World Cancer Research Fund International Systematic Literature Review

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

Analysing research on cancer prevention and survival

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Date completed:
20 November 2013

Final version:
16 December 2014

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List of Abbreviations used in the CUP SLR

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

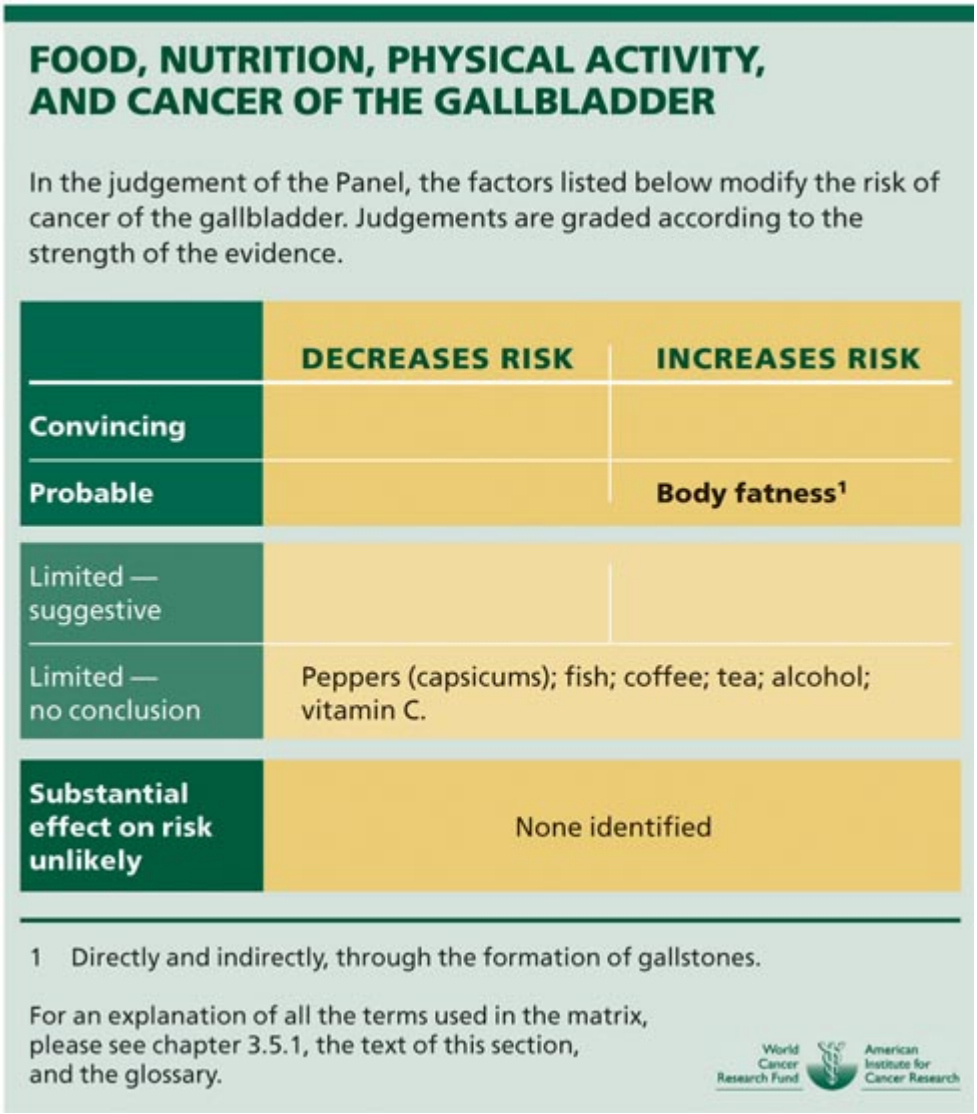
List of Abbreviations of cohort study names used in the CUP SLR

CPS II	Cancer Prevention Study II
EPIC	European Prospective Investigation into Cancer and Nutrition
JACC	Japan Collaborative Cohort study
JPHC	Japan Public Health Centre-based Prospective Study
KCPS	Korean Cancer Prevention Study
NIH-AARP	NIH-AARP Diet and Health Study
WHI	Women's Health Initiative

Background

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 gallbladder.



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

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

	DECREASES RISK	INCREASES RISK
Convincing		
Probable		**Body fatness**[1]
Limited — suggestive		
Limited — no conclusion	Peppers (capsicums); fish; coffee; tea; alcohol; vitamin C.	
Substantial effect on risk unlikely	None identified	

1 Directly and indirectly, through the formation of gallstones.

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

World Cancer Research Fund | American Institute for Cancer Research

Modifications to the existing protocol:

1. The research team composition was modified. The literature search and data extraction was conducted by Snieguole Vingeliene (SV) and double-checked by Teresa Norat. Deborah Navarro Rosenblatt and Dagfinn Aune worked as data analysts.

2. Meta-analyses were conducted when three new studies were identified even if the total number of studies was below five. This is because no meta-analysis of cohort studies was done in the 2005 SLR.

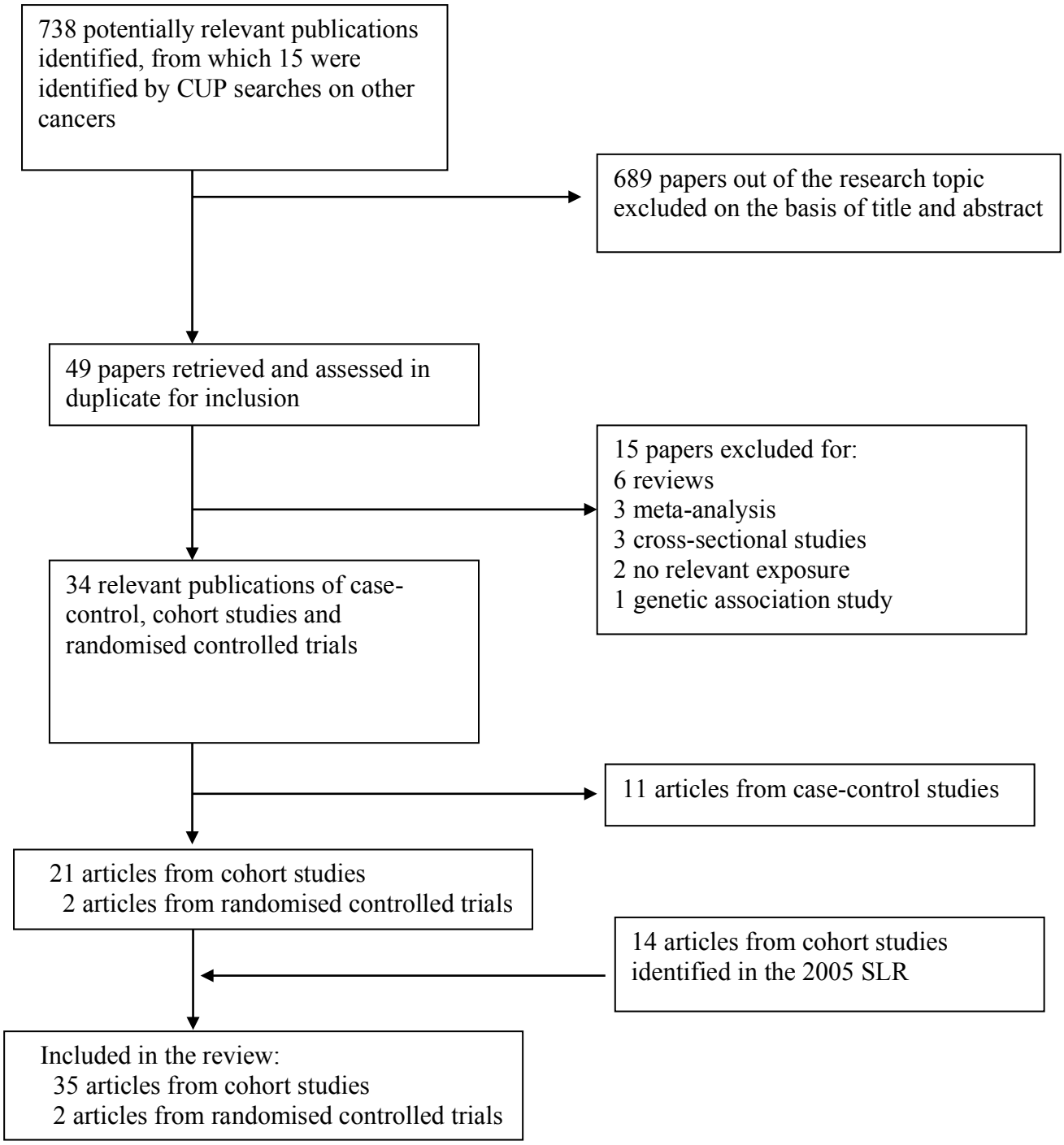
Notes on the figures and statistics used:

- Heterogeneity tests were conducted for all dose-response meta-analysis but the interpretation should be cautious when the number of studies is low because these tests have low power. Visual 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 dose-response analysis. Low heterogeneity was defined as below 30% and high heterogeneity as more than 50%. 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 combined-study summary relative risk estimates and corresponding 95% CIs. The units of increase are indicated in each figure.
- The highest vs lowest forests plots show the relative risk estimate for the highest vs the lowest category of exposure reported in each paper.
- The dose-response plots show the relative risk estimates for each exposure category as published in each relevant study. The relative risks estimates are plotted in the mid-point of each category level (x-axis) and are connected through lines.

Continuous Update Project: Results of the search

The search period is from the 1st of January 2006 until the 31st of March 2013.

Flow chart of the search for gallbladder cancer – 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 as a major disease-prevention research program assessing the risks and benefits of hormone therapy and dietary modification (low fat diet) 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.

One year later, participants in the hormone therapy and dietary modification trials were invited to enrol in the randomized trial of calcium plus vitamin D (CaD) compared to placebo. Fifty-four percent of CaD trial participants had been enrolled in the trial assessing hormone therapy, 69% had enrolled in the trial assessing dietary modification, and 14% were in both trials.

1.5 Low fat diet

In the WHI dietary modification trial (Prentice et al, 2007), the overall incidence of cancer of the biliary tract did not differ, after an average of 8.1 years of follow-up**,** between the group with dietary modification intervention and the control group (HR = 1.96, 95% CI = 0.95 to 4.03; *P* = 0.20; 30 cases), (n intervention = 11092 postmenopausal women; n control = 16537).

The goals of the dietary modification 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 percentage of energy from fat, consumed 1.1 servings more of vegetables and fruit and 0.4 servings more of grain than the comparison group.

5.6.3 Calcium and vitamin D

No significant association on gallbladder cancer risk was observed in the WHI randomized controlled trial on calcium and vitamin D (Brunner et al, 2011). After a mean follow-up of seven years, the relative risk of gallbladder cancer in the intervention group compared to controls was 1.04 (95% CI: 0.15-7.38; 4 cases).

The primary outcome was hip fracture, and gallbladder 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 to placebo. Self-reported baseline total calcium and vitamin D intakes from diet were similar in the two groups and remained similar during the trial.

2. Cohort studies. Results by exposure.

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

The first column shows the exposure code for the exposure used in the database. Only exposures identified during the CUP are shown.

Exposure code	Exposure name	Number of articles		Total number of cohort studies
		Second Expert Report	CUP	
3.6.2	Tea	0	2	2
3.6.2.2	Green tea	1	2	3
3.6.2	Black tea	0	1	1
5.1.4	Sugar (as nutrient)	0	3	3
5.4	Alcohol consumption	0	4	3*
8.1.1	BMI	6	8	14
8.1.3	Weight	0	2	2
8.3.1	Height	0	2	2

***Three cohorts from four publications reported on alcohol.**

Exposures that were reported in only one study identified during the CUP

Individual level dietary pattern, type of breakfast, carrots, Chinese cabbage, fruits, citrus fruits, mushrooms, pickled vegetables, seaweed, spinach, tomatoes, lettuce and cabbage, beans, potatoes, cereals (grains), rice, starch, dietary fibre, milk, cheese, yoghurt, chicken, liver, cod liver oil, beef, ham and sausages, fish, fish paste, fish(salted and dried), eggs, pork, poultry, energy intake, lipids, mono/disaccharides, sucrose, fructose, total carbohydrates, fat preference, margarine, butter, fried foods, fried vegetables, fruit juices, coffee, glycaemic index, glycaemic load, sugars (as foods), sweets, miso soup, tofu, multivitamin supplements, thiamine (vitamin B1), vitamin C supplements, vitamin E supplements, preference for salty foods, preserved foods, salt, physical activity (duration), walking, leisure time, sports, vigorous activity, waist circumference, hip circumference, waist to hip ratio, waist to height ratio, weight at 20 years, weight change.

There were enough studies to update meta-analysis only for Sugar, Alcohol and BMI. No analysis on green tea and tea was conducted because only one study provided enough data for meta-analysis.

5.1.4 Total sugar (as nutrient)

Methods

Up to March 2013, reports from three cohort studies were identified; all of them were identified during the CUP. The CUP meta-analysis included two studies. For one study (Tasevska et al, 2012) intake was rescaled from g/1000 kcal/day to g/day using the average energy intake (kcals/day) reported in the article. The dose-response results are presented for an increment of 50 grams of total sugar per day.

The EPIC study (Fedirko et al, 2013) and the NIH-AARP study (Tasevska et al, 2012) reported on biliary tract cancers (including cancers of the gallbladder, ampulla of Vater and extrahepatic bile ducts). The EPIC study (Fedirko et al, 2013) also reported on gallbladder. The summary RR for an increase of 50 gr per day of total sugar intake was 0.95 (0.64-1.41), a similar result to that obtained for biliary tract cancers. Tasevka et al, 2012 did not report on gallbladder cancer.

Main results

The summary RR per 50 g/d was 0.88 (95% CI: 0.69-1.13; I^2=0%, $P_{heterogeneity}$ =0.89) for the two studies combined.

Heterogeneity

There was no evidence of heterogeneity across the limited number of studies (I^2=0%, p=0.89).

Comparison with the Second Expert Report

No meta-analysis was conducted in the second report.

Published meta-analysis

No meta-analysis was identified

Table 2 Studies on total sugar 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 Study	236	14.8	All	0.78 0.90	0.52 0.60	1.18 1.33	149.95 g/d vs 65.85 g/d Per 50 g/d increase
Tasevska, 2012	USA	NIH-American Association of Retired People Diet and Health Study	98 66	7.2	M F	0.82 0.80	0.46 0.39	1.48 1.67	76.9 vs 38.7 g per 1000 kcal/d 83.1 vs 38.7 g per 1000 kcal/d
Iso, 2007	Japan	Japan Collaborative Cohort Study for Evaluation of Cancer	71 88	~12	M F	0.88 1.03	0.46 0.61	1.69 1.74	Modification of sugar intake vs no change

Table 3 Overall evidence on total sugar consumption and gallbladder/biliary tract cancer

	Summary of evidence
2005 SLR	No study was identified on total sugar intake and gallbladder cancer during the 2005 SLR
Continuous Update Project	Three studies were identified; two could be included in the meta-analysis. Non significant (inverse) associations were observed in the studies

Table 4 Summary of results of the dose response meta-analysis of total sugar consumption and gallbladder/biliary tract cancer

Gallbladder/biliary tract cancer		
	2005 SLR*	Continuous Update Project
Studies (n)	-	2
Cases (n)	-	400
Increment unit used	-	Per 50 g/day
Overall RR (95%CI)	-	0.88 (0.69-1.13)
Heterogeneity (I^2,p-value)	-	0%, p=0.89

*No meta-analysis was conducted in the 2005 SLR

Table 5 Inclusion/exclusion table for meta-analysis of total sugar consumption and gallbladder/biliary tract 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
GAL00161	Fedirko	2013	Prospective Cohort study	European Prospective Investigation into Cancer and Nutrition Study	All	Incidence	No	Yes	Yes	-	-
GAL00152	Tasevska	2012	Prospective Cohort study	NIH-American Association of Retired People Diet and Health Study	M F	Incidence	No	Yes	Yes	Person-years Exposure rescaled to g/day	-
GAL00146	Iso	2007	Prospective Cohort study	Japan Collaborative Cohort Study for Evaluation of Cancer	M F	Mortality	No	No	Yes	-	No quantitative intake levels

Figure 1 Highest versus lowest forest plot of total sugar consumption and gallbladder/ tract cancer

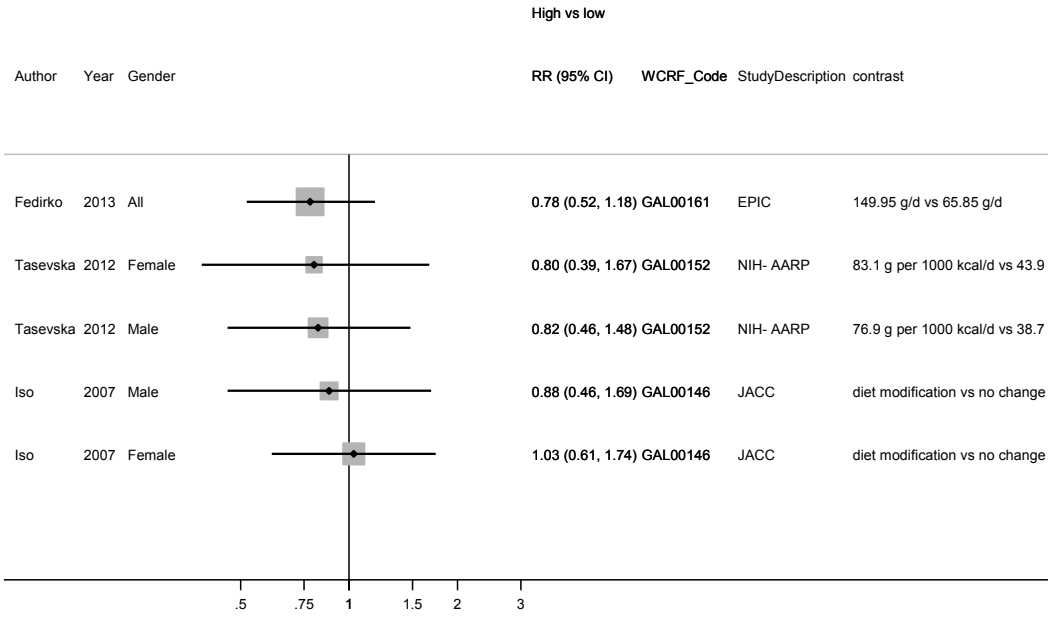


Figure 2 Dose-response meta-analysis of total sugar and gallbladder cancer/bilia per 50 g/day

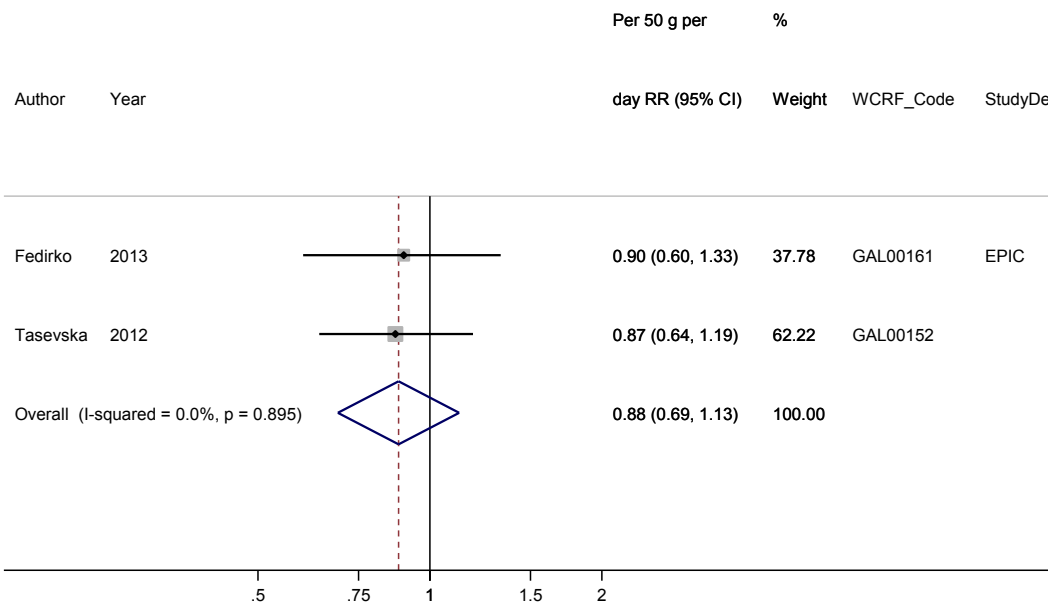
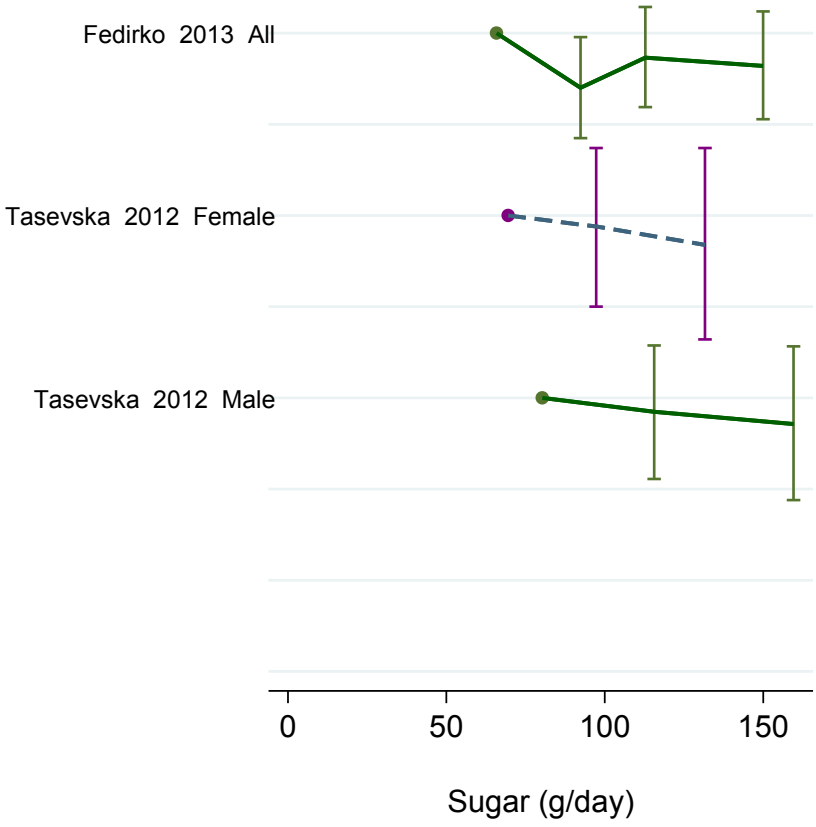


Figure 3 Dose-response graph of total sugar and gallbladder/biliary tract cancer



5.4.1 Total Alcohol (from ethanol)

Methods

Up to March 2013, reports from three cohort studies and four publications were identified; all of them are from Asian countries, were identified during the CUP. The CUP meta-analysis included three studies but for two of them only the results for men could be included. The endpoint was mortality in two studies. For the dose-response analyses results were converted to a common scale of exposure level (grams per day) of ethanol intake. The dose-response results are presented for an increment of 10 grams of ethanol per day.

The outcomes investigated were incidence of biliary tract cancer (Ishiguro et al, 2008), mortality for gallbladder cancer (Yagyu et al, 2008; Osaza et al, 2008) and mortality for extrahepatic bile duct cancer (Yi et al, 2010).

Main results

The summary RR per 10 g/d was 1.07 (95% CI: 0.98-1.17; I^2=26.2%, $P_{heterogeneity}$ =0.25) for the three studies combined.

Heterogeneity

There was no evidence of heterogeneity across the limited number of studies (I^2=26.2%, p=0.25). There was no indication of publication bias with Egger's test (p=0.93).

Comparison with the Second Expert Report

No meta-analysis was conducted in the second report.

Published meta-analysis

In a published meta-analysis (Li et al, 2011) of two case-control studies (467 cases and 1315 controls), the summary RR for gallbladder cancer was 0.70 (95% CI: 0.49-1.00, I^2= 16%, $P_{heterogeneity}$ =0.27), among alcohol drinkers vs. non-drinkers.

Table 6 Studies on alcohol consumption identified in the CUP

Author, year	Country	Study name	Cases	Years of follow up	Sex	RR	LCI	UCI	Contrast
Yi, 2010	Korea	Kangwha Cohort Study	17	20.8	M F	3.06 7.01	0.49 0.77	19.1 63.6	>= 540 g/week vs non drinkers >= 12 g/week vs non drinkers
Yagyu, 2008	Japan	Japan Collaborative Cohort Study for Evaluation of Cancer	165	15	M F	3.07 0.62	0.90 0.09	10.44 4.55	>= 72 g/day vs non drinkers >= 24 g/day vs non drinkers
Ishiguro, 2008	Japan	Japan Public Health Center-based Prospective Study	235	10.9	M F	1.04 1.06	0.65 0.50	1.66 2.22	>= 150 g/week vs non drinkers <150 g/week vs non drinkers
Ozasa, 2007	Japan	Japan Collaborative Cohort Study for Evaluation of Cancer	72	~12	M F	3.21 2.17	1.09 0.29	9.44 15.8	>=81 ml alcohol/day vs non drinkers 54-80 ml alcohol/day vs non drinkers

Table 7 Overall evidence on alcohol consumption and gallbladder cancer

	Summary of evidence
2005 SLR	No study was identified on total ethanol intake and gallbladder cancer during the 2005 SLR
Continuous Update Project	Four publications from three cohorts were identified. Three studies were included in the meta-analysis. Only one study showed a significant positive association among women.

Table 8 Summary of results of the dose response meta-analysis of alcohol consumption and gallbladder cancer

Gallbladder cancer		
	2005 SLR*	Continuous Update Project
Studies (n)	-	3
Cases (n)	-	417
Increment unit used	-	Per 10 g/day
Overall RR (95%CI)	-	1.07 (0.98-1.17)
Heterogeneity (I^2,p-value)	-	26.2%, p=0.25

*No meta-analysis was conducted in the second report

Table 9 Inclusion/exclusion table for meta-analysis of alcohol consumption and gallbladder 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
GAL00162	Yi	2010	Prospective Cohort study	Kangwha Cohort Study	M F	Mortality	No	Yes No	Yes	Mid-points	Only results in men were included. Ethanol intake for females was very low, with small amount of cases, giving a very high RR with extreme CI.
GAL00143	Yagyu	2008	Prospective Cohort study	Japan Collaborative Cohort Study for Evaluation of Cancer	M F	Mortality	No	Yes	Yes	Mid-points	-
GAL00144	Ishiguro	2008	Prospective Cohort study	Japan Public Health Center-based Prospective Study	M F	Incidence	No	Yes	Yes	Person-years and mid-points per category	Only results in men were included. Women only 2 categories
GAL00141	Ozasa	2007	Prospective Cohort study	Japan Collaborative Cohort Study for Evaluation of Cancer	M F	Mortality	No	No	No	--	Superseded by Ozasa el at, 2007 (GAL00141)

Figure 4 Highest versus lowest forest plot of alcohol consumption and gallbladd

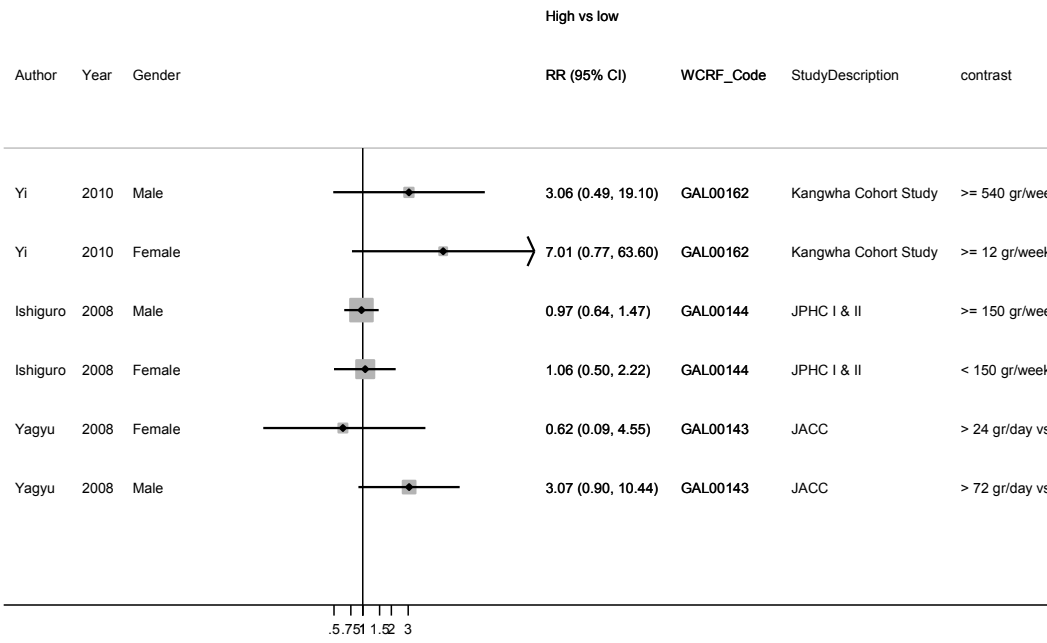


Figure 5 Dose-response meta-analysis of alcohol consumption and gallbladder ca 10 g/day

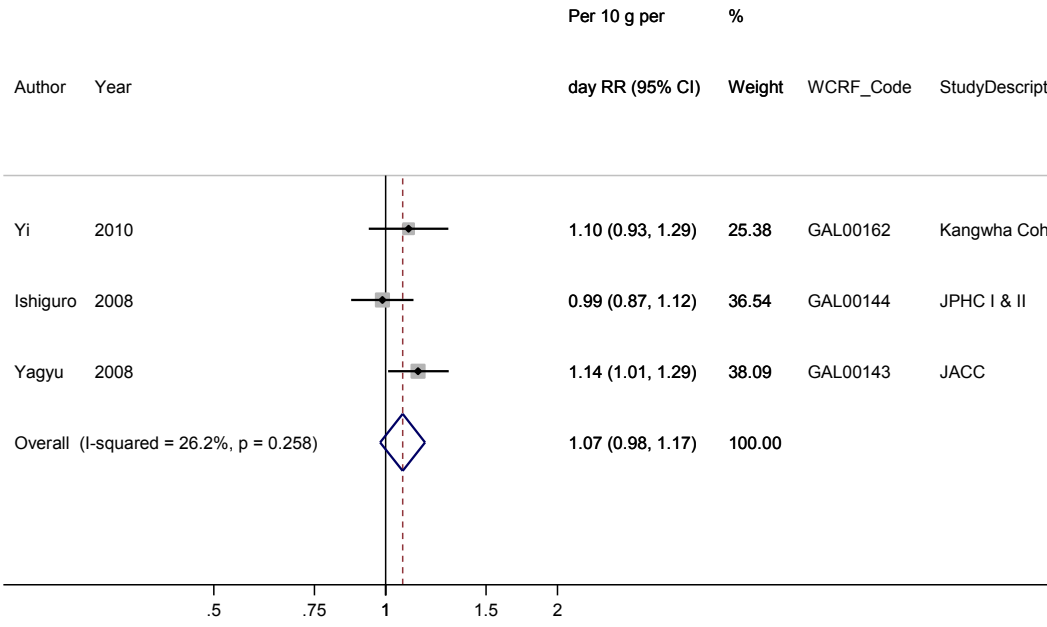
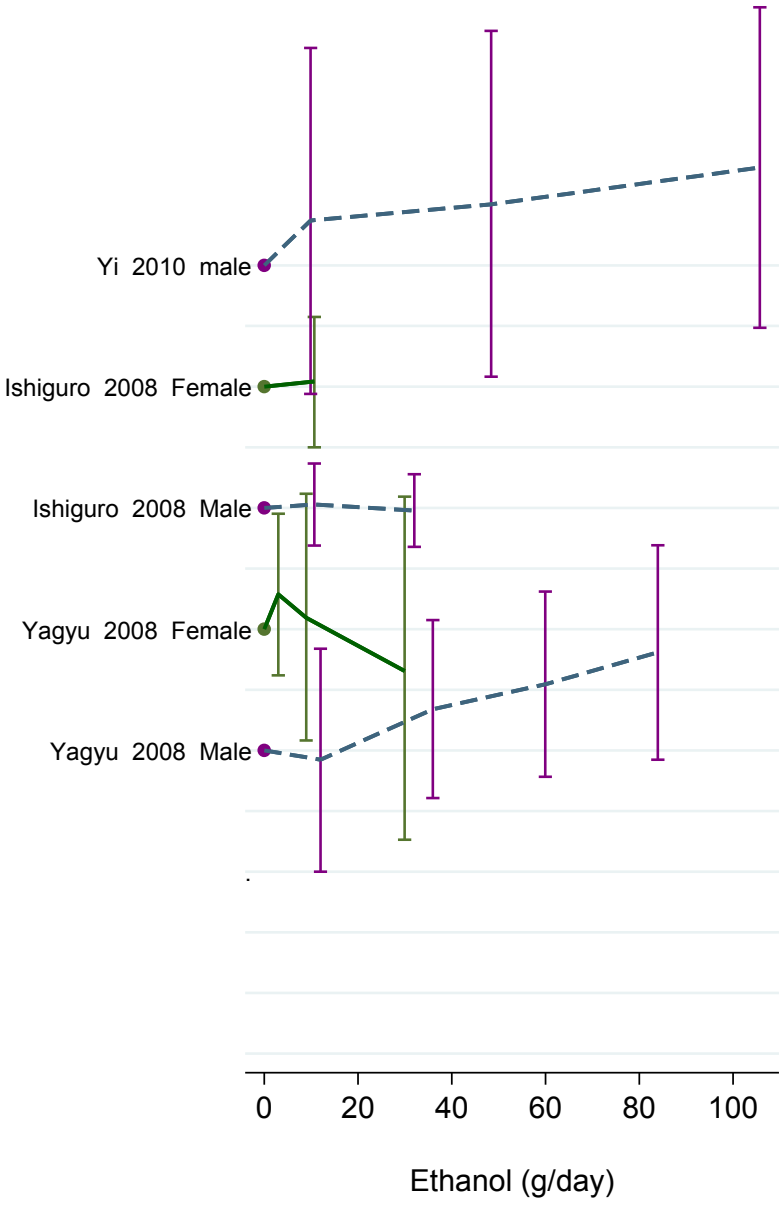


Figure 6 Dose-response graph of alcohol consumption and gallbladder cancer



8 Anthropometry

8.1.1 BMI

Methods

Up to March 2013, reports from 11 cohort studies (14 publications) were identified; six of them were identified during the 2005 SLR and five during the CUP. Two multi-site papers were missed in the 2005 SLR, but have been added during the CUP (Moller et al., 1994, GAL00164 and Oh et al., 2005, GAL00163). The CUP dose-response meta-analysis included eight studies. Dose-response analyses were conducted per 5 units increase in BMI (kg/m^2).

The outcome was gallbladder cancer in all the studies.

Three studies used the second lowest category as a reference category due to limited number of cases in the lowest category and when this was the case we converted the risk estimates using the method by Hamling et al, 2008, so the lowest category was the reference.

Main results

The summary RR per 5 units increase in BMI (kg/m^2) was 1.25 (95% CI: 1.15-1.37; I^2=52.3%, $P_{heterogeneity}$ =0.04) for all studies combined.

When stratifying by sex, the summary RR for males was 1.23 (95% CI: 1.13-1.33; I^2=0%, $P_{heterogeneity}$ =0.91), and 1.25 (95% CI: 1.07-1.46; I^2=69.3%, $P_{heterogeneity}$ =0.006) for females.
When stratifying by outcome, the association was statistically significant for incidence (summary RR: 1.23; 95% CI: 1.10-1.39; I^2=64.3%, $P_{heterogeneity}$ 0.02), but not for mortality, summary RR: 1.31; 95% CI: 1.18-1.46; I^2=0%, $P_{heterogeneity}$ =0.87).
When stratified by geographic location the summary RR was 1.32 (95% CI: 1.24-1.41, I^2=0%, $p_{heterogeneity}$=0.43) for three studies from Europe, 1.22 (95% CI: 0.98-1.52, I^2=56.3%, $p_{heterogeneity}$=0.08) for four Asian studies, and 1.32 (95% CI: 1.18-1.47) for an American study.

There was evidence of nonlinearity for the association between BMI and gallbladder cancer, $p_{nonlinearity}$<0.01, with an increased risk from BMI of approximately 24 or greater.

In influence analysis the summary RR ranged from 1.23 (95% CI: 1.11-1.36, I^2=42.6%, $p_{heterogeneity}$=0.11) when excluding the Norwegian Tuberculosis Screening Study (Engeland et al, 2005) to 1.29 (95% CI: 1.18-1.41, I^2=31.6%, $p_{heterogeneity}$=0.19) when excluding the Korean Cancer Prevention Study (Jee et al, 2008) and there was also less heterogeneity in the analyses when these two studies were excluded.

Heterogeneity

There was evidence of heterogeneity across the studies (I^2=52.3%, p=0.04). When stratified by sex there was no heterogeneity among men, I^2= 0%.
There was no indication of publication bias with Egger's test (p=0.89).

Comparison with the Second Expert Report

Six publications from five cohorts were identified during the Second Expert Report. From these, only four studies provided suitable information to be used in the meta-analysis. The summary RR per 5 units of BMI increment was 1.23 (95% CI: 1.15-1.32; I^2=44.7%, $P_{heterogeneity}$=0.061).

Published meta-analysis and pooled analysis

In a published meta-analysis (Renehan et al, 2008) of four prospective studies, the summary RR per 5 units increment of BMI in males was 1.09 (95% CI: 0.99-1.21, I^2= 0%, $P_{heterogeneity}$ =0.12, 928 cases, n=4 studies) and 1.59 (95% CI: 1.02-2.47, I^2= 67%, $P_{heterogeneity}$ =0.04, 1111 cases, n=2 studies) for females.

In another published meta-analysis (Larsson et al, 2007) of eight prospective and three case-control studies, that compared obese individuals vs those who are normal weight, the summary RR was 1.66 (95% CI: 1.47-1.88, I^2= 12%, $P_{heterogeneity}$ =0.31) for all studies. The summary RR was 1.69 (95% CI: 1.48-1.92, I^2= 14.1%, $P_{heterogeneity}$ =0.30) for the eight prospective studies and 1.42 (95% CI: 0.89-2.24, I^2= 16.1%, $P_{heterogeneity}$ =0.31) for the three case-control studies. When stratified by sex, the summary RR for males was 1.35 (95% CI: 1.09–1.68) and for females was RR 1.88 (95% CI: 1.66–2.13).

A pooled analysis of 57 prospective studies (222 deaths) reported a HR for gallbladder cancer death of 1.12 (95% CI: 0.90-1.38) for a 5 unit increase in BMI (Prospective Studies Collaboration, Whitlock et al, 2009).

Table 10 Studies on BMI identified in the CUP

Author, year	Country	Study name	Cases	Years of follow up	Sex	RR	LCI	UCI	Contrast
Schlesinger, 2013	Europe	European Prospective Investigation into Cancer and Nutrition	76	8.6	All	1.28	0.99	1.65	Per 5 BMI units
Ishiguro, 2008	Japan	Japan Public Health Center-based Prospective Study	93 63 30	10.9	All M F	1.06 1.39 0.94	0.59 0.45 0.48	1.90 4.34 1.88	>= 27 kg/m^2 vs <= 22.9 kg/m^2
Jee, 2008	Korea	Korean Cancer Prevention Study	2276 1062	10.8	M F	1.65 1.44	1.11 0.98	2.44 2.12	>= 30 kg/m^2 vs <= 20 kg/m^2
Song, 2008	Korea	Korean Cancer Prevention Study	181	8.75	F	2.10 1.04	0.97 0.99	4.51 1.10	>=30.0 kg/m2 vs <18.5kg/m2 Per 1BMI units
Fujino 2007	Japan	Japan Collaborative Cohort Study for Evaluation of Cancer	66 90	~12	M F	0.56 3.47	0.07 0.84	4.06 14.35	>=30.0 kg/m^2 vs <18.5kg/m^2
Samanic, 2006	Sweden	Swedish Construction Workers Cohort	109	19	M	1.40	0.73	2.70	>=30.0 kg/m^2 vs 18.5-24.9 kg/m^2

Table 11 Overall evidence on BMI and gallbladder cancer

	Summary of evidence
2005 SLR	Six studies were identified on BMI and gallbladder cancer during the 2005 SLR. A total of four studies were included in the meta-analysis, with a summary RR of 1.23 (95% CI: 1.15-1.32; I^2=44.7%, $P_{heterogeneity}$=0.061), per 5 units of BMI increment.
Continuous Update Project	A total of six new studies were identified. Overall, eight studies were included in the CUP meta-analysis. The meta-analysis showed a significant positive association between BMI and gallbladder cancer overall, among females and males, and for incidence, but not mortality.

Table 12 Summary of results of the dose response meta-analysis of BMI and gallbladder cancer

Gallbladder cancer		
	2005 SLR	Continuous Update Project
Studies (n)	4	8
Cases (n)	2561	6004
Increment unit used	Per 5 kg/m^2 increase	Per 5 kg/m^2 increase
Overall RR (95%CI)	1.23 (1.15-1.32)	1.25 (1.15-1.37)
Heterogeneity (I^2, p-value)	44.7%, p=0.061	52.3%, p=0.04
Male		
Overall RR (95%CI)	1.16 (1.07-1.25)	1.23 (1.13-1.33), n=6
Heterogeneity (I^2, p-value)	0%, p=0.519	0%, p=0.91
Female		
Overall RR (95%CI)	1.29 (1.16-1.43)	1.25 (1.07-1.46), n=6
Heterogeneity (I^2, p-value)	70.8%, p=0.016	69.3%, p=0.006
Incidence		
Overall RR (95%CI)	1.21 (1.12-1.32)	1.23 (1.10-1.39), n=6
Heterogeneity (I^2, p-value)	51.6%, p=0.044	64.3%, p=0.02
Mortality		
Overall RR (95%CI)	-	1.31 (1.18-1.46), n=2
Heterogeneity (I^2, p-value)	-	0%, p=0.87

Table 13 Inclusion/exclusion table for meta-analysis of BMI and gallbladder 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
GAL00145	Schlesinger	2013	Nested Case-Control Study	European Prospective Investigation into Cancer and Nutrition	All	Incidence	No	Yes	No	--	Only continuous values for gallbladder cases
GAL00144	Ishiguro	2008	Prospective Cohort study	Japan Public Health Center-based Prospective Study	M F	Incidence	No	Yes	Yes	Mid-points	-
GAL00142	Jee	2008	Prospective Cohort study	Korean Cancer Prevention Study	M F	Incidence	No	Yes	Yes	Mid-points, person-years Rescaled categories	
GAL00149	Song	2008	Prospective Cohort study	Korean Cancer Prevention Study	F	Incidence	No	No	No	--	Superseded by Jee, 2008 (GAL00142)
GAL00159	Fujino	2007	Prospective Cohort study	Japan Collaborative Cohort Study for Evaluation of Cancer	M F	Mortality	No	Yes	Yes	Rescaled categories and midpoints	
GAL00140	Samanic	2006	Prospective Cohort study	Swedish Construction Workers Cohort	M	Incidence	No	Yes	Yes	Mid-points and person-years	
GAL00137	Engeland	2005	Prospective Cohort study	Norwegian Cohort Study	M F	Incidence	Yes	Yes	Yes	Mid-points and rescaled categories	
GAL00135	Kuriyama	2005	Prospective	Japan, Cohort	M	Incidence	Yes	Yes	Yes		(Male subgroup reported only two categories of BMI and used only for

GAL00134	Samanic	2004	Prospective Cohort study	US male veterans, cohort	M	Incidence	Yes	No	Yes		Only two categories of exposure
GAL00005	Calle	2003	Prospective Cohort study	Cancer Prevention Study II	M F	Mortality	Yes	Yes	Yes	Mid-points, person-years and rescaled categories	-
GAL00030	Wolk	2001	Prospective Cohort study	Swedish obesity cohort	M F	Incidence	Yes	No	Yes	-	Only two categories of exposure
GAL00037	Robsahm	1999	Prospective Cohort study	Norwegian Cohort Study	M F	Incidence	Yes	No	No	-	Superseded by Engeland, 2005 (GAL00137)
GAL00164	Moller	1994	Prospective Cohort study	Danish Obesity Cohort	M F	Incidence	No	No	Yes		Only two categories of exposure

[1]GAL00163 and GAL00164 were missed by the 2005 SLR as they were multi-site cancer publications, but have been added during the CUP.

Figure 7 Highest versus lowest forest plot of BMI and gallbladder cancer

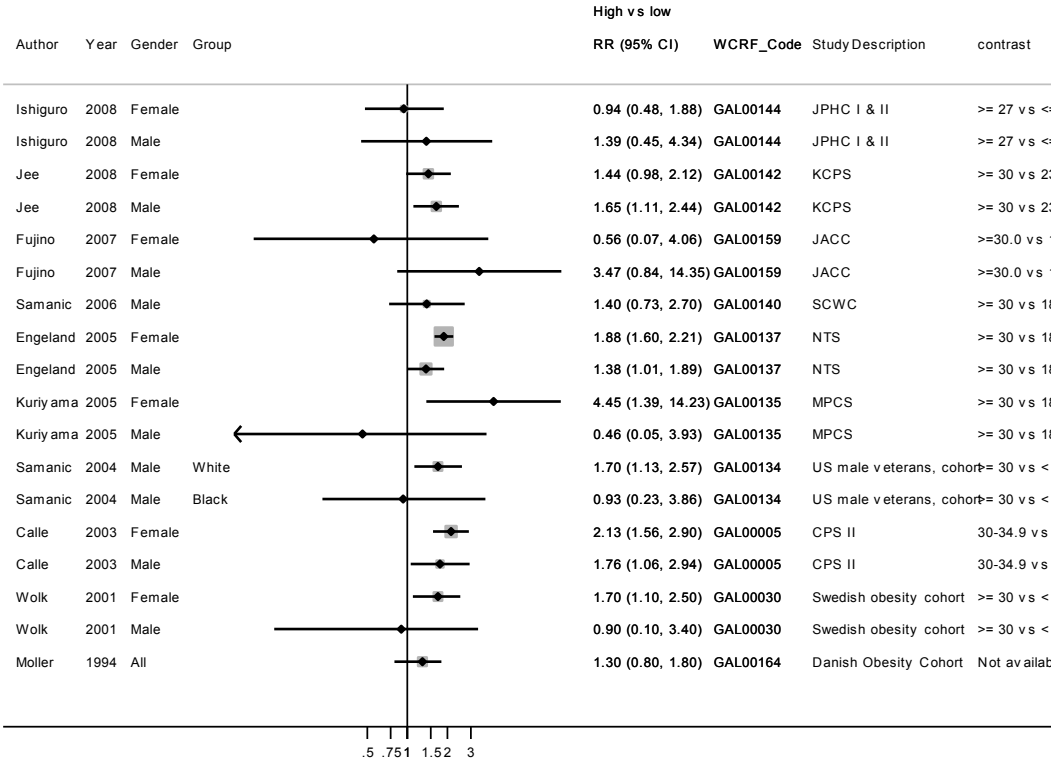


Figure 8 Dose-response meta-analysis of BMI and gallbladder cancer, per 5 BMI units (kg/m^2)

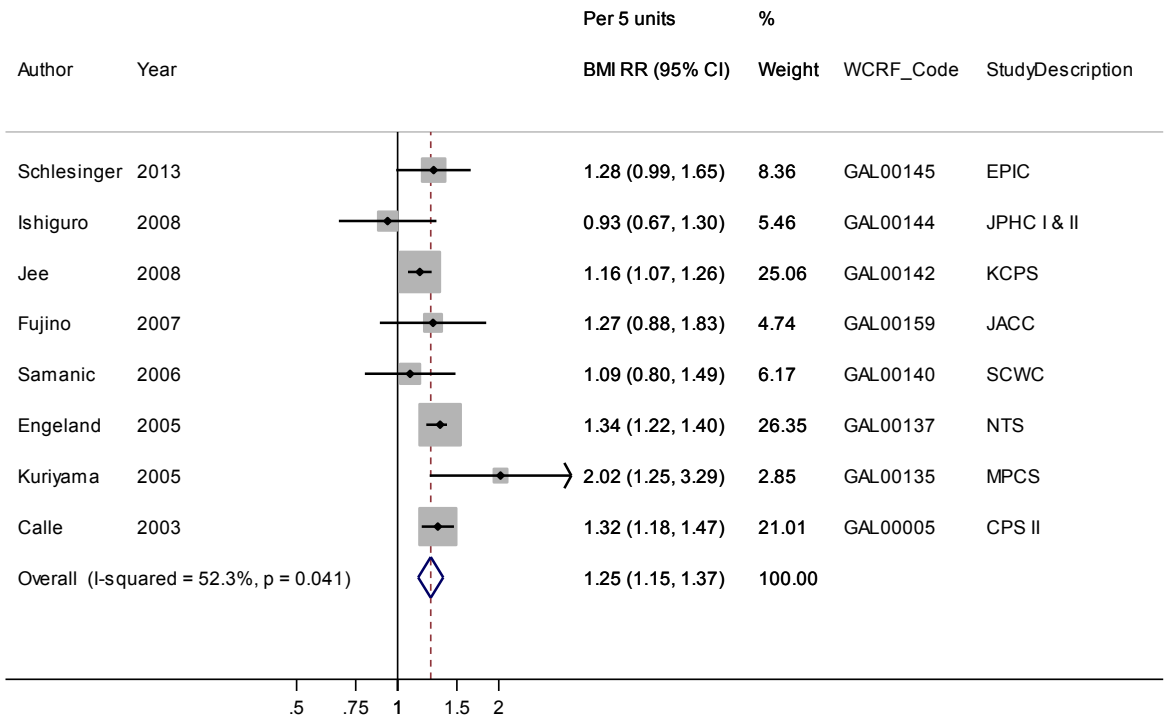


Figure 9 Dose-response meta-analysis of BMI and gallbladder cancer by outcome type, per 5 BMI units (kg/m^2)

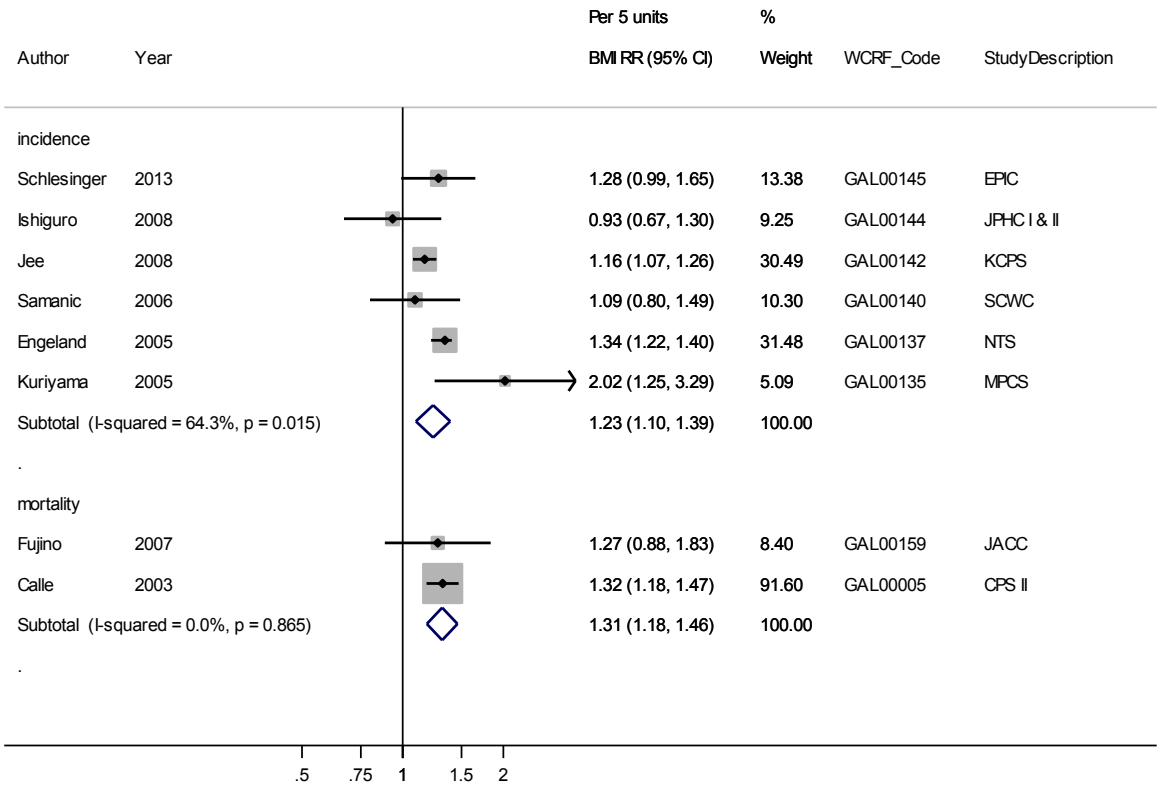


Figure 10 Dose-response meta-analysis of BMI and gallbladder cancer by sex, per 5 BMI units (kg/m^2)

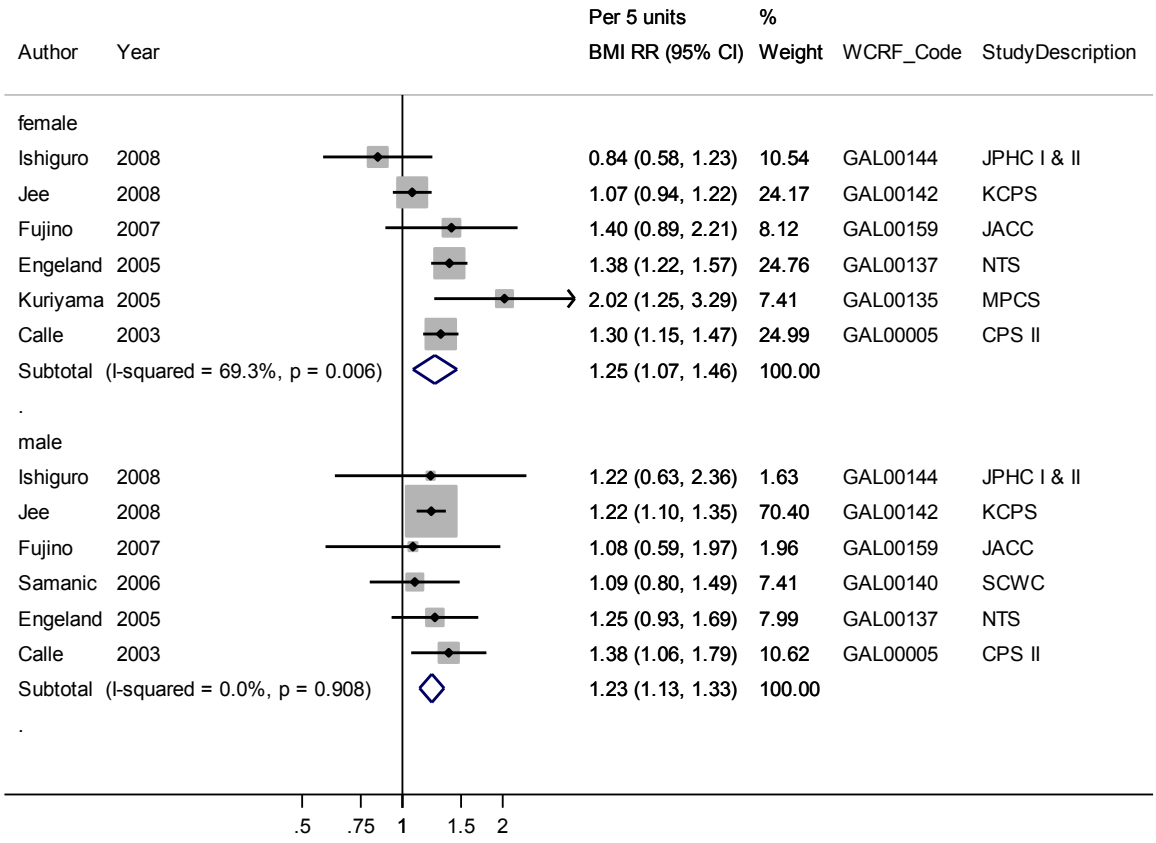


Figure 11 Dose-response meta-analysis of BMI and gallbladder cancer by geographic location, per 5 BMI units (kg/m2)

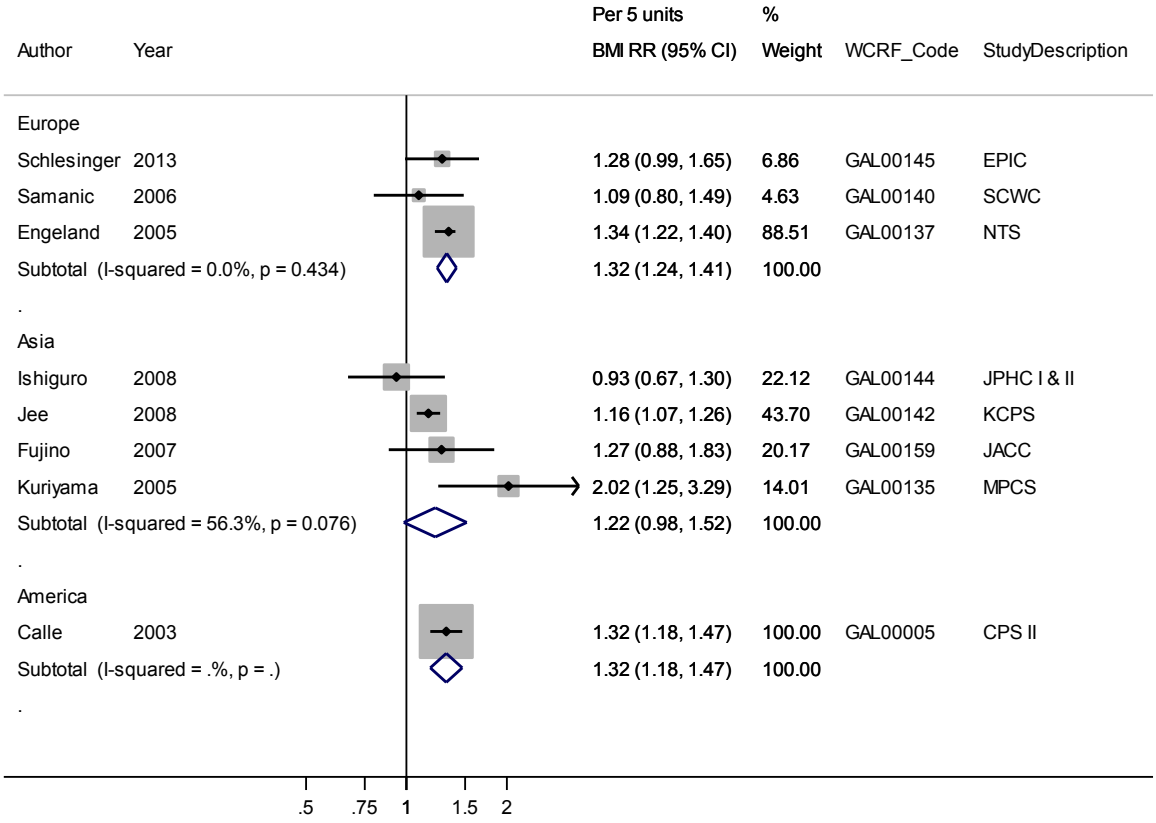
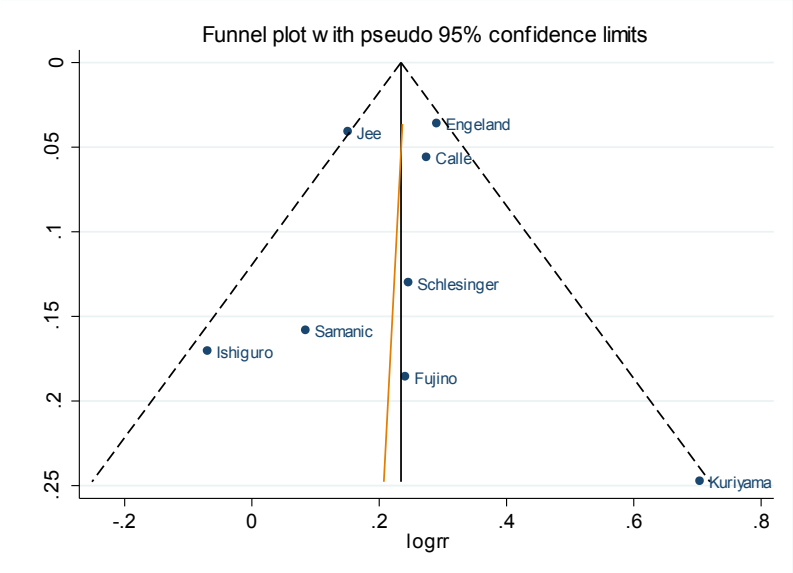


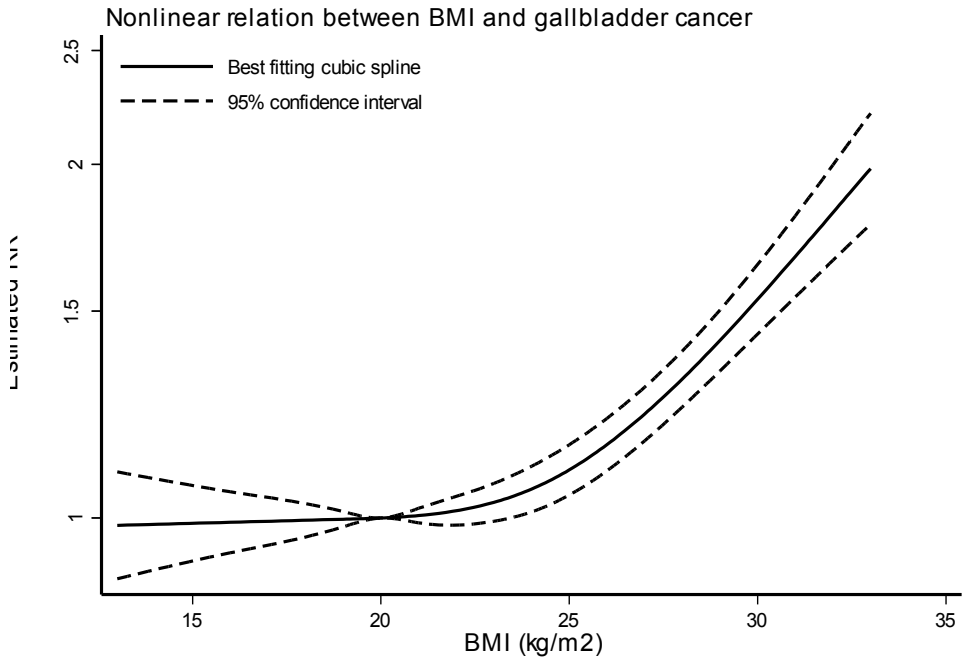
Figure 12 Funnel plot of BMI and gallbladder cancer



Egger's test p=0.89

Figure 13 Dose-response graph of BMI and gallbladder cancer

Figure 14 Non-linear dose-response figure for BMI and gallbladder cancer



$P_{nonlinearity}<0.01$

Figure 15 Scatter plot of risk estimates for BMI and gallbladder cancer

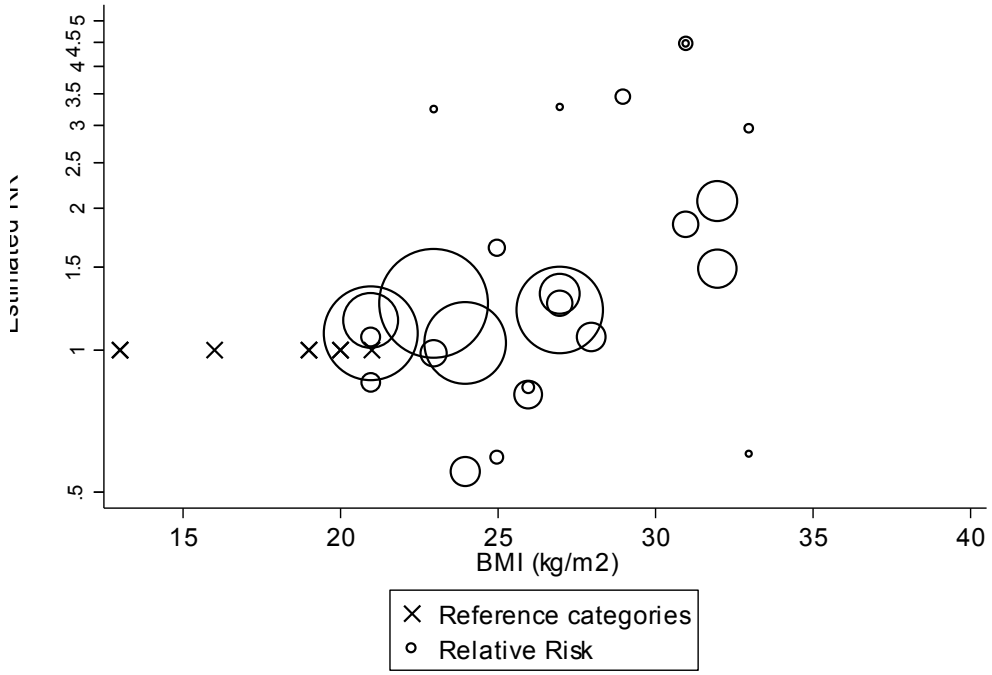


Table 14 RRs from the nonlinear analysis for BMI and gallbladder cancer

BMI (kg/m^2)	RR (95% CI)
13	0.99 (0.89-1.09)
16	0.99 (0.93-1.05)
19	1.00 (0.98-1.01)
20	1.00
23	1.03 (0.99-1.07)
24	1.06 (1.01-1.11)
25	1.10 (1.05-1.15)
26	1.15 (1.10-1.22)
27	1.23 (1.16-1.29)
28	1.31 (1.24-1.39)
29	1.42 (1.33-1.50)
31	1.67 (1.54-1.81)
32	1.82 (1.66-2.00)
33	1.98 (1.78-2.21)

8.1.3 Weight

Methods

Up to March 2013, reports from two cohort studies were identified; all of them were identified during the CUP. The CUP meta-analysis included two studies. The dose-response results are presented for an increment of 5 kg.

One study has incidence of gallbladder cancer as outcome and the other has mortality for gallbladder cancer.

Main results

The summary RR per 5 kg was 1.05 (95% CI: 0.92-1.19; I^2=57.9%, $P_{heterogeneity}$ =0.12) for the two studies combined.

Heterogeneity

There was no evidence of heterogeneity across the limited number of studies (I^2=57.9%, p=0.12).

Comparison with the Second Expert Report

No meta-analysis was conducted in the second report.

Published meta-analysis

No meta-analysis was identified

Table 15 Studies on weight identified in the CUP

Author, year	Country	Study name	Cases	Years of follow up	Sex	RR	LCI	UCI	Contrast
Schlesinger, 2013	Europe	European Prospective Investigation into Cancer and Nutrition Study	76	8.6	All	1.11	1.00	1.22	Per 5 kg increase
Fujino 2007	Japan	Japan Collaborative Cohort Study for Evaluation of Cancer	67 93	~12	M F	0.74 1.07	0.39 0.66	1.40 1.73	>= 63 kg vs < 55 kg >= 55 kg vs < 49 kg

Table 16 Overall evidence on weight and gallbladder cancer

	Summary of evidence
2005 SLR	No study was identified on weight and gallbladder cancer during the 2005 SLR
Continuous Update Project	Two studies were identified; two studies could be included in the meta-analysis. Neither of the studies showed significant association.

Table 17 Summary of results of the dose response meta-analysis of weight and gallbladder cancer

Gallbladder cancer		
	2005 SLR*	Continuous Update Project
Studies (n)	-	2
Cases (n)	-	236
Increment unit used	-	Per 5 kg
Overall RR (95%CI)	-	1.05 (0.92-1.19)
Heterogeneity (I^2,p-value)	-	57.9%, p=0.12

*No meta-analysis was conducted in the second report

Table 18 Inclusion/exclusion table for meta-analysis of weight and gallbladder 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
GAL00145	Schlesinger	2013	Nested Case-Control Study	European Prospective Investigation into Cancer and Nutrition Study	All	Incidence	No	Yes	No	-	Only continuous values for gallbladder cancer
GAL00159	Fujino	2007	Prospective Cohort study	Japan Collaborative Cohort Study for Evaluation of Cancer	M F	Mortality	No	Yes	Yes	Mid-exposure values, person-years per category (there was a mistake in the paper, hence we had to recalculated person-years)	-

Figure 16 Highest versus lowest forest plot of weight and gallbladder cancer

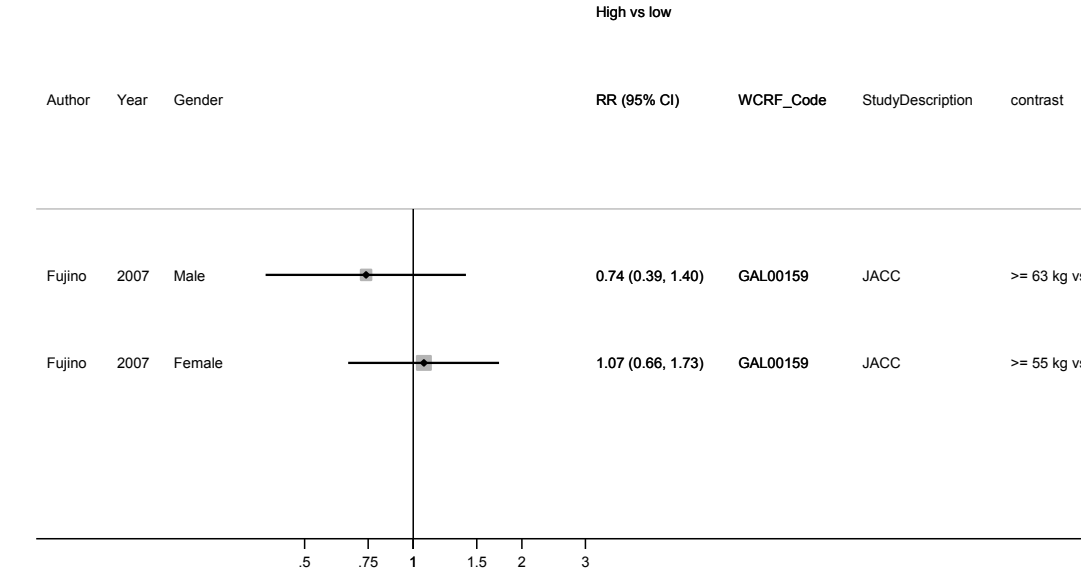


Figure 17 Dose-response meta-analysis of weight and gallbladder cancer, per 5 k

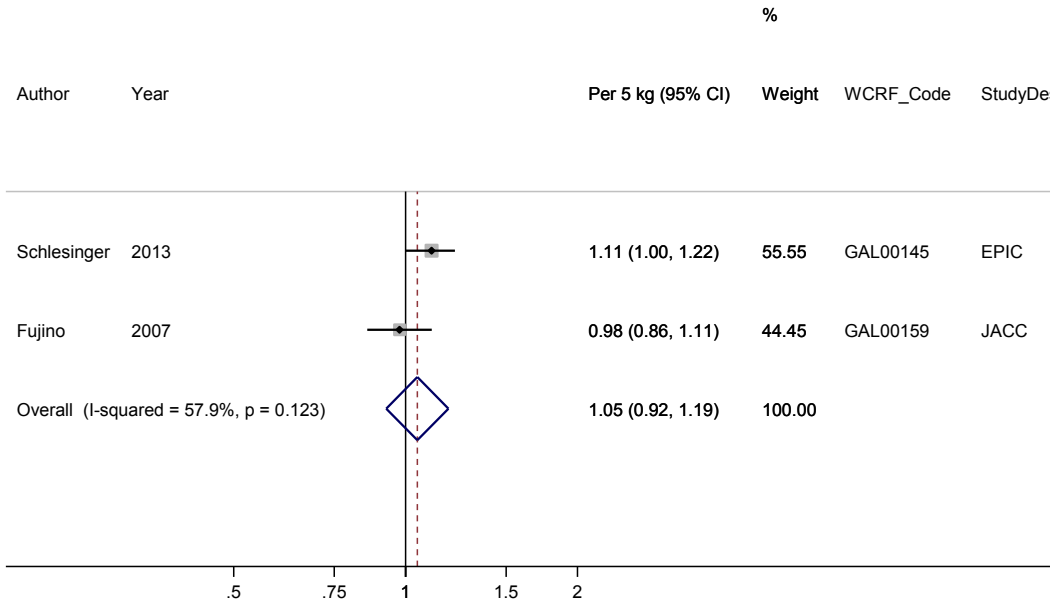
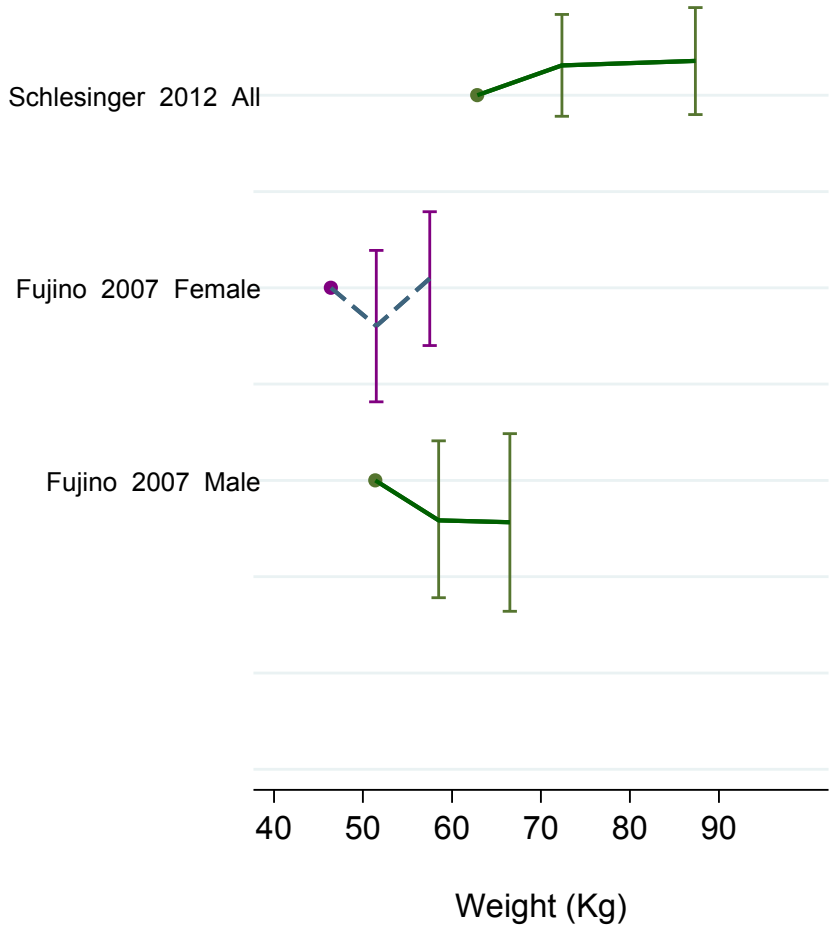


Figure 18 Dose-response graph of weight and gallbladder cancer



8.3.1 Height

Methods

Up to March 2013, reports from two cohort studies were identified; all of them were identified during the CUP. The CUP meta-analysis included two studies. The dose-response results are presented for an increment of 5 cm.

The Korea National Health Insurance Corporation study (Sung et al, 2009) reported on biliary tract cancers (ICD-10 C23, C24). The Japan Collaborative Cohort Study for Evaluation of Cancer (Fujino et al, 2007) was on gallbladder cancer.

Main results

The summary RR per 5 cm was 1.03 (95% CI: 0.92-1.17; I^2=38.1%, $P_{heterogeneity}$ =0.20) for all studies combined.

Heterogeneity

There was of evidence of moderate heterogeneity across the limited number of studies (I^2=38.1%, p=0.20).

Comparison with the Second Expert Report

No meta-analysis was conducted in the second report.

Published meta-analysis

No meta-analysis was identified

Table 19 Studies on height identified in the CUP

Author, year	Country	Study name	Cases	Years of follow up	Sex	RR	LCI	UCI	Contrast
Sung, 2009	Korea	Korea National Health Insurance Corporation	941 451	8.72	M F	1.24 1.08 1.22 1.06	1.03 1.01 0.92 0.97	1.49 1.15 1.62 1.17	> 171 cm vs <= 164.5 cm Per 5 cm increase > 158 cm vs <= 151 cm Per 5 cm increase
Fujino 2007	Japan	Japan Collaborative Cohort Study for Evaluation of Cancer	67 90	~12	M F	0.46 1.14	0.23 0.67	0.92 1.94	>= 165 cm vs < 160cm >= 154 cm vs < 159 cm

Table 20 Overall evidence on height and gallbladder cancer

	Summary of evidence
2005 SLR	No study was identified on height and gallbladder cancer during the 2005 SLR
Continuous Update Project	Two studies were identified; two studies could be included in the meta-analysis. There was no significant (weak positive) association.

Table 21 Summary of results of the dose response meta-analysis of height and gallbladder cancer

Gallbladder cancer		
	2005 SLR*	Continuous Update Project
Studies (n)	-	2
Cases (n)	-	1549
Increment unit used	-	Per 5 cm
Overall RR (95%CI)	-	1.03 (0.92-1.17)
Heterogeneity (I^2, p-value)	-	38.1%, p=0.204

*No meta-analysis was conducted in the second report

Table 22 Inclusion/exclusion table for meta-analysis of height and gallbladder 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
GAL00150	Sung	2009	Prospective Cohort study	Korea National Health Insurance Corporation	M F	Incidence	No	Yes	Yes	-	-
GAL00159	Fujino	2007	Prospective Cohort study	Japan Collaborative Cohort Study for Evaluation of Cancer	M F	Mortality	No	Yes	Yes	Mid-points and person-years	-

Figure 19 Highest versus lowest forest plot of height and gallbladder cancer

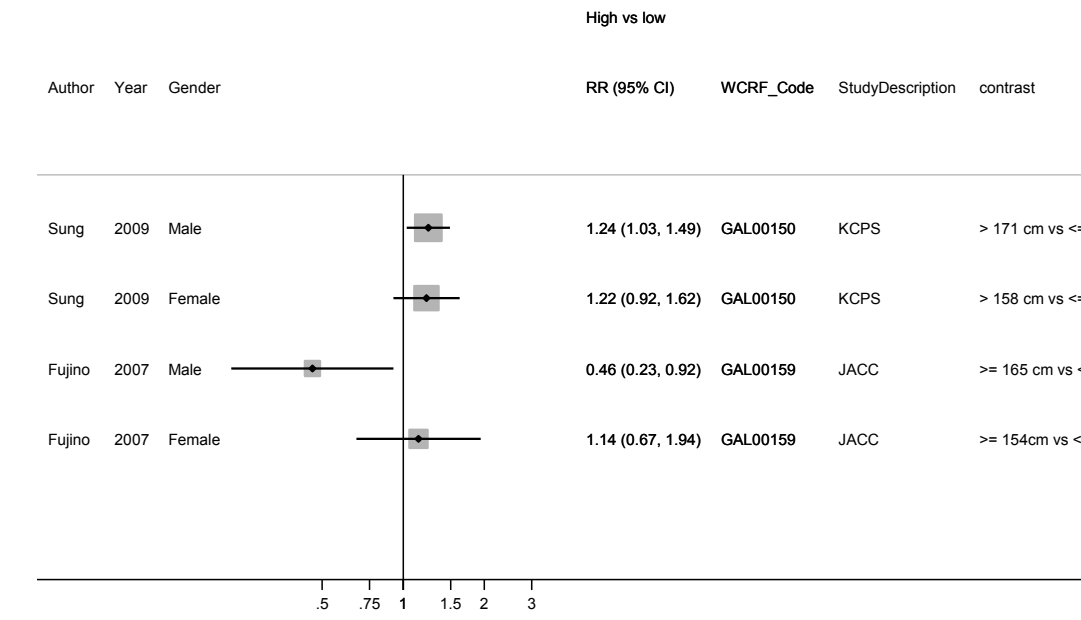


Figure 20 Dose-response meta-analysis of height and gallbladder cancer, per 5 c

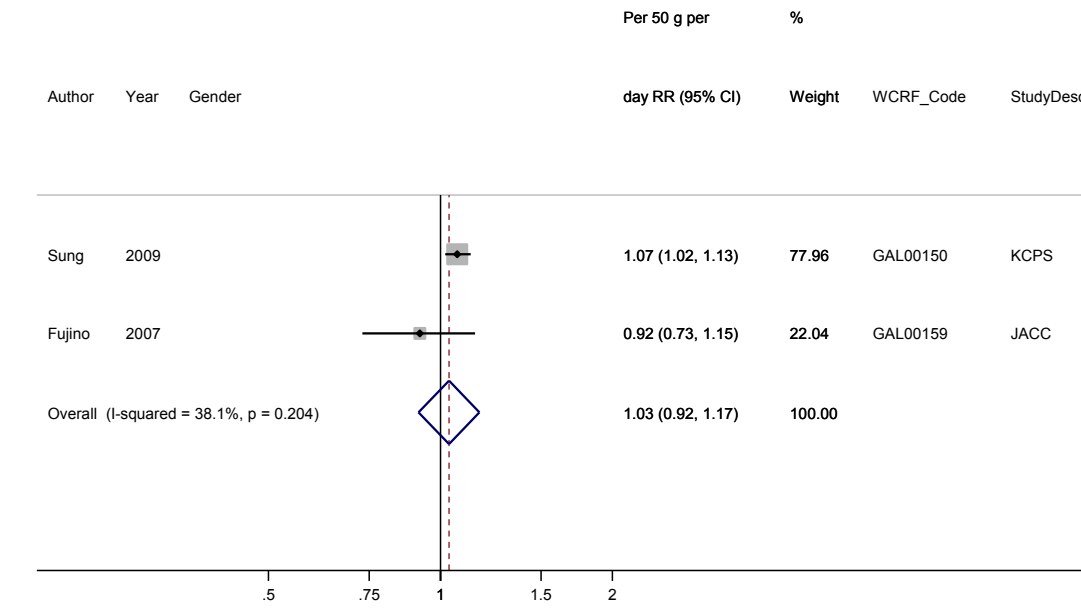
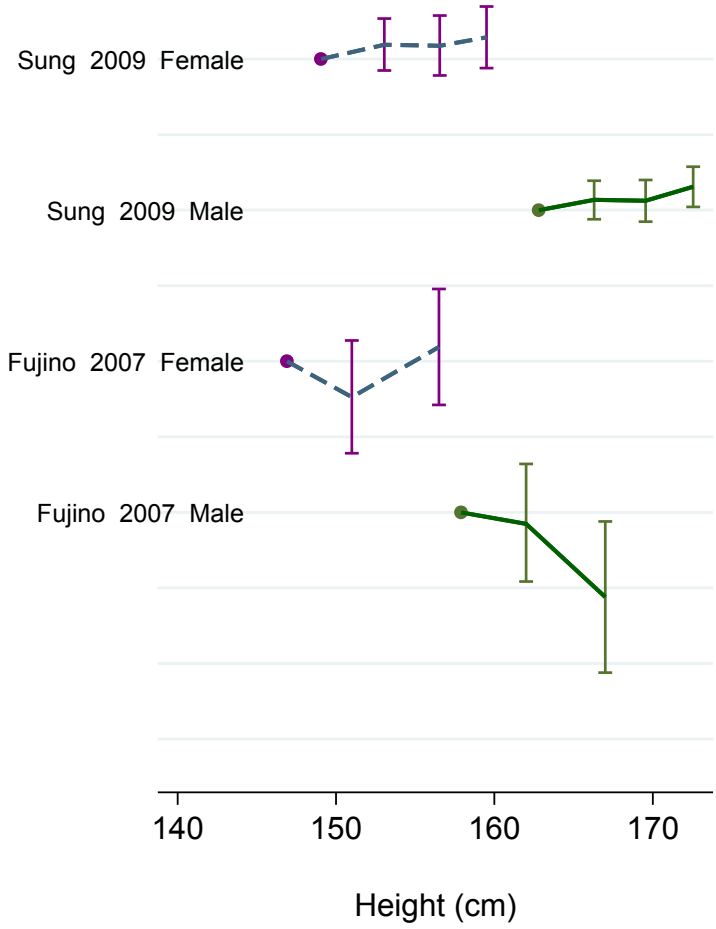


Figure 21 Dose-response graph of height and gallbladder cancer



Anthropometric characteristics investigated by each study

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

			Anthropometric characteristic		
First author	Year	Study name	BMI	Weight	Height
Schlesinger	2013	European Prospective Investigation into Cancer and Nutrition	x	x	
Sung	2009	Korea National Health Insurance Corporation			x
Ishiguro	2008	Japan Public Health Center-based Prospective Study	x		
Jee	2008	Korean Cancer Prevention Study	x		
Song	2008				
Oh	2005				
Fujino	2007	Japan Collaborative Cohort Study for Evaluation of Cancer	x	x	x
Samanic	2006	Swedish Construction Workers Cohort	x		
Engeland	2005	Norwegian Cohort Study	x		
Kuriyama	2005	Japan, Cohort Study	x		
Samanic	2004	US male veterans, cohort	x		
Calle	2003	Cancer Prevention Study II	x		
Wolk	2001	Swedish obesity cohort	x		
Robsahm	1999	Norwegian screening programme for tuberculosis	x		
Moller	1994	Danish Obesity Cohort	x		

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