WCRF/AICR Systematic Literature Review
Continuous Update Project

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

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List of Abbreviations used in the CUP SLR

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

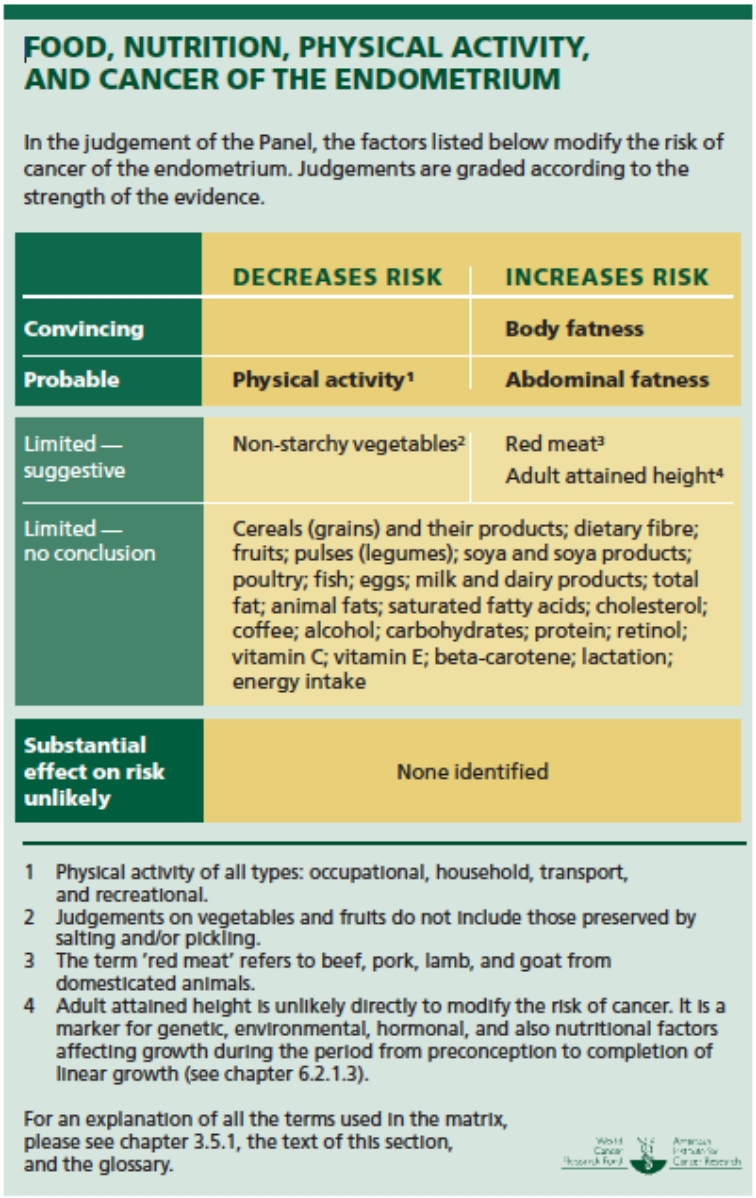
List of Abbreviations of cohort study names used in the CUP SLR

CTS	California Teachers Study
BSC	Breast Screening Cohort
BCDDP	Breast Cancer Detection Demonstration Project
CNBSS	Canada National Breast Screening Study
Sweden	Census and Cancer Environment Register
CPS II	Cancer Prevention Study II
EPIC	European Prospective Investigation into Cancer and Nutrition
EDGE	The Estrogen, Diet, Genetics, and Endometrial Study
IWHS (or IOWA)	Iowa Women's Health Study Cohort
HHC	Hawaii Historical Cohort
HUNT I & II	North-Trondelag Health Study
JCCS	Japan Collaborative Cohort study
JPHC	Japan Public Health Centre-based Prospective Study
KCPS	Korean Cancer Prevention Study
Lund Cohort	Lund University Cohort
MCS	Miyagi Cohort Study
MWS	Million Women's Study
MEC	Multiethnic Cohort Study
NSPT&NHS	Norwegian Health Surveys
NHS	Nurses' Health Study
NIH-AARP	NIH-AARP Diet and Health Study
NLCS (or NCS)	The Netherlands Cohort Study
NNHSS (or NHSS)	Cohort from Norwegian National Health Screening
NYUWHS	New York University Women's Health Study
OVS	Oxford Vegetarian Study
SFCTS	Sweden, Finland Co-twin study
SFB	San Francisco Bay Study
SMC	Swedish Mammography Cohort Study
STC (or STR)	Swedish Twin Cohort
SSC	Swedish Screening Cohort
VIP	Västerbotten Intervention Project
VHM &PP	The Vorarlberg Health Monitoring and Promotion Program
WHI	Women's Health Initiative
WHS	Women Health Study
WLHS	Women's Lifestyle and Health Study

Background

Matrices presented in the WCRF/AICR 2007 Expert Report

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



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

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

	DECREASES RISK	INCREASES RISK
Convincing		**Body fatness**
Probable	**Physical activity[1]**	**Abdominal fatness**
Limited — suggestive	Non-starchy vegetables[2]	Red meat[3] Adult attained height[4]
Limited — no conclusion	Cereals (grains) and their products; dietary fibre; fruits; pulses (legumes); soya and soya products; poultry; fish; eggs; milk and dairy products; total fat; animal fats; saturated fatty acids; cholesterol; coffee; alcohol; carbohydrates; protein; retinol; vitamin C; vitamin E; beta-carotene; lactation; energy intake	
Substantial effect on risk unlikely	None identified	

1 Physical activity of all types: occupational, household, transport, and recreational.
2 Judgements on vegetables and fruits do not include those preserved by salting and/or pickling.
3 The term 'red meat' refers to beef, pork, lamb, and goat from domesticated animals.
4 Adult attained height is unlikely directly to modify the risk of cancer. It is a marker for genetic, environmental, hormonal, and also nutritional factors affecting growth during the period from preconception to completion of linear growth (see chapter 6.2.1.3).

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

Modifications to the existing protocol

1. The search team composition was modified. Deborah Navarro, Leila Abar and Snieguole Vingeliene worked in the search, article selection, data extraction and data analysis. Dagfinn Aune worked in data analysis.

2. In the original protocol, meta-analysis for a particular exposure would be conducted when 3 or more trials or cohort studies had been published after 2006, and if the total number of studies in the database totalised to more than 3 trials or 5 cohort studies. This was modified and the CUP team conducted meta-analysis for an exposure when the total number of cohort studies with enough data was two. This is because for many exposures no meta-analysis was conducted during the SLR 2005 for the Second Expert Report.

3. Meta-analyses for highest versus lowest categories have been conducted for physical activity. This is because no dose-response analyses were possible due to differences in assessing physical activity across studies.

4. Case-control studies were used in the meta-analysis of isoflavones by special request of one of the panel leaders (E Bandera).

5. Restricted cubic splines were used to model the nonlinear association of alcohol and endometrial cancer (Figure 48) because fractional polynomial models were not robust.

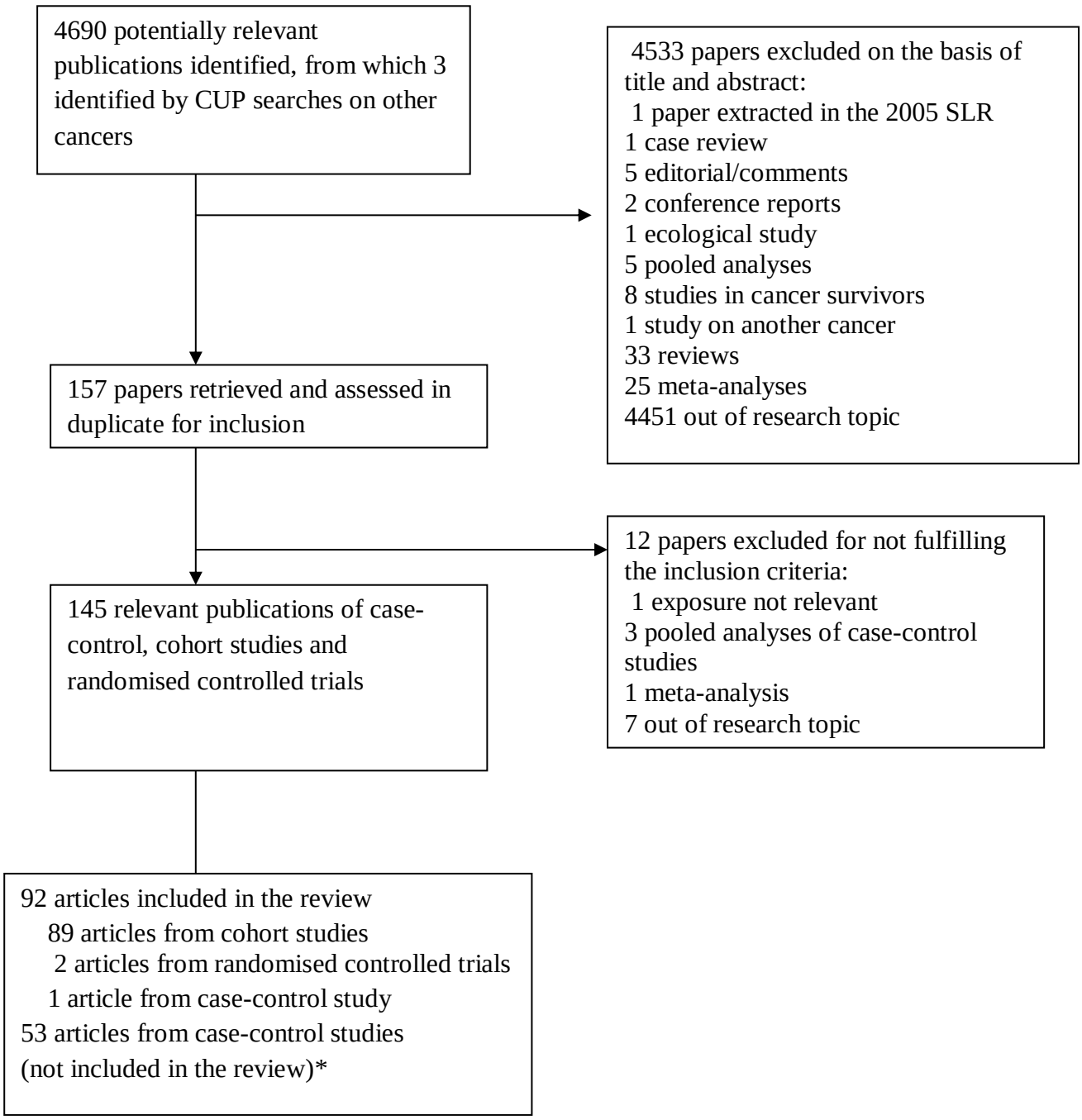
Notes on the figures and statistics used:

- Heterogeneity tests were conducted for dose-response meta-analysis but the interpretation should be cautious when the number of studies is often very low because these tests have low power. Inspection of the forest plots and funnel plots is recommended.
- I^2 statistic was calculated to give an indication of the extent of heterogeneity in dose-response analysis. Low heterogeneity might account for less than 30 per cent of the variability in point estimates, and high heterogeneity for more than 50 per cent. These values are tentative, because the practical impact of heterogeneity in a meta-analysis also depends on the size and direction of effects.
- Heterogeneity test and I2 statistics are shown for "Highest vs Lowest" meta-analysis when this is the only type of meta-analyses conducted for an exposure.
- Only random effect models are shown in Tables and Figures.
- The dose-response forests plots show the relative risk estimate in each study, expressed per unit of increase. The relative risk is denoted by boxes (larger boxes indicate that the study has higher precision, and greater weight). Horizontal lines denote 95% Confidence intervals (CIs). Arrowheads indicate truncations. The diamond at the bottom shows combined-study summary relative risk estimates and corresponding 95% CIs. The units of increase are indicated in each figure. Only summary estimates using random effect models are shown.
- In Highest vs Lowest forest plots, the box represents the relative risk estimate for the highest vs the lowest category of exposure reported in the paper. An overall summary estimate is not shown. The summary estimates for the highest vs the lowest category of exposure using random effect models is shown in tables.
- The dose-response plot shows the relative risk estimates for each exposure category as published by each study. The relative risks estimates are plotted in the mid-point of each category level (x-axis) and are connected through lines.

Continuous Update Project: Results of the search

The search period is from the 1st of January 2006 until the 31st of December 2012. The number of studies showing separate results for pre- and post-menopausal women was low and analyses stratified by menopausal status could not be conducted.

Flow chart of the search for endometrial cancer – Continuous update project
Search period January 1st 2006-December 31st 2012¶



¶ *125 articles from case-control studies, 65 from cohort studies and 3 from randomised controlled trials were identified in the 2005 SLR*

**Data from case-control studies on endometrial cancer identified during the CUP are not extracted to the CUP database and not included in this SLR, with the exception of one case-control study on isoflavones (by request of the Panel)*

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

Two publications of The Women's Health Initiative (WHI) (Prentice et al, 2007; Brunner et al, 2011) were identified.

The Women's Health Initiative was initiated in 1992 as a major disease-prevention research program assessing the risks and benefits of hormone therapy and dietary modification among postmenopausal women. The average age of the participants was 62.3 years, about three-quarters were overweight or obese (BMI ≥ 25 kg/m2), and more than 40% reported a history of hypertension.

One year later, participants in the hormone therapy and dietary modification trials were invited to enrol in the randomized trial of calcium plus vitamin D (CaD) compared to placebo. The majority of study women (91%) joined the CaD trial during their first annual clinic visit with 9% the following year. Fifty-four per cent of CaD trial participants had been enrolled in one of the trials assessing hormone therapy, 69% had been enrolled in the trial assessing dietary modification, and 14% were in both trials.

1.5 Low fat diet

One publication of the dietary modification trial and endometrial cancer was identified (Prentice et al, 2007). No significant effect on endometrial cancer survival was observed.

The goals of the dietary modification intervention were reduced fat intake (20% or less of energy from fat), and increased intake of vegetables and fruit (5 or more servings/day) and grains (6 or more servings/day).

The primary cancer outcomes were colorectal and breast cancer. Endometrial cancer was listed as cancer site that would potentially benefit from the dietary modification intervention.

At 6 years, the intervention group had 8.1% lower percentage of energy from fat, consumed 1.1 servings more of vegetables and fruit and 0.4 servings more of grain than the comparison group.

The overall incidence of cancer of the endometrium did not differ between the intervention and the control groups (HR = 1.11, 95% CI = 0.88 to 1.40; *P* = .18), based on 27629 women (n = 11092 intervention, n = 16537 comparison) with a uterus at baseline. No indication of an intervention effect later in the intervention period was observed.

5.6.3 Calcium and vitamin D

One publication of the calcium plus vitamin D trial and endometrial cancer was identified (Brunner et al, 2011). No effect on endometrial cancer was observed.

The primary outcome was hip fracture. Endometrial cancer was a secondary outcome.

Postmenopausal women (N = 36,282) were randomized to daily use of 1,000 mg of calcium carbonate combined with 400 IU of vitamin D3 or placebo. Self-reported baseline total calcium and vitamin D intakes from diet were similar in the randomization groups and remained similar during the trial.

After a mean follow-up of seven years, the relative risk of endometrial cancer of cases compared to controls was 0.95 (95% CI: 0.71-1.28) (Brunner et al, 2011).Calcium and vitamin D supplementation in the dosage provided in this trial did not reduce the incidence of invasive cancers or cancer mortality in postmenopausal women. However, women who received calcium and vitamin D and were in the active arm of the dietary modification trial had a significantly lower risk of developing cancer. About one quarter of the participants stopped taking pills by the end of the study and serum 25(OH)D values were not measured.

2 Cohort studies. Results by exposure.

Table 1 Number of relevant articles identified during the Second Expert Report and the CUP and total number of cohorts by exposure.
The exposure code is the exposure identification in the database. Only exposures identified during the CUP are shown.
**The total number does not correspond to the sum of the number of articles because some cohort studies have published more than one article on the same exposure*

Exposure code	Exposure name	Number of articles		Total number of cohort studies
		Second Report	CUP	
1.4	Individual level dietary patterns	2	2	4
1.6.1	Breastfeeding- Child		2	2
2.1.1	Corn		1	1
2.1.1	Rye		1	1
2.1.1	Oatmeal		1	1
2.1.1.3	Rye bread		1	1
2.1.1.3	Wholegrain bread		1	1
2.1.1.0.3	Crispbread		1	1
2.1.2.1	Sweet Potatoes		1	1
2.1.2.4	Wholegrain foods		1	1
2.1.3	Wheat		1	1
2.2.1	Non-starchy vegetables		1	1
2.2.1.1	Carrots and Celery (umbelliferea)		1	1
2.2.1.4.2	Spinach		1	1
2.2.1.4.3	Lettuce		1	1
2.2.1.5	Solanaceae		1	1
2.2.2	Fruits		2	2
2.2.2.1	Citrus fruits		1	1
2.2.2.1	Rutaceae		1	1
2.2.2.2	Rosaceae		1	1
2.2.2.2.1	Bananas		1	1
2.2.2.2.11	Grape		1	1
2.2.2.2.4	Watermelon		1	1
2.3	Legumes		1	1
2.3	Leguminosae		1	1
2.3.1	Soya foods		1	1
2.3.2.2	Tofu		1	1
2.5.1	Meat	1	1	2
2.5.1.5	Liver		1	1
2.5.1.2	Processed meat	1	3	4
2.5.2.2.9	Sausages		1	1
2.5.1.3	Red meat	1	4	5
2.5.1.4	Poultry	1	1	2
2.6.4	Fructose		1	1

Number of relevant articles (cont.)

Exposure code	Exposure name	Number of articles		Total number of cohort studies
		Second Report	CUP	
2.6.4	Sugars (as foods)		1	1
2.7	Dairy foods		1	1
2.7.1.1	Whole milk		1	1
2.7.1.2	Low-fat milk		1	1
2.7.2	Hard cheese		1	1
2.7.3	Yoghurt		1	1
2.9	Jam & Jellies		1	1
2.9.1	Sweet foods		1	1
2.9.18	Cookies		1	1
3.4	Soft drinks		1	1
3.6.1	Coffee	2	6	8
3.6.1	Decaffeinated coffee		3	3
3.6.2	Tea	1	2	3
3.6.2.2	Green tea		1	1
3.7.1	Alcoholic drinks		2	2
3.7.1.1	Beers		1	1
4.4.2	Acrylamide		3	3
5.1	Carbohydrate	3	3	5*
5.1.2	Fibre		3	3
5.1.2.1	Cereal fibre		2	2
5.1.2.2	Vegetable fibre		1	1
5.1.2.3	Fruit fibre		1	1
5.1.3	Starch		1	1
5.1.4	Sugars (as nutrients)	1	1	2
5.1.4	Mono/disaccharides		1	1
5.1.4	Sucrose		2	2
5.1.5	Glycaemic index	2	3	5
5.1.5	Glycaemic load	2	4	6
5.2	Total fats	2	1	3
5.2	Animal fats		1	1
5.2	Vegetable fats		1	1
5.2.2	Saturated fatty acids		1	1
5.2.3	Monounsaturated fatty acids	1	1	2
5.2.4	Polyunsaturated fatty acids		1	1
5.2.4.1	n-3 fatty acids		1	1
5.2.5	Trans fatty acids		1	1
5.3.1	Methionine		1	1
5.4	Alcohol (as ethanol)	5	7	9*
5.4	Ethanol from beer		4	4
5.4	Ethanol from spirit (hard liquor)		4	4
5.4	Ethanol from wine		4	4

Number of relevant articles (cont.)

Exposure code	Exposure name	Number of articles		Total number of cohort studies
		Second Expert Report	CUP	
5.4.1	Alcohol from beer		1	1
5.4.2	Alcohol from wine		1	1
5.5.1	Vitamin A		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
5.5.10	Plasma vitamin D		1	1
5.5.10	Dietary vitamin D		1	1
5.5.11	Vitamin E		1	1
5.5.13	Antioxidant indices		1	1
5.5.13	Multivitamin supplement		3	3
5.5.2	Lutein and zeaxanthin		1	1
5.5.2	Lycopene		1	1
5.5.2	Total carotenoids		1	1
5.5.3	Dietary folate	1	2	2*
5.5.4	Riboflavin		1	1
5.5.5	Thiamin (vitamin B1)		1	1
5.5.6	Niacin		1	1
5.5.7	Pyridoxine (vitamin B6)		1	1
5.5.8	Cobalamin (vitamin B12)		1	1
5.5.9	Vitamin C		1	1
5.6.2	Dietary heme iron		1	1
5.6.2	Iron		2	2
5.6.2	Heme iron		1	1
5.6.6	Cadmium		2	2
5.7.5	Daidzein		1	1
5.7.5	Genistein		1	1
5.7.5	Glycitein		1	1
5.7.5	Enterolactone		1	1
5.7.5	Total isoflavones		1	1
5.8	Flavonoids		1	1
6.1	Total physical activity	1	1	2
6.1.1	Non-recreational activity		1	1
6.1.1.1	Occupational physical activity	3	2	5
6.1.1.2	Bicycling		1	1
6.1.1.2	Exercise/sport	1	3	4
6.1.1.2	Recreational activity	4	5	9
6.1.1.2	Stair climbing		1	1
6.1.1.2	Walking		1	1
6.1.1.3	Gardening		2	2

Number of relevant articles (cont.)

Exposure code	Exposure name	Number of articles		Total number of cohort studies
		Second Report	CUP	
6.1.1.3	Household activity	1	1	2
6.1.1.4	Transportation (walking/biking)	1	4	5
6.1.3	Vigorous activity	1	3	4
6.1.3.2	Walking pace		1	1
6.1.4	Duration of physical activity		1	1
6.1.4.1	Duration of occupation		1	1
6.1.4.2	Duration of recreational activity		1	1
6.1.4.2	Duration of walking		2	2
6.2	Sitting time		3	3
7.1	Energy Intake	1	4	5
8.1.1	BMI	17	22	35
8.1.1	BMI at age 18-25 years	3	4	7
8.1.2	Weight for height		1	1
8.1.3	Weight	3	2	4
8.1.6	BMI change		1	1
8.2.1	Waist circumference	2	3	5
8.2.2	Hips circumference		2	2
8.2.3	Waist to hip ratio	4	4	5*
8.3.1	Height	12	4	13*
8.4.1	Birthweight	1	3	4

1 Patterns of diet

1.3 -1.4 Individual level dietary pattern

Methods

Overall, four cohort studies have been identified, two studies during the CUP and two during the SLR 2005. Different definitions of dietary patterns were used and it was not possible to estimate a summary measure of association.

Main results

Risk of endometrial cancer did not differ in British vegetarians and fish eaters compared to meat eaters. The number of cases of endometrial cancer was low (Key, 2009).
In the Cancer Prevention Study II Nutrition Cohort, the risk of endometrial cancer was not related to the consumption of high-beta-carotene foods and high-lycopene foods. There was an increased risk associated with consumption of fruits and vegetables high in lutein and vitamin C (p-trend <= 0.04 and p-trend <= 0.03, respectively). The largest contributor to lutein-containing vegetables was salad (59 %), followed by broccoli (32 %) and spinach (6 %). Consuming salad three times per week as compared with less than once per week was associated with higher risk (RR = 1.46, 95 % CI: 1.12- 1.91; p-trend <0.05). For citrus fruits, the largest contributor was orange juice (49 %); orange juice was not significantly positively related to risk (McCullough et al, 2007).

Table 2 Studies on dietary patterns identified in the CUP

Author, year	Country	Study name	Cases	Years of follow-up	RR	LCI	UCI	Contrast
Key, 2009	UK	OVS, EPIC-Oxford	71 Meat eaters, 8 fish eaters, 22 vegetarians	12.2	0.61 0.75	0.29 0.45	1.30 1.28	Fish eater vs meat eater Vegetarian vs meat eater
McCullough, 2007	USA	Cancer Prevention Study II Nutrition Cohort	435	~9	0.98 1.39 p=0.04 0.87 1.31 P=0.03	0.72 1.02 0.65 0.97	1.33 1.91 1.16 1.77	High-b-carotene foods >= 2 vs <0.5 serv/wk High-lutein foods >= 5. vs <1.5 serv/wk High-lycopene foods >= 4.5 vs <0.8 serv/wk High-vitamin C foods >= 7.7 vs <1.7 serv/wk

Conclusion from the Second Expert Report

A Recommended Food Score (Mai et al 2005) was applied in the Breast Cancer Detection Demonstration Project. The score included various plant foods, chicken, turkey, fish and skimmed and semi-skimmed milk and milk beverages. No association with the index was observed (RR highest vs lowest quartile =0.87; 95% CI: 0.61-1.22).
An index of concordance with the Dietary Guidelines for Americans was applied in the Iowa's Women Cohort Study (Harnack et al, 2002). The RR for the highest vs the lowest index quintile was 0.71 (95% CI: 0.52-0.96). After exclusion of the components on BMI and physical activity, the RR was 1.28 (95% CI: 0.92-1.79).

1.6 Breastfeeding

Methods

Two studies were identified, one study during the SLR 2005 for the Second Expert Report on breastfeeding and one study during the CUP on being breast-fed.

Main results

Being breastfed was not related to the risk of endometrial cancer in the Nurses' Health Study ($HR_{\text{Been breastfed vs Not}}$=0.91; 95% CI: 0.77-1.07; 708 cases). Compared to not having been breast fed, the hazard ratios for ≤3, 4–8, and >=9 months duration of breastfed were 1.09 (0.78–1.52), 0.80 (0.59–1.09), 0.99 (0.77–1.29), respectively, of having been breastfed; *P* for trend = 0.88) (Xue et al, 2008).

Table 3 Studies on breastfeeding identified in the CUP

Author/year	Country	Study name	Cases	Years of follow-up	RR	LCI	UCI	Contrast
Xue, 2008	USA	Nurses' Health Study	708	28	0.91	0.77	1.07	Been breastfed Yes vs no
					0.99	0.77	1.29	>= 9 months vs no

Conclusion from the Second Expert Report

No studies were found on being breastfed and endometrial cancer risk.
Duration of breastfeeding was not significantly associated with the risk of endometrial cancer in women before and after adjusting by parity in a Norwegian follow up study. RR was 0.96 (95% CI: 0.90-1.02) per 2-month increment of average duration of lactation per pregnancy and 0.99 (95% CI: 0.92-1.07) per 6-month increment of total duration of breastfeeding (Kvale et al, 1987). The few case-control studies identified presented conflicting results.

2 Foods

2.2.1 Vegetables

Methods

Up to December 2012, two cohort studies were identified during the Continuous Update Project. No study was identified in the SLR 2005. The NIH-AARP Diet and Health Study (Kabat et al., 2010) reported vegetable intake in serving per 1000 kcal/ day which was converted to serving per day for comparability purposes. The, average energy intake (kcal/day) reported in a previous paper of the same study (George et al, 2009) was used in the conversion. The dose-response results are presented for an increment of 1 serving/day.

Main results

The summary RR for 1 serving per day was 1.05 (95% CI: 1.00 -1.10) for the two studies combined. The summary RR for 100 g/ day intake of vegetables was 1.04 (95% CI: 1.00 -1.08) for the two studies combined.

Only one study investigated the potential effect modification of hormone treatment. In the CPS II (McCullough et al, 2007) only among women who had never used hormone replacement therapy was the risk of endometrial cancer lower in the highest (vs. lowest) tertile of vegetable (RR = 0.80, 95% CI: 0.57- 1.13; p-interaction = 0.01, p trend =0.29) but the association was not statistically significant. Among hormone treatment users , the RR in the highest vs lowest tertile was 1.38 (0.96- 2.00) Ptrend=0.11 for vegetables.

Heterogeneity

There was no heterogeneity (I^2 = 0%, $P_{heterogeneity}$ = 0.93).

Conclusion from the Second Expert Report

No cohort study was identified during the SLR 2005. The summary estimate of 8 case-control studies per 100 g/day increase was 0.90 (95% CI: 0.86-0.95).

Published meta-analysis

A meta-analysis of 10 case-control studies conducted for the 2007 WCRF/AICR Second Expert Report found a RR of 0.71 (95% CI: 0.55-0.91) for the highest versus the lowest categories of total vegetables intake (Bandera et al, 2007). When vegetable intake was modelled as continuous variables, the summary OR was 0.90 (95% CI: 0.86-0.95) for an increment in intake of 100 g/d.

Table 4 Studies on vegetables identified in the CUP

Author, year	Country	Study name	Cases	Years of follow up	RR	LCI	UCI	Contrast
Kabat, 2010	USA	NIH-AARP Diet and Health study	1142	8	1.09	0.90	1.33	> 1.67 vs. < 0.74 servings/1000 kcal/day
					1.01	0.92	1.11	serving per 1000 kcal/day
McCullough 2007	USA	Cancer Prevention Study II Nutrition Cohort	435	9	1.21	0.89	1.65	> 2.6 vs. < 1.0 serving/day
					1.07	0.98	1.17	Per 1 serving/day
					1.18	0.88	1.58	> 1.9 vs. <0.8 serving/1000 kcal/day
					1.06	0.95	1.19	serving per 1000 kcal/day

Table 5 Overall evidence on vegetables and endometrial cancer

	Summary of evidence
SLR 2005	No cohort study was identified during the 2005 SLR
Continuous Update Project	Two cohort studies were identified during the CUP. The results from the two studies were included in the dose-response meta-analysis. None of the studies reported significant associations.

Table 6 Summary of results of the dose response meta-analysis of vegetables and endometrial cancer

Endometrial cancer incidence		
	SLR 2005*	Continuous Update Project
Studies (n)	-	2
Cases (n)	-	1577
Increment unit used	-	1 serving/day
Overall RR (95%CI)	-	1.05 (95% CI: 1.00-1.10)
Heterogeneity (I^2,p-value)	-	0%, p=0.93

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

Table 7 Inclusion/exclusion table for meta-analysis of vegetables and endometrial cancer

WCRF code	Author	Year	Study design	Study name	Cancer outcome	SLR 2005	CUP dose-response	CUP H vs. L forest plot	Estimated values	Exclusion reason
END00214	Kabat	2010	Prospective Cohort study	NIH- AARP Diet and Health Study	Incidence	No	Yes	Yes	Serving/1000Kcal/ day Rescaled to serving/day	-
END00229	McCullough	2007	Prospective Cohort study	Cancer Prevention Study ll Nutrition Cohort	Incidence	No	Yes	Yes	Serving per day	-

Figure 1 Highest versus lowest forest plot of vegetables and endometrial cancer

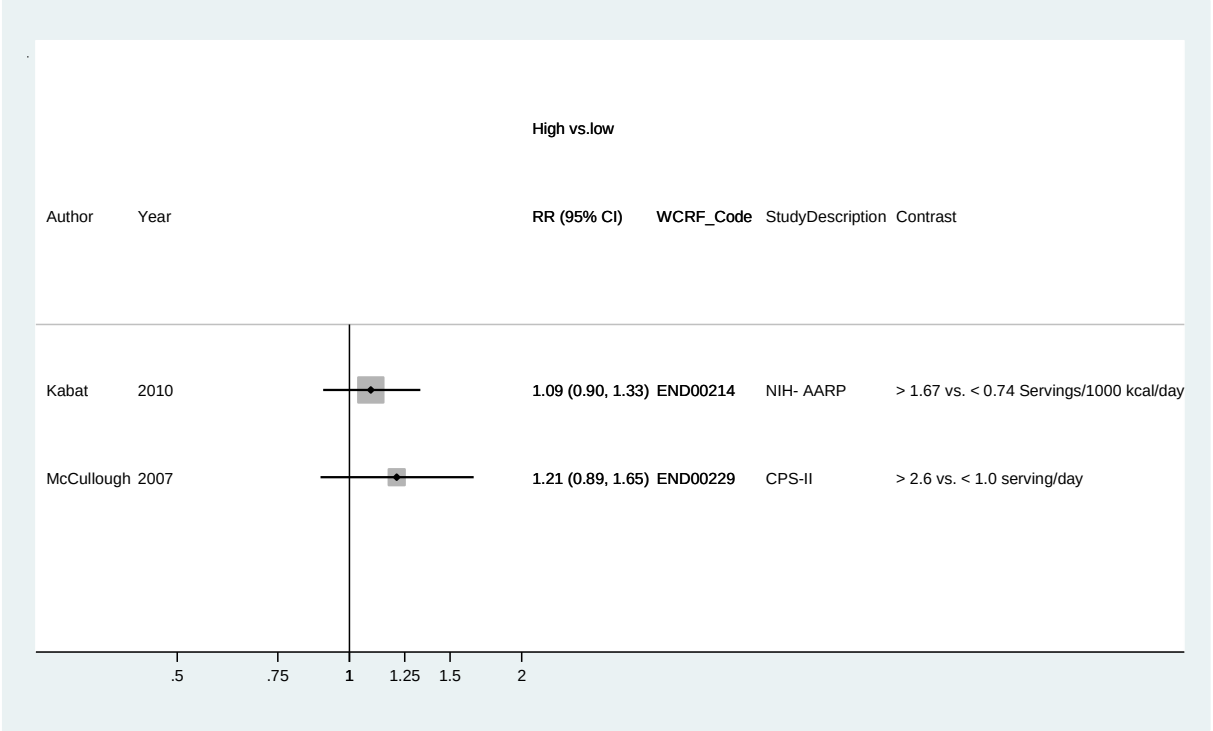


Figure 2 Dose-response meta-analysis of vegetables and endometrial cancer –per 1 serving/day

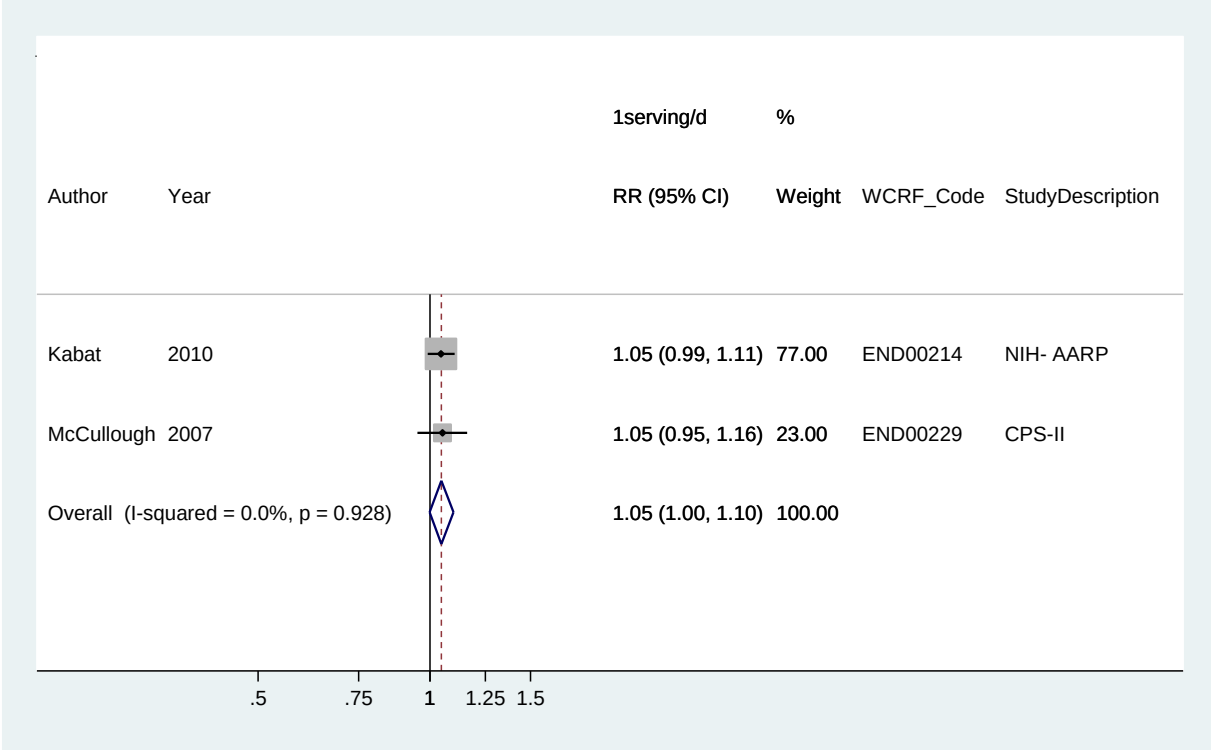
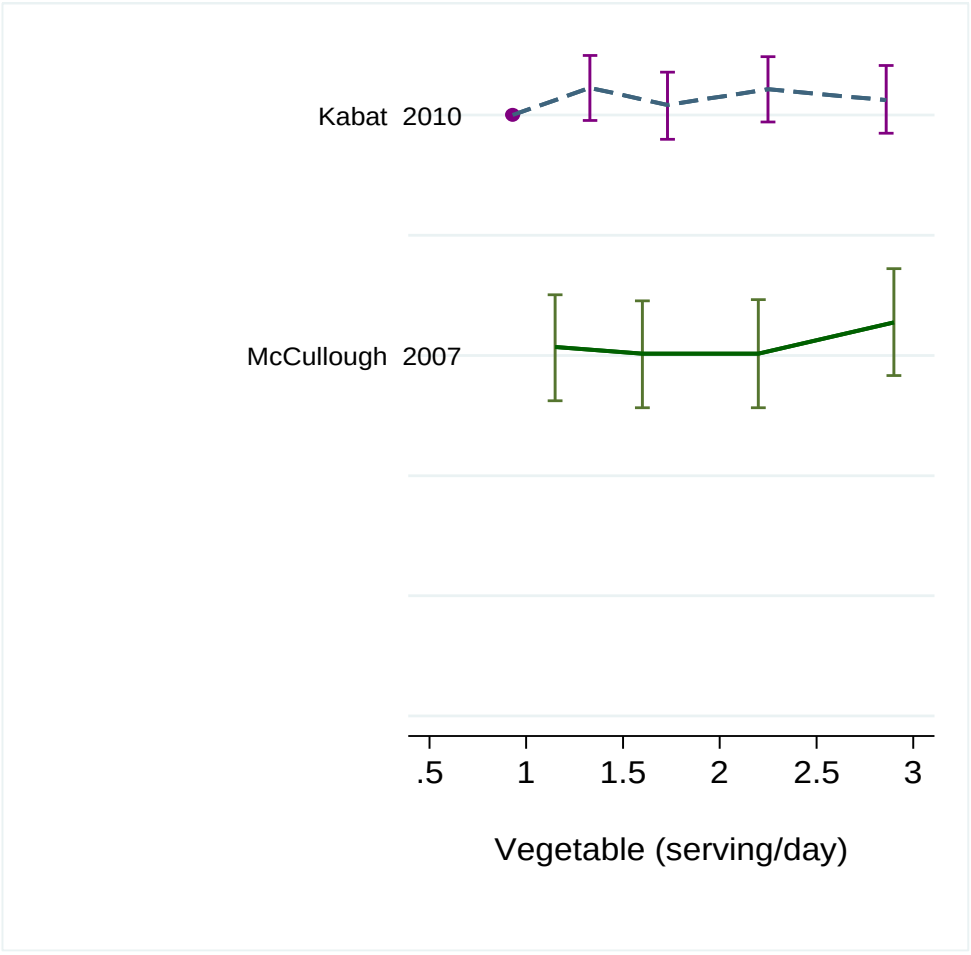


Figure 3 Dose-response graph of vegetables and endometrial cancer



2.2.2 Fruits

Methods

Up to December 2012, two cohort studies were identified during the Continuous Update Project. No study was identified during the SLR 2005. The NIH-AARP Diet and Health Study (Kabat et al., 2010) reported fruits intake in serving per 1000 kcal/ day, which was converted to serving per day for comparability purposes. The average energy intake (kcal/day) reported in a previous paper of the same study (George et al, 2009) was used in the conversion. The dose-response results are presented for an increment of 1 serving/day.

Main results

The summary RR for 1serving /day intake of total fruits was 1.07 (95% CI: 1.01-1.12) for all studies combined. The summary RR for 100g/day intake of total fruits was 1.05 (95% CI:1.01-1.10) for all studies combined.

Only one study investigated the potential effect modification of hormone treatment. In the CPS II (McCullough et al, 2007), only among women who had never used hormone replacement therapy was the risk of endometrial cancer lower in the highest (vs. lowest) tertile of fruit (RR = 0.75, 95% CI: 0.52- 1.07;p-interaction = 0.03, p trend = 0.11) but the association was not statistically significant. Among hormone treatment users , the RR in the highest vs lowest tertile of fruits was 1.41 (0.99- 2.02), Ptrend=0.08 for fruits.

Heterogeneity

There was no heterogeneity across the limited number of published studies (I^2 = 0%, $P_{heterogeneity}$ = 0.72.

Conclusion from the Second Expert Report

No cohort study was identified during the SLR 2005. The summary odds ratio of 14 case-control studies was 0.97 (95% CI 0.92-1.02) for an intake increment of 100 g/d.

Published meta-analysis

A meta-analysis of 14 case-control studies conducted for the Second Expert Report found a RR of 0.90 (95% CI 0.72-1.12) for the highest versus lowest categories of total fruits intake (Bandera et al., 2007). When fruit intake was modelled as continuous variables, the summary OR was 0.97 (95% CI 0.92-1.02) for an intake increment of 100 g/d.

Table 8 Studies on fruits identified in the CUP

Author, year	Country	Study name	Cases	Years of follow up	RR	LCI	UCI	Contrast
Kabat, 2010	USA	NIH- AARP Diet and Health Study	1142	8	1.30 1.07	1.04 0.99	1.61 1.15	> 1.91 vs. <0.61 serving/1000Kcal/day serving/1000Kcal/day
McCullough, 2007	USA	Cancer Prevention Study ll Nutrition Cohort	435	9	1.24 1.09	0.90 1.0	1.70 1.19	>2.7 vs. <0.9 serving/day Per 1 serving/day

Table 9 Overall evidence on fruits and endometrial cancer

	Summary of evidence
SLR 2005	No cohort study was identified during the 2005 SLR
Continuous Update Project	Two cohort studies were identified during the CUP and included in the dose-response meta-analysis. A weak protective association was observed in one of the studies

Table 10 Summary of results of the dose response meta-analysis of fruits and endometrial cancer

Endometrial cancer incidence		
	SLR 2005*	Continuous Update Project
Studies (n)	-	2
Cases (n)	-	1577
Increment unit used	-	1 serving/day
Overall RR (95%CI)	-	1.07 (95% CI: 1.01-1.12)
Heterogeneity (I^2,p-value)	-	0%, p=0.72

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

Table 11 Inclusion/exclusion table for meta-analysis of fruits and endometrial cancer

WCRF code	Author	Year	Study design	Study name	Cancer outcome	SLR 2005	CUP dose-response	CUP H vs. L forest plot	Estimated values	Exclusion reason
END00214	Kabat	2010	Prospective Cohort study	NIH- AARP Diet and Health Study	Incidence	No	Yes	Yes	Serving/1000/Kcal/day rescaled to serving per day	-
END00229	McCullough	2007	Prospective Cohort study	Cancer Prevention Study ll Nutrition Cohort	Incidence	No	Yes	Yes	Serving per day	-

Figure 4 Highest versus lowest forest plot of fruits and endometrial cancer

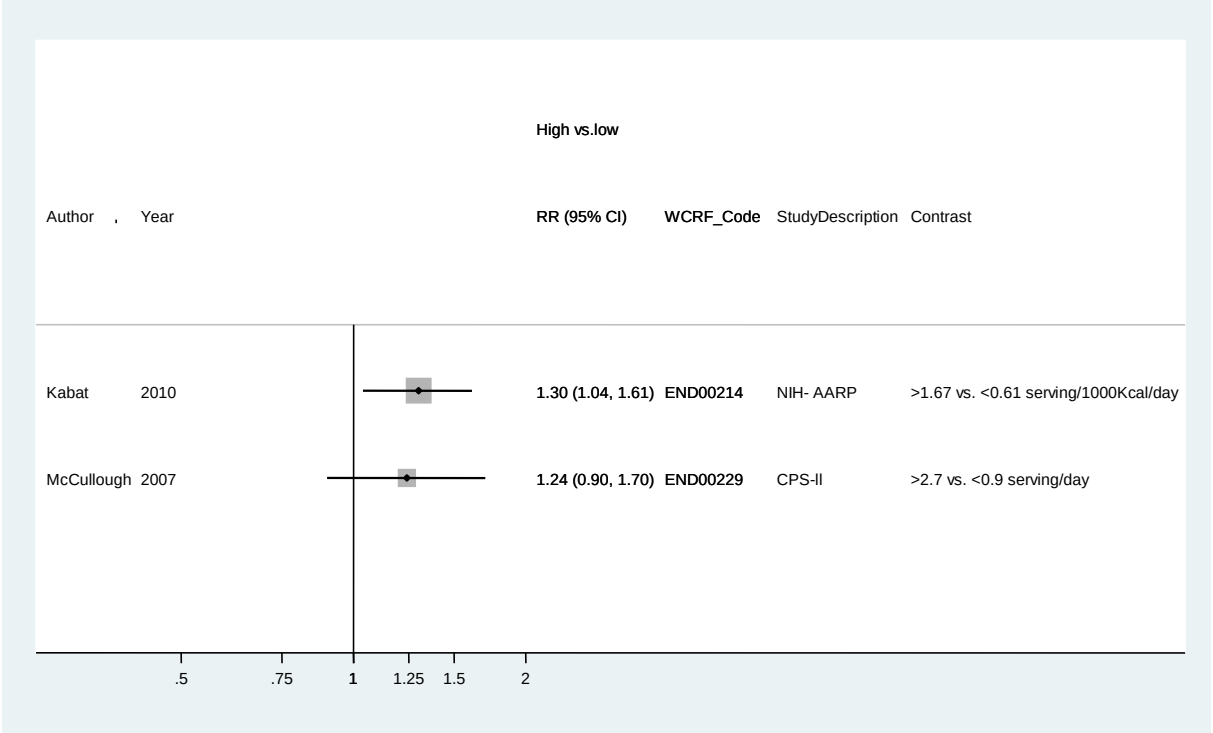


Figure 5 Dose-response meta-analysis of fruits and endometrial cancer –per 1 serving/day

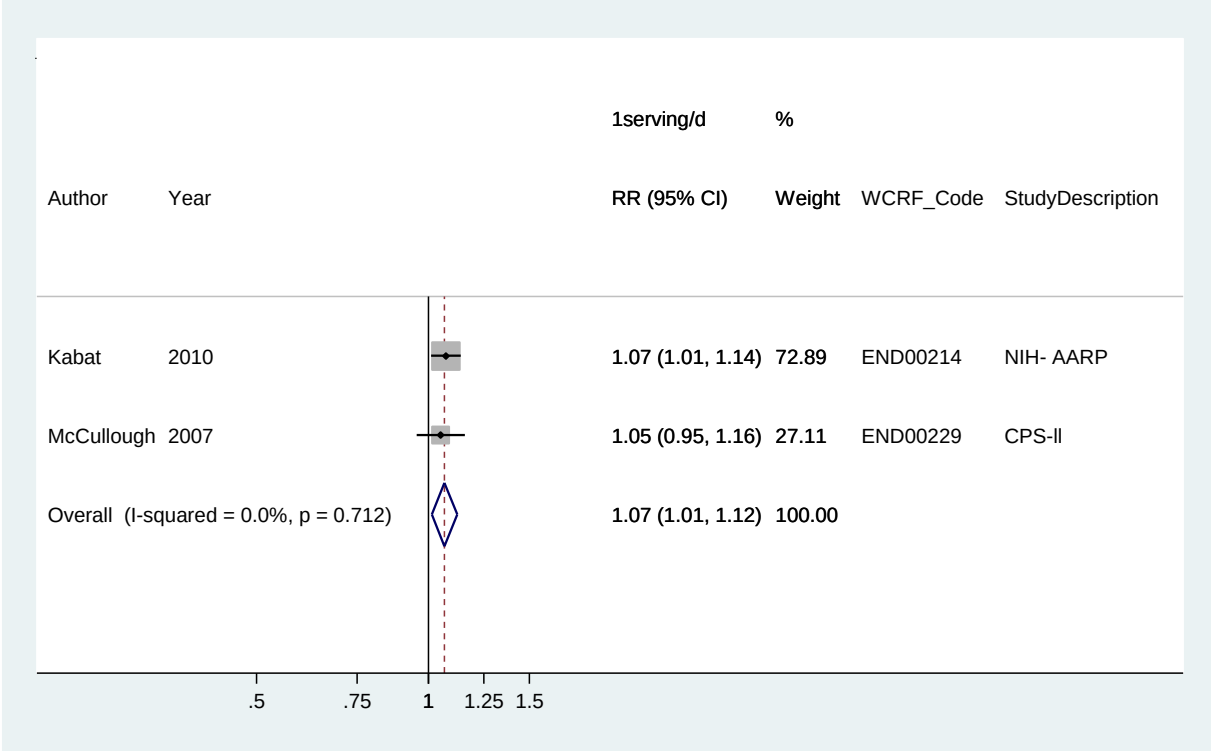
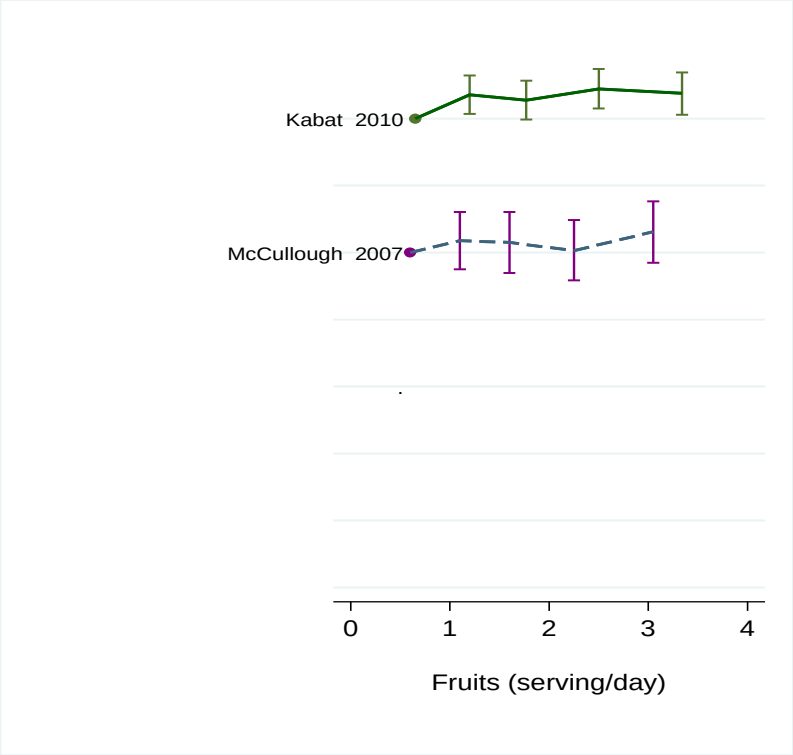


Figure 6 Dose-response graph of fruits and endometrial cancer



2.5.1.2 Processed meat

Methods

Up to December 2012, reports from four cohort studies were identified, three of which were identified during the CUP. The CUP meta-analysis included the three studies identified during the CUP.
The dose-response results are presented for an increment of 50 grams per day (the highest category of intake in one study was >23.53 g/day).

Main results

The summary RR per 50 grams per day was 1.24 (95% CI: 0.80-1.93; I^2= 16.0%, $P_{heterogeneity}$=0.30). The excluded study (Zheng et al, 1995) reported a RR estimate for the highest versus the lowest intake category of processed meat/fish of 1.5 ($p \leq 0.05$). None of the studies examined effect modification by hormone use or BMI.

Heterogeneity

There was evidence of low heterogeneity across the limited number of published studies (I^2=16%, p=0.30). There was no evidence of publication bias with Egger's test, p=0.94

Conclusion from the Second Expert Report

Only one study was identified during the SLR 2005 (Zheng et al, 1995), reporting a positive association between processed meat intake and endometrial cancer (RR=1.5, confidence intervals not available).

Table 12 Studies on processed meat consumption identified in the CUP

Author, year	Country	Study name	Cases	Years of follow up	RR	LCI	UCI	Contrast
Genkinger, 2012	Sweden	Swedish Mammography Cohort	720	21	1.12	0.84	1.49	367.40 g/week vs 53.80 g/week
van Lonkhuijzen, 2011	Canada	Canadian Study of Diet, Lifestyle, and Health Cohort	107	11	1.45	0.80	2.61	>=23.53 g/d vs <3.80 g/d
Cross, 2007	USA	The National Institutes of Health-American Association for Retired Persons	1185	8.2	1.02	0.84	1.23	22.6 g/1000 kcal/d vs 1.6 g/1000 kcal/d

Table 13 Overall evidence on processed meat consumption and endometrial cancer

	Summary of evidence
SLR 2005	One cohort study, the Iowa Women's Health Study reported a positive association between processed meat intake and endometrial cancer.
Continuous Update Project	Three additional cohort studies were identified and included in the dose-response meta-analysis. None of them reported significant results.

Table 14 Summary of results of the dose response meta-analysis of processed meat consumption and endometrial cancer

Endometrial cancer		
	SLR 2005*	Continuous Update Project
Studies (n)	-	3
Cases (n)	-	2012
Increment unit used	-	Per 50 g/day
Overall RR (95%CI)	-	1.24 (0.80-1.93)
Heterogeneity (I^2,p-value)	-	16.0%, p=0.30

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

Table 15 Inclusion/exclusion table for meta-analysis of processed meat consumption and endometrial cancer

WCRF_ Code	Author	Year	Study Design	Study Name	Cancer Outcome	SLR 2005	CUP dose-response meta-analysis	CUP HvL forest plot	Estimated values	Exclusion reasons
END00278	Genkinger	2012	Prospective Cohort study	Swedish Mammography Cohort	Incidence	No	Yes	Yes	Recalculate continuous values	---
END00273	van Lonkhuijzen	2011	Case-cohort study	Canadian Study of Diet, Lifestyle, and Health Cohort	Incidence	No	Yes	Yes	Mid-exposure values	----
END00277	Cross	2007	Prospective Cohort study	The National Institutes of Health- American Association for Retired Persons	Incidence	No	Yes	Yes	Person years	----
END00015	Zheng	1995	Prospective Cohort study	Iowa Women's Health Study	Incidence	Yes	No	No	-	No exposure quantities and confidence limits

Figure 7 Highest versus lowest forest plot of processed meat consumption and endometrial cancer

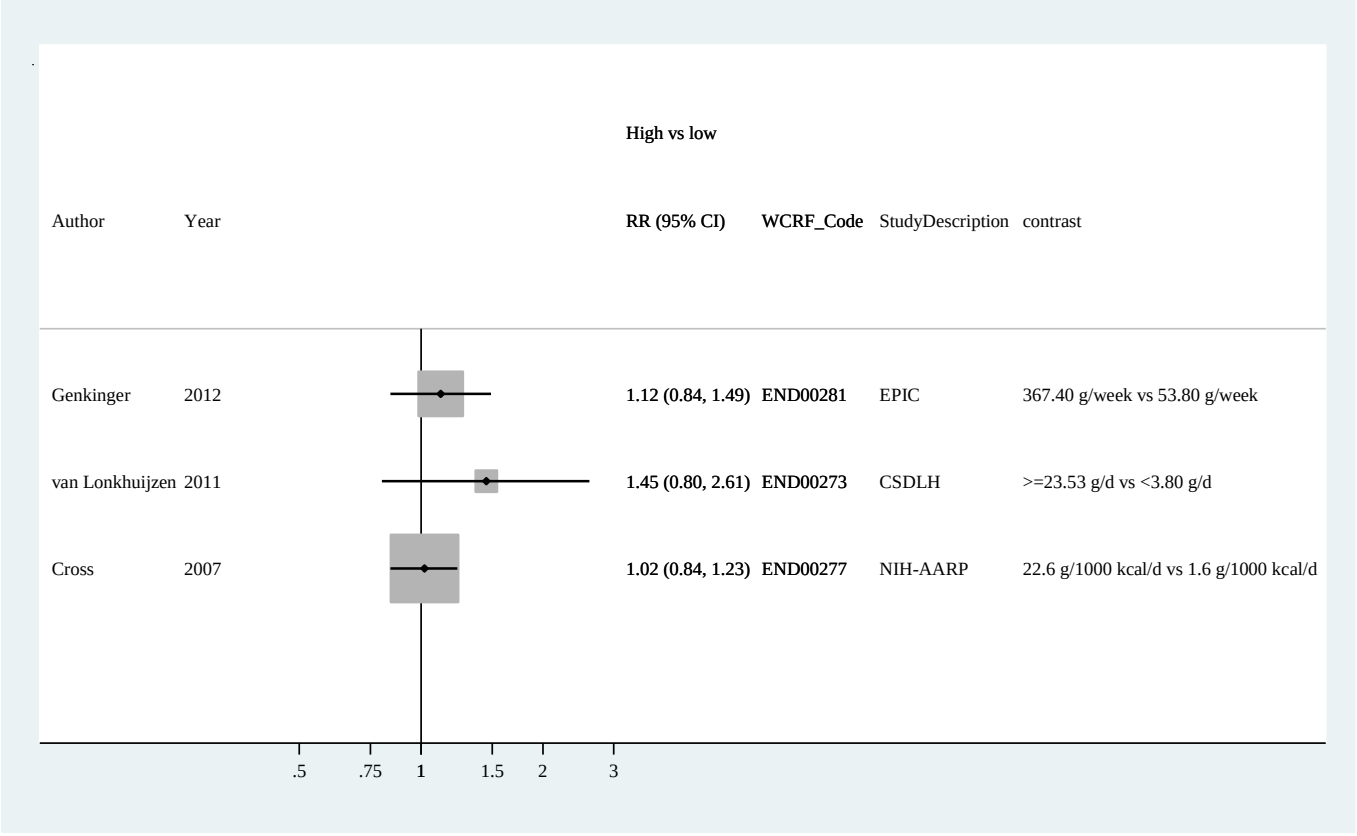


Figure 8 Dose-response meta-analysis of processed meat and endometrial cancer - per 50 g/day

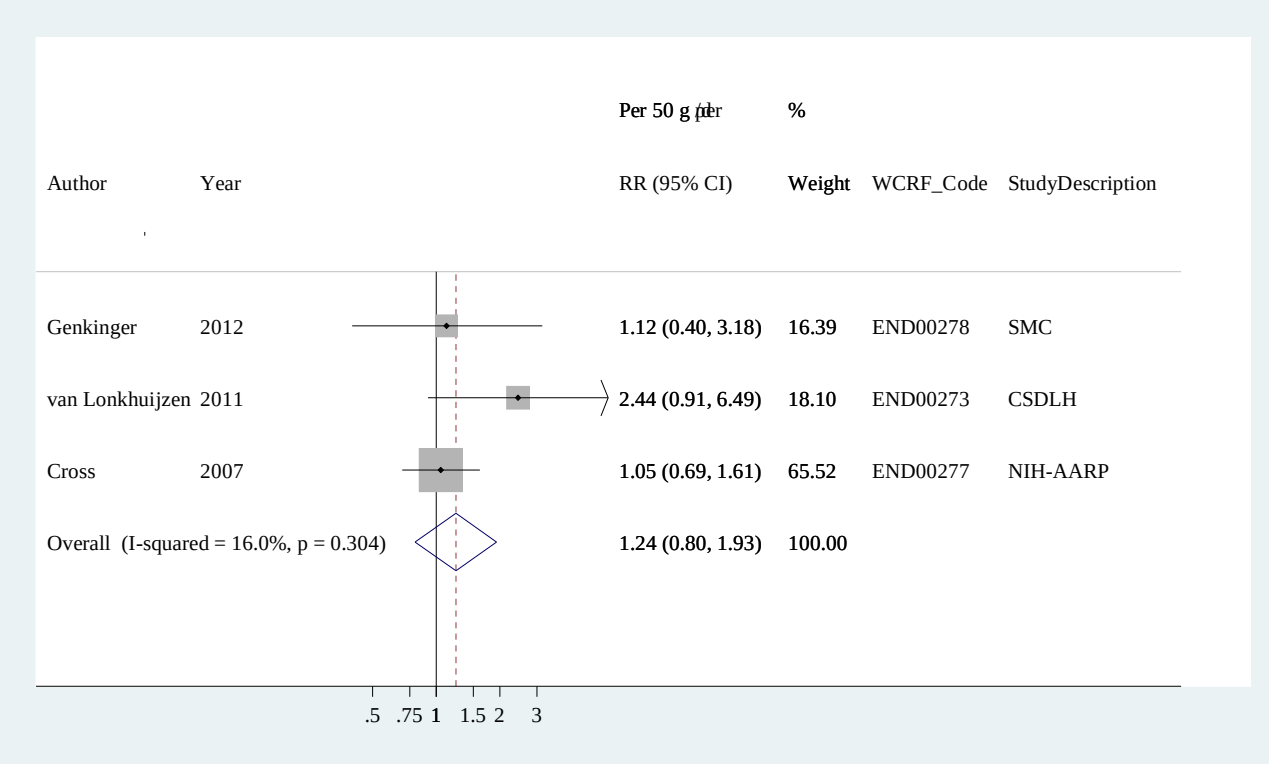
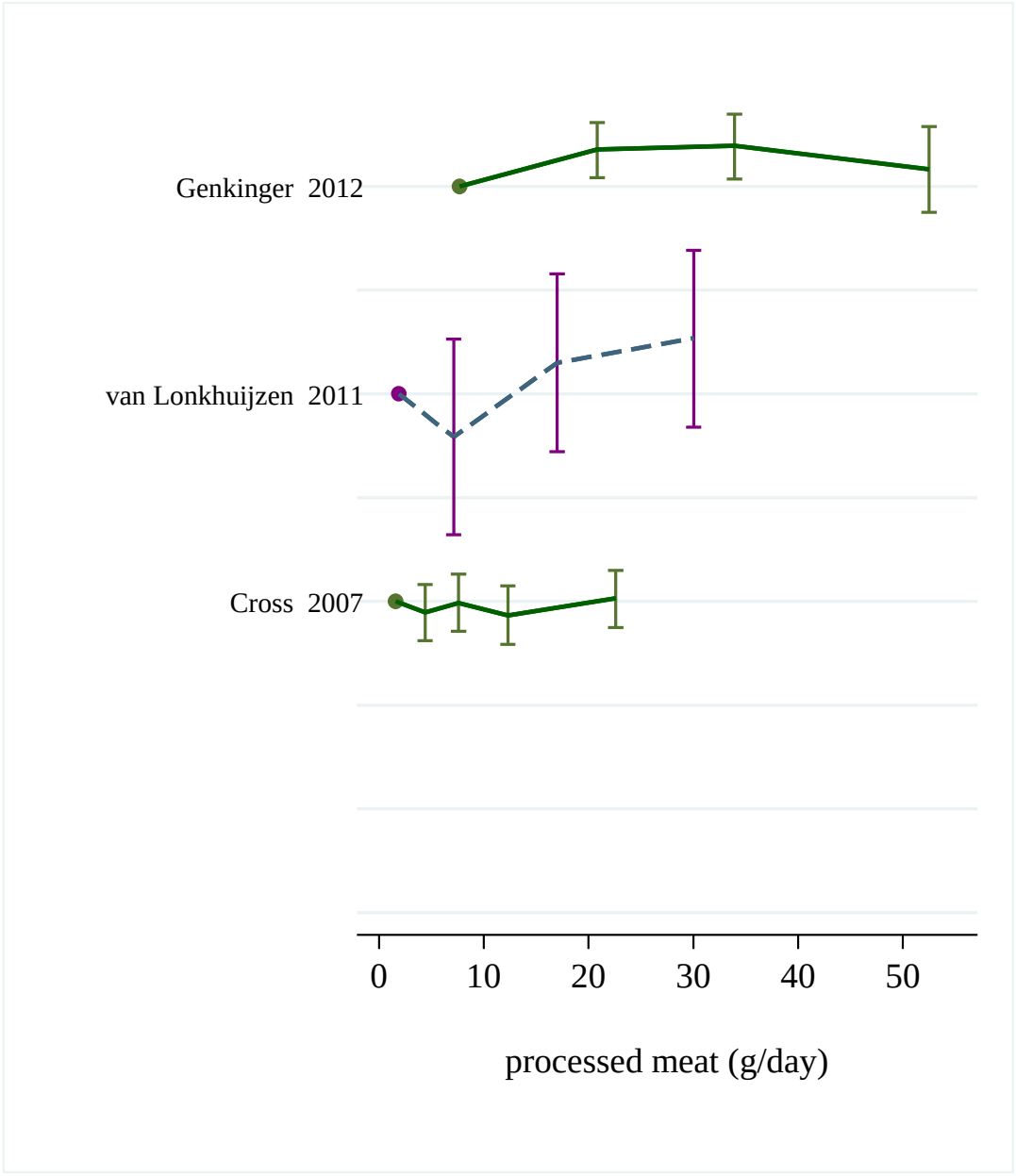


Figure 9 Dose-response graph of processed meat and endometrial cancer



2.5.1.3 Red meat

Methods

Up to December 2012, reports from five cohort studies were identified, four of which were identified during the CUP. The CUP meta-analysis included the four studies identified during the CUP. The dose-response results are presented for an increment of 50 grams per day (the highest category of intake in one study was >52.15 g/day).

Main results

The summary RR per 50 grams per day was 0.99 (95% CI: 0.83-1.17; I^2= 61.8%, $P_{heterogeneity}$=0.049). The excluded study (Zheng et al, 1995) reported no association between red meat intake and endometrial cancer risk.

Heterogeneity

There was evidence of high heterogeneity across the limited number of published studies (I^2=61.8%, p=0.049). There was borderline evidence of publication bias with Egger's test, p=0.054

Conclusion from the Second Expert Report

One cohort study was identified during the SLR 2005, with no association between red meat consumption and endometrial cancer. The summary odds ratio per 50 g/day of red meat consumption of six case-control studies was 1.21 (95% CI: 1.04-1.41; p value: 0.06).

Published meta-analysis

A meta-analysis of seven case-control studies showed a RR of 1.51 (95% CI: 1.19-1.93; I^2=44%, p=0.097) per 100 g/day of red meat consumption (Bandera et al., 2007).

Table 16 Studies on red meat consumption identified in the CUP

Author, year	Country	Study name	Cases	Years of follow up	RR	LCI	UCI	Contrast
Genkinger, 2012	Sweden	Swedish Mammography Cohort	720	21	1.06	0.68	1.66	714.07 g/week vs 40.60 g/week
van Lonkhuijze, 2011	Canada	Canadian Study of Diet, Lifestyle, and Health Cohort	107	11	1.62	0.86	3.08	>=52.15 g/d vs <22.09 g/d
Kabat, 2008	Canada	Canadian National Breast Cancer Screening Study	426	16.4	0.86	0.61	1.22	>108.99 g/d vs <48.49 g/d
Cross, 2007	USA	The National Institutes of Health-American Association for Retired Persons	1185	8.2	0.75	0.62	0.91	62.7 g/1000 kcal/d vs 9.8 g/1000 kcal/d

Table 17 Overall evidence on red meat consumption and endometrial cancer

	Summary of evidence
SLR 2005	One cohort study was identified during the SLR 2005, the Iowa Women's Health Study. This study reported no association with red meat intake and endometrial cancer.
Continuous Update Project	Four additional cohort studies were identified and included in the dose-response meta-analysis. Only one of them reported significant protective results

Table 18 Summary of results of the dose response meta-analysis of red meat consumption and endometrial cancer

Endometrial cancer		
	SLR 2005*	Continuous Update Project
Studies (n)	-	4
Cases (n)	-	2438
Increment unit used	-	Per 50 g/day
Overall RR (95%CI)	-	0.99 (0.83-1.17)
Heterogeneity (I^2,p-value)	-	61.8%, p=0.049

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

Table 19 Inclusion/exclusion table for meta-analysis of red meat consumption and endometrial cancer

WCRF_ Code	Author	Year	Study Design	Study Name	Cancer Outcome	SLR 2005	CUP dose-response meta-analysis	CUP HvL forest plot	Estimated values	Exclusion reasons
END00278	Genkinger	2012	Prospective Cohort study	Swedish Mammography Cohort	Incidence	No	Yes	Yes	Recalculate continuous values	---
END00273	van Lonkhuijzen	2011	Case-cohort study	Canadian Study of Diet, Lifestyle, and Health Cohort	Incidence	No	Yes	Yes	Mid-exposure values	----
END00223	Kabat	2008	Prospective Cohort study	Canadian National Breast Cancer Screening Study	Incidence	No	Yes	Yes	Person years and mid-exposure values	----
END00277	Cross	2007	Prospective Cohort study	The National Institutes of Health-American Association for Retired Persons	Incidence	No	Yes	Yes	Person years	----
END00015	Zheng	1995	Prospective Cohort study	Iowa Women's Health Study	Incidence	Yes	No	No	-	No exposure quantities and confidence limits

Figure 10 Highest versus lowest forest plot of red meat consumption and endometrial cancer

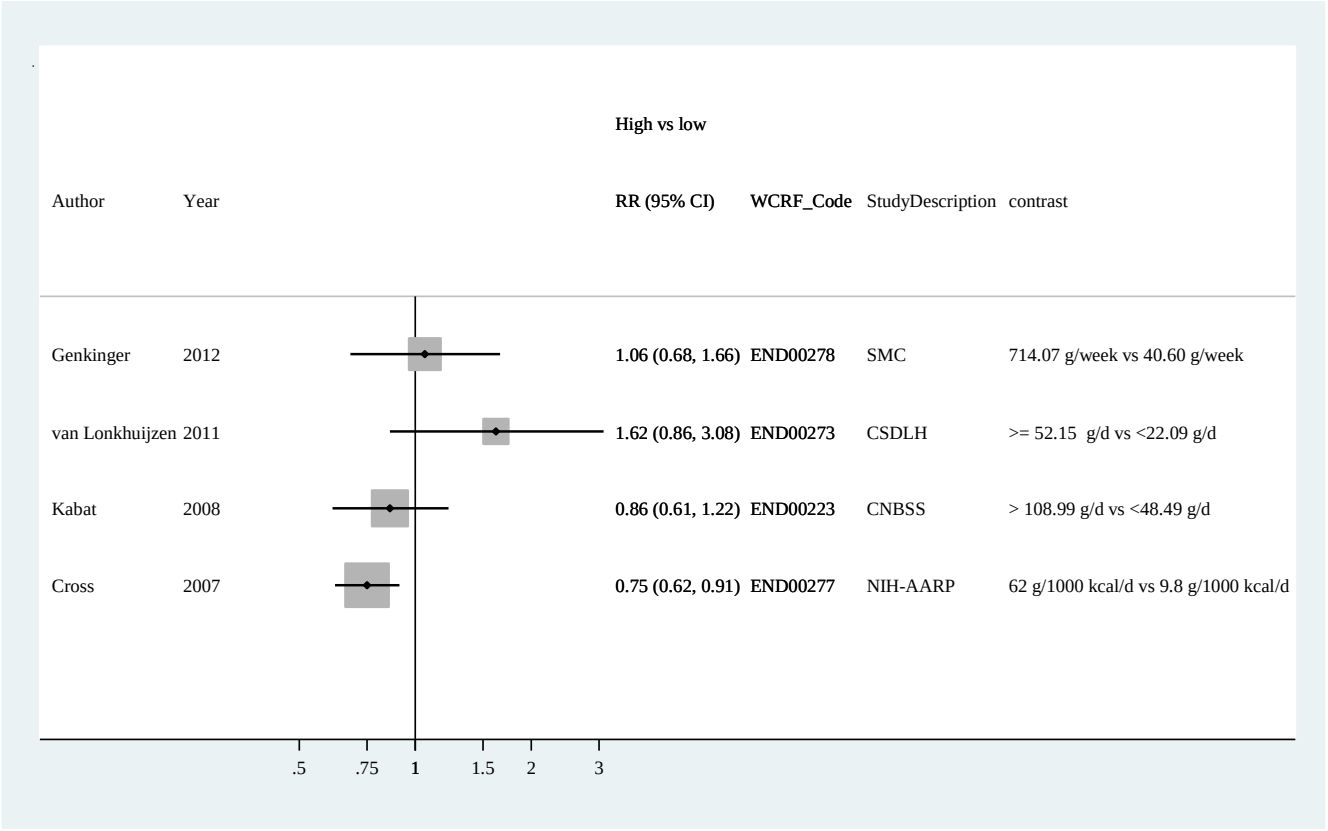


Figure 11 Dose-response meta-analysis of red meat and endometrial cancer - per 50 g/day

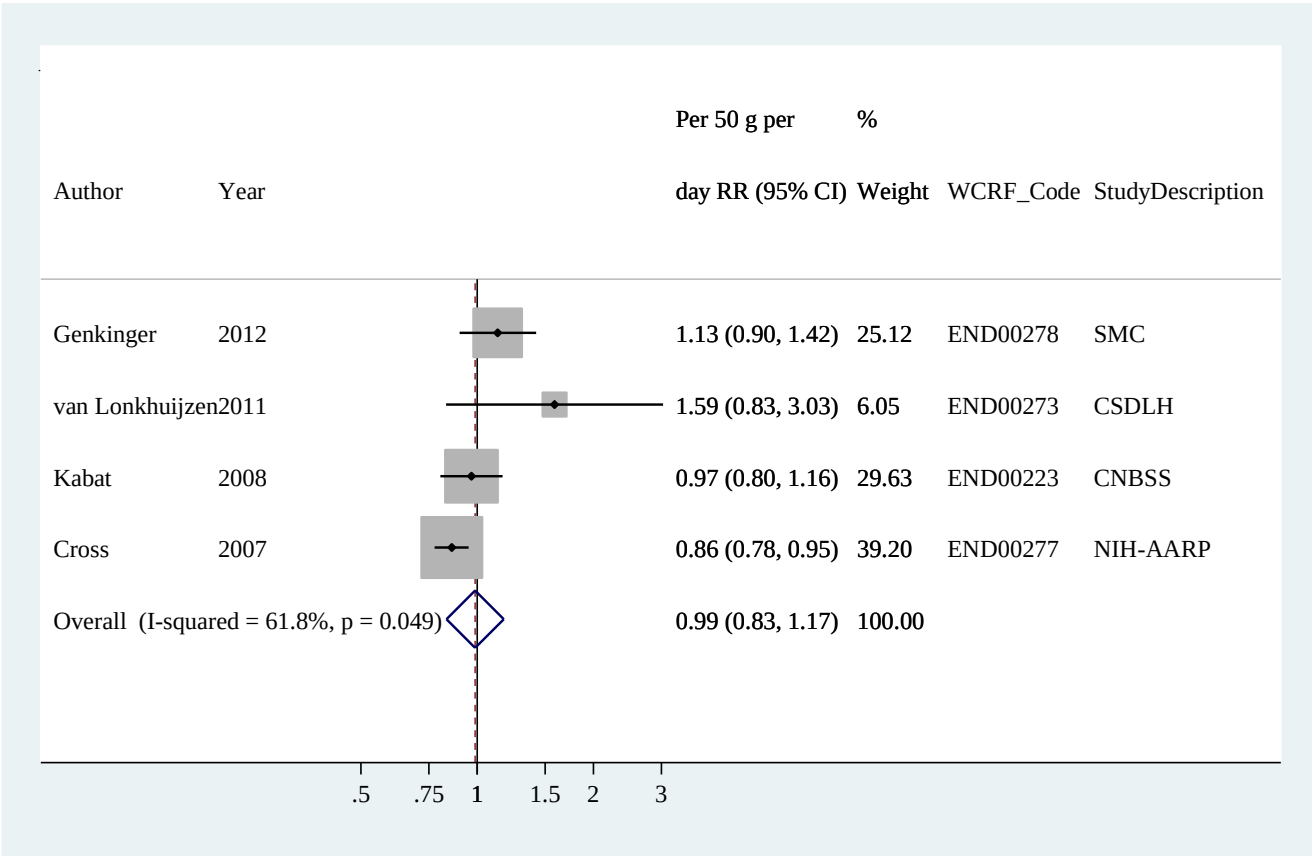
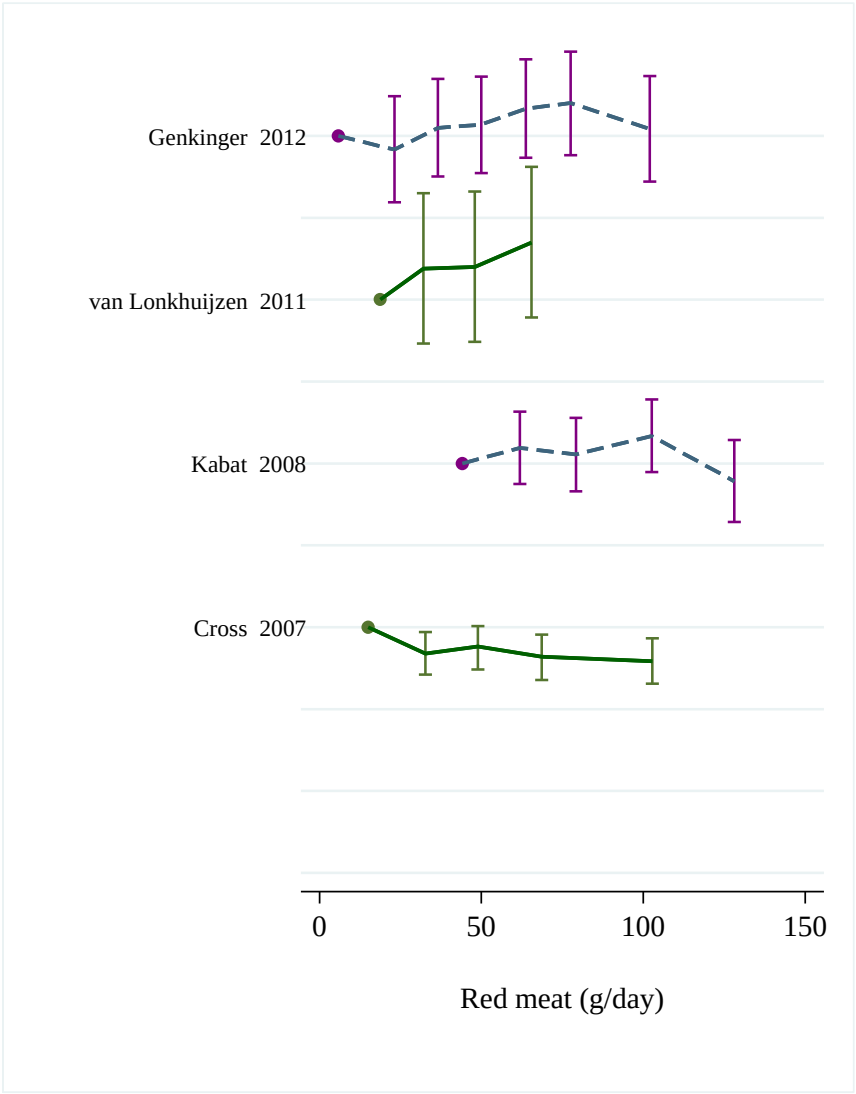


Figure 12 Dose-response graph of red meat and endometrial cancer



3 Beverages

3.6.1 Coffee

Methods
A total of 8 cohort studies have been published on coffee and endometrial cancer risk up to 2012, six of which were published after the Second Expert Report. Dose-response analyses were conducted for an increase of 1 cup per day.

Main results
The summary RR per 1 cup of coffee per day was 0.93 (95% CI: 0.91-0.96, I^2=10%, $p_{heterogeneity}$=0.35, n=7). There was no evidence of publication bias with Egger's test, p=0.39.

Two studies explored the effect modification by postmenopausal hormone use. In the NIH-AARP (Gunter et al, 2011), the relation of coffee with endometrial cancer incidence varied significantly by hormone use ($p_{interaction}$ = 0.03) with an association only apparent among never users (Hazard ratio comparing drinking >3 cups/day versus none = 0.54; 95% CI, 0.41–0.72; Ptrend = 0.0005). In the NHS (Je et al, 2011), the inverse associations with 4 or more cups of coffee seemed stronger among postmenopausal women (RR =0.74; 95% CI = 0.55–1.00; Ptrend = 0.04) and those without current hormone use (RR = 0.69; 95% CI = 0.48–1.00; Ptrend =0.03), but no significant interactions between these variables and coffee intake were observed.

Three studies investigating effect modification by body fatness support that the potential protective effect of coffee on endometrial cancer risk is more evident in overweight and obese women. In the NIH-AARP (Gunter et al, 2011) the relation of coffee with endometrial cancer incidence was only observed in women with BMI>25 kg/m2. In the NHS (Je et al, 2011), the inverse associations with 4 or more cups of coffee seemed stronger among obese women (BMI > 30 kg/m2; RR = 0.62; 95% CI: 0.38–1.01; Ptrend = 0.02), but no significant interaction was observed. In the SMC (Frieberg et al, 2009), the association with coffee seemed largely confined to overweight and obese women, who showed a respective risk reduction of 12% (95% CI 0–23%) and 20% (95% CI 7–31%) for every cup of coffee, but was not observed among normal weight women ($p_{interaction}$ <0.001).

Heterogeneity
There was low evidence of heterogeneity, I^2=9.9%, $p_{heterogeneity}$=0.35. Visual inspection of the funnel plot suggests that a small study (Shimazu et al, 2008) reported an inverse association much stronger than the association reported by other studies.

Published meta-analyses

In a meta-analysis of two cohort studies and seven case-control studies, the relative risk estimates of different coffee consumption categories compared to non coffee drinkers were 0.80 (95% CI: 0.68-0.94) for coffee drinkers; 0.87 (95% CI: 0.78-0.97) for low-to-moderate drinkers and 0.64 (95% CI: 0.48-0.86) for heavy coffee drinkers (Bravi et al, 2009). When restricted to the two cohort studies, the respective summary RRs were 0.86 (95% CI: 0.51-1.45), 0.96 (95% CI: 0.54-1.68) and 0.55 (95% CI: 0.30-1.02).

The summary RR for an increment of one cup per day was 0.93 (95%: 0.89-0.97) for all studies combined and 0.97 (95% CI: 0.89-1.04) when restricted to the two cohort studies.

Another meta-analysis of four cohort studies found a summary RR of 0.74 (95% CI: 0.63-0.84) for high vs. low coffee consumption (Yu et al, 2011).

A more recent meta-analysis of six cohort studies and ten case-control studies reported a summary RR of 0.71 (95% CI: 0.62-0.81) for high vs. low consumption for all studies combined and 0.70 (95% CI: 0.62-0.81) for cohort studies (Je & Giovannucci, 2012). The summary RR per one cup per day among cohort studies was 0.94 (95% CI: 0.90-0.97).

Conclusion from the Second Expert Report

In the SLR of the 2007 Expert Report the evidence relating coffee to endometrial cancer risk was limited and no conclusion was possible. The summary odds ratio of the highest vs lowest intake of five case-control studies was 0.85 (95% CI: 0.63-1.14)

Table 20 Studies on coffee identified in the CUP

Author/year	Country	Study name	Cases	Years of follow-up	RR	LCI	UCI	Contrast
Giri, 2011	USA	Women's Health Initiative Observational Study	427	~7.5	0.86	0.63	1.18	≥4 vs. ≤1 or 0 cups/day
Gunter, 2012	USA	NIH-AARP Diet and Health Study	1486	9.3	0.64 0.94	0.41 0.90	0.80 0.97	>3 vs. 0 cups/day Per 1 cup/day
Je, 2011	USA	Nurses' Health Study	672	26	0.75	0.57	0.97	≥4 vs. <1 cups/day
Nilsson, 2010	Sweden	Vasterbotten Intervention Program	108	15	0.88	0.44	1.78	≥4 vs. <1 times/day
Friberg, 2009	Sweden	Swedish Mammography Cohort	677	17.6	0.75 0.90	0.58 0.83	0.97 0.97	≥4 vs. ≤1 cups/day Per 1 cup/day
Shimazu, 2008	Japan	Japan Public Health Centre-based Prospective study	117	15	0.38	0.16	0.91	≥3 cups/d vs. ≤2/wk

Table 21 Overall evidence on coffee and endometrial cancer

	Summary of evidence
SLR 2005	One cohort study was identified in the SLR. Another study published before 2007 was identified in the CUP.. Both studies showed non-significant inverse associations between coffee intake and endometrial cancer risk.
Continuous Update Project	Six additional studies reported on coffee and endometrial cancer risk. All RRs were below 1, and four of the studies showed significant inverse associations.

Table 22 Summary of results of the dose-response meta-analysis of coffee and endometrial cancer

Endometrial cancer		
	SLR 2005*	Continuous Update Project
Studies (n)	-	7
Cases (n)	-	3571
RR (95% CI)	-	0.93 (0.91-0.96)
Quantity	-	Per 1 cup/d
Heterogeneity (I^2, p-value)	-	9.9%, p=0.36

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

Table 23 Inclusion/exclusion table for meta-analysis of coffee and endometrial cancer

WCRF code	Author	Year	Study design	Study name	Cancer outcome	SLR 2005	CU dose-response	CU H vs. L forest plot	Estimated values	Exclusion reason
END00257	Giri	2011	Prospective cohort study	Women's Health Initiative – Observational Study	Incidence	No	Yes	Yes	Midpoints	
END00258	Gunter	2012	Prospective cohort study	NIH-AARP Diet and Health Study	Incidence	No	Yes	Yes	Midpoints, person-years	
END00256	Je	2011	Prospective cohort study	Nurses' Health Study	Incidence	No	Yes	Yes	Midpoints	
END00279	Nilsson	2010	Prospective cohort study	Vasterbotten Intervention Project	Incidence	No	Yes	Yes	Midpoints, person-years	
END00221	Friberg	2009	Prospective cohort study	Swedish Mammography Cohort	Incidence	No	Yes	Yes	Midpoints	
END00207	Shimazu	2008	Prospective cohort study	Japan Public Health Centre-based Cohort study	Incidence	No	Yes	Yes	Midpoints	
END00280	Stensvold	1994	Prospective cohort study	Norwegian Health Screening Service	Incidence	No*	Yes	Yes	Midpoints	
END00178	Jacobsen	1986	Prospective cohort study		Incidence	Yes	No	Yes		Only high vs. low comparison

Figure 13 Highest versus lowest forest plot of coffee and endometrial cancer

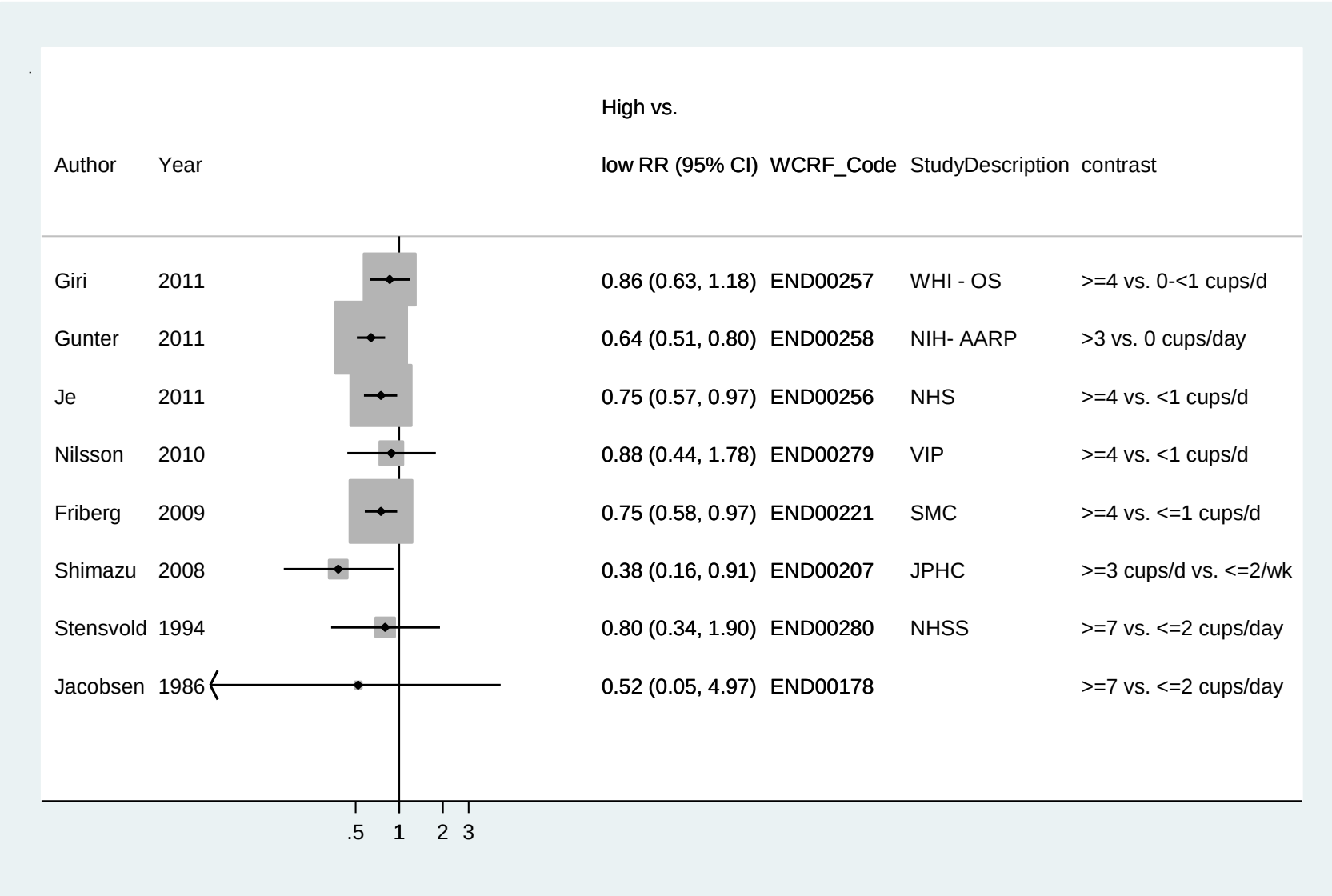


Figure 14 Dose-response meta-analysis of coffee and endometrial cancer, per 1 cup/d

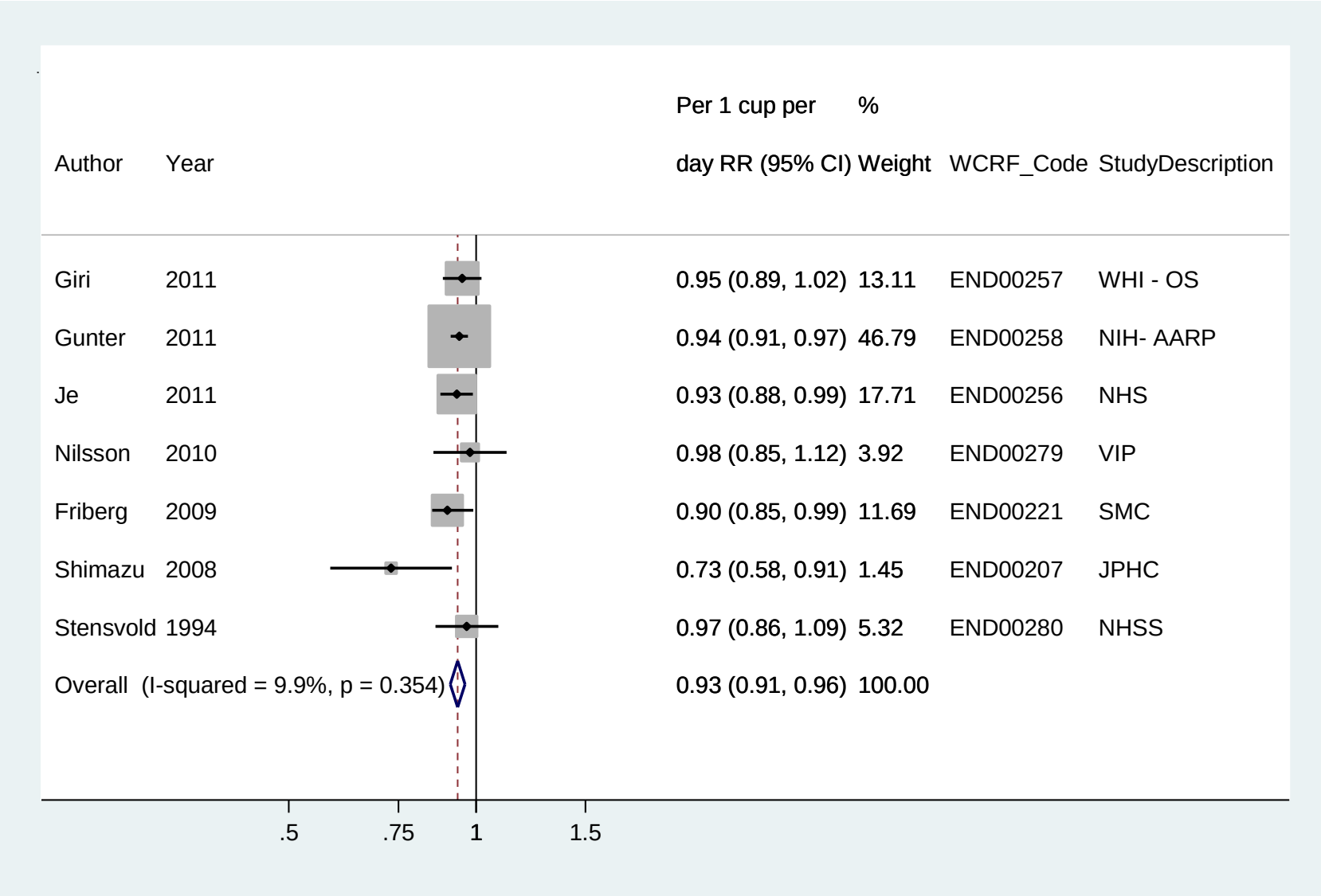


Figure 15 Funnel plot of coffee and endometrial cancer

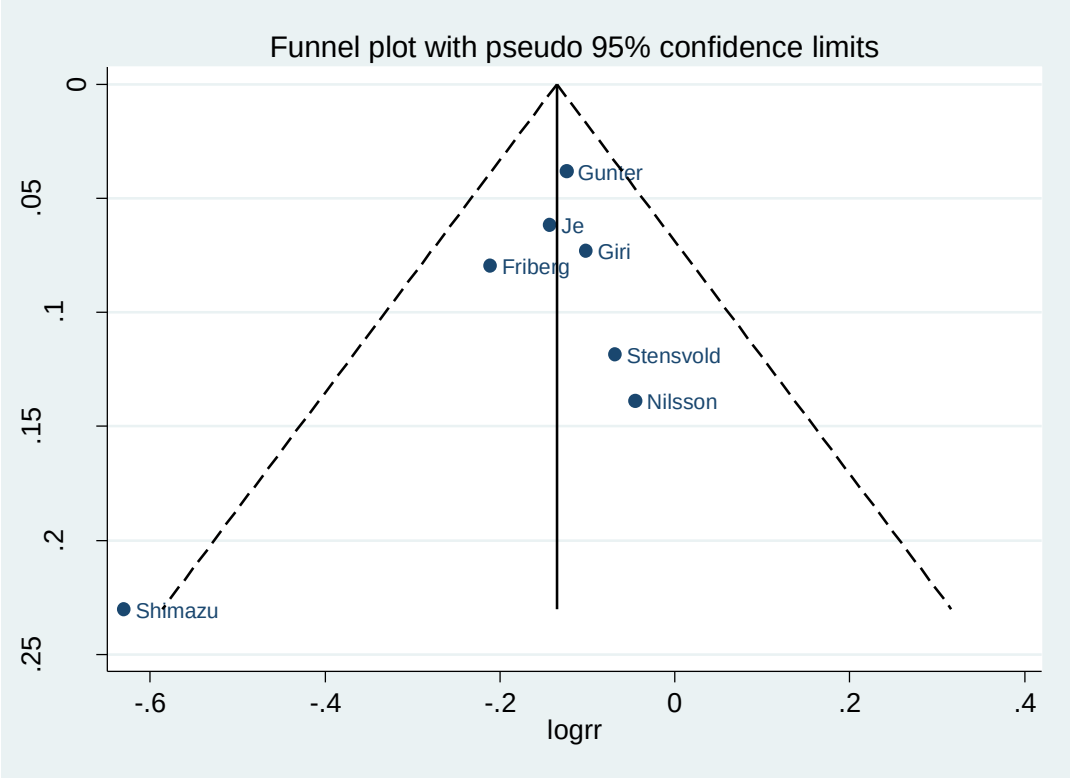
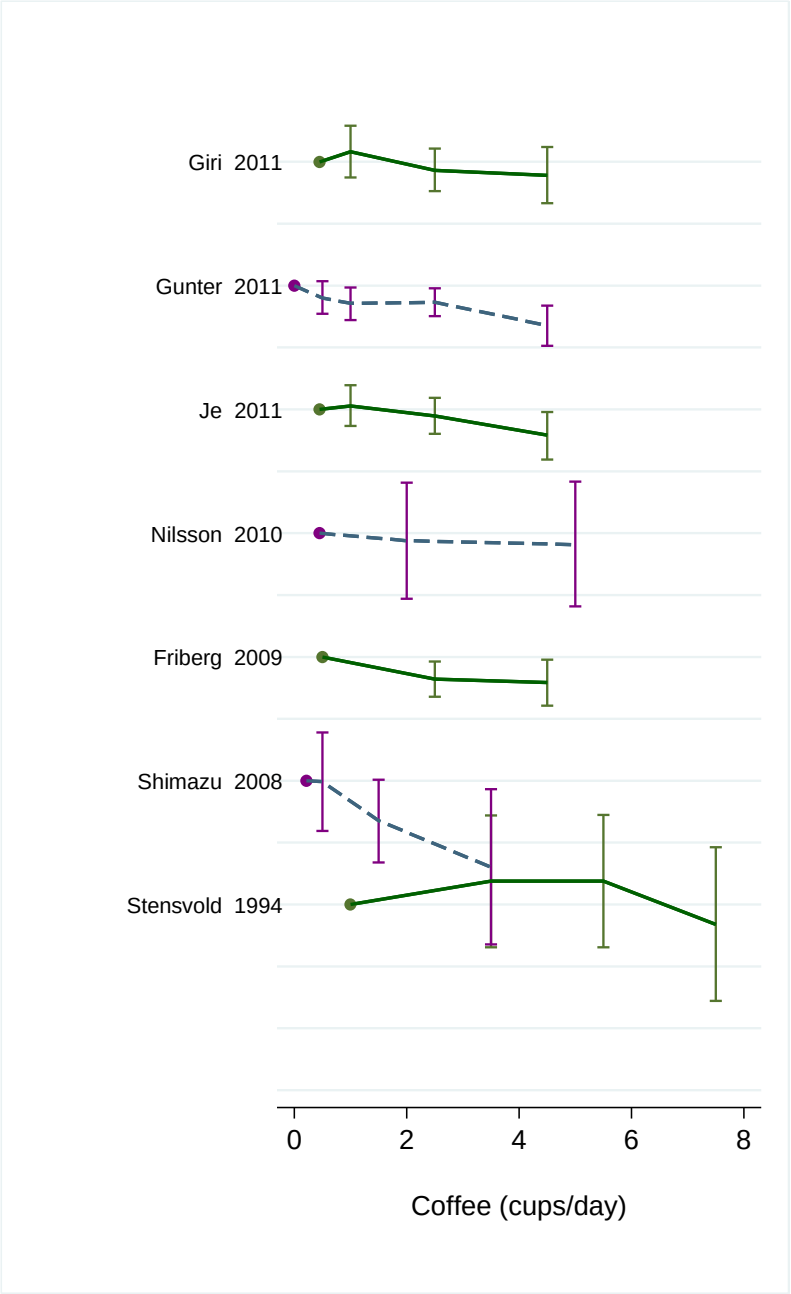


Figure 16 Dose-response graph of coffee and endometrial cancer



3.6.1.1 Decaffeinated coffee

Methods

A total of 3 cohort studies have been published on decaffeinated coffee and endometrial cancer risk up to 2012, all of which were identified in the CUP. Dose-response analysis was conducted per 1 cup per day.

Main results

The summary RR per 1 cup of decaffeinated coffee per day was 0.92 (95% CI: 0.87-0.97, I^2=0%, $p_{heterogeneity}$=0.81, n=3). There was no evidence of publication bias with Egger's test, p=0.40.

Heterogeneity

There was no heterogeneity, I^2=0%, $p_{heterogeneity}$=0.81.

Published meta-analyses

None of the three meta-analyses on coffee intake and endometrial cancer risk conducted analyses for decaffeinated coffee (Bravi et al, 2009, Yu et al, 2011, and Je & Giovannucci, 2012).

Conclusion from the Second Expert Report

No prospective study was identified

Table 24 Studies on decaffeinated coffee identified in the CUP

Author/year	Country	Study name	Cases	Years of follow-up	RR	LCI	UCI	Contrast
Giri, 2011	USA	Women's Health Initiative Observational Study	427	~7.5	0.51	0.25	1.03	≥4 vs. ≤1 or 0 cups/day
Gunter, 2012	USA	NIH-AARP Diet and Health Study	1486	9.3	0.81 0.93	0.54 0.87	1.20 0.99	>3 vs. 0 cups/day Per 1 cup/day
Je, 2011	USA	Nurses' Health Study	672	26	0.78	0.57	1.08	≥2 cups/d vs. <1 cup/mo

Table 25 Overall evidence on decaffeinated coffee and endometrial cancer

	Summary of evidence
SLR 2005	No cohort studies reported on decaffeinated coffee and endometrial cancer.
Continuous Update Project	Three cohort studies reported on decaffeinated coffee and endometrial cancer and all of these showed non-significant inverse associations.

Table 26 Summary of results of the dose-response meta-analysis of decaffeinated coffee and endometrial cancer

Endometrial cancer		
	SLR 2005*	Continuous Update Project
Studies (n)	-	3
Cases (n)	-	2585
RR (95% CI)	-	0.92 (0.87-0.97)
Quantity	-	Per 1 cup/d
Heterogeneity (I^2, p-value)	-	0%, p=0.81

No meta-analysis was conducted in the Second Expert Report

Table 27 Inclusion/exclusion table for meta-analysis of decaffeinated coffee and endometrial cancer

WCRF code	Author	Year	Study design	Study name	Cancer outcome	SLR 2005	CU dose-response	CU H vs. L forest plot	Estimated values	Exclusion reason
END00257	Giri	2011	Prospective cohort study	Women's Health Initiative – Observational Study	Incidence	No	Yes	Yes	Midpoints	
END00258	Gunter	2012	Prospective cohort study	NIH-AARP Diet and Health Study	Incidence	No	Yes	Yes	Midpoints, person-years	
END00256	Je	2011	Prospective cohort study	Nurses' Health Study	Incidence	No	Yes	Yes	Midpoints	

Figure 17 Highest versus lowest forest plot of decaffeinated coffee and endometrial cancer

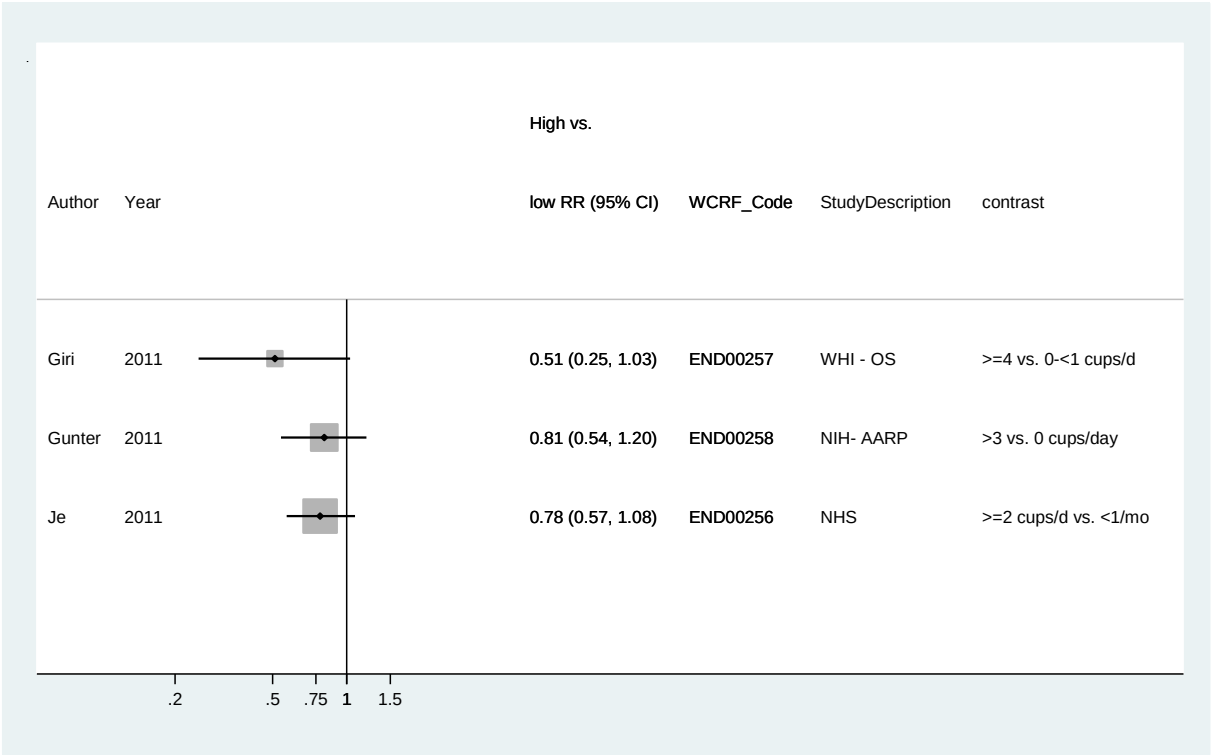


Figure 18 Dose-response meta-analysis of decaffeinated coffee and endometrial cancer, per 1 cup/d

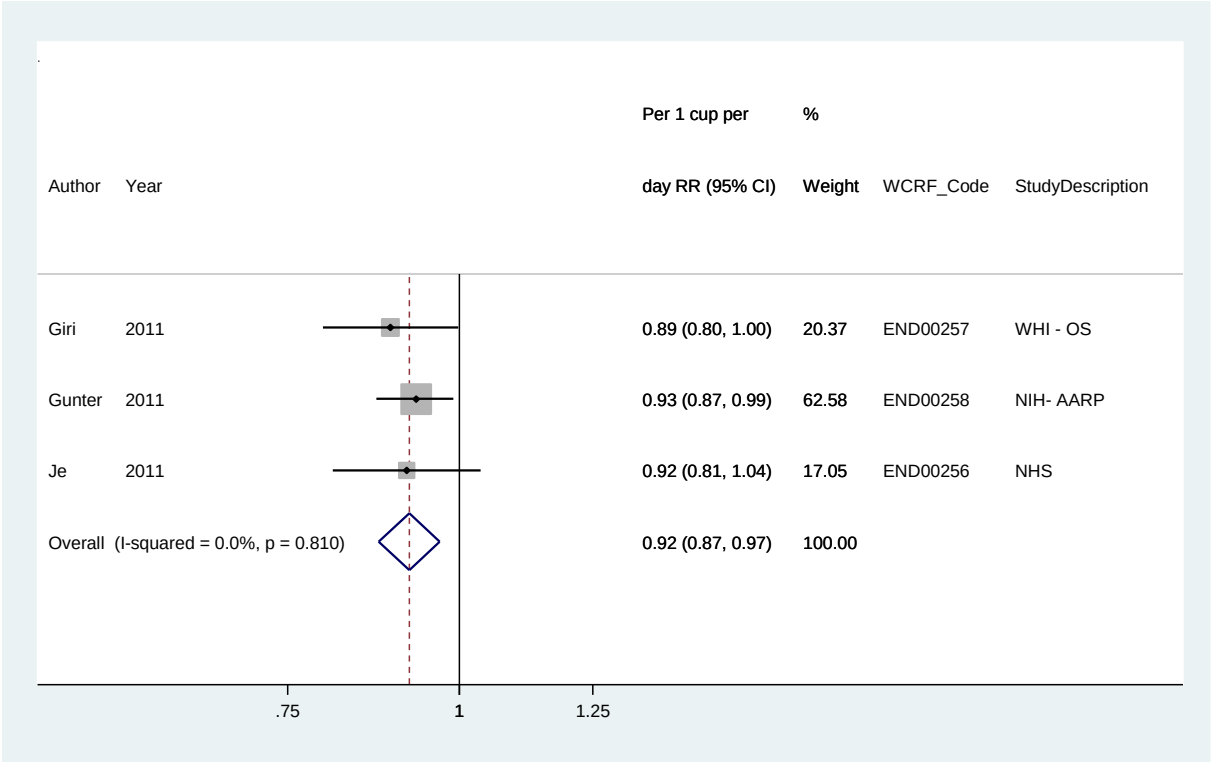
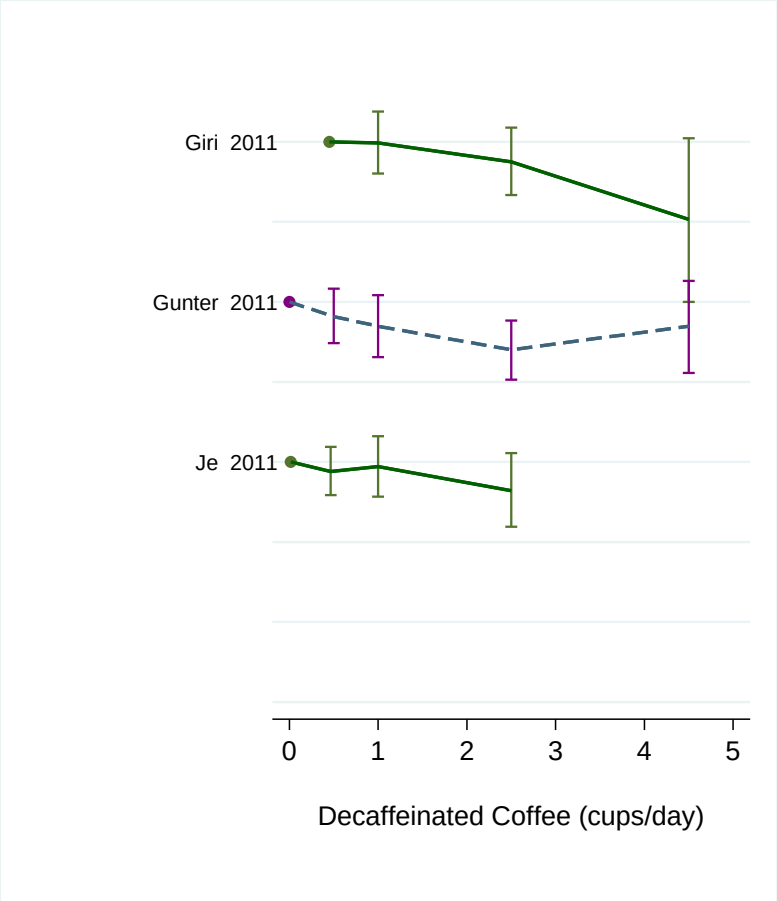


Figure 19 Dose-response graph of decaffeinated coffee and endometrial cancer



3.6.2 Tea

Methods

Up to December 2012, reports from three cohort studies were identified, two of which were identified during the CUP.
One study showing a non-significant inverse association could not be included in the dose-response meta-analysis because only reported highest vs lowest comparison. One additional Japanese study investigated green tea in relation to endometrial cancer and was not included in the meta-analysis (Shimazu et al, 2008). No association was reported in this study ($RR_{>5\ cups/day\ vs\ <4\ cups/week}$=0.75; 95% CI; 0.44-1.30).

Main results

The summary RR per 1 cup/day was 1.03 (95% CI: 0.89-1.21).

Heterogeneity

There was no evidence of heterogeneity across the limited number of published studies (I^2=0%, $P_{heterogeneity}$ =0.76).

Published meta-analyses

A meta-analysis of seven studies (two prospective and five case-control studies) (Tang et al. 2009), showed a summary RR for an increase of 2 cups/day of 0.90 (95% CI: 0.77-1.05) from two cohort studies and 0.66 (95% CI: 0.69-0.87) for four case-control studies.
In a recent meta-analysis of four case-control studies and endometrial cancer, the summary relative risk for the highest vs lowest intake was 0.78 (95% CI: 0.62, 0.98) (Butler et al. 2011).

Conclusion from the Second Expert Report

One study was identified during the SLR 2005 and showed no association between tea consumption and endometrial cancer.

Table 28 Studies on tea consumption identified in the CUP

Author, year	Country	Study name	Cases	Years of follow up	RR	LCI	UCI	Contrast
Giri, 2011	USA	Women's Health Initiative	427	7.5	1.10	0.61	1.97	>= 4 cups/d vs non-daily tea intake
Je, 2011	USA	Nurses' Health Study	672	26	0.94	0.69	1.30	>=2 cups/d vs <1 cup/month

Table 29 Overall evidence on tea consumption and endometrial cancer

	Summary of evidence
SLR 2005	One study was identified during the SLR 2005, the Iowa Women's Health Study .This study reported no association (RR: 0.76, p for trend: 0.47) between tea intake and endometrial cancer
Continuous Update Project	Two additional cohort studies were identified and included in the dose-response meta-analysis. No significant association was reported in any of them.

Table 30 Summary of results of the dose response meta-analysis of tea consumption and endometrial cancer

Endometrial cancer		
	SLR 2005*	Continuous Update Project
Studies (n)	-	2
Cases (n)	-	921
Increment unit used	-	Per 1 cup/day
Overall RR (95%CI)	-	1.03 (0.89-1.21)
Heterogeneity (I^2,p-value)	-	0%, p=0.76

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

Table 31 Inclusion/exclusion table for meta-analysis of tea consumption and endometrial cancer

WCRF_ Code	Author	Year	Study Design	Study Name	Cancer Outcome	SLR 2005	CUP dose-response meta-analysis	CUP HvL forest plot	Estimated values	Exclusion reasons
END00257	Giri	2011	Prospective Cohort study	Women's Health Initiative	Incidence	No	No	Yes	------	Two categories of exposure.
END00256	Je	2011	Prospective Cohort study	Nurses' Health Study	Incidence	No	Yes	Yes	Mid-exposure values	
END00066	Zheng	1996	Prospective Cohort study	Iowa Women's Health Study	Incidence	Yes	Yes	Yes	Person years per category and mid-exposure values	

Figure 20 Highest versus lowest forest plot of tea consumption and endometrial cancer

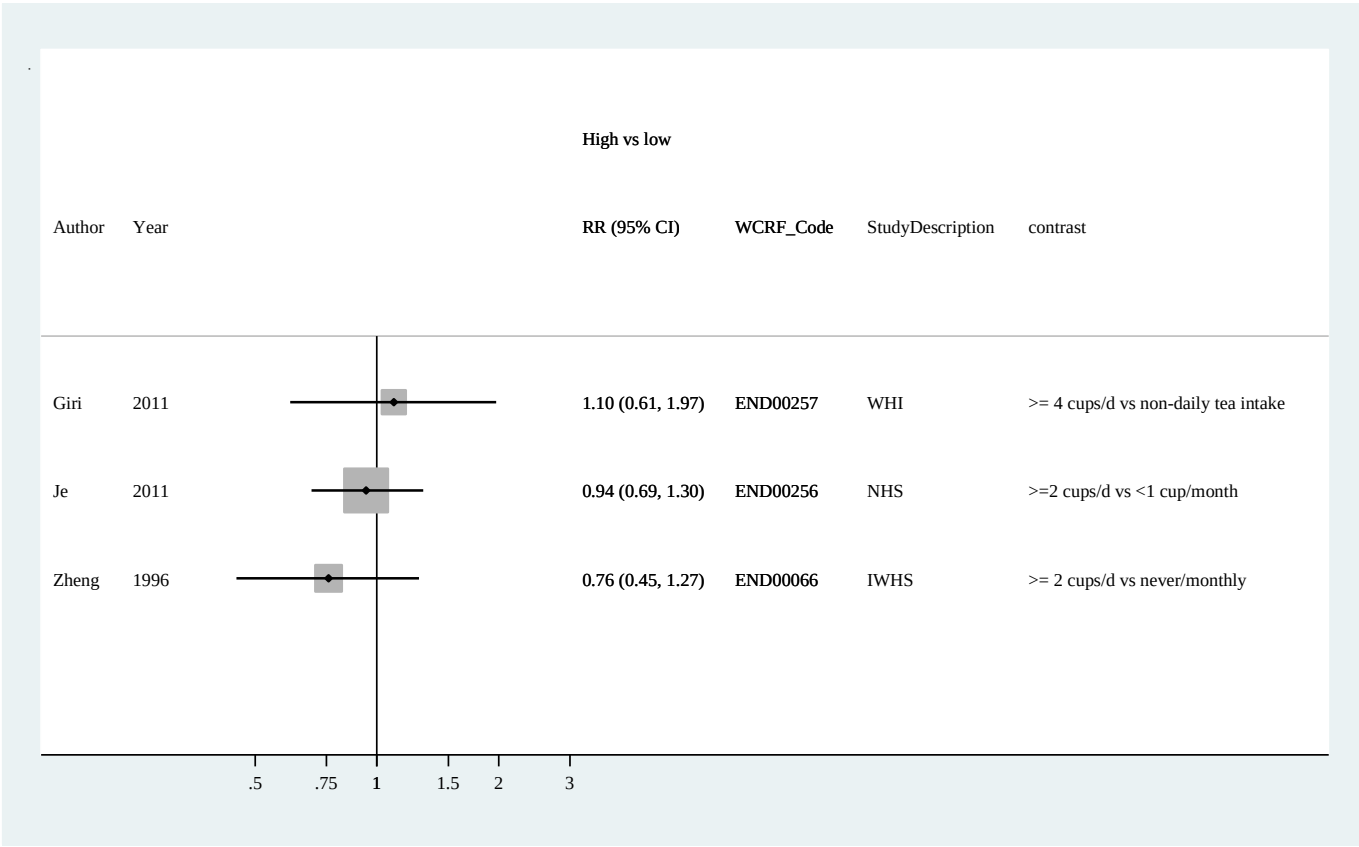


Figure 21 Dose-response meta-analysis of tea and endometrial cancer - per 1 cup/day

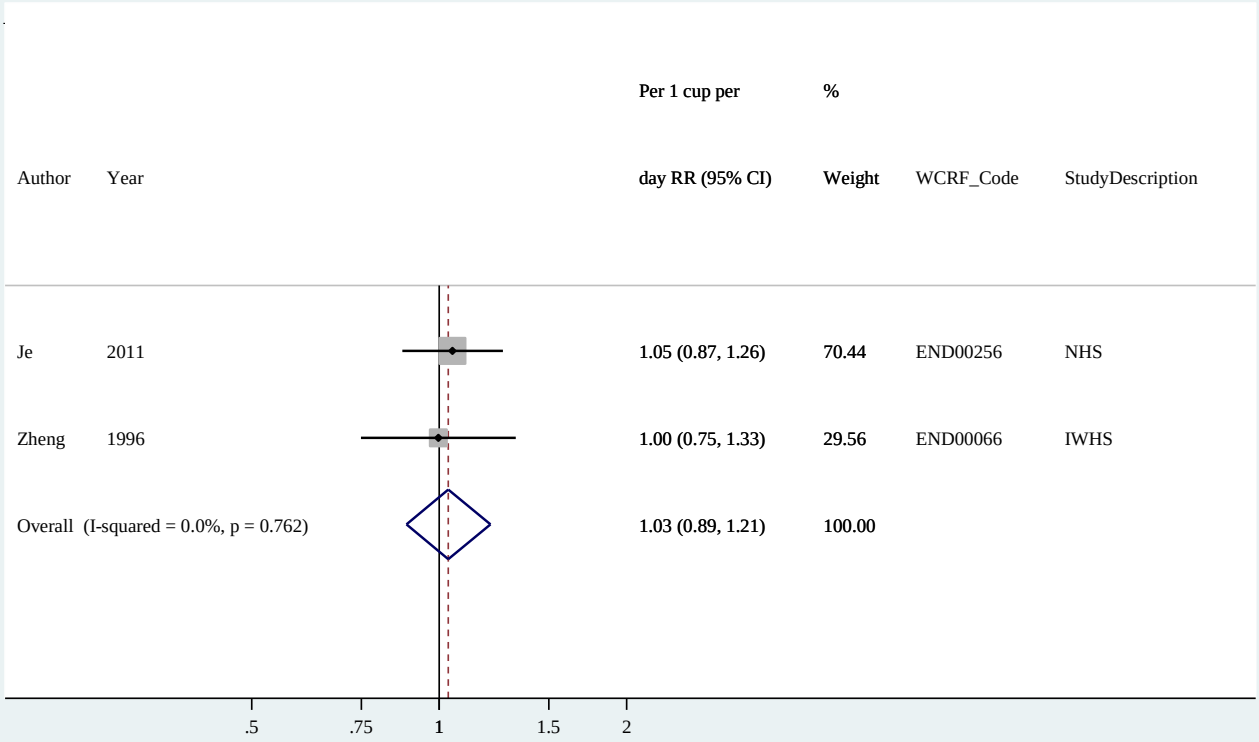
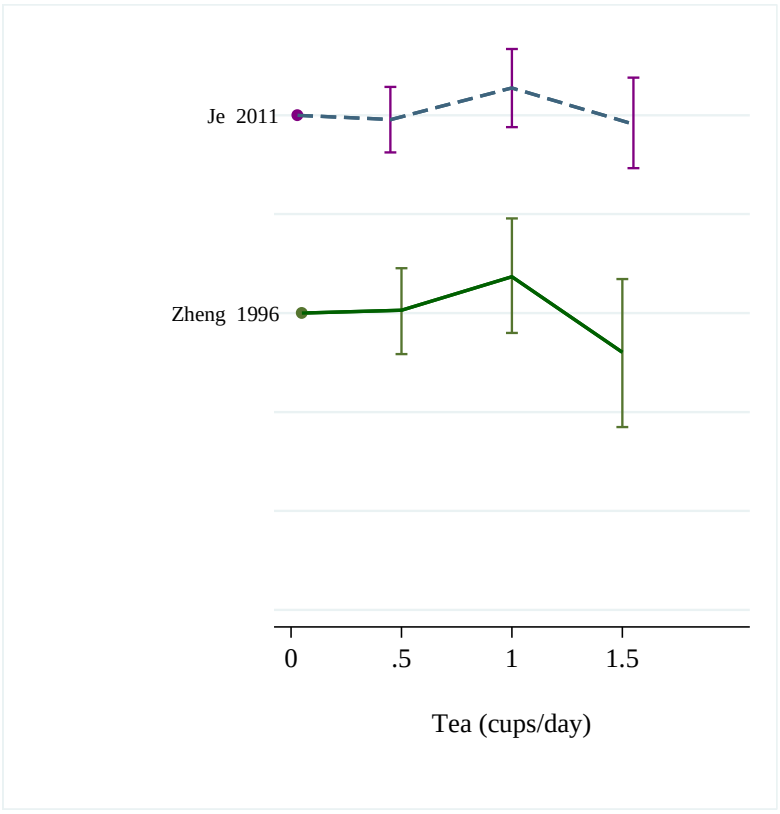


Figure 22 Dose-response graph of tea and endometrial cancer



4 Food production, preservation, processing and preparation

4.4.2 Acrylamide

Methods

A total of 3 cohort studies have been published on dietary acrylamide and endometrial cancer risk up to 2012, all of which were identified in the CUP. Dose-response analyses were conducted per 10 µg/day.

Main results

The summary RR per 10 µg/day of acrylamide was 1.07 (95% CI: 0.94-1.21, I^2=45.5%, $p_{heterogeneity}$=0.16, n=3). There was no evidence of publication bias with Egger's test, p=0.40.

Heterogeneity

There was moderate heterogeneity, I^2=45.5%, $p_{heterogeneity}$=0.16.

Published meta-analyses

A previous meta-analysis of two cohort studies showed a summary RR of 1.03 (95% CI: 0.80-1.33) for high vs. low intake and 1.01 (0.96-1.07) per 10 µg/day (Pellucci et al, 2011).

Conclusion from the Second Expert Report

No studies were identified during the SLR 2005.

Table 32 Studies on acrylamide identified in the CUP

Author/year	Country	Study name	Cases	Years of follow-up	RR	LCI	UCI	Contrast
Wilson, 2010	USA	Nurses' Health Study	484	26	1.41 1.43	1.01 0.90	1.97 2.28	25.1 vs. 8.7 µg/d, all 25.1 vs. 8.7 µg/d, never smokers
Larsson, 2009	Sweden	Swedish Mammography Cohort study	687	17.7	0.96 1.20	0.76 0.76	1.21 1.90	32.5 vs. 16.9 µg/d, long-term intake ≥29.2 vs. <20.5 µg/d, never smokers, 10-year follow-up
Hogervorst, 2007	Netherlands	Netherlands Cohort study	327	11.3	1.29 1.04 1.99 1.12	0.81 0.91 1.12 0.95	2.07 1.19 3.52 1.33	36.8 vs. 9.5 µg/d, all Per 10 µg/d 36.8 vs. 9.5 µg/d, never smokers Per 10 µg/d, never smokers

Table 33 Overall evidence on acrylamide and endometrial cancer

	Summary of evidence
SLR 2005	No cohort studies reported on acrylamide and endometrial cancer.
Continuous Update Project	Three cohort studies reported on acrylamide and endometrial cancer and one showed a significant positive association, while the other two showed no significant association; one of these showed a significant positive association in never smokers.

Table 34 Summary of results of the dose-response meta-analysis of acrylamide and endometrial cancer

Endometrial cancer		
	SLR 2005*	Continuous Update Project
Studies (n)	-	3
Cases (n)	-	1498
RR (95% CI)	-	1.07 (0.94-1.21)
Quantity	-	Per 10 µg/day
Heterogeneity (I^2, p-value)	-	45.5%, p=0.16

No meta-analysis was conducted in the Second Expert Report

Table 35 Inclusion/exclusion table for meta-analysis of acrylamide and endometrial cancer

WCRF code	Author	Year	Study design	Study name	Cancer outcome	SLR 2005	CU dose-response	CU H vs. L forest plot	Estimated values	Exclusion reason
END00209	Wilson	2010	Prospective cohort	Nurses' Health Study	Incidence	No	Yes	Yes	-	
END00215	Larsson	2009	Prospective cohort	Swedish Mammography Cohort	Incidence	No	Yes	Yes	-	
END00231	Hogervorst	2007	Case cohort	Netherlands Cohort Study	Incidence	No	Yes	Yes	-	

Figure 23 Highest versus lowest forest plot of acrylamide and endometrial cancer

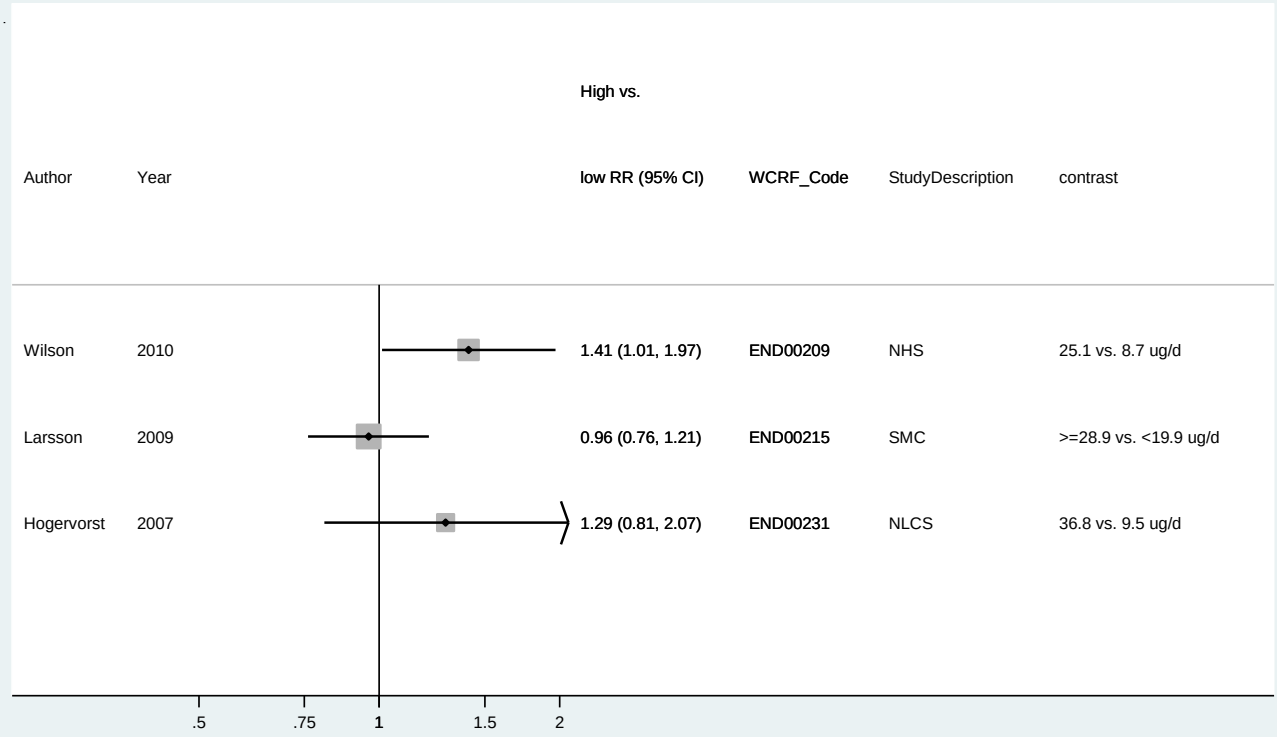


Figure 24 Dose-response meta-analysis of acrylamide and endometrial cancer, per 10 µg/d

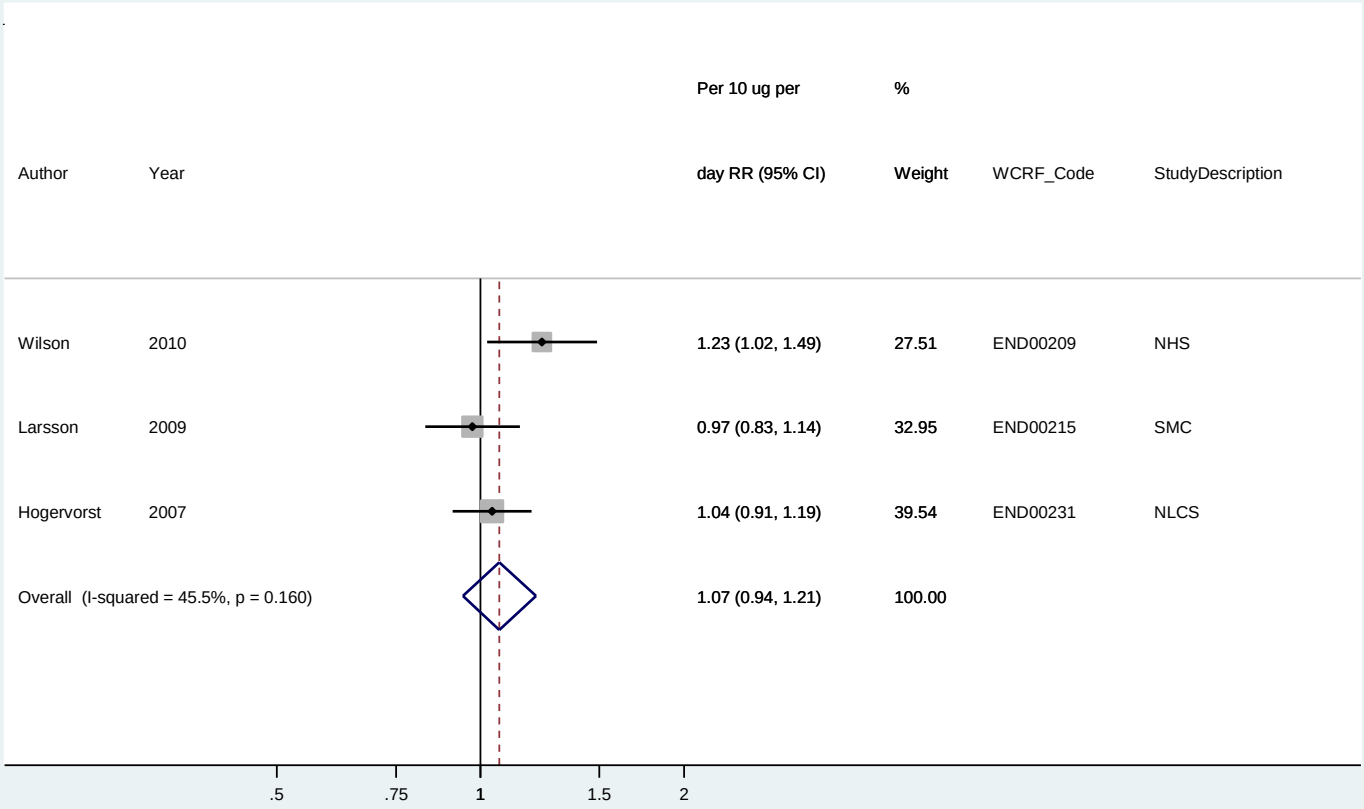
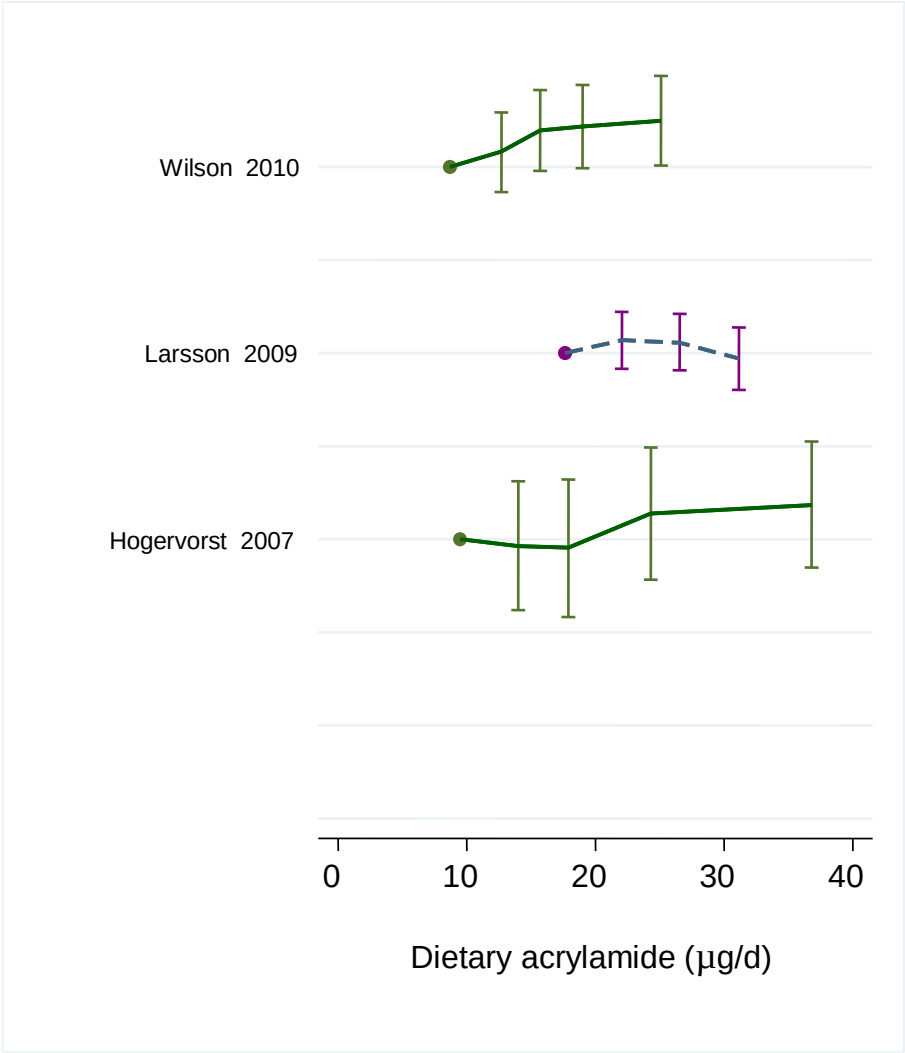


Figure 25 Dose-response graph of acrylamide and endometrial cancer



5 Dietary constituents

5.1 Carbohydrate

Methods
A total of 5 cohort studies (6 publications) have been published on carbohydrate intake and endometrial cancer risk up to 2012, three of which were identified in the CUP. Dose-response analyses were conducted per 100 g/day. For one study (Zheng et al, 1995) that reported carbohydrate intake in percentage of energy intake, we converted the results to gram per day using the median energy intake and 4 kcal/gram carbohydrate as conversion factors.

Main results
The summary RR per 100 g/day of carbohydrate intake was 1.18 (95% CI: 1.02-1.37, I^2=0%, $p_{heterogeneity}$=0.67, n=5). There was no evidence of publication bias with Egger's test, p=0.73.

All studies considered energy intake and BMI as potential confounders except Zheng et al, 1995 (IWHS) that adjusted for energy intake but not for BMI.

Studies that examined the association by menopausal status produced discordant results. In the NHS (Cui et al, 2011) a positive association with carbohydrate intake was observed among premenopausal women (top vs. bottom quintile RR = 2.87, 95% CI = 1.38–6.08) but not among postmenopausal women, although the test for heterogeneity was not significant (p heterogeneity= 0.94).

The test of heterogeneity was not significant also in EPIC (Cust et al, 2007), but contrary to the findings in the NHS, the risk estimates were significant among postmenopausal women but not among premenopausal women. Among postmenopausal women, the associations between total carbohydrates and endometrial cancer risk were significant only in never users of hormone therapy (p heterogeneity = 0.04). When stratified by body mass index subgroups, the calibrated continuous models suggested a possibly stronger association among normal-weight women, but this finding was not reflected in the quartile risk estimates

Heterogeneity
There was no evidence of heterogeneity, I^2=0%, $p_{heterogeneity}$=0.67.

Conclusion from the Second Expert Report

In the SLR of the 2007 Expert Report the evidence relating carbohydrate to endometrial cancer risk was limited and no conclusion was possible.

Table 36 Studies on carbohydrate intake identified in the CUP

Author/year		Study name	Cases	Years of follow-up	RR	LCI	UCI	Contrast
Cui, 2011	USA	Nurses' Health Study	669	26	1.29	1.00	1.67	214.8 vs. 141.0 g/d
Cust, 2007	Europe	European Prospective Investigation into Cancer and Nutrition	710	6.4	1.16 1.20 1.61	0.93 0.97 1.06	1.43 1.50 2.45	≥257 vs. <170 g/d Per 100 g/d, uncalibrated Per 100 g/d, calibrated
Larsson, 2006	Sweden	Swedish Mammography Cohort	608	15.6	1.12	0.85	1.47	256 vs. 201 g/d

Table 37 Overall evidence on carbohydrate and endometrial cancer

	Summary of evidence
2005 SLR 2005	Two cohort studies (3 publications) reported on carbohydrate intake and endometrial cancer and both found no association.
Continuous Update Project	Three cohort studies reported on carbohydrate and endometrial cancer. One showed a borderline association, another reported a significant association in analyses calibrated for diet measurement error and the third did not report any significant association

Table 38 Summary of results of the dose-response meta-analysis of carbohydrate and endometrial cancer

Endometrial cancer		
	SLR 2005	Continuous Update Project
Studies (n)	1	5
Cases (n)	426	2629
RR (95% CI)	1.03 (0.97-1.10)	1.18 (1.02-1.37)
Quantity	Per 15% energy intake	Per 100 g/day
Heterogeneity (I^2, p-value)	-	0%, p=0.67

Table 39 Inclusion/exclusion table for meta-analysis of carbohydrate and endometrial cancer

WCRF code	Author	Year	Study design	Study name	Cancer outcome	SLR 2005	CU dose-response	CU H vs. L forest plot	Estimated values	Exclusion reason
END00261	Cui	2011	Prospective cohort study	Nurses' Health study	Incidence	No	Yes	Yes	Person-years	
END00225	Cust	2007	Prospective cohort study	European Prospective Investigation into Cancer and Nutrition	Incidence	No	Yes	Yes	Midpoints	
END00243	Larsson	2006	Prospective cohort study	Swedish Mammography Cohort study	Incidence	No	Yes	Yes	-	
END00201	Silvera	2005	Prospective cohort study	Canadian National Breast Screening Study	Incidence	Yes	Yes	Yes	Midpoints	
END00009	Jain	2000	Prospective cohort study	Canadian National Breast Screening Study	Incidence	Yes	No	No	-	Overlap with END00201 by Silvera et al.
END00015	Zheng	1995	Prospective cohort study	Iowa Women's Health Study	Incidence	Yes	Yes	Yes	Recalculation from E% to grams per day	

Figure 26 Highest versus lowest forest plot of carbohydrate and endometrial cancer

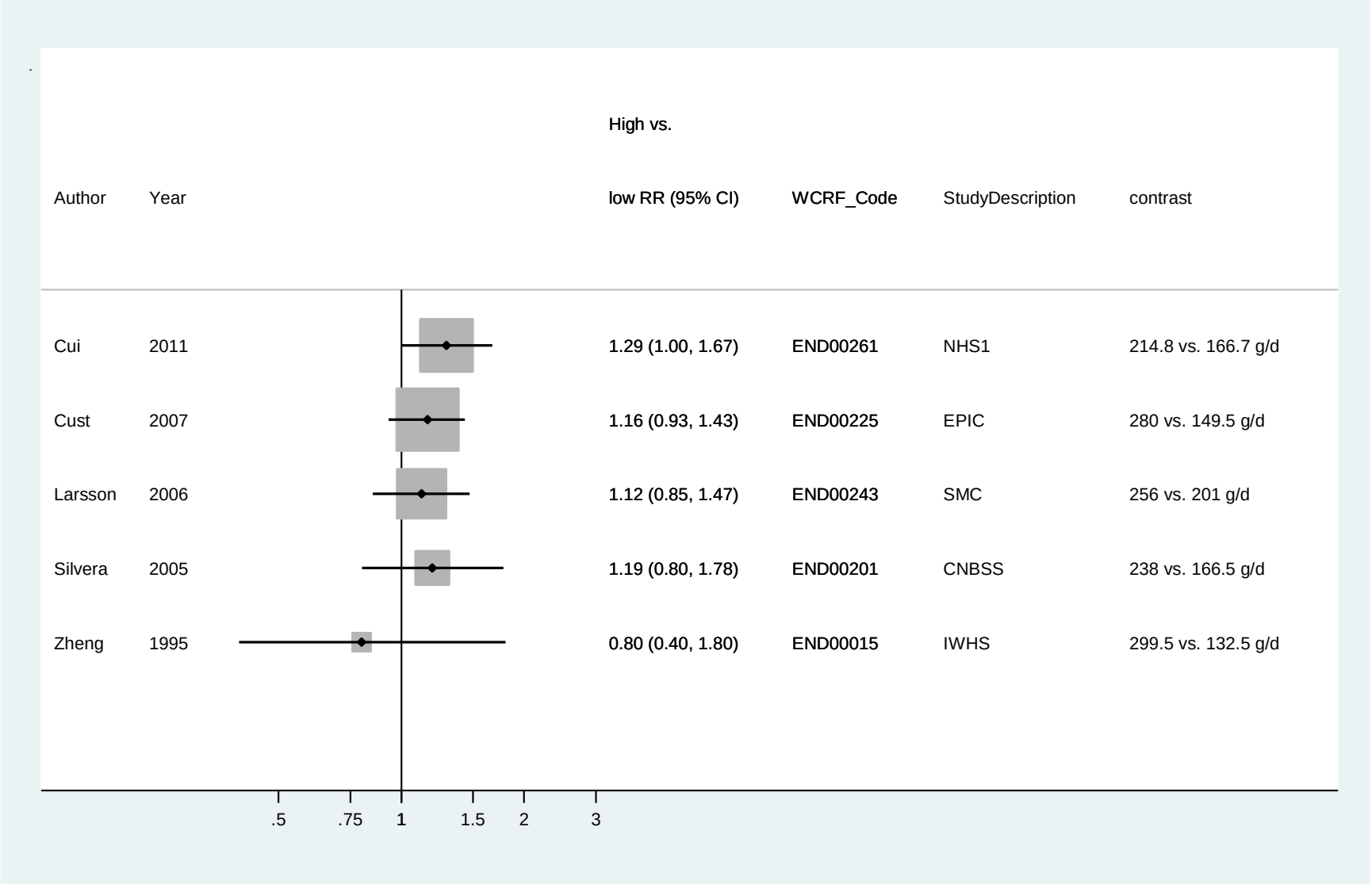


Figure 27 Dose-response meta-analysis of carbohydrate and endometrial cancer, per 100 g/d

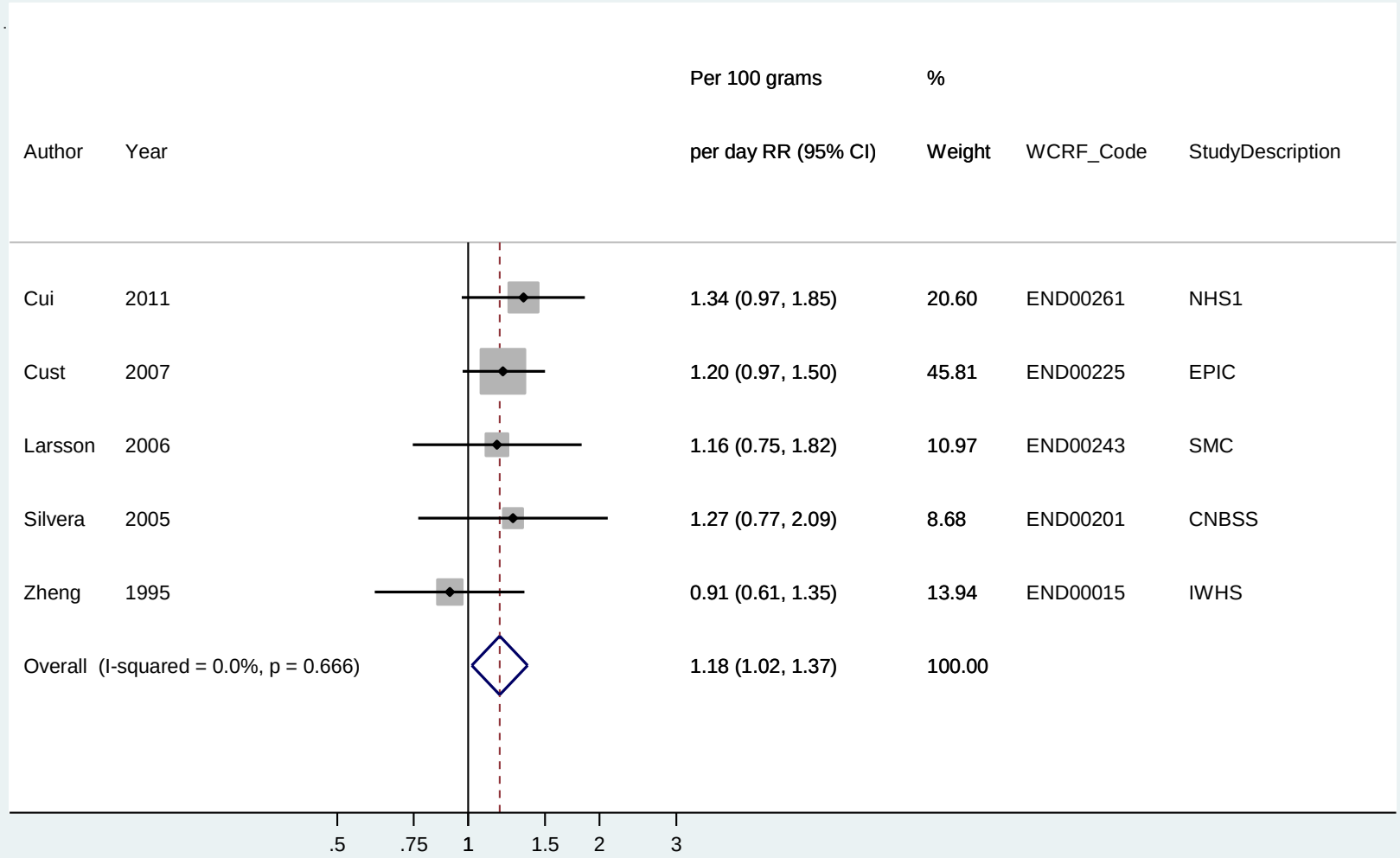


Figure 28 Funnel plot of carbohydrate intake and endometrial cancer

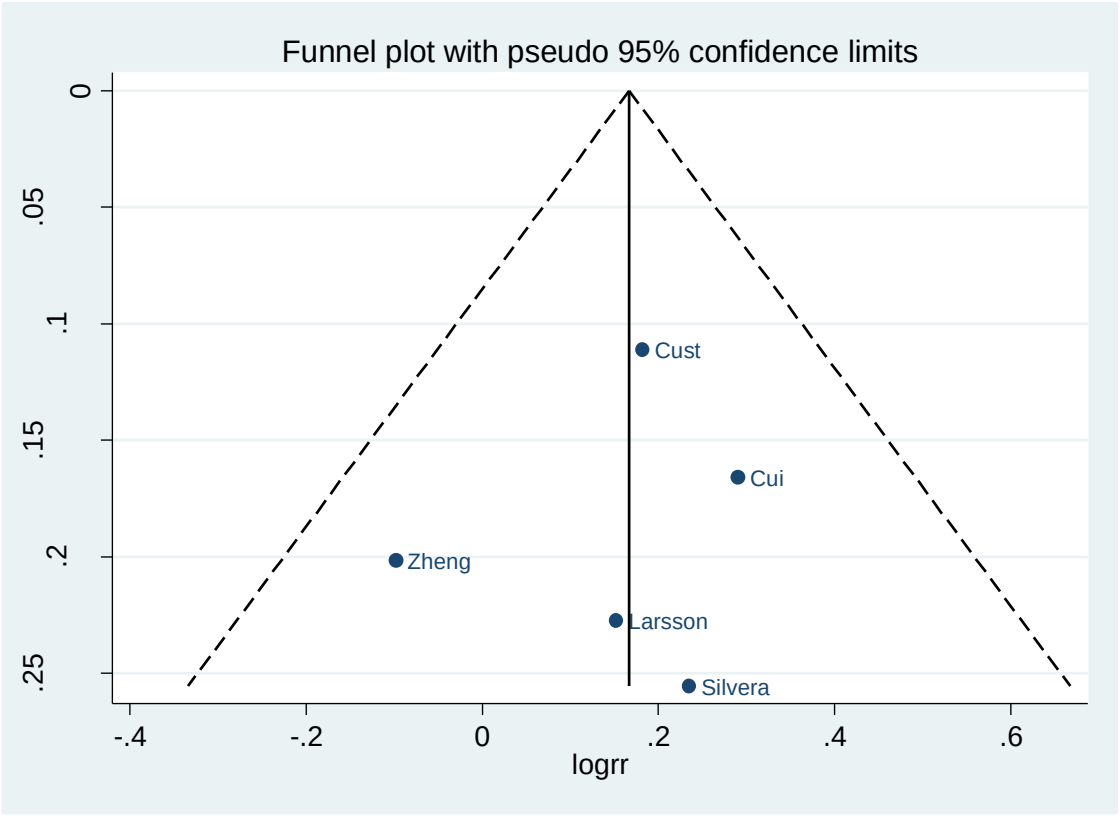
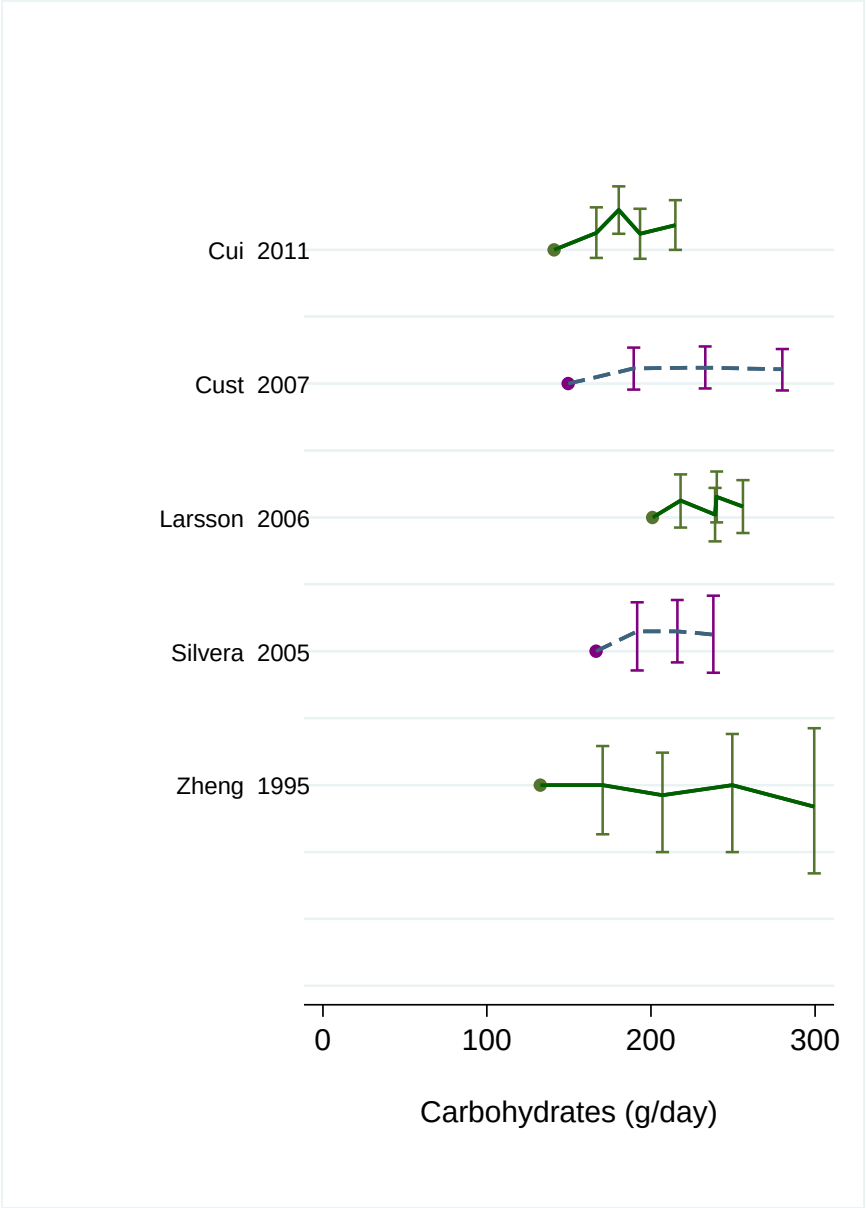


Figure 29 Dose-response graph of carbohydrate and endometrial cancer



5.1.5 Glycaemic index

Methods
A total of 5 cohort studies have been published on glycaemic index and endometrial cancer risk up to 2012, three of which were identified in the CUP. Dose-response analyses were conducted per 10 units/day.

Main results
The summary RR per 10 units/day of glycaemic index was 0.99 (95% CI: 0.90-1.10, I^2=27.7%, $p_{heterogeneity}$=0.24, n=5). There was no evidence of publication bias with Egger's test, p=0.87.

Heterogeneity
There was low heterogeneity, I^2=27.7%, $p_{heterogeneity}$=0.24.

Published meta-analyses

A meta-analysis of five cohort studies and two case-control studies found no significant association overall (high vs. low comparison), summary RR=1.15 (95% CI: 0.95-1.40) or among cohort studies, summary RR=1.00 (95% CI: 0.87-1.14). A positive association was observed among the two case-control studies, summary RR=1.56 (95% CI: 1.21-2.02) (Nagle et al, 2012). The same results were published in a meta-analysis by Galeone et al., 2012, including the same studies.

A meta-analysis of four cohort studies and one case-control study found a positive association overall, summary RR=1.22 (95% CI: 1.01-1.49), but this may have been driven by the result of the case-control study which showed a significant positive association (Gnagnarella et al, 2008).

Conclusion from the Second Expert Report

In the SLR of the 2007 Expert Report the evidence relating glycaemic index to endometrial cancer risk was limited and no conclusion was possible.

Table 40 Studies on glycaemic index intake identified in the CUP

Author/year		Study name	Cases	Years of follow-up	RR	LCI	UCI	Contrast
George, 2008	USA	NIH-AARP Diet and Health Study	1041	~8	0.85	0.70	1.04	≥56.56 vs. ≤50.43 units/day
Cust, 2007	Europe	European Prospective Investigation into Cancer and Nutrition	710	6.4	1.04 1.01 1.03	0.84 0.92 0.82	1.28 1.12 1.30	≥58.4 vs. <53.4 units/d Per 5 units, uncalibrated Per 5 units, calibrated
Larsson, 2006	Sweden	Swedish Mammography Cohort	608	15.6	1.00	0.77	1.30	85.5 vs. 73.9 units/day

Table 41 Overall evidence on glycaemic index and endometrial cancer

	Summary of evidence
2005 SLR 2005	Two cohort studies reported on glycaemic index intake and endometrial cancer and both found no significant association.
Continuous Update Project	Three cohort studies reported on glycaemic index and endometrial cancer and showed no significant association.

Table 42 Summary of results of the dose-response meta-analysis of glycaemic index and endometrial cancer

Endometrial cancer		
	SLR 2005*	Continuous Update Project
Studies (n)	-	5
Cases (n)	-	3200
RR (95% CI)	-	0.99 (0.90-1.10)
Quantity	-	Per 10 units/day
Heterogeneity (I^2, p-value)	-	27.7%, p=0.24

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

Table 43 Inclusion/exclusion table for meta-analysis of glycaemic index and endometrial cancer

WCRF code	Author	Year	Study design	Study name	Cancer outcome	SLR 2005	CU dose-response	CU H vs. L forest plot	Estimated values	Exclusion reason
END00260	George	2008	Prospective cohort study	NIH-AARP Diet and Health Study	Incidence	No	Yes	Yes	Midpoints, person-years, distribution of cases	
END00225	Cust	2007	Prospective cohort study	European Prospective Investigation into Cancer and Nutrition	Incidence	No	Yes	Yes	Midpoints	
END00243	Larsson	2006	Prospective cohort study	Swedish Mammography Cohort study	Incidence	No	Yes	Yes		
END00201	Silvera	2005	Prospective cohort study	Canadian National Breast Screening Study	Incidence	Yes	Yes	Yes	Midpoints	
END00064	Folsom	2003	Prospective cohort study	Iowa Women's Health Study	Incidence	Yes	Yes	Yes	Midpoints, person-years	

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

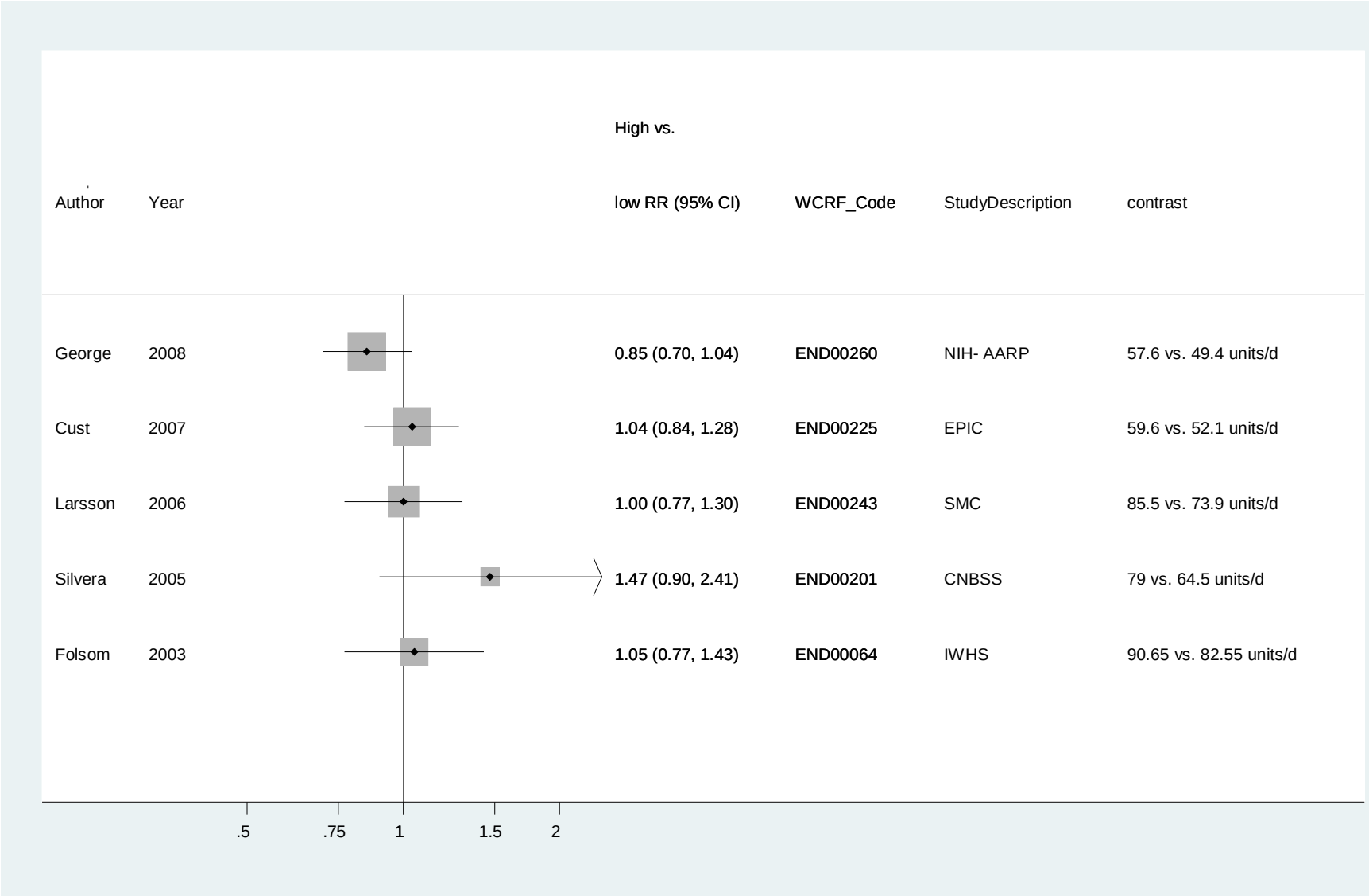


Figure 31 Dose-response meta-analysis of glycaemic index and endometrial cancer, per 10 units/d

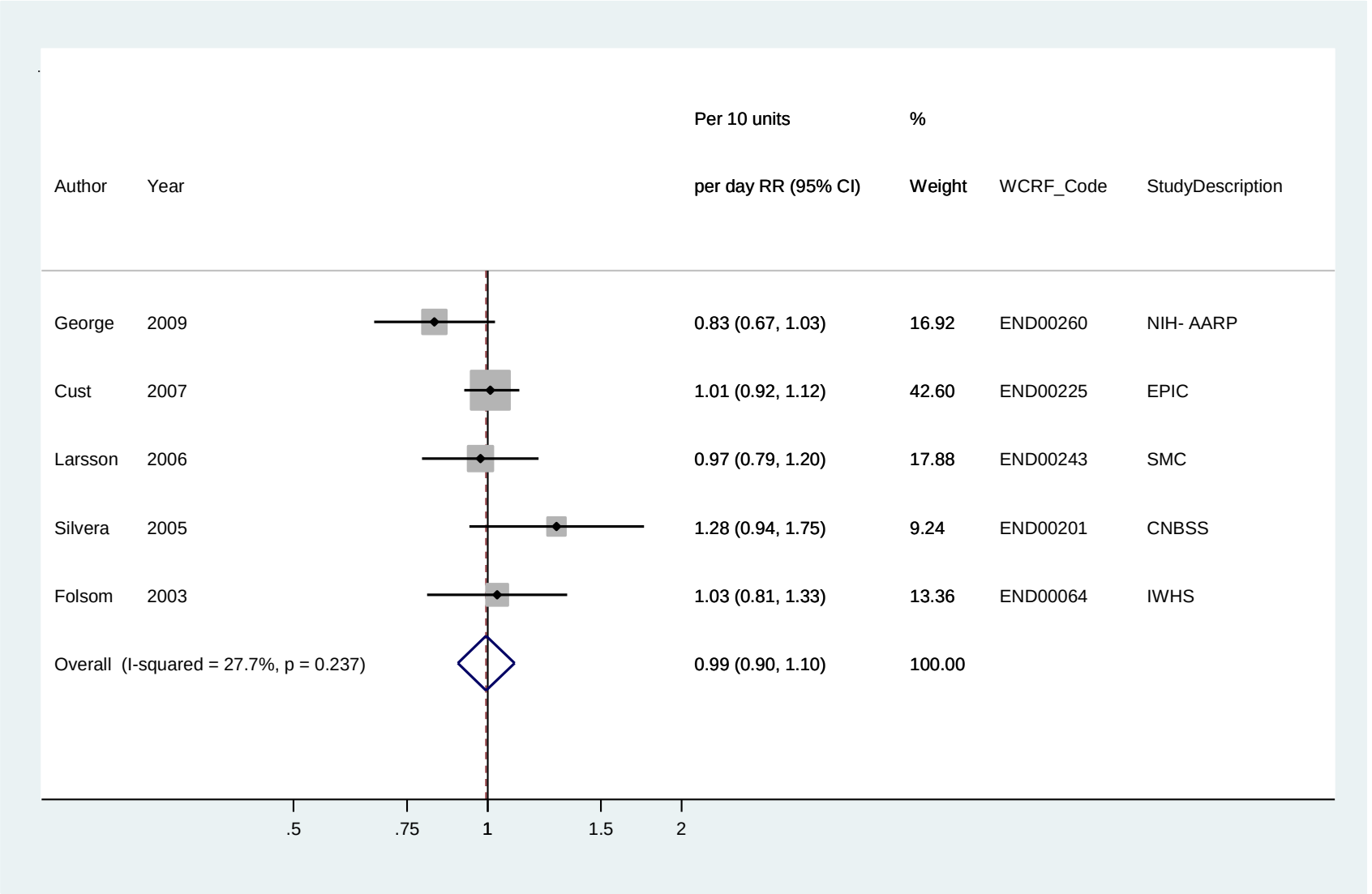


Figure 32 Funnel plot of glycaemic index and endometrial cancer

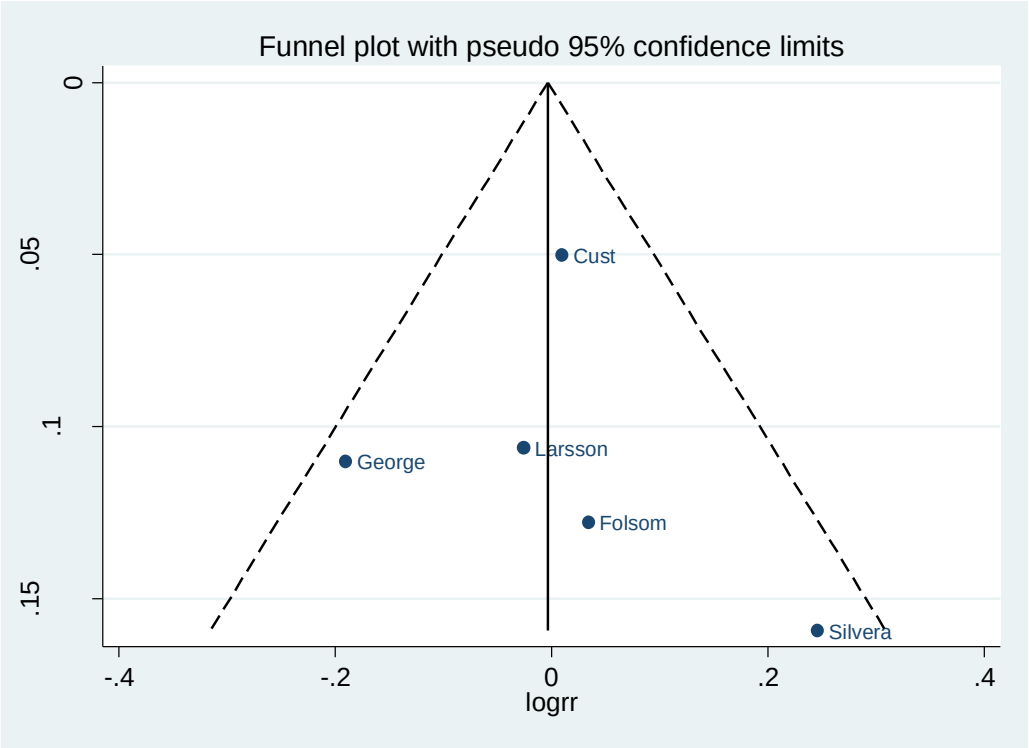
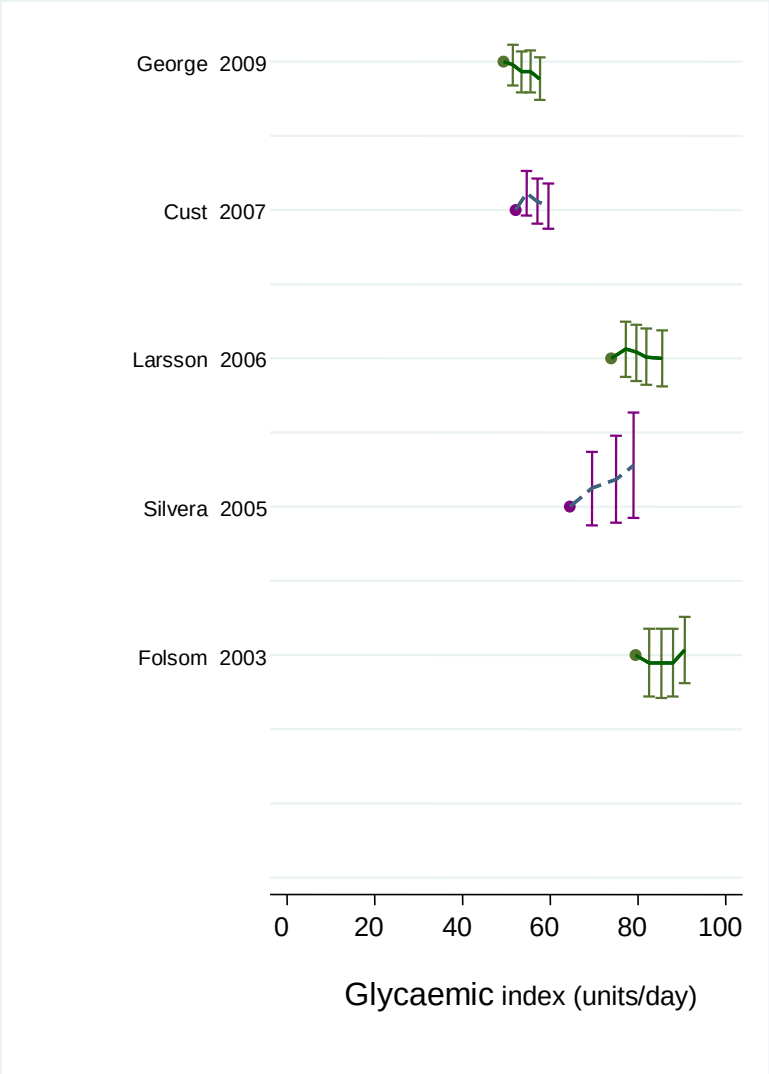


Figure 33 Dose-response graph of glycaemic index and endometrial cancer



5.1.6 Glycaemic load

Methods
A total of 6 cohort studies have been published on glycaemic load and endometrial cancer risk up to 2012, four of which were identified in the CUP. Dose-response analyses were conducted per 50 units/day.

Main results
The summary RR per 50 units/day of glycaemic load was 1.15 (95% CI: 1.06-1.25, I^2=0%, $p_{heterogeneity}$=0.86, n=6). There was no evidence of publication bias with Egger's test, p=0.13.

One study (NHS,Cui et al, 2011) , reported that the association with glycaemic load was stronger in premenopausal women . In the CBCSS (Silvera et al,2006) the association was more evident in overweight and obese women, pre-menopausal and inactive, and among postmenopausal women,in ever hormone users (although no significant). In the SMC the association was more evident in obese and inactive women (Larsson et al, 2006).

Heterogeneity
There was no evidence of heterogeneity, I^2=0%, $p_{heterogeneity}$=0.86.

Published meta-analyses

A meta-analysis of six cohort studies and two case-control studies found a significant positive association overall (high vs. low comparison), summary RR=1.21 (95% CI: 1.09-1.33) and among cohort studies, summary RR=1.22 (95% CI: 1.09-1.37), but not among the two case-control studies, summary RR=1.14 (95% CI: 0.91-1.44) (Nagle et al, 2012).

A meta-analysis of five cohort studies and two case-control studies found a positive association overall, summary RR=1.19 (95% CI: 1.06-1.34), and among cohort studies, summary RR=1.21(95% CI: 1.07-1.36), but not among the case-control studies, summary RR=1.04 (95% CI: 0.72-1.51) (Galeone et al, 2012).

A meta-analysis of four cohort studies and one case-control study found a significant positive association overall, summary RR=1.36 (95% CI: 1.14-1.62) (Gnagnarella et al, 2008).

Conclusion from the Second Expert Report

In the SLR of the 2007 Expert Report the evidence relating glycaemic load to endometrial cancer risk was limited and no conclusion was possible.

Table 44 Studies on glycaemic load intake identified in the CUP

Author/year	Country	Study name	Cases	Years of follow-up	RR	LCI	UCI	Contrast
Cui, 2011	USA	Nurses' Health Study	669	26	1.29	0.99	1.67	118.3 vs. 72.8 units/day
George, 2009	USA	NIH-AARP Diet and Health Study	1041	~8	1.25	0.86	1.81	≥135.31 vs. ≤66.91 units/day
Cust, 2007	Europe	European Prospective Investigation into Cancer and Nutrition	710	6.4	1.15 1.14 1.40	0.94 0.96 0.99	1.41 1.34 1.99	≥158 vs. <98 units/day Per 50 units/d, uncalibrated Per 50 units/d, calibrated
Larsson, 2006	Sweden	Swedish Mammography Cohort	608	15.6	1.15	0.88	1.51	210 vs. 155 units/day

Table 45 Overall evidence on glycaemic load and endometrial cancer

	Summary of evidence
2005 SLR 2005	Two cohort studies reported on glycaemic load intake and endometrial cancer and one found a significant positive association and the other found a non-significant positive association
Continuous Update Project	Four cohort studies reported on glycaemic load and endometrial cancer and showed no significant association.

Table 46 Summary of results of the dose-response meta-analysis of glycaemic load and endometrial cancer

Endometrial cancer		
	SLR 2005*	Continuous Update Project
Studies (n)	-	6
Cases (n)	-	3869
RR (95% CI)	-	1.15 (1.06-1.25)
Quantity	-	Per 50 units/day
Heterogeneity (I^2, p-value)	-	0%, p=0.86

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

Table 47 Inclusion/exclusion table for meta-analysis of glycaemic load and endometrial cancer

WCRF code	Author	Year	Study design	Study name	Cancer outcome	SLR 2005	CU dose-response	CU H vs. L forest plot	Estimated values	Exclusion reason
END00261	Cui	2011	Prospective cohort study	Nurses' Health Study	Incidence	No	Yes	Yes	Person-years	
END00260	George	2009	Prospective cohort study	NIH-AARP Diet and Health Study	Incidence	No	Yes	Yes	Midpoints, person-years, distribution of cases	
END00225	Cust	2007	Prospective cohort study	European Prospective Investigation into Cancer and Nutrition	Incidence	No	Yes	Yes	Midpoints	
END00243	Larsson	2006	Prospective cohort study	Swedish Mammography Cohort study	Incidence	No	Yes	Yes		
END00201	Silvera	2005	Prospective cohort study	Canadian National Breast Screening Study	Incidence	Yes	Yes	Yes	Midpoints	
END00064	Folsom	2003	Prospective cohort study	Iowa Women's Health Study	Incidence	Yes	Yes	Yes	Midpoints, person-years	

Figure 34 Highest versus lowest forest plot of glycaemic load and endometrial cancer

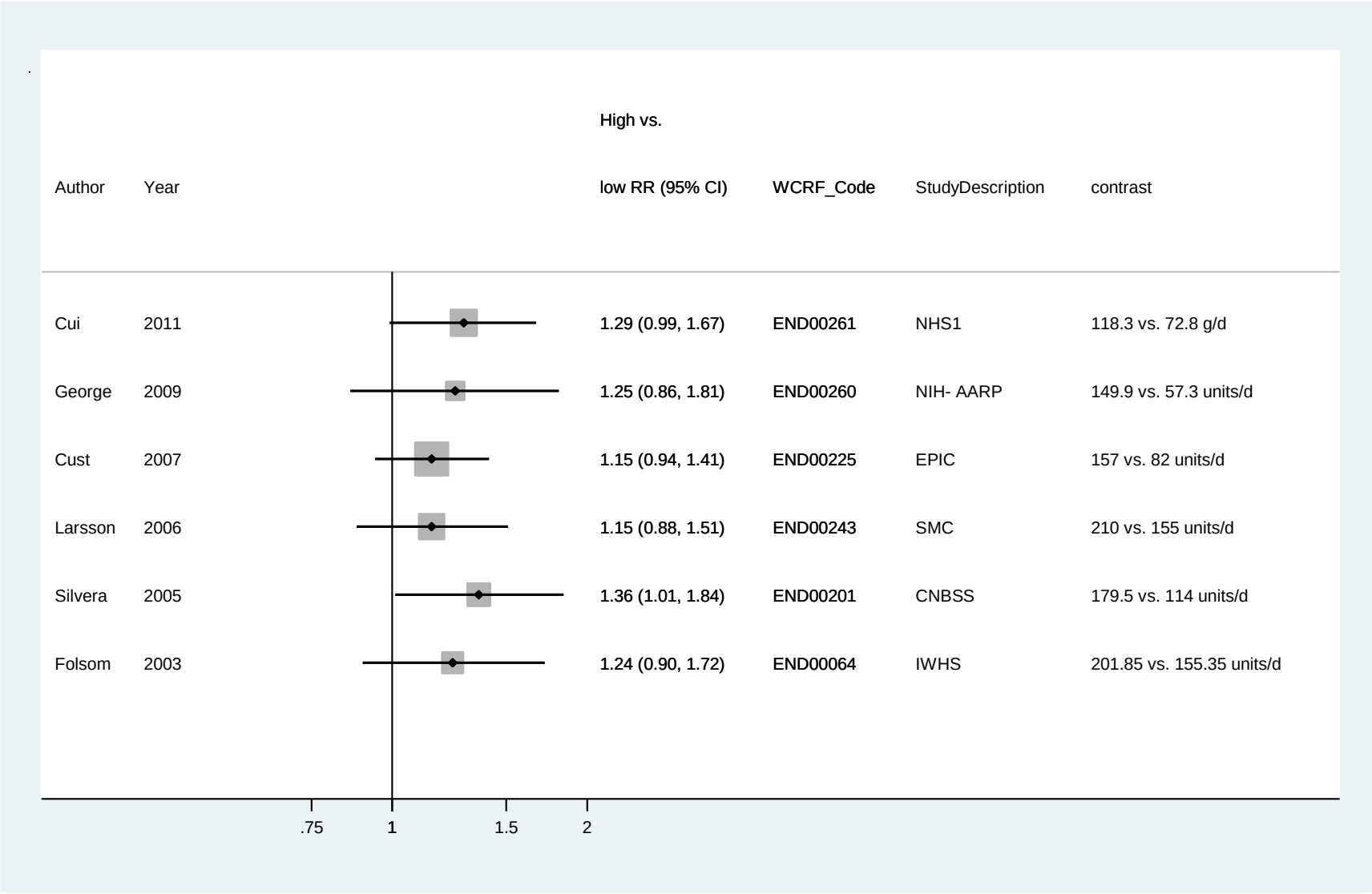


Figure 35 Dose-response meta-analysis of glycaemic load and endometrial cancer, per 50 units/day

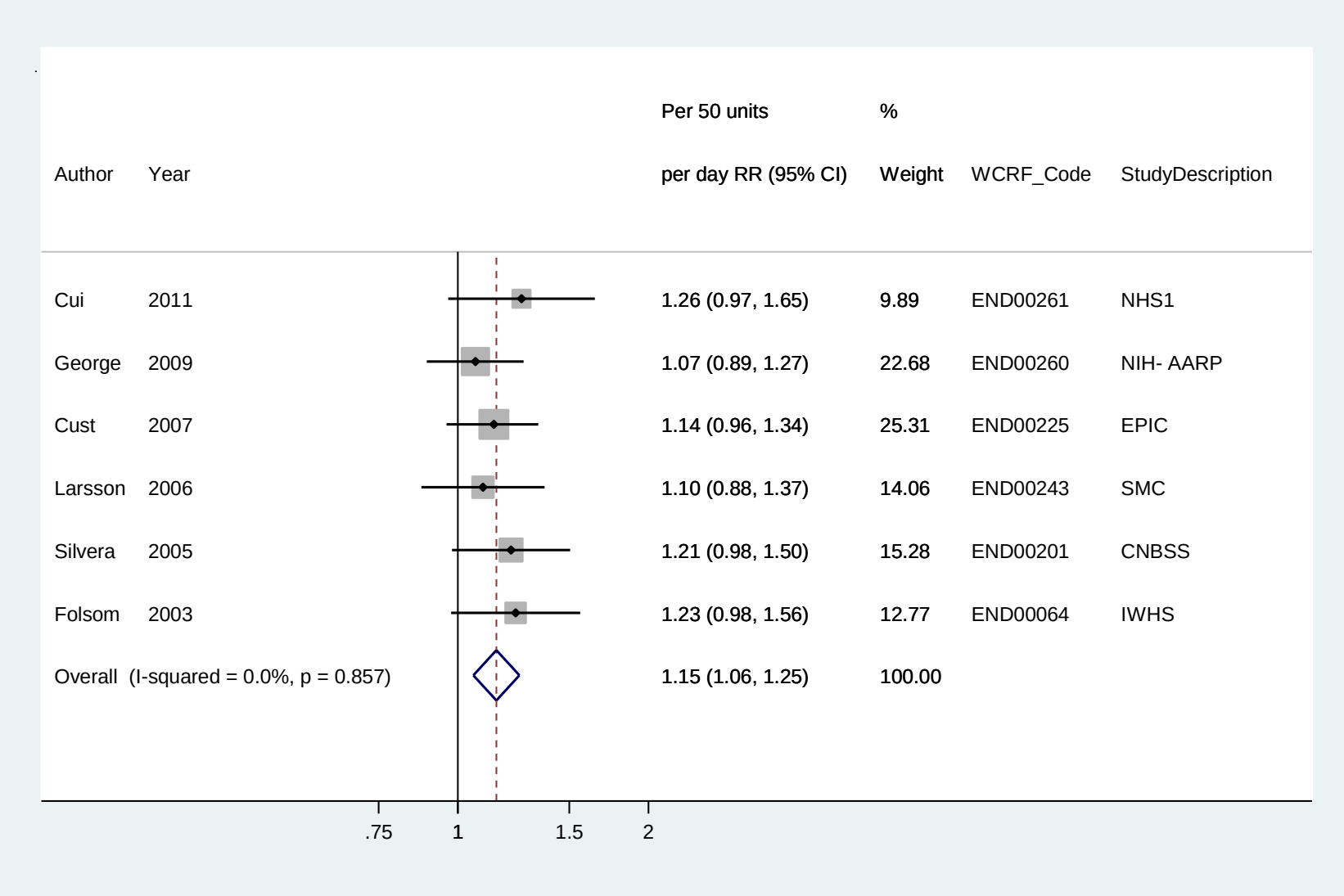


Figure 36 Funnel plot of glycaemic load and endometrial cancer

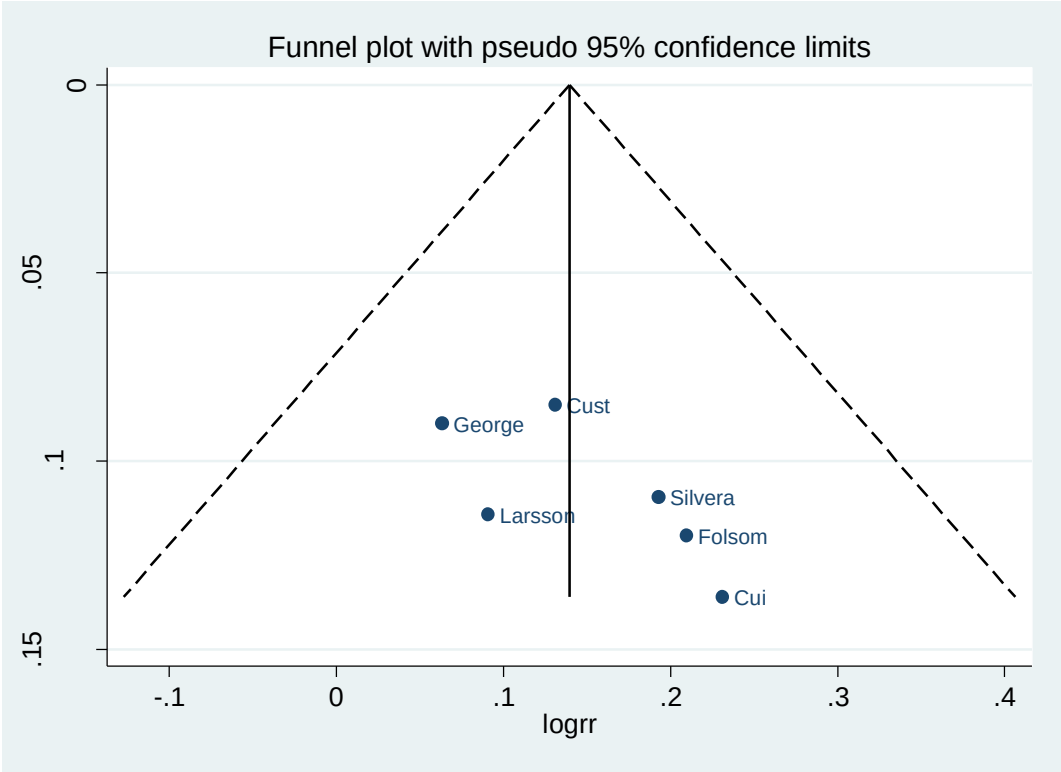


Figure 37 Dose-response graph of glycaemic load and endometrial cancer

5.1.2 Fibre

Methods
A total of 4 cohort studies have been published on fibre and endometrial cancer risk up to 2012, 3 of which were identified in the CUP. Dose-response analyses were conducted per 10 grams per day.

Main results
The summary RR per 10 grams of fibre per day was 1.09 (95% CI: 1.01-1.17, I^2=0%, $p_{heterogeneity}$=1.00, n=3).

Heterogeneity
There was no evidence of heterogeneity, I^2=0%, $p_{heterogeneity}$=0.99.

Conclusion from the Second Expert Report

In the systematic review of the 2007 expert report the evidence relating fibre intake to endometrial cancer risk was limited and no conclusion was possible.

Published meta-analyses

A meta-analysis based on the SLR of the Second Expert Report including one cohort study and 8 case-control studies found a summary RR of 0.71 (95% CI: 0.0.59-0.85) for high versus low fibre intake among case-control studies. The summary RR per 5 g/1000 kcal was 0.82 (95% CI: 0.75-0.90) with no evidence of heterogeneity, I^2=0%, $p_{heterogeneity}$=0.55 (Bandera et al, 2007). The only prospective study found no association, RR=1.15 (95% CI: 0.89-1.49) per 5 g/1000 kcal.

Table 48 Table Studies on fibre identified in the CUP

Author/year	Study name	Number of cases	Years of follow-up	RR	LCI	UCI	Comparison
Aarestrup, 2012	Diet, Cancer and Health cohort	217	13.5	1.23 1.04	0.75 0.90	2.02 1.19	>24 vs. ≤17 g/d Per 5 g/d
Cui, 2011	Nurses' Health Study	669	26	1.21	0.94	1.57	21.3 vs. 10.7 g/d
Cust, 2007	EPIC study	710	6.4	1.13 1.08 1.27	0.91 0.95 0.99	1.40 1.22 1.63	Quartile 4 vs. 1 Per 10 g/d, uncalibrated Per 10 g/d, calibrated

Table 49 Table Overall evidence on fibre and endometrial cancer

SLR	Summary of evidence
2005 SLR	One cohort study reported on fibre and endometrial cancer and found no association. Three out of six case-control studies reported significant inverse associations.
Continuous update	Three additional cohort studies reported on fibre intake and endometrial cancer and reported non-significant positive associations.

Table 50 Table Summary of results of the dose-response meta-analysis of fibre and endometrial cancer

Endometrial cancer		
	2nd Report	Updated meta-analysis
Studies (n)	-	3
Cases (n)	-	1600
RR (95% CI)	-	1.09 (95% CI: 1.01-1.17)
Quantity	-	Per 10 g/d
Heterogeneity (I^2, p-value)	-	0%, p=0.99

Table 51Table Inclusion/exclusion table for meta-analysis of fibre and endometrial cancer

WCRF code	Author	Year	Study design	Study name	Cancer outcome	SLR	CU dose-response	CU H vs. L forest plot	Estimated values	Exclusion reason
END00291	Aarestrup	2012	Prospective cohort study	The Diet, Cancer and Health Study	Incidence	No	No	No		Overlap with Cust et al, 2007 (END00225)
END00261	Cui	2011	Prospective cohort study	Nurses' Health Study	Incidence	No	Yes	Yes	Person-years	
END00225	Cust	2007	Prospective cohort study	EPIC study	Incidence	No	Yes	Yes		
END00009	Jain	2000	Case cohort study	Canadian National Breast Screening Study	Incidence	Yes	Yes	Yes	Midpoints, distribution of cases and person-years	

Figure 38 Figure Highest versus lowest forest plot of fibre and endometrial cancer

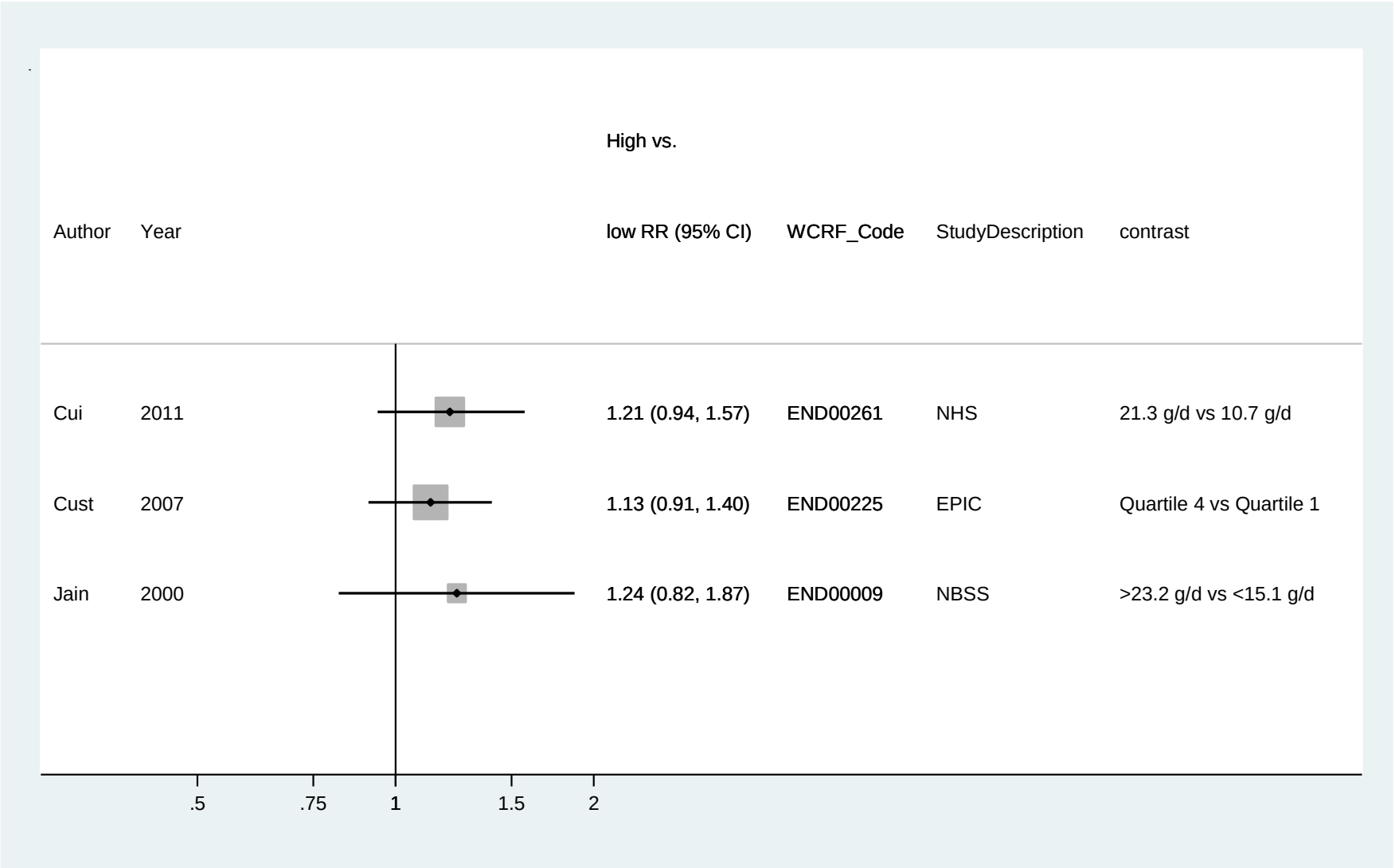


Figure 39 Figure Dose-response meta-analysis of fibre and endometrial cancer, per 10 g/d

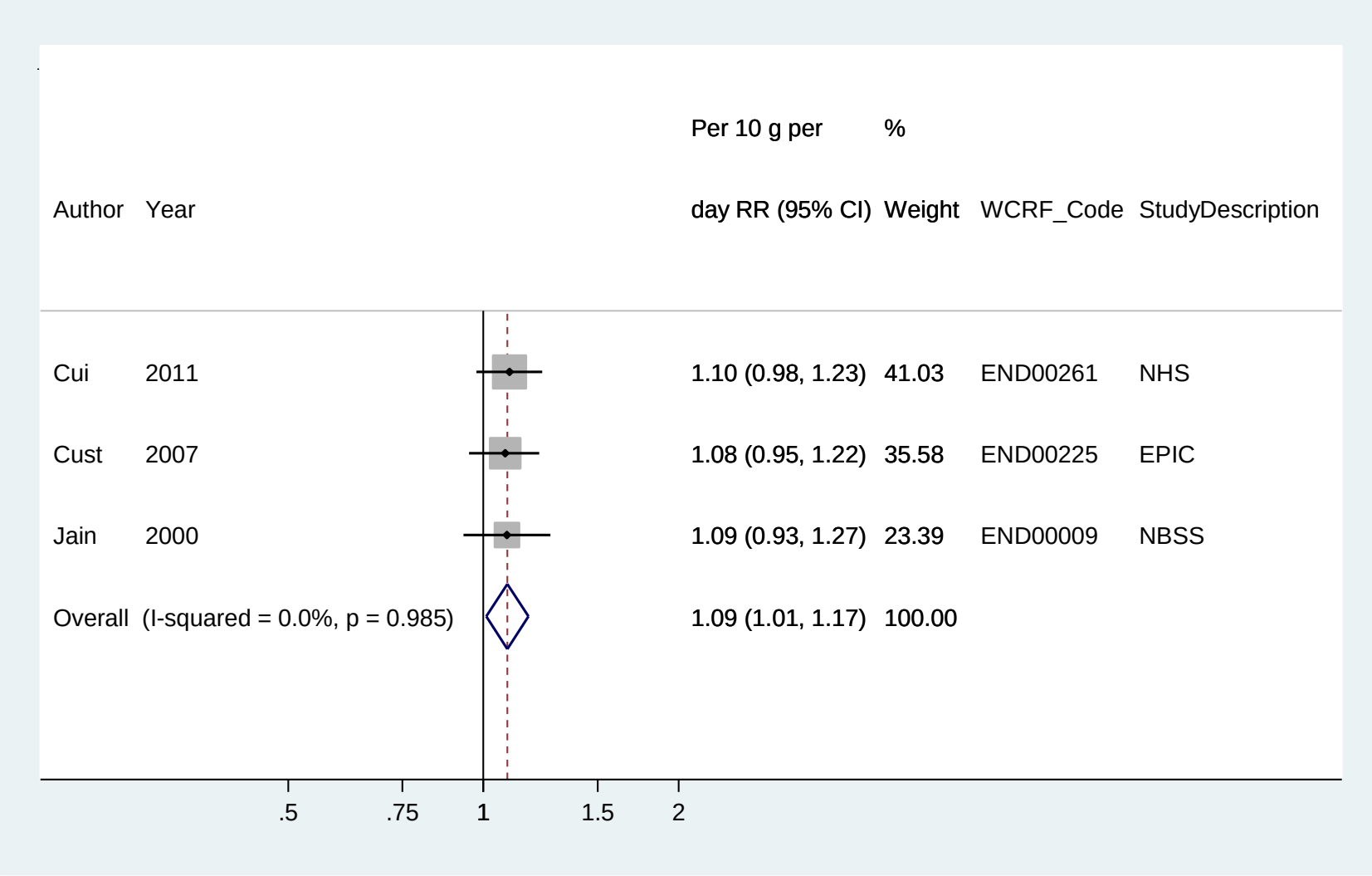
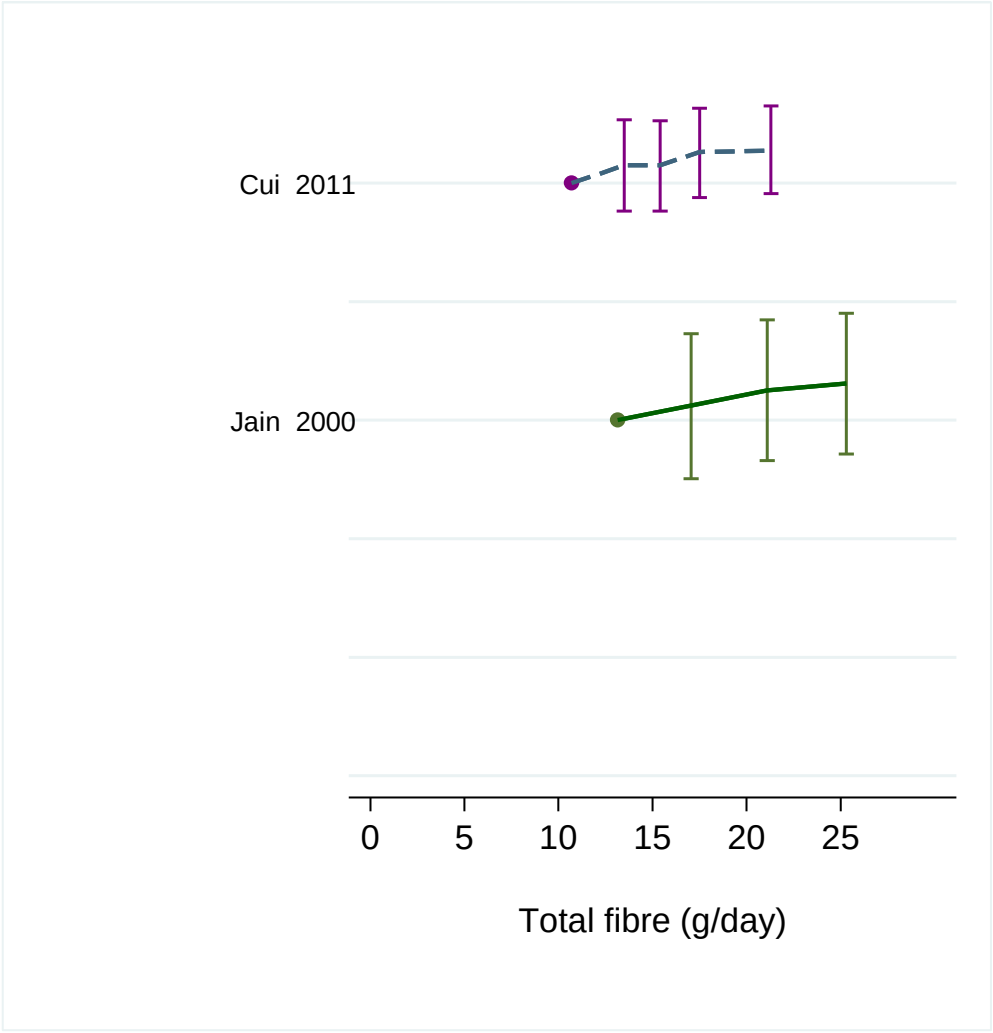


Figure 40 Figure Dose-response graph of fibre and endometrial cancer



5.2.1 Total Fat

Methods

Up to December 2012, reports from three cohort studies were identified; one of them was identified during the CUP. The CUP meta-analysis included three studies. The dose-response results are presented for an increment of 10 grams of total fat per day.

One of the studies identified during the 2005 SLR and included in the meta-analysis (Furberg, 2003) presented only age-adjusted results.

Main results

The summary RR per 10 grams per day was 1.00 (95% CI: 0.96-1.04; I^2= 68.7%, $P_{heterogeneity}$=0.04).

Heterogeneity

There was high heterogeneity across the limited number of published studies (I^2=68.7%, p=0.04).

Comparison with the Second Expert Report

Two studies were identified during the SLR 2005 (Jain, 2000 and Furberg, 2003). These studies showed no association between total fat intake and endometrial cancer

Published meta-analysis

A meta-analysis of seven case-control studies (Bandera, 2007) showed a RR of 1.24 (95% CI: 1.10- 1.41; I^2= 58.8%; $P_{heterogeneity}$ =0.03) per 10% kcal from total fat. After excluding studies that did not adjust for total energy intake, there was still suggestion of an association and no evidence of heterogeneity (RR=1.17; 95% CI: 1.08-1.28; I^2= 0.0%; $P_{heterogeneity}$ =0.67).

Table 52 Studies on total fat intake identified in the CUP

Author, year	Country	Study name	Cases	Years of follow up	RR	LCI	UCI	Contrast
Cui, 2011	USA	Nurses' Health Study	669	~26	1.17	0.91	1.49	75.4 g/d vs 50.0 g/d

Table 53 Overall evidence on total fat intake and endometrial cancer

	Summary of evidence
SLR	Two studies were identified during the SLR, showing no association between total fat intake and endometrial cancer
Continuous Update Project	One cohort study was identified and could be included in the meta-analysis. Overall, three studies were included in the CUP meta-analysis

Table 54 Summary of results of the dose response meta-analysis of total fat intake and endometrial cancer

Endometrial cancer		
	SLR*	Continuous Update Project
Studies (n)	-	3
Cases (n)	-	1020
Increment unit used	-	Per 10g/day
Overall RR (95%CI)	-	1.00 (0.96-1.04)
Heterogeneity (I^2,p-value)	-	67.8%, p=0.04

*No meta-analysis for cohort studies was conducted in the second report

Table 55 Inclusion/exclusion table for meta-analysis of total fat intake and endometrial cancer

WCRF_ Code	Author	Year	Study Design	Study Name	Cancer Outcome	SLR	CUP dose-response meta-analysis	CUP HvL forest plot	Estimated values	Exclusion reasons
END00261	Cui	2011	Prospective Cohort study	Nurses' Health Study	Incidence	No	Yes	Yes	Person years	----
END00014	Furberg	2003	Prospective Cohort study	Norwegian National Health Screening Service	Incidence	Yes	Yes	No	Rescale continuous value	---
END00009	Jain	2000	Case Cohort Study	Canadian National Breast Cancer Screening Study	Incidence	Yes	Yes	Yes	Person years and mid-exposure values	----

Figure 41 Highest versus lowest forest plot of total fat intake and endometrial cancer

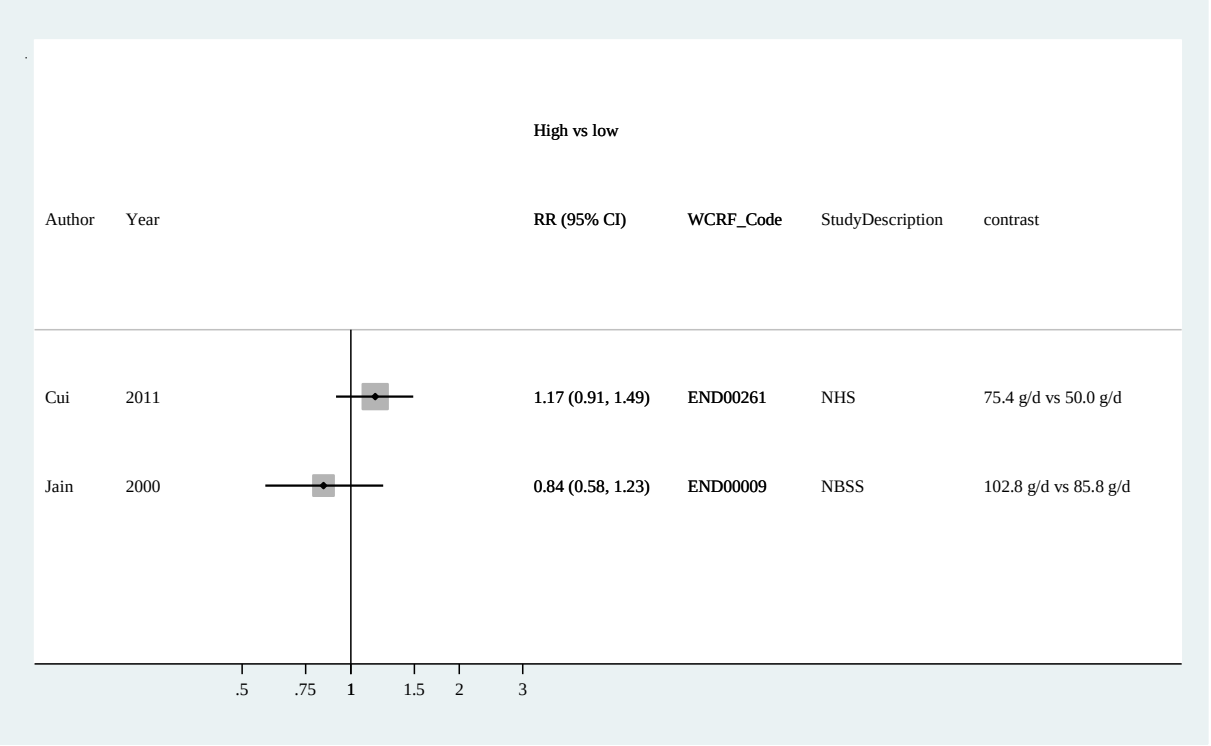


Figure 42 Dose-response meta-analysis of total fat and endometrial cancer - per 10 g/day

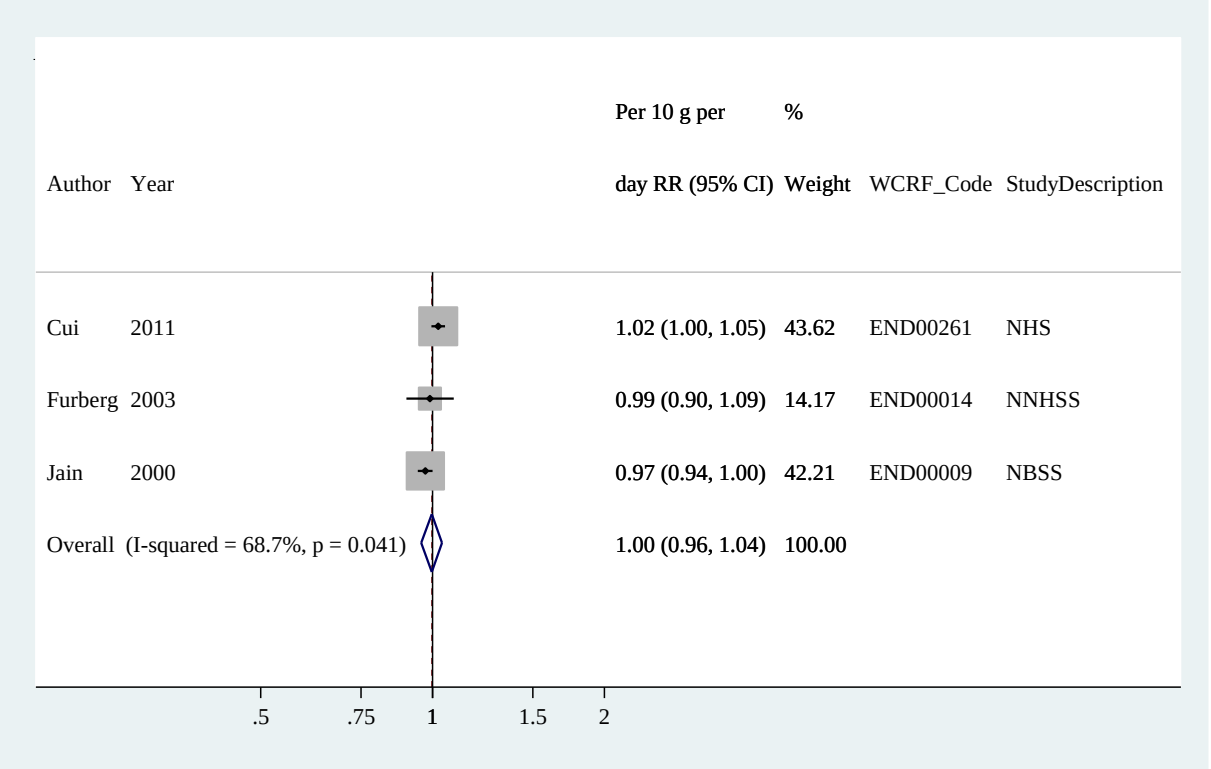
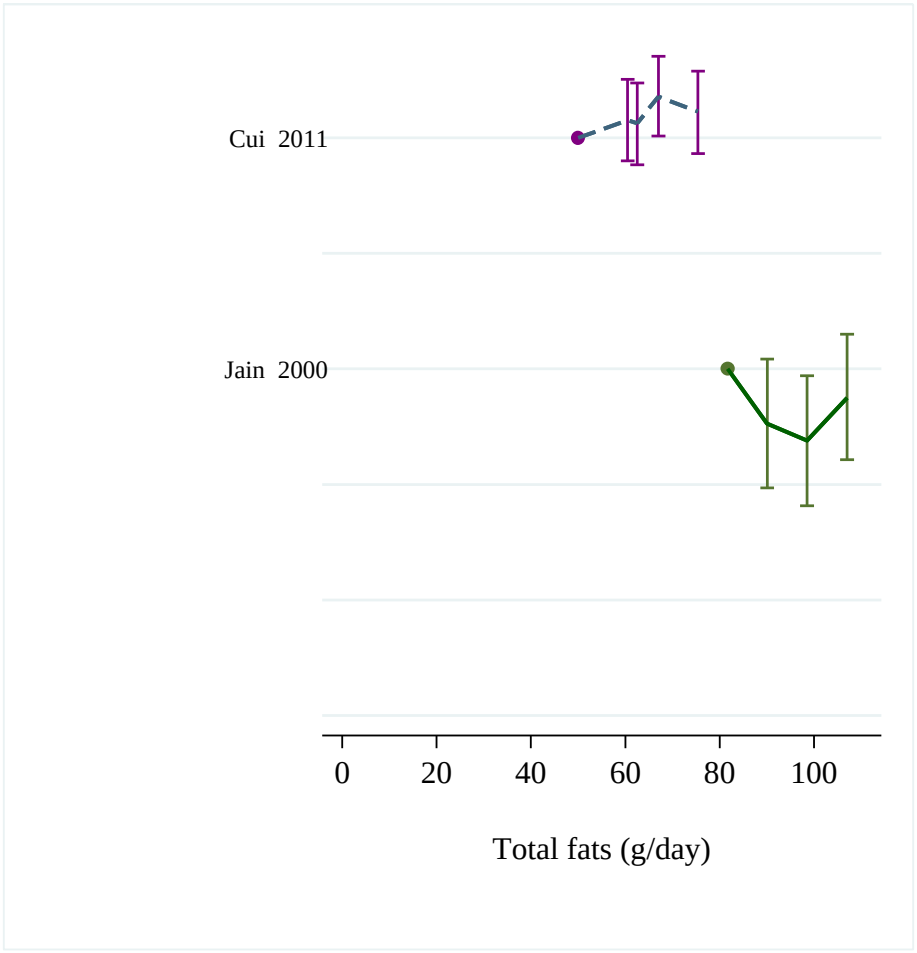


Figure 43 Dose-response graph of total fat and endometrial cancer



5.4.1 Alcohol (ethanol)

Methods

Up to December 2012, reports from ten cohort studies and 12 publications were identified; five of them were identified during the SLR 2005 and seven were identified during the CUP. The CUP meta-analysis included nine studies. Drinks per day were rescaled to g/day in one study using 13 grams of ethanol intake per drink. The dose-response results are presented for an increment of 10 grams of ethanol per day.

Main results

The summary RR per 10 g/d was 1.01 (95% CI: 0.97-1.06, I^2=29.0%, $P_{heterogeneity}$ =0.18) for all studies combined. In sensitivity analysis of the influence of individual studies, the summary RR ranged from 0.98 (95% CI: 0.95-1.02) when excluding the Multiethnic Cohort Study (Setiawan et al, 2008) to 1.03 (95% CI: 0.96-1.09) when excluding the EPIC Study (Fedirko et al, 2012).

There was no evidence of a nonlinear association. Restricted cubic splines were used to fit the data instead of fractional polynomial models because the latests were not robust.

In the NIH-AARP (Yang et al, 2011), there was some suggestion of higher risks associated with alcohol consumption among lean women (BMI, <25) (p interaction: 0.002). In contrast, significant inverse trends were observed among heavier women (p trend: 0.04). Alcohol intake was most clearly associated with increased endometrial cancer risk among postmenopausal hormone users in lean women; compared to non-drinkers, increased risk was observed for >0–12 g/day (RR = 1.33; 95% CI: 0.95–1.87), 12-<24 g/day (RR =1.60; 95% CI: 1.05–2.45) and >24 g/day (RR = 1.28; 95% CI: 0.73–2.23). Hormone use modified the association of alcohol intake with endometrial cancer (P interaction: 0.005). No association was observed in never-hormone-users, but there was some suggestion of positive association among postmenopausal hormone users.

In the SMC (Friberg et al, 2009) and in the MEC (Setiawan et al, 2008) postmenopausal hormone use did not modify the association of alcohol intake and endometrial cancer. In the MEC, the RR estimates were higher in hormone users than in non users, but the number of cases was very low (8 cases with >2 drinks/day)

Heterogeneity

There was evidence of low heterogeneity across the studies (I^2=29.0%, p=0.18). There was no indication of publication bias with Egger's test (p=0.24). The Multiethnic Cohort Study (Setiawan et al, 2008) was the only study reporting a positive significant association.

Conclusion from the Second Expert Report

Five publications from three cohorts were identified during the Second Expert Report. No meta-analysis was conducted in the Second Expert Report, only high versus low analysis.

Published meta-analysis

In a published meta-analysis (Sun et al, 2011), the summary RR of endometrial cancer for alcohol drinkers vs. non-drinkers was 1.04 (95% CI: 0.91-1.18, I^2= 6.93%, $P_{heterogeneity}$ =0.226) for six prospective studies and 0.89 (95% CI: 0.76-1.05, I^2= 50.73%, $P_{heterogeneity}$ =<0.001) for 14 case-control studies .

A meta-analysis comparing drinkers vs non-drinkers reported a summary RR of 1.01 (95% CI 0.90–1.14) for seven prospective studies and 0.90 (95% CI 0.80–1.01) for 20 case-control studies (Turati et al, 2010).

In another published meta-analysis (Friberg et al, 2010) of seven prospective studies, the summary RR for endometrial cancer was 1.17 (95% CI: 0.93-1.46, I^2= 50.0%, $P_{heterogeneity}$ =0.061) comparing highest versus lowest category of intake. There was evidence of a non-linear association. Women drinking less than one drink of alcohol (13 g of ethanol) per day had a lower risk for endometrial cancer. However, there was an increased risk for endometrial cancer for intakes higher than two alcoholic drinks per day: compared with non-drinkers, the risk was higher by 14% (95% CI: 0.95–1.36) for 2–2.5 drinks per day and by 25% (95% CI: 0.98–1.58) for more than 2.5 drinks per day.

In the CUP analysis, the non-linear association disappears after the inclusion of the results of EPIC (Fedirko et al, 2012) and the NIH-AARP (Yang et al, 2011) cohort studies in the meta-analysis.

Table 56 Studies on ethanol consumption identified in the CUP

Author, year	Country	Study name	Cases	Years of follow up	RR	LCI	UCI	Contrast
Fedirko, 2012	Europe	European Prospective Investigation into Cancer and Nutrition	1382	11	0.85	0.61	1.18	> 36 g/d vs non drinkers
Yang, 2011	USA	National Institute of Health - American Association of Retired Persons Diet and Health Study	1491	9.4	0.93	0.71	1.20	>= 24 g/d vs non drinkers
Friberg, 2009	Sweden	Swedish Mammography Study	687	17.6	1.09	0.71	1.68	>=10 g/d vs non drinkers
Allen, 2009	UK	The Million Women Study	4118	7.2	1.05 0.97	0.91 0.82	1.22 1.03	>=15 drinks/week vs non drinkers Per 10 g ethanol/day
Setiawan, 2008	USA	Multiethnic Cohort Study	324	8.3	2.01	1.30	3.11	>=24 g/d vs non drinkers
Kabat, 2008	Canada	Canada National Breast Screen Study	426	16.4	0.84	0.52	1.36	>=30 g/d vs non drinkers
Loerbroks, 2007	Netherlands	Netherlands Cohort Study	280	11.3	1.78	0.88	3.60	>=30 g/d vs non drinkers

Table 57 Overall evidence on ethanol consumption and endometrial cancer

	Summary of evidence
SLR 2005	Three cohort studies were identified, with a total of five publications. The highest vs lowest meta-analysis showed no association
Continuous Update Project	Seven additional publications were identified; only one study showed a positive association between ethanol consumption and endometrial cancer. A total of nine studies could be included in the dose-response meta-analysis.

Table 58 Summary of results of the dose response meta-analysis of ethanol consumption and endometrial cancer

Endometrial cancer		
	SLR 2005*	Continuous Update Project
Studies (n)	3	9
Cases (n)	726	8992
Increment unit used	Highest vs. lowest	Per 10g/day
Overall RR (95%CI)	1.00 (0.81, 1.24)	1.01 (0.97-1.06)
Heterogeneity (I^2,p-value)	0.0%, p=0.780	29.0%, p=0.18

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

Table 59 Inclusion/exclusion table for meta-analysis of ethanol consumption and endometrial cancer

WCRF_ Code	Author	Year	Study Design	Study Name	Cancer Outcome	SLR 2005	CUP dose-response meta-analysis	CUP HvL forest plot	Estimated values	Exclusion reasons
END00292	Fedirko	2012	Prospective Cohort study	European Prospective Investigation into Cancer and Nutrition	Incidence	No	Yes	Yes	Rescale continuous values	-
END00252	Yang	2011	Prospective Cohort study	National Institute of Health - American Association of Retired Persons Diet and Health Study	Incidence	No	Yes	Yes	Mid-points	-
END00217	Friberg	2009	Prospective Cohort study	Swedish Mammography Study	Incidence	No	Yes	Yes	Mid-points	-
END00248	Allen	2009	Prospective Cohort study	The Million Women Study	Incidence	No	Yes	Yes	-	-
END00222	Setiawan	2008	Prospective Cohort study	Multiethnic Cohort Study	Incidence	No	Yes	Yes	Person-years and mid-points per category	-
END00247	Kabat	2008	Prospective Cohort study	Canada National Breast Screen Study	Incidence	No	Yes	Yes	Person-years mid-points per category and cases number per category	-
END00224	Loerbroks	2007	Case Cohort Study	Netherlands Cohort Study	Incidence	No	Yes	Yes	-	-
END00201	Silvera	2005	Prospective Cohort study	Canada National Breast Screen Study	Incidence	Yes	No	No	-	Superseded by Kabat (END00247)

END00064	Folsom	2003	Prospective Cohort study	Iowa Women Health Study	Incidence	Yes	No	No	-	Two categories (yes vs no) Gapstur (END00041) was used instead
END00009	Jain	2000	Prospective Cohort study	Canada National Breast Screen Study	Incidence	Yes	No	No	-	Superseded by Kabat (END00247)
END00060	Terry	1999	Prospective Cohort study	Swedish Twin cohort	Incidence	Yes	Yes	Yes	Drinks rescaled to g/day. Mid-points	-
END00041	Gapstur	1993	Prospective Cohort study	Iowa Women Health Study	Incidence	Yes	Yes	Yes	Mid-points	-

Figure 44 Highest versus lowest forest plot of ethanol consumption and endometrial cancer

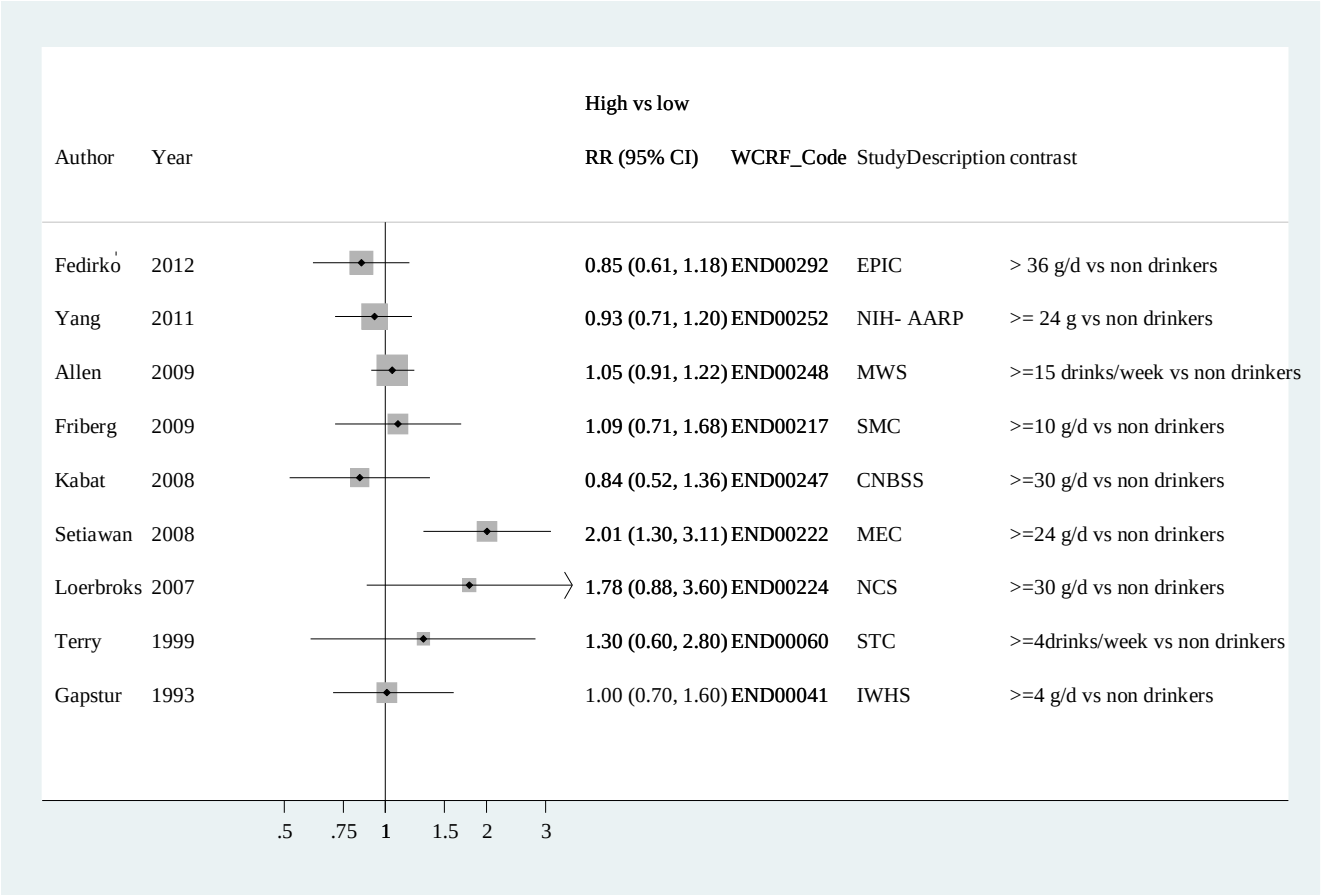


Figure 45 Dose-response meta-analysis of ethanol and endometrial cancer - per 10 g/day

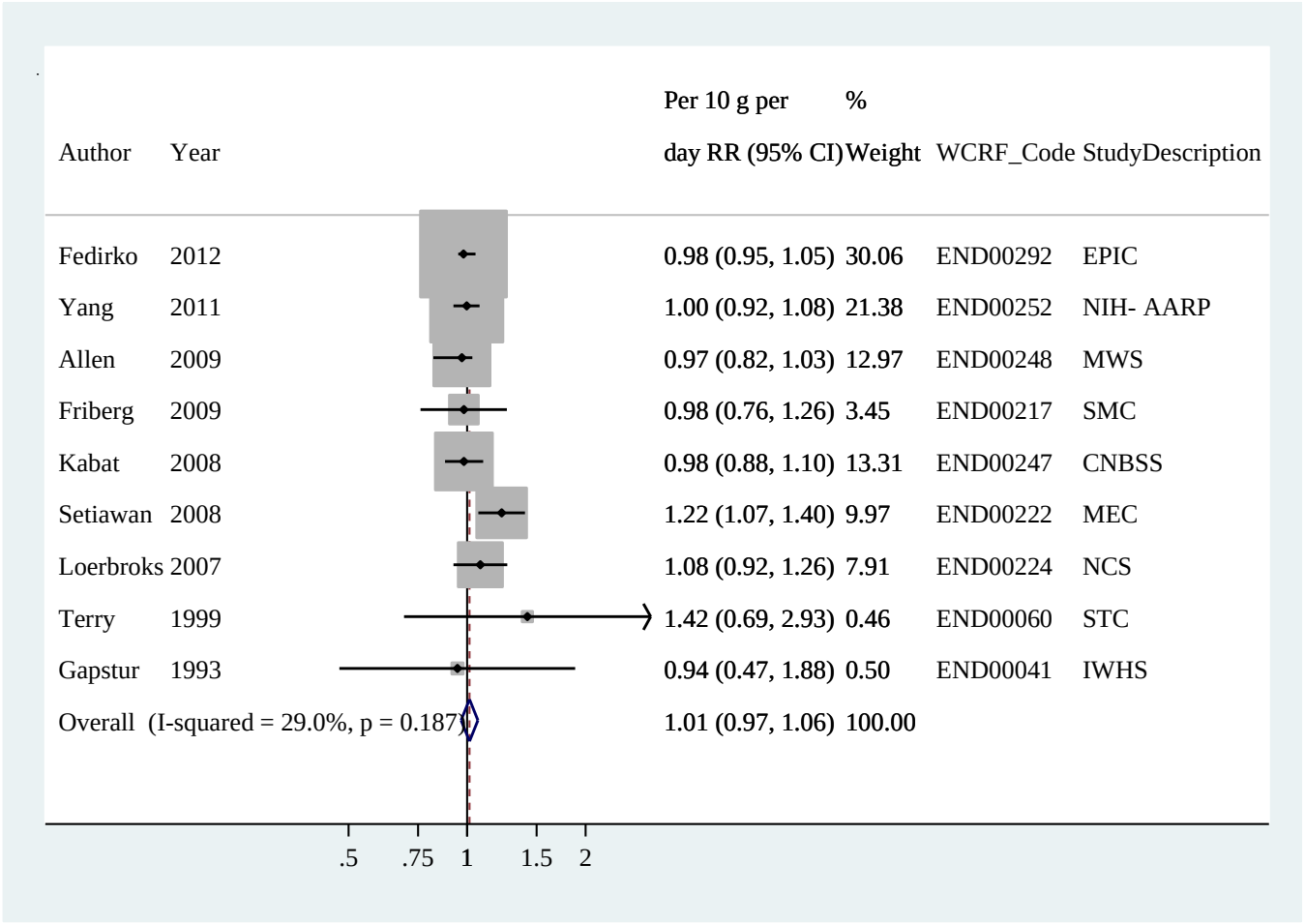


Figure 46 Funnel plot of ethanol consumption and endometrial cancer

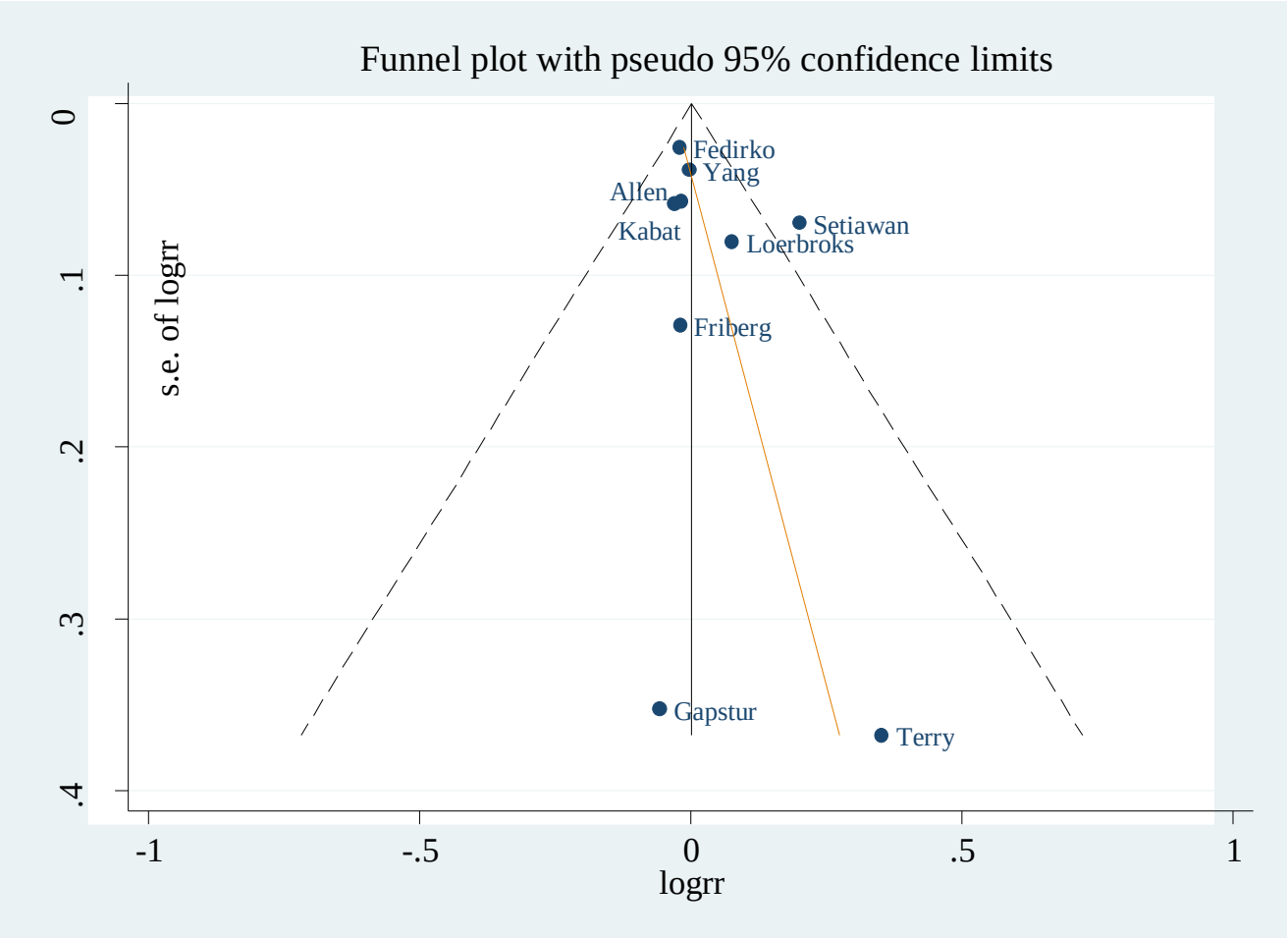


Figure 47 Dose-response graph of ethanol and endometrial cancer

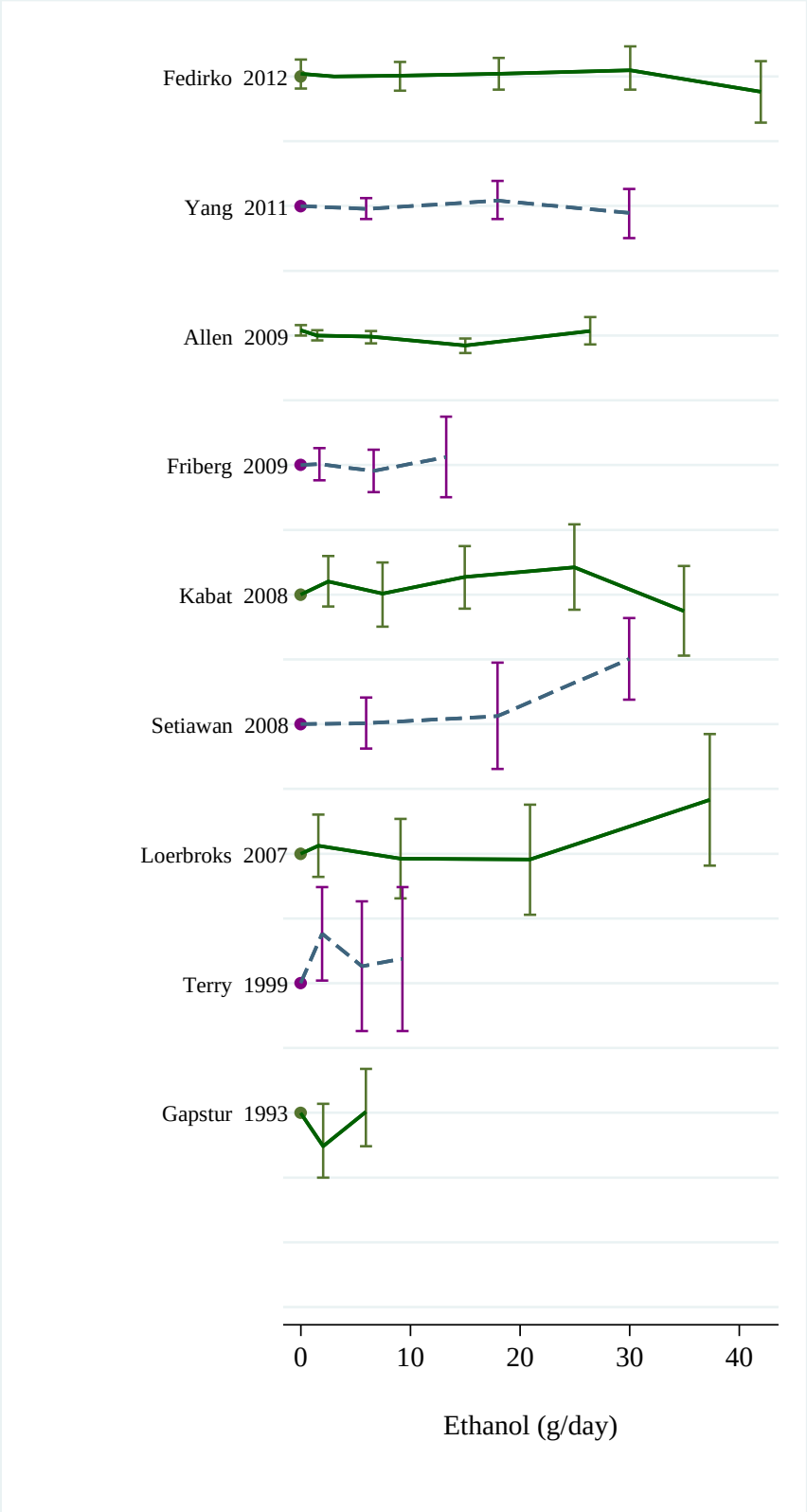


Figure 48 Nonlinear dose-response figure for total ethanol and endometrial cancer

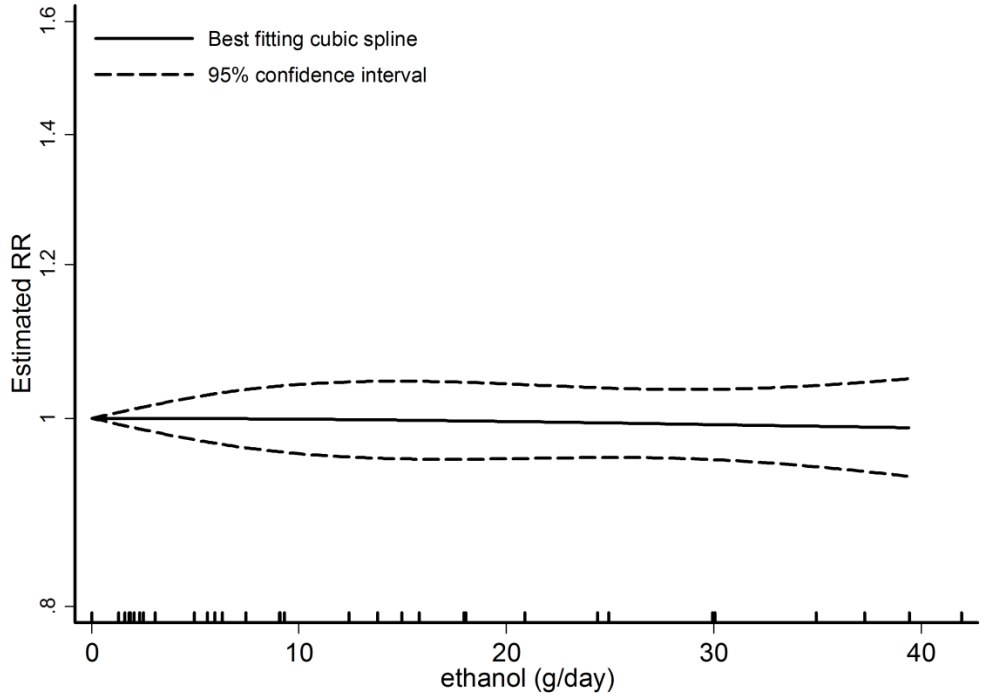
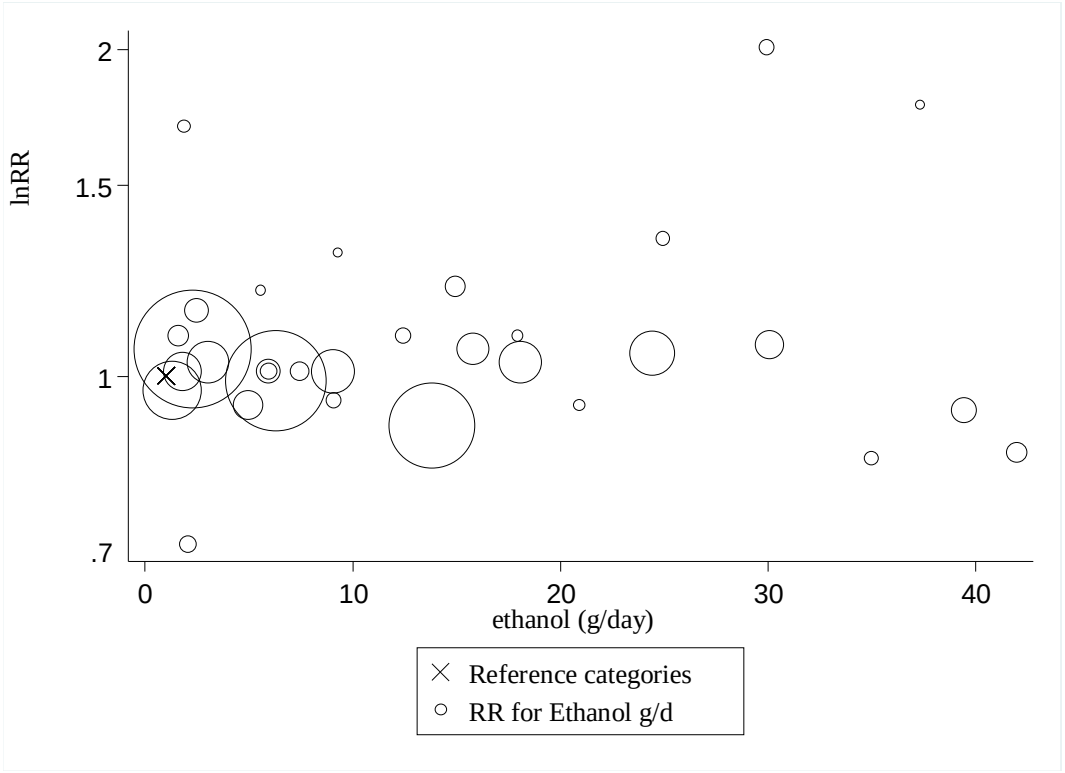


Figure 49Scatter plot of risk estimates for total ethanol and endometrial cancer



Explanation for nonlinear dose-response analyses

The nonlinear dose-response analyses was computed using the pool first command in Stata using the categorical risk estimates from each study included in the analysis. Several polynomial curves were tested, the program automatically selects the curve with the best fit. The dose-response relationship was also explored using a scatter plot. The relative risk estimates were plotted against the corresponding levels of the exposure (empty circles) compared with the reference category X. The area of the circles is proportional to the inverse of the variance and was used as weight. Larger studies with small variances are given more weight than small studies with large variances. Random effects models were used for the analysis.

Table 60 RRs (95% CIs) for nonlinear analysis of total ethanol and endometrial cancer

Ethanol (g/day)	RR (95% CI)
1.0	1.00
5.0	1.03 (0.98-1.08)
10.0	1.05 (0.96-1.14)
15.0	1.06 (0.95-1.18)
20.0	1.07 (0.94-1.21)
25.0	1.07 (0.93-1.23)
30.0	1.06 (0.90-1.24)
35.0	1.04 (0.86-1.26)

Figure 50 Dose-response meta-analysis of ethanol and endometrial cancer - per 10 g/day, stratified by hormone replacement therapy

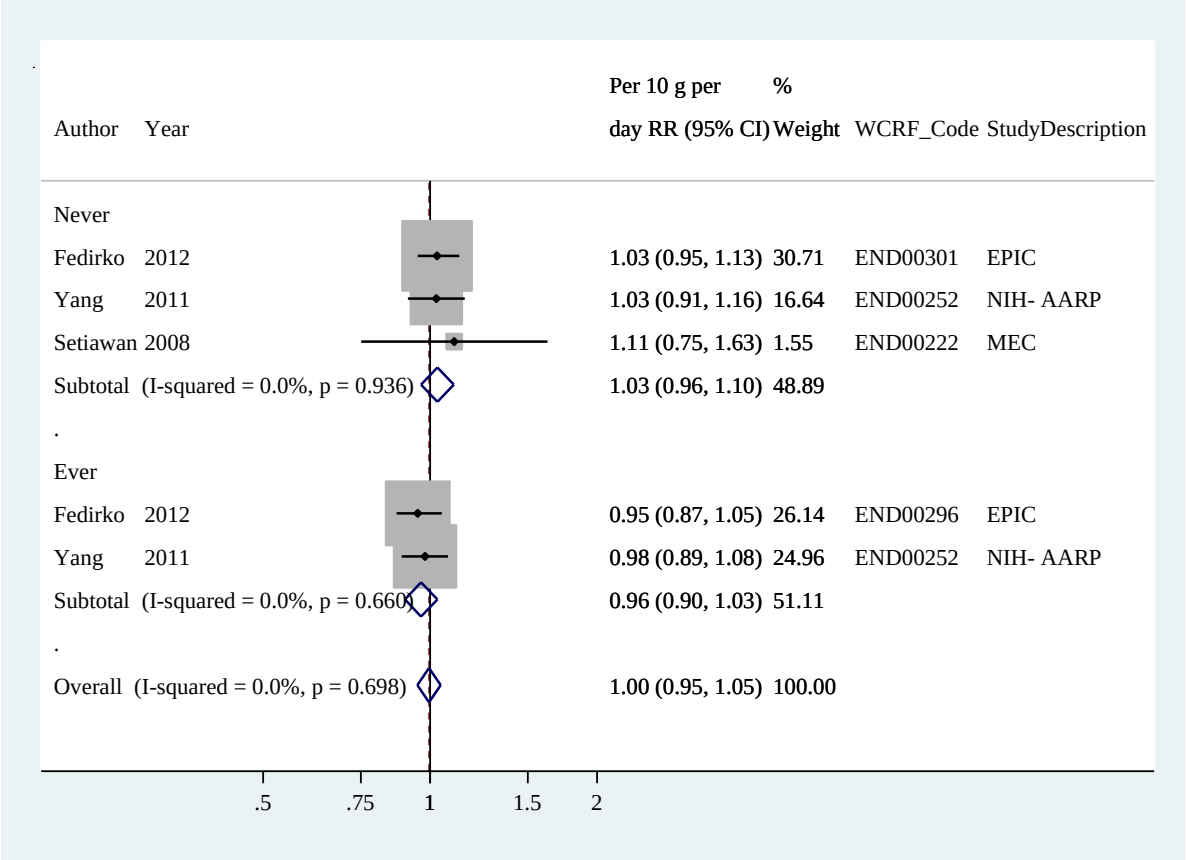
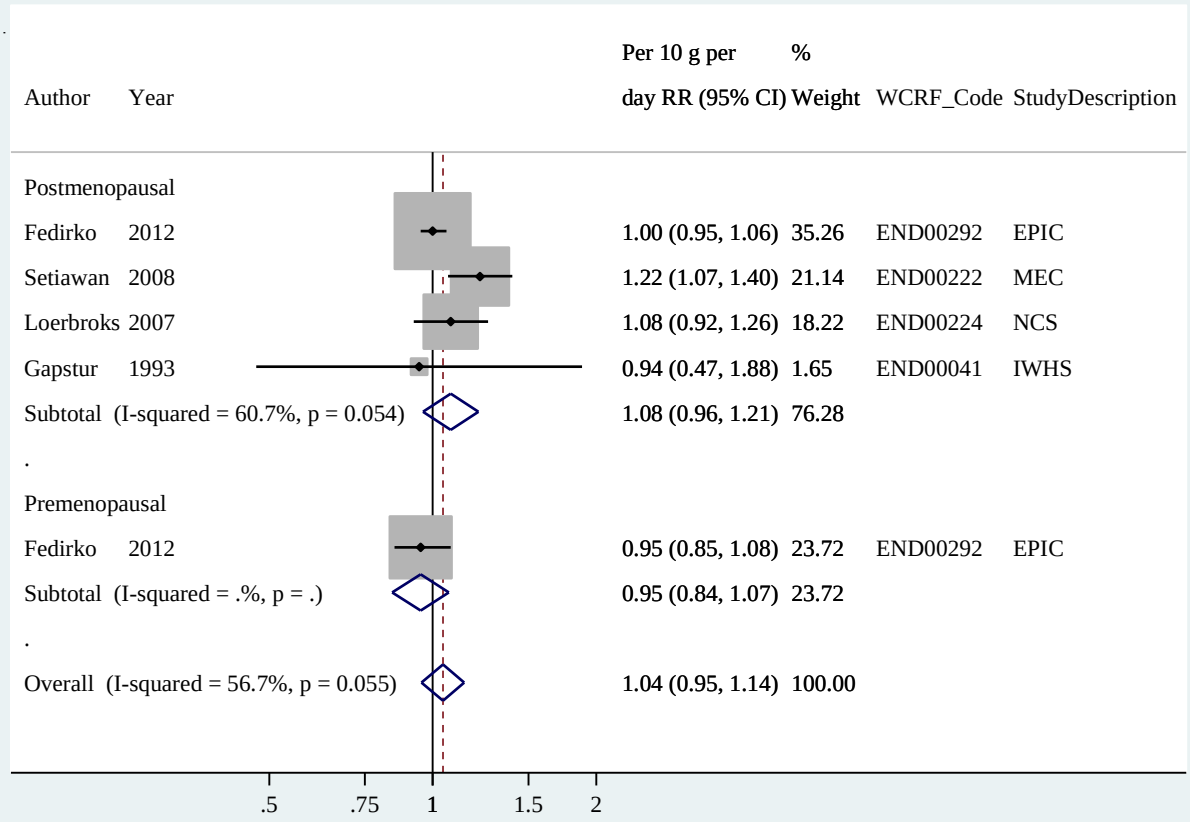


Figure 51 Dose-response meta-analysis of ethanol and endometrial cancer - per 10 g/day, stratified by menopausal status



5.4.1.1 Ethanol from beer

Methods

Up to December 2012, reports from five cohort studies were identified; all of them were identified during the CUP (including one paper missed by the SLR). The CUP meta-analysis included three studies. The dose-response results are presented for an increment of 10 grams of ethanol per day.

Main results

The summary RR per 10 grams per day was 1.02 (95% CI: 0.91-1.13; I^2= 0%, $P_{heterogeneity}$=0.36).

Heterogeneity

There was no evidence of heterogeneity across the limited number of published studies (I^2=0%, p=0.36).

Conclusion from the Second Expert Report

No study was found during the SLR 2005.

Published meta-analysis

In a published meta-analysis of three prospective and four case-control studies (Sun Q et al, 2011), the summary RR for endometrial cancer was 0.91 (95% CI: 0.75-1.11), among beer drinkers vs. non-drinkers.

Table 61 Studies on ethanol from beer intake identified in the CUP

Author, year	Country	Study name	Cases	Years of follow up	RR	LCI	UCI	Contrast
Fedirko, 2012	Europe	European Prospective Investigation into Cancer and Nutrition	1382	11	0.95	0.72	1.24	> 6 g/d vs non drinkers
Yang, 2011	USA	National Institute of Health - American Association of Retired Persons Diet and Health Study	1491	9.4	0.99	0.49	1.99	>=24 g/d vs non drinkers
Setiawan, 2008	USA	Multiethnic Cohort Study	324	8.3	1.46	0.52	4.12	>=24 g/d vs non drinkers
Loerbroks, 2007	Netherlands	Netherlands Cohort Study	280	11.3	1.30	0.82	2.07	Yes vs No
Gapstur, 1993*	USA	Iowa Women's Health Study	167	~4	0.70	0.30	1.60	>= 4 g/d vs non drinkers

*****missed by 2005 SLR

Table 62 Overall evidence on ethanol from beer intake and endometrial cancer

	Summary of evidence
SLR 2005	No study was identified during the SLR 2005 *
Continuous Update Project	Four cohort studies were identified; three of them could be included in the meta-analysis. None of the studies showed a significant association between ethanol from beer and endometrial cancer risk.

*One study was missed by the 2005 SLR

Table 63 Summary of results of the dose response meta-analysis of ethanol from beer intake and endometrial cancer

Endometrial cancer		
	SLR 2005*	Continuous Update Project
Studies (n)	-	3
Cases (n)	-	3197
Increment unit used	-	Per 10g/day
Overall RR (95%CI)	-	1.02 (0.91-1.13)
Heterogeneity (I^2,p-value)	-	0%, p=0.36

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

Table 64 Inclusion/exclusion table for meta-analysis of ethanol from beer intake and endometrial cancer

WCRF_ Code	Author	Year	Study Design	Study Name	Cancer Outcome	SLR 2005	CUP dose-response meta-analysis	CUP HvL forest plot	Estimated values	Exclusion reasons
END00292	Fedirko	2012	Prospective Cohort study	European Prospective Investigation into Cancer and Nutrition	Incidence	No	Yes	Yes	Rescale continuous values	
END00252	Yang	2011	Prospective Cohort study	National Institute of Health - American Association of Retired Persons Diet and Health Study	Incidence	No	Yes	Yes	Mid-exposure values	----
END00222	Setiawan	2008	Prospective Cohort study	Multiethnic Cohort Study	Incidence	No	Yes	Yes	Person years and mid-exposure values	----
END00224	Loerbroks	2007	Case Cohort Study	Netherlands Cohort Study	Incidence	No	No	Yes	-	Only two categories (yes vs no)
END00041	Gapstur	1993	Prospective Cohort study	Iowa Women Health Study	Incidence	No	No	Yes	-	Only two categories

Figure 52 Highest versus lowest forest plot of ethanol from beer intake and endometrial cancer

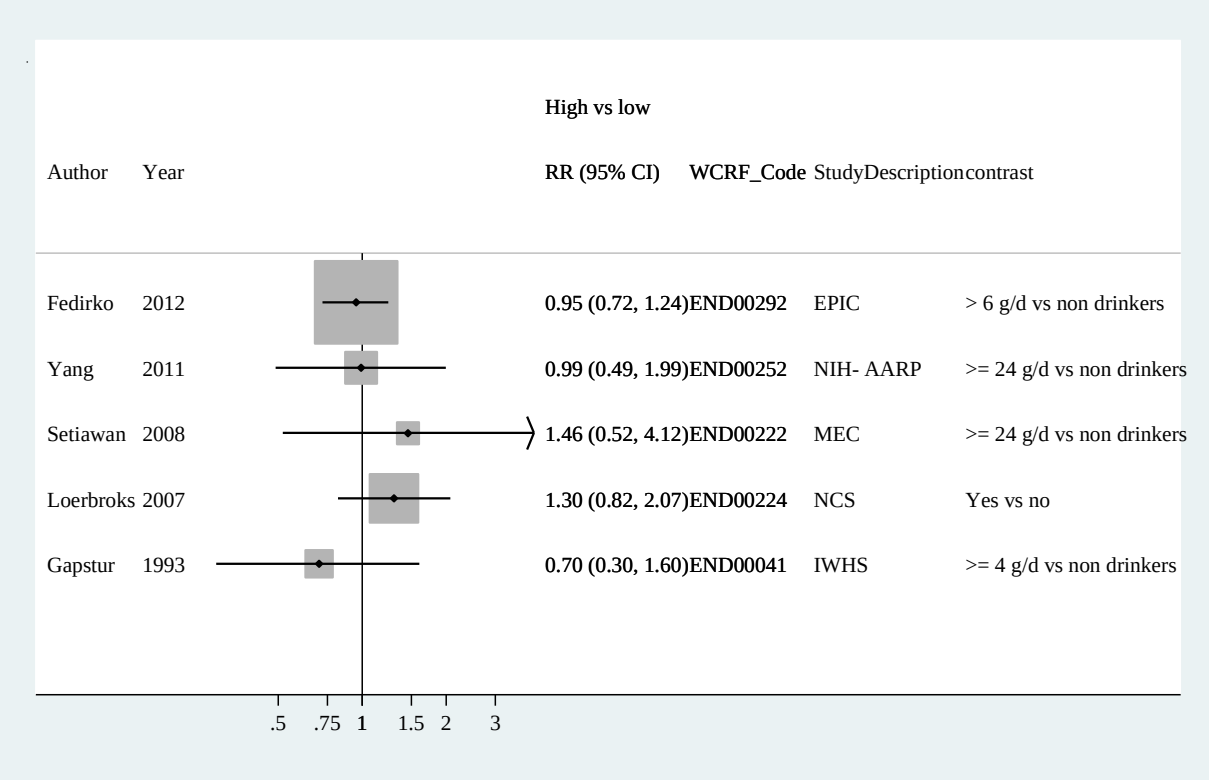


Figure 53 Dose-response meta-analysis of ethanol from beer and endometrial cancer - per 10 g/day

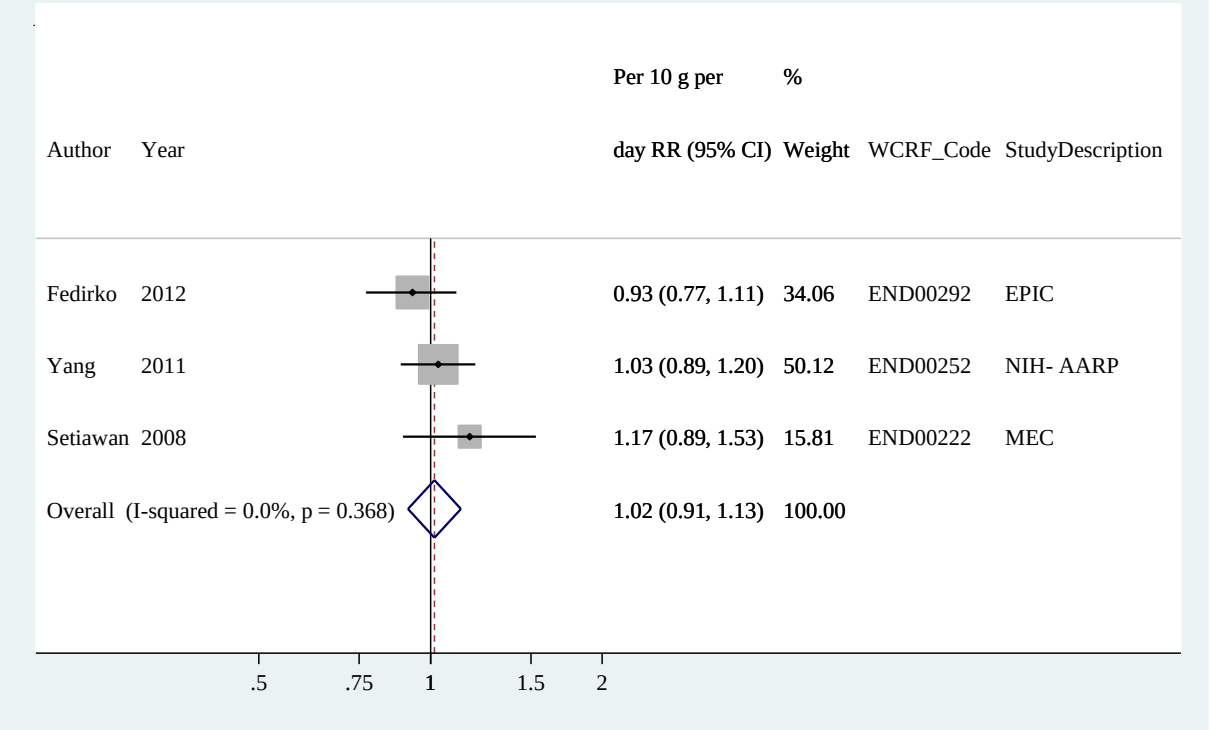
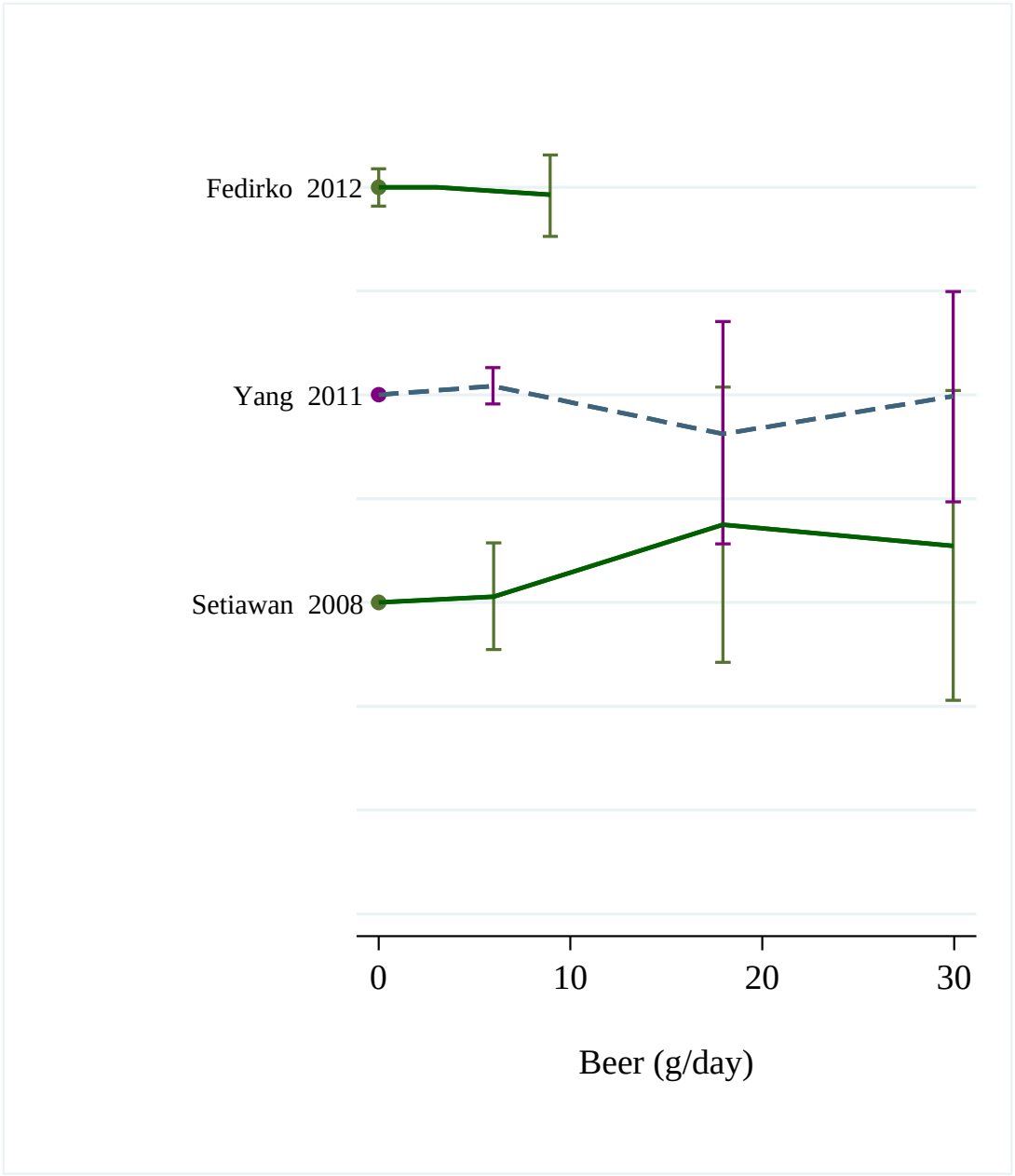


Figure 54 Dose-response graph of ethanol from beer and endometrial cancer



5.4.1.2 Ethanol from wine

Methods

Up to December 2012, reports from five cohort studies were identified; of them were identified during the CUP (including one paper missed by the SLR). The CUP meta-analysis included four studies. The dose-response results are presented for an increment of 10 grams of ethanol per day.

Main results

The summary RR per 10 grams per day was 1.07 (95% CI: 0.95-1.21; I^2= 70.5%, $P_{heterogeneity}$=0.017).

Heterogeneity

There was evidence of high heterogeneity across the limited number of published studies (I^2=70.5%, p=0.017). Egger's test did not show evidence of publication bias among the limited number of studies (p= 0.36)

Conclusion from the Second Expert Report

No study was found during the SLR 2005.

Published meta-analysis

In a published meta-analysis of three prospective and four case-control studies (Sun Q et al, 2011), the summary RR for endometrial cancer was 1.07 (95% CI: 0.92-1.25), among wine drinkers vs. non-drinkers.

Table 65 Studies on ethanol from wine intake identified in the CUP

Author, year	Country	Study name	Cases	Years of follow up	RR	LCI	UCI	Contrast
Fedirko,2012	Europe	European Prospective Investigation into Cancer and Nutrition	1382	11	1.05	0.82	1.35	> 6 g/d vs non drinkers
Yang, 2011	USA	National Institute of Health - American Association of Retired Persons Diet and Health Study	1491	9.4	0.95	0.61	1.48	>=24 g/d vs non drinkers
Setiawan, 2008	USA	Multiethnic Cohort Study	324	8.3	3.15	1.63	6.09	>=24 g/d vs non drinkers
Loerbroks, 2007	Netherlands	Netherlands Cohort Study	280	11.3	1.11	0.64	1.93	21.8 g/d vs non drinkers
Gapstur, 1993*	USA	Iowa Women's Health Study	167	~4	0.80	0.40	1.70	>= 4 g/d vs non drinkers

*****missed by 2005 SLR

Table 66 Overall evidence on ethanol from wine intake and endometrial cancer

	Summary of evidence
SLR 2005	No study was identified during the SLR 2005*
Continuous Update Project	Four cohort studies were identified. One of the studies identified showed a significant negative association. All of the studies identified could be included in the dose-response meta-analysis.

*One study was missed by the 2005 SLR

Table 67 Summary of results of the dose response meta-analysis of ethanol from wine intake and endometrial cancer

Endometrial cancer		
	SLR 2005*	Continuous Update Project
Studies (n)	-	4
Cases (n)	-	3477
Increment unit used	-	Per 10g/day
Overall RR (95%CI)	-	1.07 (0.95-1.21)
Heterogeneity (I^2,p-value)	-	70.5%, p=0.017

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

Table 68 Inclusion/exclusion table for meta-analysis of ethanol from wine intake and endometrial cancer

WCRF_ Code	Author	Year	Study Design	Study Name	Cancer Outcome	SLR 2005	CUP dose-response meta-analysis	CUP HvL forest plot	Estimated values	Exclusion reasons
END00292	Fedirko	2012	Prospective Cohort study	European Prospective Investigation into Cancer and Nutrition	Incidence	No	Yes	Yes	Rescale continuous values	-
END00252	Yang	2011	Prospective Cohort study	National Institute of Health - American Association of Retired Persons Diet and Health Study	Incidence	No	Yes	Yes	Mid-exposure values	----
END00222	Setiawan	2008	Prospective Cohort study	Multiethnic Cohort Study	Incidence	No	Yes	Yes	Person years and mid-exposure values	----
END00224	Loerbroks	2007	Case Cohort Study	Netherlands Cohort Study	Incidence	No	Yes	Yes	-	----
END00041	Gapstur	1993	Prospective Cohort study	Iowa Women Health Study	Incidence	No	No	Yes	-	Only two categories

Figure 55 Highest versus lowest forest plot of ethanol from wine intake and endometrial cancer

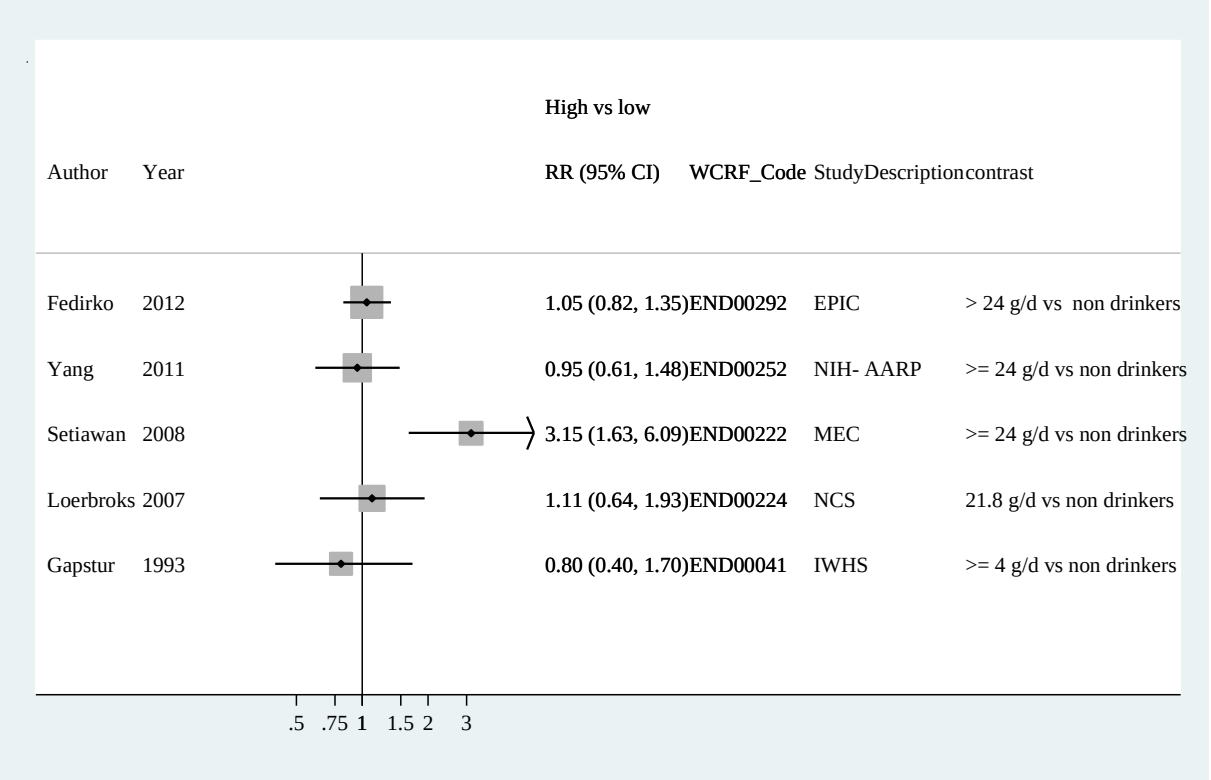


Figure 56 Dose-response meta-analysis of ethanol from wine and endometrial cancer - per 10 g/day

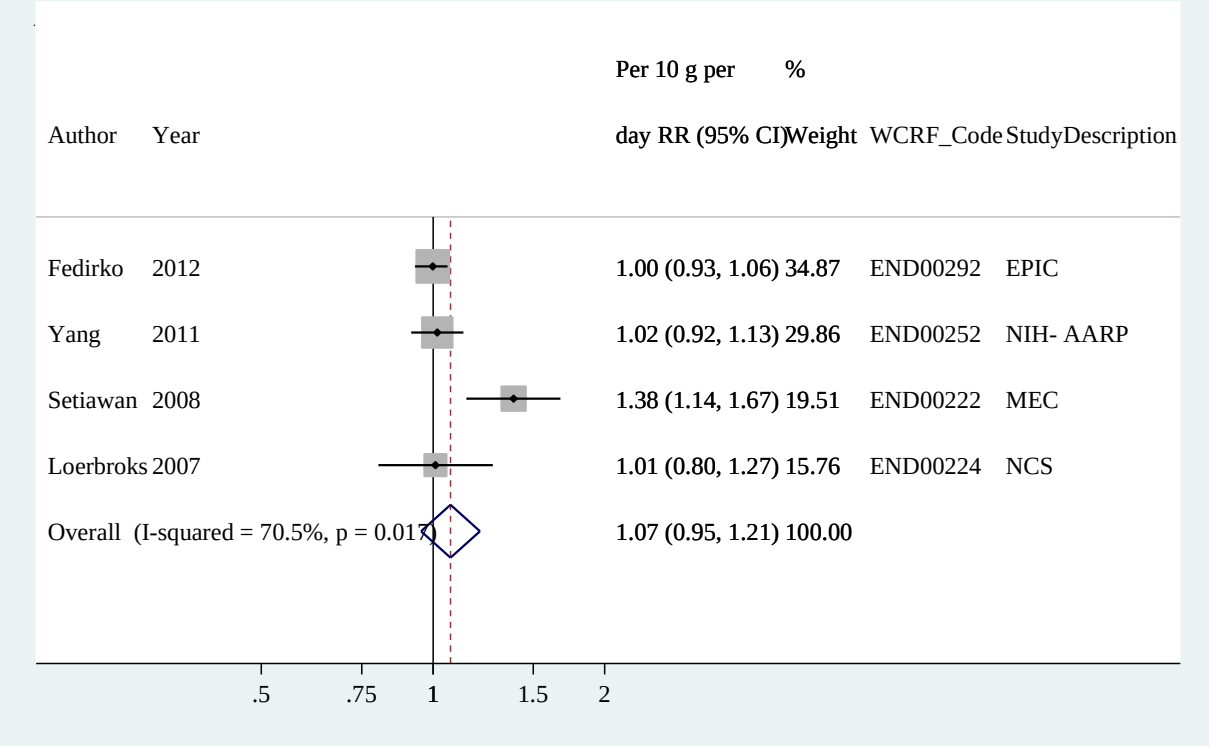
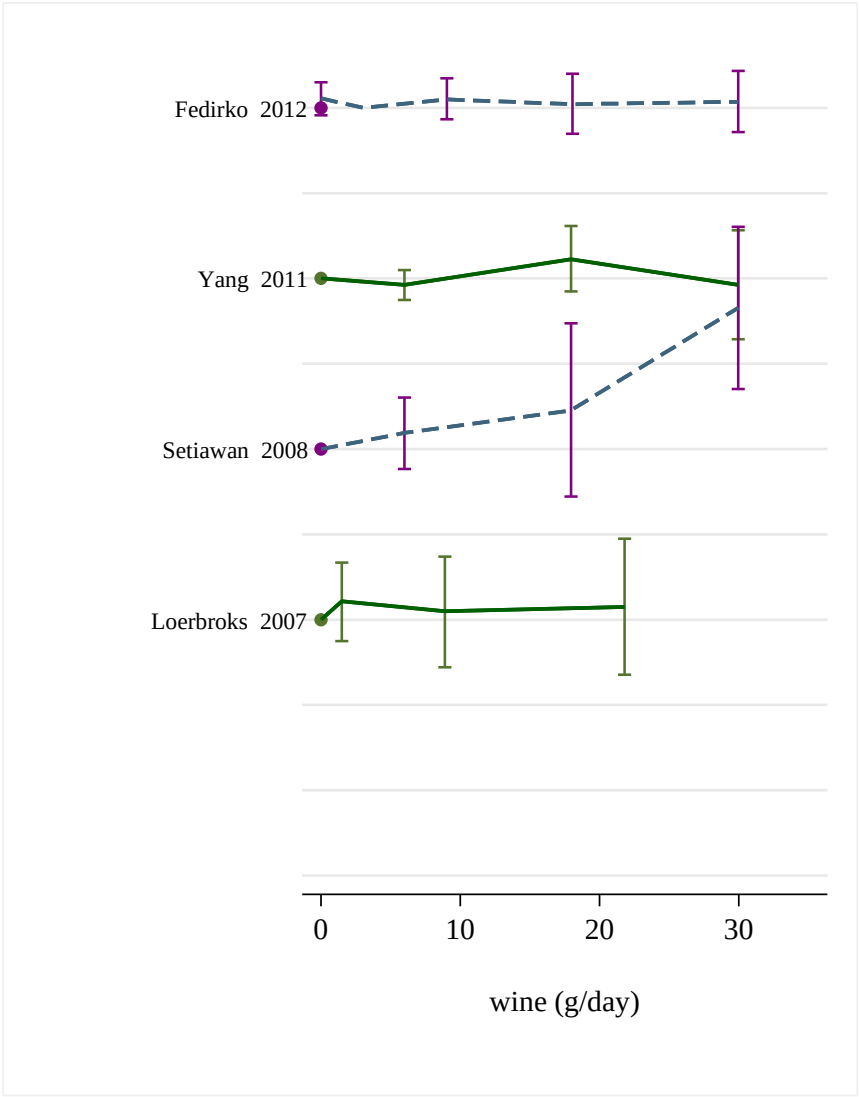


Figure 57 Dose-response graph of ethanol from wine and endometrial cancer



5.4.1.3 Ethanol from liquor

Methods

Up to December 2012, reports from five cohort studies were identified; all of them were identified during the CUP (including one paper missed by the SLR). The CUP meta-analysis included three studies. The dose-response results are presented for an increment of 10 grams of ethanol per day.

Main results

The summary RR per 10 grams per day was 1.05 (95% CI: 0.87-1.25); I^2= 76.1%, $P_{heterogeneity}$=0.015).

Heterogeneity

There was evidence of high heterogeneity across the limited number of published studies (I^2=76.1%, p=0.015).

Conclusion from the Second Expert Report

No study was found during the SLR 2005.

Published meta-analysis

In a published meta-analysis of three prospective and four case-control studies (Sun Q et al, 2011), the summary RR for endometrial cancer was 1.22 (95% CI: 1.03-1.45), among liquor drinkers vs. non-drinkers. The EPIC study (Fedirko et al, 2012) and the NIH-AARP cohort study (Yang et al, 2011) were not included in this meta-analysis. Liquor intake was not related to endometrial cancer risk in these two studies.

Table 69 Studies on ethanol from liquor intake identified in the CUP

Author, year	Country	Study name	Cases	Years of follow up	RR	LCI	UCI	Contrast
Fedirko, 2012	Europe	European Prospective Investigation into Cancer and Nutrition	1382	11	1.11	0.87	1.41	> 6 g/d vs non drinkers
Yang, 2011	USA	National Institute of Health - American Association of Retired Persons Diet and Health Study	1491	9.4	0.77	0.51	1.18	>=24 g/d vs non drinkers
Setiawan, 2008	USA	Multiethnic Cohort Study	324	8.3	1.96	0.98	3.90	>=24 g/d vs non drinkers
Loerbroks, 2007	Netherlands	Netherlands Cohort Study	280	11.3	1.11	0.73	1.68	Yes vs No
Gapstur, 1993*	USA	Iowa Women's Health Study	167	~4	1.40	0.80	2.40	>= 4 g/d vs non drinkers

*****missed by 2005 SLR

Table 70 Overall evidence on ethanol from liquor intake and endometrial cancer

	Summary of evidence
SLR 2005	No study was found during the SLR 2005 *
Continuous Update Project	Four cohort studies were identified; three of them could be included in the dose-response meta-analysis.

*One study was missed by the 2005 SLR

Table 71 Summary of results of the dose response meta-analysis of ethanol from liquor intake and endometrial cancer

Endometrial cancer		
	SLR 2005*	Continuous Update Project
Studies (n)	-	3
Cases (n)	-	3197
Increment unit used	-	Per 10g/day
Overall RR (95%CI)	-	1.05 (0.87-1.25)
Heterogeneity (I^2,p-value)	-	76.1%, p=0.015

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

Table 72 Inclusion/exclusion table for meta-analysis of ethanol from liquor intake and endometrial cancer

WCRF_ Code	Author	Year	Study Design	Study Name	Cancer Outcome	SLR 2005	CUP dose-response meta-analysis	CUP HvL forest plot	Estimated values	Exclusion reasons
END00292	Fedirko	2012	Prospective Cohort study	European Prospective Investigation into Cancer and Nutrition	Incidence	No	Yes	Yes	Rescale continuous values	-
END00252	Yang	2011	Prospective Cohort study	National Institute of Health - American Association of Retired Persons Diet and Health Study	Incidence	No	Yes	Yes	Mid-exposure values	----
END00222	Setiawan	2008	Prospective Cohort study	Multiethnic Cohort Study	Incidence	No	Yes	Yes	Person years and mid-exposure values	----
END00224	Loerbroks	2007	Case Cohort Study	Netherlands Cohort Study	Incidence	No	No	Yes	-	Only two categories (yes vs no)
END00041	Gapstur	1993	Prospective Cohort study	Iowa Women Health Study	Incidence	No	No	Yes	-	Only two categories

Figure 58 Highest versus lowest forest plot of ethanol from liquor intake and endometrial cancer

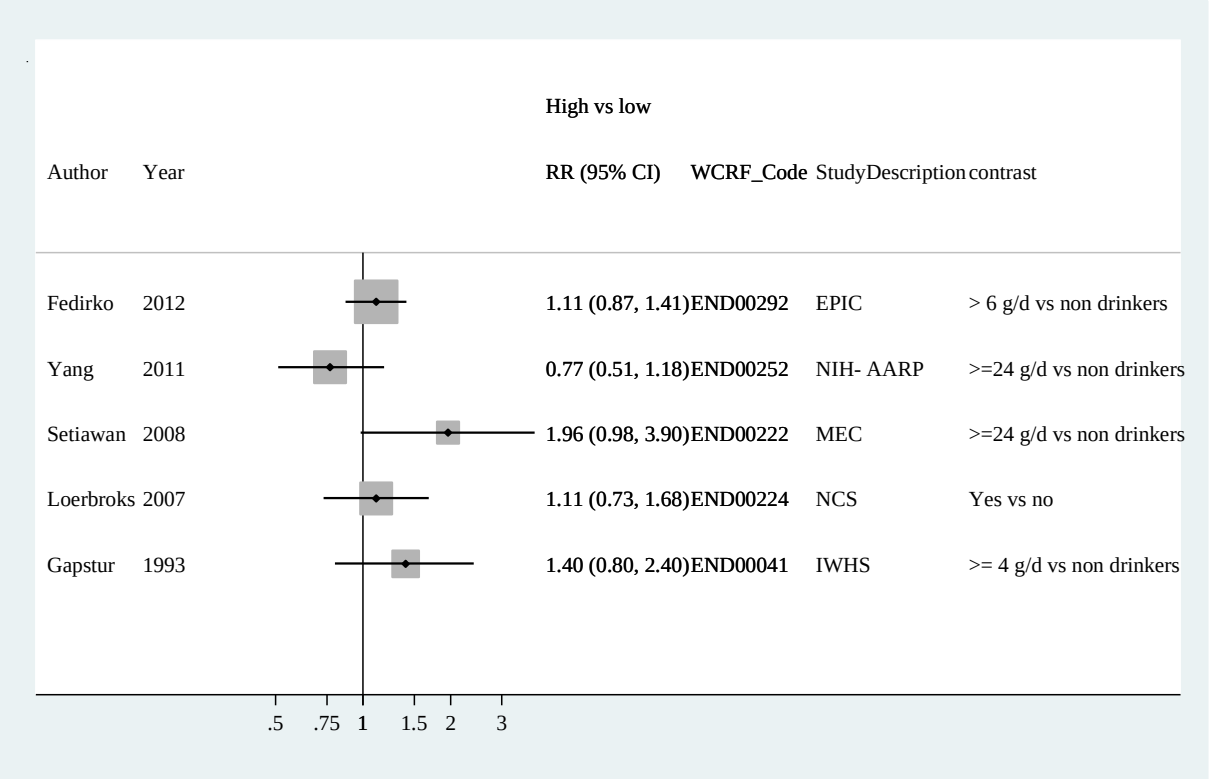


Figure 59 Dose-response meta-analysis of ethanol from liquor and endometrial cancer - per 10 g/day

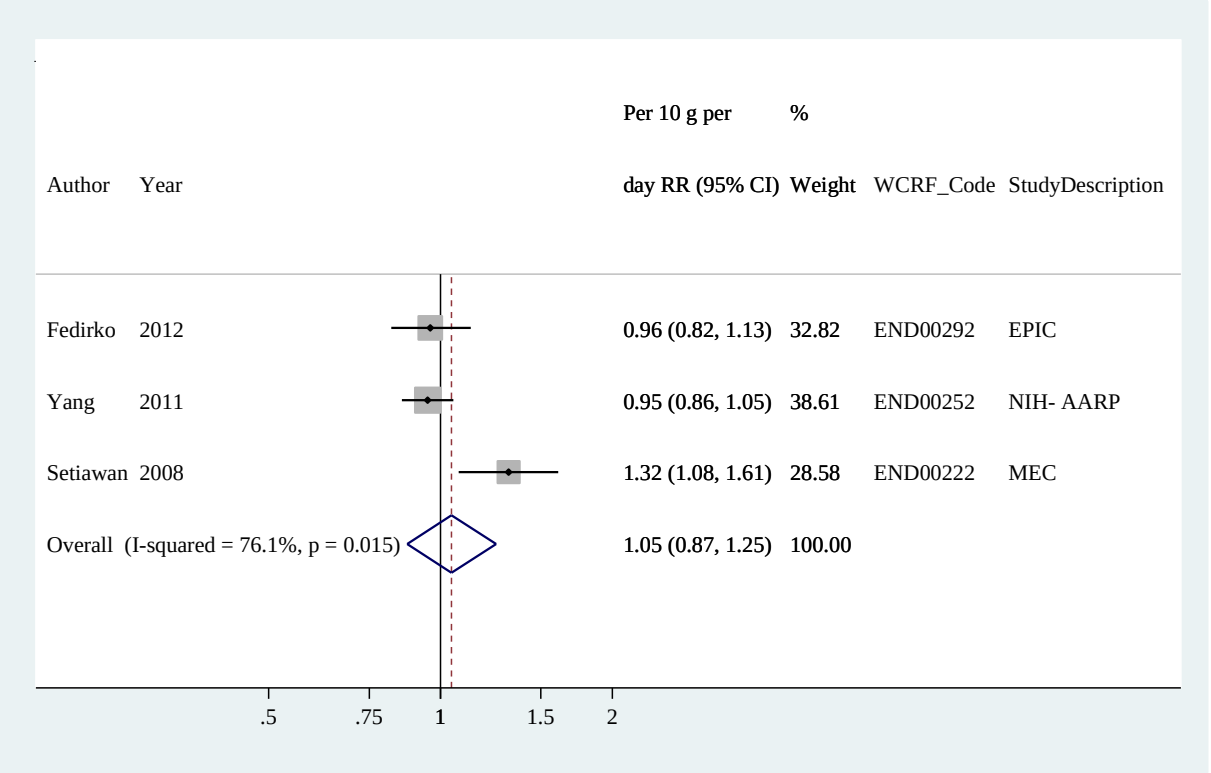
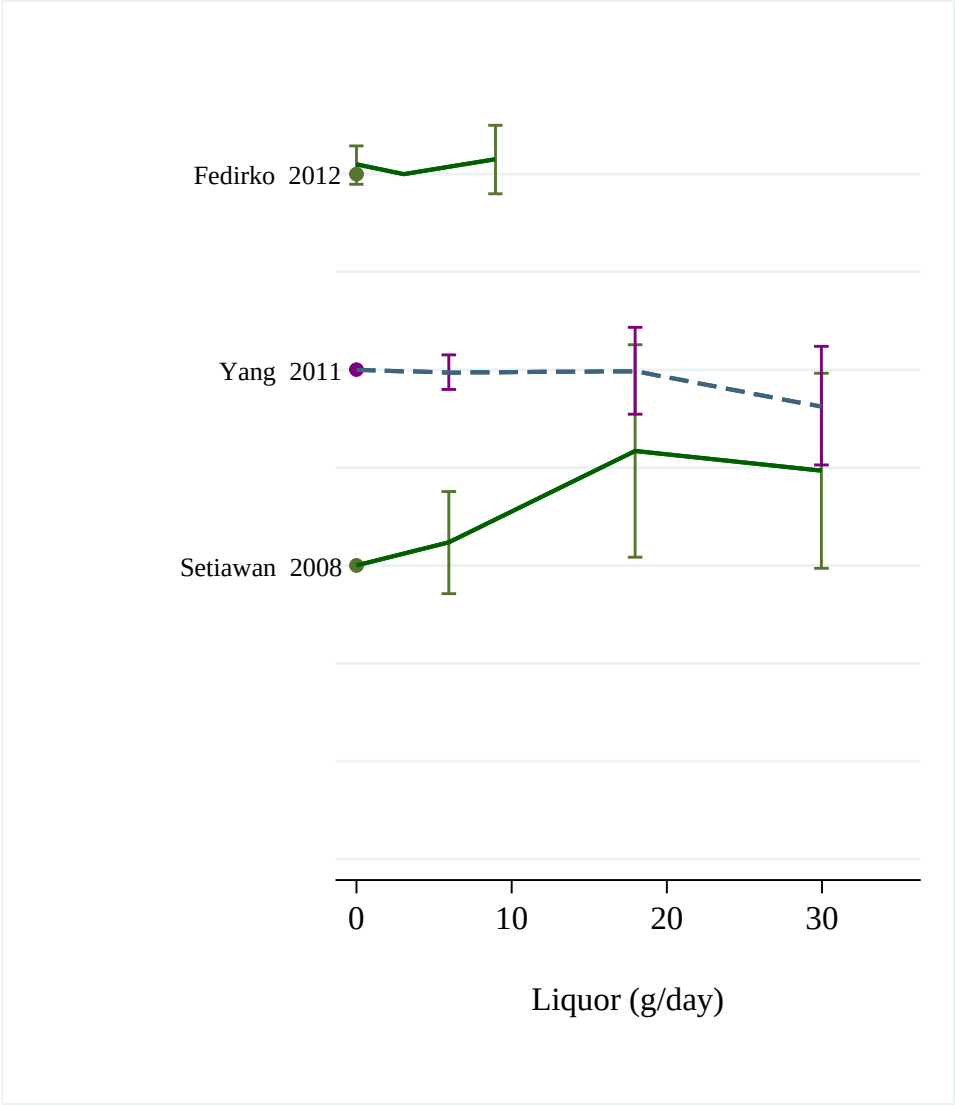


Figure 60 Dose-response graph of ethanol from liquor and endometrial cancer



5.5.3 Folate (Dietary only)

Methods

Up to December 2012, three cohort studies were identified. Two of three studies were identified during the Continuous Update Project. One study (Jain et al., 2000) was superseded by a study of Kabat et al in 2008 in the Canadian National Breast Cancer Screening Study and was excluded from the analysis. The Iowa Women Health Study (Uccella et al., 2011) reported results for type 1 and type 2 endometrial cancers. Only results of type 1 are included in dose-response meta-analysis because it includes adenocarcinomas, the most frequent histology in endometrial cancer. Two of the three studies had been included in the dose-response meta-analysis. The increment used was 50 µg/day.

Main results

The summary RR per 50 µg /day was 1.00 (95% CI: 0.97-1.02) for all studies combined.

Heterogeneity

There was no heterogeneity ($I^2 = 0\%$, $P_{heterogeneity} = 0.78$).

Conclusion from the Second Expert Report

No meta-analysis was conducted.

Table 73 Studies on dietary folate identified in the CUP

Author, year	Country	Study name	Cases	Years of follow up	RR	LCI	UCI	Contrast
Uccella, 2011	USA	Iowa Women Health Study (Type 1 endometrial cancer)	471	20	1.09	0.79	1.52	>373.7 vs. <225.1 µg/d
Uccella, 2011	USA	Iowa Women Health Study (Type 2 endometrial cancer)	71	20	1.34	0.55	3.23	>373.7 vs. <225.1 µg/d
Kabat, 2008	Canada	Canadian National Breast Cancer Screening Study	426	16.4	0.79	0.55	1.13	>400 vs. <236 µg /d

Table 74 Overall evidence on dietary folate and endometrial cancer

	Summary of evidence
SLR 2005	Only one cohort study was identified.
Continuous Update Project	Two cohort studies were identified during the CUP. The results from the two studies were included in the meta-analysis. None of the studies reported significant associations.

Table 75 Summary of results of the dose response meta-analysis of dietary folate and endometrial cancer

Endometrial cancer incidence		
	SLR 2005*	Continuous Update Project
Studies (n)	-	3
Cases (n)	-	1189
Increment unit used	-	50 μg /day
Overall RR (95%CI)	-	1.00 (0.97-1.02)
Heterogeneity (I^2,p-value)	-	0%, p=0.78

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

Table 76 Inclusion/exclusion table for meta-analysis of dietary folate and endometrial cancer

WCRF code	Author	Year	Study design	Study name	Cancer outcome	SLR 2005	CUP dose-response	CUP H vs. L forest plot	Estimated values	Exclusion reason
END00271	Uccella	2011	Prospective Cohort study	Iowa Women's Health Study	Incidence (only type 1 endometrial cancer)	No	Yes	Yes	Mid-exposure values	-
END00247	Kabat	2008	Prospective Cohort Study	Canadian National Breast Cancer Screening Study	Incidence	No	Yes	Yes	Mid-exposure values	-
END00009	Jain	2000	Case-cohort Study	National Breast Cancer Screening Study	Incidence	Yes	No	No	-	Superseded by Kabat et al., 2008

Figure 61 Highest versus lowest forest plot of dietary folate and endometrial cancer

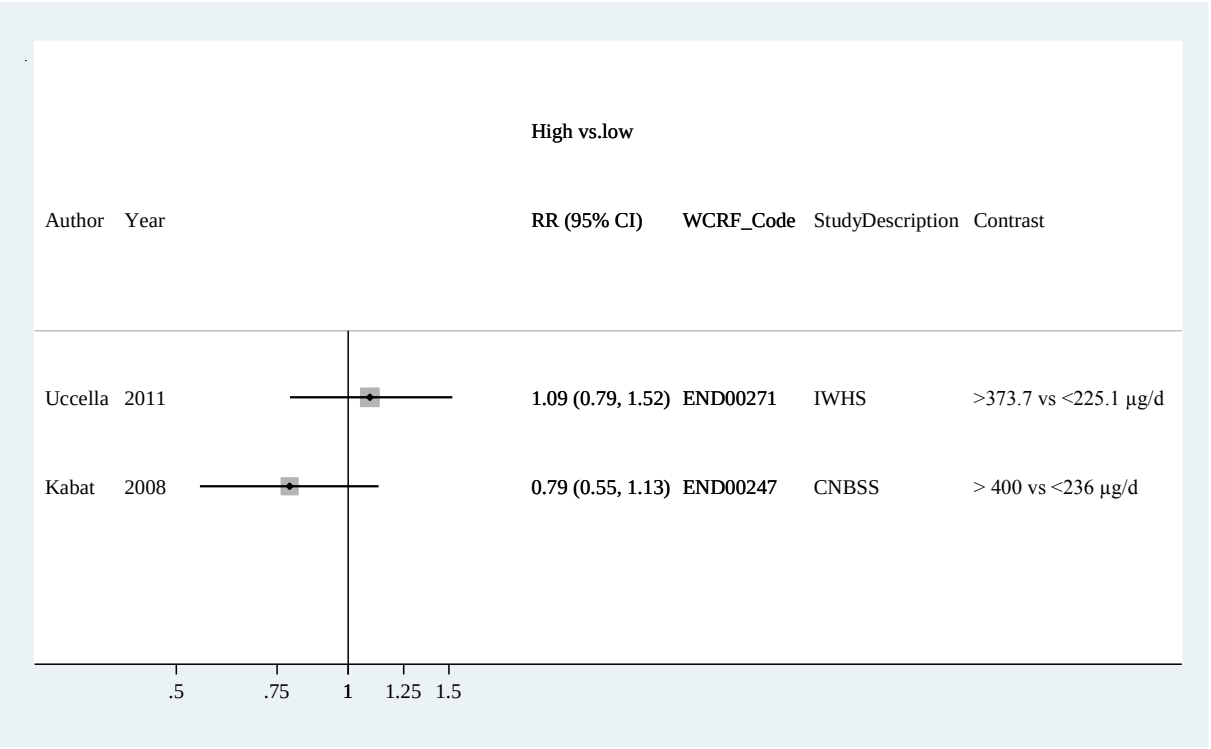


Figure 62 Dose-response meta-analysis of dietary folate and endometrial cancer - per 50

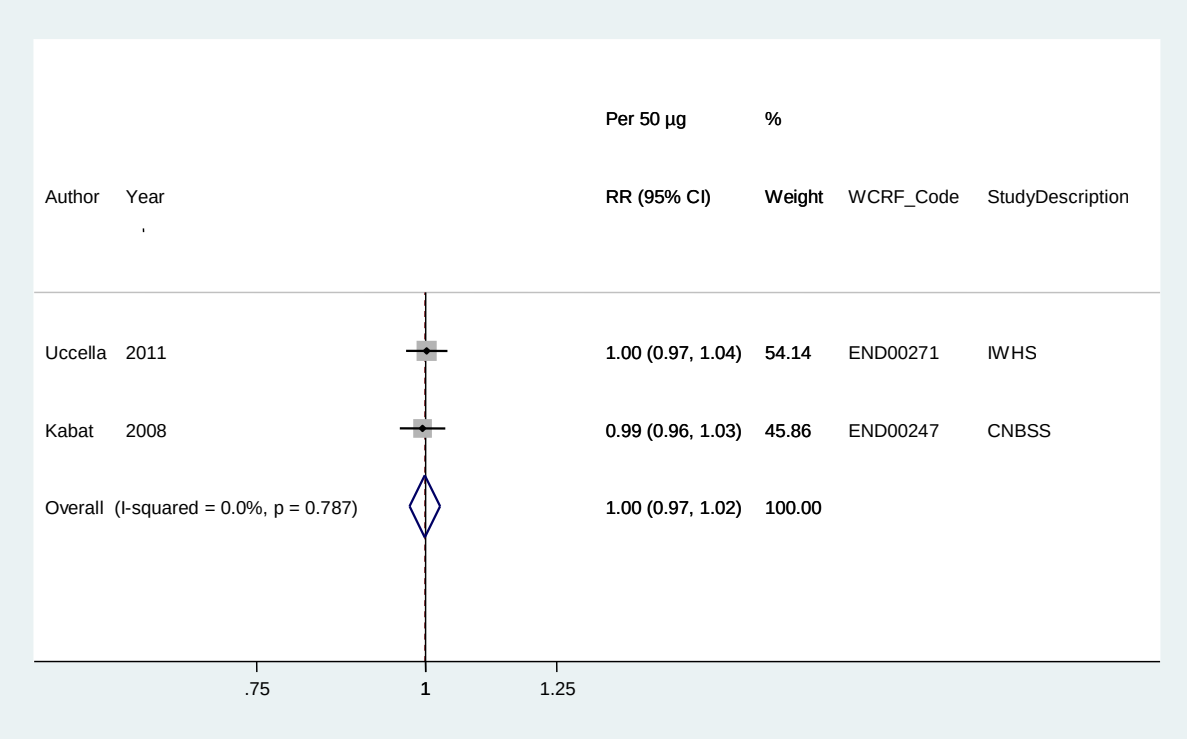
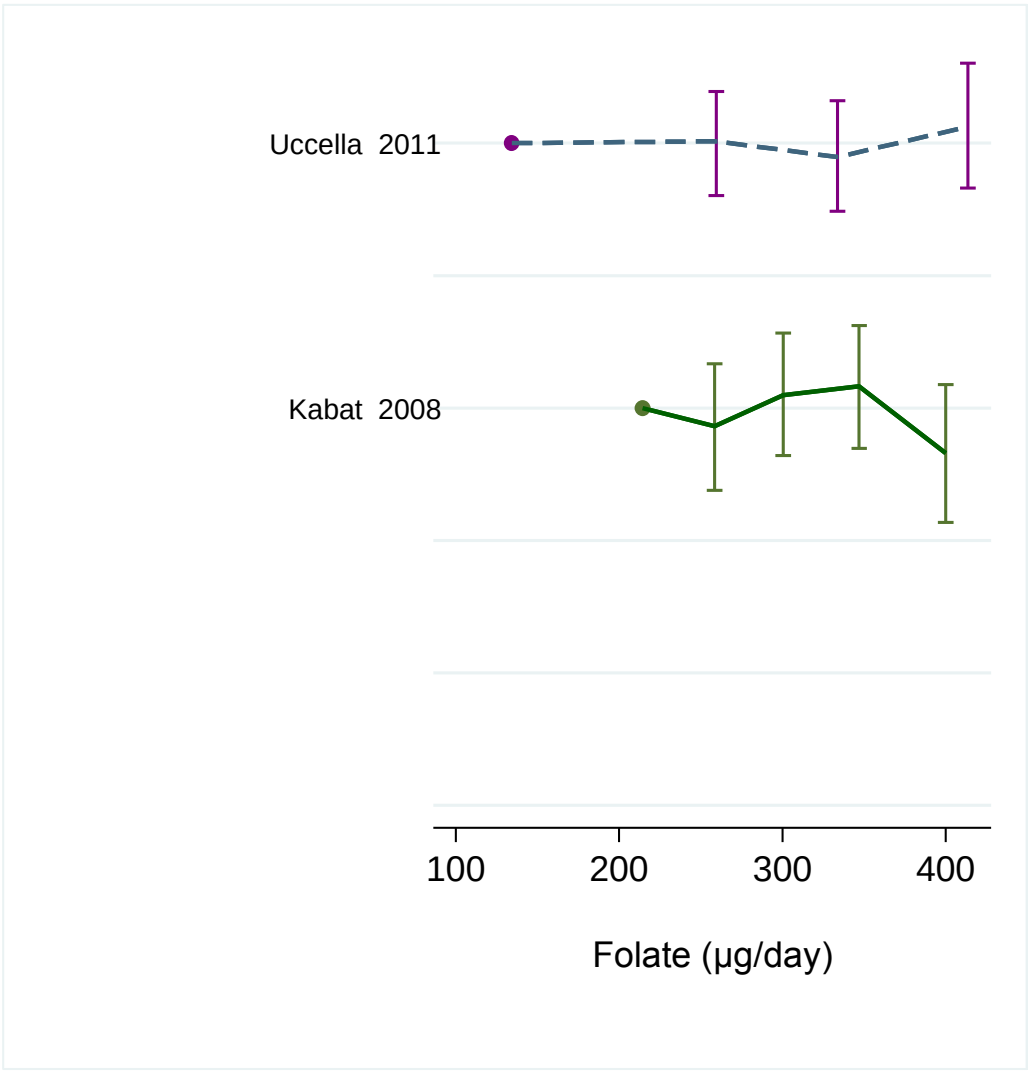


Figure 63 Dose-response graph of dietary folate and endometrial cancer



5.5.13 Multivitamins

Methods

Up to December 2012, three cohort studies were identified during the Continuous Update Project. No study was identified in the SLR 2005. One study (Cui, 2011) reported the number of supplements used per week in a categorical variable which was converted to binary variable (yes vs. no) to be comparable with the other studies included in the analysis using the Hamling method (Hamling et al, 2008). Only high versus lowe comparison of users vs non users was possible.

Main results

The summary RR when comparing multivitamin intake with no intake, was 1.03 (95% CI: 0.93- 1.13, $I^2 = 0\%$, $P_{heterogeneity} = 0.43$) for all studies combined.

Heterogeneity

There was no evidence of heterogeneity across the limited number of published studies ($I^2 = 0\%$, $P_{heterogeneity} = 0.43$).

Conclusion from the Second Expert Report

No study was identified during the SLR 2005.

Table 77 Studies on multivitamin identified in the CUP

Author, year	Country	Study name	Cases	Years of follow up	RR	LCI	UCI	Contrast
Cui, 2011	USA	Nurses' Health Study	669	26	1.09	0.69	1.73	10 pills/week vs. none
Uccella, 2011	USA	Iowa Women's Health Study	542	20	1.11	0.91	1.36	User vs non-user
Neuhouser 2009	USA	Women's Health Initiative Dietary Modification and Observational study	912	8	1.05	0.90	1.21	yes vs. no

Table 78 Overall evidence on multivitamin intake and endometrial cancer

	Summary of evidence
SLR 2005	No study was identified during the SLR 2005.
Continuous Update Project	Three cohort studies were identified; all were included in the dose-response meta-analysis. None of the studies reported significant associations.

Table 79 Summary results of meta-analysis of multivitamin intake (use vs. non-use) and endometrial cancer

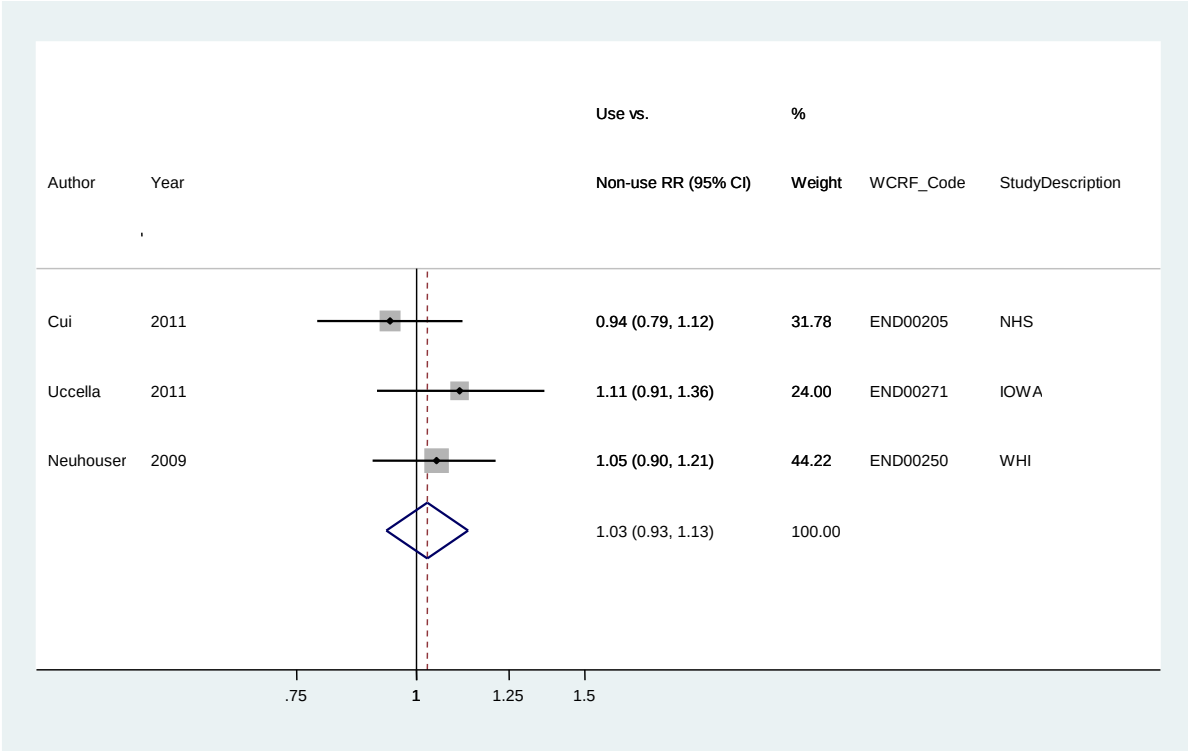
Endometrial cancer incidence		
	SLR 2005*	Continuous Update Project
Studies (n)	-	3
Cases (n)	-	2123
Increment unit used	-	Use vs. non-use
Overall RR (95%CI)	-	1.03 (0.93 - 1.13)
Heterogeneity (I^2,p-value)	-	0 %, p=0.43

*No meta-analysis was conducted in the SLR 2005

Table 80 Inclusion/exclusion table for meta-analysis of multivitamin intake and endometrial cancer

WCRF code	Author	Year	Study design	Study name	Cancer outcome	SLR 2005	CUP dose-response	CUP Yes vs. No forest plot	Estimated values	Exclusion reason
END00205	Cui	2011	Prospective Cohort study	Nurses' Health Study (NHS)	Incidence	No	No	Yes	Supplements/week rescaled to use vs non-use	-
END00271	Uccella	2011	Prospective Cohort study	Iowa Women's Health Study	Incidence (only type1 endometrial cancer)	No	No	Yes	-	-
END00250	Neuhouser	2009	Prospective Cohort study	Women's Health Initiative	Incidence	No	No	Yes	-	-

Figure 64 forest plot of multivitamin intake use vs. non-use and endometrial cancer



5.7.5 Total Isoflavones

Methods

Up to December 2012, reports from three case-control studies and one cohort study were identified; one case-control study and the only cohort study where identified during the CUP. The CUP meta-analysis included two case-control studies. The dose-response results are presented for an increment of 10000 mcg of total isoflavones intake per day.

A study among Chinese women living in Shanghai reported no association between total isoflavones consumption and endometrial cancer. This study was excluded from the dose-response meta-analysis due to the high intake values of total isoflavones that made impossible to compare this study with other populations.

Main results

The summary RR per 1000 mcg per day was 0.87 (95% CI: 0.78-0.97; I^2= 0%, $P_{heterogeneity}$=0.927).

The only cohort study identified reported a protective association between total isoflavones intake and endometrial cancer (0.87; 95% CI: 0.78-0.97, Ptrend=0.02)

Heterogeneity

There was high heterogeneity across the limited number of published studies (I^2=0%, p=0.927).

Comparison with the Second Expert Report

There was no meta-analysis in the Second Expert Report.

Published meta-analysis

There is no published meta-analysis in this topic

Table 81 Studies on total isoflavones intake identified in the CUP

Author, year	Country	Study name	Cases	Years of follow up	RR	LCI	UCI	Contrast
Ollberding, 2012	USA	Multiethnic Cohort study	489	13.6	0.66	0.47	0.90	>=7.82 mg kcal/day
Bandera, 2009	USA	The Estrogen, Diet, Genetics, and Endometrial study	424 cases & 398 controls	-	0.80	0.50	1.27	>666 mcg/ kcal per day vs 50.0 g/d

Table 82 Overall evidence on total isoflavones intake and endometrial cancer

	Summary of evidence
SLR	Two case-control studies were identified during the SLR. One study reported on Chinese woman in Shanghai and found no association between total isoflavones intake and endometrial cancer. The second study reported on US non-Asian women and found a protective effect of total isoflavones and endometrial cancer risk.
Continuous Update Project	One cohort study and one case-control study were identified. The cases-control study was included in the meta-analysis. Overall, two case-control studies were included in the CUP meta-analysis

Table 83 Summary of results of the dose response meta-analysis of total isoflavones intake and endometrial cancer

Endometrial cancer		
	SLR*	Continuous Update Project
Studies (n)	-	2
Cases (n)	-	902
Increment unit used	-	Per 1000 mcg/day
Overall RR (95%CI)	-	0.87 (0.78-0.97)
Heterogeneity (I^2,p-value)	-	0%, p=0.927

*No meta-analysis was conducted in the Second Report

Table 84 Inclusion/exclusion table for meta-analysis of total isoflavones intake and endometrial cancer

WCRF_ Code	Author	Year	Study Design	Study Name	Cancer Outcome	SLR	CUP dose-response meta-analysis	CUP HvL forest plot	Estimated values	Exclusion reasons
END00265	Ollberding	2012	Prospective Cohort study	Multiethnic Study	Incidence	No	No	No	-	Cohort study (all other studies are case-control studies)
ENDXXXX	Bandera	2009	Case-Control study	The Estrogen, Diet, Genetics, and Endometrial study	Incidence	Yes	Yes	Yes	Mid-exposure values	---
END00011	Xu	2004	Case-Control study	Shanghai Cancer Registry	Incidence	Yes	No	Yes	Mid-exposure values	Intake ranges not comparable with non-Asian populations
END00010	Horn-Ross	2003	Case-Control study	San Francisco Bay Study	Incidence	Yes	Yes	Yes	Mid-exposure values	---

Figure 65 Highest versus lowest forest plot of total isoflavones intake and endometrial cancer

Figure 66 Dose-response meta-analysis of total isoflavones and endometrial cancer - per 10 g/day

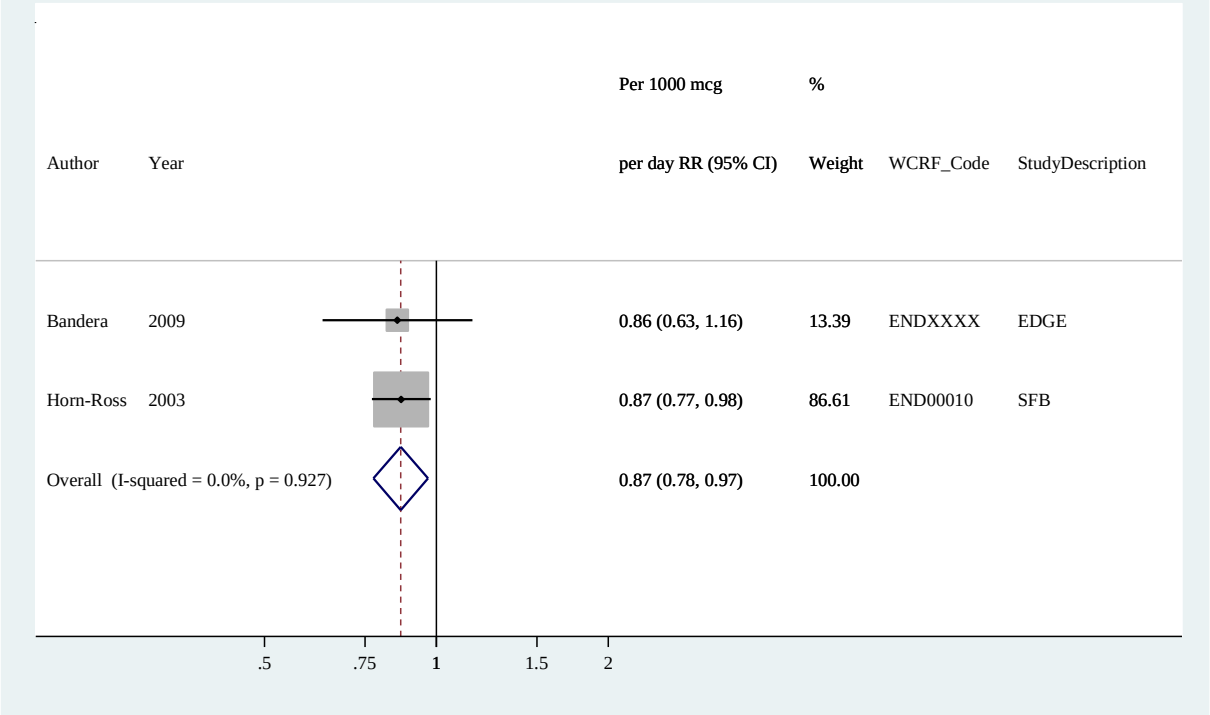
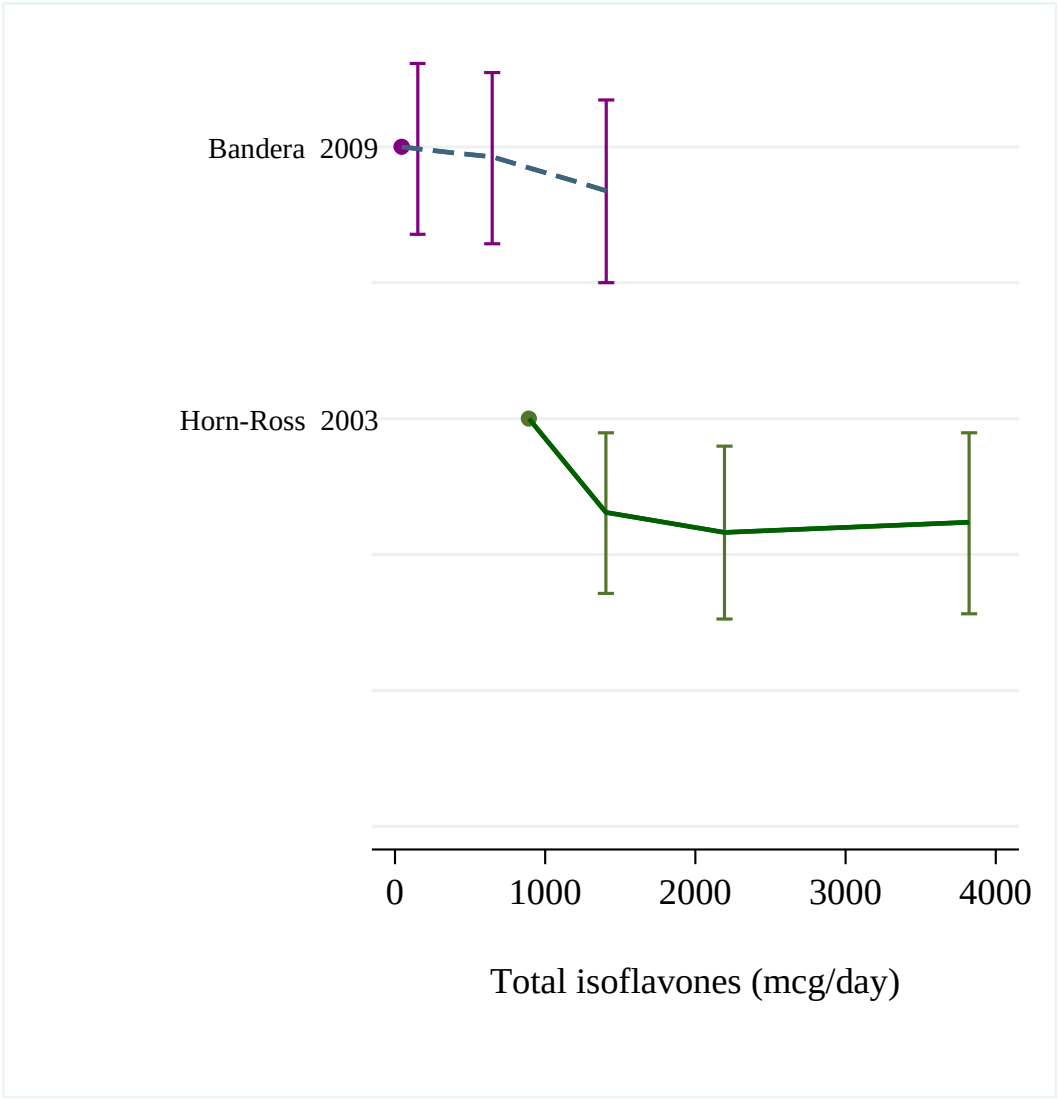


Figure 67 Dose-response graph of total isoflavones and endometrial cancer



6 Physical activity

6.1.1.1 Occupational physical activity

Methods
Five cohort studies were identified on occupational physical activity and endometrial cancer risk up to 2012, two of which were identified in the CUP. Dose-response analyses were not possible because of the differences in assessing occupational physical activity across studies. All studies were included in a highest versus lowest meta-analysis.

Main results
The summary RR for the highest vs. the lowest category of occupational physical activity reported in the articles 0.79 (95% CI: 0.71-0.88, I^2= 18.4%, $p_{heterogeneity}$=0.97, n=5). There was no evidence of publication bias with Egger test (p= 0. 946) among the limited number of studies.

In sensitivity analysis of the influence of individual studies, the relative risk for the highest vs. the lowest category of occupational physical activity ranged from 0.76 (95% CI: 0.70-0.84) when a Swedish study by Friberg et al. 2006 was excluded to 0.81(95% CI: 0.67-0.97) when another Swedish study by Moradi et al.1998 was excluded.

All studies except two (Moradi, 1998; Weiderpass, 2001) controlled for BMI. Effect modification by BMI was additionally explored in the three other studies. No significant differences in associations across BMI levels were observed in two of the studies (Friberg, 2006; Friedenreich, 2007). In one study (Furberg, 2003) occupational physical activity was especially protective in obese women (P interaction: 0.17).

Heterogeneity
There was low heterogeneity in the analysis, I^2=18.4%, $p_{heterogeneity}$=0.297.

Conclusion from the Second Expert Report

A meta-analysis of three cohort studies showed that occupational physical activity was inversely related to endometrial cancer risk.
The Second Expert Report concluded that physical activity of all types probably protects against endometrial cancer risk.

Table 85 Studies on occupational physical activity identified in the CUP

Author/year	Country	Study name	Cases	Years of follow-up	RR	LCI	UCI	Contrast
Friedenreich, 2007	Europe	EPIC	689	6.6	0.89	0.63	1.26	Manual/heavy manual vs. sedentary
Friberg, 2006	Sweden	Swedish Mammography Cohort	225	7	1.01	0.75	1.37	High vs. low

Table 86 Overall evidence on occupational physical activity and endometrial cancer

	Summary of evidence
2005 SLR 2005	Three cohort studies, all conducted in Scandinavian countries reported that greater occupational physical activity was associated with decreased risk of endometrial cancer.
Continuous Update Project	Two additional cohort studies reported no significant association of occupational physical activity and endometrial cancer.

Table 87 Summary of results of the highest vs. lowest meta-analysis of occupational physical activity and endometrial cancer

Endometrial cancer		
	SLR 2005	Continuous Update Project
Studies (n)	3	5
Cases (n)	4912	5826
RR (95% CI)	0.75 (0.68-0.83)	0.79 (0.71-0.88)
Contrast	Highest vs. Lowest	Highest vs. Lowest
Heterogeneity (I^2, p-value)	0% p=0.389	18.4%, p= 0.297

Table 88 Inclusion/exclusion table for meta-analysis of occupational physical activity and endometrial cancer

WCRF code	Author	Year	Study design	Study name	Cancer outcome	SLR 2005	CUP HvL forest plot	Estimated values	Exclusion reason
END00245	Friedenreich	2007	Prospective cohort study	European Prospective Investigation into Cancer	Incidence	No	Yes	-	-
END00283	Friberg	2006	Prospective cohort study	Swedish Mammography Cohort	Incidence	No	Yes	-	-
END00014	Furberg	2003	Prospective cohort study	Cohort from Norwegian National Health Screening	Incidence	Yes	Yes	-	-
END00111	Weiderpass	2001	Prospective cohort study	Women Occupational Cancer Study	Incidence	Yes	Yes	Relative risks estimated from Standardised incidence rates	-
END00083	Moradi	1998	Prospective cohort study	Census and Cancer Environment Register	Incidence	Yes	Yes	Relative risks recalculated because referent category was the highest level	-

Figure 68 Highest versus lowest forest plot of occupational physical activity and endometrial cancer

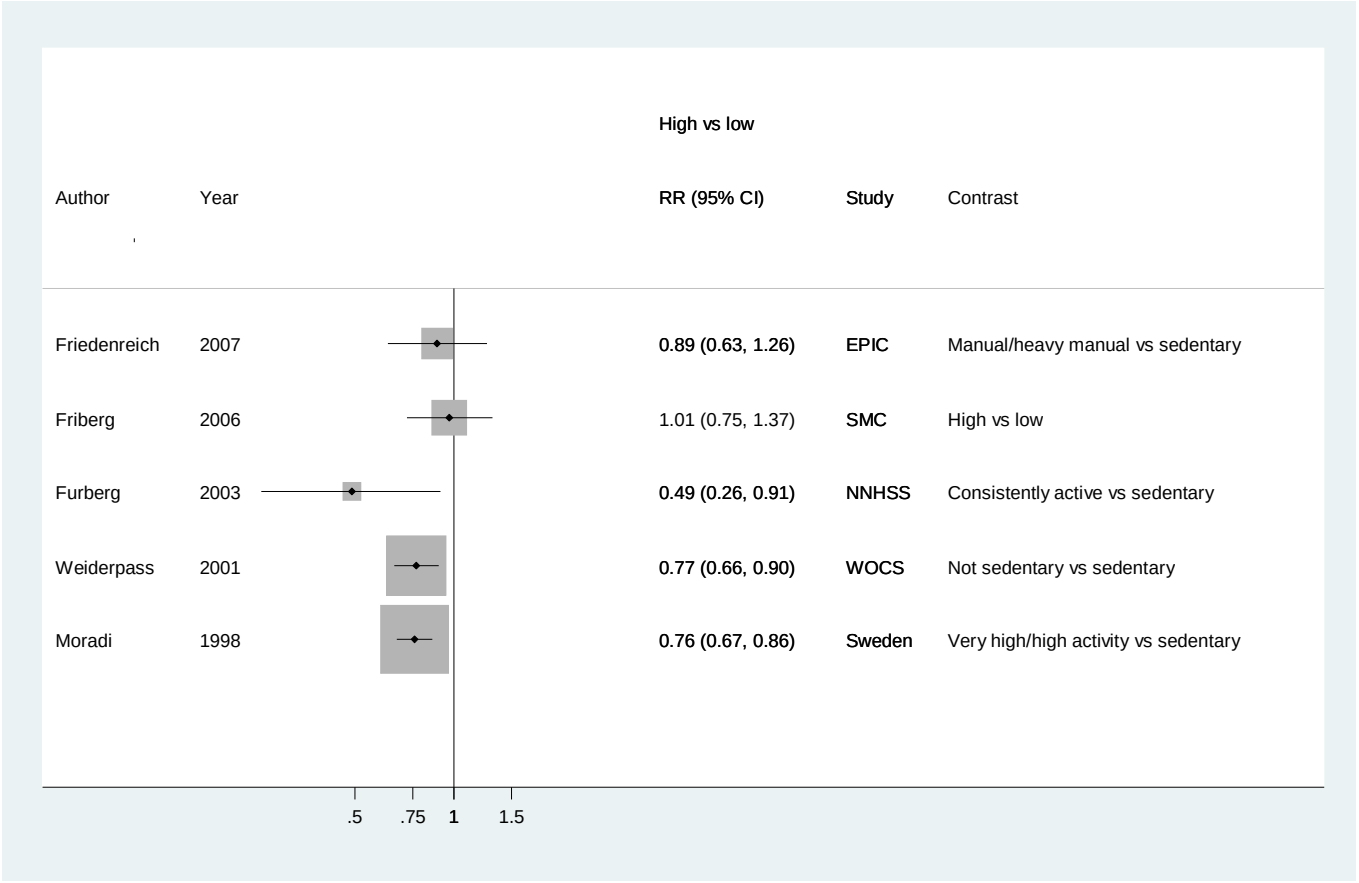
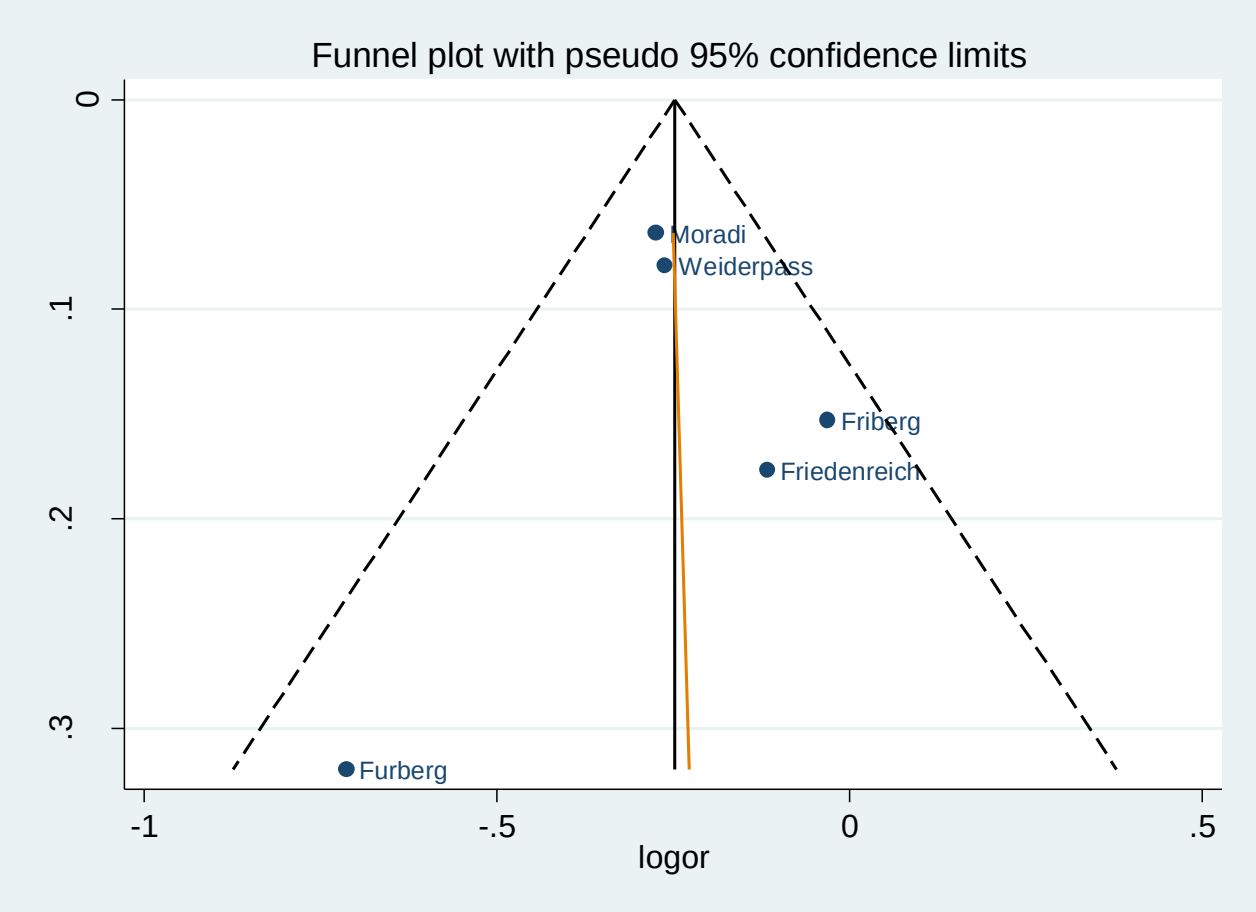


Figure 69 Funnel plot occupational physical activity and endometrial cancer



6.1.1.2 Recreational physical activity

Methods

A total of 9 cohort studies (10 publications) have been published on recreational (or leisure time) physical activity and endometrial cancer risk up to 2012, five (six publications) of which were identified in the CUP. Dose-response analyses were not possible because different measures of physical activity were used in the studies.

A highest versus lowest meta-analysis was conducted. One study reported only age-adjusted results (Folsom et al, 2003). All other studies reported multivariable adjusted results. First, we included in the analyses multivariable results not adjusted by BMI and three studies (Fuberg et al. 2003, Schouten et al. 2004, and Friedenreich et al. 2007) that provided the multivariable adjusted results including BMI as covariable.

Second, the meta-analysis was conducted including only all the results that were adjusted for BMI. Two studies did not provide results adjusted for BMI and were excluded (Folsom et al. 2003, Terry et al. 1999).

Main results

The summary RR for the highest vs. the lowest category of recreational physical activity was 0.73 (95% CI: 0.58-0.93, I^2=75.9%, $p_{heterogeneity}$=<0.0001, n=9) for all studies combined.

In analyses restricted to studies that adjusted for BMI, the RR for the highest vs. the lowest category of recreational physical activity was 0.80 (95% CI: 0.69-0.92, I^2=21.2%, $p_{heterogeneity}$=0.268, n=7)

In sensitivity analysis of the influence of individual studies, analyses the relative risk for the highest vs. the lowest category of recreational physical activity ranged from 0.69 (95% CI: 0.54-0.88) when the Iowa Women Health Study (Folsom et al. 2003) was excluded to 0.79 (95% CI: 0.63-0.98) when NIH-AARP was excluded.

Six studies investigated effect modification for BMI. Four studies reported no significant effect modification (Gierach, 2009; Friedenreich, 2007; Friberg, 2006; Schouten, 2004). In the WHEL study (Conroy, 2009) compared to normal weight active women the relative risks of endometrial cancer were 1.17 (95% CI: 0.77-1.77) for normal weight inactive women , and in overweight women, these were1.60 (95% CI: 1.01-2.54) for overweight active women and 1.85 (95% CI: 1.26-2.72) for overweight inactive women. In the Cancer Prevention Study II Nutrition Cohort, the inverse relationship with physical activity was seen only among overweight or obese women (trend p = 0.003) and not in normal weight women (trend p =0.51) (heterogeneity of trends p = 0.01). Compared to normal weight women with less than 7 MET-hr/week of activity, the hazard ratios were (1.01; 95% CI: 0.69-1.48) for normal weight women with the higher physical activity level and 0.59 (95% CI: 0.42-0.83) for obese women with the higher activity level.

The summary RR for the highest vs. the lowest category of recreational physical activity was 0.73 (95% CI: 0.58-0.93, I2=75.9%, pheterogeneity=<0.0001, n=9) for all studies combined.

In analyses restricted to studies that adjusted for BMI, the RR for the highest vs. the lowest category of recreational physical activity was 0.80 (95% CI: 0.69-0.92, I2=21.2%,p Heterogeneity=0.268, n=7).

Heterogeneity

There was high heterogeneity in the analysis for all studies combined, I^2=75.9%, $p_{heterogeneity}$=<0.0001. There was no evidence of publication bias with Egger test (p: 0.338) and the visual inspection of the funnel plot indicates that the smallest study (Terry et al, 1999) reported an inverse association outside the expected random fluctuation. Exclusion of the study by Terry et al, 1999 from the analysis did not substantially modify the summary estimate.

Low heterogeneity was observed in the meta-analysis of results adjusted for BMI (I^2=21.2 %, $p_{heterogeneity}$=0.268).

Conclusion from the Second Expert Report

In the systematic review of the 2007 expert report it was judged that physical activity (all types) probably decreases endometrial cancer risk.

Published meta-analysis

A meta-analysis of cohort studies on recreational activity was recently published (Moore et al, 2010). It includes the same studies that were included in the CUP and therefore the results are the same.

A narrative review of cohort and case-control studies concluded that about 1 hour daily of moderate-intensity activity appears to confer a benefit for endometrial cancer risk, and that there is no consistent evidence regarding the effect for different population sub-groups including different BMI categories and menopausal status (Friedenreich et al, 2010).

Table 89 Studies on recreational physical activity identified in the CUP

Author/year	Country	Study name	Cases	Years of follow-up	RR	LCI	UCI	Contrast
Gierach, 2009	USA	NIH-American Association of Retired Persons	1052	3 yrs(cases) 7 yrs (non-cases)	0.56	0.46	0.68	>=5 times/week vs. never/rarely
Conroy, 2009	USA	Women Health Study	264	8.8	1.15	0.79	1.67	≥20.4 vs. <2.7 MET-h/week
Patel, 2008	USA	Cancer Prevention Study II Nutrition Cohort	466	Baseline: 1992 End of follow-up: 2003	0.67	0.44	1.03	>=31.5 vs. 0-<7 METh/week
Friedenreich, 2007	Europe	European Prospective Investigation into Cancer	689	6.6	0.94	0.75	1.18	>=41.26 vs. <12.01 METh/week
Schouten, 2006	Netherlands	The Netherland Cohort Study	226	9.3	0.54	0.34	0.85	90 min vs. less than 30 min. per day
Friberg, 2006	Sweden	Swedish Mammography Cohort	225	7	0.90	0.67	1.21	>20 min/d vs. <20 min/d

Table 90 Overall evidence on recreational physical activity and endometrial cancer

	Summary of evidence
2005 SLR 2005	Four cohort studies reported on recreational physical activity and endometrial cancer, from which two studies reported significant inverse associations, one reported inverse but not significant association and one study did not find any association.
Continuous Update Project	Six additional cohort studies reported on recreational physical activity and endometrial cancer, and two found significant inverse association. One of these (Schouten et al, 2006) presented results already published in 2004. The other studies reported no significant inverse associations.

Table 91 Summary of results of the highest vs. lowest meta-analysis of recreational physical activity and endometrial cancer

Endometrial cancer		
	SLR 2005	Continuous Update Project
Studies (n)	4	9
Cases (n)	2696	3600
RR (95% CI)	0.57 (0.30-1.09)	0.73 (0.58-0.93)
Contrast	Highest vs. Lowest	Highest vs. Lowest
Heterogeneity (I^2, p-value)	82.2% p=0.001	75.9%, p=<0.0001
Sensitivity analysis of results adjusted by BMI	-	
Studies (n)	-	7
Cases (n)	-	3052
RR (95% CI)	-	0.80 (0.69-0.92)
Contrast	-	Highest vs. Lowest
Heterogeneity (I2, p-value)	-	21.2 %, p=0.268

Table 92 Inclusion/exclusion table for meta-analysis of recreational physical activity and endometrial cancer

WCRF code	Author	Year	Study design	Study name	Cancer outcome	SLR 2005	CUP HvL forest plot	Estimated values	Exclusion reason
END00218	Conroy	2009	Prospective cohort study	Women Health Study	Incidence	No	Yes	RR and CI recalculated because referent was highest level	-
END00216	Gierach	2009	Prospective cohort study	NIH-American Association of Retired People	Incidence	No	Yes	-	-
END00227	Patel	2008	Prospective cohort study	Cancer Prevention Study II and Nutrition	Incidence	No	Yes	-	-
END00245	Friedenreich	2007	Prospective cohort study	European Prospective Investigation into Cancer	Incidence	No	Yes	-	-
END00283	Friberg	2006	Prospective cohort study	Swedish Mammography Cohort	Incidence	No	Yes	-	-
END00246	Schouten	2006	Case-cohort study	The Netherland Cohort Study	Incidence	No	No	-	Used Schouten et al, 2004 with more data
END00119	Schouten	2004	Case-cohort study	The Netherland Cohort Study	Incidence	Yes	Yes	-	-
END00014	Furberg	2003	Prospective cohort study	Cohort from Norwegian National Health Screening	Incidence	Yes	Yes	-	-
END00160	Folsom	2003	Prospective cohort study	Iowa Women Health Study	Incidence	Yes	Yes	-	-
END00060	Terry	1999	Prospective cohort study	Cohort from Swedish Twin Registry	Incidence	Yes	Yes	-	-

Figure 70 Highest versus lowest forest plot of recreational physical activity and endometrial cancer

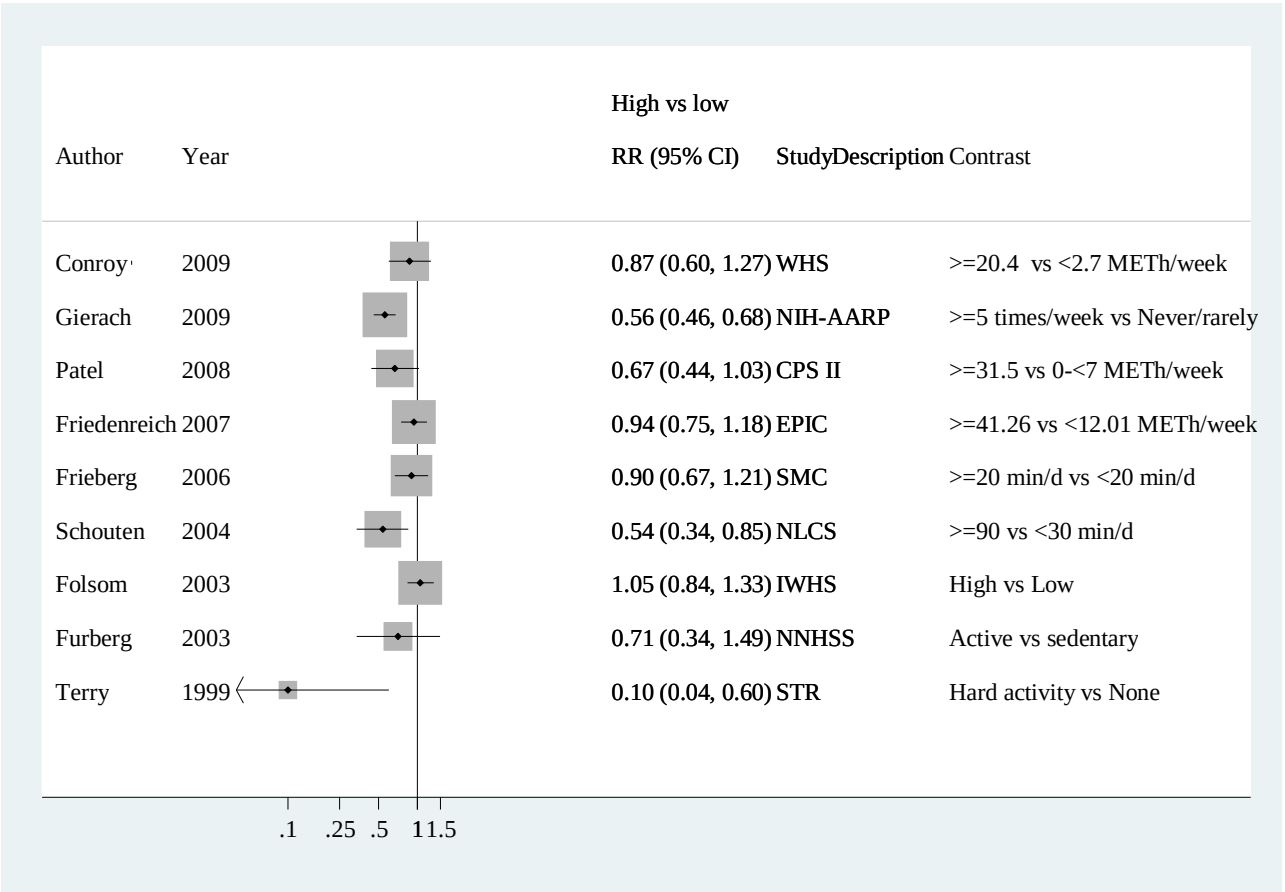


Figure 71 Funnel plot recreational physical activity and endometrial cancer

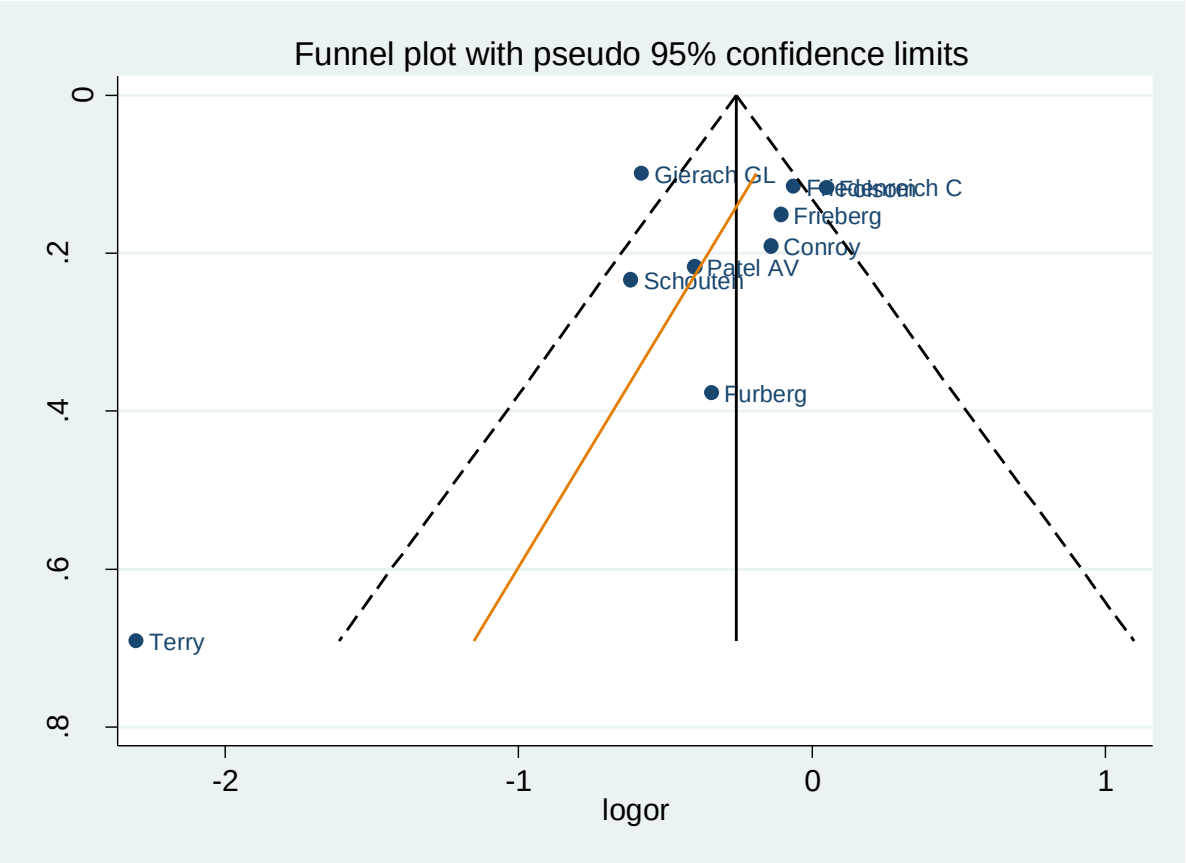
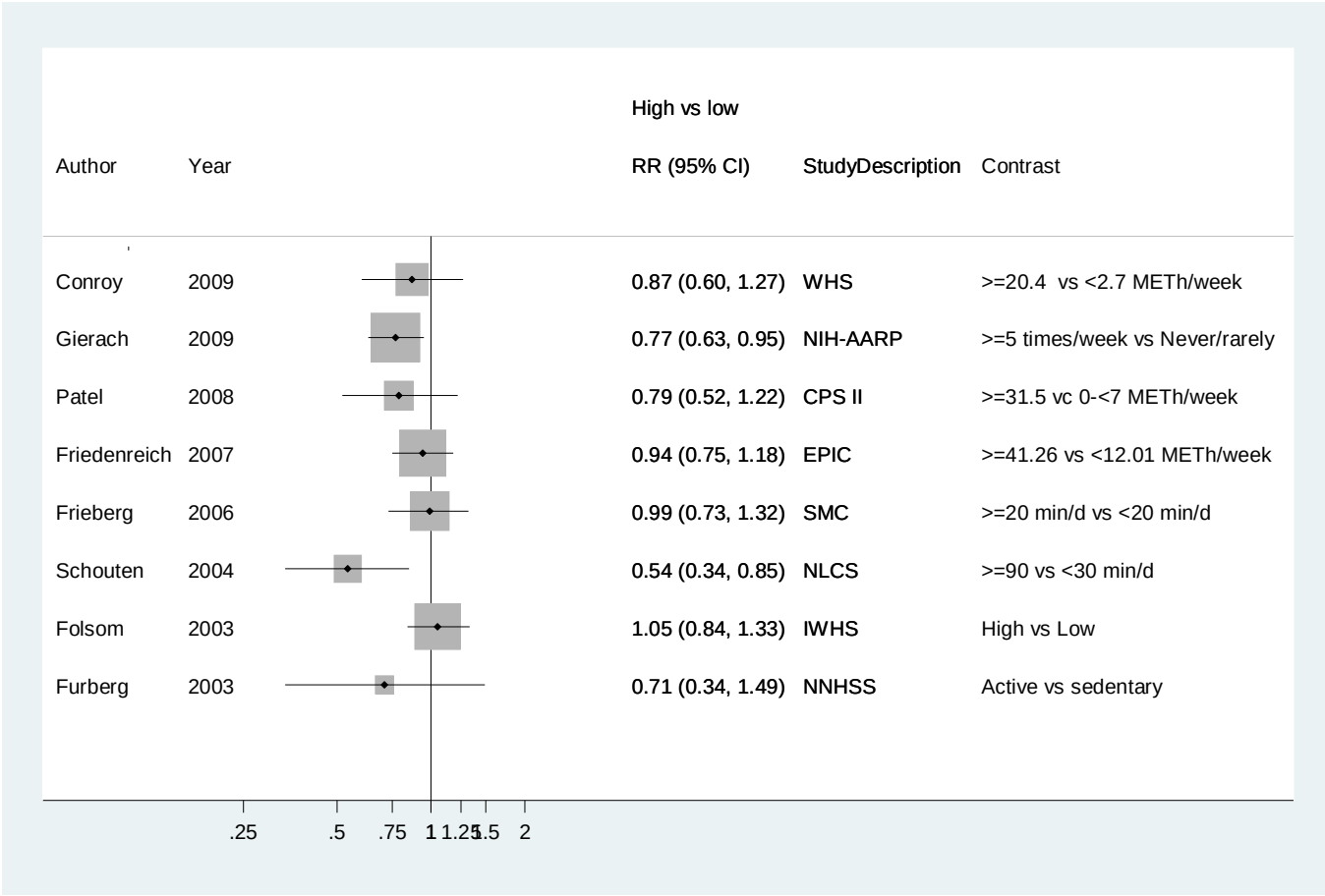


Figure 72 Highest versus lowest forest plot of recreational physical activity and endometrial cancer after adjustment for BMI



6.1.1.4 Walking/biking (mainly for transportation)

Methods

Five cohort studies have been published on walking/biking (mainly for transportation) and endometrial cancer risk up to 2012, four of which were identified in the CUP. Dose-response analyses were not possible because different measures of walking/biking were used in the studies. A highest versus lowest meta-analysis was conducted.

Main results

The summary RR for the highest vs. the lowest category of walking/biking reported in the articles was 0.88 (95% CI: 0.69-1.14, I^2=61.9%%, $p_{heterogeneity}$=0.033, n=5).

In sensitivity analysis of the influence of individual studies, analyses the relative risk estimate ranged from 0.97 (95% CI: 0.79-1.19) when the Netherlands Cohort Study was excluded (Schouten al. 2006) was excluded to 0.81 (95% CI: 0.61-1.08) when the NIH-AARP was excluded (Gierach et al. 2009).

None of the studies reported effect modification by BMI.

Heterogeneity

There was high heterogeneity across study results, I^2=61.9%, $p_{heterogeneity}$=0.033. This was due to the outlier result in the Netherlands cohort study (Schouten et al. 2006).

There was no evidence of publication bias with Egger test (p: 0.316) in the limited number of studies identified but visual inspection of the funnel plot indicates asymmetry due to a strong association observed in the Dutch study (Schouten et al. 2006).

Conclusion from the Second Expert Report

No meta-analysis was conducted. The Second Expert Report concluded that physical activity of all types probably protects against endometrial cancer risk.

Table 93 Studies on walking/biking (mainly for transportation) identified in the CUP

Author/year	Country	Study name	Cases	Years of follow-up	RR	LCI	UCI	Contrast
Conroy, 2009	USA	Women Health Study	264	8.8	1.14	0.79	1.64	>=2 h/week vs. no regular
Gierach, 2009	USA	NIH-American Association of Retired Persons	1052	3 yrs(cases) 7 yrs (non-cases)	1.17	0.88	1.54	10+ years vs. none or <1 year walked/byke to work
Friedenreich, 2007	Europe	European Prospective Investigation into Cancer	689	6.6	0.87	0.67	1.08	High vs. low
Friberg, 2006	Sweden	Swedish Mammography Cohort	225	7	0.71	0.45	1.1	High vs. low

Table 94 Overall evidence on walking/biking (mainly for transportation) and endometrial cancer

	Summary of evidence
2005 SLR 2005	A Dutch cohort study reported a significant inverse association between walking/biking (mainly for transportation) and endometrial cancer
Continuous Update Project	Four additional cohort studies were identified. None of them reported significant associations.

Table 95 Summary of results of the highest vs. lowest meta-analysis of walking/biking (mainly for transportation) and endometrial cancer

Endometrial cancer		
	SLR 2005*	Continuous Update Project
Studies (n)	-	5
Cases (n)		2456
RR (95% CI)		0.89 (95% CI: 0.69-1.14)
Contrast		Highest vs. Lowest
Heterogeneity (I^2, p-value)		61.9 %, p=0.033

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

Table 96 Inclusion/exclusion table for meta-analysis of walking/biking (mainly for transportation) and endometrial cancer

WCRF code	Author	Year	Study design	Study name	Cancer outcome	SLR 2005	CUP HvL forest plot	Estimated values	Exclusion reason
END00218	Conroy	2009	Prospective cohort study	Women Health Study	Incidence	No	Yes	RR and CI recalculated because referent was highest level	-
END00216	Gierach	2009	Prospective cohort study	NIH-American Association of Retired People	Incidence	No	Yes	-	-
END00245	Friedenreich	2007	Prospective cohort study	European Prospective Investigation into Cancer	Incidence	No	Yes	-	-
END00283	Friberg	2006	Prospective cohort study	Swedish Mammography Cohort	Incidence	No	Yes	-	-
END00119	Schouten	2004	Case-cohort study	The Netherland Cohort Study	Incidence	Yes	Yes	-	-

Figure 73 Highest versus lowest forest plot of walking/biking and endometrial cancer

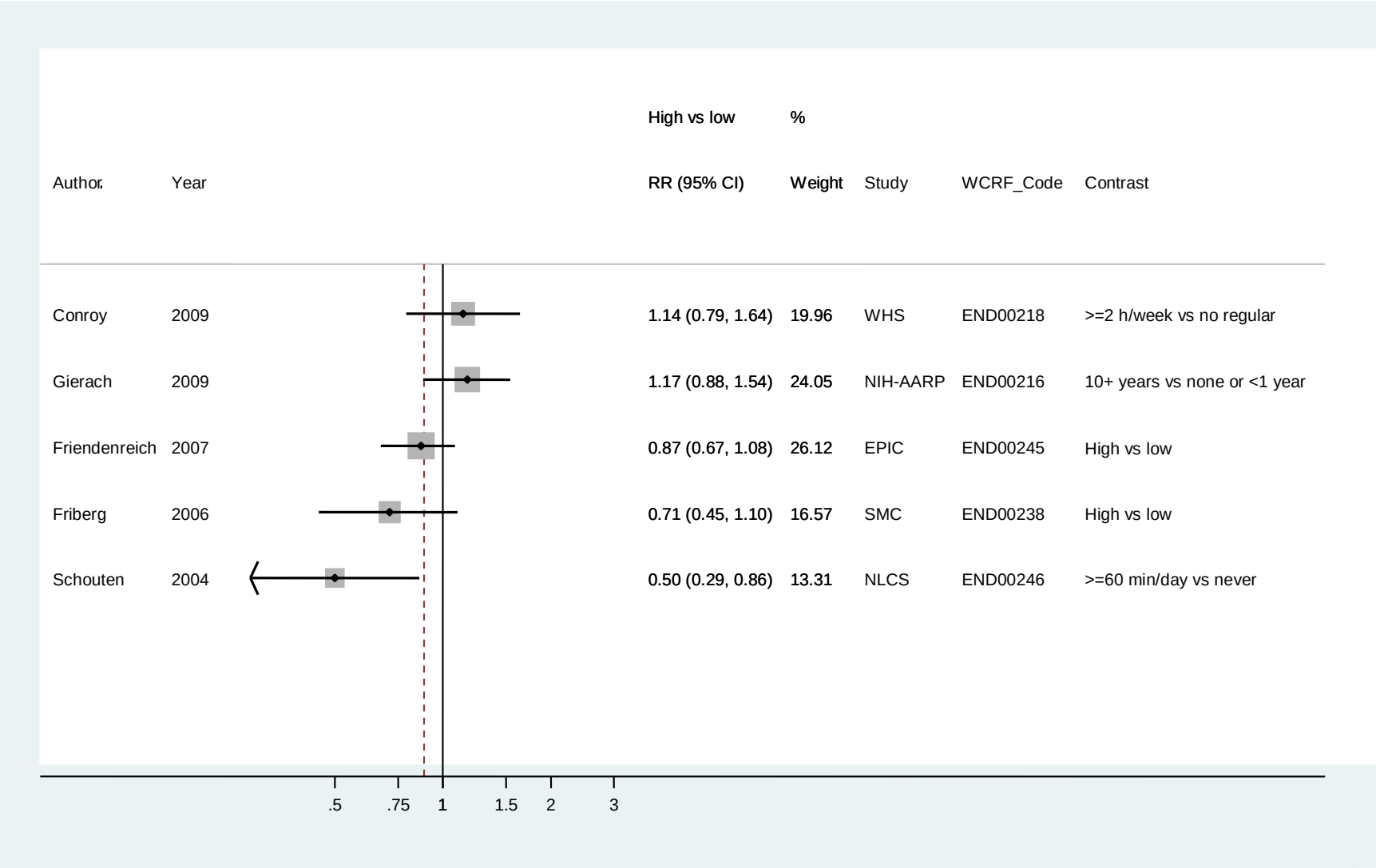
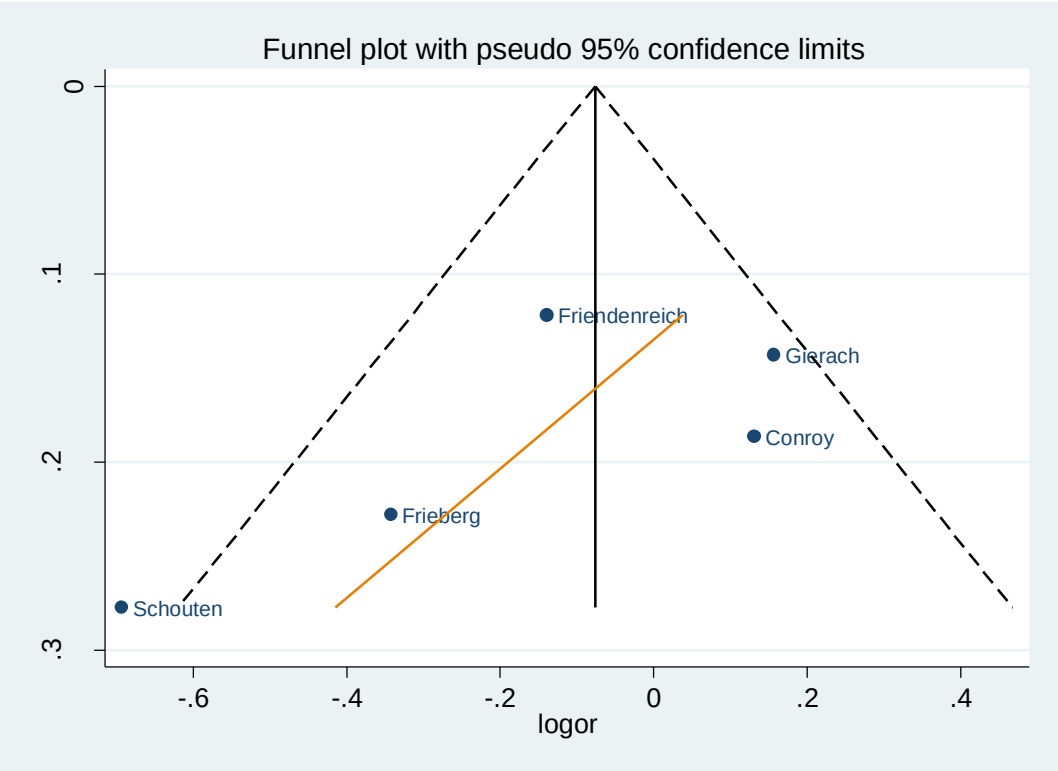


Figure 74 Funnel plot walking/biking (mainly for transportation) and endometrial cancer



6.1.1.5 Exercise/sport

Methods

Three studies on incidence and one on mortality have been identified, one during the literature review for the SLR 2005 and three during the CUP. Dose-response analyses were not possible because of different measures used in the studies. A highest versus lowest meta-analysis was conducted. The study on mortality was excluded from the analysis.

Main results

The summary RR for the highest vs. the lowest level of exercise/sport was 0.81 (95% CI: 0.56-1.17, I^2=66.2%, $p_{heterogeneity}$=0.052, n=3).

None of the studies reported effect modification by BMI.

The Japanese study with mortality for endometrial cancer as endpoint reported no association of sport activity with mortality for endometrial cancer (Khan et al, 2006).

Heterogeneity

There was evidence of high heterogeneity (I^2=66.2 %, $p_{heterogeneity}$=0.052).

Conclusion from the Second Expert Report

No meta-analysis was conducted. The Second Expert Report concluded that physical activity of all types probably protects against endometrial cancer risk.

Table 97 Studies on exercise/sport identified in the CUP

Author/year	Country	Study name	Cases	Years of follow-up	RR	LCI	UCI	Contrast
Patel, 2008	USA	Cancer Prevention Study II and Nutrition	466	Baseline: 1992 End of follow-up: 2003	0.61	0.46	0.8	Consistently high vs. none/low
Friberg, 2006	Sweden	Swedish Mammography Cohort	225	7	0.99	0.73	1.32	High vs. low
Khan, 2006	Japan	Japan Collaborative Cohort Study	22	13.3	1.16	0.41	3.28	>=1-2 hour/week vs. seldom

Table 98 Overall evidence on exercise/sport and endometrial cancer

	Summary of evidence
2005 SLR 2005	One study did not find association between sport/exercise and endometrial cancer.
Continuous Update Project	Three cohort studies, two on incidence and one on mortality have been identified. Only one study on incidence reported a significant inverse association of sport/exercise activities and endometrial cancer.

Table 99 Summary of results of the highest vs. lowest meta-analysis of exercise/sport and endometrial cancer

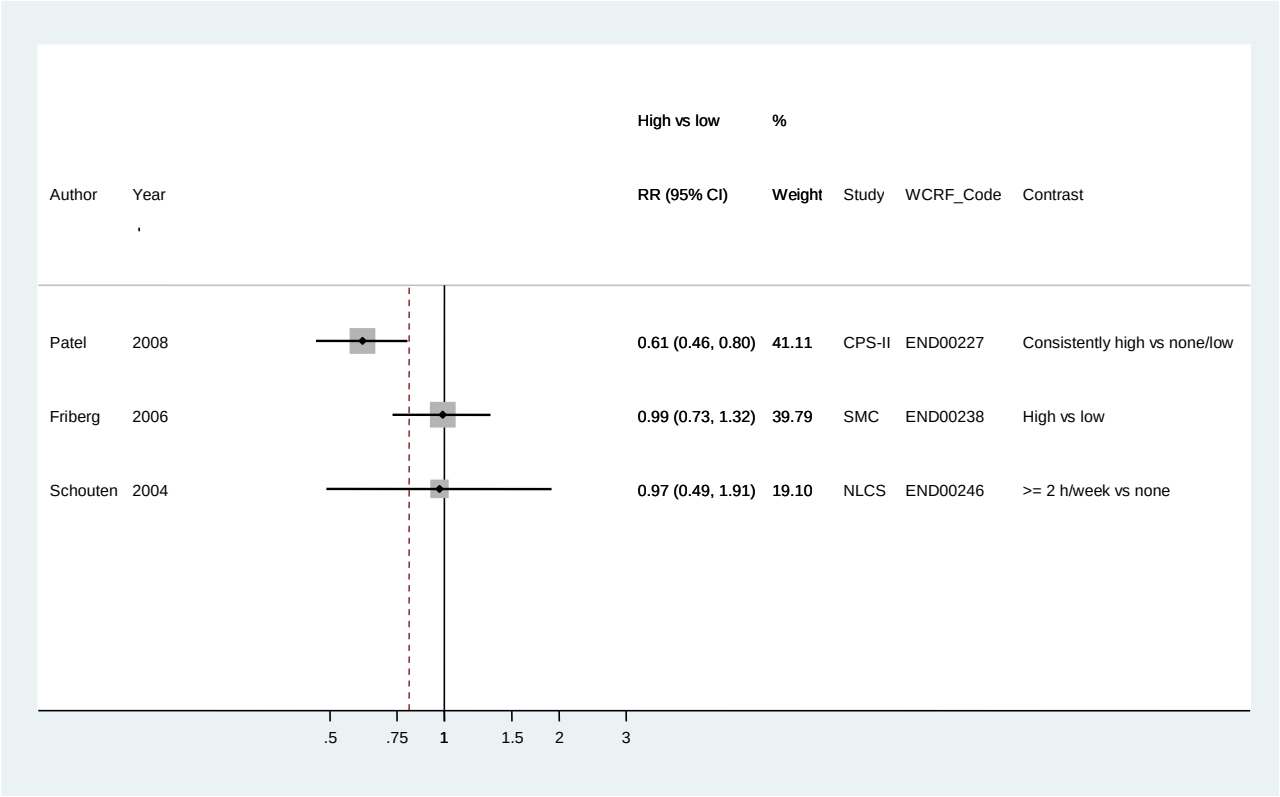
Endometrial cancer		
	SLR 2005*	Continuous Update Project
Studies (n)	-	3
Cases (n)		917
RR (95% CI)		0.81 (0.56-1.17)
Contrast		Highest vs. Lowest
Heterogeneity (I^2, p-value)		66.2%, p=0.052

*Only one study identified during the SLR 2005

Table 100 Inclusion/exclusion table for meta-analysis of exercise/sport and endometrial cancer

WCRF code	Author	Year	Study design	Study name	Cancer outcome	SLR 2005	CUP HvL forest plot	Estimated values	Exclusion reason
END00227	Patel	2008	Prospective cohort study	Cancer Prevention Study II and Nutrition	Incidence	No	Yes	-	-
END00242	Friberg,	2006	Prospective cohort study	Swedish Mammography Cohort	Incidence	No	Yes	-	-
END00238	Khan	2006	Prospective cohort study	Japan Collaborative Cohort Study	Mortality	No	No		Mortality as endpoint
END00246	Schouten	2004	Case-cohort	The Netherlands Cohort Study	Incidence	Yes	Yes	-	

Figure 75 Highest versus lowest forest plot of exercise/sport and endometrial cancer



6.1.3 Vigorous activity

Methods

Four cohort studies have been published on vigorous physical activity and endometrial cancer risk up to 2012, three of which were identified in the CUP. Dose-response analyses were not possible because different measures of physical activity were used in the studies. A highest versus lowest meta-analysis was conducted.

Main results

The summary RR for the highest vs. the lowest category of vigorous physical activity reported in the articles was 0.88 (95% CI: 0.61-1.26, I^2=85.0 % $p_{heterogeneity}$=<0.0001, n=4).

In the NIH-AARP Diet and Health Study (Gierach, 2009), there was some suggestion of an interaction for BMI (p for interaction: 0.12). The relationship of vigorous physical activity with endometrial cancer was not significant in normal weight women (P for trend: 0.92) but it was significant for all the levels of vigorous physical activity considered (from 1-3 times/month up to 5+ times/week) compared to never/rarely in obese women. A significant trend was observed in obese women (p for trend<0.0001).The three other studies don't report or don't explore effect modification.

Heterogeneity

There was high heterogeneity across study results, I^2=85.0 %, $p_{heterogeneity}$=<0.0001.

Conclusion from the Second Expert Report

No meta-analysis was conducted. The Second Expert Report concluded that physical activity of all types probably protects against endometrial cancer risk.

Table 101 Studies on vigorous physical activity identified in the CUP

Author/year	Country	Study name	Cases	Years of follow-up	RR	LCI	UCI	Contrast
Conroy, 2009	USA	Women Health Study	264	8.8	1.15	0.76	1.72	>15 MET h/week vs. None
Gierach, 2009	USA	NIH-American Association of Retired Persons	1052	3 yrs(cases) 7 yrs (non-cases)	0.56	0.46	0.68	5< times/week vs. never/rarely
Friedenreich, 2007	Europe	European Prospective Investigation into Cancer	689	6.6	0.93	0.74	1.16	High vs. low

Table 102 Overall evidence on vigorous physical activity and endometrial cancer

	Summary of evidence
2005 SLR 2005	One cohort study reported no association
Continuous Update Project	Three additional cohort studies were identified. Only one study reported significant inverse association.

Table 103 Summary of results of the highest vs. lowest meta-analysis of vigorous physical activity and endometrial cancer

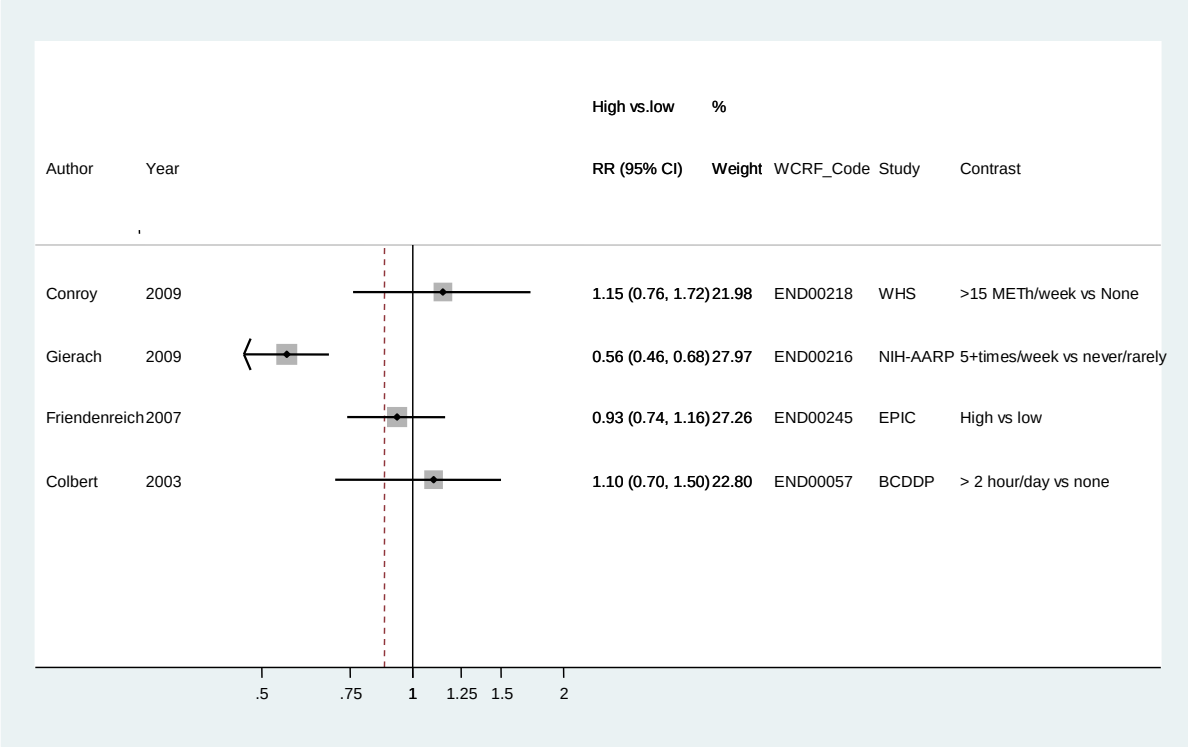
Endometrial cancer		
	SLR 2005*	Continuous Update Project
Studies (n)	-	4
Cases (n)		2258
RR (95% CI)		0.88 (0.61-1.26)
Contrast		Highest vs. Lowest
Heterogeneity (I^2, p-value)		85.0 %, p=<0.0001

*No meta-analysis was conducted for the SLR 2005

Table 104 Inclusion/exclusion table for meta-analysis of vigorous physical activity and endometrial cancer

WCRF code	Author	Year	Study design	Study name	Cancer outcome	SLR 2005	CUP HvL forest plot	Estimated values	Exclusion reason
END00218	Conroy	2009	Prospective cohort study	Women Health Study	Incidence	No	Yes	-	-
END00216	Gierach	2009	Prospective cohort study	NIH-American Association of Retired People	Incidence	No	Yes	-	-
END00245	Friedenreich	2007	Prospective cohort study	European Prospective Investigation into Cancer	Incidence	No	Yes	-	-
END00057	Colbert	2003	Prospective cohort study	Breast Cancer Diagnosis Demonstration Project	Incidence	Yes	Yes	-	-

Figure 76 Highest versus lowest forest plot of vigorous physical activity and endometrial cancer



6.2 Sitting time

Methods

Three studies were identified, all during the CUP. Dose-response analyses were not possible because different measures were used in the studies. A highest versus lowest meta-analysis was conducted.

Main results

The summary RR for the highest vs. the lowest level of time spent sitting was 1.46 (95% CI: 1.21-1.76, I^2=0%, $p_{heterogeneity}$=0.827, n=3). After adjustment for BMI, the relative risks estimates were attenuated; in one study the relative risk estimate remained significant (Friberg et al, 2006) and in another study the trend remained significant (Moore et al, 2010).

Heterogeneity

There was no evidence of heterogeneity (I^2=0 %, $p_{heterogeneity}$=0.827).

Conclusion from the Second Expert Report

No cohort study was identified in the SLR 2005.

Table 105 Studies on sitting time identified in the CUP

Author/year	Country	Study name	Cases	Years of follow-up	RR	LCI	UCI	Contrast
Moore, 2009	USA	NIH-American Association of Retired Persons	1052	3 yrs (cases) 7yrs (non-cases)	1.45	1.1	1.92	9+h/day vs. <3 h
Patel, 2008	USA	Cancer Prevention Study II and Nutrition	466	Baseline: 1992 End of follow-up: 2003	1.4	1.03	1.89	6+ vs. <3 hour/day
Friberg, 2006	Sweden	Swedish Mammography Cohort	225	7	1.66	1.05	2.61	High vs. low

Table 106 Overall evidence on sitting time activity and endometrial cancer

	Summary of evidence
2005 SLR 2005	No study identified during the SLR 2005.
Continuous update	Three cohort studies reported on sitting time and endometrial cancer; all of them found significant positive association between sitting time and endometrial cancer risk.

Table 107 Summary of results of the highest vs. lowest meta-analysis of sitting time and endometrial cancer

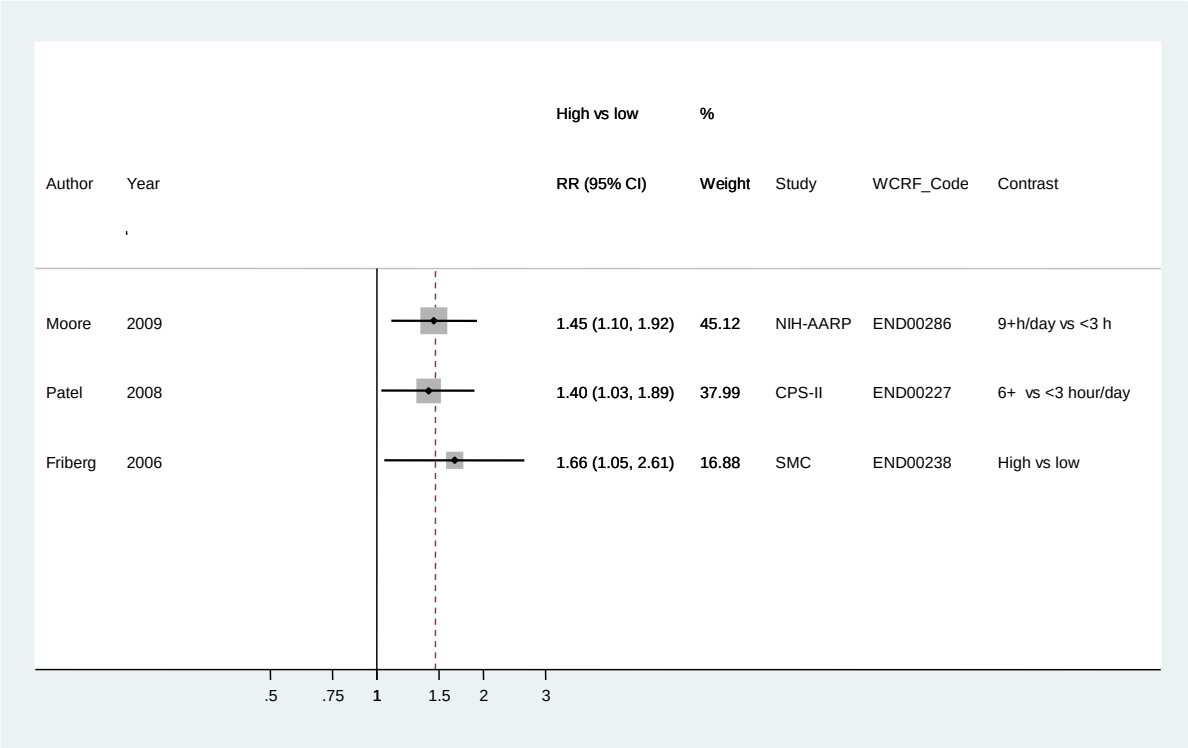
Endometrial cancer		
	SLR 2005*	Continuous Update Project
Studies (n)	-	3
Cases (n)		1579
RR (95% CI)		1.46 (1.21-1.76)
Contrast		Highest vs. Lowest
Heterogeneity (I^2, p-value)		0%, p=0.827

*No study identified during the Second Expert Report

Table 108 Inclusion/exclusion table for meta-analysis of sitting time and endometrial cancer

WCRF code	Author	Year	Study design	Study name	Cancer outcome	SLR 2005	CUP HvL forest plot	Estimated values	Exclusion reason
END00286	Moore	2009	Prospective cohort study	NIH-American Association of Retired Persons	Incidence	No	Yes	-	-
END00227	Patel	2008	Prospective cohort study	Cancer Prevention Study II and Nutrition	Incidence	No	Yes	-	-
END00242	Friberg,	2006	Prospective cohort study	Swedish Mammography Cohort	Incidence	No	Yes	-	-

Figure 77 Highest versus lowest forest plot of sitting time and endometrial cancer



8 Anthropometry

8.1.1 BMI

Methods

A total of 34 cohort studies (50 publications) have been published on BMI, at cohort enrolment, and endometrial cancer risk up to December 2012. Four studies were on endometrial cancer as second primary cancer and were not included. From the 34 cohort studies, 18 studies (24 publications) were identified in the CUP. Dose-response analyses were conducted per 5 units increase in BMI (kg/m^2). Several studies used the second lowest category as a reference category due to limited number of cases in the lowest category and when this was the case the lowest category was excluded from the analyses in the linear dose-response analyses. We also did a sensitivity analysis not excluding the lowest category, but converting the risk estimates using the method by Hamling et al, 2008, so that the lowest category was the reference. This method was also used for the nonlinear dose-response analysis. For the analysis stratified by hormone replacement therapy use, most studies reported results for ever vs. never users. For this reason we pooled the results for former and current users in one study (which did not report results for ever users) using a fixed effects model (Chang et al, 2007), so that the study could be included in the analysis of ever vs. never users.

Main results

The summary RR per 5 units increase in BMI (kg/m^2) was 1.50 (95% CI: 1.42-1.59, I^2=86.2%, $p_{heterogeneity}$<0.0001, n=26 studies, 25 risk estimates). In the sensitivity analysis using the converted risk estimates, the summary RR per 5 units increase in BMI was 1.56 (95% CI: 1.48-1.64, I^2=79.8%, $p_{heterogeneity}$<0.0001). There was no evidence of publication bias with Egger's test, p=0.21, however, the funnel plot suggested asymmetry. There was evidence of nonlinearity, $p_{nonlinearity}$<0.0001, with a steeper increase in risk at higher BMI levels. Although there was some suggestion of a J-shaped curve with a slight increase in risk at very low BMI levels it is possible that this may be an artefact due to differing reference category levels as it can be seen in the scatter plot that there are no studies suggesting increased risk at low levels of BMI.

Additional analyses were conducted by menopausal status. Two studies reported results for both premenopausal and postmenopausal women and eight reported results only for postmenopausal women. In addition, two studies reported results stratified by age (Tornberg et al, 1994: ≥55 vs. <55 years and Bjørge et al, 2006: 50-74 vs. 20-49 years) and one study reported results among women aged ≥55 years (Schouten et al, 2004). The higher and lower age ranges were considered to be approximate indicators of postmenopausal and premenopausal status, respectively, and were included in these analyses. The summary RR per 5 units increase in BMI was 1.41 (95% CI: 1.37-1.45, I^2=0%, $p_{heterogeneity}$=0.53, n=4) for

premenopausal women and 1.51 (95% CI: 1.38-1.65, I^2=91.9%, $p_{heterogeneity}$<0.0001, n=13) for postmenopausal women.

When we conducted analyses among two studies (Friedenreich, 2007 and Reeves, 2011) that also adjusted for waist-to-hip ratio, the summary RR was 1.28 (95% CI: 1.17-1.40, I^2=45.9%, $p_{heterogeneity}$=0.17) per 5 units increase in BMI.

In additional subgroup analyses by hormone replacement therapy (HRT) use, the association was much stronger among never users of HRT than among ever users, summary RR = 1.73 (95% CI: 1.44-2.08, I^2=87%) in never HRT users vs. 1.15 (95% CI: 1.06-1.25, I^2=0%) among ever HRT users.

Heterogeneity

There was high heterogeneity, I^2=89.5%, $p_{heterogeneity}$<0.0001.

Conclusion from the Second Expert Report

In the SLR of the 2007 Expert Report the evidence relating body fatness to increased endometrial cancer risk was considered convincing.

Published meta-analyses

A meta-analysis of 4 population-based case-control studies reported a summary RR of 1.10 (95% CI: 1.07-1.12) per 1 unit (Bergström et al, 2001).

A meta-analysis of 19 prospective studies reported a summary RR of 1.59 (95% CI: 1.50-1.68, I^2=77%, $p_{heterogeneity}$<0.0001) per 5 units increase in BMI (Renehan et al, 2008).

In an updated meta-analysis of 24 prospective studies, the summary RR per 5 units increase in BMI was 1.60 (95% CI: 1.52-1.68) (Crosbie et al, 2010).

Table 109 Studies on BMI identified in the CUP

Author/year	Country	Study name	Cases	Years of follow-up	RR	LCI	UCI	Contrast
Yang, 2013	USA	NIH-AARP Diet and Health Study	1312 type 1 138 type 2	9.4 years	2.93 1.83	2.62 1.27	3.28 2.63	≥30 vs. <30 ≥30 vs. <30
Yang, 2012	United Kingdom	Million Women's Study	1410	7.3 years	7.72 1.87	6.79 1.77	8.77 1.96	≥35 vs. <22.5 Per 5 units
Ollberding, 2012	USA	Multiethnic Cohort Study	489	13.6 years	2.68	2.10	3.42	≥30 vs. <25

Reeves, 2011	USA	Women's Health Initiative	806	7.8 years	1.76	1.41	2.19	≥30 vs. <25
Park, 2010	USA	Multiethnic Cohort Study	463	10.3 years	3.54	2.70	4.63	≥30 vs. <25
Dossus, 2010	Europe	European Prospective Investigation into Cancer and Nutrition	305	NA	2.02	1.26	3.23	≥30 vs. <25
Allen, 2010	Europe	European Prospective Investigation into Cancer and Nutrition	247	9 years	2.67	1.63	4.37	≥30 vs. <25
Canchola, 2010	USA	California Teachers Study	395	9.1 years	 3.5 1.07 1.6 1.04 1.0 1.03	 2.2 1.04 0.88 1.00 0.63 0.99	 5.5 1.09 2.8 1.08 1.7 1.06	never HT use: ≥30 vs. <25 Per 1 unit Ever estrogen use: ≥30 vs. <25 Per 1 unit Used estrogen and progesterone exclusively: ≥30 vs. <25 Per 1 unit
Conroy, 2009	USA	Women's Health Study	264	8.8 years	2.49	1.73	3.59	≥30 vs. <22.5
Epstein, 2009	Sweden	Lund Cohort	166	15.5 years	3.5	2.2	5.4	>29 vs. <25
Lindemann, 2009	Norway	Hunt II	100	9 years	8.59	3.29	22.44	≥40 vs. <25
Lindemann, 2009	Norway	Hunt I	224	17.8 years	8.3	4.1	16.7	≥40 vs. <20
Lindemann, 2008	Norway	Hunt I	222	15.7 years	6.36	3.08	13.16	≥40 vs. <20
McCullough, 2008	USA	CPS II Nutrition Cohort	318	11 years	4.70	3.12	7.07	≥35 vs. <22.5
Song, 2008	Korea	Korean Cancer Prevention Study	112	8.75 years	2.95	1.20	7.24	≥30 vs. 21-22.9
Lundqvist, 2007	Sweden	Sweden, Finland Co-twin study	214	26.3 years	3.2 1.11 2.9 1.09	2.1 1.06 1.4 1.04	4.8 1.15 5.9 1.14	≥30 vs. 18.5-<25 Per unit ≥30 vs. 18.5-<25 Per unit
Chang, 2007	USA	NIH-AARP Diet and Health Study	677	4.6 years	3.03	2.50	3.68	≥30 vs. <25
Friedenreich, 2007	Europe	European Prospective Investigation into Cancer and Nutrition	567	6.4 years	3.02 1.06	1.66 1.04	5.52 1.08	≥40 vs. <25 Per 1 unit
Reeves, 2007	UK	The Million Women Study	2657	5.4 years	2.73 2.89	2.55 2.62	2.92 3.18	≥30 vs. <22.5 Per 10 units

Löf, 2007	Sweden	Women's Lifestyle and Health Study	73	~12 years	3.05	1.6	5.82	≥30 vs. <25
Bjørge, 2007	Norway	Norwegian Health Surveys	9227	25 years	2.51	2.38	2.66	≥30 vs. <18.5
Khan, 2006	Japan	Japan Collaborative Cohort Study	14 deaths	13.3 years	0.79	0.08	7.70	≥25 vs. <18.5
Setiawan, 2006	USA	Multiethnic Cohort Study	321	7.3 years	3.14	2.33	4.22	≥30 vs. <25
Yamazawa, 2006	Japan	NA	6	122 months	0.65	0.07	5.42	≥25 vs. <25

NA: Not available

Table 110 Overall evidence on BMI and endometrial cancer

	Summary of evidence
2005 SLR 2005	Twenty two cohort studies reported on BMI and endometrial cancer and found a significant positive association. All of the nineteen studies included in the high vs. low analysis showed positive associations, with only four of these showing non-significant associations.
Continuous Update Project	Eleven additional cohort studies (not included in the 2005 SLR) reported on BMI and endometrial cancer and all found increased risk.

Table 111 Summary of results of the dose-response meta-analysis of BMI and endometrial cancer

Endometrial cancer		
	SLR 2005	Continuous Update Project
Studies (n)	15	25[1]
Cases (n)	3484	18717
RR (95% CI)	1.52 (1.48-1.57)	1.50 (1.42-1.59)
Quantity	Per 5 units BMI kg/m^2	Per 5 units BMI kg/m^2
Heterogeneity (I^2, p-value)	88.0%, p<0.001	86.2%, p<0.0001

[1] One publication (Lundqvist et al, 2007) was from a combined analysis of two studies (25 risk estimates, 26 studies).

Table 112 Inclusion/exclusion table for meta-analysis of BMI and endometrial cancer

WCRF code	Author	Year	Study design	Study name	Cancer outcome	SLR 2005	CUP dose-response	CUP H vs. L forest plot	Estimated values	Exclusion reason
END00293	Yang	2013	Prospective Cohort Study	NIH-AARP Diet and Health Study	Incidence	No	No	Yes		Only high vs. low comparison
END00295	Yang	2012	Prospective Cohort Study	The Million Women Study	Incidence	No	No	No		Overlap with Reeves et al, 2007, END00251, which had a larger number of cases
END00265	Ollberding	2012	Prospective Cohort Study	Multiethnic Cohort Study	Incidence	No	No	No		Overlap with END00206 by Park et al, 2010 which provided the distribution of cases and controls
END00253	Reeves	2011	Prospective Cohort Study	Women's Health Initiative	Incidence	No	Yes	Yes	Midpoints, person-years	
END00206	Park	2010	Prospective Cohort Study	Multiethnic Cohort Study	Incidence	No	Yes	Yes	Midpoints, person-years	
END00236	Dossus	2010	Nested case-control study	European Prospective Investigation into Cancer and Nutrition	Incidence	No	No	No		Overlap with END00237 by Friedenreich et al, 2007
END00244	Allen	2010	Nested case-control study	European Prospective Investigation into Cancer and Nutrition	Incidence	No	No	No		Overlap with END00237 by Friedenreich et al, 2007
END00213	Canchola	2010	Prospective cohort study	California Teacher's Study	Incidence	No	Yes	Yes	Midpoints	

END00218	Conroy	2009	Prospective cohort study	Women's Health Study	Incidence	No	Yes	Yes	Midpoints, person-years	
END00219	Epstein	2009	Prospective cohort study	Lund Cohort	Incidence	No	Yes	Yes	Midpoints, person-years	
END00281	Lindemann	2009	Prospective cohort study	Hunt II	Incidence	No	Yes	Yes	Midpoints, cases, person-years	
END00284	Lindemann	2009	Prospective cohort study	Hunt I	Incidence	No	No	No		Overlap with END00228 by Lindemann et al, 2008
END00228	Lindemann	2008	Prospective cohort study	Hunt I	Incidence	No	Yes	Yes	Midpoints, person-years	
END00208	McCullough	2008	Prospective cohort study	CPS II Nutrition Cohort	Incidence	No	Yes	Yes	Midpoints	
END00267	Song	2008	Prospective cohort study	Korean Cancer Prevention Study	Incidence	No	Yes	Yes	Midpoints	
END00268	Lundqvist	2007	Prospective cohort study	Sweden, Finland Co-twin study	Incidence	No	Yes	Yes	Midpoints, person-years	
END00241	Chang	2007	Prospective cohort study	NIH-AARP Diet and Health Study	Incidence	No	Yes	Yes	Midpoints	
END00237	Friedenreich	2007	Prospective cohort study	European Prospective Investigation into Cancer and Nutrition	Incidence	No	Yes	Yes	Midpoints	
END00251	Reeves	2007	Prospective cohort study	The Million Women Study	Incidence Mortality	No	Yes	Yes	Midpoints, person-years	
END00230	Löf	2007	Prospective cohort study	Women's Lifestyle and Health Study	Incidence	No	Yes	Yes	Midpoints, person-years	
END00272	Bjørge	2007	Prospective cohort study	Norwegian Health Surveys	Incidence	No	Yes	Yes	Midpoints	
END00196	Lukanova	2006	Prospective cohort study	Northern Sweden Health and Disease	Incidence	Yes	Yes	Yes	Midpoints	

				Cohort						
END00238	Khan	2006	Prospective cohort study	Japan Collaborative Cohort Study	Mortality	No	No	No		Outcome was mortality
END00232	Setiawan	2006	Prospective cohort study	Multiethnic Cohort Study	Incidence	No	No	No		Overlap with END00206 by Park et al, 2010
END00198	Yamazawa	2006	Prospective cohort study	NA	Incidence	No	No	No		Study population consisted of breast cancer cases so outcome was secondary cancer
END00180	Kuriyama	2005	Prospective cohort study	Miyagi Cohort Study	Incidence	Yes	Yes	Yes	Midpoints, person-years	
END00191	Lacey	2005	Prospective cohort study	Breast Cancer Detection Demonstration Project	Incidence	Yes	Yes	Yes	Cases, midpoints	
END00199	Rapp	2005	Prospective cohort study	The Vorarlberg Health Monitoring and Promotion Program	Incidence	Yes	Yes	Yes	Midpoints	
END00201	Silvera	2005	Prospective cohort study	Canadian National Breast Screening Study	Incidence	Yes	Yes	Yes	Midpoints	
END00246	Schouten	2004	Prospective cohort study	Netherlands Cohort Study	Incidence	Yes	Yes	Yes	Midpoints	
END00064	Folsom	2003	Prospective cohort study	Iowa Women's Health Study	Incidence	Yes	Yes	Yes	Midpoints	
END00014	Furberg	2003	Prospective cohort study	Norwegian National Health Screening Survey	Incidence	Yes	No	No		Overlap with Bjørge et al, 2006, END00272
END00074	Jonsson	2003	Prospective cohort study	Swedish Twin Cohort	Incidence	Yes	No	No		Overlap with END00268 by Lundqvist et al, 2007
END00135	Calle	2003	Prospective	Cancer	Mortality	Yes	No	No		Overlap with

			cohort study	Prevention Study II (ACS cohort)						END00208 by McCullough et al, 2008 which reported on incidence and therefore was preferred
END00124	Pukkala	2002	Prospective cohort study	Finnish Breast Cancer Cohort	Incidence	Yes	No	No		Study population consisted of breast cancer cases so outcome was secondary cancer
END00132	Zeleniuch-Jacquotte	2001	Nested case-control study	New York University Women's Health Study	Incidence	Yes	No	No		No risk estimates
END00126	Anderson	2001	Prospective cohort study	Iowa Women's Health Study	Incidence	Yes	No	No		Overlap with END00064 by Folsom et al, 2003
END00160	Folsom	2000	Prospective cohort study	Iowa Women's Health Study	Incidence	Yes	No	No		Overlap with END00064 by Folsom et al, 2003
END00009	Jain	2000	Prospective cohort study	Canadian National Breast Screening Study	Incidence	Yes	No	No		Overlap with END00201 by Silvera et al, 2005
END00149	Olson	1999	Prospective cohort study	Iowa Women's Health Study	Incidence	Yes	No	No		Overlap with END00064 by Folsom et al, 2003
END00116	Bernstein	1999	Prospective cohort study	NA	Incidence	Yes	No	No		Study population consisted of breast cancer cases so outcome was secondary cancer
END00137	Tulinius	1997	Prospective cohort study	Icelandic Cohort	Incidence	Yes	Yes	No		Only continuous risk estimate
END00094	De Waard	1996	Case cohort study	Breast Screening Cohort	Incidence	Yes	Yes	Yes	Midpoints, confidence intervals, person-years	

END00133	Tornberg	1994	Prospective cohort study	Swedish Screening Cohort	Incidence	Yes	Yes	Yes	Midpoints, confidence intervals	
END00041	Gapstur	1993	Prospective cohort study	Iowa Women's Health Study	Incidence	Yes	No	No		Overlap with END00064 by Folsom et al, 2003
END00069	Le Marchand	1991	Prospective cohort study	Hawaii Historical Cohort	Incidence	Yes	No	Yes		BMI was not quantified
END00073	Tretli	1990	Prospective cohort study	Norwegian National Health Screening Service	Incidence	Yes	No	No		Overlap with END00272 by Bjorge et al, 2007
END00058	Folsom	1989	Prospective cohort study	Iowa Women's Health Study	Incidence	Yes	No	No		Overlap with END00064 by Folsom et al, 2003
END00072	Baanders-van-Halewijn	1985	Prospective cohort study	The Dioagnostisch Underzoek Mamma-carcinom (DOM) project	Incidence	Yes	No	No		Overlap with END00094, by de Waard et al, 1996
END00071	Ewertz	1984	Nested case-control study	Danish CC	Incidence	Yes	No	No		Study population consisted of breast cancer cases so outcome was secondary cancer

NA: Not available

Figure 78 Highest versus lowest forest plot of BMI and endometrial cancer

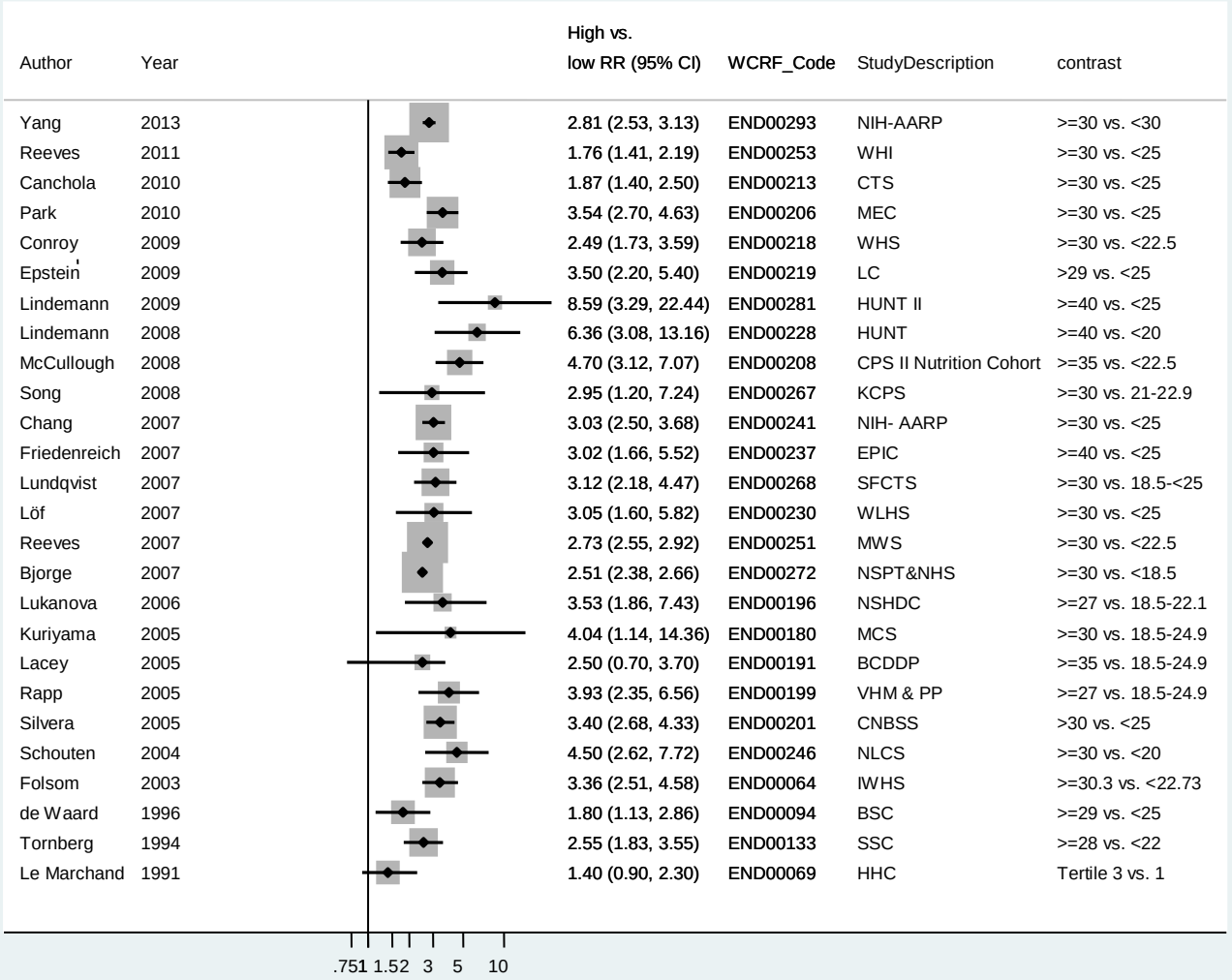


Figure 79 Dose-response meta-analysis of BMI and endometrial cancer, per 5 units

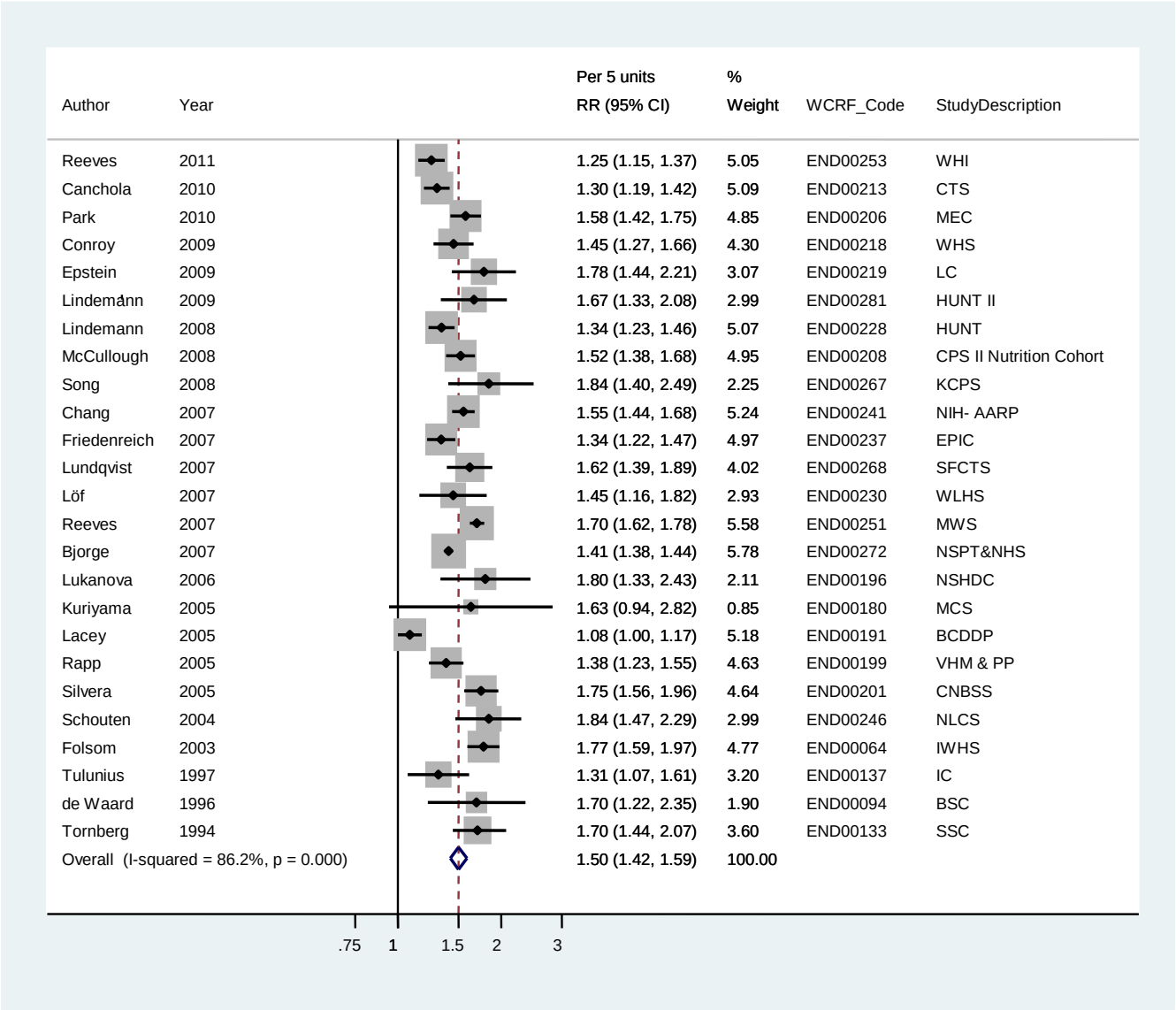


Figure 80 Figure Dose-response meta-analysis of BMI and endometrial cancer, per 5 units, stratified by menopausal status

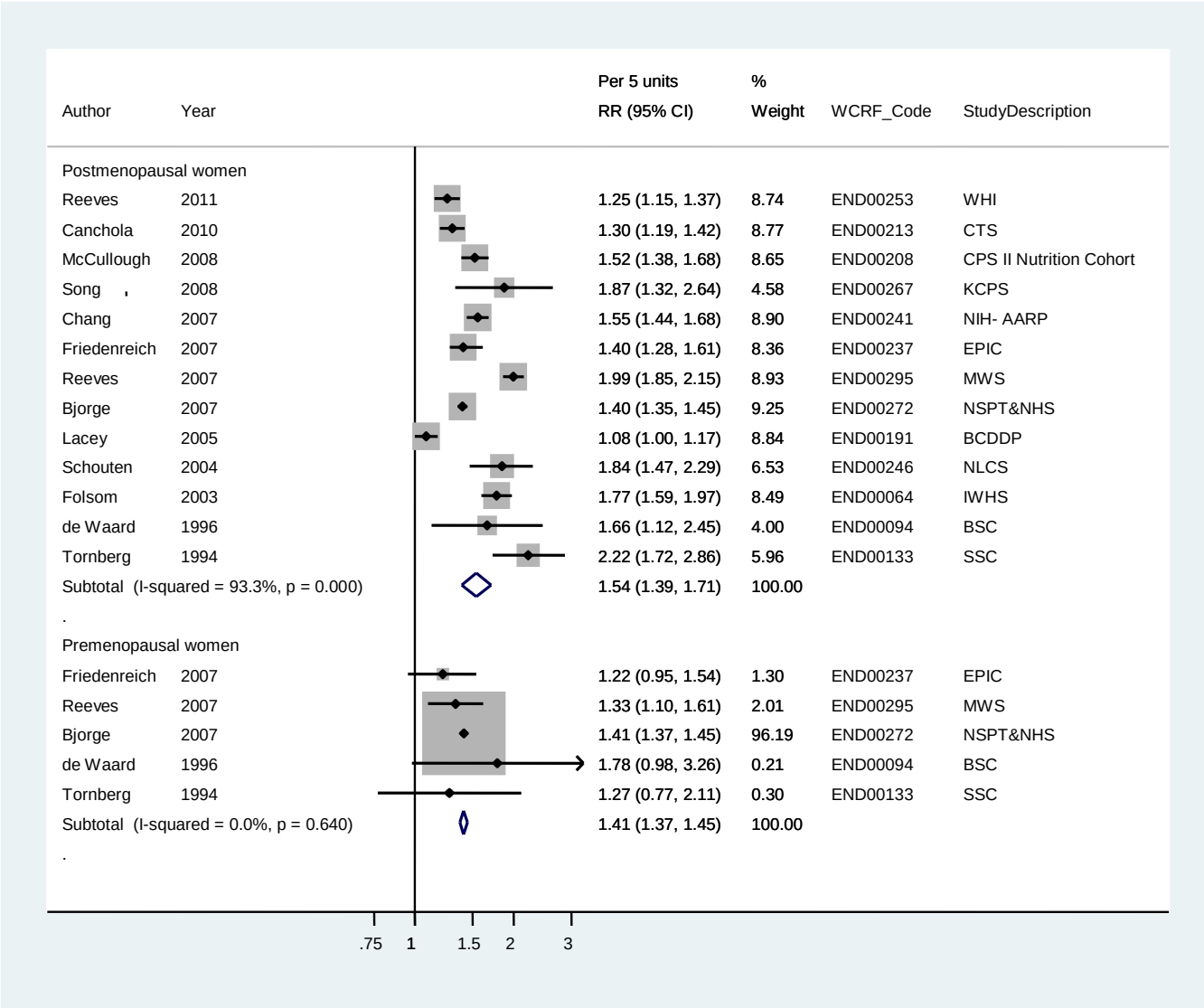


Figure 81 Dose-response meta-analysis of BMI and endometrial cancer, per 5 units, stratified by hormone replacement therapy use

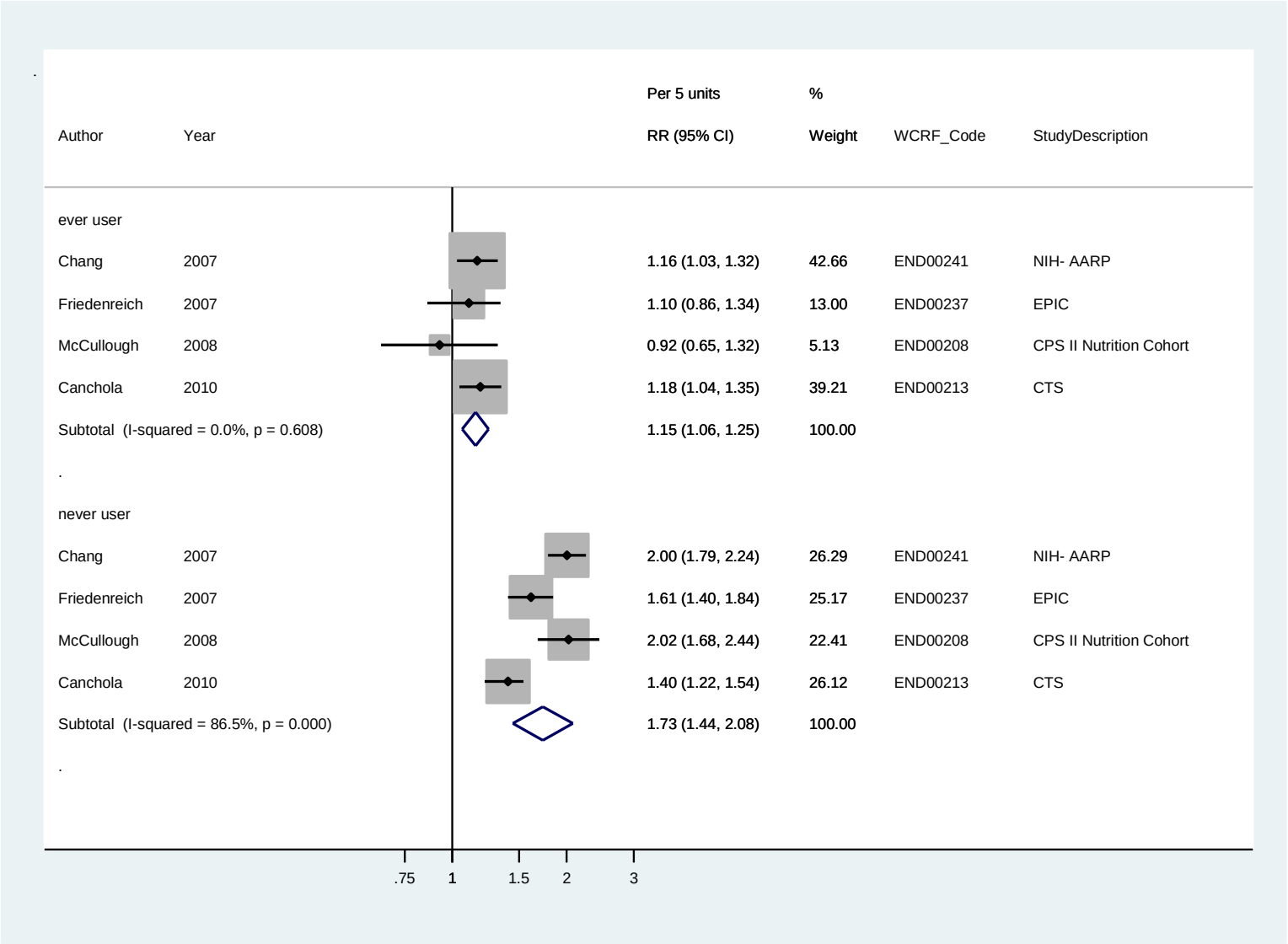


Figure 82 Funnel plot of BMI and endometrial cancer

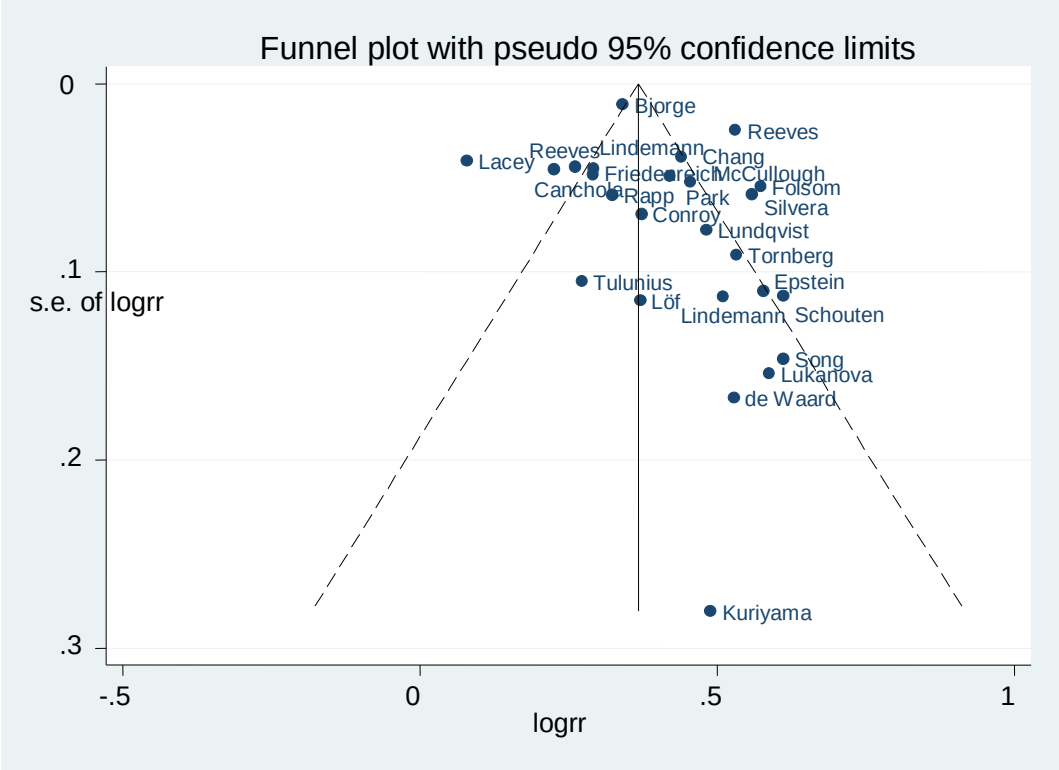


Figure 83 Dose-response graph of BMI and endometrial cancer

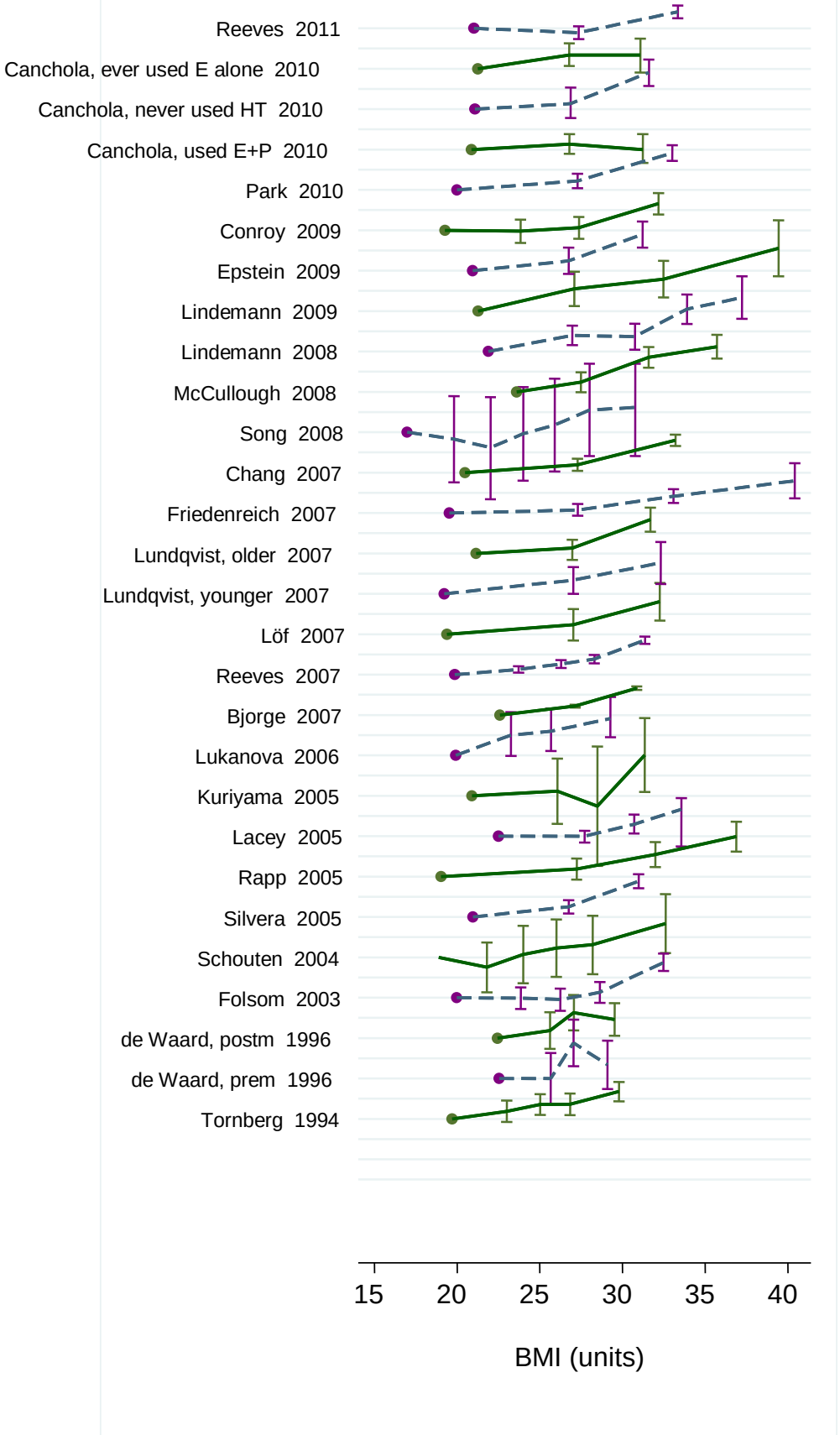


Figure 84 Nonlinear dose-response figure for BMI and endometrial cancer

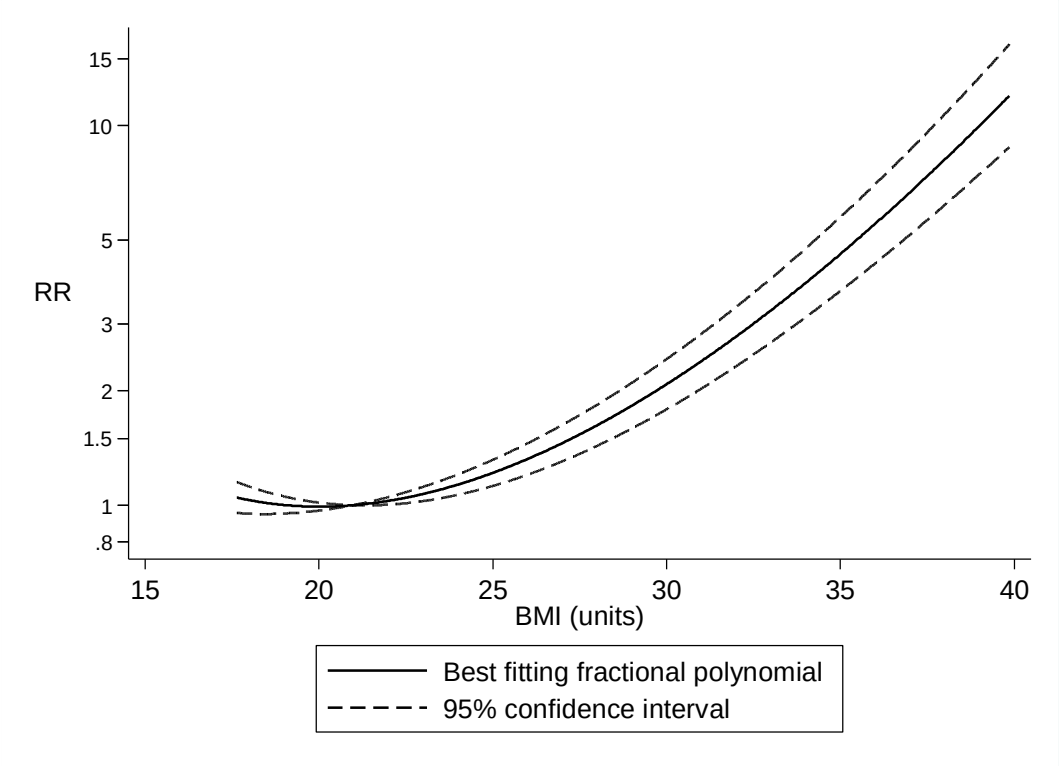
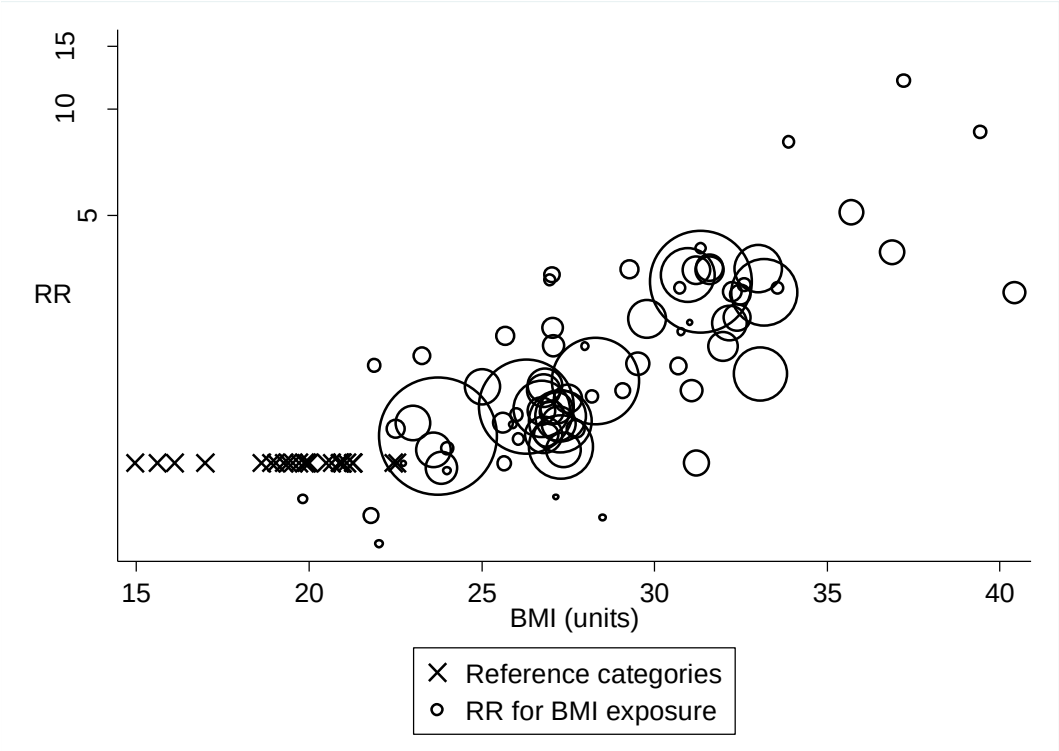


Figure 85 Scatter plot of risk estimates for BMI and endometrial cancer



Explanation for nonlinear dose-response analyses

The nonlinear dose-response analyses was computed using the pool first command in Stata using the categorical risk estimates from each study included in the analysis. Several polynomial curves were tested, but the program automatically selects the curve with the best fit. The dose-response relationship was also explored using a scatter plot. The relative risk estimates were plotted against the corresponding levels of the exposure (empty circles) compared with the reference category X. The area of the circles is proportional to the inverse of the variance and was used as weights. Larger studies with small variances are therefore given more weight than small studies with large variances. Random effects models were used for the analysis.

Table 113 RRs (95% CIs) for nonlinear analysis of BMI and endometrial cancer

BMI	RR (95% CI)
17.5	1.05 (0.96-1.16)
20	0.99 (0.97-1.02)
21	1.00
22.5	1.04 (1.01-1.08)
25	1.22 (1.12-1.32)
27.5	1.54 (1.37-1.73)
30	2.09 (1.79-2.44)
32.5	3.02 (2.51-3.64)
35	4.59 (3.67-5.74)
37.5	7.37 (5.65-9.61)
40	12.37 (9.03-16.94)

8.1.1 BMI at age 18-25 years

Methods

A total of 8 cohort studies have been published on BMI at age 18-25 years and endometrial cancer risk up to December 2012, five of which were identified in the CUP. Four studies investigated BMI at age 18 years, two at age 20, one at age 21 and another at age 25 years. In this analysis, all studies were pooled together under BMI at age 18-25 years. Dose-response analyses were conducted per 5 units.

Main results

The summary RR per 5 kg/m^2 increase in BMI at age 18-25 years was 1.42 (95% CI: 1.22-1.66, I^2=79%, $p_{heterogeneity}$<0.001, n=7). There was no evidence of publication bias with Egger's test, p=0.54, although some slight asymmetry when inspecting the funnel plot. There was some indication of a nonlinear association, $p_{nonlinearity}$=0.07, with a slight J-shaped curve, with the lowest risk for BMI around 15-16, however, the confidence intervals were wide. Four studies reported attenuation of the associations when further adjusted for current BMI (Chang et al, 2007, McCullough et al, 2008, Canchola et al, 2010, Yang et al, 2012), but only two of these could be included in dose-response analyses (Chang et al, 2007, Yang et al, 2012), and the summary RR was 1.02 (95% CI: 0.94-1.11, I^2=0%, $p_{heterogeneity}$=0.58) per 5 BMI units.

Heterogeneity

There was high heterogeneity, I^2=79%, $p_{heterogeneity}$<0.0001, which appeared to be driven by one study (Million Women's Study) and when this study was excluded, I^2=0%, $p_{heterogeneity}$=0.48, and the summary RR was 1.28 (95% CI: 1.20-1.37).

Conclusion from the Second Expert Report

In the SLR of the 2007 Expert Report the evidence that greater body fatness increases endometrial cancer risk was considered convincing. There was no separate judgement for body fatness in young adulthood.

Table 114 Studies on BMI at age 18-25 years identified in the CUP

Author/year	Country	Study name	Cases	Years of follow-up	RR	LCI	UCI	Contrast
Yang, 2012	United Kingdom	Million Women's Study	1410	7.3	1.95	1.67	2.27	Per 5 units
Park, 2010	USA	Multiethnic Cohort Study	463	10.3	1.71	1.31	2.25	≥21.897 vs. <18.840
Canchola, 2010	USA	California Teachers Study	395	9.1	1.8 1.07 1.2 1.03 1.4 1.02	1.1 1.03 0.64 0.97 0.89 0.97	2.9 1.12 2.3 1.09 2.3 1.07	never HT use: ≥25 vs. <25 units Per 1 unit Ever estrogen use: ≥25 vs. <25 units Per 1 unit Used estrogen and progesterone excusively: ≥25 vs. <25 units Per 1 unit
McCullough, 2008	USA	Cancer Prevention Study 2 Nutrition Cohort	318 cases	11	2.01	1.34	3.01	≥25 vs. 18.5-<20.0
Chang, 2007	USA	NIH-AARP Diet and Health Study	677 cases	4.6	1.98	1.09	3.52	≥30 vs. <25

Table 115 Overall evidence on BMI at age 18-25 years and endometrial cancer

	Summary of evidence
2005 SLR 2005	Three cohort studies reported on BMI at age 18-25 years and endometrial cancer and all found a significant positive association.
Continuous Update Project	Five additional cohort studies reported on BMI at age 18-25 years and endometrial cancer and all found a significant increased risk, although risk estimates were attenuated in four studies when further adjusted for current BMI.

Table 116 Summary of results of the dose-response meta-analysis of BMI at age 18-25 years and endometrial cancer

Endometrial cancer		
	SLR 2005	Continuous Update Project
Studies (n)	3	7
Cases (n)	466	3740
RR (95% CI)	1.31 (1.12-1.54)	1.42 (1.22-1.66)
Quantity	Per 5 kg/m^2	Per 5 kg/m^2
Heterogeneity (I^2, p-value)	0%, p=0.46	78.8%, p<0.0001

Table 117 Inclusion/exclusion table for meta-analysis of BMI at age 18-25 years and endometrial cancer

WCRF code	Author	Year	Study design	Study name	Cancer outcome	SLR 2005	CU dose-response	CU H vs. L forest plot	Estimated values	Exclusion reason
END00295	Yang	2012	Prospective cohort study	Million Women's Study	Incidence	No	Yes	No	Midpoints	Continuous result only
END00206	Park	2010	Prospective cohort study	Multiethnic Cohort Study	Incidence	No	Yes	Yes	Midpoint, person-years	
END00213	Canchola	2010	Prospective cohort study	California Teacher's Study	Incidence	No	Yes	Yes	-	
END00241	Chang	2007	Prospective cohort study	NIH-AARP Diet and Health Study	Incidence	No	Yes	Yes	Midpoints	
END00208	McCullough	2008	Prospective cohort study	Cancer Prevention Study 2 - Nutrition Cohort	Incidence	No	No	Yes	-	Only high vs. low comparison
END00246	Schouten	2004	Prospective cohort study	Netherlands Cohort Study	Incidence	Yes	Yes	Yes	Midpoints	
END00074	Jonsson	2003	Prospective cohort study	Swedish Twin Cohort	Incidence	Yes	Yes	Yes	-	
END00041	Gapstur	1993	Prospective cohort study	Iowa Women's Health Study	Incidence	Yes	Yes	Yes	-	

Figure 86 Highest versus lowest forest plot of BMI at age 18-25 years and endometrial cancer (units=kg/m2)

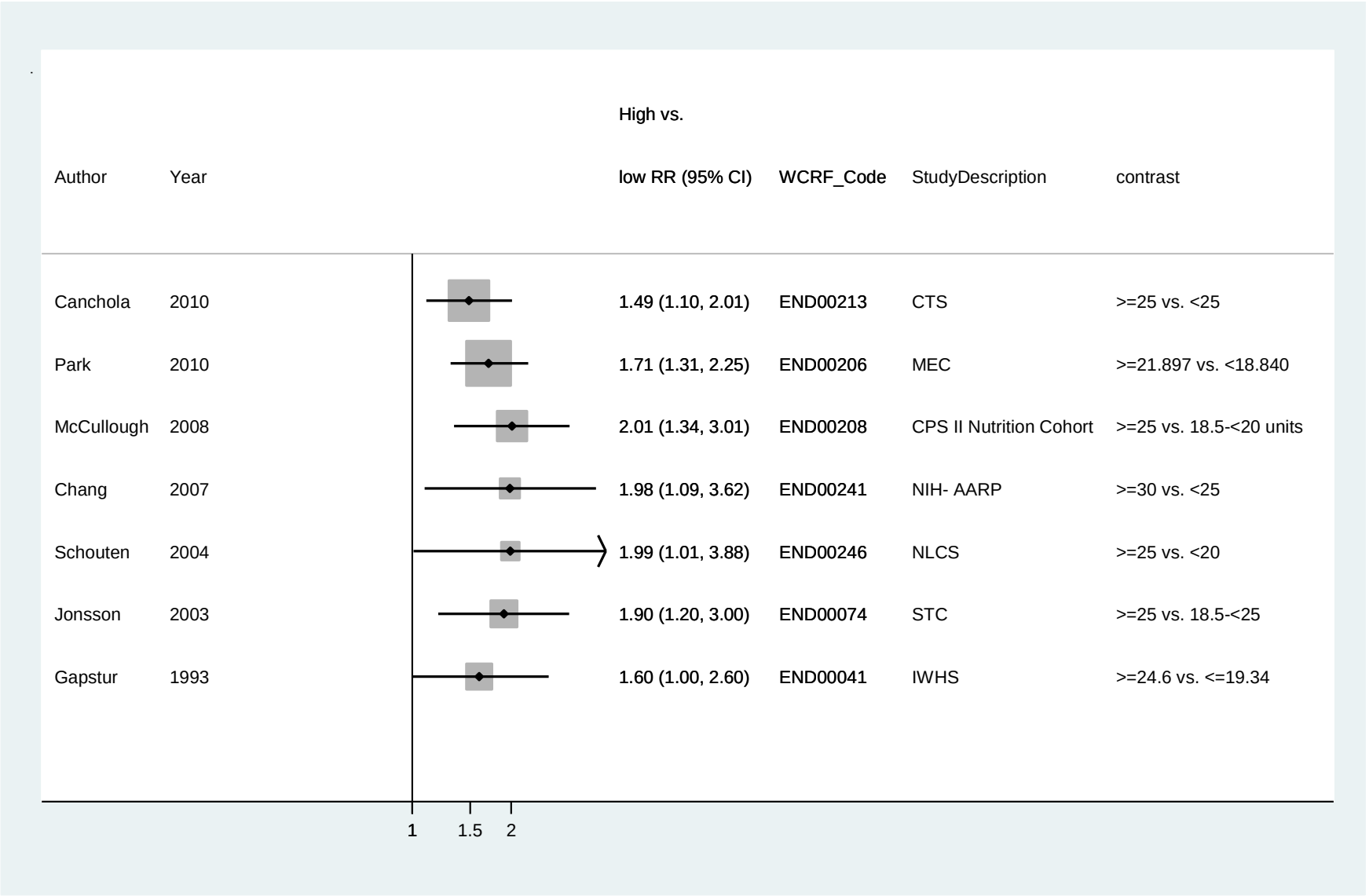


Figure 87 Dose-response meta-analysis of BMI at age 18-25 years and endometrial cancer, per 5 kg/m2

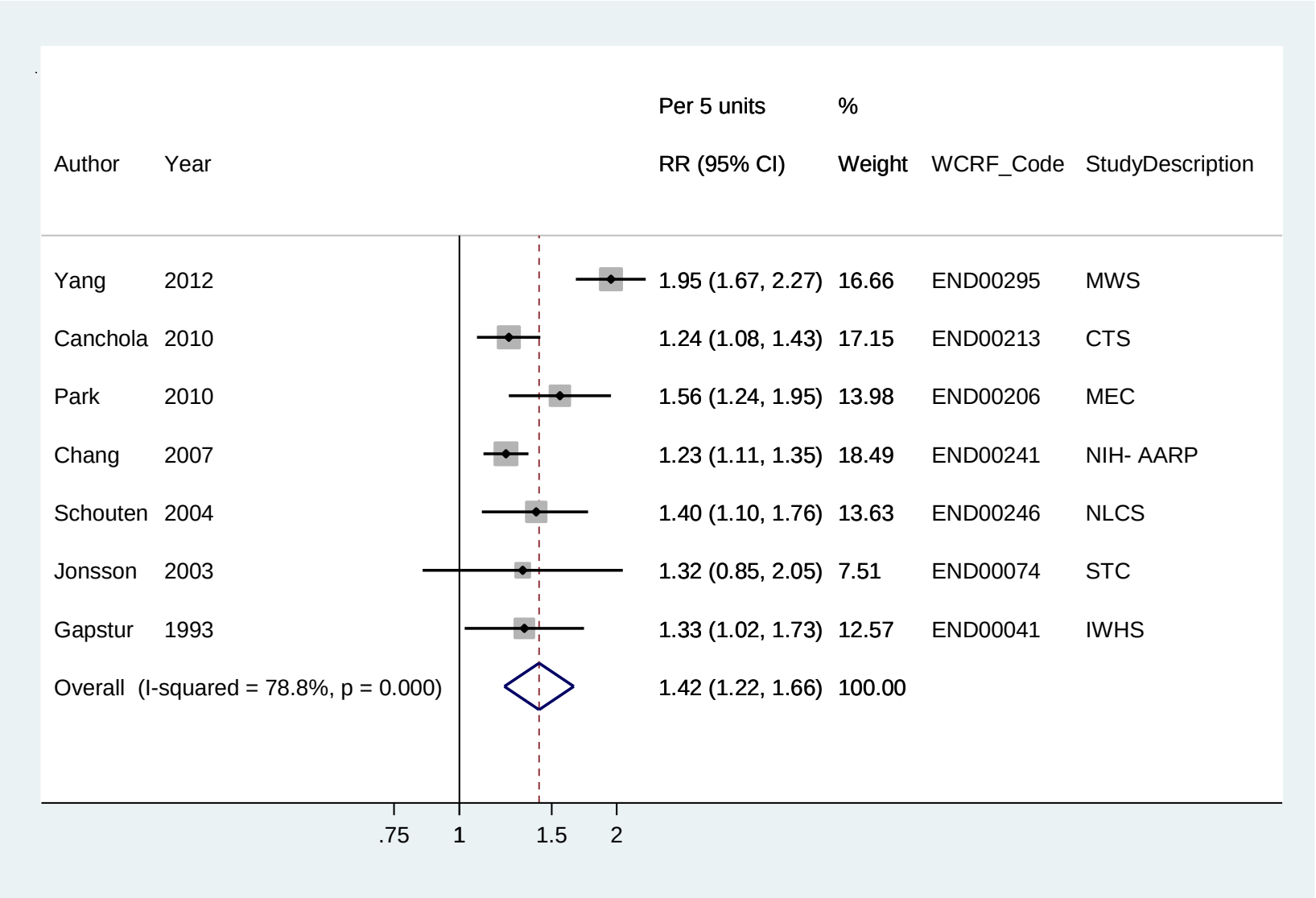


Figure 88 Funnel plot of BMI at age 18-25 years and endometrial cancer

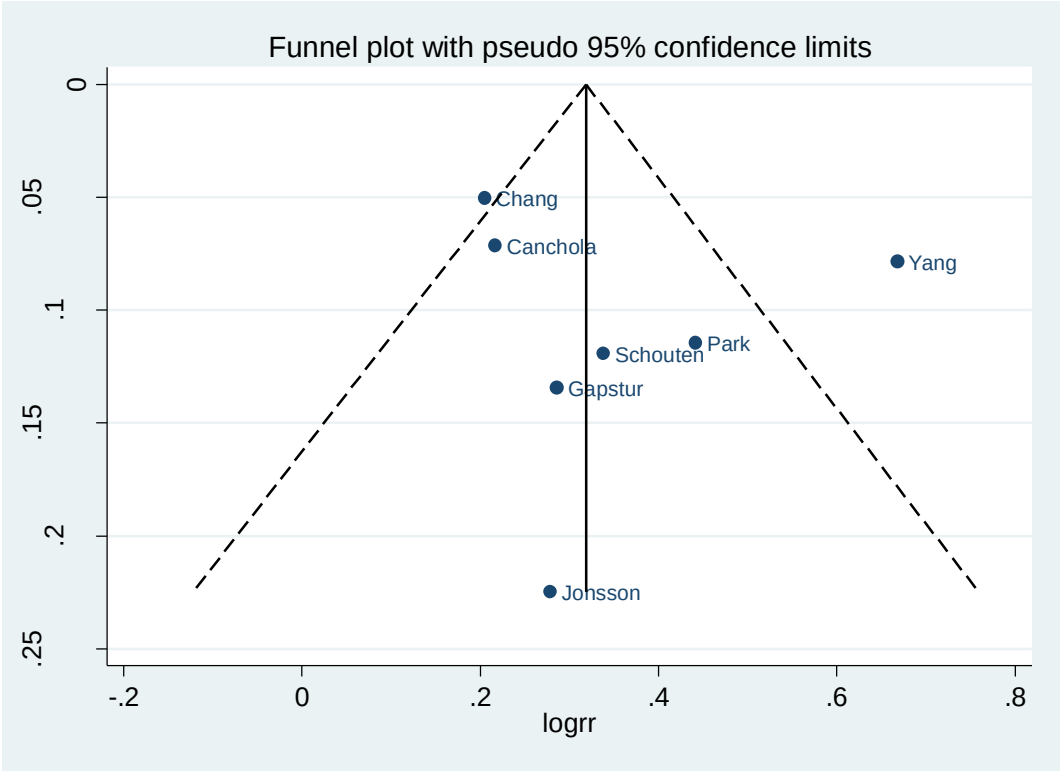


Figure 89 Dose-response graph of BMI at age 18-25 years and endometrial cancer

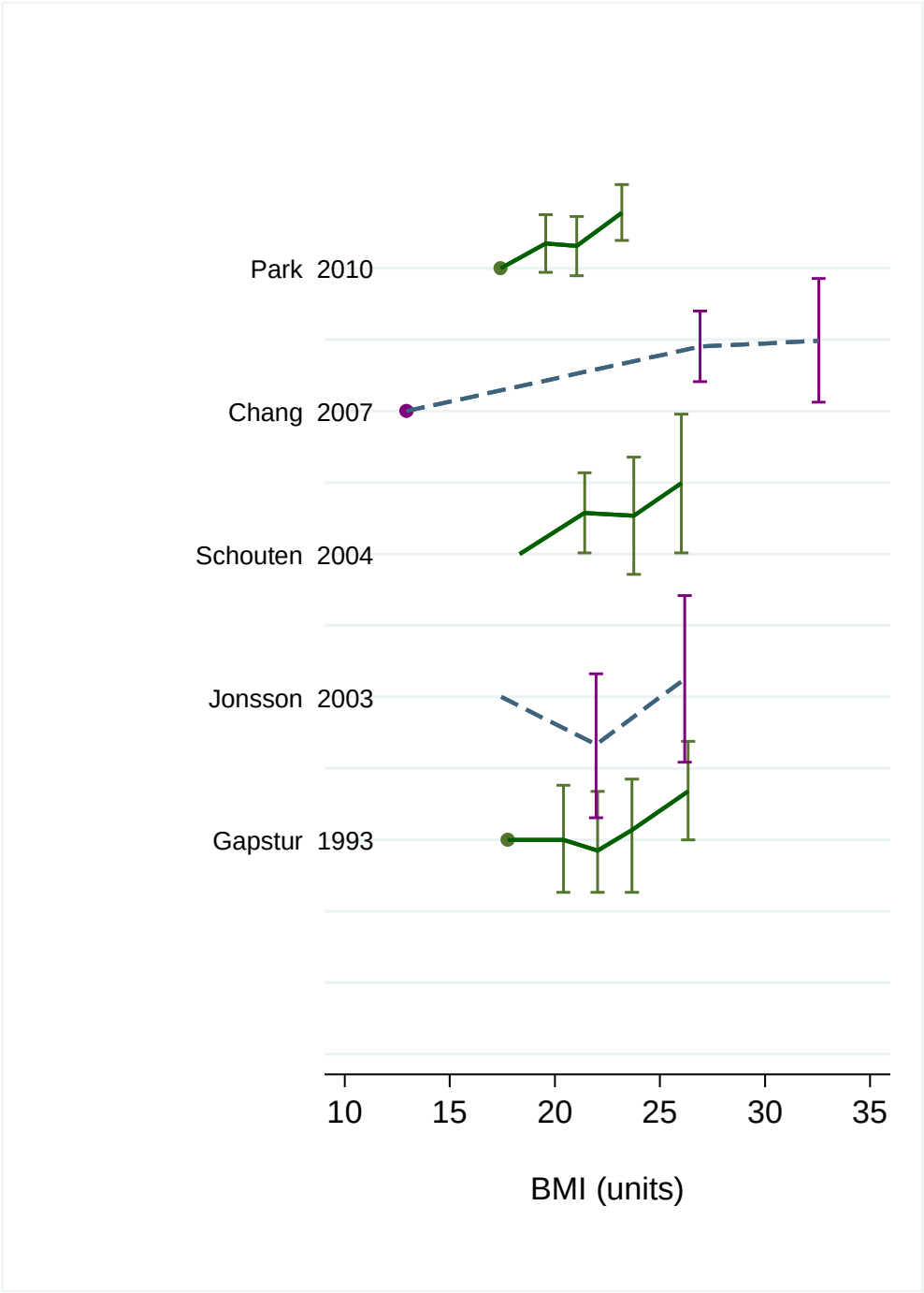


Figure 90 Nonlinear dose-response figure for BMI at age 18-25 and endometrial cancer

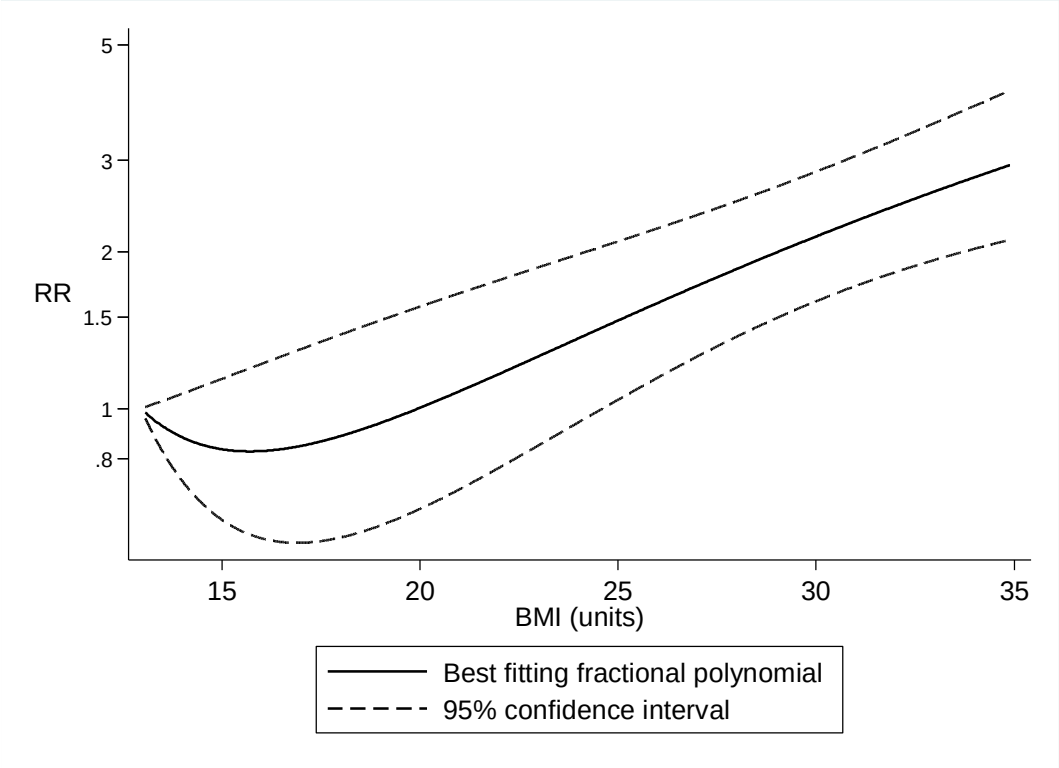


Figure 91 Scatter plot of risk estimates for BMI at age 18-25 and endometrial cancer

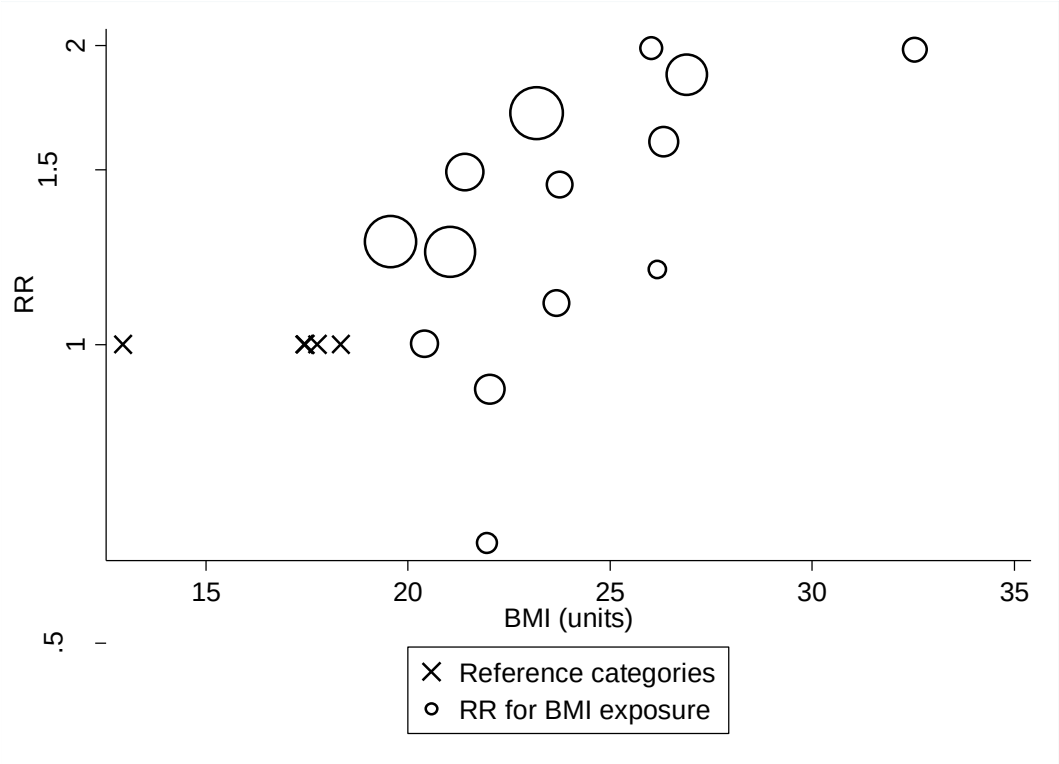


Table 118 RRs (95% CIs) for nonlinear analysis of BMI at age 18-25 and endometrial cancer

BMI	RR (95% CI)
13	1.00
15	0.83 (0.61-1.14)
17.5	0.86 (0.56-1.34)
20	1.00 (0.64-1.57)
22.5	1.21 (0.81-1.82)
25	1.48 (1.04-2.10)
27.5	1.79 (1.32-2.43)
30	2.14 (1.61-2.86)
32.5	2.54 (1.88-3.42)
35	2.96 (2.12-4.13)

8.1.6 Weight change

Methods

A total of 5 cohort studies have been published on weight change between early adulthood (age 18-25 years) and baseline and endometrial cancer risk up to 2012, four of which were identified in the CUP. Dose-response analyses were conducted per 5 kg of weight gained. It was not possible to conduct dose-response analyses for weight loss because the studies had <3 categories for weight loss. Estimates that were stratified by hormone therapy use in the study by Canchola et al were pooled using a fixed effects model.

Main results

The summary RR per 5 kg increase in weight gain was 1.16 (95% CI: 1.10-1.22, I^2=66%, $p_{heterogeneity}$=0.02, n=4).

Heterogeneity

There was high heterogeneity, I^2=66%, $p_{heterogeneity}$=0.02.

Comparison with the Second Expert Report

In the systematic review of the 2007 expert report there was only one cohort study on weight change and endometrial cancer and no meta-analysis was conducted.

Table 119 Studies on weight change identified in the CUP

Author/year	Country	Study name	Number of cases	Years of follow-up	RR	LCI	UCI	Comparison
Canchola, 2010	USA	California Teachers Study	395	9.1 years				never HT use:
					3.7	2.0	7.1	+≥40 lb vs. stable
					1.10	1.05	1.14	Per 10 lb
								Ever estrogen use:
					0.85	0.50	1.40	+≥40 lb vs. stable
					1.05	0.98	1.13	Per 10 lb
								Used estrogen and progesterone exclusively:
					1.5	0.93	2.3	+≥40 lb vs. stable
					1.04	0.99	1.10	Per 10 lb
Park, 2010	USA	Multiethnic Cohort Study	463	10.3 years	3.47	1.81	6.67	+≥42.80% vs. <23.59%, African American
					2.02	1.25	3.26	+≥20.10% vs. <8.18%, Japanese American
					3.08	1.66	5.71	+≥35.45% vs. <18.46%, Latinas
					1.83	1.17	2.86	+≥26.19% vs. <10.00%, Whites
Chang, 2007	USA	NIH-AARP Diet and Health Study	677	4.6	2.75	1.96	3.86	+≥20 vs. -5 to +4.9 kg
Friedenreich, 2007	10 European Countries	European Prospective Investigation into Cancer and Nutrition	264	6.4 years	1.75	1.11	2.77	+≥20 kg vs. -3 to <3 kg
					1.13	1.06	1.19	Per 5 kg

Table 120 Overall evidence on weight change and endometrial cancer

SLR	Summary of evidence
2005 SLR	One cohort study reported on weight change intake and endometrial cancer and found a significant positive association.
Continuous update	Four additional cohort studies reported on weight change and endometrial cancer and all found increased risk, although in one study the association was restricted to never users of hormone therapy.

Table 121 Summary of results of the dose-response meta-analysis of weight change and endometrial cancer

Endometrial cancer		
	2nd Report	Updated meta-analysis
Studies (n)	-	5
Cases (n)	-	1971
RR (95% CI)	-	1.16 (1.10-1.22)
Quantity	-	Per 5 kg
Heterogeneity (I^2, p-value)	-	65.5%, p=0.02

Table 122 Inclusion/exclusion table for meta-analysis of weight change and endometrial cancer

WCRF code	Author	Year	Study design	Study name	Cancer outcome	SLR	CU dose-response	CU H vs. L forest plot	Estimated values	Exclusion reason
END00213	Canchola	2010	Prospective cohort study	California Teacher's Study	Incidence	No	Yes	Yes		
END00206	Park	2010	Prospective cohort study	Multiethnic Cohort Study	Incidence	No	Yes	Yes	Midpoints, person-years, exposure was converted from % weight change to kg weight change	
END00241	Chang	2007	Prospective cohort study	NIH-AARP Diet and Health Study	Incidence	No	Yes	Yes	Midpoints	
END00237	Friedenreich	2007	Prospective cohort study	European Prospective Investigation into Cancer and Nutrition	Incidence	No	Yes	Yes	Midpoints	
END00074	Jonsson	2003	Prospective cohort study	Swedish Twin Cohort	Incidence	Yes	Yes	Yes	Midpoints, person-years	

Figure 92 Highest versus lowest forest plot of weight change and endometrial cancer

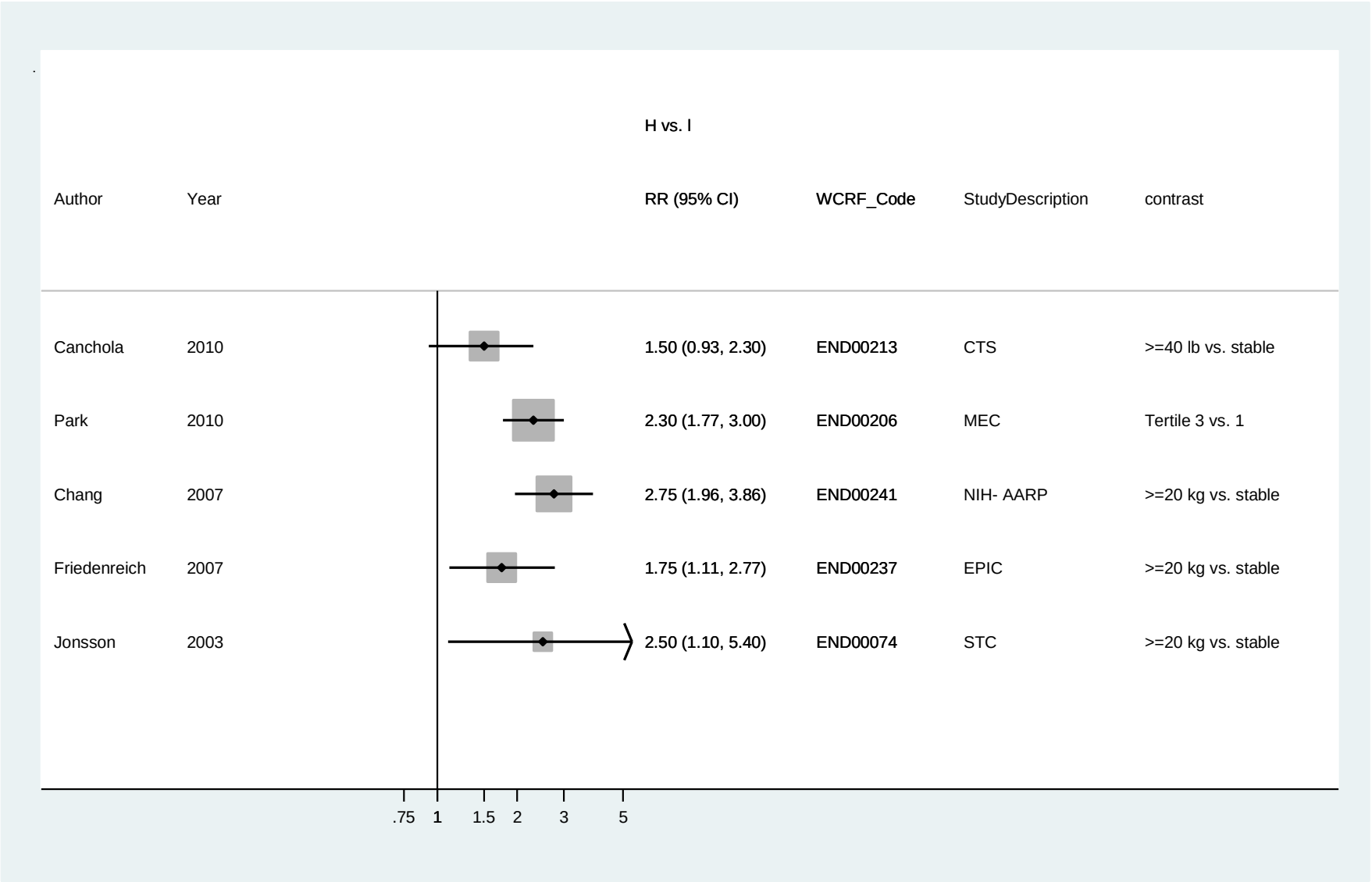


Figure 93 Dose-response meta-analysis of weight change and endometrial cancer, per 5 kg

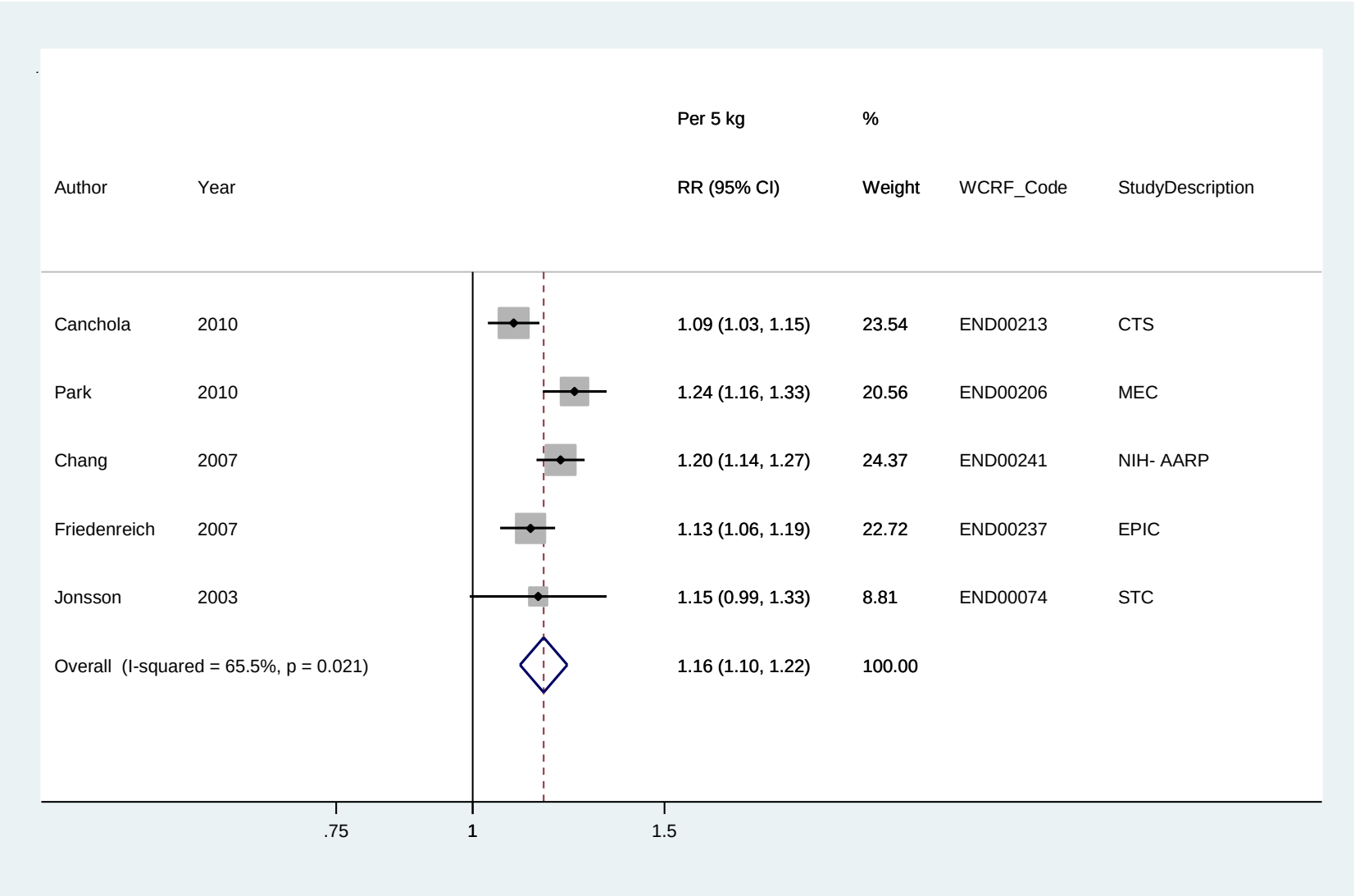
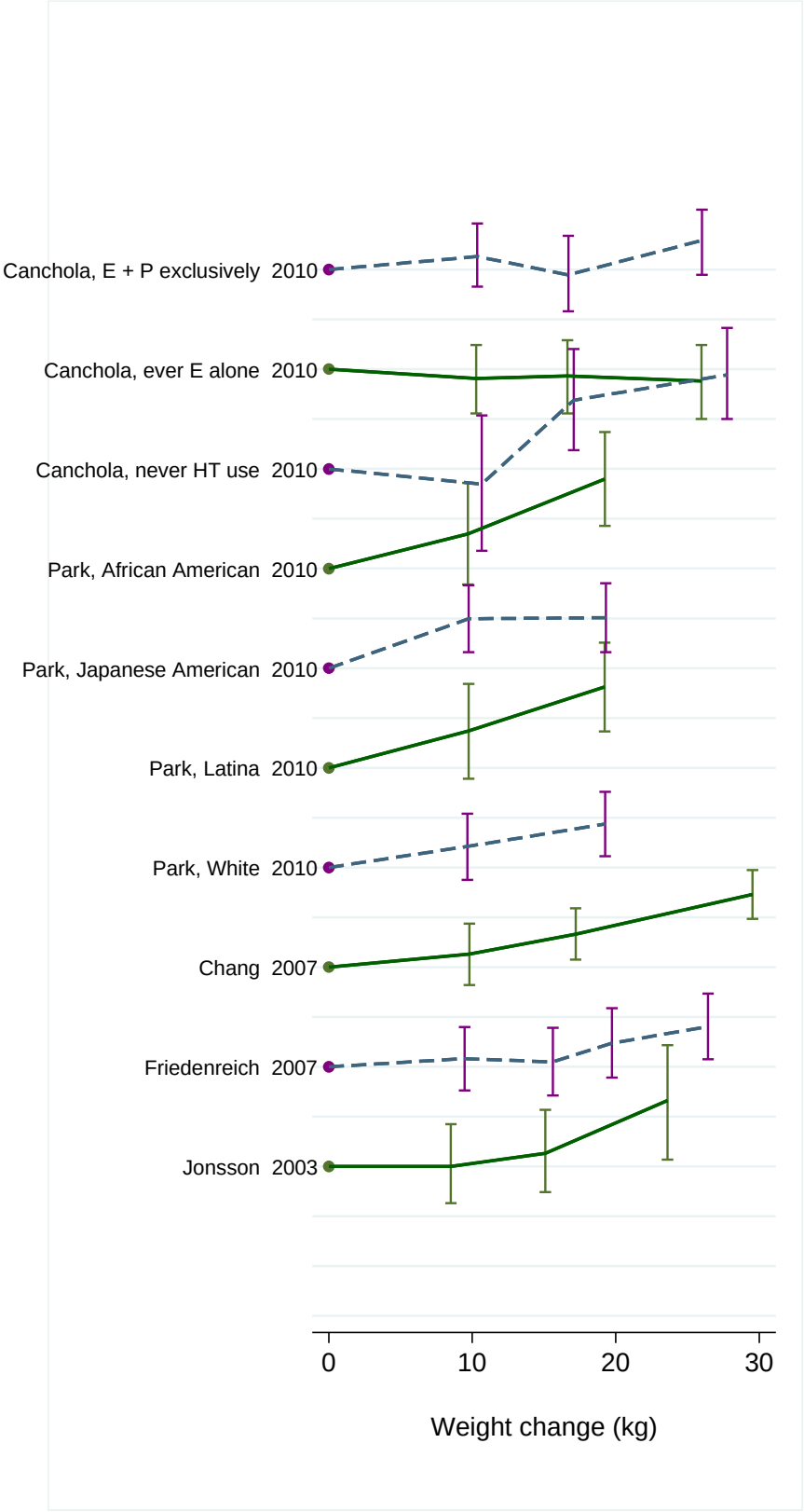


Figure 94 Dose-response graph of weight change and endometrial cancer



8.2.1 Waist circumference

Methods

A total of 4 cohort studies have been published on waist circumference and endometrial cancer risk up to December 2012, three of which were identified in the CUP. Dose-response analyses were conducted per 5 cm increase in waist circumference. Estimates that were stratified by hormone therapy use in the study by Canchola et al were pooled using a fixed effects model.

Main results

The summary RR per 5 cm increase in waist circumference was 1.13 (95% CI: 1.08-1.18, I^2=70.5%, $p_{heterogeneity}$=0.02, n=4). For two studies which further adjusted for BMI (Friedenreich et al, 2007 and Conroy et al, 2009), the summary RR was 1.12 (95% CI: 1.05-1.20, I^2=19.6%, $p_{heterogeneity}$=0.27). There was evidence of a nonlinear association between waist circumference and endometrial cancer risk, $p_{nonlinearity}$<0.0001, with a steeper increase in risk at higher levels of waist circumference.

Two studies which further adjusted for BMI could be included in a meta-analysis (Friedenreich et al, 2007 and Conroy et al, 2009), and the summary RR was 1.12 (95% CI: 1.05-1.20, I^2=20%, $p_{heterogeneity}$=0.27).

Heterogeneity

There was high heterogeneity, I^2=70.5%, $p_{heterogeneity}$=0.02.

Conclusion from the Second Expert Report

In the SLR of the 2007 Expert Report the evidence relating abdominal fatness to endometrial cancer risk was considered probable. The conclusion was based in the positive associations observed in the four case-control studies identified.

Table 123 Studies on waist circumference identified in the CUP

Author/year	Country	Study name	Cases	Years of follow-up	RR	LCI	UCI	Contrast
Canchola, 2010	USA	California Teachers Study	395	9.1	2.7 1.09 1.3 1.02 1.3 1.02	1.5 1.02 0.78 0.97 0.85 0.98	4.8 1.08 2.2 1.08 2.0 1.06	never HT use: ≥35 vs. <35 inches Per 1 inch Ever estrogen use: ≥35 vs. <35 inches Per 1 inch Used estrogen and progesterone exclusively: ≥35 vs. <35 inches Per 1 inch
Conroy, 2009	USA	Women's Health Study	264	8.8	1.61	0.91	2.83	≥39.0 vs. <31.0 inches
Friedenreich, 2007	Europe	European Prospective Investigation into Cancer and Nutrition	567	6.4	1.76 1.13	1.42 1.09	2.19 1.17	≥88 vs. <88 cm Per 5 cm

Table 124 Overall evidence on waist circumference and endometrial cancer

	Summary of evidence
2005 SLR 2005	One cohort study reported on waist circumference intake and endometrial cancer and found a significant positive association.
Continuous Update Project	Three additional cohort studies reported on waist circumference and endometrial cancer and two found significantly increased risk, while one reported no significant association. In one of the studies the positive association was restricted to never users of hormone therapy.

Table 125 Summary of results of the dose-response meta-analysis of waist circumference and endometrial cancer

Endometrial cancer		
	SLR 2005*	Continuous Update Project
Studies (n)	-	4
Cases (n)	-	1641
RR (95% CI)	-	1.13 (1.08-1.18)
Quantity	-	Per 5 cm
Heterogeneity (I^2, p-value)	-	70.5%, p=0.02

*No meta-analysis was conducted in the SLR 2005

Table 126 Inclusion/exclusion table for meta-analysis of waist circumference and endometrial cancer

WCRF code	Author	Year	Study design	Study name	Cancer outcome	SLR 2005	CU dose-response	CU H vs. L forest plot	Estimated values	Exclusion reason
END00213	Canchola	2010	Prospective cohort study	California Teacher's Study	Incidence	No	Yes	Yes		
END00218	Conroy	2009	Prospective cohort study	Women's Health Study	Incidence	No	Yes	Yes	Midpoints, person-years	
END00237	Friedenreich	2007	Prospective cohort study	European Prospective Investigation into Cancer and Nutrition	Incidence	No	Yes	Yes	Midpoints	
END00160	Folsom	2000	Prospective cohort study	Iowa Women's Health Study	Incidence	Yes	Yes	Yes	Midpoints	

Figure 95 Highest versus lowest forest plot of waist circumference and endometrial cancer

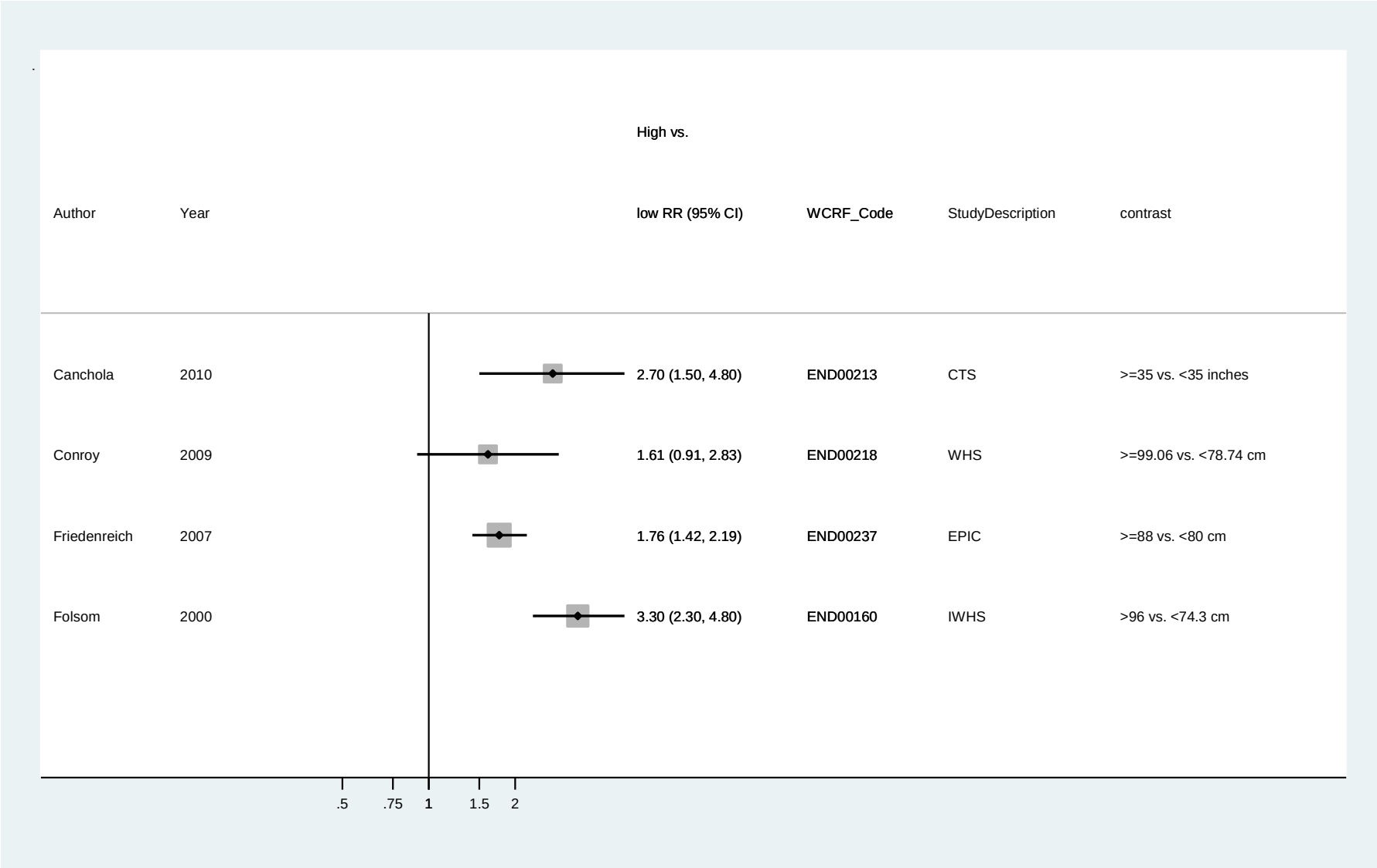


Figure 96 Dose-response meta-analysis of waist circumference and endometrial cancer, per 5 cm

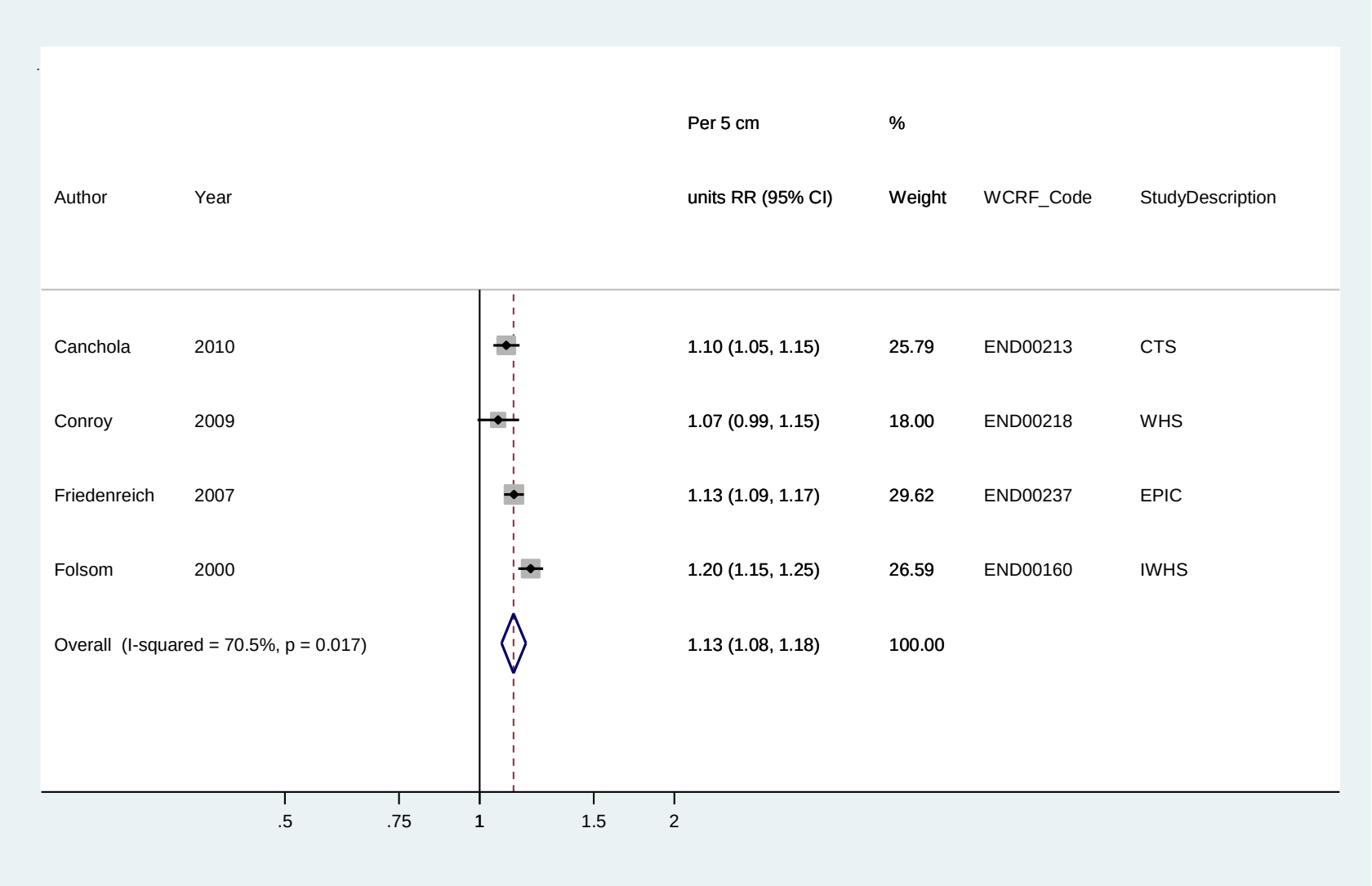


Figure 97 Dose-response graph of waist circumference and endometrial cancer

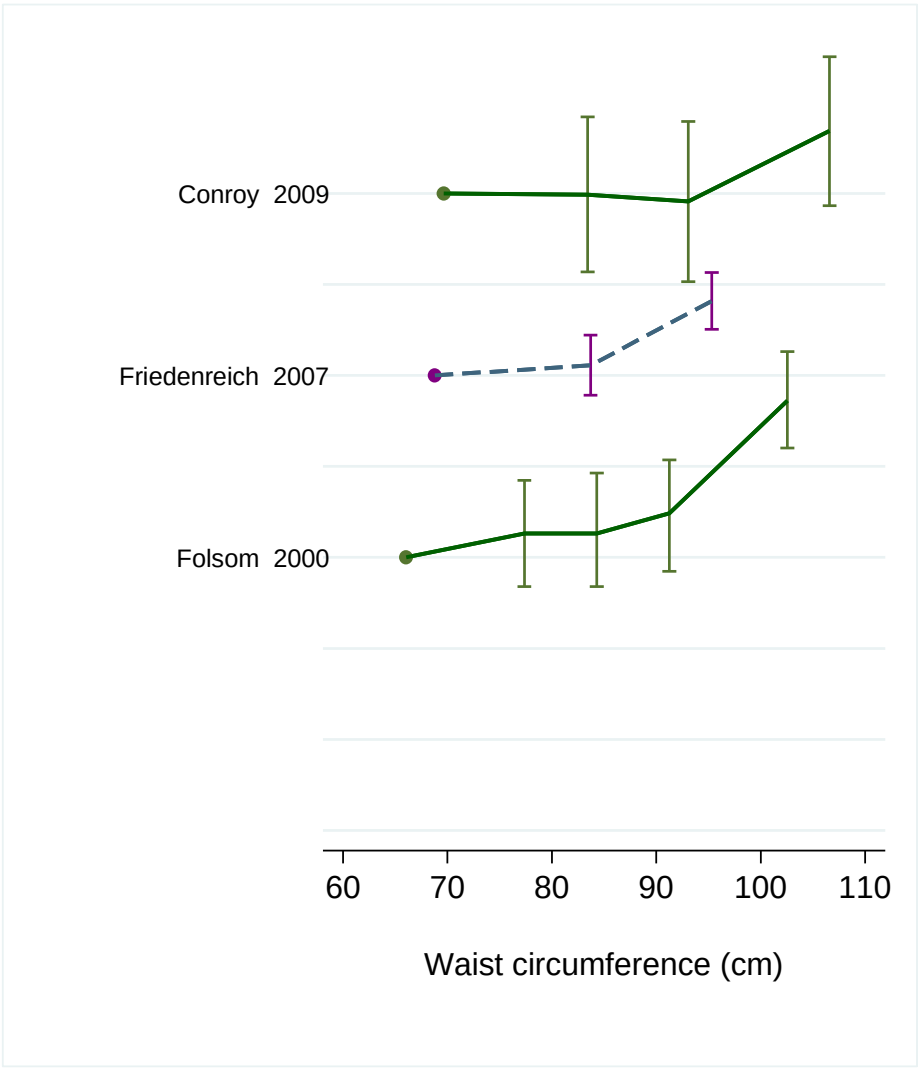


Figure 98 Nonlinear dose-response figure for waist circumference and endometrial cancer

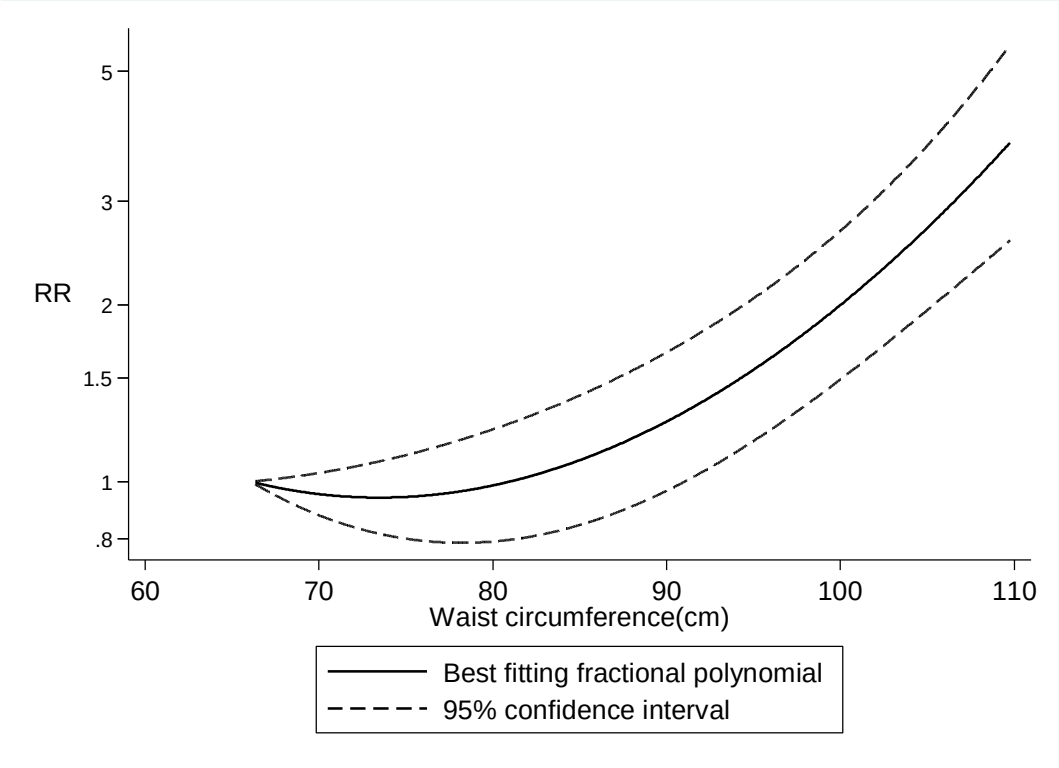


Figure 99 Scatter plot of risk estimates for waist circumference and endometrial cancer

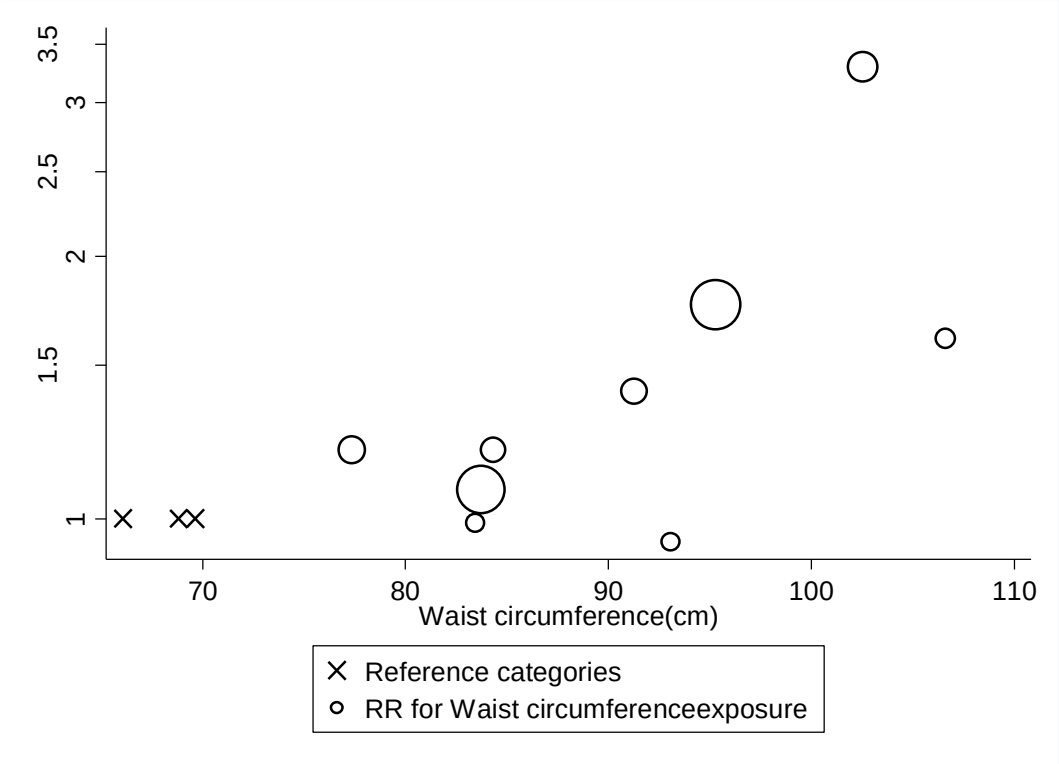


Table 127 RRs (95% CIs) for nonlinear analysis of waist circumference and endometrial cancer

Waist circumference	RR (95% CI)
66.17	1.00
70	0.95 (0.88-1.03)
75	0.94 (0.80-1.11)
80	0.99 (0.79-1.23)
85	1.09 (0.84-1.40)
90	1.27 (0.97-1.66)
95	1.55 (1.18-2.06)
100	2.01 (1.50-2.69)
105	2.72 (1.97-3.76)
110	3.84 (2.61-5.65)

8.2.3 Waist-to-hip ratio

Methods

A total of 5 cohort studies (9 publications) have been published on waist-to-hip ratio and endometrial cancer risk up to December 2012, four of which were identified in the CUP. Dose-response analyses were conducted per 0.1 units.

Main results

The summary RR per 0.1 units increase in waist-to-hip ratio was 1.21 (95% CI: 1.13-1.29, I^2=0%, $p_{heterogeneity}$=0.48, n=5). For three studies that further adjusted for BMI (Friedenreich et al, 2007, Conroy et al, 2009, Reeves et al, 2011), the summary RR was 1.07 (95% CI: 0.97-1.17, I^2=0%, $p_{heterogeneity}$=0.99). There was no evidence of a nonlinear association between waist-to-hip ratio and endometrial cancer, $p_{nonlinearity}$=0.29.

Heterogeneity

There was no evidence of heterogeneity, I^2=0%, $p_{heterogeneity}$=0.48.

Conclusion from the Second Expert Report

In the SLR of the 2007 Expert Report the evidence relating abdominal fatness to endometrial cancer risk was considered probable. Only one cohort was identified. The summary odds ratio for 0.1 increment from four cohort studies was 1.45 (95% CI: 1.00-2.09).

Table 128 Studies on waist-to-hip ratio identified in the CUP

Author/year	Country	Study name	Cases	Years of follow-up	RR	LCI	UCI	Contrast
Reeves, 2011	USA	Women's Health Initiative	806	7.8	1.33	1.04	1.70	≥0.8530 vs. <0.7554
Canchola, 2010	USA	California Teachers Study	395	9.1	2.7 1.31 1.5 1.10 1.1 1.01	1.3 1.02 0.83 0.85 0.70 0.78	5.6 1.68 2.6 1.43 1.6 1.31	never HT use: ≥0.80 vs. <0.80 units Per 0.1 unit Ever estrogen use: ≥0.80 vs. <0.80 units Per 0.1 unit Used estrogen and progesterone exclusively: ≥0.80 vs. <0.80 units Per 0.1 unit
Conroy, 2009	USA	Women's Health Study	264	8.8	1.34	0.75	2.37	≥0.87 vs. <0.78 units
Friedenreich, 2007	Europe	European Prospective Investigation into Cancer and Nutrition	567	6.4	1.58 1.17	1.19 1.03	2.10 1.32	>0.831 vs. ≤0.742 units Per 0.1 unit

Table 129 Overall evidence on waist-to-hip ratio and endometrial cancer

	Summary of evidence
2005 SLR 2005	One cohort study (four publications) reported on waist-to-hip ratio and endometrial cancer and found a significant positive association.
Continuous Update Project	Four additional cohort studies reported on waist-to-hip ratio and endometrial cancer and all found increased risk, although risk estimates were non-significant in one study and in another study the association was restricted to never users of hormone therapy.

Table 130 Summary of results of the dose-response meta-analysis of waist-to-hip ratio and endometrial cancer

Endometrial cancer		
	SLR 2005*	Continuous Update Project
Studies (n)	-	5
Cases (n)	-	2330
RR (95% CI)	-	1.21 (1.13-1.29)
Quantity	-	Per 0.1 units
Heterogeneity (I^2, p-value)	-	0%, p=0.48

*No meta-analysis was conducted in the SLR 2005

Table 131 Inclusion/exclusion table for meta-analysis of waist-to-hip ratio and endometrial cancer

WCRF code	Author	Year	Study design	Study name	Cancer outcome	SLR 2005	CU dose-response	CU H vs. L forest plot	Estimated values	Exclusion reason
END00253	Reeves	2011	Prospective cohort study	Women's Health Initiative	Incidence	No	Yes	Yes	Midpoints, person-years	
END00213	Canchola	2010	Prospective cohort study	California Teacher's Study	Incidence	No	Yes	Yes		
END00218	Conroy	2009	Prospective cohort study	Women's Health Study	Incidence	No	Yes	Yes	Midpoints, person-years	
END00237	Friedenreich	2007	Prospective cohort study	European Prospective Investigation into Cancer and Nutrition	Incidence	No	Yes	Yes	Midpoints	
END00064	Folsom	2003	Prospective cohort study	Iowa Women's Health Study	Incidence	Yes	Yes	Yes	Midpoints	
END00126	Anderson	2001	Prospective cohort study	Iowa Women's Health Study	Incidence	Yes	No	No		Overlap with END00160 by Folsom et al, 2000, no risk estimates presented
END00160	Folsom	2000	Prospective cohort study	Iowa Women's Health Study	Incidence	Yes	No	No		Overlap with Folsom et al, 2003 END00064
END00041	Gapstur	1993	Prospective cohort study	Iowa Women's Health Study	Incidence	Yes	No	No		Overlap with END00160 by Folsom et al, 2000
END00058	Folsom	1989	Prospective cohort study	Iowa Women's Health Study	Incidence	Yes	No	No		Overlap with END00160 by Folsom et al, 2000

Figure 100 **Highest versus lowest forest plot of waist-to-hip ratio and endometrial cancer**

Figure 101 Dose-response meta-analysis of waist-to-hip ratio and endometrial cancer, per 0.1 units

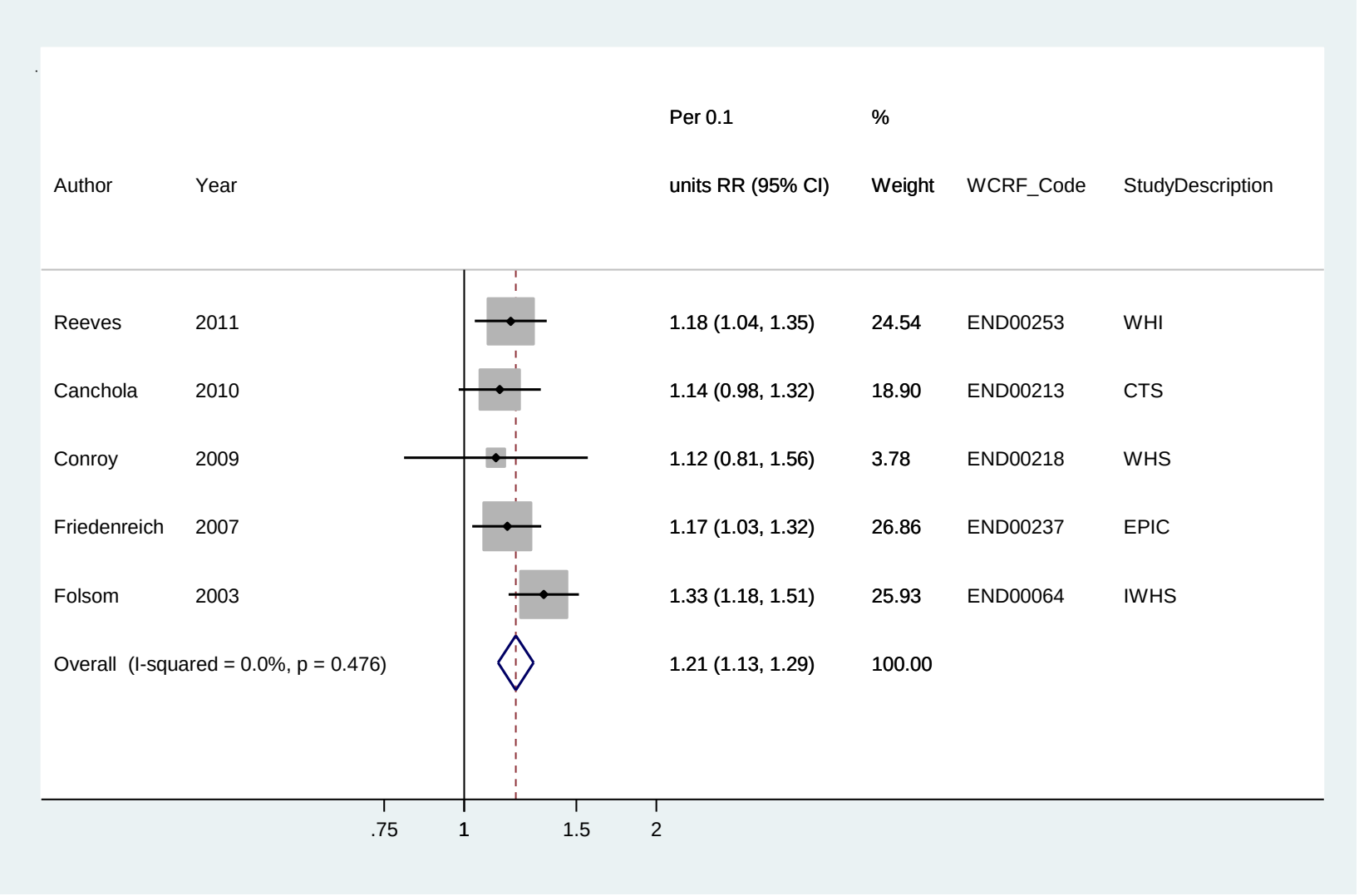


Figure 102 Dose-response graph of waist-to-hip ratio and endometrial cancer

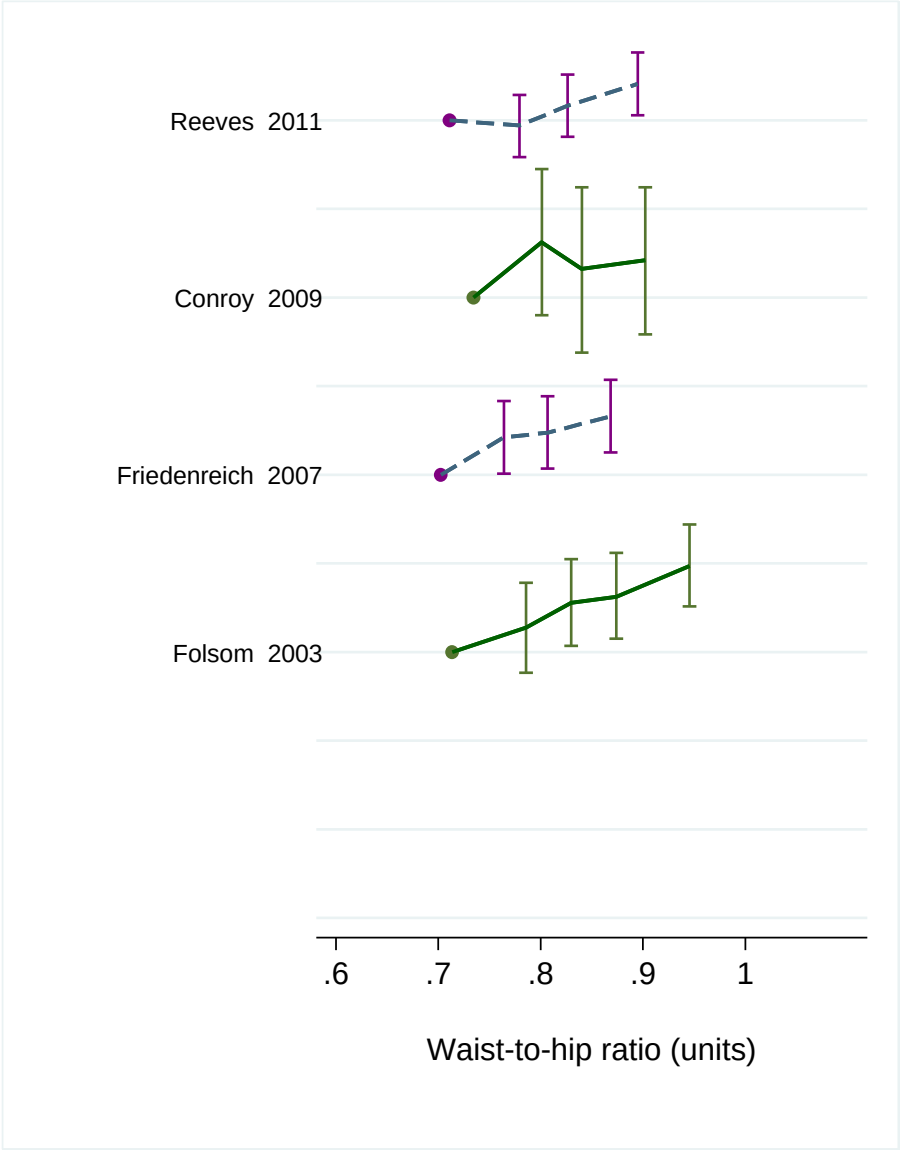


Figure 103 Nonlinear dose-response for waist-to-hip ratio and endometrial cancer

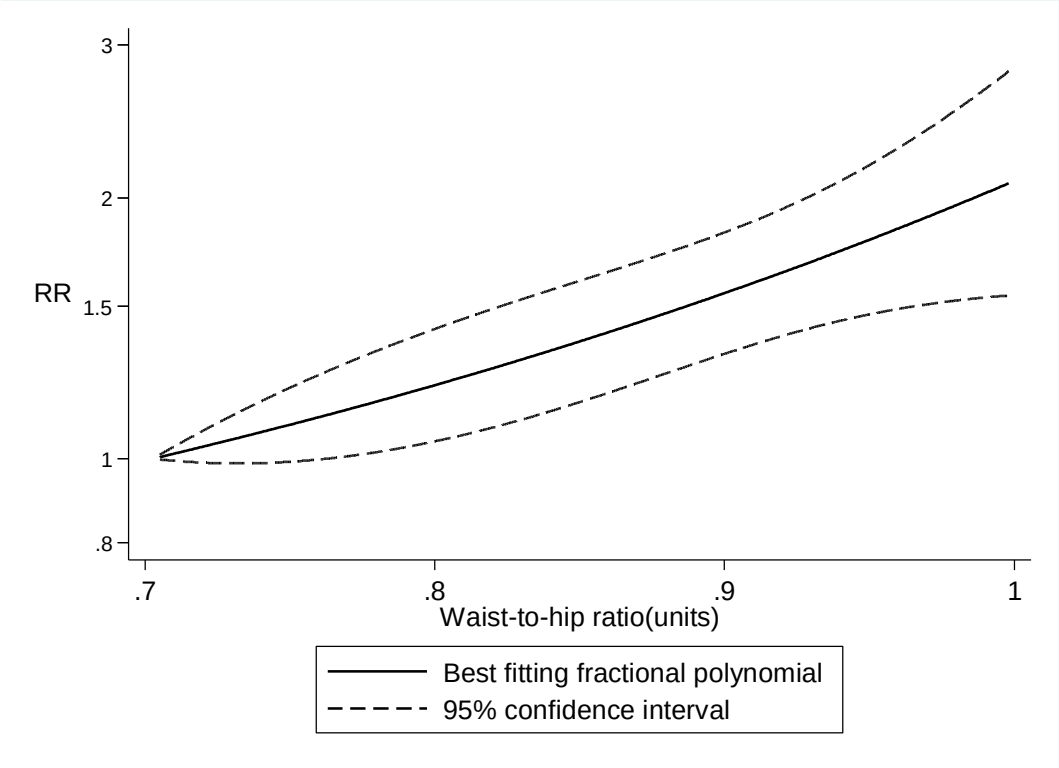


Figure 104 Scatter plot of risk estimates for waist-to-hip ratio and endometrial cancer

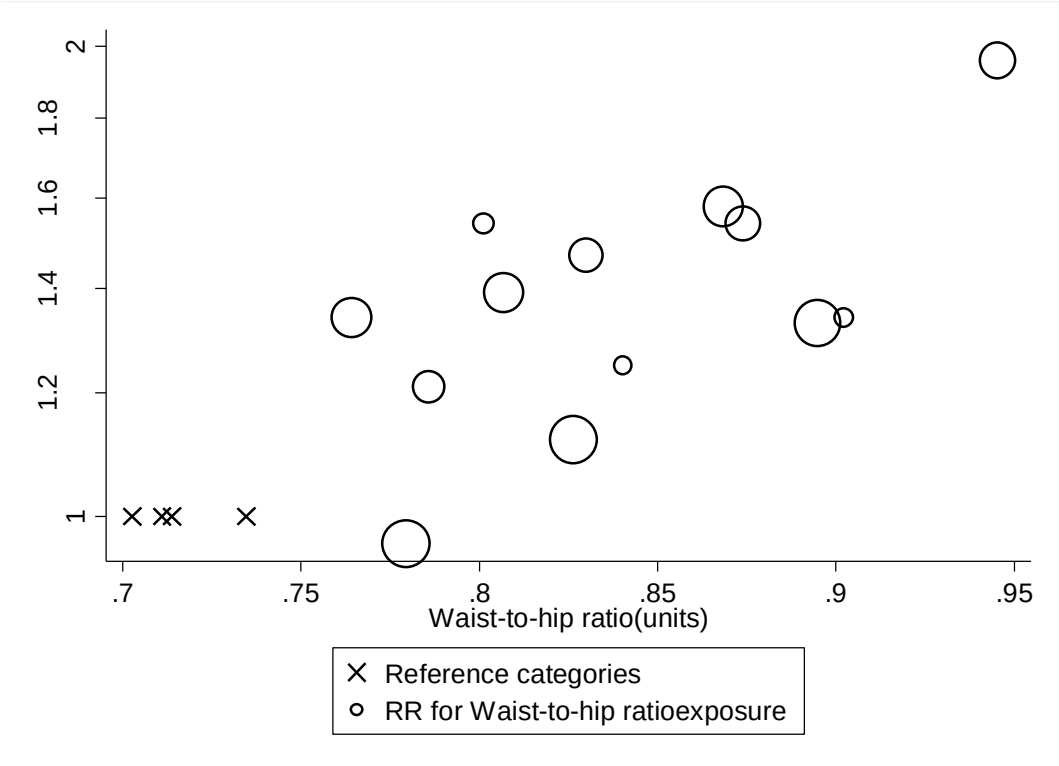


Table 132 RRs (95% CIs) for nonlinear analysis of waist-to-hip ratio and endometrial cancer

WHR	RR (95% CI)
0.7035	1.00
0.7508	1.10 (0.99-1.21)
0.8009	1.22 (1.05-1.42)
0.8501	1.37 (1.16-1.60)
0.9002	1.55 (1.32-1.83)
0.9503	1.79 (1.47-2.18)
1.0004	2.09 (1.54-2.84)

8.3.1 Height

Methods

A total of 13 cohort studies and one ancillary analysis on a randomised trial (18 publications) have been published on height and endometrial cancer risk up to December 2012, eight (7 publications) of which were identified in the CUP. Dose-response analyses were conducted per 5 cm. We used the method by Hamling et al to convert risk estimates for studies that used the second lowest category as the reference category.

Main results

The summary RR per 5 cm increase in height was 1.07 (95% CI: 1.03-1.11, I^2=69.0%, $p_{heterogeneity}$=0.001, n=9). There was no evidence of a nonlinear association between height and endometrial cancer, $p_{nonlinearity}$=0.39

Heterogeneity

There was high heterogeneity, I^2=69.0%, $p_{heterogeneity}$=0.001.

Conclusion from the Second Expert Report

In the systematic review of the 2007 expert report the evidence relating height to increased endometrial cancer risk was considered limited suggestive.

Table 133 Studies on height identified in the CUP

Author/ year	Country	Study name	Cases	Years of follow-up	RR	LCI	UCI	Contrast
Kabat, 2013	Canada	Canadian National Breast Screening Study	780	16.2	1.36	1.22	1.52	Per 10 cm
Green, 2011	UK	The Million Women Study	5810	9.4	1.19	1.12	1.26	Per 10 cm
Park, 2010	USA	Multiethnic Cohort Study	463	10.3	0.97	0.72	1.32	≥165.1 vs. <157.0 cm
Sung, 2009	Korea	Korean Cancer Prevention Study	298	~9	1.24	1.08	1.41	Per 5 cm increment
Lundqvist, 2007	Sweden, Finland	Sweden, Finland co-	214	26.3	0.9	0.6	1.2	Quartile 4 vs. 1

		Twin study						
Friedenreich, 2007	Europe	European Prospective Investigation into Cancer and Nutrition	567	6.4	1.09 1.01	0.83 0.94	1.42 1.09	>166.5 vs. ≤157.0 cm Per 5 cm
Bjorge, 2007	Norway	Norwegian Health Surveys	9227	25	1.11	1.04	1.19	≥170 vs. 160-169 cm

Table 134 Overall evidence on height and endometrial cancer

	Summary of evidence
2005 SLR 2005	Ten cohort studies reported on height and endometrial cancer, but only four of these could be included in dose-response and high vs. low analyses respectively. Three studies found a significant positive association, which was limited to older women in one of these studies. The remaining studies showed non-significant associations.
Continuous Update Project	Eight additional follow-up studies reported on height and endometrial cancer, and four (three estimates) found no significant association, but four other studies found a significant positive association.

Table 135 Summary of results of the dose-response meta-analysis of height and endometrial cancer

Endometrial cancer		
	SLR 2005	Continuous Update Project
Studies (n)	4	9*
Cases (n)	-	17732
RR (95% CI)	1.17 (0.96-1.42)	1.07 (1.03-1.11)
Quantity	Per 10cm	Per 5 cm
Heterogeneity (I^2, p-value)	0%	69.0%, p=0.001

* Nine risk estimates (10 studies), one publication included results from an analysis of two studies combined (Lundqvist et al, 2007).

Table 136 Inclusion/exclusion table for meta-analysis of height and endometrial cancer

WCRF code	Author	Year	Study design	Study name	Cancer outcome	SLR 2005	CU dose-response	CU H vs. L forest plot	Estimated values	Exclusion reason
END00297	Kabat	2013	Prospective cohort study	Canadian National Breast Screening Study	Incidence	No	Yes	No		Only continuous estimate
END00259	Green	2011	Prospective cohort study	The Million Women Study	Incidence	No	Yes	No		Only continuous estimate
END00206	Park	2010	Prospective cohort study	Multiethnic Cohort Study	Incidence	No	Yes	Yes	Midpoints, person-years	
END00282	Sung	2009	Prospective cohort study	Korean Cancer Prevention Study	Incidence	No	Yes	Yes	Midpoints	
END00237	Friedenreich	2007	Prospective cohort study	European Prospective Investigation into Cancer and Nutrition	Incidence	No	Yes	Yes	Midpoints	
END00268	Lundqvist	2007	Prospective cohort study	Sweden, Finland Co-twin study	Incidence	No	Yes	Yes	Midpoints, person-years	
END00272	Bjørge	2007	Prospective cohort study	Norwegian Health Surveys	Incidence	No	Yes	Yes	Midpoints	
END00246	Schouten	2004	Prospective cohort study	Netherlands Cohort Study	Incidence	Yes	Yes	Yes		
END00172	Unfer	2004	Ancillary analysis in Randomised Controlled	NA	Incidence	Yes	No	No		No risk estimates, not endometrial cancer cases

			Trial (5 years follow-up)							
END00014	Furberg	2003	Prospective cohort study	Norwegian Health Screening Service	Incidence	Yes	No	No		Overlap with Bjorge et al, 2006 END00272
END00074	Jonsson	2003	Prospective cohort study	Swedish Twin Registry	Incidence	Yes	No	No		Overlap with Lundqvist et al, 2007, END00268
END00014	Zeleniuch-Jacquotte	2001	Nested case-control study	New York University Women's Health Study	Incidence	Yes	No	No		No risk estimates (only mean height)
END00060	Terry	1999	Prospective cohort study	Swedish Twin Registry	Incidence	Yes	No	No		Overlap with END00074 by Jonsson et al, 2003
END00094	de Waard	1996	Prospective cohort study	Breast Cancer Screening	Incidence	Yes	Yes	Yes	Midpoints, confidence intervals	
END00069	Le Marchand	1991	Prospective cohort study	Hawaii Historical Cohort	Incidence	Yes	No	Yes		No measure of height provided
END00073	Tretli	1990	Prospective cohort study	Norwegian National Health Screening Study	Incidence	Yes	No	No		Overlap with Bjorge et al, 2006 END00272
END00072	Baanders-van Halewijn	1985	Nested case-control study	Netherlands Breast Cancer Screening	Incidence	Yes	No	No		Overlap with END00094, de Waard et al, 1996
END00071	Ewertz	1984	Nested case-control study	Danish CC	Incidence	Yes	No	No		Participants were patients with breast cancer

Figure 105 Highest versus lowest forest plot of height and endometrial cancer

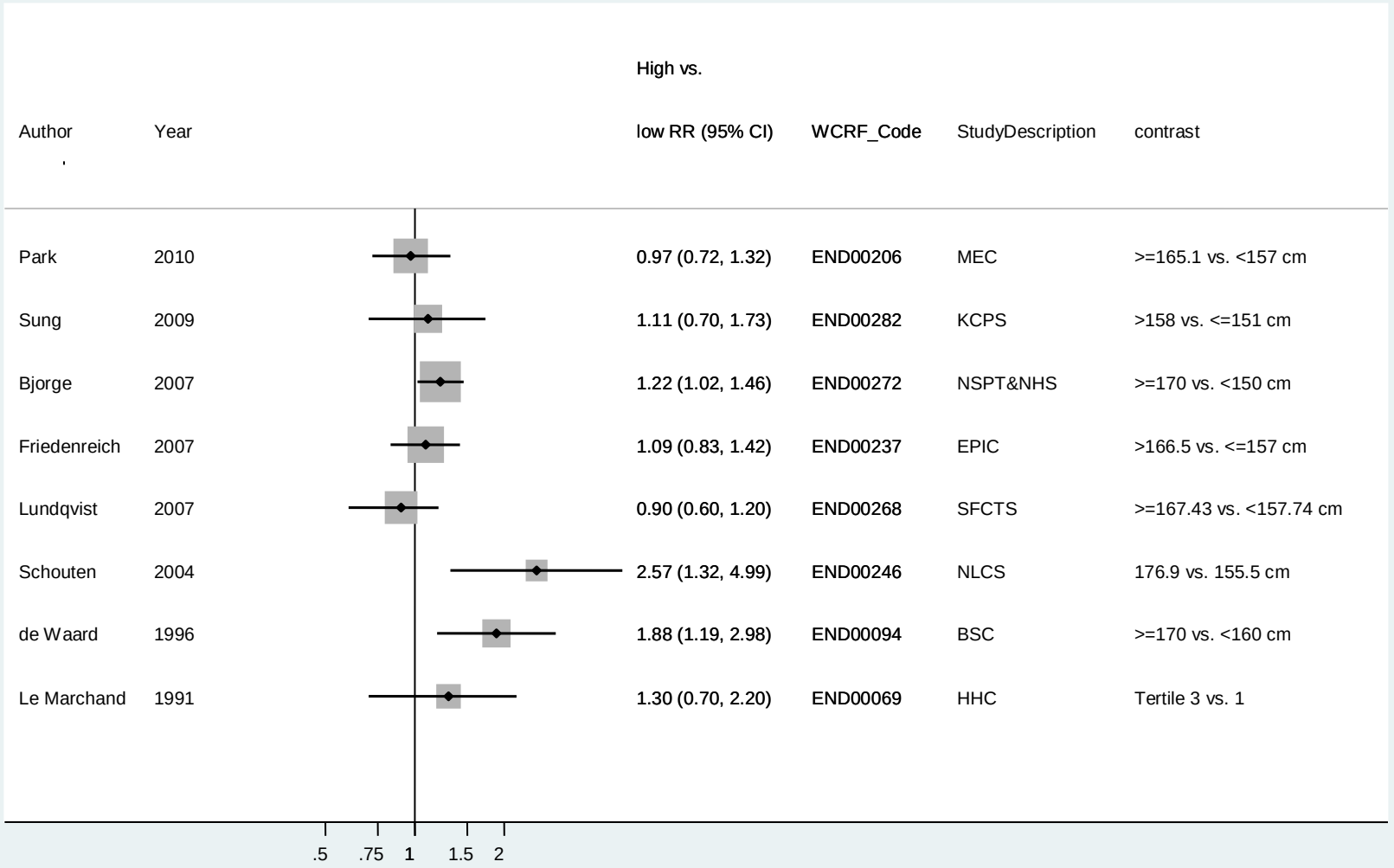


Figure 106 Dose-response meta-analysis of height and endometrial cancer, per 5 cm

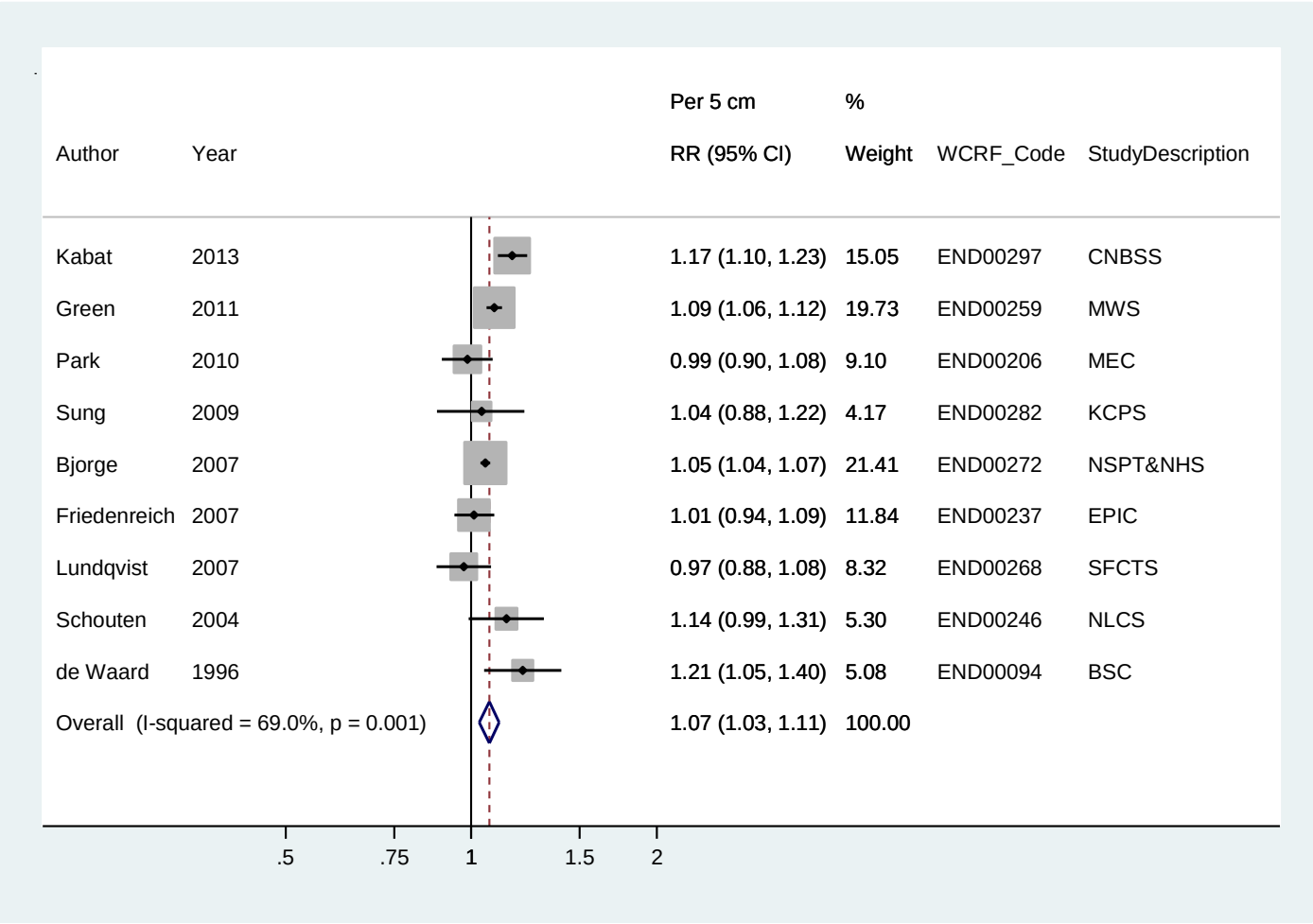


Figure 107 Dose-response graph of height and endometrial cancer

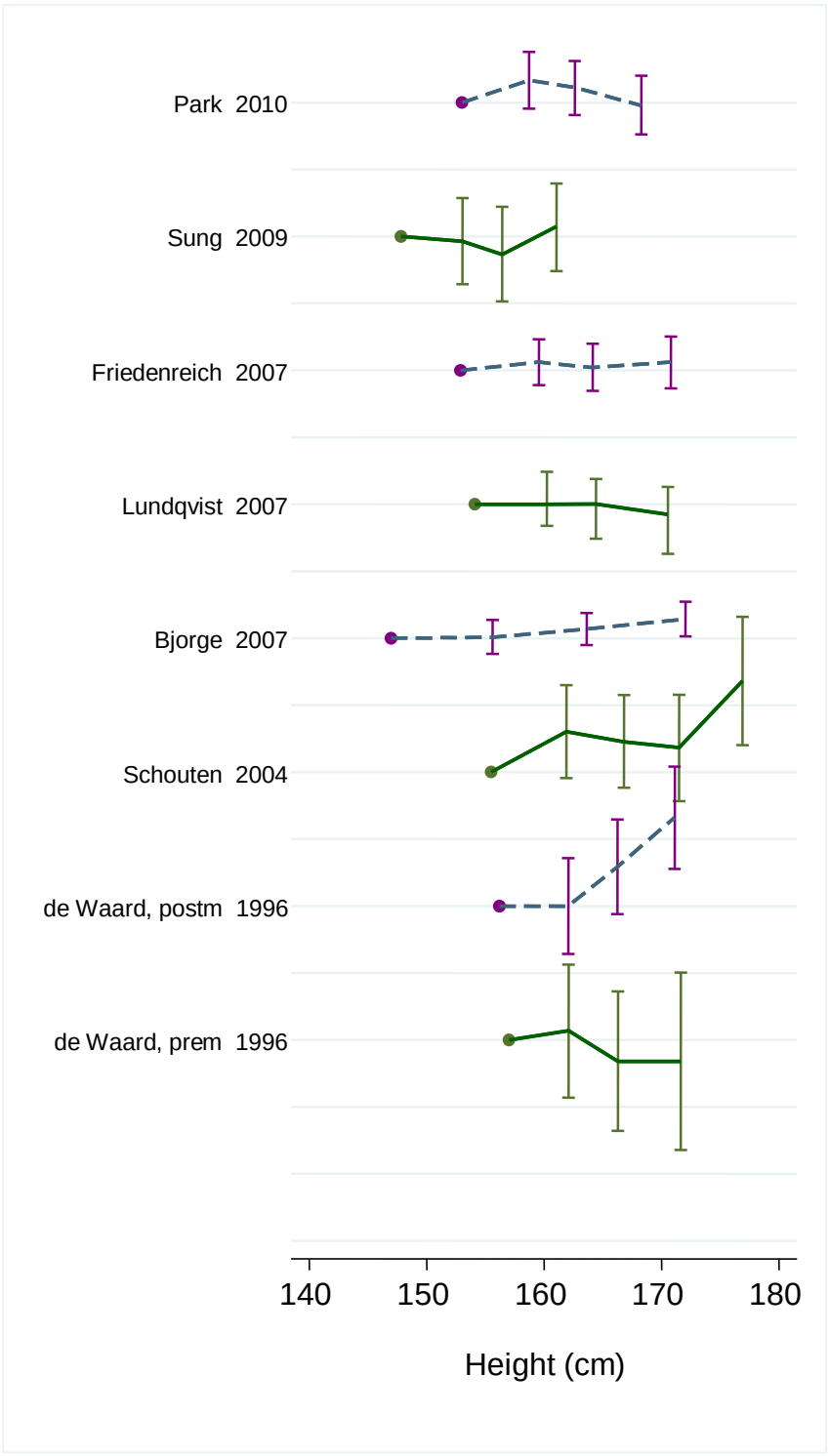


Figure 108 Nonlinear dose-response figure for height and endometrial cancer

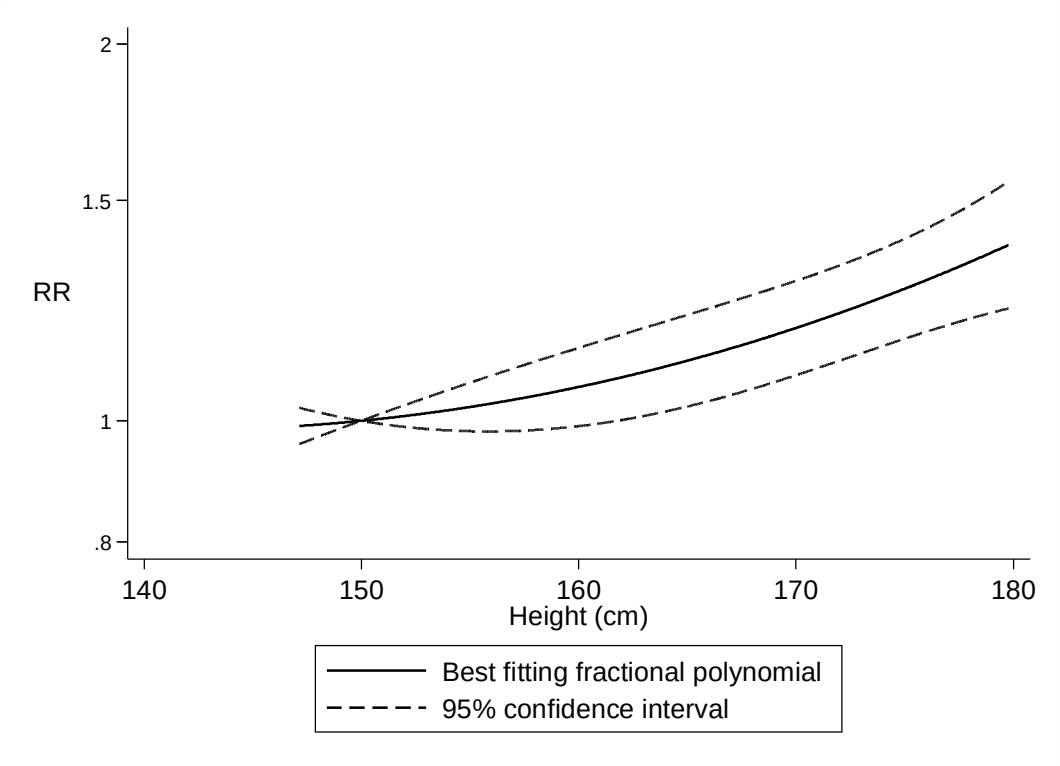


Figure 109 Scatter plot of risk estimates for height and endometrial cancer

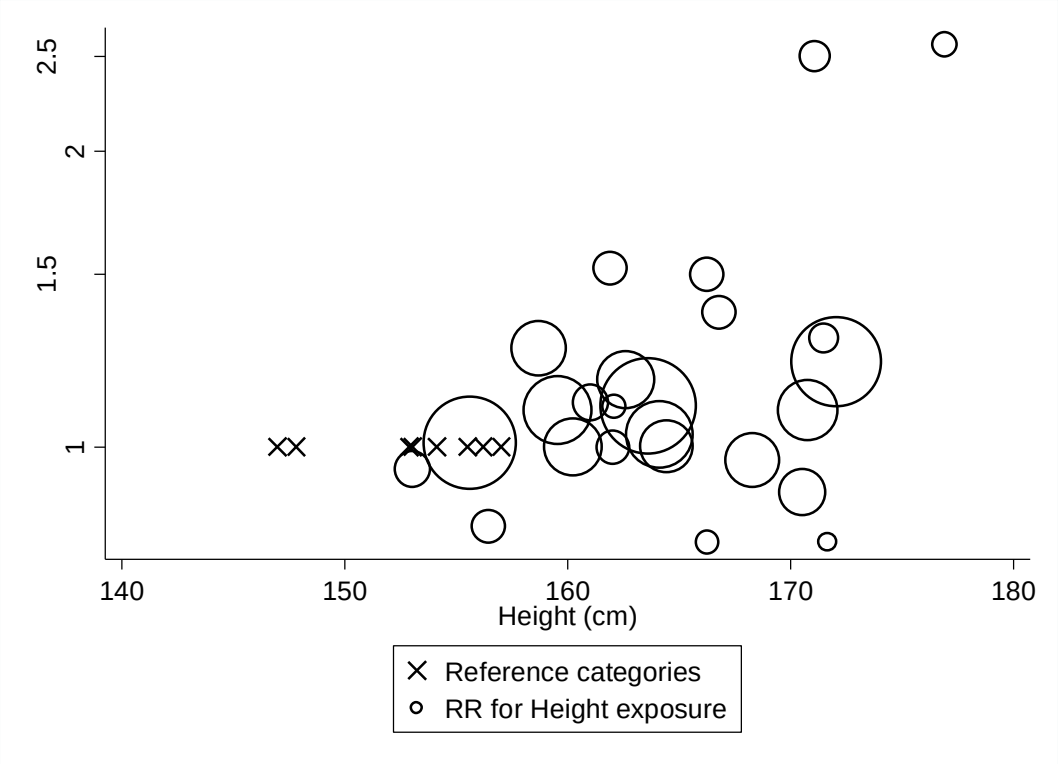


Table 137 RRs (95% CIs) for nonlinear analysis of height and endometrial cancer

Height (cm)	RR (95% CI)
150	1.00
155	1.03 (0.98-1.07)
160	1.06 (0.99-1.14)
165	1.13 (1.03-1.22)
170	1.19 (1.09-1.29)
175	1.28 (1.16-1.40)
180	1.39 (1.23-1.56)

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