World Cancer Research Fund International Systematic Literature Review

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

Analysing research on cancer prevention and survival

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List of Abbreviations

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
HCC	Hepatocellular carcinoma

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

EPIC	European Prospective Investigation into Cancer and Nutrition
HCAS	Haimen City Anti-Epidemic Station
JACC	Japan Collaborative Cohort study for Evaluation of Cancer Risk
JPHC	Japan Public Health Centre-based Prospective Study
KCPS	Korean Cancer Prevention Study
KMCC	Korean Multi-Centre Cancer Cohort
KNHIC	Korean National Health Insurance Corporation
LSS	Life Span Study
MWS	The Million Women Study
NIH-AARP	NIH-AARP Diet and Health Study
SCHS	Singapore Chinese Health study
SMHS	Shanghai Men's Health Study
SWHS	Shanghai Women's Health Study
TSP	Taiwan Screening Project
WHI	Women's Health Initiative

Introduction

Matrices presented in the WCRF/AICR 2007 Expert Report

In the judgment of the Panel of the WCRF-AICR Second Expert Report the factors listed below modify the risk of cancers of the liver.

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

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

	DECREASES RISK	INCREASES RISK
Convincing		**Aflatoxins[1]**
Probable		**Alcoholic drinks[2]**
Limited — suggestive	Fruits[3]	Body fatness
Limited — no conclusion	Cereals (grains) and their products[1]; non-starchy vegetables; peanuts (groundnuts)[1]; fish; salted fish; water source; coffee; tea	
Substantial effect on risk unlikely	None identified	

1 Foods that may be contaminated with aflatoxins include cereals (grains), and also pulses (legumes), seeds, nuts, and some vegetables and fruits (see chapter 4.2).
2 Cirrhosis is an essential precursor of liver cancer caused by alcohol. The International Agency for Research on Cancer has graded alcohol as a Class 1 carcinogen for liver cancer. Alcohol alone only causes cirrhosis in the presence of other susceptibility factors.
3 Judgements on vegetables and fruits do not include those preserved by salting and/or pickling.

Modifications to the existing protocol

The research team composition was modified. The literature search and data extraction was conducted by Leila Abar and checked by Teresa Norat. Leila Abar and Deborah Navarro worked in data extraction. Deborah Navarro and Dagfinn Aune worked as data analysts. Deborah Navarro put together the document. Other responsibilities remain as listed in the Protocol.

Meta-analyses were conducted when three studies were identified in the CUP even if no article was identified in the 2005 SLR. This is because only a few meta-analyses of cohort studies were conducted in the 2005 SLR.

Notes on the figures and statistics used:

- Heterogeneity tests were conducted for dose-response meta-analysis. The interpretation of the test for heterogeneity should be cautious when the number of studies is low because these tests have low power. Inspection of the forest plots and funnel plots is recommended.

- I^2 statistic was calculated to give an indication of the extent of heterogeneity in the dose-response meta-analysis. Low heterogeneity might account for less than 30 per cent of the variability in point estimates, and high heterogeneity for more than 50 per cent. These values are tentative, because the practical impact of heterogeneity in a meta-analysis also depends on the size and direction of effects.

- Heterogeneity test and I^2 statistics are shown for "Highest vs Lowest" meta-analysis when this is the only type of meta-analyses conducted for an exposure.

- Only random effect models are shown in Tables and Figures.

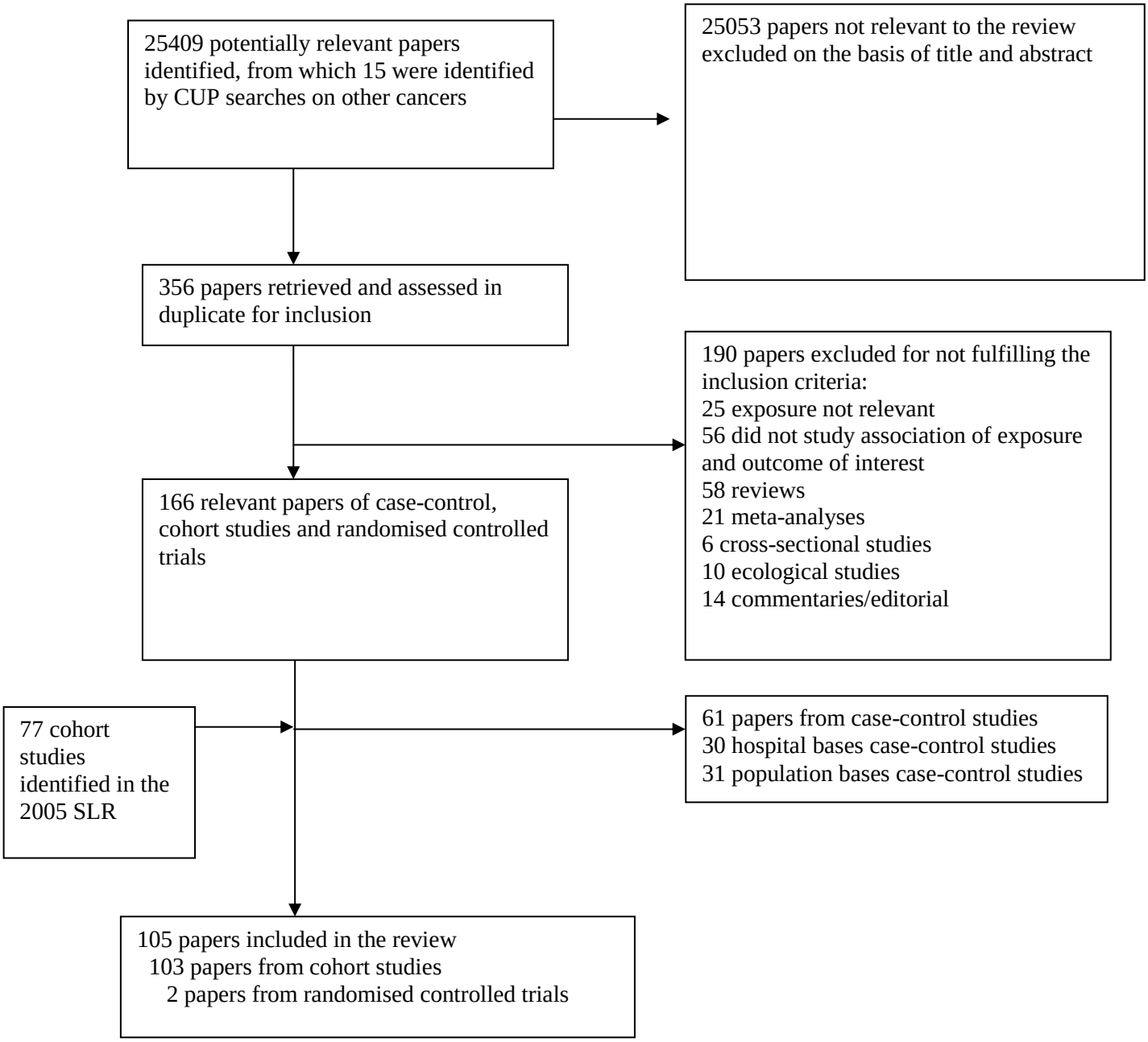
- The dose-response forests plots show the relative risk estimate in each study, expressed per unit of increase. The relative risk is denoted by boxes (larger boxes indicate that the study has higher precision, and greater weight). Horizontal lines denote 95% Confidence intervals (CIs). Arrowheads indicate truncations. The diamond at the bottom shows the summary relative risk estimates and corresponding 95% CIs. The units of increase are indicated in each figure.

- The Highest vs Lowest forest plots show the relative risk estimate for the highest compared to the lowest category of exposure reported in each paper. An overall summary estimate is not shown in the figure.

- The dose-response plot shows the relative risk estimates for each exposure category with respect to the referent category as published by each study. The relative risks estimates are plotted in the mid-point of each category (x-axis) and they are connected through lines.

Continuous Update Project: Results of the search

Flow chart of the search for liver – Continuous Update Project Search period January 1st 2006-March 31st 2013¶



1. Randomised controlled trials (RCT). Results by exposure.

Two publications of The Women's Health Initiative (WHI) (Prentice et al, 2007; Brunner et al, 2011) were identified. The Women's Health Initiative was initiated in 1992 to assess the risks and benefits of hormone therapy (HT) and dietary modification (DM) among postmenopausal women. The average age of the participants was 62.3 years, about three-quarters were overweight or obese (BMI ≥ 25 kg/m2), and more than 40% reported a history of hypertension.

After one year, participants in the HT and DM trials were invited to enrol in the randomised trial of calcium plus vitamin D (CaD) compared to placebo. The majority of the women in the study joined the CaD trial; 54% of CaD trial participants had been enrolled in the trial assessing hormone therapy, 69% had been enrolled in the trial assessing dietary modification, and 14% were in both trials.

1.5 Low fat diet

A publication on the WHI Dietary modification trial including liver cancer as endpoint was identified (Prentice et al, 2007). Breast and colorectal cancers were the primary outcomes. Coronary heart disease was listed as secondary outcome. The goals of the DM intervention was to reduced fat intake (20% or less of energy from fat), and increase the intake of vegetables and fruit (5 or more servings/day) and grains (6 or more servings/day). At 6 years, the intervention group had 8.1% lower of energy intake from fat, consuming 1.1 more servings of vegetables and fruit and 0.4 more servings of grain than the comparison group.

The overall risk of liver cancer, after an average of 8.1 years of follow-up, did not differ between the intervention and the control groups (HR = 2.30, 95% CI = 0.89 to 5.93; *P* = 0.31; 11 cases in the intervention and seven cases in the control). The number of women in the trial was 27629 women (n = 11092 intervention, n = 16537 comparison).

5.6.3 Calcium and vitamin D

One publication on the effect of calcium and vitamin D in postmenopausal women and liver cancer was identified (WHI, Brunner et al, 2011). The primary outcome was hip fracture and liver cancer was a secondary outcome. Postmenopausal women (N = 36,282) were randomized to daily use of 1,000 mg of calcium carbonate combined with 400 IU of vitamin D3 or placebo. Self-reported baseline total calcium and vitamin D intakes from diet were similar in the randomization groups and remained similar during the trial.

After a mean follow-up of seven years, the relative risk of liver cancer of intervention compared to placebo was 0.45 (95% CI: 0.14-1.47; 4 cases in the intervention group and 9 cases in the placebo group).

2. Cohort studies. Results by exposure

(Only exposures with at least two studies identified in the CUP are reviewed).

Table of counts

Number of relevant articles identified during the Second Expert Report and the CUP

The exposure code is the exposure identification in the database.

1. Included in the CUP Review				
Exposure code	**Exposure name**	**Number of relevant articles identified**		
		2005 SLR	**CUP**	Total Number of Cohort Studies
2.2.2	Fruits	2	3	5
2.5.1.2	Processed meat	-	3	3
2.5.1.3	Red meat	-	3	3
2.5.1.4	Poultry	-	2	2
2.5.2	Fish	3	4	7
3.6.1	Coffee	4	7	11
3.6.2.2	Green tea	1	7	8
5.1.5	Glycaemic load	-	4	4
5.1.5	Glycaemic index	-	3	3
5.4	Alcohol	16	14	30
5.4.1	Sake	-	4	4
5.5.9.2	Dietary vitamin C	-	3	3
8.1.1	BMI	7	34	41
Not included in the CUP Review				
Only 2 articles identified in the CUP: Dietary pattern, Vegetables, Beef, Vitamin C supplement, Serum lycopene, Multivitamin supplement, Vitamin E from supplements, Serum tocopherol serum levels, Serum alpha-tocopherol, Serum alpha-carotene, Serum retinol, Dietary retinol, Calcium supplement, Sugars, Lipids, Carbohydrates, Height , Weight.				
Only one article identified in the CUP: Cadmium, Selenium, Dietary calcium, Iron, Heme iron, Niacin, Thiamin (vitamin B1), Total vitamin B2 intake, Serum folate, Folic acid, Folate, Serum total carotenoids, Serum beta-carotene, Beta-carotene(dietary), Serum zeaxanthin Xanthophylls, Serum lutein, Serum Canthaxanthin,Vitamin B supplement,Vitamin E from foods,Vitamin beta-E + gamma-E,Vitamin alpha-E,Plasma 25-hydroxyvitamin D, Serum beta-cryptoxanthin, n-3 fatty acids, EPA fatty acid, DPA fatty acid, DHA fatty acid, Alpha-linolenic acid, Polyunsaturated fat, Monounsaturated fatty acids, Saturated fat, Sugars (as nutrients), Sucrose, Fructose, Mono/disaccharides, Starch, Fruit fibre, Vegetable fibre, Grains/cereals fibre, Total fibre, PhIP, MelQx, DiMelQx, Nitrite, Nitrate, Salt, Urinary aflatoxins/ DNA-adducts, Arsenic, Serum DDT, Serum DDE, Sweets, , Dairy foods, Milk, Yoghurt, Cheese, Genistein, Daidzein, Margarine, Cod liver oil, Butter, Fat preference, Eggs, Liver, Beans, Citrus fruits, Tomatoes, Pickles, Seaweed, Spinach, Green leafy vegetables, Chinese cabbage, Carrots, Energy Intake, Walking, Physical activity (duration), Total vigorous physical activity, Sports, Leisure time physical activity score,Physical activity level, Waist-to-thigh ratio, Waist to hip ratio, Hips circumference, Waist circumference, Weight change, BMI change, Weight at 20 years				

2.2.2 Fruits

Methods

Up to June 2013, five publications from the same number of cohort studies were identified; three of these were identified during the CUP. Three studies could be included in dose-response meta-analysis. The dose-response results are presented for an increment of 100 grams of fruits per day.

Fruit intake in times or servings was converted to grams using a standard portion size of 80g.

George et al. (2009) reported in cup-equivalents/1000kcal, which was converted to g/day using the standard portion size of 80g and the average energy intake provided in the paper, which was 1990 kcal/day for males and 1500kcal/day for females.

Main results

The summary RR per 100 g/d was 1.00 (95% CI: 0.91-1.09; I^2=4.7%, $P_{heterogeneity}$ =0.35) for the all studies combined. The NIH-AARP (George et al, 2009a) had 89% weight in the analysis.

Heterogeneity

There was low evidence of heterogeneity (I^2=4.7%, p=0.35) and no significant evidence of publication bias with Egger's test (p=0.52) in the limited number of studies included in the analysis.

Comparison with the Second Expert Report

In the Second Report, the evidence was judged as limited suggestive of protective effect. No meta-analysis of cohort studies was conducted. The summary of five case-control studies was 0.69 (95% CI 0.54-0.89) for the highest compared to the lowest category in fixed effect models (I^2:47.7%, heterogeneity=0.107) and 0.73 (95% CI=0.51-1.05) in random effect model.

Published meta-analysis

No published meta-analyses were identified.

Table 1 Studies on fruit consumption and liver cancer identified in the CUP

Author, year	Country	Study name	Cases	Years of follow up	Sex	RR	LCI	UCI	Contrast
Songserm, 2012	Thailand	Khon Kaen Cohort Study	219	Not available	All	0.60	0.33	0.98	>=35 average times/month vs < 35 average times/month
George, 2009a	USA	NIH-AARP Diet and Health Study	394	~ 8	F M	0.93	0.47	1.84	1.9-5.58 cups/ 1000 kcal/day vs 0-0.60 cups/ 1000 kcal/day
						0.90	0.62	1.32	1.59-5.13 cups/ 1000 kcal/day vs 0-0.44 cups/ 1000 kcal/day
Kurahashi, 2009	Japan	Japan Public Health Center-based Prospective Study	101	~11.8	All	1.45	0.85	2.48	120.3 g/d vs 13.4 g/d

Table 2 Overall evidence on fruit consumption and liver cancer

	Summary of evidence
2005 SLR	Two publications from the same cohort were identified during the 2005 SLR. None of them showed significant associations.
Continuous Update Project	Three publications from three cohort studies were identified during the CUP. Overall, a null association was observed.

Table 3 Summary of results of the dose response meta-analysis of fruit consumption and liver cancer

Liver cancer		
	2005 SLR*	Continuous Update Project
Studies (n)	-	3
Cases (n)	-	1050
Increment unit used	-	Per 100 g/day
Overall RR (95%CI)	-	1.00 (0.91-1.09
Heterogeneity (I^2,p-value)	-	4.7%, p=0.35

*No meta-analysis was conducted during the 2005 SLR

Table 4 Inclusion/exclusion table for meta-analysis of fruit consumption and liver cancer

WCRF_ Code	Author	Year	Study Design	Study Name	Subgroup	Cancer Outcome	2005 SLR	CUP dose-response meta-analysis	CUP HvL forest plot	Estimated values	Exclusion reasons
LIV00424	Songserm	2012	Nested case-control study	Khon Kaen Cohort Study (KKCS)	All	Incidence	No	No	Yes	-	Only two categories
LIV00455	Kurahashi	2009	Prospective Cohort study	Japan Public Health Center-based Prospective Study	All	Incidence	No	Yes	Yes	-	
LIV00435	George(a)	2009	Prospective Cohort study	NIH- AARP Diet and Health Study	M F	Incidence	No	Yes	Yes	Mid-points values, cases and person-years	--
LIV00473	Sauvaget	2004	Prospective Cohort study	Life Span Study	All	Mortality	Yes	Yes	Yes	-	No risk estimates, only two categories, LIV00334 (Sauvaget, 2003) was included instead
LIV00334	Sauvaget	2003	Prospective Cohort study	Life Span Study	All	Mortality	Yes	No	No	Mid-points values, cases and person-years	

Figure 1 Highest versus lowest forest plot of fruit consumption and liver cancer

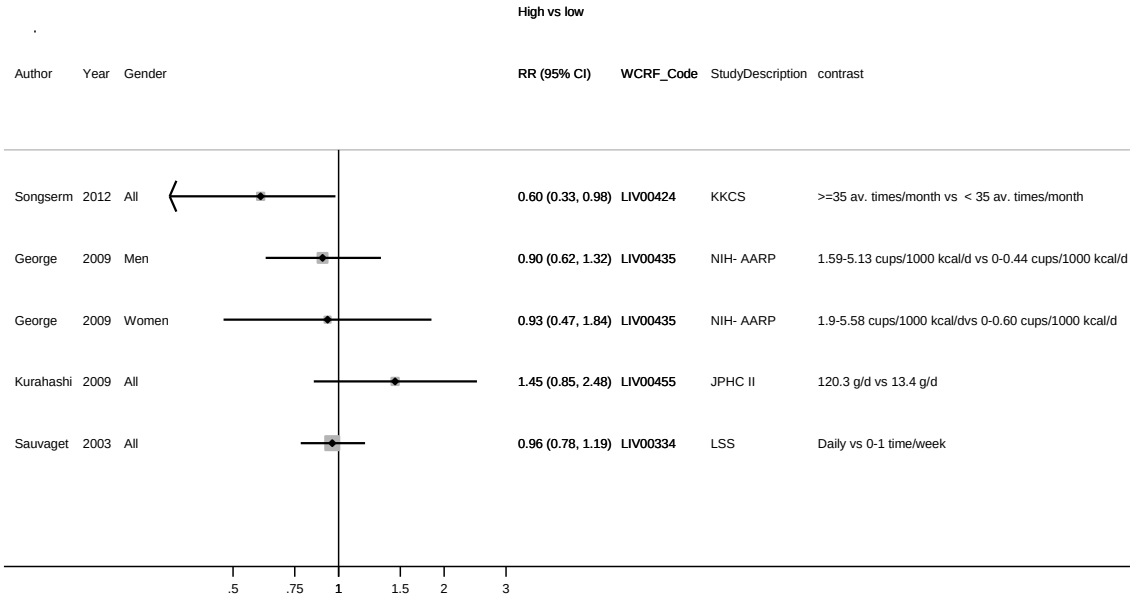


Figure 2 Dose-response meta-analysis of fruit and liver cancer - per 100 g/day

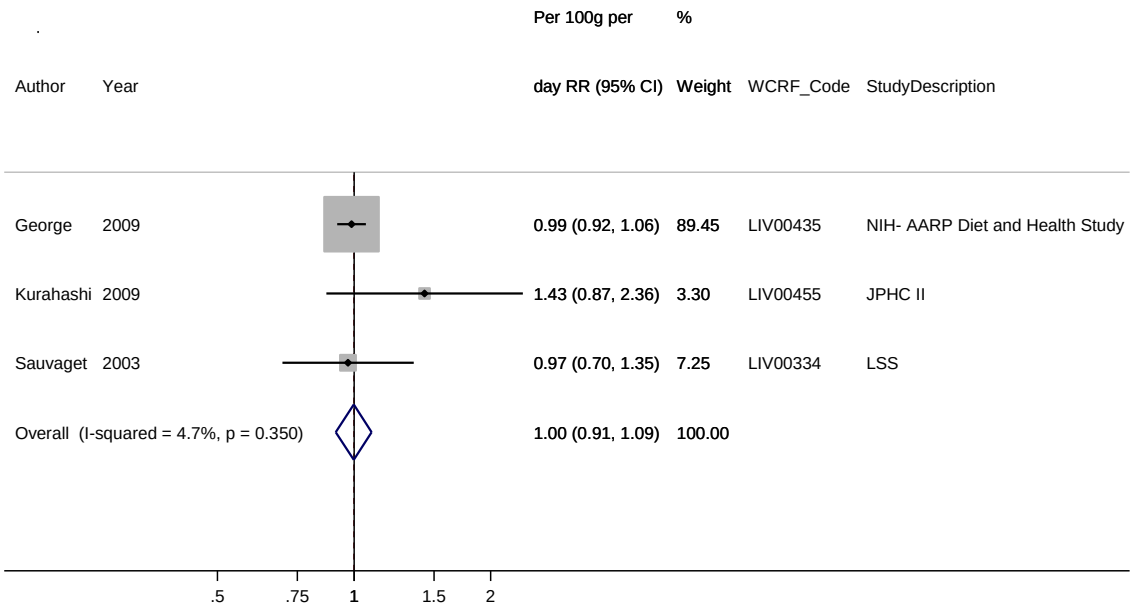


Figure 3 Funnel plot of fruit intake and liver cancer

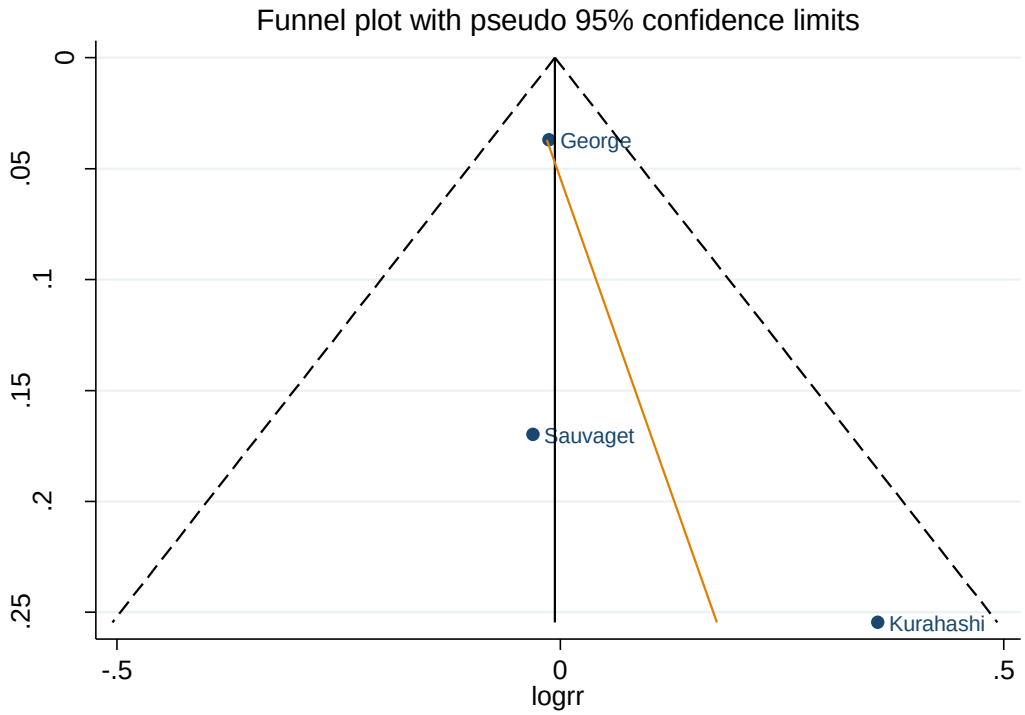
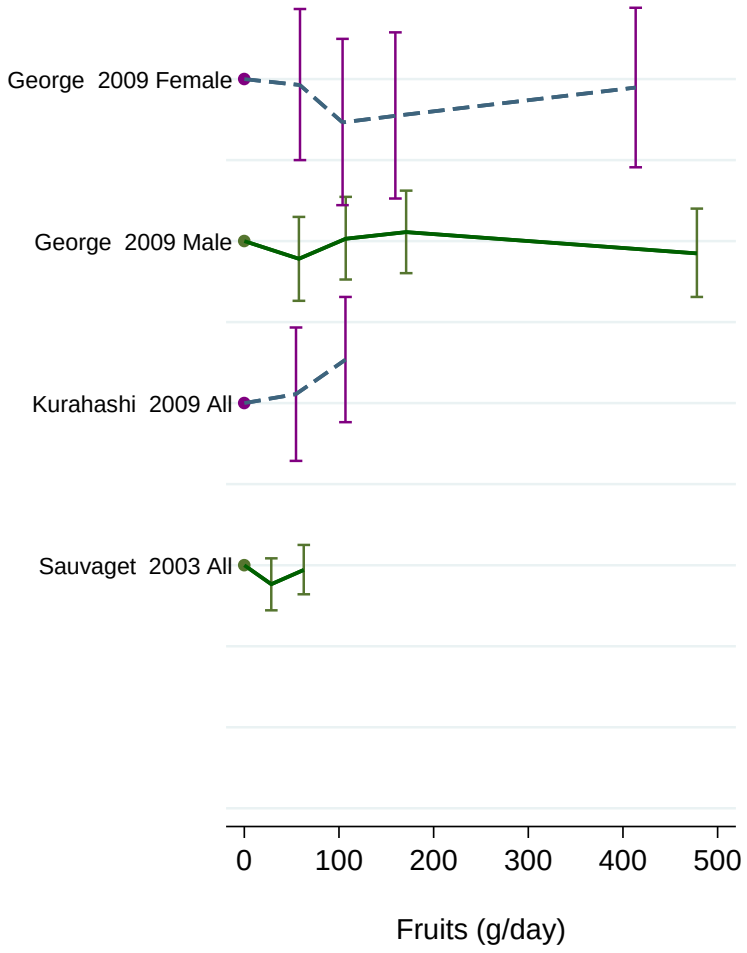


Figure 4 Dose-response graph of fruit and liver cancer



2.5.1.2 Processed meat

Methods

Up to June 2013, three publications from two cohort studies were identified, all during the CUP. The dose-response results are presented for an increment of 50 grams of processed meat per day.

One study presented results in g/1000 kcal days (Cross et al, 2007). These results were transformed to g/d using daily kcal intake mean reported in the paper.

Main results

The summary RR per 50 g/d was 0.86 (95% CI: 0.61-1.22; I^2=56.2%, $P_{heterogeneity}$ =0.13) for the two studies combined.
It was not possible to perform Egger's test because less than three studies were included in the analysis.

Heterogeneity

There was evidence of moderate to high heterogeneity across the two studies (I^2=56.2%, p=0.13).

Comparison with the Second Expert Report

No meta-analysis was conducted during the Second Expect Report

Published meta-analysis

No published meta-analyses were identified.

Table 5 Studies on processed meat consumption and liver cancer identified in the CUP

Author, year	Country	Study name	Cases	Years of follow up	Sex	RR	LCI	UCI	Contrast
Fedirko, 2013	Europe	European Prospective Investigation into Cancer and Nutrition	191	11.4	All	0.77 0.94	0.45 0.89	1.34 1.00	>44.4 g/d vs 0-11.4 g/d Per 10 g/d increment
Freedman, 2010	USA	NIH-AARP Diet and Health Study	338	~ 7	All	1.17	0.79	1.79	Quintile 5 vs quintile 1
Cross, 2007	USA	NIH-AARP Diet and Health Study	403	8.2	All	1.09	0.77	1.53	22.6 g/1000 kcal/d vs 1.6 g/1000 kcal/d

Table 6 Overall evidence on processed meat consumption and liver cancer

	Summary of evidence
2005 SLR	No study was identified during the 2005 SLR.
Continuous Update Project	Three publications from two cohort studies were identified. None of the two studies showed a significant inverse association.

Table 7 Summary of results of the dose response meta-analysis of processed meat consumption and liver cancer

Liver cancer		
	2005 SLR*	Continuous Update Project
Studies (n)	-	2
Cases (n)	-	594
Increment unit used	-	Per 50 g/day
Overall RR (95%CI)	-	0.86 (0.61-1.22)
Heterogeneity (I^2,p-value)	-	56.2%, p=0.13

*No meta-analysis was conducted during the 2005 SLR

Table 8 Inclusion/exclusion table for meta-analysis of processed meat consumption and liver cancer

WCRF_ Code	Author	Year	Study Design	Study Name	Subgroup	Cancer Outcome	2005 SLR	CUP dose-response meta-analysis	CUP HvL forest plot	Estimated values	Exclusion reasons
LIV00514	Fedirko(a)	2013	Prospective Cohort study	European Prospective Investigation into Cancer and Nutrition	All	Incidence	No	Yes	Yes	Rescale continuous values	-
LIV00439	Freedman	2010	Prospective Cohort study	NIH-AARP Diet and Health Study	All	Incidence	No	No	No	-	Only Q5 vs Q1 reported Cross et al, 2007 (LIV00475) was used.
LIV00475	Cross	2007	Prospective Cohort study	NIH-AARP Diet and Health Study	All	Incidence	No	Yes	yes	Person-years	--

Figure 5 Highest versus lowest forest plot of processed meat consumption and liver cancer

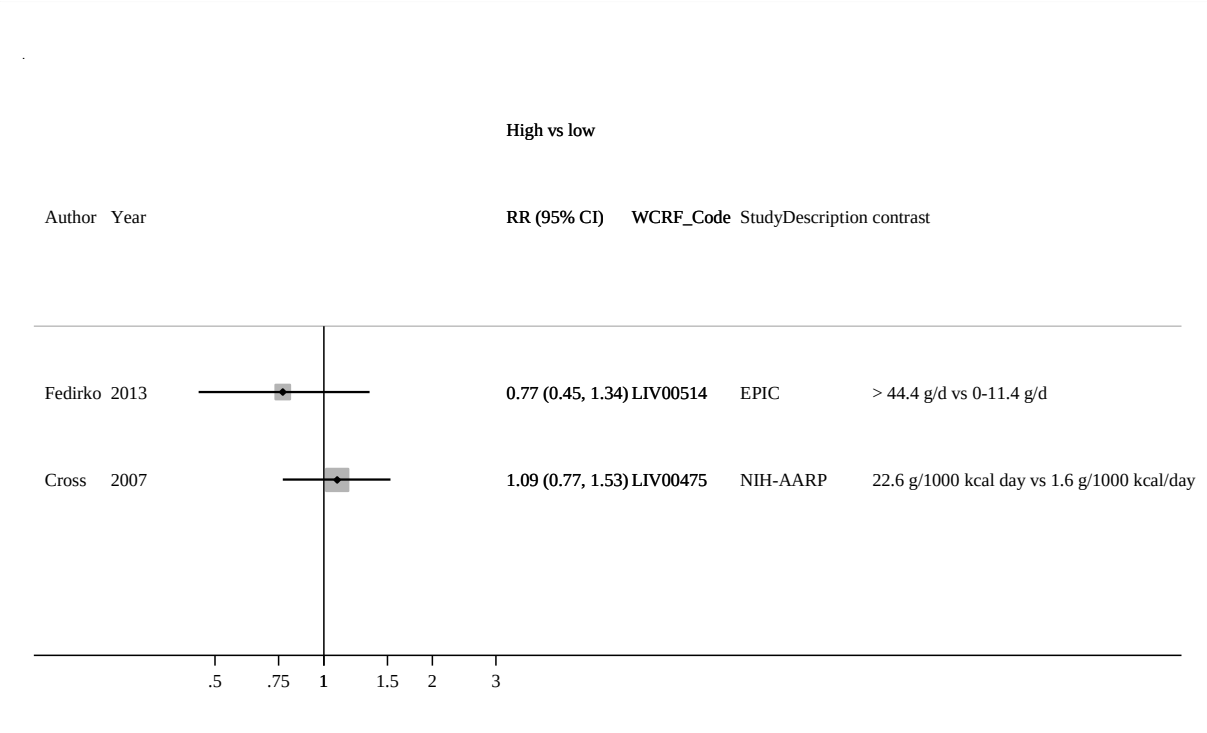


Figure 6 Dose-response meta-analysis of processed meat and liver cancer - per 50 g/day

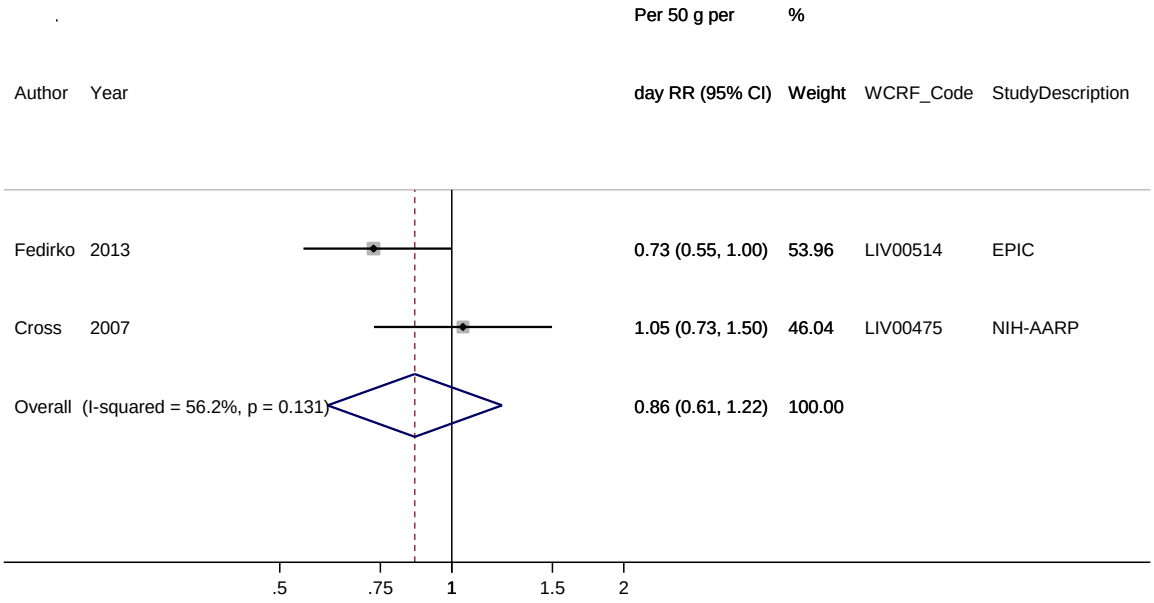
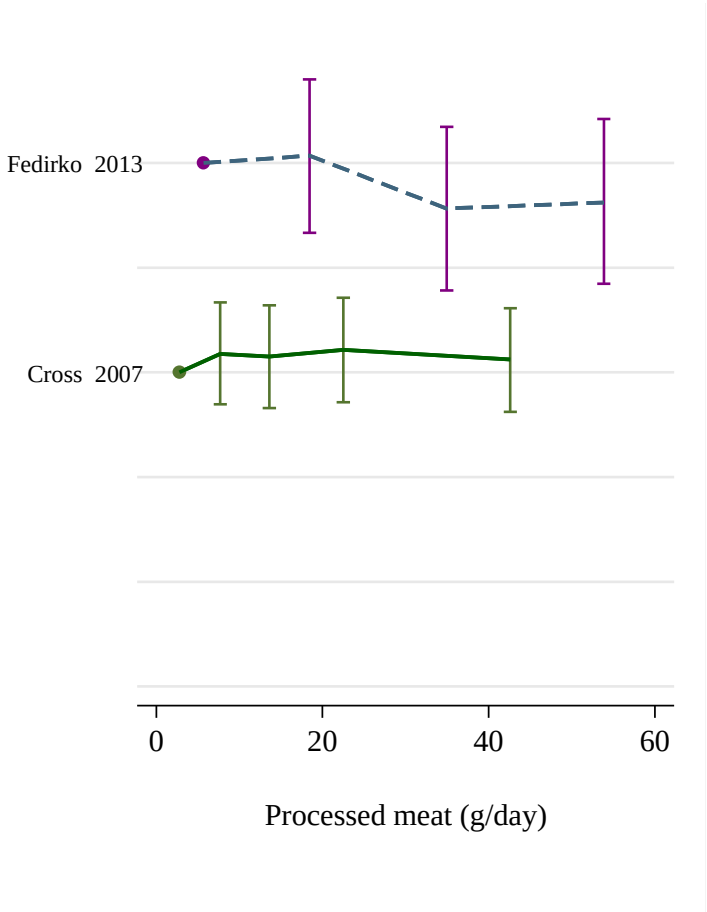


Figure 7 Dose-response graph of processed meat and liver cancer



2.5.1.3 Red meat

Methods

Up to June 2013, three publications from two cohort studies were identified (all published during the CUP). The dose-response results are presented for an increment of 100 grams of red meat per day.

One study presented results in g/1000 kcal days (Cross et al, 2007). These results were transformed to g/d using daily kcal intake mean reported in the paper.

Main results

The summary RR per 100 g/d was 1.25 (95% CI: 0.90-1.75; I^2=39.2%, $P_{heterogeneity}$ =0.20) for the two studies combined. When Freedman et al, 2010 that excluded deaths from liver cancer was included in the analysis instead of Cross et al, 2007, the summary RR was 1.21 (95% CI: 0.82-1.77; I^2=24.8%, pheterogeneity=0.25).

Heterogeneity

There was evidence of moderate heterogeneity across the two studies (I^2=39.2%, p=0.20).

It was not possible to perform Egger's test because only two studies were included in the analysis.

Comparison with the Second Expert Report

No meta-analysis was conducted during the Second Expect Report

Published meta-analysis

No published meta-analyses were identified.

Table 9 Studies on red meat consumption identified in the CUP

Author, year	Country	Study name	Cases	Years of follow up	Sex	RR	LCI	UCI	Contrast
Fedirko, 2013	Europe	European Prospective Investigation into Cancer and Nutrition	191	11.4	All	1.11 1.00	0.60 0.95	2.03 1.04	>63.4 g/d vs 0-16.6g/d Per 10 g/d increment
Freedman, 2010	USA	NIH-AARP Diet and Health Study	338	~ 7	All	1.74	1.16	2.61	52.2 g/1000 kcal/d vs 0-16.4 g/1000 kcal/d
Cross, 2007	USA	NIH-AARP Diet and Health Study	403	8.2	All	1.61	1.12	2.31	62.7 g/1000 kcal/d vs 9.8 g/1000 kcal/d

Table 10 Overall evidence on red meat consumption and liver cancer

	Summary of evidence
2005 SLR	No study was identified during the 2005 SLR.
Continuous Update Project	Three publications from two cohorts were identified; two of them could be included in the meta-analysis. One of the studies showed significant positive association. The overall estimate of two studies was not significant.

Table 11 Summary of results of the dose response meta-analysis of red meat consumption and liver cancer

Liver cancer		
	2005 SLR*	Continuous Update Project
Studies (n)	-	2
Cases (n)	-	594
Increment unit used	-	Per 100 g/day
Overall RR (95%CI)	-	1.25 (0.90-1.75)
Heterogeneity (I^2,p-value)	-	39.2%, p=0.20

*No meta-analysis was conducted during the 2005 SLR

Table 12 Inclusion/exclusion table for meta-analysis of red meat consumption and liver cancer

WCRF_ Code	Author	Year	Study Design	Study Name	Subgroup	Cancer Outcome	2005 SLR	CUP dose-response meta-analysis	CUP HvL forest plot	Estimated values	Exclusion reasons
LIV00514	Fedirko(a)	2013	Prospective Cohort study	European Prospective Investigation into Cancer and Nutrition	All	Incidence	No	Yes	Yes	Rescale continuous values	-
LIV00439	Freedman	2010	Prospective Cohort study	NIH-AARP Diet and Health Study	All	Incidence	No	No	No	-	Excluded deaths from liver cancer to avoid misclassification. Cross et al, 2007 (LIV00475) used instead for comparability with the other study
LIV00475	Cross	2007	Prospective Cohort study	NIH-AARP Diet and Health Study	All	Incidence	No	Yes	yes	Person-years	--

Figure 8 Highest versus lowest forest plot of red meat consumption and liver cancer

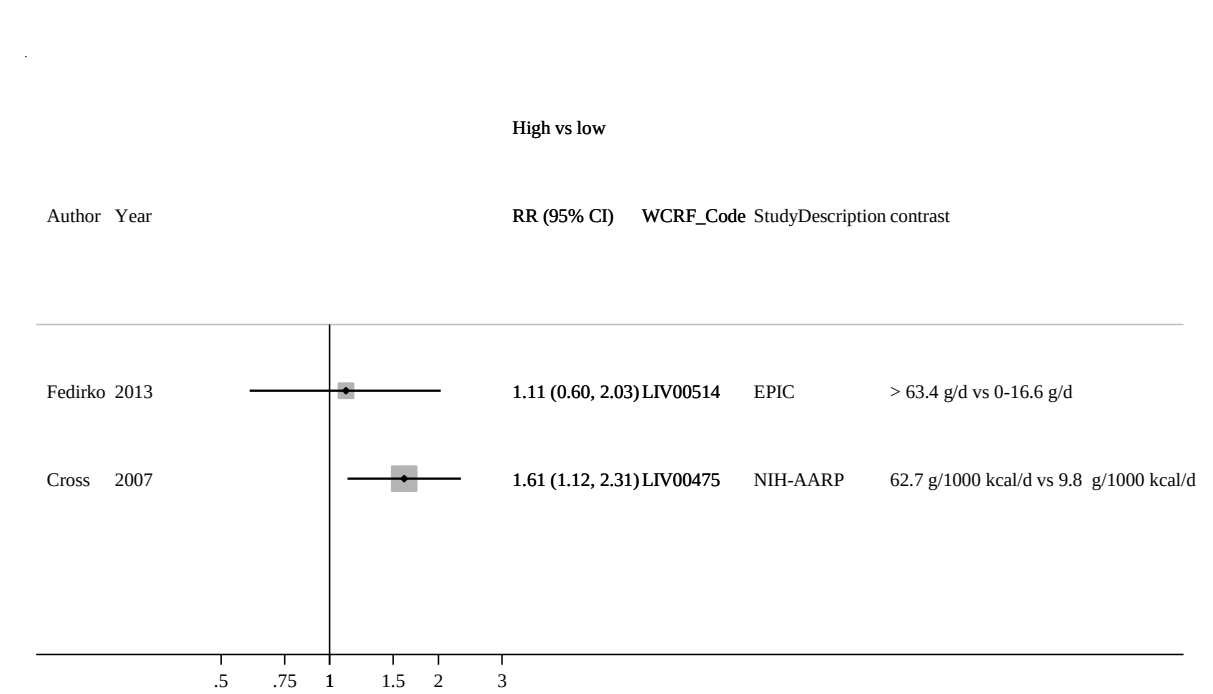


Figure 9 Dose-response meta-analysis of red meat and liver cancer - per 100 g/day

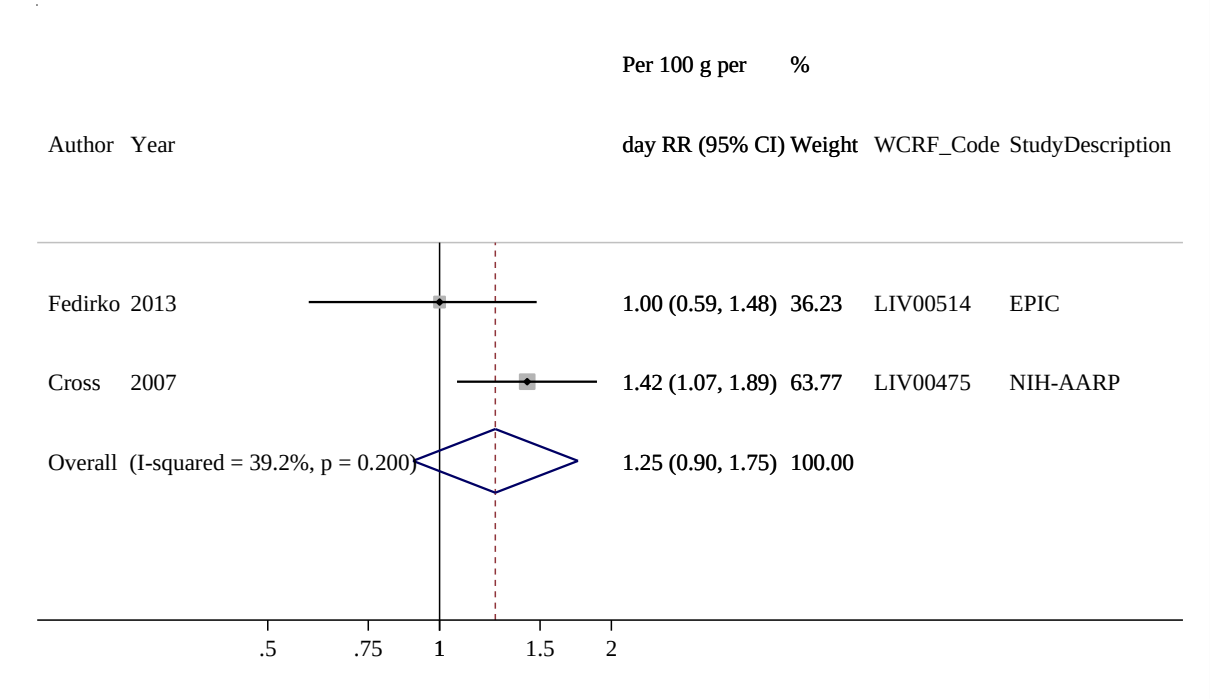
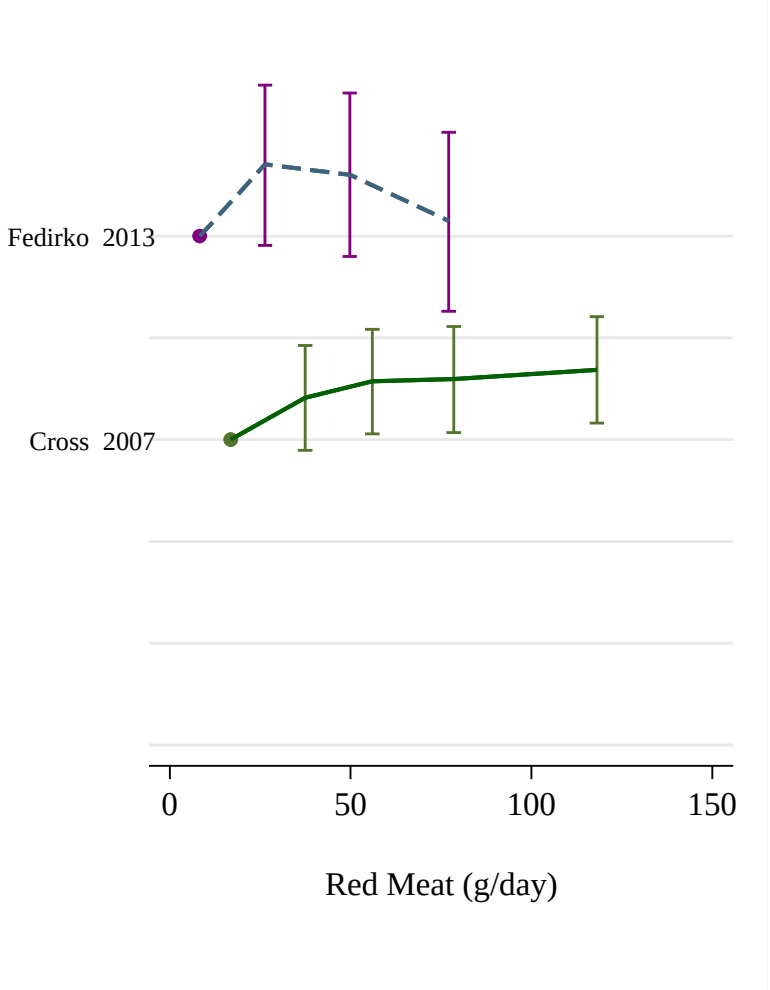


Figure 10 Dose-response graph of red meat and liver cancer



2.5.1.4 Poultry

Methods

Up to June 2013, reports from two cohort studies were identified; the two of them were identified during the CUP. The dose-response results are presented for an increment of 20 grams of poultry per day.

One study presented results in g/1000 kcal days (Daniel et al, 2011). These results were transformed to g/d using mean daily kcal intake reported in the paper.

Main results

The summary RR per 20 g/d was 0.94 (95% CI: 0.89-0.99; I^2=0%, $P_{heterogeneity}$ =0.54) for the two studies combined. The inverse association is driven by the result of the largest study (NIH-AARP, Daniel et al, 2011). The inverse association persisted in addition and substitution models with red meat and confounding was carefully examined in the NIH-AARP. The authors discussed that as high intake of poultry often clusters with a healthier overall eating pattern and lifestyle, the possibility of residual confounding by other factors remains in the study.

Heterogeneity

There was no evidence of heterogeneity across the two studies (I^2=0%, $P_{heterogeneity}$ =0.54).

It was not possible to perform Egger's test due to only two studies being included in the analysis.

Comparison with the Second Expert Report

No meta-analysis was conducted during the Second Expect Report

Published meta-analysis

No published meta-analyses were identified.

Table 13 Studies on poultry consumption identified in the CUP

Author, year	Country	Study name	Cases	Years of follow up	Sex	RR	LCI	UCI	Contrast
Fedirko, 2013	Europe	European Prospective Investigation into Cancer and Nutrition	122	11.4	All	0.87 0.99	0.54 0.91	1.40 1.06	>27.4 g/d vs 0-5.6 g/d Per 10 g/d increment
Daniel, 2011	USA	NIH-AARP Diet and Health Study	582	9.1	All	0.75	0.57	0.99	51.2 g/1000 kcal/d vs 5.3 g/1000 kcal/d

Table 14 Overall evidence on poultry consumption and liver cancer

	Summary of evidence
2005 SLR	No study was identified during the 2005 SLR.
Continuous Update Project	Two publications were identified; one study reported a significant inverse association. Overall, a significant inverse association was observed.

Table 15 Summary of results of the dose response meta-analysis of poultry consumption and liver cancer

Liver cancer		
	2005 SLR*	Continuous Update Project
Studies (n)	-	2
Cases (n)	-	704
Increment unit used	-	Per 20 g/day
Overall RR (95%CI)	-	0.94 (0.89-0.99)
Heterogeneity (I^2,p-value)	-	0%, p=0.54

*No meta-analysis was conducted during the 2005 SLR

Table 16 Inclusion/exclusion table for meta-analysis of poultry consumption and liver cancer

WCRF_ Code	Author	Year	Study Design	Study Name	Subgroup	Cancer Outcome	2005 SLR	CUP dose-response meta-analysis	CUP HvL forest plot	Estimated values	Exclusion reasons
LIV00514	Fedirko(a)	2013	Prospective Cohort study	European Prospective Investigation into Cancer and Nutrition	All	Incidence	No	Yes	Yes	Rescale continuous values	-
LIV00434	Daniel	2011	Prospective Cohort study	NIH-AARP Diet and Health Study	All	Incidence	No	Yes	Yes	Person-years, cases per category	-

Figure 11 Highest versus lowest forest plot of poultry consumption and liver cancer

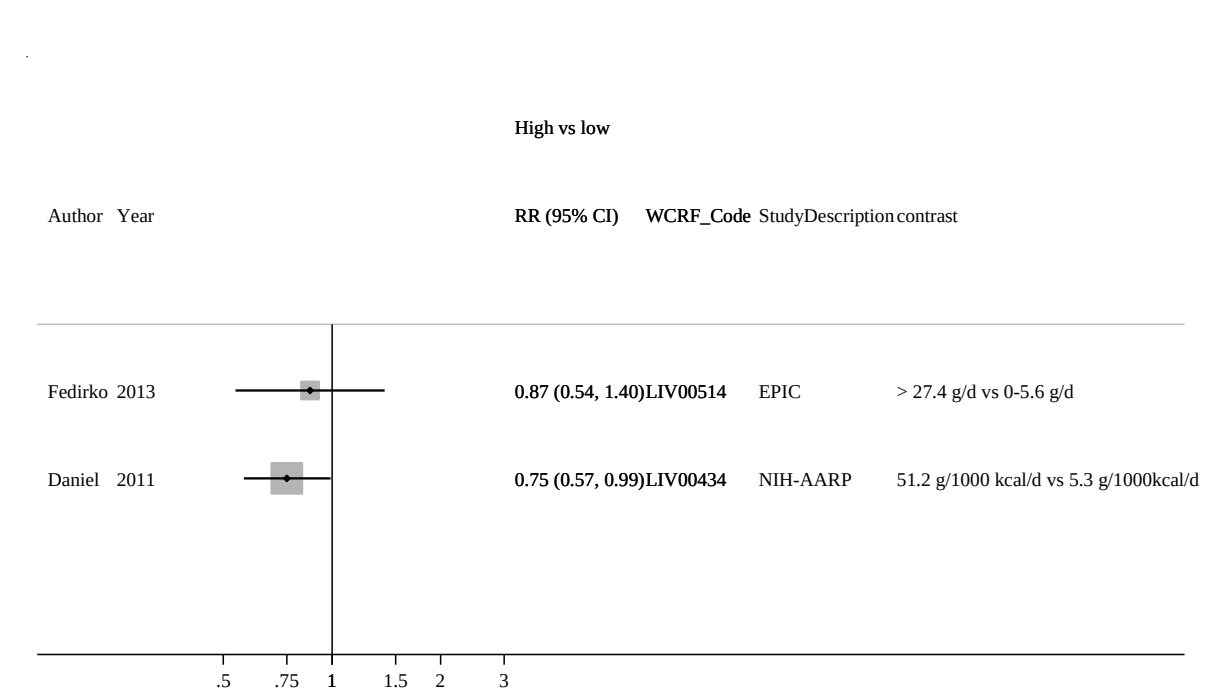


Figure 12 Dose-response meta-analysis of poultry and liver cancer - per 20 g/day

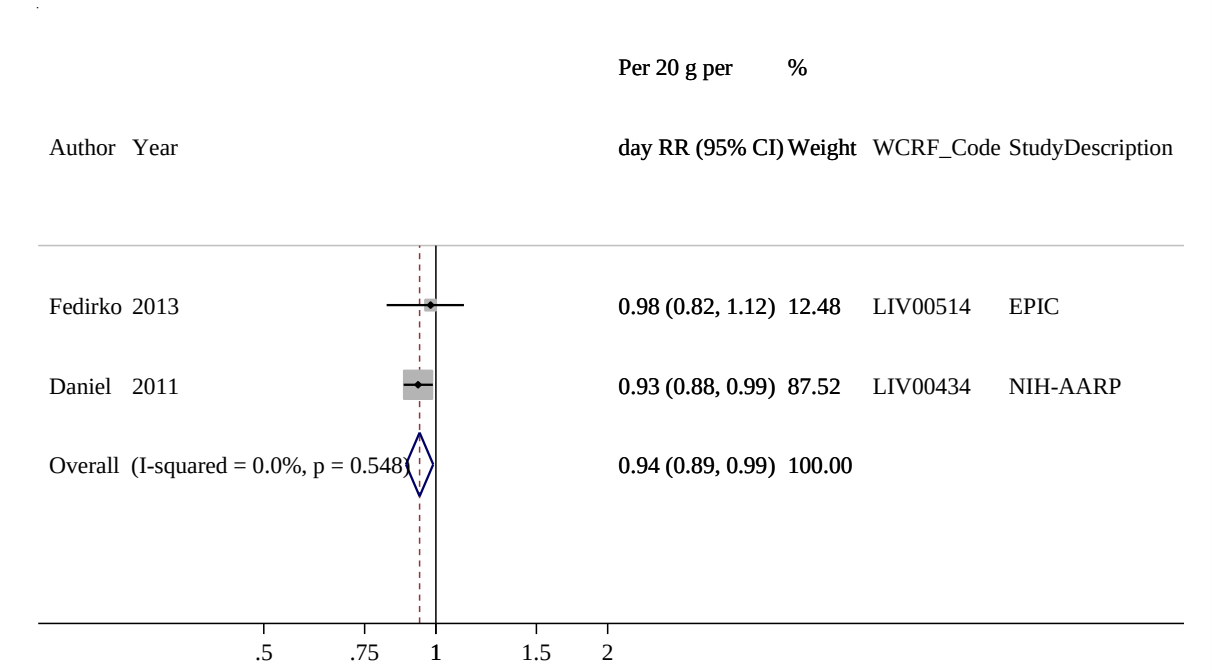
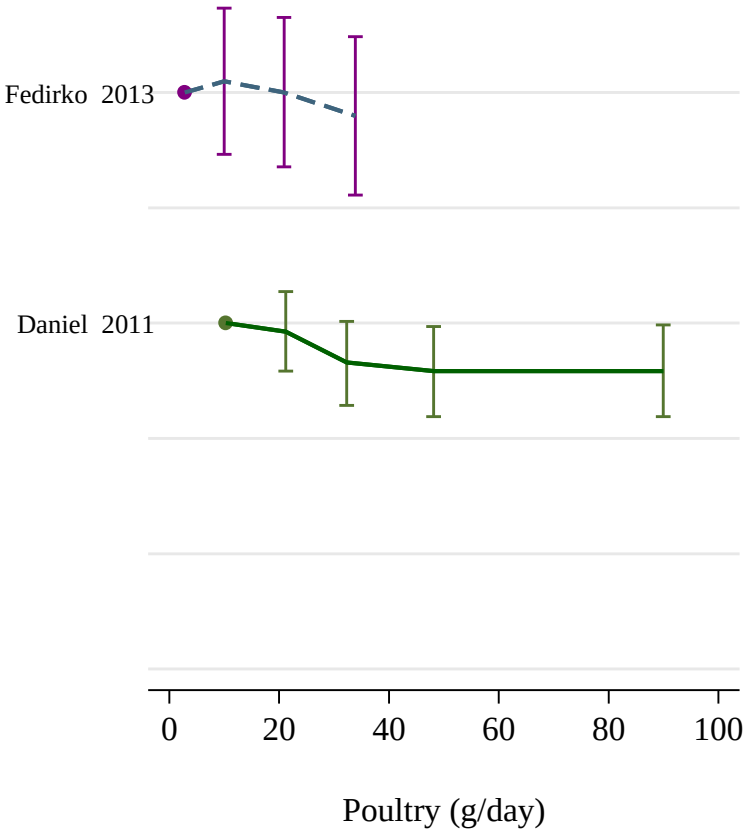


Figure 13 Dose-response graph of poultry and liver cancer



2.5.2 Fish

Methods

Up to June 2013, seven publications from six cohort studies were identified; four publications were identified during the CUP. The CUP meta-analysis included four studies. Portions or serving sizes were approximated to 120 grams per day (2005 SLR). The dose-response results are presented for an increment of 20 grams of fish intake per day.

One study presented results in g/1000 kcal days (Daniel et al, 2011). These results were transformed to g/d using the mean daily kcal intake reported in the paper.

One paper (Songserm et al, 2012) was not included in the review because reported on raw fresh water fish (*Koi-Pla*) intake in Thailand. This type of fish is the main source of liver fluke infection in that country and associated with liver cancer risk. The RR reported in this paper was 2.5 (95% CI: 1.05-5.74, p=0.04), when comparing non-consumption versus weekly intake.

Two other studies were not included in the dose-response meta-analysis and in the forest plot comparing the highest with the lowest intake level: the measure of association in Hirayama et al 1989 was age-standardized mortality ratio with no confidence interval and Ikeda, et al, 1983 reported on broiled and dried fish, and did not presented RR estimates.

Main results

The summary RR per 20 g/d was 0.94 (95% CI: 0.89-0.99; I^2=52.5%, $P_{heterogeneity}$ =0.09) for all four studies combined.

There was no significant evidence of publication bias with Egger's test (p=0.17).

Heterogeneity

There was evidence of moderate to high heterogeneity across the limited number of studies (I^2=52.5%, $P_{heterogeneity}$ =0.09). There was no indication of publication bias with Egger's test (p=0.23) but across the limited number of studies, the funnel plot suggests that small studies showing positive associations were missing. The asymmetry is also driven by the inverse association reported in Fedirko et al, 2013a (EPIC).
Only two studies could account for HBV/HVC status (Fedirko et al, 2013a; Sawada et al, 2012) and in these studies, the inverse association with fish intake was stronger than in other studies. In the European cohort (Fedirko et al, 2013a) the observed inverse association of fish intake with hepatocellular carcinoma was not altered by adjustment for HBV/HCV status or liver function score, or after exclusions of first 2 years of follow-up. The results were similar in a nested case-control study subset in which α-fetoprotein level was used to exclude metastatic cases or other types of liver cancers (78 with metastasis in the liver or ineligible histology code were excluded). In the Japanese study (Sawada et al, 2012), total fish consumption was not statistically significantly associated with the risk of HCC, with a multivariable HR for the highest compared to lowest quintile of 0.52 (95% CI, 0.20 –1.32; *P*trend = 0.31) when subjects were limited to those who were both anti-HCV or HBsAg positive (n = 1303), and the inverse association between total fish and HCC was strengthened when subjects were limited to those who were anti-
HCV positive, with a multivariable HR for the highest compared to the lowest quintile of 0.30 (95% CI: 0.11–0.82; *P*trend =0.03).

Comparison with the Second Expert Report

A highest versus lowest meta-analysis was conducted in the Second Expert Report, with a summary RR of 1.08 (95% CI: 0.65-1.80, n=2)

Published meta-analysis

No published meta-analyses were identified.

Table 17 Studies on fish consumption identified in the CUP

Author, year	Country	Study name	Cases	Years of follow up	Sex	RR	LCI	UCI	Contrast
Fedirko, 2013a	Europe	European Prospective Investigation into Cancer and Nutrition	191	11.4	All	0.63 0.83	0.39 0.74	1.01 0.95	>50.8 g/d vs 0-14.2 g/d Per 20 g/d increment
Sawada, 2012	Japan	Japan Public Health Center-based Prospective Study	398	11.2	All	0.64	0.41	1.02	160.6 g/d vs 35.5 g/d
Daniel, 2011	USA	NIH-AARP Diet and Health Study	582	9.1	All	0.86	0.65	1.13	21.4 g/1000 kcal/d vs 3.6 g/1000 kcal/d
Iso, 2007	Japan	Japan Collaborative Cohort Study for Evaluation of Cancer	436 205	~12	M F	0.97 0.92	0.76 0.64	1.25 1.32	>= 5 times/week vs < 3 times/week

Table 18 Overall evidence on fish consumption and liver cancer

	Summary of evidence
2005 SLR	Three studies were identified during the 2005 SLR on fish intake and liver cancer. One of these studies only investigated broiled and dried fish, other study reported age-standardized mortality ratios. A highest versus lowest intake meta-analysis was conducted and included two studies.
Continuous Update Project	Four publications were identified; all of them could be included in the meta-analysis. The meta-analysis showed a significant inverse association between fish intake and liver cancer.

Table 19 Summary of results of the dose response meta-analysis of fish consumption and liver cancer

Liver cancer		
	2005 SLR	Continuous Update Project
Studies (n)	2	4
Cases (n)	175	1812
Increment unit used	Highest vs lowest	Per 20 g/day
Overall RR (95%CI)	1.08 (0.65-1.80)	0.94 (0.89-0.99)
Heterogeneity (I^2,p-value)	25.8%, p=0.26	52.5%, p=0.09

Table 20 Inclusion/exclusion table for meta-analysis of fish consumption and liver cancer

WCRF_ Code	Author	Year	Study Design	Study Name	Subgroup	Cancer Outcome	2005 SLR	CUP dose-response meta-analysis	CUP HvL forest plot	Estimated values	Exclusion reasons
LIV00514	Fedirko(a)	2013	Prospective Cohort study	European Prospective Investigation into Cancer and Nutrition	All	Incidence	No	Yes	Yes	--	-
LIV00423	Sawada	2012	Prospective Cohort study	Japan Public Health Center-based Prospective Study	All	Incidence	No	Yes	Yes	--	-
LIV00434	Daniel,	2011	Prospective Cohort study	NIH-AARP Diet and Health Study	All	Incidence	No	Yes	Yes	Person-years, cases per category	-
LIV00463	Iso	2007	Prospective Cohort study	Japan Collaborative Cohort Study for Evaluation of Cancer	M F	Mortality	No	Yes	Yes	Mid-points	--
LIV00670	Kurozawa	2004	Prospective Cohort study	Japan Collaborative Cohort Study for Evaluation of Cancer	M F	Mortality	Yes	No	No	--	Superseded by Iso, 2007 (LIV00463)
LIV00158	Hirayama	1989	Prospective Cohort study	Japanese, cohort study	M F	Mortality	Yes	No	No	--	RR presented as age-standardized mortality ratio
LIV00168	Ikeda	1983	Prospective Cohort study	Japan, Adult Health Study	M F	Mortality	Yes	No	No	--	Data on broiled (no RR available) and dried fish

Figure 14 Highest versus lowest forest plot of fish consumption and liver cancer

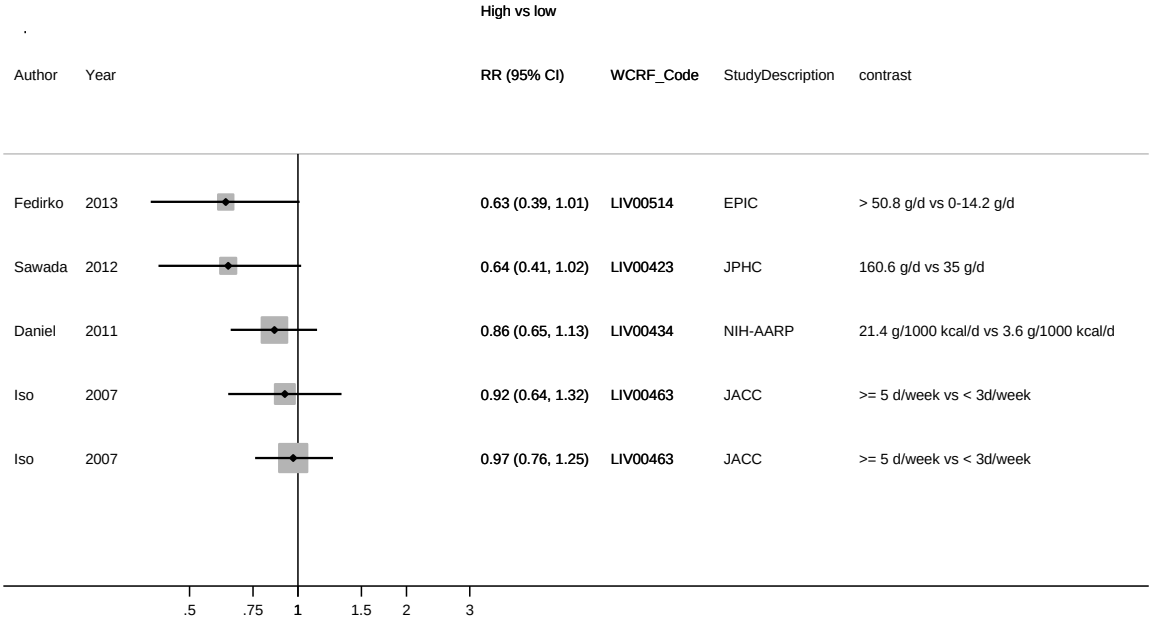


Figure 15 Dose-response meta-analysis of fish and liver cancer - per 20 g/day

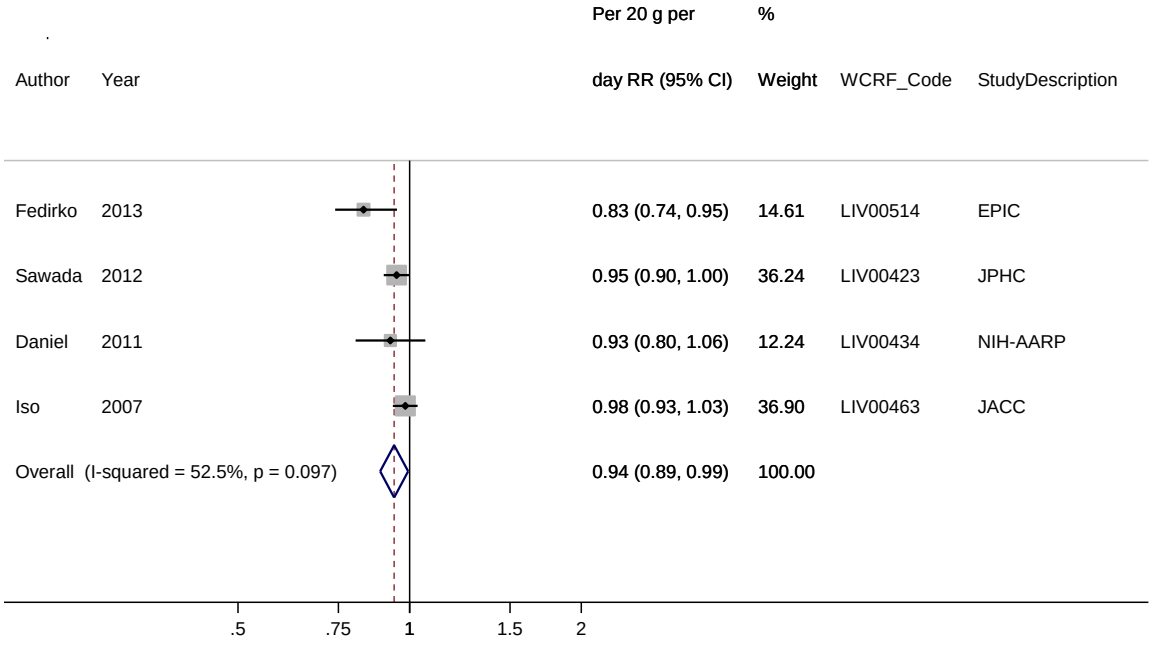


Figure 16 Funnel plot of fish intake and liver cancer

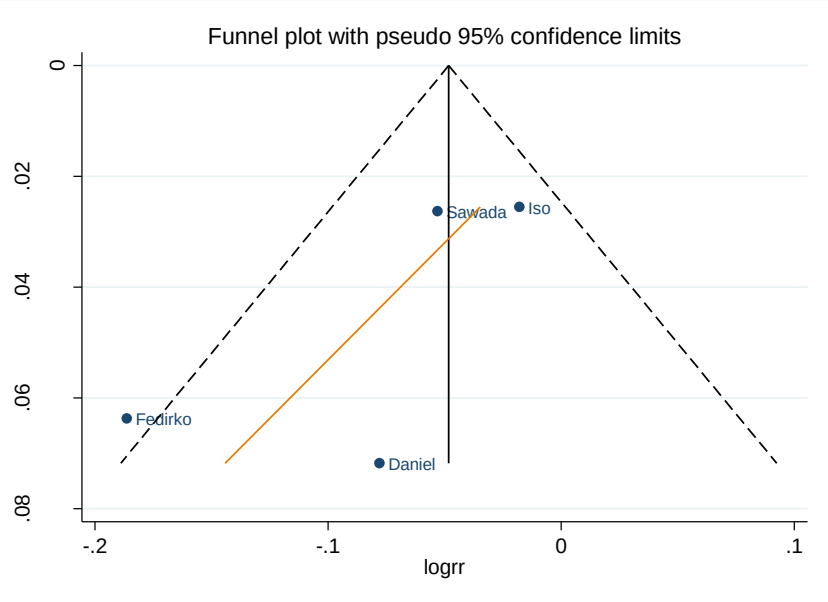
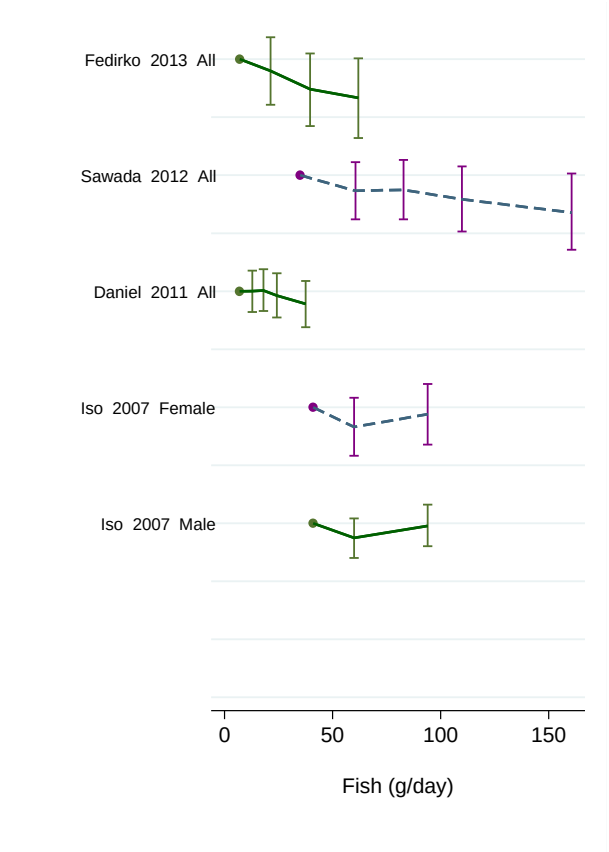


Figure 17 Dose-response graph of fish and liver cancer



3.6.1 Coffee

Methods

Up to June 2013, reports from eight cohort studies (11 publications) were identified. Four publications were identified during the 2005 SLR and seven during the CUP. The CUP meta-analysis included six cohort studies. For the dose-response analyses, coffee was rescaled assuming 1 cup was equivalent to 200 g, one drink, and one time per day. The dose-response results are presented for an increment of 1 cup of coffee per day. Only one of the included studies reported on mortality as outcome.

Main results

The summary RR per 1 cup/day was 0.86 (95% CI: 0.81-0.90; I^2=18.4%, $P_{heterogeneity}$ =0.294) for the six studies combined. In stratified analyses, the summary RR for females was 0.91 (95% CI: 0.83-1.01; I^2=0%, $P_{heterogeneity}$ =0.94), and 0.84 (95% CI: 0.78-0.90; I^2=20.6%, $P_{heterogeneity}$ =0.28) for males.

The meta-analysis included six cohorts from South-Asian populations and one from a European population. The European study included in the meta-analysis reported a significant inverse association (Hu et al, 2008). The other European study, a case-control nested in a cohort (Trichopoulos et al, 2011) was not included in the dose-response meta-analysis. This study did not find evidence of association of regular coffee intake and risk of hepatocellular carcinoma (115 cases matched to 229 control subjects) in analysis adjusted by main risk factors, including chronic HBV and HCV infections.

Three of the two cohort studies (two publications) included in the meta-analyses had information on HBV/HCB serological status in a subset of the participants. In the Singapore Chinese Health Study (Johnson et al, 2011), the point estimates of relative risk of hepatocellular carcinoma associated with high consumption of coffee in a subgroup of 92 cases and 276 matched controls with HBV/HCV serological status were very similar to those based on the entire cohort. In the Japan Public Health Centre-based Prospective Study I and II (Inoue et al, 2005), the inverse associations were similar to that observed in the entire study population when the analyses were restricted to hepatitis C virus-positive and hepatitis B virus-positive participants. A more recent analysis in the JPHC-II cohort confirmed these results (Inoue et al, 2009a).

Two other studies looked at previous history of liver disease. In the Finish study (Hu et al, 2008), the inverse association between coffee consumption and the risk of liver cancer was consistent after excluding subjects with liver chronic disease at baseline and in analysis stratified by serum levels of gamma-glutamyltransferase, an indicator of liver injury. In a Japanese study (Shimazu et al, 2005) a significant inverse association between coffee consumption and the risk of liver cancer was observed in subjects with a history of liver disease (53 cases), whereas the association was inverse but not significant in subjects without a history of liver disease (64 cases).

No information on previous liver disease was available in a Japanese study (Iso et al, 2007) on mortality for liver cancer in which a significant inverse association was observed.

Heterogeneity

There was low heterogeneity across the studies (I^2=18.4%, p=0.29). There was no indication of publication bias with Egger's test (p=0.20).

Comparison with the Second Expert Report

A highest versus lowest coffee intake meta-analysis was conducted during the Second Expert Report (RR= 0.53; 95% CI: 0.39-0.73, I^2: 0%, $P_{heterogeneity}$ =0.74, 4 studies).

Published meta-analysis

A meta-analysis (Bravi et al, 2013) reported a summary RR for any coffee intake versus no intake of 0.60 (95% CI: 0.50–0.71) (16 studies, 8 cohorts and 8 case-control, 3153 HCC cases). The RR was 0.56 (95% CI, 0.42–0.75) for the 8 case-control studies included and 0.64 (95% CI: 0.52-0.78) for 8 cohort studies (7 Asian and 1 European). The summary RR for an increment of 1 cup/day of coffee was 0.80 (95% CI: 0.77–0.84) for all studies combined, 0.77 (95% CI: 0.71–0.83) for case-control studies, and 0.83 (95% CI: 0.78–0.88) for cohort studies. The association was consistent regardless alcohol intake habits, history of hepatitis or other liver disease and sex.

In another meta-analysis (Sang et al, 2013), the RR estimates of liver cancer for the highest intake versus non/occasionally coffee drinkers was 0.50 (95% CI: 0.42–0.59; p= 0.337, $P_{heterogeneity}$ = 10.2%; 16 studies, seven cohorts and nine case-control studies). The summary RR estimates were 0.50 (95% CI: 0.40–0.63) for case–control studies and 0.48 (95%CI: 0.38–0.62) for cohort studies. The summary RRs were 0.38 (95% CI: 0.25–0.56) in men and 0.60 (95% CI: 0.33–1.10) in women. The cohort studies in this meta-analysis are the same studies included in the dose-response analysis of the CUP review.

A meta-analysis published in 2007 (Larsson et al, 2007a), presented results from four cohort and five case-control studies (2260 cases and 239146 non-cases). The RR for an increase of 2 cups/day coffee intake was 0.57 (95% CI: 0.49–0.67; p=0.17). In stratified analysis, the summary RRs of liver cancer for an increase of 2 cups/day coffee intake were 0.69 (95% CI: 0.55– 0.87) for persons without a history of liver disease and 0.56 (95% CI: 0.35– 0.91) for those with a history of liver disease.

Table 21 Studies on coffee consumption identified in the CUP

Author, year	Country	Study name	Cases	Years of follow up	Sex	RR	LCI	UCI	Contrast
Trichopoulos, 2011	Europe	European Prospective Investigation into Cancer and Nutrition	115	8.9	All M F	1.36 1.56 0.70	0.66 0.67 0.10	2.79 3.64 4.90	>= 250 g/d vs <250g/d
Johnson, 2011	Singapore (Chinese origin)	Singapore Chinese Health Study	362	6.4	All	0.56	0.31	1.00	>= 3 drinks/d vs non-drinkers
Inoue, 2009a	Japan	Japan Public Health Center-based Prospective Study II	110 73 37	12.7	All M F	0.54 0.32 0.69	0.21 0.10 0.11	1.39 1.10 4.22	>= 3 cups/d vs almost never
Hu, 2008	Finland	Finland 1972-2002	128 82 46	19.3	All M F	0.32 0.28 0.41	0.16 0.13 0.10	0.62 0.61 1.70	>= 8 cups/d vs 0-1 cups/d
Ohishi, 2008	Japan	Adult Health Study Longitudinal Cohort	224	~24	All	0.40	0.16	1.02	Daily vs never
Wakai, 2007	Japan	Japan Collaborative Cohort study	96	~10	All	0.49	0.25	0.96	>= 1 cup/d vs non-drinkers
Iso, 2007	Japan	Japan Collaborative Cohort study	434 207	~12	M F	0.73 0.80	0.58 0.56	0.93 1.15	>= 2 times/d vs <=2 times/month

Table 22 Overall evidence on coffee consumption and liver cancer

	Summary of evidence
2005 SLR	Four publications (four cohorts) were identified during the 2005 SLR on coffee intake and liver cancer. This meta-analysis showed a significant inverse association.
Continuous Update Project	Seven publications (six cohorts, four new) were identified during the CUP; three of them could be included in the meta-analysis. Overall, six cohorts were included in the meta-analysis, A significant inverse association was observed.

Table 23 Summary of results of the dose response meta-analysis of coffee consumption and liver cancer

Liver cancer		
	2005 SLR	Continuous Update Project
Studies (n)	4	6
Cases (n)	709	1582
Increment unit used	Highest versus lowest	Per 1 cup /day
Overall RR (95%CI)	0.53 (0.39-0.73)	0.86 (0.81-0.90)
Heterogeneity (I^2,p-value)	0%, p=0.74	18.4%, p=0.29
By sex		Women
Studies (n)		3
Overall RR (95%CI)		0.91 (0.83-1.01)
Heterogeneity (I^2,p-value)		0%, p=0.94
		Men
Studies (n)		3
Overall RR (95%CI)		0.84 (0.78-0.90)
Heterogeneity (I^2,p-value)		20.6%, p=0.28

Table 24 Inclusion/exclusion table for meta-analysis of coffee consumption and liver cancer

WCRF_ Code	Author	Year	Study Design	Study Name	Sub-group	Cancer Outcome	2005 SLR	CUP dose-response meta-analysis	CUP HvL forest plot	Estimated values	Exclusion reasons
LIV00425	Trichopoulos	2011	Nested Case Control	European Prospective Investigation into Cancer and Nutrition	All M F	Incidence	No	No	Yes	-	Only two categories of intake
LIV00432	Johnson	2011	Nested Case Control	Singapore Chinese Health Study	All	Incidence	No	Yes	Yes	Mid-points	-
LIV00450	Inoue (a)	2009	Prospective Cohort	Japan Public Health Center-based Prospective Study II	All M F	Incidence	No	No	No	--	LIV00633 (Inoue et al, 2005) JPHC I and II with more cases was used instead. Results of the two studies were similar
LIV00473	Hu	2008	Prospective Cohort	Finland, 1972-2002	All M F	Incidence	No	Yes	Yes	Mid-points	--
LIV00476	Ohishi	2008	Nested Case Control	Adult Health Study Longitudinal Cohort	All	Incidence	No	No	Yes	--	Only two categories of intake
LIV00463	Iso	2007	Prospective Cohort	Japan Collaborative Cohort study	M F	Mortality	No	Yes	Yes	Mid-points	-
LIV00478	Wakai	2007	Nested Case Control	Japan Collaborative Cohort study	All	Mortality	No	No	No	--	Superseded by LIV00463 (Iso el at, 2007)
LIV00543	Shimazu	2005	Prospective Cohort	Japan Miyagi Prefecture, cohort 1& 2	All	Incidence	Yes	Yes	Yes	Mid-points	--
LIV00633	Inoue	2005	Prospective Cohort	Japan Public Health Center-based Prospective Study I & II	All M F	Incidence	Yes	Yes	Yes	Mid-points	
LIV00669	Kurozawa	2005	Prospective Cohort	Japan Collaborative Cohort study	All M F	Mortality	Yes	No	No	--	Superseded by LIV00463 (Iso el at, 2007)
LIV00670	Kurozawa	2004	Prospective Cohort	Japan Collaborative Cohort study	M F	Mortality	Yes	No	No	--	Superseded by LIV00463 (Iso el at, 2007)

Figure 18 Highest versus lowest forest plot of coffee consumption and liver cancer

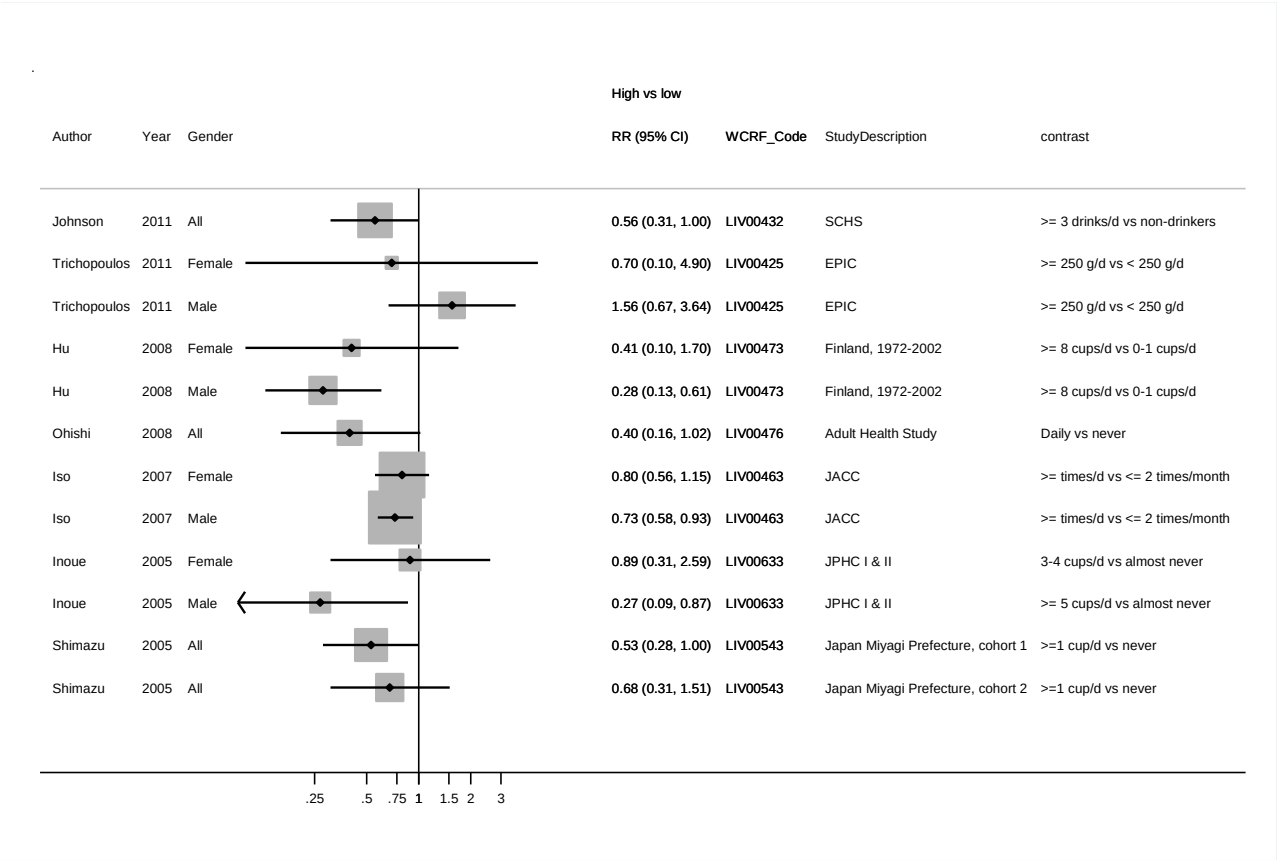
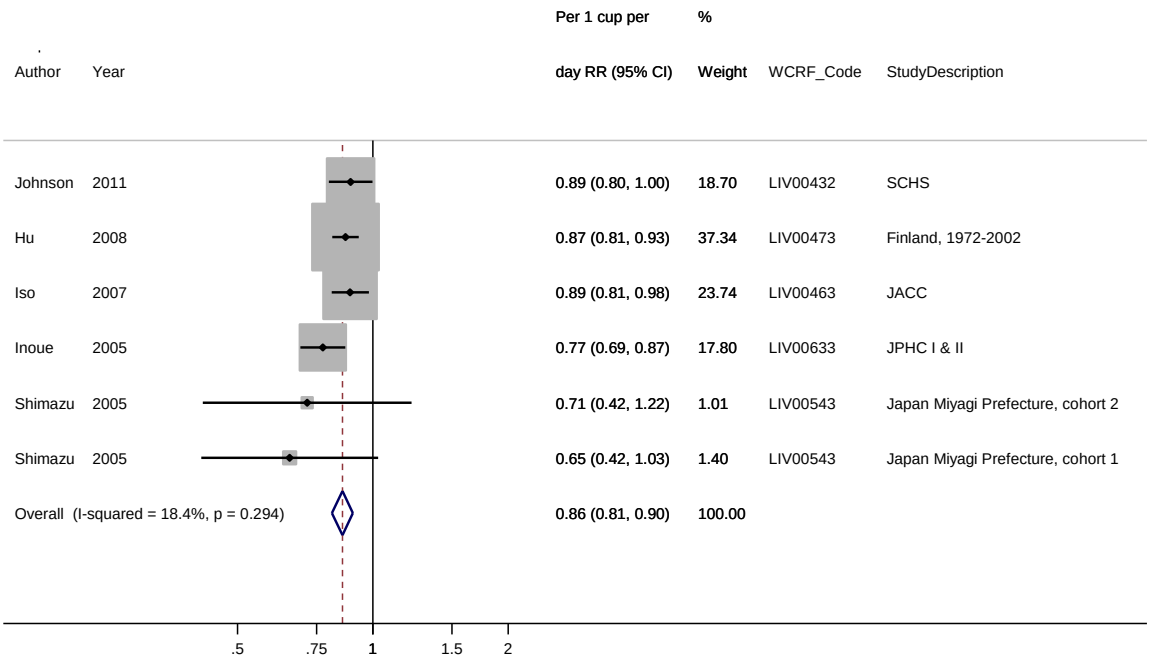


Figure 19 Dose-response meta-analysis of coffee and liver cancer - per 1 cup/day



Note: Inoue et al, 2005 included data originally from two cohort studies: JPHC I and II.

Figure 20 Figure Funnel plot of coffee intake and liver cancer

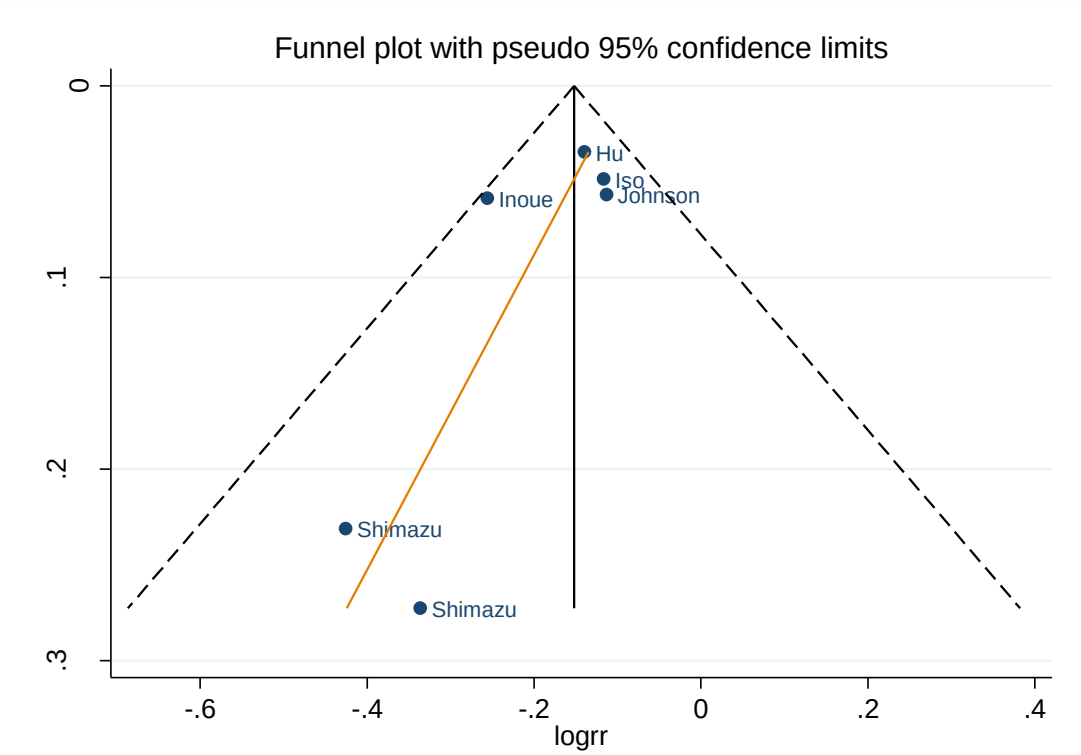


Figure 21 Dose-response graph of coffee and liver cancer

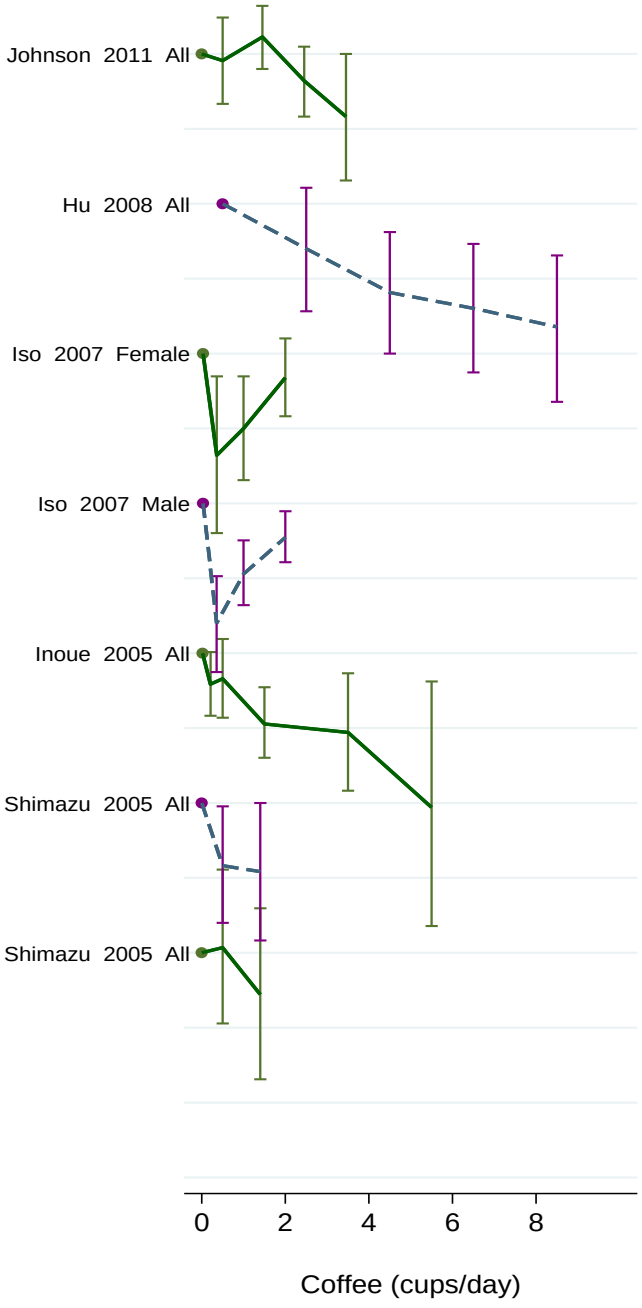
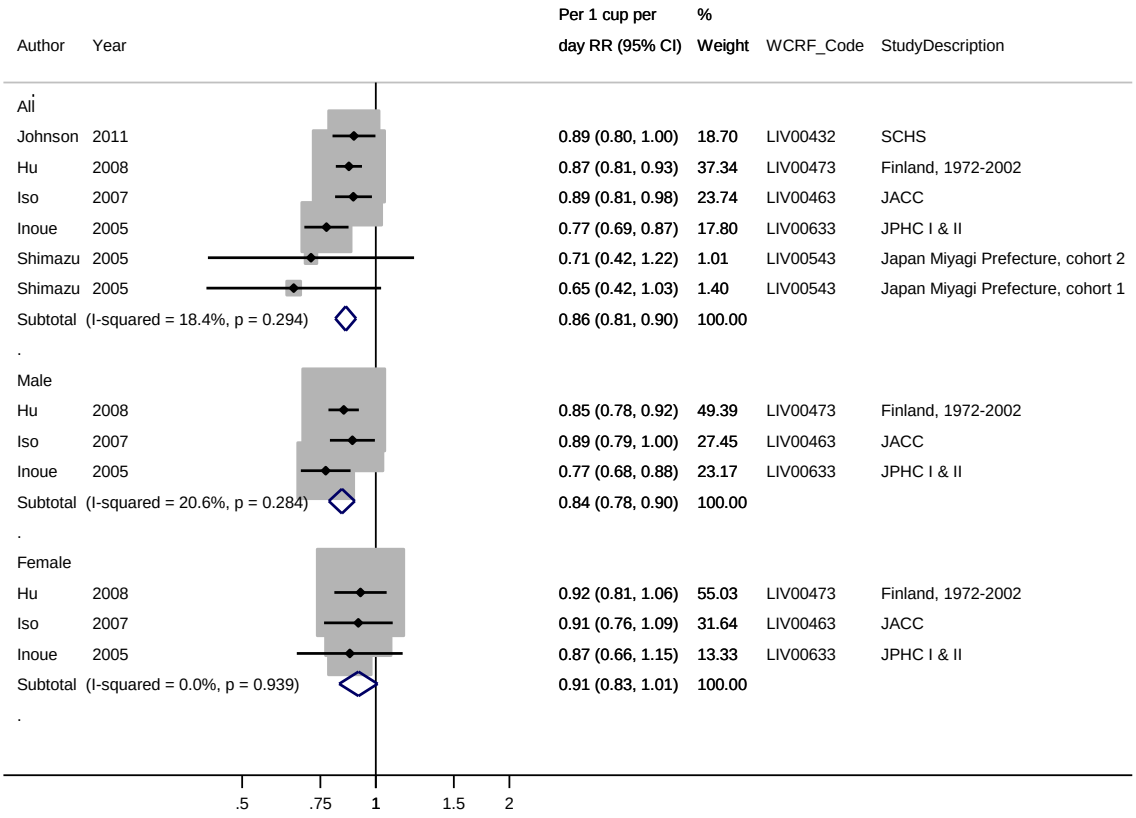


Figure 22Dose-response meta-analysis per 1 cup/day of coffee intake and liver cancer by sex



3.6.2.2 Green tea

Methods

Up to June 2013, reports from eight cohort studies were identified. Five publications were identified during the CUP. The CUP meta-analysis included four cohort studies. The dose-response results are presented for an increment of 1 cup of green tea per day.

Main results

The summary RR per cup/d was 0.99 (95% CI: 0.94-1.03; I^2=60.2%, $P_{heterogeneity}$ =0.05) for all studies combined.

Heterogeneity

There was evidence of high heterogeneity across the limited number of studies (I^2=60.2%, $P_{heterogeneity}$ =0.05). There was no indication of publication bias with Egger's test (p=0.78).

All studies were in Japanese populations. Only one study (Ui et al, 2010) reported a significant inverse association. The significant association was for more than 5 cups of green tea intake per day compared to less than one cup among participants who did not have a history of liver disease, and was inverse but not significant in participants with history of liver disease; it was significant in women but not in men. No association was observed in two Chinese studies and one Japanese study that could not be included in the dose-response meta-analysis (Nechuta et al, 2012, Johnson et al, 2011, Shimazu et al, 2005).

Comparison with the Second Expert Report

No meta-analysis was conducted during the Second Expert Report

Published meta-analysis

In a meta-analysis of 11 studies (five case–control and six prospective cohort studies) the summary RR for the highest vs the lowest consumption of green tea intake was 0.79 (95% CI: 0.68–0.93) (Sing et al, 2011). The overall estimate for any type of tea (highest vs lowest intake) was 0.77 (95% CI = 0.57-1.03; 13 studies). The summary for cohort studies for the highest vs the lowest consumption of any type of tea (6 cohort studies on green tea and one study on any type of tea) was 0.84 (95% CI: 0.69-1.02).

Table 25 Studies on green tea consumption identified in the CUP

Author, year	Country	Study name	Cases	Years of follow up	Sex	RR	LCI	UCI	Contrast
Nechuta, 2012	China	Shanghai Women's Health Study	247	11	All	0.89	0.58	1.38	Regular vs never drinkers
Ui, 2010	Japan	Ohsaki Cohort Study	247 164 83	9	All M F	0.58 0.63 0.50	0.41 0.41 0.27	0.83 0.98 0.90	>= 5 cup/d vs < 1 cup/d
Johnson, 2011	Singapore (Chinese origin)	Singapore Chinese Health Study	362	6.4	All	-	-	-	No association
Inoue, 2009a	Japan	Japan Public Health-Center-based Prospective Study	110	12.7	All	1.44	0.84	2.45	>= 5 cup/d vs < 3 cup/d
Iso, 2007	Japan	Japan Collaborative Cohort Study for Evaluation of Cancer	436 205	~12	M F	0.89 0.85	0.69 0.59	1.16 1.23	>= 4 times/d vs <= 3 times/week

Table 26 Overall evidence on green tea consumption and liver cancer

	Summary of evidence
2005 SLR	One study was identified during the 2005 SLR on green tea intake and liver cancer.
Continuous Update Project	Five publications were identified during the CUP; four studies could be included in the meta-analysis. No significant association (RR=0.99) was observed.

Table 27 Summary of results of the dose response meta-analysis of green tea consumption and liver cancer

Liver cancer		
	2005 SLR*	Continuous Update Project
Studies (n)	-	4
Cases (n)	-	1389
Increment unit used	-	Per 1 cup /day
Overall RR (95%CI)	-	0.99 (0.94-1.03)
Heterogeneity (I^2,p-value)	-	60.2%, p=0.05

*No meta-analysis of cohort studies was conducted during SLR

Table 28 Inclusion/exclusion table for meta-analysis of green tea consumption and liver cancer

WCRF_ Code	Author	Year	Study Design	Study Name	Subgroup	Cancer Outcome	2005 SLR	CUP dose-response meta-analysis	CUP HvL forest plot	Estimated values	Exclusion reasons
LIV00448	Nechuta	2012	Prospective Cohort study	Shanghai Women's Health Study	All	Incidence	No	No	Yes	--	Only two categories of intake
LIV00432	Johnson	2011	Nested Case Control	Singapore Chinese Health Study	All	Incidence	No	No	No	---	RRs by category of coffee intake and overall could not be derived
LIV00447	Ui	2009	Prospective Cohort study	Ohsaki Cohort Study	All M F	Incidence	No	Yes	Yes	Mid-points	-
LIV00450	Inoue (a)	2009	Prospective Cohort study	Japan Public Health-Center-based Prospective Study	All	Incidence	No	Yes	Yes	Mid-points	-
LIV00463	Iso	2007	Prospective Cohort study	Japan Collaborative Cohort Study for Evaluation of Cancer	M F	Mortality	No	Yes	Yes	Mid-points	--
LIV00543	Shimazu	2005	Prospective Cohort	Japan Miyagi Prefecture, cohort 1 and 2	All	Incidence	No	No	Yes		Missing number of cases and participants per category (two cohorts)
LIV00670	Kurozawa	2004	Prospective Cohort study	Japan Collaborative Cohort Study for Evaluation of Cancer	M F	Mortality	Yes	No	No	--	Superseded by LIV00463 (Iso el at, 2007)
LIV00519	Nagano	2001	Prospective Cohort study	Life Span Study	All	Incidence	No	Yes	Yes	Person-years and mid-points	-

Figure 23 Highest versus lowest forest plot of green tea consumption and liver cancer

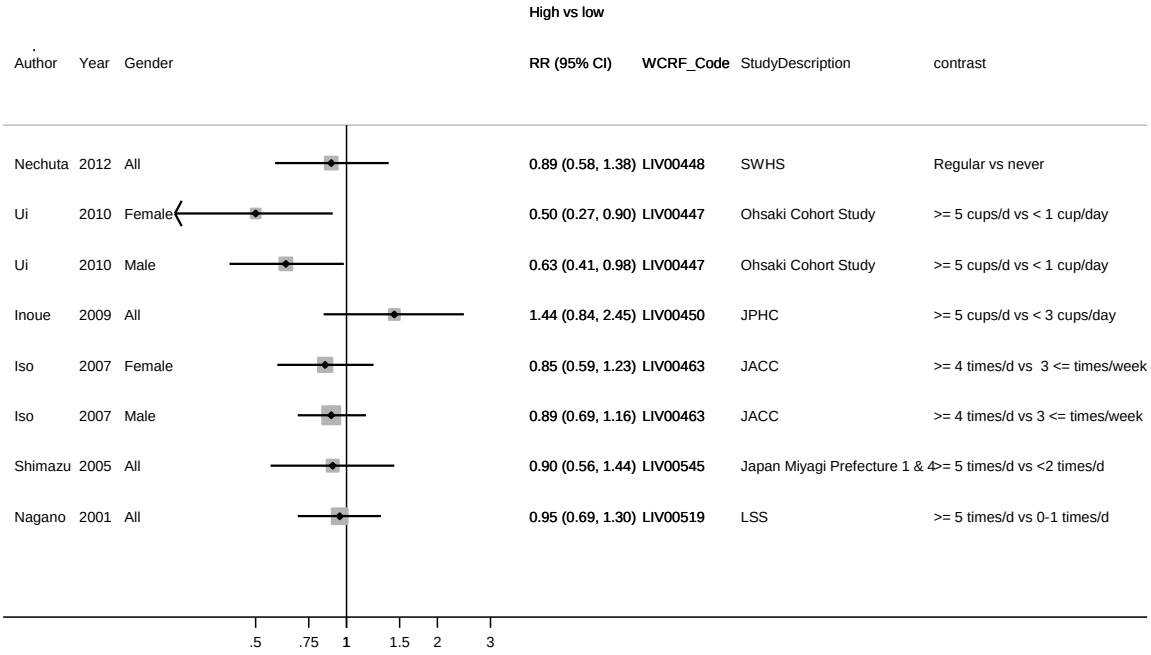


Figure 24 Dose-response meta-analysis of green tea and liver cancer - per 1 cup/day

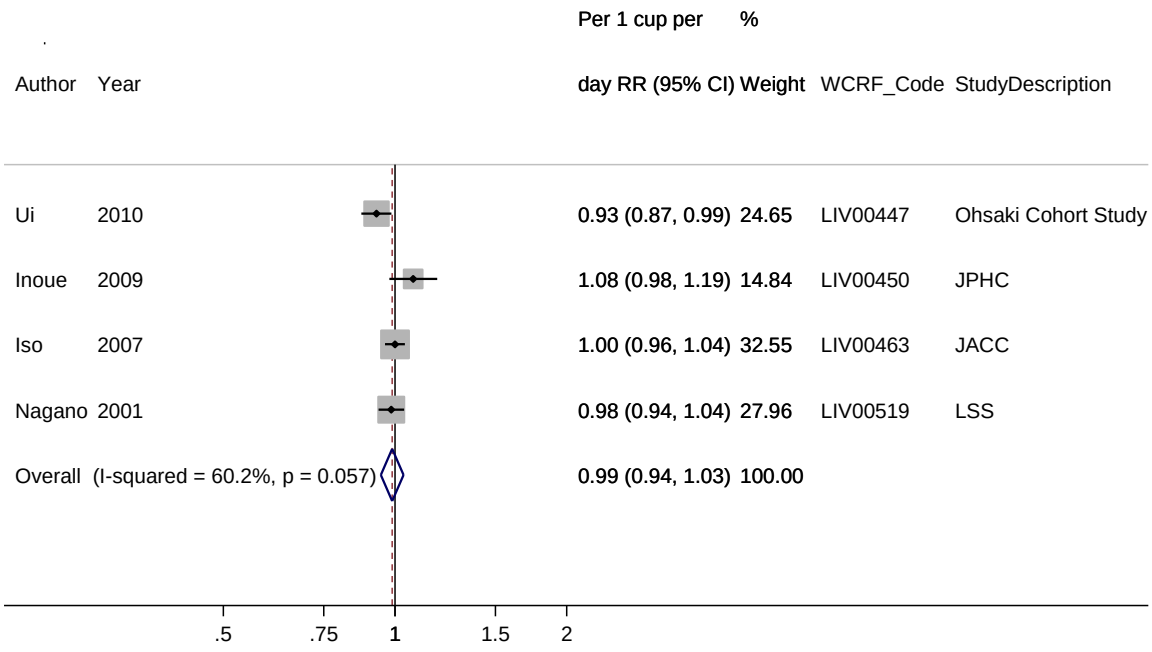


Figure 25 Funnel plot of green tea intake and liver cancer

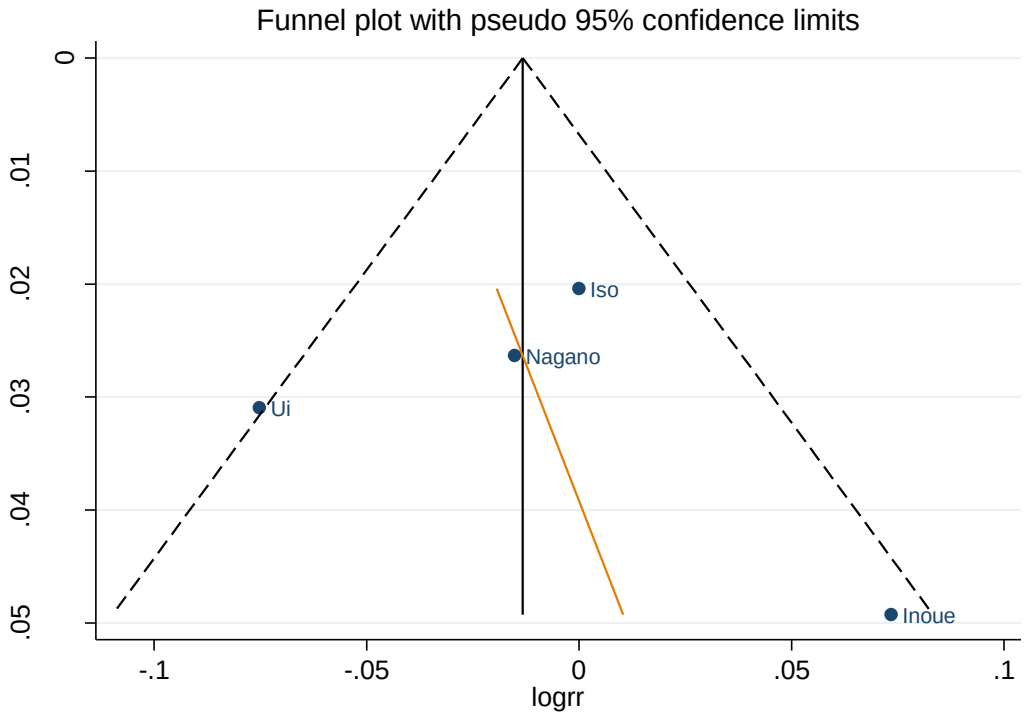
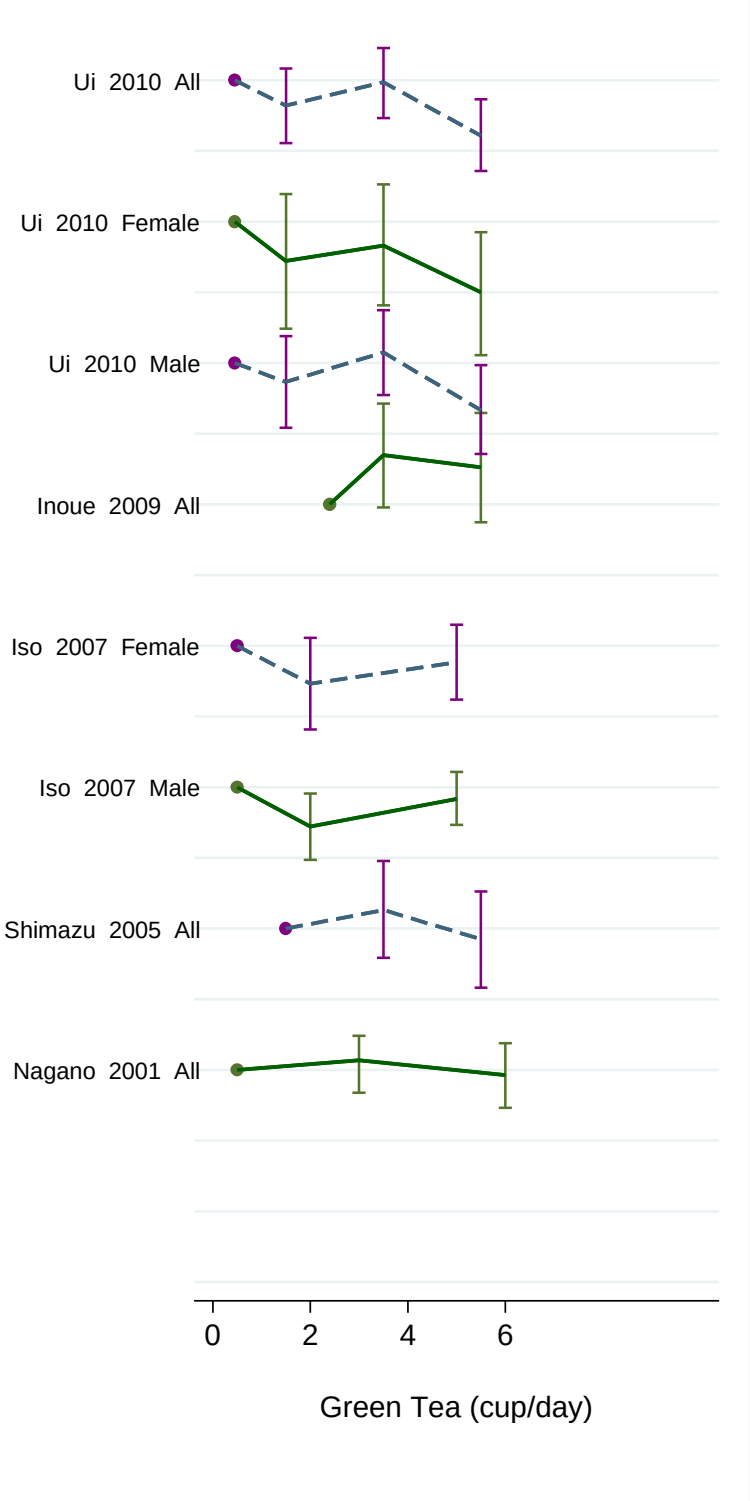


Figure 26 Dose-response graph of green tea and liver cancer



4.2.2.2.2 Aflatoxin

Only one new study (Wu, 2009) on aflatoxin and liver cancer was identified by the CUP. No meta-analysis was conducted.
Most prospective studies have been conducted in China and Taiwan. Their results are summarized in the Table below.

There are several reviews on the topic. The most recent review included 17 studies with 1680 HCC cases and 3052 controls from case-control studies and nested case-control studies conducted in China, Taiwan, or sub-Saharan Africa. The estimated RRs for aflatoxin exposure (any) was 4.75 (95% 2.78–8.11, 9 studies) in general population (HBsAg+ adjusted), 2.39 (95% CI 1.50–3.82, 11 studies) in HBsAg+ individuals, 5.91 (95% CI: 3.66-9.55, 6 studies) in HBsAg- individuals, and 54.1 (95% Ci: 21.3–137.7, 6 studies) for the combined effect of aflatoxin and HBV infection. The population attributable risk of aflatoxin-related HCC was estimated at 17% (14–19%) overall and higher in HBV+ (21%) than HBV− (8.8%) populations (Liu et al, 2013).

Table 29 Nested case-control and cohort studies on aflatoxin (any biomarker of exposure) and liver cancer identified in the CUP and 2005 SLR

Author, year	Country	Study description	Cases	Years of follow up	Sex	OR	LCI	UCI	Contrast
Wu, 2009	Taiwan	Case-control study nested within a community-based cohort, samples taken in 1990-92		13 years	M/F				AFB1-albumin adducts above mean (59.8 fmol/mg) vs below mean
			241 HCC 155 HCC 75 HCC			1.54 1.43 1.65	1.01 0.76 0.63	2.36 2.71 4.33	All participants HBsAg positive HBsAg negative Urinary AFB1 above mean (55.2 fmol/mL) vs below mean
			241 HCC			1.76	1.18	2.58	All participants
			143 HCC			1.19	0.72	1.98	HBsAg positive
			55 HCC			4.29	1.43	12.85	HBsAg negative
Yuan	2006	Case-control study nested in Shanghai Cohort Study	50 HCC	~12-15 years	M	3.25	1.63	6.48	Urinary aflatoxin biomarker positive vs negative
Sun	2001	Taiwan, chronic hepatitis B carriers	79 HCC	~ 6 years	M/F	2.0	1.1	3.7	AFB1-albumin adducts detectable vs non detectable
Sun	1999	145 men with chronic HBV, Qidong, China	22 HCC	10 years	M	3.3	1.2	8.7	Urinary AFM1 detectable (above 3.6 ng/L) vs non detectable
Yu	1997	4841 men HBsAg carriers, Taiwan	21 HCC	~4.7 years	M	12	1.2	117.4	Both markers (urinary AFM1 and AFB1-N7-guanine adducts) vs none
Chen	1996	4841 men, HbAg carriers, Taiwan	32 HCC	NA	M	3.8	1.0	14.5	AFB1-albumin adducts high vs un detectable
Wang	1996	Nested case control, Taiwan	56 HCC	~2 years	M	1.6	0.4	5.5	Serum level aflatoxin-albumin detectable vs non detectable
					M	3.8	1.1	12.8	Urinary levels of aflatoxin high vs low
Qian	1994	18 244 men Shanghai, China	55 HCC	~3-6 years	M	5.0	2.1	11.8	Any urinary aflatoxin biomarker vs none
Ross	1992	18 244 men Shanghai, China	22 liver cancer	~1-4 years	M	2.4	1.0	5.9	Any urinary aflatoxin biomarker vs none

HCC: Hepatocellular carcinoma

5.1.5 Glycaemic load

Methods

Up to June 2013, reports from four cohort studies were identified three publications), all during the CUP. All studies are included in the dose-response meta-analysis. The dose-response results are presented for an increment of 50 units of glycaemic load per day.

Main results

The summary RR per 50 units/d was 0.95 (95% CI: 0.85-1.07; I^2=69.9%, $P_{heterogeneity}$ =0.02) for all studies combined.

Heterogeneity

There was evidence of high heterogeneity across the limited number of studies (I^2=69.9%, p=0.02). Visual inspection of the forest plot shows that the results of the NIH-AARP (George et al, 2009) are discordant. The publication by George et al, 2009 was a study on many cancers. Most of the associations with glycaemic load were null. The authors indicated that although a few site-specific associations were significant, multiple comparisons may explain their significance, and many associations disappeared in subanalyses with more careful control for confounders (data not shown) There was no indication of publication bias with Egger's test (p=0.85).

Comparison with the Second Expert Report

No meta-analysis was conducted during the Second Expert Report

Published meta-analysis

No published meta-analyses were identified.

Table 30 Studies on glycaemic load identified in the CUP

Author, year	Country	Study name	Cases	Years of follow up	Sex	RR	LCI	UCI	Contrast
Fedirko, 2013b	Europe	European Prospective Investigation into Cancer and Nutrition	191	11.4	All	1.19 1.19	0.72 0.64	1.97 2.21	Quartile 4 vs Quartile 1 Per 50 units/d increment
Vogtmann, 2012	China	Shanghai Women's Health Study	139	11.2	F	1.02	0.59	1.79	241.9 units/d vs 166.3 units/d
		Shanghai Men's Health Study	208	5.3	M	1.07	0.68	1.67	286.0 units/d vs 194.4 units/d
George, 2009b	USA	NIH-AARP Diet and Health Study	72 238	6.89	F M	0.18 0.47	0.04 0.23	0.79 0.95	163.9 units/d vs 54.1 units/d 197.2 units/d vs 68.0 units/d

Table 31 Overall evidence on glycaemic load and liver cancer

	Summary of evidence
2005 SLR	No publication was identified during the 2005 SLR.
Continuous Update Project	Four cohorts were identified; all of them could be included in the meta-analysis. One study reported an inverse association. No significant association was observed in the other three studies.

Table 32 Summary of results of the dose response meta-analysis of glycaemic load and liver cancer

Liver cancer		
	2005 SLR*	Continuous Update Project
Studies (n)	-	4
Cases (n)	-	848
Increment unit used	-	Per 50 units/day
Overall RR (95%CI)	-	0. 95(0.85-1.07)
Heterogeneity (I^2,p-value)	-	69.9%, p=0.02

*No meta-analysis was conducted during the Second Expert Report

Table 33 Inclusion/exclusion table for meta-analysis of glycaemic load and liver cancer

WCRF_ Code	Author	Year	Study Design	Study Name	Subgroup	Cancer Outcome	2005 SLR	CUP dose-response meta-analysis	CUP HvL forest plot	Estimated values	Exclusion reasons
LIV00504	Fedirko(b)	2013	Prospective Cohort study	European Prospective Investigation into Cancer and Nutrition	All	Incidence	No	Yes	Yes	-	-
LIV00415	Vogtmann	2012	Prospective Cohort study	Shanghai Women's Health Study	F	Incidence	No	Yes	Yes	Person-years, cases per category	-
				Shanghai Men's Health Study	M	Incidence	No	Yes	Yes	Person-years, cases per category	-
LIV00498	George(b)	2009	Prospective Cohort study	NIH-AARP Diet and Health Study	F M	Incidence	No	Yes	Yes	Mid-points (categories 2, 3 & 4 only)	-

Figure 27 Highest versus lowest forest plot of glycaemic load and liver cancer

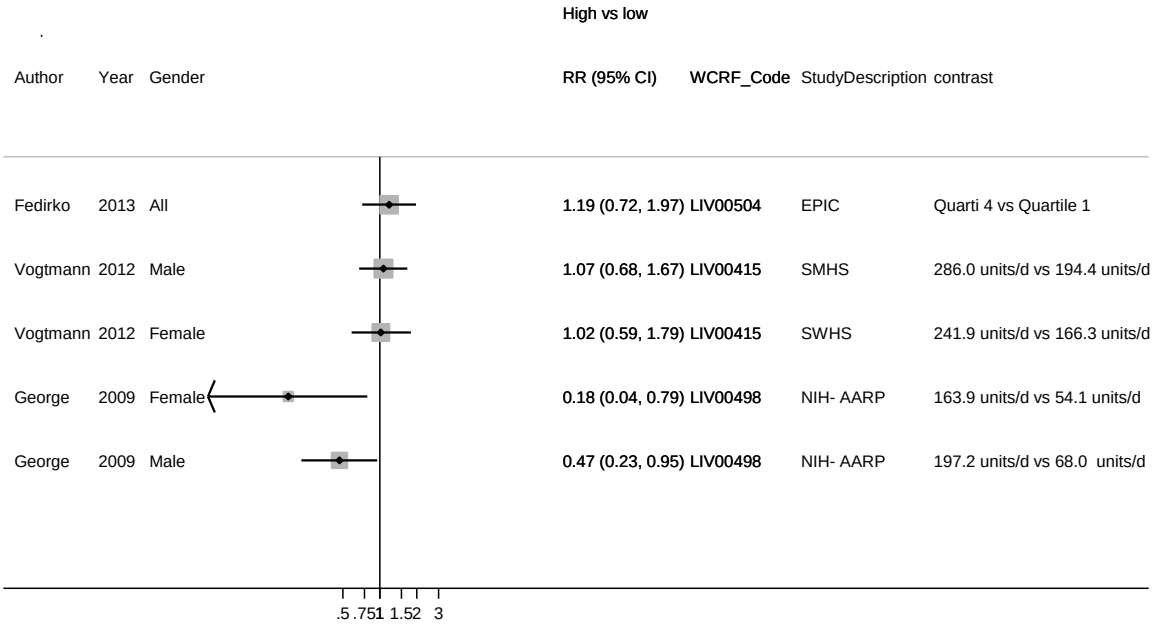


Figure 28 Dose-response meta-analysis of glycaemic load and liver cancer - per 50 units/day

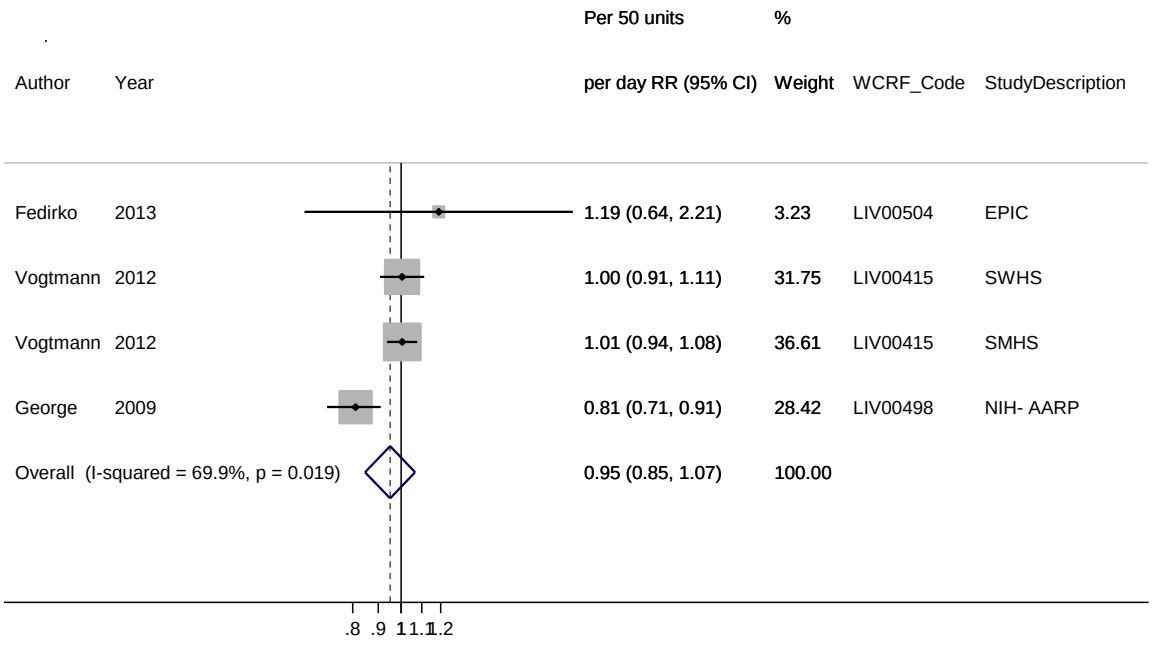


Figure 29 Dose-response graph of glycaemic load and liver cancer

5.1.5 Glycaemic index

Methods

Up to June 2013, reports from four cohort studies (three publications) were identified, all during the CUP. The dose-response results are presented for an increment of 5 units of glycaemic index per day.

Main results

The summary RR per 5 units/d was 1.02 (95% CI: 0.99-1.06; I^2=66.2%, $P_{heterogeneity}$ =0.03) for all studies combined. When stratifying by sex, the summary RR for females was 1.04 (95% CI: 1.00-1.08; I^2=23.3%, $P_{heterogeneity}$ =0.23, n=2), and for men 1.01 (95% CI: 0.97-1.05; I^2=77.2%, $P_{heterogeneity}$ =0.03, n=2).

Heterogeneity

There was evidence of high heterogeneity across the limited number of studies (I^2=66.2%, p=0.03). Visual inspection of the forest plot suggests that the heterogeneity may be explained by the increased risk observed in the Shanghai Women's Health Study (Vogtmann et al, 2012). However, the authors indicated that when GI, GL, and carbohydrates were entered as time-varying covariates, nearly all of the observed associations were closer to the null and no longer statistically significant but these result was not shown and could not be included in the analysis.

There was no indication of publication bias with Egger's test (p=0.56).

Comparison with the Second Expert Report

No meta-analysis was conducted during the Second Expert Report

Published meta-analysis

No published meta-analyses were identified.

Table 34 Studies on glycaemic index identified in the CUP

Author, year	Country	Study name	Cases	Years of follow up	Sex	RR	LCI	UCI	Contrast
Fedirko, 2013b	Europe	European Prospective Investigation into Cancer and Nutrition	191	11.4	All	1.09 1.04	0.71 0.71	1.66 1.51	Quartile 4 vs Quartile 1 Per 5 units/d increment
Vogtmann, 2012	China	Shanghai Women's Health Study	139	11.2	F	2.17	1.08	4.35	76.8 units/d vs 63.9 units/d
		Shanghai Men's Health Study	208	5.3	M	0.89	0.58	1.37	77.2 units/d vs 64.4 units/d
George 2009b,	USA	NIH-AARP Diet and Health Study	72 238	6.89	F M	0.95 1.62	0.43 1.05	2.10 2.48	58.2 units/d vs 48.8 units/d 58.5 units/d vs 49.6 units/d

Table 35 Overall evidence on glycaemic index and liver cancer

	Summary of evidence
2005 SLR	No publication was identified during the 2005 SLR.
Continuous Update Project	Four cohorts were identified; all of them could be included in the meta-analysis. Two different studies found a positive association, one in males and another in females. Overall, no significant associations were observed.

Table 36 Summary of results of the dose response meta-analysis of glycaemic index consumption and liver cancer

Liver cancer		
	2005 SLR*	Continuous Update Project
Studies (n)	-	4
Cases (n)	-	848
Increment unit used	-	Per 5 units/day
Overall RR (95%CI)	-	1.02 (0.99-1.06)
Heterogeneity (I^2,p-value)	-	66.2%, p=0.03
By sex		Female
Overall RR (95%CI)		1.04 (1.00-1.08), n=2
Heterogeneity (I^2,p-value)		28.3%,p= 0.23
		Male
Overall RR (95%CI)		1.01 (0.97-1.05) n=2
Heterogeneity (I^2,p-value)		77.2%, p=0.03

*No meta-analysis was conducted during the Second Expert Report

Table 37 Inclusion/exclusion table for meta-analysis of glycaemic index and liver cancer

WCRF_ Code	Author	Year	Study Design	Study Name	Subgroup	Cancer Outcome	2005 SLR	CUP dose-response meta-analysis	CUP HvL forest plot	Estimated values	Exclusion reasons
LIV00504	Fedirko(b)	2013	Prospective Cohort study	European Prospective Investigation into Cancer and Nutrition	All	Incidence	No	Yes	Yes	--	-
LIV00415	Vogtmann	2012	Prospective Cohort study	Shanghai Women's Health Study	F	Incidence	No	Yes	Yes	Person-years, cases per category	-
				Shanghai Men's Health Study	M	Incidence	No	Yes	Yes	Person-years, cases per category	
LIV00498	George (b)	2009	Prospective Cohort study	NIH-AARP Diet and Health Study	F M	Incidence	No	Yes	Yes	Mid-points (categories 2, 3 & 4 only)	-

Figure 30 Highest versus lowest forest plot of glycaemic index and liver cancer

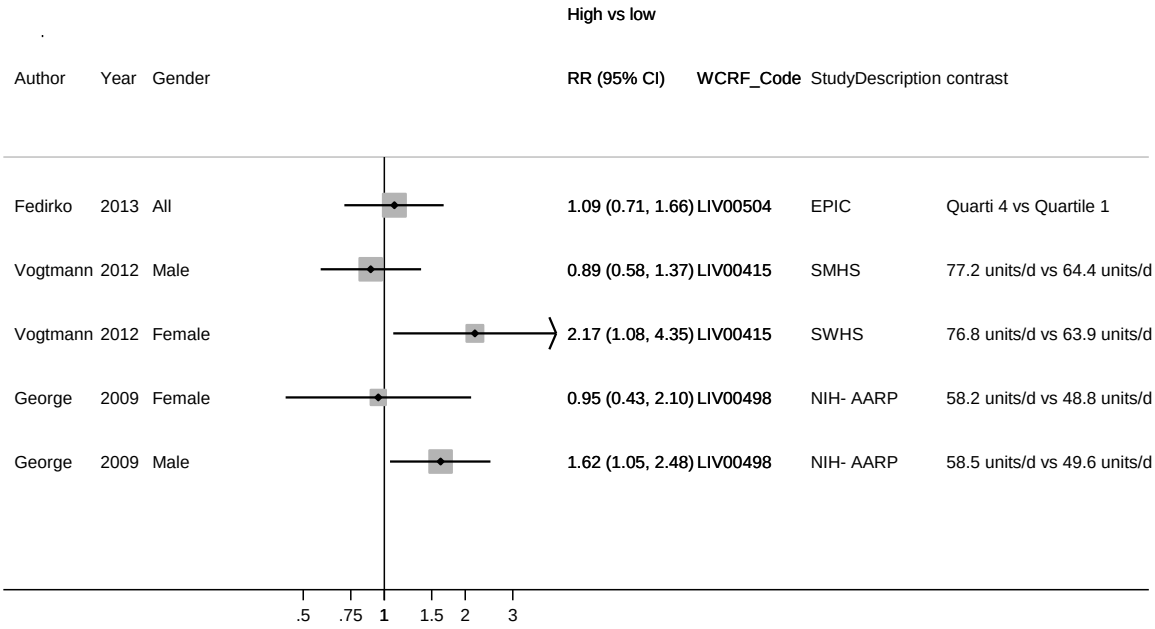


Figure 31 Dose-response meta-analysis of glycaemic index and liver cancer - per 5 units/day

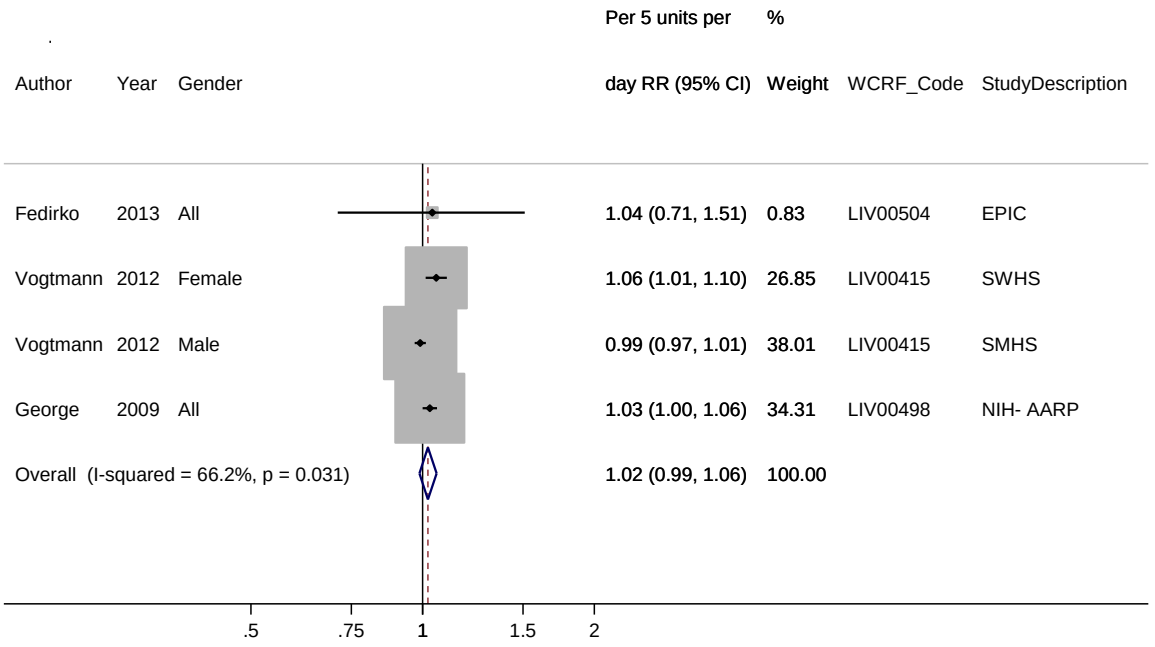


Figure 32 Dose-response graph of glycaemic index and liver cancer

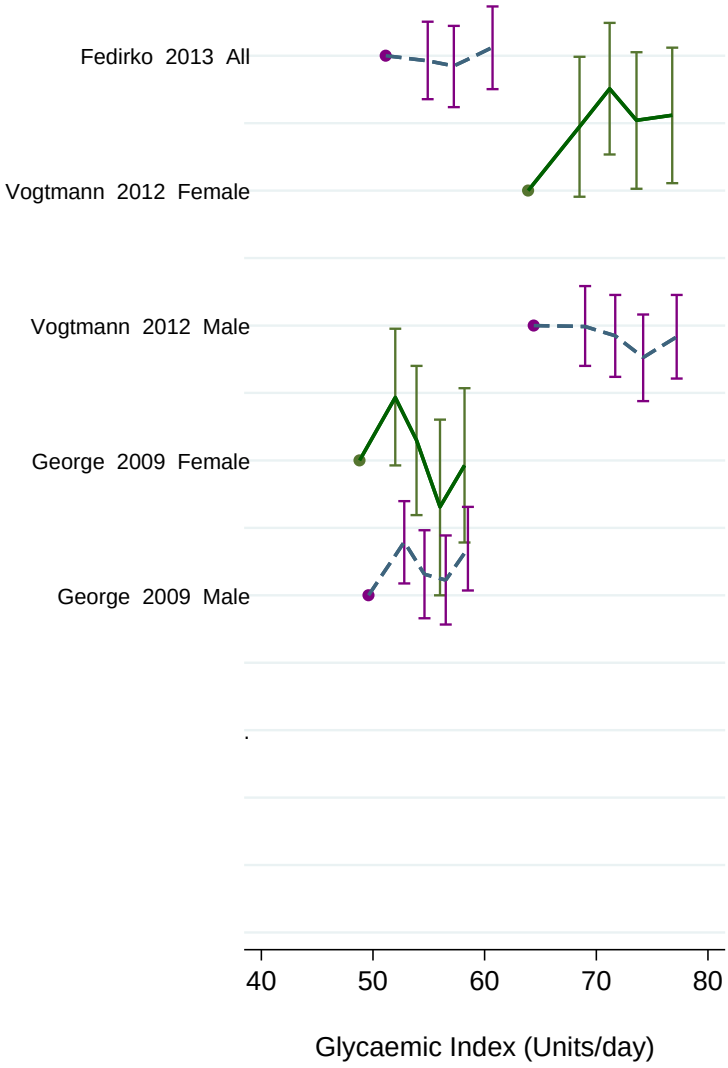
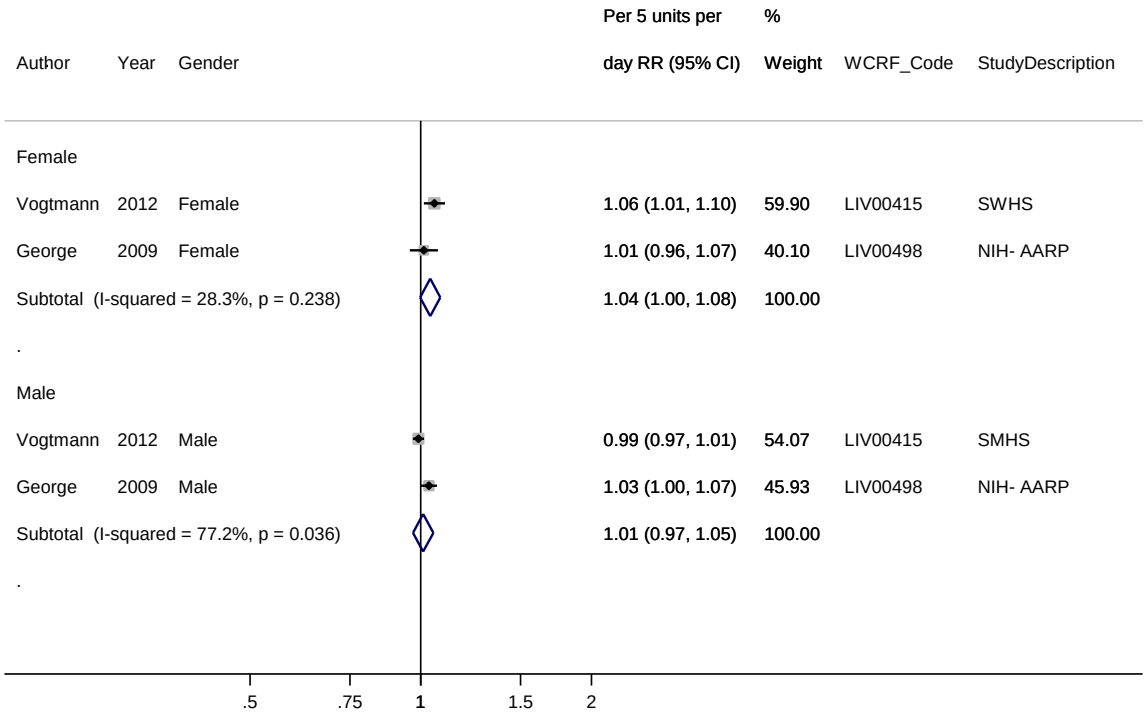


Figure 33 Dose-response meta-analysis of glycaemic index and liver cancer - per 5 units/day, by sex



5.4 Alcohol (as ethanol)

Methods

Up to June 2013, reports from 19 cohort studies and 30 publications were identified. 16 publications were identified during the 2005 SLR and 14 during the CUP. The CUP meta-analysis included 14 cohort studies; three of them were identified during the 2005 SLR and 11 during the CUP. Studies on patients with hepatic cirrhosis (15 studies), hepatitis B (8 studies), hepatitis C (6 studies), alcoholism or history of alcohol abuse (13 studies) are not included in the review.

For studies that reported on alcoholic drinks, the intake was rescaled to grams per day using 13 gr as average content of ethanol per one drink or one time. The dose-response results are presented for an increment of 10 gr ethanol per day.

Main results

The summary RR for an increase of 10 gr ethanol per day was 1.04 (95% CI: 1.02-1.06; I^2=64.0%, $P_{heterogeneity} \leq 0.01$) for all studies combined. There was significant evidence of publication bias with Egger's test, p=0.001

Exclusion of former drinkers might have attenuated the association of alcohol with liver cancer in some studies. The dose response relationship was derived from categorical data in which the reference category used was "never drinkers" in five out of 14 studies included in the dose-response meta-analysis (Jung et al, 2012; Ohishi et al, 2008; Nakaya et al, 2005; Goodman et al, 1995; Ross et al, 1992). Former drinkers were not included in the dose-response analysis in these studies.

Four studies reported the relative risk estimate for the comparison of past alcohol drinkers with never drinkers. The summary estimate for the four studies was 2.58 (95% CI= 1.76-3.77) (see figures below).

When the studies identified in the CUP were pooled with the results of the Pooled analyses of Asian cohort studies (Shimazu et al, 2012) the summary RR for an increase of 10 g/d of ethanol was 1.04 (95% CI: 1.02-1.06); I^2:=0%, Pheterogeneity=<0.39. The Miyagi cohort (Nakaya et al, 2005) was the only study in the Pooled analysis that was included in the CUP SLR.

There was no evidence of non-linearity (p nonlinearity test=0.25)

Heterogeneity

Heterogeneity was explored in stratified analyses. Stratification by sex showed the association was weaker in studies in men but with higher heterogeneity than in women. The summary RR per 10 gr ethanol intake in women was 1.19 (95% CI: 1.04-1.35; I^2=12.4%, $P_{heterogeneity}$ =0.33) and it was 1.03 (95% CI: 1.01-1.05; I^2=51.4%, $P_{heterogeneity}$ =0.04) in men.

When stratifying by outcome, stronger associations and higher heterogeneity was observed in studies with incidence as outcome. The summary RR for incidence of liver cancer was 1.12 (95% CI: 1.05-1.18; I^2=68.8%, $P_{heterogeneity}$ =0.001) and 1.02 (95% CI: 1.01-1.03; I^2=0%, $P_{heterogeneity}$ =0.48) for mortality.

The heterogeneity was not reduced when the analyses were restricted to studies in Asian countries: the summary RR for an increase of 10 gr of ethanol was 1.04 (95% CI: 1.02-1.07; I^2=62.3%, $P_{heterogeneity}$ =0.003). The association was only slightly stronger on average in one North American and two European studies (one only in women). The overall RR per 10 gr increase of ethanol intake was 1.08 (95% CI: 1.00-1.16; I^2=73.9%; $P_{heterogeneity}$ =0.02).

In two studies the analyses were adjusted by status of surface antigens for Hepatitis B virus or antibodies against Hepatitis C. In a study in Japan (Ohishi et al, 2008), alcohol consumption ≥40 g of

ethanol per day remained a significant risk factor for hepatocellular carcinoma after adjusting for viral infection status. In a study in Korean men, mortality for liver cancer was not related to alcohol intake in age-adjusted models and in multivariable models including HBsAg seropositivity (Joshi et al, 2008).

In the EPIC study, when subjects who were chronically infected with HBV or HCV were excluded from the analysis, the overall attributable fraction for high regular alcohol intake (≥40 g/d in men and ≥20 g/d in women) was 18%, compared to 10.2% when all participants were included in the analyses.

In the Taiwan Screening Project (Wang et al, 2003) that could not be included in the dose-response analysis for lack of the required information, the increase risk of hepatocellular carcinoma with increasing alcohol intake was stronger in HBsAg-negatives participants.

The remaining studies did not control for virus infection status or did not have this information

Comparison with the Second Expert Report

A meta-analysis on ethanol intake, per 10 (gr or ml) per day was conducted during the Second Expert Report (RR= 1.10; 95% CI: 1.02-1.17, I^2: 0%, p=0.49). No heterogeneity was indicated; hence results were presented based on the fixed effect model. This analysis included two papers with viral hepatitis B cases (LIV00225 and LIV00296) and one paper with viral hepatitis C cases (LIV00189). These three studies were not included in the CUP analysis.

Published meta-analysis and pooled analysis

A recent meta-analysis (Bagnardi et al, 2013) of 20 studies (7 cohorts, 13 case-control studies,4626 HCC cases) reported a summary RR of liver cancer for light alcohol intake (up to 1 drink/day) versus non-drinkers of 1.03 (95% CI: 0.90–1.20). The RRs for the same comparison was 1.00 (95% CI: 0.85–1.18) for the 7 cohorts studies and 1.10 (95% CI: 0.86-1.41) for 13 case-control studies.

In a pooled analysis of four large Japanese cohorts (Miyagi Cohort Study, The Japan Public Health Center-based prospective Study I and II and The Japan Collaborative Cohort Study ; 804 cases, 605 men and 199 women), compared with occasional drinkers the summary RRs was 1.76 (95% CI: 1.08–2.87) for men with 69-91.9 gr of ethanol intake per day and 1.66 (95% CI: 0.98–2.82) for men with intake >= 92 gr of ethanol per day. In women, the summary RR was 3.60 (95% CI: 1.22-10.66) when comparing those who drank more than 23 gr ethanol per day to occasional drinkers (Shimazu et al, 2012).

Table 38 Studies on alcohol intake identified in the CUP

Author, year	Country	Study name	Cases	Years of follow up	Sex	RR	LCI	UCI	Contrast
Loomba, 2013	Taiwan	Taiwan Screening Project	305	11.6	All	2.56	1.96	3.35	Yes vs no
Persson, 2013	USA	NIH-AARP Diet and Health Study	435	10.5	All	1.92	1.42	2.60	> 3 vs <1 drinks/day (in drinkers)
Jung, 2012	Korea	Korean Multi-center Cancer Cohort	82	9.3	All	3.50	1.40	8.78	> 504.01 vs 0.01-90 g/week
Yang, 2012	China	China Male Cohort	1115	15	M	1.21	0.92	1.44	>= 700 g/week vs non-drinkers
Koh, 2011	Singapore (Chinese origins)	Singapore Chinese Health Study	92	11.5	All	2.24	1.46	3.41	> =2 drinks/d vs non-drinkers
Schütze, 2011	Europe	European Prospective Investigation into Cancer and Nutrition	104 54	8.8	M F	1.13 1.09	1.04 0.89	1.22 1.33	Per 12 g/d increment
Trichopoulos, 2011	Europe	European Prospective Investigation into Cancer and Nutrition	115 80 35	~8.8	All M F	1.77 1.17 7.10	0.73 0.40 0.69	4.27 3.40 73.38	>= 40 g/d vs 0-10 g/d >= 20 g/d vs 0-15 g/d
Kim, 2010	Korea	Korean National Health Insurance Corporation	1506 174	5	M F	1.23 1.80	1.01 0.90	1.51 3.57	>= 90 g/d vs non-drinkers >= 15 g/d vs non-drinkers
Yi, 2010	Korea	Kangwha Cohort Study	37 8	20.8	M F	0.79 1.06	0.31 0.13	2.01 8.47	>= 540 g/week vs none >= 12 g/week vs none
Allen, 2009	UK	Million Women Study	337	7.2	F	1.70 1.24	1.12 1.02	2.56 1.51	>= 15 drinks (150 g ethanol)/week Per 10 g/d increment
Ohishi, 2008	Japan	Adult Health Study	224	~32	All	4.36 1.73	1.48 1.19	13.0 2.52	>= 40 g/d vs never Per 20 g/d increment
Joshi, 2008	Korea	Korean National Health Insurance System	998	6	M	1.09	0.77	1.54	Very heavy drinker vs non-drinker (>=100 g/d vs 0 g/d)
Lai, 2006	Taiwan	Keelung Community-Based Integrated Screening	138	2.78	All	2.37	1.15	4.88	High vs no (cumulative alcohol intake)
Yuan, 2006	China	Shanghai Cohort Study	214	15	M	2.77	1.49	5.15	>= 4 drinks/d vs non-drinkers

Table 39 Overall evidence on alcohol intake and liver cancer

	Summary of evidence
2005 SLR	Sixteen publications were identified, four publications on ethanol intake and 12 on alcohol drinks and liver cancer in healthy individuals at baseline. The 2005 SLR meta-analysis showed a significant positive association
Continuous Update Project	Fourteen publications were identified, nine publications on ethanol intake and five on alcoholic drinks from which 11 cohorts could be included in the meta-analysis. Overall, 14 cohorts were included in the meta-analysis and a significant positive association was observed.

Table 40 Summary of results of the dose response meta-analysis of alcohol intake and liver cancer

Liver cancer		
	2005 **SLR**	**Continuous Update Project**
Studies (n)	6	14
Cases (n)	400	5650
Increment unit used	Per 10 gr/ml increase	Per 10 gr increase
Overall RR (95%CI)	1.10 (1.02-1.17)	1.04 (1.02-1.06)
Heterogeneity (I^2,p-value)	0%, p=0.49	64%, p<0.01
	Continuous Update Project and Asian Pooling Project	
Studies (n)	17	
Cases (n)	6372	
Increment unit used	Per 10 gr increase	
Overall RR (95%CI)	1.04 (1.02-1.06)	
Heterogeneity (I^2,p-value)	0 %, p=<0.39	
Continuous Update Project Stratified Analyses (RR per 10 g/d increase)		
Sex	**Men**	**Women**
Studies (n)	8	4
Cases (n)	4132	637
Overall RR (95%CI)	1.03 (1.01-1.05)	1.19 (1.04-1.35)
Heterogeneity (I^2,p-value)	51.4%, p=0.04	12.4%, p=0.33
Outcome	**Incidence**	**Mortality**
Studies (n)	9	5
Cases (n)	1738	3912
Overall RR (95%CI)	1.12 (1.05-1.18)	1.02 (1.01-1.03)
Heterogeneity (I^2,p-value)	68.8%, p=0.001	0%, p=0.48
Location	**Asia**	**North America and Europe**
Studies (n)	11	3
Cases (n)	4720	930
Overall RR (95%CI)	1.04 (1.02-1.07)	1.08 (1.00-1.16)
Heterogeneity (I^2,p-value)	62.9%, p=0.003	73.9%, p=0.02

Table 41 Inclusion/exclusion table for meta-analysis of alcohol intake and liver cancer

WCRF_ Code	Author	Year	Study Design	Study Name	Subgroup	Cancer Outcome	2005 SLR	CUP dose-response meta-analysis	CUP HvL forest plot	Estimated values	Exclusion reasons
LIV00505	Loomba	2013	Prospective Cohort	Taiwan Screening Project	All	Incidence	No	No	Yes	-	Only two categories
LIV00508	Persson	2013	Prospective Cohort	NIH-AARP Diet and Health Study	All	Incidence	No	Yes	Yes	Mid-points	--
LIV00464	Jung	2012	Prospective Cohort Study	Korean Multi-Centre Cancer Cohort	All	Mortality	No	Yes	Yes	Person-years, rescale categories, mid-points	
LIV00421	Yang	2012	Prospective Cohort Study	China Male Cohort	Male	Mortality	No	Yes	Yes	Mid-points	
LIV00427	Koh	2011	Prospective Cohort	Singapore Chinese Health Study	All	Incidence	No	Yes	Yes	Mid-points and person years	--
LIV00436	Schütze	2011	Prospective Cohort Study	European Prospective Investigation into Cancer and Nutrition	Male Female	Incidence	No	Yes	No	Rescale continuous values	
LIV00425	Trichopoulos	2011	Prospective Cohort Study	European Prospective Investigation into Cancer and Nutrition	All Male Female	Incidence	No	No	No	--	Superseded by LIV00436 (Schütze et al, 2011)
LIV00433	Kim	2010	Prospective Cohort Study	Korean National Health Insurance Corporation	Male Female	Mortality	No	Yes	Yes	Mid-points, cases	
LIV00445	Yi	2010	Prospective Cohort Study	Kangwha Cohort Study	Male Female	Mortality	No	Yes	Yes	Person-years, mid-points	Excluded female from analysis because there was only 1 case in the upper category out of three
LIV00454	Allen	2009	Prospective Cohort Study	Million Women Study	Female	Incidence	No	Yes	Yes	Rescale continuous values	
LIV00476	Ohishi	2008	Nested Case-Control Study	Adult Health Study, Japan	All	Incidence	No	Yes	Yes	Rescale continuous values	
LIV00467	Joshi	2008	Prospective Cohort Study	Korean National Health Insurance System	Male	Mortality	No	Yes	Yes	Mid-points, person-years, cases	
LIV00492	Lai	2006	Prospective Cohort	Keelung Community-Based Integrated Screening, Taiwan	All	Incidence	No	No	Yes	-	Categories on cumulative alcohol intake
LIV00484	Yuan	2006	Nested Case-control	Shanghai Cohort Study	Male	Incidence	No	Yes	Yes	Mid-points	--
LIV00535	Sakoda	2005	Nested Case-Control Study	Haimen City Anti-Epidemic Station	All	Incidence	Yes	No	No	-	No RR Superseded by LIV00103

											(Evans et al, 2002)
LIV00668	Nakaya	2005	Prospective Cohort Study	Miyagi Cohort	All	Incidence	Yes	Yes	Yes	Mid-points	
LIV00534	Sharp	2005	Nested Case-Control Study	Adult Health Study	All	Mortality	Yes	No	No	--	Superseded by LIV00476 (Ohishi et al, 2008)
LIV00413	Wang	2003	Prospective Cohort	Taiwan Screening Project	M	Incidence	Yes	No	No	-	Only two categories Same study as LIV00505 (Loomba et al, 2013)
LIV00251	Meng	2002	Nested Case-Control Study	Haimen City Anti-Epidemic Station, China	All	Incidence	Yes	No	No	-	No measurement units Same as LIV00103 (Evans et al, 2002)
LIV00103	Evans	2002	Nested Case-Control Study	Haimen City Anti-Epidemic Station, China	Male Female	Incidence	Yes	No	Yes	-	Only two categories
LIV00466	Sun	2001	Nested Case-Control Study	Taiwan Screening Project	All	Incidence	Yes	No	No	-	Only two categories. Same study as LIV00505 (Loomba et al, 2013)
LIV00445	Yuan	1997	Prospective Cohort	Shanghai Cohort Study	Male	Mortality	No	No	No	-	Superseded by LIV00484 (Yuan et al, 2006)
LIV00066	Chen	1986	Prospective Cohort	Taiwan Screening Project	All	Incidence	Yes	No	No	-	Only two categories. Same study as LIV00505 (Loomba et al, 2013)
LIV00412	Wang	1986	Prospective Cohort	Taiwan Screening Project	M	Incidence	Yes	No	No	-	Only two categories. Same study as LIV00505 (Loomba et al, 2013)
LIV00228	London	1995	Nested Case-control	Haimen City Anti-Epidemic Station, China	Male	Incidence	No	No	No	-	Superseded by LIV00103 (Evans et al, 2002)
LIV00130	Goodman	1995	Prospective Cohort Study	Life Span Study, Japan	Male Female	Incidence	Yes	Yes	Yes	Mid-points	
LIV00192	Kjaerheim	1993	Prospective Cohort	Norwegian Teetotalers study	Male Female	Incidence	Yes	No	No	-	Standard Incidence Ratio (general population vs alcohol abstainers)
LIV00328	Ross	1992	Nested Case-Control Study	China study	Male	Incidence	Yes	Yes	Yes	Mid-points	
LIV00158	Hirayama	1989	Prospective Cohort	Japanese cohort study	All	Mortality	Yes	No	Yes	-	Only two categories
LIV00156	Hirayama	1985	Prospective Cohort	Japanese cohort study	Male	Mortality	No	No	No	-	Superseded by LIV00158 (Hirayama et al, 1985)

Figure 34 Highest versus lowest forest plot of alcohol intake and liver cancer

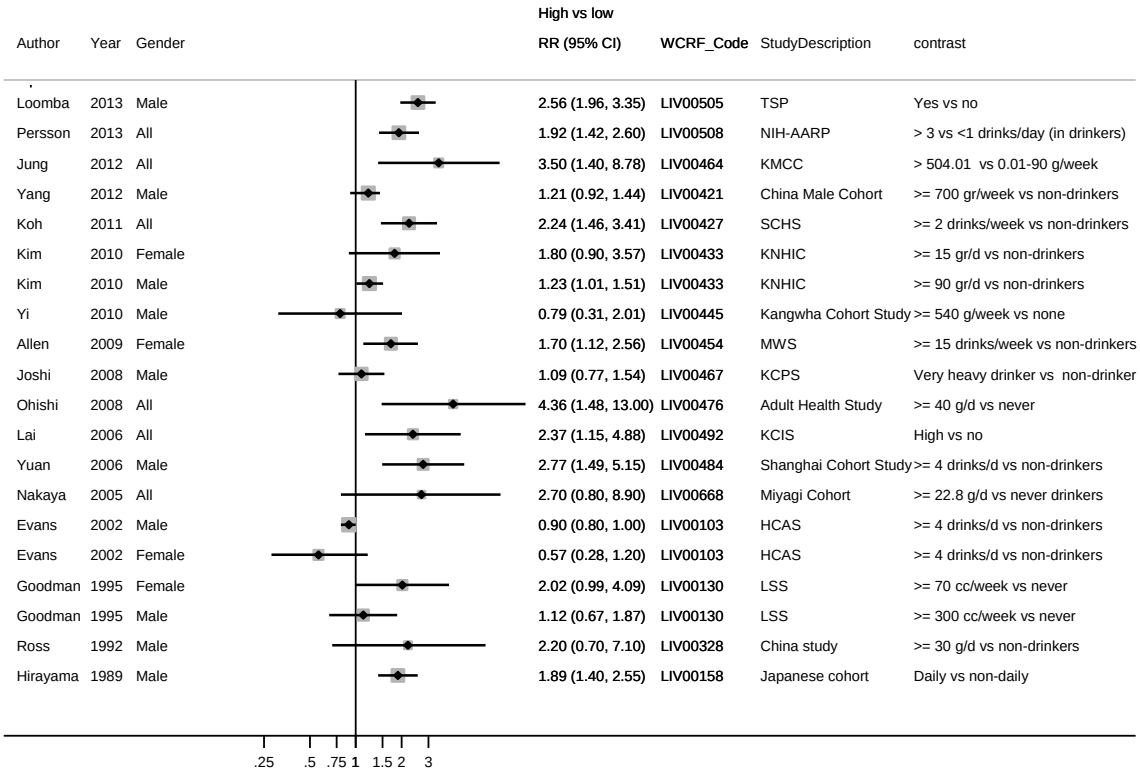


Figure 35 Highest versus lowest forest plot of alcohol intake and liver cancer by sex

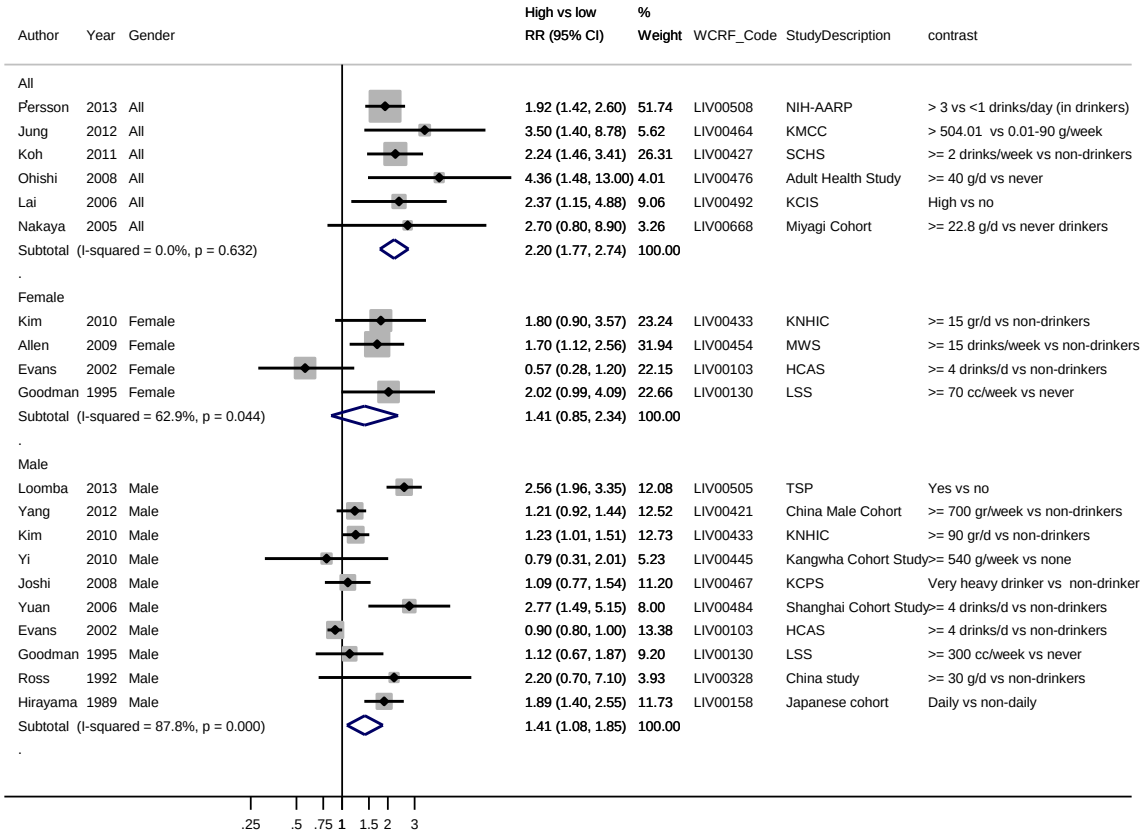


Figure 36 Dose-response meta-analysis of alcohol intake and liver cancer - per 10 g per day

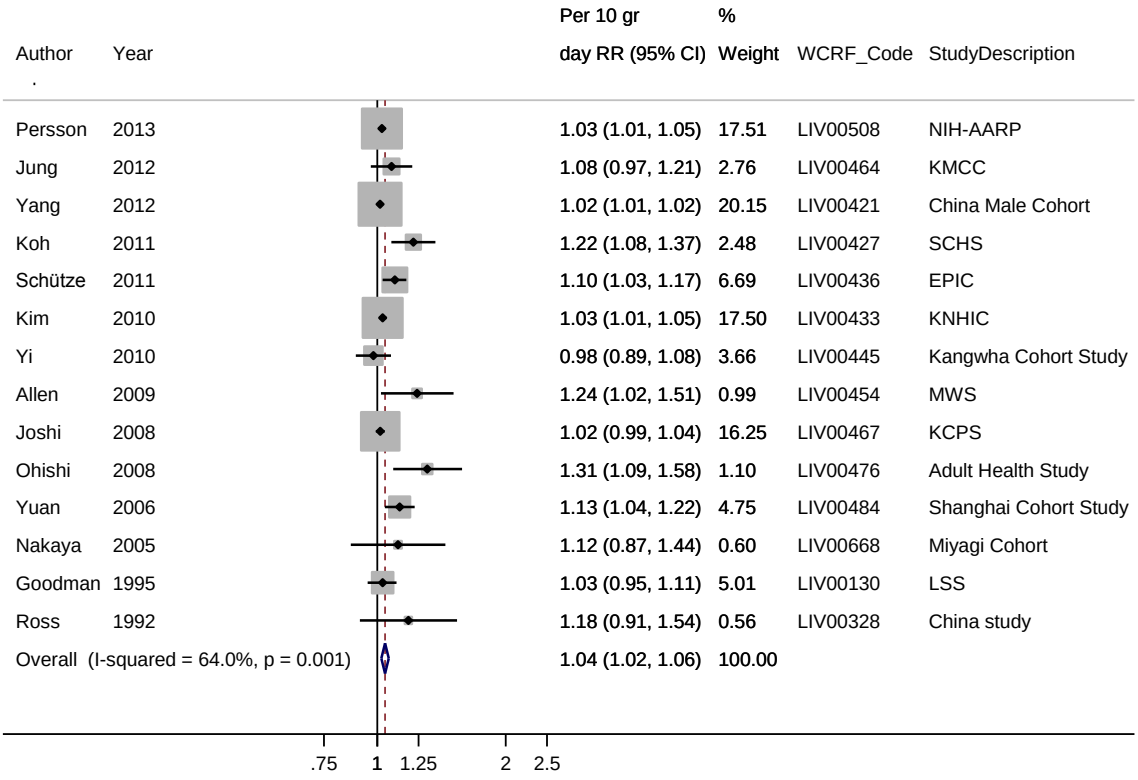


Figure 37 Dose-response meta-analysis per 10 g per day of alcohol intake and liver cancer by sex

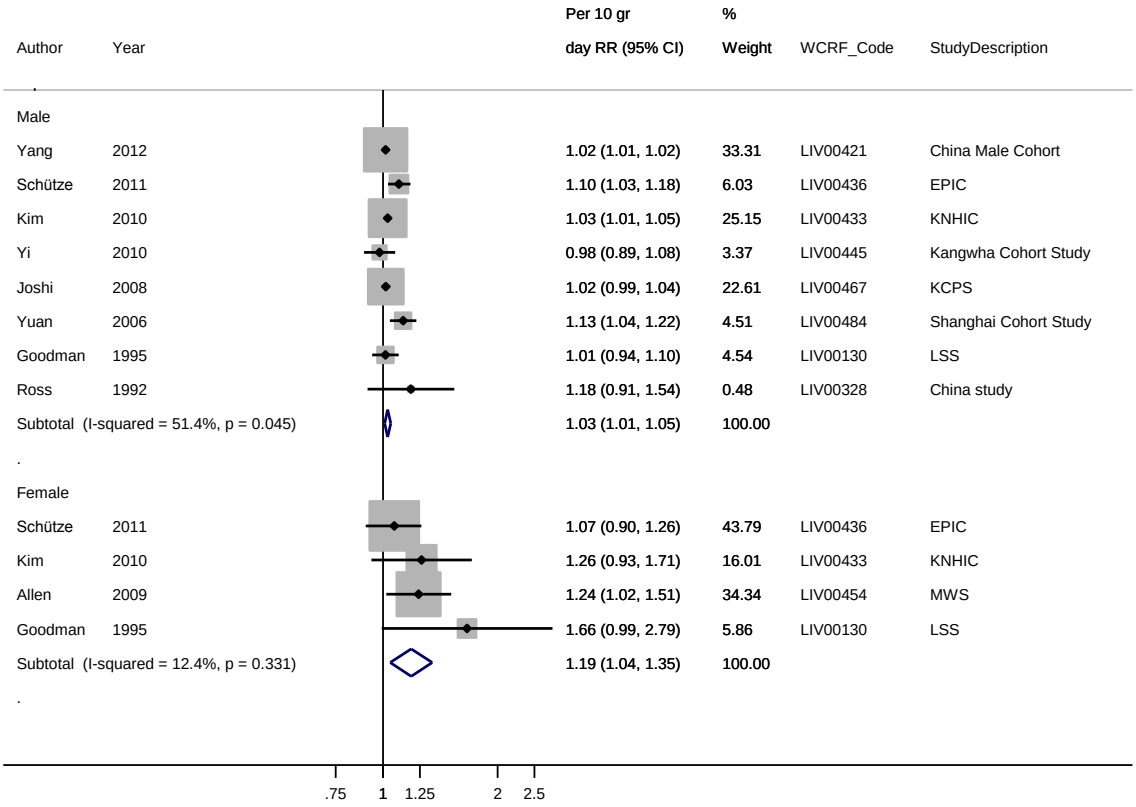


Figure 38 Dose-response meta-analysis per 10 g per day of alcohol intake and liver cancer by outcome

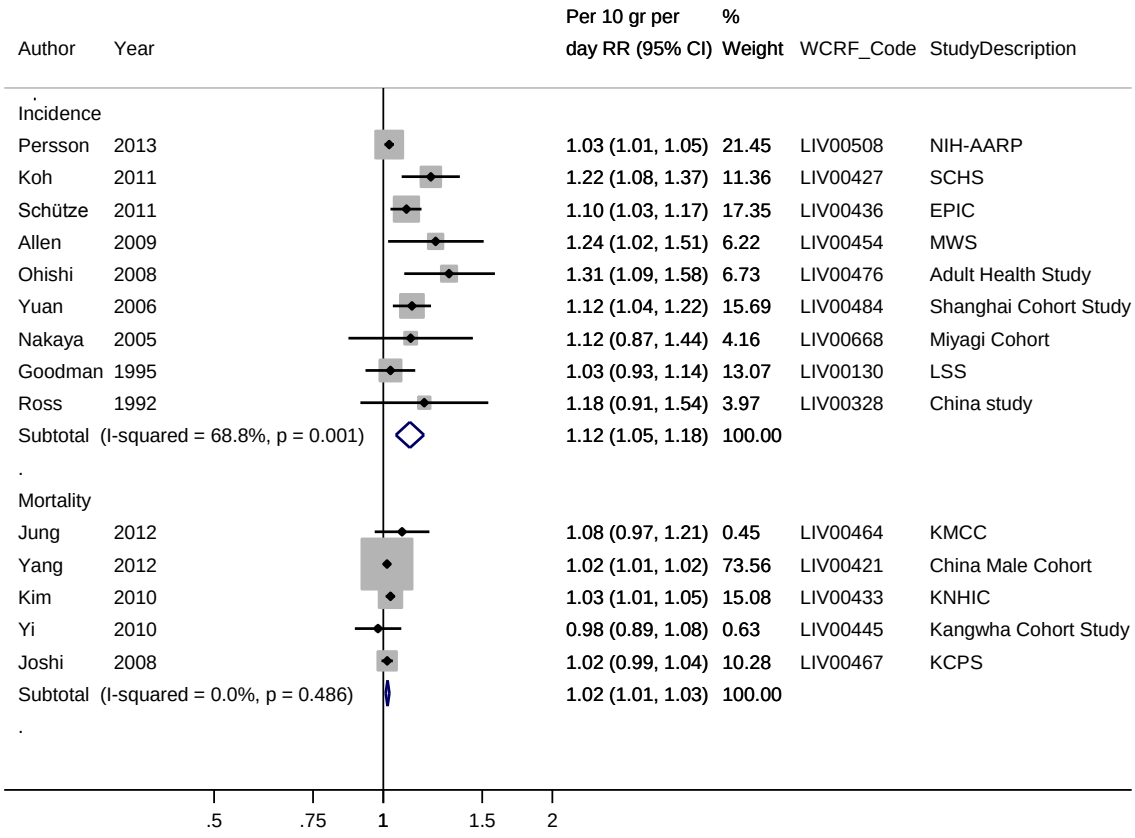
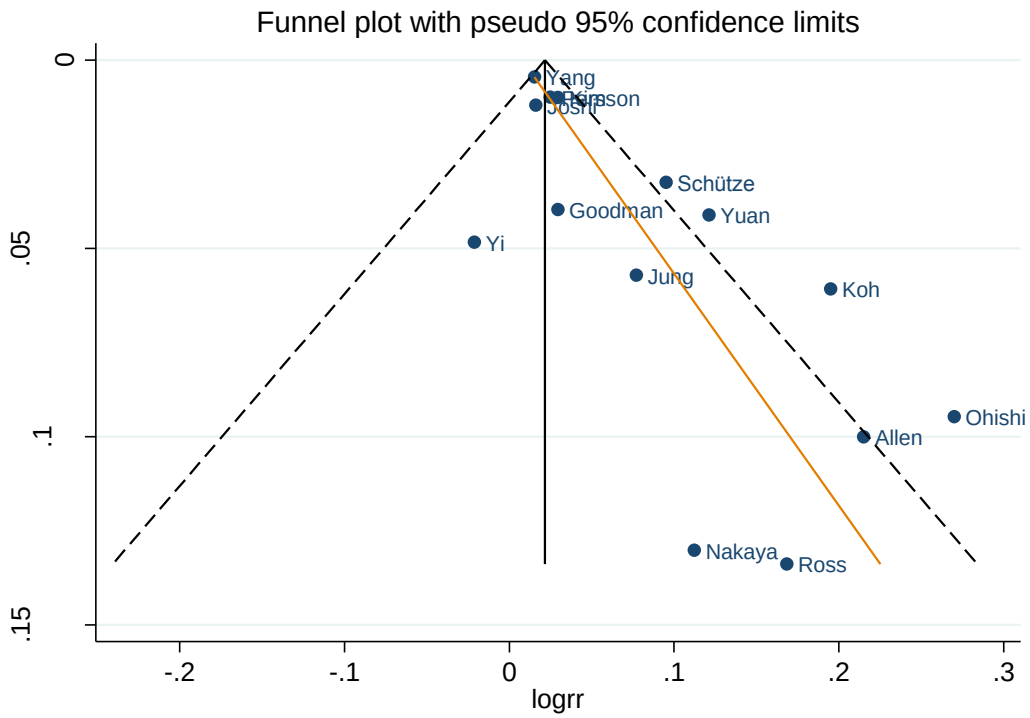


Figure 39 Figure Funnel plot of alcohol intake and liver cancer



P=0.001

Figure 40 Dose-response graph of alcohol intake and liver cancer

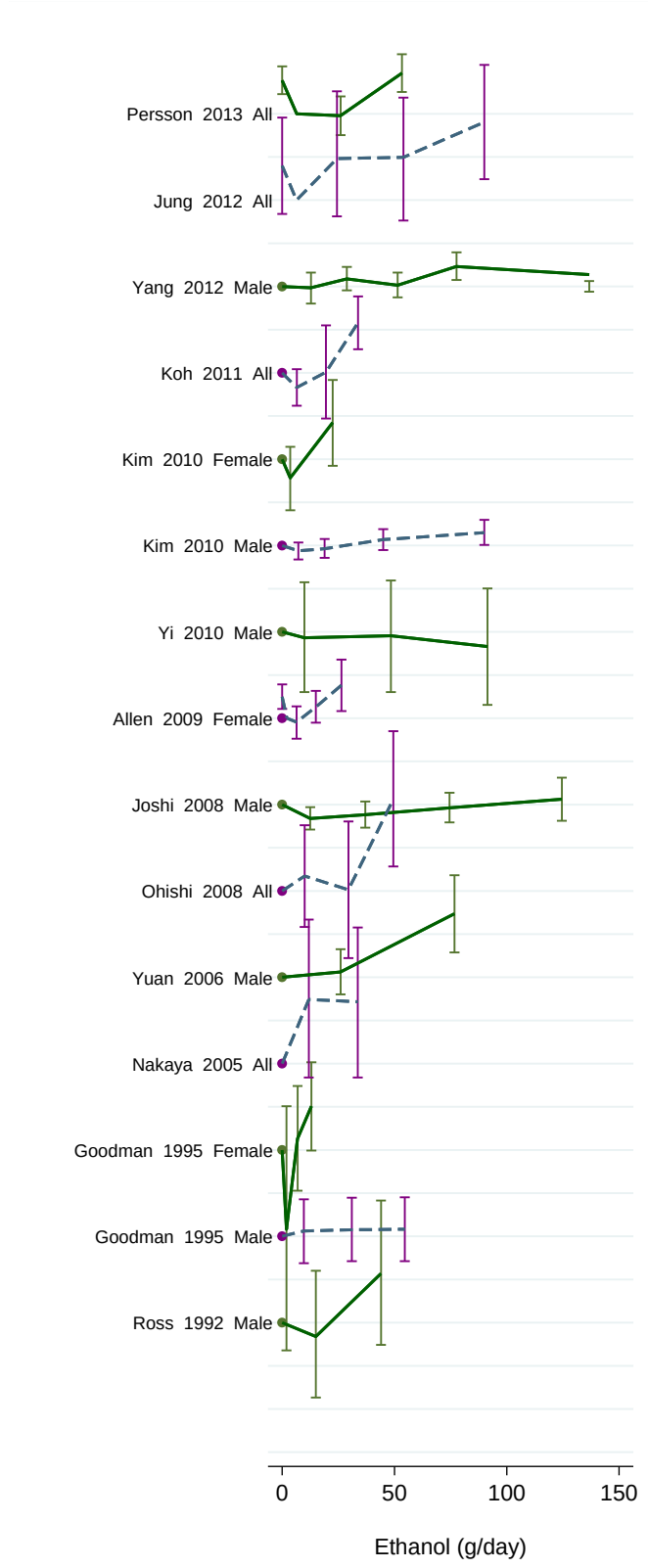


Figure 41 Dose-response meta-analysis per 10 g per day of alcohol intake and liver cancer by location

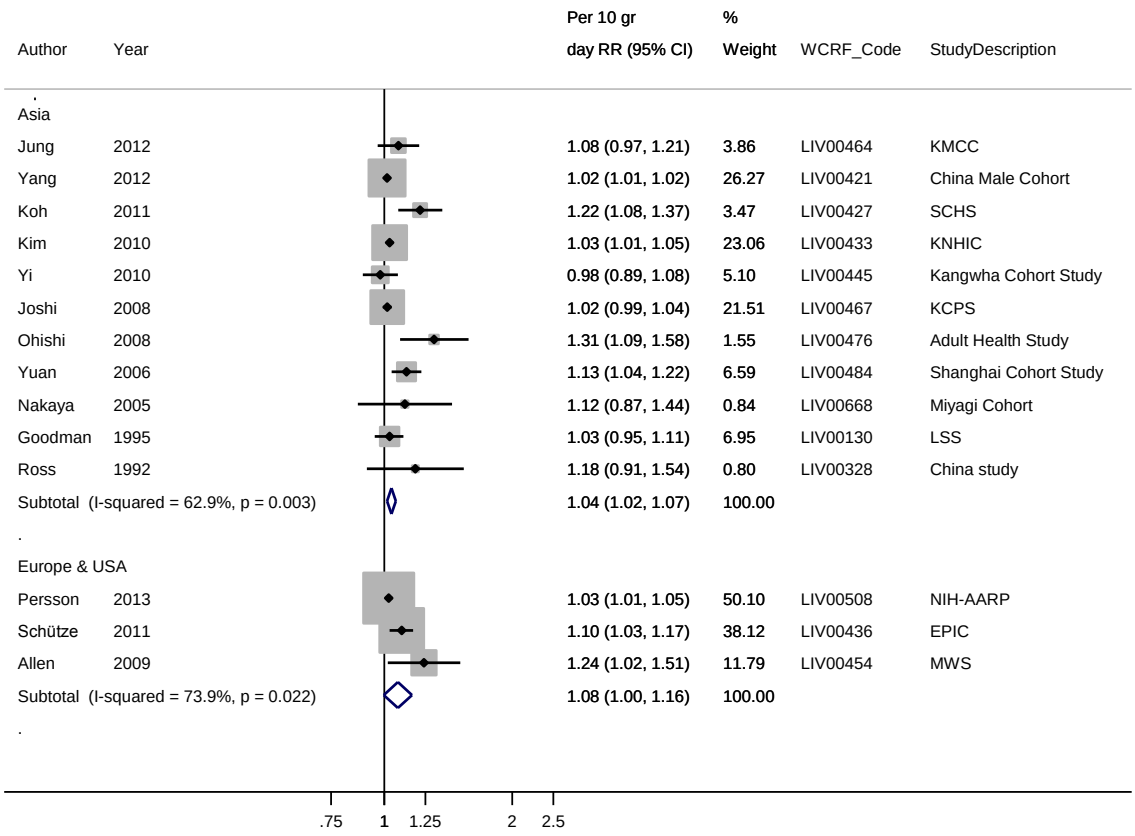


Figure 42 Forest plot of relative risks of liver cancer for former drinkers versus never drinkers

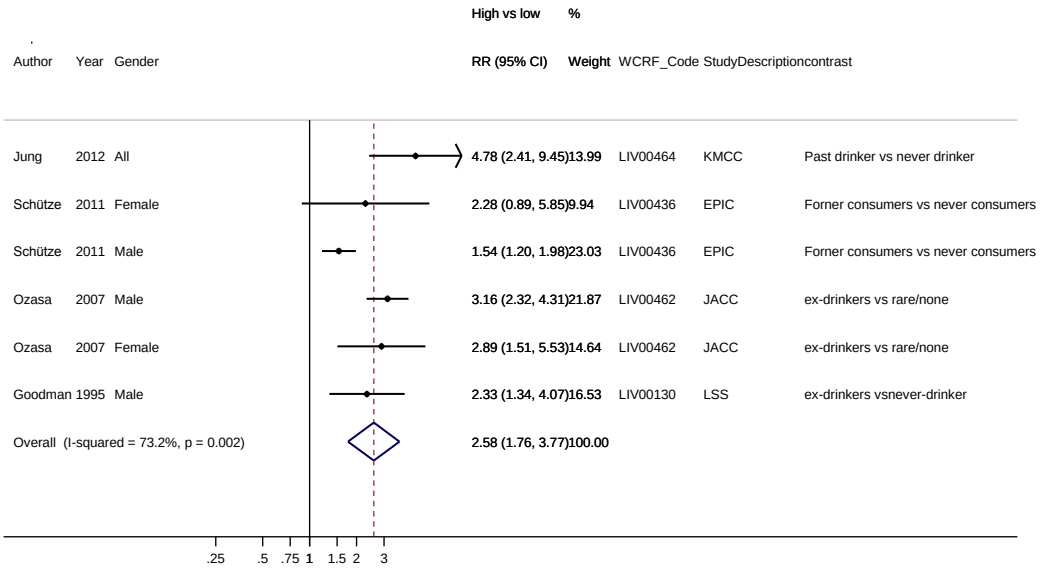


Figure 43 Forest plot of relative risks of liver cancer for former drinkers versus never drinkers by sex

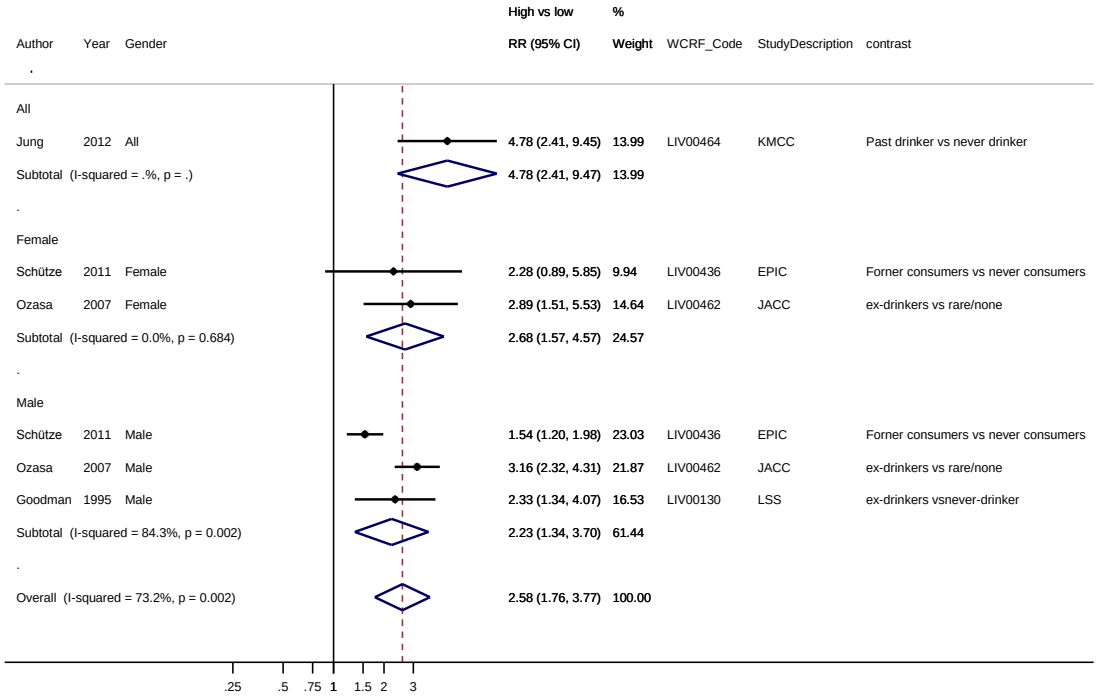
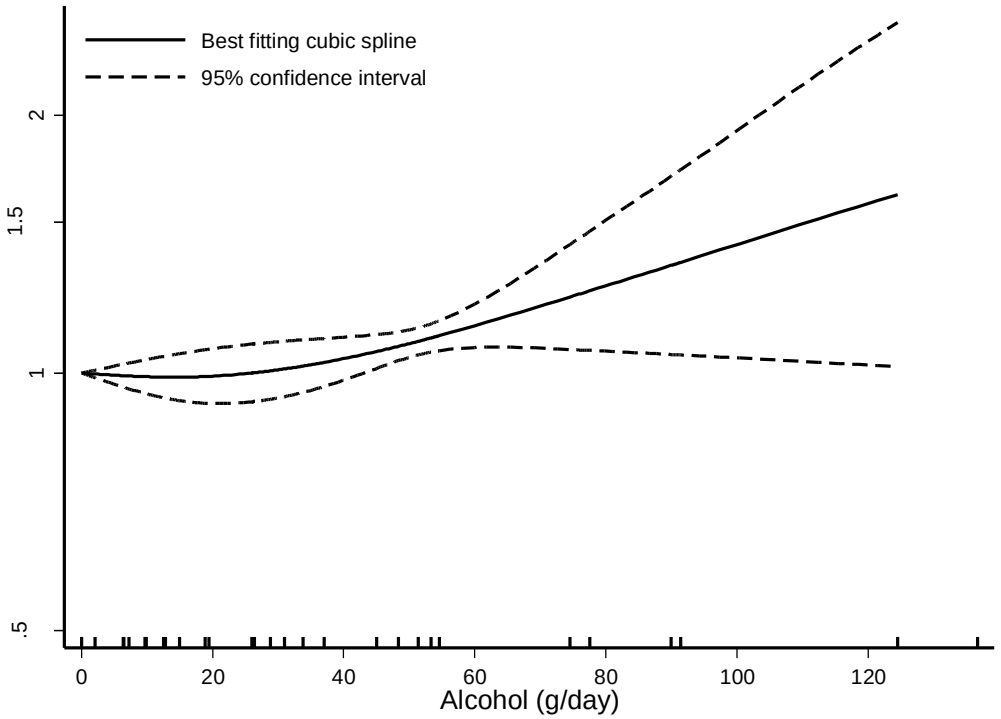


Figure 44 Non-linear dose-response figure for ethanol intake and liver cancer



p nonlinearity test=0.25

Figure 45 Scatter plot of risk estimates for BMI and liver cancer

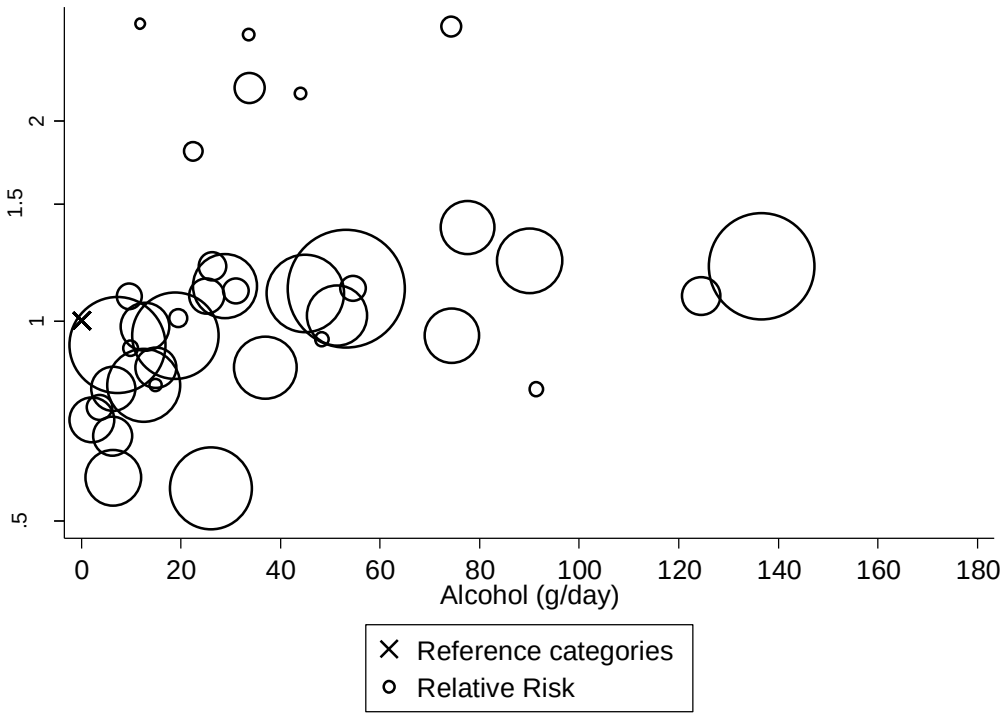


Table 42 RRs from the nonlinear analysis

Ethanol intake (grams per day)	RR (95% CI)
0	1
12.5	0.99 (0.94-1.05)
20	0.99 (0.92-1.07)
45	1.06 (1.01-1.11)
55	1.11 (1.06-1.15)
75	1.23 (1.07-1.41)

For the nonlinear analysis, studies that reported only continuous values or using three categories of intake or less were excluded (8 studies included).

5.4.1 Sake (ethanol equivalent)

Methods

Up to June 2013, reports from nine publications and five cohorts were identified. Eight publications and four cohorts were identified during the 2005 SLR and one during the CUP. The CUP meta-analysis included five cohort studies; four of them were identified during the 2005 SLR and one during the CUP. For the dose-response analyses, results were converted to a common scale of exposure level of 10 gr of sake as ethanol equivalent per day. The dose-response results are presented for an increment of 10 gr of sake (ethanol equivalent) per day.

Main results

The summary RR per 10 gr sake (ethanol equivalent) per day was 1.03 (95% CI: 1.00-1.05; I^2=8.7%, $P_{heterogeneity}$ =0.35) for all studies combined.

Heterogeneity

There was evidence of low heterogeneity across the limited number of studies combined (I^2=8.7%, p=0.35). There was no indication of publication bias with Egger's test (p=0.37).

Comparison with the Second Expert Report

No meta-analysis on sake intake as ethanol grams per day was conducted during the Second Expert Report. The three studies identified during the 2005 SLR were included in the alcoholic drinks or ethanol analyses.

Published meta-analysis

No published meta-analyses were identified.

Table 43 Studies on sake (ethanol equivalent) intake identified in the CUP

Author, year	Country	Study name	Cases	Years of follow up	Sex	RR	LCI	UCI	Contrast
Ozasa, 2007	Japan	Japan Collaborative Cohort Study for Evaluation of Cancer	243	~12	M	1.47	0.96	2.25	>= 81 ml ethanol (sake equivalent) vs none
			156		F	1.02	0.14	7.37	54-80 ml ethanol (sake equivalent) vs none

Table 44 Overall evidence on sake (ethanol equivalent) intake and liver cancer

	Summary of evidence
2005 SLR	Eight publications from four cohorts were identified during the 2005 SLR on sake equivalent intake and liver cancer in healthy individuals at baseline.
Continuous Update Project	One publication was identified during the CUP. Overall, five cohorts could be included in the CUP meta-analysis. The meta-analysis showed a marginal positive association.

Table 45 Summary of results of the dose response meta-analysis of sake (ethanol equivalent) intake and liver cancer

Liver cancer		
	2005 SLR*	**Continuous Update Project**
Studies (n)	--	5
Cases (n)		3868
Increment unit used		Per 10 gr ethanol/day (sake equivalent) increase
Overall RR (95%CI)		1.03 (1.00 -1.05)
Heterogeneity (I^2,p-value)		8.7%, p=0.35

*No meta-analysis was conducted during the 2005 SLR

Table 46 Inclusion/exclusion table for meta-analysis of sake (ethanol equivalent) and liver cancer

WCRF_ Code	Author	Year	Study Design	Study Name	Subgroup	Cancer Outcome	2005 SLR	CUP dose-response meta-analysis	CUP HvL forest plot	Estimated values	Exclusion reasons
LIV00462	Ozasa	2007	Prospective Cohort Study	Japan Collaborative Cohort Study for Evaluation of Cancer	M F	Mortality	No	Yes	Yes	Mid-points	--
LIV00632	Jee	2004	Prospective Cohort Study	Korean Cancer Prevention Study	M F	Mortality	Yes	Yes	Yes	Mid-points, person-years	Female excluded for dose-response analysis (only two categories)
LIV00531	Ogimoto	2004	Prospective Cohort Study	Japan Collaborative Cohort Study for Evaluation of Cancer	M F	Mortality	Yes	No	No	--	Superseded by LIV00462 (Ozasa et al, 2007)
LIV00268	Murata	1996	Nested Case-Control Study	Chiba Cancer Association gastric mass screening cohort	M	Incidence	Yes	Yes	Yes	Confidence intervals, mid-points, person-years	
LIV00345	Shibata	1990	Prospective Cohort Study	Kyushu Cohort Study	M, farming area	Mortality	Yes	Yes	Yes	Mid-points, person-years	--
LIV00197	Kono	1987	Prospective Cohort Study	Japanese Physician Study	M	Mortality	Yes	Yes	Yes	Mid-points, person-years, cases per category	--
LIV00196	Kono	1986	Prospective Cohort Study	Japanese Physician Study	M	Mortality	Yes	No	No	--	Superseded by LIV00197 (Kono et al, 1987)
LIV00346	Shibata	1986	Prospective Cohort Study	Kyushu Cohort Study	M, farming area	Mortality	Yes	No	No	--	Superseded by LIV00345 (Kono et al, 1990)
LIV00198	Kono	1985	Prospective Cohort Study	Japanese Physician Study	M	Mortality	Yes	No	No	--	Superseded by LIV00197 (Kono et al, 1987)

Figure 46 Highest versus lowest forest plot of sake (ethanol equivalent) intake and liver cancer

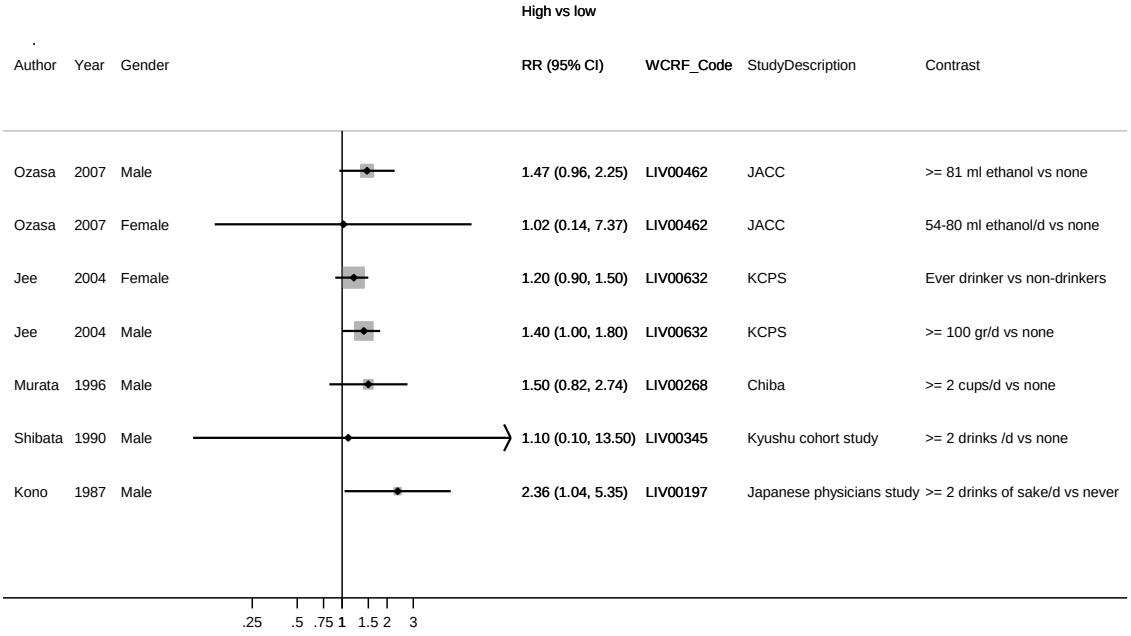


Figure 47 Dose-response meta-analysis of sake (ethanol equivalent) and liver cancer - per 10 g/day

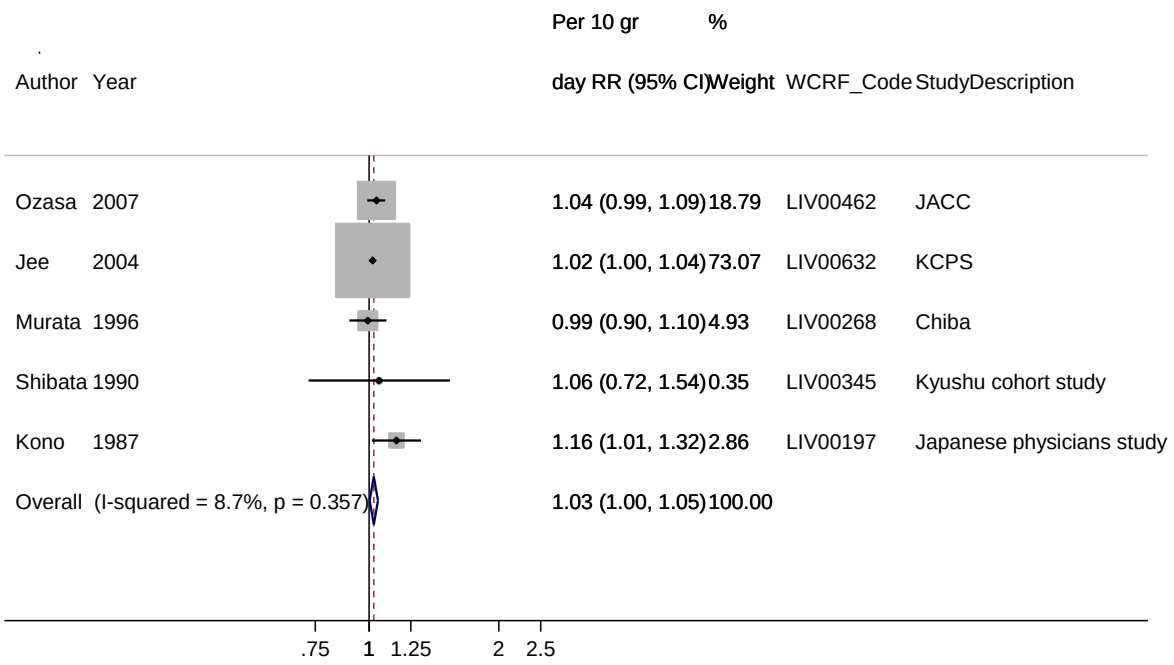
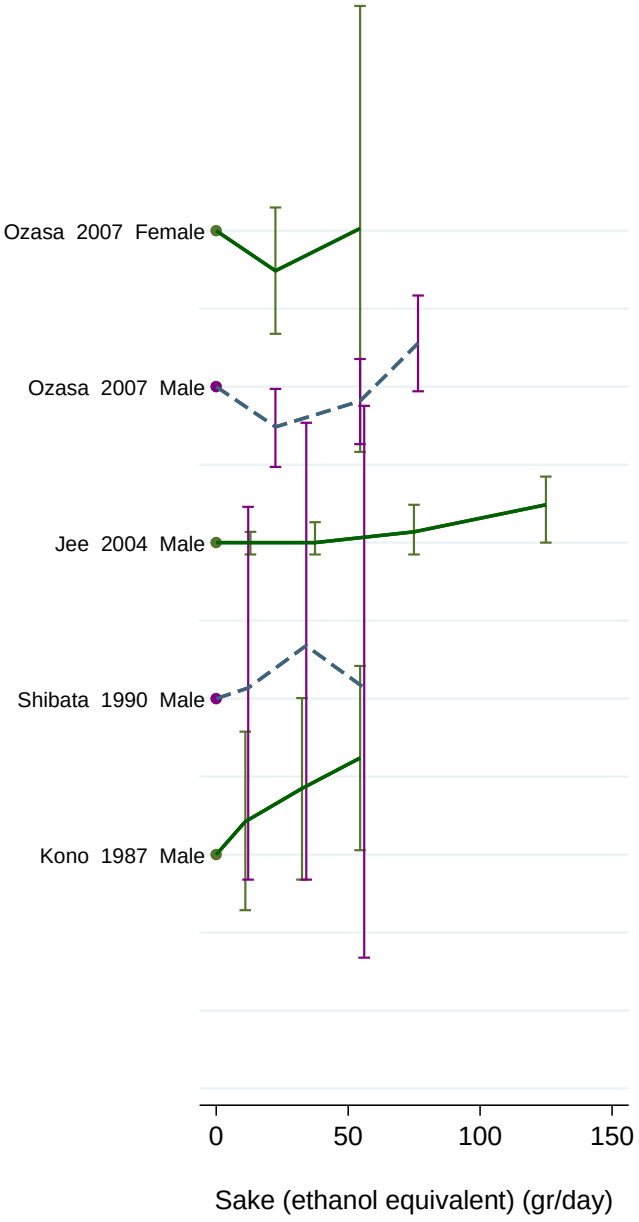


Figure 48 Dose-response graph of sake (ethanol equivalent) intake and liver cancer



5.5.9.2 Dietary vitamin C

Methods

Up to June 2013, reports from three cohort studies (two publications) were identified, all of them during the CUP. The dose-response results are presented for an increment of 25 mg of dietary vitamin C intake per day.

Main results

The summary RR per 25 mg/d was 0.97 (95% CI: 0.87-1.09; I^2=21.4%, $P_{heterogeneity}$ =0.2) for all studies combined.

Heterogeneity

Heterogeneity was low (I^2=21.4%, p=0.28). There was no indication of publication bias with Egger's test (p=0.175).

Comparison with the Second Expert Report

No analysis was conducted during the Second Expert Report

Published meta-analysis

No published meta-analyses were identified.

Table 47 Studies on dietary vitamin C consumption identified in the CUP

Author, year	Country	Study name	Cases	Years of follow up	Sex	RR	LCI	UCI	Contrast
Zhang, 2012	China	Shanghai Women's Health Study	118	10.9	F	0.87	0.47	1.58	> 109.963 mg/d vs <= 59.928 mg/d
		Shanghai Men's Health Study	149	5.5	M	0.63	0.38	1.04	> 119.799 mg/d vs <= 61.165 mg/d
Kurahashi, 2012	Japan	Japan Public Health Center-based Prospective Study	101	11.8	All	1.38	0.80	2.40	93.9 mg/d vs 36.4 mg/d

Table 48 Overall evidence on dietary vitamin C consumption and liver cancer

	Summary of evidence
2005 SLR	No study was identified during the 2005 SLR.
Continuous Update Project	Two publications (three cohorts) were identified; None of them reported a significant association. The CUP meta-analysis showed a non-significant (weak inverse) association.

Table 49 Summary of results of the dose response meta-analysis of vitamin dietary C consumption and liver cancer

Liver cancer		
	2005 SLR*	Continuous Update Project
Studies (n)	-	3
Cases (n)	-	368
Increment unit used	-	Per 25 mg/day
Overall RR (95%CI)	-	0.97 (0.87-1.09)
Heterogeneity (I^2,p-value)	-	21.4%, p=0.28

*No meta-analysis was conducted during the 2005 SLR

Table 50 Inclusion/exclusion table for meta-analysis of dietary vitamin C consumption and liver cancer

WCRF_ Code	Author	Year	Study Design	Study Name	Subgroup	Cancer Outcome	2005 SLR	CUP dose-response meta-analysis	CUP HvL forest plot	Estimated values	Exclusion reasons
LIV00416	Zhang	2012	Prospective Cohort study	Shanghai Women's Health Study	F	Incidence	No	Yes	Yes	Person-years, mid-points	-
LIV00416	Zhang	2012	Prospective Cohort study	Shanghai Men's Health Study	M	Incidence	No	Yes	Yes	Person-years, mid-points	-
LIV00455	Kurahashi	2009	Prospective Cohort study	Japan Public Health Center-based Prospective Study	All	Incidence	No	Yes	Yes	--	-

Figure 49 Highest versus lowest forest plot of dietary vitamin C consumption and liver cancer

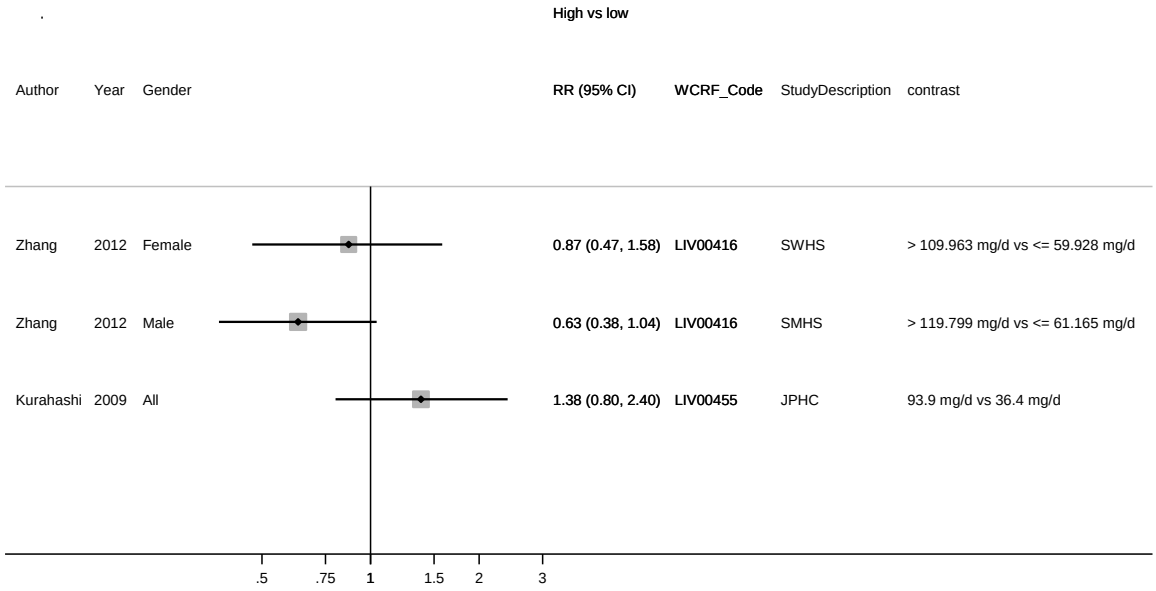


Figure 50 Dose-response meta-analysis of dietary vitamin C and liver cancer - per 25 mg/day

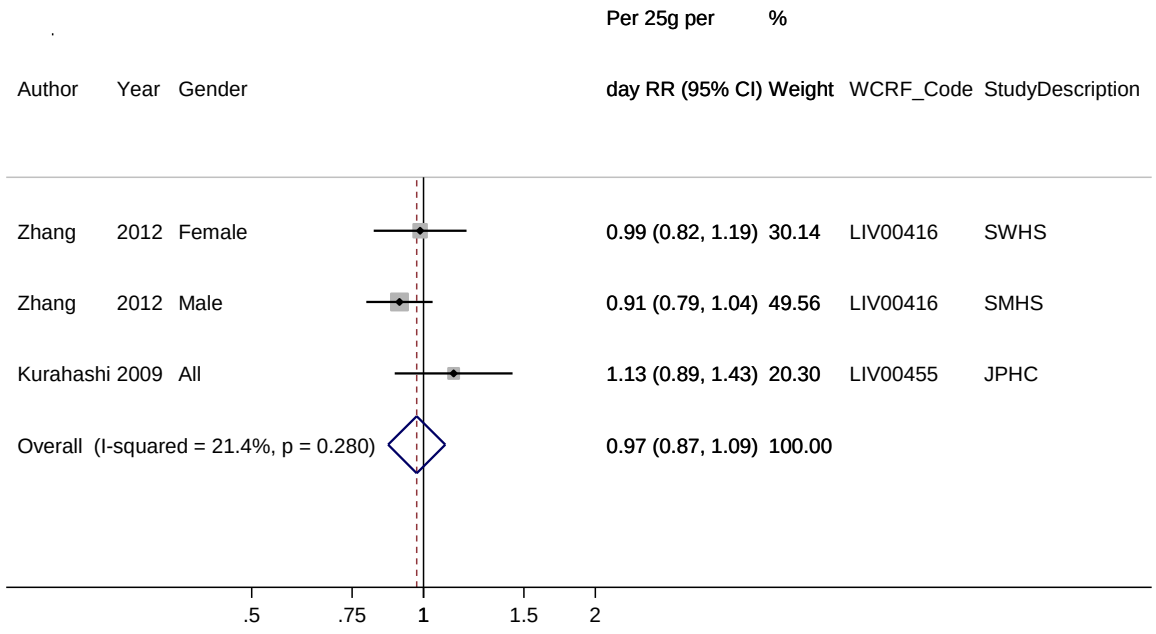
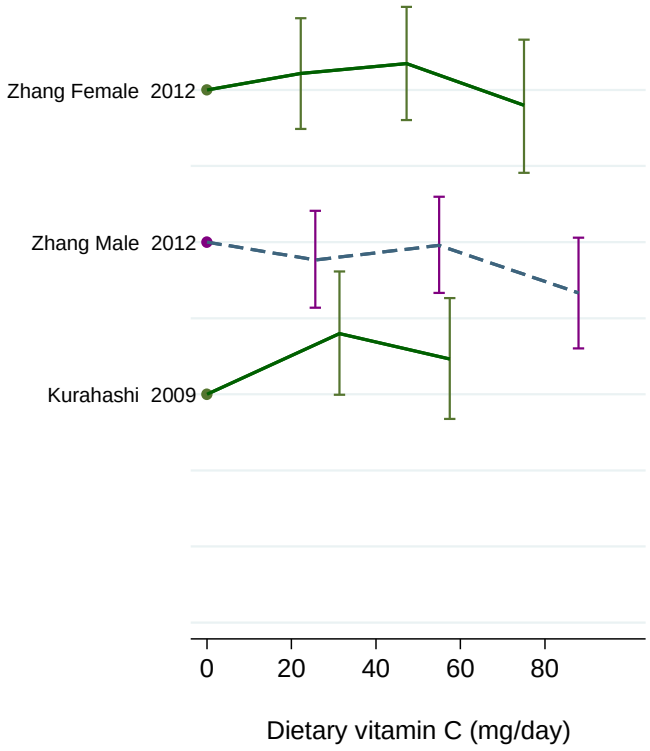


Figure 51 Dose-response graph of dietary vitamin C and liver cancer



6. Physical activity

Four cohort studies on physical activity and liver cancer had been published (Suzuki et al, 2007; Inoue et al, 2008; Yun et al, 2008; Behrens et al, 2013). The studies reported on different domains and no summary estimate could be derived. All studies except the small one (Inoue et al, 2008) reported significant associations in the domains investigated (see table below).

6.1 Total physical activity

One study in Japanese men and women (Inoue et al, 2008, JPHC) identified 64 liver cancers after 7.5 years of follow-up. The RR estimate for the highest compared to the lowest METs score of physical activity (including heavy physical work, strenuous exercise, standing, walking, sedentary, sleep or other passive activity) was 0.54 (95% CI: 0.23-1.29).

6.1.1.2 Leisure-time Physical Activity

A study (Yun et al, 2008) in Korean men identified 169 liver cancers after 6 years of follow-up. The RR was 0.88 (95% CI: 0.81-0.95) when comparing moderate-high versus low leisure-time physical activity.

A study (Suzuki et al, 2007) in Japanese men and women (JCCS) investigated times of sport activities per week and duration of sports in school-time in relation to mortality from liver cancer. During follow-up (duration not available), 377 deaths from liver cancer were identified in men and 143 in women. The HRs were 1.14 (0.83-1.58) for men and 1.57 (0.90-2.73) for women when comparing less than 1 hour per week with more than 3 hours per week of sport activities. The HRs for duration of sports in school time were 1.11 (0.85-1.46) in men and 1.11 (0.69-1.76) in women when comparing always activity with a little time of activity.

6.1.1.4 Walking

The study in Japanese men and women (JCCS) (Suzuki et al, 2007) reported a HR of mortality for liver cancer of 1.43 (95% CI: 1.10-1.86) in men and 1.84 (95% CI: 1.27-2.66) in women when comparing less than 0.5 hours/day of walking time to more than 1 hour/day.

6.1.3 Vigorous physical activity

The NIH-AARP Diet and Health Study (Behrens et al, 2013) investigated frequency of vigorous physical activity and HCC risk. After 10 years of follow-up, 415 cases of HCC were identified. The RR for 5 times per week or more of vigorous physical activity compared to none was 0.56 (0.41-0.78; Ptrend = <0.001).

6.2 Sitting time

The study in Japanese men and women (JCCS) (Suzuki et al, 2007) reported a HR of mortality for liver cancer of 1.55 (95% CI: 1.12-2.17) in men and 2.38 (95% CI: 1.41-4.02) in women when comparing more than 4 hours/day spent watching TV to less than 2 hours/day.

Table 51 Summary of physical activity studies and liver cancer

Author, year	Country	Study name	Cases	Years of follow up	Sex	RR	LCI	UCI	Contrast
Behrens, 2013	USA	NIH-AARP Diet and Health Study	415 HCC	10	M/F	0.56	0.41	0.78	Vigorous physical activity 5+ times/week vs none Ptrend<0.001
Yun, 2008	Korea	National Health Insurance Corporation Study	169 liver cancer	6	M	0.88	0.81	0.95	Leisure time physical activity Moderate-high vs low
Inoue, 2008	Japan	Japan Public Health Center-based Prospective Study	64 liver cancers	7.5	M/F	0.54	0.23	1.29	METs score (heavy physical work, strenuous exercise, standing, walking, sedentary, sleep or other passive activity) Highest vs lowest quartile
Suzuki, 2007	Japan	Japan Collaborative Cohort Study for Evaluation of Cancer Risk	377 deaths	NA	M	1.14	0.82	1.58	Sport times/week 1 h vs >3 h
						1.43	1.10	1.86	Walking time/day, <0.5 vs >1h
						1.11	0.85	1.46	Sport in school time Yes vs little duration
						1.55	1.12	2.17	Hours spent watching TV/day >4 vs <2 h/day
			143 deaths		F	1.57	0.90	2.73	Sport times/week ,1 h vs >3 h
						1.84	1.27	2.66	Walking time/day, <0.5 vs >1h
						1.11	0.69	1.76	Sport in school time Yes vs little duration
						2.38	1.41	4.02	Hours spent watching TV/day >4 vs <2 h/day

8.1.1 BMI

Methods

A total of 15 cohort studies (22 publications) have been published on BMI and liver cancer risk up to June 2013. Fourteen studies (18 publications, since 2006) were identified in the CUP. Dose-response analyses were conducted per 5 units increase in BMI (kg/m^2). We converted the risk estimates using the method by Hamling et al, 2008, when the lowest category was not the reference category so that the lowest category became the reference. This method was also used for the nonlinear dose-response analysis.

Studies on patients with hepatic cirrhosis (one study), hepatitis B (3 studies), hepatitis C (10 studies), non-alcoholic fatty liver disease (one study), non-alcoholic steato-hepatitis (one study) and patients with obesity discharge diagnosis (3 studies) are not included in the review.

Main results

The summary RR per 5 units increase in BMI (kg/m^2) was 1.30 (95% CI: 1.16-1.46, I^2=78.3%, $p_{heterogeneity}$<0.0001, n=12). There was no evidence of publication bias with Egger's test, p=0.27. There was evidence of nonlinearity, $p_{nonlinearity}$<0.0001, with a steeper increase in risk at higher BMI levels. When stratified by outcome type the summary RR was 1.43 (95% CI: 1.19-1.70, I^2=83.6%, $p_{heterogeneity}$<0.0001, n=8) for incidence and 1.13 (95% CI: 1.00-1.28, I^2=43.3%, $p_{heterogeneity}$=0.15, n=4) for mortality. When stratified by sex the summary RR was 1.21 (95% CI: 1.10-1.33, I^2=11.4%, $p_{heterogeneity}$=0.34, n=4) for women and 1.21 (95% CI: 1.02-1.44, I^2=83.8%, $p_{heterogeneity}$<0.0001, n=8) for men.
The heterogeneity was mainly due to differences in the strength of the association, as all but two studies reported associations in the direction of increased risk. With meta-regression analysis there was heterogeneity between subgroups when stratified by geographic location, with a weaker association in Asian studies, summary RR=1.18 (95% CI: 1.04-1.34, I^2=60%, $p_{heterogeneity}$=0.02) than in European studies, summary RR=1.59 (95% CI: 1.35-1.87, I^2=42%, $p_{heterogeneity}$=0.16). The heterogeneity among men was also reduced when stratified by geographic location, with summary RRs of 1.06 (95% CI: 0.97-1.16, I^2=17.4%) among four Asian studies and 1.55 (1.18-2.04, I^2=56%) among three European studies.

Heterogeneity

There was high heterogeneity, I^2=78.3%, $p_{heterogeneity}$<0.0001, which appeared to be more due to differences in the size of the effect estimates, than due to a lack of association as all apart from two studies reported positive associations. When stratified by sex there was lower heterogeneity among women (I^2=11.4%, $p_{heterogeneity}$=0.34) than among men (83.8%, $p_{heterogeneity}$<0.0001). In addition, heterogeneity was reduced when studies were stratified by geographic location.

Conclusion from the Second Expert Report

In the SLR of the 2007 Expert Report the evidence relating body fatness to increased liver cancer risk was considered limited suggestive.

Published meta-analyses and pooled analysis

A meta-analysis of 26 prospective studies found a summary RR of 1.48 (95% CI: 1.31-1.67, I^2=83.6%, $p_{heterogeneity}$<0.001) for overweight and 1.83 (95% CI: 1.59-2.11, I^2=75.0%, $p_{heterogeneity}$<0.001) for obesity compared to normal weight (Chen et al, 2012a).

A meta-analysis of 21 prospective studies found a summary RR of 1.39 (95% CI: 1.25-1.55) per 5 unit increment in BMI (Wang et al, 2012).

A meta-analysis of 8 cohort studies found summary RRs of 1.02 (95% CI: 1.02-1.03), 1.35 (95% CI: 1.24-1.47) and 2.22 (95% CI: 1.74-2.83) for BMI values of 25, 30 and 35, respectively (Rui, 2012).

A meta-analysis of 11 cohort studies reported a summary RR of 1.17 (95% CI: 1.02-1.34, I^2=52.5, $p_{heterogeneity}$=0.03) for overweight persons and 1.89 (95% CI: 1.51-2.36, I^2=86.4, $p_{heterogeneity}$<0.001) for obese persons (Larsson, 2007b).

A meta-analysis of 4 prospective studies reported a summary RR of 1.24 (95% CI: 0.95-1.62, I^2=83%, $p_{heterogeneity}$=0.12) in men and there was only one study in women (RR=1.07, 95% CI: 0.55-2.08) per 5 units increase in BMI (Renehan et al, 2008).

A pooled analysis of 44 Asian cohort studies (Asia-Pacific Cohort Studies Collaboration) including 420 liver cancer deaths reported a HR of 1.27 (0.93-1.74) for BMI ≥25 vs. 18.5-22.9 (Batty et al, 2009).

A pooled analysis of 39 Asian cohort studies (Asia-Pacific Cohort Studies Collaboration) reported a HR of 1.10 (0.63-1.91) for BMI 30-60 vs. 18.5-24.9 (Parr et al, 2010).

A pooled analysis of 7 European cohorts (Norway, Austria, Sweden) reported a RR of 1.92 (95% CI: 1.23-2.96) for the highest vs. the lowest quintile of BMI (31.3 vs. 20.7) (Borena et al, 2012).

A pooled analysis of 57 prospective studies (422 deaths) reported a HR for liver cancer death of 1.47 (1.26-1.71) for a 5 unit increase in BMI (Prospective Studies Collaboration, 2009).

Table 52 Studies on BMI identified in the CUP

Author/year	Country	Study name	Cases	Years of follow-up	RR	LCI	UCI	Contrast (BMI (kg/m^2)
Li, 2013	Japan	Japan Collaborative Cohort Study	527	19	1.15 1.42	0.83 0.95	1.60 2.13	≥25 vs. 21-22.9, men ≥25 vs. 21-22.9, women
Loomba, 2013	Taiwan	Not available	305	11.6	1.25 4.12	0.68 2.05	2.31 8.28	≥30 vs. <23, no alcohol use ≥30 vs. <23, alcohol use
Chen, 2012b	China Nationally Representative Cohort Study	Not available	884	10	0.91 1.15	0.71 0.74	1.17 1.79	Per 5 units, BMI<23.5 Per 5 units, BMI≥23.5
Schlesinger, 2012	10 European countries	European Prospective Investigation into Cancer and Nutrition	177	8.6	2.28 1.55	1.50 1.31	3.45 1.83	29.9/29.6 vs. 23.3/21.4 M/F Per 5 units
Trichopoulos, 2011	10 European countries	European Prospective Investigation into Cancer and Nutrition	125	8.9	1.81	1.06	3.10	≥30 vs. <30
Inoue, 2009b	Japan	Japan Public Health Center-based Cohort 2	102	12.7	2.72	1.51	4.89	≥27 vs. <25
Wang, 2009	Taiwan	Not available	111	8	1.70	1.02	2.80	≥30 vs. <30
Song, 2008	Korea	Korea National Health Insurance Corporation Study	676	8.75	1.63 1.03	0.96 0.99	2.75 1.07	≥30 vs. 21-22.9 Per 1 unit
Ohishi, 2008	Japan	The Adult Health Study	224	Not available	4.57	1.85	11.3	>25 vs. 21.3-22.9
Chen, 2008	Taiwan	Not available	291	14	2.36 1.36 4.13 1.86	0.91 0.64 1.38 1.14	6.17 2.89 12.4 3.04	≥30 vs. <23, HBsAg-/anti-HCV- ≥30 vs. <23, HBsAg+/anti-HCV- ≥30 vs. <23, HBsAg-/anti-HCV+ ≥30 vs. <23, pooled
Jee, 2008	Korea	Korea National Health Insurance Corporation Study	10520	14 years	1.63 1.39	1.27 1.00	2.10 1.94	≥30 vs. 23-24.9, men ≥30 vs. 23-24.9, women
Joshi, 2008	Korea	Korea	998	6 years	1.08	0.67	1.72	≥30 vs. 18.5-24.9

		National Health Insurance Corporation Study						
Batty, 2008	United Kingdom	The Whitehall Study	57	Up to 38 years	2.37 1.18	0.95 0.91	5.90 1.54	≥30 vs. 18.5-<25 Per 1 SD
Fujino, 2007	Japan	Japan Collaborative Cohort Study	637	Not available	1.46 1.09	0.65 0.44	3.28 2.69	≥30 vs. 18.5-24, men ≥30 vs. 18.5-24, men
Lai, 2006	Taiwan	Keelung Community-Based Integrated Screening Program	138	2.78 years	1.07	0.76	1.51	≥25 vs. <25
Samanic, 2006	Sweden	Swedish Construction Workers Cohort Study	297	19 years	3.62	2.62	5.00	>30 vs. <25
Kuriyama, 2005	Japan	Miyagi Prefecture Cohort Study	100	9 years	1.14 0.91	0.46 0.30	2.87 2.80	27.5-29.9 vs. 18.5-24.9, men 27.5-29.9 vs. 18.5-24.9, women
Rapp, 2005	Austria	The Vorarlberg Health Monitoring and Promotion Program	57	9.9 years	1.67	0.75	3.72	≥30 vs. 18.5-24.9

Table 53 Overall evidence on BMI and liver cancer

	Summary of evidence
2005 SLR	Five cohorts (6 publications) reported on BMI or obesity (as discharge diagnosis) and liver cancer and all of these reported increased risk. One of the studies reported a positive association in whites and an inverse association in African Americans.
Continuous Update Project	Sixteen publications from 12 cohort studies were identified on BMI and liver cancer and 9 of these reported positive significant associations,

Table 54 Summary of results of the dose-response meta-analysis of BMI and liver cancer

Liver cancer		
	2005 SLR	Continuous Update Project
Studies (n)	4	12
Cases (n)	-	14311
RR (95% CI)	1.71 (1.09-2.67)	1.30 (1.16-1.46)
Increment unit used	Highest versus lowest	Per 5 units BMI kg/m^2
Heterogeneity (I^2, p-value)	90.0%, p<0.0001	78.3%, p<0.0001
By sex		**Women**
Studies (n)		4
Overall RR (95%CI)		1.21 (1.10-1.33)
Heterogeneity (I^2,p-value)		11.4%, p=0.34
By geographic location		**Men**
Studies (n)		8
Overall RR (95%CI)		1.21 (1.02-1.44)
Heterogeneity (I2,p-value)		83.8%, p<0.0001
By geographic location		Europe
Studies (n)		4
Overall RR (95%CI)		1.59 (1.35-1.87)
Heterogeneity (I2,p-value)		42%, p=0.16
		Asia
Studies (n)		7
Overall RR (95%CI)		1.18 (1.04-1.34)
Heterogeneity (I2,p-value)		60%, p=0.02

Table 55 Inclusion/exclusion table for meta-analysis of BMI and liver cancer

WCRF code	Author	Year	Study design	Study name	Cancer outcome	2005 SLR	CUP dose-response	CUP H vs. L forest plot	Estimated values	Exclusion reason
LIV00518	Li	2013	Prospective Cohort	Japan Collaborative Cohort Study	Mortality	No	No	No		Overlap with Fujino et al, 2007 (LIV00460) which had a greater number of cases
LIV00505	Loomba	2013	Prospective Cohort	Not available	Incidence	No	No	Yes		Distribution of cases or person/years not reported
LIV00485	Chen(b)	2012	Prospective Cohort	Not available	Mortality	No	Yes	No		Only continuous estimate
LIV00419	Schlesinger	2012	Prospective Cohort	European Prospective Investigation into Cancer and Nutrition	Incidence	No	Yes	Yes	Person-years	
LIV00425	Trichopoulos	2011	Nested Case Control	European Prospective Investigation into Cancer and Nutrition	Incidence	No	No	No		Overlap with Schlesinger et al, 2012 (LIV00419)
LIV00449	Wang	2009	Prospective Cohort	Not available	Incidence	No	No	Yes		<3 categories
LIV00451	Inoue(b)	2009	Prospective Cohort	Japan Public Health Center-based Cohort 2	Incidence	No	Yes	Yes	Midpoints	
LIV00502	Song	2008	Prospective Cohort	Korea National Health Insurance Corporation Study	Incidence	No	No	No		Overlap with Jee et al, 2008 (LIV00471)
LIV00476	Ohishi	2008	Prospective Cohort	The Adult Health Study	Incidence	No	Yes	Yes	Midpoints	

LIV00474	Chen	2008	Prospective Cohort	Not available	Incidence	No	Yes	Yes	Midpoints	
LIV00471	Jee	2008	Prospective Cohort	Korea National Health Insurance Corporation Study	Incidence	No	Yes	Yes	Midpoints, person-years	
LIV00467	Joshi	2008	Prospective Cohort	Korea National Health Insurance Corporation Study	Mortality	No	No	No		Overlap with Jee et al, 2008 (LIV00471)
LIV00466	Batty	2008	Prospective Cohort	The Whitehall Study	Mortality	No	Yes	Yes	Midpoints	
LIV00460	Fujino	2007	Prospective Cohort	Japan Collaborative Cohort Study	Mortality	No	Yes	Yes	Midpoints	
LIV00492	Lai	2006	Prospective Cohort	Keelung Community-Based Integrated Screening Program	Incidence	No	No	Yes		<3 categories of BMI
LIV00483	Samanic	2006	Prospective Cohort	Swedish Construction Workers Cohort Study	Incidence	No	Yes	Yes	Midpoints, person-years	
LIV00512	Kuriyama	2005	Prospective Cohort	Miyagi Prefecture Cohort Study	Incidence	No	Yes	Yes	Midpoints	
LIV00511	Rapp	2005	Prospective Cohort	VHM&PP	Incidence	No	Yes	Yes	Midpoints	
LIV00545	Batty	2005	Prospective Cohort	The Whitehall Study	Mortality	Yes	No	No		Overlap with Batty et al, 2008 (LIV00466)
LIV00538	Oh	2005	Prospective Cohort	Korea National Health Insurance Corporation Study	Incidence	Yes	No	No		Overlap with Jee, et al, 2008 (LIV00471)
LIV00632	Jee	2004	Prospective Cohort	Korea National Health Insurance Corporation	Mortality	Yes	No	No		No risk estimates, overlap with Jee et al, 2008 (LIV00471)

				Study						
LIV00055	Calle	2003	Prospective Cohort	Cancer Prevention Study 2	Mortality	Yes	Yes	Yes	Midpoints, distribution of cases and person-years	

Figure 52 Highest versus lowest forest plot of BMI and liver cancer

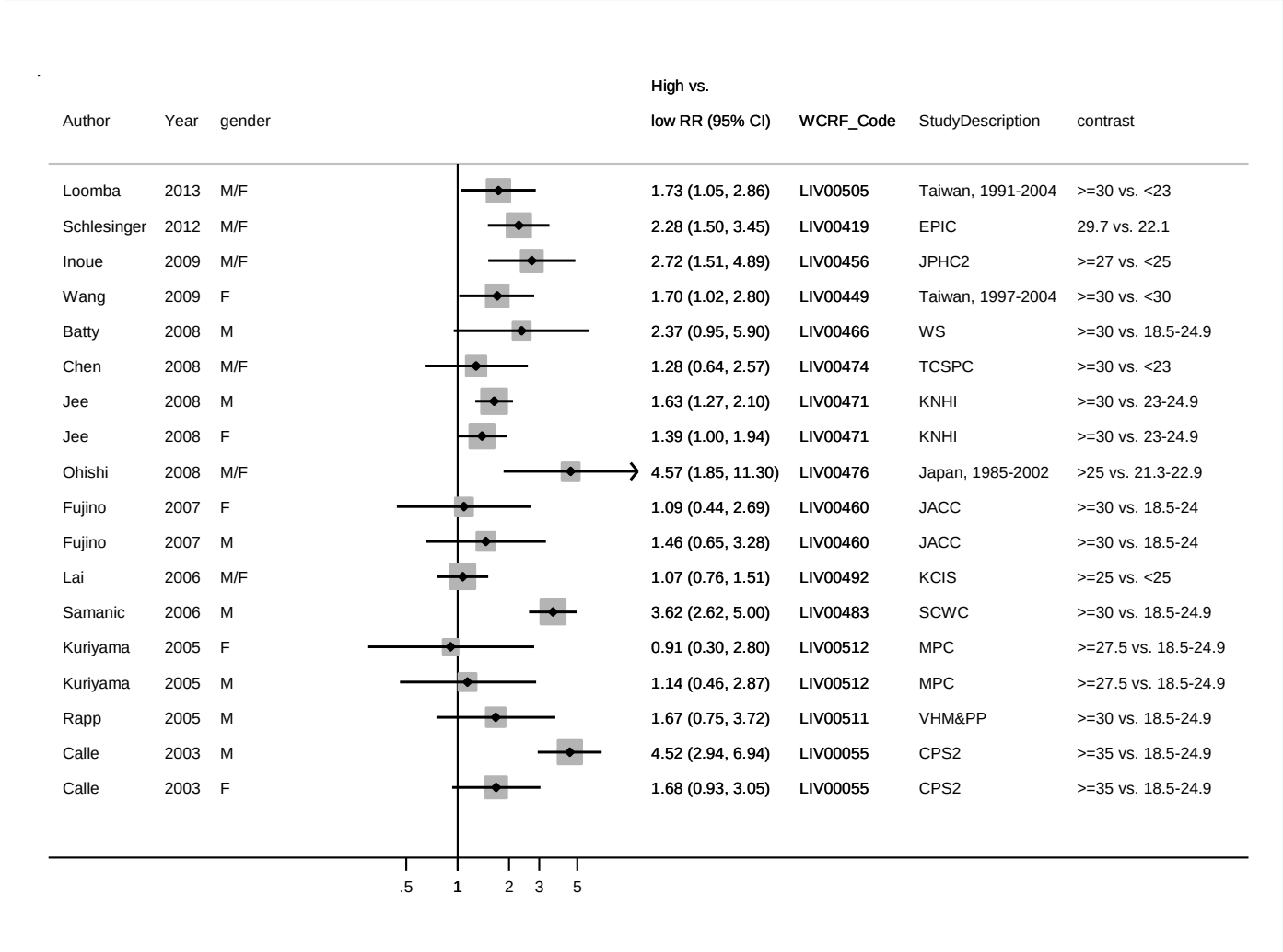


Figure 53 Dose-response meta-analysis of BMI and liver cancer, per 5 units

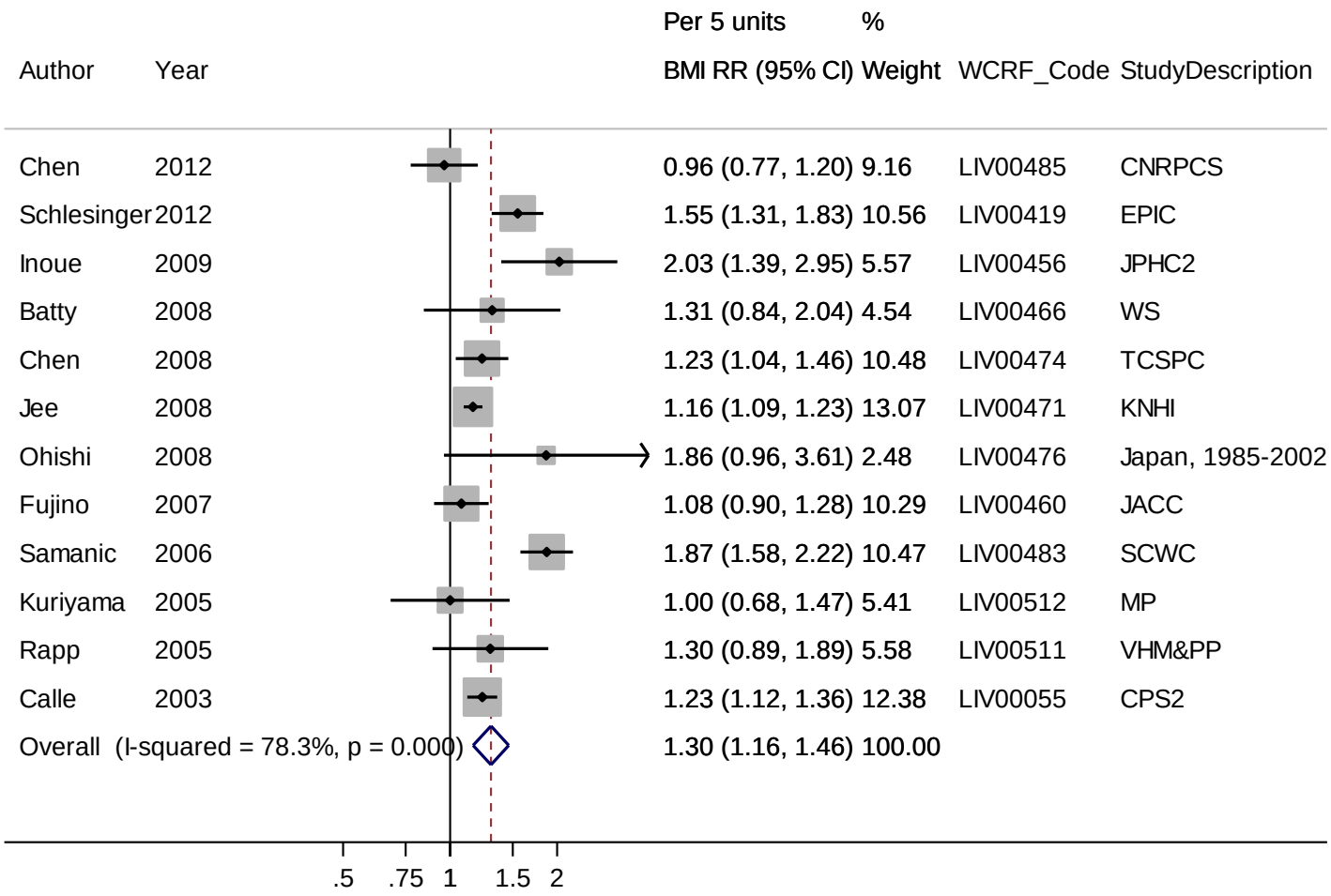


Figure 54 Dose-response meta-analysis of BMI and liver cancer, per 5 units, stratified by outcome type

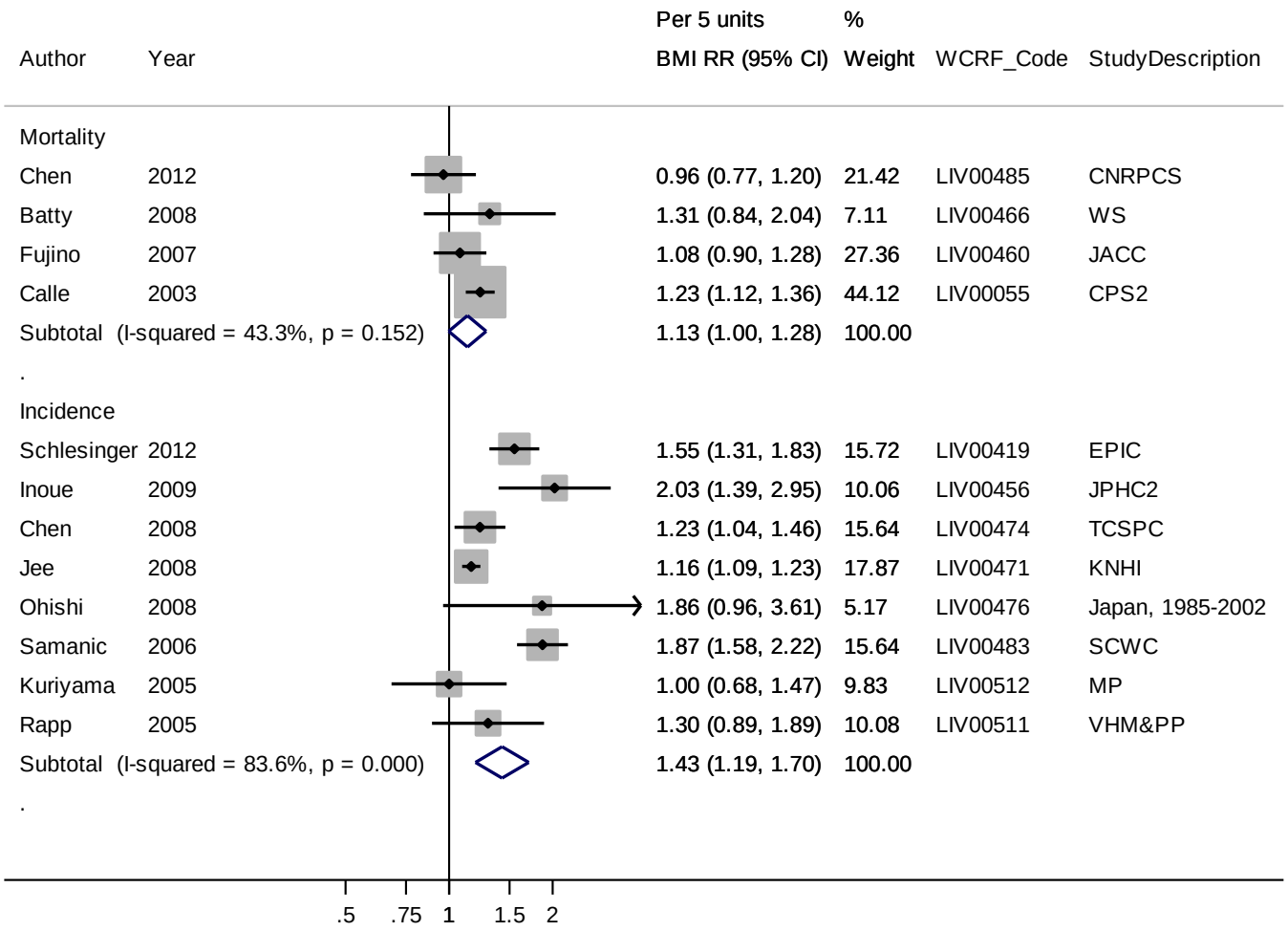


Figure 55 Dose-response meta-analysis of BMI and liver cancer, per 5 units, stratified by sex

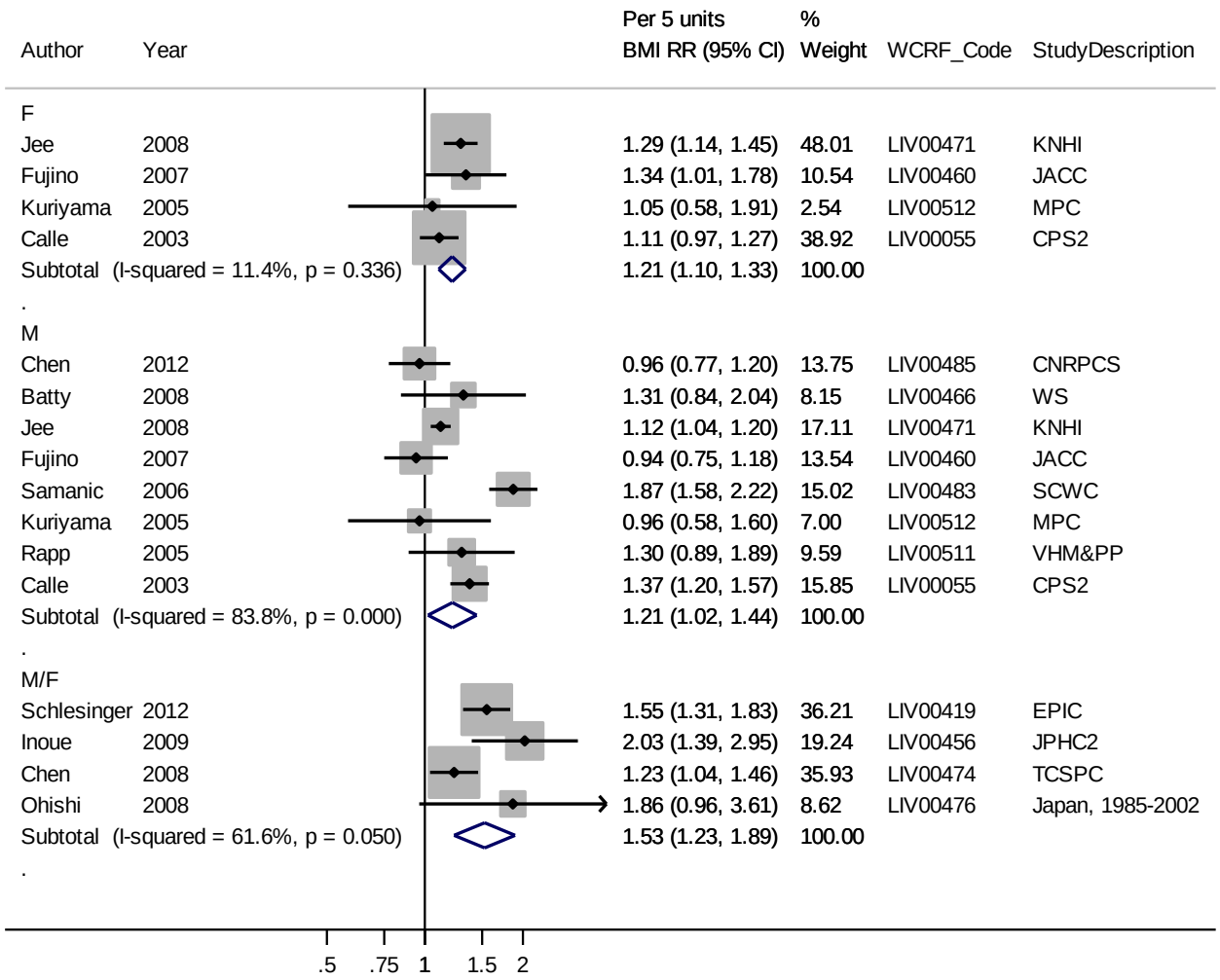


Figure 56 Figure Dose-response meta-analysis of BMI and liver cancer, per 5 units, stratified by geographic location

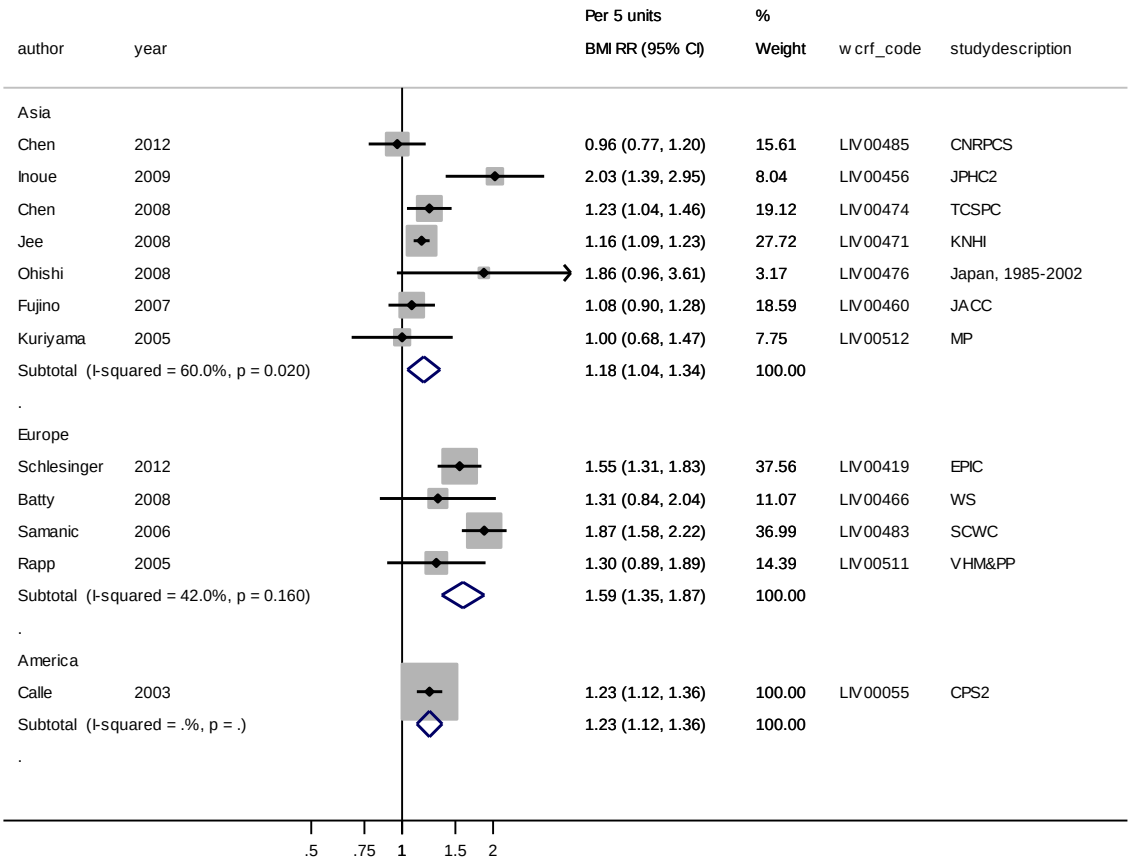


Figure 57 Funnel plot of BMI and liver cancer

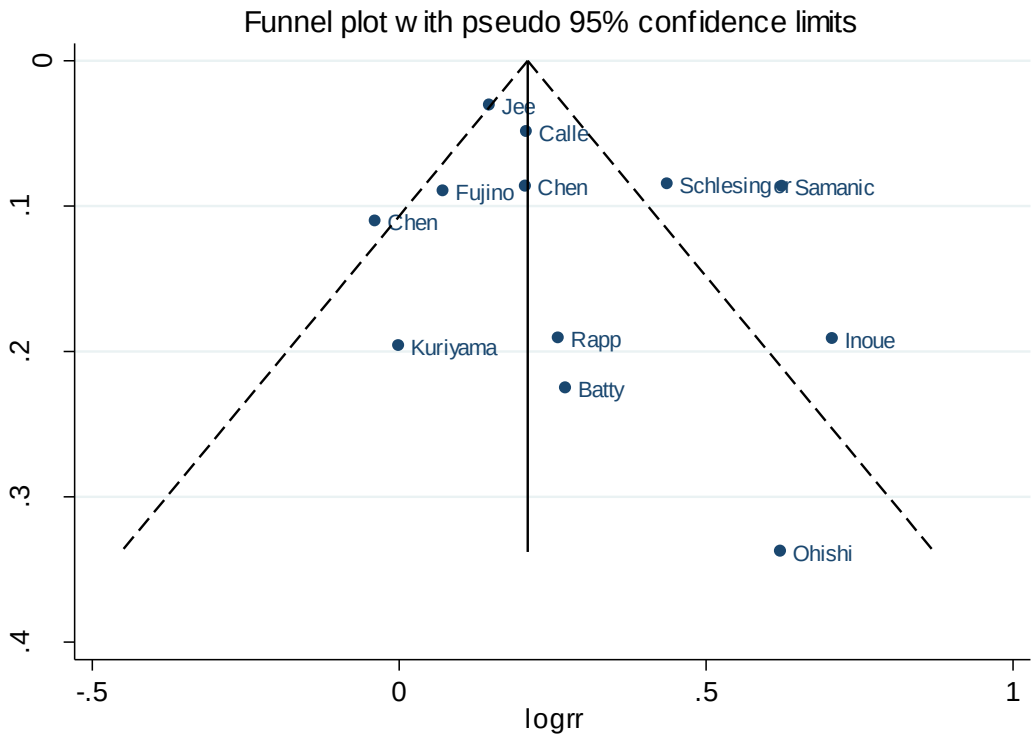


Figure 58 Dose-response graph of BMI and liver cancer

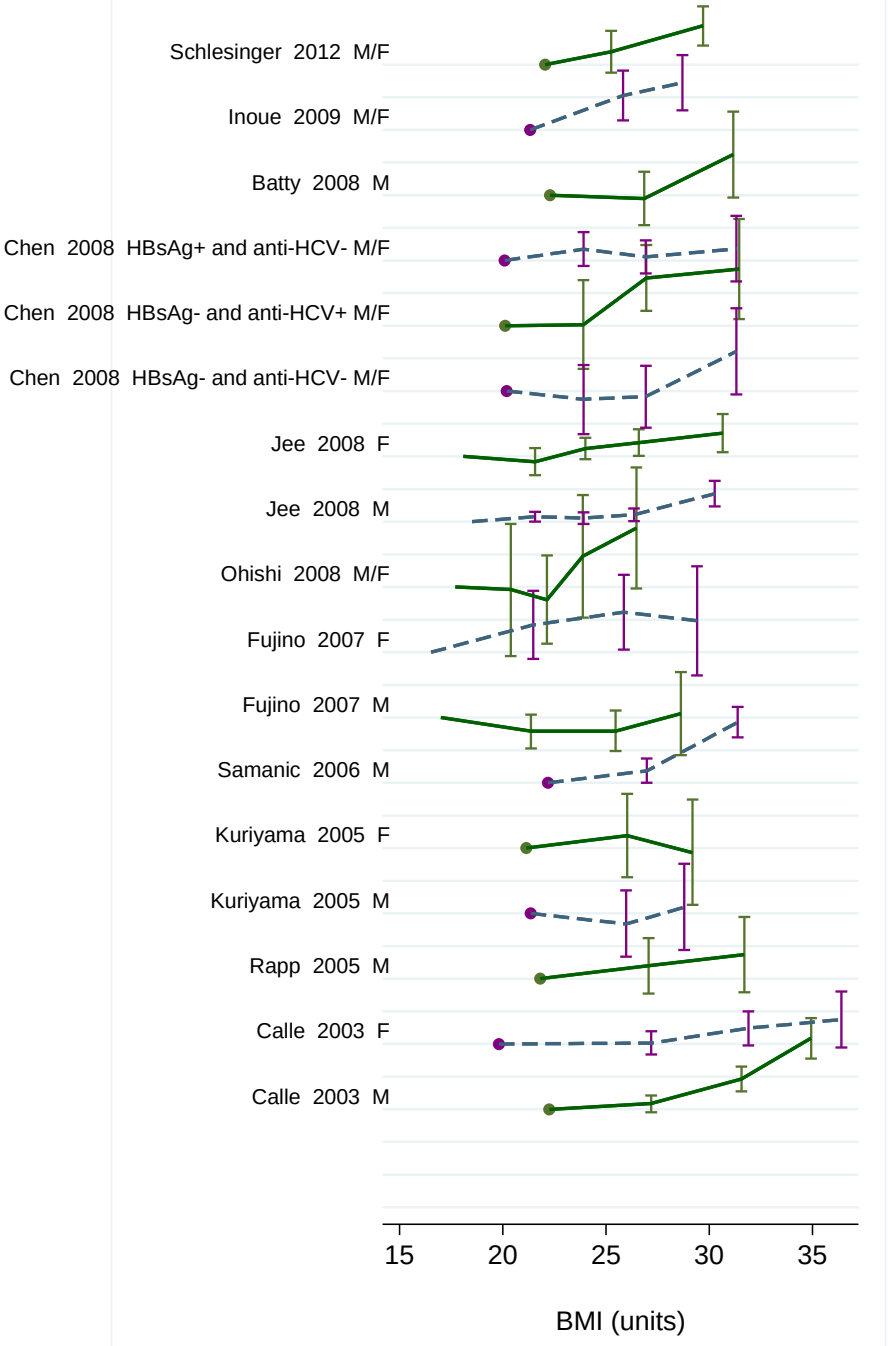


Figure 59 Non-linear dose-response figure for BMI and liver cancer

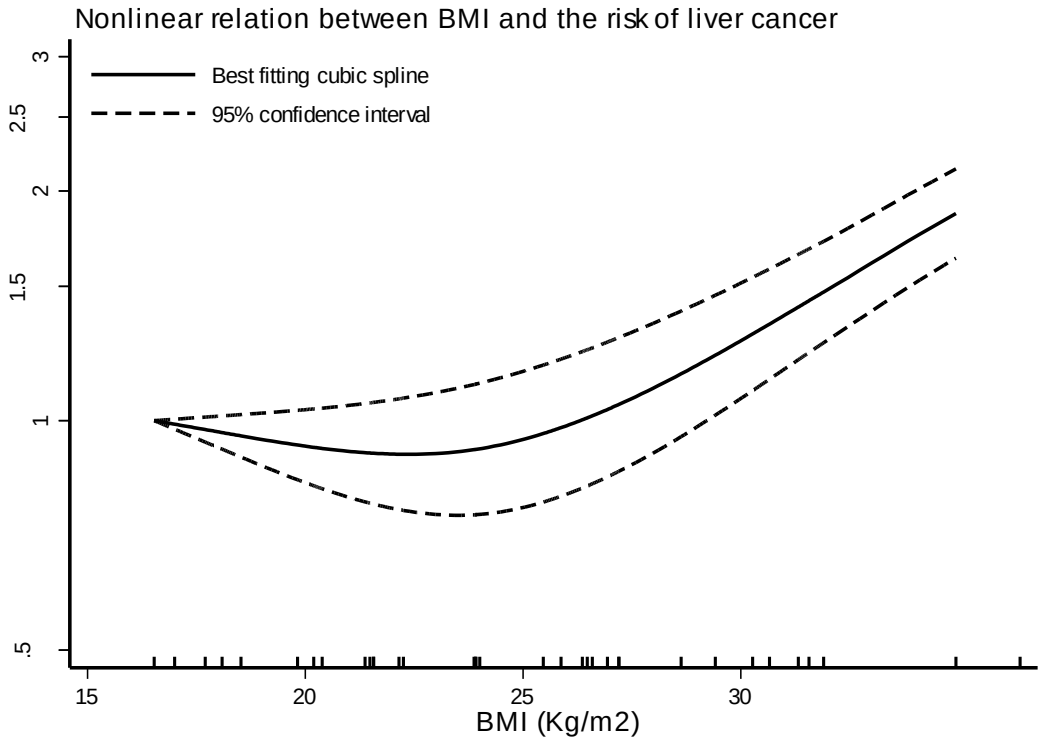


Figure 60 Scatter plot of risk estimates for BMI and liver cancer

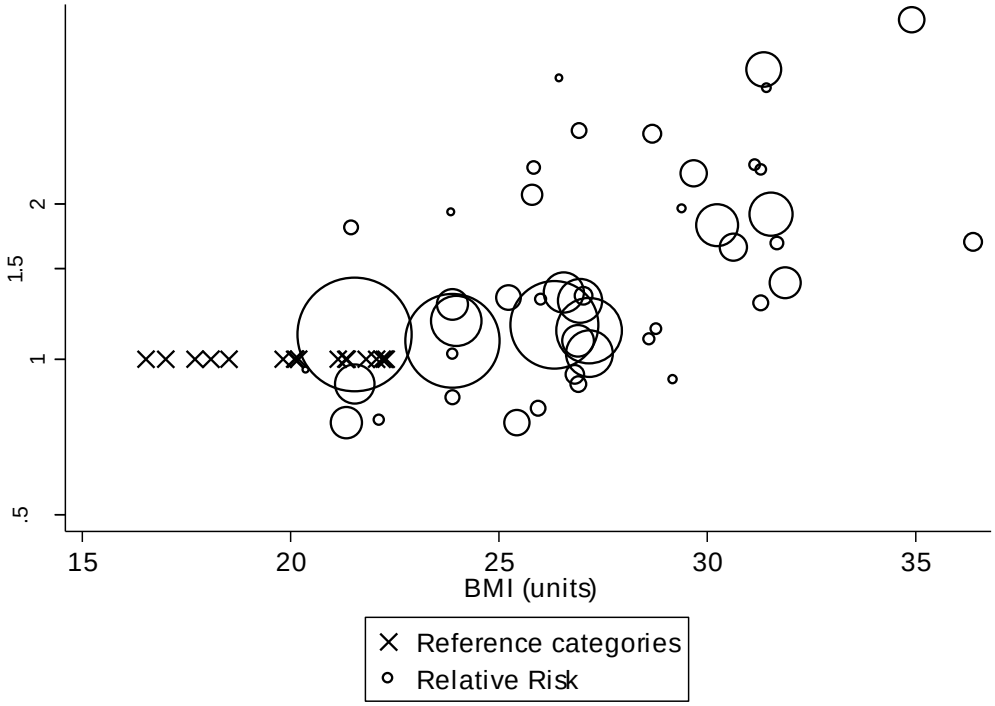


Table 56 RRs from the nonlinear analysis

BMI values	RR (95% CI)
17.0	1.00
18.0	0.99 (0.97-1.00)
20.0	0.92 (0.82-1.04)
22.5	0.90 (0.76-1.07)
25.0	0.96 (0.78-1.18)
27.0	1.05 (0.86-1.29)
30.0	1.30 (1.09-1.54)
35.0	1.87 (1.83-2.40)

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