers, cigarettes/day day), physical activity, use of oral contraceptives, HRT use	
						10 g/day (continuous)	1.03 (0.98-1.09)		
Thun, 2009 LUN20346 North America	CPS II, Prospective Cohort, Age: 30 years, M/W, non-smokers	406/ 223 216 24 years	Death certificate and national death index	Mailed questionnaire	Mortality, lung cancer, men	≥ 4 drinks/d vs nondrinker	0.84 (0.55-1.27)	Age, education, occupation, race (non-smokers only)	Mid-points of exposure categories Exposure values using standard portion size
		652			Mortality, lung cancer, women		0.69 (0.41-1.16)		
Chao, 2008 LUN20333 USA	CMHS, Prospective Cohort, Age: 45-69 years, M	210/ 78 168 4 years	Record linkage with cancer registries	Semi-quantitative FFQ	Incidence, lung cancer	≥ 3 drinks/d vs nondrinker	1.08 (0.6-1.94)	Age, ethnicity, education, household income, BMI, smoking status, cigarettes /day, smoking duration, antecedents COPD/	Distribution of cases by exposure category Distribution of person-years/non-cases 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
								emphysema	using standard portion size Mid-points of exposure categories
Kabat, 2008a LUN20311 Canada	CNBSS, Prospective Cohort, Age: 40-59 years, W	358/ 49 654 16.4 years	Record linkage to Canadian centre database and to national mortality database	FFQ	Incidence, lung cancer	≥ 30 g/d vs nondrinkers	1.03 (0.71-1.51)	Age, BMI, , pack years of smoking, parity, years of education, alcohol consumption	Distribution of cases by exposure category Distribution of person-years/non-cases by exposure category Mid-points of exposure categories
Kabak, 2008b LUN20341 USA	WHI-DM & OS, Prospective Cohort, Age: 50-79 years, W, postmenopausal women	1342/ 159 659 7.8 years	Lung cancer was not the primary outcome of the trial. Follow-up by mail or phone. Self-reported lung cancers verified by local review of pathology reports	Mailed questionnaire or telephone interview	Incidence, lung cancer	≥ 7 drinks/week vs nondrinker	1.0 (0.76-1.33)	Age, smoking status, pack years of smoking, education, ethnicity, HRT use, intakes of fat, fruits, vegetables, alcohol, total calories,	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
								physical activity, study	
Shimazu, 2008 LUN20336 Japan	JPHC, Prospective Cohort, Age: 40-69 years, M	651/ 46 347 14 years	Hospital records, population-based cancer registries and death certificates	Self-administered questionnaire	Incidence, lung cancer	≥ 450 g/week vs 1–3 d/month,	1.31 (0.89-1.94)	Age, area, smoking status, pack-years of smoking , years since cessation, passive smoking, family history of lung cancer	Rescale reference category Distribution of person-years/non-cases by exposure category Mid-points of exposure categories
Ozasa, 2007 LUN20280 Japan	JACC, Prospective Cohort, M/W	637/ 12 years	Population death registries	Questionnaire	Mortality, lung cancer, men	≥ 81 ml/d vs none	1.29 (0.98-1.71)	Age, study area	Exposure values using portion size in the publication
		209/ 12 years			Mortality, lung cancer, women	54-80 ml/d vs none	2.34 (0.74-7.40)		
Rohrmann, 2006 LUN20320 Europe	EPIC, Prospective Cohort, Age: 35-70	1119/ 478 590 6.4 years	Cancer registries, health insurance records, active	FFQ, dietary questionnaires,	Incidence, lung cancer	≥ 60 g/d vs 0.1-4.9 g/d	0.86 (0.66-1.14)	Age, sex, study centre, smoking status, smoking duration,	Rescale reference category Distribution of
		606			Incidence,		0.81 (0.59-11)		

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Missing data derived for analyses
	years, M/W		follow up confirmed with pathology and medical records	food record	lung cancer, men			cigarettes/day, height, weight, fruit consumption, red meat consumption, processed meat consumption, education, physical activity at work, total non-alcohol energy intake	person-years/non-cases by exposure category Mid-points of exposure categories
		513			Incidence, lung cancer, women		0.87 (0.42-1.82)		
		97			Incidence, lung cancer, never smokers	30-59.9 g/d vs 0.1-4.9 g/d	0.55 (0.17-1.83)		
		290			Incidence, lung cancer, former smokers	≥ 60 g/d vs 0.1-4.9 g/d	0.87 (0.46-1.67)		
		726			Incidence, lung cancer, current smokers		0.90 (0.66-1.24)		
Freidenhein, Pooling Project, 2005 USA	Prospective Cohorts, HPFS 40-75 years M	244/ 44 349 1986-1996	Follow-up questionnaires and medical records reviews, linkage with a cancer registry or both. In addition, some studies used mortality registries or	FFQ Standard drink size	Incidence, lung cancer	≥30g/d vs none	1.26 (0.86-1.86)	Education, BMI, energy intake, smoking status, smoking duration, cigarettes smoked/day in current smokers	Mid-points of exposure categories Distribution of person-years/non-cases by exposure category
Freidenhein, Pooling Project, 2005 The Netherlands	NLCS 55-69 years M/W	828 (M) 128 (W) 58 279/ 1986-1992				≥30g/d vs none	Men 1.69 (1.18-2.44)		
						≥30g/d vs none	Women 0.56 (0.21-1.4)		
Freidenhein,	NHS Section A	156/				≥30g/d vs none	0.99 (0.59-1.65)		

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	Missing data derived for analyses
Pooling Project, 2005 USA	34-59 years W	88 307 1980-1986	death certificates						
Freidenhein, Pooling Project, 2005 USA	NHS Section B 40-65 years W	379/ 68 307 1986-1996				≥30g/d vs none	1.07 (0.75-1.52)		
Freidenhein, Pooling Project, 2005 USA	IWHS 55-69 years W	433/ 33 831 1986–1996				≥30g/d vs none	1.49 (1.11-2.00)		
Freidenhein, Pooling Project, 2005 USA	NYSC 15-107 years M/W	392 (M) 130 (W)/ 27 936 (M) 21 045 (W) 1980-1987				≥30g/d vs none	Men 1.16 (0.80-1.70)		
						≥30g/d vs none	Women 1.04 (0.46- 2.38)		
Nakaya, 2005 LUN26874 Japan	MCSII Prospective cohort, 40-64 M	96/ 21 201 7 years	Miyagi Prefecture Cancer Registry	Self-administered questionnaire	Incidence, lung cancer	≥ 22.8 g/d vs never drinkers	1.3 (0.8-2.3)	Age, cigarette smoking (smoking status and cigarettes/day), education, daily consumption of orange and other fruit juice (spinach,	Exposure values using portion size in the publication Mid-points of exposure categories. Distribution of person-years/non-cases

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Missing data derived for analyses
								tomato, carrot or pumpkin)	by exposure category
Alavanja, 2004 LUN16965 USA	AHS Prospective Cohort, M/W,	213/ 89 658 6.2 years	Iowa and North Carolina cancer registries; state death registries and National Death Index	FFQ - study-specific	Mortality, lung cancer	≥1 time/week vs never	1.0 (0.7-1.5)	Age, sex, smoking status, pack-years family history of lung cancer, antecedents of respiratory diseases, educational level, intake of vegetables, fruits, race	Mid-points of exposure categories RRs for men and women combined Exposure values using standard portion size
		59			Mortality, lung cancer spouses	≥4 times/month vs never	0.2 (0.04-0.8)		
Takezaki, 2003 LUN00268 Japan	Aichi Study Prospective Cohort, Age: 30- years, M/W,	38/ 5 885 14 years	Follow-up based on data from Aichi local council	FFQ - study-specific	Incidence, lung cancer	≥ 41 g/d vs almost never drinker	0.7 (0.28-1.71)	Age sex, smoking status, cigarettes/day -2 categories- , occupation.	Exposure values using portion size in the publication Mid-points of exposure categories
Djousse, 2002 LUN00436 USA	FHS Prospective Cohort,	269/ 9 238	Self-report at clinic visits to the Framingham Study,	Dietary history questionnaire	Incidence, lung cancer	≥ 24 g/d vs 0 g/d	1.3 (0.7-2.4)	Age, sex, smoking status, pack-years of	Distribution of 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	Missing data derived for analyses
	Age: 28-62 years, M/W		surveillance of hospitalizations, National Death Index					cigarette smoking, and year of birth	category Distribution of person-years/non-cases by exposure category Mid-points of exposure categories
Lee, 2002 LUN00654 South Korea	KMIC Prospective Cohort, Age: 35-64 years, M	802/ 452 645 5 years	Death certificates, incident cases confirmed by medical charts	Questionnaire	Mortality, lung cancer	> 20 g/d vs nondrinkers	2.0 (1.5-2.6)	Age	Mid-points of exposure categories
Prescott, 1999 LUN01393 Denmark	CCHS Prospective Cohort, Age: 20- years, M	480/ 28 160 28 years	Danish Cancer Registry	Dietary history questionnaire	Incidence lung cancer, men	> 41.1 drinks/week vs < 1 drink/week	1.57 (1.06-2.33)	Age, smoking status, years of smoking, cigarettes/day, educational level, study cohort	Mid-points of exposure Distribution of person-years/non-cases by exposure category Exposure values using standard portion size
	W	194			Incidence lung cancer, women		0.8 (0.11-5.79)		
Woodson, 1999	ATBC	1059/	Finnish Cancer	FFQ - study-	Incidence lung	42 g/s vs 1.8 g/d	1.0 (0.8-1.2)	Age, BMI, years	Rescale

Author, Year, WCRF Code, Country	Study 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
LUN01299 Finland	Prospective Cohort, Age: 50-69 years, M	27 111 7.7 years	Registry and the Register of Causes of Death	specific	cancer			smoked, cigarettes per day, and intervention group.	reference category
Knekt, 1996 LUN01885 Finland	HES Finland Prospective Cohort, Age: 30-95 years, M/W	70/ 7018 14 years	Finnish Cancer Registry	Dietary history questionnaire	Incidence, lung cancer, men	>94 g/week vs 0 g/week	1.37 (0.71-2.67)	Age	Mid-points of exposure
Murata, 1996 LUN02113 Japan	CCCJ Nested Case Control, M	162/ 17 200 9 years	Cancer registry	Questionnaire	Incidence, lung cancer	2.1 cups/d vs 0 cups/d	1.8		Estimated confidence intervals Exposure values using standard portion size
Stemmermann, 1990 LUN12798 USA	HHP Prospective Cohort, Age: 45-79 years, M	209 7572 24 years	Hospital records, death certificates, cancer registry	FFQ - study-specific	Incidence, lung cancer	≥ 40 oz/month vs 0 oz/month	1.09 (0.73-1.64)	Age, current smoker status, number cigarettes, maximum number of cigarettes per day, years	Mid-points of exposure Distribution of person-years/non-cases 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
								smoked	using standard portion size
Kono, 1987 LUN09311 Japan	JPS Prospective Cohort, Age: 27-89 years, M	74 5130 19 years	Death certificates	Dietary history questionnaire	Mortality, lung cancer	≥ 1 drink/d vs never	1.0 (0.54-1.87)	Age, smoking habits (non and ex-smokers combined, cigarettes/day in smokers)	Distribution of cases by exposure category Distribution of person-years/non-cases by exposure category Exposure values using standard portion size Mid-points of exposure categories

Table 105 Alcohol consumption (ethanol) and lung cancer risk. Main characteristics of studies excluded 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	Reasons for exclusion
Butler, 2013 LUN26852	SCHS, Prospective	1130/ 61 321	Singapore cancer registry	Validated FFQ	Incidence, lung cancer	Any vs none	0.99 (0.86-1.14)	Age, dialect group, sex,	Used only in highest versus

China	Cohort, Age: 45-74 years, M/W	11.5 years	database					interview year, number of cigarettes smoked per day, years of smoking, number of years since quit smoking	lowest analysis. Only 2 categories
Lin, 2013 LUN20316 USA	NHANES III, Prospective Cohort, Age: 50- years, M/W	57/ 5204 12.4	Death certificates	FFQ & 24-hr dietary recall	Mortality, lung cancer, women	Yes vs no	1.1 (0.56-2.16)	Urinary cadmium, age, zinc, race/ethnicity, smoking status, BMI, caloric intake	Used only in highest versus lowest analysis. Only 2 categories
		98			Mortality, lung cancer, men		0.56 (0.29-1.06)		
Pavanello, 2012 LUN20332 Denmark	DCH, Nested Case Control, Age: 50-64 years, M/W	425/ 160 725	Danish cancer registry	FFQ	Incidence, lung cancer	25.39 g/d vs 7.6 g/day	1.01 (1.0-1.02)	Gender, fruit consumption, cigarettes pack years, passive smoking, occupational exposure, cyp1a2 polymorphism	Included in EPIC (LUN20320, Rohrmann, 2006)
Toriola, 2009 LUN20352 Finland	The Findrink study Prospective Cohort, M	65/ 2267	Finish cancer registry	Structured questionnaire	Incidence, lung cancer	Binge drinking vs non-binge drinking	1.89 (1.10-3.20)	Age, exam date, year of examination, family history of cancer, smoking, socio-economic status, leisure	Only two categories Binge drinking

								physical activity, BMI	
Nishino, 2006 LUN22448 Japan	JACC Prospective Cohort, Age: 40-79 years, M	377/ 28 536 10 years	Population death registries	Questionnaire	Mortality, lung cancer	≥ 50 g/d + vs never	0.98 (0.64-1.5)	Age, smoking habits, family history of specific cancer, other nutrients, foods or supplements	Superseded by LUN20280 (Ozasa, 2007)
Tamosiunas, 2003 LUN00287 Lithuania	KRIS Prospective Cohort, M	243/ 6446 18 years	Health records	Survey	Mortality, lung cancer	Alcohol users vs non-users	1.14 (0.72-1.79)		Only two categories (article in Lithuanian)
Chen, 2004 LUN17199 Taiwan	TAC Prospective Cohort, Age: 58years, M/W, Blackfoot population	139/ 10 591 8 years	National Cancer Registry	Questionnaire	Incidence, lung cancer	Yes vs no	1.15 (0.77-1.73)	Sex, age, educational level, area of residence, smoking habits	Used only in highest versus lowest analysis. Only 2 categories
Goodman, 2003 LUN00294 USA	CARET trial. Nested Case Control, Age: 45-69 years, M/W	268/ 18 314 4 years	Primary outcome of the trial. Active follow-up with confirmation by clinical records and pathology reports	FFQ - study-specific	Incidence, lung cancer	More than 7 drinks per week vs nondrinker			No measurement of association
Jeng, 2003 LUN00099 Taiwan	Cohort of cancer screening trail	58/ 23 943 10 years	National Cancer Registry		Incidence, lung cancer	Drinker vs nondrinker	p test for difference in means:0.86		No measurement of association (mean)

	Nested Case Control, Age: 30-64 years, M/W								
Ito, 2003 LUN00342 Japan	JACC Nested Case Control, Age: 40-79 years, M/W	147/ 39 140 8 years	Population death registries	Dietary history questionnaire	Mortality, lung cancer				No RR, Superseded by LUN20280 (Ozasa, 2007)
Olson, 2002 LUN00502 USA	IWHS Prospective Cohort, Age: 55-69 years, W Postmenopausal	596/ 38 006 12 years	Driving license/private health care list	FFQ - study-specific	Incidence, lung cancer	>4 g/d vs never	1.08 (0.9-1.3)	Age, Smoking habits	Only 3 intake levels. The data of the Pooling Project (Freudenheim, 2005) was used instead
Bandera, 2002 LUN00506 USA	NYSC Nested Case Control, Age: 40-80 years, M/W	395/ 57 968 7 years	Cancer registry and New York State Department of Health's Vital Statistics Section, National Death Index	FFQ - study-specific	Mortality, lung cancer, Men	≥ 11 drinks/month vs 0 drinks/month	1.32 (0.57-3.06)	Age, smoking habits, area of residence, educational level, ethnicity/race Physical activity	Nested case-control. The data of the Pooling Project (Freudenheim, 2005) was used instead
		130			Mortality, lung cancer, women	≥ 5 drinks/month vs 0 drinks/month	1.54 (0.35-6.8)		
Ratnasinghe, 2000 LUN01072	Miners, high risk population	9 142 6 years	Surveillance, Epidemiology and End Results	Dietary history questionnaire	Incidence, lung cancer		p test for difference in means:0.18		No measurement of association (mean)

China	Nested Case Control, Age: 41-79 years, M/W								
Breslow, 2000 LUN01082 USA	NHIS Prospective Cohort, Age: 18-87 years, M/W	157/ 20 195 8.5 years	National cancer record list	FFQ	Mortality, lung cancer	> 4.4 servings/week vs 0 servings/week	1.3 (0.8-2.0)	Age, sex, smoking duration, packs/day	Superseded by LUN20286 (Breslow, 2011)
Chiazze, 1997 LUN07632 USA	APC Nested Case Control, M	4 631 20 years	National death index	Questionnaire	Mortality, lung cancer	Regular drinker vs not regular drinker	1.29 (0.57-2.94)		Used only in highest versus lowest analysis. Only 2 categories
Fu, 1997 LUN01468 China	Nagoya, 1983-2000 Prospective Cohort, M		Follow-up based on data from Aichi local council	Questionnaire			M 0.67(0.43-1.04) F 0.87 (0.43-1.76)		Article in Chinese. Only two caterogies, included in HvL
Anderson, 1997 LUN01803 USA	IWHS Prospective Cohort, Age: 55-69 years, W Postmenopausal	343/ 34 480 9 years	Iowa Health Registry (part of SEER registry)	FFQ - study-specific	Incidence, lung cancer	≥ 35 vs 0 g/week	2.28 (1.80-2.89)	Age	Superseded by LUN00502 (Olson, 2002)
Bandera, 1997 LUN01693	NYSC Prospective Cohort,	395 men/ 48 000 7 years	NY Health's Vital Statistics	FFQ - study-specific	Mortality, lung cancer, men	Q3 vs Q 1	1.12 (0.88-1.41)	Age, energy intake, smoking habits,	Superseded by LUN00506 (Bandera, 2002.

USA	Age: 40-80 years, M/W	130 women	Section and Cancer Registry		Mortality, lung cancer, women		1.01 (0.64-1.58)	educational level	The data of the Pooling Project (Freudenheim, 2005) was used instead)
Potter, 1992 LUN02842 USA	IOWA Nested Case Control, Age: 55-69 years, Postmenopausal women	109 41 837 4 years	Cancer registry	FFQ - study-specific	Incidence, lung cancer		p test for difference in means<0.001 (alcohol consumption higher in cases)		No measurement of association (mean). The data of the Pooling Project (Freudenheim, 2005) was used instead
Connett, 1989 LUN03434 USA	MRFIT Nested Case Control, Age: 35-57 years, M	66/ 12 866 10 years	Active follow-up confirmed with hospital records	Recall	Mortality, lung cancer		p= 0.30		No measurement of association
Kono, 1986 LUN15000 Japan	JPS Prospective Cohort, M	n/a 5135 19 years	Local vital status registry (Honseki) and death certificates	Questionnaire	Mortality, lung cancer	Daily drinker (≥2 go/day) vs non-drinker servings/week	0.9 (0.5-1.7)	Age, smoking habits	Superseded by LUN15000 (Kono, 1987)
Jensen-O-M, 1983 LUN13314 Denmark	Seventh-Day Adventists Prospective Cohort, M	70/ 1589 34 years	National Central Danish Cancer Registry, Person Registry and National Central Death Registry		Incidence, lung cancer	Expected cases vs observed cases	1.0 (0.7-1.4)		Standard mortality ratio based on general population
Tuyns, 1976	French Second	N/A			Mortality, lung			Age	No measurement

LUN04826 France	Word War Historical Cohort, M	30 years			cancer				of association

Figure 119 RR estimates of lung cancer by levels of alcohol (ethanol) intake with Pooling Project.

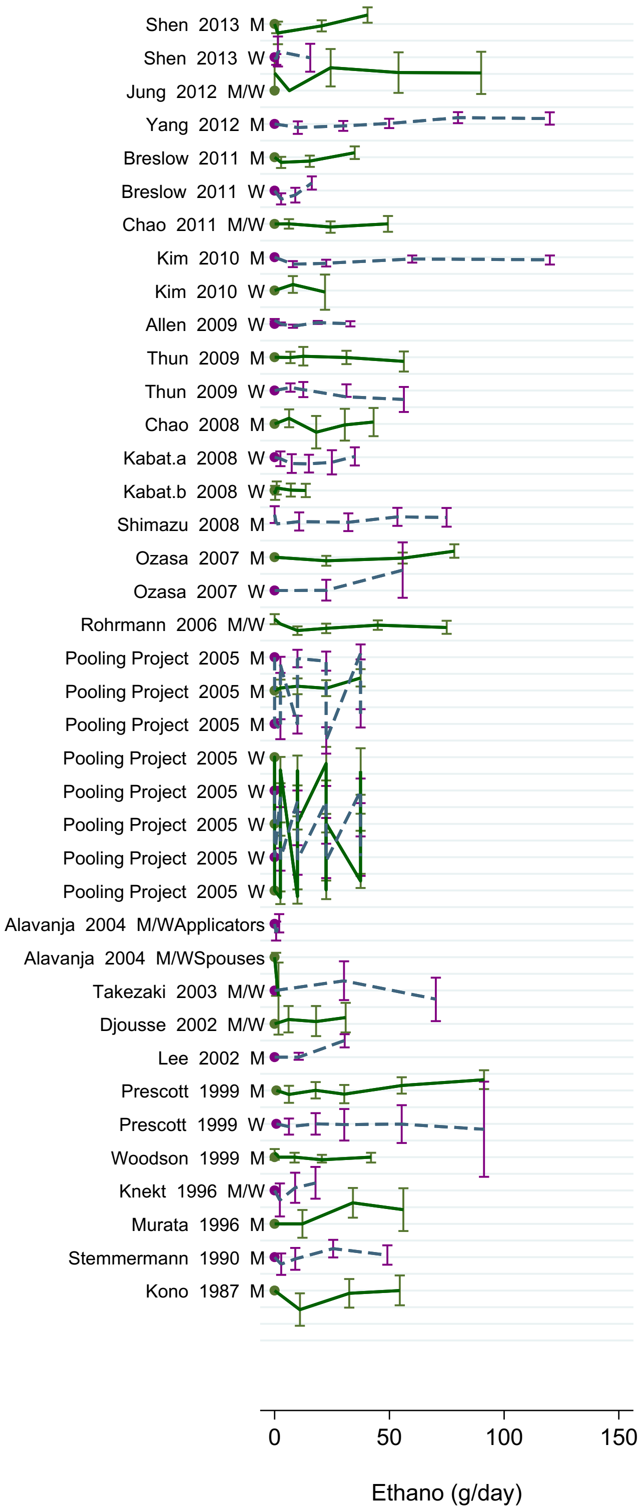


Figure 120 RR (95% CI) of lung cancer for the highest compared with the lowest level of alcohol (ethanol) intake with Pooling Project.

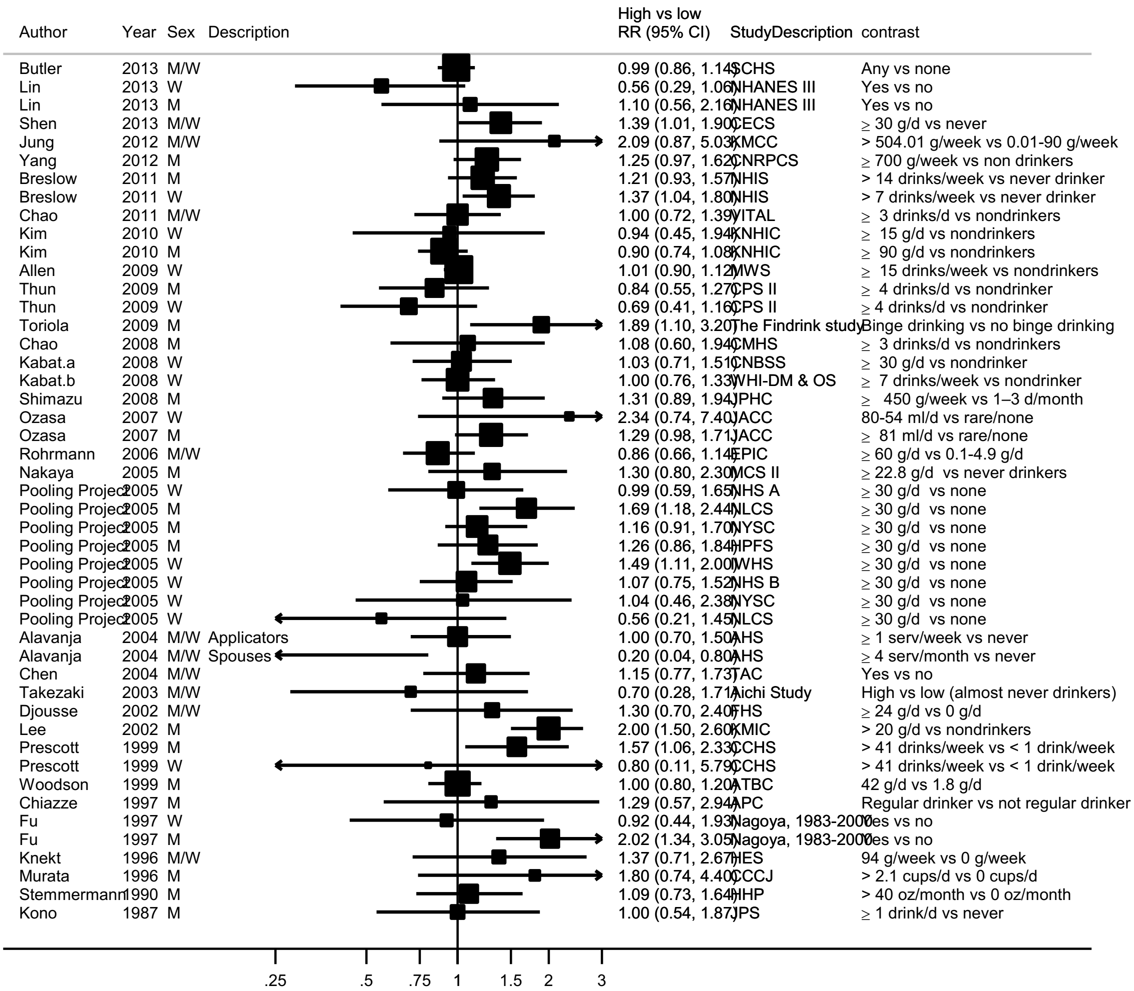
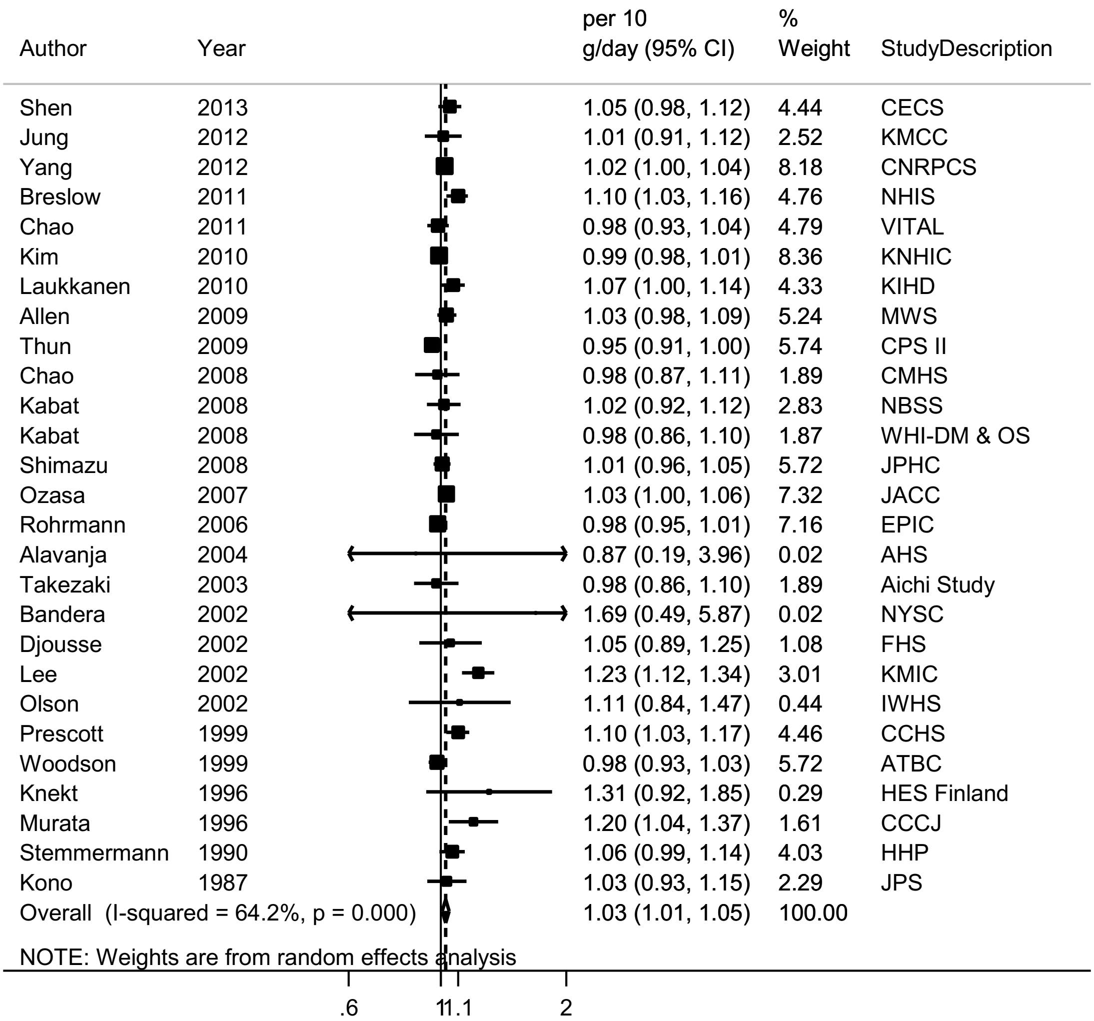


Figure 121 RR (95% CI) of lung cancer for 10 g/day increase of alcohol (ethanol) intake. CUP.



Note: Pooling project not included

Figure 122 RR (95% CI) of lung cancer for 10 g/day increase of alcohol (ethanol) intake with Pooling Project.

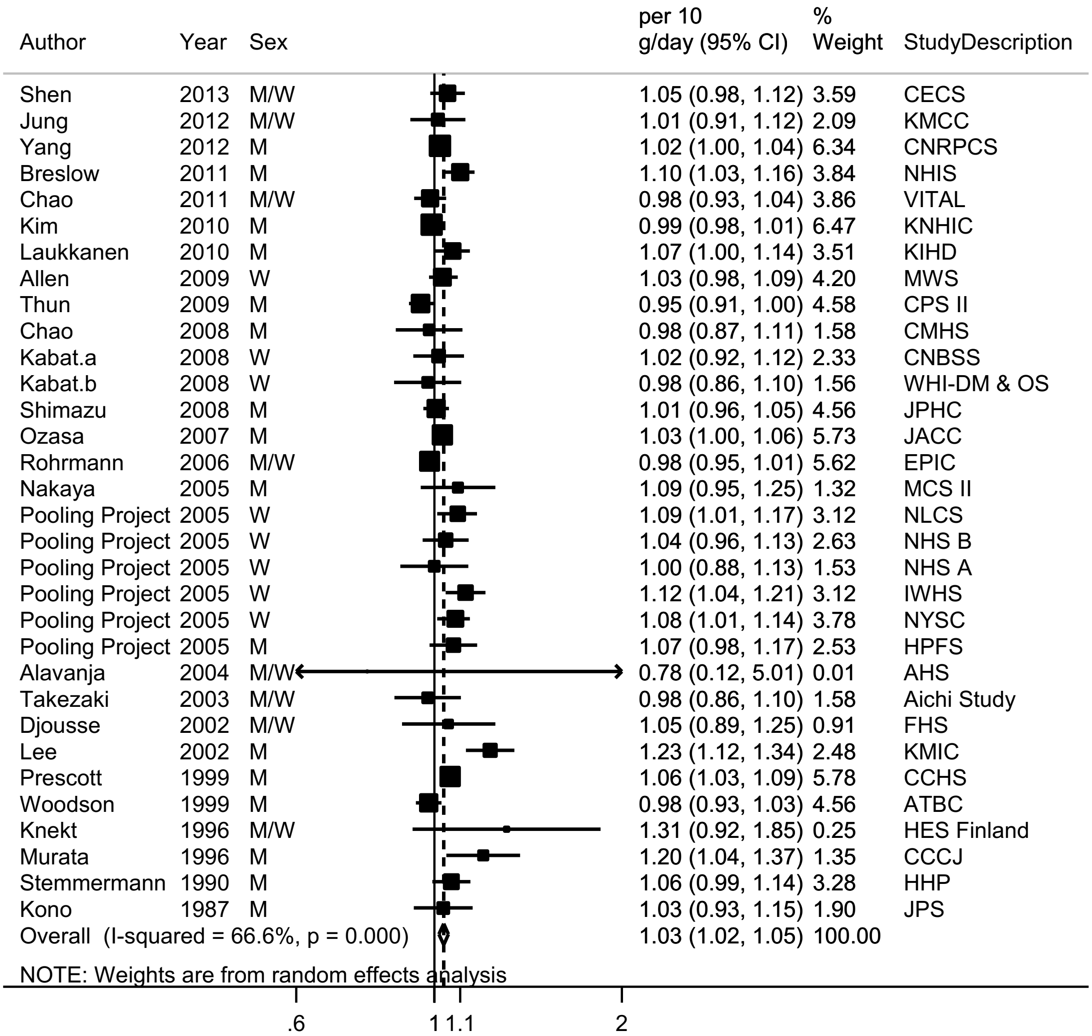
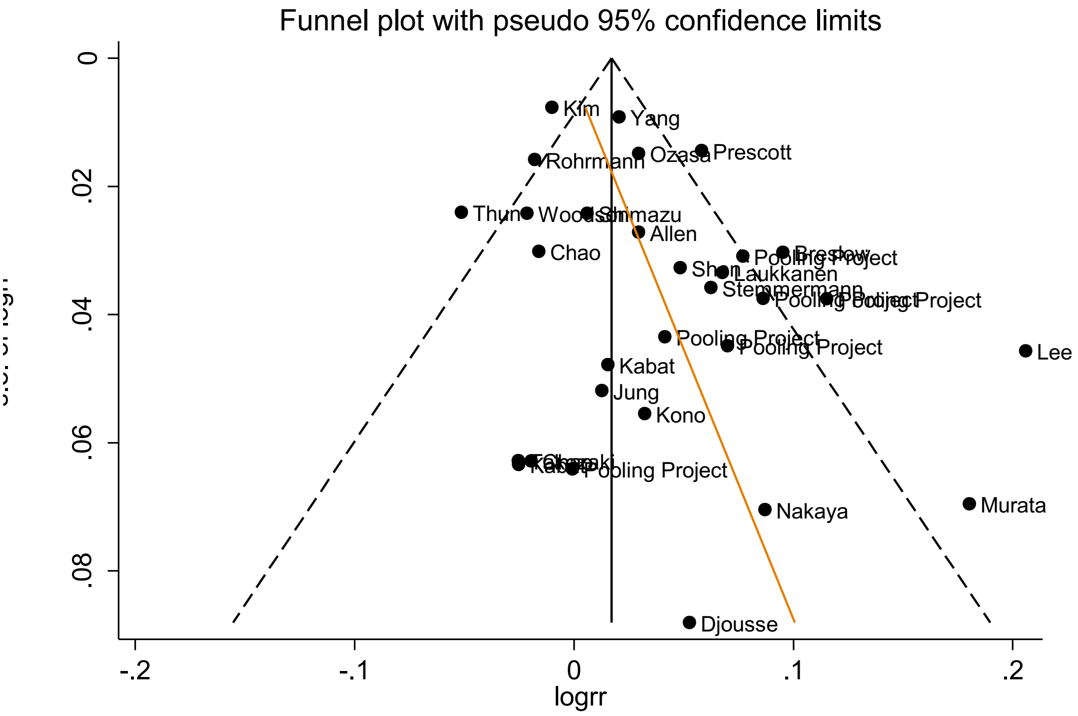


Figure 123 Funnel plot of studies included in the dose response meta-analysis of alcohol (ethanol) intake and lung cancer.



Note: Alavanja 2004 and Knekt 1996 were not included in this graph to improve visibility

Egger's test p =0.02

Figure 124 RR (95% CI) of lung cancer for 10 g/day increase of alcohol (ethanol) intake by sex with Pooling Project

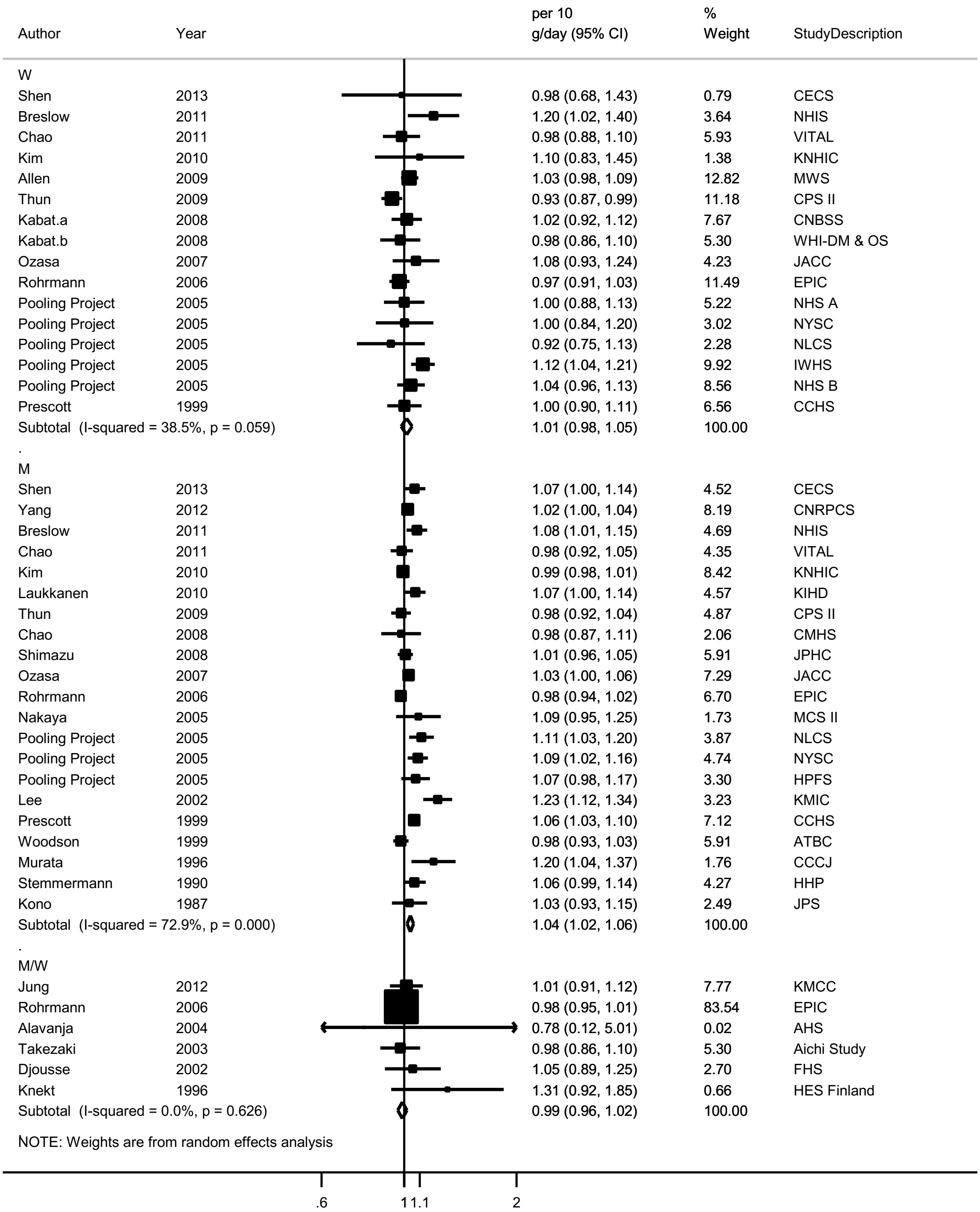


Figure 125 RR (95% CI) of lung cancer for 10 g/day increase of alcohol (ethanol) intake by cancer outcome with Pooling Project

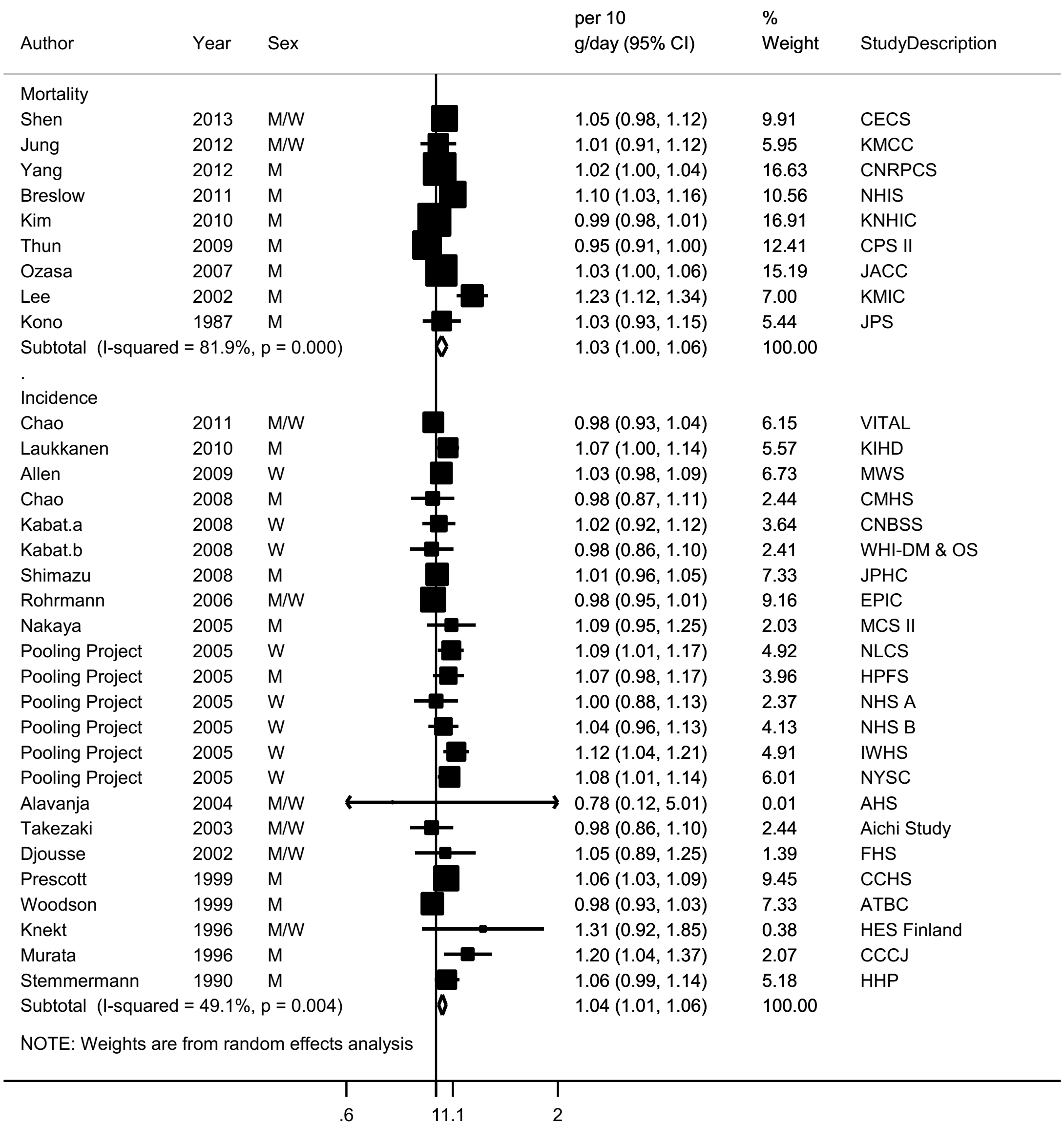
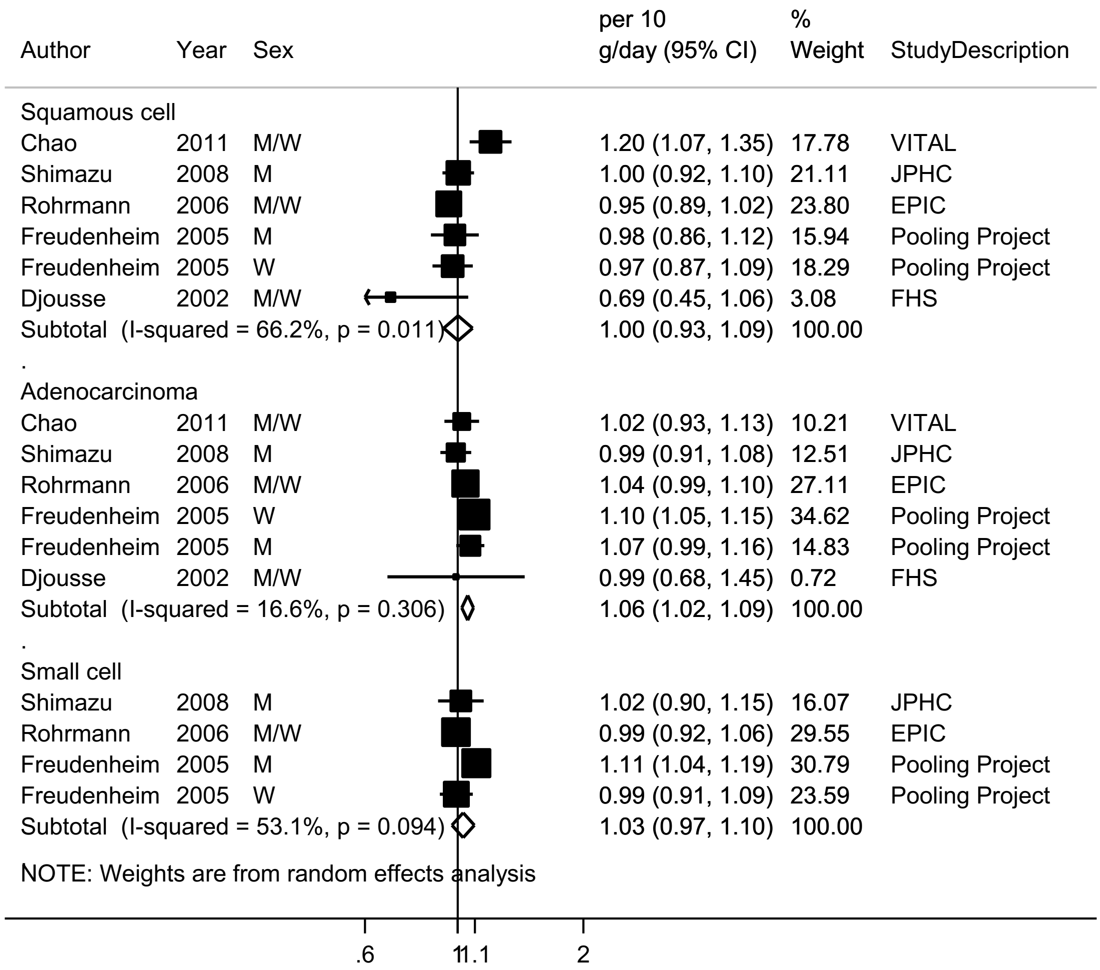


Figure 126 RR (95% CI) of lung cancer for 10 g/day increase of alcohol (ethanol) intake by cancer type (including Pooling Project)



Note: the Pooling Project provided overall data on lung cancer type

Figure 127 RR (95% CI) of lung cancer for 10 g/day increase of alcohol (ethanol) intake by smoking status (including Pooling Project)

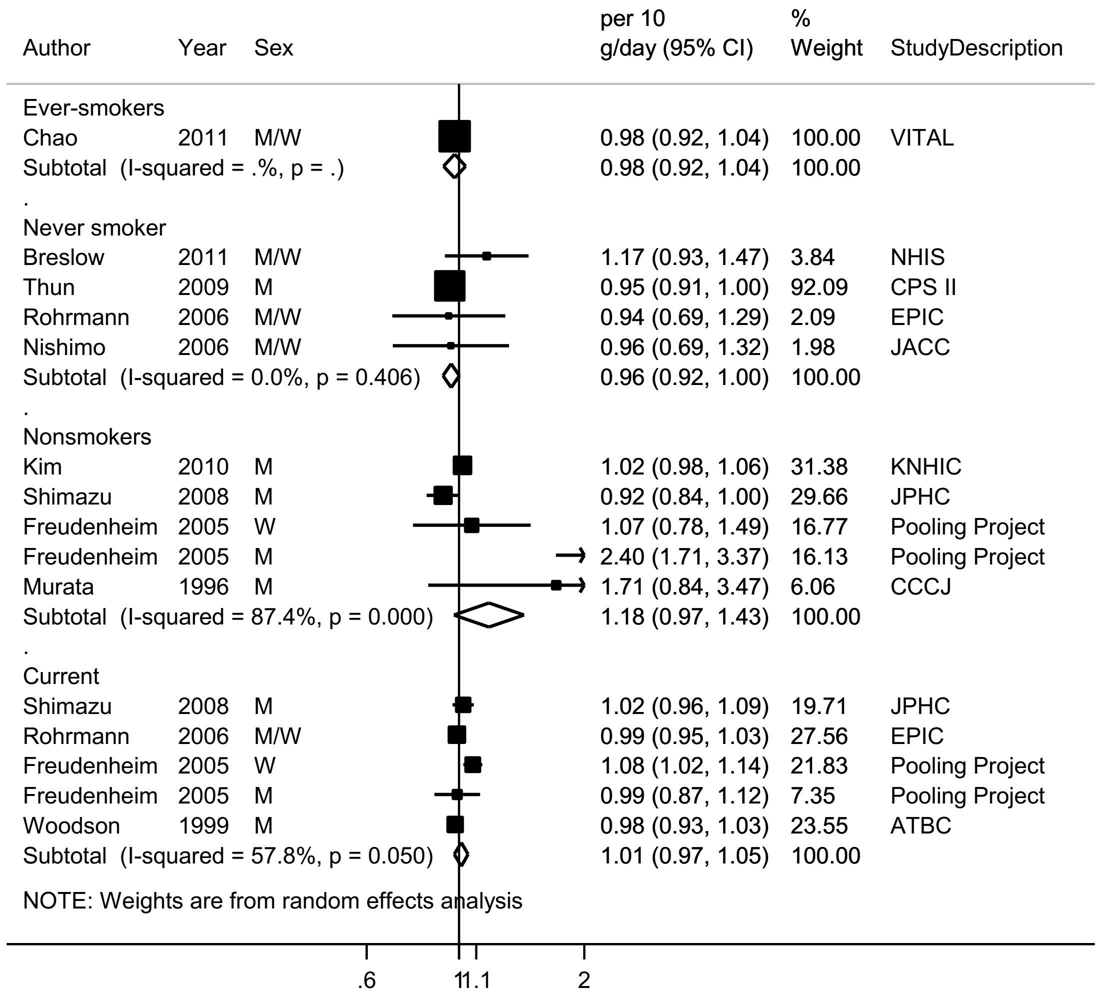


Figure 128 RR (95% CI) of lung cancer for 10 g/day increase of alcohol (ethanol) intake by smoking adjustment

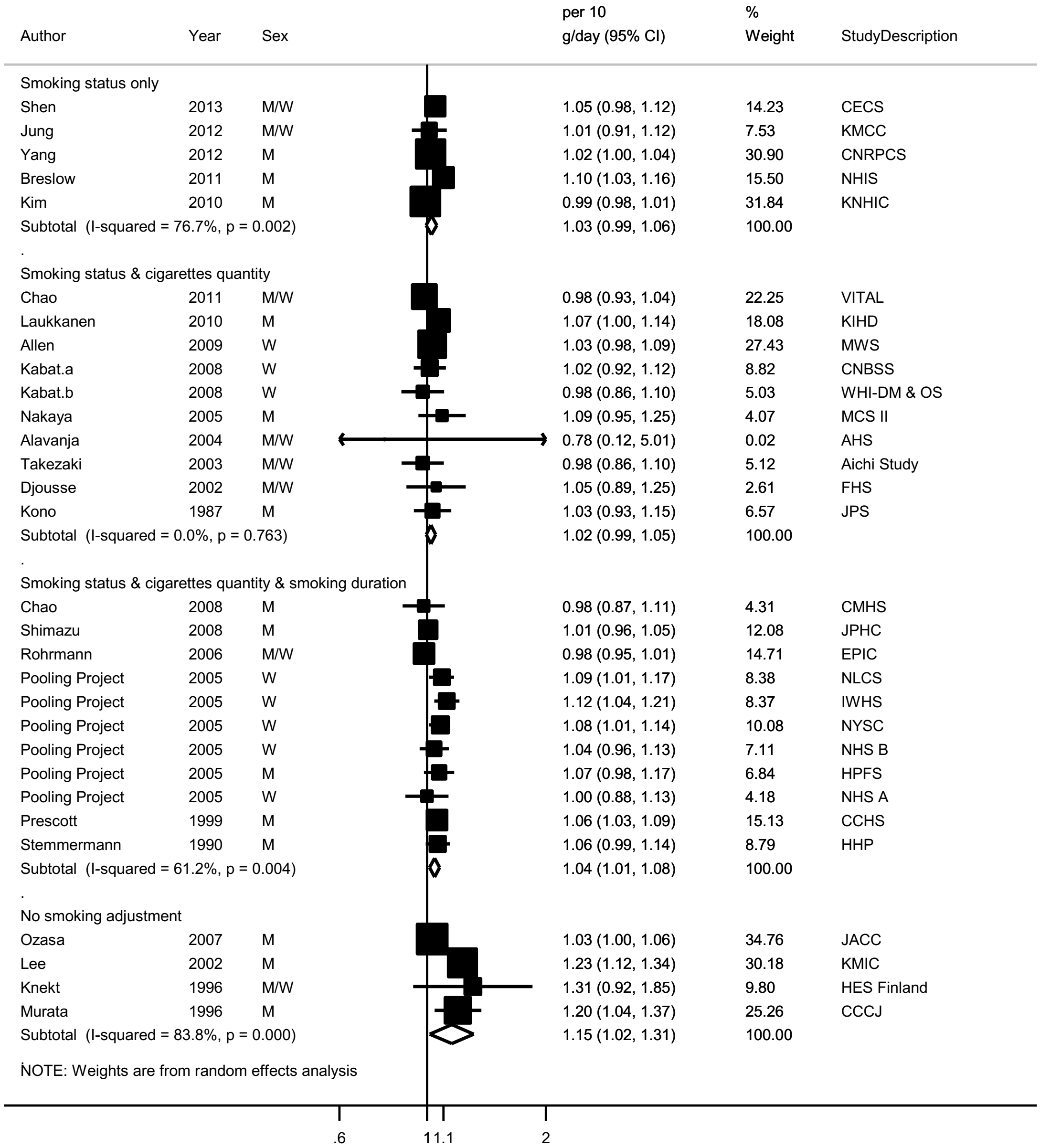


Figure 129 RR (95% CI) of lung cancer for 10 g/day increase of alcohol (ethanol) intake by ethanol intake units

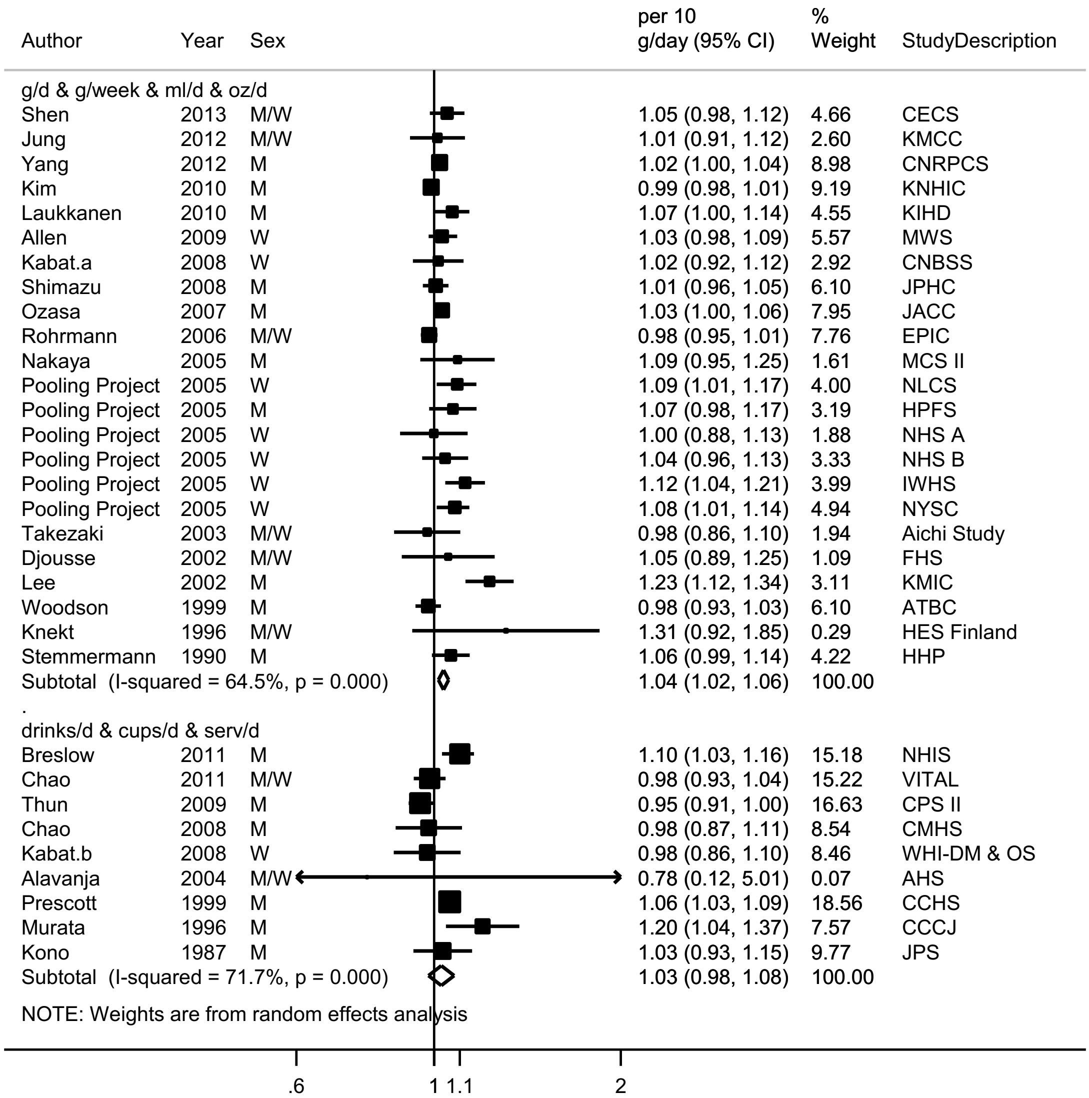


Figure 130 RR (95% CI) of lung cancer for 10 g/day increase of alcohol (ethanol) intake by geographic location

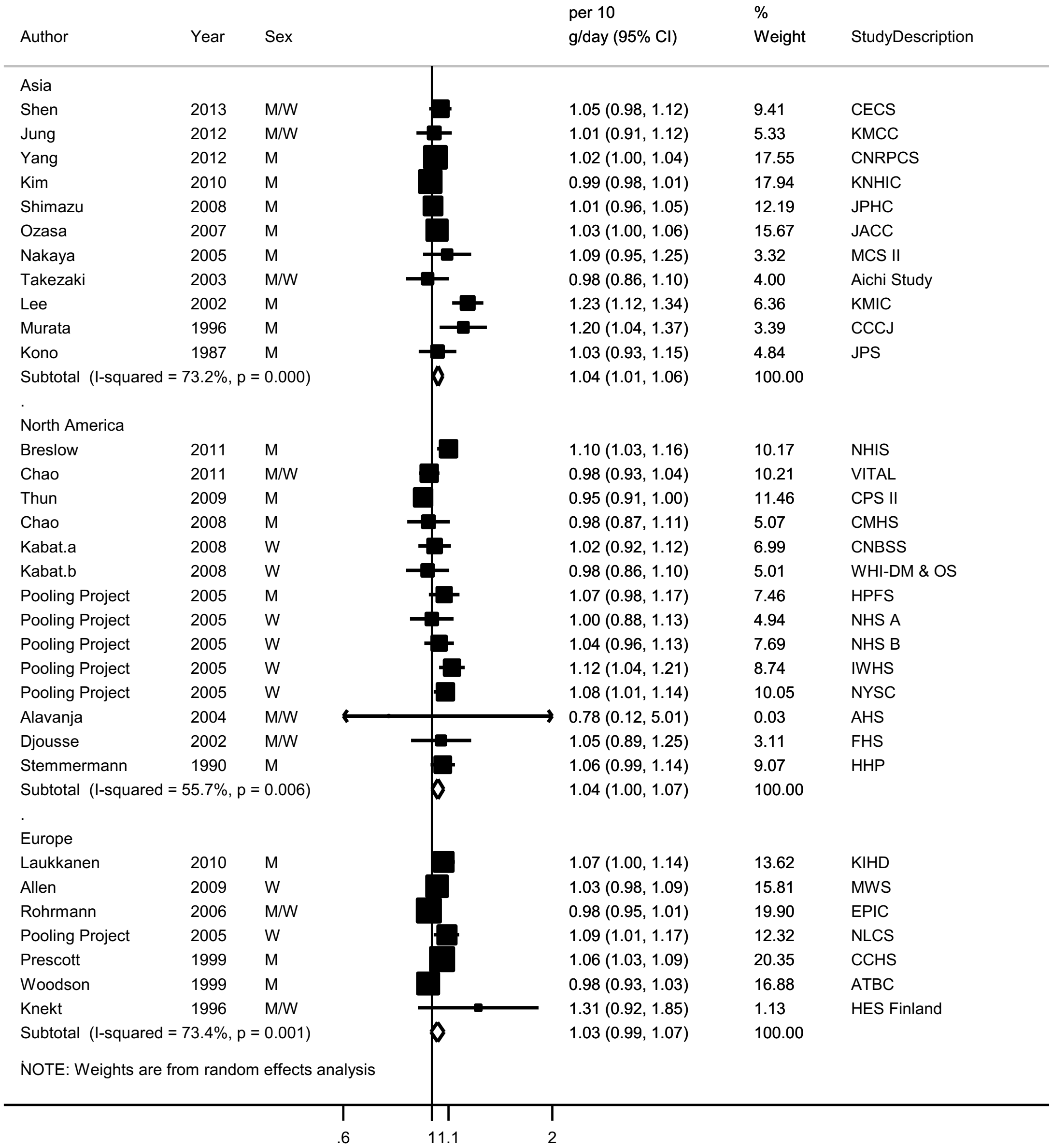
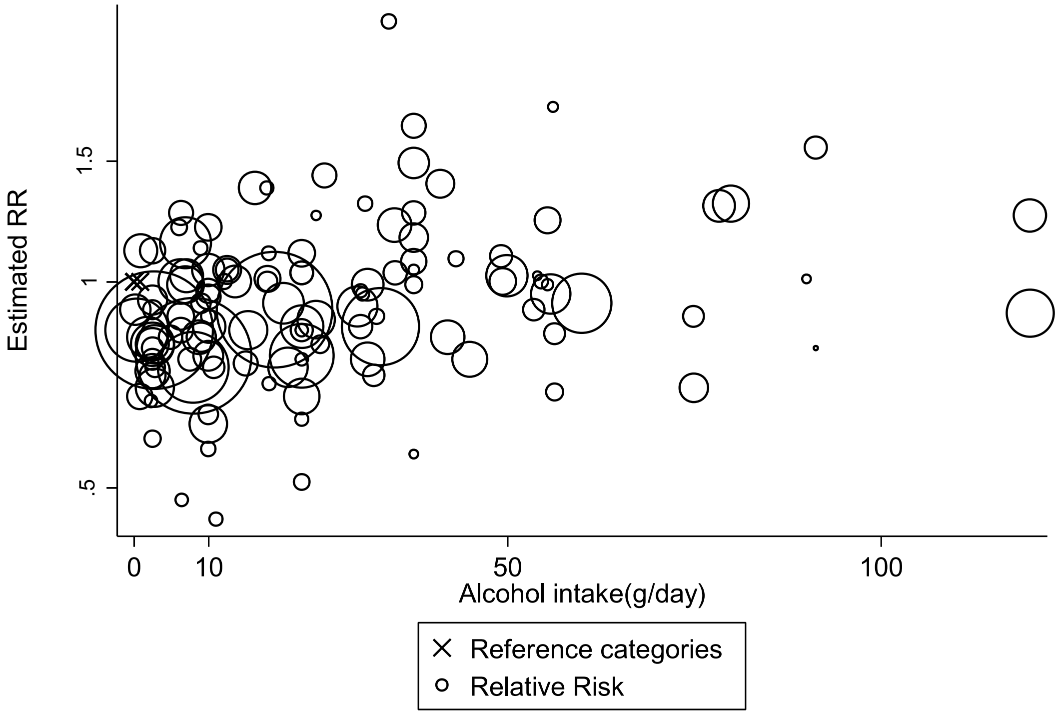
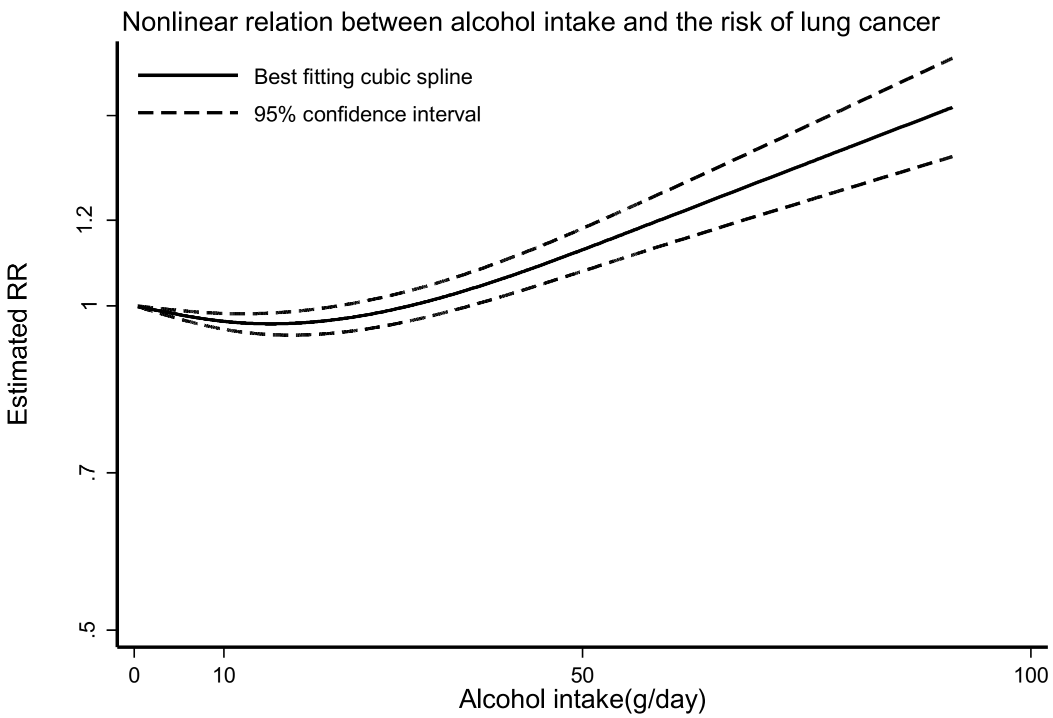


Figure 131 Relative risk of lung cancer and alcohol (ethanol) intake estimated using non-linear models



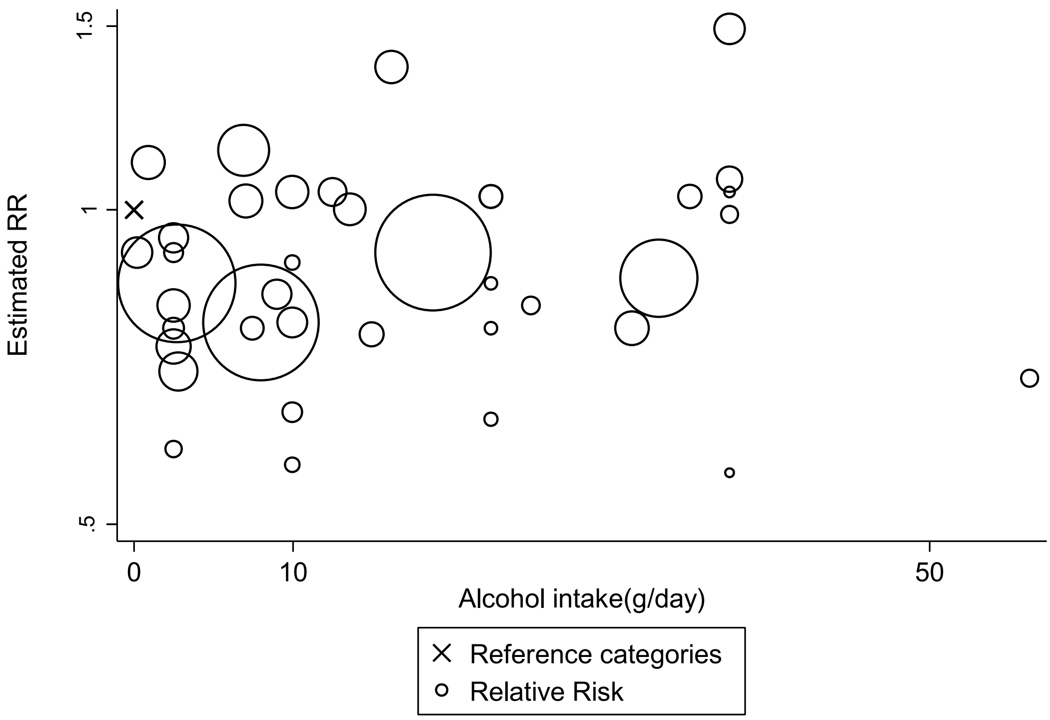


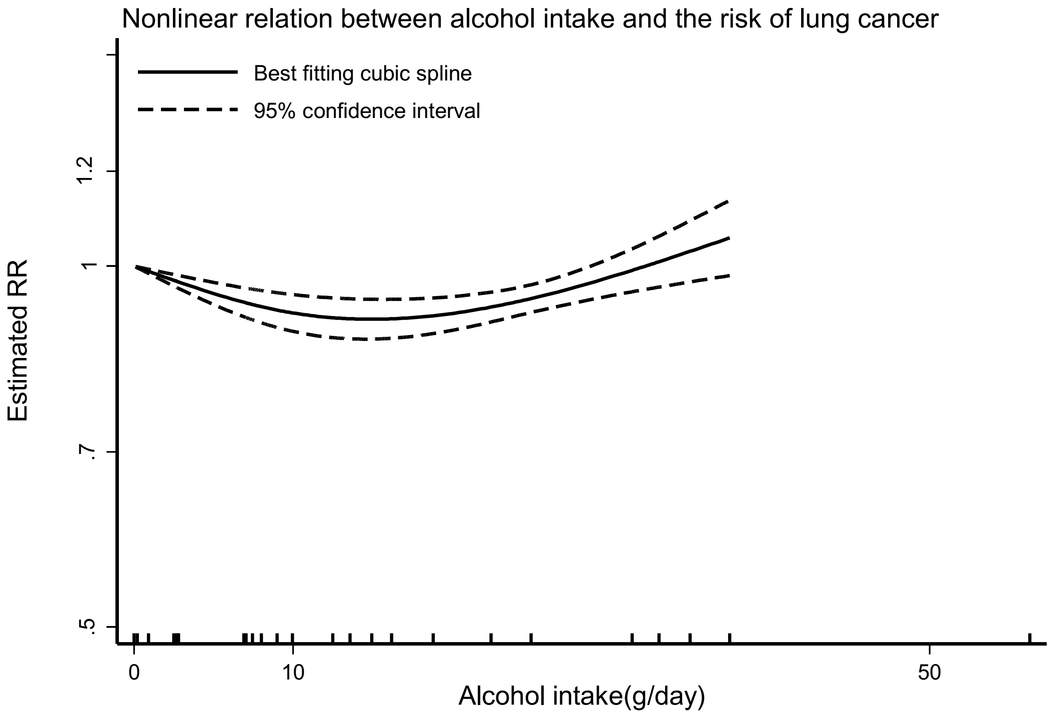
$p < 0.01$
Laukkanen 2010, Nakaya 2005, Alavanja 2004, Takezaki 2003, Lee 2002, could not be included in the non-linear analysis.

Table 106 Table with alcohol (ethanol) intake values and corresponding RRs (95% CIs) for non-linear analysis of alcohol (ethanol) intake and lung cancer

Alcohol intake (g/day)	RR (95%CI)
0	1.00
20	0.97 (0.94-0.99)
40	1.05 (1.01-1.09)
60	1.21(1.14-1.28)
80	1.40 (1.28-1.53)

Figure 132 Relative risk of lung cancer and alcohol (ethanol) intake estimated using non-linear models, women only



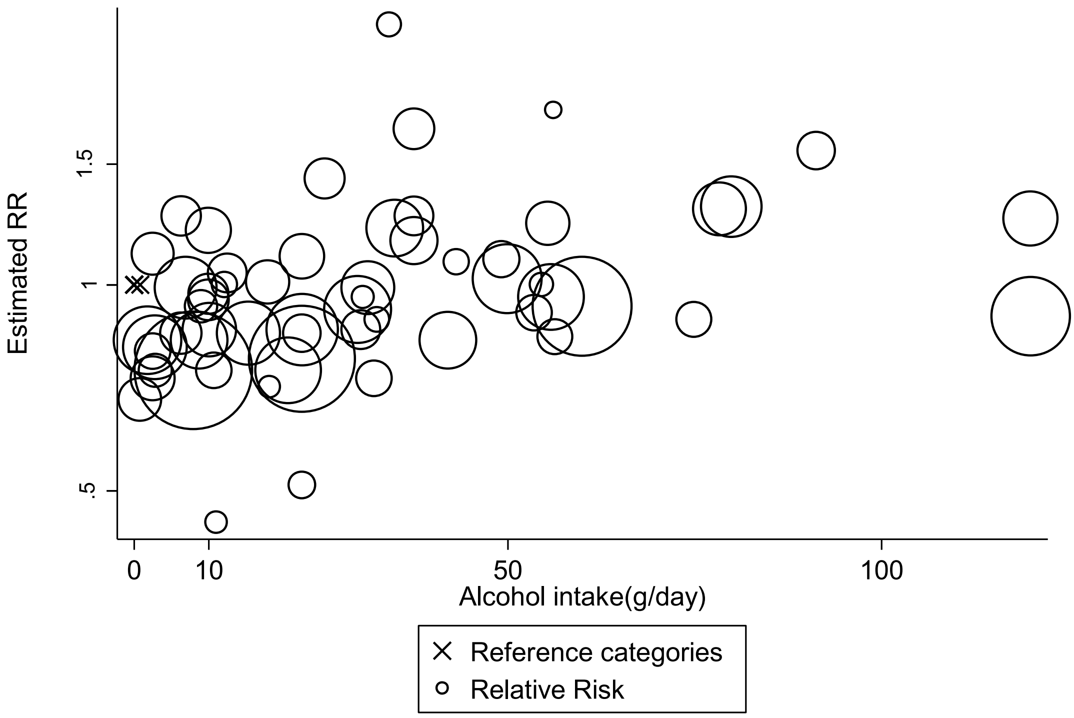


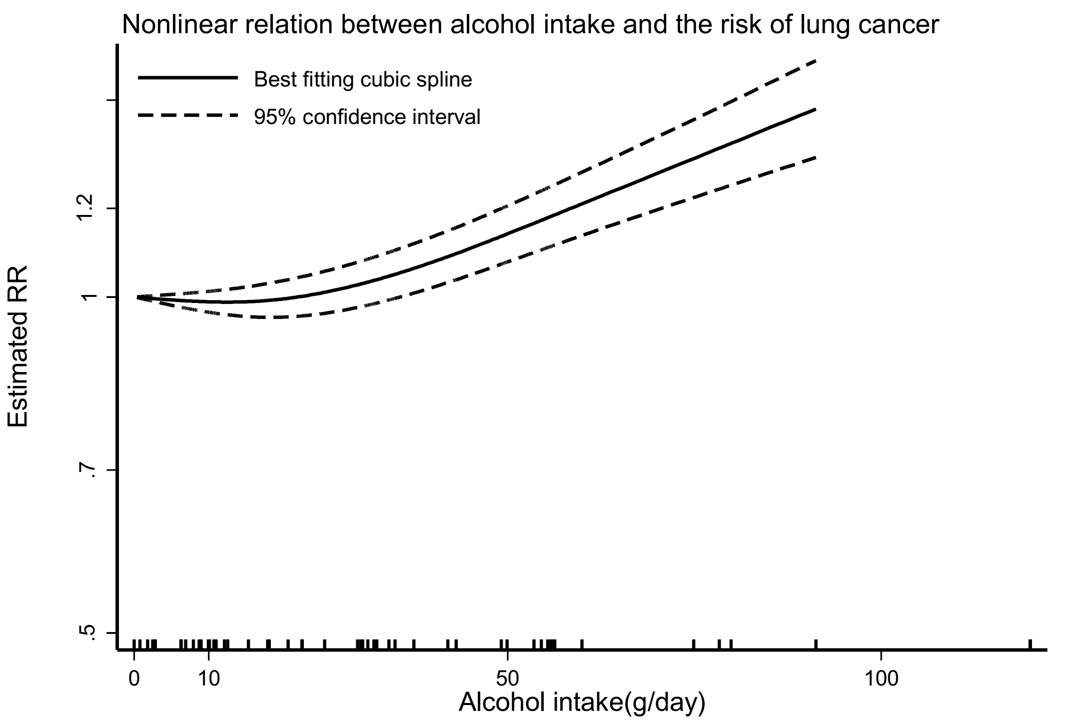
$p < 0.01$

Table 107 Table with alcohol (ethanol) intake values and corresponding RRs (95% CIs) for non-linear analysis of alcohol (ethanol) intake and lung cancer in women

Alcohol intake (g/day)	RR (95%CI)
0	1.00
10	0.92 (0.89-0.95)
20	0.92 (0.90-95)
30	0.97 (0.94-1.01)
40	1.04 (0.97-1.11)
50	1.22 (1.05-1.43)

Figure 133 Relative risk of lung cancer and alcohol (ethanol) intake estimated using non-linear models, men only





$p < 0.01$

Table 108 Table with alcohol (ethanol) intake values and corresponding RRs (95% CIs) for non-linear analysis of alcohol (ethanol) intake and lung cancer in men

Alcohol intake (g/day)	RR (95%CI)
0	1.00
20	0.99 (0.95-1.03)
40	1.08 (1.03-1.14)
60	1.21 (1.13-1.29)
80	1.37 (1.25-1.49)

Figure 134 RR (95% CI) of lung cancer for ex drinkers compared with nondrinkers of alcohol

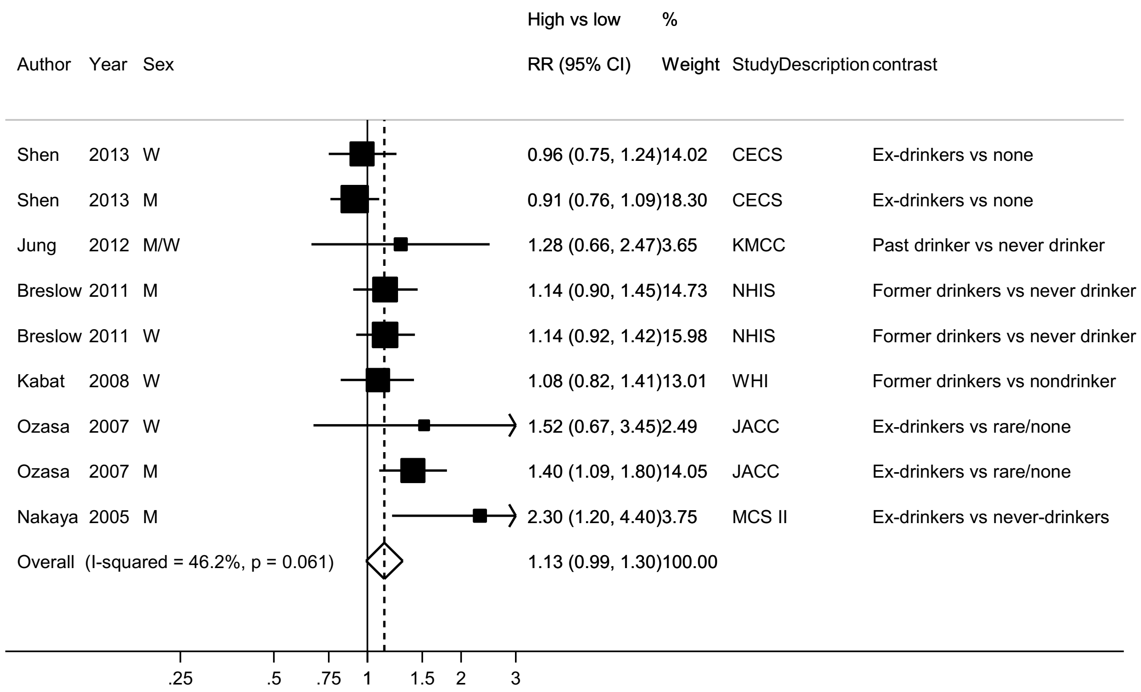
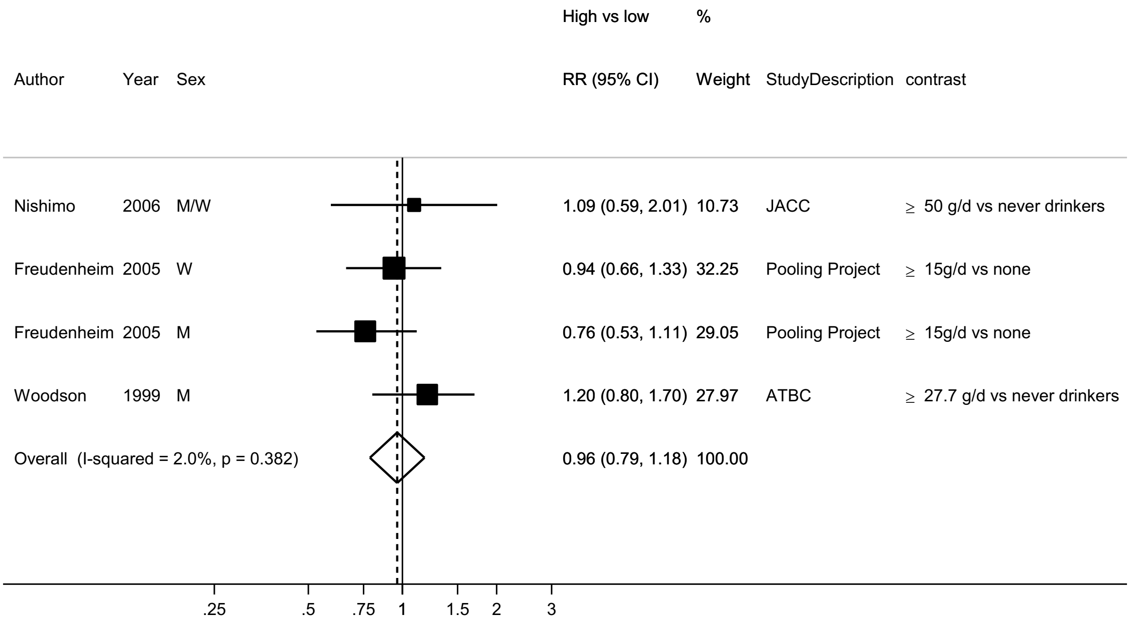


Figure 135 RR (95% CI) of lung cancer for the highest compared with the lowest level of alcohol (ethanol) intake in current smokers of less than 20 cigarettes per day



Note: this graph was added to compare the two publications that provided data on smokers of less than 20 cigarettes per data and the Pooling Project

5.4.1 Beer (ethanol)

Cohort studies

Summary

Main results:
Seven studies (3481 cases) were included in the dose-response meta-analysis. No significant association of beer intake was observed for lung cancer.
Only one (Potter, 1992) of the two publications excluded from the dose-response analysis found a significant positive association.
Results from the Pooling Project (Freudenhein, 2005) were included in this analysis.
High heterogeneity was observed.
There was no significant evidence of publication or small study bias (p=0.75).
There was a limited number of studies on lung cancer subtypes and by smoking status.

Sensitivity analyses:
The summary RRs ranged from 1.07 (95% CI=0.93-1.22) when Woodson, 1999 was omitted to 1.01 (95% CI=0.88-1.17) when Prescott, 1999 was omitted in the influence analysis. The summary RRs did not change materially when Chao, 2011 (23.46% weight) and Chao, 2008 (24.56% weight) were omitted in turn.

Study quality:
Cancer outcome was confirmed using cancer registry records in most studies and beer intake was assessed using FFQ or questionnaire in all studies.

All studies adjusted for at least smoking status.

Pooling Project of cohort studies

Lung cancer was not significantly positively associated to beer intake in the Pooling Project of Cohort Studies (Freudenheim, 2005; seven cohorts) in men (1370 cases) and significantly positively associated in women (1245 cases).

Table 109 Beer intake and lung 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	7
Studies included in 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

Table 110 Beer intake and lung cancer risk. Summary of the dose-response meta-analysis in the 2005 SLR and CUP.

	2005 SLR	**CUP**
Increment unit used	10 g/week	10 g/day
All studies		
Studies (n)	2	7
Cases (total number)	1620	3481
RR (95%CI)	1.02 (0.97-1.06)	1.04 (0.93-1.16)
Heterogeneity (I^2, p-value)	89.0%	63.8 %, 0.01
P value Egger test		0.75

All studies and Pooling Project *Indicates that the Pooling project (Freudenheim, 2005) is included		
Studies (n)		15
Cases (total number)		6146
RR (95%CI)		1.03 (0.95-1.11)
Heterogeneity (I^2, p-value)		51.6%, 0.04
P value Egger test		0.75
Men*		
Studies (n)		5
RR (95%CI)		1.03 (0.96-1.10)
Heterogeneity (I^2, p-value)		45.1%, 0.12
Women*		
Studies (n)		3
RR (95%CI)		1.17 (0.86-1.59)
Heterogeneity (I^2, p-value)		74.8%, 0.02
Incidence*		
Studies (n)		7
RR (95%CI)		1.02 (0.95-1.11)
Heterogeneity (I^2, p-value)		56.5%, 0.02

Table 111 Beer intake and lung 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								
Chao, 2007	10 Cohort 6 Case-control	4391 4119	Europe, North America, Uruguay	Incidence	≥1 drink/day vs nondrinker	1.25 (1.06-1.48) (total) 1.15 (0.85-1.55) (case-control) 1.39 (1.21-1.61) (cohort)	0.11 0.08 0.66	
Pooled-analyses								
Freudenheim, 2005	8 cohorts	1420	Europe and North America	Incidence	≥ 15 g/d vs none	1.10 (0.85-1.42) Men	0.47	0.47
		1245				1.88 (1.45-2.42) Women	< 0.01	0.43

Table 112 Beer intake and lung cancer risk. Main characteristics of studies 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	Missing data derived for analyses
Gnagnarella, 2013a LUN26858 Italy	COSMOS Prospective Cohort, Age: 50-84 years M/W heavy smokers	178/ 4336 5.7 years	Screening examinations	FFQ	Incidence, lung cancer,	330 g/d vs never	0.73 (0.29-1.85)	Age, sex, energy intake, smoking duration, average daily cigarettes consumption, years of cessation, asbestos exposure, fruits and vegetables, fish, red meat, olive oil, tea and wine intake	Mid-points of exposure categories Exposure values using standard portion size
Chao, 2011 LUN20355 USA	VITAL, Prospective Cohort, Age: 50-76 years, M/W	580/ 66 186 5.9 years	Cancer registry	FFQ	Incidence, lung cancer,	>1drink/d vs non-drinkers	1.04 (0.76-1.44)	Sex, race, education, household income, BMI, history of emphysema, cigarette smoking, family history of lung cancer, fat intake, high intensity physical activity, fruit and vegetable intake	Mid-points of exposure categories Distribution of person-years/non-cases by exposure category Exposure values using standard portion size
Chao, 2008 LUN20333	CMHS, Prospective	210/ 78 168	Record linkage with cancer	Semi-quantitative FFQ	Incidence, lung cancer	≥ 1 drink/d vs non-drinker	0.78 (0.45-1.35)	Age, ethnicity, education,	Distribution of cases by

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Missing data derived for analyses
USA	Cohort, Age: 45-69 years, M	4 years	registries			1 /drinks/month (continuous)	1.0 (0.99-1.0)	household income, BMI, smoking status, cigarettes smoked/day, smoking duration, CODP/emphysema, red wine, white wine, liquor	exposure category Distribution of person-years/non-cases by exposure category Exposure values using standard portion size Mid-points of exposure categories
Olson, 2002 LUN00502 USA	IWHS Prospective Cohort, Age: 55-69 years, W Postmenopausal	561/ 38 006 12 years	Iowa Health Registry (part of SEER registry)	FFQ - study-specific	Incidence, lung cancer	≥ weekly vs never	1.36 (1.11-1.68)	Age, smoking habits, pack year smoking	Mid-points of exposure categories
Prescott, 1999 LUN01393 Denmark	CCHS Prospective Cohort, Age: 20- years, M/W	429/ 28 160 28 years	Danish Cancer Registry	Dietary history questionnaire	Incidence, lung cancer, men	>13.1 times/week vs 0 times/week	1.36 (1.02-1.82)	Age, smoking, study cohort, educational level	Mid-points of exposure Distribution of person-years/non-cases by exposure category Exposure values
		131/ 28 160 28 years			Incidence, lung cancer, women		1.49 (0.70-3.13)		

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Missing data derived for analyses
									using standard portion size
Woodson, 1999 LUN01299 Finland	ATBC Prospective Cohort, Age: 50-69 years, M	1059/ 27 111 7.7 years	Finnish Cancer Registry and the Register of Causes of Death	FFQ - study-specific	Incidence, lung cancer	19.8 vs 0.9 g/d	0.9 (0.7-1.1)	Age, BMI, years smoked, cigarettes per day, and intervention group.	Rescale reference category
Chow, 1992 LUN02888 USA	LBS Prospective Cohort, Age: 35- years, M	213/ 17 633 20 years	Death certificates	FFQ - study-specific	Mortality, lung cancer	> 13 times/month vs never used	1.10 (0.60-1.90)	Age, smoking status, industry/occupation	Exposure values using standard portion size Mid-points of exposure categories

Table 113 Beer consumption (ethanol) and lung cancer risk. Main characteristics of studies excluded 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	Reasons for exclusion
Potter, 1992 LUN02842 USA	IWHS Nested Case Control, Age: 55-69 years, Postmenopausal women	109/ 41 837 4 years	Cancer registry	FFQ - study-specific	Incidence, lung cancer	Drinker vs non-drinker Per glass/week	1.90 (0.96-3.90) 1.06 (1.02-1.10)	Physical activity, smoking habits, educational level	Superseded by Olson, 2002, LUN00502)
Pollack, 1984 LUN04212 USA	Japan-Hawaii Cancer Study Prospective Cohort, Age: 45-79 years, M	89/ 7837 14 years	Hospital records, death certificates, Hawaii tumour registry	FFQ - study-specific	Incidence, lung cancer	500 or more oz/week vs none			No measure of association (only in a graph)

Figure 136 RR estimates of beer intake and lung cancer by levels of beer intake with Pooling Project

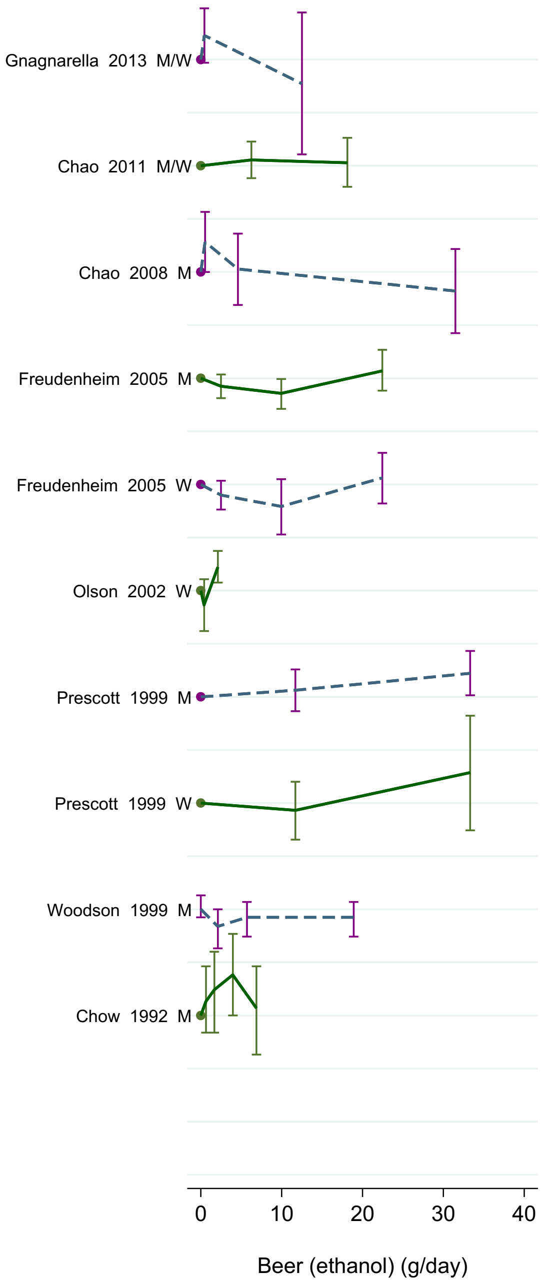


Figure 137 RR (95% CI) of lung cancer for the highest compared to the lowest level of beer intake with Pooling Project

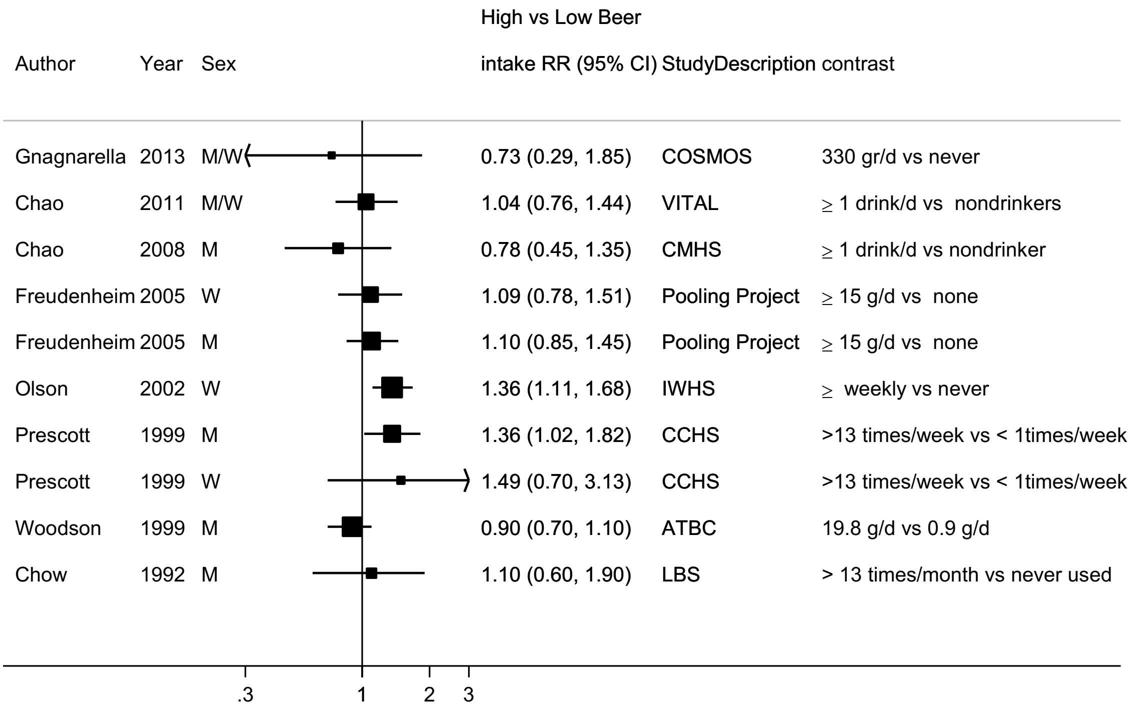


Figure 138 RR (95% CI) of lung cancer for 10 g/day increase of beer (ethanol) with Pooling Project

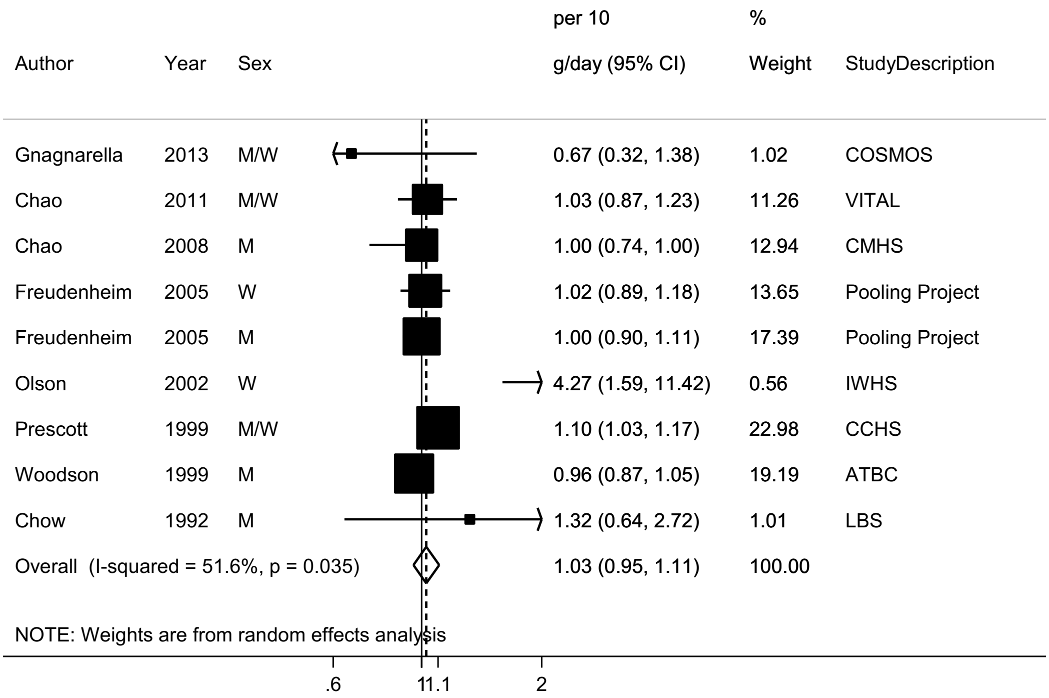
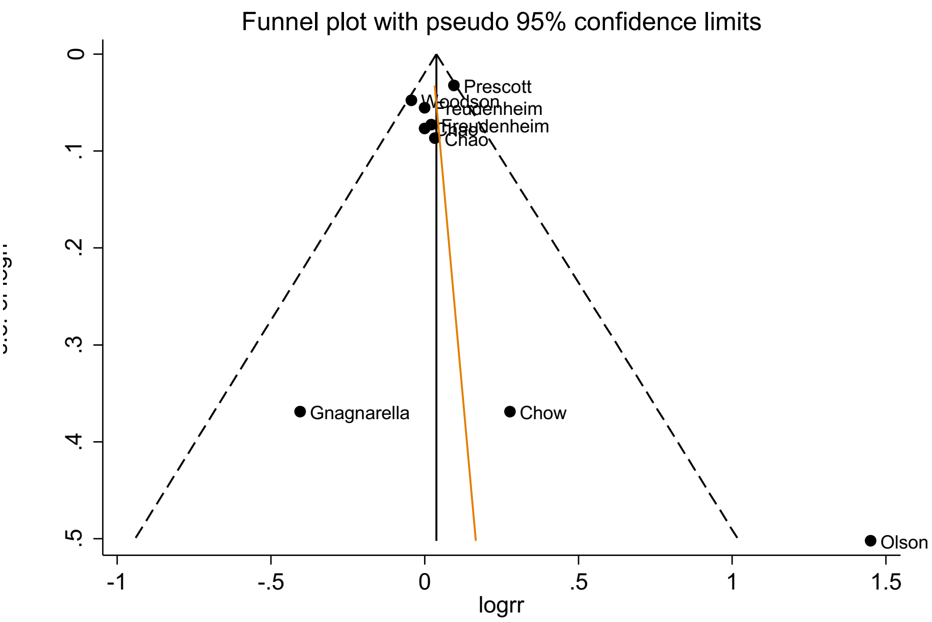


Figure 139 Funnel plot of studies included in the dose response meta-analysis of beer intake and lung cancer with Pooling Project



Egger's test p= 0.75

Figure 140 RR (95% CI) of lung cancer for 10g/day increase of beer intake by sex with Pooling Project

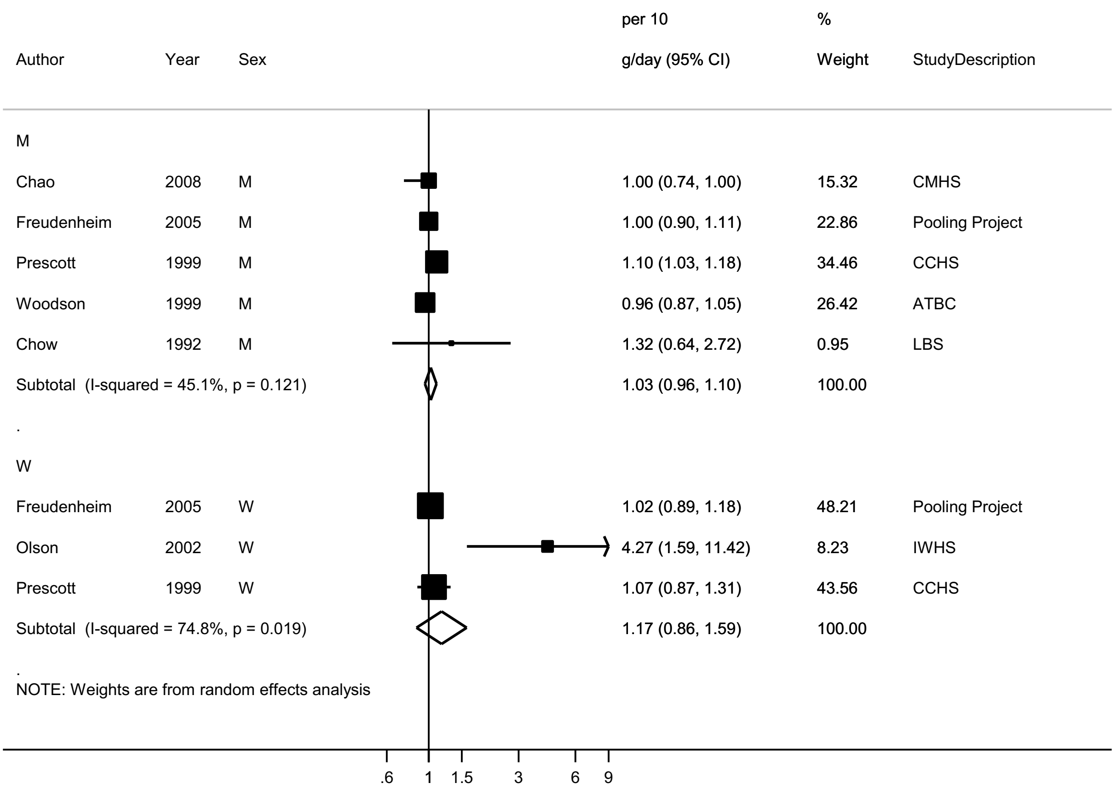
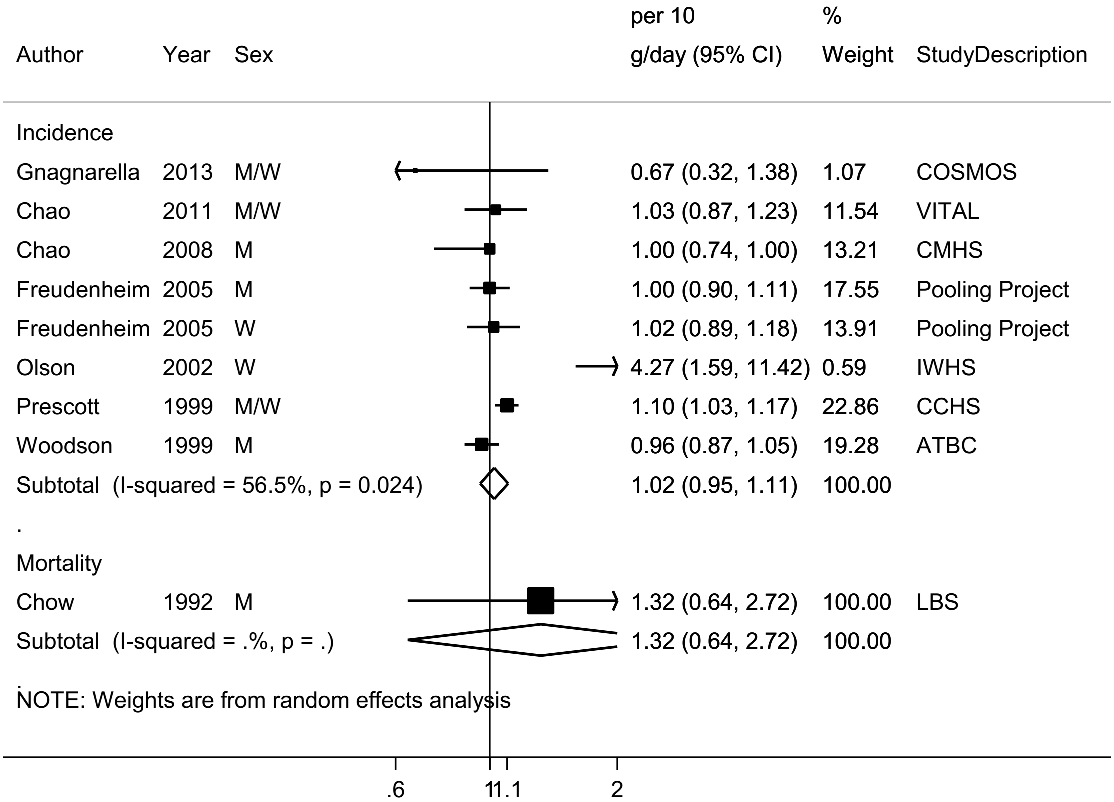


Figure 141 RR (95% CI) of lung cancer for 10g/day increase of beer intake by outcome with Pooling Project



5.4.2 Wine (ethanol)

Cohort studies

Summary

Main results:
Five studies (2701 cases) were included in the dose-response meta-analysis. A significant protective association of wine intake was observed for lung cancer.
High heterogeneity was observed.
There was a limited number of studies on lung cancer subtypes and by smoking status.
There was significant evidence of publication or small study bias (p=0.05).

Sensitivity analyses:

The summary RRs ranged from 0.82 (95% CI=0.73-0.90) when Gnagnarella, 2013a was omitted to 0.90 (95% CI=0.78-1.03) when Prescott, 1999 was omitted in the influence analysis.

Study quality:
Cancer outcome was confirmed using cancer registry records in most studies and wine intake was assessed using FFQ or questionnaire in all studies. All studies adjusted by smoking.

Several studies reported that wine drinkers tend to have higher consumption of fruits and vegetables and are less likely to be current smokers. In a study in smokers, wine consumption was inversely related to fruit and vegetables intake and positively correlated with pack-years of smoking (Gnagnarella, 2013). In another study (Chao 2011), all types of alcoholic beverages were associated with increased prevalence of ever-smoking, but wine drinkers were less likely to be current smokers, tended to consume more fruit and vegetables and less fat. .In a study in men (Chao, 2008) consumption of red wine also appeared to be associated with increased intake of fruits and vegetables; red and white wine drinkers were less likely to be current smokers. In the Pooling Project of cohort studies (Freudenheim, 2005) an inverse trend for wine was observed only in former smokers and the associations of red and white wine consumption with lung cancer risk were similar (data not shown in the publication). Finally, in an early study in Denmark (Prescott, 1999), wine drinkers differed from drinkers of beer and spirits mainly in that fewer were heavy smokers and more had a higher educational level.

Pooling Project of cohort studies

Lung cancer was not significantly associated with wine beer intake in the Pooling Project of Cohort Studies (Freudenheim, 2005; seven cohorts, men 1370 cases and women 1245 cases).

Table 114 Wine intake and lung cancer risk. Number of studies in the CUP SLR

	Number
Studies identified	7 (7 publications)
Studies included in forest plot of highest compared with lowest exposure	5
Studies included in dose-response meta-analysis	5

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

Table 115 Wine intake and lung cancer risk. Summary of the dose-response meta-analysis in the 2005 SLR and CUP.

	2005 SLR	CUP
Increment unit used	No meta-analysis	10 g/day
All studies		
Studies (n)		5
Cases (total number)		2701
RR (95%CI)		0.87 (0.76-0.98)
Heterogeneity (I^2, p-value)		62.0 %, 0.03
P value Egger test		0.07
All studies and Pooling Project		
Studies (n)		12
Cases (total number)		5366
RR (95%CI)		0.88 (0.80-0.97)
Heterogeneity (I^2, p-value)		55.9%, 0.04
P value Egger test		0.05

Table 116 Wine intake and lung 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								
Chao, 2007	8 Cohort 6 Case-control	4391 4119	Europe, North America, Japan, China	Incidence	≥1 drink/day vs nondrinker	0.78 (0.60-1.02) (total) 0.80 (0.60-1.07) (case-control) 0.66 (0.27-1.65) (cohort)	0.03 0.14 0.01	
Pooled-analyses								
Freudenheim, 2005	8 cohorts	1420	Europe and North America	Incidence	≥ 15 g/d vs none	0.87(0.55-1.39) Men	0.04	0.23
		1245				1.09 (0.78-1.51) Women	0.99	0.31

Table 117 Wine intake and lung cancer risk. Main characteristics of studies 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	Missing data derived for analyses
Gnagnarella, 2013a LUN26858 Italy	COSMOS Prospective Cohort Age: 50-84 years, M/W heavy smokers	178/ 4 336 5.7 years	Screening examinations	FFQ	Incidence, lung cancer	≥ 3 glasses/d vs < 1 glass/d	0.94 (0.65-1.36)	Age, sex, energy intake, smoking duration, average daily cigarettes consumption, years of cessation, asbestos exposure, fruits and vegetables, fish, red meat, olive oil, tea and wine intake	Mid-points of exposure categories Exposure values using standard portion size
Chao, 2011 LUN20355 USA	VITAL, Prospective Cohort, Age: 50-76 years, M/W	580/ 66 186 5.9 years	Cancer registry	FFQ	Incidence, lung cancer	>1drink/d vs non-drinkers	0.76 (0.54-1.07)	Gender, race, education, household income, body mass index, history of COPD/emphysema, cigarette smoking (duration smoked, pack-yr, pack-yr	Mid-points of exposure categories Distribution of person-years/non-cases by exposure category Exposure values using standard portion size

Author, Year, WCRF Code, Country	Study 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
								squared), family history of lung cancer, high intensity physical activity, fat intake, and fruit and vegetable intake	
Chao, 2008 LUN20333 USA	CMHS, Prospective Cohort, Age: 45-69 years, M	210/ 78 168 4 years	Record linkage with cancer registries	Semi-quantitative FFQ	Incidence, lung cancer	Red wine ≥ 1 drink/d vs non-drinker	0.55 (0.23-1.29)	Age, ethnicity, education, household income, BMI, smoking status, cigarettes smoked/day, smoking duration, COPD/emphysema, liquor	Distribution of cases by exposure category Distribution of person-years/non-cases by exposure category Exposure values using standard portion size Mid-points of exposure categories Pooled red and white wine.
						1 drinks/month (continuous)	0.98 (0.97-1.00)		
						White wine ≥ 1 drink/d vs non-drinker	0.87 (0.31-2.40)		
						1 drinks/month (continuous)	1.00 (0.98-1.01)		
Prescott, 1999 LUN01393	CCHS Prospective	429/ 28 160	Danish Cancer Registry	Dietary history	Incidence, lung cancer,	>13.1 times/week vs 0 times/week	0.44 (0.22-0.86)	Age, smoking,study	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
Denmark Prescott, 1999	Cohort, Age: 20 years, W	28 years		questionnaire	men			cohort, educational level	Distribution of person-years/non-cases by exposure category Exposure values using standard portion size
		131			Incidence, lung cancer, women		0.18 (0.03-1.33)		
Woodson, 1999 LUN01299 Finland	ATBC Prospective Cohort, Age: 50-69 years, M	1059/ 27 111 7.7 years	Finnish Cancer Registry and Register of Causes of Death	FFQ - study-specific	Incidence, lung cancer	19.8 g/d vs 0.7 g/d	0.8 (0.6-1.1)	Age, BMI, years smoked, cigarettes per day, and intervention group.	Rescale reference category

Table 118 Wine consumption (ethanol) and lung cancer risk. Main characteristics of studies excluded 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) P trend	Adjustment factors	Reasons for exclusion
Potter, 1992 LUN02842 USA	IWHS Nested Case Control, Age: 55-69 years, Postmenopausal women	109/ 41 837 4 years	Cancer registry	FFQ - study-specific	Incidence, lung cancer	Drinker vs non-drinker Per glass/week		Physical activity, smoking habits, educational level	Mean values
Pollack, 1984 LUN04212 USA	Japan-Hawaii Cancer Study Prospective Cohort, Age: 45-79 years, M	89/ 7837 14 years	Hospital records, death certificates, Hawaii tumour registry	FFQ - study-specific	Incidence, lung cancer	≥ 500 oz/week vs none			No measure of association (only in a graph)

Figure 142 RR estimates of lung cancer by levels of wine intake with Pooling Project

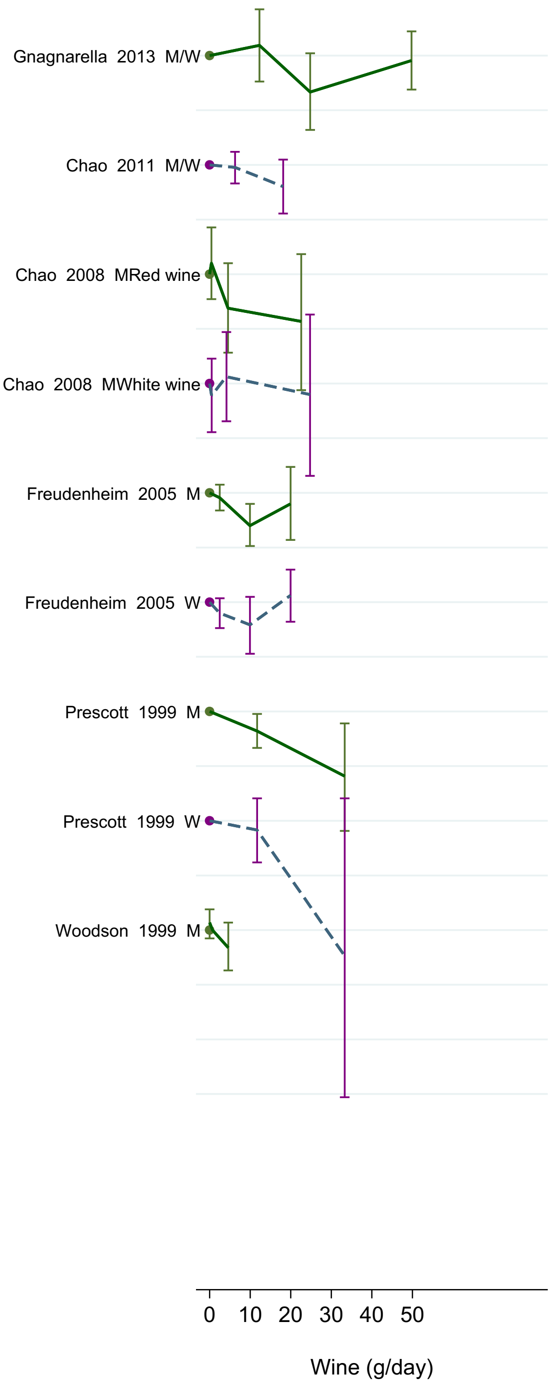


Figure 143 RR (95% CI) of lung cancer for the highest compared with the lowest level of wine intake with Pooling Project

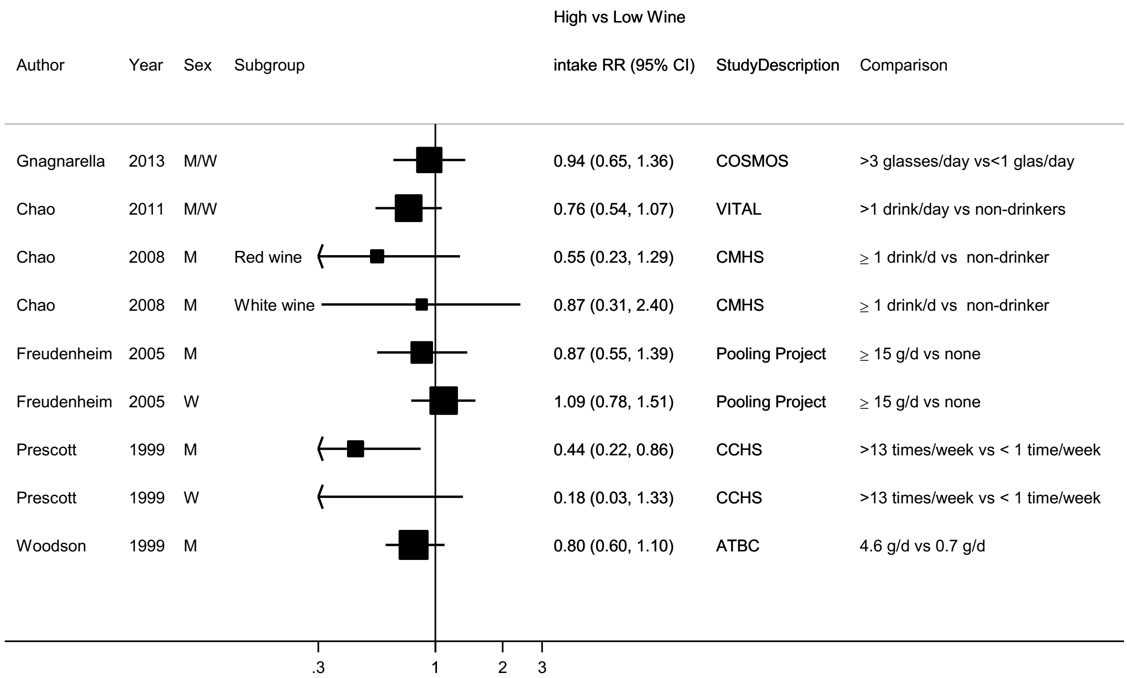


Figure 144 RR (95% CI) of lung cancer for 10 g/day increase of wine intake

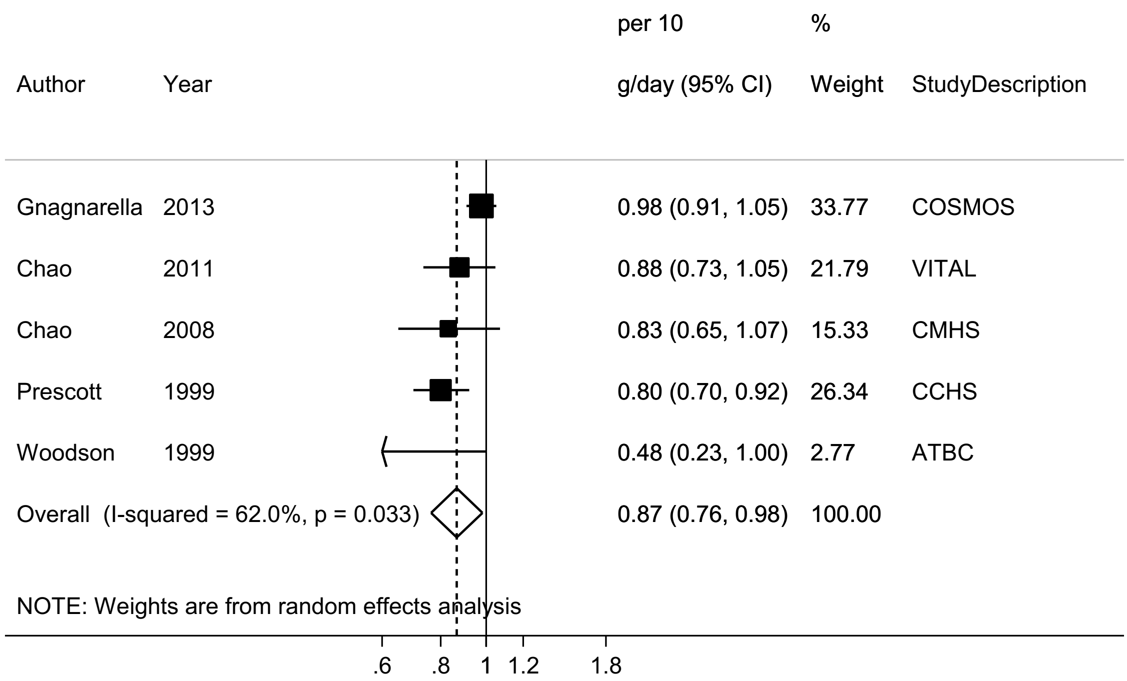


Figure 145 RR (95% CI) of lung cancer for 10 g/day increase of wine intake with Pooling Project

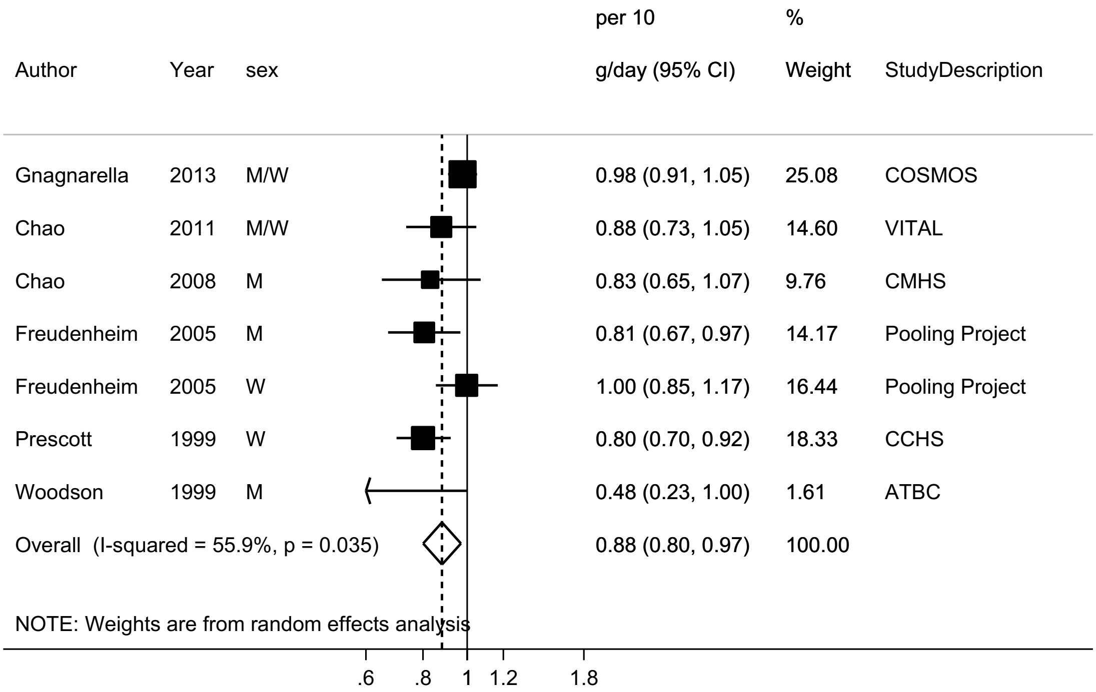
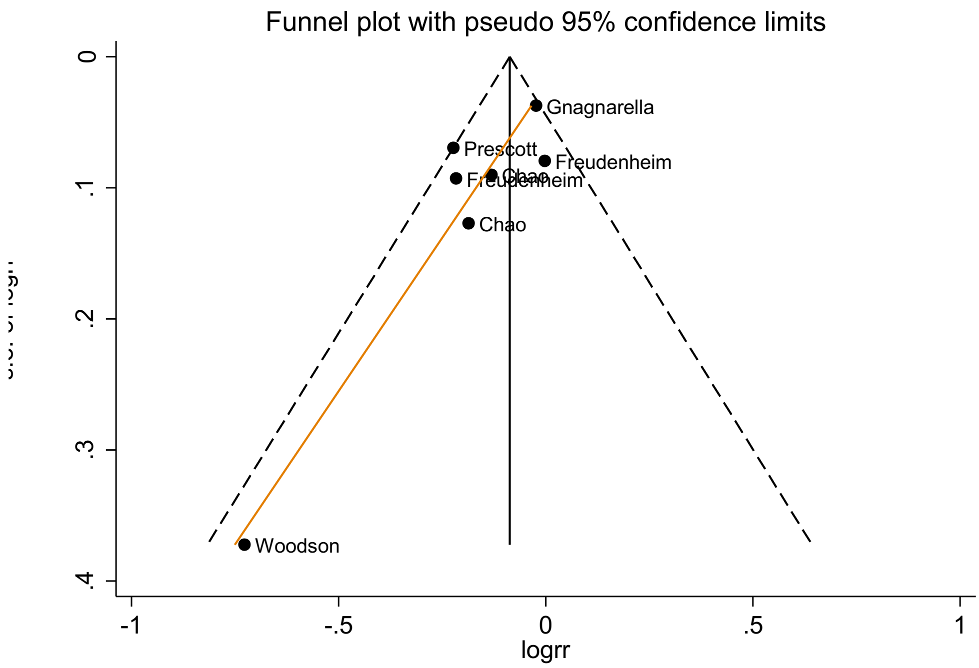


Figure 146 Funnel plot of studies included in the dose response meta-analysis of wine intake and lung cancer with Pooling Project



Egger's test p=0.05

5.4.3 Liquors (ethanol)

Cohort studies

Summary

Main results:
Six studies (2920 cases) were included in the dose-response meta-analysis. No significant association of liquors intake was observed for lung cancer.
No heterogeneity was observed.
There was no significant evidence of publication or small study bias (p=0.40).
There was a limited number of studies on lung cancer subtypes and by smoking status.

Sensitivity analyses:
The summary RRs ranged from 1.01 (95% CI=0.95-1.08) when Prescott, 1999 was omitted to 1.04 (95% CI=0.98-1.10) when Chao, 2008 was omitted in the influence analysis.

Study quality:
Cancer outcome was confirmed using cancer registry records in most studies and liquors intake was assessed using FFQ or questionnaire in all studies.
All studies adjusted for at least smoking status.

Pooling Project of cohort studies

Lung cancer was significantly positively related to liquors intake in the Pooling Project of Cohort Studies (Freudenheim, 2005; seven cohorts) in men (1370 cases), but not in women (1245 cases).

Table 119 Liquors intake and lung cancer risk. Number of studies in the CUP SLR

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

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

Table 120 Liquors intake and lung cancer risk. Summary of the dose-response meta-analysis in the 2005 SLR and CUP.

	2005 SLR	CUP
Increment unit used	No-meta-analysis	10 g/day
All studies		
Studies (n)		6
Cases (total number)		2920
RR (95%CI)		1.03 (0.98-1.10)
Heterogeneity (I^2, p-value)		0 %, 0.94
P value Egger test		0.40
All studies and Pooling Project		
Studies (n)		13
Cases (total number)		5585
RR (95%CI)		1.04 (1.00-1.09)
Heterogeneity (I^2, p-value)		0%, 0.79
P value Egger test		0.52

Table 121 Liquor intake and lung 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								
Chao, 2007	9 Cohort 6 Case-control	4391 4119	Europe, North America, Uruguay	Incidence	≥1 drink/day vs nondrinker	1.25 (1.04-1.51) (total) 1.19 (0.91-1.56) (case-control) 1.41 (0.99-1.99) (cohort)	0.02 0.03 0.06	
Pooled-analyses								
Freudenheim, 2005	8 cohorts	1420	Europe and North America	Incidence	≥ 15g/d vs none	1.34(1.09-1.66) Men	0.04	0.28
		1245				0.99 (0.80-1.22) Women	0.52	0.56

Table 122 Liquors intake and lung cancer risk. Main characteristics of studies 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	Missing data derived for analyses
Gnagnarella, 2013a LUN26858 Italy	COSMOS Age: 50-84 years M/W heavy smokers	178/ 4336 5.7 years	Screening examinations	FFQ	Incidence, lung cancer	330 g/d vs never	0.94 (0.57-1.57)	Age, sex, energy intake, smoking duration, average daily cigarettes consumption, years of cessation, asbestos exposure, fruits and vegetables, fish, red meat, olive oil, tea and wine intake	Mid-points of exposure categories Exposure values using standard portion size
Chao, 2011 LUN20355 USA	VITAL, Prospective Cohort, Age: 50-76 years, M/W	580/ 66 186 5.9 years	Cancer registry	FFQ	Incidence, lung cancer	>1drink/d vs non-drinkers	1.03 (0.77–1.36)	Sex, race, education, household income, BMI, history of emphysema, cigarette smoking, family history of lung cancer, fat intake, high intensity	Mid-points of exposure categories Distribution of person-years/non-cases by exposure category Exposure values using standard portion size

Author, Year, WCRF Code, Country	Study 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
								physical activity, fruit and vegetable intake	
Chao, 2008 LUN20333 USA	CMHS, Prospective Cohort, Age: 45-69 years, M	210/ 78 168 4 years	Record linkage with cancer registries	Semi-quantitative FFQ	Incidence, lung cancer	≥1 drink/d vs non-drinker Continuous 1 drink/month	0.93 (0.54-1.58) 1.00 (1.00-1.01)	Age, ethnicity, education, household income, BMI, smoking status, cigarettes smoked/day, smoking duration, COPD/emphysema, white and red wine	Distribution of cases by exposure category Distribution of person-years/non-cases by exposure category Exposure values using standard portion size Mid-points of exposure categories
Prescott, 1999 LUN01393 Denmark	CCHS Prospective Cohort, Age: 20- years, W	429/ 28 160 28 years	Cancer registry	Dietary history	Incidence, lung cancer men	>13.1 times/week vs < 1 times/week	1.46 (0.99-2.14)	Age, smoking, study cohort, educational level	Mid-points of exposure Distribution of person-years/non-cases by exposure category Exposure values using standard
Prescott, 1999		131		Questionnaire	Incidence, lung cancer, women		0.67 (0.21-2.18)		

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Missing data derived for analyses
									portion size
Woodson, 1999 LUN01299 Finland	ATBC Prospective Cohort, Age: 50-69 years, M	1059/ 27 111 7.7 years	Cancer registry	FFQ - study-specific	Incidence, lung cancer	19.8 g/d vs non-drinkers	1.1 (0.9-1.3)	Age, body mass index, years smoked, cigarettes per day, and intervention group.	Rescale reference category Exposure values using standard portion size Mid-points of exposure categories
Chow, 1992 LUN02888 USA	LBS Prospective Cohort, Age: 35- years, M	213/ 17 633 20 years	Death certificates	FFQ - study-specific	Mortality, lung cancer	> 13 times/month vs never used	1.0 (0.5-1.8)	Age, smoking status, industry/occupation	Exposure values using standard portion size Mid-points of exposure categories

Table 123 Liquor consumption (ethanol) and lung cancer risk. Main characteristics of studies excluded 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) P trend	Adjustment factors	Exclusion reason
Potter, 1992 LUN02842 USA	IWHS Nested Case Control, Age: 55-69 years, W, Postmenopausal	109/ 41 837 4 years	Cancer registry	FFQ - study-specific	Incidence, lung cancer	Drinker vs non-drinker Per glass/week		Physical activity, smoking habits, educational level	Mean values
Pollack, 1984 LUN04212 USA	Japan-Hawaii Cancer Study Prospective Cohort, Age: 45-79 years, M	89/ 7837 14 years	Hospital records, death certificates, Hawaii tumour registry	FFQ - study-specific	Incidence, lung cancer	≥ 500 oz/week vs none			No measure of association (only in a graph)

Figure 147 RR estimates of lung cancer by levels of liquors intake with Pooling Project

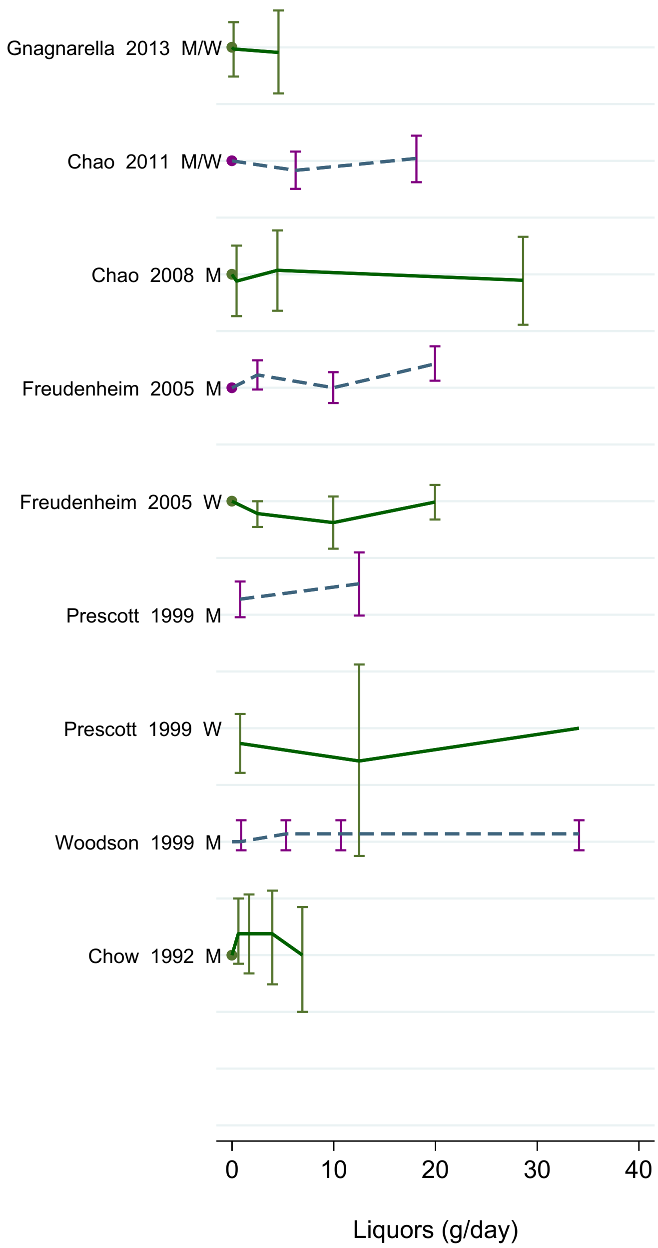


Figure 148 RR (95% CI) of lung cancer for the highest compared with the lowest level of liquors intake with Pooling

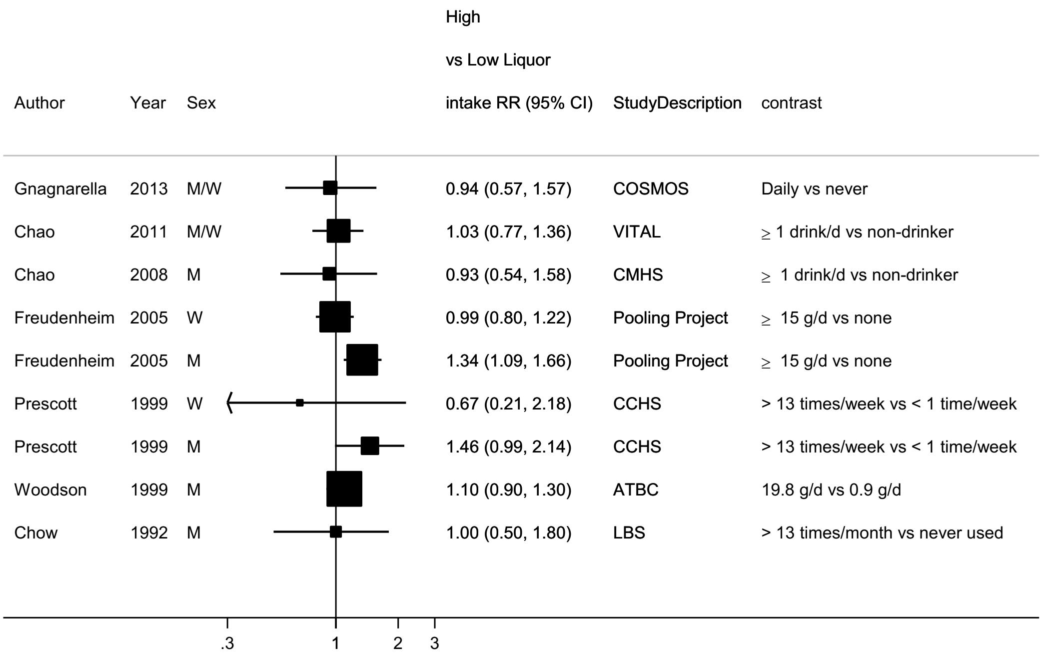


Figure 149 RR (95% CI) of lung cancer for 10 g/day increase of liquors intake

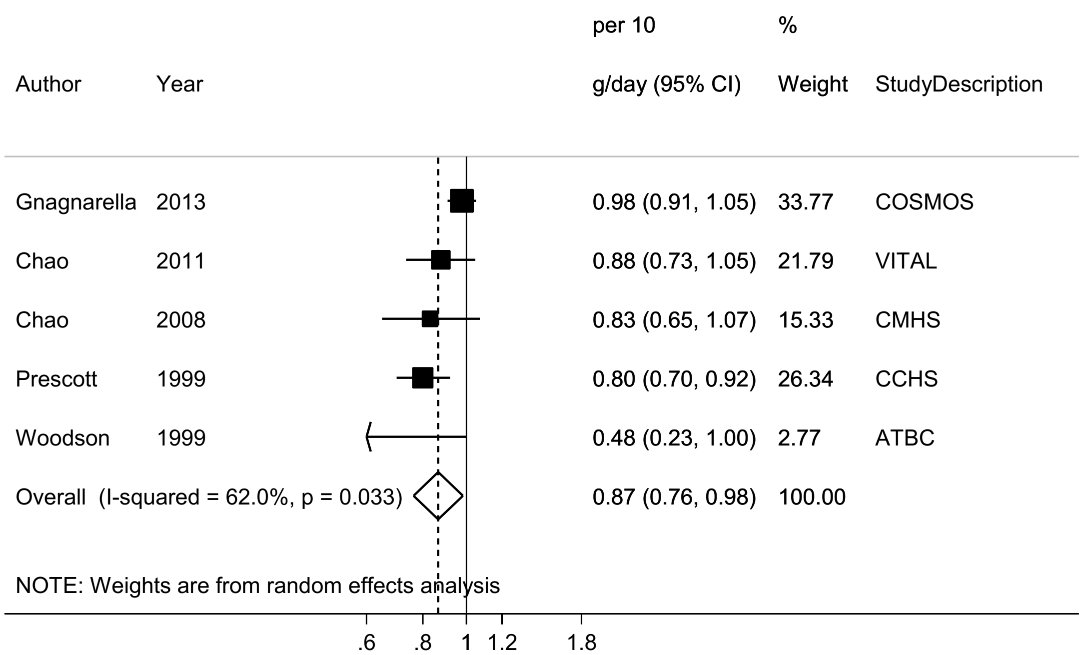


Figure 150 RR (95% CI) of lung cancer for 10 g/day increase of liquors intake with Pooling Project

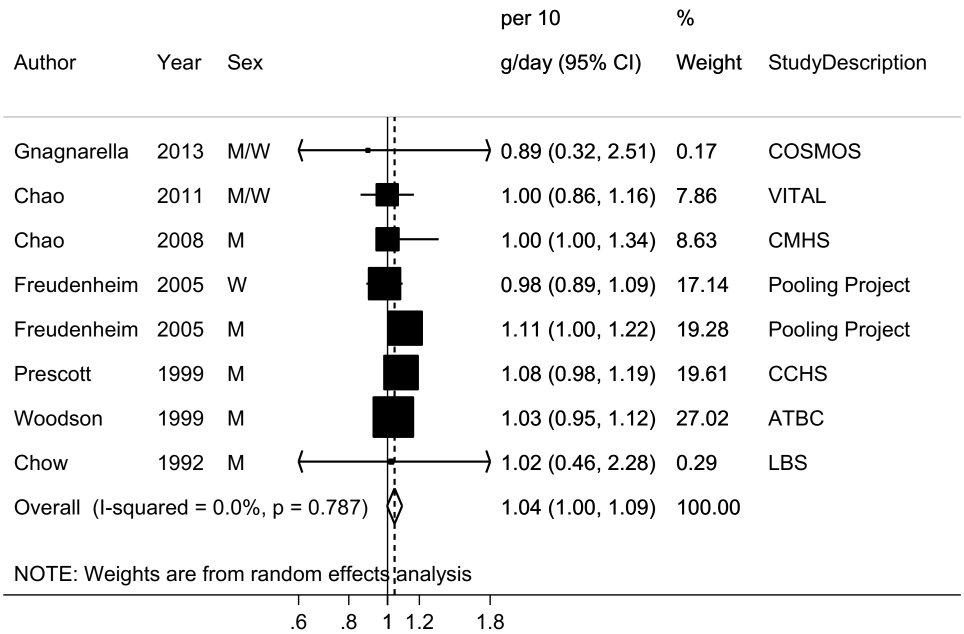
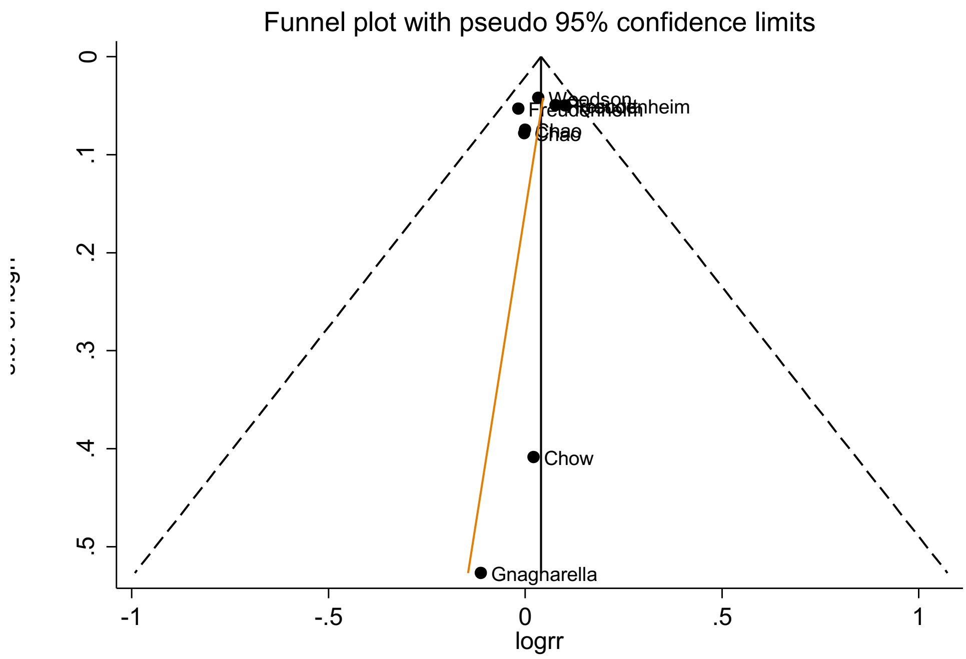


Figure 151 Funnel plot of studies included in the dose response meta-analysis of liquors intake and lung cancer with Pooling Project



Egger's test p=0.52

5.5.1.1 Dietary and supplemental retinol

This section is included here because the evidence that high-dose retinol supplements in smokers increases lung cancer risk was judged as limited suggestive in the Second Expert Report. One study on dietary retinol was identified in the CUP (Takata, 2013). The 2005 SLR provided evidence of no significant association between dietary retinol consumption and lung cancer (RR=1.00; 95% CI= 1.00-1.00 per 100 IU per day, 3 studies).

For supplemental retinol, in one intervention study identified in the 2005SLR, the relative risk of lung cancer in the retinol treated group was 0.66 (95% CI, 0.19-2.32) compared to the placebo group (Musk, 1998). Two studies (a post-intervention follow-up of a RCT and one cohort study) were identified in the CUP, both showed a non-significant association between supplemental retinol and lung cancer risk.

Table 124 Dietary retinol and lung cancer risk. Main characteristics of studies identified in CUP and 2005 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
Takata, 2013 LUN26860 China	SMHS, Prospective Cohort, Age: 40-74 years, M	359/ 61 092 6 years	Biennial home visits/linkage/cancer registry/vital stats	Validated FFQ	Incidence, lung cancer	251.7 vs 63.4 mcg/day	0.85 (0.62-1.16) Ptrend:0.32	Age, BMI, tea consumption, total caloric intake, current smoking status, education, family history of lung cancer, history of chronic bronchitis, number 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
								cigaretets smoked per day, years of smoking
Holick, 2002 LUN00515 Finland	ATBC, Prospective Cohort, Age: 50-69 years, M, Smokers only	1 644/ 29 133 11 years	Cancer registry	FFQ - study-specific	Incidence, lung cancer	>2138.03 vs 0.03-716.97 mcg/day	0.96 (0.82-1.13)	Age, years smoked, cigarettes/day, trial group, supplement use , energy intake, cholesterol, and fat
Bandera, 1997 LUN01693 USA	New York State Cohort, 1980, Prospective Cohort, Age: 40-80 years, M/W	395/ 48 000 7 years	New York State Department of Health's Vital Statistics Section and Cancer Registry,	FFQ - study-specific	Mortality, men	Tertile 3 vs tertile 1	0.87 (0.68-1.10)	Age, educational level, energy intake, smoking habits
					Mortality, women		1.44 (0.93-2.23)	
Yong, 1997 LUN01778 USA	NHANES I, Prospective Cohort, Age: 25-74 years, M/W	248/ 10 068 19 years	Hospital records and death certificate	FFQ - study-specific	Incidence, lung cancer	>1641.6 vs <399.33 iu	1.22 (0.85-1.76)	Age, sex Alcohol consumption, BMI, educational level, 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
								ethnicity/race, family history of cancer, physical activity, smoking habits
Knekt, 1993 LUN02684 Finland	Finnish Mobile Clinic Health Examination Survey, Nested Case Control, Age: 15- years, M	26/ 21 172 9 years	Cancer registry	FFQ - study-specific	Incidence, lung cancer non-smokers	Highest tertile vs lowest tertile	1.40 (0.50-3.60)	Age
					Current smokers		0.70 (0.50-1.20)	
Chow, 1992 LUN02888 USA	LBS, Prospective Cohort, Age: 35- years, M	219/ 17 633 20 years		FFQ - study-specific	Mortality, lung cancer	Quintile 5 vs quintile 1	0.90 (0.60-1.40)	Age, other, smoking habits
Shekelle, 1981 LUN04467 USA	Western Electric, Prospective Cohort, Age: 40-55 years, M	2 107 19 years		FFQ - study-specific	Incidence, lung cancer	Per 100 iu/day	1.00 (-1.00--1.00)	Age, other nutrients, foods or supplements, smoking habits

Table 125 Supplemental retinol and lung cancer risk. Main characteristics of studies identified in CUP and 2005 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
Satia, 2009 LUN20357 USA	VITAL, Prospective Cohort, Age: 50-76 years, M/W	504/ 77 126 4 years	SEER registry	Self-administered questionnaire	Incidence, lung cancer	≥4 vs no use years	1.53 (1.12-2.08) Ptrend:0.004	Age, gender, pack years squared, pack-years smoking, years of smoking
		391			Incidence, non-small cell carcinoma	≥4 vs no use years	1.80 (1.29-2.52) Ptrend:0.0003	Age, gender, pack years squared, pack-years smoking, years of smoking
		47			Women	≥4 vs no use years	1.46 (0.92-2.32) Ptrend:0.08	Age, BMI, fruit & veg consumption, physical activity, vitamin e supplement use, pack years squared, pack-years smoking, years of smoking
		53			Men	≥4 vs no use	1.58 (1.04-2.40)	Age, BMI, fruit

Author, Year, 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	Ptrend:0.02	& veg consumption, physical activity, vitamin e supplement use, pack years squared, pack-years smoking, years of smoking
		74			Incidence, small cell carcinoma	≥4 vs no use years	1.01 (0.37-2.79) Ptrend:0.89	Age, gender, pack years squared, pack-years smoking, years of smoking
		56			Incidence, other lung cancers	>1200 vs no use mcg	0.96(0.36-2.61) Ptrend:0.99	
		155			Incidence, lung cancer, current smokers	≥4 vs no use years	1.34 (0.78-2.29) Ptrend:0.53	
		47			Females	>1200 vs no use mcg	1.46 (0.92-2.32) Ptrend:0.08	
		44			Former smokers, quit 10+ years ago	≥4 vs no use years	1.05 (0.66-1.65) Ptrend:0.90	
		18			Former smokers, quit <10 y ago	≥4 vs no use years	1.43 (0.72-2.84) Ptrend:0.68	
		53			Males	>1200 vs no use	1.24 (0.84-1.85)	

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors
						mcg	Ptrend:0.56	
Kamangar, 2006 LUN20362 China	NIT Cohort, Post intervention follow-up of randomised Controlled Trial, Age: 40-69 years, M/W	29 303 Treatment 1986 to 1991 Follow-up to 2001 15 years	By interview	(Intervention in RCT)	Mortality, lung cancer	Retinol and zinc vs placebo	0.82 (0.59-1.14)	Age, sex, residence, other treatment groups
Musk, 1998 LUN01664 Australia	Wittenoom workers cohort, Non Randomised Control Trial, Age: 40-85 years, M/W, High Risk population	42	Cancer and death register	FFQ - study-specific	Mortality, lung cancer	Intervention group vs non-intervention group tablets/day	0.66 (0.19-2.32)	Age, non nutrient chemicals, smoking habits

5.5.1.1 Serum retinol

Cohort studies

Summary

Main results:
Eight studies (2855 cases) out of 15 cohort studies (20 publications) were included in the dose-response meta-analysis. A significant inverse association of lung cancer risk with serum retinol was observed. There was no evidence of heterogeneity.
Of the seven excluded studies, one study in Swiss men reported a significant inverse association (Eichholzer, 1996) among those older than 60 years and inverse but not significant in younger men; two small studies reported lower mean serum retinol levels in cases than in controls (Salonen, 1985; Wald, 1980). The four other studies reported non-significant inverse associations or non-significant lower mean levels in the cases.
There were not enough data to do stratified analyses by either histological type or smoking status.

Sensitivity analyses:
The inverse associations were statistically significant in men but not in women (three studies in women).
When the studies in high risk populations were excluded (Alfonso, 2006; Goodman, 2003; Ratnasinghe, 2003; Holick, 2002) the overall estimate was 0.96 (95% CI=0.94-0.99).
In influence analysis, the summary RRs ranged from 0.96 (95% CI=0.94-0.98) when Holick, 2002 was omitted to 0.96 (95% CI=0.95-0.98) when Yuan, 2001 was omitted.

There was evidence of a non-linear dose-response of lung cancer and serum retinol ($p < 0.01$). The curve is suggestive of a decreased risk of lung cancer with higher blood retinol levels. No significant association was observed in the MEC cohort (Epplein, 2009) in which the retinol blood levels were higher than in the other studies.

Study quality:
All studies included in the analysis were adjusted for main confounders including age and smoking status. All studies adjusted for intensity, duration of smoking and other smoking variables in addition to smoking status, except one study (Alfonso, 2006) that was adjusted only for smoking status. In the multi-ethnic study the range of blood retinol values were higher than in the other included studies (Epplein, 2009).
Retinol levels were determined by HPLC with different assays in the studies. In general, cases and controls were matched by date of blood collection.
Four studies were in high risk populations: high-risk miners (Ratnasinghe, 2003), or heavy smokers or people exposed to asbestos (Holick, 2002; Alfonso, 2006; Goodmann, 2003).

Table 126 Serum retinol and lung cancer risk. Number of studies in the CUP SLR

	Number
Studies identified	15 (20 publications)
Studies included in forest plot of highest compared with lowest exposure	11
Studies included in dose-response meta-analysis	8
Studies included in non-linear dose-response meta-analysis	6

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

Table 127 Serum retinol and lung cancer risk. Summary of the dose-response meta-analysis in the 2005 SLR and CUP

	2005 SLR	CUP
Increment unit used	0.1 µmol/L	10 µg/100 mL
All studies		
Studies (n)	4	8
Cases (total number)	2050	2855
RR (95%CI)	0.95 (0.89-1.01)	0.97 (0.95-0.98)
Heterogeneity (I^2, p-value)		0%, 0.86
P value Egger test		0.47
Stratified and sensitivity analysis		
Sex	**Men**	**Women**
Studies (n)	6	3
RR (95%CI)	0.96 (0.94-0.99)	1.00 (0.96-1.04)
Heterogeneity (I^2, p-value)	53.3%, 0.06	0%, 0.50

Table 128 Serum retinol and lung cancer risk. Main characteristics of studies included in the 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
Epplein, 2009 LUN20317 USA	MEC, Nested Case Control, Age: 45-75 years, M/W	136/ 272 controls ~ 5 years	SEER registry	94% of the blood when fasting for 8 h or more Refrigeration after ~ 3 hours Most samples collected between 2001 and 2006	Incidence, lung cancer, men	1804 vs 890 ng/mL	1.26 (0.57-2.77) Ptrend:0.61 No trend in smokers (p = 0.61)	Age at specimen collection, fasting hours before blood draw, cigarettes pack-years, and pack-years squared, years of schooling and family history of lung cancer	ng/mL converted to µg/100 mL
		71/ 142 controls			Incidence, lung cancer, women	1712 vs 777 ng/mL	0.77 (0.29-2.06) Ptrend:0.63		
Alfonso, 2006 LUN26889 Australia	Australia, Wittenoom, Prospective Cohort Age (mean): 51.5 years M, exposed to asbestos	47/ 1953 10.5 years	Cancer registry	Non-fasting plasma, HPLC used	Incidence, lung cancer	Per 1 µmol/L increase	0.90 (0.54-1.51)	Age, sex, smoking status, asbestose exposure and level of hepatic enzymes	Increment recalculated to 10 µmol/L, unit converted to µg/100 mL
Ito, 2005 LUN26888 Japan	JACC, Nested Case Control,	163/ 375 controls 10 years	Death certificate	Serum sample measured by (HPLC)	Incidence, lung cancer, men	> 3.23 vs < 2.19 ng/mL	0.49 (0.22-1.08) Ptrend: 0.42	Age, sex, smoking habits, participating	Mid-points of exposure, µmol/L

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Missing data derived for analyses
	Age: 40-79 years, M/W	48/ 112			Incidence, lung cancer, women	> 2.78 vs < 1.92 ng/mL	2.25 (0.68-7.47) Ptrend:0.16	institution and alcohol drinking	converted to µg/100 mL
Goodman, 2003 LUN00294 USA	CARET, Nested Case Control, Age: 45-69 years, M/W	276/ 276 controls 4 years	Primary outcome of the trial. Active follow-up with confirmation by clinical records and pathology reports	Non-fasting blood sample at the time of first trial visit	Incidence, lung cancer	777 vs 577 ng/mL	0.69 (0.42-1.14) Ptrend: 0.11	Age, sex, smoking, centre, year of randomization pack-years of smoking and years quit smoking	Mid-points of exposure, number of cases and controls per quartiles, ng/mL converted to µg/100 mL
		174/ 174 controls 4 years			Incidence, lung cancer, men		0.54 (0.29-1.01) Ptrend: 0.04		
		102/ 102 controls 4 years			Incidence, lung cancer, women		1.05 (0.46-2.37) Ptrend: 1.00		
Ratnasinghe, 2003 LUN00362 China	YTC, Nested Case Control, Age: 40-74 years, High-risk miners men	108/ 216 controls 6 years	Cancer registry and annual screenings	Serum collected 2 years prior to diagnosis	Incidence, lung cancer	> 60 vs < 42 µg/dL	0.70 (0.40-1.30) Ptrend: 0.7	Age, radon exposure, smoking habits, pack-years	Mid-points of exposure
Holick, 2002 LUN00515 Finland	ATBC, Prospective Cohort, Age: 50-69 years, M , smokers	1644/ 29 133 11 years	Finnish Cancer Registry and the Register of Causes of Death	Fasting (12 h) serum sample	Incidence, lung cancer	> 685 vs < 484 µg/L	0.73 (0.62-0.86) Ptrend: <0.01	Age, years smoked, cigarettes/day, trial group, supplement use , energy intake,	Distribution of person yeas per quintiles, mid-points of exposure, µg/L converted

Author, Year, WCRF Code, Country	Study 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
	and exposed to asbestos							cholesterol, and fat	to μg/100 mL
Yuan, 2001 LUN00828 China	Shanghai, China, Nested Case Control, Age: 45-64 years, M	209/ 335 controls 12 years	Active follow-up, Shanghai cancer registry, death certificates	Non-fasting blood sample processed within 3-4 hours HPLC	Incidence, lung cancer	≥ 56.58 vs < 39.61 μg/dL	0.65 (0.37-1.09) Ptrend: 0.18	Age at starting to smoke, average cigarettes /day, and smoking status at the time of blood draw (non-smoker, smoker)	Mid-points of exposure
		189/ 335			Incidence, lung cancer, ever smokers	Highest vs lowest	0.75 (0.27–2.07)		
		20/ 287			Incidence, lung cancer, never smokers		0.62 (0.40–0.96)		
Friedman, 1986 LUN03902 USA	Kaiser Permanent Medical Centre, Nested Case Control, Age: 26-78 years, M/W	151/ 302 controls 8 years	Hospital cohort, follow-up not described in the publication	Blood samples taken for health check up	Incidence, lung cancer	38.1-65.5 vs 98.7-173.3 μg/dL	1.20	Age, sex, ethnicity/race, other, smoking habits	Confidence intervals (using cases and controls numbers), mid-points of exposure, RR was recalculated using Hamling method

Table 129 Serum retinol and lung cancer risk. Main characteristics of studies excluded from the 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 LUN20287	Hokkaido, Japan, Prospective Cohort Study, Age: 39-85 years, M/W	41/ 3254 11.7 years	Mortality records	Fasting serum sample	Mortality, lung cancer	Per each logarithmically transformed serum value	0.56 (0.20-1.51)	Age, sex, smoking status, alcohol consumption, serum cholesterol and triglyceride, alanine aminotrans-ferase activity	HRs for one log increase
Ito, 2005 LUN26887 Japan	Hokkaido, Japan, Cohort Study, Prospective Cohort, Age: 39-79 years, M/W	31/ 3182 10.5 years	Death certificate	Fasting serum sample (measured in serum using HPLC method)	Mortality, lung cancer	High vs low	0.46 (0.14-1.50) Ptrend: 0.21	Age, sex, ALT activity, serum cholesterol, smoking habits	Superseded by Ito, 2006 LUN20287 No exposure levels Used in H vs L analysis only
Ito, 2003 LUN00342 Japan	JACC, Nested Case Control, Age: 40-79 years, M/W	147/ 311 controls 8 years	Population death registries	35% of participants provided blood samples	Mortality, lung cancer	≥ 2.95 vs < 2.01 µmol/L	1.02 (0.49-2.14) Ptrend: 0.83	Age, sex, participating institution, smoking and alcohol drinking	Superseded by Ito, 2005 LUN26888

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Reasons for exclusion
Eichholzer, 1996 LUN07846 Switzerland	Basel Switzerland, Prospective Cohort, Age: 20-79 years, M	87/ 2974 17 years	Death certificate	Fasting blood sample	Mortality, lung cancer	< 2.45 µmol/L vs higher and age > 60 years	2.51 (1.24-5.08)	Age, biomarkers, smoking habits, lipids	Data for lowest vs highest Recalculated to high vs low using Hamling method
						< 2.45 µmol/L vs higher and age ≤ 60 years	1.26 (0.60-3.07)		
Knekt, 1993 LUN02684 Finland	FMCHES, Nested Case Control, Age: ≥ 15 years, M	122/ 21 172 9 years	Cancer registry	Samples taken during health checks, analysed 15 years after collection	Incidence, lung cancer, current smokers	Lowest vs highest	1.5 (0.8-3.1)	Age	Only lowest vs highest tertiles Recalculated to high vs low using Hamling method
					Incidence, lung cancer, non- smokers		4.4 (0.9-21.5)		
Orentreich, 1991 LUN08914 USA	Kaiser Permanent Medical Centre, Nested Case Control, Age: 26-78 years, M/W	123/ 263 000 8 years	Hospital records	Blood samples collected during health check-ups and analysed ~15 years later	Incidence, lung cancer	Lowest vs highest	1.50		Duplicate of Friedman, 1986 LUN03902
Stahelin, 1991 LUN13357 Switzerland	Basel, Prospective Cohort, Age: 20-79 years, M	68/ 2974, 12 years	Death certificate	Fasting blood sample	Mortality, lung cancer	< 2.45 µmol/L vs higher and age > 60 years	2.54 (1.45-4.43) P: < 0.05	Age, smoking habits, lipids	Superseded by Eichholzer, 1996 LUN07846

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Reasons for exclusion
						< 2.45 µmol/L vs higher and age ≤ 60 years	1.15 (0.47-2.81)		
Knekt, 1990 LUN08960 Finland	A follow up study of FMCHES, Nested Case Control, Age: 15-99 years, M/W	108/ 36 265 8 years	Cancer Registry	Samples taken during health checks, analysed 15 years after collection	Incidence, lung cancer	Lowest vs highest	1.5 (0.9-2.7)	Age, smoking habits	Superseded by Knekt, 1993 LUN02684
Connett, 1989 LUN03434 USA	MRFIT, Nested Case Control, Age: 35-57 years, M, high risk of coronary heart disease	66/ 131 controls 10 years	Active follow-up confirmed with hospital records	Blood sample at trial baseline, same storage time in cases and controls	Mortality, lung cancer	Mean Cases: 70 µg/dL Controls: 73 µg/dL	p test difference: 0.25	Age, cigarettes per day, BMI, serum cholesterol, DBP, years of education, serum thiocyanate, leukocyte count	No OR available
Menkes, 1986 LUN03835 USA	Washington county Maryland, Nested Case Control, M/W	99/ 196 controls 5 years	Cancer registry	Blood sample Retinol difference between stored and fresh samples lower than 7%	Incidence, lung cancer	Lowest vs highest	1.13 P trend: 0.68	Age, sex, ethnicity/race, other, smoking habits	No serum levels available. Lowest vs highest recalculated to high vs low using Hamling

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Reasons for exclusion
									method
Salonen, 1985 LUN12990 Finland	NKP, Nested Case Control, Age: 30-64 years, M/W	15/ 15 controls 4 years	National death certificate register	Blood samples stored at -20 and analysed ~7 years later	Mortality, respiratory cancers	Mean Cases: 480 µg/L Controls: 568 µg/L	p difference mean <0.05		No RR available
Wald, 1980 LUN04547 UK	BUPA, Nested Case Control, Age: 35-64 years, M	14/ 172 controls 5 years	Hospital records	Blood sample taken at health check ups	Mortality, lung cancer	Mean Cases: 183 µg/L Controls: 231 µg/L	p difference mean <0.05		No RR available

Figure 152 RR estimates of lung cancer by levels of serum retinol

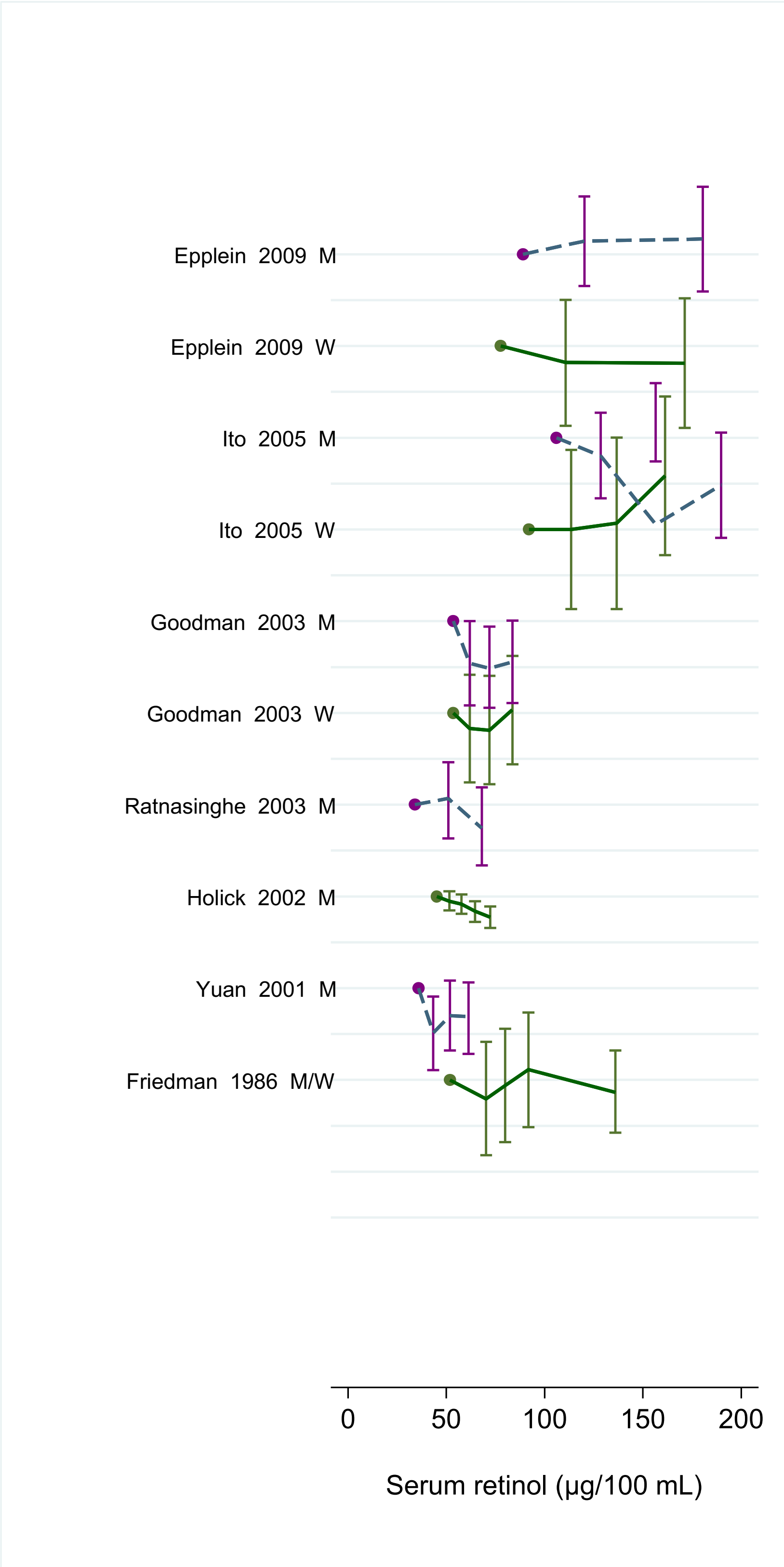
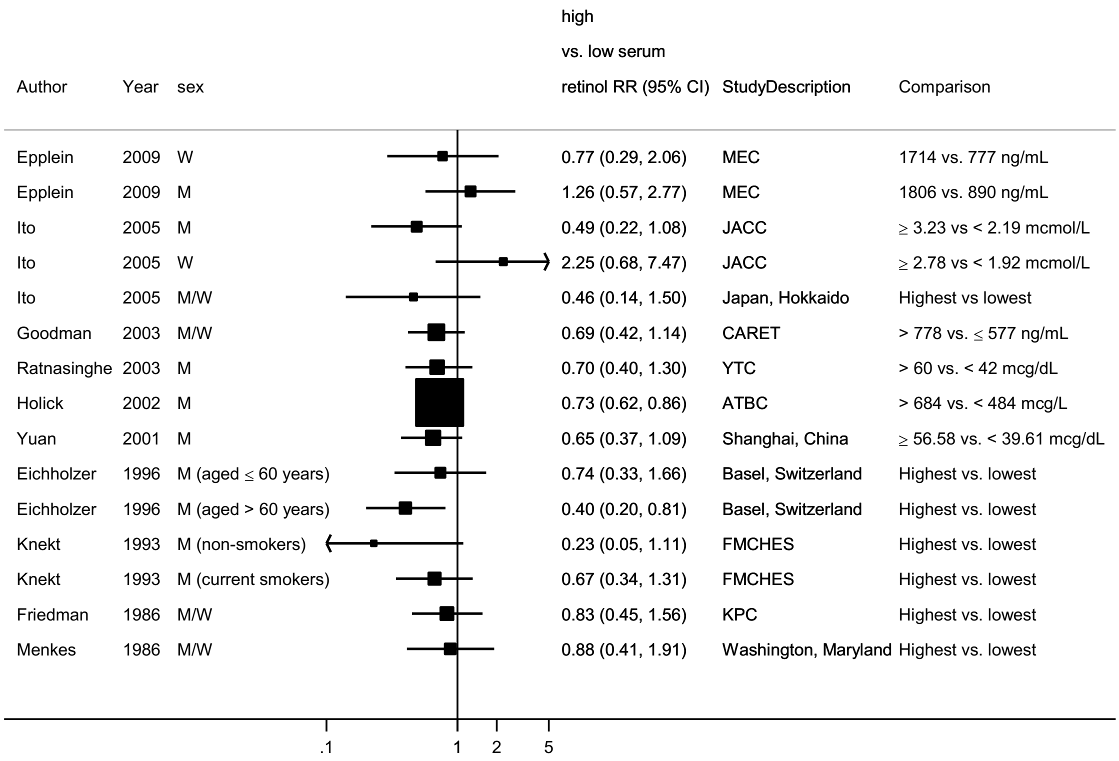


Figure 153 RR (95% CI) of lung cancer for the highest compared with the lowest level of serum retinol



*In studies of Eichholzer, 1996; Knekt, 1993; Friedman, 1986 and, Menkes, 1986, the RR's were recalculated using Hamling method (Hamling, 2008).

Figure 154 RR (95% CI) of lung cancer for 10 μg/100 mL increase of serum retinol

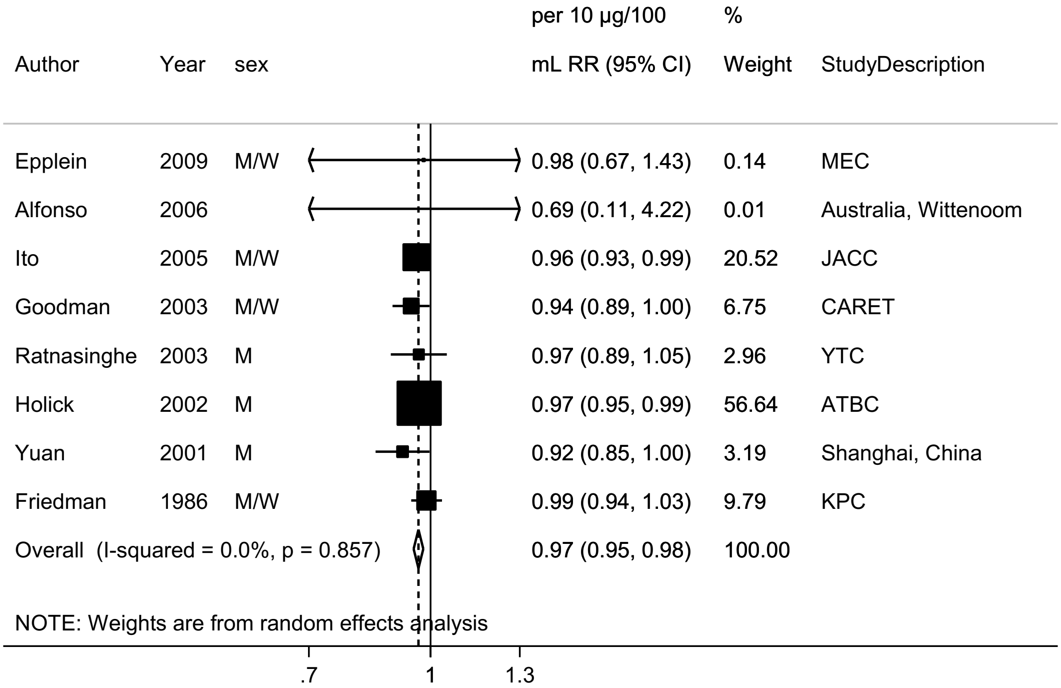
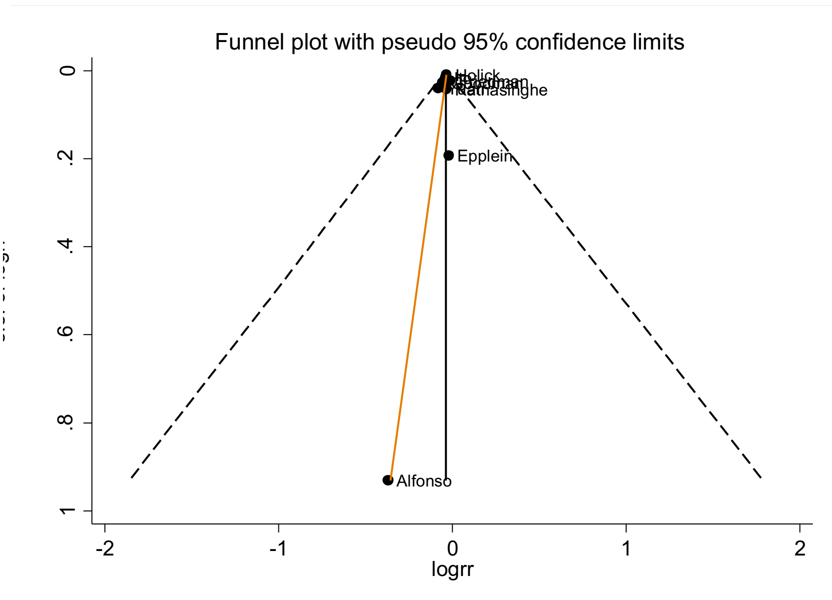


Figure 155 Funnel plot of studies included in the dose response meta-analysis of serum retinol and lung cancer



Egger's test p= 0.47

Figure 156 RR (95% CI) of lung cancer for 10 µg/100 mL increase of serum retinol by sex

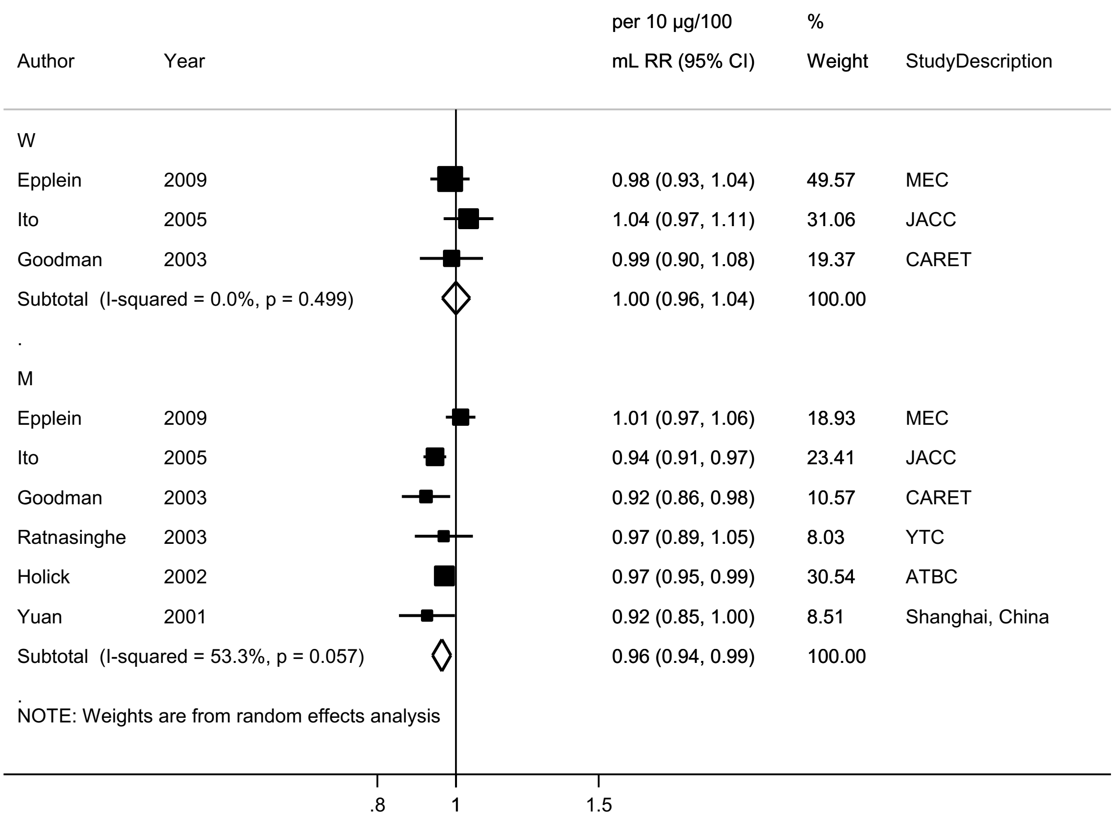
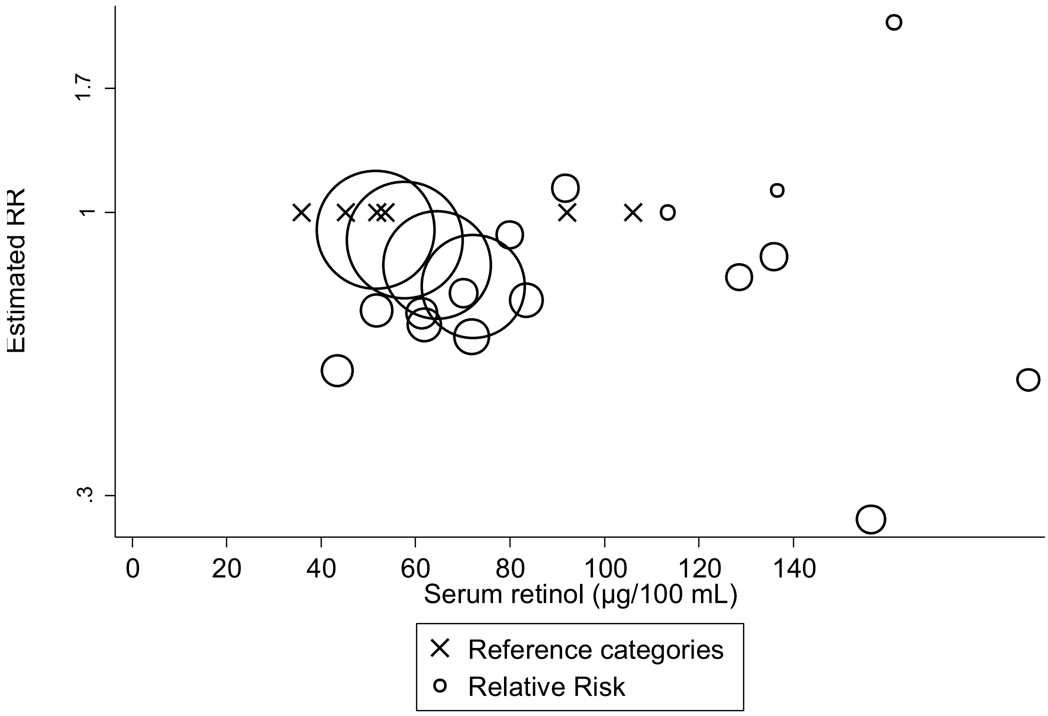
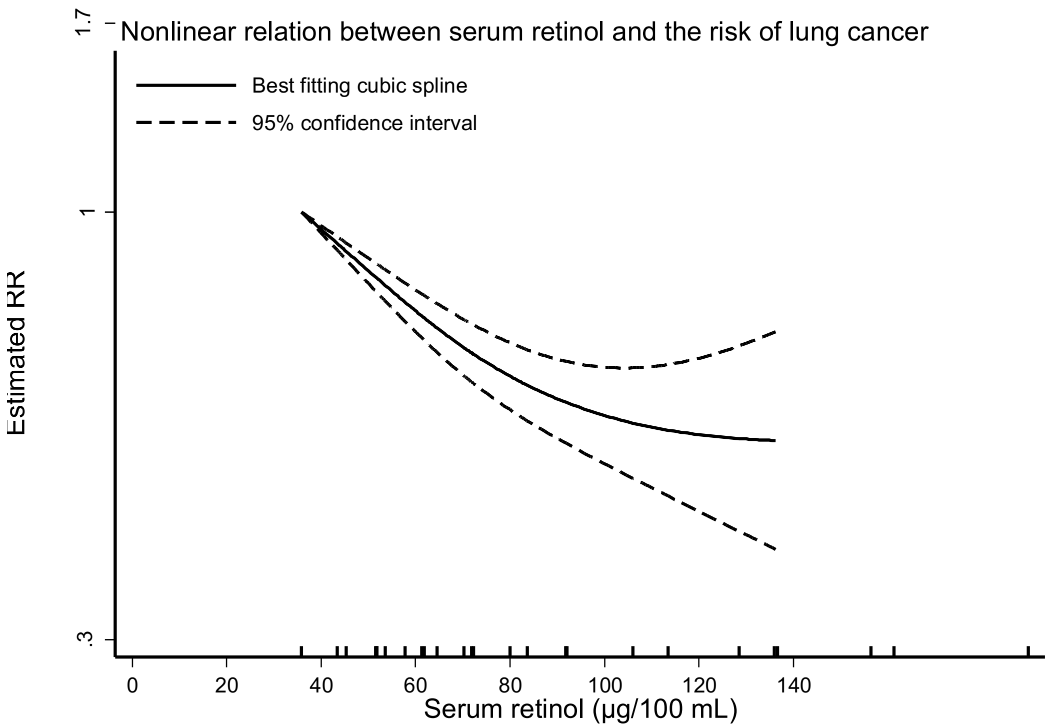


Figure 157 Relative risk of lung cancer and serum retinol estimated using non-linear models





$p < 0.01$

Table 130 Table with serum retinol values and corresponding RRs (95% CIs) for non-linear analysis of serum retinol and lung cancer

Serum retinol (µg/100 mL)	RR (95%CI)
35.8	1.00
45.2	0.90 (0.88-0.92)
64.5	0.72 (0.66-0.77)
92.05	0.58 (0.52-0.66)
189.74	0.53 (0.27-1.02)

5.5.1.2 Dietary beta-carotene

Cohort studies

Summary

Main results:
Thirteen studies (7560 cases) out of 15 cohort studies (19 publications) were included in the dose-response meta-analysis. A borderline inverse association of lung cancer risk with dietary beta-carotene was observed. In analysis stratified by smoking status, a borderline inverse association was observed in current smokers (eight studies), and no association was observed in former or never smokers (seven smokers). Low heterogeneity was observed in all analyses.
In stratified analysis by sex, a significant inverse association was observed in women, but not in men. A borderline inverse association was observed in studies in Europe, but not in North America.
There was no evidence of publication or small study bias (p=0.52).
It was not possible to include the Pooling project of cohort studies because dietary intakes were not quantified in the publication (Mannisto, 2004). Seven out of 13 studies included in the CUP dose-response meta-analyses were not included in the Pooling Project of Cohort studies. The results of the CUP meta-analysis and the Pooling project are similar. In addition, lung cancer was not associated with dietary beta-carotene in smokers, never or former smokers, or with any of the lung cancer cell types in the Pooling project.

Sensitivity analyses:
In influence analysis, the summary RR did not change materially when studies were omitted in turn. When two studies in high risk populations were excluded (Holick, 2002; Neuhouser, 2003) the overall estimate remained unchanged, 0.99 (95% CI=0.98-1.00).

There was no statistical evidence of non-linear dose-response of lung cancer and dietary beta-carotene intake ($p > 0.05$).

Study quality:
Dietary beta-carotene was estimated from food intake assessed with FFQ. Estimated intake levels were much higher in a study in a retirement community in United States (Shibata, 1992) and much lower in another study (Steinmetz, 1993) compared to the rest of the studies. Lung cancer was not associated with beta-carotene intake in the two studies.

All studies were adjusted by main confounders, including age and smoking. All studies adjusted for intensity, duration of smoking and other smoking variables in addition to smoking status, except one study (Knekt, 1999) that was adjusted only for smoking status. Two studies were in in heavy smokers or populations exposed to asbestos (Holick, 2002; Neuhouser, 2003), in which no significant (inverse) associations were observed.

Table 131 Dietary beta-carotene and lung cancer risk. Number of studies in the CUP SLR

	Number
Studies identified	15 (19 publications)
Studies included in forest plot of highest compared with lowest exposure	14
Studies included in dose-response meta-analysis	13
Studies included in non-linear dose-response meta-analysis	9

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

Table 132 Dietary beta-carotene and lung cancer risk. Summary of the dose-response meta-analysis in the 2005 SLR and CUP

	2005 SLR	**CUP**
Increment unit used	500 µg/day	700 µg/day
All studies		
Studies (n)	5	13
Cases (total number)	2502	7560
RR (95%CI)	1.00 (0.98-1.01)	0.99 (0.98-1.00)
Heterogeneity (I^2, p-value)	59%	5.3%, 0.39
P value Egger test		0.52

Stratified and sensitivity analysis (no analyses conducted in the 2005 SLR)			
Smoking status	**Never smokers**	**Current smokers**	**Former smokers**
Studies (n)	7	8	7
RR (95%CI)	0.99 (0.96-1.03)	0.99 (0.98-1.00)	0.99 (0.97-1.01)
Heterogeneity (I^2, p-value)	0%, 0.63	0%, 0.72	0%, 0.60

Sex	Men	Women	
Studies (n)	7	4	
RR (95%CI)	0.99 (0.97-1.02)	0.98 (0.96-0.99)	
Heterogeneity (I^2, p-value)	39%, 0.13	0%, 0.78	
Geographic location	**Asia**	**Europe**	**North America**
Studies (n)		5	7
RR (95%CI)		0.99 (0.98-1.00)	0.99 (0.97-1.01)
Heterogeneity (I^2, p-value)		0%, 0.50	33%, 0.19

Table 133 Dietary beta-carotene and lung 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								
Gallicchio*, 2008	7		United States, Europe, Canada and Singapore	Incidence, lung cancer	Per 500 µg /day	0.99 (0.98-1.00)		0%, 0.88
	11	5446			Highest vs lowest	0.92 (0.83-1.01)		0%, 0.85
	7			Current smokers	Highest vs lowest	0.89 (0.78-1.00)		
	5			Former smokers		0.98 (0.76-1.26)		
	5			Never smokers		0.97 (0.61-1.52)		
Pooled analyses								
Männistö, 2004	7	3155	North America and Europe	Incidence, lung cancer	Q5 vs Q1	0.98 (0.87-1.11)	0.47	0.95
		1915		Current smokers	Q4 vs Q1	0.98 (0.84-1.14)	0.62	0.89
		981		Former smokers		1.06 (0.86-1.02)	0.61	0.35
		259		Never smokers		1.02 (0.70-1.47)	0.73	0.80
		956		Adenocarcinoma		1.04 (0.85-1.27)	0.84	0.19
		538		Small cell carcinoma		1.18 (0.97-1.43)	0.21	0.85
		901		Squamous cell carcinoma		1.06 (0.89-1.27)	0.50	0.78

*Number of cases is reported only in highest vs lowest analysis which includes 11 studies.

Table 134 Dietary beta-carotene and lung cancer risk. Main characteristics of studies included in the 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
Roswall, 2009 LUN26873 Denmark	DCH, Prospective Cohort, Age: 50-64 years, M/W	721/ 55 557 10.6 years	Danish cancer registry	FFQ	Incidence, lung cancer	Per 5,000 µg/day	0.96 (0.87-1.06)	Age, sex, smoking status, intensity and duration, passive smoking, time since quitting, work exposure to carcinogenic substances, intake of supplements of folate, vitamin C, vitamin E or beta-carotene	Distribution of person-years by exposure categories, increment recalculated to 700 µg/day
						> 4377 vs 0-1194.5 µg/day	0.77 (0.60-0.98) Ptrend:0.42		
		593			Current smokers	Per 5,000 µg/day	0.97 (0.87-1.07)		
		95			Former smokers		0.79 (0.60-1.03)		
		33			Never smokers		0.97 (0.65-1.33)		
Neuhouser, 2003 LUN00354 USA	CARET, Prospective Cohort, Age: 45-69 years, M/W	326/ 14 120 8 years	Primary outcome of the trial. Active follow-up with confirmation by clinical records and pathology reports	FFQ - study-specific	Incidence, lung cancer, placebo arm	≥ 3429 vs ≤ 1156 µg /day	0.95 (0.67-1.36) Ptrend:0.89	Age, sex, smoking status, total pack-years of smoking, asbestos exposure, race/ethnicity, and enrollment center	Mid-points, distribution of person-years and cases by exposure quintiles, RRs of intervention and placebo arms combined
					Incidence, lung cancer, intervention arm		0.93 (0.68-1.26) Ptrend:0.15		

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Missing data derived for analyses
Yuan, 2003 LUN00218 Singapore	SCHS, Prospective Cohort, Age: 45-47 years, M/W	482/ 62 392 8 years	Cancer registry and, birth and death registries	FFQ - study-specific	Incidence, lung cancer	2473 vs 583 µg/1000 kcal	1.00 (0.74-1.35)	Age, sex, BMI, year of interview, education, ethnicity/race, cigarettes /day, years smoking, years since quitting smoking for former smokers	Distribution of person years by exposure quintiles, increment recalculated to 700 µg/day, µg /1000 kcal converted to µg /day
					Incidence, lung cancer	Per 1890 µg/1000 kcal	1.22 (0.70-2.13)		
		268			Current smokers		1.29 (0.59-2.80)		
		71			Former smokers		0.91 (0.23-3.99)		
		145			Never smokers		1.34 (0.50-3.53)		
Rohan, 2002 LUN00605 Canada	CNBSS, Case Cohort, Age: 40-59 years, W	155/ 5361 controls 10 years	Record linkage to Canadian Centre Database and to National Mortality Database	FFQ - study-specific	Incidence, lung cancer	Per 500 µg /day	0.99 (0.96-1.02)	Age, clinic site, energy intake, other, other nutrients, foods or supplements, smoking habits	Increment recalculated to 700 µg/day,
						6823.5 vs 3152.2 µg /day	1.40 (0.76-2.59) Ptrend:0.20		
		101			Incidence, lung cancer, current smokers	Per 500 µg /day	0.97 (0.94-1.01)		
		36			Incidence, lung cancer, former smokers		1.02 (0.98-1.07)		
		18			Incidence, lung cancer, never smokers		0.96 (0.90-1.03)		
Holick, 2002 LUN00515	ATBC, Prospective	1 644/ 29 133	Finnish Cancer Registry and the	FFQ - study-specific	Incidence, lung cancer	> 3015 vs < 977 µg /day	0.92 (0.79-1.07) Ptrend:0.24	Age, years smoked,	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
Finland	Cohort, Age: 50-69 years, M, Smokers only	11 years	Register of Causes of Death					cigarettes/day, trial group, supplement use , energy intake, cholesterol, and fat	exposure quintiles
Michaud, 2000 LUN01014 USA	HPFS, Prospective Cohort, Age: 30-75 years, M	275/ 46 924 10 years	Active follow-up, cases confirmed with medical and pathology records	FFQ - study-specific	Incidence, lung cancer, men	8950 vs 2127 µg /day	1.09 (0.73-1.63) Ptrend: 0.72	Age (5-y categories), smoking status (never, past with time since quitting, or current with 6 categories), age at start of smoking (< 15 y, 15–19 y, 20–29 y, ≥30 y, or never smokers), quintiles of energy intake, and time period	Distribution of person years by exposure quintiles, estimation of confidence intervals
	NHS, Prospective Cohort, Age: 30-75 years, W	519/ 77 283 12 years			Incidence, lung cancer, women	7071 vs 2098 µg /day	0.80 (0.60-1.07) Ptrend:0.08		Distribution of person years by exposure quintiles
	HPFS & NHS, Prospective Cohort, Age: 30-75 years,	794/ 124 207 10-12 years			Incidence, lung cancer, men and women pooled	Highest vs lowest	0.90 (0.67-1.21) Ptrend:0.15	Additionally adjusted by sex	Distribution of person years and number of cases by exposure quintiles
		357			Incidence, lung cancer, men and		0.84 (0.59-1.21)	Additionally adjusted by 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
	M/W				women pooled, current smokers			at start smoking and time since quitting	
		345			Incidence, lung cancer, men and women pooled , former smokers		1.01 (0.70-1.45)		
		84			Incidence, lung cancer, men and women pooled, never smokers		0.69 (0.32-1.48)		
Voorrips, 2000a LUN01121 Netherlands	NLCS, Case Cohort, Age: 55-69 years, M	939/ 1525 controls 6.3 years	Regional cancer registries and computerized national database of pathology report (PALGA)	FFQ - study-specific	Incidence, lung cancer	4729 vs 1470 µg /day	1.02 (0.68-1.53) Ptrend:0.38	Age, educational level, family history of specific cancer, smoking habits, years of smoking cigarettes, cigarettes per day	Distribution of number of cases and non-cases in quintiles
		487			Incidence, lung cancer, current smokers	Highest vs lowest	0.74 (0.47-1.16) Ptrend:0.05		
		312			Incidence, lung cancer, former smokers	Highest vs lowest	0.81 (053-1.34) Ptrend:0.58		
		35			Incidence, lung cancer, never smokers	Highest vs lowest	1.98 (0.75-5.26) Ptrend:0.14		
Knekt, 1999 LUN01416 Finland	FMCHES, Prospective Cohort,	138/ 4545	Cancer Registry	FFQ - study-specific	Incidence, lung cancer	1522 vs 849 µg /day	0.79 (0.50-1.24) Ptrend:0.15	Age, smoking status	Distribution of person years and number of cases

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Missing data derived for analyses
	Age: 20-69 years, M	25 years			Incidence, lung cancer, current smokers	Highest vs lowest	0.96 (0.58-1.58)	Age	in tertiles
					Incidence, lung cancer, non-smokers	Highest vs lowest	0.38 (0.12-1.18)	Age	
Steinmetz, 1993 LUN02740 USA	IWHS, Nested Case Control, Age: 55-69 years, W, Post-menopausal	138/ 2814 controls 4 years	Iowa Health Registry (part of SEER registry)	FFQ - study-specific	Incidence, lung cancer	≥ 12592 vs ≤ 4886 IU/week	0.81 (0.48-1.38)	Age, energy intake, pack years of smoking	Distribution of number of cases and non-cases per quartiles, mid-points of exposure, IU/week converted to µg /day
		81/ 431			Incidence, lung cancer, current smokers		0.96 (0.47-1.95)		
		38/ 538			Incidence, lung cancer, former smokers		0.66 (0.23-1.93)		
		19/ 1804			Incidence, lung cancer, never smokers		1.08 (0.30-3.23)	Age, energy intake	
Shibata, 1992 LUN08664 USA	LWS, Prospective Cohort, Age: 74 years, M/W	94/ 11 580 6 years	Death by reports of friends or relatives, National Death Index; incidence through hospital records	FFQ - study-specific	Incidence, lung cancer, men	≥ 9200 vs < 4000 µg /day	1.07 (0.66-1.74)	Age, smoking habits	Distribution of person-years by exposure tertiles
		70/ 11 580			Incidence, lung cancer, women	≥ 9800 vs < 4800 µg /day	0.59 (0.32-1.07)	Age, smoking habits	

Author, Year, WCRF Code, Country	Study 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
Shekelle, 1992 LUN02862 USA	WES, Prospective Cohort, Age: 41-57 years, M	57/ 1960 24 years	Annual self-reported, confirmed through medical records. Death certificates	FFQ - study-specific	Incidence, lung cancer	<3800 vs ≥ 6700 IU/day	2.5	Age, number of cigarettes smoked per day, years of smoking	Distribution of person-years and cases by exposure quartiles , estimation of confidence intervals, data for lowest vs highest recalculated to high vs low using Hamling method, increment recalculated to 700 µg/day, IU/day converted to to µg /day
						Per 6000 IU/day	2.20 (1.10-4.60)		
Kromhout, 1987 LUN03765 Netherlands	Zutphen Study, Prospective Cohort, Age: 40-59 years, M	878 12 years	Data from Central Bureau of Statistics, diagnosis verified through cancer registry, hospital	Dietary history questionnaire	Mortality, lung cancer	Highest vs lowest	0.68 (0.35-1.34)	Age, pack years of smoking	Distribution of person-years and cases by exposure quartiles, 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
			discharge or general practitioner						mg/day converted to µg /day

Table 135 Dietary beta-carotene and lung cancer risk. Main characteristics of studies excluded from the 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
Speizer, 1999 LUN01255 USA	NHS, Prospective Cohort, Age: 30-55 years, W	593/ 118 351 1 793 089 person-years	Active follow-up, cases confirmed with medical and pathology records	FFQ - study-specific	Incidence, lung cancer	Highest vs lowest	0.80 (0.60-1.10) Ptrend:0.17	Age, energy intake, smoking habits	Duplicate of Michaud, 2000 LUN01014
Ocke, 1997 LUN01851 Netherlands	Zutphen Study, Prospective Cohort, Age: 40-59 years, M	54/ 561 12 years	Data from Central Bureau of Statistics, diagnosis verified through cancer registry, hospital discharge or general	Dietary history questionnaire	Incidence, lung cancer	> 33rd vs ≤ 33rd average intake percentile	1.04 (0.60-1.83)	Age, pack years of cigarettes, energy intake	Duplicate of Kromhout, 1987 LUN03765
						> 33rd vs ≤ 33rd stable intake percentile	2.11 (1.02-4.38)		

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
			practitioner						
Knekt, 1993 LUN02684 Finland	FMCHES, Nested Case Control, Age: 15- years, M	95/ 270 controls 9 years	Cancer registry	FFQ - study-specific	Incidence, lung cancer , current smokers	Highest vs lowest	1.00 (0.60-1.70)	Age	Duplicate of Knekt, 1999 LUN01416
		26			Incidence, lung cancer, non-smokers		2.80 (0.80-10.00)		
Chow, 1992 LUN02888 USA	LBS, Prospective Cohort, Age: 35- years, M	219/ 17 633 20 years	Death certificates	FFQ - study-specific	Mortality, lung cancer	Highest vs lowest	0.80 (0.50-1.20)	Age, smoking habits, industry/occupation	Used only in highest vs lowest analysis No specific cut-points for quintiles is reported
Shibata, 1992 LUN02889 USA	LWS, Prospective Cohort, Age: 74 years, M	125/ 5080 6 years	Death by reports of friends or relatives, National Death Index; incidence through hospital records	FFQ - study-specific	Incidence, lung cancer	13 318 vs 2577 µg /day	0.98 (0.59-1.63)	Age, smoking habits	Duplicate of Shibata, 1992 LUN08664

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Reasons for exclusion
Connett, 1989 LUN03434 USA	MRFIT, Nested Case Control, Age: 35-57 years, M	66/ 131 controls 10 years	Active follow-up confirmed with hospital records	Recall	Mortality, lung cancer	Mean Cases: 2377.8 µg Controls: 3152.4 µg	p test difference ; 0.20	Age, cigarettes per day, BMI, serum cholesterol, DBP, years of education, serum thiocyanate, leukocyte count	No OR available
Paganini-Hill, 1987 LUN03731 USA	LWS, Prospective Cohort, Age: 74 years, M/W	56/ 10 473 3 years	Death by reports of friends or relatives, National Death Index; incidence through hospital records	FFQ - study-specific	Incidence, lung cancer, men	Highest intake	IRR= 1.43	Age	Only incident rate (IRR) is reported in men and women
					Incidence, lung cancer, women	High intake	IRR=0.53		

Figure 158 RR estimates of lung cancer by levels of dietary beta-carotene

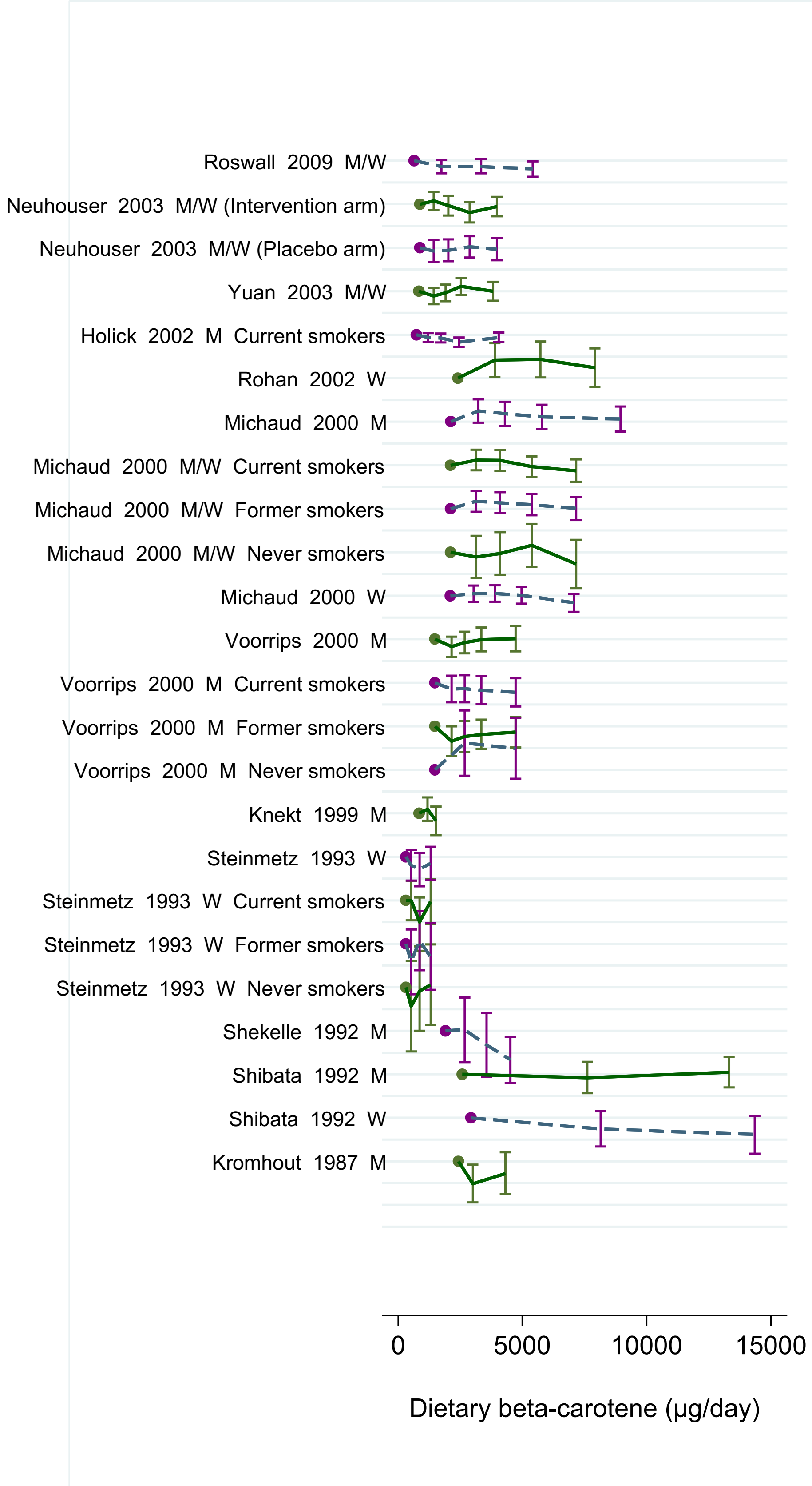


Figure 159 RR (95% CI) of lung cancer for the highest compared with the lowest level of dietary beta-carotene

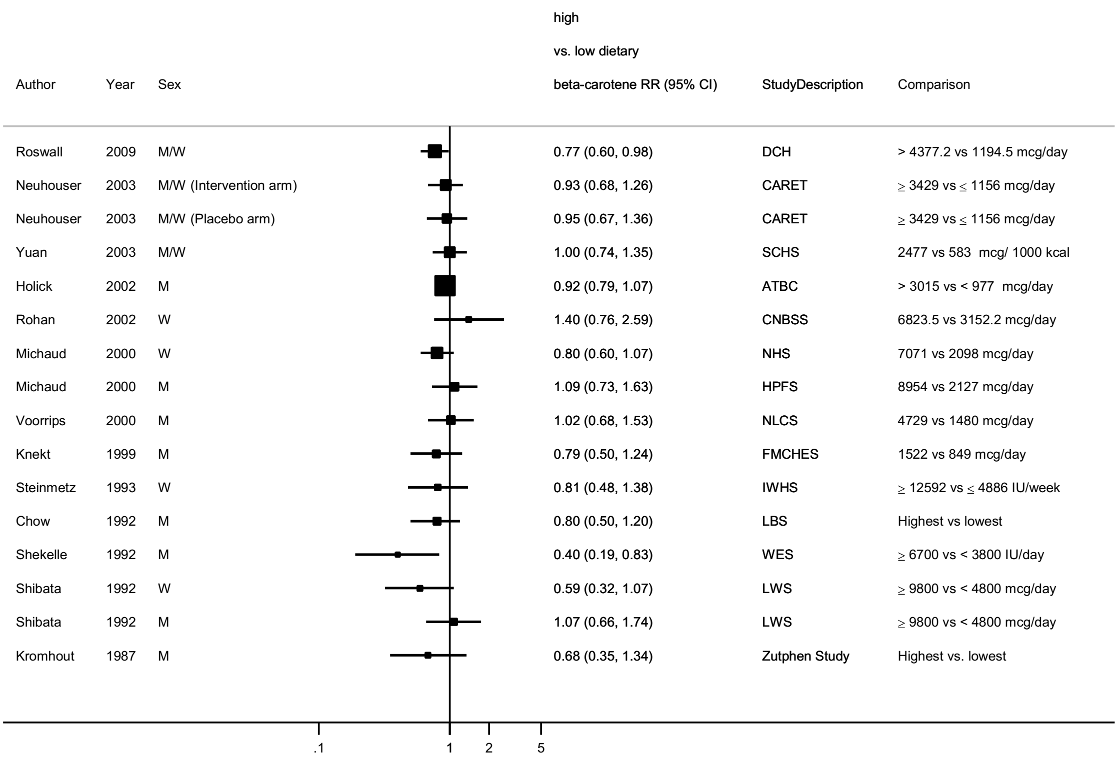


Figure 160 RR (95% CI) of lung cancer for 700 µg/day increase of dietary beta-carotene

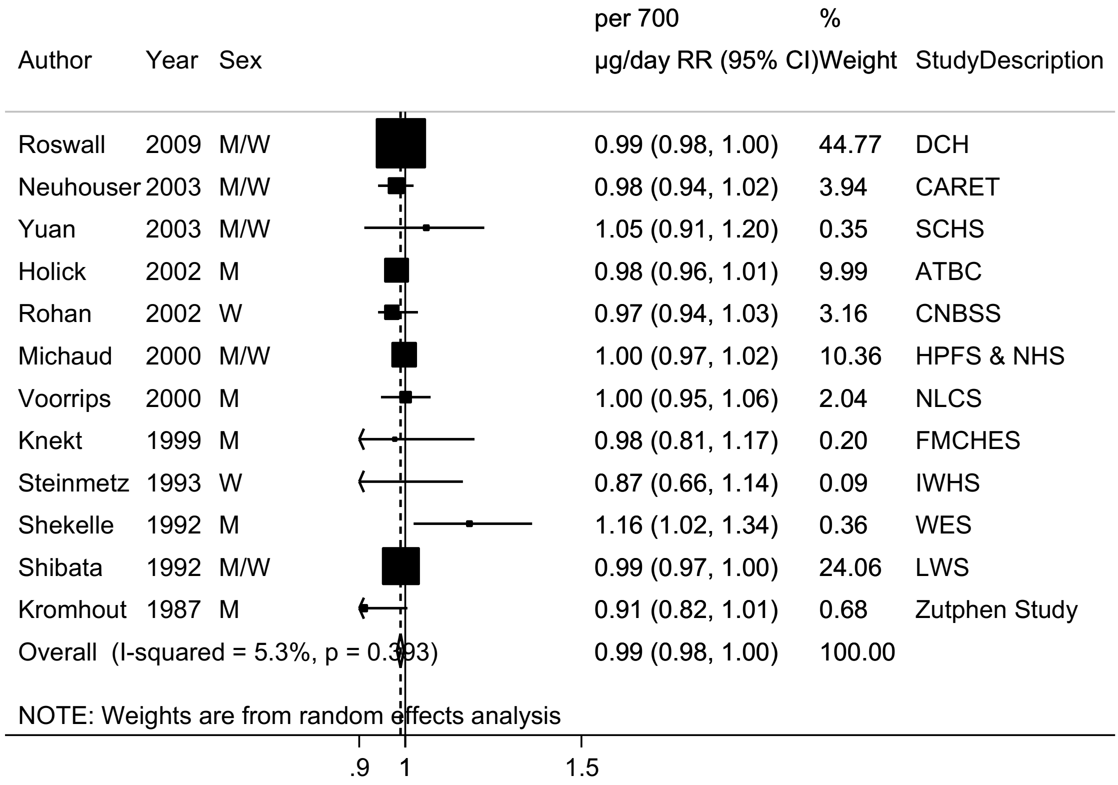
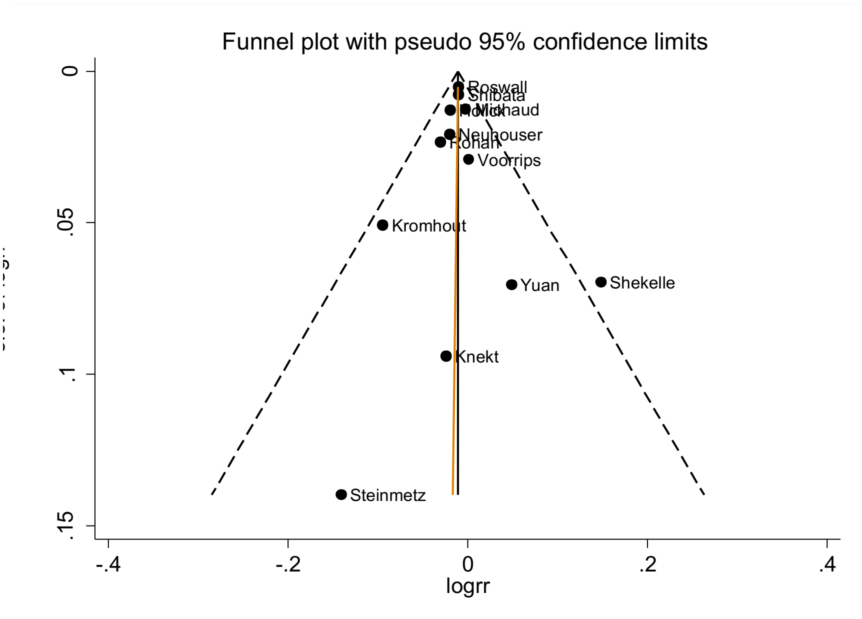


Figure 161 Funnel plot of studies included in the dose response meta-analysis of dietary beta-carotene and lung cancer



Egger’s test p=0.52

Figure 162 RR (95% CI) of lung cancer for 700 µg/day increase of dietary beta-carotene by smoking status

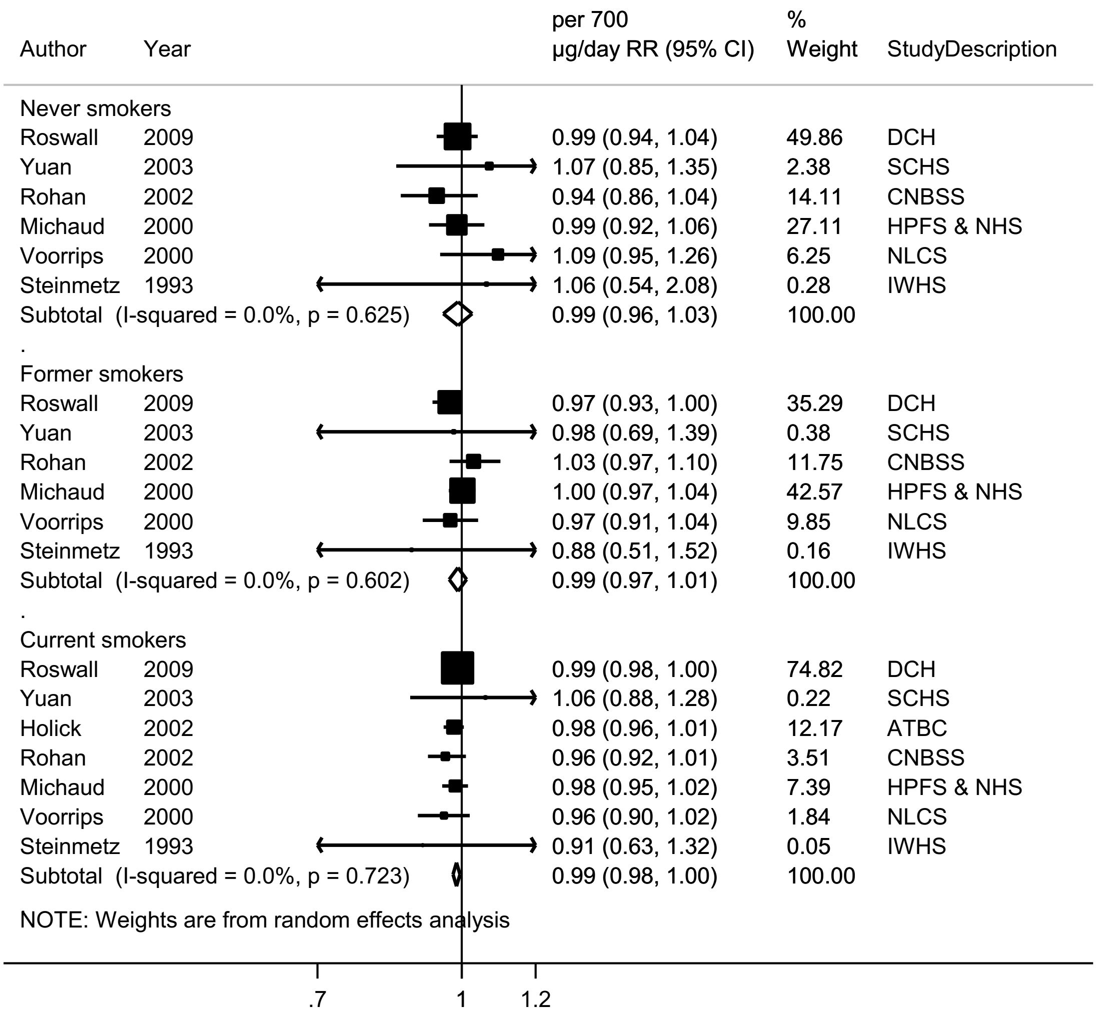


Figure 163 RR (95% CI) of lung cancer for 700 µg/day increase of dietary beta-carotene by sex

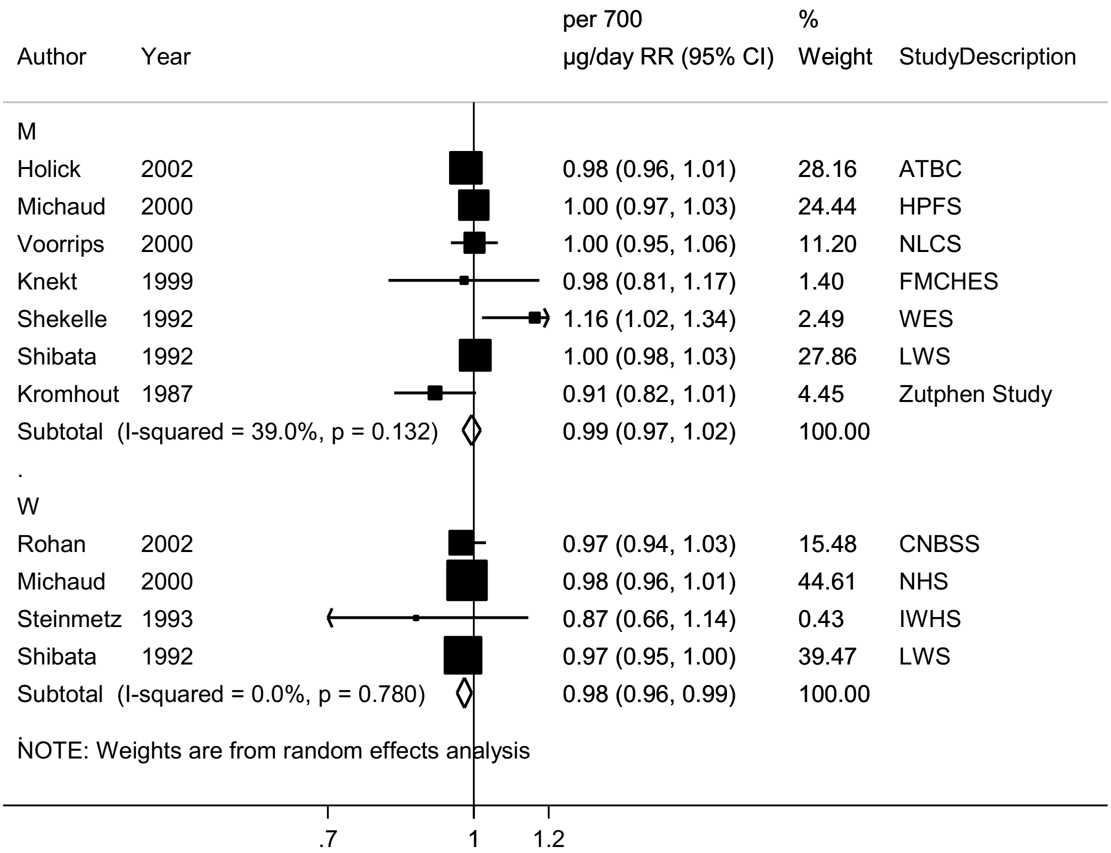
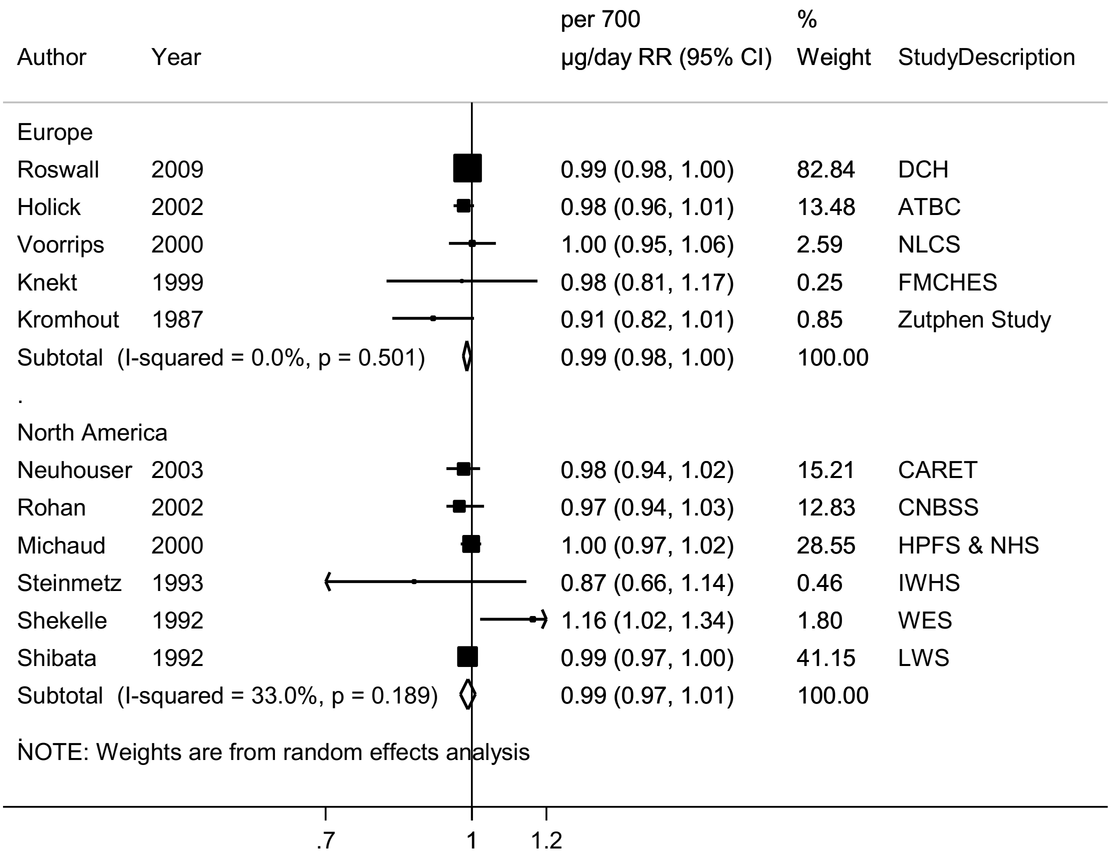


Figure 164 RR (95% CI) of lung cancer for 700 µg/day increase of dietary beta-carotene by geographic area



5.5.1.2 Supplemental beta-carotene

One RCT (Lin, 2009), one post intervention follow up study of a RCT (ATBC, Virtamo, 2014) and two cohort studies (Roswall, 2009; Satia, 2009) were identified in the CUP. The new RCT showed no association. The smoothed time curve of the 18 years post-intervention follow-up of the ATBC showed an increased risk in beta-carotene recipients compared with the nonrecipients, but the relative risk declined below 1 four years after the trial and varied nonsignificantly around 1.0 thereafter. Among prospective studies, there was a significant positive dose-response association only in a Danish prospective study in men and women (Roswall, 2009).

Table 136 RCT on supplemental beta-carotene identified in the CUP and SLR

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Main outcome	Intervention	Outcome	Comparison	RR (95%CI) Ptrend	Notes
Virtamo, 2014 LUN20385 Finland	ATBC, 18 years post-intervention follow-up study, Age: 50-69 years, M, Male Smokers	1445 active/1436 no beta-carotene incident cases/ 25 563 randomised	Lung and other cancers	20 mg of b-carotene alone, 50 mg of a-tocopherol alone, both b-carotene and a-tocopherol, or placebo	Incidence, lung cancer	Beta-carotene vs no beta-carotene	1.04 (0.96-1.11)	Baseline age, BMI, smoking, and alcohol consumption did not modify the effect of beta-carotene on lung cancer risk during the post-trial period (*P*>0.05 for interaction for each factor)
		1349 active/ 1322 no beta-carotene deaths			Mortality, lung cancer	Beta-carotene vs no beta-carotene	1.05 (0.97-1.13)	
		736 active /725 placebo incident cases			Incidence, lung cancer	Alpha-tocopherol and beta-carotene vs placebo	1.05 (0.95-1.16)	
						Beta-carotene vs placebo	1.01 (0.91-1.13)	

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Main outcome	Intervention	Outcome	Comparison	RR (95%CI) Ptrend	Notes
Lin, 2009 LUN20384 USA	WACS, Double-blind, placebo-controlled 2 × 2 × 2 factorial trial of of vitamin C, tocopherol and beta carotene (50 mg every other day) in women at high risk of cardiovascular disease Age: 40- years	41 cases beta-carotene active and 33 placebo/ 3807 active and 3820randomised; 9.4 years of treatment	Major cardiovascular events cancer events assessed by questionnaire and verified by medical records	Synthetic vitamin C (500 mg of ascorbic acid daily), natural-source vitamin E (600 IU of - tocopherol every other day), and beta carotene (50 mg of Lurotin every other day)	Incidence or mortality, lung cancer	Beta-carotene vs placebo	1.26 (0.80-1.99)	Models included main effect terms of the three antioxidants and age
Goodman, 2004 LUN17049 USA	6 years post-intervention follow-up of CARET, double-blind, placebo controlled trial, M/W, ex- and current smokers, men exposed to asbestosers Age: 45-69	376 active/311 placebo incident cases/ 8744 assigned to treatment, 8396 placebo	Lung cancer and cardiovascular disease	Combination of 30 mg/day of b-carotene and 25,000 IU/day of retinyl palmitate	Incidence, lung cancer	Beta-carotene & retinol vs placebo	1.12 (0.97 - 1.31)	
					Mortality, lung cancer		1.20 (1.01- 1.43)	
Virtamo, 2003 LUN00269	ATBC, Post-intervention	1037 cases/ 25 563	Lung and other cancers	20 mg of b-carotene alone, 50	Incidence, lung cancer	Beta-carotene vs no beta-carotene	1.06 (0.94-1.20)	

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Main outcome	Intervention	Outcome	Comparison	RR (95%CI) Ptrend	Notes
Finland	follow-up study , Age: 50-69 years, M, Smokers only			mg of a-tocopherol alone, both b-carotene and a-tocopherol, or placebo	Mortality, lung cancer		1.07 (1.02-1.12)	
Cook, 2000 LUN01029 USA	PHS, Double-blind, placebo-controlled trial 2 x 2 factorial design , Age: 40-84 years, M (Physicians)	85 cases active/93 placebo 22 071 men randomised	For the beta-carotene arm, any cancer except non-melanoma skin cancer	Aspirin (325 mg on alternate days) and beta-carotene(50 mg on alternate days in specific	Incidence, lung cancer	Beta-carotene vs placebo	0.9 (0.7-1.2) p=0.54	
		11/13			Non-smokers		0.90 (0.40-1.90)	
		34/34			Former smokers		1.00 (0.60-1.60)	
		40/45			Current smokers		0.90 (0.60-1.30)	
Lee, 1999 LUN15003 USA	WHS, Double-blind, placebo controlled 2 x 2 x 2 trial of aspirin, vitamin E, and b-carotene , Age: 45- years, W, health professionals	39 876 randomised 2.1 years' treatment plus 2.0 years' follow-up 30 cases active/21 placebo	Cardiovascular diseases	100 mg of aspirin, 600 IU of vitamin E, 50 mg of b-carotene, all on alternate days	Incidence, lung cancer	Beta-carotene vs placebo	1.43 (0.82-2.49)	
De Klerk, 1998 LUN016 63 Australia	Australian cohort of asbestos workers,	6 cases beta carotene/ 4 cases retinol	Lung and other cancers	30 mg/day b-carotene or 25,000 IU/day retinol at	Incidence, lung cancer	25,000 IU/day retinol (512 subjects) vs 30	0.66 (0.19–2.32	

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Main outcome	Intervention	Outcome	Comparison	RR (95%CI) Ptrend	Notes
	Randomized trial Age: 40-83 years, M/W	512 assigned to each treatment		least 400 days worth		mg/day b-carotene (512 subjects)		
Albanes, 1996 LUN20371 Finland	ATBC, Placebo-controlled randomised trial 2 x 2 factorial design, Age:50-69 years, Male smokers	474 cases active/ 402 placebo 29 133 male smokers randomised	Cancer including lung cancer	20 mg of b-carotene alone, 50 mg of a-tocopherol alone, both b-carotene and a-tocopherol, or placebo	Incidence, lung cancer	Beta-carotene vs placebo	1.18 (1.03-1.36)	
Omenn, 1996 LUN02019 USA	CARET, Double-blind, placebo controlled trial, Age: 45-69 M/W Current or former smokers	388 cases/ 9 420 subjects in active group/8 894 subjects in placebo group	Lung cancer and cardiovascular disease	a combination of 30 mg of b-carotene /day and 25,000 IU of retinol (vitamin A) in the form of retinyl palmitate/day	Incidence, lung cancer	Beta-carotene & retinol vs placebo	1.28 (1.04–1.57)	Risk group, time of recruitment, and study centre
Hennekens, 1996 LUN02020 USA	PHS, Double-blind, placebo controlled trial 2 x 2 factorial design , Age:40-84 years,	82 cases active/ 88 cases placebo 22 071 men randomised	For the beta-carotene arm, any cancer except non-melanoma skin cancer	Aspirin (325 mg on alternate days) and beta-carotene(50 mg on alternate days in specific	Incidence, lung cancer	Beta-carotene vs placebo		Age, other nutrients, foods or supplements
					Current smokers		0.90 (0.58-1.40)	
					Former smokers		1.00 (0.62-1.61)	
					None smokers		0.78 (0.34-1.79)	

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Main outcome	Intervention	Outcome	Comparison	RR (95%CI) Ptrend	Notes
	M (Physicians)							
Albanes, 1996 LUN01904 Finland	ATBC, Placebo-controlled randomised trial 2 x 2 factorial design, Age:50-69 years, Male smokers	474 cases active/ 402 placebo 29 133 male smokers randomised	Lung cancer	20 mg of b-carotene alone, 50 mg of a-tocopherol alone, both b-carotene and a-tocopherol, or placebo	Incidence, lung cancer	Beta-carotene vs placebo	1.16 (1.02-1.33) p=0.02	Age, anthropometry, smoking habits, other nutrients, foods or supplements
					Smokers with ≥20 cigarettes/day		1.25 (1.07-1.46)	
Heinonen, 1994 LUN02496 Finland	ATBC, Placebo-controlled randomised trial 2 x 2 factorial design, Age:50-69 years, Male smokers	474 cases active/ 402 placebo 29 133 male smokers randomised	Lung and other cancers	20 mg of b-carotene alone, 50 mg of a-tocopherol alone, both b-carotene and a-tocopherol, or placebo	Incidence, lung cancer	Beta-carotene vs placebo	1.18 (1.03-1.36)	

Table 137 Cohort Studies on supplemental beta-carotene identified in the CUP and SLR

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors
Roswall, 2009 LUN26873 Denmark	DCH, Prospective Cohort, Age: 50-64 years, M/W	721/ 55 557 10.6 years	Danish cancer registry	FFQ	Incidence, lung cancer	> 13500 vs 0 µg/day	1.56 (0.58-4.25)	Age, sex, supplements of folate, vitamin C, vitamin E, smoking status, intensity, duration, passive smoking, smoking cessation, work exposure to carcinogenic substances
						Per 5000 µg/day	1.64 (1.20-2.23)	
Satia, 2009 LUN20357 USA	VITAL, Prospective Cohort, Age: years, M/W	521/ 77 126 10 years	Seattle-Puget Sound SEER registry		Incidence, lung cancer	> 1200 µg /day vs no use	1.25 (0.91-1.71)	Age, sex, BMI, years of smoking, pack-years, and pack-years squared, fruit and vegetable intake, physical activity, supplemental vitamin E use
		297			Men		1.10 (0.71-1.70)	
		224			Women		1.49 (0.76-2.58)	
		30			Current smokers		0.96 (0.45-2.07)	
		18			Former smokers quit < 10 years		1.52 (0.64-3.60)	
		44			Former smokers quit ≥ 10 years		1.06 (0.61-1.84)	
		391			Non-small cell lung cancer		1.22 (0.85-1.76)	

		74			Small cell lung cancer		2.58 (0.99-6.72)	
		56			Other lung cancers		1.95 (0.63-6.02)	
Michaud, 2000 LUN01014 USA	HPFS, Prospective Cohort, Age: 30-75 years, M	275/ 46 924 10 years	Active follow-up, cases confirmed with medical and pathology records	FFQ - study-specific	Incidence, lung cancer, men	Use vs non-use	0.82 (0.36-1.85)	Age (5-y categories), smoking status, time since quitting, age start of smoking quintiles of energy intake, and time period
	NHS, Prospective Cohort, Age: 30-75 years, W	519/ 77 283 12 years			Incidence, lung cancer, women		1.23 (0.55-2.76)	

5.5.1.2 Serum beta-carotene

Cohort studies

Summary

Nine studies (2958 cases) out of 17 cohort studies (20 publications) were included in the dose-response meta-analysis. A significant inverse association was observed. There was evidence of moderate heterogeneity.
The excluded studies did not report significant associations with the exception of one study in which a significant inverse association was observed in women but not in men, and another study in which cases have lower mean values than controls, but the results were not adjusted for confounders.

There was not enough data to do stratified analysis by either smoking status or histological type. In the multiethnic study (Epplein, 2009), an inverse association was observed in men but not in women (p interaction=0.01) and it was mainly in non-adenocarcinomas (p interaction =0.05). There was no effect modification by smoking (ever or never smoker).
In the ATBC study (in men smokers or exposed to asbestos) (Holick, 2002), a significant inverse association was observed in men who smoked < 19 cigarettes/day (P trend =0.02) but not in the heavy smokers. In a Chinese study (Yuan, 2001) similar associations were observed in never and ever smokers, but only 20 cases were never smokers.

Sensitivity analyses:
The association remained significant in influence analysis; the summary RRs ranged from 0.90 (95% CI=0.84-0.97) when Nomura, 1985 was omitted to 0.93(95% CI=0.88-0.98) when Ito, 2005 was omitted.
After excluding the studies in high risk populations (heavy smokers or exposed to asbestos in CARET, Goodman, 2003 and ATBC, Holick, 2002; male minersin Ratnasinghe, 2003;) the inverse association was slightly strengthened from 0.92 (95% CI= 0.87-0.97) to 0.90 (95% CI=0.84-0.96).

There was no evidence of non-linear dose response of lung cancer and serum beta-carotene (p > 0.05) (Figure not shown).

Study quality:
All studies were adjusted by main confounders, including age and smoking. All studies adjusted for intensity, duration of smoking and other smoking variables in addition to smoking status. Three studies were in high risk populations: high-risk miners (Ratnasinghe, 2003), heavy smokers or exposed to asbestos (Holick, 2002; Goodmann, 2003) (see sensitivity analysis above)
All studies used HPLC. In a study in Japanese men in Hawaii in which no significant inverse association of lung cancer with serum beta-carotene levels was observed, the serum values

were higher than in other studies (Nomura, 1985). The authors reported a high coefficient of variation in a study in ten frozen samples (38.6%).

Table 138 Serum beta-carotene and lung cancer risk. Number of studies in the CUP SLR

	Number
Studies identified	17 (20 publications)
Studies included in forest plot of highest compared with lowest exposure	14
Studies included in dose-response meta-analysis	9
Studies included in non-linear dose-response meta-analysis	6

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

Table 139 Serum beta-carotene and lung cancer risk. Summary of the dose-response meta-analysis in the 2005 SLR and CUP

	2005 SLR	CUP
Increment unit used	0.1 µmol/L	10 µg/100 mL
All studies		
Studies (n)	5	9
Cases (total number)	2039	2958
RR (95%CI)	0.97 (0.93-1.02)	0.92 (0.87-0.97)
Heterogeneity (I^2, p-value)		39.7%, 0.10
P value Egger test		0.28

Stratified and sensitivity analysis (no analyses conducted in the 2005 SLR)		
Sex	**Men**	**Women**
Studies (n)	7	3
RR (95%CI)	0.90 (0.83-0.97)	0.95 (0.84-1.08)
Heterogeneity (I^2, p-value)	62.7%, 0.01	7.1%, 0.34
Outcome	**Incidence**	**Mortality**
Studies (n)	6	3
RR (95%CI)	0.94 (0.89-0.99)	0.86 (0.78-0.95)
Heterogeneity (I^2, p-value)	42.9%, 0.12	0%, 0.45
Geographic location	**Asia**	**North America**
Studies (n)	3	5
RR (95%CI)	0.94 (0.67-1.31)	0.93 (0.88-0.99)
Heterogeneity (I^2, p-value)	68.4%, 0.04	14.5%, 0.32

Table 140 Serum beta-carotene and lung 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								
Gallicchio*, 2008	6	2240	Japan, China, Finland, UK, North America	Incidence, lung cancer	Per 0.1 µmol/L	0.95 (0.87-1.03)		72%, < 0.01
	10	2846			Highest vs lowest	0.84 (0.66-1.07)		0%, 0.08

Table 141 Serum beta-carotene and lung cancer risk. Main characteristics of studies included in the 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
Min, 2014 LUN26890 USA	A follow up study of NHANES III, Prospective Cohort, Age: ≥ 20 years, M/W	161/ 10 382	Death certificate	Blood sample, measured by HPLC	Mortality, lung cancer	≥ 24 vs ≤ 8 µg/dL	0.76 (0.48-1.20)	Age , sex, smoking status, ethnicity, education, alcohol consumption, exercise, pack-year of smoking, obesity, total cholesterol,	Mid-points of exposure, person years
		91/ 2957			Mortality, lung cancer, current smokers	≥ 17 vs ≤ 6 µg/dL	0.57 (0.30-1.07)		

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Missing data derived for analyses
		70/ 7425			Mortality, lung cancer, never/former smokers	≥ 26 vs ≤ 9 µg/dL	1.08 (0.54-2.17)	daily fat intake and vegetable and fruit consumption	
Epplein, 2009 LUN20317 USA	MEC, Nested Case Control, Age: 45-75 years, M/W	136/ 272 controls Mean 1 year 8 month (cases)	SEER Registry	Blood sample, (94% fasting for 8 h or more)	Incidence, lung cancer, men	497 vs 82 ng/mL	0.30 (0.15-0.64) Ptrend:< 0.01	Age at specimen collection, fasting hours before blood draw, cigarettes pack-years, and pack-years squared, years of schooling and family history of lung cancer	ng/mL converted to µg/100 mL
		71/ 142 controls Mean 1 year 8 month (cases)			Incidence, lung cancer, women	508 vs 100 ng/mL	1.33 (0.49-3.61) Ptrend:0.53		
Goodman, 2003 LUN00294 USA	CARET, Nested Case Control, Age: 45-69 years, M/W	276/ 276 controls 4 years	Primary outcome of the trial. Active follow-up with confirmation by clinical records and pathology reports	Non-fasting blood sample	Incidence, lung cancer	255 vs 87 ng/mL	1.07 (0.63-1.83) Ptrend: 0.73	Age, sex, smoking, study centre at randomization, , year of randomization pack-years of smoking and years quit smoking	Mid-points of exposure, number of cases and controls per quartiles, ng/mL converted to µg/100 mL
		174/ 174 controls 4 years			Incidence, lung cancer, men		1.40 (0.71-2.74) Ptrend: 0.42		
		102/ 102 controls 4 years			Incidence, lung cancer, women		0.72 (0.30-1.75) 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	Missing data derived for analyses
Ito, 2005 LUN26888 Japan	JACC, Nested Case Control, Age: 40-79 years, M/W	163/ 375 controls 10 years	Death certificate	Serum sample (measured by HPLC)	Mortality, lung cancer, men	≥ 0.58 vs < 0.14 µmol/L	0.23 (0.09-0.55) Ptrend: 0.00	Age, sex, smoking habits, participating institution and alcohol drinking	Mid-points of exposure , µmol/L converted to µg/100 mL
		48/ 122			Mortality, lung cancer, women	≥ 1.21 vs < 0.40 µmol/L	0.82 (0.19-3.58) Ptrend: 0.48		
Ratnasinghe, 2003 LUN00362 China	YTC, Nested Case Control, Age: 40-74 years, High-risk miners men	108/ 216 controls 6 years	Cancer registry and annual screenings	Serum collected 2 years prior to diagnosis	Incidence, lung cancer	19-90 vs < 9 µg/dL	2.0 (0.11-3.8) Ptrend: 0.08	Age, radon exposure, smoking habits, pack-years	Mid-points of exposure
Holick, 2002 LUN00515 Finland	ATBC, Prospective Cohort, Age: 50-69 years, M , smokers and exposed to	1 644/ 29 133 11 years	Finnish Cancer Registry and the Register of Causes of Death	Fasting (12 h) serum sample	Incidence, lung cancer	> 290 vs < 99 µg/L	0.81 (0.69-0.95) Ptrend: 0.02	Age, years smoked, cigarettes per day, intervention (alpha-tocopherol and beta-carotene	Distribution of person yeas per quintiles, mid-points of exposure, µg/L converted to

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Missing data derived for analyses
	asbestos							supplement) serum cholesterol	µg/100 mL
Yuan, 2001 LUN00828 China	Shanghai, China, Nested Case Control, Age: 45-64 years, M	209/ 335 controls 12 years	Active follow-up, Shanghai cancer registry, death certificates	Non-fasting blood sample	Incidence, lung cancer	≥ 16.21 vs < 7.10 µg/dL	0.74 (0.42-1.30) Ptrend: 0.20	Age at starting to smoke, average no. of cigarettes smoked/day, and smoking status at the time of blood draw (non-smoker, smoker)	Mid-points of exposure
		189/ 335			Incidence, lung cancer, ever smokers	Highest vs lowest	0.85 (0.57–1.27)		
		20/ 287			Incidence, lung cancer, never smokers		0.69 (0.26–1.79)		
Connett, 1989 LUN03434 USA	MRFIT, Nested Case Control, Age: 35-57 years, M	66/ 131 controls 10 years	Active follow-up confirmed with hospital records, National Death Index	Serum sample	Mortality, lung cancer	Lowest vs highest	2.32	Age, cigarettes per day, BMI, serum cholesterol, DBP, years of education, serum thiocyanate, leukocyte count	Estimating CI's using cases and controls numbers RR was recalculated using Hamling method
						Per 10 µg /dL	0.72 (0.50-1.04)		
Nomura, 1985 LUN04074	HHP, Nested Case	74/ 302 controls	Continuous surveillance in	Non-fasting blood sample	Incidence, lung cancer	0-15 vs 57.1-311.5 µg /dL	2.20 (0.80-6.00)	Age, smoking habits	Mid-points of exposure

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Missing data derived for analyses
USA	Control, Age: 45-79 years, M	10 years	local hospitals and record linkage with cancer registry						RR was recalculated using Hamling method

Table 142 Serum beta-carotene and lung cancer risk. Main characteristics of studies excluded from the 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 LUN20287	Hokkaido, Japan, Prospective Cohort Study, Age: 39-85 years, M/W	41/ 3254 11.7 years	Mortality records	Fasting serum sample	Mortality, lung cancer	Per each logarithmically transformed serum value	0.91 (0.58-1.41)	Age, sex, smoking status, alcohol consumption, serum cholesterol and triglyceride, alanine aminotrans-ferase activity	HRs for one log increase
Ito, 2005 LUN26887 Japan	Japan, Hokkaido Cohort Study, Prospective Cohort,	31/ 3182 10.5 years	Death certificate	Fasting serum sample (measured in serum using	Mortality, lung cancer	High vs low	1.55 (0.53-4.56) Ptrend: 0.17	Age, sex, ALT activity, serum cholesterol, smoking habits	Superseded by Ito, 2006 LUN20287 No 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: 39-79 years, M/W			HPLC method)					levels Used in H vs L analysis only
Ito, 2003 LUN00342 Japan	JACC, Nested Case Control, Age: 40-79 years, M/W	147/ 311 controls 8 years	Death certificate	Serum sample	Mortality, lung cancer	≥ 0.76 vs < 0.19 µmol/L	0.21 (0.08-0.58) Ptrend: < 0.01	Age, sex, participating institution, smoking and alcohol drinking	Superseded by Ito, 2005 LUN26888
Comstock, 1997 LUN01716 USA	CLUE I & CLUE II, Nested Case Control, Age: 25- years, M/W	157/ 312 controls	Death certificates and hospital discharge records	Blood sample	Incidence, lung cancer, men	Highest vs lowest	0.67 Ptrend:0.10		No data available to calculate missing confidence intervals
		101/ 202 controls			Incidence, lung cancer, women		0.33 Ptrend: < 0.01		
Knekt, 1993 LUN02684 Finland	FMCHES, Nested Case Control, Age: ≥ 15 years, M	122/ 270 controls 9 years	Finnish cancer registry	Serum sample	Incidence, lung cancer, current smokers	Lowest vs highest	0.8 (0.4-1.8)	Age	Only two levels
					Incidence, lung cancer, non-smokers		2.6 (0.7-8.9)		
Orentreich, 1991 LUN08914 USA	Kaiser Permanent Medical Centre , Nested Case Control, Age: 26-78 years,	123/ 263 000 8 years	Hospital records	Serum sample	Incidence, lung cancer	Lowest vs highest	3.0		Only two 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/W								
Knekt, 1990 LUN08960 Finland	A follow up study of FMCHES, Nested Case Control, Age: 15-99 years, M/W	108/ 36 265 8 years	Cancer registry	Serum sample	Incidence, lung cancer	Lowest vs highest	1.0(0.5-1.9)	Age, smoking habits	Superseded by Knekt, 1993 LUN02684
Stahelin, 1987 LUN03811 Switzerland	Basel Study III, Prospective Cohort, Age: 20-79 years, M	2975 7 years	Death certificate	Fasting blood sample	Mortality, lung cancer	Mean exposure:0.25 µmol/L			No RR available Duplicate of Stahelin, 1984 LUN04142
Menkes, 1986 LUN03835 USA	Washington county Maryland, Nested Case Control, M/W	99/ 196 controls 5 years	Cancer registry	Blood sample	Incidence, lung cancer	Lowest vs highest	2.20 P value: 0.04	Age, sex, ethnicity/race, other, smoking habits	No cut-points level available
Stahelin, 1984 LUN04142 Switzerland	Basel Study III, Nested Case Control, Age: 20-79 years, M	35/ 108 controls 13 years	Death certificate		Mortality, lung cancer	Mean exposure; 14.8 µg/dL in cases, 23.7 µg/dL in controls	P difference < 0.05		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
Wald, 1988 LUN12818 UK	BUPA, Nested Case Control, Age: 35-64 years, M	50/ 99 controls 5 years	Hospital records	Serum sample	Mortality, lung cancer	Highest vs lowest	0.82		No cut-points for quintiles, Confidence intervals calculated

Figure 165 RR estimates of lung cancer by levels of serum beta-carotene

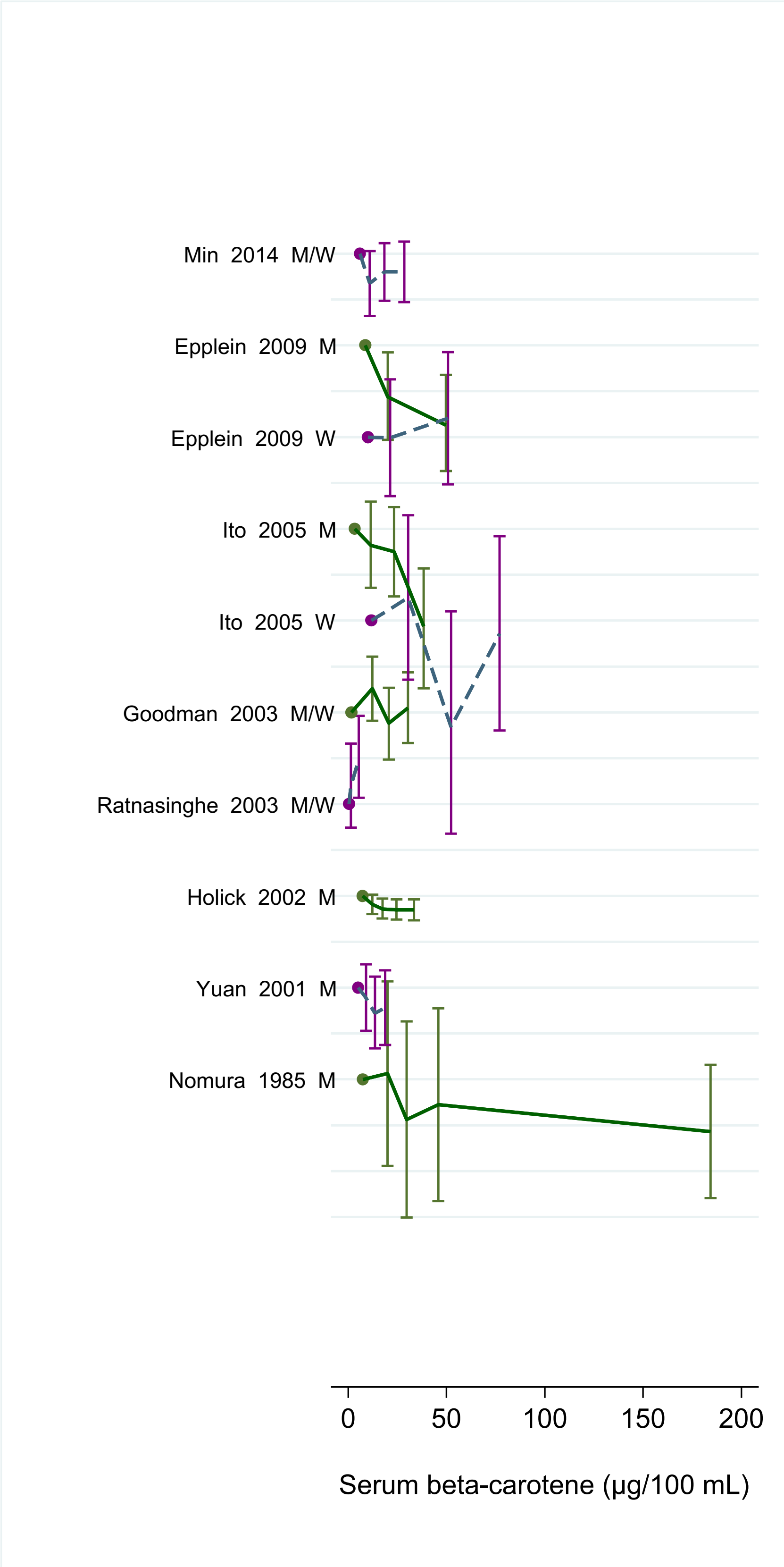
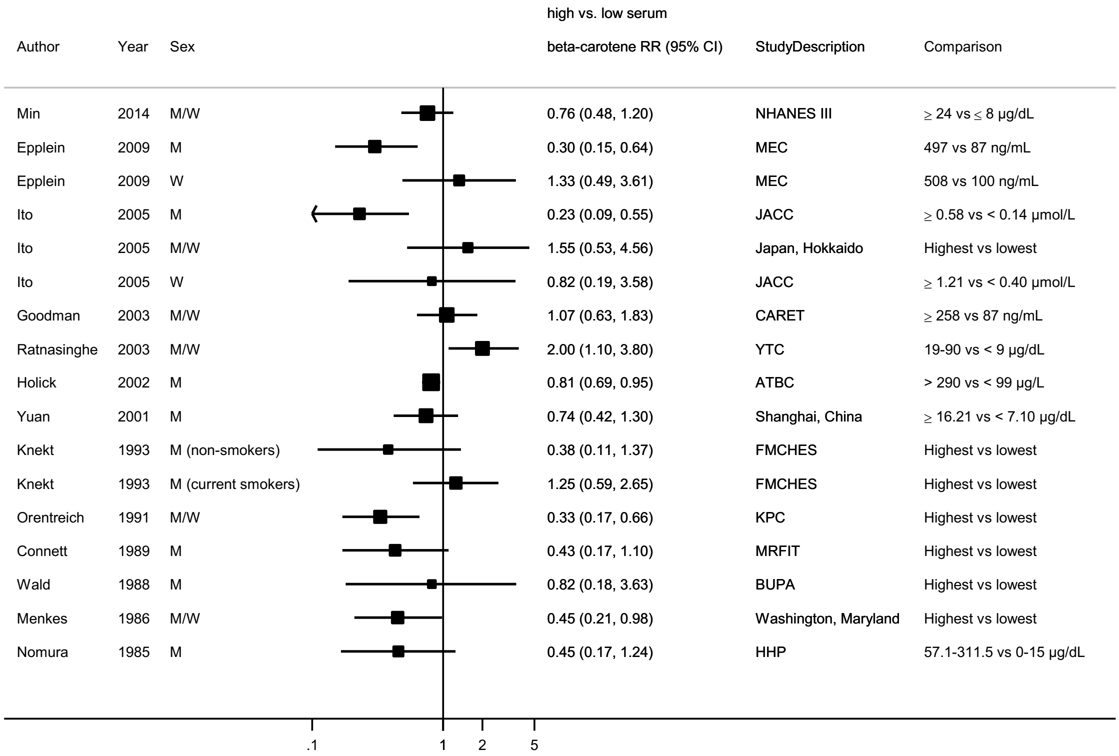


Figure 166 RR (95% CI) of lung cancer for the highest compared with the lowest level of serum beta-carotene



* RR's were recalculated using Hamling method in Knekt, 1993; Orentreich, 1991; Connett, 1989, Menkes, 1986; Nomura, 1985.

Figure 167 RR (95% CI) of lung cancer for 10 µg/100 mL increase of serum beta-carotene

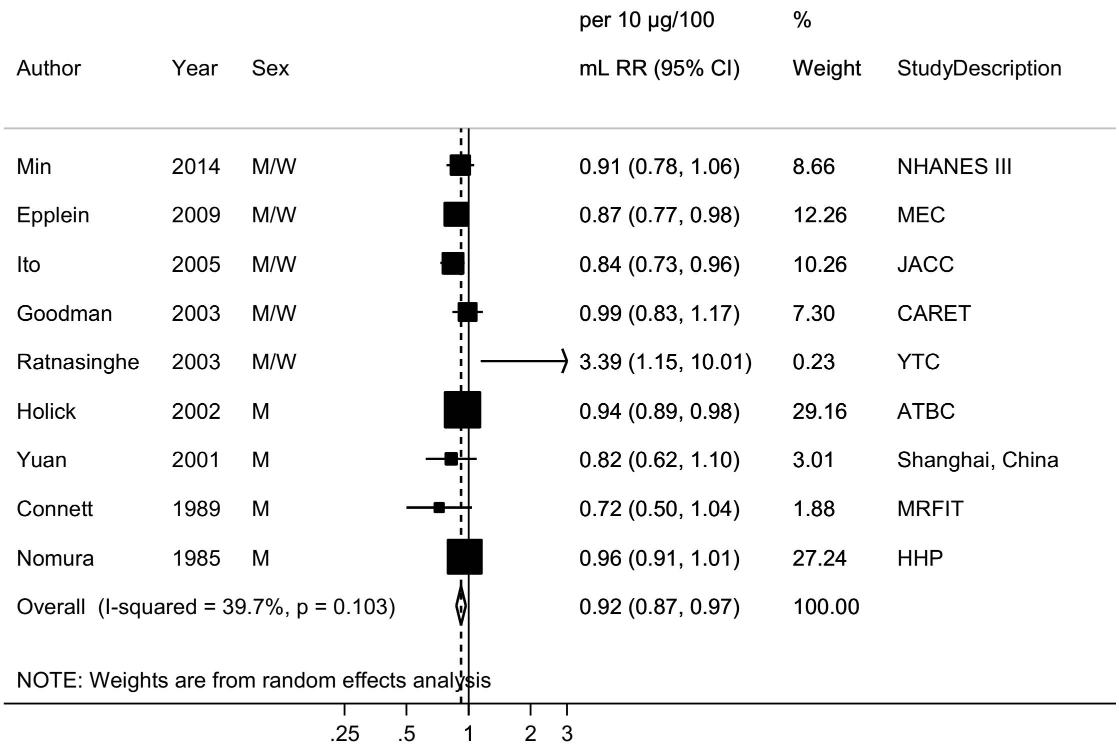
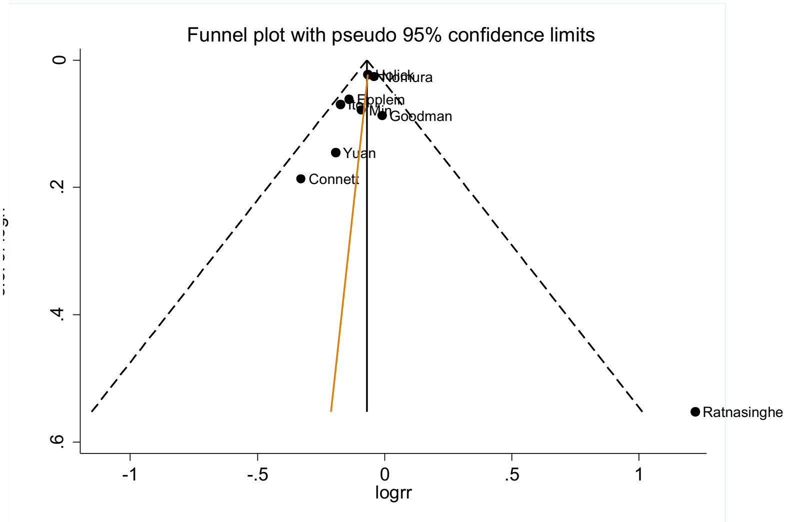


Figure 168 Funnel plot of studies included in the dose response meta-analysis of serum beta-carotene and lung cancer



Egger's test p =0.28

Figure 169 RR (95% CI) of lung cancer for 10 µg/100 mL increase of serum beta-carotene by sex

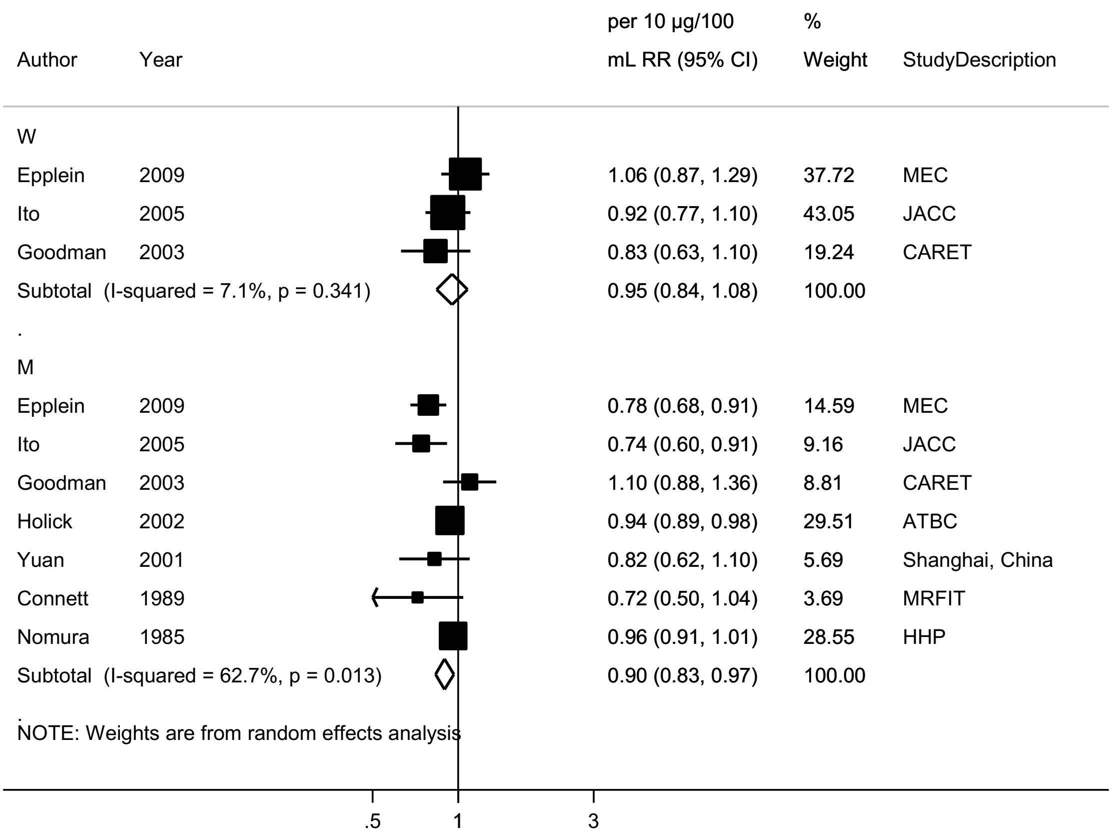


Figure 170 RR (95% CI) of lung cancer for 10 µg/100 mL increase of serum beta-carotene by outcome

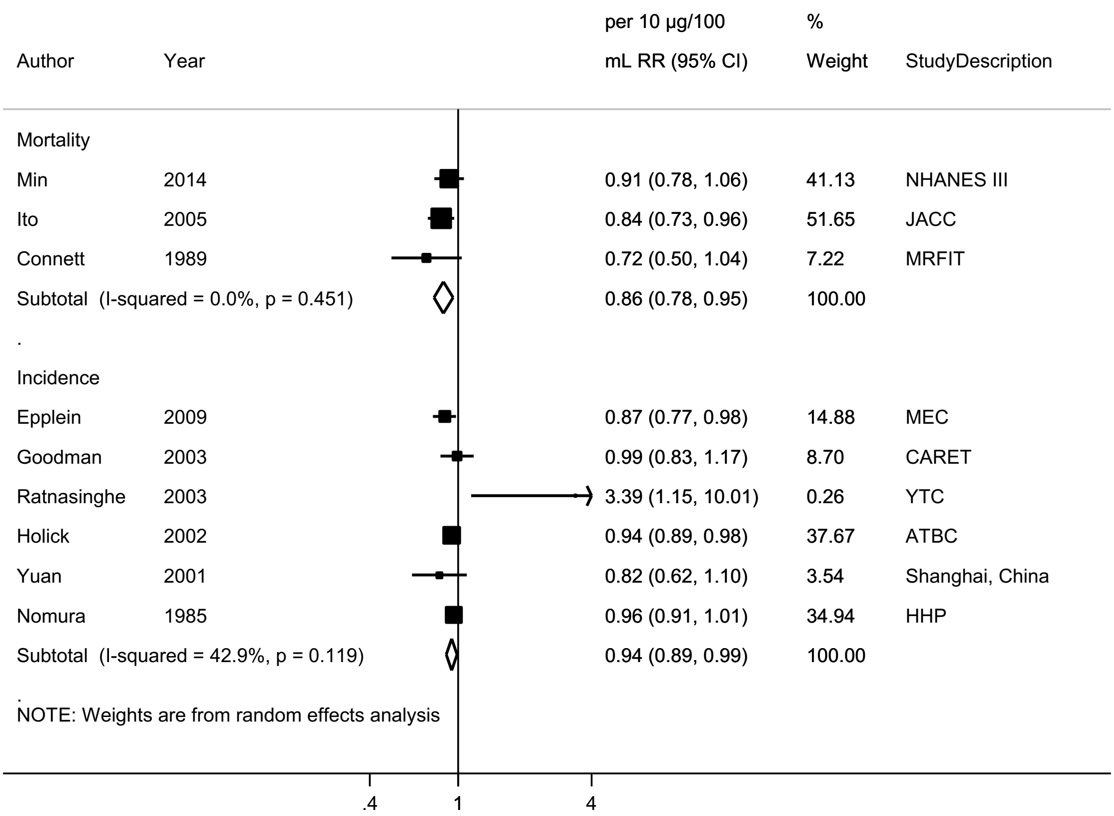
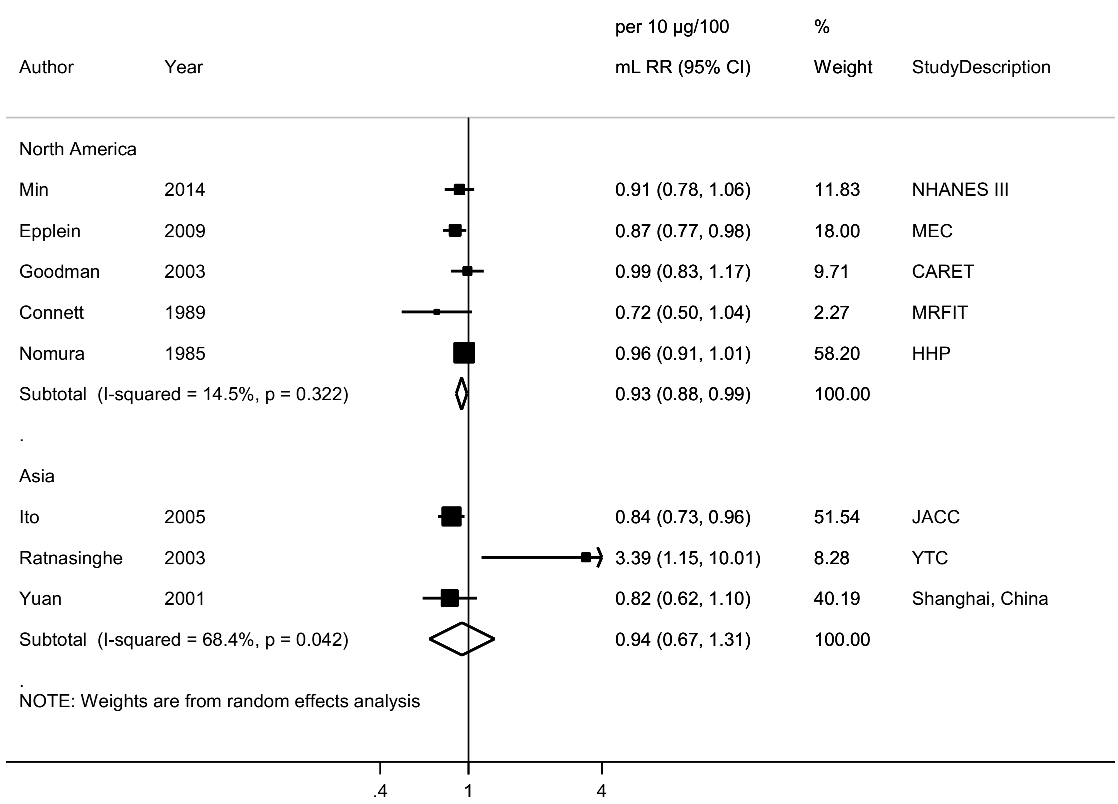


Figure 171 RR (95% CI) of lung cancer for 10 µg/100 mL increase of serum beta-carotene by geographic area



5.5.1.2 Dietary alpha-carotene

No new study identified during the CUP. The 2005 SLR included 3 studies in dose-response meta-analysis, the overall RR was 1.00; 95% CI 0.98-1.01 per 200 µg /day).

Table 143 Dietary alpha-carotene and lung cancer risk. Results of meta-analyses and pooled analyses of prospective studies

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								
Gallicchio, 2008	5	2645	Europe, North America, Australia and China	Incidence, lung cancer	Per 200 µg/day	0.99 (0.97, 1.01)		0.36, 0.18
	8	3928			Highest vs lowest	0.89(0.79, 1.00)		15%, 0.31
Pooled analysis								
Männistö, 2004	7	3155	North America and Europe	Incidence, lung cancer	Q5 vs Q1	0.93 (0.82–1.06)	0.47	0.39
		1915		Current smokers	Q4 vs Q1	0.99 (0.85–1.15)	0.97	0.45
		981		Former smokers		0.94 (0.72–1.23)	0.44	0.15
		259		Never smokers		0.92 (0.64–1.33)	0.82	0.47
		956		Adenocarcinoma		0.99 (0.84–1.17)	0.96	0.40
		538		Small cell carcinoma		1.07 (0.88–1.29)	0.53	0.68
		901		Squamous cell carcinoma		0.97 (0.80–1.16)	0.86	0.40

Table 144 Dietary alpha-carotene and lung cancer risk. Main characteristics of studies identified in the 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
Neuhouser, 2003 LUN00354 USA	CARET, Prospective Cohort, Age: 45-69 years, M/W	326/ 14 120 8 years	Clinical records and, pathology reports	FFQ - study-specific	Incidence, lung cancer, placebo arm	≥ 881 vs ≤ 214 µg /day	0.93 (0.65-1.32) Ptrend:0.89	Age, sex, clinic site, environmental factors, ethnicity/race, smoking habits
					Incidence, lung cancer, intervention arm		0.87 (0.64-1.19) Ptrend:0.15	
Yuan, 2003 LUN00218 Singapore	SCHS, Prospective Cohort, Age: 45-47 years, M/W	482/ 62 392 8 years	Cancer registry and, birth and death registries	FFQ - study-specific	Incidence, lung cancer	376 vs 23 µg/1000 kcal	1.06 (0.79-1.42)	Age, sex, BMI, year of interview, educational level, ethnicity/race, number of cigarettes smoked per day, number of years of smoking, number of years since quitting smoking for former smokers
					Incidence, lung cancer	Per 353 µg/1000 kcal	1.13 (0.62–2.08)	Age, sex, BMI, year of interview,

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors
								educational level, ethnicity/race, number of cigarettes smoked per day, number of years of smoking, number of years since quitting smoking for former smokers, measurement error
		268			Incidence, lung cancer, current smokers		1.42 (0.61–3.31)	Age, sex, BMI, year of interview, educational level, ethnicity/race, number of cigarettes smoked per day, number of years of smoking
		71			Incidence, lung cancer, former smokers		0.24 (0.04–1.47)	Age, sex, BMI, year of interview,

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors
								educational level, ethnicity/race, smoking habits, number of cigarette smoked per day, number of years of smoking , number of years of since quitting smoking, dietary measurement error
		145			Incidence, lung cancer, never smokers		1.51 (0.54–4.26)	Age, sex, BMI, year of interview, educational level, ethnicity/race, smoking habits, dietary measurement error
Rohan, 2002 LUN00605	CNBSS, Case Cohort,	155/	Cancer and Death registries	FFQ - study-specific	Incidence, lung cancer	Per 100 µg /day	1.00 (0.97–1.02)	Age, clinic site, 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
Canada	Age: 40-59 years, W	5361 controls 10 years				1495.3 vs 557.6 µg /day	0.90 (0.51–1.58) Ptrend:0.92	other, other nutrients, foods or supplements, smoking habits
		101			Incidence, lung cancer, current smokers	Per 100 µg /day	0.98 (0.96–1.01)	
		36			Incidence, lung cancer, former smokers		1.01 (0.98–1.05)	
		18			Incidence, lung cancer, never smokers		0.98 (0.94–1.02)	
Holick, 2002 LUN00515 Finland	ATBC, Prospective Cohort, Age: 50-69 years, M, Smokers only	1 644/ 29 133 11 years	Cancer registry and medical records	FFQ - study-specific	Incidence, lung cancer	> 949 vs < 180 µg /day	0.94 (0.81-1.09) Ptrend:0.47	Age, energy intake, other nutrients, foods or supplements, smoking habits
Michaud, 2000 LUN01014 USA	HPFS, Prospective Cohort, Age: 30-75 years, M	275/ 46 924 10 years	Questionnaire, medical record, pathology report	FFQ - study-specific	Incidence, lung cancer, men	1810 vs 302 µg /day	0.88 (0.60-1.29) Ptrend: 0.32	Age (5-y categories), smoking status (never, past with time since quitting, or current with 6

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors
	NHS, Prospective Cohort, Age: 30-75 years, W	519/ 77 283 12 years			Incidence, lung cancer, women	1355 vs 267 µg /day	0.68 (0.51-0.92) Ptrend:0.007	categories), age at start of smoking (< 15 y, 15–19 y, 20–29 y, ≥30 y, or never smokers), quintiles of energy intake, and time period
	HPFS & NHS, Prospective Cohort, Age: 30-75 years, M/W	794/ 124 207 10-12 years			Incidence, lung cancer, men and women pooled	Highest vs lowest	0.75 (0.59-0.96) Ptrend:0.04	Age (5-y categories), smoking status (never, past with time since quitting, or current with 6 categories), age at start of smoking (< 15 y, 15–19 y, 20–29 y, ≥30 y, or never smokers), quintiles of energy intake, and time period
		357			Incidence, lung cancer, , men and women		0.84 (0.59-1.20)	Age (5-y categories), quintiles 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
					pooled, current smokers			energy intake, and time period, age at start of smoking and current smoking
		345			Incidence, lung cancer, , men and women pooled , former smokers		0.81 (0.56-1.15)	Age (5-y categories), quintiles of energy intake, and time period, age at start of smoking and time since quitting
		84			Incidence, lung cancer, , men and women pooled, never smokers		0.37 (0.18-0.77)	Age (5-y categories), quintiles of energy intake, and time period
Voorrips, 2000 LUN01121 Netherlands	NLCS, Case Cohort, Age: 55-69 years, M	939/ 1525 controls 6.3 years	Cancer registry and pathology reports	FFQ - study-specific	Incidence, lung cancer	1300 vs 198 µg /day	1.01(0.71–1.43) Ptrend:0.29	Age, educational level, family history of specific cancer, smoking habits
		487			Incidence, lung cancer, current smokers	Highest vs lowest	0.76 (0.49–1.17) Ptrend:0.41	Age, educational level, family history of

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors
								specific cancer
		312			Incidence, lung cancer, former smokers	Highest vs lowest	0.96 (0.60–1.56) Ptrend:0.94	Age, educational level, family history of specific cancer, years of smoking cigarettes, number of cigarettes per day
		35			Incidence, lung cancer, never smokers	Highest vs lowest	1. 1.61 (0.61–4.21) Ptrend:0.27	Age, educational level, family history of specific cancer, years of smoking cigarettes, number of cigarettes per day
Knekt, 1999 LUN01416 Finland	FMCHES, Prospective Cohort, Age: 20-69 years, M	138/ 4 545 25 years	Cancer registry	FFQ - study-specific	Incidence, lung cancer	Highest vs lowest	0.61 (0.39–0.95) Ptrend:0.10	Age, smoking status
					Incidence, lung cancer, current smokers	Highest vs lowest	0.70 (0.43–1.14)	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
					Incidence, lung cancer, non-smokers	Highest vs lowest	0.33 (0.11–1.02)	Age
Speizer, 1999 LUN01255 USA	NHS, Prospective Cohort, Age: 30-55 years, W	593/ 118 351 1 793 089 person-years	Hospital records and pathology reports	FFQ - study-specific	Incidence, lung cancer	Highest vs lowest	0.60 (0.40-0.80)	Age, energy intake, smoking habits

5.5.1.2 Serum alpha-carotene

Cohort studies

Main results:
Five studies (1066 cases) out of 9 cohort studies (10 publications) were included in the dose-response meta-analysis. A significant inverse association between serum alpha-carotene and lung cancer risk was observed. There was no evidence of heterogeneity.

There was not enough data to do stratified analysis by either smoking status or histological type. In a follow up study of NHANES III, an inverse association was found in current smokers. In the Multi-ethnic study (Epplein, 2009), an inverse association was observed in men but not in women (p interaction=0.01) and it was mainly in non-adenocarcinomas (p interaction =0.08). There was no effect modification by smoking (ever or never smoker).
In a Chinese study (Yuan, 2001) similar associations were observed in never and ever smokers, but only 20 cases were never smokers.

Sensitivity analyses:
The association remained significant in influence analysis; the summary RRs ranged from 0.41 (95% CI=0.27-0.61) when Goodman, 2003 was omitted to 0.48(95% CI=0.31-0.73) when Min, 2014 was omitted.

After excluding a study in high risk populations (CARET, Goodman, 2003) the inverse association did not changed materially and remained significant.

Study quality:
All studies included in the analysis were adjusted for main confounders including age and smoking status. All studies adjusted for intensity, duration of smoking and other smoking variables in addition to smoking status. One study was in high risk populations: exposed to asbestos (Goodman, 2003).
All studies measured blood alpha carotenes levels by HPLC.

Table 145 Serum alpha-carotene and lung 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 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 146 Serum alpha-carotene and lung cancer risk. Summary of the dose-response meta-analysis in the 2005 SLR and CUP

	2005 SLR	CUP
Increment unit used	0.05 µmol/L	Per 10 µg/100 mL
All studies		
Studies (n)	2	5
Cases (total number)	255	1066
RR (95%CI)	0.81 (0.45-1.44)	0.44 (0.31-0.64)
Heterogeneity (I^2, p-value)	87%, 0.22	0%, 0.72
P value Egger test		0.64

Table 147 Serum alpha-carotene and lung 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								
Gallicchio, 2008	2	319	Europe, North America, Australia and China	Incidence, lung cancer	Per 0.05 µmol/L	0.84 (0.44, 1.59)		50%, 0.16
	5	735			Highest vs lowest	0.89 (0.59, 1.33)		52%, 0.08

Table 148 Serum alpha-carotene and lung cancer risk. Main characteristics of studies included in the 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
Min, 2014 LUN26890 USA	A follow up study of NHANES III, Prospective Cohort, Age: ≥ 20 years, M/W	161/ 10 382	Death certificate	Blood sample, measured by HPLC	Mortality, lung cancer	≥ 6 vs ≤ 1 µg/dL	0.53 (0.32–0.88)	Age , sex, smoking status, ethnicity, education, alcohol consumption, exercise, pack-year of smoking, obesity, total cholesterol, daily fat intake and vegetable and fruit consumption	Distribution of persn-years, mid-points of exposure
		91/ 2957			Mortality, lung cancer, current smokers	≥ 4 vs ≤ 1 µg/dL	0.54 (0.31-0.94)		
		70/ 7425			Mortality, lung cancer, never/former smokers	≥ 7 vs ≤ 2 µg/dL	0.87 (0.42-1.78)		
Epplein, 2009 LUN20317 USA	MEC, Nested Case Control, Age: 45-75 years, M/W	136/ 272 controls Mean 1 year 8 month (cases)	SEER	Blood sample, (94% fasting for 8 h or more) (measured by HPLC)	Incidence, lung cancer, men	100 vs 24 ng/mL	0.24 (0.11-0.53) Ptrend:< 0.01	Age at specimen collection, fasting hours before blood draw, cigarettes pack-years, and pack-years squared, years of schooling and family history of	ng/mL converted to µg/100 mL
		71/ 142 controls Mean 1 year 8 month (cases)			Incidence, lung cancer, women	109 vs 22 ng/mL	1.52 (0.53-4.38) Ptrend:0.29		

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Missing data derived for analyses
								lung cancer	
Goodman, 2003 LUN00294 USA	CARET, Nested Case Control, Age: 45-69 years, M/W	276/ 276 controls 4 years	Self-reported in the trial, checked with pathology records	Non-fasting blood sample (measured by HPLC)	Incidence, lung cancer	51.5 vs 19 ng/mL	0.77 (0.45–1.32) Ptrend: 0.26	Age, sex, smoking, study centre at randomization, year of randomization pack-years of smoking and years quit smoking	Mid-points of exposure, number of cases and controls per quartiles, ng/mL converted to µg/100 mL
		174/ 174 controls 4 years			Incidence, lung cancer, men		1.13 (0.58–2.22) Ptrend: 0.96		
		102/ 102 controls 4 years			Incidence, lung cancer, women		0.43 (0.17–1.08) Ptrend: 0.06		
Ito, 2005 LUN26888 Japan	JACC, Nested Case Control, Age: 40-79 years, M/W	163/ 375/ controls 10 years	Death certificate	Serum sample (measured by HPLC)	Mortality, lung cancer, men	≥ 0.090 vs < 0.032 µmol/L	0.40 (0.18-0.86) Ptrend=0.02	Age, sex, smoking habits, participating institution and alcohol drinking	Mid-points of exposure , µmol/L converted to µg/100 mL
		48/ 112			Mortality, lung cancer, women	≥ 0.150 vs < 0.058 µmol/L	0.39 (0.07-2.1) Ptrend: 0.41		

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Missing data derived for analyses
Yuan, 2001 LUN00828 China	Shanghai, China, Nested Case Control, Age: 45-64 years, M	209/ 335 controls 12 years	Active follow-up, Shanghai cancer registry, death certificates	Non-fasting blood sample (measured by HPLC)	Incidence, lung cancer	≥ 1.61 vs < 0.71 µg/dL	1.15 (0.62-2.15) Ptrend: 0.79	Age at starting to smoke, average no. of cigarettes smoked/day, and smoking status at the time of blood draw (non-smoker, smoker)	Mid-points of exposure
		189/ 335			Incidence, lung cancer, ever smokers	Highest vs lowest	0.83 (0.54–1.28)		
		20/ 287			Incidence, lung cancer, never smokers		0.77 (0.30–2.01)		

Table 149 Serum alpha-carotene and lung cancer risk. Main characteristics of studies excluded from the 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 LUN20287	Hokkaido, Japan, Prospective Cohort Study, Age: 39-85 years, M/W	41/ 3 254 11.7 years	Mortality records	Fasting serum sample	Mortality, lung cancer	Per each logarithmically transformed serum value	0.62 (0.39-1.03)	Age, sex, smoking status, alcohol consumption, serum cholesterol and triglyceride, alanine aminotransferas e activity	HRs for one log increase
Ito, 2005 LUN26887 Japan	Hokkaido, Japan, Cohort Study, Prospective Cohort, Age: 39-79 years, M/W	31/ 3182 10.5 years	Death certificate	Fasting serum sample (measured in serum using HPLC method)	Mortality, lung cancer	High vs low	0.97 (0.41-2.30) Ptrend: 0.14	Age, sex, ALT activity, serum cholesterol, smoking habits	Superseded by Ito, 2006 LUN20287 No exposure levels Used in H vs L analysis only
Ito, 2003 LUN00342 Japan	JACC, Nested Case Control, Age: 40-79 years, M/W	147/ 311 controls 8 years	Death certificate	Serum	Mortality, lung cancer	≥ 0.10 vs < 0.03 μmol/L	0.35 (0.14−0.88) Ptrend: 0.02	Age, gender, participating institution, smoking and alcohol drinking	Superseded by Ito, 2005 LUN26888
Ratnasinghe,	YTC,	108/	Cancer registry	Serum collected	Incidence, lung	> 1 vs < 1	1.2 (0.7-2.0)	Age, radon	Only 2

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Reasons for exclusion
2000 LUN01072 China	Nested Case Control, Age: 40-74 years, High-risk miners men	216 controls 6 years	and annual screenings	2 years prior to diagnosis	cancer	µg/dL		exposure, tobacco exposure	categories of data Used in H vs L analysis only
Comstock, 1997 LUN01716 USA	CLUE I & CLUE II, Nested Case Control, Age: 25- years, M/W	157/ 312 controls	Death certificates and hospital discharge records	Blood sample	Incidence, lung cancer, men	Highest vs lowest	0.47 Ptrend:0.02		No data available to calculate missing confidence intervals
		101/ 202 controls			Incidence, lung cancer, women	Highest vs lowest	0.43 Ptrend: 0.11		

Figure 172 RR estimates of lung cancer by levels of serum alpha-carotene

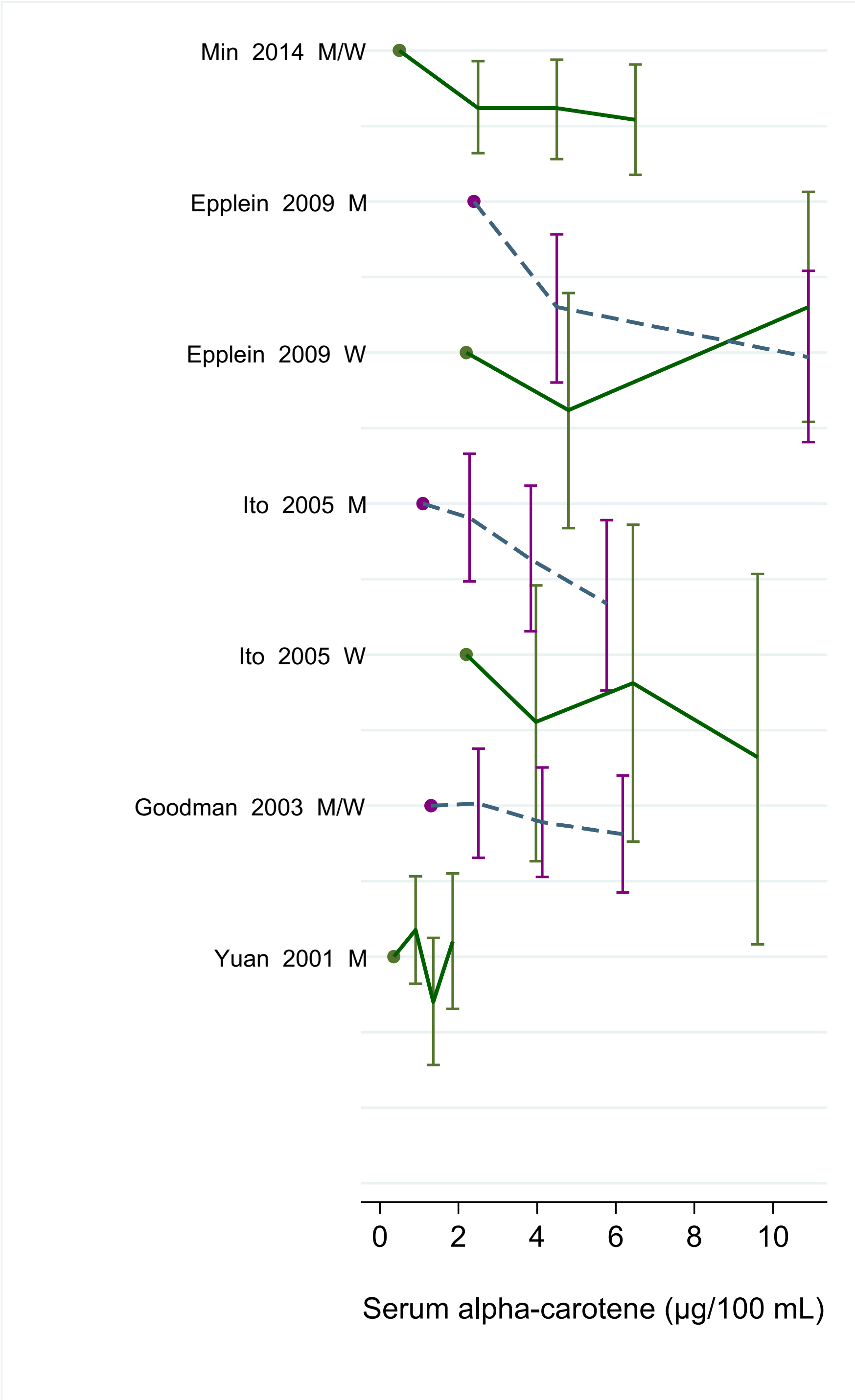


Figure 173 RR (95% CI) of lung cancer for the highest compared with the lowest level of serum alpha-carotene

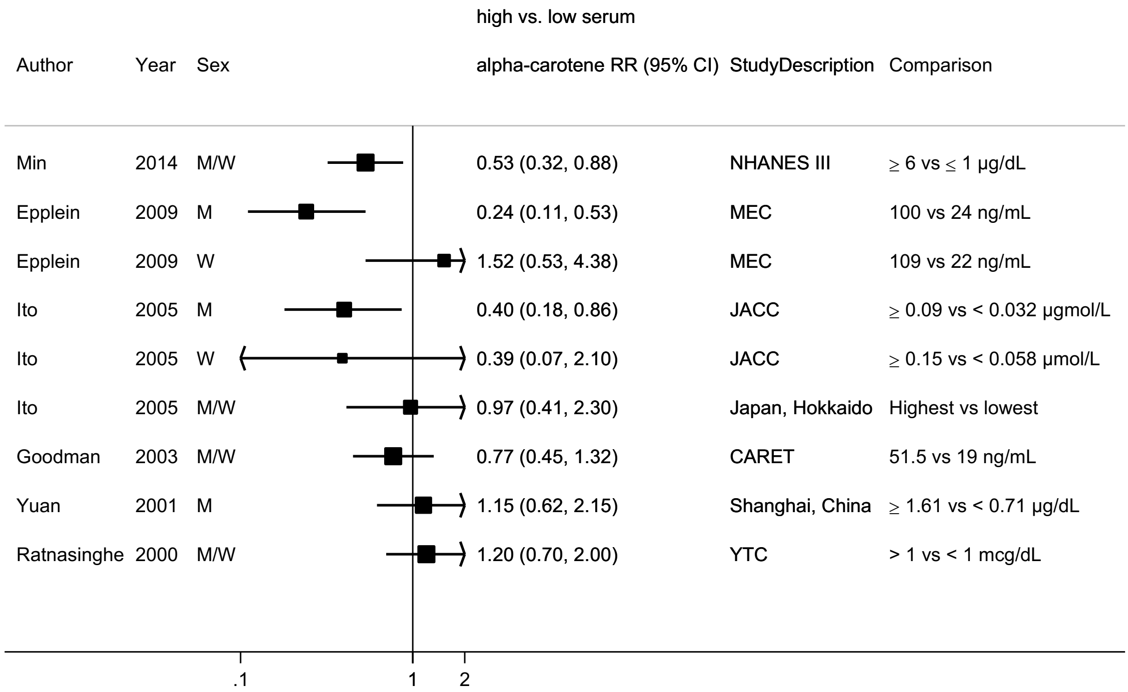


Figure 174 RR (95% CI) of lung cancer for 10 µg/100 mL increase of serum alpha-carotene

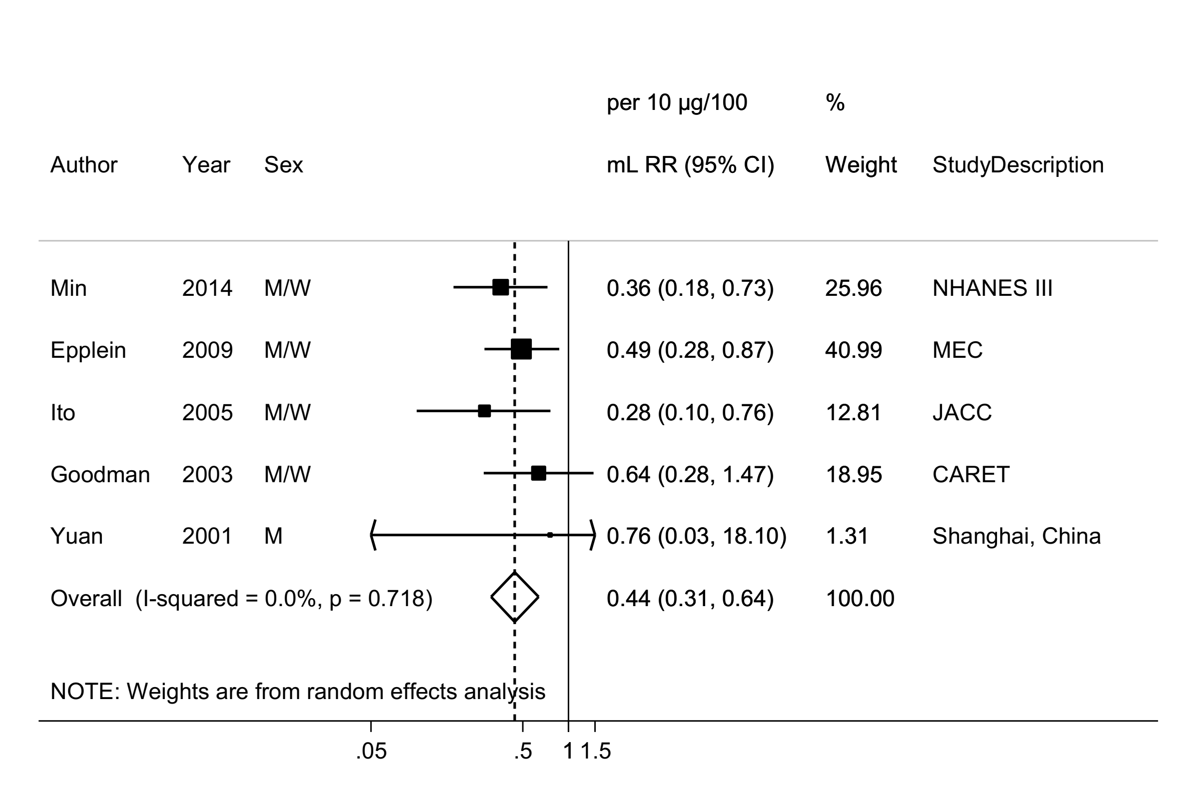
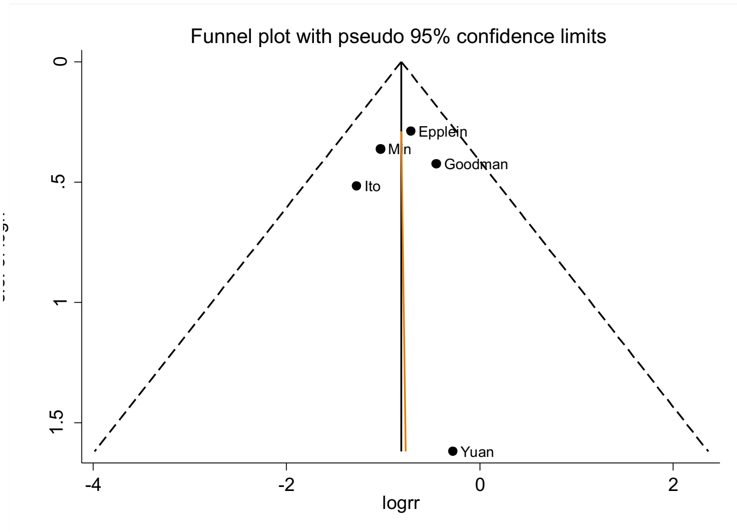


Figure 175 Funnel plot of studies included in the dose response meta-analysis of serum alpha-carotene and lung cancer



Egger's test p = 0.64

5.5.1.2 Dietary beta-cryptoxanthin

There was only one study identified in the CUP (Butler, 2013) and no meta-analysis was conducted. The 2005 SLR found a RR 0.97 (95% CI 0.960-0.998 per 10 µg /day, 2 studies).

Figure 176 Dietary beta-crytoxanthin and lung cancer risk. Results of meta-analyses and pooled analyses of prospective studies

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								
Gallicchio, 2008	5	2645	Europe, North America, Australia and China	Incidence, lung cancer	Per 1000 µg/day	0.99 (0.98, 1.00)		0.21, 0.28
	8	3928			Highest vs lowest	0.80(0.72, 0.89)		0%, 0.90
Pooled analysis								
Männistö, 2004	7	3155	North America and Europe	Incidence, lung cancer	Q5 vs Q1	0.76 (0.67–0.86)	< 0.001	0.95
		1915		Current smokers	Q4 vs Q1	0.70 (0.60–0.81)	< 0.001	0.47
		981		Former smokers		0.84 (0.69–1.03)	0.43	0.45
		259		Never smokers		0.77 (0.42–1.42)	0.80	0.02
		956		Adenocarcinoma		0.80 (0.68–0.93)	0.01	0.77
		538		Small cell carcinoma		0.66 (0.51–0.87)	0.02	0.19
		901		Squamous cell carcinoma		0.67 (0.56–0.80)	< 0.001	0.94

Table 150 Dietary beta-cryptoxanthin and lung cancer risk. Main characteristics of studies identified in the CUP and 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
Butler, 2013 LUN26852 China	SCHS, Prospective Cohort, Age: 45-74 years, M/W	1 130/ 61 321 12 years	Singapore cancer registry database	Validated FFQ	Incidence, lung cancer	Quartile 4 vs quartile 1	0.84 (0.71-0.99)	Age, sex, dialect group, interview year, number of cigarettes smoked per day, number of years since quit smoking, years of smoking
Neuhouser, 2003 LUN00354 USA	CARET, Prospective Cohort, Age: 45-69 years, M/W	742/14120 12 years	Clinical records pathology reports	FFQ - study-specific	Incidence, lung cancer	>4140 vs 1-1050 mcg/month	0.69 (0.48-0.99)	Age, sex, smoking status, total pack-years of smoking, asbestos exposure, race/ethnicity, and enrollment center
Rohan, 2002 LUN00605 USA	Canadian Screening, Case Cohort, Age: 40-59 years,	56 837 10 years	Cancer and death registries	FFQ - study-specific	Incidence, lung cancer	Per 10 mcg/day	0.97 (0.92-1.03)	Age, clinic site, energy intake, other, other nutrients, foods or supplements,

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors
	W							smoking habits
Holick, 2002 LUN00515 Finland	ATBC, Prospective Cohort, Age: 50-69 years, M, Smokers only	456/ 29 133 11 years	Cancer registry and medical record	FFQ - study-specific	Incidence, lung cancer current smokers	>56.03 vs 0.03-4.97 mcg/day	0.78 (0.58-1.05)	Age, years smoked, cigarettes/day, trial group, supplement use , energy intake, cholesterol, and fat
Michaud, 2000 LUN01014 USA	HPFS and NHS, Prospective Cohort, Age: 30-75 years, M/W,	275/ 124 207 12 years	Questionnaire, medical record and pathology report	FFQ - study-specific	Incidence, lung cancer, men	170 vs 14 mcg/day	0.73 (0.50-1.06)	Age, energy intake, other, smoking habits
		519			Women	118 vs 15 mcg/day	0.87 (0.66-1.15)	
		84			Non-smokers	Quintile 5 vs quintile 1	0.71 (0.35-1.42)	
		345			Former smokers	Quintile 5 vs quintile 1	0.69 (0.49-0.96)	
		357			Current smokers	Quintile 5 vs quintile 1	1.05 (0.75-1.49)	
					Adenocarcinom a	Quintile 5 vs quintile 1	0.57 (0.29-1.10)	
Voorrips, 2000 LUN01121	NLCS, Case Cohort,	35/ 58 279	Cancer registry and pathology	FFQ - study-specific	Incidence, lung cancer	356 vs 12 mcg/d	082 (0.59-1.13)	Age, educational level, family

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors
Netherlands	Age: 55-69 years, M,	3 years	reports					history of specific cancer
Knekt, 1999 LUN01416 Finland	Finnish Mobile Clinic Health Examination Survey, Prospective Cohort, Age: 20-69 years, M	4 545 25 years	Cancer registry	FFQ - study-specific	Incidence, lung cancer current smokers	Tertile 3 vs tertile 1	0.82 (0.51-1.33)	Age
					Non-smokers	Tertile 3 vs Tertile 1	0.37 (0.12-1.12)	
					Incidence, lung cancer	4.1 vs 1.3 mcg/day	0.72 (0.46-1.11)	Age, smoking habits

5.5.1.2 Serum Beta-cryptoxanthin

Cohort studies

Summary

Main results:
Six studies (1088 cases) out of 9 cohort studies (10 publications) were included in the dose-response meta-analysis. No significant association between serum beta-cryptoxanthin and lung cancer was observed. There was evidence of substantial heterogeneity across studies. There was not enough data to do stratified analysis by smoking status, sex, histological and outcome type.

Sensitivity analyses:
In influence analysis, a significant inverse association was observed when excluding a study in high-risk miners in China with 10.93 % of weight in the meta-analysis (Ratnasinghe, 2003). This study reported a strong positive association and visual inspection of the funnel plot shows its result is outside the expected limits.
The summary RR did not change materially when the other three studies were omitted in turn. The summary RRs ranged from 0.71 (95% CI=0.55-0.91) when Ratnasinghe, 2003 was omitted to 0.86 (95% CI=0.63-1.17) when Yuan, 2001 was omitted.

Study quality:
All studies included in the analysis were adjusted for main confounders including age and smoking status. All studies adjusted for intensity, duration of smoking and other smoking variables in addition to smoking status.

Table 151 Serum beta-cryptoxanthin and lung 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 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 152 Serum beta-cryptoxanthin and lung cancer risk. Summary of the dose-response meta-analysis in the 2005 SLR and CUP

	2005 SLR	CUP
Increment unit used	0.05 μmol/L	10 μg/100 mL
All studies		
Studies (n)	2	6
Cases (total number)	255	1088
RR (95%CI)	0.95 (0.69-1.25)	0.80 (0.57-1.12)
Heterogeneity (I^2, p-value)	97%	76.7%, 0.001
P value Egger test		0.23

Stratified and sensitivity analysis (no analyses conducted in the 2005 SLR)		
Geographic location	**Asia**	**North America**
Studies (n)	3	3
RR (95%CI)	0.82 (0.24-2.87)	0.76 (0.59-0.98)
Heterogeneity (I^2, p-value)	88.6%, < 0.001	49.3%, 0.14

Table 153 Serum beta-cryptoxanthin and lung 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								
Gallicchio*, 2008	2	319	Europe, North America, Australia and China	Incidence, lung cancer	Per 0.05 µmol/L	1.14 (0.75-1.72)		90%, < 0.02
	5	835			Highest vs lowest	0.82 (0.40-1.68)		75%, < 0.01

Table 154 Serum beta-cryptoxanthin and lung cancer risk. Main characteristics of studies included in the 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
Min, 2014 LUN26890 USA	A follow up study of NHANES III, Prospective Cohort, Age: ≥ 20 years, M/W	161/ 10 382	Death certificate	Blood sample, measured by HPLC	Mortality, lung cancer	≥ 13 vs ≤ 5 µg/dL	0.56 (0.33-0.96)	Age , sex, smoking status, ethnicity, education, alcohol consumption, exercise, pack-year of smoking, obesity, total	Mid-points of exposure, person years

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Missing data derived for analyses
		91/ 2957			Mortality, lung cancer, current smokers	≥ 10 vs ≤ 4 µg/dL	0.39 (0.19-0.80)	cholesterol, daily fat intake and vegetable and fruit consumption	
		70/ 7425			Mortality, lung cancer, never/former smokers	≥ 14 vs ≤ 6 µg/dL	0.84 (0.42-1.67)		
Epplein, 2009 LUN20317 USA	MEC, Nested Case Control, Age: 45-75 years, M/W	136/ 272 controls	SEER Registry	Fasting blood sample (94%)	Incidence, lung cancer, men	353 vs 82 ng/mL	0.33 (0.15-0.73) Ptrend:< 0.01	Age at blood draw, pack years of smoking, hours of fasting before blood draw, family history of lung cancer, matching variables, years of education	ng/mL converted to µg/100 mL
		71/ 142 controls			Incidence, lung cancer, women	413 vs 82 ng/mL	1.58 (0.59-4.23) Ptrend:0.32		
Goodman, 2003 LUN00294 USA	CARET, Nested Case Control, Age: 45-69 years, M/W	276/ 276 controls 4 years	Primary outcome of the trial. Active follow-up with confirmation by clinical records and pathology reports	Non-fasting blood sample	Incidence, lung cancer	87.0 vs 39.5 ng/mL	0.76 (0.44-1.28) Ptrend:0.07	Age, sex, smoking, study centre at randomization, year of randomization pack-years of smoking and years quit	Mid-points of exposure, number of cases and controls per quartiles, ng/mL converted to µg/ 100 mL
		174/ 174 controls			Incidence, lung cancer, men		1.21 (0.62-2.37) Ptrend:0.97		
		102/ 102 controls			Incidence, lung cancer, women		0.34 (0.14-0.81) Ptrend:<0.01		

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Missing data derived for analyses
								smoking	
Ito, 2005 LUN26888 Japan	JACC, Nested Case Control, Age: 40-79 years, M/W	163/ 375 controls 10 years	Death certificate	Serum sample (measured by HPLC)	Mortality, lung cancer, men	≥ 0.31 vs < 0.08 µmol/L	0.32 (0.13-0.78) Ptrend: 0.03	Age, sex, smoking habits, participating institution and alcohol drinking	Mid-points of exposure , µmol/L converted to µg/100 mL
		48/ 122			Mortality, lung cancer, women	≥ 0.49 vs < 0.19 µmol/L	1.00 (0.22-4.48) Ptrend: 0.74		
Ratnasinghe, 2003 LUN00362 China	YTC, Nested Case Control, Age: 40-74 years, High-risk miners men	108/ 216 controls 6 years	Cancer registry and annual screenings	Serum collected 2 years prior to diagnosis	Incidence, lung cancer	> 8 vs < 4 µg/dL	2.9 (1.4-0.58) Ptrend: 0.03	Age, radon exposure, smoking habits, pack-years	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
Yuan, 2001 LUN00828 China	Shanghai, China, Nested Case Control, Age: 45-64 years, M	209/ 335 controls 12 years	Active follow-up, Shanghai cancer registry, death certificates	Non-fasting blood sample	Incidence, lung cancer	≥ 4.54 vs < 1.81 µg/dL	0.45 (0.22-0.92) Ptrend: 0.02	Age at starting to smoke, average no. of cigarettes smoked/day, and smoking status at the time of blood draw (non-smoker, smoker)	Mid-points of exposure
		189/ 335			Incidence, lung cancer, ever smokers	Highest vs lowest	0.58 (0.36–0.93)		
		20/ 287			Incidence, lung cancer, never smokers		0.90 (0.31–2.60)		

Table 155 Serum beta-cryptoxanthin and lung cancer risk. Main characteristics of studies excluded from the 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 LUN20287	Hokkaido, Japan, Prospective Cohort Study, Age: 39-85	41/ 3254 11.7 years	Mortality records	Fasting serum sample	Mortality, lung cancer	Per each logarithmically transformed serum value	0.99 (0.63-1.56)	Age, sex, smoking status, alcohol consumption, serum	HRs for one log increase

Author, Year, WCRF Code, Country	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							cholesterol and triglyceride, alanine aminotransferase activity	
Ito, 2005 LUN26887 Japan	Japan, Hokkaido Cohort Study, Prospective Cohort, Age: 39-79 years, M/W	31/ 3182 10.5 years	Death certificate	Fasting serum sample (measured in serum using HPLC method)	Mortality, lung cancer	High vs low	0.66 (0.18-2.36) Ptrend: 0.79	Age, sex, ALT activity, serum cholesterol, smoking habits	Superseded by Ito, 2006 LUN20287 No exposure levels Used in H vs L analysis only
Ito, 2003 LUN00342 Japan	JACC, Nested Case Control, Age: 40-79 years, M/W	147/ 39 140 8 years	Population death registries	Blood sample	Mortality, lung cancer	≥ 0.35 vs < 0.09 µmol/L	0.44 (0.17-1.16) Ptrend:0.11	Age, sex, alcohol consumption, BMI, other, other nutrients, foods or supplements, smoking habits	Superseded by Ito, 2005 LUN26888
Comstock, 1997 LUN01716 USA	CLUE I & CLUE II, Nested Case Control, Age: 25- years, M/W	157/ 313 controls	Death certificates and hospital discharge records	Blood sample	Incidence, lung cancer, men	Highest vs lowest	0.32 Ptrend: < 0.01		No data available to calculate missing intervals
		101/ 102 controls			Incidence, lung cancer, women		0.20 Ptrend: < 0.01		

Figure 177 RR estimates of lung cancer by levels of serum beta-cryptoxanthin

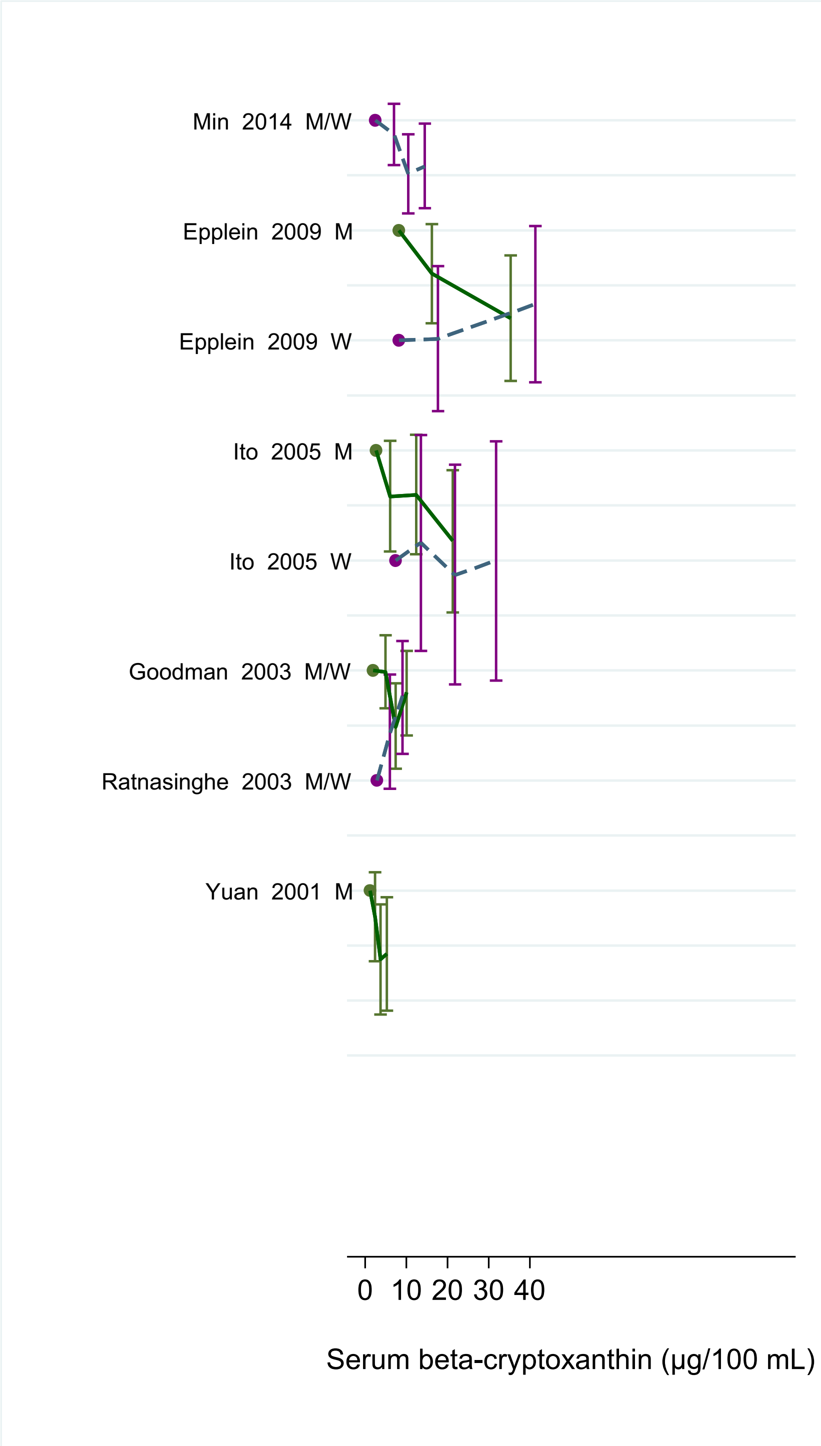


Figure 178 RR (95% CI) of lung cancer for the highest compared with the lowest level of serum beta-cryptoxanthin

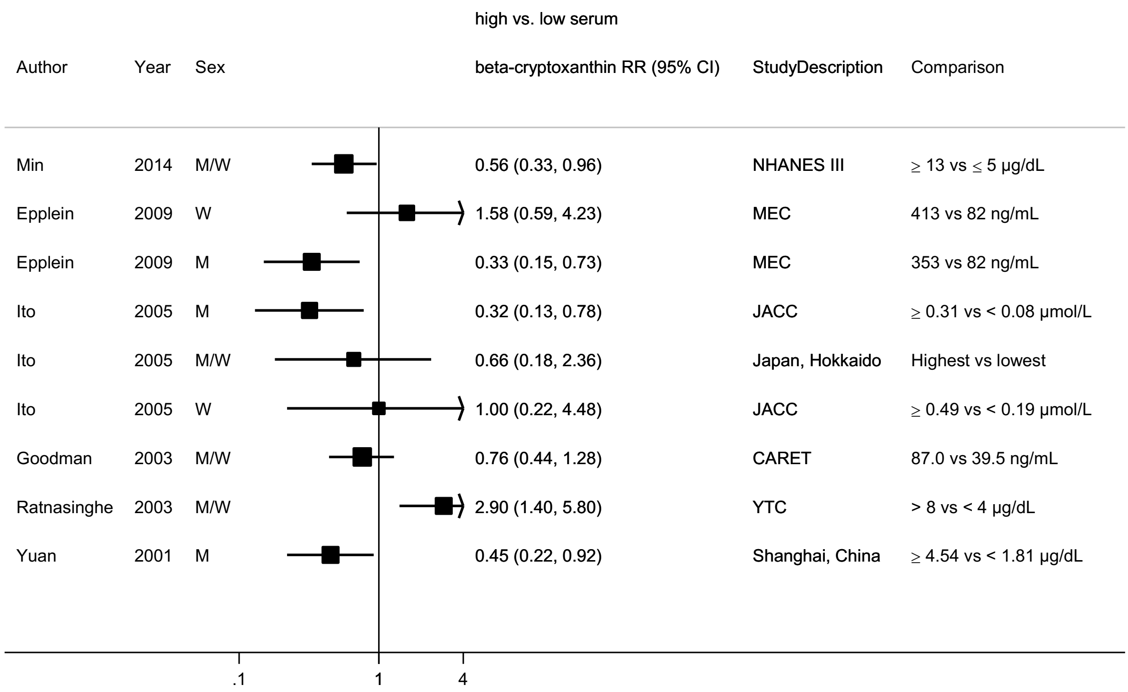


Figure 179 RR (95% CI) of lung cancer for 10 μg/100 mL increase of serum beta-cryptoxanthin

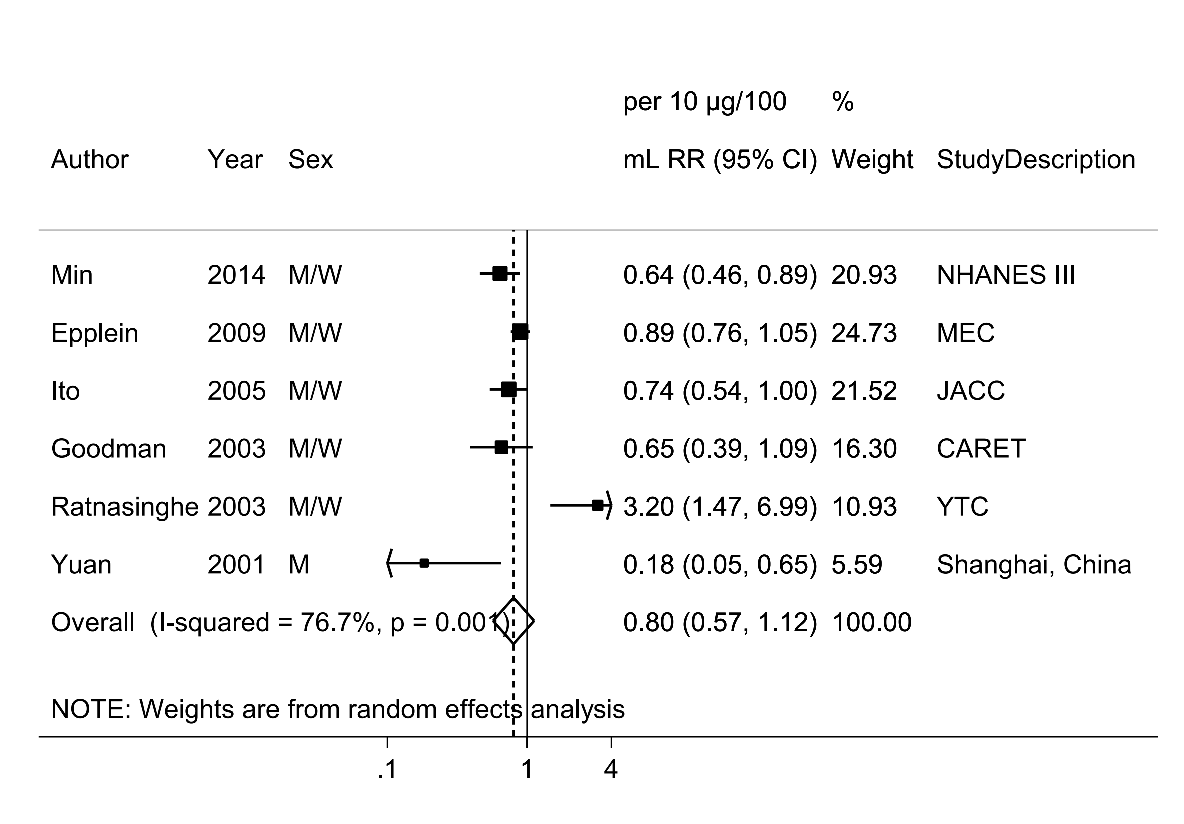
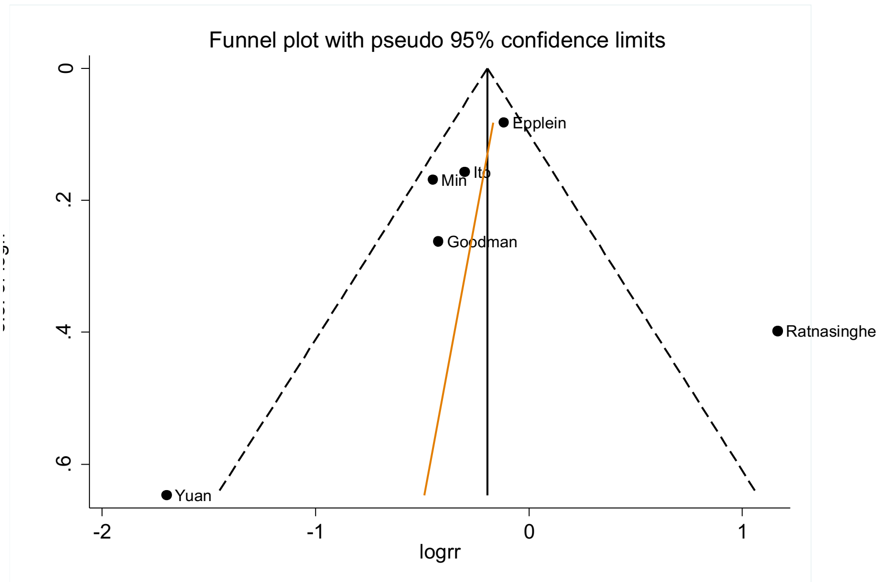
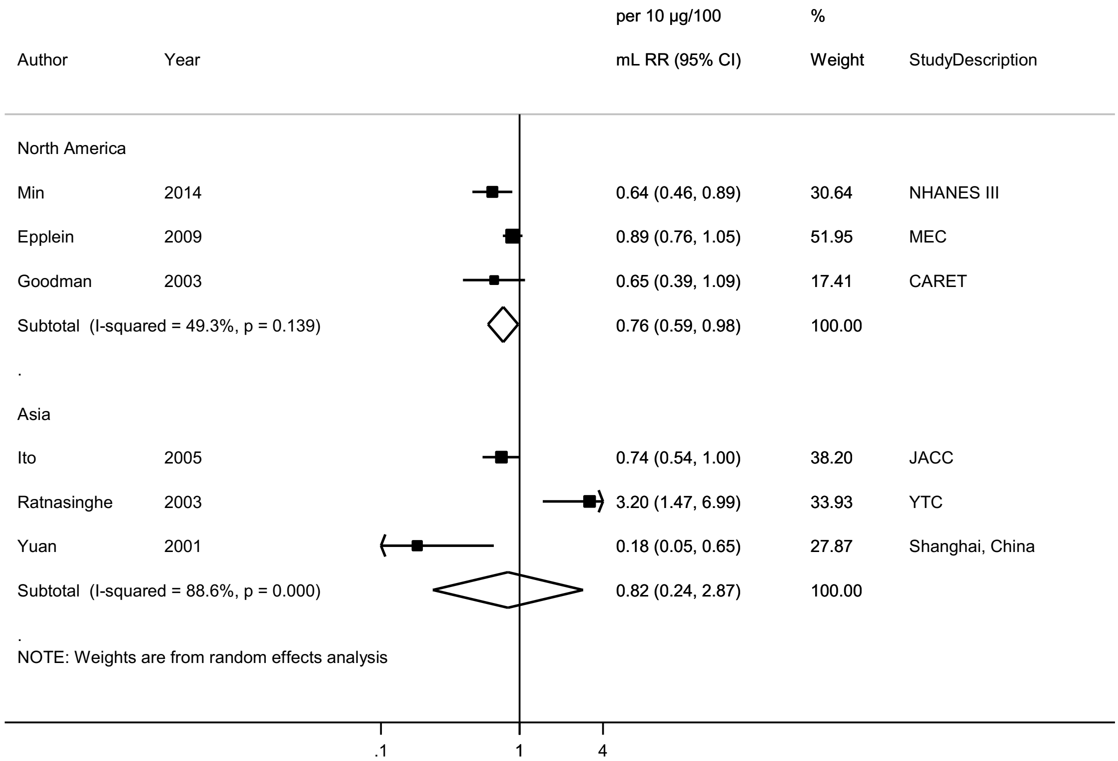


Figure 180 Funnel plot of studies included in the dose response meta-analysis of Serum beta-cryptoxanthin and lung cancer



Egger's test p=0.23

Figure 181 RR (95% CI) of lung cancer for 10 µg/100 mL increase of serum beta-cryptoxanthin by geographic area



5.5.2 Dietary Lycopene

No new study identified during the CUP. The 2005 SLR included 3 studies in dose-response meta-analysis, the overall RR was 0.89 (95% CI= 0.73-1.07) per 1000 µg /day.

Table 156 Dietary lycopene and lung cancer risk. Results of meta-analyses and pooled analyses of prospective studies

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								
Gallicchio, 2008	5	3848	Europe, North America, Australia and China	Incidence, lung cancer	Per 1000 µg/day	0.97 (0.94, 1.00)		0.81, <0.001
	9	2800			Highest vs lowest	0.86(0.77, 0.97)		20%, 0.26
Pooled analysis								
Männistö, 2004	7	3155	North America and Europe	Incidence, lung cancer	Q5 vs Q1	0.91 (0.78–1.07)	0.42	0.11
		1915		Current smokers	Q4 vs Q1	0.81 (0.70–0.94)	0.06	0.65
		981		Former smokers		1.05 (0.86–1.27)	0.76	0.42
		259		Never smokers		0.86 (0.60–1.23)	0.29	0.68
		956		Adenocarcinoma		0.93 (0.79–1.09)	0.64	0.96
		538		Small cell carcinoma		0.95 (0.79–1.14)	0.98	0.96
		901		Squamous cell carcinoma		0.86 (0.72–1.02)	0.11	0.95

Table 157 Dietary lycopene and lung cancer risk. Main characteristics of studies included in the SLR 2005

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors
Neuhouser, 2003 LUN00354 USA	CARET, Prospective Cohort, Age: 45-69 years, M/W	326/ 14 120 8 years	Primary outcome of the trial. Active follow-up with confirmation by clinical records and pathology reports	FFQ - study-specific	Incidence, lung cancer, placebo arm	≥ 7075 vs ≤ 2484 µg /day	0.94 (0.67–1.32) Ptrend:0.80	Age, sex, clinic site, environmental factors, ethnicity/race, smoking habits
					Incidence, lung cancer, intervention arm		0.78 (0.57–1.06) Ptrend:0.08	
Yuan, 2003 LUN00218 Singapore	SCHS, Prospective Cohort, Age: 45-47 years, M/W	482/ 62 392 8 years	Cancer registry and, birth and death registries	FFQ - study-specific	Incidence, lung cancer	1490 vs 70 µg/1000 kcal	0.89 (0.65–1.21)	Age, sex, BMI, year of interview, education, ethnicity/race, cigarettes /day, years smoking, years since quitting smoking for former smokers
					Incidence, lung cancer	Per 1420 µg/1000 kcal	0.65 (0.33–1.29)	
		268			Current smokers		0.74 (0.29–1.85)	
		71			Former smokers		0.70 (0.12–4.01)	
		145			Never smokers		0.53 (0.16–1.80)	
Rohan, 2002 LUN00605 Canada	CNBSS, Case Cohort, Age: 40-59 years, W	155/ 5361 controls 10 years	Record linkage to Canadian Centre Database and to National Mortality Database	FFQ - study-specific	Incidence, lung cancer	Per 1000 µg /day	1.00 (0.98-1.02)	Age, clinic site, energy intake, other, other nutrients, foods or supplements, smoking habits
						14110.4 vs 4464.3 µg /day	1.04 (0.61–1.76) Ptrend: 0.23	
		101			Incidence, lung	Per 1000	1.00 (0.98–1.02)	

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors
					cancer, current smokers	µg /day		
		36			Incidence, lung cancer, former smokers		1.00 (0.97–1.03)	
		18			Incidence, lung cancer, never smokers		0.96 (0.91–1.01)	
Holick, 2002 LUN00515 Finland	ATBC, Prospective Cohort, Age: 50-69 years, M, Smokers only	1 644/ 29 133 11 years	Finnish Cancer Registry and the Register of Causes of Death	FFQ - study-specific	Incidence, lung cancer	> 1168 vs < 232 µg /day	0.72 (0.61-0.84) Ptrend:< 0.0001	Age, energy intake, other nutrients, foods or supplements, smoking habits
Michaud, 2000 LUN01014 USA	HPFS, Prospective Cohort, Age: 30-75 years, M	275/ 46 924 10 years	Active follow-up, cases confirmed with medical and pathology records	FFQ - study-specific	Incidence, lung cancer, men	18 195 vs 3697 µg /day	0.86 (0.59 1.25) Ptrend: 0.51	Age (5-y categories), smoking status (never, past with time since quitting, or current with 6 categories), age at start of smoking (< 15 y, 15–19 y, 20–29 y, ≥30 y, or
	NHS, Prospective Cohort, Age: 30-75 years,	519/ 77 283 12 years			Incidence, lung cancer, women	14 676 vs 4398 µg /day	0.77 (0.60, 1.00) Ptrend:0.18	

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
	W							never smokers), quintiles of energy intake, and time period
	HPFS & NHS, Prospective Cohort, Age: 30-75 years, M/W	794/ 124 207 10-12 years			Incidence, lung cancer, men and women pooled	Highest vs lowest	0.80 (0.64, 0.99) Ptrend:0.10	Additionally adjusted by sex
		357			Incidence, lung cancer, men and women pooled, current smokers		0.63 (0.45, 0.88)	
		345			Incidence, lung cancer, men and women pooled , former smokers		0.96 (0.70, 1.31)	Additionally adjusted by age at start smoking and time since quitting
		84			Incidence, lung cancer, men and women pooled, never smokers		0.86 (0.44, 1.69)	
Voorrips, 2000a LUN01121 Netherlands	NLCS, Case Cohort, Age: 55-69 years, M	939/ 1525 controls 6.3 years	Regional cancer registries and computerized national database of pathology report	FFQ - study-specific	Incidence, lung cancer	2035 vs 132 µg /day	1.12 (0.77–1.61) Ptrend:0.04	Age, educational level, family history of specific cancer, smoking habits, years of
		487			Incidence, lung cancer, current smokers	Highest vs lowest	0.81 (0.53–1.23) Ptrend:0.74	

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors
		312	(PALGA)		Incidence, lung cancer, former smokers		1.06 (0.64–1.74) Ptrend:0.68	smoking cigarettes, cigarettes per day
		35			Incidence, lung cancer, never smokers		1.54 (0.61–3.90) Ptrend:0.26	
Knekt, 1999 LUN01416 Finland	FMCHES, Prospective Cohort, Age: 20-69 years, M	138/ 4545 25 years	Cancer Registry	FFQ - study-specific	Incidence, lung cancer	Highest vs lowest	1.00 (0.67–1.50) Ptrend:0.77	Age, smoking status
					Incidence, lung cancer, current smokers	Highest vs lowest	1.26 (0.81–1.96)	Age
					Incidence, lung cancer, non-smokers		0.46 (0.16–1.33)	
Steinmetz, 1993 LUN02740 USA	IWHS, Nested Case Control, Age: 55-69 years, W, Post-menopausal	138/ 2814 controls 4 years	Iowa Health Registry (part of SEER registry)	FFQ - study-specific	Incidence, lung cancer	> 5 vs 0-1 servings/week	1.21 (0.69-2.10)	Age, energy intake, pack years of smoking
Speizer, 1999 LUN01255 USA	NHS, Prospective Cohort,	593/ 118 351 1 793 089	Active follow-up, cases confirmed with	FFQ - study-specific	Incidence, lung cancer	Highest vs lowest	0.80 (0.60-1.10) Ptrend:0.76	Age, energy intake, smoking habits

Author, Year, 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: 30-55 years, W	person-years	medical and pathology records					

5.5.2 Serum Lycopene

Cohort studies

Main results:
Five studies (1066 cases) out of 8 cohort studies (9 publications) were included in the dose-response meta-analysis. A borderline significant inverse association was observed.

There was not enough data to do stratified analysis by either smoking status or histological type. In the Multi-ethnic study (Epplein, 2009), there was no effect modification by smoking (ever or never smoker); an inverse association was observed in men but not in women (p interaction=0.01) and
In a Chinese study (Yuan, 2001) similar associations were observed in never and ever smokers, but only 20 cases were never smokers.

There was evidence of moderate heterogeneity and publication or small study bias.

Sensitivity analyses:
In influence analysis the summary RRs ranged from 0.86 (95% CI=0.74-1.00) when Goodman, 2003 was omitted to 0.92(95% CI=0.86-0.99) when Ito, 2005 was omitted.

Study quality:
All studies included in the analysis were adjusted for main confounders including age and smoking status. All studies adjusted for intensity, duration of smoking and other smoking variables in addition to smoking status. One study was in high risk populations: exposed to asbestos (Goodman, 2003). All studies measured blood alpha carotenes levels by HPLC.

Table 158 Serum lycopene and lung 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 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 159 Serum lycopene and lung cancer risk. Summary of the dose-response meta-analysis in the 2005 SLR and CUP

	2005 SLR	CUP
Increment unit used		Per 10 µg/100 mL
All studies		
Studies (n)		5
Cases (total number)		1066
RR (95%CI)		0.90 (0.82-1.00)
Heterogeneity (I^2, p-value)		35.9%, 0.18
P value Egger test		< 0.01

Table 160 Serum lycopene and lung 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								
Gallicchio, 2008	1	211	North America, Japan, China,	Incidence, lung cancer	Per 0.05 µmol/L	0.82 (0.68, 0.98)		
	4	727			Highest vs lowest	0.71 (0.51, 0.98)		0%, 0.53

Table 161 Serum lycopene and lung 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
Min, 2014 LUN26890 USA	A follow up study of NHANES III, Prospective Cohort, Age: ≥ 20 years, M/W	161/ 10 382	Death certificate	Blood sample, measured by HPLC	Mortality, lung cancer	≥ 29 vs ≤ 13 µg/dL	0.67 (0.42–1.07)	Age , sex, smoking status, ethnicity, education, alcohol consumption, exercise, pack-year of smoking, obesity, total cholesterol, daily fat intake and vegetable and fruit consumption	Distribution of person-years, mid-points of exposure
		91/ 2957			Mortality, lung cancer, current smokers	≥ 25 vs ≤ 13 µg/dL	0.80 (0.41-1.56)		
		70/ 7425			Mortality, lung cancer, never/former smokers	≥ 30 vs ≤ 15 µg/dL	0.99 (0.46-2.17)		
Epplein, 2009 LUN20317 USA	MEC, Nested Case Control, Age: 45-75 years, M/W	136/ 272 controls Mean 1 year 8 month (cases)	SEER	Blood sample, (94% fasting for 8 h or more) measured by HPLC	Incidence, lung cancer, men	463 vs 164 ng/mL	0.36 (0.18-0.75) Ptrend:< 0.01	Age at specimen collection, fasting hours before blood draw, cigarettes pack-years, and pack-years squared, years of schooling and	ng/mL converted to µg/100 mL
		71/ 142 controls Mean 1 year 8 month (cases)			Incidence, lung cancer, women	401 vs 144 ng/mL	1.94 (0.72-5.22) Ptrend:0.15		

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Missing data derived for analyses
								family history of lung cancer	
Goodman, 2003 LUN00294 USA	CARET, Nested Case Control, Age: 45-69 years, M/W	276/ 276 controls 4 years	Self-reported in the trial, checked with pathology records	Non-fasting blood sample measured by HPLC	Incidence, lung cancer	437 vs 213 ng/mL	0.86 (0.52–1.43) Ptrend: 0.31	Age, sex, smoking, study centre at randomization, , year of randomization pack-years of smoking and years quit smoking	Mid-points of exposure, number of cases and controls per quartiles, ng/mL converted to µg/100 mL
		174/ 174 controls 4 years			Incidence, lung cancer, men		1.07 (0.56–2.05) Ptrend: 0.87		
		102/ 102 controls 4 years			Incidence, lung cancer, women		0.61 (0.27–1.38) Ptrend: 0.16		
Ito, 2005 LUN26888 Japan	JACC, Nested Case Control, Age: 40-79 years, M/W	163/ 375/ controls 10 years	Death certificate	Serum sample (measured by HPLC)	Mortality, lung cancer, men	≥ 0.15 vs < 0.04 µmol/L	0.44 (0.19-1.05) Ptrend=0.03	Age, sex, smoking habits, participating institution and alcohol drinking	Mid-points of exposure , µmol/L converted to µg/100 mL
		48/ 112			Mortality, lung cancer, women	≥ 0.20 vs < 0.07 µmol/L	0.63(0.12-3.25) Ptrend: 0.5		

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Missing data derived for analyses
Yuan, 2001 LUN00828 China	Shanghai, China, Nested Case Control, Age: 45-64 years, M	209/ 335 controls 12 years	Active follow-up, Shanghai cancer registry, death certificates	Non-fasting blood sample measured by HPLC	Incidence, lung cancer	≥ 4.31 vs < 1.61 µg/dL	0.59 (0.31–1.14) Ptrend: 0.15	Age at starting to smoke, average no. of cigarettes smoked/day, and smoking status at the time of blood draw (non-smoker, smoker)	Mid-points of exposure
		189/ 335			Incidence, lung cancer, ever smokers	Highest vs lowest	0.65 (0.23–1.83)		
		20/ 287			Incidence, lung cancer, never smokers		0.85 (0.55–1.30)		

Table 162 Serum lycopene and lung cancer risk. Main characteristics of studies excluded from the 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 LUN20287	Hokkaido, Japan, Prospective Cohort Study, Age: 39-85 years, M/W	41/ 3 254 11.7 years	Mortality records	Fasting serum sample	Mortality, lung cancer	Per each logarithmically transformed serum value	0.78 (0.52-1.17)	Age, sex, smoking status, alcohol consumption, serum cholesterol and triglyceride, alanine aminotransferas e activity	HRs for one log increase
Ito, 2005 LUN26887 Japan	Hokkaido, Japan, Cohort Study, Prospective Cohort, Age: 39-79 years, M/W	31/ 3182 10.5 years	Death certificate	Fasting serum sample (measured in serum using HPLC method)	Mortality, lung cancer	High vs low	0.93 (0.39-2.24) Ptrend: 0.76	Age, sex, ALT activity, serum cholesterol, smoking habits	Superseded by Ito, 2006 LUN20287 No exposure levels Used in H vs L analysis only
Ito, 2003 LUN00342 Japan	JACC, Nested Case Control, Age: 40-79 years, M/W	147/ 311 controls 8 years	Death certificate	Serum sample (measured by HPLC)	Mortality, lung cancer	≥ 0.38 vs < 0.10 μmol/L	0.46 (0.21-1.04) Ptrend: 0.09	Age, gender, participating institution, smoking and alcohol drinking	Superseded by Ito, 2005 LUN26888
Comstock, 1997	CLUE I & CLUE II,	157/ 312 controls	Death	Blood sample	Incidence, lung cancer, men	Highest vs lowest	1.10 Ptrend:0.25		No data available 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
LUN01716 USA	Nested Case Control, Age: 25- years, M/W		certificates and hospital discharge records						calculate missing confidence intervals
		101/ 202 controls			Incidence, lung cancer, women	Highest vs lowest	0.83 Ptrend: 0.83		

Figure 182 RR estimates of lung cancer by levels of serum lycopene

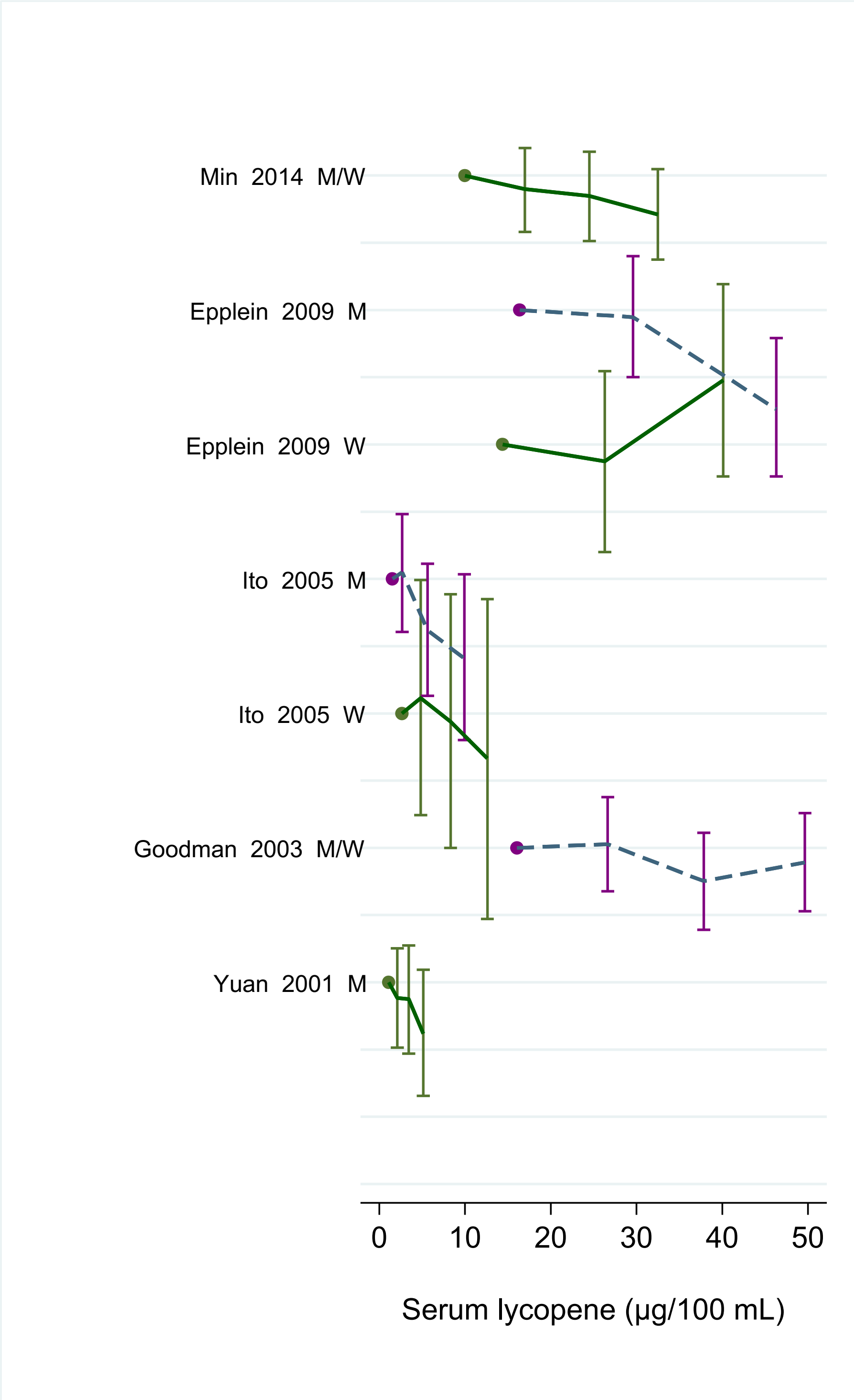


Figure 183 RR (95% CI) of lung cancer for the highest compared with the lowest level of serum lycopene

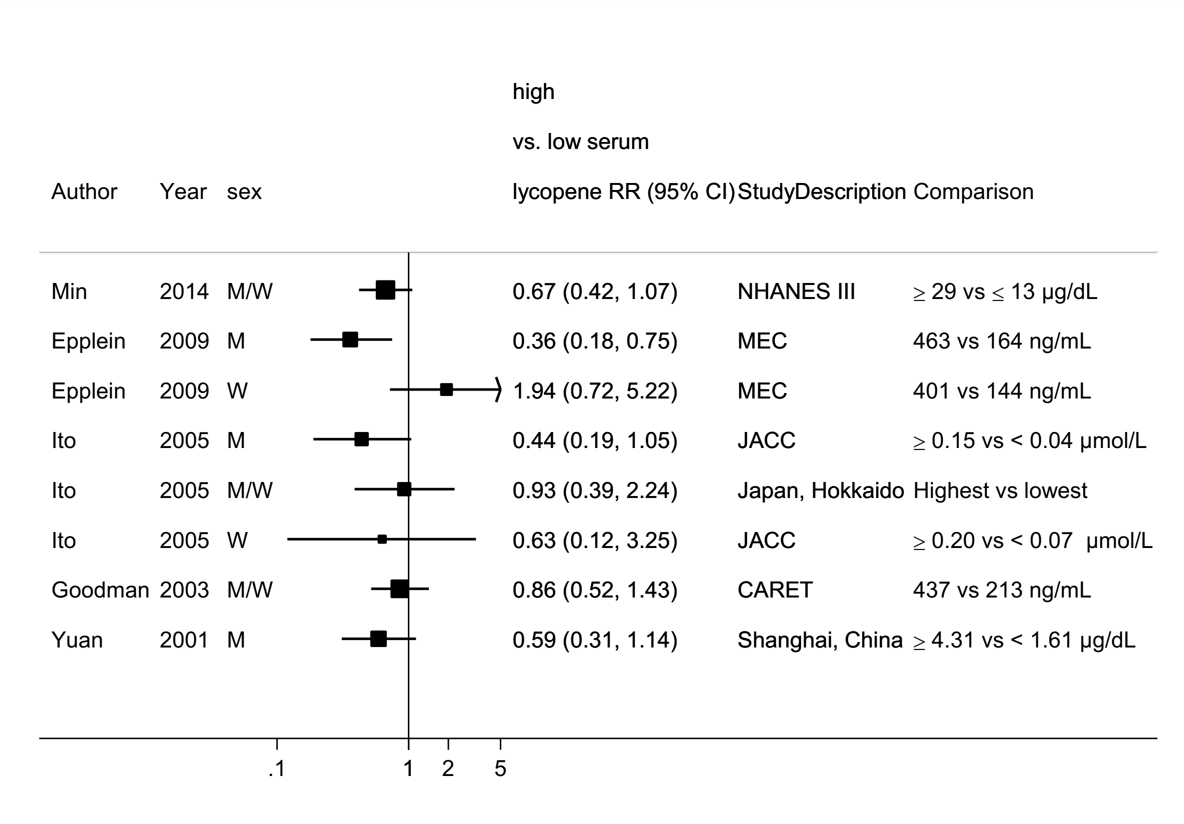


Figure 184 RR (95% CI) of lung cancer for 10 µg/100 mL increase of serum lycopene

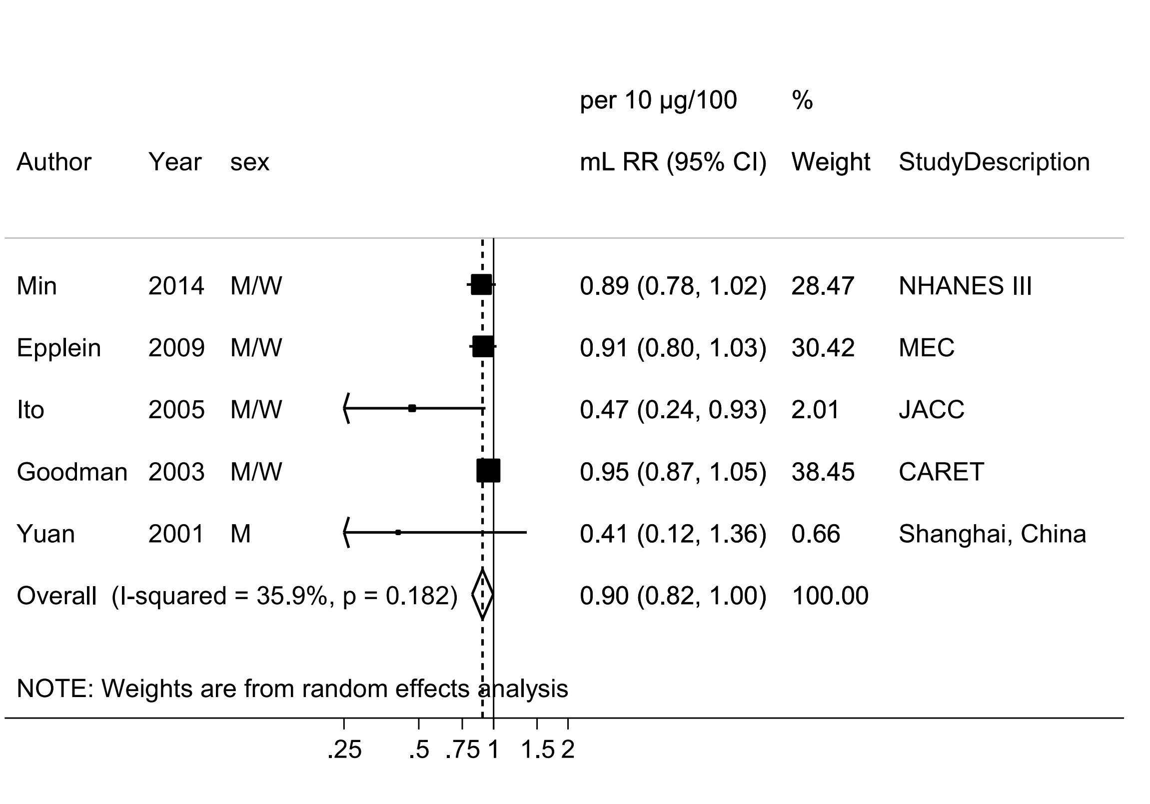
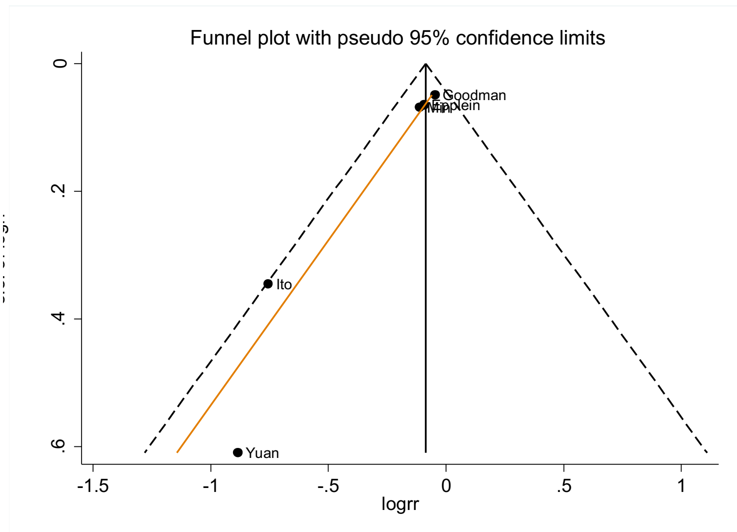


Figure 185 Funnel plot of studies included in the dose response meta-analysis of serum lycopene and lung cancer



Egger's test p≤ 0.01

5.5.2 Dietary Lutein and zeaxanthin

No new study identified during the CUP. The 2005 SLR included 2 studies in dose-response meta-analysis, the overall RR was 0.98 (95% CI= 0.81-1.18), per 1000 µg/day.

Table 163 Dietary Lutein and zeaxanthin and lung cancer risk. Results of meta-analyses and pooled analyses of prospective studies

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								
Gallicchio, 2008	2	2126	North America, Europe, China, Australia	Incidence, lung cancer	Per 1000 µg/day	0.97 (0.84-1.12)		<0.01
	5	3006			Highest vs lowest	0.89(0.79, 1.00)		0%, 0.53
Pooled analysis								
Männistö, 2004	7	3155	North America and Europe	Incidence, lung cancer	Q5 vs Q1	0.91 (0.81–1.03)	0.15	0.71
		1915		Current smokers	Q4 vs Q1	0.91 (0.79–1.05)	0.08	0.92
		981		Former smokers		1.03 (0.84–1.26)	0.69	0.51
		259		Never smokers		0.88 (0.61–1.26)	0.75	0.82
		956		Adenocarcinoma		0.86 (0.73–1.02)	0.10	0.39
		538		Small cell carcinoma		1.02 (0.85–1.23)	0.71	0.51

		901		Squamous cell carcinoma		1.01 (0.85–1.19)	0.96	0.89

Table 164 Dietary Lutein and zeaxanthin and lung cancer risk. Main characteristics of studies included in the SLR 2005

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors
Neuhouser, 2003 LUN00354 USA	CARET, Prospective Cohort, Age: 45-69 years, M/W	326/ 14 120 8 years	Primary outcome of the trial. Active follow-up with confirmation by clinical records and pathology reports	FFQ - study-specific	Incidence, lung cancer, placebo arm	≥ 1988 vs ≤ 775 µg /day	0.91 (0.65–1.28) Ptrend:0.73	Age, sex, clinic site, environmental factors, ethnicity/race, smoking habits
					Incidence, lung cancer, intervention arm		0.84 (0.61–1.15) Ptrend:0.21	
Yuan, 2003 LUN00218 Singapore	SCHS, Prospective Cohort, Age: 45-47 years, M/W	482/ 62 392 8 years	Cancer registry and, birth and death registries	FFQ - study-specific	Incidence, lung cancer	2079 vs 551 µg/1000 kcal	1.12 (0.84–1.50)	Age, sex, BMI, year of interview, education, ethnicity/race, cigarettes /day, years smoking, years since quitting smoking for former smokers
					Incidence, lung cancer	Per 1528 µg/1000 kcal	1.48 (0.89–2.45)	
		268			Current smokers		1.49 (0.75–2.97)	
		71			Former smokers		2.18 (0.61–7.82)	
		145			Never smokers		1.29 (0.53–3.13)	
Holick, 2002 LUN00515 Finland	ATBC, Prospective Cohort, Age: 50-69 years, M, Smokers only	1 644/ 29 133 11 years	Finnish Cancer Registry and the Register of Causes of Death	FFQ - study-specific	Incidence, lung cancer	> 1815 vs < 1012 µg /day	0.83 0.71, 0.99 Ptrend:< 0.001	Age, energy intake, other nutrients, foods or supplements, smoking habits

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors
Voorrips, 2000a LUN01121 Netherlands	NLCS, Case Cohort, Age: 55-69 years, M	939/ 1525 controls 6.3 years	Regional cancer registries and computerized national database of pathology report (PALGA)	FFQ - study-specific	Incidence, lung cancer	3857 vs 1388 µg /day	0.88 (0.57–1.38) Ptrend:0.39	Age, educational level, family history of specific cancer, smoking habits, years of smoking cigarettes, cigarettes per day
		487			Incidence, lung cancer, current smokers	Highest vs lowest	0.69 (0.45–1.07) Ptrend:< 0.01	
		312			Incidence, lung cancer, former smokers		0.66 (0.39–1.09) Ptrend:0.05	
		35			Incidence, lung cancer, never smokers		1.35 (0.56–3.26) Ptrend:0.42	
Knekt, 1999 LUN01416 Finland	FMCHES, Prospective Cohort, Age: 20-69 years, M	138/ 4545 25 years	Cancer Registry	FFQ - study-specific	Incidence, lung cancer	Highest vs lowest	0.87 (0.57–1.31) Ptrend:0.34	Age, smoking status
					Incidence, lung cancer, current smokers	Highest vs lowest	0.99 (0.62–1.57)	Age
					Incidence, lung cancer, non-smokers		0.46 (0.18–1.17)	

5.5.2 Serum Lutein and zeaxanthin

Cohort studies

Main results:
Five studies (1172 cases) out of 8 cohort studies (9 publications) were included in the dose-response meta-analysis. No significant association between serum lutein and zeaxanthin and lung cancer risk was observed.

There was not enough data to do stratified analysis by either smoking status or histological type. In the Multi-ethnic study (Epplein, 2009), an inverse association was observed in men but not in women (p interaction=0.01) and there was no effect modification by smoking (ever or never smoker).In a Chinese study (Yuan, 2001) significant borderline inverse associations was observed in ever smokers (189 cases), but not in never smokers (20 cases).

Sensitivity analyses:
In influence analysis the summary RRs ranged from 0.84 (95% CI=0.74-0.96) when Ratnasinghe, 2003 (study in high-risk miners) was omitted to 0.96(95% CI=0.84-1.10) when Ito, 2005 was omitted.

Study quality:
All studies included in the analysis were adjusted for main confounders including age and smoking status. All studies adjusted for intensity, duration of smoking and other smoking variables in addition to smoking status.

Table 165 Serum lutein and zeaxanthin and lung 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 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 166 Serum lutein and zeaxanthin and lung cancer risk. Summary of the dose-response meta-analysis in the 2005 SLR and CUP

	2005 SLR	CUP
Increment unit used		Per 10 µg/100 mL
All studies		
Studies (n)		5
Cases (total number)		1172
RR (95%CI)		0.90 (0.77-1.04)
Heterogeneity (I^2, p-value)		42.8%, 0.14
P value Egger test		0.63

Table 167 Serum lutein and zeaxanthin and lung 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								
Gallicchio, 2008	2	1855	North America, Europe, China, Australia	Incidence, lung cancer	Per 0.1 µmol/L	0.98 (0.90, 1.06)		84%, 0.01
	4	2095			Highest vs lowest	0.95 (0.67, 1.36)		11%, 0.34

Table 168 Serum lutein and zeaxanthin and lung cancer risk. Main characteristics of studies included in the 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
Min, 2014 LUN26890 USA	A follow up study of NHANES III, Prospective Cohort, Age: ≥ 20 years, M/W	161/ 10 382	Death certificate	Blood sample, measured by HPLC	Mortality, lung cancer	≥ 28 vs ≤ 14 µg/dL	0.73 (0.44-1.22)	Age , sex, smoking status, ethnicity, education, alcohol consumption, exercise, pack-year of smoking, obesity, total cholesterol, daily fat intake and vegetable and fruit consumption	Distribution of person-years, mid-points of exposure
		91/ 2957			Mortality, lung cancer, current smokers	29-86 vs ≤ 13 µg/dL	0.68 (0.38-1.22)		
		70/ 7425			Mortality, lung cancer, never/former smokers	≥ 30 vs ≤ 14 µg/dL	0.86 (0.40-1.85)		
Epplein, 2009 LUN20317 USA	MEC, Nested Case Control, Age: 45-75 years, M/W	136/ 272 controls Mean 1 year 8 month (cases)	SEER	Blood sample, (94% fasting for 8 h or more) measured by HPLC	Incidence, lung cancer, men	623 vs 250 ng/ml	0.45 (0.21-0.94) Ptrend:0.04	Age at specimen collection, fasting hours before blood draw, cigarettes pack-years, and pack-years squared, years of schooling and family history of	ng/mL converted to µg/100 mL
		71/ 142 controls Mean 1 year 8 month (cases)			Incidence, lung cancer, women	563 vs 236 ng/ml	2.23 (0.79-6.26) 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	Missing data derived for analyses
								lung cancer	
Ito, 2005 LUN26888 Japan	JACC, Nested Case Control, Age: 40-79 years, M/W	163/ 375/ controls 10 years	Death certificate	Serum sample (measured by HPLC)	Mortality, lung cancer, men	≥ 1.15 vs < 0.64 µmol/L	0.66 (0.33-1.35) Ptrend:0.24	Age, sex, smoking habits, participating institution and alcohol drinking	Mid-points of exposure , µmol/L converted to µg/100 mL
		48/ 112			Mortality, lung cancer, women	≥ 1.42 vs < 0.70µmol/L	0.29 (0.05-1.60) Ptrend:0.03		
Ratnasinghe, 2003 LUN00362 China	YTC, Nested Case Control, Age: 40-74 years, High-risk miners men	108/ 216 controls 6 years	Cancer registry and annual screenings	Serum collected 2 years prior to diagnosis (measured by HPLC)	Incidence, lung cancer	> 60 vs < 42 µg/dL	1.03 (0.7-2.4) Ptrend: 0.96	Age, radon exposure, smoking habits, pack-years	Mid-points of exposure
Yuan, 2001 LUN00828 China	Shanghai, China, Nested Case Control, Age: 45-64 years, M	209/ 335 controls 12 years	Active follow-up, Shanghai cancer registry, death certificates	Non-fasting blood sample (measured by HPLC)	Incidence, lung cancer	≥ 40.64 vs < 24.27 µg/dL	0.97 (0.55–1.71) Ptrend: 0.53	Age at starting to smoke, average no. of cigarettes smoked/day, and smoking status at the time of blood draw	Mid-points of exposure
		189/ 335			Incidence, lung cancer, ever	Highest vs lowest	0.68 (0.46–1.00)		

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Missing data derived for analyses
					smokers			(non-smoker, smoker)	
		20/ 287			Incidence, lung cancer, never smokers		1.82 (0.71–4.65)		

Table 169Serum lutein and zeaxanthin and lung cancer risk. Main characteristics of studies excluded from the 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 LUN20287	Hokkaido, Japan, Prospective Cohort Study, Age: 39-85 years, M/W	41/ 3 254 11.7 years	Mortality records	Fasting serum sample	Mortality, lung cancer	Per each logarithmically transformed serum value	0.90 (0.52-1.55)	Age, sex, smoking status, alcohol consumption, serum cholesterol and triglyceride, alanine aminotransferas e activity	HRs for one log increase
Ito, 2005 LUN26887 Japan	Hokkaido, Japan, Cohort Study, Prospective Cohort, Age: 39-79 years,	31/ 3182 10.5 years	Death certificate	Fasting serum sample (measured in serum using HPLC method)	Mortality, lung cancer	High vs low	1.27 (0.42-3.87) Ptrend:0.71	Age, sex, ALT activity, serum cholesterol, smoking habits	Superseded by Ito, 2006 LUN20287 No exposure levels

Author, Year, WCRF Code, Country	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								Used in H vs L analysis only
Ito, 2003 LUN00342 Japan	JACC, Nested Case Control, Age: 40-79 years, M/W	147/ 311 controls 8 years	Death certificate	Serum	Mortality, lung cancer	≥ 1.19 vs < 0.66 μmol/L	0.58 (0.26−1.29) Ptrend: 0.34	Age, gender, participating institution, smoking and alcohol drinking	Superseded by Ito, 2005 LUN26888
Comstock, 1997 LUN01716 USA	CLUE I & CLUE II, Nested Case Control, Age: 25- years, M/W	157/ 312 controls	Death certificates and hospital discharge records	Blood sample	Incidence, lung cancer, men	Highest vs lowest	0.50 Ptrend:0.01		No data available to calculate missing confidence intervals
		101/ 202 controls			Incidence, lung cancer, women	Highest vs lowest	0.24 Ptrend: 0.02		

Figure 186 RR estimates of lung cancer by levels of serum lutein and zeaxanthin

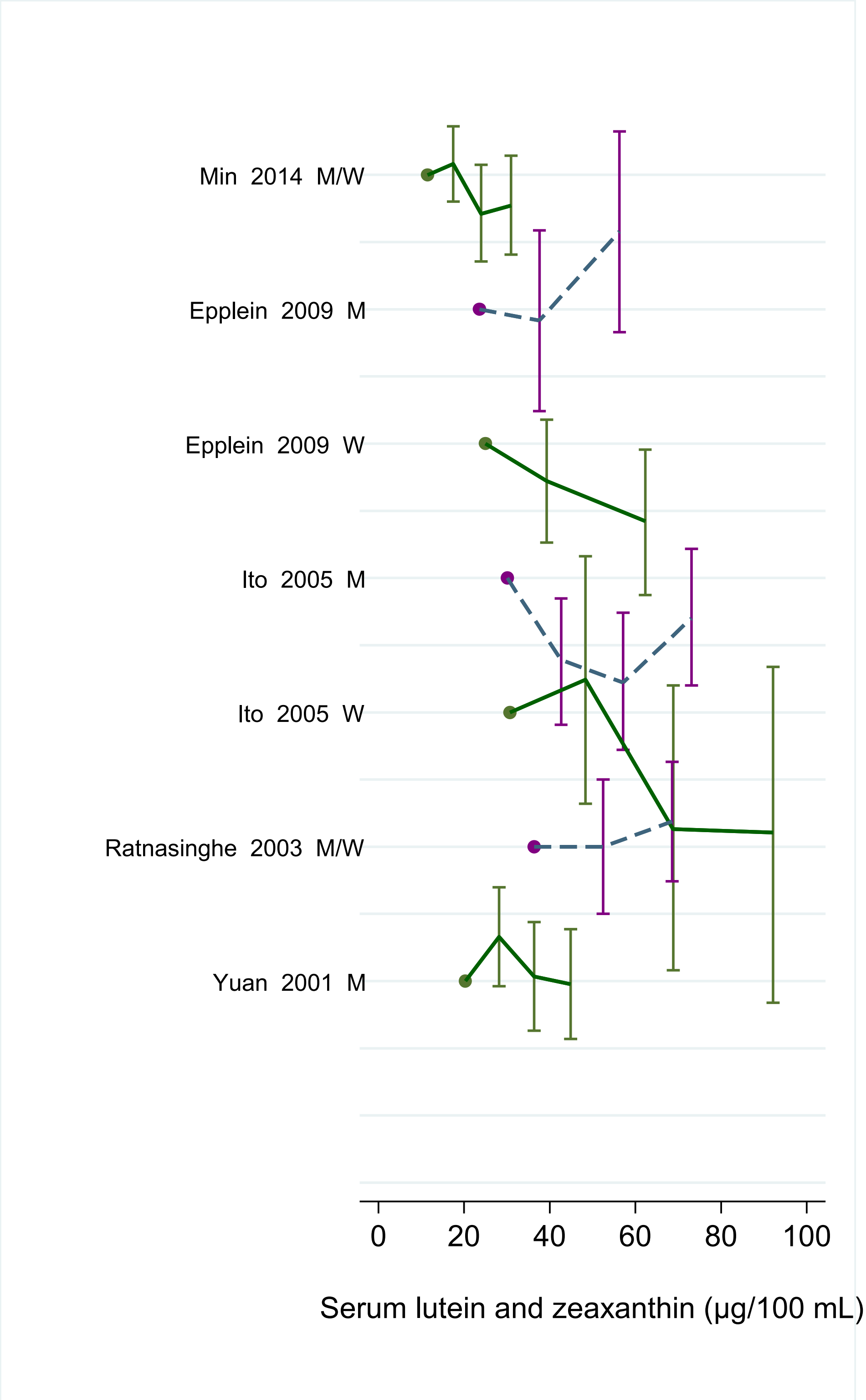


Figure 187 RR (95% CI) of lung cancer for the highest compared with the lowest level of serum lutein and zeaxanthin

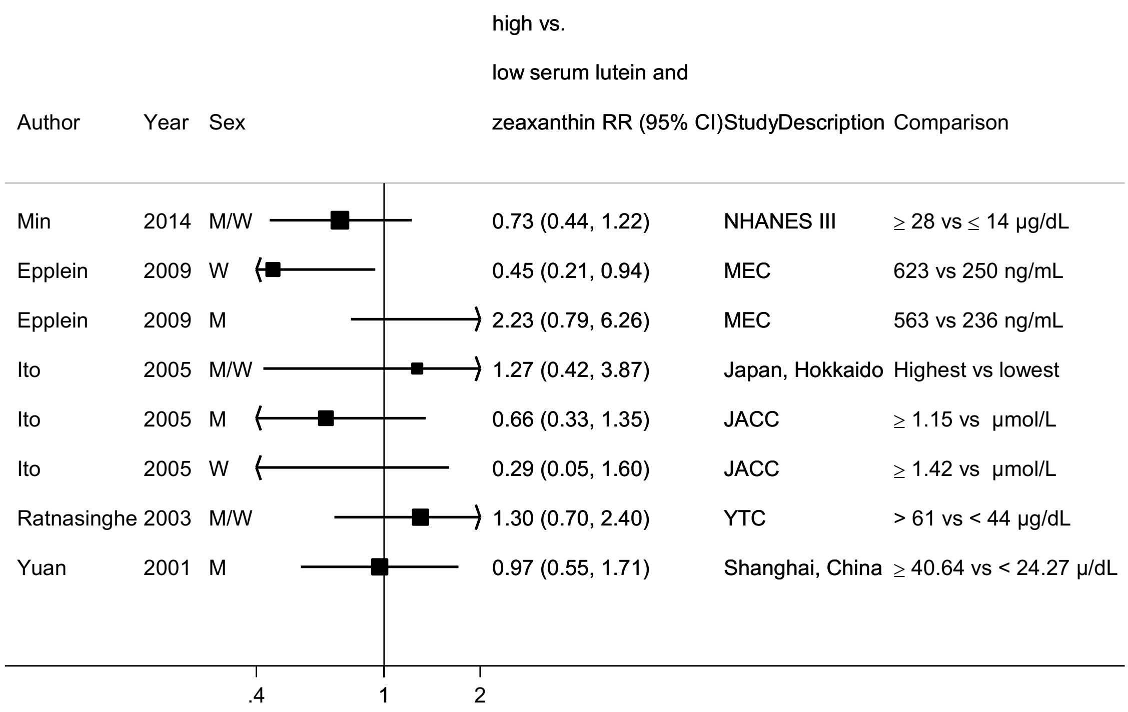


Figure 188 RR (95% CI) of lung cancer for 10 µg/100 mL increase of serum lutein and zeaxanthin

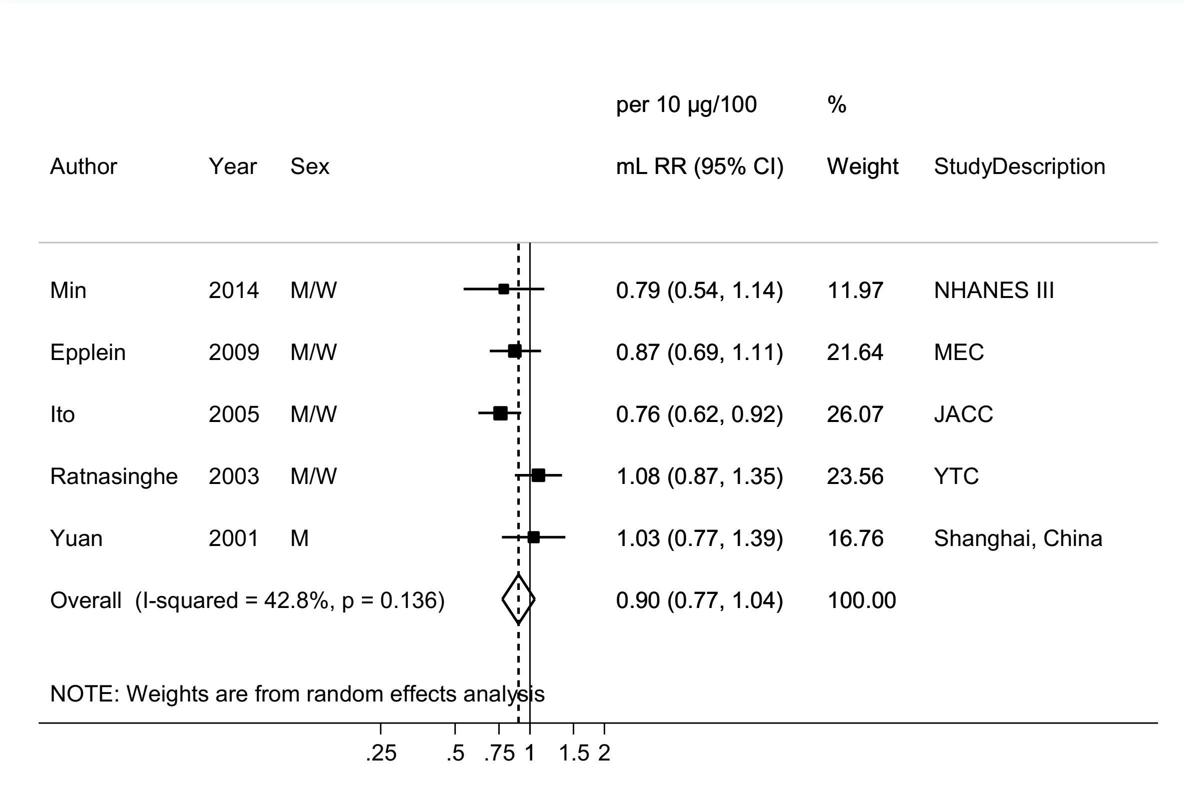
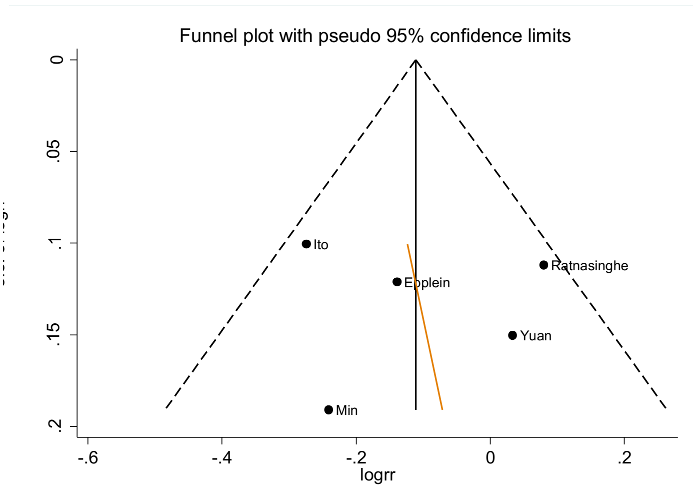


Figure 189 Funnel plot of studies included in the dose response meta-analysis of serum lutein and zeaxanthin and lung cancer



Egger's test p= 0.63

5.5.2 Total carotenoids intake

Cohort studies

Summary

Main results:

Seven studies (4491 cases) out of 9 cohort studies (10 publications) were included in the dose-response meta-analysis. A significant inverse association between total carotenoids intake and lung cancer risk was observed.

Low heterogeneity was observed in all analyses. There was no evidence of publication or small study bias (p=0.31).

There were not enough studies to do stratified analysis by either smoking status or histologic type. In the SMHS study, an inverse association was observed among heavy smokers only, and not in non-smokers or light smokers. Two other studies (FMCHES and NYSC) reported no inverse association either in current smokers (light or heavy) or in non-smokers. The studies on smokers or exposed to asbestos populations (ATBC; Wright, 2004 and CARET, Neuhouser, 2003) did not report significant associations.

Sensitivity analyses:
In influence analysis, the summary RR did not change materially when studies were omitted in turn. The summary RRs ranged from 0.98 (95%CI= 0.96-1.00) when Michaud, 2000 was omitted to 0.99 (95%CI=0.98-1.00) when Bandera, 1997 was omitted.

There were not enough studies to conduct the non-linear dose-response analysis.

Study quality:
Total carotenoids intake was estimated from food intake assessed with FFQ.
All studies were adjusted by main confounders, including age and smoking. Most studies (6 studies) adjusted for intensity, duration of smoking and other smoking variables in addition to smoking status, except one study (Knekt, 1999) that was adjusted only for smoking status.
Two studies from 3 publications (ATBC and CARET) were in in heavy smokers or populations exposed to asbestos (Wright, 2004; Neuhouser, 2003; Holick, 2002).

Table 170 Total carotenoids intake and lung 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 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

Table 171 Total carotenoids intake and lung cancer risk. Summary of the dose-response meta-analysis in the 2005 SLR and CUP

	2005 SLR	**CUP**
Increment unit used	1000 µg/day	1000 µg/day
All studies		
Studies (n)	2	7
Cases (total number)	1820	4491
RR (95%CI)	0.98 (0.96-0.99)	0.98 (0.97-0.99)
Heterogeneity (I^2, p-value)		36.7%, 0.16
P value Egger test		0.31
Stratified and sensitivity analysis		
Sex	**Men**	**Women**
Studies (n)	5	2
RR (95%CI)	0.98 (0.96-1.00)	0.99 (0.98-1.00)
Heterogeneity (I^2, p-value)	52.4%, 0.08	0%, 0.69

Table 172 Total carotenoids intake and lung cancer risk. Results of meta-analyses and pooled analyses of prospective studies

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								
Gallicchio, 2008	3	2095	North America, Europe, China, Australia	Incidence, lung cancer	Per 1000 µg/day	0.98 (0.97-0.99)		0%, 0.41
	8	4035			Highest vs lowest	0.79 (0.71-0.87)		0%, 0.80

Table 173 Total carotenoids intake and lung cancer risk. Main characteristics of studies included in the 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
Takata, 2013 LUN26860 China	SMHS, Prospective Cohort, Age: 40-74 years, M	359/ 61 092 6 years	Biennial home visits/linkage/cancer registry/vital stats	Validated FFQ	Incidence, lung cancer	5025.5 vs 1449.8 µg /day	0.64 (0.46-0.88) Ptrend:0.008	Age, BMI, current smoking status, years smoking, cigarettes/day education, family history of lung cancer, history of chronic bronchitis, tea consumption, total caloric intake	Distribution of person-years
		197			Heavy smokers	5025.5 vs 1449.8 µg /day	0.56 (0.36-0.89) Ptrend:0.02		
		116			Light smokers	5025.5 vs 1449.8 µg /day	0.70 (0.39-1.25) Ptrend:0.24		
		46			Never smokers	5025.5 vs 1449.8 µg /day	1.03 (0.42-2.53) Ptrend:0.77		
Wright, 2004 LUN05175 Finland	ATBC, Prospective Cohort, Age: 50–69 years, Male smokers	1787/ 27 111 14.4 years	Finnish Cancer Registry	Validated FFQ	Incidence, lung cancer	8320 vs 2832 µg /day	0.96 (0.91-1.02) Ptrend:0.16	Age, energy intake, number of cigarettes smoked per day, number of years of smoking, intervention assignment, BMI, and educational level	Increment unit converted to 1000 µg /day
Neuhouser, 2003 LUN00354	CARET, Prospective Cohort,	326/ 14 120 8 years	Primary outcome of the trial. Active	FFQ - study-specific	Incidence, lung cancer, placebo arm	≥ 13,244 vs ≤ 5425 µg /day	0.90 (0.64–1.37) Ptrend:0.64	Age, sex, smoking status, total pack-years	Distribution of person-years, mid-point

Author, Year, WCRF Code, Country	Study name, Characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Missing data derived for analyses
USA	Age: 45-69 years, M/W		follow-up with confirmation by clinical records and pathology reports		Incidence, lung cancer, intervention arm		0.77 (0.56–1.05) Ptrend:0.12	of smoking, asbestos exposure, race/ethnicity, and enrolment centre	exposure, number of cases in quintiles
Michaud, 2000 LUN01014 USA	HPFS, Prospective Cohort, Age: 30-75 years, M	275/ 46 924 10 years	Active follow-up, cases confirmed with medical and pathology records	FFQ - study-specific	Incidence, lung cancer, men	33 253 vs 7802 µg /day	0.64 (0.37, 1.13) Ptrend: 0.16	Age (5-y categories), smoking status (never, past with time since quitting, or current with 6 categories), age at start of smoking (< 15 y, 15–19 y, 20–29 y, ≥30 y, or never smokers), quintiles of energy intake, and time period	Distribution of person-years, missing confidence intervals calculated
	NHS, Prospective Cohort, Age: 30-75 years, W	519/ 77 283 12 years			Incidence, lung cancer, women	30 251 vs 8002 µg /day	0.69 (0.46, 1.03) Ptrend:0.01		
	HPFS & NHS, Prospective Cohort, Age: 30-75 years, M/W	794/ 124 207 10-12 years			Incidence, lung cancer, men and women pooled	Highest vs lowest	0.68 (0.49, 0.94) Ptrend:<0.01	Additionally adjusted by 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	Missing data derived for analyses
Knekt, 1999 LUN01416 Finland	FMCHES, Prospective Cohort, Age: 20-69 years, M	138/ 4545 25 years	Cancer Registry	FFQ - study-specific	Incidence, lung cancer	3830 vs 2350 µg /day	0.92 (0.60–1.41) Ptrend:0.21	Age, smoking status	Distribution of person years and number of cases in tertiles
					Incidence, lung cancer, current smokers	Highest vs lowest	1.12 (0.70–1.80)	Age	
					Incidence, lung cancer, non-smokers	Highest vs lowest	0.47 (0.17–1.31)		
Bandera, 1997 LUN01693 USA	NYSC, Prospective Cohort, Age: 40-80 years, M/W	395/ 48 000 7 years	Cancer registry and New York State Department of Health's Vital Statistics Section, National Death Index	FFQ - study-specific	Mortality, lung cancer, men	Highest vs lowest	0.73 (0.58-0.94) Ptrend:0.03	Age, educational level, energy intake, smoking habits	Tertiles from Bandera, 2002 LUN00506, distribution of person years, mid-points exposure IU/month converted to µg /day
		130			Mortality, lung cancer, women		0.82 (0.52-1.29) Ptrend:0.35		
		200			Mortality, lung cancer, men	**1-20 cigarettes/day**	0.75 (0.53-1.04) Ptrend:0.37		

Author, Year, WCRF Code, Country	Study name, Characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Missing data derived for analyses
		176			Mortality, lung cancer, men	**> 20 cigarettes/day**	0.84 (0.58-1.22) Ptrend:0.14		

Table 174 Total carotenoids intake and lung cancer risk. Main characteristics of studies excluded from the 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
Holick, 2002 LUN00515 Finland	ATBC, Prospective Cohort, Age: 50-69 years, M, Smokers only	1 644/ 29 133 11 years	Finnish Cancer Registry and the Register of Causes of Death	FFQ - study-specific	Incidence, lung cancer	> 6792 vs < 2770 µg /day	0.84 (0.72, 0.99) Ptrend:< 0.01	Age, energy intake, other nutrients, foods or supplements, smoking habits	Superseded by Wright, 2004 LUN05175
Bandera, 2002 LUN00506 USA	NYSC, Nested case-control, Age: 40-80 years, M/W	395/ 48 000 7 years	Cancer registry and New York State Department of Health's Vital Statistics Section, National Death Index	FFQ - study-specific	Mortality, lung cancer, men	Highest vs lowest	0.79 (0.62–1.02)	Age, ace, and county of residence), education (year), cigarettes/day, and years smoking	Duplicate of Bandera, 1997 LUN01693
					Mortality, lung cancer, women	Highest vs lowest	0.87 (0.56–1.34)		
Yong, 1997 LUN01778 USA	NHANES I, Prospective Cohort, Age: 25-74 years, M/W	248/ 10 068 19 years	Follow-up interviews confirmed with hospital records and death certificates	FFQ - study-specific	Incidence, lung cancer	> 113.05 vs 23.07 mg/day	0.66 (0.45-0.96)	Age, sex, educational attainment, non-recreational activity level, BMI, alcohol intake, family history, total	This exposure calculated by summing of Vitamin A 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**	**Reasons for exclusion**
								calorie intake and smoking status	
Chow, 1992 LUN02888 USA	LBS, Prospective Cohort, Age: 35- years, M	219/ 17 633 20 years	Death certificates	FFQ - study-specific	Mortality, lung cancer	Highest vs lowest	0.80 (0.50-1.20)	Age, smoking habits, industry/occupation	Used only in highest vs lowest analysis No specific cut-points for quintiles is reported

Figure 190 RR estimates of lung cancer by levels of total carotenoids intake

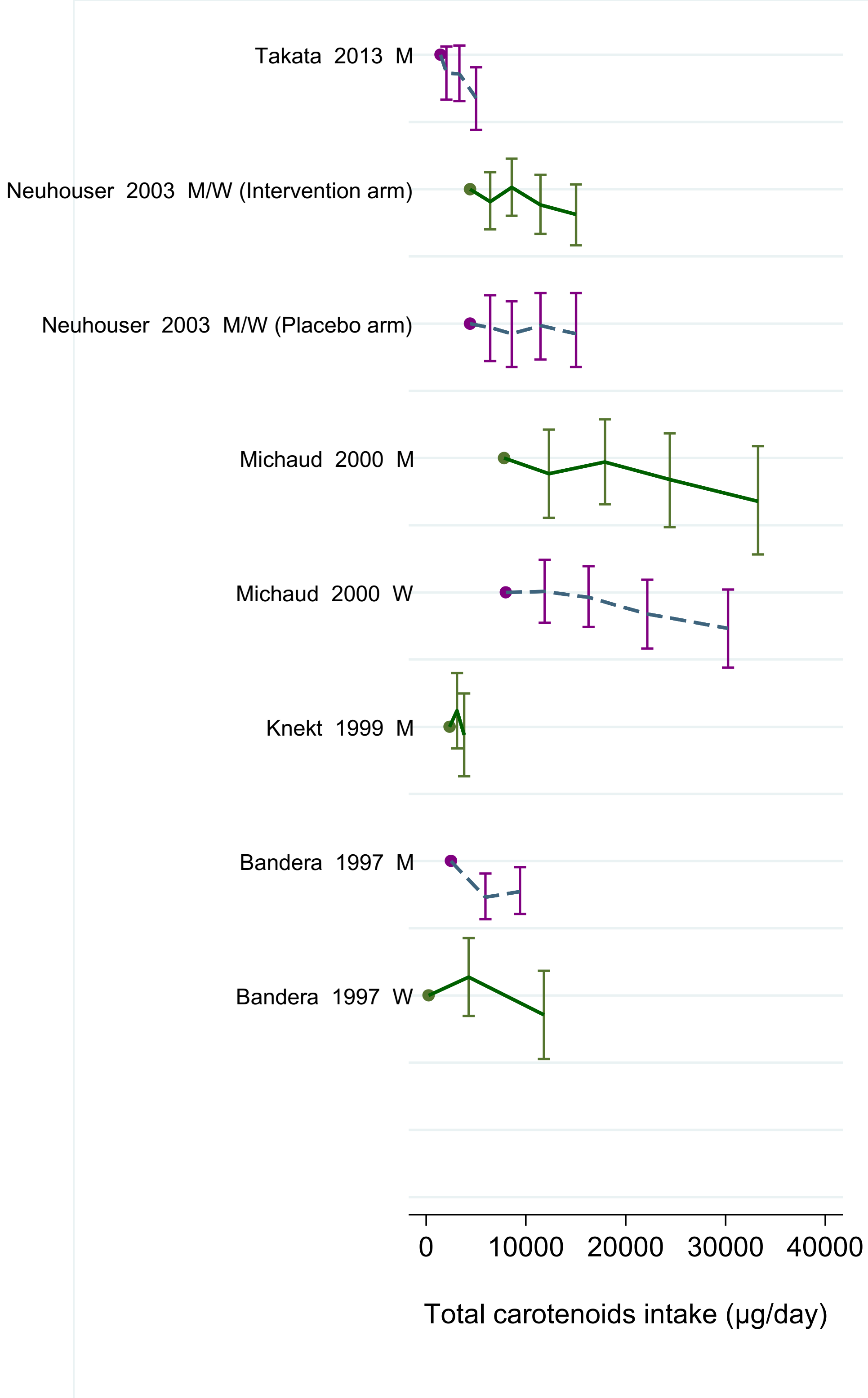


Figure 191 RR (95% CI) of lung cancer for the highest compared with the lowest level of total carotenoids intake

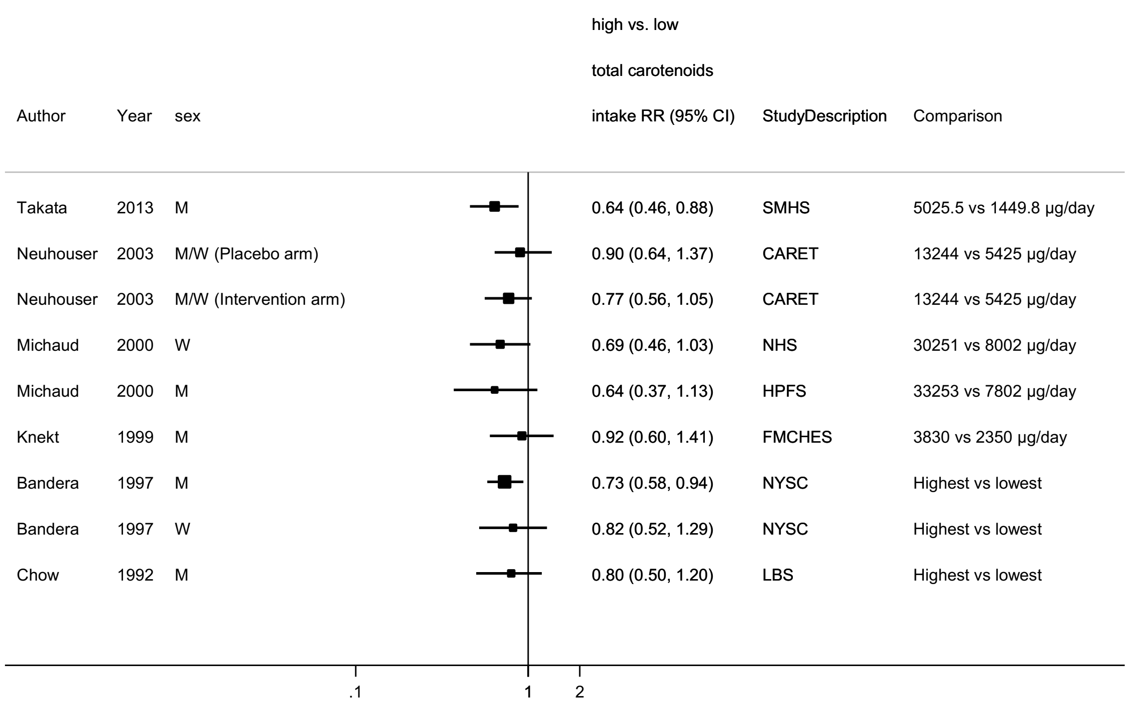


Figure 192 RR (95% CI) of lung cancer for 1000 µg/day increase of total carotenoids intake

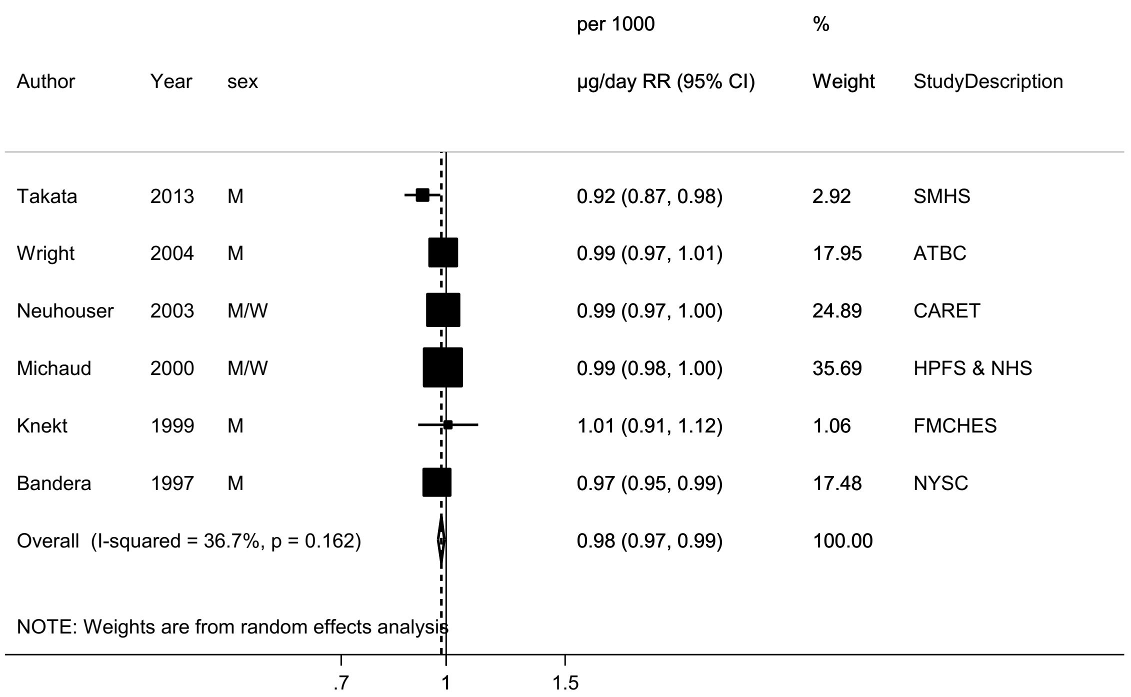
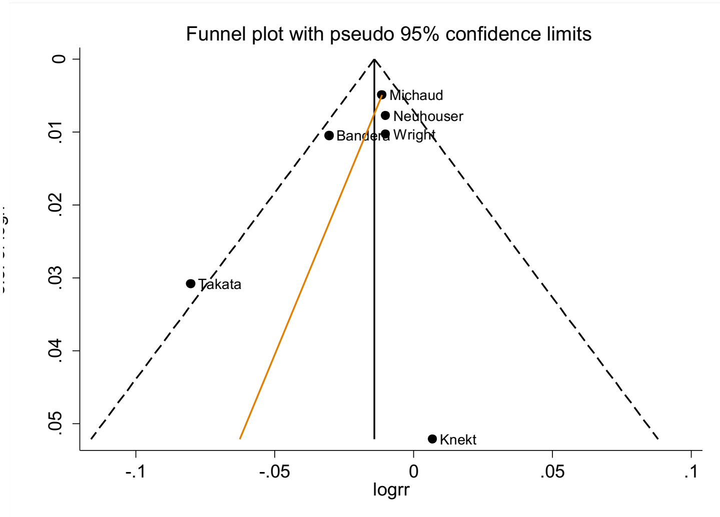
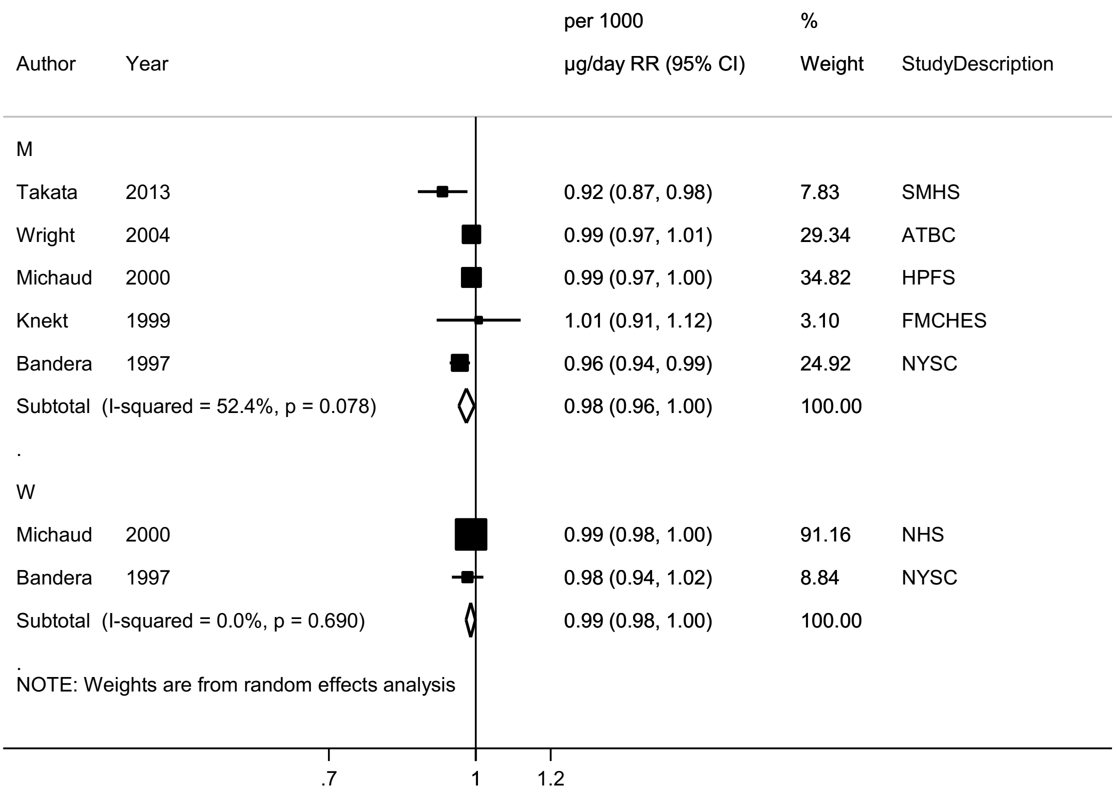


Figure 193 Funnel plot of studies included in the dose response meta-analysis of total carotenoids intake and lung cancer



Egger's test p=0.31

Figure 194 RR (95% CI) of lung cancer for 1000 µg/day increase of total carotenoids intake by sex



5.5.2.1 Serum total carotenoids

Cohort studies

Summary

Main results:
Only highest versus lowest analysis could be performed (5 studies, 724 cases). There was a significant inverse association between serum total carotenoids and lung cancer risk.

There was not enough data to do stratified analysis by either smoking status or histological type. In the Multi-ethnic cohort study (Epplein, 2009), an inverse association was observed in men but not in women (p interaction=0.01) and it was mainly in non-adenocarcinomas (p interaction =0.007). There was no effect modification by smoking (ever or never smoker).
In a Chinese study (Yuan, 2001), a significant inverse associations was observed in ever smokers (189 cases), and not in never smokers (20 cases).

Study quality:
All studies included in the analysis were adjusted for main confounders including age and smoking status. All studies adjusted for intensity, duration of smoking and other smoking variables in addition to smoking status.

Table 175 Serum total carotenoids and lung 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	
Studies included in dose-response meta-analysis	Not enough studies
Studies included in non-linear dose-response meta-analysis	Not enough studies

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

Table 176 Serum total carotenoids and lung cancer risk. Summary of the dose-response meta-analysis in the 2005 SLR and CUP

	2005 SLR	CUP
All studies		
Increment unit used	No meta-analysis	Highest vs lowest
Studies (n)		5
Cases (total number)		724
RR (95%CI)		0.64 (0.44-0.93)
Heterogeneity (I^2, p-value)		23.0%, 0.27

Table 177 Serum total carotenoids and lung 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								
Gallicchio*, 2008	2	367	Japan, China, Finland, UK, North America	Incidence, lung cancer	Per 0.75 µmol/L	0.64 (0.46-0.88)		0%, 0.89
	4	2846			Highest vs lowest	0.70 (0.44-1.11)		46%, 0.2

Table 178 Serum total carotenoids and lung cancer risk. Main characteristics of studies included in the high compared to low analysis

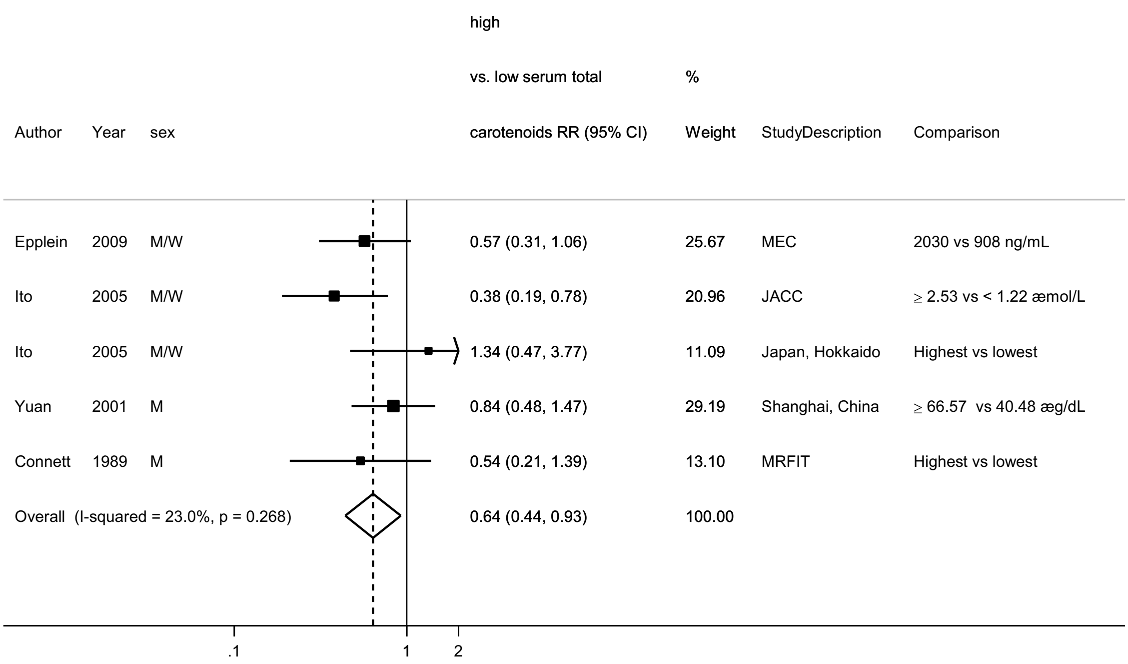
Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Missing data derived for analyses
Epplein, 2009 LUN20317 USA	MEC, Nested Case Control, Age: 45-75 years, M/W	136/ 272 controls Mean 1 year 8 month (cases)	SEER Registry	Blood sample, (94% fasting for 8 h or more)	Incidence, lung cancer, men	2030 vs 908 ng/mL	0.32 (0.15-0.68) Ptrend:< 0.01	Age at specimen collection, fasting hours before blood draw, cigarettes pack-years, and pack-years squared, years of schooling and family history of lung cancer	
		71/ 142 controls Mean 1 year 8 month (cases)			Incidence, lung cancer, women	2091 vs 818 ng/mL	1.78 (0.62-5.08) Ptrend:0.25		
Ito, 2005 LUN26888 Japan	JACC, Nested Case Control, Age: 40-79 years, M/W	163/ 375 controls 10 years	Death certificate	Serum sample (measured by HPLC)	Mortality, lung cancer, men	≥ 2.53 vs < 1.22 µmol/L	0.42 (0.19-0.95) Ptrend: 0.09	Age, participating institution, smoking habits, alcohol drinking, BMI and serum total cholesterol	
		48/ 122			Mortality, lung cancer, women	≥ 3.93 vs < 1.87 µmol/L	0.27 (0.06-1.34) Ptrend: 0.32		
Ito, 2005 LUN26887 Japan	Japan, Hokkaido Cohort Study, Prospective	31/ 3182 10.5 years	Death certificate	Fasting serum sample (measured in	Mortality, lung cancer	High vs low	1.34 (0.47-3.77) Ptrend: 0.58	Age, sex, ALT activity, serum cholesterol,	

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Missing data derived for analyses
	Cohort, Age: 39-79 years, M/W			serum using HPLC method)				smoking habits	
Yuan, 2001 LUN00828 China	Shanghai, China, Nested Case Control, Age: 45-64 years, M	209/ 335 controls 12 years	Active follow-up, Shanghai cancer registry, death certificates	Non-fasting blood sample	Incidence, lung cancer	≥ 66.57 vs < 40.48 µg/dL	0.84 (0.48–1.47) Ptrend: 0.20	Age at starting to smoke, average no. of cigarettes smoked/day, and smoking status at the time of blood draw (non-smoker, smoker)	
		189/ 335			Incidence, lung cancer, ever smokers	Highest vs lowest	0.63 (0.42–0.94)		
		20/ 287			Incidence, lung cancer, never smokers		1.09 (0.42–2.76)		
Connett, 1989 LUN03434 USA	MRFIT, Nested Case Control, Age: 35-57 years, M	66/ 131 controls 10 years	Active follow-up confirmed with hospital records, National Death Index	Serum sample	Mortality, lung cancer	Lowest vs highest	1.84	Age, cigarettes per day, BMI, serum cholesterol, DBP, years of education, serum thiocyanate, leukocyte count	
						Per 40 µg /dL	0.65 (0.44-0.97)		

Table 179 Serum total carotenoids and lung cancer risk. Main characteristics of studies excluded in the high compared to low 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 LUN20287	Hokkaido, Japan, Prospective Cohort Study, Age: 39-85 years, M/W	41/ 3254 11.7 years	Mortality records	Fasting serum sample	Mortality, lung cancer	Per each logarithmically transformed serum value	0.87 (0.46-1.64)	Age, sex, smoking status, alcohol consumption, serum cholesterol and triglyceride, alanine aminotransferase activity	HRs for one log increase
Ito, 2003 LUN00342 Japan	JACC, Nested Case Control, Age: 40-79 years, M/W	147/ 39 140 8 years	Population death registries	Blood sample	Mortality, lung cancer	> 3.02 vs < 1.34 µmol/L	0.27 (0.10-0.70) Ptrend:0.03	Age, sex, alcohol consumption, BMI, other, other nutrients, foods or supplements, smoking habits	Superseded by Ito, 2005 LUN26888

Figure 195 RR (95% CI) of lung cancer for the highest compared with the lowest level of serum total carotenoids



*In MRFIT study, the RR's were recalculated using Hamling method (Hamling, 2008).

5.5.3 Dietary folate

Cohort studies

Summary

Main results:
Nine studies (4900 cases) were included in the dose-response meta-analysis. Dietary folate was not significantly associated with lung cancer risk. No significant associations were observed in analysis stratified by smoking status (4-5 studies each strata).
Moderate heterogeneity was observed. There was evidence of publication or small study bias (p= 0.01).
The funnel plot shows that a Danish study (Roswall, 2009), reporting a significant positive association is an outlier. In this study, no significant association was observed with supplemental folic acid (p for different effect of source=0.03). The median dietary intake of folate in the cohort (325.3 g/day) was more than three times as large as the median supplemental intake (100 g/day).When the analysis on dietary folate were stratified by smoking status, the association was inverse but not significant in never smokers and positive and not significant in former and current smokers, but there was no significant interaction (p interaction =0.13) . Only 33 and 92 cases were never smokers or current smokers respectively, and 82% of the cases were current smokers. The analyses were adjusted for smoking status (never/former/present), smoking duration, smoking intensity, possible cessation and when, passive smoking, work exposure and other potential confounders.
In stratified analysis by sex and geographic area,a significant inverse association observed in only in men (not among women) and in studies in North America (not in Asia or Europe).

Sensitivity analysis:
In influence analysis, a significant inverse association was observed after excluding the DCH study (Roswall, 2009, that showed a positive significant association). The summary RRs ranged from 0.97 (95% CI=0.94-0.99) when Roswall, 2009 was omitted to 1.00 (95% CI= 0.96-1.04) when Bandera, 1997 was omitted. After exclusion of the DHC study (Roswall, 2009) the high vs low meta-analysis including the studies in the Pooling project was 0.91 (95% CI= 0.81-1.01).

There was evidence of a U-shaped dose-response association of lung cancer and dietary folate intake (P linearity < 0.01). In the studies, this shape is suggested in three studies.

Study quality:
Cancer outcome was confirmed using records in cancer registries in most studies. All studies used FFQ to assess the intake of dietary folate. In one Australian study (Bassette, 2012), the analysis could not be corrected for the wheat flour which was fortified with folate.

The study from Singapore (Yuan, 2003) corrected for measurements error in dietary assessment using regression calibrated method.
All studies included in the dose-response analysis were adjusted at least for age and smoking intensity and in one study in never smokers, for passive smoking.

Pooling Project of Cohort studies:

A pooling project of 8 prospective studies (Cho, 2006) reported a relative risk estimate of lung cancer of 0.88 (95% CI= 0.74-1.04) for the highest compared with the lowest study-specific quintile of dietary folate intake and Ptrend = 0.08, with no evidence of heterogeneity across studies. No significant associations were observed in men and women, in analyses stratified by smoking status, and cancer type (adenocarcinomas, small cell carcinomas and squamous cell carcinomas).
Six studies included in the CUP SLR were not included in the pooled analysis. In a categorical meta-analysis of the studies in the Pooling project (Cho, 2006) and the non-overlapping studies included in the CUP SLR, the RR for the highest compared to the lowest level of dietary folate was 0.95 (95% CI=0.86-1.06, 14 cohort studies). A combined dose-response analysis was not possible.

Table 180 Dietary folate intake and lung 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	9
Studies included in dose-response meta-analysis	9
Studies included in non-linear dose-response meta-analysis	6

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

Table 181 Dietary folate intake and lung cancer risk. Summary of the dose-response meta-analysis in the 2005 SLR and CUP

	2005 SLR	**CUP**
All studies		
Increment unit used	No meta-analysis	100 µg/day
Studies (n)		9
Cases (total number)		4900
RR (95%CI)		0.99 (0.95-1.02)
Heterogeneity (I^2, p-value)		44%, 0.08
p value Egger test		0.01
Pooling project of cohort studies and non-overlapping studies identified in the CUP SLR		
Comparison		Highest vs lowest

Studies (n)		14
Cases (total number)		6284
RR (95%CI)		0.95 (0.86-1.06)
Heterogeneity (I^2, p-value)		10.4%, 0.35

Stratified and sensitivity analysis (no analyses conducted in the 2005 SLR)			
Smoking status	**Never smokers**	**Current smokers**	**Former smokers**
Studies (n)	5	4	4
RR (95%CI)	0.99 (0.93-1.05)	0.94 (0.83-1.07)	0.96 (0.88-1.05)
Heterogeneity (I^2, p-value)	3.5%, 0.39	64.3%, 0.04	0%, 0.58
Sex	**Men**	**Women**	
Studies (n)	3	3	
RR (95%CI)	0.95 (0.91-0.98)	0.99 (0.95-1.03)	
Heterogeneity (I^2, p-value)	0.3%, 0.37	0%, 0.96	
Geographic location	**Asia**	**Europe**	**North America**
Studies in the CUP (n)	3	2	3
RR (95%CI)	0.98 (0.94-1.03)	1.03 (0.81-1.29)	0.96 (0.94-0.99)
Heterogeneity (I^2, p-value)	0%, 0.54	86.2%, < 0.01	0%, 0.40

Table 182 Dietary folate intake consumption and lung 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								
Zhang, 2014	9		USA, Canada, Australia, Denmark, Netherlands, China, Singapore	Incidence, lung cancer	Per 100 µg/day	0.99 (0.97-1.01)	0.32	33.6%, 0.14
Dai, 2013	6 case-control studies	3805 (5470 controls)	USA, Japan, Russia, Eastern Europe	Incidence, lung cancer	Highest vs lowest	0.73 (0.63-0.85)	< 0.001	9.6%, 0.35
Pooled analyses								
Cho, 2006	8	3155	North America and Europe	Incidence, lung cancer	Highest vs lowest	0.88 (0.74-1.04)	0.08	0.09
		1808		Men		0.80 (0.58-1.08)	0.18	0.03
		1398		Women		0.95 (0.79-1.13)	0.31	0.56
		259		Never smokers		0.69 (0.38-1.26)	0.23	0.03
		981		Former smokers		0.96 (0.78-1.17)	0.69	0.89
		1915		Current smokers		0.86 (0.75-1.00)	0.06	0.56

Table 183 Dietary folate intakes and lung cancer risk. Main characteristics of studies included in the 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
Takata, 2013 LUN26860 China	SMHS, Prospective Cohort, Age: 40-74 years, M	359/ 61 092 6 years	Biennial home visits (diagnosis verified by medical chart review), record linkage to Cancer Registry and Vital Statistics Registry	Validated FFQ	Incidence, lung cancer	474.4 vs 217.9 µg/day	0.99 (0.70-1.40) Ptrend:0.92	Age, BMI, current smoking status, years smoking, cigarettes/day education, family history of lung cancer, history of chronic bronchitis, tea consumption, total caloric intake	Distribution of person-years per quartiles
Bassett, 2012 LUN20320 Australia	MCCS, Prospective Cohort, Age: 40-69 years, M/W	348/ 37 046 15 years	Cancer registry	FFQ	Incidence, lung cancer	≥ 80th vs < 20th percentile	1.02 (0.69-1.50) Ptrend:0.60	Age, sex, BMI, alcohol consumption, beta-carotene intake, country of birth, daily caloric intake, physical activity,	Distribution of person years in smoking status subgroups, SD unit increments recalculated to 100 µg/day
						Per 1 SD units	1.03 (0.91-1.17)		
		155			Incidence, lung cancer, current smoker	≥ 80th vs < 20th percentile	1.03 (0.60-1.77) Ptrend:0.92		
						Per 1 SD units	1.01 (0.85-1.20)		
		143			Incidence, lung cancer, former	≥ 80th vs < 20th percentile	0.98 (0.56-1.70) Ptrend:0.61		

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Missing data derived for analyses
					smokers	Per 1 SD units	1.05 (0.88-1.25)	smoking status, time since smoking cessation, pack years of smoking	
		50			Incidence, lung cancer, never smokers	≥ 80th vs < 20th percentile	1.21 (0.45-3.27) Ptrend:0.62		
						Per 1 SD units	1.07 (0.80-1.44)		
Takata, 2012 LUN26859 China	SWHS, Prospective Cohort, Age: 40-70 years, Women never smokers	428/ 71 267 11 years	Shanghai cancer registry and Shanghai vital statistics registry	FFQ	Incidence, lung cancer	405 vs 185 µg/day	0.96 (0.70-1.32) Ptrend:0.79	Age, BMI, income, occupation, total caloric intake, history of asthma, passive smoking	Distribution of person-years per quartiles
Roswall, 2009 LUN26873 Denmark	DCH, Prospective Cohort, Age: 50-64 years, M/W	721/ 55 557 10.6 years	Danish cancer registry	FFQ	Incidence, lung cancer	> 383.7 vs 0- ≤ 247.9	1.37 (1.01-1.84)	Age, sex, folate supplements, intakes of vitamin C, vitamin E beta-carotene, smoking status, smoking intensity, smoking duration, passive smoking, smoking cessation, work exposure to	Distribution of person-years
		721				Per 100 µg/day	1.15 (1.03-1.28)		
		33			Incidence, lung cancer , never smokers	Per 100 µg/day	0.68 (0.46-1.01)		
		95			Incidence, lung cancer , former smokers	Per 100 µg/day	1.02 (0.83-1.25)		
		593			Incidence, lung cancer , current	Per 100 µg/day	1.02 (0.94-1.11)		

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Missing data derived for analyses
					smokers			carcinogenic substances	
Kabat, 2008a LUN20311 Canada	CNBSS, Prospective Cohort, Age: 40-59 years, W	358/ 49 654 16 years	Record linkage to Canadian Centre Database and to National Mortality Database	FFQ	Incidence, lung cancer	> 374 vs < 236.9 µg/day	1.12 (0.83-1.52) Ptrend:0.43	Age, alcohol consumption, BMI, parity, smoking status, pack years of smoking, years of education	Distribution of person years and number of cases in quintiles, Mid-points exposure
Neuhouser, 2003 LUN00354 USA	CARET, Prospective Cohort, Age: 45-69 years, M/W	326/ 14 120 12 years	Primary outcome of the trial. Active follow-up with confirmation by clinical records and pathology reports	FFQ - study-specific	Incidence, lung cancer, placebo arm	≥ 309 vs ≤ 144 µg /day	0.87 (0.61-1.23) Ptrend:0.39	Age, sex, smoking status, total pack-years of smoking, asbestos exposure, race/ethnicity, and enrollment center	Distribution of person-years and cases by exposure quintiles, mid-points of exposure quintiles, RRs for intervention and placebo combined
		414			Incidence, lung cancer, intervention arm	≥ 309 vs ≤ 144 µg /day	0.94 (0.68-1.30) Ptrend:0.53		
Yuan, 2003 LUN00218 Singapore	SCHS, Prospective Cohort, Age: 45-47 years,	482/ 62 392 8 years	Cancer registry and death registry	FFQ - study-specific	Incidence, lung cancer	141 vs 65 µg/1000 kcal	0.82 (0.60-1.11)	Age, sex, BMI, interview year, education, ethnicity/race, smoking status,	Distribution of person years in smoking status subgroups, µg / 1000 kcal
						Per 76 µg/1000 kcal	0.71 (0.40-1.25)		
		268			Incidence, lung	Per 76 µg/1000	0.67 (0.31-1.46)		

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Missing data derived for analyses
	M/W				cancer, current smokers	kcal		cigarettes/day, years smoking, years since quitting smoking	converted to µg /day, increment unit recalculated to 100 µg/day
		145			Incidence, lung cancer, never smokers	Per 76 µg/1000 kcal	0.77 (0.28-2.10)		
		71			Incidence, lung cancer, former smokers	Per 76 µg/1000 kcal	0.68 (0.16-2.93)		
Voorrips, 2000a LUN01121 Netherlands	NLCS, Case Cohort, Age: 55-69 years, M	939/ 1525 6.3 years	Regional cancer registries and computerized national database of pathology report (PALGA)	FFQ - study-specific	Incidence, lung cancer	400 vs 212 µg/day	0.83 (0.39-1.75)	Age, educational level, family history of specific cancer, smoking status, years smoking, cigarettes/day, education, family history of lung cancer	Distribution of, number of cases and non-cases in quintiles
		35			Incidence, lung cancer, never smokers	Highest vs lowest	1.09 (0.44-2.72)		
		312			Incidence, lung cancer, former smokers	400 vs 212 µg/day	0.72 (0.45-1.17)		
		487			Incidence, lung cancer, current smokers	400 vs 212 µg/day	0.63 (0.41-0.98)		
Bandera, 1997 LUN01693 USA	NYSC, Prospective Cohort, Age: 40-80 years,	395/ 48 000 7 years	Cancer registry and New York State Department of Health's Vital	FFQ - study-specific	Mortality, lung cancer, men	Highest vs lowest	0.70 (0.55-0.89) Ptrend: < 0.01	Age, educational level, energy intake, smoking habits	Tertiles from Bandera, 2002, distribution of person years, mid-points

Author, Year, WCRF Code, Country	Study 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	130	Statistics Section, National Death Index		Mortality, lung cancer, women	Highest vs lowest	0.85 (0.54-1.33) Ptrend: 0.42		exposure

Table 184 Dietary folate intake and lung cancer risk. Main characteristics of studies excluded in the 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
Sakoda, 2011 LUN20351 USA	CARET, Nested Case Control, Age: 45-69 years, M/W	365/ 18 314	Primary outcome of the trial. Active follow-up with confirmation by clinical records and pathology reports	FFQ	Incidence, lung cancer	> 256.1 vs ≤ 175.4 µg /day	ORGA 1.42 (1.02-1.97)	Age, sex, enrolment year, smoking status, occupational asbestos exposure	Only has gene interactions results Neuhouser, 2003 LUN00354 was used
		163			Incidence, lung cancer	> 256.1 vs ≤ 175.4 µg /day	ORAA 1.91 (1.15-3.16)		
					Incidence, lung cancer	> 256.1 vs ≤ 175.4 µg /day	OR per A allele 1.39 (1.10-1.76)		
Bandera, 2002 LUN00506 USA	NYSC, Nested case-control, Age: 40-80 years, M/W	395/ 48 000 7 years	Cancer registry and New York State Department of Health's Vital Statistics Section, National Death Index	FFQ - study-specific	Mortality, lung cancer, men	Highest vs lowest	0.82 (0.65-1.05) Ptrend: < 0.05	Age, ace, and county of residence), education (yr), cigarettes/day, and years smoking	Duplicate of Bandera, 1997 LUN01693
		130			Mortality, lung cancer, women	Highest vs lowest	0.88 (0.55-1.43)		

Figure 196 RR estimates of lung cancer by levels of dietary folate intake

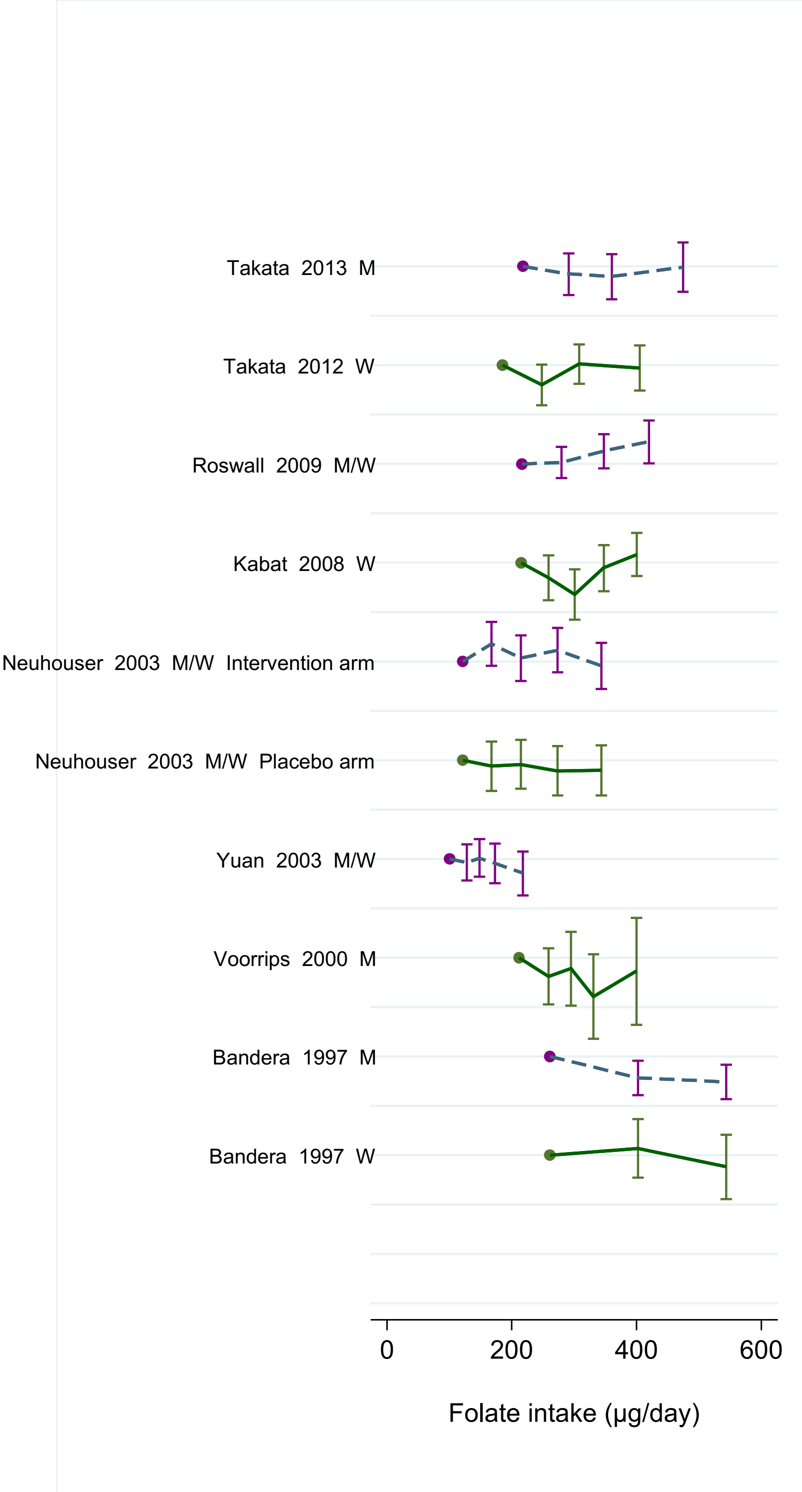


Figure 197 RR (95% CI) of lung cancer for the highest compared with the lowest level of dietary folate intake

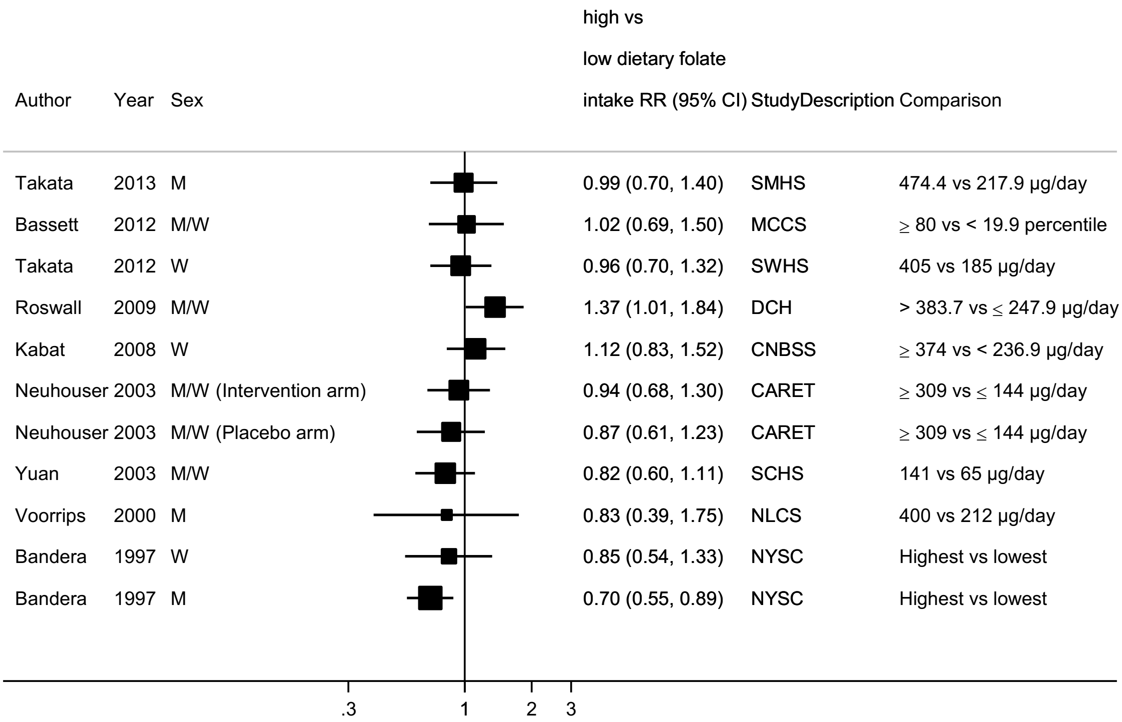


Figure 198 RR (95% CI) of lung cancer for 100 μg/day increase of dietary folate intake

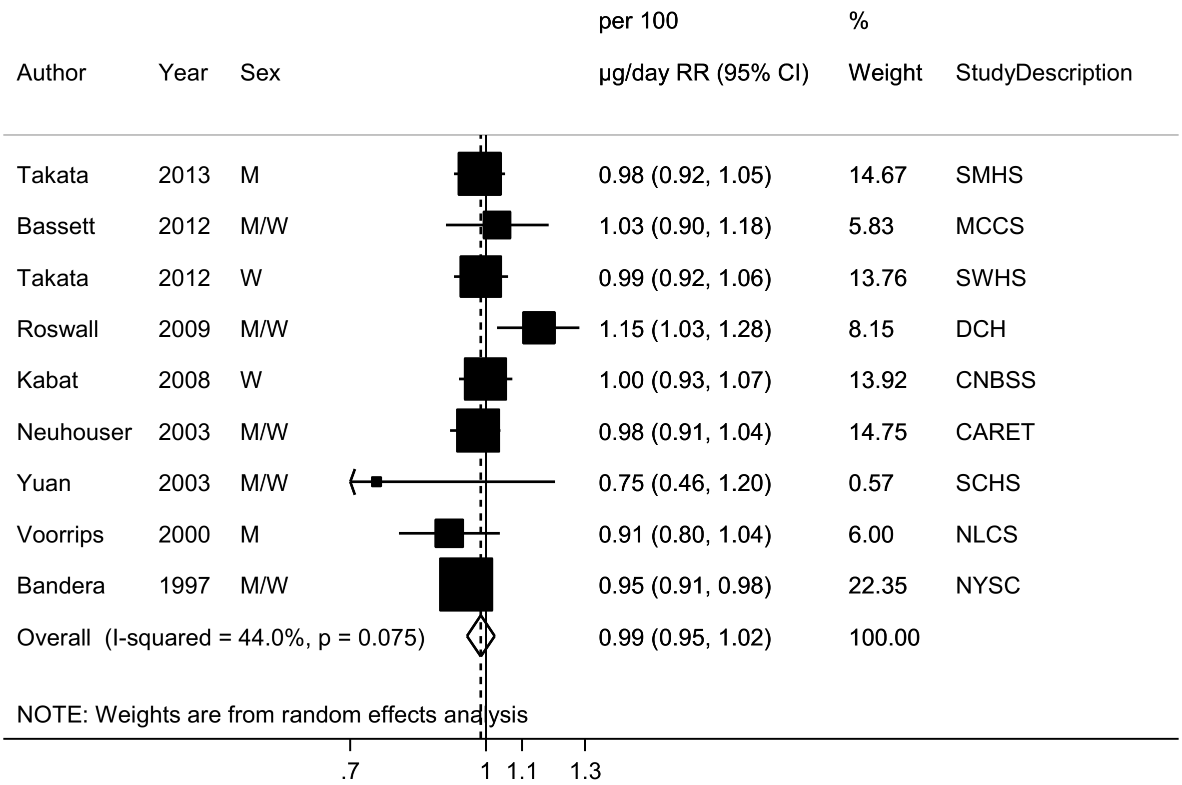
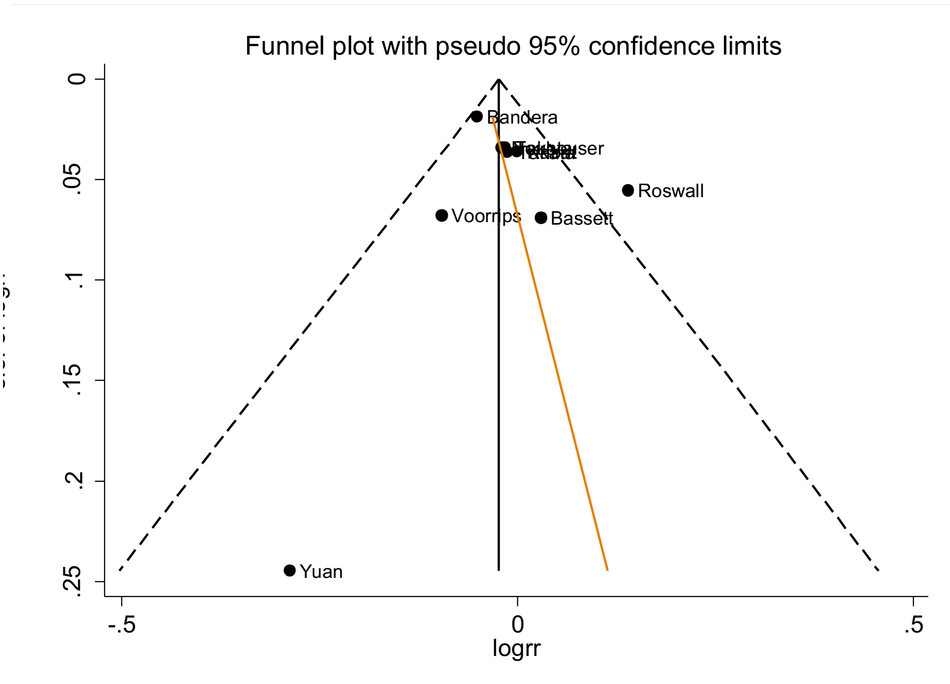


Figure 199 Funnel plot of studies included in the dose response meta-analysis of dietary folate intake and lung cancer



Egger's test p= 0.01

Figure 200 RR (95% CI) of lung cancer for 100 μg/day increase of dietary folate intake by smoking status

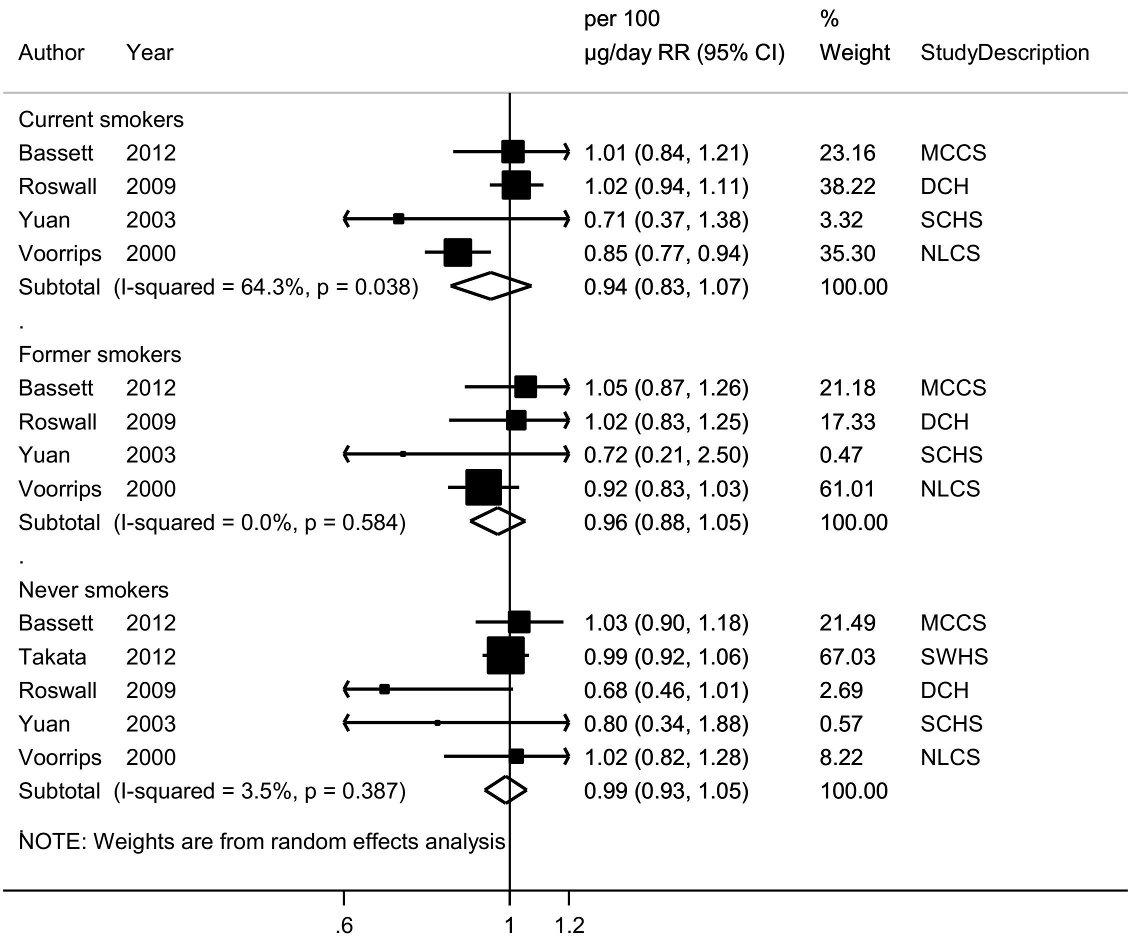


Figure 201 RR (95% CI) of lung cancer for 100 μg/day increase of dietary folate intake by sex

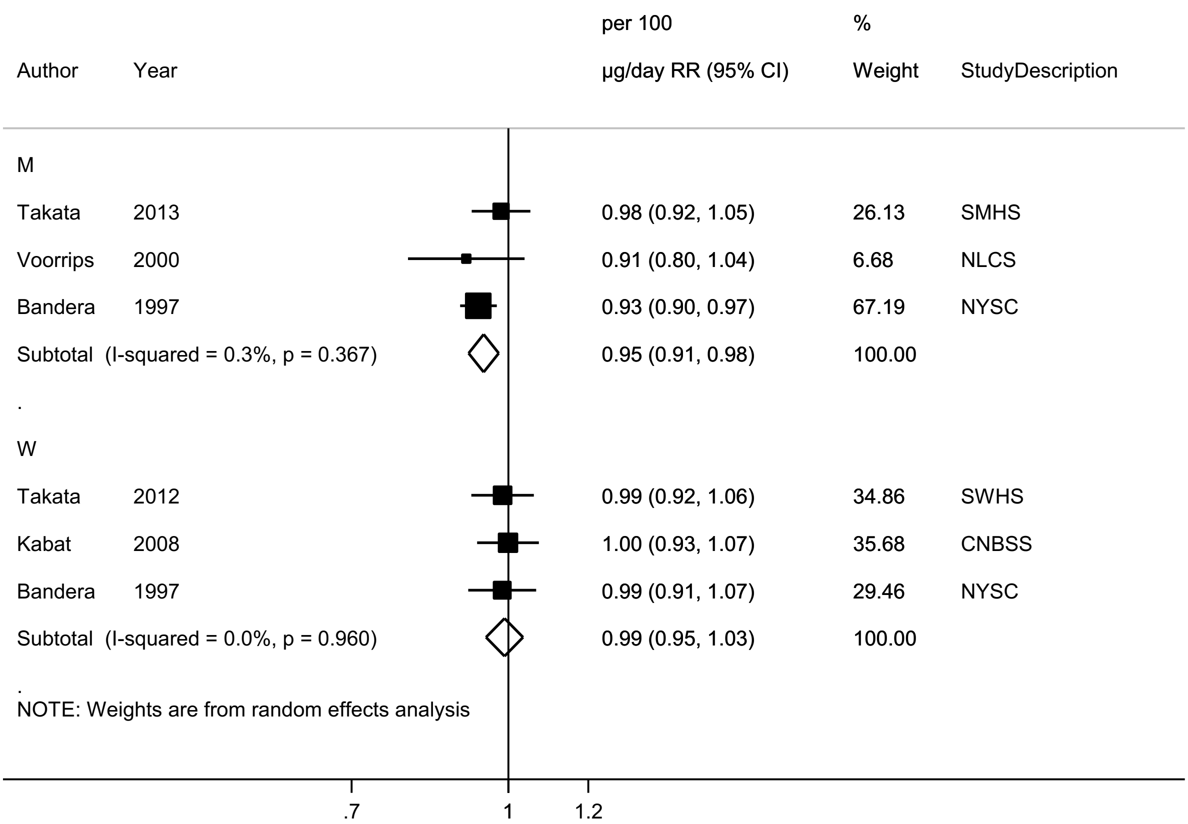


Figure 202 RR (95% CI) of lung cancer for 100 μg/day increase of dietary folate intake by geographic location

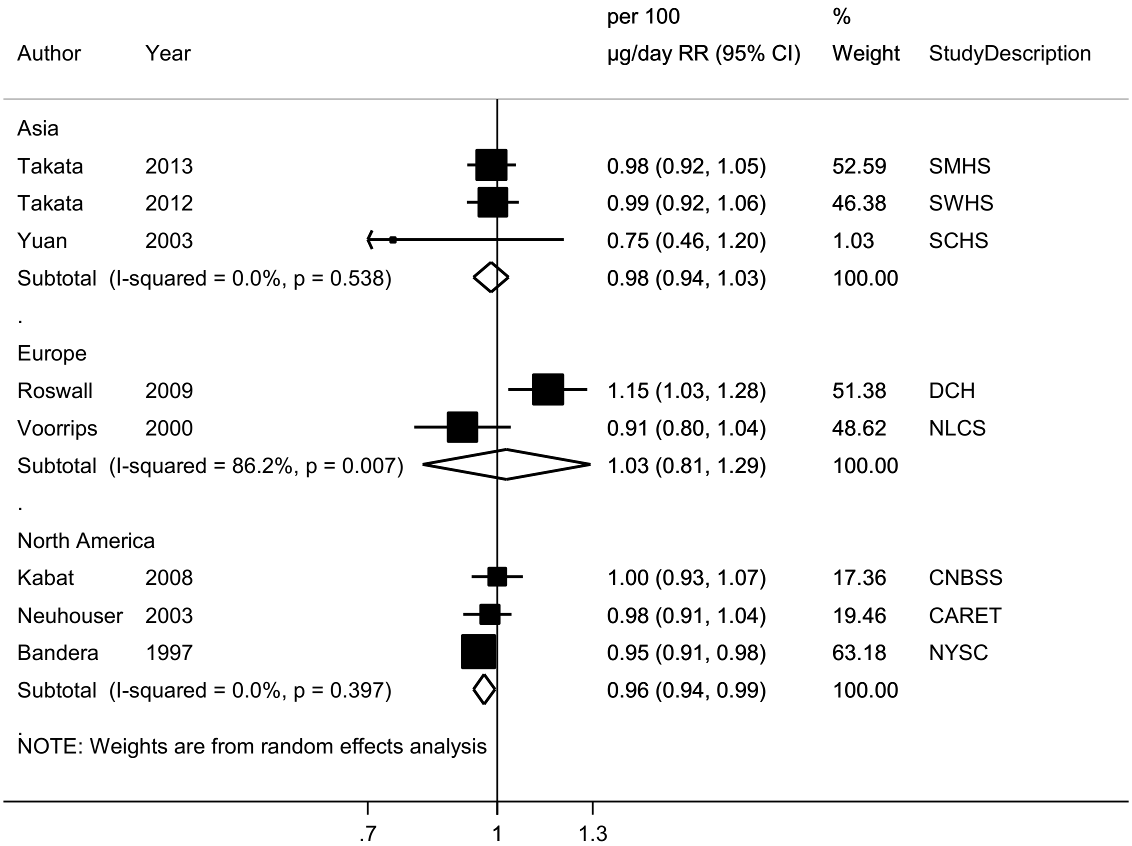


Figure 203 RR (95% CI) of lung cancer for the highest compared with the lowest level of dietary folate intake: Pooling Project of 8 cohorts and 6 studies identified in the CUP

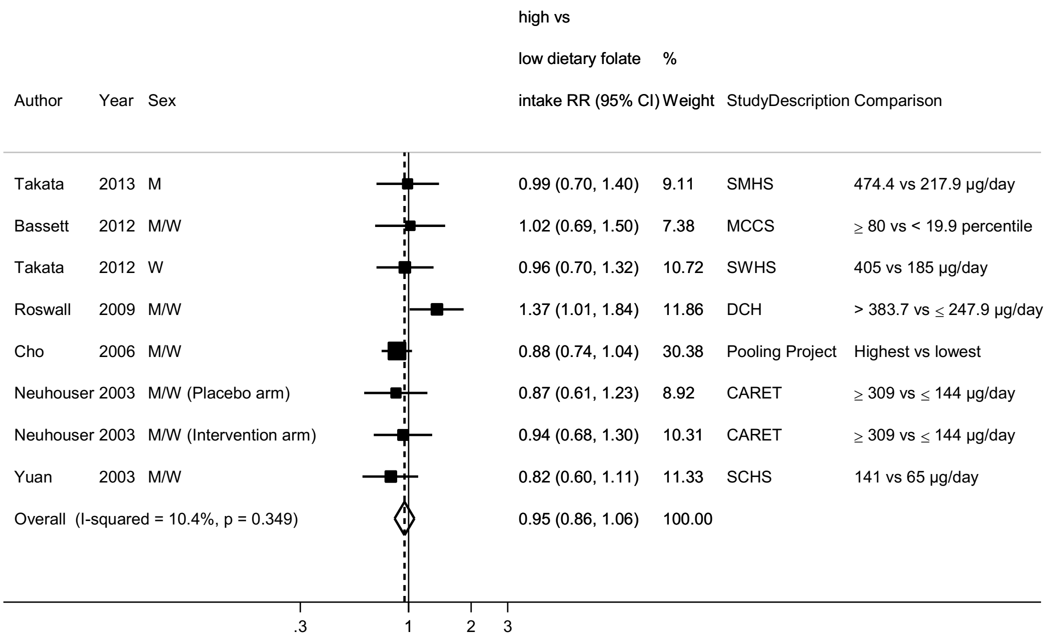
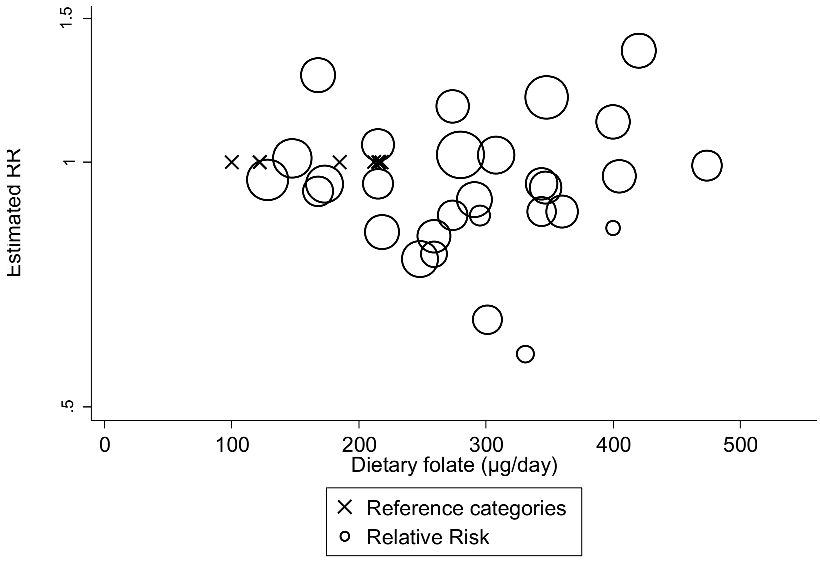
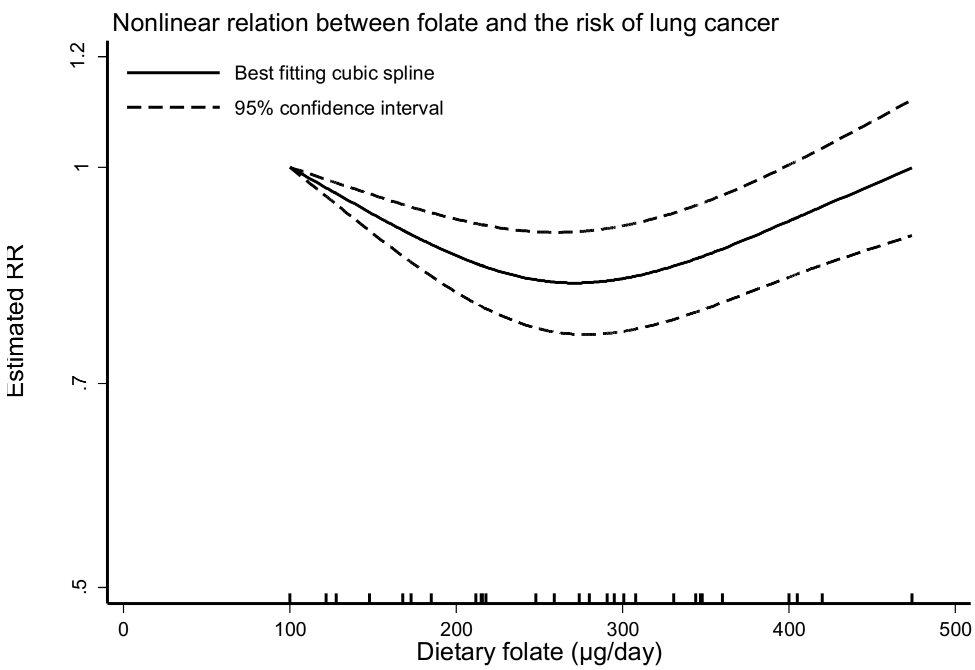


Figure 204 Relative risk of lung cancer and dietary folate intake estimated using non-linear models





$p < 0.01$

Table 185 Table with dietary folate intake values and corresponding RRs (95% CIs) for non-linear analysis of dietary folate and lung cancer

Dietary folate intake (µg/day)	RR (95%CI)
100	1.00
248	0.83 (0.77-0.90)
308	0.84 (0.77-0.91)
400	0.91 (0.83-1.00)
474	1.00 (0.89-1.12)

5.5.3 Folate supplement

No study was identified during the SLR. Two new studies were identified during the CUP. No significant association was found between folate supplement use and risk of lung cancer.

The first study (Roswall, 2009) reported no significant association for an increment of 100 µg/day of folate supplement use and risk of lung cancer (1.01; 95% CI= 0.95-1.07). This study included 55 557 Danish participants and observed 721 incident cases of lung cancer (369 men, 352 women) during an average follow up of 10.6 years.

The second study (Slatore, 2008) reported no significant association between the intake of folate supplement (10 years use) and risk of lung cancer (0.99; 95% CI= 0.79-1.23). The Vitamins And Lifestyle (VITAL) study is prospective cohort which followed 77 126 men and women for an average of 4.05 years. A total of 521 cases of lung cancer were observed.

Table 186 Studies on supplemental folate intake identified in the CUP

Author, Year, WCRF Code, Country	Study 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
Roswall, 2009 LUN26873 Denmark	DCH, Prospective Cohort, Age: 50-64 years, M/W	721/ 55 557 10.6 years	Danish cancer registry	FFQ	Incidence, lung cancer	> 133.2 vs 0 µg/day	0.99 (0.72–1.36)	Age, sex, intake of folate supplements, vitamin C, vitamin E, beta-carotene, smoking status, intensity and duration, passive smoking, smoking cessation, work exposure to carcinogenic substances	
						Per 100 µg/day	1.01 (0.95-1.07)		
		220			Incidence, lung cancer, current smokers		1.01 (0.94–1.09)		
		32			Incidence, lung cancer, former smokers		1.01 (0.91–1.12)		
		20			Incidence, lung cancer, never smokers		1.02 (0.96–1.08)		
Slatore, 2008 LUN20344 USA	VITAL, Prospective Cohort, Age: 50-76 years, M/W	517/ 77 126 4 years	Seattle–Puget Sound SEER registry		Incidence, lung cancer	≥ 400 vs no use µg/day	0.99 (0.79-1.23) Ptrend:0.68	Age, sex, pack years squared, pack-years, years of smoking	
		391			Incidence, non-small cell carcinoma	≥ 400 vs no use µg/day	1.03 (0.80-1.32) Ptrend:0.37		
		226			Incidence, lung cancer, former smokers, quit 10+ years ago	≥ 400 vs no use µg/day	0.97 (0.70-1.33) Ptrend:0.90		

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Missing data derived for analyses
		155			Incidence, lung cancer, current smokers	≥ 400 vs no use µg/day	1.08 (0.72-1.62) Ptrend:0.30		
		93			Incidence, lung cancer, former smokers, quit < 10 years ago	≥ 400 vs no use µg/day	0.76 (0.44-1.31) Ptrend:0.23		
		73			Incidence, small cell carcinoma	≥ 400 vs no use µg/day	0.61 (0.31-1.21) Ptrend:0.18		
		57			Incidence, other lung cancers	≥ 400 vs no use µg/day	1.20 (0.63-2.29) Ptrend:0.77		

5.5.3 Serum folate

In a nested case-control in the EPIC study including 899 cases of lung cancer and 1770 controls (Johansson, 2010), lung cancer was inversely related to serum folate (OR fourth vs first quartile: 0.69, 95% CI= 0.50-0.95; *P* for trend < 0.01). The association was significant for former (529 cases) and current smokers (260 cases) and inverse but not significant for never smokers (96 cases). The summary estimate in the 2005 SLR (three studies from four publications) was RR= 0.97 (95% CI= 0.92-1.03) per 2 μmol/L increase.

Table 187 Studies on serum folate identified in the CUP

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors
Johansson, 2010 LUN20318 France, Italy, Spain, UK, Netherlands, Greece, Germany, Sweden, Denmark	EPIC, Nested Case Control, Age: 35-79 years, M/W	899/ 1 770	Cancer registries, health insurance records, active follow up confirmed with pathology and medical records	Concentration of folate determined by micro-biological methods (*Lactobacillus casei*)	Incidence, lung cancer	22.5-395 vs 0.1-10 nmol/L	0.69 (0.50-0.95) Ptrend:< 0.01	Age, sex, country, year of blood collection, methionine, plasma homocysteine, plasma vit B2, B6 and B12, cotinine concentration in plasma
		529			Incidence, lung cancer, current smokers	22.5-395 vs 0.1-10 nmol/L	0.54 (0.34-0.83) Ptrend:< 0.01	Age, sex, country
		260			Incidence, lung cancer, former smokers	22.5-395 vs 0.1-10 nmol/L	0.58 (0.37-0.91) Ptrend:0.02	
		96			Incidence, lung cancer, never smokers	22.5-395 vs 0.1-10 nmol/L	0.84 (0.43-1.65) Ptrend:0.41	
Rossi, 2006 LUN21225 Australia	Busselton, Western Australia ,	44/ 1988	Death certificate	Fasting blood samples, serum folate	Mortality, Lung cancer	Per decrease of 2 µg//L	1.11 (0.85- 1.45)	Age, sex, smoking

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors
	Prospective cohort study Age: 40-90 years, M/W			levels measured within 1 week of collection		6 vs 0-2.99 µg//L	1.17 (0.44- 3.12)	
Ito, 2005 LUN26888 Japan	JACC, Nested Case Control, Age: 40-79 years, M/W	163/ 375 controls 10 years	Death certificate	Serum sample measured by (HPLC)	Incidence, lung cancer, men	> 7.5vs < 3.9 ng/mL	0.82 (0.20-3.35) Ptrend: 0.95	Age, sex, smoking habits, participating institution and alcohol drinking
		48/ 112			Incidence, lung cancer, women	> 9.9 vs < 4.7 ng/mL	0.93 (0.10-8.50) Ptrend:0.88	
Ito, 2003 LUN00342 Japan	JACC Nested Case Control, Age: 40-79 years, M/W	147/ 311 controls 8 years	Population death registries	Serum sample, analysed by HPLC	Mortality, lung cancer	18.36 vs < 9.29 nmol/L	0.52 (0.15–1.75) (Folic acid)	Age, sex, participating institution, smoking habits and alcohol drinking habits,BMI, serum cholesterol level
Hartman, 2001 LUN00887 Finland	ATBC, Nested Case Control, Age:50-69 Years, M, smokers	300 / 300 controls	Cancer registry	Serum sample, analysed by HPLC	Incidence, lung cancer	> 5.2 vs ≤3.1 µg//mL	0.96 (0.52-1.79)	Age, smoking (years and number of cigarettes smoked per day as continuous variables), BMI

5.5.9 Dietary vitamin C

Cohort studies

Summary

Main results:
Ten studies (4379 cases) out of 13 studies (17 publications) were included in the dose-response meta-analysis. A significant inverse association of lung cancer risk with vitamin C intake was observed.
High heterogeneity was observed that was partially explained in stratified analysis in which the significant inverse association was observed in current smokers but not in former or nerver smokers. There was no evidence of publication or small study bias (p= 0.54).

Sensitivity analysis:
In influence analysis, the summary RRs ranged from 0.90 (95% CI=0.87-0.95) when Shibata, 1992 was omitted to 0.93 (95% CI= 0.89-0.97) when Voorrips, 2000a was omitted.

There was evidence of a non-linear dose-response of lung cancer and dietary vitamin C intake ($p < 0.01$). There is a decreasing risk of lung cancer for increasing vitamin C intakes up to approximately 100 mg/day, little additional risk decrease is observed for higher dietary vitamin C intakes.

Study quality:
All studies used FFQ to assess the intake of dietary vitamin C. The study from Singapore (Yuan, 2003) corrected for measurements error in dietary assessment using regression calibrated method.
All studies included in the dose-response analysis were adjusted at least for age and smoking status, All studies adjusted for intensity, duration of smoking and other smoking variables in addition to smoking status

Table 188 Dietary vitamin C consumption and lung cancer risk. Number of studies in the CUP SLR

	Number
Studies identified	13 (17 publications)
Studies included in forest plot of highest compared with lowest exposure	12
Studies included in dose-response meta-analysis	10
Studies included in non-linear dose-response meta-analysis	5

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

Table 189 Dietary vitamin C consumption and lung cancer risk. Summary of the dose-response meta-analysis in the 2005 SLR and CUP

	2005 SLR	CUP
All studies		
Increment unit used	Per 50 mg/day	Per 40 mg/day
Studies (n)	2	10
Cases (total number)	412	4379
RR (95%CI)	0.93 (0.84-1.03)	0.92 (0.88-0.96)
Heterogeneity (I^2, p-value)	63%	65.9%, < 0.01
p value Egger test		0.54

Stratified and sensitivity analysis (no analyses conducted in the 2005 SLR)			
Smoking status	**Never smokers**	**Current smokers**	**Former smokers**
Studies (n)	3	4	3
RR (95%CI)	0.93 (0.79-1.08)	0.87 (0.79-0.96)	0.96 (0.87-1.05)
Heterogeneity (I^2, p-value)	0%, 0.90	61.8%, 0.05	0%, 0.80
Sex	**Men**	**Women**	
Studies (n)	5	3	
RR (95%CI)	0.92 (0.86-0.98)	0.96 (0.92-1.01)	
Heterogeneity (I^2, p-value)	80.3%, < 0.001	0%, 0.42	
Cancer Type	**Adenocarcinoma**	**Small cell carcinoma**	**Squamous cell carcinoma**
Studies in the CUP (n)	2	No data	2
RR (95%CI)	0.93 (0.87-0.99)		0.92 (0.87-0.97)
Heterogeneity (I^2, p-value)	3%, 0.31		0%, 0.37
Geographic location	**Asia**	**Europe**	**North America**
Studies in the CUP (n)	2	3	5
RR (95%CI)	0.93 (0.87-1.00)	0.86 (0.76-0.98)	0.95 (0.91-1.00)
Heterogeneity (I^2, p-value)	0%, 0.51	83.7%, < 0.01	40.4%, 0.15

Table 190 Dietary vitamin C consumption and lung 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	Outcome	Comparison	RR (95%CI)	P trend	Heterogeneity (I^2, p value)
Luo, 2014*	14 (case-control and cohort studies)	6607	Lung cancer, all	Per 100 mg/day	0.93 (0.88-0.98)		74.9%, < 0.01
	21 (case-control and cohort studies)	8938	Lung cancer, all	Highest vs lowest	0.83 (0.73-0.94)		57.8%, < 0.01
	14 cohorts	5485	Lung cancer, all	Highest vs lowest	0.83 (0.73-0.94)		48%, 0.02
	7 case-control studies	3453	Lung cancer, all	Highest vs lowest	0.84 (0.62-1.13)		73.2%, < 0.01
	8	3474	Men	Highest vs lowest	0.74 (0.63–0.87)		31.9%, 0.17
	8	2037	Women	Highest vs lowest	1.00 (0.75–1.33)		59.5%, 0.01
	4	1044	Current smokers	Highest vs lowest	0.64 (0.44–0.92)		52.2%, 0.01
	4	702	Former smokers	Highest vs lowest	0.90 (0.71–1.14)		0%, 0.92
	3	262	Never smokers	Highest vs lowest	1.02 (0.64–1.64)		0%, 0.47
	17	7104	America	Highest vs lowest	0.85 (0.73–0.98)		63.4%, < 0.01
	2	993	Europe	Highest vs lowest	0.64 (0.40–1.04)		46.8%, 0.17
	2	841	Asia	Highest vs lowest	0.82 (0.66–1.03)		0%, 0.87

Table 190(cont.)

Author, Year	Number of studies	Total number of cases	Studies country, area	Outcome	Comparison	RR (95%CI)	P trend	Heterogeneity (I^2, p value)
Pooled-analysis								
Cho, 2006	8	3206	North America and Europe	Incidence, lung cancer	Highest vs lowest	0.80 (0.71-0.91)	< 0.01	0.47
		1777		Men		0.80 (0.66–0.96)	0.08	0.33
		1378		Women		0.81 (0.68–0.97)	0.01	0.39
		259		Never smokers		0.68 (0.41–1.12)	0.41	0.11
		981		Former smokers		0.89 (0.73–1.10)	0.17	0.58
		1915		Current smokers		0.85 (0.70–1.02)	0.08	0.15
		956		Adenocarcinomas		0.90 (0.74–1.09)	0.22	0.20
		538		Small cell carcinomas		0.83 (0.68–1.00)	0.07	0.91
		901		Squamous cell carcinomas		0.84 (0.70–1.00)	0.02	0.61

*Reported on total vitamin C intake including supplements.

Table 191 Dietary vitamin C consumption and lung cancer risk. Main characteristics of studies included in the 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
Takata, 2013 LUN26860 China	SMHS, Prospective Cohort, Age: 40-74 years, M	359/ 61 092 6 years	Biennial home visits (diagnosis verified by medical chart review), record linkage to Cancer Registry and Vital Statistics Registry	Validated FFQ	Incidence, lung cancer	150.4 vs 46.2 mg/day	0.84 (0.61-1.16)	Age, BMI, tea consumption, total caloric intake, current smoking status, education, family history of lung cancer, history of chronic bronchitis, number of cigarettes smoked per day, years of smoking	Distribution of person-years per quartiles
Roswall, 2009 LUN26873 Denmark	DCH, Prospective Cohort, Age: 50-64 years, M/W	721/ 55 557 10.6 years	Danish cancer registry	FFQ	Incidence, lung cancer	Per 100 mg/day	0.94 (0.78-1.13)	Age, sex, folate supplements, intake of vitamin C, vitamin E, beta-carotene, smoking status, intensity and	Distribution of person-years, increment unit recalculated to 40 mg/day
		721				> 120.2 vs ≤ 60 mg/day	0.76 (0.58-0.9)		
		33			Incidence, lung cancer, never	Per 100 mg/day	0.82 (0.42–1.61)		

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Missing data derived for analyses
					smokers			duration, passive smoking, smoking cessation, work exposure to carcinogenic substances	
		95			Incidence, lung cancer, former smokers		0.90 (0.60–1.34)		
		593			Incidence, lung cancer, current smokers		0.91 (0.77–1.08)		
Neuhouser, 2003 LUN00354 USA	CARET, Prospective Cohort, Age: 45-69 years, M/W	326/ 14 120 8 years	Primary outcome of the trial. Active follow-up with confirmation by clinical records and pathology reports	FFQ - study-specific	Incidence, lung cancer, placebo arm	≥ 110 vs ≤ 35 mg/day	0.66 (0.47–0.94) Ptrend:0.06	Age, sex, smoking status, total pack-years of smoking, asbestos exposure, race/ethnicity, and enrollment center	Distribution of person-years and cases by exposure quintiles, mid-points of exposure quintiles, RRs for intervention and placebo combined
		414			Incidence, lung cancer, intervention arm		0.80 (0.58–1.11) Ptrend:0.04		
Yuan, 2003 LUN00218 Singapore	SCHS, Prospective Cohort, Age: 45-47 years, M/W	482/ 62 392 8 years	Cancer registry and death registries	FFQ - study-specific	Incidence, lung cancer	102 vs 19 mg/1000 kcal	0.81 (0.59–1.09)	Age, sex, BMI, year of interview, educational level, ethnicity/race,	Distribution of person years in smoking status subgroups, mg / 1000 kcal converted to
						Per 83 mg/1000 kcal	0.69 (0.42–1.15)		
		268			Incidence, lung cancer, current smokers		0.48 (0.22–1.01)		

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Missing data derived for analyses
		71			Incidence, lung cancer, never smokers		1.30 (0.38–4.44)	number of cigarettes smoked per day, number of years of smoking, number of years since quitting smoking for former smokers	mg/day, increment unit recalculated to 40 mg/day
		145			Incidence, lung cancer , former smokers		0.90 (0.38–2.12)		
Voorrips, 2000a LUN01121 Netherlands	NLCS, Case Cohort, Age: 55-69 years, M	939/ 58 279 6.3 years	Regional cancer registries and computerized national database of pathology report (PALGA)	FFQ - study-specific	Incidence, lung cancer	138 vs 51 mg/day	0.64 (0.54–0.77) Ptrend:< 0.01	Age, educational level, family history of lung cancer, smoking status, cigarettes/ day, years smoking, time since quitting	Distribution of, number of cases and non-cases in quintiles
		35			Incidence, lung cancer, never smokers		0.67 (0.25–1.79) Ptrend:0.39		
		312			Incidence, lung cancer, former smokers		0.84 (0.56–1.27) Ptrend:0.38		
		487			Incidence, lung cancer, current smokers		0.54 (0.38–0.78) Ptrend:< 0.01		
Yong, 1997 LUN01778 USA	NHANES I, Prospective Cohort, Age: 25-74 years,	248/ 10 068 19 years	Follow-up interviews confirmed with hospital records and death	FFQ - study-specific	Incidence, lung cancer	> 113.05 vs 23.07 mg/day	0.66 (0.45-0.96)	Age, sex, educational attainment, non-recreational activity level,	Distribution of person years and mid-points 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		certificates					BMI, alcohol intake, family history, total calorie intake, smoking status and pack years of smoking	
Bandera, 1997 LUN01693 USA	NYSC, Prospective Cohort, Age: 40-80 years, M/W	395/ 48 000 7 years	Cancer registry and New York State Department of Health's Vital Statistics Section, National Death Index	FFQ - study-specific	Mortality, lung cancer, men	Highest vs lowest	0.63 (0.53-0.88) Ptrend: < 0.01	Age, educational level, energy intake, smoking habits	Used tertiles from Bandera, 2002 , distribution of person years in tertiles, mid-points exposure
		130			Mortality, lung cancer, women	Highest vs lowest	0.88 (0.57-1.37) Ptrend: 0.19		
Steinmetz, 1993 LUN02740 USA	IWHS, Nested Case Control, Age: 55-69 years, Post-menopausal women	138/ 2814 controls 4 years	Iowa Health registry (part of SEER registry)	FFQ - study-specific	Incidence, lung cancer	≥ 189 vs ≤ 99 mg/week	0.81 (0.46-1.43)	Age, energy intake, pack years of smoking	Distribution of number of cases and non-cases per quartiles, mid-points of exposure
Shibata, 1992 LUN08664 USA	LWS, Prospective Cohort,	94/ 11 580 6 years	Death by reports of friends or relatives,	FFQ - study-specific	Incidence, lung cancer, men	≥ 210 vs < 145 mg/day	1.11 (0.68-1.81)	Age, smoking habits	Distribution of person-years by exposure tertiles

Author, Year, WCRF Code, Country	Study 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: 74 years, M/W	70/ 11 580	National Death Index; incidence through hospital records		Incidence, lung cancer, women	≥ 225 vs < 155 mg/day	0.56 (0.31-1.02)	Age, smoking habits	
Kromhout, 1987 LUN03765 Netherlands	Zutphen Study, Prospective Cohort, Age: 40-59 years, M	878 12 years	Data from Central Bureau of Statistics, diagnosis verified through cancer registry, hospital discharge or general practitioner, death certificate	Dietary history questionnaire	Mortality, lung cancer	Highest vs lowest	0.36 (0.18-0.75)	Age, pack-years of cigarette smoking	Distribution of person-years and cases by exposure tertiles, mid-points of exposure tertiles

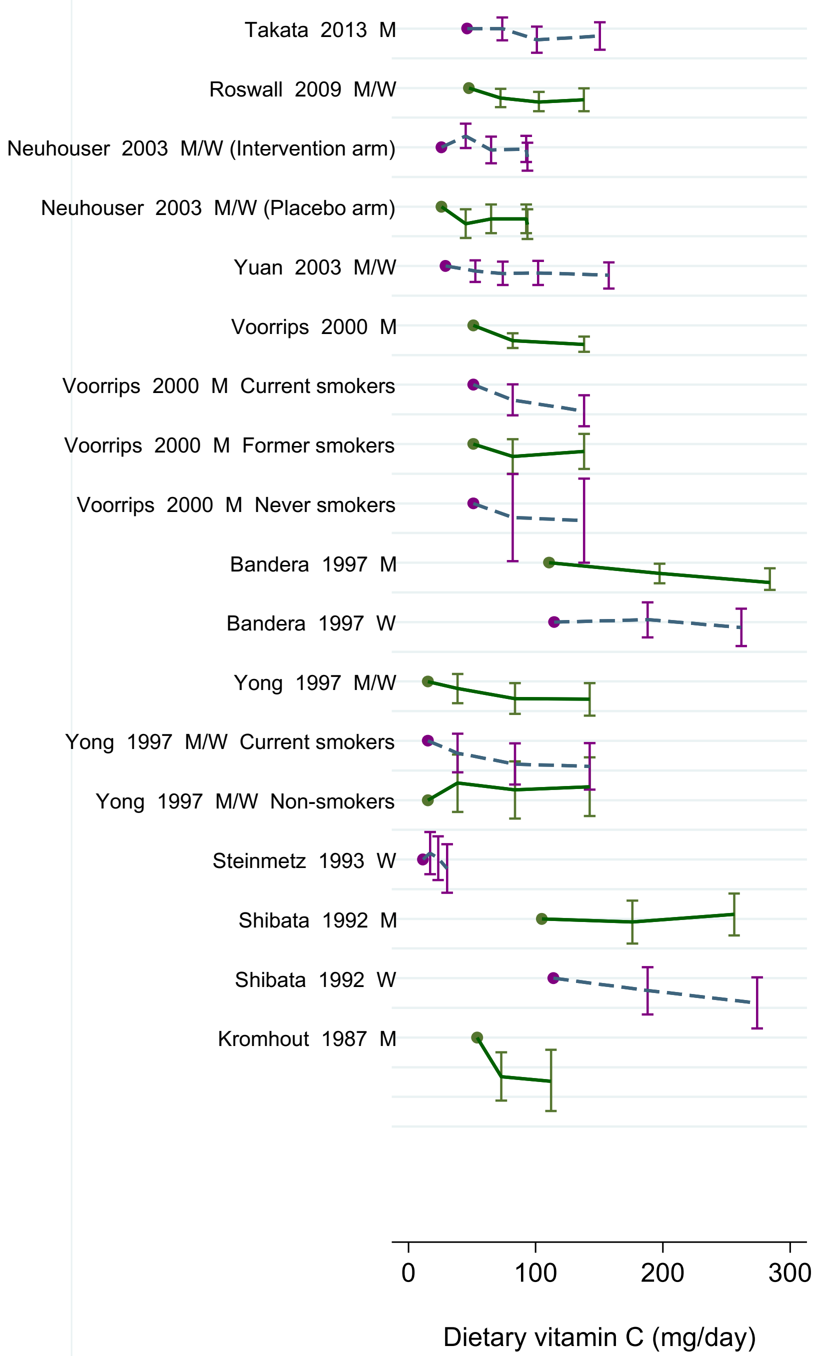
Table 192 Dietary vitamin C consumption and lung cancer risk. Main characteristics of studies excluded in the dose-response meta-analysis

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
Sakoda, 2011 LUN20351 USA	CARET, Nested Case Control, Age: 45-69 years, M/W	365/ 18 314	Primary outcome of the trial. Active follow-up with confirmation by clinical records and pathology reports	FFQ	Incidence, lung cancer	> 85.2 vs ≤ 46.1 mg/day	ORGA 1.30 (0.93–1.83)	Age, sex, enrolment year, smoking status, occupational asbestos exposure	Only has gene interactions results, Neuhouser, 2003 LUN00354 was used
		163			Incidence, lung cancer		ORAA 1.80 (1.10–2.94		
					Incidence, lung cancer		OR per A allele 1.33 (1.06–1.68)		
Bandera, 2002 LUN00506 USA	NYSC, Nested case-control, Age: 40-80 years, M/W	395/ 48 000 7 years	Cancer registry and New York State Department of Health's Vital Statistics Section, National Death Index	FFQ - study-specific	Mortality, lung cancer, men	Highest vs lowest	0.65 (0.50–0.84) Ptrend: < 0.05	Age, ace, and county of residence), education (yr), cigarettes/day, and years smoking	Duplicate of Bandera, 1997 LUN01693
					Mortality, lung cancer, women		0.80 (0.51–1.26)		
Ocke, 1997 LUN01851 Netherlands	Zutphen Study, Prospective Cohort, Age: 40-59 years, M	54/ 561 12 years	Data from Central Bureau of Statistics, diagnosis verified through cancer registry, hospital	Dietary history questionnaire	Incidence, lung cancer	> 33rd vs ≤ 33rd average intake percentile	1.43 (0.82-2.51)	Age, pack years of cigarettes, energy intake	Duplicate of Kromhout, 1987 LUN03765
						> 33rd vs ≤ 33rd stable intake percentile	1.65 (0.76-3.58)		

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Reasons for exclusion
			discharge or general practitioner						
Knekt, 1993 LUN02684 Finland	FMCHES, Nested Case Control, Age: 15- years, M	95/ 21 172 9 years	Cancer registry	FFQ - study-specific	Incidence, lung cancer, non-smokers	Lowest vs highest	3.1 (0.9-10.7)	Age	Used only in highest vs lowest analysis Hamling method used to rescale lowest vs highest to highest vs lowest
					Incidence, lung cancer, smokers		0.8 (0.4-1.3)		
Chow, 1992 LUN02888 USA	LBS, Prospective Cohort, Age: 35- years, M	219/ 17 633 20 years	Death certificates	FFQ - study-specific	Mortality, lung cancer	Highest vs lowest	0.80 (0.50-1.20)	Age, smoking habits, industry/occupation	Used only in highest vs lowest analysis, No specific cut-points for quintiles is reported
Knekt, 1991b LUN03018 Finland	FMCHES, Prospective Cohort, Age: 20-69 years, M	4583 20 years	Cancer registry	FFQ - study-specific	Incidence, , lung cancer, current smokers	Lowest vs highest	0.81	Age, smoking habits	Duplicate of Knekt, 1993 LUN02684

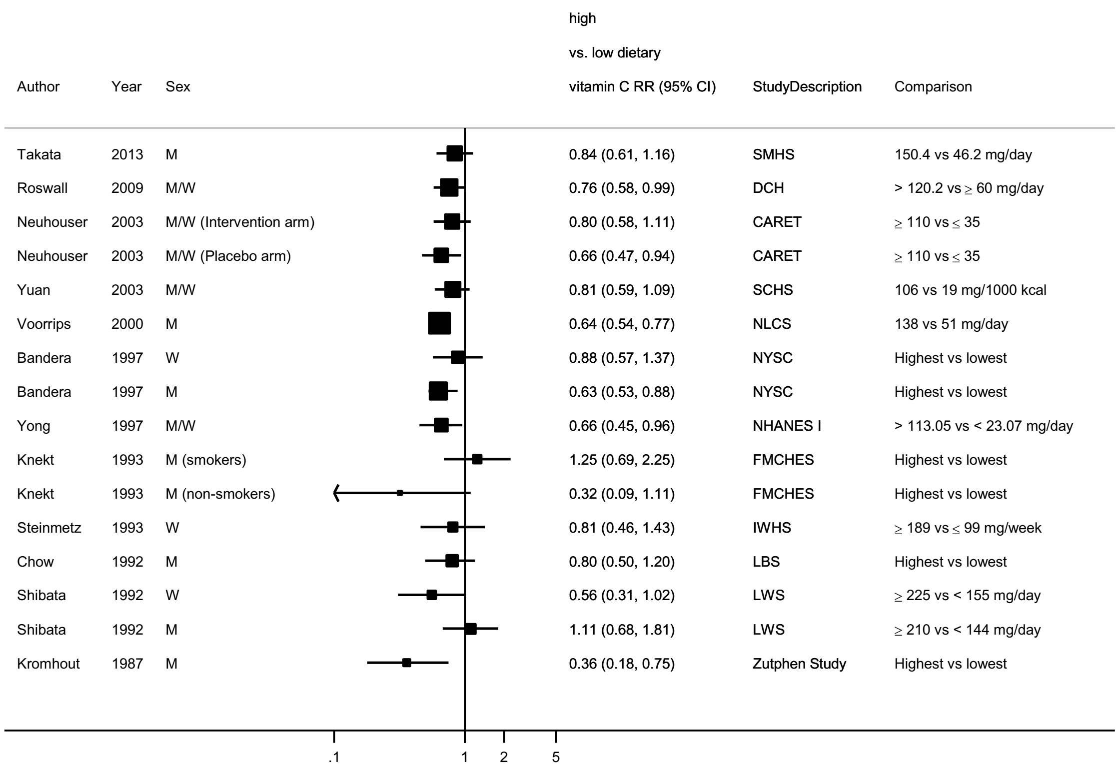
Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Reasons for exclusion
Kvåle, 1983 LUN04322 Norway	Norway, 1967-1978, Prospective Cohort, M/W	168/ 16 713 11.5 years	Cancer registry	Dietary history questionnaire	Incidence, primary tumour of lung cancer	Highest vs lowest	0.88 Pvalue: 0.65	Age, cigarette smoking, urban/rural place of residency	Intake is a score of frequency

Figure 205 RR estimates of lung cancer by levels of dietary vitamin C consumption



* In study of Yong, 1997, non-smokers defined as never smokers plus former smokers.

Figure 206 RR (95% CI) of lung cancer for the highest compared with the lowest level of dietary vitamin C consumption



*In FMCHES study, the RR's were recalculated using Hamling method (Hamling, 2008).

Figure 207 RR (95% CI) of lung cancer for 40 mg/day increase of dietary vitamin C consumption

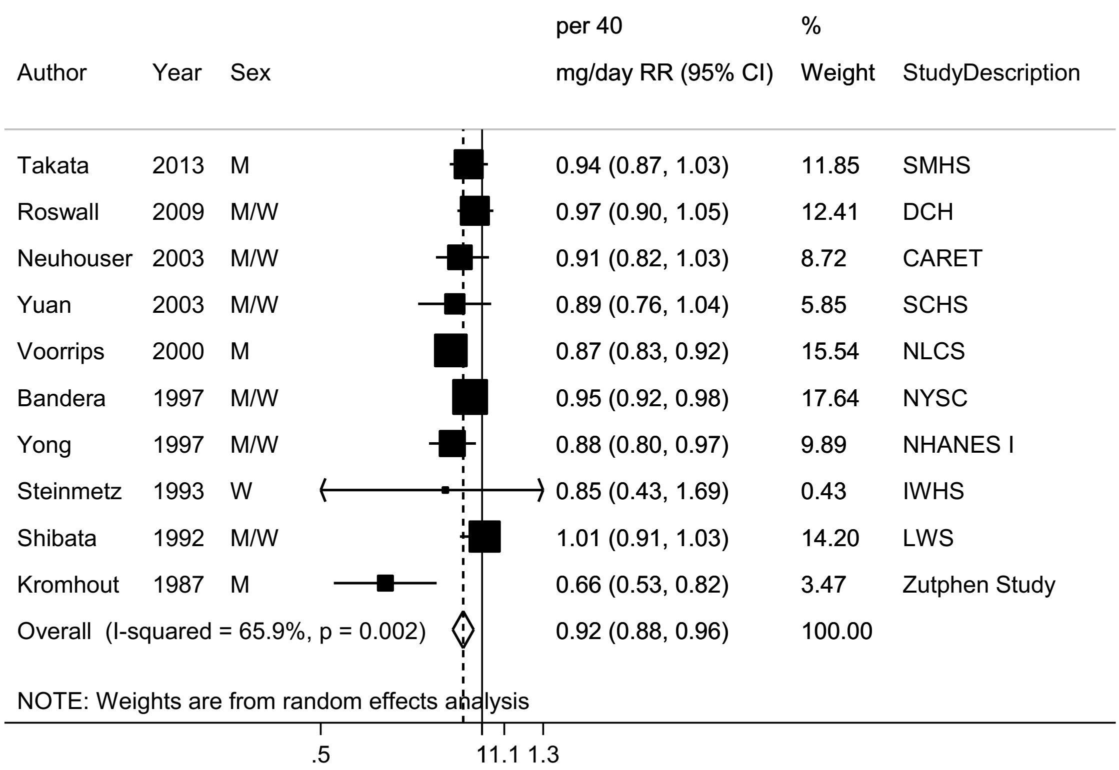
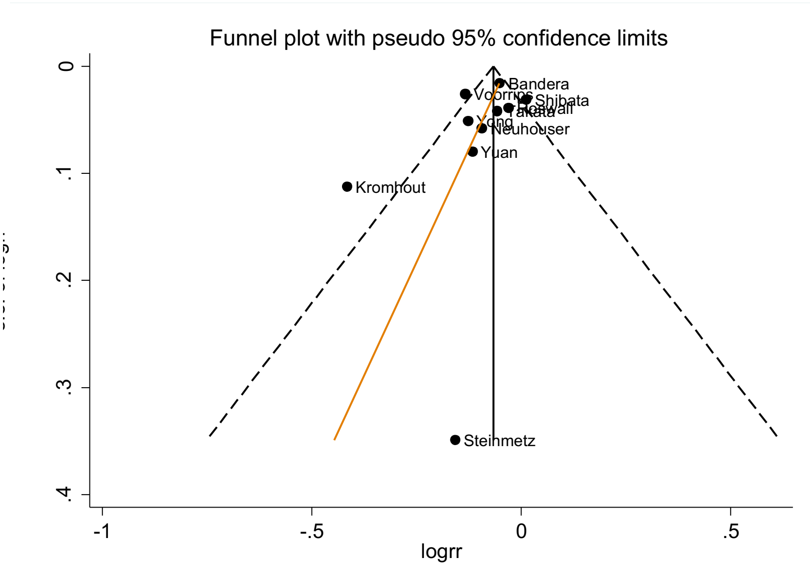


Figure 208 Funnel plot of studies included in the dose response meta-analysis of dietary vitamin C consumption and lung cancer



Egger's test p= 0.54

Figure 209 RR (95% CI) of lung cancer for 40 mg/day increase of dietary vitamin C consumption by smoking status

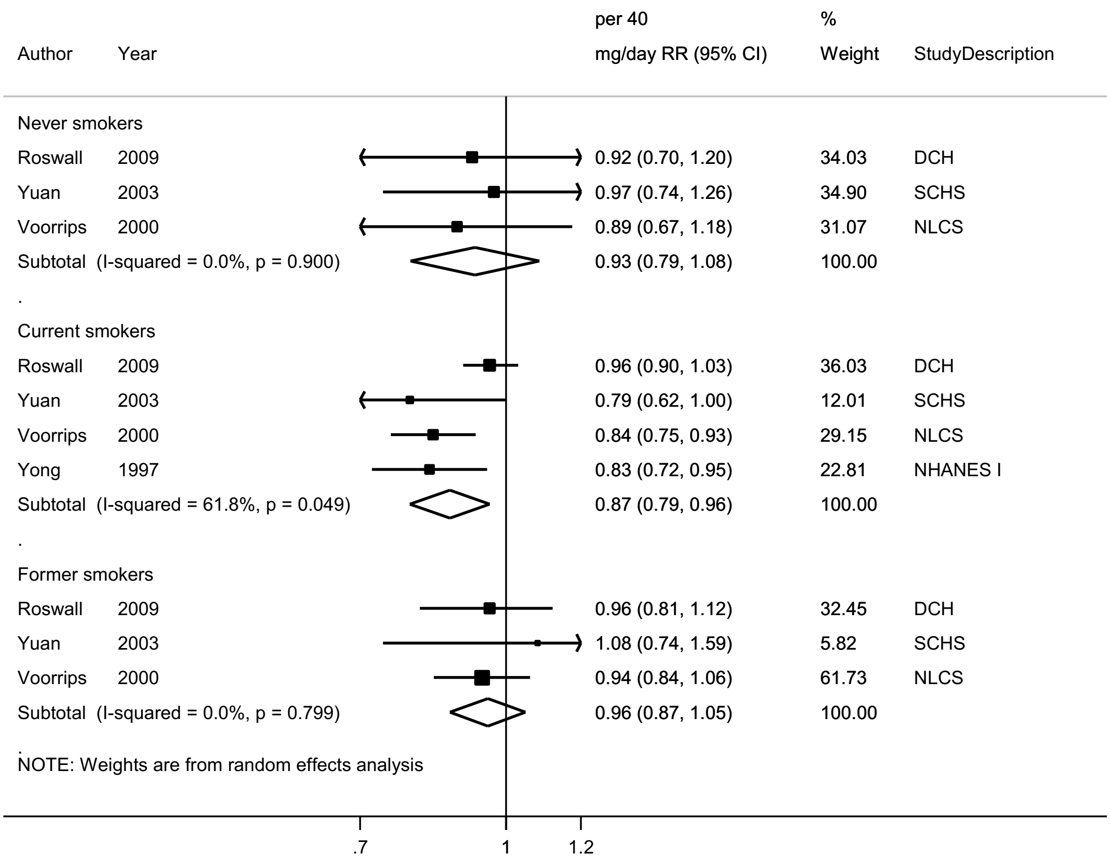


Figure 210 RR (95% CI) of lung cancer for 40 mg/day increase of dietary vitamin C consumption by sex

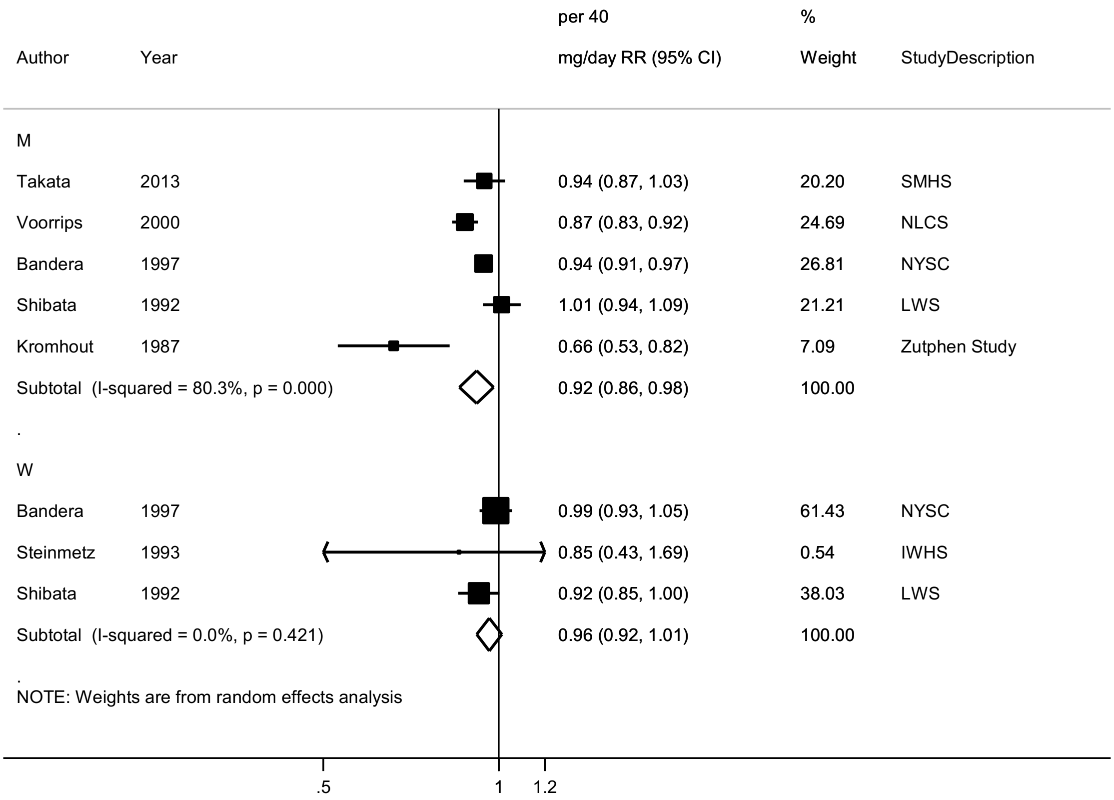


Figure 211 RR (95% CI) of lung cancer for 40 mg/day increase of dietary vitamin C consumption by cancer site

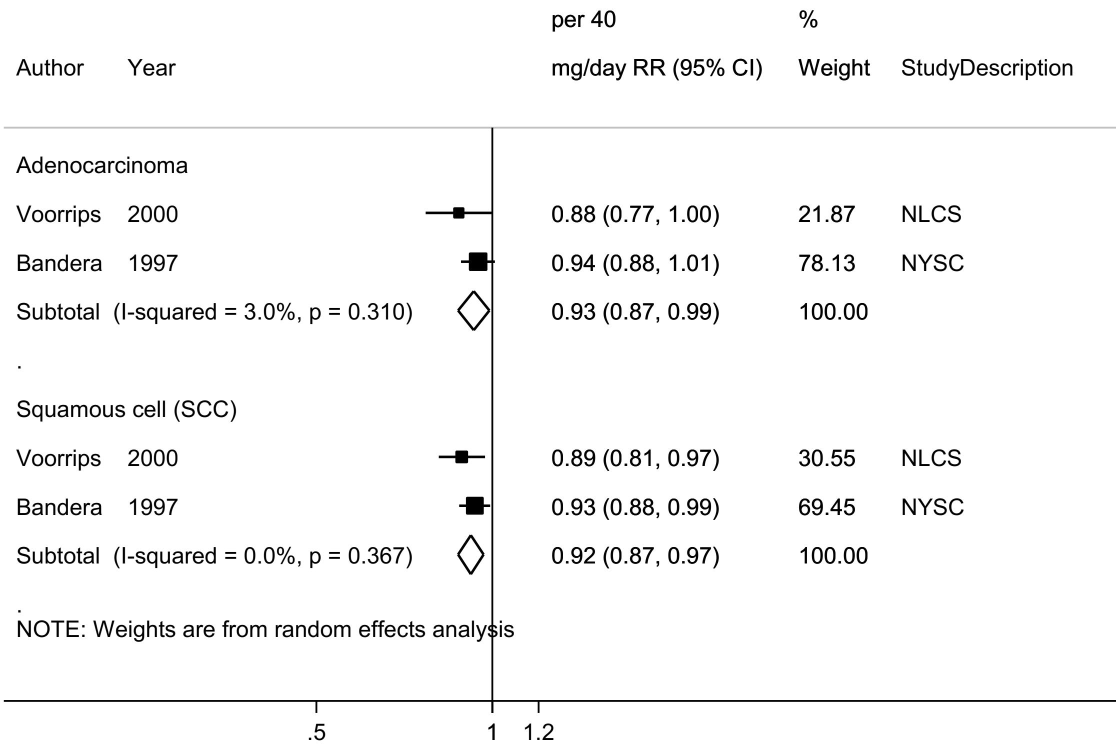


Figure 212 RR (95% CI) of lung cancer for 40 mg/day increase of dietary vitamin C consumption by geographic location

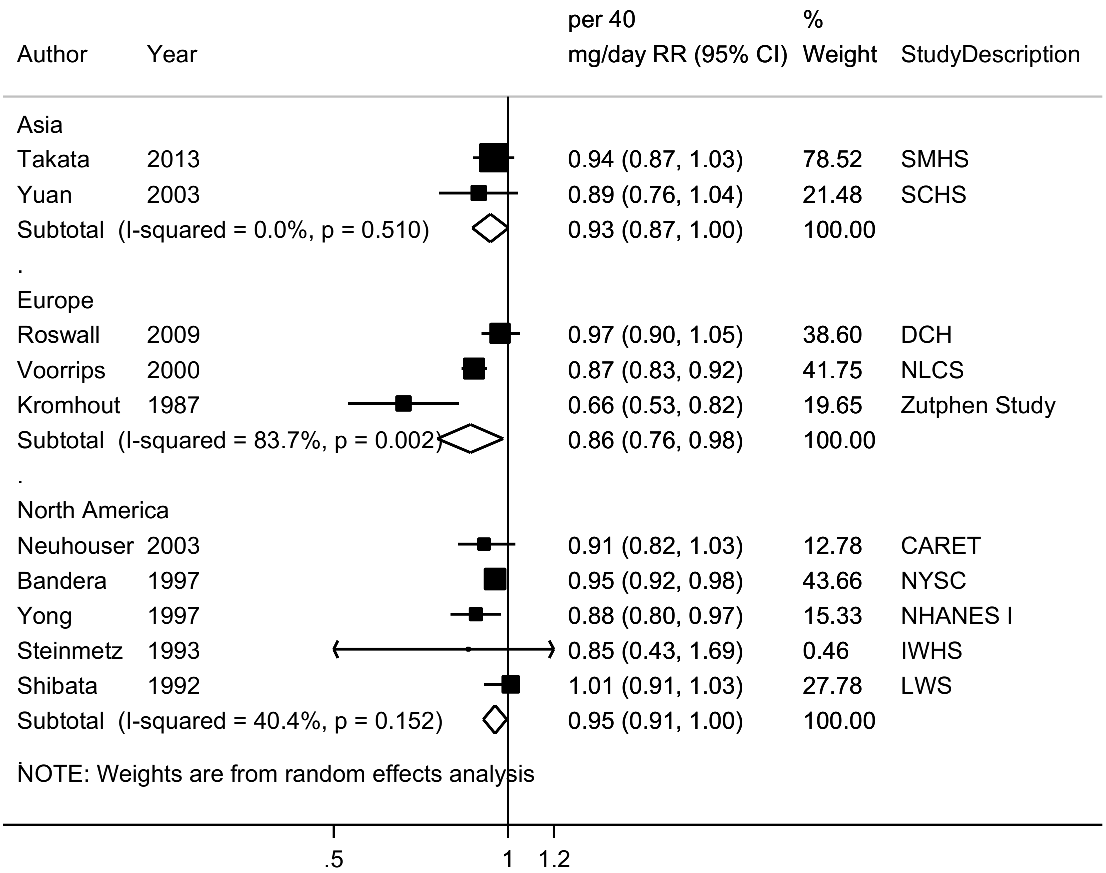
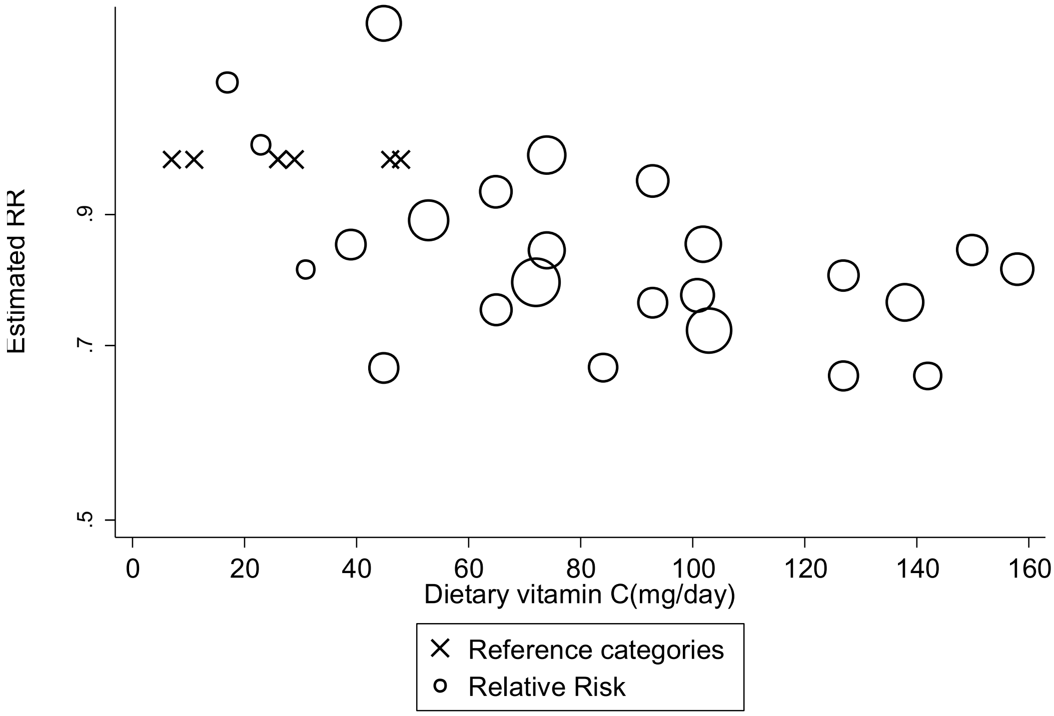
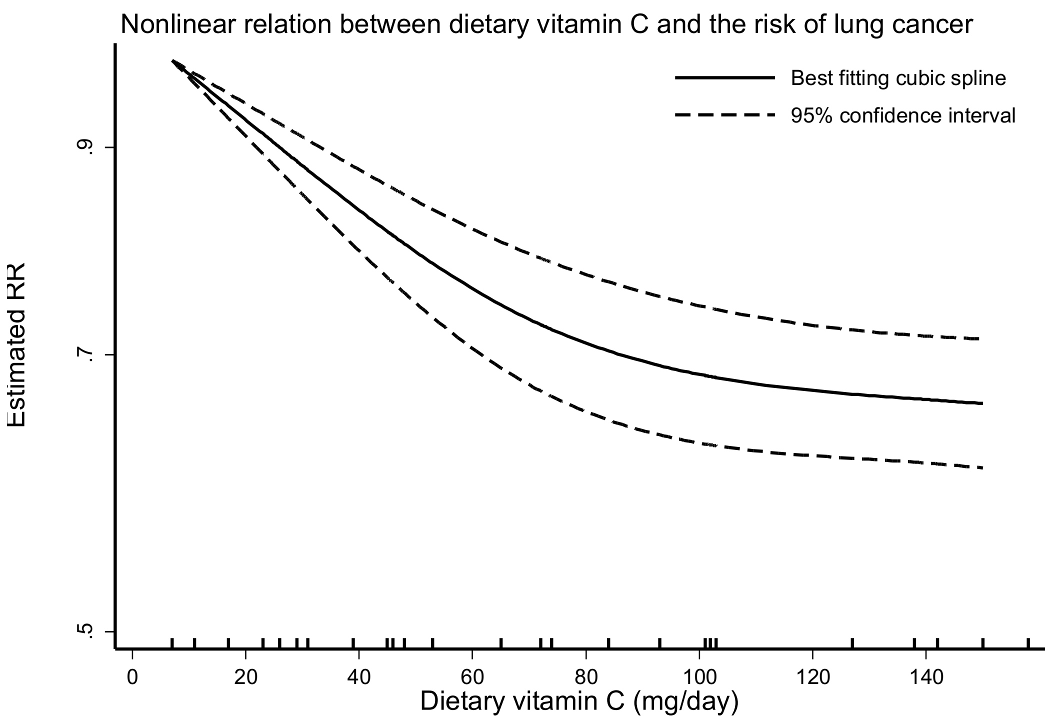


Figure 213 Relative risk of lung cancer and dietary vitamin C estimated using non-linear models





$p < 0.01$

Table 193 Table with dietary vitamin C values and corresponding RRs (95% CIs) for non-linear analysis of dietary vitamin C and lung cancer

Dietary vitamin C intake (mg/day)	RR (95%CI)
7	1.0
29	0.88 (0.86-0.91)
65	0.74 (0.69-0.80)
101	0.68 (0.63-0.74)
142	0.66 (0.61-0.72)

5.5.9 Vitamin C supplement

Randomised Controlled Trials

No randomised controlled trial study was identified during the 2005 SLR. One RCT (Wang, 2014; Gaziano, 2009) was identified during the CUP
The Physician's Health Study II is a randomised, double-blind, placebo-controlled, factorial trial of vitamin E (synthetic α-tocopherol 400 IU on alternate days) and vitamin C (500 mg daily) supplementation (Gaziano, 2009). The study included 14 641 male physicians in the United States of 50 year of age or older. During a mean follow-up of 8 years, a total of 103 lung cancer cases were confirmed. No significant difference in lung cancer incidence was observed in the vitamin C (500 mg daily) supplementation group compared to placebo (HR= 0.95 (95% CI= 0.64-1.39)). In another publication of PHS II study (Wang, 2014), the reported HR's were 0.95 (95% CI= 0.65-1.38) for lung cancer risk and 0.77 (95% CI= 0.52-1.16) for lung cancer death. After the PHS II intervention ended in 2011, the participants were followed up for an extra mean of 2.8 years and 53 lung cancer cases were identified (Wang, 2014). No effect of vitamin C on the risk of lung cancer in the active vitamin C group compared with the placebo group was observed in this posttrial follow up study (HR=1.12 (95% CI= 0.66-1.93) for lung cancer risk and 1.32 (95% CI= 0.73-2.40) for lung cancer death) (Wang, 2014).

Cohort studies

Summary

Main results:
Six studies were identified. Only one study provided data for dose-response analysis. Instead, categorical meta-analyses combining the comparisons of use vs nonuse and highest vs lowest supplement level was conducted, including 6 studies (4166 cases). There was no significant association of vitamin C supplement use and lung cancer.
No heterogeneity was observed.

The results were similar in men and women. There was not enough data to do stratified analysis by either histologic type or smoking status.

Study quality:
All studies used FFQ to assess the intake of vitamin C supplement. All studies included in the meta- analysis were adjusted at least for age and smoking status, except one study (Iso, 2007) that did not adjust for smoking. After excluding the only study not adjusted for smoking (Iso, 2007) the RR was 1.00(0.89-1.13).

Table 194 Vitamin C supplement use and lung cancer risk. Number of studies in the CUP SLR

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

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

Table 195 Vitamin C supplement use and lung cancer risk. Summary of the dose-response meta-analysis in the 2005 SLR and CUP

	2005 SLR	**CUP**
All studies		
Increment unit used	No meta-analysis	Highest vs lowest
Studies (n)		6
Cases (total number)		4166
RR (95%CI)		0.99 (0.88-1.10)
Heterogeneity (I^2, p-value)		0%, 0.53

Stratified and sensitivity analysis (no analyses conducted in the 2005 SLR)		
Sex	**Men**	**Women**
Studies (n)	3	3
RR (95%CI)	0.91 (0.72-1.15)	0.93(0.78-1.10)
Heterogeneity (I^2, p-value)	0%, 0.66	0%, 0.49

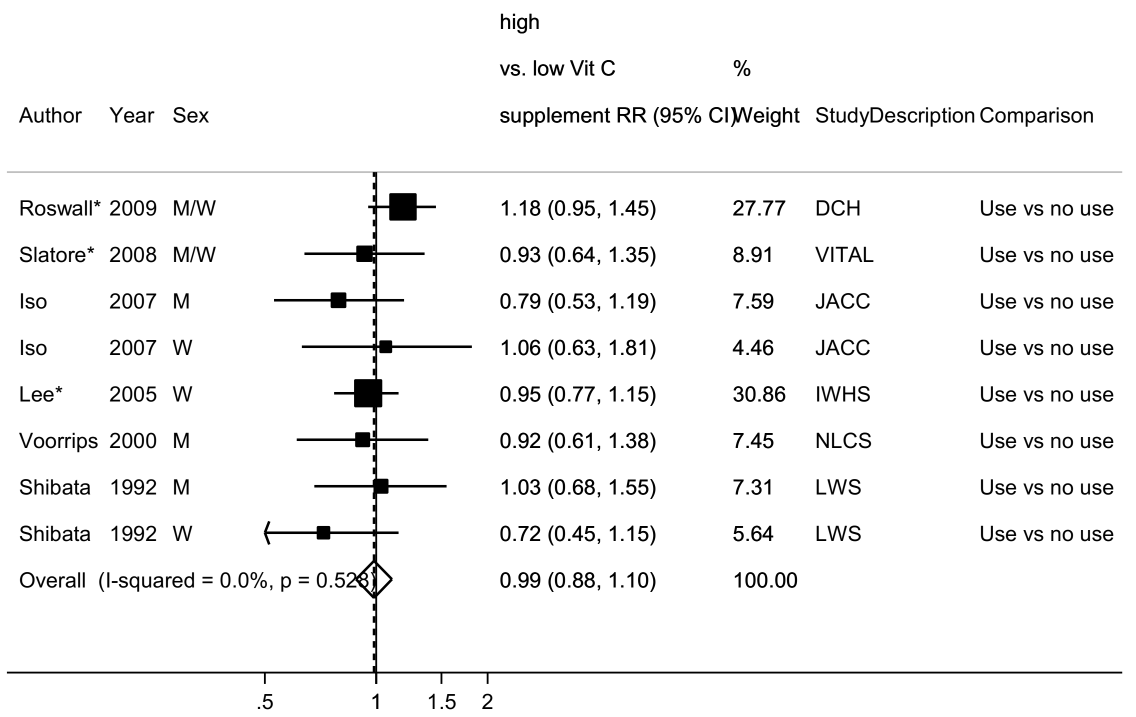
Table 196 Vitamin C supplement use and lung cancer risk. Main characteristics of studies included in the dose-response meta-analysis

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
Roswall, 2009 LUN26873 Denmark	DCH, Prospective Cohort, Age: 50-64 years, M/W	721/ 55 557 10.6 years	Danish cancer registry	FFQ	Incidence, lung cancer	Per 100 mg/day	1.00 (0.96-1.03)	Age, sex, folate supplements intake, vitamin C intake, vitamin E intake, beta-carotene intake, smoking status, smoking intensity, smoking duration, passive smoking, smoking cessation work exposure to carcinogenic substances	
		721			Incidence, lung cancer	> 66.6 vs 0 mg/day	1.23 (0.93-0.62)		
		23			Incidence, lung cancer, never smokers	Per 100 mg/day	0.92 (0.72–1.18)		
		42			Incidence, lung cancer, former smokers		0.96 (0.83–1.11)		
		278			Incidence, lung cancer, current smokers		1.01 (0.98–1.04)		
Slatore, 2008 LUN20344 USA	VITAL, Prospective Cohort, Age: 50-76 years, M/W	515/ 77 126 4 years	SEER registry/hospital records/ pathology	Self-administered questionnaire	Incidence, lung cancer	> 322 vs no use mg/day	0.97 (0.76-1.23) Ptrend:0.88	Age, sex, years smoked, pack-years, and pack-years squared	
		391			Incidence, non-small cell carcinoma		0.97 (0.74-1.29) Ptrend:0.74		
		73			Incidence, small		0.65 (0.31-1.35)		

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Missing data derived for analyses
					cell carcinoma		Ptrend:0.22		
		57			Incidence, other lung cancers		1.37 (0.67-2.79) Ptrend:0.18		
		226			Incidence, lung cancer, former smokers, quit 10+ years ago		0.92 (0.65-1.31) Ptrend:1.0		
		93			Incidence, lung cancer, former smokers, quit <10 years ago		0.90 (0.52-1.56) Ptrend:0.81		
		155			Incidence, lung cancer, current smokers		1.05 (0.67-1.66) Ptrend:0.53		
Iso, 2007 LUN20294 Japan	JACC, Prospective Cohort, Age: 40-79 years, M/W	867/ 105 500 15 years	Population death registries	Validated FFQ	Mortality, lung cancer, men	Use vs no use	0.82 (0.53-1.29)	Age, area of study	
		254			Mortality, lung cancer, women		1.06 (0.63-1.81)		
Lee, 2005 LUN17250 USA	IWHS, Prospective Cohort, Age: 55-69 years, W,	700 34 708 16 years	Health Registry of Iowa (part of SEER registry)	FFQ (study specific)	Incidence, lung cancer	≥ 701 vs 0 mg/day	1.07 Ptrend: 0.94	Age, alcohol consumption, energy intake, smoking habits	Estimation of confidence intervals

Author, Year, WCRF Code, Country	Study 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
	Post-menopausal								
Voorrips, 2000a LUN01121 Netherlands	NLCS, Case Cohort, Age: 55-69 years, M	939/ 58 279 6.3 years	Regional cancer registries and computerized national database of pathology report (PALGA)	FFQ (study specific)	Incidence, lung cancer	Yes vs no	0.92 (0.61–1.38) Ptrend: 0.54	Age, educational level, family history of specific cancer, smoking habits	
Shibata, 1992 LUN08664 USA	LWS, Prospective Cohort, Age: 74 years, M/W	94/ 11 580 6 years	Death by reports of friends or relatives, National Death Index; incidence through hospital records	FFQ (study specific)	Incidence, lung cancer, men	Yes vs no	1.03 (0.68-1.55)	Age, smoking habits	
		70/ 11 580			Incidence, lung cancer, women	Yes vs no	0.72 (0.45-1.15)	Age, smoking habits	

Figure 214 RR (95% CI) of lung cancer for the highest compared with the lowest level of Vitamin C supplement use



*RR's in 3 studies (Roswall, 2009; Slatore, 2008; Lee, 2005) recalculated to use vs non-use using Hamling method.

Figure 215 RR (95% CI) of lung cancer for the highest compared with the lowest level of Vitamin C supplement use, after excluding study not adjusted for smoking status

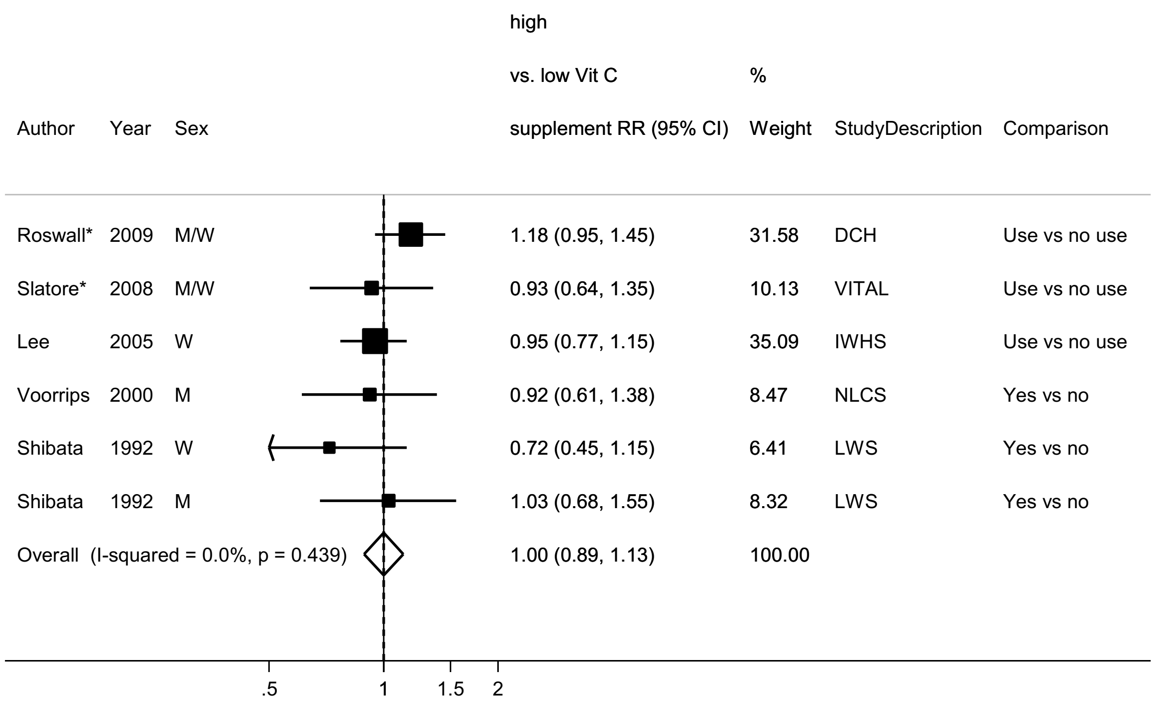
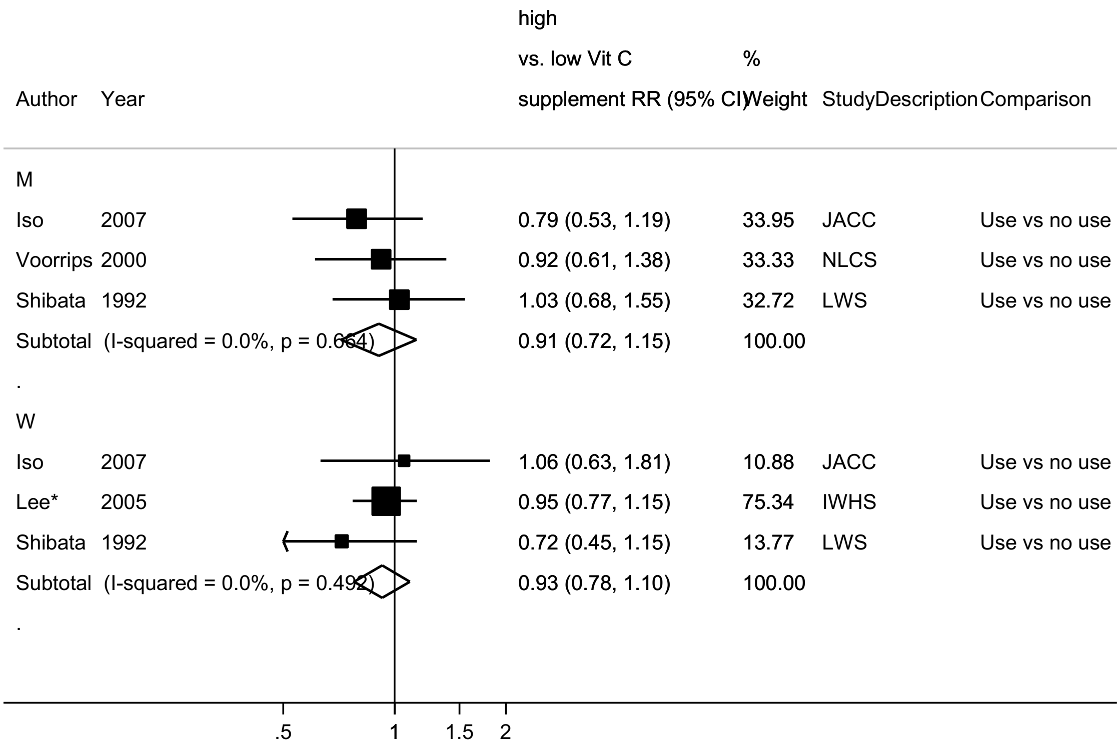


Figure 216 RR (95% CI) of lung cancer for the highest compared with the lowest level of Vitamin C supplement use by sex



*RR's in Lee, 2005 study recalculated to use vs non-use using Hamling method.

5.5.10 Plasma hydroxyvitamin D

Cohort studies

Summary

Main results:
Five studies (1126 cases) out of 6 studies (7 publicatios) were included in the dose-response meta-analysis. Plasma hydroxyvitamin D was not related to lung cancer risk. No heterogeneity was observed.
There was significant evidence of publication or small study bias (p=0.004). The asymmetry was driven by one study that reported an inverse association (Kilkkinen, 2008). When this study was omitted, there was no evidence of publication bias or small study bias (p=0.79).

Sensitivity analysis:
The summary RRs ranged from 0.97 (95% CI=0.93-1.01) when Cheng, 2012 was omitted to 0.98 (95% CI=0.95-1.02) when Kilkkinen, 2008 was omitted in the influence analysis.
Only one study reported on mortality (Cheng, 2012). When this study was excluded from the analysis the overall estimate remained the same.

Study quality:
Cancer outcome was confirmed in most studies using cancer registries or medical records. All studies adjusted by smoking status and BMI. Only two studies adjusted for season of blood extraction and two studies for supplement use.

Table 197 Plasma hydroxyvitamin D and lung 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 dose-response meta-analysis	5

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

Table 198 Plasma hydroxyvitamin D and lung cancer risk. Summary of the dose-response meta-analysis in the 2005 SLR and CUP.

	2005 SLR	**CUP**
Increment unit used	No meta-analysis	nmol/L
All studies		
Studies (n)		5
Cases (total number)		1126
RR (95%CI)		0.98 (0.94-1.01)
Heterogeneity (I^2, p-value)		0 %, 0.97
P value Egger test		< 0.01

Table 199 Plasma hydroxyvitamin D and lung cancer risk. Main characteristics of studies 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)	Adjustment factors	Missing data derived for analyses
Skaaby, 2014 LUN26878 Denmark	Monica10, Inter99, Health2006, Prospective Cohort, Age: 18-71 years, M/W	110/ 12 204 11 years	Cancer registry	Blood test	Incidence, lung and bronchus	Quartile 4 vs quartile 1	0.91 (0.51-1.62)	Study, sex, education, season during which blood was drawn, physical activity, smoking habits, alcohol intake, intake of fish, BMI	
						Per 10 nmol/L	0.98 (0.91-1.05)		
Ordonez Mena, 2013 LUN20308 Germany	ESTHER, Prospective Cohort, Age: 50-74 years, M/W	136/ 9 561 8 years	Self-report verified by medical records or by linkage with state cancer registries	Blood test	Incidence, lung cancer	Quartile 4 vs quartile 1	1.07 (0.69-1.65)	Age, sex, multivitamin use, fish intake, less than once a week, red meat consumption less than once a week, daily fruit intake, daily vegetables intake, BMI, education, physical activity, smoking, family history of cancer	Rescale reference category using the Hamling method. Mid-points of exposure using four sessions of the year

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI)	Adjustment factors	Missing data derived for analyses
Cheng, 2012 LUN20326 USA	NHANES III, Prospective Cohort, Age: 17- years, M/W	258/ 16 693	National death index	Blood test	Mortality, lung cancer	>80.4 nmol/L vs <43.9 nmol/L	0.95 (0.62-1.44)	Age, sex, BMI, race/ethnicity, smoking status, region	Mid-points of exposure
Weinstein, 2011 LUN20345 Finland	ATBC, Nested Case Control, Age: 55-62 years, M, Smokers	500/ 29 133	Finnish Cancer Registry and the Register of Causes of Death	Blood test	Incidence, lung cancer	Quintile 5 vs quintile 1	1.08 (0.67-1.75)	BMI, study supplementation group, alcohol intake, serum cholesterol, smoking	
						Per 10 nmol/L	0.98 (0.91-1.05)		
Kilkkinen, 2008 LUN20329 Finland	MFHS, Prospective Cohort, Age: 30- years, M/W	122/ 6 937 24 years	Finnish cancer registry	Blood test	Incidence, lung cancer	Tertile 3 vs tertile1	0.72 (0.43-1.19)	Age, sex, alcohol consumption, BMI, marital status, education, season of baseline measurement, smoking	Weighted average of mid-point exposure. Distribution of person-years/non-cases by category

Table 200 Plasma hydroxyvitamin D and lung cancer risk. Main characteristics of studies excluded 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) P trend	Adjustment factors	Reasons for exclusion
Afzal, 2013 LUN20304 Denmark	CCHS, Prospective Cohort, Age: 20-100 years, M/W	507/ 9791 28 years	Danish cancer registry	Blood test	Incidence, lung cancer	Per 10 nmol/L	1.19 (1.09-1.31)	Age, sex, alcohol consumption, BMI, leisure - physical activity, work - physical activity, education years, cigarettes pack years	Continuous values in decrease for 50% reduction in levels
Freedman, 2007 LUN20379 USA	NHANES III, Prospective Cohort, Age: 17 and more years, M/W	153/ 16 818 146 578 person-years	National death index	Blood test	Mortality, lung cancer	>100 nmol/L vs 49.9 nmol/L	1.14 (0.60-2.18)	Age, sex, race, smoking history	Superseded by Chen, 2012

Figure 217 RR estimates of lung cancer by levels of plasma hydroxyvitamin D

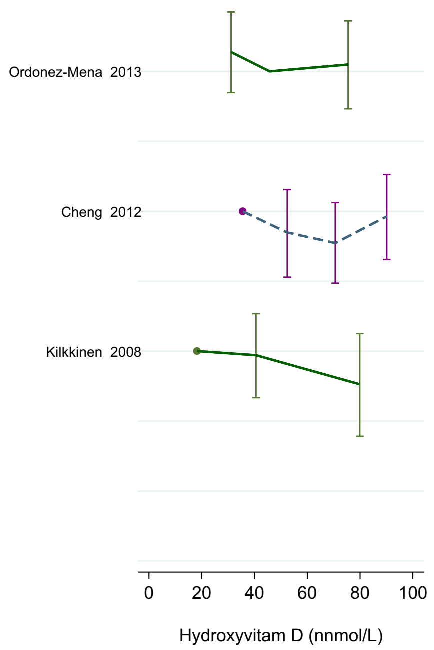


Figure 218 RR (95% CI) of lung cancer for the highest compared with the lowest level of plasma hydroxyvitamin D

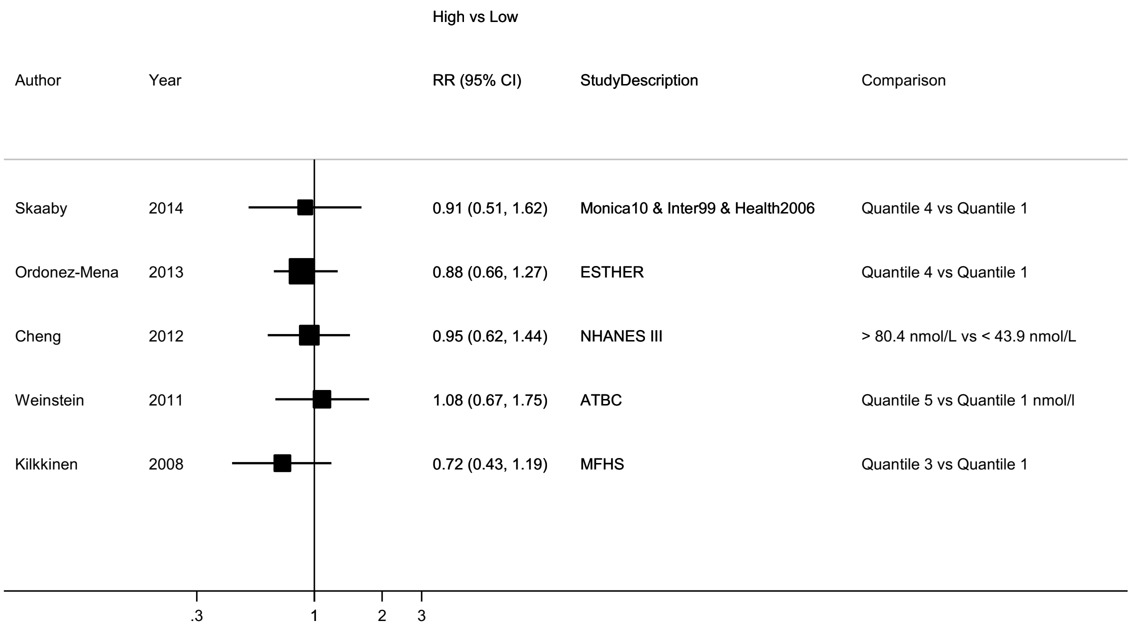


Figure 219 RR (95% CI) of lung cancer for 10 nmol/L increase of plasma hydroxyvitamin D

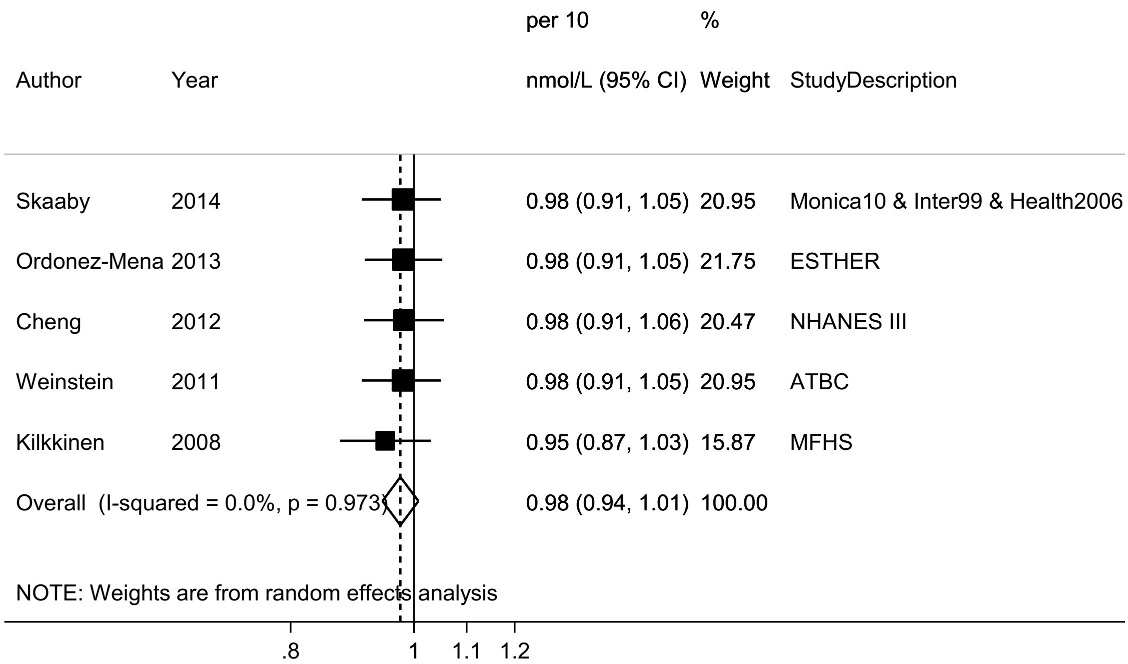
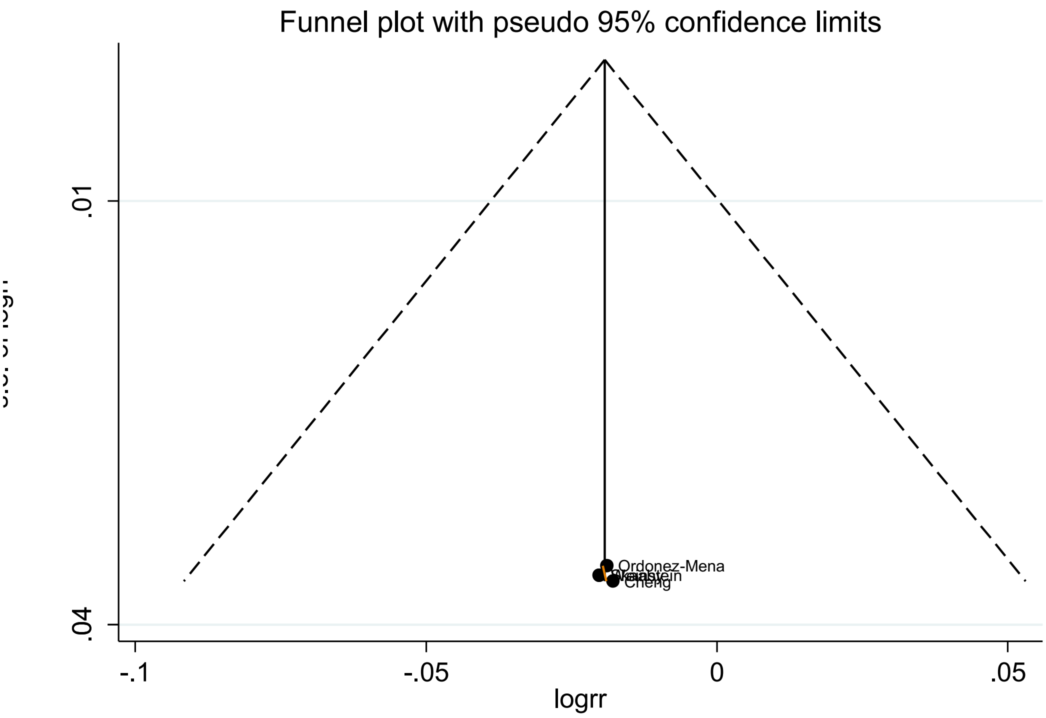


Figure 220 Funnel plot of studies included in the dose response meta-analysis of plasma hydroxyvitamin D and lung cancer



Egger's test p < 0.01 (all studies)
Kikkinen 2008, was not included for better visibility of the forest plot

5.5.11 Vitamin E supplement

Randomised controlled trials

Three randomised controlled trials were identified during the 2005 SLR. The summary of the 2005 SLR meta-analysis showed no effect of vitamin E supplement on lung cancer risk (RR= 0.94 (95% CI= 0.78-1.14) for intervention vs placebo).

A long –term follow-up of the ATBC was the only study identified in the CUP. The ATBC results were included in the meta-analysis in the 2005 SLR (Virtamo, 2014). The ATBC was a randomised, double-blind, placebo-controlled trial of α-tocopherol (50 mg daily) and beta carotene (20 mg daily) for a median 6.3 years in 29133 male smokers. After 18 years of follow-up, there was no difference on lung cancer risk in the men supplement with α-tocopherol compared to those with placebo (HR: 0.99; 0.90-1.10).Another RCT on selenium and vitamin E supplement was identified in the CUP (Lipmann, 2009), median overall

follow-up was 5.46 years, for vitamin E supplement alone the relative risk for lung cancer was 1.00 (95%CI=0.64-1.55, 67 cases) and for vitamin E and selenium the relative risk was 1.16 (95%CI=0.76-1.78, 78 cases).
In another RCT from the Physicians Health Study (PHS) II study (Wang, 2014), the reported HR was 0.86 (95% CI= 0.59-1.26) for lung cancer risk and 0.98 (95% CI= 0.65-1.47) for lung cancer death. After the PHS II intervention ended, in 2011, the participants were followed for a mean of 2.8 extra years, with 49 more lung cancer cases identified The HR for the follow-up period was (HR=1.06 (95% CI= 0.62-1.82) for lung cancer risk and 1.04 (95% CI= 0.57-1.87) for lung cancer death.

Cohort studies

Summary

Main results:
Six studies were identified. Most studies assessed use of vitamin E supplement. A categorical meta-analysis of studies comparing use vs nonuse was performed, including six studies (3946 cases). No significant association was observed.

Low heterogeneity was observed.

No association was observed in startifed analysis by sex and when excluding a study on lung cancer mortality. There was a limited number of studies on lung cancer subtypes and by smoking status, and no analysis was possible.

Study quality:
Cancer outcome was confirmed using cancer registry records in most studies and vitamin E supplement was assessed using questionnaires or interview all studies.
All studies adjusted for smoking status. All studies included in the highest versus lowest analysis were at least adjusted for age.

Table 201 Vitamin E supplement and lung cancer risk. Number of studies in the CUP SLR

	Number
Studies identified	6 (6 publications)
Studies included in forest plot of highest compared with lowest exposure	6
Studies included in dose-response meta-analysis	0

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

Table 202 Vitamin E supplement and lung cancer risk. Summary of the dose-response meta-analysis in the 2005 SLR and CUP.

	2005 SLR	CUP
Increment unit used		Highest versus lowest
All studies		
Studies (n)		6
Cases (total number)		3946
RR (95%CI)		1.05 (0.97-1.13)
Heterogeneity (I^2, p-value)		6.5 %, 0.38
P value Egger test		

Stratified and sensitivity analysis (no analyses conducted in the 2005 SLR)		
Outcome	**Incidence**	
Studies (n)	5	
RR (95%CI)	1.05 (0.94-1.18)	
Heterogeneity (I^2, p-value)	20.5%, 0.30	
Sex	**Men**	**Women**
Studies (n)	3	3
RR (95%CI)	0.99 (0.77-1.29)	1.05 (0.74-1.49)
Heterogeneity (I^2, p-value)	0%, 0.58	56.5%, 0.10

Table 203 Vitamin E supplement use and lung 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								
Alkhenizan, 2007	5 RCT	111635 (participants)			Yes vs no intake of vitamin E supplement	1.02 (0.88-1.19)		
	2 RCT	30077 (participants)			Vitamin E supplement ≥ 300 mg/d	0.97 (0.81-1.16)		
	2 RCT	41682 (participants)			Vitamin E supplement < 300 mg/d	0.97 (0.85-1.10)		
Pooled-analyses								
Cho, 2005 (Pooling Project of Prospective Studies)	7 cohort studies	3206 cases	USA, Canada, Finland, Netherlands	Incidence	Quintile 5 vs quintile 1 Dietary vitamin E	0.86 (0.76-0.99)	0.36	0.34
					Quintile 5 vs quintile 1 Total vitamin E	0.96 (0.83-1.12)	0.85	0.75
					>200 mg/d vs <6mg/d Total vitamin E	0.86 (0.72-1.03)	0.96	0.41

*Results were similar when were stratified by smoking status (never, past, current smokers) and by lung cancer type (adenocarcinoma, small cell, squamous cell)

Table 204 Vitamin E supplement and lung cancer risk. Main characteristics of studies 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)	Adjustment factors	Missing data derived for analyses
Wu, 2014 LUN26880 China	SWHS, Prospective Cohort, Age: 40-70 years, W, Non smokers	481/ 72 829 12 years	Cancer registry and annual in-person re-interviews of surviving cohort members	Validated FFQ	Incidence, lung cancer	Non-use vs use	1.33 (1.01-1.73)	Age, calcium to magnesium ratio, energy intake, tea consumption, total dietary tocopherol, vitamin e intake, multivitamin intake, passive smoking, vitamin supplement	
Roswall, 2009 LUN26873 Denmark	DCH, Prospective Cohort, Age: 50-64 years, M/W	721/ 55 557 11 years	Danish cancer registry	FFQ	Incidence, lung cancer	Per 10 mg/day	0.99 (0.96-1.01)	Age, sex, folate, smoking cessation, smoking status, vitamin e intake, beta-carotene, passive smoking, smoking duration, smoking intensity, vitamin c (diet), work exposure to cigarette smoke	
						>10 mg/days vs 0 mg/day	0.84 (0.61-1.16)		
Slatore, 2008 LUN20344	VITAL, Prospective	515 77 126	SEER registry/hospital	Self-administered	Incidence, lung cancer	> 215 mg/day vs no use	1.19 (0.95-1.50)	Age, sex, pack years squared,	

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI)	Adjustment factors	Missing data derived for analyses
USA	Cohort, Age: 50-76 years, M/W	4 years	records/ pathology	questionnaire		Per 100 mg/day	1.05 (1.00-1.09)	pack-years, years of smoking Vitamin e intake from foods	
Iso, 2007 LUN20294 Japan	JACC, Prospective Cohort, Age: 40-79 years, M/W	866/ 105 500 15 years	Population death registries	Validated FFQ	Mortality, lung cancer, men	Use vs no use	0.82 (0.53-1.29)	Age, area of study	
		254			Mortality, lung cancer, women		1.05 (0.65-1.69)		
Voorrips, 2000 LUN01121 Netherlands	NLCS, Case Cohort, Age: 55-69 years, M	487/ 58 279 3 years	Regional cancer registries and computerized national database of pathology report (PALGA)	FFQ - study-specific	Incidence, lung cancer	Yes vs no	1.10 (0.65-1.87)	Age, educational level, family history of lung cancer, smoking habits, years of smoking cigarettes, number of cigarettes per day	
Shibata, 1992 LUN08664 USA	LWS, Prospective Cohort, Age: 74 years, M	94/ 11 580 6 years	Death by reports of friends or relatives, National Death Index; incidence through hospital records	FFQ - study-specific	Incidence, lung cancer	Yes vs no	1.10 (0.73-1.65)	Age, smoking habits	

Figure 221 RR (95% CI) of lung cancer for the use compared with no use of vitamin E supplement

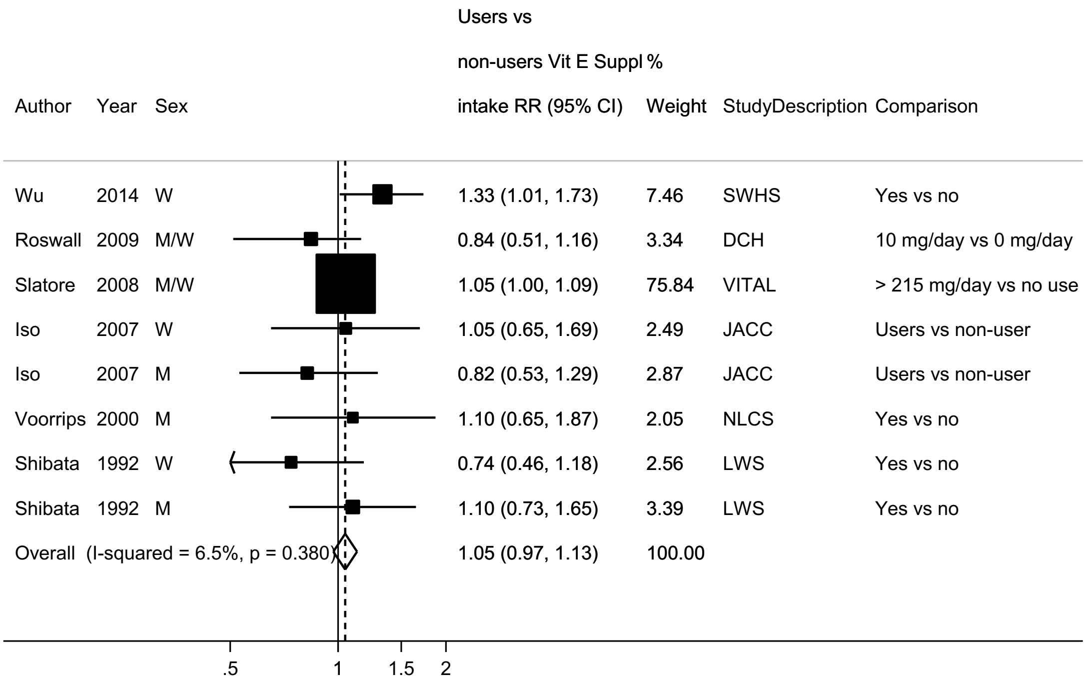


Figure 222 RR (95% CI) of lung cancer for use compared with no use of vitamin E supplement by sex

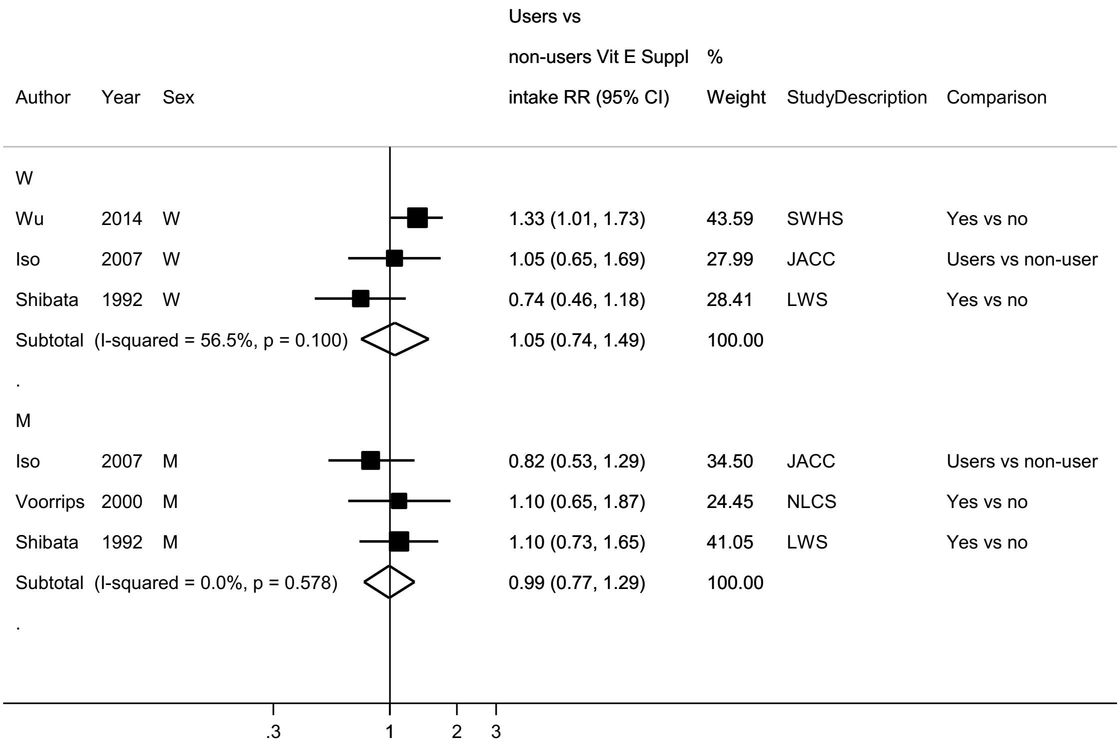
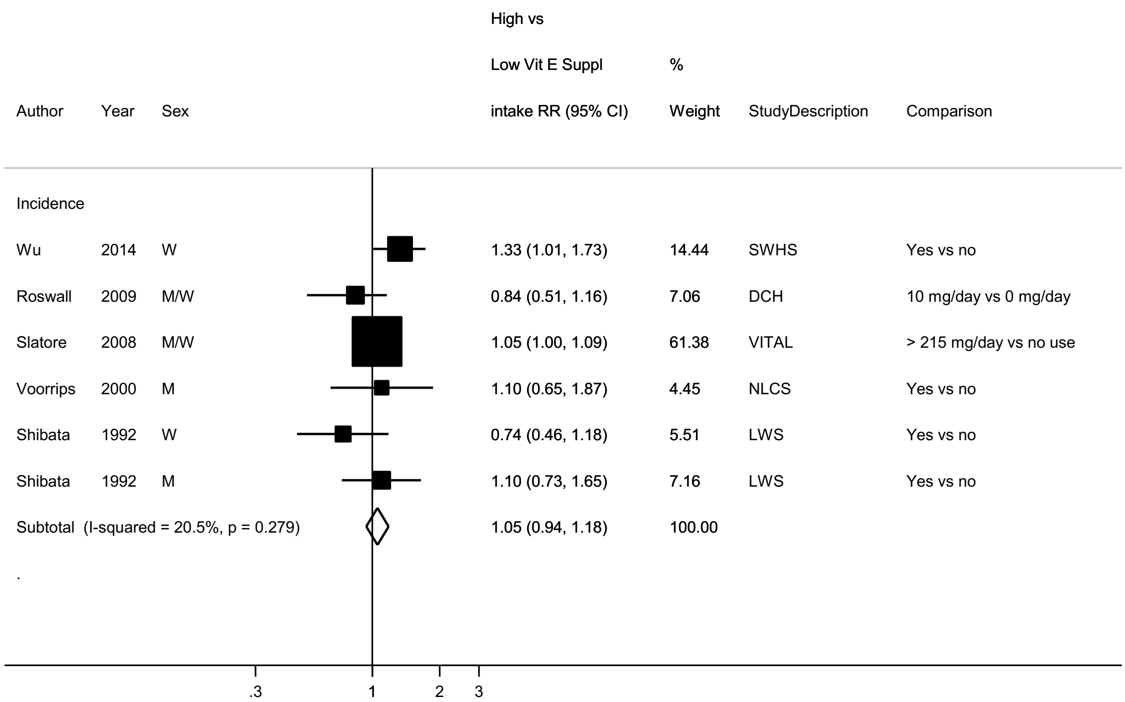


Figure 223 RR (95% CI) of lung cancer for use compared with no use of vitamin E supplement by outcome



5.5.13 Multivitamin supplement

Randomised Controlled Trials

No randomised controlled trial was identified during the 2005 SLR.
One RCT (Gaziano, 2012) was identified during the CUP. The Physician's Health Study II was a randomised, double-blind, placebo-controlled, 2 x 2 x 2 x 2 factorial trial of daily multivitamin supplementation, vitamin E (400-IU synthetic -tocopherol), vitamin C (500 mg synthetic ascorbic acid) and beta carotene (50-mg Lurotin) including 14 641 male physicians in the United States of 50 year of age or older. The trial investigated benefits and risk of supplementation on cancer, cardiovascular disease, eye disease, and cognitive function. Treatment started in 2001 and the multivitamin component continued until 2011. . Lung cancer mortality was not the main outcome. Men taking multivitamin did not have a reduction on lung cancer risk (HR= 0.89; 95% CI= 0.64-1.25 comparing active treatment -74 cases- with placebo - 88 cases).

Cohort studies

Summary

Main results:
All studies except one assessed use of multivitamin use, but not dose. Only highest versus lowest analysis could be performed (6 studies, 6688 cases). Multivitamin supplement use was not related to lung cancer risk. No heterogeneity was observed.
In stratified analysis by sex, the results were similar for men and women. There was not enough data to do stratified analysis by either histologic type or smoking status.

Study quality:
All studies used questionnaire to assess the intake of multivitamin supplement. All studies included in the high vs low analysis were adjusted for age and smoking status and other potential confounders, except one study (Iso, 2007) on mortality that did not adjust for smoking. One Chinese study in nonsmoker's women was adjusted for passive smoking (Wu, 2014). Two studies were on lung cancer mortality.

Table 205 Multivitamin supplement use and lung cancer risk. Number of studies in the CUP SLR

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

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

Table 206 Multivitamin supplement use and lung cancer risk. Summary of the dose-response meta-analysis in the 2005 SLR and CUP

	2005 SLR	**CUP**
All studies		
Increment unit used	No meta-analysis	Highest vs lowest
Studies (n)		6
Cases (total number)		6688
RR (95%CI)		1.03 (0.95-1.12)
Heterogeneity (I^2, p-value)		0%, 0.92

Stratified and sensitivity analysis (no analyses conducted in the 2005 SLR)		
Sex	**Men**	**Women**
Studies (n)	3	4
RR (95%CI)	1.01 (0.84-1.22)	1.02 (0.92-1.14)
Heterogeneity (I^2, p-value)	0%, 0.86	0%, 0.57

Table 207 Multivitamin supplement use and lung cancer risk. Main characteristics of studies included in the 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
Wu, 2014 LUN26880 China	SWHS, Prospective Cohort, Age: 40-70 years, W, Non smokers	481/ 72 829 12 years	Cancer registry and annual in-person re-interviews of surviving cohort members	Validated FFQ	Incidence, lung cancer	Use vs no use	1.17 (0.89-1.53)	Age, passive smoking, calcium to magnesium ratio, energy intake, tea consumption, total dietary tocopherol, vitamin E intake, vitamin supplements use (A, B, C, calcium and other)	
		362			Incidence, lung cancer, low* passive smokers		1.33 (0.98-1.82)		
		119			Incidence, lung cancer, high* passive smokers		0.84 (0.50-1.43)		
Takata, 2013 LUN26860 China	SMHS, Prospective Cohort, Age: 40-74 years, M	359/ 61 092 6 years	Biennial home visits/linkage/ cancer registry/vital stats	Validated FFQ	Incidence, lung cancer	Use vs no use	1.08 (0.71-0.63)	Age, BMI, current smoking status, years of smoking, cigarettes/ay, total caloric intake, education, ever consumption of tea, history of chronic bronchitis, and family history of lung cancer among first-degree relatives	
Park, 2011 LUN26855 USA	MEC, Prospective Cohort, Age: 45-75 years,	1635/ 182 099 11 years	National Death Index	Questionnaire	Mortality, lung cancer, men	Use vs no use	1.08 (0.70-1.68)	Age, BMI, smoking status, years smoking, years since quit smoking, cigarettes/day, ethnicity, physical activity, pre-existing disease, alcohol,	
		1229			Mortality,		0.73 (0.37-1.45)		

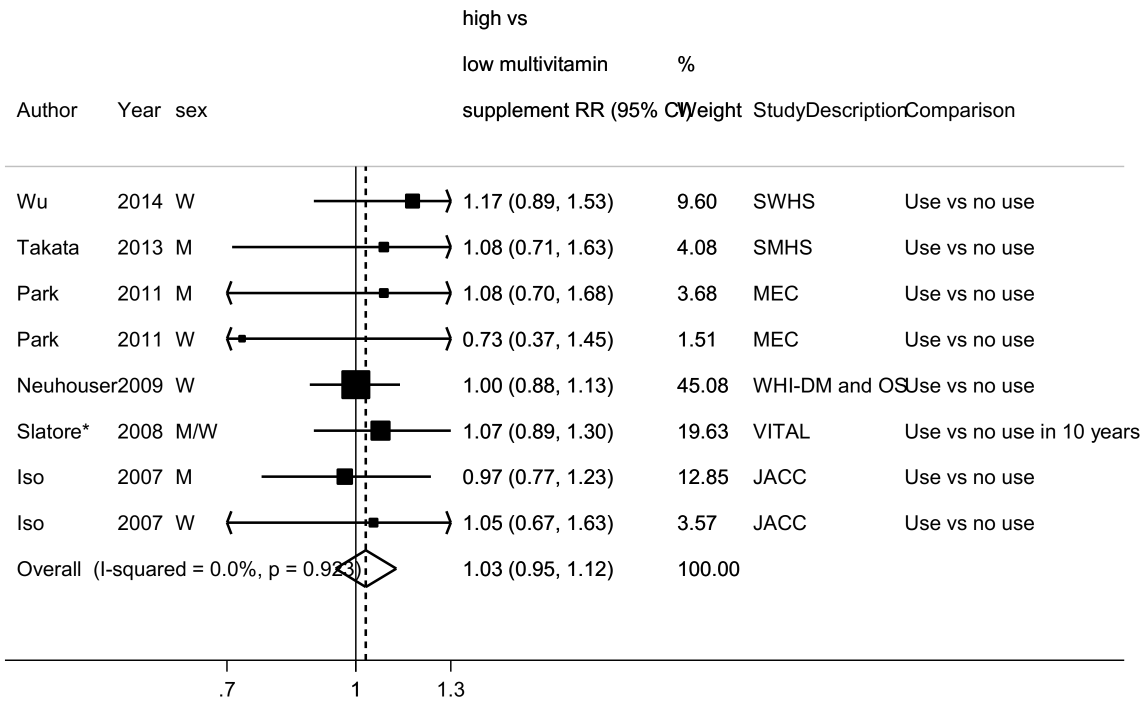
Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Missing data derived for analyses
	M/W				lung cancer, women			education, fruits and vegetables intake, energy from fat, family history of lung cancer, single supplement use, vegetable, HRT use and menopausal status (for women only)	
Neuhouser, 2009 LUN20297 USA	WHI-DM and OS, Prospective Cohort, Age: 50-79 years, W, Post-menopausal	1340/ 161 806 8 years	Self-report verified by medical record	Questionnaire	Incidence, lung cancer	Use vs no use	1.00 (0.88-1.13)	Age,BMI, smoking status, education, oestrogen plus progesterone use, family history of cancer, history of high cholesterol, physical activity, race/ethnicity, systolic blood pressure, US region, supplement of vitamin C, E, Ca, calories from fat, family history of myocardial infarction, fruit and vegetable, general health status, mammogram in the past 2y, prior bilateral oophorectomy, randomisation assignment or study enrolment, single supplement, not including vitamin C, E or calcium, treated diabetes mellitus, years since menopause	
Slatore, 2008	VITAL, Prospective	521/ 77 126	Seer registry/hospital	Self-administered	Incidence, lung cancer	> 5.6 pills/week vs	0.98 (0.78-1.22) Ptrend:0.69	Age, sex, years smoked, pack-years, and pack-years squared.	

Author, Year, WCRF Code, Country	Study 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
LUN20344 USA	Cohort, Age: 50-76 years, M/W	4 years	records/pathology	questionnaire		no use			
		391			Incidence, lung cancer, non-small cell carcinoma		0.99 (0.77-1.28) Ptrend:0.84		
		73			Incidence, lung cancer, small cell carcinoma		0.70 (0.35-1.40) Ptrend:0.31		
		57			Incidence, other lung cancers		1.23 (0.63-2.40) Ptrend:0.56		
		226			Incidence, lung cancer, former smokers, quit 10+ years ago		0.96 (0.69-1.32) Ptrend:0.60		
		155			Incidence, lung cancer, current smokers		1.02 (0.67-1.56) Ptrend:0.76		
		93			Incidence, lung cancer,		0.70 (0.39-1.25) 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
					former smokers, quit < 10 years ago				
Iso, 2007 LUN20294 Japan	JACC, Prospective Cohort, Age: 40-79 years, M/W	869/ 105 500 15 years	Municipal resident registration records, death certificates	Validated FFQ	Mortality, lung cancer, men	Use vs no use	0.97 (0.77-1.23)	Age, area of study	
		254			Mortality, lung cancer, women	Use vs no use	1.05 (0.67-1.63)		

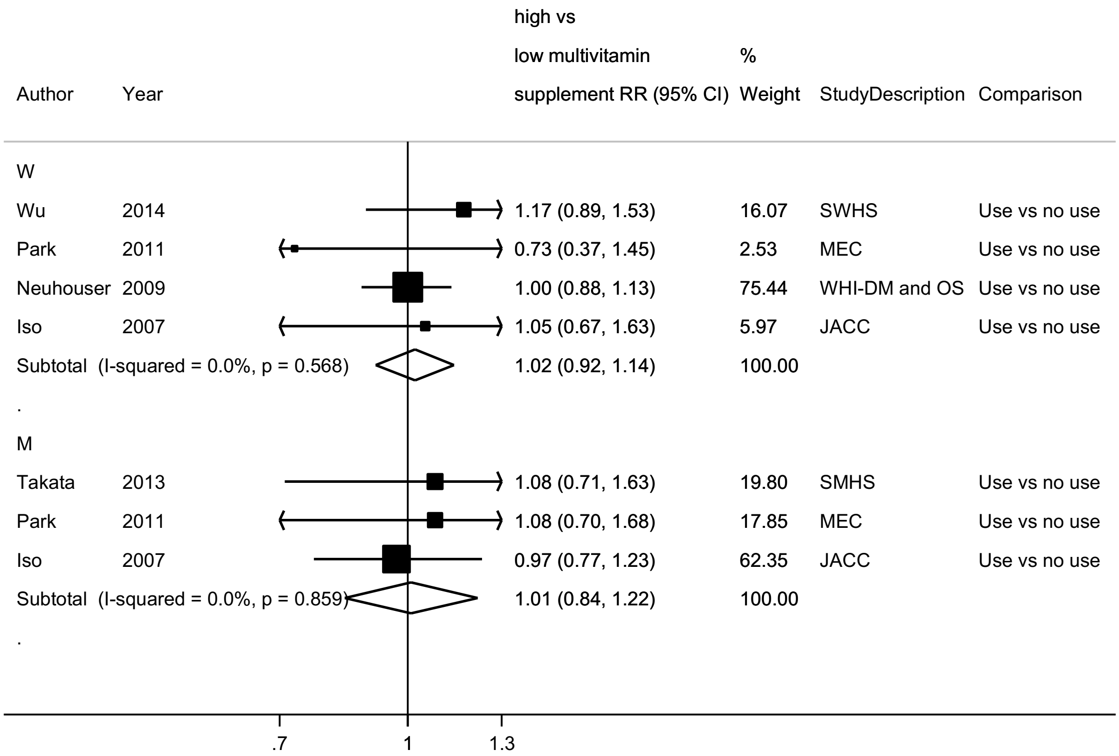
* Passive smoking: Low = never or exposure to husband or working place. High = both husband and working place tobacco smoke exposure.

Figure 224 RR (95% CI) of lung cancer for the highest compared with the lowest level of multivitamin supplement use



*RR in study of Slatore, 2008 recalculated to use vs nonuse using Hamling method.

Figure 225 RR (95% CI) of lung cancer for the highest compared with the lowest level of multivitamin supplement use by sex



5.6.4 Toenail Selenium

No studies on toenail selenium were identified in the CUP. Three studies on toenail selenium were identified in the 2005SLR. No meta-analysis was conducted. All studies were non-significant.

Table 208 Toenail selenium and lung cancer risk. Main characteristics of studies identified in CUP and 2005 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
Hartman, 2002 LUN00397 Finland	ATBC, Nested Case Control, Age: 50-69 years, M, Smokers only	29 133 6 years	Cancer registry	FFQ - study-specific	Incidence, lung cancer	Time of randomization-year 5 vs time of randomization-o years	0.61 (0.27-1.41)	Age, alcohol consumption, anthropometry, other nutrients, foods or supplements, smoking habits
						Time of randomization-year 5 vs time of randomization-year 0	1.20 (0.75-2.50)	
Garland, 1995 LUN23942 USA	Nurses Health Study, Nested Case Control, Age: 30-55 years, W, No specific	47/ 62 641 41 months	Medical records	FFQ - study-specific	Incidence, lung cancer	Tertile 3 vs tertile 1 mcg	4.33 (0.54-34.60)	Age, smoking habits

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors
	group							
van den Brandt, 1993 LUN02616 Netherlands	NLCS, Case Cohort, Age: 55-69 years, M/W, No specific group	285 2 459 3 years	Questionnaire and cancer registry	FFQ - study-specific	Incidence, lung cancer, men	>0.64 vs 0-0.48 mcg	0.50 (0.30-0.82)	Age, sex, educational level, smoking habits
		143/			Incidence, squamous cell (scc)	>0.61 vs 0-0.5 mcg	0.55 (0.30-1.04)	
		62			Incidence, adenocarcinoma,	>0.61 vs 0-0.5 mcg	0.59 (0.25-1.40)	
		57			Incidence, other tumor types,	>0.61 vs 0-0.5 mcg	0.70 (0.31-1.58)	
		5			Incidence, small cell	>0.61 vs 0-0.5 mcg	0.19 (0.04-0.87)	
		32			Incidence, lung cancer, women	0.57-0.63 vs 0-0.48 mcg	0.40 (0.13-1.24)	

5.6.4 Dietary and supplemental selenium

Two RCT's were identified in the CUP, none on selenium supplements alone. One was on selenium and vitamin E and the other was on β-carotene, α-tocopherol, and selenium. One RCT on supplemental selenium and two cohort studies on dietary selenium were identified in the 2005SLR. No meta-analysis was conducted. All studies were non-significant.

Table 209 Dietary and supplemental selenium and lung cancer risk. Main characteristics of studies identified in CUP and 2005 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	Exposure name
Lippman, 2009 LUN26853 USA, Canada	SELECT, Randomised Control Trial, Age: 50years, M	78/ 8703 5 years	Self report, medical records and national death index		Incidence, lung cancer	Selenium and vit e group vs placebo	1.16 (0.76-1.78)		Selenium supplement
		75/8752				Selenium group vs placebo	1.12 (0.73-1.72)		
Kamangar, 2006 LUN20362 China	NIT Cohort, Randomised Control Trial, Age: 40-69 years, M/W	29 303 15 years	By interview		Mortality, lung cancer	β-carotene, α-tocopherol, and selenium	0.98 (0.71-1.35)	Age, sex, residence, other treatment groups	Selenium supplement
Reid, 2002 LUN00462 USA	Nutritional Prevention of Cancer Trial, Randomised Control Trial, Age: 18-80 years, M/W	60/1250 Mean treatment years on the trial from 4.5 to 7.9y	Hospital records		Mortality, lung cancer	Se intervention vs placebo mcg/day	0.70 (0.40-1.21)	Age, smoking habits	Selenium supplement
		41			Current smokers	Se intervention	0.67 (0.36-1.26)	Age, biomarkers	

	History of Skin Cancer					vs placebo mcg/day			
		17			Former smokers	Se intervention vs placebo mcg/day	0.70 (0.26-1.81)	Age, biomarkers	
Knekt, 1991 LUN03018 Finland	Finnish Mobile Clinic Health Examination Survey, Prospective Cohort, Age: 20-69 years, M	4 583 20 years	Cancer registry	FFQ - study-specific	Incidence, lung cancer, current smokers	Lowest vs highest	0.83	Age, smoking habits	Dietary selenium
Kromhout, 1987 LUN03765 Netherlands	Zutphen Study, Prospective Cohort, Age: 40-59 years, M	878 12 years		Dietary history questionnaire	Mortality, lung cancer	Quartile 4 vs quartile 1	0.98 (0.41-2.36)	Age	Dietary selenium

5.6.4 Serum selenium

Cohort studies

Summary

Main results:
Six studies (874 cases) out of 13 cohort studies (13 publications) were included in the dose-response meta-analysis. No significant inverse association of lung cancer with serum selenium was observed.
Of the six studies excluded from dose-response meta-analysis, three studies in USA reported no significant association of selenium levels with lung cancer (Epplein, 2009; Comstok, 1997; Menkes, 1986) and three studies reported lower mean serum selenium levels in cases than in controls (Kornitzer, 2004; Ujije, 2002; Salonen 1985).
High heterogeneity was observed.
There was significant evidence of publication study bias ($p < 0.02$). The asymmetry in the funnel plot is due to one Japanese study showing an inverse association (Kabuto, 1994).

The low number of studies did not allow exploration of heterogeneity. A study of Finish population where selenium levels are 60% lower than the values observed in other European populations (Knekt, 1998) was the only study showing significant inverse association. One study (Suadicani, 2012), reported a significant increased risk of lung cancer mortality with high levels of serum selenium only among heavy smokers. In this study, selenium levels were positively related to smoking, alcohol intake, low social class and antecedents of chronic bronchitis.

Sensitivity analysis:
The summary RR ranged from 0.98 (95% CI=0.94-1.02) when excluding Suadicani, 2012 to 1.01 (95% CI=0.98-1.03) when Kabuto, 1994 was excluded.

Study quality:
Some studies were on specific populations (tin miners in China (Ratnasinghe, 2003), heavy smokers or exposed to asbestos men and women (CARET, Goodman, 2001), a Finish population where selenium levels are 60% lower than the values observed in other European populations (Knekt, 1998), atomic bomb survivors (Kabuto, 1994)). The studies on tin miners (Ratnasinghe, 2003) and the Finnish study (Knekt, 1998) reported serum values lower than in other studies. In the Finish study, the samples were stored for 20 years, but a reliability test did not indicate that storage affected selenium levels (mean selenium decreased from 58.9 µg/L to 58 µg/L). In general, the laboratory techniques vary across studies.
In four studies, mortality for lung cancer was the outcome.
All studies included in the dose-response analysis were adjusted at least for age and smoking status, except one study (Knekt, 1998) that did not adjust for age. Four studies adjusted for

smoking status, duration and intensity, and two studies adjusted for smoking status (see sensitivity analysis below).
Smoking has been shown to be a predictor of low selenium levels in some studies.

Table 210 Serum selenium and lung cancer risk. Number of studies in the CUP SLR

	Number
Studies identified	13 (13 publications)
Studies included in forest plot of highest compared with lowest exposure	8
Studies included in 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 211 Serum selenium and lung cancer risk. Summary of the dose-response meta-analysis in the 2005 SLR and CUP

	2005 SLR	**CUP**
Increment unit used	10 ug/L	10 µg/L
All studies		
Studies (n)	4	6
Cases (total number)	351	874
RR (95%CI)	0.97 (0.94-1.0)	0.99 (0.95-1.03)
Heterogeneity (I^2, p-value)		87.9%, < 0.001
p value Egger test		0.02
Stratified and sensitivity analysis		
Adjustment for smoking	**Smoking status only**	**Intensity and duration of smoking**
Studies (n)	2	4
RR (95%CI)	0.95 (0.89-1.00)	1.01 (1.00-1.03)
Heterogeneity (I^2, p-value)	36.8%, 0.21	0%, 0.66
Sex	**Men**	**Women**
Studies (n)	3	No data
RR (95%CI)	1.02 (1.00-1.04)	
Heterogeneity (I^2, p-value)	0%, 0.99	
Outcome	**Incidence**	**Mortality**
Studies (n)	4	2
RR (95%CI)	1.01 (0.97-1.05)	0.99 (0.92-1.05)
Heterogeneity (I^2, p-value)	41.6%, 0.16	96.2%, < 0.001

Table 212 Serum selenium and lung 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, 2004	6 (cohorts and case-control studies)	1029	USA, Finland, Netherlands, China	Incidence, lung cancer	Highest vs lowest	0.80 (0.58-1.10)		0.13

Table 213 Serum selenium and lung cancer risk. Main characteristics of studies included in the 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
Suadicani, 2012 LUN20330 Denmark	CMS, Prospective Cohort, Age: 53-74 years, M	167/ 3333 16 years	Death register	Blood sample (graphite furnace atomic absorption spectrophotometric method after a simple dilution with a solution containing nickel in nitric acid)	Mortality, lung cancer	1.3-3.0 vs 0.4-1.0 µmol/L	1.43 (0.96-2.14)	Age, peak flow, salt and fat intake, spirits, chronic bronchitis, pack years of smoking	Distribution of person years per category, µmol/l converted to µg/L
Ratnasinghe, 2003 LUN00362 China	YTC, Nested Case Control, Age: 40-74 years, M/W	108/ 216 controls 6 years	Annual screens and cancer registry	Blood collected 2 years prior to diagnosis (atomic absorption spectrometry; 5.3% intraset coefficient of variation)	Incidence, lung cancer genotype	> 55 vs < 39 ng/mL	1.2 (0.6-2.4) Ptrend: 0.52	Age at baseline, radon and pack years of tobacco exposure	Mid-point exposure
Goodman, 2001 LUN00774 USA	CARET, Nested Case Control, Age: 45-74 years, M/W,	356/ 356 controls 18 314	Primary outcome of the trial. Active follow-up with confirmation by clinical records	Serum samples were obtained a mean of 4.7 years before diagnosis	Incidence, lung cancer, former smokers	12.94-17.23 vs 6.39-10.55 µg/dL	1.20 (0.77-1.88) Ptrend: 0.49	Age at randomization within 5-year intervals, year of randomization, smoking habits,	Distribution of cases in quartiles, mid-point exposure, µg/dL converted to µg/L

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Missing data derived for analyses
	Former and current smokers		and pathology reports	(flameless atomic absorption)				intervention arm, exposure population, blood draw visit	
Knekt, 1998 LUN01456 Finland	FMCHES, Nested Case Control, Age: ≥ 19 years, M/W	95/ 190 controls 19 years	Cancer registry	Serum sample stored ~20 years, reliability: 0.87 (graphite furmace technique, CV:9.7%)	Incidence, lung cancer	> 60.6 vs < 45.5 μg/L	0.41 (0.17-0.94)	BMI, other nutrients, foods or supplements, smoking status	Mid-point exposure
Kabuto, 1994 LUN02419 Japan	Hiroshima Nagasaki, Nested Case Control, Age: 30-≥ 70 years, M/W	77/ 120 controls 13 years	Tumour and tissue registries and mortality register	Blood sample (fluorometry)	Mortality, lung cancer	< 99 vs >128 ng/mL	1.8 (0.7-5.0)	Age, sex, city, radiation dose and smoking status	Mid-point exposure, Hamling method used to rescale RR to highest vs lowest
Nomura, 1987 LUN22797 USA	HHP, Nested Case Control, Age: 45-65 years, M	71/ 293 controls 11 years	Continuous surveillance in local hospitals and record linkage with cancer registry	Non-fasting venous blood sample stored ~75 (neutron activation Analysis)	Incidence, lung cancer	< 10.31 vs ≥ 13.31 μg/dL	1.10	Age, current number of cigarette smoked per day	RR to highest vs lowest

Table 214 Serum selenium and lung cancer risk. Main characteristics of studies excluded in the 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
Epplein, 2009 LUN20317 USA	MEC, Nested Case Control, Age: 45-75 years, M/W	136/ 272 controls	SEER registry	Blood sample before the diagnosis	Incidence, lung cancer, men	0.15 vs 0.12 µg/ g of sodium	0.70 (0.37-1.33) Ptrend:0.30	Age at specimen collection, fasting hours before blood draw, pack-years, years of schooling and family history of lung cancer	Serum selenium reported in µg/g of sodium, used only in highest versus lowest analysis
		71/ 142 controls			Incidence, lung cancer, women		0.98 (0.42-2.29) Ptrend:0.91		
Kornitzer, 2004 LUN10733 Belgium	BIRNH, Nested Case Control, Age: 25-74 years, M/W	64/ 430 controls 10 years	Vital status was asked from all municipalities where participants used to live	Non-fasting blood sample	Mortality, lung cancer, men	Mean men cases: 76.6 (14.6) µg/L Mean men controls: 79.6 (14.2) µg/L	No p values		No OR available
Ujiie, 2002 LUN06082 Japan	Miagy Japan, Nested Case Control, M/W	314/ 2238 controls 5 years	Hospital records	Fasting blood sample	Incidence, lung cancer, men	Mean Cases: 99.5 ppb Controls: 112.5 ppb	P difference <0.01	Adjusted for age and sex	No OR available
					Incidence, lung cancer, women	Mean Cases: 86.9 ppb Controls: 102.5			No OR available

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Reasons for exclusion
						ppb			
Comstock, 1997 LUN01716 USA	CLUE I &CLUE II, Nested Case Control, Age: 25- years, M/W	157/ 313 controls	Death certificates and hospital discharge records	Blood sample	Incidence, lung cancer, men	Highest vs lowest	0.59 Ptrend:0.14		No data available to calculate missing intervals
		101/ 202 controls			Incidence, lung cancer, women		0.71 Ptrend:0.34		
Knekt, 1993 LUN02684 Finland	FMCHES, Nested Case Control, Age: ≥ 15 years, M	122/ 270 controls 9 years	Cancer registry	Serum sample	Incidence, lung cancer, current smokers	Lowest vs highest	2.40 (1.10-5.10)	Age	Superseded by Knekt, 1998 LUN01456
		22/ 270 controls 9 years			Incidence, lung cancer, non-smokers		1.6 (0.5-5.5)		
Menkes, 1986 LUN03835 USA	Washington county Maryland, Nested Case Control, M/W	99/ 196 controls 5 years	Cancer registry	Blood sample	Incidence, lung cancer	Lowest vs highest	0.68 pvalue: 0.07	Age, sex, ethnicity/race, other, smoking habits	Used only in highest versus lowest analysis (recalculated to high vs low) No cut-points level available
Salonen, 1985 LUN12990 Finland	NKP, Nested Case Control, Age: 30-64 years, M/W	15/ 15 controls 4 years	National death certificate register	Blood sample	Mortality, respiratory cancer	Mean Cases: 52.6 µg/L Controls: 62.0 µg/L	Pdifference: < 0.05		No RR available

Figure 226 RR estimates of lung cancer by levels of serum selenium

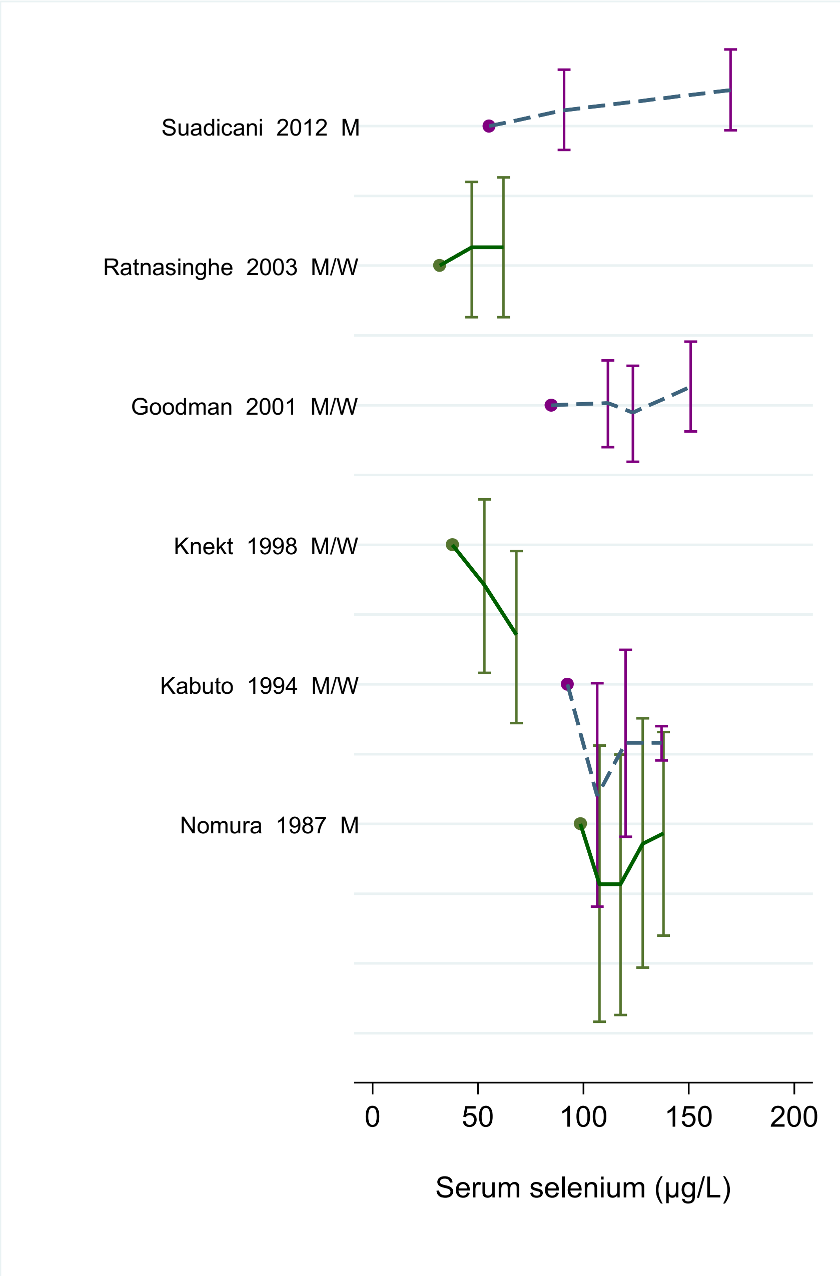
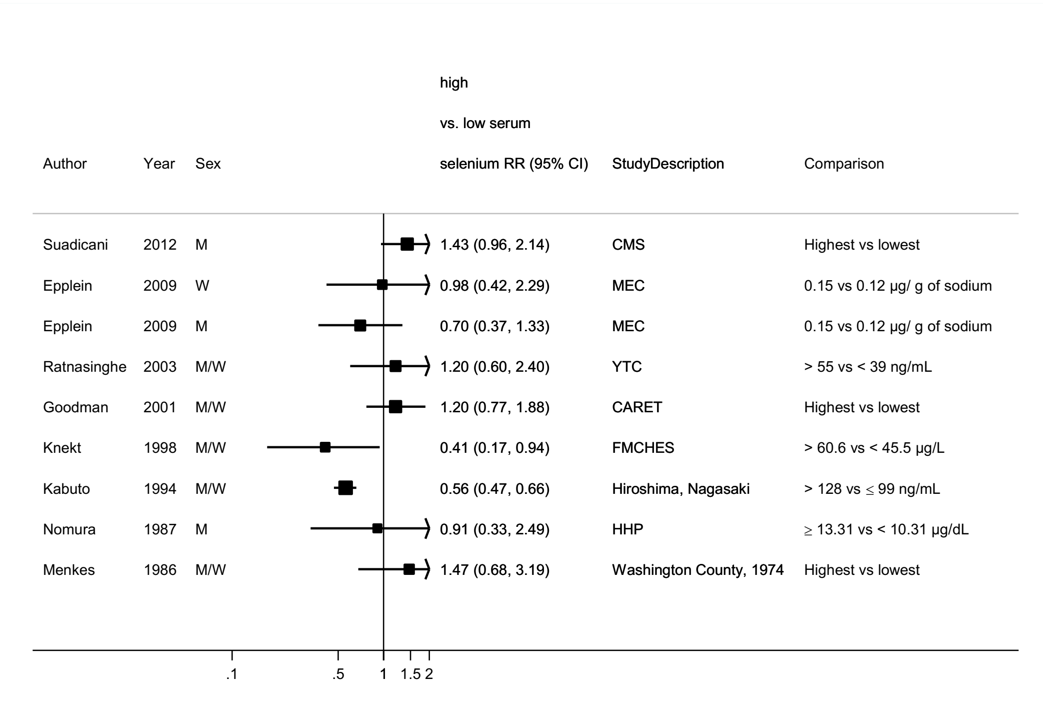


Figure 227 RR (95% CI) of lung cancer for the highest compared with the lowest level of serum selenium



The comparison is 1.3-3.0 vs 0.4-1.0 µmol/L in Saudicani, 2002, and 12.94-17.23 vs 6.39-10.55 µg/dL in Goodman, 2001. For Kabuto, 1994, Nomura, 1987, and Menkes, 1986 the RR's were recalculated to highest vs lowest (Hamling, 2008).

Figure 228 RR (95% CI) of lung cancer for 10 µg/L increase of serum selenium

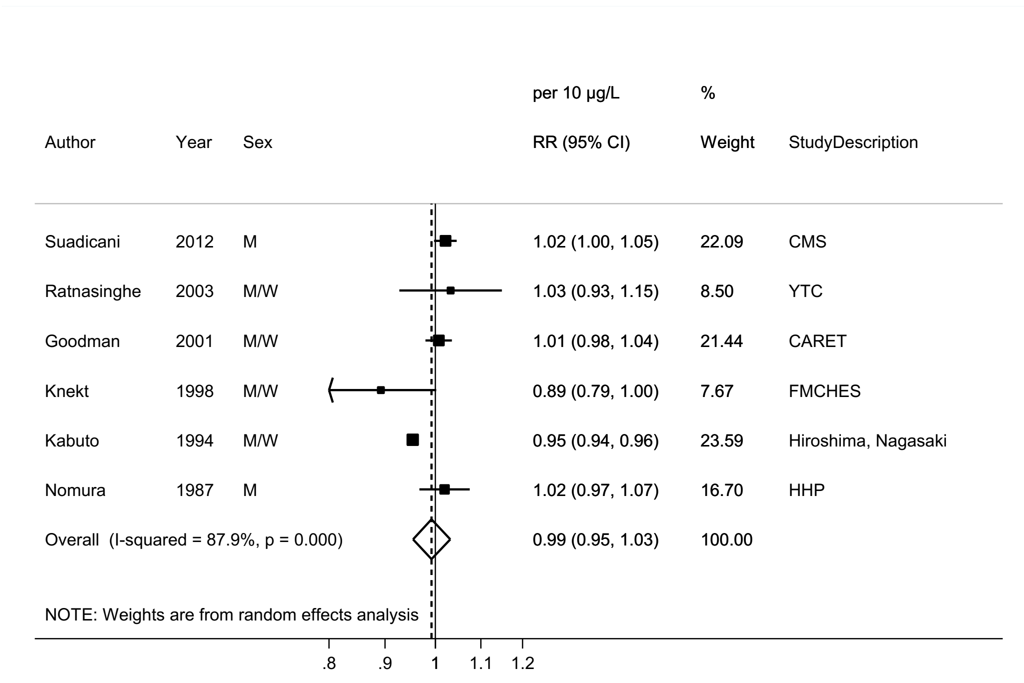
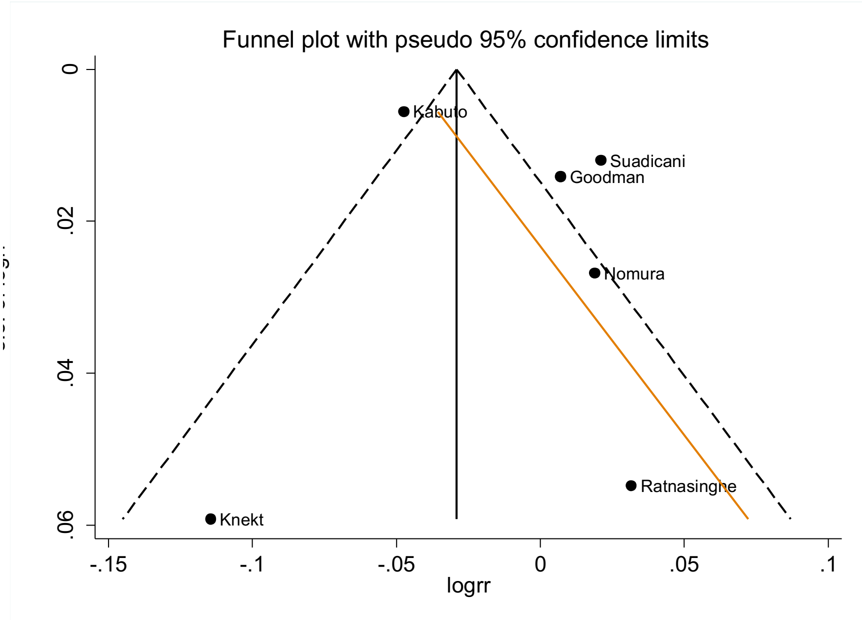


Figure 229 Funnel plot of studies included in the dose response meta-analysis of serum selenium and lung cancer



Egger's test p=0.02

Figure 230 RR (95% CI) of lung cancer for 10 µg/L increase of serum selenium by sex

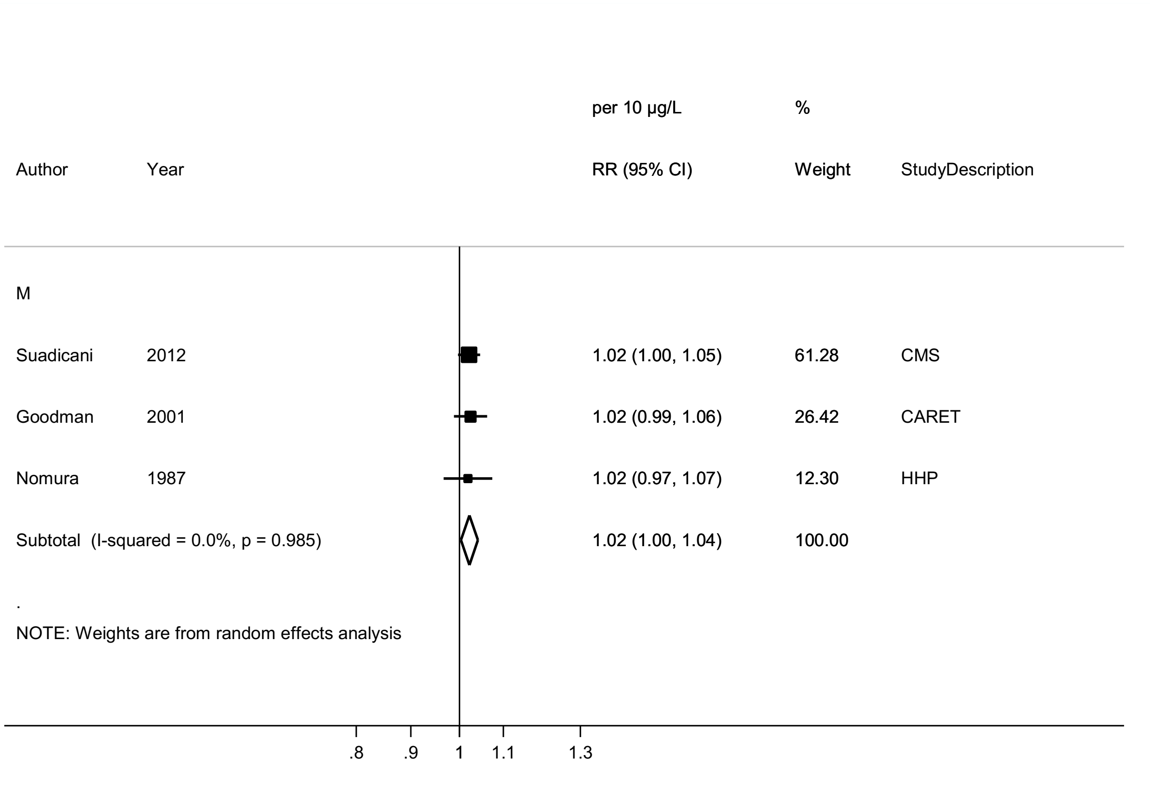
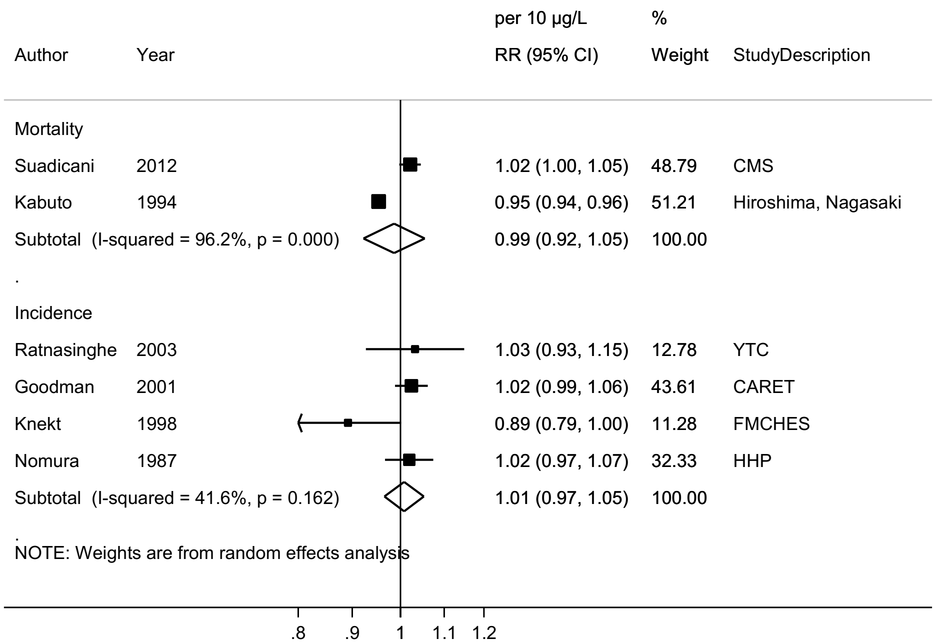


Figure 231 RR (95% CI) of lung cancer for 10 µg/L increase of serum selenium by cancer outcome



5.7.7 Quercetin (dietary)

No new study was identified in the CUP. There were two studies identified in the 2005 SLR which showed an inverse association between dietary quercetin and lung cancer. No meta-analysis was conducted. One published meta-analysis was identified. It included five case-control and cohort studies and showed an inverse association between quercetin and lung cancer risk (RR for highest compared to lowest intake=0.66 95%CI=0.47-0.92, I^2=49.6%, p= 0.09, n=4). The same meta-analysis reported an inverse association for kaempferol and no association with total dietary flavonoids (OR= 0.84, 95% CI= 0.71-1.00, I^2=58.1%, p= 0.02, n=8) (Woo, 2013).

Table 215 Quercetin and lung cancer risk. Main characteristics of studies identified in the 2005 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
Knekt, 2002 LUN00531 Finland	Finish Mobile Clinic Health Examination Survey, Prospective Cohort, Age: 39.00years, M/W,	169/ 10 054 30 years	Cancer registry	FFQ - study-specific	Incidence, lung cancer	>3.9 vs <1.4 mg/day	0.42 (0.25-0.72)	Age, sex, area of residence, BMI, energy intake, other, other nutrients, foods or supplements, smoking habits
Hirvonen, 2001 LUN00745 Finland	ATBC, Prospective Cohort, Age: 50-69 years, M, Smokers only	27 110 6 years	Cancer registry	FFQ - study-specific	Incidence, lung cancer	Highest vs Lowest	0.63 (0.52-0.78)	Age, energy intake, other nutrients, foods or supplements, smoking habits

5.8 Dietary Isoflavones

Cohort studies

Summary

Main results:
Most studies did not have the information needed for dose response meta-analysis. Only highest versus lowest analysis was performed. Four studies (2919 cases) were included in the highest versus lowest meta-analysis, all identified in the CUP. A significant inverse association of isoflavones with lung cancer was observed.

No evidence of heterogeneity was detected.

Sensitivity analyses:
In stratified analysis by smoking status, the results showed a stronger inverse association for isoflavones intake and lung cancer in never smokers but not for ever smokers.

Study quality:
All studies used FFQ or food questionnaire to assess the intake of isoflavones. All studies included in the high vs low analysis were adjusted for main confounders including age and smoking status.

Table 216 Isoflavones and lung cancer risk. Number of studies in the CUP SLR

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

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

Table 217 Isoflavones and lung cancer risk. Summary of the dose-response meta-analysis in the 2005 SLR and CUP

	2005 SLR	**CUP**
All studies		
Increment unit used		Highest vs lowest
Studies (n)		4
Cases (total number)		2919
RR (95%CI)		0.88 (0.79-0.99)
Heterogeneity (I^2, p-value)		0%, 0.72

P value Egger test		

Stratified and sensitivity analysis (no analyses conducted in the 2005 SLR)		
Smoking status	**Never smokers**	**Ever smokers**
Studies (n)	3	2
RR (95%CI)	0.66 (0.51-0.84)	1.02 (0.84-1.25)
Heterogeneity (I^2, p-value)	0%, 0.64	0%, 0.93

Table 218 Isoflavones and lung 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	6 (cohorts and case-control studies)	3093	Asia and America	Incidence, lung cancer	Per g/day	0.99 (0.97-1.01)		
					Highest vs lowest	0.80 (0.71-0.89)		
Yang*, 2012	5 (cohorts and case-control studies)		Asia and America	Incidence, lung cancer	Highest vs lowest	0.63(0.45-0.90)		81.8%, < 0.001

Table 219 Isoflavones intake and lung cancer risk. Main characteristics of studies included in the 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
Butler, 2013 LUN26852 China	SCHS, Prospective Cohort, Age: 45-74 years, M/W	1130/ 61 321 12 years	Singapore cancer registry database	Validated FFQ	Incidence, lung cancer	Highest vs lowest (mg/1000kcal /day)	0.88 (0.74-1.05)	Age, sex, number of cigarettes smoked per day, number of years since quit smoking, years of smoking, dialect group, interview year	
Yang, 2012 LUN20337 China	SWHS, Prospective Cohort, Age: 40-70 years, W	370/ 71 550 9 years	Cancer registry, death certificate, home visits and family member interview (next of kin)	FFQ and 24 hour recall	Incidence, lung cancer	> 44.23 vs ≤ 15.92 mg/day	0.72 (0.51-1.02) Ptrend:0.02	Age, BMI, smoking status, alcohol consumption, energy intake, fruits, menopausal status, non-soy calcium, non-soy vegetables, physical activity, red	
						Per 10 mg/day	0.93 (0.87-0.99)		

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Missing data derived for analyses
		340/			Never smokers	> 44.23 vs ≤ 15.92 mg/day	0.68 (0.47-0.97) Ptrend:0.02	meat intake, birth year, education, family history of lung cancer	
						Per 10 mg/day	0.93 (0.87-0.99)		
Shimazu, 2010 LUN20347 Japan	JPHC, Prospective Cohort, Age: 45-74 years, M/W	481/ 76 661 11 years	Cancer registry, hospital reports and death certificate	Validated FFQ	Incidence, lung cancer, men	48 vs 9 mg/day	0.89 (0.67-1.19) Ptrend:0.45	Age, smoking stats, alcohol consumption, fruit intake, area, fish intake, total vegetable intake, menopausal status (in women)	
		178			Incidence, lung cancer, women	48 vs 9 mg/day	0.83 (0.54-1.29) Ptrend:0.41		
		318			Incidence, lung cancer, men current smokers	48 vs 9 mg/day	1.03 (0.72-1.48) Ptrend:0.95		
		89			Incidence, lung cancer, men, former smokers	48 vs 9 mg/day	0.96 (0.50-1.82) Ptrend:0.86		
		74			Incidence, lung cancer, men, never smokers	48 vs 9 mg/day	0.43 (0.21-0.90) Ptrend:0.02		
		157			Incidence, lung cancer, women, never smokers	48 vs 9 mg/day	0.67 (0.41-1.10) Ptrend:0.13		
Cutler, 2008	IWHS,	647/	Linkage to the	Validated FFQ	Incidence, lung	1.83 vs 0.07	1.03 (0.80-1.34)	Age, BMI,	

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Missing data derived for analyses
LUN20338 USA	Prospective Cohort, Age: 55-69 years, W, postmenopausal	34 708 18 years	state health registry of IOWA, part of SEER		cancer, ever smokers	mg/day	Ptrend:0.91	education level, energy intake, multivitamin use, race, level of physical activity, pack years of smoking	
		113			Incidence, lung cancer, never smokers		0.80 (0.41-1.58) Ptrend:0.19		

Table 220 Isoflavones intake and lung cancer risk. Main characteristics of studies excluded in the 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
Seow, 2009 LUN20356 China	SCHS, Prospective Cohort, Age: 45-74 years, Women only	298/ 35 298 9.6 years	Cancer registry	Validated FFQ	Incidence, lung cancer, women	Highest vs lowest (mg/1000kcal /day	0.74 (0.53-1.04) Ptrend: 0.06		Superseded by Butler, 2013 LUN26852 which includes M/W
		138			Incidence, lung cancer, women Adenocarcinomas only		0.90 (0.55-1.47) Ptrend: 0.57		
		160			Incidence, lung cancer, women, other histologic types		0.62 (0.38-1.00) Ptrend: 0.04		
		109			Incidence, lung cancer, women, ever smokers		1.10 (0.641.89) Ptrend: 0.99		
		30			Incidence, lung cancer, women, ever smokers, Adenocarcinomas only		1.53 (0.58-4.01) Ptrend: 0.63		

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Reasons for exclusion
		79			Incidence, lung cancer, women, ever smokers, Adenocarcinomas other histologic types		0.97 (0.50-1.85) Ptrend: 0.75		
		189			Incidence, lung cancer, women, never smokers		0.59 (0.38-0.91) Ptrend: 0.02		
		108			Incidence, lung cancer, women, never smokers, Adenocarcinomas only		0.79 (0.45-1.39) Ptrend: 0.41		
		81			Incidence, lung cancer, women, never smokers, other histologic types		0.38 (0.18-0.80) Ptrend: 0.01		

Figure 232 RR (95% CI) of lung cancer for the highest compared with the lowest level of isoflavones intake

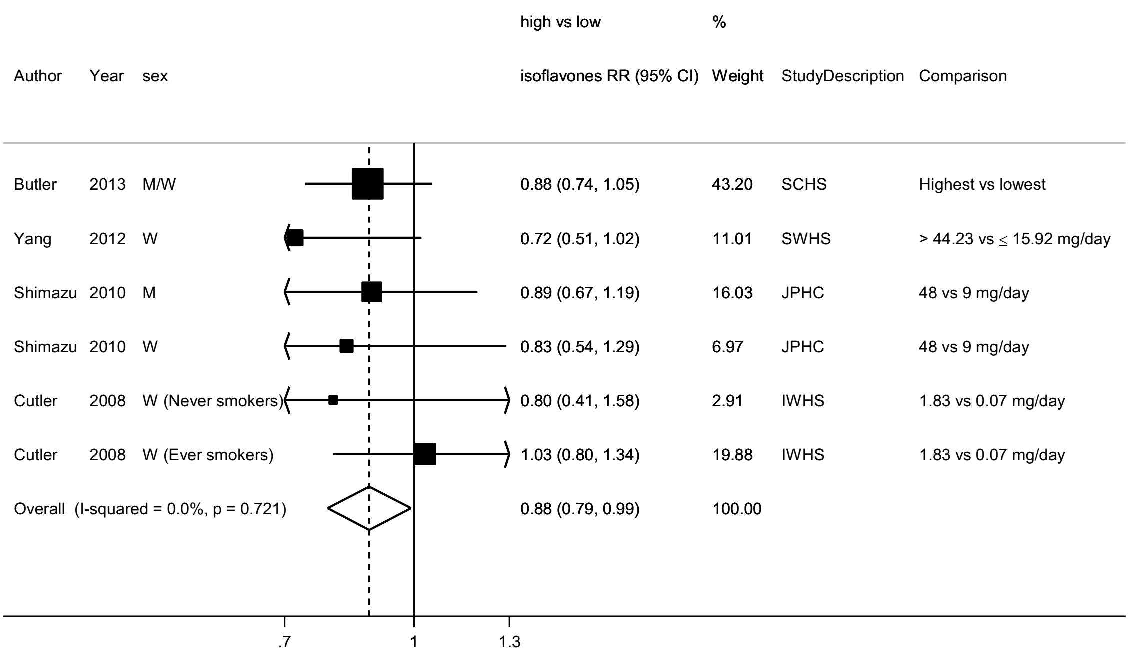
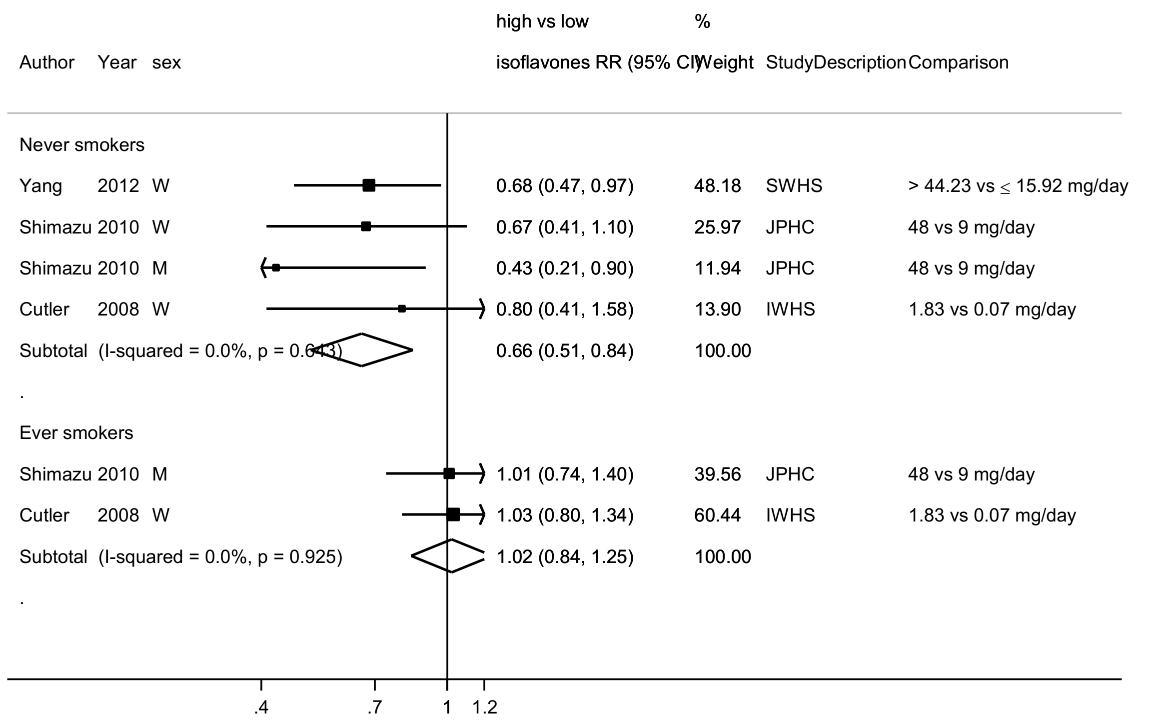


Figure 233 RR (95% CI) of lung cancer for the highest compared with the lowest level of isoflavones intake by smoking status



* In Shimazu, 2010 study, RR's of current and former smokers were combined in ever smokers.

6 Physical Activity

Physical activity was assessed using different instruments and for a variety of physical activities. Dose-response meta-analyses were not possible. The results are summarized for the highest compared to the lowest physical activity categories in the studies. The activities and levels are different and the summary is an indicative of the direction of the association.
The activities had been grouped as total physical activity, leisure time physical activity (non occupational activity, recreational or when the questionnaire did not include occupational activity) and occupational physical activity. Details of the physical activity assessment in each cohort included in the review are tabulated below. A few studies reported on sitting time and television viewing, walking or cycling, and these results are shown in tables. The association of physical activity according to smoking status and for cancer types had been reported in a limited number of studies and these are also summarized in highest vs lowest meta-analyses.

Table 221 Main characteristics of physical activity assessment in studies include in the review.

Study	Domains	Description of assessment	Validation
Alpha-Tocopherol, Beta Carotene Cancer Prevention (ATBC)	Occupational Leisure time	Two questions: 1) physical activity at work (not working; mainly sitting; walking quite a lot but not lifting or; walking and lifting; heavy physical work) 2) usual leisure-time activity in the past year as: *(i)* sedentary (*e.g.,* reading, watching television); *(ii)* moderate (*e.g.,* walking, hunting, gardening) fairly regularly; or *(iii)* heavy (*e.g.,* running, skiing, swimming) fairly regularly**.**	Not indicated
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
Beta-carotene and Retinol Efficacy Trial (CARET)	Total	Interview on time sleeping, last year frequency of vigorous, moderate and light activity, sitting (section of from Paffenbarger questionnaire)	Not validated. Significant correlation with BMI and cardiovascular diseases in the study.
Copenhagen Centre for Prospective Population Studies (CCPPS)	Leisure time	Self-administered questionnaire (Saltin & Grimby with minor modifications) on last year frequency of almost entirely sedentary activity (reading, TV, cinema) or light physical activity less than 2 hours per week; light physical activity 2–4 hours per week, e.g. walking, cycling, light gardening; light physical activity more than 4 hours per week or more vigorous physical activity 2–4 hours per week, e.g. brisk walking, fast cycling, heavy gardening, sports where you get sweaty or exhausted; highly vigorous physical activity more than 4 hours per week or regular heavy exercise or competitive sports several times per week	The questionnaire discriminates sedentary persons well from their more active counterparts with regard to maximal oxygen uptake
European Prospective Investigation into Nutrition and Cancer (EPIC)	Occupational Leisure time	Interview in part of the cohort or self-administered. Occupational activity (unemployed, sedentary, standing, manual, heavy manual and unknown), non-occupational physical activity (housework, home repair, gardening, stair climbing), recreational activities (walking, cycling and all other sports combined), vigorous nonoccupational activity (recreational and household activities causing sweating or faster heartbeat).	Relative validity and reproducibility undertaken; the questionnaire was found to be satisfactory for the ranking of subjects, less suitable for estimation of energy expenditure. Construct validity by correlation with BMI

Study	Domains	Description of assessment	Validation
Harvard University Health Study (HAHS)	Leisure time	Questionnaire of blocks walked, stairs climbed, frequency and duration of list of sport activities	Described as reliable and valid for ranking individuals. Test-retest correlation coefficient over one month: 0.72
Iowa Women's Health Study (IWHS)	Leisure time	Questions on nonoccupational physical activity level at baseline: frequency of moderate activity (such as bowling, golf, light sports or physical exercise, gardening, long walks), vigorous physical activity (such as jogging, racquet sports, swimming, aerobics, strenuous sports)	The derived physical activity level variable has predictive validity for coronary heart disease Incidence
Japan Collaborative Cohort Study for Evaluation of Cancer (JACC)	Leisure time	Questionnaire. Frequency of sport or physical exercise, time walking, time watching TV	Not indicated
Japan-Hawaii Study (Japanese in Hawaii)	Total Occupational Leisure time	Weighted sum of usual time sleeping or lying down, sitting or standing, walking, moderate and heavy activities, semiquantitative amount of physical activity at job and recreation (from Framingham study)	Not indicated
Japan Public Health Center-based Prospective Study (JPHC)	Total	Self-reported heavy physical work or strenuous exercise (4 METs), being sedentary (1.5 METs), standing or walking (2 METs), sleep or other passive activity (0.5 METs).	Validated using 4-day, 24-hour physical activity records
Korea Medical Insurance Corporation 1992-1994 (KMIC)	Leisure time	Exercise (yes or no)	Not indicated

Study	Domains	Description of assessment	Validation
Korean National Health Insurance Corporation Study 2002 (KNHIC)	Leisure time	Frequency and duration of vigorous, sweat-producing leisure physical activity	Not indicated
Kuopio Ischaemic Heart Disease Risk Factor Study	Leisure time	Interview by a nurse. Twelve-month physical activity questionnaire on frequency, duration and intensity of list of sport activities, home works and gardening, fishing and forestry, walking and biking to work	Selected activities (common activities) based in a previous population-based study in Finland
Mini-Finland health Survey 1978-80 (MFHS)	Leisure time	Exercise (three levels)	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

6.1 Total physical activity

Cohort studies

Summary

Main results:
Five studies (1457 cases) could be included in highest versus lowest meta-analysis. No significant (inverse) association was observed in men and women, and overall.There was moderate heterogeneity. The number of studies for investigating the sources of heterogeneity was low.

Sensitivity and stratified analysis
When the CARET study (Alfano, 2004) was excluded from the analysis no heterogeneity was observed and the association became significant (summary RR= 0.85; 95% CI 0.72-0.99).

Study quality:
Cancer outcome was confirmed using cancer registry records in most studies. Physical activity was assessed using different questionnaires. All studies adjusted for smoking status and intensity, BMI and other potential confounders.

Table 222 Total physical activity and lung cancer risk. Number of studies in the CUP SLR

	Number
Studies identified	5 (6 publications)
Studies included in forest plot of highest compared with lowest exposure	5
Studies included in dose-response meta-analysis	NA

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

Table 223 Total physical activity and lung cancer risk. Summary of the highest vs lowest meta-analysis in the 2005 SLR and CUP.

	2005 SLR	CUP	
All studies			
Increment unit used	No meta-analysis	Highest versus lowest	
Studies (n)		5	
Cases (total number)		1457	
RR (95%CI)		0.90 (0.77-1.04)	
Heterogeneity (I^2, p-value)		40 %, 0.10	
By sex (CUP)	**Men**	**Women**	**Men and Women**
Studies (n)	4	3	1
Cases (total number)	1134	254	263
RR (95%CI)	0.83 (0.66-1.06)	0.84 (0.57-1.24)	0.97 (0.74-1.28)
Heterogeneity (I^2, p-value)	44.4%, 0.15	0%, 0.78	78.7%, 0.03

Notes: Two risk sets from one study were included in the analysis for both sexes combined.

Table 224 Results of meta-analyses of prospective studies of physical activity and lung cancer 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 (I2, p value)
Sun, 2012	13 cohorts	14074	USA, Japan-Hawaii, South Korea Norway, UK, Europe	Incidence	Any type of physical activity High vs low	All studies 0.77 (0.73-0.81)	< 0.01	10.8%
						Men 0.78 (0.73-0.83) n=11	< 0.01	31.%
						Women 0.76 (0.69-0.84) n=7	< 0.01	0%

Note: This meta-analysis included studies on total and leisure time physical activity

Table 225 Total physical activity and lung cancer risk. Main characteristics of studies included in the CUP SLR

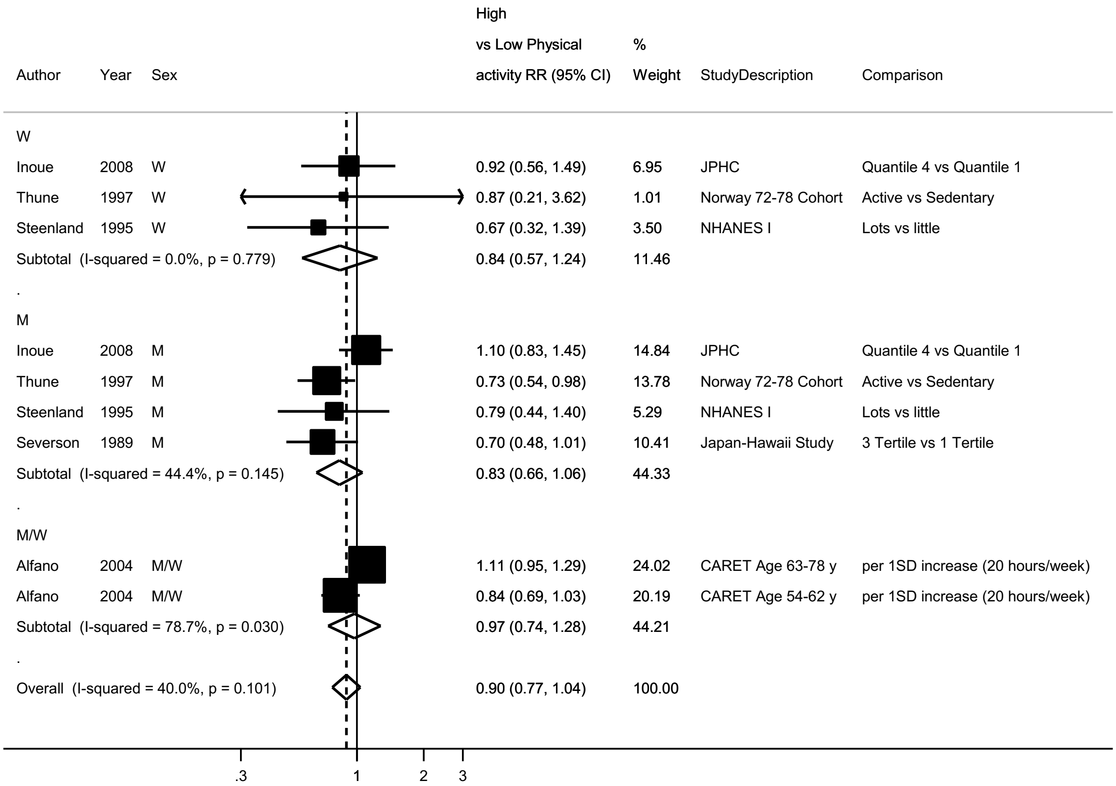
Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI)	Adjustment factors	Missing data derived for analyses
Inoue, 2008 LUN20284 Japan	JPHC, Prospective Cohort, Age: 45-74 years, M/W	388/ 79 771 8 years	Hospital notifications, linkage with population-based cancer registries, death certificate	Self-reported , questionnaire	Incidence, lung cancer, men	Quartile 4 vs quartile 1	1.10 (0.83-1.45)	Age, area, energy intake, history of diabetes, smoking status, alcohol intake status, BMI, leisure-time physical activity	
		144/			Incidence, lung cancer, women		0.92 (0.56-1.49)		
Alfano, 2004 LUN17027 USA	CARET, Prospective Cohort, Age: 50-69 years, M/W	263/ 7045 6 years	Primary outcome of the trial. Active follow-up with confirmation by clinical records and pathology reports	Interview. Questionnaire	Incidence, lung cancer	1 SD increase in physical activity	0.84 (0.69-1.03)	Age, sex, current smoking status, pack-years, BMI, education level, ethnicity, family history of cancer, intervention or placebo group, general health status, fat, fruits, vegetables and alcohol intakes	
Thune, 1997 LUN01867 Norway	Norway 1972-78 Prospective Cohort,	401/ 81 516 19 years	Cancer Registry	Self-reported and checked by nurse	Incidence, men	Active vs sedentary	0.73 (0.58-0.94)	Age, BMI, geographical region, smoking	

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI)	Adjustment factors	Missing data derived for analyses
	M/W	50					0.87 (0.21-3.62)	habits (former, pipe/cigar) number of cigarettes smoked, years of smoking	
Steenland, 1995 LUN12546 USA	NHANES I, Nested Case Control, Age: 25-74 years, M/W	151/ 14 407 8 years	Follow-up interviews confirmed with hospital records and death certificates	Two questions	Incidence, lung cancer, men	Little vs lots	1.26 (0.71-2.24)	Age, alcohol consumption, BMI, other, physical activity, smoking status (derived from a subsequent questionnaire)	Rescaled reference category using the Hamling method
		59			Incidence, lung cancer, women		1.41 (0.59-3.35)		
Severson 1989 LUN13297 USA	Japan-Hawaii Study, Prospective Cohort, M	194/ 7925 21 years	Hospital records, death certificates, Hawaii tumour registry	Questionnaire	Incidence, lung cancer	Tertile 3vs tertile 1	0.70 (0.48-1.01)	Age, BMI, smoking	

Table 226 Total physical activity and lung cancer risk. Main characteristics of studies excluded 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) P trend	Adjustment factors	Reasons for exclusion
Albanes, 1989 LUN12810 USA	NHANES I, Prospective Cohort, Age: 25-74 years, M/W	114/ 12 545 10 years	Follow-up interviews confirmed with hospital records and death certificates	Questionnaire	Incidence, lung cancer	Quite inactive vs very active	2.00 (1.20-3.50)	Age, BMI, energy intake, family history of cancer, other nutrients, foods or supplements, smoking habits	Superseded by Steenland, 1995 (LUN12546)

Figure 234 RR (95% CI) of lung cancer for the highest compared with the lowest level of total physical activity



6.1.1.1 Occupational physical activity

Cohort studies

Summary

Main results:
Five studies (3773cases) were included in highest versus lowest analysis. Lung cancer risk was not significantly associated with occupational physical activity in men and women. There was no evidence of heterogeneity.

Study quality:
Cancer outcome was confirmed using cancer registry records in most studies; occupational physical activity was assessed using questionnaires or interview all studies.
All studies adjusted for smoking status, BMI and other potential confounders.

Table 227 Occupational physical activity and lung 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 dose-response meta-analysis	NA

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

Table 228 Occupational physical activity and lung cancer risk. Summary of the dose-response meta-analysis in the 2005 SLR and CUP.

	2005 SLR	**CUP**
Increment unit used	No meta-analysis	Highest versus lowest
All studies		
Studies (n)		5
Cases (total number)		3773
RR (95%CI)		1.12 (0.99-1.28)
Heterogeneity (I^2, p-value)		0 %, 0.64

By sex	**Men**	**Women**	**Men and Women**
Studies (n)	4	2	1
RR (95%CI)	1.11 (0.95-1.30)	1.05 (0.75-1.47)	1.25 (0.90-1.74)
Cases (total number)	2656	527	320
Heterogeneity (I^2, p-value)	11.0%, 0.34	0%, 0.55	

Table 229 Occupational physical activity and lung cancer risk. Main characteristics of studies included in the CUP SLR

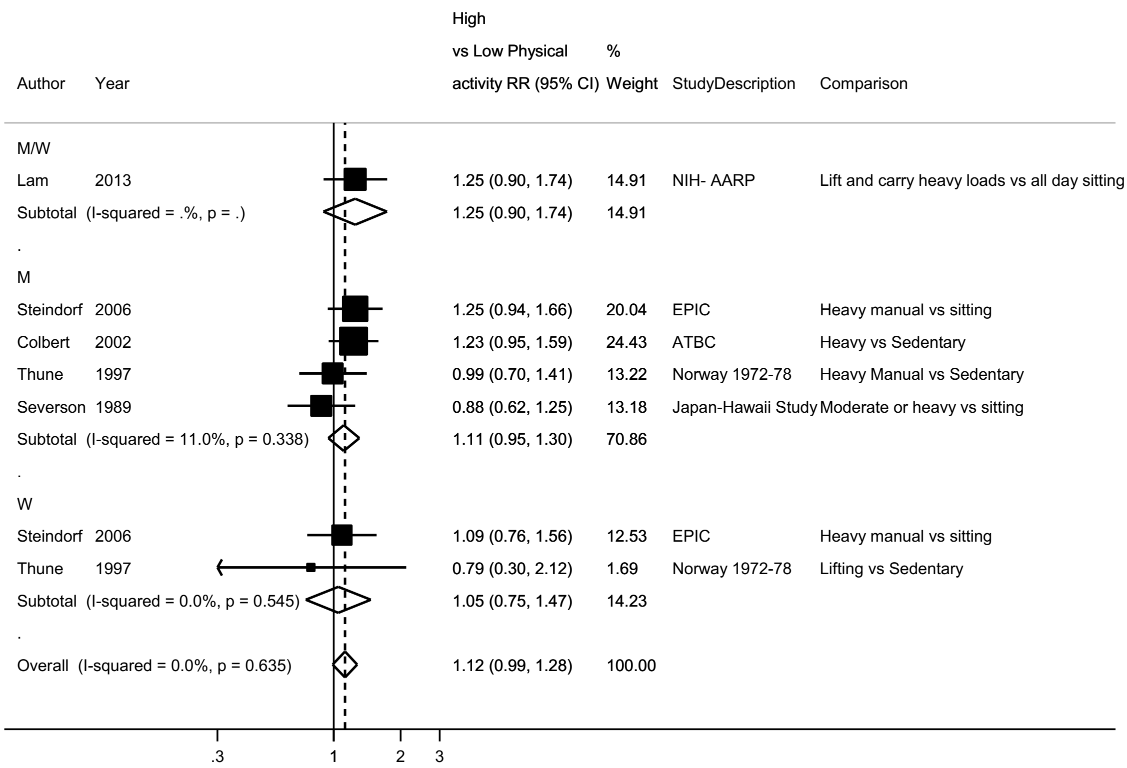
Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI)	Adjustment factors	Missing data derived for analyses
Lam, 2013 LUN26868 USA	NIH- AARP Diet and Health Study, Prospective Cohort, M/W, never smokers	320/ 158 415 10 years	Cancer registries	Questionnaire	Incidence, lung cancer	Carry and lifting heavy loads vs all day sitting	1.21 (0.84-1.76)	Age, BMI, education, ethnicity, vigorous activity, alcohol consumption, total caloric intake	Rescaled reference category using the Hamling method
Steindorf, 2006 LUN26875 Europe	EPIC, Prospective Cohort, M/W	607/ 416 227 6 years	Cancer registries, health insurance records, pathology records and active follow up	Questionnaire/ interview	Incidence, lung cancer, men	Heavy manual vs sitting	1.25 (0.94-1.66)	Age, centre, smoking weight, height, education, total energy intake without energy from alcohol, alcohol intake, intake of fruits, intake of vegetables, intake of red and processed meat and occupational exposure to lung carcinogens, household physical activity	
		476			Incidence, lung cancer, women		1.09 (0.76-1.56)		

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI)	Adjustment factors	Missing data derived for analyses
Colbert, 2002 LUN00643 Finland	ATBC Prospective Cohort, M, Smokers only	1442/ 27 087 6 years	Finnish Cancer Registry and the Register of Causes of Death	Questionnaire	Incidence, lung cancer, men	Active vs sedentary	1.23 (0.95-159)	Age, BMI, supplement group, cigarettes smoked/day, years of smoking, education, energy intake and vegetable intake	
Thune, 1997 LUN01867 Norway	Norway 1972-78 Prospective Cohort, M/W	413/ 81 516 19 years	Cancer registry	Questionnaire	Incidence, lung cancer, men	Heavy manual vs sedentary	0.99 (0.70-1.41)	Age, BMI, geographical region, smoking habits, number cigarettes smoked	
		51			Incidence, lung cancer, women		0.79 (0.30-2.12)		
Severson 1989 LUN13297 USA	,Japan-Hawaii Study Prospective Cohort, M	194/ 7925 21 years	Hospital records, death certificates, Hawaii tumour registry	Questionnaire	Incidence, lung cancer	Moderate or heavy vs mostly sitting	0.88 (0.62-1.25)	Age, BMI, smoking habits	

Table 230 Occupational physical activity and lung cancer risk. Main characteristics of studies excluded 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) P trend	Adjustment factors	Reasons for exclusion
Rundle, 2010 LUN20354 Europe	EPIC, Nested Case Control, M/W	230/ 878 7.4 years	Cancer registry, health insurance records, active follow up and mortality registry	Interview	Incidence, lung cancer	Manual/heavy vs sitting	1.03 (0.60-1.79)	Recreational physical activity, household physical activity, total years of smoking	Only never smokers. Steindorf 2006 LUN26875 was used instead
Bak, 2005 LUN18652 Denmark	DCH Prospective Cohort, M/W	194/ 54 422 7 years	Cancer registry	Questionnaire	Incidence, lung cancer, men	Heavy activity vs sedentary	1.13 (0.63-2.05)	Active/no active for of leisure time physical activity (sports, cycling gardening, housework do-it-your-self, walking), smoking ,school education, intake of fruit and vegetables and possible occupational exposure to lung carcinogen	Cohort included in EPIC (Steindorf 2006 LUN26875)
		175			Incidence, lung cancer, women		1.80 (0.75-4.31)		

Figure 235 RR (95% CI) of lung cancer for the highest compared with the lowest level of occupational physical activity



6.1.1.2 Recreational physical activity

Nonoccupational, leisure time activities, sport or exercise and summarized in this section.

Cohort studies

Summary

Main results:
A significant inverse association was observed on average in the 18 (17655 cases) studies included in the highest versus lowest analysis. There was moderate to high heterogeneity. The association was significant in men (16 studies) and inverse but borderline the statistical significance in women (eight studies). In analysis stratified by smoking status (seven studies), significant inverse associations were observed in smokers (six studies), former smokers (two studies) and in former and never smokers (three studies). No significant association was observed in never smokers (three studies).
Five studies examine the association by cancer type. The strongest inverse association was observed for adenocarcinomas; significant inverse association was also observed for squamous cell carcinomas. No significant association (inverse) with substantial heterogeneity was observed for small cell carcinomas.
In the NIH-AARP (Leitzmann, 2009), the association of physical activity and lung cancer types was analysed by smoking status. The pattern of association was similar in current and former smokers but for current smokers, the inverse association was most apparent for adenocarcinoma. No relation was observed for any cancer type in never smokers. The difference of association when comparing ever smokers with never smokers was significant only for adenocarcinoma.

Study quality:
Cancer outcome was confirmed using cancer registry records in most studies. There are differences on the type of physical activity assessed. In some studies, moderate to vigorous activity was assessed. However, no important heterogeneity was observed.
All except three studies adjusted for smoking status (and other measures of intensity or frequency), BMI and other potential confounders. In the studies that did not adjust for smoking no association was observed in the Japanese study in men and inverse but not significant in women (Suzuki, 2007); strong inverse significant association was observed in a Korean study in men (Lee, 2002) and inverse but not significant in a small study in Finland (Knekt, 1996).

Three studies did not adjusted for smoking; five studies adjusted for smoking status only, six studies adjusted for smoking status only and cigarette quantity, two studies adjusted for smoking status and smoking duration, and two studies adjusted for smoking status, intensity and duration (years smoking /time since quitting). After excluding the 3 studies not adjusting for smoking (Suzuki 2007, Lee 2002, Knekt 1996) the RR was 0.88(0.79-0.93) for men and 0.90 (0.79-1.02) for women.

Table 231 Recreational physical activity and lung cancer risk. Number of studies in the CUP SLR

	Number
Studies identified	19 (23 publications)
Studies included in forest plot of highest compared with lowest exposure	18
Studies included in dose-response meta-analysis	NA

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

Table 232 Recreational physical activity and lung cancer risk. Summary of the highest vs lowest meta-analysis in the 2005 SLR and CUP

	2005 SLR*	**CUP**
All studies		
Increment unit used		Highest versus lowest
Studies (n)		18
Cases (total number)		17655
RR (95%CI)		0.86 (0.81-0.92)
Heterogeneity (I^2, p-value)		41%, 0.02

Stratified and sensitivity analysis (no analyses conducted in the 2005 SLR)				
By sex	**Men**	**Women**		
Studies (n)	16	8		
Cases (total number)	11972	5412		
RR (95%CI)	0.85 (0.79-0.92)	0.89 (0.79-1.00)		
Heterogeneity (I^2, p-value)	47.2%, 0.02	31.0%, 0.18		
Smoking status	**Never smokers**	**Current smokers**	**Former smokers**	**Former and never smokers**
Studies (n)	3	6	3	2
RR (95%CI)	0.99 (0.76-1.31)	0.81 (0.71-0.91)	0.68 (0.51-0.90)	0.81 (0.70-0.95)
Heterogeneity (I^2, p-value)	18.9%, 0.29	64.9%, 0.01	49.9%, 0.13	5.4%, 0.30
Cancer type	**Small cell carcinoma**	**Squamous cell carcinoma**	**Adenocarcinoma**	
Studies (n)	5	5	5	
RR (95%CI)	0.88 (0.72-	0.87 (0.78-	0.82 (0.74-0.91)	

	1.07)	0.97)			
Heterogeneity (I^2, p-value)	56.8%, 0.04	0%, 0.66	0%, 0.73		
Adjustment by smoking	**No adjustment**	**Smoking status only**	**Smoking status, cigarrete quantity**	**Smoking status, duration**	**Smoking status, intensity, duration**
Studies (n)	3	5	6	2	2
RR (95%CI)	0.86 (0.70-1.06)	0.83 (0.76-0.89)	0.81 (0.72-0.91)	0.97 (0.88-1.06)	0.99 (0.85-1.16)
Heterogeneity (I^2, p-value)	54.7%, 0.09	0%, 0.82	56.7%, 0.02	0%, 0.83	0%, 0.98

*2005 SLR included publications that reported on sports, standard mortality ratio and household activities. Highest versus lowest analysis was conducted, but no overall RR was reported.

Table 233 Recreational physical activity and lung cancer risk. Results of meta-analyses and pooled analyses of prospective studies published after the 2005 SLR.

Author, year	Number of studies	Number of cases	Country	Outcome	Comparison	RR (95% CI)	Ptrend	I2 %, p heterogeneity
Buffart, 2014 (smokers only)	7 cohorts	11367	USA, Finland, Norway, Korea	Incidence	High vs low	All 0.82 (0.77-0.87)	< 0.01	21.6%, 0.19
						Men 0.85 (0.77-0.93) n=4 (10 RRs)	< 0.01	10.8%, 0.34
						Women 0.68 (0.57-0.82) n=1 (2 RR)	< 0.01	0%, 0.58
						Heavy smokers 0.83 (0.77-0.89) (9 RR)	< 0.01	0%, 0.65
						Light smokers 0.87 (0.80-0.95) (6 RR)	0.02	17.5%, 0.30

Table 234 Recreational physical activity and lung cancer risk. Main characteristics of studies 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)	Adjustment factors	Missing data derived for analyses
Batty, 2010b LUN20277 UK	Whitehall Study, Prospective Cohort, M, Civil Servants	366/ 6729 40 years	National health service central registers	Questionnaire	Mortality, lung cancer	Inactive vs active	1.25 (0.93-1.69)	Age, BMI, employment grade, forced expiratory volume in 1 second, smoking	Rescaled reference category
Laukkanen, 2010 LUN26864 Finland	Kuopio Ischaemic Heart Disease Risk Factor Study, Prospective Cohort, Age: 42-60 years, M	52/ 2268 17 years	Finnish cancer registry	Questionnaire	Incidence, lung cancer	Per 1 MET increase	0.80 (0.69-0.93)	Age, BMI, energy intake, fat intake, smoking status (cigarette pack-years per 10 years number of cigarettes smoked), alcohol, fibre intake	
Leitzmann, 2009 LUN20358 USA	NIH-AARP Study Prospective Cohort Age: 59-71 years, Retired	4419/ 501148 7.2 years	Linkage with 11 state cancer registry databases	Questionnaire	Incidence, lung cancer, men	Times per week of physical activity	0.77 (0.70-0.85)	Age, BMI, smoking (time since quitting for former smokers, smoking intensity for former and current smokers), race/ethnicity, education,, marital status, family	
		2326			Incidence, lung cancer, women		0.80 (0.69-0.92)		

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure Assessment	Outcome	Comparison	RR (95%CI)	Adjustment factors	Missing data derived for analyses
								history of cancer, intakes of fruit and vegetables, red meat, alcohol	
Kabat, 2008b LUN20341 USA	WHI, Prospective Cohort, Age: 50-79 years postmenopausal women	1304/ 159 659 8 years	Lung cancer was not the primary outcome of the trial. Follow-up by mail or phone. Self-reported lung cancers verified by local review of pathology reports	Questionnaire	Incidence, lung cancer	≥ 21.02 MET /week vs <1.38 MET /week	1.06 (0.88-1.28)	Age, smoking status, pack of smoking, education, ethnicity, hormone replacement therapy use, intakes of total fat, fruits, vegetables, alcohol, and total calories	
Sprague, 2008 LUN20331 USA	SHOW, Prospective Cohort, Age: 43-86 years, M/W	134/ 4831 13 years	Cancer registry, death certificate and national death index	Questionnaire	Incidence, lung cancer	≥875 kcal/week vs 0-174 kcal/week	0.56 (0.35-0.87)	Age, sex, BMI, pack year of smoking, time since smoking cessation, WBC count, alcohol intake, education	
Yun, 2008 LUN20276 Korea	KNHIC, Prospective Cohort,	1574/ 444 963 6 years	Linkage with cancer registry, national health	Self-report	Incidence, lung cancer	Moderate-high vs low	0.83 (0.75-0.92)	Age, BMI, dietary preference, employment,	

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure Assessment	Outcome	Comparison	RR (95%CI)	Adjustment factors	Missing data derived for analyses
	M		insurance and death report					fasting blood sugar, smoking status, alcohol drinking,	
Suzuki, 2007 LUN20282 Japan	JACC	Men 705 /456405 Women 195 /638490	Population death registries	Questionnaire	Mortality, lung cancer	>3 hr sport vs <1 hr	Men 0.97 (0.80-1.17) 1.28 (0.80-2.06)	Age, area	
Sinner, 2006 LUN20319 USA	IWHS, Prospective Cohort, W	777/ 36 410 17 years	State health registry	Questionnaire	Incidence, lung cancer	High vs low	0.77 (0.64-0.94)	BMI, education level, marital status, smoking status (current, former, never), vegetable intake, age at baseline, alcohol intake, pack years of smoking	

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure Assessment	Outcome	Comparison	RR (95%CI)	Adjustment factors	Missing data derived for analyses
Steindorf, 2006 LUN26875 Europe	EPIC, Prospective Cohort, M/W	607/ 416 227 6 years	Cancer registries, health insurance records, pathology rec & active follow up	Questionnaire/int erview	Incidence, lung cancer, men	≥ 45 MET hr/week vs <13.4 MET hr/week	1.00 (0.79-1.27)	Age, centre, smoking status (duration, intensity, time since smoking cessation). weight, height, education, total energy intake without energy from alcohol, alcohol intake, intake of fruits, intake of vegetables, intake of red and processed meat and occupational exposure to lung carcinogens, household physical activity	
		476			Incidence, lung cancer, women	≥ 42 MET hr/week vs 13.4 MET hr/week	0.99 (0.76-1.30)		
Schnohr, 2005 LUN20368 Denmark	CCPPS, Prospective Cohort, M/W	545/ 28 259 14 years	Cancer registry	Questionnaire	Incidence, lung cancer, men	Vigorous vs low physical activity in leisure time	0.92 (0.72-1.18)	Age, alcohol consumption, cohort membership, smoking duration, smoking status (interaccion	
		228			Incidence, lung cancer, women		1.06 (0.71-1.60)		

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure Assessment	Outcome	Comparison	RR (95%CI)	Adjustment factors	Missing data derived for analyses
								between smoking status and duration), occupational physical activity, birth cohort, education	
Lee, 2002 LUN00654 South Korea	KMIC, Prospective Cohort, Age: 35-64 years, M	883/ 452 645 5 years	Death certificate	Questionnaire	Mortality, lung cancer	Yes vs no	0.80 (0.70-0.90)	Age	
Colbert, 2002 LUN00643 Finland	ATBC Prospective Cohort, M, Smokers only	1442/ 27 087 6 years	Finnish Cancer Registry and the Register of Causes of Death	Questionnaire	Incidence, lung cancer	Active vs sedentary	0.97 (0.87-1.07)	Age, supplement group, BMI, cigarettes smoked/day, years of smoking, education, energy intake and vegetable intake	
Wannamethee, 2001 LUN12104 UK	BRHS, Prospective Cohort, Age: 40-59 years, M	265/ 7588 19 years	Death certificates, Cancer registry, record linkage, postal questionnaires to surviving	Questionnaire	Incidence, lung cancer	Vigorous vs none/moderate	0.76 (0.40-1.43)	Age, alcohol consumption, BMI, cigarrette smoking, social class	

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure Assessment	Outcome	Comparison	RR (95%CI)	Adjustment factors	Missing data derived for analyses
			members						
Lee, 1999 LUN01280 USA	HAHS, Prospective Cohort, Age: 58.00years, M	245/ 13 905 16 years	Self-report of physician diagnosed, site specific cancer, death certificate	Questionnaire	Incidence, lung cancer	≥12600 kJ/week vs 1-4199 kJ/week	0.61 (0.41-0.89)	Age, BMI, cigarette smoking (non-smoker, smoker, or ≤ cigarrtes day, smoker of ≥ 20 cigarrettes day or uknown quantity)	
Thune, 1997 LUN01867 Norway	Norway 1972-78 Prospective Cohort, Age: 20-49 years, M/W	413/ 81 516 19 years	Cancer Registry of Norway	Questionnaire	Incidence, lung cancer, men	Regular training vs sedentary	0.71 (0.52-0.97)	Age, BMI, geographical region, smoking habits (ex-smoking, pipe/cigar smoking, number of cigarettes smoked, years smoked),	
		51			Incidence, lung cancer, women		0.99 (0.35-2.78)		
Knekt, 1996 LUN01885 Finland	MFHS Prospective Cohort, Age: 30-95 years, M/W	70/ 7018 14 years	Cancer Registry	Questionnaire	Incidence, lung cancer, Men	High vs low	0.45 (0.17-1.18)	Age	
Severson 1989 LUN13297 USA	Japan-Hawaii Study, Prospective	194/ 7925 21 years	Hospital records, death certificates,	Questionnaire	Incidence lung cancer	3 Tertile vs 1 tertile	0.70 (0.48-1.01)	Age, BMI, cigarette smoking	

Author, Year, WCRF Code, Country	**Study name, characteristics**	**Cases/ Study size Follow-up (years)**	**Case ascertainment**	**Exposure Assessment**	**Outcome**	**Comparison**	**RR (95%CI)**	**Adjustment factors**	**Missing data derived for analyses**
	Cohort, M		Hawaii tumour registry						
Albanes, 1989 LUN12810 USA	NHANES I Prospective Cohort, Age: 25-74 years, M/W,	114/ 12 545 10 years	Follow-up interviews confirmed with hospital records and death certificates	Questionnaire	Incidence, lung cancer, men	Little or no exercise vs much exercise	0.90 (0.60-1.50)	Age, race, BMI, energy intake, economic status, family history of specific cancer, other nutrients, foods or supplements, smoking habits, pack-year smoked	Rescaled reference category using the Hamling method

Table 235 Recreational physical activity and lung cancer risk. Main characteristics of studies excluded 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) P trend	Adjustment factors	Reasons for exclusion
Rundle, 2010 LUN20354 Europe	EPIC, Nested Case Control, M/W	230/ 878 7.4 years	Cancer registry, health insurance records, active follow up and mortality registry	Interview	Incidence lung cancer	> 39.0 vs 0-12 MET-hrs/week	0.56 (0.35-0.90)	Occupational physical activity, household physical activity, total years of smoking	Nonsmokers only, Steindorf 2006 (LUN26875) used instead
Farahmand, 2003 LUN13031 Sweden	Vasaloppet cohort, Prospective Cohort, Age: 16-81 years, M/W	8/ 73 622 4 years	Mortality registries	Questionnaire	Incidence, lung cancer, men	Observed deaths vs expected deaths	0.22 (0.10-0.43)		Standardized Mortality Ratio
Linseisen, 2002 LUN00434 Germany	EPIC-Heidelberg Nested Case Control, Age: 25-70 years, M/W	15/ 482 924 2 years	By trained physician and histology	Questionnaire	Incidence, lung cancer, current smokers	(mean exposure)		Age, sex, other, smoking habits	Mean exposure Superseded by Rundle, 2010 (LUN20354)
Potter, 1992 LUN02842 USA	IWHS, Nested Case Control,	109/ 41 837 4 years	Iowa Health Registry (part of SEER registry)	Questionnaire	Incidence, lung cancer	High vs low/moderate	0.41 (0.20-0.81)	Alcohol consumption, educational	Superseded by Sinner, 2006 (LUN20319)

	Age: 55-69 years, W, Post-menopausal							level, smoking habits	
Sellers, 1991 LUN03128 USA	IWHS Nested Case-Control Age: 55-69 Women	179/ 2079 4 years	Iowa Health Registry (part of SEER registry)	Questionnaire	Incidence, lung cancer	High vs low or moderate	0.4 (0.3-0.5)		Superseded by Sinner 2006 (LUN20319)

Figure 236 RR (95% CI) of lung cancer for the highest compared with the lowest level of recreational physical activity

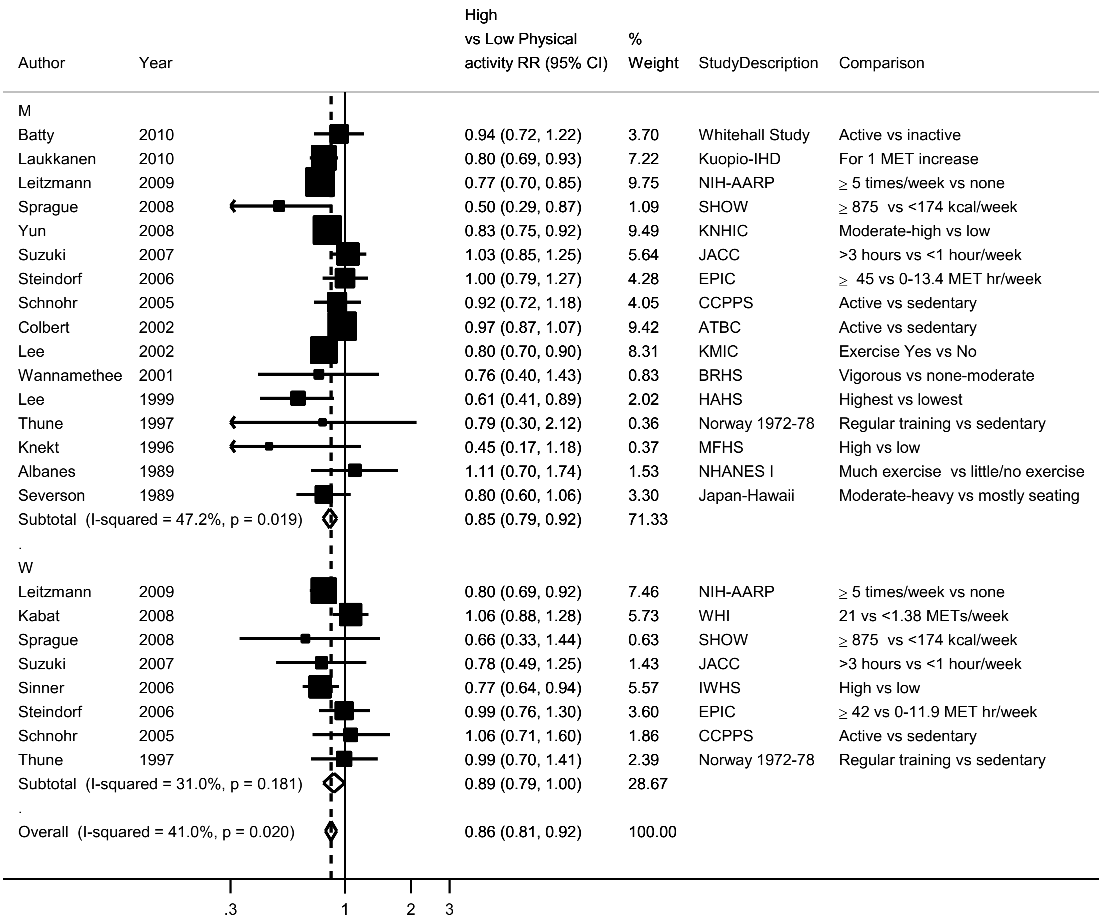


Figure 237 RR (95% CI) of lung cancer for the highest compared with the lowest level of recreational physical activity, excluding studies not adjusted for smoking status

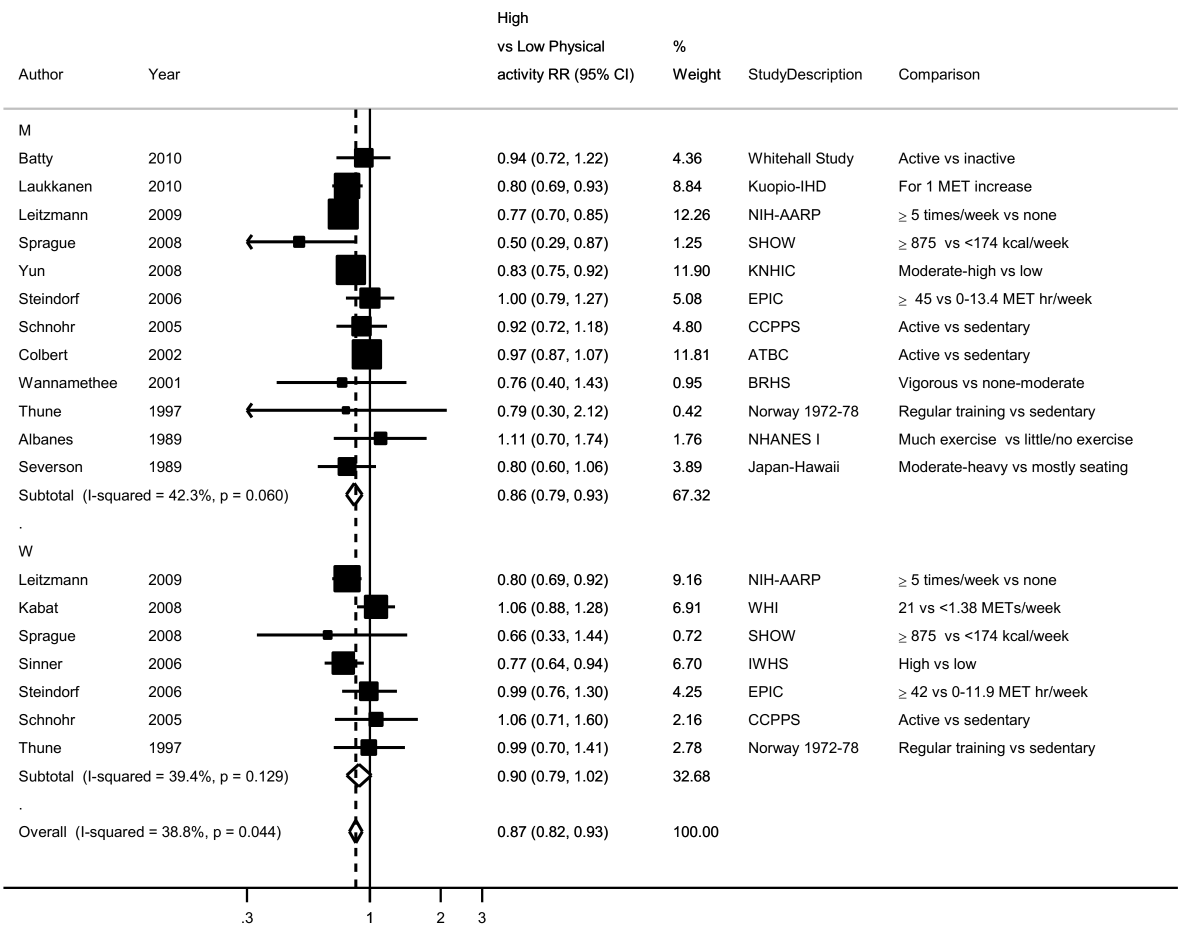


Figure 238 RR (95% CI) of lung cancer for the highest compared with the lowest level of recreational physical activity by smoking status

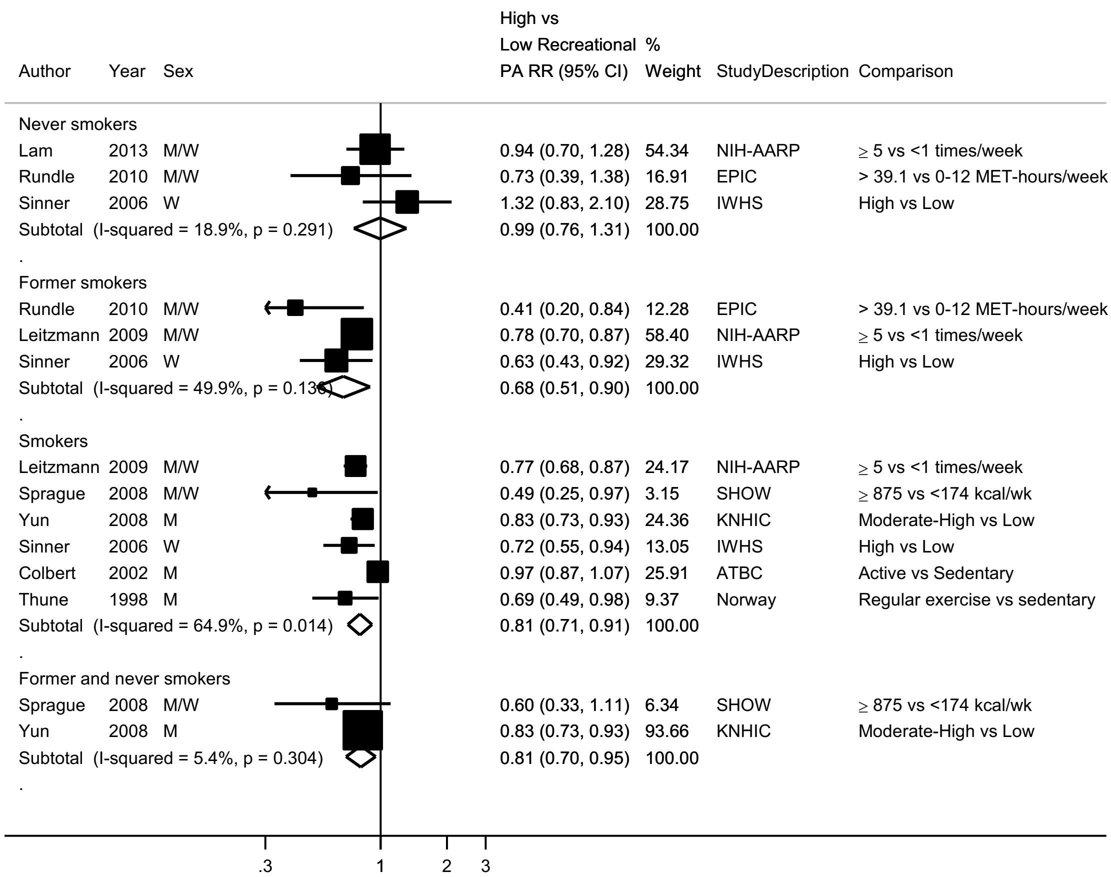
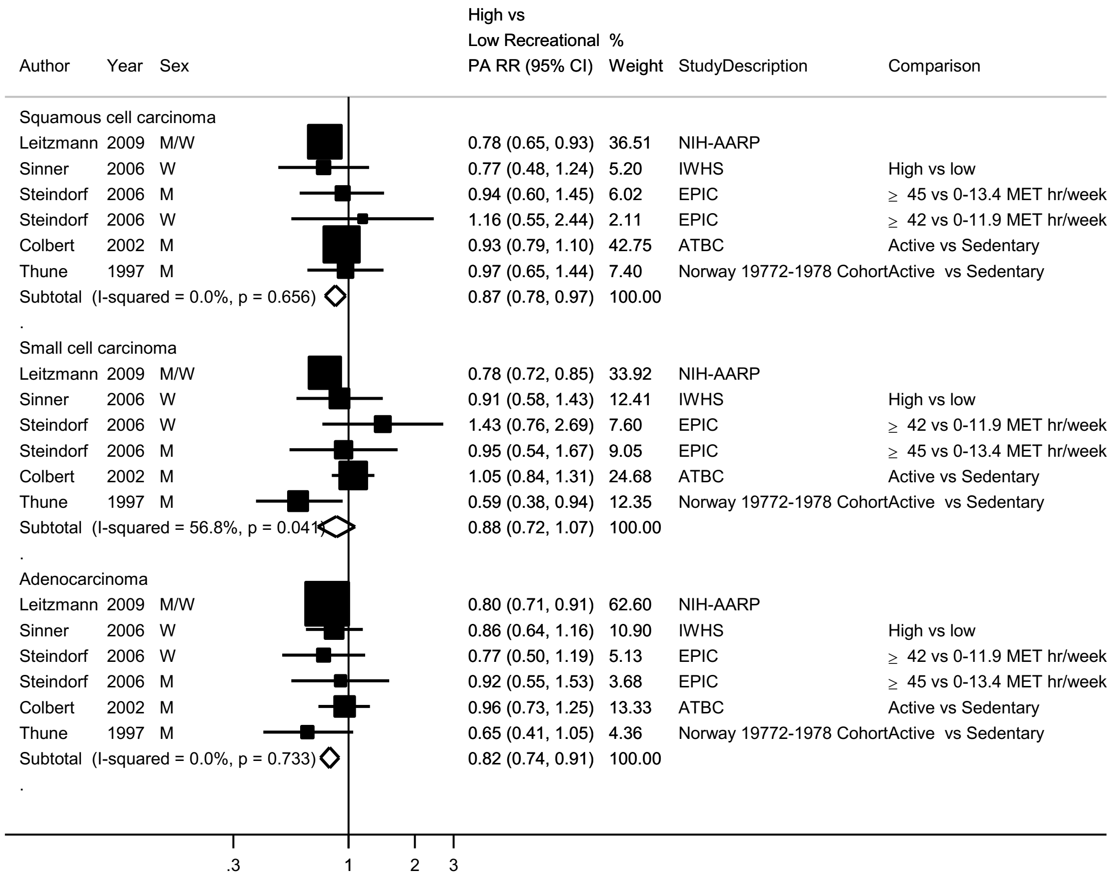


Figure 239 RR (95% CI) of lung cancer for the highest compared with the lowest level of recreational physical activity by cancer type



8 Anthropometry

8.1.1 BMI

Cohort studies

Summary

Main results:
Twenty nine studies (35 206 cases) out of 39 studies (47 publications) were included in the dose-response meta-analysis. A significant inverse association of BMI was observed. When the Pooling Project was combined with the nonoverlapping studies included in the CUP dose-response analysis a similar inverse association was observed.
Two studies were excluded because they combined larynx, trachea, bronchus and lung cancer incidence, two studies had unadjusted results, one study was in Chinese and one study did not provide quantile range or confidence intervals.
High heterogeneity was observed. In stratified analysis, the results were similar in men and women, in studies with incidence and mortality as outcome and in studies of different locations. There was a limited number of studies on lung cancer subtypes. Twelve studies were included in stratified analysis by smoking. A significant inverse association was found for current smokers and former, not for never smokers. There was high heterogeneity across studies in smoking subgroups. When the Pooling Project was added to a stratified highest versus lowest analysis by smoking status the results were similar to the dose-response analysis stratified by smoking.
There was significant evidence of publication or small study bias (p=0.02).

Sensitivity analyses:
The overall association remained statistically significant in influence analysis. The summary RRs ranged from 0.81 (95% CI=0.77-0.86) when Calle, 2003 was omitted to 0.84 (95% CI=0.82-0.88) when Lee, 2002 was omitted in the influence analysis.
There was evidence of a non-linear dose-response for lung cancer and BMI (p < 0.01).

Study quality:
Cancer outcome was confirmed using records in cancer registries in most studies.
Most studies measured weight and height to calculate BMI. Six studies used self-reported weight and height to calculated BMI and four studies used the BMI from medical records.
All studies included in the dose-response analysis were at least adjusted for age, sex, and smoking status.
Out of 29 studies, the first years of follow-up were excluded from the main analyses in four studies: Bhaskaran, 2014 (first year of follow-up excluded and no change after further exclusion on first three years of follow-up); Chen, 2012 (first 5 years of follow-up

excluded); Jee, 2008 (first 2 years excluded) and Rapp, 2005 (first year excluded). In other nine studies the results remained similar after exclusion of the first years of follow-up: Song, 2014 (first five years excluded), Smith 2012 (5 and 7 years), Leung, 2011 (3 years), Andreotti, 2010 (5 years), Kabat, 2008 (3 years), Reeves, 2007 (2 years), Calle 2003 (2 years), Olson, 2002 (5 years), Kark, 1995 (the results persisted during follow-up) . In one study (Chyou, 1994) lung cancer risk was inversely associated with subscapular skinfold in the first 10 years of follow-up (p=0.049) and inverse but no significant association later in follow-up, but a similar analysis on BMI was not shown. The remaining studies did not test whether exclusion of first years of follow-up modified the results.

Pooling project of cohort studies:
Lung cancer was significantly inversely related to BMI in the Pooling Project of Cohort Studies (Parr, 2010; 39 cohorts). The association was significant in current smokers and in never smokers. When the Pooling Project was included in the CUP dose-response meta-analysis with the nonoverlapping studies identified in the CUP a significant inverse association was observed (63 studies).

Table 236 BMI and lung cancer risk. Number of studies in the CUP SLR

	Number
Studies identified	39 (47 publications)
Studies included in forest plot of highest compared with lowest exposure	29
Studies included in dose-response meta-analysis	29
Studies included in non-linear dose-response meta-analysis	25

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

Table 237 BMI and lung cancer risk. Summary of the dose-response meta-analysis in the 2005 SLR and CUP.

	2005 SLR	**CUP**
Increment unit used	1 kg/m^2	5 kg/m^2
All studies		
Studies (n)	15	29
Cases (total number)	3565	35 206
RR (95%CI)	0.98 (0.98-0.99)	0.83(0.80-0.86)
Heterogeneity (I^2, p-value)	76%	80.3%, <0.001
P value Egger test		<0.001
All studies and Pooling Projects		
Studies (n)		63

Cases (total number)		23 565
RR (95%CI)		0.85(0.82-0.88)
Heterogeneity (I^2, p-value)		75.2%, <0.01
Highest versus Lowest stratified analysis, all studies and Pooling Project		
Smoking status	**Never smokers**	**Current smokers**
Studies (n)	48	48
RR (95%CI)	0.88 (0.66-1.09)	0.76 (0.59-0.97)
Heterogeneity (I^2, p-value)	73.8%, <0.01	77.2%, <0.01

Stratified and sensitivity analysis (no analyses conducted in the 2005 SLR)			
Smoking status	**Never smokers**	**Current smokers**	**Former smokers**
Studies (n)	12	10	7
RR (95%CI)	0.93 (0.84-1.03)	0.81 (0.73-0.89)	0.88 (0.79-0.98)
Heterogeneity (I^2, p-value)	68.9%, <0.001	83.1%, <0.001	63.9%, 0.01
Sex	**Men**	**Women**	
Studies (n)	19	14	
RR (95%CI)	0.79 (0.74-0.85)	0.87 (0.83-0.91)	
Heterogeneity (I^2, p-value)	78.3% , <0.001	55.7%, <0.01	
Outcome	**Incidence**	**Mortality**	
Studies (n)	20	10	
RR (95%CI)	0.84 (0.81-0.88)	0.79 (0.70- 0.89)	
Heterogeneity (I^2, p-value)	79.8%, < 0.001	81.4%, 0.08	
Cancer type	**Small cell carcinoma**	**Squamous cell carcinoma**	**Adenocarcinoma**
Studies (n)	2	2	3
RR (95%CI)	0.96 (0.80-1.15)	0.73 (0.40-1.33)	0.87 (0.83-0.92)
Heterogeneity (I^2, p-value)	32.4%, 0.22	89.9%, <0.01	0%, 0.66
Geographic location	**Asia**	**Europe**	**North America**
Studies (n)	9	10	11
RR (95%CI)	0.82 (0.71- 0.94)	0.80 (0.76-0.86)	0.87 (0.83-0.90)
Heterogeneity (I^2, p-value)	84.2% , <0.001	66.6% , <0.001	46.9%, 0.04
Exposure assessment	**Self-reported**	**Measured**	**Medical records**
Studies (n)	6	20	4
RR (95%CI)	0.86(0.81-0.91)	0.79 (0.73-0.85)	0.87 (0.80-0.95)
Heterogeneity (I^2, p-value)	58.5%, 0.03	76.6%, <0.001	89.7%, <0.001
Adjustment on smoking	**Smoking status**	**Intensity and duration of smoking**	**No adjustment**
Studies (n)	11	15	4
RR (95%CI)	0.82(0.81-0.83)	0.84(0.80-0.88)	0.70(0.61-0.80)
Heterogeneity (I^2, p-value)	0%, 0.74	81.2%, <0.01	33.7%, 0.24

Table 238 BMI and lung cancer risk. Results of meta-analyses and pooled analyses of prospective studies published after the 2005 SLR.

Author, Year	Number of cohort studies	Total number of cases	Studies country, area	Outcome	Comparison	RR (95%CI)	P trend	Heterogeneity (I^2, p value)
Meta-analyses								
Yang, 2013	31	26 066	20 cohort studies and 11 case-control studies from North America, Europe and Asia	Lung cancer incidence	≥25 vs 18.5-24.9 kg/m² All	0.79(0.73–0.85)		
					Current smokers	0.63 (0.57–0.70)		
					Former smokers	0.73 (0.58–0.91)		
					Never smokers	0.83 (0.70–0.98)		
					Squamous cell carcinoma	0.68(0.58–0.80)		
					Small cell carcinoma	0.99(0.66–1.48)		
					Adenocarcinoma	0.79(0.65–0.96)		
Pooled analyses								
Parr, 2010	39	1478	Asia-Pacific Cohort Studies Collaboration	Lung cancer mortality	30-60 vs 12-18.4 kg/m²	0.83 (0.64–1.08)	< 0.01	
					Per 5 units	0.86 (0.77–0.96)		
					25-29 vs 12-18.4 kg/m² smokers	0.67(0.57-0.79)	< 0.01	
					25-29 vs 12-18.4 kg/m² never smokers	0.42(0.27-0.65)	0.01	

Table 239 Table 240 BMI and lung cancer risk. Main characteristics of studies 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	Missing data derived for analyses
Wie, 2014 LUN26882 Korea	Korea 2004-2013, Prospective Cohort, M/W	36/ 8024 7 years	Cancer registry and medical records	Height and weight were measured using InBody 3.0 (Biospace)	Incidence, lung cancer	≥25 vs <25 kg/m^2	1.54 (0.44-5.38)	Age, sex, income, marital status, physical activity, alcohol, education, energy, smoking status	
						Per 1 kgm^2	1.01 (0.81-1.24)		
Song, 2014b LUN26877 Finland	FINRISK , Prospective Cohort, Age: 24-74 years, M/W	626/ 54 725 21 years	Cancer and mortality registries	Height and weight were measured on site by specially trained nurses with participants not wearing shoes and heavy clothing	Incidence, lung cancer, men	35 vs 23.0-24.9 kg/m^2	0.83 (0.44-1.59)	Age, leisure - physical activity, area, education, smoking status	Distribution of person-years by exposure category, mid-points of exposure categories.
		114			Incidence, lung cancer, women		0.80 (0.35-1.85)		
Bhaskaran, 2014 LUN26876 UK	CPRD 1987-2012, Prospective Cohort, M/W	19 339/ 5 243 978	Medical records	Extracted from GP notes in database	Incidence and mortality, lung cancer	≥35 vs 18.5-24.9 kg/m^2	0.66 (0.61-0.72)	Age, sex	Converted CIs from 99% to 95%, for the non-linear analysis, RRs with the lowermost category as
						Per 5 kg/m^2	0.82(0.81-0.83)	Age, diabetes status, smoking status, alcohol use, socioeconomic status, calendar	
					Incidence and mortality, lung cancer, never smokers		0.99(0.95-1.04)		

Author, Year, WCRF Code, Country	Study 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
								year, sex	reference was calculated using the Hamling's method
Bethea, 2013 LUN26857 USA	Black Women's Health Study, 1995, Prospective Cohort, W, Black women	323/ 56 944	Cancer registry, medical records, histology	Self-reported weight and height	Incidence, lung cancer	>30 vs 18.5-24.9 kg/m^2	0.69 (0.52-0.93) Ptrend:< 0.01	Age, age at first birth, geographic area, parity, physical activity, alcohol, education, family history of lung cancer, pack years of smoking	Mid-points of exposure categories
						>30 vs 18.5-24.9 kg/m^2	0.56 (0.33-0.97) Ptrend:<0.01		
		140			Incidence, lung cancer, former smoker	>30 vs 18.5-24.9 kg/m^2	0.90 (0.56-1.42) Ptrend:0.06		
		137			Incidence, lung cancer current smoker	>30 vs 18.5-24.9 kg/m^2	0.62 (0.38-1.00) Ptrend:<0.01		
		46			Incidence, lung cancer, never smoked	>30 vs 18.5-24.9 kg/m^2	0.83 (0.41-1.70) Ptrend:0.23		
Butler, 2013 LUN26852 China	SCHS, Prospective Cohort, Age: 45-74 years, M/W	1130/ 61 321 12 years	Singapore cancer registry database	Medical records	Incidence, lung cancer	>30 vs 18.4 kg/m^2	0.54 (0.32-0.91)	Age, sex, dialect group, interview year, number of cigarettes smoked per day, number of years since quit smoking, years of smoking	Distribution of person-years by exposure category, mid-points of exposure categories.

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Missing data derived for analyses
Lam, 2013 LUN26868 USA	NIH- AARP Diet and Health Study, Prospective Cohort, Age: 50-71 years, M/W, never smokers	532/ 158 415 10 years	Postal service, social security administration death master file, national death index	Anthropometric variables (baseline weight and height) derived from the baseline questionnaire and the second risk factor questionnaire (waist circumference, hip circumference, weight and height at 18, 35, and 50 years).	Incidence, lung cancer, never smokers	>30 vs 18.5-24.9 kg/m^2	1.21 (0.95-1.53) Ptrend:0.21	Age, alcohol consumption, ethnicity, total caloric intake, education, physical activity at work, vigorous physical activity	Used only for stratified analysis by smoking. Smith, 2012 LUN20334 used for total. Distribution of person-years by exposure category, mid-points of exposure categories.
Lin, 2013 LUN20316 USA	NHANES III, Prospective Cohort, Age: 50- years, M/W	98/ 5204 12	National Death Index	Weight and height measured	Mortality, lung cancer, men	>30 vs >24.9 kg/m^2	0.35 (0.14-0.93) Ptrend:0.11	Age, caloric intake, race/ethnicity, smoking status, current alcoholic beverage intake, urinary cadmium, zinc	Distribution of cases and person-years by exposure category, mid-points of exposure categories.
		57			Mortality, lung cancer, women	>30 vs >24.9 kg/m^2	1.76 (0.78-3.98) Ptrend:0.36		
Chen, 2012 LUN20288 China	CNRPCS, Prospective Cohort,	758/ 142 214 15 years	Review of medical records and death	Trained health workers measured height	Mortality, lung cancer, BMI 15 to <23.5kg/m²	Per 5 kg/m^2	0.70 (0.56-0.88)	Age, alcohol intake, area, education,	RR for BMI 15 to <23.5 and 23.5-35 kg/m2

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Missing data derived for analyses
	Age: 40-79 years, M		certificates	and weight.				smoking status	combined
		621			BMI 15 to <23.5kg/m² , ever-smokers	Per 5 kg/m^2	0.65 (0.50-0.83)	Age, alcohol intake, area, education, smoking	
		178			BMI 23.5 to <35kg/m²	Per 5 kg/m^2	0.89 (0.57-1.40)	Age, alcohol intake, area, education, smoking	
		137			BMI 15 to <23.5kg/m² , never-smokers	Per 5 kg/m^2	1.01 (0.58-1.77)	Age, alcohol intake, area, education, smoking	
		131			BMI 23.5 - 35kg/m² , ever-smokers	Per 5 kg/m^2	0.88 (0.51-1.50)	Age, alcohol intake, area, education, smoking	
		47			BMI 23.5 - 35kg/m² , never-smokers	Per 5 kg/m^2	0.92 (0.40-2.13)	Age, alcohol intake, area, education, smoking	
					BMI 15-23.5kg/m², current smokers	Per 5 kg/m^2	0.66 (0.45-0.95)	Age, cigarettes per day	
Smith, 2012	NIH-AARP,	6093/	Cancer registry	Height and	Incidence, lung	>35 vs 22.5-	0.81 (0.70-0.94)	Cigar or pipe	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
LUN20334 USA	Prospective Cohort, Age: 50-71 years, M/W, Retired	448 732 10 years	and national death index	weight were self-reported.	cancer, men	24.99 kg/m^2	Ptrend:<0.01	smoking, education level, history of emphysema, physical activity, race/ethnicity, age at study entry, alcohol intake, smoking status and dose	exposure categories
		3423			Men former smokers	>35 vs 22.5-24.99 kg/m^2	0.84 (0.70-1.01) Ptrend:<0.01	Cigar or pipe smoking, education level, history of emphysema, physical activity, race/ethnicity, age at study entry, alcohol intake, smoking status and dose	
						Per 5 kg/m^2	0.91 (0.87-0.96)		
		3344			Women	>35 vs 22.5-24.99 kg/m^2	0.73 (0.61-0.87) Ptrend:<0.01		
		2440			Men current smokers	>35 vs 22.5-24.99 kg/m^2	0.76 (0.58-0.98) Ptrend:<0.01		
						Per 5 kg/m^2	0.89 (0.84-0.94)		
		2021			Men former smokers, quit ≥ 10 y ago	Per 5 kg/m^2	0.96 (0.90-1.01)		
						>30 vs 18.5-24.99 kg/m^2	0.96 (0.84-1.09) Ptrend:0.47		
		1800			Women current smokers	>35 vs 22.5-24.99 kg/m^2	0.63 (0.48-0.84) Ptrend:<0.01		

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Missing data derived for analyses
						Per 5 kg/m^2	0.87 (0.83-0.92)		
		1383			Men former smokers, quit ≥ 10 y ago, >20 cigarettes/d	Per 5 kg/m^2	0.96 (0.89-1.03)		
						>30 vs 18.5-24.99 kg/m^2	0.91 (0.78-1.06) Ptrend:0.20		
		1294			Women former smokers	>35 vs 22.5-24.99 kg/m^2	0.78 (0.62-0.99) Ptrend:<0.01		
						Per 5 kg/m^2	0.91 (0.86-0.96)		
		1269			Men current smokers, >20 cigarettes/d	Per 5 kg/m^2	0.91 (0.85-0.98)		
						>30 vs 18.5-24.99 kg/m^2	0.81 (0.69-0.95) Ptrend<0.01		
		1171			Men current smokers,≤20 cigarettes/d	Per 5 kg/m^2	0.87 (0.80-0.94)		
						>30 vs 18.5-24.99 kg/m^2	0.73 (0.60-0.88) Ptrend:<0.01		
		1132			Women current smokers, ≤ 20 cigarettes/d	Per 5 kg/m^2	0.84 (0.78-0.90)		
						>30 vs 18.5-24.99 kg/m^2	0.67 (0.55-0.82) Ptrend:<0.01		
		668			Women current smokers, >20 cigarettes/d	Per 5 kg/m^2	0.92 (0.85-1.00)		
						>30 vs 18.5-24.99 kg/m^2	0.79 (0.63-1.00) Ptrend:0.08		
		638/			Men former smokers, quit ≥ 10 y ago, ≤20	Per 5 kg/m^2	0.95 (0.85-1.06)		
						>30 vs 18.5-	10.60 (0.84-		

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Missing data derived for analyses
					cigarettes/d	24.99 kg/m^2	1.34) Ptrend:0.61		
		605			Men former smokers, quit 5-9 y ago, > 20 cigarettes/d	Per 5 kg/m^2	0.88 (0.80-0.98)		
						>30 vs 18.5-24.99 kg/m^2	0.70 (0.55-0.89) Ptrend<0.01		
		599			Men former smokers, quit 1-4 y ago	Per 5 kg/m^2	0.86 (0.77-0.96)		
						>30 vs 18.5-24.99 kg/m^2	0.83 (0.66-1.05) Ptrend:0.14		
		597			Women former smokers, quit ≥ 10 y ago	Per 5 kg/m^2	0.90 (0.83-0.98)		
						>30 vs 18.5-24.99 kg/m^2	0.72 (0.58-0.91) Ptrend:<0.01		
		423			Men former smokers, quit 1-4 y ago, >20 cigarettes/d	Per 5 kg/m^2	0.85 (0.75-0.96)		
						>30 vs 18.5-24.99 kg/m^2	0.78 (0.59-1.02) Ptrend:0.10		
		390			Women former smokers, quit 5-9 y ago	Per 5 kg/m^2	0.97 (0.88-1.07)		
		311			Women former smokers, quit ≥ 10 y ago, >20 cigarettes/d	Per 5 kg/m^2	0.97 (0.87-1.08)		
						>30 vs 18.5-24.99 kg/m^2	0.94 (0.70-1.26) Ptrend:0.67		
		307			Women former	Per 5 kgm^2	0.86 (0.76-0.97)		

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Missing data derived for analyses
					smokers, quit 1-4 y ago	>30 vs 18.5-24.99 kg/m^2	0.58 (0.42-0.81) Ptrend<0.01		
		286			Women former smokers, quit ≥ 10 y ago, ≤20 cigarettes/d	Per 5 kg/m^2	0.81 (0.71-0.92)		
						>30 vs 18.5-24.99 kg/m^2	0.51 (0.35-0.73) Ptrend:<0.01		
		249			Women never smokers	>35 vs 22.5-24.99 kg/m^2	1.00 (0.58-1.74) Ptrend:0.85	Education level, physical activity, race/ethnicity, age at study entry, alcohol intake	
						Per 5 kg/m^2	0.97 (0.86-1.10)		
		233			Women former smokers, quit 5-9 y ago, > 20 cigarettes/d	Per 5 kg/m^2	1.04 (0.92-1.17)	Cigar or pipe smoking, education level, history of emphysema, physical activity, race/ethnicity, age at study entry, alcohol intake, smoking status and dose	
						>30 vs 18.5-24.99 kg/m^2	1.23 (0.80-1.72) Ptrend:0.20		
		198			Men former smokers, quit 5-9 y ago, ≤ 20 cigarettes/d	Per 5 kg/m^2	0.74 (0.60-0.90)		
						>30 vs 18.5-24.99 kg/m^2	0.51 (0.32-0.80) Ptrend:0.01		
		176			Men former smokers, quit 1-4 y ago, ≤20 cigarettes/d	Per 5 kg/m^2	0.89 (0.72-1.11)		
						>30 vs 18.5-24.99 kg/m^2	0.99 (0.64-1.54) Ptrend:0.88		
		166			Men never	>35 vs 22.5-	1.04 (0.41-2.67)	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
					smokers	24.99 kg/m^2	Ptrend:0.44	physical activity, race/ethnicity, age at study entry, alcohol intake	
						Per 5 kg/m^2	1.08 (0.88-1.33)		
						>30 vs 18.5-24.99 kg/m^2	1.32 (0.85-2.04) Ptrend:0.31		
		157			Women former smokers, quit 1-4 y ago, >20 cigarettes/d	Per 5 kg/m2	0.89 (0.76-1.04)	Cigar or pipe smoking, education level, history of emphysema, physical activity, race/ethnicity, age at study entry, alcohol intake, smoking status and dose	
						>30 vs 18.5-24.99 kg/m^2	0.71 (0.46-1.10) Ptrend:0.11		
					Women former smokers, quit 5-9 y ago, ≤ 20 cigarettes/d	Per 5 kg/m^2	0.84 (0.71-1.00)		
						>30 vs 18.5-24.99 kg/m2	0.66 (0.42-1.03) Ptrend:0.08		
		150			Women former smokers, quit 1-4 y ago,≤20 cigarettes/d	Per 5 kg/m2	0.82 (0.69-0.98)		
						>30 vs 18.5-24.99 kg/m^2	0.46 (0.28-0.76) Ptrend:<0.01		
Dehal, 2011 LUN20302 USA	NHEFS, Prospective Cohort, Age: 25-75 years, M/W	124/ 7016 17 years	Death index , social security administration death file	Measured at baseline by a trained technician.	Mortality, lung cancer	Obesity vs normal weight	0.98 (0.57-1.70) Ptrend:0.88	Age, sex, cigarette smoking, educational level, fruit and vegetable consumption, marital status, race/ethnicity,	

Author, Year, WCRF Code, Country	Study 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
								alcohol drinking, family income, type of residence area at baseline	
Leung, 2011 LUN20325 Hong Kong	CECS, Prospective Cohort, Age: 65- years, M/W, Elderly	932/ 58 931 423 061 person years	Death register	Obtained from health assessment database.	Mortality, lung cancer	>30 vs 18.5-22.9 kg/m^2	0.55 (0.38-0.80) Ptrend:<0.01	Marital status, smoking status, alcohol intake, education, gender, housing	Distribution of person-years by exposure category, mid-points of exposure categories.
						>30 vs 18.5-22.9 kg/m^2	0.49 (0.31-0.79) Ptrend:<0.01	Alcohol consumption, marital status, smoking status, education, gender, housing	
		500			Ever smoker	>30 vs 18.5-22.9 kg/m^2	0.70 (0.41-1.21) Ptrend:0.05	Alcohol consumption, marital status, education, gender, housing	
					Ever smokers	>30 vs 18.5-22.9 kg/m^2	0.59 (0.29-1.21) Ptrend:0.42	Marital status, alcohol intake, education, gender, housing	
		432			Never smokers	>30 vs 18.5-22.9	0.46 (0.27-0.79)	Marital status,	

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Missing data derived for analyses
						kg/m^2	Ptrend:0.03	alcohol intake, education, gender, housing	
						>30 vs 18.5-22.9 kg/m^2	0.44 (0.24-0.82) Ptrend:<0.01	Alcohol consumption, marital status, education, gender, housing	
Andreotti, 2010 LUN20291 USA	AHS, Prospective Cohort, M/W, Pesticide applicators and their spouses	261/ 67 947 10 years	Cancer registry	Self-reported height and weight in questionnaire, missing values were supplemented by the 5-year follow-up phone interview and from the driver's licenses	Incidence, lung cancer, men	≥35 vs 18.5-24.9 kg/m^2	0.47 (0.15-1.49)	Age, race, smoking status, state of residence, exercise, vegetable consumption, family history of cancer	Distribution of person-years by exposure category, mid-points of exposure categories.
						Per 1 kg/m^2	0.97 (0.93-1.01)		
		96			Incidence, lung cancer, women	30-34.9 vs 18.5-24.9 kg/m^2	0.67(0.33-1.38)		
						Per 1 kg/m^2	0.98(0.94-1.03)		
		228			Incidence, lung cancer, men, ever smokers	≥35 vs 18.5-24.9 kg/m^2	0.22 (0.05–0.90)	Age, race, state of residence, exercise, cigarettes pack years, vegetable consumption, family history of cancer	
						Per 1 kgm2	0.92 (0.88–0.97)		
		64			Incidence, lung cancer, women,	≥35 vs 18.5-24.9 kg/m^2	0.87 (0.40–1.90)	Age, race, state of residence,	

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Missing data derived for analyses
					ever smokers	Per 1 kg/m^2	0.99 (0.94–1.05)	exercise, pack yrs of smoking, vegetable consumption, family history of cancer, hypertension, vitamin supplements, parity;	
		21			Incidence, lung cancer, men, never smokers	Per 1 kg/m^2	0.98 (0.86–1.11)	Age, race, state of residence, exercise, vegetable consumption, family history of cancer, state	
		30			Incidence, lung cancer, women, never smokers	Per 1 kg/m^2	0.92 (0.84–1.01)	Age, race, state of residence, exercise,, vegetable consumption, family history of cancer, hypertension, vitamin supplements, parity, state	

Author, Year, WCRF Code, Country	Study 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
Koh, 2010 LUN20359 China	SCHS, Prospective Cohort, Age: 45-74 years, M/W	1042/ 63 257 13 years	Linkage with national cancer and death registries	At the time of recruitment, an in-person interview was conducted at the subject's residence by a trained interviewer using a structured questionnaire. self-reported heights and weights at baseline.	Incidence, lung cancer	<20 vs ≥28 kg/m^2	1.34 (0.98-1.83) Ptrend:<0.01	Age, sex, beta-cryptoxanthin intake, dialect group, education level, number of cigarettes smoked per day, number of years since quit smoking, years of smoking	Used only in stratified analysis by smoking (for total Butler, 2013 LUN26852 Distribution of person-years by exposure category, mid-points of exposure categories.
		599			Incidence, lung cancer, current smokers	<20 vs ≥28 kg/m^2	1.91 (1.12-3.25) Ptrend:<0.01		
		287			Incidence, lung cancer, never smokers	<20 vs ≥28 kg/m^2	0.93 (0.55-1.56) Ptrend:0.31		
		156			Incidence, lung cancer, former smokers	<20 vs ≥28 kg/m^2	0.85 (0.41-1.75) Ptrend:0.46		
Laukkanen, 2010 LUN26864 Finland	Kuopio Ischaemic Heart Disease Risk Factor Study, Prospective Cohort, Age: 42-60 years, M	52/ 2268 17	Finnish cancer registry	Weight and height measured	Incidence, lung cancer	Per 5 kg/m^2	0.62 (0.39-0.93)	Age, energy intake, fat intake, smoking status, alcohol, fibre intake, physical activity	
Inoue, 2009 LUN20272 Japan	JPHC, Prospective Cohort,	149/ 27724 10 years	Hospital records, population-	Measured by trained staff.	Incidence, lung cancer, men	Overweight (≥25) vs no overweight	1.10 (0.76-1.60)	Age, smoking status, study area, ethanol	

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Missing data derived for analyses
	Age: 40-69 years, M/W		based cancer registries and death certificates			(<25) kg/m^2		intake, serum cholesterol	
Yang, 2009 LUN20349 China	CNRPCS, Prospective Cohort, Age: 40-79 years, M	1311/ 217 180 15 years	Death register/ death certificates	Height, weight were measured.	Incidence, lung cancer, current smokers	>22.5 vs 20-22.5 kg/m^2	0.89 (0.80-0.98) Ptrend:0.01	5-yr age group, education level, fruit intake, meat intake, study area, alcohol drinking, exposure to indoor air-pollution, self reported health status	Used only in individual curves dose response graph and highest versus lowest analysis. Superseded by Chen, 2012 LUN20288 which only present continuous results
Jee, 2008 LUN20283 Korea	KNHIC, Prospective Cohort, Age: 30-95 years, M/W	9066/ 1 213 829 11 years	Linkage with cancer registry, national health insurance and death report	Height and weight measured in light clothing at physical examination.	Incidence, lung cancer, men	>30 vs 23-24.9 kg/m^2	1.29 (0.96-1.73) Ptrend:<0.01	Age, smoking	Distribution of person-years by exposure category, mid-points of exposure categories. RRs for men and women combined
		2 231/			Incidence, lung cancer, women	>30 vs 23-24.9 kg/m^2	0.91 (0.63-1.33) Ptrend:0.07		

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Missing data derived for analyses
Kabat, 2008b LUN20341 USA	WHI-DM and OS, Prospective Cohort, Age: 50-79 years, W, postmenopausal women	1353/ 159 659 8 years	Follow-up by mail or phone. Self-reported lung cancers verified by local review of pathology reports	All study participants had their weight, height, and Waist and hip circumferences measured at baseline. In addition, observational study participants provided information on weight and height at ages 18, 35, and 50 years, maximum and minimum weight, and weight loss during different periods of life.	Incidence, lung cancer	≥32.2 vs <23.1 kg/m^2	0.79 (0.65-0.96) Ptrend<0.01	Age, ethnicity, fruit intake, physical activity, smoking status, study, total caloric intake, vegetable intake, alcohol intake, education, pack yrs of smoking, total fat intake, use of HRT	Distribution of person-years by exposure category, mid-points of exposure categories
		736			Incidence, lung cancer, former smokers	≥32.2 vs <23.1 kg/m^2	0.61 (0.40-0.94) Ptrend:0.02		
		404			Incidence, lung cancer, current smokers	≥32.2 vs <23.1 kg/m^2	0.40 (0.22-0.72) Ptrend<0.01		
		248			Incidence, lung cancer, former smokers, 15-24 cigarettes/day	≥32.2 vs <23.1 kg/m^2	0.52 (0.25-1.07) Ptrend:0.18		
		197			Incidence, lung cancer, never smokers	≥32.2 vs <23.1 kg/m^2	0.91 (0.41-2.05) Ptrend:0.47	Age, ethnicity, fruit intake, height, physical activity, study, total caloric intake, vegetable intake, waist circumference, alcohol intake, education, total fat intake, use of HRT	
		178			Incidence, lung	≥32.2 vs <23.1	0.51 (0.20-1.32)	Age, ethnicity,	

Author, Year, WCRF Code, Country	Study 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, current smokers, 15-24 cigarettes/day	kg/m^2	Ptrend:0.10	fruit intake, height, physical activity, study, total caloric intake, vegetable intake, waist circumference, alcohol intake, education, total fat intake, use of HRT, years of smoking	
		162			Incidence, lung cancer, former smokers, >35 cigarettes/day	≥32.2 vs <23.1 kg/m^2	0.30 (0.13-0.71) Ptrend<0.01		
		138			Incidence, lung cancer, former smokers, 5-14 cigarettes/day	≥32.2 vs <23.1 kg/m^2	1.31 (0.47-3.65) Ptrend:0.79		
		113			Incidence, lung cancer, former smokers, 25-34 cigarettes/day	≥32.2 vs <23.1 kg/m^2	0.76 (0.26-2.22) Ptrend:0.99		
		85			Incidence, lung cancer, current smokers, 5-14 cigarettes/day	≥32.2 vs <23.1 kg/m^2	0.68 (0.28-1.62) Ptrend:0.25		
		71			Incidence, lung cancer, current smokers, 25-34 cigarettes/day	≥32.2 vs <23.1 kg/m^2	0.39 (0.09-1.80) Ptrend:0.45		
		50			Incidence, lung cancer, current smokers, >35	≥32.2 vs <23.1 kg/m^2	0.09 (0.02-0.47) Ptrend<.0.01		

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Missing data derived for analyses
					cigarettes/day				
Slatore, 2008 LUN20344 USA	VITAL, Prospective Cohort, Age: 50-76 years, M/W	494/ 77 126 4 years	SEER registry/hospital records/ pathology	Height and weight measured BMI calculated	Incidence, lung cancer	≥30 vs 18.5-24.9 kg/m^2	0.66 (0.51-0.85)	Age, sex, pack years squared, pack-years, years of smoking	Distribution of person-years by exposure category, mid-points of exposure categories
Fujino, 2007 LUN20278 Japan	JACC, Prospective Cohort, M/W	849/ 265 118 8 years	Population death registries	Obtained from survey, no further details were provided.	Mortality, lung cancer, men	>30 vs 18.5-24 kg/m^2	0.38 (0.12-1.18)	Age, study area	Mid-points of exposure categories RRs for men and women combined
		248			Mortality, lung cancer, women	>30 vs 18.5-24 kg/m^2	0.38 (0.09-1.56)		
Kabat, 2007 LUN20321 Canada	CNBSS, Prospective Cohort, Age: 40-59 years, W	520/ 89 788 16 years	Record linkage to Canadian centre database and to national mortality database	Height and weight were measured at the initial physical examination. .	Incidence, lung cancer, women current smokers	≥27.9 vs ≤21.6 kg/m^2	0.63 (0.48-0.83) Ptrend<0.01	Age, education level, menopausal status, pack yrs of cigarettes	Mid-points of exposure categories
		123			Incidence, lung cancer, women former smokers	≥27.9 vs ≤21.6 kg/m^2	0.69 (0.39-1.23) Ptrend:0.02	Age, education level, menopausal status, smoking, years since quitting, pack	

Author, Year, WCRF Code, Country	Study 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
								yrs of smoking	
		98			Incidence, lung cancer, women never smokers	≥27.9 vs ≤21.6 kg/m^2	2.19 (1.00-4.80) Ptrend<0.01	Age, education level, menopausal status	
Kondo, 2007 LUN20327 Japan	JACC, Prospective Cohort, Age: 40-79 years, M	243/ 29 350 11 years	Population death registries	We obtained self-reported weight and height at baseline, and weight around age 20 from the questionnaire.	Mortality, lung cancer, current smokers	Per 1 kg/m^2	1.01 (1.00-1.02)	Age, family history of cancer	Used only in stratified analysis by smoking (Fujino, 2007 LUN20278 for total). Rescaled RR for the increment unit used
		110			Mortality, lung cancer, 40-59 pack-years of smoking	Per 1 kg/m^2	1.01 (0.94-1.09)		
		93			Mortality, lung cancer, <40 pack-years of smoking	Per 1 kg/m^2	0.94 (0.87-1.02)		
		83			Mortality, lung cancer, former smokers	Per 1 kg/m^2	1.01 (0.93-1.09)		
		40			Mortality, lung cancer, ≥60 pack-years of smoking	Per 1 kg/m^2	0.94 (0.98-1.00)		
		22			Mortality, lung cancer, never	Per 1 kg/m^2	1.15 (1.01-1.32)		

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Missing data derived for analyses
					smokers				
Reeves, 2007 LUN20299 UK	MWS, Prospective Cohort, Age: 50-64 years, W	3559/ 1 222 630 5 years	National health records	Self-reported	Mortality, lung cancer	≥30 vs 22.5-24.9 kg/m^2	0.80 (0.74-0.88)	Age, geographic region, physical activity, reproductive history, smoking status, socio-economic status, alcohol intake	Distribution of person-years by exposure category, mid-points of exposure categories. RRs for men and women combined
						Per 10 units	0.72 (0.66-0.79)		
		3171			Incidence, lung cancer	≥30 vs 22.5-24.9 kg/m^2	0.84 (0.77-0.92)		
						Per 10 units	0.74 (0.67-0.82)		
		2257			Incidence, lung cancer, excluding first 2 years of follow-up	Per 10 units	0.77 (0.69-0.86)		
		1351			Incidence, lung cancer, postmenopausal women	Per 10 units	0.74 (0.64-0.86)		
		269			Incidence, lung cancer, never smokers	Per 10 units	0.82 (0.59-1.13)		
		64			Incidence, lung cancer, premenopausal women	Per 10 units	0.86 (0.45-1.65)		
Tsai, 2006	Shell Study,	116/	National Death	Height and	Mortality, lung	Obese vs normal	0.51 (0.26-1.03)	Age, sex,	Distribution of

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Missing data derived for analyses
LUN22336 USA	Prospective Cohort, Age: 30-69 years, M/W	7139 20 years	Index	weight measured	cancer	weight		biomarkers, smoking habits	person-years by exposure category, mid-points of exposure categories
Eichholzer, 2005 LUN17412 Switzerland	Basel Study, Prospective Cohort, Age: 20-79 years, M	87/ 2974 17 years	Death certificates	Height and weight measured in 1971/73	Mortality, lung cancer	Per 1 kg/m^2	1.00 (0.93-1.07)	Age, smoking habits	Rescaled RR for the increment unit used
Kuriyama, 2005 LUN20364 Japan	MCS I, Prospective Cohort, Age: 40- years, M/W	145/ 27 539 9 years	Cancer registry	Self-reported weight and height	Incidence, lung cancer, men	≥30 vs 18.5-24.9 kg/m^2	0.80 (0.20-3.26) Ptrend:0.08	Age, alcohol consumption, bean-paste soup intake, fruit consumption, health insurance, smoking status, fish consumption, green/yellow veg consumption, meat consumption	Distribution of person-years by exposure category, mid-points of exposure categories
		48			Incidence, lung cancer, women	≥30 vs 18.5-24.9 kg/m^2	1.72 (0.60-4.91) Ptrend:0.61	Age at menarche, menopausal	

Author, Year, WCRF Code, Country	Study 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
								status, parity, age of first live birth	
Rapp, 2005 LUN20363 Austria	VHM&PP, Prospective Cohort, Age: 18-94 years, M/W	464/ 145 931 10 years	Cancer registry and death certificates	Collected by medical staff at physical examination	Incidence, lung cancer, men	≥35 vs 18.5-24.9 kg/m^2	0.88 (0.41-1.86) Ptrend:0.15	Age, occupation, smoking status	Mid-points of exposure categories RRs for men and women combined
		126/			Incidence, lung cancer, women	≥30 vs 18.5-24.9 kg/m^2	0.87 (0.50-1.50) Ptrend:0.67		
Calle, 2003 LUN13341 USA	CPS II, Prospective Cohort, Age: 30- years, M/W	9925/ 900 053 16 years	Death certificate and national death index	Height and weight measured BMI calculated	Mortality, lung cancer, men	35-39.9 vs 18.5-24.9 kg/m^2	0.67 (0.54-0.84)	Age, alcohol consumption, ethnicity/race, marital status, other nutrients, foods or supplements, physical activity, smoking habits, vegetable intake	Distribution of person-years by exposure category, mid-points of exposure categories RRs for men and women combined
		5349			Mortality, lung cancer, women	≥40vs 18.5-24.9 kg/m^2	0.81(0.52-1.28)		
Olson, 2002 LUN00502 USA	IWHS, Prospective Cohort, Age: 55-69 years, W, Postmenopausal	532/ 38 006 12 years	Iowa Health Registry (part of SEER registry)	Using a paper tape measure mailed to subjects w/ the questionnaire. height, weight, BMI calculated	Incidence, lung cancer	≥30.70 vs ≤22.89 kg/m^2	0.43 (0.27-0.69)	Age, alcohol consumption, anthropometry, BMI, educational level, physical activity,	
						>22.90 vs ≤18.60 kg/m^2	1.08 (0.80-1.44)		
		325			Incidence, lung cancer, current	≥30.70 vs ≤22.89 kg/m^2	0.47 (0.27-0.81)		

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Missing data derived for analyses
					smokers			smoking habits	
		210			Incidence, adenocarcinoma	≥30.70 vs ≤22.89 kg/m^2	0.62 (0.30-1.32)		
		165			Incidence, adenocarcinoma	>22.90 vs ≤18.60 kg/m^2	1.19 (0.74-1.90)		
		129			Incidence, lung cancer, former smokers	≥30.70 vs ≤22.89 kg/m^2	0.32 (0.17-0.61)		
		109			Incidence, small cell carcinoma	≥30.70 vs ≤22.89 kg/m2 kg	0.60 (0.22-1.61)		
						>22.90 vs ≤18.60 kg/m2	1.02 (0.51-2.04)		
		106			Incidence, squamous cell carcinoma	≥30.70 vs ≤22.89 kg/m2 kg	0.22 (0.08-0.64)		
						>22.90 vs ≤18.60 kg/m^2	1.17 (0.67-2.05)		
		76			Incidence, lung cancer, non-smokers	≥30.70 vs ≤22.89 kg/m^2	0.44 (0.21-0.95)		

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
Lee, 2002 LUN00654 South Korea	KMICS, Prospective Cohort, Age: 35-64 years, M	883/ 452 645 5 years	Death certificates	Height and weight measured BMI calculated	Mortality, lung cancer	>24.6 vs 22.2 kg/m^2	0.90 (0.80-1.10) Ptrend:0.19	Age	Distribution of person-years by exposure category, mid-points of exposure categories
Tulinius, 1997 LUN07499 Iceland	Reykjavik Study, Prospective Cohort, M/W	273/ 22 946 16 years	Cancer registry	Height and weight measured BMI calculated	Incidence, lung cancer, men	Per 1 kg/m^2	0.93 (0.90-0.97)	Age	Rescaled RR for the increment unit used
		199			Incidence, lung cancer, women	Per 1 kg/m^2	0.93 (0.89-0.96)		
Knekt, 1996 LUN01885 Finland	HES Finland1978-1980, Prospective Cohort, Age: 30-95 years, M/W	70/ 7018 14 years	Cancer registry	Height and weight measured BMI calculated	Incidence, lung cancer, men	>27 vs <22.5 kg/m^2	0.49 (0.25-0.96)	Age	Distribution of person-years by exposure category, mid-points of exposure categories
Kark, 1995 LUN02145 Israel	ICSS, Prospective Cohort, Age: 40-69 years,	125/ 9975 23 years	Death certificates	Physical exam in 1963, measured height and weight, repeated in 1965	Mortality, lung cancer, current smokers	<22.92 vs >28.32 kg/m^2	3.69 (1.87-7.26)	Age, other, smoking habits	Distribution of person-years by exposure category, mid-points of
		85			Mortality, lung cancer,	<22.92 vs >28.32 kg/m^2	1.36(062-2.92)		

Author, Year, WCRF Code, Country	Study 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	28		and 1968; weight measured wearing light clothing with beam balance; height measured without shoes to nearest centimetre	Non-smokers	Lower 20% vs upper 60% kg/m^2	1.70 (0.70-4.30)		exposure categories
Chyou, 1994 LUN02487 USA	HHP, Prospective Cohort, Age: 45-79 years, M	236/ 7945 23 years	Hospital records, death certificates, Hawaii tumour registry	BMI calculated from height and weight	Incidence, lung cancer	≥26.0 vs <22.0 kg/m^2	0.69 (0.46-1.02)	Age, smoking habits	Distribution of person-years by exposure category, mid-points of exposure categories
Knekt, 1991c LUN03014 Finland	HES Finland1966-1972, Prospective Cohort, Age: 20-75 years, M	504/ 25 994 19 years	Cancer registry	Height and weight measured BMI calculated	Incidence, lung cancer	<22.5 vs >27 kg/m^2	1.80 (1.4-2.4)	Age, smoking habits	Distribution of person-years by exposure category, mid-points of exposure categories,
Wannamethee, 1989	BRHS, Prospective	81/ 7735	Cancer registry and National	BMI calculated from height,	Mortality, lung cancer	≥32 vs <20 kg/m^2	0.13 (0.02-1.05)	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
LUN03358 UK	Cohort, Age: 40-59 years, M	9 years	Death Index	weight					

Table 241 BMI and lung cancer risk. Main characteristics of studies excluded 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	Reasons for exclusion
Van Kruijsdijk RC, 2013 LUN20372 Netherlands	SMART, Prospective Cohort, Age: 18-80 years, M/W, High Risk population	118/ 4583 6 years	Cancer registry	Height and weight measured	Incidence, larynx, trachea, bronchus, lung	Per 4 kg/m^2	0.85 (0.68-1.07)	Age, sex, alcohol consumption, smoking status, pack years of smoking	Outcome was Incidence, larynx, trachea, bronchus, lung combined
Leitzmann, 2011 LUN26849 USA	NIH- AARP Diet and Health Study, Prospective Cohort, Age: 50-71 years, M/W	2925/ 225 712 1 961 011 person-years	Linkage to the social security administration death master file and the national death index	Participants were requested to measure their waist with a tape measure one inch above the navel while standing and to report values to the nearest quarter inch. information on body weight and height was requested in the baseline questionnaire.	Mortality, lung cancer	>35 vs 18.5-24.9 kg/m^2	0.94 (0.75-1.17) Ptrend:0.16	Age, sex, race/ethnicity, smoking status, alcohol intake	Superseded by Lam, 2013 LUN26868

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Reasons for exclusion
Prentice, 2009 LUN20263 USA	WHI, Prospective Cohort, Age: 50-79 years, W, Postmenopausal	421/ 80 816	Self report verified by medical record and pathology report		Incidence, lung cancer	Per 20 kgm^2	1.44 (0.99-2.11)	Energy intake, hypertension, race, alcohol, smoking	Superseded by Kabat, 2008b LUN20341 USA
Song, 2008 LUN20309 Korea	KNHIC, Prospective Cohort, Age: 40-64 years, Postmenopausal	560/ 170 481 9 years	Cancer registry, death report and Korea national health insurance corporation	Weights and heights were measured using standardised stadiometers and scales during a health examination with the women in light clothing.	Incidence, trachea, bronchus, lung	>30 vs 21-22.9 kg/m^2	0.48 (0.24-0.94)	Age, height, smoking status, alcohol intake, pay level at study entry, physical exercise	Outcome was Incidence, larynx, trachea, bronchus, lung combined. Jee, 2008 LUN20283 was included.
						Per 1 kg/m^2	0.97 (0.94-0.99)		
		326/				>30 vs 21-22.9 kg/m^2	0.36 (0.13-0.99)		
						Per 1 kg/m^2	0.94 (0.91-0.98)		
Oh, 2005 LUN18406 South Korea	KNHIC, Prospective Cohort, Age: 20- years, M	2 264/ 781 283 10 years	Linkage with cancer registry, national health insurance and death report	Weight and height at baseline	Incidence, lung cancer	>30 vs 18.5-22.9 kg/m^2	0.77 (0.47-1.30)	Age, alcohol consumption, family history of cancer, physical activity, smoking habits, urban/rural status	Superseded by Jee, 2008 LUN20283
Goodman, 2003 LUN00294	Carotene and Retinol Efficacy	275/ 18 314	Primary outcome of the	Weight, height, BMI	Incidence, lung cancer				Only mean 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	Reasons for exclusion
USA	Trial (CARET), Nested Case Control, Age: 45-69 years, M/W	4 years	trial. Active follow-up with confirmation by clinical records and pathology reports						
Tamosiunas, 2003 LUN00287 Lithuania	Kaunas Rotterdam Intervention Study, Prospective Cohort, Age: 45-59 years, M	6446 18 years	Death registry	Height, weight; BMI calculated	Mortality, lung cancer		0.80 (0.67-0.95)	Unadjusted	Unadjusted results
Li, 2002 LUN00629 China	Prospective Cohort Study on Coronary Heart Disease and Stroke Causes and Morbidity, Prospective Cohort, Age: 40-91 years, M/W	16/ 6209 9 years	Home visit or telephone contact, hospital record, death certificate	BMI, weight, height, blood pressure, pulse were measured	Mortality , lung cancer	< 21.2 vs 23.6-26.1 kg/m^2	5.63 (0.65-48.53)	Age, sex, alcohol consumption, smoking habits	Article in Chinese

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Reasons for exclusion
Seidell, 1996 LUN02018 Netherlands	Netherlands 1974-80,The Consultation Bureau Project on CVD, Prospective Cohort, Age: 30-54 years, M/W	48 287 12 years	Municipal registry	Weight, height, BMI calculated	Mortality, lung cancer	Underweight men vs other weights	4.57 (1.98-10.58)	Age	Only used in HvL only 2 categories
Hoffmans, 1989 LUN03512 Netherlands	Dutch Male Birth Cohort, Nested Case Control, Age: 49.00years, M	222/ 78 612 32 years	Death certificate	Height, weight, BMI	Mortality, lung cancer	Leanest group vs other groups kg/m^2	2.30 (1.34-3.87)	Unadjusted	Unadjusted results on BMI at age 18
						Leanest group vs other groups kg/m^2	2.40 (1.39-4.05)		
Lee, 1984 LUN04204 USA	MEC, Nested Case Control, Age: 18- years, M/W	55/ 50 000 7 years	SEER registry	Height and weight	Incidence, lung cancer, men	Quartile 4 vs quartile 1 kg/m^2	0.76	Age, sex, ethnicity/race	No quantile range, no confidence intervals
		26/			Incidence, lung cancer, women	Quartile 4 vs quartile 1 kg/m^2	0.09		

Figure 240 RR estimates of lung cancer by levels of BMI

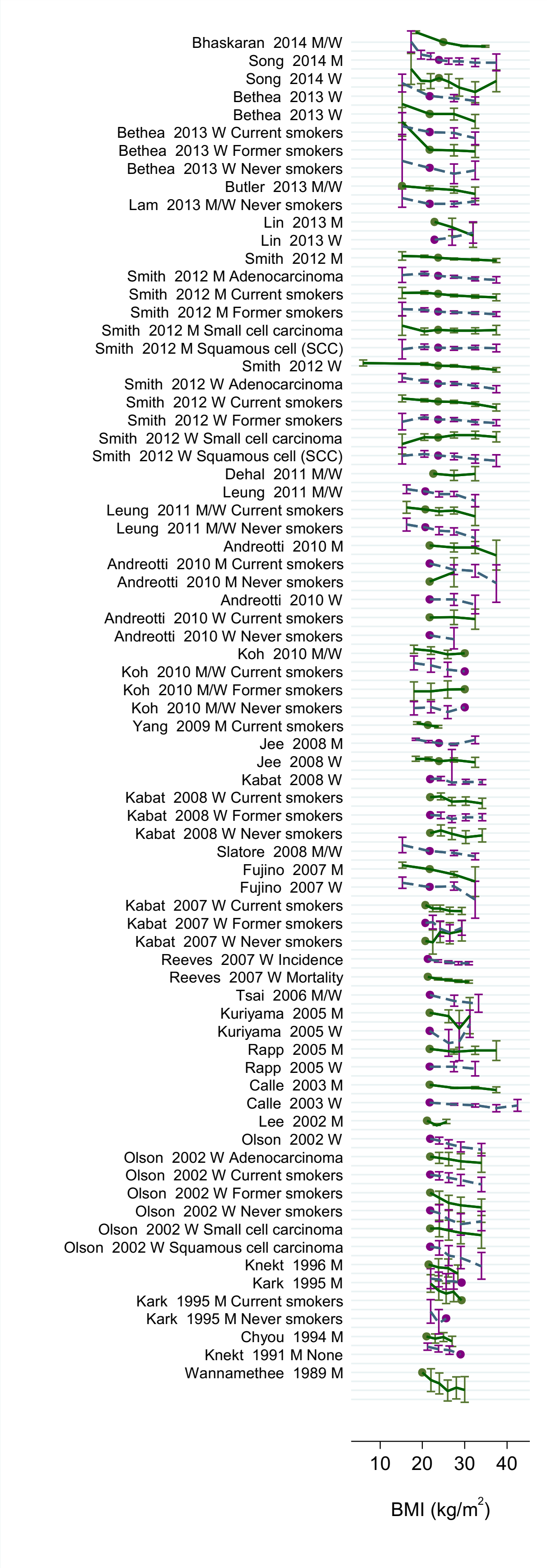


Figure 241 RR (95% CI) of lung cancer for the highest compared with the lowest level of BMI

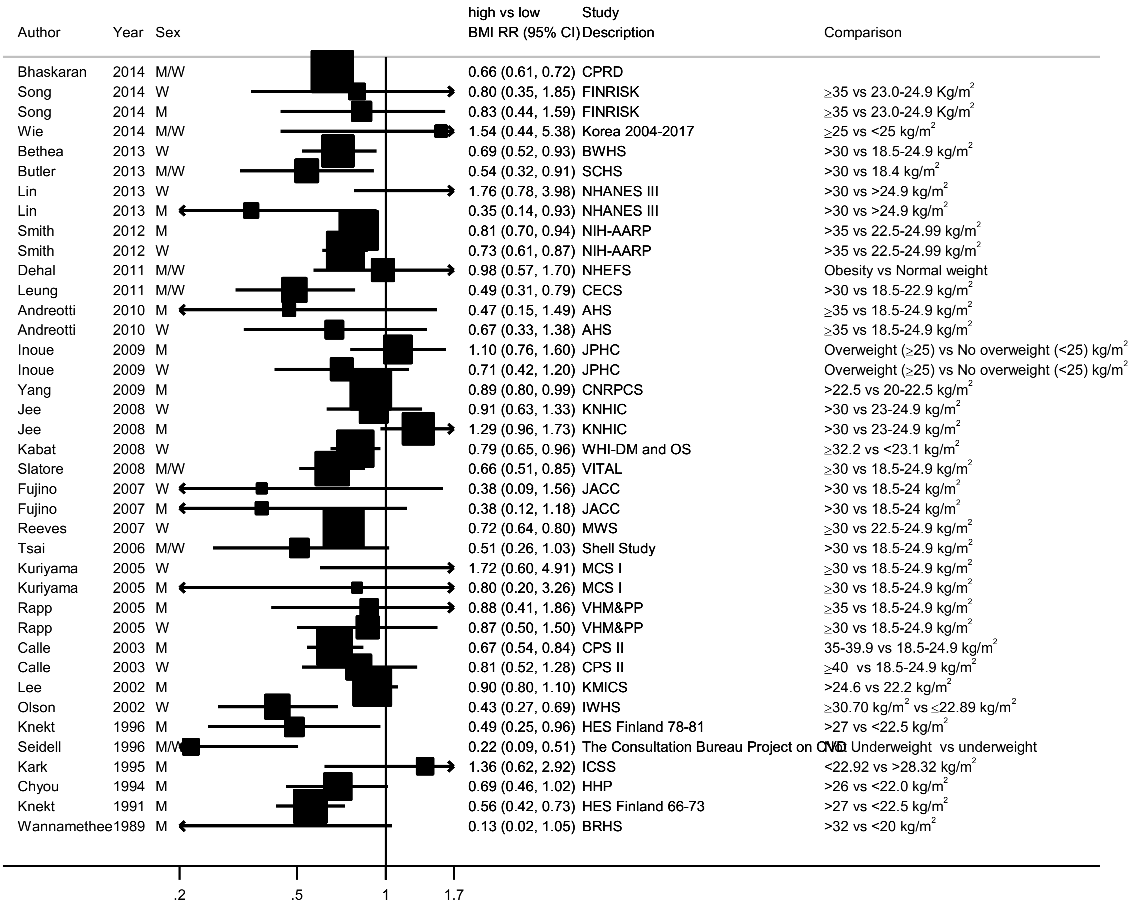


Figure 242 RR (95% CI) of lung cancer for 5 kg/m^2 increase of BMI

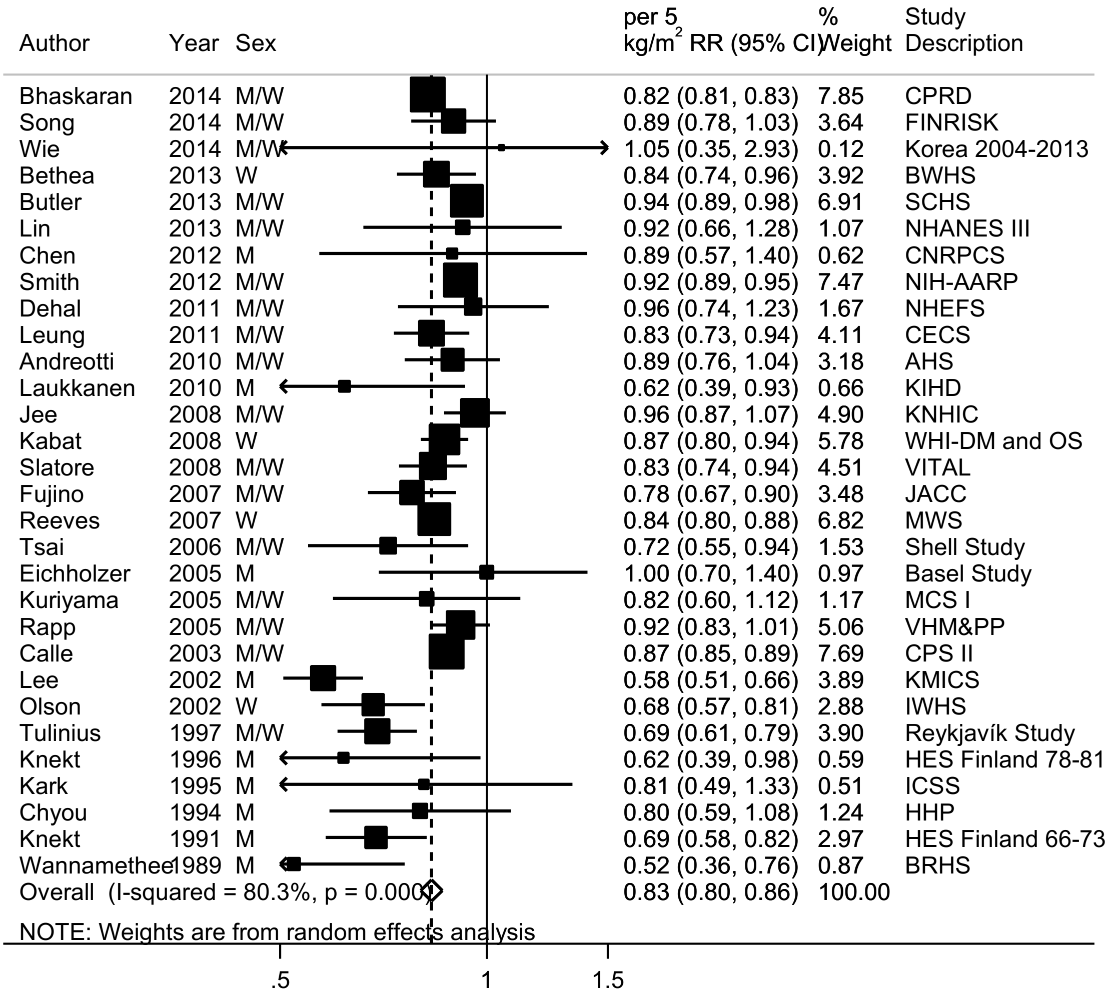
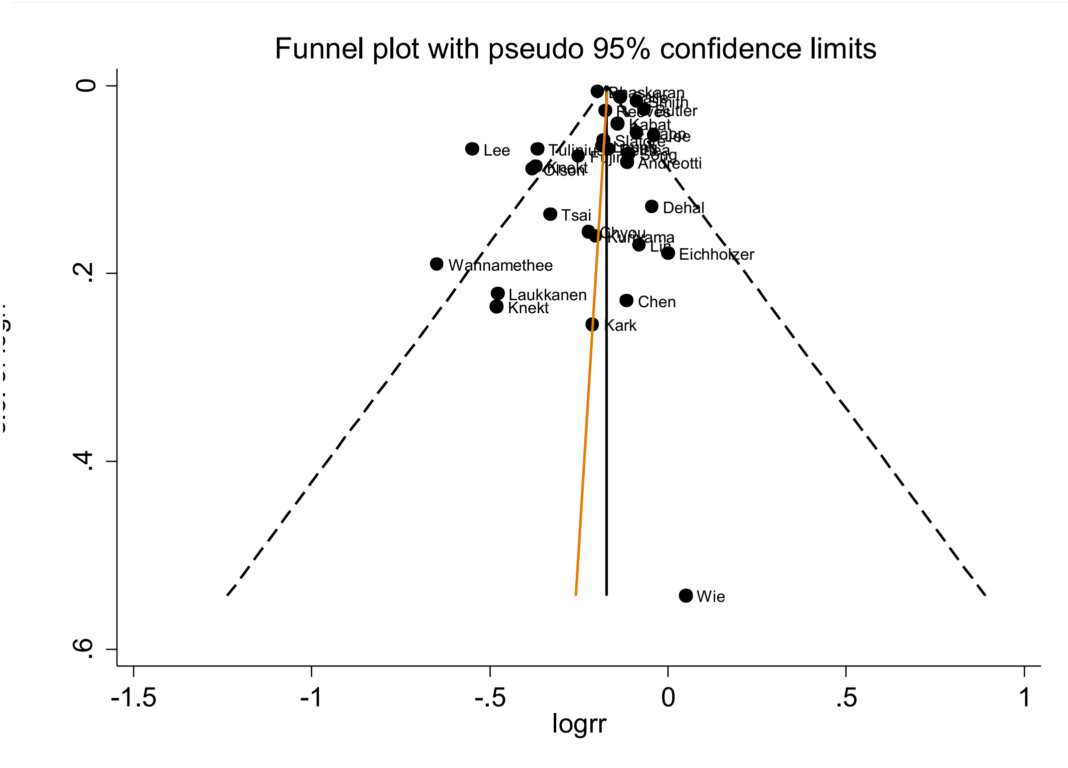


Figure 243 Funnel plot of studies included in the dose response meta-analysis of BMI and lung cancer



Egger’s test $p < 0.001$

Figure 244 RR (95% CI) of lung cancer for 5 kg/m² increase of BMI by sex

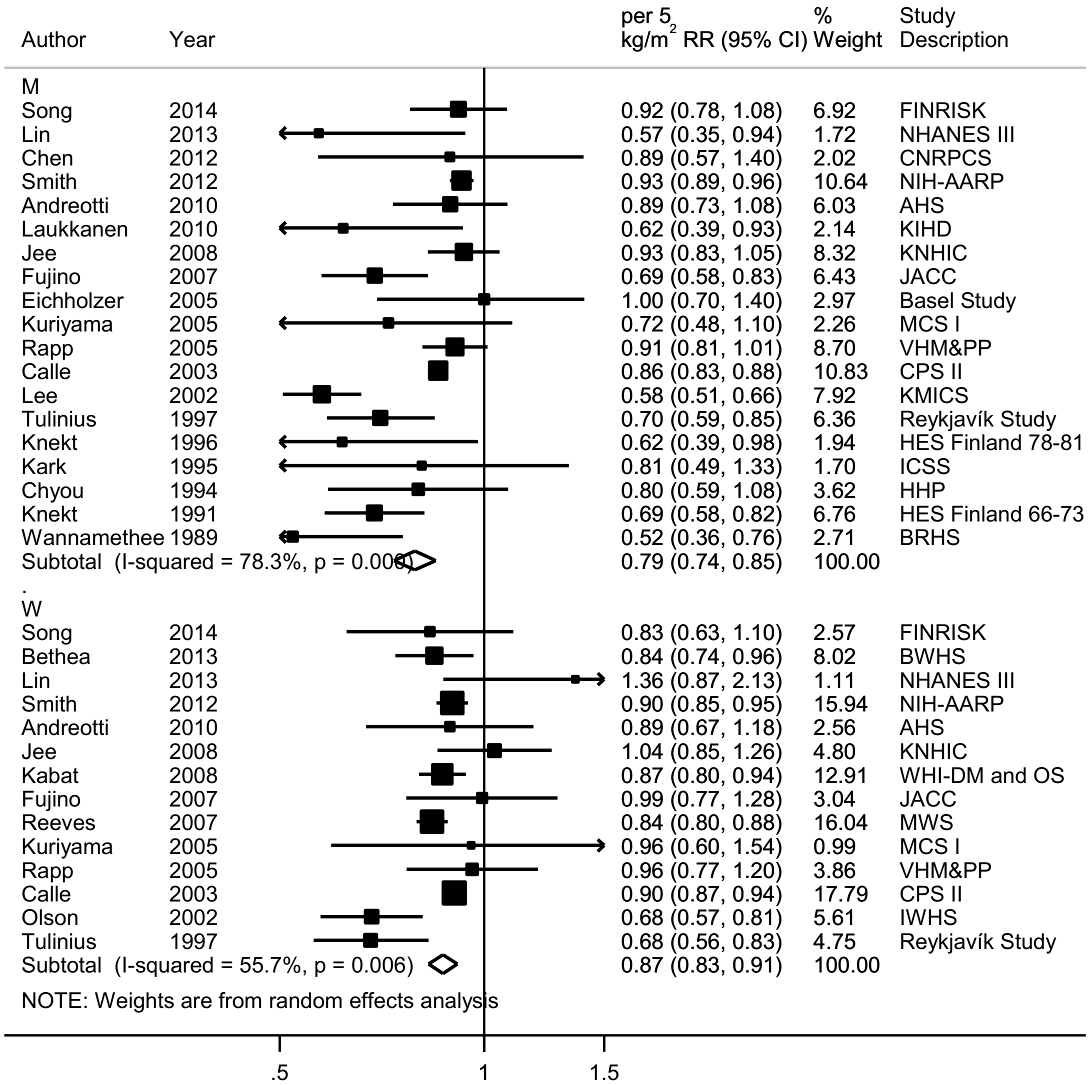


Figure 245 RR (95% CI) of lung cancer for 5 kg/m^2 increase of BMI by cancer outcome

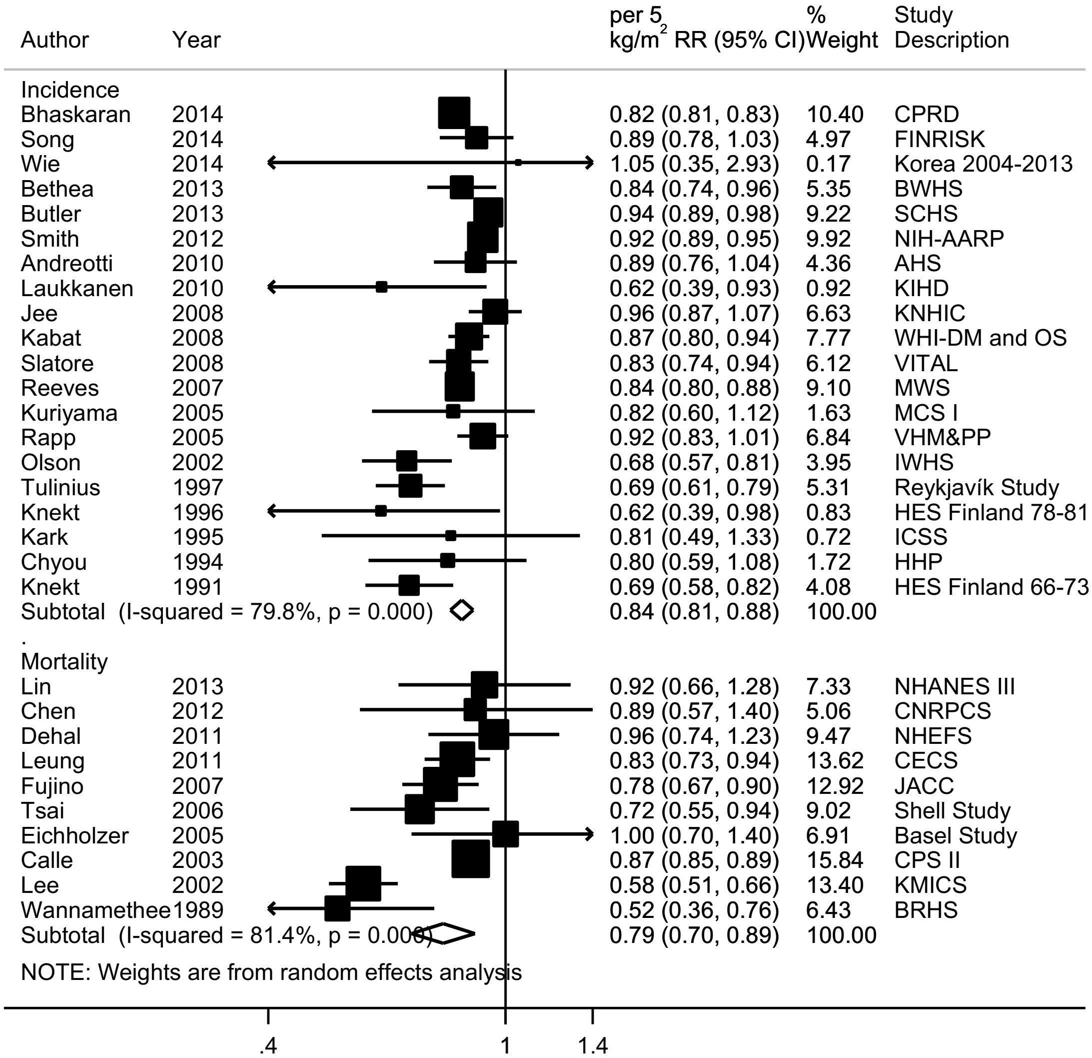


Figure 246 RR (95% CI) of lung cancer for 5 kg/m^2 increase of BMI by cancer site

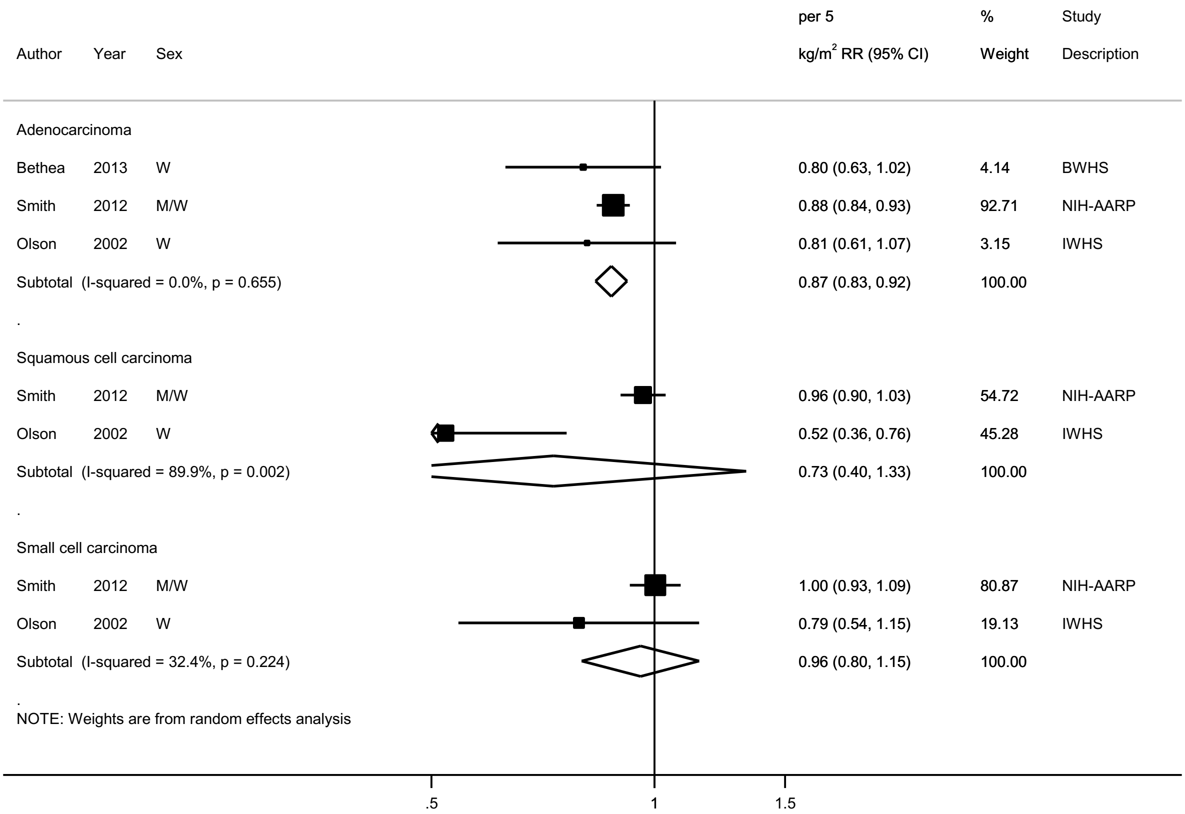


Figure 247 RR (95% CI) of lung cancer for 5 kg/m^2 increase of BMI by smoking status

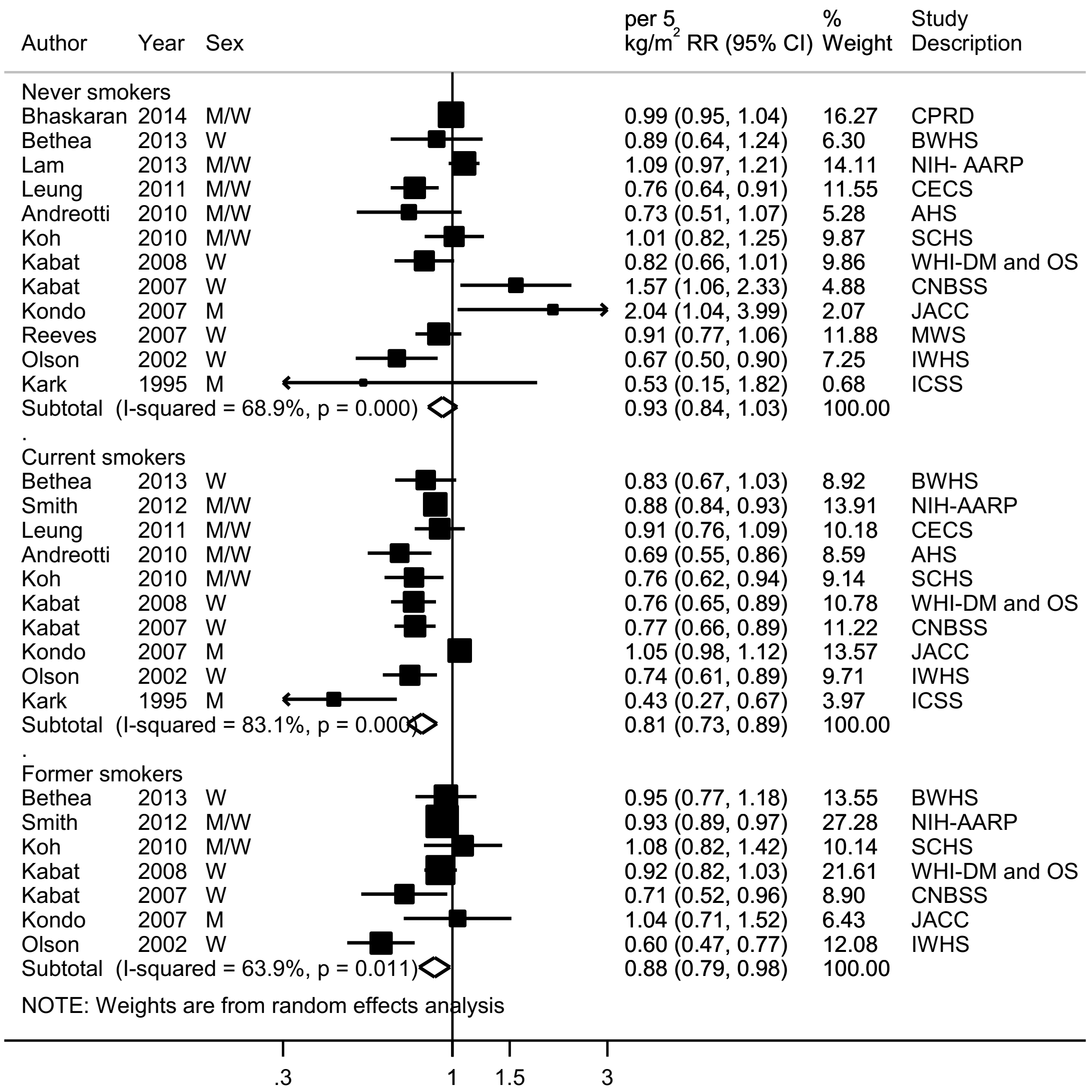


Figure 248 RR (95% CI) of lung cancer for 5 kg/m^2 increase of BMI by geographic location

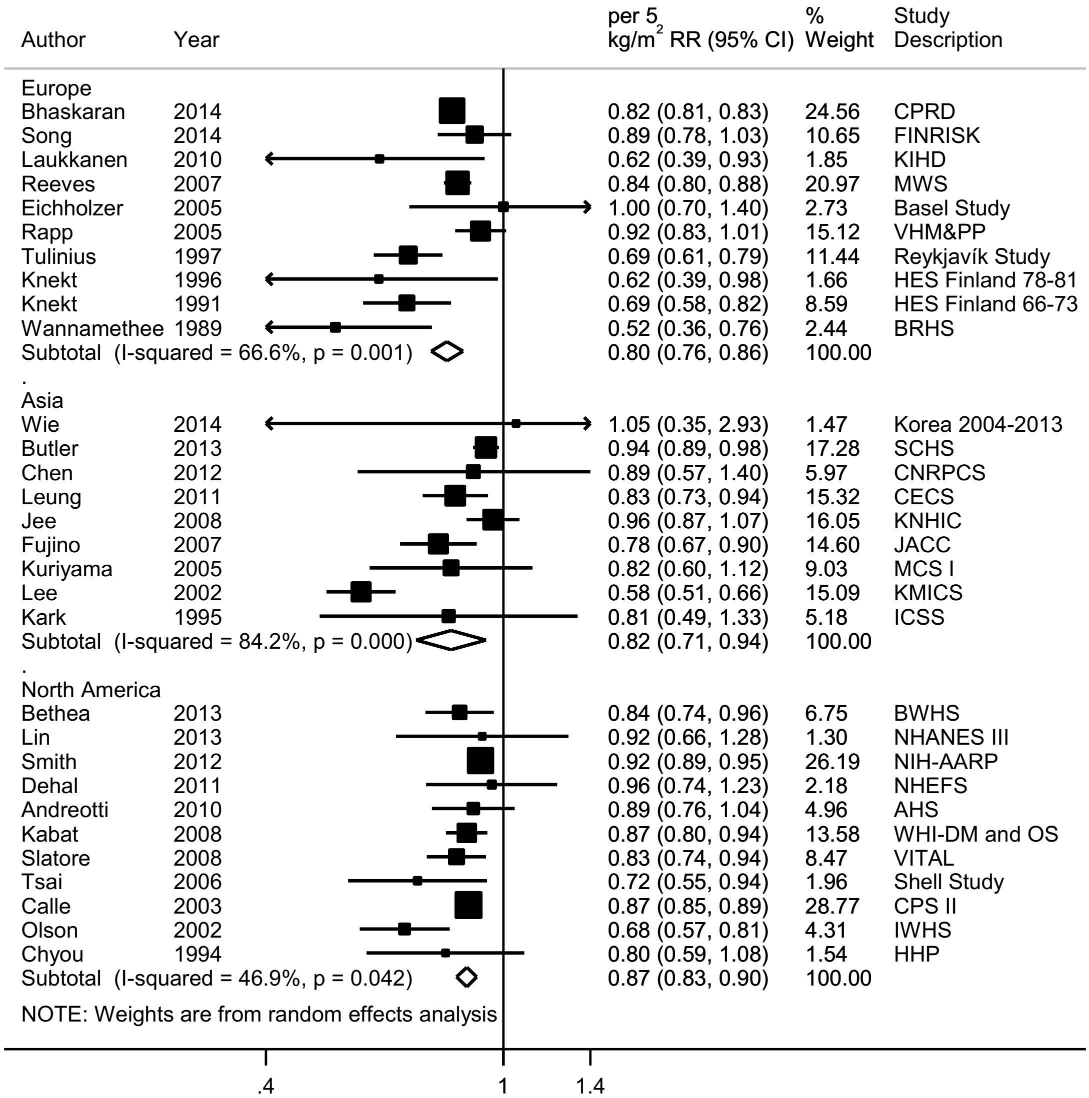


Figure 249 RR (95% CI) of lung cancer for 5 kg/m^2 increase of BMI by exposure assessment methods

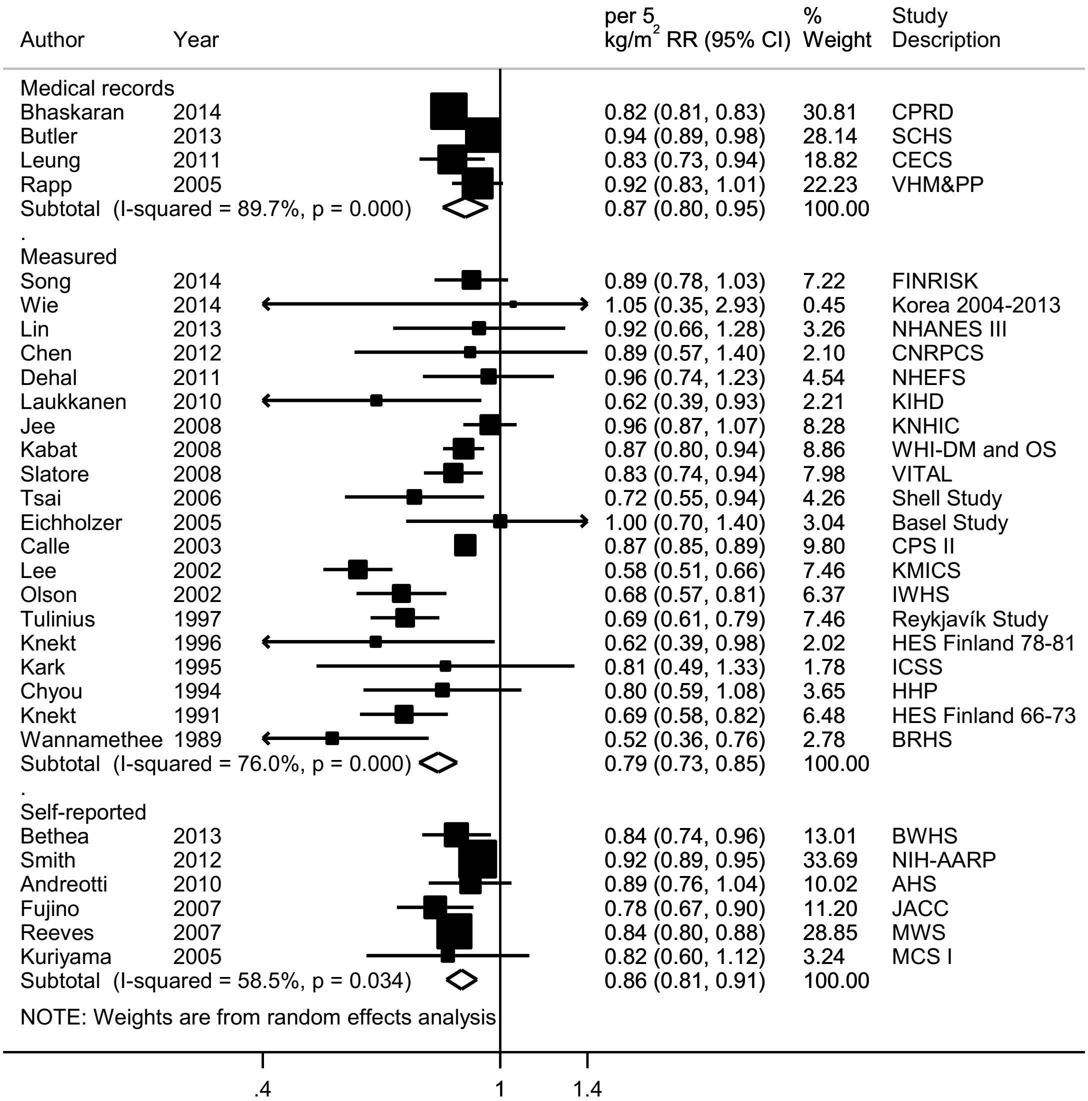
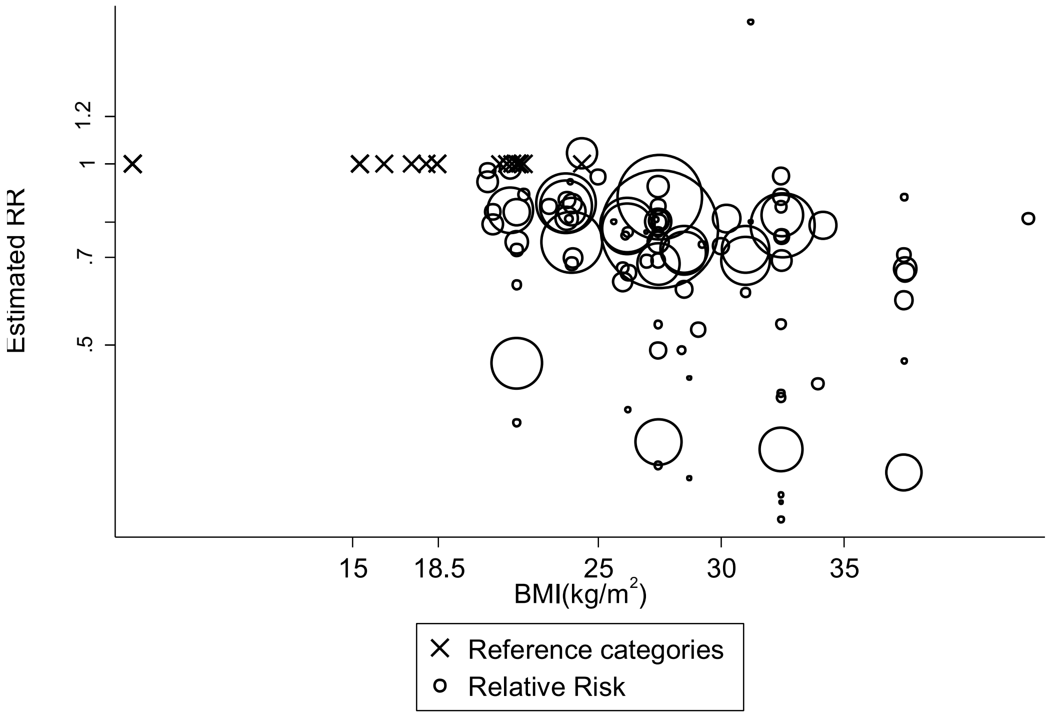
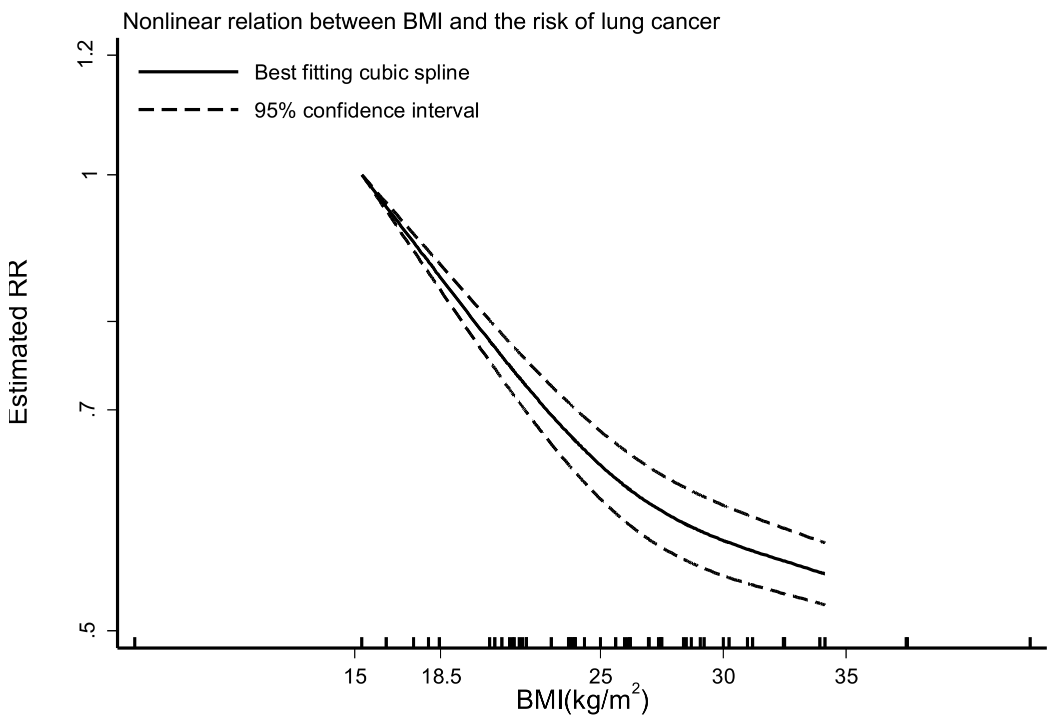


Figure 250 Relative risk of lung cancer and BMI estimated using non-linear models





$p < 0.01$

Table 242 Table with BMI values and corresponding RRs (95% CIs) for non-linear analysis of BMI and lung cancer

BMI (Kg/m^2)	RR (95%CI)
15	1
18.5	0.87(0.85-0.88)
22	0.75(0.72-0.77)
25	0.67(0.64-0.70)
30	0.60(0.57-0.63)

8.1.3 Weight

Cohort studies

Summary

Main results:
Five studies (3082 cases) out of 6 studies (6 publications) were included in the dose-response meta-analysis. A significant inverse association of weight was observed. No meta-analysis or pooling projects on weight and lung cancer were identified.

One study was excluded because it only reported interactions between weigh, height to weight and lung cancer risk.
High heterogeneity was observed. Only four studies were included in the dose-response analysis and no stratified analysis was performed. There was no evidence of publication or small study bias (p=0.98). Non-linear analysis was not performed because only 2 studies had sufficient data to use the cubic spline model.

Study quality:
Cancer outcome was confirmed using at least one of these records: cancer registries, pathology reports or National Death Index.
Two of the studies included in the dose response used measured weight, three studies used self-reported weight.
All studies included in the dose-response analysis were at least adjusted for age. After excluding studies not adjusting for smoking (Tulinius 1997, Fujino2007, Drinkard 1995) there was only one study left (Kabat, 2008) and no meta-analysis was performed.

Table 243 Weight and lung cancer risk. Number of studies in the CUP SLR

	Number
Studies identified	6 (6 publications)
Studies included in forest plot of highest compared with lowest exposure	4
Studies included in 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 244 Weight and lung cancer risk. Summary of the dose-response meta-analysis in the 2005 SLR and CUP.

	2005 SLR	**CUP**
Increment unit used	10 kg	5 kg
All studies		
Studies (n)	2	5
Cases (total number)	705	3082
RR (95%CI)	0.82 (0.64-1.06)	0.92(0.87-0.97)
Heterogeneity (I^2, p-value)	99.3%	73.7%, <0.01
P value Egger test		0.99

Table 245 Weight and lung cancer risk. Main characteristics of studies 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	Missing data derived for analyses
Kabat, 2008b LUN20341 USA	WHI-DM and OS, Prospective Cohort, Age: 50-79 years, W, postmenopausal women	736/ 159 659 8 years	Lung cancer was not the primary outcome of the trial. Follow-up by mail or phone. Self-reported lung cancers verified by local review of pathology reports	Weight measured	Incidence, lung cancer, former smokers	≥187.4 vs <132.5 pounds	0.79 (0.60-1.05) Ptrend:0.14	Age, ethnicity, fruit intake, height, physical activity, study, total caloric intake, vegetable intake, age at quitting smoking, alcohol intake, education, pack yrs of smoking, quitting smoking due to health problem (yes/no), total fat intake, use of HRT	Conversion from pound to kg using the conversion unit of 1 pound=0.45kg
		404			Incidence, lung cancer, current smokers	≥187.4 vs <132.5 pounds	0.60 (0.41-0.87) Ptrend:<0.01		
		197			Incidence, lung cancer, never smokers	≥187.4 vs <132.5 pounds	0.78 (0.47-1.30) Ptrend:0.31		
Fujino, 2007 LUN20278 Japan	JACC, Prospective Cohort, M/W	878/ 265 118 8 years	Population death registries	Obtained from survey	Mortality, lung cancer, men	>63 vs 54.9 kg	0.73 (0.61-0.88)	Age, study area	Mid-points of exposure categories RRs for men and women combined
		255/			Mortality, lung cancer, women	>55 vs 48.9 kg	0.98 (0.72-1.33)		

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Missing data derived for analyses
Tulinius, 1997 LUN07499 Iceland	Reykjavík Study, Prospective Cohort, M/W	273/ 22 946 16 years	Cancer registry	Weight measured	Incidence, lung cancer, men	Per 1 kg	0.98 (0.96-0.99)	Age	Rescaled RR for the increment unit used
		199			Incidence, lung cancer, women	Per 1 kg	0.96 (0.94-0.97)		
Key, 1996 LUN01947 UK	HFSS, Prospective Cohort, Age: 16-80 years, M/W	162/ 10 771 17 years	Death certificate	Self-reported questionnaire	Mortality, lung cancer	Tertile 3 vs Tertile 1	0.63 (0.33-1.23)	Age, sex, smoking habits	Mid-points of exposure categories
Drinkard, 1995 LUN02192 USA	IWHS, Prospective Cohort, Age: 55-69 years, W, Postmenopausal	233/ 41 837 6 years	Iowa Health Registry (part of SEER registry)	Self-reported questionnaire	Incidence, lung cancer	>77.74 vs 60.44 kg	0.58 (0.36-0.75)	Age	Mid-points of exposure categories

Table 246 Weight and lung cancer risk. Main characteristics of studies excluded 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	Reasons for exclusion
Kabat, 2012 LUN20268 Canada	CNBSS, Prospective Cohort, Age: 40-59 years	685/ 88 256 16 years	Record linkage to Canadian Centre Database and to National Mortality Database	Measured weight and height	Incidence, lung cancer, ever smokers	Quintile 5 vs quintile 1	0.50 (0.39-0.64) Ptrend:<0.01	Age, contraception, hormone use, menopausal status, education, pack yrs of smoking	No quantile range. Interaction between weight to height, weight and lung cancer risk
		104			Incidence, lung cancer, never smokers	Quintile 5 vs quintile 1	1.98 (1.03-3.80) Ptrend:<0.01		

Figure 251 RR estimates of lung cancer by levels of weight

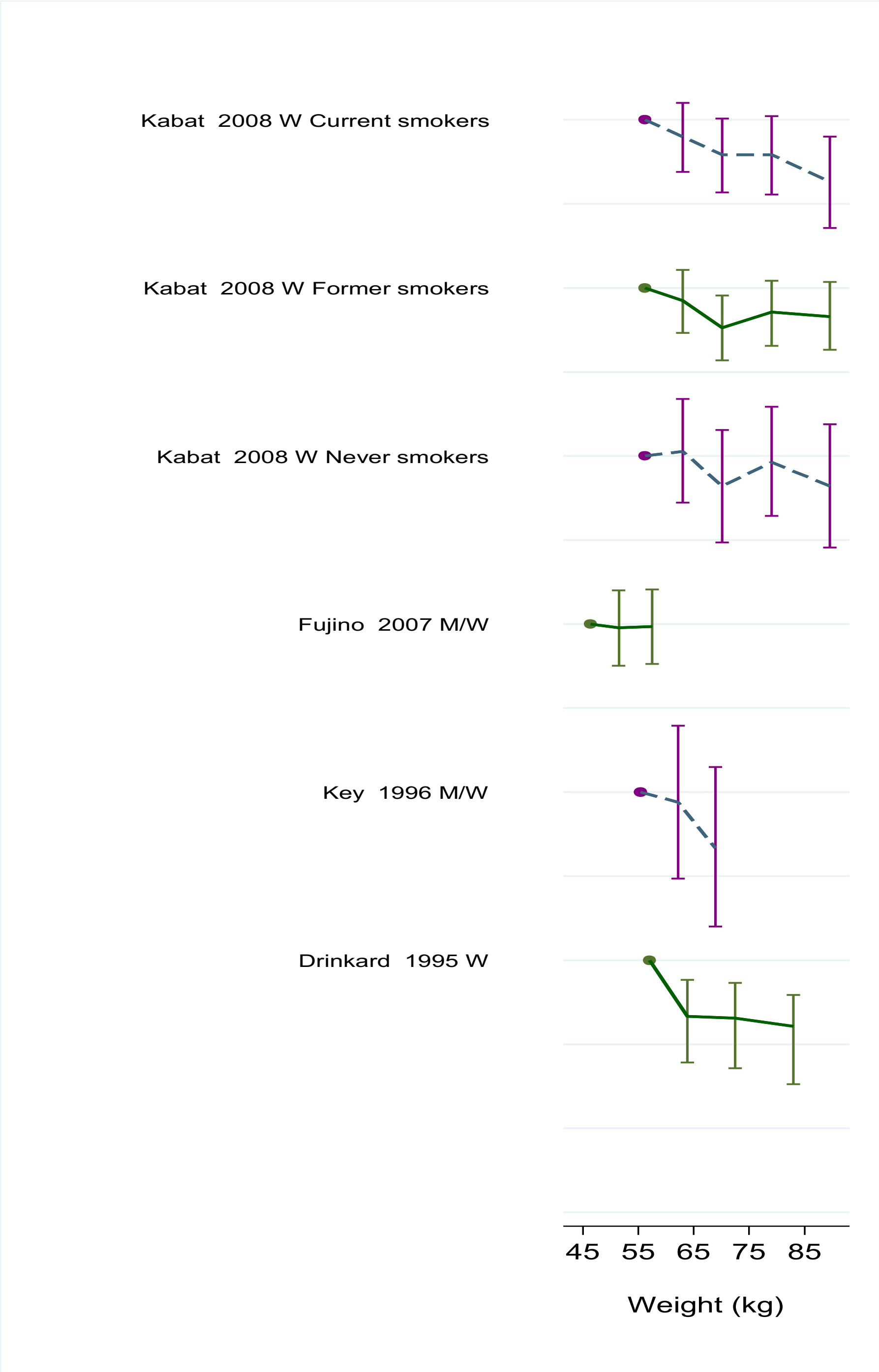


Figure 252 RR (95% CI) of lung cancer for the highest compared with the lowest level of weight

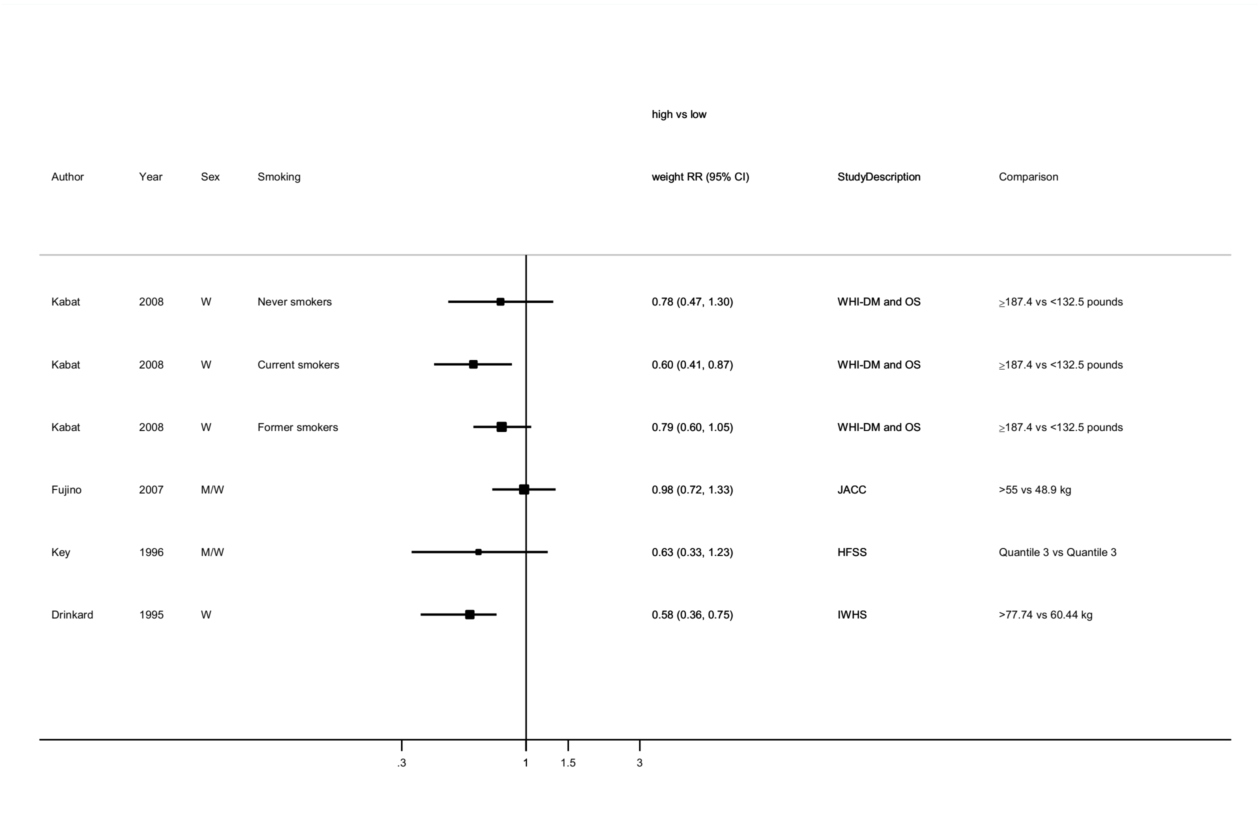


Figure 253 RR (95% CI) of lung cancer for 5 kg increase of weight

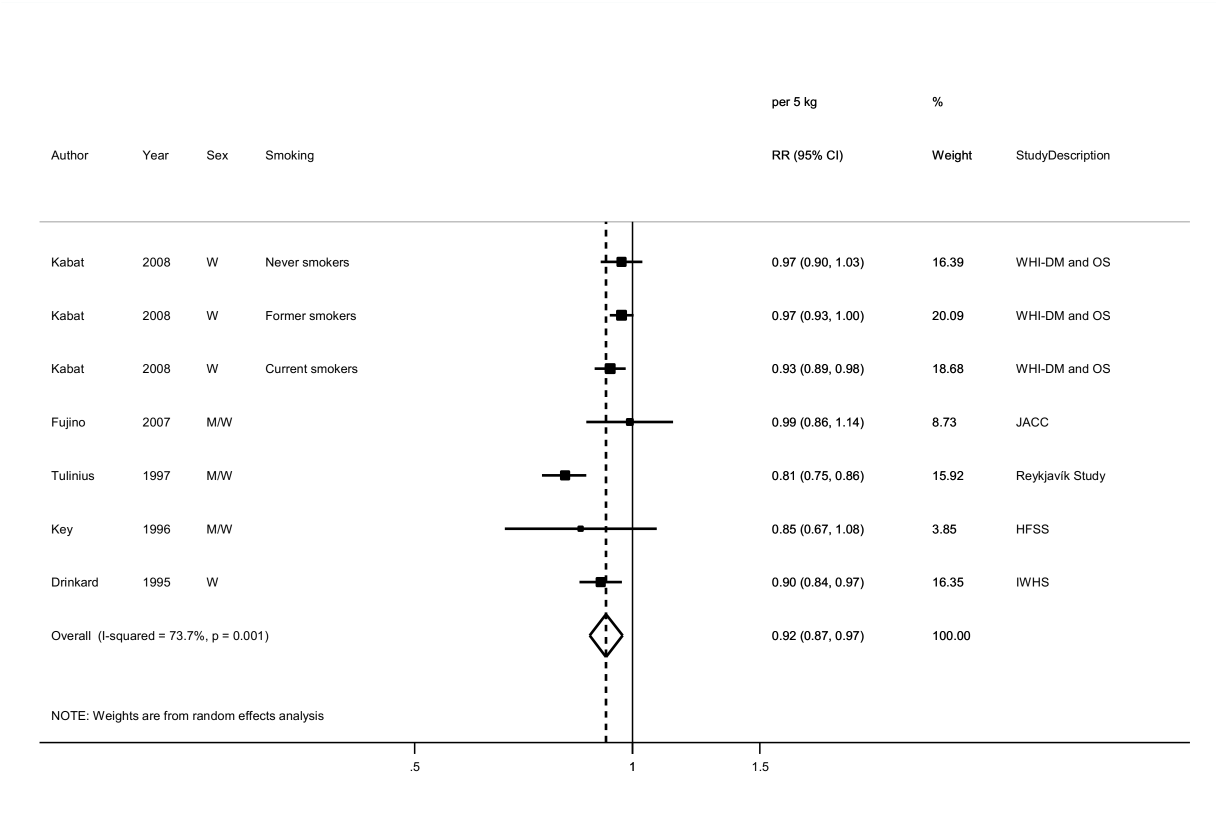
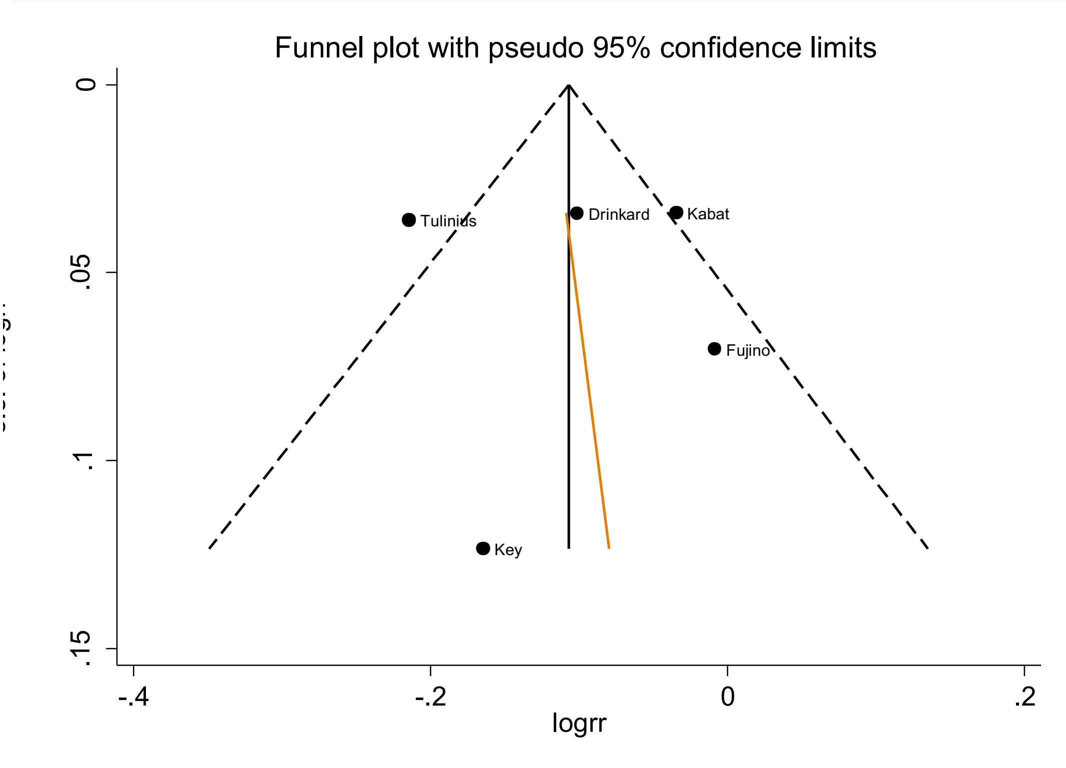


Figure 254 Funnel plot of studies included in the dose response meta-analysis of weight and lung cancer



Egger's test p=0.99

8.2.1 Waist circumference

Cohort studies

Summary

Main results:
There were a limited number of studies which could be included in the dose response meta-analysis. Only highest versus lowest analysis could be performed. There were 4 (2788 cases) studies included in highest versus lowest analysis. A significant association was observed between waist circumference and lung cancer.
There was evidence of moderate heterogeneity.

Sensitivity analyses:
In stratified analysis by smoking status, results were significant only among current and former smokers, not for never smokers.

Study quality:
Most studies used self-reported measures of waist circumference, except one study in which participant's waist circumferences were measured (Kabat, 2008).
All studies included in the high vs low analysis were in women, except the NIH- AARP study which was in men and women.
All studies were adjusted by main confounders, including age, BMI and smoking status.

The study of Lam, 2013 reported relative risk estimates of lung cancer among never smokers only.

Table 247 Waist circumference and lung 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	4
Studies included in dose-response meta-analysis	Not enough studies
Studies included in non-linear dose-response meta-analysis	Not enough studies

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

Table 248 Waist circumference and lung cancer risk. Summary of the dose-response meta-analysis in the 2005 SLR and CUP

	2005 SLR	CUP
All studies		
Increment unit used		Highest vs lowest
Studies (n)		4
Cases (total number)		2788
RR (95%CI)		1.40 (1.09-1.79)
Heterogeneity (I^2, p-value)		32%, 0.20

Stratified and sensitivity analysis (no analyses conducted in the 2005 SLR)			
Smoking status	**Never smokers**	**Current smokers**	**Former smokers**
Studies (n)	2	2	2
RR (95%CI)	1.47 (0.90-2.43)	1.70 (1.18-2. 45)	1.54 (1.07-2.19)
Heterogeneity (I^2, p-value)	24.3%, 0.25	0%, 0.67	0%, 0.85

Table 249 Waist circumference and lung cancer risk. Main characteristics of studies included in the 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
Bethea, 2013 LUN26857 USA	BWHS, 1995, Prospective Cohort, W, Black women	323/ 56 944	Cancer registry, medical records, histology	Self-reported weight and height	Incidence, lung cancer	≥ 37 vs < 28 inch	0.85 (0.54-1.35) Ptrend:0.23	Age, age at first birth, BMI, geographic area, parity, physical activity, alcohol, education, family history of lung cancer, pack years of smoking	
Lam, 2013 LUN26868 USA	NIH- AARP, Prospective Cohort, Age: 50-71 years, M/W, never smokers	532/ 158 415 10 years	Postal service, social security administration death master file, National Death Index	Through questionnaire	Incidence, lung cancer	Q4 vs Q1	1.75 (1.09-2.79) Ptrend:0.07	Age, BMI at baseline, alcohol consumption, ethnicity, hip circumference, total caloric intake, education, physical activity at work, vigorous physical activity	
Kabat, 2008 LUN20341 USA	WHI-DM and OS, Prospective	197/ 159 659 8 years	Self-reported lung cancers	All study participants had their weight,	Incidence, lung cancer, never smokers	≥ 97.6 vs < 74.6 cm	1.01 (0.45-2.28) Ptrend:0.97	Age, BMI, ethnicity, fruit intake, 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	Missing data derived for analyses
	Cohort, Age: 50-79 years, W, postmenopausal women	736/ 159 659 8 years	were verified by local review of pathology reports	height, and waist and hip circumferences measured at baseline	Incidence, lung cancer, former smokers		1.50 (0.98-2.31) Ptrend:0.004	physical activity, study, total caloric intake, vegetable intake, age at quitting smoking, alcohol intake, education, pack years of smoking, quitting smoking due to health problem (yes/no), total fat intake, use of HRT	
		404/ 159 659 8 years			Incidence, lung cancer, current smokers		1.56 (0.91-2.69) Ptrend:0.12		
Olson, 2002 LUN00502 USA	IWHS, Prospective Cohort, Age: 55-69 years, W, Post-menopausal	596/ 38 006 12 years	SEER registry	Questionnaire (paper tape measure mailed with the questionnaire)	Incidence, lung cancer	> 99.0 vs ≤ 75.56 cm	1.76 (1.14-2.73)	Age, BMI, pack-years of smoking (continuous), physical activity score, educational level, beer consumption, height, and BMI at age 18 years	
		76/ 38 006 12 years			Incidence, lung cancer, never smokers		1.43 (0.69-2.97) Ptrend:0.99		

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Missing data derived for analyses
		129/ 38 006 12 years			Incidence, lung cancer, former smokers		1.62 (0.85-3.09) Ptrend:0.25		
		325/ 38 006 12 years			Incidence, lung cancer, current smokers		1.83 (1.11-3.01) Ptrend:0.01		

Table 250 Waist circumference and lung cancer risk. Main characteristics of studies excluded from the 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
van Kruijsdijk, 2013 LUN20372 Netherlands	SMART, Prospective Cohort, Age: 18-80 years, M/W, Patients with	141/ 6172 6 years	Cancer registry	Height and weight measured	Incidence, larynx, trachea, bronchus, lung	Per 11.9 cm	0.94 (0.70-1.25)	Age, sex, alcohol consumption, smoking status, pack years of smoking	Outcome is larynx, trachea, bronchus and lung cancer

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Reasons for exclusion
	manifest vascular disease								
Leitzmann, 2011 LUN26849 USA	NIH- AARP Diet and Health Study, Prospective Cohort, Age: 50-71 years, M/W	2925/ 225 712 1 961 011 person-years	Linkage to the social security administration death master file and the National Death Index	Participants were requested to measure their waist with a tape measure one inch above the navel while standing and to report values to the nearest quarter inch. .	Mortality, lung cancer	≥ 96 (women); ≥ 118 men) vs < 80 (women); < 94 (men)	1.77 (1.41-2.23) Ptrend:< 0.01	Age, sex, BMI, race/ethnicity, smoking status, alcohol intake	Superseded by Lam, 2013 (LUN26868)

Figure 255 RR (95% CI) of lung cancer for the highest compared with the lowest level of waist circumference

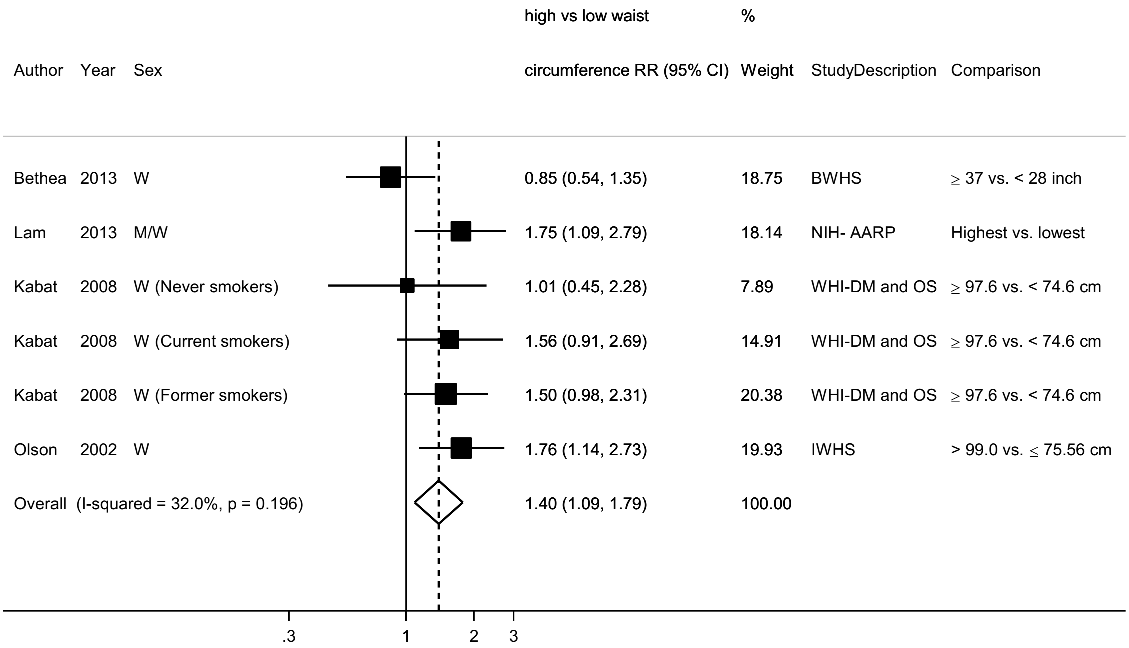
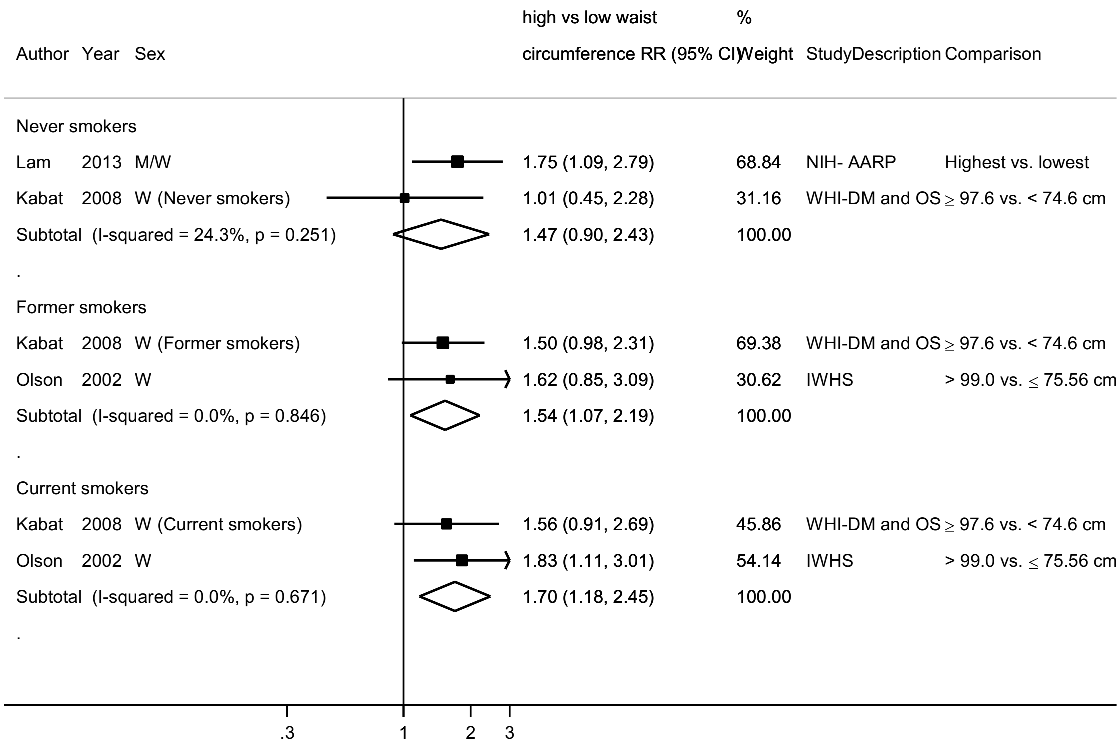


Figure 256 RR (95% CI) of lung cancer for the highest compared with the lowest level of waist circumference by smoking status



8.2.3 Waist to hip ratio

Cohort studies

Summary

Main results:
Only highest versus lowest analysis could be performed as there were a limited number of studies which could be included in the dose response meta-analysis. There were 4 (2388 cases) studies included in highest versus lowest analysis. No significant association was observed for waist to hip ratio and lung cancer.

No heterogeneity was observed.

There was not enough data to do stratified analysis by either histologic type or smoking status.

Study quality:
All studies used self-measured or measured waist and hip circumferences. All studies included in the high vs low analysis were adjusted at least for age and smoking status, except one study (Lam, 2013) that did not adjust for smoking.

Table 251 Waist to hip ratio and lung 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	4
Studies included in dose-response meta-analysis	Not enough studies
Studies included in non-linear dose-response meta-analysis	Not enough studies

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

Table 252 Waist to hip ratio and lung cancer risk. Summary of the dose-response meta-analysis in the 2005 SLR and CUP

	2005 SLR	CUP
All studies		
Increment unit used	No meta-analysis	Highest vs lowest
Studies (n)		4
Cases (total number)		2388
RR (95%CI)		1.11 (0.96-1.28)
Heterogeneity (I^2, p-value)		0%, 0.61

Table 253 Waist to hip ratio and lung cancer risk. Main characteristics of studies included in the dose-response meta-analysis

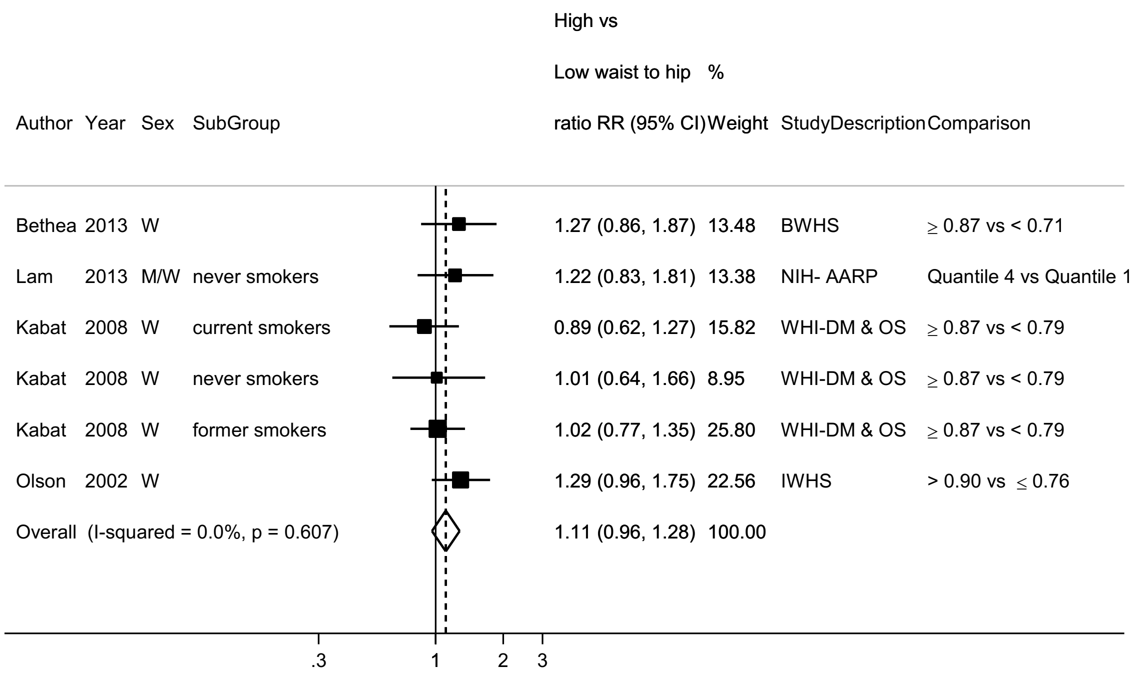
Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI)	Adjustment factors	Missing data derived for analyses
Bethea, 2013 LUN26857 USA	Black Women's Health Study, 1995, Prospective Cohort, W, Black women	281/ 56 944	Cancer registry, medical records, histology	Self-measured	Incidence	> 0.87 vs < 0.71 ratio	1.27 (0.86-1.87)	Age, age at first birth, BMI, geographic area, parity, physical activity, alcohol, education, family history of lung cancer, pack years of smoking	
Lam, 2013 LUN26868 USA	NIH- AARP Diet and Health Study, Prospective Cohort, Age: 50-71 years, M/W, Never smokers	241/ 158 415 10 years	Linkage with 10 state cancer registry databases that included the 8 original states and 3 additional states (Arizona, Nevada, and Texas)	Self-measured	Incidence	Quartile 4 vs quartile 1	1.22 (0.83-1.81)	Age, alcohol consumption, BMI at baseline, ethnicity, total caloric intake, education, physical activity at work, vigorous physical activity	
Kabat, 2008 LUN20341 USA	WHI-DM and OS, Prospective Cohort, Age: 50-79	736/ 159 659 8 years	Questionnaire, medical records or pathology reports reviewed by physicians	Weight, height, and waist and hip circumferences measured at	Incidence former smokers	≥0.87 vs < 0.75 ratio	1.02 (0.77-1.35)	Age, ethnicity, fruit intake, height, physical activity, study, total caloric	
		404			Current smokers		0.89 (0.62-1.27)		

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI)	Adjustment factors	Missing data derived for analyses
	years, W, Postmenopausal women			baseline.				intake, vegetable intake, age at quitting smoking, alcohol intake, education, pack years of smoking, quitting smoking due to health problem (yes/no), total fat intake, use of HRT	
		197			Never smokers		1.01 (0.64-1.66)		
Olson, 2002 LUN00502 USA	IWHS, Prospective Cohort, Age: 55-69 years, W Postmenopausal	529/ 38 006 12 years	State Health Registry of Iowa, part of the National Cancer Institute's SEER program	Using a paper tape measure mailed to subjects with the questionnaire.	Incidence	>0.90 vs ≤0.76	1.29 (0.96-1.75)	Age, pack-years of smoking, smoking status, physical activity score, educational level, and beer consumption.	

Table 254 Waist to hip ratio and lung cancer risk. Main characteristics of studies excluded 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) P trend	Adjustment factors	Reasons for exclusion
Linseisen, 2002 LUN00434 Germany	EPIC-Heidelberg, Nested Case Control, Age: 25-70 years, M/W	20/ 482 924 2 years	Trained physician and histology	Height and weight, BMI, and weight-hip ratio	Incidence			Age, sex, other, smoking habits	Only mean exposure

Figure 257 RR (95% CI) of lung cancer for the highest compared with the lowest level of waist to hip ratio



8.3.1 Height

Cohort studies

Summary

Main results:
12 studies (19 750 cases) out of 14 studies (15 publications) were included in the dose-response meta-analysis. A borderline significant association was observed.
High heterogeneity was observed. There was evidence of publication or small study bias (p= 0. 08).
In one excluded study, a relative risk of 0.94 (0.78-1.14) was reported per 1 SD increase in height for lung cancer risk.
The Emerging Risk Factors Collaboration (ERFC) study (Emerging Risk Factors Collaboration, 2012) which included 121 cohort studies and Asia Pacific Cohort Studies Collaboration (APCSC) study (Batty, 2010a), including 38 cohort studies, were meta-analysed with 6 studies (Kabat, 2013a; Walter, 2013; Green, 2011; Fujino, 2007; Olson, 2002; Knekt, 1991a), identified in the CUP SLRs and the the summary RR was 1.01 (95%CI= 1.00-1.02). In stratified analysis by sex, smoking status, outcome and geographic

location, the association remained borderline significant only in studies in men and the studies with incidence as outcome.

Sensitivity analyses:
The summary RRs ranged from 1.00 (95% CI=0.99-1.01) when Sung, 2009 was omitted to 1.02 (95% CI=1.00-1.03) when Olson, 2002 was omitted.
There was evidence of a non-linear dose-response of lung cancer and height ($p < 0.01$). The curve suggests an increased risk of lung cancer with the height higher than 170 cm.

Study quality:
Cancer outcome was confirmed using records in cancer and death registries in most studies. Most studies adjusted for main confounders including age and smoking. Nine studies adjusted for smoking status, duration and intensity, and two studies adjusted only for smoking status (see sensitivity analysis below).

Table 255 Height and lung cancer risk. Number of studies in the CUP SLR

	Number
Studies identified	14 (15 publications)
Studies included in forest plot of highest compared with lowest exposure	7
Studies included in dose-response meta-analysis	12
Studies included in non-linear dose-response meta-analysis	5

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

Table 256 Height and lung cancer risk. Summary of the dose-response meta-analysis in the 2005 SLR and CUP

	2005 SLR	CUP
Increment unit used	Per 5 cm	Per 5 cm
All studies		
Studies (n)	5	12
Cases (total number)	1 762	19 750
RR (95%CI)	1.07 (1.0-1.15)	1.01 (1.00-1.02)
Heterogeneity (I^2, p-value)	40%	81.3%, < 0.001
P value Egger test		0.08
All studies pooled with ERFC and APCSC		
Studies (n)		165
RR (95%CI)		1.01 (1.00-1.02)
Heterogeneity (I^2, p-value)		72.3%, < 0.01
P value Egger test		0.17

Stratified and sensitivity analysis			
Smoking status	**Ever smokers**	**Never smokers**	
Studies (n)	2	3	
RR (95%CI)	1.00 (0.93-1.08)	1.06 (0.99-1.12)	
Heterogeneity (I^2, p-value)	76.5%, 0.04	0%, 0.91	
Adjustment for smoking	**No smoking adjustment**	**Intensity and duration of smoking**	
Studies (n)	2	9	
RR (95%CI)	1.00 (1.00-1.01)	1.02 (1.00-1.04)	
Heterogeneity (I^2, p-value)	0%, 0.72	85.8%, <0.001	
Sex	**Men**	**Women**	
Studies (n)	7	6	
RR (95%CI)	1.02 (1.0-1.03)	1.00 (0.99-1.01)	
Heterogeneity (I^2, p-value)	84.6%, < 0.001	49.7%, 0.08	
Outcome Type	**Incidence**	**Mortality**	**Incidence and mortality**
Studies (n)	8	2	2
RR (95%CI)	1.01 (1.00-1.03)	1.06 (0.94-1.19)	1.04 (0.87-1.25)
Heterogeneity (I^2, p-value)	82.4%, < 0.001	93.3%, < 0.001	71.2%, 0.06
All studies pooled with ERFC and APCSC			
Geographical area	**Europe and North America**	**Asia and Australia**	

Studies (n)	126	40	
RR (95%CI)	1.01 (0.99-1.02)	1.04 (0.99-1.09)	
Heterogeneity (I^2, p-value)	73.7%, < 0.01	94.4%, < 0.001	

Table 257 Height and lung 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								
Emerging Risk Factors Collaboration (ERFC), 2012	121	10 045	Europe and North America	Lung cancer, mortality	Per 6.5 cm	1.04 (1.02-1.06)		0%
Asia Pacific Cohort Studies Collaboration (APCSC), 2010	38	506 648	Asia and Australia	Lung cancer, mortality	Per 6 cm in men	1.06 (1.00-1.12)		
					Per 6 cm in women	1.08 (0.97-1.21)		

Table 258 Height and lung cancer risk. Main characteristics of studies included in the dose-response meta-analysis

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Missing data derived for analyses
Kabat, 2013a LUN20369 USA	WHI, Prospective Cohort, Age: 50-79 years, W, Postmenopausal	1466/ 144 701 12 years	Follow-up by mail or phone. Self-reported lung cancers verified by local review of pathology reports	Measured by trained staff	Incidence, lung cancer, ever smokers	Per 10 cm increase	1.09 (1.00-1.19)	Age, alcohol, pack years of smoking, education, ethnicity, hormone therapy, randomisation, status, site-specific scaling of W/HX	Increment recalculated from 10 cm to 5 cm, results of ever and never smokers subgroups were combined to be included in the meta-analysis
		269/ 144 701 12 years			Incidence, lung cancer, never smokers	Per 10 cm increase	1.12 (0.92-1.38)	Age, alcohol, hormone therapy, education, ethnicity, randomization status, site-specific scaling of W/HX	
Kabat, 2013b LUN20274 Canada	CNBSS, Prospective Cohort, Age: 40-59	657/ 88 256 16 years	Record linkages to cancer database and to the national	Height and weight measured at the initial examination.	Incidence and mortality, lung cancer, ever smokers	Per 10 cm increase	0.93 (0.82-1.06)	Age at entry, BMI, menopausal status, pack	Increment recalculated from 10 cm to 5 cm,

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Missing data derived for analyses
	years, W	100/ 88 256 16 years	mortality database		Incidence and mortality, lung cancer, never smokers	Per 10 cm increase	1.07 (0.78-1.47)	years of smoking, years of education	results of ever and never smokers subgroups were combined to be included in the meta-analysis
Walter, 2013 LUN20382 USA	VITAL, Prospective Cohort, Age: 50-76 years, M/W	743/ 65 038 7 years	Cancer registry	Self-reported questionnaire	Incidence, lung cancer	Per 5 inches increase	1.04 (0.90-1.19) Pvalue:0.62	Age, sex, race	Inch converted to cm, increment per 5 cm calculated, person years
Green, 2011 LUN26869 UK	MWS, Prospective Cohort, Age: 56.1 years, W, middle-aged adults	8074/ 1 297 124	NHS registers	Questionnaire calibrated by sample measurements (high correlation between measured and reported height was observed).	Incidence, lung cancer	Per 10 cm	1.03 (0.98-1.08)	Age, age at first birth, age at menarche, BMI, parity, socio-economic status, alcohol intake, region, smoking, status, cigarettes per day, strenuous exercise	Increment recalculated from 10 cm to 5 cm
		5 425			Incidence, lung cancer, current smokers	Per 10 cm	1.04 (0.97-1.10)	Age, age at first birth, age at menarche, 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
		667			Incidence, lung cancer , never smokers	Per 10 cm	1.15 (0.96-1.38)	parity, socio-economic status, alcohol intake, region, strenuous exercise	
Sung, 2009 LUN20261 Korea	KNHIC, Prospective Cohort, Age: 40-64 years, M/W, middle-class adults	4453/ 788 789 9 years	Linkage with cancer registry, national health insurance and death report	Measured by a trained nurse	Incidence, lung cancer, men	> 171.1 vs 164.6-168.0 cm	1.18 (1.09-1.29)	Age, BMI, alcohol consumption, area of residence, cigarette smoking habits, level of monthly salary, occupation, regular exercise	Mid-point exposure, results of men and women were combined to be included in the meta-analysis
						Per 5 cm increase	1.07 (1.04-1.10)		
		943/ 788 789 9 years			Incidence, lung cancer, women	> 158.1 vs 151.1-155.0 cm	1.08 (0.88-1.31)		
						Per 5 cm increase	1.05 (0.99-1.13)		
Fujino, 2007 LUN20278 Japan	JACC, Prospective Cohort, M/W	853	Population death registries	Obtained from survey	Mortality, lung cancer, men	≥ 165 vs 160.0 cm	1.04 (0.87-1.23)	Age, study area	Mid-point exposure, results from men and women combined to be included in the meta-analysis
		251			Mortality, lung cancer, women	≥ 154 vs 149.0 cm	1.18 (0.85-1.65)		

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	Missing data derived for analyses
Batty, 2006 LUN21130 UK	WHITE, Prospective Cohort, Age: 40-64 years, M, non-industrial, London-based, male government employees	801/ 17 312 35 years	Death certificate and National Health Registry	Height measured (subjects measured with shoes with to nearest 1/2 inch below point of measurement)	Mortality, lung cancer	≥ 181 vs < 171 cm	1.62 (1.28-2.06)	Age, BMI, employment grad e, physical activity, smoking habit, marital status, triceps skinfold thickness, systolic blood pressure, cholesterol, forced vital, impaired glucose tolerance, diabetes, disease at entry	Mid-point exposure, person years
						Per 5 cm increase	1.13 (1.06-1.20)		
Gunnell, 2003 LUN00114 UK	Caerphilly, Prospective Cohort, Age: 45-59 years, M, Residents from the town of Caerphilly and	78/ 2393 19 years	Death and cancer registry	Height recorded during examination	Mortality, lung cancer	Per 6 cm increase	1.21 (0.96-1.51)	Age, BMI, smoking habits (never smoked, ex-smoker (>10 yr, 5–9 yr, 1–4 yr, <1 yr), cigar or pipe smoker, and current cigarette smoker (1–14, 15–24,	Increment recalculated to 5 cm, person years

Author, Year, WCRF Code, Country	Study name, characteristics	Cases/ Study size Follow-up (years)	Case ascertainment	Exposure assessment	Outcome	Comparison	RR (95%CI) Ptrend	Adjustment factors	Missing data derived for analyses
	five adjacent villages in South Wales							25+ per day), father's occupation, unemployment of the father during the subject's childhood, subject's occupation, household size in childhood	
Olson, 2002 LUN00502 USA	IWHS, Prospective Cohort, Age: 55-69 years, W, Post-menopausal	596/ 38 006 12 years	State Health Registry of Iowa	Self-reported questionnaire (paper tape measure mailed to subjects)	Incidence, lung cancer	> 167.6 cm vs ≤ 157.5 cm	1.05 (0.81-1.36) Ptrend: 0.78	Age, BMI, waist circumference, BMI at age 18 years, beer consumption, educational level, physical activity, smoking status, pack years of smoking	Mid-point exposure
Hebert, 1997 LUN01785 USA	PHS, Prospective Cohort, Age: 40-84 years,	170/ 22 017 12 years	Self-reported questionnaire reviewed by medical records	Self-reported	Incidence, lung cancer	≥ 73 vs ≤ 67 inch	1.07 (0.63-1.83) Ptrend:0.65	Age, BMI, alcohol consumption, physical activity,	Distribution of person years per categories, mid-point exposure, Inch converted

Author, Year, WCRF Code, Country	Study 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							smoking habits, beta-carotene assignments, aspirin assignment	to cm and increment recalculated
Knekt, 1991a LUN03143 Finland	FMCHES, 1966, Prospective Cohort, Age: 20-69 years, M	117/ 4 538 20 years	Finnish cancer registry	Height was measured	Incidence, lung cancer	> 178 vs ≤ 169 cm	1.20 (0.60-2.10)	Age, smoking habits	Mid-point exposure
Albanes, 1988 LUN26870 USA	NHANES I, Prospective Cohort, Age: 25-74 years, M	114/ 5141 10 years	Follow-up interviews confirmed with hospital records and death certificates	Measured to the nearest millimetre	Incidence, lung cancer, men	> 178.7 vs < 169 cm	1.10 (0.60-2.00)	Age, race, cigarette-smoking status, family income, and BMI,	Distribution of person years and number of cases in quartiles, mid-points exposure

Table 259 Height and lung cancer risk. Main characteristics of studies excluded from the 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
Whitley, 2009 LUN20312 UK	BOCS, Historical Cohort, M/W	97/ 2642 59 years	Cancer registry and death certificates	Height measured at age 2-14 years to the nearest millimetre using a stadiometer	Mortality, lung cancer	Per 1 SD	0.94 (0.78-1.14)	Age, sex	No clear definition of 1 SD increment; reported in age subgroups, boys and girls only
Kabat, 2008b LUN20341 USA	WHI-DM and OS, Prospective Cohort, Age: 50-79 years, W, postmenopausal women	736/ 159 659 8 years	Follow-up by mail or phone, self-reported lung cancers verified by local review of pathology reports	Measured at baseline	Incidence, lung cancer, current smokers	≥ 167.1 vs < 156.5 cm	1.19 (0.83-1.70) Ptrend:0.35	Age, education, ethnicity, use of hormone replacement therapy (never/ever), intakes of total fat (g/day), fruits (servings/day), vegetables (servings/day), alcohol (drinks/week), and total calories (kcal/day), physical activity, study	Superseded by Kabat, 2013a LUN20369
		404/ 159 659 8 years			Incidence, lung cancer, former smokers	≥ 167.1 vs < 156.5 cm	1.17 (0.89-1.53) Ptrend:0.26		
		197/ 159 659 8 years			Incidence, lung cancer, never smokers	≥ 167.1 vs < 156.5 cm	1.44 (0.91-2.27) 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	Reasons for exclusion
								(Observational Study/Clinical Trial), pack years of smoking	
Chyou, 1994 LUN02487 USA	HHP, Prospective Cohort, Age: 45-79 years, M, Japanese live in Hawaii	236/ 7945 23 years	Hospital records, death certificates, Hawaii tumour registry	Obtained during examination	Incidence, lung cancer, Standing height (STH)	Mean exposure:163.4 cm		Age	No RR available
					Incidence, lung cancer, Sitting height (SIH)	Mean exposure:86.7 cm			

Figure 258 RR estimates of lung cancer by levels of height

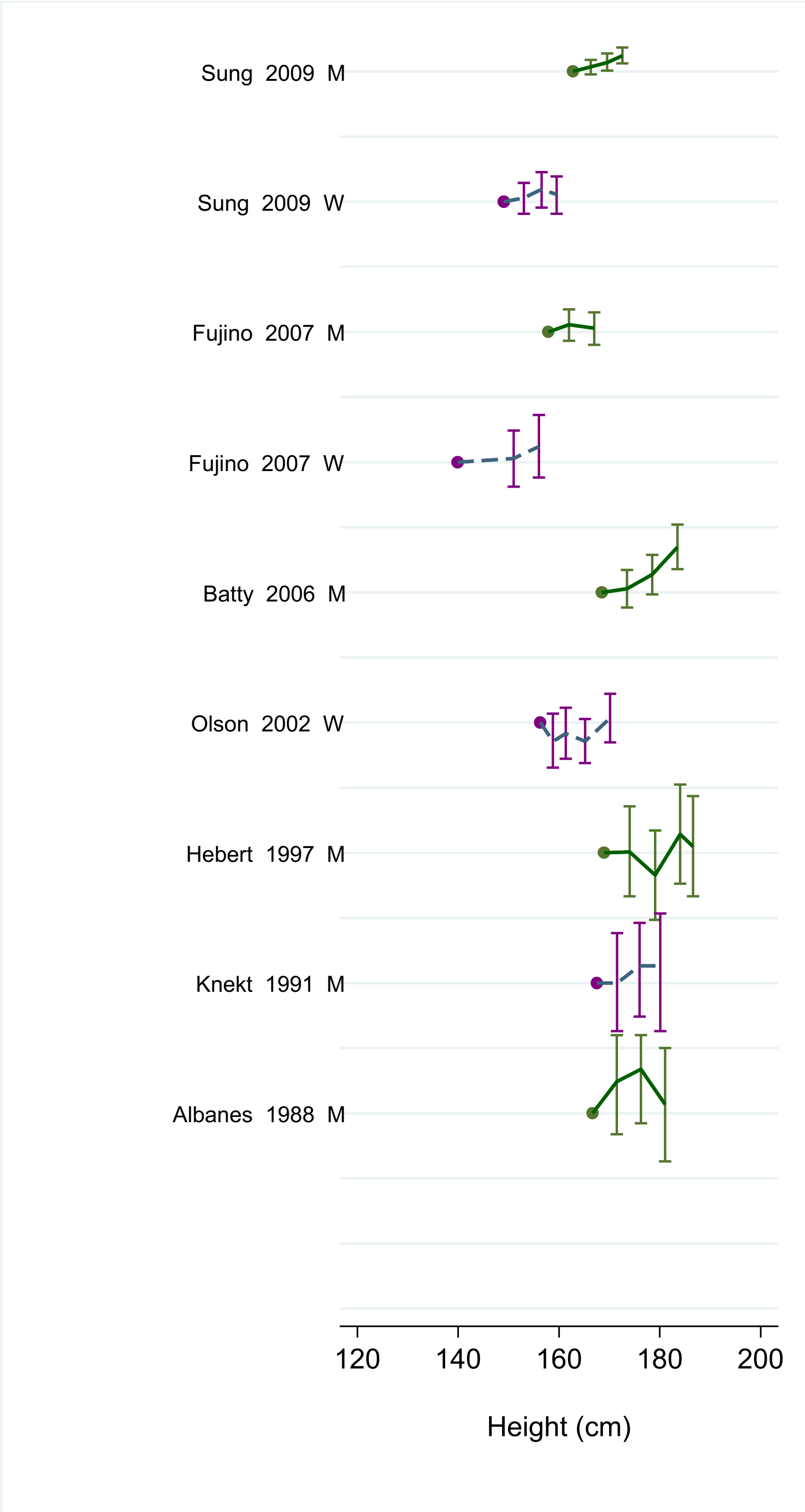


Figure 259 RR (95% CI) of lung cancer for the highest compared with the lowest level of height

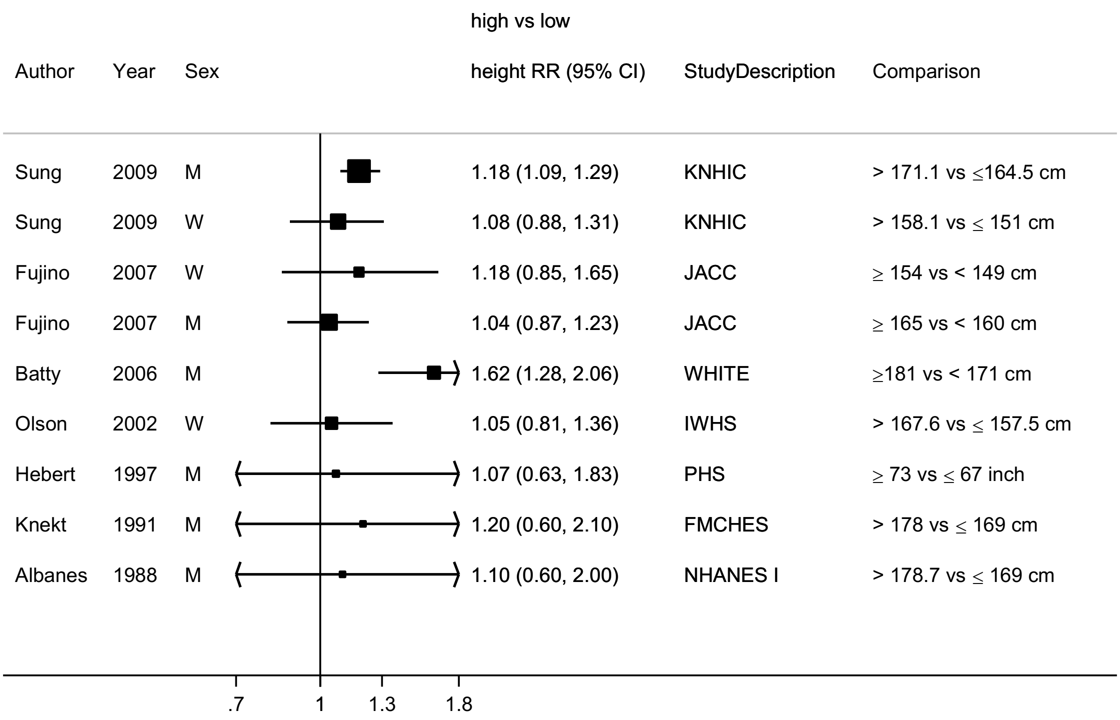


Figure 260 RR (95% CI) of lung cancer for 5 cm increase of height

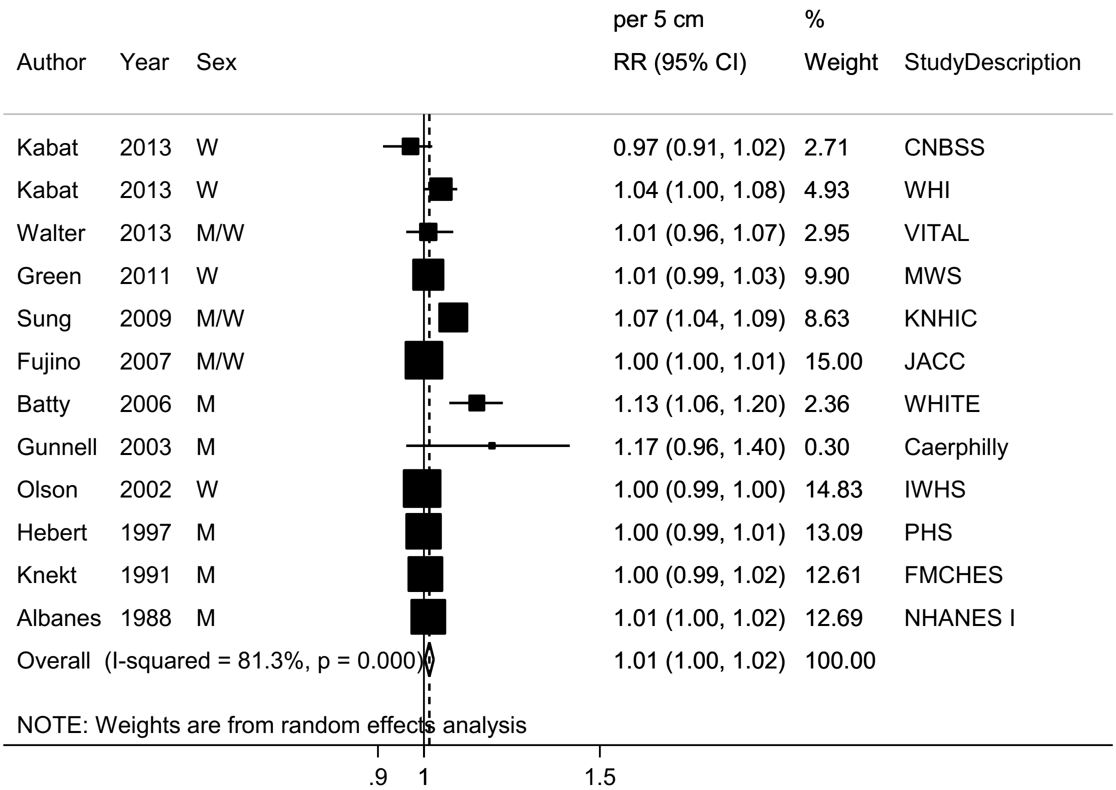
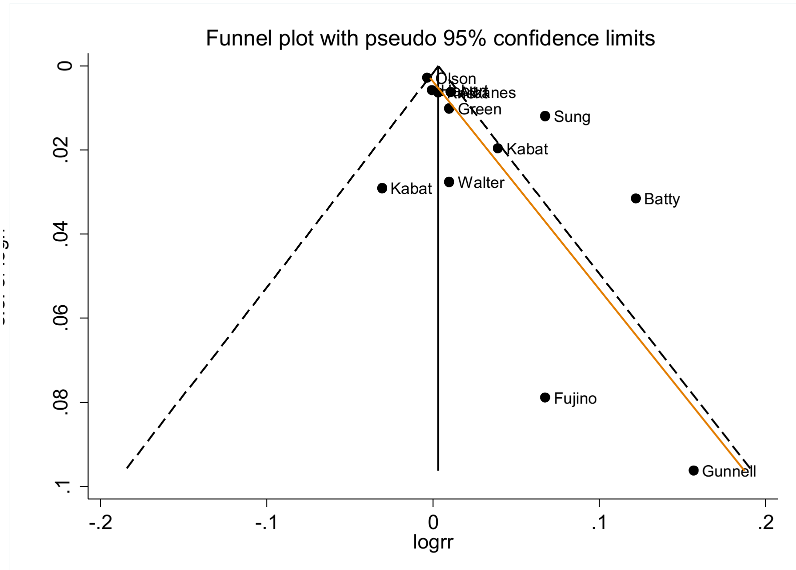


Figure 261 Funnel plot of studies included in the dose response meta-analysis of height and lung cancer



Egger's test p= 0.08

Figure 262 RR (95% CI) of lung cancer for 5 cm increase of height pooled with ERFC and APCSC

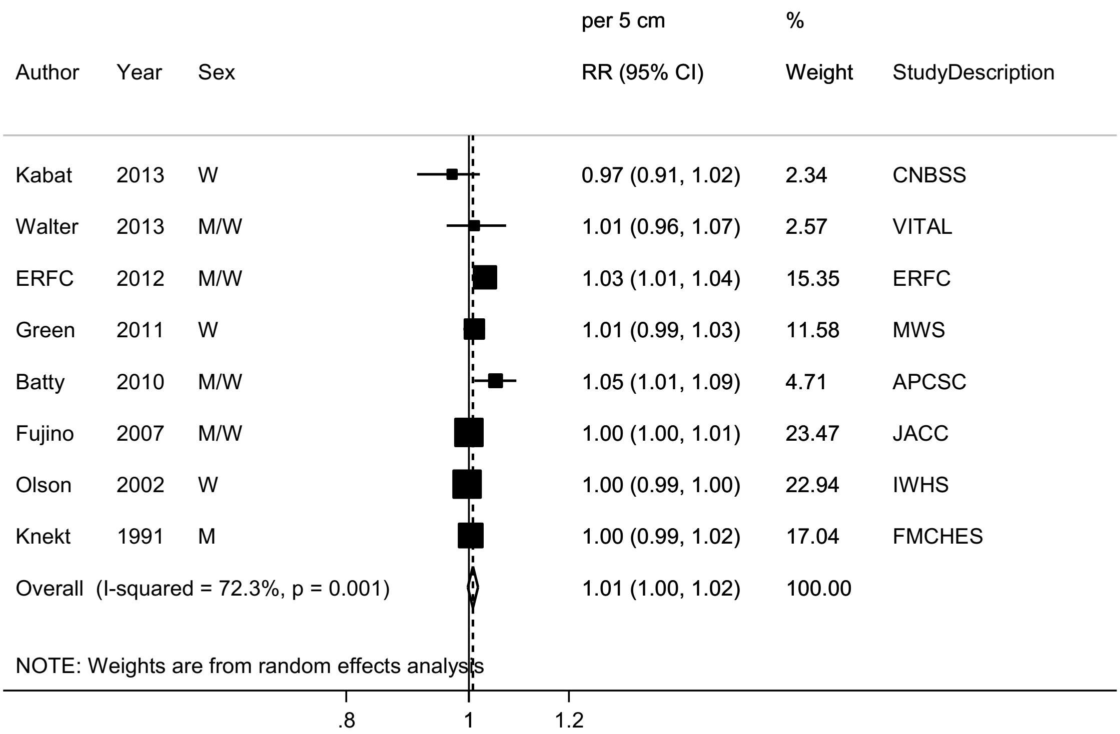


Figure 263 RR (95% CI) of lung cancer for 5 cm increase of height by geographical area pooled with ERFC and APCSC

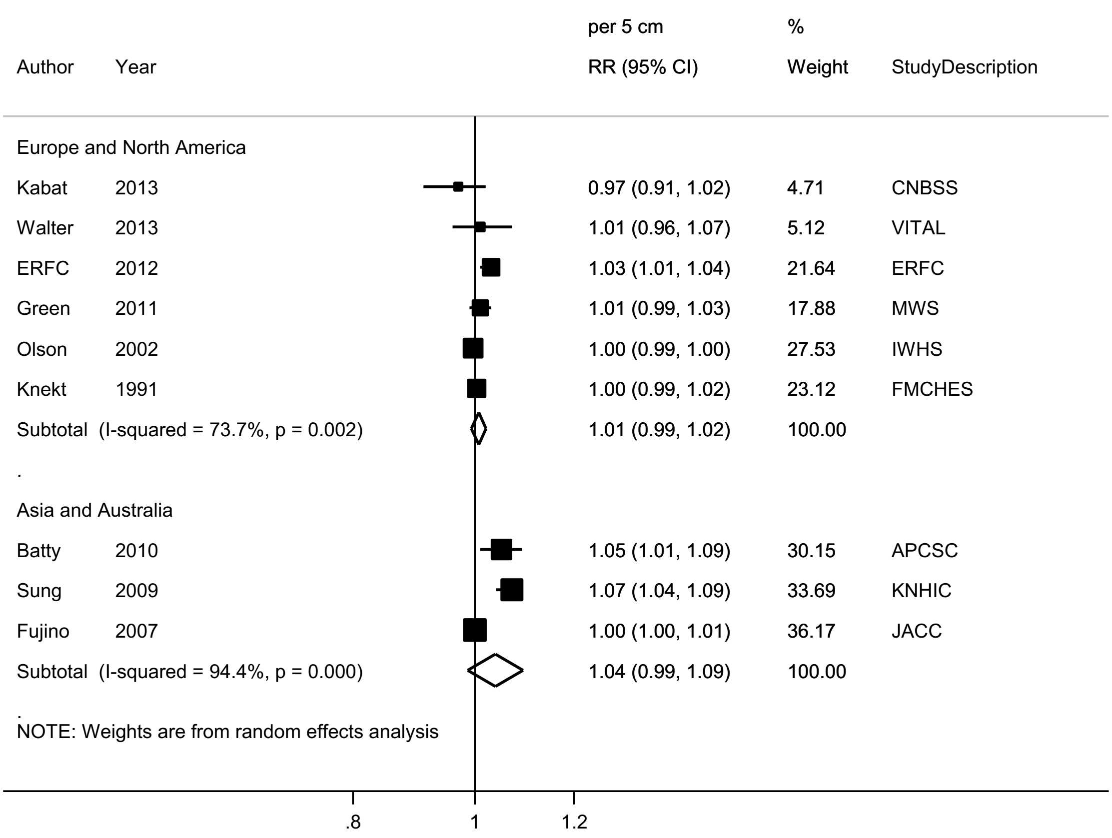


Figure 264 RR (95% CI) of lung cancer for 5 cm increase of height by sex

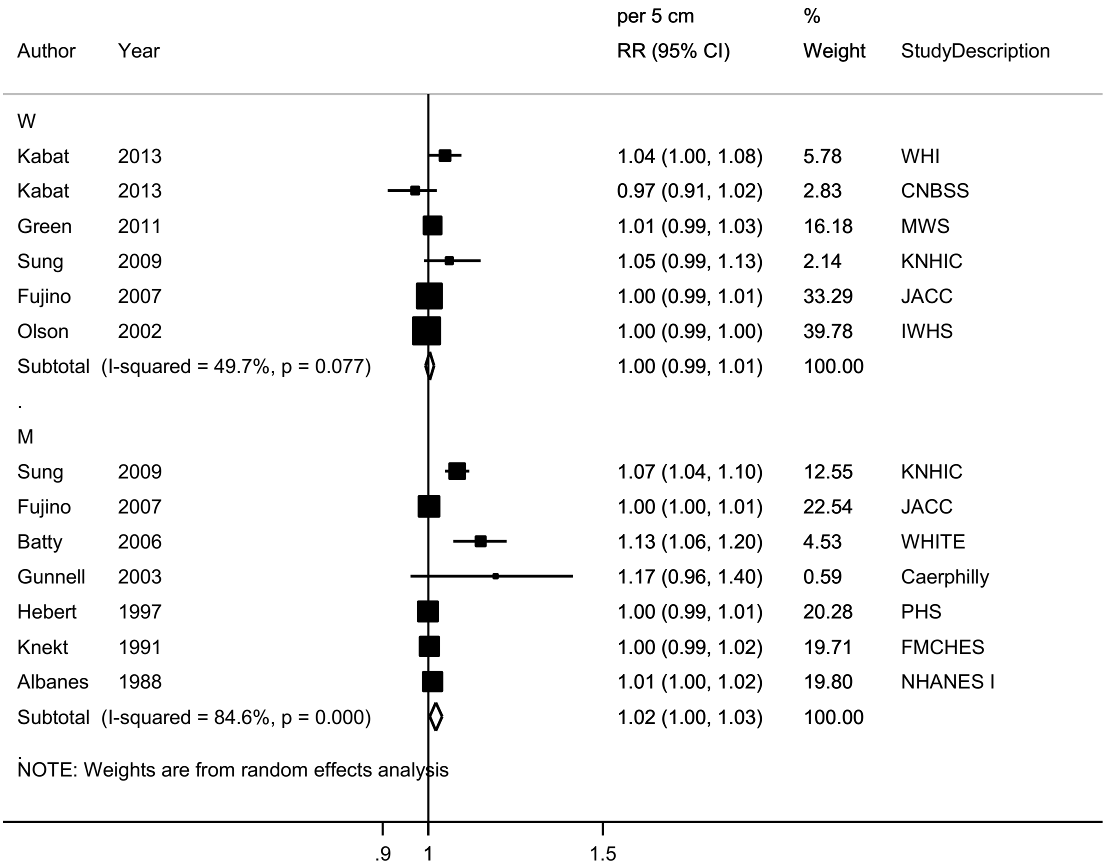


Figure 265 RR (95% CI) of lung cancer for 5 cm increase of height by cancer outcome

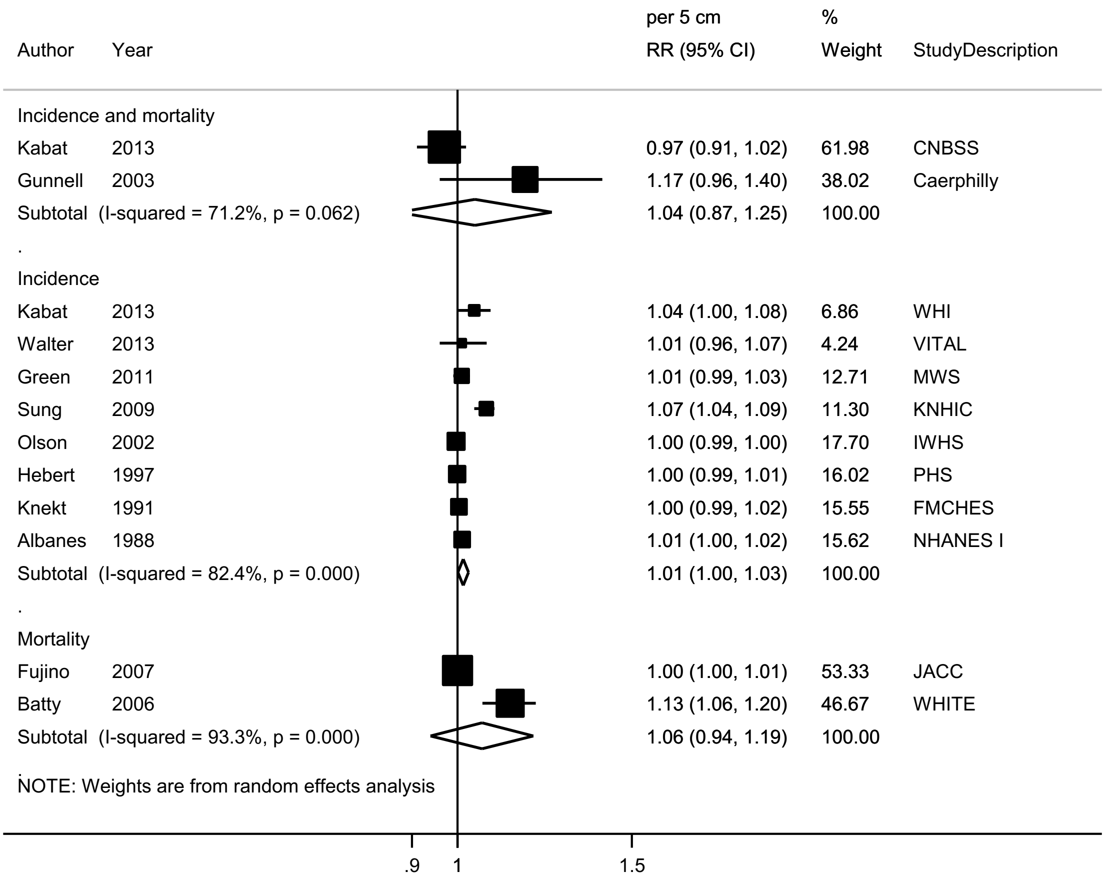


Figure 266 RR (95% CI) of lung cancer for 5 cm increase of height by smoking status

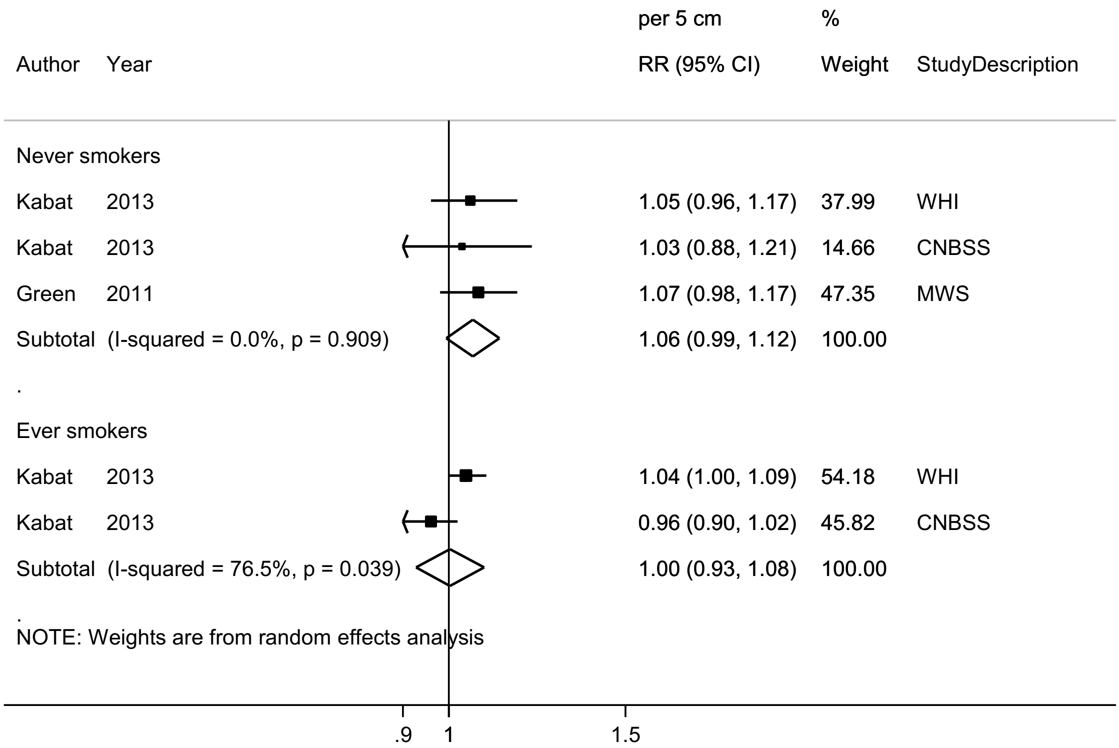
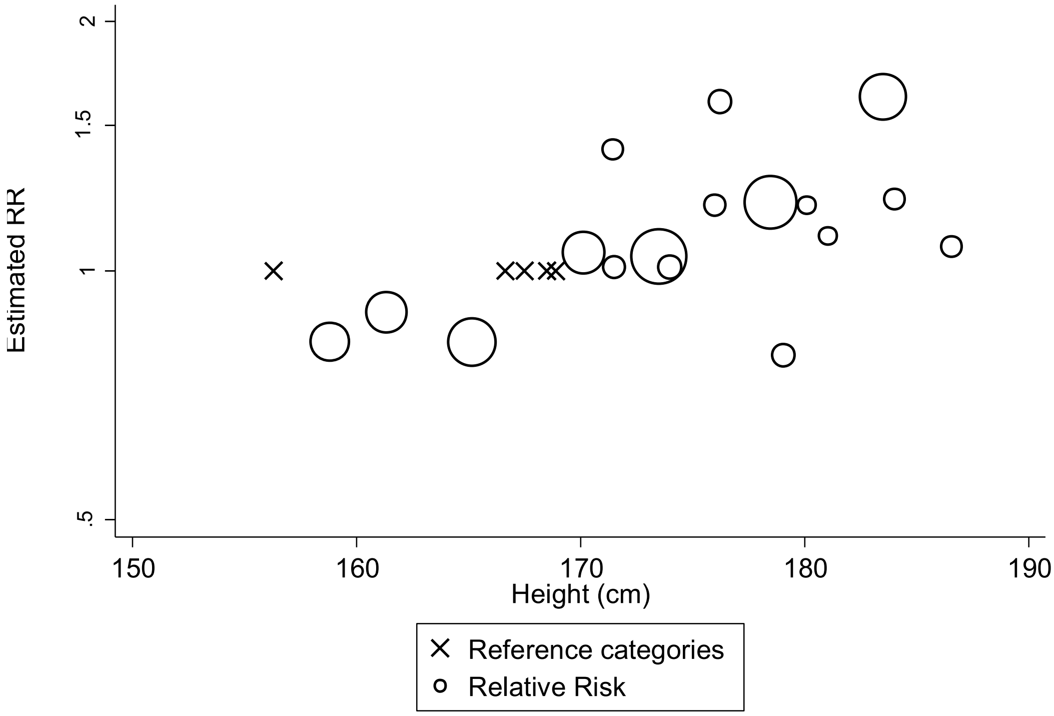
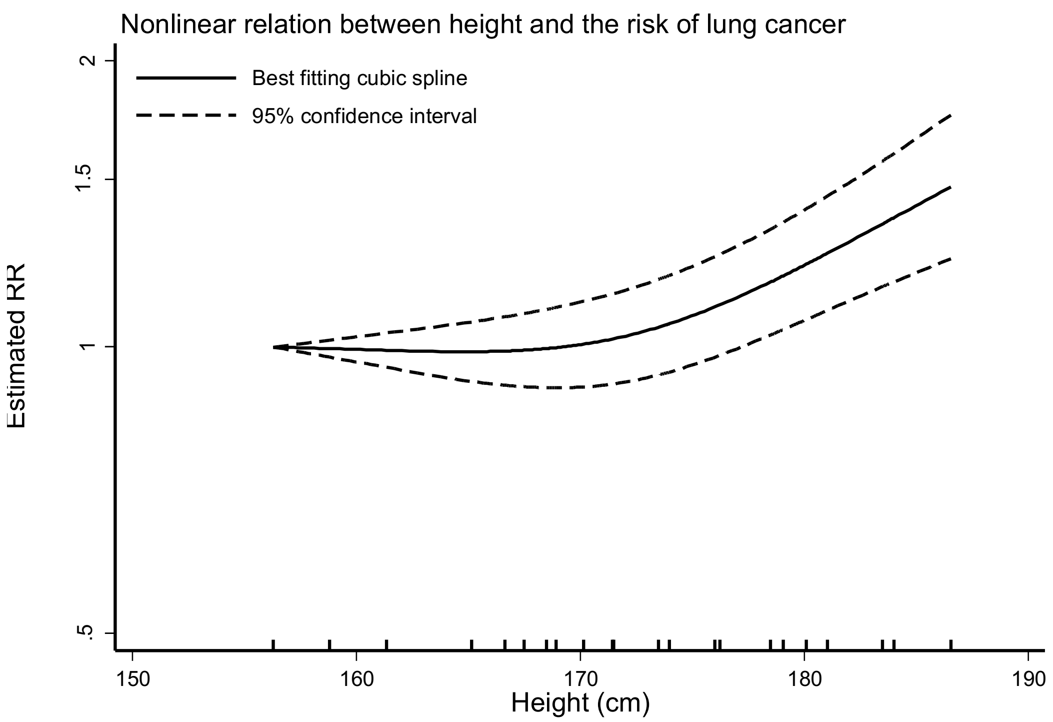


Figure 267 Relative risk of lung cancer and height estimated using non-linear models





$p < 0.01$

Table 260 Table with height values and corresponding RRs (95% CIs) for non-linear analysis of height and lung cancer

Height (cm)	RR (95%CI)
156.3	1.0
167.5	0.99 (0.91-1.08)
170	1.01 90.91-1.12)
176	1.10 (0.98-1.24)
186.5	1.47 (1.24-1.75)

Reference List

1. Adult height and the risk of cause-specific death and vascular morbidity in 1 million people: individual participant meta-analysis. Int J Epidemiol 2012; 41: 1419-33.
2. Afzal, Shoaib, Bojesen et al. Low plasma 25-hydroxyvitamin D and risk of tobacco-related cancer. Clin Chem 2013; 59: 771-80.
3. Alavanja MC, Dosemeci M, Samanic C et al. Pesticides and lung cancer risk in the agricultural health study cohort. Am J Epidemiol 2004; 160: 876-85.
4. Albanes D, Blair A, TAYLOR P. Physical Activity And Risk Of Cancer In The Nhanes I Population. American-Journal-of-Public-Health 744; 1989.
5. Albanes D, Jones DY, Schatzkin A et al. Adult stature and risk of cancer. Cancer Res 1988; 48: 1658-62.
6. Albanes D, Heinonen OP, Huttunen JK et al. Effects of alpha-tocopherol and beta-carotene supplements on cancer incidence in the Alpha-Tocopherol Beta-Carotene Cancer Prevention Study. Am J Clin Nutr 1995; 62: 1427S-30S.
7. Albanes D, Heinonen OP, Taylor PR et al. Alpha-Tocopherol and beta-carotene supplements and lung cancer incidence in the alpha-tocopherol, beta-carotene cancer prevention study: effects of base-line characteristics and study compliance. J Natl Cancer Inst 1996; 88: 1560-70.
8. Alfano CM, Klesges RC, Murray DM et al. Physical activity in relation to all-site and lung cancer incidence and mortality in current and former smokers. Cancer Epidemiol Biomarkers Prev 2004; 13: 2233-41.
9. Alfonso HS, Fritschi L, de Klerk NH et al. Plasma vitamin concentrations and incidence of mesothelioma and lung cancer in individuals exposed to crocidolite at Wittenoom, Western Australia. Eur J Cancer Prev 2006; 15: 290-4.
10. Allen NE, Beral V, Casabonne D et al. Moderate alcohol intake and cancer incidence in women. J Natl Cancer Inst 2009; 101: 296-305.
11. Andreotti, Gabriella, Hou et al. Body mass index, agricultural pesticide use, and cancer incidence in the Agricultural Health Study cohort. Cancer Causes Control 2010; 21: 1759-75.
12. Baastrup R, Sorensen M, Balstrom T et al. Arsenic in drinking-water and risk for cancer in Denmark. Environ Health Perspect 2008; 116: 231-7.
13. Bagnardi V, Rota M, Botteri E et al. Alcohol consumption and lung cancer risk in never smokers: a meta-analysis. Ann Oncol 2011; 22: 2631-9.
14. Bak H, Christensen J, Thomsen BL et al. Physical activity and risk for lung cancer in a Danish cohort. Int J Cancer 2005; 116: 439-44.
15. Balder HF, Goldbohm RA, van den Brandt PA. Dietary patterns associated with male lung cancer risk in the Netherlands Cohort Study. Cancer Epidemiol Biomarkers Prev 2005; 14: 483-90.

16. Bandera EV, Freudenheim JL, Marshall JR et al. Diet and alcohol consumption and lung cancer risk in the New York State Cohort (United States). Cancer Causes Control 1997; 8: 828-40.
17. Bandera EV, Freudenheim JL, Marshall JR et al. Impact of losses to follow-up on diet/alcohol and lung cancer analyses in the New York State Cohort. Nutr Cancer 2002; 42: 41-7.
18. Bassett JK, Hodge AM, English DR et al. Dietary intake of B vitamins and methionine and risk of lung cancer. Eur J Clin Nutr 2012; 66: 182-7.
19. Batty GD, Shipley MJ, Langenberg C et al. Adult height in relation to mortality from 14 cancer sites in men in London (UK): evidence from the original Whitehall study. Ann Oncol 2006; 17: 157-66.
20. Batty GD, Barzi F, Woodward M et al. Adult height and cancer mortality in Asia: the Asia Pacific Cohort Studies Collaboration. Ann Oncol 2010; 21: 646-654a.
21. Batty GD, Shipley MJ, Kivimaki M et al. Walking pace, leisure time physical activity, and resting heart rate in relation to disease-specific mortality in London: 40 years follow-up of the original Whitehall study. An update of our work with professor Jerry N. Morris (1910-2009). Ann Epidemiol 2010; 20: 661-669b.
22. Bethea, Traci N, Rosenberg et al. Obesity in relation to lung cancer incidence in African American women. Cancer Causes Control 2013; 24: 1695-703.
23. Bhaskaran K, Douglas I, Forbes H et al. Body-mass index and risk of 22 specific cancers: a population-based cohort study of 5.24 million UK adults. Lancet 2014; 384: 755-65.
24. Bradbury KE, Appleby PN, Key TJ. Fruit, vegetable, and fiber intake in relation to cancer risk: findings from the European Prospective Investigation into Cancer and Nutrition (EPIC). Am J Clin Nutr 2014; 100: 394S-8S.
25. Brenner DR. Cancer incidence due to excess body weight and leisure-time physical inactivity in Canada: implications for prevention. Prev Med 2014; 66: 131-9.
26. Breslow RA, Graubard BI, Sinha R et al. Diet and lung cancer mortality: a 1987 National Health Interview Survey cohort study. Cancer Causes Control 2000; 11: 419-31.
27. Breslow RA, Chen CM, Graubard BI et al. Prospective study of alcohol consumption quantity and frequency and cancer-specific mortality in the US population. Am J Epidemiol 2011; 174: 1044-53.
28. Buchner FL, Bueno-de-Mesquita HB, Ros MM et al. Variety in fruit and vegetable consumption and the risk of lung cancer in the European prospective investigation into cancer and nutrition. Cancer Epidemiol Biomarkers Prev 2010; 19: 2278-2286a.
29. Buchner FL, Bueno-de-Mesquita HB, Linseisen J et al. Fruits and vegetables consumption and the risk of histological subtypes of lung cancer in the European Prospective Investigation into Cancer and Nutrition (EPIC). Cancer Causes Control 2010; 21: 357-371b.
30. Buffart LM, Singh AS, van Loon EC et al. Physical activity and the risk of developing lung cancer among smokers: a meta-analysis. J Sci Med Sport 2014; 17: 67-71.

31. Butler LM, Montague JA, Koh WP et al. Fried meat intake is a risk factor for lung adenocarcinoma in a prospective cohort of Chinese men and women in Singapore. Carcinogenesis 2013; 34: 1794-9.
32. Calle EE, Rodriguez C, Walker-Thurmond K et al. Overweight, obesity, and mortality from cancer in a prospectively studied cohort of U.S. adults. 348: 1625-38.
33. Chao C. Associations between beer, wine, and liquor consumption and lung cancer risk: a meta-analysis. Cancer Epidemiol Biomarkers Prev 2007; 16: 2436-47.
34. Chao C, Slezak JM, Caan BJ et al. Alcoholic beverage intake and risk of lung cancer: the California Men's Health Study. Cancer Epidemiol Biomarkers Prev 2008; 17: 2692-9.
35. Chao C, Li Q, Zhang F et al. Alcohol consumption and risk of lung cancer in the VITamins And Lifestyle Study. Nutr Cancer 2011; 63: 880-8.
36. Chen CJ, Wu MM, Lee SS et al. Atherogenicity and carcinogenicity of high-arsenic artesian well water. Multiple risk factors and related malignant neoplasms of blackfoot disease. Arteriosclerosis 1988; 8: 452-60.
37. Chen CL, Hsu LI, Chiou HY et al. Ingested arsenic, cigarette smoking, and lung cancer risk: a follow-up study in arseniasis-endemic areas in Taiwan. JAMA 2004; 292: 2984-90.
38. Chen CL, Chiou HY, Hsu LI et al. Ingested arsenic, characteristics of well water consumption and risk of different histological types of lung cancer in northeastern Taiwan. Environ Res 2010; 110: 455-62.
39. Chen K, Liao QL, Ma ZW et al. Association of soil arsenic and nickel exposure with cancer mortality rates, a town-scale ecological study in Suzhou, China. Environ Sci Pollut Res Int 2014.
40. Chen Z, Yang G, Offer A et al. Body mass index and mortality in China: a 15-year prospective study of 220 000 men. Int J Epidemiol 2012; 41: 472-81.
41. Cheng TY, Neuhouser ML. Serum 25-hydroxyvitamin D, vitamin A, and lung cancer mortality in the US population: a potential nutrient-nutrient interaction. Cancer Causes Control 2012; 23: 1557-65.
42. Chiazze L, Watkins DK, Fryar C. Historical cohort mortality study of a continuous filament fiberglass manufacturing plant: I. White men. 1997; 39: 432-41.
43. Chiou HY, Hsueh YM, Liaw KF et al. Incidence of internal cancers and ingested inorganic arsenic: a seven-year follow-up study in Taiwan. Cancer Res 1995; 55: 1296-300.
44. Cho E, Hunter DJ, Spiegelman D et al. Intakes of vitamins A, C and E and folate and multivitamins and lung cancer: a pooled analysis of 8 prospective studies. Int J Cancer 2006; 118: 970-8.
45. Chow WH, Schuman LM, McLaughlin JK et al. A cohort study of tobacco use, diet, occupation, and lung cancer mortality. Cancer Causes Control 1992; 3: 247-54.
46. Chung CJ, Huang YL, Huang YK et al. Urinary arsenic profiles and the risks of cancer mortality: a population-based 20-year follow-up study in arseniasis-endemic areas in Taiwan. Environ Res 2013; 122: 25-30.

47. Chyou PH, Nomura AM, Stemmermann GN. A prospective study of weight, body mass index and other anthropometric measurements in relation to site-specific cancers. Int J Cancer 1994; 57: 313-7.
48. Colbert LH, Hartman TJ, Tangrea JA et al. Physical activity and lung cancer risk in male smokers. 2002; 98: 770-3.
49. Comstock GW, Alberg AJ, Huang HY et al. The risk of developing lung cancer associated with antioxidants in the blood: ascorbic acid, carotenoids, alpha-tocopherol, selenium, and total peroxyl radical absorbing capacity. Cancer Epidemiol Biomarkers Prev 1997; 6: 907-16.
50. Connett JE, Kuller LH, Kjelsberg MO et al. Relationship between carotenoids and cancer. The Multiple Risk Factor Intervention Trial (MRFIT) Study. Cancer 1989; 64: 126-34.
51. Cook NR, Le IM, Manson JE et al. Effects of beta-carotene supplementation on cancer incidence by baseline characteristics in the Physicians' Health Study (United States). Cancer Causes Control 2000; 11: 617-26.
52. Cross AJ, Leitzmann MF, Gail MH et al. A prospective study of red and processed meat intake in relation to cancer risk. PLoS Med 2007; 4: e325.
53. Cutler GJ, Nettleton JA, Ross JA et al. Dietary flavonoid intake and risk of cancer in postmenopausal women: the Iowa Women's Health Study. Int J Cancer 2008; 123: 664-71.
54. Dai WM, Yang B, Chu XY et al. Association between folate intake, serum folate levels and the risk of lung cancer: a systematic review and meta-analysis. Chin Med J (Engl) 2013; 126: 1957-64.
55. Daniel CR, Cross AJ, Graubard BI et al. Prospective investigation of poultry and fish intake in relation to cancer risk. Cancer Prev Res (Phila) 2011; 4: 1903-11.
56. Dartois, Laureen, Fagherazzi et al. Association between five lifestyle habits and cancer risk: Results from the E3N cohort. Cancer Prev Res (Phila) 2014.
57. de Klerk NH, Musk AW, Ambrosini GL et al. Vitamin A and cancer prevention II: comparison of the effects of retinol and beta-carotene. Int J Cancer 1998; 75: 362-7.
58. Dehal, Ahmed, Garrett et al. Body mass index and death rate of colorectal cancer among a national cohort of U.S. adults. Nutr Cancer 2011; 63: 1218-25.
59. Djousse L, Dorgan JF, Zhang Y et al. Alcohol consumption and risk of lung cancer: the Framingham Study. 2002; 94: 1877-82.
60. Drinkard CR, Sellers TA, Potter JD et al. Association of body mass index and body fat distribution with risk of lung cancer in older women. 1995; 142: 600-7.
61. Eichholzer M, Stahelin HB, Gey KF et al. Prediction of male cancer mortality by plasma levels of interacting vitamins: 17-year follow-up of the prospective Basel study. Int J Cancer 1996; 66: 145-50.
62. Eichholzer M, Bernasconi F, Jordan P et al. Body mass index and the risk of male cancer mortality of various sites: 17-year follow-up of the Basel cohort study. Swiss Medical Weekly 2005; 135: 27-33.
63. Epplein M, Franke AA, Cooney RV et al. Association of plasma micronutrient levels and urinary isoprostane with risk of lung cancer: the multiethnic cohort study. Cancer Epidemiol Biomarkers Prev 2009; 18: 1962-70.

64. Fan L, Cai L. [Meta-analysis on the relationship between alcohol consumption and lung cancer risk]. Wei Sheng Yan Jiu 2009; 38: 85-9.
65. FARAHMAND BY, AHLBOM A, EKBLOM O et al. Mortality amongst participants in Vasaloppet: a classical long-distance ski race in Sweden. 276; 2003; 253: 3.
66. Feskanich D, Ziegler RG, Michaud DS et al. Prospective study of fruit and vegetable consumption and risk of lung cancer among men and women. 2000; 92: 1812-23.
67. Fowke JH, Gao YT, Chow WH et al. Urinary isothiocyanate levels and lung cancer risk among non-smoking women: a prospective investigation. Lung Cancer 2011; 73: 18-24.
68. Fraser GE, Beeson WL, Phillips RL. Diet and lung cancer in California Seventh-day Adventists. Am J Epidemiol 1991; 133: 683-93.
69. Fraser GE. Associations between diet and cancer, ischemic heart disease, and all-cause mortality in non-Hispanic white California Seventh-day Adventists. Am J Clin Nutr 1999; 70: 532S-8S.
70. Freedman DM, Looker AC, Chang SC et al. Prospective study of serum vitamin D and cancer mortality in the United States. J Natl Cancer Inst 2007; 99: 1594-602.
71. Freudenheim JL, Ritz J, Smith-Warner SA et al. Alcohol consumption and risk of lung cancer: a pooled analysis of cohort studies. Am J Clin Nutr 2005; 82: 657-67.
72. Friedman GD, Blaner WS, Goodman DS et al. Serum retinol and retinol-binding protein levels do not predict subsequent lung cancer. Am J Epidemiol 1986; 123: 781-9.
73. Fu YY, Takezaki T, Tajima K. [Risk factors of lung cancer--follow-up studies in Nagoya Japan]. 1997; 18: 328-30.
74. Fujino, Yoshihisa. Anthropometry, development history and mortality in the Japan Collaborative Cohort Study for Evaluation of Cancer (JACC). Asian Pac J Cancer Prev 2007; 8 Suppl: 105-12.
75. Gallicchio L, Boyd K, Matanoski G et al. Carotenoids and the risk of developing lung cancer: a systematic review. Am J Clin Nutr 2008; 88: 372-83.
76. Garland M, Morris JS, Stampfer MJ et al. Prospective study of toenail selenium levels and cancer among women. J Natl Cancer Inst 1995; 87: 497-505.
77. Gaziano JM, Sesso HD, Christen WG et al. Multivitamins in the prevention of cancer in men: the Physicians' Health Study II randomized controlled trial. JAMA 2012; 308: 1871-80.
78. George SM, Park Y, Leitzmann MF et al. Fruit and vegetable intake and risk of cancer: a prospective cohort study. Am J Clin Nutr 2009; 89: 347-53.
79. Gnagnarella, P, Maisonneuve et al. Red meat, Mediterranean diet and lung cancer risk among heavy smokers in the COSMOS screening study. Ann Oncol 2013; 24: 2606-2611a.
80. Gnagnarella, Patrizia, Maisonneuve et al. Nutrient intake and nutrient patterns and risk of lung cancer among heavy smokers: results from the COSMOS screening study with annual low-dose CT. Eur J Epidemiol 2013; 28: 503-511b.
81. Goodman GE, Schaffer S, Bankson DD et al. Predictors of serum selenium in cigarette smokers and the lack of association with lung and prostate cancer risk. Cancer Epidemiol Biomarkers Prev 2001; 10: 1069-76.

82. Goodman GE, Schaffer S, Omenn GS et al. The association between lung and prostate cancer risk, and serum micronutrients: results and lessons learned from beta-carotene and retinol efficacy trial. Cancer Epidemiol Biomarkers Prev 2003; 12: 518-26.
83. Green J, Cairns BJ, Casabonne D et al. Height and cancer incidence in the Million Women Study: prospective cohort, and meta-analysis of prospective studies of height and total cancer risk. Lancet Oncol 2011; 12: 785-94.
84. Gunnell D, May M, Ben-Shlomo Y et al. Height, leg length, and cancer: the Caerphilly Study. Nutr Cancer 2003; 47: 34-9.
85. Harnack L, Nicodemus K, Jacobs DR, Jr. et al. An evaluation of the Dietary Guidelines for Americans in relation to cancer occurrence. Am J Clin Nutr 2002; 76: 889-96.
86. Hartman TJ, Taylor PR, Alfthan G et al. Toenail selenium concentration and lung cancer in male smokers (Finland). Cancer Causes Control 2002; 13: 923-8.
87. Hebert PR, Ajani U, Cook NR et al. Adult height and incidence of cancer in male physicians (United States). Cancer Causes Control 1997; 8: 591-7.
88. Heinonen O, Huttunen J, Albanes D et al. The effect of vitamin E and beta carotene on the incidence of lung cancer and other cancers in male smokers. The Alpha-Tocopherol, Beta Carotene Cancer Prevention Study Group. N Engl J Med 1994; 330: 1029-35.
89. Hennekens CH, Buring JE, Manson JE et al. Lack of effect of long-term supplementation with beta carotene on the incidence of malignant neoplasms and cardiovascular disease. N Engl J Med 1996; 334: 1145-9.
90. Hirvonen, T, Kontto et al. Dietary acrylamide intake and the risk of cancer among Finnish male smokers. Cancer Causes Control 2010; 21: 2223-9.
91. Hirvonen T, Virtamo J, Korhonen P et al. Flavonol and flavone intake and the risk of cancer in male smokers (Finland). 2001; 12: 789-96.
92. Hoffmans MD, Kromhout D, Coulander CD. Body Mass Index at the age of 18 and its effects on 32-year-mortality from coronary heart disease and cancer. A nested case-control study among the entire 1932 Dutch male birth cohort. 1989; 42: 513-20.
93. Holick CN, Michaud DS, Stolzenberg-Solomon R et al. Dietary carotenoids, serum beta-carotene, and retinol and risk of lung cancer in the alpha-tocopherol, beta-carotene cohort study. Am J Epidemiol 2002; 156: 536-47.
94. IARC. IARC Monographs on the Evaluation of Carcinogenic Risk to Humans. A Review of Human Carcinogens: Arsenic, Metals Fibers and Dusts. Volume 100C. 2012. Lyon, France: International Agency for Research on Cancer.
Ref Type: Report
95. Inoue M, Yamamoto S, Kurahashi N et al. Daily total physical activity level and total cancer risk in men and women: results from a large-scale population-based cohort study in Japan. Am J Epidemiol 2008; 168: 391-403.
96. Inoue M, Noda M, Kurahashi N et al. Impact of metabolic factors on subsequent cancer risk: results from a large-scale population-based cohort study in Japan. Eur J Cancer Prev 2009; 18: 240-7.

97. Iso, Hiroyasu, Kubota et al. Nutrition and disease in the Japan Collaborative Cohort Study for Evaluation of Cancer (JACC). Asian Pac J Cancer Prev 2007; 8 Suppl: 35-80.
98. Ito Y, Wakai K, Suzuki K et al. Serum carotenoids and mortality from lung cancer: a case-control study nested in the Japan Collaborative Cohort (JACC) study. Cancer Sci 2003; 94: 57-63.
99. Ito Y, Kurata M, Hioki R et al. Cancer mortality and serum levels of carotenoids, retinol, and tocopherol: a population-based follow-up study of inhabitants of a rural area of Japan. Asian Pac J Cancer Prev 2005; 6: 10-5.
100. Ito Y, Wakai K, Suzuki K et al. Lung cancer mortality and serum levels of carotenoids, retinol, tocopherols, and folic acid in men and women: a case-control study nested in the JACC Study. J Epidemiol 2005; 15 Suppl 2: S140-S149.
101. Ito Y, Suzuki K, Ishii J et al. A population-based follow-up study on mortality from cancer or cardiovascular disease and serum carotenoids, retinol and tocopherols in Japanese inhabitants. Asian Pac J Cancer Prev 2006; 7: 533-46.
102. Jansen MC, Bueno-de-Mesquita HB, Rasanen L et al. Cohort analysis of fruit and vegetable consumption and lung cancer mortality in European men. 2001; 92: 913-8.
103. Jansen MC, Bueno-de-Mesquita HB, Feskens EJ et al. Quantity and variety of fruit and vegetable consumption and cancer risk. Nutr Cancer 2004; 48: 142-8.
104. Jee, Sun H, Yun et al. Body mass index and cancer risk in Korean men and women. Int J Cancer 2008; 123: 1892-6.
105. Jeng YL, Wu MH, Huang HB et al. The methylenetetrahydrofolate reductase 677C-->T polymorphism and lung cancer risk in a Chinese population. 2003; 23: 5149-52.
106. Jensen OM. Cancer risk among Danish male Seventh-Day Adventists and other temperance society members. 1983; 70: 1011-4.
107. Johansson M, Relton C, Ueland PM et al. Serum B vitamin levels and risk of lung cancer. JAMA 2010; 303: 2377-85.
108. Jung EJ, Shin A, Park SK et al. Alcohol consumption and mortality in the Korean Multi-Center Cancer Cohort Study. J Prev Med Public Health 2012; 45: 301-8.
109. Kabat, G C, Miller et al. Dietary intake of selected B vitamins in relation to risk of major cancers in women. Br J Cancer 2008; 99: 816-821a.
110. Kabat GC, Miller AB, Rohan TE. Body mass index and lung cancer risk in women. Epidemiology 2007; 18: 607-12.
111. Kabat GC, Kim M, Hunt JR et al. Body mass index and waist circumference in relation to lung cancer risk in the Women's Health Initiative. Am J Epidemiol 2008; 168: 158-169b.
112. Kabat GC, Anderson ML, Heo M et al. Adult stature and risk of cancer at different anatomic sites in a cohort of postmenopausal women. Cancer Epidemiol Biomarkers Prev 2013; 22: 1353-1363a.
113. Kabat GC, Heo M, Kamensky V et al. Adult height in relation to risk of cancer in a cohort of Canadian women. Int J Cancer 2013; 132: 1125-1132b.
114. Kabat GC, Heo M, Miller AB et al. Scaling of weight for height in relation to risk of cancer at different sites in a cohort of Canadian women. Am J Epidemiol 2013; 177: 93-101c.

115. Kabuto M, Imai H, Yonezawa C et al. Prediagnostic serum selenium and zinc levels and subsequent risk of lung and stomach cancer in Japan. Cancer Epidemiol Biomarkers Prev 1994; 3: 465-9.
116. Kamangar F, Qiao YL, Yu B et al. Lung cancer chemoprevention: a randomized, double-blind trial in Linxian, China. Cancer Epidemiol Biomarkers Prev 2006; 15: 1562-4.
117. Kapila K, Al-Ayadhy B, Francis IM et al. Subclassification of pulmonary non-small cell lung carcinoma in fine needle aspirates using a limited immunohistochemistry panel. J Cytol 2013; 30: 223-5.
118. Kark JD, Yaari S, Rasooly I et al. Are lean smokers at increased risk of lung cancer? The Israel Civil Servant Cancer Study. 1995; 155: 2409-16.
119. Key TJ, Thorogood M, Appleby PN et al. Dietary habits and mortality in 11,000 vegetarians and health conscious people: results of a 17 year follow up. 1996; 313: 775-9.
120. Key TJ, Appleby PN, Spencer EA et al. Cancer incidence in British vegetarians. Br J Cancer 2009; 101: 192-7.
121. Khan MM, Goto R, Kobayashi K et al. Dietary habits and cancer mortality among middle aged and older Japanese living in hokkaido, Japan by cancer site and sex. Asian Pac J Cancer Prev 2004; 5: 58-65.
122. Kilkkinen A, Knekt P, Heliovaara M et al. Vitamin D status and the risk of lung cancer: a cohort study in Finland. Cancer Epidemiol Biomarkers Prev 2008; 17: 3274-8.
123. Kim MK, Ko MJ, Han JT et al. Alcohol consumption and mortality from all-cause and cancers among 1.34 million Koreans: the results from the Korea national health insurance corporation's health examinee cohort in 2000. Alcohol use and mortality in the Japan Collaborative Cohort Study for Evaluation of Cancer (JACC). Cancer Causes Control 2010; 21: 2295-302.
124. Knekt P, Aromaa A, Maatela J et al. Serum vitamin A and subsequent risk of cancer: cancer incidence follow-up of the Finnish Mobile Clinic Health Examination Survey. Am J Epidemiol 1990; 132: 857-70.
125. Knekt P, Seppanen R, Jarvinen R et al. Dietary cholesterol, fatty acids, and the risk of lung cancer among men. Nutr Cancer 1991; 16: 267-275a.
126. Knekt P, Jarvinen R, Seppanen R et al. Dietary antioxidants and the risk of lung cancer. Am J Epidemiol 1991; 134: 471-479b.
127. Knekt P, Heliovaara M, Rissanen A et al. Leanness and lung-cancer risk. Int J Cancer 1991; 49: 208-213c.
128. Knekt P. Vitamin E and smoking and the risk of lung cancer. Ann N Y Acad Sci 1993; 686: 280-7.
129. Knekt P, Raitasalo R, Heliovaara M et al. Elevated lung cancer risk among persons with depressed mood. 1996; 144: 1096-103.
130. Knekt P, Marniemi J, Teppo L et al. Is low selenium status a risk factor for lung cancer? Am J Epidemiol 1998; 148: 975-82.

131. Knekt P, Jarvinen R, Teppo L et al. Role of various carotenoids in lung cancer prevention. J Natl Cancer Inst. J.Natl.Cancer Inst. 91, 182-184. 1999.
Ref Type: Journal (Full)
132. Knekt P, Kumpulainen J, Jarvinen R et al. Flavonoid intake and risk of chronic diseases. Am J Clin Nutr 2002; 76: 560-8.
133. Koh WP, Yuan JM, Wang R et al. Body mass index and smoking-related lung cancer risk in the Singapore Chinese Health Study. Br J Cancer 2010; 102: 610-4.
134. Kondo T, Hori Y, Yatsuya H et al. Lung cancer mortality and body mass index in a Japanese cohort: findings from the Japan Collaborative Cohort Study (JACC Study). Cancer Causes Control 2007; 18: 229-34.
135. Kono S, Ikeda M, Tokudome S et al. Cigarette smoking, alcohol and cancer mortality: A cohort study of male Japanese physicians. 1987; 78: 1323-8.
136. Kornitzer M, Valente F, De BD et al. Serum selenium and cancer mortality: a nested case-control study within an age- and sex-stratified sample of the Belgian adult population. Eur J Clin Nutr 2004; 58: 98-104.
137. Kromhout D. Essential micronutrients in relation to carcinogenesis. 1987; 45: 1361-7.
138. Kuriyama S, Tsubono Y, Hozawa A et al. Obesity and risk of cancer in Japan. Int J Cancer 2005; 113: 148-57.
139. Kuriyama S, Shimazu T, Ohmori K et al. Green tea consumption and mortality due to cardiovascular disease, cancer, and all causes in Japan: the Ohsaki study. JAMA 2006; 296: 1255-65.
140. Kvale G, Bjelke E, Gart JJ. Dietary habits and lung cancer risk. Int J Cancer 1983; 31: 397-405.
141. Lam, Tram K, Moore et al. Anthropometric measures and physical activity and the risk of lung cancer in never-smokers: a prospective cohort study. PloS one 2013; 8: 70672.
142. Lam TK, Ruczinski I, Helzlsouer KJ et al. Cruciferous vegetable intake and lung cancer risk: a nested case-control study matched on cigarette smoking. Cancer Epidemiol Biomarkers Prev 2010; 19: 2534-40.
143. Laukkanen, Jari A, Pukkala et al. Cardiorespiratory fitness, lifestyle factors and cancer risk and mortality in Finnish men. Eur J Cancer 2010; 46: 355-63.
144. Lee IM, Paffenbarger RSJ. Physical activity and its relation to cancer risk: a prospective study of college alumni. 1994; 26: 831-7.
145. Lee IM, Sesso HD, Paffenbarger RSJ. Physical activity and risk of lung cancer. 1999; 28: 620-5.
146. Lee IM, Cook NR, Manson JE et al. Beta-carotene supplementation and incidence of cancer and cardiovascular disease: the Women's Health Study. J Natl Cancer Inst 1999; 91: 2102-6.
147. Lee SY, Kim MT, Jee SH et al. Does hypertension increase mortality risk from lung cancer? A prospective cohort study on smoking, hypertension and lung cancer risk among Korean men. 2002; 20: 617-22.
148. Leitzmann, Michael F, Moore et al. Waist circumference as compared with body-mass index in predicting mortality from specific causes. PloS one 2011; 6: 18582.

149. Leitzmann MF, Koebnick C, Abnet CC et al. Prospective study of physical activity and lung cancer by histologic type in current, former, and never smokers. Am J Epidemiol 2009; 169: 542-53.
150. Leung CC, Lam TH, Yew WW et al. Lower lung cancer mortality in obesity. Int J Epidemiol 2011; 40: 174-82.
151. Li, Kuanrong, Kaaks et al. Dietary calcium and magnesium intake in relation to cancer incidence and mortality in a German prospective cohort (EPIC-Heidelberg). Cancer Causes Control 2011; 22: 1375-82.
152. Li K, Yao C, Dong L. [Correlationship between body mass index and mortality in the middle-aged and elderly population of Beijing City]. 2002; 36: 34-7.
153. Li Q, Kakizaki M, Kuriyama S et al. Green tea consumption and lung cancer risk: the Ohsaki study. Br J Cancer 2008; 99: 1179-84.
154. Li WQ, Kuriyama S, Li Q et al. Citrus consumption and cancer incidence: the Ohsaki cohort study. Int J Cancer 2010; 127: 1913-22.
155. Li Y, Yang H, Cao J. Association between alcohol consumption and cancers in the Chinese population--a systematic review and meta-analysis. PLoS One 2011; 6: e18776.
156. Lin J, Cook NR, Albert C et al. Vitamins C and E and beta carotene supplementation and cancer risk: a randomized controlled trial. J Natl Cancer Inst 2009; 101: 14-23.
157. Lin YS, Caffrey JL, Lin JW et al. Increased risk of cancer mortality associated with cadmium exposures in older Americans with low zinc intake. J Toxicol Environ Health A 2013; 76: 1-15.
158. Linseisen J, Wolfram G, Miller AB. Plasma 7beta-hydroxycholesterol as a possible predictor of lung cancer risk. 2002; 11: 1630-7.
159. Linseisen J, Rohrmann S, Miller AB et al. Fruit and vegetable consumption and lung cancer risk: updated information from the European Prospective Investigation into Cancer and Nutrition (EPIC). Int J Cancer 2007; 121: 1103-14.
160. Linseisen J, Rohrmann S, Bueno-de-Mesquita B et al. Consumption of meat and fish and risk of lung cancer: results from the European Prospective Investigation into Cancer and Nutrition. Cancer Causes Control 2011; 22: 909-18.
161. Lippman SM, Klein EA, Goodman PJ et al. Effect of selenium and vitamin E on risk of prostate cancer and other cancers: the Selenium and Vitamin E Cancer Prevention Trial (SELECT). JAMA 2009; 301: 39-51.
162. Liu Y, Sobue T, Otani T et al. Vegetables, Fruit Consumption and Risk of Lung Cancer Among Middle-Aged Japanese Men and Women: Jphc Study. 2004; 15: 349-57.
163. Luo J, Shen L, Zheng D. Association between vitamin C intake and lung cancer: a dose-response meta-analysis. Sci Rep 2014; 4: 6161.
164. Mai V, Kant AK, Flood A et al. Diet quality and subsequent cancer incidence and mortality in a prospective cohort of women. Int J Epidemiol 2005; 34: 54-60.
165. Mannisto S, Smith-Warner SA, Spiegelman D et al. Dietary carotenoids and risk of lung cancer in a pooled analysis of seven cohort studies. Cancer Epidemiol Biomarkers Prev 2004; 13: 40-8.

166. Menkes MS, Comstock GW, Vuilleumier JP et al. Serum beta-carotene, vitamins A and E, selenium, and the risk of lung cancer. N Engl J Med 1986; 315: 1250-4.
167. Michaud DS, Feskanich D, Rimm EB et al. Intake of specific carotenoids and risk of lung cancer in 2 prospective US cohorts. Am J Clin Nutr 2000; 72: 990-7.
168. Miller AB. Vegetables and fruits and lung cancer. 2002; 156: 85-7.
169. Miller AB, Altenburg HP, Bueno-de-Mesquita B et al. Fruits and vegetables and lung cancer: Findings from the European Prospective Investigation into Cancer and Nutrition. 2004; 108: 269-76.
170. Min KB, Min JY. Serum carotenoid levels and risk of lung cancer death in US adults. Cancer Sci 2014; 105: 736-43.
171. Murata M, Takayama K, Choi BC et al. A nested case-control study on alcohol drinking, tobacco smoking, and cancer. 1996; 20: 557-65.
172. Musk AW, de Klerk NH, Ambrosini GL et al. Vitamin A and cancer prevention I: observations in workers previously exposed to asbestos at Wittenoom, Western Australia. Int J Cancer 1998; 75: 355-61.
173. Nagano J, Kono S, Preston DL et al. A prospective study of green tea consumption and cancer incidence, Hiroshima and Nagasaki (Japan). 2001; 12: 501-8.
174. Nakachi K, Matsuyama S, Miyake S et al. Preventive effects of drinking green tea on cancer and cardiovascular disease: epidemiological evidence for multiple targeting prevention. Biofactors 2000; 13: 49-54.
175. Nakadaira H, Endoh K, Katagiri M et al. Elevated mortality from lung cancer associated with arsenic exposure for a limited duration. J Occup Environ Med 2002; 44: 291-9.
176. Nakaya N, Tsubono Y, Kuriyama S et al. Alcohol consumption and the risk of cancer in Japanese men: the Miyagi cohort study. Eur J Cancer Prev 2005; 14: 169-74.
177. Neuhouser, Marian L, Wassertheil S et al. Multivitamin use and risk of cancer and cardiovascular disease in the Women's Health Initiative cohorts. Arch Intern Med 2009; 169: 294-304.
178. Neuhouser ML, Patterson RE, Thornquist MD et al. Fruits and vegetables are associated with lower lung cancer risk only in the placebo arm of the beta-carotene and retinol efficacy trial (CARET). Cancer Epidemiol Biomarkers Prev 2003; 12: 350-8.
179. Nishino, Yoshikazu, Wakai et al. Alcohol consumption and lung cancer mortality in Japanese men: results from Japan collaborative cohort (JACC) study. J Epidemiol 2006; 16: 49-56.
180. Nomura A, Heilbrun LK, Stemmermann GN. Prospective study of coffee consumption and the risk of cancer. 1986; 76: 587-90.
181. Nomura A, Heilbrun LK, Morris JS et al. Serum selenium and the risk of cancer, by specific sites: case-control analysis of prospective data. J Natl Cancer Inst 1987; 79: 103-8.
182. Nomura AM, Stemmermann GN, Heilbrun LK et al. Serum vitamin levels and the risk of cancer of specific sites in men of Japanese ancestry in Hawaii. Cancer Res 1985; 45: 2369-72.

183. Ocke MC, Bueno-de-Mesquita HB, Feskens EJ et al. Repeated measurements of vegetables, fruits, beta-carotene, and vitamins C and E in relation to lung cancer. The Zutphen Study. Am J Epidemiol 1997; 145: 358-65.
184. Oh SW, Yoon YS, Shin SA. Effects of excess weight on cancer incidences depending on cancer sites and histologic findings among men: Korea National Health Insurance Corporation Study. J Clin Oncol 2005; 23: 4742-54.
185. Olson JE, Yang P, Schmitz K et al. Differential association of body mass index and fat distribution with three major histologic types of lung cancer: evidence from a cohort of older women. Am J Epidemiol 2002; 156: 606-15.
186. Omenn GS, Goodman GE, Thornquist MD et al. Effects of a combination of beta carotene and vitamin A on lung cancer and cardiovascular disease. N Engl J Med 1996; 334: 1150-5.
187. Ordonez-Mena JM, Schottker B, Haug U et al. Serum 25-hydroxyvitamin d and cancer risk in older adults: results from a large german prospective cohort study. Cancer Epidemiol Biomarkers Prev 2013; 22: 905-16.
188. Orentreich N, Matias JR, Vogelman JH et al. The predictive value of serum (beta)-carotene for subsequent development of lung cancer. 1991; 16: 167-9.
189. Ozasa K, Watanabe Y, Ito Y et al. Dietary habits and risk of lung cancer death in a large-scale cohort study (JACC Study) in Japan by sex and smoking habit. Jpn J Cancer Res 2001; 92: 1259-69.
190. Ozasa K. Alcohol use and mortality in the Japan Collaborative Cohort Study for Evaluation of Cancer (JACC). Asian Pac J Cancer Prev 2007; 8 Suppl: 81-8.
191. Paganini-Hill A, Chao A, Ross RK et al. Vitamin A, beta-carotene, and the risk of cancer: a prospective study. J Natl Cancer Inst 1987; 79: 443-8.
192. Park SY, Murphy SP, Wilkens LR et al. Multivitamin use and the risk of mortality and cancer incidence: the multiethnic cohort study. Am J Epidemiol 2011; 173: 906-14.
193. Parr CL, Batty GD, Lam TH et al. Body-mass index and cancer mortality in the Asia-Pacific Cohort Studies Collaboration: pooled analyses of 424,519 participants. Lancet Oncol 2010; 11: 741-52.
194. Pavanello S, Fedeli U, Mastrangelo G et al. Role of CYP1A2 polymorphisms on lung cancer risk in a prospective study. Cancer Genet 2012; 205: 278-84.
195. Pollack ES, Nomura AM, Heilbrun LK et al. Prospective study of alcohol consumption and cancer. N Engl J Med 1984; 310: 617-21.
196. Potter JD, Sellers TA, Folsom AR et al. Alcohol, beer, and lung cancer in postmenopausal women. The Iowa Women's Health Study. 1992; 2: 587-95.
197. Prentice RL, Thomson CA, Caan B et al. Low-fat dietary pattern and cancer incidence in the Women's Health Initiative Dietary Modification Randomized Controlled Trial. J Natl Cancer Inst 2007; 99: 1534-43.
198. Prentice RL, Shaw PA, Bingham SA et al. Biomarker-calibrated energy and protein consumption and increased cancer risk among postmenopausal women. Am J Epidemiol 2009; 169: 977-89.
199. Prescott E, Gronbaek M, Becker U et al. Alcohol intake and the risk of lung cancer: influence of type of alcoholic beverage. 1999; 149: 463-70.

200. Rapp K, Schroeder J, Klenk J et al. Obesity and incidence of cancer: a large cohort study of over 145,000 adults in Austria. Br J Cancer 2005; 93: 1062-7.
201. Ratnasinghe D, Forman MR, Tangrea JA et al. Serum carotenoids are associated with increased lung cancer risk among alcohol drinkers, but not among non-drinkers in a cohort of tin miners. Alcohol Alcohol 2000; 35: 355-60.
202. Ratnasinghe DL, Yao SX, Forman M et al. Gene-environment interactions between the codon 194 polymorphism of XRCC1 and antioxidants influence lung cancer risk. Anticancer Res 2003; 23: 627-32.
203. Reeves GK, Pirie K, Beral V et al. Cancer incidence and mortality in relation to body mass index in the Million Women Study: cohort study. BMJ 2007; 335: 1134.
204. Reid ME, Duffield-Lillico AJ, Garland L et al. Selenium supplementation and lung cancer incidence: an update of the nutritional prevention of cancer trial. Cancer Epidemiol Biomarkers Prev 2002; 11: 1285-91.
205. Rohan TE, Jain M, Howe GR et al. A cohort study of dietary carotenoids and lung cancer risk in women (Canada). Cancer Causes Control 2002; 13: 231-7.
206. Rohrmann S, Linseisen J, Boshuizen HC et al. Ethanol intake and risk of lung cancer in the European Prospective Investigation into Cancer and Nutrition (EPIC). Am J Epidemiol 2006; 164: 1103-14.
207. Roswall N, Olsen A, Christensen J et al. Source-specific effects of micronutrients in lung cancer prevention. Lung Cancer 2009; 67: 275-81.
208. Rundle A, Richie J, Steindorf K et al. Physical activity and lung cancer among non-smokers: a pilot molecular epidemiological study within EPIC. Biomarkers 2010; 15: 20-30.
209. Sakoda LC, Loomis MM, Doherty JA et al. Chromosome 15q24-25.1 variants, diet, and lung cancer susceptibility in cigarette smokers. Cancer Causes Control 2011; 22: 449-61.
210. Salonen JT, Salonen R, Lappetelainen R et al. Risk of cancer in relation to serum concentrations of selenium and vitamins A and E: matched case-control analysis of prospective data. Br Med J (Clin Res Ed) 1985; 290: 417-20.
211. Satia JA, Littman A, Slatore CG et al. Long-term use of beta-carotene, retinol, lycopene, and lutein supplements and lung cancer risk: results from the VITamins And Lifestyle (VITAL) study. Am J Epidemiol 2009; 169: 815-28.
212. Sauvaget C, Nagano J, Hayashi M et al. Vegetables and fruit intake and cancer mortality in the Hiroshima/Nagasaki Life Span Study. 2003; 88: 689-94.
213. Sawada N, Iwasaki M, Inoue M et al. Dietary arsenic intake and subsequent risk of cancer: the Japan Public Health Center-based (JPHC) Prospective Study. Cancer Causes Control 2013; 24: 1403-15.
214. Schmid D, Leitzmann MF. Television viewing and time spent sedentary in relation to cancer risk: a meta-analysis. J Natl Cancer Inst 2014; 106.
215. Schnohr P, Gronbaek M, Petersen L et al. Physical activity in leisure-time and risk of cancer: 14-year follow-up of 28,000 Danish men and women. 2005; 33: 244-9.
216. Seidell JC, Verschuren WM, van Leer EM et al. Overweight, underweight, and mortality. A prospective study of 48,287 men and women. 1996; 156: 958-63.

217. Sellers TA, Potter JD, Folsom AR. Association of incident lung cancer with family history of female reproductive cancers: the Iowa Women's Health Study. 1991; 8: 199-208.
218. Seow A, Koh WP, Wang R et al. Reproductive variables, soy intake, and lung cancer risk among nonsmoking women in the Singapore Chinese Health Study. Cancer Epidemiol Biomarkers Prev 2009; 18: 821-7.
219. SEVERSON RK, Nomura AMY, Gove JS et al. A prospective analysis of physical activity and cancer. American-journal-of-epidemiology 522; 1989; 130: 3.
220. Shekelle RB, Rossof AH, Stamler J. Dietary cholesterol and incidence of lung cancer: the Western Electric Study. Am J Epidemiol 1991; 134: 480-4.
221. Shekelle RB, Tangney CC, Rossof AH et al. Serum cholesterol, beta-carotene, and risk of lung cancer. Epidemiology 1992; 3: 282-7.
222. Shen C, Schooling CM, Chan WM et al. Alcohol intake and death from cancer in a prospective Chinese elderly cohort study in Hong Kong. J Epidemiol Community Health 2013; 67: 813-20.
223. Shibata A, Paganini-Hill A, Ross RK et al. Intake of vegetables, fruits, beta-carotene, vitamin C and vitamin supplements and cancer incidence among the elderly: a prospective study. Br J Cancer 1992; 66: 673-9.
224. Shibata A, Paganini-Hill A, Ross RK et al. Dietary beta-carotene, cigarette smoking, and lung cancer in men. 1992; 3: 207-14.
225. Shimazu T, Inoue M, Sasazuki S et al. Alcohol and risk of lung cancer among Japanese men: data from a large-scale population-based cohort study, the JPHC study. Cancer Causes Control 2008; 19: 1095-102.
226. Shimazu T, Inoue M, Sasazuki S et al. Isoflavone intake and risk of lung cancer: a prospective cohort study in Japan. Am J Clin Nutr 2010; 91: 722-8.
227. Sinner P, Folsom AR, Harnack L et al. The association of physical activity with lung cancer incidence in a cohort of older women: the Iowa Women's Health Study. Cancer Epidemiol Biomarkers Prev 2006; 15: 2359-63.
228. Skaaby T, Husemoen LL, Thuesen BH et al. Prospective population-based study of the association between serum 25-hydroxyvitamin-D levels and the incidence of specific types of cancer. Cancer Epidemiol Biomarkers Prev 2014; 23: 1220-9.
229. Skuladottir H, Tjoenneland A, Overvad K et al. Does insufficient adjustment for smoking explain the preventive effects of fruit and vegetables on lung cancer? 2004; 45: 1-10.
230. Slatore CG, Littman AJ, Au DH et al. Long-term use of supplemental multivitamins, vitamin C, vitamin E, and folate does not reduce the risk of lung cancer. Am J Respir Crit Care Med 2008; 177: 524-30.
231. Smith-Warner SA, Ritz J, Hunter DJ et al. Dietary fat and risk of lung cancer in a pooled analysis of prospective studies. Cancer Epidemiol Biomarkers Prev 2002; 11: 987-92.
232. Smith-Warner SA, Spiegelman D, Yaun SS et al. Fruits, vegetables and lung cancer: a pooled analysis of cohort studies. Int J Cancer 2003; 107: 1001-11.
233. Smith L, Brinton LA, Spitz MR et al. Body mass index and risk of lung cancer among never, former, and current smokers. J Natl Cancer Inst 2012; 104: 778-89.

234. Song J, Su H, Wang BL et al. Fish consumption and lung cancer risk: systematic review and meta-analysis. Nutr Cancer 2014; 66: 539-549a.
235. Song X, Pukkala E, Dyba T et al. Body mass index and cancer incidence: the FINRISK study. Eur J Epidemiol 2014; 29: 477-487b.
236. Song YM, Sung J, Ha M. Obesity and risk of cancer in postmenopausal Korean women. J Clin Oncol 2008; 26: 3395-402.
237. Sormunen, Jorma, Backmand et al. Lifetime physical activity and cancer incidence-A cohort study of male former elite athletes in Finland. J Sci Med Sport 2013.
238. Speizer FE, Colditz GA, Hunter DJ et al. Prospective study of smoking, antioxidant intake, and lung cancer in middle-aged women (USA). Cancer Causes Control 1999; 10: 475-82.
239. Sprague BL, Trentham-Dietz A, Klein BE et al. Physical activity, white blood cell count, and lung cancer risk in a prospective cohort study. Cancer Epidemiol Biomarkers Prev 2008; 17: 2714-22.
240. Stahelin HB, Rosel F, Buess E et al. Cancer, vitamins, and plasma lipids: prospective Basel study. J Natl Cancer Inst 1984; 73: 1463-8.
241. Stahelin HB, Gey KF, Brubacher G. Plasma vitamin C and cancer death: the prospective Basel Study. 1987; 498: 124-31.
242. Steenland K, Nowlin S, Palu S. Cancer Incidence in the National-Health-and-Nutrition-Survey-I Follow-up Data - Diabetes, Cholesterol, Pulse, and Physical-Activity. 1995; 4: 807-11.
243. Steindorf K, Friedenreich C, Linseisen J et al. Physical activity and lung cancer risk in the European Prospective Investigation into Cancer and Nutrition Cohort. Int J Cancer 2006; 119: 2389-97.
244. Steinmetz KA, Potter JD, Folsom AR. Vegetables, fruit, and lung cancer in the Iowa Women's Health Study. Cancer Res 1993; 53: 536-43.
245. Stemmermann GN, Nomura AMY, Chyou PH et al. Prospective Study Of Alcohol Intake And Large Bowel Cancer. Digestive-Diseases-and-Sciences 1414; 1990.
246. Stensvold I, Jacobsen BK. Coffee and cancer: a prospective study of 43,000 Norwegian men and women. 1994; 5: 401-8.
247. Suadicani P, Hein HO, Gyntelberg F. Serum selenium level and risk of lung cancer mortality: a 16-year follow-up of the Copenhagen Male Study. Eur Respir J 2012; 39: 1443-8.
248. Sugiyama K, Kuriyama S, Akhter M et al. Coffee consumption and mortality due to all causes, cardiovascular disease, and cancer in Japanese women. J Nutr 2010; 140: 1007-13.
249. Sun JY, Shi L, Gao XD et al. Physical activity and risk of lung cancer: a meta-analysis of prospective cohort studies. Asian Pac J Cancer Prev 2012; 13: 3143-7.
250. Sung J, Song YM, Lawlor DA et al. Height and site-specific cancer risk: A cohort study of a korean adult population. Am J Epidemiol 2009; 170: 53-64.
251. Suzuki E, Yorifuji T, Takao S et al. Green tea consumption and mortality among Japanese elderly people: the prospective Shizuoka elderly cohort. Ann Epidemiol 2009; 19: 732-9.

252. Takata, Yumie, Cai et al. Dietary B vitamin and methionine intakes and lung cancer risk among female never smokers in China. Cancer Causes Control 2012; 23: 1965-75.
253. Takata Y, Xiang YB, Yang G et al. Intakes of fruits, vegetables, and related vitamins and lung cancer risk: results from the Shanghai Men's Health Study (2002-2009). Nutr Cancer 2013; 65: 51-61.
254. Takezaki T, Inoue M, Kataoka H et al. Diet and lung cancer risk from a 14-year population-based prospective study in Japan: with special reference to fish consumption. Nutr Cancer 2003; 45: 160-7.
255. Tamosiunas A, Reklaitiene R, Jureniene K et al. [Time trends in mortality from malignant tumors and lung cancer during the period 1971-2000 and the risk of death in the middle-aged Kaunas men]. 2003; 39: 596-603.
256. Tang N, Wu Y, Zhou B et al. Green tea, black tea consumption and risk of lung cancer: a meta-analysis. Lung Cancer 2009; 65: 274-83.
257. Tang N, Wu Y, Ma J et al. Coffee consumption and risk of lung cancer: a meta-analysis. Lung Cancer 2010; 67: 17-22.
258. Tardon A, Lee WJ, Delgado-Rodriguez M et al. Leisure-time physical activity and lung cancer: a meta-analysis. Cancer Causes Control 2005; 16: 389-97.
259. Tasevska N, Sinha R, Kipnis V et al. A prospective study of meat, cooking methods, meat mutagens, heme iron, and lung cancer risks. Am J Clin Nutr 2009; 89: 1884-94.
260. Tasevska N, Cross AJ, Dodd KW et al. No effect of meat, meat cooking preferences, meat mutagens or heme iron on lung cancer risk in the prostate, lung, colorectal and ovarian cancer screening trial. Int J Cancer 2011; 128: 402-11.
261. Thun MJ, Hannan LM, DeLancey JO. Alcohol consumption not associated with lung cancer mortality in lifelong nonsmokers. Cancer Epidemiol Biomarkers Prev 2009; 18: 2269-72.
262. Thune I, Lund E. The influence of physical activity on lung-cancer risk: A prospective study of 81,516 men and women. 1997; 70: 57-62.
263. Toriola AT, Kurl S, Laukkanen JA et al. Does binge drinking increase the risk of lung cancer: results from the Findrink study. Eur J Public Health 2009; 19: 389-93.
264. Tsai SP, Donnelly RP, Wendt JK. Obesity and mortality in a prospective study of a middle-aged industrial population. J Occup Environ Med 2006; 48: 22-7.
265. Tsuda T, Nagira T, Yamamoto M et al. Malignant neoplasms among residents who drank well water contaminated by arsenic from a king's yellow factory. 1989; 11 Suppl: 289-301.
266. Tsuda T, Babazono A, Yamamoto E et al. Ingested arsenic and internal cancer: a historical cohort study followed for 33 years. Am J Epidemiol 1995; 141: 198-209.
267. Tulinius H, Sigfusson N, Sigvaldason H et al. Risk factors for malignant diseases: a cohort study on a population of 22,946 Icelanders. Cancer Epidemiol Biomarkers Prev 1997; 6: 863-73.
268. Tuyns AJ, Audigier JC. Double wave cohort increase for oesophageal and laryngeal cancer in France in relation to reduced alcohol consumption during the second world war. 1976; 14: 197-208.

269. Uehara Y, Kiyohara C. Alcohol consumption and lung cancer risk among Japanese: a meta-analysis. Fukuoka Igaku Zasshi 2010; 101: 101-8.
270. Ujiie S, Kikuchi H. The relation between serum selenium value and cancer in Miyagi, Japan: 5-year follow up study. Tohoku J Exp Med 2002; 196: 99-109.
271. van den Brandt PA, Goldbohm RA, van ', V et al. A prospective cohort study on selenium status and the risk of lung cancer. Cancer Res 1993; 53: 4860-5.
272. van Kruijsdijk RC, van der Graaf Y, Peeters PH et al. Cancer risk in patients with manifest vascular disease: effects of smoking, obesity, and metabolic syndrome. Cancer Epidemiol Biomarkers Prev 2013; 22: 1267-77.
273. Veierod MB, Laake P, Thelle DS. Dietary fat intake and risk of lung cancer: a prospective study of 51,452 Norwegian men and women. Eur J Cancer Prev 1997; 6: 540-9.
274. Virtamo J, Pietinen P, Huttunen JK et al. Incidence of cancer and mortality following alpha-tocopherol and beta-carotene supplementation: a postintervention follow-up. JAMA 2003; 290: 476-85.
275. Virtamo J, Taylor PR, Kontto J et al. Effects of alpha-tocopherol and beta-carotene supplementation on cancer incidence and mortality: 18-year postintervention follow-up of the Alpha-tocopherol, Beta-carotene Cancer Prevention Study. Int J Cancer 2014; 135: 178-85.
276. Voorrips LE, Goldbohm RA, Brants HA et al. A prospective cohort study on antioxidant and folate intake and male lung cancer risk. Cancer Epidemiol Biomarkers Prev 2000; 9: 357-365a.
277. Voorrips LE, Goldbohm RA, Verhoeven DT et al. Vegetable and fruit consumption and lung cancer risk in the Netherlands Cohort Study on diet and cancer. Cancer Causes Control 2000; 11: 101-115b.
278. Wakai K, Matsuo K, Nagata C et al. Lung cancer risk and consumption of vegetables and fruit: an evaluation based on a systematic review of epidemiological evidence from Japan. Jpn J Clin Oncol 2011; 41: 693-708.
279. Wald N, Idle M, Boreham J et al. Low serum-vitamin-A and subsequent risk of cancer. Preliminary results of a prospective study. Lancet 1980; 2: 813-5.
280. Walter, Roland B, Brasky et al. Height as an explanatory factor for sex differences in human cancer. J Natl Cancer Inst 2013; 105: 860-8.
281. Wang L, Zhang X, Liu J et al. Tea consumption and lung cancer risk: a meta-analysis of case-control and cohort studies. Nutrition 2014; 30: 1122-7.
282. Wang L, Sesso HD, Glynn RJ et al. Vitamin E and C supplementation and risk of cancer in men: posttrial follow-up in the Physicians' Health Study II randomized trial. Am J Clin Nutr 2014; 100: 915-23.
283. Wang LD, Hammond EC. Lung cancer, fruit, green salad and vitamin pills. 1985; 98: 206-10.
284. Wang Y, Yu X, Wu Y et al. Coffee and tea consumption and risk of lung cancer: a dose-response analysis of observational studies. Lung Cancer 2012; 78: 169-70.
285. Wannamethee G, Shaper AG. Body weight and mortality in middle aged British men: impact of smoking. 1989; 299: 1497-502.

286. Wannamethee SG, Shaper AG, Walker M. Physical Activity and Risk of Cancer in Middle-Aged Men. 2001; 85: 1311-6.
287. Weinstein SJ, Yu K, Horst RL et al. Serum 25-hydroxyvitamin D and risk of lung cancer in male smokers: a nested case-control study. PLoS One 2011; 6: e20796.
288. Whitley E, Martin RM, Smith GD et al. Childhood stature and adult cancer risk: the Boyd Orr cohort. Cancer Causes Control 2009; 20: 243-51.
289. Wie GA, Cho YA, Kang HH et al. Red meat consumption is associated with an increased overall cancer risk: a prospective cohort study in Korea. Br J Nutr 2014; 112: 238-47.
290. Woo HD, Kim J. Dietary flavonoid intake and smoking-related cancer risk: a meta-analysis. PLoS One 2013; 8: e75604.
291. Woodson K, Tangrea JA, Barrett MJ et al. Serum alpha-tocopherol and subsequent risk of lung cancer among male smokers. 1999; 91: 1738-43.
292. Wright ME, Park Y, Subar AF et al. Intakes of fruit, vegetables, and specific botanical groups in relation to lung cancer risk in the NIH-AARP Diet and Health Study. Am J Epidemiol 2008; 168: 1024-34.
293. Wu QJ, Xie L, Zheng W et al. Cruciferous vegetables consumption and the risk of female lung cancer: a prospective study and a meta-analysis. Ann Oncol 2013; 24: 1918-24.
294. Wu QJ, Xiang YB, Yang G et al. Vitamin E intake and the lung cancer risk among female nonsmokers: A report from the Shanghai Women's Health Study. Int J Cancer 2014.
295. Wu SH, Liu Z. Soy food consumption and lung cancer risk: a meta-analysis using a common measure across studies. Nutr Cancer 2013; 65: 625-32.
296. Xue XJ, Gao Q, Qiao JH et al. Red and processed meat consumption and the risk of lung cancer: a dose-response meta-analysis of 33 published studies. Int J Clin Exp Med 2014; 7: 1542-53.
297. Yang G, Shu XO, Chow WH et al. Soy food intake and risk of lung cancer: evidence from the Shanghai Women's Health Study and a meta-analysis. Am J Epidemiol 2012; 176: 846-55.
298. Yang L, Yang G, Zhou M et al. Body mass index and mortality from lung cancer in smokers and nonsmokers: a nationally representative prospective study of 220,000 men in China. Int J Cancer 2009; 125: 2136-43.
299. Yang L, Zhou M, Sherliker P et al. Alcohol drinking and overall and cause-specific mortality in China: nationally representative prospective study of 220,000 men with 15 years of follow-up. Int J Epidemiol 2012; 41: 1101-1113a.
300. Yang WS, Wong MY, Vogtmann E et al. Meat consumption and risk of lung cancer: evidence from observational studies. Ann Oncol 2012; 23: 3163-3170b.
301. Yang Y, Dong J, Sun K et al. Obesity and incidence of lung cancer: a meta-analysis. Int J Cancer 2013; 132: 1162-9.
302. Yong LC, Brown CC, Schatzkin A et al. Intake of vitamins E, C, and A and risk of lung cancer. The NHANES I epidemiologic followup study. First National Health and Nutrition Examination Survey. 1997; 146: 231-43.

303. Yuan JM, Ross RK, Chu XD et al. Prediagnostic levels of serum beta-cryptoxanthin and retinol predict smoking-related lung cancer risk in Shanghai, China. Cancer Epidemiol Biomarkers Prev 2001; 10: 767-73.
304. Yuan JM, Stram DO, Arakawa K et al. Dietary cryptoxanthin and reduced risk of lung cancer: the Singapore Chinese Health Study. Cancer Epidemiol Biomarkers Prev 2003; 12: 890-8.
305. Yun, Young H, Lim et al. Dietary preference, physical activity, and cancer risk in men: national health insurance corporation study. BMC Cancer 2008; 8: 366.
306. Zhang YF, Zhou L, Zhang HW et al. Association between folate intake and the risk of lung cancer: a dose-response meta-analysis of prospective studies. PLoS One 2014; 9: e93465.
307. Zhuo H, Smith AH, Steinmaus C. Selenium and lung cancer: a quantitative analysis of heterogeneity in the current epidemiological literature. Cancer Epidemiol Biomarkers Prev 2004; 13: 771-8.

Appendix 1

a) Fruit or vegetable items investigated by each study

Several studies investigated fruit and vegetables, vegetables, cruciferous vegetables, green leafy vegetables, fruits, and citrus fruits and lung cancer risk. The fruit or vegetable items investigated by each study are indicated with a cross in the list below:

WCRF code	Author	Year	Country	Study Description	Fruit and vegetables	Vegetables	Cruciferous Vegetables	Green leafy vegetables	Fruits	Citrus fruit
LUN26882	Wie	2014	Korea	Korea 2004-2013	x					
LUN26881	Bradbury	2014	Europe	EPIC		x			x	
LUN26858	Gnagnarella	2013	Italy	COSMOS	x	x			x	x
LUN26860	Takata	2013	China	SMHS	x	x		x	x	x
LUN26862	Wu	2013	China	SWHS			x			
LUN20332	Pavanello	2012	Europe	DCH		x			x	
LUN26859	Takata	2012	China	SWHS		x	x	x	x	
LUN20351	Sakoda	2011	USA	CARET		x	x		x	x
LUN20324	Fowke	2011	China	SWHS			x			
LUN20322	Büchner	2010	Europe	EPIC	x	x				
LUN20360	Büchner	2010	Europe	EPIC	x	x		x	x	x
LUN20328	Lam	2010	USA	CLUE II			x			
LUN26872	Li	2010	Japan	OCS						x
LUN20353	Tasevska	2009	USA	NIH-AARP	x					
LUN20265	George	2009	USA	NIH- AARP		x			x	
LUN20344	Slatore	2008	USA	VITAL	x					
LUN20306	Wright	2008	USA	NIH-AARP	x	x	x		x	x
LUN20338	Cutler	2008	USA	IWHS						x

WCRF code	Author	Year	Country	Study Description	Fruit and vegetables	Vegetables	Cruciferous Vegetables	Green leafy vegetables	Fruits	Citrus fruit
LUN20341	Kabat	2008	USA	WHI-DM and OS					x	
LUN20323	Linseisen	2007	Europe	EPIC	x	x		x	x	x
LUN20294	Iso	2007	Japan	JACC						x
LUN00068	Khan	2004	Japan	Hokkaido Study	x	x		x		
LUN10203	Liu	2004	Japan	JPHC	x	x			x	
LUN00169	Miller	2004	Europe	EPIC	x		x	x	x	
LUN05185	Skuladottir	2004	Denmark	DCHS	x	x			x	
LUN16965	Alavanja	2004	USA	AHS		x			x	
LUN19603	Jansen	2004	Netherlands	Zutphen Study		x			x	
LUN00354	Neuhouser	2003	USA	CARET	x	x	x			x
LUN05721	Sauvaget	2003	Japan	LSS		x			x	
LUN00268	Takezaki	2003	Japan	Aichi Study		x		x	x	
LUN00442	Miller	2002	Europe	EPIC	x	x	x		x	
LUN00515	Holick	2002	Finland	ATBC		x			x	
LUN00857	Jansen	2001	Europe	SCS	x				x	
LUN00725	Ozasa	2001	Japan	JACC	x	x		x	x	x
LUN00745	Hirvonen	2001	Finland	ATBC					x	
LUN00986	Feskanich	2000	USA	NHS+ HPFS	x	x	x	x	x	x
LUN01162	Voorrips	2000	Netherlands	NLCS	x	x	x	x	x	x
LUN01416	Knekt	1999	Finland	HES Finland	x	x			x	
LUN01255	Speizer	1999	USA	NHS	x		x	x	x	x
LUN01778	Yong	1997	USA	NHANES I	x					
LUN01779	Knekt	1997	Finland	HES Finland	x	x			x	
LUN01851	Ocke	1997	Netherlands	Zutphen Study		x			x	
LUN01468	Fu	1997	Japan	Nagoya,1983-2000					x	
LUN01947	Key	1996	UK	HFSS	x				x	

WCRF code	Author	Year	Country	Study Description	Fruit and vegetables	Vegetables	Cruciferous Vegetables	Green leafy vegetables	Fruits	Citrus fruit
LUN02740	Steinmetz	1993	USA	IWHS	x	x	x	x	x	
LUN02684	Knekt	1993	Finland	HES Finland					x	
LUN08664	Shibata	1992	USA	LWS	x	x			x	
LUN02888	Chow	1992	USA	LBS		x	x		x	
LUN03076	Fraser	1991	USA	AHS	x				x	
LUN03018	Knekt	1991	Finland	HES Finland		x			x	
LUN03076	Fraser	1991	USA	AHS					x	x
LUN03765	Kromhout	1987	Netherlands	Zutphen Study					x	x
LUN03946	Stahelin	1986	Switzerland	Basel Study						x
LUN04098	Wang	1985	USA	USA 1959-1970	x	x			x	
LUN04322	Kvåle	1983	Norway	Norway, 1967-1978	x	x	x	x	x	

b) Anthropometric characteristics investigated by each study

Several studies investigated BMI, weight, height, waist circumference, and waist-to-hip ratio and lung cancer risk. The anthropometric characteristics investigated by each study are indicated with a cross in the list below:

WCRF code	Author	Year	Country	Study description	BMI	Height	Weight	Waist circumference	Waist-to-hip-ratio
LUN26876	Bhaskaran	2014	UK	CPRD	x				
LUN26877	Song	2014	Finland	FINRISK	x				
LUN26882	Wie	2014	Korea	Korea 2004-2013	x				
LUN26857	Bethea	2013	USA	BWHS	x			x	x
LUN26852	Butler	2013	China	SCHS	x				
LUN20274	Kabat	2013	Canada	CNBSS		x			
LUN20369	Kabat	2013	USA	WHI		x			
LUN26868	Lam	2013	USA	NIH-AARP	x			x	x
LUN20316	Lin	2013	USA	NHANES III	x				
LUN20372	van Kruijsdijk	2013	Netherlands	SMART	x			x	
LUN20382	Walter	2013	USA	VITAL		x			
LUN20288	Chen	2012	China	CNRPCS	x				
LUN20268	Kabat	2012	Canada	CNBSS			x		
LUN20334	Smith	2012	USA	NIH-AARP	x				
LUN20302	Dehal	2011	USA	NHEFS	x				
LUN26869	Green	2011	UK	MWS		x			
LUN26849	Leitzmann	2011	USA	NIH- AARP	x			x	
LUN20325	Leung	2011	Hong Kong	CECS	x				
LUN20291	Andreotti	2010	USA	AHS	x				
LUN20359	Koh	2010	China	SCHS	x				
LUN26864	Laukkanen	2010	Finland	KIHD	x				

WCRF code	Author	Year	Country	Study description	BMI	Height	Weight	Waist circumference	Waist-to-hip-ratio
LUN20272	Inoue	2009	Japan	JPHC	x				
LUN20263	Prentice	2009	USA	WHI	x				
LUN20261	Sung	2009	Korea	KNHIC		x			
LUN20312	Whitley	2009	UK	BOCS		x			
LUN20349	Yang	2009	China	CNRPCS	x				
LUN20283	Jee	2008	Korea	KNHIC	x				
LUN20341	Kabat	2008	USA	WHI-DM and OS	x	x	x	x	x
LUN20344	Slatore	2008	USA	VITAL	x				
LUN20309	Song	2008	Korea	KNHIC	x				
LUN20278	Fujino	2007	Japan	JACC	x	x	x		
LUN20327	Kondo	2007	Japan	JACC	x				
LUN20299	Reeves	2007	UK	MWS	x				
LUN21130	Batty	2006	UK	WHITE		x			
LUN22336	Tsai	2006	USA	Shell Study	x				
LUN17412	Eichholzer	2005	Switzerland	Basel Study	x				
LUN20364	Kuriyama	2005	Japan	MCS I	x				
LUN18406	Oh	2005	Korea	KNHIC	x				
LUN20363	Rapp	2005	Austria	VHM&PP	x				
LUN13341	Calle	2003	USA	CPS II	x				
LUN00294	Goodman	2003	USA	CARET	x				
LUN00114	Gunnell	2003	UK	Caerphilly		x			
LUN00287	Tamosinas	2003	Lithuania	Kaunas Rotterdam Intervention Study	x				
LUN00654	Lee	2002	South Korea	KMICS	x				
LUN00629	Li	2002	China	Beijing 1991-1999	x				
LUN00502	Olson	2002	USA	IWHS	x	x		x	x

WCRF code	Author	Year	Country	Study description	BMI	Height	Weight	Waist circumference	Waist-to-hip-ratio
LUN01785	Hebert	1997	USA	PHS		x			
LUN07499	Tulinius	1997	Iceland	Reykjavík Study	x		x		
LUN01947	Key	1996	USA	HPFS			x		
LUN01885	Knekt	1996	Finland	HES Finland 78-81	x				
LUN02192	Drinkard	1995	USA	IWHS			x		
LUN02145	Kark	1995	Israel	ICSS	x				
LUN02487	Chyou	1994	USA	HHP	x	x			
LUN03143	Knekt	1991	Finland	FMCHES		x			
LUN03014	Knekt	1991	Finland	HES Finland 66-73	x				
LUN03512	Hoffmanns	1989	Netherlands	Dutch Male Birth Cohort	x				
LUN03358	Wannamethee	1989	UK	BRHS	x				
LUN26870	Albanes	1988	USA	NHANES I		x			
LUN02018	Seidell	1986	Netherlands	Netherlands 1974-80	x				
LUN04204	Lee	1984	USA	MEC	x				

Protocol

Continuous Update and Systematic Literature Review of Randomised Controlled Trials and Prospective Studies on Food, Nutrition, Physical Activity and the Risk of Lung Cancer.

Reviewed by: CUP Team, Imperial College London, July 2013

INTRODUCTION

The World Cancer Research Fund/ American Institute for Cancer Research: (WCRF/AICR) has been a global leader in elucidating the relationship between food, nutrition, physical activity and cancer. The First and Second Expert Reports (1;2) represent the most extensive analyses of the existing science on the subject to date.

The Second Expert Report features eight general and two special recommendations based on solid evidence (**Figure 1**) which, when followed, will be expected to reduce the incidence of cancer. More recently, empirical evidence from a large European cohort study showed that people with lifestyle in agreement with the WCRF/AICR recommendations experienced decreased risk of cancer after an average follow-up time of ten years (3). The main risk reductions were for cancers of the colon and rectum, and lung cancer, and significant associations were observed for cancers of the breast, endometrium, lung, kidney, upper aerodigestive tract, liver, and oesophagus.

The Second Expert Report was informed by a process of seventeen systematic literature reviews (SLRs) all of the evidence published. To keep the evidence current and updated into the future, WCRF/AICR is undertaking the Continuous Update Project (CUP) in collaboration with Imperial College London (ICL). The CUP [http://www.wcrf.org/cancer_research/cup/index.php] is an on-going systematic literature review on food, nutrition, physical activity and body fatness, and cancer risk. The project ensures that the evidence, on which the WCRF/AICR recommendations are based, continues to be the most-up-to-date and comprehensive available.

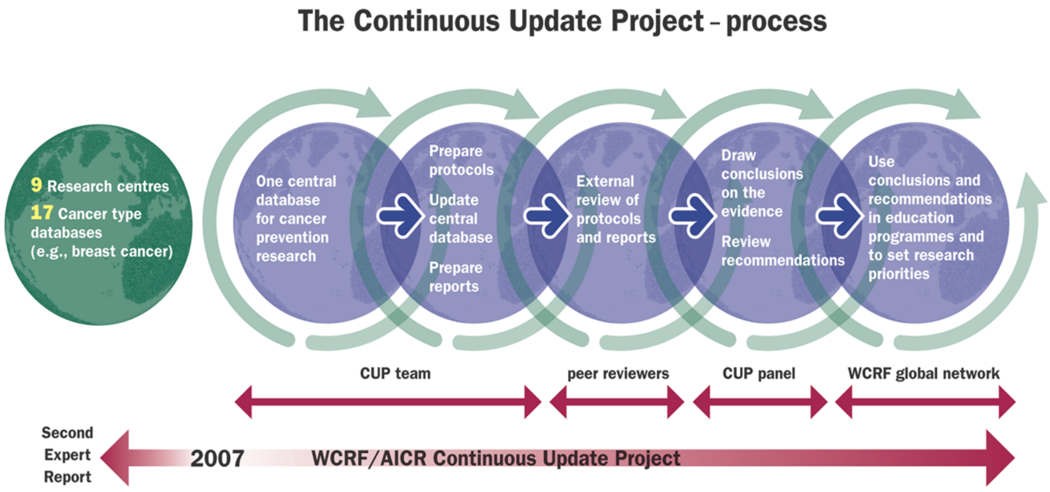
WCRF/AICR has convened a panel of experts for the CUP consisting of leading scientists in the field of diet, physical activity, obesity and cancer, who will consider the evidence produced by the systematic literature reviews conducted by the research team at ICL. The CUP Panel will judge the evidence, draw conclusions and make recommendations for cancer prevention. The entire CUP process will provide a transparent analysis and interpretation of the data as a basis for reviewing and where necessary revising the 2007 WCRF/AICR's cancer prevention recommendations (**Figure 2**).

Figure 1. 2007 World Cancer Research Fund/ American Institute for Cancer Research recommendations for cancer prevention.

RECOMMENDATIONS
BODY FATNESS Be as lean as possible within the normal range of body weight
PHYSICAL ACTIVITY Be physically active as part of everyday life
FOODS AND DRINKS THAT PROMOTE WEIGHT GAIN Limit consumption of energy-dense foods Avoid sugary drinks
PLANT FOODS Eat mostly foods of plant origin
ANIMAL FOODS Limit intake of red meat and avoid processed meat
ALCOHOLIC DRINKS Limit alcoholic drinks
PRESERVATION, PROCESSING, PREPARATION Limit consumption of salt Avoid mouldy cereals (grains) or pulses (legumes)
DIETARY SUPPLEMENTS Aim to meet nutritional needs through diet alone
BREASTFEEDING Mothers to breastfeed; children to be breastfed
CANCER SURVIVORS Follow the recommendations for cancer prevention

Source: WCRF/AICR Second Expert Report (2)

Figure 2. The Continuous Update Process



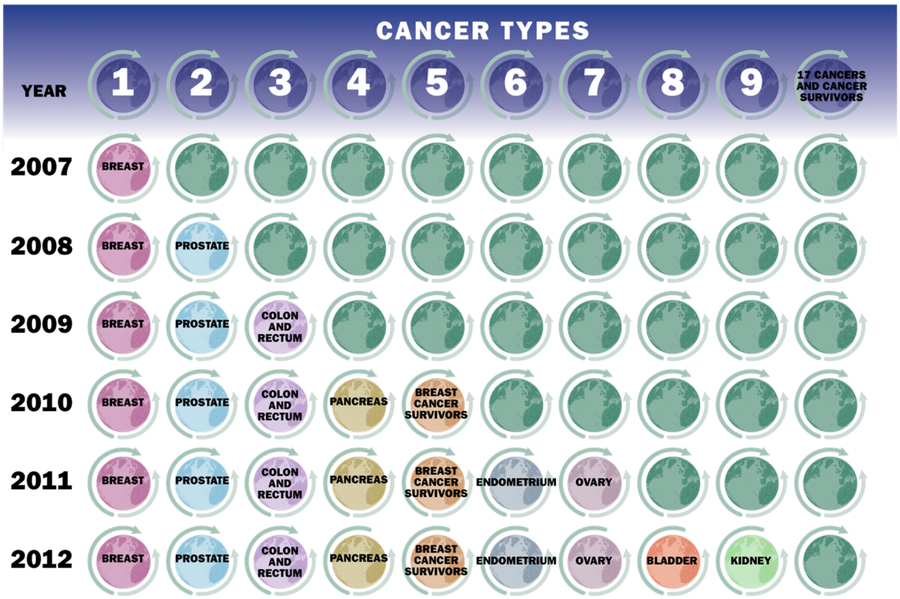
The CUP builds on the foundations of the Second Expert Report to ensure a consistent approach to reviewing the evidence SLR (4). A key step of the CUP is the update of the central database with the results of randomised controlled trials and prospective studies. The CUP Expert Panel advised that these are the study designs that should be prioritized for update because the 2007 WCRF recommendations had been mainly based on the results of randomised controlled trials and prospective cohort studies. A team at ICL conducts the CUP SLRs, where a central database has been created by merging the cancer-specific databases generated in the 2007 SLR's.

The WCRF database is being updated at ICL in a rolling programme. The CUP started in 2007 and breast cancer was the first cancer to be updated, followed by prostate and colorectal cancers. When a cancer site is included in the CUP, the team at ICL keeps updating the database for that cancer and all the other cancers already included in the CUP (**Figure 3**). Currently, the central database is continuously updated for cancers of the breast, prostate, colon and rectum, pancreas, ovary, endometrium, bladder, kidney, gallbladder, liver, stomach and oesophageal cancers.

Periodically, the CUP team at ICL prepares SLR reports with updated meta-analyses by request of the CUP Panel and Secretariat. The protocols and reports of systematic literature reviews by the IC team are available at http://www.dietandcancerreport.org/cancer_resource_center/continuous_update_project.php).

The present document is the protocol for the continuous update and the SLR on food, nutrition, physical activity and the risk of lung cancer. The peer-reviewed protocol will represent the agreed plan. Should departure from the agreed plan be considered necessary at a later stage, the CUP Expert Panel must agree with the modifications and the reasons be documented.

Figure 3. The Continuous Update Project- rolling programme

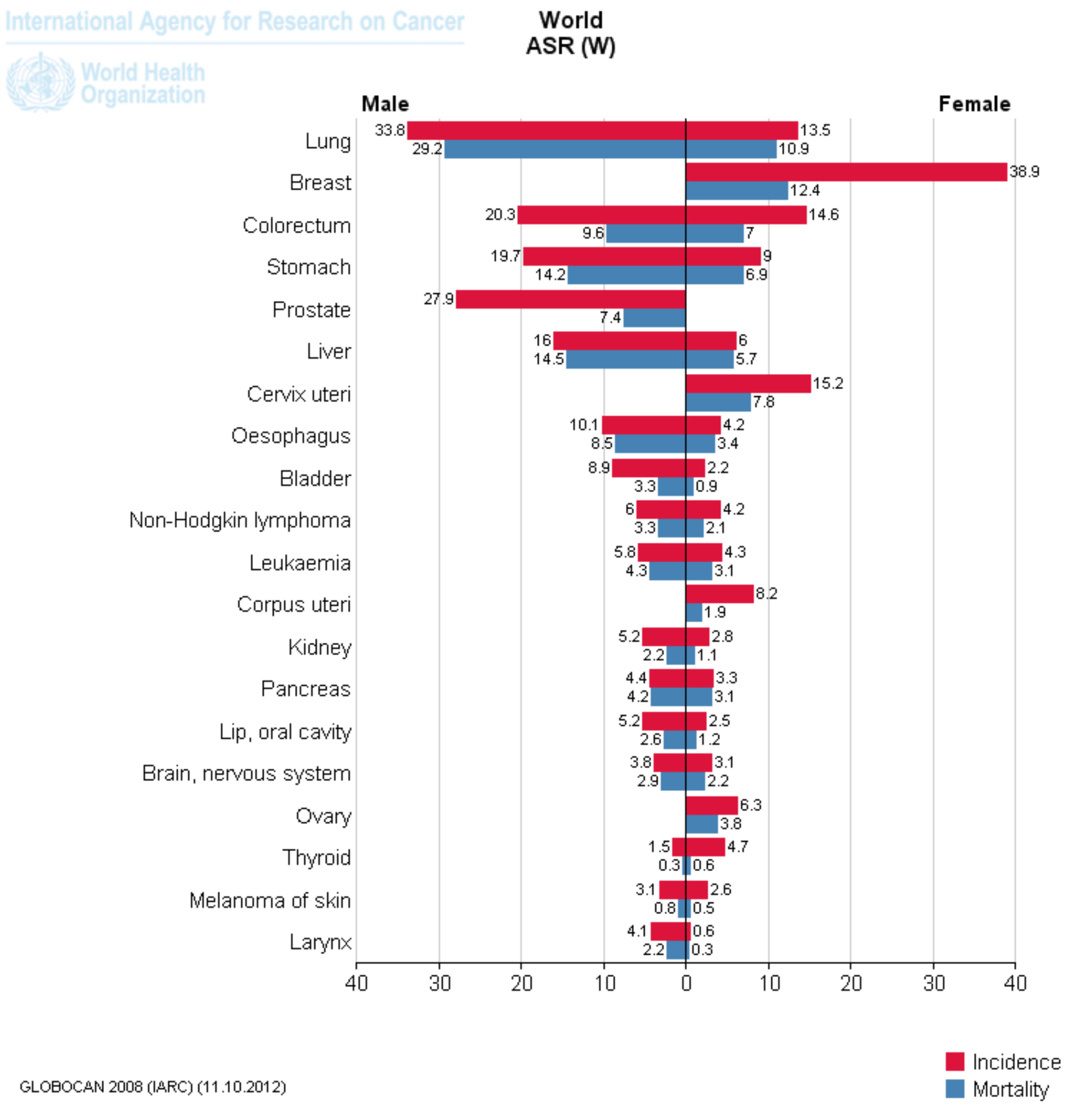


LUNG CANCER: EPIDEMIOLOGY AND RISK FACTORS.

Lung cancer is the most common cause of cancer and the leading cause of cancer death in males worldwide, and the fourth most commonly diagnosed cancer and second leading cause of cancer death in women. Most lung cancers are diagnosed at an advanced stage due to the relative lack of clinical symptoms during early stages. The 5-year survival of lung cancer is only 16% (5). In 2008, lung cancer accounted for 13% (1.6 million) of the total cases and 18% (1.4 million) of the cancer deaths (**Figure 4**).

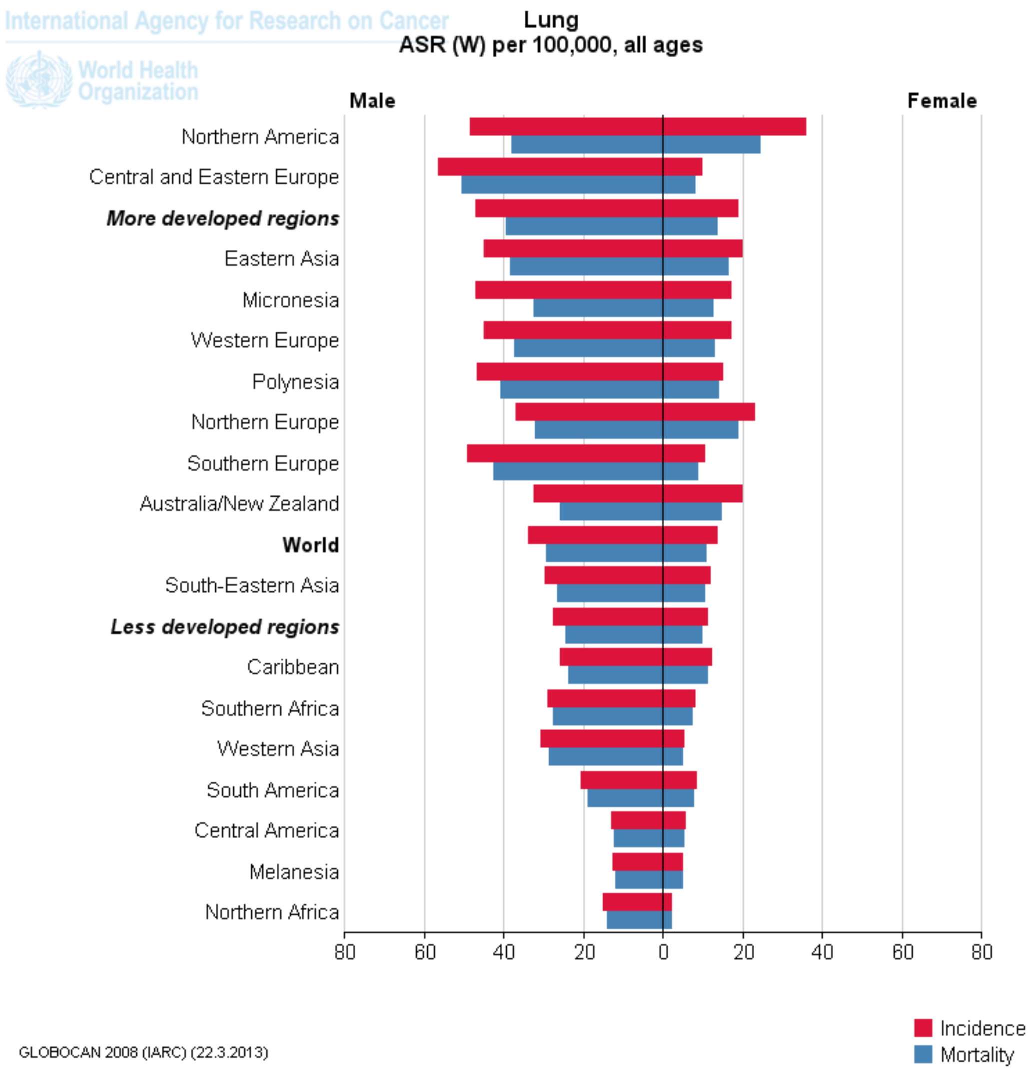
Tobacco is the main risk factor of lung cancer. Tobacco smoking accounts for 80% of the worldwide lung cancer burden in males and at least 50% of the burden in females (6;7). The geographic variation on lung cancer rates and trends across countries or between males and females within each country mainly reflects differences in tobacco smoking prevalence (**Figure 5**) (8). Male lung cancer death rates are declining in North America, some European countries, and Australia, where smoking prevalence is decreasing, but lung cancer rates are increasing in other countries, such as China and several other countries in Asia and Africa, where the smoking prevalence continues to either increase or show signs of stability (9).

Figure 4. Estimated age (world)-standardized incidence and mortality rates by sex of selected cancers (per 100 000). World. 2008



Source: Ferlay J, Shin HR, Bray F, Forman D, Mathers C and Parkin DM. GLOBOCAN 2008 v2.0, Cancer Incidence and Mortality Worldwide: IARC CancerBase No. 10 [Internet]. Lyon, France: International Agency for Research on Cancer; 2010. Available from: http://globocan.iarc.fr, accessed on 20/03/2013

Figure 5. Estimated age-standardized incidence of lung cancer (per 100 000). World 2008



Source: Ferlay J, Shin HR, Bray F, Forman D, Mathers C and Parkin DM. GLOBOCAN 2008 v2.0, Cancer Incidence and Mortality Worldwide: IARC CancerBase No. 10 [Internet].Lyon, France: International Agency for Research on Cancer; 2010. Available from: http://globocan.iarc.fr, accessed on 20/03/2013

Non-smokers exposed to environmental tobacco smoke have an increased risk for developing lung cancer and there is also evidence that air pollution is a risk factor of lung cancer (10). Known risk factors for lung cancer include exposure to several occupational and environmental carcinogens such as asbestos, arsenic, radon, and polycyclic aromatic hydrocarbons (11;12).

There are two main classes of lung cancer: small cell lung cancer (SCLC) and non-SCLC. Non-SCLC accounts for approximately more than 85% of all lung cancer cases and includes two major types: nonsquamous carcinoma (including adenocarcinoma, large-cell carcinoma, other cell types) and squamous cell (epidermoid) carcinoma. Adenocarcinoma is the most frequently occurring cell type in non-smokers. Small-cell lung cancer is an aggressive form of lung cancer, strongly associated with cigarette smoking (13).

There is evidence that nutritional factors play a role in lung cancer development. The expert panel of the 2007 WCRF/AICR Second Report concluded that the evidence that arsenic in drinking water and beta-carotene supplements (high doses in smokers) increases the risk of lung cancer was convincing; fruits and foods containing carotenoids probably decrease the risk of lung cancer. The evidence suggesting a protective effect of non-starchy vegetables, foods containing selenium, foods containing quercitin, selenium (supplements) and physical activity was limited. There was limited evidence suggesting that red meat, processed meat, total fat intake, butter and retinol supplements and low body fatness increase the risk of lung cancer. There was not enough evidence to allow conclusions on other nutritional factors investigated (**Figure 6**).

Figure 6. Summary of judgements of the 2007 Second Expert Report on lung cancer 2007

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

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

	DECREASES RISK	INCREASES RISK
Convincing		**Arsenic in drinking water**[1] **Beta-carotene supplements**[2]
Probable	**Fruits**[3] **Foods containing carotenoids**[4]	
Limited — suggestive	Non-starchy vegetables[3] Foods containing selenium[4] Foods containing quercetin[4] Selenium[5] Physical activity[6]	Red meat[7] Processed meat[8] Total fat Butter Retinol supplements[2] Low body fatness
Limited — no conclusion	Cereals (grains) and their products; starchy tubers; dietary fibre; pulses (legumes); poultry; fish; eggs; milk and dairy products; total fat; animal fats; plant oils; soft drinks; coffee; tea; alcohol; preservation, processing, and preparation; carbohydrate; protein vitamin A; thiamin; riboflavin; niacin; vitamin B6; folate; vitamin C; vitamin E; multivitamins; calcium; copper; iron; zinc; pro-vitamin A carotenoids; lycopene; flavonoids; culturally-defined diets; body size, shape, and composition (except low body fatness); energy intake	
Substantial effect on risk unlikely	None identified	

1 The International Agency for Research on Cancer has graded arsenic and arsenic compounds as Class 1 carcinogens. The grading for this entry applies specifically to inorganic arsenic in drinking water.
2 The evidence is derived from studies using high-dose supplements (20 mg/day for beta-carotene; 25 000 international units/day for retinol) in smokers.
3 Judgements on vegetables and fruits do not include those preserved by salting and/or pickling.
4 Includes both foods naturally containing the constituent and foods which have the constituent added (see chapter 3.5.3).
5 The evidence is derived from studies using supplements at a dose of 200 µg/day.
6 Physical activity of all types: occupational, household, transport, and recreational.
7 The term 'red meat' refers to beef, pork, lamb, and goat from domesticated animals.
8 The term 'processed meat' refers to meats preserved by smoking, curing, or salting, or addition of chemical preservatives.

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

World Cancer Research Fund — American Institute for Cancer Research

Source: WCRF/AICR Second Expert report world (2)

SYSTEMATIC LITERATURE REVIEW ON LUNG CANCER

1. RESEARCH QUESTION

The research topic is:

The associations between food, nutrition and physical activity and the risk of lung cancer.

The main objective is:

To summarize the evidence from prospective studies and randomised controlled trials on the association between foods, nutrients, physical activity, body adiposity and the risk of lung cancer in men and women.

2. REVIEW TEAM

Name	Current position at IC	Role within team
Teresa Norat	Principal Research Fellow	Principal investigator
Doris Chan	Research Assistant	Supervisor of data extraction. Data analyst, SLR report preparation
Ana Rita Vieira	Research Assistant	Data analyst, SLR report preparation
Leila Abar	Research Assistant	Systematic search, article selection, data extraction
Deborah Navarro	Research Assistant	Systematic search, article selection, data extraction
Snieguole Vingeliene	Research Assistant	Systematic search, article selection, data extraction

Review coordinator, WCRF: Rachel Thompson
Statistical advisor: Darren Greenwood, senior Research Lecturer, University of Leeds

All the reviewers are trained in the procedures for literature search, data selection and extraction for systematic literature reviews. The reviewers that will conduct the data analyses have experience in meta-analyses. Selected CUP SLRs published by members of the ICL team are in the References Section (14-22).

3. TIMELINE

The SLRs for the Second Expert Report ended in December 30th 2005. The SLR centre extracted all the data from relevant articles published up to this date for the Second Expert Report.

The CUP team at IC will search and extract data of the articles from prospective studies and randomised controlled trials published from January 1st 2006. The reviewers will verify that there are not duplicities in the database using a module for article search implemented in the interface for data entry.

List of tasks and deadlines for the continuous update on lung cancer:

Task	Deadline
Start Medline search of relevant articles published from January 1st 2006	1st October 2013
Start review of title and abstracts of articles identified in electronic search and select papers for complete review	1st November 2013
Download papers and select relevant papers for data extraction	1st December 2013
Start data extraction	6th January 2014
Start hand search of references	6th January 2014
Start quantitative analysis of articles included in PubMed up to 30th March 2014*	1st April 2014
Start writing SLR report	1st July 2014
Send SLR report for review to CUP secretariat	30th September 2014
Review and modify SLR report according to reviewer's comments	December 2014
Send reviewed SLR report to CUP secretariat	21st December
Transfer Endnote files to SLR CUP Secretariat	21st December
Panel meeting	April 2015

*End date of the intermediate systematic literature review to the CUP Panel

4. SEARCH STRATEGY

4.1. Search database

The Medline database (includes coverage from 70 countries) will be searched using PubMed as platform. The rationale for searching only in Medline is the results of the SLR's for the Second Expert Report indicated that searching reports of prospective studies in databases other than Medline was not cost effective (23). Central and ClinialTrials.gov will be searched for evidence of trials relevant to this review. A study comparing different electronic databases concluded that "The publications found in only one database were not unique with regard to access by the other databases to each reference, but rather to our particular search strategy" (24). We conducted a test using two published systematic literature reviews randomly selected from reviews on oesophageal cancer and diet (25;26). Although the authors reported searching in several electronic databases, all the articles included in the reviews were identified in PubMed if the CUP search strategy was used. Therefore, the inclusion of other electronic databases does not appear to confer further advantage to our specific search strategy.

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. The full search strategy is in **Annex** 1.

A first search will be conducted using as date limits January 1st 2006 to September 30th 2013 and subsequent searches will be conducted every month. The relevant articles published before January 2006 were identified and the data extracted into the WCRF database during the SLR for the Second Expert Report.

5. STUDY SELECTION CRITERIA FOR THE UPDATE

5.1 Inclusion criteria

The articles to be included in the review:

- Must have as exposures/interventions one of the following: dietary patterns, foods, nutrients –dietary, supplemental or both-, diet biomarkers, food contaminants, food additives, indicators of body adiposity in early life, adolescence or adulthood, changes in body adiposity, height, breastfeeding, physical activity.
- Must have as outcome of interest incidence or mortality of lung cancer
- Have to present results from an epidemiologic study in men and/or women of one of the following types:
    - o Randomized controlled trial
    - o Prospective cohort study
    - o Nested case-control study
    - o Case-cohort study
    - o Historical cohort study

- Studies in individuals free of cancer at the moment of exposure assessment or intervention (except non melanoma skin cancer)

5.2 Exclusion criteria

- Studies with designs not listed in the Inclusion criteria (e.g. case-control studies, case-only studies, ecological studies, non-randomized clinical trials, cross-sectional studies, 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 that cannot be translated (members in the review team can read Chinese, French, Italian, Spanish and Portuguese).

6. ARTICLE SELECTION

First, all references obtained with the searches in PubMed will be imported in a Reference Manager Database using the filter Medline.

The article selection will follow three steps:

1. An electronic search will first be undertaken within Reference Manager to facilitate the identification of irrelevant records by using the terms indicated below. Relevance will be assessed upon reading of the titles and abstracts of the articles identified by the electronic search.

List of terms for use within Reference Manager Database

Radiotherapy
Chemotherapy
Cisplatinum
Docetaxel
Cell
Inhibitor
Novel
Model
Receptor
Antibody
Transgenic
Mice
Hamster
Rat
Dog
Cat
In vitro

2. In a second step, two reviewers will assess the titles and abstracts of the remaining articles.

3. In a third step, the reviewers will assess the full manuscripts of all papers for which eligibility could not be determined by reading the title and abstract.

The reviewers will solve any disagreements about the study or exposure relevance by discussion with the principal investigator.

6.1 Reference Manager Files

Five user-defined fields (**Table 1**) will be created in the Reference Manager database where the reviewers will indicate:

1) if the study was selected upon reading of title and abstract, or entire article
2) the study design of articles on exposures/interventions and outcome relevant to the review
3) the status of data extraction of included articles
4) the WCRF code assigned to included studies during data extraction
5) reasons for exclusion of articles on exposures/interventions and outcome relevant to the review

Relevant case-control studies will be labelled in the Reference manager database as Included for the purpose of identification, but the results of case-control studies will not be included in the WCRF database or in the meta-analysis.

Table 1. User-defined fields and terms to be used in the Reference Manager database for identification of the status of articles identified in the searches

Field	Use	Terms	Notes
User Def 1	Indicate result of assessment for inclusion	Excludedabti	Excludedabti: paper exclusion based on abstract and title
		Excluded	Excluded: paper exclusion based on full paper text
		Included	Included: reports of case-control studies, cohort studies, pooled analysis and trials relevant to the review.
User Def 2	Reasons for exclusion	No measure of association No original data Commentary, no original data	No original data uses data from others No adequate study design includes non-

		Foreign article in [*language*] No adequate study design Meta-analysis Already extracted Cancer survivors	controlled trials, cross-sectional analysis, and ecological studies. Already extracted refers to studies identified by another search Cancer survivors for studies that are not in people free of cancer at baseline
User Def 3	Study design	Randomized controlled trial (RCT) Prospective cohort study Retrospective cohort study Nested case-control study Case cohort study Population-based case-control study Hospital-based case-control study Case-control study- other Pooled analysis of cohort studies Pooled analysis of case-control studies	Case-control study-other: when the comparison populations are neighbours, friends, and any other case in which the controls are not population- or hospital- based. Case-control studies and pooled analyses are identified as included but the data are not extracted to the database.
User Def 4	WCRF code	LUN+ consecutive digits	WCRF codes are assigned automatically by the data extraction software when performing the data extraction.
User Def 5	Cancer group	Indicates if the study report aggregative cancer types such as gastro-lung cancer, upper aero-digestive or other	The data should be extracted in the article has inclusion criteria

7. DATA EXTRACTION

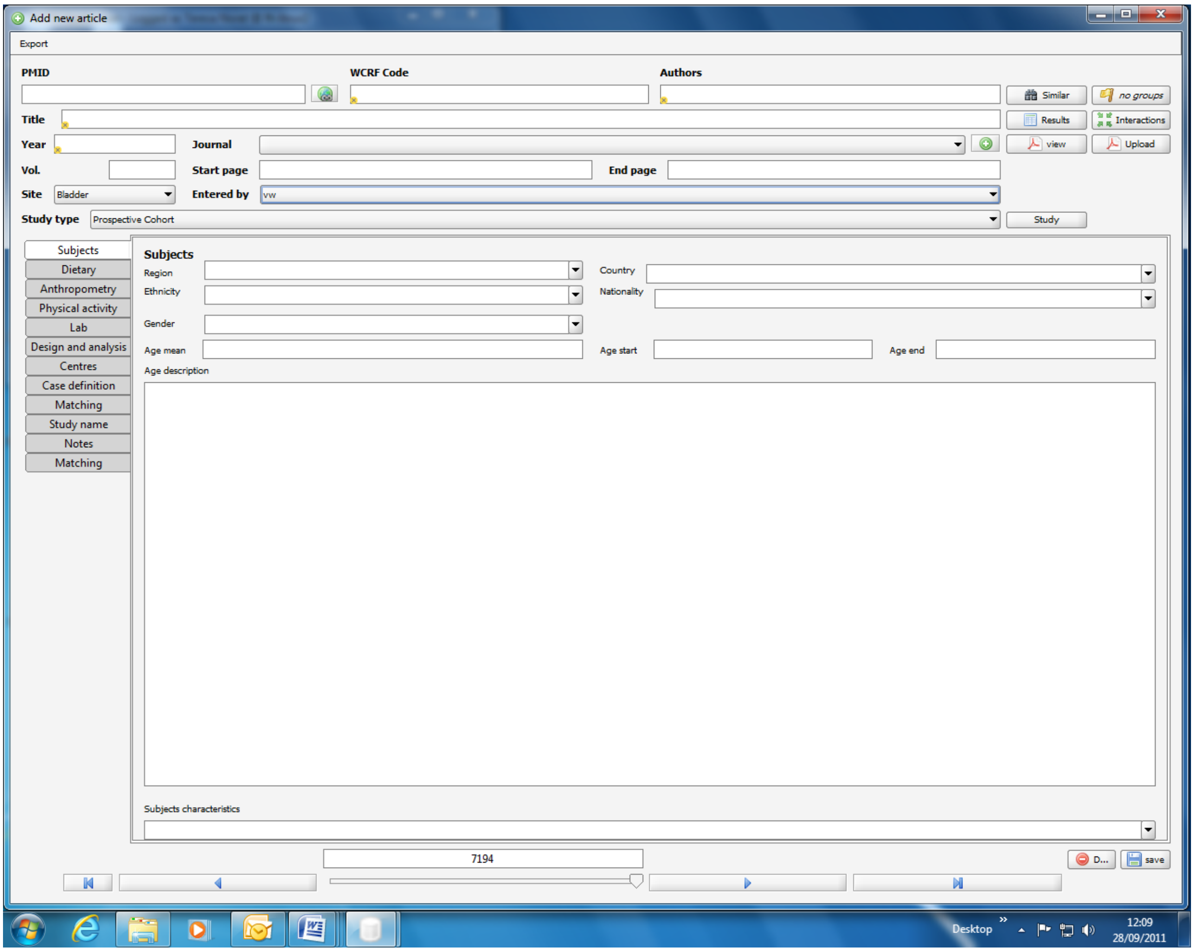
The IC team will update the WCRF-AICR central database using an interface created or this purpose **(Figure 6)**. The application will automatically check that the paper

has not already been extracted to the database using author name, publication year and journal references. The data extracted will be double-checked by a second reviewer. The data to be extracted include study design, name, characteristics of study population, mean age, distribution by sex, country, recruitment year, methods of exposure assessment, definition of exposure, definition of outcome, method of outcome assessment, study size, length of follow up, lost to follow-up, analytical methods and whether methods for correction of measurement error were used.
The ranges, means or median values for each level of the exposure will be extracted as reported in the paper.
For each result, the reviewers will extract the covariates included in the analytical models and the matching variables.
Measures of association, number of cases and number of comparison individuals or person years for each category of exposure will be extracted for each model reported in the paper. The reviewer will not do any calculation during this phase. Stratified and subgroup analyses, and results of interaction analyses will be extracted (e.g. by sex, age group, smoking status, BMI category, alcohol intake level, etc.)
The reviewer should extract the results for each type of cancer (non-SCC, SCC, lung cancer site not specified, and indicate histological type if provided), for each gender, for each subgroup, in stratified and interaction analysis.

7.1 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: LUN (lung cancer), followed by a 5-digit number that will be generated sequentially by the software during data extraction.

Figure 6. CUP interface. Example of screen for data entry.



7.2 Codification of exposures/interventions.

The exposures/interventions will be codified during data extraction as in the Second Expert Report. The main headings and sub-headings codes are in **Annex 2**. Wherever possible, the reviewer will use the sub-heading codes. Additional codes have been programmed in the database to facilitate the data entry. The reviewer should also extract the description of the exposure/intervention definition in the free text box provided for that purpose in the data entry screen. The definition will be extracted as it appears in the paper.

The main headings for codification of the exposure groups are:

1. **Patterns of diet**, includes regionally defined diets, socio-economically defined diets, culturally defined diets, individual level dietary patterns, other dietary patterns, breastfeeding and other issues
2. **Foods**, including starchy foods; fruit and (non-starchy) vegetables; pulses (legumes); nuts and seeds; meat, poultry, fish and eggs; fats, oils and sugars; milk and dairy products; and herbs, spices, and condiments, and composite foods.
3. **Beverages**, including total fluid intake, water, milk, soft drinks, fruit juices, hot drinks and alcoholic drinks.

4. **Food production** including traditional methods and chemical contaminants, food preservation, processing and preparation.
5. **Dietary constituents**, including carbohydrate, lipids, protein, alcohol, vitamins, minerals, phytochemicals, nutrient supplements and other bioactive compounds
6. **Physical activity**, including total physical activity, physical inactivity and surrogate markers for physical activity.
7. **Energy balance**, including energy intake, energy density and energy expenditure.
8. **Anthropometry**, including markers of body composition, markers of body fat distribution, height and other skeletal measures, and growth in foetal life, infancy or childhood.

7.3 Codification of biomarkers of exposure

Biomarkers of exposure will be included under the heading and with the code of the corresponding exposure.

During the SLR for the Second Expert Report, some review centres opted for including in the review only biomarkers for which there was strong evidence on reliability or validity whereas other centres opted for including results on all the biomarkers retrieved in the search, independently of their validity. For the evaluation of the evidence, the Panel of Experts took in consideration the validity of the reported biomarkers.

However, since the identification and validation of other biomarkers is an expanding area (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 Codification of outcomes.

The reviewer will indicate in the field: outcome type, whether the outcome is incidence or mortality and in outcome subtype, if the results are on lung adenocarcinoma, squamous cell carcinoma or lung cancer not specified.

7.5 Extraction and labelling of study results

The reviewer will extract the measures of association (RR estimates and confidence intervals) for the relevant exposures from all the statistical models shown in the paper, including subgroups, stratified analyses, interactions and sensitivity analyses. These results can be shown in tables, in the text or as supplemental information of the paper.

The reviewer should label the results as unadjusted, intermediately adjusted, or most adjusted model, depending on the models:

- Univariate models in the paper will be labelled “unadjusted”.

- If the paper shows several multivariable models, the multivariable model with the highest number of covariables in the paper will be labelled "most adjusted".
- Other models in the paper that are not the "unadjusted" or the "most adjusted" model will be labelled "intermediately" adjusted.

In addition, the reviewer will indicate the "best model" for meta-analyses. The "best model" for meta-analysis will be the most adjusted model from the paper. In some papers, the researchers report models that include variables likely to be in the causal pathway of an exposure-outcome relationship. The purpose of these models is the exploration of possible mechanisms. When "mechanistic" models are reported, the "intermediately" adjusted result with the highest number of covariables will be indicated as "best model". The "mechanistic" model will be labelled as "most adjusted" model, but not as "best model" for meta-analysis. If there are enough papers with "mechanistic" models, these results will be meta-analysed independently of the "best models".

If a model is not adjusted for smoking and smokers are included in the study population, the results obtained with this model will not be labelled as "best model".

8. QUALITY CONTROL OF THE ARTICLE SELECTION AND DATA EXTRACTION.

A second reviewer at ICL will check the article selection and the data extraction. If there are discrepancies between the reviewers, the discrepancy will be discussed with the Principal Investigator.

9. DATA ANALYSIS

9.1 Meta-analysis

Dose-response meta-analyses will be conducted, such as in the SLR for the Second Report. The meta-analysis will include studies identified during the 2005 SLR and studies identified during the CUP SLR.

The meta-analyses will be conducted separately for:

- Small cell lung cancer, non- small cell lung cancer, lung cancers any histocytology or non-specified
- Incidence, mortality
- Men, women, both gender
- Smokers, ex-smokers, never smokers (or equivalent groups shown in the papers), smoking status not specified
- Geographic area, race or ethnicity, other sub-groups reported in the papers

When possible, the results of each study from a published pooled analysis will be included individually, instead of using the pooled result reported in the paper. The purpose is to look at heterogeneity across study results. The reviewers will check that the same study is not included twice in the meta-analysis. If this is not possible, meta-analyses will be conducted with and without the overall results of pooled analyses.

The measure of association for the highest vs. the lowest comparison for each study will be displayed graphically in forests plots, but a summary estimate will not be calculated, to avoid pooling exposure levels that are different across studies. However, categorical meta-analyses will be conducted for exposures categorised in two levels (e.g. breastfeeding categorised as yes vs. no, use of multivitamins categorised as yes vs. no).

Dose-response meta-analysis (log-linear models) will be conducted to express the results of each study in the same increment unit for a given exposure. The results will be shown in a dose-response forest plot with the studies ordered by publication year, the most recent being on the top.

Non-linear dose-response meta-analyses will be conducted as exploratory analysis.

Table 2.Recommended increment units for meta-analyses.

Exposure	Increment unit
Total fruits and vegetables	100 g
Non starchy vegetables	100 g
Fruits	100 g
Citrus fruits	50 g
Red meat	100 g
Processed meat	50 g
Poultry	100 g
Fish	50 g
Eggs	25 g
Salt	1 g
Coffee	1 cup
Tea	1 cup
Alcoholic drinks	1 drink/day
Alcohol (as ethanol)	10 g
Dietary calcium	200 mg
Dietary fibre	10 g
Folate	100 µg
Blood selenium	10 µg/L
Alcohol from beer	10 g/day (approx. one drink)
Alcohol from wine	10 g/day (approx. one drink)
BMI	5 kg/m^2
Waist	2.5 cm (1 inch)

Waist-to-hip	0.1 unit
Height	5 cm
Physical activity	5 MET-h per week

9.2 Selection of exposures for a dose-response meta-analysis

A dose-response meta-analysis will be conducted when at least two new reports of trials or two news reports of cohort studies with enough data for dose-response meta-analysis are identified during the CUP and if there are in total five cohort studies or five randomised controlled trials. The minimum number of two studies was not derived statistically but it is a number of studies that can be reasonable expected to have been published after the Second Expert Report.

Where a particular study has published more than one paper on the same exposure, the analysis using the larger number of cases will be selected but if the most recent paper does not provide enough information for the dose-response meta-analysis, the previous publication will be used. The results section will indicate whether the reports of the same study are similar or not.

For comparability, the increment units for the log-linear dose-response analyses will be those used in the meta-analyses in the previous SLRs (**Table 2**). If most of the identified studies report servings, times, these will be used as increment unit.

9.3 Selection of results for meta-analyses

The results based on "best" adjusted models will be used in the dose-response meta-analyses. The log-linear dose-response estimates reported in the article will be used in the CUP dose-response meta-analysis. If the results are presented only for categorical data (quantiles or pre-defined categories), the slope of the dose-response relationship for each study will be derived from the categorical data.

9.4 Derivation of data required for meta-analyses.

The data required to derive the dose-response slope from categorical data are:

1. number of cases for each exposure category
2. person-years -or number of comparison individuals nested case-control analyses- for each exposure category
3. median, mean or cut-offs of exposure categories.

The information provided in the articles is often incomplete and this may result in exclusions of results from meta-analyses. In the SLR on lung and prostate cancers for the Second Expert Report, only 64% of the cohort studies provided enough data to be included in dose-response meta-analysis. There was empirical evidence that studies that showed a significant association were more likely to be usable in dose-response meta-analysis than studies that did not show any evidence of association (28)

The failure to include all available evidence will reduce precision of summary estimates and may lead to bias if propensity to report results in sufficient detail is associated with the magnitude and/or direction of associations. To address the data incompleteness, a number of approaches will be undertaken to derive the missing data from the available data where possible. The approaches are in **Table 3.**

Table 3. Approaches to derive missing information for meta-analyses in the CUP

Type of data	Problem	Approach
Dose-response data	Serving size is not quantified or ranges are missing, but group descriptions are given	Use serving size recommended in SLR
	Standard error missing	Use p value (either exact or the upper bound) to estimate the standard error
Quantile-based data	Numbers of controls (or the denominator in cohort studies) are missing	Group sizes are assumed to be approximately equal
	Confidence interval is missing	Use raw numbers of cases and person years (or controls in nested case-control studies) to calculate confidence interval (although doing so may result in a somewhat smaller standard error than would be obtained in an adjusted analysis)
	Group mean are missing	Estimate using the method of Chêne and Thompson (29) with a normal or lognormal distribution, as appropriate- detailed instructions are in the 2005 SLR Guidelines (30)- 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)
	Upper boundary for the highest category not reported	Assume that the boundary had the same amplitude as the nearest category
Category data	Numbers of controls (or the denominator in cohort studies) is missing	Derive these numbers from the numbers of cases and the reported odds ratios (proportions will be correct unless adjustment for confounding factors considerably alter the crude odds ratios)

Where the units of measurement differ between results, the units would be converted to a common scale. Where assumptions had to be made on portion or serving sizes the assumptions used in the WCRF/AICR Second Expert Report will be applied (4) (**Table 4**). For studies reporting intakes in grams/1000 kcal/day, the intake in grams/day will be approximated using the average energy intake per quantile reported in the article.

Table 4. List of conversion units

Item	Conversion of one unit
Beer	400ml serving
Cereals	60g serving
Cheese	35g serving
Dried fish	10g serving
Eggs	55g serving (1 egg)
Fats	10g serving
Fruit & Vegetables	80g serving
Fruit Juice	125ml serving
General drinks inc. soft & hot drinks	200ml serving
Meat & Fish	120g serving
Milk	50ml serving
Milk as beverage	200ml serving
Processed cheese slice	10g serving
Processed meat	50g serving
Shellfish	60g serving
Spirits	25ml serving
Staple foods (rice, pasta, potatoes, beans & lentils, foods boiled in soy sauce)	150g serving
Water & Fluid intake	8oz cup
Wine	125ml serving

9.5 Statistical Methods

When not provided, the slopes of a dose-response relationship will be derived from categorical data using generalized least-squares for trend estimation (command GLST in Stata) (31). This method accounts for the correlation between relative risks estimates with respect to the same reference category (32). The dose-response model is forcing the fitted line to go through the origin and whenever the assigned dose corresponding to the reference group (RR=1) is different from zero, this is rescaled to zero and the assigned doses to the other exposure categories are rescaled accordingly.

The study specific log odds ratios per unit increase in exposure will be combined in a random effect model using the method of DerSimonian and Laird (33), with the estimate of heterogeneity being taken from the inverse-variance fixed-effect model.

Publication and related bias (e.g. small study bias) will be explored through visual examination of funnel plots using precision (1/SE(β)) in the vertical axis and Egger's test (34). Funnel plots will be shown when there are at least five studies included in the analysis.

Heterogeneity between studies will be quantified with the I^2 statistic - where cut points I^2 values of 30%, and 50% (35). Mild heterogeneity might account for less than 30 per cent of the variability in point estimates, and notable heterogeneity substantially more than 50 per cent. Heterogeneity will be assessed visually from forest plots and with statistical tests (P value <0.05 will be considered statistically significant) but the interpretation will rely mainly in the I^2 values as the test has low power and the number of studies for some exposures will probably be limited.

Potential sources of heterogeneity will be explored by stratified analyses when the number of studies allows it (at least two studies in each stratum). The variables that will be explored as sources of heterogeneity are gender, smoking status, geographic area, level of control for confounder, publication year, length of follow-up. Meta-regression will be conducted if the number of studies allows it. The interpretation of stratified analysis should be cautious. If a considerable number of study characteristics are investigated in a meta-analysis containing only a small number of studies, then there is a high probability that one or more study characteristics will be found to explain heterogeneity, even in the absence of real associations.

Potential non-linear dose-response relationships will be explored using fractional polynomial models (36). The best fitting second order fractional polynomial regression model defined as the one with the lowest deviance will be determined. Non-linearity will be tested using the likelihood ratio test (37). The non-linear dose-response analyses will be conducted using a program prepared by D. Greenwood, statistical advisor of the project.

All analyses will be conducted in Stata/SE 12.1.

9.6 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 analyses will be done as a minimum in the following cases:

- Excluding studies that did not adjust for smoking or that did it very crudely (e.g. ever/never).
- Including and excluding studies where exposure level was inferred by the authors (for example assigning a standard portion size when this is not provided) or other missing information was derived from the data.
- Influence-analyses where each individual study will be omitted in turn in order to investigate the sensitivity of the pooled estimates to inclusion or exclusion of particular studies (38)

10. SYSTEMATIC LITERATURE REVIEW REPORT

An updated SLR report will be sent to the CUP Secretariat on January 30, 2015 for discussion in the Expert Panel.

The SLR report will include the following elements:

1. Modifications of the approved protocol

    Any modification required during the review will be described

2. Results of the search

    Flowchart with number of records downloaded, number of papers thought potentially relevant after reading titles and abstracts and number of papers included. The reasons for excluding papers should also be described.

3. Summary tables of studies identified in the continuous update

    Number of studies by study design and publication year.

    Number of studies by exposure (main heading and selected subheadings) and publication year

    Number of studies by exposure and outcome subtype

4. Tabulation of study characteristics

The tables will include study characteristics (e.g. population, exposure, outcome, study design) and main study results.

The tables will include the information required by the Panel to judge the quality of the studies included in the analyses (Newcastle –Ottawa quality assessment scale (39) for cohort studies and the Cochrane Collaboration's tool for assessing risk of bias (40)).

Example of table of study characteristics for cohort studies (in two parts below):

Author, Year, country,	Study design	Country, Ethnicity, other characteristics	Age (mean)	Cases (n)	Non cases (n/person-years)	Case ascertainment	Follow-up (years)

WCRF Code							

Assessment details	Category of exposure	Subgroup	No cat	RR	(95% CI)	p trend	Adjustment factors						
							A	B	C	D	E	F	G

5. Graphic presentation of individual studies

Tabular presentation will be complemented with graphic displays when two or more new studies have been published during the CUP. Study results will be displayed in forest plots showing relative risk estimates and 95% confidence interval of ''high versus low'' comparisons for each study. Dose-response graphs will be given for individual studies for which the information is available. Funnel plots will be shown when there are at least four studies.

6. Results of the dose-response meta-analysis

Main characteristics of included and excluded studies in dose-response meta-analysis will be tabulated, and reasons for exclusions will be detailed.

The results of meta-analysis will be presented in tables and forest plots. The tables will include a comparison with the results of the meta-analyses undertaken during the SLR for the Second Expert Report.

All forest plots in the report will have the same format. Footnotes will provide quantified information (statistical tests and I^2 statistics) on the degree of heterogeneity between the displayed studies.

Meta-regression, stratified analyses and sensitivity analyses results will be presented in tables and, if the number of studies justifies it, in forest plots.

Reference List

1. World Cancer Research Fund / American Institute for Cancer Research. Food, Nutrition and the Prevention of Cancer: a Global Perspective. Washington, DC: AICR, 1997.

2. World Cancer Research Fund / American Institute for Cancer Research. Food, Nutrition, Physical Activity, and the Prevention of Cancer: a Global Perspective. Washington DC: AICR, 2007.

3. Romaguera D, Vergnaud AC, Peeters PH et al. Is concordance with World Cancer Research Fund/American Institute for Cancer Research guidelines for

cancer prevention related to subsequent risk of cancer? Results from the EPIC study. Am J Clin Nutr 2012;96:150-63.

4. World Cancer Research Fund/ American Institute for Cancer Research. Systematic Literature Review. The SLR Specification Manual In . In: AICR, ed. Food, Nutrition, Physical Activity and the Prevention of Cancer: A Global Perspective (Support Resource) . Washington DC: 2007.

5. Heuvers ME, Hegmans JP, Stricker BH, Aerts JG. Improving lung cancer survival; time to move on. BMC Pulm Med 2012;12:77.:77.

6. Ezzati M, Lopez AD. Regional, disease specific patterns of smoking-attributable mortality in 2000. Tob Control 2004;13:388-95.

7. Ezzati M, Henley SJ, Lopez AD, Thun MJ. Role of smoking in global and regional cancer epidemiology: current patterns and data needs. Int J Cancer 2005;116:963-71.

8. Bray FI, Weiderpass E. Lung cancer mortality trends in 36 European countries: secular trends and birth cohort patterns by sex and region 1970-2007. Int J Cancer 2010;126:1454-66.

9. de GP, Munden RF. Lung cancer epidemiology, risk factors, and prevention. Radiol Clin North Am 2012;50:863-76.

10. Vineis P, Hoek G, Krzyzanowski M et al. Lung cancers attributable to environmental tobacco smoke and air pollution in non-smokers in different European countries: a prospective study. Environ Health 2007;6:7.:7.

11. Spitz M, Wu X, Wilkinson A, Wei Q. Cancer of the Lung. Oxford, UK: 2006.

12. Liu BQ, Peto R, Chen ZM et al. Emerging tobacco hazards in China: 1. Retrospective proportional mortality study of one million deaths. BMJ 1998;317:1411-22.

13. Jackman DM, Johnson BE. Small-cell lung cancer. The Lancet 1915;366:1385-96.

14. Aune D, Chan DS, Lau R et al. Dietary fibre, whole grains, and risk of colorectal cancer: systematic review and dose-response meta-analysis of prospective studies. BMJ 2011;343:d6617. doi: 10.1136/bmj.d6617.:d6617.

15. Chan DS, Lau R, Aune D et al. Red and processed meat and colorectal cancer incidence: meta-analysis of prospective studies. PLoS One 2011;6:e20456.

16. Aune D, Lau R, Chan DS et al. Nonlinear reduction in risk for colorectal cancer by fruit and vegetable intake based on meta-analysis of prospective studies. Gastroenterology 2011;141:106-18.

17. Touvier M, Chan DS, Lau R et al. Meta-analyses of vitamin D intake, 25-hydroxyvitamin D status, vitamin D receptor polymorphisms, and colorectal cancer risk. Cancer Epidemiol Biomarkers Prev 2011;20:1003-16.

18. Aune D, Chan DS, Vieira AR et al. Fruits, vegetables and breast cancer risk: a systematic review and meta-analysis of prospective studies. Breast Cancer Res Treat 2012;134:479-93.

19. Aune D, Vieira AR, Chan DS et al. Height and pancreatic cancer risk: a systematic review and meta-analysis of cohort studies. Cancer Causes Control 2012;23:1213-22.

20. Aune D, Chan DS, Vieira AR et al. Dietary fructose, carbohydrates, glycemic indices and pancreatic cancer risk: a systematic review and meta-analysis of cohort studies. Ann Oncol 2012;23:2536-46.

21. Aune D, Greenwood DC, Chan DS et al. Body mass index, abdominal fatness and pancreatic cancer risk: a systematic review and non-linear dose-response meta-analysis of prospective studies. Ann Oncol 2012;23:843-52.

22. Aune D, Chan DS, Greenwood DC et al. Dietary fiber and breast cancer risk: a systematic review and meta-analysis of prospective studies. Ann Oncol 2012;23:1394-402.

23. Kaiser Permanente SLR Team. Food, Nutrition, Physical Activity and the Prevention of Cancer: A Global Perspective (Support Resource). Washington DC: 2007.

24. Lemeshow AR, Blum RE, Berlin JA, Stoto MA, Colditz GA. Searching one or two databases was insufficient for meta-analysis of observational studies. J Clin Epidemiol 2005;58:867-73.

25. Choi Y, Song S, Song Y, Lee JE. Consumption of red and processed meat and esophageal cancer risk: Meta-analysis. World J Gastroenterol 2013;19:1020-9.

26. Liu J, Wang J, Leng Y, Lv C. Intake of fruit and vegetables and risk of esophageal squamous cell carcinoma: A meta-analysis of observational studies. Int J Cancer 2013;10.

27. Jenab M, Slimani N, Bictash M, Ferrari P, Bingham SA. Biomarkers in nutritional epidemiology: applications, needs and new horizons. Hum Genet 2009;125:507-25.

28. Bekkering GE, Harris RJ, Thomas S et al. How much of the data published in observational studies of the association between diet and prostate or bladder cancer is usable for meta-analysis? Am J Epidemiol 2008;167:1017-26.

29. Chene G, Thompson SG. Methods for summarizing the risk associations of quantitative variables in epidemiologic studies in a consistent form. Am J Epidemiol 1996;144:610-21.

30. World Cancer Research Fund/ American Institute for Cancer Research. Systematic Literature Review. The SLR Specification Manual. Food, Nutrition, Physical Activity and the Prevention of Cancer: A Global Perspective (Support Resource). Washington DC: AICR 2007.

31. Orsini N, Bellocco R, Greenland S. Generalized least squares for trend estimation of summarized dose-response data . Stata J 2006;6:40-57.

32. Greenland S, Longnecker MP. Methods for trend estimation from summarized dose-response data, with applications to meta-analysis. Am J Epidemiol 1992;135:1301-9.

33. DerSimonian R, Laird N. Meta-analysis in clinical trials. Control Clin Trials 1986;7:177-88.

34. Egger M, Davey SG, Schneider M, Minder C. Bias in meta-analysis detected by a simple, graphical test. BMJ 1997;315:629-34.

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

36. Royston P. A strategy for modelling the effect of a continuous covariate in medicine and epidemiology. Stat Med 2000;19:1831-47.

37. Rota M, Bellocco R, Scotti L et al. Random-effects meta-regression models for studying nonlinear dose-response relationship, with an application to alcohol and esophageal squamous cell carcinoma. Stat Med 2010;%20;29:2679-87.

38. Tobias A. Assessing the influence of a single study in meta-analysis. Stata Tech Bull 1999;47:15-7.

39. Stang A. Critical evaluation of the Newcastle-Ottawa scale for the assessment of the quality of nonrandomized studies in meta-analyses. Eur J Epidemiol 2010;25:603-5.

40. Cochrane Handbook for Systematic Reviews of Interventions. http://www.cochrane.org/training/cochrane-handbook. 2012.

Annex 1. WCRF - PUBMED SEARCH STRATEGY

1) Searching for all studies relating to food, nutrition and physical activity:

#1 diet therapy[MeSH Terms] OR nutrition[MeSH Terms]
#2 diet[tiab] OR diets[tiab] OR dietetic[tiab] OR dietary[tiab] OR eating[tiab] OR intake[tiab] OR nutrient*[tiab] OR nutrition[tiab] OR vegetarian*[tiab] OR vegan*[tiab] OR "seventh day adventist"[tiab] OR macrobiotic[tiab]
#3 food and beverages[MeSH Terms]
#4 food*[tiab] OR cereal*[tiab] OR grain*[tiab] OR granary[tiab] OR wholegrain[tiab] OR wholewheat[tiab] OR roots[tiab] OR plantain*[tiab] OR tuber[tiab] OR tubers[tiab] OR vegetable*[tiab] OR fruit*[tiab] OR pulses[tiab] OR beans[tiab] OR lentils[tiab] OR chickpeas[tiab] OR legume*[tiab] OR soy[tiab] OR soya[tiab] OR nut[tiab] OR nuts[tiab] OR peanut*[tiab] OR groundnut*[tiab] OR (seeds[tiab] and (diet*[tiab] OR food*[tiab])) OR meat[tiab] OR beef[tiab] OR pork[tiab] OR lamb[tiab] OR poultry[tiab] OR chicken[tiab] OR turkey[tiab] OR duck[tiab] OR fish[tiab] OR ((fat[tiab] OR fats[tiab] OR fatty[tiab]) AND (diet*[tiab] or food*[tiab] or adipose[tiab] or blood[tiab] or serum[tiab] or plasma[tiab])) OR egg[tiab] OR eggs[tiab] OR bread[tiab] OR (oils[tiab] AND and (diet*[tiab] or food*[tiab] or adipose[tiab] or blood[tiab]or serum[tiab] or plasma[tiab])) OR shellfish[tiab] OR seafood[tiab] OR sugar[tiab] OR syrup[tiab] OR dairy[tiab] OR milk[tiab] OR herbs[tiab] OR spices[tiab] OR chilli[tiab] OR chillis[tiab] OR pepper*[tiab] OR condiments[tiab] OR tomato*[tiab]
#5 fluid intake[tiab] OR water[tiab] OR drinks[tiab] OR drinking[tiab] OR tea[tiab] OR coffee[tiab] OR caffeine[tiab] OR juice[tiab] OR beer[tiab] OR spirits[tiab] OR liquor[tiab] OR wine[tiab] OR alcohol[tiab] OR alcoholic[tiab] OR beverage*[tiab] OR (ethanol[tiab] and (drink*[tiab] or intake[tiab] or consumption[tiab])) OR yerba mate[tiab] OR ilex paraguariensis[tiab]
#6 pesticides[MeSH Terms] OR fertilizers[MeSH Terms] OR "veterinary drugs"[MeSH Terms]
#7 pesticide*[tiab] OR herbicide*[tiab] OR DDT[tiab] OR fertiliser*[tiab] OR fertilizer*[tiab] OR organic[tiab] OR contaminants[tiab] OR contaminate*[tiab] OR veterinary drug*[tiab] OR polychlorinated dibenzofuran*[tiab] OR PCDF*[tiab] OR polychlorinated dibenzodioxin*[tiab] OR PCDD*[tiab] OR polychlorinated biphenyl*[tiab] OR PCB*[tiab] OR cadmium[tiab] OR arsenic[tiab] OR chlorinated hydrocarbon*[tiab] OR microbial contamination*[tiab]
#8 food preservation[MeSH Terms]
#9 mycotoxin*[tiab] OR aflatoxin*[tiab] OR pickled[tiab] OR bottled[tiab] OR bottling[tiab] OR canned[tiab] OR canning[tiab] OR vacuum pack*[tiab] OR refrigerate*[tiab] OR refrigeration[tiab] OR cured[tiab] OR smoked[tiab] OR preserved[tiab] OR preservatives[tiab] OR nitrosamine[tiab] OR hydrogenation[tiab] OR fortified[tiab] OR additive*[tiab] OR colouring*[tiab] OR coloring*[tiab] OR

flavouring*[tiab] OR flavoring*[tiab] OR nitrates[tiab] OR nitrites[tiab] OR solvent[tiab] OR solvents[tiab] OR ferment*[tiab] OR processed[tiab] OR antioxidant*[tiab] OR genetic modif*[tiab] OR genetically modif*[tiab] OR vinyl chloride[tiab] OR packaging[tiab] OR labelling[tiab] OR phthalates[tiab] or bisphenol a[tiab]

#10 cookery[MeSH Terms]

#11 cooking[tiab] OR cooked[tiab] OR grill[tiab] OR grilled[tiab] OR fried[tiab] OR fry[tiab] OR roast[tiab] OR bake[tiab] OR baked[tiab] OR stewing[tiab] OR stewed[tiab] OR casserol*[tiab] OR broil[tiab] OR broiled[tiab] OR boiled[tiab] OR (microwave[tiab] and (diet*[tiab] or food*[tiab])) OR microwaved[tiab] OR re-heating[tiab] OR reheating[tiab] OR heating[tiab] OR re-heated[tiab] OR heated[tiab] OR poach[tiab] OR poached[tiab] OR steamed[tiab] OR barbecue*[tiab] OR chargrill*[tiab] OR heterocyclic amines[tiab] OR polycyclic aromatic hydrocarbons[tiab] OR dietary acrylamide[tiab]

#12 ((carbohydrates[MeSH Terms] OR proteins[MeSH Terms]) and (diet*[tiab] or food*[tiab])) OR sweetening agents[MeSH Terms]

#13 salt[tiab] OR salting[tiab] OR salted[tiab] OR fiber[tiab] OR fibre[tiab] OR polysaccharide*[tiab] OR starch[tiab] OR starchy[tiab] OR carbohydrate*[tiab] OR lipid*[tiab] OR ((linoleic acid*[tiab] OR sterols[tiab] OR stanols[tiab]) AND (diet*[tiab] or food*[tiab] or adipose [tiab] or blood[tiab] or serum[tiab] or plasma[tiab])) OR sugar*[tiab] OR sweetener*[tiab] OR saccharin*[tiab] OR aspartame[tiab] OR acesulfame[tiab] OR cyclamates[tiab] OR maltose[tiab] OR mannitol[tiab] OR sorbitol[tiab] OR sucrose[tiab] OR xylitol[tiab] OR cholesterol[tiab] OR protein[tiab] OR proteins[tiab] OR hydrogenated dietary oils[tiab] OR hydrogenated lard[tiab] OR hydrogenated oils[tiab]

#14 vitamins[MeSH Terms]

#15 supplements[tiab] OR supplement[tiab] OR vitamin*[tiab] OR retinol[tiab] OR carotenoid*[tiab] OR tocopherol[tiab] OR folate*[tiab] OR folic acid[tiab] OR methionine[tiab] OR riboflavin[tiab] OR thiamine[tiab] OR niacin[tiab] OR pyridoxine[tiab] OR cobalamin[tiab] OR mineral*[tiab] OR (sodium[tiab] AND (diet*[tiab] or food*[tiab])) OR iron[tiab] OR ((calcium[tiab] AND (diet*[tiab] or food*[tiab] or supplement*[tiab])) OR selenium[tiab] OR (iodine[tiab] AND and (diet*[tiab] or food*[tiab] or supplement*[tiab] or deficiency)) OR magnesium[tiab] OR potassium[tiab] OR zinc[tiab] OR copper[tiab] OR phosphorus[tiab] OR manganese[tiab] OR chromium[tiab] OR phytochemical[tiab] OR allium[tiab] OR isothiocyanate*[tiab] OR glucosinolate*[tiab] OR indoles[tiab] OR polyphenol*[tiab] OR phytoestrogen*[tiab] OR genistein[tiab] OR saponin*[tiab] OR coumarin*[tiab] OR lycopene[tiab]

#16 physical fitness[MeSH Terms] OR exertion[MeSH Terms] OR physical endurance[MeSH Terms] or walking[MeSH Terms]

#17 recreational activit*[tiab] OR household activit*[tiab] OR occupational activit*[tiab] OR physical activit*[tiab] OR physical inactivit*[tiab] OR exercise[tiab] OR exercising[tiab] OR energy intake[tiab] OR energy expenditure[tiab] OR energy

balance[tiab] OR energy density[tiab]
#18 body weight [MeSH Terms] OR anthropometry[MeSH Terms] OR body composition[MeSH Terms] OR body constitution[MeSH Terms] OR obesity [MeSH Terms] OR obesity [MeSH Terms]
#19 weight loss[tiab] or weight gain[tiab] OR anthropometry[tiab] OR birth weight[tiab] OR birthweight[tiab] OR birth-weight[tiab] OR child development[tiab] OR height[tiab] OR body composition[tiab] OR body mass[tiab] OR BMI[tiab] OR obesity[tiab] OR obese[tiab] OR overweight[tiab] OR over-weight[tiab] OR over weight[tiab] OR skinfold measurement*[tiab] OR skinfold thickness[tiab] OR DEXA[tiab] OR bio-impedence[tiab] OR waist circumference[tiab] OR hip circumference[tiab] OR waist hip ratio*[tiab] OR weight change [tiab] OR adiposity [tiab] OR abdominal fat [tiab] OR body fat distribution [tiab] OR body size [tiab] OR waist-to-hip ratio [tiab]
#20 #1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19
#21 animal[MeSH Terms] NOT human[MeSH Terms]
#22 #20 NOT #21

2) Searching for all studies relating to lung cancer:

#23 lung neoplasm [MeSH Terms] OR (lung AND (carcinoma[tiab] OR neoplasm*[tiab] OR tumor*[tiab]))

3) Searching for all studies relating lung cancer, and food, nutrition and physical activity:

#**24** #22 AND #23

Annex 2. LIST OF HEADINGS AND EXPOSURE CODES (minimum list)

**Indicates codes added during the CUP*

1 Patterns of diet

1.1 Regionally defined diets

*1.1.1 Mediterranean diet

Include all regionally defined diets, evident in the literature. These are likely to include Mediterranean, Mesoamerican, oriental, including Japanese and Chinese, and "western type".

1.2 Socio-economically defined diets

To include diets of low-income, middle-income and high-income countries (presented, when available in this order). Rich and poor populations within low-income, middle-income and high-income countries should also be considered. This section should also include the concept of poverty diets (monotonous diets consumed by impoverished populations in the economically-developing world mostly made up of one starchy staple, and may be lacking in micronutrients).

1.3 Culturally defined diets

To include dietary patterns such as vegetarianism, vegan diets, macrobiotic diets and diets of Seventh-day Adventists.

1.4 Individual level dietary patterns

To include work on factor and cluster analysis, and various scores and indexes (e.g. diet diversity indexes) that do not fit into the headings above.

1.5 Other dietary patterns

Include under this heading any other dietary patterns present in the literature, that are not regionally, socio-economically, culturally or individually defined.

1.6 Breastfeeding

1.6.1 Mother

Include here also age at first lactation, duration of breastfeeding, number of children breast-fed

1.6.2 Child

Results concerning the effects of breastfeeding on the development of cancer should be disaggregated into effects on the mother and effects on the child. Wherever possible detailed information on duration of total and exclusive breastfeeding, and of complementary feeding should be included.

1.7 Other issues

For example, results related to 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, e.g. salted root vegetables (i.e. 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 when there are data for wild and non-domesticated animals, please show these separately under this general heading as a subcategory.

2.5.1.1 Fresh Meat
2.5.1.2 Processed meat

*2.5.1.2.1 Ham
*2.5.1.2.1.7 Burgers
*2.5.1.2.8 Bacon
*2.5.1.2.9 Hot dogs
*2.5.1.2.10 Sausages

Repeat results concerning processed meat here and under the relevant section under 4. Food Production and Processing. Please record the definition of 'processed meat' used by each study.

2.5.1.3 Red meat

*2.5.1.3.1 Beef
*2.5.1.3.2 Lamb
*2.5.1.3.3 Pork
*2.5.1.3.6 Horse, rabbit, wild meat (game)

Where results are available for a particular type of meat, e.g. beef, pork or lamb, please report under a separate heading.

Show any data on wild meat (game) under this heading as a separate sub-category.

2.5.1.4 Poultry

Show any data on wild birds under this heading as a separate sub-category.

*2.5.1.5 Offals, offal products (organ meats)

2.5.2 Fish

*2.5.2.3 Fish, processed (dried, salted, smoked)
*2.5.2.5 Fatty Fish
*2.5.2.7 Dried Fish
*2.5.2.9 White fish, lean fish

2.5.3 Shellfish and other seafood

2.5.4 Eggs

2.6 Fats, oils and sugars

2.6.1 Animal fats

*2.6.1.1 Butter
*2.6.1.2 Lard
*2.6.1.3 Gravy

*2.6.1.4 Fish oil

2.6.2 Plant oils
2.6.3 Hydrogenated fats and oils

*2.6.3.1 Margarine

Results concerning hydrogenated fats and oils should be reported twice, here and under 4.3.2 Hydrogenation

2.6.4 Sugars

This heading refers to added (extrinsic) sugars and syrups as a food that is refined sugars, such as table sugar, or sugar used in bakery products.

2.7 Milk and dairy products

Results concerning milk should be reported twice, here and under 3.3 Milk

*2.7.1 Milk, fresh milk, dried milk

*2.7.1.1 Whole milk, full-fat milks
*2.7.1.2 Semi skimmed milk, skimmed milk, low fat milk, 2% Milk

*2.7.2 Cheese

*2.7.2.1 Cottage cheese
*2.7.2.2 Cheese, low fat

*2.7.3 Yoghurt, buttermilk, sour milk, fermented milk drinks

*2.7.3.1 Fermented whole milk
*2.7.3.2 Fermented skimmed milk

*2.7.7 Ice cream

2.8 Herbs, spices, condiments

*2.8.1 Ginseng
*2.8.2 Chili pepper, green chili pepper, red chili pepper

2.9 Composite foods

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 Mate
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, lung 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 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 Glycaemic index, glycaemic load

This heading refers to intrinsic sugars that are naturally incorporated into the cellular structure of foods, and 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 e.g. genistein
5.7.6 Caffeine
5.7.7 Other

Where available report results relating to other phytochemicals such as saponins and coumarins. Results concerning any other bioactive compounds, which are not phytochemicals should be reported under the separate heading 'other bioactive compounds'. 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 foetal life, infancy or childhood

8.4.1 Birthweight
8.4.2 Weight at one year