WCRF/AICR Systematic Literature Review Continuous Update Project Report

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

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Background

Matrices presented in the WCRF/AICR 2007 Expert Report

CANCER OF THE PANCREAS

	DECREASES RISK	**INCREASES RISK**
Convincing		Body fatness
Probable	Foods containing folate	Abdominal fatness Adult attained height
Limited –suggestive	Fruits Physical activity	Red meat
Limited –no conclusion	Cereals (grains) and their products; dietary fibre; vegetables; pulses (legumes); soya and soya products; processed meat; poultry; fish; eggs; milk and dairy products; total fat; butter; plant oils; margarine; cholesterol; sugar (sucrose); black tea; green tea; alcohol; nitrate and nitrite/ total carbohydrate/ folic acid supplements; vitamin C; vegetarianism; age at menarche; lactation; energy intake	
Substantial effect on risk unlikely	Coffee	

An independent panel of experts (the CUP panel) is responsible for reviewing the CUP findings and for making judgements and recommendations based on the body of scientific evidence. This was already done for the CUP reports on breast and colorectal cancer and the summaries are available at:

http://www.dietandcancerreport.org/cancer_resource_center/cup_summaries.php.

The pancreatic cancer report will be discussed by the CUP Panel in June 2012.

Changes to the approved protocol

In this report, influence analyses and funnel plots are presented when there are 5 or more studies included in the dose-response analysis. The review team conducted nonlinear dose-response analyses for some exposures for papers submitted for publication in peer reviewed journals. These nonlinear dose-response analyses have been included in the present report for those exposures. A separate section on study quality was included for exposures where there was a change in the results compared with the WCRF/AICR 2007 report.
In the approved protocol (Appendix 1), a meta-analysis for a particular exposure and outcome will be conducted when three or more trials or cohort studies have been published in the period reviewed, and if the total number of studies in the database totalise to more than three trials or five cohort studies with enough information to conduct a dose-response meta-analysis, or providing data to calculate the information required to do it (Protocol Section 14.1 When to do a meta-analysis). However, in the present report, additional meta-analyses were exceptionally conducted for some exposures with less than three cohort studies published in the period reviewed. These are exposures classified under the same main food group (exposure heading) as other exposures with three or more publications in the period reviewed and for which meta-analyses were conducted. The purpose of conducting additional meta-analysis was to complement other analysis for the same food group. The exposures with less than three cohort studies published in the period for which meta-analysis were conducted are indicated below under the corresponding food group (exposure heading):

2.5 Meat, poultry, fish and eggs.

Processed meat: Two studies were published during the Continuous Update Project. An updated meta-analysis was conducted to complement the updated meta-analyses on red meat (three studies identified during the CUP).

Eggs: A meta-analysis was conducted (two studies during the update). All other food items under 2.5 Meat, poultry, fish and eggs were therefore updated.

3.4 Soft drinks.

Diet soft drinks: Only one new publication was identified. A meta-analysis was conducted (three studies overall) to complement the meta-analysis of soft drinks (four new publications identified during the update) in the present report.

3.6 Hot drinks.

Coffee: An updated meta-analysis adding two new publications on coffee identified during the update is presented. The reason for conducted meta-analysis was the inconsistent results of two meta-analyses published in 2011 (see "Published meta-analysis" in 3.6.1 Coffee).

5.2 Lipids.

Updated meta-analyses on monounsaturated and polyunsaturated fatty acids, linolenic acid, linoleic acid and dietary cholesterol (two new publications identified in the update each) are included, to complement the updated analyses on lipids and saturated fats with four publications each identified in the Continuous Update Project.

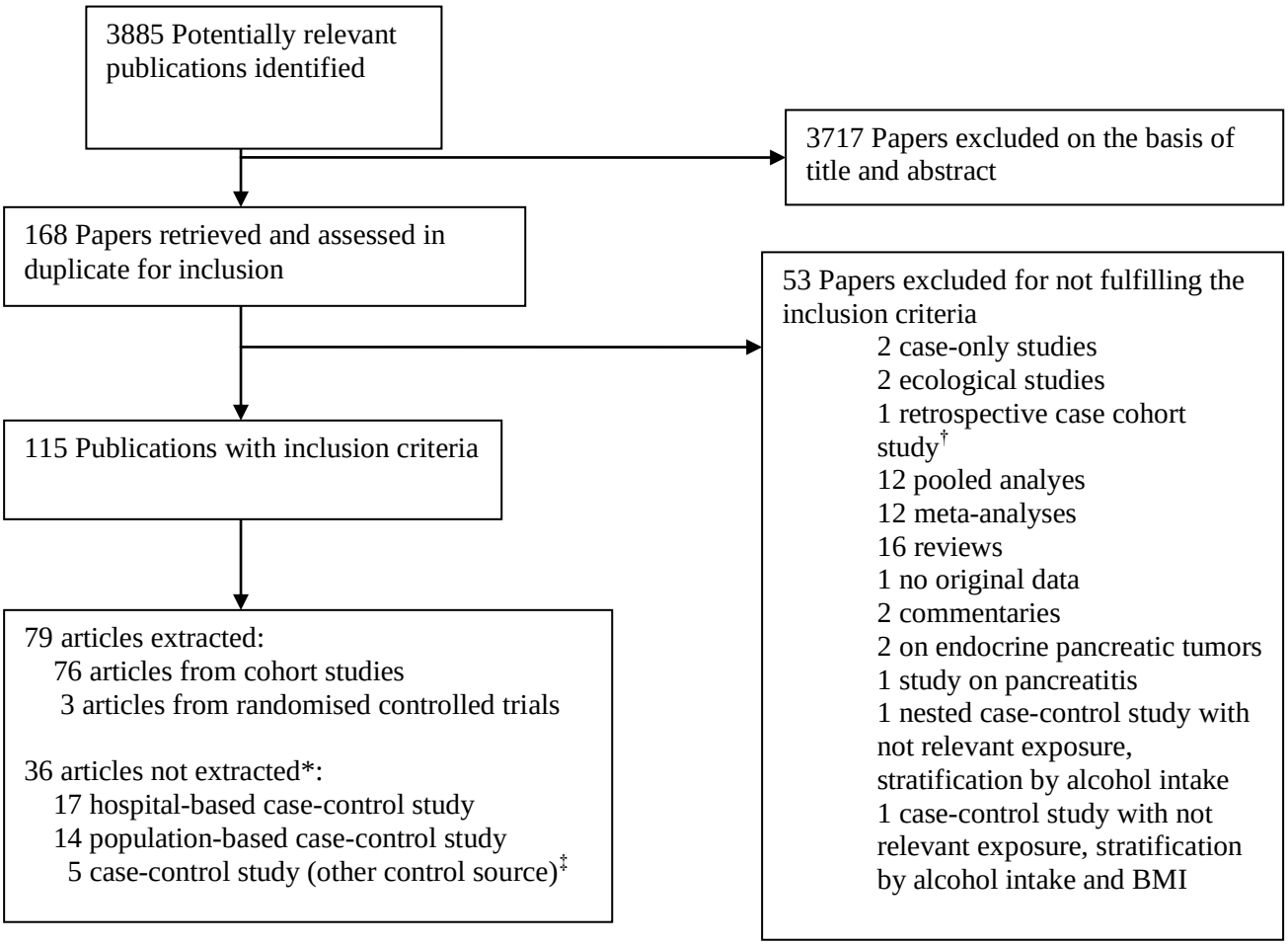
5.5.3 Folates and associated compounds.

Total folate: A meta-analysis is included (two publications identified in the update) to complement the meta-analysis on dietary folate (three publications identified during the update).

Results of the search

The search period is from the 1st of January 2006 until the 28th of September 2011. An updated search was conducted up to 31st of December 2011, which identified two relevant articles in addition to those shown in the flow-chart.

Flow chart of the search for pancreatic cancer – Continuous update project



**Data from case-control studies on pancreatic cancer identified during the CUP are not extracted nor included in the meta-analyses of this report. The reference list of case-control studies is stored in a Reference Manager database.*

† Excluded because diet was assessed retrospectively with next of kins.

‡ Controls were either spouses or friends, or outpatients, or restricted populations.

Randomised controlled trials

Three studies were identified during the update. The results by exposure are reviewed below.

5.6.3 Calcium and vitamin D

In the Women's Health Initiative (WHI) trial of calcium plus vitamin D (CaD), 36,282 postmenopausal women were randomized to 1,000 mg of elemental calcium with 400 IU vitamin D3 or placebo (Brunner et al, 2011). After seven years, 1,306 invasive cancers were diagnosed in the supplement group and 1,333 in the placebo group and 32 and 36 women respectively were diagnosed with pancreatic cancer during follow-up. Calcium/vitamin D supplementation did not reduce invasive total cancer incidence or mortality, and no reduction in pancreatic cancer risk was observed (HR: 0.88; 95% CI: 0.55- 1.41). Supplementation lowered total cancer risk in the WHI healthy diet trial arm and in women without a first degree relative with cancer, but the observed interactions were considered only suggestive given multiple testing considerations. Some study limitations were that one-quarter of the participants stopped taking study pills by the end of the study, the dose of vitamin D was low, and serum 25(OH)D values were not available.

5.5 Vitamin E, vitamin C

The Physicians' Health Study II, a randomized, double-blind, placebo-controlled factorial trial, did not find any effect of long-term supplementation of 400 IU of vitamin E every other day and 500 mg of vitamin C daily on the risk of total or prostate cancer, which was the main study outcome, or in any of the cancer sites investigated. The study included 14,641 male physicians in the United States initially aged 50 years or older. During a mean follow-up of 8.0 years, there were 1943 confirmed cancer cases. Compared to the placebo group, the hazard ratios of pancreatic cancer were 1.14 (95% CI, 0.67-1.93) for vitamin E (29 cases of pancreatic cancer in the treatment group) and 0.97 (95% CI, 0.57-1.64) for vitamin C (27 cases of pancreatic cancer in the treatment group). Adherence to the treatment was good (Gaziano et al, 2009).

5.5 Antioxidants (vitamin C, vitamin E or beta carotene)

Supplementation with vitamin C (500 mg of ascorbic acid daily), vitamin E (600 IU of alfa - tocopherol every other day), or beta carotene (50 mg every other day), did not show overall benefits in the primary prevention of total cancer incidence or cancer mortality in 8171 women in the Women's Antioxidant Cardiovascular Study, a double-blind, placebo-controlled factorial trial .During an average 9.4 years of treatment, 624 women developed incident invasive cancer and 176 women died from cancer. Only 14, 10 and 11 pancreatic cancer cases were identified during follow-up in each of the treatment groups and no significant effects were observed (Lin et al, 2009).

Cohort studies: Number of cohort studies by exposure

Table 1 Total number and number of prospective cohorts identified in the CUP by exposure.
Exposures not identified in the CUP are omitted; articles on one exposure superseded by new publications of the same cohort are in brackets.

Code	Name	CUP	Total
1.1.1	Mediterranean diet	1	1
1.2	Socio-economically defined diets	1	1
1.4	Flavonol- rich foods	1	1
1.5	Other dietary patterns	1	1
1.6.1	Breastfeeding - Mother	1	3
2.2	Fruit and (non-starchy) vegetables	4	5
2.2.1	Total vegetables	(1)+7	10
2.2.1	Fruiting vegetables	1	1
2.2.1.1.1	Carrots	1	1
2.2.1.2	Brassica vegetables	1	1
2.2.1.2	Cruciferous vegetables	2	4
2.2.1.2.3	Cabbage	4	4
2.2.1.2.4	Broccoli	1	1
2.2.1.2.5	Cauliflower	1	1
2.2.1.3	Allium vegetables	1	1
2.2.1.3.5	Onion	1	1
2.2.1.4	Green leafy vegetables	1	1
2.2.1.4.2	Spinach	2	2
2.2.1.5	Dark green vegetables	1	1
2.2.1.5	Leafy vegetables	1	1
2.2.1.5	Leafy vegetables, cooked	1	1
2.2.1.5	Raw leafy vegetables	1	1
2.2.1.5	Light green vegetables	1	1
2.2.1.5	Mushrooms	1	2
2.2.1.5	Pickles	1	1
2.2.1.5	Yellow-orange vegetables	1	1
2.2.1.5.13	Tomatoes	2	3
2.2.2	Fruits	7+(1)	12
2.2.2.1	Citrus fruits	5+(1)	8
2.2.2.2	Berries	2	2
2.2.2.2	Fruit, cooked	1	1
2.2.2.2	Other fruits (non-citrus)	1	3
2.2.2.2	Stone fruit	1	1
2.2.2.2	Yellow-Orange fruits	1	1
2.2.2.2.8	Apples	1	1
2.2.2.2.11	Grape	1	1
2.3	Legumes	2	2
2.3.2	Beans	1	1

2.3.2.2	Tofu	1	1
2.5.1	Meat	1	1
2.5.1	Total meat	2	2
2.5.1	Broiled meat	1	1
2.5.1	Rare/medium done red and processed meat	1	1
2.5.1	Fried meat	1	1
2.5.1	Well done red and processed meat	1	1
2.5.1	White meat	1	1
2.5.1.2	Processed meat	2+(1)	8
2.5.1.2	Ham and sausages	1	1
2.5.1.2	Nitrate processed meat	1	1
2.5.1.3	Red meat	3+(1)	10
2.5.1.3	Minced red meat	1	1
2.5.1.3.1	Beef	2	4
2.5.1.3.3	Pork	2	4
2.5.1.4	Chicken	2	2
2.5.1.4	Poultry	2	8
2.5.1.5	Liver	1	1
2.5.2	Fish	3	10
2.5.2	Fish paste	1	1
2.5.2.3	Dried and salted fish	1	1
2.5.4	Eggs	(1)+1	9
2.6.4	Sugars (as foods)	1	1
2.6.4	Sugar added to coffee, tea, or lemonade	1	1
2.6.4	Sugar added to drinks and desserts	1	1
2.9.1	Desserts	1	1
2.9.13	Sugar and sweets	1	1
2.9.13	Sweets	1	1
3.4	Soft drinks	4	7
3.4.1	Diet soft drinks	1	3
3.4.2	Soda pop	1	1
3.5	Fruit juices	5	5
3.5.1	Citrus fruit juice	1	1
3.6.1	Coffee	2	19
3.6.2	Tea	2+(1)	10
3.6.2.2	Green tea	2	4
3.7.1	Alcohol consumption	1	1
3.7.1	Total alcoholic drinks	3+(1)	9
3.7.1.1	Beers	3	8
3.7.1.2	Wines	4	7
3.7.1.3	Spirits	3	8
4.3.5.4.1	Dietary nitrate	1	3
4.3.5.4.1	Dietary nitrite	1	2
4.3.5.4.1	Nitrite	1	1
4.4.2.3	Baked meat	1	1
4.4.2.6	Grilled meat	1	1

4.4.2.7	BaP	1	1
4.4.2.8	MeIQx	1	1
4.4.2.8	DiMeIQx	1	1
4.4.2.8	PhIP	1	1
4.4.2.9	Mutagen index, meat	1	1
5.1	Carbohydrate	5	10
5.1.3	Starch	2	3
5.1.4	Sugars (as nutrients)	2	3
5.1.4	Galactose	1	1
5.1.4	Glucose	1	1
5.1.4	Lactose	1	1
5.1.4	Maltose	1	1
5.1.4	Mono/disaccharides	1	1
5.1.4	Fructose	5	7
5.1.4	Sucrose	6	9
5.1.5	Glycemic index	5+(1)	8
5.1.5	Glycemic load	6+(1)	9
5.2	Cholesterol	1	1
5.2	Meat fat	1	1
5.2	Ratio n-3/n-6 fatty acids	1	1
5.2	Vegetable fat	1	1
5.2.1	Total fat	3+(1)	8
5.2.2	Saturated fat	3+(1)	5
5.2.2	Palmitic acid	1	1
5.2.2	Stearic acid	1	1
5.2.3	Monounsaturated fat	2	4
5.2.3	Oleic acid	1	1
5.2.3	Palmitoleic acid (16:1)	1	1
5.2.4	Polyunsaturated fat	2	4
5.2.4.1	DHA (Docosahexaenoic acid)	2	2
5.2.4.1	EPA (Eicosapentaenoic fatty acid)	2	2
5.2.4.1	Linolenic acid	2	4
5.2.4.1	n-3 fatty acids	1	3
5.2.4.2	Arachidonic acid	1	1
5.2.4.2	Linoleic acid	2	4
5.2.4.2	n-6 fatty acids	1	1
5.2.5	Trans 18:1 fatty acid	1	1
5.2.5	Trans Unsaturated Fatty Acids	2	2
5.2.6	Cholesterol, dietary	2	5
5.4	Alcohol (as ethanol)	3+(1)	9
5.4	Ethanol from beer	1	1
5.4	Ethanol from liquor	1	1
5.4	Ethanol from wine	1	1
5.5	Vitamin B	1	1
5.5.1.1	Retinol	1	1
5.5.1.2	Alpha-carotene	1	1

5.5.1.2	Beta-carotene	1	1
5.5.1.2	beta-cryptoxanthin	1	1
5.5.2	Lutein and zeaxanthin	1	1
5.5.2	Lycopene	1	1
5.5.3	Total folate	2	4
5.5.3	Dietary folate	3	6
5.5.3	10-formyldihydrofolate	1	1
5.5.3	5-formyltetrahydrofolate	1	1
5.5.3	5-methyltetrahydrofolate	1	1
5.5.3	Folate Supplement	1	1
5.5.3	Folic acid	2	2
5.5.3	Monoglutamates	1	1
5.5.3	Plasma folate	1	1
5.5.3	Plasma homocysteine	1	1
5.5.3	Polyglutamates	1	1
5.5.3	Tetrahydrofolate	1	1
5.5.3	Methionine	2	5
5.5.4	Riboflavin, biomarker	1	1
5.5.7	Plasma Pyridoxine (vitamin B6)	1	1
5.5.8	Plasma Cobalamin (vitamin B12)	1	1
5.5.9	Vitamin C	2	5
5.5.9	Vitamin C from multivitamins and individual supplements	1	1
5.5.10	Serum 25-Hydroxyvitamin D	1	1
5.5.10	Vitamin D	1	1
5.5.11	Alpha-tocopherol	1	1
5.5.11	Alpha-tocopherol serum levels	1	1
5.5.11	Beta tocopherol	1	1
5.5.11	Delta-tocopherol	1	1
5.5.11	Gamma tocopherol	1	1
5.5.11	Vitamin E	3	4
5.5.11	Vitamin E from multivitamins and individual supplements	1	1
5.5.13	Multivitamin supplement	2	6
5.6.2	Iron	1	3
5.6.3	Calcium	1	1
5.6.6	Magnesium	1	1
5.7	Kaempferol	2	2
5.7.4	Catechin	1	1
5.8	Flavan-3-ols	1	1
5.8	Flavones	1	1
5.8	Flavonoids	1	2
5.8	Flavonols	2	2
5.8	Myricetin	2	2
5.8	Quercetin	2	2
6.1	Total physical activity (overall summary measures)	4	5
6.1.1.1	Occupational physical activity	1	5
6.1.1.2	Leisure physical activity	7+(1)	17

6.1.1.2	Sports, at different age	1	1
6.1.1.2	Walking	1	5
6.1.3	Low intensity	1	1
6.1.3	Moderate physical activity	1	3
6.1.3	Vigorous activity	3	6
6.2	Sitting time	1	1
7.1	Energy Intake	1	4
7.2	Energy expenditure	1	1
7.2	Metabolic equivalents (metab rate / resting MR)	1	1
8.1.1	BMI	13+(4)	33
8.1.1	BMI at 20 yrs	3	6
8.1.3	Weight	3	7
8.1.6	Adult weight change	1	1
8.1.6	BMI change	1	1
8.1.6	Change in body composition	1	1
8.1.6	Weight change	3	8
8.2.1	Waist circumference	3	5
8.2.2	Hips circumference	3	3
8.2.3	Waist to hip ratio	3	4
8.3.1	Height	3+(3)	11

Cohort studies: Results by exposure
(the number indicates the exposure code in the database)

2 Foods

2.2 Fruits and non-starchy vegetables

Methods

A total of 5 cohort studies on total fruit and vegetable intake and pancreatic cancer incidence have been published up to September 2011, four of which were identified in the Continuous Update Project.

Dose-response analyses of fruit and vegetable intake and risk of pancreatic cancer were conducted. For the dose-response analyses all results were converted to a common scale (grams per day) and 80 grams was used as an average serving size for studies that presented the results only by frequency (two studies). The dose-response results are presented for an increment of 100 grams per day.

Main results

Five studies were included in the dose-response analysis of fruit and vegetables combined and pancreatic cancer risk. There was no significant association (summary RR=1.00, 95% CI: 0.97-1.03) per 100 g/d, with no evidence of heterogeneity, I^2=0%, p=0.65. There was no evidence of publication bias with Egger's test, p=0.41. The summary RR ranged from 1.00 (95% CI: 0.96-1.03) when the Iowa cohort study in post-menopausal women (Inoue-Choi et al, 2011) was excluded to 1.01 (95% CI: 0.96-1.06) when the EPIC Study (Vrieling et al, 2002) was excluded.

Heterogeneity

There was no evidence of heterogeneity in the analyses (I^2=0%).
Note: In the ATBC Cancer Prevention Study legumes were included together with fruits and non-starchy vegetables

Comparison with the Second Expert Report

In the systematic review of the 2007 expert report, no significant inverse association was observed in the only cohort study identified that reported on total fruit and vegetables combined. Two out of four case-control studies identified reported significant inverse associations. The prospective studies identified in the CUP confirm a lack of an association between fruit and vegetable intake and pancreatic cancer.

Fruit and non-starchy vegetables

Table 2 Studies on fruit and non-starchy vegetables identified in the CUP

Author, year	Country	Study name	Number of cases	Years of follow-up	Sex	RR	LCI	UCI	Contrast
Heinen, 2011	Netherlands	Netherlands Cohort Study	423	16.3	M/F	0.89 1.0	0.64 0.98	1.24 1.02	528/589.8 vs. 175.1/213.7 g/d (M/F) Per 25 g/d increase
Inoue-Choi, 2011	USA	Iowa Women's Health Study	256	16.3	F	1.18	0.79	1.77	64.5 vs 22.0 serv/wk
Vrieling, 2009	Europe	European Prospective Investigation into Cancer and Nutrition	555	8.9	M/F	0.92 1.0	0.68 0.96	1.25 1.04	>588 vs. <255 g/d Per 100 g/d
Larsson, 2006	Sweden	Swedish Mammography Cohort & Cohort of Swedish Men	135	6	M/F	1.13	0.66	1.94	≥5.5 vs. <2.5 serv/d

Table 3 Overall evidence on fruit and non-starchy vegetables and pancreatic cancer

	Summary of evidence
SLR	Only one cohort study reported on fruit and vegetables combined and found a non-significant inverse association.
Continuous Update Project	Four cohort studies were identified. None of the identified studies found any significant association between fruit and vegetable intake and pancreatic cancer risk.

Table 4 Summary of results of the dose response meta-analysis on fruit and non-starchy vegetables and pancreatic cancer

Pancreatic cancer		
	SLR*	Continuous Update Project
Studies (n)	-	5
Cases (n)	-	1532
Increment unit used	-	Per 100 g/d
Overall RR (95%CI)	-	1.00 (0.97-1.03)
Heterogeneity (I^2, p-value)	-	0%, p=0.65

*No meta-analysis was conducted in the 2nd report. Only one study was identified.

Table 5 Inclusion/exclusion table for meta-analysis of fruits and non-starchy vegetables and pancreatic cancer

WCRF code	Author	Year	Study design	Study name	Subgroup	Cancer outcome	SLR	CUP dose-response meta-analysis	CUP HvL forest plot	Estimated values	Exclusion reason*
PAN70064	Heinen	2011	Case cohort study	Netherlands Cohort study	Men/women	Incidence	New	Yes	Yes		
PAN70063	Inoue-Choi	2011	Prospective Cohort study	Iowa Women's Health Study	Women	Incidence	New	Yes	Yes	Person-years	
PAN70020	Vrieling	2009	Prospective Cohort study	European Prospective Investigation into Nutrition and Cancer	Men/women	Incidence	New	Yes	Yes		
PAN70018	Larsson	2006	Prospective Cohort study	Swedish Mammography Cohort & Cohort of Swedish Men	Men/women	Incidence	New	Yes	Yes		
PAN07590	Stolzenberg-Solomon	2002	Prospective Cohort study	ATBC Cancer Prevention Study	Men smokers	Incidence	Yes	Yes	Yes	Mid-exposure values, person-years	

*All studies are included in dose-response meta-analysis

Figure 1 Highest versus lowest forest plot of fruits and non-starchy vegetables intake and pancreatic cancer

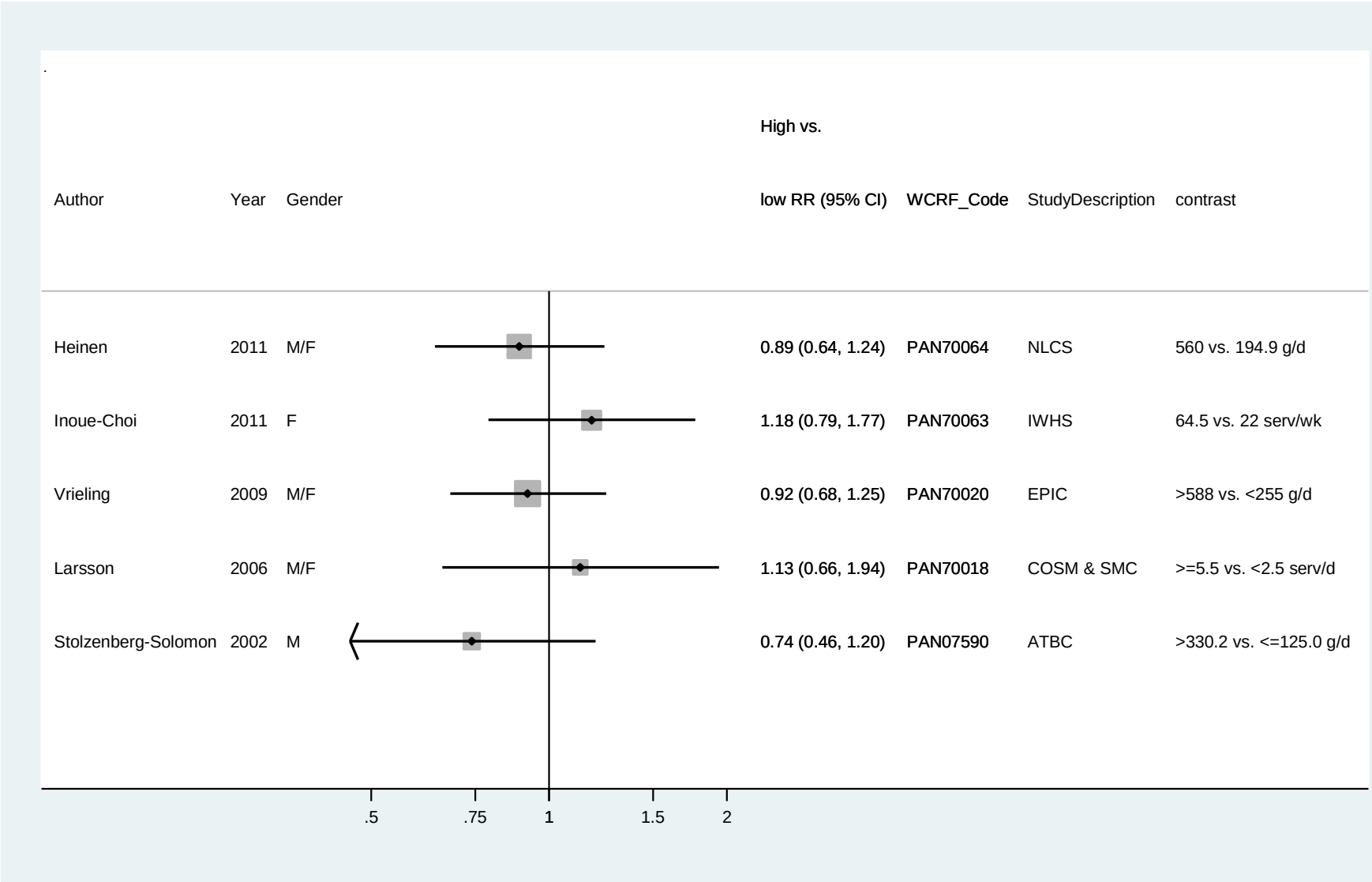


Figure 2 Dose-response meta-analysis of fruits and non-starchy vegetables intake and pancreatic cancer - per 100 g/d

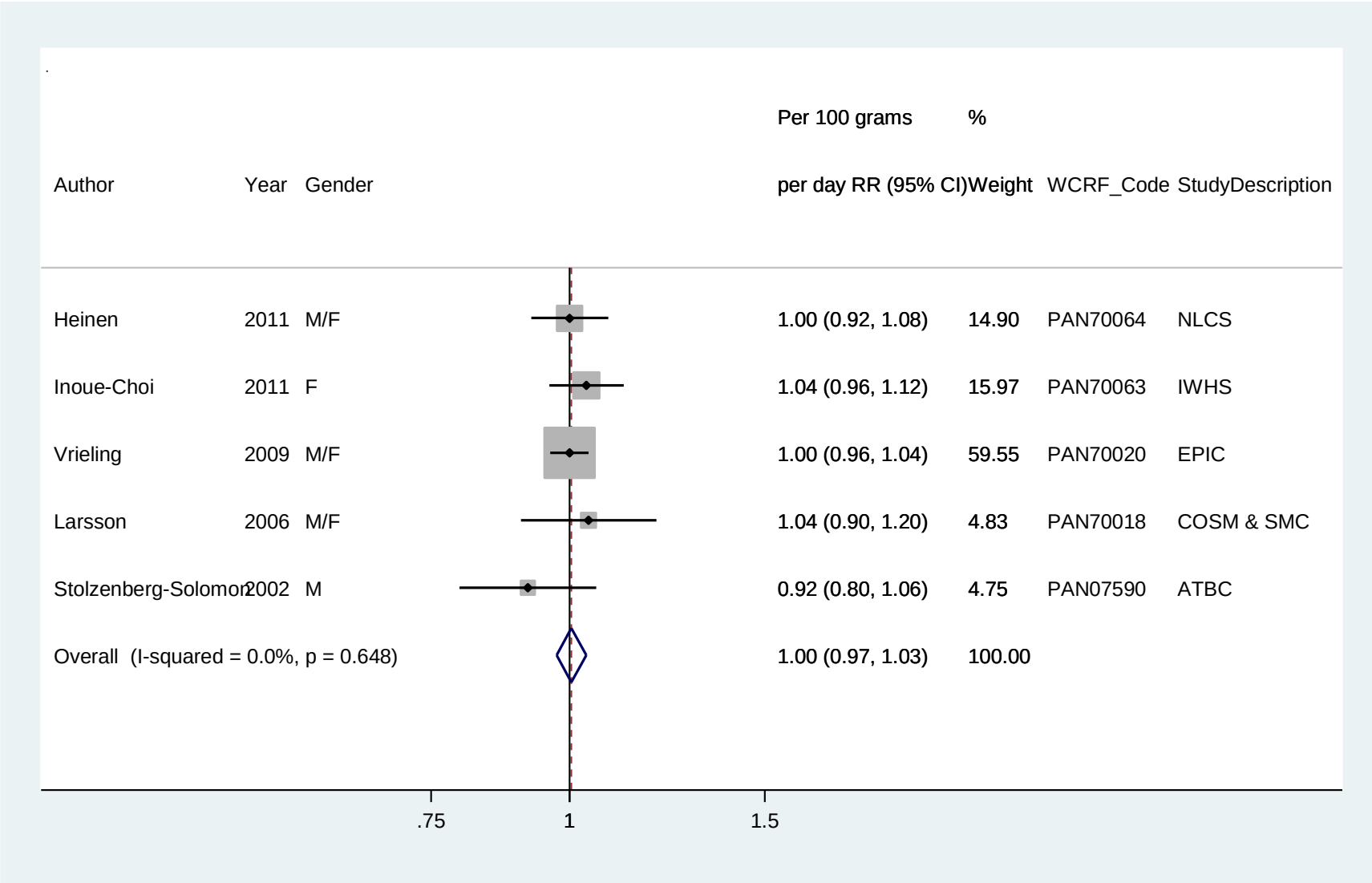


Figure 3 Funnel plot of fruit and non-starchy vegetables and pancreatic cancer

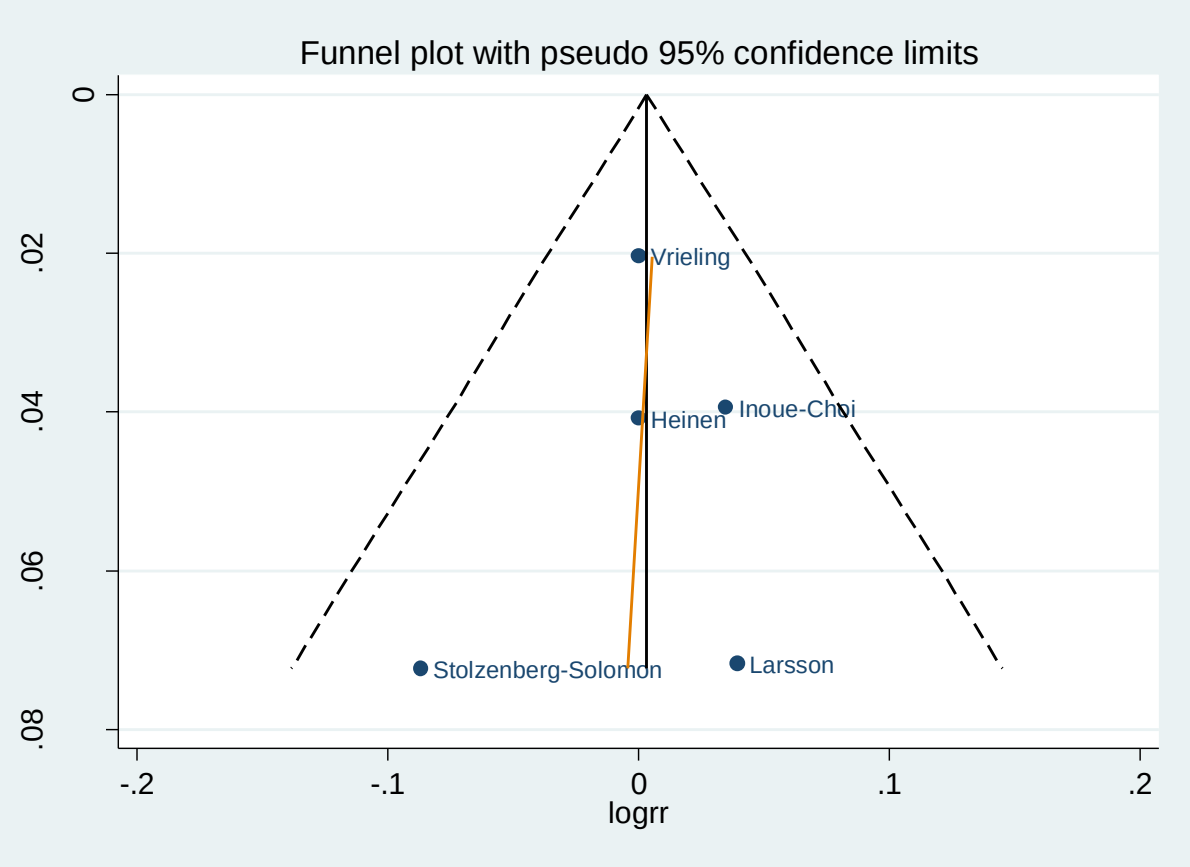
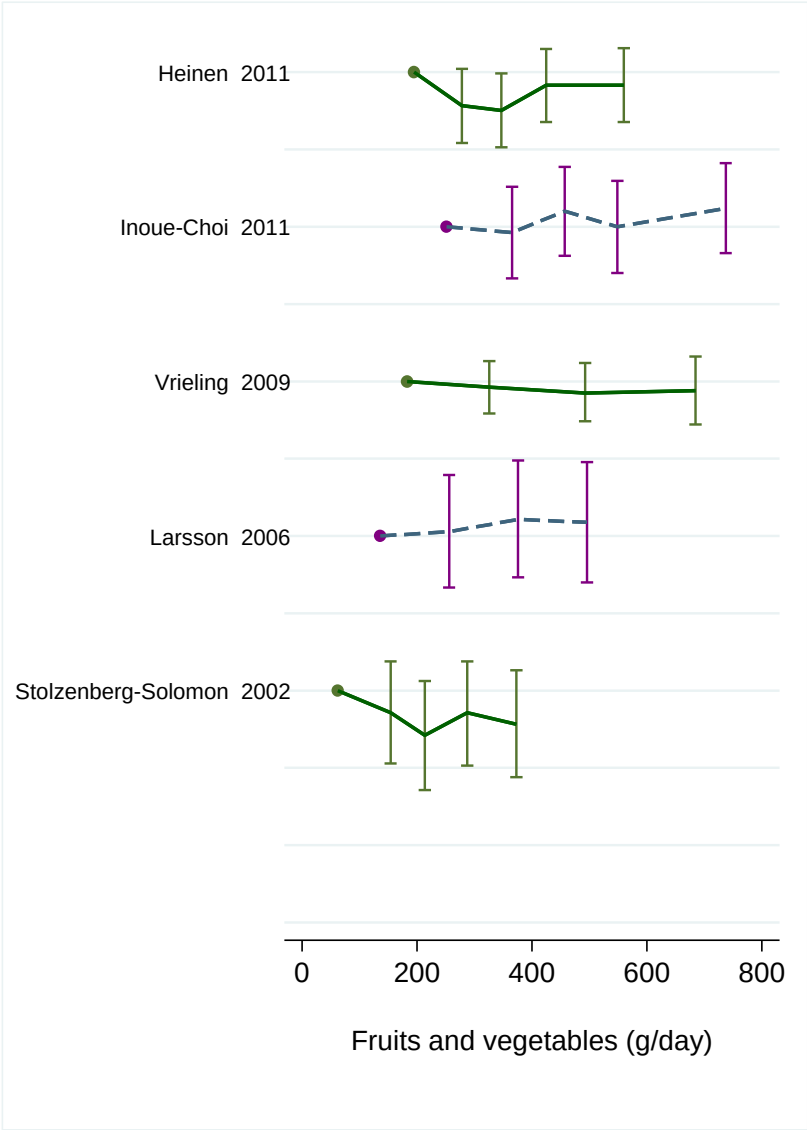


Figure 4 Dose-response graph of fruit and non-starchy vegetable intake and pancreatic cancer



2.2.1 Vegetables

Methods

A total of 10 cohort studies (11 publications) have been published on vegetables and pancreatic cancer incidence and mortality, 8 of which were identified in the Continuous Update Project.

For the dose-response analyses all results were converted to a common scale (grams per day) and 80 grams was used as an average serving size for studies that presented the results only by frequency. For studies that presented the results in grams per 1000 kcal per day the intakes were converted to absolute intakes using the mean or median energy intake reported in the same article, e.g. if the median energy intake was 2000 kcal/day the intake in grams per 1000 kcal per day was multiplied by a factor of 2 (2000/1000=2).

Two articles were excluded. One article, because a more recent report of the same cohort was included. The report of the Cancer Prevention Study II on pancreatic cancer mortality (Coughlin et al, 2000) was not included because vegetable intakes in servings or grams were not provided. No significant association was observed in this study in analysis stratified by gender. A modest inverse association was observed when the results for men and women were pooled by the review team using fixed effect models. The dose-response results are presented for an increment of 100 grams per day.

Main results

The summary RR per 100 grams per day of vegetable intake was 1.00 (95% CI: 0.96-1.03, I^2=14.6%, $P_{heterogeneity}$ =0.31) for studies with incidence or mortality as endpoint (n=9) and 1.00 (95% CI: 0.97-1.03, I^2=0.7%, $P_{heterogeneity}$ =0.42) for pancreatic cancer incidence (n=8). The summary RR ranged from 0.99 (95% CI: 0.94-1.04) when excluding the NIH-AARP Diet and Health Study (George et al, 2009) to 1.01 (95% CI: 0.98-1.05) when excluding the Multiethnic Cohort Study (Nothlings et al, 2006). There was no evidence of publication bias with Egger's test, p=0.49.

Heterogeneity

There was generally little evidence of heterogeneity in the analyses (I^2 ranged from 0.7-14.6%).

Published meta-analysis

In a published meta-analysis the summary RR of pancreatic cancer for high vs. low intake of vegetables was 0.80 (95% CI: 0.69-0.93), based on 5 case-control studies. There was significant heterogeneity in the analysis, p=0.02 (Vainio, 2006). No dose-response analyses were conducted. In the overall evaluation, the reviewers indicated that although inverse associations for vegetable consumption were seen in many case-control studies, these had largely not been replicated in the two identified cohort studies.

Comparison with the Second Expert Report

In the systematic review of the 2007 expert report the evidence for an association between intake of vegetables and pancreatic cancer risk was considered to be limited and no conclusion was possible.

Table 6 Studies on vegetables identified in the CUP

Author/year	Country	Study name	Number of cases	Years of follow-up	Sex	RR	LCI	UCI	Contrast
Heinen, 2011	Netherlands	Netherlands Cohort Study	423	16.3	M/F	1.23	0.86	1.75	287.5/299.4 vs. 103.6/106.2 g/d
Inoue-Choi, 2011	USA	Iowa Women's Health Study	256	16.3	F	1.21	0.81	1.80	40.0 vs. 11.5 serv/wk
Vrieling, 2009	Europe	European Prospective Investigation into Cancer and Nutrition	555	8.9	M/F	0.99	0.73	1.33	>276 vs. <110 g/d
George, 2009	USA	NIH-AARP Diet and Health Study	713 377	8	F M	0.82 1.03	0.59 0.81	1.13 1.32	≥1.43 vs. ≤0.56 cup equivalents/1000 kcal/d ≥1.10 vs. ≤0.44 cup equivalents/1000 kcal/d
Bobe, 2008	Finland	Alpha-Tocopherol and Beta-Carotene Cancer Prevention Study	306	16.1	M	0.78	0.54	1.12	>373.0 vs. ≤208.3 g/d
Nothlings, 2006	USA	Multiethnic Cohort Study	529	8.3	M/F	0.86	0.65	1.14	266.28 vs. 78.14 g/1000 kcal/d
Lin, 2006	Japan	Japan Collaborative Cohort Study	300	~10	M F	0.64 0.90	0.38 0.55	1.09 1.48	Quartile 4 vs. 1 Quartile 4 vs. 1
Larsson, 2006	Sweden	Swedish Mammography Cohort & Cohort of Swedish Men	135	6	M/F	1.08	0.63	1.85	≥2.5 vs. <1.0 serv/d

Table 7 Overall evidence on vegetables and pancreatic cancer

	Summary of evidence
SLR	Three studies were identified and all showed non-significant inverse associations. Two of these were included in the meta-analysis.
Continuous Update Project	Eight cohort studies were identified. None of the studies reported statistically significant associations. Non-significant inverse associations were present in 4 studies and non-significant positive associations were present in 2 studies.

Table 8 Summary of results of the dose response meta-analysis on vegetables and pancreatic cancer

Pancreatic cancer		
	SLR	Continuous Update Project
Studies (n)	2	9
Cases (n)	228	3657
Increment unit used	Per 100 g/d	Per 100 g/d
Overall RR (95%CI)	0.92 (0.79-1.08)	1.00 (0.96-1.03)
Heterogeneity (I^2, p-value)	0%, p=0.60	14.6%, p=0.31

Table 9 Inclusion/exclusion table for meta-analysis of vegetables and pancreatic cancer

WCRF code	Author	Year	Study design	Study name	Subgroup	Cancer outcome	SLR	CUP dose-response meta-analysis	CUP HvL forest plot	Estimated values	Exclusion reason
PAN70064	Heinen	2011	Case cohort study	Netherlands Cohort study	Men/ women	Incidence	New	Yes	Yes		
PAN70063	Inoue-Choi	2011	Prospective Cohort study	Iowa Women's Health Study	Women	Incidence	New	Yes	Yes	Person-years	
PAN70020	Vrieling	2009	Prospective Cohort study	European Prospective Investigation into Nutrition and Cancer	Men/ women	Incidence	New	Yes	Yes		
PAN70057	George	2009	Prospective Cohort study	NIH-AARP Diet and Health Study	Men/ women	Incidence	New	Yes	Yes	Mid-exposure values, person-years	
PAN70010	Bobe	2008	Prospective Cohort study	ATBC Cancer Prevention Study	Men	Incidence	New	Yes	Yes	Mid-exposure values	
PAN70019	Nothlings	2006	Prospective Cohort study	Multiethnic Cohort Study	Men/ women	Incidence	New	Yes	Yes	Person-years	
PAN70018	Larsson	2006	Prospective Cohort study	Swedish Mammography Cohort & Cohort of Swedish Men	Men/ women	Incidence	New	Yes	Yes		
PAN70051	Lin	2006	Prospective Cohort study	Japan Collaborative Cohort Study	Men/ women	Mortality	New	Yes	Yes	Mid-exposure values, person-years, quantities taken from another paper from the same study (Nagura et al, Br J Nutr 2009;102(2): 285-92)	
PAN07590	Stolzenberg -Solomon	2002	Prospective Cohort study	ATBC Cancer Prevention Study	Men	Incidence	Yes	No	No		Surpassed by Bobe et al, 2008, PAN70010
PAN07195	Coughlin	2000	Prospective Cohort study	Cancer Prevention Study II	Men/ women	Mortality	Yes	No	Yes		No quantities provided
PAN07562	Shibata	1994	Prospective Cohort study	Leisure World Cohort Study	Men/ women	Incidence	Yes	Yes	Yes	Mid-exposure values, person-years	

Figure 5 Highest versus lowest forest plot of vegetables and pancreatic cancer

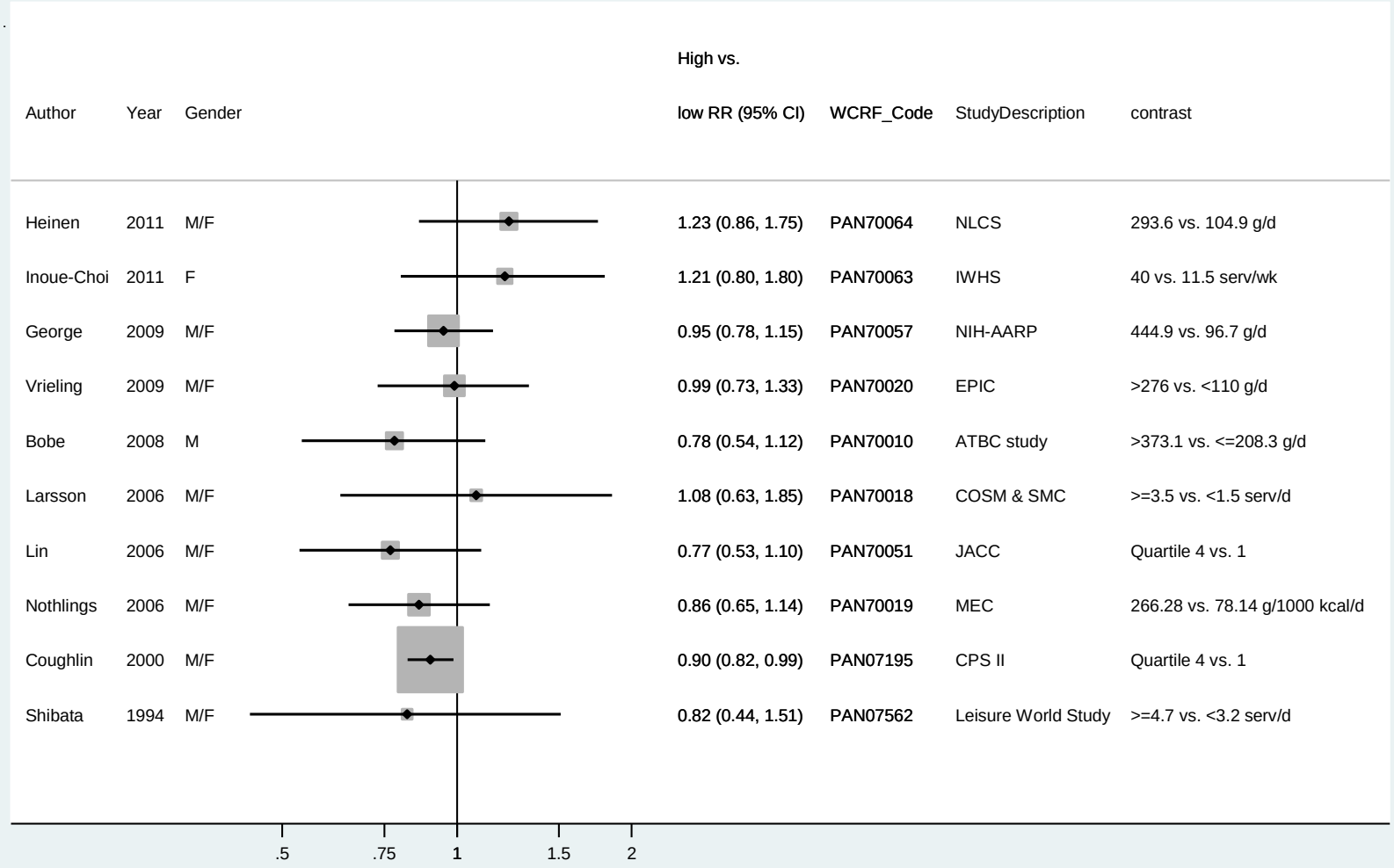


Figure 6 Dose-response meta-analysis of vegetables and pancreatic cancer, stratified by outcome type - per 100 g/d

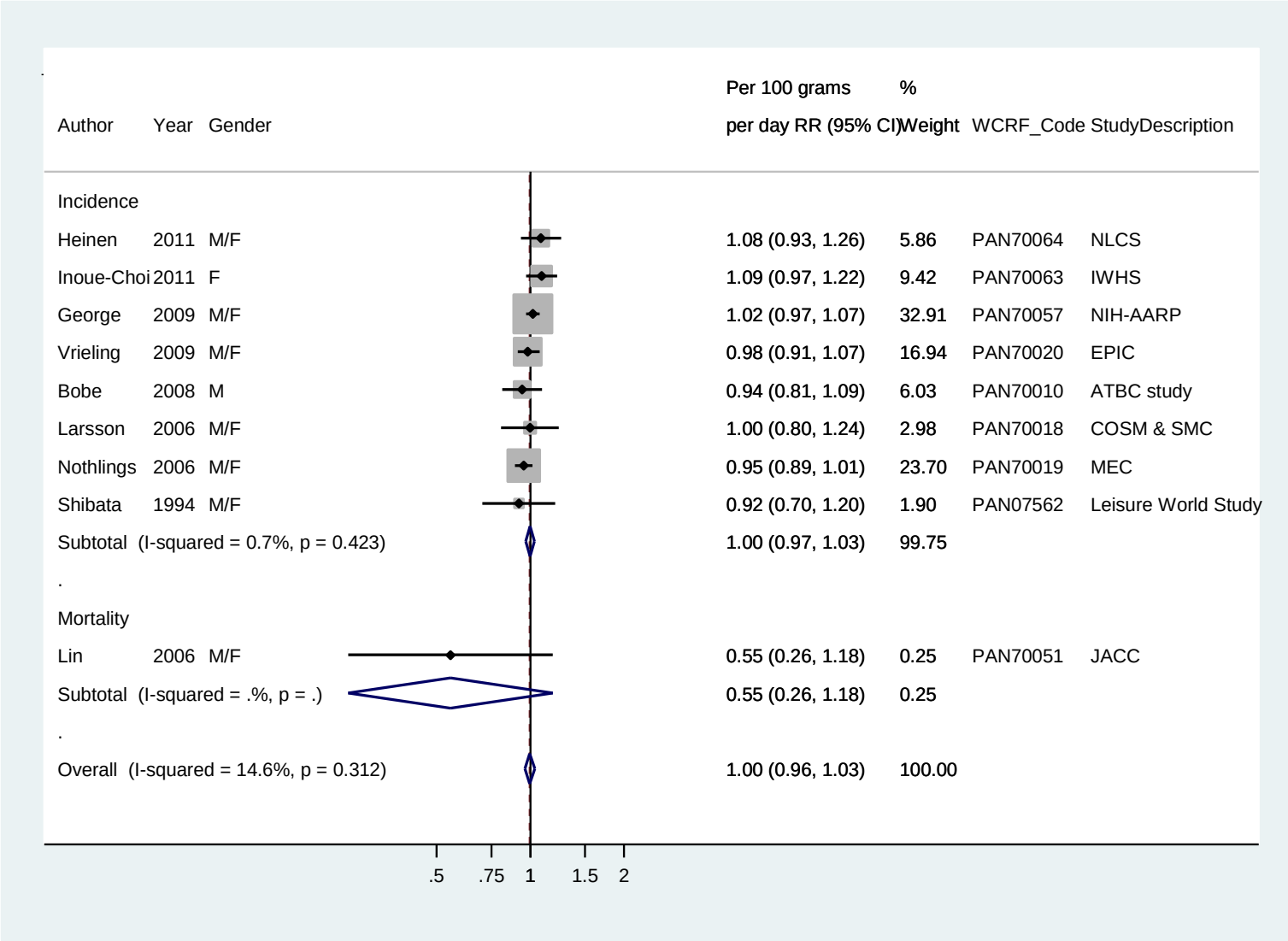


Figure 7 Funnel plot of vegetables and pancreatic cancer

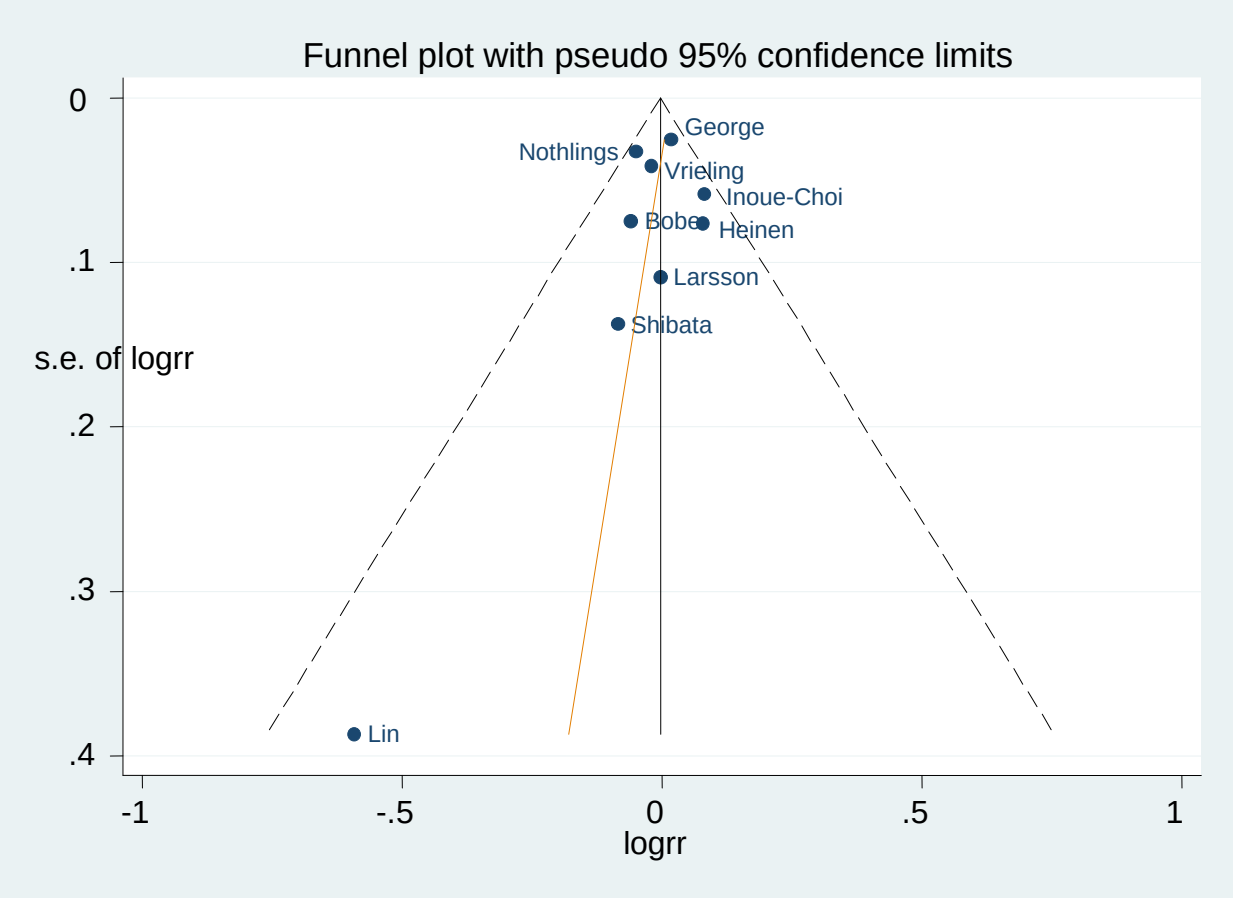
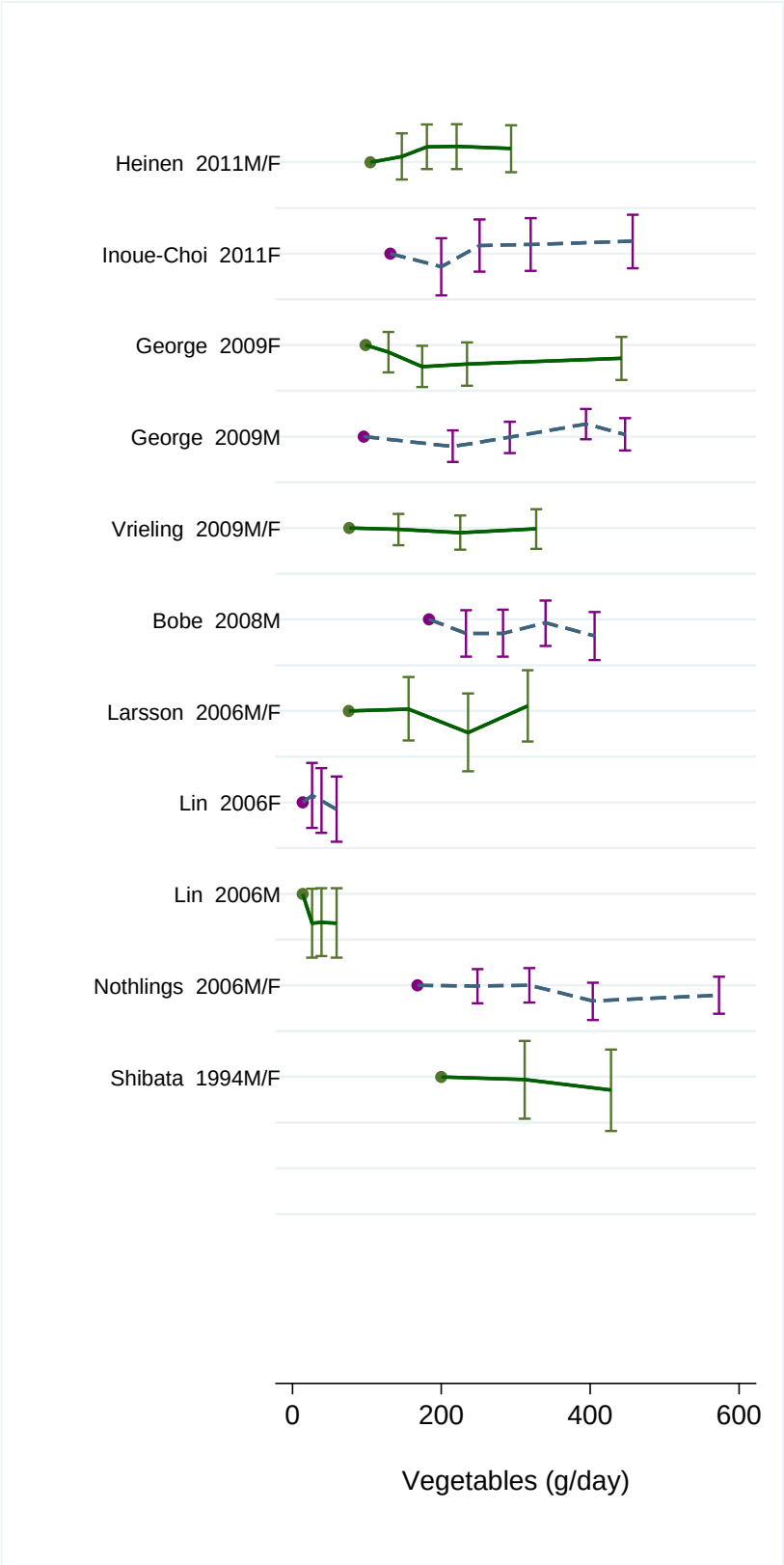


Figure 8 Dose-response graph of vegetable intake and pancreatic cancer



2.2.1.2.3 Cabbage

Methods

A total of 4 cohort studies have been published on cabbage intake and pancreatic cancer up to 28th of September 2011, and all the 4 studies were identified in the Continuous Update Project. Dose-response analyses were conducted per 50 g/d (80 grams was used as a standard serving size for conversion to g/d).

Main results

The summary RR per 50 g/d of cabbage intake was 0.97 (0.74-1.26, I^2=0%, $p_{heterogeneity}$=0.92, 4 studies). There was no evidence of publication bias with Egger's test, p=0.23. One study could not be included in dose-response meta-analysis because exposure was presented only in two categories. In this study (Larsson et al, 2006) cabbage consumption was associated with a statistically significant lower risk of pancreatic cancer. Other findings from this prospective study do not support a relationship of overall fruit and vegetable consumption with pancreatic cancer risk.

Heterogeneity

There was no evidence of heterogeneity (I^2=0%, p=0.92).

Comparison with the Second Expert Report

In the systematic review of the 2007 expert report there were no studies reporting on cabbage intake and pancreatic cancer risk.

Table 10 Studies on cabbage identified in the CUP

Author, year	Country	Study name	Number of cases	Years of follow-up	Sex	RR	LCI	UCI	Contrast
Vrieling, 2009	Europe	European Prospective Investigation into Nutrition and Cancer	555	8.9	M/F	0.95 0.99 0.99	0.69 0.92 0.79	1.29 1.07 1.25	>36 vs. <5 g/d Per 25 g/d, observed Per 25 g/d, calibrated
Bobe, 2008	Finland	ATBC Cohort study	306	16.1	M	0.98	0.68	1.40	>4.3 vs. 0 g/d
Larsson, 2006	Sweden	Swedish Mammography Cohort & Cohort of Swedish Men	135	6	M/F	0.62	0.39	0.99	≥1 serv/wk vs. never
Lin, 2006	Japan	Japan Collaborative Cohort Study for Evaluation of Cancer Risk	300 deaths	~10	M F	0.85 0.97	0.45 0.49	1.60 1.92	Almost every day vs. 0-2 times/mo Almost every day vs. 0-2 times/mo

Table 11 Overall evidence on cabbage and pancreatic cancer

	Summary of evidence
SLR	No cohort studies were available on cabbage intake and pancreatic cancer risk.
Continuous Update Project	Four cohort studies have been published. The Swedish study reported a significant inverse association, while the remaining three found no significant association.

Table 12 Summary of results of the dose-response meta-analysis of cabbage intake and pancreatic cancer

Pancreatic cancer		
	SLR*	Continuous Update Project
Studies (n)	-	4
Cases (n)	-	1161
Increment unit	-	Per 50 g/d
RR (95% CI)	-	0.97 (0.74-1.26)
Heterogeneity (I^2, p-value)	-	0%, p=0.92

*No meta-analysis was conducted in the 2nd report

Table 13 Inclusion/exclusion table for meta-analysis of cabbage intake and pancreatic cancer

WCRF code	Author	Year	Study design	Study name	Subgroup	Cancer outcome	SLR	CUP dose-response	CUP dose-response meta-analysis	CUP HvL forest plot	Exclusion reason
PAN70020	Vrieling	2009	Prospective Cohort study	European Prospective Investigation into Nutrition and Cancer	Men/Women	Incidence	New	Yes	Yes	Mid-exposure values	
PAN70010	Bobe	2008	Prospective Cohort study	ATBC Cancer Prevention Study	Men	Incidence	New	Yes	Yes	Mid-exposure values	
PAN70018	Larsson	2006	Prospective Cohort study	Swedish Mammography Cohort & Cohort of Swedish Men	Men/Women	Incidence	New	No	Yes		Only two categories
PAN70051	Lin	2006	Prospective Cohort study	Japan Collaborative Cohort Study for Evaluation of Cancer risk	Men/Women	Mortality	New	Yes	Yes	Mid-exposure values, grams per day	

Figure 9 Highest versus lowest forest plot of cabbage intake and pancreatic cancer

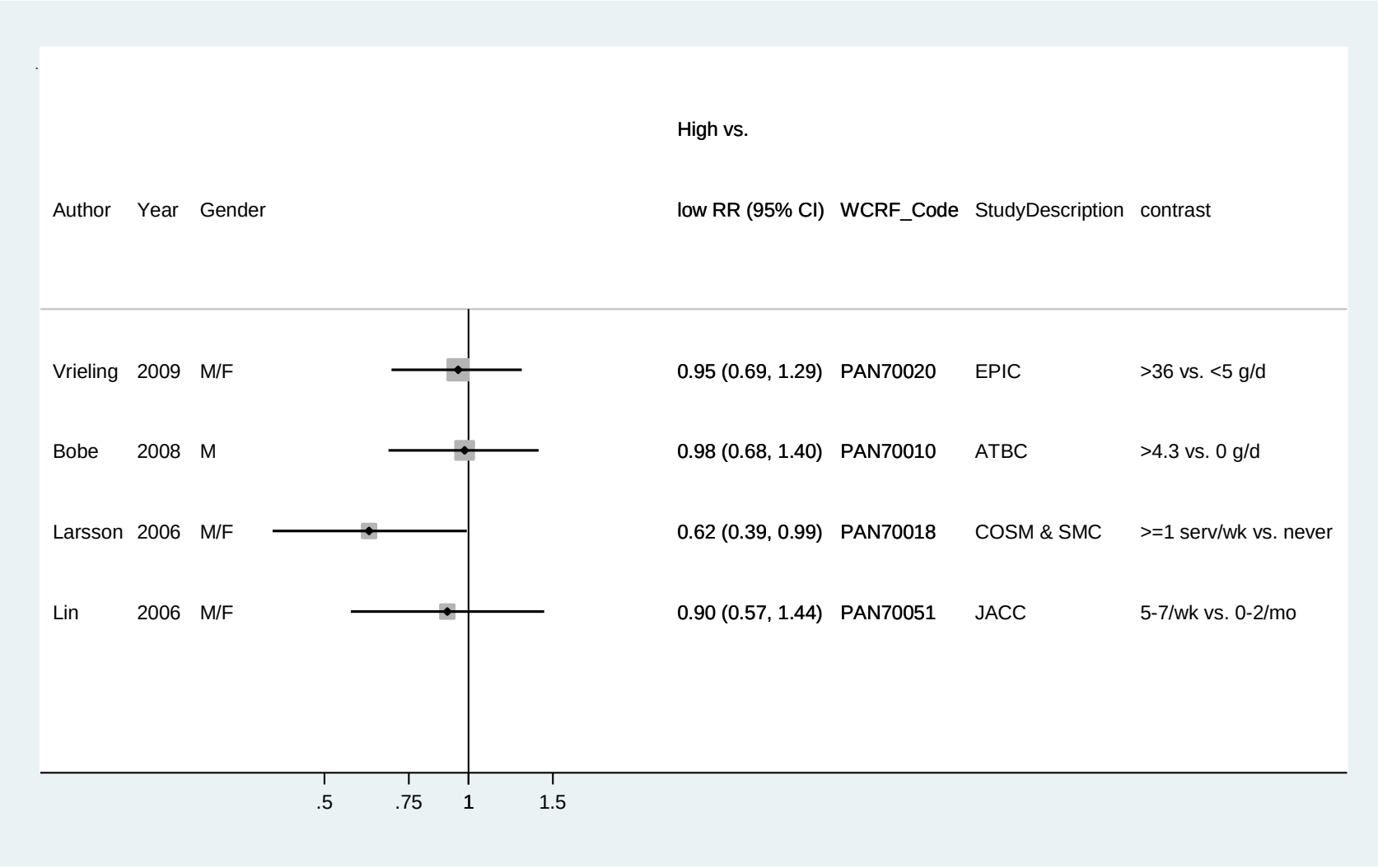


Figure 10 Dose-response meta-analysis for cabbage and pancreatic cancer, per 50 g/d

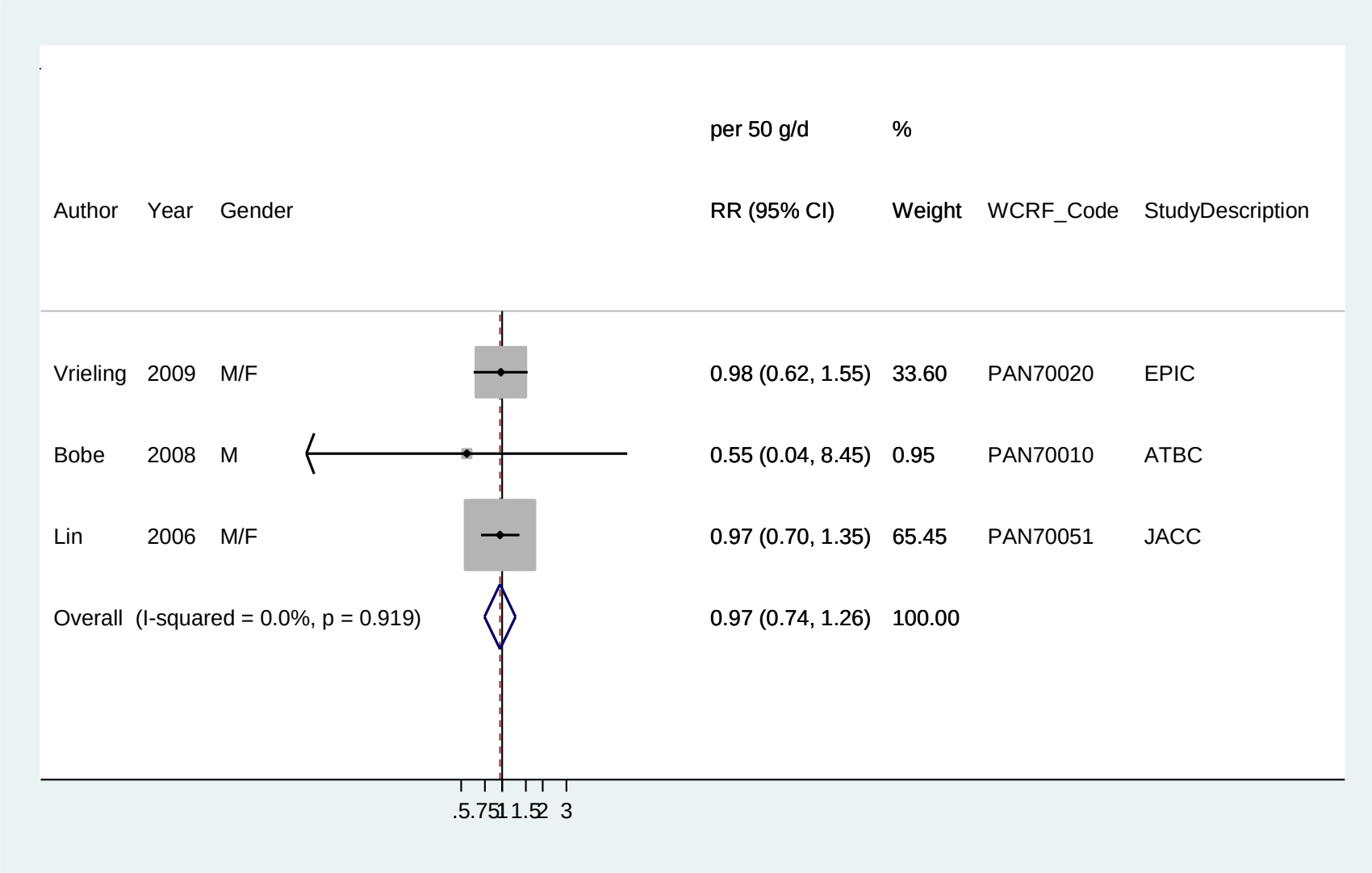
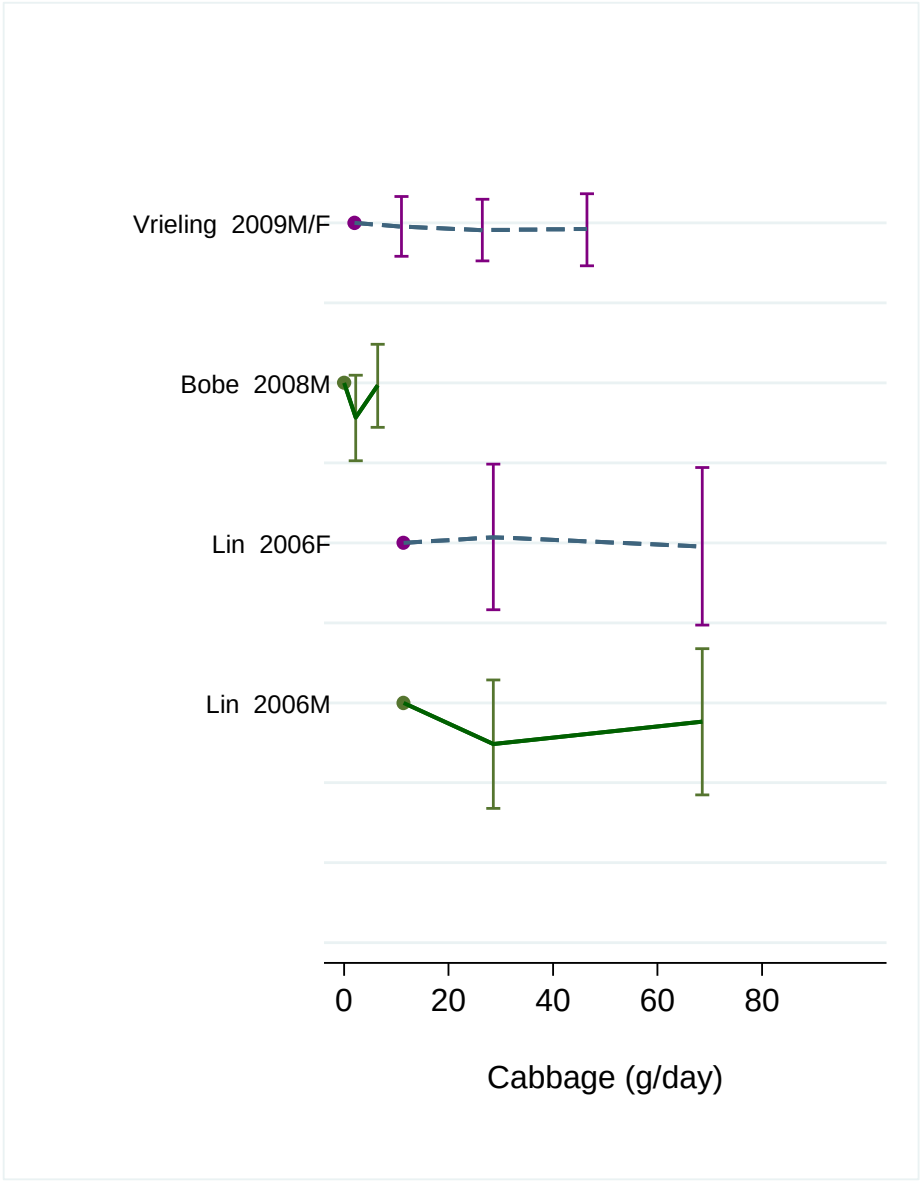


Figure 11 Dose-response graph of cabbage intake and pancreatic cancer



2.2.2 Fruits

Methods

A total of 12 cohort studies (13 publications) on fruit intake and pancreatic cancer incidence and mortality have been published, 8 of which were identified in the Continuous Update Project.

Main results

Ten studies were included in the meta-analysis. Two studies, one in Health Food shoppers in UK and the second from Japan (Appleby et al, 2002 and Khan et al, 2004) were excluded because only two categories of fruit intake were presented. None of the two excluded studies reported significant associations (the study results are in Figure 10).

The summary RR per 100 grams per day of fruit intake was 1.00 (95% CI: 0.95-1.05, I^2=15.2%, $P_{heterogeneity}$=0.30) for studies with incidence or mortality as endpoint (n=10); 1.01 (95% CI: 0.97-1.05, I^2=0%, $P_{heterogeneity}$=0.60) for pancreatic cancer incidence (n=8) and 0.64 (95% CI: 0.43-0.95, I^2=0%, $P_{heterogeneity}$=0.54) for pancreatic cancer mortality (n=2).

In sensitivity analyses excluding one study at a time the summary RR ranged from 0.97 (0.93-1.02) when excluding the Multiethnic Cohort Study (Nothlings et al, 2007) to 1.01 (95% CI: 0.96-1.06) when excluding the NIH-AARP Diet and Health Study (George et al, 2009).

Heterogeneity

There was evidence of small study bias with Egger's test, p=0.03, which was explained by the two studies of mortality with small number of cases that found inverse associations. When the analysis was restricted to the studies of incidence there was no evidence of publication bias, p=0.31 and there was little evidence of heterogeneity in the analyses (I^2 ranged from 0-15.2%).

Published meta-analysis

A meta-analysis of case-control studies found a significant inverse association between fruit intake and the risk of pancreatic cancer (Vainio, 2006). The summary RR from 6 case-control studies for high vs. low intake was 0.72 (95% CI: 0.63-0.83). There was significant heterogeneity in the analyses, p=0.0007. No dose-response analysis was conducted. In the overall evaluation, the reviewers indicated that although inverse associations for fruit consumption were seen in several case-control studies, these had largely not been replicated in the four identified cohort studies.

Comparison with the Second Expert Report

In the systematic review of the 2007 expert report there was limited suggestive evidence that fruit intake reduces pancreatic cancer risk based on meta-analysis of three cohort studies.

Table 14 Studies on fruits identified in the CUP

Author, year	Country	Study name	Number of cases	Sex	Years of follow-up	RR	LCI	UCI	Contrast
Heinen, 2011	Netherlands	Netherlands Cohort Study	423	M/F	16.3	0.90	0.66	1.24	292.8/344.2 vs. 31.3/64.1 g/d (m/w)
Inoue-Choi, 2011	USA	Iowa Women's Health Study	256	F	16.3	0.98	0.64	1.50	≥29.5 vs. ≤6.5 serv/wk
Vrieling, 2009	Europe	European Prospective Investigation into Cancer and Nutrition	555	M/F	8.9	1.02	0.77	1.36	>329 vs. <112 g/d
Bobe, 2008	Finland	Alpha-Tocopherol and Beta-Carotene Cancer Prevention Study	306	M	16.1	0.95	0.67	1.34	>191.3 vs. ≤52.33 g/d
George, 2009	USA	NIH-AARP Diet and Health Study	713 /377	M F	8	1.21 0.73	0.87 0.57	1.70 0.95	≥1.90 vs. ≤0.60 cup equivalents/1000 kcal/d ≥1.59 vs. ≤0.44 cup equivalents/1000 kcal/d
Nothlings, 2007	USA	Multethnic Cohort Study	434	M/F	8	1.42	1.05	1.93	178.4 vs. <53.3 g/1000 kcal/d
Lin, 2006	Japan	Japan Collaborative Cohort Study	300	M F	~10	0.71 0.65	0.35 0.36	1.45 1.15	Quartile 4 vs. 1 Quartile 4 vs. 1
Larsson, 2006	Sweden	Swedish Mammography Cohort & Cohort of Swedish Men	135	M/F	6	1.10	0.64	1.88	≥2.5 vs. <1.0 serv/d

Table 15 Overall evidence on fruits and pancreatic cancer

	Summary of evidence
SLR	All the five cohort studies identified reported non-significant inverse associations.
Continuous Update Project	Of the 8 studies identified, one study in American retired individuals reported an inverse association among men, but not women; a Japanese study reported a non-significant inverse association in both genders, one multiethnic study in USA reported a significant positive association and five studies reported no clear association.

Table 16 Summary of results of the dose response meta-analysis on fruits and pancreatic cancer

Pancreatic cancer		
	SLR	Continuous Update Project
Studies (n)	3	10
Cases (n)	345	3739
Increment unit used	Per 100 g/d	Per 100 g/d
Overall RR (95%CI)	0.92 (0.81-1.04)	1.00 (0.95-1.05)
Heterogeneity (I^2, p-value)	0%, p=0.60	15.2%, p=0.30

Table 17 Inclusion/exclusion table for meta-analysis of fruits and pancreatic cancer

WCRF code	Author	Year	Study design	Study name	Subgroup	Cancer outcome	SLR	CUP dose-response meta-analysis	CUP HvL forest plot	Estimated values	Exclusion reason
PAN70064	Heinen	2011	Case cohort study	Netherlands Cohort study	Men/women	Incidence	New	Yes	Yes		
PAN70063	Inoue-Choi	2011	Prospective Cohort study	Iowa Women's Health Study	Women	Incidence	New	Yes	Yes	Person-years	
PAN70020	Vrieling	2009	Prospective Cohort study	European Prospective Investigation into Nutrition and Cancer	Men/women	Incidence	New	Yes	Yes		
PAN70010	Bobe	2008	Prospective Cohort study	ATBC Cancer Prevention Study	Men	Incidence	New	Yes	Yes	Mid-exposure values	
PAN70057	George	2009	Prospective Cohort study	NIH-AARP Diet and Health Study	Men/women	Incidence	New	Yes	Yes	Mid-exposure values, person-years	
PAN70003	Nothlings	2007	Prospective Cohort study	Multethnic Cohort Study	Men/women	Incidence	New	Yes	Yes	Person-years	
PAN70018	Larsson	2006	Prospective Cohort study	Swedish Mammography Cohort & Cohort of Swedish Men	Men/women	Incidence	New	Yes	Yes		
PAN70051	Lin	2006	Prospective Cohort study	Japan Collaborative Cohort Study	Men/women	Mortality	New	Yes	Yes	Mid-exposure values, person-years, quantities taken from another paper from the same study (Nagura et al, Br J Nutr 2009;102(2):285-92)	

PAN20239	Khan	2004	Prospective Cohort study	Hokkaido Cohort	Men/women	Mortality	Yes	No	Yes		Only high vs. low comparison
PAN11533	Sauvaget	2003	Prospective cohort study	The Hiroshima/ Nagasaki Life Span Study	Men/women	Mortality	Yes	Yes	Yes	Mid-exposure values, person-years	
PAN60026	Appleby	2002	Prospective cohort study	Health Food Shoppers Cohort study	Men/women	Mortality	Yes	No	Yes		Only high vs. low comparison
PAN07590	Stolzenberg-Solomon	2002	Prospective Cohort study	ATBC Cancer Prevention Study	Men	Incidence	Yes	No	No	Mid-exposure values, person-years	Overlap with Bobe et al, 2008, PAN70010
PAN07562	Shibata	1994	Prospective Cohort study	Leisure World Cohort Study	Men/women	Incidence	Yes	Yes	Yes	Mid-exposure values, person-years	

Figure 12 Highest versus lowest forest plot of fruits and pancreatic cancer

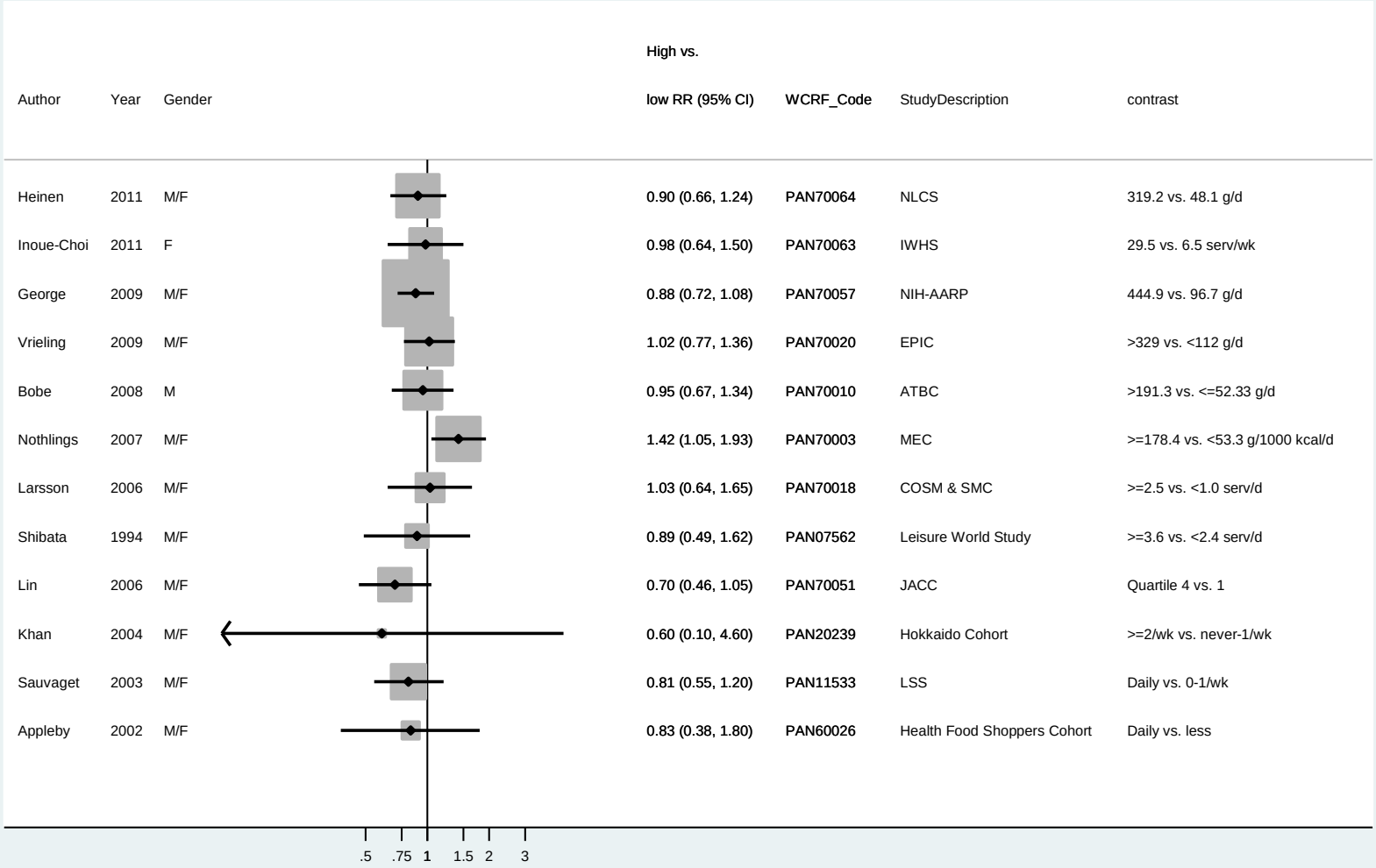


Figure 13 Dose-response meta-analysis of fruits and pancreatic cancer - per 100 g/d

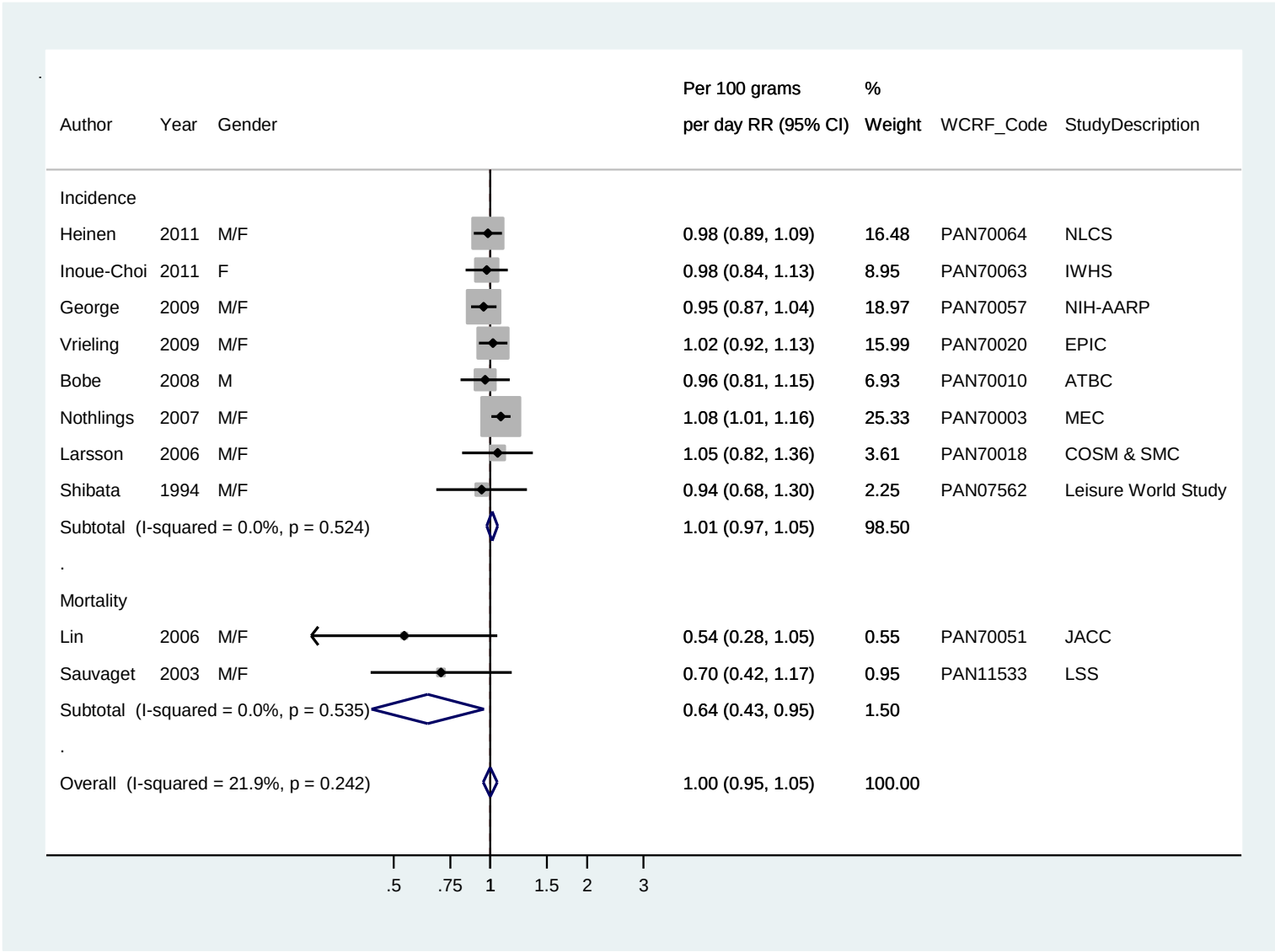


Figure 14 Funnel plot of fruits and pancreatic cancer

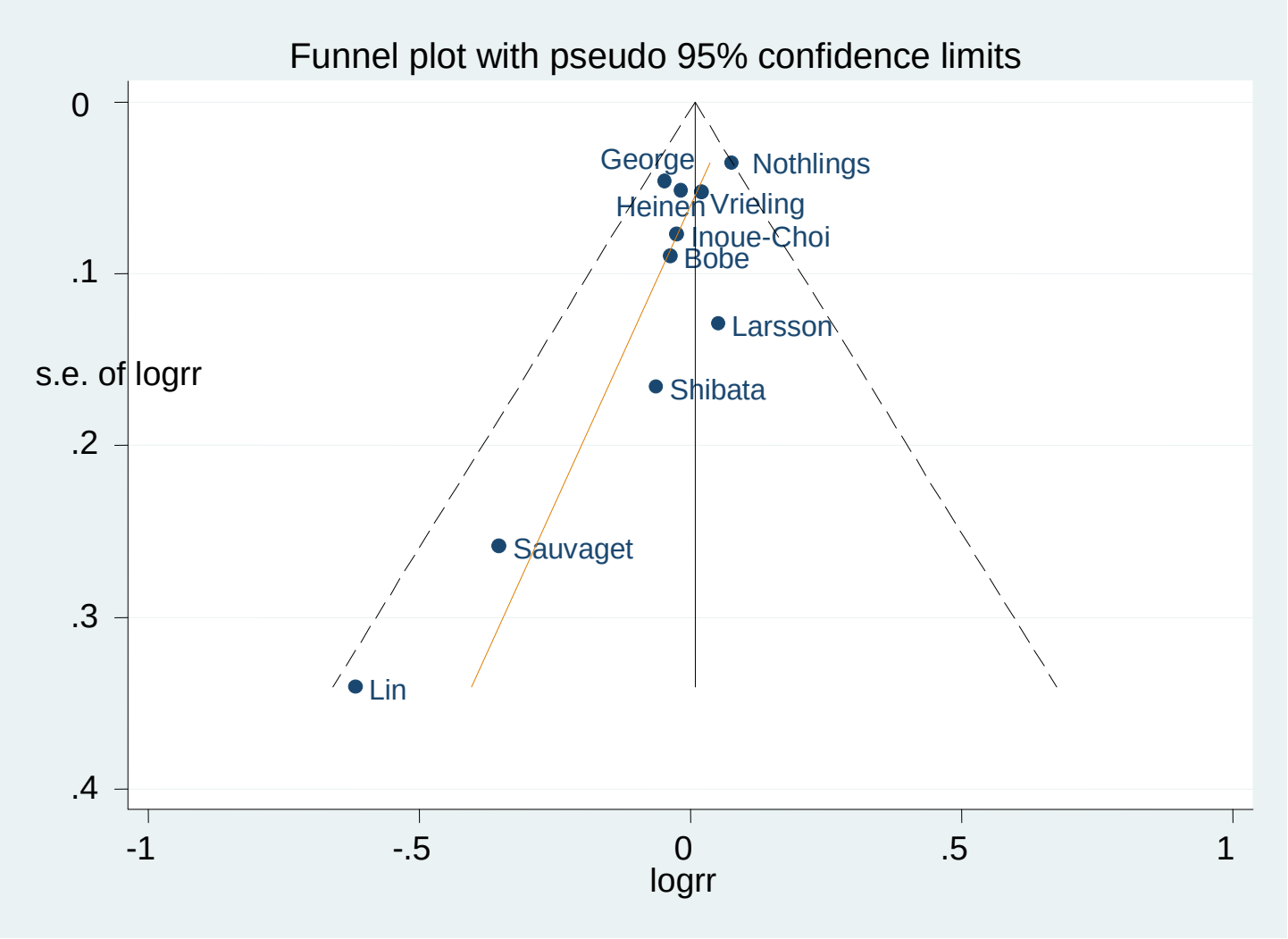
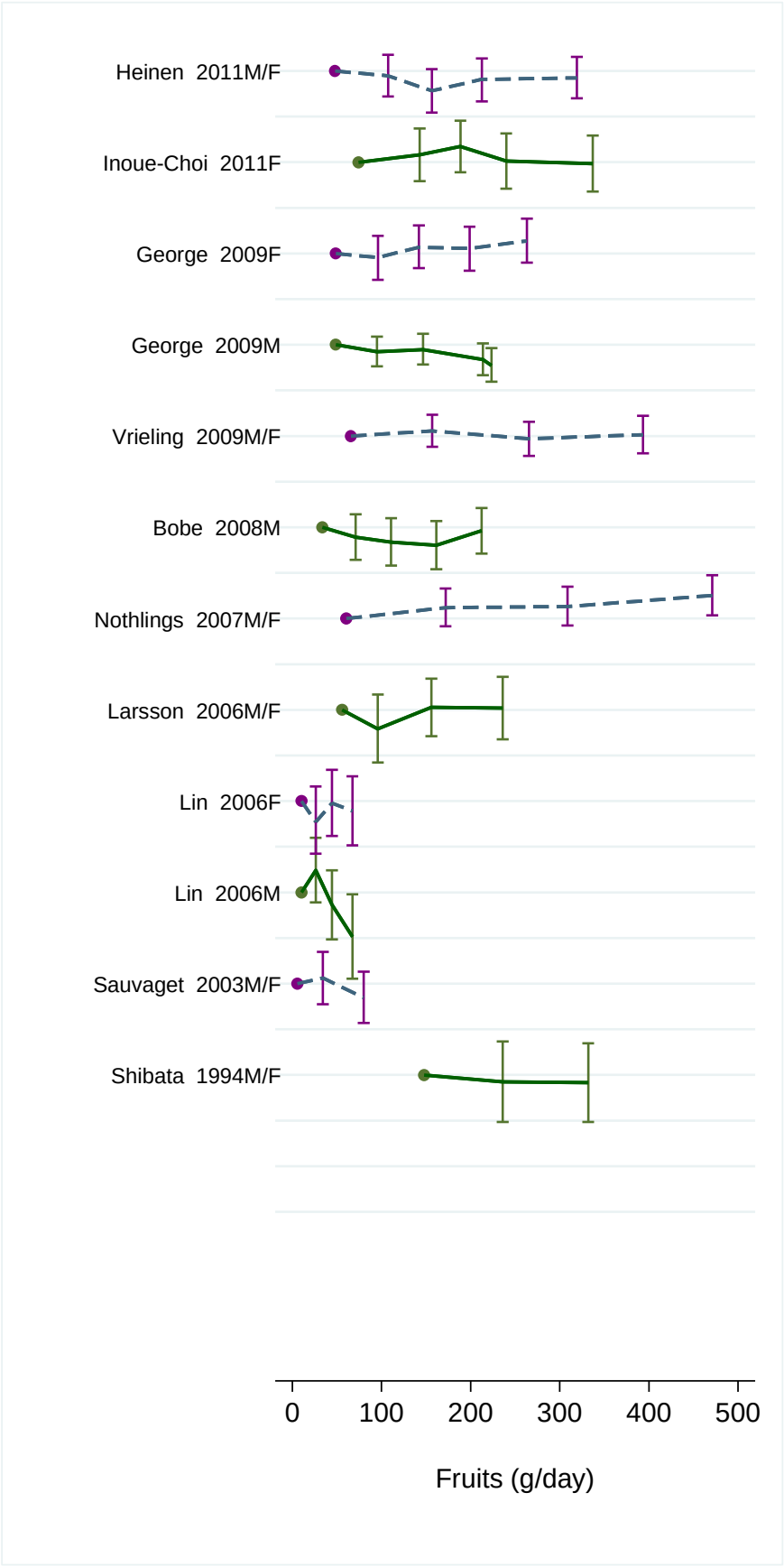


Figure 15 Dose-response graph of fruit intake and pancreatic cancer



2.2.2.1 Citrus fruit

Methods

A total of 8 cohort studies (9 publications) have been published on citrus fruit intake and pancreatic cancer up to 28th of September 2011. Six of these were identified in the CUP. Dose-response analyses including six studies were conducted and the increment used was 100 g/d (150 g was used as a standard unit for conversion of results from frequency to g/d).

Main results

Two cohort studies, the Adventist Health cohort Study (Mills et al, 1988) and the Cancer Prevention Study II (Coughlin et al, 2000) could not be included in meta-analysis because the reports did not provide enough data. The two studies reported null associations.
The summary RR per 100 g/d of citrus fruit intake was 1.02 (0.93-1.13, I^2=0%, $p_{heterogeneity}$=0.98, 6 studies). The summary RR ranged from 1.01 (95% CI: 0.81-1.27) when the Multiethnic Cohort Study was excluded to 1.03 (95% CI: 0.93-1.14) when the Japan Collaborative Cohort Study was excluded. There was no evidence of publication bias with Egger's test, p=0.83.

Heterogeneity

There was no evidence of heterogeneity (I^2=0%, p=0.98).

Comparison with the Second Expert Report

In the systematic review of the 2007 expert report there was no judgement of the association between citrus fruit intake and pancreatic cancer risk because it was not possible to conduct a meta-analysis of the available studies.

Table 18 Studies on citrus fruit identified in the CUP

Author, year	Country	Study name	Number of cases	Years of follow-up	Sex	RR	LCI	UCI	Contrast
Heinen, 2011	Netherlands	Netherlands Cohort Study	423	16.3	M/F	0.79 0.99	0.57 0.96	1.10 1.03	128.7/170.4 vs. 0/3.7 g/d Per 25 g/d
Vrieling, 2009	Europe	European Prospective Investigation into Nutrition and Cancer	555	8.9	M/F	1.12 1.00 1.00	0.86 0.96 0.94	1.45 1.03 1.08	>68 vs. <8 g/d Per 25 g/d, observed Per 25 g/d, calibrated
Bobe, 2008	Finland	ATBC Cohort study	306	16.1	M	1.05	0.74	1.49	>58.80 vs. ≤4.43 g/d
Nothlings, 2007	USA	Multiethnic Cohort study	434	8	M/F	1.08	0.82	1.43	≥93.9 vs. <13.4 g/d
Larsson, 2006	Sweden	Swedish Mammography Cohort & Cohort of Swedish Men	135	6	M/F	1.12	0.68	1.83	≥7 serv/wk vs. <1 serv/wk

Lin, 2006	Japan	Japan Collaborative Cohort Study for Evaluation of Cancer Risk	300	~10	M F	0.85 1.07	0.47 0.57	1.51 1.98	Almost every day vs. 0-2 times/mo Almost every day vs. 0-2 times/mo

Table 19 Overall evidence on citrus fruit and pancreatic cancer

	Summary of evidence
SLR	Three cohort studies were available on citrus fruit intake and pancreatic cancer risk, one showed no association and the other reported that there was no significant association, but did not provide a risk estimate.
Continuous Update Project	Six cohort studies have been published. All the studies reported no significant association.

Table 20 Summary of results of the dose-response meta-analysis of citrus fruit intake and pancreatic cancer

Pancreatic cancer		
	SLR*	Continuous Update Project
Studies (n)	-	6
Cases (n)	-	2153
Increment unit	-	Per 100 g/d
RR (95% CI)	-	1.02 (0.93-1.13)
Heterogeneity (I^2, p-value)	-	0%, p=0.98

*No meta-analysis was conducted in the 2nd report.

Table 21 Inclusion/exclusion table for meta-analysis of citrus fruit intake and pancreatic cancer

WCRF code	Author	Year	Study design	Study name	Subgroup	Cancer outcome	SLR	CUP dose-response meta-analysis	CUP HvL forest plot	Estimated values	Exclusion reason
PAN70064	Heinen	2011	Case cohort study	Netherlands Cohort study	Men/women	Incidence	New	Yes	Yes		
PAN70020	Vrieling	2009	Prospective Cohort study	European Prospective Investigation into Nutrition and Cancer	Men/women	Incidence	New	Yes	Yes	Mid-exposure values	
PAN70010	Bobe	2008	Prospective Cohort study	ATBC Cancer Prevention Study	Men	Incidence	New	Yes	Yes	Mid-exposure values	
PAN70003	Nothlings	2007	Prospective Cohort study	Multiethnic Cohort Study	Men/women	Incidence	New	Yes	Yes	Person-years	
PAN70018	Larsson	2006	Prospective Cohort study	Swedish Mammography Cohort & Cohort of Swedish Men	Men/women	Incidence	New	Yes	Yes	Mid-exposure values	
PAN70051	Lin	2006	Prospective Cohort study	Japan Collaborative Cohort Study for Evaluation of Cancer risk	Men/women	Mortality	New	Yes	Yes	Mid-exposure values	
PAN07589	Stolzenberg-Solomon	2002	Prospective Cohort study	ATBC Cancer Prevention Study	Men	Incidence	Yes	No	No		Superseded by Bobe, 2008
PAN07195	Coughlin	2000	Prospective Cohort study	Cancer Prevention Study II	Men/women	Mortality	Yes	No	Yes		Quantity not reported
PAN07449	Mills	1988	Prospective Cohort study	Adventist Health Study	Men/women	Mortality	Yes	No	No		No risk estimate provided

Figure 16 Highest versus lowest forest plot on citrus fruit and pancreatic cancer

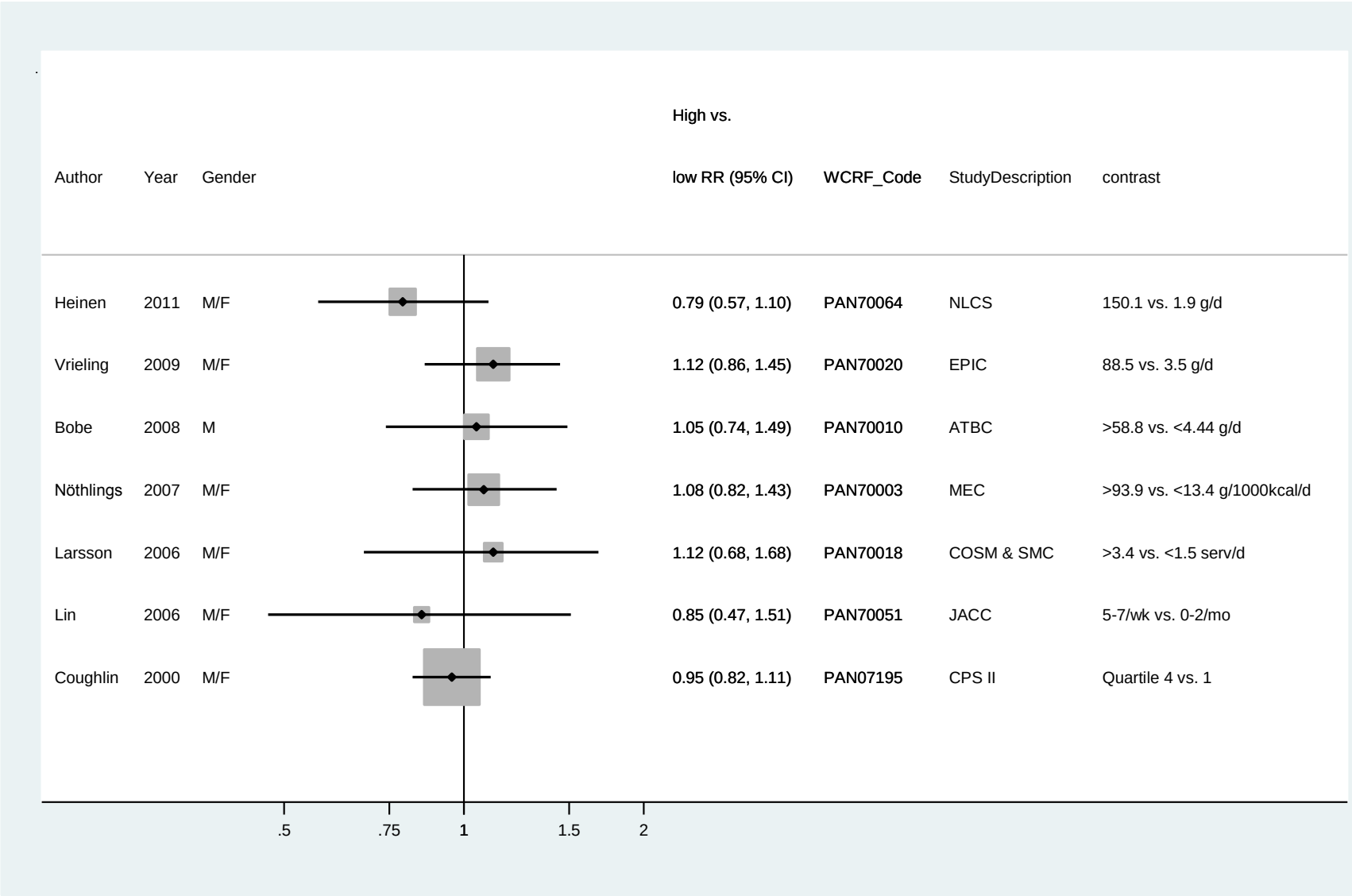


Figure 17 Dose-response meta-analysis of citrus fruit and pancreatic cancer - per 100 g/d

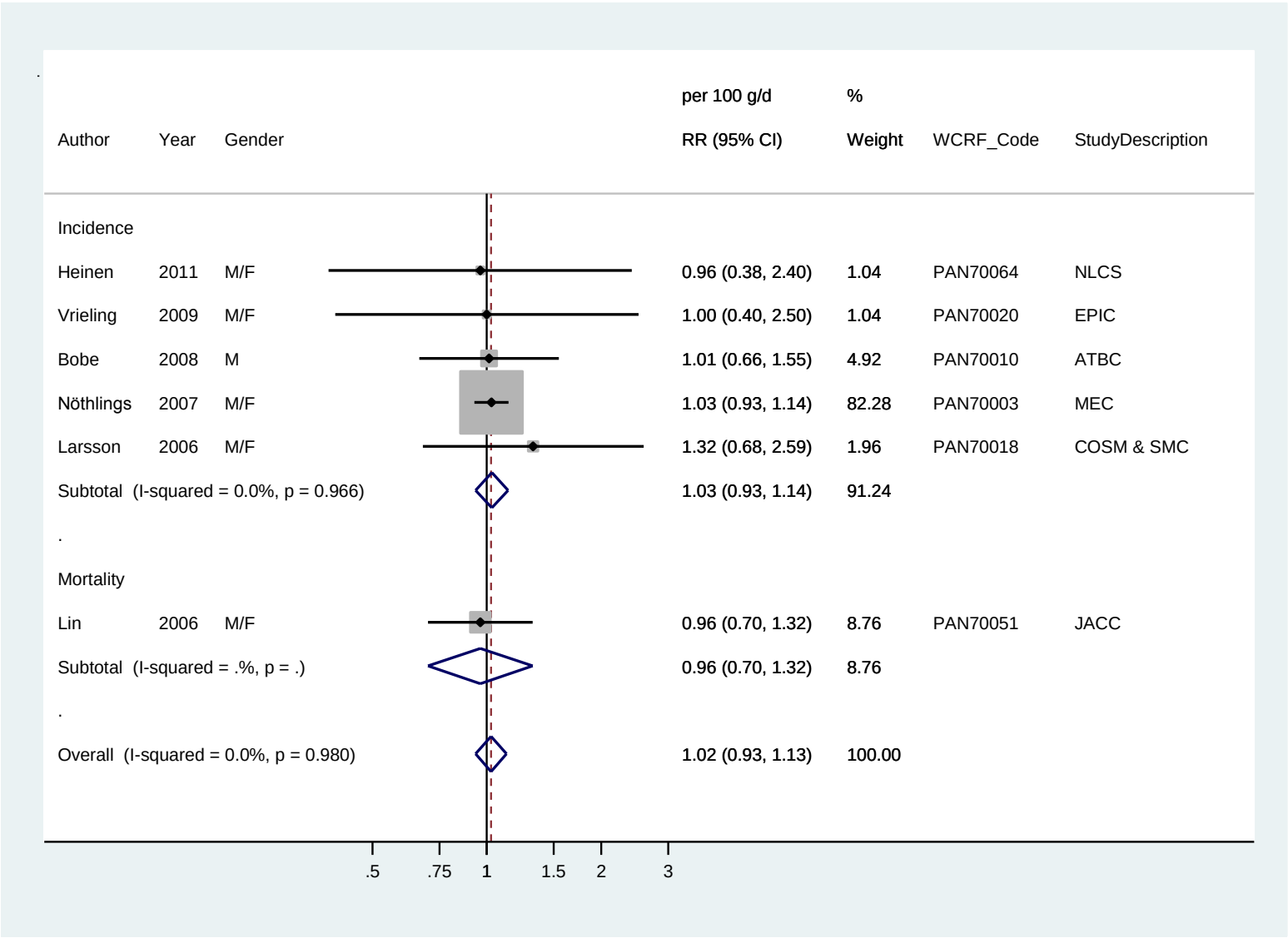


Figure 18 Funnel plot of citrus fruit and pancreatic cancer

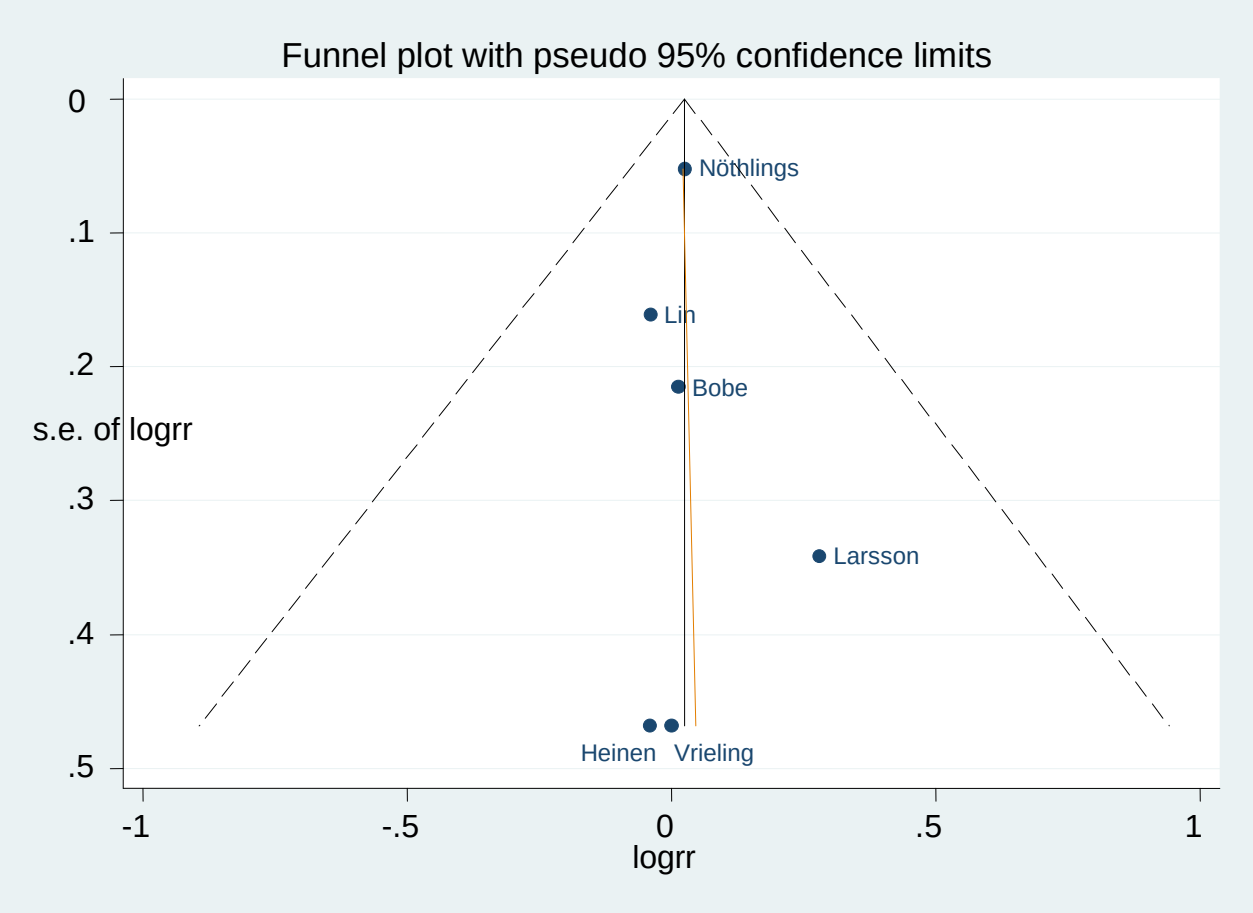
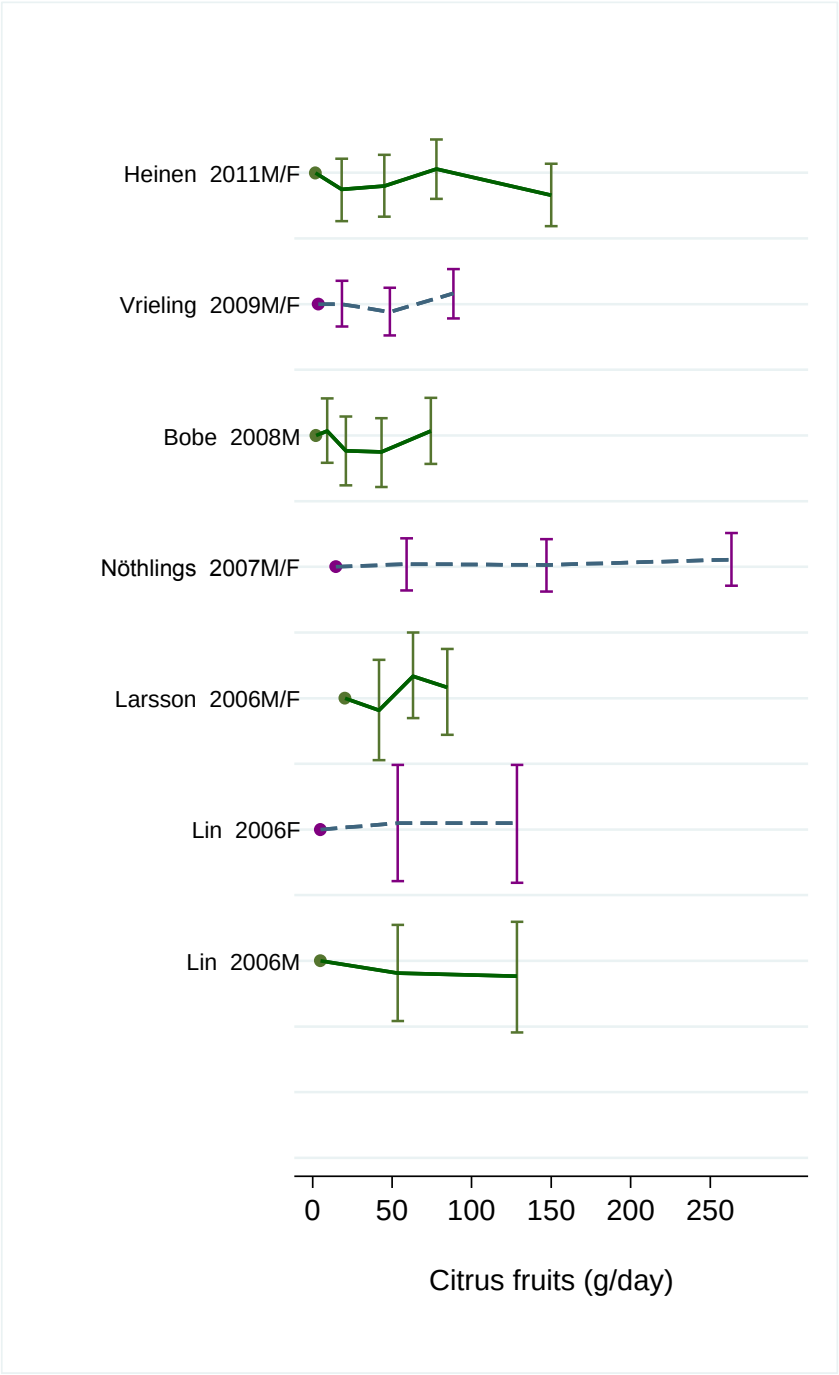


Figure 19 Dose-response graph of citrus fruit intake and pancreatic cancer



2.5.1.2 Processed meat

Methods

Eight cohort studies (9 publications) have published on processed meat and pancreatic cancer, two of which were identified in the Continuous Update Project.
Overall and stratified dose-response analyses of processed meat intake and pancreatic cancer risk were conducted. A serving size of 50 grams was used for converting results reported by frequency to grams per day. The results of dose-response analyses are presented for an increment of 50 grams per day.

Main results

Seven studies (one in pancreatic cancer mortality) could be included in meta-analysis. One study excluded because exposure was presented in only two categories (Hokkaido Cohort Study, Khan et al, 2004) reported a non-significant inverse association of pancreatic cancer mortality and processed meat intake.

The summary RR per 50 g/d was 1.16 (95% CI: 1.00-1.33, I^2=0%, $P_{heterogeneity}$ =0.43) for pancreatic cancer incidence (n=6) and 1.17 (95% CI: 1.01-1.34, I^2=0%, $P_{heterogeneity}$ =0.51) for studies on pancreatic cancer incidence and mortality combined (n=7). In a sensitivity analysis the summary RR ranged from 1.12 (95% CI: 0.94-1.33) when excluding the NIH-AARP Diet and Health Study to 1.21 (95% CI: 1.03-1.42) when excluding the ATBC Cancer Prevention Study. There was no indication of publication bias with Egger's test, p=0.95. There was a significant positive association between processed meat intake and pancreatic cancer among men, summary RR=1.21 (95% CI: 1.01-1.45, I^2=0%, 3 studies), but not among women, summary RR=1.09 (95% CI: 0.69-1.73, I^2=43%, 4 studies).

Heterogeneity

There was no evidence of significant heterogeneity in the analyses. However, in subgroup analyses by sex a positive association of processed meat was found in men, but not in women. Study results in women were inconsistent, with two studies showing non-significant inverse associations and two studies showing non-significant or significant positive associations (I^2=43.4 %, Figure 23).

Comparison with the Second Expert Report

In the systematic review of the 2007 expert report there was limited and inconclusive evidence for an association between processed meat intake and pancreatic cancer based on meta-analysis of 3 cohort studies.

Published meta-analysis

A meta-analysis of 7 prospective studies reported a summary RR of 1.19 (95% CI: 1.04-1.36, I^2=0%, $p_{heterogeneity}$=0.46) per 50 g/day increase in processed meat consumption (Larsson et al, 2012).

Table 22 Studies on processed meat identified in the CUP

Author, year	Country	Study name	Number of cases	Years of Follow-up	Sex	RR	LCI	UCI	Contrast
Heinen, 2009	Netherlands	Netherlands Cohort Study	350	13.3	M F	0.93 0.98	0.65 0.87	1.35 1.11	35.7/25.6 vs. 0/0 g/d Per 15 g/d
Cross, 2007	USA	NIH-AARP Diet and Health Study	1103	6.8	M F	1.31 0.86	1.01 0.60	1.68 1.22	22.6 vs. 1.6 g/d
Stolzenberg-Solomon, 2007	USA	NIH-AARP Diet and Health Study	836	5	M/F	0.97	0.76	1.23	>16.0 vs. ≤3.0 g/d

Table 23 Overall evidence on processed meat and pancreatic cancer

	Summary of evidence
SLR	Six cohort studies (processed meat, processed pork and pork products) were identified and showed no significant associations overall.
Continuous Update Project	Two additional prospective studies (three publications) were identified. One study reported a significant increase in risk among men, but not in women, while the other study reported no significant association.

Table 24 Summary of results of the dose response meta-analysis on processed meat and pancreatic cancer

Pancreatic cancer incidence		
	SLR	Continuous Update Project
Studies (n)	3	6
Cases (n)	513	2448
Increment unit	20 g/d	Per 50 g/d
RR (95% CI)	0.93 (0.82-1.05)	1.16 (1.00-1.33)
Heterogeneity (I^2, p-value)	63%, p=0.06	0%, p=0.43
Pancreatic cancer incidence and mortality combined		
Studies (n)	-	7
Cases (n)	-	2748
Increment unit	-	Per 50 g/d
RR (95% CI)	-	1.17 (1.01-1.34)
Heterogeneity (I^2, p-value)	-	0%, p=0.51
By gender		
Men	-	1.21 (95% CI: 1.01-1.45), n=3
Heterogeneity (I^2,p-value)		0%, p=0.39
Women	-	1.09 (95% CI: 0.69-1.73), n=4
Heterogeneity (I^2,p-value)		43.4%, p=0.15

Table 25 Inclusion/exclusion table for meta-analysis of processed meat and pancreatic cancer

WCRF code	Author	Year	Study design	Study name	Subgroup	Cancer outcome	SLR	CUP dose-response meta-analysis	CUP HvL forest plot	Estimated values	Exclusion reason
PAN70056	Heinen	2009	Case cohort study	Netherlands Cohort Study	Men/women	Incidence	New	Yes	Yes		
PAN70017	Stolzenberg-Solomon	2007	Prospective cohort study	NIH-AARP Diet and Health Study	Men/women	Incidence	New	No	No	Mid-exposure values	Overlapped with PAN70016 which had a larger number of cases
PAN70016	Cross	2007	Prospective cohort study	NIH-AARP Diet and Health Study	Men/women	Incidence	New	Yes	Yes	Person-years	
PAN60002	Larsson	2006	Prospective cohort study	Swedish Mammography Cohort Study	Women	Incidence	Yes	Yes	Yes	Mid-exposure values	
PAN70051	Lin	2006	Prospective cohort study	Japan Collaborative Cohort Study	Men/women	Mortality	Yes	Yes	Yes	Person-years, Mid-exposure values	
PAN61048	Nothlings	2005	Prospective cohort study	Multiethnic Cohort Study	Men/women	Incidence	Yes	Yes	Yes	Person-years	
PAN20239	Khan	2004	Prospective cohort study	Hokkaido Cohort study	Men/women	Mortality	Yes	No	Yes		Only two categories
PAN07442	Michaud	2003	Prospective cohort study	Nurses' Health Study	Women	Incidence	Yes	Yes	Yes		
PAN07590	Stolzenberg-Solomon	2002	Prospective cohort study	ATBC Cohort Study	Male smokers	Incidence	Yes	Yes	Yes	Mid-exposure values, distribution of cases and person-years	

Figure 20 Highest versus lowest forest plot of processed meat and pancreatic cancer

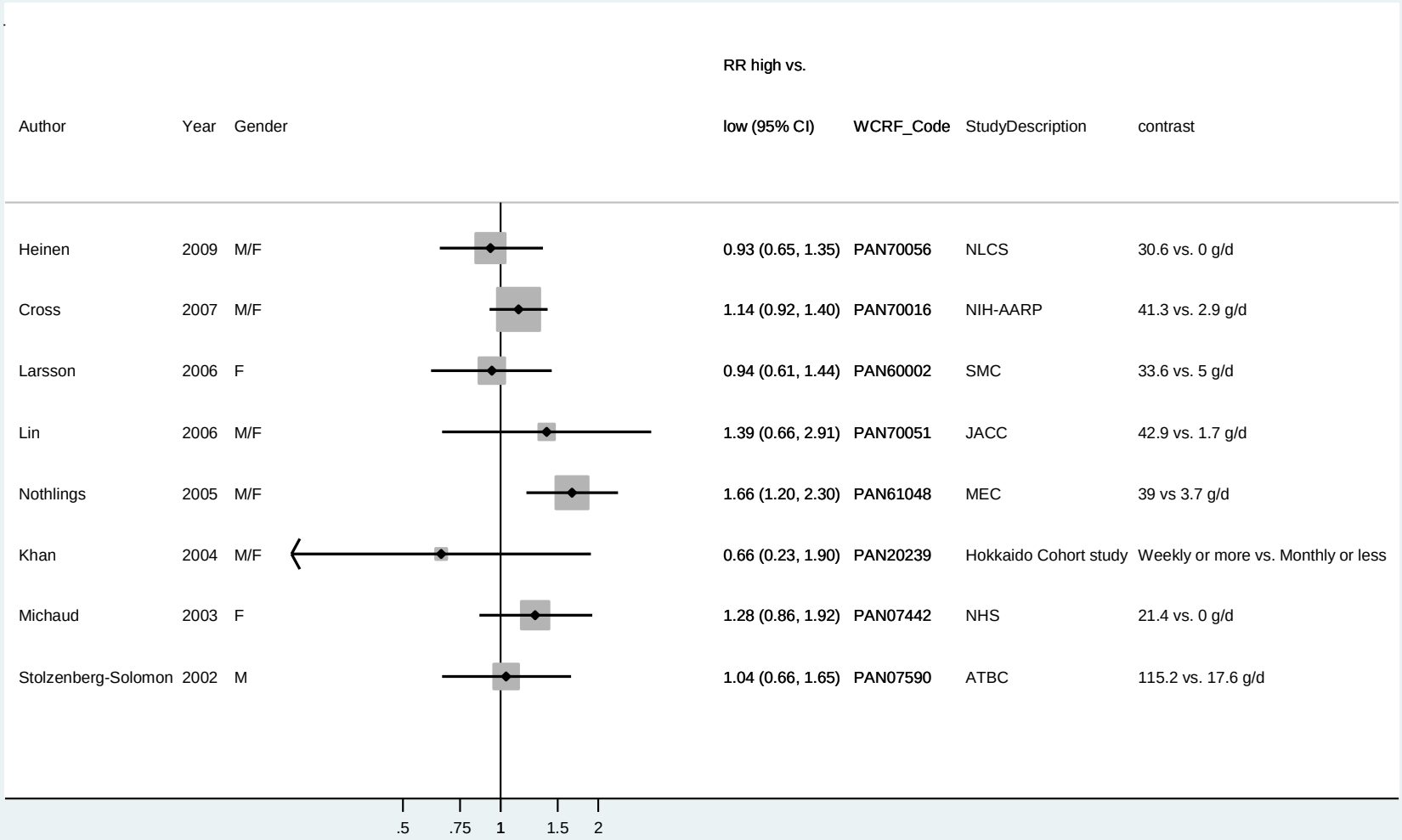


Figure 21 Dose-response meta-analysis of processed meat and pancreatic cancer - per 50 g/day

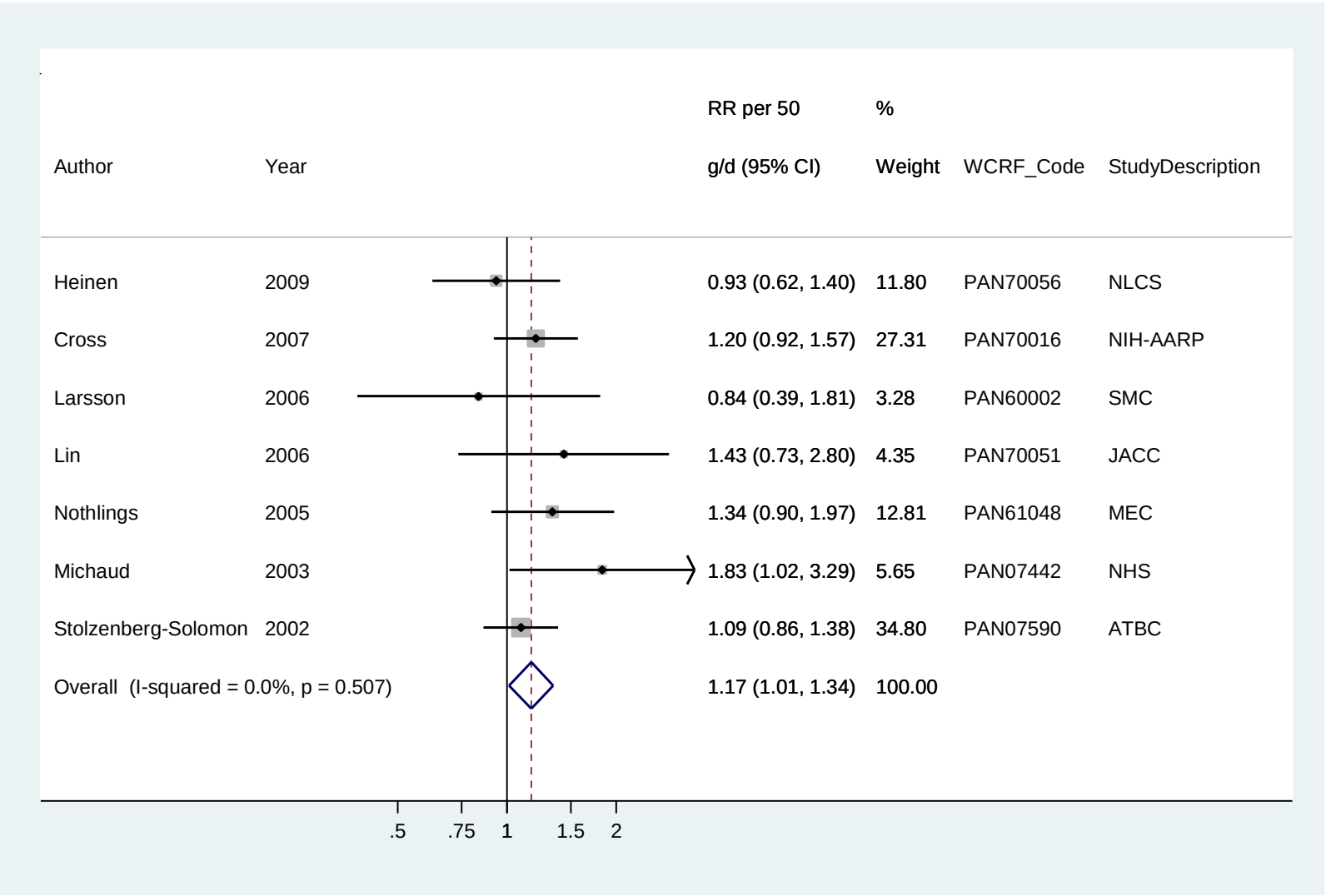


Figure 22 Dose-response graph of processed meat and pancreatic cancer

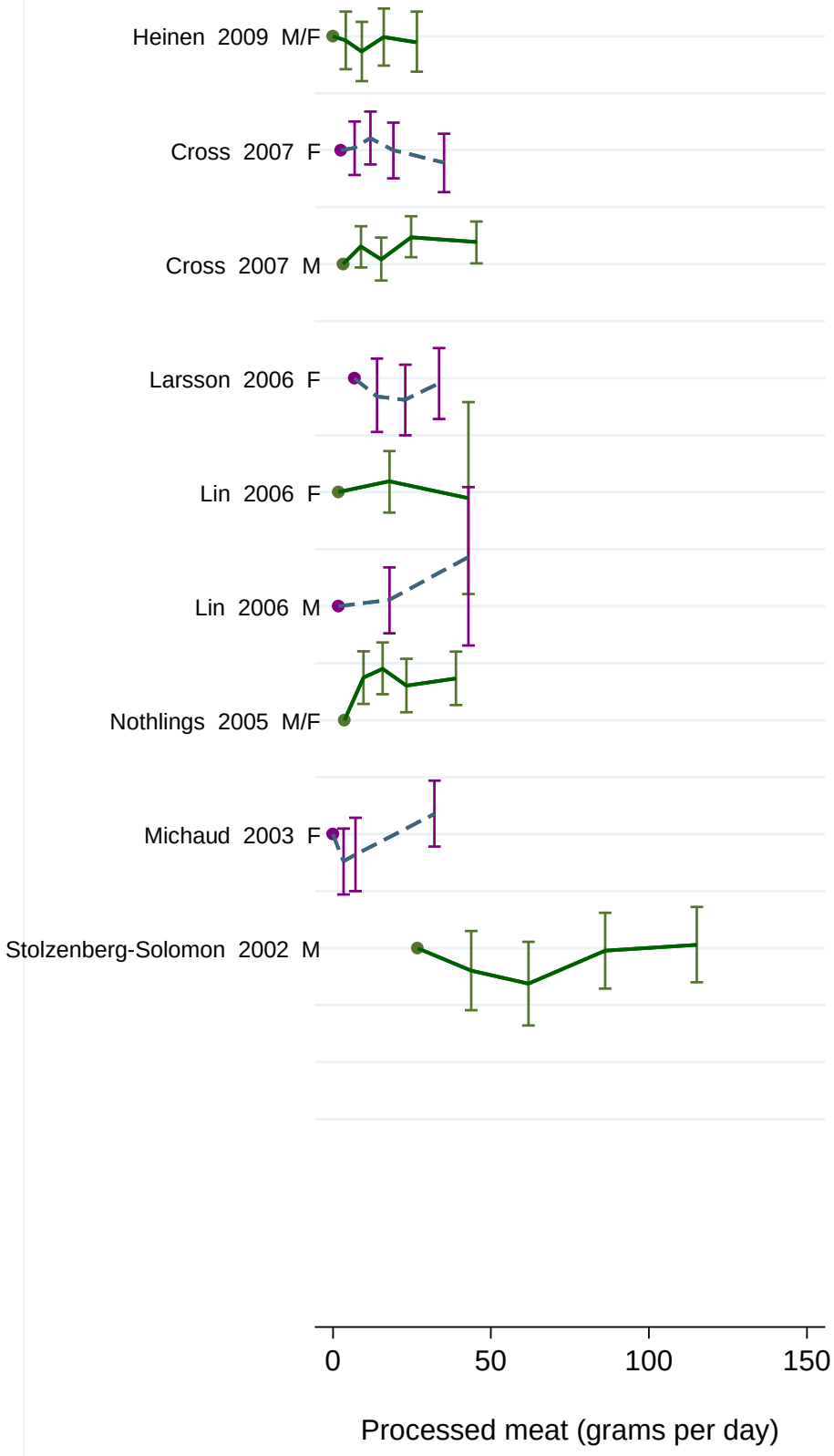
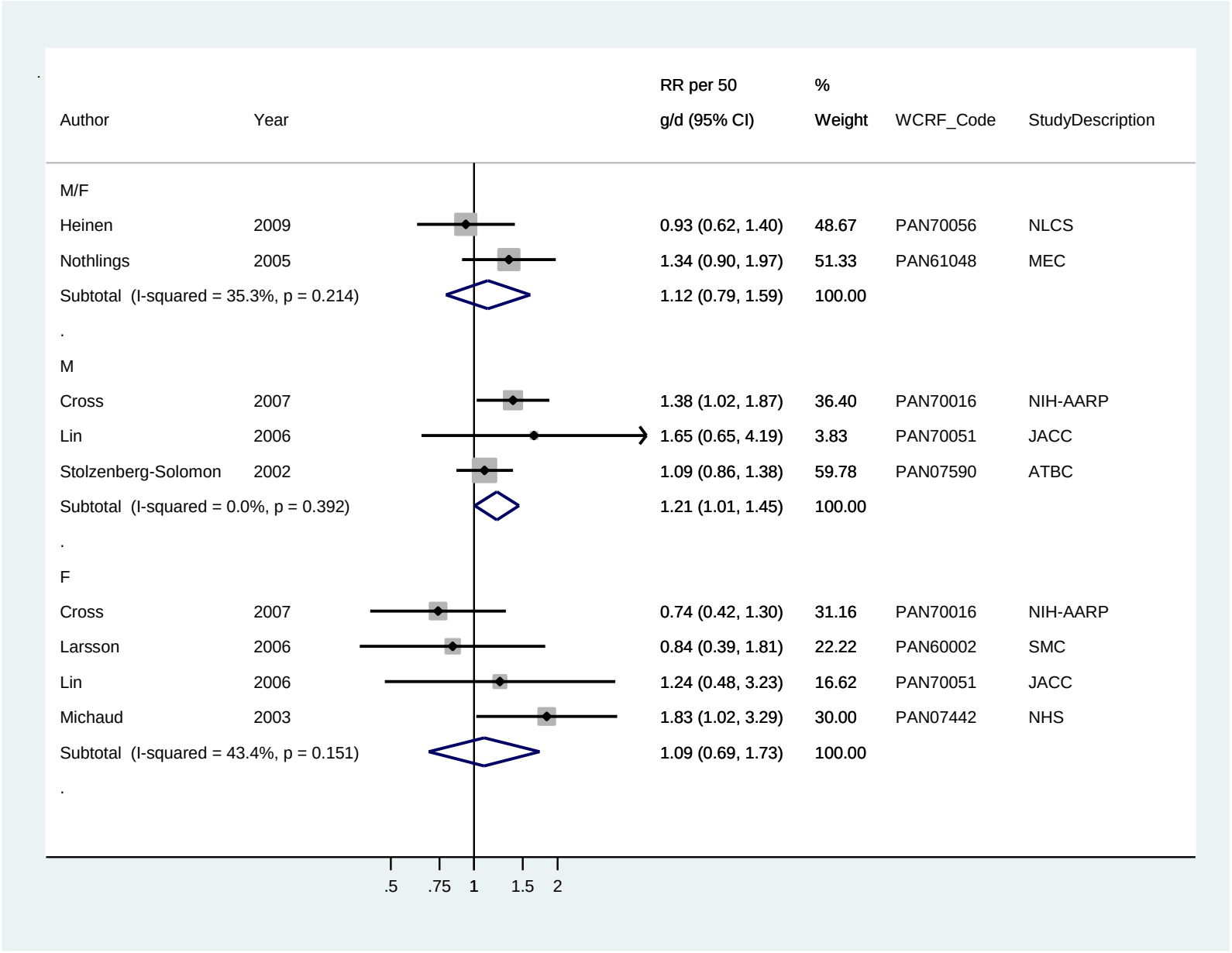


Figure 23 Dose-response meta-analysis of processed meat and pancreatic cancer, stratified by sex - per 50 g/day



2.5.1.3 Red meat

Methods

Overall 10 cohort studies (11 publications) on red meat and pancreatic cancer were identified, of which four publications from three cohort studies were identified in the Continuous Update Project.

Dose-response analyses and stratified analyses of red meat and pancreatic cancer risk were conducted. The dose-response results are presented for an increase of 100 grams per day. A serving size of 120 grams was used for converting the intake to grams per day in studies that reported intake by frequency.

Main results

Eight cohort studies were included in the meta-analysis (one cohort in pancreatic cancer mortality). Two other cohort studies did not provide enough data and were excluded from the meta-analysis: the Hokkaido Cohort Study (Khan et al, 2004) reported a non-significant positive association of pancreatic cancer mortality and red meat intake, and the Cancer Prevention Study II (Coughlin et al, 2000) reported no association.

The definition of red meat varied in the studies included in the meta-analysis. In two studies it was not clear if red and processed meats were combined into a group, in two studies red meat included also preserved or processed red meat (such as hot dogs, bacon, sausages, ham) and in two studies only fresh red meat was examined.

The summary RR per 100 g/d was 1.14 (95% CI: 0.95-1.38, I^2=47%, $P_{heterogeneity}$ =0.08) for pancreatic cancer incidence and 1.18 (95% CI: 0.98-1.45, I^2=52%, $P_{heterogeneity}$ =0.04) for studies on pancreatic cancer incidence and mortality. The summary RR ranged from 1.12 (95% CI: 0.94-1.33) when the Multiethnic Cohort Study (Nothlings et al, 2005) was excluded to 1.22 (95% CI: 1.04-1.42) when the Netherlands Cohort Study (Heinen et al, 2009) was excluded. There was no indication of publication bias with Egger's test, p=0.13.

Heterogeneity

There was evidence of moderate heterogeneity in the analyses. In the analysis stratified by sex there was a significant association among three studies of men, summary RR = 1.37 (1.03-1.83, I^2=43%), but not in four studies among women, summary RR = 1.06 (0.86-1.31, I^2=0%). The cohort studies included in the gender specific analyses were not the same for men and women with the exception of the NIH-AARP Diet and Health Study (Cross et al, 2007) that showed a positive significant trend in men but not in women.

Comparison with the Second Expert Report

In the systematic review of the 2007 expert report there was limited suggestive evidence that red meat intake increases pancreatic cancer risk, based on meta-analysis of two cohort studies and review of 5 additional cohort studies that were not included in the meta-analysis.

Published meta-analysis

A meta-analysis of six cohort studies reported a RR of 1.14 (95% CI: 0.94-1.38) for high vs. low red meat intake (Paluszkiewicz et al, 2011). Another recently published meta-analysis reported a RR of 1.13 (95% CI: 0.93-1.39) per 120 g/day increase in red meat intake (Larsson et al, 2012).

Table 26 Studies on red meat identified in the CUP

Author, year	Country	Study name	Number of cases	Years of Follow-up	Sex	RR	LCI	UCI	Contrast
Inoue-Choi, 2011	USA	Iowa Women's Health Study	256	16.3	F	0.97	0.65	1.44	9.0 vs. 2.0 serv/wk
Heinen, 2009	Netherlands	Netherlands Cohort Study	350	13.3	M F	0.75 0.98	0.52 0.94	1.09 1.02	145.9/130.4 vs. 45.8/36.2 g/d (m/w) Per 100 g/d
Cross, 2007	USA	NIH-AARP Diet and Health Study	1103	6.8	M F	1.43 0.92	1.11 0.64	1.83 1.32	67.0 vs. 12.0 g/1000 kcal/d 54.7 vs. 7.8 g/1000 kcal/d
Stolzenberg-Solomon, 2007	USA	NIH-AARP Diet and Health Study	836	5	M F	1.36 0.66	1.0 0.43	1.84 1.01	>54.7 vs. 19.0 g/1000 kcal/d >43.7 vs. 13.0 g/1000 kcal/d

Table 27 Overall evidence on red meat and pancreatic cancer

	Summary of evidence
SLR	Three cohort studies showed no significant association, while four cohort studies showed an increased risk which was significant in three of the studies.
Continuous Update Project	Three prospective studies (four publications) evaluated red meat intake and pancreatic cancer risk. One large study found an increased risk in men, but not in women, but two other studies found no association.

Table 28 Summary of results of the dose response meta-analysis on red meat and pancreatic cancer

Pancreatic cancer incidence		
	SLR	Continuous Update Project
Studies (n)	2	7
Cases (n)	341	2704
Increment unit	20 g/d	Per 100 g/d
RR (95% CI)	1.00 (0.95-1.05)	1.14 (0.95-1.38)
Heterogeneity (I^2, p-value)	0%, 0.8	47%, p=0.08

Pancreatic cancer incidence and mortality combined		
	SLR	Continuous Update Project
Studies (n)	-	8
Cases (n)	-	2761
Increment unit	-	Per 100 g/d
RR (95% CI)	-	1.19 (0.98-1.45)
Heterogeneity (I^2, p-value)	-	52%, p=0.04
By gender		
Men	-	1.43 (1.10-1.86), n=3
Heterogeneity (I^2,p-value)		27%, p=0.25
Women	-	1.06 (0.86-1.30), n=4
Heterogeneity (I^2,p-value)		0%, p=0.52

Table 29 Inclusion/exclusion table for meta-analysis of red meat intake and pancreatic cancer

WCRF code	Author	Year	Study design	Study name	Subgroup	Cancer outcome	SLR	CUP dose-response meta-analysis	CUP HvL forest plot	Estimated values	Exclusion reason
PAN70063	Inoue-Choi	2011	Prospective cohort study	Iowa Women's Health Study	Women	Incidence	New	Yes	Yes	Mid-exposure values, person-years	
PAN70056	Heinen	2009	Case cohort study	Netherlands Cohort Study	Men/women	Incidence	New	Yes	Yes		
PAN70017	Stolzenberg-Solomon	2007	Prospective cohort study	NIH-AARP Diet and Health Study	Men/women	Incidence	New	No	No		Duplicate, PAN70016 had a greater number of cases and was used for the analysis
PAN70016	Cross	2007	Prospective cohort study	NIH-AARP Diet and Health Study	Men/women	Incidence	New	Yes	Yes	Person-years	
PAN60002	Larsson	2006	Prospective cohort study	Swedish Mammography Cohort Study	Women	Incidence	Yes	Yes	Yes	Mid-exposure values	
PAN61048	Nothlings	2005	Prospective cohort study	Multiethnic Cohort Study	Men/women	Incidence	Yes	Yes	Yes	Person-years	
PAN20239	Khan	2004	Prospective cohort study	Hokkaido Cohort study	Men/women	Mortality	Yes	No	Yes		Only two categories
PAN07442	Michaud	2003	Prospective cohort study	Nurses' Health Study	Women	Incidence	Yes	Yes	Yes		
PAN07590	Stolzenberg-Solomon	2002	Prospective cohort study	ATBC Cohort Study	Male smokers	Incidence	Yes	Yes	Yes	Mid-exposure values, distribution of cases and person-years	
PAN07195	Coughlin	2000	Prospective cohort study	Cancer Prevention Study II	Men/women	Mortality	Yes	No	Yes		Quantities not provided
PAN07668	Zheng	1993	Prospective cohort study	Lutheran Brotherhood Cohort study	Men	Mortality	Yes	Yes	Yes	Quantities were not provided in the original publication, but were adopted from PRO03129	

Figure 24 Highest versus lowest forest plot of red meat and pancreatic cancer

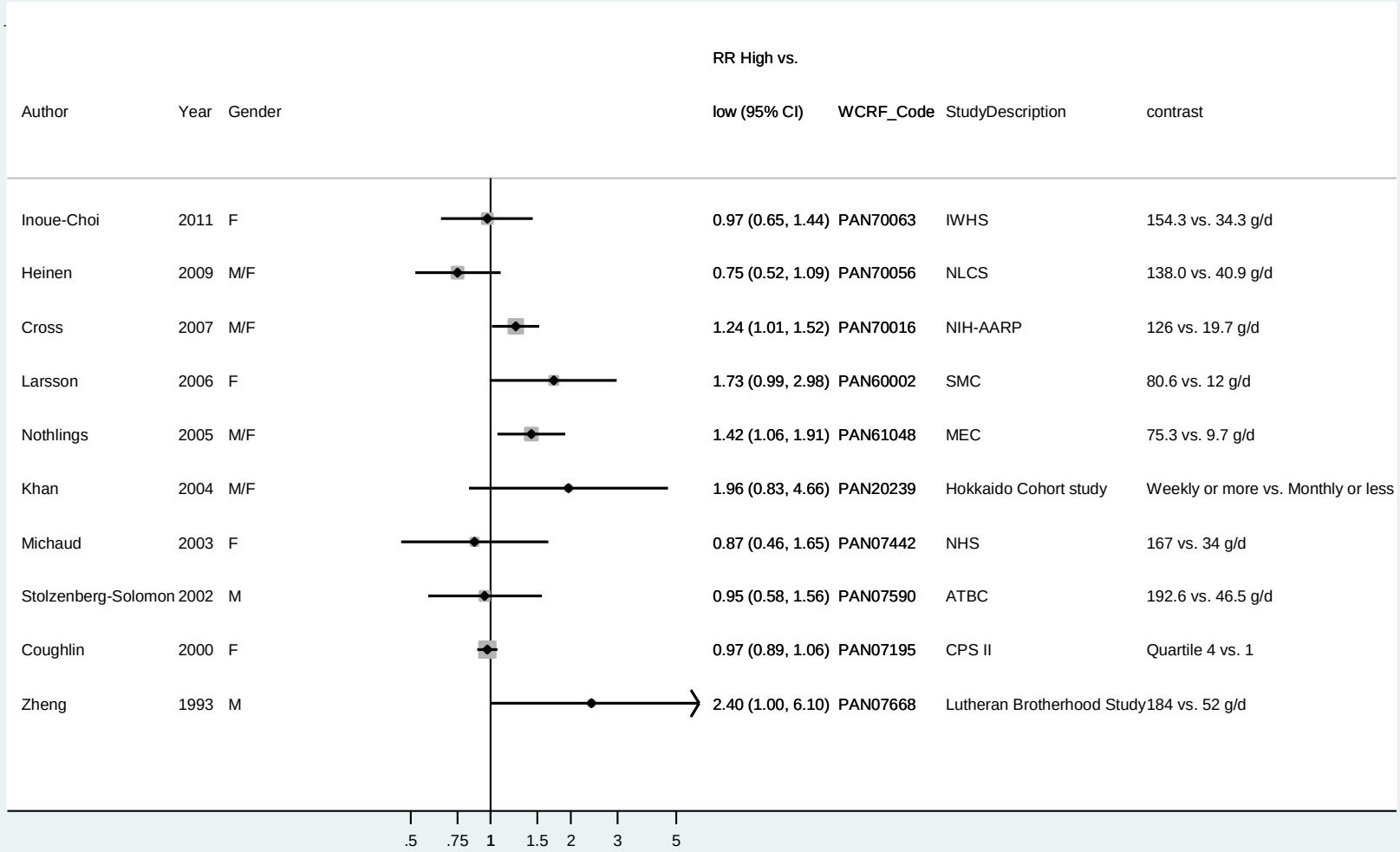


Figure 25 Dose-response meta-analysis of red meat and pancreatic cancer - per 100 g/d

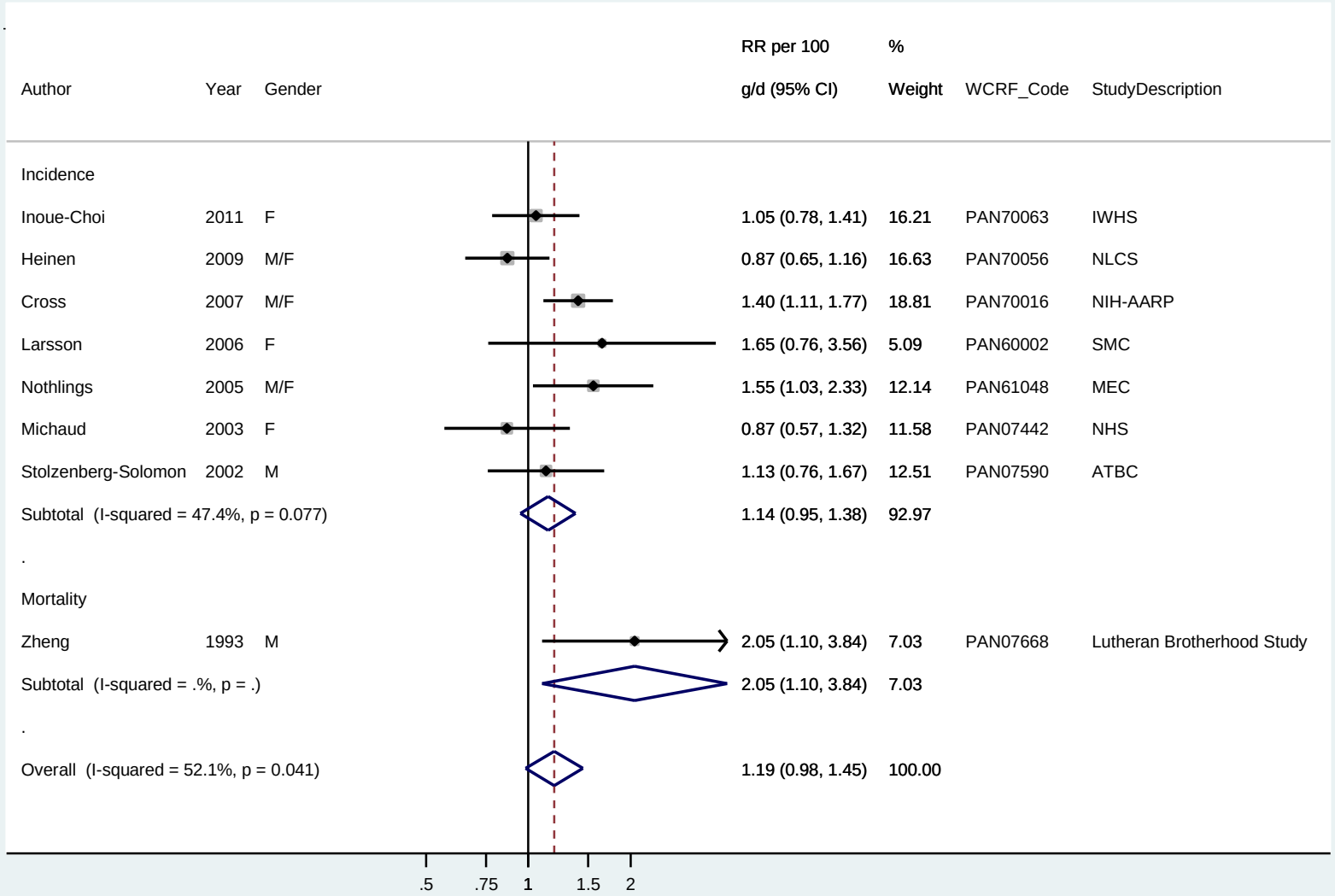


Figure 26 Funnel plot of red meat and pancreatic cancer

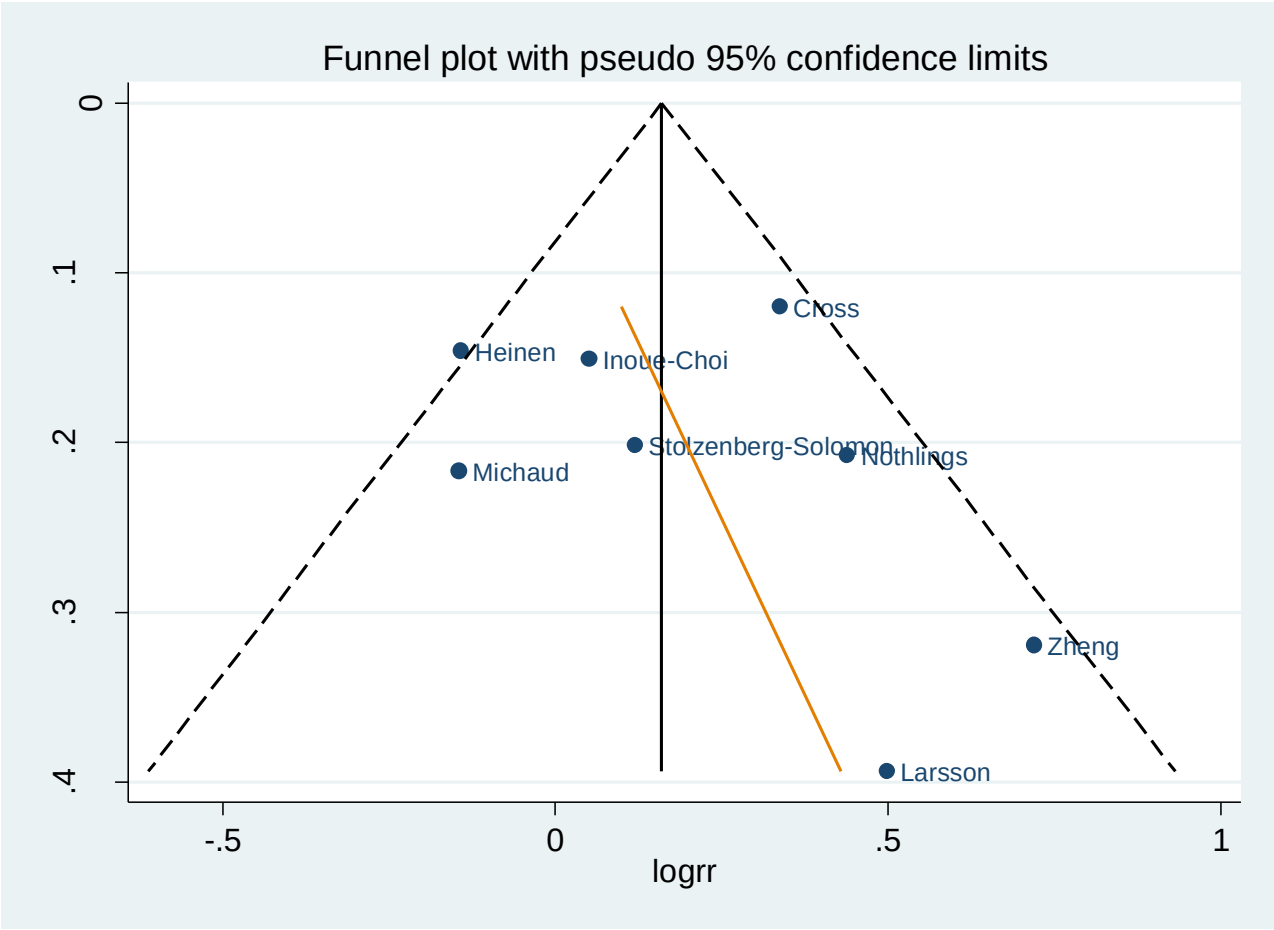


Figure 27 Dose-response graph of red meat and pancreatic cancer

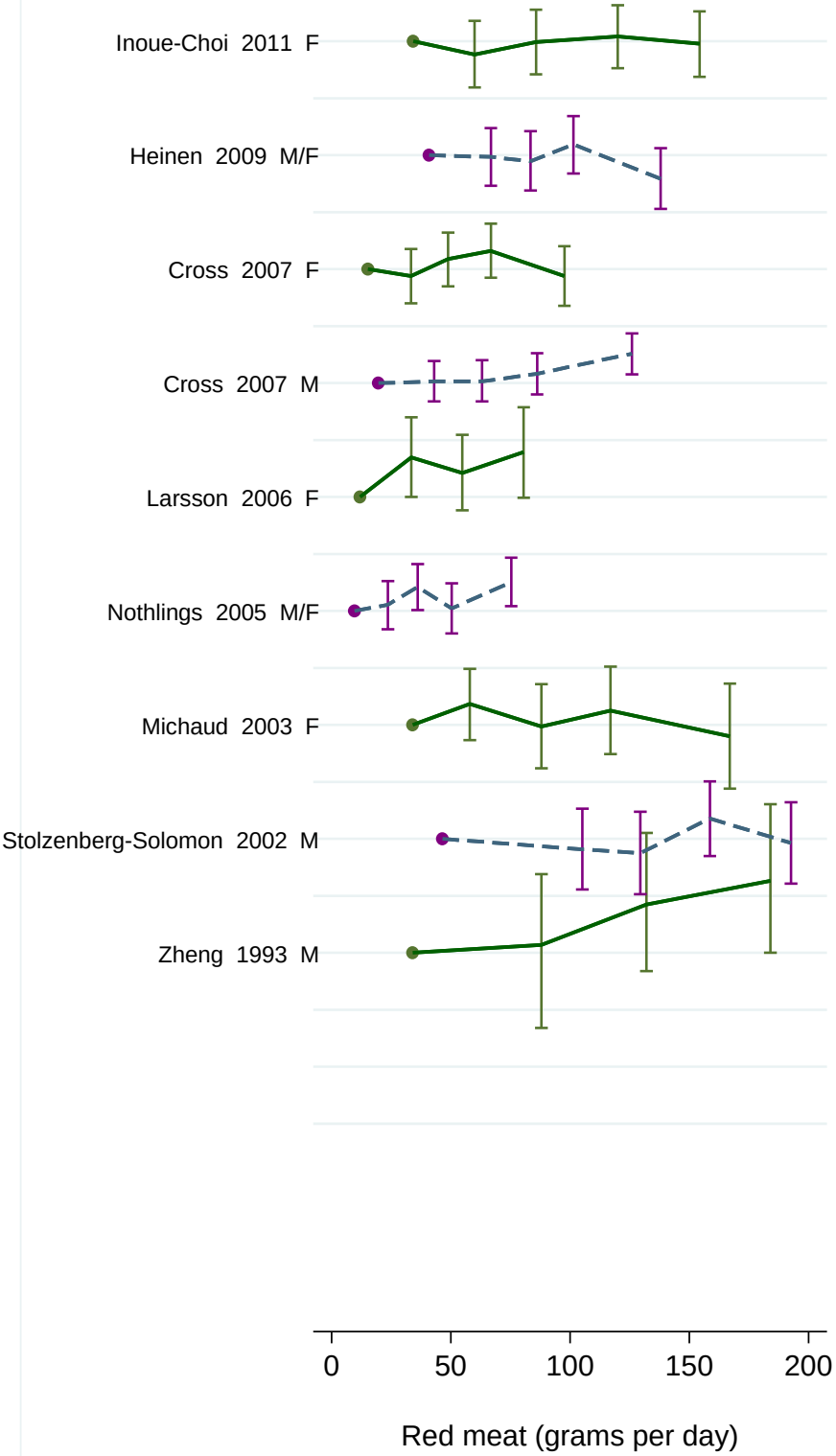
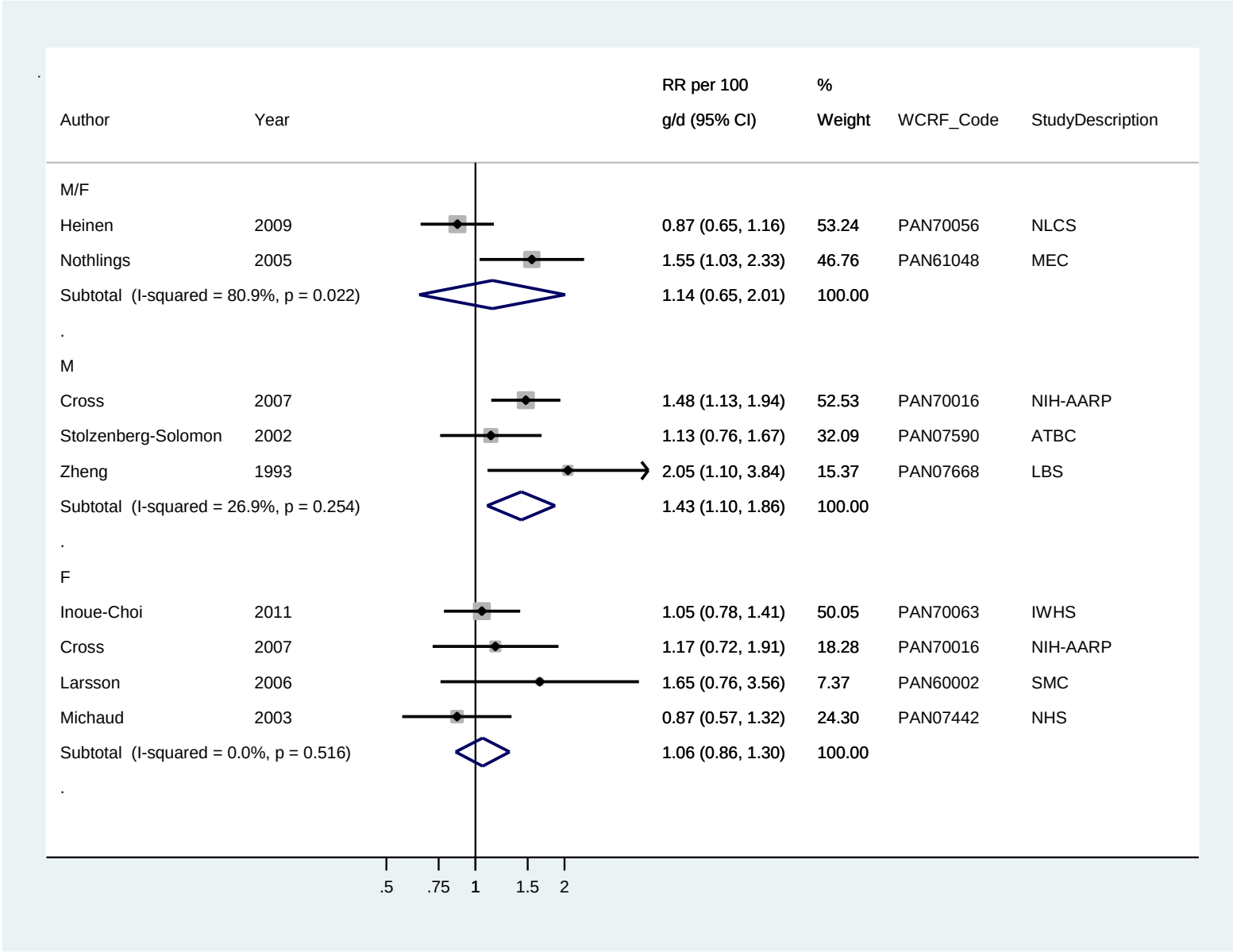


Figure 28 Dose-response meta-analysis of red meat and pancreatic cancer, stratified by sex - per 100 g/d



2.5.2 Fish

Methods

Ten cohort studies on fish and pancreatic cancer have been published up to September 2011. Three studies were identified during the CUP and 7 during the SLR for the Second Expert Report. Fish assessment varied across studies. In some studies total fish intake included all types of fish, shellfish and canned fish whereas in others shellfish was not included in the food group.

For the dose-response analyses all results were converted to a common scale (grams per day) and 120 grams was used as standard serving or portion size for studies that presented the intake only by frequency. The dose-response analyses were presented for an increment of 20 grams per day. Two studies (NIH-AARP, Daniel et al. 2011 and the MEC study, Nothlings et al, 2005) presented the fish intake in grams per 1000 kcal and these were converted to absolute intakes using the median energy intake reported by the study.

Main results

Seven studies were included in dose-response meta-analysis (3 studies identified during the CUP and 4 studies identified during the 2007 SLR). Two studies on mortality were not included because fish intake was categorized only into two groups (Khan et al, 2004; Hirayama et al, 1990), and a third study because amount or frequency of intake was not reported (Zheng et al, 1993). No associations were seen in the studies excluded from the meta-analysis.

The summary RR per 20g/day was 1.03 (95% CI: 0.97-1.08; I^2= 0%, $P_{heterogeneity}$=0.76, 7 studies) for incidence and mortality of pancreatic cancer. The observed associations were similar for men and women, RR per 20g/day was 1.02 (95% CI: 0.89-1.15) for women and 0.98 (95% CI: 0.89-1.08) in men.

The overall results remained the same when one study with mortality as outcome was excluded from the analysis (RR: 1.03, 95% CI: 0.97-1.10). The RR ranged from 1.00 (95% CI: 0.93-1.07) when excluding the NIH-AARP (Daniel et al, 2011) to 1.03 (95% CI: 0.98-1.09) when excluding the ATBC study (Stolzenberg-Solomon et al, 2002).Sensitivity analyses to explore the effect of expressing servings in grams using a standard portion size were conducted as the number of studies allowed it. Similar results were obtained when the analyses were restricted to the four studies that reported intake in grams per day (RR per 20g/day: 1.02 (95% CI: 0.96-1.09; $P_{heterogeneity}$=0.57) and to the three studies that reported intake in frequency (RR per an increase of one serving/week: 1.06; 95% CI: 0.87-1.29).

Heterogeneity

There was no evidence of heterogeneity (I^2= 0%, p=0.76) between studies. Egger's tests suggested no evidence of publication bias (p=0.20).

Comparison with the Second Expert Report

Overall, fish was not associated with the risk of pancreatic cancer. The RR for an increase of 20g/day = 1.02 (95%CI: 0.97-1.07) in the updated report. The only study with information available for meta-analysis in the 2007 SLR was the study of Stolzenberg-Solomon et al, 2002 (RR per 20g/day: 1.00; 95% CI: 0.86, 1.15).

Table 30 Studies on fish intake identified in the CUP

Author, year	Country	Study name	Cases	Years of follow up	Sex	RR	LCI	UCI	Contrast
Daniel, 2011	USA	NIH- AARP Diet and Health Study	1727	9	M/F	1.12	0.96	1.31	21.4 vs 3.6 g/1000 kcal
Heinen, 2009	Netherlands	The Netherlands Cohort study	350	13.3	M/F	1.05	0.75	1.47	>=20 g/day vs none
Lin, 2006	Japan	Japan Collaborative Cohort study for Evaluation of Cancer Risk	300	9.4	M F	1.27 0.88	0.58 0.45	2.77 1.73	5/7 vs 0-2 times a week

Table 31 Overall evidence on fish intake and pancreatic cancer

	Summary of evidence
SLR	Seven studies were identified but only one study was considered suitable for dose-response meta-analysis (the ATBC cohort of male smokers; RR= 1.00 (95% CI: 0.86-1.15) per 20 g/day). None of the studies reported an association of fish consumption and risk of pancreatic cancer.
Continuous Update Project	Three cohort studies were identified. None reported significant associations between fish consumption and pancreatic cancer.

Table 32 Summary of results of the dose response meta-analysis on fish intake and pancreatic cancer

Pancreatic cancer		
	SLR	Continuous Update Project
Studies (n)	-	7
Cases (n)	-	3372
Increment unit used	-	Per 20g/day
Overall RR (95%CI)	-	1.03 (0.97-1.08)
Heterogeneity (I^2,p-value)	-	0%, p=0.76
Stratified analysis		
Men		
RR (95%CI)	-	0.98 (0.89-1.08)
Heterogeneity (I^2,p-value)		0%, p=0.66
Studies		2
Cases (n)		294
Women		
RR (95%CI)	-	1.02(0.89-1.15)
Heterogeneity (I^2,p-value)		24.1%, p=0.27
Studies		3
Cases (n)		487
	Sensitivity analysis	
Fish intake in grams		
Studies	-	4
Cases (n)		2722
Increment unit used		20g/day
Overall RR (95%CI)		1.02 (0.96-1.09)
Heterogeneity (I^2,p-value)		0%, p=0.57
Fish intake in serving/week	-	
Studies		3
Cases (n)		650
Increment unit used		Per 1 serving/week
Overall RR (95%CI)		1.03 (0.94-1.13)
Heterogeneity (I^2,p-value)		0%, p=0.38

Table 33 Inclusion/exclusion table for meta-analysis on fish intake and pancreatic cancer

WCRF_ Code	Author	Year	Study Design	Study Name	Subgroup	Cancer Outcome	SLR	CUP dose-response meta-analysis	CUP HvL forest plot	Estimated values	Exclusion reasons
PAN70069	Daniel	2011	Prospective Cohort study	NIH- AARP Diet and Health Study	Men/Women	Incidence	New	Yes	Yes	Cases and person/ years per quintile g/day per quintile and mid-exposure values	
PAN70056	Heinen	2009	Prospective Cohort study	The Netherlands Cohort study	Men/Women	Incidence	New	Yes	Yes	Mid-exposure values, person years per quintile	
PAN70051	Lin	2006	Prospective Cohort study	Japan Collaborative Cohort study for Evaluation of Cancer Risk	Men/Women	Mortality	New	Yes	Yes	Mid-exposure values	
PAN60002	Larsson	2006	Prospective Cohort study	Sweden mammography screening cohort	Women	Incidence	Yes	Yes	Yes	Mid-exposure values	
PAN61048	Nöthlings	2005	Prospective Cohort study	Hawaii-Los Angeles Multiethnic Cohort (MEC) Study	Men/Women	Incidence	Yes	Yes	Yes	Person/ years per quintile	
PAN20239	Khan	2004	Prospective Cohort study	Hokkaido Cohort, Japan	Men/Women	Mortality	Yes	No	Yes		Only two categories
PAN07442	Michaud	2003	Prospective Cohort study	The Nurses' Health Study Cohort	Women	Mortality /incidence	Yes	Yes	Yes	Mid-exposure values	
PAN07590	Stolzenberg-Solomon	2002	Prospective Cohort study	Alpha Tocopherol Beta Carotene Cancer Prevention Study - Finland	Men	Incidence	Yes	Yes	Yes	Mid-exposure values , cases/person-years per quintile	

PAN07668	Zheng	1993	Prospective Cohort study	Lutheran Brotherhood Cohort study, USA	Men	Mortality	Yes	No	Yes		no information on exposure frequency or intake
PAN00247	Hirayama	1990	Prospective Cohort study	6 Prefecture Cohort, Japan	Men/Women	Mortality	Yes	No	Yes		Only two categories

Figure 29 Highest versus lowest forest plot of fish intake and pancreatic cancer

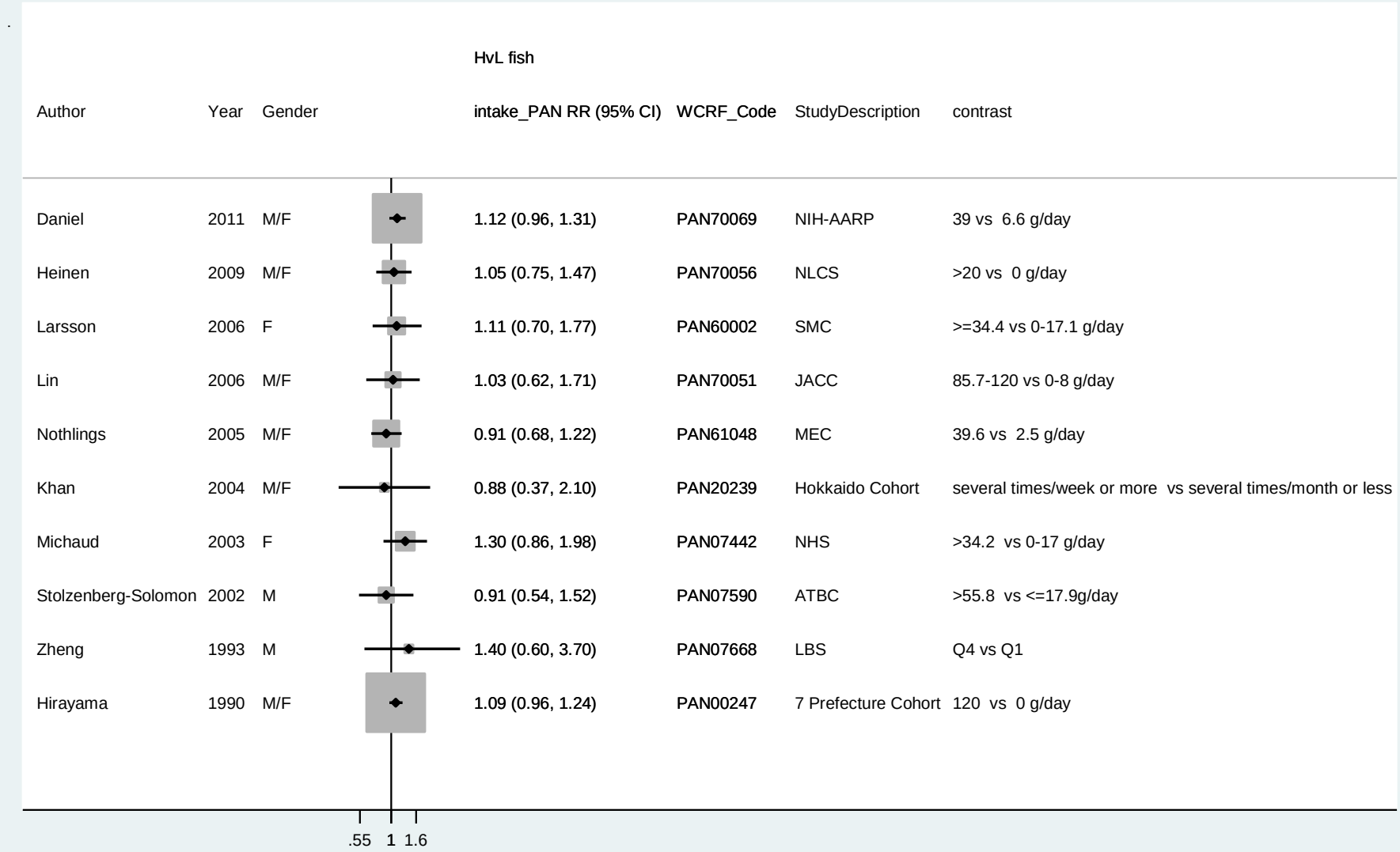


Figure 30 Dose-response meta-analysis of fish intake and pancreatic cancer – per 20g/day

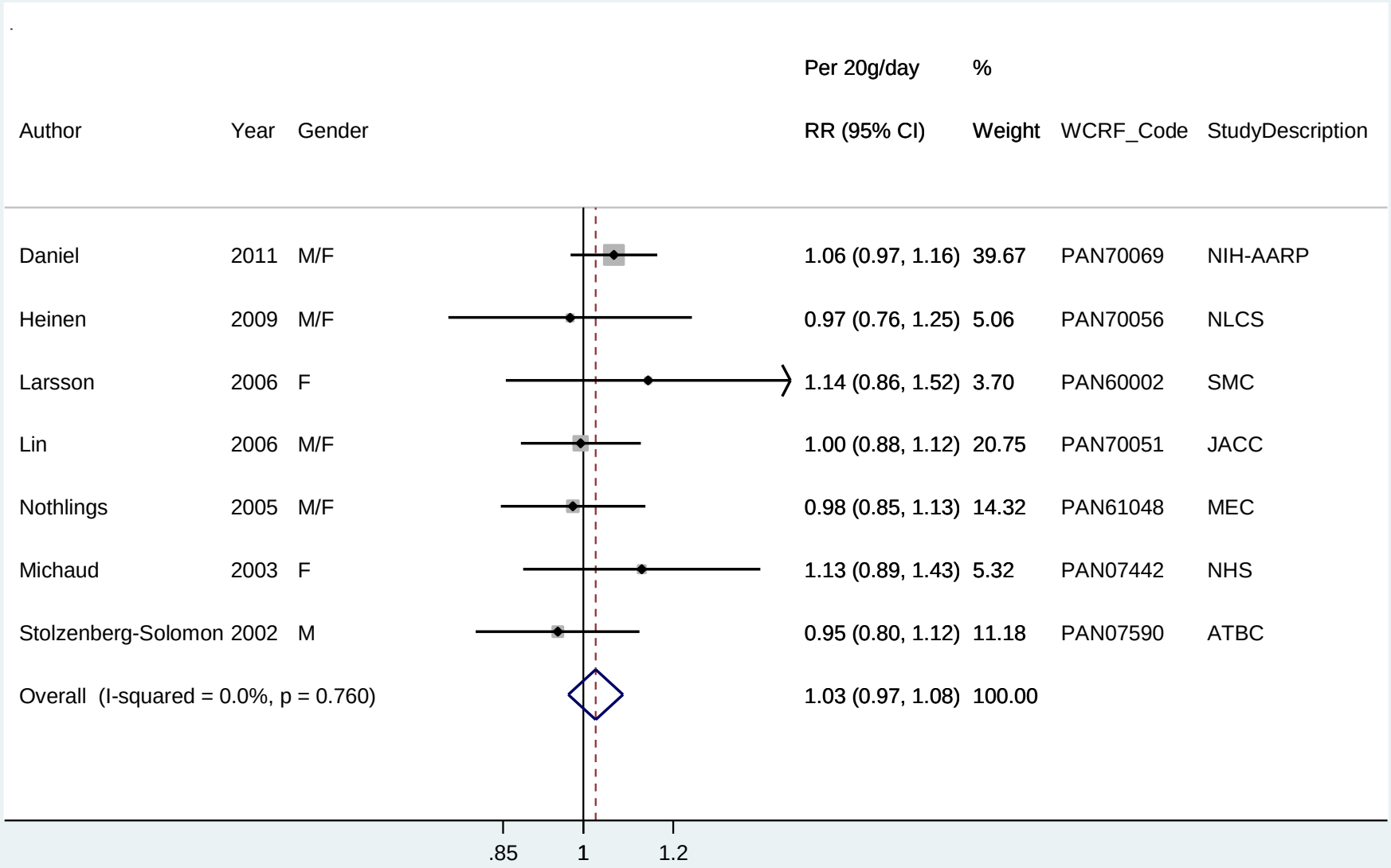


Figure 31 Funnel plot of fish intake and pancreatic cancer

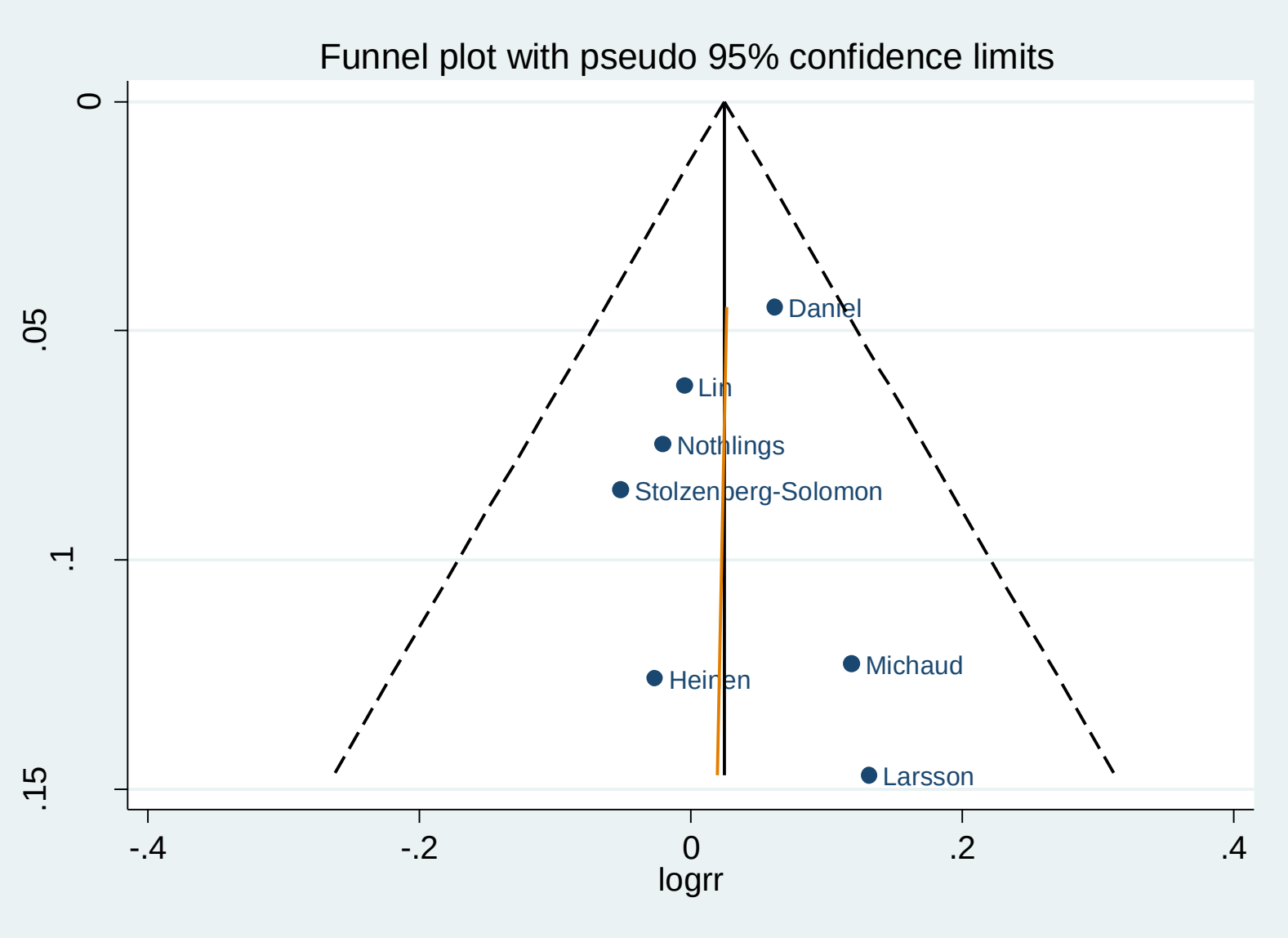


Figure 32 Dose-response graph of fish intake and pancreatic cancer

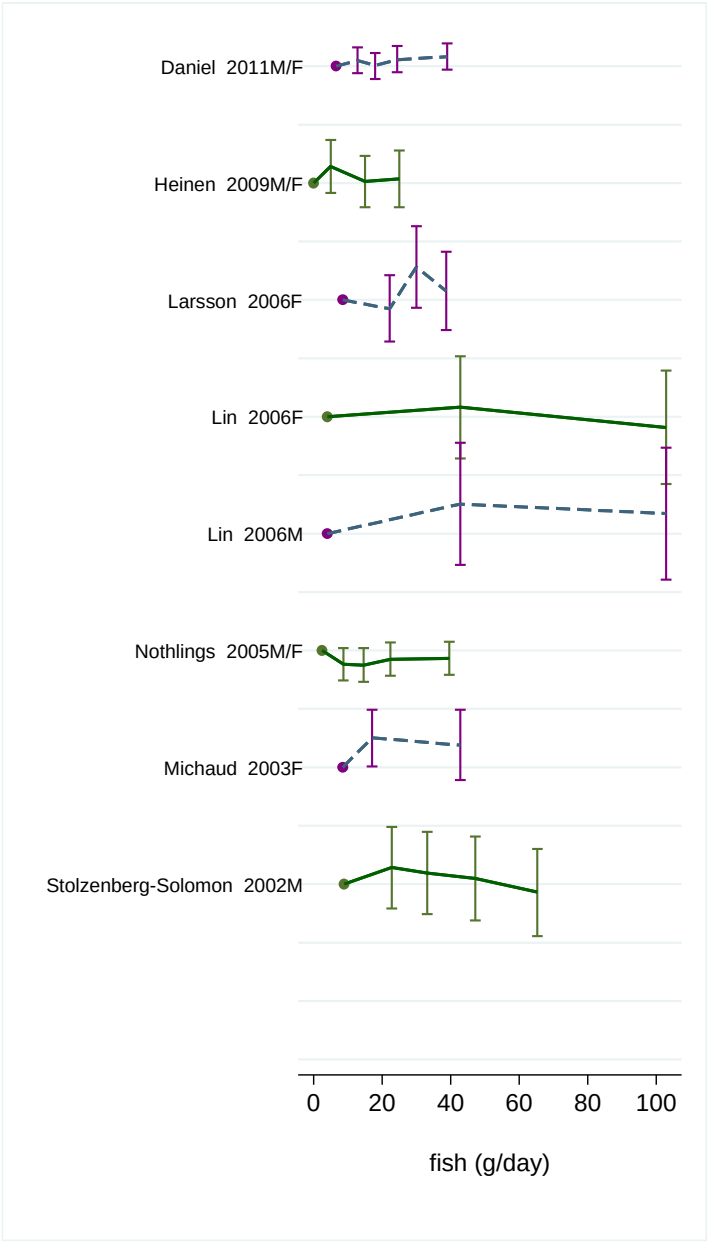


Figure 33 Dose-response meta-analysis of fish intake and pancreatic cancer, stratified by sex – per 20g/day

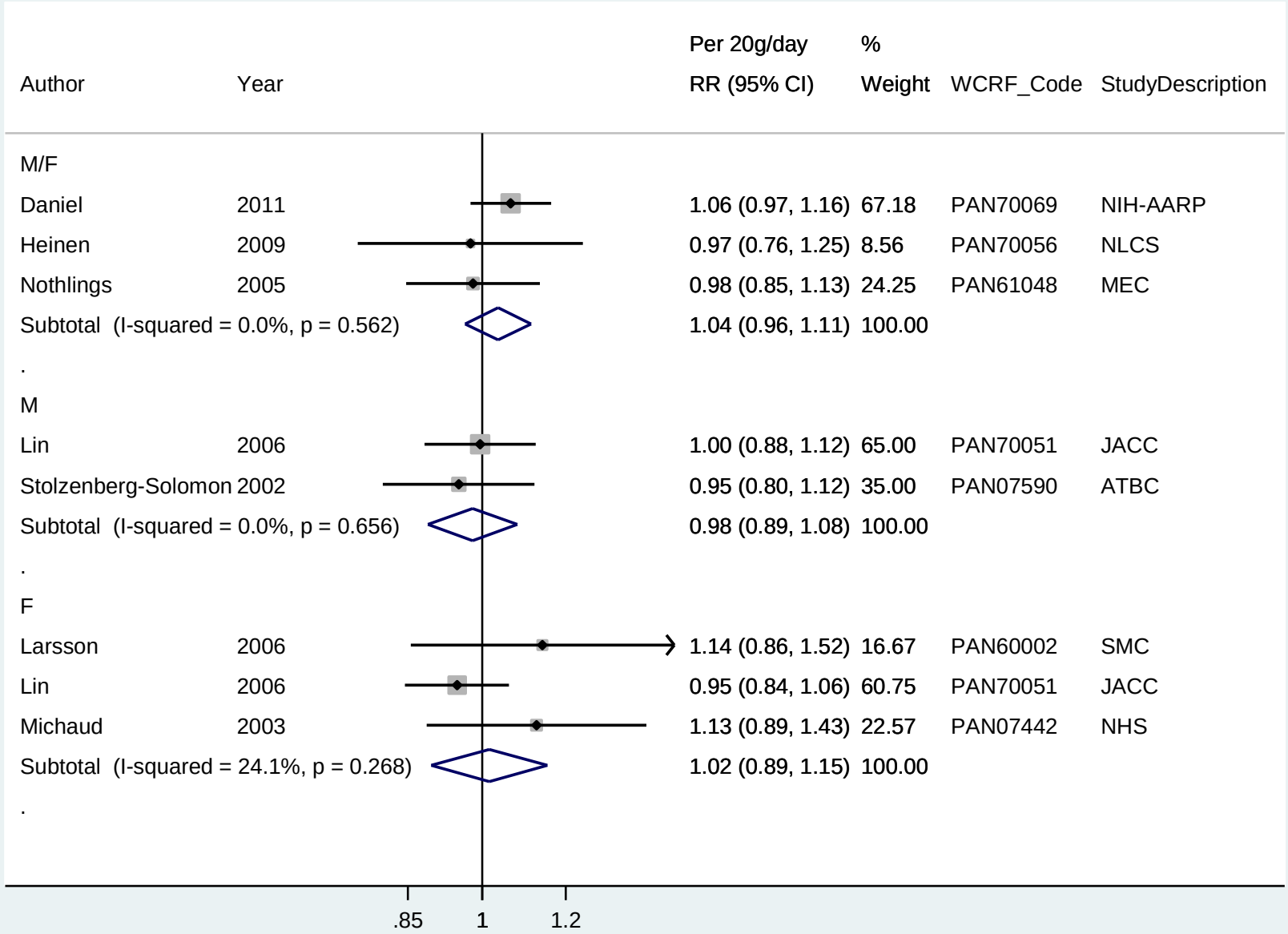


Figure 34 Dose-response meta-analysis of fish intake and pancreatic cancer, stratified by outcome type – per 20g/day

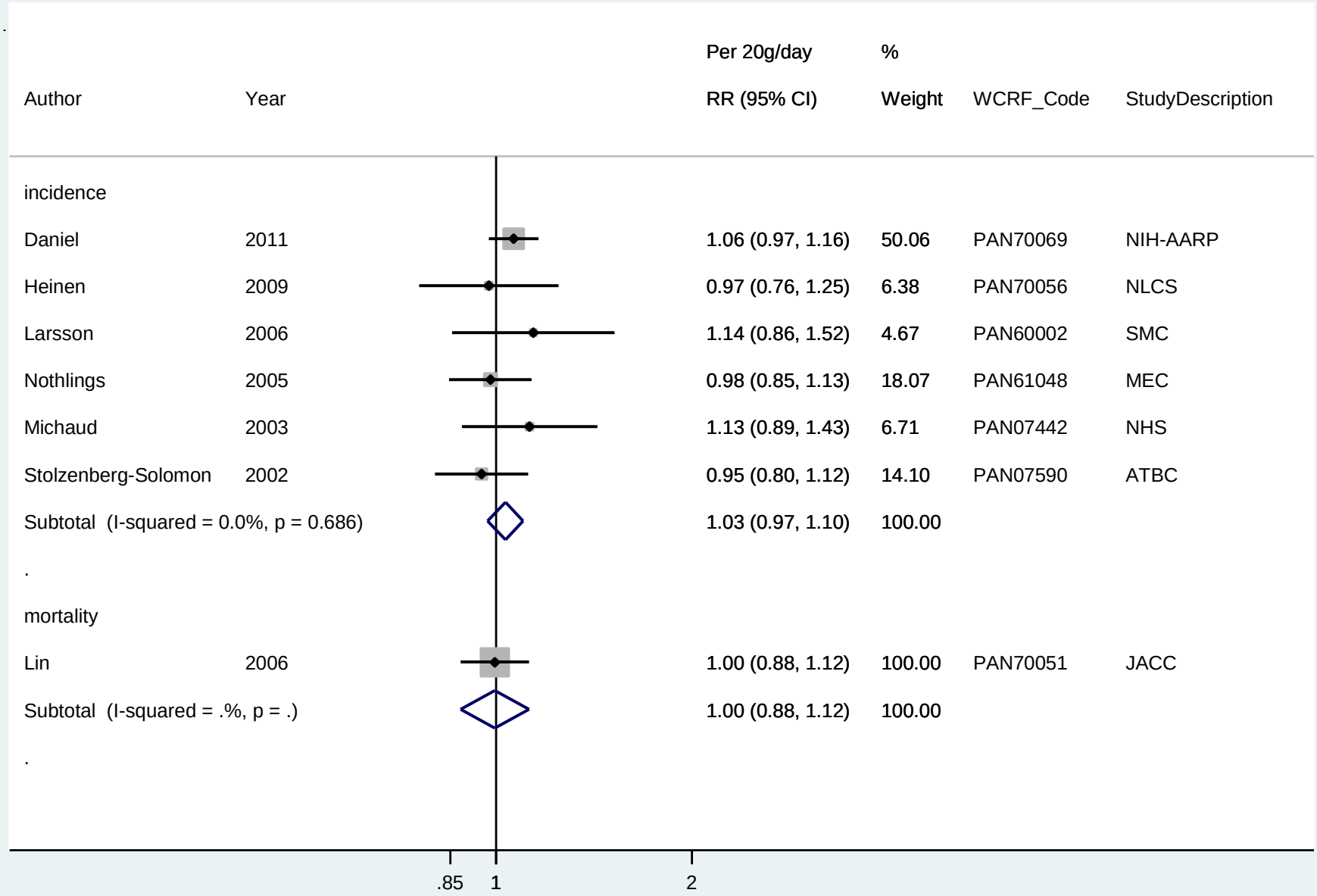
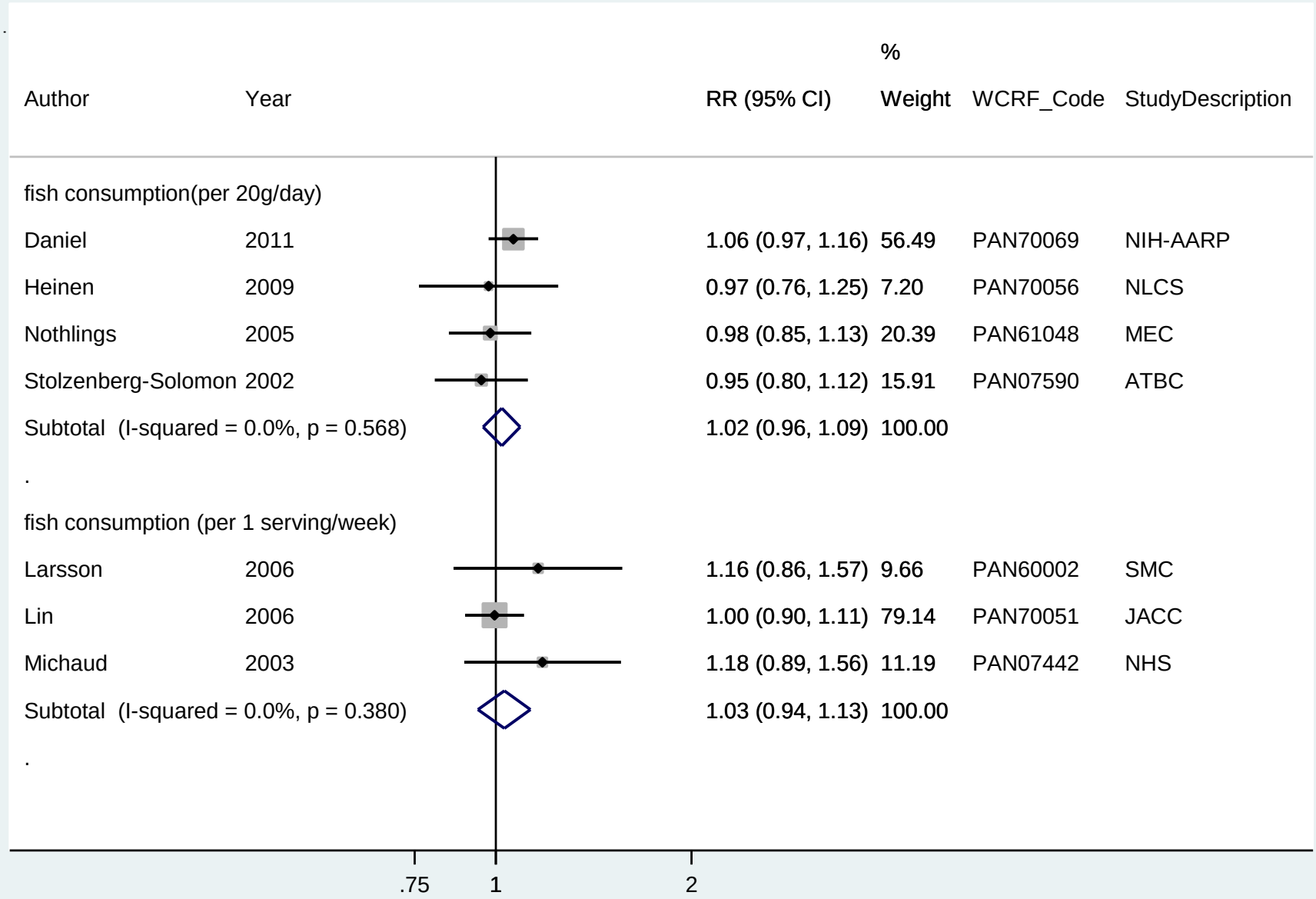


Figure 35 Dose-response meta-analysis of fish intake and pancreatic cancer, stratified by exposure type



2.5.4 Egg

Methods

Up to September 2011, reports from nine cohort studies were identified, two of which were identified during the CUP. The dose-response meta-analysis for pancreatic cancer performed in the previous SLR report included three studies. In the updated meta-analysis, 6 studies (2 studies identified during the CUP and 4 studies identified during the 2007 SLR) were included.

Main results

The summary RR per 20 g/day was 1.02 (95%CI: 0.90-1.17; $P_{heterogeneity}$=0.26, 6 studies) for pancreatic cancer incidence and mortality. The overall results remained the same when one study with mortality as outcome was excluded from the analysis, RR= 1.01 (95% CI: 0.88-1.16). The RR ranged from 0.99 (95% CI: 0.85-1.15) when excluding the NHS (Michaud et al, 2003) to 1.04(95% CI: 0.84-1.29) when excluding the MEC study (Nöthlings et al, 2005).

Heterogeneity

Low heterogeneity was observed (I^2= 22.1%, p=0.26). In stratified analysis by sex, the RR for males was 1.02 (95% CI: 0.87-1.20) and 1.14 (95%: 0.81-1.59) for females. Egger's tests did not show evidence of publication bias (p=0.96).

Comparison with the Second Expert Report

The results are consistent with the previous conclusion of no evidence of an association between the egg intake and pancreatic cancer.

Table 34 Studies on egg consumption identified in the CUP

Author, year	Country	Study name	Cases	Years of follow up	Sex	RR	LCI	UCI	Contrast
Heinen, 2009	Netherlands	The Netherlands Cohort study	350	13.3	M/F	0.85	0.60	1.22	28.5 vs 7.1 g/day
Skinner, 2006	USA	Nurse's Health Study and Health Professionals Follow-Up Study	365	16	M/F	0.87	-	-	Highest vs lowest

Table 35 Overall evidence on egg consumption and pancreatic cancer

	Summary of evidence
SLR	Data were extracted from 7 prospective cohort studies. Of these, 3 provided data in a format appropriate for inclusion in a meta-analysis. The summary relative risk from the cohort studies was 1.10 (95% CI: 0.90 to 1.36) per 20 g/day (p=0.09). Studies not included in the meta-analysis showed non-significant and inconsistent associations.
Continuous Update Project	Two cohort studies were identified. Both reported on male and female. None of the studies found an association between egg consumption and pancreatic cancer.

Table 36 Summary of results of the dose response meta-analysis of egg consumption and pancreatic cancer

Pancreatic cancer		
	SLR	Continuous Update Project
Studies (n)	3	6
Cases (n)	381	1385
Increment unit used	Per 20g/day	Per 20g/day
Overall RR (95%CI)	1.10 (0.90 -1.36)	1.02 (0.90-1.17)
Heterogeneity (I^2,p-value)	59%, p=0.09	22.1%, p=0.26
Stratified analysis		
Men	-	1.02 (0.87-1.20) (n=1)
Heterogeneity (I^2,p-value)		-
Women		1.14(0.81-1.59) (n=2)
Heterogeneity (I^2,p-value)		0%, p=0.53

Table 37 Inclusion/exclusion table for meta-analysis of egg consumption and pancreatic cancer

WCRF_ Code	Author	Year	Study Design	Study Name	Subgroup	Cancer Outcome	SLR	CUP dose-response meta-analysis	CUP HvL forest plot	Estimated values	Exclusion reasons
PAN70056	Heinen	2009	Prospective Cohort study	The Netherlands Cohort study	Men /Women	Incidence	New	Yes	Yes	Mid-exposure values	
PAN70024	Skinner	2006	Prospective Cohort study	Nurse's Health Study and Health Professionals Follow-Up Study	Men /Women	Incidence	New	No	No		Not enough data on egg as exposure
PAN60002	Larsson	2006	Prospective Cohort study	Swedish Mammography Cohort (SMC)	Women	Incidence	Yes	Yes	Yes	Mid-exposure values	
PAN61048	Nöthlings	2005	Prospective Cohort study	Hawaii-Los Angeles Multiethnic Cohort (MEC) Study	Men /Women	Incidence	Yes	Yes	Yes	person-years per quintile	
PAN20239	Khan	2004	Prospective Cohort study	Hokkaido Cohort, Japan	Men /Women	Mortality	Yes	No	Yes (women)		Unable to accurately quantify exposure levels
PAN07442	Michaud	2003	Prospective Cohort study	Nurse's Health Study	Women	Mortality /incidence	Yes	Yes	Yes	Mid-exposure values	
PAN07590	Stolzenberg -Solomon	2002	Prospective Cohort study	Alpha Tocopherol Beta Carotene Cancer Prevention Study - Finland	Men	Incidence	Yes	Yes	Yes	Mid-exposure values , cases/person-years per quintile	
PAN07668	Zheng	1993	Prospective Cohort study	Lutheran Brotherhood Insurance Society	Men	Mortality	Yes	No	No		Eggs and dairy products as exposure
PAN07449	Mills	1988	Prospective Cohort study	Californian Seventh Day Adventists	Men /Women	Mortality	Yes	Yes	Yes	Mid-exposure values	

Figure 36 Highest versus lowest forest plot of egg consumption and pancreatic cancer

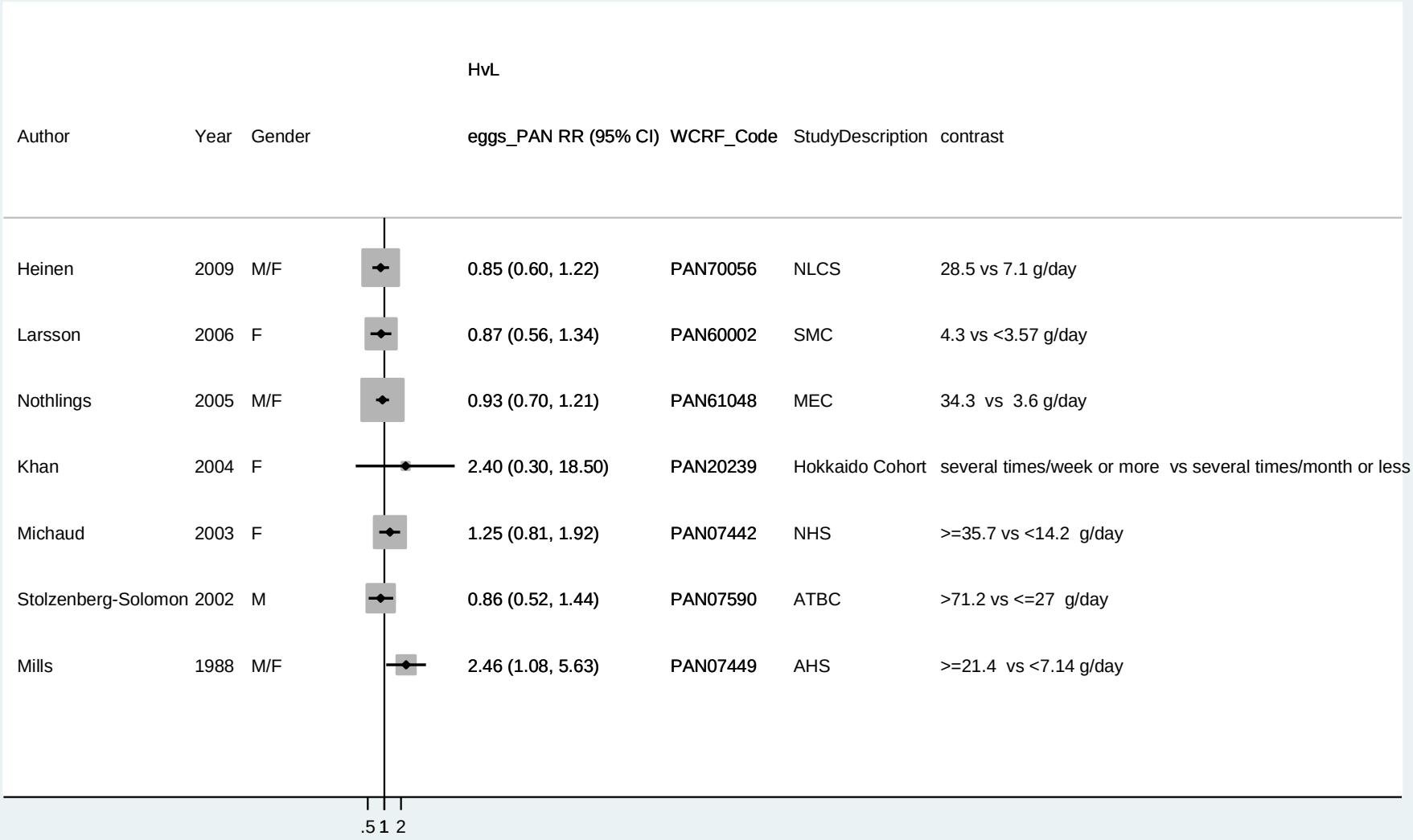


Figure 37 Dose-response meta-analysis of egg consumption and pancreatic cancer – per 20g/day

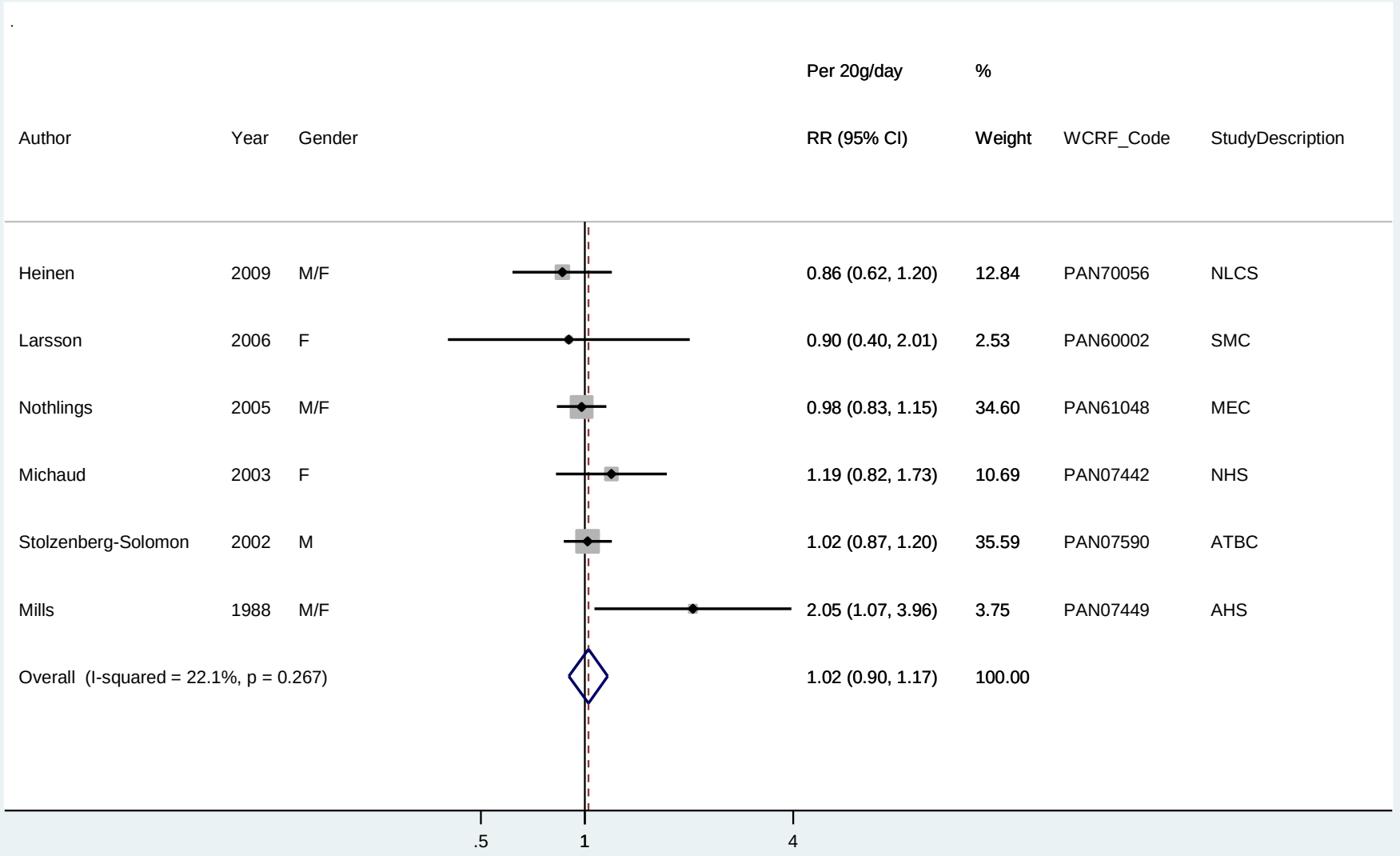


Figure 38 Funnel plot of egg consumption and pancreatic cancer

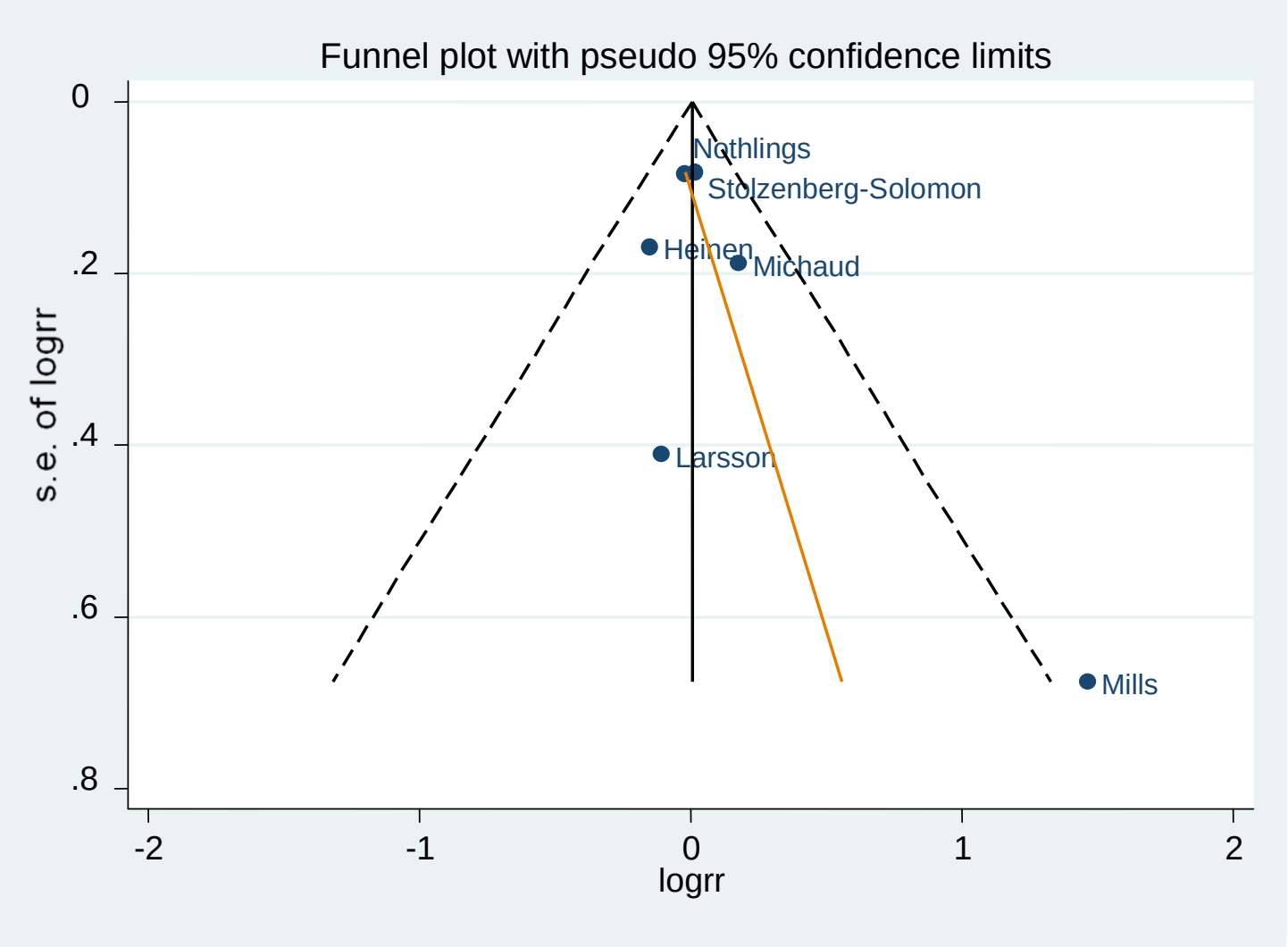
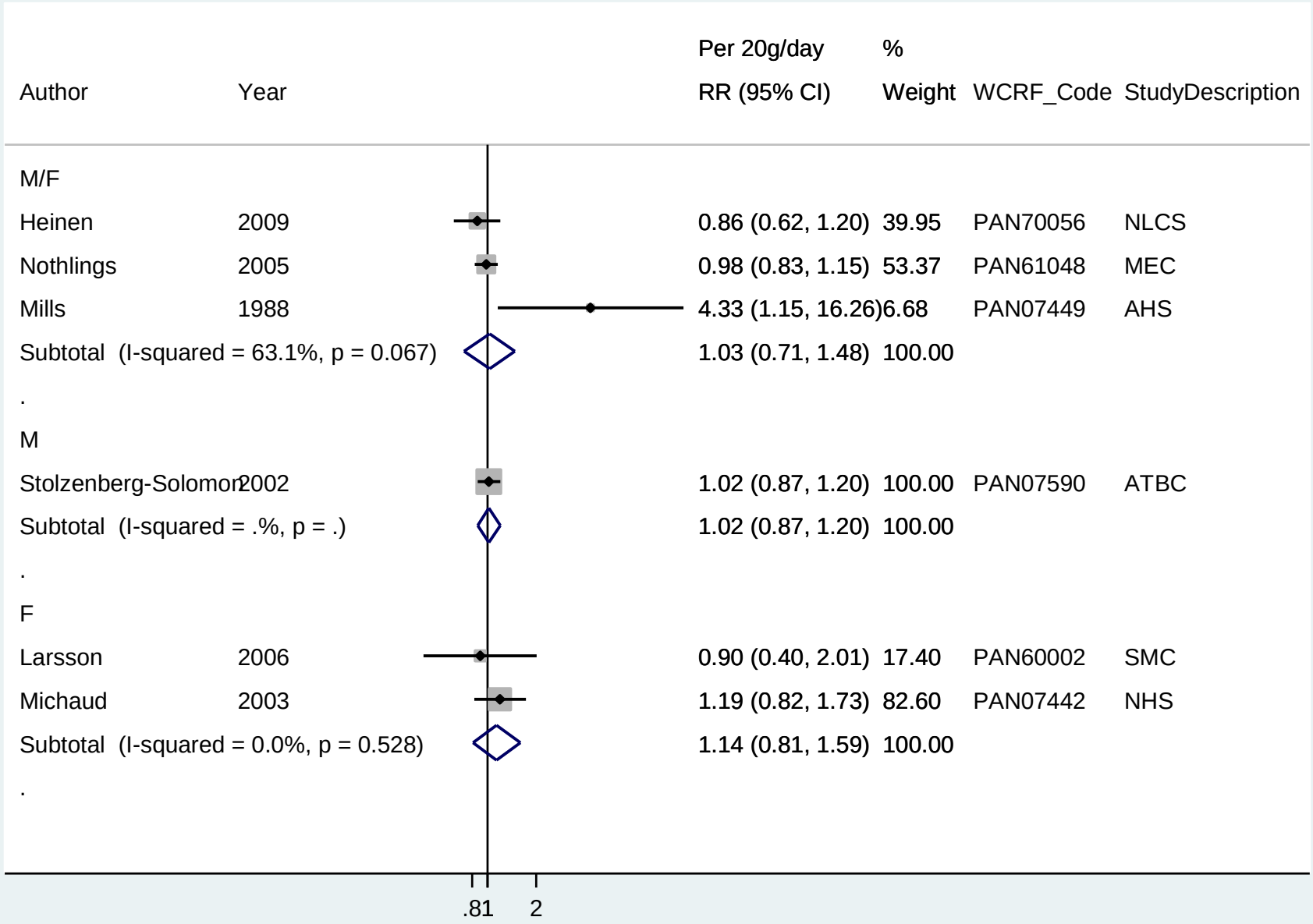


Figure 39 Dose-response graph of egg and pancreatic cancer

Figure 40 Dose-response meta-analysis of egg consumption and pancreatic cancer, stratified by sex – per 20g/day



3 Beverages

3.4 Soft drinks

Methods

A total of 7 cohort studies have been published on intake of soft drinks and pancreatic cancer risk up to September 2011, four of which were identified in the Continuous Update Project. Dose-response analyses were conducted per 200 ml/d (200 ml was used as a standard serving size for conversion to ml/d). For studies reporting the intake in grams we converted the intake to ml using a 1:1 conversion ratio.

Main results

Six studies were included in the meta-analyses. One small study reporting no association reported intake in only two categories of exposure and could not be included (Khan et al, 2004). The summary RR per 200 ml/d of soft drink intake was 1.22 (0.98-1.51, I^2=66.9%, $P_{heterogeneity}$=0.01, 7 studies). The summary RR ranged from 1.15 (95% CI: 0.94-1.39) when the Singapore Chinese Health Study was excluded to 1.33 (95% CI: 0.99-1.79) when the NIH-AARP Diet and Health Study was excluded. There was no evidence of publication bias with Egger's test, p=0.24.

Heterogeneity

There was high unexplained heterogeneity (I^2=66.9%, $P_{heterogeneity}$=0.01). In subgroup and meta-regression analyses no explanation for this heterogeneity was found (I^2 ranged from 55% to 74% in subgroup analyses by duration of follow-up, geographic location, number of cases and adjustment for possible confounding factors (alcohol, smoking, diabetes, body mass index, physical activity, meat, and energy intake) and there was no evidence of heterogeneity between subgroups, p≥0.16. Heterogeneity was not explained by the most influential studies (I^2 ranged from 59% to 61%).

Comparison with the Second Expert Report

No meta-analysis was conducted in the Second Expert Report.

Published pooled analysis and meta-analysis

A pooled analysis of 14 cohort studies reported a pooled RR of 1.19 (95% CI: 0.98-1.46) for ≥250 vs. 0 g/day of sugar-sweetened soft drink intake (Genkinger, 2011). On a continuous scale there was a significant association between sugar-sweetened soft drinks and pancreatic cancer risk, pooled RR=1.06 (95% CI: 1.02-1.12) per 177.5 g/day increment, which was significant among men, pooled RR=1.08 (1.02-1.14), but not in women, pooled RR=1.03 (95% CI: 0.93-1.13), $p_{interaction}$=0.38. A meta-analysis of seven cohort studies (included in this report) reported a summary RR of 1.05 (95% CI: 0.94-1.17) for soft drink consumers vs. non-consumers (n=7) and a summary RR of 1.21 (95% CI: 0.90-1.63) for high vs. low soft drink consumption (n=6) (Gallus, 2011), but dose-response analyses were not conducted

Table 38 Studies on soft drinks identified in the CUP

Author, year	Country	Study name	Number of cases	Years of follow-up	Sex	RR	LCI	UCI	Contrast
Mueller, 2010	Singapore	Singapore Chinese Health Study	140	Up to 14	M/F	1.87	1.10	3.15	≥2 serv./wk vs. none
Bao, 2008	USA	NIH-AARP Diet and Health Study	1258	7.2	M/F	1.01	0.77	1.31	512.8 vs. 0 g/d
Nothlings, 2007	USA	Multiethnic Cohort Study	434	8	M/F	1.07	0.82	1.41	≥75.7 vs 0 g/1000 kcal/d
Larsson, 2006	Sweden	Swedish Mammography Cohort & Cohort of Swedish Men	131	7.2	M/F	1.93	1.18	3.14	2.1 vs. 0 serv./d

Table 39 Overall evidence on soft drinks and pancreatic cancer

	Summary of evidence
SLR	Three cohort studies reported on carbonated soft drinks and pancreatic cancer. One study reported a significant increase in risk, while the two other studies reported no significant association.
Continuous Update Project	Two new studies reported significantly increased risk, while two other studies found no association.

Table 40 Summary of results of the dose-response meta-analysis of soft drink intake and pancreatic cancer

Pancreatic cancer		
	SLR*	Continuous Update Project
Studies (n)	-	6
Cases (n)	-	2342
Increment unit	-	Per 200 ml/d
RR (95% CI)	-	1.22 (0.98-1.51)
Heterogeneity (I^2, p-value)	-	66.9%, p=0.01

*No meta-analysis was conducted in the 2nd report

Table 41 Inclusion/exclusion table for meta-analysis of soft drink intake and pancreatic cancer

WCRF code	Author	Year	Study design	Study name	Subgroup	Cancer outcome	SLR	CUP dose-response meta-analysis	CUP HvL forest plot	Estimated values	Exclusion reason
PAN70008	Mueller	2010	Prospective Cohort study	Singapore Chinese Health Study	Men/Women	Incidence	New	Yes	Yes	Mid-exposure values	
PAN70009	Bao	2008	Prospective Cohort study	NIH-AARP Diet and Health Study	Men/Women	Incidence	New	Yes	Yes		
PAN70003	Nothlings	2007	Prospective Cohort study	Multiethnic Cohort Study	Men/Women	Incidence	New	Yes	Yes	Mid-exposure values, g/1000 kcal/d-> ml/d, person-years	
PAN70005	Larsson	2006	Prospective Cohort study	Swedish Mammography Cohort & Cohort of Swedish Men	Men/Women	Incidence	New	Yes	Yes		
PAN61070	Schernhammer	2005	Prospective Cohort study	Health Professionals Follow-up Study	Men	Incidence	Yes	Yes	Yes	Mid-exposure values, frequency -> ml/d	
PAN61070	Schernhammer	2005	Prospective Cohort study	Nurses' Health Study	Women	Incidence	Yes	Yes	Yes	Mid-exposure values, frequency -> ml/d	
PAN20239	Khan	2004	Prospective cohort study	Hokkaido Cohort	Men/Women	Mortality	Yes	No	Yes		Only high vs. low comparison

Figure 41 Highest versus lowest forest plot of soft drinks intake and pancreatic cancer

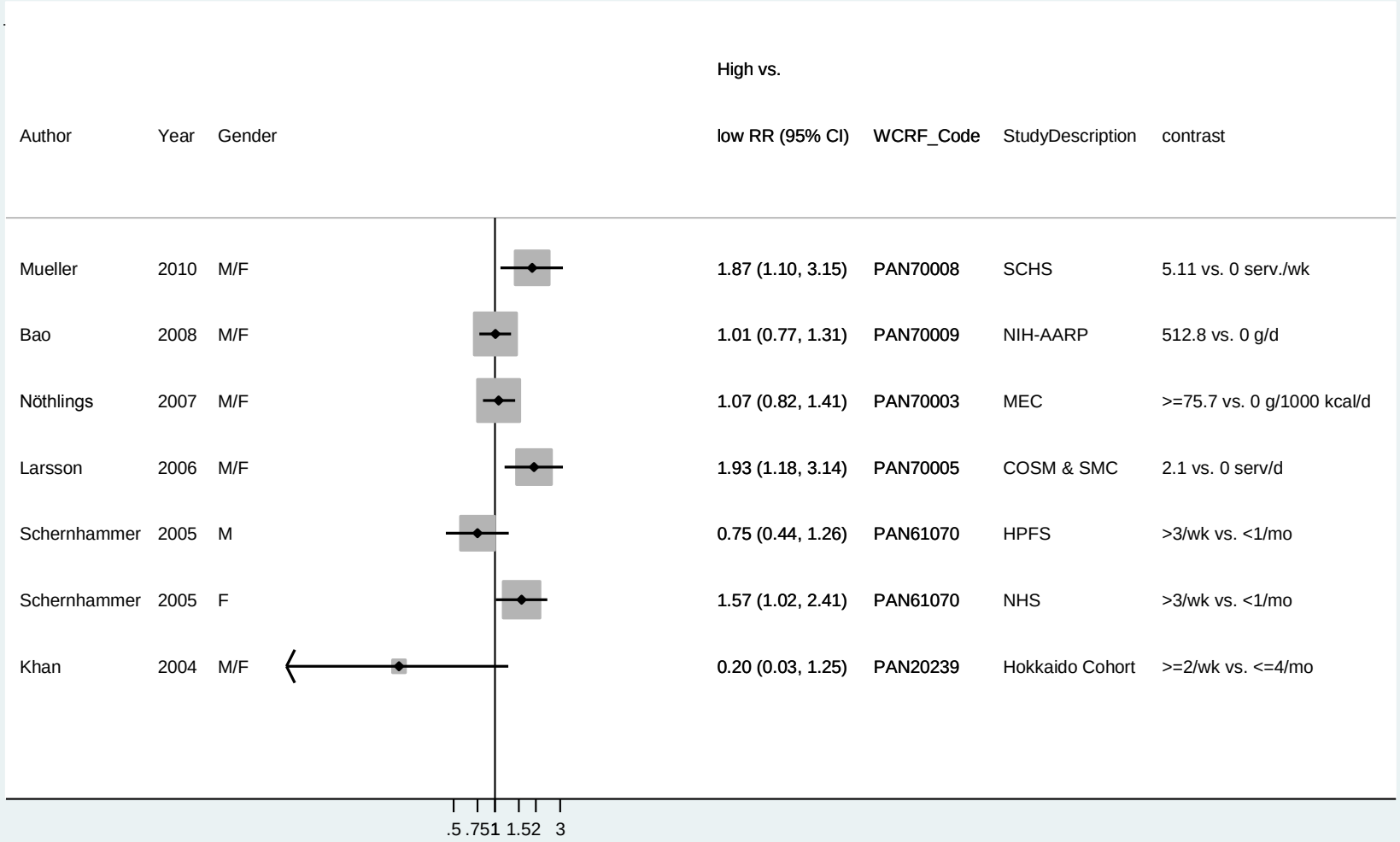


Figure 42 Dose-response meta-analysis of soft drinks and pancreatic cancer - per 200 ml/d

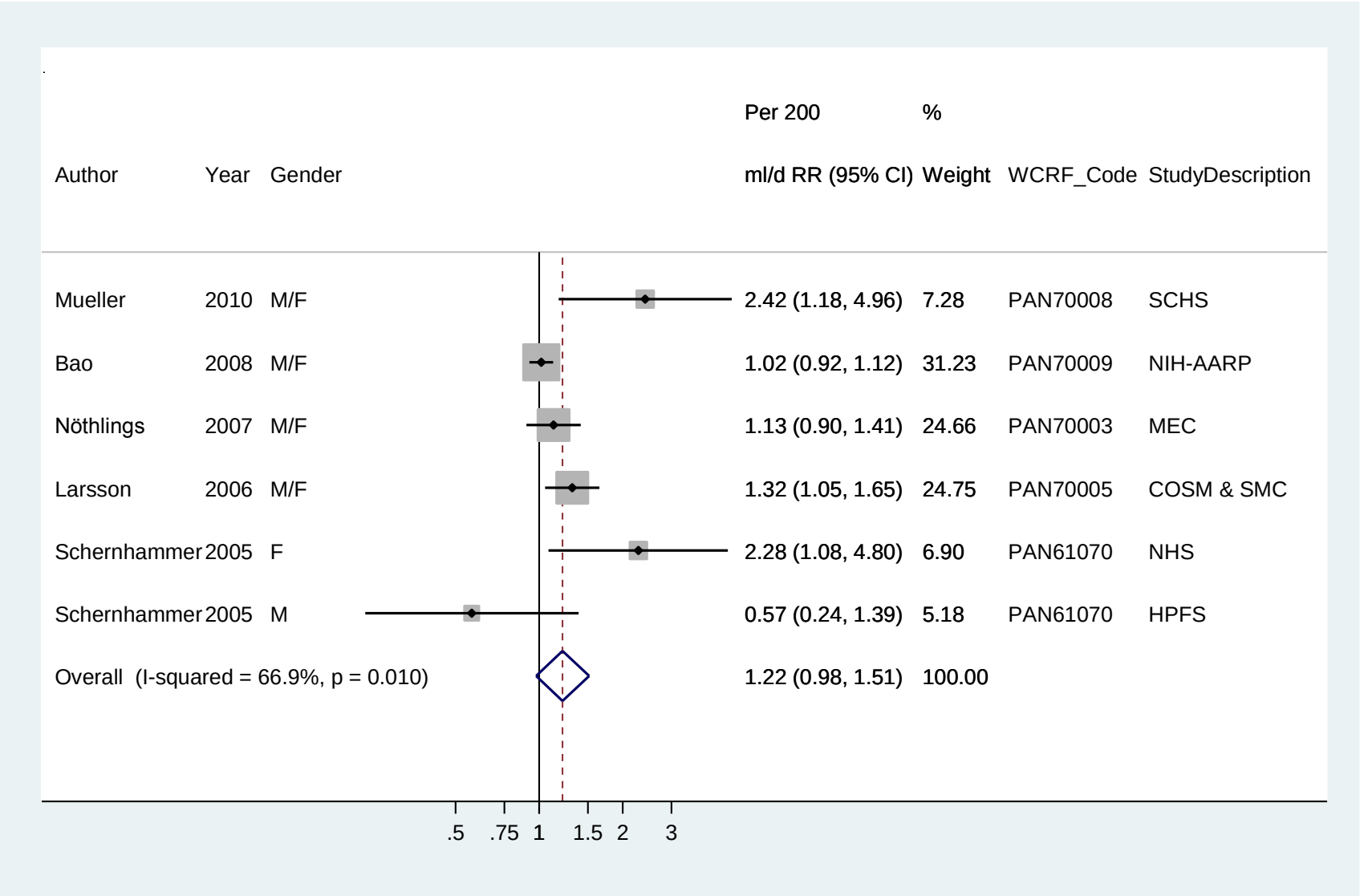


Figure 43 Funnel plot of soft drinks and pancreatic cancer

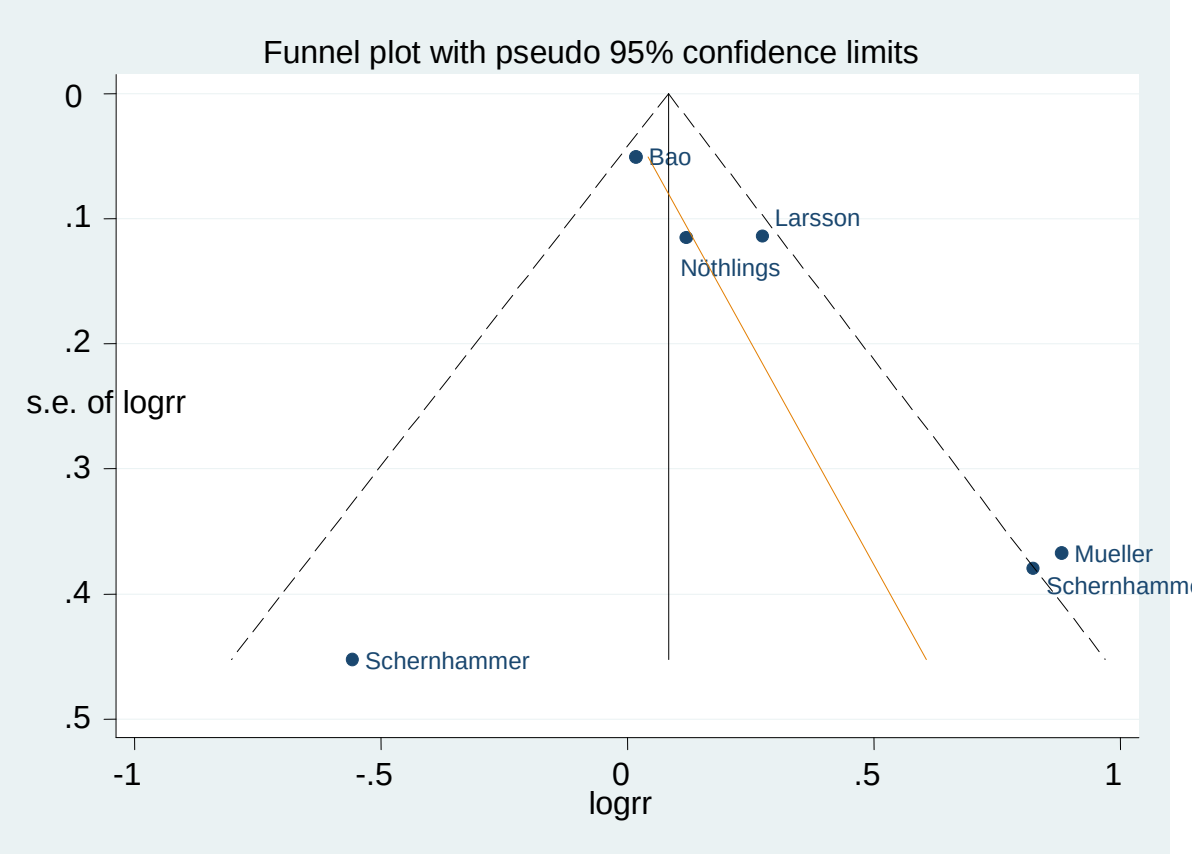
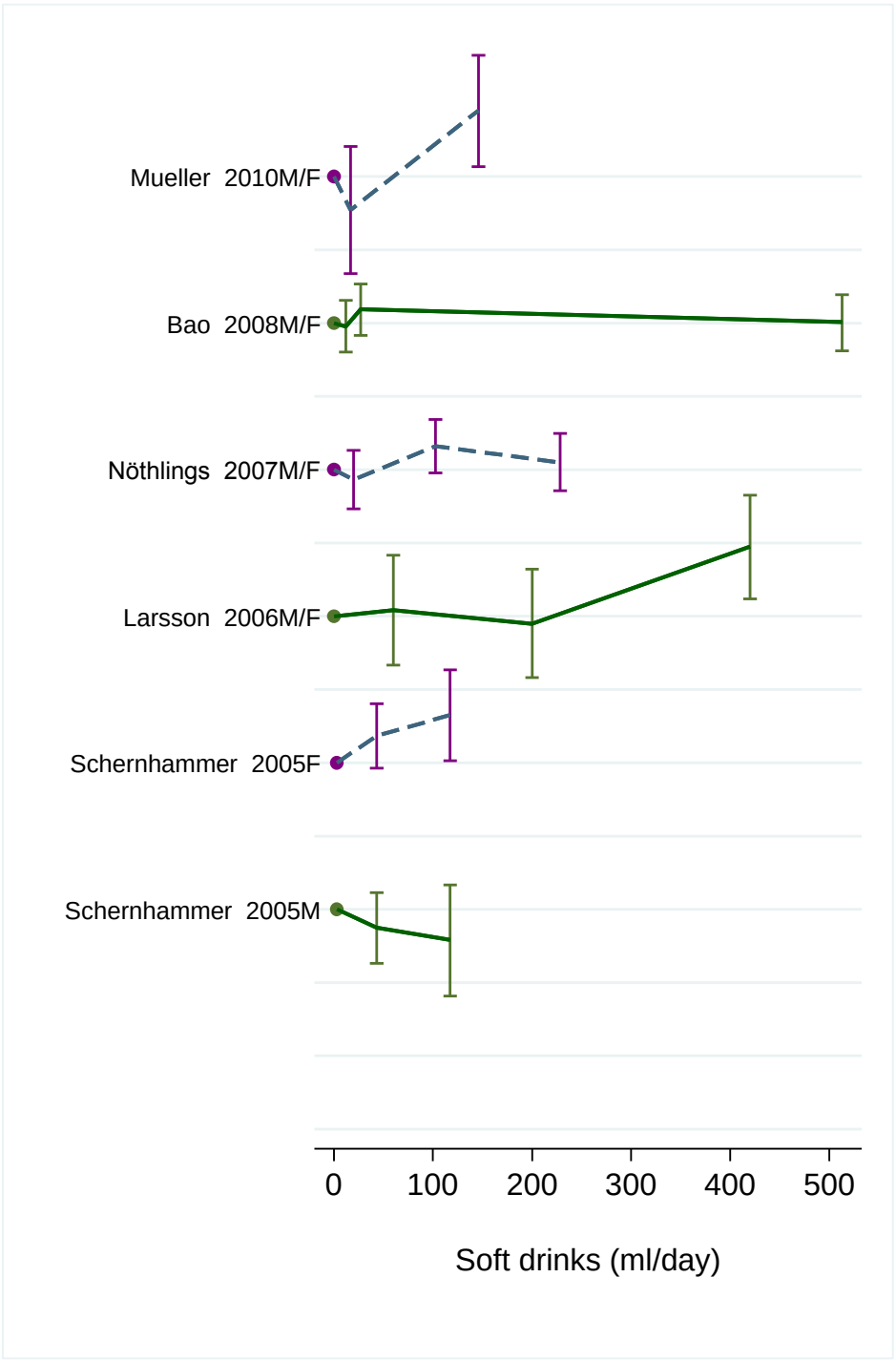


Figure 44 Dose-response graph of soft drink intake and pancreatic cancer



3.4.1 Diet soft drinks

Methods

A total of 3 cohort studies (2 publications) have been published on intake of diet soft drinks and pancreatic cancer risk up to September 2011, of which one study was identified in the Continuous Update Project. Dose-response analyses were conducted per 200 ml/d (200 ml was used as a standard serving size for conversion from frequency to ml/d). For studies reporting the intake in grams we converted the intake to ml using a 1:1 conversion ratio.

Main results

The three studies were included in dose-response meta-analysis. The summary RR per 200 ml/d of diet soft drink intake was 1.03 (0.97-1.09, I^2=0%, $p_{heterogeneity}$=0.71, 3 studies). Because of the few studies we did not test for publication bias.

Heterogeneity

There was no evidence of heterogeneity (I^2=0%, p=0.71).

Comparison with the Second Expert Report

No meta-analysis was conducted in the Second Expert Report.

Table 42 Studies on diet soft drinks identified in the CUP

Author, year	Country	Study name	Number of cases	Years of follow-up	Sex	RR	LCI	UCI	Contrast
Bao, 2008	USA	NIH-AARP Diet and Health Study	1258	7.2	M/F	1.11	0.86	1.44	816.9 vs. 0 g/d

Table 43 Overall evidence on diet soft drinks and pancreatic cancer

	Summary of evidence
SLR	Two cohort studies were available on carbonated diet drinks and pancreatic cancer risk, but were not included in the report
Continuous Update Project	One cohort study has been published and found no significant association.

Table 44 Summary of results of the dose-response meta-analysis of diet soft drink intake and pancreatic cancer

Pancreatic cancer		
	SLR*	Continuous Update Project
Studies (n)	-	3
Cases (n)	-	1637
Increment unit	-	Per 200 ml/d
RR (95% CI)	-	1.03 (0.97-1.09)
Heterogeneity (I^2, p-value)	-	0%, p=0.71

*No meta-analysis was conducted in the 2nd report.

Table 45 Inclusion/exclusion table for meta-analysis of diet soft drink intake and pancreatic cancer

WCRF code	Author	Year	Study design	Study name	Subgroup	Cancer outcome	SLR	CUP dose-response meta-analysis	CUP Hv L forest plot	Estimated values	Exclusion reason
PAN70009	Bao	2008	Prospective Cohort study	NIH-AARP Diet and Health Study	Men/Women	Incidence	New	Yes	Yes		
PAN61070	Schernhammer	2005	Prospective Cohort study	Health Professionals Follow-up Study	Men	Incidence	Yes	Yes	Yes	Mid-exposure values, frequency -> ml/d	
PAN61070	Schernhammer	2005	Prospective Cohort study	Nurses' Health Study	Women	Incidence	Yes	Yes	Yes	Mid-exposure values, frequency -> ml/d	

Figure 45 Highest versus lowest forest plot of diet soft drinks intake and pancreatic cancer

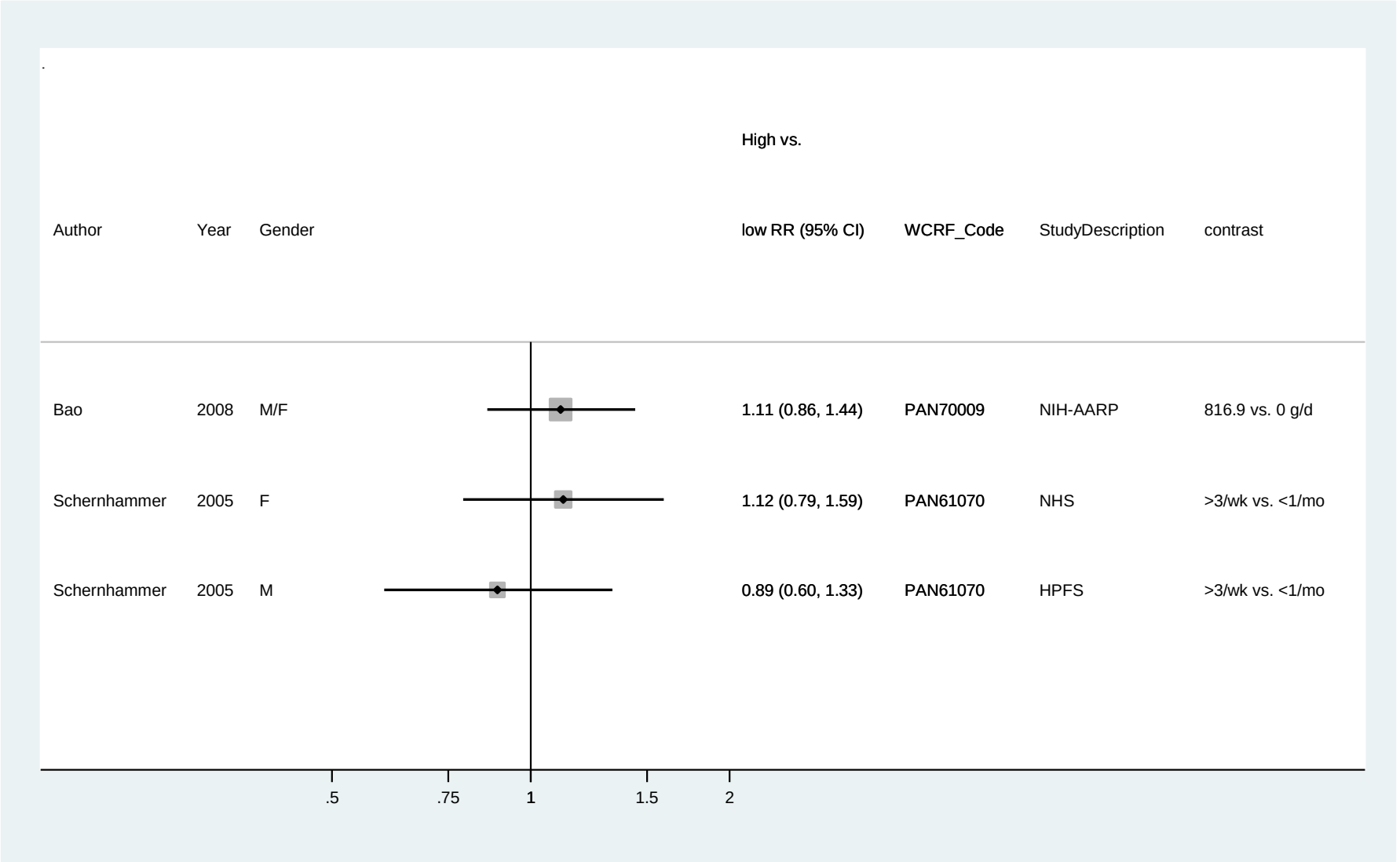


Figure 46 Dose-response meta-analysis of diet soft drinks and pancreatic cancer - per 200 ml/d

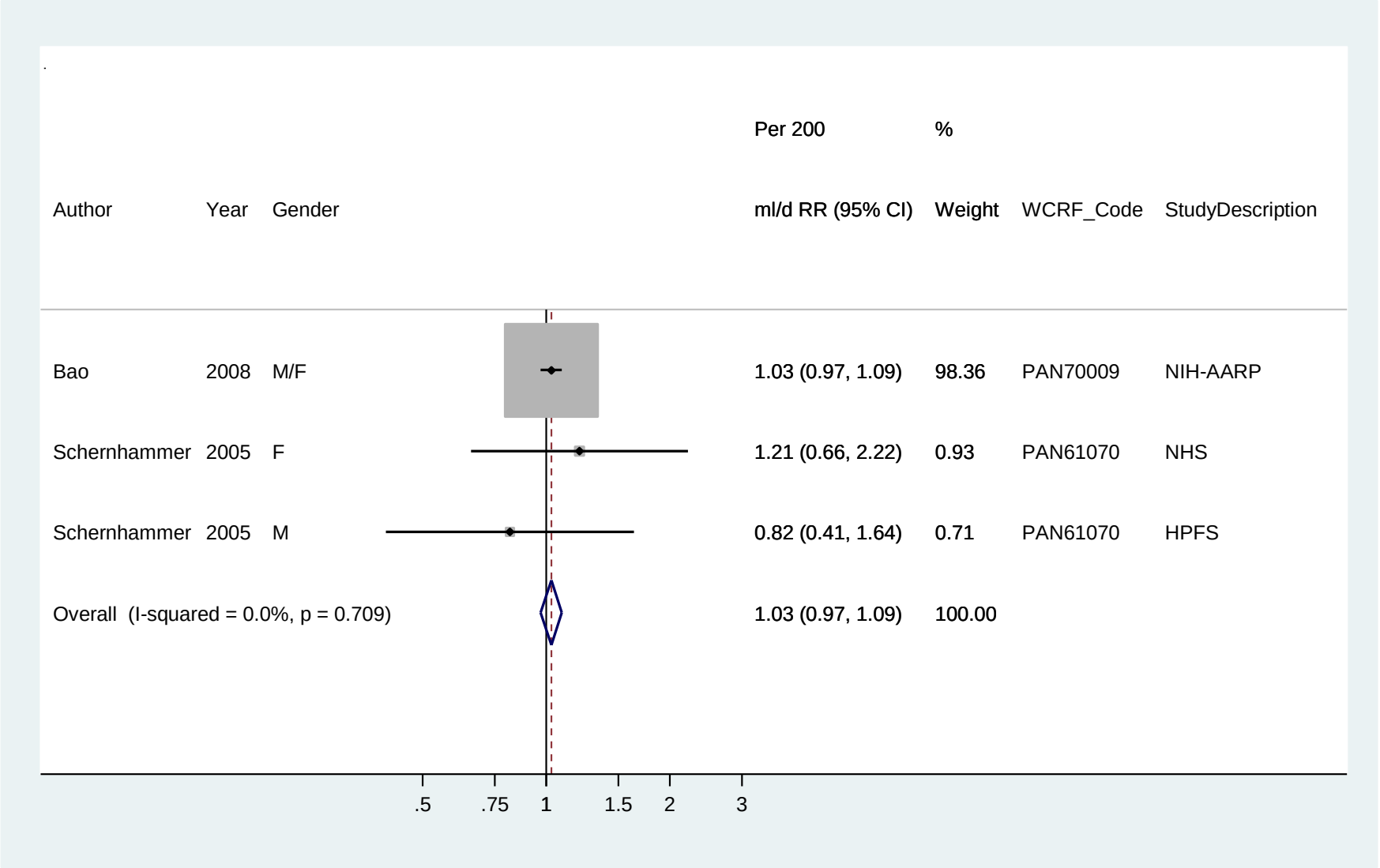
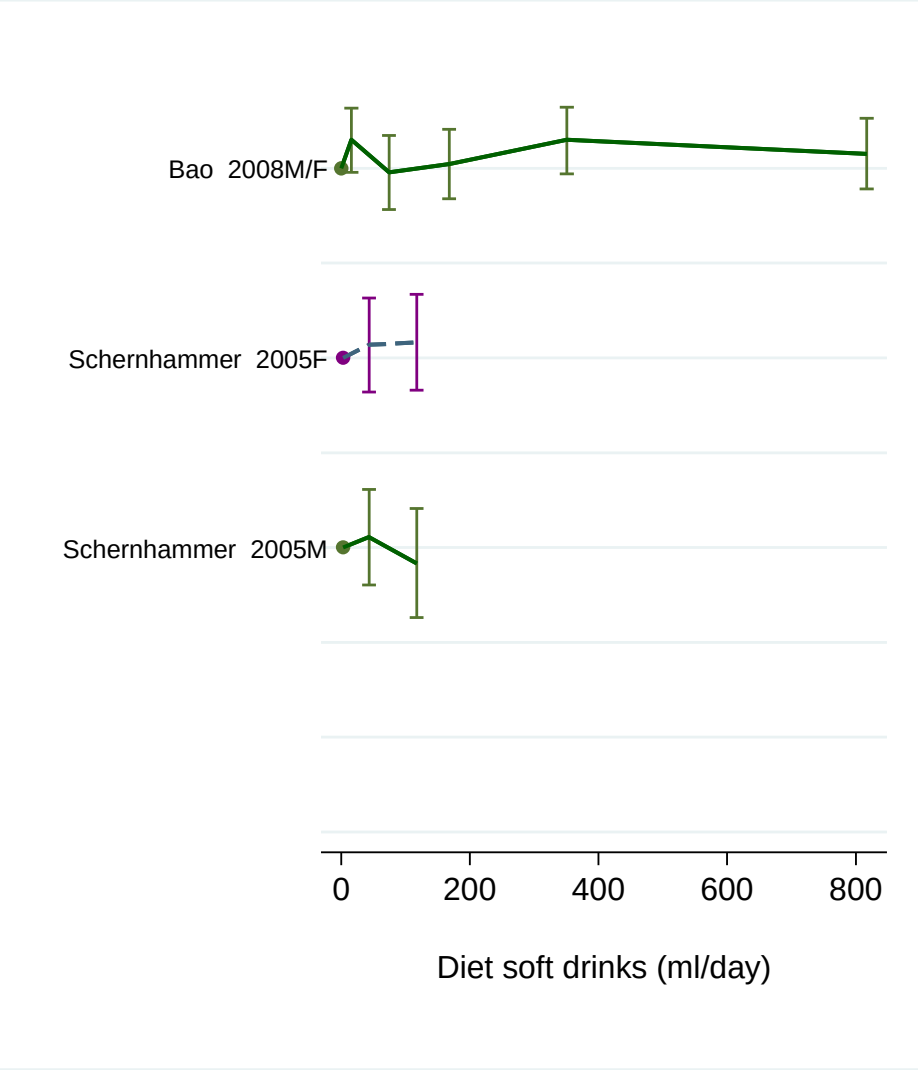


Figure 47 Dose-response graph of diet soft drink intake and pancreatic cancer



3.5 Fruit juices

Methods

A total of 5 cohort studies have published on intake of fruit juices and pancreatic cancer risk up to September 2011, all of which were identified in the Continuous Update Project. Dose-response analyses were conducted per 200 ml/d (125 ml was used as a standard serving size for conversion from frequency to ml/d). For studies reporting the intake in grams we converted the intake to ml using a 1:1 conversion ratio.

Main results

All studies were included in the meta-analysis. The summary RR per 200 ml/d of fruit juice intake was 0.89 (0.70-1.13, I^2=28%, $p_{heterogeneity}$=0.24, 5 studies). The summary RR ranged from 0.78 (95% CI: 0.61-0.99) when excluding the Multiethnic Cohort study to 0.94 (95% CI: 0.71-1.24) when excluding the Netherlands Cohort Study. There was no evidence of publication bias with Egger's test, p=0.92.

Heterogeneity

There was little evidence of heterogeneity (I^2=9.8%, p=0.35).

Comparison with the Second Expert Report

No meta-analysis was conducted in the Second Expert Report.

Table 46 Studies on fruit juices identified in the CUP

Author, year	Country	Study name	Number of cases	Years of follow-up	Sex	RR	LCI	UCI	Contrast
Mueller, 2010	Singapore	Singapore Chinese Health Study	140	Up to 14	M/F	1.31	0.74	2.30	≥2 serv./wk vs. none
Vrieling, 2009	Europe	European Prospective Investigation into Nutrition and Cancer	555	8.9	M/F	0.79	0.47	1.33	>68 vs. 0 g/d
Bobe, 2008	Finland	ATBC Cancer Prevention study	306	16.1	M	0.84	0.60	1.17	>121.5 vs. 0 g/d
Nothlings, 2007	USA	Multiethnic Cohort Study	434	8	M/F	1.08	0.83	1.41	≥60 vs. <4.7 g/1000 kcal/d
Lin, 2006	Japan	Japan Collaborative Cohort Study for Evaluation of Cancer Risk	300	9.9	M F	0.33 1.09	0.13 0.62	0.84 1.90	Almost every day vs. 0-2/mo Almost every day vs. 0-2/mo

Table 47 Overall evidence on fruit juices and pancreatic cancer

	Summary of evidence
SLR	No cohort studies were available on intake of fruit juices and pancreatic cancer risk.
ContinuousUpdate Project	Five cohort studies were published on fruit juices and pancreatic cancer risk. Only one of these studies reported a significant inverse association, which was limited to men, while the remaining studies reported no significant association.

Table 48 Summary of results of the dose-response meta-analysis of fruit juice intake and pancreatic cancer

Pancreatic cancer		
	SLR*	Continuous Update Project
Studies (n)	-	5
Cases (n)	-	1735
Increment unit	-	Per 200 ml/d
RR (95% CI)	-	0.89 (0.70-1.13)
Heterogeneity (I^2, p-value)	-	28%, p=0.24

*No meta-analysis was conducted in the 2nd report

Table 49 Inclusion/exclusion table for meta-analysis of fruit juice intake and pancreatic cancer

WCRF code	Author	Year	Study design	Study name	Subgroup	Cancer outcome	SLR	CUP dose-response meta-analysis	CUP HvL forest plot	Estimated values	Exclusion reason
PAN70008	Mueller	2010	Prospective Cohort study	Singapore Chinese Health Study	Men/Women	Incidence	New	Yes	Yes	Mid-exposure values	
PAN70020	Vrieling	2009	Prospective Cohort study	European Prospective Investigation into Nutrition and Cancer	Men/Women	Incidence	New	Yes	Yes		
PAN70003	Nothlings	2007	Prospective Cohort study	Multiethnic Cohort Study	Men/Women	Incidence	New	Yes	Yes	Mid-exposure values, g/1000 kcal/d-> ml/d, person-years	
PAN70010	Bobe	2008	Prospective Cohort study	ATBC Cancer Prevention Study	Men	Incidence	New	Yes	Yes	Mid-exposure values	
PAN70051	Lin	2006	Prospective Cohort study	JACC study	Men/Women	Incidence	New	Yes	Yes	Mid-exposure values, frequency to ml/d	

Figure 48 Highest versus lowest forest plot of fruit juice intake and pancreatic cancer

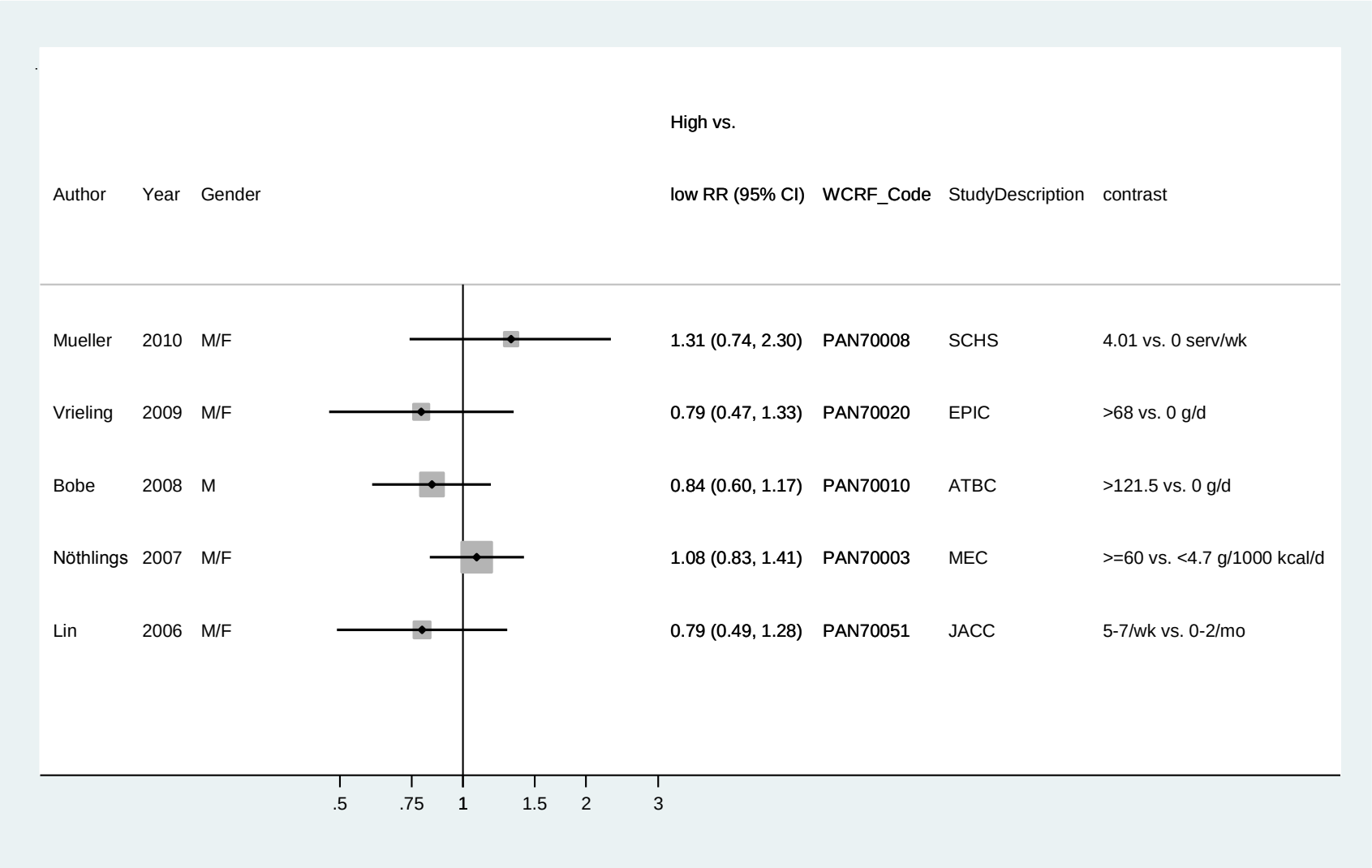


Figure 49 Dose-response meta-analysis of fruit juices and pancreatic cancer - per 200 ml/d

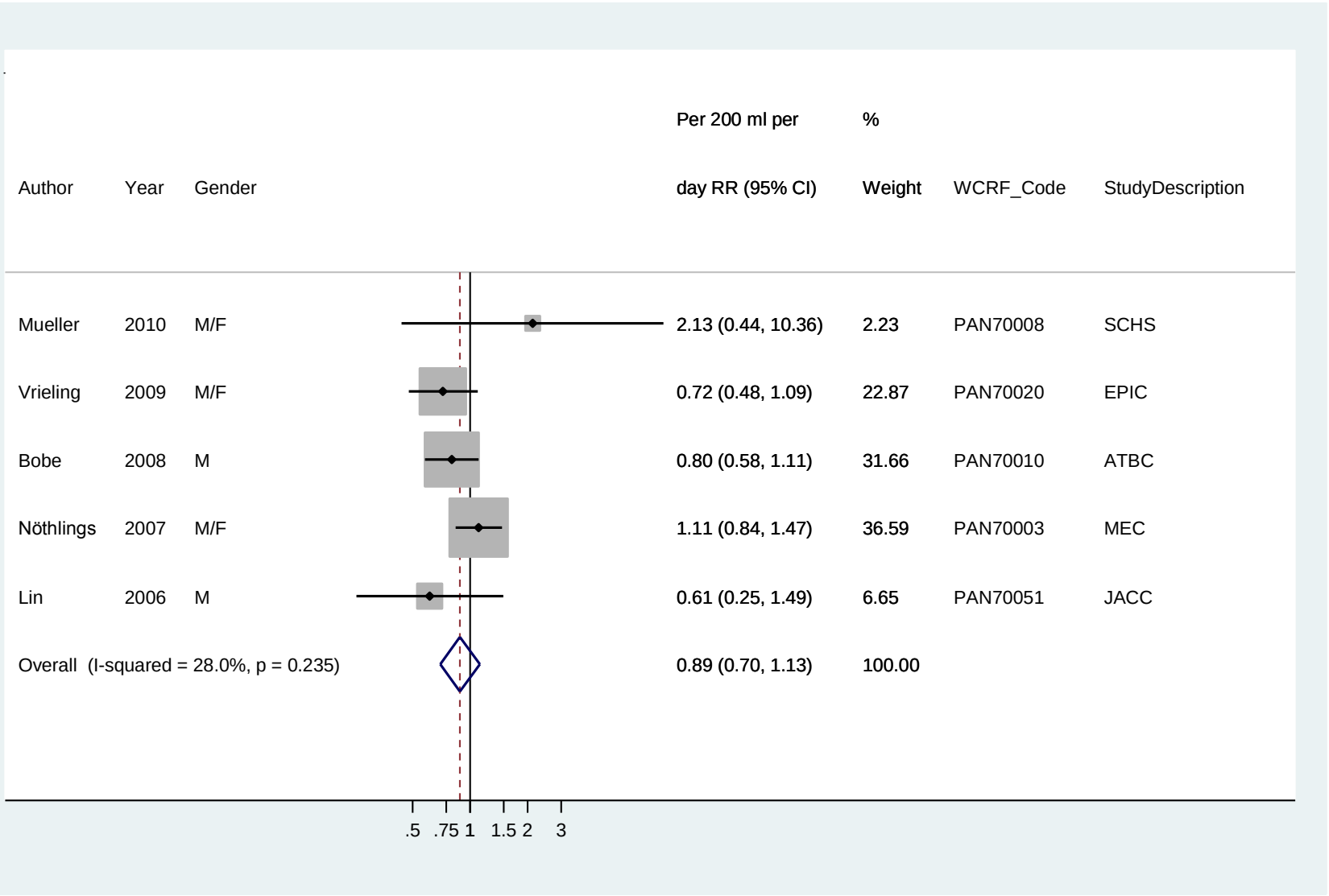


Figure 50 Funnel plot of fruit juice intake and pancreatic cancer

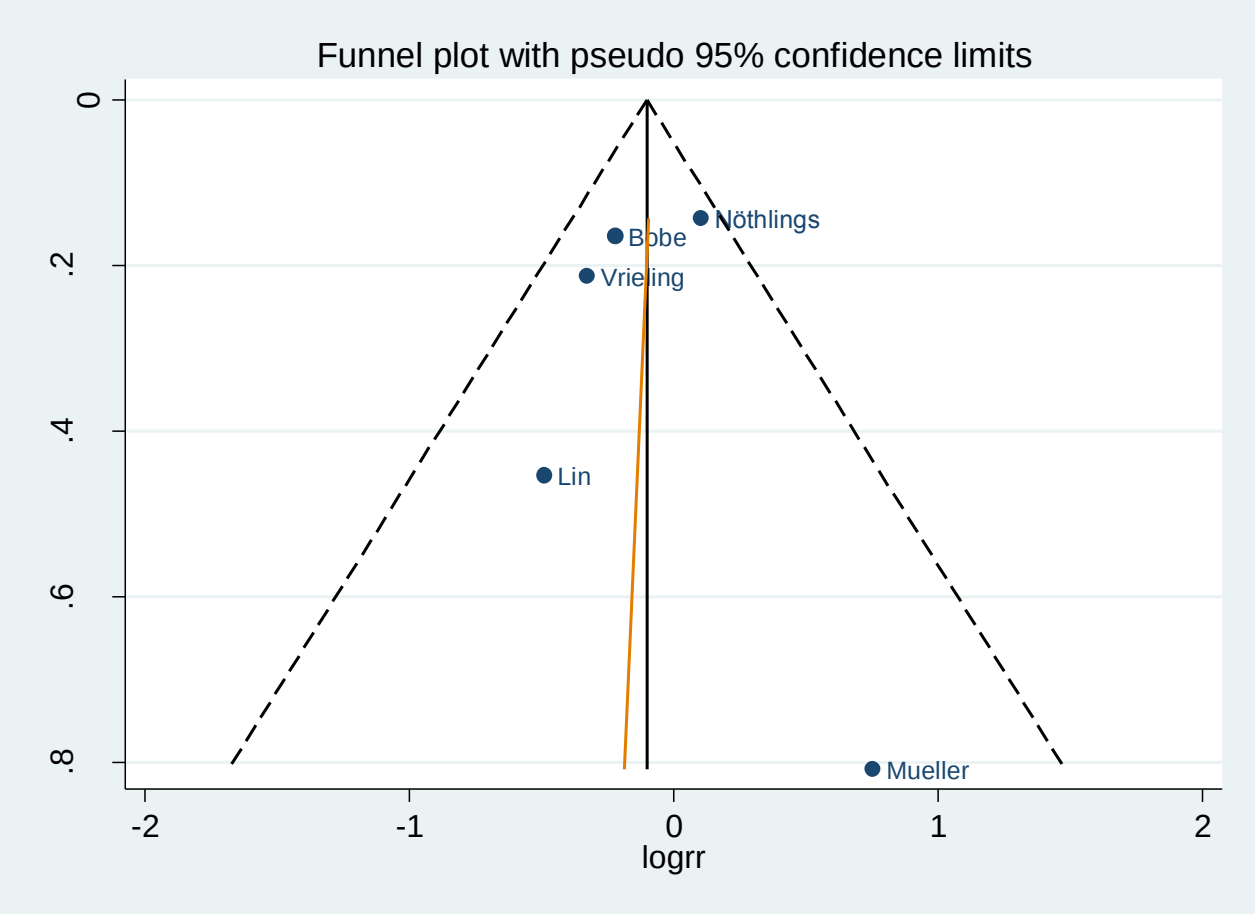
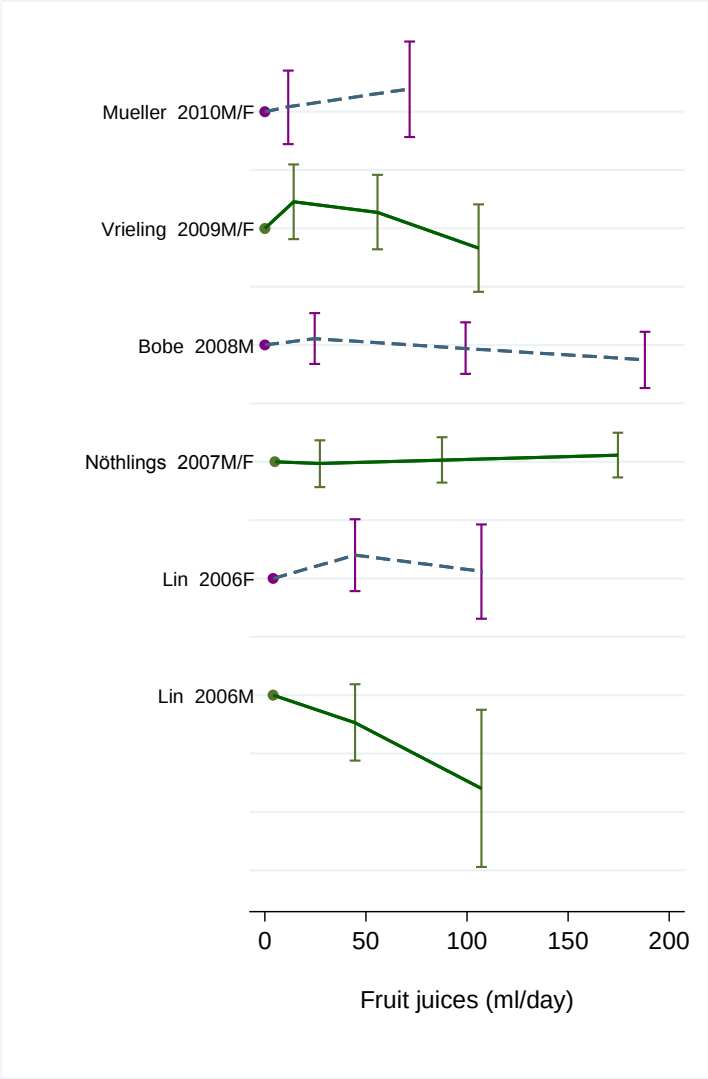


Figure 51 Dose-response graph of fruit juice intake and pancreatic cancer



3.6.1 Coffee

Methods

Twenty-three reports from twenty cohort studies were identified, from which two studies were identified during the CUP. Dose-response meta-analysis for cohort studies was performed in the previous SLR report. In this report, an updated meta-analysis including 11 studies identified during the 2007 SLR and the two studies identified during the CUP was performed. The reason for conducted meta-analysis was the inconsistent results of two meta-analyses published in 2011 (see below "Published meta-analysis").

For the dose-response analyses all results were converted to a common scale (cups per day) and one cup was equivalent to 240 ml and used as the standard serving or portion size.

Main results

Thirteen studies were included in the meta-analysis. The summary RR per 1 cup/day was 1.02 (95% CI: 0.95-1.09; $P_{heterogeneity}$=0.15, 13 studies) for incidence or mortality of pancreatic cancer. The overall results remained the same when three studies with mortality as outcome were excluded from the analysis (RR= 1.03; 95% CI: 0.95-1.11). The RR ranged from 0.99 (95% CI: 0.92-1.06) when excluding the JACC study (Lin et al, 2002) to 1.03 (95% CI: 0.96-1.11) when excluding the HPFS (Michaud et al, 2001).

We calculated the overall RR for the comparison of the highest versus the lowest category of intake reported in the articles. The overall RR was 1.06 (95% CI: 0.79 -1.42; I^2=45.3% $P_{heterogeneity}$ =0.04) which is comparable with the meta-analysis published by Turatti et al, 2011.

Heterogeneity

Moderate heterogeneity was observed overall (I^2= 29.3%, p=0.15). Egger's tests suggested no evidence of publication bias, p=0.87.

Comparison with the Second Expert Report

Overall, coffee intake was not associated with the risk of pancreatic cancer. RR for an increase of one cup/day was 1.02 (95% CI: 0.95-1.09), similar to that reported in the previous SLR report (RR for one cup/day was 1.00 (95% CI: 0.94 -1.07).

Published meta-analysis

A pooled analysis of 14 cohort studies reported no statistically significant association between pancreatic cancer risk and intake of coffee, RR was 1.10 (95% CI: 0.81–1.48) comparing ≥900 to <0 g/d (Genkinger et al, 2011). A recent meta-analysis (Turati et al, 2011) based on 12 cohort studies, reported a pooled RR per 1 cup/day (1 cup was defined as 180g of coffee) of 1.00 (95% CI: 0.95–1.05) and a RR for the high versus low of 1.04 (95% CI: 0.80–1.36).
In another meta-analysis by Dong et al, 2011 using most of the same cohort studies as in the meta-analysis by Turati et al, 2011, a suggestive inverse association of pancreatic cancer risk

with coffee intake was concluded, based on separate analyses of three different comparisons of categories of coffee drinkers defined by the authors (drinkers, low to moderate coffee drinkers, and high coffee drinkers compared to non/lowest drinkers from included studies). The pooled RR of pancreatic cancer was 0.82 (95% CI: 0.69-0.95) for coffee drinkers, 0.86 (0.76-0.96) for low to moderate coffee drinkers, and 0.68 (0.51-0.84) for high drinkers compared to never/lowest coffee drinkers. However, the dose-response meta-analysis did not support an association (RR per 1 cup/day increase: 0.96; 95% CI: 0.90-1.02). It was assumed that 125ml of coffee was equivalent to 1 cup.

Table 50 Studies on coffee intake identified in the CUP

Author, year	Country	Study name	Cases	Years of follow up	Sex	RR	LCI	UCI	Contrast
Nilsson, 2010	Sweden	Vasterbotten - Northern Sweden	74	15	M F	1.50	0.57	3.92	≥ 4 vs < 1 cups/day
Luo, 2007	Japan	Japan Public Health Center-based Prospective Study	223	11	M F	0.6 1.3	0.3 0.5	1.1 3.3	> 3 cups/day vs rarely

Table 51 Overall evidence on coffee intake and pancreatic cancer

	Summary of evidence
SLR	Data were extracted from 19 studies, and 9 included sufficient information to be included in a meta analysis. The summary relative risk from the cohort studies was 1.003 (95% CI: 0.94- 1.07) per 1 cup/day (p=0.9).
Continuous Update Project	Two cohort studies were identified and reported non-significant associations with pancreatic cancer.

Table 52 Summary of results of the dose response meta-analysis of coffee intake and pancreatic cancer

Pancreatic cancer		
	SLR	Continuous Update Project
Studies (n)	9	13
Cases (n)	1092	1460
Increment unit used	Per cup/day	Per cup/day
Overall RR (95%CI)	1.00 (0.94-1.07)	1.02(0.95-1.09)
Heterogeneity (I^2,p-value)	29%, p=0.2	29.3%, p=0.15
Stratified analysis		
Men	-	0.98 (0.88-1.11) (n=7)
Heterogeneity (I^2,p-value)		59.3%, p=0.02
Women		1.06(0.92-1.22) (n=4)
Heterogeneity(I^2,p-value)		28.5%, p=0.24

Table 53 Inclusion/exclusion table for meta-analysis of coffee intake and pancreatic cancer

WCRF_ Code	Author	Year	Study Design	Study Name	Subgroup	Cancer Outcome	SLR	CUP dose-response meta-analysis	CUP HvL forest plot	Estimated values	Exclusion reasons
PAN70027	Nilson	2010	Prospective Cohort study	Vasterbotten - Northern Sweden	Men/Women	Incidence	New	Yes	Yes	person years, Mid-exposure values	
PAN70025	Luo	2007	Prospective Cohort study	Japan Public Health Center-based Prospective Study	Men/Women	Mortality/ incidence	New	Yes	Yes	Mid-exposure values	
PAN20239	Khan	2004	Prospective Cohort study	Hokkaido Cohort	Men/Women	Mortality	Yes	No	Yes		Only two categories
PAN07590	Stolzenberg-Solomon	2002	Prospective Cohort study	Alpha Tocopherol Beta Carotene Cancer Prevention Study Cohort	Men	Incidence	Yes	Yes	Yes	Mid-exposure values , cases/person-years per quintile	
PAN07389	Lin	2002	Prospective Cohort study	Japan Collaborative Cohort Study for Evaluation of Cancer Risk	Men/Women	Mortality/ incidence	Yes	Yes	Yes	Mid-exposure values	
PAN70058	Isaksson	2002	Prospective Cohort study	Swedish Twin cohort	Men/Women	Incidence	No	No	No		Letter to the editor
PAN07588	Stolzenberg-Solomon	2001	Nested Case Control	Alpha Tocopherol Beta Carotene Cancer Prevention Study Cohort	Men	Incidence	No	No	No		Only mean values
PAN07440	Michaud	2001	Prospective Cohort study	The Nurse's Health Study Cohort and Health Professional Study	Men/Women	Mortality/ incidence	Yes	Yes	Yes	Mid-exposure values	
PAN07288	Harnack	1997	Prospective Cohort study	Iowa Women’s Health Study	Women	Mortality/ incidence	Yes	Yes	Yes	Mid-exposure values	

PAN07562	Shibata	1994	Prospective Cohort study	Leisure World Cohort Study	Men/Women	Incidence	Yes	Yes	Yes	Mid-exposure values	
PAN07582	Stensvold	1994	Prospective Cohort study	Norwegian Cardiovascular Screening Cohort	Men/Women	Mortality/ incidence	Yes	Yes	Yes	Mid-exposure values	
PAN07668	Zheng	1993	Prospective Cohort study	Lutheran Brotherhood Insurance Society	Men	Mortality	Yes	Yes	Yes	Mid-exposure values	
PAN04147	Friedman	1993	Nested Case Control study	Members of the Kaiser Permanent Medical Care Program including Oakland	Men/Women	Incidence	Yes	No	Yes		Only two categories
PAN60025	Klatsky	1993	Prospective Cohort study	Members of the Kaiser Permanent Medical Care Program including Oakland	Men/Women	Mortality	Yes	No	No		No measure of the relationship
PAN07299	Hirayama	1989	Prospective Cohort study	Japan Cohort	Men/Women	Mortality	Yes	No	No		No number of cases per category, no confidence intervals
PAN07449	Mills	1988	Prospective Cohort study	Californian Seventh Day Adventists	Men/Women	Mortality	No	Yes	Yes	Mid-exposure values	SLR used the Snowdon 1984
PAN07294	Hiatt	1988	Case Cohort study	Members of the Kaiser Permanent Medical Care Program including Oakland	Men/Women	Incidence	Yes	No	No (Superseded by Friedman 1993)		No number of cases per category
PAN07471	Nomura	1986	Prospective Cohort study	Japan - Hawaii Centre	Men	Incidence	Yes*	Yes	Yes	Mid-exposure values, person years	
PAN09619	Jacobsen	1986	Prospective Cohort study	Combined Norwegian Cohorts	Men/Women	Mortality/ incidence	Yes	No	Yes		Only two categories
PAN11810	Snowdon	1984	Prospective	Adventist Mortality	Men/Women	Mortality	Yes	Yes	Yes		

			Cohort	Study							
PAN07637	Whittemore	1983	Nested Case Control	College Alumni Health Study	Men	Mortality	Yes	No	Yes		Only two categories
PAN07291	Heuch	1983	Prospective Cohort study	Combined Norwegian Cohorts	Men/Women	Incidence	No	No	No		Supersede by Jacobsen 1986
PAN00004	Elinder	1981	Historical Cohort	Swedish Twin Registry	Men/Women	Mortality	Yes	No	No		Only mean values

*** Nomura et al, 1986 was identified during the 2007 SLR but was not included in the meta-analysis because it does not present the confidence intervals, which were estimated for the CUP report**

Figure 52 Highest versus lowest forest plot of coffee intake and pancreatic cancer

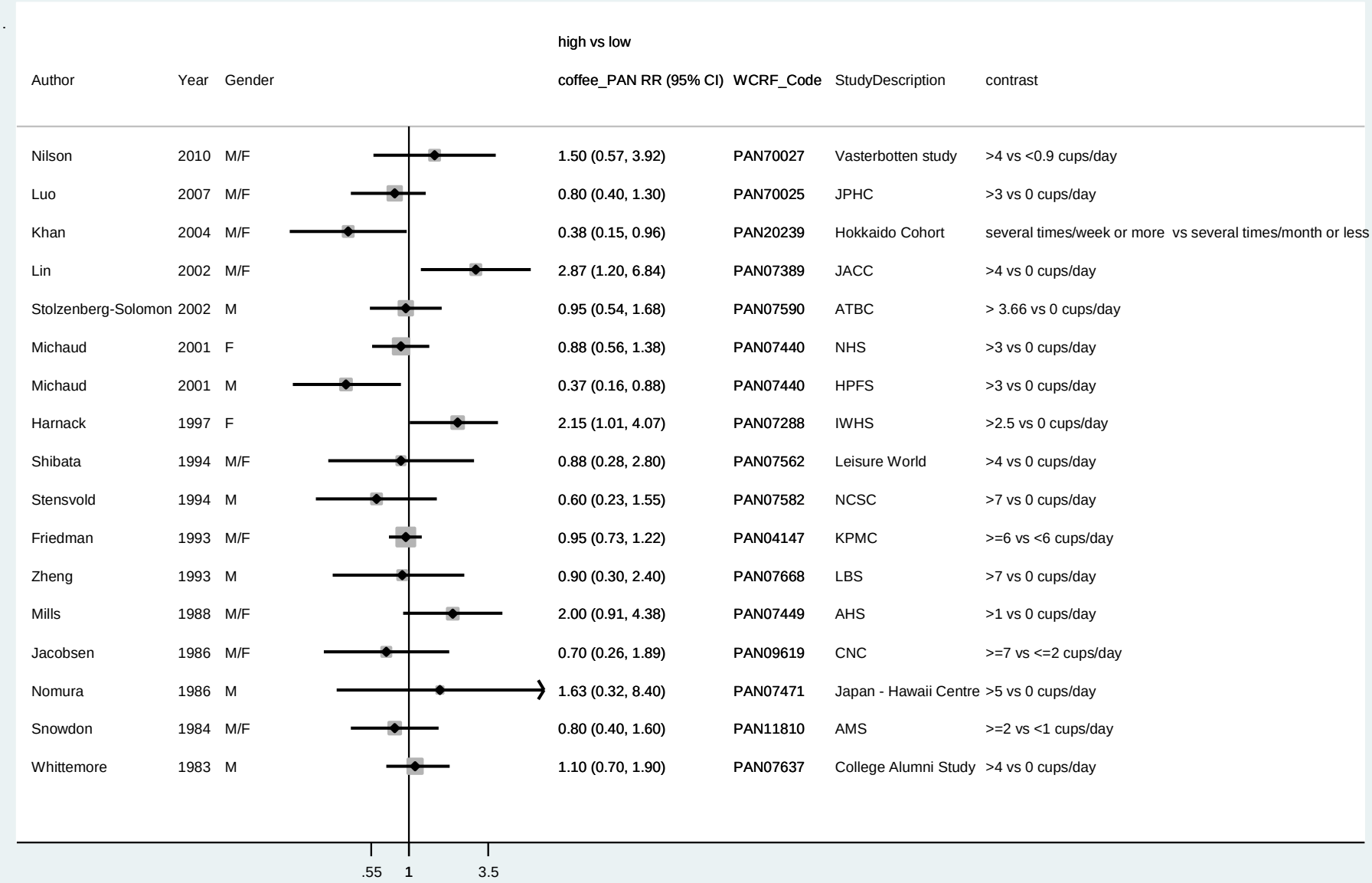


Figure 53 Dose-response meta-analysis of coffee intake and pancreatic cancer – per cup/day

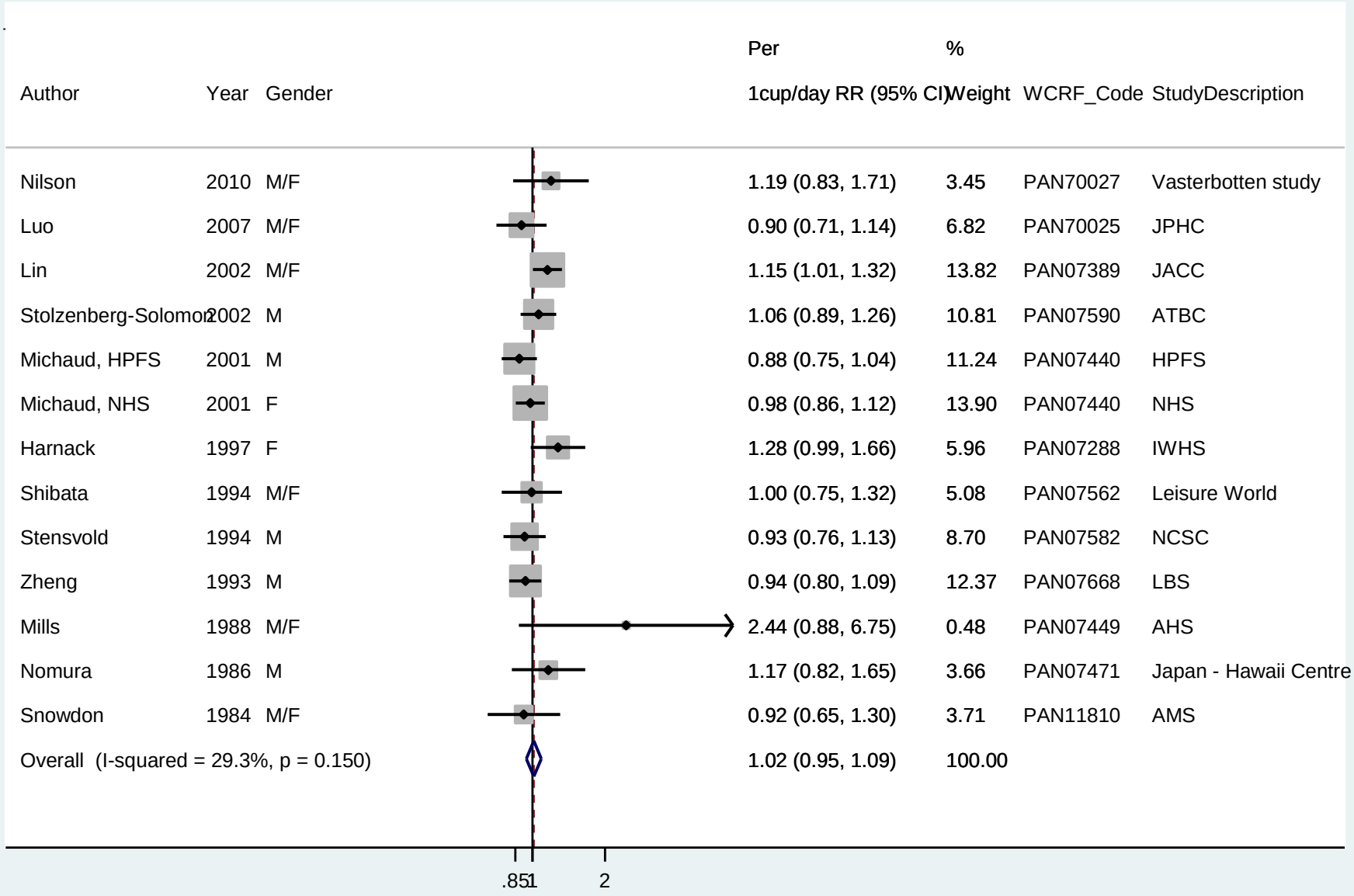


Figure 54 Funnel plot of coffee intake and pancreatic cancer

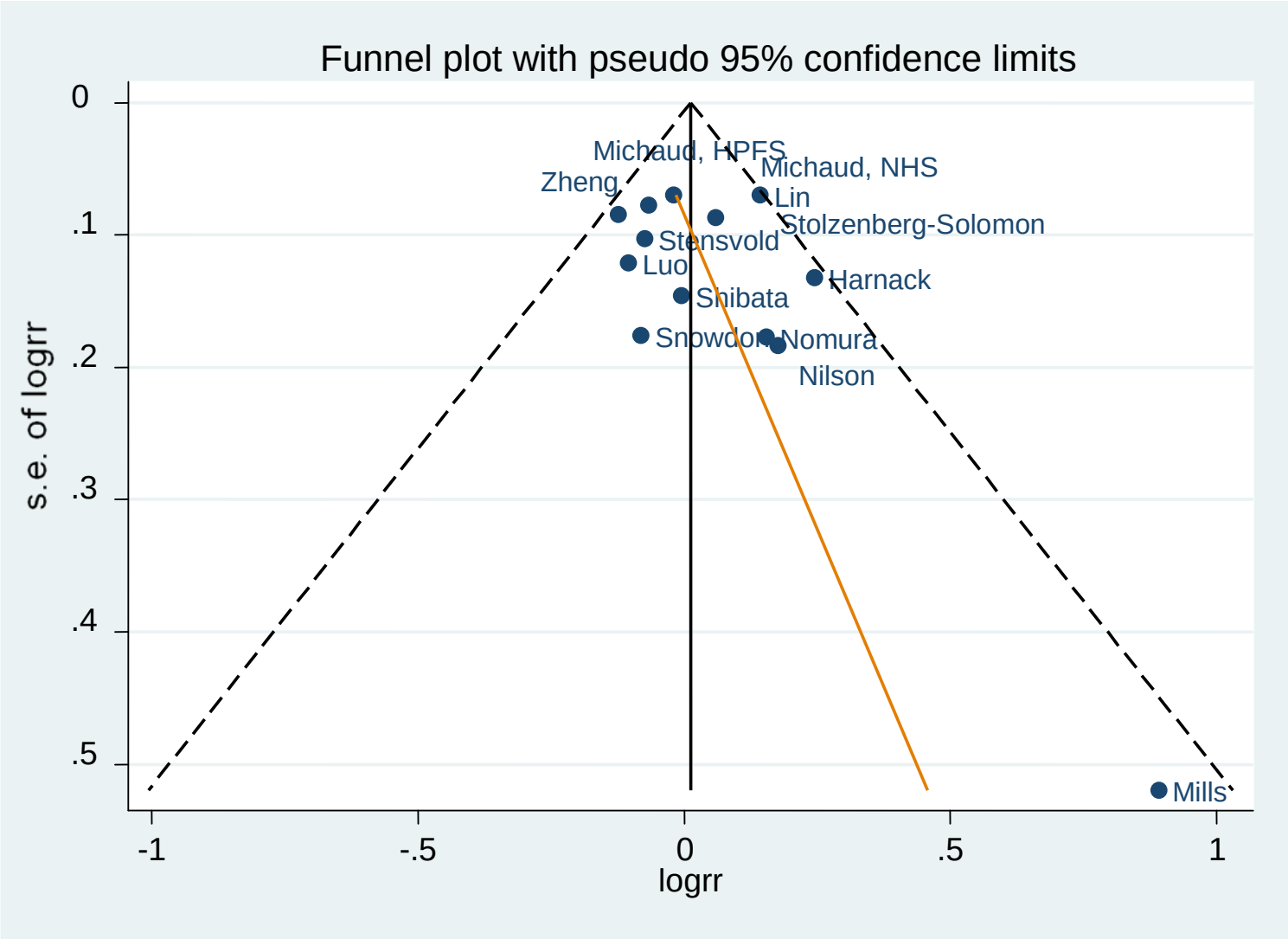


Figure 55 Dose-response graph of coffee intake and pancreatic cancer

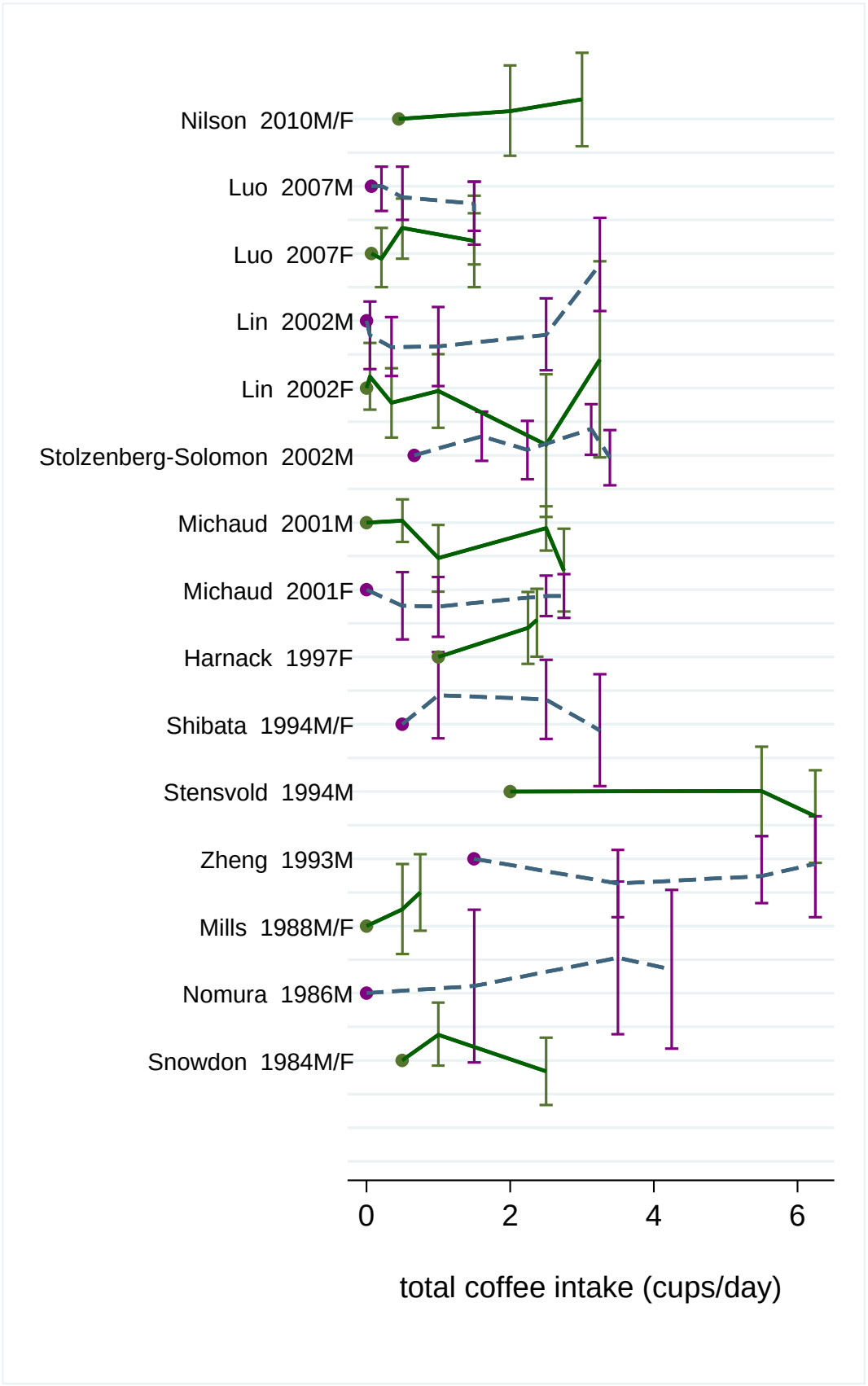


Figure 56 Dose-response meta-analysis of coffee intake and pancreatic cancer, stratified by sex – per cup/day

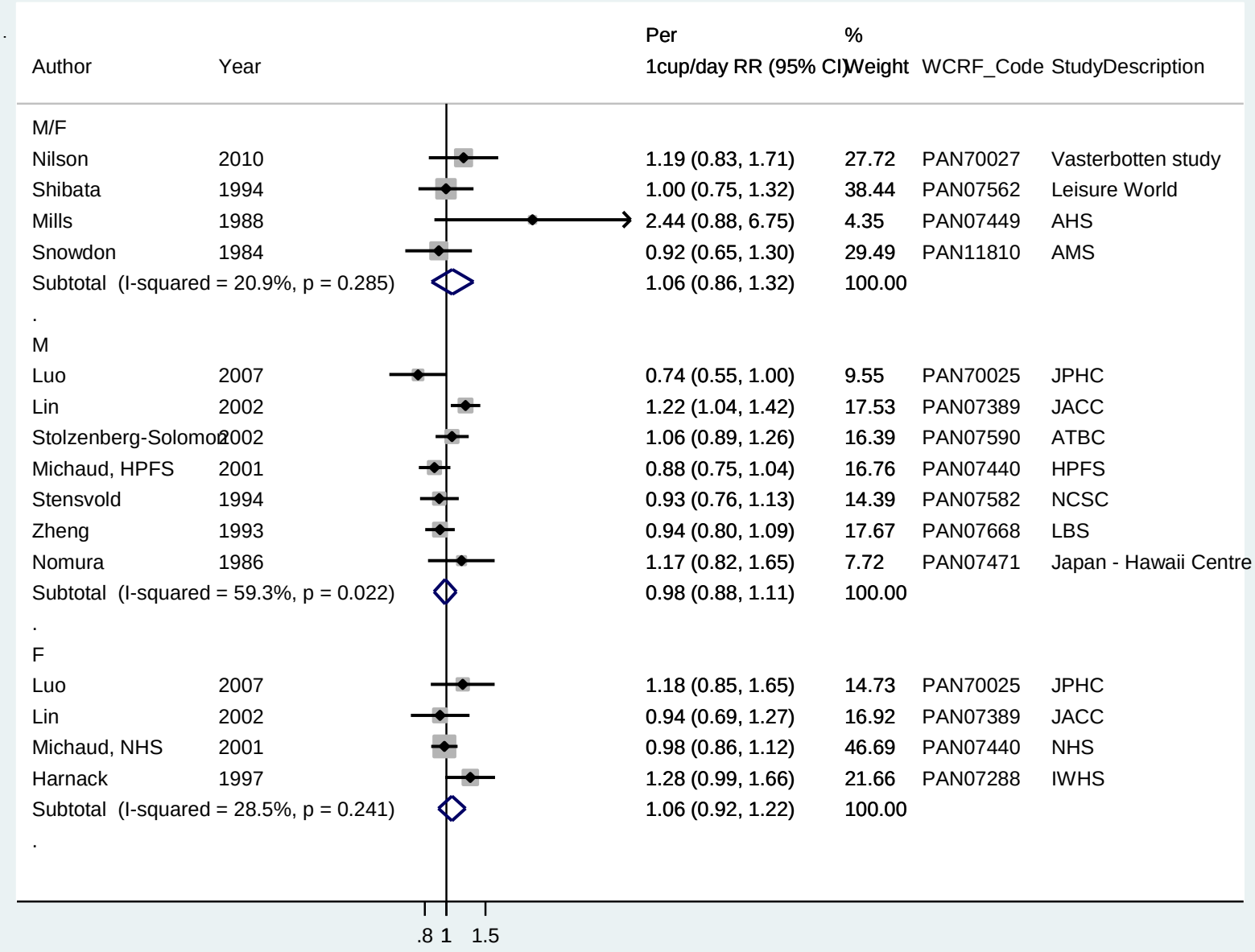
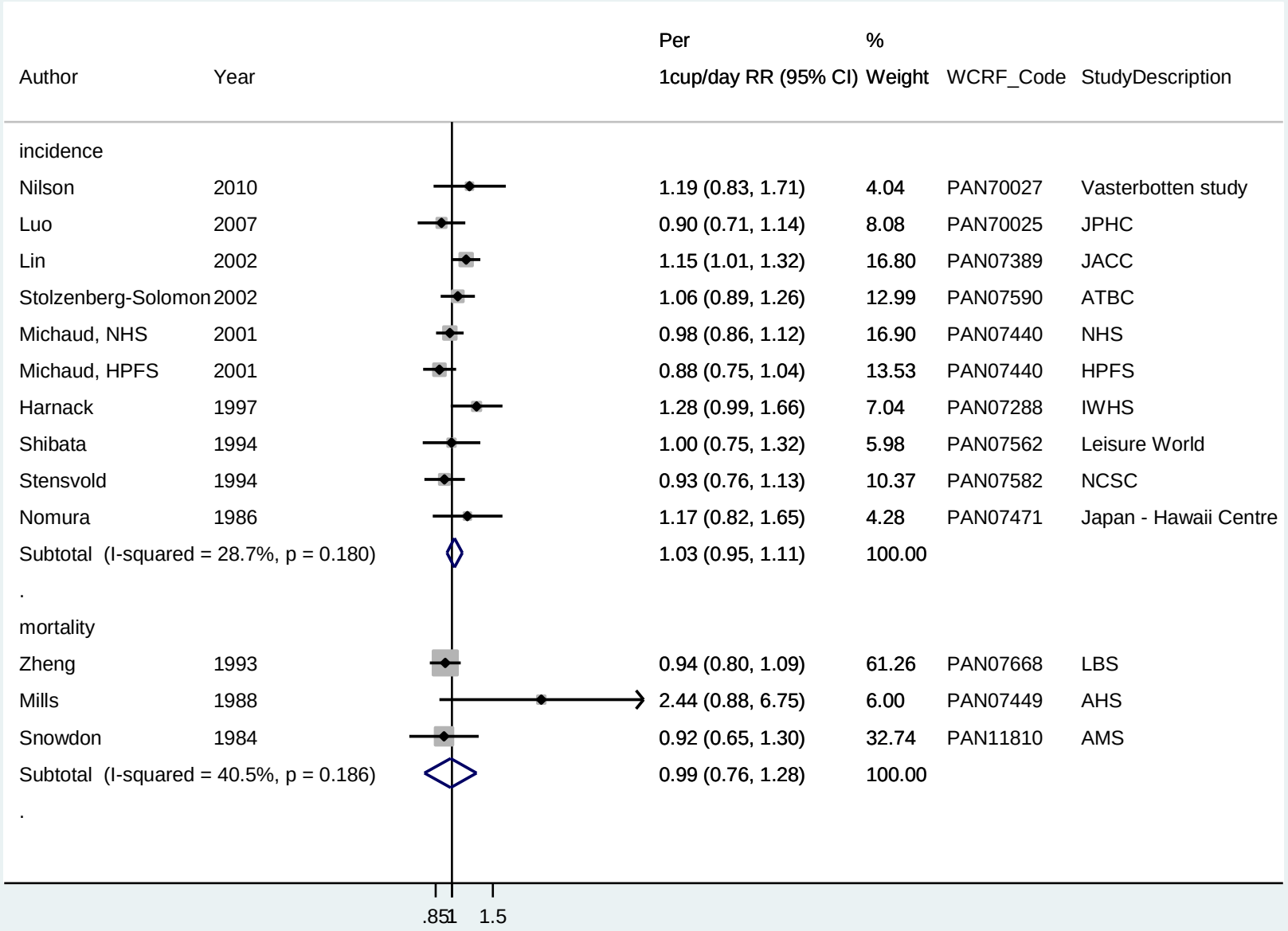


Figure 57 Dose-response meta-analysis of coffee intake and pancreatic cancer, stratified by outcome type – per cup/day



3.6.2 Tea

Methods

Eleven publications from 10 different cohorts were identified, three of these during the CUP. Dose-response meta-analysis for cohort studies was performed in the previous SLR report. In this report, a meta-analysis including 7 different studies (3 studies identified during the CUP and 4 studies identified during the 2007 SLR) was performed.

For the dose-response analyses all results were converted to a common scale (cups per day) and one cup was equivalent to 240 ml and used as the standard serving or portion size.

Main results

Seven studies were included in the meta-analysis. The summary RR per 1 cup/day was 0.91 (95% CI: 0.74-1.12; $P_{heterogeneity}$=0.11, 7 studies). The RR ranged from 0.82 (95% CI: 0.68-0.99) when excluding the EPIC study (Nöthlings et al, 2008) to 0.96 (95% CI: 0.79-1.18) when excluding the Leisure World Study (Shibata et al, 1994).

Heterogeneity

Moderate heterogeneity was found (I^2= 41.5%, p=0.11) between studies. No evidence of publication bias with Egger's test, p=0.53.

Comparison with the Second Expert Report

Overall, total tea intake was not associated with the risk of pancreatic cancer. RR for an increase of one cup/day = 0.91 (95% CI: 0.74-1.12) was similar to the previous SLR report (RR for one cup/day was 0.95 (95% CI: 0.82 - 1.09).

Published meta-analysis

A pooled analysis of 14 cohort studies reported no statistically significant associations between tea and pancreatic cancer, RR was 0.96 (95% CI, 0.78–1.16) comparing ≥400 to 0 g/d (Genkinger at al, 2011).

Table 54 Studies on tea intake identified in the CUP

Author, year	Country	Study name	Cases	Years of follow up	Sex	RR	LCI	UCI	Contrast
Bobe, 2008	Finland	Alpha Tocopherol Beta Carotene Cancer Prevention Study Cohort	306	16.1	M	0.96	0.71	1.29	> 0.65 vs 0 cups/day
Nöthlings, 2008	USA	Multiethnic Cohort	610	10	M/F	0.83	0.64	1.07	>1 vs 0 cups/day
Nöthlings, 2008	Europe	European Prospective Investigation into Cancer and Nutrition	517	13	M/F	1.53	0.80	2.92	> 2.38 vs 0 cups/day

Table 55 Overall evidence on tea intake and pancreatic cancer

	Summary of evidence
SLR	Data were extracted from 8 publications on 6 different cohort studies. Of these, 5 publications contributed information to the meta-analysis. The summary relative risk from the cohort studies was 0.95 (95% CI: 0.82 1.09) per 1 cup/day (p=0.5).
Continuous Update Project	Two publications from three cohort studies were identified. Two studies showed an inverse association between tea intake and pancreatic cancer and the other one showed a positive association, however none of the relationships was statistically significant. Eight studies were included in the high versus low forest plot.

Table 56 Summary of results of the dose response meta-analysis of tea intake and pancreatic cancer

Pancreatic cancer		
	SLR	Continuous Update Project
Studies (n)	5	7
Cases (n)	576	2075
Increment unit used	Per cup/day	Per cup/day
Overall RR (95%CI)	0.95 (0.82-1.09)	0.91(0.74-1.12)
Heterogeneity (I^2,p-value)	27%, p=0.2	41.5%, p=0.11
Stratified analysis		
Men	-	0.83 (0.56-1.22) (n=2)
Heterogeneity (I^2,p-value)		0%, p=0.60
Women		1.03 (0.67-1.57) (n=2)
Heterogeneity (I^2,p-value)		0%, p=0.76

Table 57 Inclusion/exclusion table for meta-analysis of tea and pancreatic cancer

WCRF_ Code	Author	Year	Study Design	Study Name	Subgroup	Cancer Outcome	SLR	CUP dose-response meta-analysis	CUP HvL forest plot	Estimated values	Exclusion reasons
PAN70010	Bobe	2008	Prospective Cohort study	Alpha Tocopherol Beta Carotene Cancer Prevention Study Cohort	Men	Incidence	New	Yes	Yes	Mid-exposure values	
PAN70053	Nöthlings	2008	Prospective Cohort study	Multiethnic Cohort and European Prospective Investigation into Cancer and Nutrition	Men/Women	Incidence	New	Yes	Yes	Mid-exposure values	
PAN07590	Stolzenberg-Solomon	2002	Prospective Cohort study	Alpha Tocopherol Beta Carotene Cancer Prevention Study Cohort	Men	Incidence	Yes	No	No		Superseded by Bobe 2008
PAN07440	Michaud	2001	Prospective Cohort study	The Nurse's Health Study Cohort and Health Professional Study	Men/Women	Mortality/ incidence	Yes	Yes	Yes	Mid-exposure values	
PAN07288	Harnack	1997	Prospective Cohort study	Iowa Women's Health Study	Women	Mortality/ incidence	Yes	Yes	Yes	Mid-exposure values	
PAN12667	Zheng	1996	Prospective Cohort study	Iowa Women's Health Study	Women	Incidence	No	No	No		Superseded by Hamack 1997
PAN07562	Shibata	1994	Prospective Cohort study	Leisure World Cohort Study	Men/Women	Incidence	Yes	Yes	Yes	Mid-exposure values	
PAN60025	Klatsky	1993	Prospective Cohort study	Members of the Kaiser Permanent Medical Care Program including Oakland	Men/Women	Mortality	Yes	No	No		No measure of the relationship

PAN00627	Kinlen.	1988	Prospective Cohort study	UK study	Men	Mortality	Yes	No	No		Did not present data in an appropriate format (only unadjusted results)
PAN07638	Whittemore	1985	Nested Case Control study	College Alumni Health Study	Men/Women	Mortality/ Incidence	Yes	No	Yes		Only two categories
PAN07637	Whittemore	1983	Nested Case Control study	College Alumni Health Study	Men	Mortality	Yes	No	No		Superseded by Whittemore 1985

Figure 58 Highest versus lowest forest plot of tea intake and pancreatic cancer

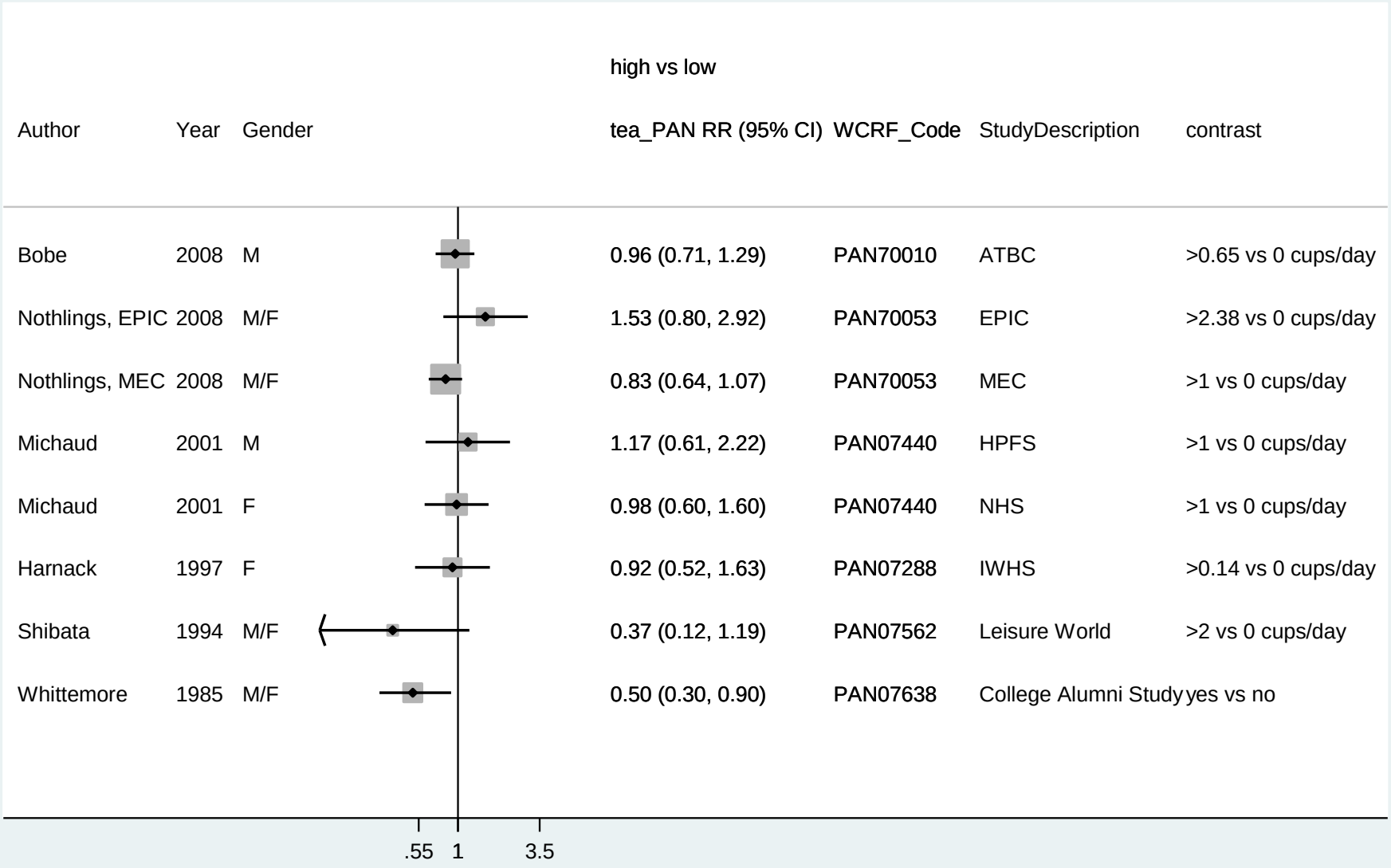


Figure 59 Dose-response meta-analysis of tea intake and pancreatic cancer– per cup/day

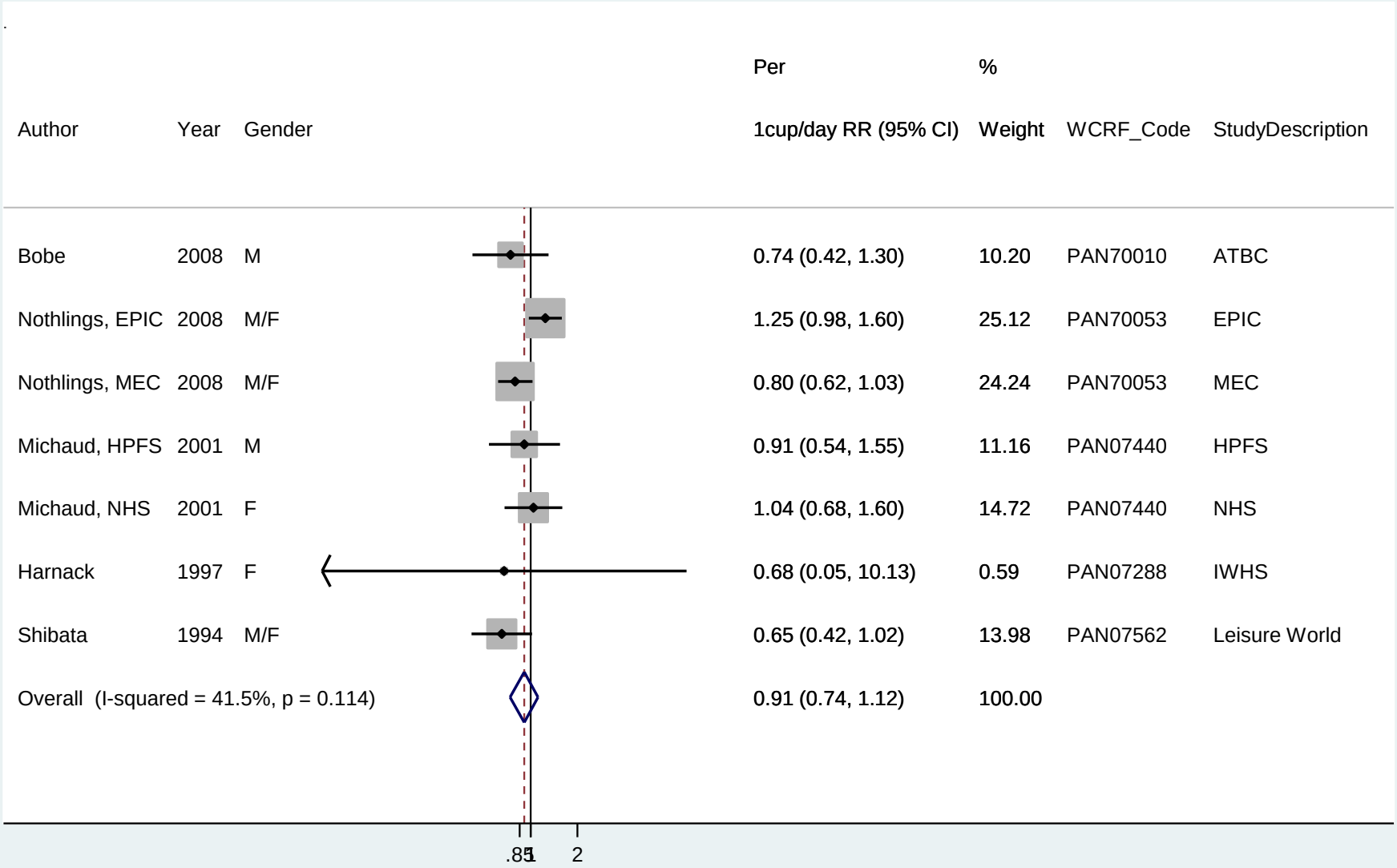


Figure 60 Funnel plot of tea intake and pancreatic cancer

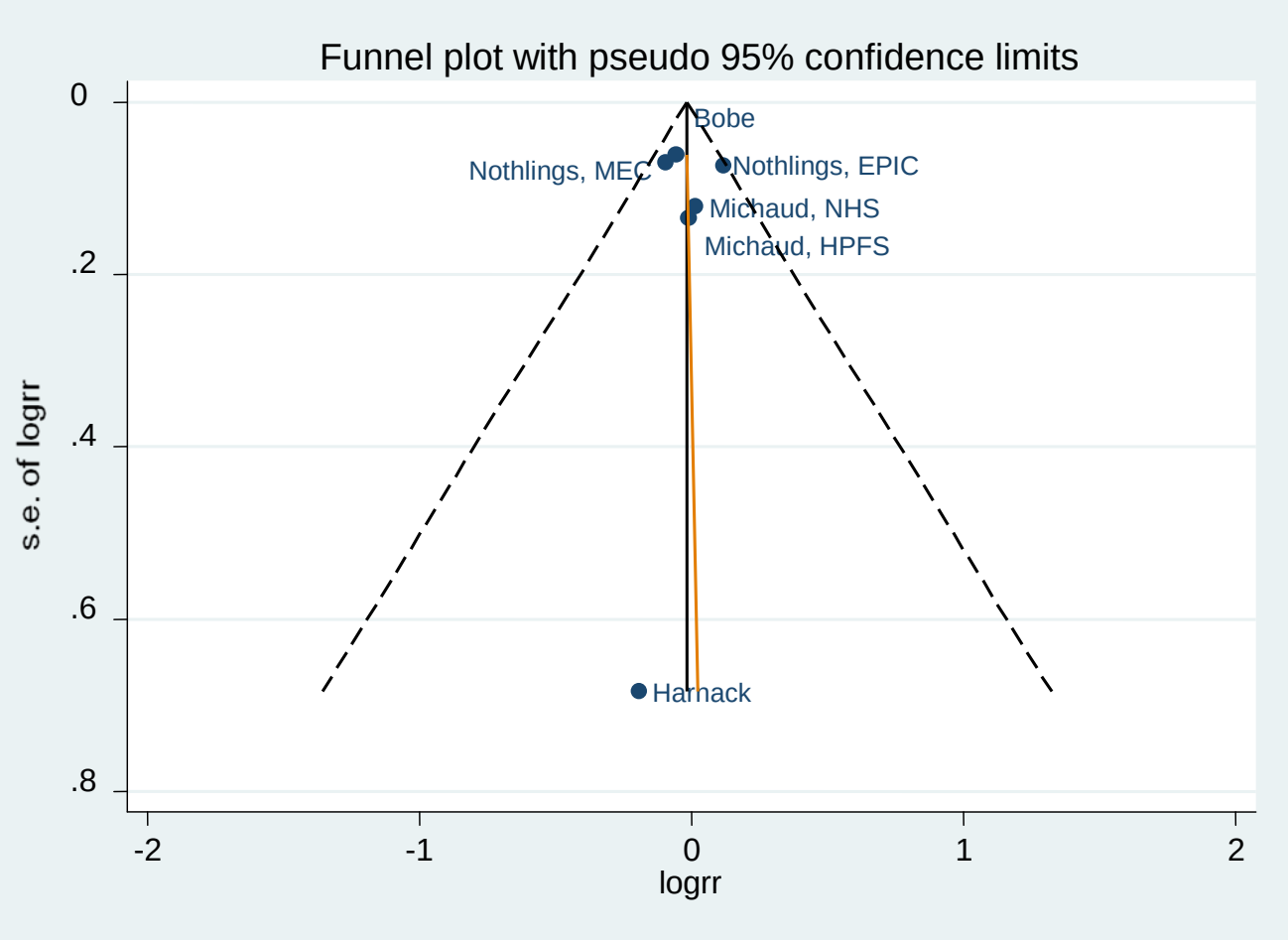


Figure 61 Dose-response graph of tea intake and pancreatic cancer

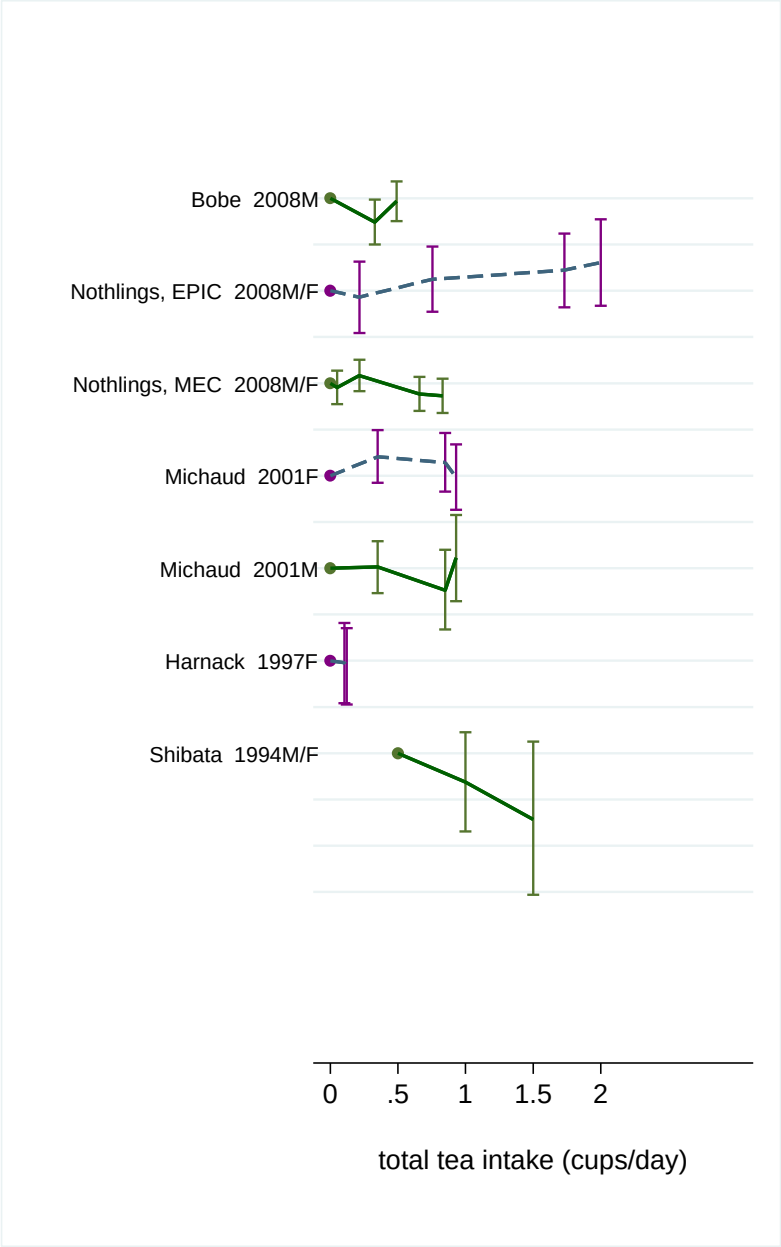
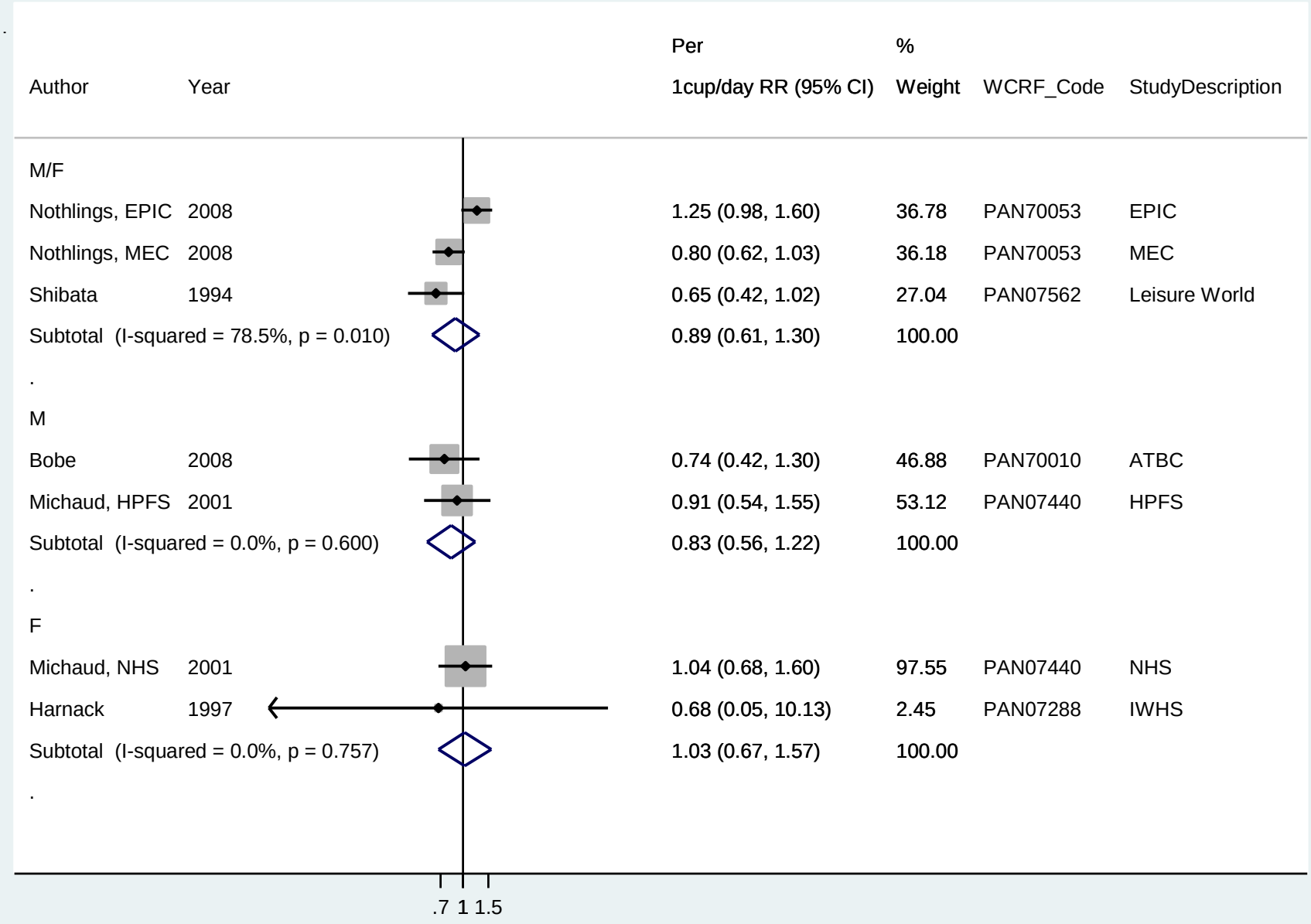


Figure 62 Dose-response meta-analysis of tea intake and pancreatic cancer, stratified by sex – per cup/day



3.7.1 Total alcoholic drinks

Methods

Nine cohort studies (12 publications) were identified, three of which were identified during the CUP. Studies reporting ethanol from alcoholic drinks (g/day) are reviewed in Section 5.4 and not here. Dose-response meta-analysis for pancreatic cancer was performed in the previous SLR report. In this report, a meta-analysis including 6 different studies (3 studies identified during the CUP and 3 studies identified during the 2007 SLR) was performed.

Main results

The summary RR per 1 drink/week was 1.00 (95% CI: 0.99-1.01; $P_{heterogeneity}<0.001$, 6 studies) for incidence or mortality of pancreatic cancer. The RR ranged from 0.99 (95% CI: 0.98-1.01) when excluding the NIH-AARP study (Jiao et al, 2009) to 1.00 (95% CI: 0.99-1.01) when excluding the MWS (Stevens et al, 2009).

Of the three excluded studies, one study in Norwegians did not report association with alcoholic drinks categorized only in two groups of alcohol consumption (Nilsen et al, 2000), one small study in US did not find any association (Hiatt et al, 1988) and one study that reported a U-shaped association of alcohol and mortality on Health Professionals men in US (Gaziano et al, 2000) did not find a significant association with pancreatic cancer mortality. There was evidence of a nonlinear association between total alcoholic drinks and pancreatic cancer risk, $p_{nonlinearity}<0.0001$.

Heterogeneity

High heterogeneity was observed overall ($I^2= 93.0\%$, $p<0.001$). This is probably explained by one small study on men (Zheng et al, 1993) that reported strong positive associations. Although Egger's tests was not statistically significant (p= 0.10) the funnel plot suggested small study bias. The small study of Zheng et al, 1993 was an outlier and there were no studies of similar precision showing inverse or null effect.

Comparison with the Second Expert Report

Overall, in the updated meta-analysis, alcohol was not associated with the risk of pancreatic cancer. RR for an increase of one drink/week = 1.00 (95% CI: 0.99-1.01) was compatible to that reported in the previous SLR report (RR for one drink/week was 0.98 (95% CI= 0.97 to 0.99).

Published meta-analysis

A meta-analysis of cohort and case control studies (Tramacere et al, 2009) reported an overall significant inverse association of moderate alcohol intake (<3 drinks/day) and pancreatic cancer risk (pooled RR = 0.92 (95%CI: 0.86–0.97) and a significant increased association for higher levels of alcohol intake (pooled RR=1.22 (95% CI: 1.12–1.34) compared with non-drinking. This meta-analysis included studies that reported on alcoholic drinks and on ethanol from alcoholic drinks. Reports on ethanol from alcoholic beverages are included in Section Section 5.4 in the CUP report.
A pooled analysis of the PanScan project investigated ethanol from alcoholic drinks. It is reviewed under Section 5.4.

Table 58 Studies on total alcoholic drinks identified in the CUP

Author, year	Country	Study name	Cases	Years of follow up	Sex	RR	LCI	UCI	Contrast
Gapstur, 2011	USA	Cancer Prevention Study II	6847	24	M/F	1.17	1.06	1.29	≥28 vs 0 drinks/week
Stevens, 2009	United Kingdom	The Million Women Study	1338	7	F	1.01	0.94	1.09	≥ 14 vs 0 drinks/week
Jiao L, 2009	USA	NIH- AARP Diet and Health Study	1149	7.3	M F	1.70 1.24	1.20 0.72	2.38 2.13	≥ 6 vs 0 drinks/week 3-3.99 vs 0 drinks/week
Jiao L, 2009	USA	NIH- AARP Diet and Health Study	1057	7.2	M F	0.78 1.11	0.64 0.82	0.95 1.51	≤ 2 vs 2 drinks/day ≤1 vs >1 drinks/day

Table 59 Overall evidence on total alcoholic drinks and pancreatic cancer

	Summary of evidence
SLR	Data were extracted from 8 publications from 7 studies. The summary relative risk from the 4 cohort studies included was 0.98 (95% CI: 0.97 - 0.99) per 1 drink/week (p=0.004).
Continuous Update Project	Four publications from three cohort studies were identified. One study reported on female and the others on male and female. All studies found positive associations between alcoholic drinks and pancreatic cancer, but only two were statistically significant.

Table 60 Summary of results of the dose response meta-analysis of total alcoholic drinks and pancreatic cancer

Pancreatic cancer		
	SLR	Continuous Update Project
Studies (n)	4	6
Cases (n)	4039	9522
Increment unit used	Per drink/week	Per drink/week
Overall RR (95%CI)	0.98 (0.97-0.99)	1.00 (0.99-1.01)
Heterogeneity (I^2,p-value)	0%, p=0.6	93.0%, p<0.001
Stratified analysis		
Men	-	1.01 (1.00-1.02) (n=3)
Heterogeneity (I^2,p-value)		74.7%, p=0.02
Women		1.00 (0.98-1.01) (n=4)
Heterogeneity (I^2,p-value)		92.2%, p<0.001

Table 61 Inclusion/exclusion table for meta-analysis of total alcoholic drinks and pancreatic cancer

WCRF_ Code	Author	Year	Study Design	Study Name	Subgroup	Cancer Outcome	SLR	CUP dose-response meta-analysis	CUP HvL forest plot	Estimated values	Exclusion reasons
PAN70070	Gapstur	2011	Prospective Cohort study	Cancer Prevention Study II	Men/Women	Mortality	New	Yes	Yes	Mid-exposure values	
PAN70044	Stevens	2009	Prospective Cohort study	The Million Women Study	Women	Incidence	New	Yes	Yes	Confidence intervals, Mid-exposure values	
PAN70046	Jiao	2009	Prospective Cohort study	NIH- AARP Diet and Health Study	Men/Women	Incidence	New	Yes	Yes	Mid-exposure values	
PAN70054	Jiao	2009	Prospective Cohort study	NIH- AARP Diet and Health Study	Men/Women	Incidence	New	No	No		Superseded by Jiao L, 2009 (PAN70046)
PAN07195	Coughlin	2000	Prospective Cohort study	Cancer Prevention Study II	Men/Women	Mortality	Yes	No	No		Superseded by Gapstur 2011
PAN14732	Nilsen	2000	Prospective Cohort study	Nord-Trondelag, Norway	Men/Women	Incidence	Yes	No	Yes		Only two categories
PAN69934	Gaziano	2000	Prospective Cohort study	Physician's Health Study	Men	Mortality	Yes	No	Yes		No number of cases per category
PAN07288	Harnack	1997	Prospective Cohort study	Iowa Women's Health Study	Women	Mortality/ Incidence	Yes	Yes	Yes	Mid-exposure values	
PAN07562	Shibata	1994	Prospective Cohort study	Leisure World Cohort Study	Men/Women	Incidence	Yes	Yes	Yes	Mid-exposure values	
PAN07668	Zheng	1993	Prospective Cohort study	Lutheran Brotherhood Insurance Society	Men	Mortality	Yes	Yes	Yes	Mid-exposure values	
PAN04147	Friedman	1993	Nested case control study	Members of the Kaiser Permanent Medical Care Program including Oakland	Men/Women	Incidence	Yes	No	Yes		No number of cases per category

PAN07294	Hiatt	1988	Case-cohort study	Members of the Kaiser Permanent Medical Care Program	Men/Women	Incidence	Yes	No	No (Superseded by Friedman 1993)		No number of cases per category (Same cohort as Friedman 1993)

Figure 63 Highest versus lowest forest plot of total alcoholic drinks and pancreatic cancer

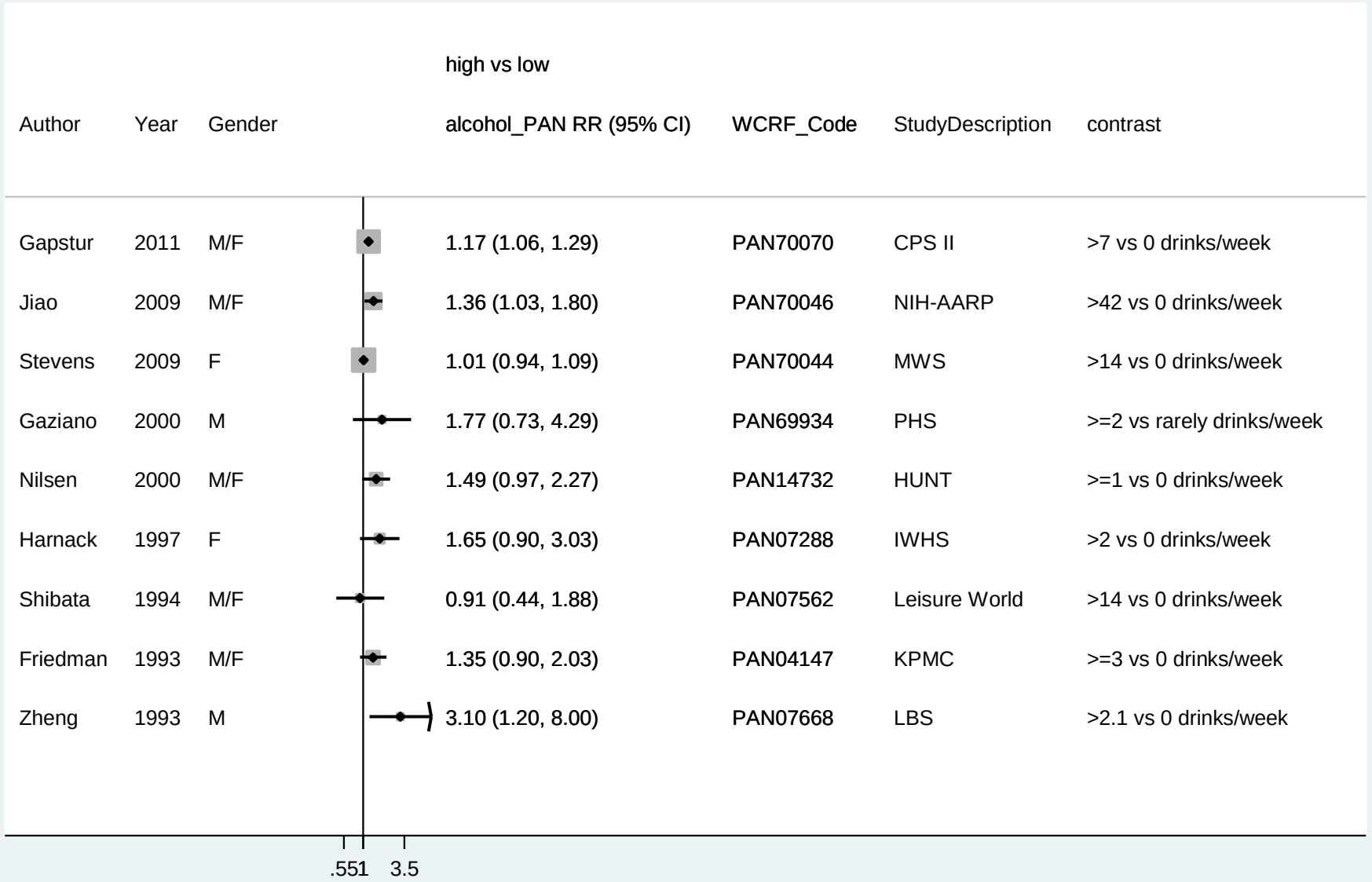


Figure 64 Dose-response meta-analysis of total alcoholic drinks and pancreatic cancer – per drink/week

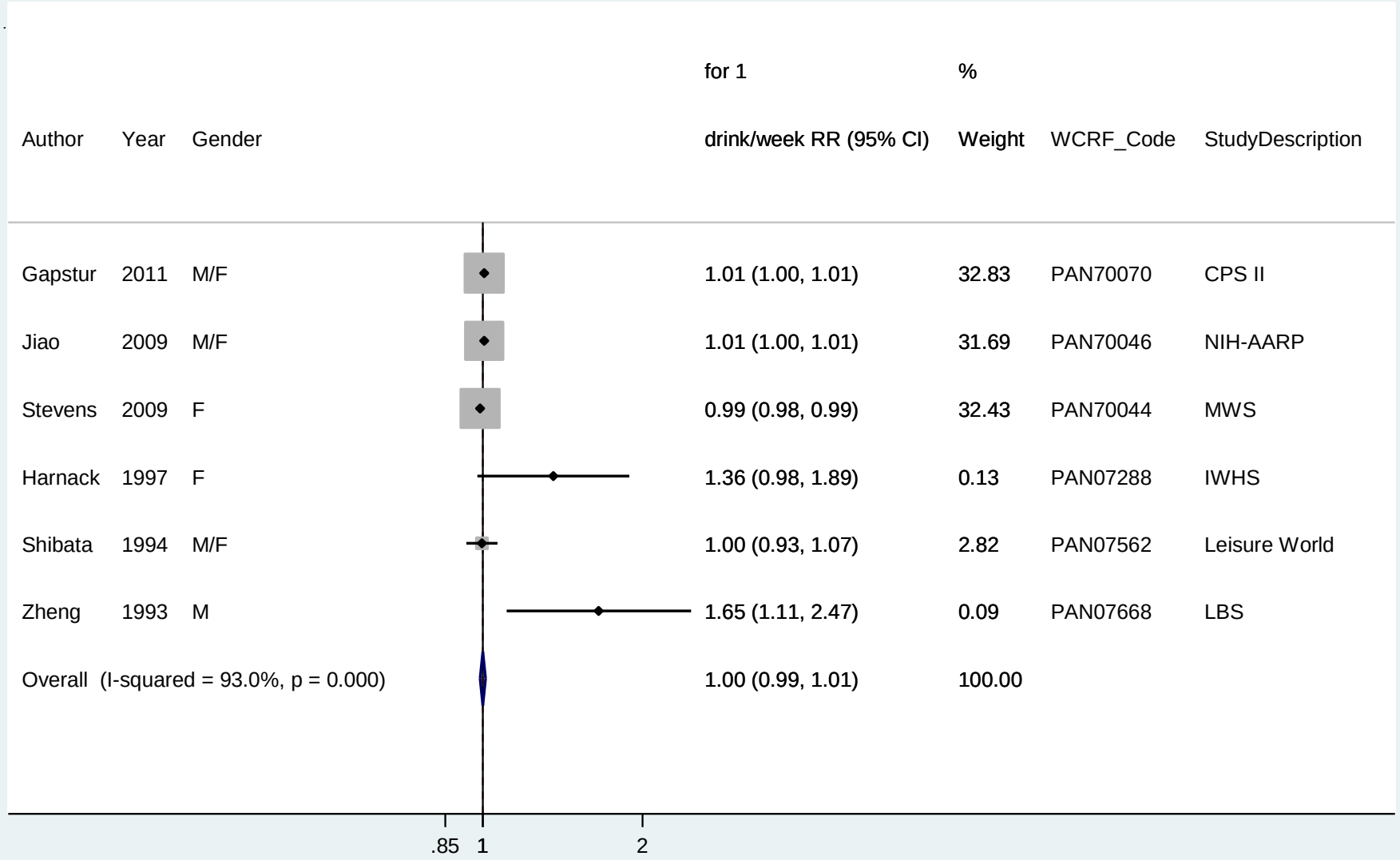


Figure 65 Funnel plot of total alcoholic drinks and pancreatic cancer

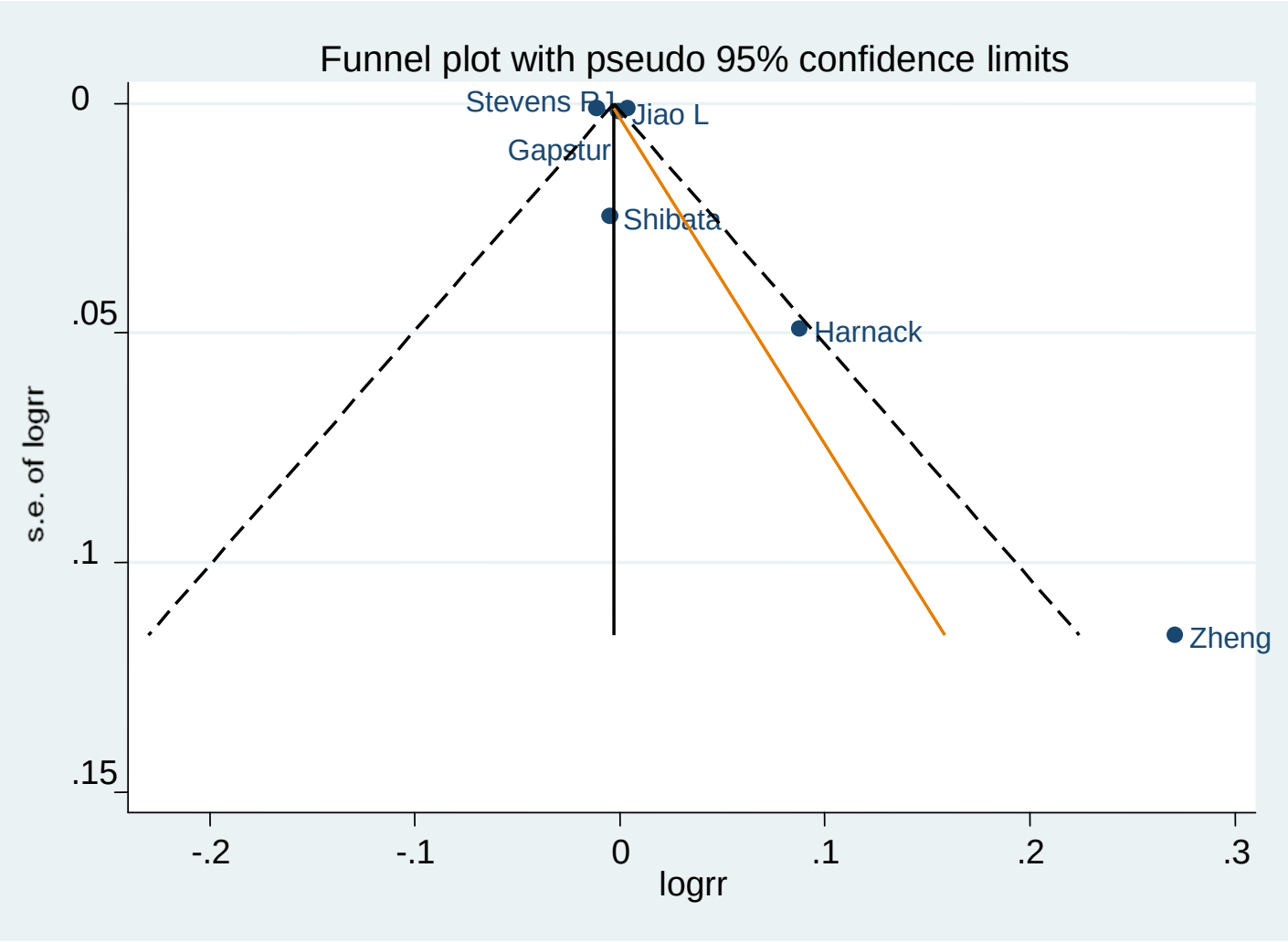


Figure 66 Dose-response graph of total alcoholic drinks and pancreatic cancer

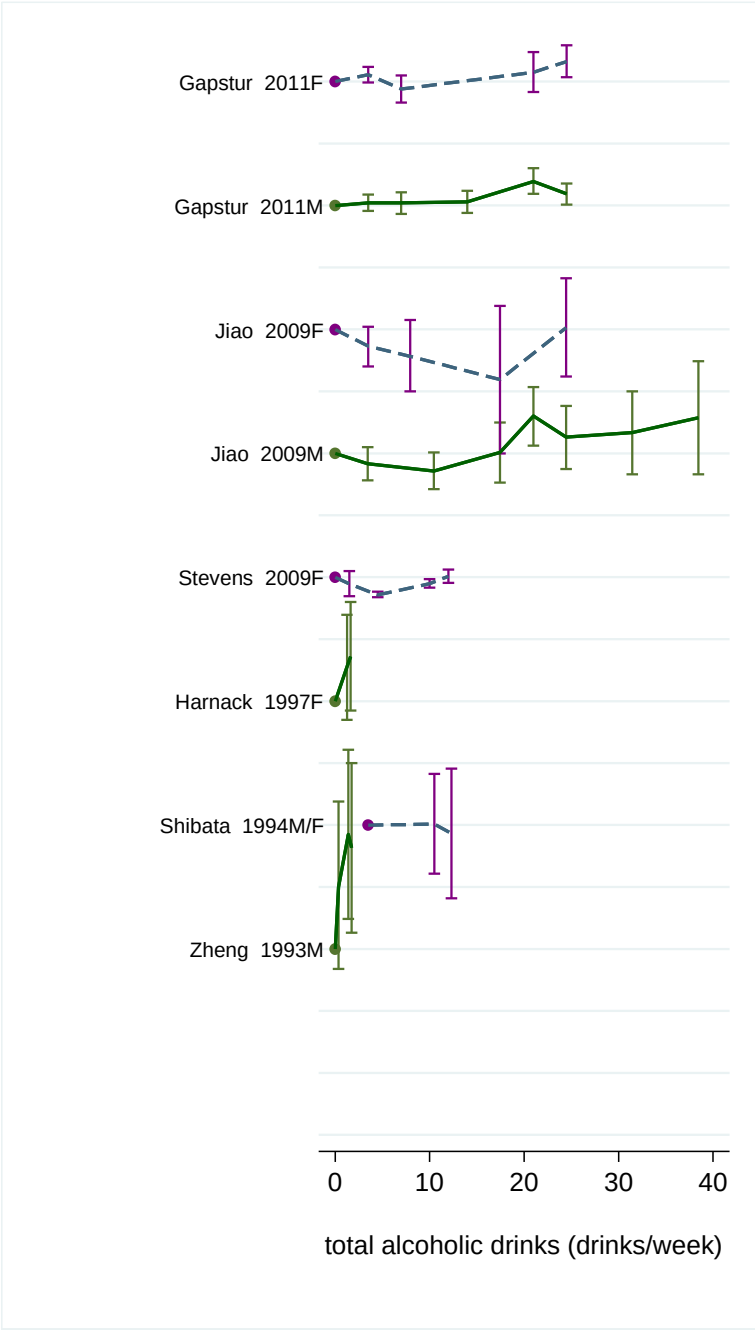


Figure 67 Dose-response meta-analysis of total alcoholic drinks and pancreatic cancer, stratified by sex– per drink/week

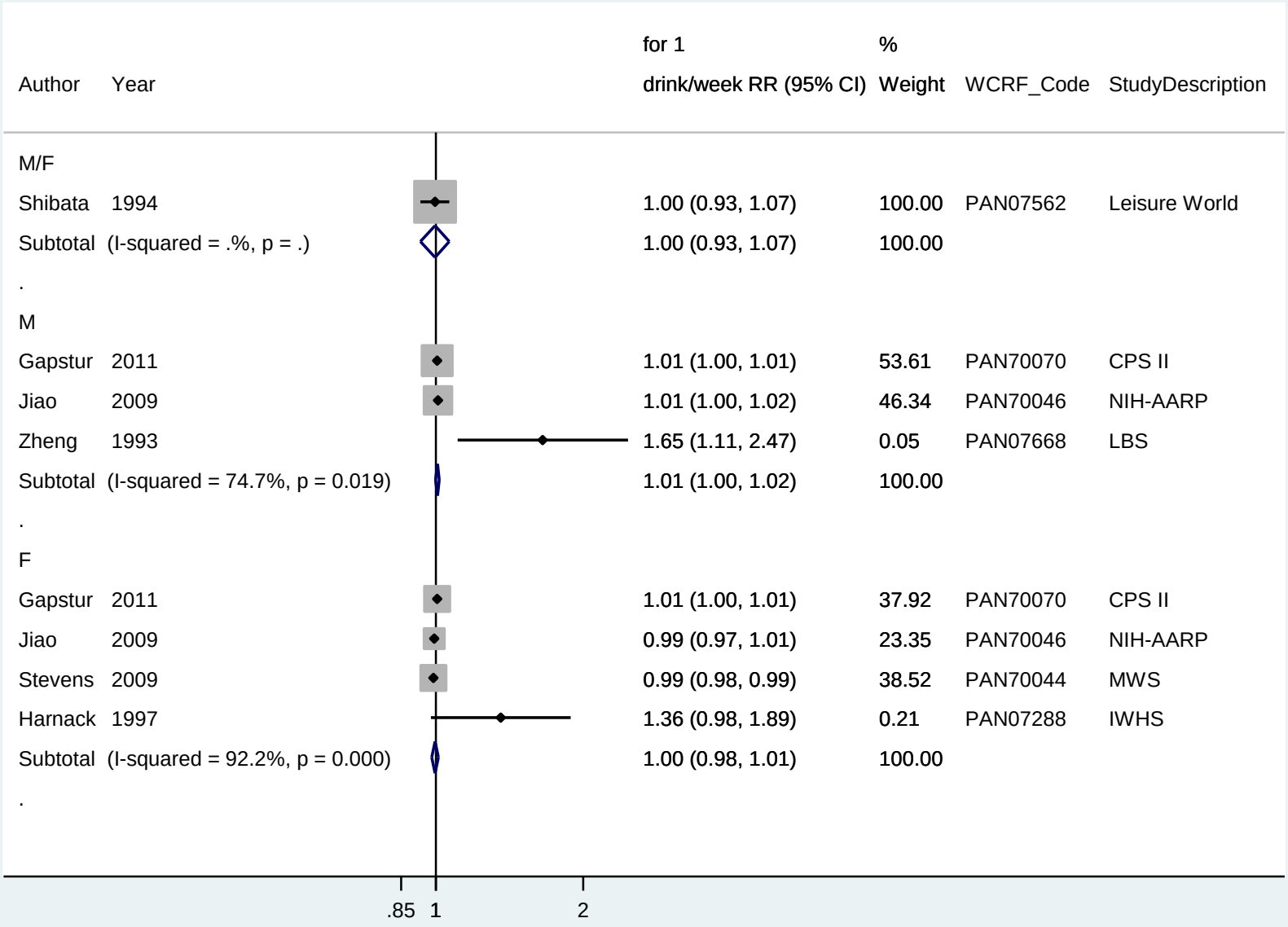


Figure 68 Dose-response meta-analysis of total alcoholic drinks and pancreatic cancer, stratified by outcome type – per drink/week

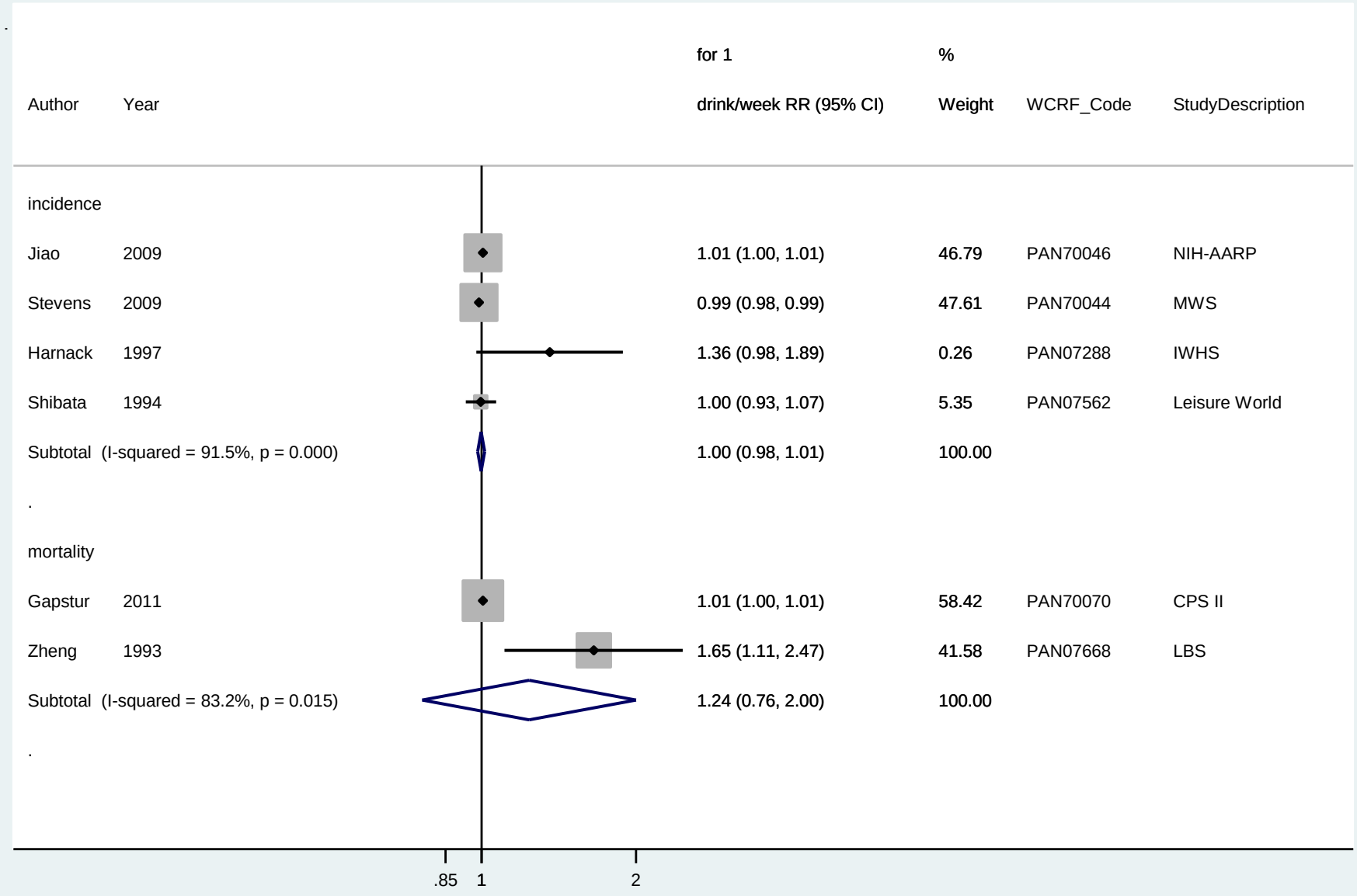


Figure 69 Nonlinear dose-response analysis of total alcoholic drinks and pancreatic cancer

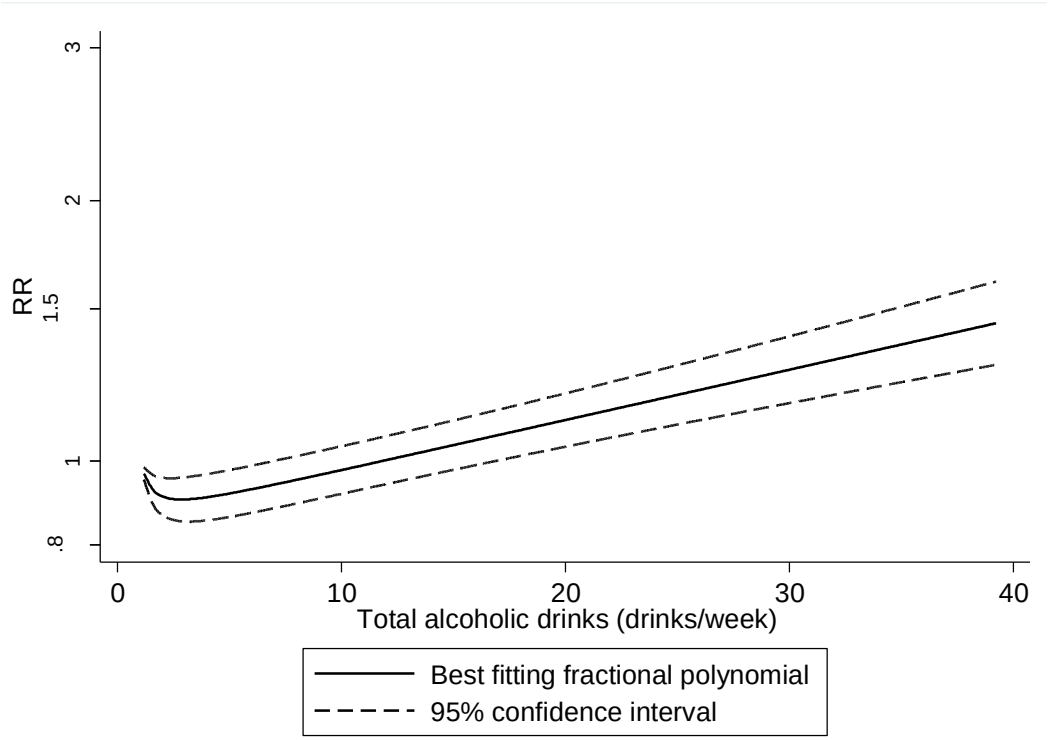


Figure 70 Scatter plot of risk estimates of total alcoholic drinks and pancreatic cancer

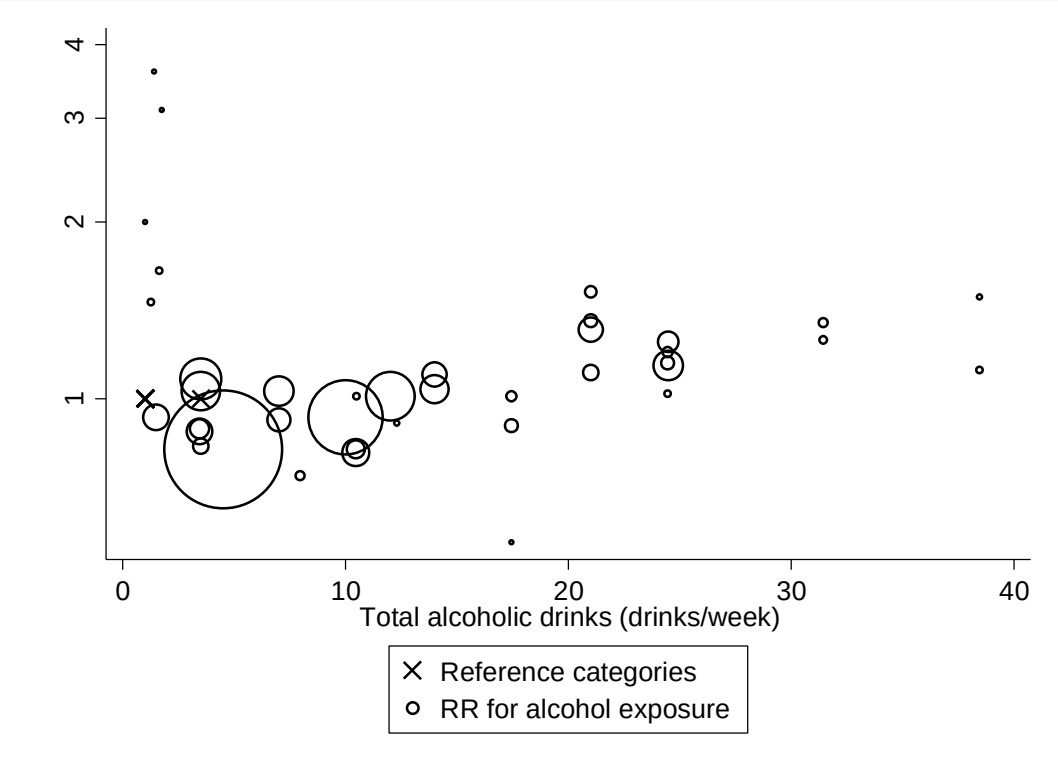


Table 62 Table with total alcoholic drinks values and corresponding RRs (95% CIs) for nonlinear analysis of total alcoholic drinks and pancreatic cancer

Total alcoholic drinks (drinks/week)	RR (95% CI)
1	1.00
7	0.93 (0.88-1.0)
10	0.97 (0.91-1.04)
15	1.04 (0.97-1.11)
20	1.11 (1.03-1.20)
30	1.27 (1.16-1.39)

3.7.1.1 Beers

Methods

Overall, eight cohort studies have been identified up to September 2011, of which three studies were identified during the CUP. Dose-response meta-analysis for pancreatic cancer was performed in the previous SLR report. In this report, a meta-analysis including 5 different studies (3 studies identified during the CUP and 2 studies identified during the 2007 SLR) was performed.

Main results

Dose-response meta-analysis showed a summary RR for an increase of one drink/week of 1.00 (95% CI: 0.98-1.01; $P_{heterogeneity}$=0.03, 5 studies) for incidence or mortality of pancreatic cancer. The overall results remained the same when two studies with mortality as outcome were excluded from the analysis (RR= 0.99 (95% CI: 0.98-1.01). The RR ranged from 0.99 (95% CI: 0.97-1.02) when excluding the CPS II (Gapstur et al, 2011) to 1.00 (95% CI: 0.98-1.02) when excluding the NIH-AARP (Jiao et al, 2009).

Heterogeneity

Moderate heterogeneity was observed overall (I^2= 61.6%, p=0.03). This is explained by the extreme result of a small study in men (Zheng et al, 1993) (see funnel plot). Egger's tests suggested some evidence of publication bias, p= 0.02.

Comparison with the Second Expert Report

Overall, 1 drink/week was not associated with the risk of pancreatic cancer. The RR for an increase of one drink/week = 1.00 (95%CI: 0.98-1.01) in the updated report. The only study with information available for meta-analysis in the 2007 SLR was the study of Zheng et al, 1993 (RR per 1 drink/week: 1.30; 95% CI: 1.06, 1.60). The results of this study were not consistent with those of other studies (see forest plot).

Table 63 Studies on beers identified in the CUP

Author, year	Country	Study name	Cases	Years of follow up	Sex	RR	LCI	UCI	Contrast
Gapstur, 2011	USA	Cancer Prevention Study II	6847	24	M/F	1.08	0.90	1.30	≥21 vs 0 drinks/week
Heinen , 2009	Netherlands	The Netherlands Cohort study	350	13.3	M/F	0.79	0.52	1.20	≥ 5.0 vs 0 drinks/week
Jiao, 2009	USA	NIH- AARP Diet and Health Study	1149	7.3	M F	1.14 0.53	0.89 0.17	1.46 1.67	≥ 1.0 vs > 0-0.99 drinks/week

Table 64 Overall evidence on beers and pancreatic cancer

	Summary of evidence
SLR	Data were extracted from 5 studies, but the information provided was not enough for meta-analysis.
Continuous Update Project	Three cohort studies were identified. All reported on male and female and none of the studies found a significant association with pancreatic cancer risk. Six studies were included in the high versus low forest plot.

Table 65 Summary of results of the dose response meta-analysis of beers and pancreatic cancer

Pancreatic cancer		
	SLR*	Continuous Update Project
Studies (n)	-	5
Cases (n)	-	8469
Increment unit used	-	Per drink/week
Overall RR (95%CI)	-	1.00 (0.98-1.01)
Heterogeneity (I^2,p-value)		61.6%, p=0.03
Stratified analysis		
Men	-	1.11 (0.85-1.44) (n=2)
Heterogeneity (I^2,p-value)		78.8%, p=0.03
Women		1.09 (0.74-1.59) (n=2)
Heterogeneity (I^2,p-value)		51.6%, p=0.15

*No meta-analysis was conducted in the 2nd report.

Table 66 Inclusion/exclusion table for meta-analysis of beers and pancreatic cancer

WCRF_ Code	Author	Year	Study Design	Study Name	Subgroup	Cancer Outcome	SLR	CUP dose-response meta-analysis	CUP HvL forest plot	Estimated values	Exclusion reasons
PAN70070	Gapstur	2011	Prospective cohort study	Cancer Prevention Study II	Men/ Women	Mortality	New	Yes	Yes	Mid-exposure values, person years	
PAN70048	Heinen	2009	Prospective Cohort study	The Netherlands Cohort study	Men/ Women	Incidence	New	Yes	Yes	Mid-exposure values	
PAN70046	Jiao	2009	Prospective Cohort study	NIH- AARP Diet and Health Study	Men/ Women	Incidence	New	Yes	Yes	Mid-exposure values	
PAN07288	Harnack	1997	Prospective Cohort study	Iowa Women's Health Study	Women	Mortality/ Incidence	Yes	Yes	Yes	Mid-exposure values	
PAN07668	Zheng	1993	Prospective Cohort study	Lutheran Brotherhood Insurance Society	Men	Mortality	Yes	Yes	Yes	Mid-exposure values	
PAN07339	Kato	1992	Prospective Cohort study	Japan - Hawaii Centre	Men	Incidence	Yes	No	No		Only mean values
PAN07299	Hirayama	1989	Prospective Cohort study	6 Prefecture Cohort, Japan	Men/ women	Mortality	Yes	No	Yes		Only two categories
PAN07294	Hiatt	1988	Case-cohort study	Members of the Kaiser Permanent Medical Care Program	Men/Women	Incidence	Yes	No	No		Only mean values

Figure 71 Highest versus lowest forest plot of beers and pancreatic cancer

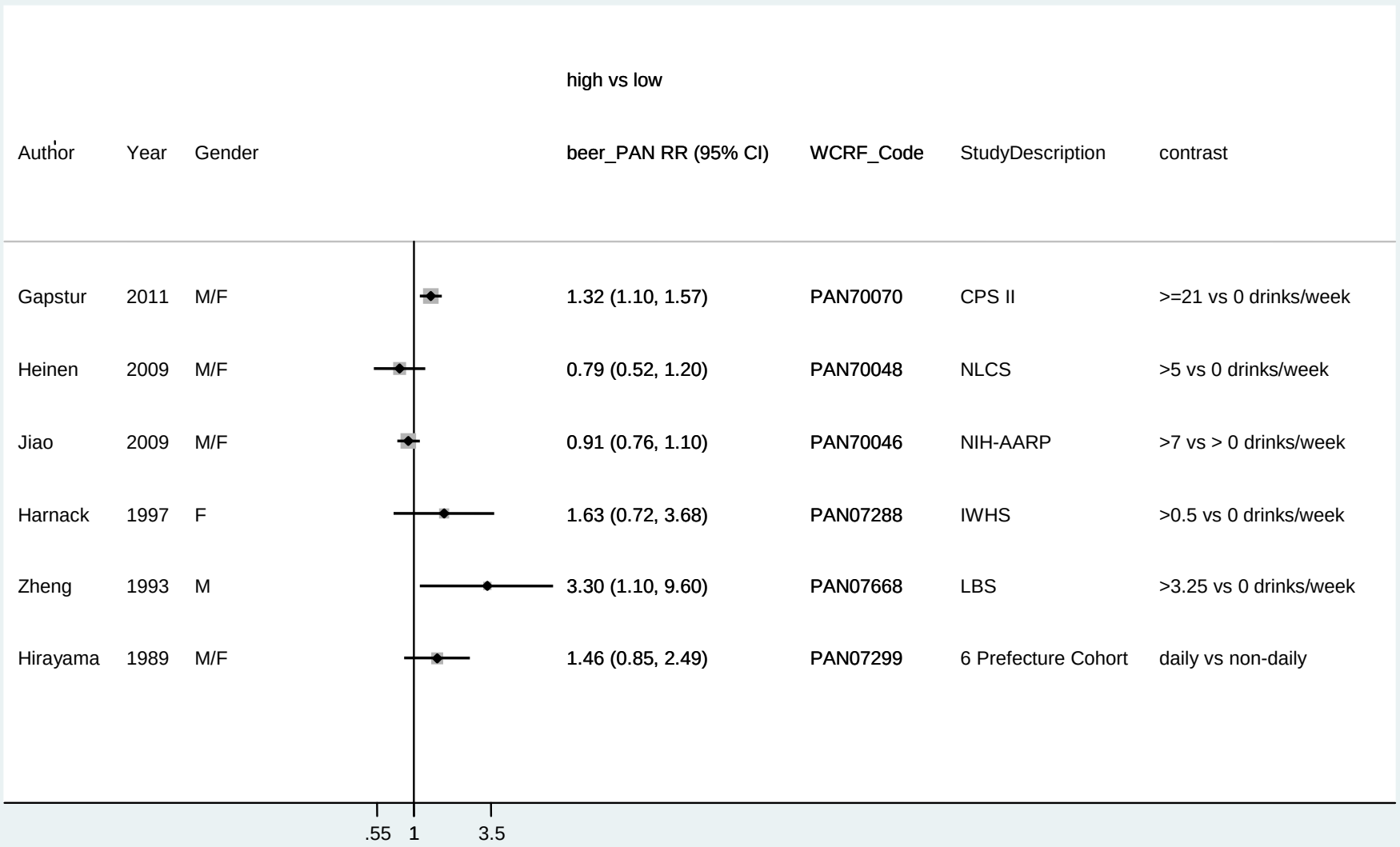


Figure 72 Dose-response meta-analysis of beers and pancreatic cancer – per drink/week

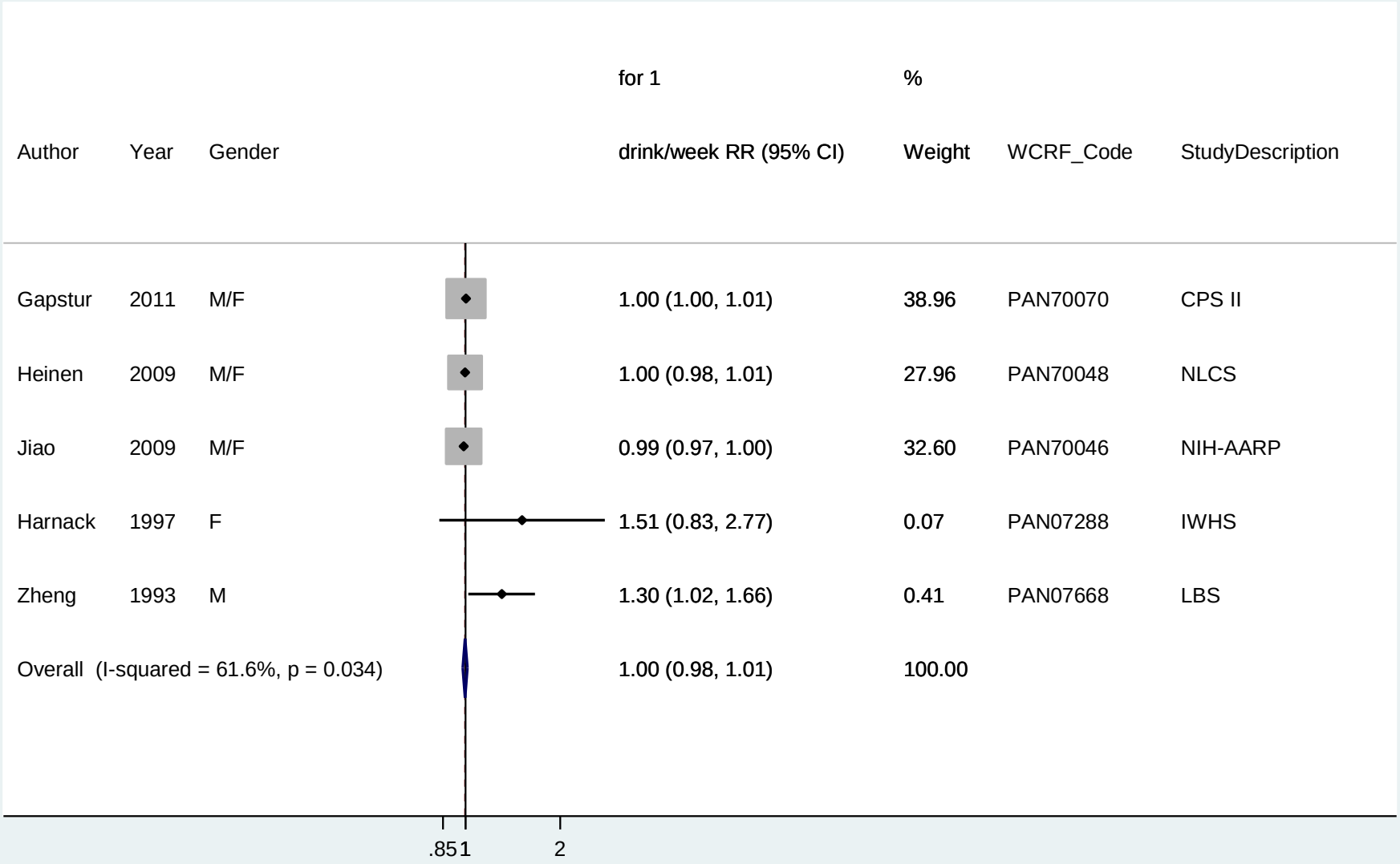


Figure 73 Funnel plot of beers and pancreatic cancer

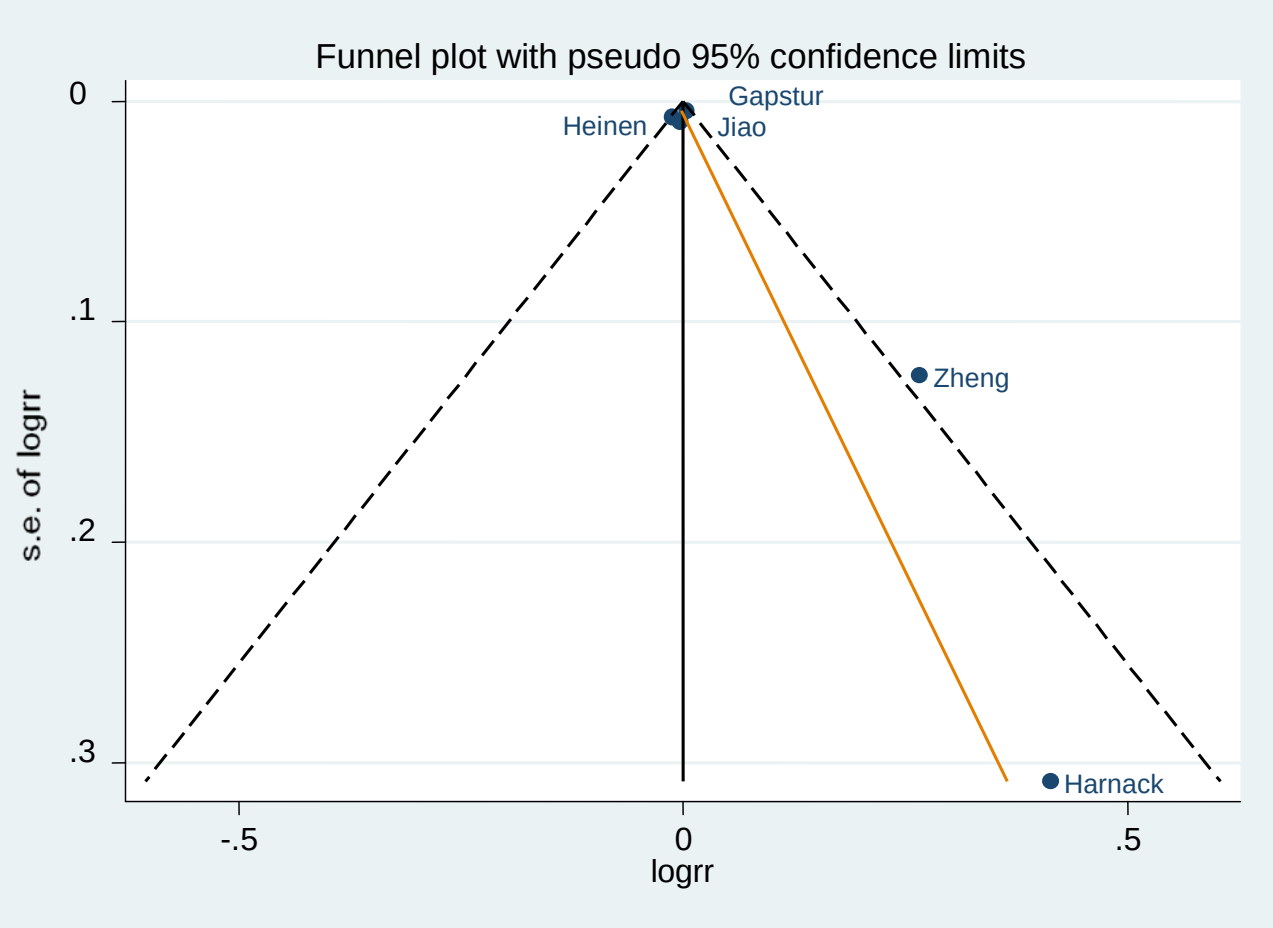


Figure 74 Dose-response graph of beers and pancreatic cancer

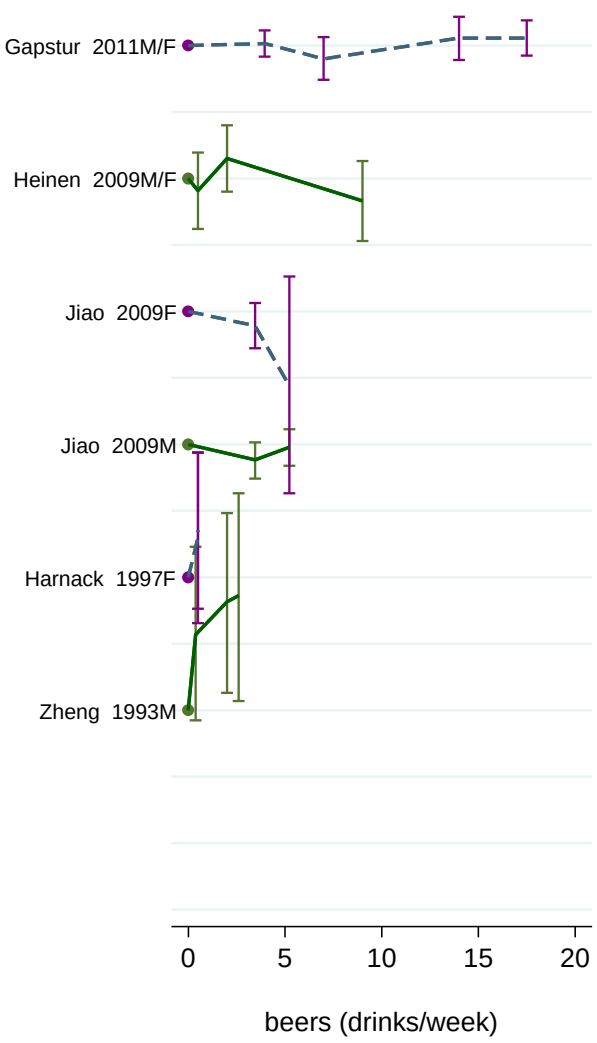


Figure 75 Dose-response meta-analysis of beers and pancreatic cancer, stratified by sex – per drink/week

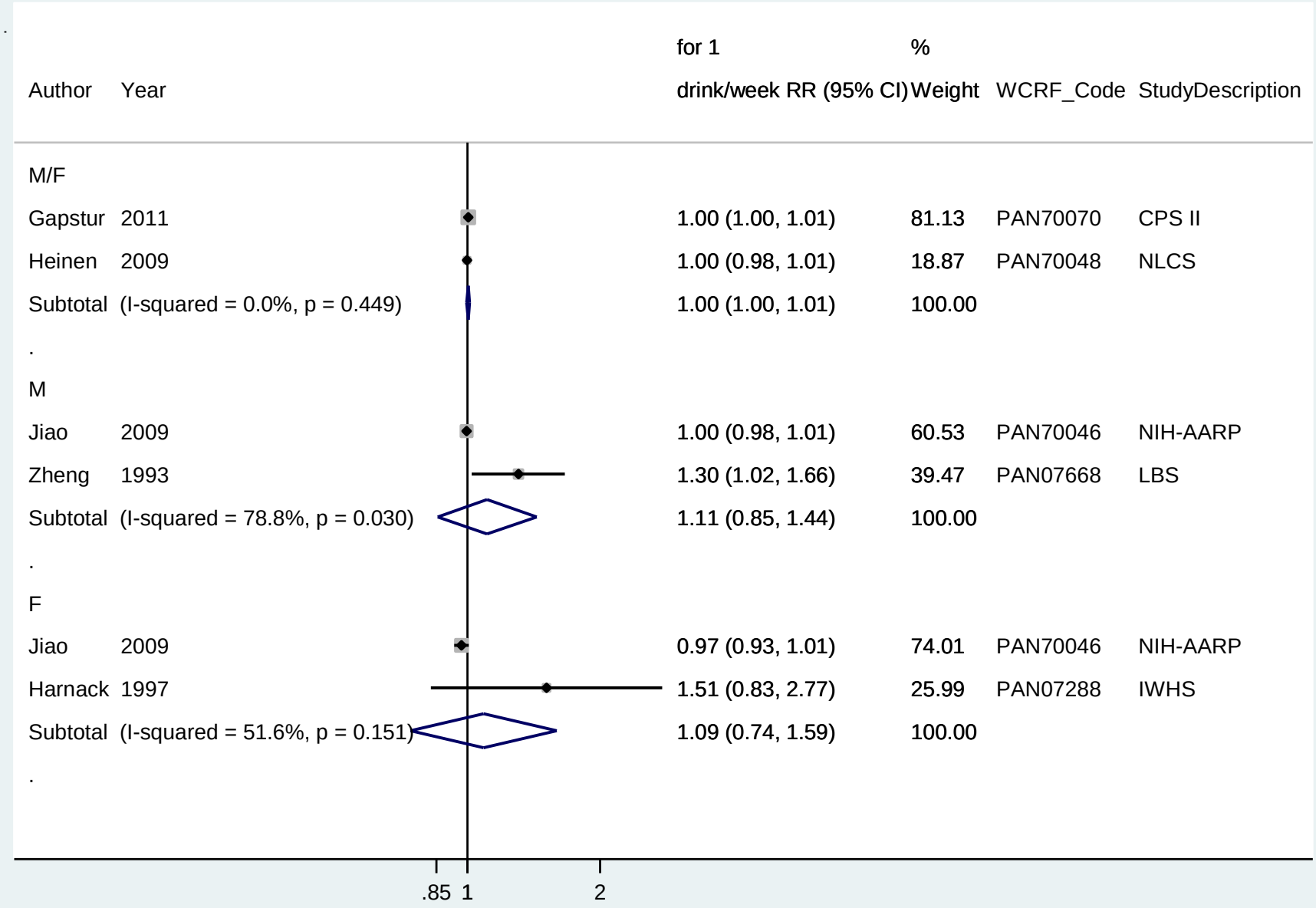
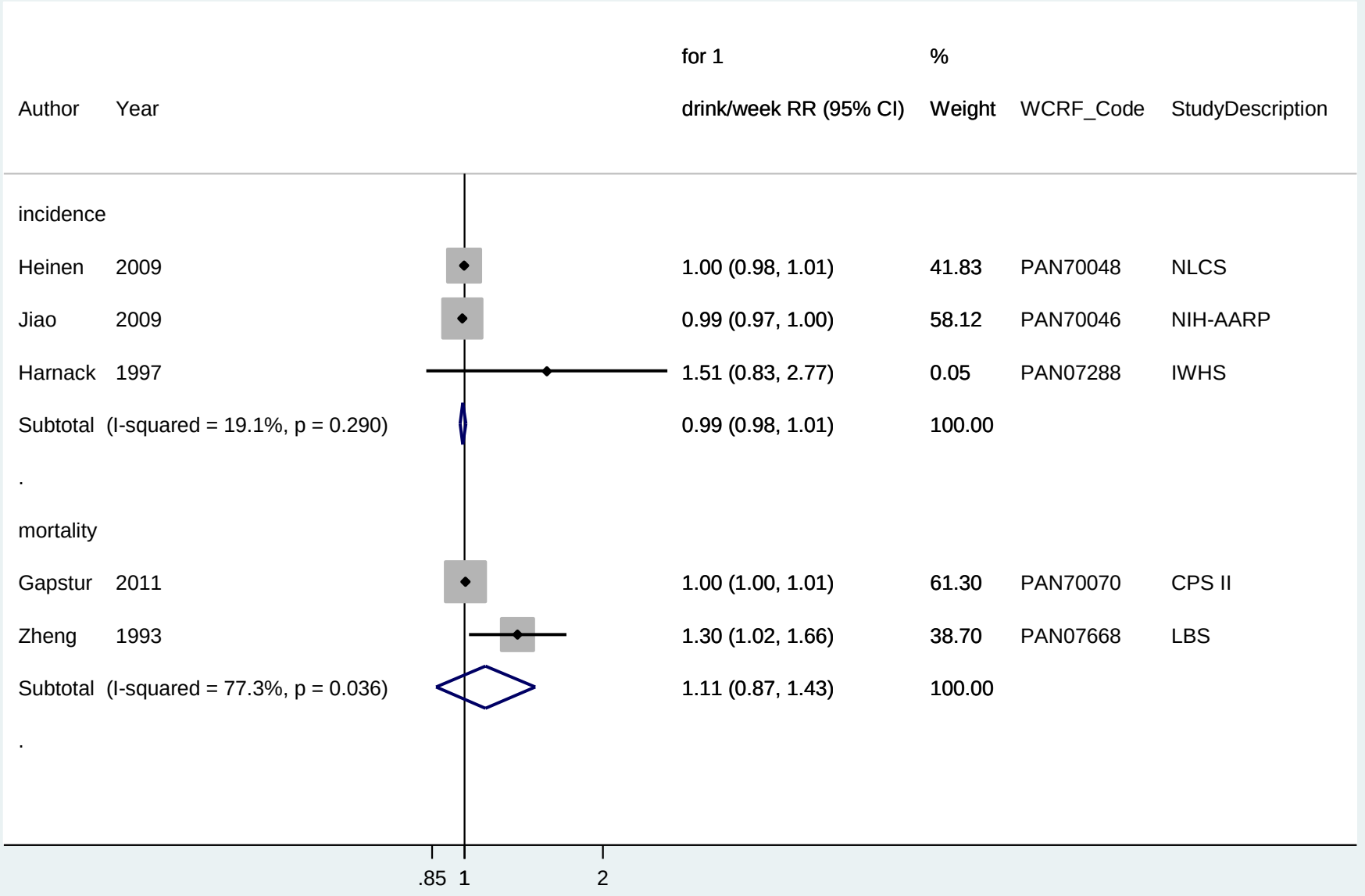


Figure 76 Dose-response meta-analysis of beers and pancreatic cancer, stratified by outcome type – per drink/week



3.7.1.2 Wine

Methods

Seven cohort studies were identified, from which four were identified during the CUP. Dose-response meta-analysis for cohort studies was not performed in the previous SLR report. In this report, a meta-analysis including 5 different studies (4 studies identified during the CUP and 1 study identified during the 2007 SLR) was performed. One study (ATBC, Bobe et al. 2008) presented the wine intake in grams per day and this was converted to servings per week using as conversion 1 serving=125g of wine.

Main results

The summary RR per 1 drink/week was 1.00 (95% CI: 0.99-1.01; $P_{heterogeneity}$=0.33, 5 studies) for incidence or mortality of pancreatic cancer. The overall results remained the same when one study with mortality as outcome was excluded from the analysis (RR= 1.01 (95% CI: 0.99-1.03). The RR ranged from 1.00 (95% CI: 0.99-1.01) when excluding the ATBC study (Bobe et al, 2008) to 1.00 (95% CI: 0.99-1.03) when excluding the NIH-AARP study (Jiao et al, 2009).

Heterogeneity

Low heterogeneity was observed overall (I^2=13.7%, p=0.33). Egger's tests suggested no evidence of publication bias, p= 0.48, but visual inspection shows the smallest study (Harnack et al, 1997) shows a stronger association compared with the other studies.

Comparison with the Second Expert Report

Overall, in the updated meta-analysis, wine was not associated with the risk of pancreatic cancer. RR for an increase of one drink/week = 1.00 (95% CI: 0.99-1.01) Dose-response meta-analysis for cohort studies was not performed in the previous SLR report.

Table 67 Studies on wine identified in the CUP

Author, year	Country	Study name	Cases	Years of follow up	Sex	RR	LCI	UCI	Contrast
Gapstur, 2011	USA	Cancer Prevention Study II	6847	24	M/F	1.09	0.79	1.49	≥21 vs 0 drinks/week
Heinen , 2009	Netherlands	The Netherlands Cohort study	350	13.3	M/F	1.18	0.84	1.66	≥ 5.0 vs 0 drinks/week
Jiao, 2009	USA	NIH- AARP Diet and Health Study	1149	7.3	M F	0.99 0.94	0.74 0.59	1.32 1.52	≥ 1.0 vs > 0-0.99 drinks/week
Bobe, 2008	Finland	Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study	306	16.1	M	1.02	0.70	1.49	>24.3 vs 0 g/day

Table 68 Overall evidence on wine and pancreatic cancer

	Summary of evidence
SLR	Three studies were identified. No meta-analysis was possible because two of the studies did not report measure of association.
Continuous Update Project	Four studies were identified. All reported on male and female. None of the studies reported significant association

Table 69 Summary of results of the dose response meta-analysis of wine and pancreatic cancer

Pancreatic cancer		
	SLR*	Continuous Update Project
Studies (n)	-	5
Cases (n)	-	8718
Increment unit used	-	Per drink/week
Overall RR (95%CI)	-	1.00 (0.99-1.01)
Heterogeneity (I^2,p-value)		13.7%, p=0.33
Stratified analysis		
Men	-	1.01 (0.99-1.04) (n=2)
Heterogeneity (I^2,p-value)		18.3%, p=0.27
Women		1.06 (0.84-1.35) (n=2)
Heterogeneity (I^2,p-value)		68.3%, p=0.08

* No meta-analysis was conducted in the 2nd report.

Table 70 Inclusion/exclusion table for meta-analysis of wine and pancreatic cancer

WCRF_ Code	Author	Year	Study Design	Study Name	Subgroup	Cancer Outcome	SLR	CUP dose-response meta-analysis	CUP HvL forest plot	Estimated values	Exclusion reasons
PAN70070	Gapstur	2011	Prospective cohort study	Cancer Prevention Study II	Men/ Women	Mortality	New	Yes	Yes	Mid-exposure values, person years	
PAN70048	Heinen	2009	Prospective cohort study	The Netherlands Cohort study	Men/ Women	Incidence	New	Yes	Yes	Mid-exposure values	
PAN70046	Jiao	2009	Prospective cohort study	NIH- AARP Diet and Health Study	Men/ Women	Incidence	New	Yes	Yes	Mid-exposure values	
PAN70010	Bobe	2008	Prospective cohort study	Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study	Men	Incidence	New	Yes	Yes	Mid-exposure values	
PAN07288	Harnack	1997	Prospective cohort study	Iowa Women's Health Study	Women	Mortality/ Incidence	Yes	Yes	Yes	Mid-exposure values	
PAN07339	Kato	1992	Prospective Cohort study	Japan - Hawaii Centre	Men	Incidence	Yes	No	No		Only mean values
PAN07294	Hiatt	1988	Case-cohort	Members of the Kaiser Permanent Medical Care Program	Men/Women	Incidence	Yes	No	No		Only mean values

Figure 77 Highest versus lowest forest plot of wine and pancreatic cancer

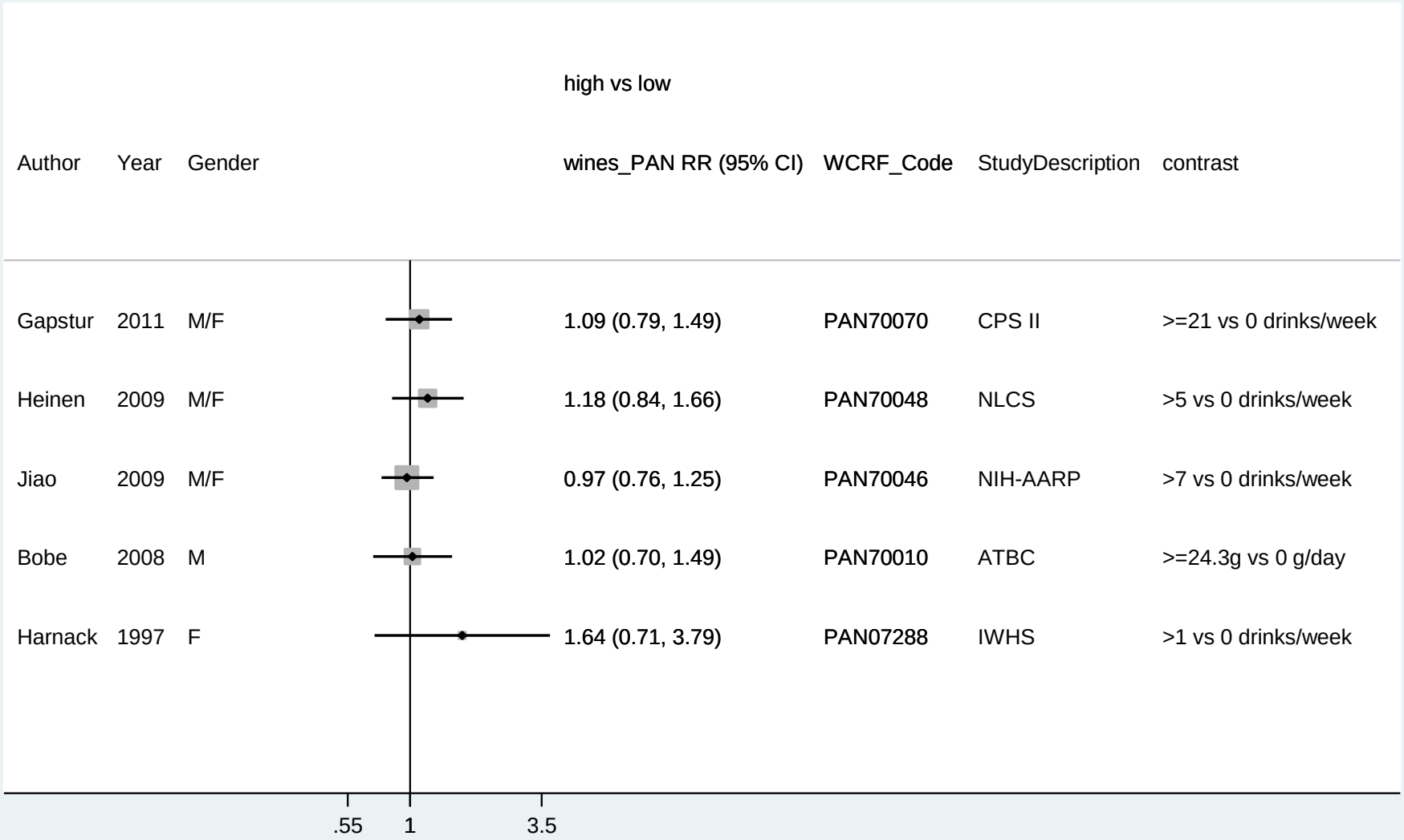


Figure 78 Dose-response meta-analysis of wine and pancreatic cancer – per drink/week

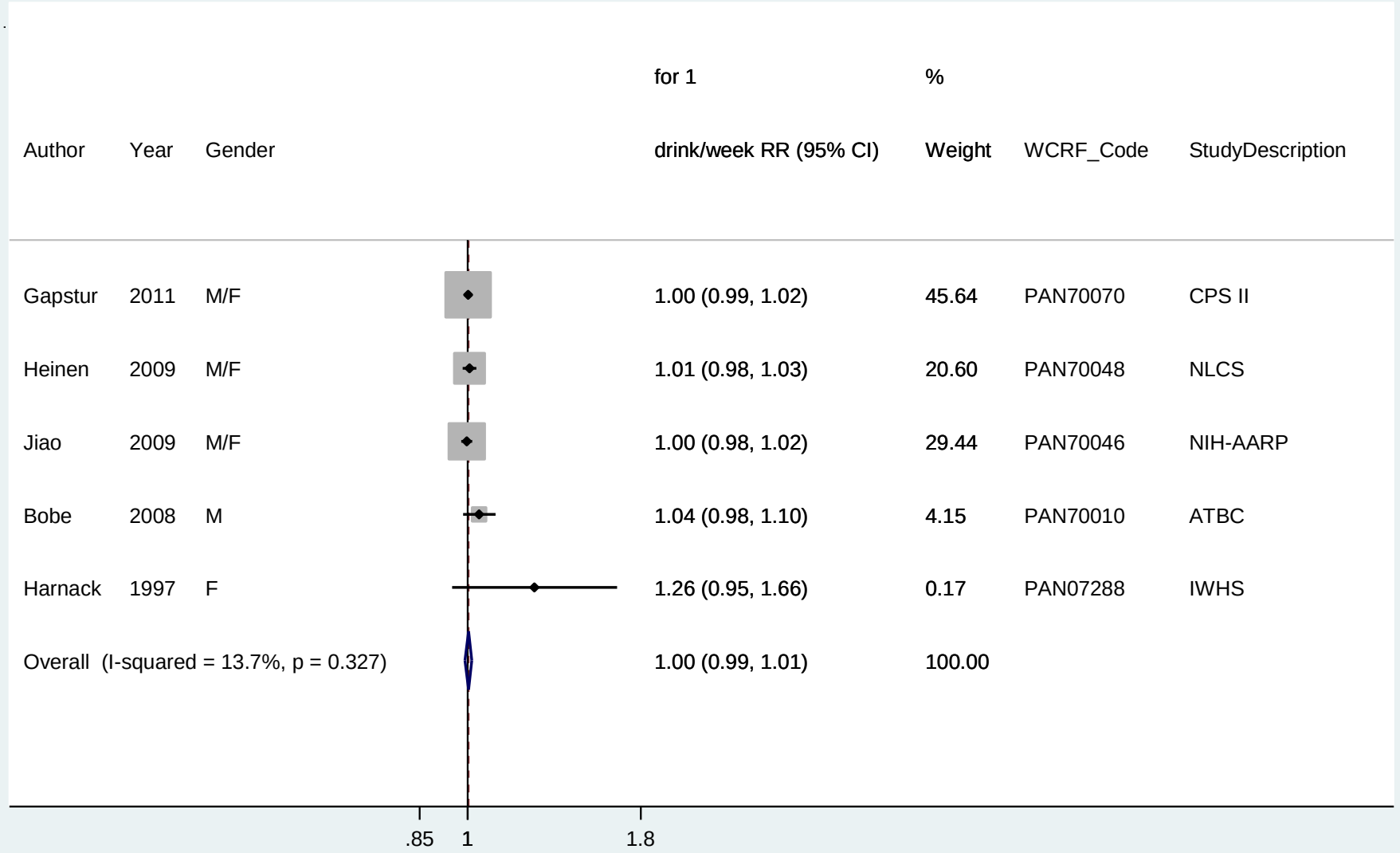


Figure 79 Funnel plot of wine and pancreatic cancer

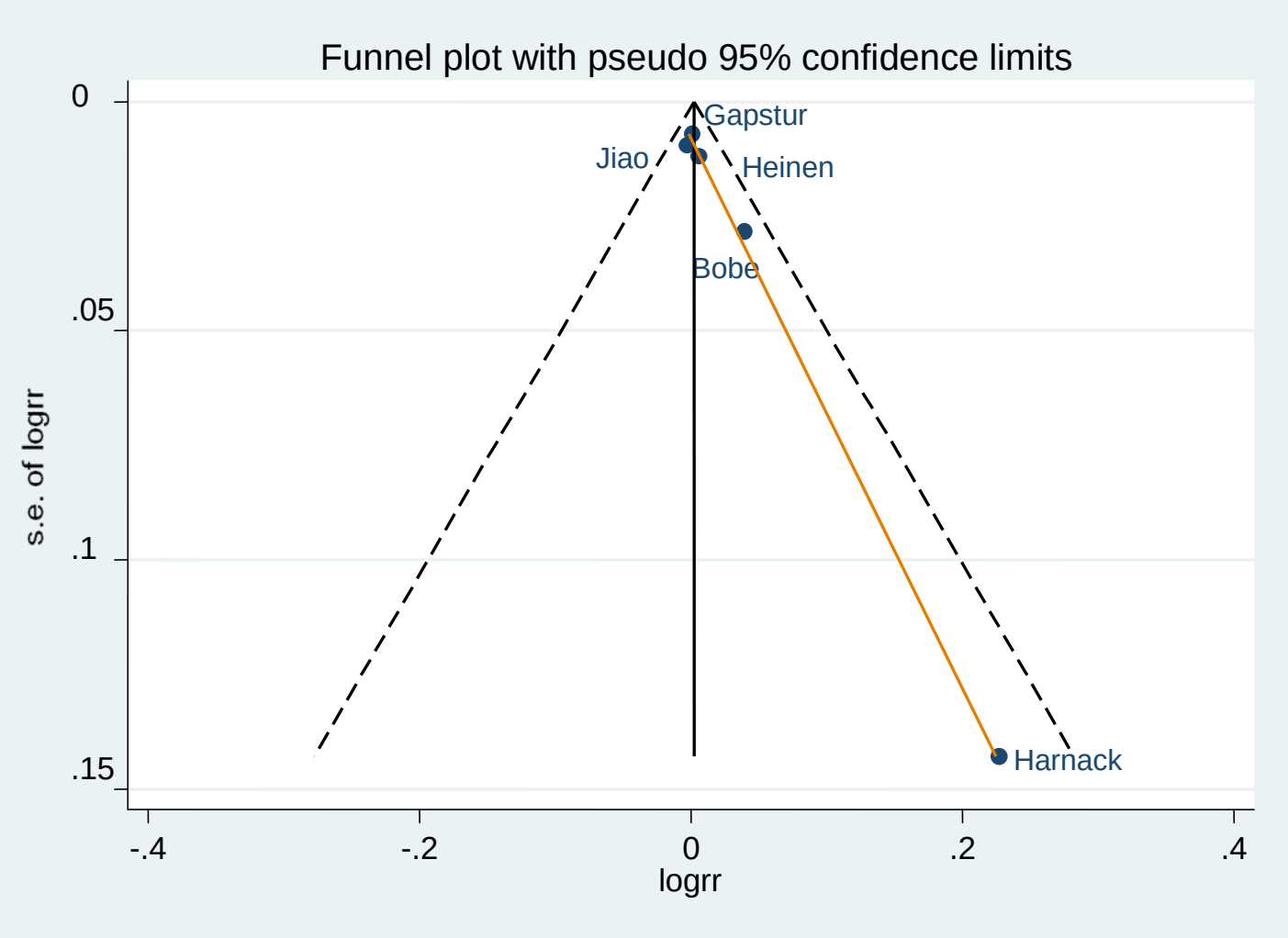


Figure 80 Dose-response graph of wine and pancreatic cancer

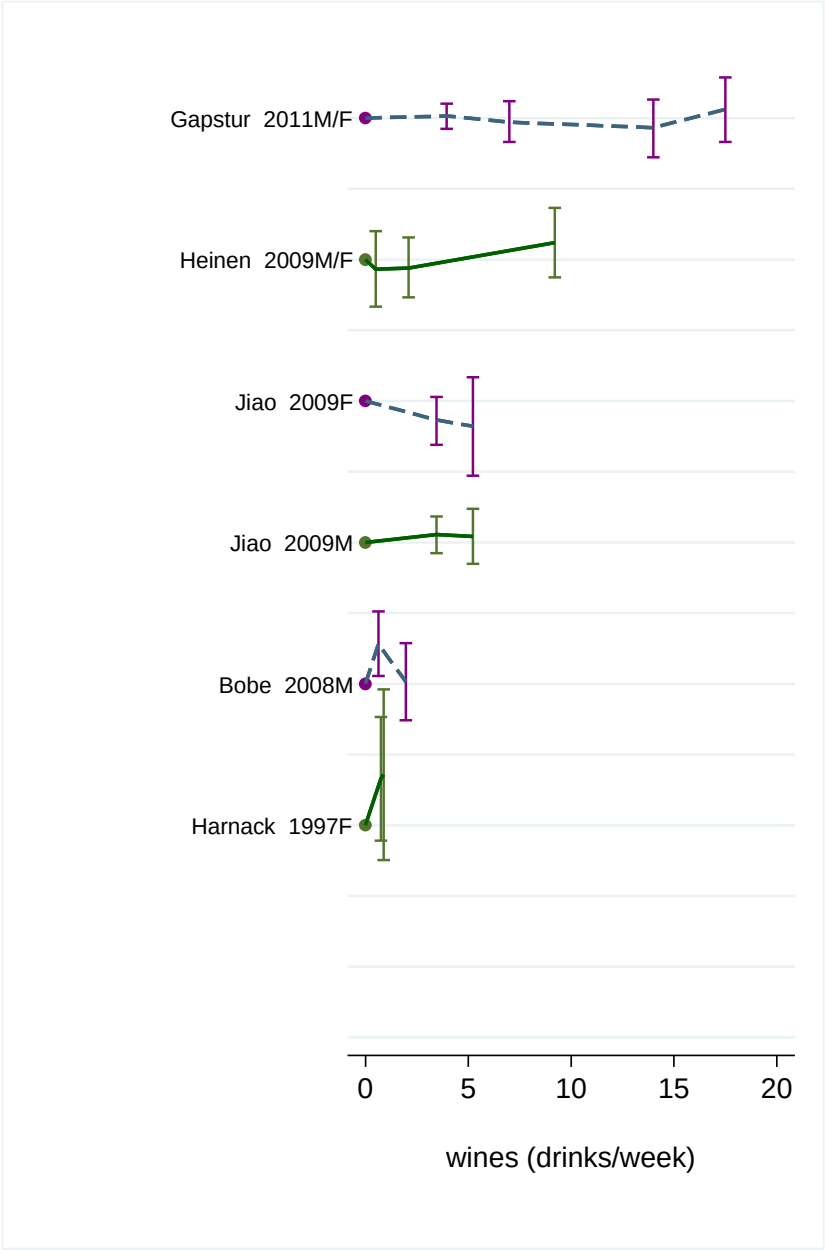


Figure 81 Dose-response meta-analysis of wine and pancreatic cancer, stratified by sex – per drink/week

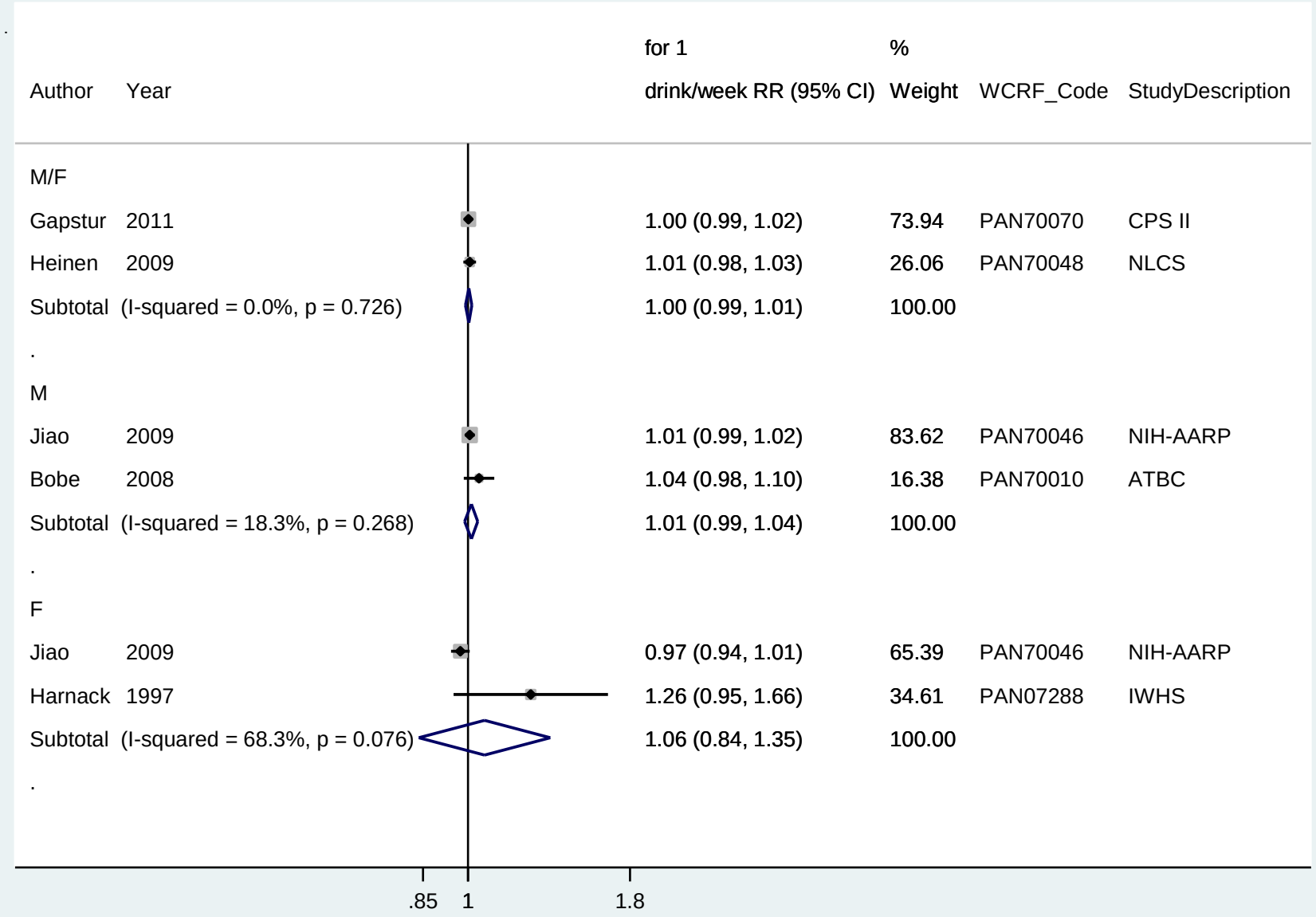
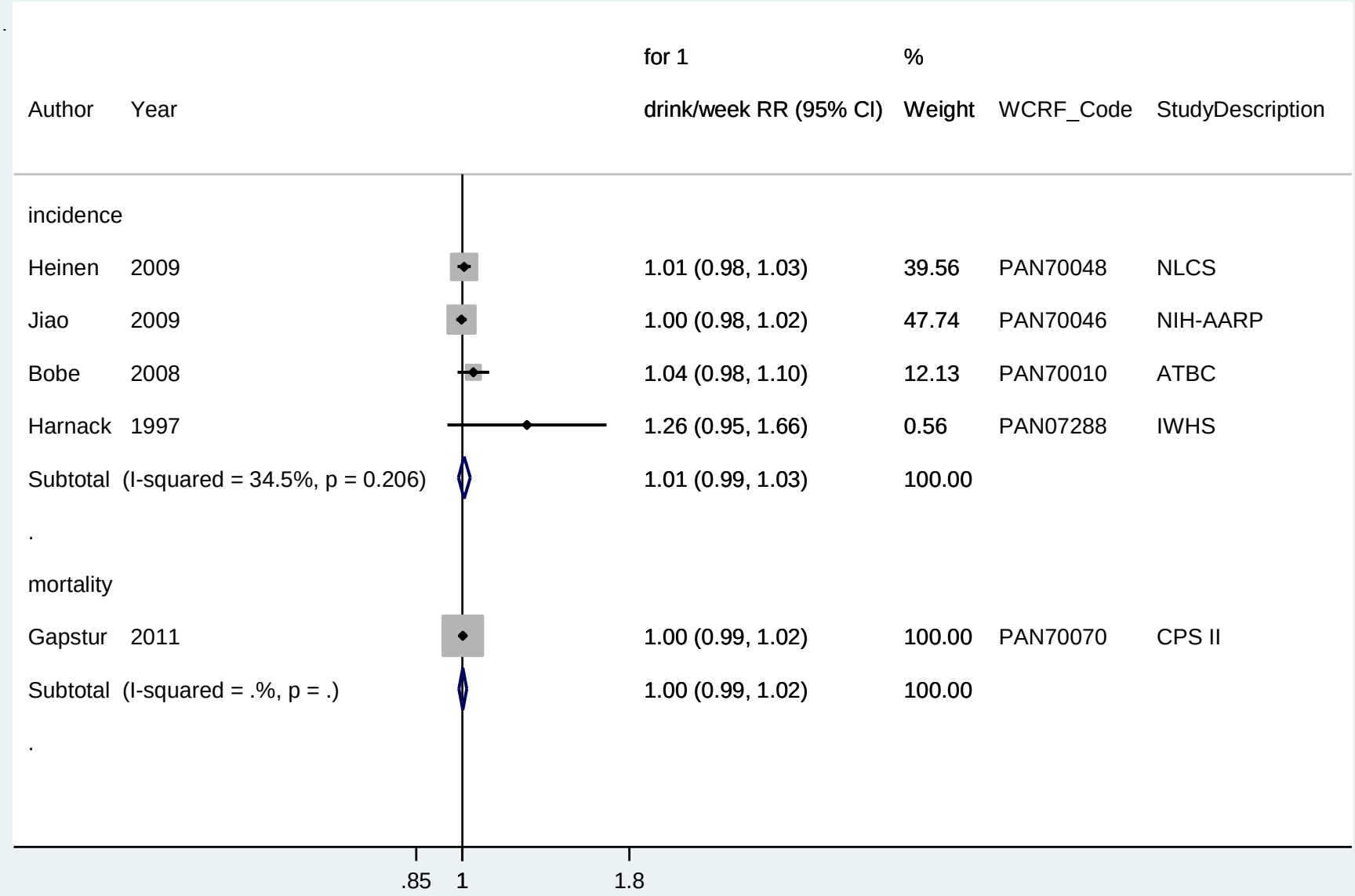


Figure 82 Dose-response meta-analysis of wine and pancreatic cancer, stratified by outcome type – per drink/week



3.7.1.3 Spirits

Methods

Eight cohort studies were identified, three of these during the CUP. Dose-response meta-analysis for cohort studies was performed in the previous SLR report. In this report, a meta-analysis including 5 different studies (3 studies identified during the CUP and 2 studies identified during the 2007 SLR) was performed.

Main results

The summary RR per 1 drink/week was 1.01 (95% CI: 1.00-1.02; $P_{heterogeneity}$=0.10, 5 studies) for incidence or mortality of pancreatic cancer. The overall results remained the same when two studies with mortality as outcome were excluded from the analysis (RR= 1.01; 95% CI: 0.99-1.03). The RR ranged from 1.01 (95% CI: 1.00-1.37) when excluding the LBS (Zheng et al, 1993) to 1.01 (95% CI: 0.99-1.03) when excluding the NIH-AARP study (Jiao et al, 2009).

Heterogeneity

Moderate heterogeneity was observed overall (I^2= 48.7%, p=0.10). Visual inspection of the funnel plot suggests that heterogeneity is due to the extreme results by Harnack et al, 1997 in a small American study in women and Zheng et al, 1993 in the Lutheran Brotherhood Insurance Society study and that no small studies showing inverse or null associations were published. Egger's tests for publication bias was not significant, p=0.21.

Comparison with the Second Expert Report

The RR for an increase of one drink/week of spirits (RR= 1.01; 95% CI: 1.00-1.02) was weaker than the results of two cohort studies that reported measures of association and were identified in the 2007 SLR (Harnack et al, 1997 and Zheng et al, 1993).

Published meta-analysis

The Pancreatic Cancer Cohort Consortium – PanScan (Michaud et al, 2009) observed a statistically significant increase in risk among men consuming 45 or more grams of alcohol from liquor per day (OR = 2.23, 95% CI: 1.02–4.87, compared to 0 g/day of alcohol from liquor, P-trend = 0.12), but not among women (OR = 1.35, 95% CI: 0.63–2.87, for 30 or more g/day of alcohol from liquor, compared to none).

Table 71 Studies on spirits identified during the CUP

Author, year	Country	Study name	Cases	Years of follow up	Sex	RR	LCI	UCI	Contrast
Gapstur, 2011	USA	Cancer Prevention Study II	6847	24	M/F	1.32	1.10	1.57	≥21 vs 0 drinks/week
Heinen , 2009	Netherlands	The Netherlands Cohort study	350	13.3	M/F	0.96	0.68	1.35	≥ 5.0 vs 0 drinks/week
Jiao, 2009	USA	NIH- AARP Diet and Health Study	1149	7.3	M F	1.66 1.46	1.24 0.80	2.23 2.67	≥ 3.0 vs 0-0.99 drinks/week

Table 72 Overall evidence on spirits and pancreatic cancer

	Summary of evidence
SLR	Data were extracted from four cohort studies and one case cohort study. The result of one cohort study was reported RR=1.27 (95% CI: 1.03, 1.56) per 1 drink/week (p=0.02).
Continuous Update Project	Three cohort studies were identified. All reported on male and female. Two studies reported a significant positive association between spirits drinking and pancreatic cancer. Six studies were included in the high versus low forest plot.

Table 73 Summary of results of the dose response meta-analysis of spirits and pancreatic cancer

Pancreatic cancer		
	SLR*	Continuous Update Project
Studies (n)	-	5
Cases (n)	-	8469
Increment unit used	-	Per drink/week
Overall RR (95%CI)	-	1.01 (1.00-1.02)
Heterogeneity (I^2,p-value)		48.7%, p=0.10
Stratified analysis		
Men	-	1.05 (0.92-1.19) (n=2)
Heterogeneity (I^2,p-value)		46.0%, p=0.17
Women		1.11 (0.88-1.39) (n=2)
Heterogeneity (I^2,p-value)		81.4%, p=0.02

*No meta-analysis was conducted in the 2nd report.

Table 74 Inclusion/exclusion table for meta-analysis of spirits and pancreatic cancer

WCRF_ Code	Author	Year	Study Design	Study Name	Subgroup	Cancer Outcome	SLR	CUP dose-response meta-analysis	CUP HvL forest plot	Estimated values	Exclusion reasons
PAN70070	Gapstur	2011	Prospective cohort study	Cancer Prevention II	Men/ Women	Mortality	New	Yes	Yes	Mid-exposure values, person years	
PAN70048	Heinen	2009	Prospective cohort study	The Netherlands Cohort study	Men/ Women	Incidence	New	Yes	Yes	Mid-exposure values	
PAN70046	Jiao	2009	Prospective cohort study	NIH- AARP Diet and Health Study	Men/ Women	Incidence	New	Yes	Yes	Mid-exposure values	
PAN07288	Harnack	1997	Prospective cohort study	Iowa Women's Health Study	Women	Mortality/ Incidence	Yes	Yes	Yes	Mid-exposure values	
PAN07668	Zheng	1993	Prospective cohort study	Lutheran Brotherhood Insurance Society	Men	Mortality	Yes	Yes	Yes	Mid-exposure values	
PAN07339	Kato	1992	Prospective Cohort study	Japan - Hawaii Centre	Men	Incidence	Yes	No	No		Only mean values
PAN07299	Hirayama	1989	Prospective Cohort study	6 Prefecture Cohort, Japan	Men/ women	Mortality	Yes	No	Yes		Only two categories
PAN07294	Hiatt	1988	Case-cohort	Members of the Kaiser Permanent Medical Care Program	Men/Women	Incidence	Yes	No	No		Only mean values

Figure 83 Highest versus lowest forest plot of spirits and pancreatic cancer

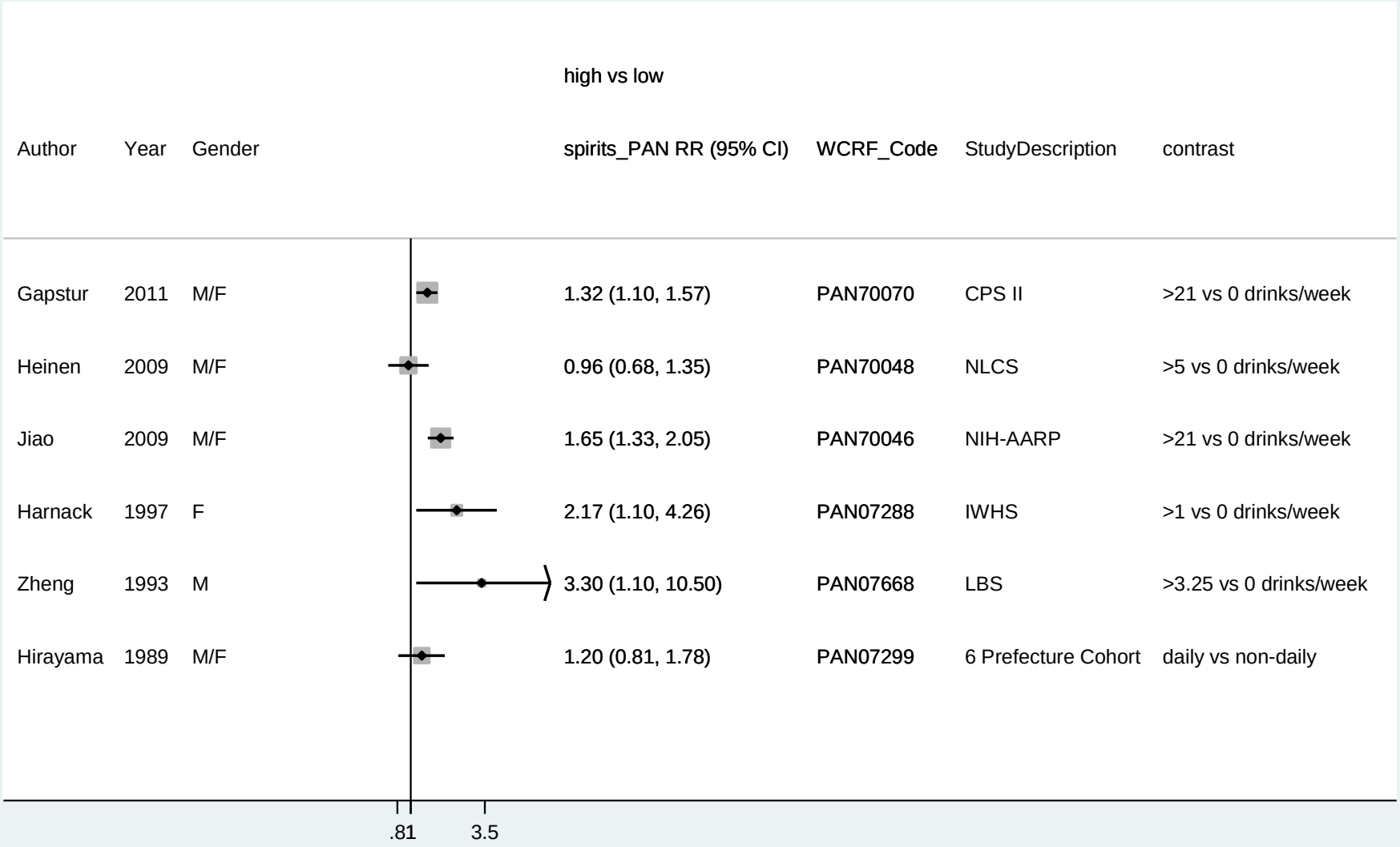


Figure 84 Dose-response meta-analysis of spirits and pancreatic cancer – per drink/week

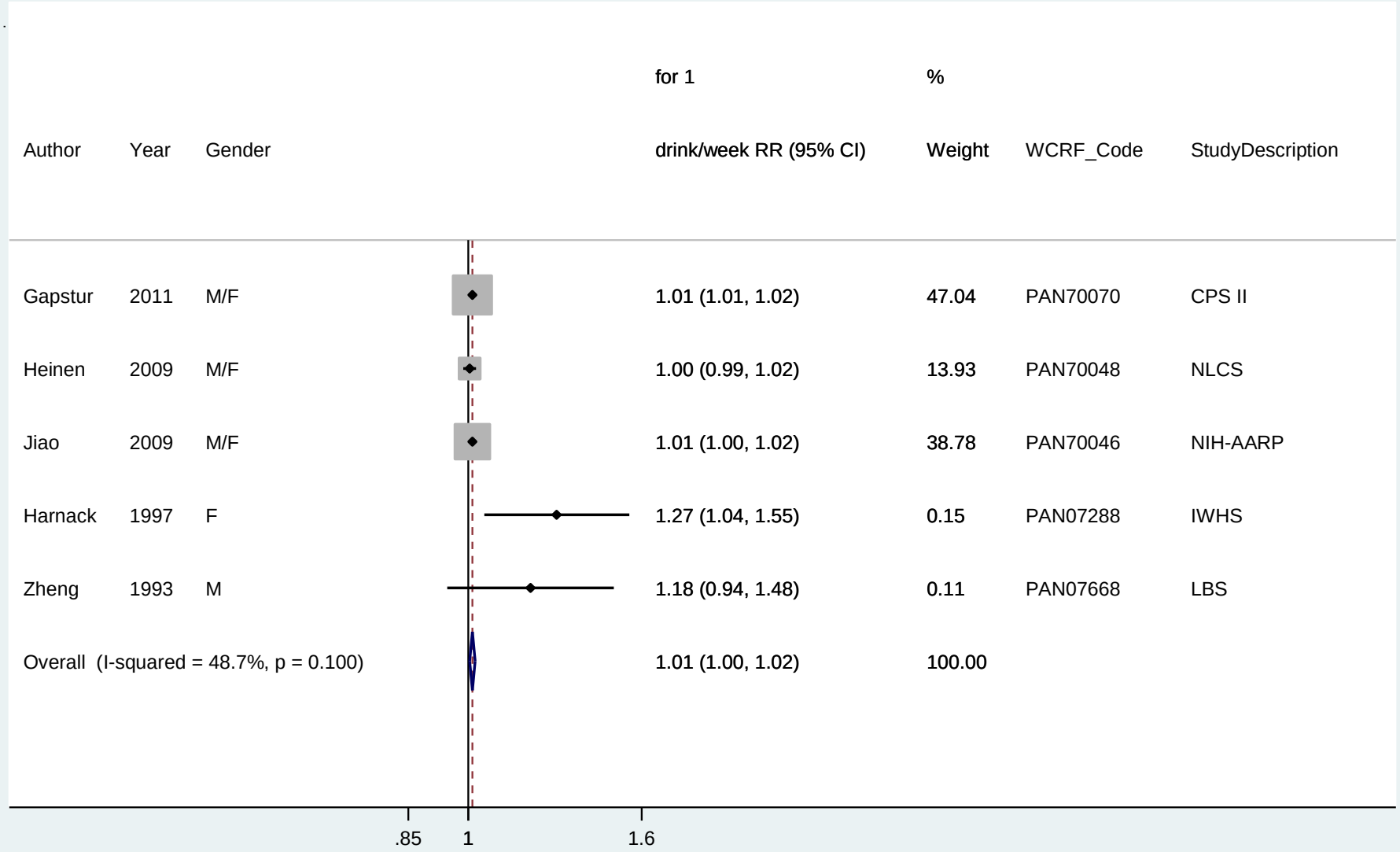


Figure 85 Funnel plot of spirits and pancreatic cancer

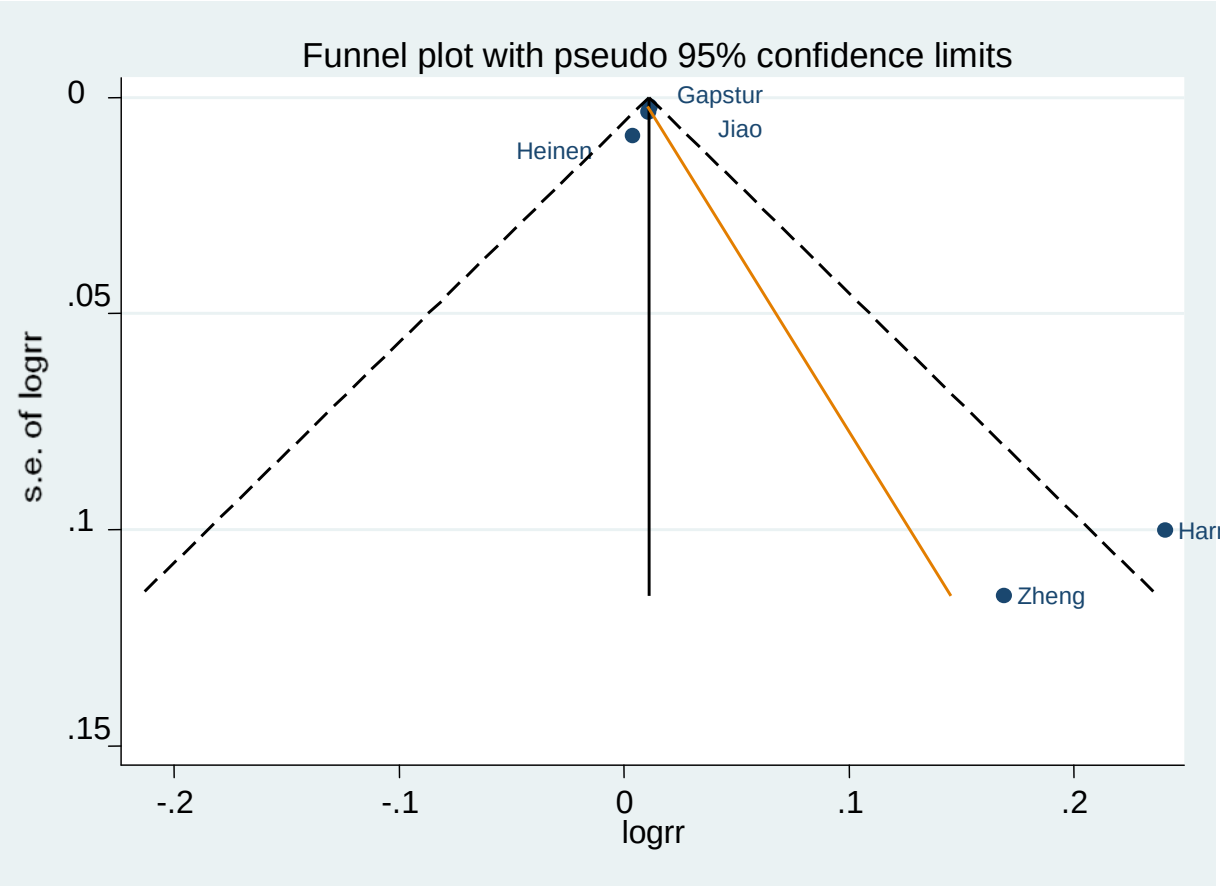


Figure 86 Dose-response graph of spirits and pancreatic cancer

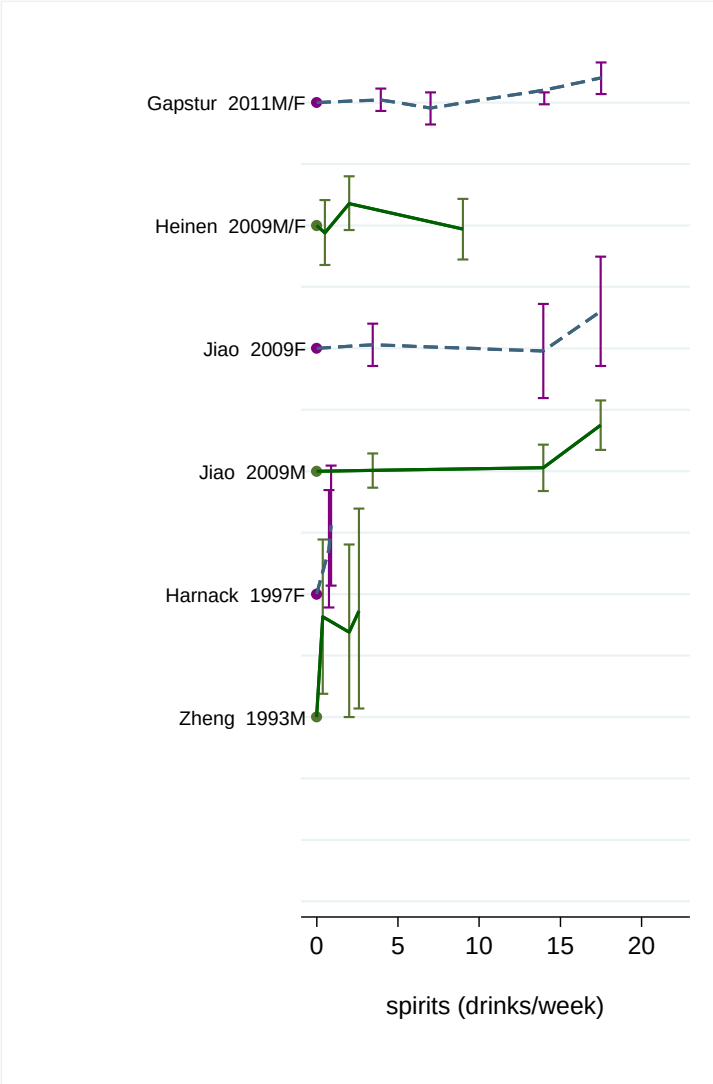


Figure 87 Dose-response meta-analysis of spirits and pancreatic cancer, stratified by sex – per drink/week

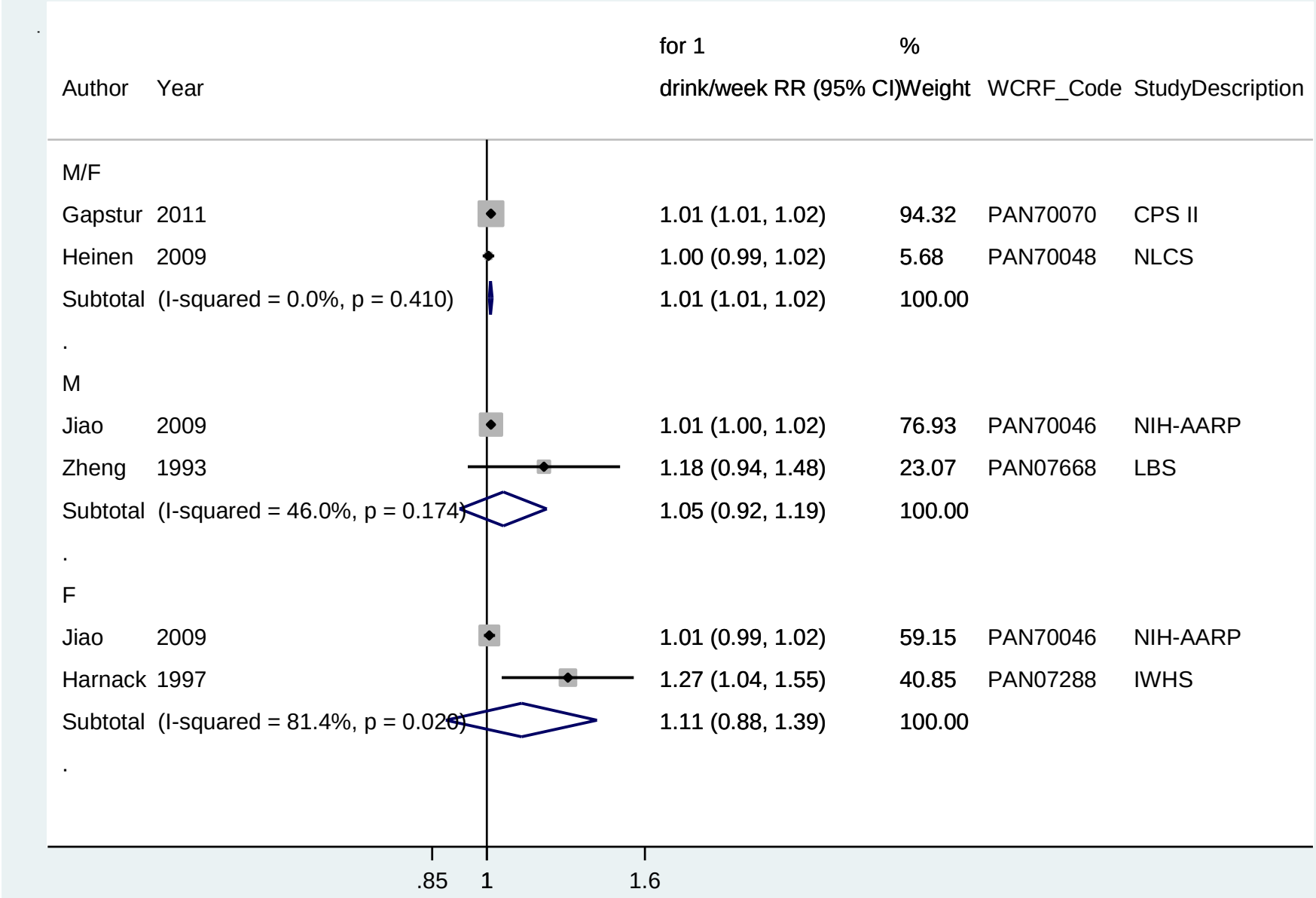
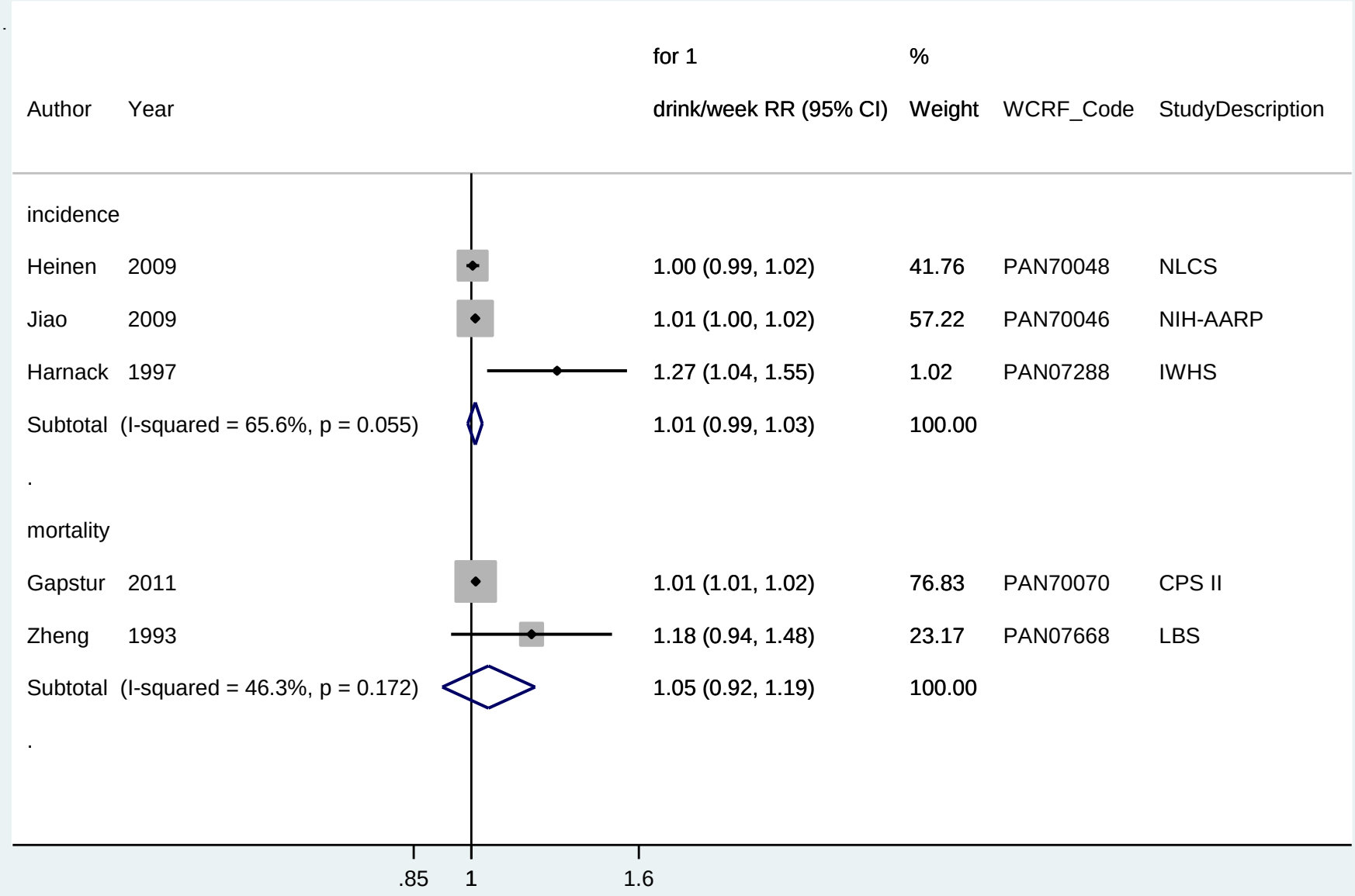


Figure 88 Dose-response meta-analysis of spirits and pancreatic cancer, stratified by outcome type – per drink/week



5 Dietary constituents

5.1 Carbohydrates

Methods

Overall ten cohort studies on carbohydrates and pancreatic cancer were identified of which five publications (five cohort studies) were identified in the Continuous Update Project. Nine studies could be included in updated meta-analysis. The excluded study did not report any measure of association.

Main results

The summary RR per 100 g/d was 0.97 (95% CI: 0.81-1.16, I^2=35%, $p_{heterogeneity}$=0.14, 9 studies). The summary RR ranged from 0.92 (95% CI: 0.75-1.13) when excluding the NIH-AARP Diet and Health Study to 1.04 (95% CI: 0.90-1.21) when excluding the Alpha-Tocopherol and Beta-Carotene Cancer Prevention Study. There was no evidence of publication bias with Egger's test, p=0.42. There was no evidence of a nonlinear association between carbohydrates and pancreatic cancer risk, $p_{nonlinearity}$=0.32.

Heterogeneity

There was little evidence of heterogeneity (I^2=35%, $p_{heterogeneity}$=0.14) in the analyses.

Comparison with the Second Expert Report

Carbohydrate intake was not associated with pancreatic cancer risk in this updated analysis and these results are consistent with the Second Expert Report which reported a pooled estimate from cohort studies of 0.95 (95% CI: 0.79 to 1.15) per 50 g/day (p=0.6).

Table 75 Studies on carbohydrate identified in the CUP

Author,year	Country	Study name	Number of cases	Years of Follow-up	Sex	RR	LCI	UCI	Contrast
Simon, 2010	USA	Women's Health Initiative	287	8	F	0.80	0.56	1.15	285 vs. 203 g/d
Jiao, 2009	USA	NIH-AARP Diet and Health Study	1151	7.2	M/F	1.12	0.84	1.50	≥151.5 vs. 9.0-111.2 g/1000 kcal/d
Heinen, 2008	Netherlands	Netherlands Cohort Study	408	13.3	M/F	1.03 1.04	0.69 0.85	0.85 1.27	256 vs. 155 g/d Per 50 g/d
Patel, 2007	USA	Cancer Prevention Study II Nutrition Cohort	401	9	M/F	1.28 0.90	0.83 0.56	1.96 1.41	>218.94 vs. ≤162.56 g/d >177.15 vs. ≤129.98 g/d
Nothlings, 2007	USA	Multiethnic Cohort Study	434	8	M/F	1.04	0.75	1.46	≥58.7 vs. <46.7 g/1000 kcal/d

Table 76 Overall evidence on carbohydrate and pancreatic cancer

	Summary of evidence
SLR	Five cohort studies were included in the review, and four of these contributed to the meta-analysis. Two studies reported significant inverse associations, one reported no association, and one study reported a non-significant positive association.
Continuous Update Project	Five studies were published on carbohydrate intake and pancreatic cancer risk. None of the studies reported statistically significant associations.

Table 77 Summary of results of the dose response meta-analysis on carbohydrate and pancreatic cancer

Pancreatic cancer		
	SLR	Continuous Update Project
Studies (n)	4	9
Cases (n)	521	3202
Increment unit	50 g/d	Per 100 g/d
RR (95% CI)	0.95 (0.79-1.15)	0.97 (0.81-1.16)
Heterogeneity (I^2, p-value)	72%, p=0.02	35.2%, p=0.14
By gender		
Men	-	0.80 (0.41-1.57), n=2
Heterogeneity (I^2,p-value)	-	74%, p=0.05
Women	-	0.91 (0.70-1.19), n=5
Heterogeneity (I^2,p-value)	-	28%, p=0.24

Table 78 Inclusion/exclusion table for meta-analysis of carbohydrate and pancreatic cancer

WCRF code	Author	Year	Study design	Study name	Subgroup	Cancer outcome	SLR	CUP dose-response meta-analysis	CUP HvL forest plot	Estimated values	Exclusion reason
PAN70015	Simon	2010	Prospective cohort study	Women's Health Initiative	Women	Incidence	New	Yes	Yes	Mid-exposure values	
PAN70006	Jiao	2009	Prospective cohort study	NIH-AARP Diet and Health Study	Men/women	Incidence	New	Yes	Yes	Mid-exposure values, person-years	
PAN70004	Heinen	2008	Case cohort study	Netherlands Cohort Study	Men/women	Incidence	New	Yes	Yes		
PAN70003	Nothlings	2007	Prospective cohort study	Multiethnic Cohort Study	Men/women	Incidence	New	Yes	Yes	Mid-exposure values	
PAN70061	Patel	2007	Prospective cohort study	Cancer Prevention Study II Nutrition Cohort	Men/women	Incidence	New	Yes	Yes	Mid-exposure values	
PAN60006	Silvera	2005	Prospective cohort study	Canadian National Breast Screening Study	Women	Incidence	Yes	Yes	Yes	Mid-exposure values	
PAN07441	Michaud	2002	Prospective cohort	Nurses' Health Study	Women	Incidence	Yes	Yes	Yes		
PAN07590	Stolzenberg-Solomon	2002	Prospective cohort study	ATBC Cancer Prevention Study	Men (smokers)	Incidence	Yes	Yes	Yes	Mid-exposure values, person-years, cases in each quintile	
PAN07288	Harnack	1997	Prospective cohort study	Iowa women's Health Study	Women	Incidence	Yes	Yes	Yes	Mid-exposure values	
PAN07339	Kato	1992	Prospective Cohort study	Japan - Hawaii Centre	Men	Incidence	Yes	No	No		No measure of the relationship

Figure 89 Highest versus lowest forest plot of carbohydrate and pancreatic cancer

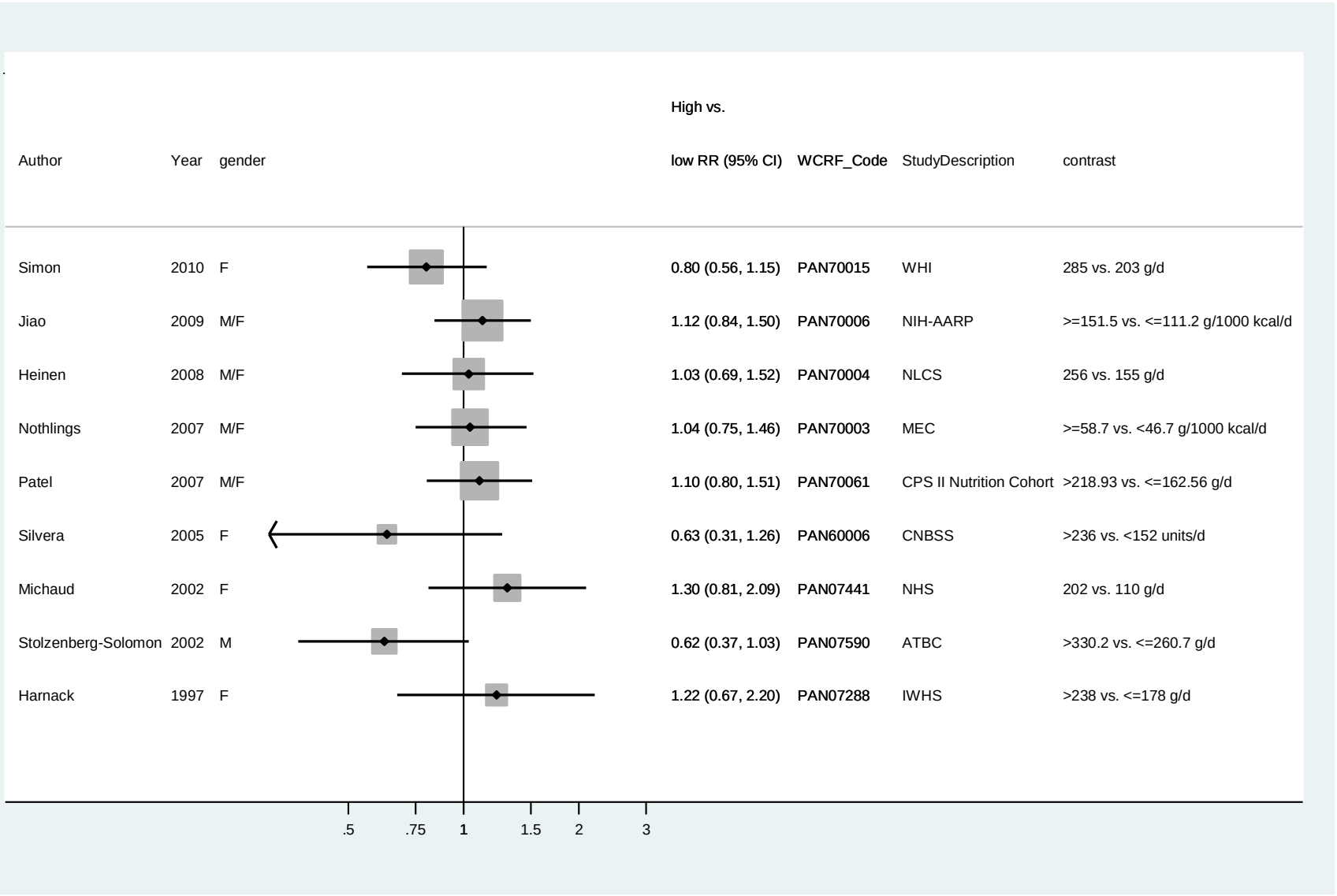


Figure 90 Dose-response meta-analysis of carbohydrate and pancreatic cancer - per 100 grams per day

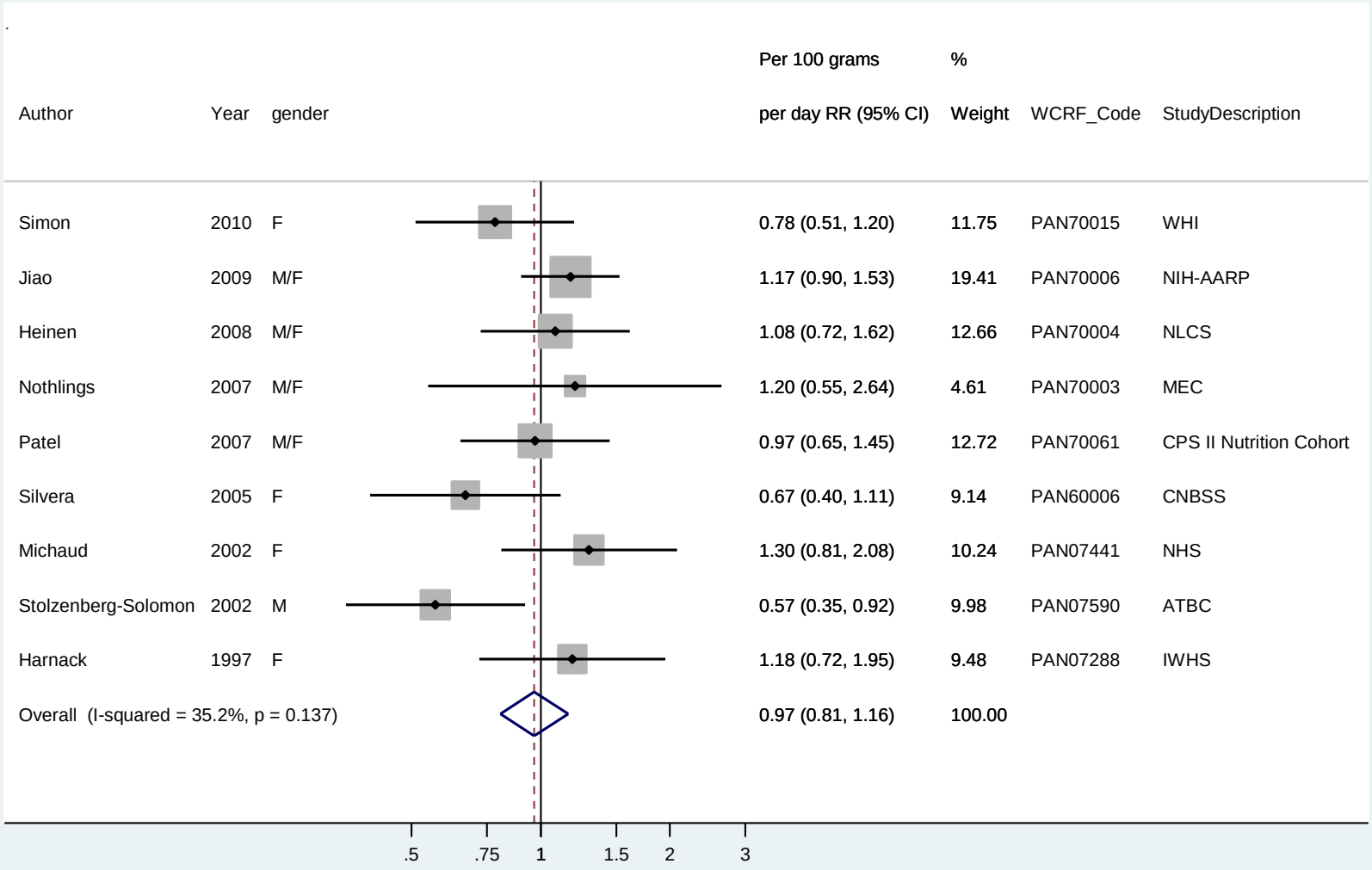


Figure 91 Funnel plot of carbohydrate intake and pancreatic cancer

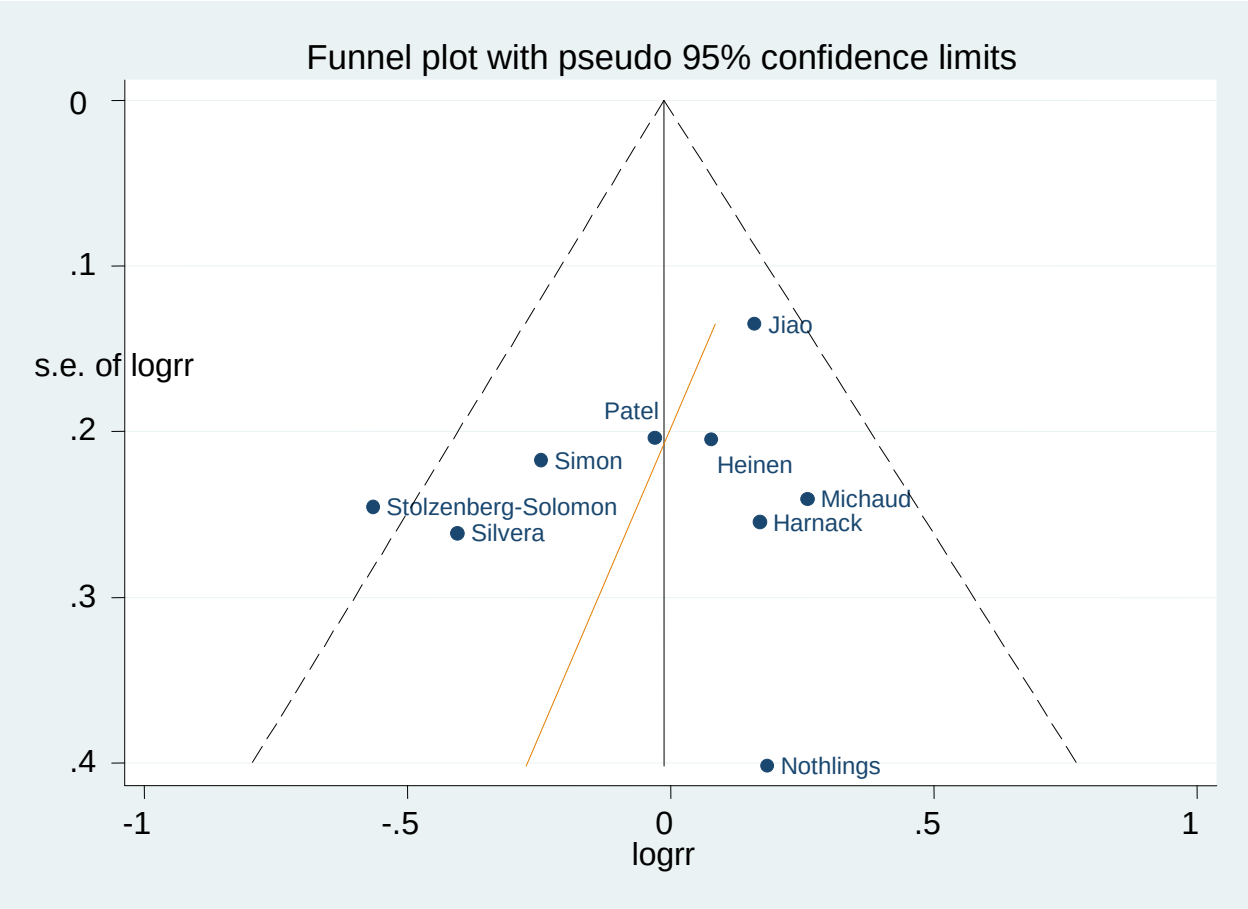


Figure 92 Dose-response graph of carbohydrate and pancreatic cancer

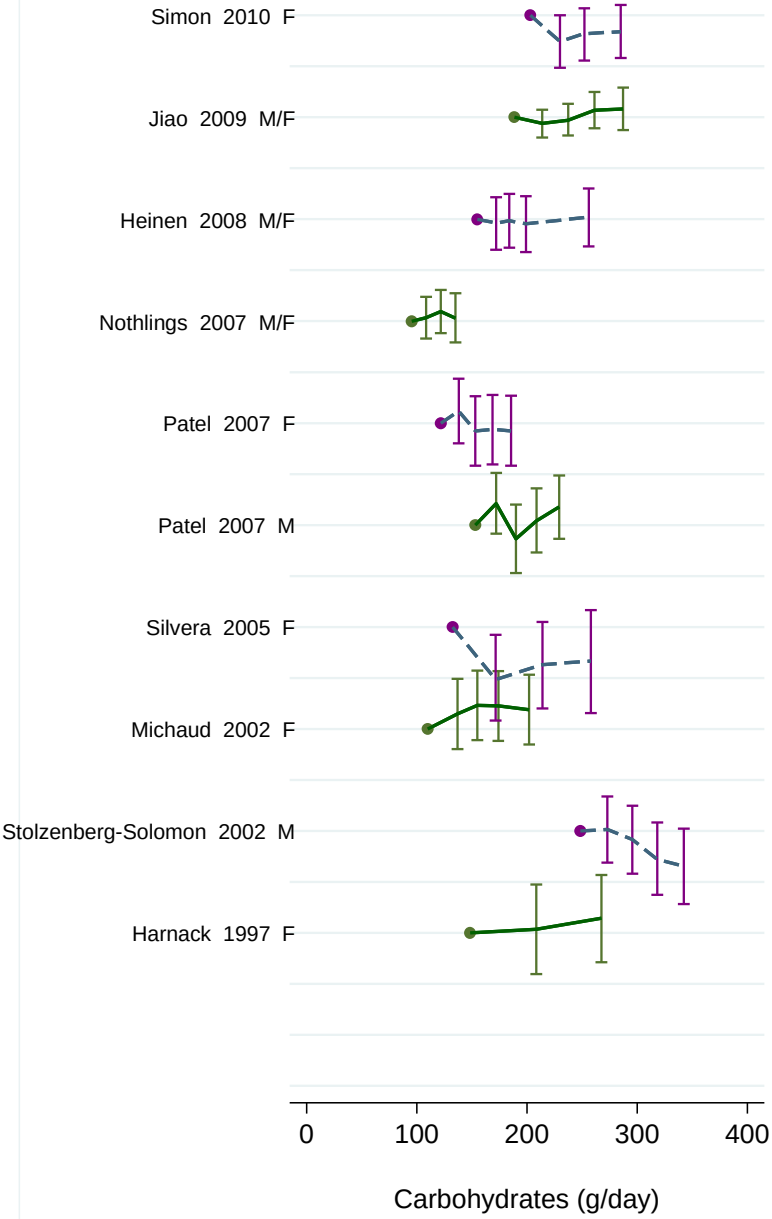


Figure 93 Dose-response meta-analysis of carbohydrate and pancreatic cancer, stratified by sex - per 100 grams per day

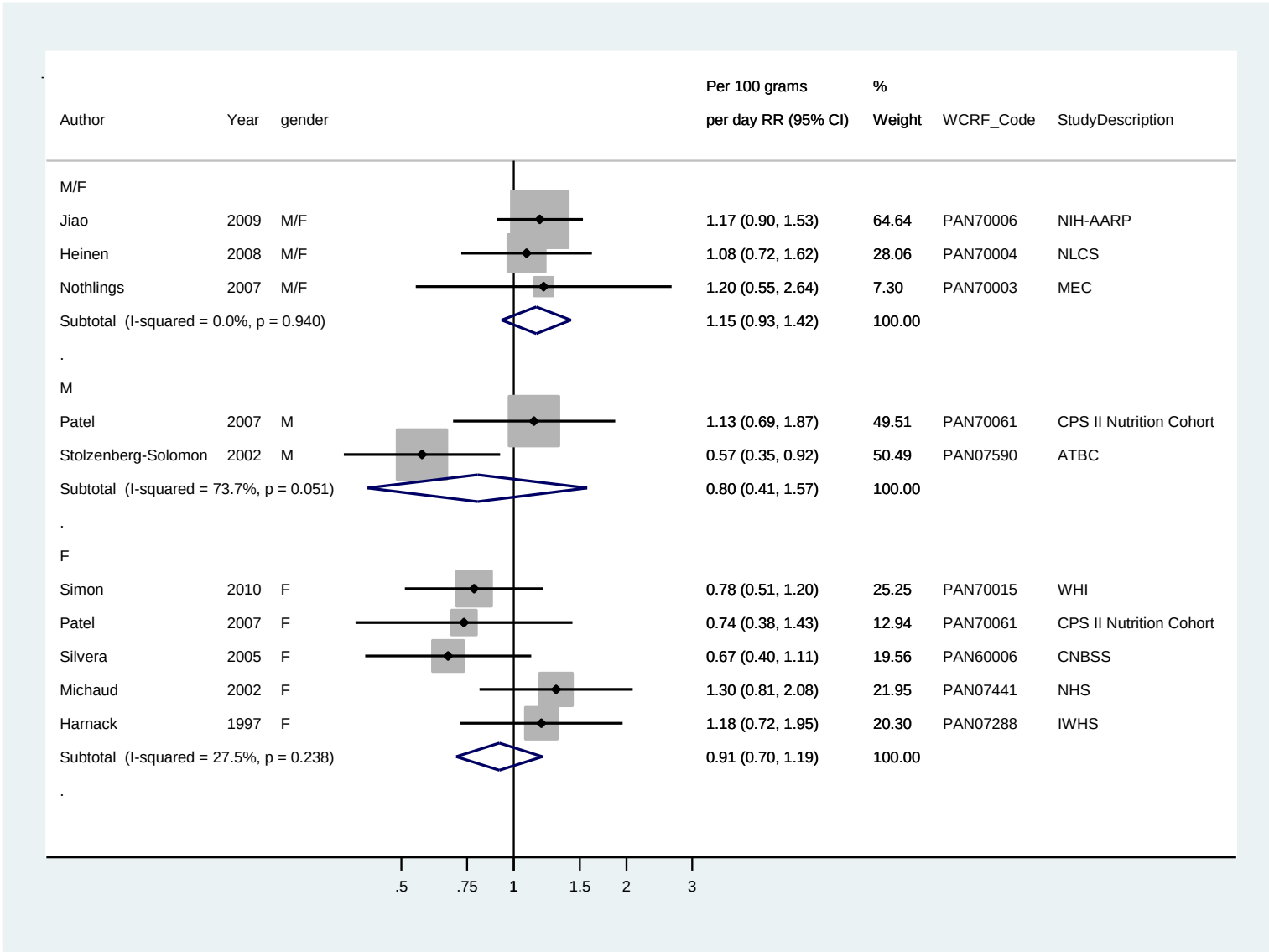


Figure 94 Nonlinear dose-response analysis of carbohydrate intake and pancreatic cancer

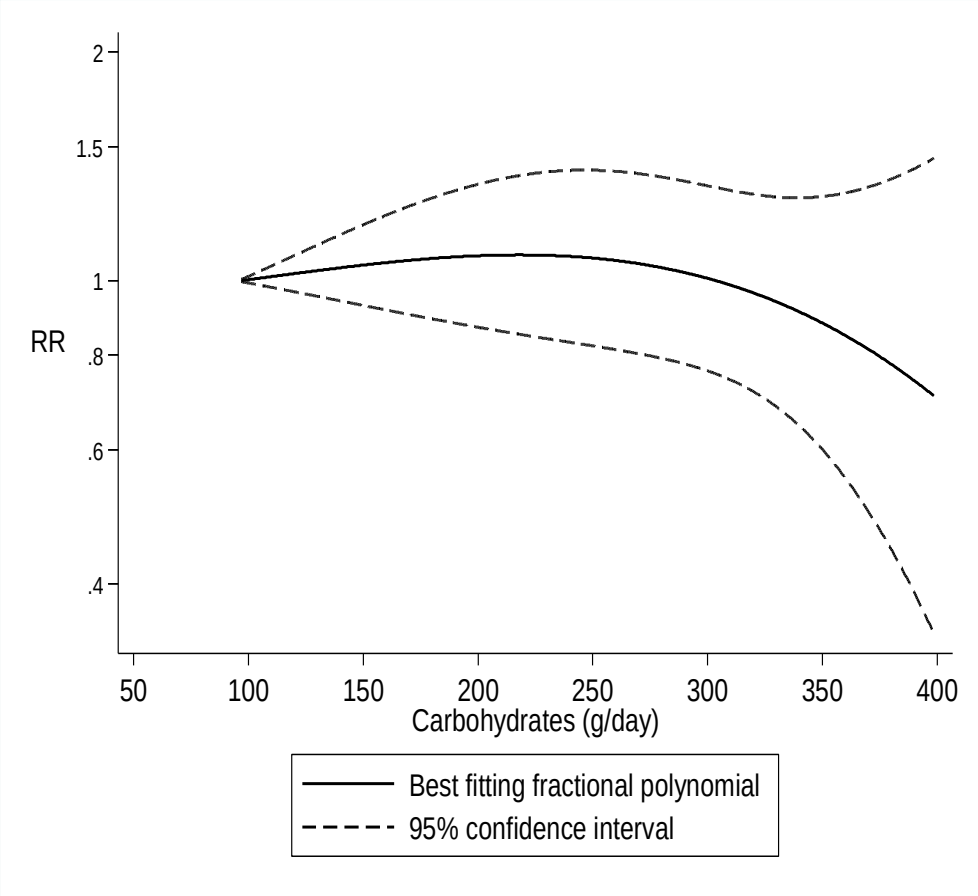


Figure 95 Scatter plot of risk estimates of carbohydrate intake and pancreatic cancer

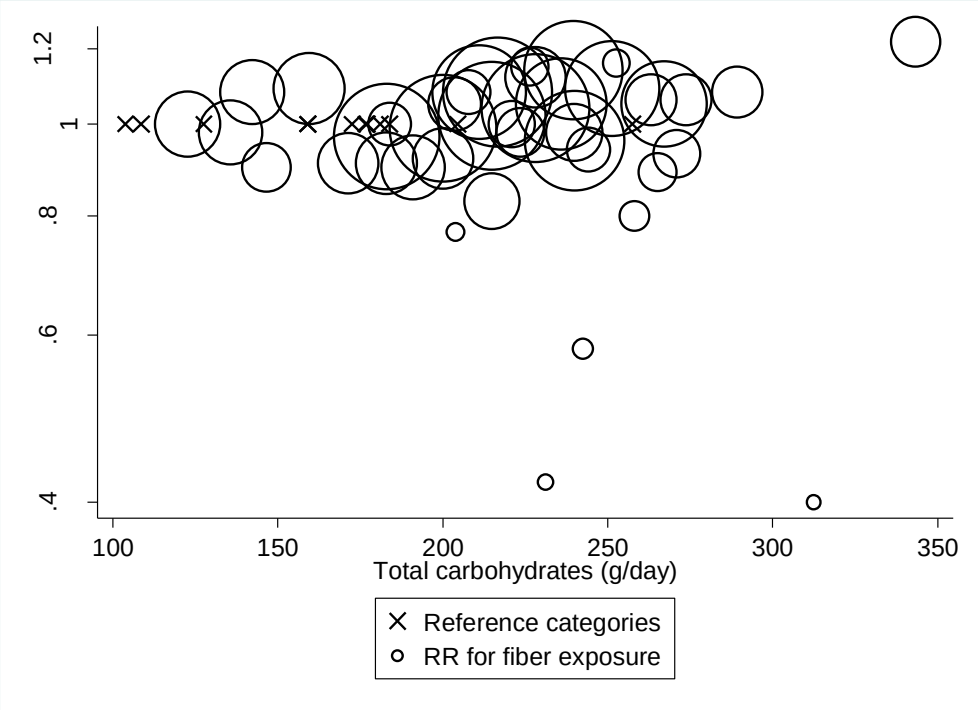


Table 79 Table with carbohydrate values and corresponding RRs (95% CIs) for nonlinear analysis of carbohydrate and pancreatic cancer

Carbohydrate (g/day)	RR (95% CI)
95.4	1.00
100	1.00 (0.99-1.01)
150	1.05 (0.93-1.19)
200	1.08 (0.87-1.34)
250	1.07 (0.82-1.40)
300	1.01 (0.76-1.33)
350	0.88 (0.60-1.29)
400	0.70 (0.34-1.46)

5.1.4 Fructose

Methods

Seven cohort studies were published on fructose intake and pancreatic cancer and five of these were identified in the Continuous Update Project.
Dose-response analyses and stratified analyses of fructose intake and pancreatic cancer risk were conducted. The dose-response results are presented per 25 grams per day. The Cancer Prevention Study II Nutrition cohort only reported the relative risk estimate for the highest versus the lowest intake category (RR: 1.00; 95% CI: 0.73-1.36) and could not be included in the dose-response analysis.

Main results

The summary RR for a 25 gram per day increment was 1.22 (95% C: 1.08-1.37) and there was no evidence of heterogeneity, I^2=0%, $p_{heterogeneity}$=0.43 (n=6). The summary RR ranged from 1.16 (95% C: 0.99-1.36) when excluding the NIH-AARP Diet and Health study to 1.26 (95% CI: 1.12-1.42) when excluding the Women's Health Initiative. There was no evidence of publication bias with Egger's test, p=0.22. There was no evidence of a nonlinear association between fructose intake and pancreatic cancer, $p_{nonlinearity}$=1.00.

Heterogeneity

There was little evidence of heterogeneity (I^2=0%, $p_{heterogeneity}$ =0.43) in the analysis.

Study quality

Six studies were from the USA and one from Canada. One study was conducted among nurses (NHS), two studies included participants in cancer screening programmes (CNBSS, PLCO), one study was part of a randomized clinical trial (WHI) and the remaining studies were conducted among retired persons (NIH-AARP), in a multiethnic population (MEC) and the general population (CPS2). All the studies used validated food frequency questionnaires for the dietary assessment. All studies adjusted for age, smoking, BMI and energy intake.

Fewer studies adjusted for diabetes, physical activity, intake of alcohol and meat. The number of cases in the studies ranged from 112 to 1151.

Comparison with the Second Expert Report

There was a positive association between fructose intake and pancreatic cancer in this updated analysis of prospective studies, however, no meta-analysis was conducted in the Second Expert Report.

Table 80 Studies on fructose identified in the CUP

Author, year	Country	Study name	Number of cases	Years of follow-up	Sex	RR	LCI	UCI	Contrast
Simon, 2010	USA	Women's Health Initiative	287	8	F	0.79	0.54	1.17	33 vs. 13 g/d
Meinhold, 2010	USA	Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial	266	6.5	M/F	1.20	0.83	1.75	≥17.48 vs. ≤7.59 g/1000 kcal/d
Jiao, 2009	USA	NIH-AARP Diet and Health Study	1151	7.2	M/F	1.29	1.04	1.59	≥18.4 vs. 0.10-7.29 g/1000 kcal/d
Patel, 2007	USA	Cancer Prevention Study II Nutrition Cohort	401	9	M/F	1.00	0.73	1.36	Quintile 5 vs. 1
Nothlings, 2007	USA	Multiethnic Cohort Study	434	8	M/F	1.35	1.02	1.80	≥15.4 vs. <7.3 g/1000 kcal/d

Table 81 Overall evidence on fructose and pancreatic cancer

	Summary of evidence
SLR	Two studies reported on fructose intake. One reported a non-significant positive association and one study reported no association.
Continuous Update Project	Five cohort studies have published results for fructose intake and pancreatic cancer risk and two of these found statistically significant positive associations, while the remaining three studies reported no significant association.

Table 82 Summary of results of the dose response meta-analysis on fructose and pancreatic cancer

Pancreatic cancer		
	SLR*	Continuous Update Project
Studies (n)	-	6
Cases (n)	-	2831
Increment unit	-	Per 25 g/d
RR (95% CI)	-	1.22 (1.08-1.37)
Heterogeneity (I^2, p-value)	-	0%, p=0.43
Men	-	-
Heterogeneity (I^2, p-value)	-	-
Women	-	1.05 (0.73-1.49), n=3
Heterogeneity (I^2, p-value)	-	38.6%, p=0.20

*No meta-analysis was conducted in the 2nd report.

Table 83 Inclusion/exclusion table for meta-analysis of fructose and pancreatic cancer

WCRF code	Author	Year	Study design	Study name	Subgroup	Cancer outcome	SLR	CUP dose-response meta-analysis	CUP HvL forest plot	Estimated values	Exclusion reason
PAN70015	Simon	2010	Prospective cohort study	Women's Health Initiative	Women	Incidence	New	Yes	Yes	Mid-exposure values	
PAN70007	Meinhold	2010	Prospective cohort study	Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial	Men/women	Incidence	New	Yes	Yes	Mid-exposure values, person-years	
PAN70006	Jiao	2009	Prospective cohort study	NIH-AARP Diet and Health Study	Men/women	Incidence	New	Yes	Yes	Mid-exposure values, person-years	
PAN70003	Nothlings	2007	Prospective cohort study	Multiethnic Cohort Study	Men/women	Incidence	New	Yes	Yes	Mid-exposure values	
PAN70061	Patel	2007	Prospective cohort study	Cancer Prevention Study II Nutrition Cohort	Men/women	Incidence	New	No	Yes	Mid-exposure values	Only highest vs. lowest comparison
PAN60006	Silvera	2005	Prospective cohort study	Canadian National Breast Screening Study	Women	Incidence	Yes	Yes	Yes	Mid-exposure values	
PAN07441	Michaud	2002	Prospective cohort study	Nurses' Health Study	Women	Incidence	Yes	Yes	Yes		

Figure 96 Highest versus lowest forest plot of fructose and pancreatic cancer

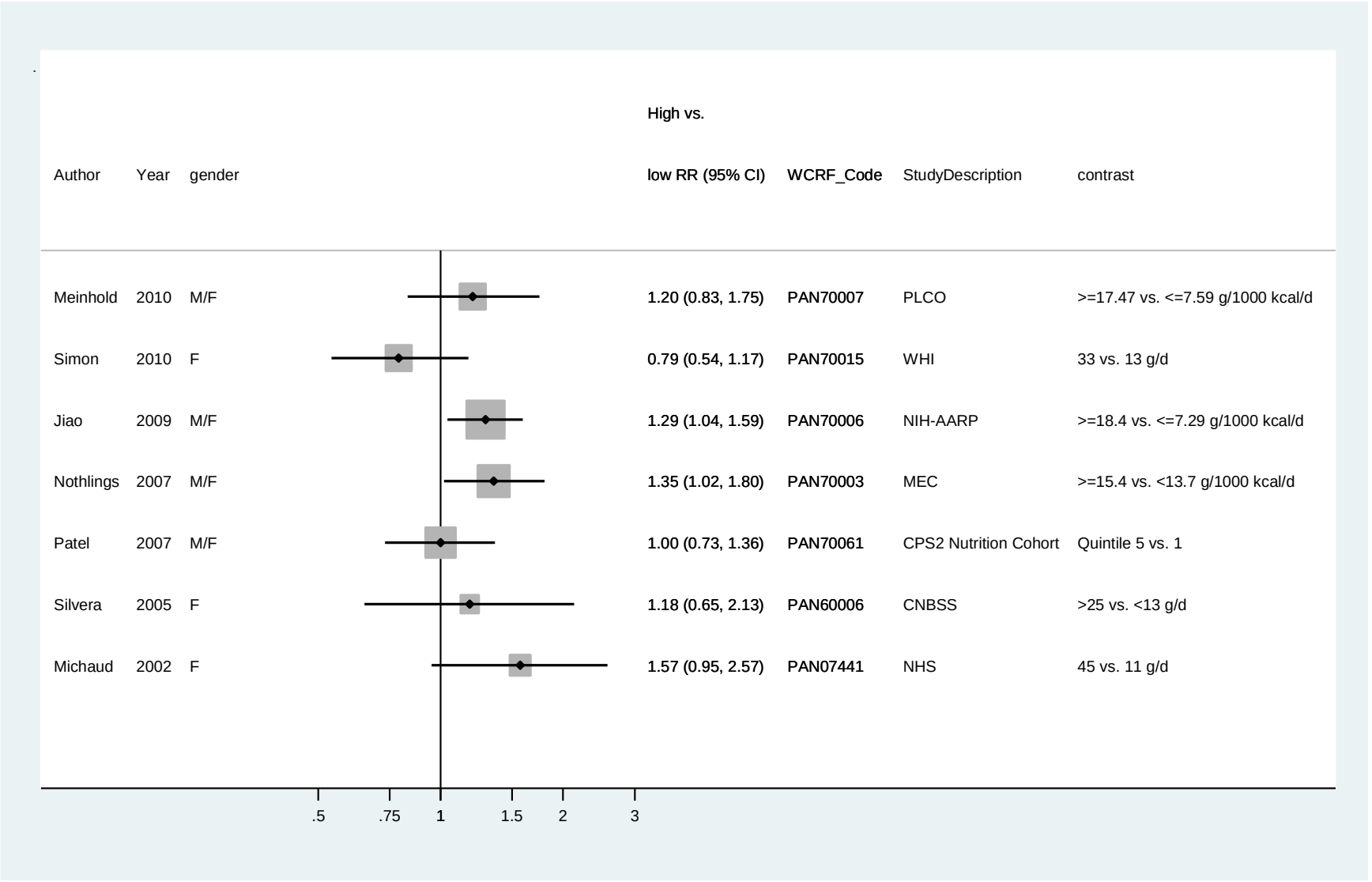


Figure 97 Dose-response meta-analysis of fructose and pancreatic cancer - per 25 grams per day

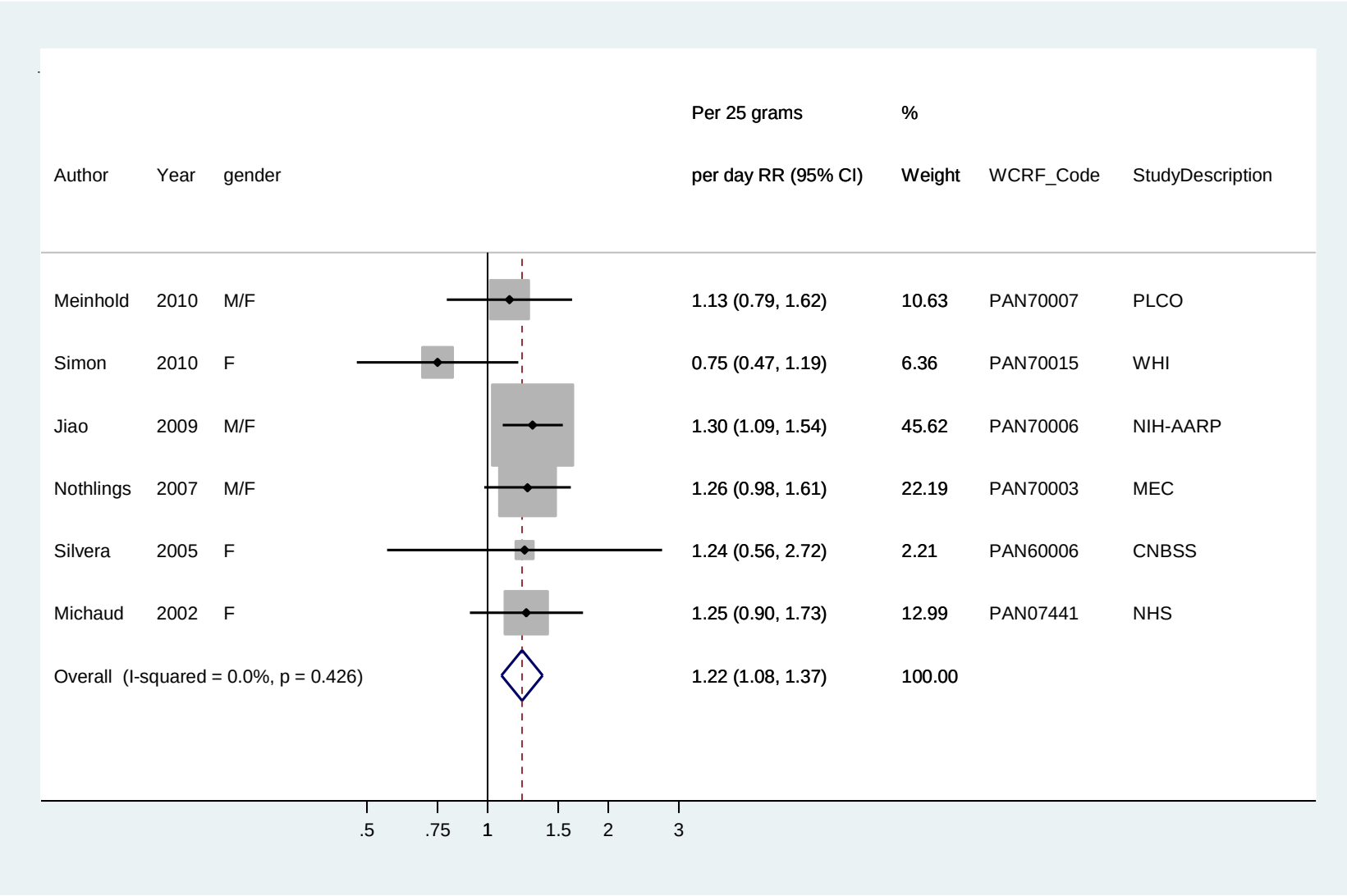


Figure 98 Funnel plot of fructose and pancreatic cancer

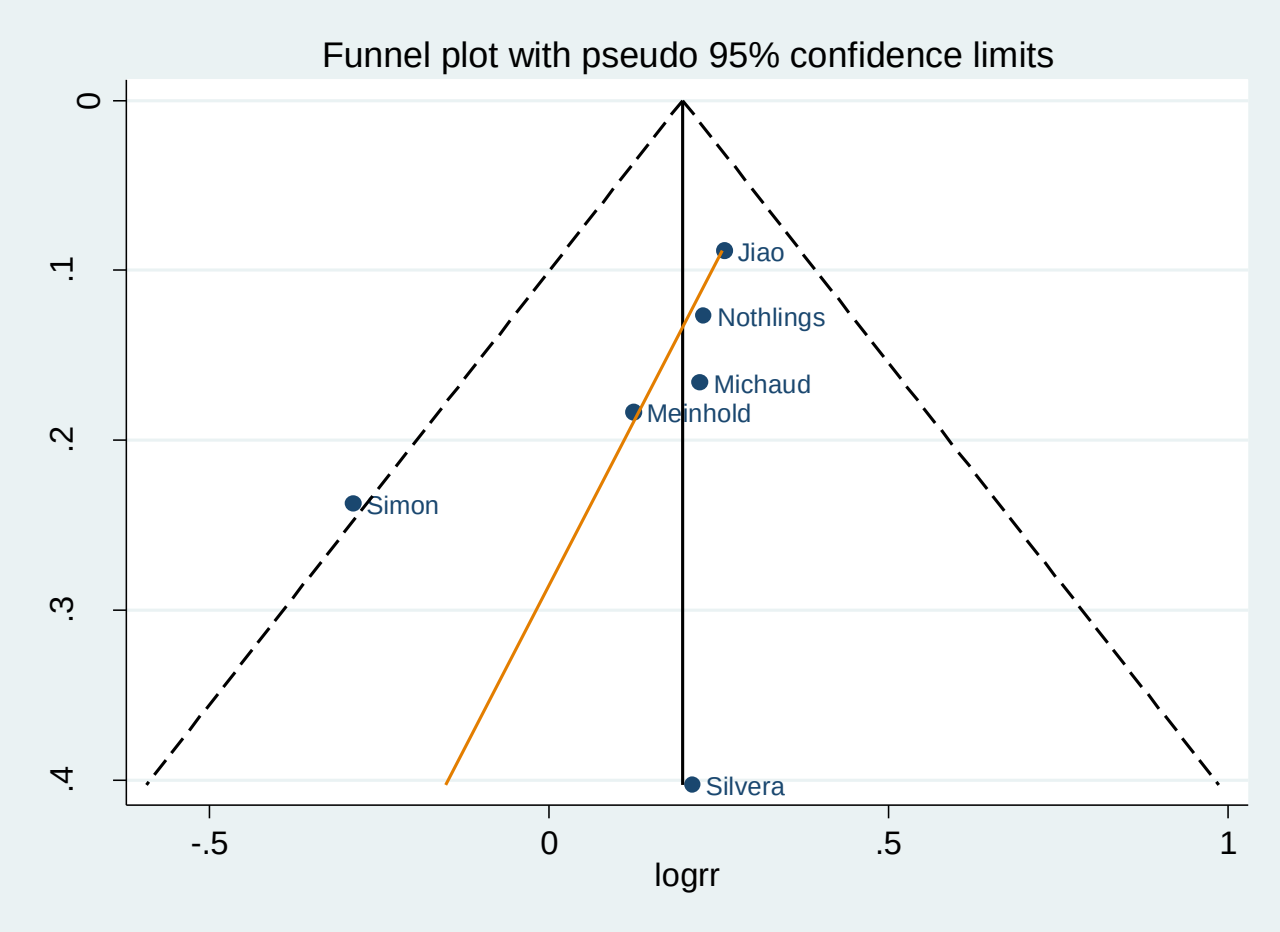


Figure 99 Dose-response graph of fructose and pancreatic cancer

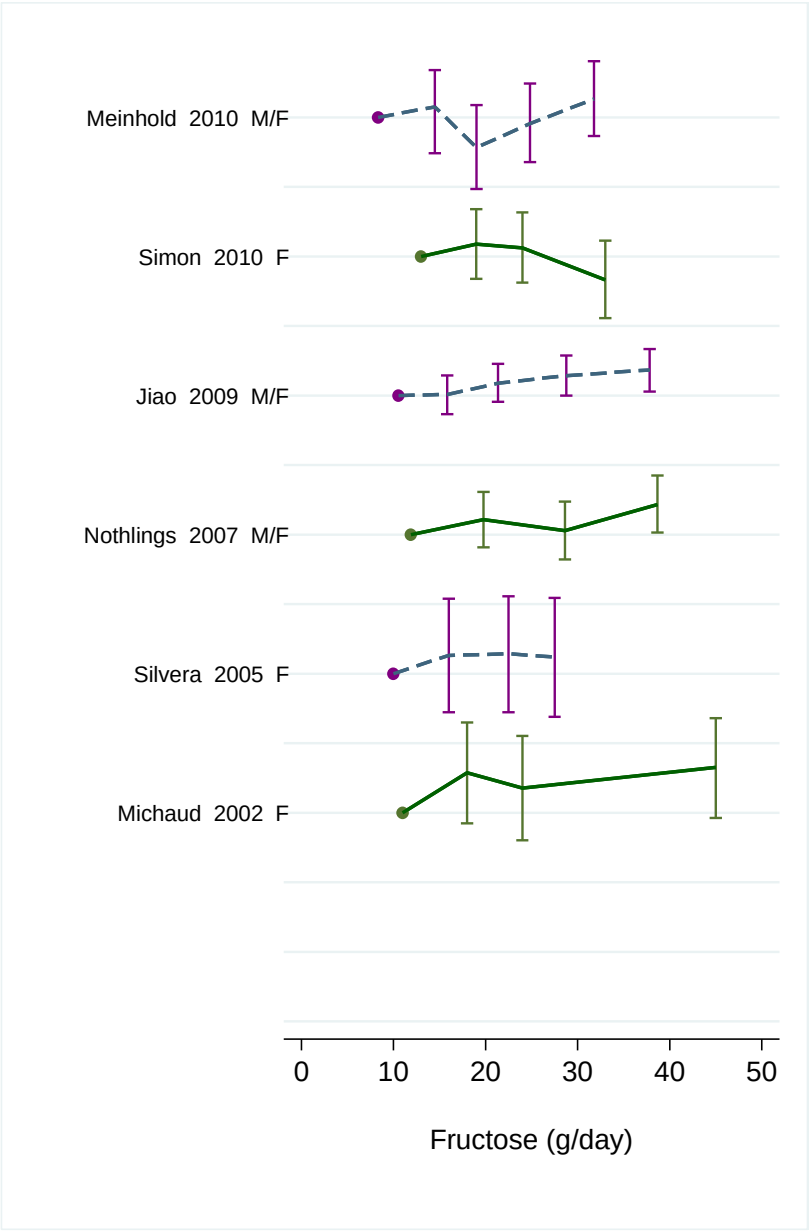


Figure 100 Dose-response meta-analysis of fructose and pancreatic cancer, stratified by sex - per 25 grams per day

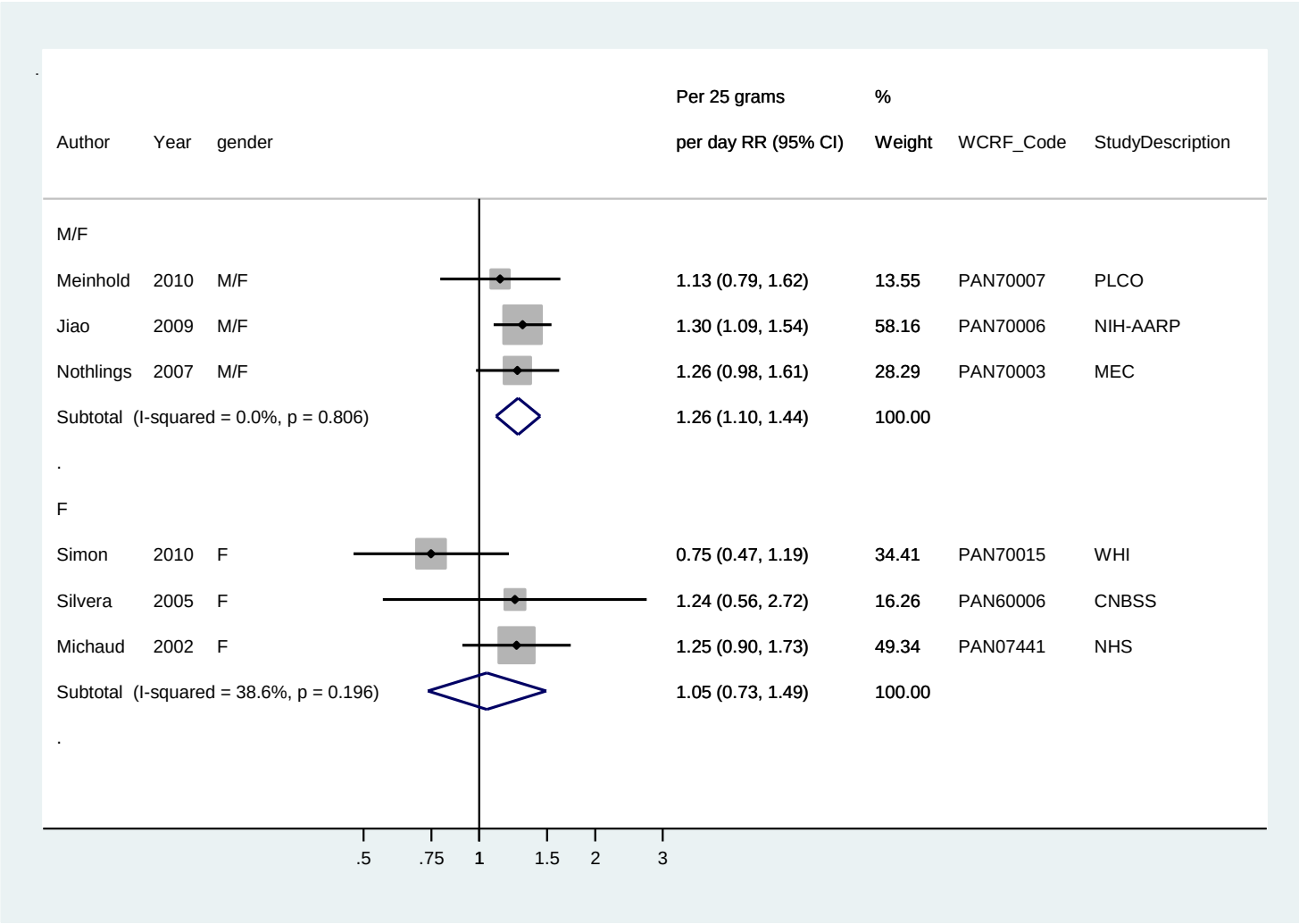


Figure 101 Nonlinear dose-response analysis of fructose and pancreatic cancer

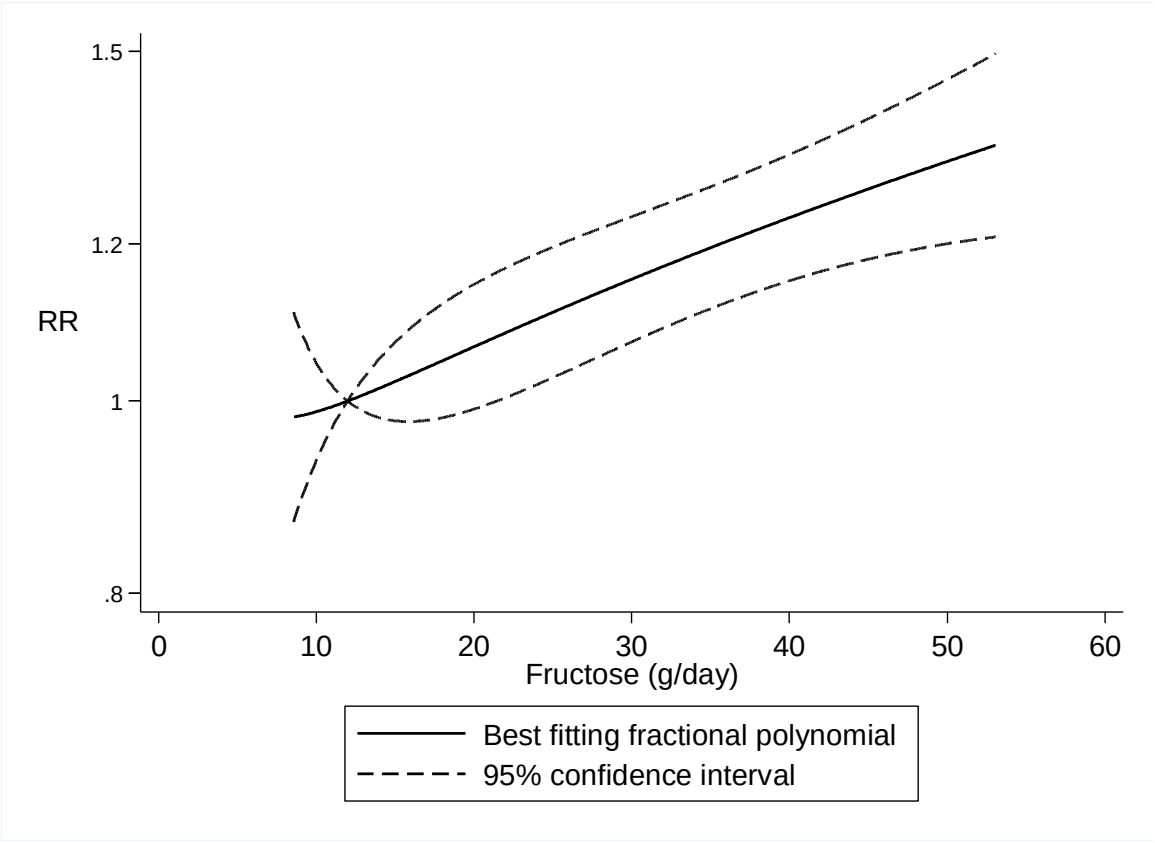


Figure 102 Scatter plot of risk estimates for fructose and pancreatic cancer risk

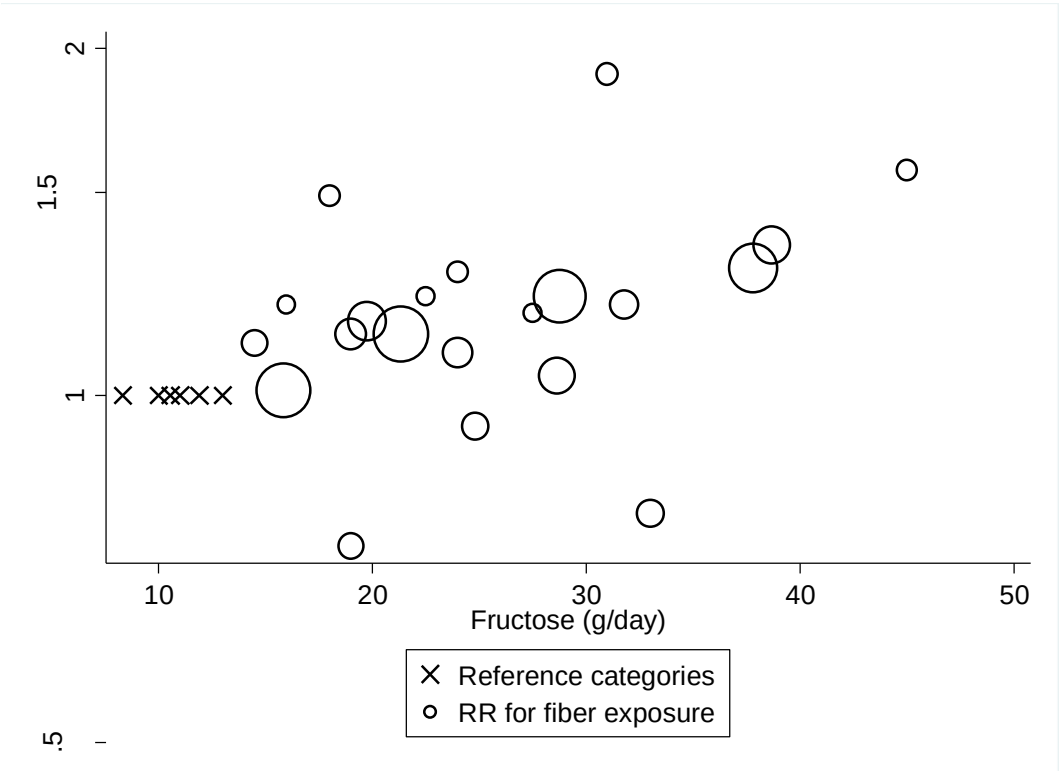


Table 84 Table with fructose values and corresponding RRs (95% CIs) for nonlinear analysis of fructose and pancreatic cancer

Fructose (g/day)	RR (95% CI)
12	1.00
15	1.02 (0.98-1.07)
20	1.07 (0.99-1.15)
25	1.11 (1.03-1.20)
30	1.15 (1.07-1.24)
35	1.19 (1.11-1.28)
40	1.24 (1.15-1.33)
45	1.28 (1.18-1.39)
50	1.32 (1.20-1.45)

5.1.4 Sucrose

Methods

Overall nine studies of sucrose and pancreatic cancer have been published up to September 2011, of which six studies were identified in the Continuous Update Project.
Dose-response analyses including eight studies and stratified analyses of sucrose intake and pancreatic cancer risk were conducted. The dose-response results are presented per 25 grams per day. The Cancer Prevention Study II Nutrition cohort only reported the relative risk estimate for the highest versus the lowest intake category (RR: 0.84; 95% CI: 0.62-1.14) and could not be included in the dose-response meta-analysis.

Main results

The summary RR per 25 grams per day was 1.05 (95% C: 0.92-1.19, I^2=53%, $p_{heterogeneity}$=0.04, 8 studies). The summary RR ranged from 1.02 (95% C: 0.89-1.16) when the PLCO study was excluded to 1.10 (95% C: 0.97-1.24) when the ATBC study was excluded. There was no evidence of publication bias with Egger's test, p=0.71. There was no evidence of a nonlinear association between sucrose and pancreatic cancer risk, $p_{nonlinearity}$=0.14.

Heterogeneity

There was significant evidence of moderate heterogeneity (I^2=53%, $p_{heterogeneity}$ =0.04).

Comparison with the Second Expert Report

The results are consistent with the analysis in the Second Expert Report in finding no association between sucrose intake and pancreatic cancer risk.

Table 85 Studies on sucrose identified in the CUP

Author, year	Country	Study name	Number of cases	Years of Follow-up	Sex	RR	LCI	UCI	Contrast
Simon, 2010	USA	Women's Health Initiative	287	8	F	1.30	0.89	1.89	60 vs. 32 g/d
Meinhold, 2010	USA	Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial	266	6.5	M/F	1.55	1.06	2.27	≥29.71 vs. ≤17.04 g/1000 kcal/d
Jiao, 2009	USA	NIH-AARP Diet and Health Study	1151	7.2	M/F	0.95	0.78	1.16	≥30.0 vs. 0.45-14.9 g/1000 kcal/d
Meinhold, 2009	Finland	Alpha-Tocopherol Beta-Carotene Cancer Prevention Study	305	19.4	M	0.68	0.47	0.98	84.3 vs. 24.9 g/d
Patel, 2007	USA	Cancer Prevention Study 2 Nutrition Cohort	401	9	M/F	0.84	0.62	1.14	Quintile 5 vs. 1
Nothlings, 2007	USA	Multiethnic Cohort Study	434	8	M/F	1.23	0.91	1.65	≥22.1 vs. <13.7 g/1000 kcal/d

Table 86 Overall evidence on sucrose and pancreatic cancer

	Summary of evidence
SLR	Three cohort studies reported on sucrose intake. One study reported a non-significant positive association, and the two other studies reported non-significant inverse associations.
Continuous Update Project	Six cohort studies have published results for sucrose intake and pancreatic cancer risk, of which one found a significant positive association, four found no significant association and one found a significant inverse association.

Table 87 Summary of results of the dose-response meta-analysis of sucrose and pancreatic

Pancreatic cancer		
	SLR	Continuous Update Project
Studies (n)	2	8
Cases (n)	246	3202
Increment unit	Per 10 g/d	Per 25 g/d
RR (95% CI)	1.06 (0.95-1.18)	1.05 (0.92-1.19)
Heterogeneity (I^2, p-value)	0%, p=0.6	53%, p=0.04
By gender		
Men	-	0.87 (0.75-1.00), n=1
Heterogeneity (I^2, p-value)	-	-
Women	-	1.02 (0.78-1.34), n=4
Heterogeneity (I^2, p-value)	-	47%, p=0.13

Table 88 Inclusion/exclusion table for meta-analysis of sucrose and pancreatic cancer

WCRF code	Author	Year	Study design	Study name	Subgroup	Cancer outcome	SLR	CUP dose-response meta-analysis	CUP HvL forest plot	Estimated values	Exclusion reason
PAN70015	Simon	2010	Prospective cohort study	Women's Health Initiative	Women	Incidence	New	Yes	Yes	Mid-exposure values	
PAN70007	Meinhold	2010	Prospective cohort study	Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial	Men/women	Incidence	New	Yes	Yes	Mid-exposure values, person-years	
PAN70006	Jiao	2009	Prospective cohort study	NIH-AARP Diet and Health Study	Men/women	Incidence	New	Yes	Yes	Mid-exposure values, person-years	
PAN70045	Meinhold	2009	Prospective cohort study	Alpha-Tocopherol Beta-Carotene Cancer Prevention Study	Men	Incidence	New	Yes	Yes	Mid-exposure values, person-years	
PAN70003	Nothlings	2007	Prospective cohort study	Multiethnic Cohort Study	Men/women	Incidence	New	Yes	Yes	Mid-exposure values	
PAN70061	Patel	2007	Prospective cohort study	Cancer Prevention Study II Nutrition Cohort	Men/women	Incidence	New	No	Yes	Mid-exposure values	Only highest vs. lowest comparison
PAN60006	Silvera	2005	Prospective cohort study	Canadian National Breast Screening Study	Women	Incidence	Yes	Yes	Yes	Mid-exposure values	
PAN07441	Michaud	2002	Prospective cohort study	Nurses' Health Study	Women	Incidence	Yes	Yes	Yes		
PAN07288	Harnack	1997	Prospective cohort study	Iowa Women's Health Study	Women	Incidence	Yes	Yes	Yes	Mid-exposure values	

Figure 103 Highest versus lowest forest plot of sucrose and pancreatic cancer

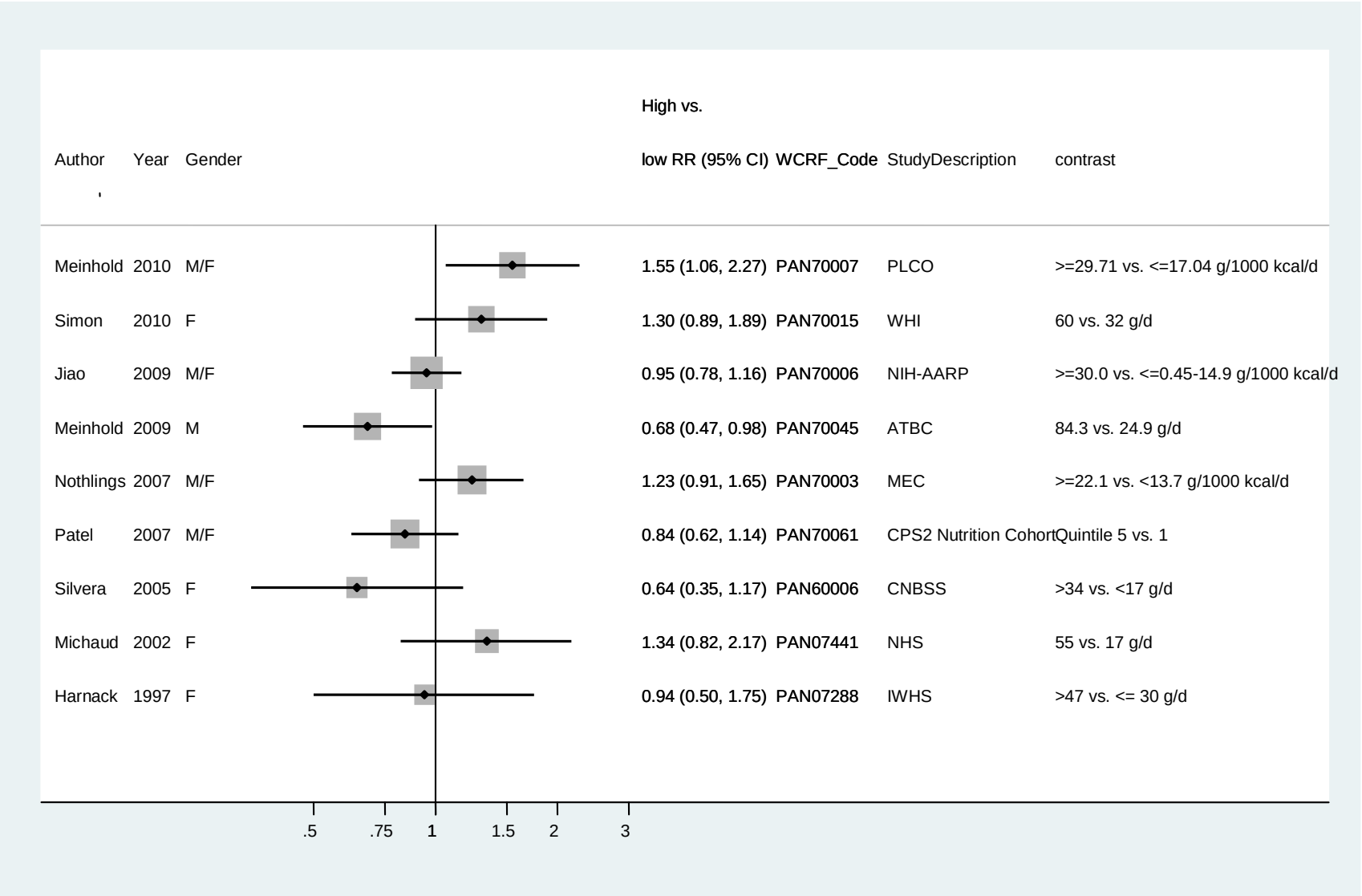


Figure 104 Dose-response meta-analysis of sucrose and pancreatic cancer - per 25 grams per day

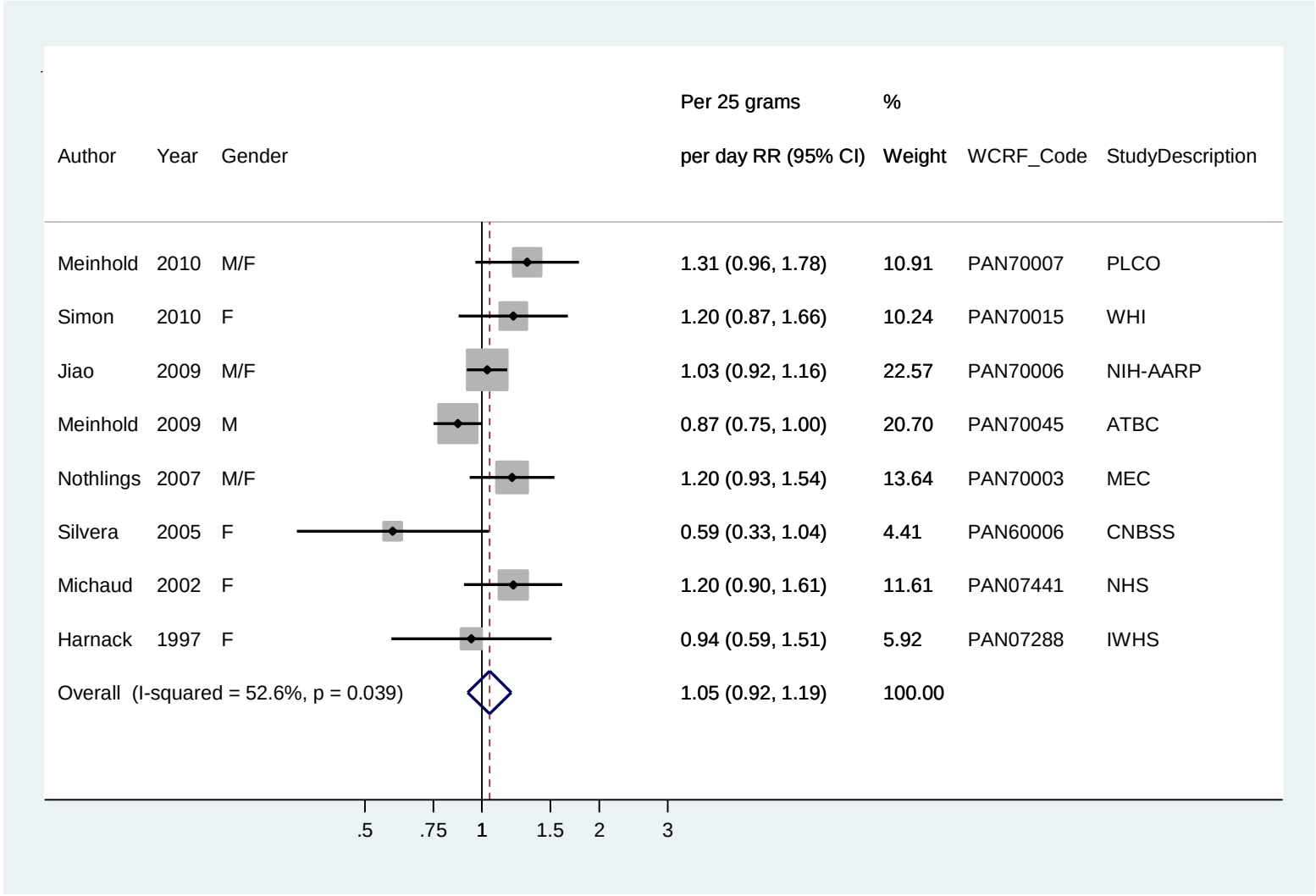


Figure 105 Funnel plot of sucrose and pancreatic cancer

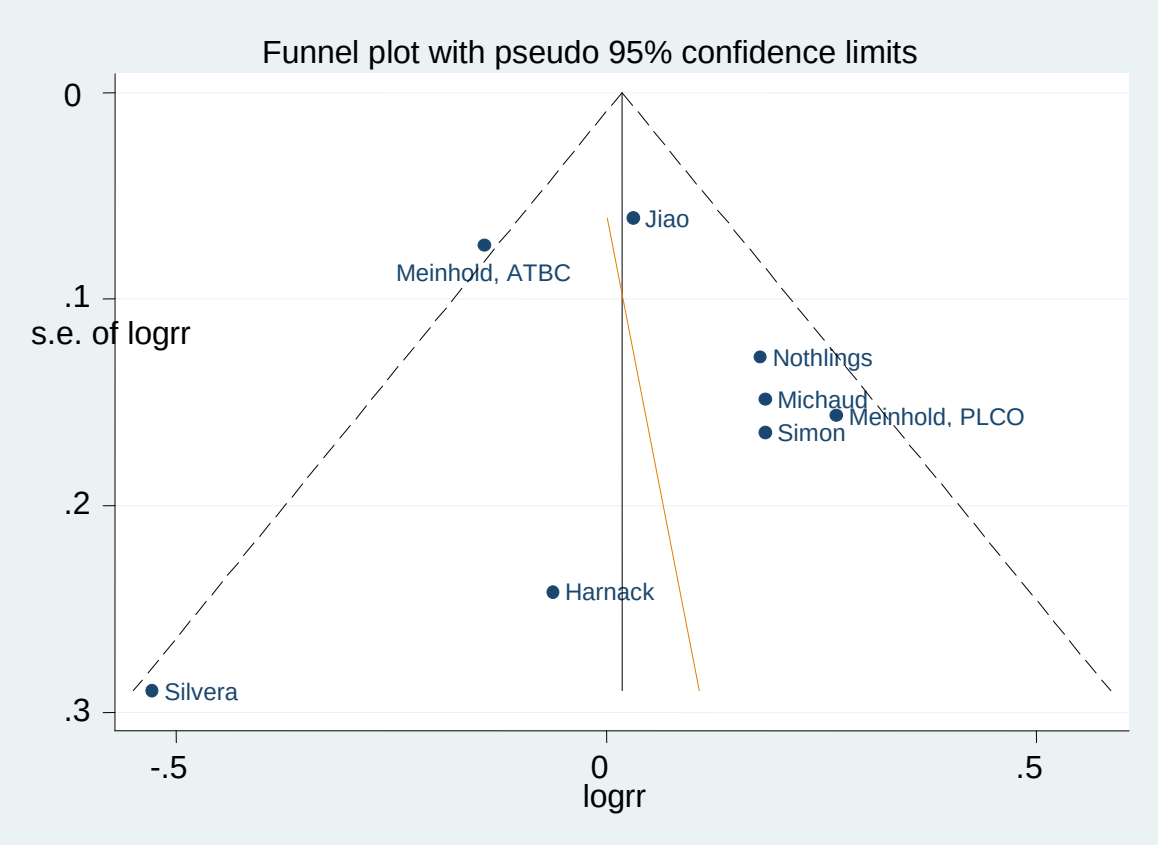


Figure 106 Dose-response graph of sucrose and pancreatic cancer

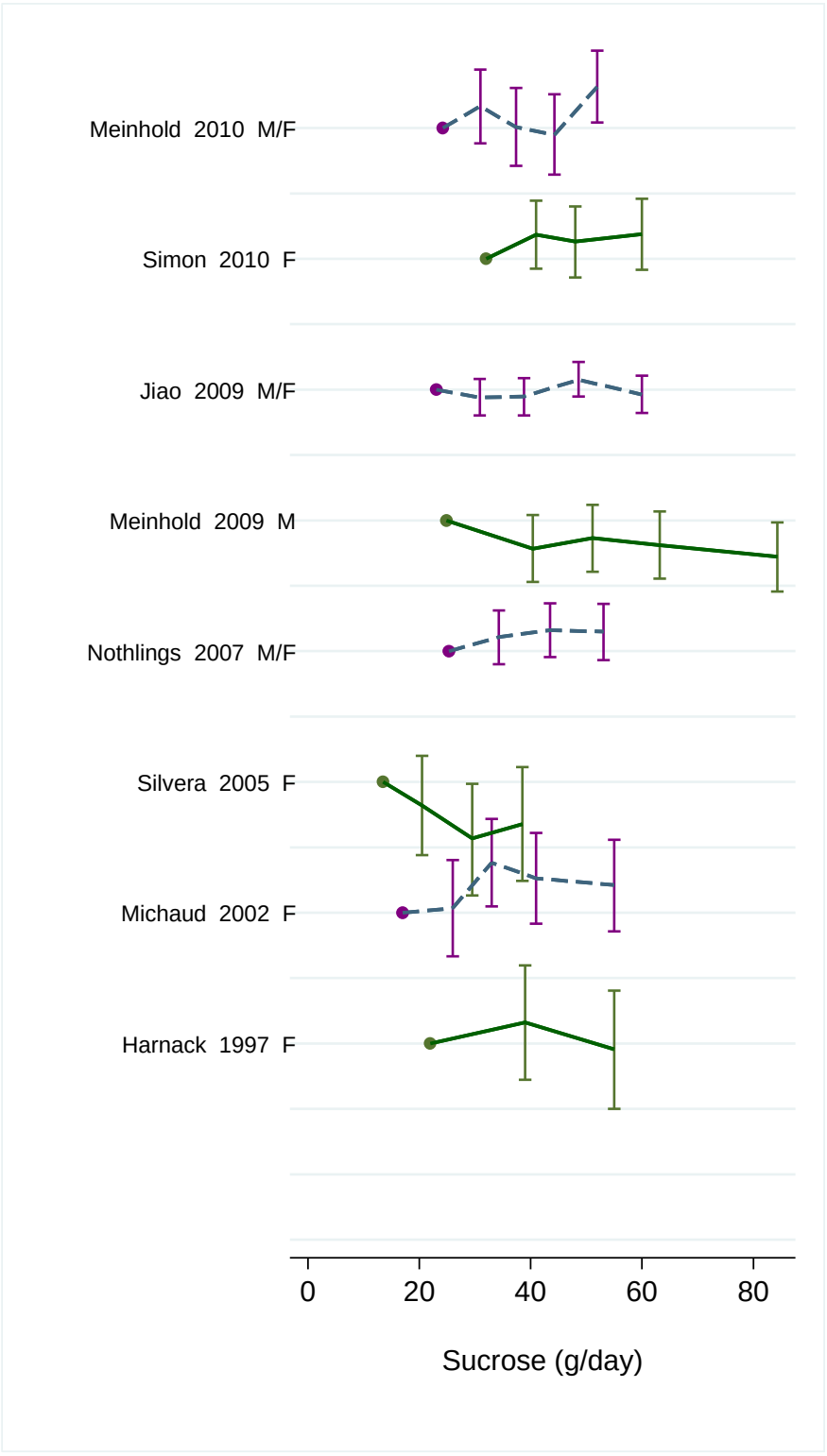


Figure 107 Dose-response meta-analysis of sucrose and pancreatic cancer, stratified by sex - per 25 grams per day

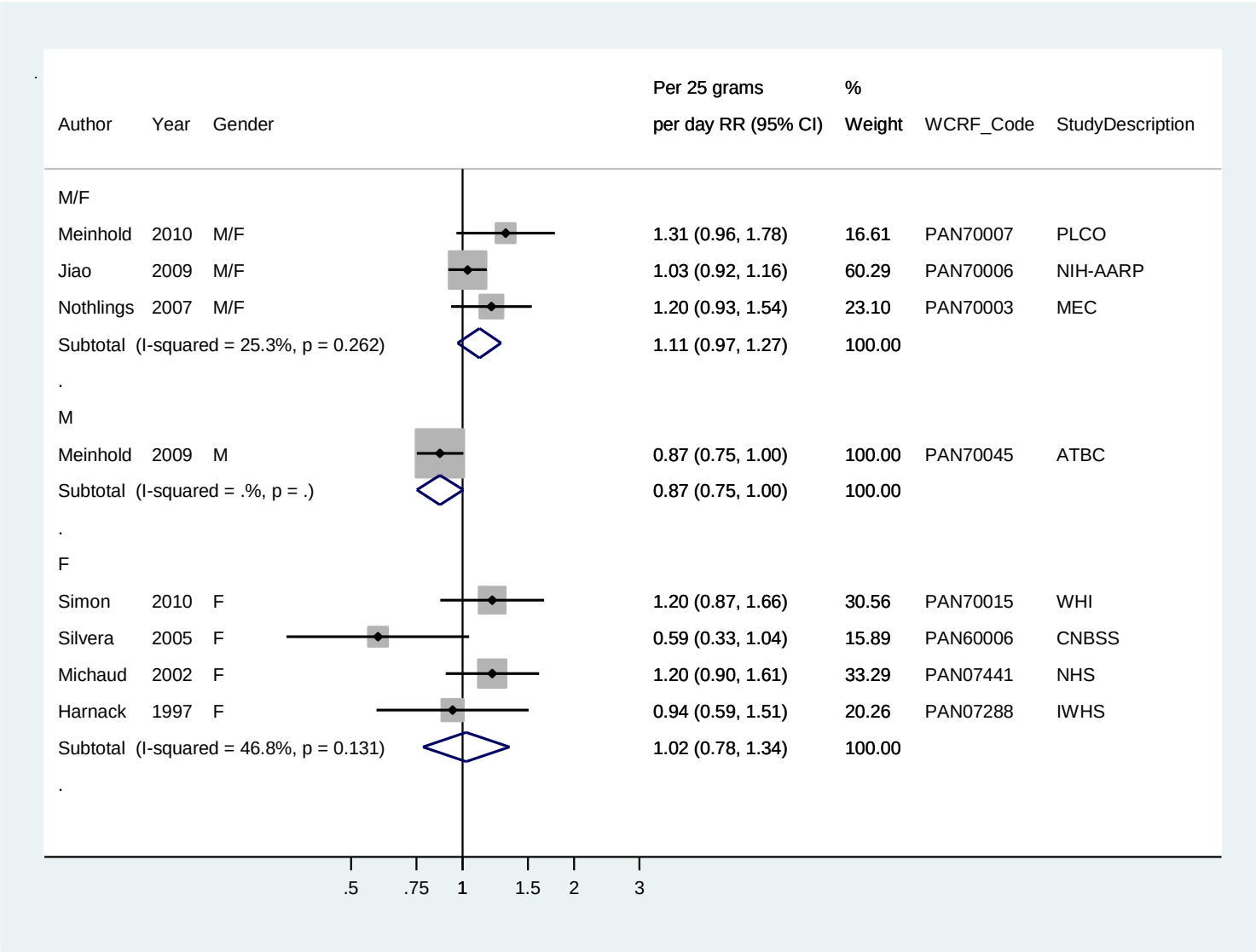


Figure 108 Nonlinear dose-response analysis of sucrose and pancreatic cancer

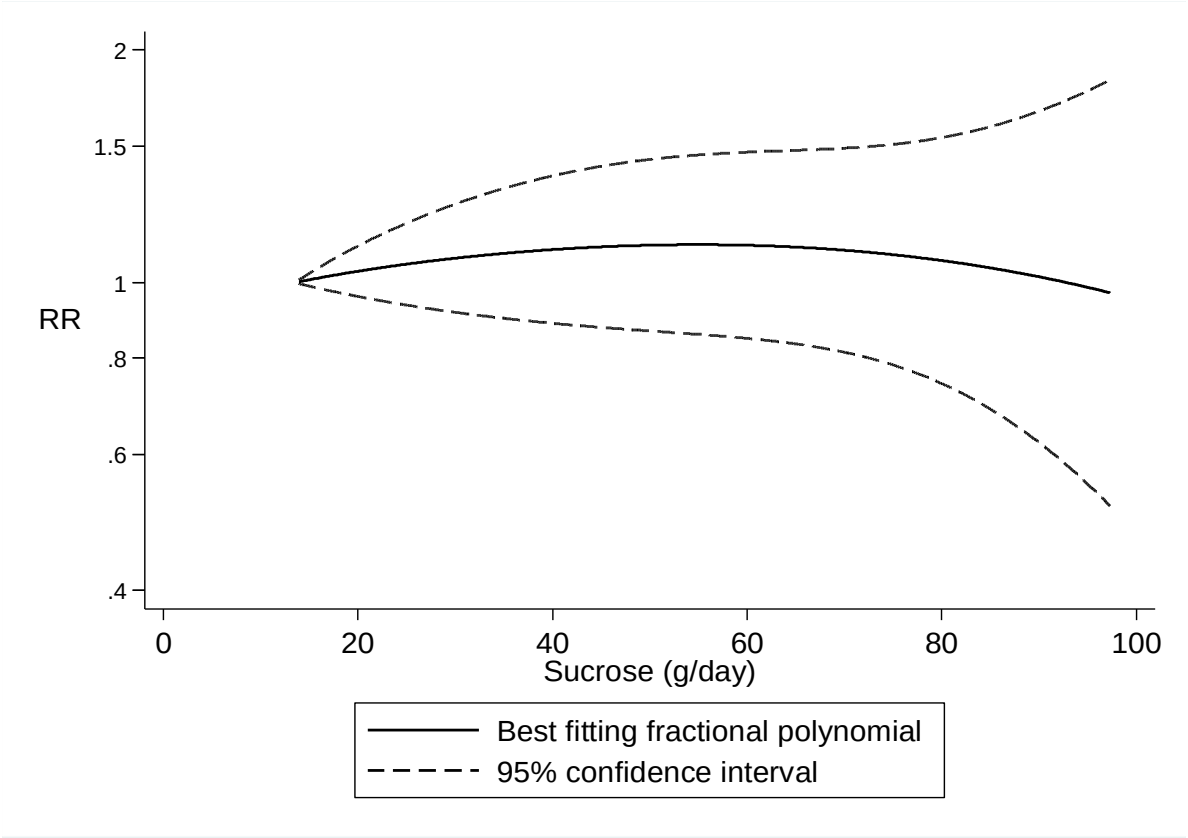


Figure 109 Scatter plot of risk estimates for sucrose and pancreatic cancer risk

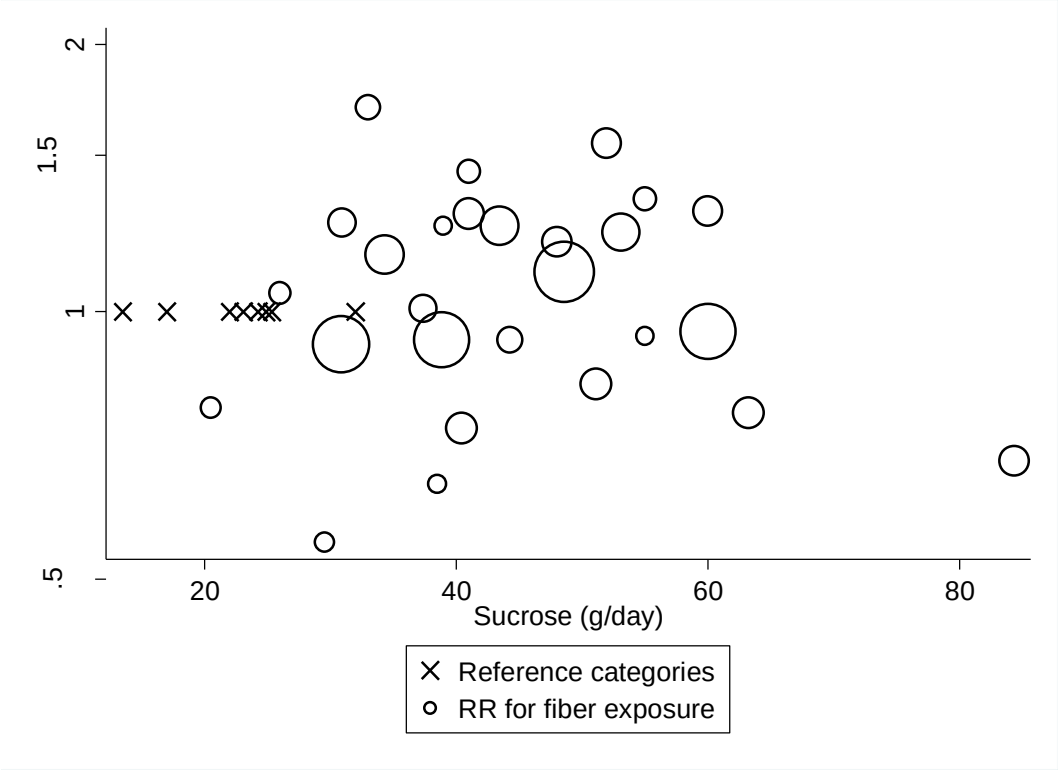


Table 89 Table with sucrose values and corresponding RRs (95% CIs) for nonlinear analysis of sucrose and pancreatic cancer

Sucrose (g/day)	RR (95% CI)
13.6	1.00
20	1.03 (0.96-1.12)
40	1.10 (0.89-1.37)
60	1.12 (0.85-1.47)
80	1.07 (0.74-1.54)
90	1.02 (0.62-1.67)

5.1.5 Glycemic index

Methods

Overall, eight cohort studies have investigated on glycemic index and pancreatic cancer. Six new publications from five cohort studies of glycemic index and pancreatic cancer were identified in the Continuous Update Project.
Dose-response analyses and stratified analyses of glycemic index and pancreatic cancer risk were conducted. The dose-response results are presented per 10 glycemic index units per day.

Main results

The summary RR per 10 glycemic index units per day was 1.02 (95% CI: 0.93-1.11), I^2=0%, $P_{heterogeneity}$ =0.97) for pancreatic cancer. The summary RR for ranged from 1.01 (95% CI: 0.91-1.11) when the Canadian National Breast Cancer Screening Study was excluded to 1.05 (95% CI: 0.94-1.17) when the Cancer Prevention Study 2 Nutrition Cohort was excluded. There was no indication of publication bias with Egger's test, p=0.54. There was no evidence of a nonlinear association between glycemic index and pancreatic cancer risk, $p_{nonlinearity}$= 1.00.

Heterogeneity

There was generally little evidence of heterogeneity in the analyses (I^2=0%, p= 0.97).

Comparison with the Second Expert Report

The results are consistent with the findings from the Second Expert Report which found no significant association between glycemic index and pancreatic cancer risk.

Published meta-analysis

Two previous meta-analyses of glycemic index and pancreatic cancer risk are consistent with our results and found no significant associations. The summary RR for high vs. low glycemic index was 0.99 (95% CI: 0.83-1.19, I^2=0%, $p_{heterogeneity}$=0.78, n=5) (Mulholland, 2009) and 1.11 (95% CI: 0.86-1.43, I^2=0%, $p_{heterogeneity}$=0.68, n=5) for (Gnagnarella, 2008), respectively.

Table 90 Studies on glycemic index identified in the CUP

Author, year	Country	Study name	Number of cases	Years of Follow-up	Sex	RR	LCI	UCI	Contrast
Simon, 2010	USA	Women's Health Initiative	287	8	F	1.13	0.78	1.63	56 vs. 48 units/d
Meinhold, 2010	USA	Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial	266	6.5	M/F	1.00	0.69	1.47	≥56.17 vs. ≤50.89 units/d
Jiao, 2009	USA	NIH-AARP Diet and Health Study	1151	7.2	M/F	1.09	0.90	1.32	≥52.6 vs. 24.5-46.2 units/d
George, 2009	USA	NIH-AARP Diet and Health Study	949	8	F M	1.00 1.19	0.71 0.92	1.40 1.55	≥56.56 vs. ≤50.43 units/d ≥57.02 vs. ≤51.26 units/d
Heinen, 2008	Netherlands	Netherlands Cohort Study	408	13.3	M/F	0.87 0.98	0.59 0.81	1.29 1.19	64 vs. 55 units/d Per 5 units
Patel, 2007	USA	Cancer Prevention Study II Nutrition Cohort	401	9	M/F	0.80 1.11	0.53 0.71	1.20 1.74	>81.83 vs. ≤69.61 units/d >79.96 vs. ≤68.42 units/d

Table 91 Overall evidence on glycemic index and pancreatic cancer

	Summary of evidence
SLR	Three studies of glycemic index were published. One showed a non-significant positive association, while the others were not associated with pancreatic cancer risk.
Continuous Update Project	Six publications from five cohort studies were identified. None of the studies reported significant associations between glycemic index and pancreatic cancer risk.

Table 92 Summary of results of the dose-response meta-analysis of glycemic index and pancreatic cancer

Pancreatic cancer		
	SLR	Continuous Update Project
Studies (n)	3	8
Cases (n)	473	2986
Increment unit	Per 10 units	Per 10 units/day
RR (95% CI)	1.09 (0.96-1.24)	1.02 (0.93-1.11)
Heterogeneity (I^2, p-value)	6%, p=0.30	0%, p=0.97
By gender		
Men	-	0.97 (0.78-1.22), n=2
Heterogeneity (I^2, p-value)	-	72%, p=0.06
Women	-	1.04 (0.95-1.13), n=6
Heterogeneity (I^2, p-value)	-	0%, p=0.98

Table 93 Inclusion/exclusion table for meta-analysis of glycemic index and pancreatic cancer

WCRF code	Author	Year	Study design	Study name	Subgroup	Cancer outcome	SLR	CUP dose-response meta-analysis	CUP HvL forest plot	Estimated values	Exclusion reason
PAN70015	Simon	2010	Prospective cohort study	Women's Health Initiative	Women	Incidence	New	Yes	Yes	Mid-exposure values	
PAN70007	Meinhold	2010	Prospective cohort study	Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial	Men/women	Incidence	New	Yes	Yes	Mid-exposure values, person-years	
PAN70006	Jiao	2009	Prospective cohort study	NIH-AARP Diet and Health Study	Men/women	Incidence	New	Yes	Yes	Mid-exposure values, person-years	
PAN70062	George	2009	Prospective cohort study	NIH-AARP Diet and Health Study	Men/ women	Incidence	New	No	No	Mid-exposure values, distribution of person-years and cases	Overlapped with Jiao, 2009 PAN70006 which had more cases
PAN70004	Heinen	2008	Case cohort study	Netherlands Cohort Study	Men/women	Incidence	New	Yes	Yes		
PAN70061	Patel	2007	Prospective cohort study	Cancer Prevention Study II Nutrition Cohort	Men/women	Incidence	New	Yes	Yes	Mid-exposure values	
PAN61271	Johnson	2005	Prospective cohort study	Iowa Women's Health Study	Women	Incidence	Yes	Yes	Yes	Mid-exposure values, person-years	
PAN60006	Silvera	2005	Prospective cohort study	Canadian National Breast Screening Study	Women	Incidence	Yes	Yes	Yes	Mid-exposure values	
PAN07441	Michaud	2002	Prospective cohort study	Nurses' Health Study	Women	Incidence	Yes	Yes	Yes		

Figure 110 Highest versus lowest forest plot of glycemic index and pancreatic cancer

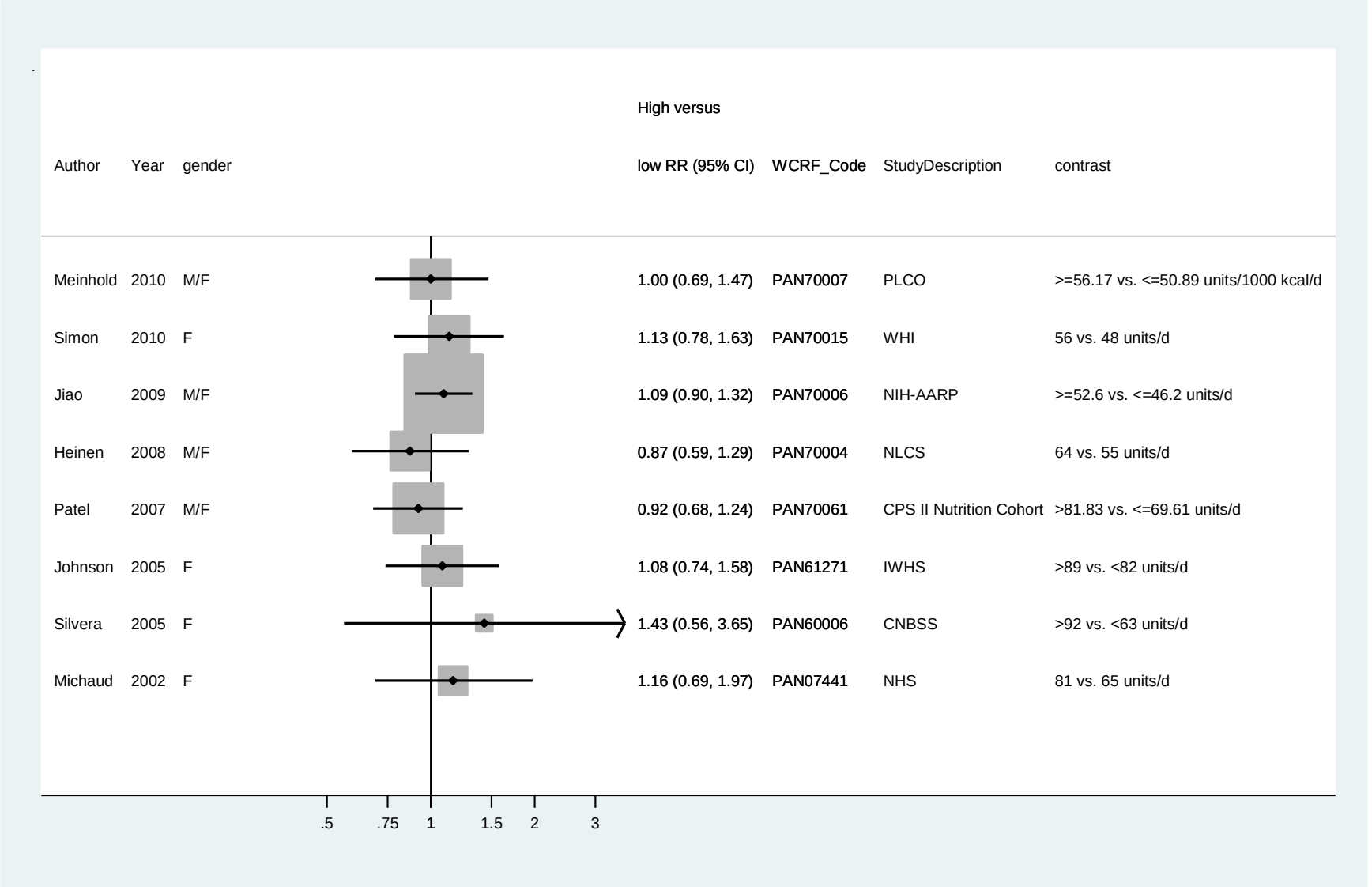


Figure 111 Dose-response meta-analysis of glycemic index and pancreatic cancer - per 10 units

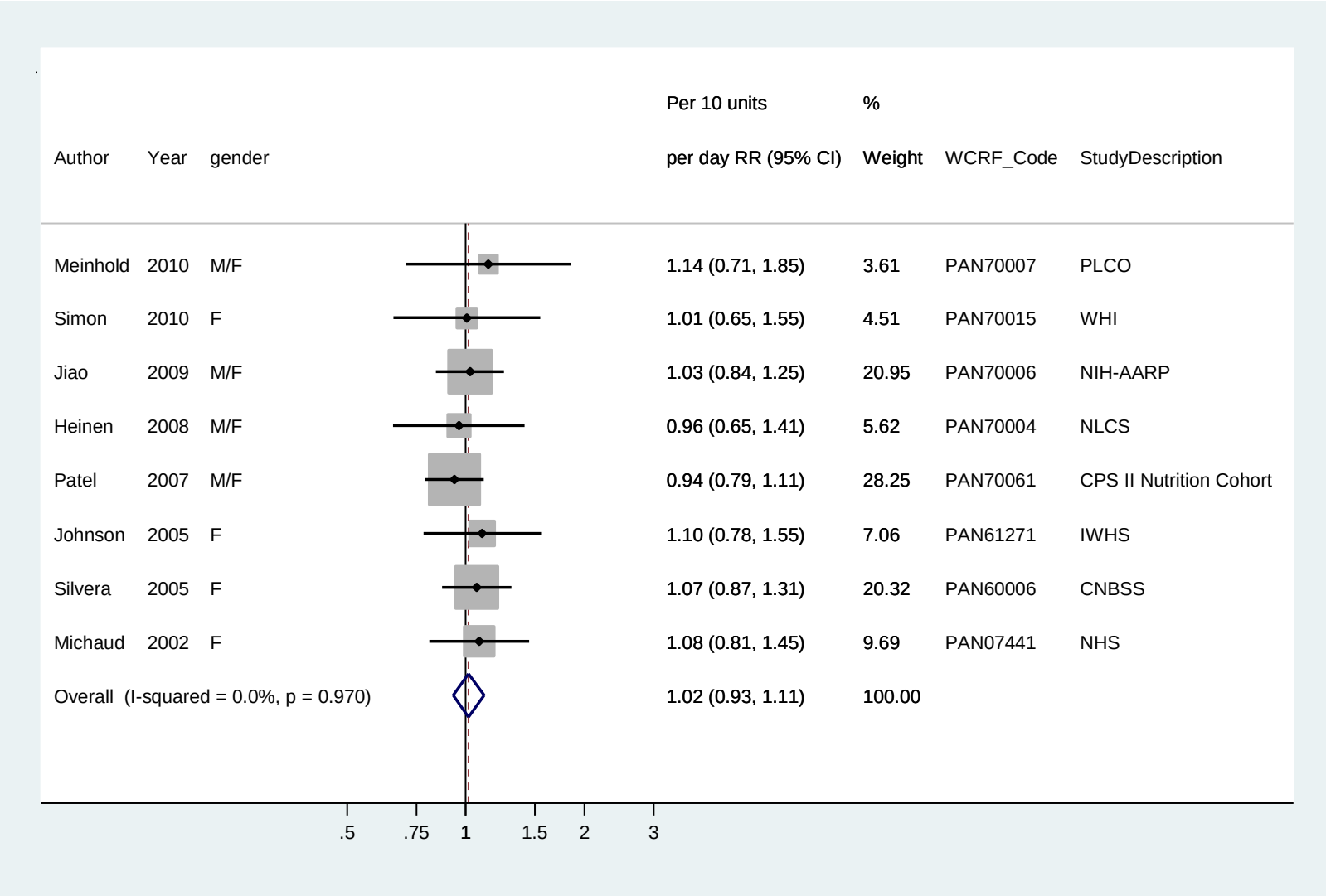


Figure 112 Funnel plot of glycemic index and pancreatic cancer

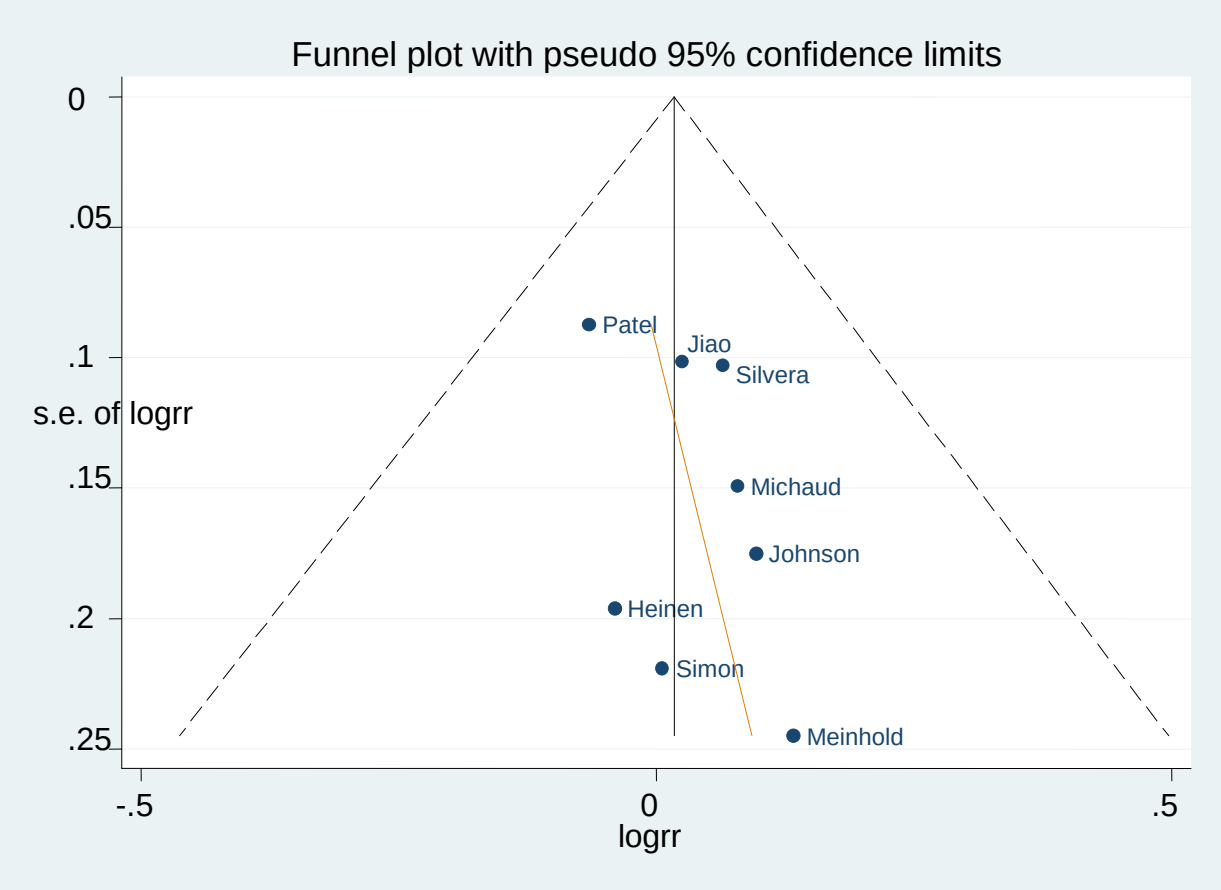


Figure 113 Dose-response graph of glycemic index and pancreatic cancer

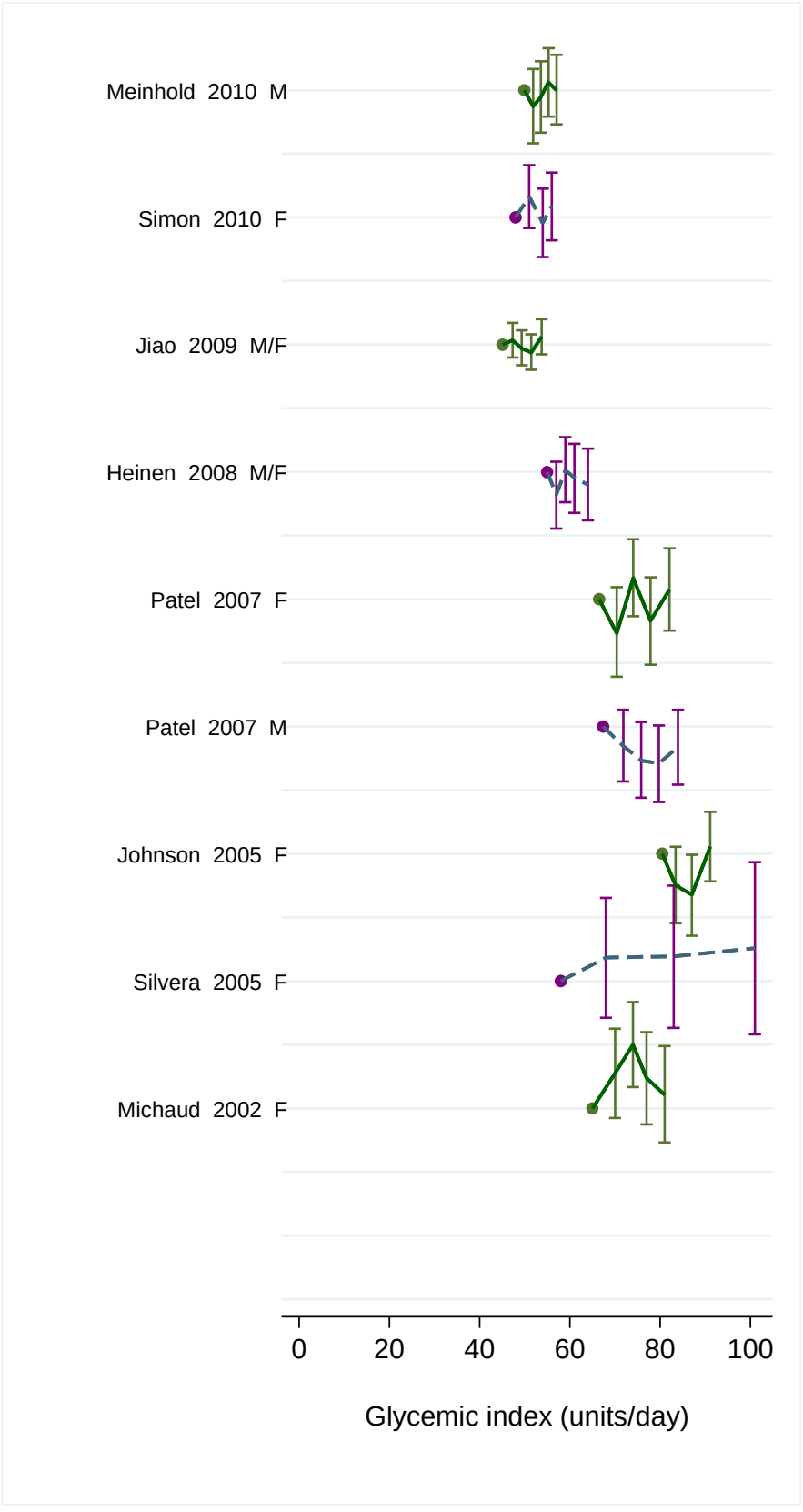


Figure 114 Dose-response meta-analysis of glycemic index and pancreatic cancer, stratified by sex - per 10 units

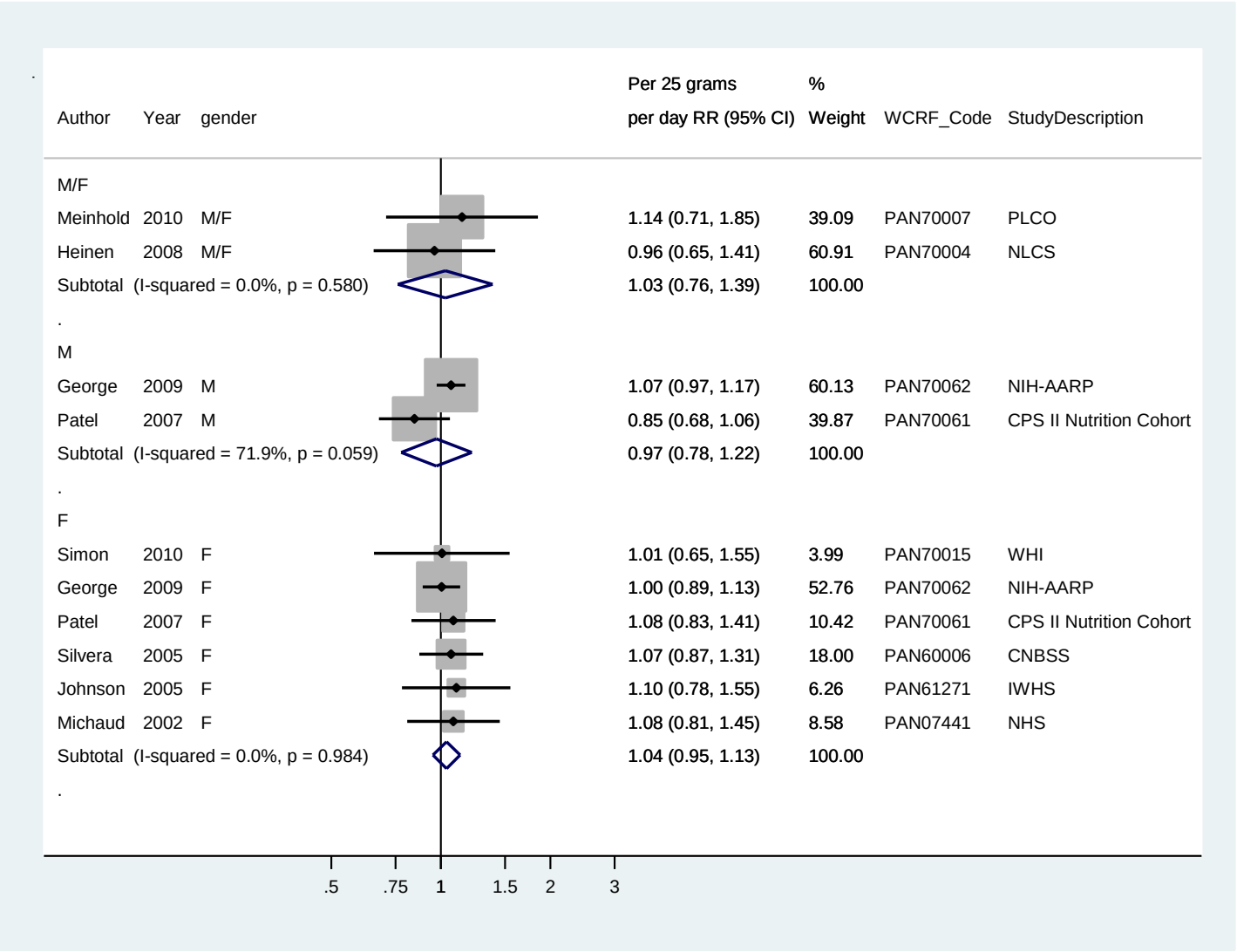


Figure 115 Nonlinear dose-response analysis of glycemic index and pancreatic cancer

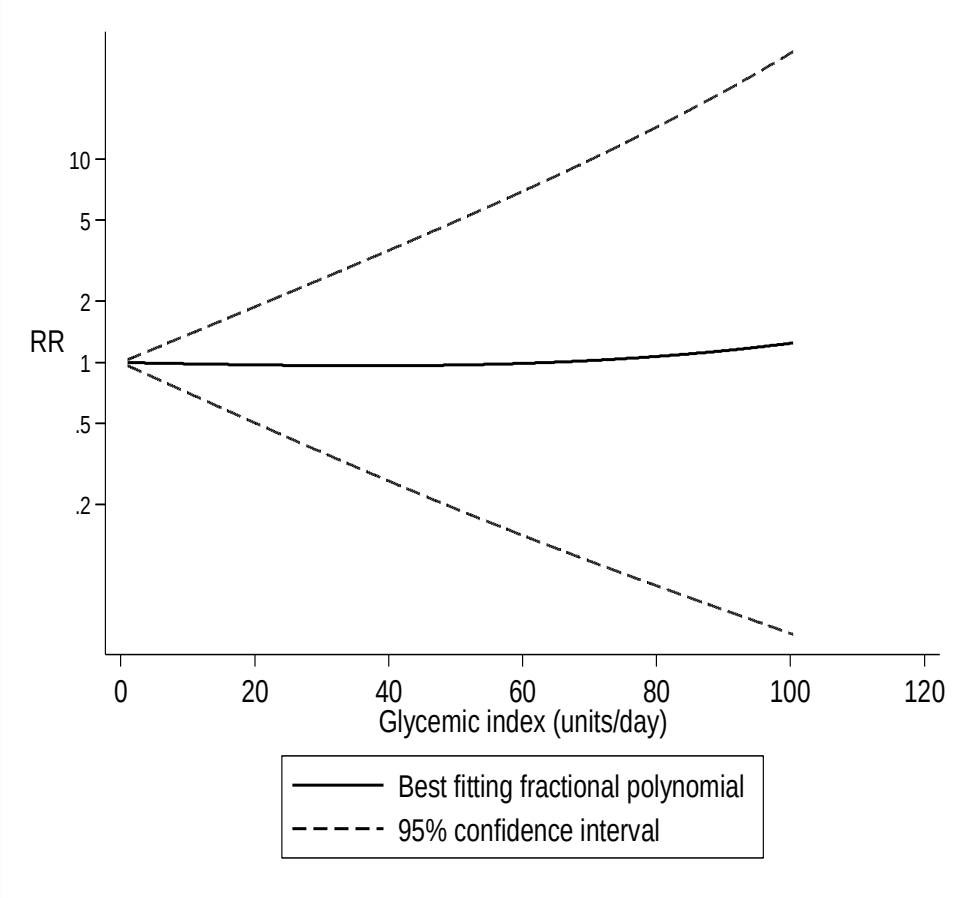


Figure 116 Scatter plot of risk estimates for glycemic index and pancreatic cancer risk

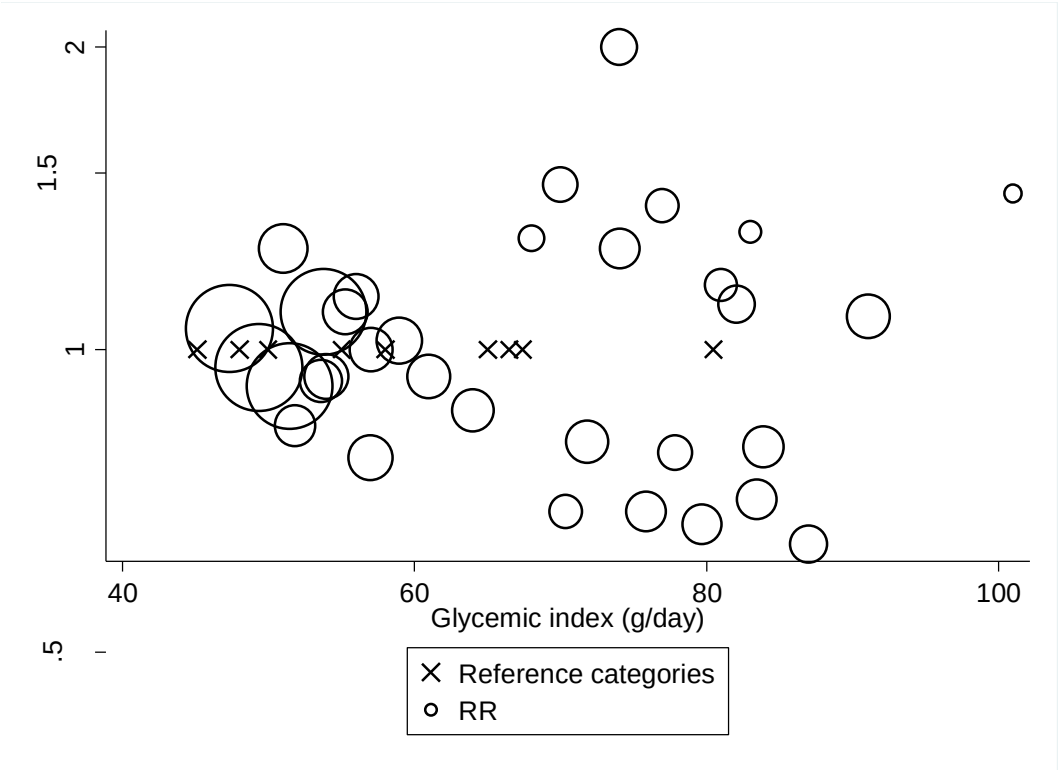


Table 94 Table with glycemic index values and corresponding RRs (95% CIs) for nonlinear analysis of glycemic index and pancreatic cancer

Glycemic index	RR (95% CI)
45.2	1.00
50	1.03 (0.73-1.46)
60	1.08 (0.41-2.85)
80	1.14 (0.15-8.78)
100	1.11 (0.04-28.14)

5.1.5 Glycemic load

Methods

Overall, nine studies have reported results on glycemic load and pancreatic cancer. Seven new publications from six cohort studies of glycemic load and pancreatic cancer were identified in the Continuous Update Project.

Dose-response analyses and stratified analyses of glycemic load and pancreatic cancer risk were conducted. The dose-response results are presented per 50 glycemic load units per day.

Main results

The summary RR per 50 glycemic load units per day was 1.03 (95% CI: 0.93-1.14, for pancreatic cancer. In a sensitivity analysis the summary RR ranged from 1.01 (95% CI: 0.91-1.12) when excluding the Nurses' Health Study to 1.05 (95% CI: 0.95-1.16) when excluding the NIH-AARP Diet and Health Study. There was no indication of publication bias with Egger's test, p=0.68. There was no evidence of a nonlinear association between glycemic load and pancreatic cancer risk, $p_{nonlinearity}$=0.51

Heterogeneity

There was generally little evidence of heterogeneity (I^2=10%, $P_{heterogeneity}$ =0.35) in the analyses.

Comparison with the Second Expert Report

The results are consistent with the findings from the Second Expert Report which found no significant association between glycemic load and pancreatic cancer risk.

Published meta-analysis

Two previous meta-analyses of glycemic load and pancreatic cancer risk found no significant associations. The summary RR for high vs. low glycemic load was 1.01 (95% CI: 0.86-1.19, I^2=0%, $p_{heterogeneity}$=0.39, n=6) (Mulholland, 2009) and 1.00 (95% CI: 0.94-1.53, I^2=11%, $p_{heterogeneity}$=0.34, n=4) (Gnagnarella, 2008), respectively.

Table 95 Studies on glycemic load identified in the CUP

Author, year	Country	Study name	Number of cases	Years of Follow-up	Sex	RR	LCI	UCI	Contrast
Simon, 2010	USA	Women's Health Initiative	287	8	F	0.80	0.55	1.15	150 vs. 105 units/d
Meinhold, 2010	USA	Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial	266	6.5	M/F	1.41	0.97	2.07	≥73.57 vs. ≤54.28 g/1000 kcal/d
Jiao, 2009	USA	NIH-AARP Diet and Health Study	1151	7.2	M/F	0.95	0.74	1.22	≥74.9 vs. 4.0-54.5 units/d
George, 2009	USA	NIH-AARP Diet and Health Study	949	8	F M	0.49 0.67	0.26 0.42	0.94 1.08	135.31 vs. 66.91 units/d 164.44 vs. 83.20 units/d
Heinen, 2008	Netherlands	Netherlands Cohort Study	408	13.3	M/F	0.85 1.03	0.58	1.24	156 vs. 88 units/d Per 50 g/d
Patel, 2007	USA	Cancer Prevention Study II Nutrition Cohort	401	9	M F	1.10 0.89	0.73 0.56	1.64 1.41	>169.89 vs. ≤119.02 units/d >132.37 vs. ≤95.13 units/d
Nothlings, 2007	USA	Multiethnic Cohort Study	434	8	M/F	1.10	0.80	1.52	≥82.3 vs. <63.3 g/1000 kcal/d

Table 96 Overall evidence on glycemic load and pancreatic cancer

	Summary of evidence
SLR	Three cohort studies were identified of which one showed a non-significant positive association and the two others no clear association.
Continuous Update Project	Six cohort studies (7 publications) were identified. One study reported a significant inverse association among women, but results for men were not significant. Another study reported a marginally increased risk, while the four other studies found no clear association.

Table 97 Summary of results of the dose-response meta-analysis of glycemic load and pancreatic cancer

Pancreatic cancer		
	SLR	Continuous Update Project
Studies (n)	3	9
Cases (n)	473	3420
Increment unit CI)	Per 20 g/d	Per 50 units/day
RR (95%	1.01 (0.92-1.11)	1.03 (0.93-1.14)
Heterogeneity (I^2, p-value)	50%, p=0.10	10%, p=0.35
By gender		
Men	-	0.93 (0.80-1.08), n=2
Heterogeneity (I^2, p-value)	-	0%, p=0.33
Women	-	0.89 (0.75-1.06), n=6
Heterogeneity (I^2, p-value)	-	37%, p=0.16

Table 98 Inclusion/exclusion table for meta-analysis of glycemic load and pancreatic cancer

WCRF code	Author	Year	Study design	Study name	Subgroup	Cancer outcome	SLR	CUP dose-response meta-analysis	CUP HvL forest plot	Estimated values	Exclusion reason
PAN70015	Simon	2010	Prospective cohort study	Women's Health Initiative	Women	Incidence	New	Yes	Yes	Mid-exposure values	
PAN70007	Meinhold	2010	Prospective cohort study	Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial	Men/women	Incidence	New	Yes	Yes	Mid-exposure values, person-years	
PAN70006	Jiao	2009	Prospective cohort study	NIH-AARP Diet and Health Study	Men/women	Incidence	New	Yes	Yes	Mid-exposure values, person-years	
PAN70062	George	2009	Prospective cohort study	NIH-AARP Diet and Health Study	Men/ women	Incidence	New	No	No	Mid-exposure values, distribution of person-years and cases	Overlapped with Jiao, 2009 PAN70006 which had more cases, but included in gender stratified analyses
PAN70004	Heinen	2008	Case cohort study	Netherlands Cohort Study	Men/women	Incidence	New	Yes	Yes		
PAN70003	Nothlings	2007	Prospective cohort study	Multiethnic Cohort Study	Men/women	Incidence	New	Yes	Yes	Mid-exposure values	
PAN70061	Patel	2007	Prospective cohort study	Cancer Prevention Study II Nutrition Cohort	Men/women	Incidence	New	Yes	Yes	Mid-exposure values	
PAN61271	Johnson	2005	Prospective cohort study	Iowa Women's Health Study	Women	Incidence	Yes	Yes	Yes	Mid-exposure values, person-years	
PAN60006	Silvera	2005	Prospective cohort study	Canadian National Breast Screening Study	Women	Incidence	Yes	Yes	Yes	Mid-exposure values	
PAN07441	Michaud	2002	Prospective cohort study	Nurses' Health Study	Women	Incidence	Yes	Yes	Yes		

Figure 117 Highest versus lowest forest plot of glycemic load and pancreatic cancer

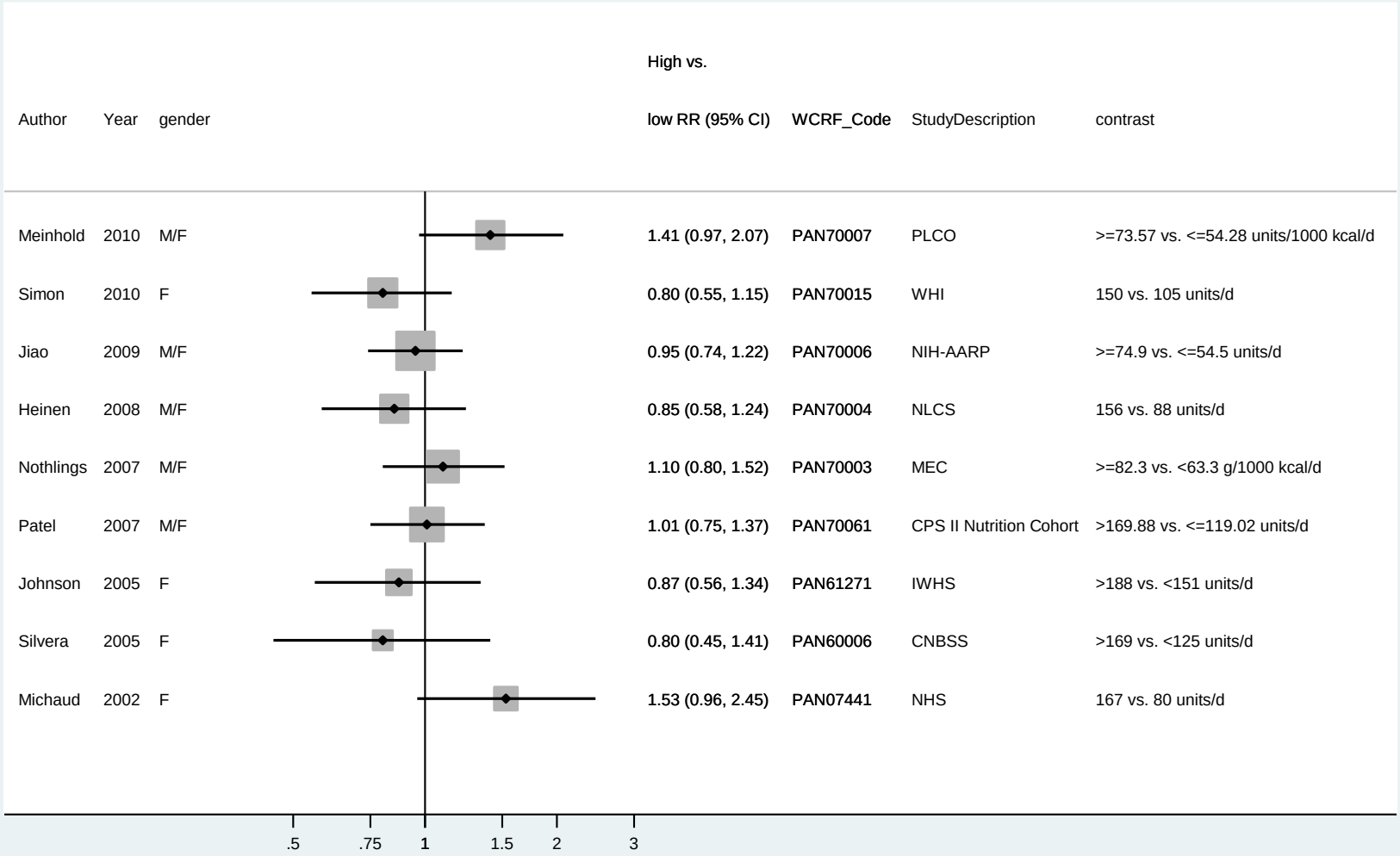


Figure 118 Dose-response meta-analysis of glycemic load and pancreatic cancer - per 50 units/day

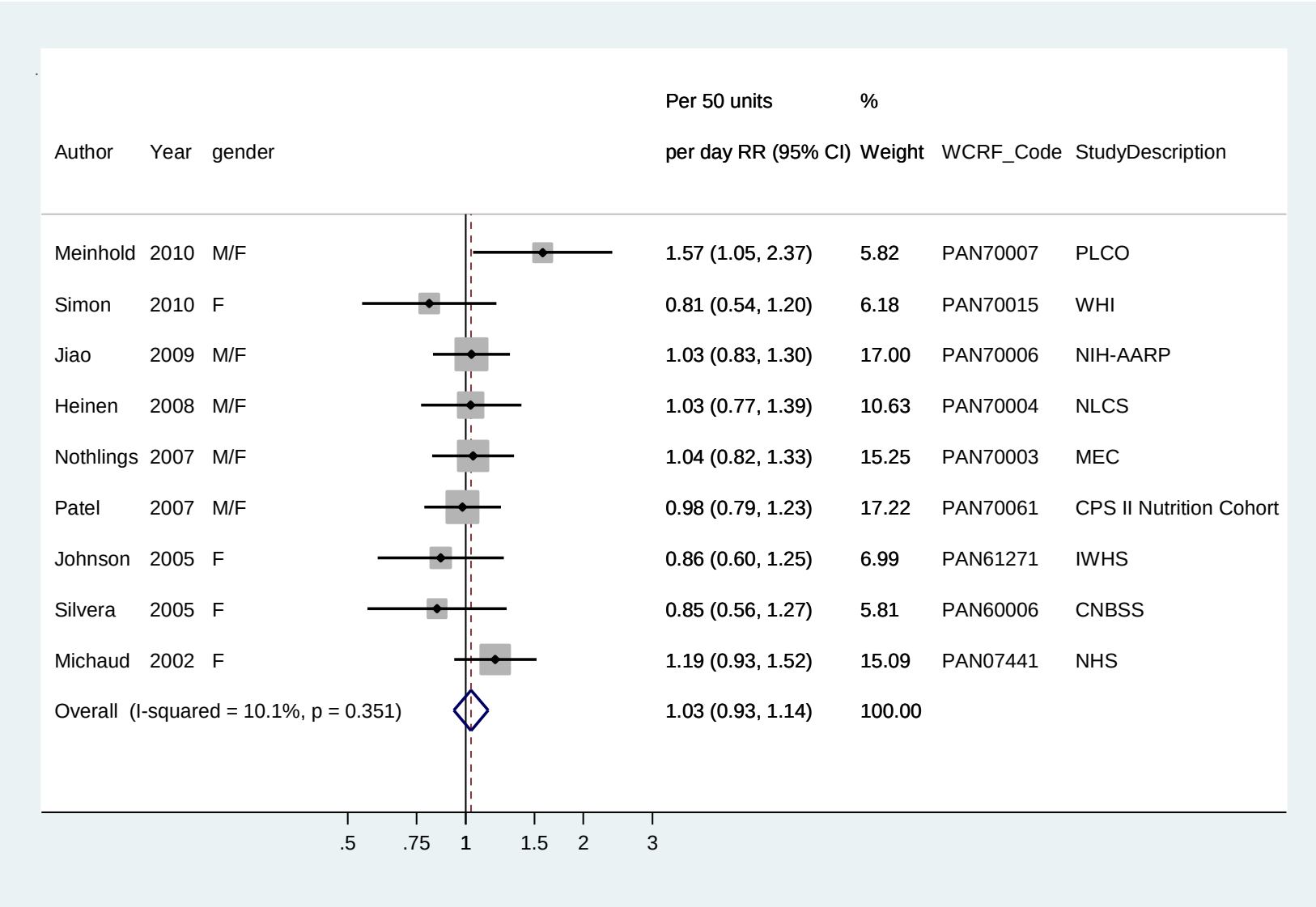


Figure 119 Funnel plot of glycemic load and pancreatic cancer

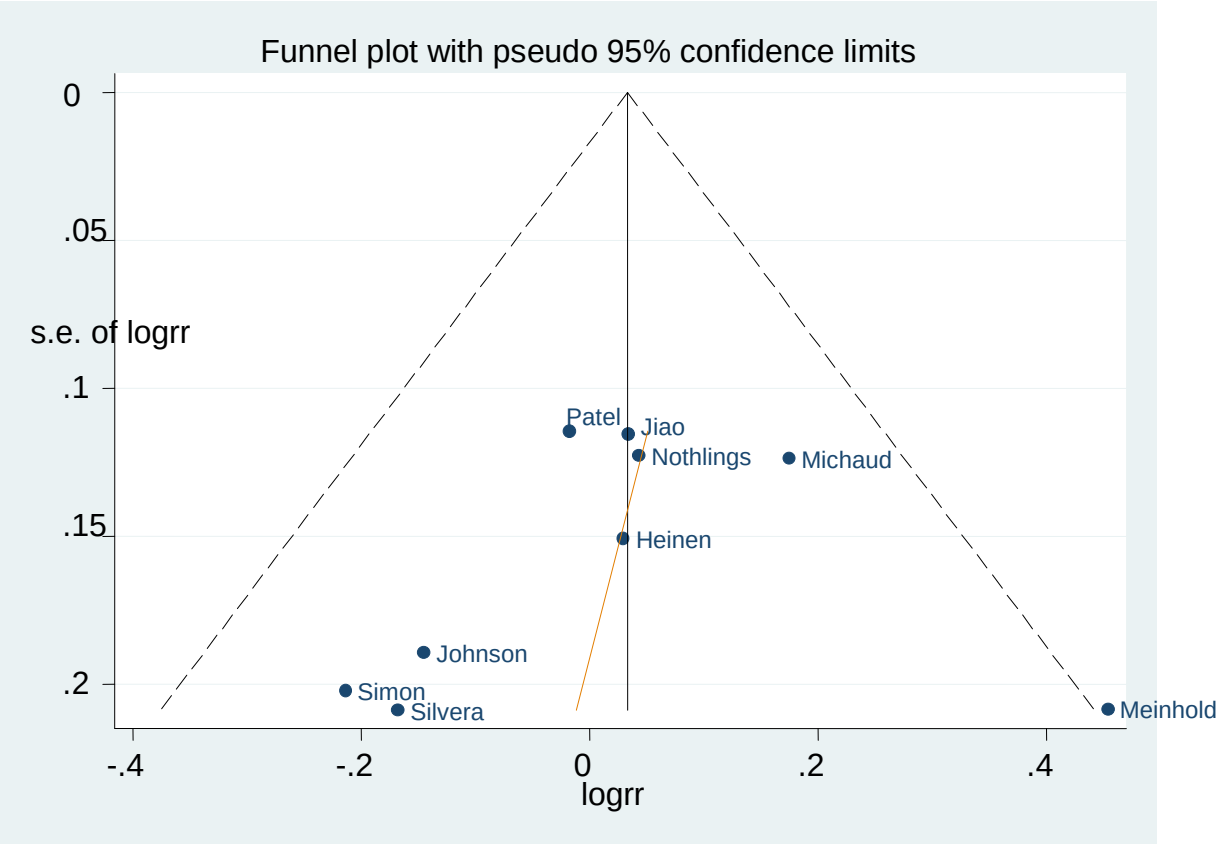


Figure 120 Dose-response graph of glycemic load and pancreatic cancer

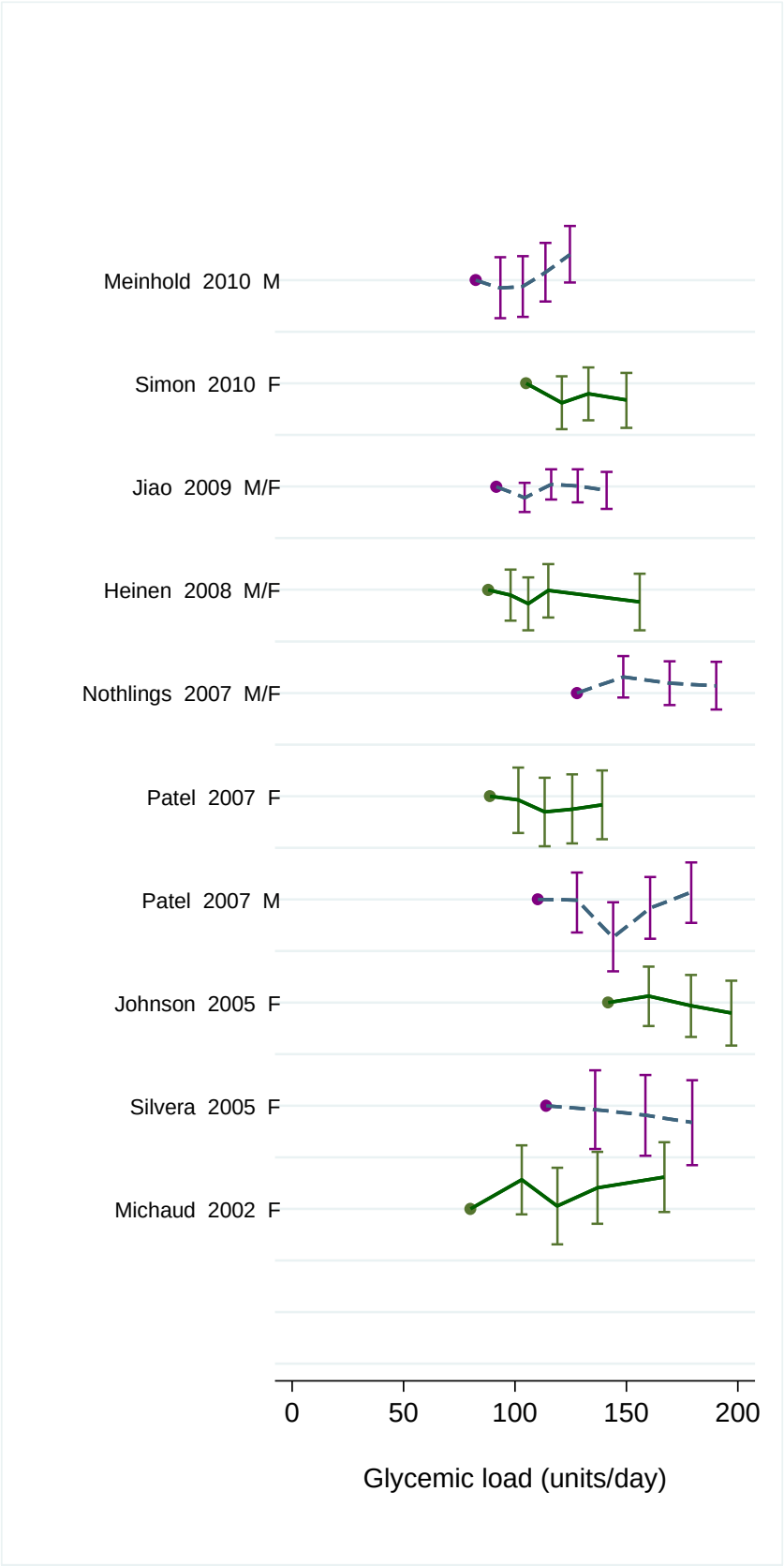


Figure 121 Dose-response meta-analysis of glycemic load and pancreatic cancer, stratified by sex - per 50 units/day

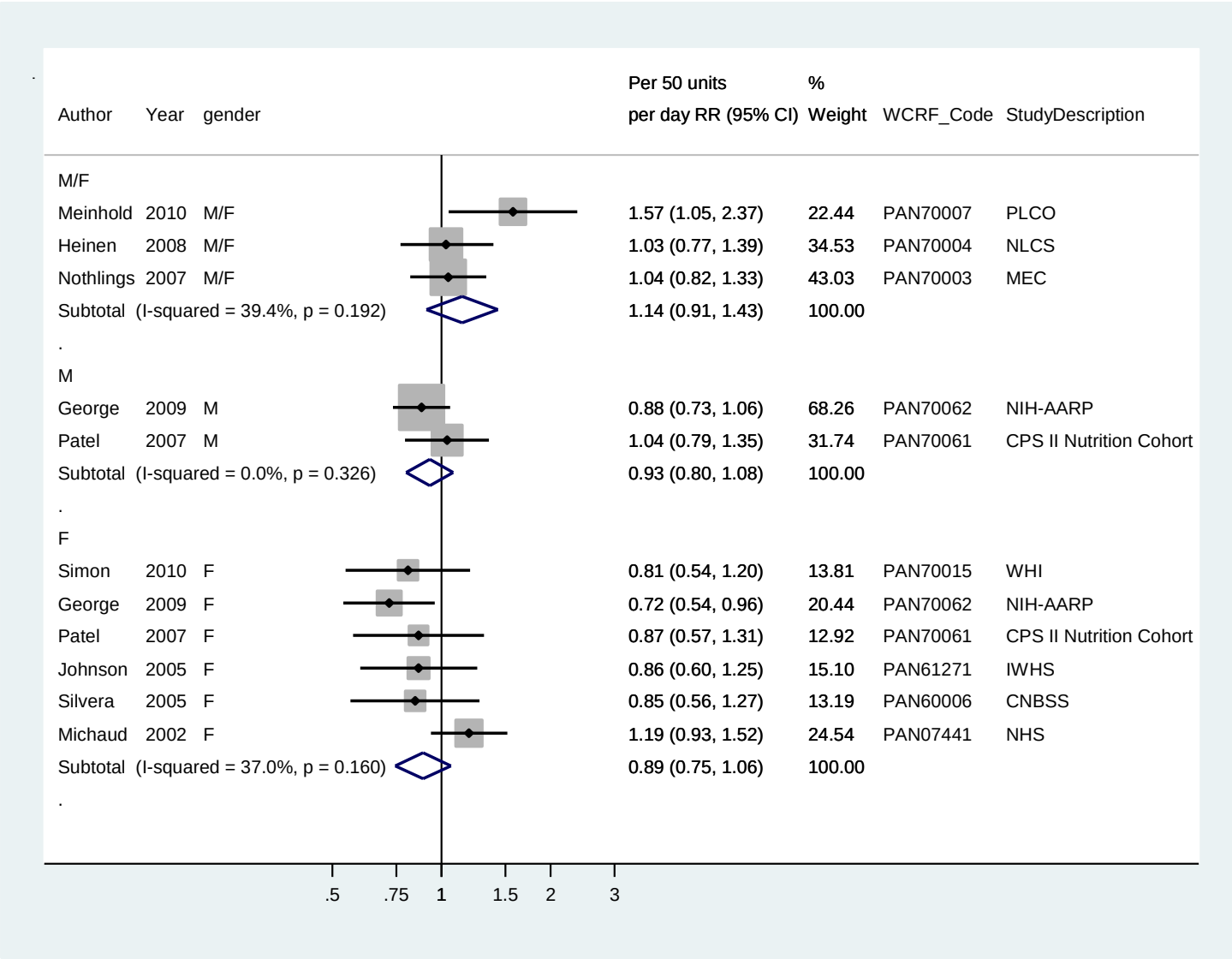


Figure 122 Nonlinear dose-response analysis of glycemic load and pancreatic cancer

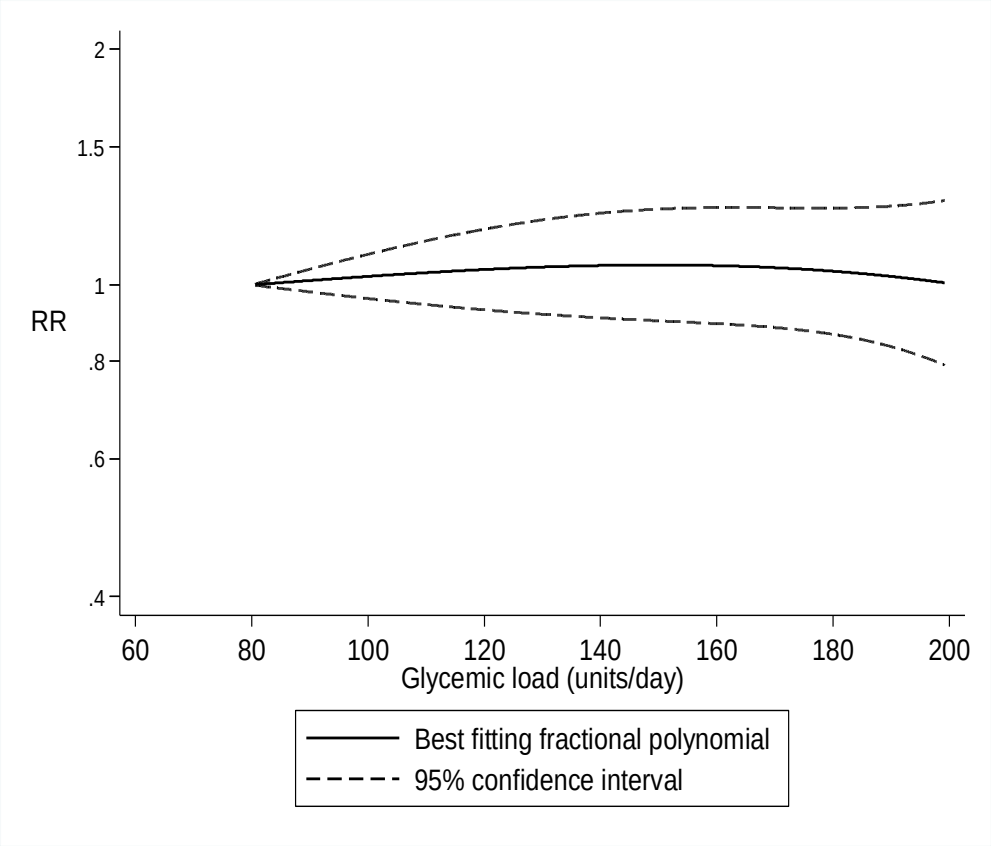


Figure 123 Scatter plot of risk estimates for glycemic load and pancreatic cancer risk

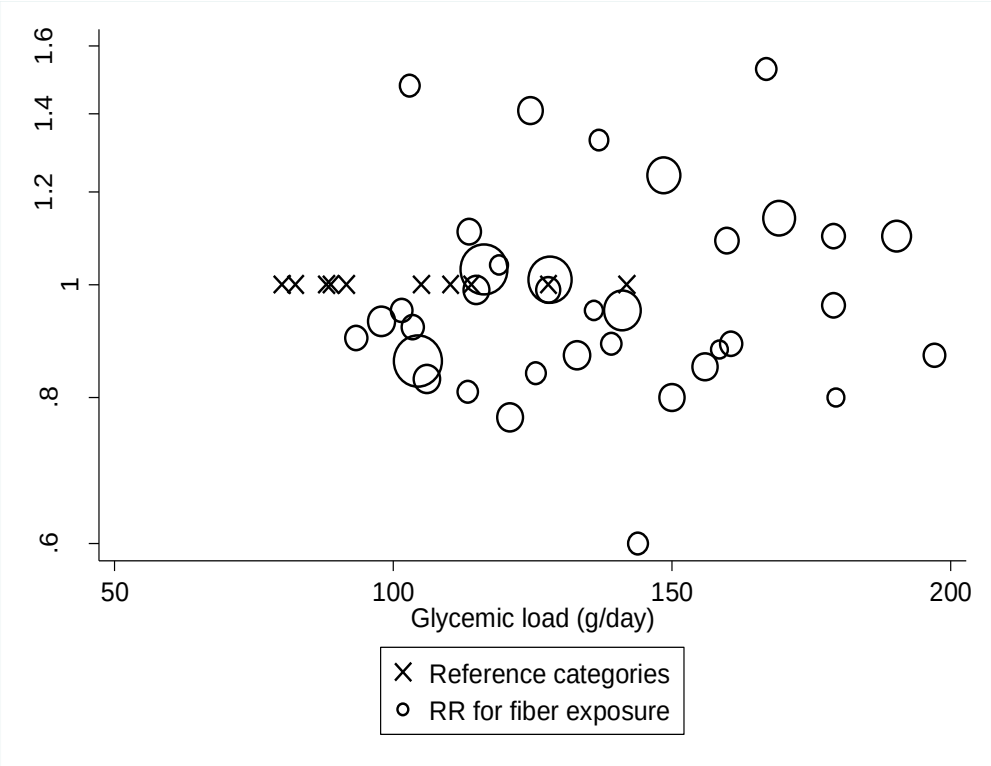


Table 99 Table with glycemic load values and corresponding RRs (95% CIs) for nonlinear analysis of glycemic load and pancreatic cancer

Glycemic load	RR (95% CI)
80	1.00
100	1.03 (0.96-1.09)
120	1.05 (0.93-1.18)
140	1.06 (0.91-1.23)
160	1.06 (0.89-1.26)
180	1.04 (0.86-1.25)
200	1.00 (0.79-1.28)

5.2.1 Total Fat (dietary)

Methods

Eight cohort studies were identified, from which four were identified during the CUP. Dose-response meta-analysis for pancreatic cancer was performed in the previous SLR report. In this report, a meta-analysis including 6 different studies (3 studies identified during the CUP and 3 studies identified during the 2007 SLR) was performed.

Two studies, NIH-AARP study (Thiebaut et al, 2009) and the MEC study (Nothlings et al, 2005) reported the fat intake using as measure unit the percentage of energy from fat. The percentage of energy from fat was converted to grams of fat per day. For the conversion in the NIH-AARP study, the mean total energy intake in the third quintile for men and women was assigned as total energy intake to all participants and 1g of fat was considered equivalent to 9 kcal. For the MEC study, the weighted average of energy intake was estimated and 1g of fat was considered equivalent to 9 kcal. In a sensitivity analysis, the dose-response relationship was estimated excluding the NIH-AARP study and the MEC study from the analysis.

Main results

The summary RR per 20g/day was 1.05 (95% CI: 1.0-1.12; $P_{heterogeneity}$=0.55, 6 studies) for incidence or mortality of pancreatic cancer. In sensitivity analysis, the RR was 1.05 (95% CI: 0.94-1.17) when the NIH-AARP study (Thiebaut et al, 2009) and the MEC study (Nothlings et al, 2005) were excluded. In influence analysis, the RR ranged from 1.01 (95% CI: 0.94-1.10) when the NIH-AARP study (Thiebaut et al, 2009) was excluded to 1.07 (95% CI: 1.0-1.15) when the MEC study (Nothlings et al, 2005) was excluded.The PLCO study (Meinhold et al, 2010) found evidence for reverse causation as there was a significant interaction after 4 years, the high versus low RR for total fat was 1.20, (95%: 0.72-2.01). It was not possible to conduct a dose-response analysis stratified by the duration of follow-up because this study only presented the high versus low relative risk.

Heterogeneity

No evidence of heterogeneity (I^2= 0%, p=0.55) All studies reported on incidence, therefore no stratification by outcome type was performed. Egger's tests suggested no evidence of publication bias, p= 0.72.

Comparison with the Second Expert Report

Overall, total fat intake was associated with the risk of pancreatic cancer. RR for an increase of 20g/day was 1.05 (95% CI: 1.0-1.12). The 2007 SLR reported a (RR for 20g/day of 1.11 (95% CI: 0.98 -1.26).

Table 100 Studies on total fat intake identified in the CUP

Author, year	Country	Study name	Cases	Years of follow up	Sex	RR	LCI	UCI	Contrast
Meinhold, 2010	USA	PLCO Cancer Screening Trial	266	6.5	M/F	0.80	0.57	1.12	73.9 vs 39.3 g/day
Thiebaut, 2009	USA	Health AARP Diet and Health Study	1337	7.2	M/F	1.23	1.03	1.46	40 vs 20.8 % E from fat
Meinhold 2009	Finland	Alpha Tocopherol Beta Carotene Cancer Prevention Study	305	16.1	M	1.52	1.04	2.22	>=112.5 vs <89.7 g/day
Heinen, 2009	Netherlands	The Netherlands Cohort study	350	13.3	M/F	0.95	0.67	1.34	98.3 vs 68.3 g/day

Table 101 Overall evidence on total fat intake and pancreatic cancer

	Summary of evidence
SLR	Six reports from four prospective cohort studies provided data. Three of these were included in the meta-analysis. The summary relative risk from the cohort studies was 1.11 (95% CI: 0.98 - 1.26) per 20g/day (p=0.1).
Continuous Update Project	Four reports from cohort studies were identified. One is an updated analysis from previous publications on male smokers and found a positive association between total fat and pancreatic cancer risk. The other three studies, reported on male and female. Two studies found no association. One study found a positive association of pancreatic cancer with percentage of energy from fat. Seven studies were included in the high versus low forest plot.

Table 102 Summary of results of the dose response meta-analysis on total fat intake and pancreatic cancer

Pancreatic cancer		
	SLR	Continuous Update Project
Studies (n)	3	6
Cases (n)	407	2718
Increment unit used	Per 20g/day	Per 20g/day
Overall RR (95%CI)	1.11 (0.98 -1.26)	1.05 (1.0-1.12)
Heterogeneity (I^2,p-value)	0%, p=0.4	0%, p=0.55
Stratified analysis		
Men	-	1.14 (0.95-1.38) (n=1)
Heterogeneity (I^2,p-value)		--
Women		1.04(0.87-1.24) (n=2)
Heterogeneity (I^2,p-value)		0%, p=0.72

Table 103 Inclusion/exclusion table for meta-analysis total fat intake and pancreatic cancer

WCRF_ Code	Author	Year	Study Design	Study Name	Subgroup	Cancer Outcome	SLR	CUP dose-response meta-analysis	CUP HvL forest plot	Estimated values	Exclusion reasons
PAN70007	Meinhold	2010	Prospective Cohort study	PLCO Cancer Screening Trial	Men/Women	Incidence	New	No	Yes		Only high vs. low comparison
PAN70012	Thiebaut	2009	Prospective Cohort study	Health AARP Diet and Health Study	Men/Women	Incidence	New	Yes	Yes	Mid-exposure values	
PAN70045	Meinhold	2009	Prospective Cohort study	Alpha Tocopherol Beta Carotene Cancer Prevention Study - Finland	Men	Incidence	New	Yes	Yes	Person years per quintile, mid-exposure values	
PAN70056	Heinen	2009	Prospective Cohort study	The Netherlands Cohort study	Men/Women	Incidence	New	Yes	Yes	Mid-exposure values	
PAN20232	Stolzenberg-Solomon	2004	Nested case control study	Alpha Tocopherol Beta Carotene Cancer Prevention Study - Finland	Men	Incidence	No	No	No		No measure of relationship, only mean values
PAN61048	Nöthlings	2005	Prospective Cohort study	Hawaii-Los Angeles Multiethnic Cohort (MEC) Study	Men/Women	Incidence	Yes	Yes	Yes		
PAN07442	Michaud	2003	Prospective Cohort study	The Nurses' Health Study Cohort	Women	Mortality /incidence	Yes	Yes	Yes		
PAN07590	Stolzenberg-Solomon	2002	Prospective Cohort study	Alpha Tocopherol Beta Carotene Cancer Prevention Study - Finland	Men	Incidence	Yes	No	No		Superseded by Meinhold 2009
PAN07288	Harnack	1997	Prospective Cohort study	Iowa Women's Health Study	Women	Mortality/ incidence	Yes	Yes	Yes	Mid-exposure values	
PAN07339	Kato	1992	Prospective Cohort study	Japan - Hawaii Centre	Men	Incidence	Yes	No	No		No measure of relationship, only mean values

Figure 124 Highest versus lowest forest plot of total fat intake and pancreatic cancer

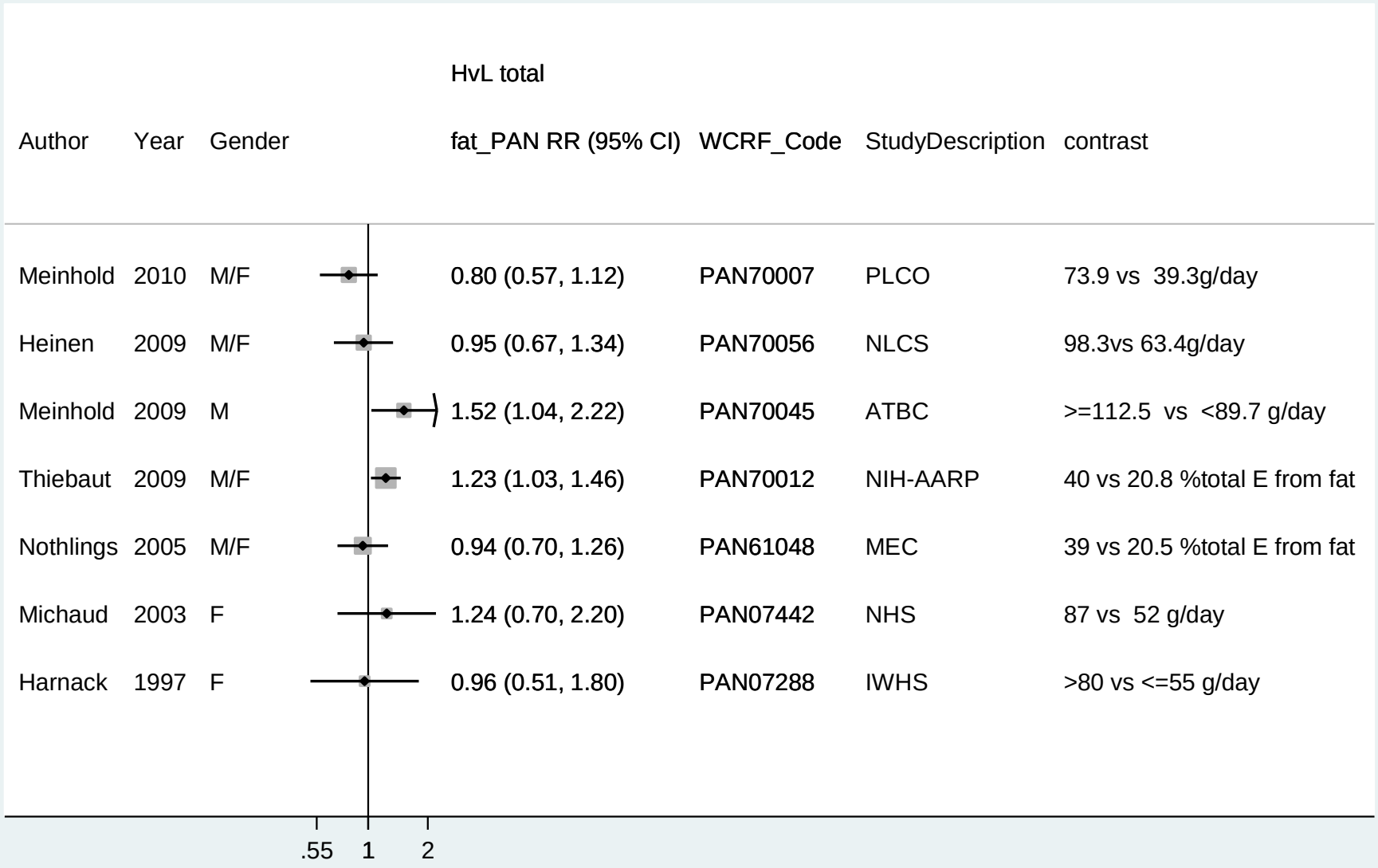


Figure 125 Dose-response meta-analysis of total fat intake and pancreatic cancer – per 20g/day

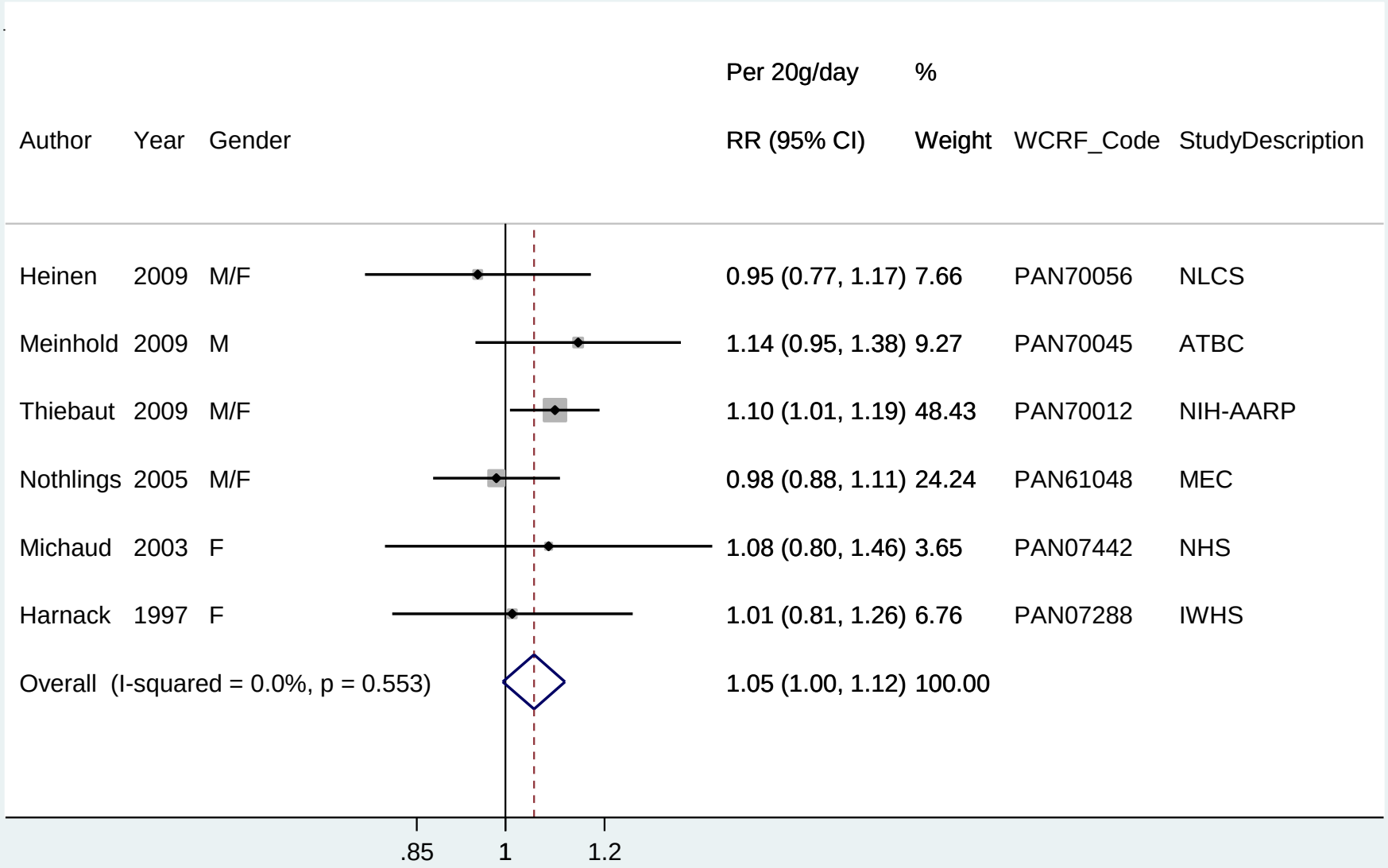


Figure 126 Funnel plot of total fat intake and pancreatic cancer

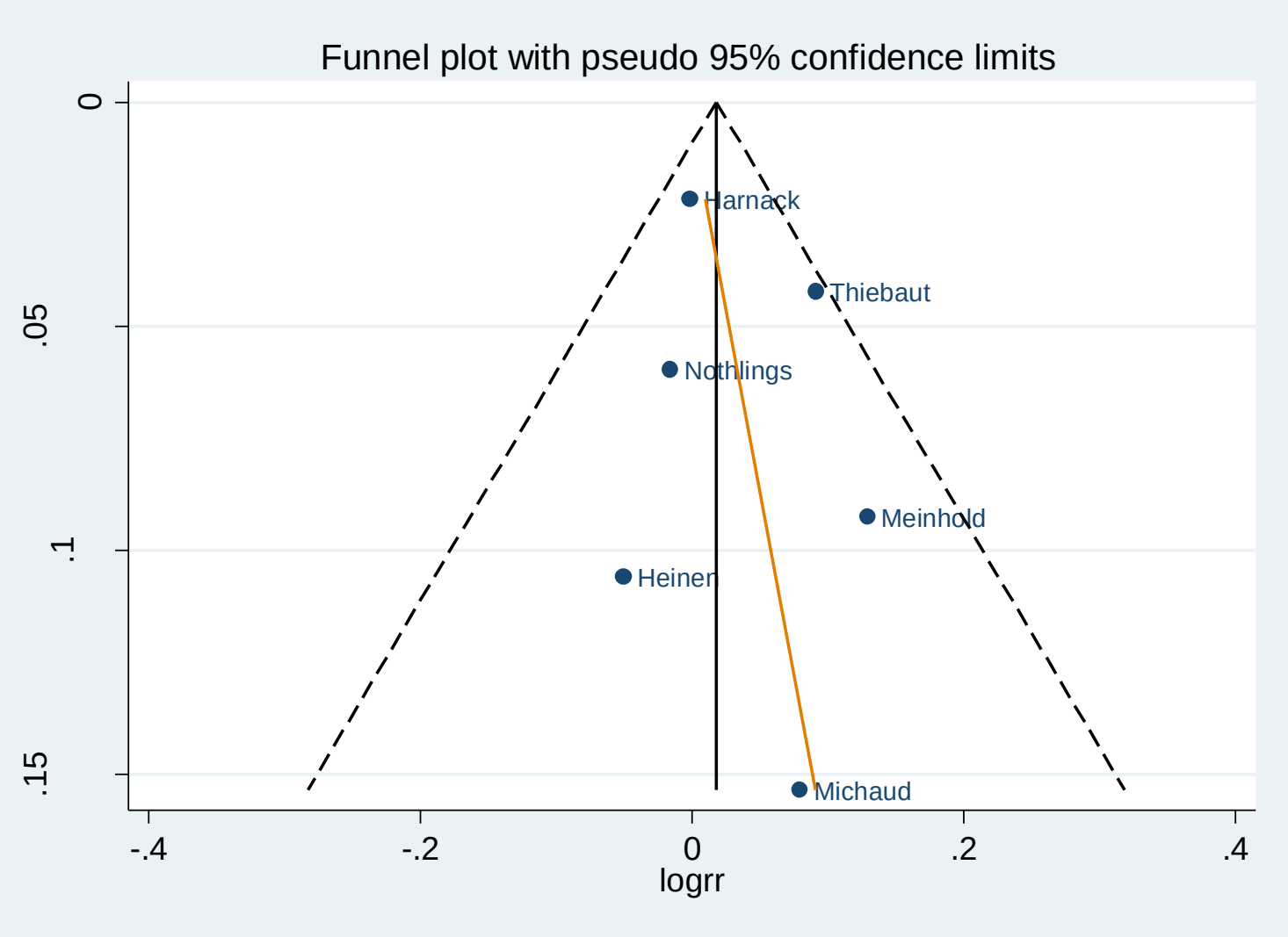


Figure 127 Dose-response graph of total fat intake and pancreatic cancer

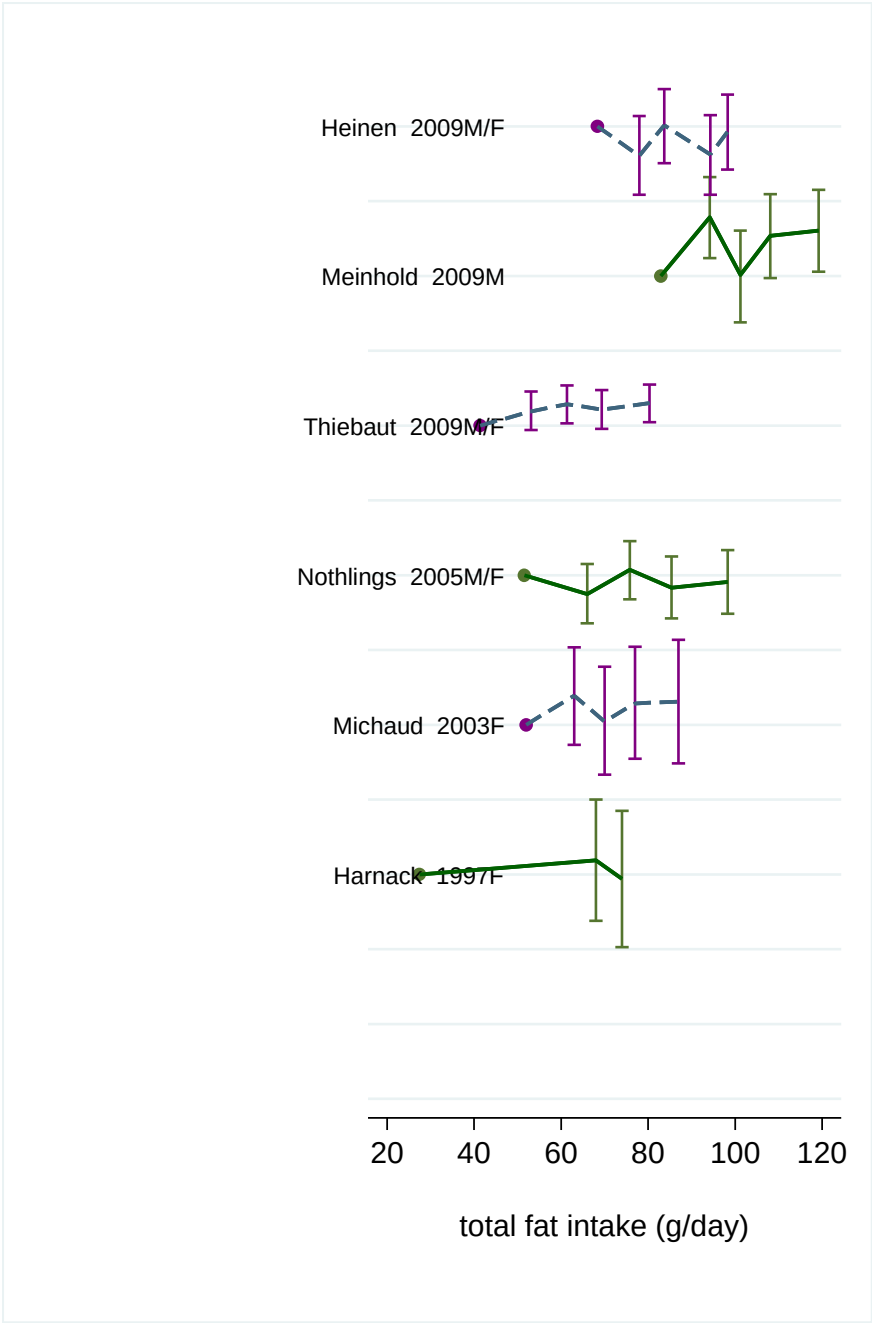
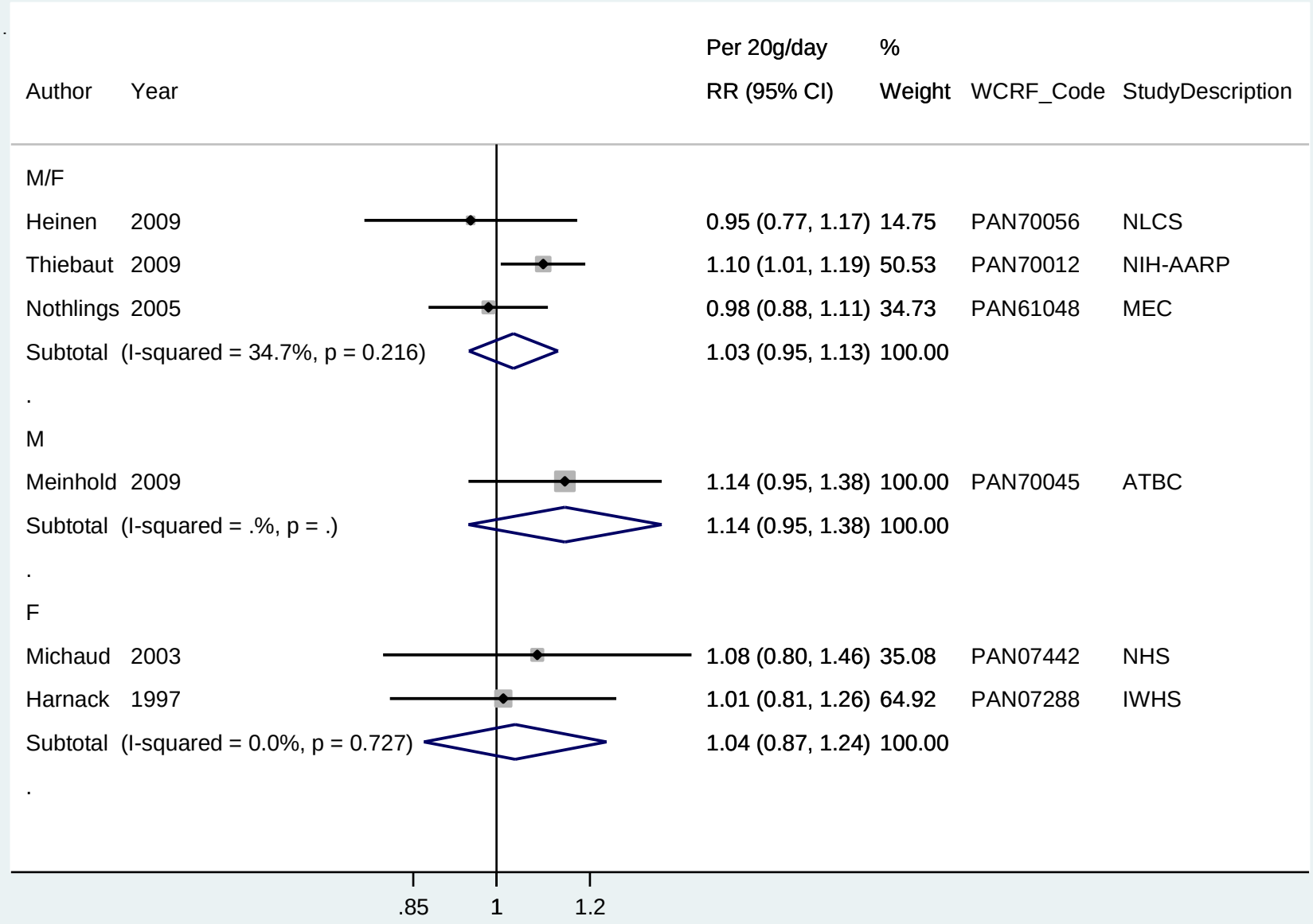


Figure 128 Dose-response meta-analysis of total fat intake and pancreatic cancer, stratified by sex – per 20g/day



5.2.2 Saturated Fat

Methods

Six cohort studies were identified, from which four were identified during the CUP. One cohort had published three reports. Dose-response meta-analysis for pancreatic cancer was performed in the previous SLR report. In this report, a meta-analysis including 5 different studies (3 studies identified during the CUP and 2 study identified during the 2007 SLR) was performed.

For the two studies, NIH-AARP study (Thiebaut et al, 2009) and MEC study (Nothlings et al, 2005) reporting fat intake as the percentage of energy from fat the same conversion method referred in section 5.2.1 Total fat was used. In a sensitivity analysis, the dose-response relationship was estimated excluding the NIH-AARP study and the MEC study from the analysis.

Main results

The summary RR per 10g/day was 1.11 (95% CI: 1.01-1.21, $P_{heterogeneity}$=0.13; 5 studies) for incidence or mortality of pancreatic cancer. The only study on men reported a RR per 10g/day of 1.12 (95% CI: 1.01-1.23) and the only study on women reported a RR per 10g/day of 0.88 (95% CI: 0.64-1.22).

In sensitivity analysis, the RR was 1.08 (95% CI: 0.99-1.19) when the NIH-AARP study (Thiebaut et al, 2009) and the MEC study (Nothlings et al, 2005) were excluded. In influence analysis, the RR ranged from 1.07(95% CI: 0.99-1.16) when the NIH-AARP study (Thiebaut et al, 2009) was excluded to 1.13 (95% CI: 1.04-1.22) when the NHS study (Michaud et al, 2003) was excluded.

Heterogeneity

Moderate heterogeneity was found (I^2= 43.3%, p=0.13) between studies. All studies reported on incidence, therefore no stratification by outcome type was performed. Egger's tests suggested no evidence of publication bias, p= 0.46.

Comparison with the Second Expert Report

Overall, saturated fat intake was associated with the risk of pancreatic cancer. RR for an increase of 10g/day was 1.11 (95% CI: 1.01-1.21, $P_{heterogeneity}$=0.13), therefore stronger than that reported in the previous SLR report (RR for 10g/day was 1.08 (95% CI: 0.89 -1.31).

Table 104 Studies on saturated fat intake identified in the CUP

Author, year	Country	Study name	Cases	Years of follow up	Sex	RR	LCI	UCI	Contrast
Meinhold, 2010	USA	PLCO Cancer Screening Trial	266	6.5	M/F	0.63	0.45	0.88	24.9 vs 11.3 g/day
Heinen, 2009	Netherlands	The Netherlands Cohort study	350	13.3	M/F	0.95	0.62	1.46	42.1 vs 25.5g/day
Thiebaut, 2009	USA	Health AARP Diet and Health Study	1337	7.2	M/F	1.36	1.14	1.62	13.2 vs 5.85 % E from fat
Meinhold, 2009	Finland	Alpha Tocopherol Beta Carotene Cancer Prevention Study	305	16.1	M	1.40	0.98	2.01	>63.2 vs <41.9 g/day

Table 105 Overall evidence on saturated fat intake and pancreatic cancer

	Summary of evidence
SLR	Three reports from two prospective cohort studies provided data. The estimated of relative risk from two cohort studies was 1.08 (95% CI: 0.88-1.31) per 10 g/day (p=0.5).
Continuous Update Project	Four cohort studies were identified. One (ATBC cohort) was an update on a study on male smokers and found a non-significant positive association between saturated fat and pancreatic cancer risk. The other two studies, reported on male and female, one found a positive association and the other found no association.

Table 106 Summary of results of the dose response meta-analysis on saturated fat intake and pancreatic cancer

Pancreatic cancer		
	SLR	Continuous Update Project
Studies (n)	2	5
Cases (n)	341	2740
Increment unit used	Per 10g/day	Per 10g/day
Overall RR (95%CI)	1.08 (0.89 -1.31)	1.11 (1.01-1.21)
Heterogeneity (I^2,p-value)	44%, p=0.2	43.3%, p=0.13

Table 107 Inclusion/exclusion table for meta-analysis on saturated fat intake and pancreatic cancer

WCRF_ Code	Author	Year	Study Design	Study Name	Subgroup	Cancer Outcome	SLR	CUP dose-response meta-analysis	CUP HvL forest plot	Estimated values	Exclusion reasons
PAN70007	Meinhold	2010	Prospective Cohort study	PLCO Cancer Screening Trial	Men/Women	Incidence	New	No	Yes		Only high vs. low comparison
PAN70045	Meinhold	2009	Prospective Cohort study	Alpha Tocopherol Beta Carotene Cancer Prevention Study - Finland	Men	Incidence	New	Yes	Yes	Person year by quintile, mid-exposure values	
PAN70012	Thiebaut	2009	Prospective Cohort study	AARP Diet and Health Study	Men/Women	Incidence	New	Yes	Yes	Mid-exposure values	
PAN70056	Heinen	2009	Prospective Cohort study	The Netherlands Cohort study	Men/Women	Incidence	New	Yes	Yes	Mid-exposure values	
PAN061048	Nothlings	2005	Prospective Cohort study	Multiethnic Cohort (MEC) Study	Men/Women	Incidence	Yes	Yes	Yes		
PAN20232	Stolzenberg-Solomon	2004	Nested case control study	Alpha Tocopherol Beta Carotene Cancer Prevention Study - Finland	Men	Incidence	No	No	No		No measure of the relationship, only mean values
PAN07442	Michaud	2003	Prospective Cohort study	The Nurses' Health Study Cohort	Women	Mortality /incidence	Yes	Yes	Yes		
PAN07590	Stolzenberg-Solomon	2002	Prospective Cohort study	Alpha Tocopherol Beta Carotene Cancer Prevention Study - Finland	Men	Incidence	Yes	No	No		Superseded by Meinhold 2009

Figure 129 Highest versus lowest forest plot of saturated fat intake and pancreatic cancer

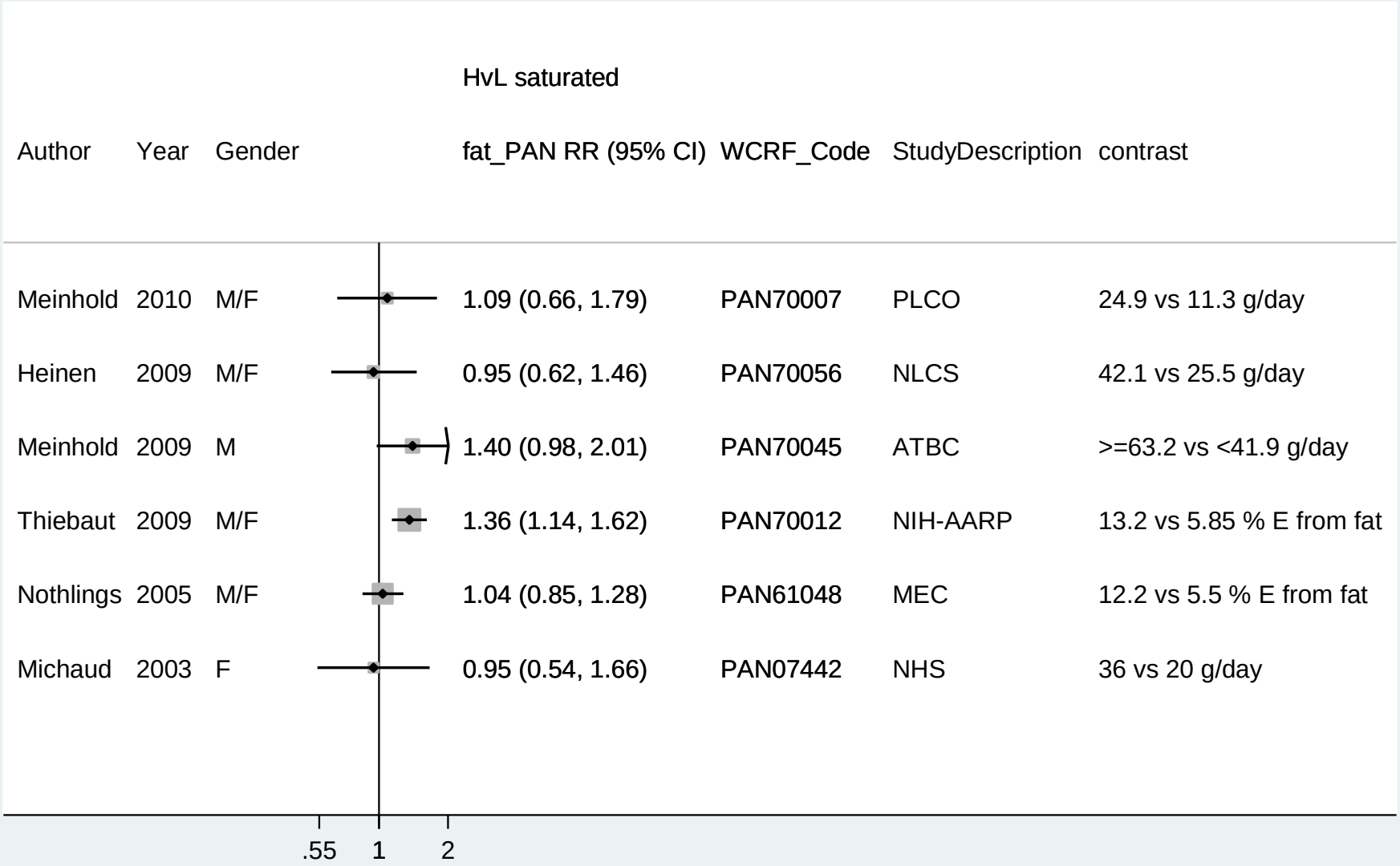


Figure 130 Dose-response meta-analysis of saturated fat intake and pancreatic cancer – per 10g/day

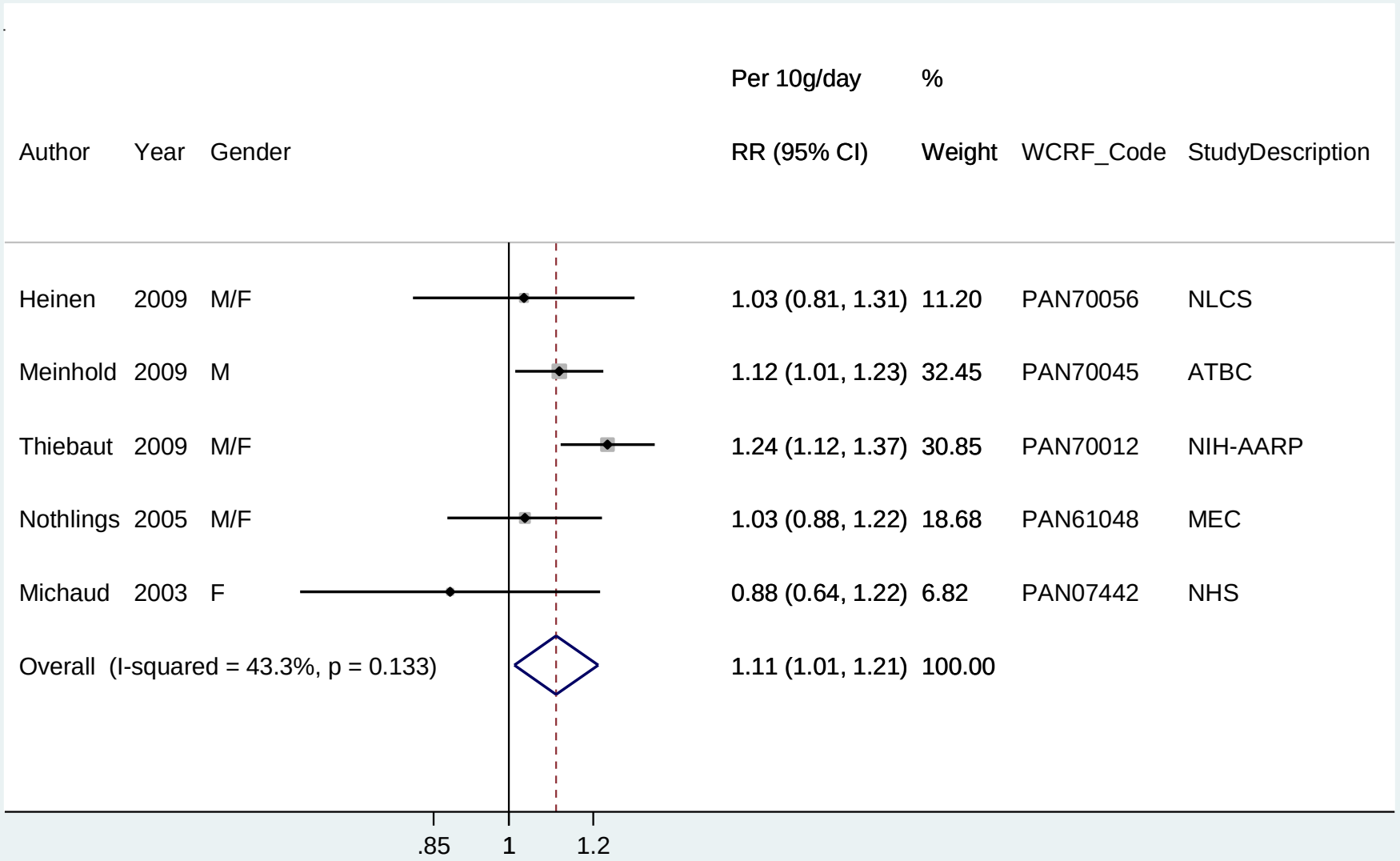


Figure 131 Funnel plot of saturated fat intake and pancreatic cancer

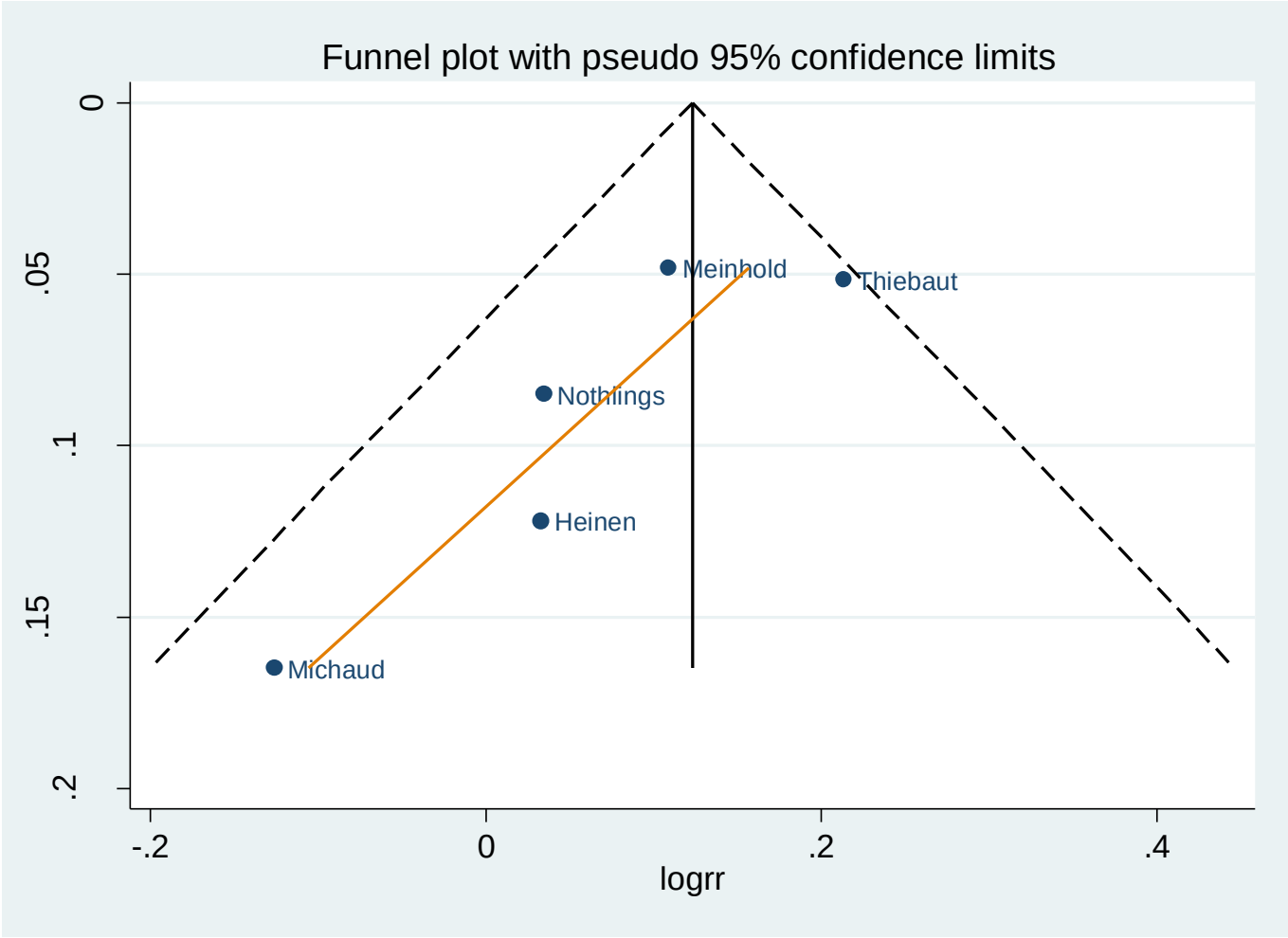
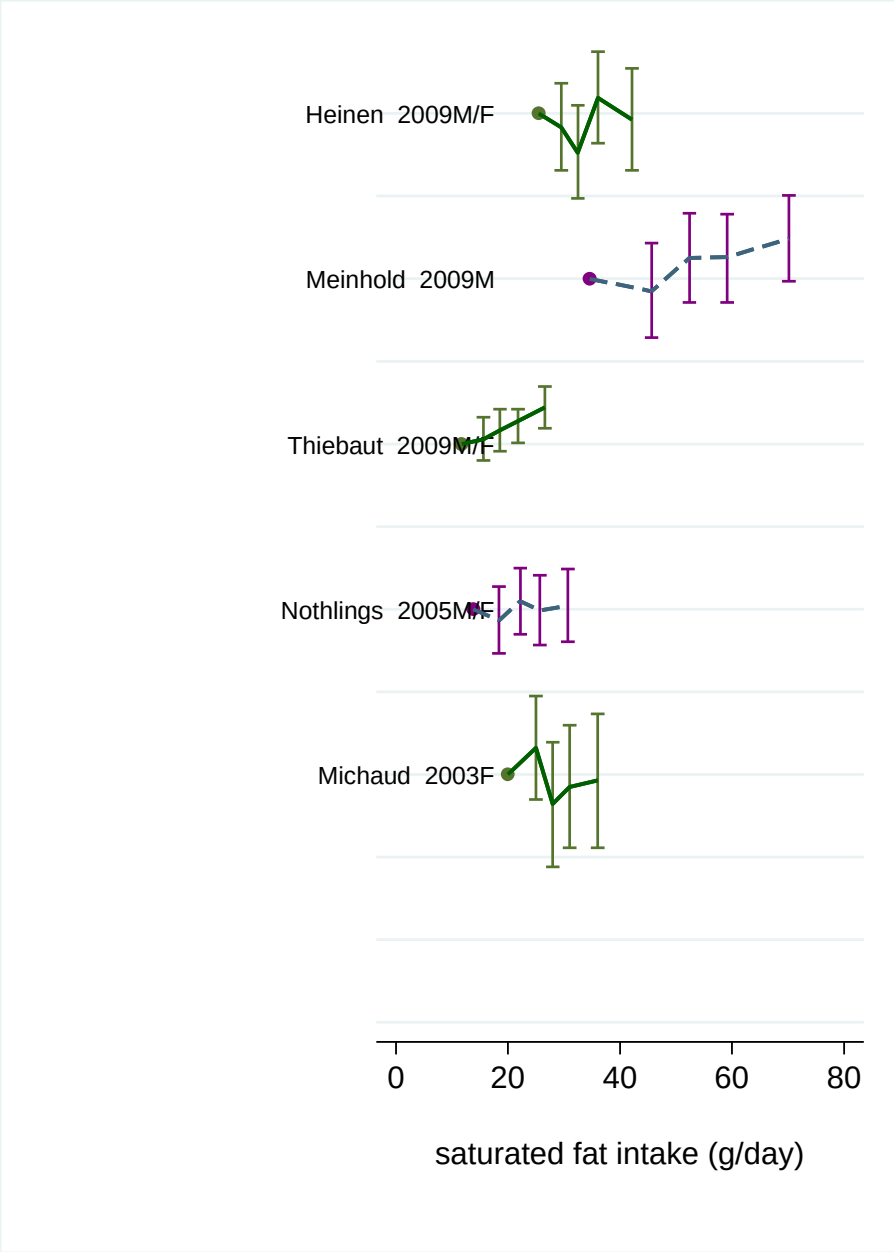


Figure 132 Dose-response graph of saturated fat intake and pancreatic cancer



5.2.3 Monounsaturated Fat

Methods

Four cohort studies were identified, two were identified during the CUP. Dose-response meta-analysis for pancreatic cancer was performed in the previous SLR report. In this report, a meta-analysis including all 4 different studies was performed.

For the only study NIH-AARP study (Thiebaut et al, 2009) reporting fat intake as the percentage of energy from fat the same conversion method referred in section 5.2.1 Total fat was used. In a sensitivity analysis, the dose-response relationship was estimated excluding the NIH-AARP from the analysis.

Main results

The summary RR per 10g/day was 1.07 (95% CI: 0.98-1.18, $P_{heterogeneity}$=0.64; 4 studies) for incidence or mortality of pancreatic cancer. The only study on men reported a RR per 10g/day of 1.10 (95% CI: 0.77-1.57) and the only study on women reported a RR per 10g/day of 1.02 (95% CI: 0.76-1.37).
In sensitivity analysis, the RR was 1.00 (95% CI: 0.83-1.20) when the NIH-AARP study (Thiebaut et al, 2009) was excluded. In influence analysis, the RR ranged from 0.99(95% CI: 0.82-1.20) when the NIH-AARP study (Thiebaut et al, 2009) was excluded to 1.09 (95% CI: 0.99-1.19) when the NLCS (Heinen et al, 2009) was excluded.

Heterogeneity

No evidence of heterogeneity (I^2= 0%, p=0.64) between studies. Egger's tests suggested no evidence of publication bias, p= 0.25.

Comparison with the Second Expert Report

Overall, monounsaturated fat intake was not associated with the risk of pancreatic cancer. RR for an increase of 10g/day was 1.07 (95% CI: 0.98-1.18, $P_{heterogeneity}$=0.64), therefore similar to that reported in the previous SLR report (RR for 10g/day was 1.08 (95% CI: 0.87 - 1.33).

Table 108 Studies on monounsaturated fat intake identified in the CUP

Author, year	Country	Study name	Cases	Years of follow up	Sex	RR	LCI	UCI	Contrast
Heinen, 2009	Netherlands	The Netherlands Cohort study	350	13.3	M/F	0.85	0.51	1.40	38.5 vs 24.5 g/day
Thiebaut, 2009	USA	Health AARP Diet and Health Study	1337	7.2	M/F	1.22	1.02	1.46	15.4 vs 7.4 % E from fat

Table 109 Overall evidence on monounsaturated fat intake and pancreatic cancer

	Summary of evidence
SLR	Two cohort studies provided data. Both were included in the meta-analysis. The summary relative risk from the cohort studies was 1.08 (95% CI: 0.87 to 1.33) per 10 g/day (p=0.5).
Continuous Update Project	Two cohort studies were identified. One study reported a positive association between monounsaturated fat (as % of E from fat) and pancreatic cancer.

Table 110 Summary of results of the dose response meta-analysis on monounsaturated fat intake and pancreatic cancer

Pancreatic cancer		
	SLR	Continuous Update Project
Studies (n)	2	4
Cases (n)	341	2028
Increment unit used	Per 10g/day	Per 10g/day
Overall RR (95%CI)	1.08 (0.87 -1.33)	1.07 (0.98-1.18)
Heterogeneity (I^2,p-value)	0%, p=0.8	0%, p=0.64

Table 111 Inclusion/exclusion table for meta-analysis monounsaturated fat intake and pancreatic cancer

WCRF_ Code	Author	Year	Study Design	Study Name	Subgroup	Cancer Outcome	SLR	CUP dose-response meta-analysis	CUP HvL forest plot	Estimated values	Exclusion reasons
PAN70056	Heinen	2009	Prospective Cohort study	The Netherlands Cohort study	Men/Women	Incidence	New	Yes	Yes	Mid-exposure values	
PAN70012	Thiebaut	2009	Prospective Cohort study	Health AARP Diet and Health Study	Men/Women	Incidence	New	Yes	Yes	Mid-exposure values	
PAN07442	Michaud	2003	Prospective Cohort study	The Nurses' Health Study Cohort	Women	Mortality /incidence	Yes	Yes	Yes		
PAN07590	Stolzenberg-Solomon	2002	Prospective Cohort study	Alpha Tocopherol Beta Carotene Cancer Prevention Study - Finland	Men	Incidence	Yes	Yes	Yes	Mid-exposure values , cases/person-years per quintile	

Figure 133 Highest versus lowest forest plot of monounsaturated fat intake and pancreatic cancer

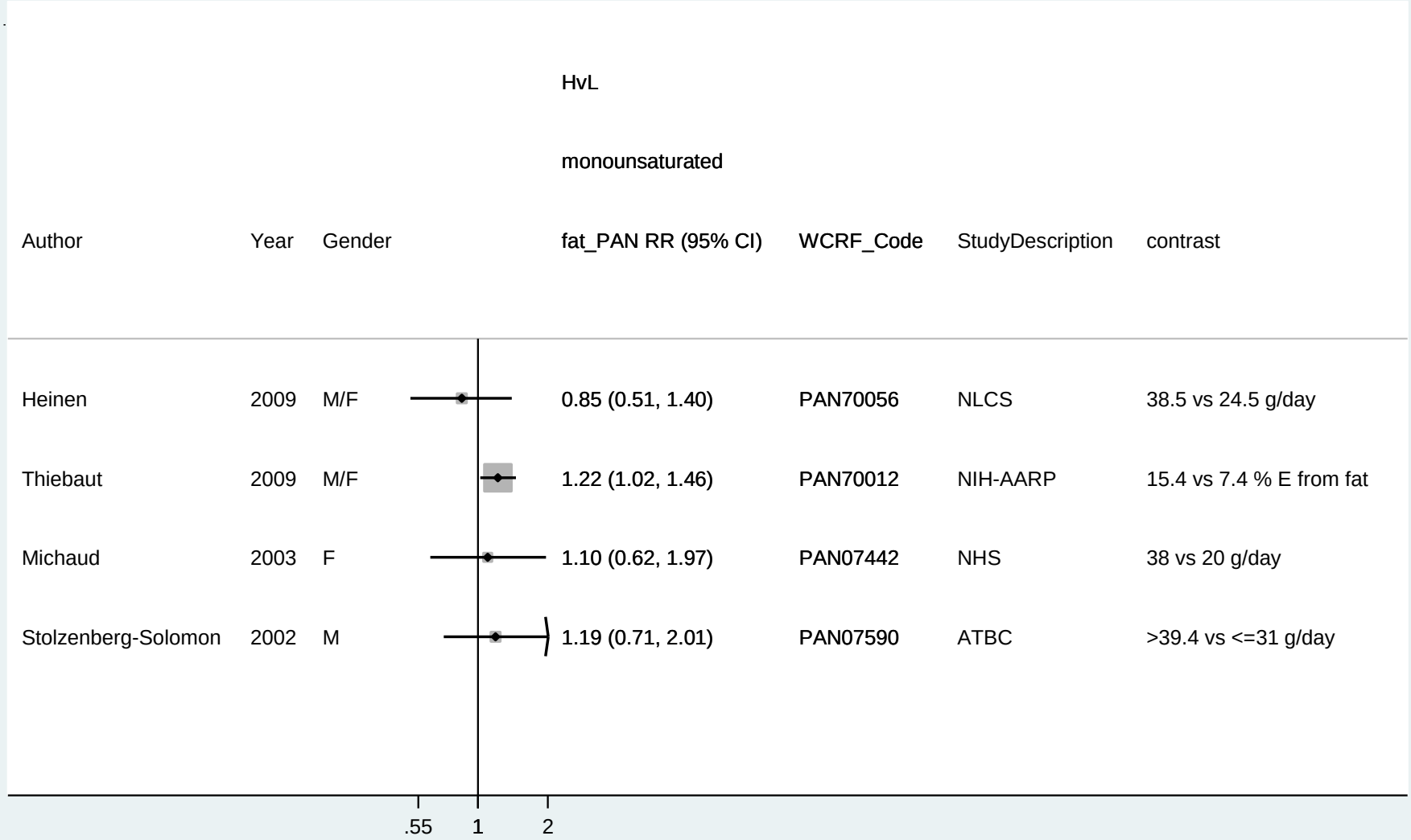


Figure 134 Dose-response meta-analysis of monounsaturated fat intake and pancreatic cancer – per 10g/day

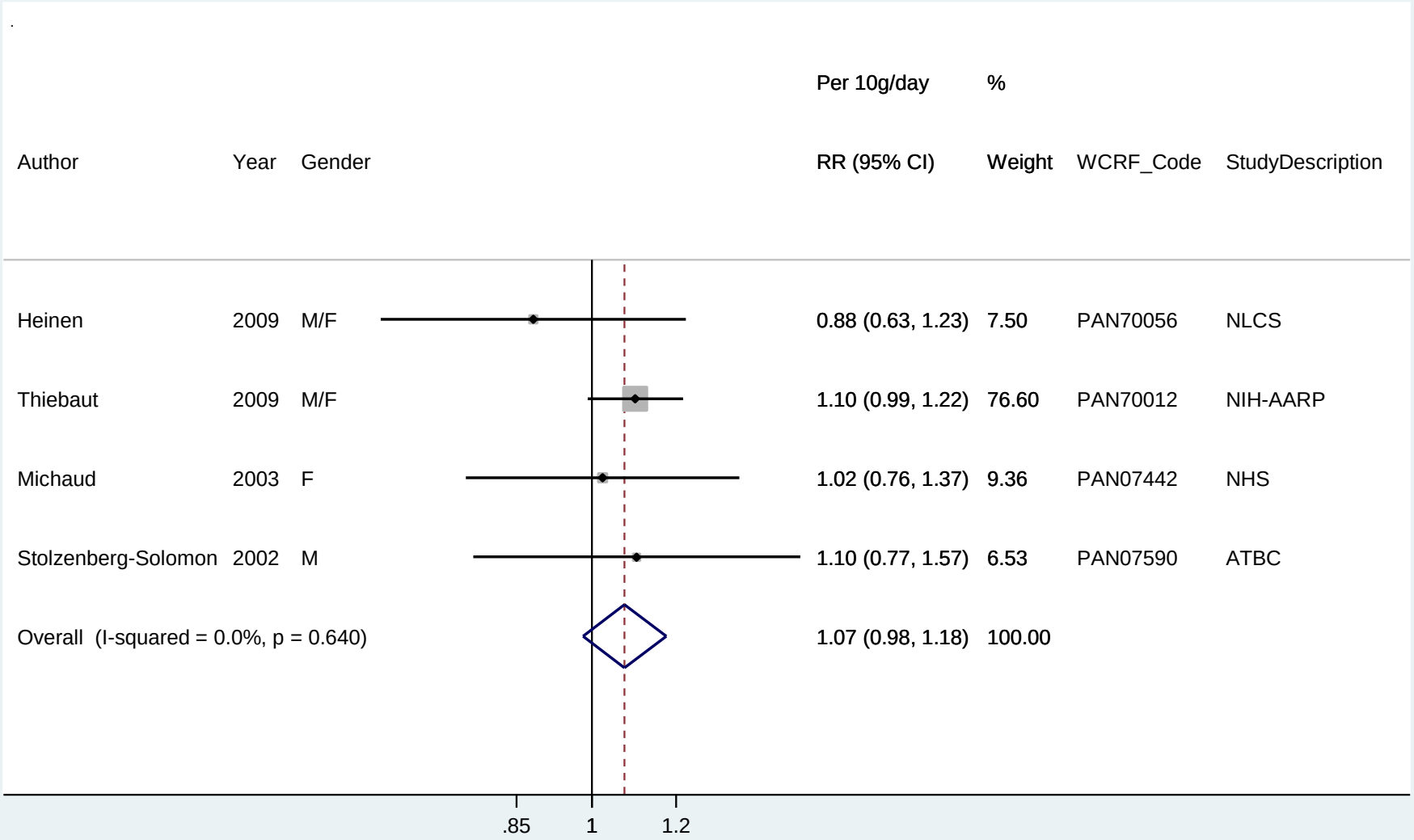
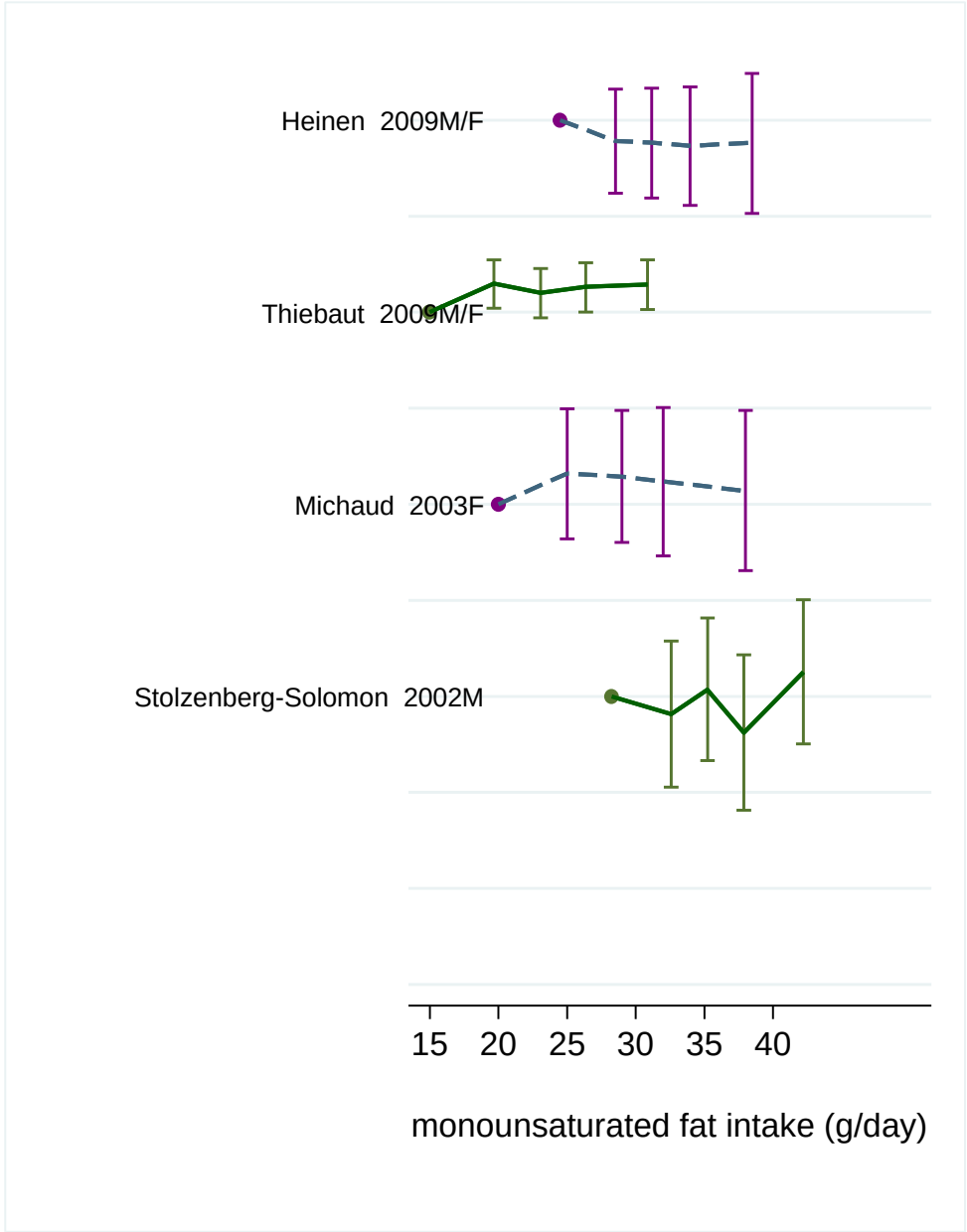


Figure 135 Dose-response graph of monounsaturated fat intake and pancreatic cancer



5.2.4 Polyunsaturated Fat

Methods

Four cohort studies were identified, of which two were identified during the CUP. Dose-response meta-analysis for pancreatic cancer was performed in the previous SLR report. In this report, a meta-analysis including all 4 different studies was performed.

For the only study NIH-AARP study (Thiebaut et al, 2009) reporting fat intake as the percentage of energy from fat the same conversion method referred in section 5.2.1 Total fat was used. In a sensitivity analysis, the dose-response relationship was estimated excluding the NIH-AARP from the analysis.

Main results

The summary RR per 10g/day was 1.05 (95% CI: 0.94-1.17, $P_{heterogeneity}$=0.92; 4 studies) for incidence or mortality of pancreatic cancer. The only study on men reported a RR per 10g/day of 1.16 (95% CI: 0.81-1.67) and the only study on women reported a RR per 10g/day of 0.92 (95% CI: 0.48-1.75).
In sensitivity analysis, the RR was 1.05 (95% CI: 0.89-1.23) when the NIH-AARP study (Thiebaut et al, 2009) was excluded. In influence analysis, the RR ranged from 1.03 (95% CI: 0.92-1.16) when the ATBC study (Stolzenberg-Solomon et al, 2002) was excluded to 1.05 (95% CI: 0.92-1.20) when the NLCS (Heinen et al, 2009) was excluded.

Heterogeneity

No evidence of heterogeneity (I^2= 0%, p=0.92) between studies. Egger's tests suggested no evidence of publication bias, p= 072.

Comparison with the Second Expert Report

Overall, polyunsaturated fat intake was not associated with the risk of pancreatic cancer. RR for an increase of 10g/day was 1.05 (95%CI: 0.94-1.17), similar to that reported in the previous SLR report (RR for 10g/day was 1.02 (95% CI: 0.76 -1.36).

Table 112 Studies on polyunsaturated fat intake identified in the CUP

Author, year	Country	Study name	Cases	Years of follow up	Sex	RR	LCI	UCI	Contrast
Heinen, 2009	Netherlands	The Netherlands Cohort study	350	13.3	M/F	0.98	0.69	1.40	26.8 vs 9.4 g/day
Thiebaut, 2009	USA	Health AARP Diet and Health Study	1337	7.2	M/F	1.00	0.84	1.18	9.8 vs 4.5 % E from fat

Table 113 Overall evidence on polyunsaturated fat intake and pancreatic cancer

	Summary of evidence
SLR	Two cohort studies provided data. Both were included in the meta-analysis. The summary relative risk from the cohort studies was 1.02 (95% CI: 0.76 to 1.36) per 10 g/day (p=0.5).
Continuous Update Project	Two cohort studies were identified and found no association between polyunsaturated fat and pancreatic cancer. Overall, four cohort studies have provided data on polyunsaturated fat intake and pancreatic cancer.

Table 114 Summary of results of the dose response meta-analysis on polyunsaturated fat intake and pancreatic cancer

Pancreatic cancer		
	SLR	Continuous Update Project
Studies (n)	2	4
Cases (n)	341	2028
Increment unit used	Per 10g/day	Per 10g/day
Overall RR (95%CI)	1.02 (0.76 -1.36)	1.05 (0.94-1.17)
Heterogeneity (I^2,p-value)	0%, p=0.4	0%, p=0.92

Table 115 Inclusion/exclusion table for meta-analysis polyunsaturated fat intake and pancreatic cancer

WCRF_ Code	Author	Year	Study Design	Study Name	Subgroup	Cancer Outcome	SLR	CUP dose-response meta-analysis	CUP HvL forest plot	Estimated values	Exclusion reasons
PAN70056	Heinen	2009	Prospective Cohort study	The Netherlands Cohort study	Men/Women	Incidence	New	Yes	Yes	Mid-exposure values	
PAN70012	Thiebaut	2009	Prospective Cohort study	Health AARP Diet and Health Study	Men/Women	Incidence	New	Yes	Yes	Mid-exposure values	
PAN07442	Michaud	2003	Prospective Cohort study	The Nurses' Health Study Cohort	Women	Mortality /incidence	Yes	Yes	Yes	Mid-exposure values	
PAN07590	Stolzenberg-Solomon	2002	Prospective Cohort study	Alpha Tocopherol Beta Carotene Cancer Prevention Study - Finland	Men	Incidence	Yes	Yes	Yes	Mid-exposure values , cases/person-years per quintile	

Figure 136 Highest versus lowest forest plot of polyunsaturated fat intake and pancreatic cancer

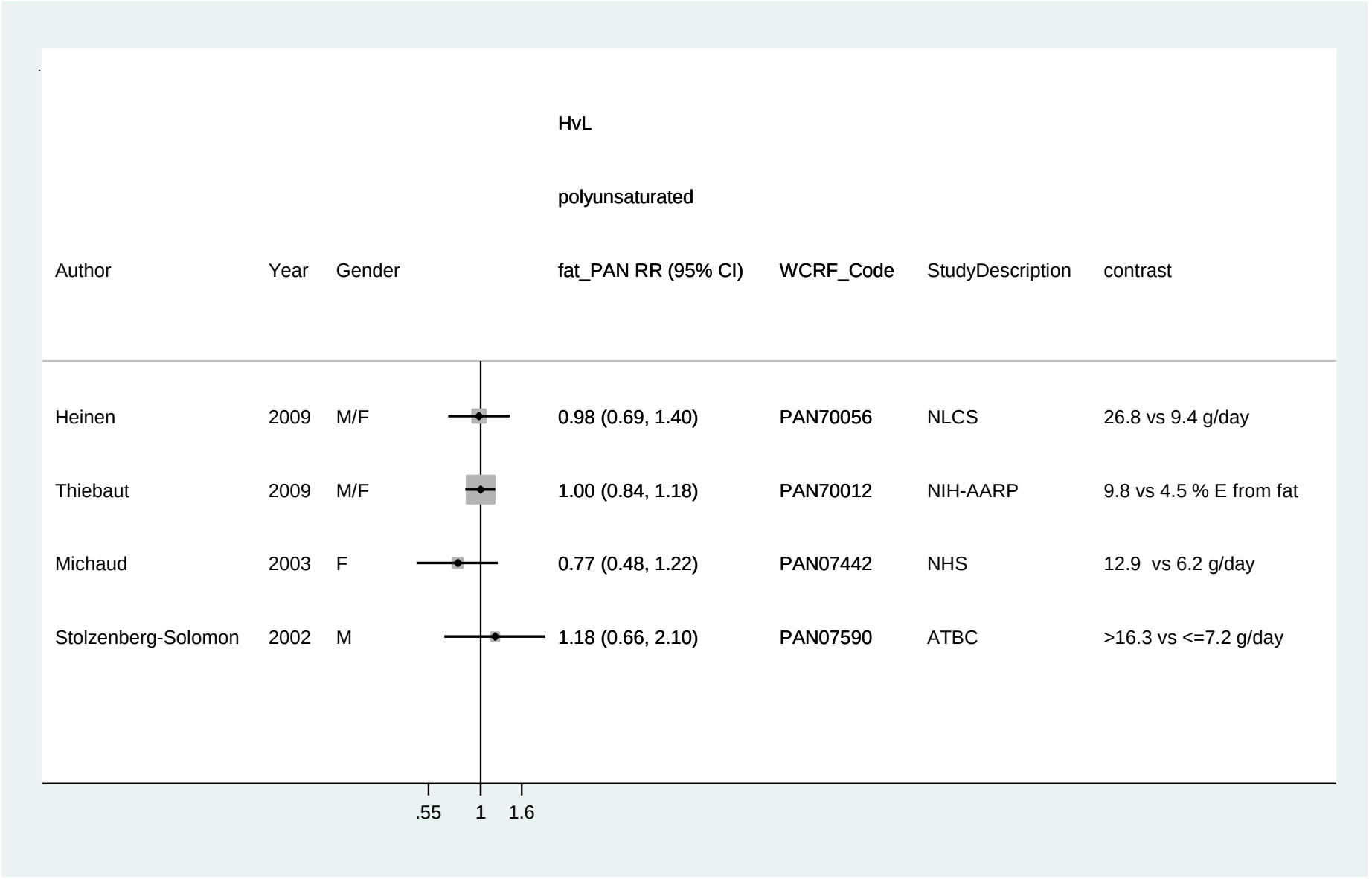


Figure 137 Dose-response meta-analysis of polyunsaturated fat intake and pancreatic cancer – per 10g/day

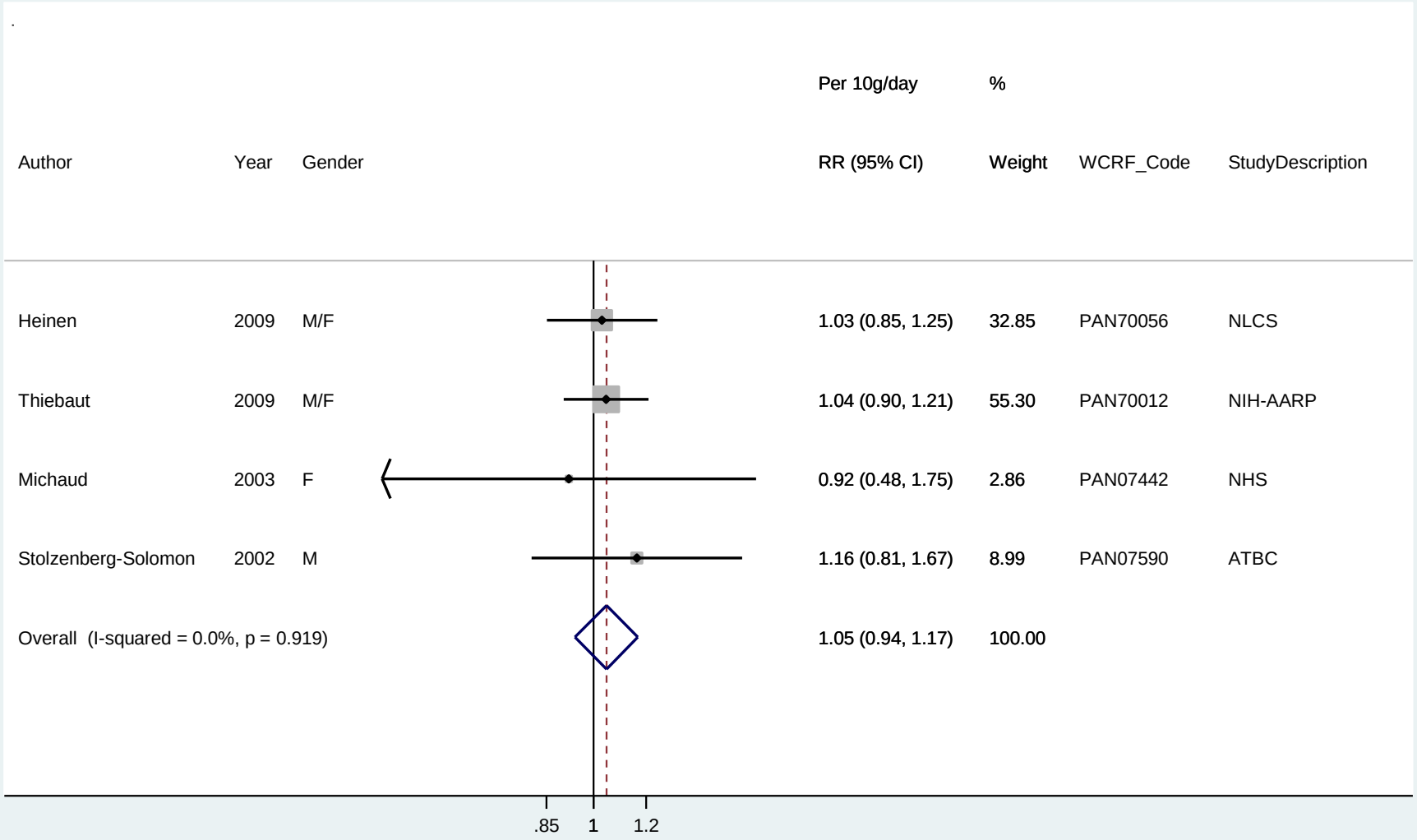
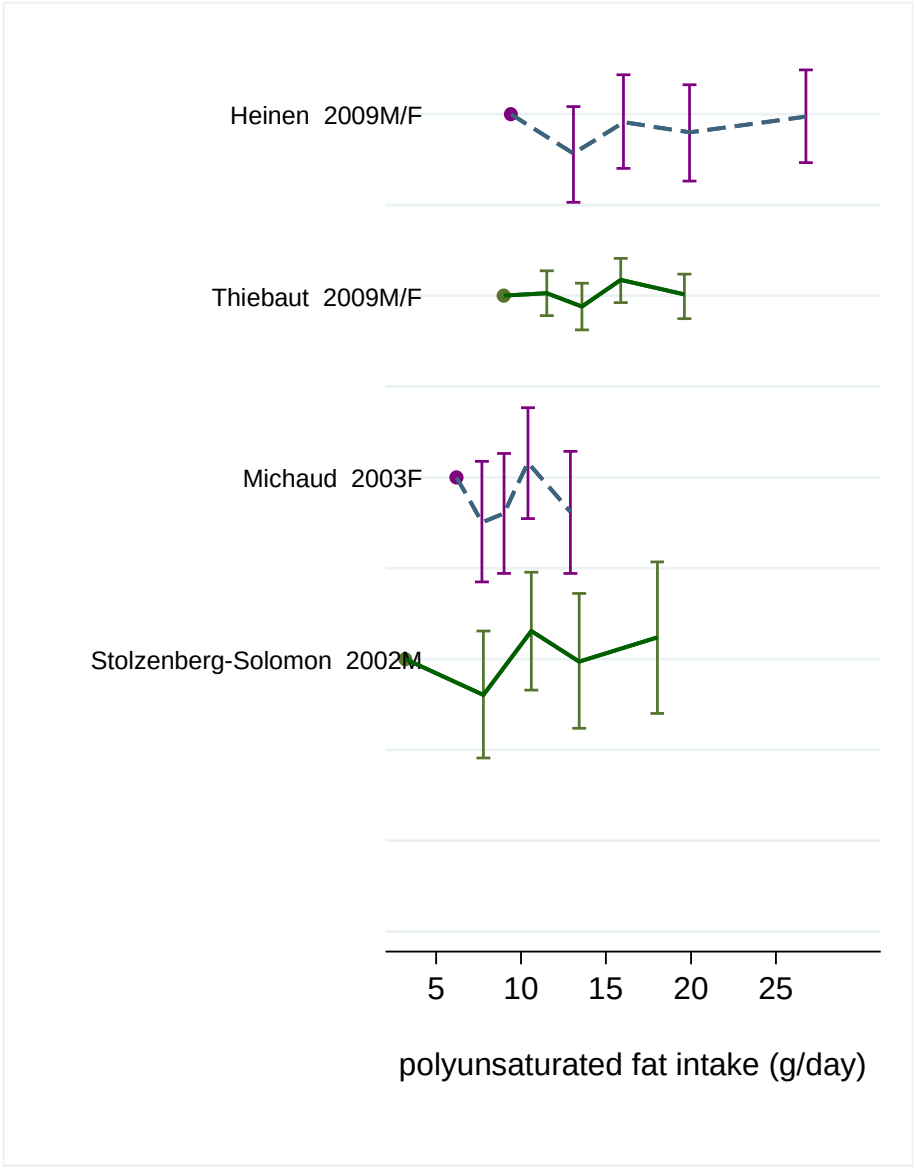


Figure 138 Dose-response graph of polyunsaturated fat intake and pancreatic cancer



5.2.4.1 Linolenic acid

Methods

Four cohort studies were identified, two were identified during the CUP. Dose-response meta-analysis for pancreatic cancer was performed in the previous SLR report. In this report, a meta-analysis including all 3 different studies was performed.

Main results

The summary RR per 1g/day was 0.96 (95% CI: 0.79-1.18, $P_{heterogeneity}$=0.34; 3 studies) for incidence or mortality of pancreatic cancer. The only study on men reported a RR per 1g/day of 1.04 (95% CI: 0.79-1.37) and the only study on women reported a RR per 1g/day of 0.45 (95% CI: 0.15-1.35).

Heterogeneity

Low heterogeneity was observed (I^2= 8.2%, p=0.34). Egger's tests suggested no evidence of publication bias, p= 0.66.

Comparison with the Second Expert Report

Overall, linolenic acid intake was not associated with the risk of pancreatic cancer. RR for an increase of 1g/day was 0.96 (95% CI: 0.79-1.18), therefore similar to that reported in the previous SLR report (RR for 1g/day was 0.92 (95% CI: 0.54 -1.57).

Table 116 Studies on linolenic acid intake identified in the CUP

Author, year	Country	Study name	Cases	Years of follow up	Sex	RR	LCI	UCI	Contrast
Heinen, 2009	Netherlands	The Netherlands Cohort study	350	13.3	M/F	0.97	0.67	1.40	1.89 vs 0.65 g/day
Thiebaut, 2009	USA	Health AARP Diet and Health Study	1337	7.2	M/F	1.13	0.95	1.34	Q5 vs Q1

Table 117 Overall evidence on linolenic acid intake and pancreatic cancer

	Summary of evidence
SLR	Two cohort studies provided data. Both studies investigated the consumption of alpha-linolenic acid and both studies were included in the meta-analysis. The summary relative risk was 0.92 (95% CI: 0.54 to 1.57) per 1 g/day (p=0.8).
Continuous Update Project	Two cohort studies were identified, but only one found an association between linolenic acid and pancreatic cancer. Four studies were included in the high versus low forest plot.

Table 118 Summary of results of the dose response meta-analysis on linolenic acid intake and pancreatic cancer

Pancreatic cancer		
	SLR	Continuous Update Project
Studies (n)	2	3
Cases (n)	341	691
Increment unit used	Per 1g/day	Per 1g/day
Overall RR (95%CI)	0.92 (0.54 -1.57)	0.96 (0.79-1.18)
Heterogeneity (I^2,p-value)	34%, p=0.2	8.2%, p=0.34

Table 119 Inclusion/exclusion table for meta-analysis linolenic acid intake and pancreatic cancer

WCRF_ Code	Author	Year	Study Design	Study Name	Subgroup	Cancer Outcome	SLR	CUP dose-response meta-analysis	CUP HvL forest plot	Estimated values	Exclusion reasons
PAN70056	Heinen	2009	Prospective Cohort study	The Netherlands Cohort study	Men/Women	Incidence	New	Yes	Yes	Mid-exposure values	
PAN70012	Thiebaut	2009	Prospective Cohort study	Health AARP Diet and Health Study	Men/Women	Incidence	New	No	Yes		No quintile range for intake
PAN07442	Michaud	2003	Prospective Cohort study	The Nurses' Health Study Cohort	Women	Mortality/incidence	Yes	Yes	Yes	Mid-exposure values	
PAN07590	Stolzenberg-Solomon	2002	Prospective Cohort study	Alpha Tocopherol Beta Carotene Cancer Prevention Study - Finland	Men	Incidence	Yes	Yes	Yes	Mid-exposure values , cases/person-years per quintile	

Figure 139 Highest versus lowest forest plot of linolenic acid intake and pancreatic cancer

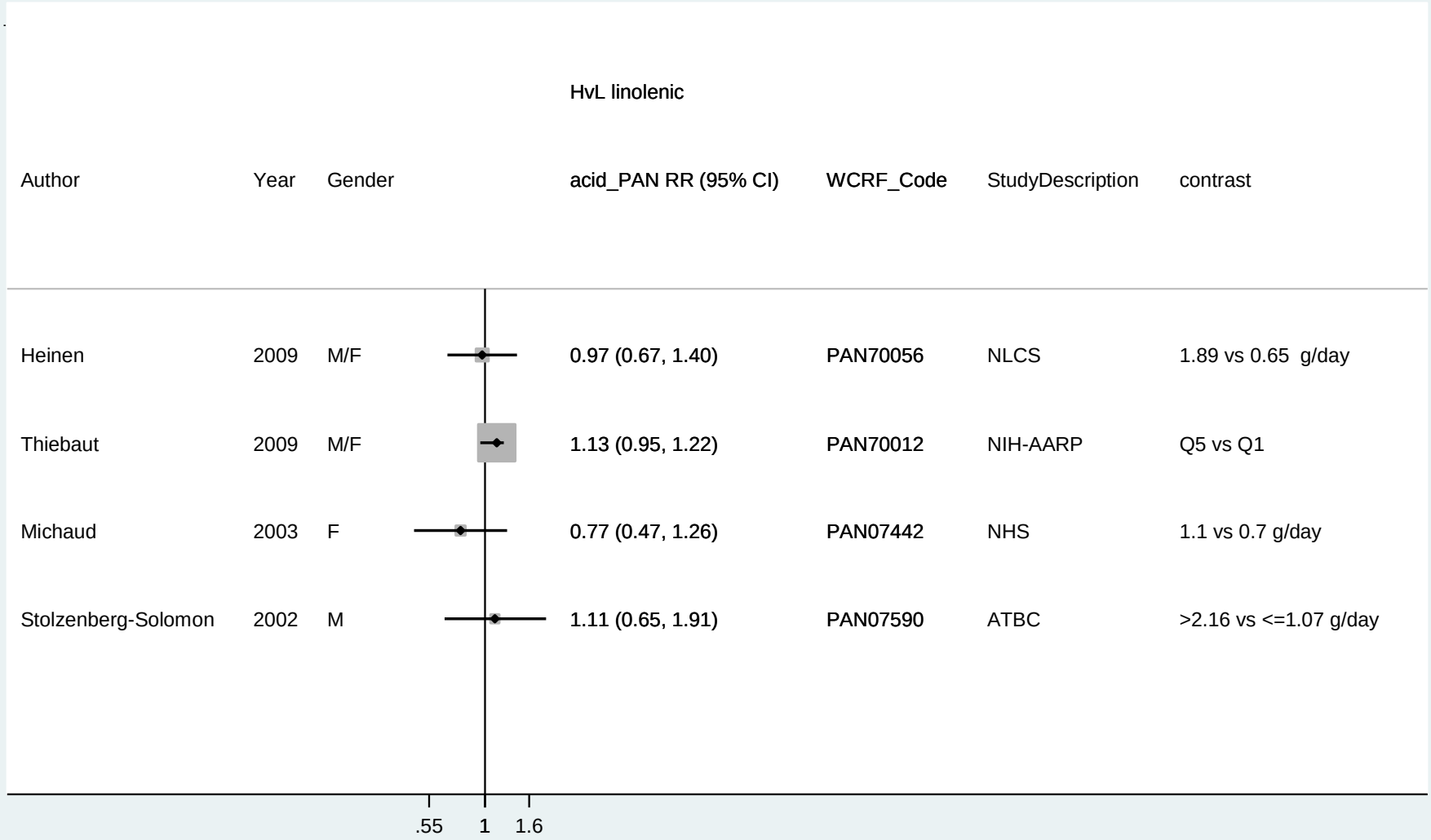


Figure 140 Dose-response meta-analysis of linolenic acid intake and pancreatic cancer – per 1g/day

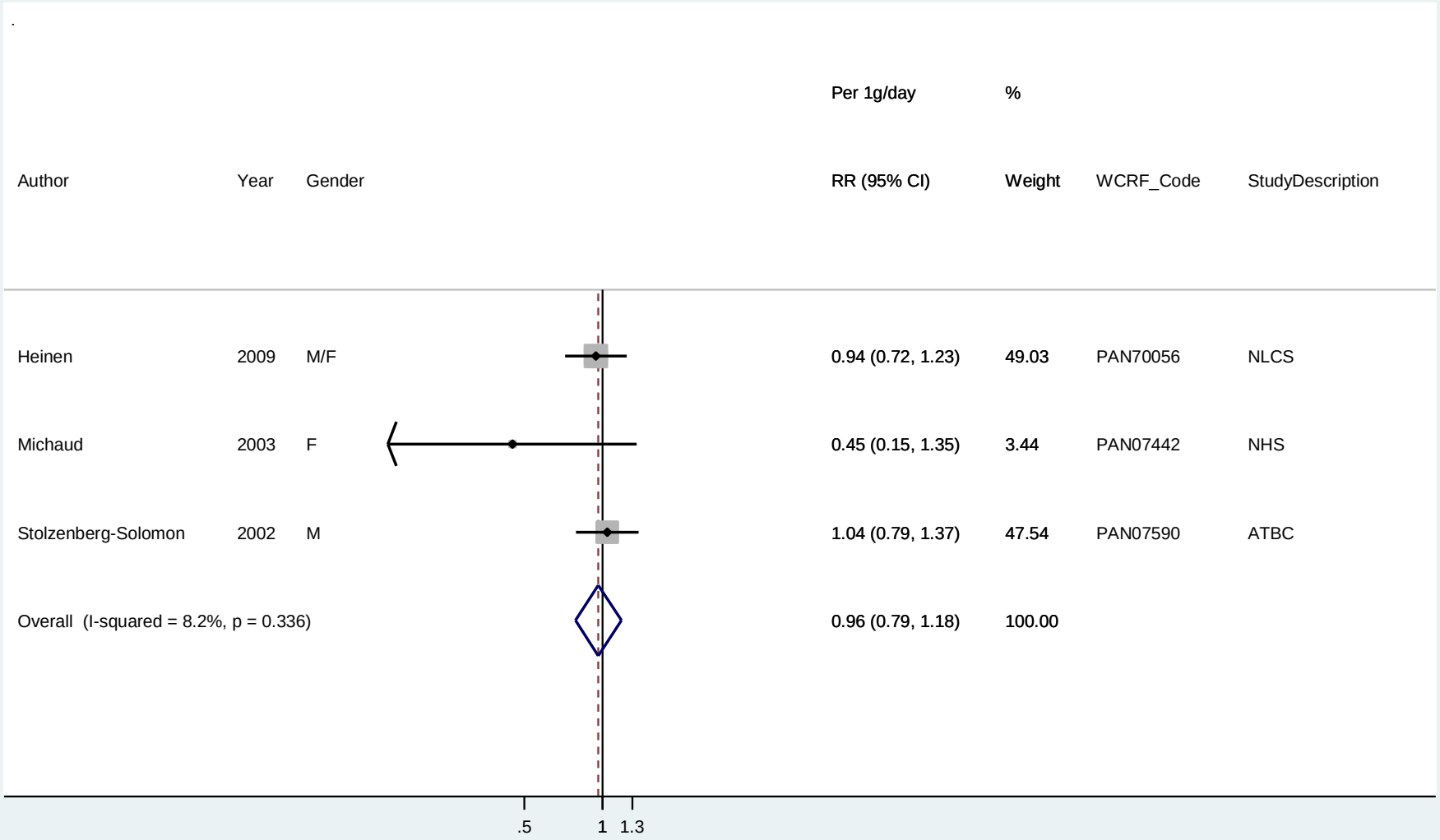
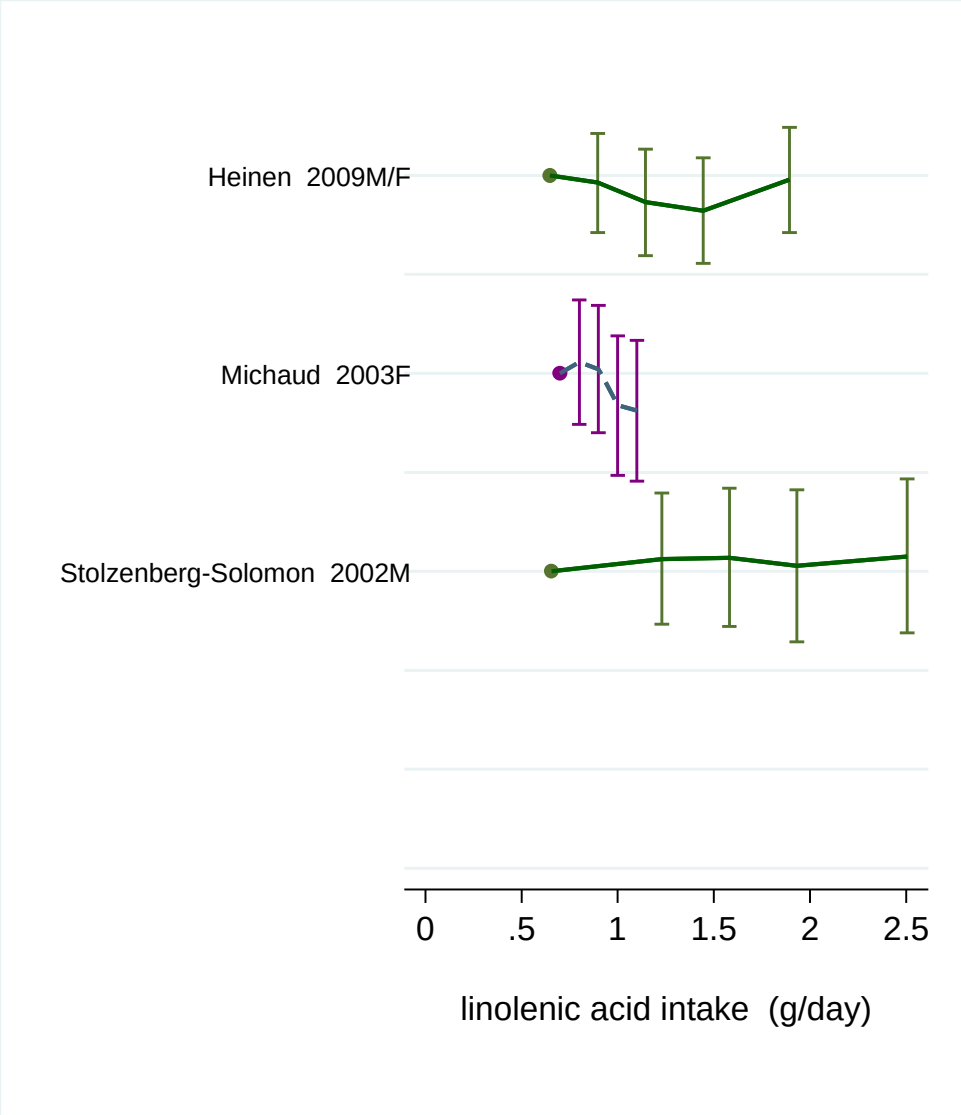


Figure 141 Dose-response graph of linolenic acid intake and pancreatic cancer



5.2.4.2 Linoleic acid

Methods

Four cohort studies were identified, two were identified during the CUP. Dose-response meta-analysis for pancreatic cancer was performed in the previous SLR report. In this report, a meta analysis including all 3 different studies was performed.

Main results

The summary RR per 1g/day was 1.01 (95% CI: 0.99-1.02, $P_{heterogeneity}$=0.79; 3 studies) for incidence or mortality of pancreatic cancer. The only study on men reported a RR per 1g/day of 1.02 (95% CI: 0.98-1.06) and the only study on women reported a RR per 1g/day of 1.00 (95% CI: 0.93-1.07).

Heterogeneity

No evidence of heterogeneity (I^2= 0%, p=0.79) between studies. Egger's tests suggested no evidence of publication bias, p= 0.58.

Comparison with the Second Expert Report

Overall, linoleic acid intake was not associated with the risk of pancreatic cancer. RR for an increase of 1g/day was 1.01 (95% CI: 0.99-1.02, $P_{heterogeneity}$=0.79), therefore similar to that reported in the previous SLR report (RR for 1g/day was 1.01 (95% CI: 0.98 -1.04).

Table 120 Studies on linoleic acid intake identified in the CUP

Author, year	Country	Study name	Cases	Years of follow up	Sex	RR	LCI	UCI	Contrast
Heinen, 2009	Netherlands	The Netherlands Cohort study	350	13.3	M/F	1.05	0.74	1.49	25.3 vs 7.7 g/day
Thiebaut, 2009	USA	Health AARP Diet and Health Study	1337	7.2	M/F	0.99	0.83	1.17	Q5 vs Q1

Table 121 Overall evidence on linoleic acid intake and pancreatic cancer

	Summary of evidence
SLR	Two cohort studies provided data. Both studies were included in the meta-analysis. The summary relative risk was 1.01 (95% CI: 0.98 to 1.04) per 1 g/day (p=0.6).
Continuous Update Project	Two cohort studies were identified and found no association between linoleic acid and pancreatic cancer. Four studies were included in the high versus low forest plot.

Table 122 Summary of results of the dose response meta-analysis on linoleic acid intake and pancreatic cancer

Pancreatic cancer		
	SLR	Continuous Update Project
Studies (n)	2	3
Cases (n)	341	691
Increment unit used	Per 1g/day	Per 1g/day
Overall RR (95%CI)	1.01 (0.98 -1.04)	1.01 (0.99-1.02)
Heterogeneity (I^2,p-value)	0%, p=0.4	0%, p=0.79

Table 123 Inclusion/exclusion table for meta-analysis linoleic acid intake and pancreatic cancer

WCRF_ Code	Author	Year	Study Design	Study Name	Subgroup	Cancer Outcome	SLR	CUP dose-response meta-analysis	CUP HvL forest plot	Estimated values	Exclusion reasons
PAN70056	Heinen	2009	Prospective Cohort study	The Netherlands Cohort study	Men/Women	Incidence	New	Yes	Yes	Non cases	
PAN70012	Thiebaut	2009	Prospective Cohort study	Health AARP Diet and Health Study	Men/Women	Incidence	New	No	Yes		No quintile range for intake
PAN07442	Michaud	2003	Prospective Cohort study	The Nurses' Health Study Cohort	Women	Mortality/incidence	Yes	Yes	Yes	Non cases	
PAN07590	Stolzenberg-Solomon	2002	Prospective Cohort study	Alpha Tocopherol Beta Carotene Cancer Prevention Study - Finland	Men	Incidence	Yes	Yes	Yes	Non cases and cases per quintile	

Figure 142 Highest versus lowest forest plot of linoleic acid intake and pancreatic cancer

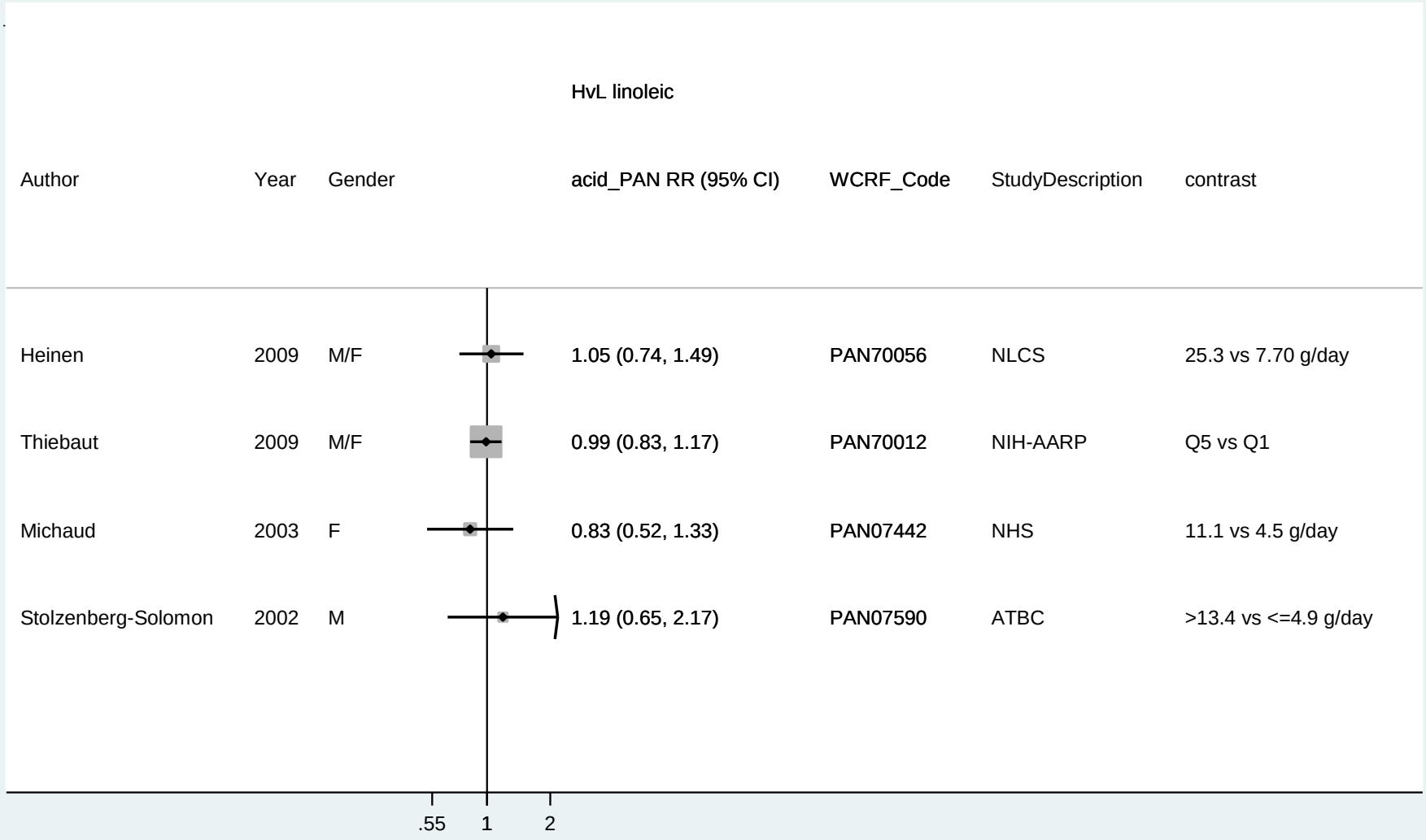


Figure 143 Dose-response meta-analysis of linoleic acid intake and pancreatic cancer – per 1g/day

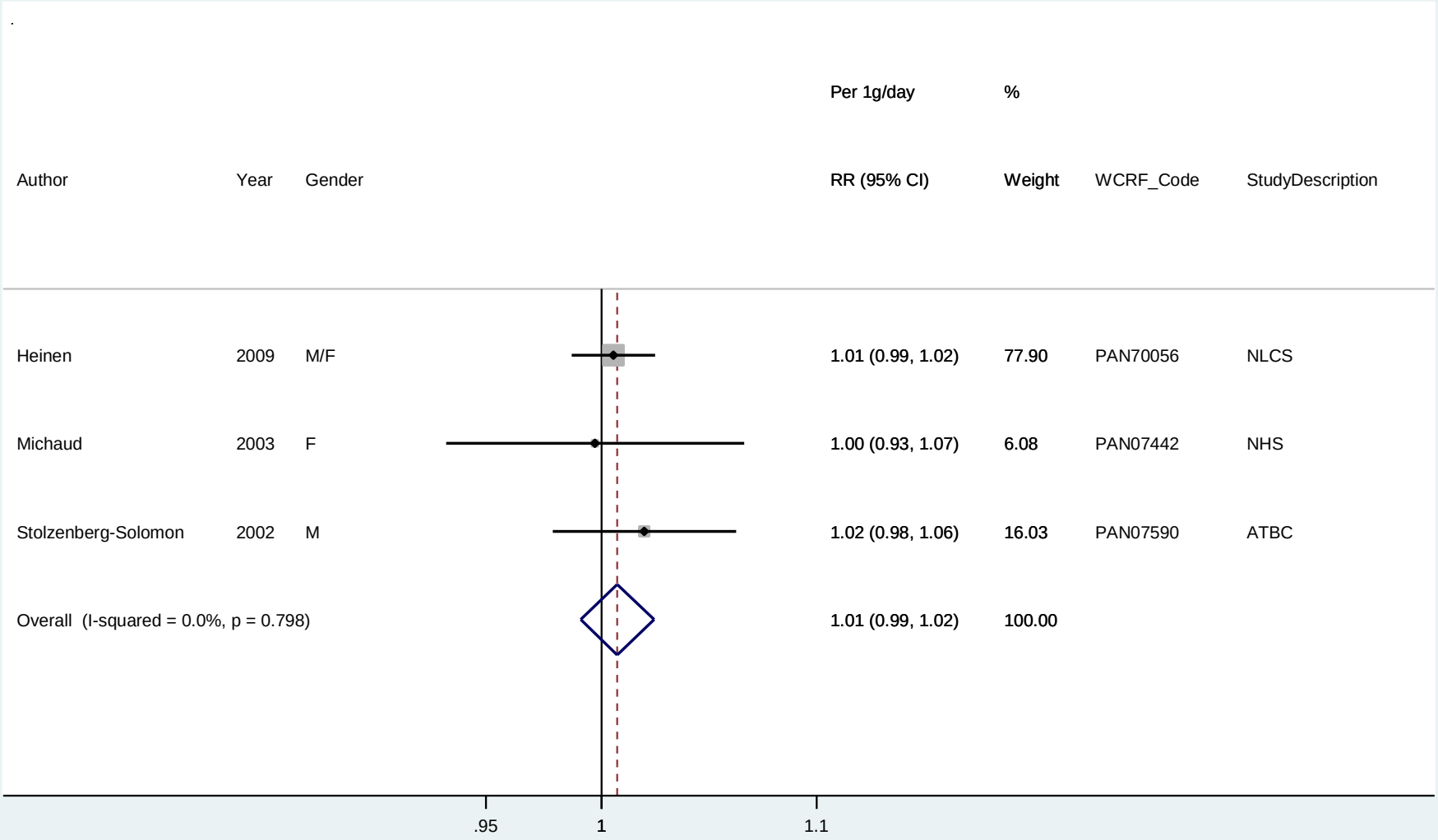
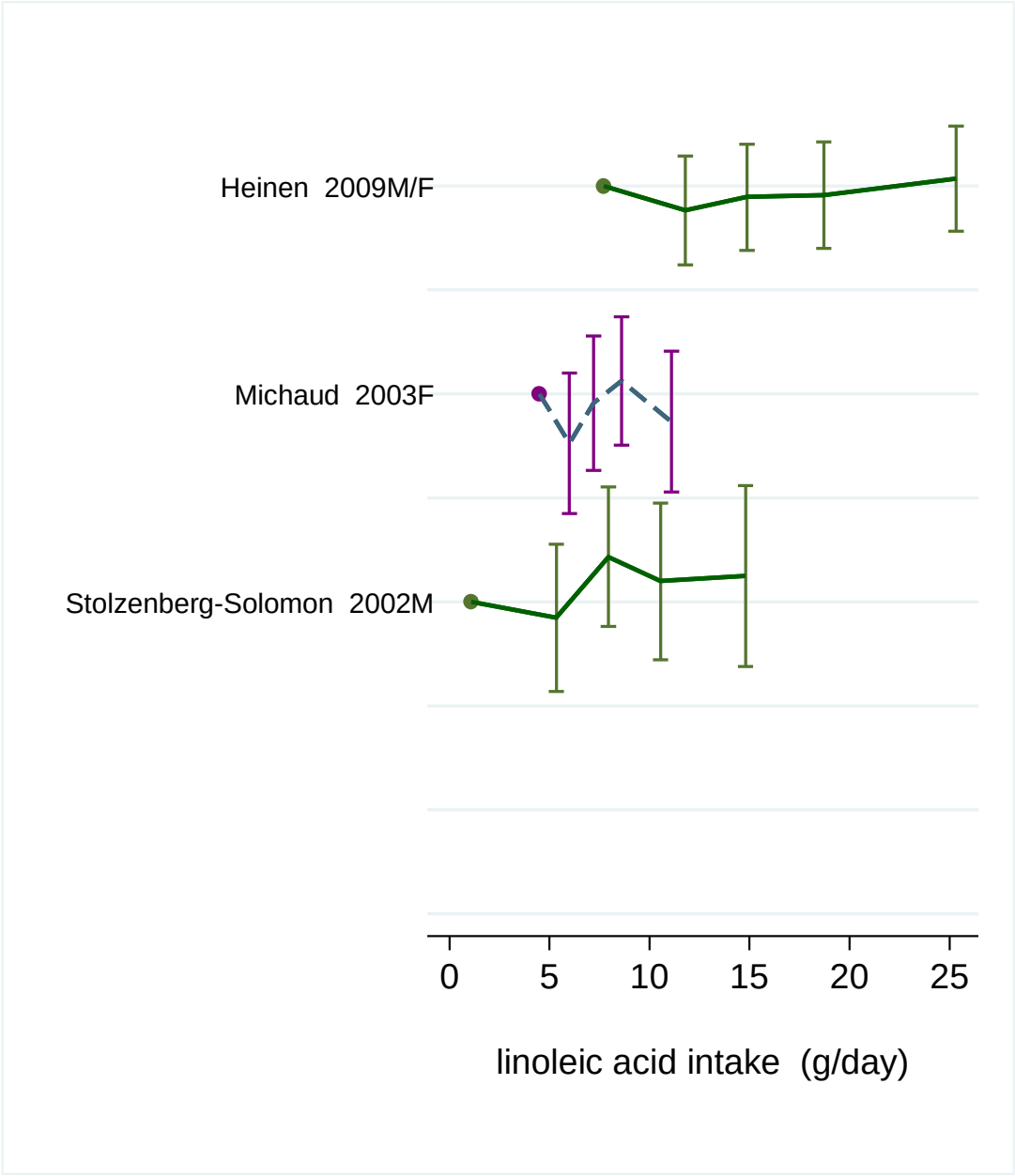


Figure 144 Dose-response graph of linoleic acid intake and pancreatic cancer



5.2.6 Cholesterol, dietary

Methods

Five cohort studies were identified, from which two were identified during the CUP. Dose-response meta-analysis for pancreatic cancer was performed in the previous SLR report. In this report, a meta-analysis including four studies was performed.

Main results

The summary RR per 0.200g/day was 1.05 (95% CI: 0.90-1.22, $P_{heterogeneity}$=0.91; 4 studies) for incidence or mortality of pancreatic cancer. The only study on men reported a RR per 0.200g/day of 1.01 (95% CI: 0.78-1.31) and the only study on women reported a RR per 0.200g/day of 1.19 (95% CI: 0.82-1.71).

Heterogeneity

No evidence of heterogeneity (I^2= 0%, p=0.91). Egger's tests suggested no evidence of publication bias, p= 0.45.

Comparison with the Second Expert Report

Overall, dietary cholesterol was not associated with the risk of pancreatic cancer. However, the NIH-AARP study (Thiebaut et al, 2009) reported a positive significant association between cholesterol intake and pancreatic cancer in the high versus low analysis. RR for an increase of 0.200g/day was 1.05 (95% CI: 0.90-1.22), therefore similar to that reported in the previous SLR report (RR for 0.200g/day was 1.06 (95% CI: 0.86 -1.30).

Table 124 Studies on dietary cholesterol identified in the CUP

Author, year	Country	Study name	Cases	Years of follow up	Sex	RR	LCI	UCI	Contrast
Heinen, 2009	Netherlands	The Netherlands Cohort study	350	13.3	M/F	0.78	0.52	1.18	0.34 vs 0.17 g/day
Thiebaut, 2009	USA	Health AARP Diet and Health Study	1337	7.2	M/F	1.28	1.08	1.52	Highest vs lowest

Table 125 Overall evidence on dietary cholesterol and pancreatic cancer

	Summary of evidence
SLR	Three prospective cohort studies provided data. Two studies were included in the meta-analysis. The summary relative risk from these studies was 1.06 (95% CI: 0.86 to 1.30) per 0.2 g/day).
Continuous Update Project	Two cohort studies were identified. One found no association between dietary cholesterol and pancreatic cancer and the other, expressed cholesterol in mg/1000Kcal, reported a significant RR (p<0.001) in the high versus low analysis. Five studies were included in the high versus low forest plot.

Table 126 Summary of results of the dose response meta-analysis on dietary cholesterol and pancreatic cancer

Pancreatic cancer		
	SLR	Continuous Update Project
Studies (n)	2	4
Cases (n)	341	1173
Increment unit used	Per 0.200g/day	Per 0.200g/day
Overall RR (95%CI)	1.06 (0.86 -1.30)	1.05 (0.90-1.22)
Heterogeneity (I^2,p-value)	0%, p=0.4	0%, p=0.91

Table 127 Inclusion/exclusion table for meta-analysis on dietary cholesterol and pancreatic cancer

WCRF_ Code	Author	Year	Study Design	Study Name	Subgroup	Cancer Outcome	SLR	CUP dose-response meta-analysis	CUP HvL forest plot	Estimated values	Exclusion reasons
PAN70056	Heinen	2009	Prospective Cohort study	The Netherlands Cohort study	Men/Women	Incidence	New	Yes	Yes	Mid-exposure values	
PAN70012	Thiebaut	2009	Prospective Cohort study	Health AARP Diet and Health Study	Men/Women	Incidence	New	No	Yes		No quintile range for intake
PAN61048	Nöthlings	2005	Prospective Cohort study	Hawaii-Los Angeles Multiethnic Cohort (MEC) Study	Men/Women	Incidence	Yes	Yes	Yes	Person years per quintile	
PAN07442	Michaud	2003	Prospective Cohort study	The Nurses' Health Study Cohort	Women	Mortality/ incidence	Yes	Yes	Yes		
PAN07590	Stolzenberg-Solomon	2002	Prospective Cohort study	Alpha Tocopherol Beta Carotene Cancer Prevention Study - Finland	Men	Incidence	Yes	Yes	Yes	Mid-exposure values , cases/person-years per quintile	

Figure 145 Highest versus lowest forest plot of dietary cholesterol and pancreatic cancer

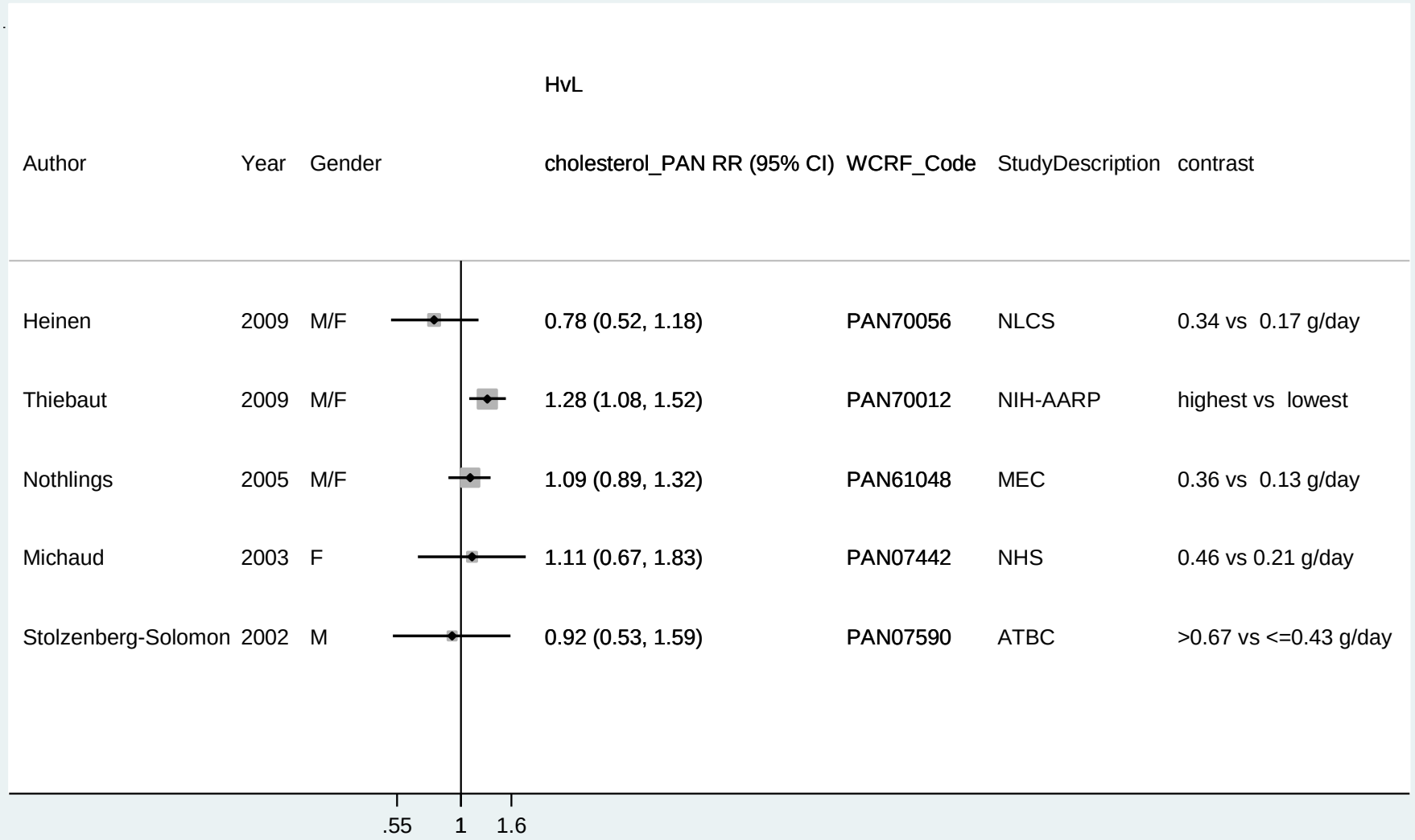


Figure 146 Dose-response meta-analysis of dietary cholesterol and pancreatic cancer – per 0.200g/day

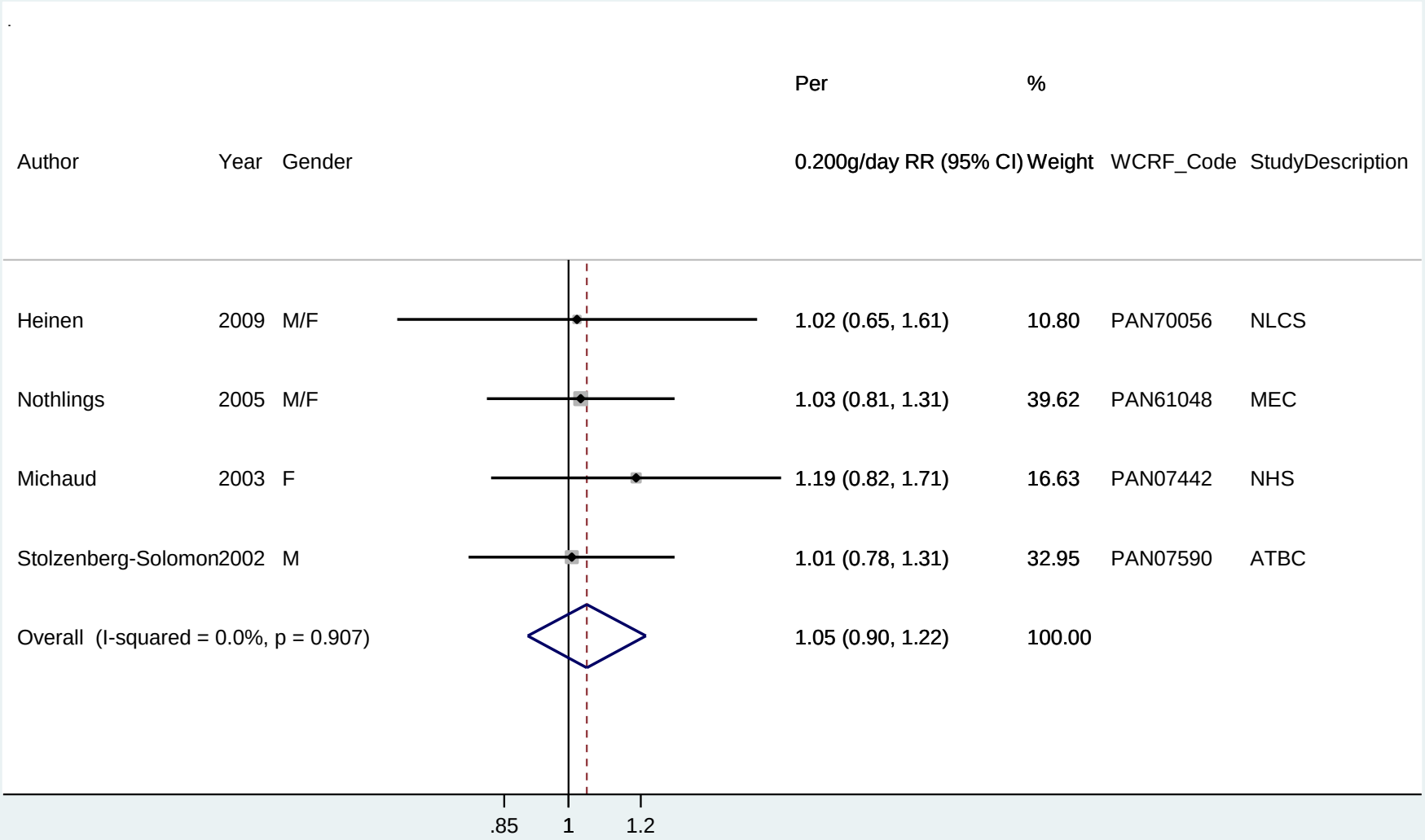
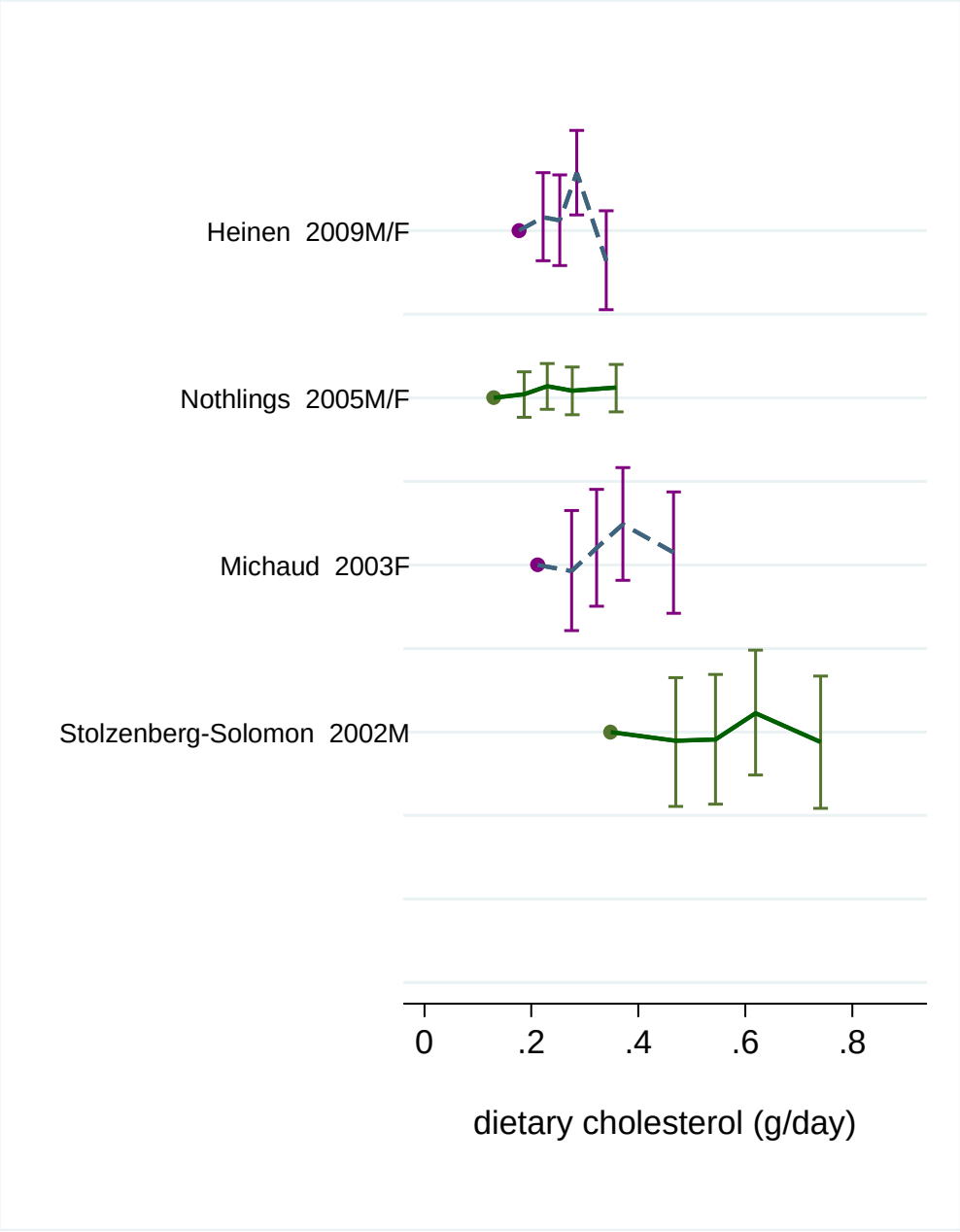


Figure 147 Dose-response graph of dietary cholesterol and pancreatic cancer



5.4 Alcohol (as ethanol)

Methods

Ten cohort studies were identified, four were identified during the CUP. Only studies reporting on ethanol from alcoholic drinks (g/day) are reviewed in this section, studies reporting on total alcoholic drinks (drinks/week) are included on section 3.7.1. Dose-response meta-analysis for cohort studies was performed in the previous SLR report. In this report, a meta-analysis including 9 different studies (4 studies identified during the CUP and 5 studies identified during the 2007 SLR) was performed.

One study (NIH-AARP, Jiao et al. 2009) presented the total alcohol intake in drinks per day and this was converted to grams per day using as conversion 1 drink=13g of alcohol, as referred in the study.

Main results

The summary RR per 10g/day was 1.00 (95% CI: 0.99-1.01 $P_{heterogeneity}$=0.88; 9 studies) for incidence or mortality of pancreatic cancer. The RR ranged from 0.99 (95% CI: 0.98-1.01) when excluding the NLCS (Heinen et al, 2009) to 1.01 (95% CI: 0.98-1.04) when excluding the NIH-AARP study (Jiao et al, 2009).
Only 3 studies reported separate results by smoking status and could be included in a dose-response meta-analysis stratified by smoking. For each 10g of alcohol a day the RR was 0.99 (95%CI: 0.95-1.02) for ever smokers and 1.02 (95%CI: 0.96-1.09) for never smokers which is similar to the overall result, RR= 1.00 (95% CI: 0.99-1.01). There was evidence of a nonlinear association between alcohol (as ethanol) and pancreatic cancer risk, $p_{nonlinearity}$<0.0001.

In a sensitivity analysis we included in the high versus low forest plot the studies from the Pooling Project and the PanScan (which were not included in this analysis) and the RR was 1.29 (95%CI: 1.13-1.48; $P_{heterogeneity}$=0.96, 4795cases), therefore similar to the overall positive association found in the high versus low including only the studies referred in table 131, RR=1.30 (95% CI: 1.09-1.54; $P_{heterogeneity}$=0.58, 3096 cases).

Heterogeneity

No heterogeneity was observed (I^2=0%, p=0.88). Egger's tests suggested no evidence of publication bias, p= 0.09.

Comparison with the Second Expert Report

Overall, there is no evidence of an association between alcohol (as ethanol) and the risk of pancreatic cancer. The summary RR per 10g/day found was similar to the relative risk reported on the previous SLR, RR= 1.00 (95% CI: 0.98 to 1.02) per 10 g/day. However, as mentioned in the main results, heavy drinking might have an effect on pancreatic cancer risk.

Published meta-analysis

The Pancreatic Cancer Cohort Consortium-PanScan, (Michaud et al, 2009 observed no significant overall association between total alcohol (ethanol) intake and pancreatic cancer risk (OR = 1.38, 95% CI: 0.86–2.23, for 60 or more g/day vs. 0 to\5 g/day). However, a statistically significant increase in risk was observed among men consuming 45 or more grams of alcohol from liquor per day (OR = 2.23, 95% CI: 1.02–4.87, compared to 0 g/day of alcohol from liquor, P-trend = 0.12), but not among women (OR = 1.35, 95% CI: 0.63–2.87, for 30 or more g/day of alcohol from liquor, compared to none). No associations were noted for wine or beer intake. Overall, no significant increase in risk was observed, but a small effect among heavy drinkers cannot be ruled out. In a pooled analysis of fourteen cohort studies (Genkinger et al, 2009) a slight positive association with pancreatic cancer risk was observed for alcohol intake (pooled multivariate RR= 1.22; 95% CI: 1.03-1.45 comparing >or=30 to 0 grams/day of alcohol). The association was only statistically significant among women although the difference in the results by gender was not statistically significant.

Table 128 Studies on alcohol (as ethanol) identified in the CUP

Author, year	Country	Study name	Cases	Years of follow up	Sex	RR	LCI	UCI	Contrast
Meinhold, 2009	Finland	Alpha Tocopherol Beta Carotene Cancer Prevention Study Cohort	305	16.1	M	1.17	0.82	1.66	≥ 29.5g vs <1.6g/day
Rohrmann, 2009	Europe	European Prospective Investigation into Nutrition and Cancer	555	8.9	M/F	1.00	0.96	1.05	Per 10g/day
Heinen, 2009	Netherlands	The Netherlands Cohort study	350	13.3	M/F	1.06	0.98	1.13	Per 10g/day
Jiao L, 2009	USA	NIH- AARP Diet and Health Study	1149	7.3	M F	1.70 1.24	1.20 0.72	2.38 2.13	≥ 81 vs 0 g/day 40.5-54 vs 0 g/day

Table 129 Overall evidence on alcohol (as ethanol) and pancreatic cancer

	Summary of evidence
SLR	Seven studies provided data. Of these, five studies were included in a meta-analysis. The summary relative risk from these studies was 1.00 (95% CI: 0.98 to 1.02) per 10 g/day (p=0.2) (half a pint of beer/glass wine/single spirit).
Continuous Update Project	Four cohort studies were identified, three reported on males and females. One study found no association between alcohol (as ethanol) and pancreatic cancer, while the other three studies found positive associations.

Table 130 Summary of results of the dose response meta-analysis of alcohol (as ethanol) and pancreatic cancer

Pancreatic cancer		
	SLR	Continuous Update Project
Studies (n)	5	9
Cases (n)	763	3096
Increment unit used	Per 10g/day	Per 10g/day
Overall RR (95%CI)	1.0 (0.98-1.02)	1.00 (0.99-1.01)
Heterogeneity (I^2,p-value)	0%, p=0.8	0%, p=0.88
Stratified analysis		
Men	-	1.02 (0.99-1.04) (n=5)
Heterogeneity (I^2,p-value)		0%, p=0.94
Women		0.99(0.95-1.02) (n=3)
Heterogeneity (I^2,p-value)		17.1%, p=0.29
Stratified analysis by smoking*		
Ever smokers		0.99 (95%CI: 0.95-1.02) (n=2)
Heterogeneity (I^2,p-value)		0%, p=0.69
Never smokers		1.02 (95%CI: 0.96-1.09) (n=3)
Heterogeneity (I^2,p-value)		26.4%, p=0.26

*Only 3 studies reported separate results by smoking status and could be included in a dose-response meta-analysis stratified by smoking.

Table 131 Inclusion/exclusion table for meta-analysis of alcohol (as ethanol) and pancreatic cancer

WCRF_ Code	Author	Year	Study Design	Study Name	Subgroup	Cancer Outcome	SLR	CUP dose-response meta-analysis	CUP HvL forest plot	Estimated values	Exclusion reasons
PAN70045	Meinhold	2009	Prospective cohort study	Alpha Tocopherol Beta Carotene Cancer Prevention Study Cohort	Men	Incidence	New	Yes	Yes	Mid-exposure values, person years per quintile	
PAN70047	Rohrmann	2009	Prospective cohort study	European Prospective Investigation into Nutrition and Cancer	Men/ Women	Incidence	New	Yes	Yes	Mid-exposure values, person years	
PAN70048	Heinen	2009	Prospective cohort study	The Netherlands Cohort study	Men/ Women	Incidence	New	Yes	Yes	Mid-exposure values	
PAN70046	Jiao	2009	Prospective Cohort study	NIH- AARP Diet and Health Study	Men/ Women	Incidence	New	Yes	Yes	Mid-exposure values	
PAN20232	Stolzenberg-Solomon	2004	Nested case control study	Alpha Tocopherol Beta Carotene Cancer Prevention Study Cohort	Men	Incidence	Yes	No	No		No measure of relationship, only mean values
PAN07389	Lin	2002	Prospective cohort study	Japan Collaborative Cohort Study for Evaluation of Cancer Risk	Men/ Women	Mortality/ Incidence	Yes	Yes	Yes	Mid-exposure values	
PAN07589	Stolzenberg-Solomon	2001	Prospective cohort study	Alpha Tocopherol Beta Carotene Cancer Prevention Study Cohort	Men	Incidence	Yes	No	No		Superseded by Meinhold, 2009
PAN07440	Michaud	2001	Prospective cohort study	The Nurses' Health Study Cohort and Health Professional Study	Men/ Women	Mortality/ Incidence	Yes	Yes	Yes	Mid-exposure values	
PAN62091	Theobald	2001	Prospective cohort study	Stockholm county cohort	Men/ Women	Mortality/ Incidence	Yes	Yes	Yes	Mid-exposure values, person	

										years	
PAN65764	Murata	1996	Nested case control study	Chiba Cancer Cohort, Japan	Men	Incidence	Yes (total alcoholic drinks as exposure)	Yes	Yes	Mid-exposure values, person years	
PAN07339	Kato	1992	Prospective cohort study	Japan - Hawaii Centre	Men	Incidence	Yes	No	No		Only mean values

Figure 148 Highest versus lowest forest plot of alcohol (as ethanol) and pancreatic cancer

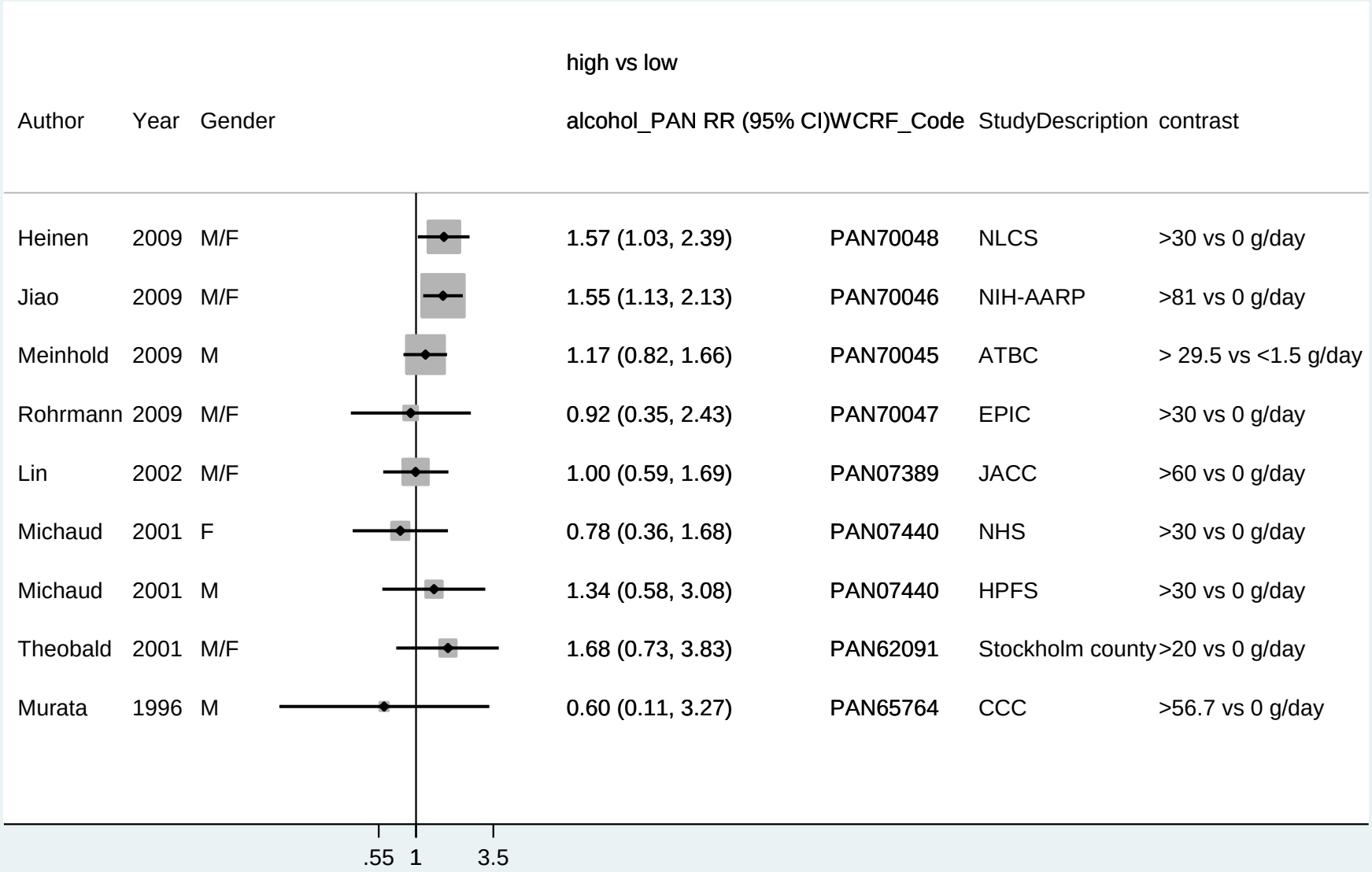


Figure 149 Dose-response meta-analysis of alcohol (as ethanol) and pancreatic cancer – per 10g /day

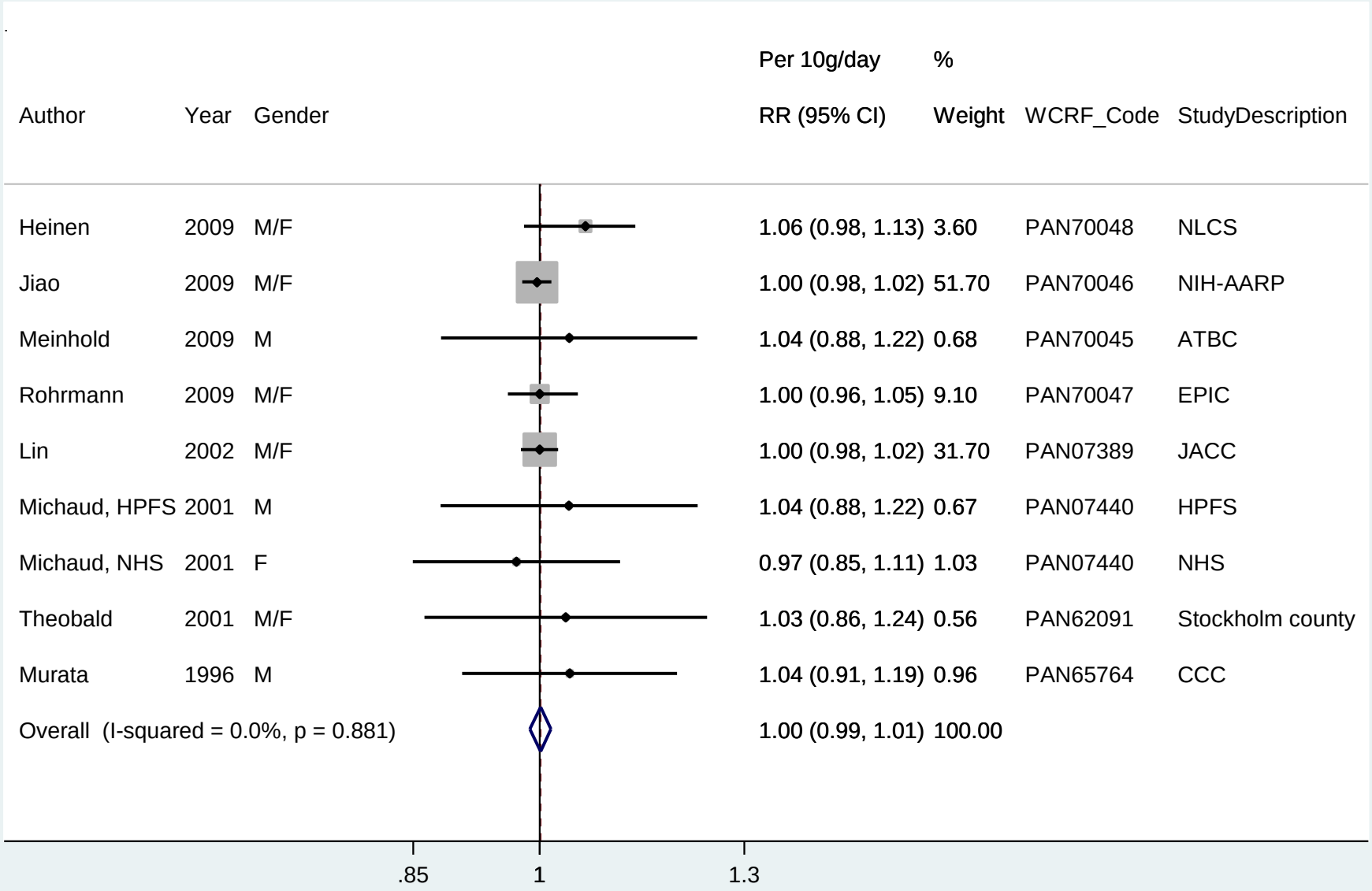


Figure 150 Funnel plot of alcohol (as ethanol) and pancreatic cancer

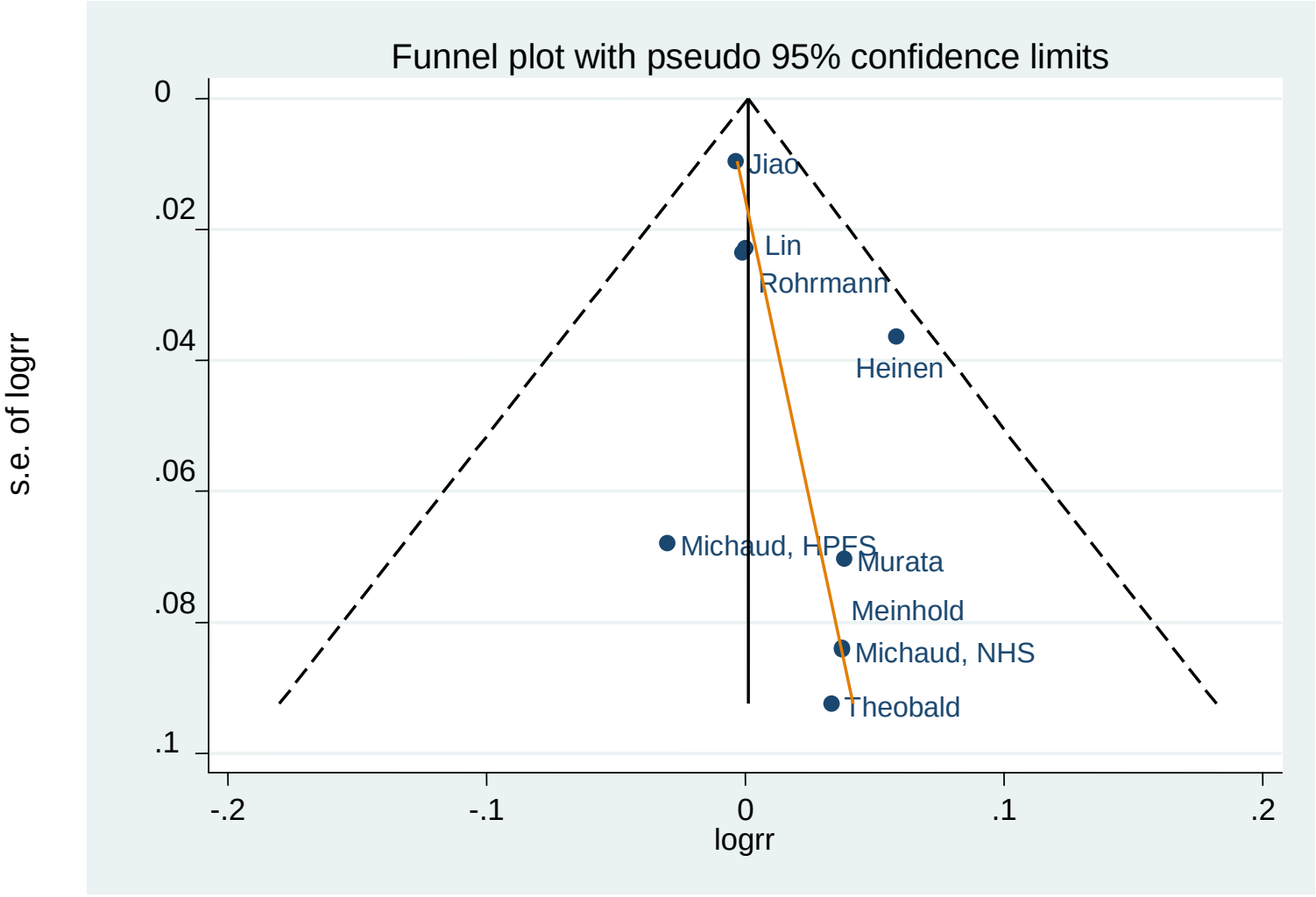


Figure 151 Dose-response graph of alcohol (as ethanol) and pancreatic cancer

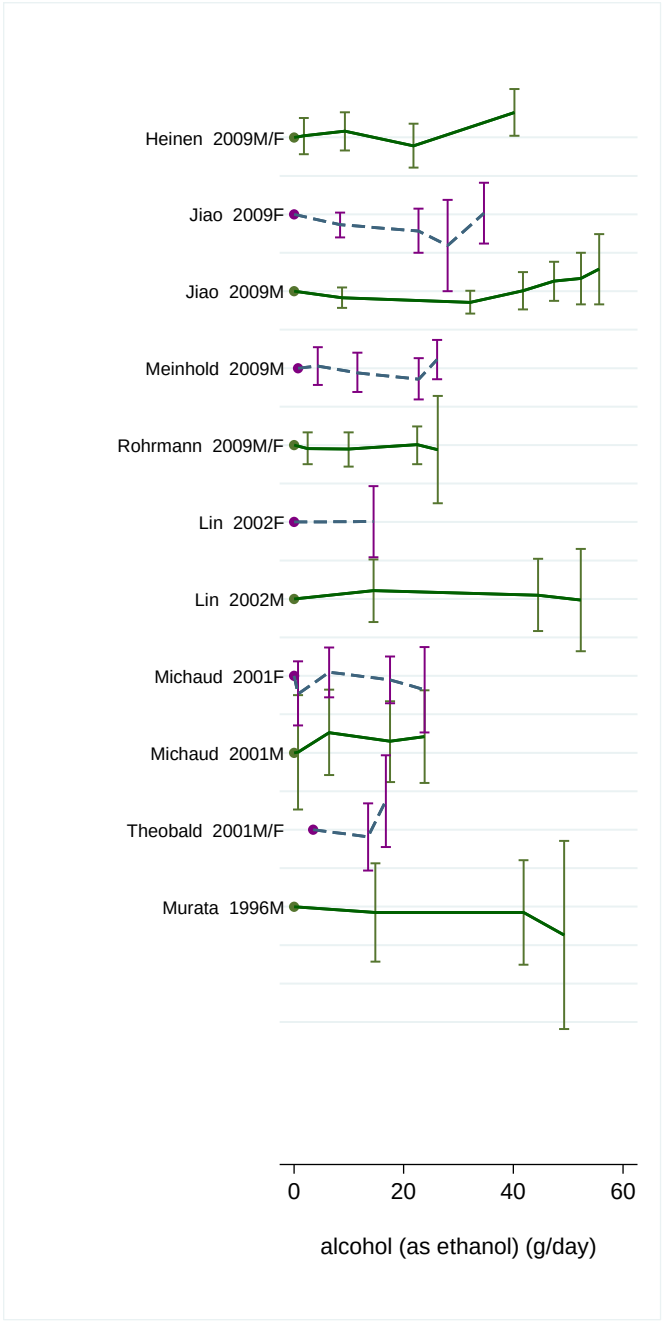


Figure 152 Dose-response meta-analysis of alcohol (as ethanol) and pancreatic cancer, stratified by sex – per 10g /day

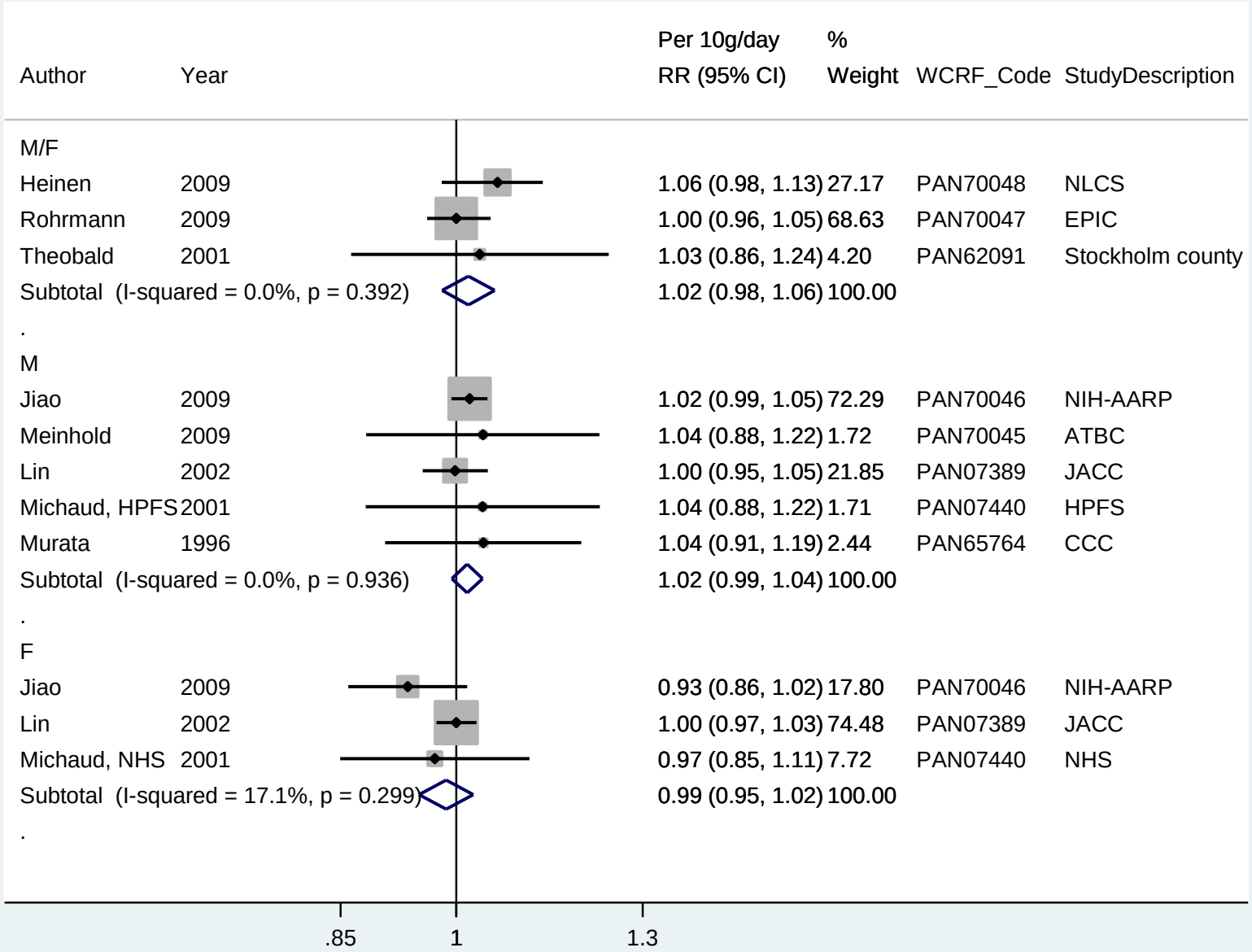


Figure 153 Nonlinear dose-response analysis of alcohol (as ethanol) and pancreatic cancer

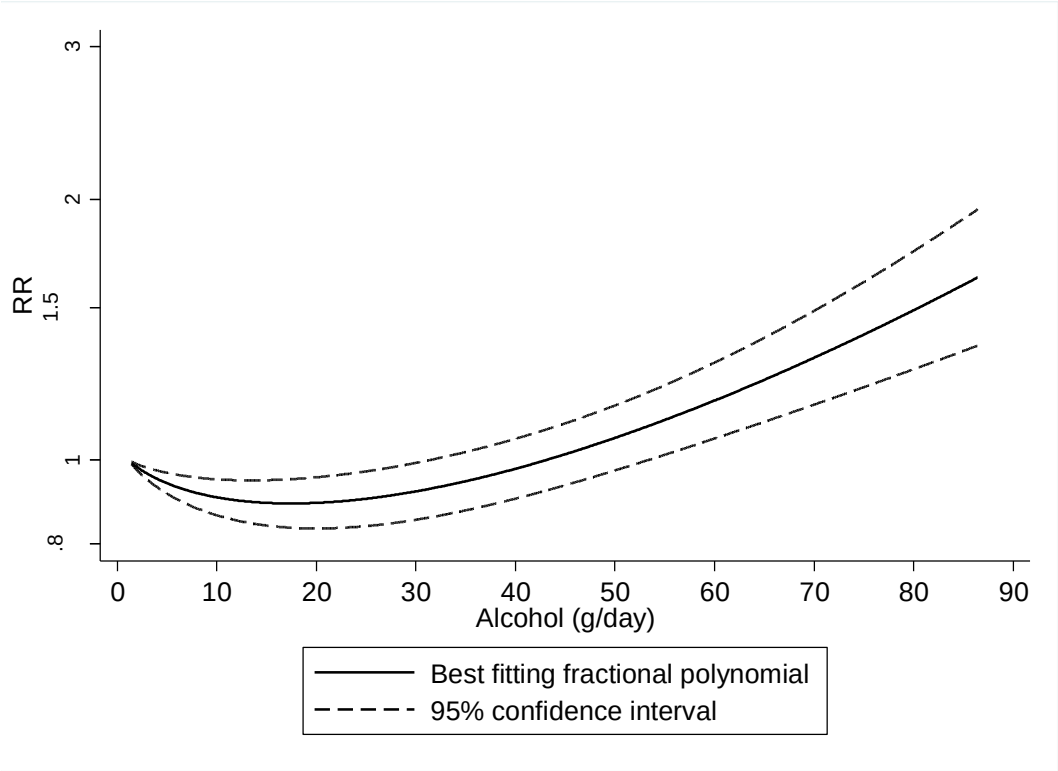


Figure 154 Scatter plot of risk estimates for alcohol (as ethanol) and pancreatic cancer risk

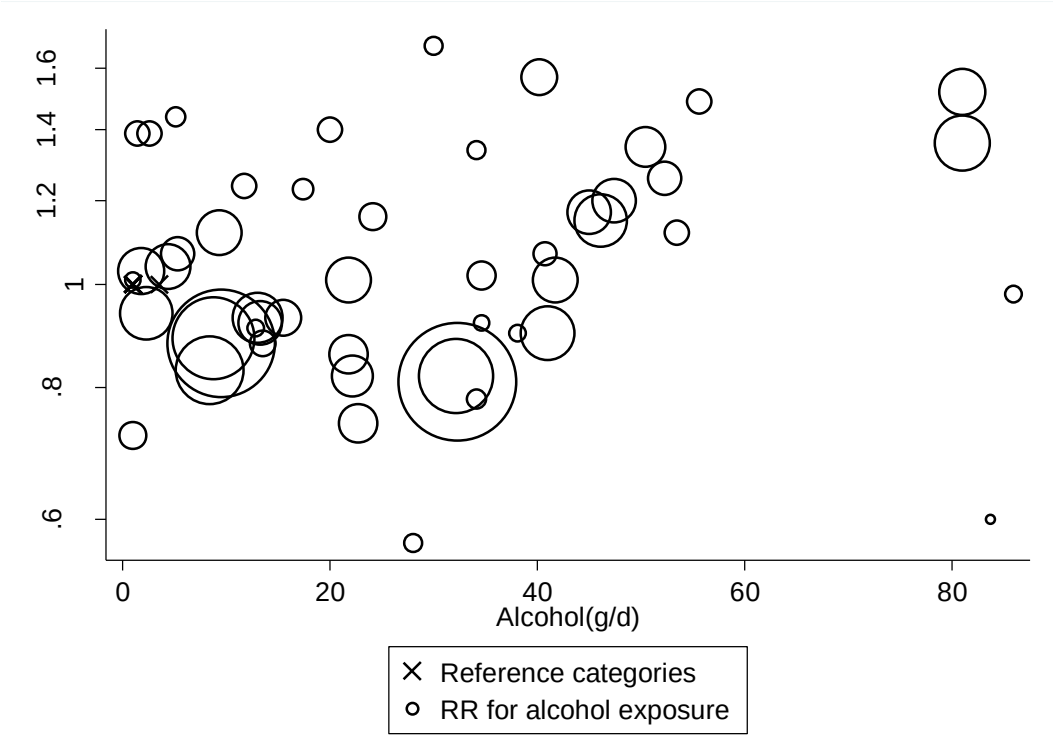
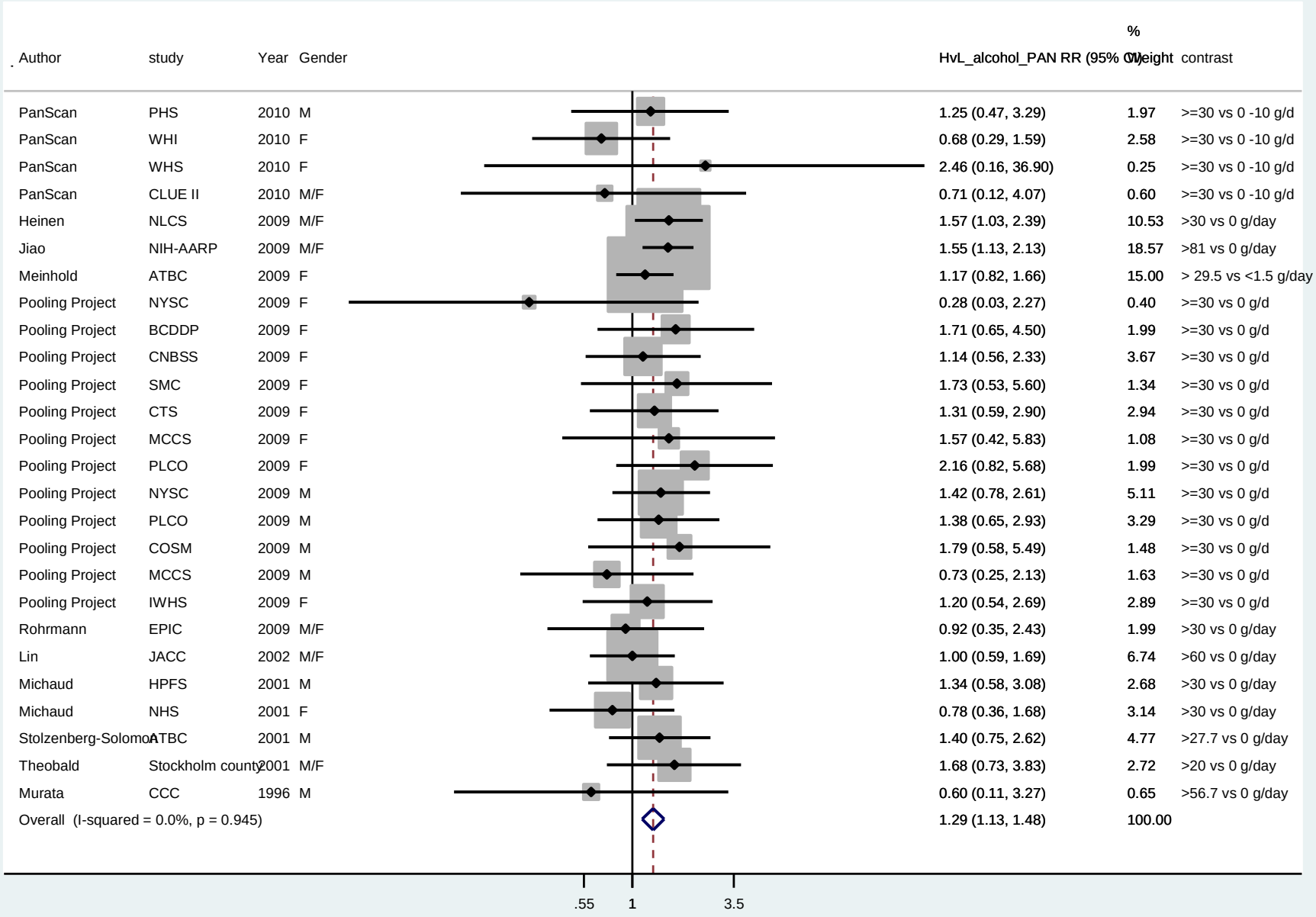


Table 132 Table with alcohol (as ethanol) values and corresponding RRs (95% CIs) for nonlinear analysis of alcohol (as ethanol) and pancreatic cancer incidence

Alcohol (as ethanol) g/day	RR (95% CI)
1.0	1.00
10	0.90 (0.86-0.94)
20	0.89 (0.83-0.95)
40	0.97 (0.90-1.05)
60	1.17 (1.05-1.29)

Figure 155 Highest versus lowest forest plot of alcohol (as ethanol) and pancreatic cancer including studies from the Pooling Project and the PanScan



5.5.3 Folate

5.5.3 Dietary folate

Methods
Six cohort studies were identified (the Cohort of Swedish Men and the Swedish Mammography Cohort are counted as one because only pooled results were published). Three publications were identified in the Continuous Update Project. Dose-response analyses of dietary folate intake and risk of pancreatic cancer incidence were conducted. The dose-response results are presented for an increment of 100 µg per day.

Main results

Six studies were included in the dose-response analysis of dietary folate intake and pancreatic cancer risk. There was no significant association (summary RR=0.89, 95% CI: 0.74-1.07) per 100 µg/d, with moderate-to high heterogeneity, I^2=59.6%, p=0.03. The summary RR ranged from 0.84 (95% CI: 0.74-0.95) when the study by Keszei et al, 2009 was excluded to 0.93 (95% CI: 0.80-1.10) when the study by Larsson, et al, 2006 was excluded. The heterogeneity was reduced when the study by Keszei et al, 2009, was excluded as well, I^2=18.2%, $p_{heterogeneity}$=0.30. There was no evidence of publication bias with Egger's test, p=0.73. There was no evidence of a nonlinear association between dietary folate and pancreatic cancer risk, $p_{nonlinearity}$=1.00

Heterogeneity

There was moderate to high heterogeneity in the analyses (I^2 =59.6%), which was explained by one outlying study.

Study quality

Two European studies were from general population cohorts (NLCS, SMC&COSM), and a third among male Finnish smokers (ATBC). Two US cohorts were conducted among male and female health professionals (NHS, HPFS) and a third within a cancer screening study (PLCO). All the studies used validated food frequency questionnaires for the dietary assessment. Most of the studies adjusted for age, BMI, smoking and energy intake. The number of cases in the studies ranged from 135 to 363.

Comparison with the Second Expert Report

The Second Expert Report found a marginally significant inverse association between dietary folate and pancreatic cancer risk in cohort studies. However, the result was based on only 2 studies. Several additional studies have been published during the CUP, but the result is not significant. Moderate heterogeneity was observed, mainly due to one study which in contrast to the remaining studies found a positive association.

Published meta-analysis and pooled analysis

A meta-analysis by Larsson et al, 2006 found an inverse association between dietary folate intake and pancreatic cancer risk. The summary RR for high vs. low intake was 0.49 (95% CI: 0.35-0.67), with little heterogeneity, I^2=17.1%, $P_{heterogeneity}$ =0.31, based on results from one case-control study and four cohort studies.

A recent pooled analysis of 14 prospective cohort studies including 319716 men and 542948 women and 2195 cases found no association between dietary folate intake and pancreatic cancer risk (Bao, 2011). The summary RR for the highest vs. the lowest quintile of folate intake was 1.06 (95% CI: 0.90-1.25, $P_{heterogeneity}$ =0.15). When the analysis was restricted to nonusers of supplements containing folic acid the summary RR for the highest vs. the lowest quintile of dietary folate intake was 1.20 (95% CI: 1.01-1.43, $P_{heterogeneity}$ =0.42), although the increased risk was only observed in the highest quintile and there was no linear trend across increasing quintiles. When the analyses were repeated by excluding the follow-up time after the folate fortification (January 1998) for studies conducted in North America, the results did not materially change (highest vs lowest quintile: for dietary folate intake, pooled multivariable RR = 0.99, 95% CI = 0.84 to 1.16, *P*trend = .95).

The six cohort studies included in the meta-analysis of the Continuous Update Project (1102 pancreatic cancer cases) were included in the Pooled Analysis of Prospective Cohort Studies (2195 cases), which with higher number of cases provides stronger evidence of a null association. The summary relative risk estimate per 100 µg/d was 0.89, 95% CI: 0.74-1.07 in the Continuous Update Project and 1.01 (95% CI: 0.95-1.07) in the pooled analysis of cohort studies (Bao, 2011).

Table 133 Studies on dietary folate identified in the CUP

Author, year	Country	Study name	Number of cases	Years of follow-up	Sex	RR	LCI	UCI	Contrast
Keszei, 2009	Netherlands	Netherlands Cohort Study	363	13.3	M/F	1.37	0.97	1.94	>259.1 vs >233.1 vs. <176.3 vs <154.1 µg/d
Oaks, 2009	USA	PLCO Cancer Screening trial	266	6.5	F M	0.47 1.20	0.23 0.70	0.94 2.04	≥253.3 vs ≤179.1 µg/d ≥229.6 vs ≤158.0 µg/d
Larsson, 2006	Sweden	Cohort of Swedish Men and Swedish Mammography Cohort	147	7	M/F	0.37	0.19	0.74	≥350 vs <200 µg/d

Table 134 Overall evidence on dietary folate and pancreatic cancer

	Summary of evidence
SLR	Two cohort studies reported on dietary folate intake and found non-significant inverse associations.
Continuous Update Project	Three cohort studies were identified. Two of the studies found significant inverse associations, which was limited to women in one of these studies. The last study found a non-significant positive association.

Table 135 Summary of results of the dose response meta-analysis of dietary folate and pancreatic cancer

Pancreatic cancer		
	SLR	Continuous Update Project
Studies (n)	2	6[1]
Cases (n)	326	1102
Increment unit used	Per 100 µg/d	Per 100 g/d
Overall RR (95% CI)	0.86 (0.73-1.00)	0.88 (0.74-1.05)
Heterogeneity (I^2, p-value)	0%, p=0.90	59.6%, p=0.03

[1] One study was included in the analysis of total folate intake in the 2nd report, however, it stated in the text that dietary folate was analysed (Stolzenberg-Solomon, 2001).

Table 136 Inclusion/exclusion table for meta-analysis of dietary folate and pancreatic cancer

WCRF code	Author	Year	Study Design	Study name	Subgroup	Cancer outcome	SLR	CUP dose-response meta-analysis	CUP HvL forest plot	Estimated values	Exclusion reason
PAN70000	Keszei	2009	Prospective cohort study	Netherlands Cohort Study	Men/Women	Incidence	New	Yes	Yes		
PAN70002	Oaks	2009	Prospective cohort study	PLCO Cancer Screening Trial	Men/Women	Incidence	New	Yes	Yes	Person-years, Mid-exposure values	
PAN70001	Larsson	2006	Prospective cohort study	Cohort of Swedish Men and Swedish Mammography Cohort	Men/Women	Incidence	New	Yes	Yes	Mid-exposure values	
PAN00006	Skinner	2004	Prospective cohort study	Nurses' Health Study	Women	Incidence	Yes	Yes	Yes	Mid-exposure values	
PAN00006	Skinner	2004	Prospective cohort study	Health Professional's Follow-up Study	Men	Incidence	Yes	Yes	Yes	Mid-exposure values	
PAN07589	Stolzenberg-Solomon	2001	Prospective cohort study	ATBC Study	Men	Incidence	Yes	Yes	Yes		

Figure 156 Highest versus lowest forest plot of dietary folate and pancreatic cancer

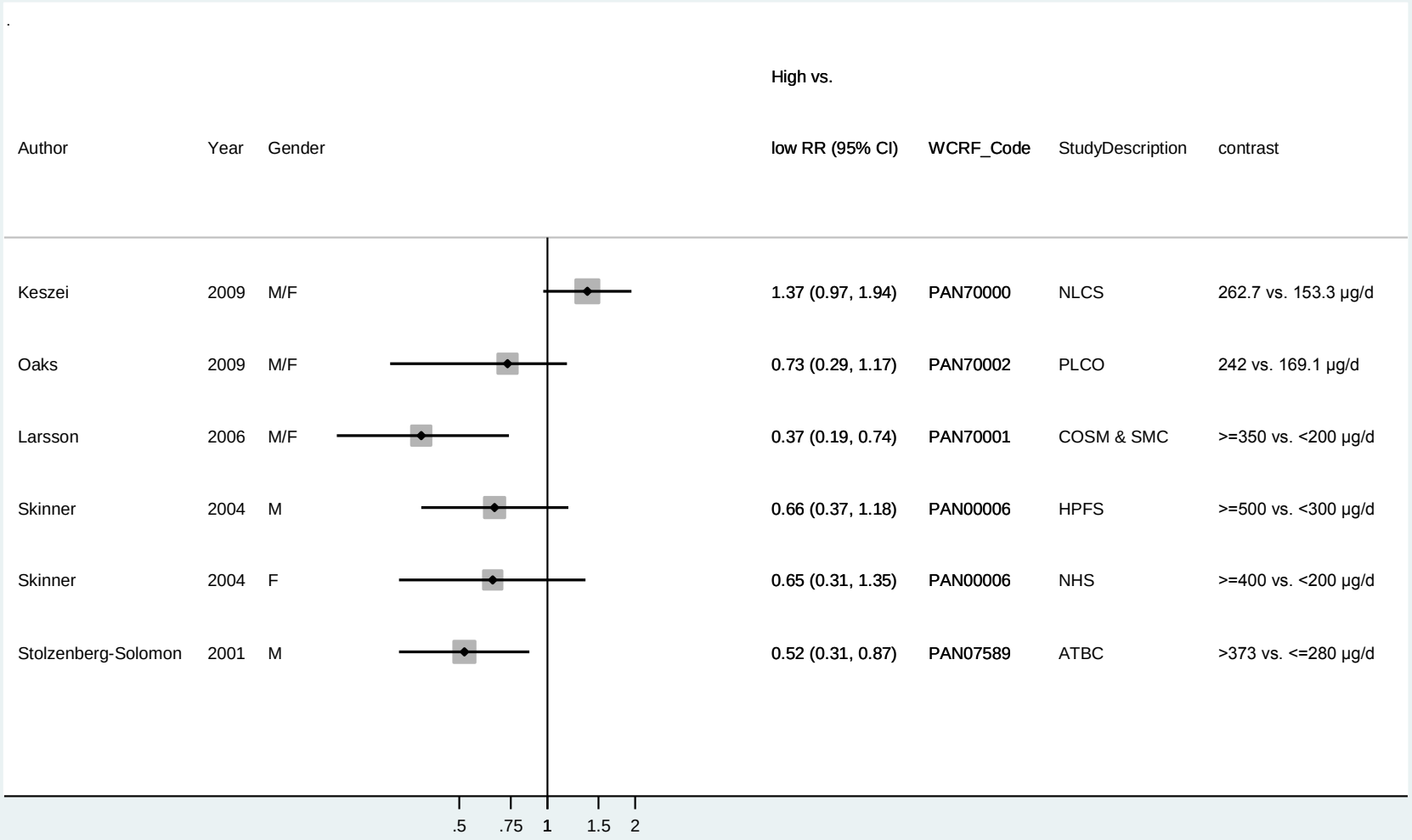


Figure 157 Dose-response meta-analysis of dietary folate and pancreatic cancer - per 100 µg/d

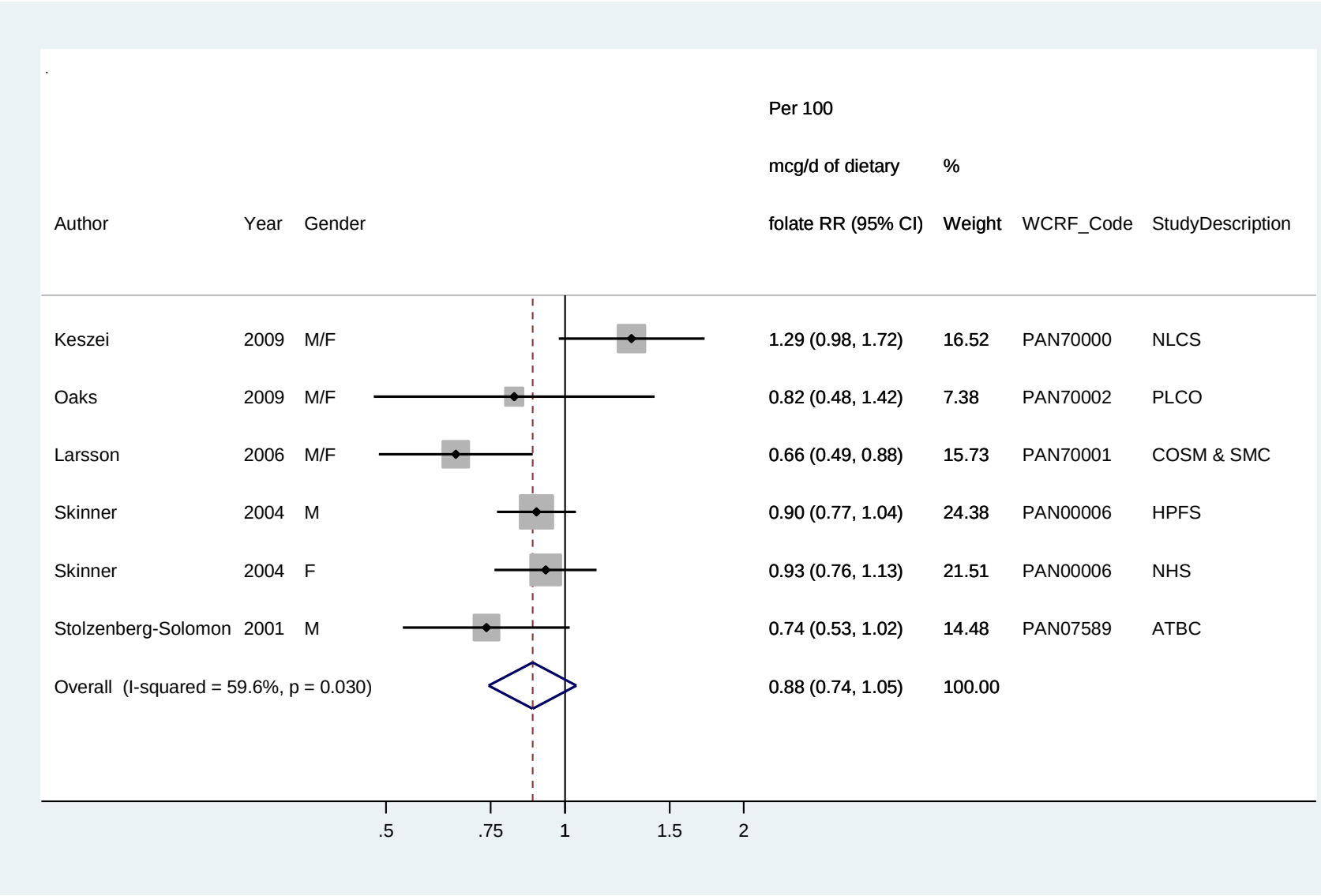


Figure 158 Funnel plot of dietary folate and pancreatic cancer

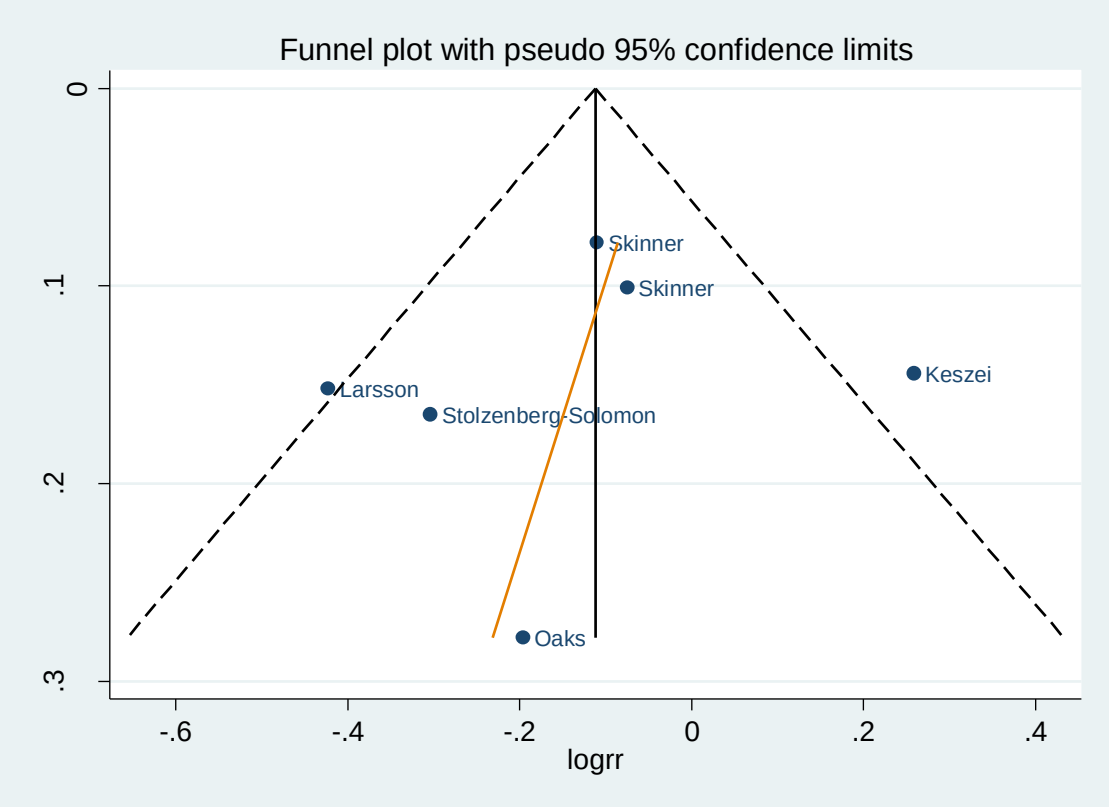


Figure 159 Dose-response graph of dietary folate intake and pancreatic cancer risk

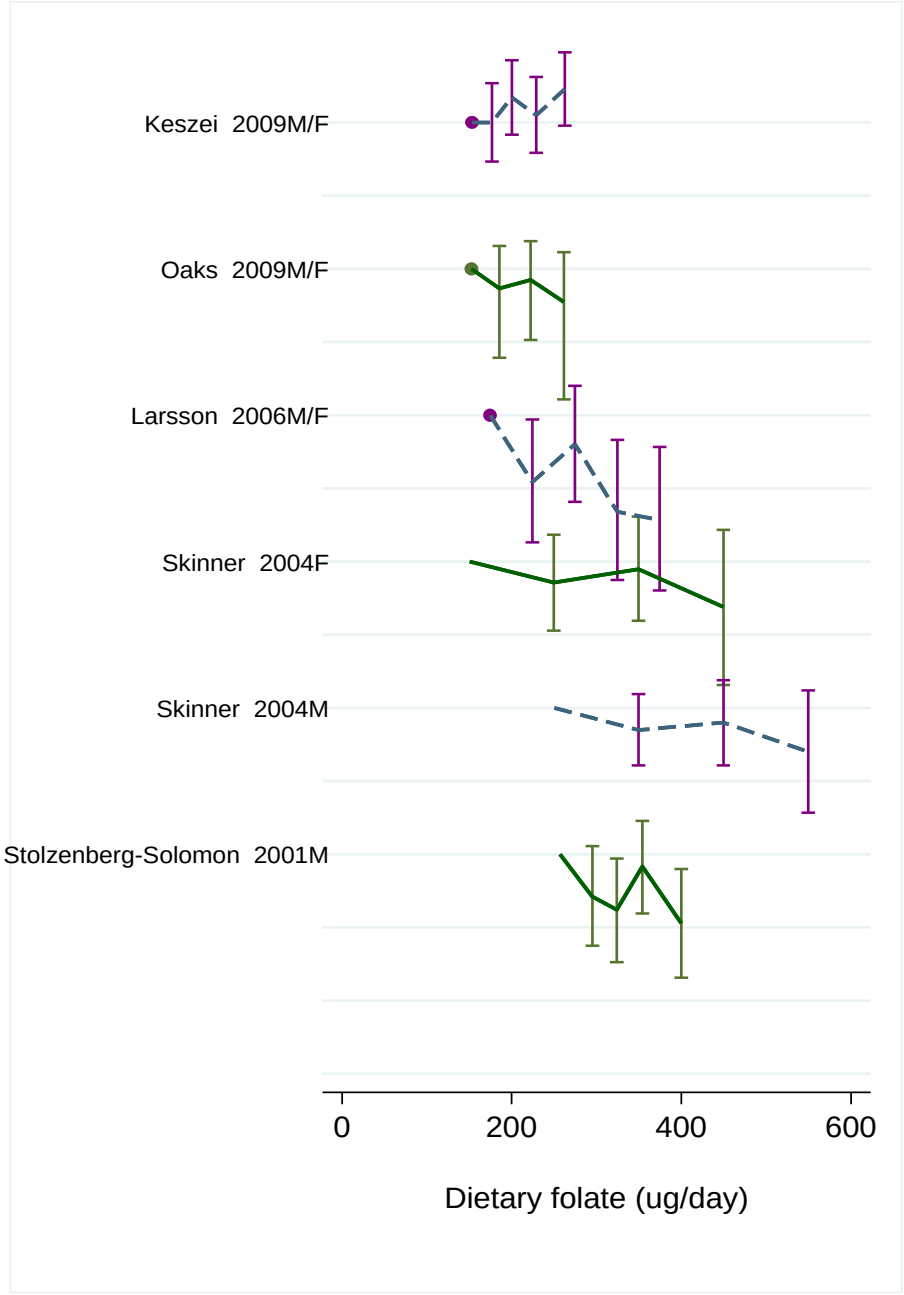


Figure 160 Nonlinear dose-response analysis of dietary folate and pancreatic cancer

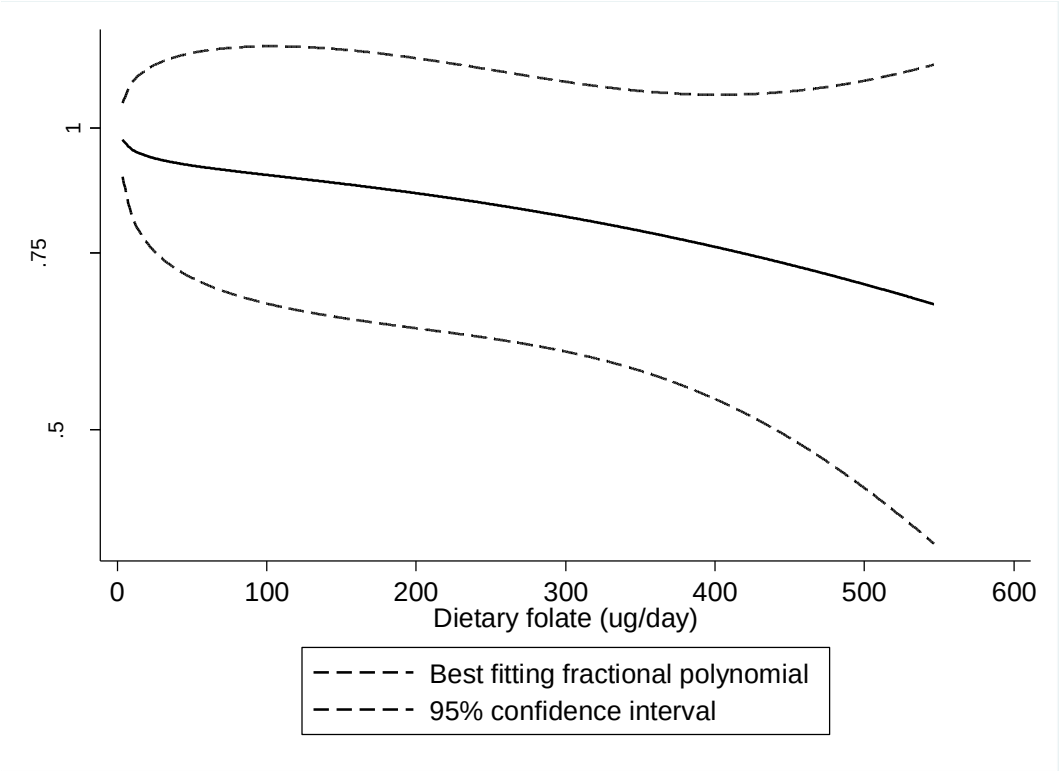


Figure 161 Scatter plot of risk estimates for dietary folate and pancreatic cancer risk

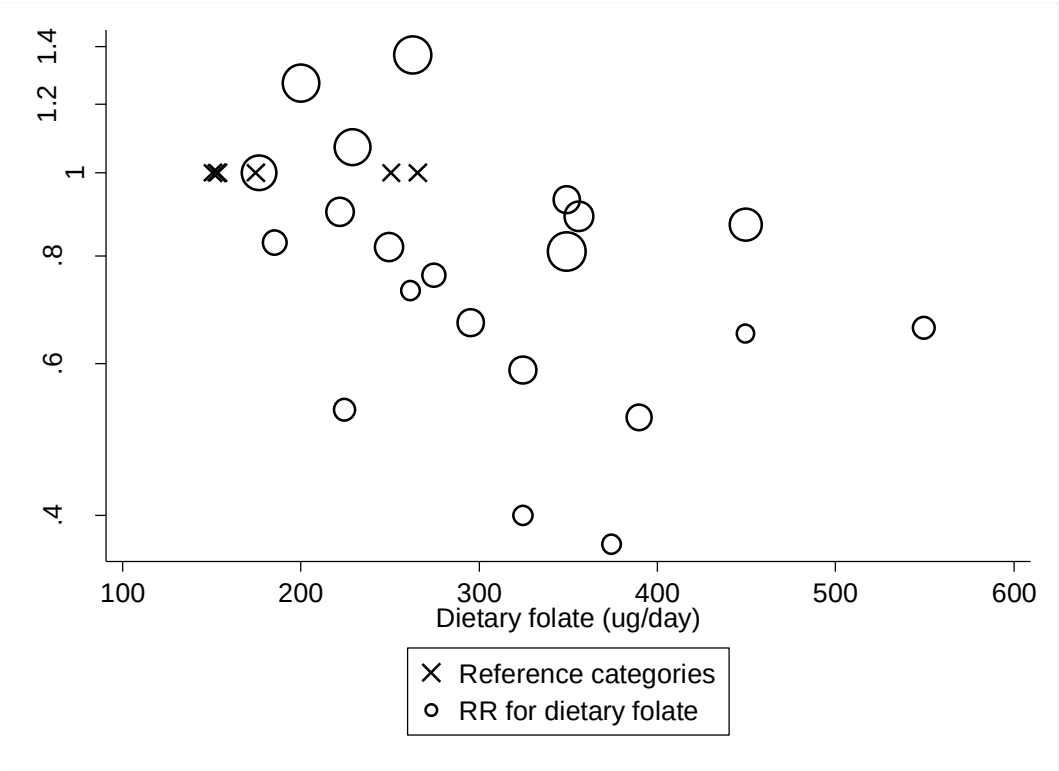


Table 137 Table with dietary folate values and corresponding RRs (95% CIs) for nonlinear analysis of dietary folate and pancreatic cancer

Dietary folate	RR (95% CI)
0 ug/d	1.00
100	0.90 (0.67-1.21)
200	0.86 (0.63-1.17)
300	0.82 (0.60-1.11)
400	0.76 (0.54-1.08)
500	0.70 (0.44-1.11)

5.5.3 Total folate

Methods

A total of four prospective studies have published on total folate intake, two of which were identified in the Continuous Update Project. Dose-response analyses of total folate intake and risk of pancreatic cancer incidence were conducted. The dose-response results are presented for an increment of 100 µg per day.

Main results

Four studies were included in the dose-response analysis of total folate intake and pancreatic cancer risk. There was no significant association (summary RR=0.95, 95% CI: 0.85-1.05) per 100 µg/d, with moderate heterogeneity, I^2=51.2%, p=0.11. The heterogeneity was reduced when the study by Larsson et al, 2006, was excluded, I^2=0%, $P_{heterogeneity}$ =0.59 and the summary RR was similar, summary RR=0.97 (95% CI: 0.91-1.04). There was no evidence of publication bias with Egger's test, p=0.48. It was not possible to fit a nonlinear curve for total folate.

Heterogeneity

There was moderate to high heterogeneity in the analyses (I^2 =51.2%), which was explained by one outlying study.

Comparison with the Second Expert Report

Three cohort studies were included in the 2nd report. The summary RR per 100 µg per day was 0.94 (95% CI: 0.80-1.11, I^2=66.7%, $p_{heterogeneity}$=0.05).

Published pooled analysis

A pooled analysis of 14 prospective cohort studies including 319716 men and 542948 women and 2195 cases found no association between total folate intake and pancreatic cancer risk (Bao, 2011). The summary RR for the highest vs. the lowest quintile of total folate intake was

0.96 (95% CI: 0.80-1.16, $P_{heterogeneity}$ =0.90). When the analyses were repeated by excluding the follow-up time after the folate fortification (January 1998) for studies conducted in North America, the results did not materially change (highest vs lowest quintile: for total folate intake, pooled multivariable RR = 0.92, 95% CI = 0.75 to 1.13, *P*trend = .95).

The four cohort studies included in the meta-analysis of the Continuous Update Project (739 pancreatic cancer cases) were included in the Pooled Analysis of Prospective Cohort Studies (2195 cases) and the relative risks estimates were similar. The summary relative risk estimate per 100 µg/d was 0.95, 95% CI: 0.85-1.05 in the Continuous Update Project and 1.00 (95% CI: 0.97-1.02) in the pooled analysis of cohort studies (Bao, 2011).

Table 138 Studies on total folate identified in the CUP

Author, year	Country	Study name	Number of cases	Years of follow-up	Sex	RR	LCI	UCI	Contrast
Oaks, 2009	USA	PLCO Cancer Screening trial	266	6.5	F M	0.56 0.95	0.30 0.59	1.06 1.54	≥534.3 vs ≤238.9 µg/d ≥413.6 vs ≤186.9 µg/d
Larsson, 2006	Sweden	Cohort of Swedish Men and Swedish Mammograpy Cohort	147	7	M/F	0.42	0.22	0.78	≥350 vs <200 µg/d

Table 139 Overall evidence on total folate and pancreatic cancer

	Summary of evidence
SLR	Three cohort studies were extracted. Two cohort studies reported on total folate intake and found no significant association.
Continuous Update Project	Two cohort studies were identified. One study reported a significant inverse association, while the last study reported no association.

Table 140 Summary of results of the dose response meta-analysis of total folate and pancreatic cancer.

Pancreatic cancer		
	SLR	Continuous Update Project
Studies (n)	3	4
Cases (n)	483	739
Increment unit used	Per 100 µg/d	Per 100 µg /d
Overall RR (95% CI)	0.94 (0.80-1.11)	0.95 (0.85-1.05)
Heterogeneity (I^2, p-value)	0%, p=0.90	51.2%, p=0.11

Table 141 Inclusion/exclusion table for meta-analysis of total folate and pancreatic cancer

WCRF code	Author	Year	Study Design	Study name	Subgroup	Cancer outcome	SLR	CUP dose-response meta-analysis	CUP HvL forest plot	Estimated values	Exclusion reason
PAN70002	Oaks	2009	Prospective cohort study	PLCO Cancer Screening Trial	Men/Women	Incidence	New	Yes	Yes	Person-years, Mid-exposure values	
PAN70001	Larsson	2006	Prospective cohort study	Cohort of Swedish Men and Swedish Mammography Cohort	Men/Women	Incidence	New	Yes	Yes	Mid-exposure values	
PAN00006	Skinner	2004	Prospective cohort study	Nurses' Health Study	Women	Incidence	Yes	Yes	Yes	Mid-exposure values	
PAN00006	Skinner	2004	Prospective cohort study	Health Professional's Follow-up Study	Men	Incidence	Yes	Yes	Yes	Mid-exposure values	

Figure 162 Highest versus lowest forest plot of total folate and pancreatic cancer

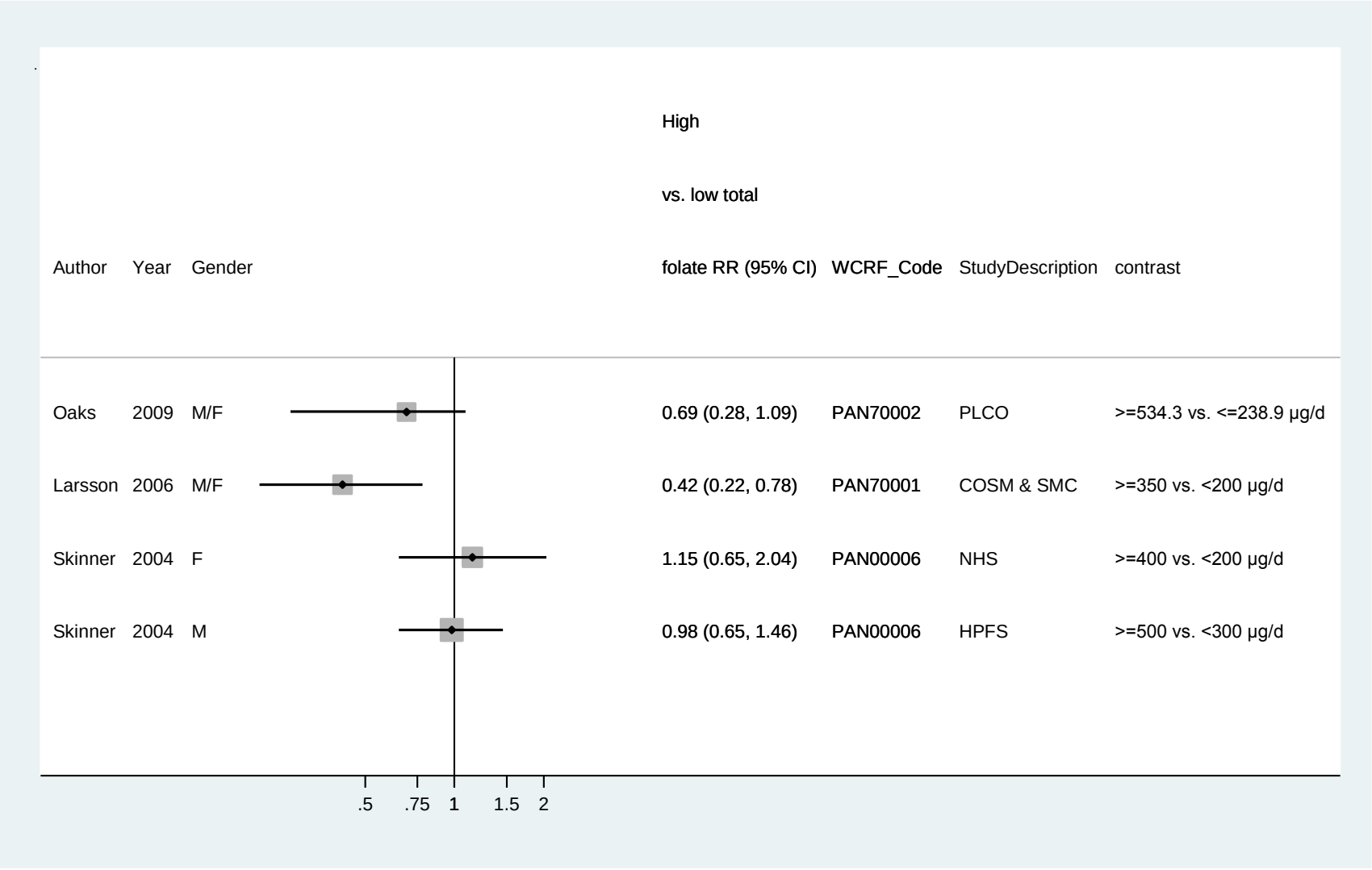


Figure 163 Dose-response meta-analysis of total folate and pancreatic cancer - per 100 µg/d

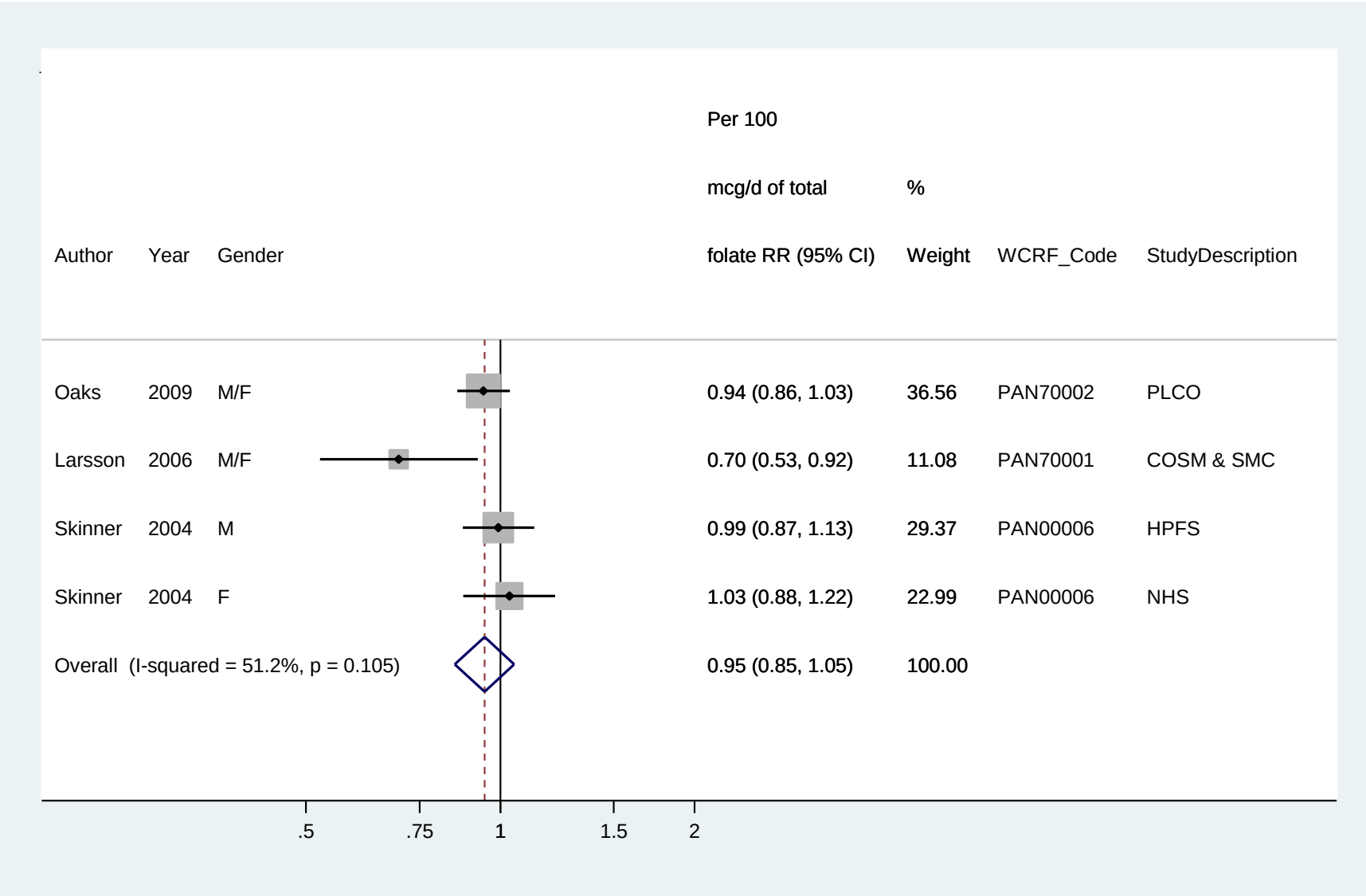
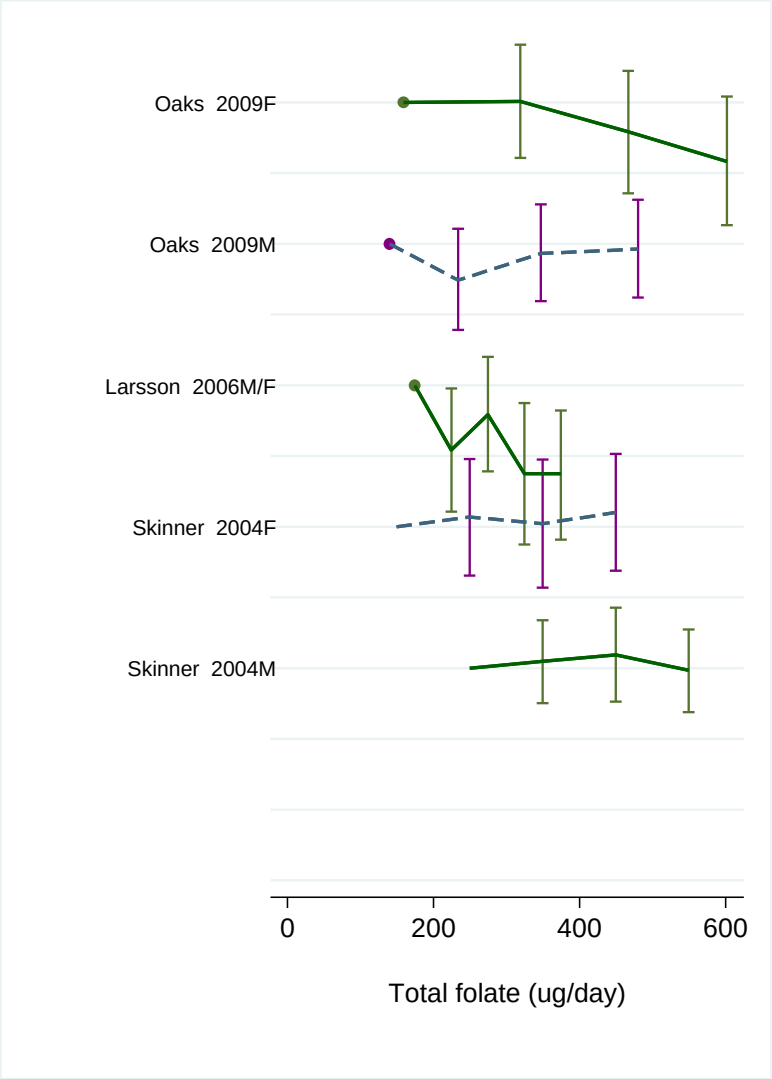


Figure 164 Dose-response graph of total folate intake and pancreatic cancer



5.5.3 Folate, blood

One report from the EPIC study was identified during the continuous update (Chuang, 2011). The results suggest a weak inverse U-shaped association between pancreatic cancer risk but none of the relative risk estimates were statistically significant. Compared to those with adequate plasma folate concentrations (10–15 nmol/L), participants with high plasma folate concentrations (>20 nmol/L) had a similar risk (RR= 1.34; 95% CI: 0.89–2.02) as those with moderate deficiency (5–10 nmol/L)(RR= 1.39; 95% CI: 0.93–2.08).
Serum folate was inversely related to pancreatic cancer risk in male smokers in a nested case-control study identified during the review for the Second Expert Report ($RR_{>4.45 \text{ vs } <3.33 \text{ ng/mL}}$ = 0.45; 95% CI: 0.24–0.82) (Stolzenberg-Solomon, 1999).

5.5.9 Vitamin C

Methods

Five cohort studies were identified, two of which were identified during the CUP. Dose-response meta-analysis for pancreatic cancer was performed in the previous SLR report. In this report, a meta-analysis including 4 different studies (2 studies identified during the CUP and 2 studies identified during the 2007 SLR) was performed.

Main results

The summary RR per 30mg/day was 1.00 (95% CI: 0.96-1.05; $P_{heterogeneity}$=0.27, 4 studies) for incidence or mortality of pancreatic cancer. The overall results remained the same when one study with mortality as outcome was excluded from the analysis, RR= 0.96 (95% CI: 0.90-1.02). The only study on men reported a RR per 30mg/day of 0.96 (95% CI: 0.83-1.12) and the only study on women reported a RR per 30mg/day of 0.96 (95% CI: 0.87-1.05).

Heterogeneity

Low heterogeneity was observed overall (I^2= 23.0%, p=0.27). Egger's tests suggested some evidence of publication bias, p= 0.03.

Comparison with the Second Expert Report

Overall, vitamin C was not associated with the risk of pancreatic cancer. RR for an increase of 30mg/day = 1.00 (95% CI: 0.96-1.05) was similar to that reported in the previous SLR report (RR for 30mg/day was 0.96 (95% CI: 0.88 -1.04).

Table 142 Studies on dietary vitamin C intake identified in the CUP

Author, year	Country	Study name	Cases	Years of follow up	Sex	RR	LCI	UCI	Contrast
Inoue-Choi M, 2011	USA	Iowa Women's Health Study	256	16.3	F	0.99	0.66	1.49	678.55 vs 82.40 mg/day
Heinen, 2011	Netherlands	Netherlands Cohort Study	423	16.3	M/F	1.0	0.74	1.33	135.4 vs 55.6 mg/day

Table 143 Overall evidence on dietary vitamin C intake and pancreatic cancer

	Summary of evidence
SLR	Three prospective cohort studies provided data. Two were used in the meta-analysis. The summary relative risk from these two studies was 0.96 (95% CI: 0.88 to 1.04) p=0.3 per 30 mg/day of vitamin C.
Continuous Update Project	Two cohort studies were identified. One reported on females and the other on male and female. None of the studies found an association between dietary vitamin C intake and pancreatic cancer. Four studies were included in the high versus low analysis.

Table 144 Summary of results of the dose response meta-analysis of dietary vitamin C intake and pancreatic cancer

Pancreatic cancer		
	SLR	Continuous Update Project
Studies (n)	2	4
Cases (n)	228	907
Increment unit used	Per 30mg/day	Per 30mg/day
Overall RR (95%CI)	0.96 (0.88 -1.04)	1.00 (0.96-1.05)
Heterogeneity (I^2,p-value)	0%, p=0.9	23.0%, p=0.27

Table 145 Inclusion/exclusion table for meta-analysis of dietary vitamin C intake and pancreatic cancer

WCRF_Code	Author	Year	Study Design	Study Name	Subgroup	Cancer Outcome	SLR	CUP dose-response meta-analysis	CUP HvL forest plot	Estimated values	Exclusion reasons
PAN70063	Inoue-Choi M	2011	Prospective Cohort study	Iowa Women's Health Study	Women	Incidence	New	Yes	Yes	Person years per quintile	
PAN70064	Heinen	2011	Prospective Cohort study	Netherlands Cohort Study	Men/Women	Mortality	New	Yes	Yes	Mid-exposure values	
PAN07590	Stolzenberg-Solomon	2002	Prospective Cohort study	Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study	Men	Incidence	Yes	Yes	Yes	Mid-exposure values, cases/person years per quintile	
PAN07562	Shibata	1994	Prospective Cohort study	Leisure World Cohort Study	Men/Women	Incidence	Yes	Yes	Yes	Mid-exposure values	
PAN66832	Enstrom	1992	Prospective Cohort study	National Health and Nutrition Examination Survey (NHANES I)	Men/Women	Mortality	Yes	No	No		only unadjusted results

Figure 165 Highest versus lowest forest plot of dietary vitamin C intake and pancreatic cancer

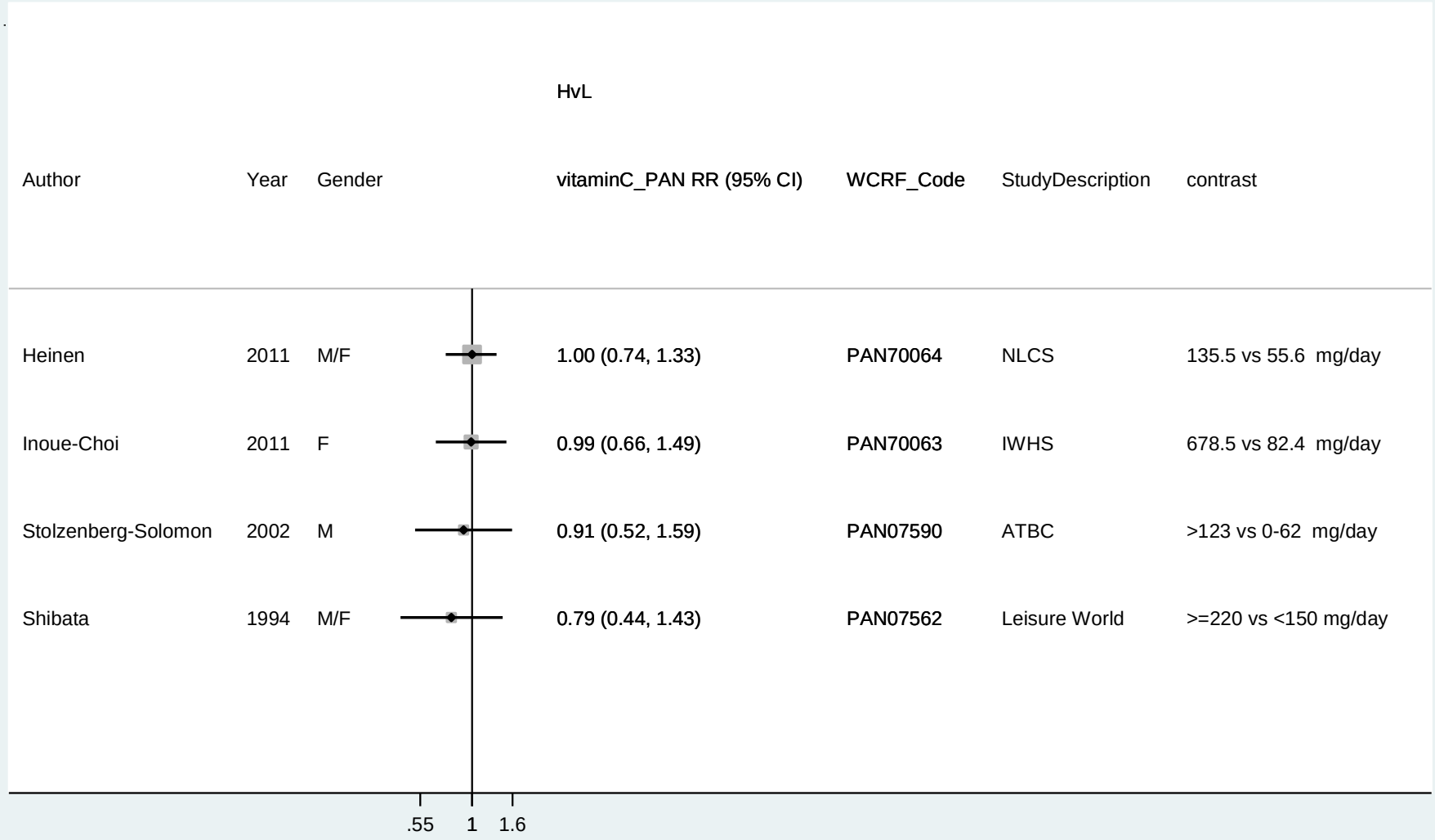


Figure 166 Dose-response meta-analysis of dietary vitamin C intake and pancreatic cancer – per 30mg/day

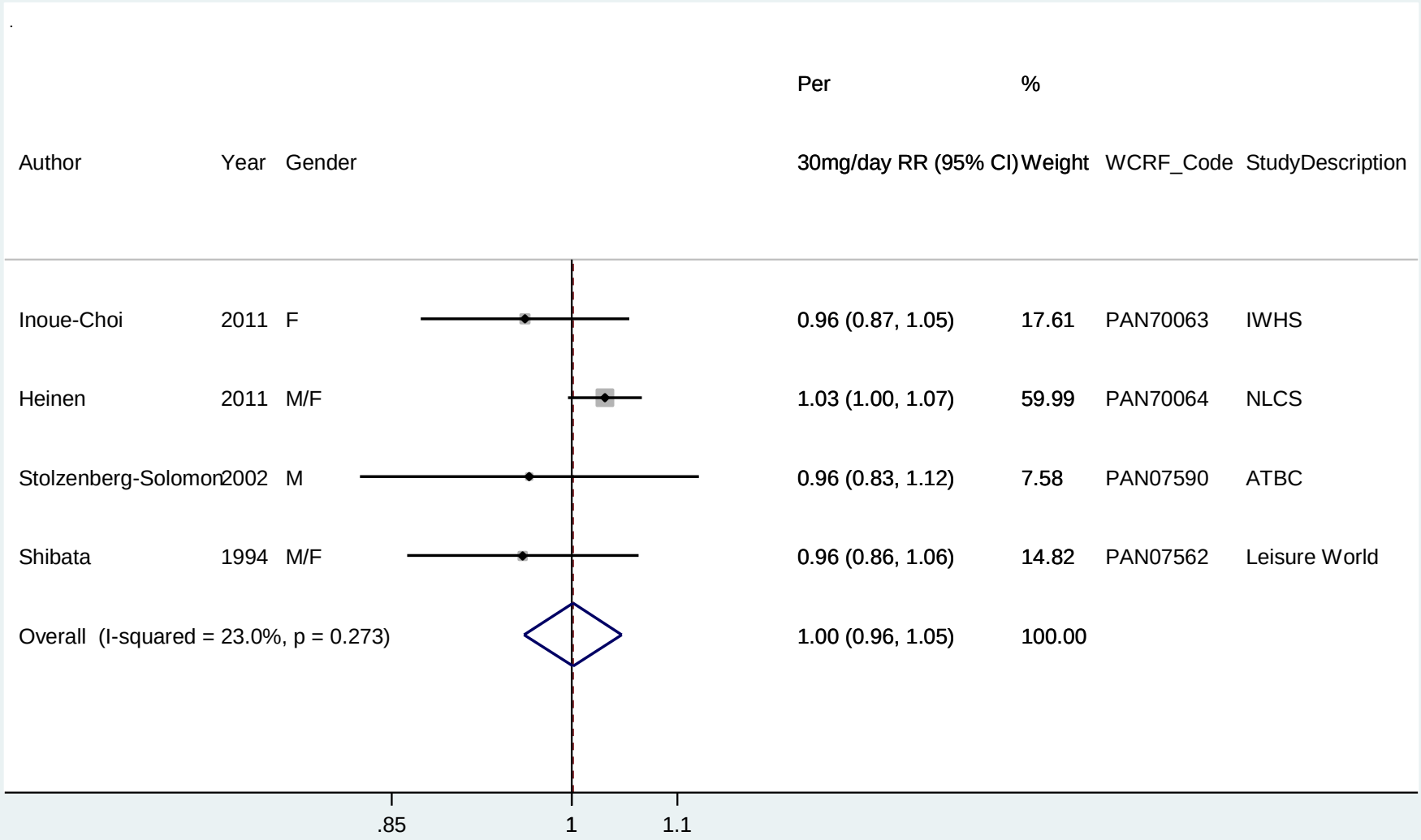
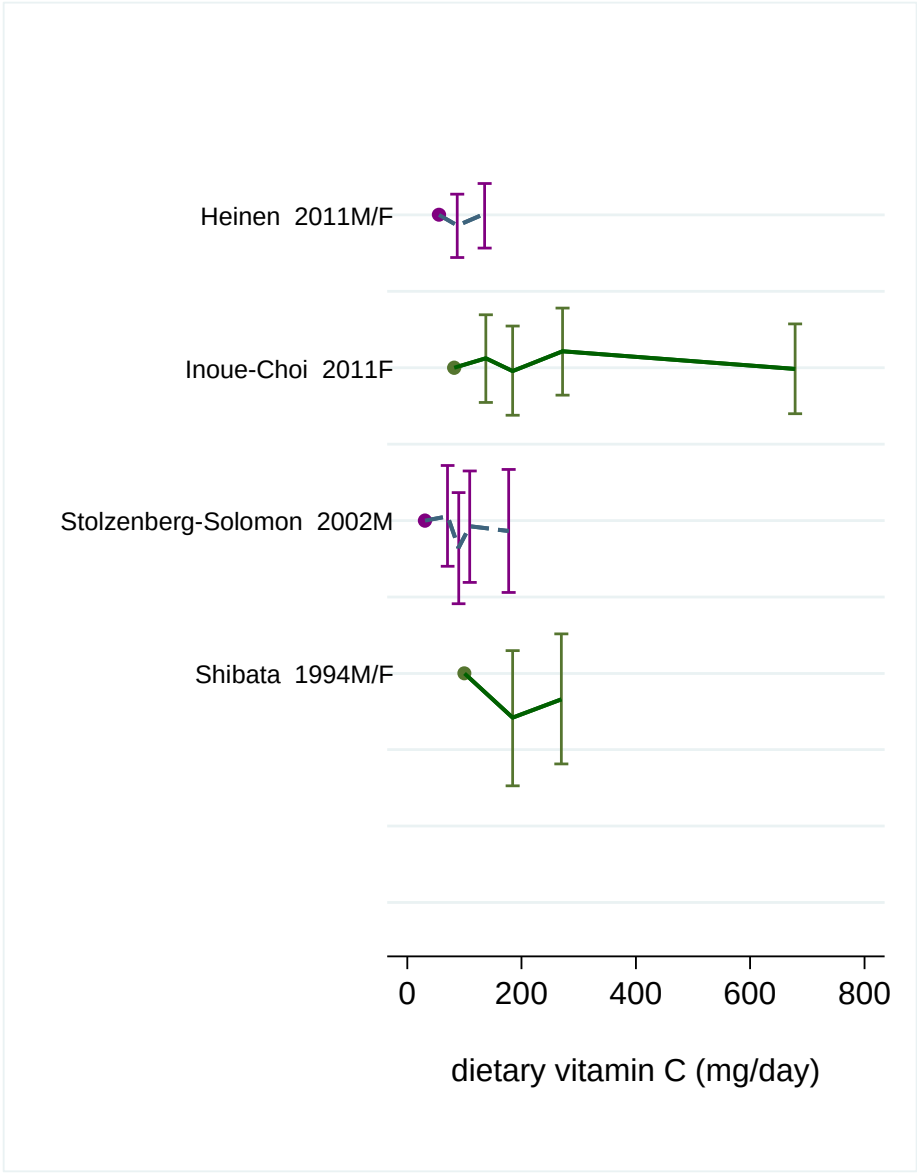


Figure 167 Dose-response graph of dietary vitamin C and pancreatic cancer



5.5.13 Multivitamin/mineral supplements

Methods

Overall six cohort studies on multivitamin/mineral supplements and pancreatic cancer (the Cohort of Swedish Men and the Swedish Mammography Cohort are counted as one because pooled results were published), three cohort studies were identified on in the Continuous Update Project.

Dose-response analyses were not conducted because the results in most of the studies were reported comparing users with nonusers of multivitamin/mineral supplements.

Main results

The summary RR for users compared with nonusers of multivitamin/mineral supplements was 1.03 (95% CI: 0.75-1.42) with substantial heterogeneity I^2=71.7%, p=0.007. Excluding one study with minimal adjustments (age, diabetes, smoking) reduced the heterogeneity and the summary RR became 1.20 (95% CI: 0.96-1.49, I^2=39.4%, $p_{heterogeneity}$=0.18). There was some suggestion of small study effects with Egger's test, p=0.07, with small positive studies missing. However, when excluding the minimally adjusted study Egger's test showed p=0.35.

Heterogeneity

There was high heterogeneity (I^2=71.7%, p=0.007) in the analyses, but this was explained by one study.

Comparison with the Second Expert Report

There was no association between use of multivitamins and pancreatic cancer risk in this meta-analysis. No meta-analysis was conducted in the Second Expert Report.

Table 146 Studies on multivitamin supplements identified in the CUP

Author, year	Country	Study name	Number of cases	Sex	Years of follow-up	RR	LCI	UCI	Contrast
Oaks, 2009	USA	PLCO Cancer Screening Trial	266	M/F	6.5	0.86	0.53	1.19	Use vs. non-use
Larsson, 2006	Sweden	Cohort of Swedish Men and Swedish Mammography Cohort	135	M/F	6.8	1.11	0.70	1.77	Use vs. non-use

Table 147 Overall evidence on multivitamin supplements and pancreatic cancer

	Summary of evidence
SLR	Three studies that reported risk estimates were identified. One study reported a significant reduction in risk, one reported a significant increase in risk and another study reported a non-significant increase in risk.
Continuous Update Project	Two studies have been published up to 2011, and both of these reported no significant association.

Table 148 Summary of results of the meta-analysis of multivitamin/mineral supplements and pancreatic cancer

Pancreatic cancer		
	SLR*	Continuous Update Project
Studies (n)	-	5
Cases (n)	-	672
Increment unit	-	Use vs. non-use
RR (95% CI)	-	1.03 (0.75-1.42)
Heterogeneity (I^2, p-value)	-	71.7%, p=0.007

*No meta-analysis was conducted in the 2nd report.

Table 149 Inclusion/exclusion table for meta-analysis of multivitamin/minerals and pancreatic cancer

WCRF code	Author	Year	Study design	Study name	Subgroup	Cancer outcome	SLR	CUP dose-response meta-analysis	CUP HvL forest plot	Estimated values	Exclusion reason
PAN70002	Oaks	2009	Prospective cohort study	PLCO Cancer Screening Trial	Men/women	Incidence	New	No	Yes		
PAN70001	Larsson	2006	Prospective cohort study	Cohort of Swedish Men/ Swedish Mammography Cohort Study	Men/women	Incidence	New	No	Yes		
PAN00006	Skinner	2004	Prospective cohort study	Health Professionals Follow-up study	Men	Incidence	Yes	No	Yes	Results for former and current users were combined	
PAN00006	Skinner	2004	Prospective cohort study	Nurses' Health Study	Women	Incidence	Yes	No	Yes	Results for former and current users were combined	
PAN15635	Anderson	2002	Prospective cohort study	Iowa Women's Health Study	Women	Incidence	Yes	No	Yes		
PAN07562	Shibata	1994	Prospective cohort study	Leisure World Cohort study	Men/women	Incidence	Yes	No	No		No measure of the association

Figure 168 Highest versus lowest forest plot of multivitamin/mineral supplements and pancreatic cancer - use vs. no use

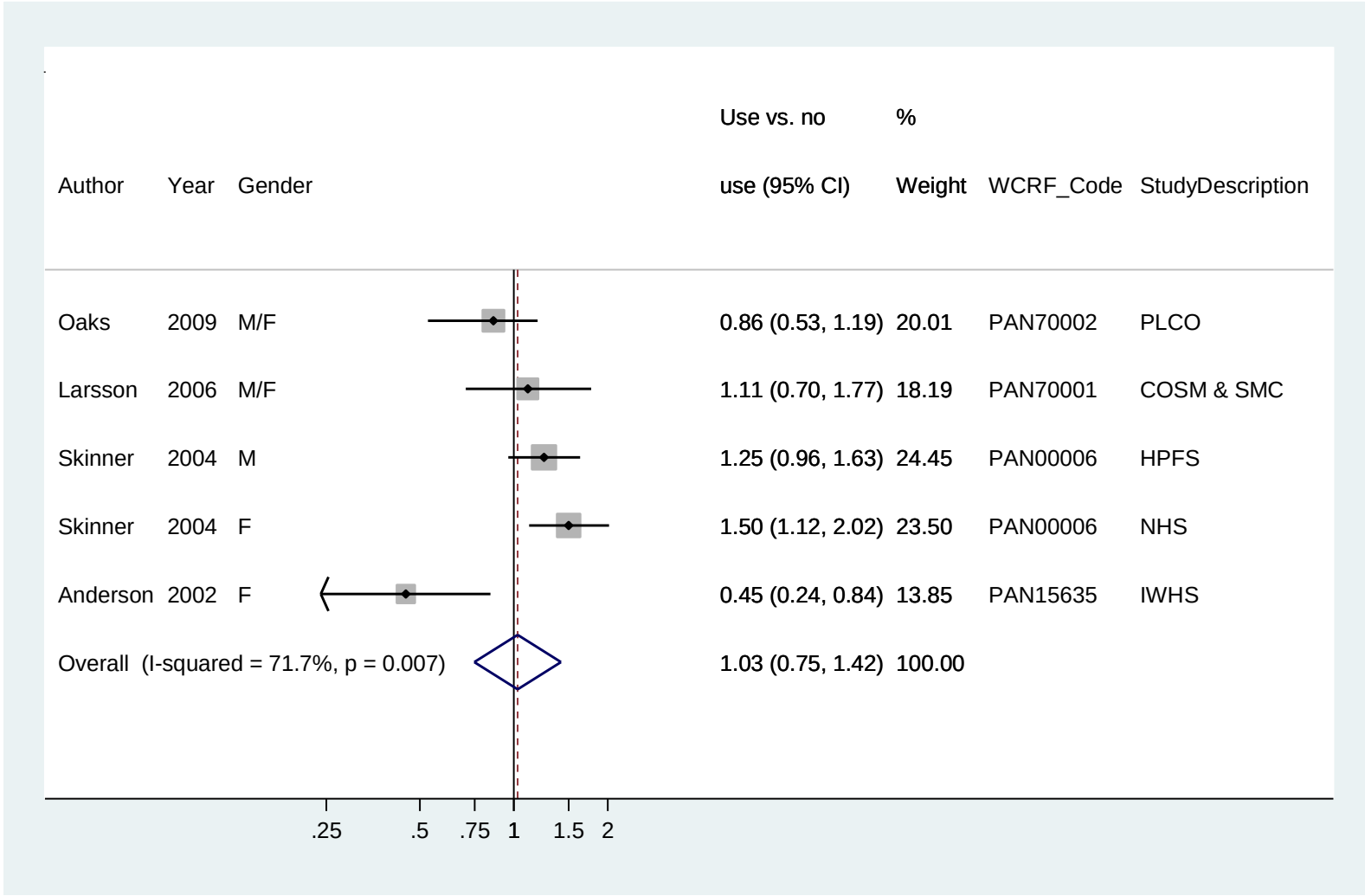
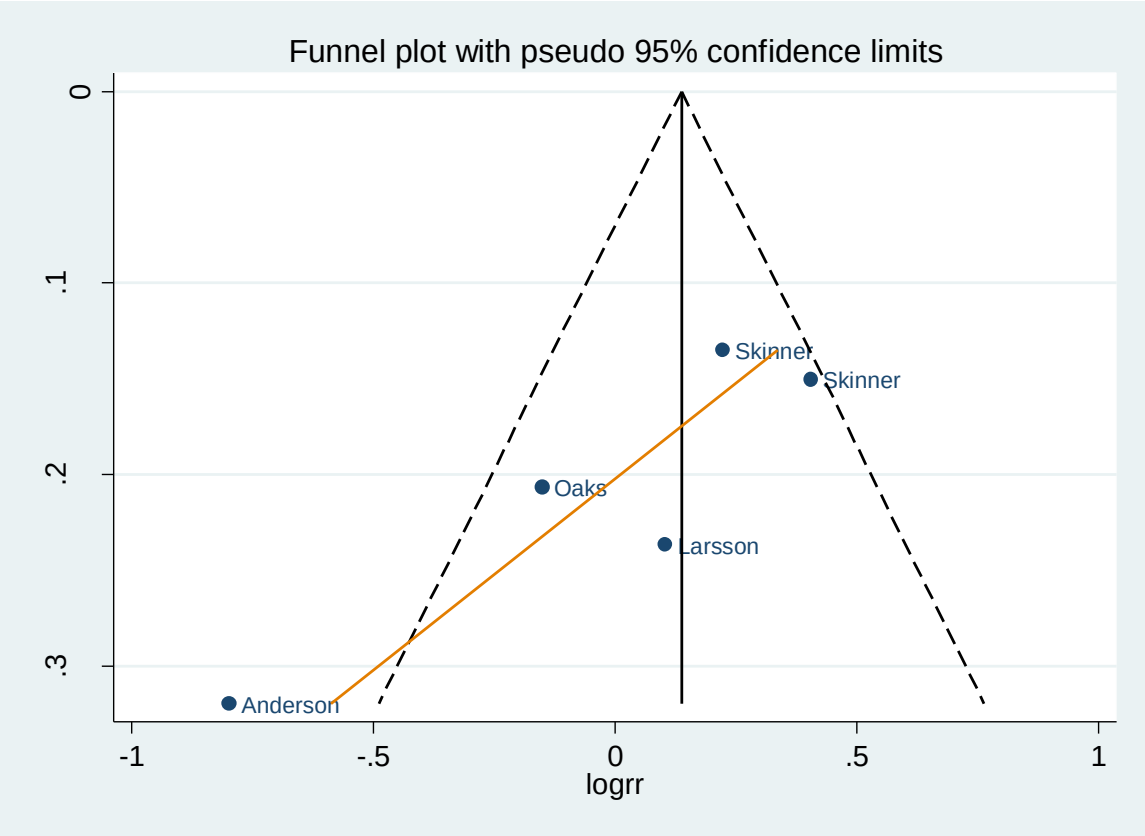


Figure 169 Funnel plot of multivitamin use and pancreatic cancer



6 Physical activity

Methods

Thirteen reports from eleven cohort studies on physical activity and pancreatic cancer risk were identified in the Continuous Update Project.

Four of these studies reported on total physical activity, nine studies from eight cohort studies reported on physical activity during leisure time- including walking, exercising, stair climbing, sports- and three studies reported on vigorous or strenuous activities. Two studies reported on moderate activities and one study each on light activities, occupational activity and time spent watching television.

Physical activity was assessed through different questionnaires and the data were presented differently. For this reason, dose-response meta-analyses were not always possible and when conducted, some studies could not be included in these.

Overall, most of the results are null for all types of activities investigated.

In a pooled analysis of seven prospective cohorts including 2,454 incident pancreatic cancer cases, high levels of physical activity were associated with significantly reduced risk for all the participants (RR 0.90; 95% CI 0.82–0.99, adjusting for sex, BMI, smoking history, cohort and diabetes), but not for never smokers (RR 1.04; 95% CI 0.88–1.24) (Jiao et al, 2009). In a sensitivity analysis including all the studies published so far and the results of the pooling project (excluding the AARP and the ATBC studies which were included in the pooling project), the overall estimate for the highest compared to the lowest level of leisure-time physical activity is: 0.94 (95% CI: 0.87-1.01, I^2=10.1%, $p_{heterogeneity}$=0.34).

6.1 Total physical activity

Methods

Total physical activity was defined as the total amount of leisure-time and occupational physical activities. A total of five studies were included in the analysis of total physical activity and pancreatic cancer incidence, four of which were identified in the Continuous Update Project. Three of the studies could be included in dose-response meta-analysis. A dose-response meta-analysis was not conducted in the 2007 WCRF/AICR report.

Main results

The summary RR of the three studies that reported on METs was 0.81 (95% CI: 0.64-1.02, I^2=0%, $P_{heterogeneity}$ =0.39) per 20 METs per day (n=3). Because of the low number of studies no tests for publication bias were carried out.

Heterogeneity

There was no evidence of heterogeneity in the overall analysis.

Comparison with the Second Expert Report

There was a non-significant inverse association between total physical activity and pancreatic cancer risk in this meta-analysis. No meta-analysis was conducted in the Second Expert Report.

Published meta-analyses

A meta-analysis of four cohort studies found no significant association between high total physical activity and pancreatic cancer risk, summary RR = 0.76 (95% CI: 0.53-1.09) (Bao, 2008).

A more recent meta-analysis which included five cohort studies found a reduced risk for high vs. low total physical activity, summary RR= 0.72 (95% CI: 0.52-0.99) (O'Rorke, 2010). No dose-response analyses were conducted.

In comparison with these meta-analyses the summary RR for high vs. low total physical activity in our analysis was 0.74 (95% CI: 0.55-1.00, I^2=48%).

In a pooled analysis of primary data of seven prospective cohorts including in which 2,454 patients with incident pancreatic cancer were identified during an average 6.9 years of follow-up, high levels of physical activity were associated with significantly reduced risk for all the participants (RR 0.90; 95% CI 0.82–0.99, adjusting for sex, BMI, smoking history, cohort and diabetes), but not for never smokers (RR 1.04; 95% CI 0.88–1.24) (Jiao et al, 2009).

Table 150 Studies on total physical activity identified in the CUP

Author, year	Country	Study name	Number of cases	Sex	Years of Follow-up	RR	LCI	UCI	Contrast
Calton, 2008	USA	Breast Cancer Detection Demonstration Project	70	F	12 years	0.52	0.26	1.05	63.44+ vs. 50.1 METs/d
Inoue, 2008	Japan	Japan Public Health Center-based Prospective Study	145	M F	7.5 years	0.55 1.29	0.30 0.62	1.00 2.67	42.65 vs. 25.45 METs/d 42.65 vs. 26.1 METs/d
Nothlings, 2007	USA	Multiethnic Cohort Study	472	M F	8 years	1.24 0.81	0.85 0.55	1.84 1.20	1.82 vs. 1.46 METs/hr 1.76 vs. 1.41 METs/hr
Berrington de Gonzalez, 2006	European countries	EPIC study	324 cases	M/F	6 years	0.82	0.50	1.35	Very active vs. inactive

Table 151 Overall evidence on total physical activity and pancreatic cancer

	Summary of evidence
SLR	Three publications from two studies were included, but showed no clear association. No meta-analysis was conducted. There was limited suggestive evidence that physical activity decreases pancreatic cancer risk.
Continuous Update Project	Four new studies on total physical activity and pancreatic cancer have been published. Three studies reported non-significant inverse associations between total physical activity and pancreatic cancer. One of these studies reported a non-significant positive association among men.

- The three publications reviewed under Total Physical Activity in the 2007 SLR are reviewed in the CUP under Leisure Time Physical Activity.

Table 152 Summary of results of the dose-response meta-analysis of total physical activity and pancreatic cancer

Pancreatic cancer incidence		
	SLR	Continuous Update Project
Studies (n)	-	3
Cases (n)	-	687
Increment unit	-	Per 20 METs/d
RR (95% CI)	-	0.81 (0.64-1.02)
Heterogeneity (I^2, p-value)	-	0%, p=0.39
By gender		
Men	-	0.83 (0.31-2.20), n=2
Heterogeneity (I^2, p-value)	-	80%, p=0.03
Women	-	0.77 (0.58-1.02), n=3
Heterogeneity (I^2, p-value)	-	0%, p=0.43

Table 153 Inclusion/exclusion table for meta-analysis of total physical activity and pancreatic cancer

WCRF code	Author	Year	Study design	Study name	Subgroup	Cancer outcome	SLR	CUP dose-response meta-analysis	CUP HvL forest plot	Estimated values	Exclusion reason
PAN70040	Calton	2008	Prospective Cohort study	Breast Cancer Detection Demonstration Project	Women	Incidence	New	Yes	Yes	Mid-exposure values	
PAN70081	Inoue	2008	Prospective Cohort study	Japan Public Health Center-based Prospective Study	Men/women	Incidence	New	Yes	Yes		
PAN70035	Nothlings	2007	Prospective Cohort study	Multiethnic Cohort Study	Men /women	Incidence	New	Yes	Yes	Mid-exposure values, person-years	
PAN70038	Berrington de Gonzalez	2006	Prospective Cohort study	The EPIC study	Men /women	Incidence	New	No	Yes		No quantification of total physical activity
PAN07586	Stolzenberg-Solomon	2002	Prospective Cohort study	ATBC Cohort study	Men (smokers)	Incidence	Yes	No	Yes		No quantification of total physical activity

Figure 170 Highest versus lowest forest plot of total physical activity pancreatic cancer

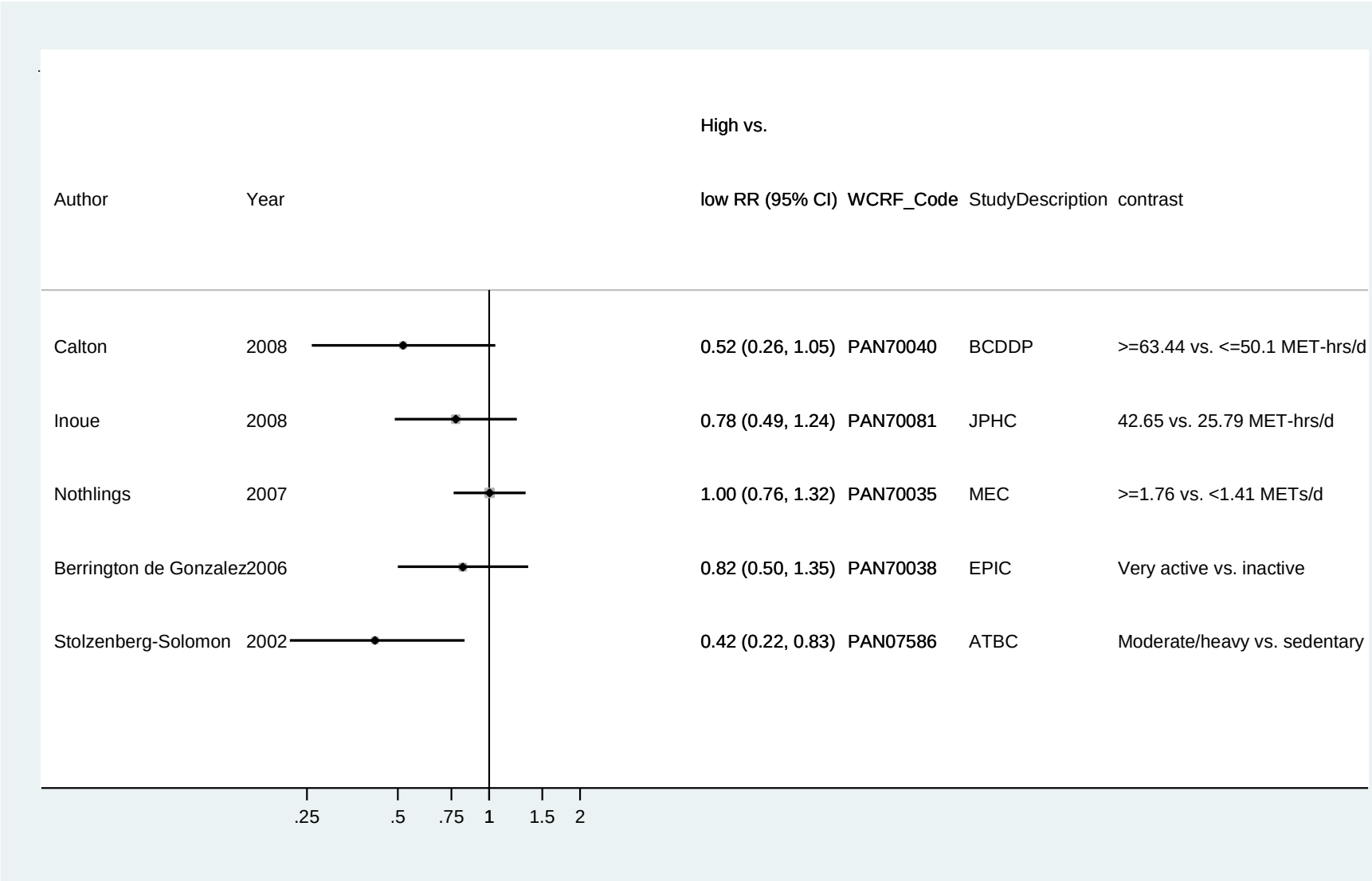


Figure 171 Dose-response meta-analysis of total physical activity and pancreatic cancer - per 20 METs per day

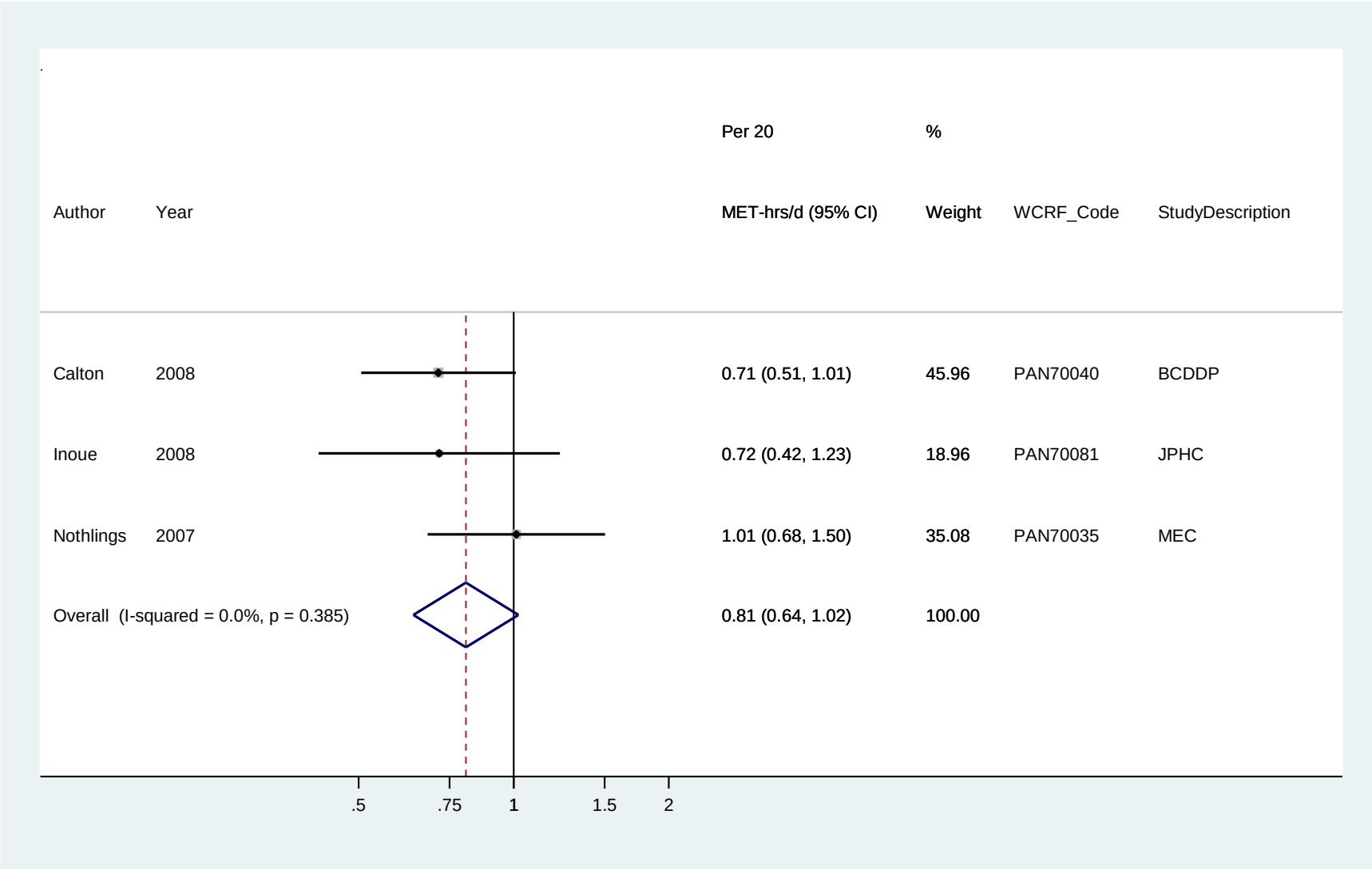


Figure 172 Dose-response graph of total physical activity and pancreatic cancer

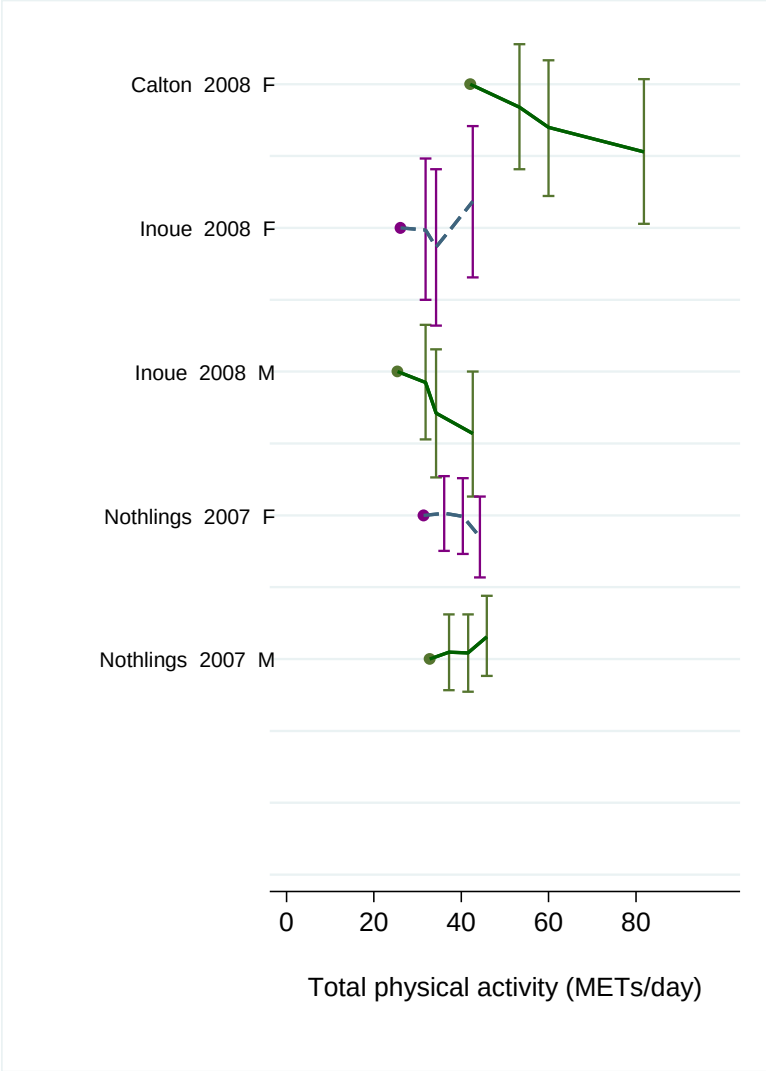
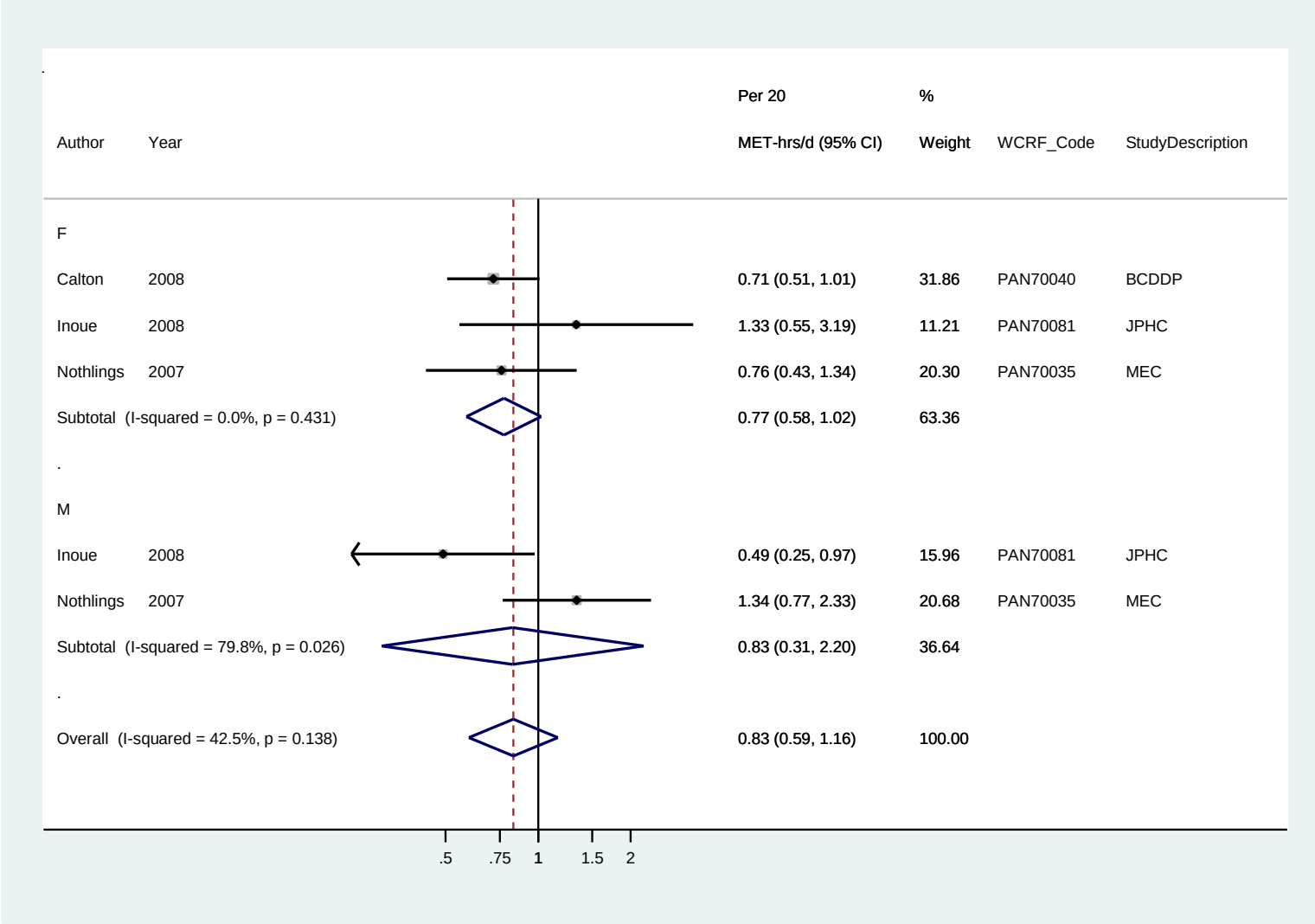


Figure 173 Dose-response meta-analysis of total physical activity and pancreatic cancer, stratified by sex - per 20 METs per day



6.1.1.1 Occupational activity

Methods

One study was identified during the Continuous Update Project (EPIC). No significant association with pancreatic cancer was observed.

Four other studies were published before the SLR for the Second Expert Report 2007. Significant increased risks of pancreatic cancer were observed in individuals with "sedentary" occupation compared to "physical" in a twin study in Sweden (Isaksson 2002 PAN70058) and in one study comparing men and women who felt 'worn out' after work compared to those in the lowest tertile of occupational activity (Nilsen, 2000 PAN14732). No significant association was observed with energy level at work in one study (Paffenbarger PAN18101*) and for* moderate/heavy work compared to sedentary work in the other study (Stolzenberg-Solomon, 2002 PAN07586).

Comparison with the Second Expert Report

No meta-analysis was conducted in the Second Expert Report.

Published meta-analyses

A meta-analysis of case-control and cohort studies found a reduced risk with occupational physical activity, summary RR = 0.75 (95% CI: 0.58-0.96) (Bao, 2008).

A more recent meta-analysis also found a reduced risk with occupational physical activity, summary RR = 0.75 (95% CI: 0.59-0.96) (O'Rorke, 2010).

Table 154 Studies on occupational physical activity identified in the CUP

Author, year	Country	Study name	Number of cases	Sex	Years of Follow-up	RR	LCI	UCI	Contrast
Berrington de Gonzalez, 2006	European countries	EPIC	324	M/F	6 years	0.88	0.60	1.29	Manual, heavy manual vs. sitting

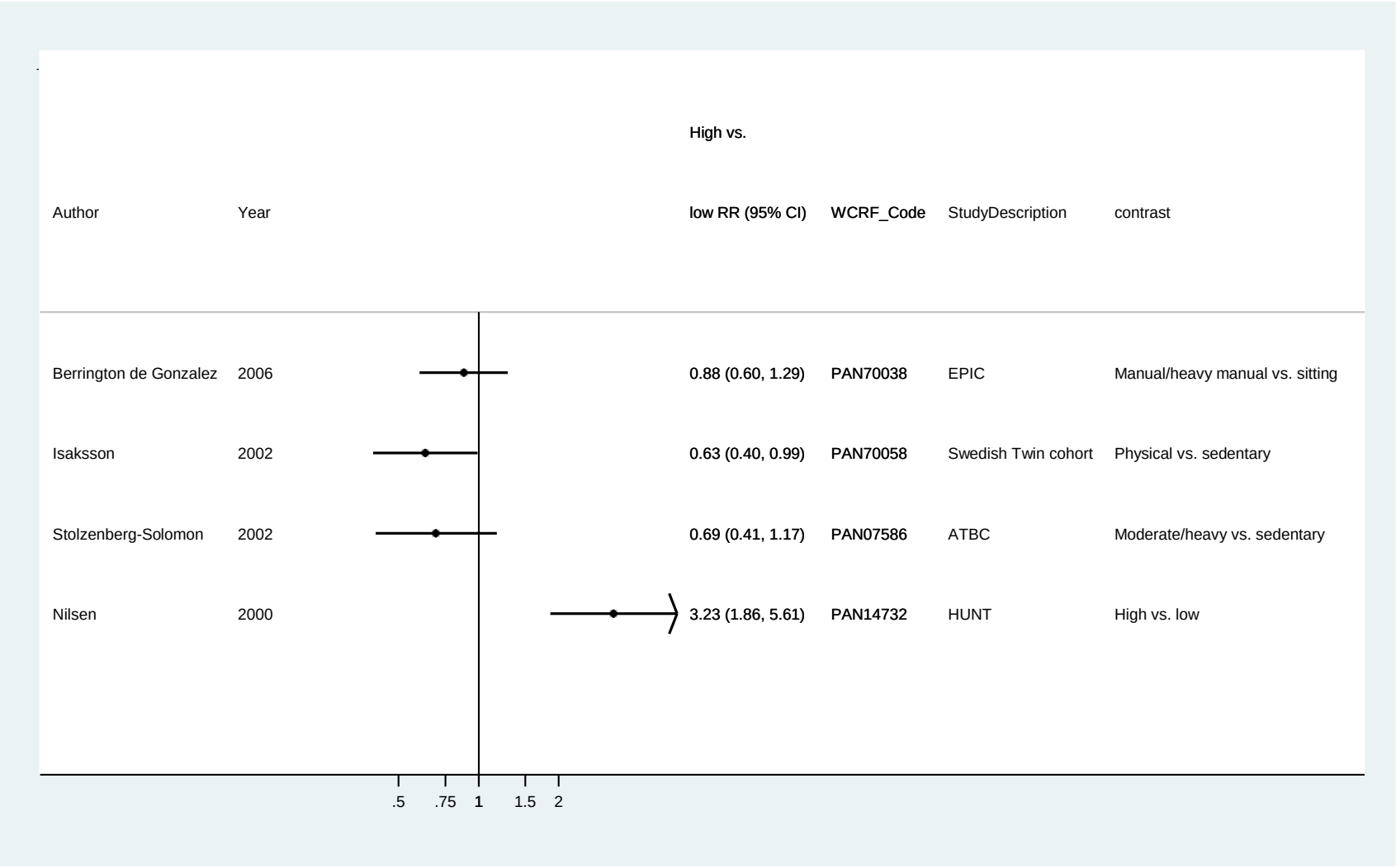
Table 155 Overall evidence on occupational activity and pancreatic cancer

	Summary of evidence
SLR	Three cohort studies provided data, of which one cohort study found a significantly reduced risk, one found a non-significantly reduced risk and one study found a significant increase in risk. One additional study was missed by the search.
Continuous Update Project	One new publication found no significant association.

Table 156 Inclusion/exclusion table for meta-analysis of occupational physical activity and pancreatic cancer

WCRF code	Author	Year	Study design	Study name	Subgroup	Cancer outcome	SLR	CUP dose-response meta-analysis	CUP HvL forest plot	Estimated values	Exclusion reason
PAN70038	Berrington de Gonzalez	2006	Prospective Cohort study	The EPIC study	Men/women	Incidence	New	No	Yes		No quantification of exposure
PAN70058	Isaksson	2002	Prospective cohort study	Swedish Twin Registry cohort study	Men/women	Incidence	No	No	Yes		Only two categories of exposure
PAN07586	Stolzenberg-Solomon	2002	Prospective cohort study	ATBC Cohort study	Men	Incidence	Yes	No	Yes		No quantification of exposure
PAN14732	Nilsen	2000	Prospective cohort study	Nord Trondelag Health Survey	Men/women	Incidence	Yes	No	Yes		No quantification of exposure
PAN18101	Paffenbarger	1978	Prospective cohort study	San Francisco Longshoremen	Men	Mortality	Yes	No	No		No risk estimates

Figure 174 Highest versus lowest forest plot of occupational physical activity and pancreatic cancer



6.1.1.2 Leisure-time physical activity

Methods

Eighteen studies on leisure-time physical activity and pancreatic cancer risk were identified. Ten new publications from 8 cohort studies were identified in the Continuous Update Project. Two of these reported only on mortality, while one study reported on both incidence and mortality. One additional study has been identified after the searches were completed, but does not alter the results and is not included in the analysis (Heinen et al, 2011).

Dose-response analyses and stratified analyses of leisure-time physical activity and pancreatic cancer risk were conducted. The dose-response results are presented per 10 MET-hrs per week.

Main results

The summary RR per 10 MET-hours per week of leisure-time physical activity was 0.99 (95% CI: 0.95-1.02, I^2=0%, $P_{heterogeneity}$ =0.67) for five studies on pancreatic cancer incidence and 0.99 (95% CI: 0.96-1.03, I^2=0%, $P_{heterogeneity}$ =0.57) for pancreatic cancer incidence and mortality combined (n=6). In sensitivity analyses, the summary RR for ranged from 0.99 (95% CI: 0.95-1.02) when the NIH AARP Diet and Health Study was excluded to 1.00 (95% CI: 0.97-1.04) when the Health Professionals Follow-up Study was excluded. There was no indication of publication bias with Egger's test, p=0.47.

Heterogeneity

There was no evidence of heterogeneity in the analyses.

Comparison with the Second Expert Report

Our results are consistent with the Second Expert Report in finding no significant association between leisure-time physical activity (recreational activity) and pancreatic cancer risk.

Published meta-analyses and pooled analysis

A meta-analysis found no significant association between high vs. low leisure-time physical activity and pancreatic cancer risk, summary RR=0.94 (95% CI: 0.83-1.05). No association was found for various intensities of physical activity as well, summary RR = 1.01 (95% CI: 0.77-1.34) for light activity, 0.83 (95% CI: 0.58-1.18) for moderate activity and 0.94 (95% CI: 0.80-1.12) for vigorous activity (Bao & Michaud, 2008).

A more recent meta-analysis also found no significant association between recreational physical activity and pancreatic cancer risk, summary RR=0.94 (95% CI: 0.88-1.01) (O'Rorke MA et al, 2009). No association was observed for transport physical activity, summary RR=0.77 (95% CI: 0.55-1.09), moderate activity, summary RR=0.79 (95% CI: 0.52-1.20), vigorous activity, summary RR=0.97 (95% CI: 0.85-1.11) and low intensity physical activity, summary RR=1.01 (0.77-1.34). No dose-response analyses were conducted.

In a pooled analysis of primary data of seven prospective cohorts including in which 2,454 patients with incident pancreatic cancer were identified during an average 6.9 years of follow-up, high levels of physical activity were associated with significantly reduced risk for all the participants (RR 0.90; 95% CI 0.82–0.99, adjusting for sex, BMI, smoking history, cohort and diabetes), but not for never smokers (RR 1.04; 95% CI 0.88–1.24) (Jiao et al, 2009).

Table 157 Studies on Leisure-time physical activity identified in the CUP

Author, year	Country	Study name	Number of cases	Years of Follow-up	Sex	RR	LCI	UCI	Contrast
Nakamura, 2011	Japan	Takayama Study	33 19	7	M F	1.03 3.29	0.41 0.96	2.60 11.20	67.2 vs. 1.44 MET-hrs/wk 51.6 vs. 0.88 MET-hrs/wk
Batty, 2009	UK	The Whitehall study	163	Up to 38	M	0.76	0.49	1.19	High vs. sedentary
Stevens, 2009	UK	Million Women's Health Study	1338 cases 1710 deaths	7.2 incidence 8.9 mortality	F	1.00 incidence 0.97 mortality	0.91 0.88	1.10 1.07	≥4 vs. <1/wk
Jiao, 2009	USA	NIH-AARP Diet and Health Study	1057	7.2	M/F	0.93	0.80	1.08	≥3-4/wk vs. never to <3-4 times/wk
Yun YH, 2008	Korea	National Health Insurance Corporation	223	6	M	1.00	0.84	1.24	Moderate/high vs. low
Suzuki, 2008	Japan	Japanese Collaborative Cohort study	170 167	NA	M F	0.97 0.87	0.65 0.54	1.45 1.39	>3 vs. 1 hrs/wk >3 vs. 1 hrs/wk
Stolzenberg-Solomon, 2008	USA	NIH-AARP Diet and Health Study	399	~3.4 years	M/F	0.96	0.69	1.32	≥61 vs. <14.3 MET-hrs/wk
Luo, 2007	Japan	Japan Public Health Center-based Prospective Study	224	11 years	M F	1.1 1.0	0.6 0.5	1.9 1.9	>2 vs. <1 day/wk >2 vs. <1 day/wk
Lin, 2007	Japan	Japanese Collaborative Cohort study	402	~11.8 years	M F	1.04 0.88	0.63 0.44	1.72 1.74	≥5 vs. <1 hr/wk ≥5 vs. <1 hr/wk
Berrington de Gonzalez, 2006	Europe	EPIC study	324	6 years	M/F	0.96	0.66	1.39	Quartile 4 vs. 1

Table 158 Overall evidence on leisure-time physical activity and pancreatic cancer

	Summary of evidence
SLR	Eight cohort studies provided data, of which one cohort study found a non-significant reduced risk. The remaining studies showed results close to the null, and two showed non-significant positive associations.
Continuous Update Project	Ten new publications from 8 prospective studies were identified in the CUP. None of the studies reported a statistically significant association between leisure-time physical activity and pancreatic cancer risk and most of the risk estimates were close to 1.

Numbers do not coincide with the numbers in table 152 because some studies included as total physical activity in the SLR were on leisure-time physical activity

Table 159 Summary of results of the dose-response meta-analysis of leisure-time physical activity and pancreatic cancer

Pancreatic cancer incidence		
	SLR	Continuous Update Project
Studies (n)	3	5
Cases (n)	592	1315
Increment unit	Per 10 MET-hrs	Per 10 MET-hrs
RR (95% CI)	0.98 (0.91-1.05)	0.99 (0.96-1.03)
Heterogeneity (I^2, p-value)	0%, p=0.4	0%, p=0.67

Pancreatic cancer incidence and mortality		
	SLR	Continuous Update Project
Studies (n)	-	6
Cases (n)	-	1367
Increment unit	-	Per 10 MET-hrs
RR (95% CI)	-	0.99 (0.96-1.02)
Heterogeneity (I^2, p-value)	-	0%, p=0.57

Table 160 Inclusion/exclusion table for meta-analysis of leisure-time physical activity and pancreatic cancer

WCRF code	Author	Year	Study design	Study name	Subgroup	Cancer outcome	SLR	CUP dose-response meta-analysis	CUP HvL forest plot	Estimated values	Exclusion reason
PAN70066	Nakamura	2011	Prospective Cohort study	Takayama Study	Men/women	Mortality	New	Yes	Yes		
PAN70039	Batty	2009	Prospective Cohort study	The Whitehall study	Men	Mortality	New	No	Yes		Did not quantify physical activity level
PAN70044	Stevens	2009	Prospective Cohort study	Million Women's Health Study	Women	Incidence Mortality	New	No No	Yes Yes		Reported on frequency
PAN70054	Jiao	2009	Prospective Cohort study	NIH-AARP Diet and Health Study	Men/women	Incidence	New	No	No		Overlap with Stolzenberg-Solomon, 2008 which was more detailed
PAN70067	Yun	2008	Prospective Cohort study	National Health Insurance Corporation	Men	Incidence	New	No	Yes		Only high vs. low comparison
PAN70065	Suzuki	2008	Prospective Cohort study	Japanese Collaborative Cohort study for Evaluation of Cancer Risk	Men/women	Mortality	New	No	No		Overlapped with Lin et al, 2007
PAN70041	Stolzenberg-Solomon	2008	Prospective Cohort study	NIH-AARP Diet and Health Study	Men/women	Incidence	New	Yes	Yes	Mid-exposure values	
PAN70036	Luo	2007	Prospective Cohort study	Japan Public Health Center-based Prospective Study	Men/women	Incidence	New	No	Yes		Reported on frequency, not MET-hrs
PAN70037	Lin	2007	Prospective Cohort study	Japanese Collaborative Cohort study for	Men/women	Mortality	New	No	Yes		Reported on frequency, not MET-hrs

				Evaluation of Cancer Risk							
PAN70038	Berrington de Gonzalez	2006	Prospective Cohort study	The EPIC study	Men/women	Incidence	New	Yes	Yes	No quantification of LTPA was provided, but external reference was used: Van Veldhoven, Eur J Cancer. 2011 Mar;47(5):748-60	
PAN61473	Patel	2005	Prospective Cohort study	Cancer Prevention Study II Nutrition Cohort	Men/women	Incidence	Yes	Yes	Yes	Mid-exposure values	
PAN61272	Sinner	2005	Prospective Cohort study	Iowa Women's Health Study	Women	Incidence	Yes	No	Yes		No quantification of physical activity level
PAN07377	Lee	2003	Prospective Cohort study	The College Alumni Health Study	Men/women	Mortality	Yes	No	Yes		Physical activity level reported in kJ/week – not combineable with other studies
PAN07312	Inoue	2003	Nested case-control study	HERPACC	Men/women	Incidence	Yes	No	Yes		Only high vs. low comparison
PAN70058	Isaksson	2002	Prospective cohort study	Swedish Twin Registry cohort study	Men/women	Incidence	No	No	Yes		Only two categories of exposure
PAN07586	Stolzenberg-Solomon	2002	Prospective cohort study	ATBC Cohort study	Men	Incidence	Yes	No	Yes		Two categories of exposure only
PAN07439	Michaud	2001	Prospective cohort study	Health Professionals Follow-up Study	M en	Incidence	Yes	Yes	Yes	Mid-exposure values	
PAN07439	Michaud	2001	Prospective cohort study	Nurses' Health Study	Women	Incidence	Yes	Yes	Yes	Mid-exposure values	
PAN14732	Nilsen	2000	Prospective cohort study	Nord Trondelag Health Survey	Men/women	Incidence	Yes	No	Yes		Only two categories
PAN20241	Davey Smith	2000	Prospective cohort study	The Whitehall Study	Men	Mortality	Yes	No	No		Surpassed by Batty et al, 2009

Figure 175 Highest vs. lowest forest plot of leisure-time physical activity and pancreatic cancer

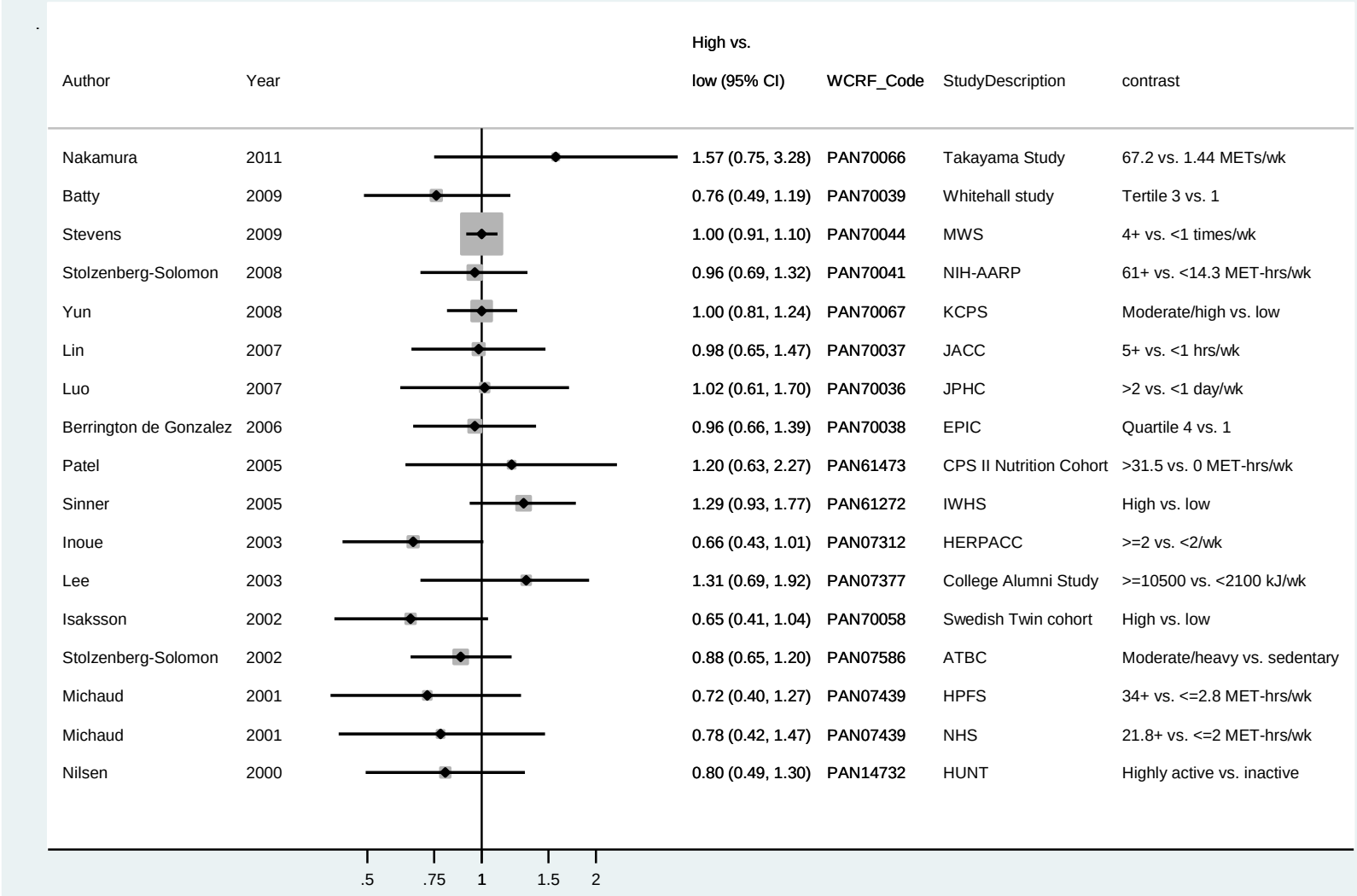


Figure 176 Dose-response meta-analysis of leisure-time physical activity and pancreatic cancer - per 10 MET-hours per week

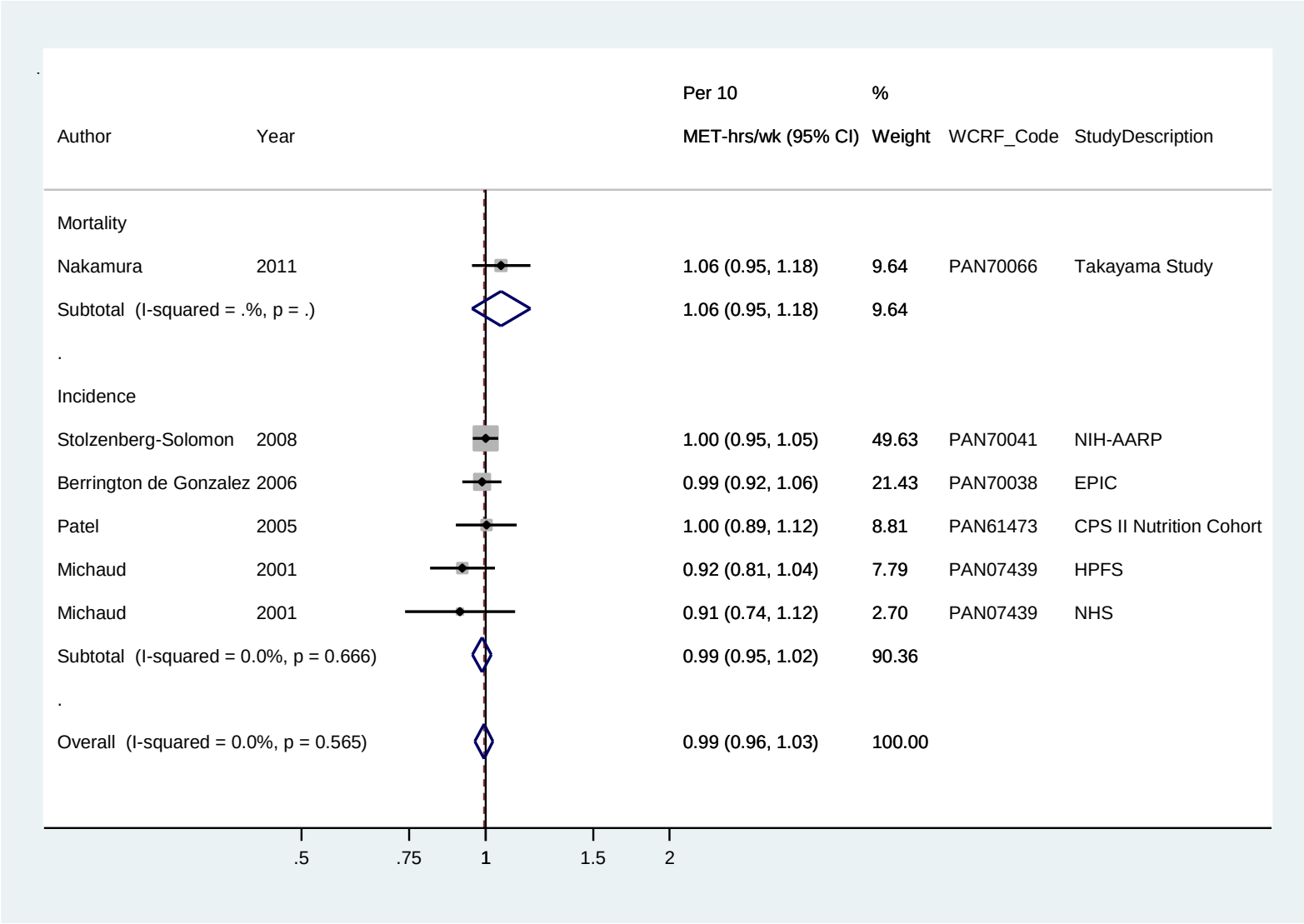


Figure 177 Funnel plot of leisure-time physical activity and pancreatic cancer

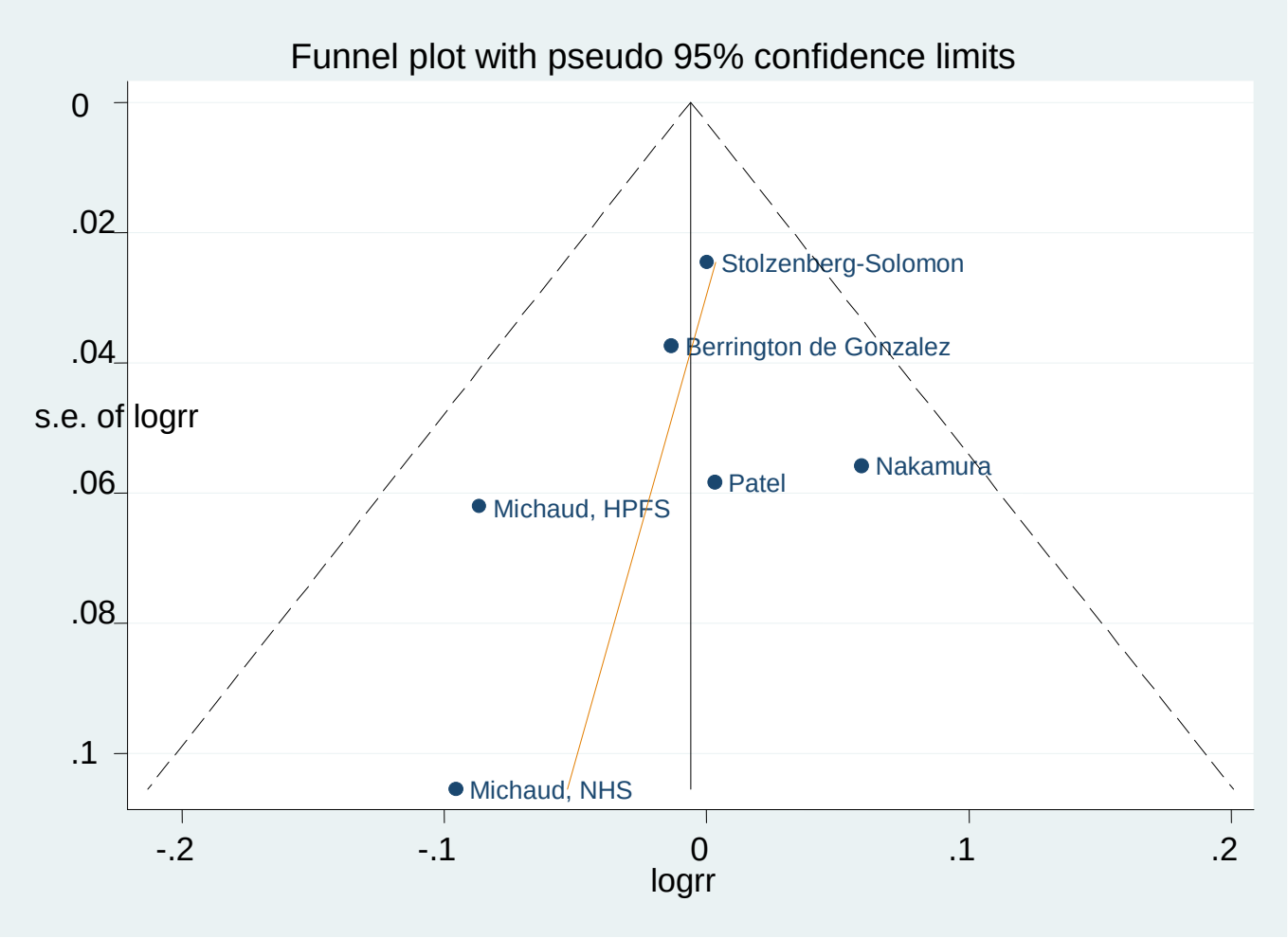


Figure 178 Dose-response graph of leisure-time physical activity and pancreatic cancer

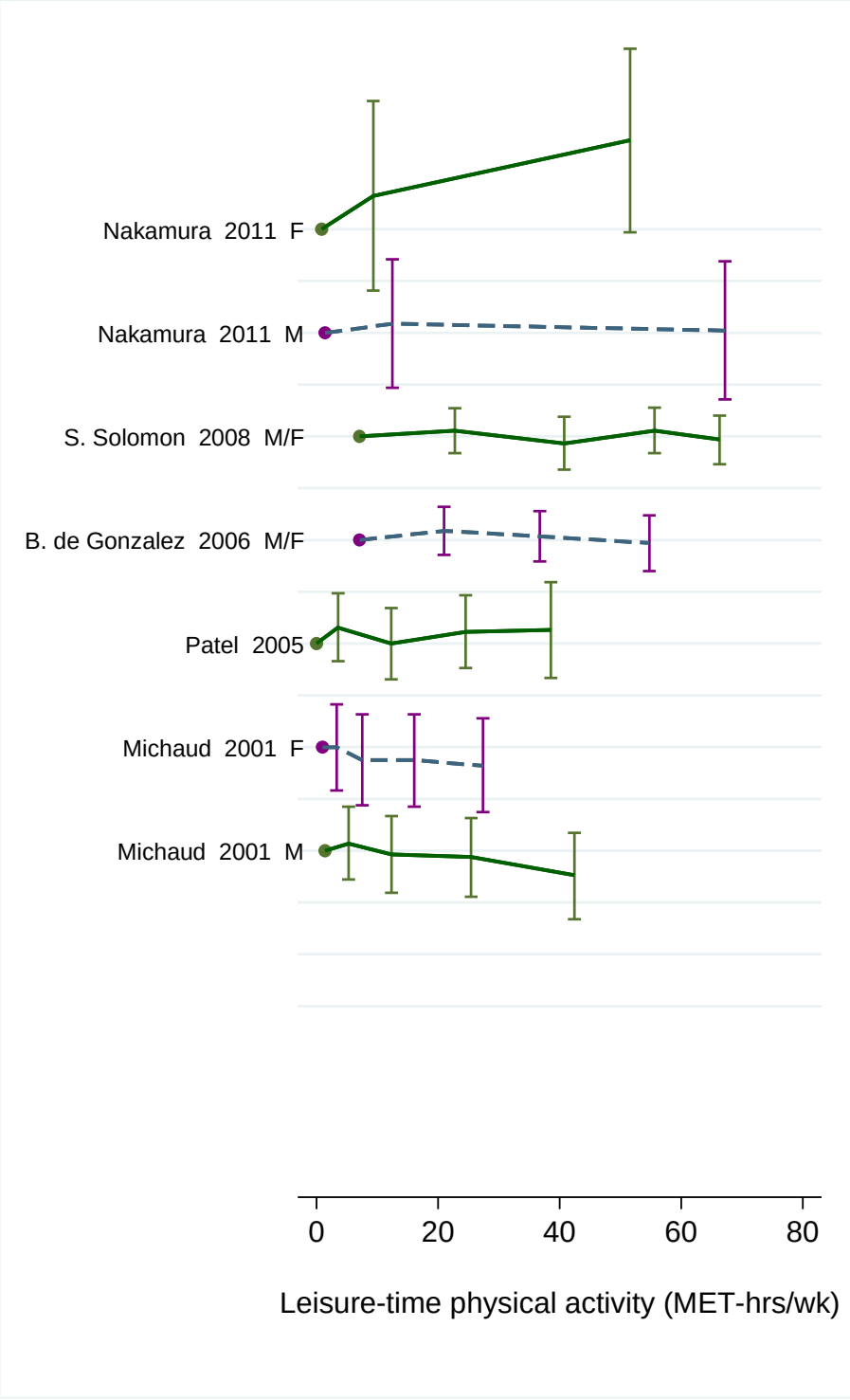
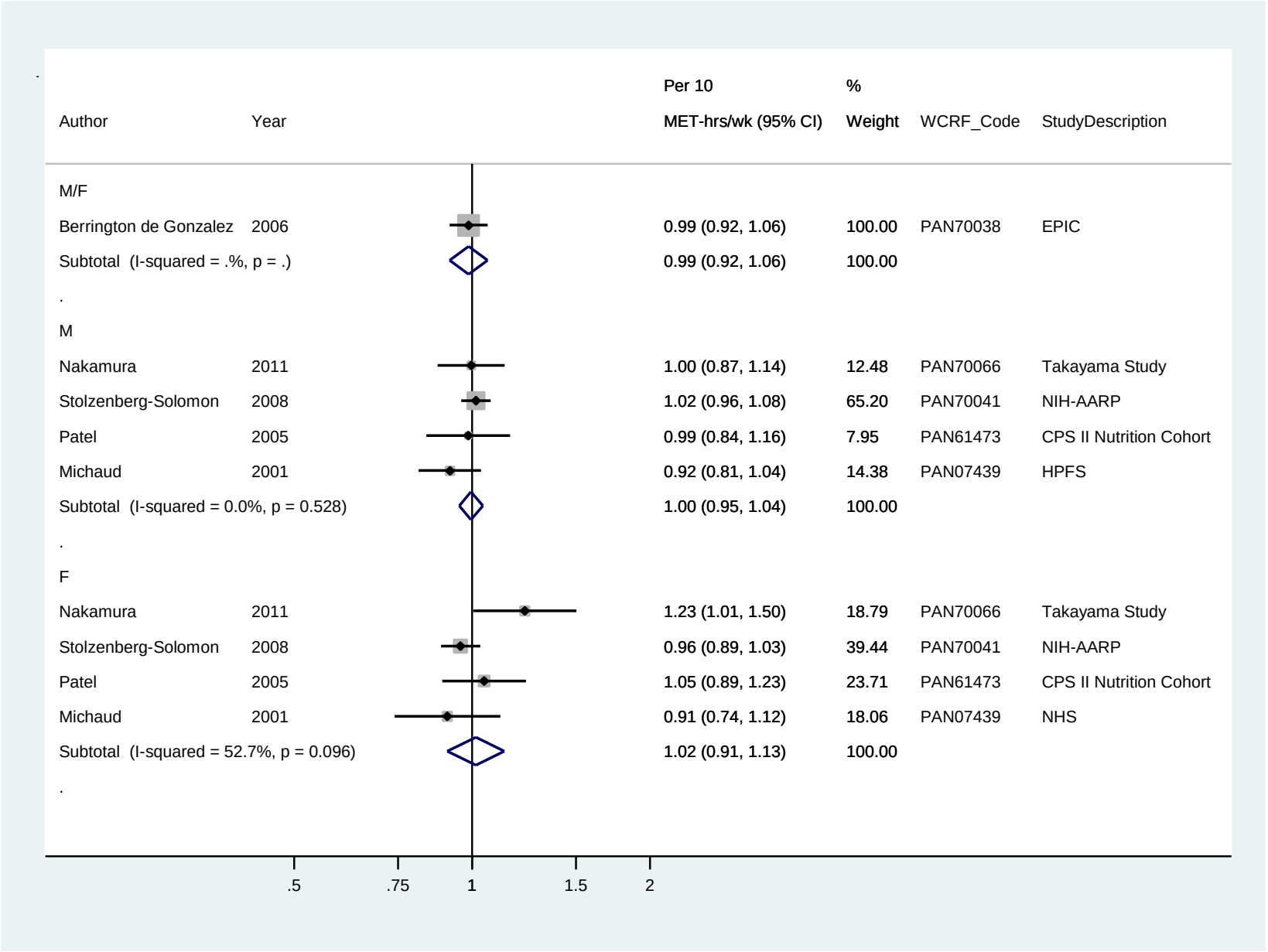


Figure 179 Dose-response meta-analysis of leisure-time physical activity and pancreatic cancer, stratified by sex - per 10 MET-hrs/wk



8 Anthropometry

8.1.1 BMI

Methods

Twenty-three new publications (from 17 prospective studies) were identified in the Continuous Update Project. A total of twenty-three studies (twelve of which were new) were included in the dose-response analysis of BMI and pancreatic cancer incidence and seven studies (five of which were new) were included in the dose-response analysis of BMI and pancreatic cancer mortality.
Dose-response analyses and stratified analyses of BMI and pancreatic cancer risk were conducted and are presented per 5 BMI units. Analyses of pancreatic cancer incidence and mortality were conducted separately in contrast to the 2nd Expert Report to be consistent with the analyses for the other cancer sites and because mixing incidence and mortality studies may cause heterogeneity in the results.

Main results

The summary RR for a 5 unit increment in BMI was 1.10 (95% CI: 1.07-1.14, I^2=19%, p=0.20, 23 studies) for pancreatic cancer incidence. The summary RR ranged from 1.09 (95% CI: 1.06-1.12) when excluding the Cancer Prevention Study 2 Nutrition Cohort to 1.11 (95% CI: 1.08-1.14) when excluding the Multiethnic Cohort Study. The summary RR was similar for men and women, summary RR= 1.10 (95% CI: 1.04-1.16) for women and 1.13 (95% CI: 1.04-1.22) for men, with moderate heterogeneity, I^2=41.8%, p=0.05 and I^2=45.6%, p=0.03, respectively. There was no evidence of publication bias with Egger's test, p=0.36. There was evidence of a nonlinear association between BMI and pancreatic cancer incidence, $p_{nonlinearity}$=0.005.

The summary RR for a 5 unit increment in BMI was 1.10 (95%: 1.02-1.19) for studies of pancreatic cancer mortality (n=7), but there was moderate to high heterogeneity, I^2=60.7%, p=0.02. Excluding either the large Cancer Prevention Study 2 or the Million Women's Study from the analysis, reduced the heterogeneity and the summary RR was 1.06 (95% CI: 1.01-1.11) with no evidence of heterogeneity (I^2=0%, p=0.53) and 1.14 (95% CI: 1.06-1.23) with little heterogeneity (I^2=14.8%, p=0.32), respectively. There was evidence of a nonlinear association between BMI and pancreatic cancer mortality, $p_{nonlinearity}$=0.0001.

Heterogeneity

There was little evidence of heterogeneity (I^2=19%, p=0.20) in the analysis for incidence, and the heterogeneity that was present in the mortality analysis was explained by either of the two largest studies.

Comparison with the Second Expert Report

Our results are consistent with the Second Expert Report in finding a positive association between BMI and pancreatic cancer risk.

Published meta-analysis and pooled analysis

A pooled analysis of 14 prospective studies (846340 participants, 2135 cases) found an increased pancreatic cancer risk with greater BMI, pooled multivariate RR = 1.47 (95% CI: 1.23-1.75) for BMI ≥30 vs. 21-22.9 (Genkinger et al, 2011). A pooled analysis from the Pancreatic Cancer Cohort Consortium (PanScan) including 2170 cases and 2209 controls reported a pooled OR of 1.55 (95% CI: 1.16-2.07) for BMI ≥35 compared with 18.5-24.9 (Arslan et al, 2010). This was attenuated when adjusted for history of diabetes mellitus (which may be an intermediate factor), pooled OR = 1.26 (95% CI: 0.93-1.71), but strengthened when the analysis was restricted to never smokers, pooled OR = 1.62 (95% CI: 1.19-2.21). A pooled analysis of seven cohort studies reported a summary RR of 1.06 (95% CI: 0.99-1.13) per 5 BMI units for men and a summary RR of 1.12 (95% CI: 1.05-1.19) for women (Jiao, 2010). A pooled analysis of 39 studies in the Asia-Pacific Cohort Studies Collaboration (424519 participants: 301 deaths) reported a RR of 0.90 (95% CI: 0.54-1.49) for BMI ≥30 vs. 18.5-24.9 (Parr et al, 2010).
A meta-analysis of 6 case-control studies and 8 cohort studies published in 2003 found an increased risk of pancreatic cancer with greater BMI, summary RR per 1 unit increment in BMI =1.02 (95% CI: 1.01-1.03) for all studies combined and 1.03 (95% CI: 1.01-1.04) for cohort studies (Berrington de Gonzalez et al, 2003). A meta-analysis of 21 prospective studies from 2007 reported a summary RR of 1.12 (95% CI: 1.06-1.17) per 5 units increase in BMI (Larsson et al, 2007). A meta-analysis of 12 prospective studies in men and 11 prospective studies in women reported a summary of 1.07 (95% CI: 0.93-1.23) for men and 1.12 (1.02-1.22) for women (Renehan et al, 2008). A meta-analysis of 12 prospective studies from 2009 reported summary RRs of 1.28 (95% CI: 0.94-1.75) and 1.24 (95% CI: 0.98-1.56) for overweight men and women, respectively, and summary RRs of 2.29 (95% CI: 1.65-3.19) and 1.60 (95% CI: 1.17-2.20) for obese men and women, respectively (Guh et al, 2009).

Table 161 Studies on BMI identified in the CUP

Author, year	Country	Study name	Number of cases	Years of Follow-up	Sex	RR	LCI	UCI	Contrast
Nakamura, 2011	Japan	The Takayama Study	33 19	7	M F	0.59 1.42	0.23 0.52	1.50 3.85	>23.6 vs. <21.3 >23.0 vs. <20.7
Andreotti, 2010	USA	Agricultural Health Study	45 21	10	M F	1.06 2.48	0.42 0.79	2.65 7.83	30-34.9 vs. 18.5-24.9 30-34.9 vs. 18.5-24.9
Andreotti, 2009	USA	Agricultural Health Study	64 29	9	M F	1.0 1.9	0.4 0.7	2.7 5.0	≥30 vs. <25 ≥30 vs. <25
Stevens, 2009	UK	The Million Women Study	1338 cases 1710 deaths	7.2, incidence 8.9, mortality	F	1.42 1.36	1.12 1.12	1.80 1.65	≥32.5 vs. 22.5-<25.0 ≥32.5 vs. 22.5-<25.0

Arnold, 2009	USA	Cancer Prevention Study II Cohort	360 deaths, blacks 5883 deaths, whites	20	M/F	1.06 1.40	0.80 1.28	1.42 1.52	≥30 vs. 18.5-<25 ≥30 vs. 18.5-<25
Jiao, 2009	USA	NIH-AARP Diet and Health Study	1057	7.2	M/F M F	0.88 0.84 0.88	0.77 0.71 0.78	0.99 0.99 1.00	18.5-25 vs. >25
Meinhold, 2008	Finland	ATBC Cancer Prevention Study	305	19.4	M	1.42	0.69	2.93	36.9 vs. 23.1
Batty , 2009	UK	The Whitehall Study	163	38	M	1.18 1.03	0.79 0.87	1.75 1.23	Tertile 3 vs. 1 Per 2.98 units
Johansen , 2009	Sweden	Malmoe Preventive Project	187	22.1	M/F	1.38 1.04	0.83 0.99	2.28 1.08	≥30 vs. 20-<25 Per 1 unit
Inoue, 2009	Japan	Japan Public Health Center-based Prospective Study	24 41	10	M F	0.33 1.16	0.10 0.81	1.12 2.22	≥25 vs. <25 ≥25 vs. <25
Berrington de Gonzalez, 2008	Korea	Korea National Health Insurance Corporation study	2194	12	M/F	0.95	0.80	1.12	27.5 vs. 18.5-22.9
de Martel, 2008	USA	Multiphase Check-up Study	141	>31	M/F	0.99	0.44	2.25	≥30 vs. <25
Stolzenberg-Solomon, 2008	USA	NIH-AARP Diet and Health Study	654	~5	M/F M F	1.33 1.48 1.19	0.95 0.96 0.71	1.86 2.30 1.99	≥35 vs. 18.5-<25.0 ≥35 vs. 18.5-<25.0 ≥35 vs. 18.5-<25.0
Jee, 2008	Korea	Korea National Health Insurance Corporation Study	1860 791	10.8	M F	1.34 1.80	0.75 1.14	2.38 2.86	≥30 vs. 23-24.9 ≥30 vs. 23-24.9
Luo, 2008	USA	Women's Health Initiative	251	7.7	F	0.8	0.5	1.3	≥35 vs. 22-24.9
Verhage, 2007	Netherlands	Netherlands Cohort Study	446	13.3	M F	2.54 1.27	1.47 0.73	4.41 2.22	≥30 vs. <23 ≥30 vs. <23
Lin, 2007	Japan	Japan Collaborative Cohort Study	402	14	M F	0.58 1.04	0.08 0.37	4.16 2.89	≥30 vs. 20-22.4 ≥30 vs. 20-22.4
Luo, 2007	Japan	Japan Public Health Center-based Prospective Study	224	11.7	M F	0.7 1.1	0.4 0.7	1.1 1.6	25-40 vs. 21-<25 25-40 vs. 21-<25
Reeves, 2007	UK	The Million Women Study	795 cases 1130 deaths	5.4, incidence 7.0, mortality	F	1.37 1.24 1.32 1.21	1.18 1.03 1.16 1.04	1.60 1.48 1.51 1.41	≥30 vs. 22.5-24.9 Per 10 units ≥30 vs. 22.5-24.9 Per 10 units

Nothlings, 2007	USA	Multiethnic Cohort Study	472	7.5	M F	1.51 0.65	1.02 0.43	2.26 0.99	≥30 vs. <25 ≥30 vs. <25
Berrington De Gonzalez, 2006	Europe	European Prospective Investigation into Cancer and Nutrition	324	6.5	M/F	1.19 1.09	0.64 0.95	2.23 1.24	35+ vs. <20 Per 5 units
Samanic, 2006	Sweden	The Swedish Construction Worker's Study	698	19	M	1.16	0.87	1.53	≥30 vs. <25
Yun, 2006	Korea	Korea National Health Insurance Corporation study	863 cases 816 deaths	10	M	1.0 (incidence) 0.8 (mortality)	0.8 0.7	1.1 1.0	≥25 vs. <25 ≥25 vs. <25

Table 162 Overall evidence on BMI and pancreatic cancer

	Summary of evidence
SLR	Seventeen cohort studies were included in the meta-analysis and 18 of 23 risk estimates from these studies showed positive associations, of which five were statistically significant and five risk estimates showed non-significant inverse associations.
Continuous Update Project	Seventeen studies (23 publications) were identified in the CUP and 6 of these reported significant positive associations (two of which was positive in men, but not in women). The remaining studies reported non-significant associations.

Table 163 Summary of results of the dose-response meta-analysis of BMI and pancreatic cancer

Pancreatic cancer incidence and mortality*		
	SLR	Continuous Update Project
Studies (n)	17	23
Cases (n)	6450	9504
Increment unit	5 units	5 units
RR (95% CI)	1.14 (1.07-1.22)	1.10 (1.07-1.14)
Heterogeneity (I^2, p-value)	51%, p=0.002	19%, p=0.20
By gender		
Men	1.24 (1.06-1.46)	1.13 (1.04-1.22)
Heterogeneity (I^2, p-value)	-	46%, p=0.03
Women	1.08 (0.97-1.20)	1.10 (1.04-1.16)
Heterogeneity (I^2, p-value)	-	42%, p=0.045

* In the CUP only studies of incidence was included in this analysis

Pancreatic cancer mortality *		
	SLR	Continuous Update Project
Studies (n)	-	7
Cases (n)	-	8869
Increment unit	-	5 units
RR (95% CI)	-	1.10 (1.02-1.19)
Heterogeneity (I^2, p-value)	-	60.7, p=0.02

* The 2nd report included studies of pancreatic cancer mortality in the overall summary. To decrease potential heterogeneity we have conducted analyses separately for incidence and mortality.

Table 164 Inclusion/exclusion table for meta-analysis of BMI and pancreatic cancer

WCRF code	Author	Year	Study design	Study name	Subgroup	Cancer outcome	SLR	CUP dose-response meta-analysis	CUP HvL forest plot	Estimated values	Exclusion reason
PAN70066	Nakamura	2011	Prospective cohort study	Takayama Study	Men/women	Mortality	New	Yes	Yes	Mid-exposure values	
PAN70060	Andreotti	2010	Prospective cohort study	Agricultural Health Study	Men/ women	Incidence	New	Yes	Yes	Person-years, mid-exposure values	
PAN70068	Andreotti	2009	Prospective cohort study	Agricultural Health Study	Men/ women	Incidence	New	No	No		Duplicate, surpassed by PAN70060
PAN70044	Stevens	2009	Prospective cohort study	The Million Women Study	Women	Incidence Mortality	New	Yes	Yes	Person-years, mid-exposure values	
PAN70043	Arnold	2009	Prospective cohort study	Cancer Prevention Study II	Men/women Black/white	Mortality	New	Yes	Yes	Person-years, mid-exposure values	
PAN70054	Jiao	2009	Prospective cohort study	NIH-AARP Diet and Health Study	Men/ women	Incidence	New	No	No		Duplicate, excluded because PAN70041 provided more detailed BMI analyses
PAN70045	Meinhold	2009	Prospective cohort study	ATBC Cancer Prevention Study	Men	Incidence	New	Yes	Yes	Unit increment, person-years	
PAN70039	Batty	2009	Prospective cohort study	The Whitehall Study	Men	Mortality	New	Yes	Yes	Unit increment	
PAN70033	Johansen	2009	Prospective cohort study	The Malmo Preventive Project	Men/ women	Incidence	New	Yes	Yes	Person-years, mid-exposure values	
PAN70032	Inoue	2009	Prospective cohort study	Japan Public Health Center-based Prospective	Men/women	Incidence	New	No	No		Duplicate, PAN70036 by Luo et al, 2007 was used because

				Study							it presented more detail in the analyses
PAN70049	Berrington de Gonzalez	2008	Prospective cohort study	National Health Insurance Corporation Study	Men/women	Incidence	New	No	No		Duplicate, PAN70031 was preferred because it had more cases
PAN70034	de Martel	2008	Nested case-control study	Multiphase Check-up Study	Men/women	Incidence	New	No	Yes	Mid-exposure values	Unadjusted results, results from a previous publication was used for the dose-response because they were adjusted PAN04147, Friedman et al, 1993
PAN70029	Luo	2008	Prospective cohort study	Women's Health Initiative	Women	Incidence	New	Yes	Yes	Person-years	
PAN70041	Stolzenberg-Solomon	2008	Prospective cohort study	NIH-AARP Diet and Health Study	Men/women	Incidence	New	Yes	Yes	Mid-exposure values	
PAN70031	Jee	2008	Prospective cohort study	National Health Insurance Corporation Study	Men/women	Incidence	New	Yes	Yes	Mid-exposure values, person-years	
PAN70042	Verhage	2007	Case-cohort study	Netherlands Cohort Study	Men/women	Incidence	New	Yes	Yes		
PAN70037	Lin	2007	Prospective cohort study	Japan Collaborative Cohort Study	Men/women	Mortality	New	Yes	Yes	Mid-exposure values	
PAN70036	Luo	2007	Prospective cohort study	Japan Public Health Center-based Prospective Study	Men/women	Incidence	New	Yes	Yes	Mid-exposure values	
PAN70030	Reeves	2007	Prospective	The Million	Women	Incidence	New	No	No		Duplicate,

			cohort study	Women Study		Mortality					surpassed by PAN70044 by Stevens et al, 2009
PAN70035	Nothlings	2007	Prospective cohort study	Multiethnic Cohort Study	Men/women	Incidence	New	Yes	Yes	Mid-exposure values, person-years	
PAN70038	Berrington de Gonzalez	2006	Prospective cohort study	European Prospective Investigation into Nutrition and Cancer	Men/women	Incidence	New	Yes	Yes	Mid-exposure values, person-years	
PAN70059	Samanic	2006	Prospective cohort study	The Swedish Construction Worker's Study	Men	Incidence	New	Yes	Yes	Mid-exposure values, person-years	
PAN70028	Yun	2006	Prospective cohort study	National Health Insurance Corporation Study	Men	Incidence	New	No	No		Duplicate, surpassed by PAN70031 by Jee et al, 2008
PAN69932	Lukanova	2006	Prospective cohort study	The Northern Sweden Health and Disease Cohort	Men/women	Incidence	Yes	Yes (sex-stratified analyses only)	No	Mid-exposure values, person-years	The paper was excluded in the overall analysis because the population overlapped with the EPIC-study, PAN70038 by Berrington de Gonzalez et al, 2006, but it was included in the sex-specific analyses as EPIC-did not report sex-specific results
PAN60007	Navarro	2005	Prospective cohort study	Canadian National Breast Screening Study	Women	Incidence	Yes	No	No		Mean exposure only

PAN61473	Patel	2005	Prospective cohort study	Cancer Prevention Study II – Nutrition Cohort	Men/women	Incidence	Yes	Yes	Yes	Mid-exposure values	
PAN61272	Sinner	2005	Prospective cohort study	Iowa Women's Health Study	Women	Incidence	Yes	Yes	Yes	Mid-exposure values	
PAN61184	Oh	2005	Prospective cohort study	National Health Insurance Corporation Study	Men/women	Incidence	Yes	No	No		Duplicate
PAN60981	Larsson	2005	Prospective cohort study	Swedish Mammography Cohort Study	Women	Incidence	Yes	Yes	Yes		
PAN60981	Larsson	2005	Prospective cohort study	Cohort of Swedish Men	Men	Incidence	Yes	Yes	Yes		
PAN61020	Rapp	2005	Prospective cohort study	The Vorarlberg Health Monitoring & Promotion Program Study Cohort	Men/women	Incidence	Yes	Yes	Yes	Mid-exposure values	
PAN60032	Kuriyama	2005	Prospective cohort study	Miyagi Prefecture Cohort	Men/women	Incidence	Yes	Yes	Yes	Mid-exposure values, person-years,	
PAN69933	Batty	2004	Prospective cohort study	The Whitehall Study	Men	Mortality	Yes	No	No		No risk estimates
PAN20232	Stolzenberg-Solomon	2004	Nested case-control study	ATBC Cancer Prevention Study	Men	Incidence	Yes	No	No		Only mean exposure, no risk estimates
PAN07377	Lee	2003	Prospective cohort study	The College Alumni Health Study	Men	Mortality	Yes	Yes	Yes	Mid-exposure values, person-years	
PAN08316	Calle	2003	Prospective cohort study	Cancer Prevention Study II	Men/women	Mortality	Yes	No	No		Duplicate, surpassed by Arnold et al, 2009
PAN15635	Anderson	2002	Prospective cohort study	Iowa Women's Health Study	Women	Incidence	Yes	No	No		No risk estimates
PAN07590	Stolzenberg-	2002	Prospective	ATBC Cancer	Men	Incidence	Yes	No	No		No risk estimates

	Solomon		cohort study	Prevention Study							
PAN07586	Stolzenberg-Solomon	2002	Prospective cohort study	ATBC Cancer Prevention Study	Men	Incidence	Yes	No	No		Duplicate
PAN70058	Isaksson	2002	Prospective cohort study	Swedish Twin Cohort Study	Men/women	Incidence	No, missed	Yes	Yes	Mid-exposure values, person-years	
PAN07439	Michaud	2001	Prospective cohort study	Nurses' Health Study	Women	Incidence	Yes	Yes	Yes		
PAN07439	Michaud	2001	Prospective cohort study	Health Professionals Follow-up Study	Men	Incidence	Yes	Yes	Yes		
PAN14732	Nilsen	2000	Prospective cohort study	HUNT	Men/women	Incidence	Yes	No	Yes		Only two categories of exposure
PAN07249	Gapstur	2000	Prospective cohort study	Chicago Heart Association	Men/women	Mortality	Yes	Yes	Yes	Mid-exposure values	
PAN07195	Coughlin	2000	Prospective cohort study	Cancer Prevention Study II	Men/women	Mortality	Yes	No	No		Duplicate
PAN63854	Robsahm	1999	Prospective cohort study	Norwegian screening programme for tuberculosis	Men/women	Incidence	Yes	No	No		No risk estimates provided
PAN07587	Stolzenberg-Solomon	1999	Prospective cohort study	ATBC Cancer Prevention Study	Men	Incidence	Yes	No	No		No risk estimates, duplicate
PAN15306	Tulinius	1997	Prospective cohort study	Reykjavik Study/Icelandic Cancer Registry study	Men/women	Incidence	Yes	No	No		No risk estimates provided
PAN07562	Shibata	1994	Prospective cohort study	World Leisure Cohort Study	Men/women	Incidence	Yes	Yes	Yes	Mid-exposure values	
PAN04147	Friedman	1993	Prospective cohort study	Multiphase Check-up Study	Men/women	Incidence	Yes	Yes	No		Only continuous result reported

Figure 180 Highest versus lowest forest plot of BMI and pancreatic cancer incidence

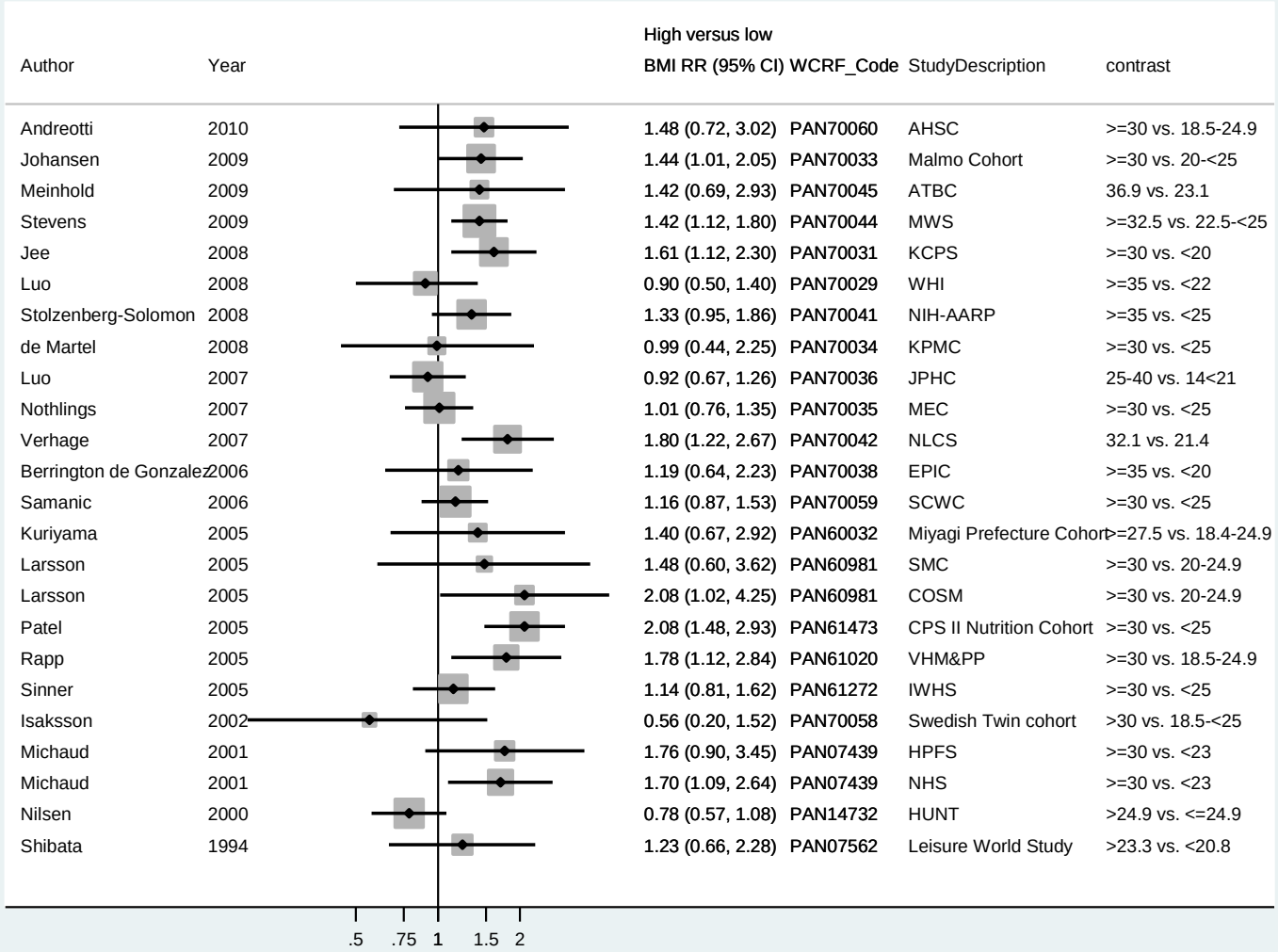


Figure 181 Dose-response meta-analysis of BMI and pancreatic cancer incidence - per 5 units

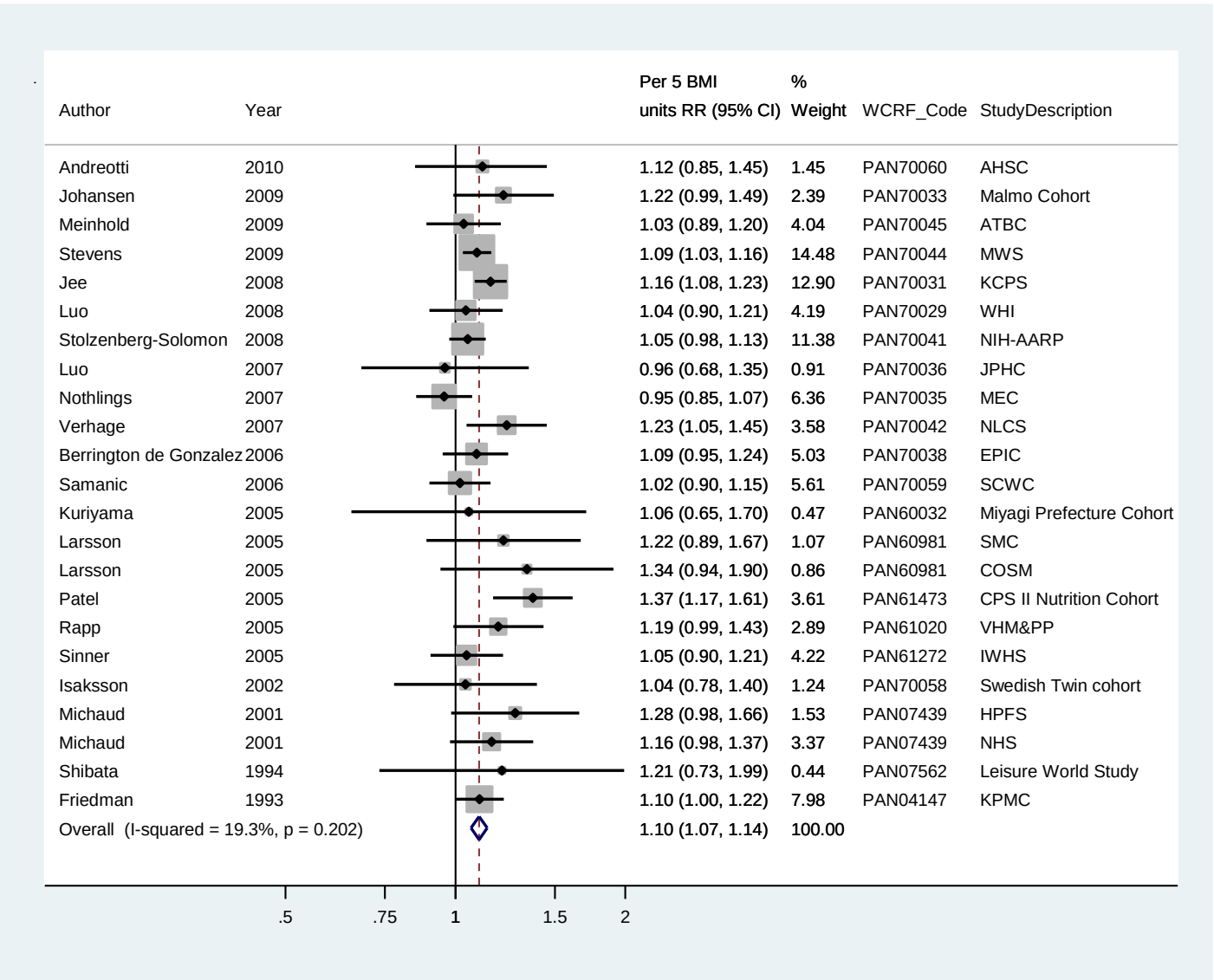


Figure 182 Funnel plot of BMI and pancreatic cancer incidence

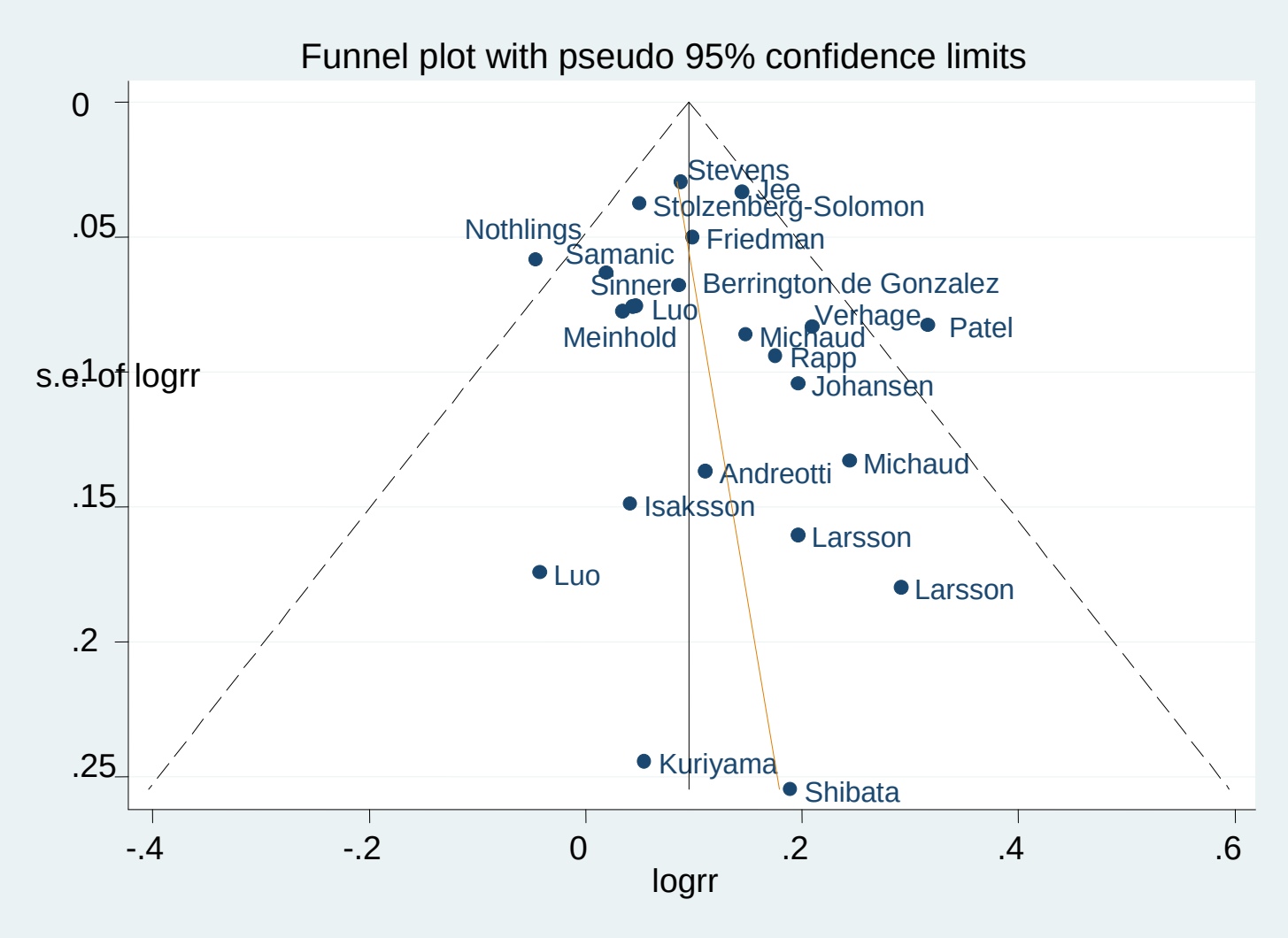


Figure 183 Dose-response graph of BMI and pancreatic cancer incidence

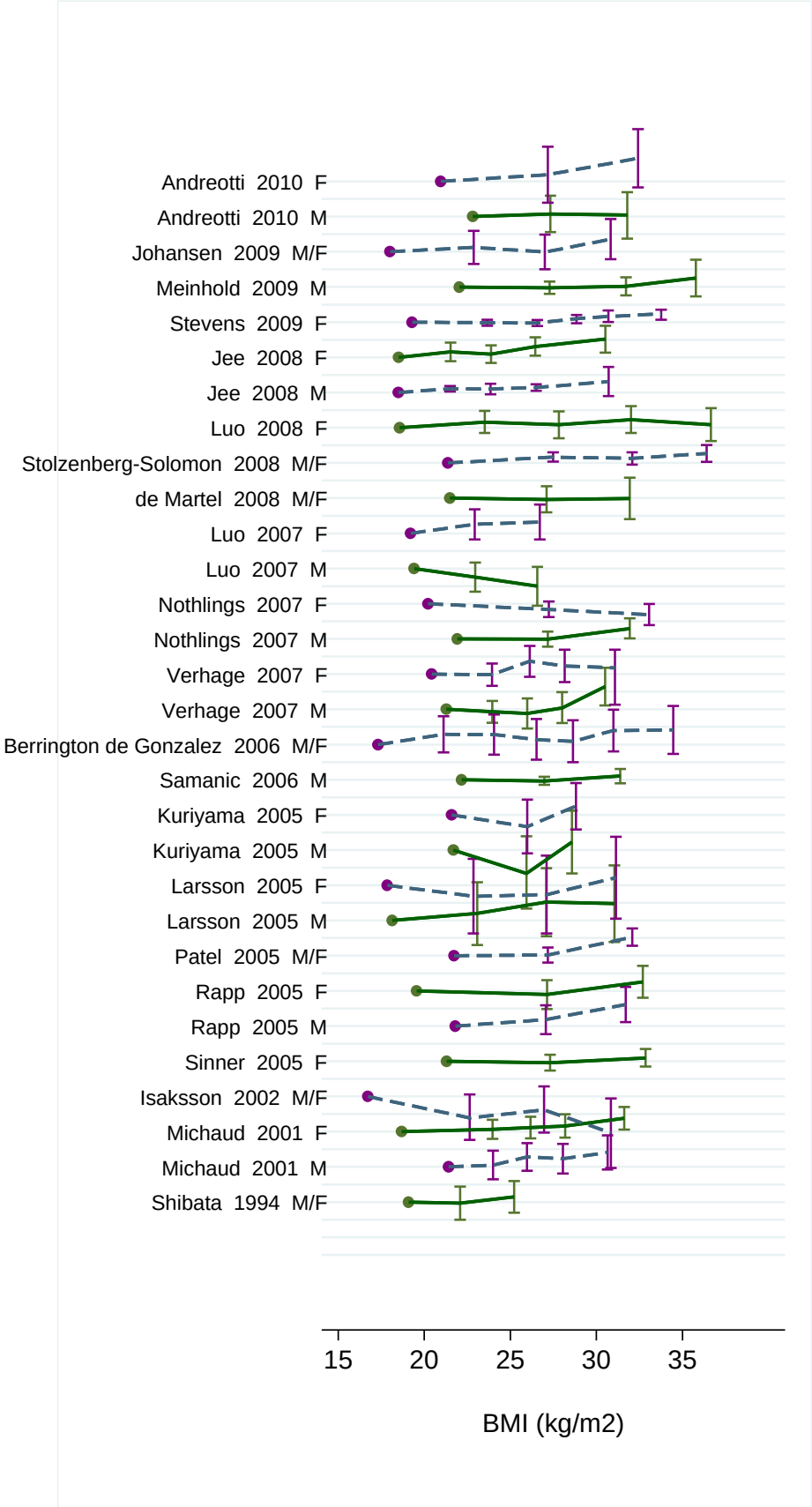


Figure 184 Dose-response meta-analysis of BMI and pancreatic cancer incidence, stratified by sex - per 5 unit

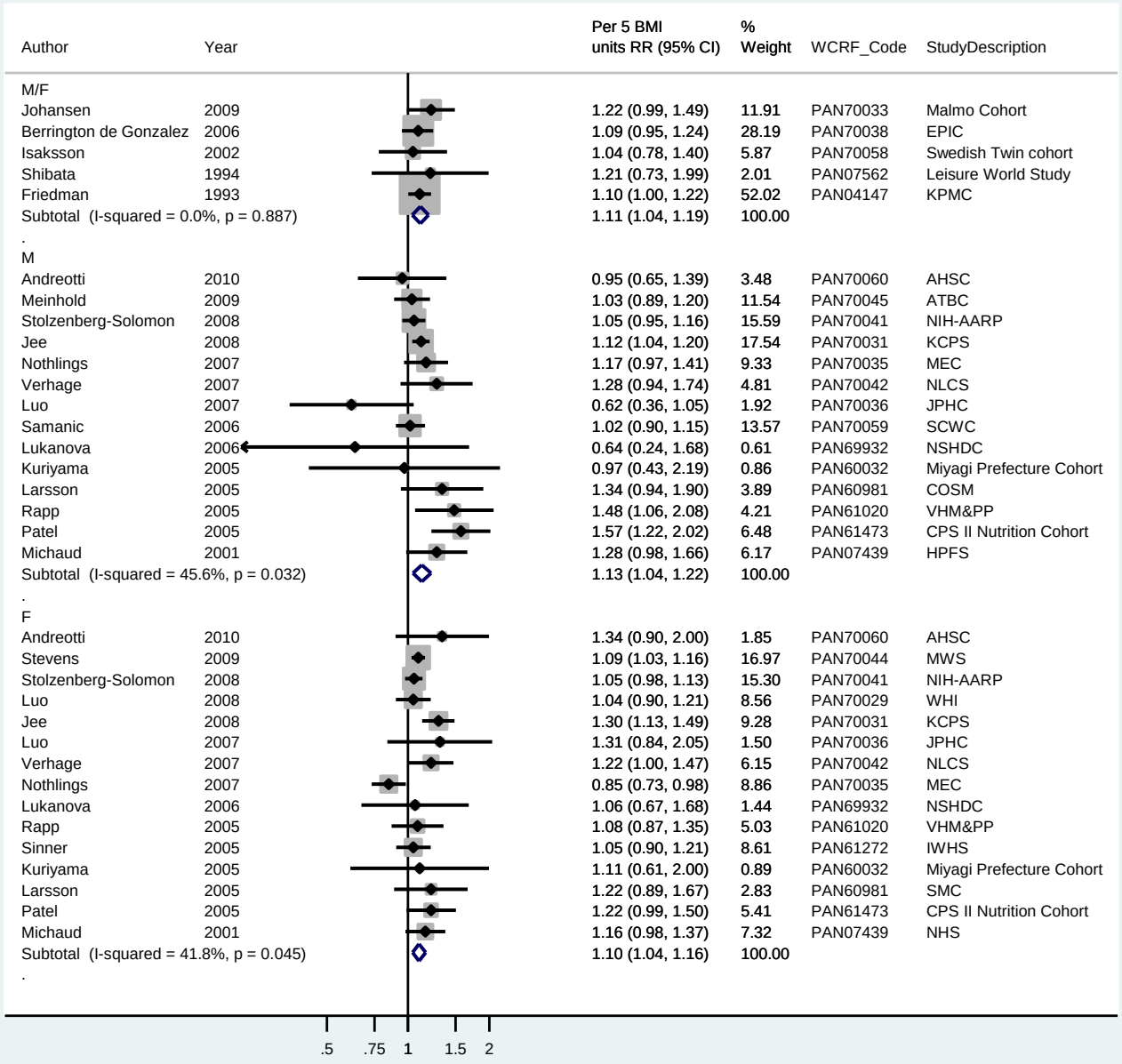


Figure 185 Nonlinear dose-response analysis of BMI and pancreatic cancer incidence

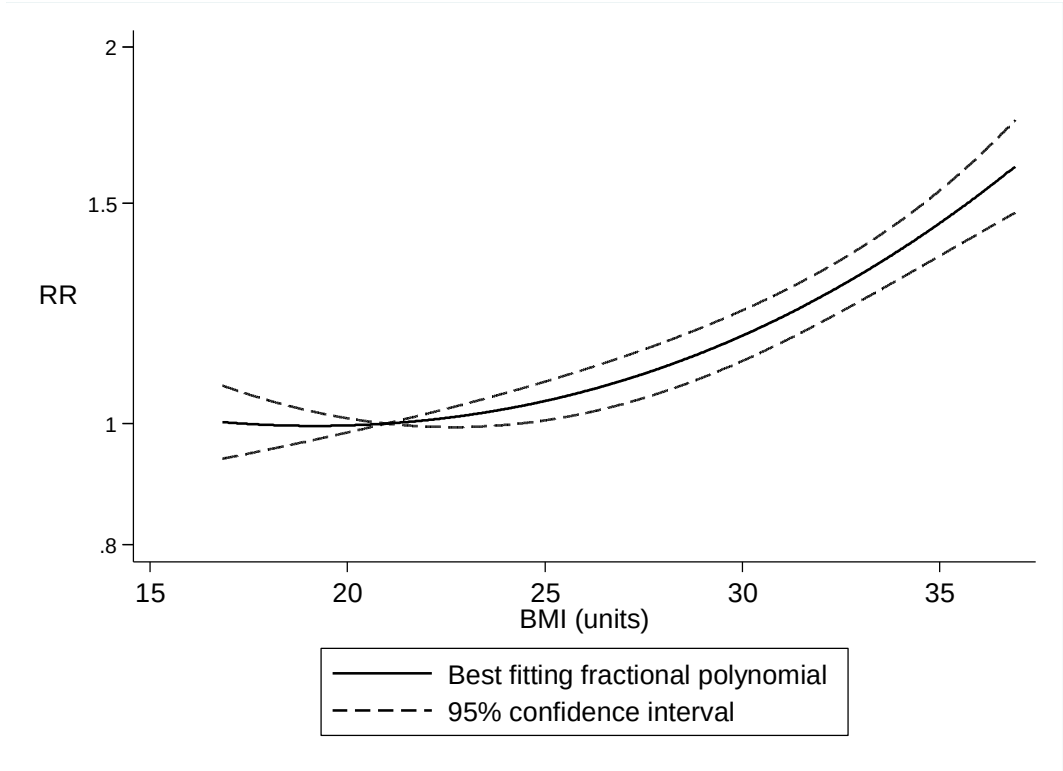


Figure 186 Scatter plot of risk estimates for BMI and pancreatic cancer incidence

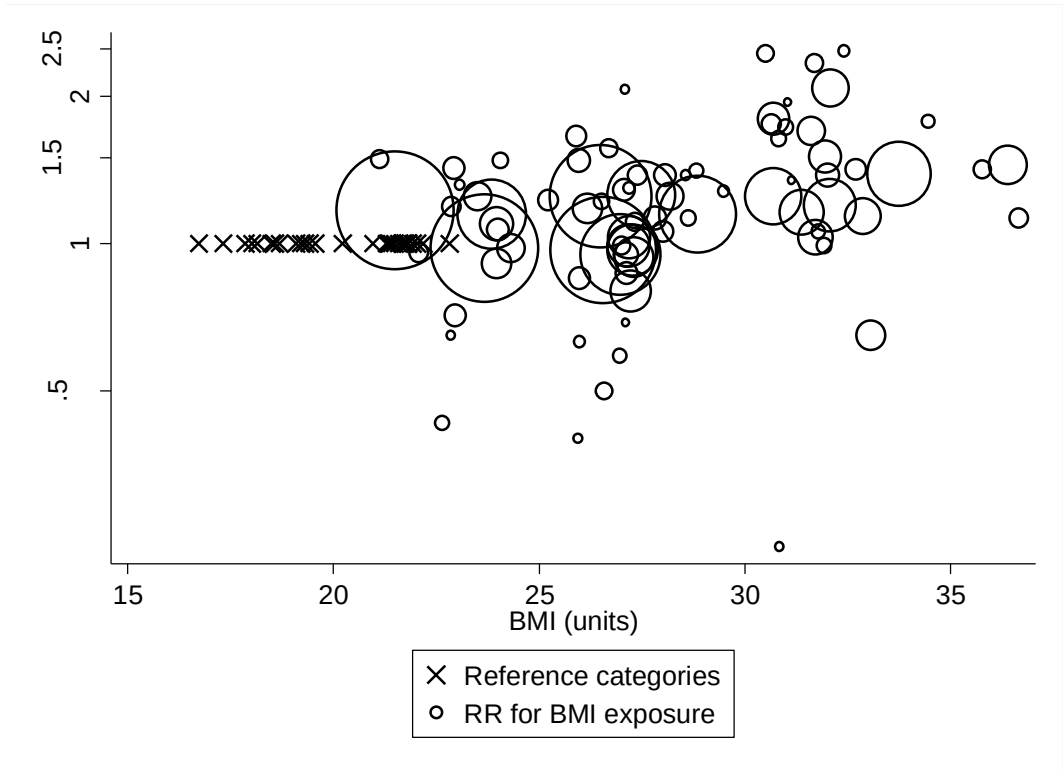


Table 165 Table with BMI values and corresponding RRs (95% CIs) for nonlinear analysis of BMI and pancreatic cancer incidence

BMI	RR (95% CI)
21	1.00
22.5	1.01 (0.99-1.03)
25	1.04 (1.01-1.08)
27.5	1.10 (1.05-1.15)
30	1.18 (1.12-1.23)
32.5	1.29 (1.23-1.35)
35	1.45 (1.36-1.53)
37.5	1.66 (1.51-1.83)

Figure 187 Highest versus lowest forest plot of BMI and pancreatic cancer mortality

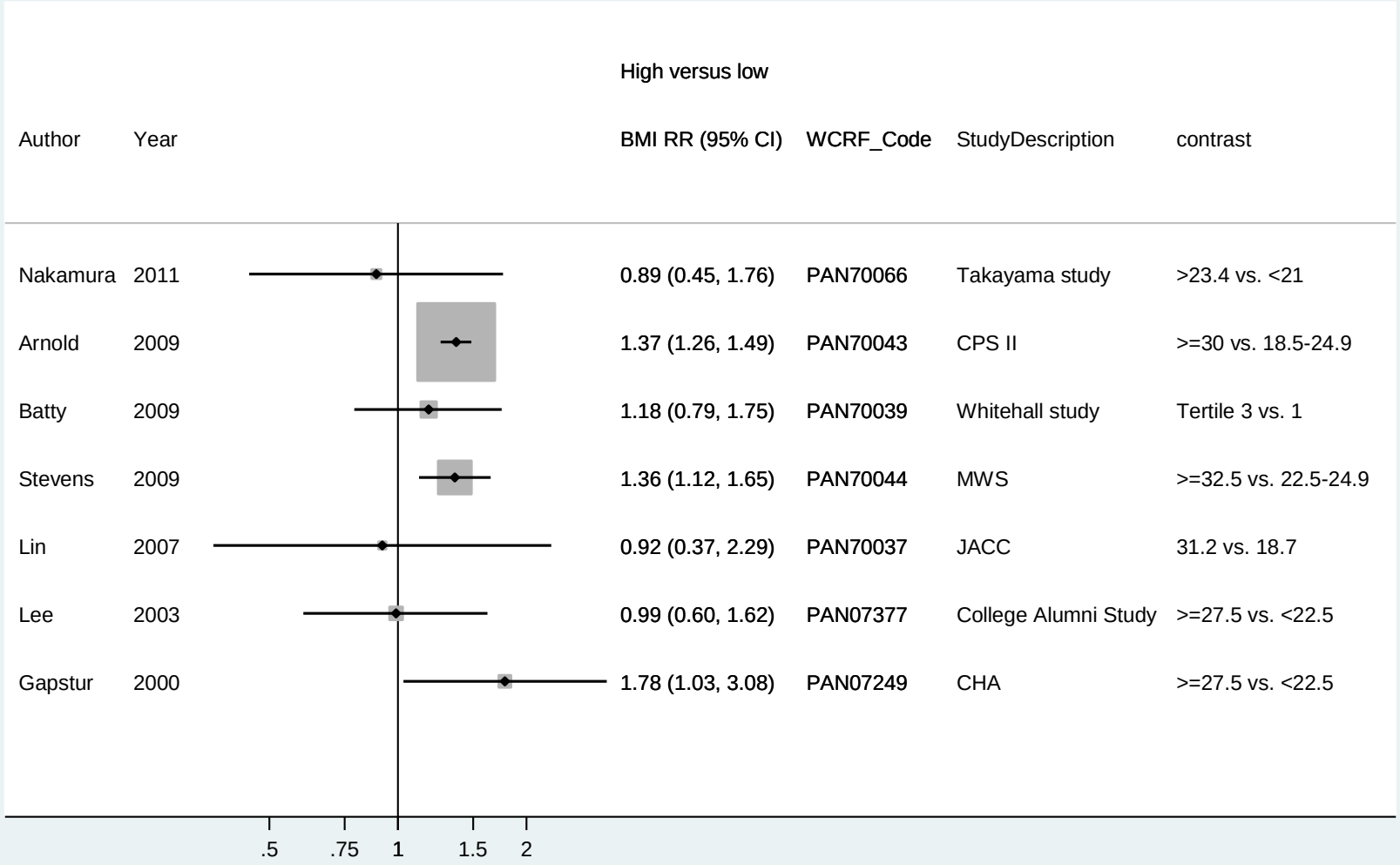


Figure 188 Dose-response meta-analysis of BMI and pancreatic cancer mortality - per 5 units

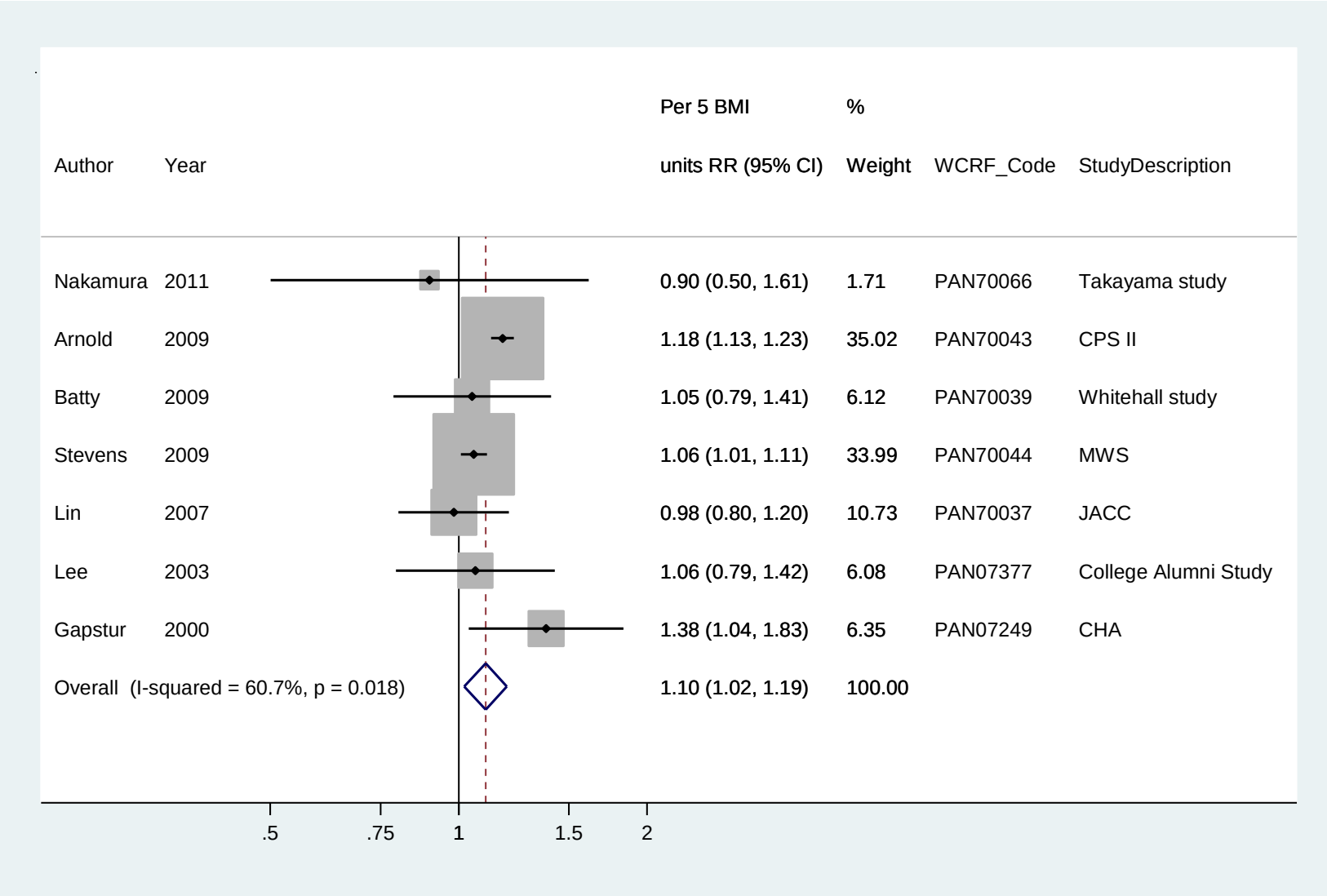


Figure 189 Funnel plot of BMI and pancreatic cancer mortality

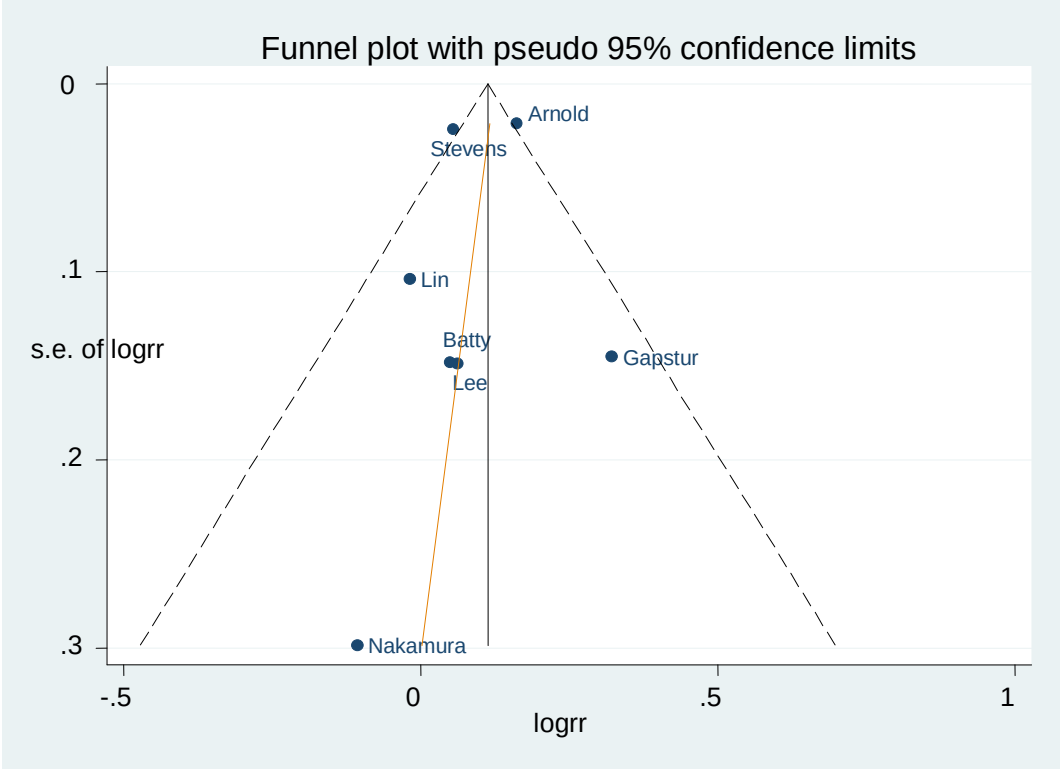


Figure 190 Dose-response graph of BMI and pancreatic cancer mortality

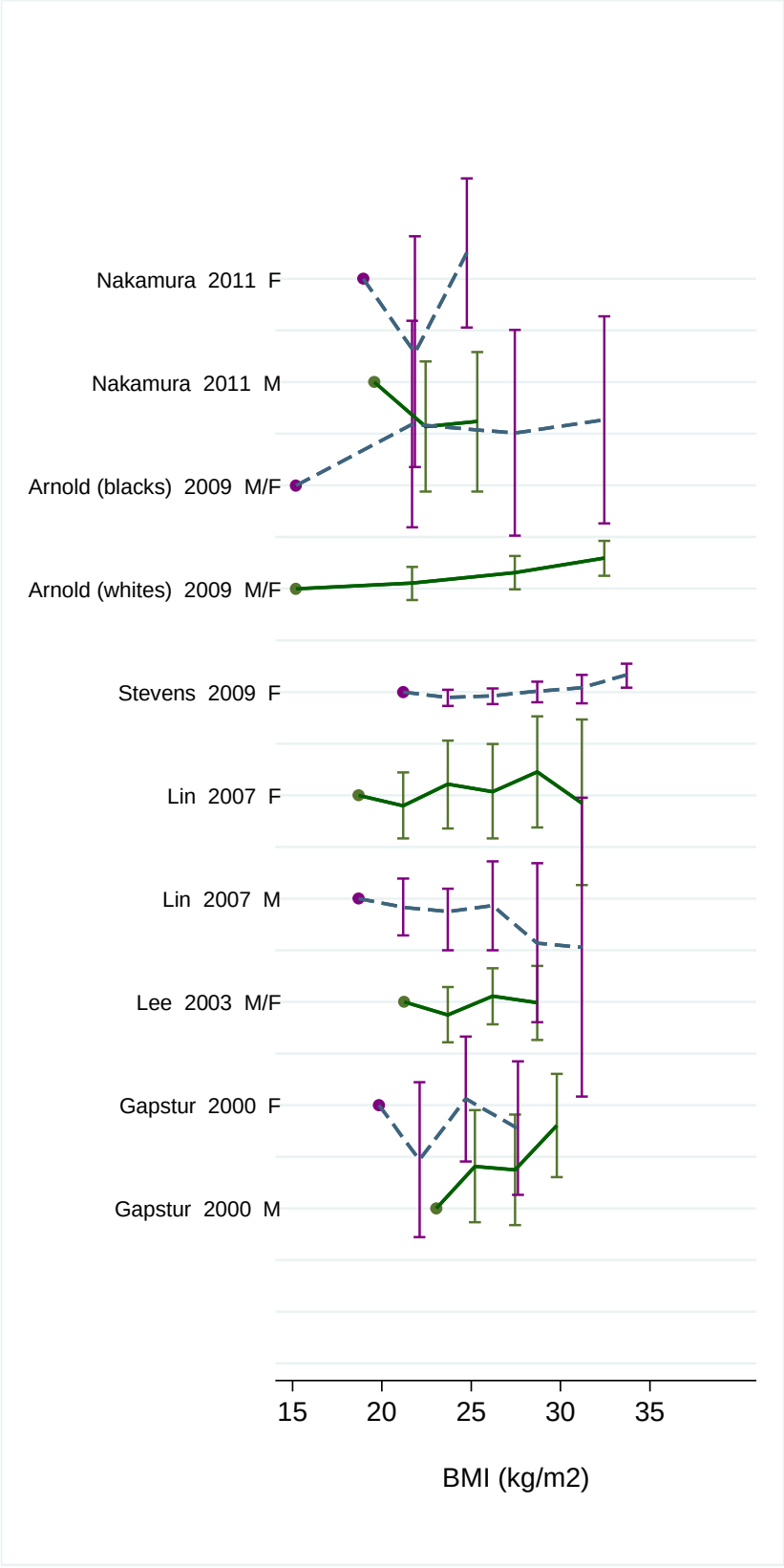


Figure 191 Nonlinear dose-response analysis of BMI and pancreatic cancer mortality

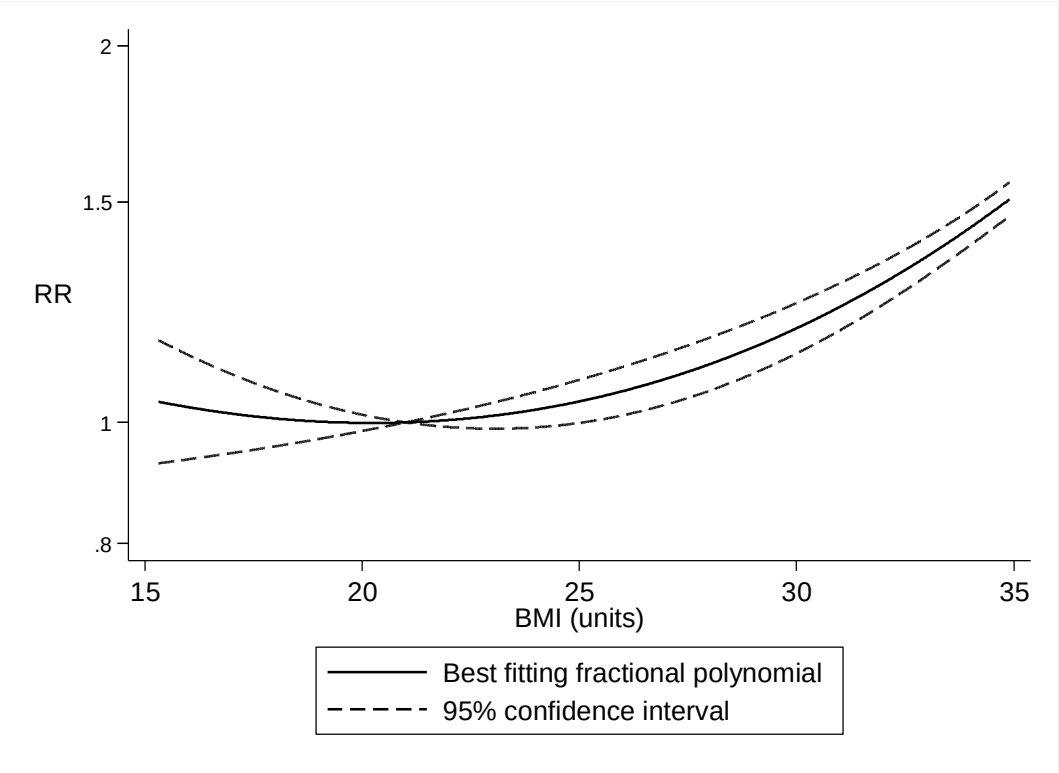


Figure 192 Scatter plot of risk estimates for BMI and pancreatic cancer mortality

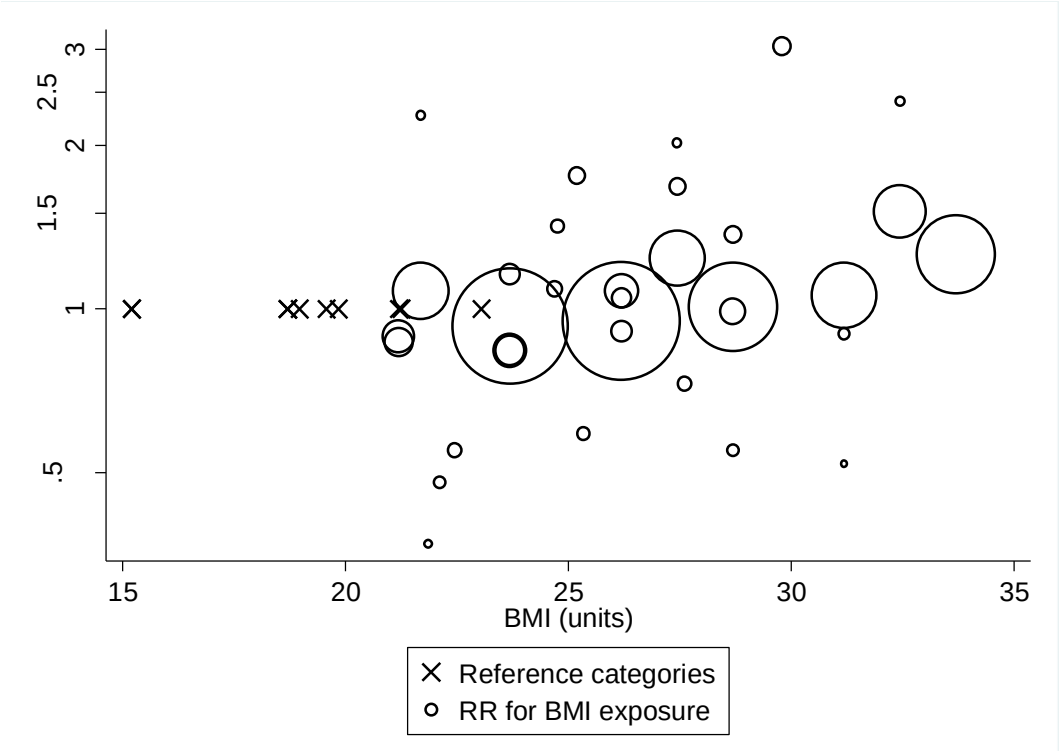


Table 166 Table with BMI values and corresponding RRs (95% CIs) for nonlinear analysis of BMI and pancreatic cancer mortality

BMI	RR (95% CI)
21	1.00
22.5	1.01 (0.99-1.03)
25	1.04 (1.00-1.08)
27.5	1.10 (1.05-1.15)
30	1.19 (1.14-1.25)
32.5	1.32 (1.27-1.37)
35	1.52 (1.47-1.56)

8.1.1 BMI at age ~20 years

Methods

Six studies were included in the review of BMI at age ~20 years and pancreatic cancer risk, three of which were identified in the Continuous Update Project up to 28th of September 2011. Four of the studies could be included in the dose-response analysis which is presented per 5 BMI units.

Main results

The summary RR for a 5 unit increment in BMI was 1.12 (95% CI: 0.97-1.29, I^2=0%, p=0.61, 3 studies).

Heterogeneity

There was no evidence of heterogeneity (I^2=0%, p=0.61) in the analyses.

Comparison with the Second Expert Report

There was no significant association between BMI at age ~20 years and pancreatic cancer. No meta-analysis was conducted in the Second Expert Report.

Published pooled analysis

A pooled analysis of 11 prospective studies found an increased pancreatic cancer risk with greater BMI in young adulthood, pooled multivariate RR = 1.30 (95% CI: 1.09-1.56) for BMI ≥30 vs. 23-24.9 (Genkinger et al, 2011) and this remained significant after further adjustment for BMI in adulthood, pooled RR = 1.21 (95% CI: 1.01-1.45).

Table 167 Studies on BMI at age ~20y identified in the CUP

Author, year	Country	Study name	Number of cases	Years of Follow-up	Sex	RR	LCI	UCI	Contrast
Nakamura, 2011	Japan	The Takayama Study	33 19	7	M F	0.71 1.05	0.31 0.33	1.62 3.36	≥22.3 vs. <20.3 ≥22.1 vs. <20
Verhage, 2007	Netherlands	Netherlands Cohort Study	446	13.3	M F	1.07 0.97	0.67 0.66	1.73 1.44	≥23 vs. <20 ≥23 vs. <20
Lin, 2007	Japan	Japan Collaborative Cohort Study	402	14	M F	3.51 0.43	1.26 0.06	9.78 3.15	≥30 vs. 20-22.4 ≥30 vs. 20-22.4

Table 168 Overall evidence on BMI at age ~20y and pancreatic cancer

	Summary of evidence
SLR	Three cohort studies reported non-significant positive associations between BMI at age ~20 years and risk of pancreatic cancer. No meta-analysis was conducted.
Continuous Update Project	Three new studies were identified. One study reported a significantly increased risk among men, but not women, while the two remaining studies reported no significant association.

Table 169 Summary of results of the dose-response meta-analysis of BMI at age ~20 years and pancreatic cancer

Pancreatic cancer incidence and mortality		
	SLR*	Continuous Update Project
Studies (n)	-	4
Cases (n)	-	900
Increment unit	-	Per 5 units
RR (95% CI)	-	1.12 (0.97-1.29)
Heterogeneity (I^2, p-value)	-	0%, p=0.61

*No meta-analysis was conducted in the 2nd report.

Table 170 Inclusion/exclusion for meta-analysis table of BMI at age ~20 years and pancreatic cancer

WCRF code	Author	Year	Study design	Study name	Subgroup	Cancer outcome	SLR	CUP dose-response meta-analysis	CUP HvL forest plot	Estimated values	Exclusion reason
PAN70066	Nakamura	2011	Prospective cohort study	Takayama Study	Men/women	Mortality	New	Yes	Yes	Mid-exposure values	
PAN70042	Verhage	2007	Case-cohort study	Netherlands Cohort Study	Men/women	Incidence	New	Yes	Yes		
PAN70037	Lin	2007	Prospective cohort study	Japan Collaborative Cohort Study	Men/women	Incidence	New	Yes	Yes	Mid-exposure values	
PAN61473	Patel	2005	Prospective cohort study	Cancer Prevention Study II – Nutrition Cohort	Men/women	Incidence	Yes	Yes	Yes	Mid-exposure values	
PAN07439	Michaud	2001	Prospective cohort study	Nurses' Health Study	Women	Incidence	Yes	No	Yes		Only high vs. low comparison
PAN07439	Michaud	2001	Prospective cohort study	Health Professionals Follow-up Study	Men	Incidence	Yes	No	Yes		Only high vs. low comparison

Figure 193 Highest versus lowest forest plot of BMI at age ~20 years and pancreatic cancer

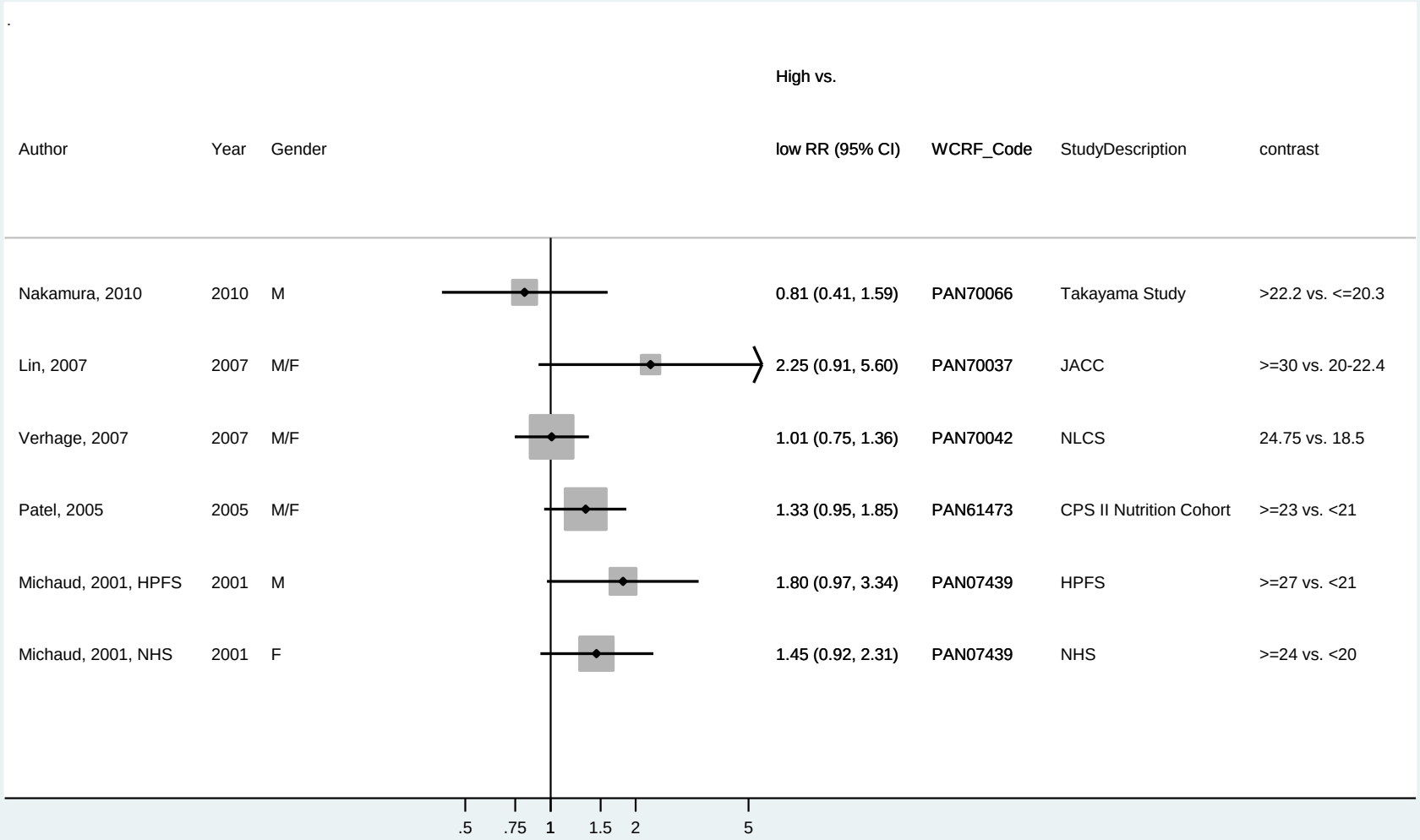


Figure 194 Dose-response meta-analysis of BMI at age ~20 years and pancreatic cancer - per 5 units

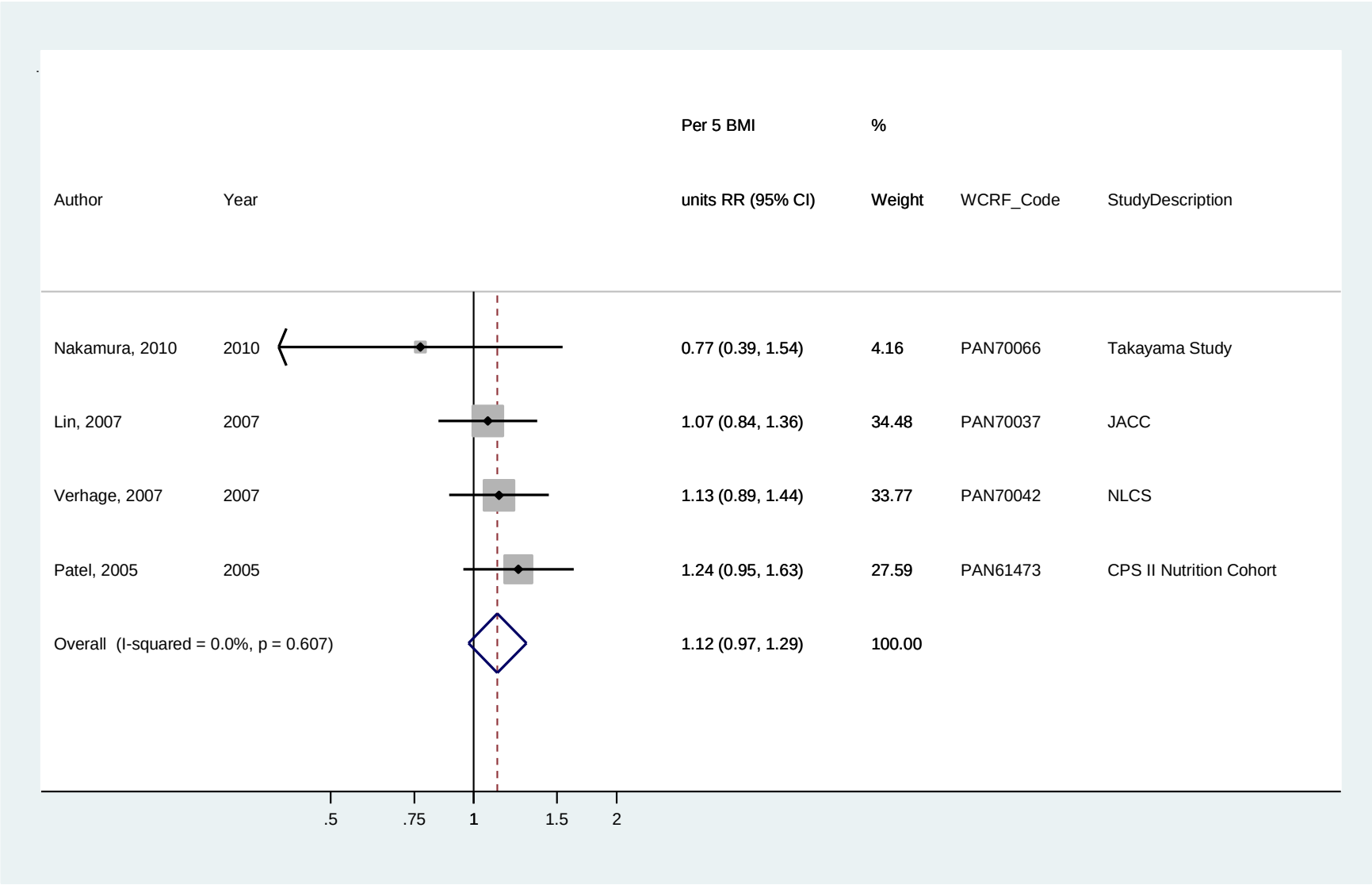
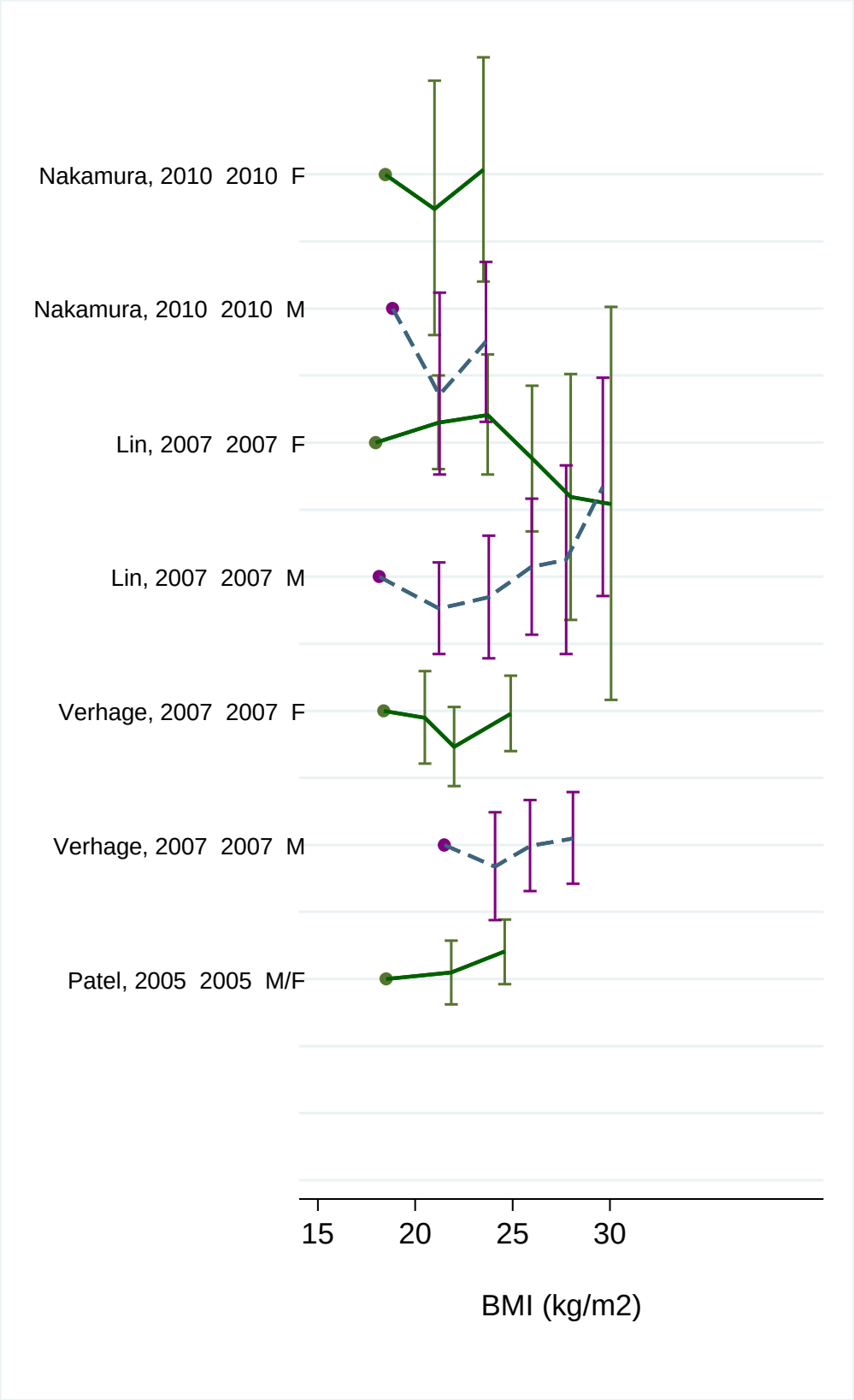


Figure 195 Dose-response graph of BMI at age ~20 years and pancreatic cancer



8.1.3 Weight

Methods

Eight publications (seven studies) were included in the review of weight and pancreatic cancer risk, three of which were identified in the Continuous Update Project up to 28th of September 2011. Five of the studies could be included in the dose-response analysis which is presented per 5 kg.

Main results

The summary RR for a 5 kg increment in weight was 1.04 (95% CI: 1.00-1.08) with high heterogeneity, I^2=68.1%, p=0.01 (n=5). The summary RR ranged from 1.03 (95% CI: 1.00-1.06) when excluding the study by Verhage et al, 2007 to 1.05 (95% CI: 1.01-1.09) when excluding the study by Berrington de Gonzalez et al, 2008. The heterogeneity was reduced when excluding the study by Verhage et al, 2007, I^2=44%, $p_{heterogeneity}$=0.15. There was no evidence of publication bias with Egger's test, p=0.70.

Heterogeneity

There was high heterogeneity in the analyses which was partly explained by one study.

Comparison with the Second Expert Report

Our results are consistent with the Second Expert Report in finding a borderline significant positive association between weight and pancreatic cancer risk.

Pooled analysis

A pooled analysis in the Pancreatic Cancer Cohort Consortium found an increased pancreatic cancer risk with greater weight, the pooled OR was 1.30 (95% CI: 1.09-1.54) for the highest vs. the lowest quartile (Arslan, 2010).

Table 171 Studies on weight identified in the CUP

Author/year	Country	Study name	Number of cases	Years of Follow-up	Sex	RR	LCI	UCI	Contrast
Berrington de Gonzalez, 2008	Korea	Korea National Health Insurance Corporation study	2194	12	M/F	1.04	0.90	1.19	>68.11 vs.<53.44
Verhage, 2007	Netherlands	Netherlands Cohort Study	446	13.3	M F	1.55 1.64	0.99 1.07	2.45 2.52	95.1 vs. 68.5 86.1 vs. 58.5
Berrington De Gonzalez, 2006	Europe	European Prospective Investigation into Cancer and Nutrition	324	6.5	M/F	1.14	0.82	1.61	>77.18 vs.<62.87

Table 172 Overall evidence on weight and pancreatic cancer

	Summary of evidence
SLR	Four cohort studies were available. Three were included in the dose-response analysis. All studies showed no significant association between weight and pancreatic cancer risk.
Continuous Update Project	Three new studies were identified. One study reported a significant increase in women and a marginally significant positive association among men. The two other new studies reported no significant association.

Table 173 Summary of results of the dose-response meta-analysis of weight and pancreatic cancer

Pancreatic cancer incidence		
	SLR	Continuous Update Project
Studies (n)	3	5
Cases (n)	665	3586
Increment unit	Per 1 kg	Per 5 kg
RR (95% CI)	1.004 (0.991-1.018)	1.04 (1.00-1.08)
Heterogeneity (I^2, p-value)	60%, p=0.084	68.1%, p=0.01

Table 174 Inclusion/exclusion table for meta-analysis of weight and pancreatic cancer

WCRF code	Author	Year	Study design	Study name	Subgroup	Cancer outcome	SLR	CUP dose-response meta-analysis	CUP HvL forest plot	Estimated values	Exclusion reason
PAN70049	Berrington de Gonzalez	2008	Prospective cohort study	National Health Insurance Corporation Study	Men/women	Incidence	New	Yes	Yes	Mid-exposure values, person-years, distribution of cases	
PAN70042	Verhage	2007	Case-cohort study	Netherlands Cohort Study	Men/women	Incidence	New	Yes	Yes		
PAN70038	Berrington de Gonzalez	2006	Prospective cohort study	European Prospective Investigation into Nutrition and Cancer	Men/women	Incidence	New	Yes	Yes	Mid-exposure values, person-years	
PAN20232	Stolzenberg-Solomon	2004	Nested case-control study	ATBC Cancer Prevention Study	Men	Incidence	Yes	No	No		Mean exposure, duplicate
PAN07586	Stolzenberg-Solomon	2002	Prospective cohort study	ATBC Cancer Prevention Study	Men	Incidence	Yes	Yes	Yes	Mid-exposure values	
PAN14732	Nilsen	2000	Prospective cohort study	HUNT	Men/women	Incidence	Yes	No	Yes		Only two categories
PAN07481	Ogren	1996	Prospective cohort study	Malmo Preventive Project Cohort Study	Men/women	Incidence	Yes	No	No		Mean exposure
PAN04147	Friedman	1993	Nested case-control study	Kaiser Permanente Medical Check-up Phase	Men/women	Incidence	Yes	Yes	No		Only continuous result

Figure 196 Highest versus lowest forest plot of weight and pancreatic cancer

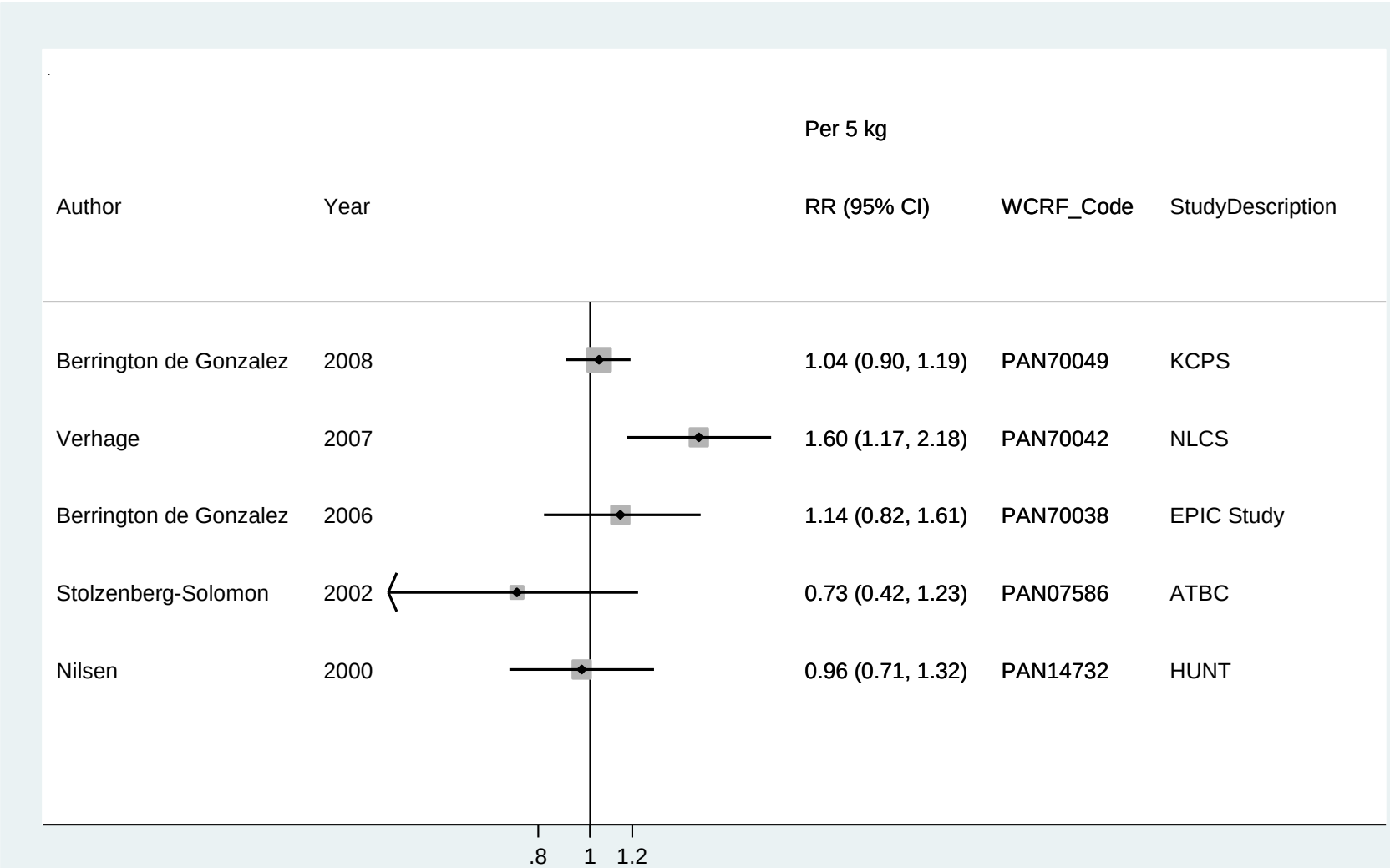


Figure 197 Dose-response meta-analysis of weight and pancreatic cancer - per 5 kg

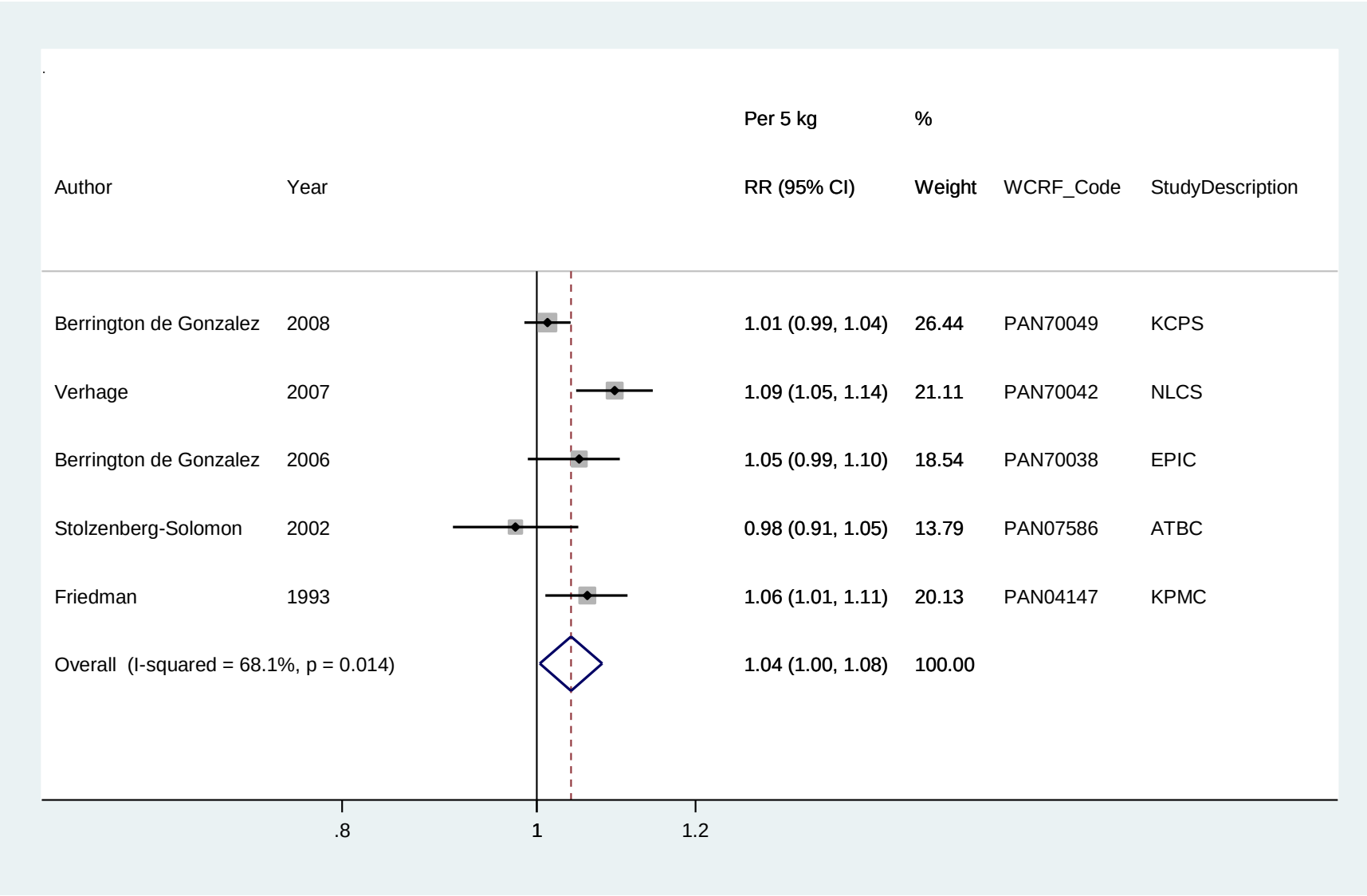


Figure 198 Funnel plot of weight and pancreatic cancer

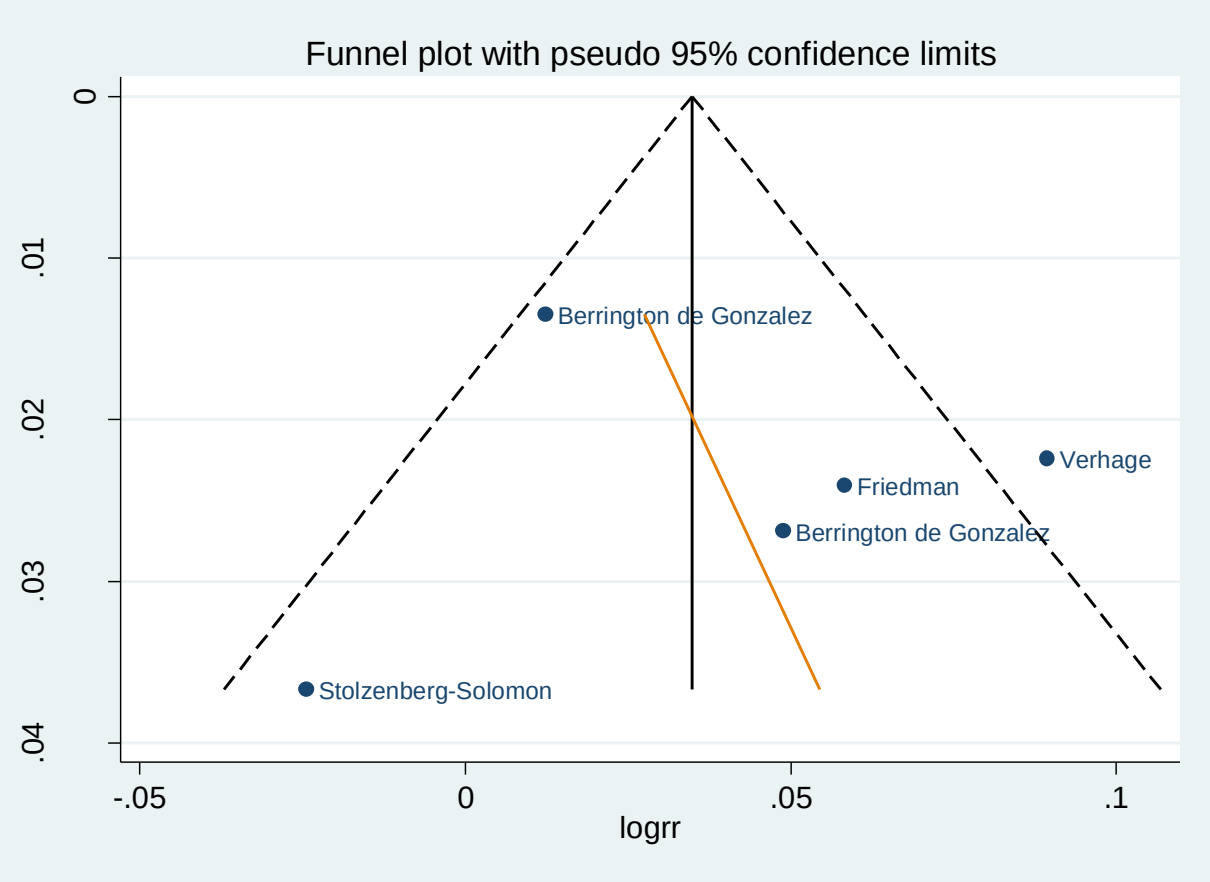
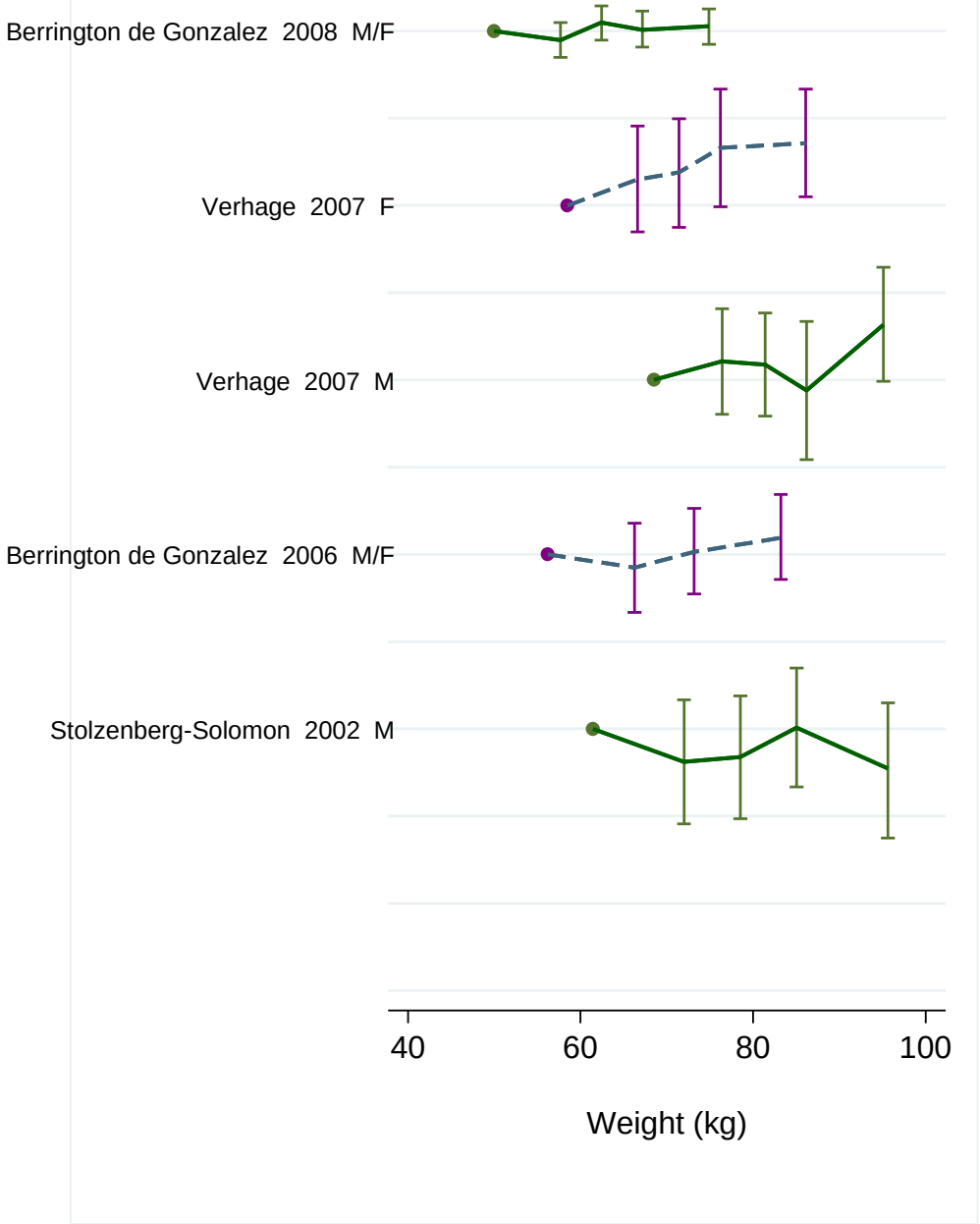


Figure 199 Dose-response graph of weight and pancreatic cancer risk



8.1.6 Change in body composition (including weight gain)

In the Netherland Cohort Study (Verhage et al, 2007) BMI change since age 20 years was positively associated with pancreatic cancer risk (HR for 1 kg/m^2 increase =1.07 ; 95% CI= 0.99-1.15). The association was statistically significant only when the analyses were restricted to microscopically verified cases (HR: 1.12; 95% CI=1.04-1.21).

Three studies on weight change were identified during the Continuous Update Project. Meta-analysis was not possible because weight change was reported in different ways. None of the studies reported statistically significant associations. In the Women's Health Initiative clinical trial and observational study, none of the types of weight changes investigated (steady gain in weight , lost weight and kept it off and weight up and down) were related to pancreatic cancer risk when compared to stable weight (Luo et al 2008). In the Malmo Preventive Project, weight gain above 10 kg was not related to risk of pancreatic cancer compared to weight gain below 10 kg (Johansen, 2009). In the Japanese Collaborative Cohort study for Evaluation of Cancer Risk (JACC), the risk of death from pancreatic cancer was not associated with weight gain between age 20 years and baseline age in either men or women (Lin, 2007).

Five studies on weight change were identified during the Second Expert Report. None of the studies provided evidence of an association. In a case-control study nested in an American cohort, decreased risk was noted for a weight gain of more than 10 lb in the 6 months preceding the questionnaire. This result might have been explained by chance as in a study with multiple comparisons. In the same study BMI was positively related to pancreatic cancer (Friedman, 1993). In a small case-control study nested in the Malmo Preventive Cohort Study weight gain of 10 kg or more since age 30 years was associated with a two-fold increased risk of pancreatic cancer (Ogren, 1996). In the Nurses'Health Study and the Health Professional Follow-up Study, participants reporting 6.75 kg or more weight loss between two consecutive biennial questionnaire experienced higher risk of pancreatic cancer compared to those whose weight had not changed more than 2.5 kg. This finding was attributed to pre-clinical disease (Michaud, 2001). In the Swedish Twin registry (Isaksson et al, 2002) the relative risk comparing individuals with weight gain of 12 kg or more compared to those with 2-6 kg weight gain was 1.46 (95% CI=0.87–2.45). In the Cancer Prevention Study II, adult weight change was not associated to pancreatic cancer risk. However, after adjustment for baseline BMI, risk of pancreatic cancer was increased among men and women who reported a tendency for central weight gain compared with men and women reporting a tendency for peripheral weight gain (RR, 1.45; 95% CI, 1.02-2.07) (Patel, 2005). In summary, although most studies reported null results, it cannot be excluded that weight gain may increase the risk of pancreatic cancer. Consistent with this is the finding of a pooled analysis of 14 prospective studies which found an increased risk among persons who increased their BMI from <25 in early adulthood to ≥30 at baseline of the studies, pooled RR = 1.38 (95% CI: 1.14-1.66) (Genkinger et al, 2011). There was also an increased pancreatic cancer risk among persons who increased their BMI by >10 units from early adulthood to baseline in the studies, pooled RR=1.40 (95% CI: 1.13-1.72).

8.2.1 Waist circumference

Methods

A total of 4 publications from 5 different cohort studies have been published on waist circumference and pancreatic cancer risk up to 28th of September 2011, three of which were identified during the Continuous Update Project. Dose-response analyses of waist circumference and pancreatic cancer were conducted and results are reported for a 10 cm increment.

Main results

The summary RR for a 10 cm increase in waist circumference was 1.11 (95% CI: 1.05-1.18, I^2=0%, p=0.74, 5 studies). The summary RR ranged from 1.11 (95% CI: 1.04-1.17) when excluding the Cohort of Swedish Men (Larsson et al, 2005) to 1.14 (95% CI: 1.06-1.22) when excluding the Women's Health Initiative (Luo et al, 2008). There was no evidence of publication bias with Egger's test, p=0.11. There was no evidence of a nonlinear association between waist circumference and pancreatic cancer risk, $p_{nonlinearity}$=0.28.

Heterogeneity

There was no evidence of heterogeneity (I^2=0%, p=0.74) in the studies.

Comparison with the Second Expert Report

This meta-analysis found a positive association between waist circumference and pancreatic cancer risk and thus are consistent with the results from the Second Expert Report.

Pooled analysis

A pooled analysis of 7 prospective studies (743 cases) found no significant association between greater waist circumference and pancreatic cancer risk, pooled multivariate RR = 1.16 (95% CI: 0.92-1.46) for the highest vs. the lowest quartile (Genkinger et al, 2011) and this was attenuated after further adjustment for BMI, pooled RR= 1.04 (95% CI: 0.73-1.47). A pooled analysis from the Pancreatic Cancer Cohort Consortium (812 cases) reported a significant positive trend with greater waist circumference, summary OR=1.23 (95% CI: 0.94-1.62, p_{trend}=0.04) Arslan, 2010).

Table 175 Studies on waist circumference identified in the CUP

Author, year	Country	Study name	Number of cases	Years of Follow-up	Sex	RR	LCI	UCI	Contrast
Luo, 2008	USA	Women's Health Initiative	251	7.7	F	1.1 1.05	0.7 0.95	1.6 1.15	105 vs. 70.5 cm Per 10 cm
Stolzenberg-Solomon, 2008	USA	NIH-AARP Diet and Health Study	654	4.5	M F	1.07 2.52	0.69 1.33	1.64 4.77	106+ vs. <88.9 cm 92.1 vs. <74.9 cm
Berrington de Gonzalez, 2006	Europe	European Prospective Investigation into Nutrition and Cancer	324	6.5	M/F	1.14 1.13	0.79 1.01	1.63 1.26	101+/88+ vs <88/<77 cm Per 10 cm

Table 176 Overall evidence on waist circumference and pancreatic cancer

	Summary of evidence
SLR	Two studies were included in the meta-analysis, both showed non-significant positive associations.
Continuous Update Project	Three new studies were identified. All the studies show positive associations which are significant in two studies, although in one of these the association was significant only among women.

Table 177 Summary of results of the dose-response meta-analysis of waist circumference and pancreatic cancer

Pancreatic cancer incidence		
	SLR	Continuous Update Project
Studies (n)	2	5
Cases (n)	136	949
Increment unit	Per 1 cm	Per 10 cm
RR (95% CI)	1.02 (1.00-1.04)	1.11 (1.05-1.18)
Heterogeneity (I^2, p-value)	0%, p=0.5	0%, p=0.74
Stratified analyses		
Men	-	1.13 (0.89-1.44), n=2
Heterogeneity (I^2, p-value)	-	61%, p=0.11
Women	-	1.14 (1.02-1.28), n=3
Heterogeneity (I^2, p-value)	-	29%, p=0.24

Table 178 Inclusion/exclusion table for meta-analysis of waist circumference and pancreatic cancer

WCRF code	Author	Year	Study design	Study name	Subgroup	Cancer outcome	SLR	CUP dose-response meta-analysis	CUP HvL forest plot	Estimated values	Exclusion reason
PAN70029	Luo	2008	Prospective cohort study	Women's Health Initiative	Women	Incidence	New	Yes	Yes	Mid-exposure values	
PAN70041	Stolzenberg-Solomon	2008	Prospective cohort study	NIH-AARP Diet and Health Study	Men/women	Incidence	New	Yes	Yes	Mid-exposure values	
PAN70038	Berrington de Gonzalez	2006	Prospective cohort study	European Prospective Investigation into Nutrition and Cancer	Men/women	Incidence	New	Yes	Yes	Mid-exposure values, person-years	
PAN60981	Larsson	2005	Prospective cohort study	Swedish Mammography Cohort	Women	Incidence	Yes	Yes	Yes		
PAN60981	Larsson	2005	Prospective cohort study	Cohort of Swedish Men	Men	Incidence	Yes	Yes	Yes		

Figure 200 Highest versus lowest forest plot of waist circumference and pancreatic cancer

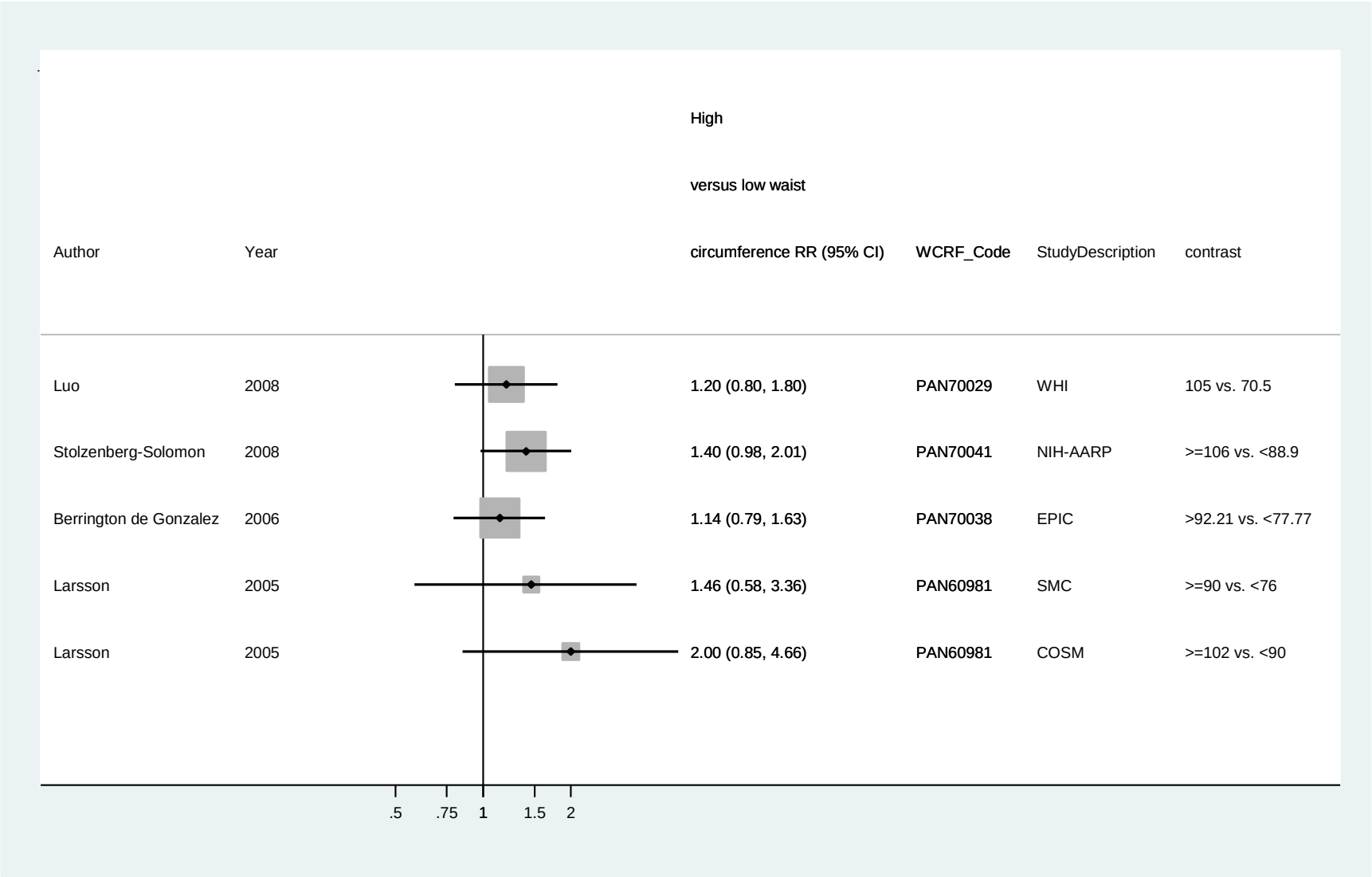


Figure 201 Dose-response meta-analysis of waist circumference and pancreatic cancer - per 10 cm

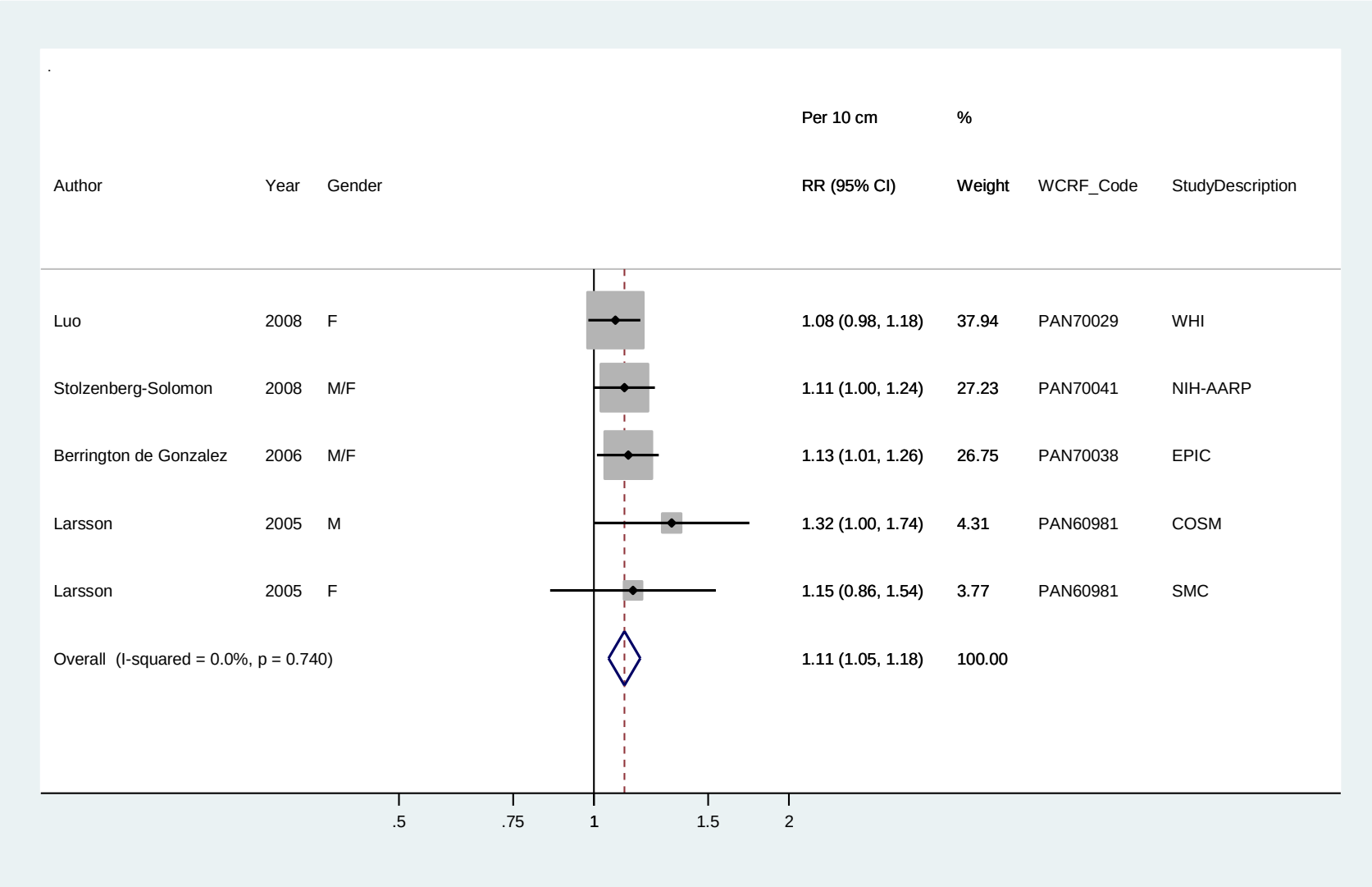


Figure 202 Funnel plot of waist circumference and pancreatic cancer

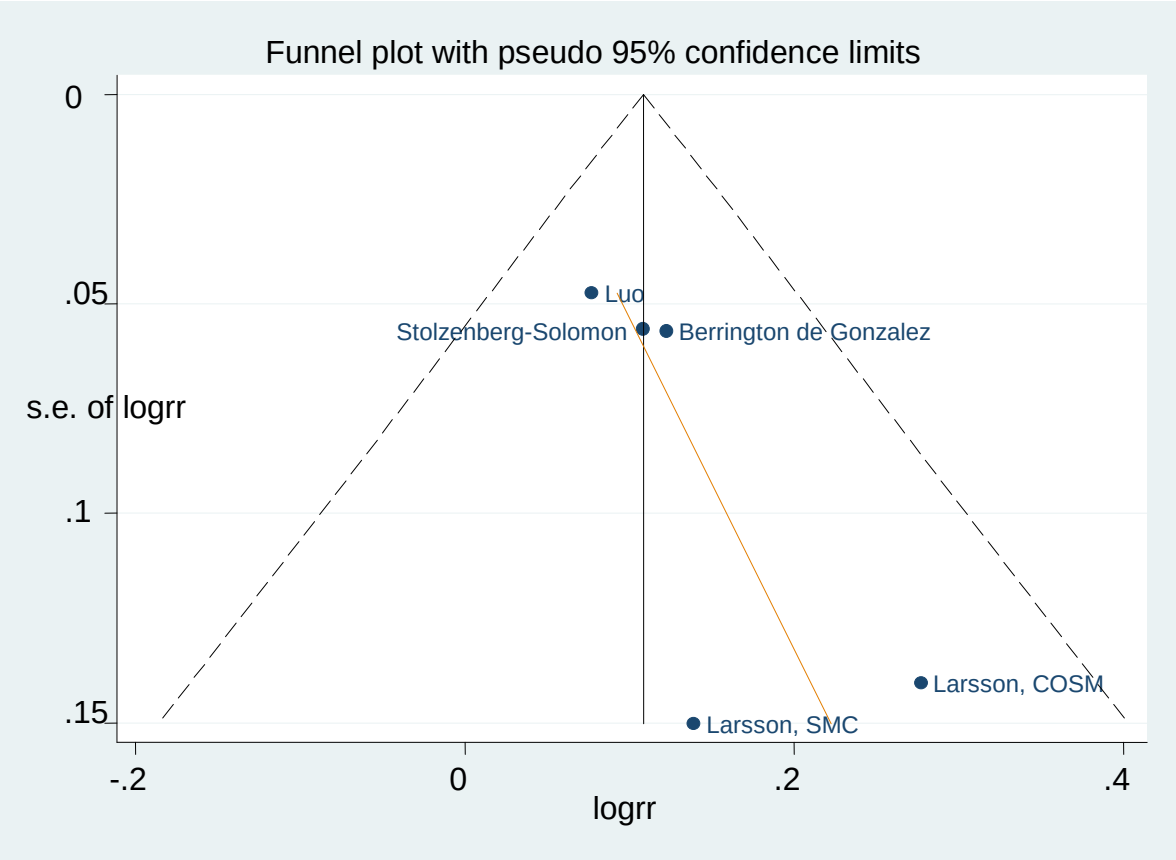


Figure 203 Dose-response graph of waist circumference and pancreatic cancer

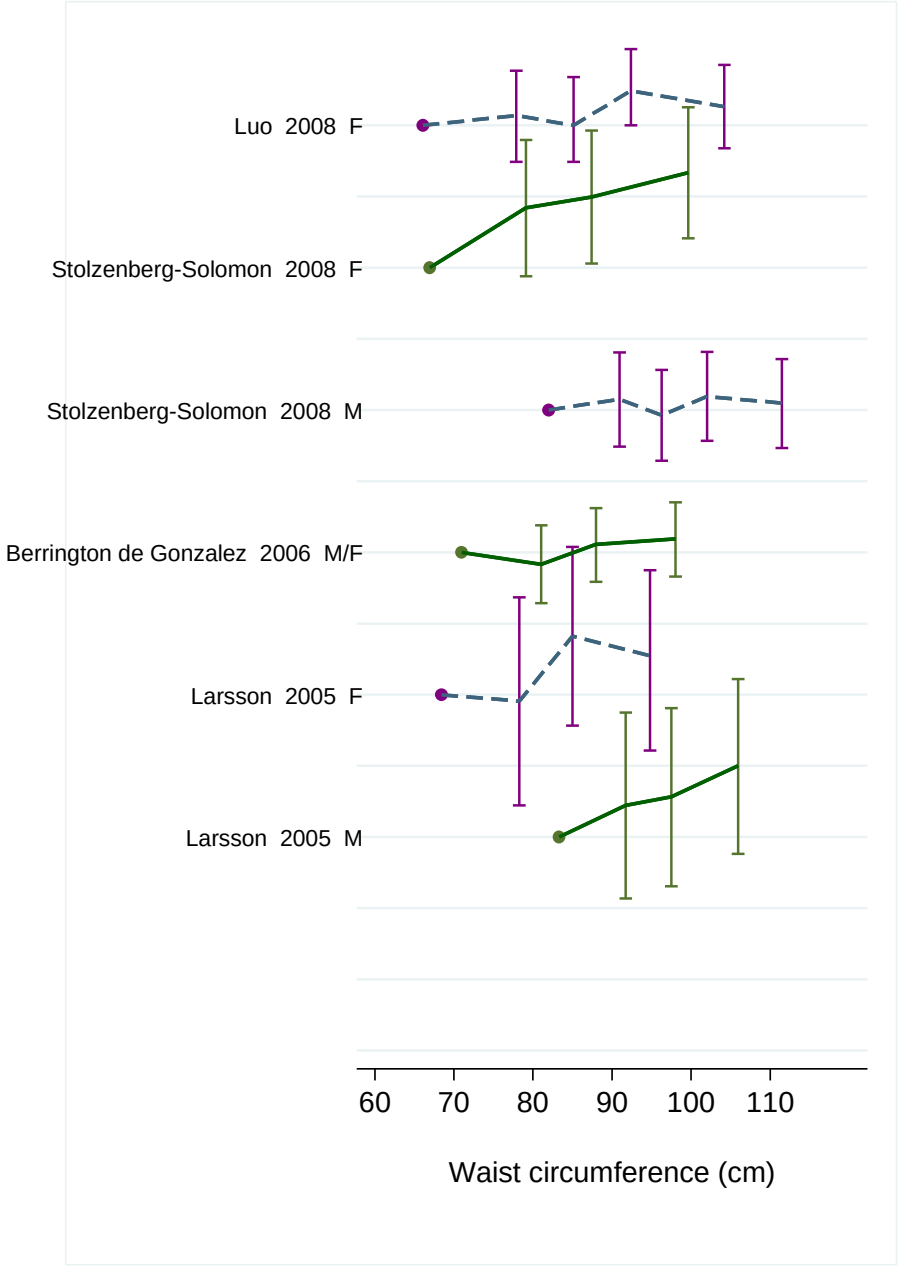


Figure 204 Dose response meta-analysis of waist circumference and pancreatic cancer, stratified by sex - per 10 cm

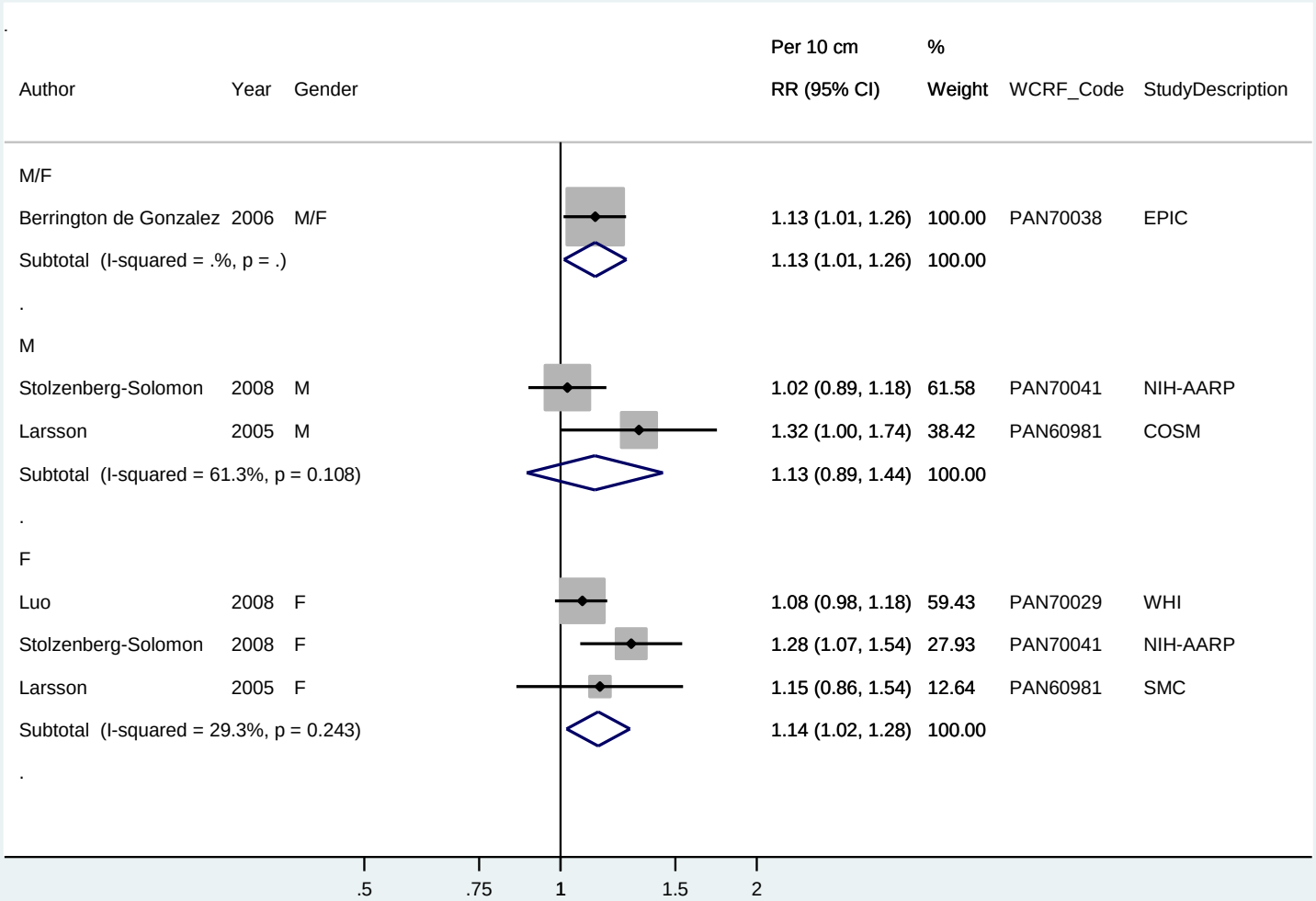


Figure 205 Nonlinear dose-response analysis of waist circumference and pancreatic cancer

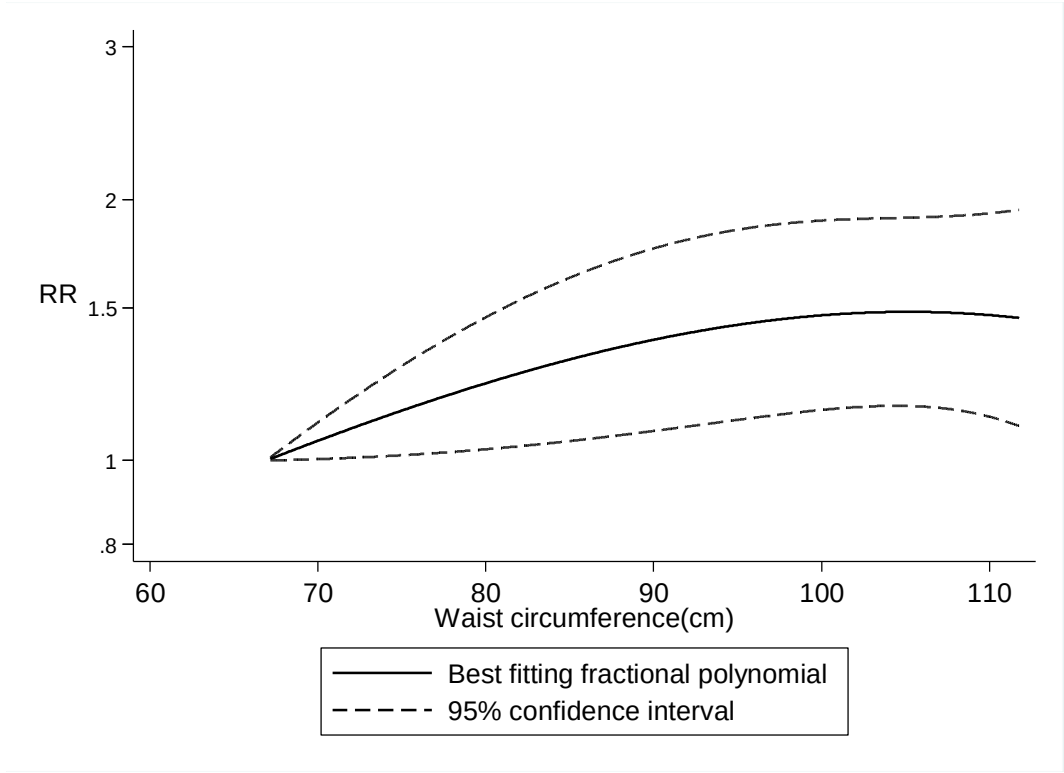


Figure 206 Scatter plot of risk estimates for waist circumference and pancreatic cancer

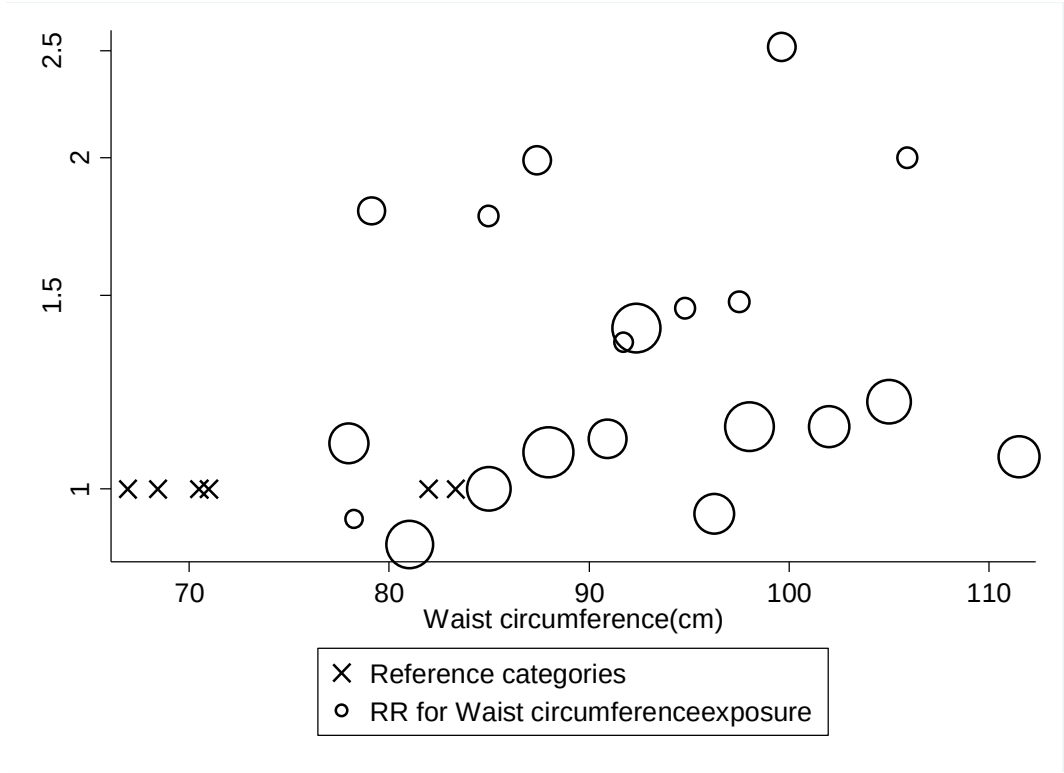


Table 179 Table with waist circumference values and corresponding RRs (95% CIs) for nonlinear analysis of waist circumference and pancreatic cancer

Waist circumference	RR (95% CI)
67 cm	1.00
70	1.05 (1.00-1.11)
75	1.14 (1.01-1.28)
80	1.23 (1.03-1.46)
85	1.31 (1.05-1.62)
90	1.38 (1.08-1.76)
95	1.43 (1.11-1.85)
100	1.47 (1.14-1.89)
105	1.48 (1.16-1.91)
110	1.47 (1.12-1.93)

8.2.2 Hips circumference

Methods

A total of 3 cohort studies have been published on waist-to-hip ratio and pancreatic cancer up to 28th of September 2011, all of which were identified in the Continuous Update Project. Dose-response analyses of hips circumference and pancreatic cancer were conducted. For the dose-response analyses we used a 10 cm increment in hips circumference.

Main results

The summary RR for a 10 cm increment in hips circumference was 1.05 (95% CI: 0.97-1.14, I^2=0%, p=0.48, 3 studies).

Heterogeneity

There was no evidence of heterogeneity (I^2=0%, p=0.61) in the analyses.

Comparison with the Second Expert Report

This meta-analysis found no significant association between hips circumference and pancreatic cancer risk. No meta-analysis was conducted in the Second Expert Report.

Pooled analysis

A pooled analysis of 6 prospective studies (567 cases) found no significant association between greater hips circumference and pancreatic cancer risk, pooled multivariate RR = 1.07 (95% CI: 0.85-1.35) for the highest vs. the lowest quartile (Genkinger et al, 2011) and this was attenuated after further adjustment for BMI, pooled RR= 0.95 (95% CI: 0.69-1.30).

Table 180 Studies on Hips Circumference identified in the CUP

Author, year	Country	Study name	Number of cases	Years of Follow-up	Sex	RR	LCI	UCI	Contrast
Luo, 2008,	USA	Women's Health Initiative	251	7.7	F	1.10	0.70	1.60	122.5 vs. 93.0
Stolzenberg-Solomon, 2008	USA	NIH-AARP Diet and Health Study	290	4.5	M F	1.04 2.07	0.64 1.03	1.70 4.14	≥109.2 vs. <95.9 cm ≥109.2 vs. <95.9 cm
Berrington de Gonzalez, 2006	Europe	European Prospective Investigation into Nutrition and Cancer	280	6.5	M/F	1.20 1.09	0.86 0.94	1.68 1.26	≥105/≥107 vs. <97/<95 cm Per 10 cm

Table 181 Overall evidence on hips circumference and pancreatic cancer

	Summary of evidence
SLR	No studies were identified.
Continuous Update Project	Three studies were identified. Only one study showed a significant positive association, which was restricted to women, while the remaining studies found no association.

Table 182 Summary of results of the dose-response meta-analysis of hips circumference and pancreatic cancer

Pancreatic cancer incidence		
	SLR*	Continuous Update Project
Studies (n)	-	3
Cases (n)	-	821
Increment unit	-	Per 10 cm
RR (95% CI)	-	1.05 (0.97-1.14)
Heterogeneity (I^2, p-value)	-	0%, p=0.48

*No meta-analysis was conducted in the 2nd report.

Table 183 Inclusion/exclusion table for meta-analysis of hips circumference and pancreatic cancer

WCRF code	Author	Year	Study design	Study name	Subgroup	Cancer outcome	SLR	CUP dose-response meta-analysis	CUP HvL forest plot	Estimated values	Exclusion reason
PAN70029	Luo	2008	Prospective cohort study	Women's Health Initiative	Women	Incidence	New	Yes	Yes		
PAN70041	Stolzenberg-Solomon	2008	Prospective cohort study	NIH-AARP Diet and Health Study	Men/women	Incidence	New	Yes	Yes	Mid-exposure values	
PAN70038	Berrington de Gonzalez	2006	Prospective cohort study	European Prospective Investigation into Nutrition and Cancer	Men/women	Incidence	New	Yes	Yes	Mid-exposure values, person-years	

Figure 207 Highest versus lowest forest plot of hips circumference and pancreatic cancer

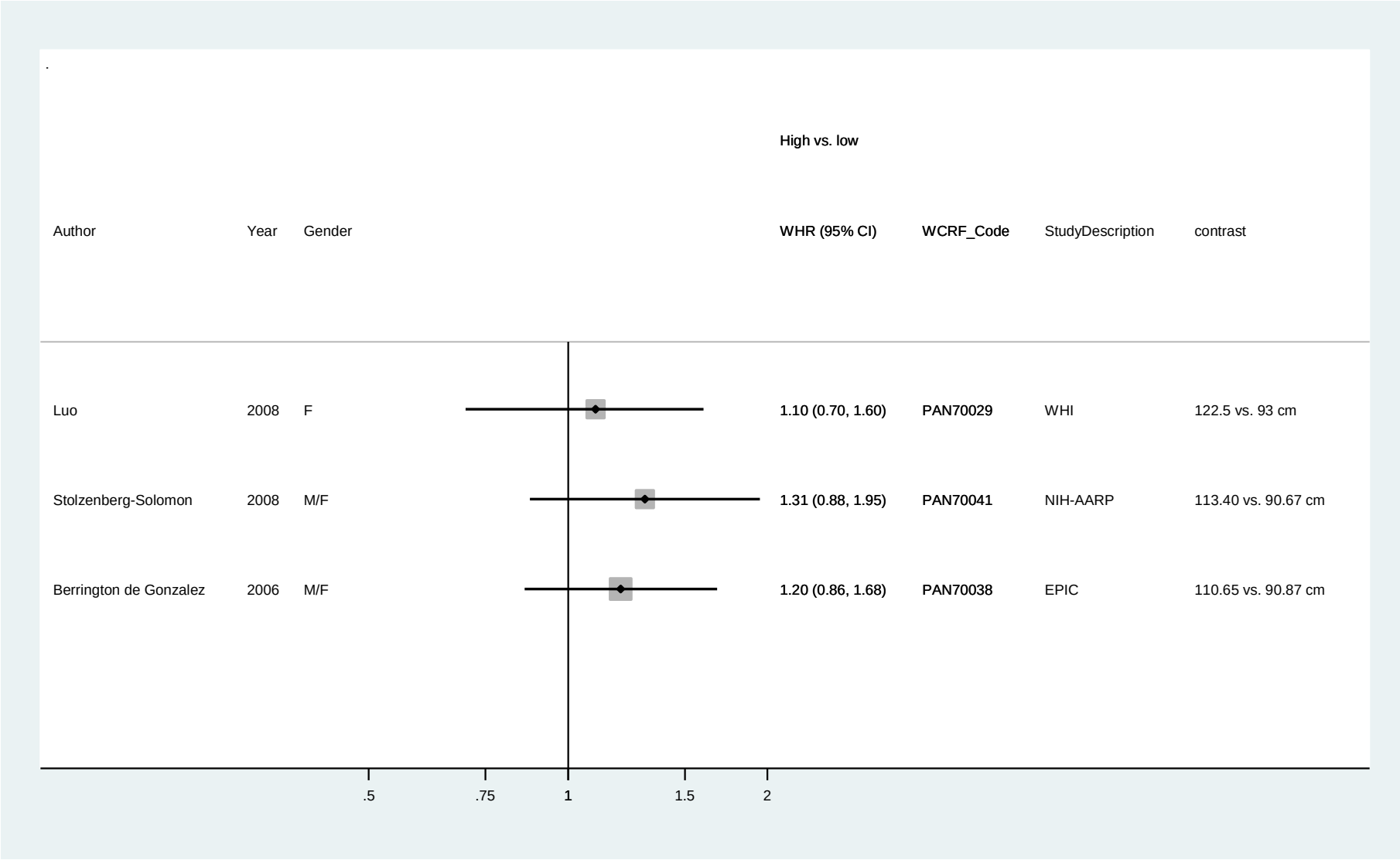


Figure 208 Dose-response meta-analysis of hips circumference and pancreatic cancer - per 10 cm

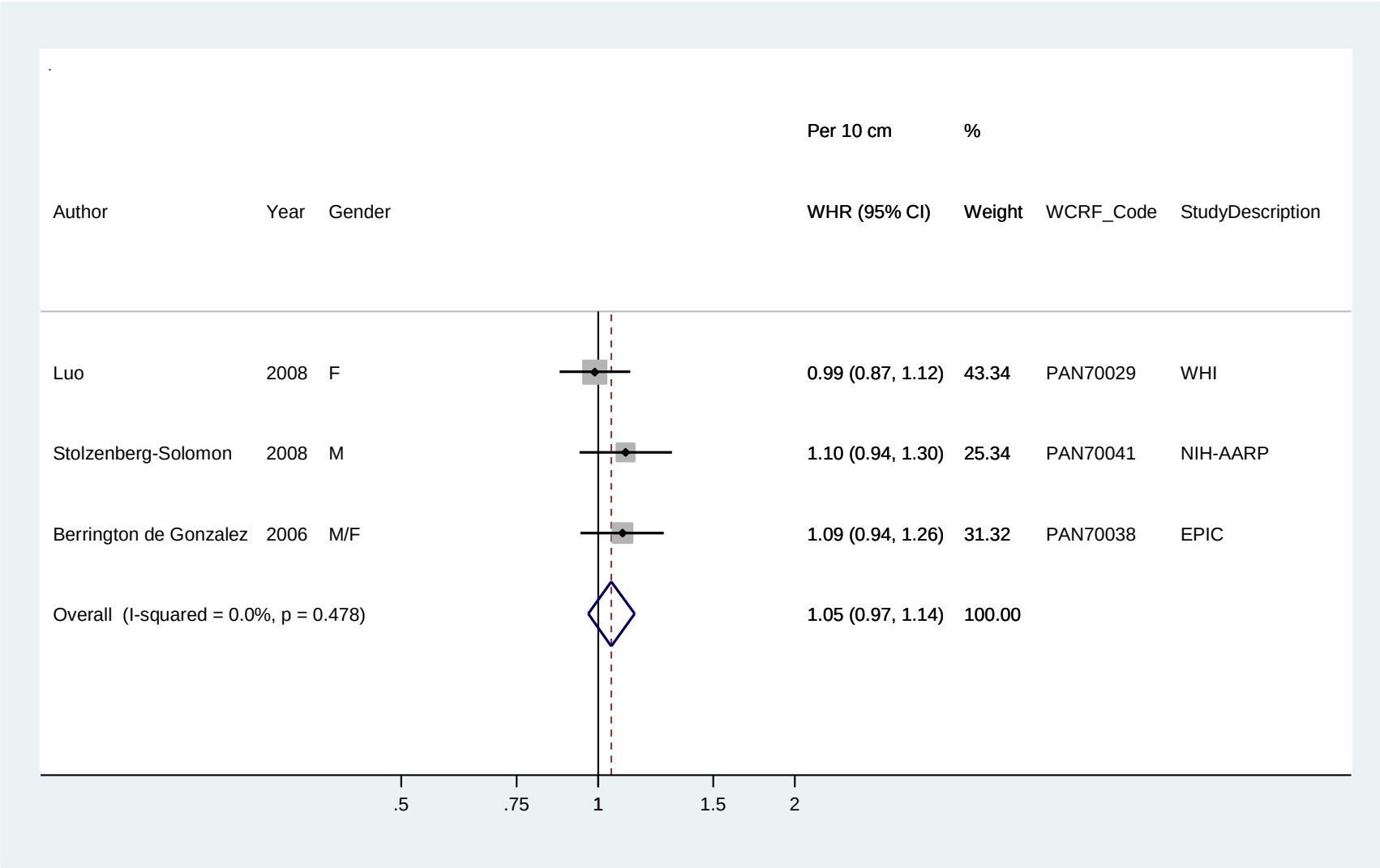
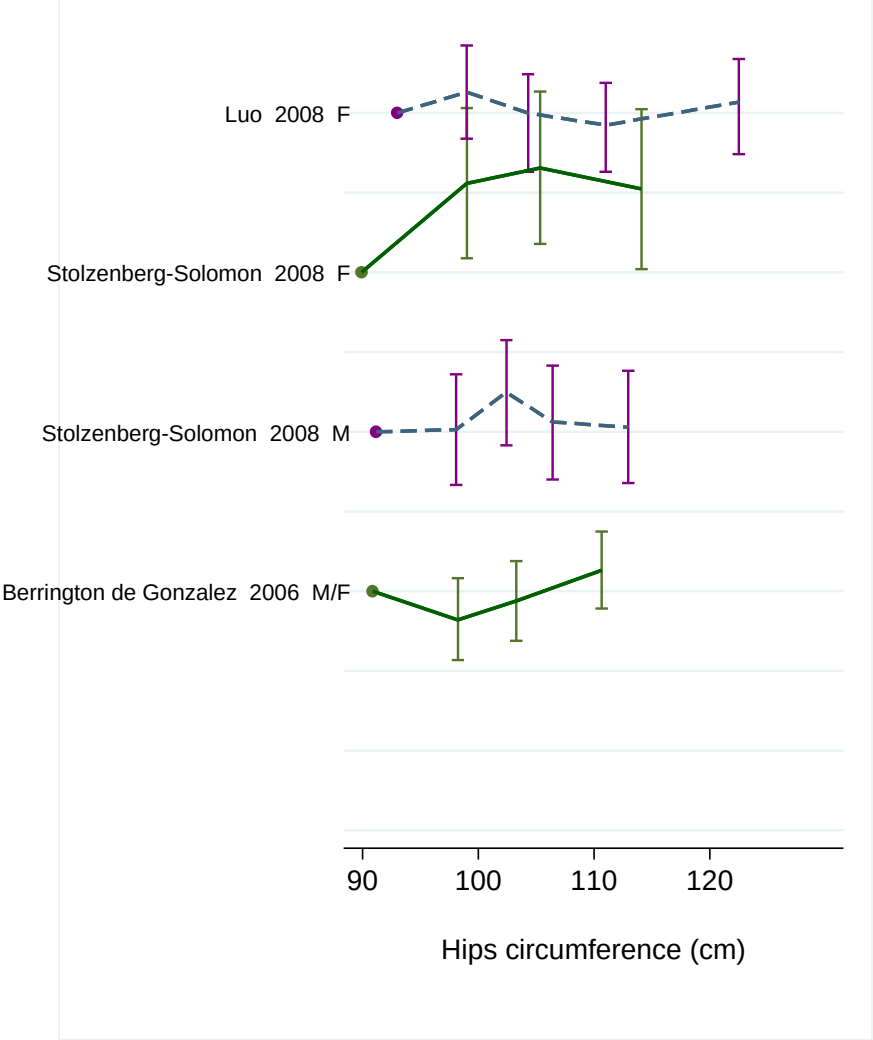


Figure 209 Dose-response graph of hips circumference and pancreatic cancer



8.2.3 Waist-to-hip ratio

Methods

A total of 4 cohort studies have been published on waist-to-hip ratio and pancreatic cancer up to 28th of September 2011, three of which were identified in the Continuous Update Project. Dose-response analyses of waist-to-hip ratio and pancreatic cancer were conducted. For the dose-response analyses we used a 0.1 unit increment in waist-to-hip ratio.

Main results

The summary RR for a 0.1 unit increment in waist-to-hip ratio was 1.19 (95% CI: 1.09-1.31, I^2=11%, p=0.34, 4 studies). There was no evidence of a nonlinear association between waist-to-hip ratio and pancreatic cancer risk, $p_{nonlinearity}$=0.29.

Heterogeneity

There was little evidence of heterogeneity (I^2=11%, p=0.34) in the analyses.

Comparison with the Second Expert Report

This meta-analysis found an increased risk of pancreatic cancer with greater waist-to-hip ratio. No meta-analysis was conducted in the Second Expert Report.

Pooled analysis

A pooled analysis of 6 cohort studies (552 cases) found a positive association between greater waist-to-hip ratio and pancreatic cancer risk, pooled multivariate RR=1.35 (95% CI: 1.03-1.78), which was not materially affected by further adjustment for BMI at baseline, pooled RR=1.34 (95% CI: 1.00-1.79) (Genkinger et al, 2011). A pooled analysis from the Pancreatic Cancer Cohort Consortium (PanScan) also reported a positive association between greater waist-to-hip ratio and pancreatic cancer risk, summary OR=1.71 (95% CI: 1.27-2.30) for the highest vs. the lowest quartile (Arslan, 2010). This was slightly strengthened when excluding former and current smokers from the analysis, summary OR=1.83 (95% CI: 1.32-2.53).

Table 184 Studies on Waist-to-hip ratio identified in the CUP

Author, year	Country	Study name	Number of cases	Years of Follow-up	Sex	RR	LCI	UCI	Contrast
Luo, 2008,	USA	Women's Health Initiative	251	7.7	F	1.7 1.27	1.1 1.07	2.6 1.50	0.91 vs. 0.72 Per 0.1 units
Stolzenberg-Solomon, 2008	USA	NIH-AARP Diet and Health Study	654	4.5	M F	1.34 1.19	0.86 0.66	2.08 2.15	≥1.00 vs. <0.90 ≥0.86 vs. <0.76
Berrington de Gonzalez, 2006	Europe	European Prospective Investigation into	324	6.5	M/F	1.33 1.24	0.93 1.04	1.92 1.48	≥0.98/≥0.84 vs. <0.90/<0.75 Per 0.1 unit

		Nutrition and Cancer							

Table 185 Overall evidence on waist-to-hip ratio and pancreatic cancer

	Summary of evidence
SLR	One study was identified and showed a non-significant positive association.
Continuous Update Project	Three new studies were identified. All the studies showed positive associations, two of which were significant.

Table 186 Summary of results of the dose-response meta-analysis of waist-to-hip ratio and pancreatic cancer

Pancreatic cancer incidence		
	SLR*	Continuous Update Project
Studies (n)	-	4
Cases (n)	-	1047
Increment unit	-	Per 0.1 units
RR (95% CI)	-	1.19 (1.09-1.31)
Heterogeneity (I^2, p-value)	-	11.0%, p=0.34

*No meta-analysis was conducted in the 2nd report.

Table 187 Inclusion/exclusion table for meta-analysis of waist-to-hip ratio and pancreatic cancer

WCRF code	Author	Year	Study design	Study name	Subgroup	Cancer outcome	SLR	CUP dose-response meta-analysis	CUP HvL forest plot	Estimated values	Exclusion reason
PAN70029	Luo	2008	Prospective cohort study	Women's Health Initiative	Women	Incidence	New	Yes	Yes	Mid-exposure values	
PAN70041	Stolzenberg-Solomon	2008	Prospective cohort study	NIH-AARP Diet and Health Study	Men/women	Incidence	New	Yes	Yes	Mid-exposure values	
PAN70038	Berrington de Gonzalez	2006	Prospective cohort study	European Prospective Investigation into Nutrition and Cancer	Men/women	Incidence	New	Yes	Yes	Mid-exposure values, person-years	
PAN61272	Sinner	2005	Prospective cohort study	Iowa Women's Health Study	Women	Incidence	Yes	Yes	Yes	Mid-exposure values	

Figure 210 Highest versus lowest forest plot of waist-to-hip ratio and pancreatic cancer

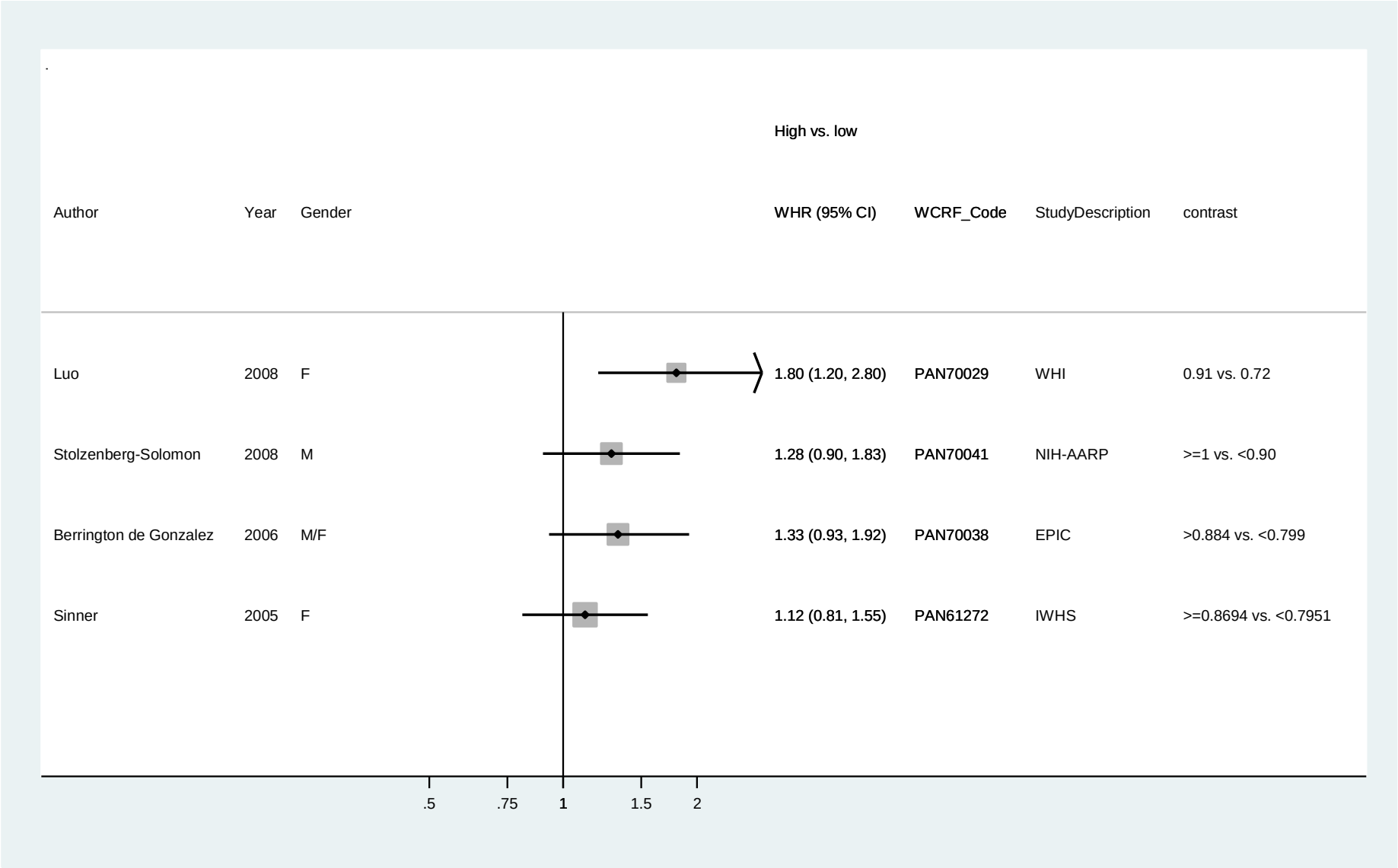


Figure 211 Dose-response meta-analysis of waist-to-hip ratio and pancreatic cancer - per 0.1 units

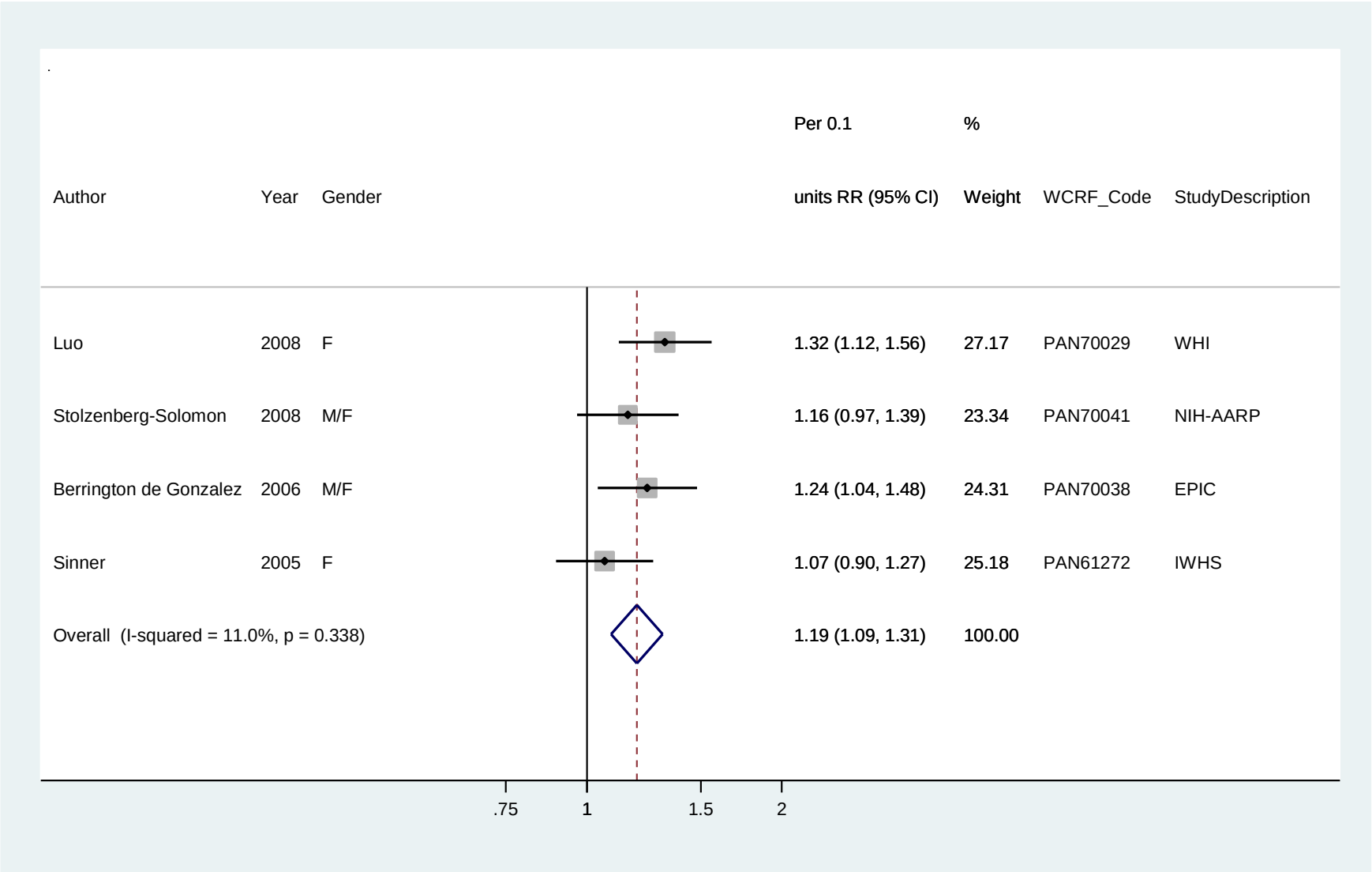


Figure 212 Dose-response graph of waist-to-hip ratio and pancreatic cancer

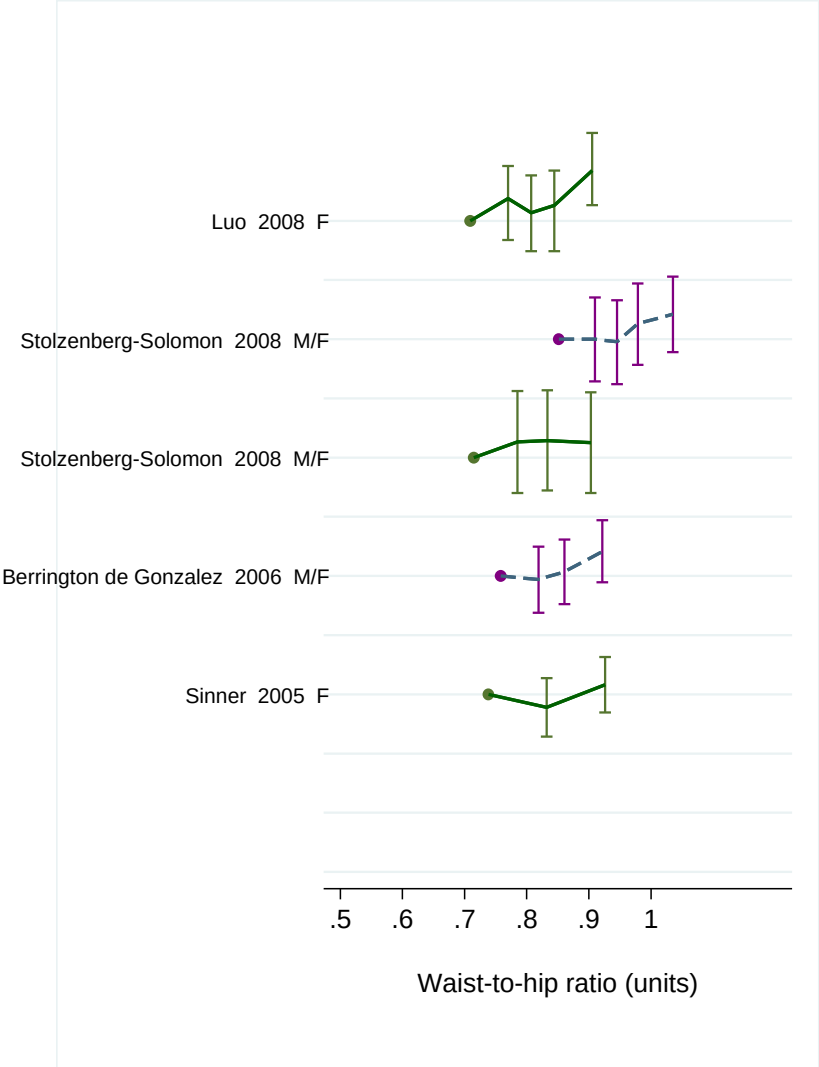


Figure 213 Nonlinear dose-response analysis of waist-to-hip ratio and pancreatic cancer

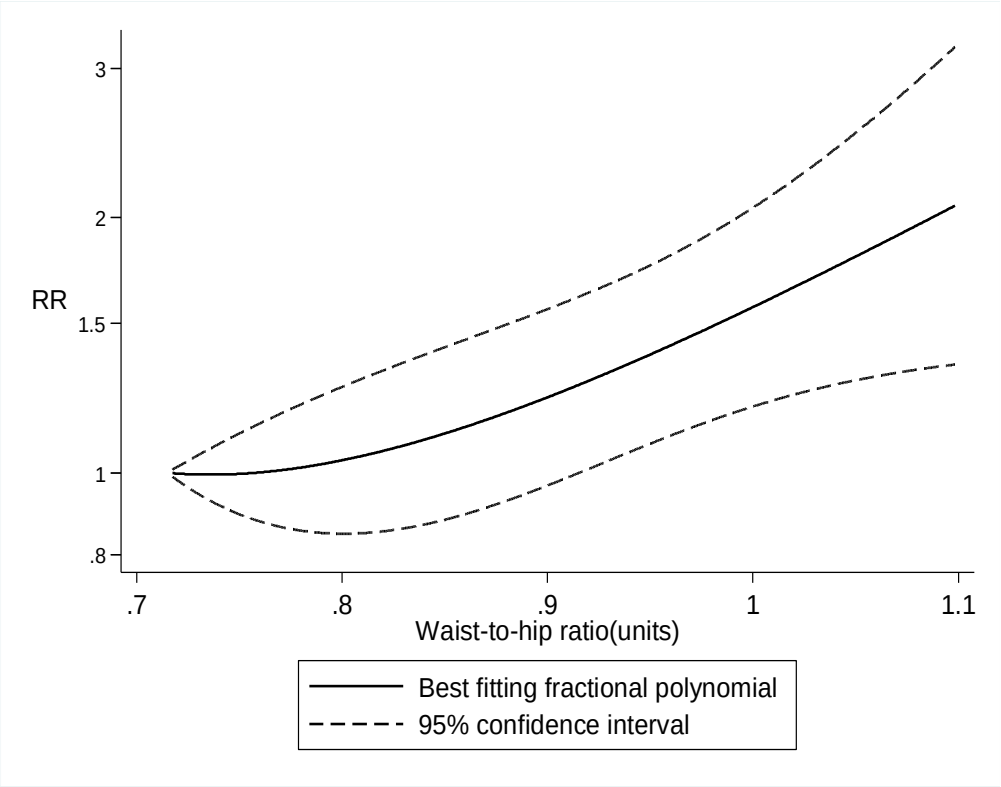


Figure 214 Scatter plot of risk estimates for waist-to-hip ratio and pancreatic cancer

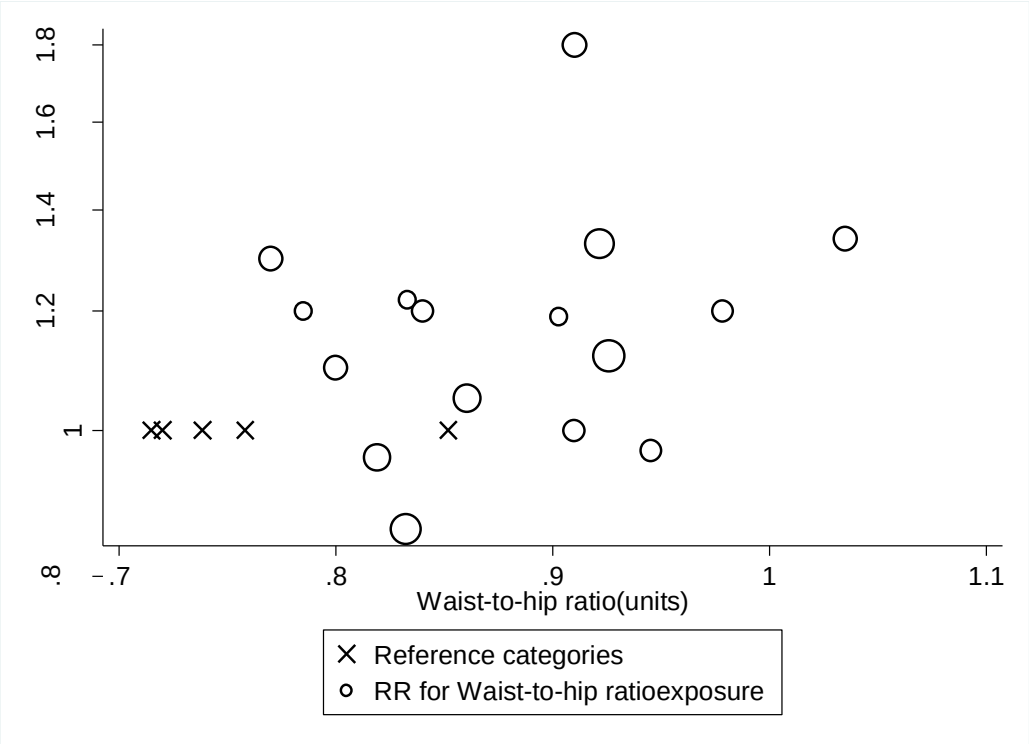


Table 188 Table with waist-to hip ratio values and corresponding RRs (95% CIs) for nonlinear analysis of waist-to-hip ratio and pancreatic cancer

Waist-to-hip ratio	RR (95% CI)
0.72	1.00
0.75	1.00 (0.89-1.11)
0.80	1.03 (0.85-1.26)
0.85	1.11 (0.88-1.41)
0.90	1.23 (0.97-1.56)
0.95	1.38 (1.08-1.76)
1.00	1.57 (1.20-2.06)
1.05	1.80 (1.29-2.52)
1.10	2.08 (1.34-3.22)

8.3.1 Height

Methods

Overall fourteen cohort studies were identified, from which eight were identified during the CUP. Dose-response meta-analysis for pancreatic cancer was performed in the previous SLR report. In this report, a meta-analysis including 10 different studies (7 studies identified during the CUP and 3 studies identified during the 2007 SLR) was performed.

Main results

The summary RR per 5cm increase was 1.07 (95% CI: 1.03-1.12; $P_{heterogeneity}$=0.005; 10 studies) for incidence or mortality of pancreatic cancer. The RR ranged from 1.06 (95% CI: 1.02-1.10) when excluding the NHS (Michaud et al, 2001) to 1.08 (95% CI: 1.04-1.12) when excluding the WHI (Luo et al, 2008). There was no evidence of a nonlinear association between height and pancreatic cancer, $p_{nonlinearity}$= p= 0.14.

Heterogeneity

High heterogeneity was observed overall (I^2= 57.1%, p=0.01). Meta-regression analysis by sex did not explain the heterogeneity between studies. There was some indication that number of cases might explain part of the heterogeneity although the test for heterogeneity was not significant, $p_{heterogeneity}$=0.10. The heterogeneity was reduced when an analysis stratified by the number of cases was conducted, the RRs were 1.03 (95% CI: 1.00-1.06, I^2=0%), 1.06 (95% CI: 0.98-1.14, I^2=64.5%) and 1.14 (95% CI: 1.05-1.23 I^2=39.5%) for studies with ≥500 cases, 250-499 and <250 cases respectively. Egger's test was not significant, p=0.15, but there was some evidence of asymmetry in the funnel plot.

Comparison with the Second Expert Report

Overall, height was associated with a significant increased risk of pancreatic cancer. The positive association with pancreatic cancer was similar in both genders. In the previous report the RR per 5cm increase in height was 1.11 (95% CI: 1.05 to 1.17).

Published meta-analysis

The Pancreatic Cancer Cohort Consortium (PanScan) including 2095 cases found no association between greater height and pancreatic cancer risk, summary OR=0.99 (95% CI: 0.83-1.18) (Arslan et al, 2010). A pooled analysis of 14 cohort studies (2135 cases) also found no significant association between greater height and pancreatic cancer risk, pooled RRs were 1.06 (95% CI: 0.87-1.29) for ≥170 vs. <160 cm among women and 1.20 (95% CI: 0.96-1.51) for ≥180 vs. <170 cm among men (Genkinger et al, 2011). The Asia Pacific Cohort Studies Collaboration found no association between greater height and pancreatic cancer risk in a pooled analysis of 38 cohort studies involving 506648 participants and 294 pancreatic cancer deaths (Batty et al, 2010), summary RR = 1.08 (95% CI: 0.95-1.24) per 6 cm increase in height for men and 0.99 (95% CI: 0.82-1.21) per 6 cm increase in height among women.

Table 189 Studies on height identified in the CUP

Author, year	Country	Study name	Cases	Years of follow up	Sex	RR	LCI	UCI	Contrast
Green, 2011	United Kingdom	Million Women Cohort	2044	9.4	F	1.05	0.95	1.17	Per 10 cm
Meinhold, 2009	Finland	Alpha Tocopherol Beta-carotene Cancer Prevention Study	305	16.1	M/F	1.23	0.87	1.75	≥180 vs <170 cm
Stevens, 2009	United Kingdom	Million Women Cohort	1338	7	F	1.18	0.97	1.44	>170 vs <155 cm
Sung, 2009	Korea	Korean Cancer Prevention Study	1254	8.7	M M F F	0.98 0.99 1.12 1.03	0.81 0.93 0.80 0.92	1.19 1.06 1.57 1.14	>171 vs. ≤151 cm Per 5 cm >158 vs. ≤151 cm Per 5 cm
Berrington de Gonzalez, 2008	Korea	Korean Cancer Prevention Study	2194	12	M/F	1.09	0.94	1.25	≥165.4 vs <155.9 cm
Stolzenberg-Solomon, 2008	USA	NIH-AARP Diet and Health Study	654	~5	M F	1.14 0.77	0.82 0.52	1.60 1.12	≥183 vs. <170 cm ≥168 vs. <157 cm
Luo, 2008	USA	Women's Health Initiative	251	7.7	F	0.9	0.6	1.3	170 vs. 153.6 cm
Song, 2008	Korea	Korean Cancer Prevention Study	262	9.86	F	1.22 0.99	0.71 0.87	2.11 1.11	≥161 vs. <149 cm Per 5cm
Verhage, 2007	Netherlands	The Netherlands Cohort Study	428	13.3	M F M F	0.99 1.32 1.01 1.02	0.56 0.67 0.99 1.00	1.75 2.60 1.03 1.05	≥185 vs <170cm ≥175 vs <160cm Per cm Per cm

Berrington de Gonzalez, 2006	Europe	European Prospective Investigation into Cancer and Nutrition	324	6.4	M/F M/F	1.74 1.37	1.20 1.15	2.52 1.64	≥171 vs <161.6 Per 10 cm
Batty, 2006	United Kingdom	The Whitehall Study	150	~30	M	1.26 1.02	0.71 0.90	2.22 1.15	≥181 vs. <171 cm Per 5 cm
Stolzenberg-Solomon, 2004	Finland	Alpha Tocopherol Beta Carotene Cancer Prevention Study	93	12.7	M	-	-	-	Only mean exposure reported

Table 190 Overall evidence on height and pancreatic cancer

	Summary of evidence
SLR	Six cohort studies showed increased risk with greater adult attained height, which was statistically significant in one. One study showed no effect on risk. Another stated that there was no significant association. Meta-analysis was possible on six cohort studies, giving a summary effect estimate of 1.11 (95% CI 1.05–1.17) per 5cm (2 inches), with low heterogeneity.
Continuous Update Project	Eleven new publications from eight cohort studies were identified. Five studies reported on males and females and three on females. Six of these studies found positive associations between height and pancreatic cancer, but only one was significant. One study showed a non-significant inverse association among, women, but a non-significant positive association in men. The last study showed a RR below 1, but was not significant. Eight studies were included in the highest vs. lowest forest plot, seven showed positive associations and two of them were significant.

Table 191 Summary of results of the dose response meta-analysis of height and pancreatic cancer

Pancreatic cancer		
	SLR	Continuous Update Project
Studies (n)	6	10
Cases (n)	1076	6147
Increment unit used	Per 5cm	Per 5cm
Overall RR (95%CI)	1.11 (1.05-1.17)	1.07 (1.03-1.12)
Heterogeneity (I^2,p-value)	8%, p=0.4	57.1%, p=0.01
Stratified analysis		
Men	-	1.07 (1.01-1.14) (n=6)
Heterogeneity (I^2,p-value)		52%, p=0.06
Women		1.07 (0.99-1.15) (n=6)
Heterogeneity (I^2,p-value)		61.4%, p=0.02

Table 192 Inclusion/exclusion table for meta-analysis of height and pancreatic cancer

WCRF_ Code	Author	Year	Study Design	Study Name	Subgroup	Cancer Outcome	SLR	CUP dose-response meta-analysis	CUP HvL forest plot	Estimated values	Exclusion reasons	Remarks
PAN70071	Green	2011	Prospective Cohort study	The Million Women Study	Women	Incidence	New	Yes	No			Provided only continuous data Self-reported height
PAN70044	Stevens	2009	Prospective Cohort study	The Million Women Study	Women	Incidence/ Mortality	New	No	Yes	Confidence interval, person years, mid-exposure values	Superseded by Green, 2011	Self-reported height
PAN70045	Meinhold	2009	Prospective Cohort study	Alpha Tocopherol Beta Carotene Cancer Prevention Study Cohort	Men	Incidence	New	Yes	Yes	Mid-exposure values, person years per quintile		Measured height
PAN70085	Sung	2009	Prospective Cohort study	Korean Cancer Prevention Study	Men/women	Incidence	New	Yes, only in sex-stratified analyses	No	Mid-exposure values, cases per category	Duplicate of PAN70049 (Berrington de Gonzalez, 2008) which had a larger number of cases	Was only included in sex-stratified analyses
PAN70049	Berrington de Gonzalez	2008	Prospective Cohort study	Korean Cancer Prevention Study	Men/women	Incidence/ Mortality	New	Yes	Yes	Mid-exposure vaues, person years per quintile		Measured height
PAN70086	Song	2008	Prospective Cohort study	Korean Cancer Prevention Study	Men/women	Mortality	New	No	No		Duplicate of PAN70049 (Berrington de	

											Gonzalez, 2008)	
PAN70041	Stolzenberg-Solomon	2008	Prospective cohort study	NIH-AARP Diet and Health Study	Men/women	Incidence	New	No	Yes		Only high vs. low comparison reported	
PAN70029	Luo	2008	Prospective cohort study	Women's Health Initiative	Women	Incidence	New	Yes	Yes	Person-years		
PAN70042	Verhage	2007	Case Cohort study	The Netherlands Cohort Study	Men/women	Incidence	New	Yes	Yes	Mid-exposure values		Provided Categorical and continuous data Self-reported height
PAN70038	Berrington de Gonzalez	2006	Prospective Cohort study	EPIC cohort	Men/women	Incidence	New	Yes	Yes	Mid-exposure vaues, person years per quintile		Provided Categorical and continuous data Self-reported and measured height
PAN70084	Batty	2006	Prospective Cohort study	The Whitehall Study	Men/women	Mortality	New	Yes	Yes	Mid-exposure values, person-years		
PAN20232	Stolzenberg-Solomon	2004	Nested Case Control study	Alpha Tocopherol Beta Carotene Cancer Prevention Study - Finland	Men	Incidence	New	No	No		Only mean exposure	
PAN00016	Giovannucci	2004	Prospective Cohort study	Health Professionals Follow-up Study	Men	Incidence	Yes	No	No		Overlapping Superseded by Michaud 2001	
PAN60747	Song	2003	Prospective Cohort study	Korean Cancer Prevention Study	Men	Mortality	Yes	No	No		Superseded by Berrington de Gonzalez A, 2008	
PAN07586	Stolzenberg-Solomon	2002	Prospective Cohort study	Alpha Tocopherol Beta Carotene Cancer Prevention Study - Finland	Men	Incidence	Yes	No	No		Superseded by Meinhold 2009	
PAN07439	Michaud	2001	Prospective Cohort study	Health Professionals Follow-up Study/ The Nurses' Health Study	Men/ women	Mortality/ incidence	Yes (women)	Yes	Yes	Mid-exposure values		Provided categorical and continuous data Self-reported height

				Cohort								
PAN14732	Nilsen	2000	Prospective Cohort study	Nord-Trondelag, Norway	Men/ women	Incidence	Yes	No	Yes		Only two categories of exposure	Self-reported height
PAN63854	Robsahm	1999	Prospective Cohort study	Norwegian screening programme for tuberculosis	Men/ women	Mortality/ incidence	Yes	No	No		No measure of the relationship	
PAN15306	Tulinius	1997	Historical Cohort study	Reykjavik Study/Icelandic Cancer Registry	Men/ women	Incidence	Yes	Yes	No		Only continuous results	Measured height
PAN07481	Ogren	1996	Nested Case Control	Malmo Preventive Project Cohort Study	Men/ women	Mortality/ incidence	Yes	No	No		Only means reported	

Figure 215 Highest versus lowest forest plot of height and pancreatic cancer

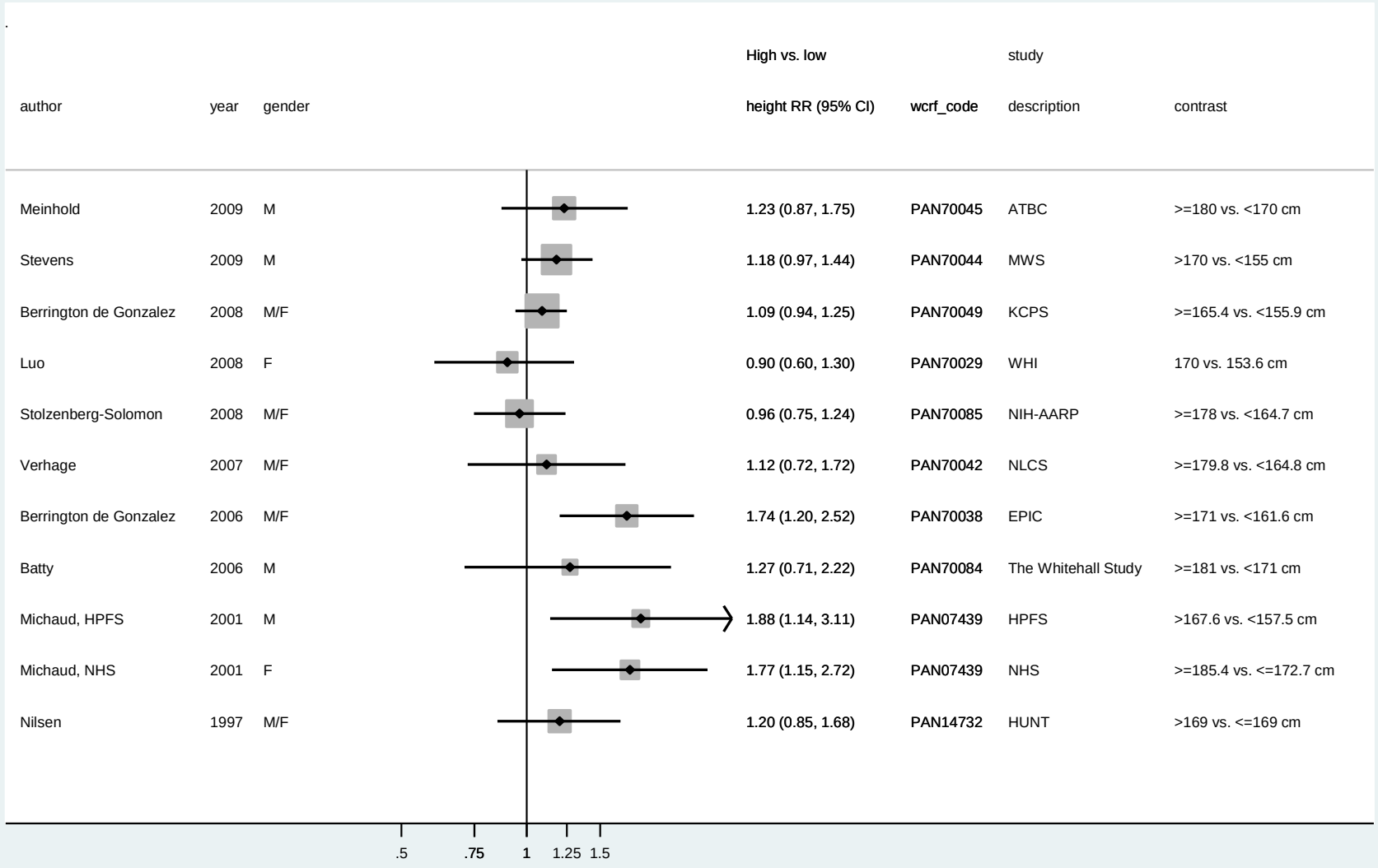


Figure 216 Dose-response meta-analysis of height and pancreatic cancer – per 5cm

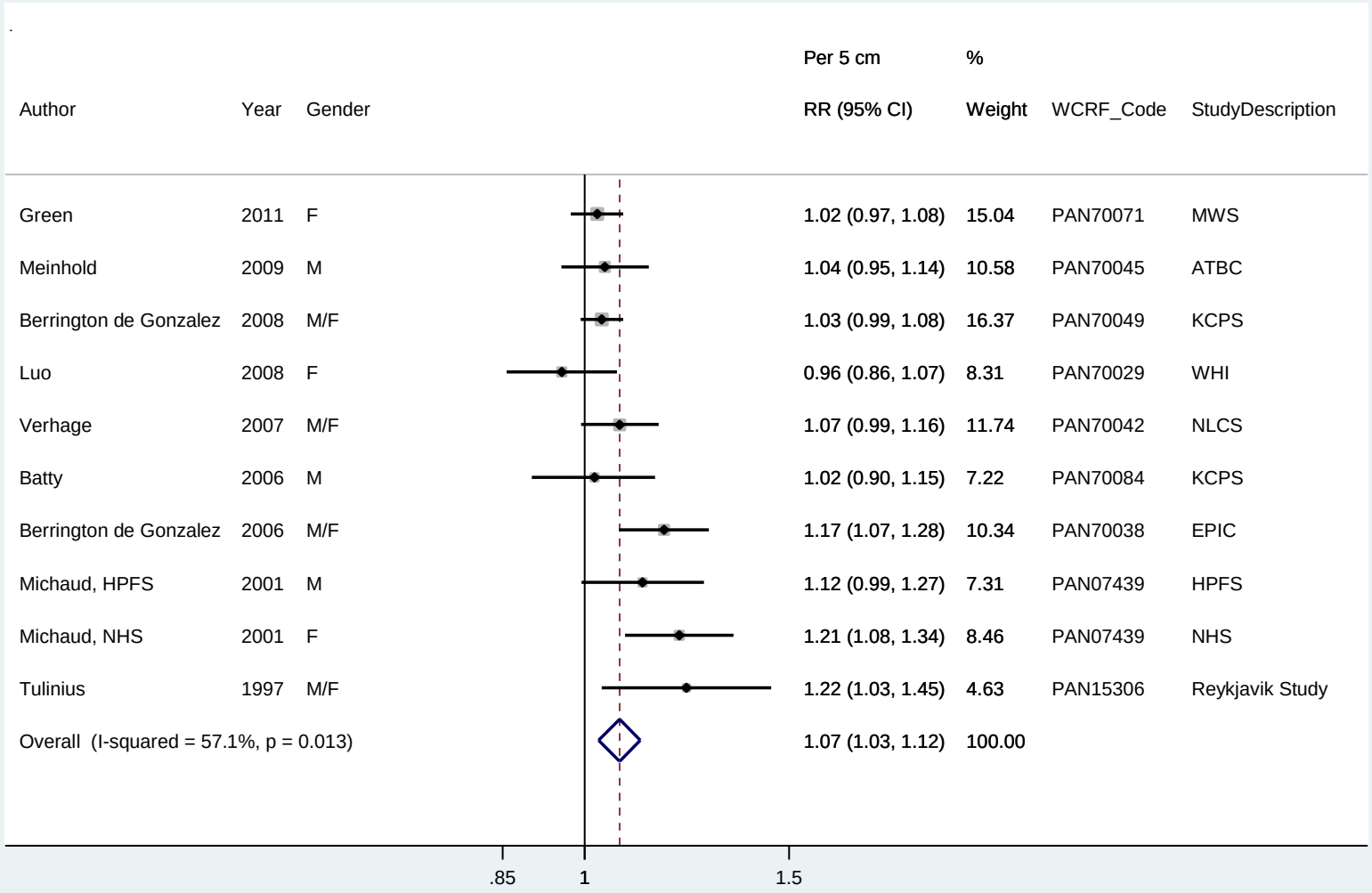


Figure 217 Funnel plot of height and pancreatic cancer

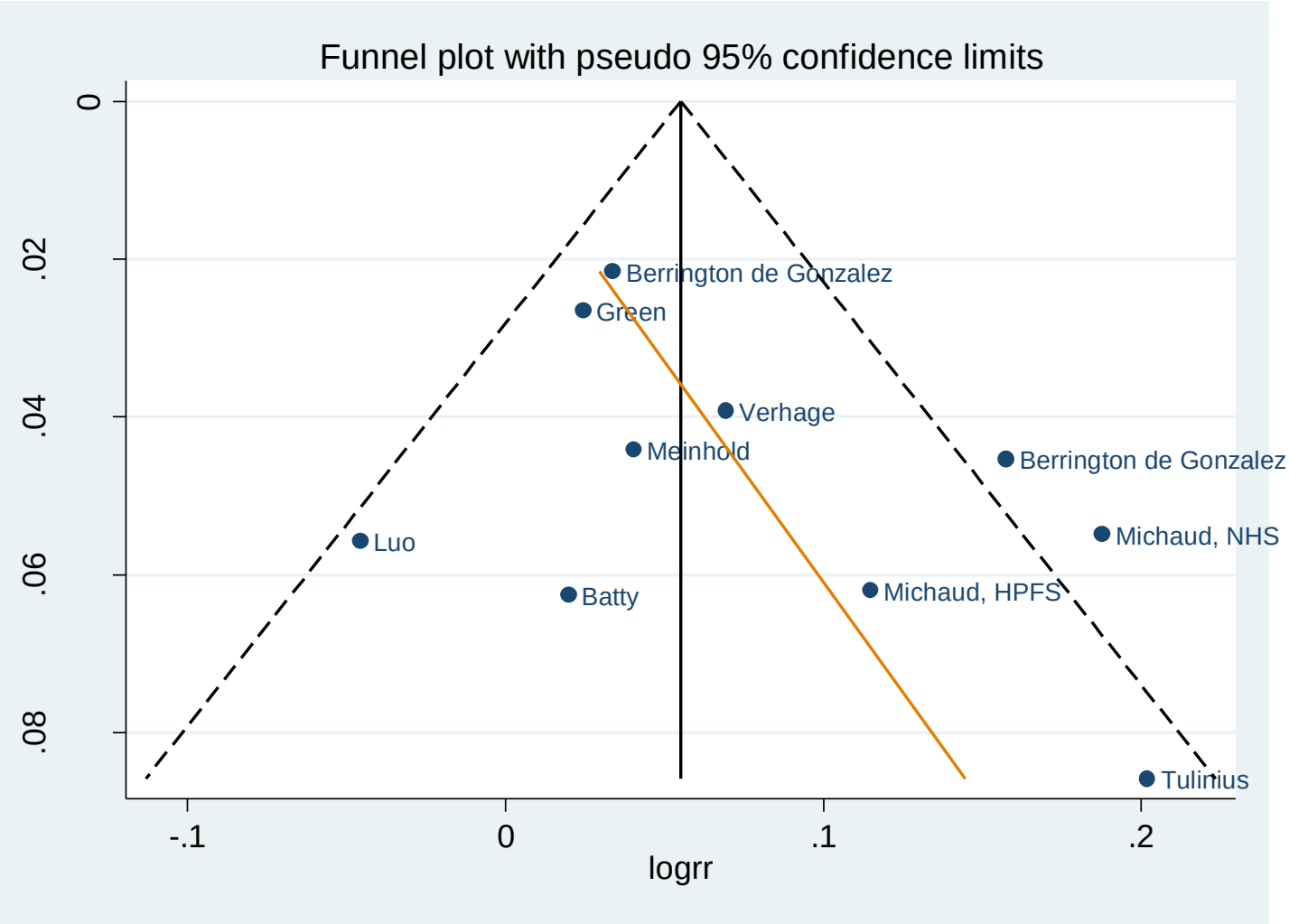


Figure 218 Dose-response graph of height and pancreatic cancer

Figure 219 Dose-response meta-analysis of height and pancreatic cancer, stratified by sex – per 5cm

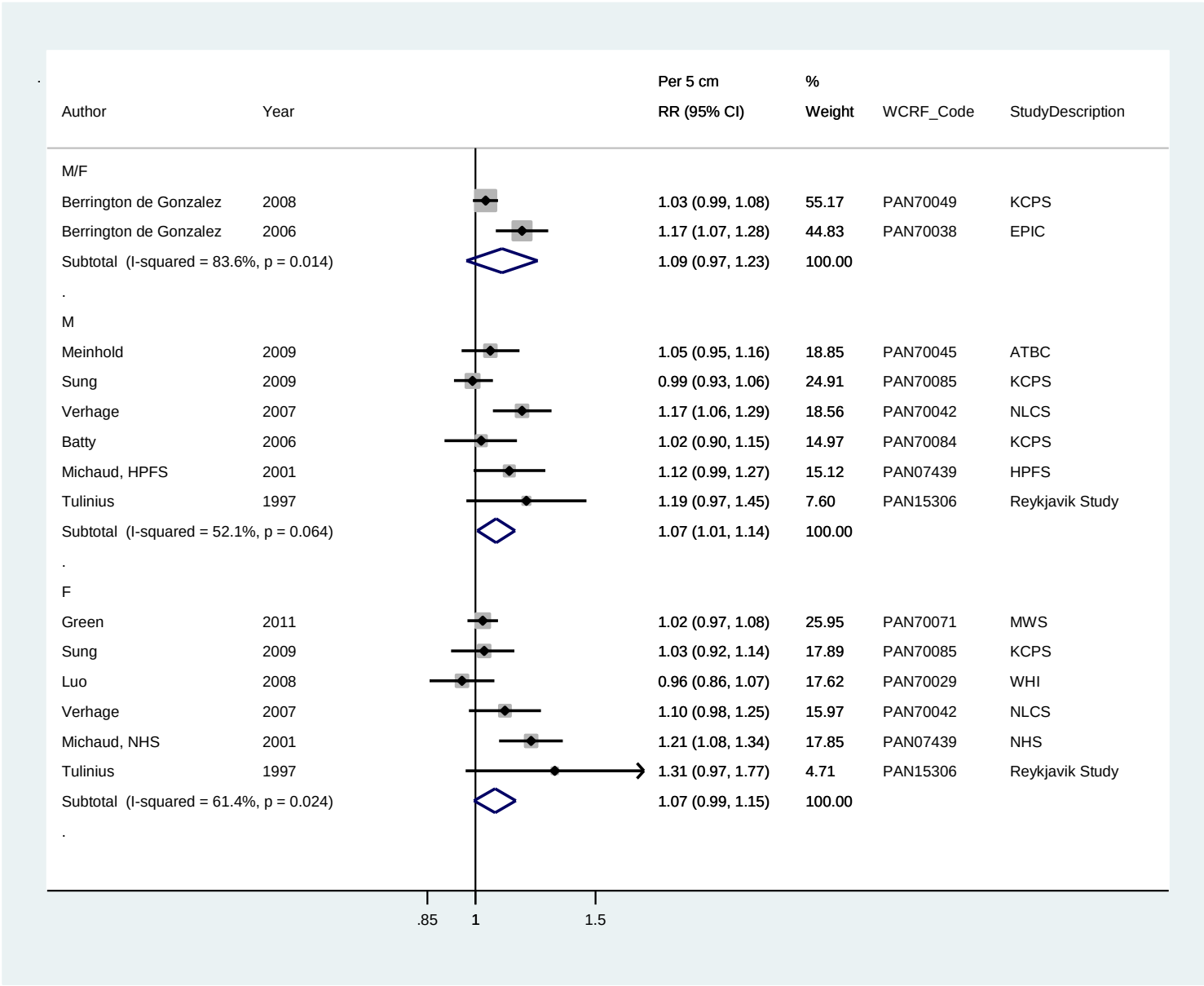


Figure 220 Nonlinear dose-response analysis of height and pancreatic cancer

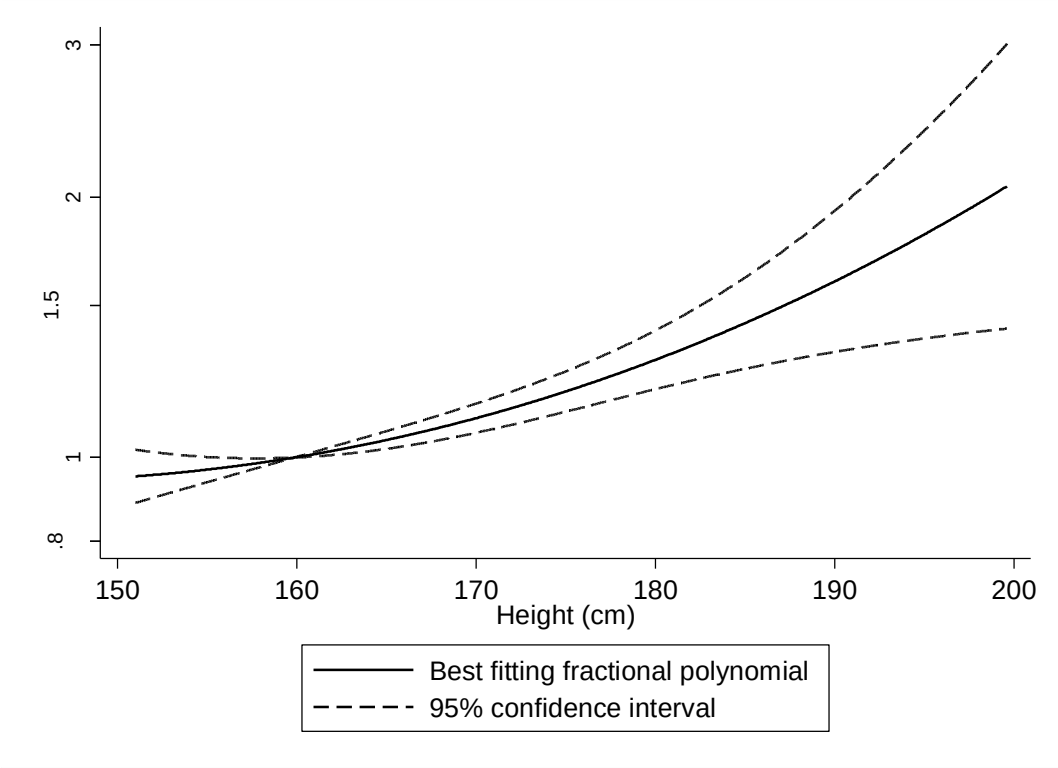


Figure 221 Scatter plot of risk estimates for height and pancreatic cancer incidence

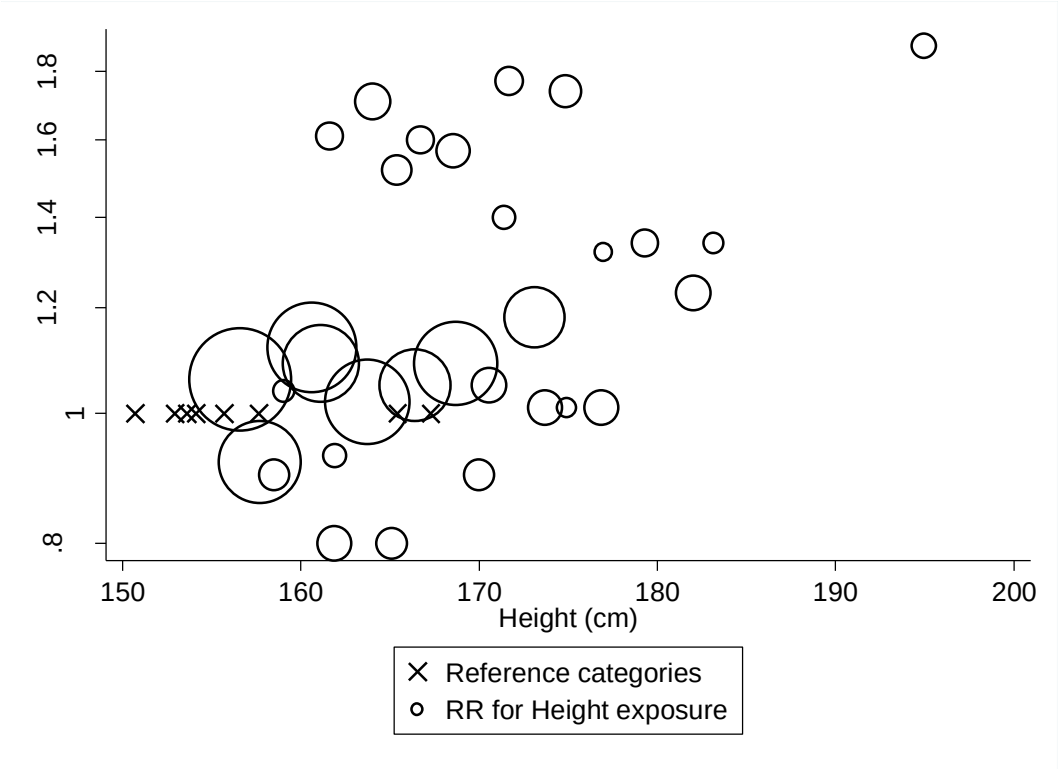


Table 193 Table with height values and corresponding RRs (95% CIs) for nonlinear analysis of height and pancreatic cancer risk

Height (cm)	RR (95% CI)
160	1.00
165	1.05 (1.02-1.07)
170	1.11 (1.07-1.15)
175	1.19 (1.13-1.26)
180	1.30 (1.20-1.40)
185	1.43 (1.27-1.62)
190	1.60 (1.33-1.93)
195	1.81 (1.37-2.38)
200	2.08 (1.41-3.07)

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Appendices

Appendix 1 Pancreatic cancer Continuous Update Project protocol

Continuous update of the WCRF-AICR report on diet and cancer

Protocol: Pancreatic Cancer

Prepared by: Imperial College Team

Teresa Norat, PhD
Doris Chan, MSc
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Rui Vieira, Database manager

WCRF/AICR has been the global leader in elucidating the relationship between food, nutrition, physical activity and cancer. The first and second expert reports represent the most extensive analysis of the existing science on the subject to date. To keep the evidence current and updated into the future, WCRF/AICR is undertaking the Continuous Update project, in collaboration with Imperial College London (ICL).
The Continuous Update will provide the scientific community with a comprehensive and up to date depiction of scientific developments on the relationship between diet, physical activity, obesity and cancer. It will also provide an impartial analysis and interpretation of the data as a basis for reviewing and where necessary revising WCRF/AICR's cancer prevention recommendations based on the 2007 Second Expert Report.
WCRF/AICR has convened a panel of experts (the Continuous Update Panel) consisting of leading scientists in the field of diet, physical activity, obesity and cancer who will consider the evidence produced by the systematic literature review and meta-analysis, and will consider the results and draw conclusions before making recommendations.
In the same way that the Second Expert Report was informed by a process of systematic literature reviews (SLRs), the continuous update will systematically review all of the science as it is published. The ongoing systematic literature review will be conducted by a team of scientists at ICL in liaison with the SLR centres where possible.
The current protocol for the continuous update of pancreatic cancer should ensure consistency of approach to the evidence, common approach to the analysis and format for displaying the evidence used in the literature reviews[1] for the Second Expert Report.
The starting point for this protocol are:

- The convention for conducting systematic reviews[1] developed by WCRF International for the Second Expert Report.
- The protocol developed by the SLR group on pancreatic cancer for the Second Expert Report (Leeds) [2].

The peer-reviewed protocol will represent the agreed plan for the Continuous Update. Should departure from the agreed plan be considered necessary at a later stage, this must be agreed by the Continuous Update Panel (CUP) and the reasons documented.

Background.

In the judgment of the Panel of the **WCRF-AICR Second Expert Report** [3], the factors listed below modify the risk of pancreatic cancer. Judgments are graded according to the strength of the evidence.

PANCREATIC CANCER		
	DECREASES RISK	INCREASES RISK
Convincing	No factor identified	Body fatness
Probable	Foods containing folate	Abdominal fatness Adult attained height
Limited –suggestive	Fruits Physical activity	Red meat
Limited –no conclusion	Cereals (grains) and their products; dietary fibre; vegetables; pulses (legumes); soya and soya products; processed meat; poultry, fish ; eggs; milk and dairy products; total fat; butter; plant oils; margarine,; cholesterol; sugar (sucrose); black tea; green tea; alcohol; nitrate and nitrite; total carbohydrate; folic acid supplements; vitamin C; vegetarianism; age at menarche; lactation; energy intake	
Substantial effect on risk unlikely	Coffee	

1. Research question

The research topic is:

The associations between food, nutrition and physical activity and the risk of pancreatic cancer.

2. Review team

Name	Current position at IC	Role within team
Teresa Norat	Principal Research Fellow	Principal investigator
Rui Vieira	Data manager	Responsible of the data management, the design and architecture of the database
Dagfinn Aune	Research Assistant	Nutritional epidemiologist, supervisor of data entry, analyst
Ana Rita Vieira	Research Assistant	Nutritional epidemiologist, reviewer
Doris Chan	Research Assistant	Nutritional epidemiologist, supervisor of data entry, analyst

Review coordinator, WCRF: Rachel Thompson

Statistical advisor: Darren Greenwood, senior Research Lecturer, University of Leeds

3. Timeline.

The SLR on pancreatic cancer for the Second Expert Report[2] ended in December 30th 2005. A pre-publication update extended the search to June 30th 2006 for exposures and cancer sites with suggestive, probable, convincing associations with the exposure of interest.

In order to ensure the completeness of the database, the ICL team will repeat the search conducted for the pre-publication update. Therefore, the Continuous Update will include the articles added to Medline from January 1st 2006. The reviewer will verify that there are not duplicities in the database. With that purpose, a module for article search has been implemented in the interface for data entry.

List of tasks and deadlines for the Continuous Update on pancreatic cancer:

Task	Deadline
Start Medline search of relevant articles published between January 2006 and December 2009	1st March, 2010*
Review abstracts and citations identified in initial electronic search. Select papers for complete review	Monthly **
Review relevant papers. Select papers for data extraction	Monthly **
Data extraction	Monthly **
End data extraction	30th August 2010
Start quantitative analysis	1st September 2010
End of quantitative analysis	30th November 2010
Send report to WCRF-AICR	20th December 2010
Transfer Endnote files to WCRF	20th December 2010

*Assuming the research assistant to be named as reviewer starts working at Imperial College in March 2010.
** Until the end of data extraction programmed to be 30th August 2010

4. Search strategy

The search will be conducted in Medline using PubMed as interface. The ICL team will use the search strategy established in the SLR Guidelines with the modifications implemented by the SLR centre (Leeds)[2] for the 2nd Expert Report[1] . The search will not be limited to "human studies" as it can not be guaranteed that all studies on PubMed have been coded as human. The full search strategy is in Annex 1.

5. Selection of articles

Only articles that match the inclusion criteria (see 5.1) will be updated in the database. Pooled analysis and meta-analysis will be identified in the search, but they will not be included in the database. The results of these studies will be used as support document in the preparation of the report.

5.1 Inclusion criteria

The articles to be included in the review:

- Have to be included in Medline from January 1st 2006 (closure date of the database for the Second Expert Report[1]).
- Have to present results from an epidemiologic study of one of the following types†:
  - Randomized controlled trial
  - Group randomized controlled trial (Community trial)
  - Prospective cohort study
  - Nested case-control study
  - Case-cohort study
  - Historical cohort study

- Must have as outcome of interest pancreatic cancer incidence or mortality.
- Have to present results on the relevant exposures
- Published in English language*

† *The selection of these study designs is based on the short life expectancy of pancreatic cancer cases after diagnosis and the potential bias of case-control studies. Filters for study design will not be implemented in the search strategy.*

* *The extent of the update has to be adequate to time and resources. For this reason the proposal is to give priority to articles published in English language. Most, if not all, high quality studies will be published in peer-reviewed journals in English language and referenced in the Medline database.*

5.2 Exclusion criteria

The articles to be excluded from the review:

- Are out of the research topic
- Do not report measure of association between the exposure and the risk of pancreatic cancer
- The measure of the relationship between exposure and outcome is only the mean difference of exposure
- Are supplement to the main manuscript (e.g. Authors' Reply).
- Are published on-line only as "Epub ahead of print" or "In Press". The data of these articles will be extracted after the definitive version is released.
- Are not in English language

6. Exposures

The Continuous Update will use the labels and exposure codes listed in the SLR Guidelines[1] for the Second Expert Report.

During the SLR for the Second Expert Report, the SLR centres assigned subcodes for exposures that were more detailed than the WCRF list of exposures. The codification used was not the same in all centres. These differences did not affect the quality of the review in each centre for the Second Expert Report. However, the codes and labels of the sub-exposures were recoded to ensure the identity of sub-exposure codes and labels in the MySQL database generated at Imperial College from the ACCESS databases for each cancer site generated for the SLRs.

The updated list of sub-exposures and codes is in Annex 2. The codes defined in the SLR Guidelines remained the same. The exposures listed represent the minimum list of exposures to be examined. These exposures are programmed in the interface for data entry to facilitate this process.

6.1 Biomarkers of exposure

In the SLR for the Second Expert Report[1], biomarkers of exposure were included under the heading and with the code of the corresponding exposure. Some review centres decided to include only biomarkers for which there was some evidence on reliability or validity, while other centres included in the database results on all the biomarkers retrieved in the search, independently of their validity. During the process of evaluation of the evidence, the Panel of Experts took in consideration the validity of the reported biomarkers.

The SLR centre on prostate cancer (Bristol) prepared a list of biomarkers to be included and excluded, based on data of studies on validity and repeatability of the biomarkers. The list of included and excluded biomarkers and the reasons for exclusion prepared by the SLR Bristol are in Annex 3.

Study results on all biomarkers of diet will be extracted in the database of the Continuous Update, including "new" biomarkers whose validity has not yet been fully proved. For the preparation of reports and meta-analysis, the Continuous Update on pancreatic cancer will use the same guidelines for exclusion of biomarkers proposed by the SLR Bristol (Annex 3).

The excluded biomarkers are:

Vit D: 1.25 $(OH)_2D$, Alkaline phosphatase activity (serum)

Iron (serum, hair, nails)

Copper (plasma, serum, hair)

Glutathione peroxidase (plasma, serum, erythrocytes, blood)

Zinc, metallotein levels (any)

Lipids: total fats (any)

Cholesterol, LDL (any)

Lipoprotein levels (serum)

Monounsaturated fatty acids (oleic acid) (plasma, adipose tissue)

Saturated fatty acids (palmitic acid, stearic acids) (plasma)

Protein (any)

Biomarkers of effect of exposure and biomarkers of cancer are not included in this review.

7. Outcome

The outcome of interest is pancreatic cancer encompassing incidence and mortality. Pancreatic cancer has one major histological morphology, adenocarcinoma that represents more than 95% of all diagnoses[4]. This nearly always represents a tumour located in the ductal exocrine cells of the pancreas and thus almost all epidemiological studies have either only considered this single entity or, under the general heading of "pancreatic cancer" have considered this along with a very small proportion of variant types. Islet cell (endocrine) tumours are much rarer, representing less than 5% of total cases. Hardly any studies have been conducted specifically on endocrine pancreatic tumours [2].

Most pancreas cancer is located at the 'head' of the pancreas with varying proportions, usually less than 10%, located in the body or tail regions[4]. Although this topology is important for clinical management, epidemiology studies hardly ever discriminate risks in relation to tumour location. However, whenever studies report on pancreatic cancer at specific locations, the information will be extracted in the database.

Pancreatic cancer is also nearly always diagnosed at a very advanced stage and survival rates beyond a few months are extremely low. As a result, there are virtually no differences between cancer incidence and cancer mortality rates. For cohort studies, this means that there is no particular advantage in distinguishing between incidence and mortality as outcomes (assuming the information concerning both registrations and deaths is equally valid and reliable). For that reason, study results on incidence and mortality will be presented and analyzed altogether. When provided by the papers, the proportion of incident and fatal cases in the study will be noted in the database.

8. Search databases

Only the Medline database will be initially searched. Data provided from the Second Expert Report[1] indicates that 95% of the articles included in the review have been retrieved from the Medline database. However, in the SLR of pancreatic cancer, 168 (77%) out of 219 articles identified electronically and included in the review were identified through PubMed and another 30 articles were identified through hand searching.

9. Hand searching for cited references

For feasibility reasons, it was decided that journals will not be hand searched in the Continuous Update. In addition, most articles included in the SLR of breast, colorectal and prostate cancer were identified through PubMed.
However, due to the relatively high number of articles (30) identified by hand searching in review articles during the SLR of pancreatic cancer, the ICL team will check the reference list of all review articles identified in the search. This will allow identifying potentially missing articles published after 2005. If there are articles missed by PubMed, the Imperial College team will consider other strategies, such as modifying the search strategy and looking into other databases.

10. Selecting articles

The results of the PubMed searches will be downloaded into a Reference Manager Database monthly.

Initially a further electronic search will be undertaken within Reference Manager to identify and remove irrelevant records. This will be achieved by generating a list of stop words. The list of stop words was developed and tested by the SLR Leeds during the preparation of the WCRF-AICR 2nd expert report on pancreatic cancer. The list of stop words was compiled from terms that describe surgical, diagnostic or oncology procedures relevant to pancreatic cancer. Also included in the stop word are terms referring to animal studies and in vitro studies. These terms will be used to identify non human studies. All references that include any of these stop words in the title of the citation will be excluded and stored in a separate Reference Manager database.

In a second step the remaining articles downloaded from PubMed will be inspected by a reviewer, who will indicate which articles are potentially relevant, articles to be excluded and articles that cannot be classified upon reading the title and abstracts.

The complete article of potentially relevant references and of references that cannot be excluded upon reading the title and abstracts will be retrieved. A second assessment will be done after review of the complete papers.

The assessment of papers will be checked by a second reviewer. It is envisaged that 10% of the non relevant articles will be randomly selected and double-checked.

11. Labelling of references

For consistency, the ICL team will use the same labelling of articles employed during the SLR process for the Second Expert Report[1]: the unique identifier for an article will be constructed using a 3-letter code to represent the cancer site (e.g. PAN for pancreatic cancer), followed by a 5-digit number that will be allocated in sequence.

12. Reference Manager Files

Reference Manager files containing the references retrieved on the initial search are generated in the Continuous Update. The variables contained in the Reference manager files are those generated using the filter Medline for importing data. Additionally, customized fields will be implemented.

Three Reference Manager files will be created:

1) A file containing the results of the initial search. The study identifier should be entered under a customized field titled 'label'. Another customised field named 'inclusion' should be marked 'in' or 'out' for each paper, thereby indicating which papers were deemed potentially relevant based on an assessment of the title and abstract.
2) A file containing the excluded papers. The study identifier should be entered under a customized field titled 'label'. Another customised field named 'reasons' should include the reason for exclusion for each paper. This file will be named Pancreas excluded.
3) A file containing the included papers. The study identifier should be entered under a customized field titled 'label'. Another customised field named "study design" should include a letter (A-Q) representing the study design of each paper, allocated using a study design algorithm. This file will be named Pancreas included.

The Reference Management databases will be converted to EndNote and sent once per year to the WCRF Secretariat.

13. Data extraction

The ICL team will update the database using the interface created at Imperial College for this purpose. The interface allows the update of all the information included in the Access databases generated during the SLRs for the Second Expert Report. This includes information on study design, name of cohort study, characteristics of study population, methods of exposure assessment, study results, analytical methods, adjustment variables, matching variables, and whether methods for correction of measurement error were used.

The study design algorithm devised for use of the SLR centres for the Second Expert Report will be used to allocate study designs to papers. In some cases it will be appropriate to assign more than one design to a particular paper (e.g. analyses in the entire cohort and nested case-control).

13.1 Quality control

Data extraction will not be performed in duplicate. This would have required important resources. Instead, 10% of the data extracted throughout the continuous update will be checked by a second reviewer at Imperial College.

The extracted data will be also checked automatically by the data manager, who will prepare monthly reports of the errors identified for its correction by the reviewer. Examples of automatic checks are checking if the confidence interval contains the effect estimate and if it is symmetrical, checking that the sum of cases and non case individuals by categories of exposure add up to the total number of cases and non case individuals.

13.2 Choice of Result

There could be several results for a particular exposure within a study according to the number of models presented in the article (unadjusted, minimally, maximally) and the number of subgroup or stratified analyses conducted (by gender, race, outcome type, etc.)

The results obtained using all the models reported in the paper and all the subgroup or stratified analysis should be extracted by the reviewer.

The reviewer should label the results as not adjusted, minimally adjusted, intermediately adjusted and maximally adjusted. In addition, the IC reviewer should indicate results obtained with a "best model" for inclusion in reports. This serves the dual purpose of marking that result to be exported to the reports and also flagging it as the best model for potential inclusion in a meta-analysis.

The identification of "best model" will be undertaken firstly on the appropriateness of adjustment. The most adjusted one will be considered to be the best model. Exception to this criterion will be "mechanistic" models, adjusting for variables likely to be in the causal pathway. When such results (over adjusted results) are reported, the most adjusted results that are not over adjusted will be extracted. Smoking is the main lifestyle risk factor identified so far and the evidence on the association of body fatness with pancreatic cancer is considered convincing [2] . The "best model" has to be controlled for confounding by smoking and body fatness. Models adjusted only for age, gender and energy intake are considered "intermediately adjusted models". In the case that there is no "best model", the maximally adjusted model reported in the paper will be used in the meta-analysis and sensitivity tests will be conducted excluding these models from the analysis.

Potential risk factors of pancreatic cancer are:

Sex
Age
Race
Energy intake
Height
Socioeconomic status
Physical activity
Body mass index
Tobacco smoking and environmental tobacco exposure
Personal history of diabetes

Chronic pancreatitis
Family history of pancreatic cancer in a parent, sibling or child.

Sometimes, potential risk factors are not kept in the model because their inclusion does not modify the risk estimates. If this is specified in the article text, this model should also be considered the "best model".
Other subsidiary criteria to consider for identifying the 'best model' for meta-analysis are the number of cases (highest), and in certain circumstances the completeness of the data (e.g. where quantile ranges are provided over where missing).

13.3 Effect modification and interaction

The ICL team should report whether interaction or heterogeneity tests were conducted and extract the results of these tests.
In the SLR for the 2nd Expert Report, the results of interaction analyses were extracted using the same module of data entry by creating new "double entry" sub-exposures (e.g. alcohol and folate intake as a single sub-exposure). The results of stratified analyses following a significant interaction test were included in the database as subgroup analyses.
To avoid the creation of new "double entry" exposures in the Continuous Update, the ICL team has developed a new module for data entry of results of interaction analysis. The module 'interaction' allows the use of existing headings of single exposures during data entry that will be automatically linked in the database. The reviewer will not need to create new sub-exposures codes. The results of stratified analyses will be extracted using the module "Subgroup analysis", similarly to what has been done in the SLR for the Second Report.

13.4 Gene-nutrient interaction

No attempt was made to critically appraise or analyse the studies that reported gene-nutrient interactions in the Second Expert Report. The results of these studies were described in the narrative review under the relevant exposures.
In the Continuous Update, the information on gene-nutrient interactions in the articles retrieved will be extracted in the database using the module "Interaction".

13.5 Multiple articles

The data of all relevant papers should be extracted, even if there is more than one paper from the same study reporting the same results. The most appropriate data set for analyses will be selected to ensure there is no duplication of data from the same study. Multiple reports from the same study will be identified using first the study name but also geographic location, recruitment dates and participant characteristics. The criteria for selecting the best data set for meta-analyses are listed under Section 14.2.

If needed, the ICL team should contact the authors for clarification. If the matter remains unresolved the review coordinator of the Continuous Update will discuss the issue with the WCRF Secretariat and the CUP, if necessary.

14. Data analysis

Meta-analytic and narrative aspects of the data analysis will complement each other. The meta-analyses will examine the evidence for dose-response effects.

Non-linear dose-response meta-analysis will be conducted if the data suggest a non-linear shape.

STATA version 11.0 (College Station, TX, USA) will be used to analyse the data.

14.1 When to do a meta-analysis

A meta-analysis for a particular exposure and outcome will be conducted when 3 or more trials or cohort studies have been published in the period reviewed, and if the total number of studies in the database totalise to more than 3 trials or 5 cohort studies with enough information to conduct a dose-response meta-analysis or providing data to calculate the required information.

The study results extracted during the SLR and the studies identified in the Continuous Update will be included in the meta-analysis. Special care will be taken to avoid including the results of the same study more than once (see 14.2).

14.2 Selection of results for meta-analyses and reporting.

The following guidelines for inclusion of studies in the meta-analysis will be applied:

1. Where more than one paper was published from the same study, the paper using the larger number of cases for analysis will be selected. This is often the most recent paper.

2. Where the same exposure was analysed in more than one way with different levels of adjustment, the best model will be the one with the most appropriate adjustment for confounding. This is often the maximally adjusted analysis (except mechanistic models) (see 13.2).

3. Where an exposure was presented for all study participants, and by subgroup, the analysis of all study participants will be used.

4. Where an exposure was presented only by subgroup, the subgroups will be pooled first and then included in the meta-analysis. This is essentially equivalent to including the overall estimate and will provide a better estimate of heterogeneity across studies.

5. Where a paper presented results from two separate studies and included a pooled analysis of different studies (e.g. the Nurses Health Study and the Health Professionals Follow-up Study), then the studies will be included separately and the pooled result will not be included. This maintains the independence of observations included and permits to look at heterogeneity across study results. The results of the pooled analysis will be mentioned in the narrative review.

14.3 Statistical Methods

To enable comparison of different studies, the relative risk for a linear dose-response across the exposure will be estimated. This will be done using the methods of Greenland & Longnecker[5] (the pool last approach) and Chêne and Thompson[6]. The same methods were used to do the linear dose-response meta-analyses in the SLRs for the Second Expert Report. The advantage of the method proposed by Greenland & Longnecker[5] is that it provides dose-response estimates that take account of the correlation induced by using the same reference group. The relative risk estimates for each unit of increase of the exposure will be derived with the method of DerSimonian and Laird[7] using the assumption of a random effects model that incorporates between-study variability. The unit of increment will be kept as the same unit used in the SLR. We will use the "best" (most adjusted risk estimate) from each study. The Stata command "glst" will be used to run all the dose-response analyses.

14.4 Derivation of data required for meta-analyses.

The information required for data to be usable for meta-analysis, for each type of result is:

Dose-response data (regression coefficients)

-Estimated odds, risk, or hazard ratio per unit increase in exposure with confidence interval (or standard error of log ratio or p value)
-Unit of measurement

Quantile-based or category data

-No. of cases and non cases (or person-time denominator for cohort studies) in each group; or total number of cases and non cases (or study size) plus explicitly defined equal-sized groups (for quantile-based data)
-Estimated odds, risk, or hazard ratios with confidence intervals (or standard error of log ratio or p value) compared with the baseline group, for each non baseline group.
-Range, mean, or median of exposure in each group
-Unit of measurement

The data needed to estimate the dose-response associations are often incompletely reported, which may result in exclusion of results from meta-analyses. Failure to include all available evidence will reduce precision of summary estimates and may also lead to bias if propensity to report results in sufficient detail is associated with the magnitude and/or direction of associations.

A number of approaches have to be taken in order to derive the information required. These will be applied in the following order of priority:

1. Where the exposure was measured as a continuous variable, and the dose-response slope given, then this will be used directly.

2. Where the slope (and its standard error or confidence interval) was not given in the text, these will be estimated applying the methods of Greenland & Longnecker[5] and using the mean exposure in each category given in the paper. No additional assumptions are required.

3. Greenland & Longnecker's method[5] requires the total numbers of cases and controls to be known, and starting estimates for the number of cases in each category. Where these were not presented, values will be estimated based on the categorisation into quantiles or on the information contained in each category estimated from the width of the confidence intervals.

4. Mean exposure for each category is rarely given, so the methods of Chene & Thompson[6] will be used to estimate the means. This approach made the assumption of a normally distributed exposure, or a distribution that could be transformed to normality.

5. Where it is not possible to derive mean exposures in each category, the midpoints will be used instead as a basis for the Greenland & Longnecker[5] method.

6. Where no confidence intervals were given in the paper, but approximate standard errors can be obtained from the cell counts, these will be used to derive approximate confidence intervals for the adjusted relative risks. Greenland & Longnecker's method[5] will then be applied using means given in the paper or estimated assuming normality, based on these derived confidence intervals.

7. Where there is a category representing a zero exposure, such as "non-drinker" or "not consumed", this will be treated separately for the purposes of estimating means in each category. Such "never" categories often lead to a peak in the distribution at zero, and the data will not follow neither a normal nor a lognormal distribution. By using a mean of zero for the "never" category and estimating means for the other categories separately, distributional assumptions could be made and more studies could be included in the meta-analysis.

8. The decision whether to log-transform will be made on an exposure by exposure basis. This will based on the SLR on pancreatic cancer (Leeds)[2] for the Second Expert Report and on the estimated means derived for use in the Greenland & Longnecker's method[5] for deriving dose-response estimates.

14.4 Missing values.

A recent review showed that only 64% of the results of cohort studies provide enough data to be included in dose-response meta-analysis[8]. Moreover, results that showed evidence of an association were more likely to be usable in dose-response meta-analysis than results that found no such evidence. Insufficient detail in reporting of results of observational studies can lead to exclusion of these results from meta-analyses and is an important threat to the validity of systematic reviews of such research.

The most frequently occurring problems in reporting and the suggested solutions to make results usable in a dose-response meta-analysis are [8] :

Type of data	Problem	Assumptions
Dose-response data	Serving size is not quantified or ranges are missing, but group descriptions are given	Use serving size recommended in SLR Prostate (Annex 6)
	Standard error missing	The p value (either exact or the upper bound) is used to estimate the standard error
Quantile-based data	Numbers of controls (or the denominator in cohort studies) are missing	Group sizes are assumed to be approximately equal
	Odds ratio is missing	Unadjusted odds ratios are calculated by using numbers of cases and controls in each group
	Confidence interval is missing	Standard error and hence confidence interval were calculated from raw numbers (although doing so may result in a somewhat smaller standard error than would be obtained in an adjusted analysis)
	Group means are missing	This information may be estimated by using the method of Chene and Thompson [6] with a normal or lognormal distribution, as appropriate, or by taking midpoints (scaled in unbounded groups according to group numbers) if the number of groups is too small to calculate a distribution (see 14.3)
Category data	Numbers of cases and controls (or the denominator in cohort studies) is missing	These numbers may be inferred based on numbers of cases and the reported odds ratio (proportions will be correct unless adjustment for confounding factors considerably alter the crude odds ratios)

14. 5 Analysis of heterogeneity and potential bias

Heterogeneity between studies will be assessed with the I^2 statistic as a measure of the proportion of total variation in estimates that is due to heterogeneity, where I^2 values of 25%, 50%, and 75% correspond to cut-off points for low, moderate, and high degrees of heterogeneity [9].

Meta-regression will be performed to investigate sources of heterogeneity if there are enough studies to do it. The variables that will be examined as sources of heterogeneity are geographic area (North-America –Non black population, North-America –Black population, Europe, Asia, Other), gender, outcome (proportion of fatal cases), and if possible number of categories used in the adjustment for smoking

Length of follow-up is a concern in prospective studies of cancer due to the long latency of the disease. As most diagnoses of pancreatic cancer are made at advanced stages[4], it is likely that there is a fairly long pre-diagnostic period when malignant disease is present. Pancreatic cancer has few early symptoms and most individuals should not have experienced changes in patterns of physical activity or diet due to cancer-related symptoms. Biomarker level might be modified during asymptomatic pre-clinical disease. If the number of cohort studies in the database allows it, we will investigate the effect of length of follow-up on heterogeneity of study results.

Other variables that may be considered as source of heterogeneity are characterisation of the exposure (FFQ, recall, diary, anthropometry etc.), exposure range (including correction for measurement error, length of intervention) and age at recruitment.

The interpretation of the exploration of heterogeneity should be cautious. If a considerable number of study characteristics are considered as possible explanations for heterogeneity in a meta-analysis containing only a small number of studies, then there is a high probability that one or more will be found to explain heterogeneity, even in the absence of real associations between the study characteristics and the size of associations.

Small study bias (e.g. publication bias) was explored through visual examination of funnel plots and through Egger's test.

We will do influence-analyses where each individual study will be omitted in turn to investigate the sensitivity of the pooled estimates to inclusion or exclusion of particular studies [10] .

14.6 Non linear trends in meta-analysis.

Non-linear meta-analysis will be applied when the data suggest that the dose-response curve is non-linear and when detecting a threshold of exposure might be of interest.

Considering a non-linear dose-response curve using the Greenland and Longnecker's pool-last approach is not possible[6] but it is possible if means and covariances of the individual studies are pooled before estimating the slope (pool first approach).

Non-linear dose-response meta-analysis will be conducted using the pool first approach method implemented within Stata by Darren Greenwood (personal communication). The best fitting nonlinear dose-response curve from a family of fractional polynomials will be selected. The best model will be the one that gave the most improvement (decrease) in deviance compared to the linear model.

15. Reports

Annual reports will be produced by the IC team. The report will include the following elements:

15.1 Results of the search

Information on number of records downloaded, number of papers thought potentially relevant after reading titles and abstracts and number of papers included. The reasons for excluding papers should also be described.

This information will be summarised in a flowchart.

15. 2 Description of studies identified in the Continuous Update

Number of studies by study design and publication year.

Number of studies by population characteristics (gender, geographic area, others)

Number of studies by exposure (main heading and selected subheadings) and publication year

Number of studies by exposure and outcome subtype

15.3 Summary of number of studies by exposure and study type in the database, separated on studies identified in the continuous update and in the SLR.

Example of table of summary study numbers:

Exposure Code	Exposure Name	Outcome	Number of controlled trials			Number of cohort studies		
			Total	SLR	Continuous update	Total	SLR	Continuous update

15.4 Tabulation of study characteristics

Information on the characteristics (e.g. population, exposure, outcome, study design) and results of the study (e.g. direction and magnitude) of the new studies will be summarised in tables using the same format as for the SLR for the Second Expert Report[1].
Within this table the studies should be ordered according to design (trials, cohort studies).

Example of table of study characteristics (in two parts below):

Author, Year, country, WCRF Code	Study design	Country, Ethnicity, other characteristics	Age (mean)	Cases (n)	Non cases (n/person-years)	Case ascertainment	Follow-up (years)

Assessment details	Category of exposure	Subgroup	No cat	OR	(95% CI)	p trend	Adjustment factors						
							A	B	C	D	E	F	G

Where
A : Age, sex
B : Socioeconomic status
C : Smoking
D : Anthropometry: height, BMI, others
E : Energy intake, other dietary factors
F: Personal antecedents of disease: diabetes, chronic pancreatitis
G : Others, e.g. family history, physical activity, marital status, race

15. 5 Graphic presentation

Tabular presentation may be complemented with graphic displays when the number of studies justifies it. Study results will be displayed in forest plots showing relative risk estimates and 95% confidence interval of ‘‘high versus low’’ comparisons for each study. No summary effect estimate of high versus low comparison will be calculated. Studies will be ordered chronologically.
Dose-response graphs are given for individual studies in which the information is available.

15.6 Results of meta-analysis

Main characteristics of included and excluded studies in dose-response meta-analysis will be tabulated, and reasons for exclusions will be detailed.
The results of meta-analysis will be presented in tables and dose-response forest plots, as well as the results of the exploration of heterogeneity and sensitivity analyses.
Studies already included in a meta-analysis during the SLR for the Second Expert Report will be identified with asterisks (*). Studies will be labelled “I” or “M” if only incident cases (I) or fatal cases (M) were included.

References

1. World Cancer Research Fund/ American Institute for Cancer Research. Systematic Literature Review. ***The SLR Specification Manual*** In : Food, Nutrition, Physical Activity and the Prevention of Cancer: A Global Perspective (Support Resource).Washington DC: AICR , 2007

2. World Cancer Research Fund/ American Institute for Cancer Research. Systematic Literature Review. ***The associations between food, nutrition and physical activity and the risk of pancreatic cancer and underlying mechanisms.*** In: Food, Nutrition, Physical Activity and the Prevention of Cancer: A Global Perspective (Support Resource).Washington DC: AICR , 2007

3. World Cancer Research Fund/ American Institute for Cancer Research. Food, Nutrition, Physical Activity and the Prevention of Cancer: A Global Perspective.page 305 Washington DC: AICR , 2007

4. Megan Dann Fesinmeyer MD et al . Differences in Survival by Histologic Type of Pancreatic Cancer Cancer Epidemiol Biomarkers Prev 2005;14(7):1766–73

5. Greenland S, Longnecker MP. Methods for trend estimation from summarized dose-response data, with applications to meta-analysis. Am J Epidemiol 1992; 135:1301-9.

6. Chêne G, Thompson SG. Methods for summarizing the risk associations of quantitative variables in epidemiologic studies in a consistent form.Am J Epidemiol. 1996;144(6):610-21.

7. DerSimonian R, Laird N (1986) Meta-analysis in clinical trials. Control Clin Trials 7:177–188

8. Bekkering GE et al. How much of the data published in observational studies of the association between diet and prostate or bladder cancer is usable for meta-analysis? Am J Epidemiol (2008);167(9):1017-26.

9. JP Higgins and SG Thompson, Quantifying heterogeneity in a meta-analysis, Stat Med 21 (2002), pp. 1539–1558.

10. A Tobias. Assessing the influence of a single study in meta-analysis, Stata Tech Bull 47 (1999), pp. 15–17.

Annex 1: Search strategy

We will use the standard search strategy for systematic literature review in PubMed developed by WCRF. This standard search uses a combination of subject heading terms e.g. MeSH in PubMed and has been structured to include all the exposures cited in the SLR Specification Manual (see below).

This search strategy will be combined with the following search questions:

#1 pancreatic neoplasms[MeSH terms]) OR (pancreatic neoplas*[tiab] OR pancreas neoplas*) OR (pancreatic cancer*[tiab] OR pancreas cancer*) OR (pancreatic carcin*[tiab] OR pancreas carcin*) OR (pancreatic tumo*[tiab] OR pancreas tumo*) OR (pancreatic metasta*[tiab] OR pancreas metasta*) OR (pancreatic malign*[tiab] OR pancreas malign*) OR (pancreatic adenocarcinoma*[tiab] OR pancreas adenocarcinoma*

Search strategy from WCRF Guidelines (version 15) for search literature review (relating to food, nutrition and physical activity):

#1 diet therapy[MeSH Terms] OR nutrition[MeSH Terms]
#2 diet[tiab] OR diets[tiab] OR dietetic[tiab] OR dietary[tiab] OR eating[tiab] OR intake[tiab] OR nutrient*[tiab] OR nutrition[tiab] OR vegetarian*[tiab] OR vegan*[tiab] OR "seventh day adventist"[tiab] OR macrobiotic[tiab] OR breastfeed*[tiab] OR breast feed*[tiab] OR breastfed[tiab] OR breast fed[tiab] OR breastmilk[tiab] OR breast milk[tiab]

#3 food and beverages[MeSH Terms]

#4 food*[tiab] OR cereal*[tiab] OR grain*[tiab] OR granary[tiab] OR wholegrain[tiab] OR wholewheat[tiab] OR roots[tiab] OR plantain*[tiab] OR tuber[tiab] OR tubers[tiab] OR vegetable*[tiab] OR fruit*[tiab] OR pulses[tiab] OR beans[tiab] OR lentils[tiab] OR chickpeas[tiab] OR legume*[tiab] OR soy[tiab] OR soya[tiab] OR nut[tiab] OR nuts[tiab] OR peanut*[tiab] OR groundnut*[tiab] OR seeds[tiab] OR meat[tiab] OR beef[tiab] OR pork[tiab] OR lamb[tiab] OR poultry[tiab] OR chicken[tiab] OR turkey[tiab] OR duck[tiab] OR fish[tiab] OR fat[tiab] OR fats[tiab] OR fatty[tiab] OR egg[tiab] OR eggs[tiab] OR bread[tiab] OR oils[tiab] OR shellfish[tiab] OR seafood[tiab] OR sugar[tiab] OR syrup[tiab] OR dairy[tiab] OR milk[tiab] OR herbs[tiab] OR spices[tiab] OR chilli[tiab] OR chillis[tiab] OR pepper*[tiab] OR condiments[tiab]

#5 fluid intake[tiab] OR water[tiab] OR drinks[tiab] OR drinking[tiab] OR tea[tiab] OR coffee[tiab] OR caffeine[tiab] OR juice[tiab] OR beer[tiab] OR spirits[tiab] OR liquor[tiab] OR wine[tiab] OR alcohol[tiab] OR alcoholic[tiab] OR beverage*[tiab] OR ethanol[tiab] OR yerba mate[tiab] OR ilex paraguariensis[tiab]

#6 pesticides[MeSH Terms] OR fertilizers[MeSH Terms] OR "veterinary drugs"[MeSH Terms]

#7 pesticide*[tiab] OR herbicide*[tiab] OR DDT[tiab] OR fertiliser*[tiab] OR fertilizer*[tiab] OR organic[tiab] OR contaminants[tiab] OR contaminate*[tiab] OR

veterinary drug*[tiab] OR polychlorinated dibenzofuran*[tiab] OR PCDF*[tiab] OR polychlorinated dibenzodioxin*[tiab] OR PCDD*[tiab] OR polychlorinated biphenyl*[tiab] OR PCB*[tiab] OR cadmium[tiab] OR arsenic[tiab] OR chlorinated hydrocarbon*[tiab] OR microbial contamination*[tiab]

#8 food preservation[MeSH Terms]

#9 mycotoxin*[tiab] OR aflatoxin*[tiab] OR pickled[tiab] OR bottled[tiab] OR bottling[tiab] OR canned[tiab] OR canning[tiab] OR vacuum pack*[tiab] OR refrigerate*[tiab] OR refrigeration[tiab] OR cured[tiab] OR smoked[tiab] OR preserved[tiab] OR preservatives[tiab] OR nitrosamine[tiab] OR hydrogenation[tiab] OR fortified[tiab] OR additive*[tiab] OR colouring*[tiab] OR coloring*[tiab] OR flavouring*[tiab] OR flavoring*[tiab] OR nitrates[tiab] OR nitrites[tiab] OR solvent[tiab] OR solvents[tiab] OR ferment*[tiab] OR processed[tiab] OR antioxidant*[tiab] OR genetic modif*[tiab] OR genetically modif*[tiab] OR vinyl chloride[tiab] OR packaging[tiab] OR labelling[tiab] OR phthalates[tiab]

#10 cookery[MeSH Terms]

#11 cooking[tiab] OR cooked[tiab] OR grill[tiab] OR grilled[tiab] OR fried[tiab] OR fry[tiab] OR roast[tiab] OR bake[tiab] OR baked[tiab] OR stewing[tiab] OR stewed[tiab] OR casserol*[tiab] OR broil[tiab] OR broiled[tiab] OR boiled[tiab] OR microwave[tiab] OR microwaved[tiab] OR re-heating[tiab] OR reheating[tiab] OR heating[tiab] OR re-heated[tiab] OR heated[tiab] OR poach[tiab] OR poached[tiab] OR steamed[tiab] OR barbecue*[tiab] OR chargrill*[tiab] OR heterocyclic amines[tiab] OR polycyclic aromatic hydrocarbons[tiab]

#12 dietary carbohydrates[MeSH Terms] OR dietary proteins[MeSH Terms] OR sweetening agents[MeSH Terms]

#13 salt[tiab] OR salting[tiab] OR salted[tiab] OR fiber[tiab] OR fibre[tiab] OR polysaccharide*[tiab] OR starch[tiab] OR starchy[tiab] OR carbohydrate*[tiab] OR lipid*[tiab] OR linoleic acid*[tiab] OR sterols[tiab] OR stanols[tiab] OR sugar*[tiab] OR sweetener*[tiab] OR saccharin*[tiab] OR aspartame[tiab] OR acesulfame[tiab] OR cyclamates[tiab] OR maltose[tiab] OR mannitol[tiab] OR sorbitol[tiab] OR sucrose[tiab] OR xylitol[tiab] OR cholesterol[tiab] OR protein[tiab] OR proteins[tiab] OR hydrogenated dietary oils[tiab] OR hydrogenated lard[tiab] OR hydrogenated oils[tiab]

#14 vitamins[MeSH Terms]

#15 supplements[tiab] OR supplement[tiab] OR vitamin*[tiab] OR retinol[tiab] OR carotenoid*[tiab] OR tocopherol[tiab] OR folate*[tiab] OR folic acid[tiab] OR methionine[tiab] OR riboflavin[tiab] OR thiamine[tiab] OR niacin[tiab] OR pyridoxine[tiab] OR cobalamin[tiab] OR mineral*[tiab] OR sodium[tiab] OR iron[tiab] OR calcium[tiab] OR selenium[tiab] OR iodine[tiab] OR magnesium[tiab] OR potassium[tiab] OR zinc[tiab] OR copper[tiab] OR phosphorus[tiab] OR manganese[tiab] OR chromium[tiab] OR phytochemical[tiab] OR allium[tiab] OR isothiocyanate*[tiab] OR glucosinolate*[tiab] OR indoles[tiab] OR polyphenol*[tiab] OR phytoestrogen*[tiab] OR genistein[tiab] OR saponin*[tiab] OR coumarin*[tiab]

#16 physical fitness[MeSH Terms] OR exertion[MeSH Terms] OR physical endurance[MeSH Terms] or walking[MeSH Terms]

#17 recreational activit*[tiab] OR household activit*[tiab] OR occupational activit*[tiab] OR physical activit*[tiab] OR physical inactivit*[tiab] OR exercise[tiab] OR exercising[tiab] OR energy intake[tiab] OR energy expenditure[tiab] OR energy balance[tiab] OR energy density[tiab]

#18 growth[MeSH Terms] OR anthropometry[MeSH Terms] OR body composition[MeSH Terms] OR body constitution[MeSH Terms]

#19 weight loss[tiab] or weight gain[tiab] OR anthropometry[tiab] OR birth weight[tiab] OR birthweight[tiab] OR birth-weight[tiab] OR child development[tiab] OR height[tiab] OR body composition[tiab] OR body mass[tiab] OR BMI[tiab] OR obesity[tiab] OR obese[tiab] OR overweight[tiab] OR over-weight[tiab] OR over weight[tiab] OR skinfold measurement*[tiab] OR skinfold thickness[tiab] OR DEXA[tiab] OR bio-impedence[tiab] OR waist circumference[tiab] OR hip circumference[tiab] OR waist hip ratio*[tiab]

#20 #1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19

Optional:
#21 animal[MeSH Terms] NOT human[MeSH Terms]

#22 #20 NOT #21

Annex 2 - Exposure codes

1 Patterns of diet

1.1 Regionally defined diets

*1.1.1 Mediterranean diet

Include all regionally defined diets, evident in the literature. These are likely to include Mediterranean, Mesoamerican, oriental, including Japanese and Chinese, and "western type".

1.2 Socio-economically defined diets

To include diets of low-income, middle-income and high-income countries (presented, when available in this order). Rich and poor populations within low-income, middle-income and high-income countries should also be considered. This section should also include the concept of poverty diets (monotonous diets consumed by impoverished populations in the economically-developing world mostly made up of one starchy staple, and may be lacking in micronutrients).

1.3 Culturally defined diets

To include dietary patterns such as vegetarianism, vegan diets, macrobiotic diets and diets of Seventh-day Adventists.

1.4 Individual level dietary patterns

To include work on factor and cluster analysis, and various scores and indexes (e.g. diet diversity indexes) that do not fit into the headings above.

1.5 Other dietary patterns

Include under this heading any other dietary patterns present in the literature, that are not regionally, socio-economically, culturally or individually defined.

1.6 Breastfeeding

1.6.1 Mother

Include here also age at first lactation, duration of breastfeeding, number of children breast-fed

1.6.2 Child

Results concerning the effects of breastfeeding on the development of cancer should be disaggregated into effects on the mother and effects on the child. Wherever possible detailed information on duration of total and exclusive breastfeeding, and of complementary feeding should be included.

1.7 Other issues

For example results related to diet diversity, meal frequency, frequency of snacking, dessert-eating and breakfast-eating should be reported here. Eating out of home should be reported here.

2 Foods

*2.0.1 Plant foods

2.1 Starchy foods

2.1.1 Cereals (grains)

* 2.1.1.0.1 Rice, pasta, noodles
* 2.1.1.0.2 Bread
* 2.1.1.0.3 Cereal

** Report under this subheading the cereals when it is not specified if they are wholegrain or refined cereals (e.g. fortified cereals)*

2.1.1.1 Wholegrain cereals and cereal products

* 2.1.1.1.1 Wholegrain rice, pasta, noodles
* 2.1.1.1.2 Wholegrain bread
* 2.1.1.1.3 Wholegrain cereal

2.1.1.2 Refined cereals and cereal products

* 2.1.1.2.1 Refined rice, pasta, noodles
* 2.1.1.2.2 Refined bread
* 2.1.1.2.3 Refined cereal

2.1.2 Starchy roots, tubers and plantains

* 2.1.2.1 Potatoes

2.1.3 Other starchy foods

**Report polenta under this heading*

2.2 Fruit and (non-starchy) vegetables

Results for "fruit and vegetables" and "fruits, vegetables and fruit juices" should be reported here. If the definition of vegetables used here is different from that used in the first report, this should be highlighted.

2.2.1 Non-starchy vegetables

This heading should be used to report total non-starchy vegetables. If results about specific vegetables are reported they should be recorded under one of the sub-headings below or if not covered, they should be recorded under '2.2.1.5 other'.

2.2.1.1 Non-starchy root vegetables and tubers
    *2.2.1.1.1 Carrots
2.2.1.2 Cruciferous vegetables
2.2.1.3 Allium vegetables
2.2.1.4 Green leafy vegetables (not including cruciferous vegetables)
2.2.1.5 Other non-starchy vegetables
    *2.2.1.5.13 Tomatoes
    *2.2.1.5.1 Fresh beans (e.g. string beans, French beans) and peas

Other non-starchy vegetables' should include foods that are botanically fruits but are eaten as vegetables, e.g. courgettes. In addition vegetables such as French beans that do not fit into the other categories, above.

If there is another sub-category of vegetables that does not easily fit into a category above eg salted root vegetables (ie you do not know if it is starchy or not) then report under 2.2.1.5. and note the precise definition used by the study. If in doubt, enter the exposure more than once in this way.

2.2.1.6 Raw vegetables

This section should include any vegetables specified as eaten raw. Results concerning specific groups and type of raw vegetable should be reported twice i.e. also under the relevant headings 2.2.1.1 –2.2.1.5.

2.2.2 Fruits
    *2.2.2.0.1 Fruit, dried
    *2.2.2.0.2 Fruit, canned
    *2.2.2.0.3 Fruit, cooked
2.2.2.1 Citrus fruit
    2.2.2.1.1 Oranges
    2.2.2.1.2 Other citrus fruits (e.g. grapefruits)
2.2.2.2 Other
    *2.2.2.2.1 Bananas
    *2.2.2.2.4 Melon
    *2.2.2.2.5 Papaya
    *2.2.2.2.7 Blueberries, strawberries and other berries
    *2.2.2.2.8 Apples, pears
    *2.2.2.2.10 Peaches, apricots, plums
    *2.2.2.2.11 Grapes

If results are available that consider other groups of fruit or a particular fruit please report under 'other', specifying the grouping/fruit used in the literature.

2.3 Pulses (legumes)

*2.3.1 Soya, soya products
*2.3.1.1 Miso, soya paste soup
*2.3.1.2 Soya juice
*2.3.1.4 Soya milk
*2.3.1.5 Tofu
*2.3.2 Dried beans, chickpeas, lentiles
*2.3.4 Peanuts, peanut products

Where results are available for a specific pulse/legume, please report under a separate heading.

2.4 Nuts and Seeds

To include all tree nuts and seeds, but not peanuts (groundnuts). Where results are available for a specific nut/seed, e.g. brazil nuts, please report under a separate heading.

2.5 Meat, poultry, fish and eggs

Wherever possible please differentiate between farmed and wild meat, poultry and fish.

2.5.1 Meat

This heading refers only to red meat: essentially beef, lamb, pork from farmed domesticated animals either fresh or frozen, or dried without any other form of preservation. It does not refer to poultry or fish.

Where there are data for offal (organs and other non-flesh parts of meat) and also when there are data for wild and non-domesticated animals, please show these separately under this general heading as a subcategory.

2.5.1.1 Fresh Meat
2.5.1.2 Processed meat
*2.5.1.2.1 Ham
*2.5.1.2.1.7 Burgers
*2.5.1.2.8 Bacon
*2.5.1.2.9 Hot dogs
*2.5.1.2.10 Sausages

Repeat results concerning processed meat here and under the relevant section under 4. Food Production and Processing. Please record the definition of 'processed meat' used by each study.

2.5.1.3 Red meat
*2.5.1.3.1 Beef

*2.5.1.3.2 Lamb
*2.5.1.3.3 Pork
*2.5.1.3.6 Horse, rabbit, wild meat (game)

Where results are available for a particular type of meat, e.g. beef, pork or lamb, please report under a separate heading.

Show any data on wild meat (game) under this heading as a separate sub-category.

2.5.1.4 Poultry

Show any data on wild birds under this heading as a separate sub-category.

*2.5.1.5 Offals, offal products (organ meats)

2.5.2 Fish
*2.5.2.3 Fish, processed (dried, salted, smoked)
*2.5.2.5 Fatty Fish
*2.5.2.7 Dried Fish
*2.5.2.9 White fish, lean fish

2.5.3 Shellfish and other seafood

2.5.4 Eggs

2.6 Fats, oils and sugars

2.6.1 Animal fats
*2.6.1.1 Butter
*2.6.1.2 Lard
*2.6.1.3 Gravy
*2.6.1.4 Fish oil
2.6.2 Plant oils
2.6.3 Hydrogenated fats and oils
*2.6.3.1 Margarine

Results concerning hydrogenated fats and oils should be reported twice, here and under 4.3.2 Hydrogenation

2.6.4 Sugars

This heading refers to added (extrinsic) sugars and syrups as a food, that is refined sugars, such as table sugar, or sugar used in bakery products.

2.7 Milk and dairy products

Results concerning milk should be reported twice, here and under 3.3 Milk

**2.7.1 Milk, fresh milk, dried milk*

*2.7.1.1 Whole milk, full-fat milks
*2.7.1.2 Semi skimmed milk, skimmed milk, low fat milk, 2% Mil

*2.7.2 Cheese
*2.7.2.1 Cottage cheese
* 2.7.2.2 Cheese, low fat

*2.7.3 Yoghurt, buttermilk, sour milk, fermented milk drinks
*2.7.3.1Fermented whole milk
*2.7.3.2Fermented skimmed milk

*2.7.7 Ice cream

2.8 Herbs, spices, condiments
*2.8.1 Ginseng
*2.8.2 Chili pepper, green chili pepper, red chili pepper

2.9 Composite foods

Eg, snacks, crisps, desserts, pizza. Also report any mixed food exposures here ie if an exposure is reported as a combination of 2 or more foods that cross categories (eg bacon and eggs). Label each mixed food exposure.

*2.9.1 Cakes, biscuits and pastry
*2.9.2 Cookies
*2.9.3 Confectionery
*2.9.4 Soups
*2.9.5 Pizza
*2.9.6 Chocolate, candy bars
*2.9.7 Snacks

3 Beverages

3.1 Total fluid intake
3.2 Water
3.3 Milk

For results concerning milk please report twice, here and under 2.7 Milk and Dairy Products.

3.4 Soft drinks

Soft drinks that are both carbonated and sugary should be reported under this general heading. Drinks that contain artificial sweeteners should be reported separately and labelled as such.

3.4.1 Sugary (not carbonated)

3.4.2 Carbonated (not sugary)

The precise definition used by the studies should be highlighted, as definitions used for various soft drinks vary greatly.

3.5 *Fruit and vegetable juices

*3.5.1 Citrus fruit juice
*3.5.2 Fruit juice
*3.5.3 Vegetable juice
*3.5.4 Tomato juice

3.6 Hot drinks

3.6.1 Coffee
3.6.2 Tea

Report herbal tea as a sub-category under tea.

3.6.2.1 Black tea
3.6.2.2 Green tea
3.6.3 Maté
3.6.4 Other hot drinks

3.7 Alcoholic drinks

3.7.1 Total

3.7.1.1 Beers
3.7.1.2 Wines
3.7.1.3 Spirits
3.7.1.4 Other alcoholic drinks

4 Food production, preservation, processing and preparation

4.1 Production

4.1.1 Traditional methods (*to include 'organic')*
4.1.2 Chemical contaminants

Only results based on human evidence should be reported here (see instructions for dealing with mechanistic studies). Please be comprehensive and cover the exposures listed below:

4.1.2.1 Pesticides
4.1.2.2 DDT
4.1.2.3 Herbicides
4.1.2.4 Fertilisers
4.1.2.5 Veterinary drugs
4.1.2.6 Other chemicals

4.1.2.6.1 Polychlorinated dibenzofurans (PCDFs)

4.1.2.6.2 Polychlorinated dibenzodioxins (PCDDs)
4.1.2.6.3 Polychlorinated biphenyls (PCBs)

4.1.2.7 Heavy metals

4.1.2.7.1 Cadmium
4.1.2.7.2 Arsenic

4.1.2.8 Waterborne residues

4.1.2.8.1 Chlorinated hydrocarbons

4.1.2.9 Other contaminants

Please also report any results that cover the cumulative effect of low doses of contaminants in this section.

4.2 Preservation

4.2.1 Drying

4.2.2 Storage
4.2.2.1 Mycotoxins
4.2.2.1.1 Aflatoxins
4.2.2.1.2 Others

4.2.3 Bottling, canning, vacuum packing
4.2.4 Refrigeration
4.2.5 Salt, salting
4.2.5.1 Salt
4.2.5.2 Salting
4.2.5.3 Salted foods

4.2.5.3.1 Salted animal food
4.2.5.3.2 Salted plant food

4.2.6 Pickling
4.2.7 Curing and smoking
4.2.7.1 Cured foods

4.2.7.1.1 Cured meats
4.2.7.1.2 Smoked foods

For some cancers e.g. colon, rectum, stomach and pancreas, it may be important to report results about specific cured foods, cured meats and smoked meats. *N*-nitrososamines should also be covered here.

4.3 Processing

4.3.1 Refining

Results concerning refined cereals and cereal products should be reported twice, here and under 2.1.1.2 refined cereals and cereal products.

4.3.2 Hydrogenation

Results concerning hydrogenated fats and oils should be reported twice, here and under 2.6.3 Hydrogenated fats and oils

4.3.3 Fermenting
4.3.4 Compositional manipulation

4.3.4.1 Fortification
4.3.4.2 Genetic modification
4.3.4.3 Other methods

4.3.5 Food additives

4.3.5.1 Flavours

Report results for monosodium glutamate as a separate category under 4.3.5.1 Flavours.

4.3.5.2 Sweeteners (non-caloric)
4.3.5.3 Colours
4.3.5.4 Preservatives

4.3.5.4.1 Nitrites and nitrates

4.3.5.5 Solvents
4.3.5.6 Fat substitutes
4.3.5.7 Other food additives

Please also report any results that cover the cumulative effect of low doses of additives.
Please also report any results that cover synthetic antioxidants

4.3.6 Packaging

4.3.6.1 Vinyl chloride
4.3.6.2 Phthalates

4.4 Preparation

4.4.1 Fresh food

4.4.1.1 Raw

Report results regarding all raw food other than fruit and vegetables here. There is a separate heading for raw fruit and vegetables (2.2.1.6).

4.4.1.2 Juiced

4.4.2 Cooked food

4.4.2.1 Steaming, boiling, poaching
4.4.2.2 Stewing, casseroling
4.4.2.3 Baking, roasting
4.4.2.4 Microwaving
4.4.2.5 Frying
4.4.2.6 Grilling (broiling) and barbecuing
4.4.2.7 Heating, re-heating

Some studies may have reported methods of cooking in terms of temperature or cooking medium, and also some studies may have indicated whether the food was cooked in a direct or indirect flame. When this information is available, it should be included in the SLR report.

Results linked to mechanisms e.g. heterocyclic amines, acrylamides and polycyclic aromatic hydrocarbons should also be reported here. There may also be some literature on burned food that should be reported in this section.

5 Dietary constituents

Food constituents' relationship to outcome needs to be considered in relation to dose and form including use in fortified foods, food supplements, nutrient supplements and specially formulated foods. Where relevant and possible these should be disaggregated.

5.1 Carbohydrate

5.1.1 Total carbohydrate
5.1.2 Non-starch polysaccharides/dietary fibre

5.1.2.1 Cereal fibre
5.1.2.2 Vegetable fibre
5.1.2.3 Fruit fibre

5.1.3 Starch

5.1.3.1 Resistant starch

5.1.4 Sugars

*5.1.5 Glycemic index, glycemic load

This heading refers to intrinsic sugars that are naturally incorporated into the cellular structure of foods, and also extrinsic sugars not incorporated into the cellular structure of foods. Results for intrinsic and extrinsic sugars should be presented separately. Count honey and sugars in fruit juices as extrinsic. They can be natural and unprocessed, such as honey, or refined such as table sugar. Any results related to specific sugars e.g. fructose should be reported here.

5.2 Lipids

5.2.1 Total fat
5.2.2 Saturated fatty acids
5.2.3 Monounsaturated fatty acids
5.2.4 Polyunsaturated fatty acids
5.2.4.1 n-3 fatty acids

Where available, results concerning alpha linolenic acid and long chain n-3 PUFA should be reported here, and if possible separately.

5.2.4.2 n-6 fatty acids
5.2.4.3 Conjugated linoleic acid

5.2.5 Trans fatty acids
5.2.6 Other dietary lipids, cholesterol, plant sterols and stanols.

For certain cancers, e.g. endometrium, lung, and pancreas, results concerning dietary cholesterol may be available. These results should be reported under this section.

5.3 Protein

5.3.1 Total protein
5.3.2 Plant protein
5.3.3 Animal protein

5.4 Alcohol

This section refers to ethanol the chemical. Results related to specific alcoholic drinks should be reported under 3.7 Alcoholic drinks. Past alcohol refers, for example, to intake at age 18, during adolescence, etc.

**5.4.1 Total Alcohol (as ethanol)*

*5.4.1.1 Alcohol (as ethanol) from beer
*5.4.1.2 Alcohol (as ethanol) from wine
*5.4.1.3 Alcohol (as ethanol) from spirits
*5.4.1.4 Alcohol (as ethanol) from other alcoholic drinks
** 5.4.1.5 Total alcohol (as ethanol), lifetime exposure*

* 5.4.1.6 Total alcohol (as ethanol), past

5.5 Vitamins

**5.5.0 Vitamin supplements*

**5.5.0.1 Vitamin and mineral supplements*

**5.5.0.2 Vitamin B supplement*

5.5.1 Vitamin A

5.5.1.1 Retinol
5.5.1.2 Provitamin A carotenoids

5.5.2 Non-provitamin A carotenoids

Record total carotenoids under 5.5.2 as a separate category marked Total Carotenoids.

5.5.3 Folates and associated compounds
*5.5.3.1 Total folate
*5.5.3.2 Dietary folate
*5.5.3.3 Folate from supplements

Examples of the associated compounds are lipotropes, methionine and other methyl donors.

5.5.4 Riboflavin
5.5.5 Thiamin (vitamin B1)
5.5.6 Niacin
5.5.7 Pyridoxine (vitamin B6)
5.5.8 Cobalamin (vitamin B12)
5.5.9 Vitamin C
5.5.10 Vitamin D (and calcium)
5.5.11 Vitamin E
5.5.12 Vitamin K
5.5.13 Other

If results are available concerning any other vitamins not listed here, then these should be reported at the end of this section. In addition, where information is available concerning multiple vitamin deficiencies, these should be reported at the end of this section under 'other'.

6 Physical activity

6.1 Total physical activity (overall summary measures)

6.1.1 Type of activity

6.1.1.1 Occupational
6.1.1.2 Recreational
6.1.1.3 Household
6.1.1.4 Transportation

6.1.2 Frequency of physical activity
*6.1.2.1 Frequency of occupational physical activity
*6.1.2.2 Frequency of recreational physical activity
6.1.3 Intensity of physical activity
*6.1.3.1 Intensity of occupational physical activity
*6.1.3.2 Intensity of recreational physical activity

6.1.4 Duration of physical activity
*6.1.4.1 Duration of occupational physical activity
*6.1.4.2 Duration of recreational physical activity

6.2 Physical inactivity
6.3 Surrogate markers for physical activity e.g. occupation

7 Energy balance
7.1 Energy intake
*7.1.0.1 Energy from fats
*7.1.0.2 Energy from protein
*7.1.0.3 Energy from carbohydrates
*7.1.0.4 Energy from alcohol
*7.1.0.5 Energy from all other sources

8 Anthropometry
8.1 Markers of body composition

8.1.1 BMI
8.1.2 Other weight adjusted for height measures
8.1.3 Weight
8.1.4 Skinfold measurements
8.1.5 Other (e.g. DEXA, bio-- impedance, etc)
8.1.6 Change in body composition (including weight gain)

8.2 Markers of distribution of fat

8.2.1 Waist circumference
8.2.2 Hips circumference
8.2.3 Waist to hip ratio
8.2.4 Skinfolds ratio
8.2.5 Other e.g. CT, ultrasound

8.3 Skeletal size

8.3.1 Height (and proxy measures)
8.3.2 Other (e.g. leg length)

8.4 Growth in fetal life, infancy or childhood

8.4.1 Birthweight,
8.4.2 Weight at one year

Annex 3. Tables of excluded and included biomarkers proposed by the SLR centre Bristol (SLR prostate cancer)

Extracted from: Food, Nutrition, Physical Activity and the Prevention of Cancer: A Global Perspective
Systematic Literature Review – Support Resource
SLR Prostate Cancer (pp 1185-1186)

The reviewers of the SLR centre Bristol used two chapters (Willet: Nutritional epidemiology (Chapter 9), 1998; Margetts and Nelson: Design concepts in nutritional epidemiology (Chapter 7), 1997) to guide their decisions. If there was no info, the biomarker was excluded. If one of the chapters stated the biomarker was useful, the data on validity were checked. Biomarkers with a correlation >0.20 were included. If the chapters stated that there were no good biomarkers for a nutrient or that the biomarker was valid for certain range of intake only, the biomarker was excluded. It was assumed that if biomarkers measured in plasma were valid, this would also be true for serum and vice versa.
The reviewers of the SLR centre Bristol have been more inclusive with respect to the validation required for biomarkers of important nutrients and have therefore added serum/plasma retinol, retinol binding protein, vit B6, ferritin, magnesium, erythrocyte superoxide dismutase (more details below). They have also included biomarkers where validity is not possible: this happens in the case of toxins and phytochemicals where dietary data are sparse. Various contaminants, such as cadmium, lead, PCBs in the serum are also included now although validity data are not available. The level of these chemicals in human tissues is often the only available measure of ingestion.

Measured in	Include	Exclude
Serum	Provit A carotenoids: Carotene, B-carotene, Alpha-carotene Nonprovit A carotenoids: Carotenoids, Lycopene, Cryptoxanthin (B-), Lutein+zeaxanthin Vit E: alpha-tocopherol, gamma tocopherol Selenium n-3 fatty acids: EPA (Eicosapentaenoic), DHA (Docosahexaenoic) Magnesium Vit A: Retinol &Retinol Binding Protein Pyridoxic acid (vit B6) Phytoestrogen: Genistein, Daidzein Chemical food contaminants Polychlorinated biphenyls (PCBs) Phytochemicals	Prealbumin Minerals: Zinc, Copper, Copper/zinc ratio, Zinc/retinol ratio Other dietary lipids: Cholesterol, Triglycerides Saturated fatty acids, Monounsaturated fatty acids, Polyunsaturated fatty acids Lipids (as nutrients), Total fat (as nutrients), Total protein
Urine	4-pyridoxic acid (vit B6) in 24-h urine	Nitrosamines Xanthurenic acid in 24-h urine Arsenic Ferritin
Saliva		Other dietary lipids: Cholesterol, Triglycerides
Erythrocyte	Linoleic acid Selenium Superoxide dismutase Cadmium	Minerals: Zinc, Copper Monounsaturated fatty acids n-3 fatty acids: EPA (Eicosapentaenoic), DHA (Docosahexaenoic) n-6 fatty acids (other than linoleic acid) Polyunsaturated fatty acids, Saturated fatty acids Glutathione peroxidase

Measured in	**Include**	**Exclude**
Plasma	Vit D Vit E: alpha-tocopherol, gamma tocopherol Vit C Provit A carotenoids: Carotene, Alpha-carotene, B-carotene Nonprovit A carotenoids: Lycopene, Cryptoxanthin (B-), zeaxanthin, Lutein Selenium, Selenoprotein Folate, Iron: ferritin Vit A Retinol: Retinol Binding Protein Cadmium, Cadmium/zinc ratio EPA DHA fatty acids	Alkaline phosphatase Minerals: Zinc, Copper, caeruloplasmin Other dietary lipids: Cholesterol, Triglycerides, LDL, HDL
Adipose tissue	n-3 fatty acids: EPA (Eicosapentaenoic), DHA (Docosahexaenoic) n-6 fatty acids Trans fatty acids , Polyunsaturated fatty acids, Saturated fatty acids	Unsaturated fat, Monounsaturated fatty acids n-9 fatty acids other measures of polyunsat fa: M:S ratio, M:P ratio, n3-n6 ratio
leucocyte	Vit C	Zinc
Erythrocyte membrane	n-6 fatty acids: linoleic	n-6 fatty acids (other than linoleic) n-3 fatty acids: EPA (Eicosapentaenoic), DHA (Docosahexaenoic)
Hair		Minerals: Zinc, Copper, Manganese, Iron Cadmium
Toenails or fingernails	Selenium	Cadmium, zinc

Reasons for exclusion and inclusion of biomarkers proposed by the SLR centre Bristol.

Extracted from: Food, Nutrition, Physical Activity and the Prevention of Cancer: A Global Perspective
Systematic Literature Review – Support Resource
SLR Prostate Cancer (pp 1187-1189)
(Source: Willet: Nutritional epidemiology (Chapter 9), 1998; Margetts and Nelson: Design concepts in nutritional epidemiology (Chapter 7), 1997)

Exposure	Measured in	Valid?	Reason (Willett)	Reason (Margetts / Nelson)
Retinol	Plasma/serum	Yes	Can be measured adequately, but limited interpretability in well-nourished population (p 190).	Main biochemical marker of vit A intake is serum retinol (p 194) although in western countries dietary intake of this vitamin is only a very minor determinant of its plasma levels.
Retinol-Binding protein	Serum	Yes	Retinol levels are highly correlated to RBP(p192).	May be measure of physiologically available form. Not if certain disease processes exist (p 192).
Beta-carotene	Plasma	Yes	Yes (p 194) although blood levels much more responsive to supplemental beta-carotene than beta-carotene from food sources (p 193)	Yes (p 197)
Alpha-carotene Beta-cryptoxanthin Lutein+zeaxanthin Lycopene	Plasma	Yes	Yes (p 194)	There is some evidence for interaction between carotenoids during intestinal absorption, which may complicate relationship between intake and blood levels (p 198)
Vit E	Plasma	Yes	Yes (p 196) NB. Strong confounding with serum cholesterol and total lipid concentrations (p 196).	Plasma, red and white blood cells. Yes, if used for vit E supplements. Yes, although if used for diet, associations are only moderate (p199)

Exposure	Measured in	Valid?	Reason (Willett)	Reason (Margetts / Nelson)
Vit D: D25 (OH)D	Plasma Serum	Yes	Yes (P 198/199) NB. Seasonal variation exists, especially in elderly populations, decreasing in winter and rising during summer (p 198) Sunshine exposure is most important determinant; level is better marker of dietary intake in subjects with low sun exposure	Both can be used to measure vit D status, but the higher plasma concentration and lesser metabolic control of d25 makes this, by far, the better option (p 198).
Vit D: 1.25 (OH)2D		No	No. Influenced by calcium and phosphate levels and parathyroid hormone (p 199).	
Vit D: Alkaline phosphatase activity	Serum	No	No. Is indirect measure of vit D status and is susceptible to other disease processes (p 199)	No info
Vit C	Plasma Leukocyte Serum	Yes	Yes (p 200). Leukocyte may be preferred for long-term intake and plasma and serum reflects more recent intake (p 201)	Yes (p 209), vit C exhibits the strongest and most significant correlation between intake and biochemical indices. Known confounders are: gender, smoking
Vitamin B6	Plasma	Yes	Yes response to supplementation shows response in PLP. PLP better measure of short term rather than long term	Recent studies show that there is unlikely to be a strong correlation between dietary intake and plasma pyridoxal phosphate levels (PPL)
PLP and 4 Pyridoxic acid	Urinary	Yes	Urinary B6 may be more responsive to recent dietary intake than plasma PLP. Random samples of urine 4 –pyridoxic acid correlate well with 24 hour collections	
Folacin (folate)	Serum Erythrocyte	Yes	Yes good correlation with dietary folate in both serum and erythrocytes	Used for assessing folate status Table 7.11p
Magnesium	Serum	Yes	Yes stronger correlation with supplement users than with dietary Mg	
Iron	Serum Hair/nails	No No	No, short-term variability is very high (p 208). No, remains to be determined	
Iron: Ferritin	Serum	Yes	Meat intake predicts serum ferritin level (p 208)	No marker of iron intake is satisfactory (p. 192)

Exposure	Measured in	Valid?	Reason (Willett)	Reason (Margetts / Nelson)
Copper : Superoxide dismutase	Erythrocyte	Yes	Among four men fed a copper deficient diet for 4 months, erythrocyte S.O.D declined for all 4. Copper repletion restored S.O.D levels	
Copper	Plasma/serum	No	No (p 211): large number of lifestyle factors/pathologic conditions probably alter blood copper concentrations (smoking, infections)	
Copper	Hair	No	No evidence (212) and data suggests influenced by external contamination	No. Copper-dependent enzyme superoxide dismutase in erythrocytes and copper-protein complex caeroplasmin in serum have been shown to be associated with copper intake, but these markers may be influenced by nondietary factors (p 193)
Selenium	Blood components Toenails	Yes	Yes. Erythrocyte is probably superior to serum as measure of long-term intake (p 206). Lower influence of environment in countries where wearing shoes is norm (toenails). Selenium status is reduced by smoking, also in older persons (p 207); Relationship of selenium with disease may be modified by other antioxidants (vit E and C)	Yes (p 193). Relationship between selenium intake and biomarkers is reasonably good. Urine: reasonable marker, plasma reflects intake provided that the range of variation is large. Red cell and glutathione perioxidase are markers of longer-term intakes. Hair and toenails are alternative possibilities, although contamination of hair samples with shampoo must be controlled for
Glutathione perioxidase	Plasma Serum Erythrocytes Blood	No	Is poor measure of selenium intake among persons with moderate and high exposure (p 206)	

Exposure	Measured in	Valid?	Reason (Willett)	Reason (Margetts / Nelson)
Zinc Metallothionein levels	Any	No No	No (p 212) May be marker of short-term intake (p 213)	No biochemical marker is a good indicator of zinc intake (p 192/193). This is, in general terms, also true for other trace metal nutrients such as copper, manganese, chromium, etc
Lipids: total fats	Any	No	No (p 213)	No, there are no markers of total fat intake (p 215)
Cholesterol, LDL Lipoprotein levels	Serum	No	No, but may be useful to predict dietary changes but not for dietary intake (p 215)	No, relationship dietary cholesterol and lipoprotein levels of cholesterol are complex and appears to vary across range of intake (p218)
Linoleic acid	Plasma Adipose tissue	No Yes	Plasma linoleic acid can discriminate between groups with relatively large differences in intake but performs less well on an individual basis (p 220) Yes (p 220)	No consistent relation between dietary linoleic acid intake and plasma linoleic acid (p 220). Across the range of fatty acids in the diet, fatty acids levels in blood and other tissue (adipose tissue) reflect the dietary levels. NB levels are not comparable across tissues
Marine omega-3 fatty acids (EPA, DHA)	Serum Plasma Adipose tissue	Yes	Yes (p 222/223), although dose-response relation remains to be determined	
Monounsat fatty acids (oleic acid)	Plasma Adipose tissue	No No	No, plasma levels are poor predictors of oleic acid intake, but adipose tissue may weakly reflect oleic acid intake (p. 224). Validity is too low	
Polyunsat fatty acids	Adipose tissue	Yes	Yes (p 220)	No info

Exposure	Measured in	Valid?	Reason (Willett)	Reason (Margetts / Nelson)
Saturated fatty acids (Palmitic acid, stearic acids)	Adipose tissue Plasma	Yes No	Yes, long term sat fatty acid intake may be reflected in adipose tissue levels (p 224) No, levels of palmitic and stearic acids in plasma do not provide a simple index of intake (p 224).	No info
Trans-fatty acids	Adipose tissue	Yes	Yes (p 225)	No info
Protein	Any	No	No (p 226)	No info
Nitrogen	Urine	Yes	Yes, but several 24-h samples are needed to provide a stable estimate of nitrogen intake (p 227) Nitrogen excretion increases with body size and exercise and decreased caloric intake	Yes (p 219) One assumes that subjects are in nitrogen Balance

Data on validity and reliability of included biomarkers
Extracted from: Food, Nutrition, Physical Activity and the Prevention of Cancer: A Global Perspective
Systematic Literature Review – Support Resource
SLR Prostate Cancer (pp 1187-1189)

Nutrient	Biologic tissue	Val./reproduc	Coef	Details
Retinol	Plasma	Validity	0.17	Borderline Correlation between pre-formed vit A intake and plasma retinol. However plasma retinol is a recognized marker of vit A nutritional status for undernourished populations
Beta-carotene			0.51	Correlation between plasma beta-carotene level (averaged from 2 samples taken 1 week apart) and a 7-day diet record estimate of beta-carotene in 98 non-smoking women (Willett, p 194).
			0.38	Cross-sectional correlation between dietary intake of carotene and plasma betacarotene in 902 adult females. In males (n=880): r=0.20 (Margetts, table 7.9a).
	Plasma	Reproducibility	0.45	Correlation for carotene (80% beta-carotene, 20% alpha-carotene) between two measurements taken 6 years apart (Willett, p 194).
Beta-cryptoxanthin	Plasma	Validity	0.49	Correlation between plasma beta-carotene level (averaged from 2 samples taken 1 week apart) and a 7-day diet record estimate of beta carotene in 98 non-smoking women (Willett, p 194)
Lutein+zeaxanthin	Plasma	Validity	0.31	
Lycopene	Plasma	Validity	0.50	
Alpha-carotene	Plasma	Validity	0.58	
Alpha-carotene	Plasma	Validity	0.43	Cross-sectional correlation between dietary intake of carotene and plasma alphacarotene in 902 adult females. In males (n=880): r=0.41 (Margetts, table 7.9a).
Carotenoids	Plasma	Reproducibility	≥080	Within-person variability of plasma levels over 1 week (Willett, p 194).
Vitamin E	Plasma	Validity	0.53	Lipid-adjusted alpha-tocopherol measurements and estimated intake (incl. supplements). After excluding supplement users: r=0.35 (Willett, p 196)
	Plasma	Reproducibility	0.65	Unadjusted repeated measures over a 6-year period (p 188). Adjusting for serum cholesterol reduced correlation to r=0.46 (p 188). Also r=0.65 was found over a 4-year period in 105 adults in Finland (Willett, p 196).
	Plasma	Validity	0.20	Cross-sectional correlation between dietary intake of vit E and plasma vit E in 880 adult males. In females (n=906): r=0.14 (Margetts, table 7.9a)

Nutrient	Biologic tissue	Val./reproduc	Coef	Details
Vitamin D: D25 (OH)D	Plasma	Validity	0.35	Correlation between FFQ estimate of vit D intake (including supplements) with plasma D25 (OH)D (n=139). Correlation excluding supplement users: r=0.25 (Willett, p 199)
			0.18	Cross-sectional correlation between dietary intake of nutrients and biochemical markers in UK pre-school child study in females (n=350). In males (n=365) r=0.06 (Margetts, table 7.9b).
	Serum	Validity	0.24	Correlation between estimated vit D intake from food and supplements (based on 24 h recall) and serum D25 (OH)D (n=373 healthy women). Food only: r=0.11 (Willett, p 199).
Vitamin C	Plasma	Validity	0.43	Unadjusted correlation between questionnaire-derived dietary ascorbic acid intake and plasma ascorbic acid concentration in a heterogeneous population. Diet only: r=38 (Table 9.1). Correlation is 0.31 for leukocyte ascorbic acid concentration.(Willett, p 200)
		Reproducibility	0.28	Repeated measures in men obtained 6 years apart (Willett, p 201)
		Validity	0.43	Cross-sectional correlation between dietary intake of nutrients and biochemical markers in UK pre-school child study in males (n=369). In females (n=354) r=0.39 (Margetts, table 7.9b).
	Serum	Validity	0.55	Correlation between food-frequency questionnaire estimate of vit C intake and serum vit C values (in smokers) in 196 men in Scotland (adjusted for total energy intake, BMI and serum cholesterol level). Non-smokers: 0.58 (Willett, p 200/201)
	Leukocyte	Validity	0.49	Correlation between one week of intake data and a single leukocyte ascorbate measurement for men. For women: r=0.36. Nutrition survey of elderly in UK (Margetts, p 211)
Vitamin B6	Plasma Urinary	Validity Validity	0.37 -	Correlation between B6 and plasma pyridoxal phosphate levels in 280 healthy men =0.37 (Willett p203)
Folacin	Serum Erythrocyte	Validity	0.56 0.51	Correlation of 0.56 in Framington Heart study 385 subjects (serum) Correlation in 19 elderly subjects (erythrocyte) (Willet p204)
Magnesium	Serum	Validity	0.27	Correlation between intake with supplements 0.27 in 139 men and 0.15 without supplements (Willett p211)

Nutrient	Biologic tissue	Val./reproduc	Coef	Details
Iron (ferritin)	Serum	Validity	0.16	Borderline 0.16 correlation with heme intake but only r-0.15 with total iron intake (Willett p 208). Included as marker of iron storage
Copper (Superoxide dismutase)	Erythrocyte	-	-	S.O.D levels reflect both depletion and repletion of Cu (Willett p 212)
Selenium	Serum	Validity	0.63	Correlation between selenium intake and serum selenium in South Dakotans (n=44)(Willett, p 186)
		Reproducibility	0.76	Average correlation between repeated measurements at four 3-month intervals in 78 adults (Willett, p 188)
	Toenails	Validity	0.59	Correlation between selenium intake and toenail selenium level in South Dakotans (n=44) (Willett, p 186)`
		Reproducibility	0.48	Correlation for selenium levels in toenails collected 6 years apart from 127 US women (Willett, p 206)
	Whole blood	Validity	0.62	Correlation between selenium intake and whole blood selenium in South Dakotans (n=44) (Willett, p 186)
		Reproducibility	0.95	Average correlation between repeated measurements at four 3-month intervals in 78 adults (Willett, p 188)
Linoleic acid	Adipose tissue	Validity	0.57	Correlation between dietary linoleic acid intakes determined from 7-day weighted diet records and the relative proportion of linoleic acid in adipose tissue in Scottish men (n=164). Also correlation between linoleic acid measured in adipose tissue and calculated from FFQ in 118 Boston-area men (Willett, p 220)
Eicosapentaenoic (n-3)	Adipose tissue	Validity	0.40	Correlation with intake estimated from three 7-day weighted food records (Willett, p 223).
		Reproducibility	0.68	Correlation over 8 months in 27 men and women aged 20-29 (Willett, p 223).
	Plasma	Validity	0.23	Correlation of cholesterol ester fraction and intake in 3,570 adults (Willett, p 223)
		Reproducibility	0.38	Correlation of two measurements taken 6 years apart in study of 759 Finnish youths (Willett, p 219)

Nutrient	Biologic tissue	Val./reproduc	Coef	Details
Docosahexaenoic (n-3)	Adipose Tissue	Validity	0.66	Correlation with intake estimated from three 7-day weighted food records (Willett, p 223)
		Reproducibility	0.93	Correlation over 8 months in 27 men and women aged 20-29 (Willett, p 223).
	Plasma	Validity	0.42	Correlation of cholesterol ester fraction and intake in 3,570 adults (Willett, p 223)
		Reproducibility	0.38	Correlation of two measurements taken 6 years apart in study of 759 Finnish youths (Willett, p 219)
Polyunsaturated fatty acids	Adipose tissue	Validity	0.80	Correlation between % of polyunsaturated fatty acid relative to total fatty acid intake and relative % of adipose tissue polyunsaturated fatty acid (Willett, p 220)
Palmitic acid	Adipose tissue	Validity	0.27	Correlation adipose tissue measurement with a FFQ estimate among 118 men. A correlation of 0.14 was reported among women. Among 20 healthy subjects, correlations between normal intake of total saturated fatty acids and fatty acid composition of triglycerides in adipose tissue was 0.57 (Willett, p 224)
Stearic acid	Adipose tissue	Validity	0.56	Among 20 healthy subjects, correlations between normal intake of total saturated fatty acids and fatty acid composition of triglycerides in adipose tissue (Willett, p 224)
Trans fatty acids	Adipose tissue	Validity	0.40	Correlation between adipose trans and intake estimated from the average of two FFQ among 140 Boston-area women. Previous study: 115 Boston area women, correlation of 0.51 between trans intake estimated from a single FFQ and a fatty acid measurement. Among 118 Boston-area men: correlation of 0.29 between trans fatty acid measured in adipose and by FFQ (Willett, p 225)
Nitrogen	Urine	Validity	0.69	Correlation between nitrogen intakes estimated from weighted food records of 16 days and the average of six 24-h urine nitrogen levels (160 women) (Willett, p 227)
Phyto Oestrogens Genistein, daidzein	Plasma 24 hr urine	Validity	0.97 0.92	Urinary excretion (24 h) and plasma concentrations of PO were significantly related to measured dietary PO intake (r 0.97, P<0.001 and r 0.92, P<0.001 respectively). These findings validate the PO database and indicate that 24 h urinary excretion and timed plasma concentrations can be used as biomarkers of PO intake. Br J Nutr. 2004 Mar;91(3):447-57

Nutrient	Biologic tissue	Val./reproduc	Coef	Details
Enterodiol Enterolactone	Serum Urine	Validity	0.13 to 0.29	Urinary enterodiol and enterolactone and serum enterolactone were significantly correlated with dietary fiber intake (r = 0.13-0.29) Cancer Epidemiol Biomarkers Prev. 2004 May;13(5):698-708

Annex 3. List of conversion units (as used in the SLR prostate, Bristol)

In cases where the units of measurement differed between results the units would be converted, where possible, such that all results used the same measurement. Where assumptions had to be made on portion or serving sizes an agreement was reached after discussion between team members and consultation of various sources. The following general sizes were agreed upon:

Beer	400ml serving
Cereals	60g serving
Cheese	35g serving
Dried fish	10g serving
Eggs 55g serving	(1 egg)
Fats	10g serving
Fruit & Vegetables	80g serving
Fruit Juice	125ml serving
General drinks inc soft & hot drinks	200ml serving
Meat & Fish	120g serving
Milk	50ml serving
Milk as beverage	200ml serving
Processed cheese slice	10g serving
Processed meat	50g serving
Shellfish	60g serving
Spirits	25ml serving
Staple foods (rice, pasta, potatoes, beans & lentils, foods boiled in soy sauce)	150g serving
Water & Fluid intake	8oz cup
Wine	125ml serving

(End of Protocol)

Appendix 2 List of prospective studies used in the report

Full name of the study	Abbreviation
6 Prefecture Cohort, Japan	6 Prefecture Cohort
Agricultural Health Study Cohort	AHSC
Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study	ATBC
Adventist Mortality Study	AMS
Breast Cancer Detection Demonstration Project	BCDDP
Californian Seventh Day Adventists	AHS
Canadian National Breast Screening Study	CNBSS
Cancer Prevention Study II	CPS II
Cancer Prevention Study II -Nutrition Cohort	CPS II - Nutrition Cohort
Chiba Cancer Cohort, Japan	CCC
Chicago Heart Association	CHA
Cohort of Swedish Men	COSM
Swedish Mammography Cohort	SMC
College Alumni Health Study	College Alumni Study
Combined Norwegian Cohorts	CNC
European Prospective Investigation into Nutrition and Cancer	EPIC
Hawaii-Los Angeles Multiethnic Cohort (MEC) Study	MEC
Health Food Shoppers Cohort study	
Health Professionals Follow-up Study	HPFS
Hokkaido Cohort, Japan	Hokkaido Cohort
Hospital-based Epidemiologic Research Program at Aichi Cancer Center	HERPACC
Iowa Women's Health Study	IWHS
Japan Collaborative Cohort Study for Evaluation of Cancer risk	JACC
Japan Public Health Center-based Prospective Study	JPHC
Japan - Hawaii Centre	
Korean Cancer Prevention Study	KCPS
Members of the Kaiser Permanent Medical Care Program including Oakland/Multiphase Check-up Study	KPMC
Leisure World cohort study	Leisure World
Lutheran Brotherhood Cohort study	LBS
Malmo Preventive Project Cohort Study	Malmo Cohort
Miyagi Prefecture Cohort, Japan	Miyagi Prefecture Cohort
NIH-AARP Diet and Health Study (NIH-AARP)	NIH-AARP
National Health and Nutrition Examination Survey	NHANES I
Nord-Trondelag Health Study (The HUNT Study)	HUNT
Norwegian Breast Screening Cohort	NBSC
Norwegian Cardiovascular Screening Cohort	NCSC
Norwegian screening programme for tuberculosis	
Physicians' Health Study	PHS
Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial	PLCO

Reykjavik Study/Icelandic Cancer Registry	Reykjavik Study
San Francisco Longshoremen	
Singapore Chinese Health Study	SHS
Swedish Mammography Cohort	SMC
Swedish Twin cohort	Swedish Twin cohort
Takayama City Cohort, Japan	Takayama City Cohort
The Hiroshima/ Nagasaki Life Span Study	LSS
The Million Women Study	MWS
The Netherlands Cohort Study (NLCS)	NLCS
The Northern Sweden Health and Disease Cohort	NSHDC
The Nurses' Health Study Cohort	NHS
The Swedish Construction Worker's Study	SCWC
The Women's Health Study	WHS
UK Study	
Vasterbotten - Northern Sweden, 1993	Vasterbotten study
The Vorarlberg Health Monitoring & Promotion Program Study Cohort	VHM&PP
Whitehall study, London	WS
Women's Health Initiative	WHI

Appendix 3 List of abbreviations

25(OH)D - 25 hydroxyvitamin D
BMI - body mass index
CI - confidence interval
CUP - Continuous Update Project
DIS - distal colon cancer
E – energy
F - female
HR - hazards ratio
HRT - hormone replacement therapy
I - incidence
IU - International unit
ICL - Imperial College London
Kcal - kilocalorie
Kg/m^2 - Kilogram/metre^2
L - liter
LCI - lower confidence interval
M – male
MET - metabolic equivalent of task or metabolic equivalent
M/F - male/female
Mg - milligram
Ng - nanogram
OR - odds ratio
PA - physical activity
PAN - pancreatic cancer
RCT - randomised controlled trial
RR - relative risk
SLR - systematic literature review
UCI - upper confidence interval
WC - waist circumference
WHR - waist-hip-ratio