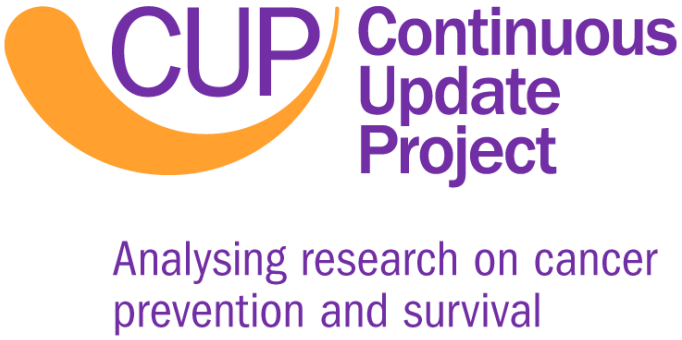
World Cancer Research Fund International Systematic Literature Review

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

ACLS	Aerobics Centre Longitudinal Study
AgriHSC	Agricultural Health Study Cohort
AHS	Californian Seventh Day Adventists
AMS	Adventists Mortality Study
ATBC	Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study
BLSA	Baltimore Longitudinal Study of Aging
BRHS	British Regional Heart Study
CARET	Carotene and Retinol Efficacy Trial
CHAC	The Chicago Heart Association Detection Project in Industry Cohort
CHS	Cardiovascular Health Study
CMHS	California Men's Health Study
CCPS/CHS	Copenhagen City Heart Study
CMS	Copenhagen Male Study
CCPM	Copenhagen County Centre of Preventive Medicine
CLUE	Campaign Against Cancer and Stroke, Washington County, Maryland
CPS	Cancer Prevention Study
CSDLH	Canadian Study of Diet, Lifestyle and Health
CSM	Cohort of Swedish Men
DCS	Danish Diet, Cancer and Health study
EPIC	European Prospective Investigation into Cancer and Nutrition
ESTHER	Epidemiologische Studie zu Chancen der Verhütung, Früherkennung und optimierten Therapie chronischer Erkrankungen in der älteren Bevölkerung
FMCHS	Finnish Mobile Clinic Health Examination Survey
FHS	Framingham Heart Study
GPRD	General Practice Research Database
Harvard Alumni	Harvard Alumni Health Study
HHS	Helsinki Heart Study
HPFS	Health Professionals Follow-up Study
HPP	Honolulu Heart Program
HUNT	The Nord-Trøndelag Health Study

I65	Iowa's 65+ Study
ICRFS	Iceland Cardiovascular Risk Factor Study
IFS	Iowa's Farmers Study
IWMS	Iowa Men's Health Study
JAN PRO	Janus Project in Norway
JACC	Japan Collaborative Cohort Study
JPHC	The Japan Public Health Centre-based Prospective Study
KNHICS	Korea National Health Insurance Corporation Study
KPMCP	Kaiser Permanente Medical Care Program
LBCS	Lutheran Brotherhood Cohort Study
LWS	Leisure World Study, Laguna Hills Study USA
LSA	Longitudinal Study on Aging
LSS	Life Span Study, atomic bomb survivors, Japan
MCCS	The Melbourne Collaborative Cohort Study
MDCS	Malmö Diet and Cancer Study
MEC	Multiethnic Cohort Study
MONICA	WHO Northern Sweden Monitoring Trends and Determinants of Cardiovascular Disease (MONICA) study
MrOS	Osteoporotic Fractures in Men (MrOS) study
NHANES	National Health and Nutrition Examination Survey
NHEFS	Nutrition Examination Survey Epidemiology Follow-up Study
NHIS	National Health Interview Survey
NIH-AARP	NIH-AARP Diet and Health Study
NLCS	The Netherlands Cohort Study
NPCT	Nutritional Prevention of Cancer Trial
NSHDC	Northern Sweden Health and Disease
OCS	Ohsaki Cohort Study
PCPT	Prostate Cancer Prevention Trial
PLCO	Prostate, Lung, Colorectal, and Ovarian (PLCO) Cancer Screening Study
PRHP	Puerto Rico Heart Health Program
RHS	Rural Health Study
SABOR	San Antonio Centre for Biomarkers of Risk of Prostate Cancer
SCHS	Singapore Chinese Health Study
SCWC	Swedish Construction Workers' Cohort Study
SELECT	The Selenium and Vitamin E Cancer Prevention Trial
SMART	Second Manifestations of ARTerial disease (SMART) study
STC	Swedish Twin Cohort
ULSAM	Uppsala Longitudinal Study of Adult Men
VHM&PP	The Vorarlberg Health Monitoring and Prevention Program
VIP	The Vasterbotten Intervention Project
VITAL	VITamins And Lifestyle cohort
WS	Whitehall Study

Background

Matrices presented in the WCRF/AICR 2007 Expert Report

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

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

	DECREASES RISK	INCREASES RISK
Convincing		
Probable	**Foods containing lycopene[1 2]** **Foods containing selenium[1]** **Selenium[3]**	**Diets high in calcium[4 5]**
Limited — suggestive	Pulses (legumes)[6] Foods containing vitamin E[1] Alpha-tocopherol[7]	Processed meat[8] Milk and dairy products[5]
Limited — no conclusion	Cereals (grains) and their products; dietary fibre; potatoes; non-starchy vegetables; fruits; meat; poultry; fish; eggs; total fat; plant oils; sugar (sucrose); sugary foods and drinks; coffee; tea; alcohol; carbohydrate; protein; vitamin A; retinol; thiamin; riboflavin; niacin; vitamin C; vitamin D; gamma-tocopherol; vitamin supplements; multivitamins; iron; phosphorus; zinc; other carotenoids; physical activity; energy expenditure; vegetarian diets; Seventh-day Adventist diets; body fatness; abdominal fatness; birth weight; energy intake	
Substantial effect on risk unlikely	Beta-carotene[1 9]	

1 Includes both foods naturally containing the constituent and foods which have the constituent added (see chapter 3.5.3).
2 Mostly contained in tomatoes and tomato products. Also fruits such as grapefruit, watermelon, guava, and apricot.
3 The evidence is derived from studies using supplements at a dose of 200 µg/day. Selenium is toxic at high doses.
4 Includes diets that naturally contain calcium and that contain foods fortified with calcium. See box 4.10.1.
5 Effect only apparent at high calcium intakes (around 1.5 g/day or more). Evidence for milk and dairy products (but not calcium) was derived only from countries with populations that have high calcium and dairy consumption.
6 Including soya and soya products.
7 The evidence is derived from studies using supplements at a dose of 50 mg/day.
8 The term 'processed meat' refers to meats preserved by smoking, curing, or salting, or addition of chemical preservatives.
9 The evidence is derived from studies using supplements at doses of 20, 30, and 50 mg/day.

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

World Cancer Research Fund | American Institute for Cancer Research

Modifications to the existing protocol

The protocol on prostate cancer was prepared in 2008. The following modifications had been introduced:

Review team: Ana Rita Vieira, Dagfinn Aune, Deborah Navarro, Leila Abar and Snieguole Vingeliene joined the team as reviewers. Ana Rita Vieira organized the writing of the SLR manuscript and put together the final document. Christophe Stevens join the team as database manager. Teresa Norat and Doris Chan had the responsibilities indicated in the protocol. Darren Greenwood worked as Statistical Advisor. Rosa Lau and Rui Vieira are not part of the team.

Timeline: The current review includes articles published until 30 April 2013 and the first draft of the review was rescheduled for submission to the WCRF Secretariat on 5 December 2013.

Methods: Nonlinear dose response relationship was explored for selected exposures. Nonlinear dose response curves were plotted using restricted cubic splines for each study, with knots fixed at percentiles 10%, 50%, and 90% through the distribution. These were combined using multivariate meta-analysis. The analyses were performed in Stata 12.0. When the number of studies with three or more categories of exposure – a requirement of the method- was low or there was no suggestion of nonlinear dose response association from the studies, nonlinear meta-analysis analyses were not conducted and there is no mention of nonlinear dose response meta-analysis for those exposures in the text.

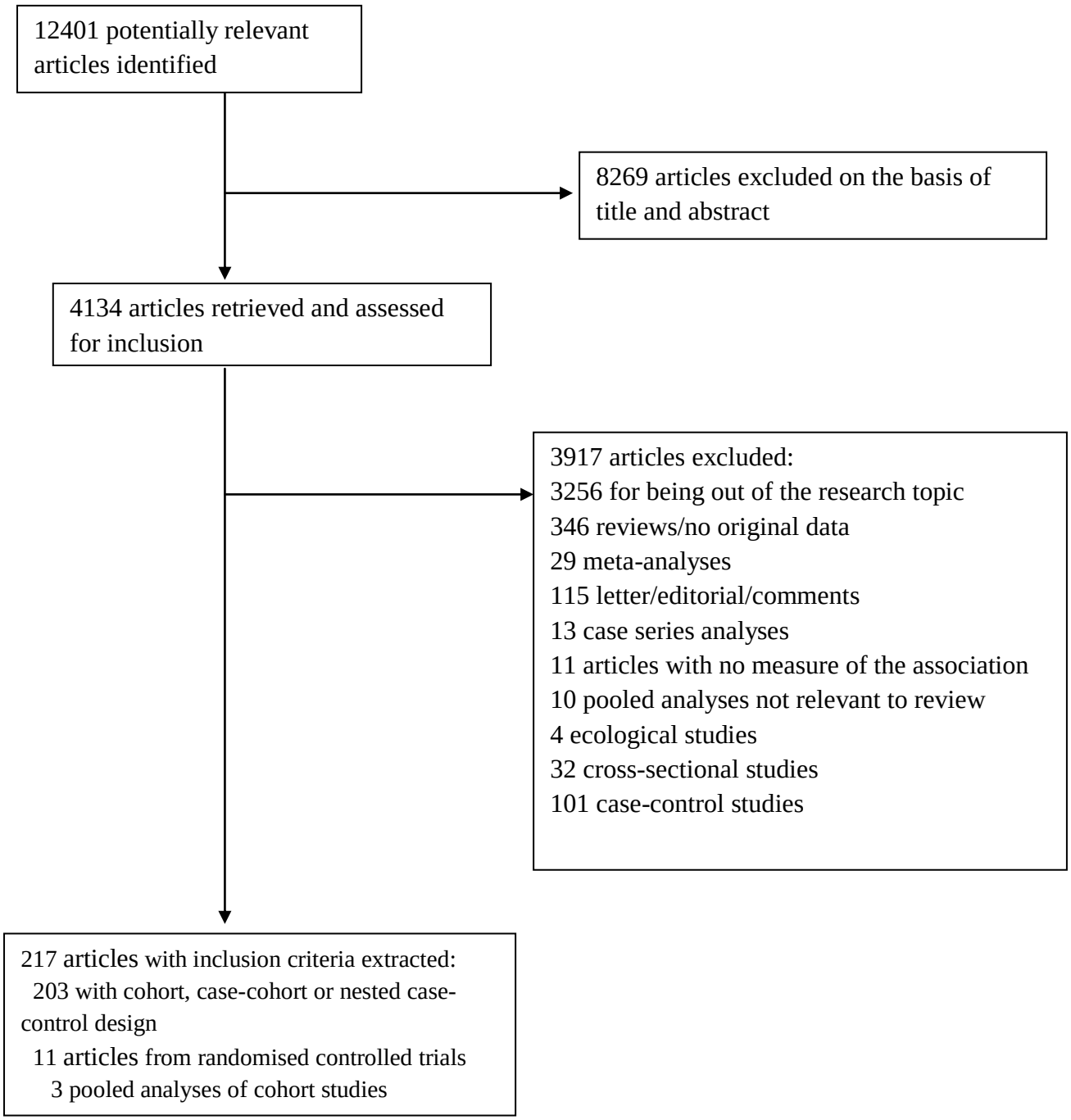
Most of the studies don't have information of prostate cancers diagnosed through screening (PSA or digital examination). Some studies collected PSA use at baseline. These data are described for Calcium and BMI because there were a relatively high number of studies providing some information.

Notes on figures and statistics used

- The statistical methods used are described in the protocol.
- The method by Hamling et al, 2008 was used to convert risk estimates when the reference category was not the lowest category, as indicated in the text.
- The interpretation of heterogeneity tests should be cautious when the number of studies is low. Visual inspection of the forest plots and funnel plots is recommended.
- The I^2 statistic describes the proportion of total variation in study estimates that is due to heterogeneity. Low heterogeneity might account for less than 30 per cent of the variability in point estimates, and high heterogeneity for substantially more than 50 per cent. These values are tentative, because the practical impact of heterogeneity in a meta-analysis also depends on the size and direction of effects (Higgins and Thompson, 2002).
- Heterogeneity test and I^2 statistics are shown for a "Highest vs Lowest" meta-analysis when this is the only type of meta-analysis conducted.
- Only summary relative risks estimated with random effect models are shown.
- Highest vs. lowest forest plots show the relative risk estimate for the highest vs the reference category used in each study. The comparisons used in each study are shown in the corresponding Figure. The overall summary estimate was not calculated (except for physical activity domains).
- The dose-response forest plots show the relative risk estimates for each study, expressed per unit of increase. The relative risk is denoted by a box (larger boxes indicate that the study has higher precision, and greater weight). Horizontal lines denote 95% confidence intervals (CIs). Arrowheads indicate truncations. The diamond at the bottom shows the summary relative risk estimate and corresponding 95% CI. The unit of increase is indicated in each figure and summary table.
- The dose-response plots show the results for each study included in the review for that exposure. The relative risks estimates are plotted in the mid-point of each category level (x-axis) and are connected through lines.
- Where results were only presented separately for specific cancer types (e.g. advanced and localised), these were first combined before inclusion in the analysis on total prostate cancer.
- Whenever possible, stratified analysis by prostate cancer type was performed. The subgroups used in the stratified analysis are defined in the protocol. Across exposures, the name of the subgroups may differ according to the classification used in the available studies provided, eg advanced/aggressive, advanced/high grade, etc. The first dose-response forest plot is the analysis of all studies combined. This is followed by analyses by cancer type, showing the subgroup of advanced/aggressive, localised/low grade and a third group of the remaining studies (any type). When there were at least two studies on prostate cancer mortality, these studies were combined separately in a meta-analysis. In some exposures, it was possible to stratify by incidence or mortality as outcome.
- Nonlinearity was explored when there were at least five studies with enough data to do it and the study results suggested a nonlinear association. The nonlinear graphs are presented when the p-value for non-linearity is statistically significant. Otherwise only the p-value is reported in the text.

Continuous Update Project: Results of the search

Flow chart of the search for prostate cancer – Continuous Update Project Search period January 1st 2006-April 30th 2013



Randomised controlled trials (RCT)

A total of four randomised controlled trials (seven publications) on prostate cancer were identified: the Selenium and Vitamin E Cancer Prevention Trial (SELECT), the Physician's Health Study II (PHS II), the Carotene and Retinol Efficacy Trial (CARET) and the Aspirin/Folate Polyp Prevention Study. The main characteristics of the trials are in **Table 1**.

Table 1 Characteristics of randomized controlled trials identified during the CUP

Trial name	Design	Participants, country, date	Intervention	Main outcome	Author, year of publication	Intervention
Selenium and Vitamin E Cancer Prevention Trial (SELECT)	Double-blind randomized placebo controlled 2 x 2 factorial trial	35,533 men from US, Canada and Puerto Rico, enrolment August 2001 to June 2004	Selenium (200 mcg L-selenomethionine daily) and/or vitamin E (400 IU all-rac-α-tocopheryl acetate daily)	Prostate cancer (there were no differences between groups in the intensity of PSA testing, PSA levels, PSA change, nor rates of testing)	Klein, 2011	Vitamin E Selenium Selenium and Vitamin E
					Dunn, 2010	Superseded by Klein, 2010. Not included
					Lippman, 2009	Superseded by Klein, 2010. Not included
Physician's Health Study II (PHS II)	Double-blind randomized placebo controlled 2x2x2x2 factorial trial	14,641 male physicians from US, enrolment began in 1997, treatment through June 2011	Multivitamin daily, vitamin E (400-IU synthetic α-tocopherol) on alternate days, vitamin C (500-mg synthetic ascorbic acid) daily, beta carotene (50-mg Lurotin) on alternate days	Total cancer and major cardiovascular events Secondary outcomes (cancer): prostate, other site-specific cancers	Gaziano, 2012	Multivitamins
					Gaziano, 2009	Vitamin E Vitamin C
Carotene and Retinol Efficacy Trial (CARET)	Double-blind randomized placebo controlled trial	18,314 men and women from US (current and former heavy smokers, or asbestos-exposed workers) enrolled before 1995. Trial stopped in 1996 (increased lung cancer incidence)	β-carotene (30 mg daily) and retinyl palmitate (25,000 IU daily)	Lung cancer incidence, cardiovascular mortality, all-cause mortality	Neuhouser, 2009	β-carotene and retinyl palmitate

Aspirin/Folate Polyp Prevention Study	Double-blind randomized placebo controlled 3 × 2 factorial trial	1021 men and women with previous colorectal adenomas from US, Canada and Puerto Rico, enrolled before April 1998. Intervention until October 2004	81 mg/d of aspirin, 325 mg/d of aspirin, 1 mg/d of folic	Colorectal adenoma	Figueiredo, 2009	Folic acid

Results of RCTs by intervention

5.5.3 Folic acid

There was an increased risk of prostate cancer in the folic acid supplementation group compared to placebo (HR 2.58; 95% CI 1.14-5.86; p < 0.02; 32 cases, median follow-up= 7 years) in a secondary analysis of the Aspirin/Folate Polyp Prevention Study. Colorectal adenoma was the main outcome (Figueiredo et al, 2009).

In a recent meta-analysis of randomized controlled trials, supplementation with folic acid had no significant effect on the incidence of prostate cancer, even in the period more than 3 years after randomization (Vollset et al, 2013). The meta-analysis included individual patient data in all randomized placebo-controlled trials of folic acid for prevention of cardiovascular disease (10 trials, n = 46,969) or colorectal adenoma (3 trials, n = 2652). The Aspirin/Folate Polyp Prevention study was included in the analysis. The median daily dose of folic acid in the trials was 2.0 mg. The RR of prostate cancer was 1.15 (95% CI 0.94-1.41) compared with placebo (351 cases in folic acid supplement arm, 305 cases in the placebo arm).

5.5.9 Vitamin C

In the Physician's Health Study II, prostate cancer risk did not differ between groups receiving vitamin C (508 cases, HR 1.02 (95% CI 0.90-1.15) and placebo (515 cases) after a mean follow-up of 8 years (Gaziano et al, 2009).

5.5.11 Vitamin E

Four publications from two trials (SELECT and PHS) reported on the efficacy of vitamin E in the prevention of prostate cancer. No intervention study was identified in the 2005 SLR.

In the SELECT trial (Klein et al, 2011) a significant increased risk of prostate cancer was observed in the group receiving vitamin E (620 cases, HR 1.17; 99% CI 1.004-1.36; p = 0.008) compared to placebo (529 cases). The absolute increase in risk of prostate cancer

for vitamin E was 1.6 per 1000 person-years. The elevated risk for vitamin E was consistent across low- and high-grade disease. The risk increase did not appear to be due to an increased biopsy rate prompted by changes in digital rectal examination, PSA, or unblinding. An interim analysis was published (Lippman et al, 2009). The analysis by Klein et al, 2011 was on the data collected up to May 2011, 7 years after the last patient was randomized as planned, and published by recommendation of the safety monitoring committee.

In the Physician's Health Study II no significant difference in prostate cancer risk was found in the group receiving vitamin E (493 cases; HR 0.97; 95% CI 0.85-1.09) and placebo (515 cases) after a mean follow-up of 8 years (Gaziano et al, 2009). The cumulative incidence curves indicated that the lack of effect did not vary for up to 10 years of treatment and follow-up (log-rank p = 0.53). Further restriction to events and time after 4 and 6 years of treatment similarly found no apparent relationships. Censoring participants at the time of vitamin E non adherence did not impact the results (HR 0.95; 95% CI 0.84-1.07; p = 0.38).

The SELECT and the PHS II used different doses. A dose of 400-IU of vitamin E was used daily in the SELECT trial and the same dose but on alternate days was used on the PHS II trial.

The Alpha Tocopherol Beta Carotene Prevention Trial (ATBC) study group reported an update of the trial results (Ahn, 2008). The post-trial follow-up period was 1991-2003. During the trial, there was a protective effect of alfa-tocopherol supplementation that disappeared during the six years posttrial follow-up (RR: 0.80; 95% CI: 0.76-1.03 for intervention compared with placebo) (Virtano, 2003). In the recent post trial follow-up study (Ahn, 2008), the RR of prostate cancer in the alfa-tocopherol intervention arm (50 mg/day) was 0.83 (95 % CI 0.74-0.94) among men without family history and among men with family history of prostate cancer the relative risks were 1.70 (95% CI 1.09-2.33) in the placebo group and 1.90 (95 % CI 1.35-2.68) in the intervention group. The relative risks were compared with men in the placebo arm without family history of prostate cancer.

5.5.1.2 Beta-carotene (and retinyl palmitate)

Three trials were identified in the SLR for the Second Expert Report. Two updated reports were identified in the CUP.

In the CARET trial (testing 30 mg β-carotene + 25,000 IU retinyl palmitate on lung cancer risk) (Neuhouser et al, 2009), men in the active CARET arm not using dietary supplements at baseline had a RR of prostate cancer of 0.80 (95 % CI 0.60-1.04; 99 cases) and 0.89 (95% CI 0.58-1.35) of aggressive cancer (44 cases) (Gleason ≥7 or stage III/IV) compared with men in the CARET placebo arm not using dietary supplements at baseline (108 cases). The RR was 1.10 (95% CI 0.81-1.48, 69 cases) for total prostate cancer and 1.36 (95% CI 0.87-2.13; 34 cases) for aggressive prostate cancer in men in the CARET active arm using dietary supplements at baseline for the same comparison. Any suggestion of increased risk disappeared in the post-intervention phase (follow-up through 2005).

When participants using CARET vitamins or other supplements were compared with those with placebo or not taking any supplements, the RR for total prostate were 1.26 (96% CI 0.96-1.64) for total prostate cancer and 1.52 (95% CI 1.03-2.24; p < 0.05) for aggressive prostate cancer. The significant increased risk of aggressive prostate cancer in men in the active CARET arm or taking supplements disappeared in the post-intervention period (0.75;

95% CI 0.51-1.09). There was no significant association of CARET plus other supplements with nonaggressive disease, relative to all others.

CARET only included smokers.

The Alpha Tocopherol Beta Carotene Prevention Trial (ATBC) study group reported an update of the trial results (Ahn, 2008). The post-trial follow-up period was 1991-2003. During the trial, no effect of beta-carotene was observed (Virtamo, 2003). In the recent post trial follow-up study (Ahn, 2008), the RR of prostate cancer in the beta-carotene intervention arm (20 mg/day) was 1.09 (95 % CI 0.97-1.23) among men without family history and among men with family history of prostate cancer the relative risks were 1.98 (95% CI: 1.37-1.86) in the placebo group and 2.02 (95% CI 1.42-2.88) in the intervention group. The relative risks were compared with men in the placebo arm without family history of prostate cancer.

The publication of the CARET study (Omenn, 1996) has been superseded by a more recent publication identified during the CUP (Neuhouser, 2009).

The publication of the ATBC study (Virtamo, 2003) has been superseded by a more recent publication identified during the CUP (Ahn, 2008).

In the Physicians' Health Study randomized trial no effect of beta-carotene on prostate cancer risk was observed. The relative risk of prostate cancer (1117 cases) comparing beta-carotene (50 mg on alternate days) (551 cases) with placebo (566 cases) was 1.0 (95% CI 0.9-1.1) (Cook, 2000). In a previous report (Cook, 1999) the authors reported a significant reduction of prostate cancer risk in the intervention group among men with low blood levels of beta-carotene at baseline)

5.5.13 Multivitamin supplements

In the Physician's Health Study II prostate cancer risk did not differ in the groups receiving multivitamin C (683 cases, HR: 0.98; 95% CI 0.88-1.09; p = 0.76) and placebo (690 cases) after a mean follow-up of 11.2 years (Gaziano et al, 2012).

5.6.4 Selenium

Three publications of the SELECT trial were identified (Klein et al, 2011; Dunn et al, 2010, Lipmann et al, 2009). The trial concluded that selenium did not prevent prostate cancer (HR: 1.09; 99% CI 0.93-1.27; 575 cases compared with placebo group; 529 cases) (Klein, 2011). The HR of high grade prostate cancer (GS $\geq$ 7) was 1.21 (99% CI 0.90-1.63; 161 cases) for those receiving selenium compared with placebo (133 cases).

The Nutritional Prevention of Cancer Trial was a randomized controlled trail on men with a history of either a basal cell or squamous cell carcinoma in low selenium areas of Eastern USA. Participants were randomised to receive either high-selenium yeast, providing 200 μg of selenium per day, or a yeast placebo. After a mean follow-up of 6.5 years (1983-1993) the RR of prostate cancer in the selenium group was 0.37 (99% CI 0.18-0.71; 13 cases) compared to placebo (35 cases) (Duffield-Lillico et al, 2003; Clark et al, 1998). After further follow-up

until 1996 (mean 7.5 years), the RR of prostate cancer was 0.51 (99% CI 0.29-0.88; 22 cases) compared to placebo (42 cases) (Duffield-Lillico et al, 2003).

5.6.6 Selenium and Vitamin E

In the SELECT trial the HR of prostate cancer in selenium plus vitamin E group was 1.05 (99% CI 0.89-1.22; 555 cases) compared to placebo (529 cases) (Klein et al, 2011). In this trial, vitamin E increased the risk of prostate cancer but there was no increased risk of prostate cancer when vitamin E and selenium were taken together. The risk of prostate cancer with Gleason 7 or higher was 1.23 (99% CI 0.91-1.66) for the two supplements combined compared to placebo.

Cohort studies. Results by exposure.

Table 2 Number of relevant articles identified during the 2005 SLR and the CUP and total number of articles by exposure.

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

Exposure Code	Exposure Name	Number of articles		Total number of articles
		2005 SLR	CUP	
1.4	Vegetarian diet	6	1	7
1.4	Other dietary patterns	0	5	5
2.1.1	Low fibre cereal	0	1	1
2.1.1.0.2	Refined cereals	0	1	1
2.1.1.0.4	Breakfast cereals	1	2	3
2.1.1	Oatmeal	0	2	2
2.1.1	Pasta and rice	0	1	1
2.1.1.1.4	High-fibre cereal	0	1	1
2.1.1.0.3	Bread	3	1	4
2.1.1.1.3	Pasta	1	1	2
2.1.1.1.3	Rye bread	0	2	2
2.1.1.1.3	Whole wheat bread	0	1	1
2.1.1.1.3	Wholegrain bread	0	1	1
2.1.1.2	Rice and pasta	0	1	1
2.1.1.2.3	Rice	3	2	5
2.1.1.4	Whole grains	0	1	1
2.1.1.1.3	French fries	0	1	1
2.1.2.1	Potatoes	3	4	7
2.1.2.1	Fries and chips	0	1	1
2.1.2.4	Wholegrain foods	0	2	2
2.2	Fruit and (non-starchy) vegetables	6	0	6
2.2	Carotene-rich fruits and vegetables	0	1	1
2.2	Total fruits	15	8	23
2.2	Total fruits and vegetables	0	1	1
2.2.1	Carotene-rich vegetables	0	1	1
2.2.1	Total vegetables	12	9	21
2.2.1.1.1	Carrots	3	2	5
2.2.1.2	Cruciferous vegetables	4	4	8
2.2.1.2.2	Chinese cabbage	0	1	1
2.2.1.2.3	Cabbage	2	3	5
2.2.1.2.4	Broccoli	2	3	5
2.2.1.2.5	Cauliflower	3	2	5
2.2.1.2.6	Brussels sprouts	2	1	3

2.2.1.2.7	Kale	3	1	4
2.2.1.3.1	Garlic	0	1	1
2.2.1.3.1	Garlic supplements	0	1	1
2.2.1.4	Green leafy vegetables	0	1	1
2.2.1.4.2	Spinach	2	2	4
2.2.1.4.3	Lettuce	2	1	3
2.2.1.4.4	Seaweed	2	1	3
2.2.1.5	Dark green vegetables	0	2	2
2.2.1.5	Deep yellow vegetables and tomatoes	0	1	1
2.2.1.5	Light green vegetables	0	1	1
2.2.1.5	Mushrooms	1	1	2
2.2.1.5	Peppers	1	1	2
2.2.1.5	Pickles	0	1	1
2.2.1.5	Tomato sauce	1	2	3
2.2.1.5	Vitamin c-rich vegetables	0	1	1
2.2.1.5	Wild plants	0	1	1
2.2.1.5	Yellow vegetables	0	1	1
2.2.1.5.13	Tomato juice	2	2	4
2.2.1.5.13	Tomatoes	6	6	12
2.2.2	Non citrus fruit	0	1	1
2.2.2.1	Citrus fruits	2	3	5
2.2.2.1	Oranges	3	1	4
2.2.2.2	Other fruits	0	1	1
2.2.2.2	Yellow-orange fruits	0	1	1
2.2.2.2.11	Grape	2	1	3
2.2.2.2.4	Watermelon	1	1	2
2.2.2.2.5	Papaya	0	1	1
2.2.2.2.8	Apples	2	1	3
2.2.2.2.9	Avocado	0	1	1
2.3	Legumes	0	2	2
2.3.1	Soy products	0	1	1
2.3.1	Soya foods	0	1	1
2.3.1.1	Miso soup	2	2	4
2.3.1.5	Tofu, soybeans	0	1	1
2.3.2	Beans, lentils	3	2	5
2.3.2.2	Tofu	3	1	4
2.3.4	Peanut butter	0	1	1
2.5.1	Total meat (red, white, processed, liver)	10	2	12
2.5.1	Meat, prefer well done	0	1	1
2.5.1	Broiled meat	0	1	1
2.5.1	Cooked meat	0	1	1
2.5.1	Rare/medium done red and processed meat	0	1	1

2.5.1	Well done red and processed meat	0	1	1
2.5.1	Well-/very well done meat	0	1	1
2.5.1	White meat	0	2	2
2.5.1.2	Processed meat	5	10	15
2.5.1.2	Ham and sausages	0	1	1
2.5.1.2	Lunchmeat	0	1	1
2.5.1.2.1	Ham	2	1	3
2.5.1.2.8	Bacon	3	2	5
2.5.1.2.9	Hot dog	0	1	1
2.5.1.2.9	Sausages	3	2	5
2.5.1.3	Red meat	10	12	22
2.5.1.3	Steak	0	1	1
2.5.1.3.1	Beef	5	4	9
2.5.1.3.1	Beef steak	0	1	1
2.5.1.3.3	Pork	5	3	8
2.5.1.3.3	Pork chops / ham steaks	0	1	1
2.5.1.4	Chicken	5	2	7
2.5.1.4	Poultry	2	6	8
2.5.1.5	Liver	2	1	3
2.5.2.1.7	Hamburger	0	1	1
2.5.2	Fish	13	8	21
2.5.2	Fish paste	0	1	1
2.5.2	Fresh fish	0	1	1
2.5.2	Smoked fish	0	1	1
2.5.2.3	Dried and salted fish	0	1	1
2.5.2.5	Fatty fish	0	1	1
2.5.2.9	White fish	0	1	1
2.5.3	Seafood	1	1	2
2.5.3	Shellfish	0	2	2
2.5.4	Eggs	12	3	15
2.6	Fat preference	0	1	1
2.6	Fats (all)	2	2	4
2.6.1.1	Butter	2	4	6
2.6.1.1	Dairy cream	0	2	2
2.6.1.1	Dairy fats	0	1	1
2.6.1.4	Fish oil	2	3	5
2.6.3	Margarine	1	2	3
2.6.4	Fructose	4	1	5
2.6.4	Sugars (as foods)	0	1	1
2.7	Cultured milk	0	1	1
2.7	Dairy products	11	16	27
2.7.1	Milk	14	8	22

2.7.1.1	Whole milk	7	4	11
2.7.1.2	Low fat milk	3	4	7
2.7.1.2	Skimmed milk	6	2	8
2.7.2	Cheese	6	10	16
2.7.2	Fresh curd cheese	0	1	1
2.7.2	Hard cheese	0	1	1
2.7.3	Sour milk products	0	2	2
2.7.3	Yoghurt	0	7	7
2.7.7	Ice cream	4	3	7
2.8.1.3	Ginseng	0	1	1
2.8.1.4	Chili	0	1	1
2.9	Spaghetti	0	2	2
2.9.1	Cakes, biscuits and pastry	0	1	1
2.9.1	Sweet baked goods	0	1	1
2.9.11	Vegetable soup	0	1	1
2.9.13	Sugar and sweets	0	1	1
2.9.13	Sweets	0	1	1
2.9.14	Pizza	1	2	3
3.4.1	Sugary drinks	1	1	2
3.5	Fruit juices	1	4	5
3.5.1	Citrus fruit juice	1	0	1
3.5.1	Orange / grapefruit juice	0	1	1
3.6.1	Caffeinated coffee	0	1	1
3.6.1	Coffee	11	6	17
3.6.1	Decaffeinated coffee	0	1	1
3.6.2	Tea	5	1	6
3.6.2	Black tea	3	2	5
3.6.2.2	Green tea	2	4	6
3.7.1	Alcohol consumption	0	7	7
3.7.1	Total alcoholic drinks	29	12	41
3.7.1	Alcoholic drinks - currency of use	0	1	1
3.7.1	Alcoholic drinks - age at first use	0	1	1
3.7.1	Alcoholic drinks - years since stopping	0	1	1
3.7.1	Alcoholism	0	1	1
3.7.1	Drinking duration	0	1	1
3.7.1	Drinking frequency	0	2	2
3.7.1	Lifetime alcohol consumption	0	1	1
3.7.1.1	Beers	5	3	8
3.7.1.2	Wines	6	3	9
3.7.1.3	Spirits	6	3	9
4.1.2.1	Pesticides	0	2	2
4.1.2.7.2	Arsenic	1	1	2

4.2	Preserved foods	0	1	1
4.2.5.1	Salt	0	1	1
4.2.5.1	Salt preference	0	1	1
4.3.5.4.1	Dietary nitrate	0	1	1
4.3.5.4.1	Dietary nitrite	0	2	2
4.3.5.4.1	Nitrite	0	1	1
4.4.2	Acrylamide	0	4	4
4.4.2	Rare/medium done red meat	0	1	1
4.4.2.4	Microwaving	0	1	1
4.4.2.5	Fried foods	0	1	1
4.4.2.5	Pan frying	0	2	2
4.4.2.6	Broiling	0	2	2
4.4.2.6	Grilling (broiling) and barbecuing	0	1	1
4.4.2.7	BaP	1	2	3
4.4.2.8	Heterocyclic amines	0	1	1
4.4.2.8	DimeIqx	0	1	1
4.4.2.8	MeIqx	1	4	5
4.4.2.8	PhIP	1	4	5
4.4.2.9	Mutagen index	1	1	2
5.1	Carbohydrate	6	4	10
5.1.2	Dietary fibre	2	3	5
5.1.2.1	Cereal fibre	0	1	1
5.1.2.2	Vegetable fibre	0	1	1
5.1.2.3	Fruit fibre	0	1	1
5.1.4	Sugars (as nutrients)	0	1	1
5.1.4	Lactose	0	1	1
5.1.4	Mono/disaccharides	0	1	1
5.1.4	Monosaccharides	0	1	1
5.1.4	Sucrose	0	2	2
5.1.5	Glycaemic index	0	3	3
5.1.5	Glycaemic load	0	3	3
5.2	Total fat (as nutrients)	9	8	17
5.2	Animal fat	2	2	4
5.2	Animal fat from dairy	2	1	3
5.2	Cholesterol, diet	0	2	2
5.2	Cholesterol, blood	12	2	14
5.2	Ratio n-3/n-6 fatty acids	0	4	4
5.2	Ratio polyunsaturated/saturated fat	2	2	4
5.2	Serum triglycerides	0	1	1
5.2.2	Saturated fatty acids	5	8	13
5.2.2	Myristic acid	2	2	4
5.2.2	Palmitic acid	3	2	5

5.2.2	Serum palmitic acid	0	1	1
5.2.2	Stearic acid (18:0)	3	2	5
5.2.3	Monounsaturated fatty acids	4	4	8
5.2.3	Oleic acid	3	2	5
5.2.3	Palmitoleic acid (16:1)	2	2	4
5.2.4	Polyunsaturated fatty acids	3	5	8
5.2.4	Eicosatrienoic	0	1	1
5.2.4.1	Alpha-linolenic acid (18:3 n-3), dietary	6	5	11
5.2.4.1	Alpha-linolenic acid (18:3 n-3), serum	3	5	8
5.2.4.1	DHA (docosahexaenoic acid), dietary	3	2	5
5.2.4.1	DHA (docosahexaenoic acid), serum	3	5	8
5.2.4.1	DPA (docosapentanoic acid), serum	1	4	5
5.2.4.1	EPA (eicosapentaenoic acid), dietary	2	2	4
5.2.4.1	EPA (eicosapentaenoic acid), serum	3	5	8
5.2.4.1	Fish fatty acids (EPA and DHA)	0	3	3
5.2.4.1	Serum PUFA n-3	0	1	1
5.2.4.1	n-3 fatty acids	0	2	2
5.2.4.2	n-6 fatty acids, dietary	0	4	4
5.2.4.2	Alpha-linoleic acid	0	1	1
5.2.4.2	Arachidonic fatty acid (20:4)	5	6	11
5.2.4.2	Dihomo-gamma-linoleic	2	3	5
5.2.4.2	Eicosadienoic acid	0	1	1
5.2.4.2	Gamma-linolenic acid	0	2	2
5.2.4.2	Linoleic acid, dietary	6	2	8
5.2.4.2	Serum pufa n-6	1	1	2
5.2.5	Trans 18:1 fatty acid	0	1	1
5.2.5	Trans fatty acids	0	4	4
5.3	Protein	7	3	10
5.3.1	Methionine	0	4	4
5.3.2	Plant protein	1	1	2
5.3.2	Vegetable protein	0	1	1
5.3.3	Animal protein	3	2	5
5.4	Alcohol (as ethanol)	3	8	11
5.4.1	Alcohol from beer	2	1	3
5.4.2	Alcohol from wine	1	2	3
5.4.3	Alcohol from spirit (hard liquor)	1	1	2
5.5	B vitamins	0	3	3
5.5	Vitamins, supplement	0	1	1
5.5.1	Vitamin A, serum	0	2	2
5.5.1	Vitamin A	8	1	9
5.5.1	Vitamin A, supplement	0	1	1
5.5.1.1	Retinol, serum	13	7	20

5.5.1.2	Alpha-carotene, serum	6	3	9
5.5.1.2	Alpha-carotene, dietary	2	2	1
5.5.1.2	Beta-carotene, serum	11	6	17
5.5.1.2	Beta-carotene, supplements	0	3	3
5.5.1.2	Beta-carotene, dietary	7	6	13
5.5.1.2	Beta-carotene, total	0	1	1
5.5.1.2	Beta-cryptoxanthin	0	3	3
5.5.1.2	Beta-cryptoxanthin, serum	0	2	2
5.5.10	Dietary vitamin D	0	1	1
5.5.10	Blood 25-hydroxyvitamin D	10	14	24
5.5.10	Vitamin D supplement	0	2	2
5.5.11	Alpha-tocopherol, serum	12	5	17
5.5.11	Alpha-tocopherol, dietary	0	3	3
5.5.11	Alpha-tocopherol supplement	0	1	1
5.5.11	Delta-tocopherol, dietary	0	4	4
5.5.11	Gamma tocopherol, serum	8	3	11
5.5.11	Serum vitamin E	0	1	1
5.5.11	Total vitamin E	0	3	3
5.5.11	Dietary vitamin E	4	5	9
5.5.11	Supplemental vitamin E	11	10	21
5.5.12	Vitamin K	0	2	2
5.5.13	Duration of multivitamin use	0	1	1
5.5.13	Multivitamin supplement	10	8	18
5.5.13	Other vitamins (including multivitamins)	0	1	1
5.5.2	Carotenoids	4	1	5
5.5.2	Carotenoids (no lycopenes)	0	1	1
5.5.2	Total carotenoids, serum levels	0	1	1
5.5.2	Canthaxanthin	0	1	1
5.5.2	Lutein	3	2	5
5.5.2	Lutein and zeaxanthin, blood	0	1	1
5.5.2	Lutein and zeaxanthin, dietary	0	1	1
5.5.2	Lycopene, dietary	7	5	12
5.5.2	Serum lutein	0	1	1
5.5.2	Serum lycopene	8	6	14
5.5.2	Serum zeaxanthin	0	1	1
5.5.2	Zeaxanthin	2	1	3
5.5.3	Total folate	5	4	9
5.5.3	Dietary folate	1	4	5
5.5.3	Supplemental Folate	0	3	3
5.5.3	Folate & alcohol	0	1	1
5.5.3	Homocysteine	0	1	1
5.5.3	Red cell folate	0	1	1

5.5.3	Serum folate	2	5	7
5.5.3	Serum homocysteine	0	1	1
5.5.4	Riboflavin	0	2	2
5.5.7	Plasma pyridoxine (vitamin B6)	0	1	1
5.5.7	Pyridoxine (vitamin B6)	1	2	3
5.5.8	Dietary vitamin B12 intake	0	1	1
5.5.8	Plasma cobalamin (vitamin B12)	0	2	2
5.5.8	Serum cobalamin (vitamin B12)	0	1	1
5.5.8	Vitamin B12, blood	0	1	1
5.5.9	Dietary vitamin C	6	5	11
5.5.9	Supplemental vitamin C	4	7	11
5.5.9	Total vitamin C	1	1	2
5.5.9	Vitamin C, from fruit	0	1	1
5.6	Mineral supplements	0	2	2
5.6.2	Haeme iron	0	2	2
5.6.2	Iron	0	2	2
5.6.2	Iron, serum	0	1	1
5.6.3	Total calcium	2	10	12
5.6.3	Dietary calcium	7	11	18
5.6.3	Supplemental calcium	4	8	12
5.6.3	Calcium from non-dairy foods	0	1	1
5.6.3	Calcium from plant sources	0	2	2
5.6.3	Calcium, blood	0	3	3
5.6.3	Calcium:phosphorus ratio	0	1	1
5.6.3	Dairy calcium	1	7	8
5.6.3	Non-dairy calcium	1	3	4
5.6.4	Serum/plasma selenium	13	4	17
5.6.4	Selenium, supplements	2	4	6
5.6.6	Boron	1	1	2
5.6.6	Cadmium	0	3	3
5.6.6	Magnesium	0	1	1
5.6.6	Phosphate	1	1	2
5.6.6	Phosphorus	6	1	7
5.6.6	Other minerals	0	1	1
5.6.7	Zinc	1	3	4
5.6.7	Zinc supplements	0	1	1
5.6.7	Zinc, serum	0	1	1
5.7	Phytochemicals	0	2	2
5.7.3	Glucosinolates and indoles	0	1	1
5.7.5	Biochanin a	0	1	1
5.7.5	Coumestrol	0	1	1
5.7.5	Daidzein	1	6	7

5.7.5	Enterodiol	0	1	1
5.7.5	Enterolactone	1	3	4
5.7.5	Equol	1	3	4
5.7.5	Formononetin	0	1	1
5.7.5	Genistein	1	6	7
5.7.5	Glycitein	0	3	3
5.7.5	Lignans	0	3	3
5.7.5	Matairesinol	0	1	1
5.7.5	O-dma	0	1	1
5.7.5	Plasma daidzein	0	2	2
5.7.5	Plasma enterolactone	0	1	1
5.7.5	Blood equol	0	3	3
5.7.5	Plasma genistein	0	3	3
5.7.5	Blood glycitein	0	2	2
5.7.5	Secoisolariciresiniol	0	1	1
5.7.5	Serum daidzein	0	1	1
5.7.5	Serum enterodiol	0	1	1
5.7.5	Serum enterolactone	0	1	1
5.7.5	Serum genistein	0	1	1
5.7.5	Serum o-DMA	0	1	1
5.7.5	Total isoflavones	0	3	3
5.7.6	Caffeine	0	1	1
5.8	Anthocyanidins	0	1	1
5.8	Flavan-3-ols	0	1	1
5.8	Flavanones	0	1	1
5.8	Flavones	0	1	1
5.8	Flavonoids	2	1	3
5.8	Flavonols	0	1	1
6.1	Total physical activity	13	5	18
6.1.1.1	Occupational physical activity	13	4	17
6.1.1.2	Bicycling	0	1	1
6.1.1.2	Exercise	0	1	1
6.1.1.2	Recreational physical activity	21	9	30
6.1.1.2	Sports	0	2	2
6.1.1.2	Stair climbing	0	1	1
6.1.1.2	Walking	0	3	3
6.1.1.3	Gardening	0	1	1
6.1.1.4	Travel activity	0	1	1
6.1.3	Light physical activity	0	1	1
6.1.3	Moderate and vigorous physical activity	0	1	1
6.1.3	Vigorous activity	4	1	5
6.1.3.2	Walking pace	0	1	1

6.1.4	Duration of physical activity	2	1	3
6.1.4.2	Duration of walking	0	1	1
7.1	Energy intake	8	8	16
8.1.1	BMI	75	39	114
8.1.1	BMI 18-21 years	5	6	11
8.1.1	BMI at 30 years	0	2	2
8.1.1	BMI at 40 years	0	1	1
8.1.1	BMI at certain age	0	1	1
8.1.2	Obesity	0	1	1
8.1.3	Weight	20	7	27
8.1.3	Weight at 18 years	0	3	3
8.1.3	Weight at 20 years	0	1	1
8.1.3	Weight at age 18 years	0	1	1
8.1.5	Body fat	2	1	3
8.1.6	BMI change	0	1	1
8.1.6	Weight change	0	6	6
8.1.6	Weight change since 18 years	0	1	1
8.2.1	Waist circumference	4	8	12
8.2.2	Hips circumference	2	1	3
8.2.3	Waist to hip ratio	3	3	6
8.2.5	Other marker for fat distribution eg ct, ultrasound	3	1	4
8.2.5	Waist-to-thigh ratio	0	1	1
8.3.1	Height (and proxy measures)	33	20	53
8.3.2	Biacromial diameter	1	1	2
8.3.2	Leg length	3	2	5
8.3.2	Other skeletal size (e.g. leg length)	1	1	2
8.3.2	Trunk length	1	2	3
8.4.1	Birth weight	6	3	9

1 Patterns of diet

1.3 Vegetarianism

Six studies (five cohorts) were identified in the 2005 SLR. One study in non-Hispanic Seven Day Adventists in USA (Fraser et al, 1999), showed an increased risk of prostate cancer in non-vegetarians compared to vegetarians (RR: 1.54; 95% CI 1.05- 2.26). No significant association was observed in the remaining studies.

One study was identified in the CUP (Key et al, 2009). This study on British vegetarians with a follow-up of 12.2 years as average, reported that compared with being meat eater, being fish eater was associated with a reduced risk of prostate cancer (RR 0.57; 95% CI 0.33-0.99) and being vegetarian was not associated with prostate cancer risk (RR 0.87; 95% CI 0.64-1.18).

1.4 Individual level dietary patterns

The characteristics and results of the identified studies are in **Table 3**.

Four studies, all identified during the CUP, investigated predefined dietary patterns. The dietary patterns investigated varied across studies and no summary was possible. A study in the NIH-AARP reported an inverse association of prostate cancer risk with higher score of the Healthy Eating Index (HEI) and the alternate HEI but only in cancers detected through PSA screening. No significant association was observed for the group with cancer not detected through PSA screening, for advanced or fatal cancers. No significant associations were observed with the Mediterranean score or with dietary preferences in the Australian, Korean and Japanese studies.

Two studies investigated dietary patterns identified from the data (*a posteriori*), one of which was identified during the CUP. None of them reported significant associations of dietary patterns and prostate cancer. Results and study characteristics are tabulated below.

Table 3 Studies identified during the CUP investigating dietary patterns

Author/year	Country	Study name	Cases	Years of follow-up	RR	LCI	UCI	Contrast
Predefined patterns								
Bosire, 2013	USA	NIH-AARP Diet and Health Study	23,453	8.9				Highest vs. lowest score quintile
					Healthy eating index 2005			
			PSA screening		0.92	0.86	0.98	
			No PSA screening		0.95	0.83	1.09	
			Advanced cancer		0.97	0.84	1.12	
			Fatal cancer		1.06	0.76	1.48	
					Alternate Mediterranean Score			
			PSA screening		0.97	0.91	1.03	
			No PSA screening		0.98	0.86	1.11	
			Advanced cancer		1.00	0.87	1.15	
			Fatal cancer		0.80	0.59	1.10	
					Alternate healthy eating index 2010			
			PSA screening		0.93	0.88	0.99	
			No PSA screening		0.98	0.86	1.13	
			Advanced cancer		1.10	0.96	1.26	
			Fatal cancer		0.96	0.71	1.30	
Muller, 2009	Australia	Melbourne Collaborative Cohort Study	1018	13.6	Mediterranean score			Highest vs. lowest score quartile
			Overall		0.93	0.74	1.18	
			Non aggressive		0.91	0.71	1.16	
			Aggressive		1.05	0.68	1.63	
					Dietary preference			
Yun, 2008	Korea	Korea National Health Insurance Study	307	6	0.95	0.59	1.51	Vegetables vs. mixture of vegetables and meat
Iso, 2007	Japan	Japan Collaborative Cohort Study for Evaluation of Cancer Risk	169 (mortality)	15	1.09	0.65	1.84	Japanese style breakfast (yes vs. no)
					1.1	0.66	1.83	Western style breakfast (yes vs. no)
					1.17	0.43	3.18	Chagayu (tea gruel) at breakfast (yes vs. no)
					0.62	0.09	4.43	Skipping breakfast (yes vs. no)
					1.52	0.61	3.74	Supper at ordinary time (yes vs. no)

Data derived patterns								
Muller, 2010	Australia	Melbourne Collaborative Cohort Study	1018	13.6				Highest vs. lowest score quintile
			Overall		1.12	0.90	1.40	Vegetable pattern
			Nonaggressive		1.12	0.88	1.44	Vegetable pattern
			Aggressive		1.11	0.71	1.73	Vegetable pattern
			Overall		0.87	0.71	1.08	Meat and potatoes
			Nonaggressive		0.87	0.69	1.10	Meat and potatoes
			Overall		1.00	0.81	1.23	Fruit and salad
			Nonaggressive		1.07	0.85	1.33	Fruit and salad
			Aggressive		0.74	0.47	1.15	Fruit and salad
Wu, 2006	USA	Health Professionals Follow-up Study	3002	13				Highest vs. lowest score quartile
			Overall		0.95	0.84	1.07	Prudent pattern
			Organ confined		0.91	0.78	1.07	Prudent pattern
			Advanced		1.01	0.73	1.41	Prudent pattern
			Overall		1.02	0.91	1.15	Western pattern
			Organ confined		1.01	0.86	1.18	Western pattern
			Advanced		1.16	0.88	1.53	Western pattern

2 Foods

2.2.1 Total vegetables

Methods
Twenty-one publications from seventeen studies were identified, from which nine publications from eight studies were identified during the CUP.

The details given on the definition of the vegetables group varied across studies. Two studies reported on a combination of starchy and non-starchy vegetables (Ambrosini et al, 2008; Shibata et al, 1992). Three studies included potatoes (Kirsh et al, 2007; Kilkkinen et al, 2003; Hsing et al, 1990). One study excluded potatoes (Snowdon et al, 1984) and another excluded white potatoes (George et al, 2009).

Vegetable intake in times or servings was converted to grams using a standard portion size of 80 g (Ambrosini et al, 2008; Gonzalez et al, 2007; Kirsh et al, 2007; Smit et al, 2007; Shibata et al, 1992; Hsing et al, 1990). George et al (2009) reported in cup-equivalents/1000 kcal, which was converted to g/day using the standard portion size of 80 g and the average energy intake of 1990 kcal/day reported in the study. Stram et al (2006) also reported in g/1000 kcal that were converted to g/day using the average energy intake of 2380 kcal/day reported in another publication of the same study (Multiethnic Cohort Study).

Thirteen studies could be included in the dose-response meta-analysis on prostate cancer. The increment unit used in the analysis was 100 g/day. From the studies included in the dose-response meta-analysis, seven studies reported on total prostate cancer (Ambrosini et al, 2008; Gonzalez et al, 2007; Key et al, 2004; Alavanja et al, 2003; Chan et al, 2000; Schuurman et al, 1998; Shibata et al, 1992), one study on total, advanced, and localised prostate cancer (Takachi et al, 2010), two studies on total and advanced/aggressive prostate cancer (George et al, 2009; Kirsh et al, 2007), one study on total and non-localised/high grade prostate cancer (Stram et al, 2006), and two studies on fatal cancer cases only (Smit et al, 2007; Hsing et al, 1990). Advanced, aggressive, high grade and fatal cancers were combined in a sub-group for separate meta-analysis.

Two studies (Harvard Alumni Health Study 1962-1966 and USA California 1960-1980) could not be included in the forest plot (Lee et al, 2001; Snowdon et al, 1984). Two publications (Kilkkinen et al, 2003; Hirvonen et al, 2001) from the ATBC study reported mean values only but a further publication (Chan et al, 2000) could be included in the analysis.

Main results
The summary RR per 100g/day was 0.99 (95% CI 0.98-1.00, $I^2 = 0\%$, $p_{heterogeneity} = 0.76$; n = 13) (all studies combined). The summary RR did not change materially when studies were omitted in turn in the influence analysis. One study (NIH-AARP, George et al, 2009) had 67% weight in the analysis. There was no evidence of publication bias with Egger's test, p = 0.76.

After stratification by prostate cancer type, the summary RRs per 100 g/day were 0.99 (95% CI 0.98-1.00; $I^2 = 0\%$; $p_{heterogeneity}=0.76$; n = 11) for total prostate cancer (excluding two studies which reported on mortality) and 1.01 (95% CI 0.97-1.04; $I^2 = 18.9\%$, $p_{heterogeneity} = 0.29$; n = 6) for advanced/high grade prostate cancer.

There was statistical evidence of non-linearity relationship with vegetable intake for total prostate cancer and for advanced prostate cancer (both $p < 0.0001$). The curves suggest a decreased risk from intake levels above 300-350 g/day but the relative risks estimates were not statistically

significant. Only two studies (Kirsh et al, 2007; Stram et al, 2006) in the total prostate cancer analysis and one study (Smit et al, 2007) in the advanced prostate cancer analysis have vegetable intake above 350g/day and the curves are flat in most of the range of intake below this value.

Heterogeneity
Overall there was no evidence of heterogeneity, $I^2 = 0\%$, $p_{heterogeneity} = 0.76$.

Comparison with the Second Expert Report
In the 2005 SLR, the meta-analysis on vegetables intake and prostate cancer showed an overall non-significant association (see Table 6).

Published meta-analysis or pooled analysis
Twelve studies were included in a highest versus lowest meta-analysis (Meng et al, 2013). The summary RR was 0.97 (95% CI 0.93-1.01; $I^2 = 0\%$, $p_{heterogeneity} = 0.51$). All the studies included in the meta-analysis are included in the CUP review. No pooled analysis was identified.

Table 4 Studies on vegetables intake identified in the CUP

Author, year	Country	Study name	Cases	Years of follow up	RR	LCI	UCI	Contrast
Drake, 2012	Sweden	Malmo Diet and Cancer Study cohort	817	15 years	1.06	0.83	1.34	Median 296.1 vs. 70.2 g/day
Takachi, 2010	Japan	JPHC study I and II	339	321061 person-years	1.33	0.93	1.91	Median 327 vs. 78 g/day
					0.99	0.91	1.08	Per 100 g/day
George, 2009	USA	NIH- AARP Diet and Health Study	17034	8 (max)	0.97	0.93	1.02	1.10-3.25 vs. 0-0.44 cup-equivalents/ 1000 kcal
Gonzalez, 2009	USA	VITAL	832	3.3 years	1.15	0.93	1.42	≥ 2.51 vs. 0-1.2 servings/day
Ambrosini, 2008	Australia	Wittennoom Gorge, West Australian cohort 1990-2004	97	12.7 years	0.73	0.38	1.40	≥2.81 vs. 0-1.6 servings/day
Gonzalez, 2007	USA	VITAL	832	3.3 years	1.15	0.93	1.42	≥ 2.51 vs. 0-1.2 servings/day
Kirsh, 2007	USA	PLCO	1338	4.2 years	0.88	0.71	1.08	Median 8.6 vs. 2.6 servings/day
Smit, 2007	Puerto Rico	PR Heart Health Study	167	40 years (max)	1.61	0.68	3.83	8.1-9.0 vs. ≤3.0 servings/day
Stram, 2006	USA	Multi-ethnic Cohort Study	3922	8 years	1.00	0.91	1.15	≥193.95 vs. ≤ 90.7 g/ 1000kcal

Table 5 Overall evidence on vegetables intake and prostate cancer

	Summary of evidence
2005 SLR	Nine prospective studies (twelve publications) were identified during the 2005 SLR and six studies were included in the meta-analysis. All studies reported statistically non-significant results.
Continuous Update Project	Eight prospective studies were identified in the CUP, all showed non-significant results. Six new studies reported on advanced prostate cancer, of which five showed non-significant association and one (George, 2009) showed a significant positive association with vegetables intake. No significant association was observed in the CUP meta-analysis.

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

Prostate cancer		
	2005 SLR	CUP
Studies (n)	6	13
Cases (n)	2372	26433
Increment unit used	Per serving/day	Per 100 g/day
Overall RR (95% CI)	0.98 (0.92-1.04)	0.99 (0.98-1.00)
Heterogeneity (I^2, p-value)	0%, p = 0.85	0%, p = 0.76
Stratified analysis		
Advanced/high grade cancer		
Overall RR (95% CI)	0.95 (0.80-1.13)	1.01 (0.97-1.04)
Heterogeneity (I^2, p-value)	(only 1 study)	18.9%, p = 0.29, n = 6
Non-advanced/low grade cancer		
Overall RR (95% CI)		0.99 (0.90-1.09)
Heterogeneity (I^2, p-value)		(only 1 study)

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

WCRF code	Author	Year	Study design	Study name	Cancer outcome	2005 SLR	CUP dose-response meta-analysis	CUP HvL forest plot	Estimated values	Exclusion reasons
PRO100139	Drake	2012	Prospective Cohort study	Malmo Diet and Cancer Study cohort	Incidence	No	No	Yes		Two exposure categories only (also reported on advanced prostate cancer)
PRO100062	Takachi	2010	Prospective Cohort study	JPHC I and II	Incidence	No	Yes	Yes		
PRO100125	George	2009	Prospective Cohort study	NIH- AARP Diet and Health Study	Incidence	No	Yes	Yes	Conversion from cup-equivalents/1000kcal to g/day using standard portion size 80g and average energy intake 1990 kcal/day, mid-exposure values, cases and person-years per quintile	
PRO100066	Gonzalez	2009	Prospective Cohort study	VITAL	Incidence/ Mortality	No	No	No		Duplicate data as in Gonzalez, 2007
PRO99954	Ambrosini	2008	Prospective Cohort study	Wittennoom Gorge, West Australian cohort 1990-2004	Incidence	No	Yes	Yes	Conversion from servings/day to g/day using standard portion size 80g, mid-exposure values	
PRO100035	Gonzalez	2007	Prospective Cohort study	VITAL	Incidence/ Mortality	No	Yes	Yes	Conversion from servings/day to g/day using standard portion size 80g, mid-exposure values	
PRO99982	Kirsh	2007	Prospective Cohort study (Follow-up of screening arm in trial)	PLCO	Incidence/ Mortality	No	Yes	Yes	Conversion from servings/day to g/day using standard portion size 80g ; cases and person-years per	

									quintile	
PRO100019	Smit	2007	Prospective Cohort study	PR Heart Health Study	Mortality	No	Yes	Yes	Conversion from servings/day to g/day using standard portion size 80g, mid-exposure values, cases and person-years per quartile	
PRO99986	Stram	2006	Prospective Cohort study	Multiethnic Cohort Study	Incidence/ Mortality	No	Yes	Yes	Conversion from g/1000kcal to g/day using average energy intake 2380 kcal/day from another paper of the same study, mid-exposure values, cases and person-years per quintile	
PRO00148	Key	2004	Prospective Cohort study	EPIC	Incidence	Yes	Yes	Yes	Used estimated mean exposure values provided in article, person-years per quintile	
PRO03999	Wu	2004	Nested case-control study	Health Professionals Follow-up Study	Incidence/ Mortality	Yes	No	No		Duplicate publication with only number of cases and non-cases per category only – no measure of association
PRO00442	Alavanja	2003	Prospective Cohort study	Agricultural Health Study Cohort	Incidence	Yes	Yes	Yes	Mid-exposure values	
PRO00142	Kilkkinen	2003	Nested case-control study	ATBC	Incidence/ Mortality	Yes	No	No		Duplicate publication with only mean exposure values
PRO01034	Hirvonen	2001	Prospective Cohort study	ATBC	Incidence/ Mortality	Yes	No	No		Duplicate publication with only mean exposure values
PRO01290	Lee	2001	Prospective Cohort study	Harvard Alumni Health Study 1962-	Incidence/ Mortality	Yes	No	No		Identified and included in the

				1966						unadjusted meta-analysis in the 2005 SLR; excluded in the CUP as only number of cases and person-years per category were reported – no measure of association
PRO01426	Chan	2000	Prospective Cohort study	ATBC	Incidence	Yes	Yes	Yes	Cases and person-years per quintile	
PRO02061	Schuurman	1998	Case-cohort study	The Netherlands Cohort Study	Incidence	Yes	Yes	Yes		
PRO02629	Giovannucci	1995	Prospective Cohort study	Health Professionals Follow-up Study	Incidence/ Mortality	Yes	No	Yes		Only two exposure categories for total vegetable intake
PRO13404	Shibata	1992	Prospective Cohort study	USA California 1981-1985	Incidence/ Mortality	Yes	Yes	Yes	Conversion from servings/day to g/day using standard portion size 80g, person-years per tertile	
PRO03129	Hsing	1990 b	Prospective Cohort study	Lutheran Brotherhood Cohort Study	Mortality	Yes	Yes	Yes	Conversion from times/month to g/day using standard portion size 80g, mid-exposure values, cases and person-years per quartile	
PRO03474	Snowdon	1984	Prospective Cohort study	USA California 1960-1980	Mortality	Yes	No	No		No measure of association, reported in text there was no significant association between vegetable intake and prostate cancer

Figure 1 Highest versus lowest forest plot of vegetables intake and prostate cancer

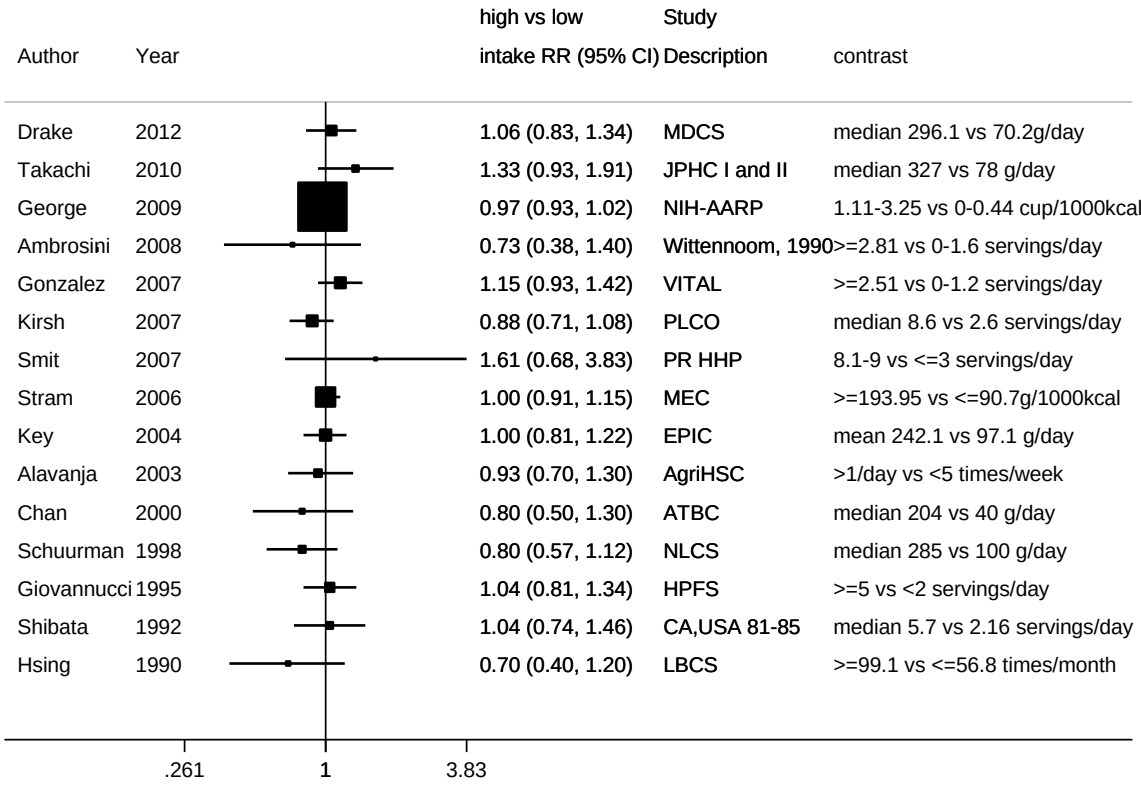


Figure 2 Dose-response meta-analysis of vegetables intake and prostate cancer – per 100g/day

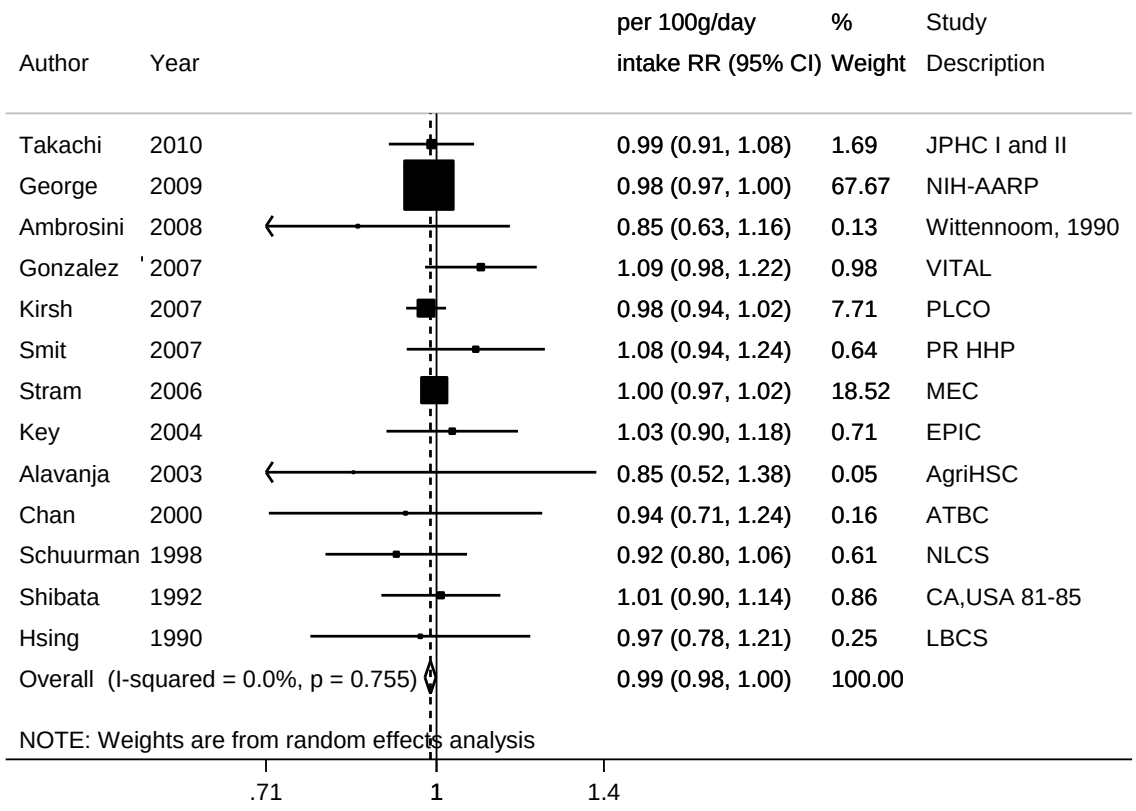
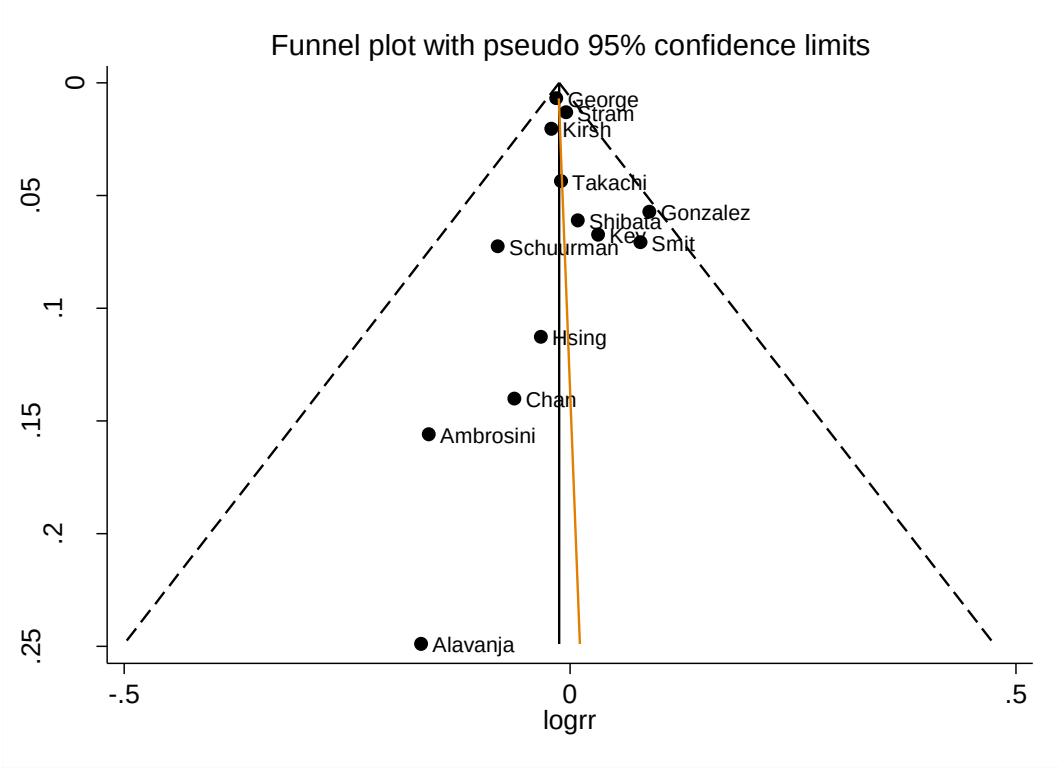


Figure 3 Funnel plot of vegetables intake and prostate cancer



Egger's test p = 0.76

Figure 4 Dose-response graph of vegetables intake and prostate cancer

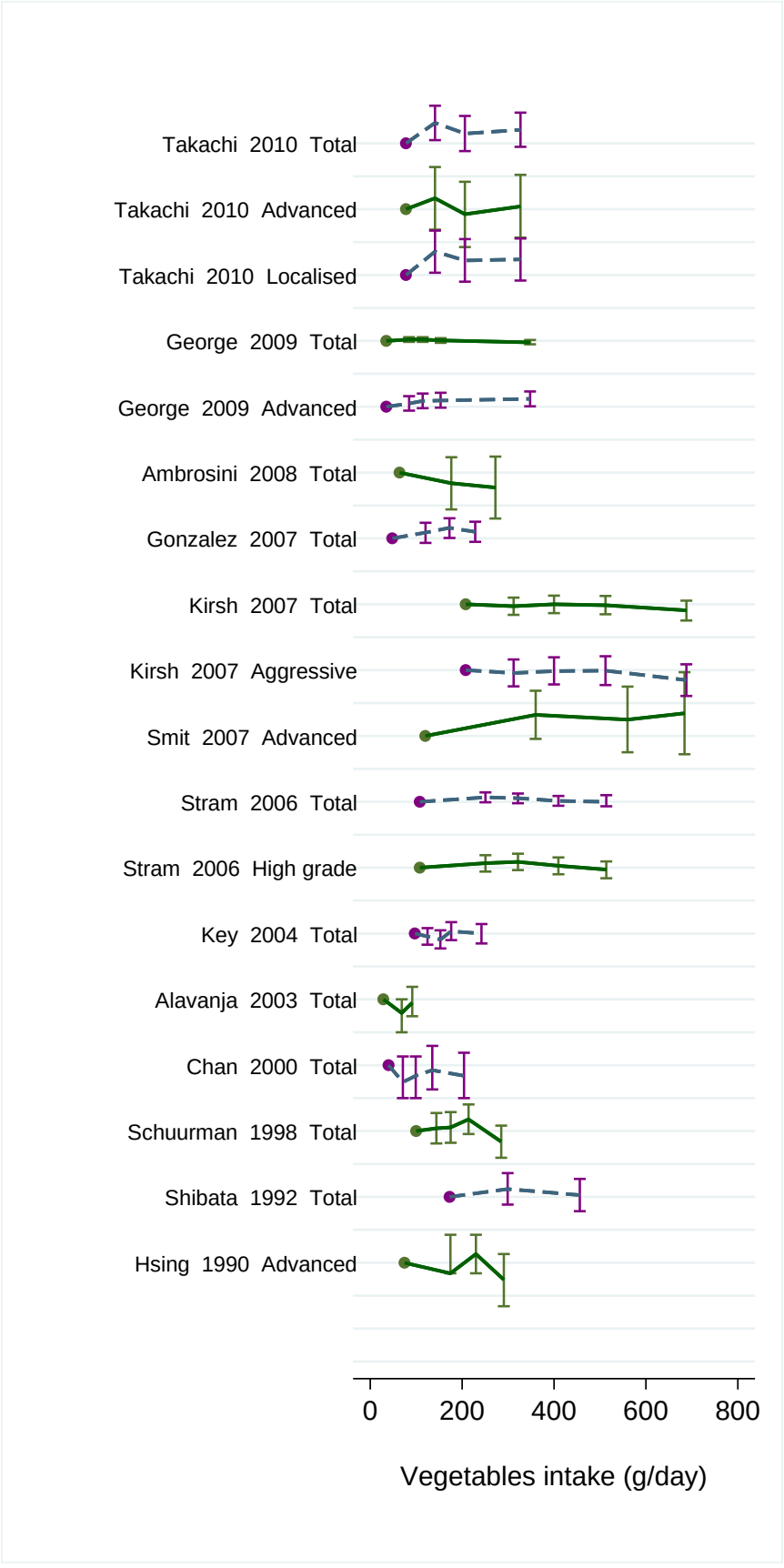


Figure 5 Dose-response meta-analysis of vegetables intake and prostate cancer, per 100 g/day, stratified by prostate cancer type

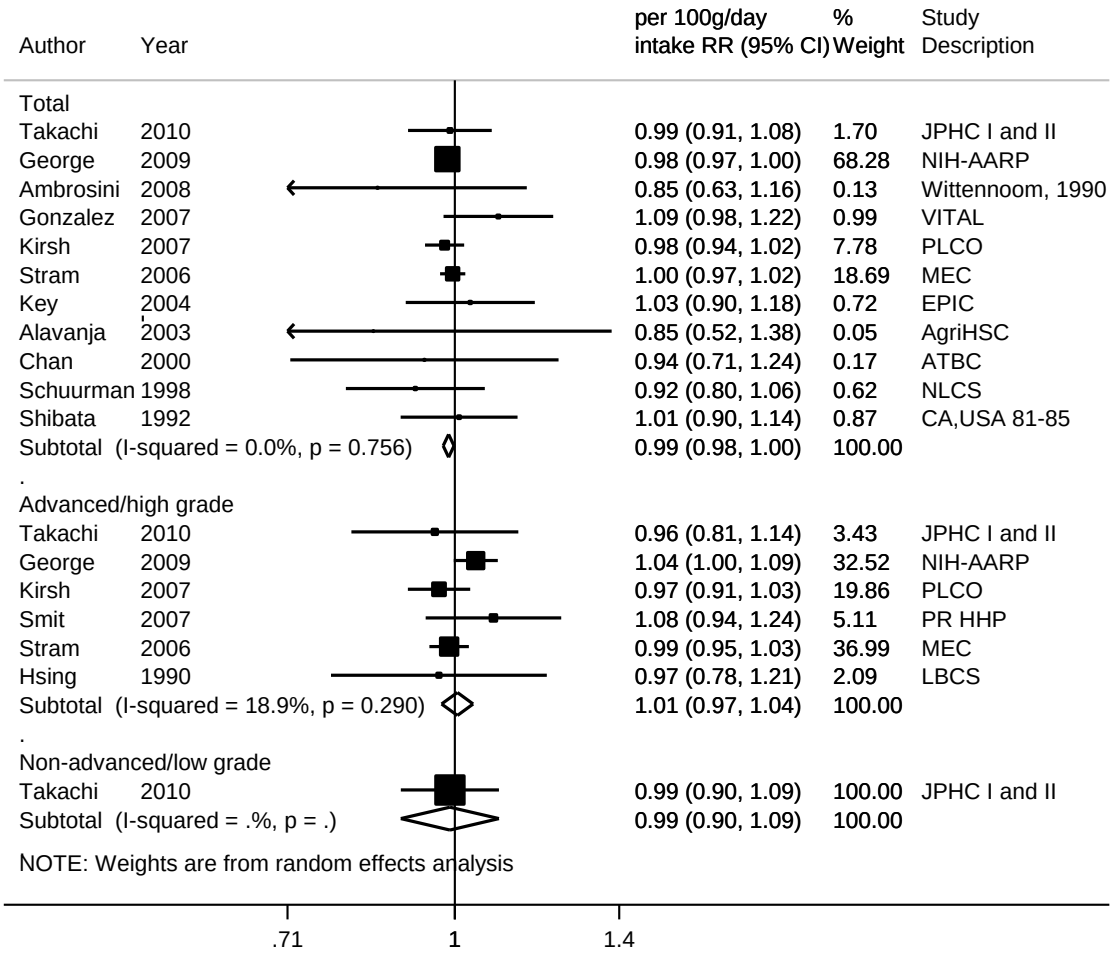
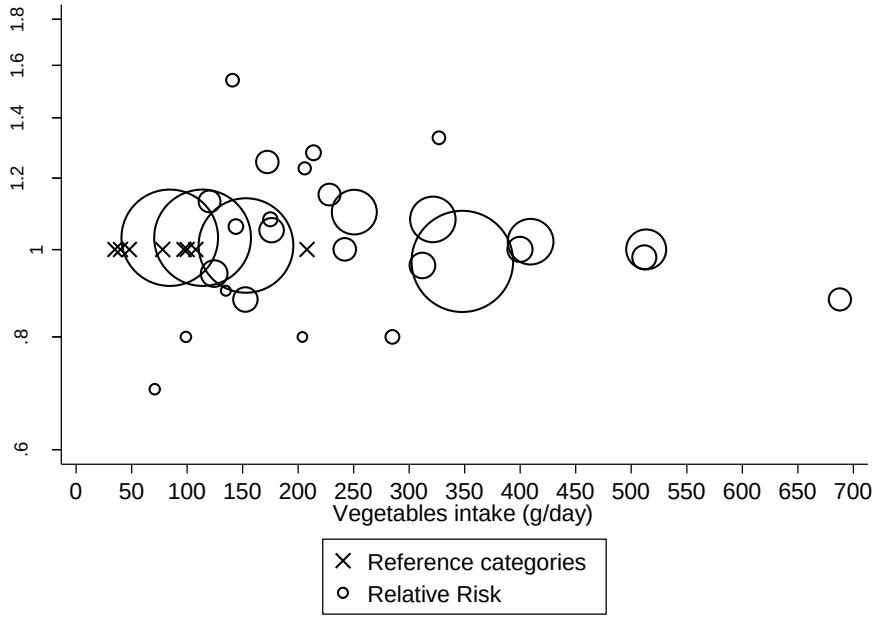


Figure 6 Non-linear dose-response analysis of vegetables intake and total prostate cancer



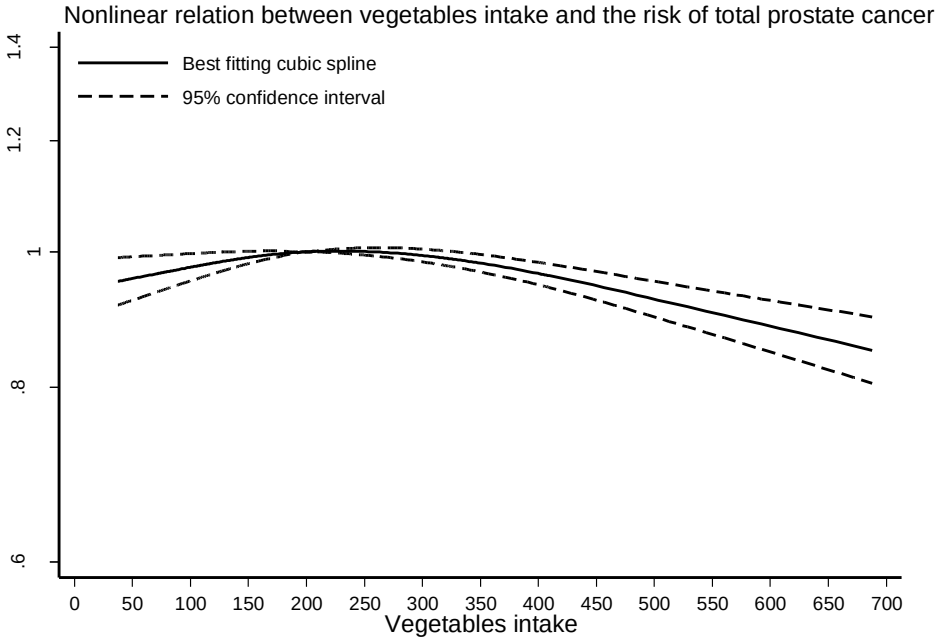
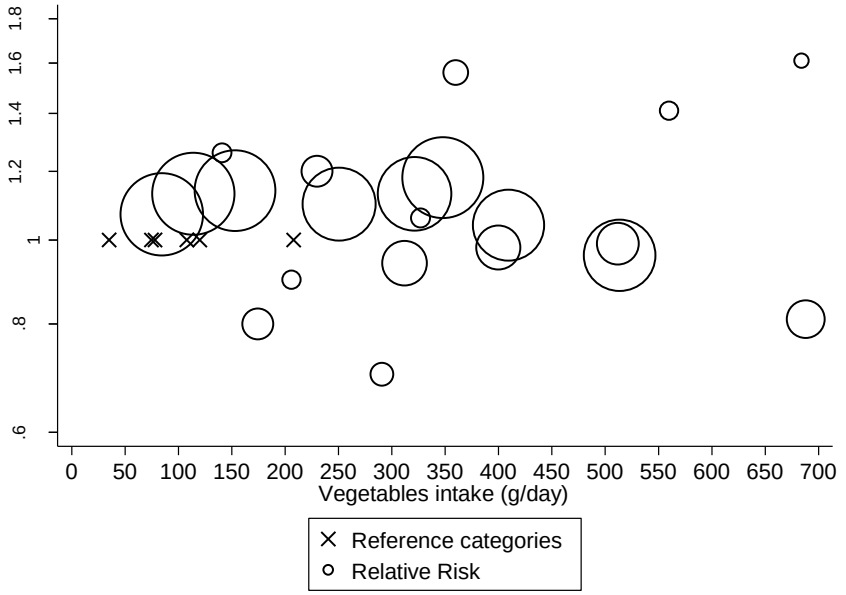


Table 8 Table with vegetables intake values and corresponding RRs (95% CIs) for non-linear analysis of vegetable intake and total prostate cancer

Vegetables intake (g/day)	RR (95% CI)
100.0	0.97 (0.95-1.00)
152.7	0.99 (0.98-1.00)
204.0	1.00
312.0	0.99 (0.98-1.00)
400.0	0.96 (0.95-0.98)

$p_{non\text{-}linearity} < 0.0001$

Figure 7 Non-linear dose-response analysis of vegetables intake and advanced prostate cancer



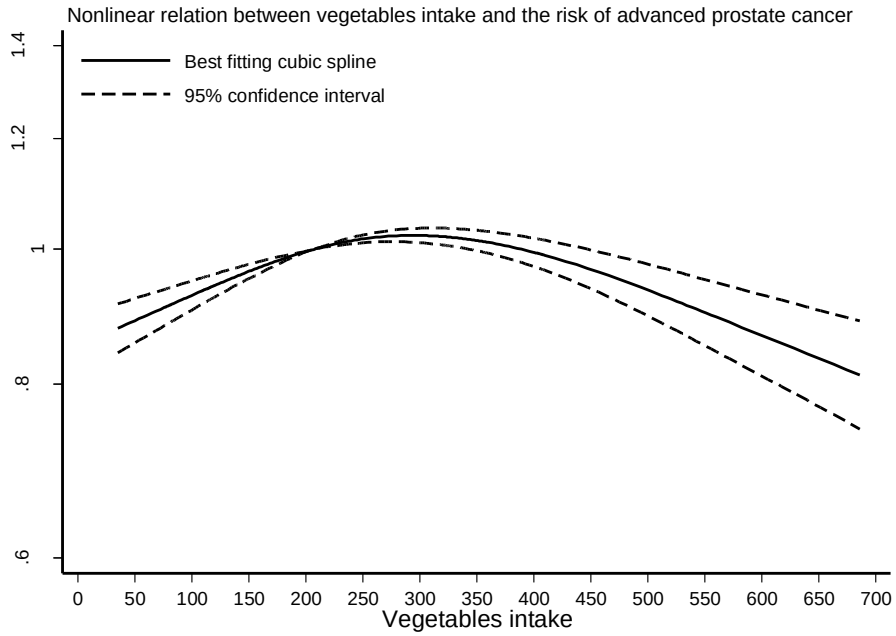


Table 9 Table with vegetable intake values and corresponding RRs (95% CIs) for non-linear analysis of vegetables intake and advanced prostate cancer

Vegetables intake (g/day)	RR (95% CI)
107.9	0.93 (0.91-0.95)
153.2	0.97 (0.96-0.98)
206.0	1.00
312.0	1.02 (1.01-1.04)
400.0	0.99 (0.97-1.02)

$p_{non\text{-}linearity} < 0.0001$

2.2.1.2 Cruciferous vegetables

Methods

Eight prospective studies were identified, four of which were identified during the CUP. All studies could be included in the dose-response meta-analysis on prostate cancer. The increment unit used in the analysis was 50 g/day.

The definition of brassicas or cruciferous vegetables varied between the studies that reported details.

Cruciferous vegetables intake in times or servings was converted to grams using a standard portion size of 80 g for 3 studies (Kirsh, 2007; Giovannucci, 2003; Hsing, 1990). For Stram et al (2006) that reported intake in g/1000 kcal, the average energy intake of 2380 kcal/day reported in another publication of the same study (Multiethnic Cohort Study) was used in the conversion.

From the studies included in the dose-response meta-analysis, three studies reported on total prostate cancer (Stram, 2006; Key, 2004; Schuurman, 1998), three studies on total, advanced, and non-advanced/localised/organ-confined prostate cancer (Agalliu, 2011; Takachi, 2010; Giovannucci, 2003), one study on total and aggressive prostate cancer (Kirsh, 2007), and one study on fatal cancer cases only (Hsing, 1990).

Main results

The summary RR of prostate cancer per 50g/day increase of cruciferous vegetable intake was 0.96 (95% CI 0.92-1.00; $I^2 = 2.6\%$; $p_{heterogeneity} = 0.41$; n = 8) (all studies combined). In influence analysis, the summary RRs ranged from 0.93 (95% CI 0.88-0.98) when the Multiethnic Cohort Study (Stram, 2006) was omitted to 0.97 (95% CI 0.93-1.02) when the PLCO study (Kirsh, 2007) was omitted. There was no evidence of publication bias with Egger's test, p = 1.00.

After stratification by prostate cancer type, the summary RRs per 50g/day were 0.96 (95% CI 0.92-1.00; $I^2 = 0\%$; $p_{heterogeneity} = 0.46$; n = 7) for total prostate cancer (excluding one study reporting on mortality), 0.94 (95% CI 0.84-1.07; $I^2 = 10.5\%$; $p_{heterogeneity} = 0.35$; n = 5) for advanced/high grade prostate cancer and 0.94 (95% CI 0.87-1.01; $I^2 = 0\%$; $p_{heterogeneity} = 0.95$; n = 3) for non-advanced/low grade prostate cancer.

There was no evidence of a non-linear relationship with total prostate cancer (p = 0.18).

Heterogeneity
Overall, there was no evidence of heterogeneity, $I^2 = 2.6\%$, $p_{heterogeneity} = 0.41$.

Comparison with the Second Expert Report
In the 2005 SLR, the meta-analysis on cruciferous vegetables intake and prostate cancer showed an overall non-significant association (RR 0.97).

Published meta-analysis or pooled analysis
A recent meta-analysis of seven cohort and six population-based case-control studies reported a significant inverse association between cruciferous vegetables intake and the risk of prostate cancer (Liu, 2012). The summary RR for the highest versus the lowest intake was 0.90 (95% CI 0.85-0.96; $I^2 = 32.7\%$; $p_{heterogeneity} = 0.12$). When stratified by study design, the significant inverse association was only observed in case-control studies (RR 0.79; 95% CI 0.69-0.89), but not in cohort studies (RR 0.95; 95% CI 0.89-1.02). All cohort studies included in this published meta-analysis were included in the CUP SLR. No pooled analysis was identified.

Table 10 Studies on cruciferous vegetables intake identified in the CUP

Author, year	Country	Study name	Cases	Years of follow up	RR	LCI	UCI	Contrast
Agalliu, 2011	Canada	CSDLH	661	7.7 years	1.01	0.75	1.37	Median 75.7 vs. 8.4g
Takachi, 2010	Japan	JPHC Study I and II	339	321 641 person-years	0.92	0.66	1.30	Median 95 vs. 16 g/day
					0.97	0.92	1.03	Per 25 g/day
Kirsh, 2007	USA	PLCO	1338	4.2 years	0.85	0.71	1.02	Median 1.1 vs. 0.1 serving/day
Stram, 2006	USA	Multiethnic Cohort Study	3922	8.0 years	1.03	0.92	1.14	≥ 29.0 vs. < 7.2 g/1000kcal

Table 11 Overall evidence on cruciferous vegetables intake and prostate cancer

	Summary of evidence
2005 SLR	Four prospective studies were identified during the 2005 SLR and three studies were included in the meta-analysis. All studies observed statistically non-significant results.
Continuous Update Project	Four new prospective studies were identified in the CUP, all showed non-significant results. Three new studies reported on advanced prostate cancer and showed a non-significant association with cruciferous vegetables intake. No significant association was observed in the CUP meta-analysis.

Table 12 Summary of results of the dose response meta-analysis of cruciferous vegetables intake and prostate cancer

Prostate cancer		
	2005 SLR	CUP
All studies		
Studies (n)	3	8
Cases (n)	3760	11124
Increment unit used	Per serving/week	Per 50 g/day
Overall RR (95% CI)	0.97 (0.94-1.01)	0.96 (0.92-1.00)
Heterogeneity (I^2, p-value)	23.0%, p = 0.27	2.6%, p = 0.41
Stratified analysis		
Advanced/high grade cancer		
Overall RR (95% CI)	1.25 (0.87-1.81)	0.94 (0.84-1.07)
Heterogeneity (I^2, p-value)	(only 1 study)	10.5%, p = 0.35, n = 5
Non-advanced/low grade cancer		
Overall RR (95% CI)		0.94 (0.87-1.01)
Heterogeneity (I^2, p-value)		0%, p = 0.95, n = 3

Table 13 Inclusion/exclusion table for meta-analysis of cruciferous vegetables intake and prostate cancer

WCRF code	Author	Year	Study design	Study name	Cancer outcome	2005 SLR	CUP dose-response meta-analysis	CUP HvL forest plot	Estimated values	Exclusion reasons
PRO100199	Agalliu	2011	Case Cohort study	Canadian Study of Diet, Lifestyle and Health cohort (CSDLH)	Incidence	No	Yes	Yes	Person-years per quintile	
PRO100062	Takachi	2010	Prospective Cohort study	JPHC Study I and II	Incidence	No	Yes	Yes		
PRO99982	Kirsh	2007	Prospective Cohort study (Follow-up of screening arm in trial)	PLCO	Incidence/ Mortality	No	Yes	Yes	Conversion from servings/day to g/day using standard portion size 80g , cases and person-years per quintile	
PRO99986	Stram	2006	Prospective Cohort study	Multiethnic Cohort Study	Incidence/ Mortality	No	Yes	Yes	Conversion from g/1000kcal to g/day using average energy intake 2380 kcal/day from another paper of the same study, mid-exposure values, cases and person-years per quintile	
PRO00148	Key	2004	Prospective Cohort study	EPIC	Incidence	Yes	Yes	Yes	Cases and person-years per quintile; used estimated mean exposure values provided in article	
PRO04079	Giovannucci	2003 b	Prospective Cohort study	Health Professionals Follow-up Study	Incidence/ Mortality	Yes	Yes	Yes	Conversion from servings/week to g/day using standard portion size 80g , mid-exposure values, person-years per category from cases	

									and RRs	
PRO02061	Schuurman	1998	Case-cohort study	The Netherlands Cohort Study	Incidence	Yes	Yes	Yes		
PRO03129	Hsing	1990 b	Prospective Cohort study	Lutheran Brotherhood Cohort Study	Mortality	Yes	Yes	Yes	Conversion from times/month to g/day using standard portion size 80g, mid-exposure values, cases and person-years per quartile	

Figure 8 Highest versus lowest forest plot of cruciferous vegetables intake and prostate cancer

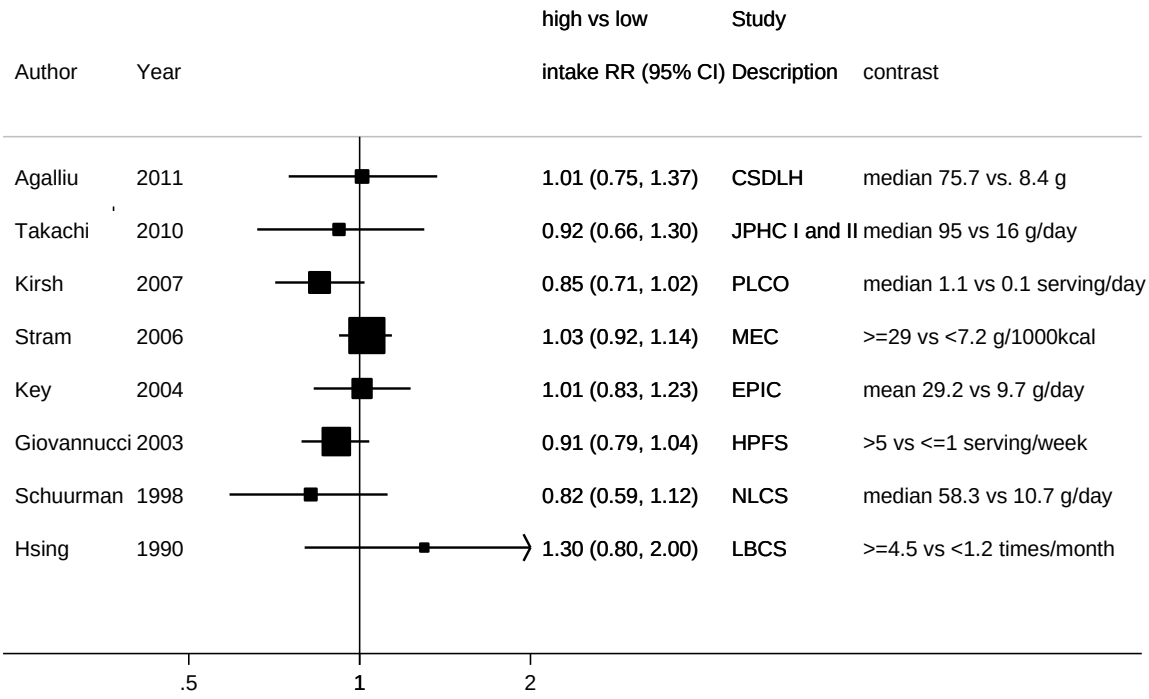


Figure 9 Dose-response meta-analysis of cruciferous vegetables intake and prostate cancer – per 50 g/day

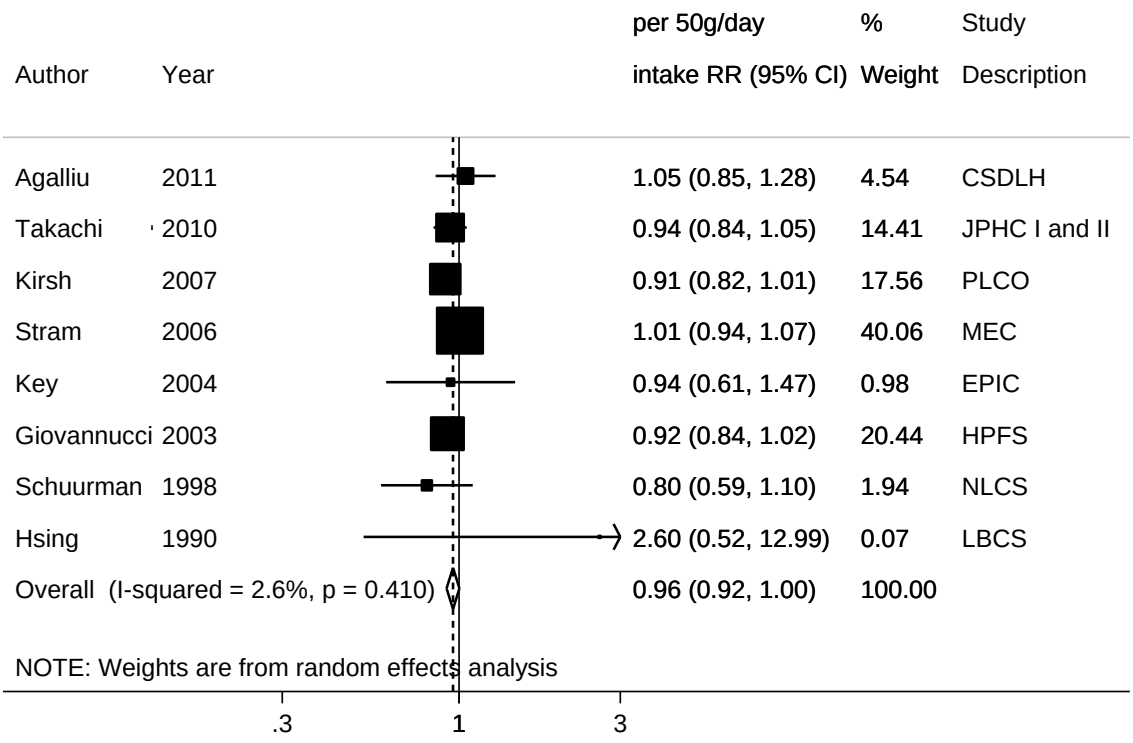
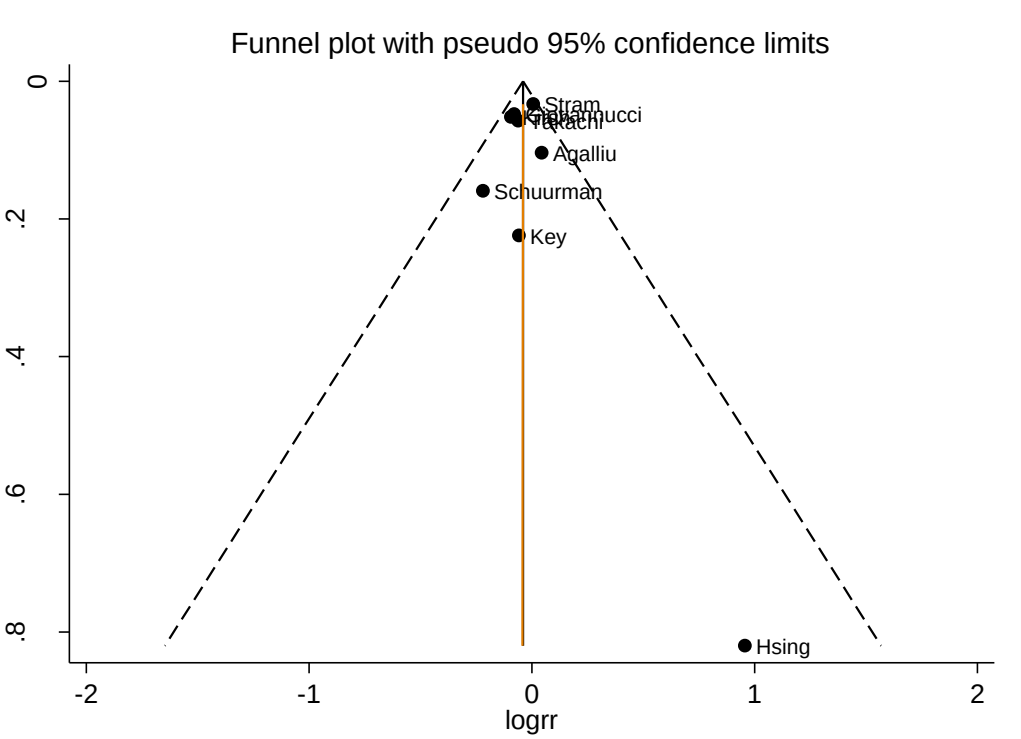


Figure 10 Funnel plot of cruciferous vegetables intake and prostate cancer



Egger's test p = 1.00

Figure 11 Dose-response graph of cruciferous vegetables intake and prostate cancer

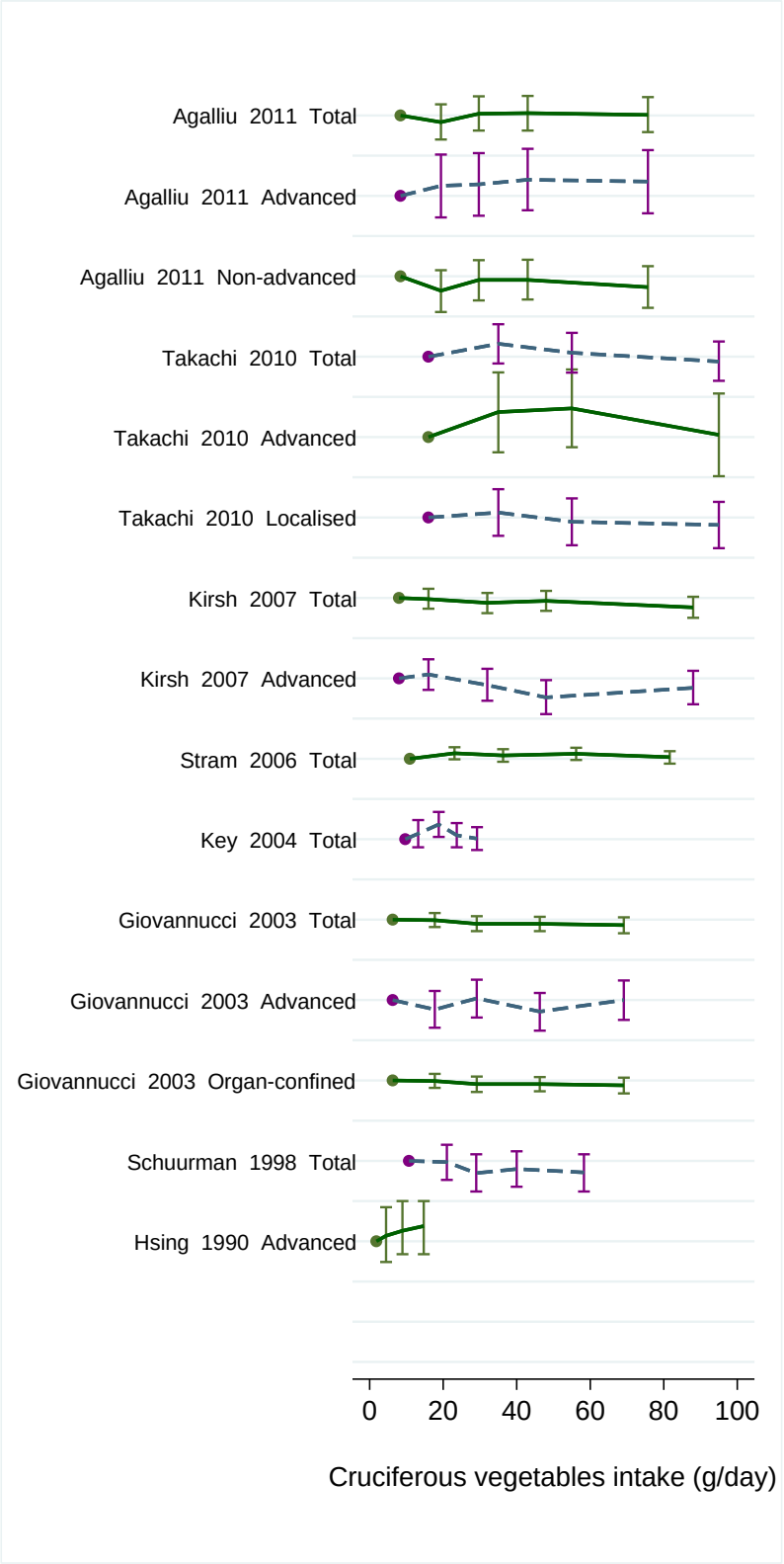
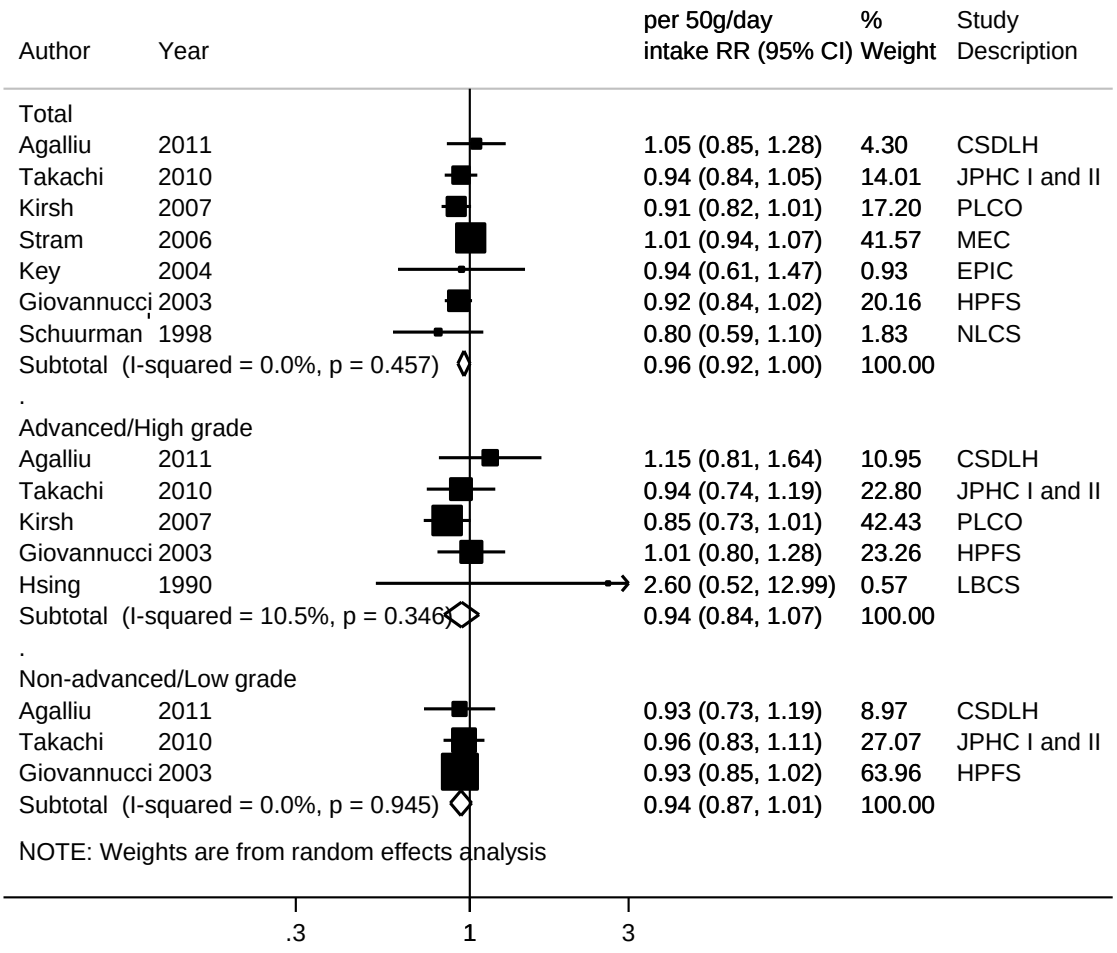


Figure 12 Dose-response meta-analysis of cruciferous vegetables intake and prostate cancer, per 50 g/day, stratified by prostate cancer type



2.2.1.5.13 Tomatoes

Methods

Ten studies from twelve publications were identified, five (from six publications) of which were identified during the CUP. Two studies identified in the 2005 SLR (Platz, 2004b; Hsing, 1990b) only reported mean values and could not be included in the analysis. There were no new updates for these studies.

The increment used in the dose-response analysis was 1 serving/day. Two studies (Takachi, 2010; Schuurman 1998) reported tomato intake in grams per day which was converted to servings/day using a conversion unit of 80 g equivalent to 1 serving.

One study (Stram, 2006) reported tomato intake in gram/1000 kcal per day, which was converted to g/day using the median energy intake reported in another publication of the Multiethnic Cohort Study.

Two studies (Stram, 2006; Ambrosini, 2008) analysed raw and cooked tomatoes separately. Ambrosini, 2008 did not report on total tomato intake and was excluded from the dose-response analysis. Stram, 2006 also reported on total tomato intake and was included.

Meta-analyses were conducted for all studies combined (all prostate cancers) and for the studies that reported results for advanced (Takachi, 2010) or aggressive prostate cancer (Kirsh, 2007). One study (Iso, 2007) reported on cancer mortality.

Main results

The summary RR per 1 serving/day was 0.93 (95% CI 0.79-1.09; $I^2 = 52.0\%$; $p_{heterogeneity} = 0.05$; n = 7). There was no significant evidence of publication bias with Egger's test, p = 0.25 but the funnel plot suggests that small studies with RRs above the average are missing.

After excluding the only study on mortality the result remained the same. The summary RR ranged from 0.86 (95% CI 0.65-1.13) when MEC Study was excluded to 0.97 (95% CI 0.87-1.09) when the HPFS was excluded. The results were similar for advanced/high grade cancers (RR per 1 serving/day was 0.96 (95% CI 0.78-1.19,; $I^2 = 0\%$; $p_{heterogeneity} = 0.93$; n = 3). There was no evidence of a non-linear relationship between tomato intake and total prostate cancer (p=0.13) or advanced prostate cancer (p = 0.85).

Heterogeneity

Overall, there was moderate evidence of heterogeneity, $I^2 = 52.0\%$, $p_{heterogeneity} = 0.05$. The two first publications (Mills, 1989; Giovannucci, 1995) reported stronger inverse associations than the average.

Comparison with the Second Expert Report

In the 2005 SLR the meta-analysis on tomatoes and prostate cancer showed an overall non-significant association. From the three studies included in the meta-analysis, only the HPFS reported an inverse significant association of tomato intake with prostate cancer risk.

Published meta-analysis or pooled analysis

A meta-analysis of cohort studies and nested case-control studies found no significant association between the consumption of raw and cooked tomato and prostate cancer incidence. The RR for highest versus lowest intake was 0.81 (95%CI 0.59-1.10; 3 studies) for raw tomato and 0.85 (95% CI 0.96-1.06; 2 studies) for cooked tomato (Chen, 2013).
A previous meta-analysis (Etminam, 2004) reported a RR of prostate cancer per additional serving of raw tomato daily (200 g) of 0.97 (95% CI 0.85–1.10) for 7 case-control studies and 0.78 (95% CI 0.66–0.92) for 2 cohort studies. The RR for moderate intake of cooked tomato products was 1.07

(95% CI 1.06–1.08) and for high intake of cooked tomato products, this RR was 0.81 (95% CI 0.71–0.92) for 6 case-control studies and 1 cohort, compared to low consumption. No pooled analysis was identified.

Table 14 Studies on tomatoes identified in the CUP

Author, year	Country	Study name	Cases	Years of follow up	RR	LCI	UCI	Contrast
Takachi, 2010	Japan	Japan Public Health Centre-Based Prospective Study I and II	339	7.3 years	1.16	0.84	1.59	68 vs. 1.2 g/d
					1.03	0.99	1.07	Per 25 g/d
Ambrosini, 2008	Australia	Wittenoom, Western Australia 1990	97	12.7 years	0.67	0.38	1.16	Cooked tomato > 2.2 vs. 0-0.6 servings/w
					1.04	0.60	1.80	Raw tomato >4.1 vs. 0-1.7 servings/w
Iso, 2007	Japan	Japan Collaborative Cohort Study (JACC Study)	149	12 years	0.92	0.60	1.41	≥ 3-4 vs. < 1/week
Kirsh, 2007	USA	Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial	1338	4.2 years	0.98	0.80	1.20	1.5 vs. 0.3 servings/d
Stram, 2006	USA and Hawai	Multiethnic Cohort Study	3922	8 years	1.02	0.92	1.14	37.3 vs. 12 g/1000 kcal
Kirsh, 2006	USA	Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial	1338	4.2 years	0.99	0.81	1.21	1.47 vs. 0.33 servings/d

Table 15 Overall evidence on tomatoes and prostate cancer

	Summary of evidence
2005 SLR	Four studies were identified during the 2005 SLR and included in the meta-analysis. Only one study (Giovannucci, 1995) showed a protective effect of tomato against prostate cancer.
Continuous Update Project	Five new studies were identified in the CUP, all showed non-significant results. No significant association was observed in the CUP meta-analysis.

Table 16 Summary of results of the dose response meta-analysis of tomatoes and prostate cancer

Prostate cancer		
	2005 SLR	CUP
All studies		
Studies (n)	4	7
Cases (n)	1866	7350
Increment unit used	Per 1 serving/day	Per 1 serving/day
Overall RR (95% CI)	0.69 (0.43-1.08)	0.93 (0.79-1.09)
Heterogeneity (I^2,p-value)	62.8%, p = 0.04	52.0%, p = 0.05
Stratified analysis		
Advanced/high grade cancer		
Overall RR (95% CI)		0.96 (0.78-1.19)
Heterogeneity (I^2,p-value)		0%, p = 0.93, n = 3
Non-advanced/low grade cancer		
Overall RR (95% CI)		1.16 (0.78-1.73)
Heterogeneity (I^2, p-value)		(only 1 study)

Table 17 Inclusion/exclusion table for meta-analysis of tomatoes and prostate cancer

WCRF code	Author	Year	Study design	Study name	Cancer outcome	2005 SLR	CUP dose-response meta-analysis	CUP HvL forest plot	Estimated values	Exclusion reasons
PRO100062	Takachi	2010	Prospective Cohort study	Japan Public Health Centre-Based Prospective Study I and II	Incidence	No	Yes	Yes	Conversion from grams/day to servings/day	
PRO99954	Ambrosini	2008	Nested case-control study	Wittenoom, Western Australia 1990	Incidence	No	No	Yes		The study did not present total tomato intake only raw and cooked tomato separately
PRO100042	Iso	2007	Prospective Cohort study	Japan Collaborative Cohort Study (JACC Study)	Mortality	No	Yes	Yes	Conversion from servings/week to servings/day	
PRO99982	Kirsh	2007	Prospective Cohort study	Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial	Incidence/ Mortality	No	Yes	Yes	Event rate and cases per quintile	
PRO99986	Stram	2006	Prospective Cohort study	Multiethnic Cohort Study	Incidence	No	Yes	Yes	Conversion from g/1000kcal to servings/day	
PRO99965	Kirsh	2006a	Prospective Cohort study	Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial	Incidence/ Mortality	No	No	No		Superseded by Kirsh, 2007
PRO10700	Platz	2004 b	Nested case-control study	CLUE II	Incidence	Yes	No	No		Only mean values
PRO02061	Schuurman	1998	Case-cohort study	Netherlands Cohort Study	Incidence	Yes	Yes	No	Conversion from g/day to servings/day	Only continuous results (not in H vs L)
PRO02629	Giovannucci	1995	Prospective Cohort study	Health Professionals Study	Incidence/ Mortality	Yes	Yes	Yes	Event rate per category	

PRO02808	Mills	1994	Prospective Cohort study	Adventist Health Study	Incidence	Yes	No	No		Only mean values. Mills 1989 included
PRO03129	Hsing	1990 b	Prospective Cohort study	Lutheran Brotherhood Study	Mortality	Yes	No	No		Insufficient data. Mentioned in the text that there is no significant association
PRO03196	Mills	1989	Prospective Cohort study	Adventist Health Study	Incidence	Yes	Yes	Yes		

Figure 13 Highest versus lowest forest plot of tomatoes and prostate cancer

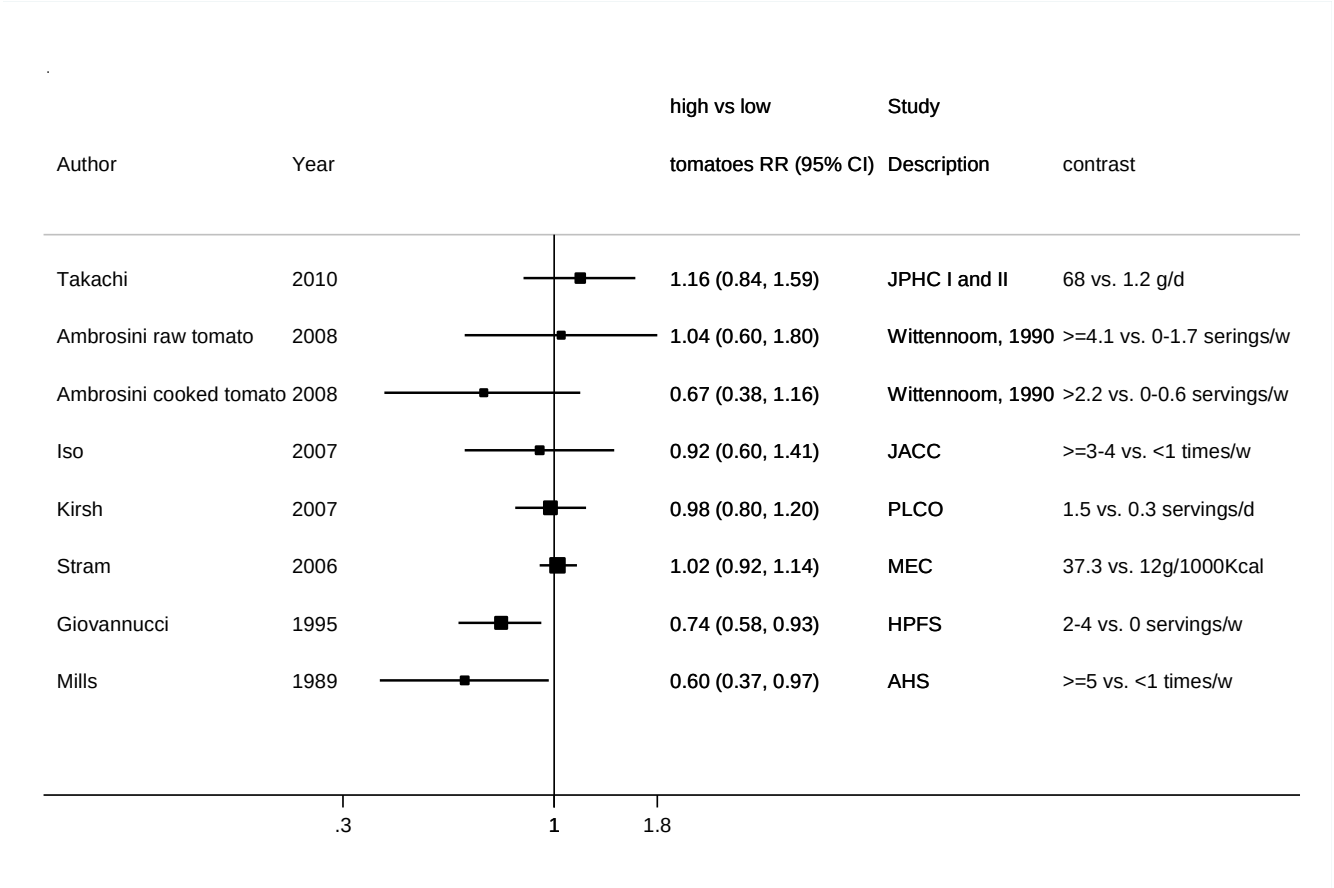


Figure 14 Dose-response meta-analysis of tomatoes and prostate cancer – per 1 serving/day

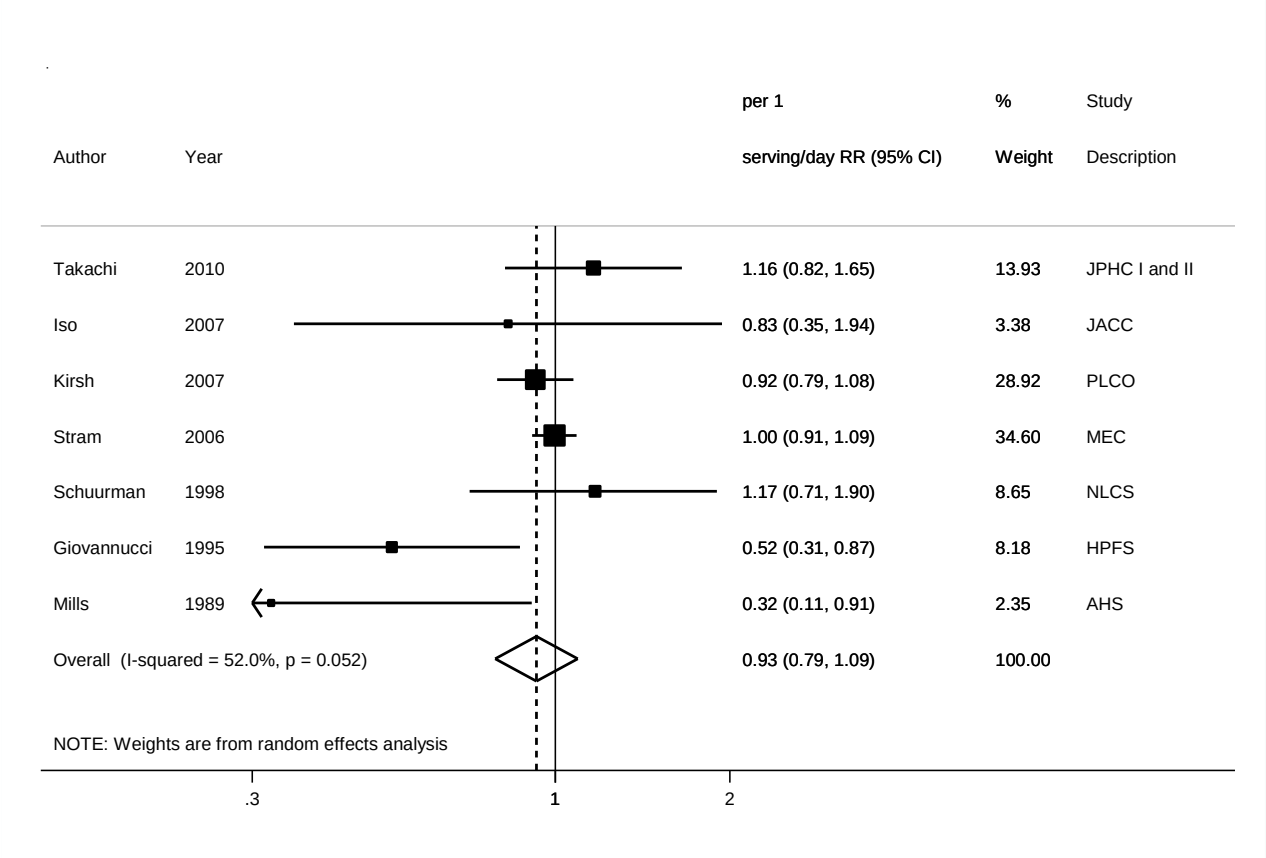
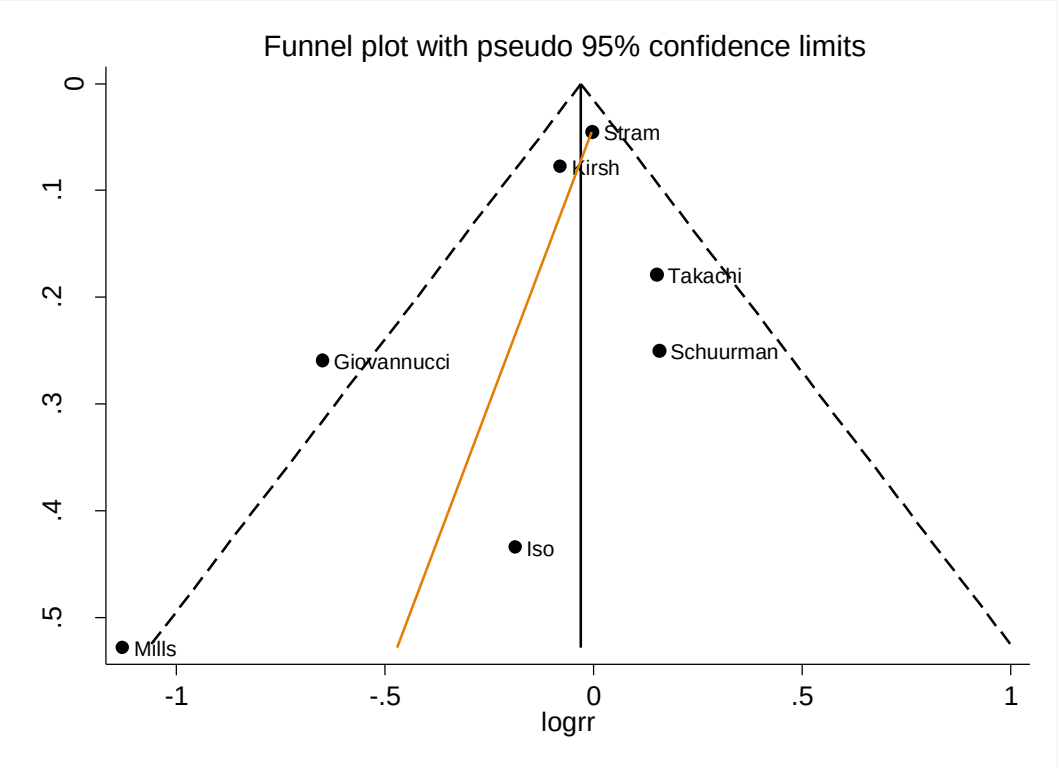


Figure 15 Funnel plot of tomatoes and prostate cancer



Egger's test p = 0.25

Figure 16 Dose-response graph of tomatoes and prostate cancer

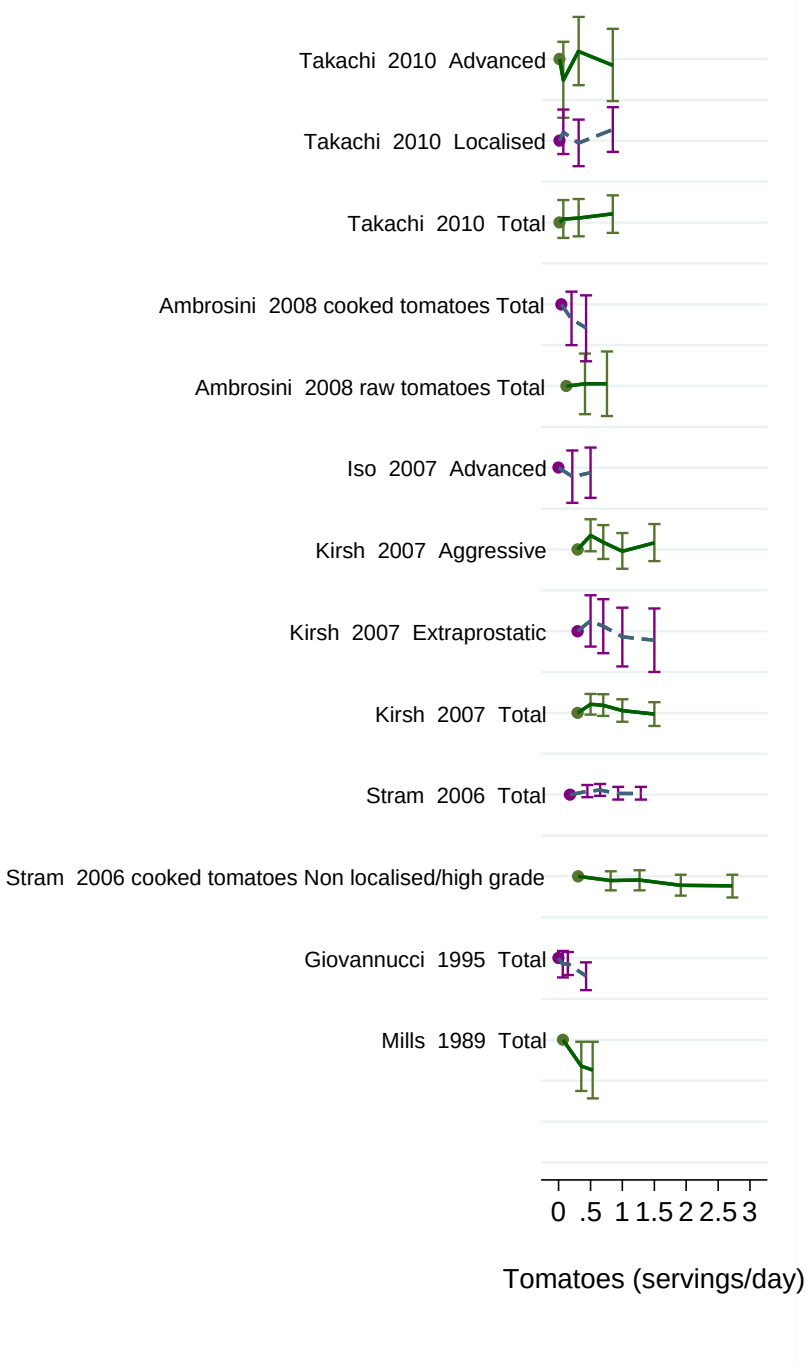
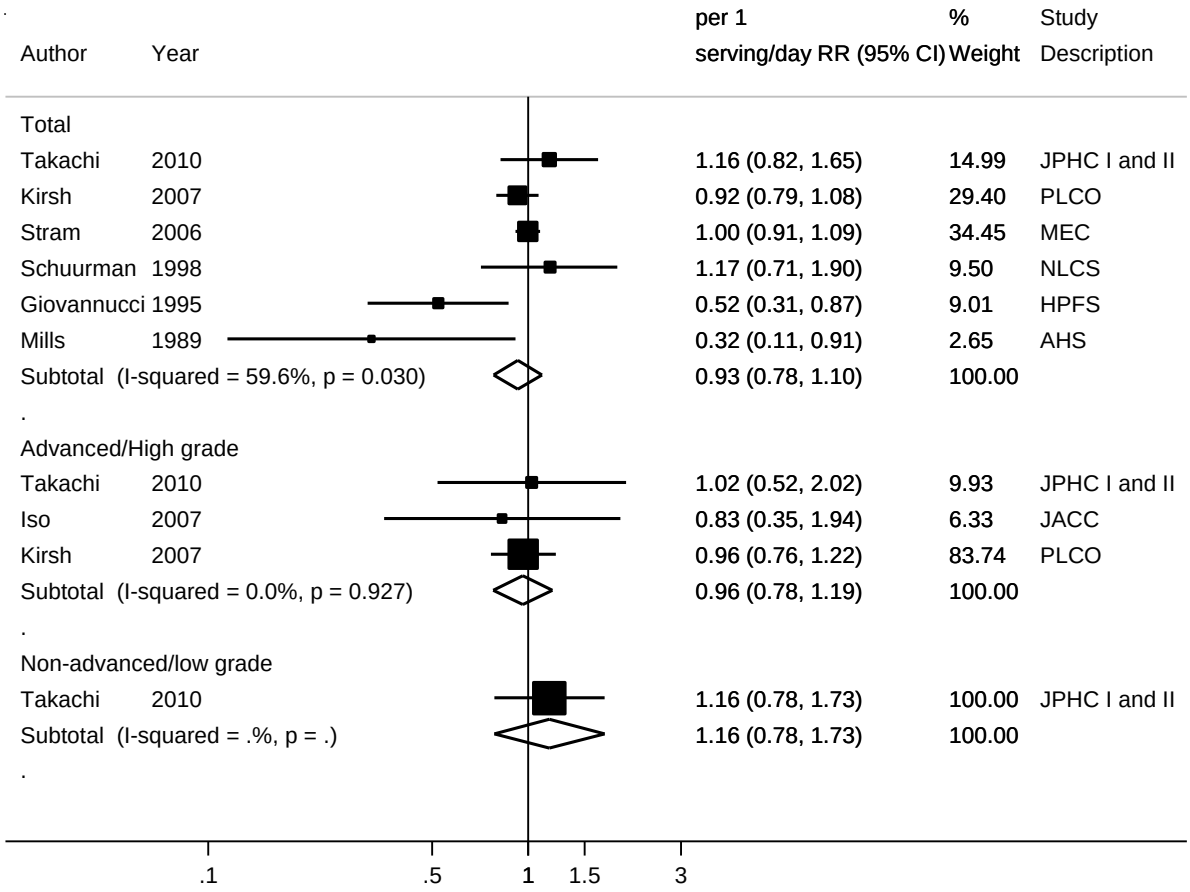


Figure 17 Dose-response meta-analysis of tomatoes and prostate cancer, per 1 serving/day stratified by prostate cancer type



2.2.1.5.13 Tomato juice/sauce

Four studies (Giovannucci, 1995; Schuurman, 1998; Stram, 2006; Kirsh, 2006) reported on tomato sauce or juice and prostate cancer. The exposure definition varied and a meta-analysis could not be conducted. The results are described to complement the review on tomato intake.

Tomato sauce: Two studies (3 publications were identified). The HPFS (Giovannucci, 1995) was identified in the 2005 SLR and later updated (Giovannucci, 2007). The HPFS (Giovannucci, 2007) reported a RR of 0.80 (95% CI 0.68-0.93) for > 2 vs. < 0.25 servings of tomato sauce intake per week. The association was not significant when the analysis was restricted to fatal prostate cancers (RR 0.91 (95% CI 0.54-1.54 for > 2 vs. < 0.25 servings of tomato sauce per week). The PLCO study (Kirsh, 2006) reported that spaghetti/tomato sauce was not associated with prostate cancer (RR0.96; 95% CI 0.76-1.19 for ≥ 2 servings/week vs. < 1 serving/month). After stratification by cancer type (advanced and non-advanced cancer) or family history of prostate cancer the relationship was still not significant. No significant association was observed with ketchup intake (RR 0.99 (95% CI 0.82-1.19) for > 2 per week vs. < 1 servings of tomato ketchup per week).

Tomato juice: Two studies were identified. The HPFS (Giovannucci, 1995) reported a significant inverse association. The result was not updated in the most recent publication (Giovannucci, 2007). The NLCS (Schuurman, 1998) reported no significant association.

Tomato and vegetable juice: The two studies identified, PLCO (Kirsh, 2006) and MEC (Stram, 2006) reported no significant association.

2.2.2 Fruits

Methods
Twenty-three publications from nineteen studies were identified, from which eight publications from eight studies were identified in the CUP.

The definition of fruit intake varied between the studies that reported details. Three studies reported on fruit and fruit juices (Stram, 2006; Kilkkinen, 2003; Hsing, 1990). One study reported on a fruit index that measured the frequency of canned, frozen, fresh, and dried fruit consumed in a month (Mills, 1989).

Fruit intake in times or servings was converted to grams using a standard portion size of 80 g (Ambrosini, 2008; Gonzalez, 2007; Kirsh, 2007; Allen, 2004; Shibata, 1992; Hsing, 1990; Mills, 1989; Severson, 1989). For Smit (2007), the reported serving size of 100 g reported in the study was used in the conversion. George (2009) reported in cup-equivalents/1000 kcal, which was converted to g/day using a standard portion size of 80 g and the average energy intake of 1990 kcal/day reported in the study. Stram (2006) also reported in g/1000 kcal and intake was converted to g/day using the average energy intake of 2380 kcal/day reported in another publication of the same study (Multiethnic Cohort Study).

Sixteen studies could be included in the dose-response meta-analysis on prostate cancer. The increment unit used in the analysis was 100 g/day. From the studies included in the dose-response meta-analysis, ten studies reported on total prostate cancer (Ambrosini, 2008; Gonzalez, 2007; Allen, 2004; Key, 2004; Chan, 2000; Schuurman, 1998; Le Marchand, 1994; Shibata, 1992; Mills, 1989; Severson, 1989), one study on total, advanced, and localised prostate cancer (Takachi, 2010), two studies on total and advanced/aggressive prostate cancer (George, 2009; Kirsh, 2007), one study on total and non-localised/high grade prostate cancer (Stram, 2006), and two studies on fatal cancer cases only (Smit, 2007; Hsing, 1990).

One study (California, USA 1960-1980) was not included in forest plots (Snowdon, 1984). Two publications (Kilkkinen, 2003; Hirvonen, 2001) from the ATBC study reported mean values only but a further publication (Chan, 2000) could be included in the analysis.

Main results
The summary RR of prostate cancer per 100 g/day was 1.00 (95% CI 0.99-1.01; $I^2 = 0\%$; $p_{heterogeneity} = 0.61$; n = 16) (all studies combined). Although the NIH-AARP (George et al, 2009) and the MEC (Stram et al, 2006) had 58% and 31% weights respectively in the analyses, the summary RR did not change materially when the studies were omitted in turn in influence analysis. The Egger's test of publication bias was not significant (p = 0.09) but the funnel plot suggests that smaller studies reported stronger positive associations than expected.

The summary RRs per 100 g/day was 1.00 (95% CI 0.98-1.02; $I^2 = 0\%$; $p_{heterogeneity} = 0.88$; n = 6) for advanced/high grade prostate cancer.

There was statistical evidence of non-linearity for total prostate cancer (p = 0.01). The curve shows a significant light increase in risk for intake in the range 200-600 grams driven by a few observations but a risk increase is not observed above this level. For advanced prostate cancer, p for non-linearity was 0.90.

Heterogeneity
Overall, there was no evidence of heterogeneity, $I^2 = 0\%$, $p_{heterogeneity} = 0.61$.

Comparison with the Second Expert Report
In the 2005 SLR, the meta-analysis on fruit intake and prostate cancer showed non-significant association.

Published meta-analysis or pooled analysis
Fourteen studies were included in a meta-analysis (Meng, 2013). The summary RR for the highest versus lowest intake was 1.02 (95% CI 0.98-1.07, $I^2 = 0\%$, $p_{heterogeneity} = 0.93$). All studies included in this published meta-analysis were included in the present review. No pooled analysis was identified.

Table 18 Studies on fruit intake identified in the CUP

Author, year	Country	Study name	Cases	Years of follow up	RR	LCI	UCI	Contrast
Drake, 2012	Sweden	Malmo Diet and Cancer Study cohort	817	15 years	1.15	0.90	1.46	Median 335 vs. 44.9 g/day
Takachi, 2010	Japan	JPHC study- I and II	339	321061 person-years	1.09	0.77	1.53	Median 335 vs. 38 g/day
					1.01	0.94	1.09	Per 100 g/day
George, 2009	USA	NIH- AARP Diet and Health Study	17034	8 years (max)	1.01	0.95	1.06	1.6-5.13 vs. 0-0.44 cup/1000 kcal
Ambrosini, 2008	Australia	Wittennoom Gorge, West Australian cohort 1990-2004	97	12.7 years	0.94	0.46	1.89	≥ 2.31 vs. < 1 servings/day
Gonzalez, 2007	USA	VITAL	832	3.3 years	1.19	0.96	1.47	≥ 2.07 vs. ≤ 0.63 servings/day
Kirsh, 2007	USA	PLCO	1338	4.2 years	0.94	0.77	1.15	Median 6 vs. 1 servings/day
Smit, 2007	Puerto Rico	PR Heart Health Study	167	40 years	1.13	0.45	2.79	2.1-3.0 vs. 0 servings/day
Stram, 2006	USA	MEC	3922	8 years	1.05	0.94	1.16	≥221.2 vs. ≤51.5 g/1000kcal

Table 19 Overall evidence on fruit intake and prostate cancer

	Summary of evidence
2005 SLR	Eleven prospective studies were identified during the 2005 SLR and nine studies were included in the meta-analysis. All studies reported statistically non-significant results.
Continuous Update Project	Eight prospective studies were identified in the CUP; none showed significant associations. Six studies reported on advanced prostate cancer and showed a non-significant association with fruit intake. No significant association was observed in the CUP meta-analysis.

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

Prostate cancer		
	2005 SLR	CUP
All studies		
Studies (n)	9	16
Cases (n)	2343	26671
Increment unit used	Per serving/day	Per 100 g/day
Overall RR (95% CI)	1.03 (0.98-1.10)	1.00 (0.99-1.01)
Heterogeneity (I^2, p-value)	20.8%, p = 0.26	0%, p = 0.61
Stratified analysis		
Advanced/high grade cancer		
Overall RR (95% CI)	0.96 (0.81-1.14)	1.00 (0.98-1.02)
Heterogeneity (I^2, p-value)	(only 1 study)	0%, p = 0.88, n = 6
Non-advanced/low grade cancer		
Overall RR (95% CI)		1.02 (0.94-1.11)
Heterogeneity (I^2, p-value)		(only 1 study)

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

WCRF code	Author	Year	Study design	Study name	Cancer outcome	2005 SLR	CUP dose-response meta-analysis	CUP HvL forest plot	Estimated values	Exclusion reasons
PRO100139	Drake	2012	Prospective Cohort study	Malmö Diet and Cancer Study cohort	Incidence	No	No	Yes		Two exposure categories only (also for advanced prostate cancer)
PRO100062	Takachi	2010	Prospective Cohort study	JPHC Study I and II	Incidence	No	Yes	Yes		
PRO100125	George	2009	Prospective Cohort study	NIH- AARP Diet and Health Study	Incidence	No	Yes	Yes	Conversion from cup-equivalents/1000kcal to g/day using standard portion size 80g and average energy intake 1990 kcal/day, mid-exposure values, cases and person-years per quintile	
PRO99954	Ambrosini	2008	Prospective Cohort study	Wittennoom Gorge, West Australian cohort 1990-2004	Incidence	No	Yes	Yes	Conversion from servings/day to g/day using standard portion size 80g, mid-exposure values	
PRO100035	Gonzalez	2007	Prospective Cohort study	VITAL	Incidence/ Mortality	No	Yes	Yes	Conversion from servings/day to g/day using standard portion size 80g, mid-exposure values	
PRO99982	Kirsh	2007	Prospective Cohort study (Follow-up of screening arm in trial)	PLCO	Incidence/ Mortality	No	Yes	Yes	Conversion from servings/day to g/day using standard portion size 80g , cases and person-years per quintile	

PRO100019	Smit	2007	Prospective Cohort study	PR Heart Health Study	Mortality	No	Yes	Yes	Conversion from servings/day to g/day using portion size 100g as used in study, mid-exposure values, cases and person-years per tertile	
PRO99986	Stram	2006	Prospective Cohort study	MEC	Incidence/ Mortality	No	Yes	Yes	Conversion from g/1000kcal to g/day using average energy intake 2380 kcal/day from another article of the same study, mid-exposure values, cases and person-years per quintile	
PRO97367	Allen	2004	Prospective Cohort study	Life Span Study	Incidence	Yes	Yes	Yes	Conversion from times/week to g/day using standard portion size 80g, mid-exposure values	
PRO00148	Key	2004	Prospective Cohort study	EPIC	Incidence	Yes	Yes	Yes	Used estimated mean exposure values provided in the article	
PRO03999	Wu	2004	Nested case-control study	Health Professionals Follow-up Study	Incidence/ Mortality	Yes	No	No		Number of cases and non-cases per category only - no measure of association Giovannucci 1995 - used
PRO00142	Kilkkinen	2003	Nested case-control study	ATBC	Incidence/ Mortality	Yes	No	No		Duplicate publication with only mean exposure values
PRO01034	Hirvonen	2001	Prospective Cohort study	ATBC	Incidence/ Mortality	Yes	No	No		Duplicate publication with only mean exposure values
PRO01426	Chan	2000	Prospective	ATBC	Incidence	Yes	Yes	Yes	Cases and person-years	

			Cohort study						per quintile	
PRO02192	Giovannucci	1998 b	Prospective Cohort study	Health Professionals Follow-up Study	Incidence/ Mortality	Yes	No	No		Advanced prostate cancer; two exposure categories only. Same study as Giovannucci 1995 which was used for total cancer
PRO02061	Schuurman	1998	Case-cohort study	The Netherlands Cohort Study	Incidence	Yes	Yes	Yes		
PRO02629	Giovannucci	1995	Prospective Cohort study	Health Professionals Follow-up Study	Incidence/ Mortality	Yes	No	Yes		Two exposure categories only
PRO02788	Le Marchand	1994	Prospective Cohort study	USA Hawaii 1975-1980	Incidence	Yes	Yes	Yes	Cases and person-years per quartile, mid-exposure values	
PRO13404	Shibata	1992	Prospective Cohort study	USA California 1981-1985	Incidence/ Mortality	Yes	Yes	Yes	Conversion from servings/day to g/day using standard portion size 80g, person-years per tertile	
PRO03129	Hsing	1990 b	Prospective Cohort study	Lutheran Brotherhood Cohort Study	Mortality	Yes	Yes	Yes	Conversion from times/month to g/day using standard portion size 80g, person-years per quartile, mid-exposure values	
PRO03196	Mills	1989	Prospective Cohort study	Adventist Health Study	Incidence	Yes	Yes	Yes	Fruit index; conversion from times/month to g/day using standard portion size 80g, mid-exposure values	
PRO03210	Severson	1989 b	Prospective Cohort study	USA Hawaii 1965-1968	Incidence	Yes	Yes	Yes	Conversion from times/week to g/day using standard portion size 80g, mid-exposure values	
PRO03474	Snowdon	1984	Prospective Cohort study	USA California 1960-1980	Mortality	Yes	No	No		Identified in 2005 SLR, no measure of

										association -reported no significant association

Figure 18 Highest versus lowest forest plot of fruit intake and prostate cancer

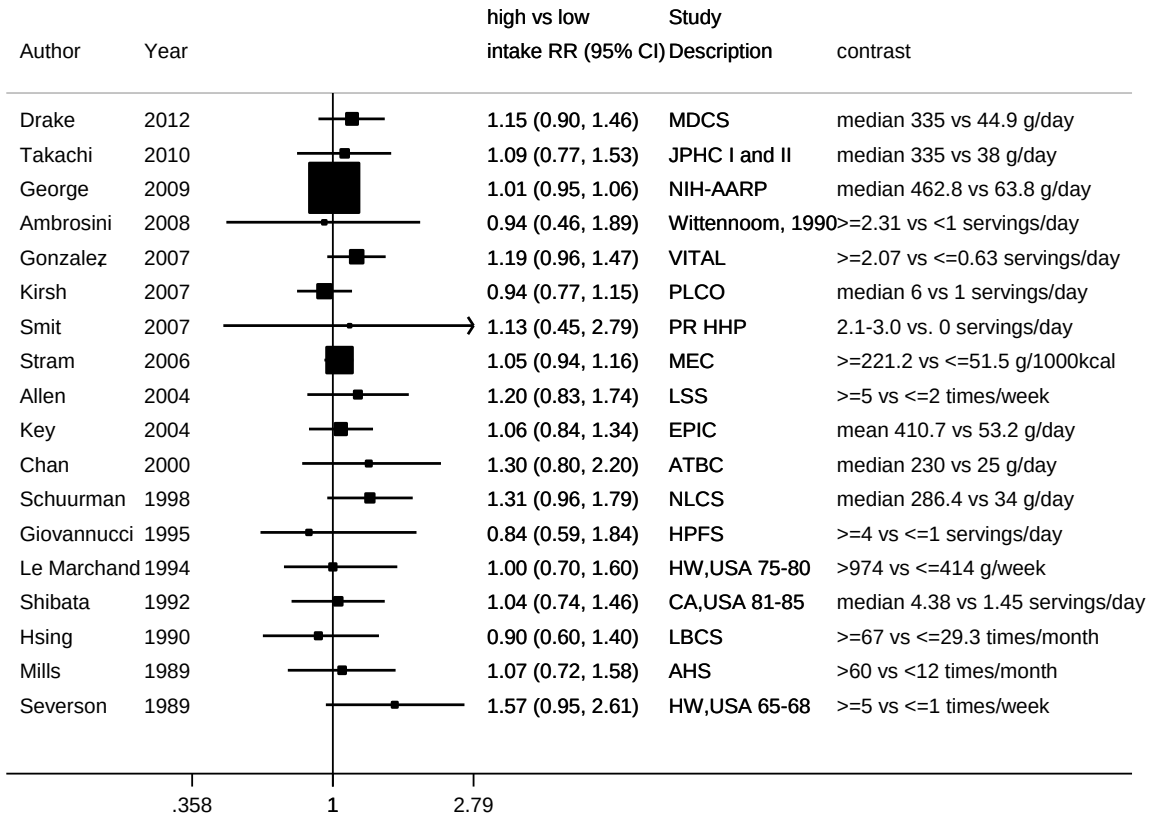


Figure 19 Dose-response meta-analysis of fruit intake and prostate cancer – per 100 g/day

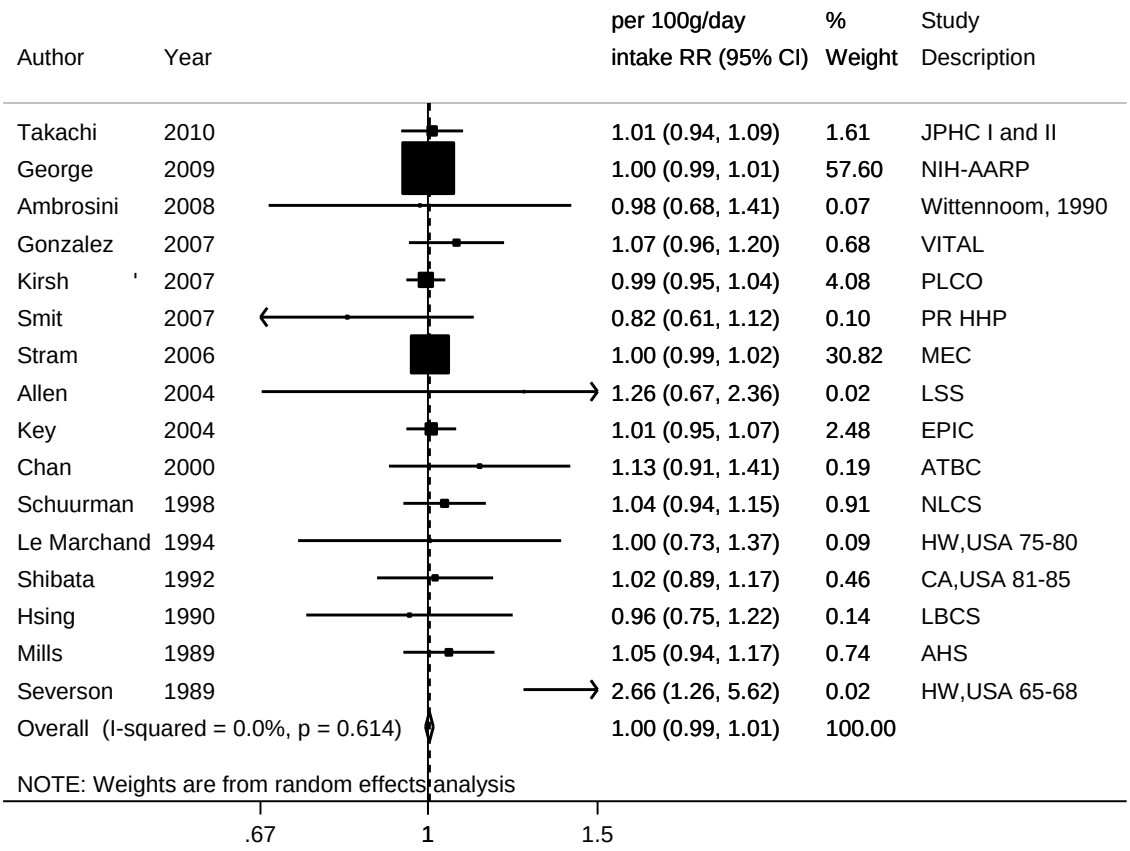
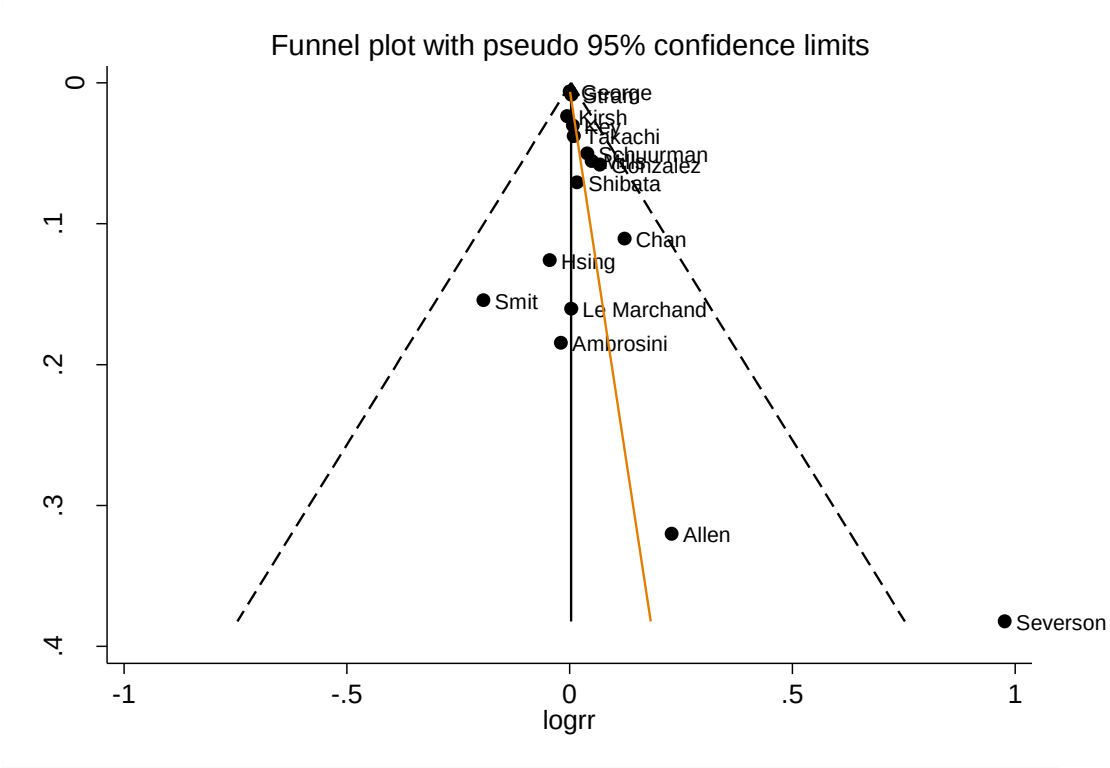


Figure 20 Funnel plot of fruit intake and prostate cancer



Egger's test p = 0.09

Figure 21 Dose-response graph of fruit intake and prostate cancer

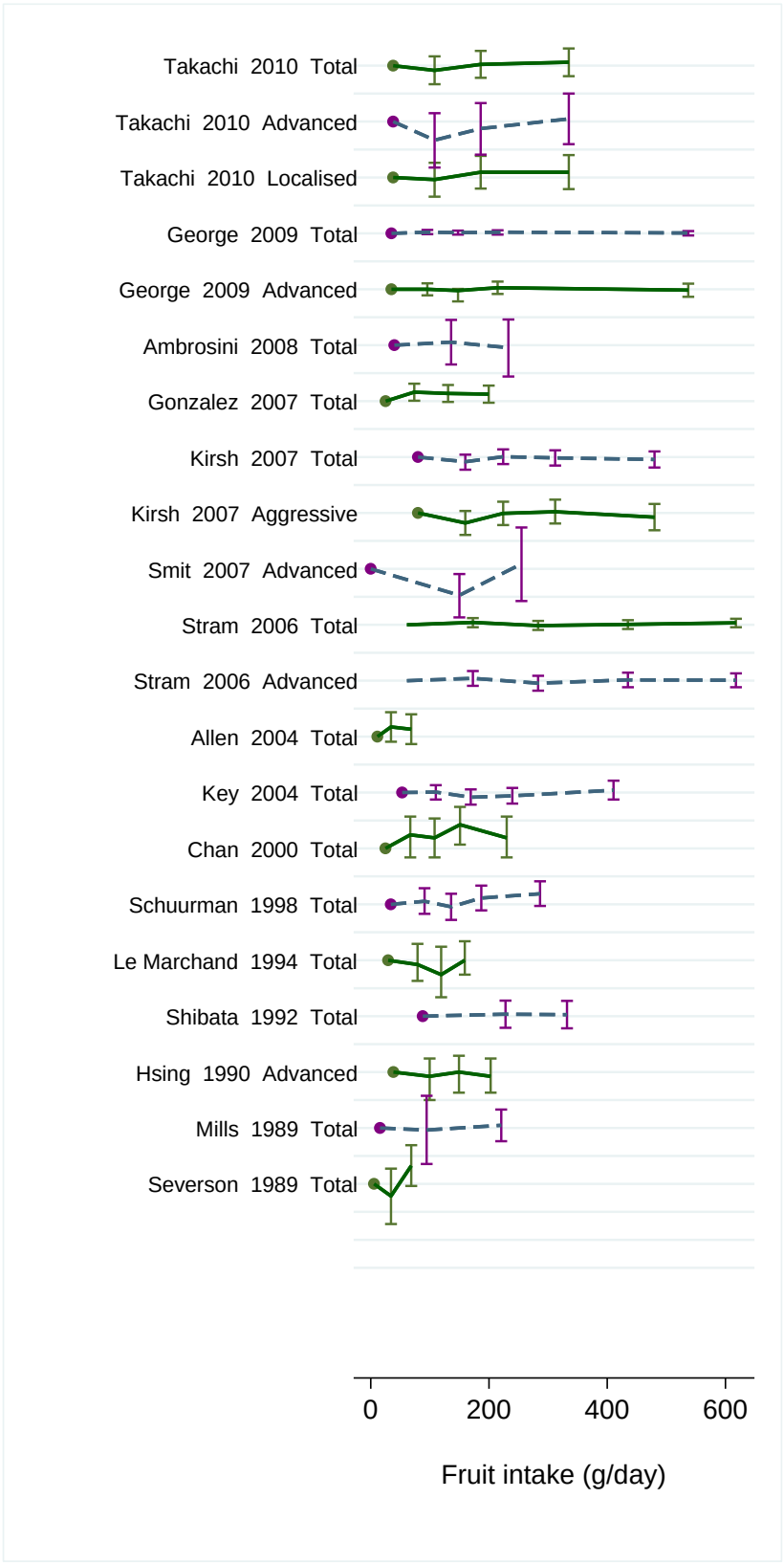


Figure 22 Dose-response meta-analysis of fruit intake and prostate cancer, per 100 g/day, stratified by prostate cancer type

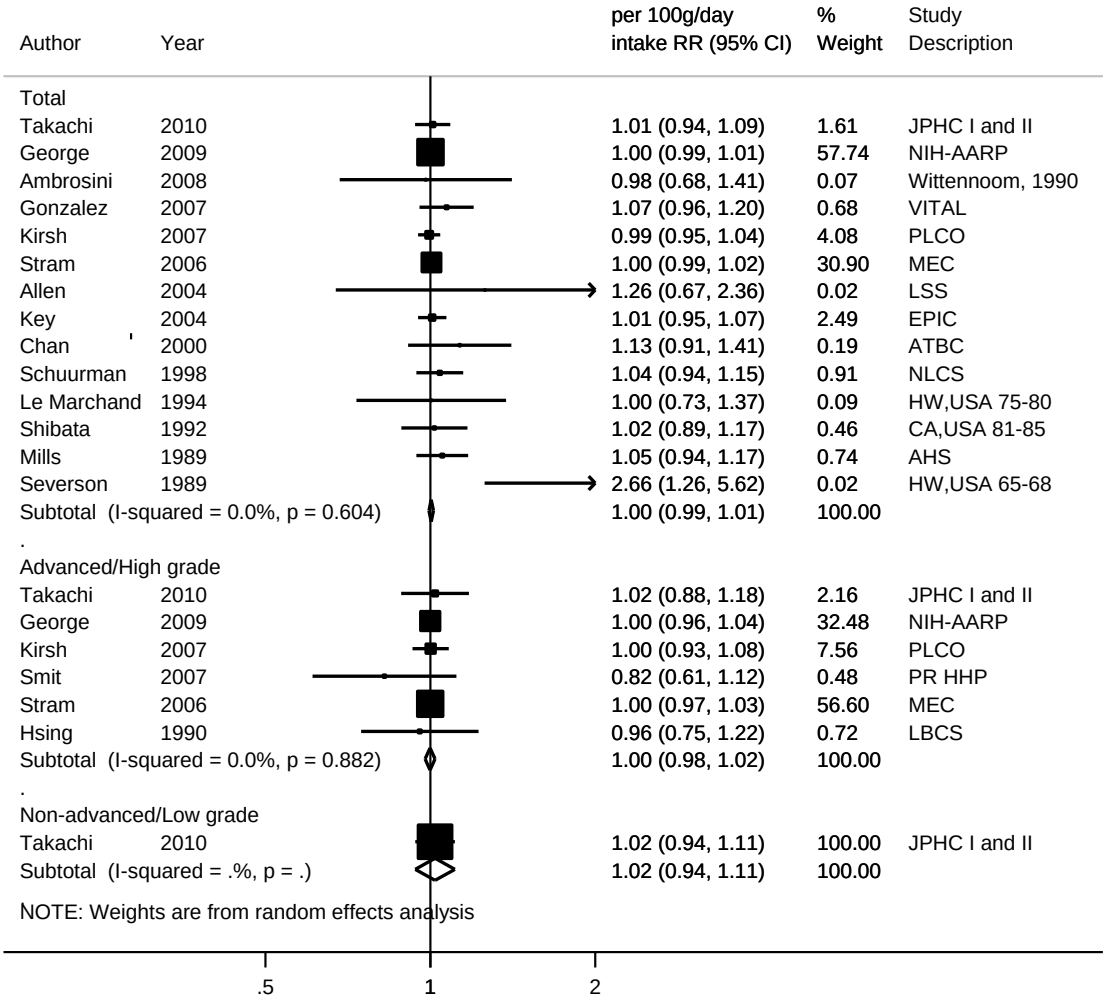
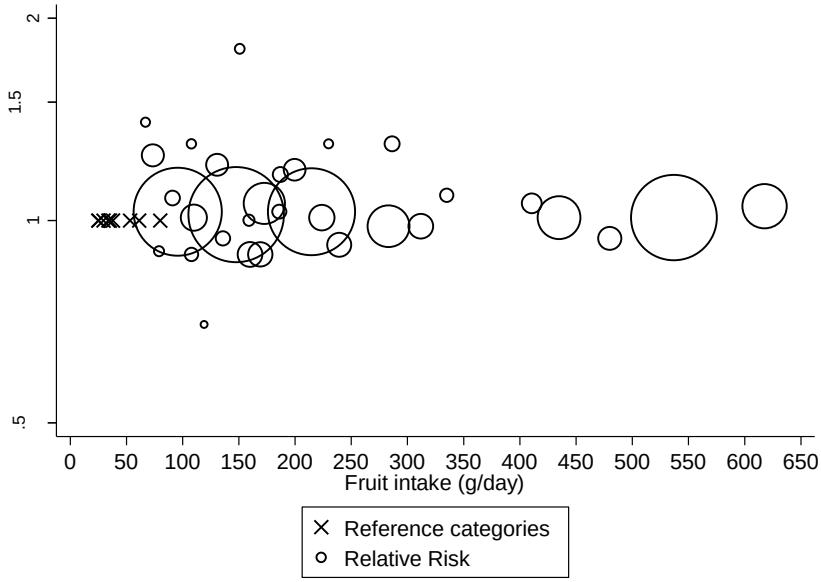


Figure 23 Non-linear dose-response analysis of fruit intake and total prostate cancer



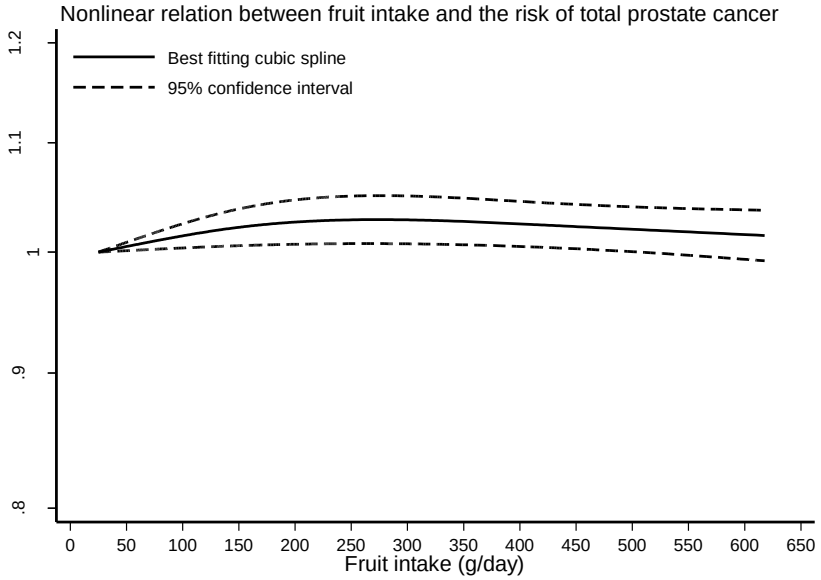


Table 22 Table with fruit intake values and corresponding RRs (95% CIs) for non-linear analysis of fruit intake and total prostate cancer

Fruit intake (g/day)	RR (95% CI)
25.0	1
199.6	1.03 (1.01-1.05)
410.7	1.02 (1.00-1.04)
617.7	1.01 (0.99-1.04)

$p_{non\text{-}linearity} = 0.01$

2.3 Pulses (legumes)

Methods
Three prospective studies on pulses (legumes) had been identified, from which two studies were identified in the CUP (Park, 2008; Smit, 2007).
Two other studies reported on boiled and dried beans respectively (Iso, 2007; Kirsh, 2007).
Two studies on beans, lentils and peas (Mills, 1989; Hsing, 1990) were also identified in the 2005 SLR.
There was no enough information to do dose-response meta-analysis.

Main results
Two out of the three studies on pulses reported inverse associations. In the Multiethnic Cohort Study (Park, 2008), a significant inverse association was observed for advanced prostate cancer (HR 0.72; 95% CI 0.59-0.89; n = 1278 cases; $p_{trend} = 0.01$). A significant inverse trend was observed for total prostate cancer (HR 0.90; 95% CI 0.81-1.01; n = 4404 cases; $p_{trend} = 0.01$). The cohort study in The Netherlands (Schuurman, 1998) reported a significant inverse association of prostate cancer (HR 0.71; 95% CI 0.51-0.98) in relation to higher intake of legumes. Prostate cancer mortality was not associated with intake of pulses (legumes) in a study in Porto Rico (Smit, 2007).

The study on boiled beans (Iso, 2007) in Japanese men reported no association with prostate cancer mortality (HR 1.11; 95% CI 0.71-1.76 for ≥ 3 vs < 1 times/week). No association of dried beans intake was observed in the PLCO study (Kirsh, 2007) (HR 1.01; 95% CI 0.84-1.22 for 0.49 vs < 0.06 servings/day).

Discordant results were observed in the two studies on beans, lentils and peas. The Adventists Health Study (Mills, 1989) reported significant decreased risk with increased intake of beans, lentils and peas (HR 0.53; 93% CI 0.31-0.90 for intake of more than three times/week compared to less than once/month. serving/week). The Lutheran Brotherhood Study reported no association (Hsing, 1990).

Comparison with the Second Expert Report
In the 2005 SLR, the meta-analysis of case-control studies gave a significant inverse association of pulses (legumes) intake and prostate cancer risk (OR for one serving/week: 0.95; 95% CI 0.91-0.99).

Published meta-analysis or pooled analysis
No study was identified.

Table 23 Overall evidence on pulses (legume) intake and prostate cancer

	Summary of evidence
2005 SLR	One cohort study was identified during the 2005 SLR and reported significant inverse association. One study on beans, lentils and peas reported no association and the other, significant inverse association.
Continuous Update Project	Two prospective studies were identified in the CUP; one showed significant associations. Two other studies on dried or boiled beans intakes reported no association. No meta-analysis was conducted.

Table 24 Studies on pulses (legumes) identified in the CUP

Author, year	Country	Study name	Cases	Years of follow up	RR	LCI	UCI	Contrast
Park, 2008	USA	MEC	All cases: 4404	8	0.90	0.81	1.01	> 21.3 vs. < 3.6 g/1000 kcal
			Advanced* 1278		0.72	0.59	0.89	
Smit, 2007	Puerto Rico	PR Heart Health Study	167	40 (max)	1.06	0.48	2.32	3.1-4.0 vs. 0 servings/day
Iso, 2007	Japan	JACC	169	15	1.11	0.71	1.76	Boiled beans ≥ 3 vs. < 1 times/week
Kirsh, 2007	USA	PLCO	1338	4.2	1.01	0.84	1.22	Dried beans Median 0.49 vs. 0.06 servings/day

*Advanced: nonlocalised or high grade cancers

2.3.1 Soya, soya products

Methods
Five cohort studies on different soya foods were identified during the CUP. There was no appropriate data to do dose-response meta-analysis.

Main results
Two studies on soya foods (Park, 2008; Kurahashi, 2007) reported no significant inverse associations. No associations were reported in two studies on miso soup (Iso, 2007; Kurahashi, 2007) and in the studies on tofu and soyabeans (Kirsh, 2007) or tofu (Iso, 2007).

Comparison with the Second Expert Report
Similar results were observed in the 2005 SLR. No association of prostate cancer was reported for soya products or soya beans (Hirayama, 1978, Allen 2004), miso soup (Severson, 1989; Allen, 2004), tofu (Hsing, 1990; Mills,1994; Nomura, 2004) foods boiled in soya sauce (Severson, 1989).
Only one cohort study reported a significant inverse association with soy milk intake (Jacobsen, 1998).

Published meta-analysis or pooled analysis

In a meta-analysis of case-control and cohort studies comparing the highest with the lowest intake reported in the studies, the combined relative risks were 0.70 (95% CI 0.56-0.88; 5 case-control studies and 3 cohorts) for nonfermented soya foods and 1.02 (95% CI 0.73- 1.42; 3 case-control studies and 3 cohorts) for fermented soya foods (Yan, 2009).

Table 25 Overall evidence on soya foods intake and prostate cancer

	Summary of evidence
2005 SLR	Seven publications on different soya foods were identified during the 2005 SLR. Only one study reported a significant (inverse) association and it was with soya milk.
Continuous Update Project	Four prospective studies investigating soya foods, miso soup, tofu or soya beans or tofu in relation with prostate cancer were identified in the CUP; none of the studies showed significant associations. No meta-analysis was conducted.

Table 26 Studies on soya and soya products identified in the CUP

Author, year	**Country**	**Study name**	**Cases**	**Years of follow up**	**RR**	**LCI**	**UCI**	**Contrast**
Soya foods								
Park, 2008	USA	MEC	4404	8	0.90	0.80	1.01	≥ 2.8 vs. 0 g/1000kcal
Kurahashi, 2007	Japan	JPHC I and II	307	325371 person-years	0.82	0.57	1.19	≥ 107.40 vs. ≤ 46.59 g/day
Miso soup								
Iso, 2007	Japan	JACC	169	15	0.95	0.59	1.51	≥ 2.0 vs. ≤ 0.5 bowls/day
Kurahashi, 2007	Japan	JPHC I and II	307	325371 person-years	1.04	0.72	1.50	≥ 356.0 vs. < 110.0 ml/day
Tofu, soyabeans								
Kirsh, 2007	USA	PLCO	1338	4.2	0.98	0.79	1.22	Median 0.51 vs. 0 servings/day
Tofu								

Iso, 2007	Japan	JACC	169	15	1.07	0.70	1.63	≥ 5 vs. < 3 times/week

2.5.1.2 Processed meat

Methods

Fifteen publications from 11 cohort studies were identified. Ten publications (seven cohort studies) were identified during the CUP. The CUP meta-analysis included 11 studies; seven of these were identified during the CUP. The dose-response results are presented for an increment of 50 g per day.

The definition of processed meat varied across study. One study presented results only on red processed meat (Richman, 2011), other study presented results on bacon and sausages (Koutros, 2009), and another study reported on cured meats (boiled ham, bacon, smoked beef and other sliced cold meats) (Schuurman, 1999).

In one study (Richman, 2011) servings/weeks were converted to grams/day using 57 grams as one serving, as reported in the article. Two studies presented intake in g/1000 kcal/day. For one study (Sinha, 2009), it was rescaled to g/d using the average daily caloric intake of all participants. In another study (Park, 2007a) in a multi-ethnic population, the conversion to g/d from g/1000 kcal/day of processed meat intake was calculated using the weighted daily caloric intake obtained from a previously published study of the MEC study (Kolonel, 2000).

For the studies included in the dose-response meta-analysis, nine included total prostate cancer (Sinha, 2009; Allen, 2008a; Koutros, 2008; Park, 2007a; Rohrmann, 2007; Rodriguez, 2006; Cross, 2005; Schuurman, 1999; Veierod, 1997), for advanced/high grade cases (Sinha, 2009; Park, 2007; Rohrmann, 2007; Cross, 2005; Schuurman, 1999; Le Marchand, 1994, n = 6), and for fatal cases (Richman, 2011; Sinha, 2009; Rodriguez, 2006, n = 3).

Advanced and high grade cancers were combined in an advanced/high grade subgroup for stratified analyses.

Main results

The summary RR per 50 g/day was 1.03 (95% CI 0.98-1.08; $I^2 = 28.9\%$; $p_{heterogeneity} = 0.17$) for all studies combined. After stratification by cancer subtype, the RR per 50 g/day was 1.09 (95% CI 0.94-1.25; $I^2 = 54.2\%$; $p_{heterogeneity} = 0.05$; n = 6) for advanced/high grade and 1.02 (95% CI 0.79-1.32; $I^2 = 0\%$; $p_{heterogeneity} = 0.41$; n = 3) for fatal prostate cancer.
There was no significant evidence of publication bias with Egger's test, p = 0.14. Some asymmetry in the funnel plots shows that earlier smaller studies tended to report strong positive associations.

Heterogeneity

Overall, there was low heterogeneity, $I^2 = 28.9\%$, $p_{heterogeneity} = 0.17$.

Comparison with the Second Expert Report

In the 2005 SLR the meta-analysis on processed meat and prostate cancer the RR for an increase of one serving/week was 1.11 (95% CI 0.99-1.25; $I^2 = 68.9\%$; $p_{heterogeneity} = 0.02$; n = 4) for all prostate cancers and 1.09 (95% CI 0.97-1.22; $I^2 = 50.5\%$; $p_{heterogeneity} = 0.15$; n = 2) for advanced/high grade prostate cancers.

Published meta-analysis or pooled analysis

A meta-analysis of 10 cohorts (Alexander, 2010) reported a summary RR of prostate cancer for an increment of 30 g/d of 1.02 (95% CI 1.00-1.04; $p_{heterogeneity} = 0.27$). The summary RR of advanced prostate cancer for an increment of 30 g/d of processed meat was 1.01 (95% CI 0.90-1.14, $p_{heterogeneity} = 0.02$). No pooled analysis was identified.

Table 27 Studies on processed meat consumption identified in the CUP

Author, year	Country	Study name	Cases	Years of follow up	RR	LCI	UCI	Contrast
Richman, 2011	USA	Health Professionals Follow-up study	199	14 years	0.64	0.38	1.06	≥ 3 serving/week vs. < 0.5 servings/week
Major, 2011	USA	NIH- AARP Diet and Cancer study	1089	~10 years	0.94	0.76	1.14	Q5 vs. Q1
Sinha, 2009	USA	NIH- AARP Diet and Cancer study	10313	9 years	1.07	1.00	1.14	24.6 g/1000 kcal/ vs. 2.2 g/1000 kcal/
Allen, 2008a	Europe	European Prospective Investigation into Cancer and Nutrition	2727	8.7 years	0.93	0.79	1.09	78 g/d vs. 18 g/d
Koutros, 2008	USA	Agricultural Health Study Cohort	668	~8.5 years	0.98	0.78	1.24	17.2 g/d vs. 0 g/d
Park, 2007a	USA	Multi-ethnic Cohort study	4404	8 years	1.01	0.91	1.12	20 g/1000 kcal/d vs. 2.2 g/1000 kcal/d
Cross, 2007	USA	NIH- AARP Diet and Cancer study	17235	6.8 years	1.02	0.97	1.07	22.6 1000 kcal/d vs. 1.6 g 1000 kcal/d
Rohrmann, 2007	USA	CLUE II cohort study	199	15 years	1.53	0.98	2.39	≥ 5 times/week vs. <1 time/week
Rodriguez, 2006	USA	Cancer Prevention Study II Nutrition Cohort	85 Black	9 years	2.4	1.2	4.9	≥ 247 g/week 0-<59 g/week vs.
			5028 White		1.00	0.9	1.1	
Wu, 2006	USA	Health Professionals Follow-up study	3002	13	0.95	0.84	1.07	Q5 vs. Q1

Table 28 Overall evidence on processed meat consumption and prostate cancer

	Summary of evidence
2005 SLR	Five studies were identified during the 2005 SLR. All of them were included in the 2005 SLR meta-analysis. Two of these studies (Schuurman, 1999; Veierod, 1997) reported significant positive association between processed meat intake and prostate cancer.
Continuous Update Project	Ten additional publications (seven studies) reported on processed meat and prostate cancer risks, seven of these were used in the meta-analysis. One of these studies (Sinha, 2009) reported a significant positive association. The CUP meta-analysis showed no significant association of processed meat and prostate cancer

Table 29 Summary of results of the dose response meta-analysis of processed meat consumption and prostate cancer

Prostate cancer		
	2005 SLR	CUP
Studies (n)	4	11
Cases (n)	1857	25963
Increment unit used	Servings/week	Per 50 g/day
Overall RR (95%CI)	1.11 (1.00-1.25)	1.03 (0.98-1.08)
Heterogeneity (I^2, p-value)	68.9%, p = 0.02	28.9%, p = 0.17
Stratified analysis		
Advanced/high grade cancer		
Overall RR (95% CI)	1.09 (0.98-1.22)	1.09 (0.94-1.25)
Heterogeneity (I^2, p-value)	50.5%, p = 0.15, n = 2	54.2%, p = 0.05, n = 6
Mortality*		
Overall RR (95% CI)		1.02 (0.79-1.32)
Heterogeneity (I^2, p-value)		0 %, p = 0.41, n = 3

* No meta-analysis was conducted in the 2005 SLR.

Table 30 Inclusion/exclusion table for meta-analysis of processed meat consumption and prostate cancer

WCRF code	Author	Year	Study design	Study name	Cancer outcome	2005 SLR	CUP dose-response meta-analysis	CUP HvL forest plot	Estimated values	Exclusion reasons
PRO100106	Richman	2011	Prospective Cohort	Health Professionals Follow-up study	Mortality	No	Yes	Yes	Person-years, mid-exposure values	
PRO100104	Major	2011	Prospective Cohort	NIH- AARP Diet and Cancer study	Incidence	No	No	No		Superseded by PRO100051 (Sinha, 2009), only African-American
PRO100051	Sinha	2009	Prospective Cohort	NIH- AARP Diet and Cancer study	Mortality	No	Yes	Yes	Person-years, mid-exposure values	
PRO99955	Allen	2008a	Prospective Cohort	European Prospective Investigation into Cancer and Nutrition	Incidence	No	Yes	Yes	Person-years	
PRO99998	Koutros	2008	Prospective Cohort	Agricultural Health Study Cohort	Incidence	No	Yes	Yes	Person-years	
PRO99977	Park	2007a	Prospective Cohort	Multi-ethnic Cohort study	Incidence	No	Yes	Yes	Cases per category, person-years	
PRO99970	Rohrmann	2007	Prospective Cohort	CLUE II	Incidence	No	Yes	Yes	Mid-exposure values	
PRO100037	Cross	2007	Prospective Cohort	NIH- AARP Diet and Cancer study	Incidence	No	No	No		Superseded by PRO100051 (Sinha, 2009)
PRO99988	Wu	2006	Prospective Cohort	Health Professionals Follow-up study	Incidence	No	No	No		Superseded by PRO100106 (Richman, 2011)
PRO99984	Rodriguez	2006	Prospective Cohort	Cancer Prevention Study II Nutrition Cohort	Incidence	No	Yes	Yes	Person-years, mid-exposure values	

PRO99850	Cross	2005	Prospective Cohort	Prostate, Lung, Colorectal and Ovarian Cancer Screening Trial	Incidence	Yes	Yes	Yes	Mid-exposure values	
PRO01122	Michaud	2001	Prospective Cohort	Health Professionals Follow-up study	Incidence	Yes	No	No		Superseded by PRO100106 (Richman, 2011)
PRO01759	Schuurman	1999b	Case-cohort	Netherlands Cohort study	Incidence	Yes	Yes	Yes	Rescale continuous values	
PRO02242	Veierod	1997	Prospective Cohort	Norway 1977-1983	Incidence	Yes	Yes	Yes	Person-years, mid-exposure values	
PRO02788	Le Marchand	1994	Prospective Cohort	USA Hawaii 1975-1980 Cohort study	Incidence	Yes	Yes	Yes	Mid-exposure values	

Figure 24 Highest versus lowest forest plot of processed meat consumption and prostate cancer

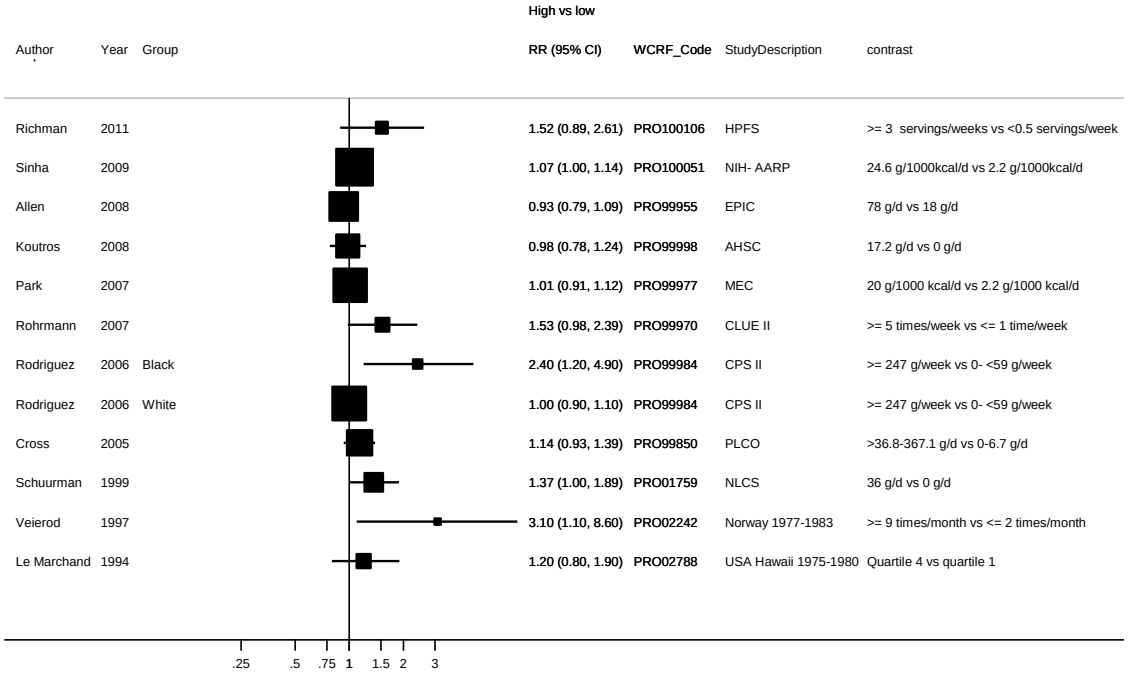


Figure 25 Dose-response meta-analysis of processed meat intake and prostate cancer, per 50 g/day

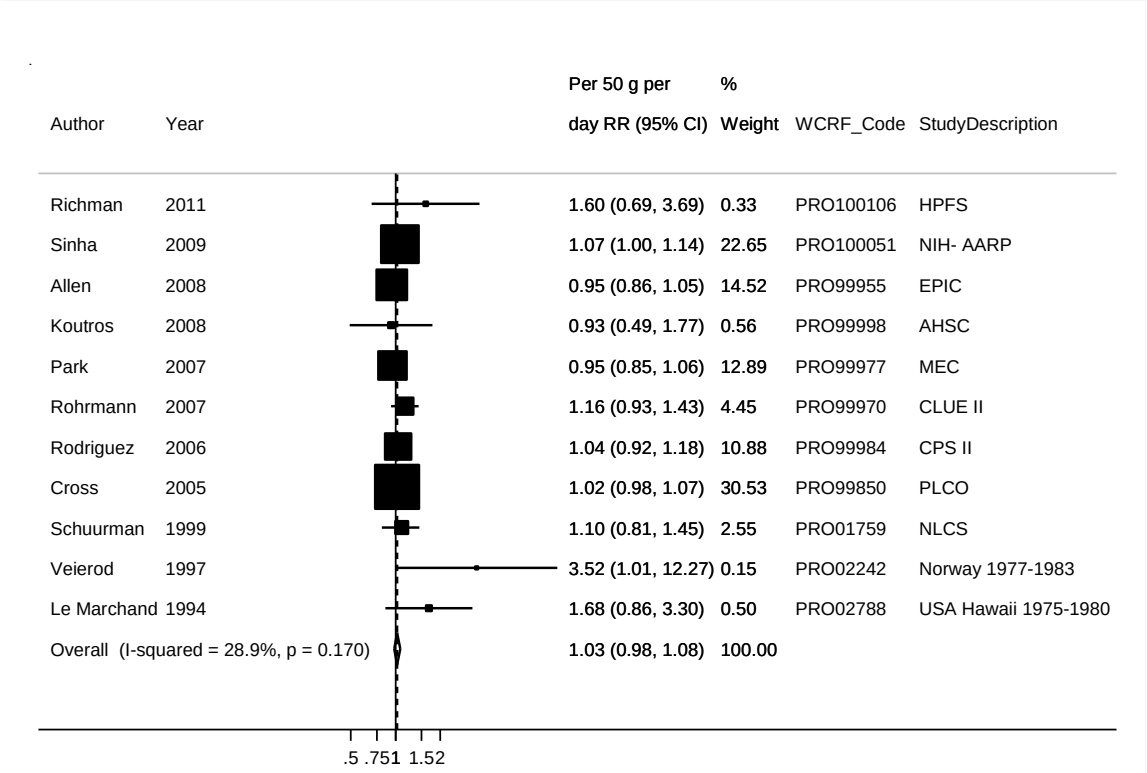
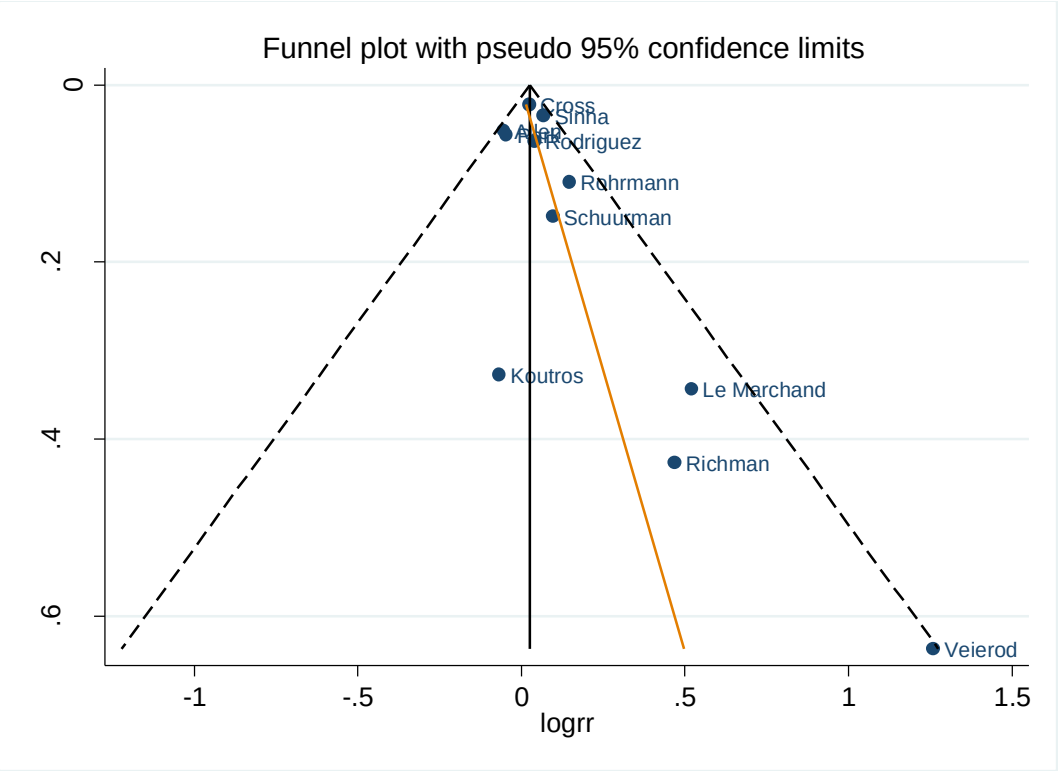


Figure 26 Funnel plot of processed meat intake and prostate cancer



Egger's test p = 0.14

Figure 27 Dose-response graph of processed meat and prostate cancer

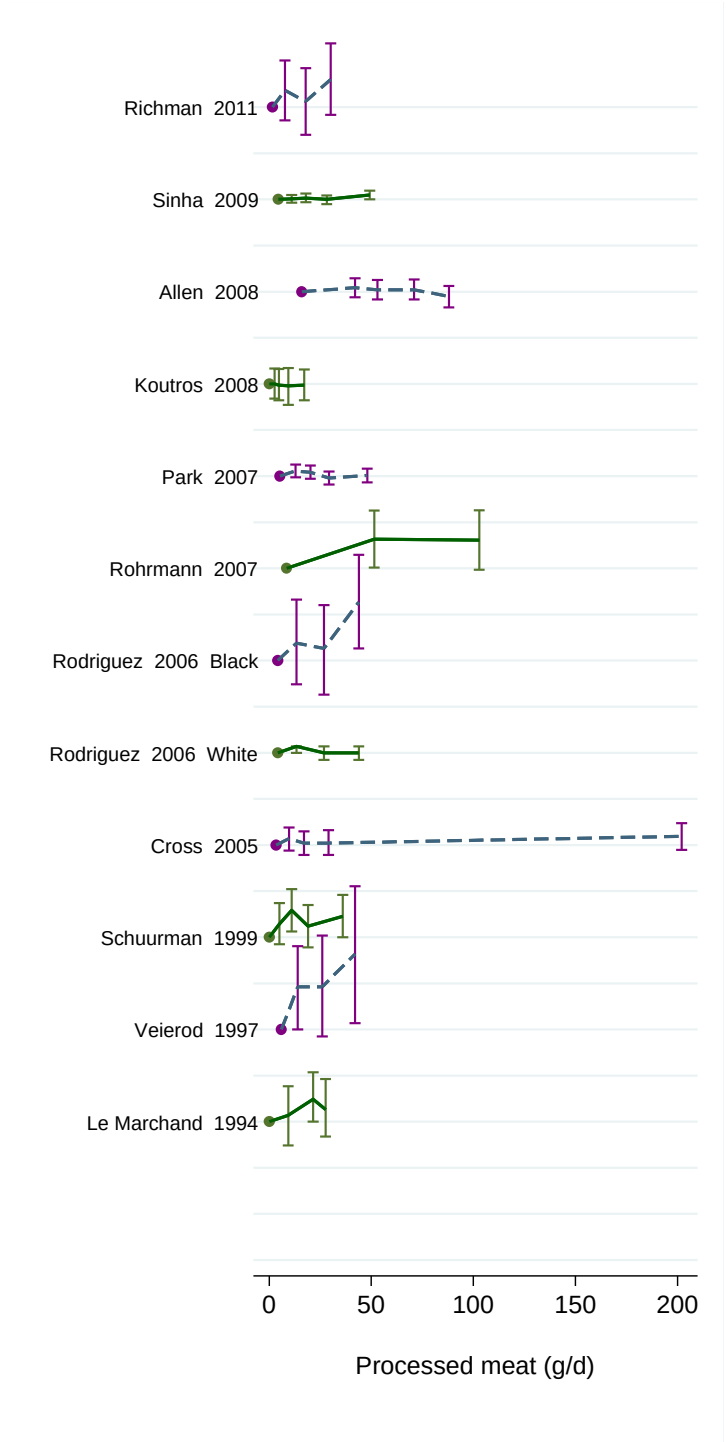
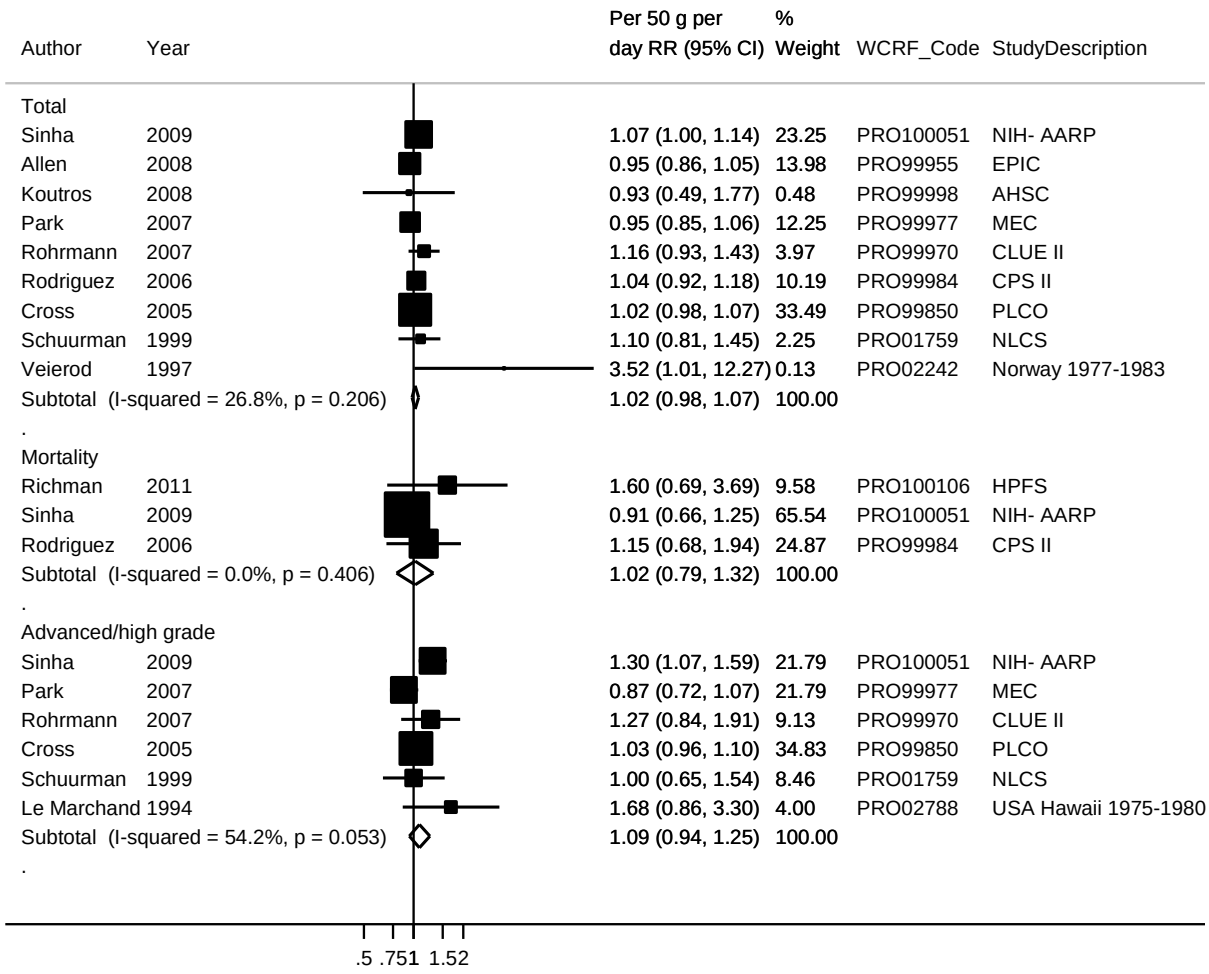


Figure 28 Dose-response meta-analysis of processed meat intake and prostate cancer, per 50 g/day, stratified by prostate cancer type



2.5.1.3 Red meat

Methods
Twenty two publications from fourteen cohorts were identified. Twelve publications (nine cohorts) were identified during the CUP. The CUP meta-analysis included ten cohort studies; eight of these were identified during the CUP. The dose-response results are presented for an increment of 100 g per day.

Two studies presented intake in g/1000 kcal/day. Exposure was rescaled to g/day using the average daily caloric intake of all participants in one study (Sinha, 2009) and in another study (Park, 2007a) that included multi-ethnic individuals, the conversion was calculated using weighted daily caloric intake of each ethnic group obtained from a previously published study of the MEC study (Kolonel, 2000).

For the studies included in the dose-response meta-analysis, eight included total prostate cancer (Agalliu, 2011; Sinha, 2009; Allen, 2008a; Koutros, 2008; Park, 2007a; Rohrmann, 2007; Rodriguez, 2006; Cross, 2005), seven studies reported invasive causes (Agalliu, 2011; Sinha, 2009; Koutros, 2008; Park, 2007; Rohrmann, 2007; Cross, 2005; Chan, 2000), and two study presented fatal cases (Richman, 2011; Sinha, 2009).

Stratified analysis by prostate cancer type was conducted combining advanced and high grade cancers into a subgroup.

Main results
The summary RR per 100 g/day was 0.99 (95% CI 0.94-1.05; $I^2 = 55.8\%$, $p_{heterogeneity} = 0.02$) for all studies combined. After stratification by cancer subtype, the RR per 100 g/day was 0.99 (95% CI 0.89-1.11; $I^2 = 36.3\%$, $p_{heterogeneity}=0.15$, n=7) for advanced/high grade and 1.19 (95% CI 0.88-1.59; $I^2 = 36.8\%$, $p_{heterogeneity}=0.21$, n=2) for fatal cases.

Heterogeneity
Overall, there was evidence of moderate heterogeneity, $I^2 = 55.8\%$, $p_{heterogeneity} =0.02$. The strongest positive association was observed in the Canadian Study of Diet, Lifestyle and Health Study (Agalliu, 2011). In this study, the largest confounders of the association between meat intake and prostate cancer were age, race, BMI, exercise and education. In a sensitivity analysis, the exclusion of this study did not substantially modified the results (RR for 100 g/d increase: 0.99 (95% CI 0.95-1.04) but the heterogeneity decreased ($I^2 = 46.9\%$; p = 0.05). There was no significant evidence of publication bias with Egger's test, p = 0.86.

Comparison with the Second Expert Report
In the 2005 SLR the meta-analysis on red meat and prostate cancer showed a summary RR of 0.98 (95% CI 0.97-1.00; $I^2 =12.1\%$; $p_{heterogeneity}=0.33$; n=7) for all prostate cancer types together and 1.00 (95% CI 0.97-1.03; $I^2 = 49.3\%$; $p_{heterogeneity}=0.12$; n=4) for advanced/high grade cases.

Published meta-analysis or pooled analysis
A meta-analysis of 9 cohorts (Alexander, 2010) the summary RR for an increment of 100 g/d of red meat was 1.00 (95% CI 0.95-1.05; $p_{heterogeneity} < 0.01$) for all prostate cancers and 0.97 (95% CI 0.91-1.02; $p_{heterogeneity}=0.57$; n = 5) for advanced prostate cancer. No pooled analysis was identified.

Table 31 Studies on red meat consumption identified in the CUP

Author, year	Country	Study name	Cases	Years of follow up	RR	LCI	UCI	Contrast
Wright, 2012	Finland	Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study	1929	21 years	0.89	0.78	1.01	Q4 vs. Q1
Agalliu, 2011	Canada	Canadian Study of Diet, Lifestyle and Health	661	7.7 years	1.44	1.06	1.95	3.1 oz/d vs 0.7 oz/d
Richman, 2011	USA	Health Professionals Follow-up study	199	14 years	1.07	0.66	1.75	≥ 8 serving/week vs. < 3 servings/week
Major, 2011	USA	NIH- AARP Diet and Cancer study	1089	~10 years	0.92	0.75	1.14	Q5 vs. Q1
Sinha, 2009	USA	NIH- AARP Diet and Cancer study	10313	9 years	1.12	1.04	1.21	66.1 g/1000 kcal/ vs. 11.6 g/1000 kcal/
Allen, 2008a	Europe	European Prospective Investigation into Cancer and Nutrition	2727	8.7 years	0.96	0.82	1.12	90 g/d vs. 28 g/d
Koutros, 2008	USA	Agricultural Health Study Cohort	668	~8.5 years	1.10	0.85	1.43	122.3 g/d vs. 23.2 g/d
Park, 2007a	USA	Multi-ethnic Cohort study	4404	8 years	0.97	0.87	1.07	37 g/1000 kcal/d vs. 5.5 g/1000 kcal/d
Cross, 2007	USA	NIH- AARP Diet and Cancer study	17235	6.8 years	1.01	0.96	1.07	62.7 1000 kcal/d vs. 9.8 g 1000 kcal/d
Rohrmann, 2007	USA	CLUE II cohort study	199	15 years	0.87	0.59	1.32	120.64 g/d vs. 70.14 g/d
Rodriguez,	USA	Cancer	85	9 years				≥ 423 g/week vs.

2006		Prevention Study II Nutrition Cohort	Black 5113 White		0.97	0.91	1.03	0- <137 g/week
Wu, 2006	USA	Health Professionals Follow-up study	3002	13 years	1.21	0.85	1.74	Q5 vs. Q1

Table 32 Overall evidence on red meat consumption and prostate cancer

	Summary of evidence
2005 SLR	Ten studies were identified during the 2005 SLR. Seven of them were included in the 2005 SLR meta-analysis. One of these studies (Chan, 2000) reported an inverse association between red meat intake and prostate cancer.
Continuous Update Project	Twelve additional publications (eight cohorts) reported on red meat and prostate cancer risks, eight of these were used in the meta-analysis. Two of these studies (Agalliu, 2011; Sinha, 2009) reported a significant positive association. No significant association was observed in the CUP meta-analysis.

Table 33 Summary of results of the dose response meta-analysis of red meat consumption and prostate cancer

Prostate cancer		
	2005 SLR	CUP
Studies (n)	7	10
Cases (n)	5236	25806
Increment unit used	Servings/week	Per 100 g/day
Overall RR (95%CI)	0.99 (0.98-1.00)	0.99 (0.94-1.05)
Heterogeneity (I^2, p-value)	12.1%, p= 0.33	55.8%, p=0.02
Stratified analysis		
Advanced/high grade cancer		
Overall RR (95%CI)	1.00 (0.97-1.03)	0.99 (0.89-1.11)
Heterogeneity (I^2,p-value)	49.3%, p = 0.12, n = 4	36.3%, p = 0.15, n = 7
Mortality		
Overall RR (95%CI)		1.19 (0.88-1.59)
Heterogeneity (I^2, p-value)		36.8%, p = 0.21, n = 2

Table 34 Inclusion/exclusion table for meta-analysis of red meat consumption and prostate cancer

WCRF code	Author	Year	Study design	Study name	Cancer outcome	2005 SLR	CUP dose-response meta-analysis	CUP HvL forest plot	Estimated values	Exclusion reasons
PRO100113	Wright	2012	Prospective Cohort	Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study	Incidence	No	No	No		No quantities reported, superseded by PRO01426 (Chan, 2000)
PRO100199	Agalliu	2011	Prospective Cohort	Canadian Study of Diet, Lifestyle and Health	Incidence	No	Yes	Yes	Person-years	
PRO100106	Richman	2011	Prospective Cohort	Health Professionals Follow-up study	Mortality	No	Yes	Yes	Person-years, mid-exposure values	
PRO100104	Major	2011	Prospective Cohort	NIH- AARP Diet and Cancer study	Incidence	No	No	No		Superseded by PRO100051 (Sinha, 2009), only African-American
PRO100051	Sinha	2009	Prospective Cohort	NIH- AARP Diet and Cancer study	Mortality	No	Yes	Yes	Person-years, mid-exposure values	
PRO99955	Allen	2008a	Prospective Cohort	European Prospective Investigation into Cancer and Nutrition	Incidence	No	Yes	Yes	Person-years	
PRO99998	Koutros	2008	Prospective Cohort	Agricultural Health Study Cohort	Incidence	No	Yes	Yes	Person-years	
PRO99977	Park	2007a	Prospective	Multi-ethnic	Incidence	No	Yes	Yes	Cases per category, person-	

			Cohort	Cohort study					years	
PRO99970	Rohrmann	2007	Prospective Cohort	CLUE II	Incidence	No	Yes	Yes	Mid-exposure values	
PRO100037	Cross	2007	Prospective Cohort	NIH- AARP Diet and Cancer study	Incidence	No	No	No		Superseded by PRO100051 (Sinha, 2009)
PRO99988	Wu	2006	Prospective Cohort	Health Professionals Follow-up study	Incidence	No	No	No		Superseded by PRO100106 (Richman, 2011)
PRO99984	Rodriguez	2006	Prospective Cohort	Cancer Prevention Study II Nutrition Cohort	Incidence	No	Yes	Yes	Person-years, mid-exposure values	
PRO99850	Cross	2005	Prospective Cohort	Prostate, Lung, Colorectal and Ovarian Cancer Screening Trial	Incidence	Yes	Yes	Yes	Mid-exposure values	
PRO10575	Platz	2004c	Nested case-control study	Health Professionals Follow-up study	Incidence	Yes	No	No		Superseded by PRO100106 (Richman, 2011)
PRO00442	Alavanja	2003	Prospective Cohort	Agricultural Health Study Cohort	Incidence	Yes	No	No		Superseded by PRO99998 (Koutros , 2008)
PRO01122	Michaud	2001	Prospective Cohort	Health Professionals Follow-up study	Mortality	Yes	No	No		Superseded by PRO100106 (Richman, 2011)
PRO01290	Lee	2001	Prospective Cohort	Harvard Alumni Health Study	Incidence	Yes	No	No		Only mean provided
PRO01426	Chan	2000	Prospective Cohort	Alpha-Tocopherol, Beta-Carotene Cancer	Incidence	Yes	Yes	Yes	Cases per category, person-years	

				Prevention Study						
PRO01759	Schuurman	1999b	Case-cohort	Netherlands Cohort study	Incidence	Yes	No	No		Other red meats (horsemeat, lamb and mutton)
PRO02814	Gann	1994	Nested case-control study	Physicians' Health Study	Incidence	Yes	No	No		No measurement units
PRO02875	Giovannucci	1993	Prospective Cohort	Health Professionals Follow-up study	Incidence	Yes	No	No		Superseded by PRO100106 (Richman, 2011)
PRO03129	Hsing	1990b	Prospective Cohort	Lutheran Brotherhood Cohort Study	Mortality	Yes	No	No		Used total meats

Figure 29 Highest versus lowest forest plot of red meat consumption and prostate cancer

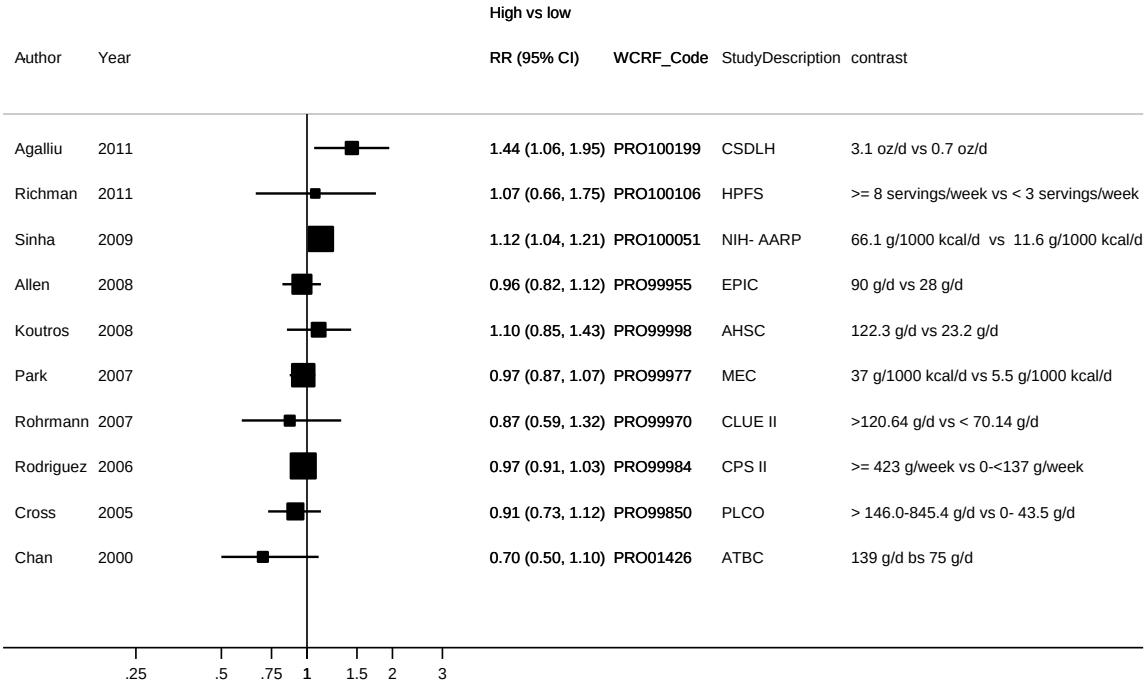


Figure 30 Dose-response meta-analysis of red meat intake and prostate cancer, per 100 g/day

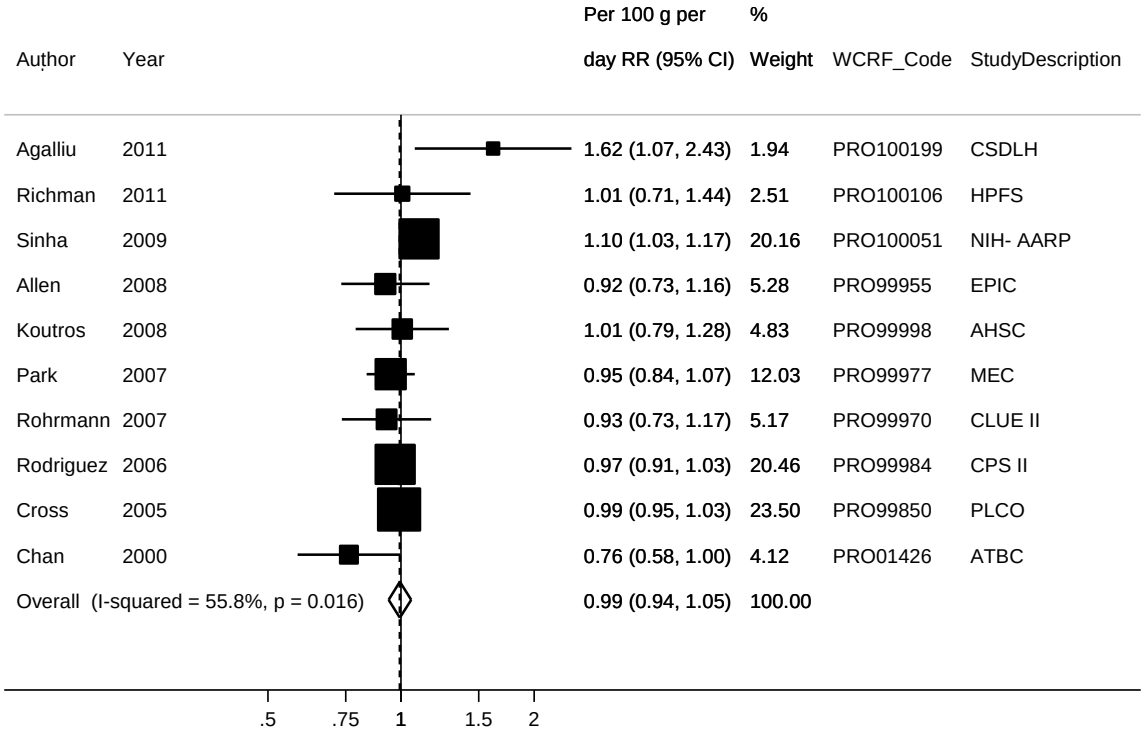
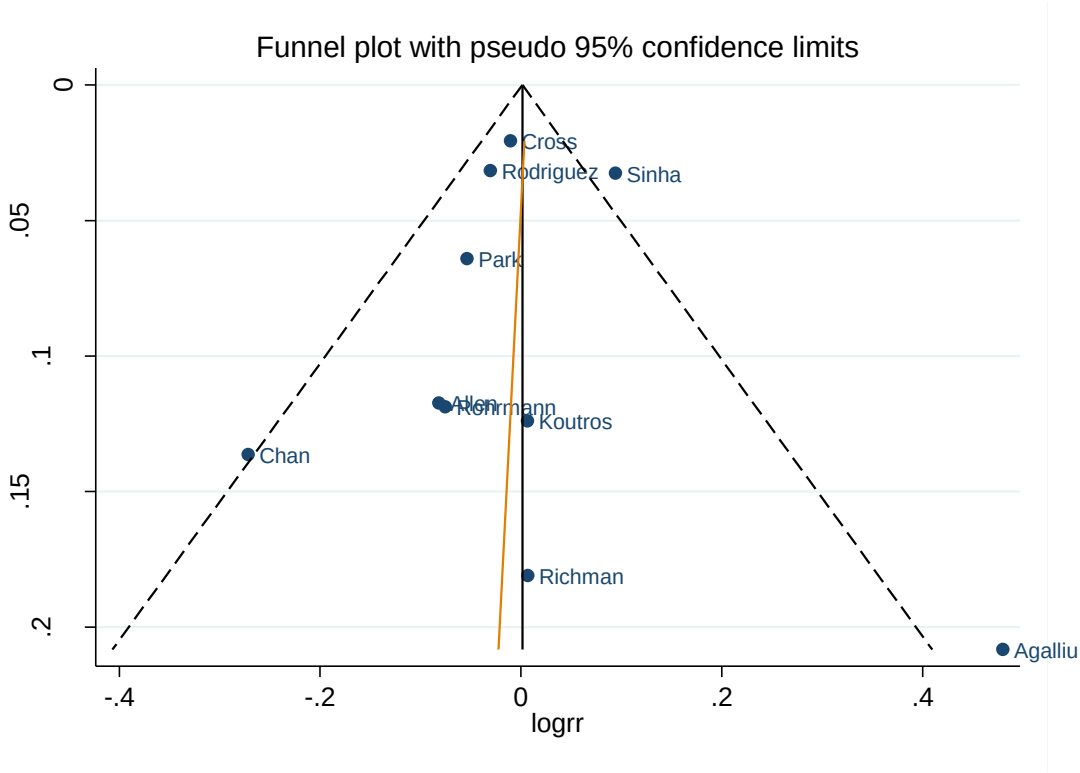


Figure 31 Funnel plot of red meat intake and prostate cancer



Egger's test p = 0.86

Figure 32 Dose-response graph of red meat and prostate cancer

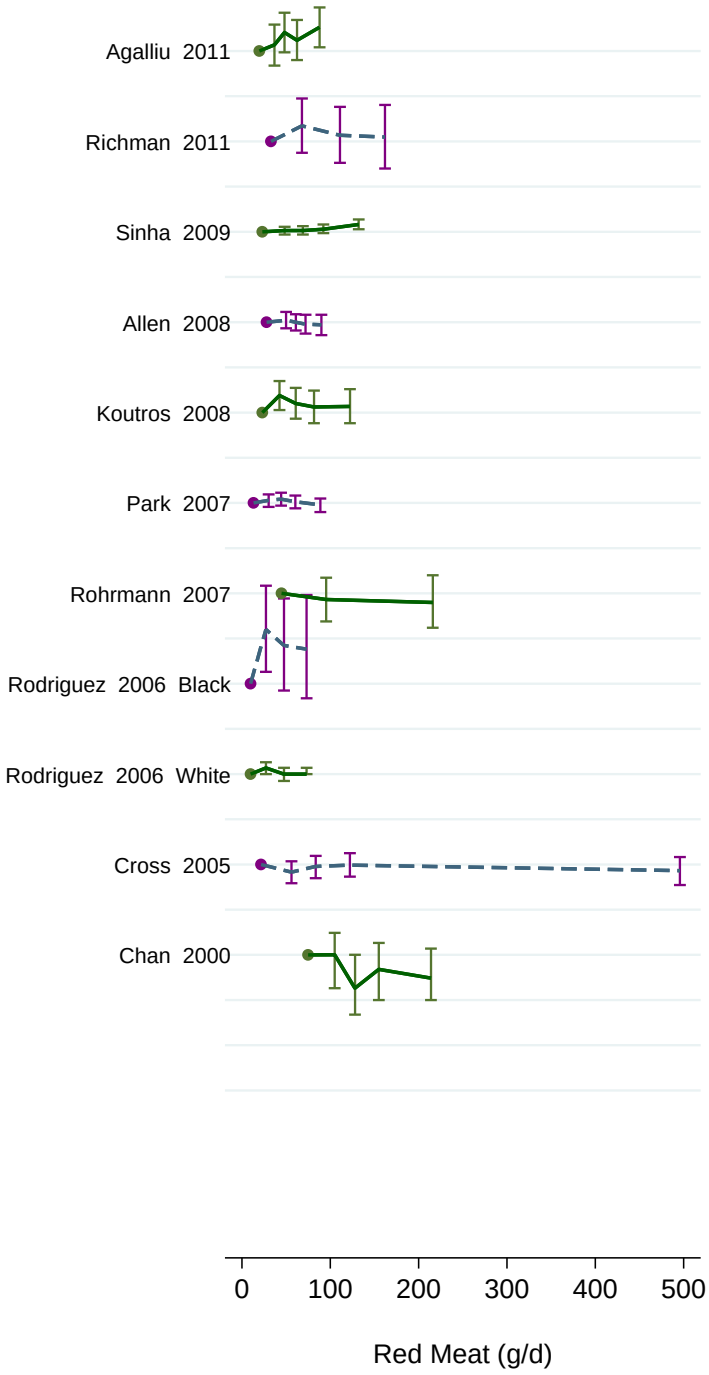
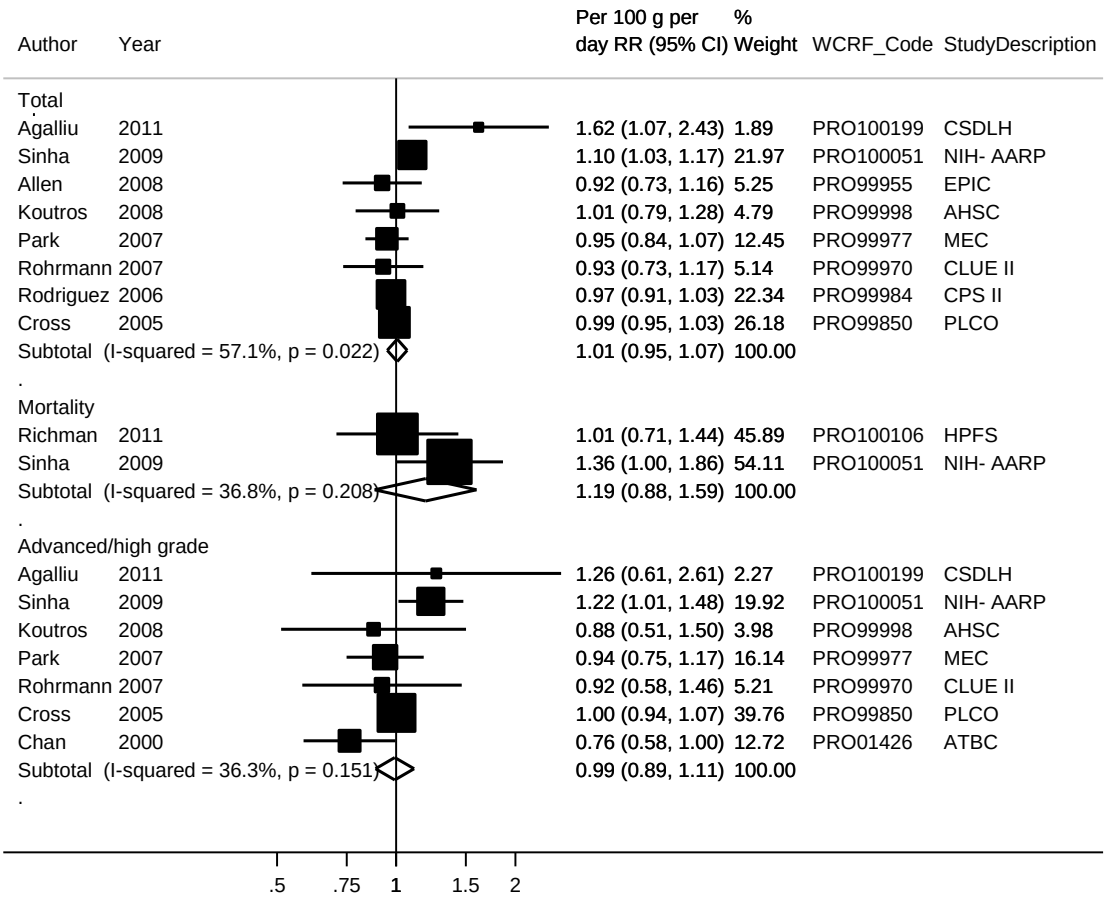


Figure 33 Dose-response meta-analysis of red meat intake and prostate cancer, per 100g/dayday, stratified by prostate cancer type



2.5.1.3.1 Beef

Methods

Ten publications from 10 cohort studies were identified, from which five publications were identified during the CUP. The CUP meta-analysis included seven studies; four of these were identified during the CUP. The dose-response results are presented for an increment of 100 gr per day.

One study presented beef intake in grams/1000 kcal/day (Park, 2007a) that was approximated to grams/day assuming as energy intake the mean caloric intake reported in a previous publication of the same study (Kolonel, 2000). In one study (Mills et al, 1989), the confidence interval in the manuscript for the highest vs lowest comparison appears to be wrong and for the dose-response meta-analysis, CIs were derived from number of cases and person/years.

A study on beef hamburgers was not included in the updated review (Michaud, 2001) although it was included in the "Beef group" in the 2005 SLR.

Six of the studies reported on total prostate cancers and high stage (III-IV), high grade (Gleason $\geq$ 7) or advanced/high grade and these were combined into a group of aggressive/advanced prostate cancers in stratified analysis (five studies).

Main results

The summary RR per 100 g/day was 1.17 (95% CI 0.89-1.53; I^2 = 49.3%, $p_{heterogeneity}$ = 0.07, n = 7) for all studies combined. The RR per 100 g/day for total prostate cancer (removing the study reporting on mortality) was 1.05 (95% CI 0.85-1.30; I^2 = 25.4%, $p_{heterogeneity}$ = 0.24; n = 6) and 1.04 (95% CI 0.70-1.53; I^2 = 40.6%, $p_{heterogeneity}$ = 0.15, n = 5) for advanced/high grade prostate cancer.

Heterogeneity

Overall, there was evidence of moderate heterogeneity, I^2 = 49.3%, $p_{heterogeneity}$ = 0.07, explained by extreme associations reported by the smaller studies. There was no significant evidence of publication bias with Egger's test, p = 0.28.

Comparison with the Second Expert Report

In the 2005 SLR the meta-analysis on beef and prostate cancer showed a summary RR of 1.05 (95% CI 0.99-1.12; I^2 = 8.47%; $p_{heterogeneity}$ = 0.350; n = 4) for all prostate cancer types together and 0.97 (95% CI 0.87-1.08; I^2 = 0%, $p_{heterogeneity}$ = 0.32, n = 2) when only including advanced cases.

Published meta-analysis or pooled analysis

No published meta-analysis or pooled analysis were identified.

Table 35 Studies on beef consumption identified in the CUP

Author, year	Country	Study name	Cases	Years of follow up	RR	LCI	UCI	Contrast
Wright, 2011	Finland	Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study	1929	21 years	0.97	0.85	1.10	Q4 vs. Q1
Koutros, 2008	USA	Agricultural Health Study Cohort	668	~8.5 years	1.03	0.71	1.49	63.0 g/d vs. 4.2 g/d
Park, 2007a	USA	Multi-ethnic Cohort study	4404 1278	8 years	0.98	0.88	1.08	27.7 g/1000 kcal/d vs. 3.7 g/1000 kcal/d
Iso, 2007	Japan	Japan Collaborative Cohort study	169	~12 years	1.61	0.85	3.07	3-4 times/week vs. never
Rohrmann, 2007	USA	CLUE II cohort study	199	15 years	1.16	0.74	1.81	≥ 5 times/week vs. ≤ 1 time/week

Table 36 Overall evidence on beef consumption and prostate cancer

	Summary of evidence
2005 SLR	Five studies were identified during the 2005 SLR. Four of them were included in the 2005 SLR meta-analysis. One of these studies (Le Marchand, 1994) reported significant positive association between beef intake and prostate cancer.
Continuous Update Project	Five additional studies reported on beef and prostate cancer risks, four of these were used in the meta-analysis. All showed no significant association. No significant association was observed in the CUP meta-analysis.

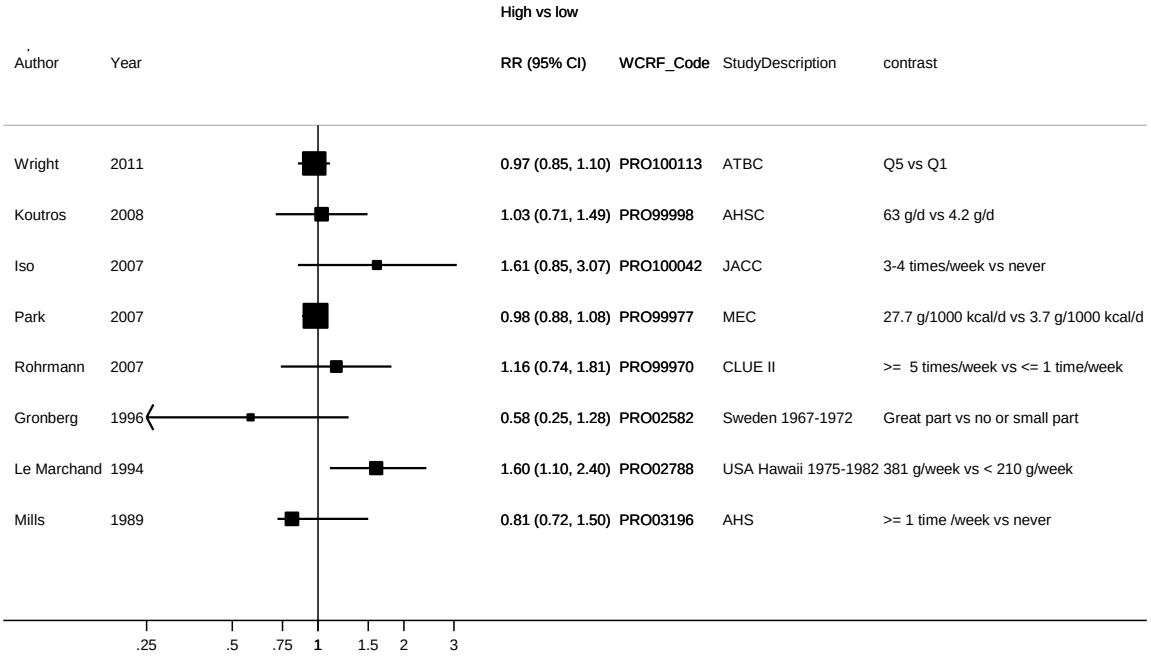
Table 37 Summary of results of the dose response meta-analysis of beef consumption and prostate cancer

Prostate cancer		
	2005 SLR	CUP
Studies (n)	4	7
Cases (n)	1269	6460
Increment unit used	Servings/week	Per 100 g/day
Overall RR (95% CI)	1.05 (0.99-1.12)	1.17 (0.89-1.53)
Heterogeneity (I^2, p-value)	8.47%, p = 0.35	49.3%, p = 0.07
Stratified analysis		
Advanced/high grade cancer		
Overall RR (95% CI)	0.97 (0.87-1.08)	1.04 (0.70-1.53)
Heterogeneity (I^2, p-value)	0%, p = 0.32, n = 2	40.6%, p = 0.15, n = 5

Table 38 Inclusion/exclusion table for meta-analysis of beef consumption and prostate cancer

WCRF code	Author	Year	Study design	Study name	Cancer outcome	2005 SLR	CUP dose-response meta-analysis	CUP HvL forest plot	Estimated values	Exclusion reasons
PRO100113	Wright	2012	Prospective Cohort	Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study	Incidence	No	No	Yes		No quantification of exposure
PRO99998	Koutros	2008	Prospective Cohort	Agricultural Health Study Cohort	Incidence	No	Yes	Yes	Person-years	
PRO100042	Iso	2007	Prospective Cohort	Japan Collaborative Cohort study	Mortality	No	Yes	Yes	Mid-exposure values	
PRO99977	Park	2007a	Prospective Cohort	Multi-ethnic Cohort study	Incidence	No	Yes	Yes	Cases per category, person-years g/1000 kcal/d rescaled to g/d	
PRO99970	Rohrmann	2007	Prospective Cohort	CLUE II	Incidence	No	Yes	Yes	Mid-exposure values	
PRO01122	Michaud	2001	Prospective Cohort	Health Professional Follow-up Study	Incidence	Yes	No	No		Reported on hamburgers
PRO01759	Schuurman	1999b	Case-cohort	Netherlands Cohort study	Incidence	Yes	Yes	Yes	Rescale continuous values	
PRO02582	Gronberg	1996	Nested Case-Control	Sweden 1967-1970	Incidence	Yes	No	Yes		No quantification of exposure
PRO02788	LeMarchand	1994	Prospective Cohort	USA Hawaii 1975-1980	Incidence	Yes	Yes	Yes	Mid-exposure values, person-years	
PRO03196	Mills	1989	Prospective Cohort	Adventist Health Study	Incidence	Yes	Yes	Yes	Mid-exposure values	

Figure 34 Highest versus lowest forest plot of beef consumption and prostate cancer



Note: Confidence interval in Mills et al, 1989 appears to be wrong in the manuscript

Figure 35 Dose-response meta-analysis of beef intake and prostate cancer (all studies), per 100 g/day

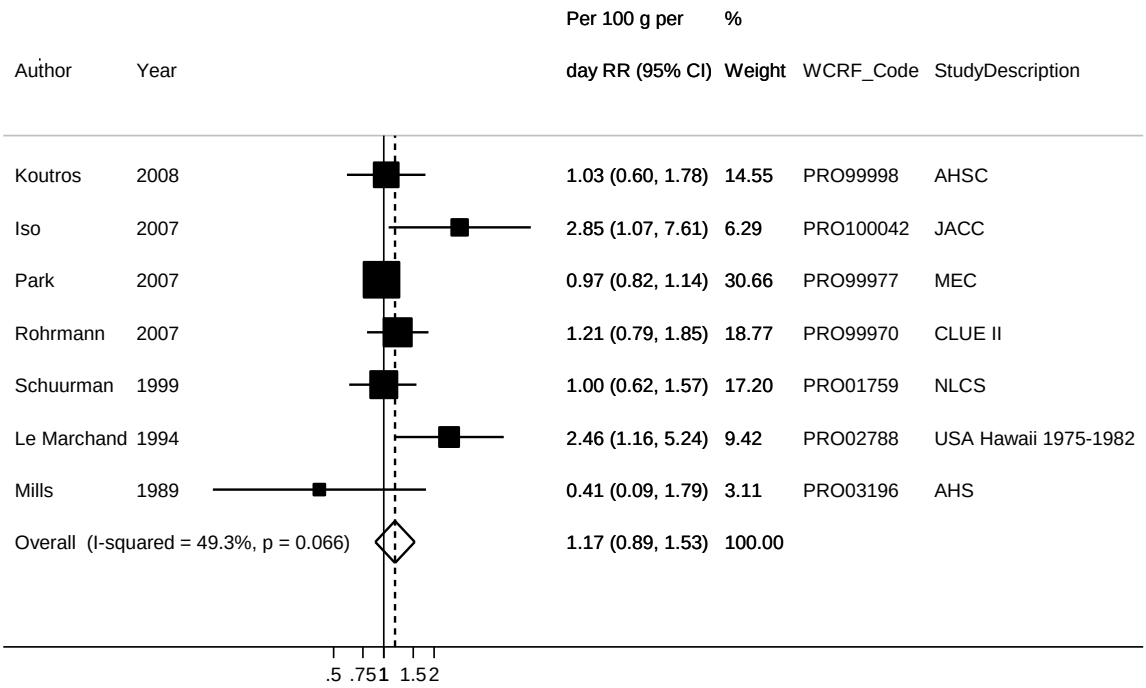
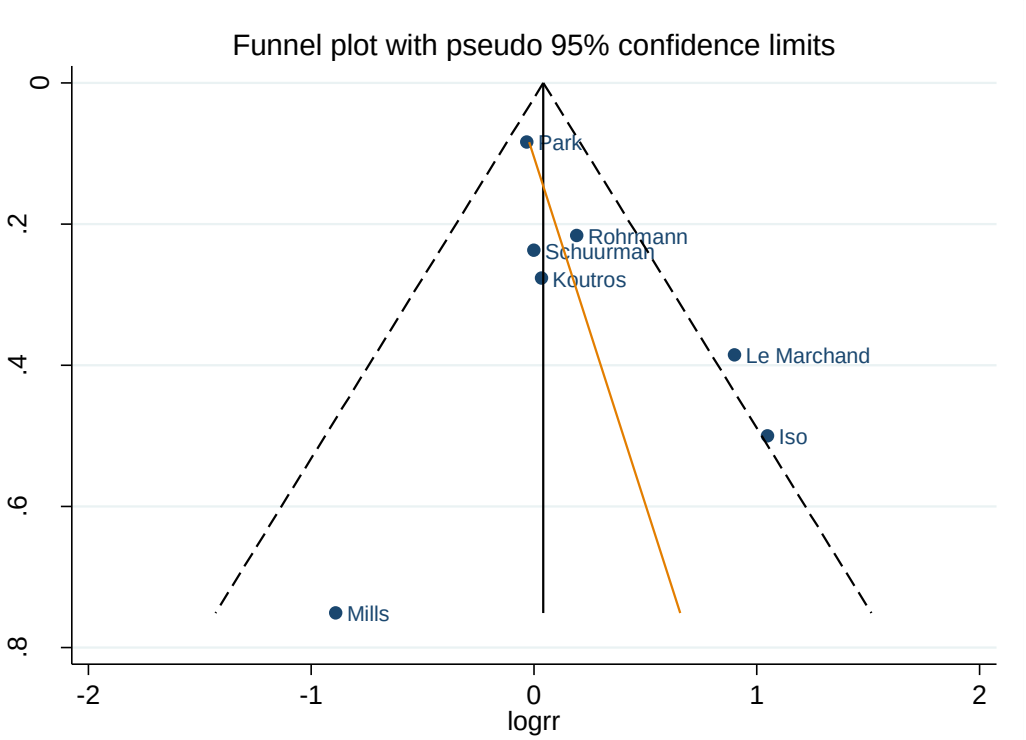


Figure 36 Funnel plot of beef intake and prostate cancer



Egger's test p = 0.28

Figure 37 Dose-response graph of beef and prostate cancer

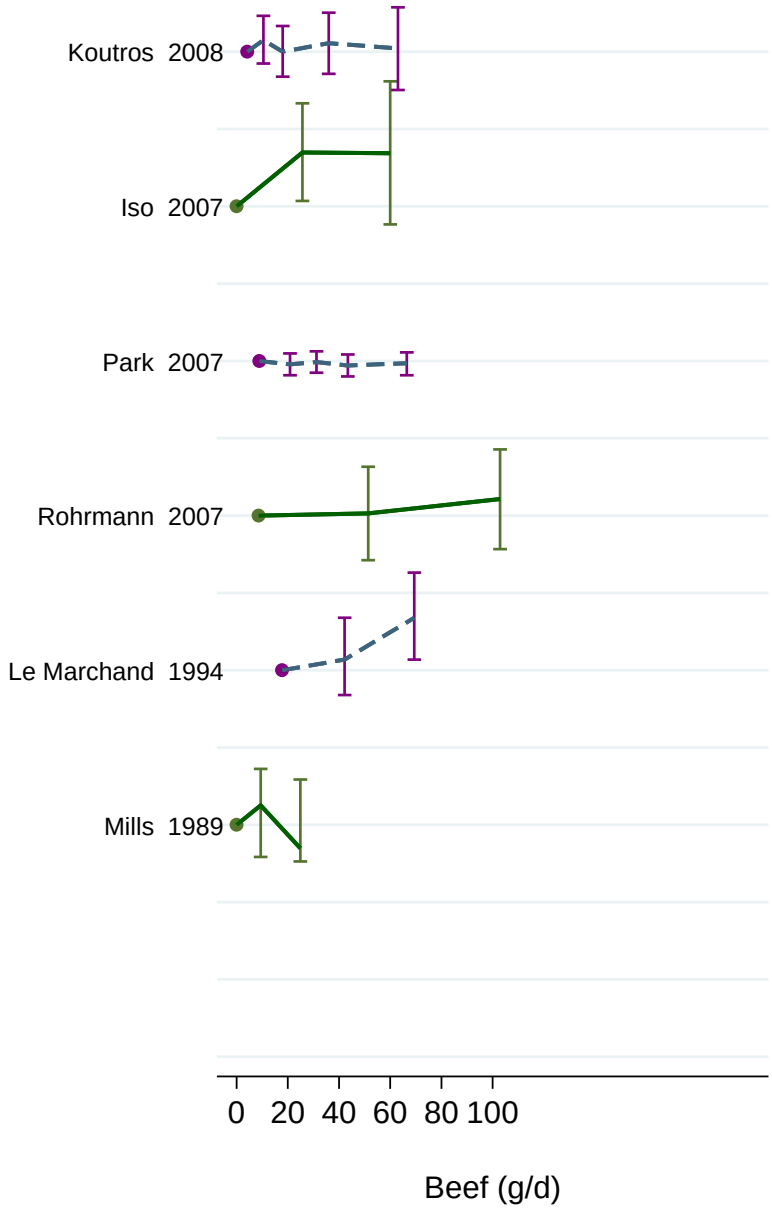
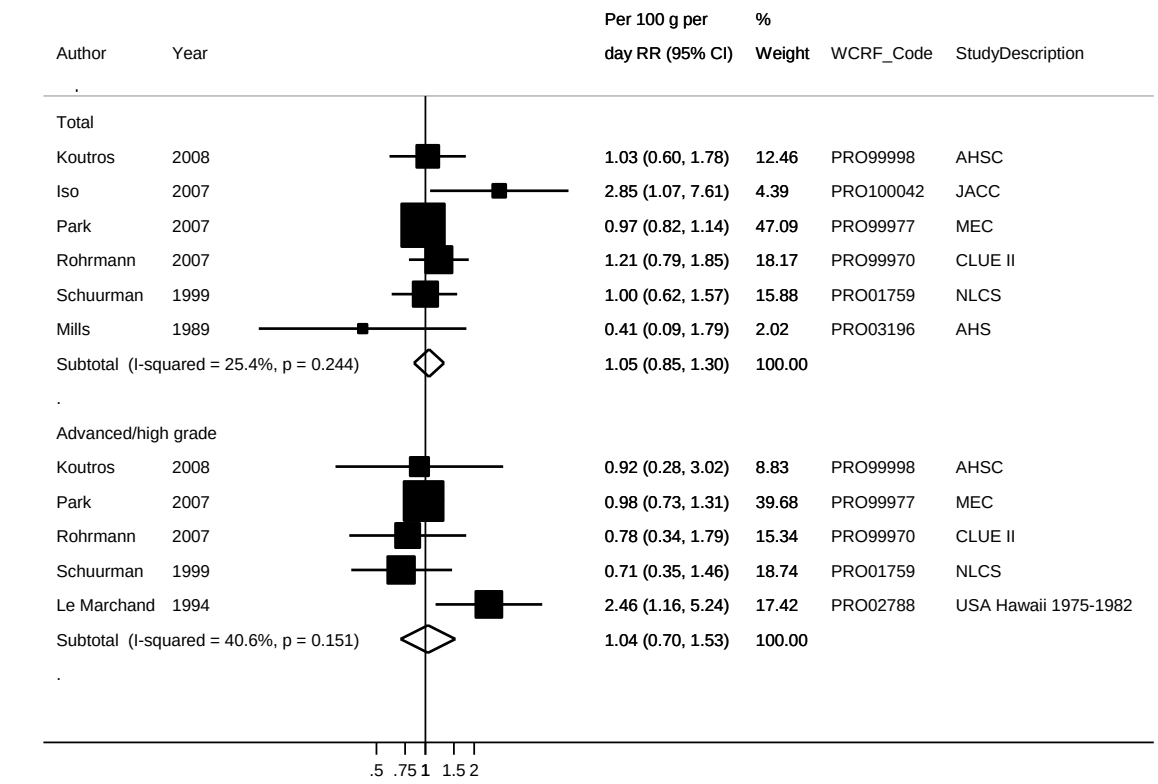


Figure 38 Dose-response meta-analysis of beef intake and prostate cancer, per 100 g/day, stratified by prostate cancer type



2.5.1.3.3 Pork

Methods
Eight publications from nine cohort studies were identified, from which three studies (publications) were identified during the CUP. The CUP meta-analysis included six studies; three of these were identified during the CUP. The dose-response results are presented for an increment of 50 g per day.

One study presented pork intake in grams/1000 kcal/day (Park, 2007a) that was approximated to grams/day assuming as energy intake the mean caloric intake reported in a previous publication of the same study (Kolonel, 2000).

Stratified analysis by prostate cancer type was conducted combining advanced and high grade cancers into a subgroup.

Main results
The summary RR per 50 g/day was 1.06 (95% CI 0.93-1.20; $I^2 = 0\%$; $p_{heterogeneity} = 0.47$; n = 6) for all studies combined. The RR per 50 g/day for prostate cancer (removing the studies reporting on mortality) was 1.06 (95% CI 0.80-1.41; $I^2 = 44.0\%$; $p_{heterogeneity} = 0.17$; n = 3) and 1.01 (95% CI 0.75-1.38; $I^2 = 26.2\%$; $p_{heterogeneity} = 0.26$; n = 4) for advanced/high grade prostate cancer.

Heterogeneity
Overall, there was evidence of low heterogeneity, $I^2 = 0\%$, $p_{heterogeneity} = 0.47$. There was no significant evidence of publication bias with Egger's test, p=0.28.

Comparison with the Second Expert Report
In the 2005 SLR the meta-analysis on pork and prostate cancer showed a summary RR of 1.05 (95% CI 1.00-1.12; $I^2 = 0\%$, $p_{heterogeneity} = 0.80$; n=3) for all prostate cancer types.

Published meta-analysis or pooled analysis
No published meta-analysis or pooled analysis was identified.

Table 39 Studies on pork consumption identified in the CUP

Author, year	Country	Study name	Cases	Years of follow up	RR	LCI	UCI	Contrast
Park, 2007a	USA	Multi-ethnic Cohort study	4404	8 years	0.97	0.88	1.08	10.2 g/1000 kcal/d vs. 0.5 g/1000 kcal/d
Iso, 2007	Japan	Japan Collaborative Cohort study	169	~12 years	1.16	0.66	2.03	3-4 times/week vs. never

Rohrmann, 2007	USA	CLUE II cohort study	199	15 years	1.17	0.77	1.78	≥ 1 times/week vs. never

Table 40 Overall evidence on pork consumption and prostate cancer

	Summary of evidence
2005 SLR	Six cohort studies (five publications) were identified during the 2005 SLR. Five of them were included in the 2005 SLR meta-analysis. One of these studies (Rodriguez, 2002) reported on two cohorts and showed a significant positive association between pork intake and prostate cancer.
Continuous Update Project	Three additional studies reported on pork and prostate cancer risk, all were used in the meta-analysis. All showed no significant association. No significant association was observed in the CUP meta-analysis.

Table 41 Summary of results of the dose response meta-analysis of pork consumption and prostate cancer

Prostate cancer		
	2005 SLR	CUP
Studies (n)	3	6
Cases (n)	1036	5808
Increment unit used	Servings/week	Per 50 g/day
Overall RR (95%CI)	1.05 (1.00-1.12)	1.06 (0.93-1.20)
Heterogeneity (I^2,p-value)	0%, p = 0.80	0%, p = 0.47
Stratified analysis		
Advanced/High grade cancer		
Overall RR (95%CI)		1.01 (0.75-1.38)
Heterogeneity (I^2,p-value)		26.2%, p = 0.26, n = 4

Table 42 Inclusion/exclusion table for meta-analysis of pork consumption and prostate cancer

WCRF code	Author	Year	Study design	Study name	Cancer outcome	2005 SLR	CUP dose-response meta-analysis	CUP HvL forest plot	Estimated values	Exclusion reasons
PRO100042	Iso	2007	Prospective Cohort	Japan Collaborative Cohort study	Mortality	No	Yes	Yes	Mid-exposure values	
PRO99977	Park	2007a	Prospective Cohort	Multi-ethnic Cohort study	Incidence	No	Yes	Yes	Cases per category, person-years g/1000 kcal/d rescaled to g/d	
PRO99970	Rohrmann	2007	Prospective Cohort	CLUE II	Incidence	No	Yes	Yes	Mid-exposure values	
PRO97367	Allen	2004	Prospective Cohort	Life Span Study	Incidence	Yes	Yes	Yes	Mid-exposure values	
PRO00881	Rodriguez	2002	Prospective Cohort	CPS I	Incidence	Yes	No	Yes		Highest versus lowest only
PRO00881	Rodriguez	2002	Prospective Cohort	CPS ll	Incidence	Yes	No	Yes		Highest versus lowest only
PRO01759	Schuurman	1999b	Case-cohort	Netherlands Cohort study	Incidence	Yes	Yes	Yes	Rescale continuous values	
PRO02582	Gronberg	1996	Nested Case-Control	Sweden 1967-1970	Incidence	Yes	No	Yes		No quantification of exposure
PRO02788	LeMarchand	1994	Prospective Cohort	USA Hawaii 1975-1980	Incidence	Yes	Yes	Yes	Mid-exposure values, person-years	

Figure 39 Highest versus lowest forest plot of pork consumption and prostate cancer

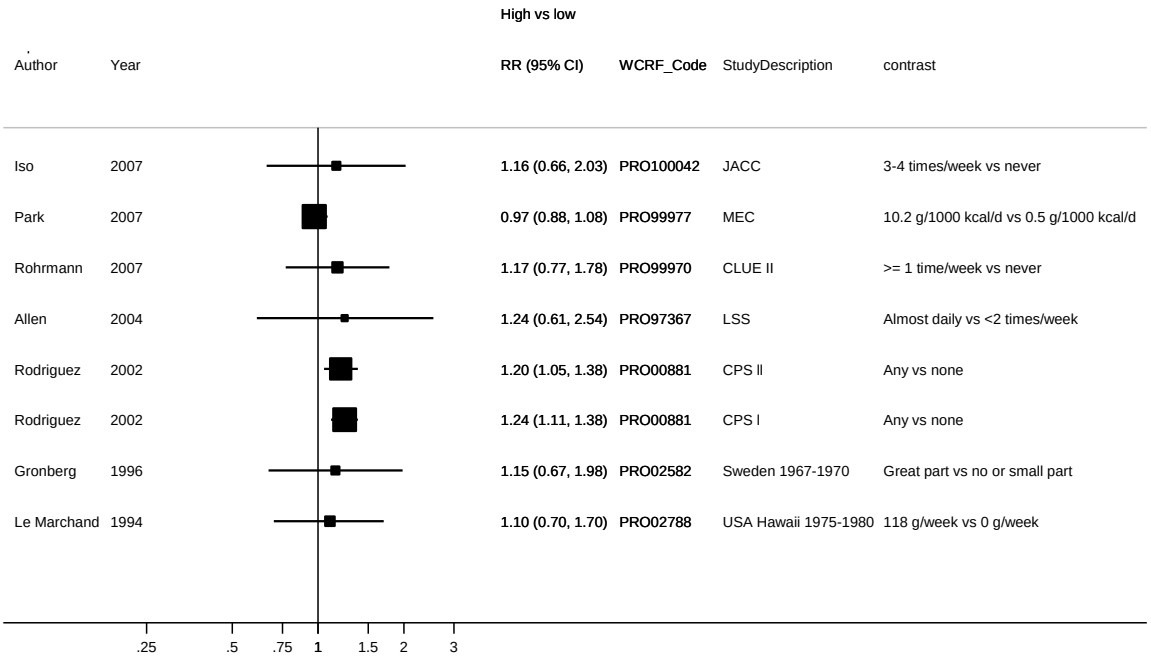


Figure 40 Dose-response meta-analysis of pork intake and prostate cancer, per 50 g/day

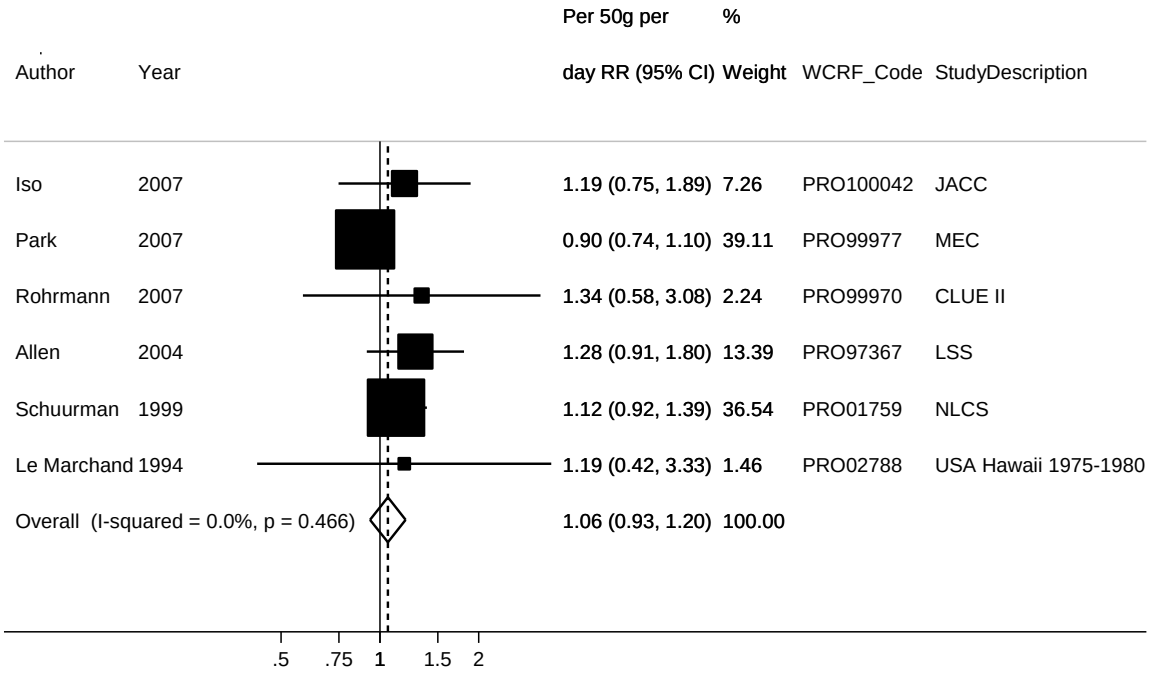
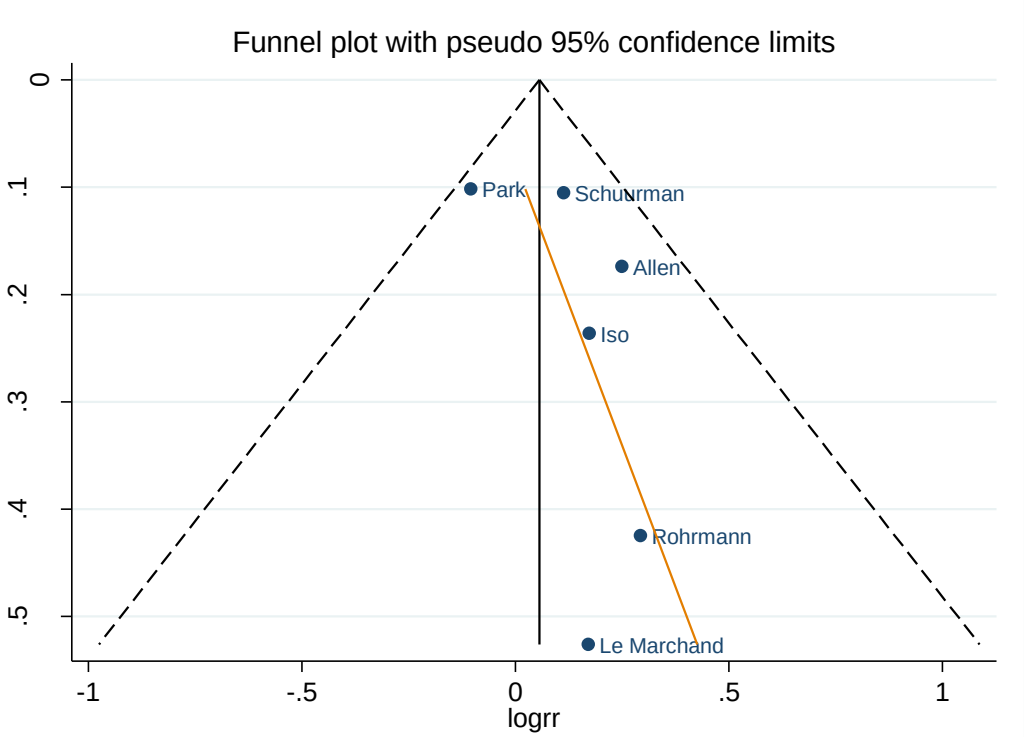


Figure 41 Funnel plot of pork intake and prostate cancer



Egger's test p = 0.28

Figure 42 Dose-response graph of pork and prostate cancer

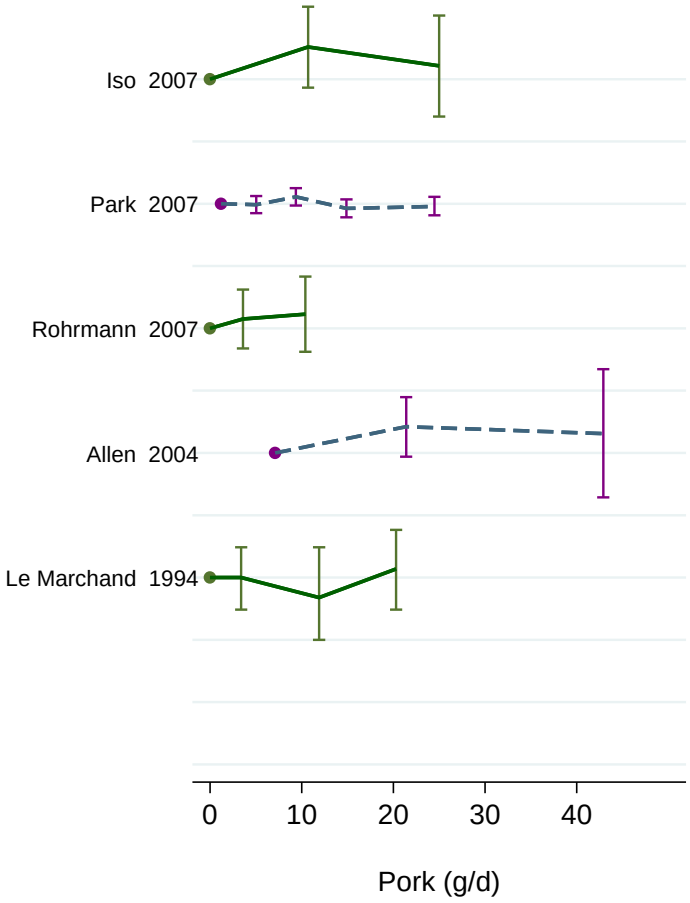
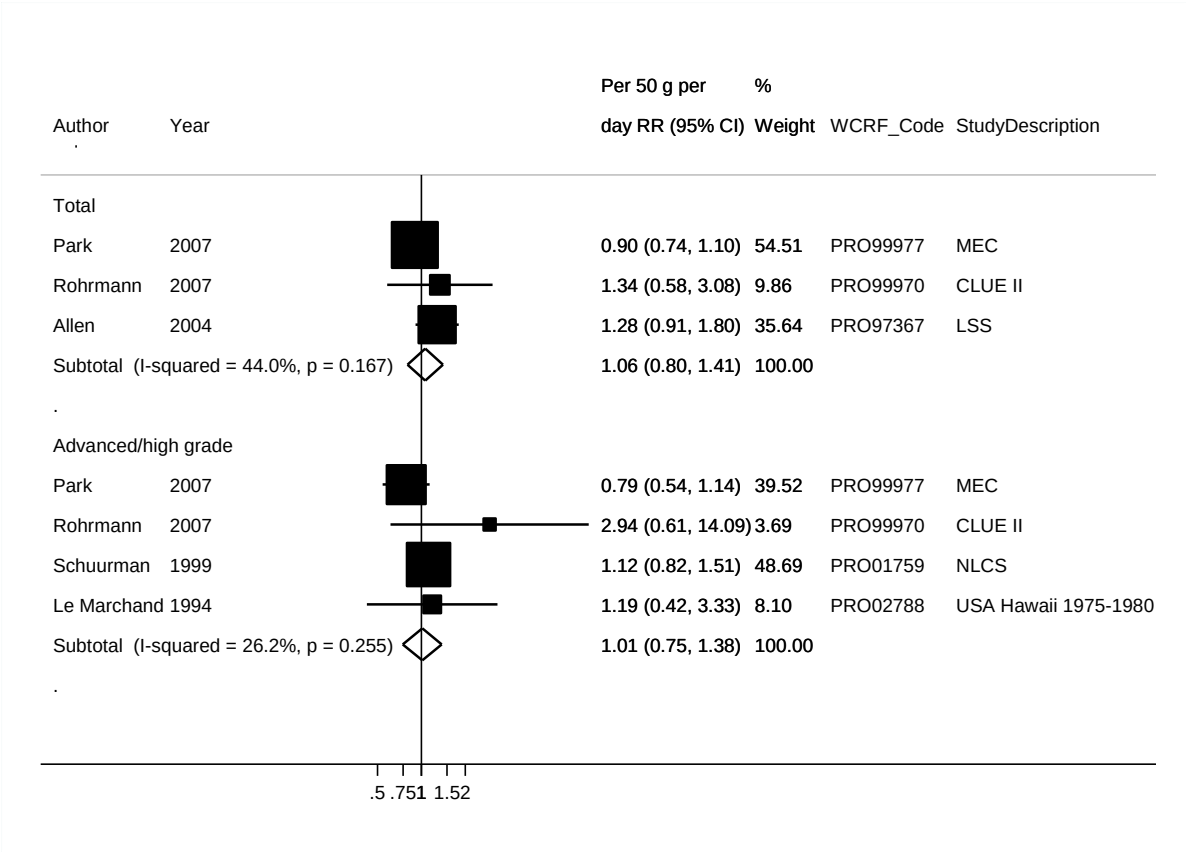


Figure 43 Dose-response meta-analysis of pork intake and prostate cancer, per 50 g/day, stratified by prostate cancer type



2.5.1.4 Poultry

Methods
Fifteen publications from 13 cohorts were identified. Eight publications (eight cohorts) were identified during the CUP. The CUP meta-analysis included 12 studies; seven of these were identified during the CUP.

Eight studies investigated poultry intake and five studies investigated chicken intake. All the studies are included under "Poultry" in this review.

In one study (Park, 2007) in a multi-ethnic population, the conversion to g/d from g/1000 kcal/day of poultry intake was calculated using the weighted daily caloric intake obtained from a previously published study of the MEC study (Kolonel, 2000).

For the studies included in the dose-response meta-analysis, eight included total prostate cancer (Allen, 2008a; Koutros, 2008; Park, 2007a; Rohrmann, 2007; Rodriguez, 2006; Allen, 2004; Schuurman, 1999; Mills, 1989), five studies reported in advanced/high grade cases (Koutros, 2008; Park, 2007; Rohrmann, 2007; Schuurman, 1999; Le Marchand, 1994) and four studies reported in fatal cases (Richman 2011; Iso, 2007; Rodriguez, 2006; Hsing, 1990).

Advanced and high grade cancers were combined in an advanced/high grade subgroup for stratified analyses.

Main results
The summary RR per 100 g/day was 1.01(95% CI 0.93-1.10; $I^2 = 0\%$; $p_{heterogeneity} = 0.46$; n = 12) for all studies combined. After stratification by cancer subtype, the RR per 100 g/day was 1.12 (95% CI 0.92-1.36; $I^2 = 0\%$; $p_{heterogeneity} = 0.73$; n = 5) for advanced/high grade and 0.87 (95% CI 0.41-1.84; $I^2 = 48.3\%$; $p_{heterogeneity} = 0.12$; n = 4) for fatal cancers.

Heterogeneity
Overall, there was evidence of moderate heterogeneity, $I^2 = 0\%$, $p_{heterogeneity} = 0.46$. There was no significant evidence of publication bias with Egger's test, p = 0.19.

Comparison with the Second Expert Report
In the 2005 SLR the meta-analysis on poultry and prostate cancer showed a summary RR of 1.15 (95% CI 0.92-1.45; $I^2 = 0\%$, $p_{heterogeneity} = 0.45$; n = 2). For chicken the RRs were 0.95 (95% CI 0.90-1.02; $I^2=0\%$, $p_{heterogeneity} = 0.48$, n = 4) for all prostate cancer and 0.96 (95% CI 0.85-1.08; $I^2 = 26.9\%$, $p_{heterogeneity} = 0.25$; n = 3) for advanced/aggressive prostate cancers.

Published meta-analysis or pooled analysis
No previous meta-analysis or pooled analysis was identified.

Table 43 Studies on poultry consumption identified in the CUP

Author, year	Country	Study name	Cases	Years of follow up	RR	LCI	UCI	Contrast
Daniel, 2011	USA	NIH-AARP Diet and Health Study	23453	9.1	1.05	1.00	1.09	Q5 vs. Q1
Richman, 2011	USA	Health Professionals Follow-up study	199	14 years	1.15	0.74	1.78	≥ 3.5 serving/week vs. < 1.5 servings/week
Allen, 2008a	Europe	European Prospective Investigation into Cancer and Nutrition	2727	8.7 years	1.12	0.98	1.27	32 g/d vs. 9 g/d
Koutros, 2008	USA	Agricultural Health Study Cohort	668	~8.5 years	1.04	0.78	1.39	42.0 g/d vs. 2.8 g/d
Park, 2007a	USA	Multi-ethnic Cohort study	4404	8 years	1.01	0.92	1.12	39.9 g/1000 kcal/d vs. 5.9 g/1000 kcal/d
Rohrmann, 2007	USA	CLUE II cohort study	199	15 years	1.14	0.77	1.70	≥ 5 times/week vs. < 1 time/week
Iso, 2007	Japan	Japan Collaborative Cohort study	169	~12 years	1.33	0.81	2.21	3-4 times/week vs. never
Rodriguez, 2006	USA	Cancer Prevention Study II Nutrition Cohort	85 Black	9 years	0.7	0.40	1.3	≥279 g/week vs. 0- <91 g/week
			5028 White		1.0	0.9	1.1	

Table 44 Overall evidence on poultry consumption and prostate cancer

	Summary of evidence
2005 SLR	Seven publications (6 studies) were identified during the 2005 SLR. None of these studies reported a significant association.
Continuous Update Project	Eight studies (one update) were identified; seven of these were used in the meta-analysis. No significant associations were observed in the studies and in the CUP meta-analysis.

Table 45 Summary of results of the dose response meta-analysis of poultry consumption and prostate cancer

Prostate cancer		
	2005 SLR	CUP
Studies (n)	2	12
Cases (n)	378	14844
Increment unit used	Servings/week	Per 100 g/day
Overall RR (95% CI)	1.15 (0.93-1.45)	1.01 (0.93-1.10)
Heterogeneity (I^2, p-value)	0%, p = 0.45	0%, p = 0.46
Stratified analysis		
Advanced/high grade cancer		
Overall RR (95% CI)		1.12 (0.92-1.36)
Heterogeneity (I^2,p-value)		0%, p = 0.73, n = 5
Mortality		
Overall RR (95% CI)		0.87 (0.41-1.84)
Heterogeneity (I^2, p-value)		48.3%, p = 0.12, n = 4

Table 46 Inclusion/exclusion table for meta-analysis of poultry consumption and prostate cancer

WCRF code	Author	Year	Study design	Study name	Cancer outcome	2005 SLR	CUP dose-response meta-analysis	CUP HvL forest plot	Estimated values	Exclusion reasons
PRO100126	Daniel	2011	Prospective Cohort	NIH-AARP Diet and Health Study	Incidence	No	No	Yes		No intake levels
PRO100106	Richman	2011	Prospective Cohort	Health Professionals Follow-up study	Mortality	No	Yes	Yes	Person-years, mid-exposure values	
PRO99955	Allen	2008a	Prospective Cohort	European Prospective Investigation into Cancer and Nutrition	Incidence	No	Yes	Yes	Person-years	
PRO99998	Koutros	2008	Prospective Cohort	Agricultural Health Study Cohort	Incidence	No	Yes	Yes	Person-years	
PRO99977	Park	2007a	Prospective Cohort	Multi-ethnic Cohort study	Incidence	No	Yes	Yes	Cases per category, person-years	
PRO99970	Rohrmann	2007	Prospective Cohort	CLUE II	Incidence	No	Yes	Yes	Mid-exposure values	
PRO100042	Iso	2007	Prospective Cohort	Japan Collaborative Cohort study for Evaluation of Cancer Risk	Mortality	No	Yes	Yes	Mid-exposure values	
PRO99984	Rodriguez	2006	Prospective Cohort	Cancer Prevention Study II Nutrition Cohort	Incidence	No	Yes	Yes	Person-years, mid-exposure values	
PRO97367	Allen	2004	Prospective Cohort	Life Spam Study	Incidence	Yes	Yes	Yes	Mid-exposure values	
PRO01122	Michaud	2001	Prospective Cohort	Health Professionals Follow-up study	Mortality	Yes	No	No		Superseded by PRO100106 (Richman, 2011)

PRO01759	Schuurman	1999b	Case-cohort	Netherlands Cohort study	Incidence	Yes	Yes	Yes	Rescale continuous values	
PRO02788	Le Marchand	1994	Prospective Cohort	USA Hawaii 1975-1980 Cohort study	Incidence	Yes	Yes	Yes	Mid-exposure values	
PRO02875	Giovannucci	1993	Prospective Cohort	Health Professionals Follow-up study	Incidence	Yes	No	No		Superseded by PRO100106 (Richman, 2011)
PRO03129	Hsing	1990b	Prospective Cohort	Lutheran Brotherhood Cohort Study	Mortality	Yes	Yes	Yes	Mid-exposure values, person-years	
PRO03196	Mills	1989	Prospective Cohort	Adventist Health Study	Incidence	Yes	Yes	Yes	Mid-exposure values	

Figure 44 Highest versus lowest forest plot of poultry consumption and prostate cancer

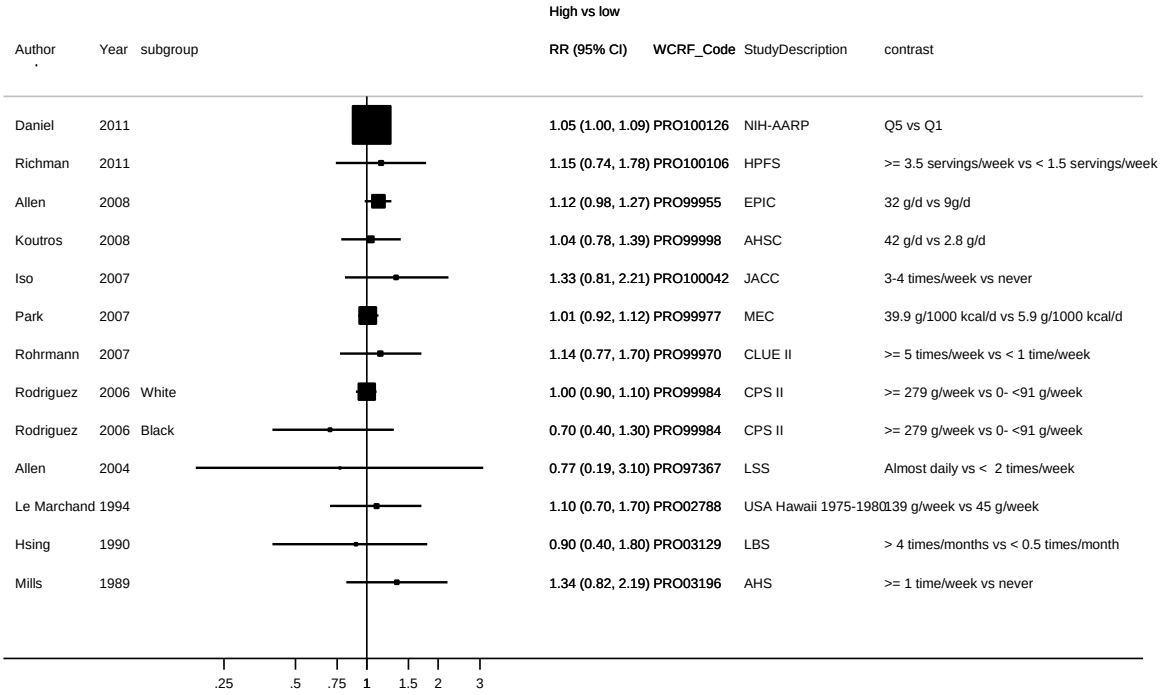


Figure 45 Dose-response meta-analysis of poultry intake and prostate cancer, per 100 g/day

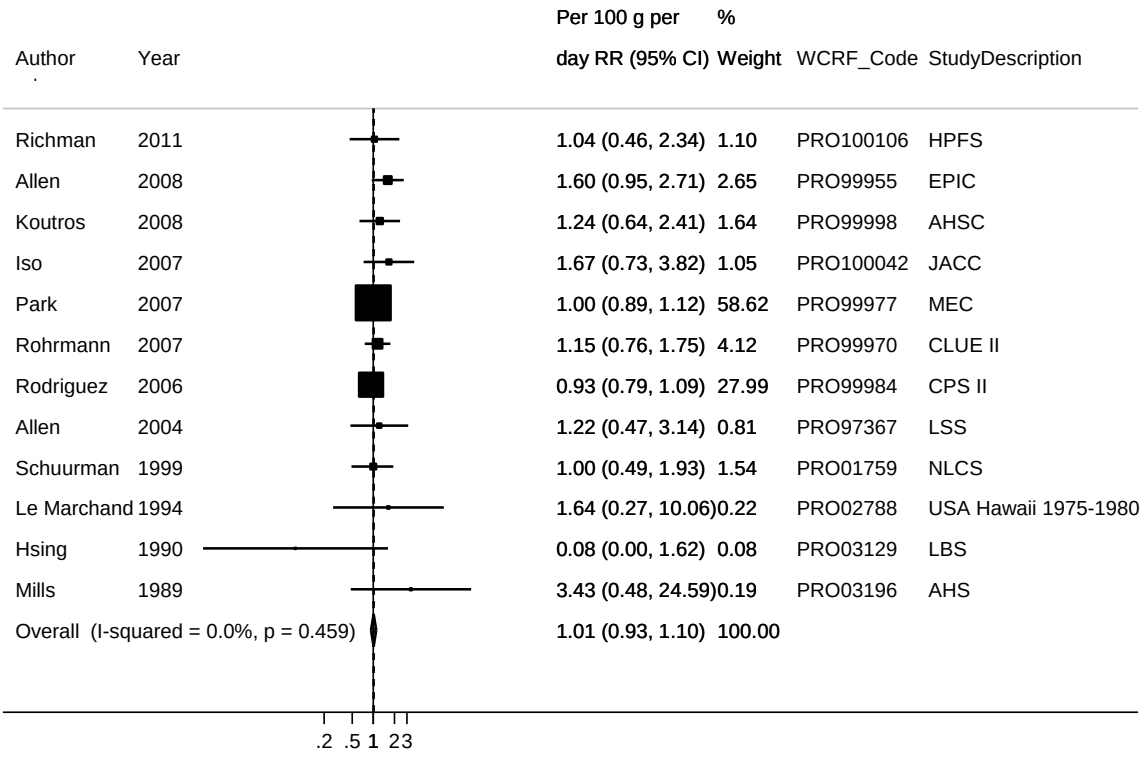
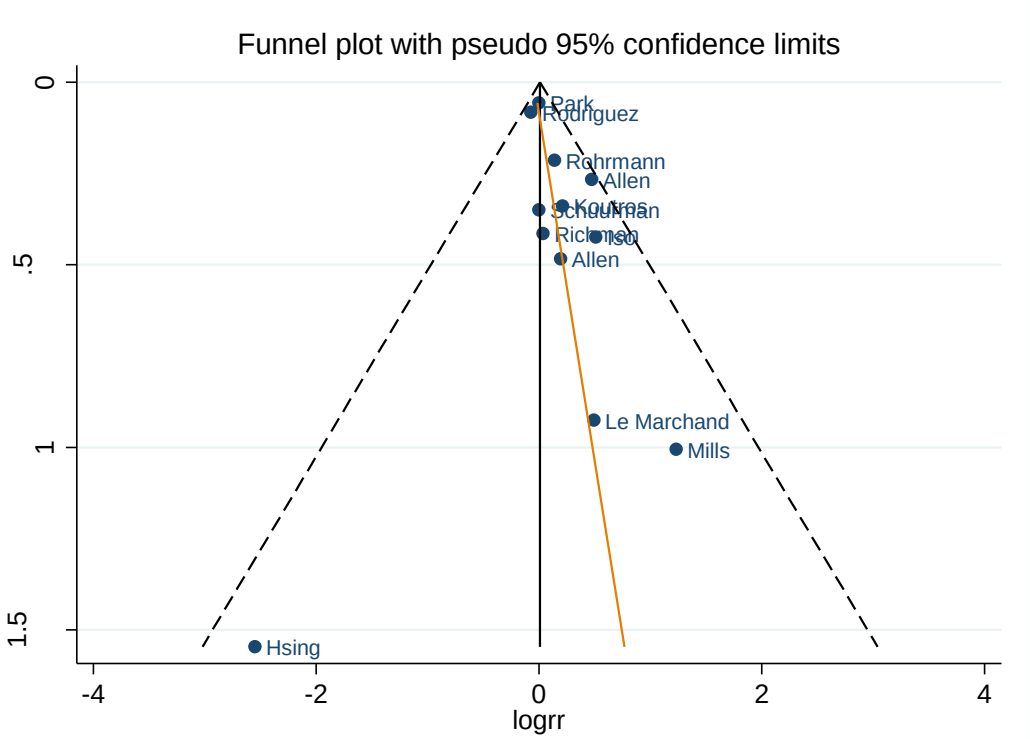


Figure 46 Funnel plot of poultry intake and prostate cancer



Egger's test p = 0.19

Figure 47 Dose-response graph of poultry and prostate cancer

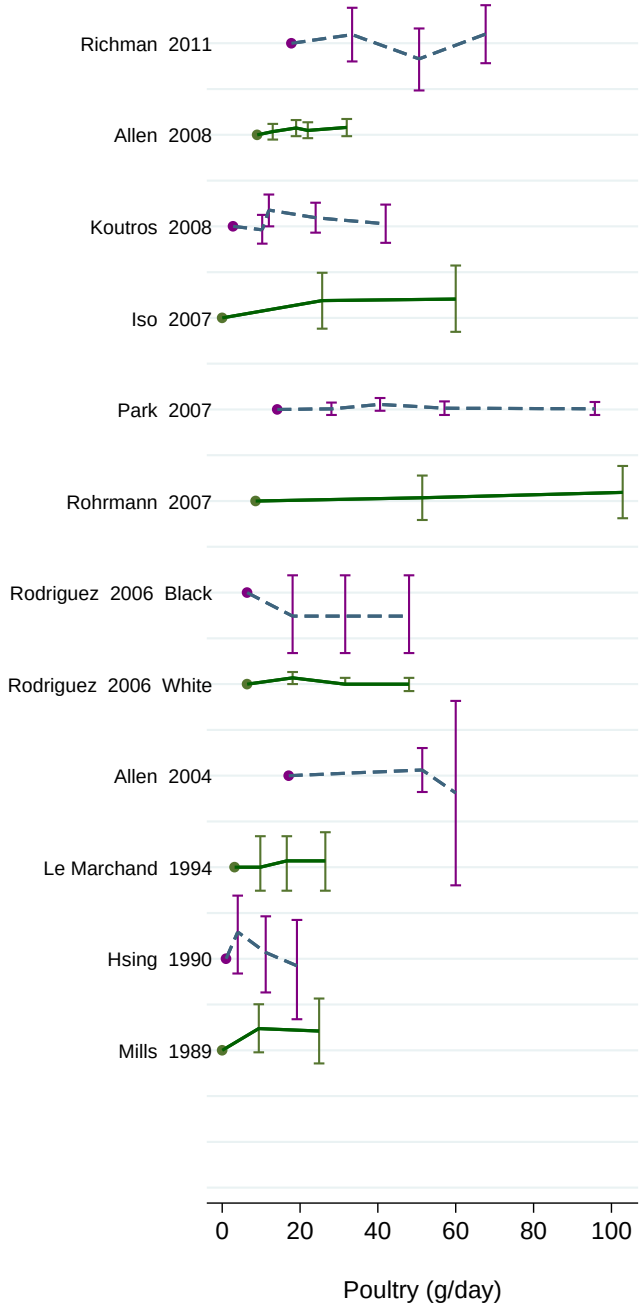
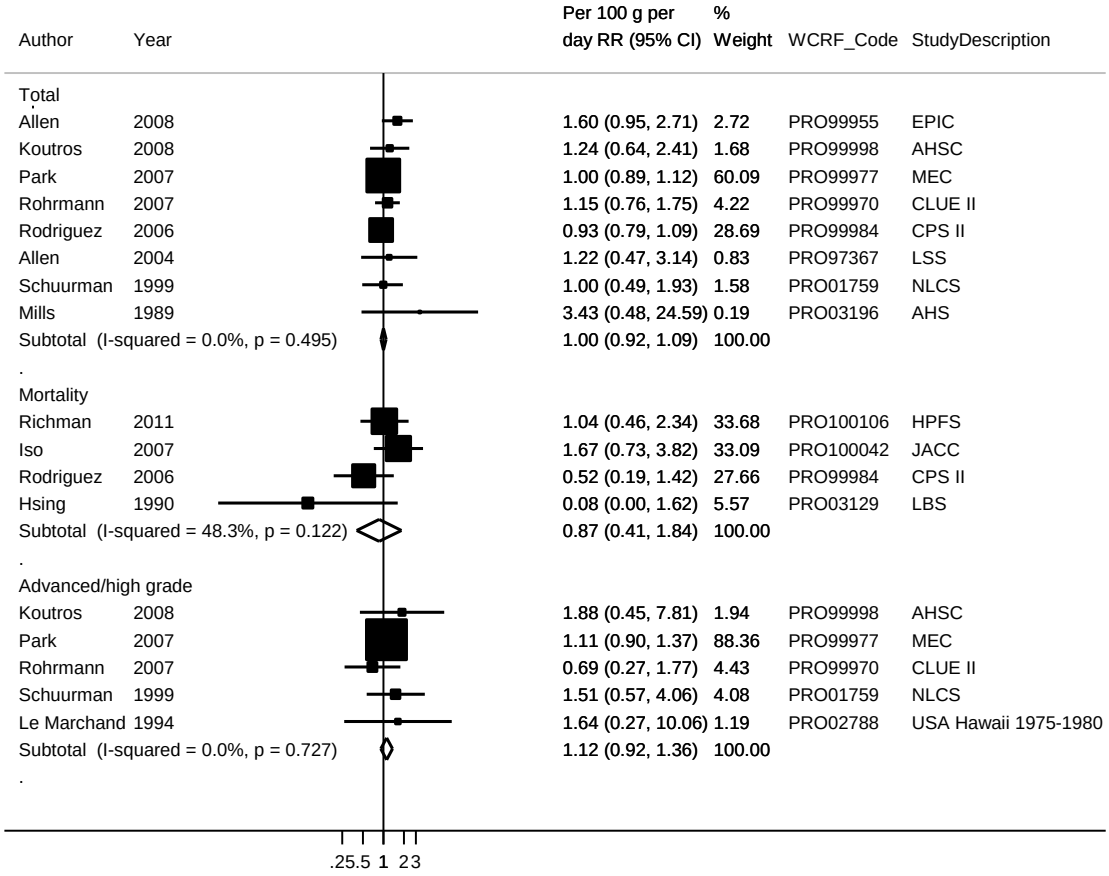


Figure 48 Dose-response meta-analysis of poultry intake and prostate cancer, per 100 g/day, stratified by prostate cancer type



2.5.2 Fish

Methods

Twenty one publications from 19 cohorts were identified. Eight publications (eight cohorts) were identified during the CUP. The CUP meta-analysis included 13 cohort studies; six of which were identified during the CUP. The dose-response results are presented for an increment of 25 g per day.

One study reported on fresh fish (Iso et al, 2007).

For the studies included in the dose-response meta-analysis, 10 included total prostate cancer (Torfadottir, 2013; Allen, 2008a; Chavarro, 2008; Park, 2007a; Rohrmann, 2007; Allen, 2004; Augustsson, 2003; Schuurman, 1999; Mills, 1989; Severson, 1989), five studies reported in advanced/high grade cases (Park, 2007; Rohrmann, 2007; Augustsson, 2003; Schuurman, 1999; Le Marchand, 1994) and two studies reported in fatal cases (Iso, 2007; Hsing, 1990).

Advanced and high grade cancers were combined in an advanced/high grade subgroup for stratified analyses.

Main results

The summary RR per 25 g/day was 1.00 (95% CI 0.97-1.03; $I^2 = 21.9\%$; $p_{heterogeneity} = 0.22$) for all studies combined. After stratification by cancer subtype, the RR per 25 g/day for total cancer was 1.00 (95% CI 0.97-1.03; $I^2 = 24.8\%$; $p_{heterogeneity} = 0.20$; n = 11) and 1.00 (95% CI 0.93 -1.07; $I^2 = 0\%$; $p_{heterogeneity} = 0.91$; n = 5) for advanced/high grade prostate cancer.

Heterogeneity

Overall, there was evidence of low heterogeneity, $I^2 = 21.9\%$, $p_{heterogeneity} = 0.22$. There was no significant evidence of publication bias with Fisher's test, p = 0.84.

Comparison with the Second Expert Report

In the 2005 SLR the meta-analysis on fish and prostate cancer, the summary RR for an increase of one serving/week was 1.00 (95% CI 0.95-1.05; $I^2 = 44.6\%$; $p_{heterogeneity} = 0.07$; n=8) for all prostate cancers and 0.97 (95% CI 0.89-1.06; $I^2 = 4.8\%$; $p_{heterogeneity} = 0.35$; n = 3) advanced/fatal prostate cancers.

Published meta-analysis or pooled analysis

In a meta-analysis of 12 case-control studies and 12 cohort studies (Szymanski et al, 2010) the summary RR for the highest versus the lowest fish intake level was 0.85 (95% CI 0.72-1.00; 5777 cases and 9805 controls) for the case control studies and 1.01 (95% CI 0.90-1.14; $I^2 = 0\%$; $p_{heterogeneity} < 0.01$; 445820 men and 13924 cases) for the cohort studies. No pooled analysis was identified.

Table 47 Studies on fish consumption identified in the CUP

Author, year	Country	Study name	Cases	Years of follow up	RR	LCI	UCI	Contrast
Torfadottir, 2013	Iceland	AGES-Reykjavik	347	7 years	0.87	0.66	1.13	≥ 4 portions/week vs ≤ 2 portions/week
					1.05	0.71	1.57	
Daniel, 2011	USA	NIH-AARP Diet and Cancer	23453	9.1 years	1.02	0.98	1.06	Q5 vs Q1
Wright, 2011	Finland	Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study	1929	21 years	0.90	0.79	1.02	Q4 vs Q1
Allen, 2008a	Europe	European Prospective Investigation into Cancer and Nutrition	2727	8.7 years	1.05	0.91	1.20	43 g/d vs 13 g/d
Chavarro, 2008	USA	Physician's Health Study	2161	19 years	1.11	0.95	1.30	≥ 5 times/week vs <1 time/week
Iso, 2007	Japan	Japan Collaborative Cohort study	169	~12 years	0.61	0.39	0.95	≥ 5 times/week vs <3 time/week
Park, 2007a	USA	Multi-Ethnic Cohort Study	4404	8 years	1.04	0.93	1.15	Q5 vs Q1
Rohrmann, 2007	USA	CLUE ll	199	12.9 years	0.86	0.44	1.67	> 5 times/ week vs <= 1 time/week

Table 48 Overall evidence on fish consumption and prostate cancer

	Summary of evidence
2005 SLR	13 studies were identified during the 2005 SLR. One study (Allen et al, 2004) showed a positive association between prostate cancer and fish intake.
Continuous Update Project	Eight additional studies reported on fish and prostate cancer risks, six of these were used in the meta-analysis. One study (Iso et al, 2007) showed an inverse association between prostate cancer mortality and fish intake. No significant association was observed in the CUP meta-analysis.

Table 49 Summary of results of the dose response meta-analysis of fish consumption and prostate cancer

Prostate cancer

	2005 SLR	CUP
Studies (n)	9	13
Cases (n)	4745	14028
Increment unit used	Servings/week	Per 25 g/day
Overall RR (95% CI)	1.00 (0.95-1.05)	1.00 (0.97-1.03)
Heterogeneity (I^2, p-value)	44.6%, p = 0.07	21.9%, p = 0.22
Stratified analysis		
Advanced/high grade		
Overall RR (95% CI)	0.98 (0.89-1.06), n = 3	1.00 (0.93-1.07), n = 5
Heterogeneity (I^2, p-value)	4.81%, p = 0.35	0%, p = 0.91
Mortality		
Overall RR (95% CI)		0.83 (0.71-0.96), n = 2
Heterogeneity (I^2, p-value)		0%, p = 0.47

Table 50 Inclusion/exclusion table for meta-analysis of fish consumption and prostate cancer

WCRF code	Author	Year	Study design	Study name	Cancer outcome	2005 SLR	CUP dose-response meta-analysis	CUP HvL forest plot	Estimated values	Exclusion reasons
PRO100160	Torfadottir	2013	Prospective Cohort	AGES-Reykjavik	Incidence	No	Yes	Yes	Mid-points, person-years	
PRO100126	Daniel	2011	Prospective Cohort	NIH-AARP Diet and Cancer	Incidence	No	No	Yes		No quantities
PRO100113	Wright	2011	Prospective Cohort	Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study	Incidence	No	No	Yes		No quantities
PRO99955	Allen	2008a	Prospective Cohort	European Prospective Investigation into Cancer and Nutrition	Incidence	No	Yes	Yes	Person-years	
PRO100024	Chavarro	2008	Prospective Cohort	Physician's Health Study	Incidence	No	Yes	Yes	Mid-points	
PRO100042	Iso	2007	Prospective Cohort	Japan Collaborative Cohort study for Evaluation of Cancer Risk	Mortality	No	Yes	Yes	Mid-points	
PRO99977	Park	2007a	Prospective Cohort	Multi-Ethnic Cohort Study	Incidence	No	Yes	Yes	Cases per category, person-years	
PRO99970	Rohrmann	2007	Prospective Cohort	CLUE ll	Incidence	No	Yes	Yes	Mid-points	
PRO97367	Allen	2004	Prospective Cohort	Life Spam Study	Incidence	Yes	Yes	Yes	Mid-points	
PRO10700	Platz	2004b	Nested Case-Control	CLUE ll	Incidence	Yes	No	No		No measure of association. Superseded by Rohrmann 2007
PRO10575	Platz	2004c	Nested Case-	Health Professionals	Incidence	Yes	No	No		No measure of association

			Control	Follow-up Study						Augustsson, 2003was included instead
PRO00545	Augustsson	2003	Prospective Cohort	Health Professionals Follow-up Study	Incidence	Yes	Yes	Yes	Mid-points	
PRO01191	Terry	2001	Prospective Cohort	Sweden 1967-1997	Incidence	Yes	No	No		No intake quantities
PRO01759	Schuurman	1999b	Case-cohort	Netherlands Cohort study	Incidence	Yes	Yes	Yes		
PRO02242	Veierod	1997	Prospective Cohort	Norway 1977-1983	Incidence	Yes	No	No		No measure of association
PRO02582	Gronberg	1996	Nested Case-Control	Sweden 1967-1970	Incidence	Yes	No	No		No intake quantities
PRO02788	Le Marchand	1994	Prospective Cohort	USA Hawaii 1975-1980 Cohort study	Incidence	Yes	Yes	Yes	Mid-points	
PRO03129	Hsing	1990b	Prospective Cohort	Lutheran Brotherhood Cohort Study	Mortality	Yes	Yes	Yes	Mid-points, person-years	
PRO03196	Mills	1989	Prospective Cohort	Adventist Health Study	Incidence	Yes	Yes	Yes	Mid-points	
PRO03210	Severson	1989b	Prospective Cohort	Hawaii 1965-1968	Incidence	Yes	Yes	Yes	Mid-points	
PRO03648	Hirayama	1979	Prospective Cohort	Japan 1966-1973	Mortality	Yes	No	No		No measure of association

Figure 49 Highest versus lowest forest plot of fish consumption and prostate cancer

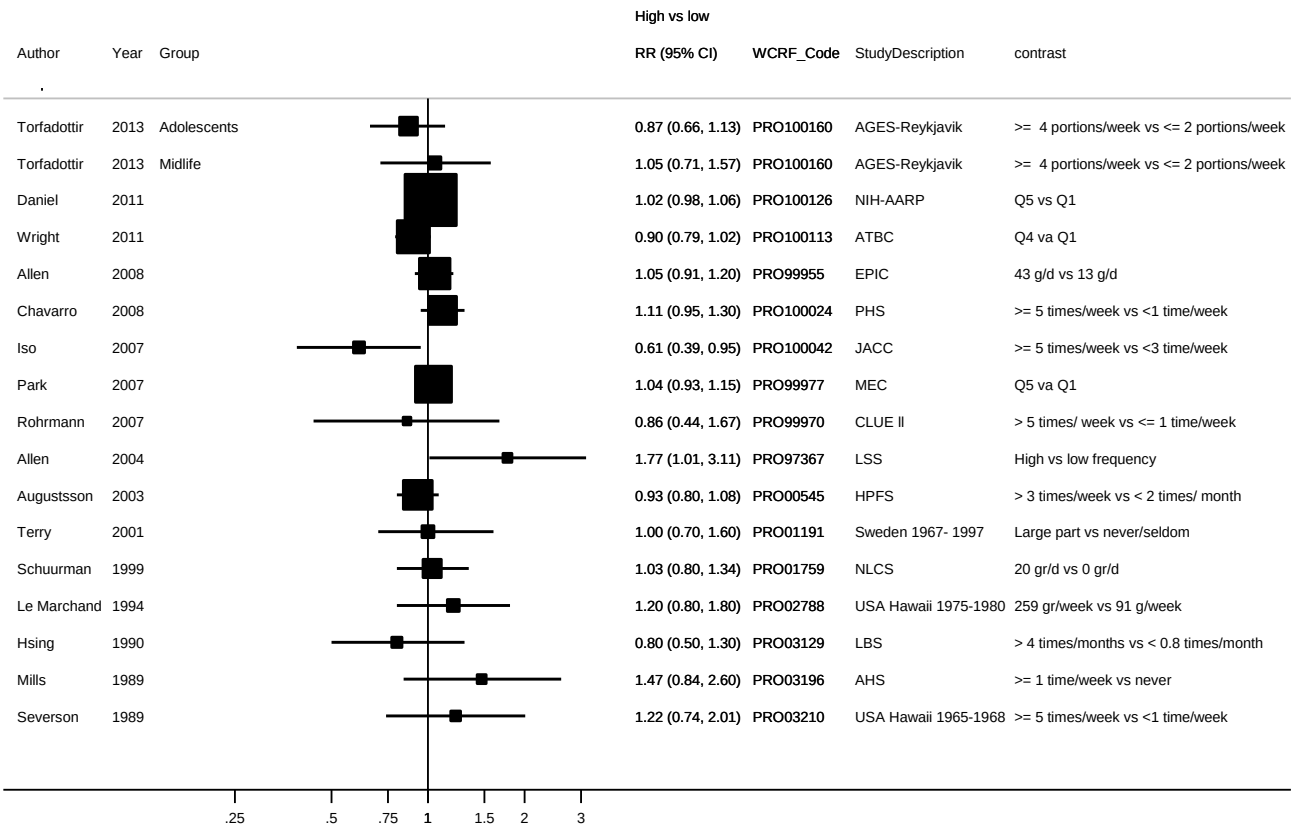


Figure 50 Dose-response meta-analysis of fish intake and prostate cancer, per 25 g/day

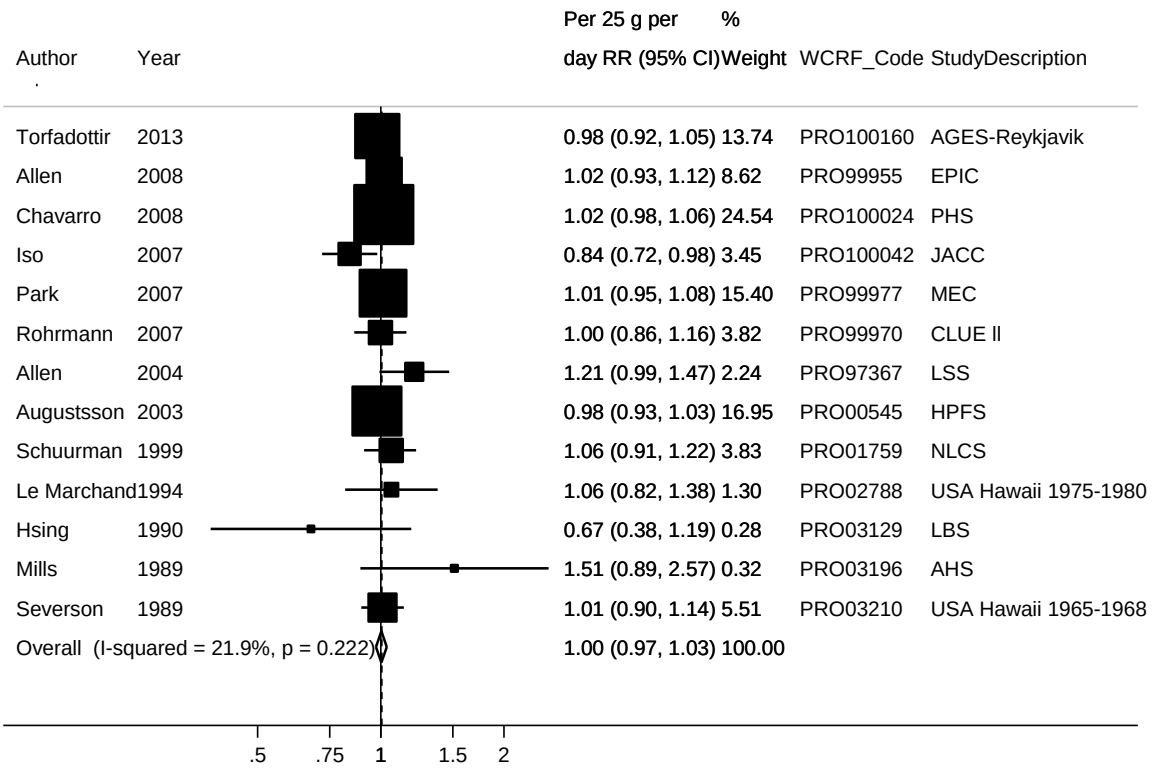
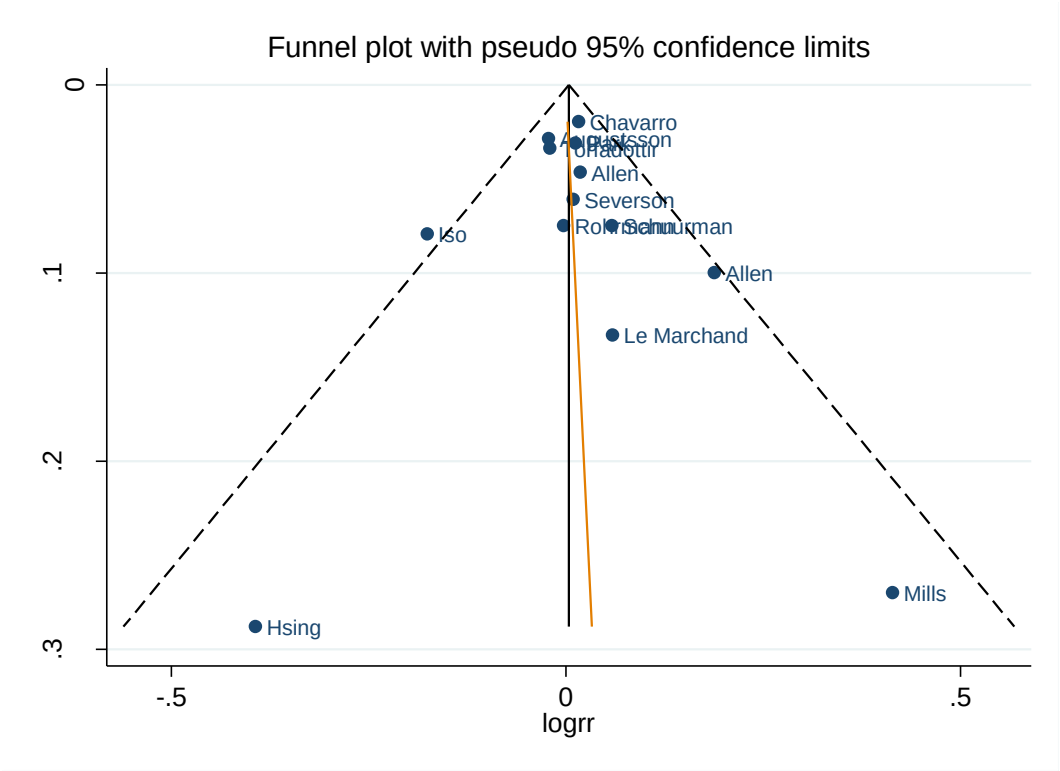


Figure 51 Funnel plot of fish intake and prostate cancer



Fisher's test p = 0.84

Figure 52 Dose-response graph of fish and prostate cancer

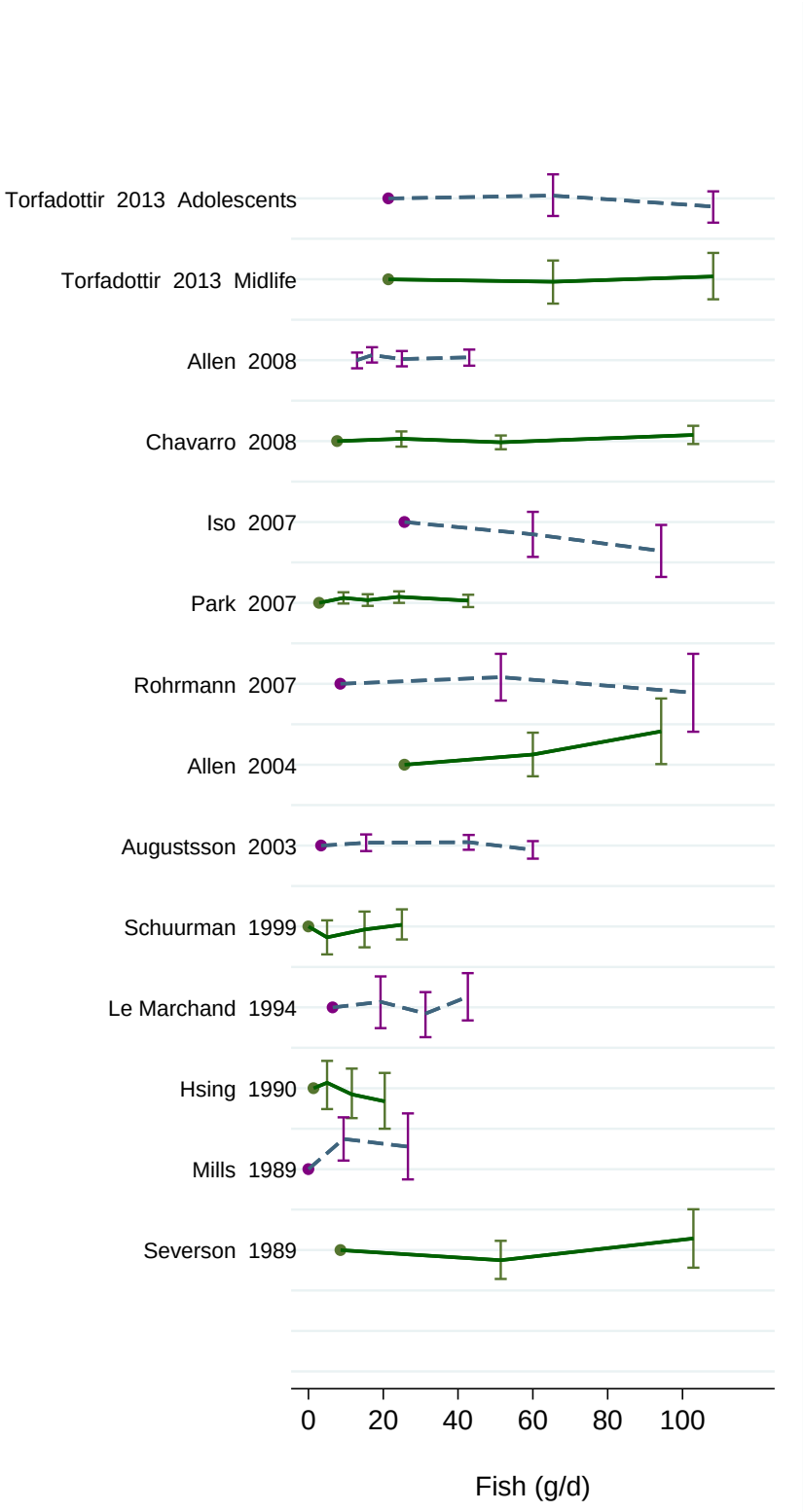
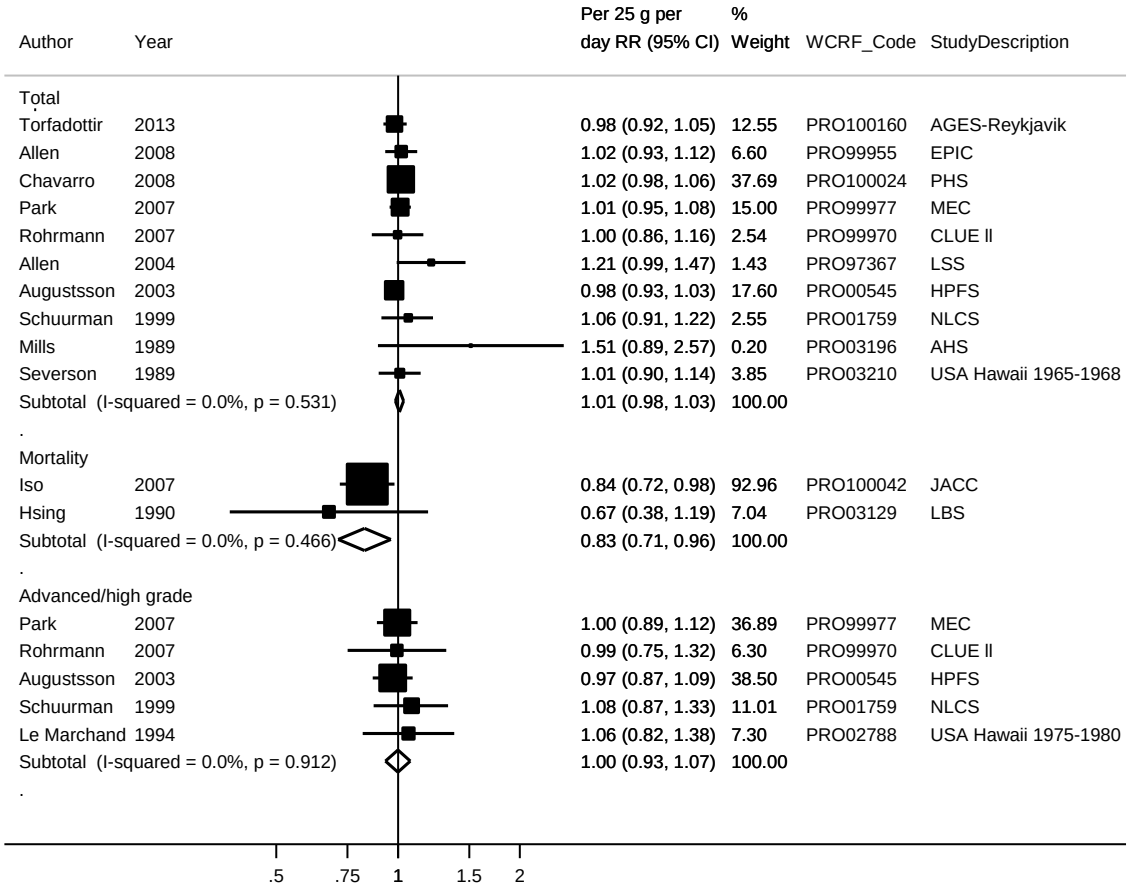


Figure 53 Dose-response meta-analysis of fish intake and prostate cancer, per 25 g/day, stratified by prostate cancer outcome



2.5.4 Eggs

Methods
Fifteen publications from 13 cohorts were identified. Three publications were identified during the CUP. The CUP meta-analysis included 11 studies; three of these were identified during the CUP.
The dose-response results are presented for an increment of 20 g per day. Servings and times were rescaled to grams assuming a standard portion size of 55 grams for consistency with the 2005 SLR.

Main results
The summary RR per 20 g/day was 1.04 (95% CI 0.97-1.11; I^2 = 22.9%, $p_{heterogeneity}$ = 0.23, n = 11) for all studies combined.
When the analysis was restricted to fatal prostate cancers, the RR per 20 g/day was 1.20 (95% CI 1.00-1.43; I^2 = 40.4%; $p_{heterogeneity}$ = 0.17; n = 4). The RR per 20 g/day after exclusion of studies with mortality as outcome was 1.00 (95% CI 0.94-1.07; I^2 = 0%; $p_{heterogeneity}$ = 0.67; n = 7). Only one study reported on advanced prostate cancer (Schuurman et al, 1999). The RR of advanced prostate cancer for an increase of 20 g/day of egg intake in this study was 0.70 (95% CI 0.53-0.93).

Heterogeneity
Overall, there was evidence of moderate heterogeneity, I^2 = 22.9%, $p_{heterogeneity}$=0.23. There was no significant evidence of publication bias with Egger's test, p = 0.10.

Comparison with the Second Expert Report
In the 2005 SLR the meta-analysis on eggs and prostate cancer showed a summary RR of 1.01 (95% CI 0.98-1.04; I^2 = 0%, pheterogeneity=0.57; n=8) for all prostate cancers and 0.97 (95% CI 0.86-1.09; I^2=67.0%; pheterogeneity=0.05; n=2) advanced/aggressive prostate cancers.

Published meta-analysis or pooled analysis
A meta-analysis (Xie et al, 2012) reported summary RRs for the highest versus lowest egg intake of 1.09 (95% CI 0.86-1.31; I^2 = 52.2%, $p_{heterogeneity}$ = 0.02) for 11 case-control studies and 0.97 (95% CI 0.87-1.07; I^2 = 0%; $p_{heterogeneity}$ = 0.44) for 6 cohort studies. No pooled analysis was identified.

Table 51 Studies on eggs consumption identified in the CUP

Author, year	Country	Study name	Cases	Years of follow up	RR	LCI	UCI	Contrast
Richman, 2011	USA	Health Professionals Follow-up study	199	14 years	1.81	1.13	2.89	≥ 2.5 serving/week vs. < 0.5 servings/week
Allen, 2008a	Europe	European Prospective Investigation into Cancer and Nutrition	2727	8.7 years	0.96	0.84	1.10	32 g/d vs. 9 g/d
Iso,	Japan	Japan	169	~12	1.17	0.80	1.71	>5 times/week

2007		Collaborative Cohort study		years				vs. <2 times/week

Table 52 Overall evidence on eggs consumption and prostate cancer

	Summary of evidence
2005 SLR	Twelve studies were identified during the 2005 SLR. None of these studies reported a significant association.
Continuous Update Project	Three additional studies reported on eggs and prostate cancer risks. One study reported a significant positive association. No significant association was observed in the CUP meta-analysis.

Table 53 Summary of results of the dose response meta-analysis of eggs consumption and prostate cancer

Prostate cancer		
	2005 SLR	CUP
Studies (n)	8	11
Cases (n)	1686	4781
Increment unit used	Servings/week	Per 20 g/day
Overall RR (95% CI)	1.01 (0.99-1.04)	1.04 (0.97-1.11)
Heterogeneity (I^2, p-value)	0%, p = 0.57	22.9%, p = 0.23
Stratified analysis		
		Incidence
Overall RR (95% CI)		1.00 (0.94-1.07) n = 7
Heterogeneity (I^2,p-value)		0%, p = 0.67
		Mortality
Overall RR (95% CI)		1.20 (1.00-1.43), n = 4
Heterogeneity (I^2, p-value)		40.4%, p = 0.17

No stratified analysis were conducted in the SLR

Table 54 Inclusion/exclusion table for meta-analysis of eggs consumption and prostate cancer

WCRF code	Author	Year	Study design	Study name	Cancer outcome	2005 SLR	CUP dose-response meta-analysis	CUP HvL forest plot	Estimated values	Exclusion reasons
PRO100106	Richman	2011	Prospective Cohort	Health Professionals Follow-up study	Mortality	No	Yes	Yes	Person-years, Mid-exposure values	
PRO99955	Allen	2008a	Prospective Cohort	European Prospective Investigation into Cancer and Nutrition	Incidence	No	Yes	Yes	Person-years	
PRO100042	Iso	2007	Prospective Cohort	Japan Collaborative Cohort study for Evaluation of Cancer Risk	Mortality	No	Yes	Yes	Mid-exposure values	
PRO97367	Allen	2004	Prospective Cohort	Life Spam Study	Incidence	Yes	Yes	Yes	Mid-exposure values	
PRO01759	Schuurman	1999b	Case-cohort	Netherlands Cohort study	Incidence	Yes	Yes	Yes		
PRO02242	Veierod	1997	Prospective Cohort	Norway 1977-1983	Incidence	Yes	No	No		No RR, no CI
PRO02582	Gronberg	1996	Nested Case-Control	Sweden 1967-1970	Incidence	Yes	No	No		No quantification of exposure
PRO02629	Giovannucci	1995	Prospective Cohort	Health Professionals Follow-up study	Incidence	Yes	No	No		No measure of association. PRO100106 (Richman, 2011) was used.
PRO02788	Le Marchand	1994	Prospective Cohort	USA Hawaii 1975-1980 Cohort study	Incidence	Yes	Yes	Yes	Mid-exposure values	
PRO03129	Hsing	1990b	Prospective Cohort	Lutheran Brotherhood	Mortality	Yes	Yes	Yes	Mid-exposure values, person-years	

				Cohort Study						
PRO03216	Thompson	1989	Prospective Cohort	Lipid Research Clinics Prevalence Study	Incidence	Yes	Yes	No	Rescale continuous values	H vs L: Only RR for continuous increment
PRO03196	Mills	1989	Prospective Cohort	Adventist Health Study	Incidence	Yes	Yes	Yes	Mid-exposure values	
PRO03210	Severson	1989b	Prospective Cohort	Hawaii 1965-1968	Incidence	Yes	Yes	Yes	Mid-exposure values	
PRO03244	Snowdon	1988	Prospective Cohort	USA California 1960-1980	Mortality	Yes	No	No		No RR, no CI, superseded by PRO03474 (Snowdon, 1984)
PRO03474	Snowdon	1984	Prospective Cohort	USA California 1960-1980	Mortality	Yes	Yes	Yes	Mid-exposure values	

Figure 54 Highest versus lowest forest plot of eggs consumption and prostate cancer

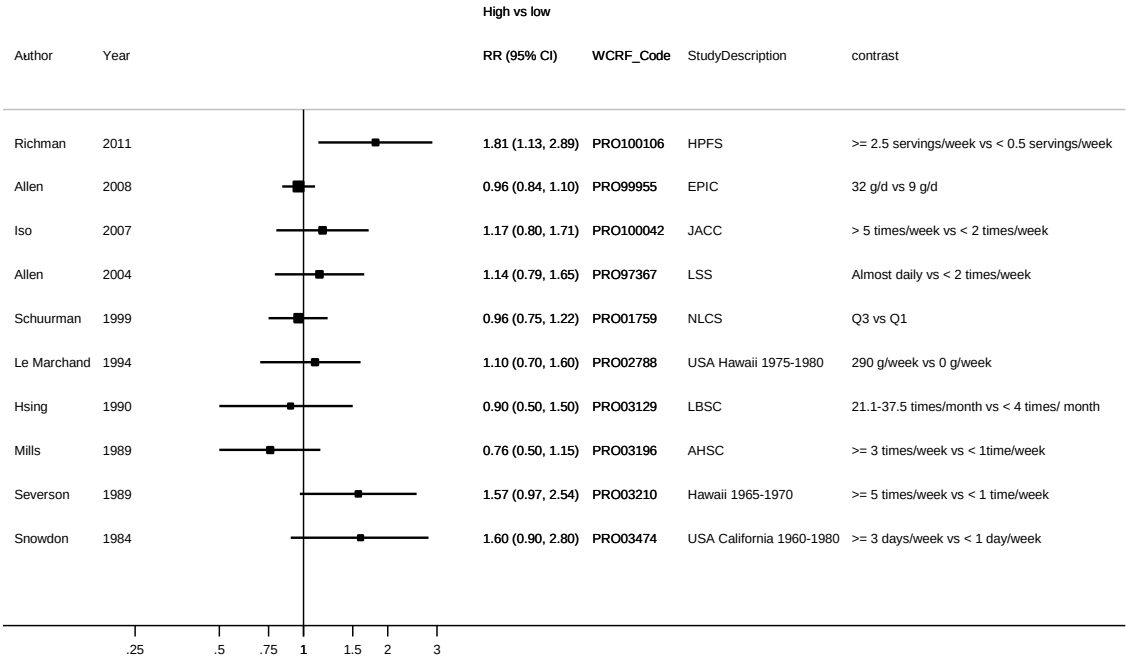


Figure 55 Dose-response meta-analysis of eggs intake and prostate cancer, per 20 g/day

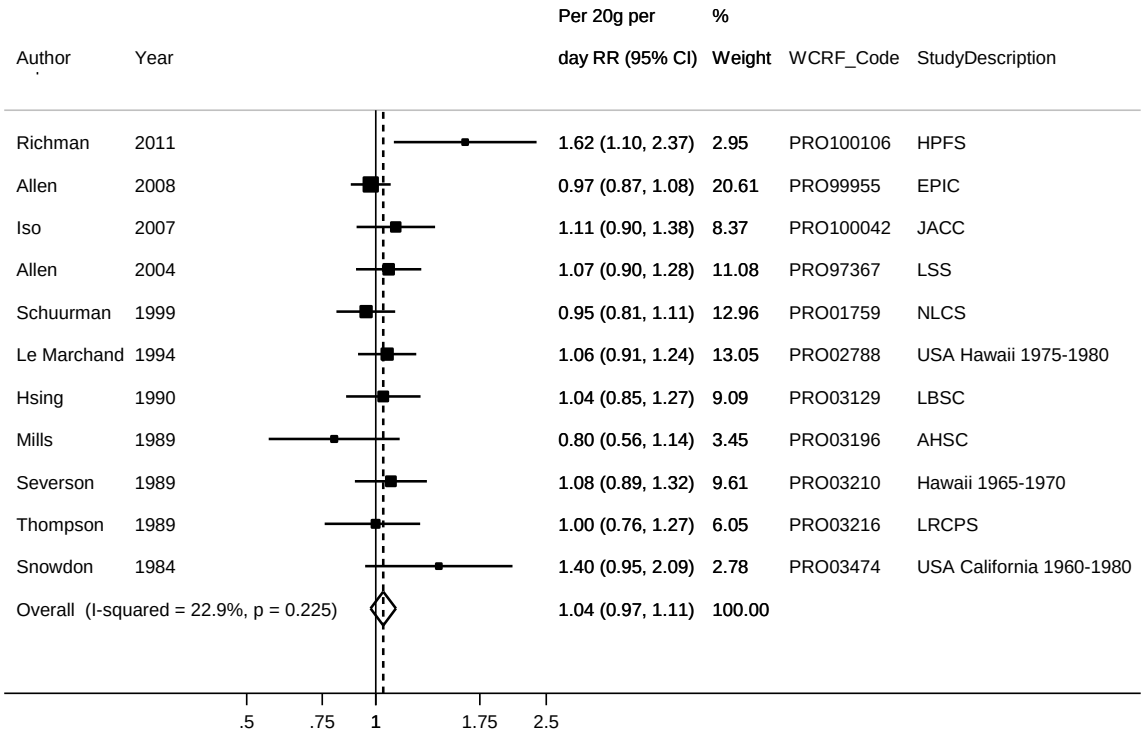
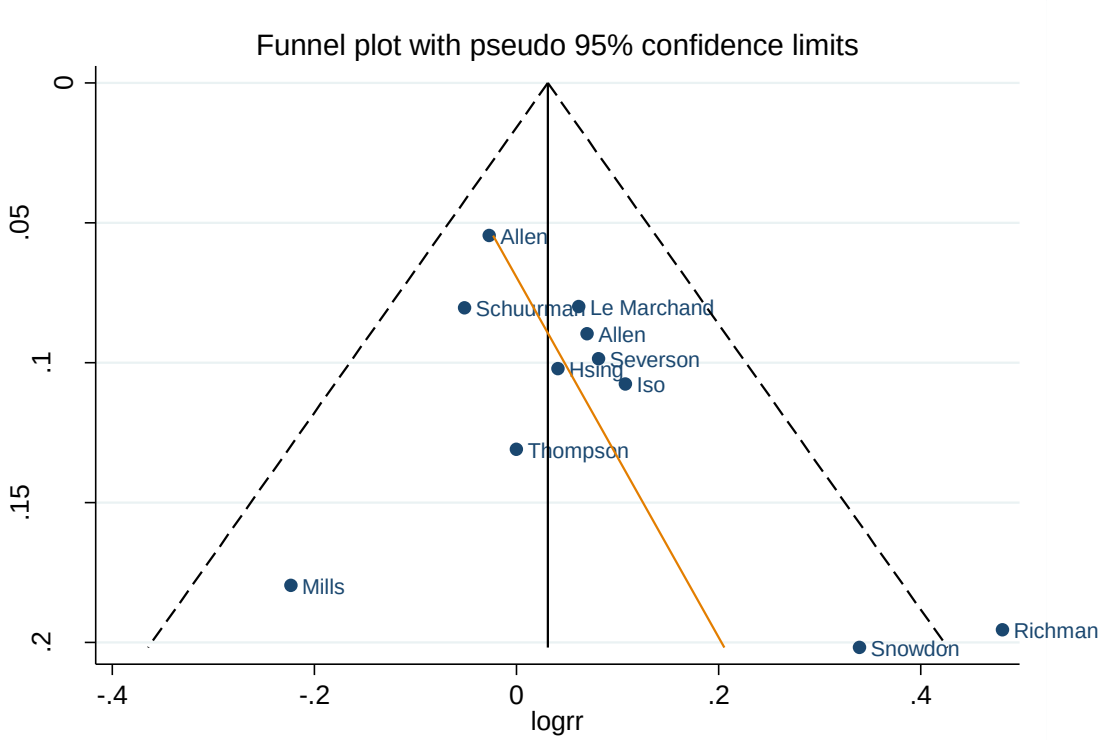


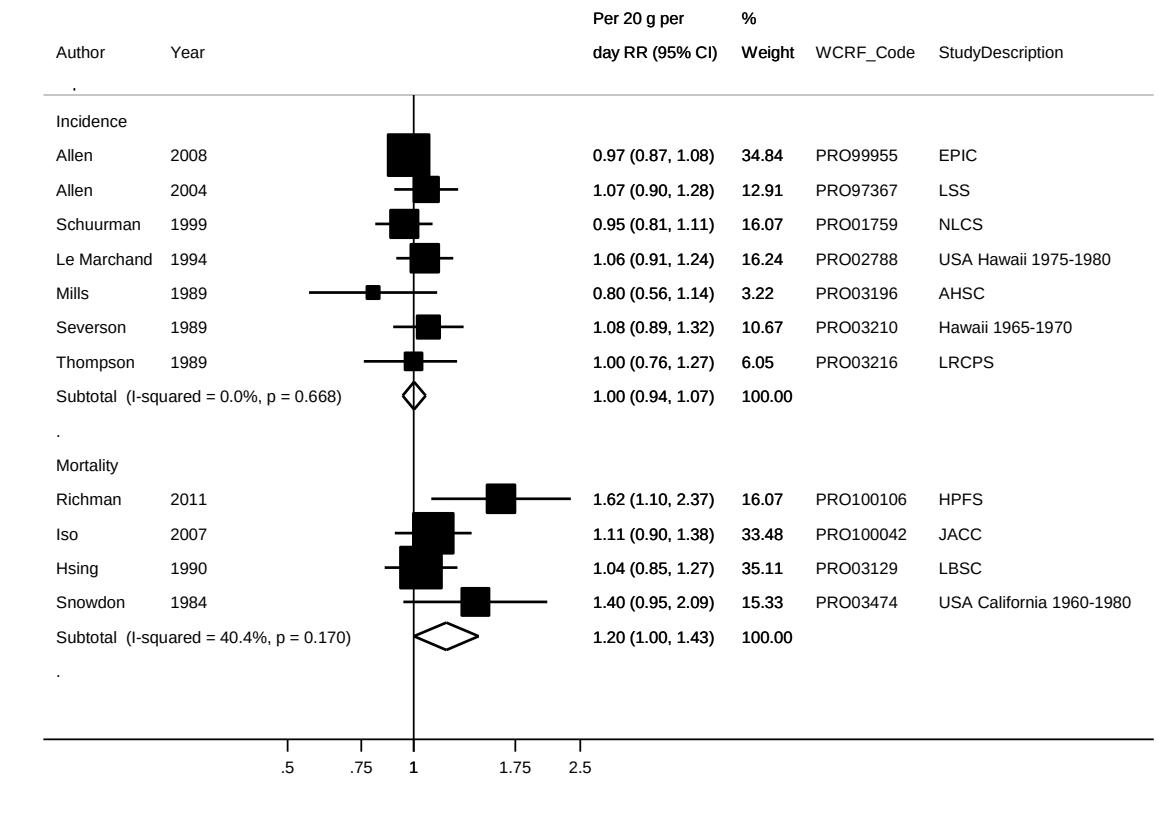
Figure 56 Funnel plot of eggs intake and prostate cancer



Egger's test p = 0.10

Figure 57 Dose-response graph of eggs and prostate cancer

Figure 58 Dose-response meta-analysis of eggs intake and prostate cancer, per 20 g/day, stratified by prostate cancer outcome



2.7 Dairy foods

Methods

A total of 21 cohort studies (25 publications) have been published on total dairy products and prostate cancer risk. Fourteen studies (15 publications) were identified in the CUP. Servings and times per day were rescaled to grams/day assuming an average portion size of 177 g (serving size reported in the US Department of Agriculture Food and Nutrient Database for Dietary Studies as most studies were from USA). Dose-response analyses were conducted per 400 g per day increase in dairy product intake.

Analyses were stratified by outcome type: aggressive or advanced cancers were grouped together (indicated as advanced in the figures and tables), nonadvanced or localised cancers were grouped and indicated as nonadvanced in graphs and figures and a third group included the subgroups of fatal prostate cancers.

Of the studies included in the dose-response analysis fifteen studies reported on total dairy and total prostate cancer: Berndt, 2002; Rodriguez, 2007; Tseng, 2005; Severi, 2006; Kesse et al, 2006; Giovannucci et al, 2006; Rohrmann et al, 2007; Park et al, 2007b (MEC); Neuhouser et al, 2007; Mitrou et al, 2007; Ahn et al, 2007; Kurahashi et al, 2008a; Park et al, 2009; Song et al, 2013.

Eight studies reported on total dairy products and non-advanced, non-aggressive, localised, low-grade, or Gleason score 2-7 prostate cancer: Severi et al, 2006; Rohrmann et al, 2007; Park et al, 2007b (MEC); Park Yet al, 2007 (NIH-AARP Diet and Health Study); Neuhouser et al, 2007; Ahn et al, 2007; Kurahashi et al, 2008a; Song et al, 2013.

Ten studies reported on total dairy products and advanced, aggressive, high-stage or Gleason score 8-10 prostate cancer: Rodriguez et al, 2003; Severi et al, 2006; Giovannucci et al, 2006; Rohrmann et al, 2007; Park et al, 2007b (MEC); Park Y et al, 2007 (NIH-AARP Diet and Health Study); Neuhouser et al, 2007; Ahn et al, 2007; Kurahashi et al, 2008a; and Song et al, 2013.

Five studies reported on total dairy products and fatal prostate cancer: Hsing et al, 1990; Koh et al, 2007; Smit et al, 2007; Park et al, 2007; and Song et al, 2013.

Three studies were not included in the forest plots because of unspecific exposure which included eggs (Allen et al, 2004), only a high vs. low comparison with outcome of mortality (Rodriguez et al, 2002) and one study used household consumption, not individual intake, when assessing dairy intake (van Der Pols et al, 2007).

Main results

The summary RR per 400 g/d increase in total dairy intake was 1.07 (95% CI 1.02-1.12; $I^2 = 43.9\%$; $p_{heterogeneity} = 0.06$; n = 15). Although there was no statistical evidence of publication bias with Egger'stest (p = 0.10), the funnel plot shows that small studies tended to report stronger associations than the average and that small studies showing inverse associations are missing.

There was no evidence of nonlinearity, $p_{non\text{-}linearity} = 0.20$.

The association remained statistically significant in influence analysis. The RR (95% CI) ranged from 1.05 (1.02-1.09) when the NHANES study (Tseng et al, 2005) was excluded to 1.07 (1.02-1.12) when either the MCCS (Severi et al, 2006) or CPSII (Rodriguez et al, 2005) were excluded.

When stratified by outcome type the summary RR was 1.09 (95% CI 1.00-1.18; I^2 = 53.0%; $p_{heterogeneity}$ = 0.04; n = 8) for nonadvanced cancers, 0.97 (95% CI 0.91-1.05; I^2 = 0%; $p_{heterogeneity}$ = 0.71; n = 10) for advanced cancers and 1.11 (95% CI 0.92-1.33; I^2 = 20.1%; $p_{heterogeneity}$ = 0.29; n = 5) for fatal cancers.

Heterogeneity
There was moderate heterogeneity in the overall analysis, I^2 = 38.9%, $p_{heterogeneity}$ = 0.06. The smaller studies, published before 2007, tended to show stronger positive associations than the most recent and larger studies.

Conclusion from the Second Expert Report
In the 2005 SLR the evidence relating dairy foods intake to increased prostate cancer risk was considered limited suggestive.

Published meta-analyses
A meta-analysis of 11 cohort studies reported a summary RR of 1.11 (95% CI 1.03-1.19; $p_{heterogeneity}$ = 0.33) for high vs. low intake (Huncharek et al, 2009).

A meta-analysis of 9 cohort studies reported a summary RR of 1.18 (95 % CI 1.07-1.30) for high vs. low dairy product intake (Qin et al, 2007).

Table 55 Studies on total dairy products identified in the CUP

Author/year	Country	Study name	Cases	Years of follow-up	RR	LCI	UCI	Contrast
Song, 2013	USA	Physician's Health Study	2806	28 years	1.12	0.93	1.35	> 2.5 vs. ≤ 0.5 serv/d
Park, 2009	USA	NIH-AARP Diet and Health Study	17189	8 years	1.06	1.01	1.12	1.4 vs. 0.2 serv/1000 kcal/d
Kurahashi, 2008a	Japan	JPHC study-cohort I and II	329	7.5 years	1.63	1.14	2.32	339.8 vs. 12.8 g/d
van der Pols, 2007	England and Scotland	Boyd Orr Cohort	41	57 years	0.55	0.21	1.42	471 vs. 89 g/d
Smit, 2007	Puerto Rico	Puerto Rico	167 deaths	41 years	1.75	0.76	4.05	≥ 7 vs. ≤ 2 serv/d
Rohrmann, 2007	USA	CLUE II	199	13 years	1.08	0.78	1.54	> 1.9 vs. < 0.9 serv/d
Park Y, 2007	USA	NIH- AARP Diet and Health Study	10180	6 years	0.96	0.87	1.06	≥ 3 vs. < 0.5 serv/d
Park, 2007b	USA	Multiethnic Cohort Study	4404	8 years	1.03	0.92	1.16	≥ 332 vs. < 49 g/d
Neuhouser, 2007	USA	CARET	890	11 years	0.82	0.66	1.02	≥ 2.2 vs. < 0.9 serv/d
Mitrou, 2007	Finland	Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study	1267	17 years	1.26	1.04	1.51	1220.2 vs. 380.9 g/d
Ahn, 2007	USA	PLCO Cancer Screening Trial	1910	8.9 years	1.12	0.97	1.30	≥ 2.75 vs. ≤ 0.98 serv/d
Severi, 2006	Australia	The Melbourne collaborative cohort study	674	10.9 years	0.99	0.78	1.26	56 vs. 10 times/week
Koh, 2006	USA	Harvard Alumni Health Study	815	10 years	1.11	0.85	1.46	≥ 3.25 vs. 0-< 1.25 serv/d

		1962-1966						
Kesse, 2006	France	SU.VI.MAX	69	7.7 years	2.16	0.96	4.85	> 396 vs. < 160 g/d
Giovannucci, 2006a	USA	Health Professionals Follow-up Study	3544	16 years	1.07	0.95	1.20	3.72 vs. 0.50 serv/d

Table 56 Overall evidence on total dairy products and prostate cancer

	Summary of evidence
2005 SLR	Eleven cohort studies reported on total dairy intake and prostate cancer and the summary of these was increased risk.
Continuous Update Project	Fifteen studies reported on total dairy and prostate cancer, and 3 of these reported significant positive associations, while the remaining twelve studies reported no significant association. A positive association was observed for total prostate cancers and the RR for advanced prostate cancers was of borderline significance.

Table 57 Summary of results of the dose-response meta-analysis of total dairy products and prostate cancer

Prostate cancer		
	2005 SLR	CUP
Studies (n)	8	15
Cases (n)	7367	38107
RR (95% CI)	1.06 (1.01-1.11)	1.07 (1.02-1.12)
Increment unit used	Per 1 serving/day	Per 400 g/d
Heterogeneity (I^2, p-value)	52.6%, p = 0.04	43.9%, p = 0.06
	Non advanced cancers	
Studies (n)	-	8
Cases (n)		16749
RR (95% CI)		1.09 (1.00-1.18)
Increment unit used		Per 400 g/d
Heterogeneity (I^2, p-value)		53.0%, p= 0.04
	Advanced cancers	
Studies (n)	-	10
Cases (n)		4465
RR (95% CI)		0.97 (0.91-1.05)
Increment unit used		Per 400 g/d
Heterogeneity (I^2, p-value)		0.0%, p = 0.71
	Fatal cancers	
Studies (n)	-	5
Cases (n)		898
RR (95% CI)		1.11 (0.92-1.33)
Increment unit used		Per 400 g/d
Heterogeneity (I^2, p-value)		20.2%, p = 0.29

Table 58 Inclusion/exclusion table for meta-analysis of total dairy products and prostate cancer

WCRF code	Author	Year	Study design	Study name	Cancer outcome	2005 SLR	CUP dose-response	CUP H vs. L forest plot	Estimated values	Exclusion reason
PRO100162	Song,	2013	Prospective Cohort	Physician's Health Study	Incidence	No	Yes	Yes	Mid-exposure values, Intake rescaled from servings to grams	
PRO100146	Park	2009	Prospective Cohort	NIH-AARP Diet and Health Study	Incidence	No	Yes	Yes	Cases/person-years. Intake rescaled from kg/100kcal/d to g/d	
PRO100000	Kurahashi	2008a	Prospective Cohort	JPHC study-cohort I and II	Incidence	No	Yes	Yes		
PRO99981	van der Pols	2007	Prospective Cohort	Boyd Orr Cohort	Incidence	No	No	No		Household consumption, childhood intake
PRO100019	Smit	2007	Prospective Cohort	Puerto Rico	Mortality	No	Yes	Yes	Mid-exposure values, cases, person-years	Included only in analyses of fatal cancers
PRO99970	Rohrmann	2007	Prospective Cohort	CLUE II	Incidence	No	Yes	Yes	Mid-exposure value. Intake rescaled from servings to grams	
PRO100005	Park Y	2007	Prospective Cohort	NIH- AARP Diet and Health Study	Incidence	No	Yes	No		Only included for advanced, and non advanced prostate cancer analysis. For total overlap with Park et al, 2009 (PRO100146)

PRO99976	Park	2007b	Prospective Cohort	Multiethnic Cohort Study	Incidence	No	Yes	Yes	Mid-exposure values, person-years	
PRO100002	Neuhouser	2007	Prospective Cohort	CARET	Incidence	No	Yes	Yes	Mid-exposure values, person-years	
PRO99979	Mitrou	2007	Prospective Cohort	Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study	Incidence	No	Yes	Yes		
PRO100039	Ahn	2007	Prospective Cohort	PLCO Cancer Screening Trial	Incidence	No	Yes	Yes	Mid-exposure values, person-years	
PRO99990	Severi	2006	Prospective Cohort	The Melbourne collaborative cohort study	Incidence	No	Yes	Yes	Mid-exposure values, cases, person-years	
PRO99962	Koh	2006	Prospective Cohort	Harvard Alumni Health Study 1962-1966	Incidence	No	Yes	Yes	Mid-exposure values, person-years	
PRO99957	Kesse	2006	Prospective Cohort	SU.VI.MAX	Incidence	No	Yes	Yes	Mid-exposure values, person-years	
PRO99968	Giovannucci	2006a	Prospective Cohort	Health Professionals Follow-up Study	Incidence	No	Yes	Yes	Person-years	
PRO97221	Tseng	2005	Prospective Cohort	NHANESI	Incidence	Yes	Yes	Yes		
PRO97367	Allen	2004	Prospective Cohort	Life Span Study	Incidence	Yes	No	No		Nonspecific exposure (included eggs)
PRO00127	Rodriguez	2003	Prospective Cohort	Cancer Prevention Study ll Nutrition Cohort	Incidence	Yes	Yes	Yes	Mid-exposure values	
PRO00881	Rodriguez	2002	Prospective Cohort	CPS l / CPS ll	Mortality	Yes	No	No		<3 categories, mortality

PRO00628	Berndt	2002	Prospective Cohort	Baltimore Longitudinal Study of Aging	Incidence	Yes	Yes	Yes		
PRO01122	Michaud	2001	Prospective Cohort	Health Professionals Follow-up study	Incidence	Yes	Yes	Yes		Included for metastatic prostate cancer (Total and advanced prostate cancer: overlap with Giovannucci et al, 2006 (PRO99968))
PRO01091	Chan	2001	Prospective Cohort	Physicians' Health Study	Incidence	Yes	No	No		Overlap with Song et al, 2013 (PRO100162)
PRO01426	Chan	2000	Prospective Cohort	Alpha Tocopherol Beta Carotene Cancer Prevention	Incidence	Yes	No	No		Overlap with Mitrou et al, 2007 (PRO99979)
PRO02814	Gann	1994	Nested Case Control	Physicians' Health Study	Incidence	Yes	No	No		No risk estimates
PRO03129	Hsing	1990b	Prospective Cohort	Lutheran Brotherhood Cohort Study	Mortality	Yes	Yes	No	Mid-exposure values	Included only in analysis of fatal cases

Figure 59 Highest versus lowest forest plot of total dairy products and prostate cancer

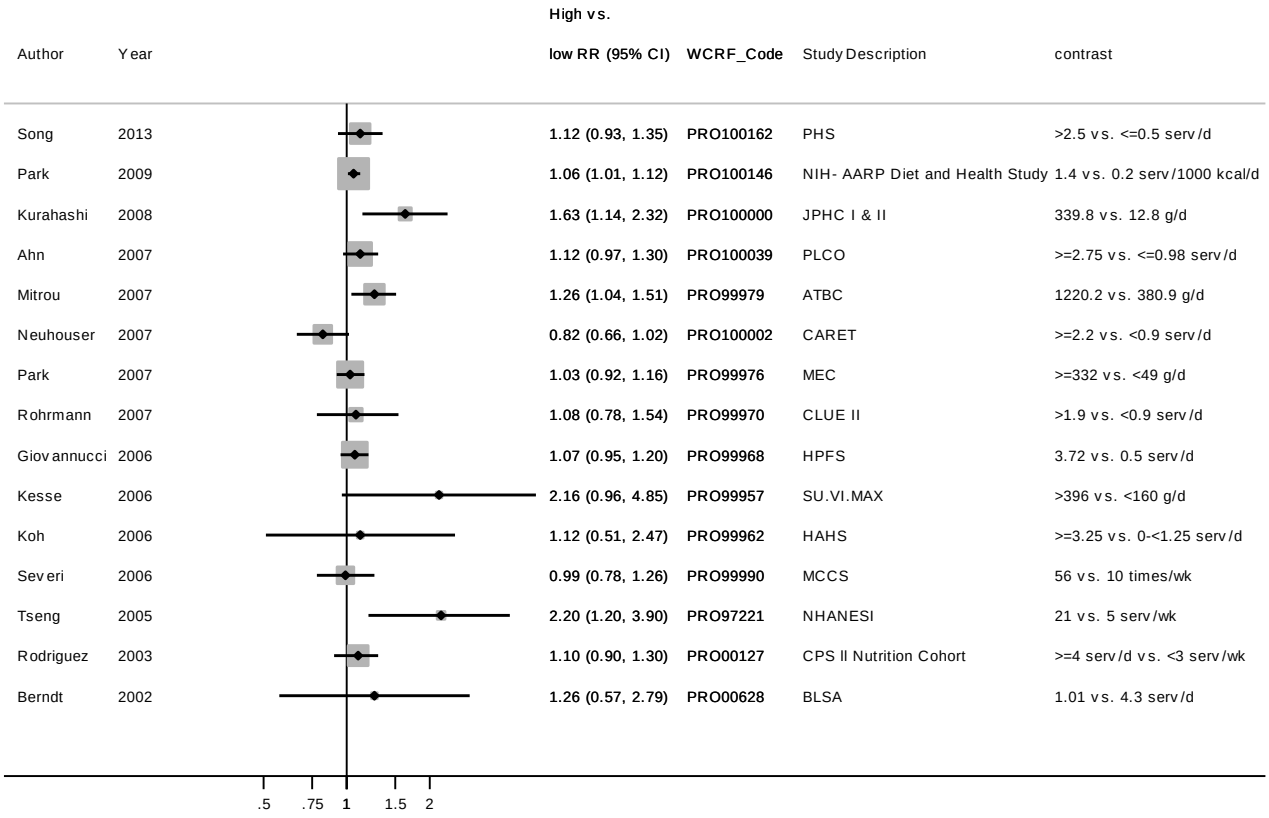


Figure 60 Dose-response meta-analysis of total dairy products and prostate cancer, per 400 g/day

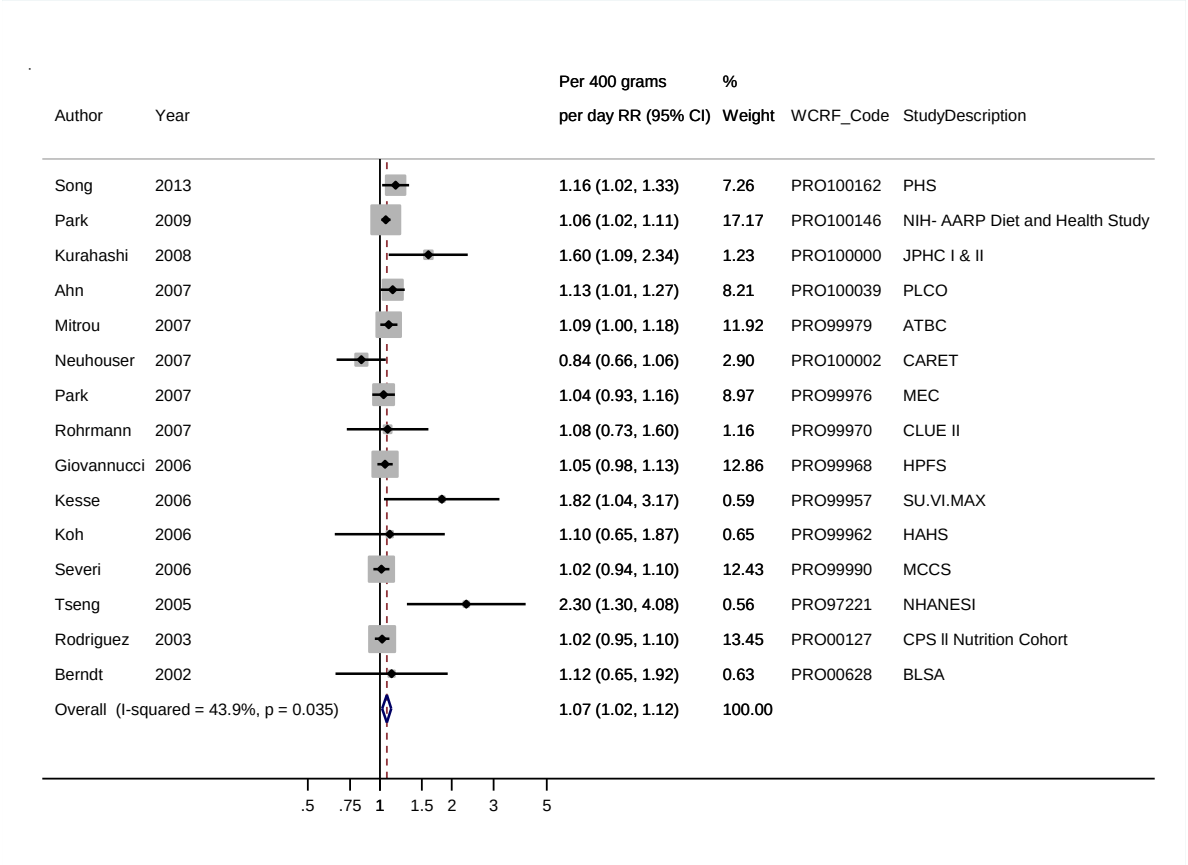
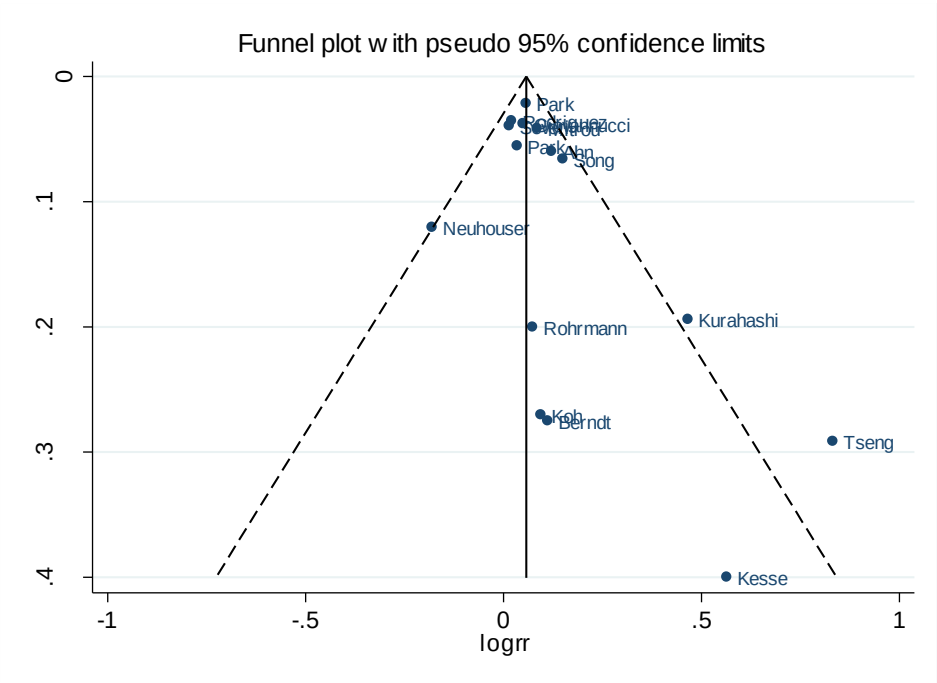


Figure 61 Funnel plot of total dairy products and prostate cancer



Egger's test p = 0.10

Figure 62 Dose-response graph of total dairy products and total prostate cancer

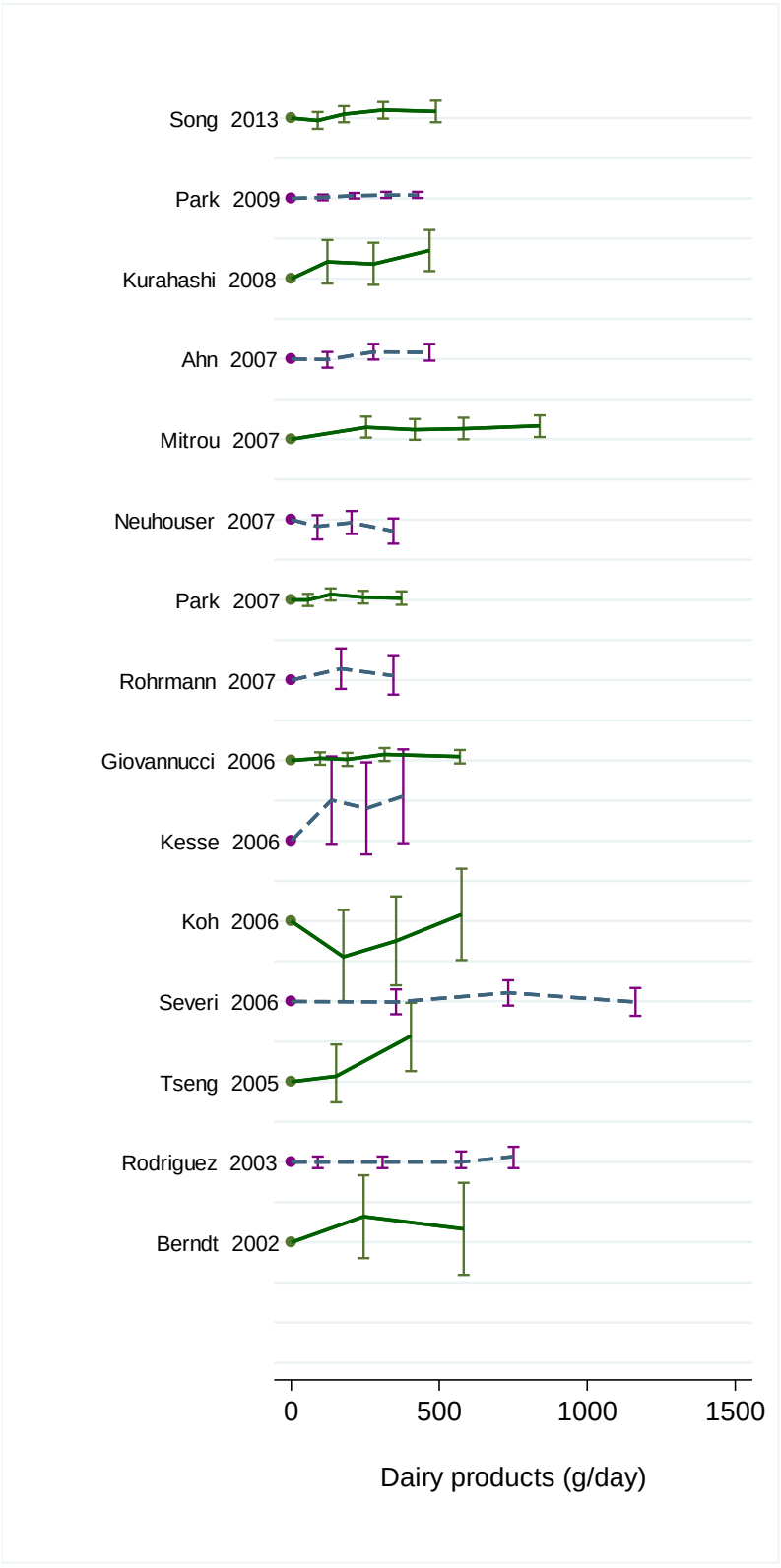
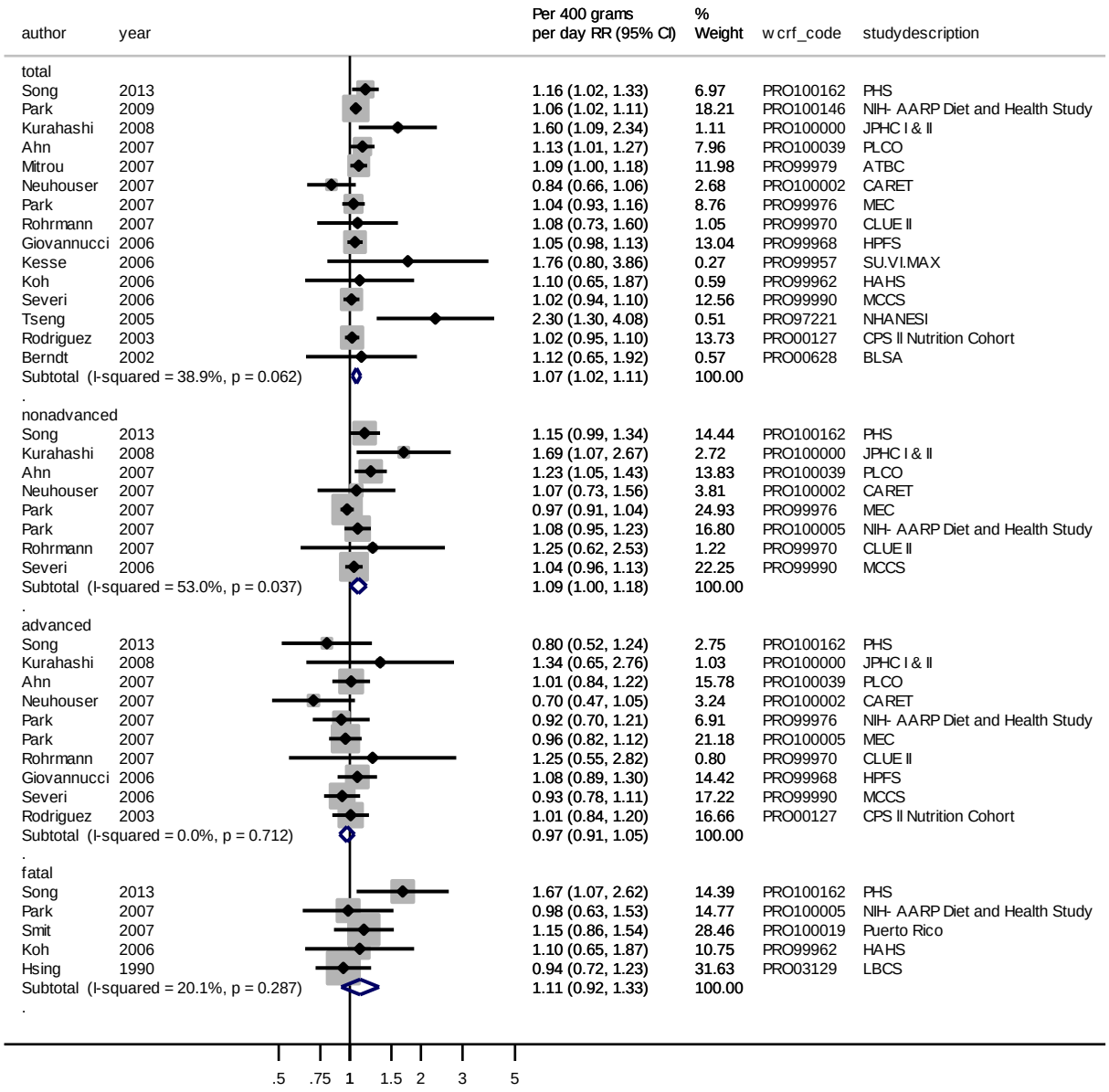


Figure 63 Dose-response meta-analysis of total dairy products and prostate cancer, per 400 g/day, stratified by outcome type



2.7.1 Milk

Methods
A total of 22 cohort studies have been published on milk intake and prostate cancer risk. Eight cohort studies were identified in the CUP. Dose-response analyses were conducted per 200 g per day increase in milk intake.

When milk intake was expressed in serving, glass or time it was rescaled in grams assuming a standard portion size of 244 g.

Of the studies included in the dose-response analysis fourteen studies reported on milk and total prostate cancer: Severson et al, 1989; Le Marchand et al, 1994; Gronberg et al, 1996; Schuurman et al, 1999; Berndt et al, 2002; Allen et al, 2004; Tseng et al, 2005; Kesse et al, 2006; Tande et al, 2006; Mitrou et al, 2007; Park et al, 2007b; Rohrmann et al, 2007; Allen et al, 2008a and Kurahashi et al, 2008a. Four studies reported on localised or low-stage prostate cancer and on high-stage, regional/distant or advanced prostate cancer: Le Marchand et al, 1994; Schuurman et al, 1999; Rohrmann et al, 2007: and Park et al, 2007b. Two studies reported on fatal PC: Snowdon et al, 1984 and Iso et al, 2007 and were only included in the analysis of mortality.

Four studies were not included in the high vs. low or dose-response analyses because no risk estimates were reported.

Main results
The summary RR per 200 g/day increase in total milk intake was 1.03 (95% CI 1.00-1.06, $I^2 = 9.1\%$, $p_{heterogeneity} = 0.35$, n = 14). There was no evidence of publication bias in the funnel plot, Egger's test, p = 0.06. There was evidence of nonlinearity, $p_{non\text{-}linearity} = 0.01$ with a slight flattening of the dose-response curve at higher intake.

When stratified by outcome type the summary RR was 1.06 (95% CI 1.00-1.13; $I^2 = 0\%$, $p_{heterogeneity} = 0.59$, n = 4) for nonadvanced cancers, 0.98 (95% CI 0.89-1.09; $I^2 = 0\%$, $p_{heterogeneity} = 0.84$, n = 4) for advanced cancers and 1.04 (95% CI 0.73-1.50; $I^2 = 67.8\%$, $p_{heterogeneity} = 0.08$, n = 2) for mortality.

Heterogeneity
There was low heterogeneity, $I^2 = 9.1\%$, $p_{heterogeneity} = 0.35$.

Conclusion from the Second Expert Report
In the 2005 SLR the evidence relating milk and dairy products to increased prostate cancer risk was considered limited suggestive.

Published meta-analyses
A meta-analysis of 8 cohort studies reported a summary RR of 1.21 (95% CI 1.00-1.47) for high vs. low milk (Qin et al, 2007).

A meta-analysis of 11 cohort studies reported a summary RR of 1.06 (95% CI 0.91-1.23) for high vs. low milk intake (Huncharek et al, 2009).

Table 59 Studies on total milk identified in the CUP

Author/year	Country	Study name	Cases	Years of follow-up	RR	LCI	UCI	Contrast
Kurahashi, 2008a	Japan	JPHC study-cohort I and II	329	7.5 years	1.53	1.07	2.19	290.5 vs. 2.3 g/d
Allen, 2008a	Ten European countries	European Prospective Investigation into Cancer and nutrition (EPIC)	2727	8.7 years	1.01	0.89	1.16	466 vs. 34 g/d
Rohrmann, 2007	USA	CLUE II	199	13 years	1.26	0.91	1.74	≥ 5 vs. ≤ 1 time/week
Park, 2007b	USA	Multiethnic Cohort Study	4404	8 years	1.07	0.95	1.19	≥ 256 vs. <17 g/d
Mitrou, 2007	Finland	Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study	1267	17 years	1.08	0.91	1.30	993.5 vs. 152.6 g/d
Iso, 2007	Japan	Japan Collaborative Cohort Study	142 deaths	≈12 years	0.84	0.57	1.22	≥ 5/week vs. <1 time/month
Tande, 2006	USA	The Atherosclerosis Risk in Communities Study	385	12.1 years	1.46	1.06	2.01	≥ 1.0 vs. < 0.07 serv/d
Kesse, 2006	France	SU.VI.MAX	69	7.7 years	1.13	0.54	2.34	> 253 vs. <2 5 g/d

Table 60 Overall evidence on total milk and prostate cancer

	Summary of evidence
2005 SLR	Nine of 14 prospective studies that reported on milk intake and prostate cancer provided risk estimates for the association between total milk and prostate cancer and three reported a significant positive association, while the remaining studies found no significant association.
Continuous Update Project	Eight additional studies were identified and two of these reported significant positive associations, while the remaining six studies found no significant association. RRs of borderline significance were obtained in the CUP meta-analysis for total and non advanced prostate cancers.

Table 61 Summary of results of the dose-response meta-analysis of total milk and prostate cancer

Prostate cancer		
	2005 SLR	CUP
Studies (n)	8	14
Cases (n)	1469	11151
RR (95% CI)	1.05 (0.98-1.14)	1.03 (1.00-1.06)
Increment unit used	Per 1 serving/day	Per 200 g/day
Heterogeneity (I^2, p-value)	25%, p = 0.23	9.3%, p = 0.35
	Non advanced cancers	
Studies (n)	-	4
Cases (n)		4092
RR (95% CI)		1.06 (1.00-1.13)
Increment unit used		Per 200 g/day
Heterogeneity (I^2, p-value)		0%, p = 0.59
	Advanced cancers	
Studies (n)	-	4
Cases (n)		1072
RR (95% CI)		0.98 (0.89-1.09)
Increment unit used		Per 200 g/day
Heterogeneity (I^2, p-value)		0%, p = 0.84
	Fatal cancers	
Studies (n)	-	2
Cases (n)		253
RR (95% CI)		1.04 (0.73-1.50)
Increment unit used		Per 200 g/day
Heterogeneity (I^2, p-value)		67.8%, p = 0.08

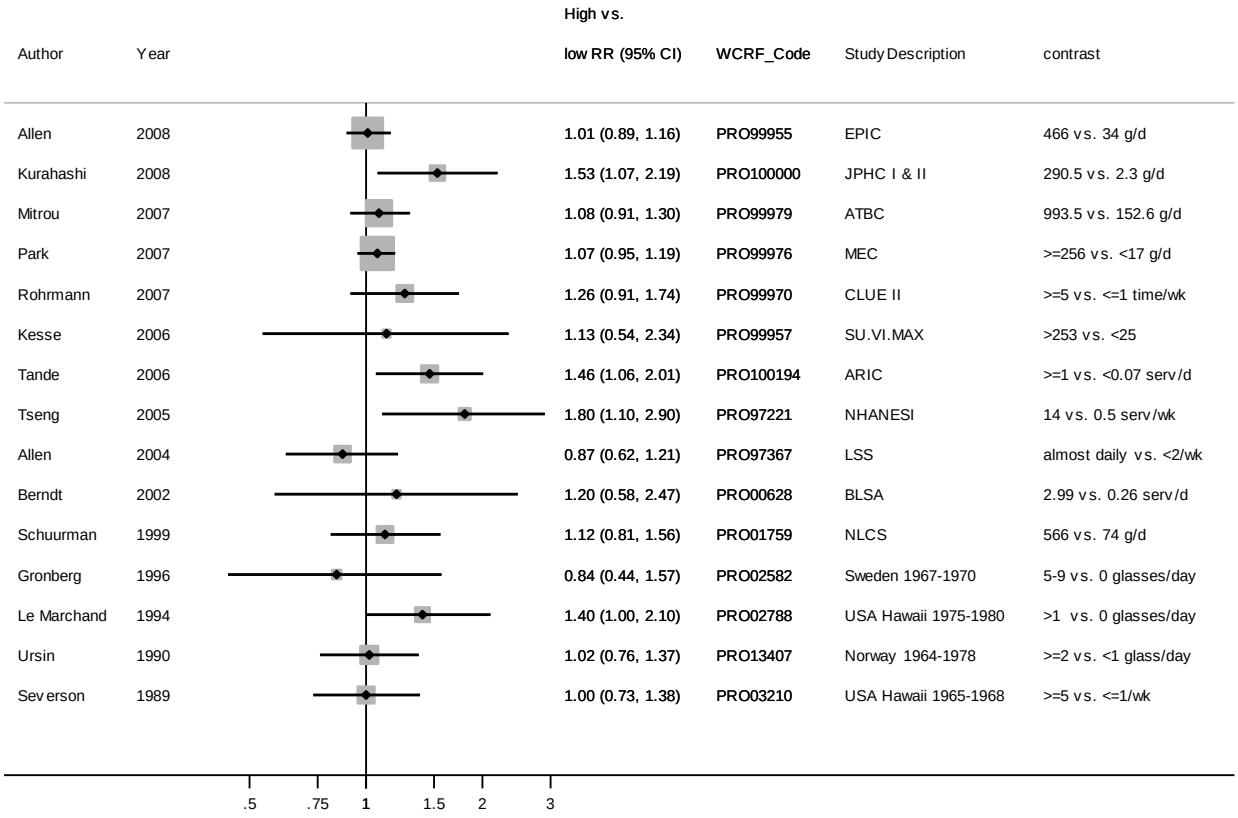
Table 62 Inclusion/exclusion table for meta-analysis of total milk and prostate cancer

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
PRO100000	Kurahashi	2008a	Prospective Cohort	JPHC study-cohort I and II	Incidence	No	Yes	Yes		
PRO99955	Allen	2008a	Prospective Cohort	European Prospective Investigation into Cancer and nutrition (EPIC)	Incidence	No	Yes	Yes	Person-years	
PRO99970	Rohrmann	2007	Prospective Cohort	CLUE II	Incidence	No	Yes	Yes	Mid-exposure values	
PRO99976	Park	2007b	Prospective Cohort	Multiethnic Cohort Study	Incidence	No	Yes	Yes	Mid-exposure values, person-years	
PRO99979	Mitrou	2007	Prospective Cohort	Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study	Incidence	No	Yes	Yes		
PRO100042	Iso	2007	Prospective Cohort	Japan Collaborative Cohort Study	Mortality	No	Yes	Yes	Mid-exposure values	Only included in mortality analysis
PRO100194	Tande	2006	Prospective Cohort	The Atherosclerosis Risk in Communities Study	Incidence	No	Yes	Yes	Mid-exposure values	
PRO99957	Kesse	2006	Prospective Cohort	SU.VI.MAX	Incidence	No	Yes	Yes	Mid-exposure values, person-years	

PRO97221	Tseng	2005	Prospective Cohort	NHANESI	Incidence	Yes	Yes	Yes		
PRO97367	Allen	2004	Prospective Cohort	Life Span Study	Incidence	Yes	Yes	Yes	Mid-exposure values	
PRO00127	Rodriguez	2003	Prospective Cohort	Cancer Prevention Study ll Nutrition Cohort	Incidence	Yes	No	No		No risk estimates
PRO00628	Berndt	2002	Prospective Cohort	Baltimore Longitudinal Study of Aging	Incidence	Yes	Yes	Yes		
PRO01091	Chan	2001	Prospective Cohort	Physicians' Health Study	Incidence	Yes	No	No		No risk estimates
PRO01759	Schuurman	1999b	Case cohort	Netherlands Cohort Study	Incidence	Yes	Yes	No		
PRO02242	Veierod	1997	Prospective Cohort	Norway 1977-1983	Incidence	Yes	No	No		Analysis compared types of milk, not quantities of total milk
PRO02582	Gronberg	1996	Nested case-control study	Sweden 1967-1970	Incidence	Yes	Yes	Yes	Mid-exposure values	
PRO02788	Le Marchand	1994	Prospective Cohort	USA Hawaii 1975-1980	Incidence	Yes	Yes	Yes	Mid-exposure values, distribution of cases and person-years	
PRO13407	Ursin	1990	Prospective Cohort	Norway 1964-1978	Incidence	Yes	No	Yes		Missing risk estimates for middle category
PRO03129	Hsing	1990b	Prospective Cohort	Lutheran Brotherhood Cohort Study	Mortality	Yes	No	No		No risk estimates
PRO03210	Severson	1989b	Prospective	USA Hawaii	Incidence	Yes	Yes	Yes	Mid-exposure	

			Cohort	1965-1968					values	
PRO03244	Snowdon	1988	Prospective Cohort	Adventist Mortality Study	Mortality	Yes	Yes	Yes	Mid-exposure values	Only included in mortality analysis
PRO03648	Hirayama	1979	Prospective Cohort	Japan 1966-1973	Mortality	Yes	No	No		No risk estimates

Figure 64 Highest versus lowest forest plot of total milk and prostate cancer



*Tande et al, 2006 was missed in the 2005 SLR. It has been included in the WCRF Database.

Figure 65 Dose-response meta-analysis of total milk and prostate cancer, per 200 g/day

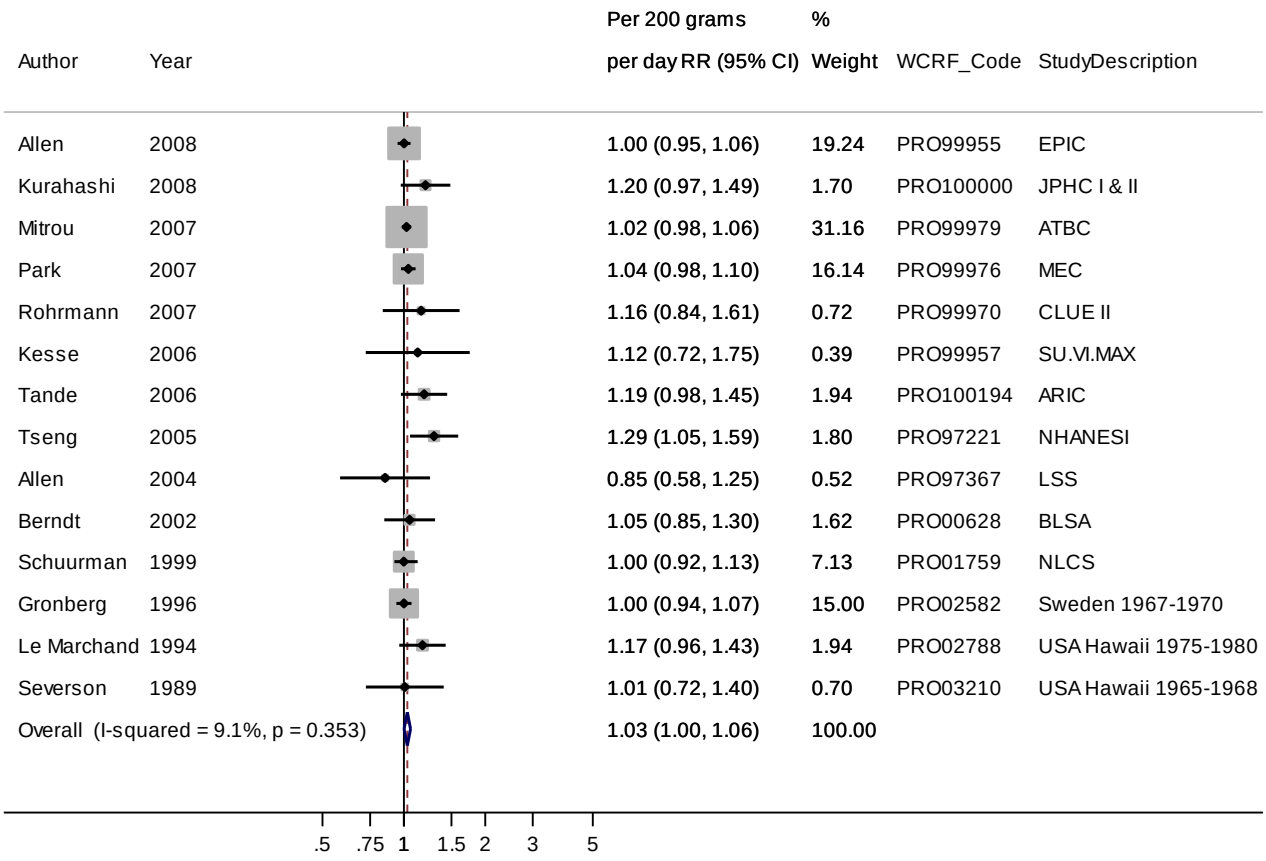
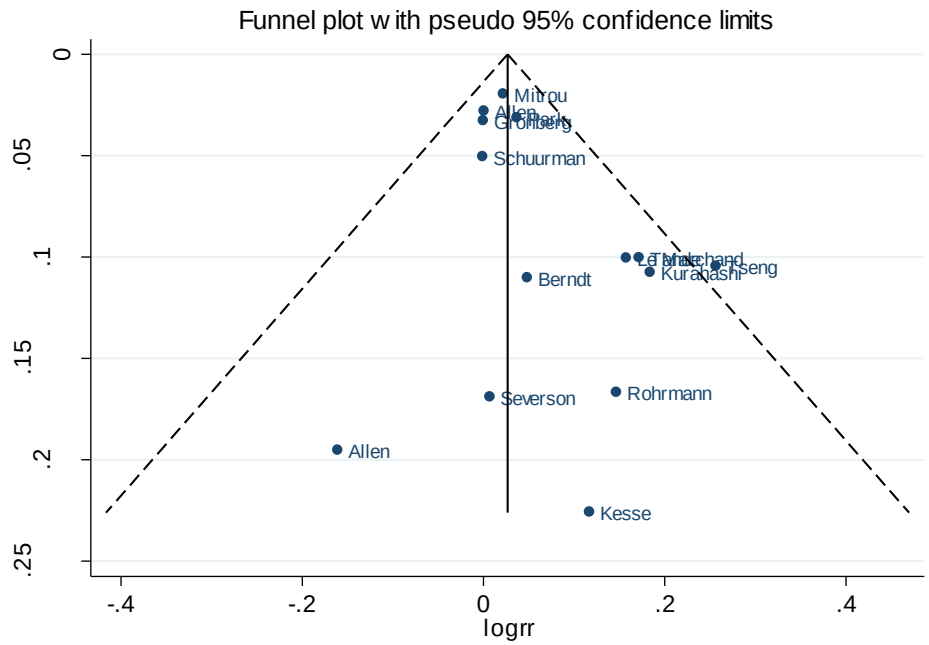


Figure 66 Funnel plot of total milk and prostate cancer



Egger's test p = 0.06

Figure 67 Dose-response graph of total milk and total prostate cancer

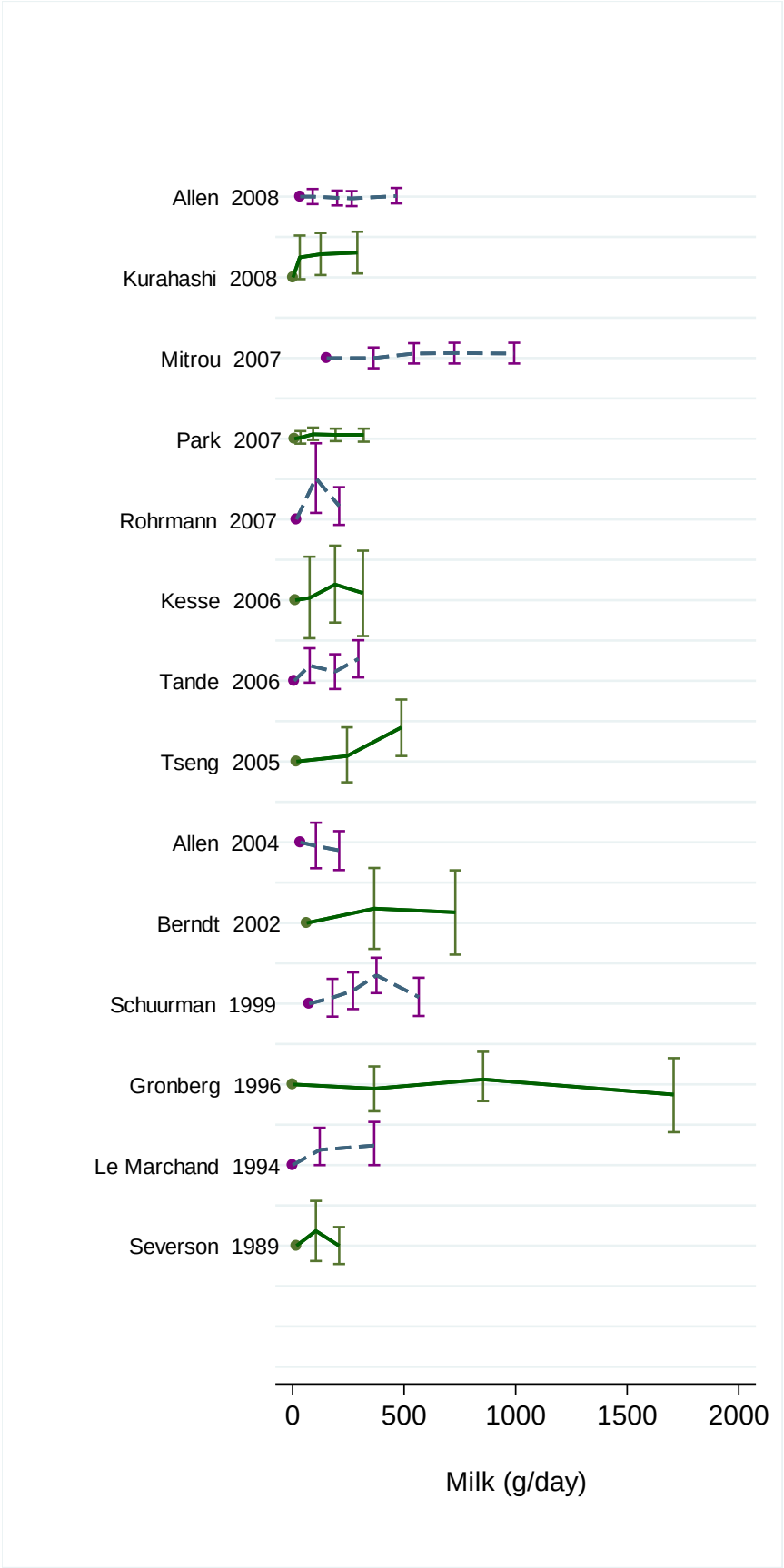


Figure 68 Dose-response meta-analysis of total milk and prostate cancer, per 200 g/day, stratified by outcome type

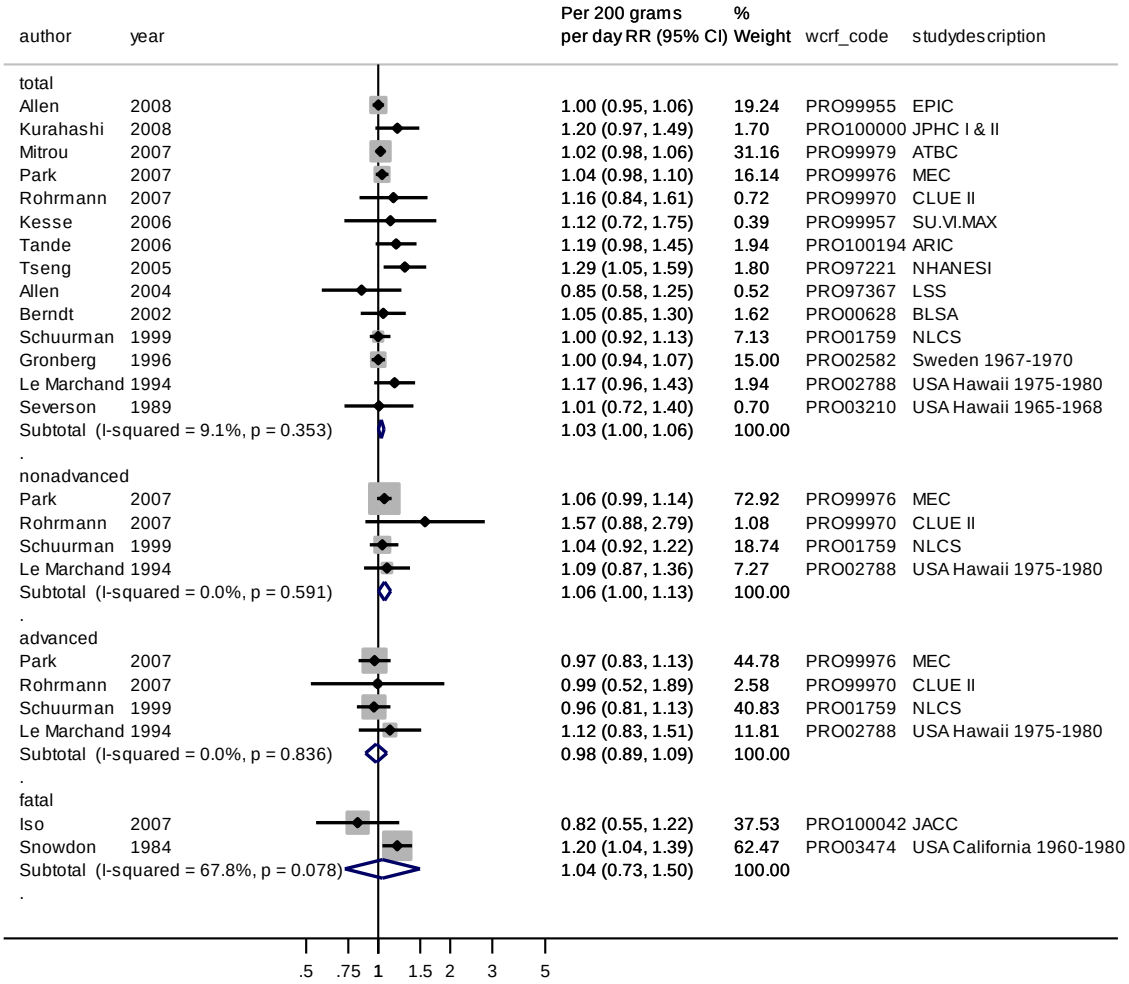


Figure 69 Nonlinear dose-response analysis of milk intake and total prostate cancer

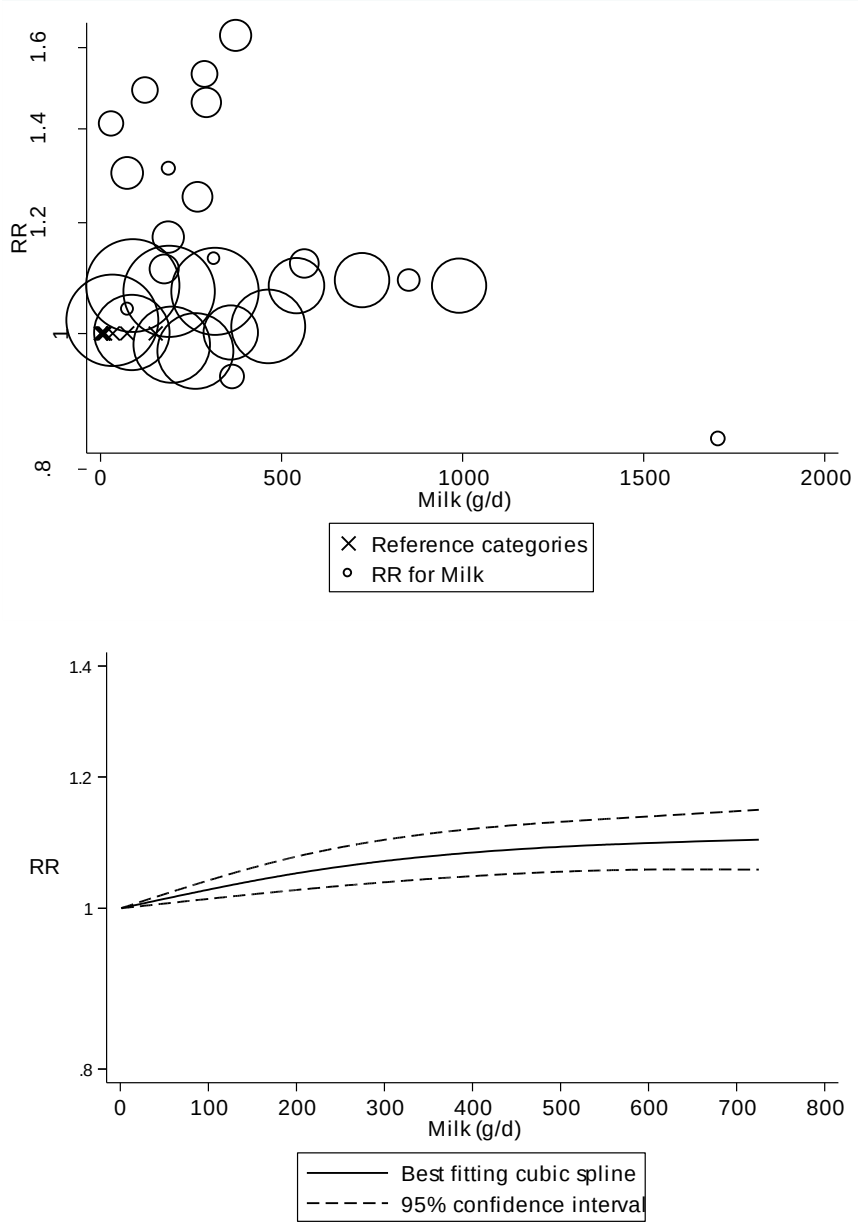


Table 63 Table with milk intake values and corresponding RRs (95% CIs) for non-linear analysis of milk intake and total prostate cancer

Milk intake (g/day)	RR (95% CI)
0	1
91.9	1.02 (1.01-1.04)
200	1.05 (1.03-1.07)
295	1.07 (1.04-1.10)
376	1.08 (1.04-1.11)
466	1.09 (1.05-1.12)
566	1.09 (1.05-1.13)

$p_{non\text{-}linearity} = 0.01$

2.7.1.1 Whole milk

Methods

A total of 10 cohort studies (11 publications) have been published on whole milk and prostate cancer risk. Four cohort studies were identified in the CUP. Dose-response analyses were conducted per 200 g increase per day in whole milk intake. When whole milk intake was expressed in serving, glass or time it was rescaled in grams assuming a standard portion size of 244 g.

Of the studies included in the dose-response analysis eight studies reported on whole milk and total prostate cancer: Thompson et al, 1989; Mills et al, 1989; Schuurman et al, 1999; Tseng et al, 2005; Park et al, 2007b (MEC); Park Y et al, 2007 (NIH-AARP Diet and Health Study); Mitrou et al, 2007 and Song et al, 2013. Four studies reported on whole milk and non-advanced or localised prostate cancer and on whole milk and advanced prostate cancer: Schuurman et al, 1999b; Park et al, 2007b (NIH-AARP Diet and Health Study); Park et al, 2007b (MEC); and Song et al, 2013. Two studies reported on fatal prostate cancer: Park et al, 2007; and Song et al, 2013. Only one study reported on metastatic PC: Michaud et al, 2001 and is not shown in the forest plots. Two studies did not report risk estimates and were excluded (Chan et al, 2001 and Berndt et al, 2002).

Main results
The summary RR per 200 g/day increase in whole milk intake was 0.98 (95% CI 0.95-1.01; $I^2 = 0\%$; $p_{heterogeneity} = 0.46$; n=8) for total PC. There was indication of publication bias with Egger's test, p = 0.04. When stratified by stage/grade the summary RR was 0.94 (95% CI 0.88-1.00; $I^2 = 33.7\%$; $p_{heterogeneity} = 0.21$, n = 4) for nonadvanced cancers, 0.96 (95% CI 0.87-1.06; $I^2 = 0\%$; $p_{heterogeneity} = 0.97$; n = 4) for advanced cancers and 1.29 (95% CI 0.97-1.70; $I^2 = 45.1\%$; $p_{heterogeneity} = 0.18$; n = 2) for fatal cancers. There was no evidence of a nonlinear association between whole milk intake and total prostate cancer, $p_{non\text{-}linearity} = 0.36$.

Heterogeneity
There was low heterogeneity, $I^2 = 0\%$, $p_{heterogeneity} = 0.46$.

Conclusion from the Second Expert Report
In the SLR of the 2007 Expert Report there was limited suggestive evidence of increased risk of prostate cancer with milk and dairy food intake, but there was no separate judgement specifically for whole milk intake.

Published meta-analyses
The previously published meta-analyses on dairy food intake and prostate cancer risk did not report summary estimates for the association between whole milk intake and prostate cancer risk (Gao, 2005, Qin et al, 2007, Huncharek et al, 2009).

Table 64 Studies on whole milk identified in the CUP

Author/ year	Country	Study name	Cases	Years of follow-up	RR	LCI	UCI	Contrast
Song, 2013	USA	Physician's Health Study	2806	28 years	0.95	0.81	1.10	≥ 1 serv/d vs. rarely
Park Y, 2007	USA	NIH- AARP Diet and Health Study	10180	6 years	0.91	0.76	1.09	≥ 2 vs. 0 serv/d
Park, 2007b	USA	Multiethnic Cohort Study	4404	8 years	0.88	0.77	1.00	≥ 163 vs. 0 g/d
Mitrou, 2007	Finland	Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study	1267	17 years	1.05	0.86	1.29	667.9 vs. 0 g/d

Table 65 Overall evidence on whole milk and prostate cancer

	Summary of evidence
2005 SLR	Five of seven studies reported risk estimates for the association between whole milk intake and prostate cancer and none of the studies reported a significant association.
Continuous Update Project	Four additional studies were identified and all reported no significant association between whole milk and prostate cancer risk. No significant association was observed in the CUP meta-analysis.

Table 66 Summary of results of the dose-response meta-analysis of whole milk and prostate cancer

Prostate cancer		
	2005 SLR	CUP
Studies (n)	5	8
Cases (n)	1256	19664
RR (95% CI)	0.95 (0.85-1.05)	0.98 (0.95-1.01)
Increment unit used	Per 1 serving/day	Per 200 g/day
Heterogeneity (I^2, p-value)	0%, p=0.57	0%, p=0.46
	Advanced cancers	
Studies (n)	-	4
Cases (n)		2649
RR (95% CI)		0.96 (0.87-1.06)
Increment unit used		Per 200 g/day
Heterogeneity (I^2, p-value)		0%, p = 0.97
	Non advanced cancers	
Studies (n)	-	4
Cases (n)		14401
RR (95% CI)		0.94 (0.88-1.00)
Increment unit used		Per 200 g/day
Heterogeneity (I^2, p-value)		33.7%, p = 0.21
	Fatal cancers	
Studies (n)	-	2
Cases (n)		483
RR (95% CI)		1.29 (0.97-1.70)
Increment unit used		Per 200 g/day
Heterogeneity (I^2, p-value)		45.1%, p = 0.18

Table 67 Inclusion/exclusion table for meta-analysis of whole milk and prostate cancer

WCRF code	Author	Year	Study design	Study name	Cancer outcome	2005 SLR	CUP dose-response	CUP H vs. L forest plot	Estimated values	Exclusion reason
PRO100162	Song	2013	Prospective Cohort	Physician's Health Study	Incidence	No	Yes	Yes	Mid-exposure values	
PRO100005	Park Y	2007	Prospective Cohort	NIH- AARP Diet and Health Study	Incidence	No	Yes	Yes	Mid-exposure values, person-years	
PRO99976	Park	2007b	Prospective Cohort	Multiethnic Cohort Study	Incidence	No	Yes	Yes	Mid-exposure values, person-years	
PRO99979	Mitrou	2007	Prospective Cohort	Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study	Incidence	No	Yes	Yes		
PRO97221	Tseng	2005	Prospective Cohort	NHANESI	Incidence	Yes	Yes	Yes		
PRO00628	Berndt	2002	Prospective Cohort	Baltimore Longitudinal Study of Aging	Incidence	Yes	No	No		No risk estimates
PRO01122	Michaud	2001	Prospective Cohort	Health Professional's Follow-up Study	Incidence	Yes	No	No		Not enough studies for metastatic cancer
PRO01091	Chan	2001	Prospective Cohort	Physicians' Health Study	Incidence	Yes	No	No		No risk estimates, superseded by Song et al, 2013 (PRO100162)
PRO01759	Schuurman	1999b	Case cohort	Netherlands Cohort Study	Incidence	Yes	Yes	No		Only continuous estimate
PRO03216	Thompson	1989	Prospective Cohort	USA California 1972-1974	Incidence	Yes	Yes	No		Only continuous estimate

				(Lipid Research Clinic Prevalence Study)						
PRO03196	Mills	1989	Prospective Cohort	Adventist Health Study	Incidence	Yes	Yes	Yes	Mid-exposure values	

Figure 70 Highest versus lowest forest plot of whole milk and total prostate cancer

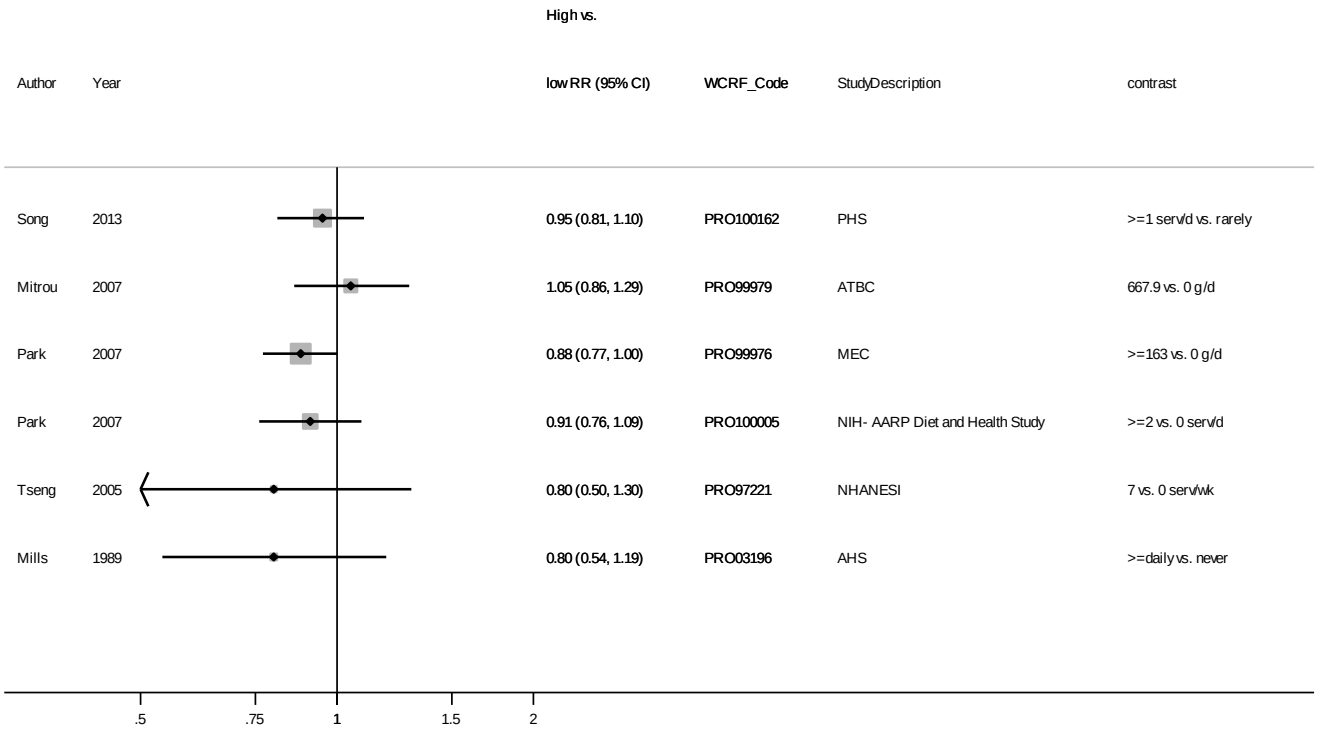


Figure 71 Dose-response meta-analysis of whole milk and total prostate cancer, per 200 g/day

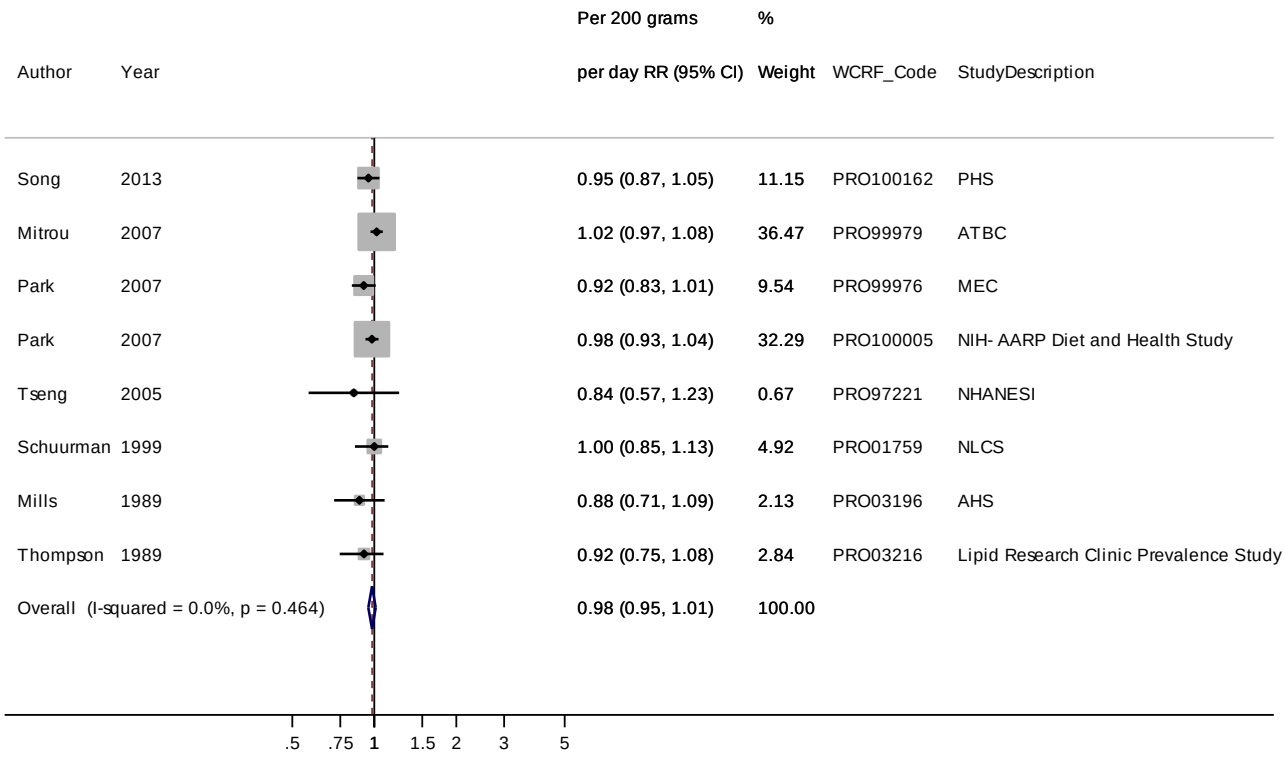
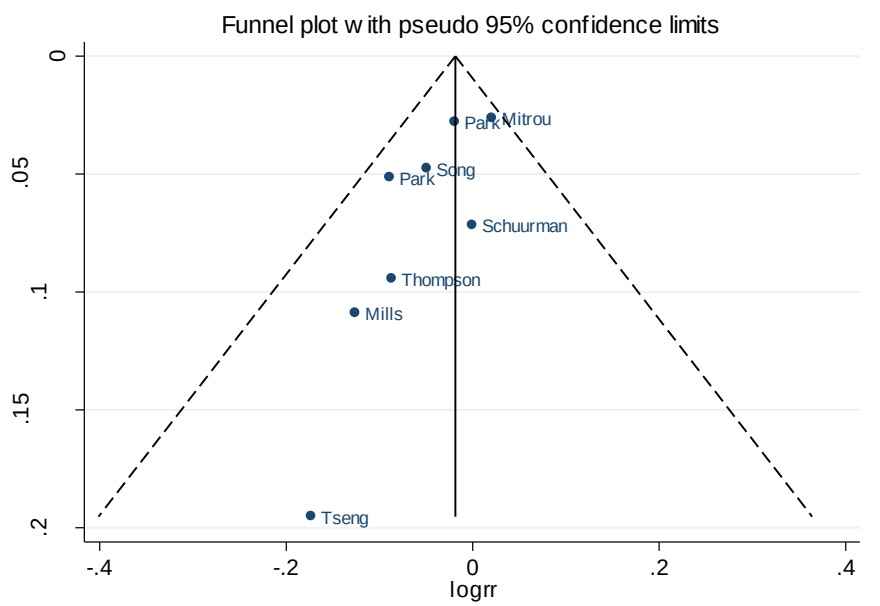


Figure 72 Funnel plot of whole milk and prostate cancer



Egger's test p = 0.04

Figure 73 Dose-response graph of whole milk and total prostate cancer

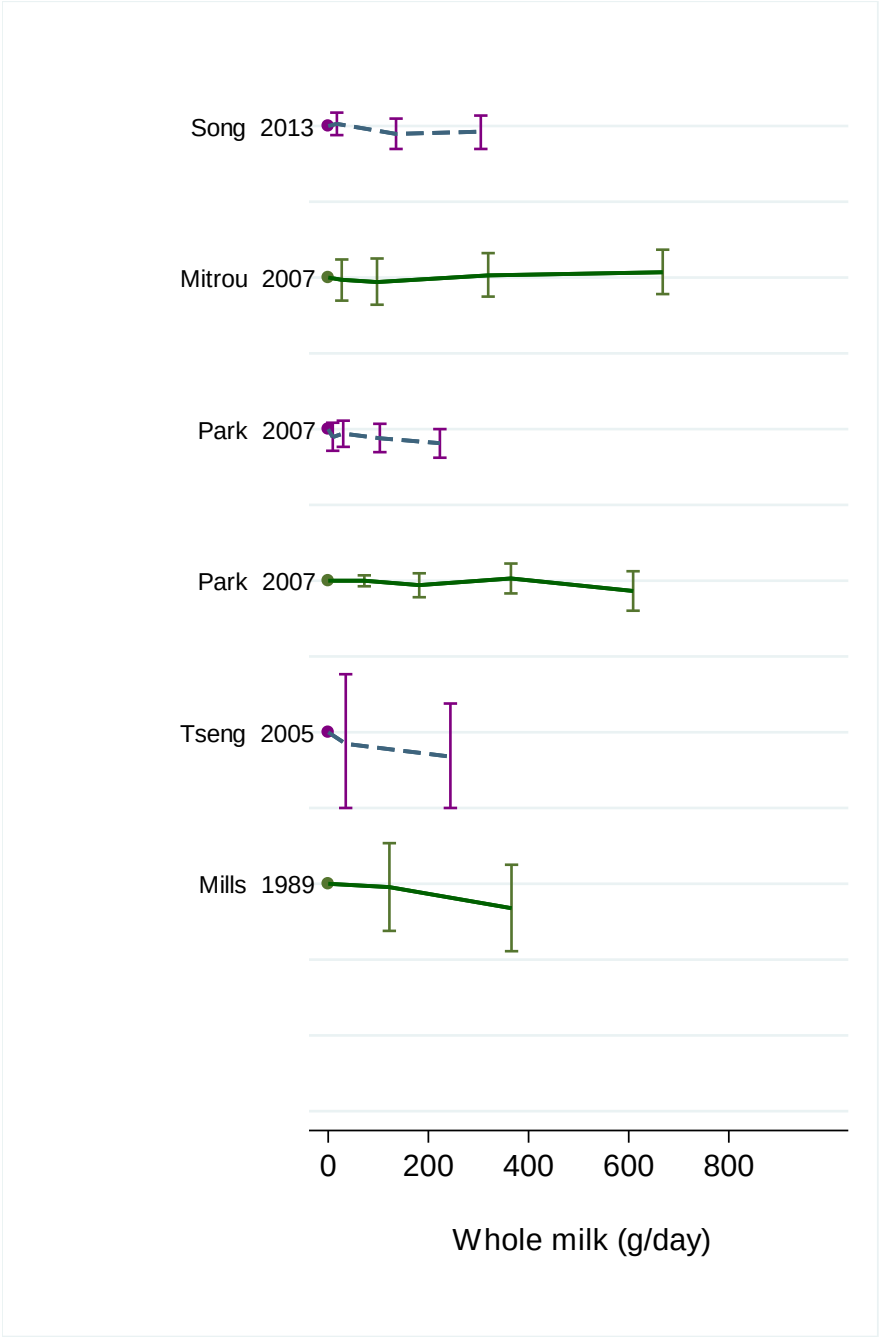
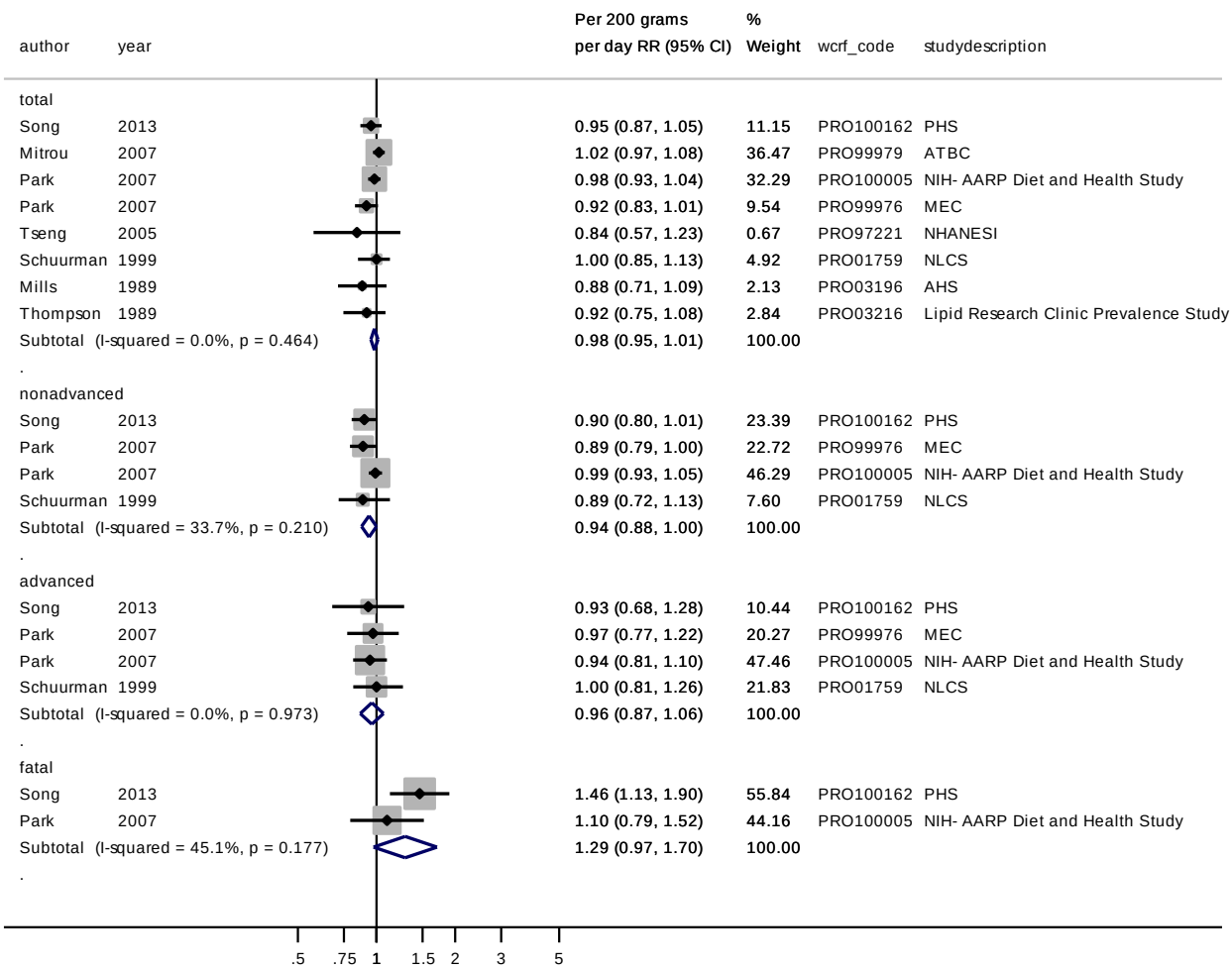


Figure 74 Dose-response meta-analysis of whole milk and prostate cancer, per 200 g/day, stratified by outcome type



2.7.1.2 Low-fat milk

Methods
A total of 7 cohort studies (7 publications) have been published on low-fat milk and prostate cancer risk up. Four cohort studies were identified in the CUP. Dose-response analyses were conducted per 200 g increase per day in low-fat milk intake. When low-fat milk intake was expressed in serving, glass or time it was rescaled in grams assuming a standard portion size of 244 g. In a few studies low-fat milk was combined with skim milk (Michaud, et al, 2001; Park et al, 2007b (MEC); Song et al, 2013).

Of the studies included in the dose-response analysis six studies reported on low-fat milk and total prostate cancer: Schuurman et al, 1999; Tseng et al, 2005; Park et al, 2007b (MEC); Park Y et al, 2007 (NIH-AARP Diet and Health Study); Mitrou et al, 2007 and Song et al, 2013. Four studies reported on low-fat milk and non-advanced or localised prostate cancer and on low-fat milk and advanced prostate cancer: Schuurman et al, 1999; Park Y et al, 2007 (NIH-AARP Diet and Health Study); Park et al, 2007b (MEC); and Song et al, 2013. Only one study reported on metastatic PC: Michaud et al, 2001 and is included among the advanced cancers. Two studies reported on fatal prostate cancer: Park et al, 2007; and Song et al, 2013.

Main results
The summary RR per 200 g/d increase in low-fat milk intake was 1.06 (95% CI 1.01-1.11; I^2 = 66.5%; $p_{heterogeneity}$ = 0.01; n = 6) for total prostate cancer. There was indication of publication bias with Egger's test, p = 0.06, but this was explained by one outlying study and when excluded Egger's test was, p = 0.22 and the summary RR was 1.05 (95% CI 1.01-1.09; I^2 = 57.5%; $p_{heterogeneity}$ = 0.05). When stratified by stage/grade the summary RR was 1.09 (95% CI: 1.01-1.17; I^2=77.1%; pheterogeneity = 0.004; n = 4) for nonadvanced cancers, 1.02 (95% CI: 0.95-1.08; I^2=35.6%; pheterogeneity = 0.18; n = 5) for advanced cancers and 1.06 (95% CI: 0.92-1.22; I^2=0%; pheterogeneity = 0.64; n = 2) for fatal cancers. There was evidence of a non-linear association between low-fat milk intake and total prostate cancer, $p_{non\text{-}linearity}$<0.01.

Heterogeneity
There was high heterogeneity, I^2 = 66.5%, $p_{heterogeneity}$ = 0.01.

Conclusion from the Second Expert Report
In the SLR of the 2007 Expert Report there was limited suggestive evidence of increased risk of prostate cancer with milk and dairy food intake, but there was no separate judgement specifically for low-fat milk intake.

Published meta-analyses
The previously published meta-analyses on dairy food intake and prostate cancer risk did not report summary estimates for the association between low-fat milk intake and prostate cancer risk (Gao, 2005, Qin et al, 2007, Huncharek et al, 2009).

Table 68 Studies on low-fat milk identified in the CUP

Author/ year	Country	Study name	Cases	Years of follow-up	RR	LCI	UCI	Contrast
Song, 2013	USA	Physician's Health Study	2806	28 years	1.19	1.06	1.33	≥ 1 serv/d vs. rarely
Park Y, 2007	USA	NIH- AARP Diet and Health Study	10180	6 years	1.03	0.95	1.13	≥ 2 vs. 0 serv/d
Park, 2007b	USA	Multiethnic Cohort Study	4404	8 years	1.16	1.04	1.29	≥ 243 vs. 0 g/d
Mitrou, 2007	Finland	Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study	1267	17 years	1.18	0.97	1.44	773.1 vs. 75.9 g/d

Table 69 Overall evidence on low-fat milk and prostate cancer

	Summary of evidence
2005 SLR	Low fat milk was not evaluated in the previous SLR.
Continuous Update Project	Four additional studies were identified and two reported significant positive associations between low-fat milk and prostate cancer risk while two reported no significant association.

Table 70 Summary of results of the dose-response meta-analysis of low-fat milk and prostate cancer

Prostate cancer		
	2005 SLR	CUP
Studies (n)	-	6
Cases (n)		19430
RR (95% CI)		1.06 (1.01-1.11)
Increment unit used		Per 200 g/day
Heterogeneity (I^2, p-value)		66.5%, p = 0.01
	Non advanced cancers	
Studies (n)	-	4
Cases (n)		14401
RR (95% CI)		1.09 (1.01-1.17)
Increment unit used		Per 200 g/day
Heterogeneity (I^2, p-value)		77.1%, p = 0.004
	Advanced cancers	
Studies (n)	-	5
Cases (n)		2898
RR (95% CI)		1.02 (0.95-1.08)
Increment unit used		Per 200 g/day
Heterogeneity (I^2, p-value)		35.6%, p = 0.18
	Fatal cancers	
Studies (n)	-	2
Cases (n)		483
RR (95% CI)		1.06 (0.92-1.22)
Increment unit used		Per 200 g/day
Heterogeneity (I^2, p-value)		0%, p = 0.64

Table 71 Inclusion/exclusion table for meta-analysis of low-fat milk and prostate cancer

WCRF code	Author	Year	Study design	Study name	Cancer outcome	2005 SLR	CUP dose-response	CUP H vs. L forest plot	Estimated values	Exclusion reason
PRO100162	Song	2013	Prospective Cohort	Physician's Health Study	Incidence	No	Yes	Yes	Mid-exposure values	
PRO100005	Park Y	2007	Prospective Cohort	NIH- AARP Diet and Health Study	Incidence	No	Yes	Yes	Mid-exposure values, person-years	
PRO99976	Park	2007b	Prospective Cohort	Multiethnic Cohort Study	Incidence	No	Yes	Yes	Mid-exposure values, person-years	
PRO99979	Mitrou	2007	Prospective Cohort	Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study	Incidence	No	Yes	Yes		
PRO97221	Tseng	2005	Prospective Cohort	NHANESI	Incidence	Yes	Yes	Yes		
PRO01122	Michaud	2001	Prospective Cohort	Health Professional's Follow-up Study	Incidence	Yes	Yes	No		
PRO01759	Schuurman	1999b	Case cohort	Netherlands Cohort Study	Incidence	Yes	Yes	No		Only continuous estimate

Figure 75 Highest versus lowest forest plot of low-fat milk and prostate cancer

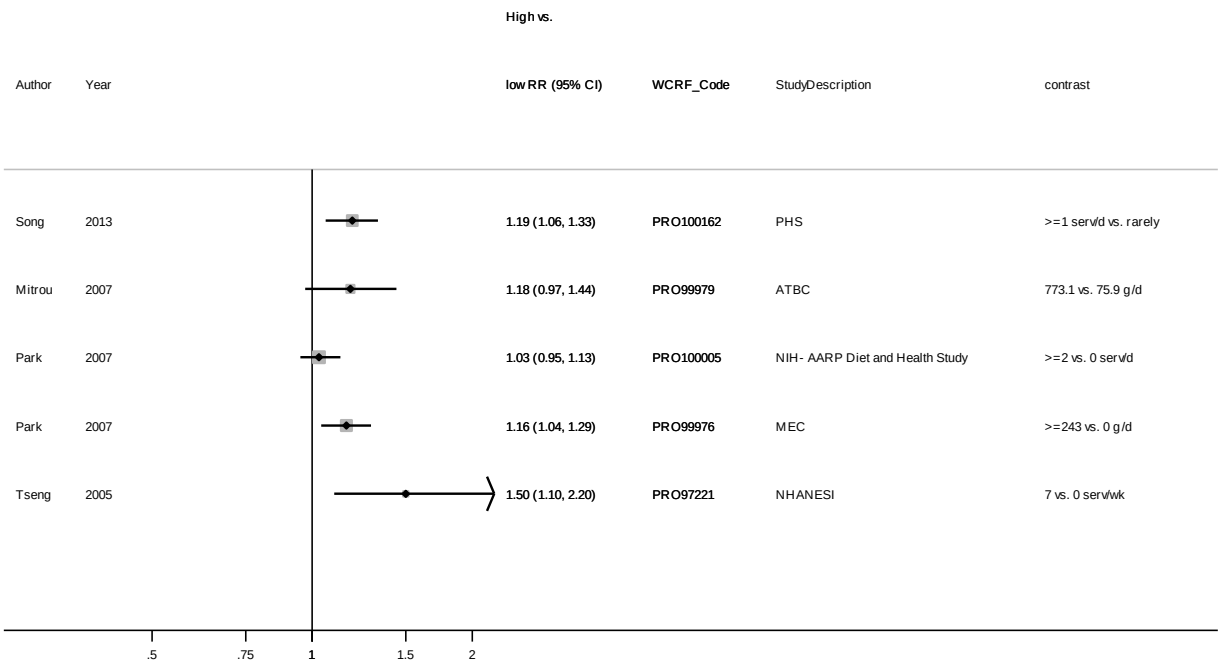


Figure 76 Dose-response meta-analysis of low-fat milk and prostate cancer, per 200 g/day

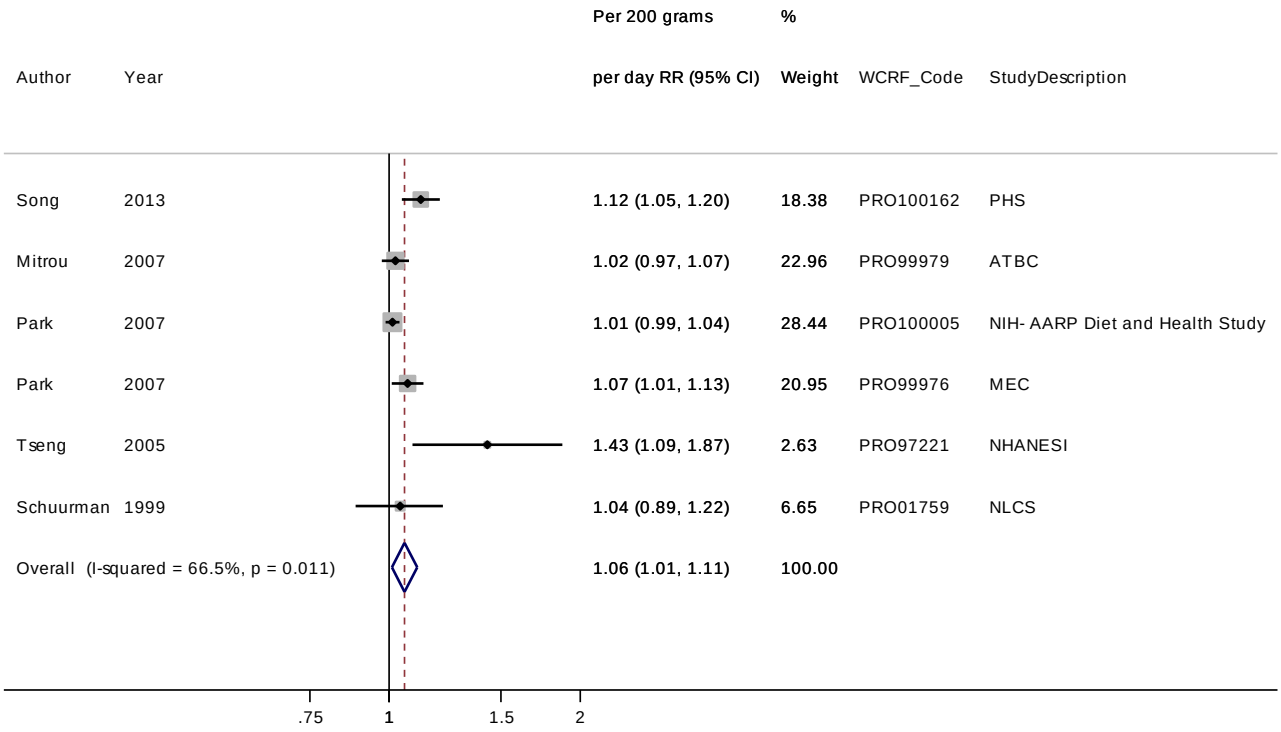
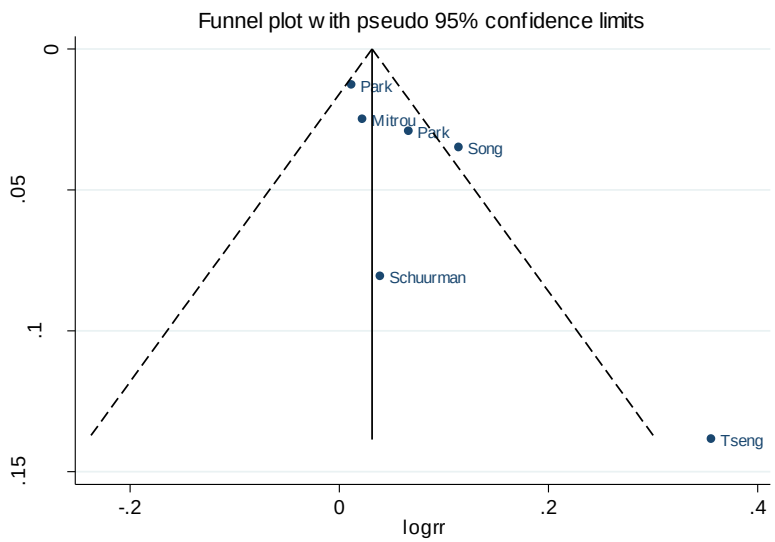


Figure 77 Funnel plot of low-fat milk and prostate cancer



Egger's test p = 0.06

Figure 78 Dose-response graph of low-fat milk and total prostate cancer

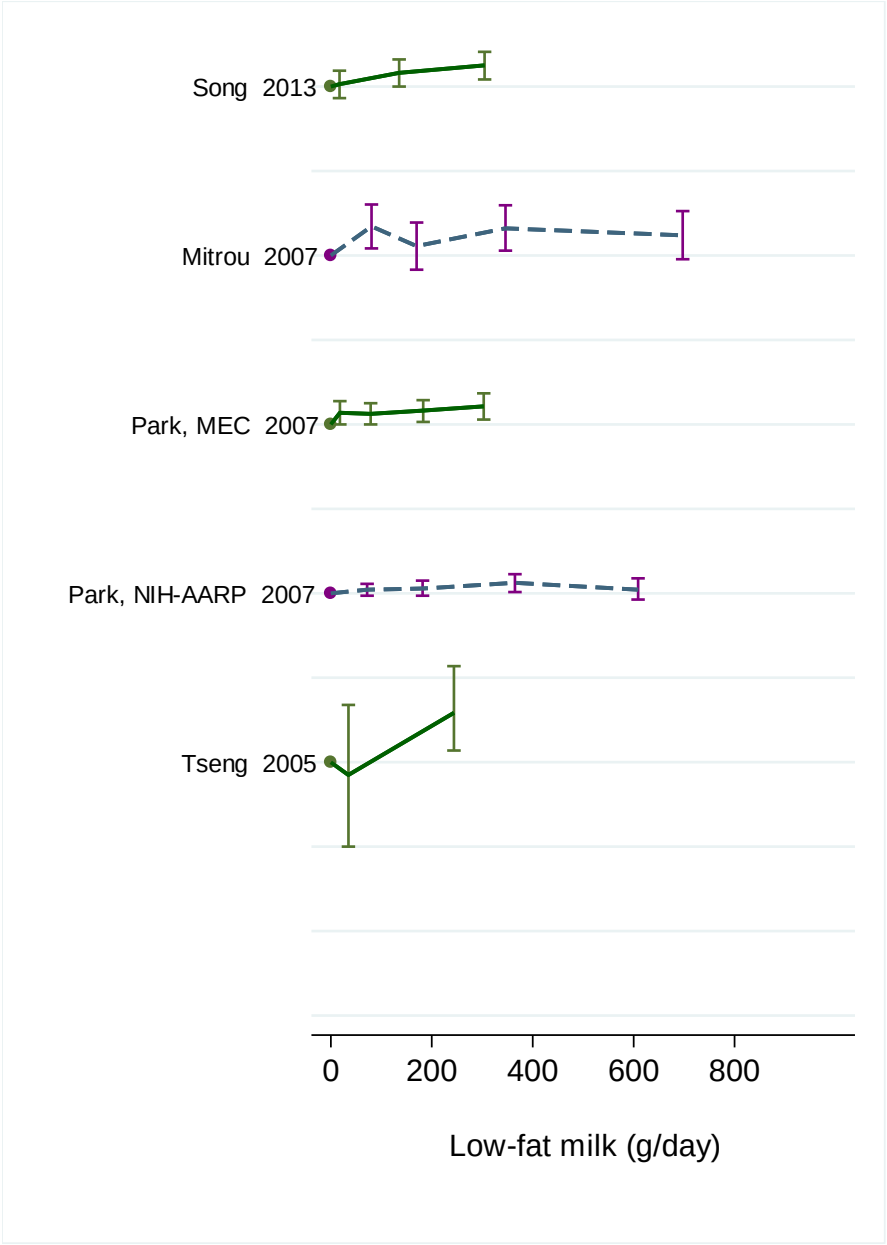


Figure 79 Dose-response meta-analysis of low-fat milk and prostate cancer, per 200 g/day, stratified by outcome type

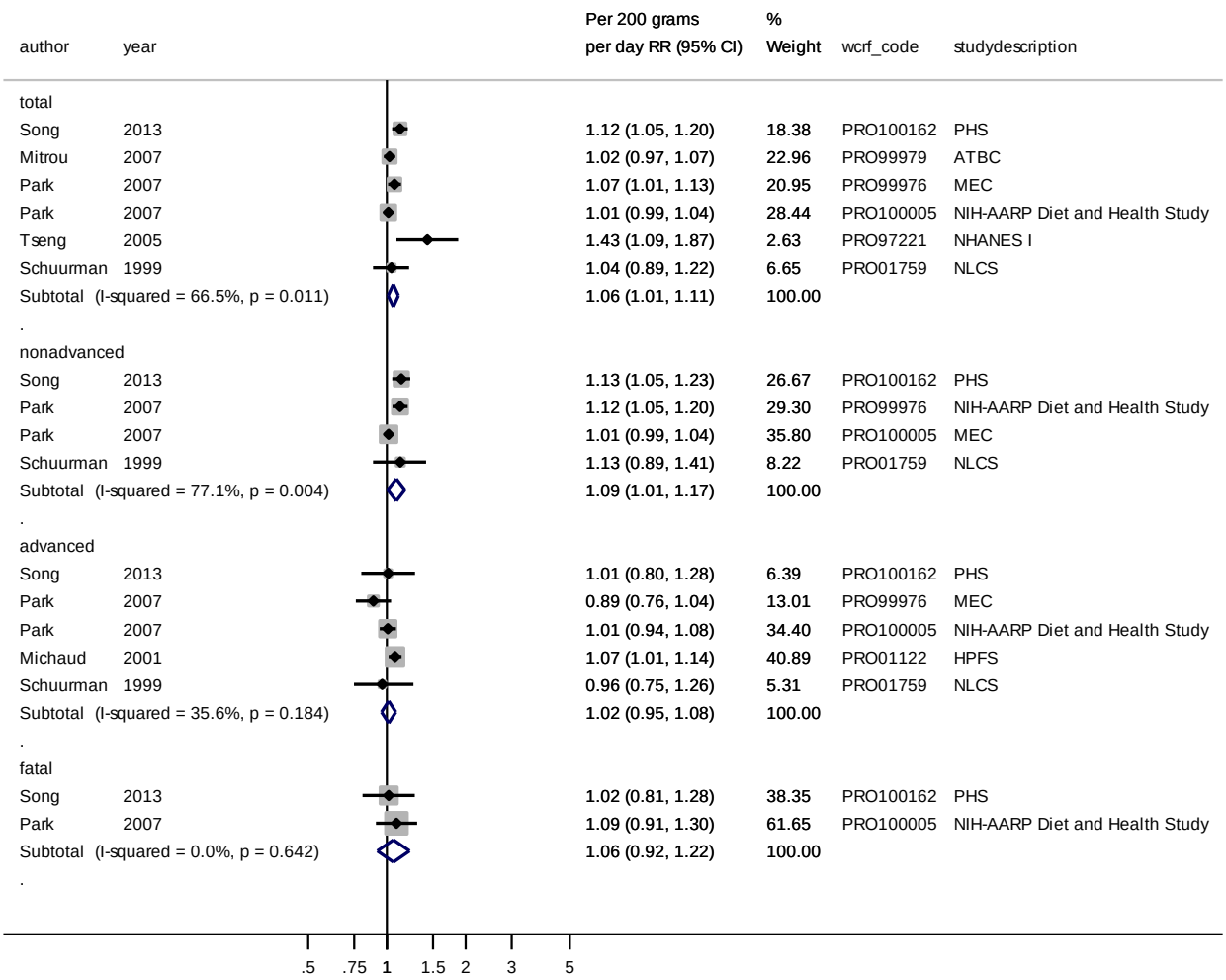


Figure 80 Non-linear dose-response analysis of low-fat milk intake and total prostate cancer

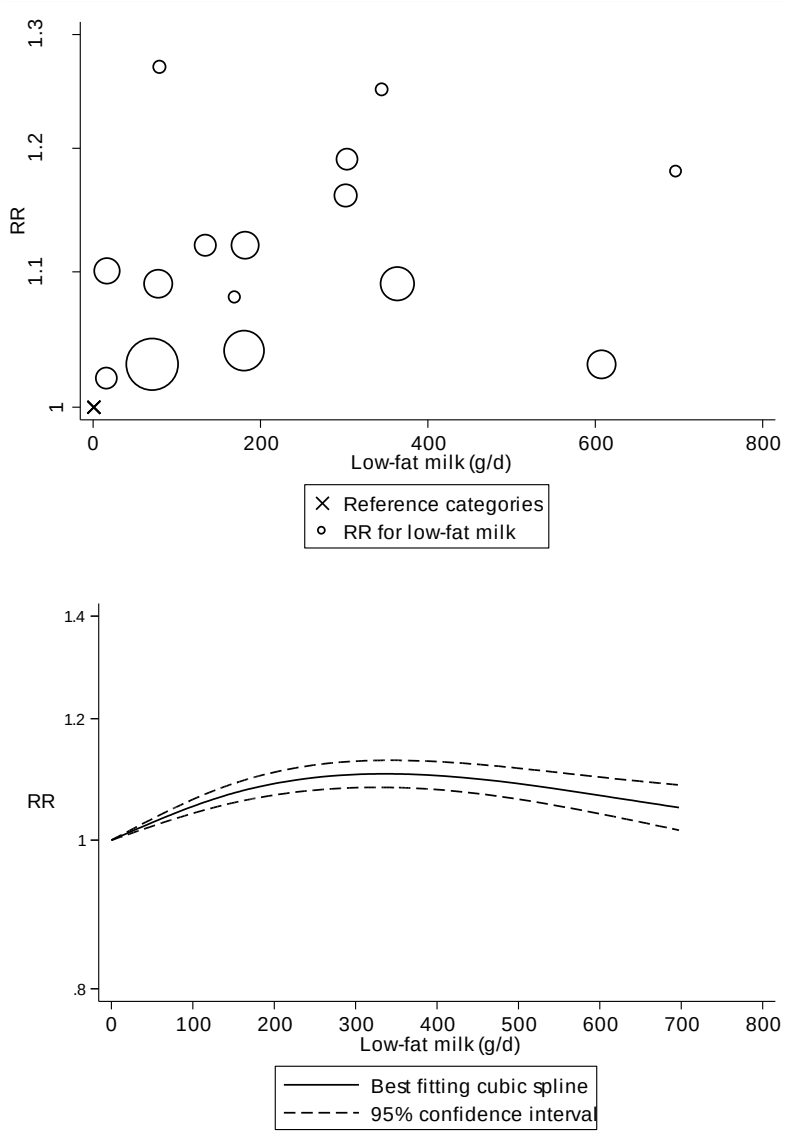


Table 72 Table with low-fat milk intake values and corresponding RRs (95% CIs) for non-linear analysis of low-fat milk intake and total prostate cancer

Low fat milk intake (g/day)	RR (95% CI)
0	1
81	1.04 (1.03-1.05)
183	1.08 (1.07-1.10)
303	1.10 (1.08-1.13)
346	1.10 (1.08-1.13)
697	1.05 (1.02-1.09)

$p_{non\text{-}linearity} < 0.01$

2.7.2 Cheese

Methods
A total of 14 cohort studies (16 publications) have been published on cheese and prostate cancer risk. Nine studies were identified in the CUP. Dose-response analyses were conducted per 50 g/day increase in cheese intake. Servings were rescaled to grams using 43 g as standard portion size.

Eleven studies reported on cheese and total prostate cancer: Schuurman et al, 1999; Allen et al, 2004; Tseng et al, 2005; Kesse et al, 2006; Rohrmann et al, 2007; Park et al, 2007b (MEC); Park Yet al, 2007 (NIH-AARP Diet and Health Study); Mitrou et al, 2007; Kurahashi et al, 2008a; Allen et al, 2008a and Song et al, 2013.

Four studies reported on localised, non-advanced or low-stage prostate cancer: Schuurman et al, 1999b and Park et al, 2007b (MEC); Park Yet al, 2007 (NIH-AARP Diet and Health Study); and Rohrmann et al, 2007.

Five studies reported on advanced or high-stage prostate cancer: Schuurman et al, 1999; Leitzmann et al, 2004; Park et al, 2007; Park et al, 2007b; and Song et al, 2013.
Three studies reported on fatal PC: Snowdon et al, 1984; Iso et al, 2007 and Park et al, 2007 and two of these were only included in the analysis of mortality (Snowden et al, 1984 and Iso et al, 2007).

Only one study reported on metastatic PC: Michaud et al, 2001 and is not shown in the forest plots. Two studies did not report risk estimates and were excluded (Chan et al, 2001 and Berndt et al, 2002).

Main results
The summary RR per 50 gram per day increase in cheese intake was 1.09 (95% CI 1.02-1.18; I^2=0%; $p_{heterogeneity}$ = 0.84; n = 11) for total PC. There was no evidence of publication bias with Egger's test, p = 0.99. When stratified by outcome type the summary RR was 1.16 (95% CI 0.96-1.40; I^2 = 39.7%; $p_{heterogeneity}$ = 0.17; n = 4) for nonadvanced prostate cancer, 1.06 (95% CI 0.76-1.48; I^2 = 57.2%; $p_{heterogeneity}$ = 0.05; n = 5) for advanced prostate cancer and 1.17 (95% CI 0.62-2.23; I^2 = 0%; $p_{heterogeneity}$ = 0.39; n = 3) for fatal prostate cancer. There was no evidence of a non-linear association between cheese intake and total prostate cancer, $p_{nonlinearity}$=0.99.

Heterogeneity
There was no evidence of heterogeneity, I^2 = 0%, $p_{heterogeneity}$ = 0.84.

Conclusion from the Second Expert Report
In the 2005 SLR there was no statement specifically on cheese intake, although there was limited suggestive evidence that milk and dairy products overall was associated with increased prostate cancer risk.

Published meta-analyses
A meta-analysis of 5 cohort studies reported a summary RR of 1.18 (95% CI 1.03-1.32) for high vs. low cheese intake (Qin et al, 2007).

A meta-analysis of 7 cohort studies reported a summary RR of 1.11 (95% CI 0.99-1.25) (Huncharek et al, 2009).

Table 73 Studies on cheese intake identified in the CUP

Author/year	Country	Study name	Cases	Years of follow-up	RR	LCI	UCI	Contrast
Song, 2013	USA	Physician's Health Study	2806	28 years	1.05	0.85	1.30	≥ 1 serv/d vs. ≤ 1 serv/wk
Kurahashi, 2008a	Japan	JPHC study-cohort I and II	329	7.5 years	1.32	0.93	1.89	6.2 vs. 1.9 g/d
Allen, 2008a	Ten European countries	European Prospective Investigation into Cancer and nutrition (EPIC)	2727	8.7 years	1.04	0.90	1.20	57 vs. 15 g/d
Iso, 2007	Japan	Japan Collaborative Cohort Study	142 deaths	≈ 12 years	0.70	0.32	1.52	≥ 3-4 vs. < 1/wk
Rohrmann, 2007	USA	CLUE II	199	13 years	1.43	1.01	2.03	≥ 5 vs. ≤ 1/wk
Park Y, 2007	USA	NIH- AARP Diet and Health Study	10180	6 years	1.08	0.96	1.22	≥ 0.75 vs. < 0.1 serv/d
Park, 2007b	USA	Multiethnic Cohort Study	4404	8 years	1.01	0.91	1.12	≥ 14 vs. 0 g/d
Mitrou, 2007	Finland	Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study	1267	17 years	1.13	0.95	1.36	54.6 vs. 3.0 g/d
Kesse, 2006	France	SU.VI.MAX	69	7.7 years	0.90	0.42	1.91	> 71 vs. < 25 g/d

Table 74 Overall evidence on cheese and prostate cancer

	Summary of evidence
2005 SLR	Five cohorts reported on cheese and prostate cancer and all of these reported non-significant positive associations.
Continuous Update Project	Nine cohort studies were identified on cheese and prostate cancer and one of these reported a significant positive association, while the remaining studies reported no significant association. A positive association was

	observed for total prostate cancer in the CUP meta-analysis.

Table 75 Summary of results of the dose-response meta-analysis of cheese and prostate cancer

Prostate cancer		
	2005 SLR	CUP
Studies (n)	5	11
Cases (n)	1514	22950
RR (95% CI)	1.21 (0.96-1.53)	1.09 (1.02-1.18)
Increment unit used	Per serving/day	Per 50 g/day
Heterogeneity (I^2, p-value)	7.7%, p = 0.36	0%, p = 0.84
	Non advanced cancers	
Studies (n)	-	4
Cases (n)		12459
RR (95% CI)		1.16 (0.96-1.40)
Increment unit used		Per 50 g/day
Heterogeneity (I^2, p-value)		39.7%, p = 0.17
	Advanced cancers	
Studies (n)	-	5
Cases (n)		2879
RR (95% CI)		1.06 (0.76-1.48)
Increment unit used		Per 50 g/day
Heterogeneity (I^2, p-value)		57.2%, p = 0.05
	Fatal cancers	
Studies (n)	-	3
Cases (n)		431
RR (95% CI)		1.17 (0.62-2.23)
Increment unit used		Per 50 g/day
Heterogeneity (I^2, p-value)		0%, p = 0.39

Table 76 Inclusion/exclusion table for meta-analysis of cheese and prostate cancer

WCRF code	Author	Year	Study design	Study name	Cancer outcome	2005 SLR 2005	CUP dose-response	CUP H vs. L forest plot	Estimated values	Exclusion reason
PRO100162	Song,	2013	Prospective Cohort	Physician's Health Study	Incidence	No	Yes	Yes	Mid-exposure values	
PRO100000	Kurahashi	2008a	Prospective Cohort	JPHC study-cohort I and II	Incidence	No	Yes	Yes		
PRO99955	Allen	2008a	Prospective Cohort	European Prospective Investigation into Cancer and nutrition (EPIC)	Incidence	No	Yes	Yes	Person-years	
PRO100042	Iso	2007	Prospective Cohort	Japan Collaborative Cohort Study	Mortality	No	Yes	Yes		
PRO99970	Rohrmann	2007	Prospective Cohort	CLUE II	Incidence	No	Yes	Yes	Mid-exposure values	
PRO100005	Park Y	2007	Prospective Cohort	NIH- AARP Diet and Health Study	Incidence	No	Yes	Yes		
PRO99976	Park	2007b	Prospective Cohort	Hawaii-Los Angeles Multiethnic Cohort (MEC) Study	Incidence	No	Yes	Yes	Mid-exposure values, person-years	
PRO99979	Mitrou	2007	Prospective Cohort	Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study	Incidence	No	Yes	Yes		

PRO99957	Kesse	2006	Prospective Cohort	SU.VI.MAX	Incidence	No	Yes	Yes	Mid-exposure values, person-years	
PRO97221	Tseng	2005	Prospective Cohort	NHANESI	Incidence	Yes	Yes	Yes		
PRO97679	Leitzmann	2004	Prospective Cohort	Health Professionals Follow-up Study	Incidence	Yes	No	No		
PRO97367	Allen	2004	Prospective Cohort	Life Span Study	Incidence	Yes	No	No	Mid-exposure values	Nonspecific exposure (included eggs)
PRO01122	Michaud	2001	Prospective Cohort	Health Professionals Follow-up study	Incidence	Yes	Yes	Yes		Included for metastatic prostate cancer, total: overlap with Giovannucci et al, 2006 (PRO99968)
PRO01091	Chan	2001	Prospective Cohort	Physicians' Health Study	Incidence	Yes	No	No		Overlap with Song et al, 2013 (PRO100162)
PRO01759	Schuurman	1999b	Case cohort	Netherlands Cohort Study	Incidence	Yes	Yes	Yes		
PRO03474	Snowdon	1984	Prospective Cohort	Adventist Mortality Study	Mortality	Yes	Yes	Yes		

Figure 81 Highest versus lowest forest plot of cheese and total prostate cancer

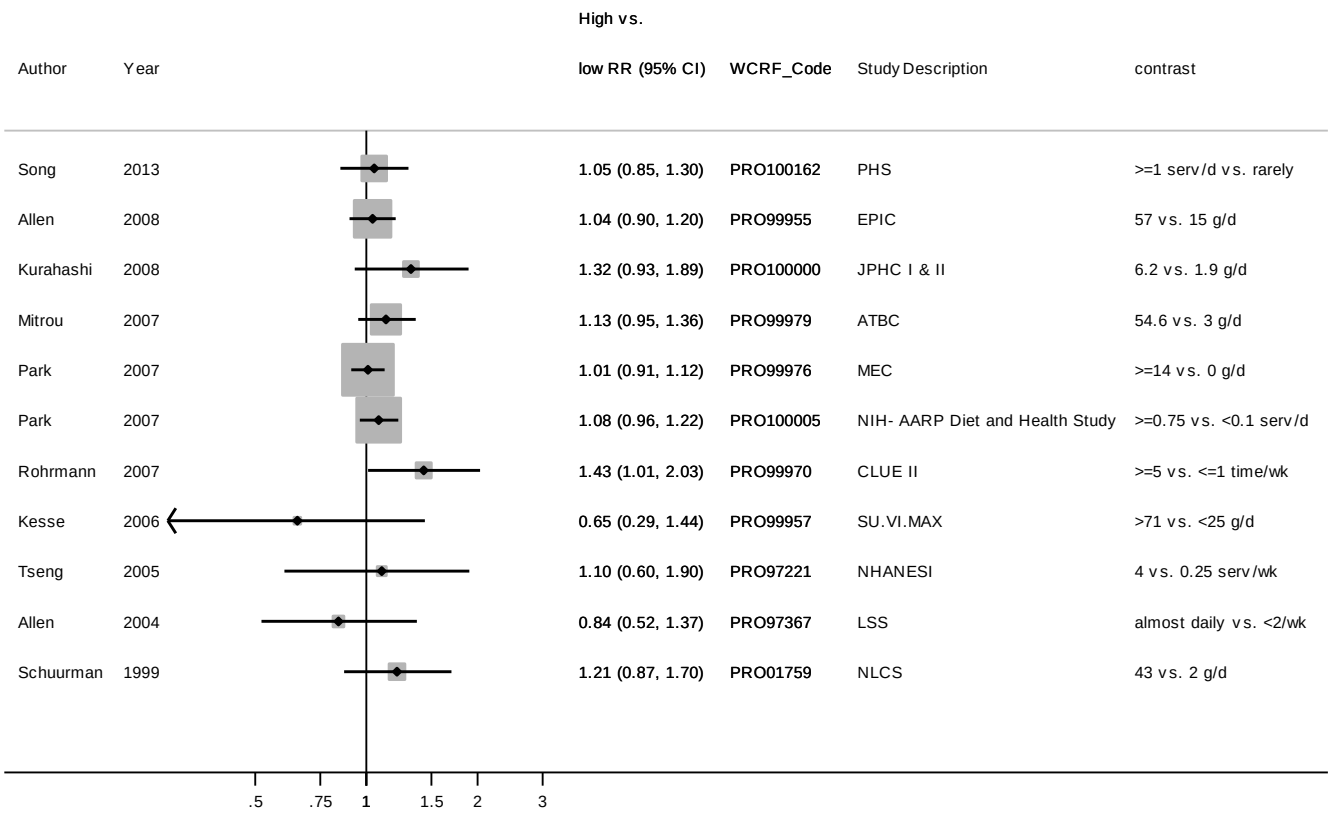


Figure 82 Dose-response meta-analysis of cheese and total prostate cancer, per 50 g/day

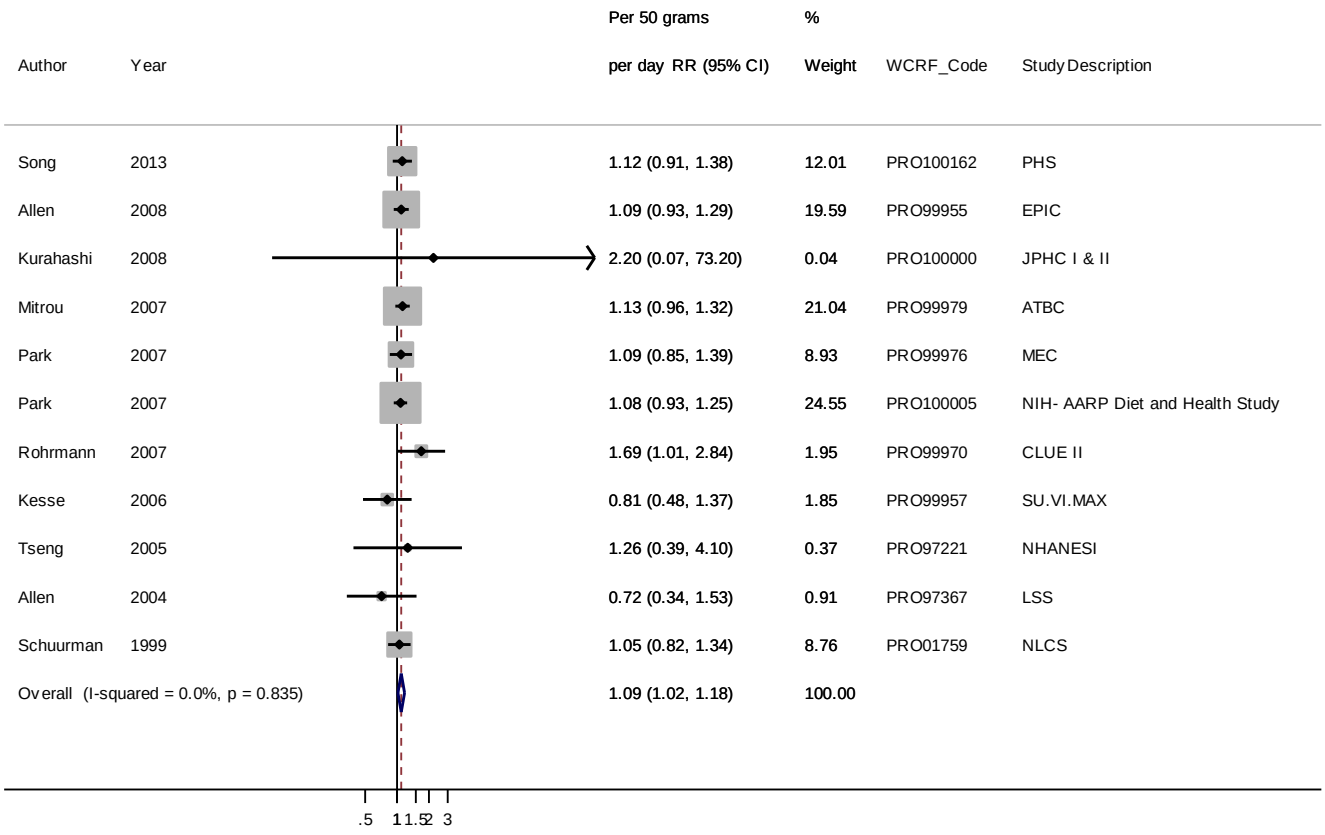
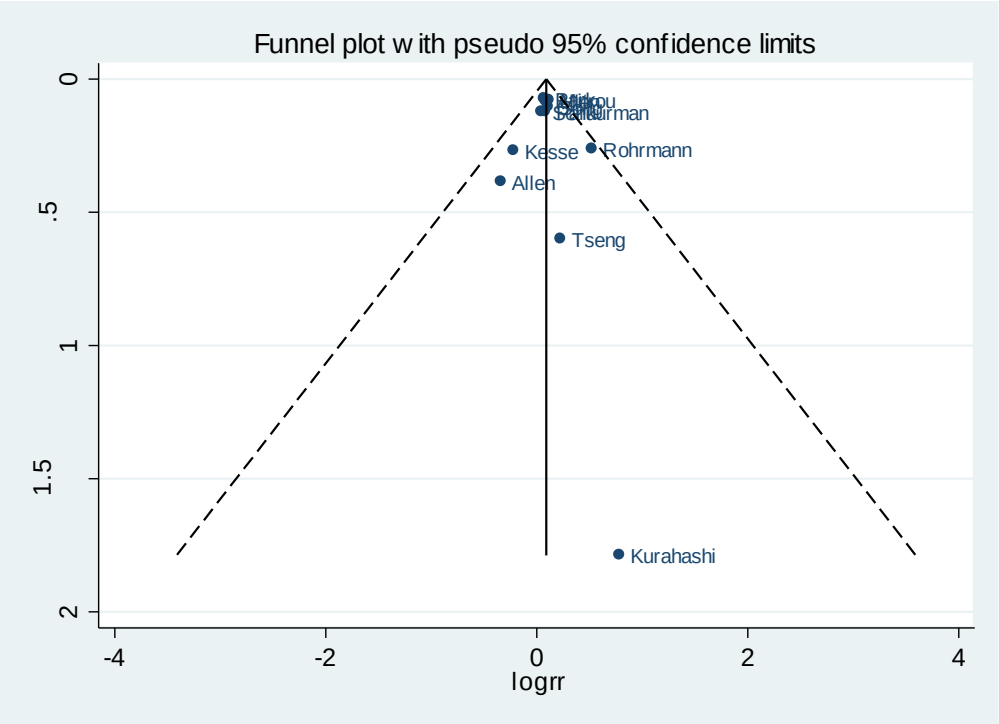


Figure 83 Funnel plot of cheese and prostate cancer



Egger's test p = 0.99

Figure 84 Dose-response graph of cheese and total prostate cancer

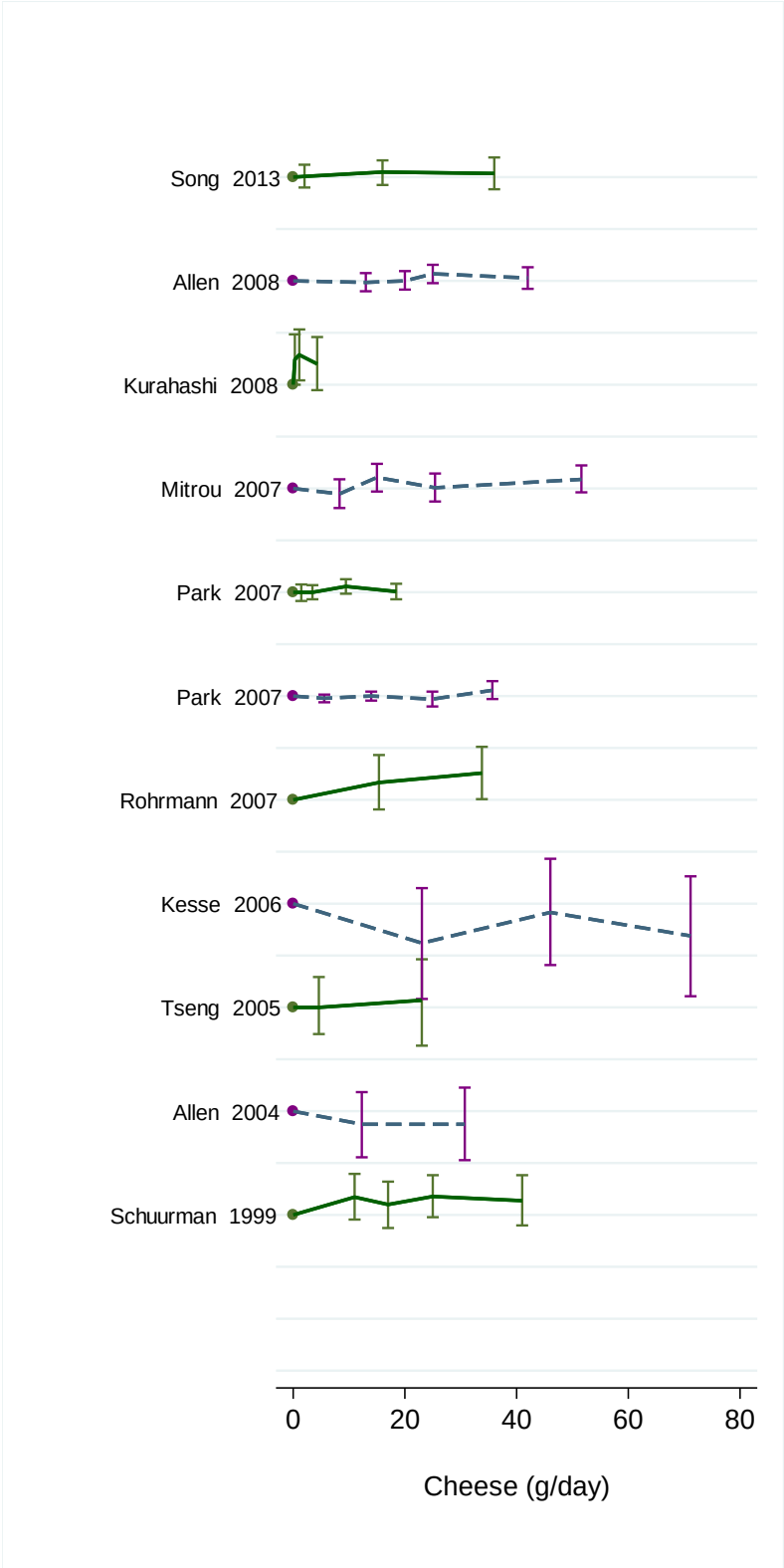
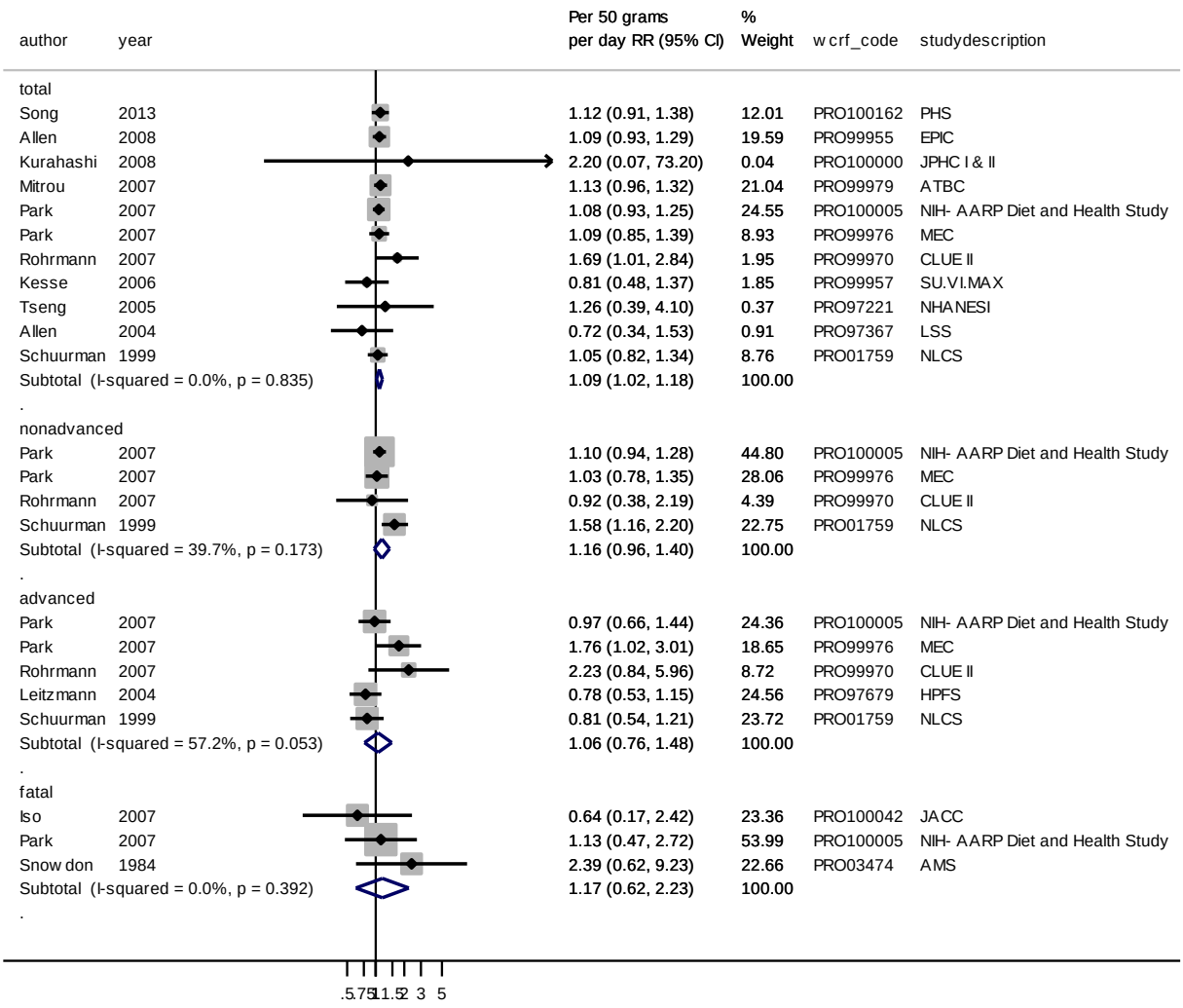


Figure 85 Dose-response meta-analysis of cheese and prostate cancer, per 50 g/day, stratified by outcome type



2.7.3 Yoghurt

Methods
A total of 7 cohort studies have been published on yoghurt and prostate cancer risk and six of these were identified in the CUP. Dose-response analyses were conducted per 100 g/day increase in yoghurt intake.

Six studies reported on total prostate cancer: Schuurman et al, 1999; Kesse et al, 2006; Park et al, 2007b (MEC); Park Y et al, 2007 (NIH-AARP Diet and Health Study); Allen et al, 2008; and Kurahashi et al, 2008a. Only two studies reported on advanced and non-advanced or localised prostate cancer (Park et al, 2007b (MEC); Park Y et al, 2007 (NIH-AARP Diet and Health Study)), and one study reported only on mortality (Iso et al, 2007) and the latter is not shown in any forest plots.

Main results
The summary RR per 100 g/d increase in yoghurt intake was 1.08 (95% CI 0.93-1.24; $I^2 = 81.6\%$; $p_{heterogeneity} < 0.01$; n = 6) for total prostate cancer. There was no evidence of publication bias with Egger's test, p = 0.62. There was no evidence of a non-linear association between yoghurt intake and total prostate cancer risk, $p_{non\text{-}linearity} = 0.99$. The summary RR per 100 g/day increase in yoghurt intake was 0.97 (95% CI 0.82-1.15; $I^2 = 54.5\%$; $p_{heterogeneity} = 0.14$; n = 2) for non advanced prostate cancer and 0.96 (95% CI 0.71-1.30; $I^2=37.8\%$; $p_{heterogeneity} = 0.21$; n = 2) for advanced prostate cancer.

Heterogeneity
There was high heterogeneity, $I^2 = 81.6\%$, $p_{heterogeneity} < 0.01$.

Conclusion from the Second Expert Report
In the 2005 SLR the evidence relating dairy intake to increase prostate cancer risk was considered limited suggestive, but it was possible to evaluate yoghurt because only one prospective study was available.

Published meta-analyses
None of the previous meta-analyses on dairy products and prostate cancer evaluated yoghurt intake in relation to prostate cancer risk (Gao et al, 2005, Qin et al, 2007, Huncharek et al, 2009).

Table 77 Studies on yoghurt identified in the CUP

Author/year	Country	Study name	Cases	Years of follow-up	RR	LCI	UCI	Contrast
Kurahashi, 2008a	Japan	JPHC study-cohort I and II	329	7.5 years	1.52	1.10	2.12	31.5 vs. 1.9 g/d
Allen, 2008a	Ten European countries	European Prospective Investigation into Cancer and nutrition (EPIC)	2727	8.7 years	1.17	1.04	1.31	135 vs. 12 g/d
Park, 2007	USA	NIH- AARP Diet and Health Study	10180	6 years	1.01	0.89	1.15	≥ 0.5 vs. 0 serv/d
Park, 2007b	USA	Multiethnic Cohort Study	4404	8 years	0.96	0.84	1.09	≥ 40 vs. 0 g/d
Iso, 2007	Japan	Japan Collaborative Cohort Study	142 deaths	NA	1.31	0.63	2.71	≥ 5 vs. < 3/week
Kesse, 2006	France	SU.VI.MAX	69	7.7 years	1.81	0.87	3.76	> 100 vs. 0 g/d

Table 78 Overall evidence on yoghurt and prostate cancer

	Summary of evidence
2005 SLR	One cohort study was identified and reported a non-significant inverse association.
Continuous Update Project	Six additional studies were identified and two reported significant positive associations while the remaining four studies found no significant association. No significant association was observed in the CUP meta-analysis.

Table 79 Summary of results of the dose-response meta-analysis of yoghurt and prostate cancer

Prostate cancer		
	2005 SLR	CUP
Studies (n)	-	6
Cases (n)	-	18282
RR (95% CI)	-	1.08 (0.93-1.24)
Increment unit used	-	Per 100 g/day
Heterogeneity (I^2, p-value)	-	81.6%, $p < 0.0001$

Table 80 Inclusion/exclusion table for meta-analysis of yoghurt and prostate cancer

WCRF code	Author	Year	Study design	Study name	Cancer outcome	2005 SLR 2005	CUP dose-response	CUP H vs. L forest plot	Estimated values	Exclusion reason
PRO100000	Kurahashi	2008a	Prospective Cohort	JPHC study-cohort I and II	Incidence	No	Yes	Yes		
PRO99955	Allen	2008a	Prospective Cohort	European Prospective Investigation into Cancer and nutrition (EPIC)	Incidence	No	Yes	Yes	Person-years	
PRO100005	Park Y	2007	Prospective Cohort	NIH- AARP Diet and Health Study	Incidence	No	Yes	Yes		
PRO99976	Park	2007b	Prospective Cohort	Multiethnic Cohort Study	Incidence	No	Yes	Yes	Mid-exposure values, person-years	
PRO100042	Iso	2007	Prospective Cohort	Japan Collaborative Cohort Study	Mortality	No	Yes	Yes	Mid-exposure values	
PRO99957	Kesse	2006	Prospective Cohort	SU.VI.MAX	Incidence	No	Yes	Yes	Mid-exposure values, person-years	
PRO01759	Schuurman	1999b	Case cohort	Netherlands Cohort Study	Incidence	Yes	Yes	No		

Figure 86 Highest versus lowest forest plot of yoghurt and prostate cancer

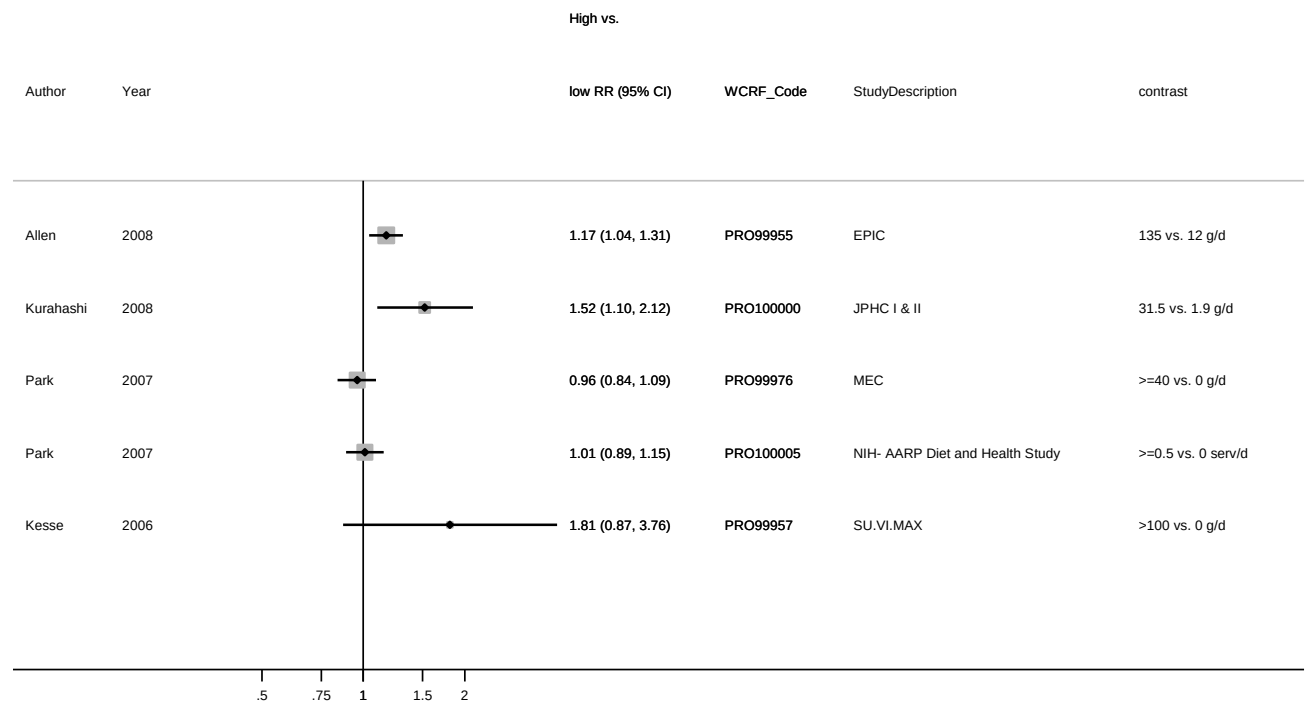


Figure 87 Dose-response meta-analysis of yoghurt and prostate cancer, per 100 g/d

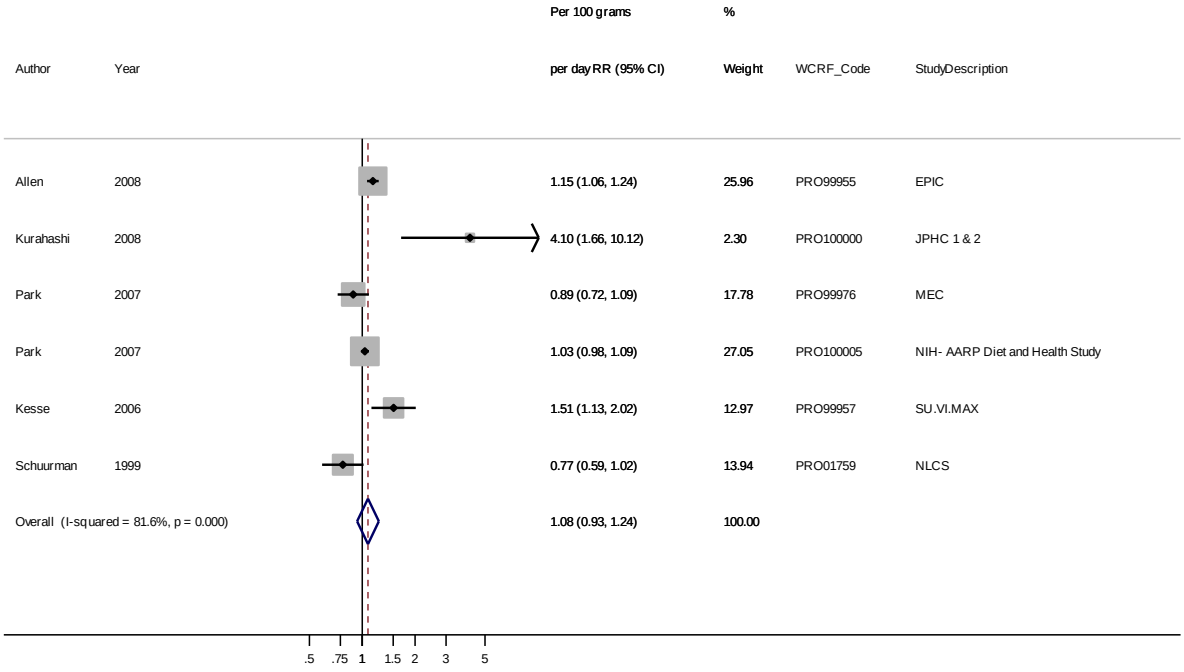
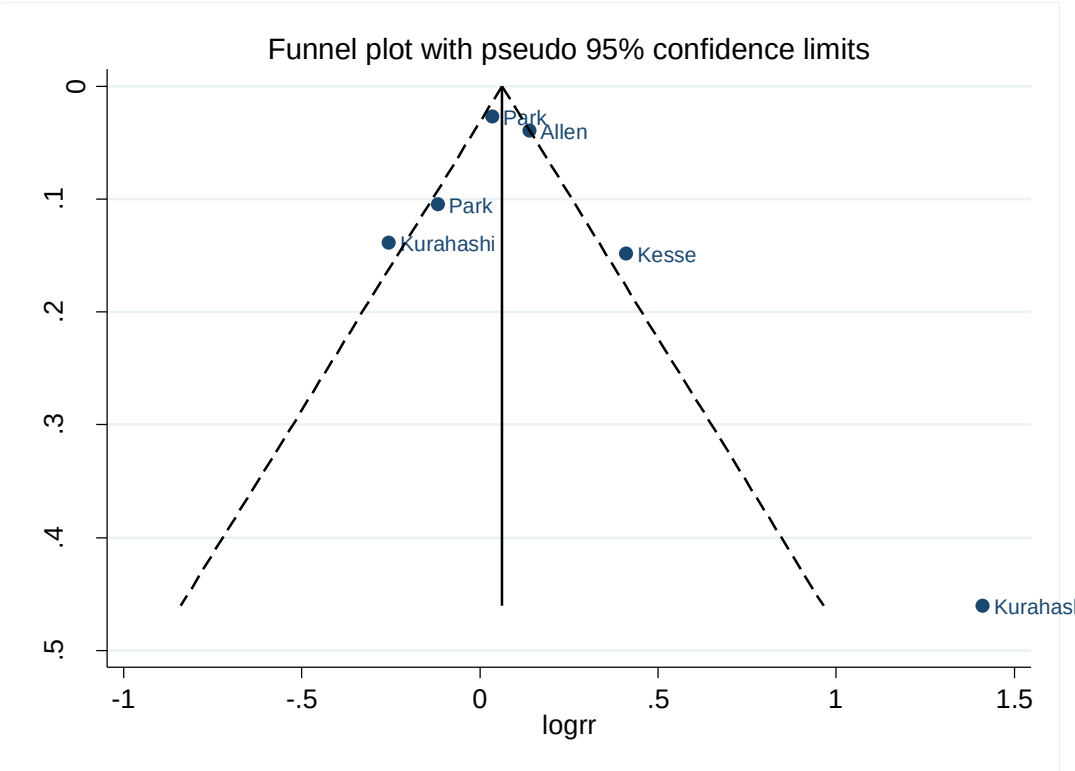


Figure 88 Funnel plot of yoghurt and prostate cancer



Egger's test p = 0.62.

Figure 89 Dose-response graph of yoghurt and total prostate cancer

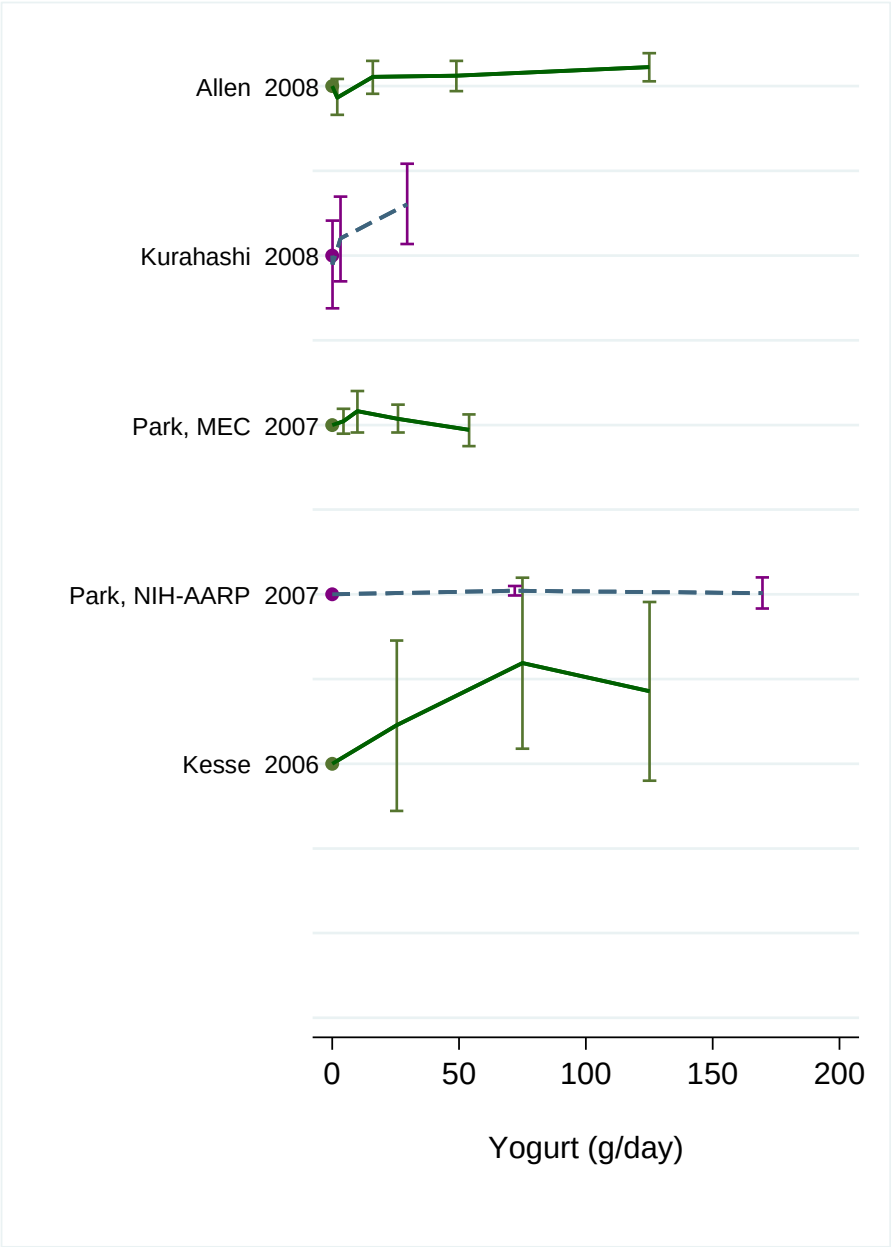
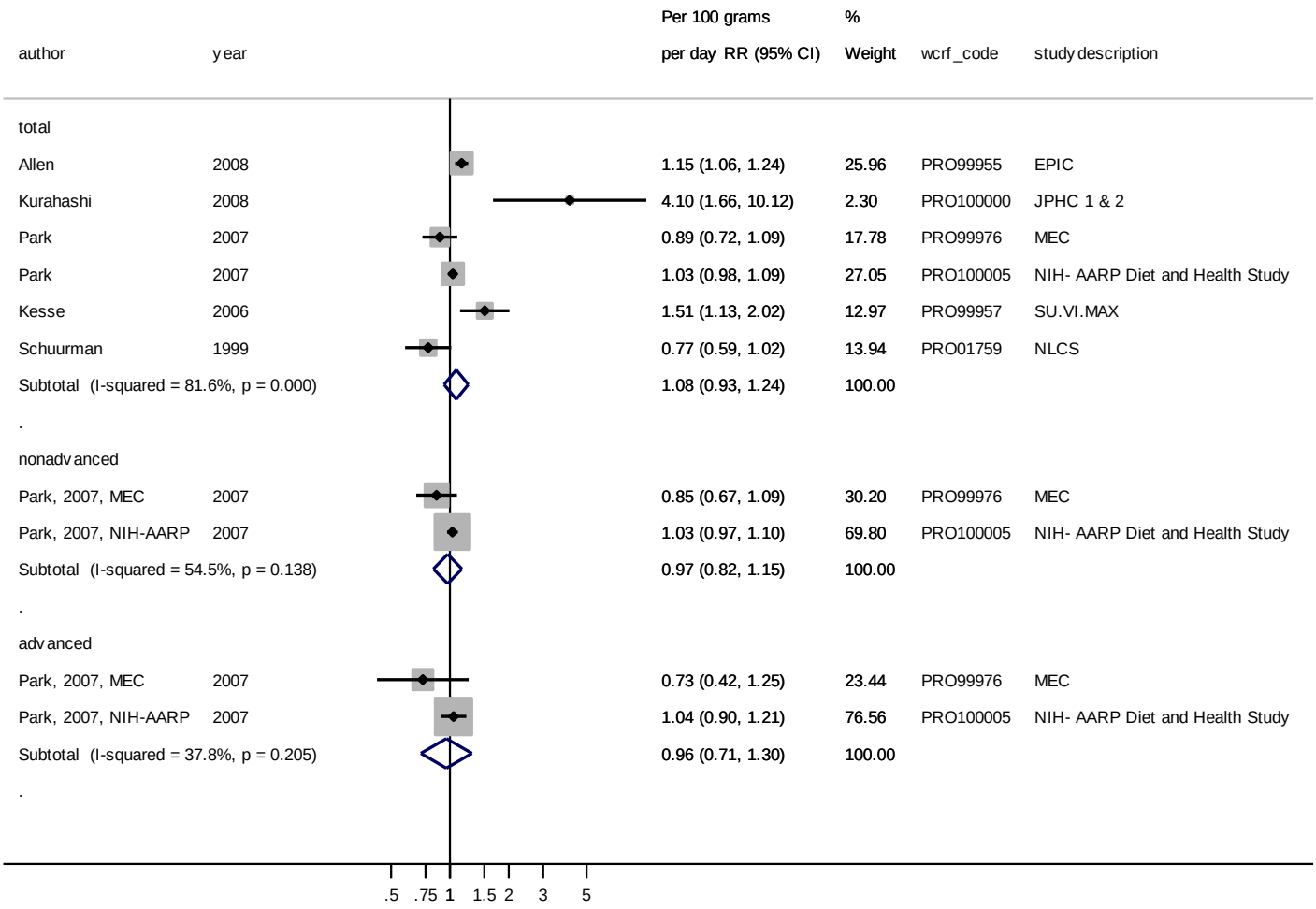


Figure 90 Dose-response meta-analysis of yogurt and prostate cancer, per 100 g/day, stratified by outcome type



3 Beverages

3.6.1 Coffee

Methods
A total of 17 publications from 15 cohort studies were identified. Six publications (five studies) were identified during the CUP. The CUP meta-analysis included 12 studies; five of these were identified during the CUP.

The dose-response results are presented for an increment of 1 cup of coffee per day. Times per day was considered equivalent to cups per day.

Of the studies included in the dose-response meta-analysis, eight reported on total prostate cancer (Shafique, 2012; Wilson, 2011; Nilsson, 2010; Allen, 2004; Ellison, 2000; Gronberg, 1996; Stensvold, 1994; Severson, 1989b) and four studies reported in fatal cases (Discacciati, 2013; Wilson, 2012; Iso, 2007; Hsing, 1990b).

Main results
Summary RR per 1 cup/day was 0.99 (95% CI 0.98-1.00; $I^2 = 0\%$, $p_{heterogeneity} = 0.82$) for all studies combined. After stratification by cancer subtype, the RR per 1 cup/day for total cancer (removing studies reporting on mortality) was 0.99 (95% CI 0.98-1.01; $I^2=0\%$; $p_{heterogeneity} = 0.65$; n = 8) and the summary RR for mortality per 1 cup/day was 0.97 (95% CI 0.93-1.00; $I^2=0\%$; $p_{heterogeneity} = 0.55$; n = 4).

There was no indication of publication bias with Egger's test (p = 0.16)

Heterogeneity
There was no evidence of heterogeneity ($I^2 = 0\%$, $p_{heterogeneity} = 0.82$).

Comparison with the Second Expert Report
A meta-analysis of six cohort studies showed a summary RR of 1.00 (95% CI 0.94-1.07; $I^2 = 31.0\%$, $p_{heterogeneity} = 0.20$)

Published meta-analyses
A meta-analysis of five cohort studies (Yu et al 2011), showed a summary RR for drinkers versus none drinkers or seldom drinkers of coffee of 0.79 (95% CI 0.61-0.98; $I^2 = 57.1\%$; $p_{heterogeneity} = 0.05$). In another meta-analysis of 12 studies (eight case-control studies and four cohort studies) (Park et al, 2010), the summary RR when comparing highest versus lowest coffee intake for all studies was 1.16 (95% CI 1.01-1.33; $I^2 = 6.5\%$.). The RR was 1.21 (95% CI 1.03-1.43; $I^2 = 27.4\%$) when including only the eight case-control studies, and 1.06 (95% CI 0.85-1.35; $I^2 = 0\%$), when only including the four cohort studies

Table 81 Studies on coffee consumption identified in the CUP

Author, year	Country	Study name	Cases	Years of follow up	Sub group	RR	LCI	UCI	Contrast
Discacciati, 2013	Sweden	Sweden 1998-2010 follow-up	2368	13 years	Localised	0.81	0.69	0.96	≥ 6 cups/day vs. none
			918		Advanced	0.87	0.66	1.16	
			515		Fatal	0.88	0.58	1.31	
					Localised	0.97	0.95	0.99	Per 1 coffee cup
					Advanced	0.98	0.95	1.02	
					Fatal	0.98	0.93	1.03	
Shafique, 2012b	United Kingdom	The Collaborative Cohort Study	318	28 years		0.93	0.66	1.31	≥ 3 cups/day vs. none
						0.96	0.81	1.13	Per 1 coffee cup
Wilson, 2011	USA	The Health Professional Follow-up Study	5035	20 years		0.82	0.68	0.98	≥ 6 cups/day vs. none
Wilson, 2012	USA	The Health Professional Follow-up Study	5025	20 years		0.89	0.81	0.99	Q5 vs. Q1
Nilsson, 2010	Sweden	The Vasterbotten Intervention Project	653	15 years		1.03	0.77	1.38	≥ 1 vs. < 1 occasions/ day
Iso, 2007	Japan	Japan Collaborative Cohort	161	12 years		1.33	0.73	1.75	≥ 2 times/day vs. <1 -2 times/month

Table 82 Overall evidence on coffee consumption and prostate cancer

	Summary of evidence
2005 SLR	11 articles (10 cohorts) were identified during the 2005 SLR. Two of them reported from the same cohort. Six studies were included in the 2005 SLR meta-analysis. All studies reported no significant association between coffee intake and prostate cancer.
Continuous Update Project	Six additional publications (five studies) reported on coffee and prostate cancer risk. Five of them could be included in the meta-analysis, in addition to one article that was not included in the 2005 SLR. Overall, 12 studies were included in the meta-analysis. No significant association was observed in the CUP meta-analysis.

Table 83 Summary of results of the dose response meta-analysis of coffee consumption and prostate cancer

Prostate cancer		
	2005 SLR	CUP
Studies (n)	6	12
Cases (n)	1157	9841
Increment unit used	1 Cups/day	Per 1 cup/day
Overall RR (95% CI)	1.00 (0.94-1.07)	0.99 (0.98-1.00)
Heterogeneity (I^2, p-value)	31.0%, p= 0.20	0%, p = 0.82
Stratified analysis		
Mortality*		
Overall RR (95% CI)		0.97 (0.93-1.00)
Heterogeneity (I^2, p-value)		0%, p = 0.55, n = 4

* No meta-analysis was conducted in the 2005 SLR.

Table 84 Inclusion/exclusion table for meta-analysis of coffee consumption and prostate cancer

WCRF code	Author	Year	Study design	Study Name	Cancer outcome	2005 SLR	CUP dose-response meta-analysis	CUP HvL forest plot	Estimated values	Exclusion reasons
PRO100156	Discacciati	2013	Prospective Cohort study	Sweden 1998-2010 follow-up	Mortality	No	Yes	Yes		
PRO100136	Shafique	2012	Prospective Cohort study	The Collaborative Cohort Study	Incidence	No	Yes	Yes		
PRO100100	Wilson	2011	Prospective Cohort study	The Health Professional Follow-up Study	Incidence /Mortality	No	Yes	Yes	Mid-exposure values, person-years per category	
PRO100101	Wilson	2012	Prospective Cohort study	The Health Professional Follow-up Study	Incidence	No	No	No		Superseded by PRO100100 (Wilson, 2011)
PRO100082	Nilsson	2010	Prospective Cohort study	The Vasterbotten Intervention Project	Incidence	No	Yes	Yes	Mid-exposure values	
PRO100042	Iso	2007	Prospective Cohort study	Japan Collaborative Cohort	Mortality	No	Yes	Yes	Mid-exposure values	
PRO97367	Allen	2004	Prospective Cohort study	Life Span Study	Incidence	Yes	Yes	Yes	Mid-exposure values	
PRO01564	Ellison	2000	Retrospectiv e Cohort study	Nutrition Canada Survey	Incidence	Yes	Yes	Yes	Mid-exposure values	
PRO02582	Gronberg	1996	Twin Cohort	Sweden 1967-1970 Twin Cohort	Incidence	Yes	Yes	Yes	Mid-exposure values, person-years per category	
PRO13405	Stensvold	1994	Prospective Cohort study	Norway 1977-1982	Incidence	Yes	Yes	No	Rescale continuous values	
PRO02788	Le Marchand	1994	Twin cohort	USA Hawaii 1975-1980	Incidence	Yes	Yes	Yes	Mid-exposure values, person-years & cases per category	
PRO03129	Hsing	1990 b	Prospective Cohort study	Lutheran Brotherhood Study	Mortality	No	Yes	Yes	Mid-exposure values, person-years & cases per category	

PRO03210	Severson	1989 b	Prospective Cohort study	USA Hawaii 1965-1968	Incidence	Yes	Yes	Yes	Mid-exposure values, person-years per category	
PRO09091	Nomura	1986	Prospective Cohort study	USA Hawaii 1965-1968	Incidence	No	No	No		No cases, no confidence interval per category available. Superseded by PRO03210 (Severson, 1989) that was included
PRO13395	Jacobsen	1986	Prospective Cohort study	Norway 1967-1969	Mortality	No	No	No		No confidence intervals, only two categories reported
PRO03451	Whittemore	1985	Prospective Cohort study	Harvard and Pennsylvania Alumni Study 1916-1950	Mortality	No	No	No		No measure of association
PRO03534	Phillips	1983	Prospective Cohort study	Californian Seventh Day Adventists	Mortality	No	No	No		No measure of association

Figure 91 Highest versus lowest forest plot of coffee consumption and prostate cancer

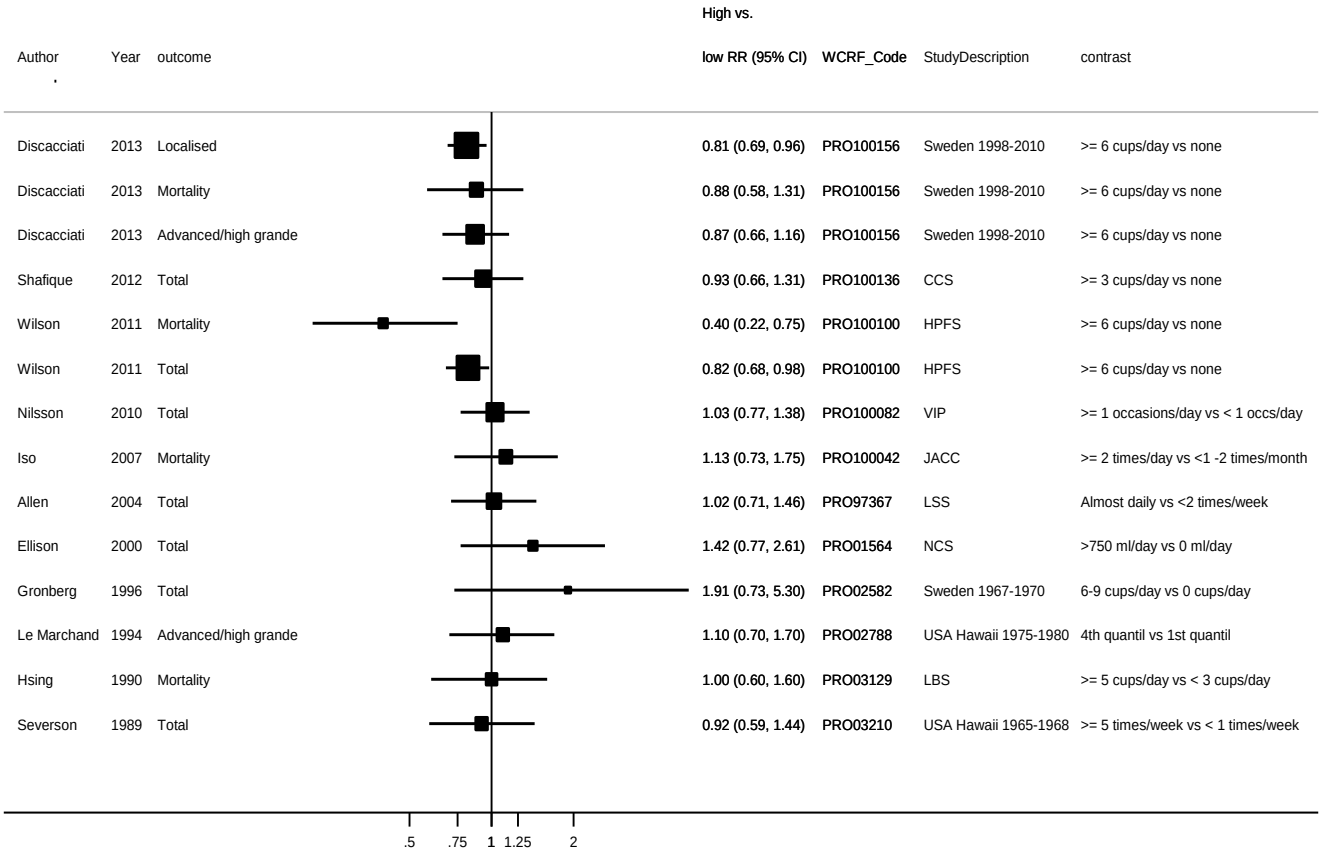


Figure 92 Dose-response meta-analysis of coffee and prostate cancer, per 1 cup/day

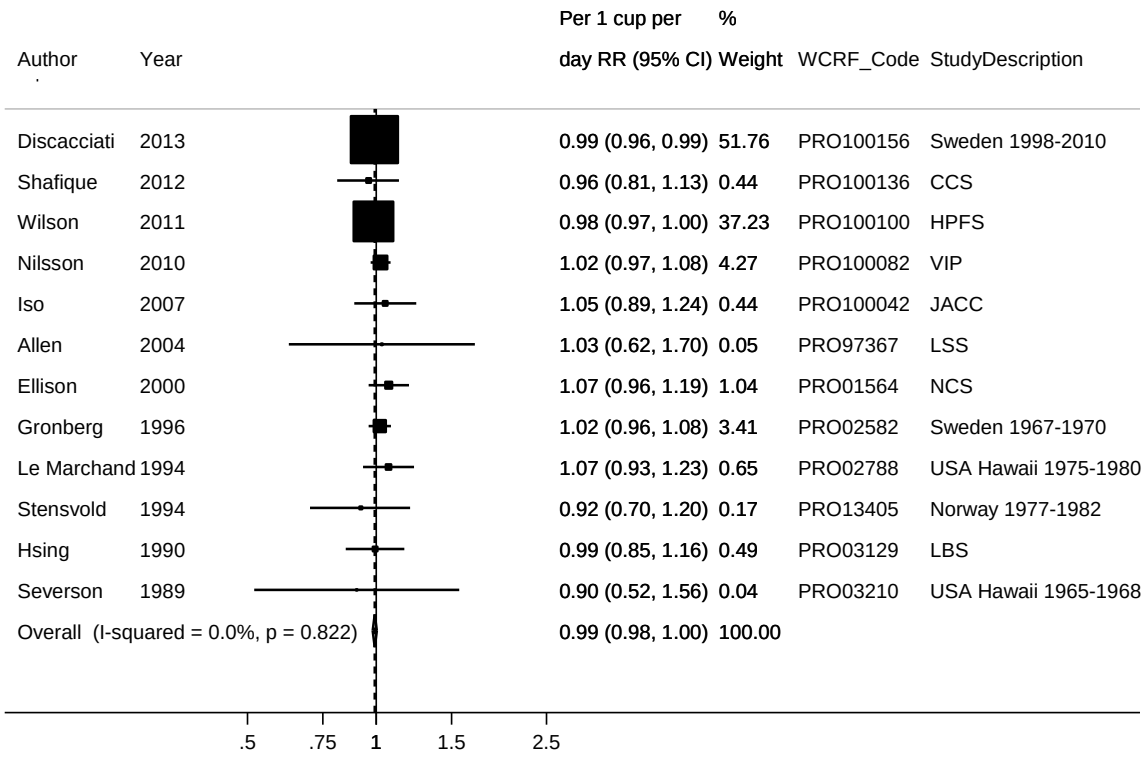
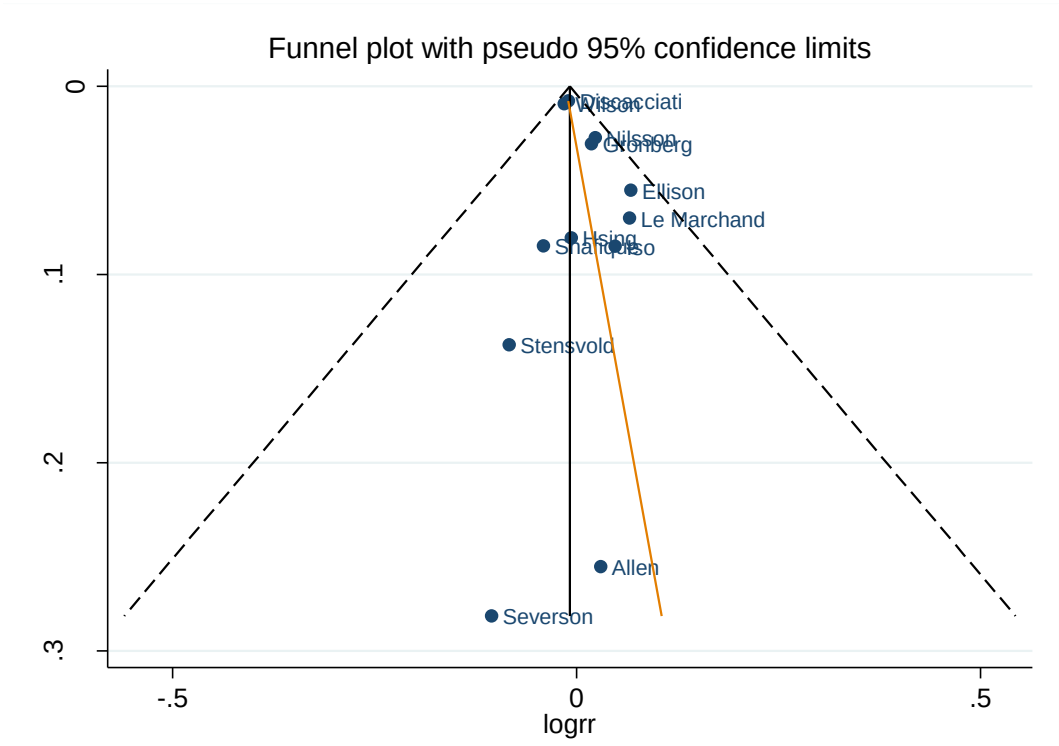


Figure 93 Funnel plot of coffee consumption and prostate cancer



Egger's test p = 0.16

Figure 94 Dose-response graph of coffee and prostate cancer

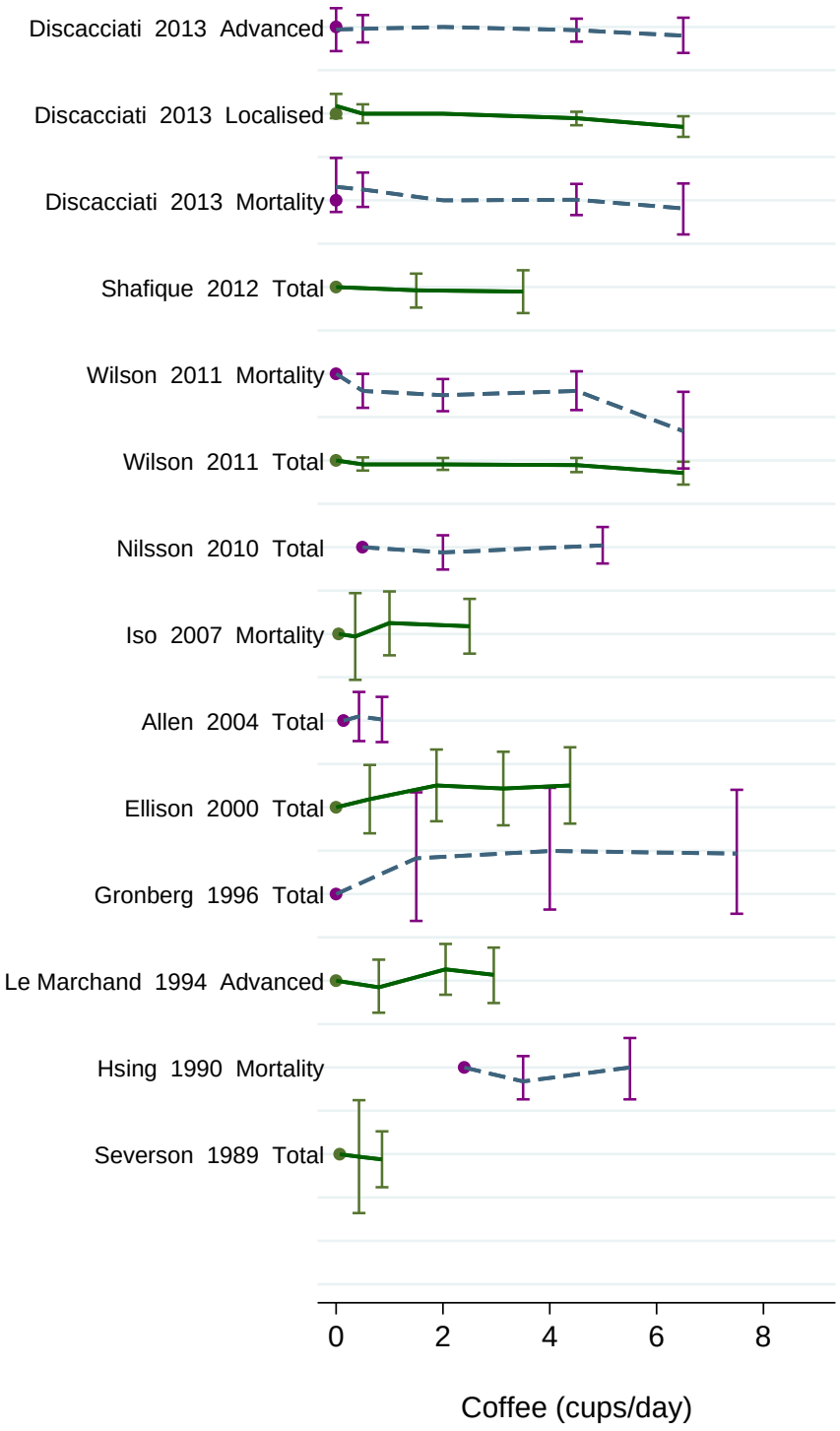
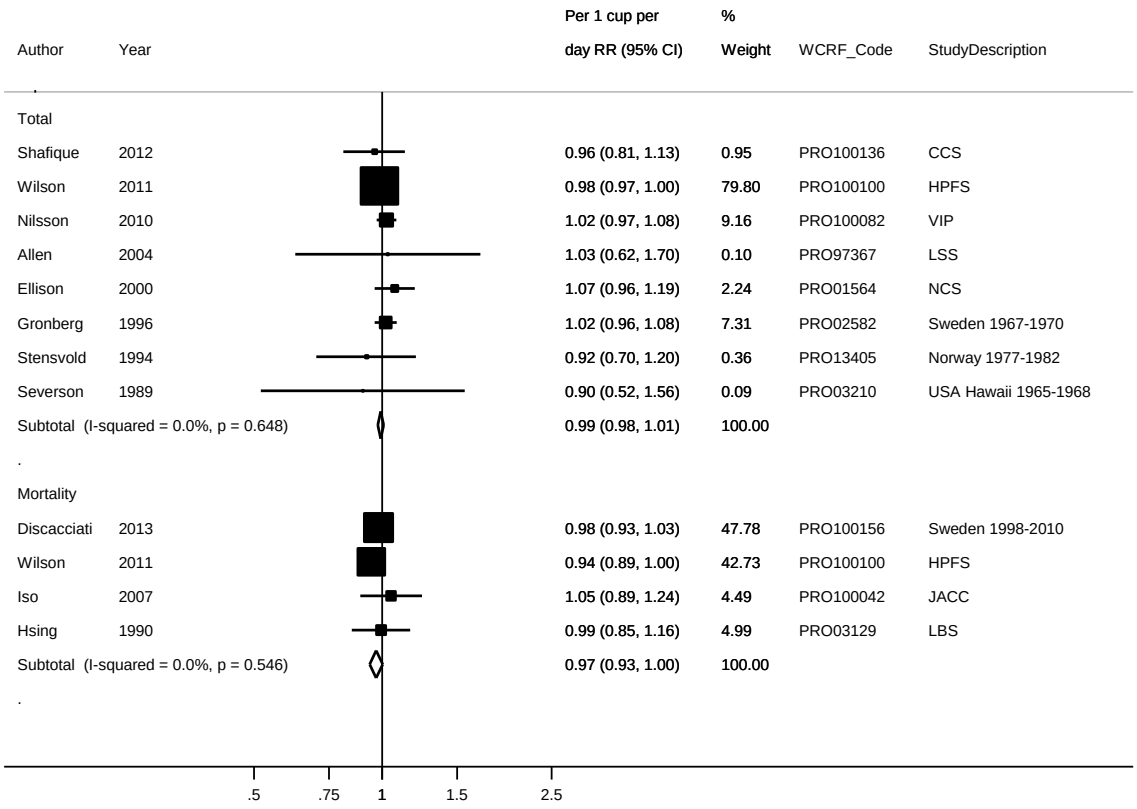


Figure 95 Dose-response meta-analysis of coffee intake and prostate cancer, per 1 cup/day, stratified by prostate cancer type



3.6.2.2 Green tea

Methods

A total of six publications from six cohort studies were identified, four of which were identified during the CUP. The CUP meta-analysis included five studies, one study from Singapore and the remaining studies from Japan.

The results presented as times per day of green tea intake (two studies) were considered equivalent to cups per day. The dose-response results are presented for an increment of 1 cup of green tea per day.

Stratified analyses were not conducted.

Main results

The summary RR per 1 cup/day was 1.01 (95% CI 0.97-1.04; $I^2 = 0\%$; $p_{heterogeneity} = 0.58$; n = 5) for all studies combined.

Heterogeneity

There was no evidence of heterogeneity across the limited number of published studies ($I^2 = 0\%$, $p_{heterogeneity} = 0.58$). There was no indication of publication bias with Egger's test ($p = 0.72$).

Comparison with the Second Expert Report

Two cohort studies were identified during the 2005 SLR (no meta-analysis for cohort studies was done). Both studies showed no evidence of association between green tea consumption and prostate cancer.

Published meta-analyses

A meta-analysis of seven studies (four prospective and three case-control studies) (Zheng et al 2011), showed a summary RR for highest versus lowest/none consumption of green tea of 0.72 (95% CI 0.45-1.15; $I^2 = 80.6\%$; $p_{heterogeneity} < 0.01$). The RR was 1.00 (95% CI 0.66-1.13; $I^2 = 7.3\%$; $p_{heterogeneity} = 0.02$), when including only the four cohort studies and 0.43 (95% CI 0.25-0.73; $I^2 = 48.8\%$; $p_{heterogeneity} = 0.15$), when including only the case-control studies.

Table 85 Studies on green tea consumption identified in the CUP

Author, year	Country	Study name	Cases	Years of follow up	RR	LCI	UCI	Contrast
Montague, 2012	Singapore	Singapore Chinese Health Study	298	11.2 years	0.95	0.62	1.45	≥2 cups/day vs. none
Iso, 2007	Japan	Japan Collaborative Cohort	153	15 years	0.96	0.60	1.53	≥ 4 times/day vs. ≤ 4 times/week

Kurahashi, 2008b	Japan	Japan Public Health Centre-based Prospective Study	404	14 years	0.89	0.65	1.21	≥ 5 cups/day vs. < 1 cup day
Kikuchi, 2006	Japan	Ohsaki Cohort Study	110	7 years	0.85	0.50	1.43	≥5 cups/day vs. < 1 cup/day

Table 86 Overall evidence on green tea consumption and prostate cancer

	Summary of evidence
2005 SLR	Two studies were identified during the 2005 SLR. Both of them reported a non-significant positive association between green tea intake and prostate cancer.
Continuous Update Project	Four additional cohort studies were identified and included in the meta-analysis. A non-significant association was reported in all of them. No significant association was observed in the CUP meta-analysis.

Table 87 Summary of results of the dose response meta-analysis of green tea consumption and prostate cancer

Prostate cancer		
	2005 SLR*	CUP
Studies (n)	-	5
Cases (n)	-	1161
Increment unit used	-	Per 1 cup/day
Overall RR (95%CI)	-	1.01 (0.97-1.04)
Heterogeneity (I^2, p-value)	-	0%, p = 0.58

*No meta-analysis was conducted in the Second Report

Table 88 Inclusion/exclusion table for meta-analysis of green tea consumption and prostate cancer

WCRF Code	Author	Year	Study design	Study name	Cancer outcome	2005 SLR	CUP dose-response meta-analysis	CUP HvL forest plot	Estimated values	Exclusion reasons
PRO100147	Montague	2012	Prospective Cohort study	Singapore Chinese Health Study	Incidence	No	Yes	Yes	Person years per category and mid-exposure values	
PRO100042	Iso	2007	Prospective Cohort study	Japan Collaborative Cohort	Mortality	No	Yes	Yes	Mid-exposure values	
PRO99963	Kurahashi	2008 b	Prospective Cohort study	Japan Public Health Centre-based Prospective Study	Incidence	No	Yes	Yes	Person years per category and mid-exposure values	
PRO99960	Kikuchi	2006	Prospective Cohort study	Ohsaki Cohort Study	Incidence	No	Yes	Yes	Mid-exposure values	
PRO97367	Allen	2004	Prospective Cohort study	Life Span Study	Incidence	Yes	Yes	Yes	Mid-exposure values	
PRO03210	Severson	1989 b	Prospective Cohort study	Japan-Hawaii Cancer Study	Incidence	Yes	No	Yes		Two categories of exposure

Figure 96 Highest versus lowest forest plot of green tea consumption and prostate cancer

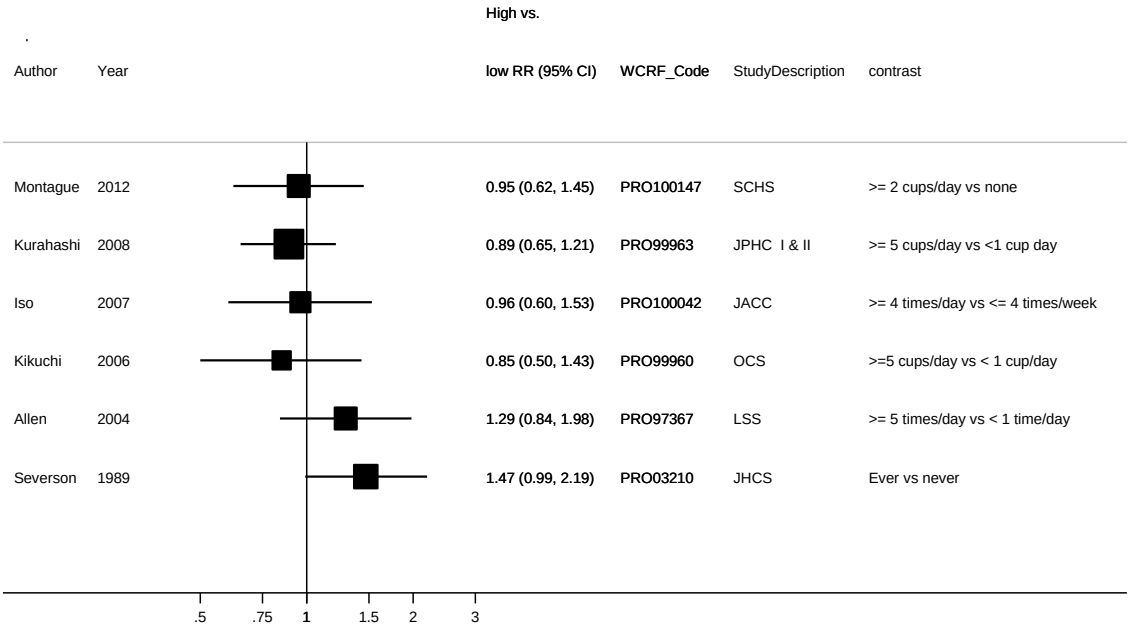


Figure 97 Dose-response meta-analysis of green tea and prostate cancer - per 1 cup/day

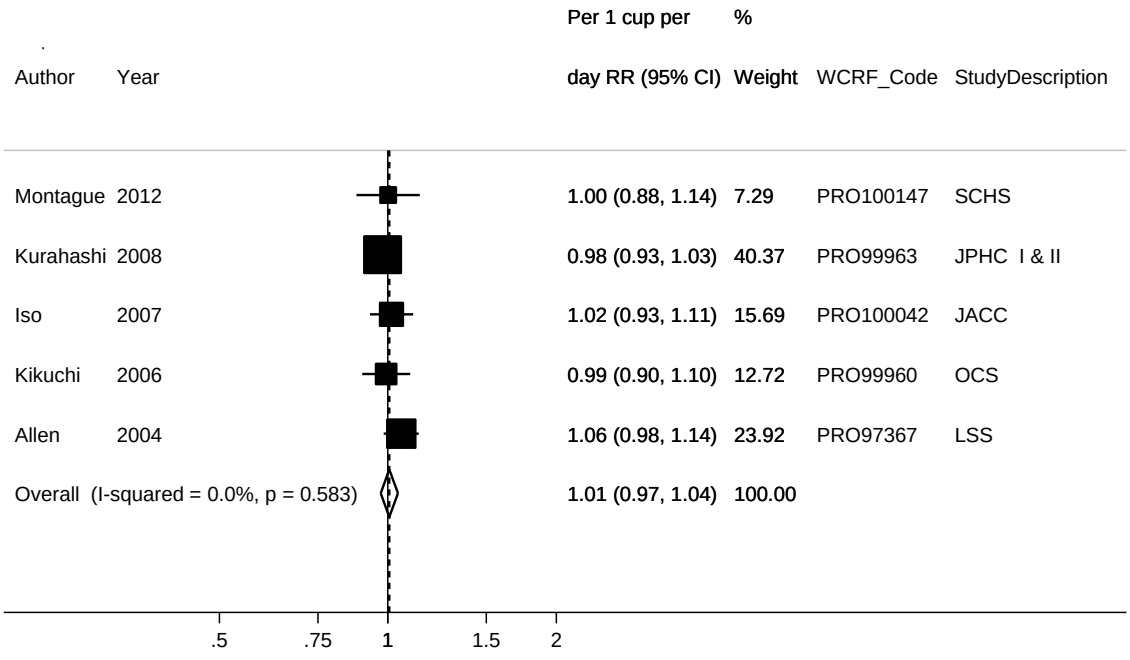
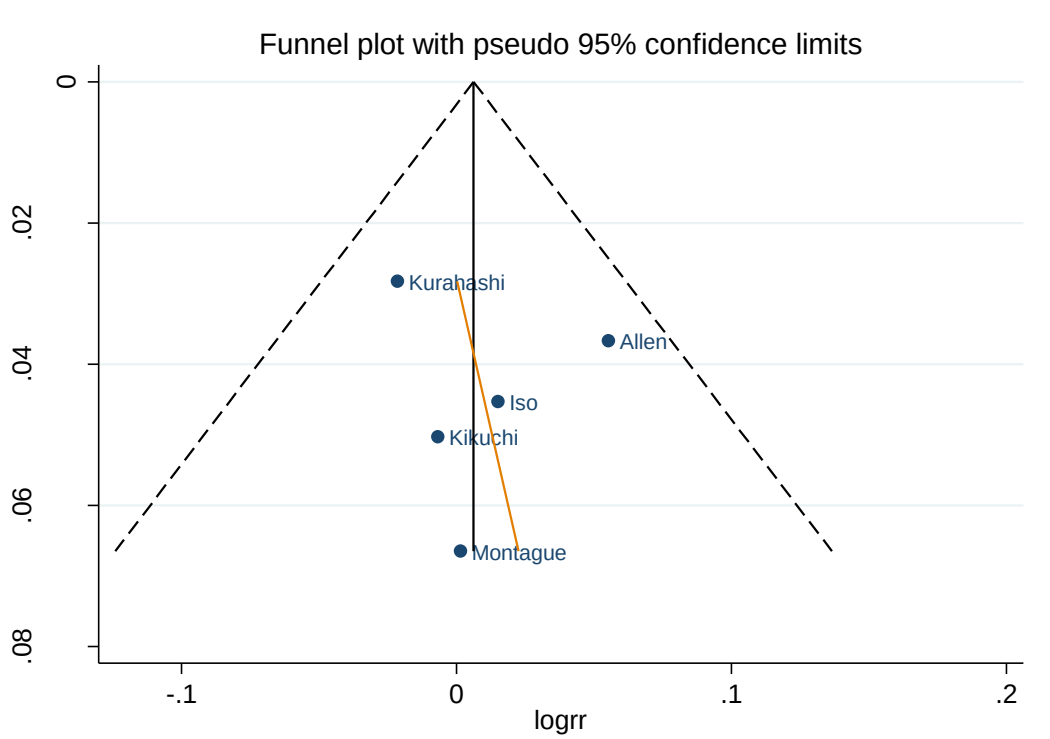
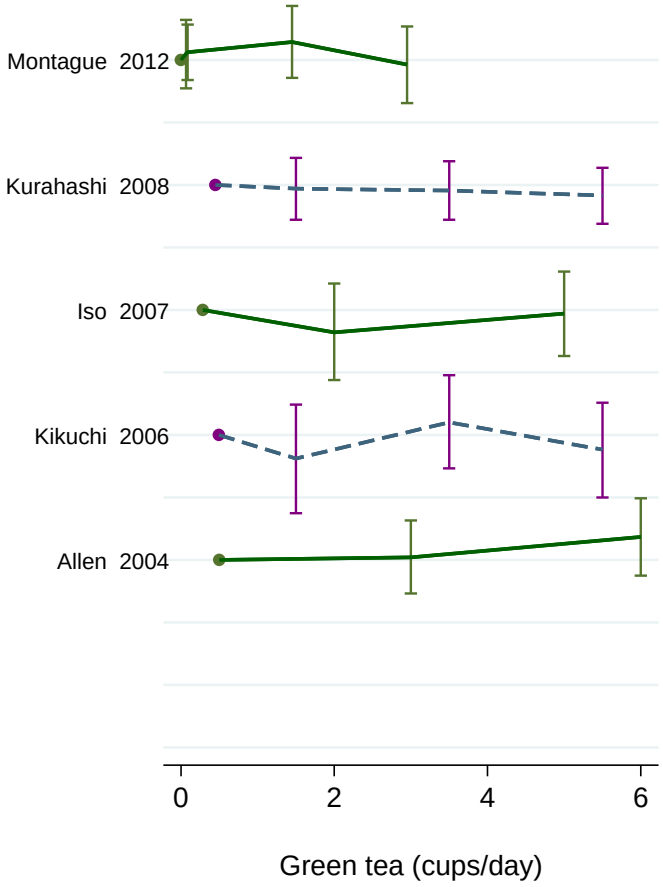


Figure 98 Funnel plot of green tea consumption and prostate cancer



Egger's test p = 0.72

Figure 99 Dose-response graph of green tea and prostate cancer



3.7 Total alcoholic drinks

Methods

Fifty-two publications from forty studies were identified, from which 17 studies from 21 publications were identified in the CUP. Two studies were updated publications of a study identified in the 2005 SLR. From the 22 studies identified in the 2005 SLR, 12 could not be used because they reported only mean values.

From the 21 publications identified in the CUP there were three studies with more than one publication – PCPT study with two publications, ATBC study with two publications and VITAL study with three publications. For each study only the publication used in the analysis was included in the table of studies identified in the CUP. This is because the number of studies was very high.

Twenty-five studies were included in the dose-response meta-analysis. The increment unit used in the dose-response analysis was 1 drink/day because most of the studies used that unit. Studies which reported alcoholic drinks and alcohol as ethanol were analysed together in order to include all the available data. The unit used for the conversion of grams per day of alcohol to drinks per day was the conversion units referred in the study. For studies that did not provide a conversion unit, one alcoholic drink was considered equivalent to 200 ml and 12.5 g of alcohol.

Most of the studies considered as referent group no alcohol consumption. In four studies (Weinstein et al, 2006; Rohrmann et al, 2008; Albertsen et al, 2002; Sesso et al,2001) the referent group was <3.7 g/day, 0.1-4.9 g/day, <1 drink/week and almost/never, respectively.

From the studies included in the dose-response meta-analysis: twelve studies reported on total prostate cancer (Severson et al, 1989b; Le Marchand et al, 1994; Breslow et al, 1999; Ellison et al, 2000; Nilsen et al, 2000; Sesso et al, 2001; Albertsen et al, 2002; Weinstein et al, 2006; Sutcliffe et al, 2007; Gonzalez et al, 2009; Chao et al, 2010; Shafique et al, 2012), four studies reported on prostate cancer mortality (Ozasa et al, 2007; Kim et al, 2010; Breslow et al, 2011; Batty et al, 2011), one study reported on total, advanced, non-advanced and fatal prostate cancer (Watters et al, 2010), one study reported on Gleason score < 7 and Gleason score ≥ 7 prostate cancer (Kristal et al, 2010), one studied reported on total, localised, advanced, low and high grade prostate cancer (Rohrmann et al, 2008), one study reported on aggressive and non-aggressive prostate cancer (Baglietto et al, 2006), one study reported on total, localised and regional/distant disease prostate cancer (Putnam et al, 2000), one study reported on total, advanced and localised prostate cancer (Geybels et al, 2012) and one study on total, advanced and non-advanced prostate cancer (Agalliu et al, 2011). In order to conduct stratified analysis by prostate cancer type, advanced, aggressive, high grade, distant disease and Gleason score ≥7 prostate cancer were combined into advance/high grade subgroup and non-advanced, non-aggressive, localised, low grade, Gleason score < 7 prostate cancers were combined into non-advanced/low grade subgroup.

As the number of studies allows it, stratified analyses were conducted for incident prostate cancer (studies that specifically reported on incidence), incidence and mortality (studies that indicated in the text incident prostate cancer and also reported number of deaths) and fatal prostate cancers.

Main results
The summary RR for an increase of one alcoholic drink per day was 1.01 (95% CI 0.99-1.02; I^2=34.4%; pheterogeneity=0.06; n=25), all studies combined. There was evidence of publication bias with Egger's test, p=0.02, that was explained by the inverse association observed in a small study (Ellison et al, 2000). When this study is removed from the analysis, the P value for Egger's test is 0.85 and the overall results remained the same.

After stratification by outcome the results remained non-significant. The RR for 1 drink per day increase was 1.03 (95% CI 0.96-1.11; I^2 = 24.2%; $p_{heterogeneity}$ = 0.27; n = 4) for fatal prostate cancer, 0.99 (95% CI 0.98-1.01; I^2 = 0%; $p_{heterogeneity}$ = 0.49; n = 13) for prostate cancer incidence, 1.00 (95% CI 0.96-1.03; I^2 = 41.9%; $p_{heterogeneity}$ = 0.11; n = 7) for advanced/high grade prostate cancer and 1.00 (95% CI 0.97-1.03; I^2 = 63.0%; $p_{heterogeneity}$=0.01; n = 7) for non-advanced/low grade prostate cancer.
There was no evidence of non-linearity for total prostate cancer (p = 0.35) but there was statistical evidence of non-linearity for advanced prostate cancer (p = 0.03). The deviation was for a small decrease in risk for intakes at around 7 drinks/day. This could be due to misclassification of sicker men who had stopped drinking at baseline, but drank before (Watters et al, 2010).

Heterogeneity
Overall, there was moderate evidence of heterogeneity, I^2 = 34.4%, $p_{heterogeneity}$ = 0.06. Visual inspection of the forest plots indicate that the heterogeneity is explained by extreme results of early small studies.

Comparison with the Second Expert Report
In the 2005 SLR, the meta-analysis on alcohol and prostate cancer was considered limited-no conclusion.

Published meta-analysis or pooled analysis
In a previous meta-analysis of 50 case–control and 22 cohort studies, including a total of 52 899 prostate cancer cases the summary relative risk for any alcohol drinking compared with non/occasional drinking was 1.06 (95% CI 1.01-1.10). The RRs for the same comparison were 1.06 (95% CI 0.98-1.14) for case-control studies and 1.06 (95% CI 0.99-1.14) for cohort studies. Compared to non/occasional drinking, the summary relative risks (all studies combined) were 1.05 (95% CI 1.02–1.08) for light drinking (≤ 1 drink/day), 1.06 (95% CI 1.01-1.11) moderate (> 1 to < 4 drinks/day) and 1.08 (95% CI 0.97-1.20) for heavy alcohol drinking (≥ 4 drinks/day) (Rota et al, 2011). No pooled analysis was identified.

Table 89 Studies on total alcoholic drinks identified in the CUP

Author, year	Country	Study name	Cases	Years of follow up	RR	LCI	UCI	Contrast
Lin, 2013	USA	NHANES III 1988/1994-2006	61	12.4 years	1.13	0.63	2.02	Yes vs. No
Geybels, 2012	Netherlands	Netherlands Cohort Study	3451	17.3 years	1.01	0.81	1.26	40.97 vs. 0 g/d
Shafique, 2012	UK	Collaborative cohort study	318	28 years	0.98	0.69	1.39	> 21 vs. 0 drinks/w
Agalliu, 2010	USA	Canadian Study of Diet, Lifestyle, and Health cohort	661	7.7 years	1.07	0.78	1.47	41.4 vs. 0 g/d
Batty, 2011	UK	Whitehall study	578	40 years	1.52	0.60	3.85	> 35 vs. 0 g/d
Breslow, 2011	USA	National Health Interview Survey (NHIS) 1988-2004	438	18 years	0.89	0.51	1.56	> 14 vs. 0 drinks/w
Chao, 2010	USA	California Men's Health Study (CMHS)	1340	5 years	1.16	0.83	1.63	≥ 5 vs. 0 drinks/d
Kim, 2010	Korea	Korea national health insurance corporation's health examinee cohort (KNHIC)	46	5 years	2.39	0.83	6.89	≥ 90 vs. 0 g/d
Watters, 2010	USA	NIH–AARP	17227	7 years	1.21	1.11	1.33	≥ 6 vs. 0 drinks/d
Kristal, 2010	USA and Canada	PCPT Prostate Cancer Prevention Trial	1703	9 years	1.11	0.93	1.31	GS 2-7 ≥ 14 vs. <1 drinks/w
					1.63	0.98	2.71	GS 8-10 ≥ 14 vs. <1 drinks/w
					1.15	0.98	1.36	Pooled ≥14 vs. <1 drinks/w

Gonzalez, 2009	USA	VITAL study	832	4 years	1.27	0.92	1.76	≥ 28 vs. <1 drinks/month
Rohrmann, 2008	Europe	EPIC	2655	8.7 years	0.88	0.72	1.08	≥ 60 vs. 0.1-4.9 g/d
Sutcliffe, 2007	USA	Health Professionals Study	3348	16 years	1.14	0.99	1.31	≥ 16.5 vs. 0 g/d
Ozasa, 2007	Japan	Japan Collaborative Cohort Study (JACC Study)	169	≈23 years	0.82	0.37	1.79	> 81 vs. 0 ml/d
Baglietto, 2006	Australia	The Melbourne Collaborative Cohort Study (MCCS)	732	9 years	0.94	0.67	1.30	> 60 vs. 0 g/d
Weinstein, 2006	Finland	ATBC study	1270	≤17 years	0.94	0.76	1.16	> 32.2 vs. < 3.7 g/d

Note: Saieva, 2012 was not included as it only reported SMR.

Table 90 Overall evidence on total alcoholic drinks and prostate cancer

	Summary of evidence
2005 SLR	Ten studies were included in the 2005 SLR meta-analysis. All were non-significant.
Continuous Update Project	Seventeen studies (twenty-one publications) were identified in the CUP and could be included in the meta-analysis; all showed a non-significant association towards an increase of risk. No significant association was observed for all studies combined.

Table 91 Summary of results of the dose response meta-analysis of total alcoholic drinks and prostate cancer

Prostate cancer		
	2005 SLR	CUP
Studies (n)	10	25
Cases (n)	4471	36942
Increment unit used	Per 1 drink/day	Per 1 drink/day
Overall RR (95% CI)	1.03 (0.99-1.07)	1.01 (0.99-1.02)
Heterogeneity (I^2, p-value)	25.0%, p = 0.23	34.4%, p = 0.06
Stratified analysis		
Incidence		
Overall RR (95% CI)		0.99 (0.98-1.01)
Heterogeneity (I^2, p-value)		0%, p = 0.49, n = 13
Mortality		
Overall RR (95% CI)		1.03 (0.96-1.11)
Heterogeneity (I^2, p-value)		24.2%, p = 0.27, n = 4
Advanced/high grade cancer		
Overall RR (95% CI)		1.00 (0.96-1.03)
Heterogeneity (I^2, p-value)		41.9%, p = 0.11, n = 7
Non-advanced/low grade cancer		
Overall RR (95% CI)		1.00. (0.97-1.03)
Heterogeneity (I^2, p-value)		63.0%, p = 0.01, n = 7

Table 92 Inclusion/exclusion table for meta-analysis of total alcoholic drinks and prostate cancer

WCRF code	Author	Year	Study design	Study name	Cancer outcome	2005 SLR	CUP dose-response meta-analysis	CUP HvL forest plot	Estimated values	Exclusion reasons
PRO100149	Lin	2013	Prospective Cohort study	NHANES III 1988/1994-2006	Mortality	No	No	Yes		Alcohol use (binary variable)
PRO100198	Geybels	2012	Case Cohort study	Netherlands Cohort Study	Incidence	No	Yes	Yes	Conversion from g/day to drinks/day	
PRO100136	Shafique	2012	Prospective Cohort study	Collaborative cohort Study, (Midspan, Scotland)	Incidence	No	Yes	Yes	Mid-exposure values, Person-years	
PRO100124	Saieva	2012	Prospective Cohort study	Cohort study of Italian alcoholics	Incidence	No	No	No		Only provide SMR
PRO100170	Batty	2011	Prospective Cohort study	Whitehall study, UK	Mortality	No	Yes	Yes	Mid-exposure values, conversion from g/day to drinks/day	
PRO100103	Breslow	2011	Prospective Cohort study	National Health Interview Survey (NHIS) 1988-2004	Mortality	No	Yes	Yes	Mid-exposure values, Person-years	
PRO100199	Agalliu	2011	Case-cohort study	Canadian Study of Diet, Lifestyle, and Health cohort	Incidence/ Mortality	No	Yes	Yes	Person-years, conversion from g/day to drinks/day	
PRO100049	Chao	2010	Prospective Cohort study	California Men's Health Study (CMHS)	Incidence	No	Yes	Yes		
PRO100123	Kim	2010	Prospective Cohort study	Korea national health insurance corporation's health examinee cohort (KNHIC)	Mortality	No	Yes	Yes	Cases and person-years per category, conversion from g/day to drinks/day	
PRO100077	Watters	2010	Prospective Cohort study	NIH–AARP	Incidence/ Mortality	No	Yes	Yes	Mid-exposure values	
PRO100078	Kristal	2010	Nested case-control study	PCPT Prostate Cancer Prevention	Incidence	No	Yes	Yes	Conversion from drinks/week to drinks/day	

				Trial						
PRO100069	Gong	2009	Follow-up of a RCT	PCPT Prostate Cancer Prevention Trial	Incidence	No	No	No		Superseded by Kristal, 2010
PRO100066	Gonzalez	2009	Prospective Cohort study	VITAL study	Incidence/ Mortality	No	Yes	Yes	Mid-exposure values , conversion from drinks/month to drinks/day	
PRO100021	Rohrmann	2008	Prospective Cohort study	EPIC	Incidence/ Mortality	No	Yes	Yes	Mid-exposure values , person-years, conversion from g/day to drinks/day	
PRO100022	Ahn	2008a	Prospective Cohort study	ATBC	Incidence/ Mortality	No	No	No		Interactions only, used Weinstein 2006
PRO100003	Sutcliffe	2007	Prospective Cohort study	Health Professionals Study	Incidence	No	Yes	Yes	Mid-exposure values, conversion from g/day to drinks/day	
PRO100131	Ozasa	2007	Prospective Cohort study	Japan Collaborative Cohort Study (JACC Study)	Mortality	No	Yes	Yes	Mid-exposure values, conversion from ml/day to drinks/day	
PRO100035	Gonzalez	2007	Prospective Cohort study	VITAL study	Incidence/ Mortality	No	No	No		Superseded by Gonzalez, 2009
PRO99959	Baglietto	2006	Prospective Cohort study	The Melbourne Collaborative Cohort Study (MCCS)	Incidence	No	Yes	Yes	Mid-exposure values, person-years, conversion from g/day to drinks/day	
PRO99989	Weinstein	2006	Prospective Cohort study	ATBC	Incidence/ Mortality	No	Yes	Yes	Mid-exposure values, conversion from g/day to drinks/day	
PRO100020	Velicer	2006	Prospective Cohort study	VITAL study	Incidence/ Mortality	No	No	No		Superseded by Gonzalez, 2009

PRO97224	King	2005	Nested case-control study	B-Carotene and Retinol Efficacy Trial, CARET	Incidence	Yes	No	No		Mean values used in 2005 SLR
PRO97367	Allen	2004	Prospective Cohort study	The Life Span Study cohort	Incidence/ Mortality	Yes	No	Yes		Binary variable
PRO97667	Jacobs	2004	Nested case-control study	Nutritional Prevention of Cancer	Incidence	Yes	No	No		Mean values used in 2005 SLR
PRO97676	Laaksonen	2004	Prospective Cohort study	Kuopio Ischaemic Heart Disease Risk Factor Study KIHDRFS	Incidence	Yes	No	No		Identified in the 2005 SLR, not used
PRO97715	Zhu	2004	Prospective Cohort study	Physician's Health Study	Incidence	Yes	No	No		Identified in the 2005 SLR, not used
PRO03860	Platz	2004a	Prospective Cohort study	Health Professionals Study	Incidence					Superseded by Sutcliffe, 2007
PRO00214	Goodman	2003	Nested case control study	B-Carotene and Retinol Efficacy Trial, CARET	Incidence	Yes	No	No		Mean values used in 2005 SLR
PRO00764	Schuurman	2002	Case-cohort study	Netherlands Cohort Study	Incidence	Yes	No	No		Mean values used in 2005 SLR
PRO00754	Albertsen	2002	Prospective Cohort study	Copenhagen City Heart Study/ Copenhagen Male Study/ Copenhagen County Centre of Preventive Medicine*	Incidence/ mortality	Yes	Yes	Yes	Mid-exposure values, person-years, conversion from drinks/week to drinks/day	
PRO01124	Sesso	2001	Prospective Cohort study	Harvard Alumni Health Study (HAHS)	Incidence/ mortality	Yes	Yes	Yes	Mid-exposure values	
PRO01602	Nilsen	2000	Prospective Cohort study	Norway 1984-1986	Incidence/ mortality	Yes	Yes	Yes	Mid-exposure values, conversion from drinks/week to drinks/day	
PRO01564	Ellison	2000	Retrospective cohort study	National Canada Survey cohort	Incidence/ mortality	Yes	Yes	Yes	Mid-exposure values, conversion from ml/d to	

									drinks/day	
PRO01487	Putnam	2000	Retrospective cohort study	Iowa's Men Study	Incidence/ mortality	Yes	Yes	Yes	Mid-exposure values, conversion from g/week to drinks/day	
PRO01898	Schuurman	1999a	Case-cohort study	Netherlands Cohort Study	Incidence	Yes	No	No		Superseded by Geybels, 2012
PRO01770	Breslow	1999	Prospective Cohort study	NHANES I COHORT I 1971/75-1992 and COHORT II 1982/84-1992 (NHEFS)	Incidence/ mortality	Yes	Yes	No		Lin, 2013 used in the high versus low analysis
PRO01737	Parker	1999	Retrospective cohort study	Iowa's Men Study	Incidence/ mortality	Yes	No	No		Superseded by Putnam, 2000
PRO02014	Nomura	1998	Nested case-control study	Honolulu Heart Program	Incidence	Yes	No	No		Mean values used in 2005 SLR The same as Severson, 1989, which was used
PRO02364	Cerhan	1997	Retrospective cohort study	Iowa's 65+ rural health study	Incidence/ mortality	Yes	No	No		Superseded by Putnam, 2000
PRO12752	Friedman	1997	Prospective Cohort study	KPMCP	Incidence/ mortality	No	No	Yes		Mean values used in 2005 SLR
PRO02418	Guess	1997	Nested case-control study	KPMCP	Incidence/ mortality	Yes	No	No		Superseded by Friedman 1997
PRO02582	Gronberg	1996	Nested case-control study	Swedish twin cohort	Incidence	Yes	No	Yes		Alcohol use (binary variable)
PRO05236	Murata	1996	Nested case-control study	Chiba Cancer Registry Japan		Yes	No	No		Identified in 2005 SLR, not used. Unadjusted results
PRO02788	Le Marchand	1994	Prospective Cohort study	Hawai 1975/1980 - 1989	Incidence	Yes	Yes	Yes	Mid-exposure values, cases and person-years, conversion from g/week to drinks/day	
PRO02822	Hiatt	1994	Prospective Cohort study	KPMCP	Incidence/ mortality	No	No	No		Superseded by Friedman, 1997

PRO03125	Stemmerman n	1990	Prospective Cohort study	Honolulu Heart Program	Incidence/ mortality	Yes	No	No		The same as Severson, 1989, which was used
PRO03129	Hsing	1990b	Prospective Cohort study	Lutheran Brotherhood Cohort Study	Mortality	Yes	No	No		Identified in 2005 SLR, not used. Unadjusted results
PRO03196	Mills	1989	Prospective Cohort study	Adventist Health Study	Incidence	Yes	No	Yes		Alcohol use (binary variable)
PRO03210	Severson	1989b	Prospective Cohort study	Honolulu Heart Program	Incidence/ mortality	Yes	Yes	Yes	Mid-exposure values, person-years, conversion from g/day to drinks/day	
PRO10360	Schmidt	1981	Prospective Cohort study	Canada Ontario 1951-1970	Mortality	Yes	No	No		Identified in the 2005 SLR, not used. Compare alcoholics vs. non alcoholics
PRO03648	Hiryama	1979	Prospective Cohort study	Japan, 1975	Mortality	Yes	No	No		Identified in the 2005 SLR, not used. Mentioned in the text that there was no relationship
PRO13452	Jensen	1979	Prospective Cohort study	Cohort of Danish brewer workers compared with general population	Incidence	Yes	No	No		Identified in the 2005 SLR, not used. Only SMR.

* Albertsen, 2002 counted as 3 studies.

Figure 100 Highest versus lowest forest plot of total alcoholic drinks and prostate cancer

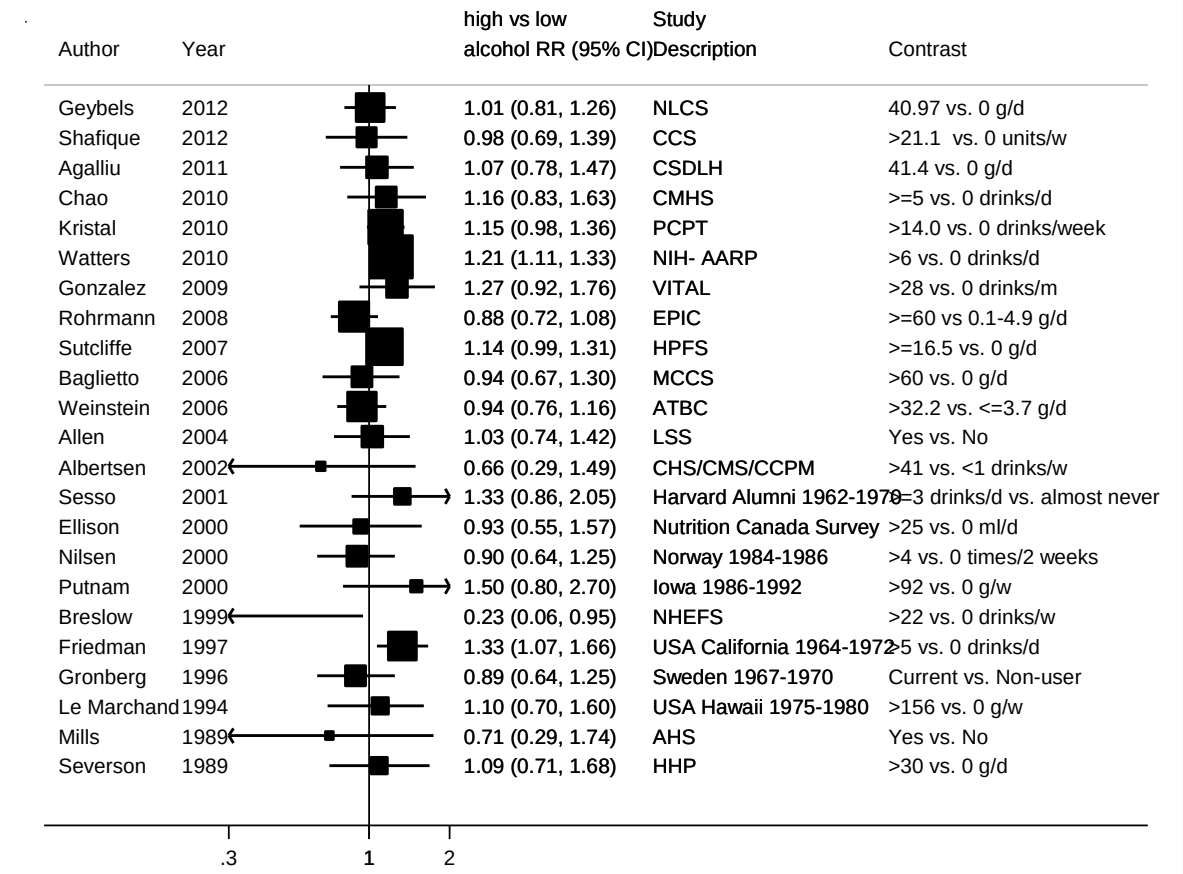


Figure 101 Dose-response meta-analysis of total alcoholic drinks and prostate cancer risk– per 1 drink/day

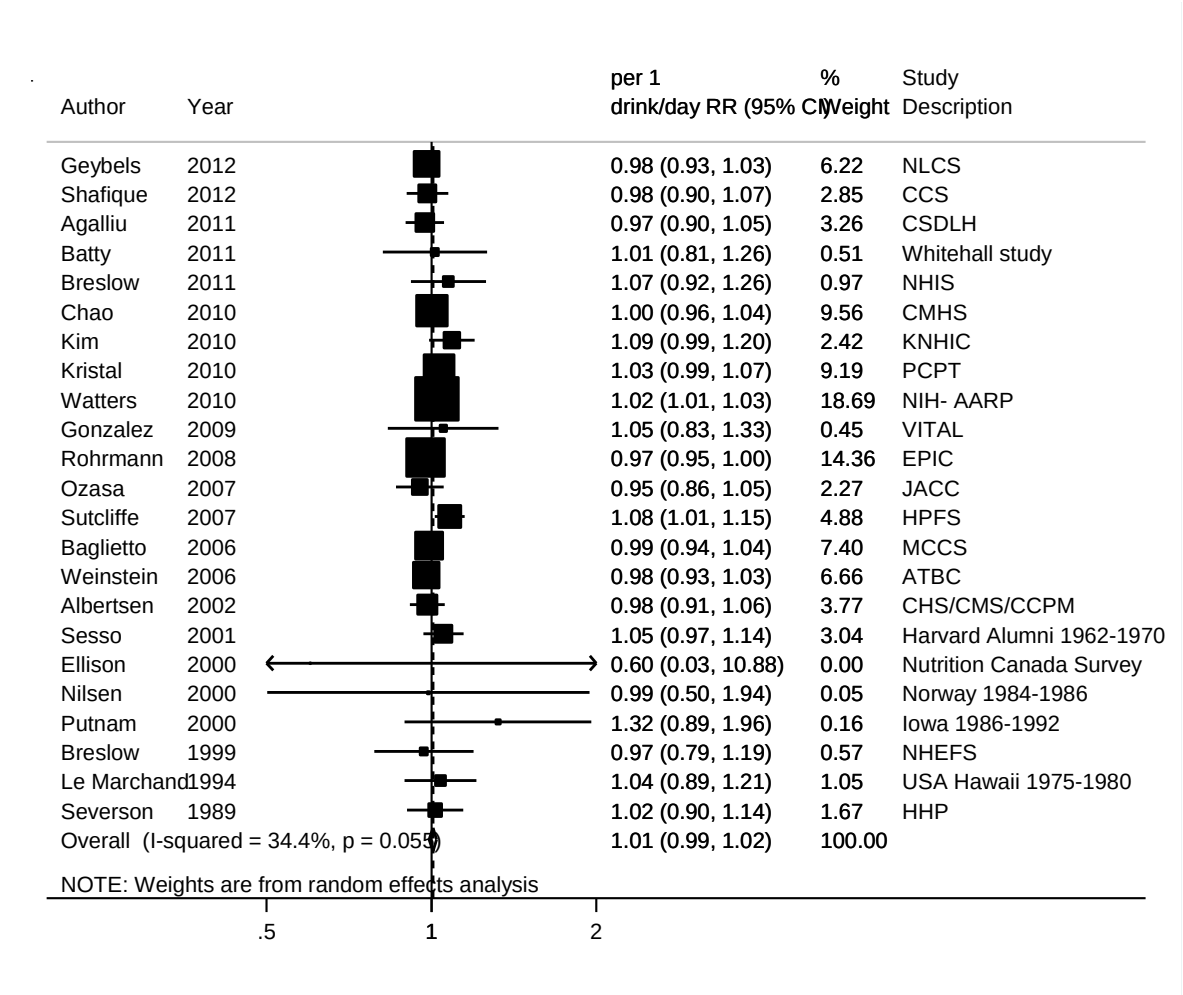
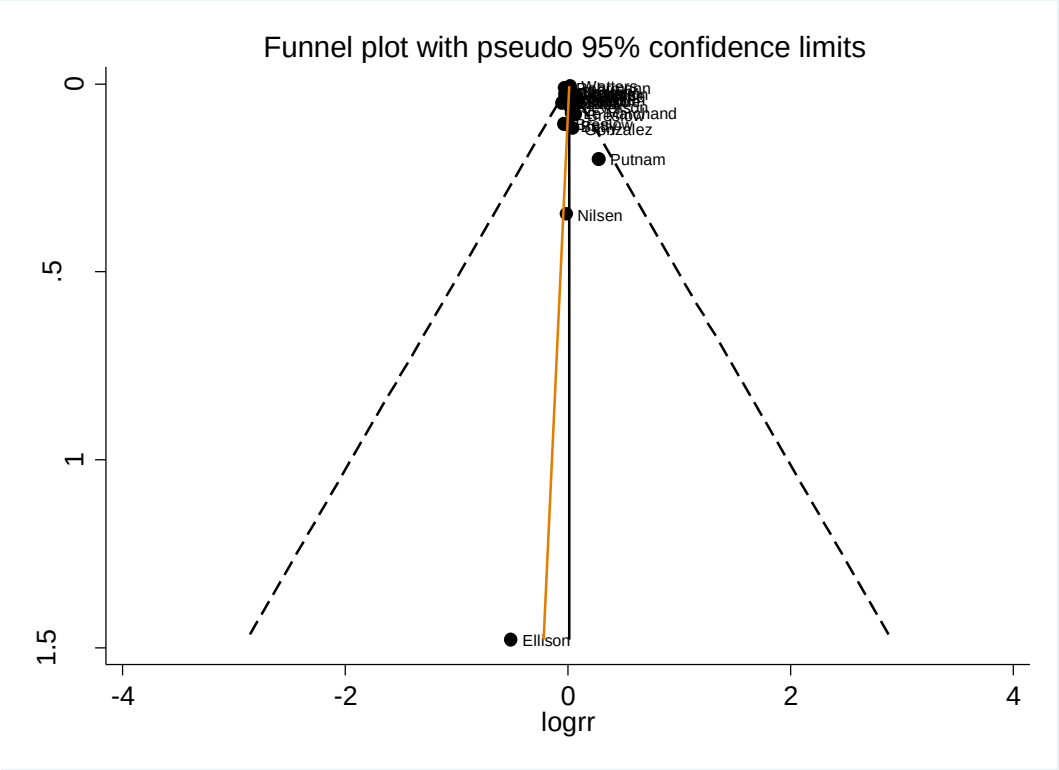


Figure 102 Funnel plot of total alcoholic drinks and prostate cancer



Egger's test p = 0.02

Figure 103 Dose-response graph of total alcoholic drinks and prostate cancer

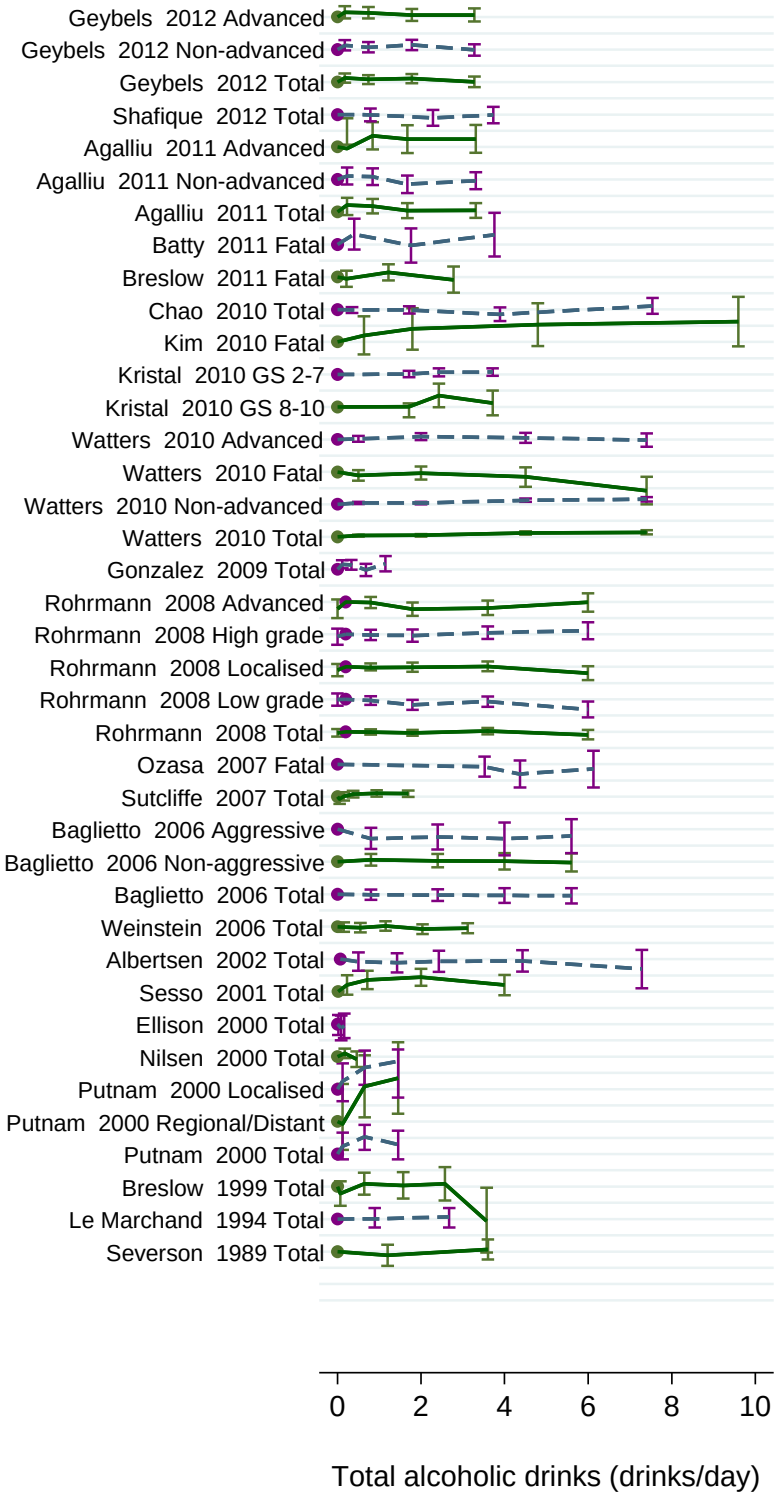


Figure 104 Dose-response meta-analysis of total alcoholic drinks and prostate cancer, per 1 drink/day, stratified by outcome type

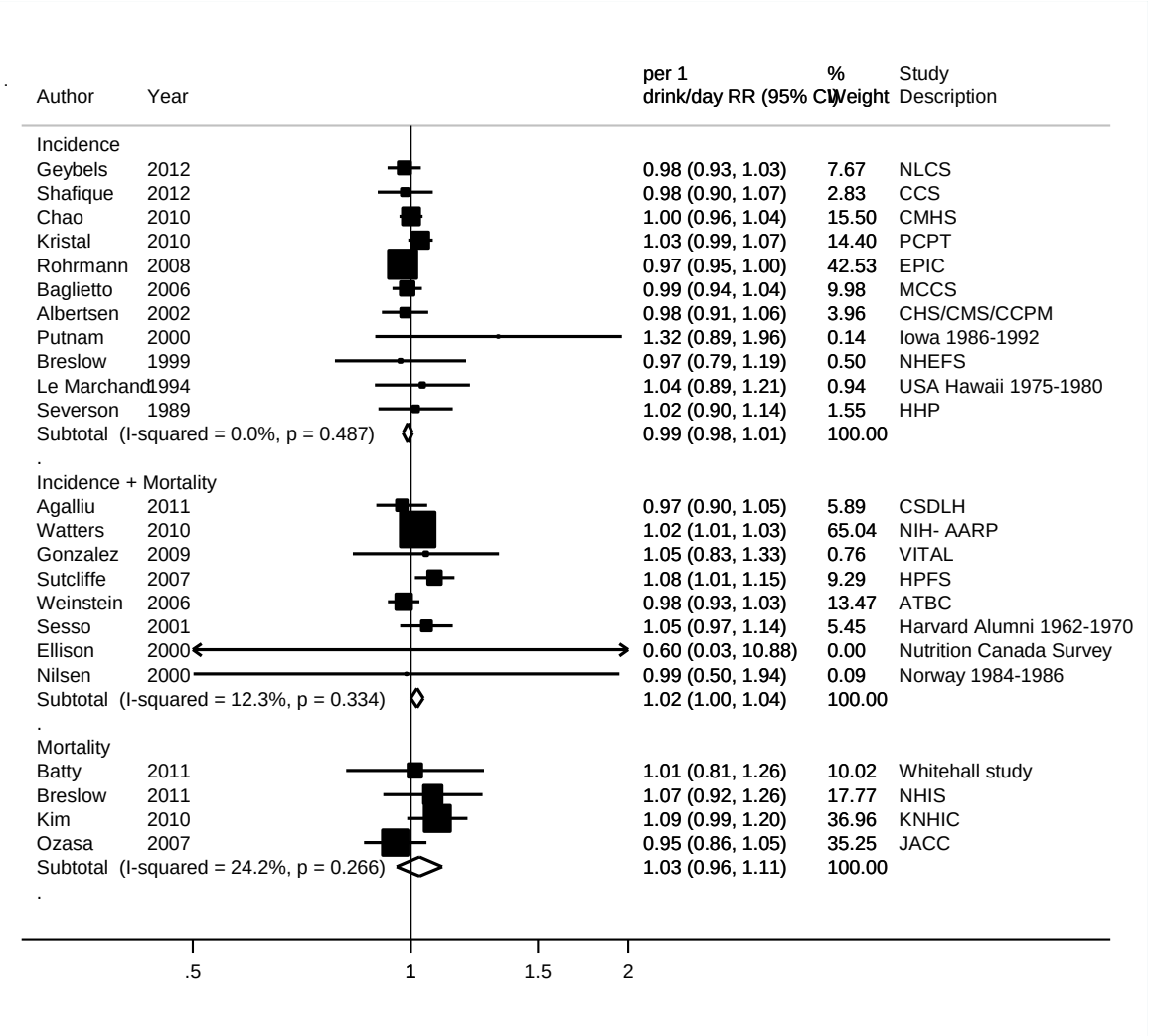


Figure 105 Dose-response meta-analysis of total alcoholic drinks and prostate cancer, per 1 drink/day, stratified by prostate cancer type

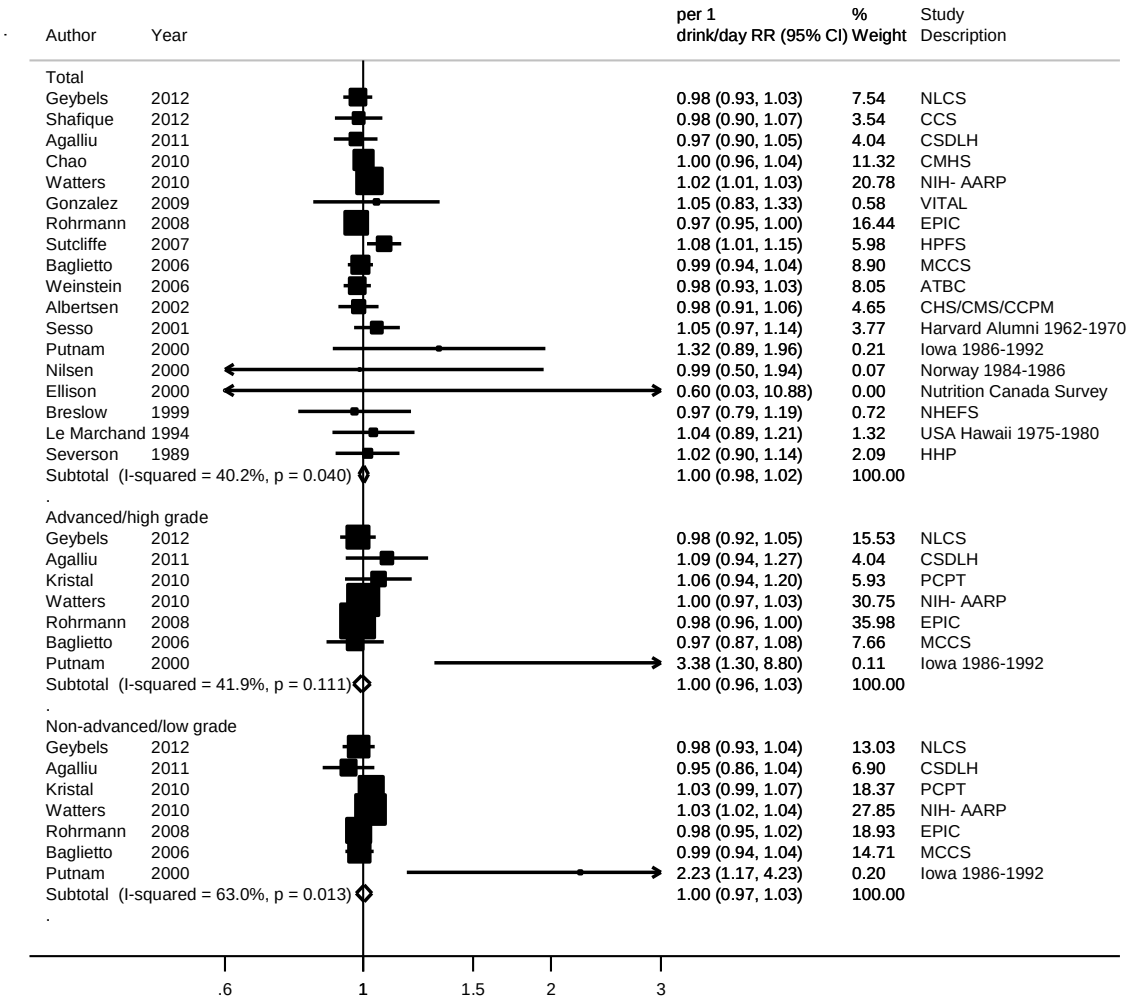
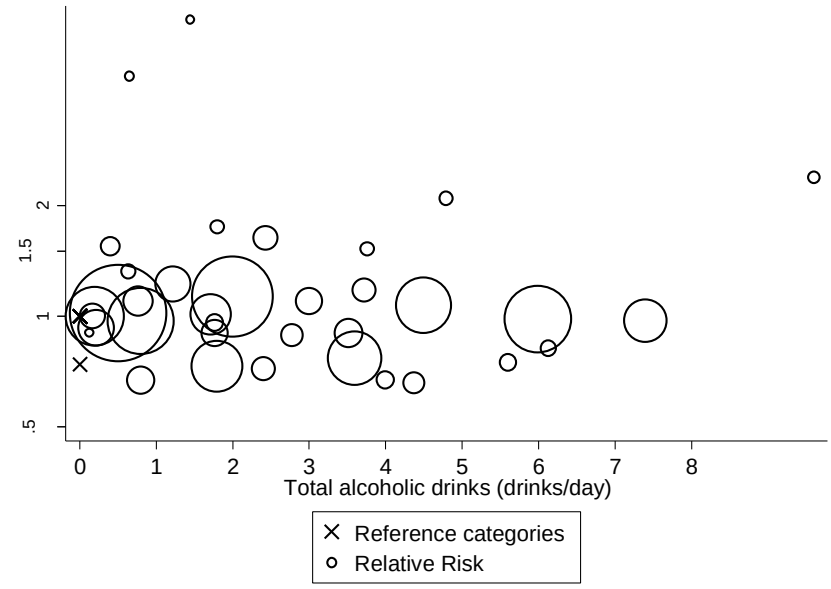


Figure 106 Non-linear dose-response analysis of total alcoholic drinks and advanced prostate cancer



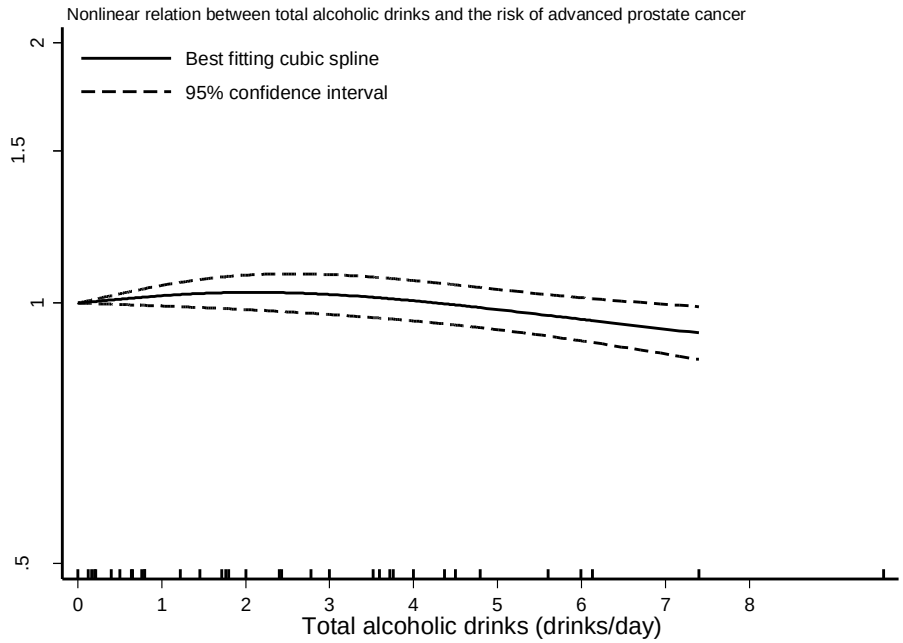


Table 93 Table with total alcoholic drinks values and corresponding RRs (95% CIs) for non-linear analysis of total alcoholic drinks and advanced prostate cancer

Total alcoholic drinks (drinks/day)	RR (95% CI)
0	1
2.0	1.02 (0.98-1.07)
4.79	0.98 (0.94-1.04)
7.4	0.92 (0.86-0.99)

$p_{non\text{-}linearity} = 0.03$

3.7.1.1 Beers

Methods
Eleven publications from thirteen studies were identified, from which 4 studies were identified in the CUP.

The increment unit used in the dose-response analysis was 1 drink/day. Whenever possible the unit used for the conversion of grams per day to drinks per day was the one referred in the study. For studies that did not provide a conversion unit, one beer was considered equivalent to 400 ml.

From the studies included in the dose-response meta-analysis all were on total prostate cancer, except two which reported on total, aggressive and non-aggressive cancer (Baglietto et al, 2006) and non-advanced and fatal prostate cancer (Watters et al, 2010). The combined estimated for non-advanced and fatal prostate cancers from Watters al, 2010 were included in the meta-analysis.

Main results
The summary RR per 1 drink per day was 1.00 (95% CI 0.99-1.02, $I^2 = 0\%$; $p_{heterogeneity} = 0.61$; n = 12). There was no evidence of publication bias with Egger's test, p = 0.17. No stratified analysis was conducted.

There was some evidence of non-linearity for total prostate cancer (p = 0.02) but the relative risk estimates were not statistically significant.

Heterogeneity
Overall, there was no evidence of heterogeneity, $I^2 = 0\%$, $p_{heterogeneity} = 0.61$.

Comparison with the Second Expert Report
In the 2005 SLR, the meta-analysis on beers and prostate cancer showed a non-significant relationship.

Published meta-analyses or pooled analyses
No published meta-analyses or pooled analyses were identified.

Table 94 Studies on beers identified in the CUP

Author, year	Country	Study name	Cases	Years of follow up	RR	LCI	UCI	Contrast
Chao, 2010	USA	California Men's Health Study (CMHS)	1340	5 years	0.96	0.78	1.18	≥ 1 vs. 0 drinks/d
Watters, 2010	USA	NIH–AARP	17227	7 years	1.09	1.00	1.20	Non-advanced > 3 vs. 0 drinks/d
					0.80	0.49	1.31	Fatal >3 vs. 0 drinks/d
Sutcliffe, 2007	USA	Health Professionals Study	3348	16 years	1.09	0.89	1.34	≥ 16.5 vs. 0 g/d
Baglietto, 2006	Australia	The Melbourne Collaborative Cohort Study (MCCS)	732	9 years	0.96	0.69	1.34	> 40 vs. 0 g/d

Table 95 Overall evidence on beers and prostate cancer

	Summary of evidence
2005 SLR	Six studies were included in the 2005 SLR meta-analysis. All were non-significant.
Continuous Update Project	Four new studies were identified in the CUP, all showed non-significant results towards an increase of risk. No significant association was observed in the CUP meta-analysis.

Table 96 Summary of results of the dose response meta-analysis of beers and prostate cancer

Prostate cancer		
	2005 SLR	CUP
Studies (n)	6	12
Cases (n)	952	24685
Increment unit used	Per 1 drink/day	Per 1 drink/day
Overall RR (95%CI)	0.93 (0.73-1.17)	1.01 (0.99-1.02)
Heterogeneity (I^2, p-value)	42.7%, p = 0.15	0%, p = 0.61

Table 97 Inclusion/exclusion table for meta-analysis of beers and prostate cancer

WCRF code	Author	Year	Study design	Study name	Cancer outcome	2005 SLR	CUP dose-response meta-analysis	CUP HvL forest plot	Estimated values	Exclusion reasons
PRO100049	Chao	2010	Prospective Cohort study	California Men's Health Study (CMHS)	Incidence	No	Yes	Yes		
PRO100077	Watters	2010	Prospective Cohort study	NIH–AARP	Incidence/ Mortality	No	Yes	Yes	Mid-exposure values	
PRO100003	Sutcliffe	2007	Prospective Cohort study	Health Professionals Study	Incidence	No	Yes	Yes	Mid-exposure values, conversion from g/day to drinks/day	
PRO99959	Baglietto	2006	Prospective Cohort study	The Melbourne Collaborative Cohort Study (MCCS)	Incidence	No	Yes	Yes	Mid-exposure values, person-years, conversion from g/day to drinks/day	
PRO00754	Albertsen	2002	Prospective Cohort study	Copenhagen City Heart Study/ Copenhagen Male Study/ Copenhagen County Centre of Preventive Medicine*	Incidence/ mortality	Yes	Yes	Yes	Mid-exposure values, person-years, conversion from drinks/week to drinks/day	
PRO01124	Sesso	2001	Prospective Cohort study	Harvard Alumni Health Study (HAHS)	Incidence/ mortality	Yes	Yes	Yes	Mid-exposure values	
PRO01487	Putnam	2000	Retrospective cohort study	Iowa's Men Study	Incidence/ mortality	Yes	Yes	Yes	Mid-exposure values, conversion from g/week to drinks/day	
PRO01770	Breslow	1999	Prospective Cohort study	NHANES I COHORT I 1971/75-1992 and COHORT II 1982/84-1992	Incidence/ mortality	Yes	Yes	Yes		

				(NHEFS)						
PRO01898	Schuurman	1999a	Case-cohort study	Netherlands Cohort Study	Incidence	Yes	Yes	Yes		
PRO02582	Gronberg	1996	Nested case-control study	Swedish twin cohort	Incidence	Yes	Yes	Yes		
PRO03129	Hsing	1990b	Prospective Cohort study	Lutheran Brotherhood Cohort Study	Mortality	Yes	No	No		Identified in 2005 SLR, not used. Unadjusted results

*Albertsen, 2002 counted as 3 studies.

Figure 107 Highest versus lowest forest plot of beers and prostate cancer

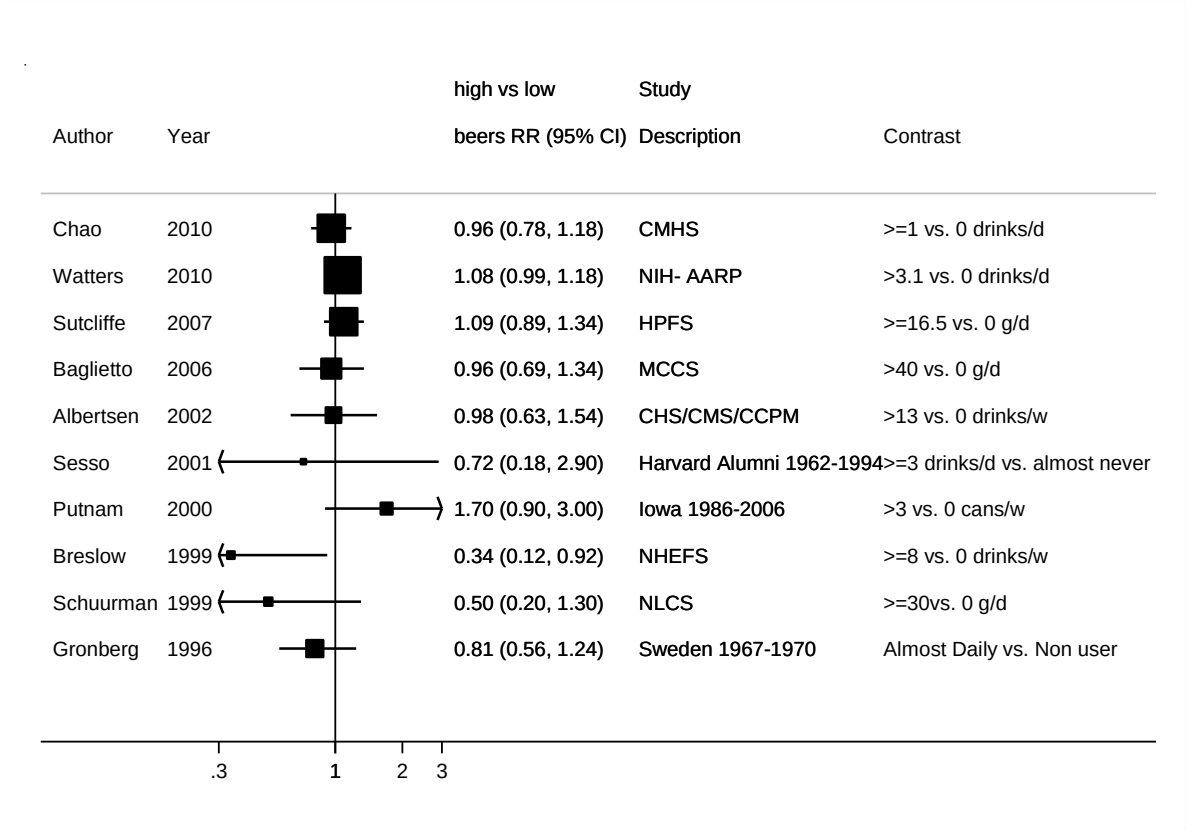


Figure 108 Dose-response meta-analysis of beers and prostate cancer – per 1 drink/day

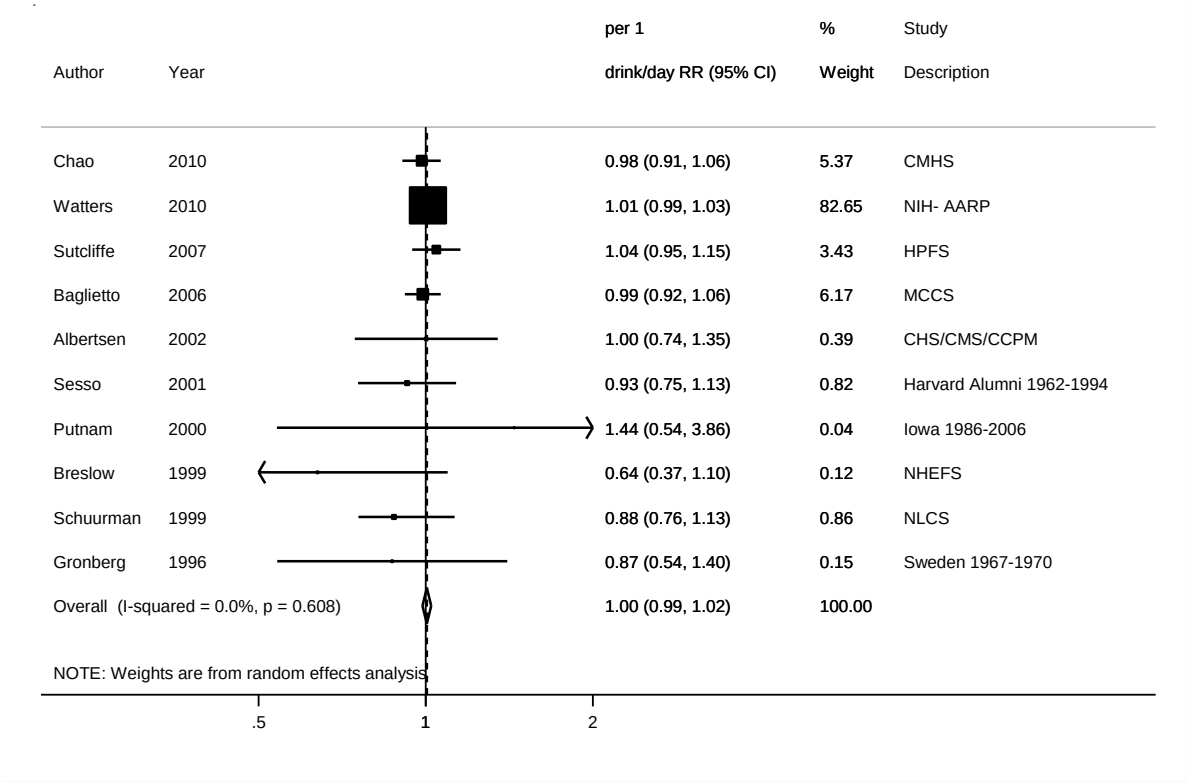
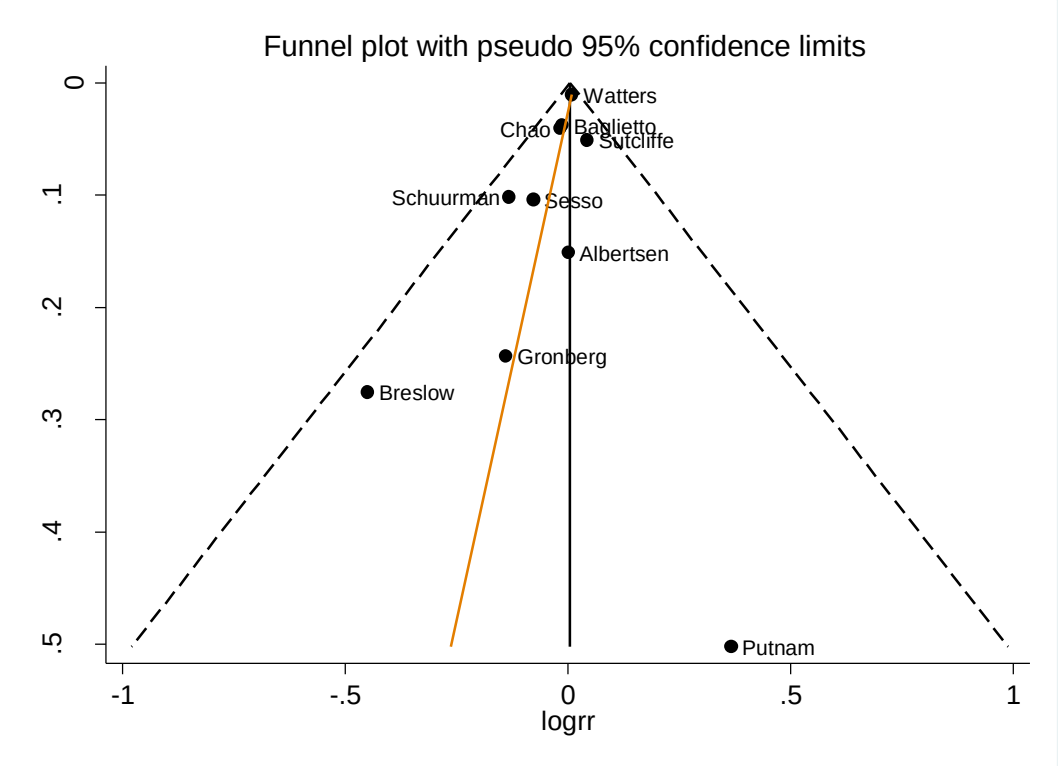


Figure 109 Funnel plot of beers and prostate cancer



Egger's test p = 0.17

Figure 110 Dose-response graph of beers and prostate cancer

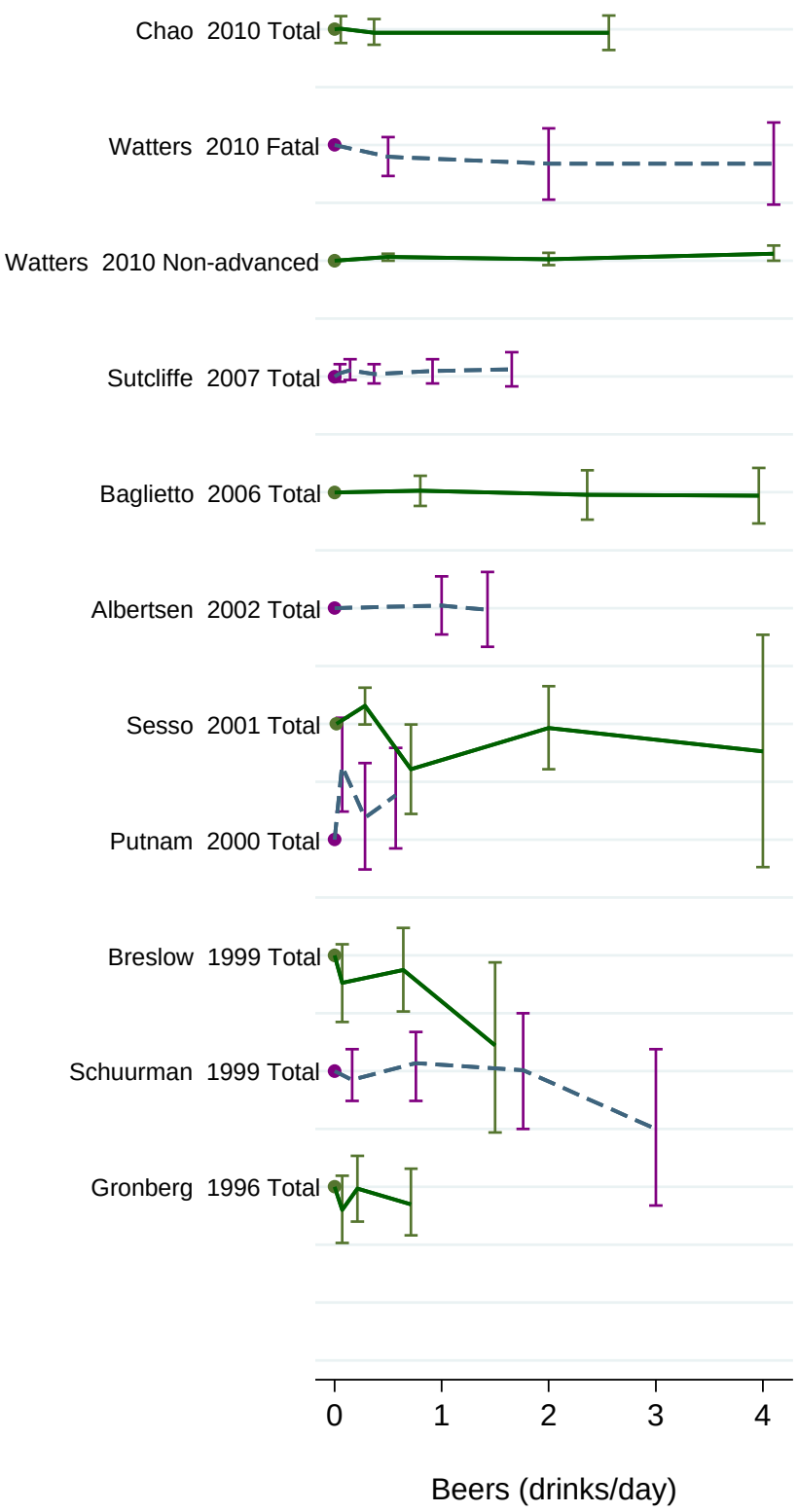


Figure 111 Non-linear dose-response analysis of beers and total prostate cancer

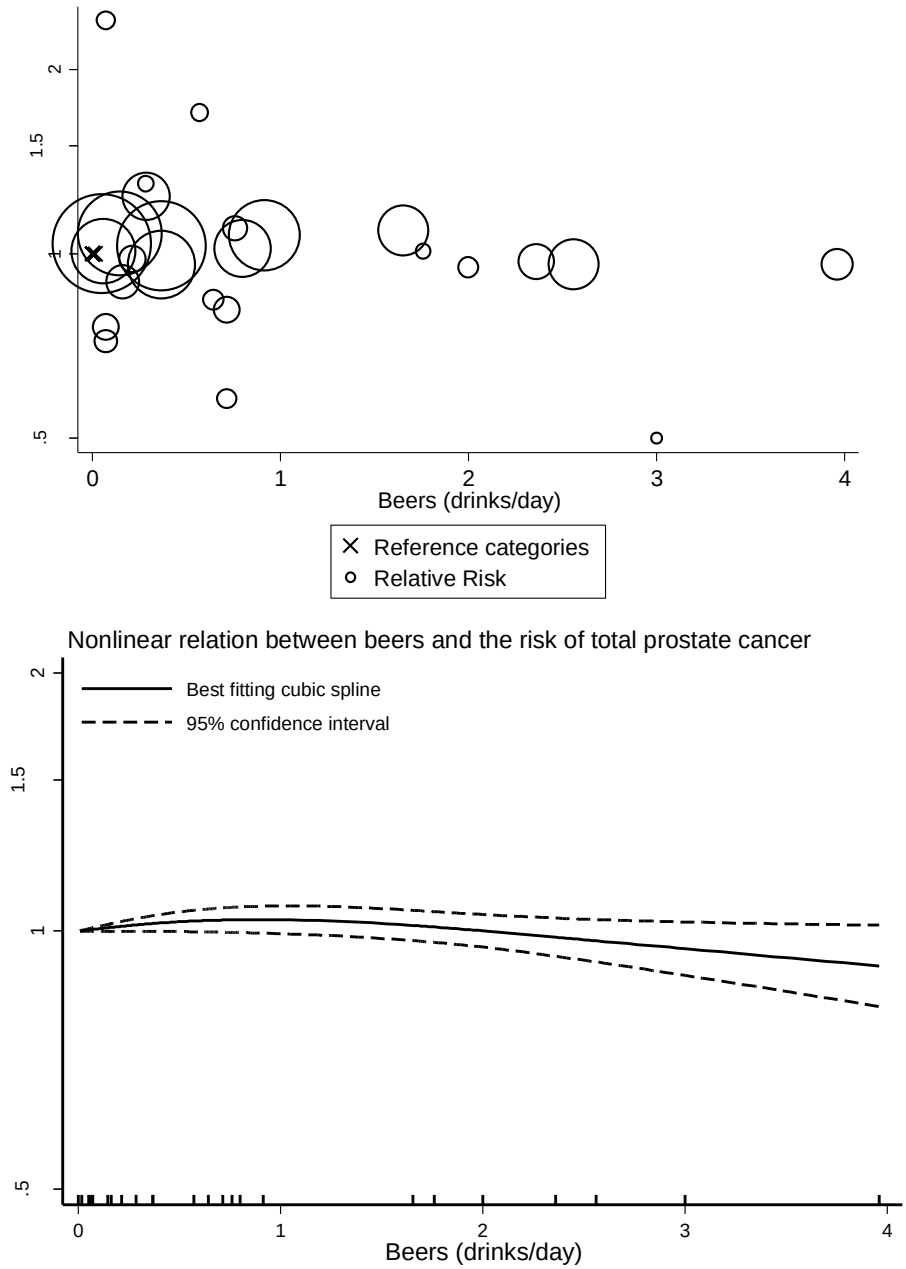


Table 98 Table with beers values and corresponding RRs (95% CIs) for non-linear analysis of beers and total prostate cancer

Beers (drinks/day)	RR (95% CI)
0	1
2.0	1.00 (0.96-1.05)
3.0	0.96 (0.89-1.02)
4.0	0.91 (0.82-1.01)

$p_{non\text{-}linearity} = 0.02$

3.7.1.2 Wines

Methods
Twelve publications from fourteen studies were identified, from which 5 studies were identified in the CUP.

The increment unit used in the dose-response analysis was 1 drink/day. Whenever possible the unit used for the conversion of grams per day to drinks per day was the one referred in the study. For studies that did not provide a conversion unit, one serving of wine was considered equivalent to 125 ml.

Nine studies were on wines in general and 3 studies stratified the analysis in red and white wine. For studies that present red and white separately the results were combined before inclusion in the meta-analysis.

From the studies included in the dose-response meta-analysis: seven were on total prostate cancer (Gronberg et al, 1996; Breslow et al, 1999; Schuurman et al, 1999a; Putnam et al, 2000; Sesso et al, 2001; Albertsen et al, 2002; Gonzalez et al, 2007), one study reported on total, stage 2-4, intermediate and high grade prostate cancer for red wine and total cancer for white wine (Chao et al, 2010), one study reported on non-advanced and fatal prostate cancer (Watters et al, 2010), one study reported on total, aggressive and non-aggressive cancer (Baglietto et al, 2006) and one study reported on total, localised, advanced, high grade and low grade prostate cancer for red wine and total prostate cancer for white wine (Sutcliffe et al, 2007). For Watters et al, 2010 the results of non-advanced and fatal prostate cancer were combined.

Main results
The summary RR per 1 drink per day was 1.02 (95% CI 1.00-1.04; $I^2 = 0\%$; $p_{heterogeneity} = 0.53$; n = 13). After excluding the Iowa's Study (Putnam et al, 2000) –showing positive association stronger than other studies- the overall result remained the same. There was no evidence of publication bias with Egger's test, p = 0.39. There was no evidence of non-linearity for total prostate cancer (p = 0.19).

Heterogeneity
Overall, there was no evidence of heterogeneity, $I^2 = 0\%$, $p_{heterogeneity} = 0.53$.

Comparison with the Second Expert Report
In the 2005 SLR, the meta-analysis on wines and prostate cancer showed a non-significant positive relationship.

Published meta-analyses or pooled analyses
No published meta-analyses or pooled analyses were identified.

Table 99 Studies on wines identified in the CUP

Author, year	Country	Study name	Cases	Years of follow up	RR	LCI	UCI	Contrast
Chao, 2010	USA	California Men's Health Study (CMHS)	1340	5 years	0.88	0.70	1.12	Red wine ≥ 1 vs. 0 drinks/d
					1.10	0.81	1.49	White wine ≥ 1 vs. 0 drinks/d
Watters, 2010	USA	NIH–AARP	17227	7 years	1.14	0.89	1.47	Non-advanced > 3 vs. 0 drinks/d
					0.90	0.58	1.37	Fatal 1-3 vs. 0 drinks/d
Sutcliffe, 2007	USA	Health Professionals Study	3348	16 years	1.06	0.72	1.56	Red wine ≥ 16.5 vs. 0 g/d
					1.19	0.89	1.60	White wine ≥ 16.5 vs. 0 g/d
Gonzalez, 2007	USA	VITAL study	832	3.3 years	1.23	0.94	1.62	Red wine 2.9-63.2 vs. 0 servings/w
					1.30	1.02	1.65	White wine 2.9-63.2 vs. 0 servings/w
Baglietto, 2006	Australia	The Melbourne Collaborative Cohort Study (MCCS)	732	9 years	0.98	0.70	1.37	> 40 vs. 0 g/d

Table 100 Overall evidence on wines and prostate cancer

	Summary of evidence
2005 SLR	Six studies were included in the 2005 SLR meta-analysis. All were non-significant.
Continuous Update Project	Five new studies were identified in the CUP; one study showed an increased risk of cancer for high consumptions (≈ 5 drinks/day) of white wine, all the others showed non-significant results towards an increase of risk. A weak positive association of borderline significance was obtained in the CUP meta-analysis.

Table 101 Summary of results of the dose response meta-analysis of wines and prostate cancer

Prostate cancer		
	2005 SLR	CUP
Studies (n)	6	13
Cases (n)	952	9314
Increment unit used	Per 1 drink/day	Per 1 drink/day
Overall RR (95% CI)	1.07 (0.86-1.35)	1.02 (1.00-1.04)
Heterogeneity (I^2, p-value)	30.8%, p = 0.23	0%, p = 0.53

Table 102 Inclusion/exclusion table for meta-analysis of wines and prostate cancer

WCRF code	Author	Year	Study design	Study name	Cancer outcome	2005 SLR	CUP dose-response meta-analysis	CUP HvL forest plot	Estimated values	Exclusion reasons
PRO100049	Chao	2010	Prospective Cohort study	California Men's Health Study (CMHS)	Incidence	No	Yes	Yes		
PRO100077	Watters	2010	Prospective Cohort study	NIH–AARP	Incidence/ Mortality	No	Yes	Yes	Mid-exposure values	
PRO100003	Sutcliffe	2007	Prospective Cohort study	Health Professionals Study	Incidence	No	Yes	Yes	Mid-exposure values, conversion from g/day to drinks/day	
PRO100035	Gonzalez	2007	Prospective Cohort study	VITAL study	Incidence/ Mortality	No	Yes	Yes	Mid-exposure values, person-years	
PRO99959	Baglietto	2006	Prospective Cohort study	The Melbourne Collaborative Cohort Study (MCCS)	Incidence	No	Yes	Yes	Mid-exposure values, person-years, conversion from g/day to drinks/day	
PRO00754	Albertsen	2002	Prospective Cohort study	Copenhagen City Heart Study/ Copenhagen Male Study/ Copenhagen County Centre of Preventive Medicine*	Incidence/ mortality	Yes	Yes	Yes	Mid-exposure values, person-years, conversion from drinks/week to drinks/day	
PRO01124	Sesso	2001	Prospective Cohort study	Harvard Alumni Health Study (HAHS)	Incidence/ mortality	Yes	Yes	Yes	Mid-exposure values	
PRO01487	Putnam	2000	Retrospective cohort study	Iowa's Men Study	Incidence/ mortality	Yes	Yes	Yes	Mid-exposure values, conversion from g/week to drinks/day	

PRO01770	Breslow	1999	Prospective Cohort study	NHANES I COHORT I 1971/75-1992 and COHORT II 1982/84-1992 (NHEFS)	Incidence/ mortality	Yes	Yes	Yes		
PRO01898	Schuurman	1999a	Case-cohort study	Netherlands Cohort Study	Incidence	Yes	Yes	Yes		
PRO02582	Gronberg	1996	Nested case-control study	Swedish twin cohort	Incidence	Yes	Yes	Yes		
PRO03129	Hsing	1990b	Prospective Cohort study	Lutheran Brotherhood Cohort Study	Mortality	Yes	No	No		Identified in 2005 SLR, not used. Unadjusted results

* Albertsen, 2002 counted as 3 studies.

Figure 112 Highest versus lowest forest plot of wines and prostate cancer

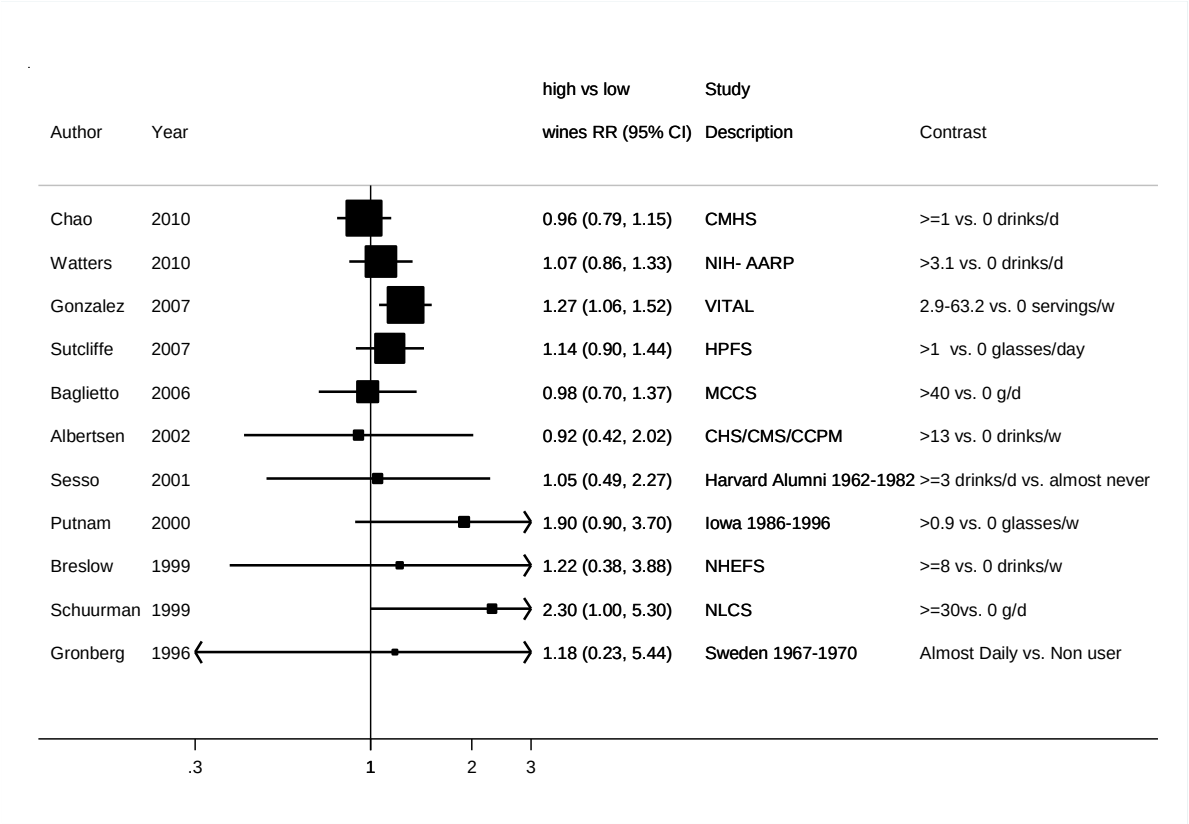


Figure 113 Dose-response meta-analysis of wines and prostate cancer – per 1 drink/day

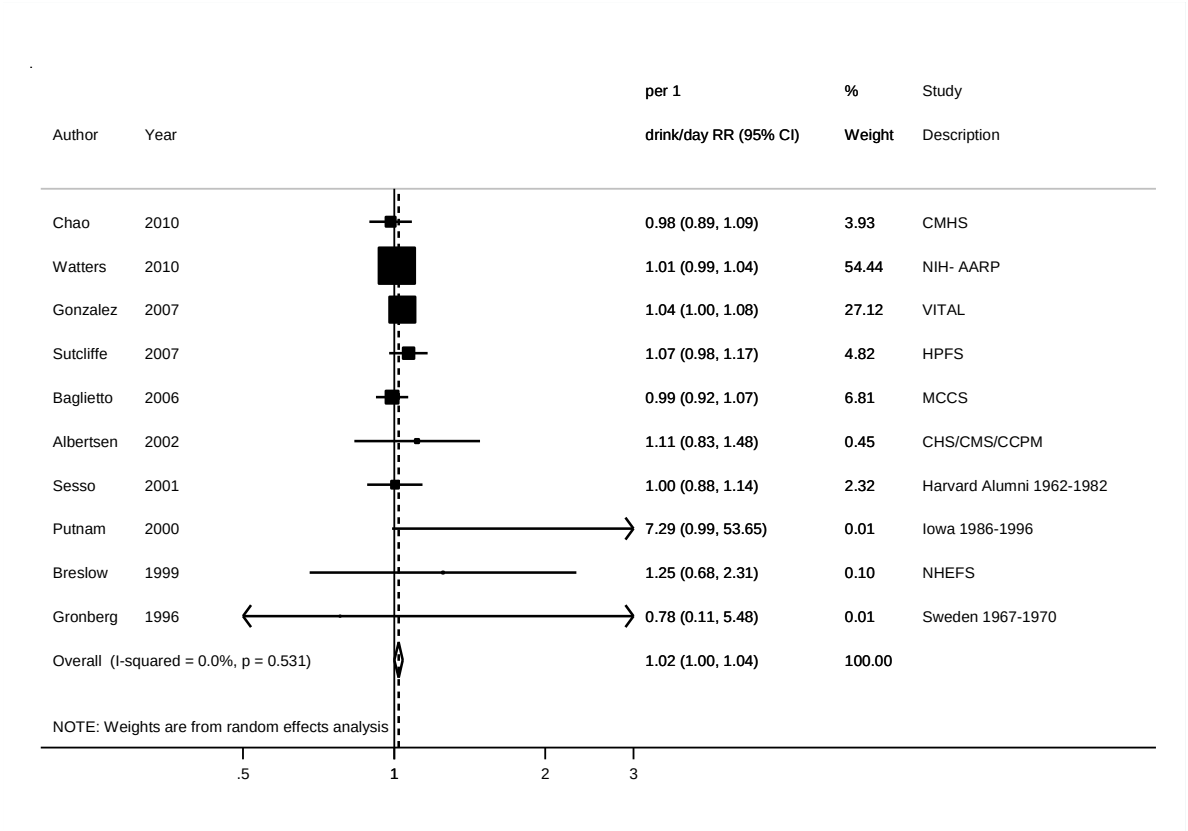
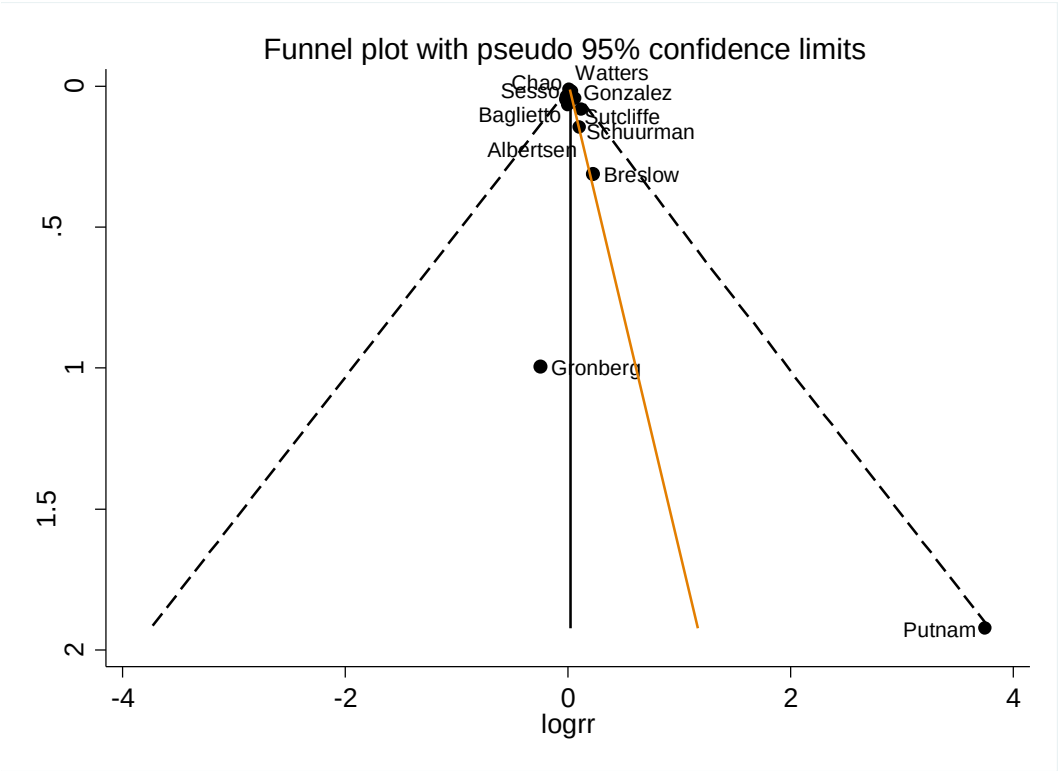
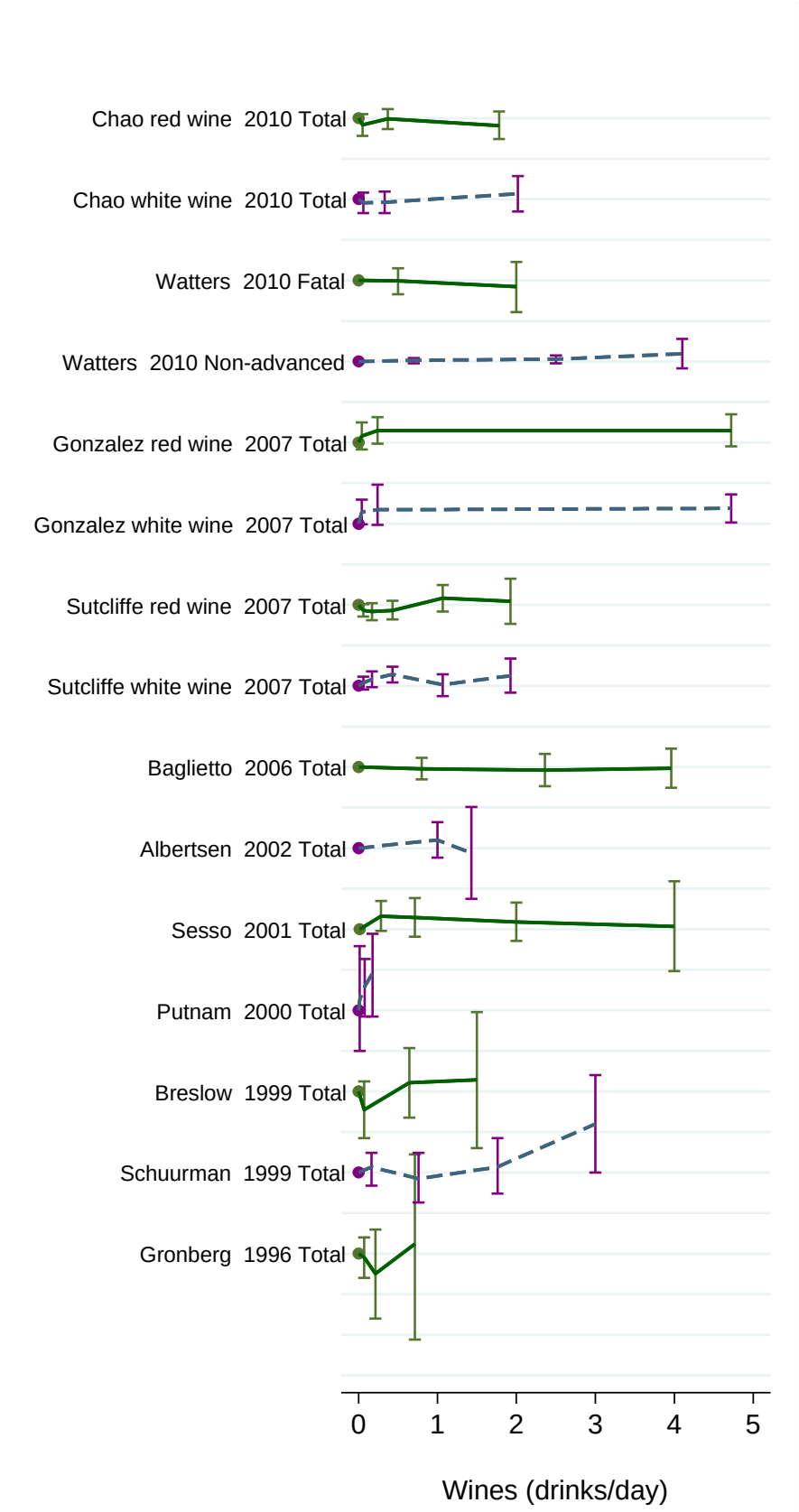


Figure 114 Funnel plot of wines and prostate cancer



Egger's test p = 0.39

Figure 115 Dose-response graph of wines and prostate cancer



3.7.1.3 Spirits

Methods
Eleven publications from thirteen studies were identified, from which 4 studies were identified in the CUP.
The increment unit used in the dose-response analysis was 1 drink/day. Whenever possible the unit used for the conversion of grams per day to drinks per day was the one referred in the study. For studies that did not provide a conversion unit, one unit of spirits was considered equivalent to 25 ml.

From the studies included in the dose-response meta-analysis all were on total prostate cancer, except one which reported on non-advanced and fatal prostate cancer (Watters et al, 2010). In this last case the results of non-advanced and fatal prostate cancer were combined.

Main results
The summary RR per 1 drink per day was 1.04 (95% CI 1.02-1.05; $I^2 = 0\%$, $p_{heterogeneity} = 0.65$; n = 11). This association is mainly due to the result of the NIH-AARP study (Watters et al, 2010) which has a weight of 88.6%. There was no evidence of publication bias with Egger's test, p=0.07. There was evidence of non-linearity for total prostate cancer ($p<0.01$) for consumptions between 1 and 3 drinks/day.

Heterogeneity
Overall, there was no evidence of heterogeneity, $I^2 = 0\%$, $p_{heterogeneity} = 0.65$.

Comparison with the Second Expert Report
In the 2005 SLR, the meta-analysis on spirits and prostate cancer showed a positive non-significant relationship.

Published meta-analyses or pooled analyses
No published meta-analyses or pooled analyses were identified.

Table 103 Studies on spirits identified in the CUP

Author, year	Country	Study name	Cases	Years of follow up	RR	LCI	UCI	Contrast
Chao, 2010	USA	California Men's Health Study (CMHS)	1340	5 years	1.05	0.82	1.33	≥ 1 vs. 0 drinks/d
Watters, 2010	USA	NIH–AARP	17227	7 years	1.15	1.06	1.24	Non-advanced > 3 vs. 0 drinks/d
					0.73	0.45	1.19	Fatal > 3 vs. 0 drinks/d
Sutcliffe, 2007	USA	Health Professionals Study	3348	16 years	1.10	0.96	1.27	≥ 16.5 vs. 0 g/d
Baglietto, 2006	Australia	The Melbourne Collaborative Cohort Study (MCCS)	732	9 years	1.14	0.96	1.35	> 1 vs. 0 g/day

Table 104 Overall evidence on spirits and prostate cancer

	Summary of evidence
2005 SLR	Six studies were included in the 2005 SLR meta-analysis. All, except one (Sesso et al, 2001), showed a positive non-significant association.
Continuous Update Project	Four new studies were identified in the CUP, only one showed an increased risk for non-advanced prostate cancer, all the other showed non-significant results towards an increase of risk. A weak positive association was observed in the CUP meta-analysis.

Table 105 Summary of results of the dose response meta-analysis of spirits and prostate cancer

Prostate cancer		
	2005 SLR	CUP
Studies (n)	6	11
Cases (n)	952	23953
Increment unit used	Per 1 drink/day	Per 1 drink/day
Overall RR (95%CI)	1.12 (0.92-1.37)	1.04 (1.02-1.05)
Heterogeneity (I^2, p-value)	37.6%, p = 0.19	0%, p = 0.65

Table 106 Inclusion/exclusion table for meta-analysis of spirits and prostate cancer

WCRF code	Author	Year	Study design	Study name	Cancer outcome	2005 SLR	CUP dose-response meta-analysis	CUP HvL forest plot	Estimated values	Exclusion reasons
PRO100049	Chao	2010	Prospective Cohort study	California Men's Health Study (CMHS)	Incidence	No	Yes	Yes		
PRO100077	Watters	2010	Prospective Cohort study	NIH–AARP	Incidence/ Mortality	No	Yes	Yes	Mid-exposure values	
PRO100003	Sutcliffe	2007	Prospective Cohort study	Health Professionals Study	Incidence	No	Yes	Yes	Mid-exposure values, conversion from g/day to drinks/day	
PRO99959	Baglietto	2006	Prospective Cohort study	The Melbourne Collaborative Cohort Study (MCCS)	Incidence	No	No	Yes		Only two categories.
PRO00754	Albertsen	2002	Prospective Cohort study	Copenhagen City Heart Study/ Copenhagen Male Study/ Copenhagen County Centre of Preventive Medicine*	Incidence/ mortality	Yes	Yes	Yes	Mid-exposure values, person-years, conversion from drinks/week to drinks/day	
PRO01124	Sesso	2001	Prospective Cohort study	Harvard Alumni Health Study (HAHS)	Incidence/ mortality	Yes	Yes	Yes	Mid-exposure values	
PRO01487	Putnam	2000	Retrospective cohort study	Iowa's Men Study	Incidence/ mortality	Yes	Yes	Yes	Mid-exposure values, conversion from g/week to drinks/day	
PRO01770	Breslow	1999	Prospective Cohort study	NHANES I COHORT I 1971/75-1992 and COHORT II 1982/84-1992 (NHEFS)	Incidence/ mortality	Yes	Yes	Yes		

PRO01898	Schuurman	1999a	Case-cohort study	Netherlands Cohort Study	Incidence	Yes	Yes	Yes		
PRO02582	Gronberg	1996	Nested case-control study	Swedish twin cohort	Incidence	Yes	Yes	Yes		
PRO03129	Hsing	1990b	Prospective Cohort study	Lutheran Brotherhood Cohort Study	Mortality	Yes	No	No		Identified in 2005 SLR, not used. Unadjusted results

* Albertsen, 2002 counted as 3 studies.

Figure 116 Highest versus lowest forest plot of spirits and prostate cancer

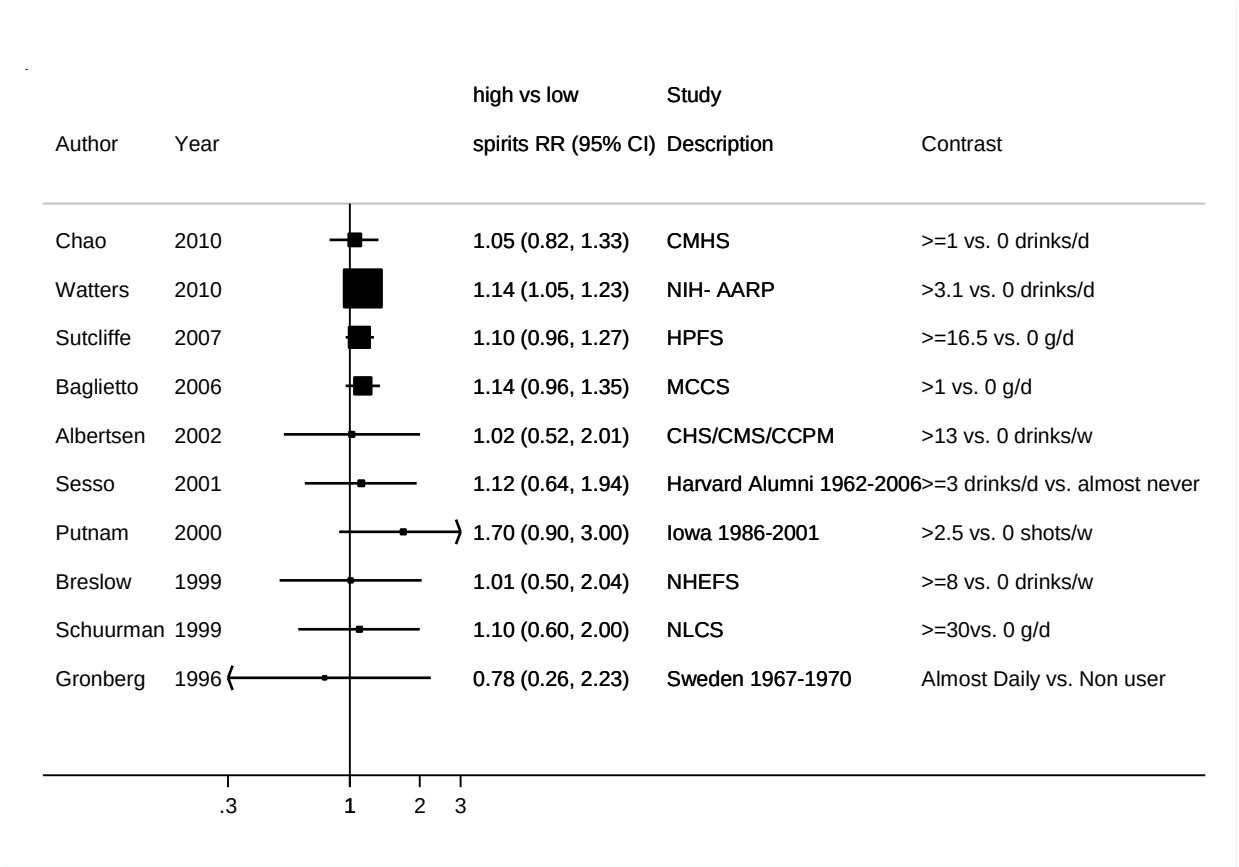


Figure 117 Dose-response meta-analysis of spirits and prostate cancer – per 1 drink/day

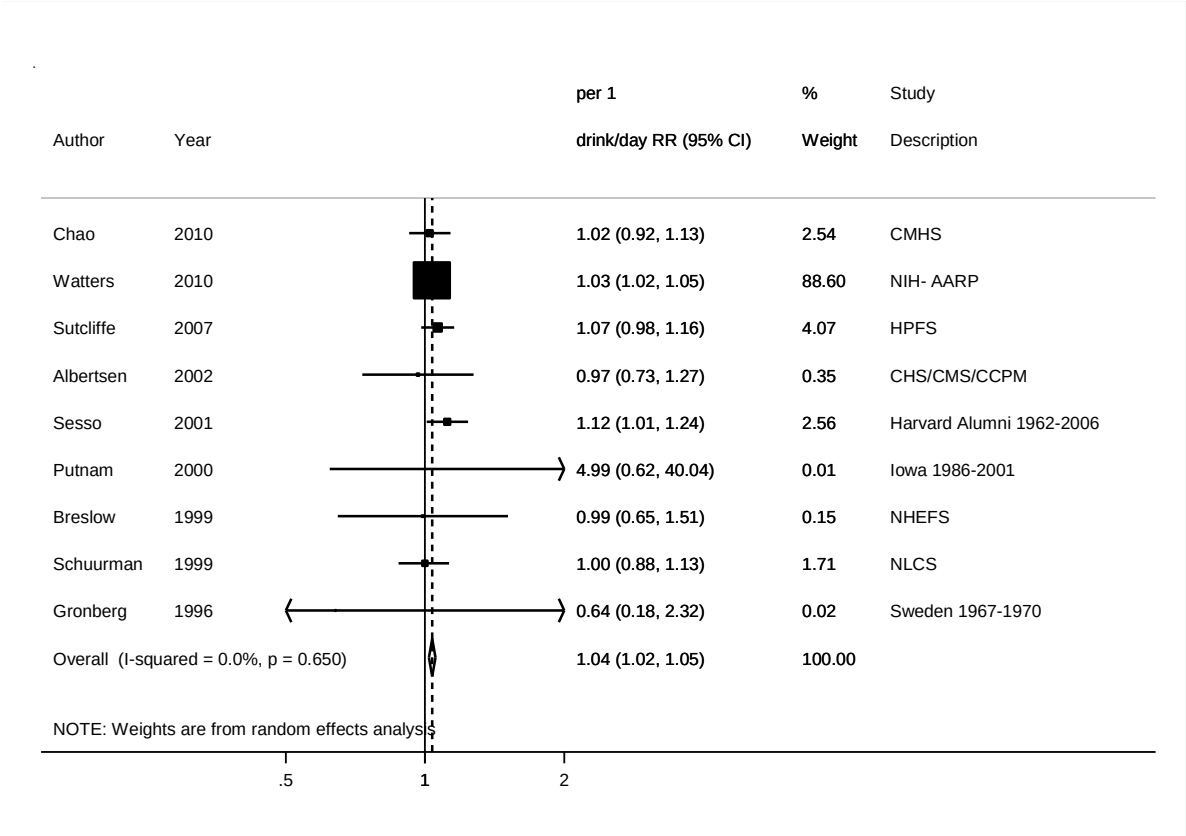
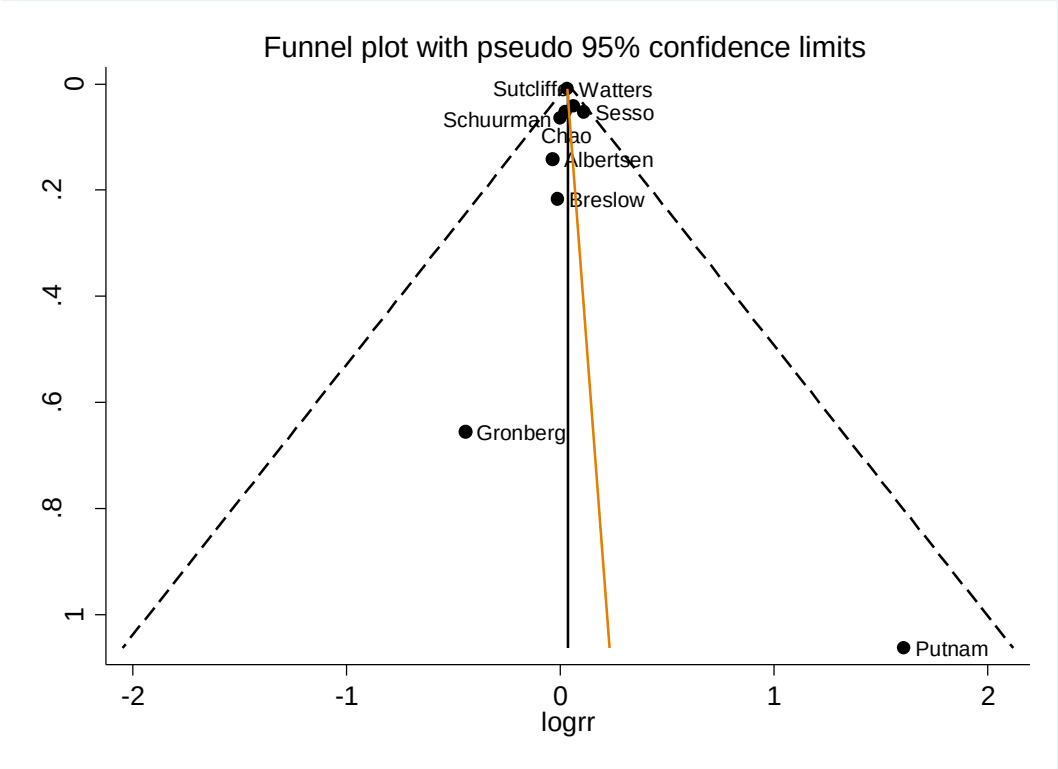


Figure 118 Funnel plot of spirits and prostate cancer



Egger's test p = 0.07

Figure 119 Dose-response graph of spirits and prostate cancer

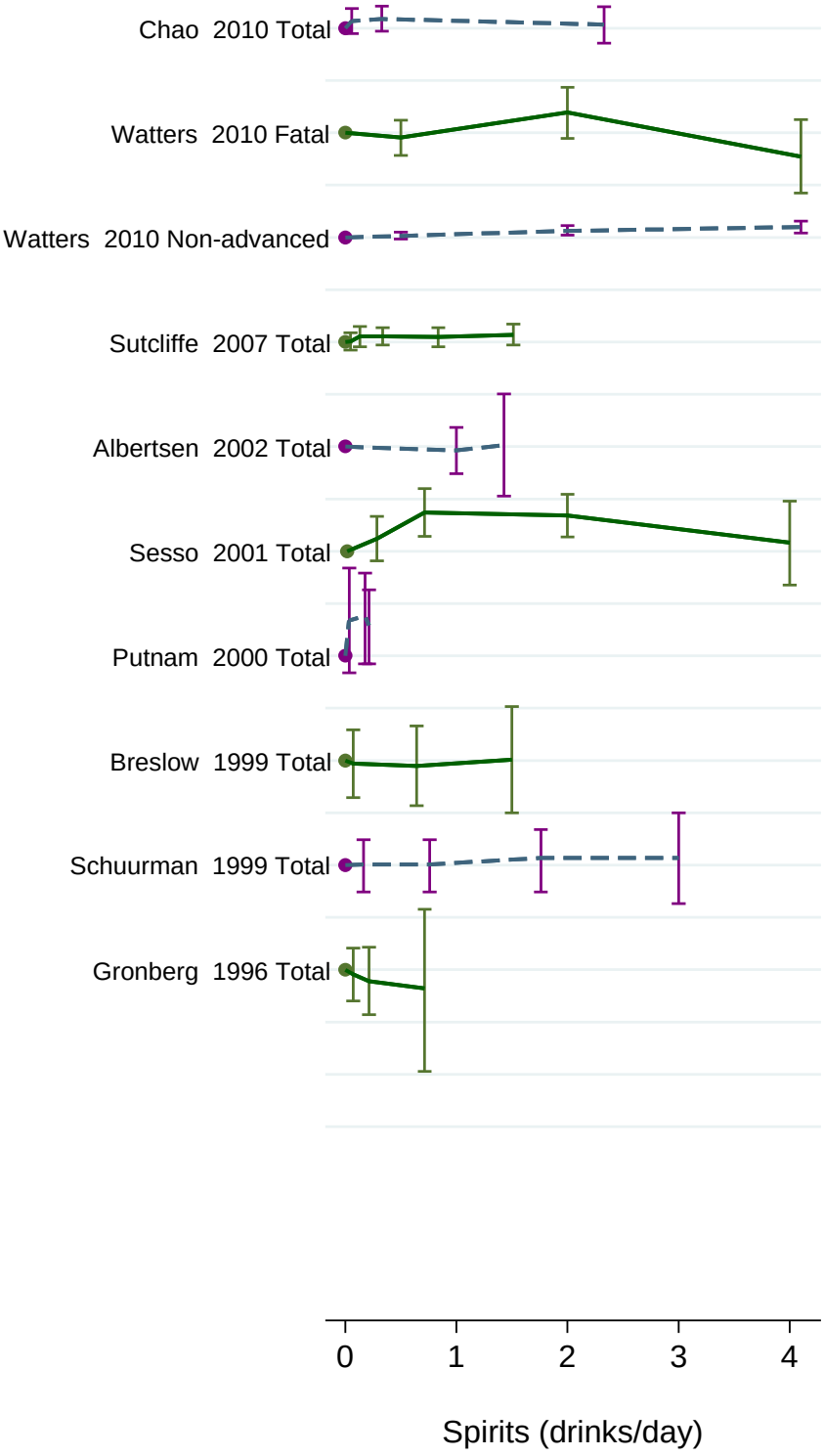
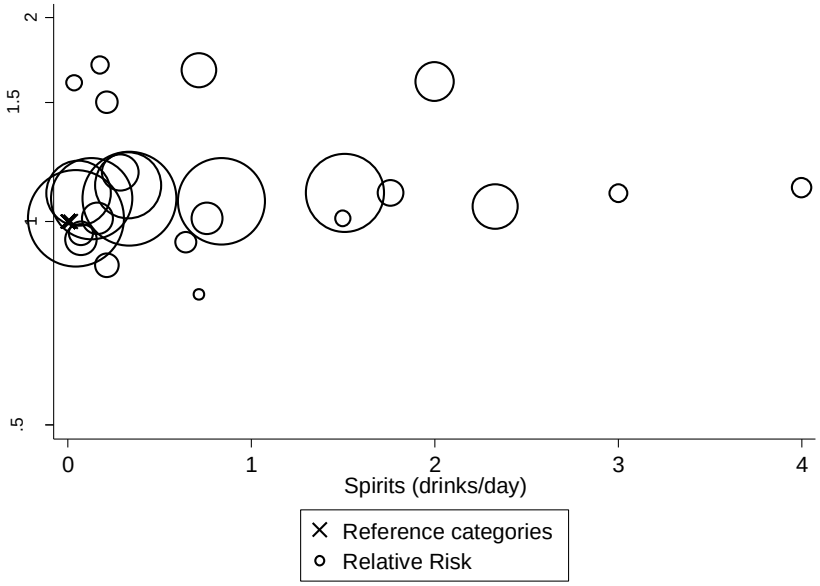


Figure 120 Non-linear dose-response analysis of spirits and total prostate cancer



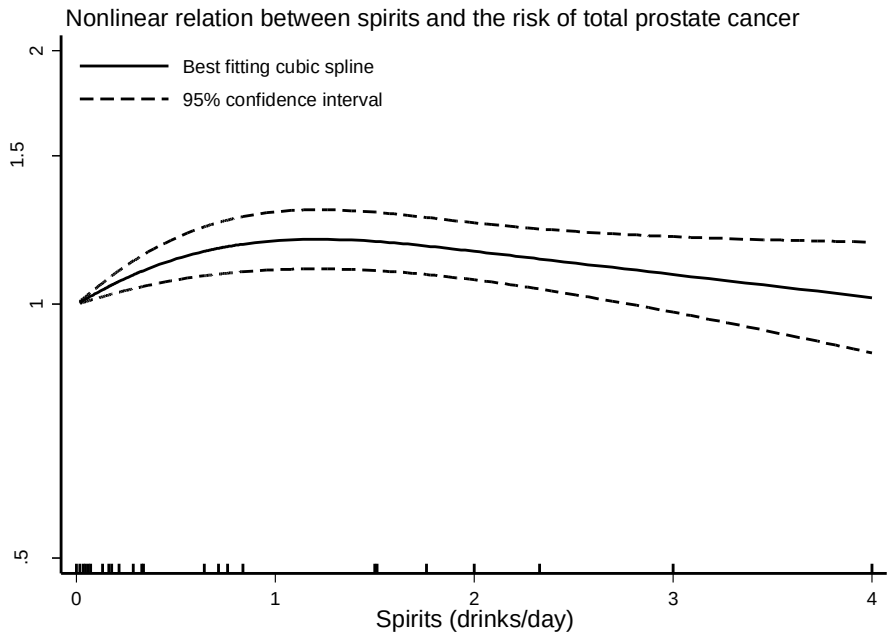


Table 107 Table with spirits values and corresponding RRs (95% CIs) for non-linear analysis of spirits and total prostate cancer

Spirits (drinks/day)	RR (95% CI)
0	1
1.5	1.21 (1.11-1.32)
2.0	1.17 (1.08-1.28)
3.0	1.07 (0.96-1.20)

$p_{non\text{-}linearity} < 0.01$

5 Dietary constituents

5.1 Carbohydrate

Methods

Ten publications from 9 cohort studies on carbohydrate and prostate cancer risk were identified; 4 publications were identified during the CUP. Dose-response analyses were conducted per 100 g/day.

In the Prostate Cancer Prevention Trial study (Kristal et al, 2010), carbohydrate intake was expressed in kcal/day which and it was rescaled to g/d using the conversion unit of 1 g equivalent to 4 kcal.

One study (Shikany et al, 2011) investigated available carbohydrates (grams of carbohydrate per serving minus value for grams of dietary fibre per serving).

From the studies included in the dose-response meta-analysis: five studies investigated total prostate cancer (Shikany et al, 2011; Chan et al, 2000; Parker et al, 1999; Severson et al, 1989b), one study reported on total and advanced prostate cancer (Shikany et al, 2010), one study in advanced prostate cancer (Giovannucci et al, 1998b) and one study (Kristal et al, 2010) on high and low grade prostate cancer. The outcome in Smit et al, 2007 was mortality for prostate cancer.

Overall, 5 cohort studies were included in dose-response analysis for total prostate cancer and 3 studies were included in stratified analysis for advanced prostate cancer. In stratified analysis by prostate cancer type, advanced, high grade and high risk cancers were combined in an advanced subgroup. No dose-response meta-analysis conducted on low grade prostate cancer.

Main results

The summary RR of total prostate cancer per 100 g/day increase of carbohydrate intake was 1.01 (95% CI 0.93-1.10; $I^2 = 56.4\%$ $p_{heterogeneity} = 0.06$) for all studies combined.
The summary RR was 1.02 (95% CI 0.91-1.14) when the study on mortality was excluded (PRHHP, Smit et al, 2007). The RR for advanced/high grade cancer per 100 g/day of carbohydrate was 0.87 (95% CI 0.71-1.07; $I^2 = 86.9\%$; $p_{heterogeneity} < 0.01$).
There was no evidence of publication bias with Egger's test, $p = 0.18$.

Heterogeneity

There was evidence of moderate heterogeneity for total prostate cancer ($I^2 = 56.4\%$; $p_{heterogeneity} = 0.06$). Visual inspection of the forest and funnel plots show that the smallest study reported stronger than average positive associations (Parker et al, 1999).

Comparison with the Second Expert Report

The meta-analysis on carbohydrate and prostate cancer during the 2005 SLR showed no significant association.

Published meta-analysis or pooled analysis

No published meta-analyses or pooled studies were identified.

Table 108 Studies on carbohydrate identified in the CUP

Author, year	Country	Study name	Cases	Years of follow up	RR	LCI	UCI	Contrast
Drake, 2012	Sweden	Malmo Preventive Project Cohort Study	817	15 years	1.10	0.84	1.42	333.7 g/day vs. 219.4 g/day
Shikany, 2011	USA	PLCO Cancer Screening Trial	2436	9.2 years	0.86	0.67	1.10	≥ 350.1 g/day vs. ≤ 188.6 g/day
Kristal, 2010	USA and Canada	The Prostate Cancer Prevention Trial	1703	7 years	0.64	0.31	1.31	> 1304 kcal/day vs. < 755 kcal/day
Smit, 2007	Puerto Rico	Puerto Rico Heart Health Program	167	40 years	1.27	0.76	2.12	≤ 341 g/day vs. ≤ 202 g/day

Table 109 Overall evidence on carbohydrate and total prostate cancer

	Summary of evidence
2005 SLR	Five cohort studies identified; four of them were included in the meta-analysis during the 2005 SLR. Results showed a non-significant association.
Continuous Update Project	Four new studies were identified in the CUP; three of them were included in the meta-analysis. Overall five studies included in the meta-analysis, all showed no significant association. No significant association was observed in the CUP meta-analysis.

Table 110 Summary of results of the dose-response meta-analysis of carbohydrate and total prostate cancer

Prostate cancer incidence and mortality		
	2005 SLR	CUP
Studies (n)	4	5
Cases (n)	1808	3859
Increment unit used	Per 100 g/day	Per 100 g/day
Overall RR (95% CI)	1.11 (0.82-1.51)	1.01 (0.93-1.10)
Heterogeneity (I^2, p-value)	I^2 = 78.7%, p < 0.01	I^2 = 56.4%, p = 0.06
Stratified analysis	Prostate cancer incidence	
Advanced/high grade cancer		
Overall RR (95% CI)		0.87 (0.71-1.07)
Heterogeneity (I^2, p-value)		I^2 = 86.9%, p < 0.01, n = 3

Table 111 Inclusion/exclusion table for meta-analysis of carbohydrate and total prostate cancer

WCRF code	Author	Year	Study design	Study name	Cancer outcome	2005 SLR	CUP dose-response meta-analysis	CUP HvL forest plot	Estimated values	Exclusion reasons
PRO100139	Drake	2012	Prospective cohort study	Malmo Preventive Project Cohort Study	Incidence	No	No	Yes		Results for highest vs. lowest only
PRO100098	Shikany	2011	Prospective cohort study	PLCO Cancer Screening Trial	Incidence	No	Yes	Yes	Mid-exposure values Person/years	
PRO100078	Kristal*	2010	Follow up of randomized trial in men with severe lower urinary tract symptoms	The Prostate Cancer Prevention Trial	Incidence	No	Yes	Yes	Mid-exposure values Person/years per quintiles Kcal/day rescaled to g/day	
PRO100019	Smit	2007	Prospective cohort study	Puerto Rico Heart Health Program	Mortality	No	Yes	Yes	Mid-exposure values Person/years Number of cases per quintiles	
PRO00515	Hsieh	2003	Prospective cohort study	Baltimore Longitudinal Study of Aging	Incidence and prevalence	Yes	No	No		Combined results for prevalent and incidence cases
PRO01426	Chan	2000	Prospective cohort study	Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study	Incidence Stage II-IV prostate cancer	Yes	Yes	Yes	Person/years Number of cases per quintiles	
PRO01737	Parker	1999	Prospective cohort study	USA Iowa 1986-1989	Incidence	Yes	Yes	Yes	Mid-exposure values	

PRO02192	Giovannucci *	1998 b	Prospective cohort study	Health Professionals Follow-up study	Incidence	Yes	Yes	Yes	Confidence intervals	
PRO03125	Stemmermann	1990	Prospective cohort study	USA Hawaii 1965-1968	Mortality and incidence	Yes	No	No		No RR available Duplicate of Severson et al, 1989 study
PRO03210	Severson	1989 b	Prospective cohort study	USA Hawaii 1965-1968	Incidence	Yes	Yes	Yes	Person/years per category Mid-exposure values	

*The studies of Kristal, 2010 and Giovannucci, 1998, were included only in advanced cancer meta-analysis.

Figure 121 Highest versus lowest forest plot of carbohydrate and total prostate cancer

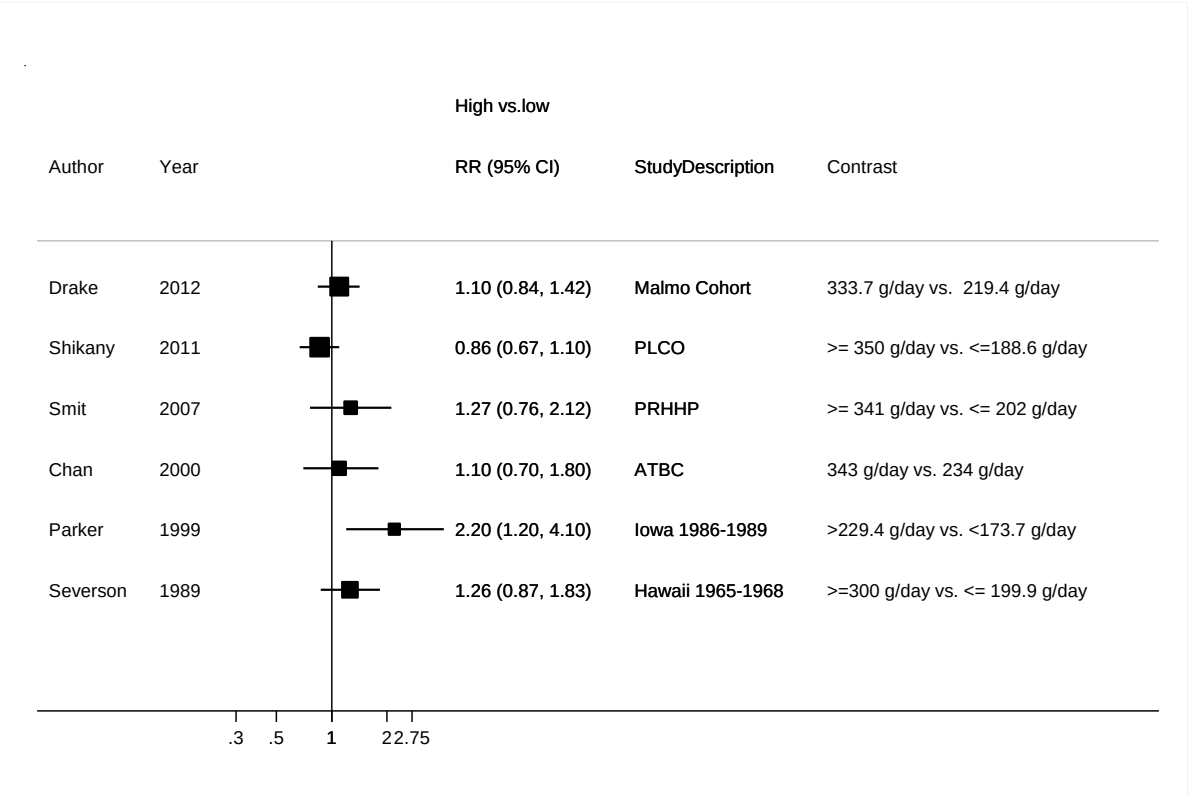


Figure 122 Dose-response meta-analysis of carbohydrate and total prostate cancer, per 100 g/day

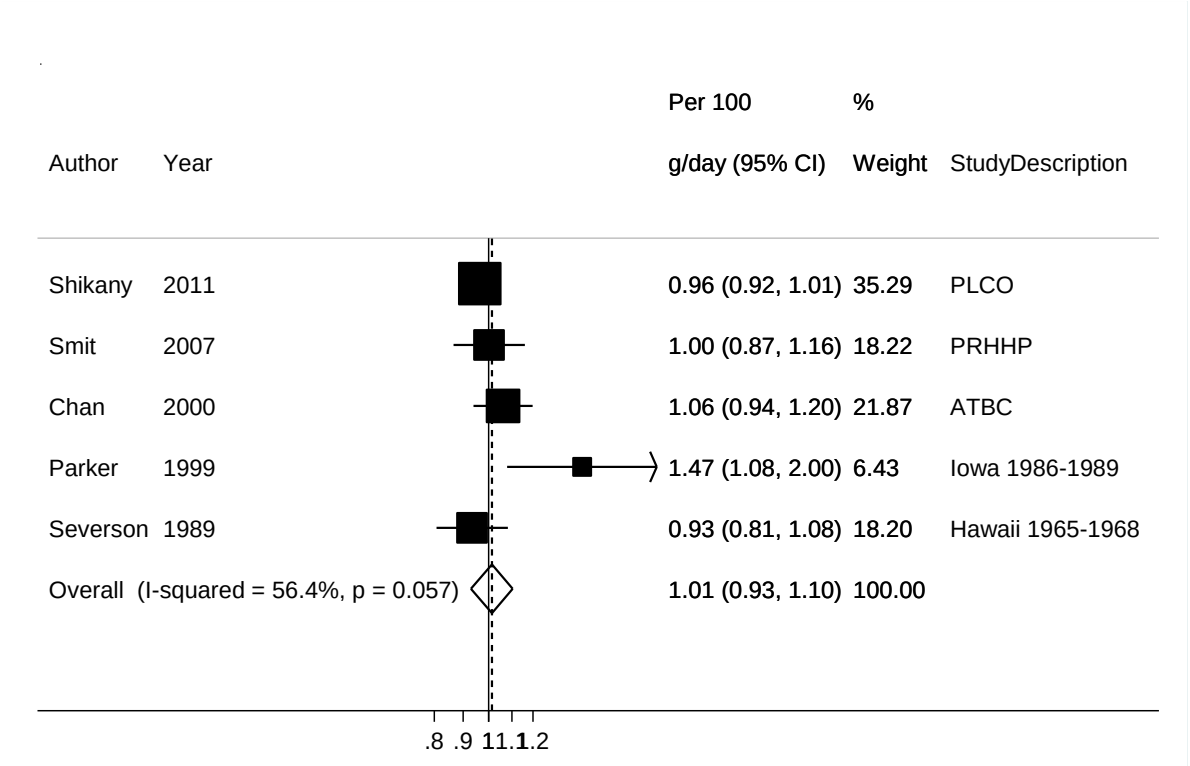
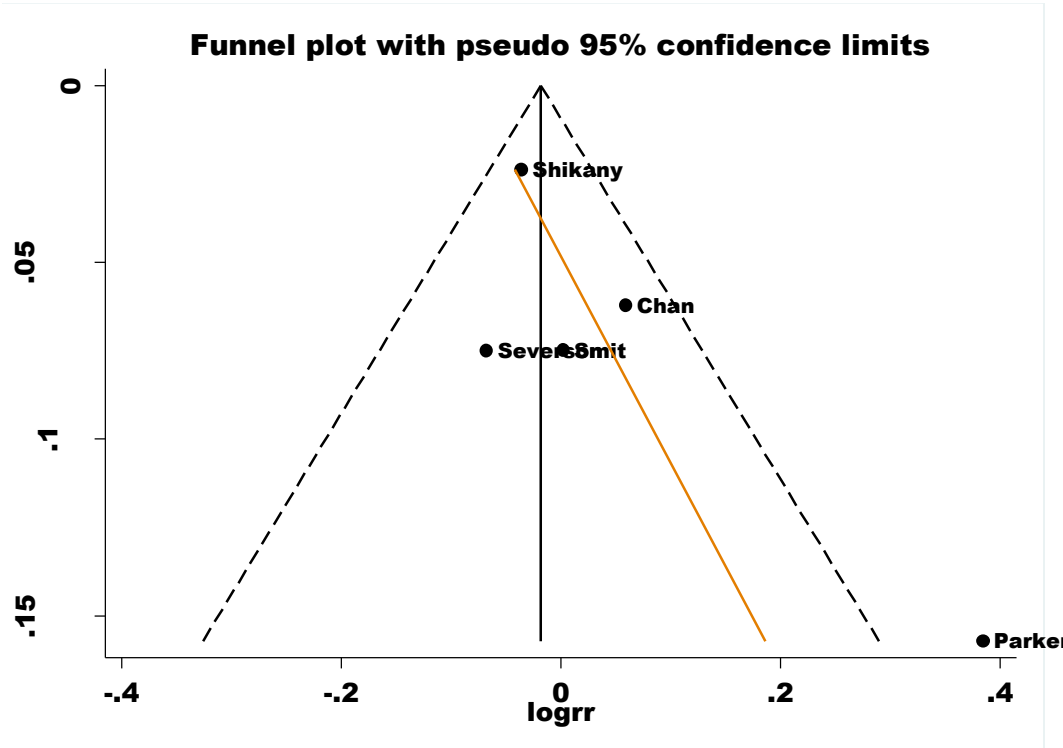


Figure 123 Funnel plot of carbohydrate and total prostate cancer



Egger's test p = 0.18

Figure 124 Dose-response graph of carbohydrate and prostate cancer

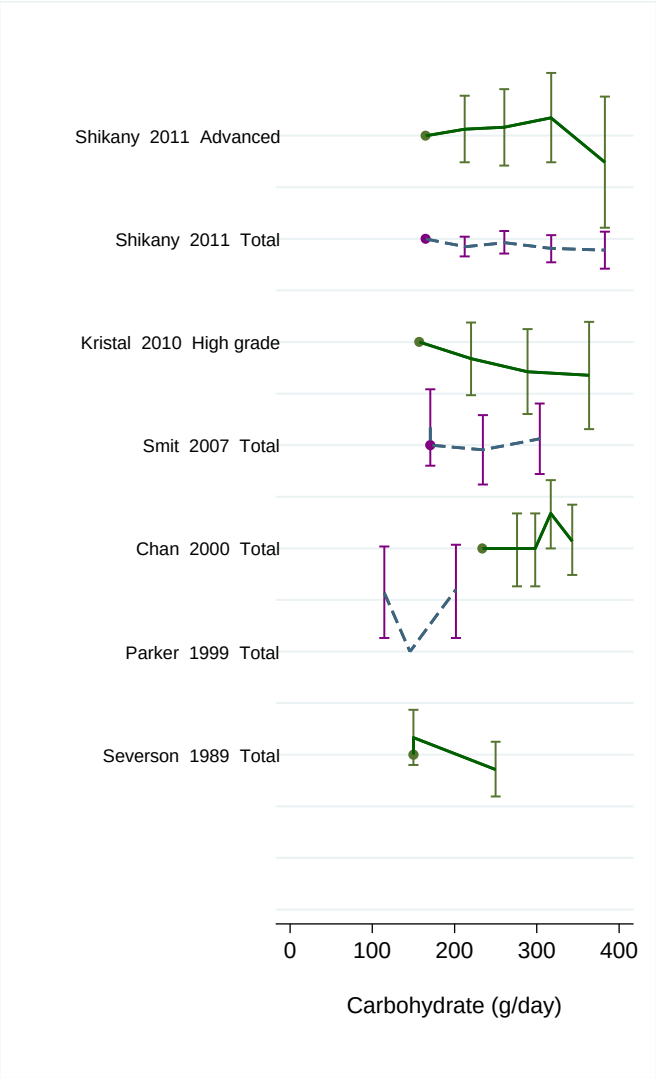
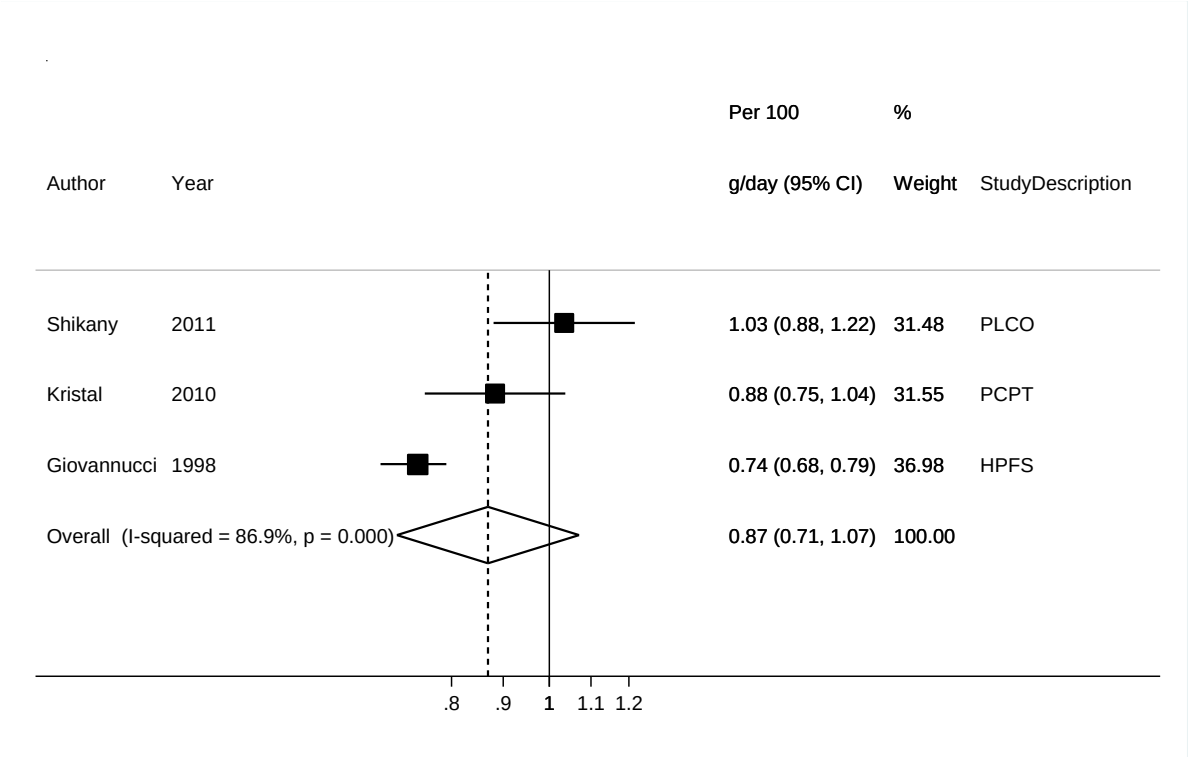


Figure 125 Dose-response meta-analysis of carbohydrate and advanced prostate cancer, per 100 g/day



5.2 Total fat

Methods

Fourteen publications from 13 cohort studies were identified on total fat and prostate cancer; 5 were identified during the CUP. There were two publications of the Health Professional Follow- up Study.

In the Prostate Cancer Prevention Trial study (Kristal et al, 2010), total fat intake was reported in kcal/day and it was rescaled to g/day using 9 kcal for 1 g of fats.

From the studies included in the meta-analysis, four studies (Neuhouser et al, 2007; Smit et al, 2007; Chan et al, 2000; Severson et al, 1989b) reported on total prostate cancer, one study (Schuurman et al, 1999) on total, localised, advanced cancers and latent and non-latent tumours; one study (Giovanucci et al, 1998b) reported on total, advanced and metastatic prostate cancer, one study (Wallström et al, 2007) on total and advanced prostate cancer, one study on prostate adenocarcinoma (Veierod et al, 1997) and one study (Kristal et al, 2010) on prostate cancers with Gleason score 2-7 and 8-10.

For analysis on total prostate cancer risk, the dose response estimates of the study of Kristal et al, 2010, on high-grade (Gleason score 8-10) and low-grade (Gleason score 2-7) prostate cancers were combined before inclusion in the analysis.

In stratified analysis, advanced and high grade (Gleason score 8-10) cancers were combined into advanced/high grade subgroup. No meta-analysis could be conducted for low grade (Gleason score 2-7) and for metastatic prostate cancer.

Overall, 9 studies were included in the meta-analysis for total prostate cancer and 3 studies were included for advanced/high grade prostate cancer.

The dose-response association was expressed for an increase of 10 g/day of fat intake.

Main results

The summary RR per 10 g/day of total fat for total prostate cancer was 1.00 (95% CI 0.99-1.01; $I^2 = 0\%$; $p_{heterogeneity} = 0.94$). The RR per 10 g/day was 1.01 (95% CI 0.98-1.03; $I^2 = 0\%$; $p_{heterogeneity} = 0.43$; n = 3) for advanced/high grade cancers.

Heterogeneity

There was no evidence of heterogeneity ($I^2 = 0\%$, $p_{heterogeneity} = 0.94$). Egger's test showed no evidence of publication bias (p = 0.21).

Comparison with the Second Expert Report

The meta-analysis on total fat and prostate cancer during the 2005 SLR showed a non-significant association.

Published meta-analysis or pooled analysis

No published meta-analysis or pooled analysis was identified.

Table 112 Studies on total fat identified in the CUP

Author/year	Country	Study name	Cases	Years of follow-up	RR	LCI	UCI	Contrast
Kristal, 2010	USA and Canada	The Prostate Cancer Prevention Trial	1703	9 years	1.07	0.86	1.33	> 919 kcal/day vs. < 454 kcal/day among cases with Gleason score 2-7
					1.23	0.58	2.60	> 919 kcal/day vs. < 454 kcal/day among cases with Gleason score 8-10
Wallström, 2007	Sweden	Malmo Diet and Cancer	817	11 years	0.99	0.79	1.24	≤ 188.6 g/day vs. ≥ 11.2 g/day
Neuhouser, 2007	USA	Beta-Carotene and Retinol Efficacy Trial (CARET)	890	11 years	1.19	0.84	1.67	≥ 93 g/day vs. < 53 g/day
Smit, 2007	Puerto Rico	Puerto Rico	167	~ 41 years	1.12	0.70	1.80	≤ 118 g/day vs. < 64 g/day
Iso, 2007	Japan	Japan Collaborative Cohort study for Evaluation of Cancer Risk	169	15 years	1.13	0.75	1.69	Modified vs. no change

Table 113 Overall evidence on total fat and total prostate cancer

	Summary of evidence
2005 SLR	Nine publications from 8 studies were identified during the 2005 SLR; seven studies were included in the meta-analysis. All showed a non-significant association.
Continuous update Project	Five new studies were identified during the CUP. Overall, 9 studies were included in the meta-analysis. No significant association was observed in the CUP meta-analysis.

Table 114 Summary of results of the dose-response meta-analysis of total fat and total prostate cancer

Total prostate cancer incidence and mortality		
	2005 SLR	Continuous Update Project
Studies (n)	7	9
Cases (n)	2600	6063
Increment unit used	Per 10 g/day	Per 10 g/day
Overall RR (95% CI)	1.00 (0.97-1.03)	1.00 (0.99-1.01)
Heterogeneity (I^2, p-value)	I^2 = 0%, p = 0.84	I^2 = 0%, p = 0.94
Stratified analysis		
Advanced/high grade cancer		
Overall RR (95% CI)		1.01 (0.98-1.03)
Heterogeneity (I^2, p-value)		I^2 = 0%, p = 0.43, n = 3

Table 115 Inclusion/exclusion table for meta-analysis of total fat and total prostate cancer

WCRF code	Author	Year	Study design	Study name	Cancer outcome	2005 SLR	CUP dose-response meta-analysis	CUP HvL forest plot	Estimated values	Exclusion reasons
PRO100078	Kristal	2010	Prospective Cohort Study	The Prostate Cancer Prevention Trial	Incidence	No	Yes	Yes	Mid-exposure values Combined results of cases with Gleason score 2-7 and 8-10 Conversion of kcal/day to g/day	
PRO99966	Wallström	2007	Prospective Cohort Study	Malmo Diet and Cancer	Incidence	No	Yes	Yes	Person years	
PRO100019	Neuhouser	2007	Prospective Cohort Study	Beta-Carotene and Retinol Efficacy Trial (CARET)	Incidence	No	Yes	Yes	Mid-exposure values Person years	
PRO100019	Smit	2007	Prospective Cohort Study	Puerto Rico	Mortality	No	Yes	Yes	Mid-exposure values Number of cases per quartiles	
PRO100042	Iso	2007	Prospective Cohort Study	Japan Collaborative Cohort study for Evaluation of Cancer Risk	Mortality	No	No	No		Exposure is fat intake modification
PRO97676	Laaksonen	2004	Prospective Cohort Study	Kuopio Ischaemic Heart Disease Risk Factor Study	Incidence	Yes	No	No		Only means were shown

PRO00515	Hsieh	2003	Prospective Cohort Study	Baltimore Longitudinal Study of Aging	Incidence and prevalence	Yes	No	No		Includes prevalent cases
PRO01426	Chan	2000	Prospective Cohort Study	Alpha Tocopherol Beta Carotene Cancer Prevention	Incidence	Yes	Yes	Yes	Person years Number of cases per quintiles	
PRO01683	Schuurman	1999	Case-cohort Study	Netherland Cohort Study	Incidence	Yes	Yes	Yes		
PRO02192	Giovannucci	1998 b	Prospective Cohort Study	Health Professional Follow up Study (HPFS)	Mortality and incidence	Yes	Yes	No	Person years	
PRO02242	Veierod	1997	Prospective Cohort Study	Norway 1977-1983	Incidence	Yes	Yes	Yes	Mid-exposure values Person years	
PRO02875	Giovannucci	1993	Prospective Cohort Study	Health Professional Follow up Study (HPFS)	Mortality and incidence	Yes	No	Yes		Superseded by Giovannucci et al, 1998 for dose-response
PRO03125	Stemmermann	1990	Prospective Cohort Study	Honolulu Heart Programme (HHP)	Mortality and incidence	Yes	No	No		Only means is shown
PRO03210	Severson	1989 b	Prospective Cohort Study	USA Hawaii 1965-1968	Incidence	Yes	Yes	Yes	Mid-exposure values Person years of follow up per category	

Figure 126 Highest versus lowest forest plot of total fat and total prostate cancer

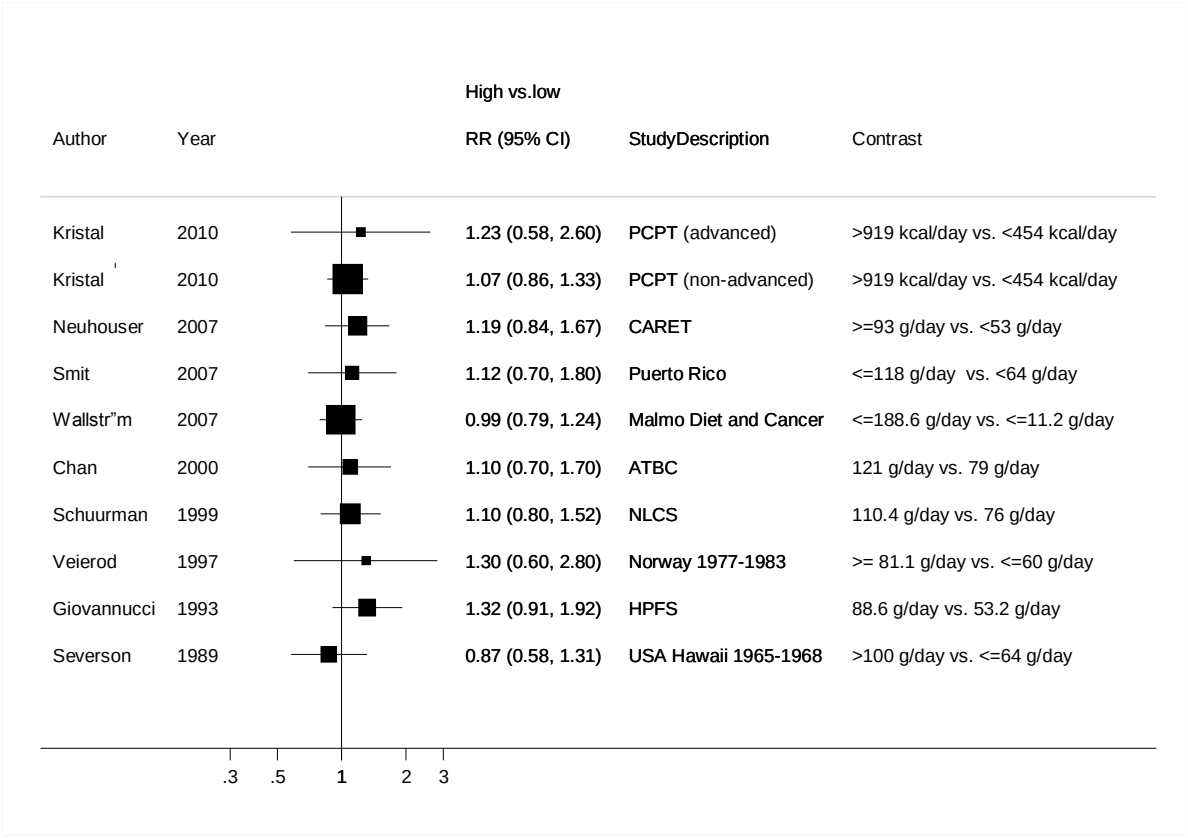


Figure 127 Dose-response meta-analysis of total fat and total prostate cancer, per 10 g/day

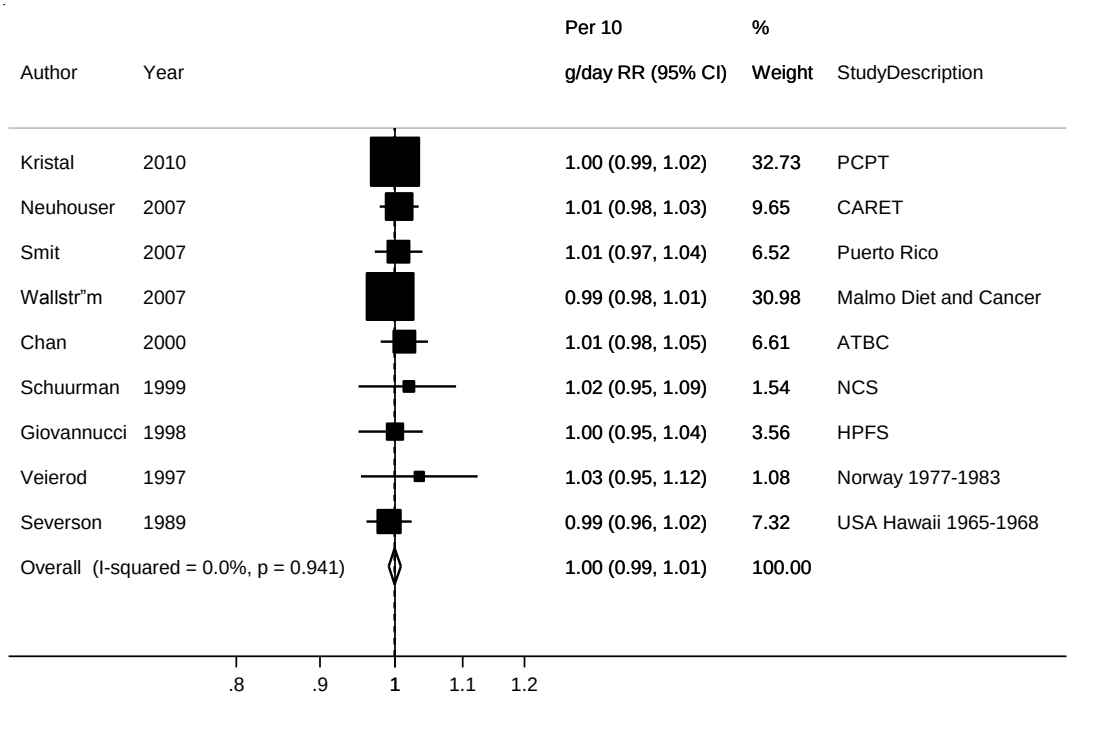
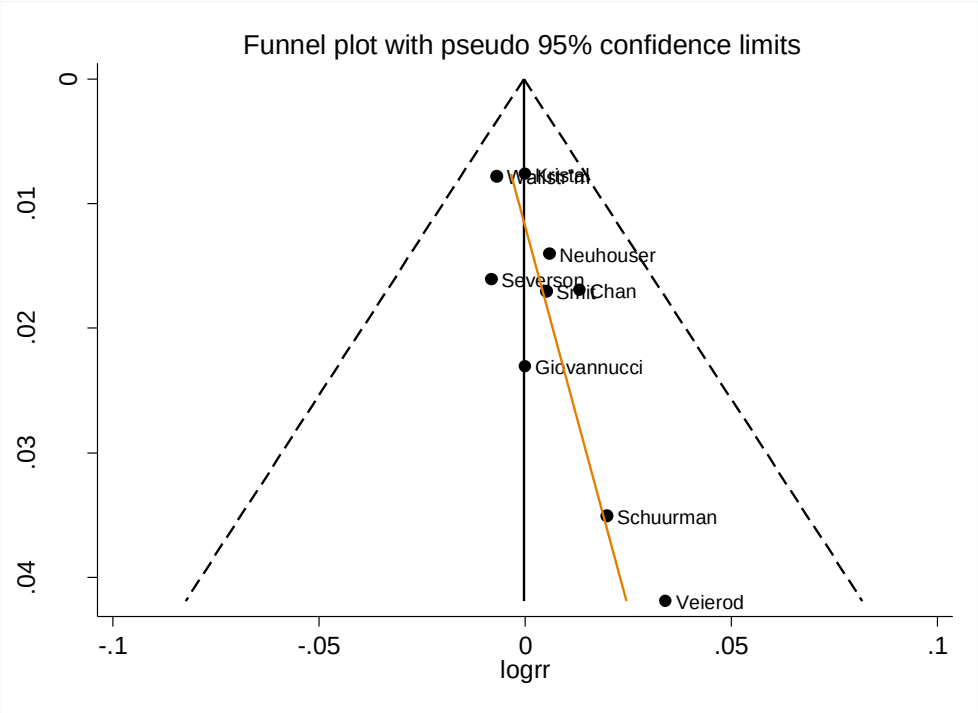


Figure 128 Funnel plot of total fat and total prostate cancer



Egger's test showed no evidence of publication bias (p = 0.21)

Figure 129 Dose-response graph of total fat and prostate cancer

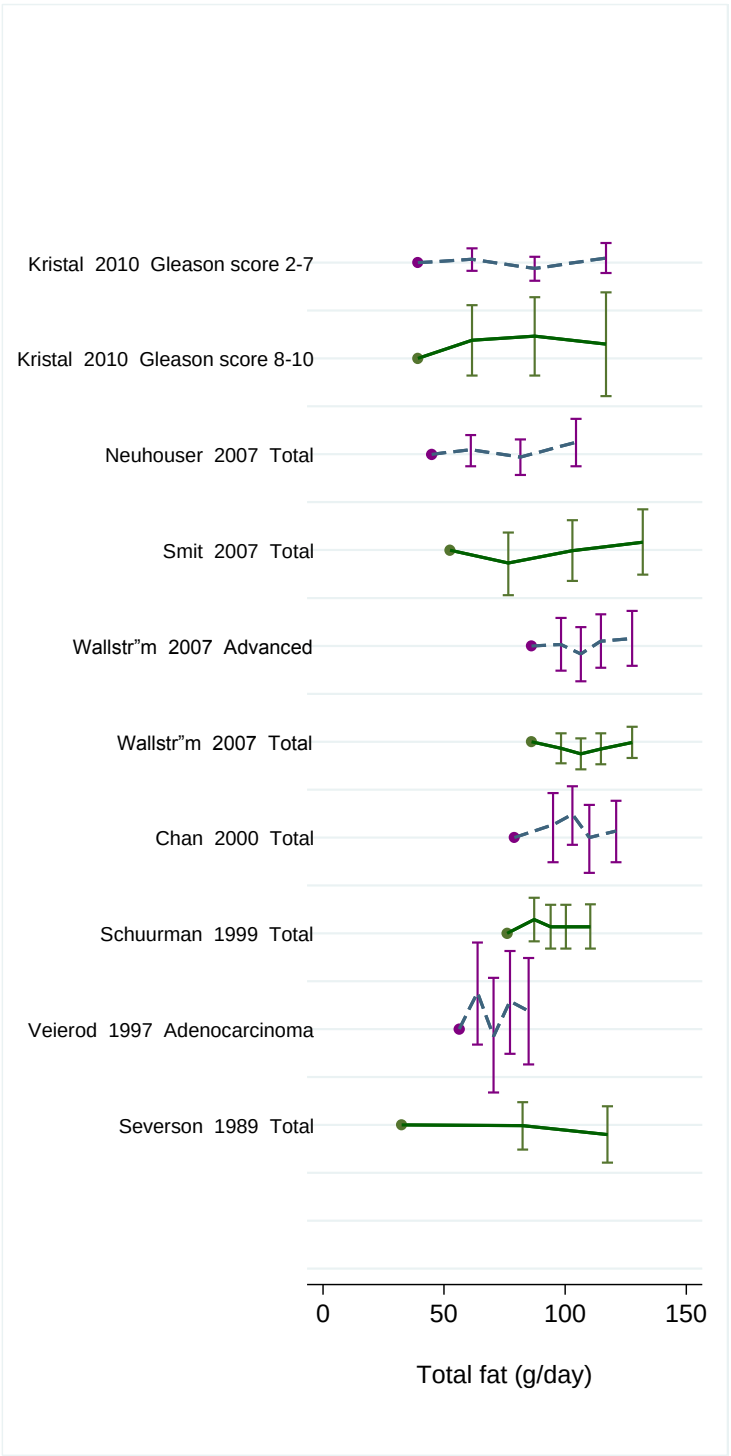
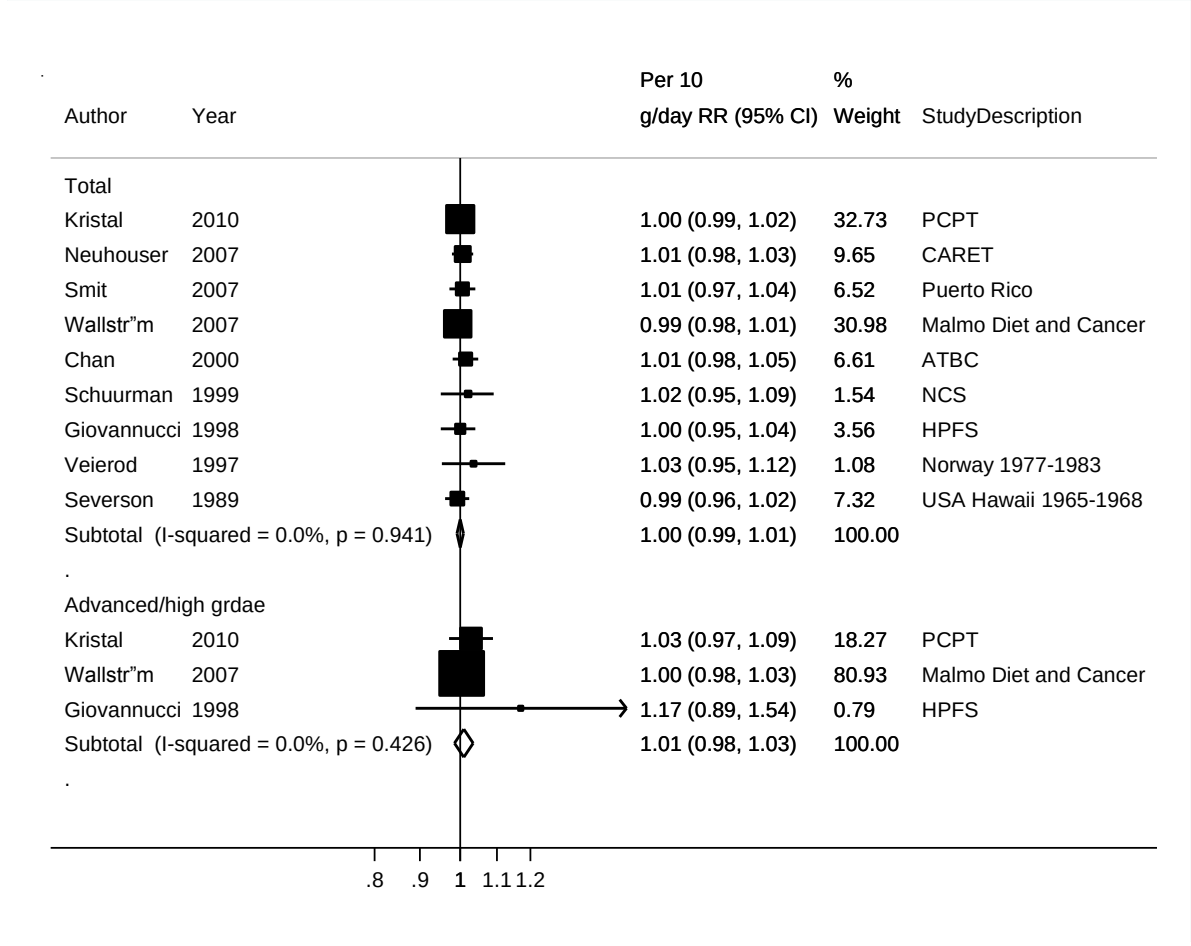


Figure 130 Dose-response meta-analysis of total fat and advanced prostate cancer, per 10 g/day



5.2 Total fat (% energy)

Methods
A total of five publications from 5 cohort studies were identified; all were identified during the CUP. Dose-response analyses were conducted per 10 % increase in energy from total fat. Two of the studies reported also in total fat intake in g/day and were included in the meta-analysis in the precedent section (PCPT, Kristal et al, 2010; CARET, Neuhouser et al, 2007).

From the studies included in the dose-response meta-analysis: one study reported on total, localised, advanced, low grade and high grade prostate cancer (Crowe et al, 2008), one study reported on advanced, non-advanced and fatal cancer (Pelser et al, 2013), one study reported on cancers with Gleason scores of 2-7 and 8-10 (Kristal et al, 2010), one study reported total, non-localised or high-grade cancer (Park et al, 2007) and one study reported on prostate cancer (Neuhouser et al, 2007).

Advanced prostate cancer, cancers with Gleason score 8-10 and non-localised cancers were included in the advanced/high grade subgroup. Crowe et al, 2008 study reported for both advanced and high grade cancer separately; the result of advanced prostate cancer was used in the subgroup analysis.

Overall, 5 studies were included in the meta-analysis for total prostate cancer, 4 studies included for advanced/high grade prostate cancer and 3 studies were included for non-advanced/low grade prostate cancer.

Main results
The summary RR per 10% energy of total fat and total prostate cancer was 1.00 (95% CI 0.99-1.01; I^2 = 0%; $p_{heterogeneity}$ = 0.49). In stratification analysis by prostate cancer type, the RR per 10% energy from total fat was 1.01 (95% CI 0.97-1.05; I^2 = 47.5%; $p_{heterogeneity}$ = 0.13; n=4) for advanced/high grade cancers and 1.00 (95% CI: 0.98-1.02, I^2=22.3%, $p_{heterogeneity}$ = 0.28, n = 3) for non-advanced/low grade cancers.

Heterogeneity
There was no heterogeneity (I^2 = 0%, $p_{heterogeneity}$ = 0.49). Egger's test showed no evidence of publication bias (p = 0.24).

Comparison with the Second Expert Report
No study was identified during the 2005 SLR.

Published meta-analysis or pooled analysis
No published meta-analysis or pooled analysis was identified.

Table 116 Studies on total fat identified in the CUP

Author/year	Country	Study name	Cases	Years of follow-up	RR	LCI	UCI	Contrast
Pelser, 2013	USA	NIH-AARP Diet and Health Study	23281	9 years	1.01	0.96	1.06	40.0 vs. 20.3% energy among non-advanced cases
					1.07	0.95	1.21	40.0 vs. 20.3% energy among advanced cases
Kristal, 2010	USA and Canada	The Prostate Cancer Prevention Trial	1703	9 years	0.90	0.77	1.06	>37.9 vs. <27.4% energy among cases with Gleason score 2-7
					1.36	0.78	2.39	>37.9 vs. <27.4% energy among cases with Gleason score 8-10
Crowe, 2008a	Europe	European Prospective Investigation into Cancer and Nutrition	2727	8.7 years	0.96	0.84	1.09	40.4 vs. 31.3 % energy
					0.90	0.79	1.02	Per 10% increase
Neuhouser, 2007	USA	Beta-Carotene and Retinol Efficacy Trial (CARET)	890	11 years	1.08	0.88	1.32	>=42.5 vs. <33.3% energy/day
Park, 2007a	USA	Multi-ethnic Cohort Study	4404	8 years	0.99	0.89	1.09	Q5 vs. Q1

Table 117 Overall evidence on total fat and total prostate cancer

	Summary of evidence
2005 SLR	No study was identified during the 2005 SLR.
Continuous update	Five new cohort studies were identified during the CUP; all were included in the meta-analysis. No significant association was observed in the CUP meta-analysis.

Table 118 Summary of results of the dose-response meta-analysis of total fat and total prostate cancer

Total prostate cancer incidence and mortality		
	2005 SLR*	Continuous Update Project
Studies (n)	-	5
Cases (n)	-	33005
Increment unit used	-	Per 10% energy
Overall RR (95% CI)	-	1.00 (0.99-1.01)
Heterogeneity (I^2, p-value)	-	I^2 = 0%, p = 0.49
Stratified analysis		
Advanced/high grade cancer		
Overall RR (95%CI)		1.01(0.97-1.05)
Heterogeneity (I^2, p-value)		I^2 = 47.5%, p = 0.13, n = 4
Non-advanced/low grade cancer		
Overall RR (95%CI)		1.00 (0.98-1.02)
Heterogeneity (I^2, p-value)		I^2 = 22.3%, p = 0.28, n = 3

Table 119 Inclusion/exclusion table for meta-analysis of total fat and total prostate cancer

WCRF code	Author	Year	Study design	Study name	Cancer outcome	2005 SLR	CUP dose-response meta-analysis	CUP HvL forest plot	Estimated values	Exclusion reasons
PRO100158	Pelser	2013	Prospective Cohort Study	NIH-AARP Diet and Health Study	Mortality and incidence	No	Yes	Yes	Person years per quintile	
PRO100078	Kristal	2010	Follow-up of subjects in finasteride trial	The Prostate Cancer Prevention Trial	Incidence	No	Yes	Yes	Mid-exposure values Person years per quartiles	
PRO99956	Crowe	2008a	Prospective Cohort Study	European Prospective Investigation into Cancer and Nutrition	Incidence	No	Yes	Yes	Person years per quintile	
PRO100019	Neuhouser	2007	Prospective Cohort Study	Beta-Carotene and Retinol Efficacy Trial (CARET)	Incidence	No	Yes	Yes	Mid-exposure values Person years per quartiles	
PRO99977	Park	2007a	Prospective Cohort Study	Multi-ethnic Cohort Study	Mortality and incidence	No	Yes	Yes	Person years per quintile Number of cases per quintile	

Figure 131 Highest versus lowest forest plot of total fat and total prostate cancer

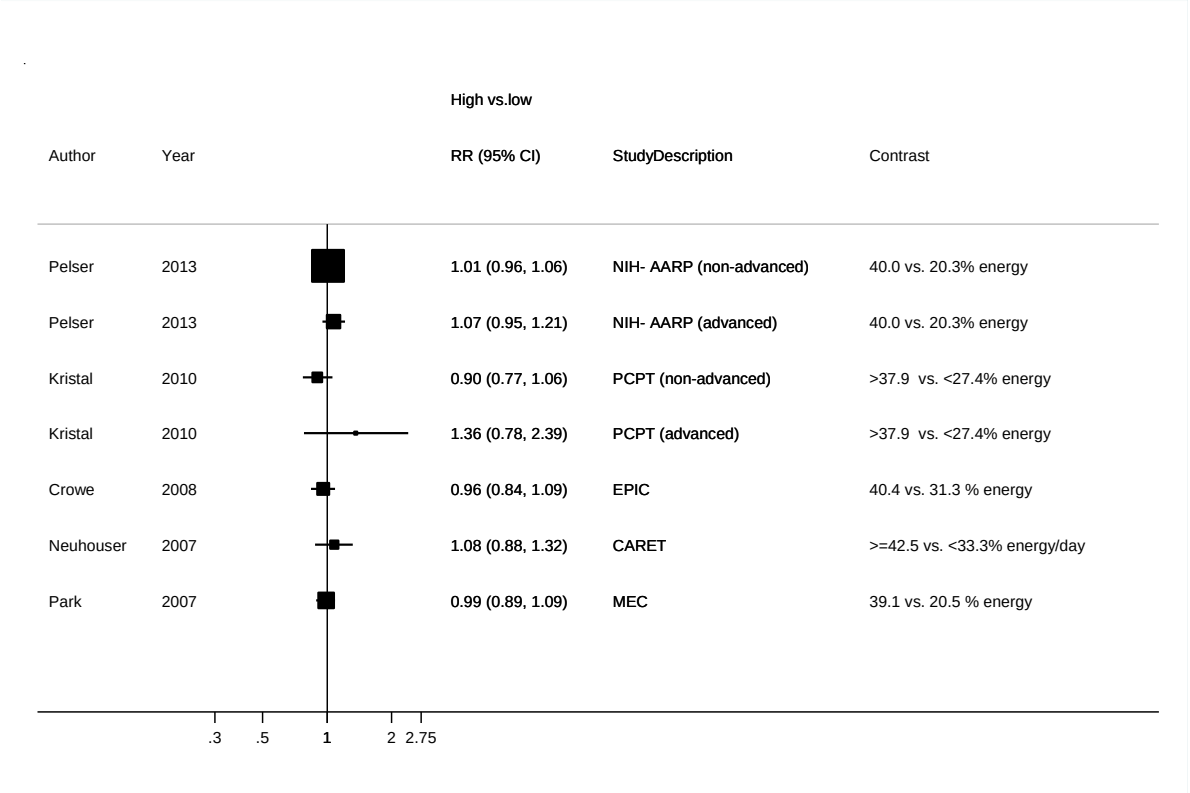


Figure 132 Dose-response meta-analysis of total fat and total prostate cancer, per 10% increase

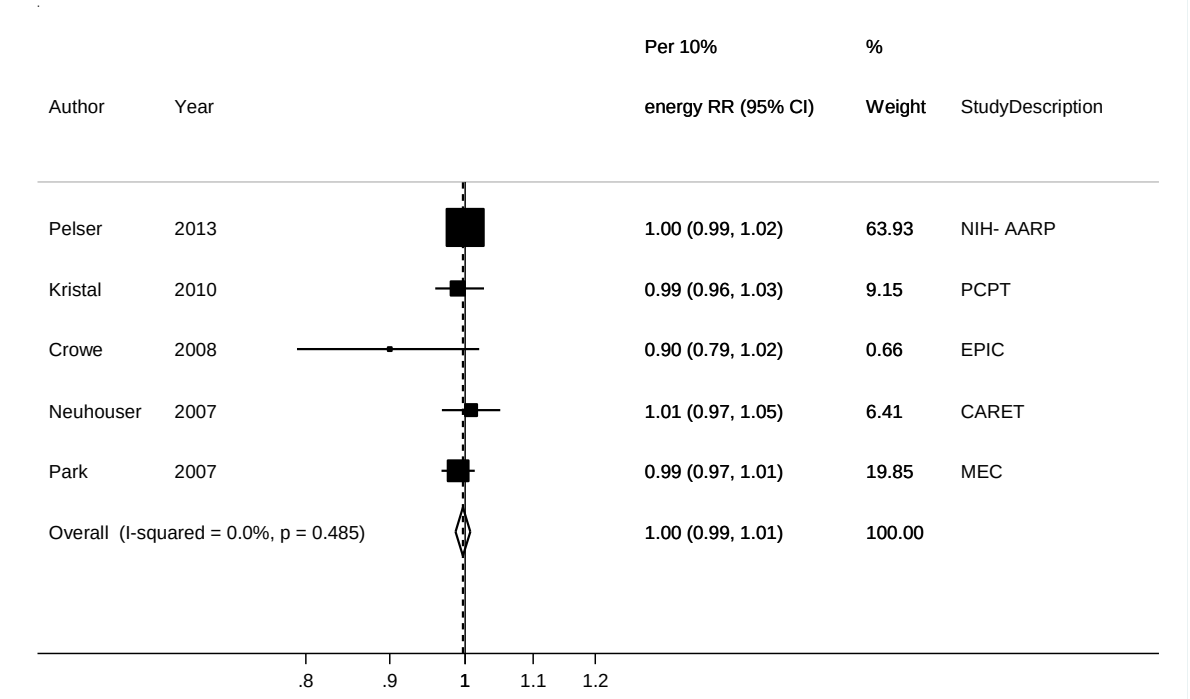
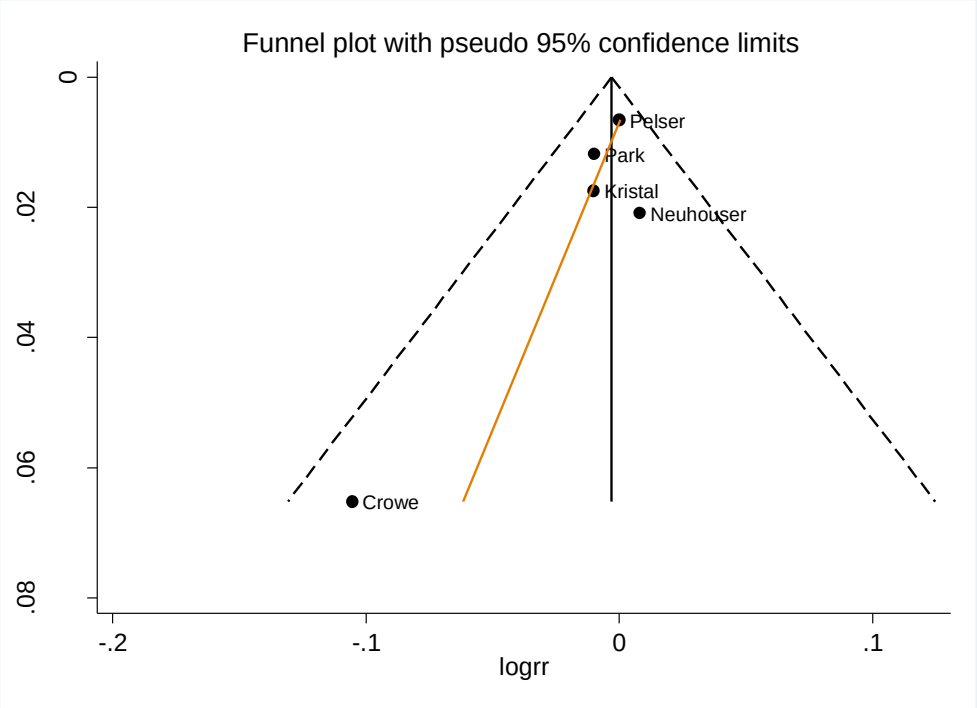


Figure 133 Funnel plot of total fat and total prostate cancer



Egger's test showed no evidence of publication bias (p = 0.24).

Figure 134 Dose-response graph of total fat and prostate cancer

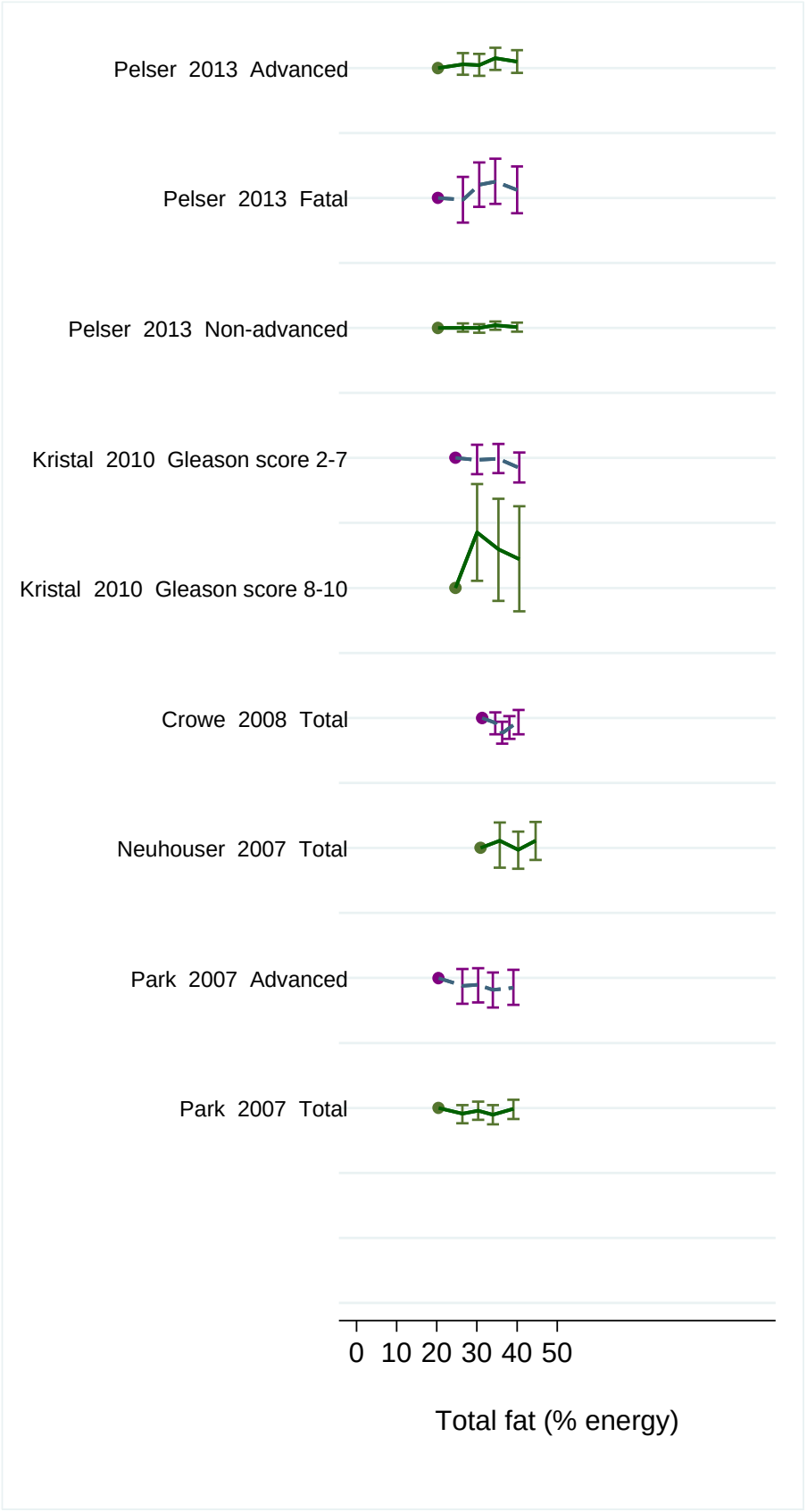
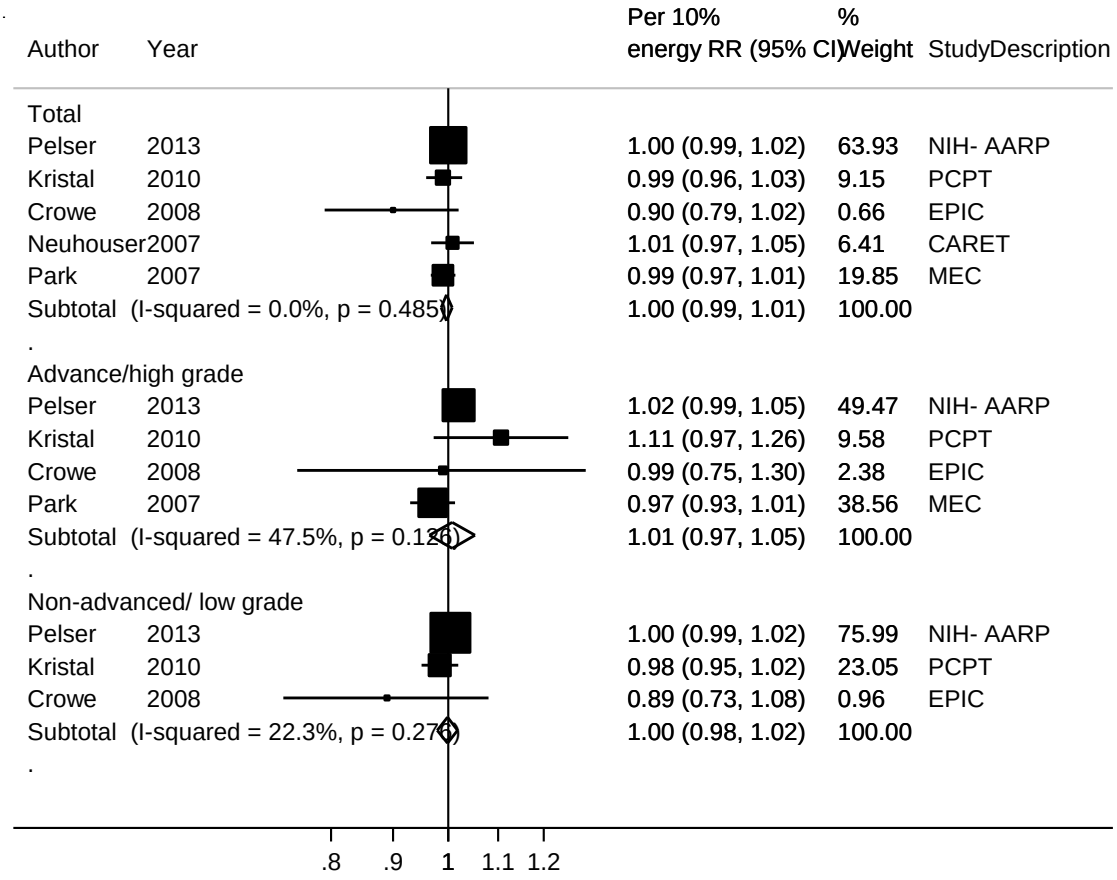


Figure 135 Dose-response meta-analysis of total fat and advanced prostate cancer, per 10% energy increase



5.2.2 Saturated fatty acids (g/day)

Methods
Ten publications (10 cohort studies) were identified, 5 of which were identified during the Continuous Update Project. The unit used in the dose-response analysis was 10 g/day. Saturated fat intake of kcal/day reported in Kristal et al, 2010 study was converted to g/day, using 9 kcal per 1 g of fat.

One study (Batty et al, 2011) investigated prostate cancer mortality. From the studies included in the dose-response meta-analysis: four studies reported on total prostate cancer (Severson et al, 1989; Veierød et al, 1997; Neuhouser et al, 2007; Batty et al, 2011), two reported on total, localised and advanced prostate cancer (Schuurman et al, 1999; Kurahashi et al, 2008a), one study reported on total and advanced cancer (Wallström et al, 2007) and one study excluded stage A1 adenocarcinomas (Giovannucci et al, 1993)

Kristal et al, 2010 reported RRs for low-grade (GS 2-7) and high-grade (GS 8-10) prostate cancer separately. The dose response associations for each cancer type were estimated and combined before inclusion in the meta-analysis of total prostate cancer risk.

In order to conduct stratified analysis by prostate cancer type, advanced and high grade cancers were combined in an advanced/high grade subgroup and non-advanced, localised, and low grade were combined in non-advanced/low grade subgroup.

Main results
The summary RR per 10 g/day increase was 0.99 (95% CI 0.96-1.03; I^2=0%; $p_{heterogeneity}$ = 0.59) (all studies combined). There was no significant evidence of publication bias with Egger's test, p=0.93.

The RR per 10 g per day was 1.07 (95% CI 0.93-1.23; I^2=36.6%; $p_{heterogeneity}$ = 0.21; n=3) for non-advanced/low grade and 1.00 (95% CI 0.90-1.12; I^2=0.3%; $p_{heterogeneity}$ = 0.40; n=5) for advanced/high grade cancer.

Heterogeneity
Overall, there was no evidence of heterogeneity, I^2 = 0%, $p_{heterogeneity}$ = 0.59.

Comparison with the Second Expert Report
In the 2005 SLR the meta-analysis on saturated fatty acids and prostate cancer showed borderline non-significant association.

Published meta-analysis or pooled analysis
No published meta-analyses or pooled studies were identified.

Table 120 Studies on saturated fat consumption identified in the CUP

Author, year	Country	Study name	Cases	Years of follow up	RR	LCI	UCI	Contrast
Batty, 2011	UK	Whitehall study, London	60	40 years	0.85	0.65	1.12	Per 15 g/day
					0.68	0.34	1.35	≥62.1 vs. <50.5 g/day
Kristal, 2010	USA and Canada	Prostate Cancer Prevention Trial	1576	10 years maximum	1.01	0.77	1.34	GS 2-7 >301 vs. <144 kcal/day
			127		0.37	0.13	1.00	GS 8-10 > 301 vs. < 144 kcal/day
			1703					
Kurahashi, 2008a	Japan	Japan Public Health Centre-based Prospective Study	329	7.5 years	1.37	0.97	1.95	22.9 vs. 9.7 g/day
Wallström, 2007	Sweden	Malmö Diet and Cancer Study	817	11 years	0.98	0.79	1.22	58.8 vs. 33.1 g/day
Neuhouser, 2007	USA	The Carotene and Retinol Efficacy Trial	811	11 years	0.98	0.71	1.35	≥33.6 vs. < 18.3 g/day

Table 121 Overall evidence on saturated fat consumption and prostate cancer

	Summary of evidence
2005 SLR	Five studies were identified during the 2005 SLR. Four studies were included in the 2005 SLR meta-analysis. All studies reported no significant association between saturated fat intake and prostate cancer.
Continuous Update Project	Five additional studies reported on saturated fat and prostate cancer risk. No significant association was observed in the CUP meta-analysis.

Table 122 Summary of results of the dose response meta-analysis of saturated fat consumption and prostate cancer

Prostate cancer		
	2005 SLR	CUP
Studies (n)	4	9
Cases (n)	1167	4887
Increment unit used	Per 10g/day	Per 10 g/day
Overall RR (95%CI)	0.99 (0.94-1.03)	0.99 (0.96-1.03)
Heterogeneity (I^2,p-value)	0%, p = 0.66	0%, p = 0.59
Stratified analysis		
Advanced/high grade cancer		
Overall RR (95%CI)	1.00 (0.81-1.25)	1.00 (0.90-1.12)
Heterogeneity (I^2,p-value)	0%, p = 0.84, n = 2	0.3%, p = 0.40, n = 5
Non-advanced/low grade cancer*		
Overall RR (95%CI)		1.07 (0.93-1.23)
Heterogeneity (I^2,p-value)		36.6%, p = 0.21, n = 3

* No meta-analysis was conducted in the 2005 SLR.

Table 123 Inclusion/exclusion table for meta-analysis of saturated fat consumption and prostate cancer

*Age adjusted results.

WCRF code	Author	Year	Study design	Study name	Cancer outcome	2005 SLR	CUP dose-response meta-analysis	CUP HvL forest plot	Estimated values	Exclusion reasons
PRO100170	Batty	2011	Prospective Cohort study	Whitehall study, London	Mortality	No	Yes	Yes	Continuous RR rescaled per 10g/day increase Mid-exposure values	
PRO100078	Kristal	2010	Follow-up of subjects in finasteride trial	Prostate Cancer Prevention Trial	Incidence	No	Yes	Yes	Person years per quintile and mid-exposure values Conversion of kcal/day to g/day	
PRO100000	Kurahashi	2008a	Prospective Cohort study	Japan Public Health Centre-based Prospective Study	Incidence	No	Yes	Yes		
PRO99966	Wallström	2007	Prospective Cohort study	Malmö Diet and Cancer Study	Incidence	No	Yes	Yes	Person years per quintile	
PRO100002	Neuhouser	2007	Prospective Cohort study	Carotene and Retinol Efficacy Trial	Incidence	No	Yes	Yes	Person years per quintile and mid-exposure values	
PRO97676	Laaksonen	2004	Prospective Cohort study	Kuopio Ischaemic Heart Disease Risk Factor Study	Incidence	Yes	No	No		Only means
PRO01683	Schuurman	1999	Case-cohort study	Netherlands Cohort Study	Incidence	Yes	Yes	Yes		
PRO02242	Veierød	1997	Prospective Cohort study	Norway 1977-1983	Incidence	Yes	Yes	Yes	Person years per quintile	
PRO02875	Giovannucci	1993	Prospective Cohort study	Health Professionals Follow-up Study	Incidence and mortality	Yes	Yes	Yes	localised	
PRO03210	Severson*	1989b	Prospective Cohort study	Japan-Hawaii Cancer Study	Incidence	Yes	Yes	Yes	Person years per category and mid-exposure values	

Figure 136 Highest versus lowest forest plot of saturated fat consumption and prostate cancer

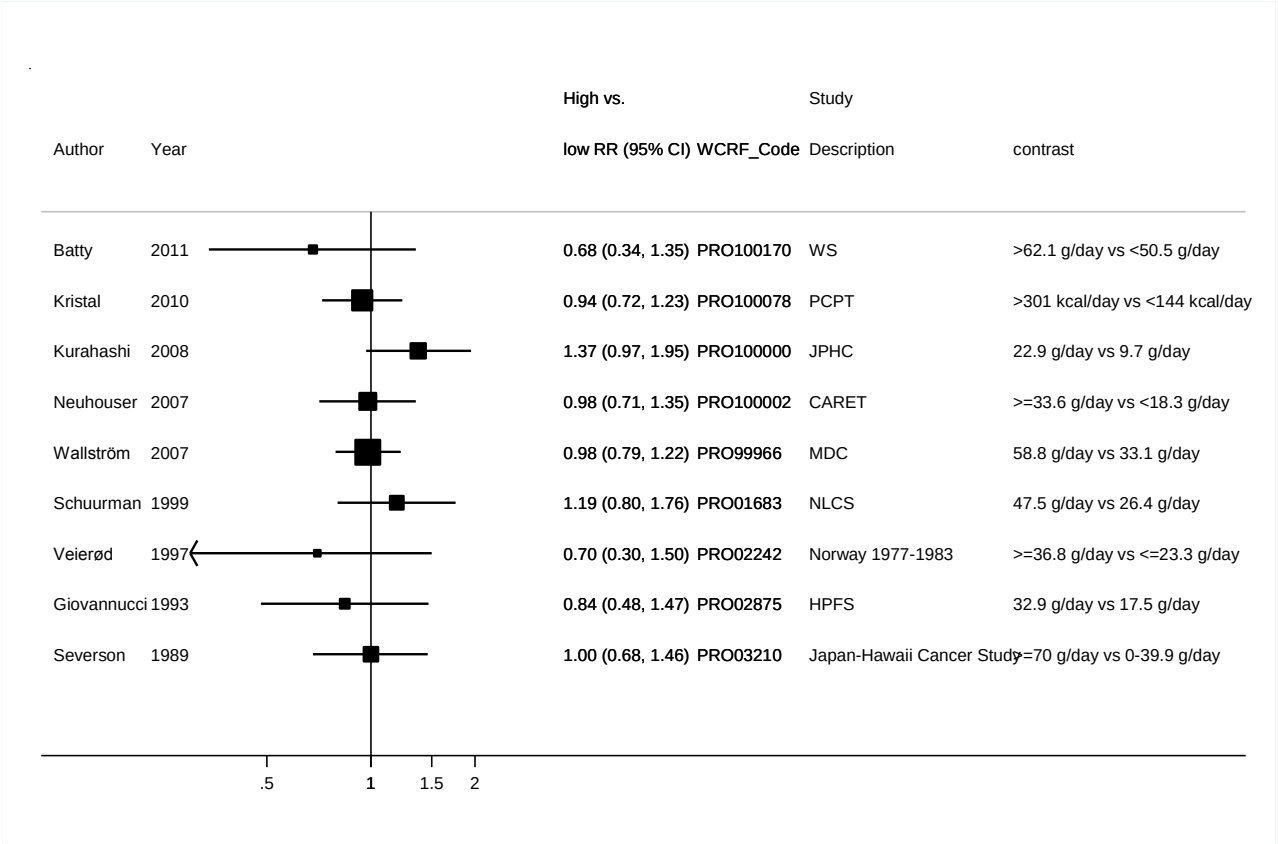


Figure 137 Dose-response meta-analysis of saturated fat intake and prostate cancer, per 10 g/day, stratified by cancer subtype

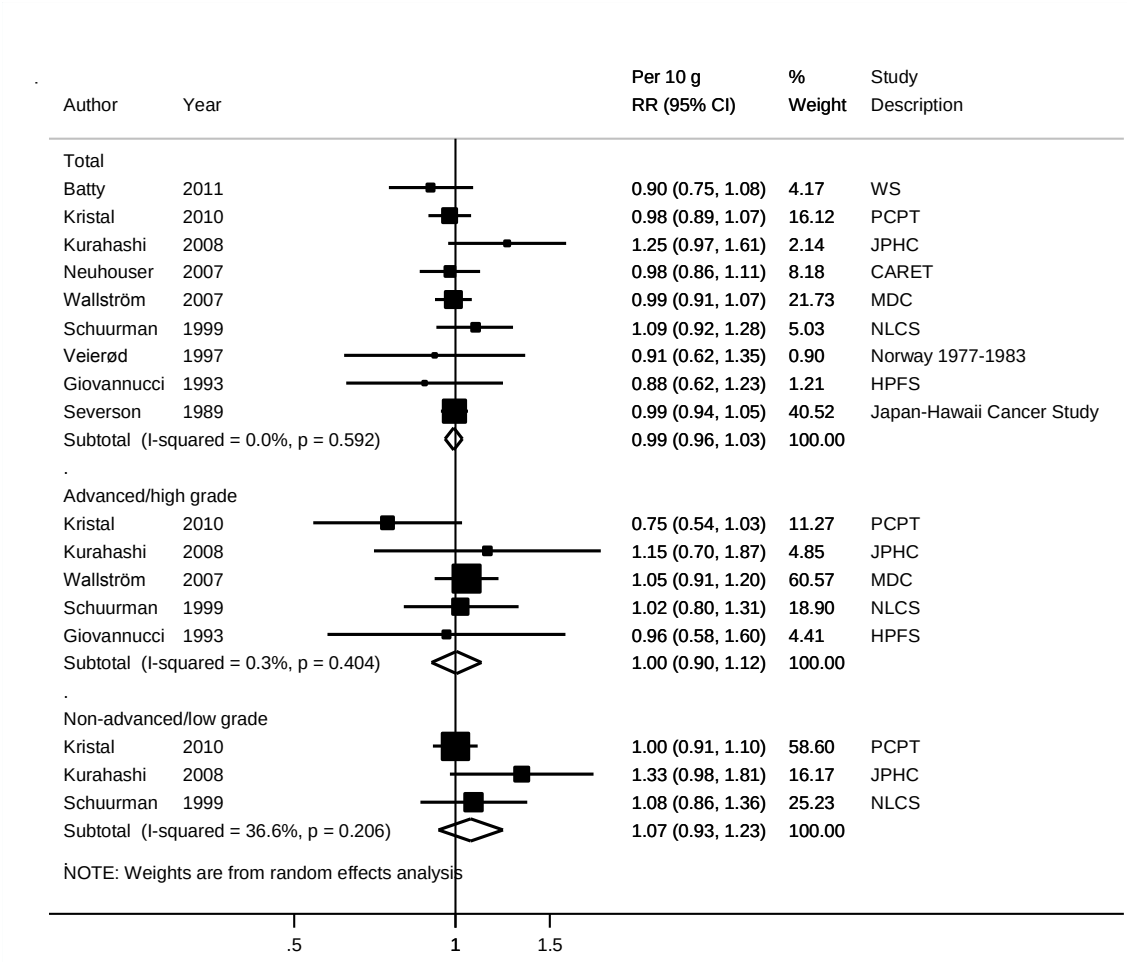
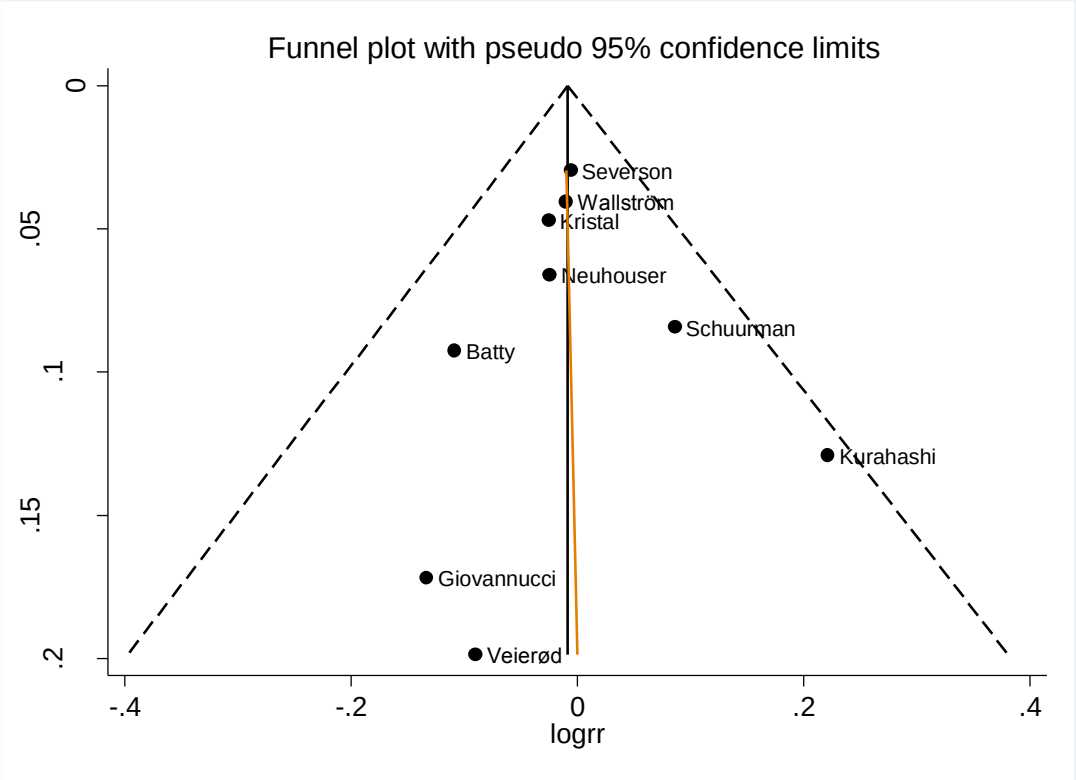
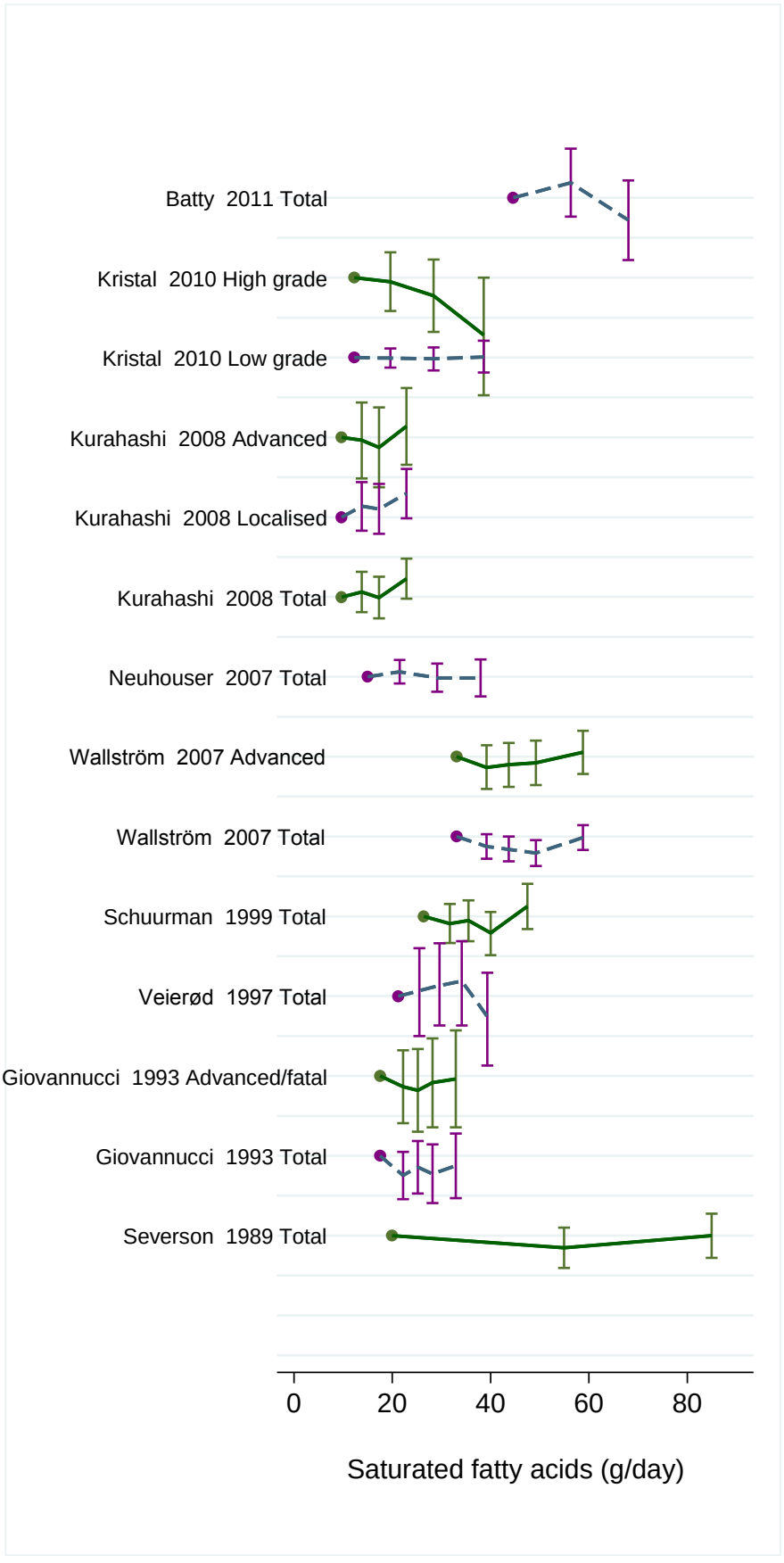


Figure 138 Funnel plot of saturated fat intake and prostate cancer



Egger's test p = 0.93

Figure 139 Dose-response graph of saturated fat and prostate cancer



5.2.2 Saturated fatty acids (% energy)

Methods

A total of 5 publications (5 cohort studies) were identified, four of which were identified during the Continuous Update Project. Four studies were included in the meta-analysis. Only one study (PCPT, Kristal et al, 2010) was included in the precedent section on saturated fats (g/day). The unit used in the dose-response analysis was 5% increase in energy from saturated fat.

All studies reported on cancer incidence except Pelser et al, 2013 that investigated incidence and mortality from prostate cancer.

Kristal et al (2010) reported RR for low-grade (GS 2-7) and high-grade (GS 8-10) prostate cancer separately. The RRS were pooled before inclusion in the high vs. low forest plots and meta-analysis for total prostate cancer risk.

Advanced cancers, cancers with Gleason score 8-10 and non-localised cancers were combined in advanced/high grade subgroup. Crowe et al (2008) reported for both advanced and high grade cancer separately; the result of advanced prostate cancer was used in the subgroup analysis.

Main results

The summary RR per 5% energy increase from saturated fat was 0.97 (95% CI 0.92-1.03; $I^2 = 53.3\%$; $p_{heterogeneity} = 0.09$). Egger's test showed significant evidence of asymmetry, $p = 0.01$; only four studies were in the analysis.

The RR per 5% energy increase from saturated fat was 0.98 (95% CI 0.92-1.04; $I^2 = 22.8\%$; $p_{heterogeneity} = 0.27$; n = 3) for non-advanced/low grade cancer and 0.98 (95% CI 0.83-1.16; $I^2=69.2\%$; $p_{heterogeneity} = 0.02$; n = 4) for advanced/high grade prostate cancer.

Heterogeneity

High heterogeneity was observed, $I^2 = 53.3\%$, $p_{heterogeneity} = 0.09$. The low number of studies did not allow exploration of heterogeneity sources.

Comparison with the Second Expert Report

No meta-analysis was conducted in the Second Expert Report. The CUP found no significant association between energy intake from saturated fat and prostate cancer risk.

Published meta-analysis or pooled analysis

No published meta-analyses or pooled studies were identified.

Table 124 Studies on % energy intake from saturated fat identified in the CUP

Author, year	Country	Study name	Cases	Years of follow up	RR	LCI	UCI	Contrast
Pelser, 2013	USA	NIH-AARP Diet and Health Study	18934	9 years	1.01	0.94	1.08	Nonadvanced 13.3 vs. 5.8% energy
			2930		1.21	1.00	1.46	Advanced 13.3 vs. 5.8% energy, P_{trend} = 0.03
			725		1.47	1.01	2.15	Fatal 13.3 vs. 5.8% energy, P_{trend} = 0.04
Kristal, 2010	USA and Canada	Prostate Cancer Prevention Trial	1576	10 years maximum	0.89	0.76	1.05	GS 2-7 > 12.4 vs. < 8.5 % energy
			127		0.73	0.43	1.26	GS 8-10 > 12.4 vs. < 8.5 % energy
Crowe, 2008a	Europe	European Prospective Investigation into Cancer and Nutrition	2727	8.7 years	0.93	0.84	1.02	Per 5% increase in energy from saturated fat
					0.97	0.85	1.11	17.2 vs. 10.1% energy
Park, 2007a	USA	Multiethnic Cohort Study	4404	8 years	0.94	0.85	1.04	12.3 vs. 5.5 % energy

*P_{trend} = 0.045

Table 125 Overall evidence on % energy intake from saturated fat and prostate cancer

	Summary of evidence
2005 SLR	One study was identified during the 2005 SLR
Continuous Update Project	Four studies reported on saturated fat and prostate cancer risk. All studies reported non-significant associations. One study reported a significant inverse association for high grade cancer (Crowe, 2008). Pelser, 2013 study reported significantly higher risk of mortality in highest vs. lowest analysis. No significant association was observed in the CUP meta-analysis.

Table 126 Summary of results of the dose response meta-analysis of % energy intake from saturated fat and prostate cancer

Prostate cancer		
	2005 SLR*	CUP
Studies (n)	-	4
Cases (n)	-	30698
Increment unit used	-	Per 5% energy
Overall RR (95% CI)	-	0.97 (0.92-1.03)
Heterogeneity (I^2, p-value)	-	53.3%, p = 0.09
Stratified analysis		
Advanced/high grade cancer		
Overall RR (95% CI)	-	0.98 (0.83-1.16)
Heterogeneity (I^2, p-value)	-	69.2%, p = 0.02, n = 4
Non-advanced/low grade cancer		
Overall RR (95% CI)	-	0.98 (0.92-1.04)
Heterogeneity (I^2, p-value)	-	22.8%, p = 0.27, n = 3

* No meta-analysis was conducted in the 2005 SLR.

Table 127 Inclusion/exclusion table for meta-analysis of % energy intake from saturated fat and prostate cancer

WCRF code	Author	Year	Study design	Study name	Cancer outcome	2005 SLR	CUP dose-response meta-analysis	CUP HvL forest plot	Estimated values	Exclusion reasons
PRO100158	Pelser	2013	Prospective Cohort study	NIH-AARP Diet and Health Study	Incidence; mortality	No	Yes	Yes	Person years per quintile	
PRO100078	Kristal	2010	Follow-up of subjects in finasteride trial	Prostate Cancer Prevention Trial	Incidence	No	Yes	Yes	Person years per quintile and mid-exposure values	
PRO99956	Crowe	2008a	Prospective Cohort study	European Prospective Investigation into Cancer and Nutrition	Incidence	No	Yes	Yes	Person years per quintile	
PRO99977	Park	2007a	Prospective Cohort study	Multiethnic Cohort Study	Incidence	No	Yes	Yes	Person years per quintile Cases per quintile	
PRO97676	Laaksonen	2004	Prospective Cohort study	Kuopio Ischaemic Heart Disease Risk Factor Study	Incidence	Yes	No	No		Only means

Figure 140 Highest versus lowest forest plot of % energy intake from saturated fat and prostate cancer

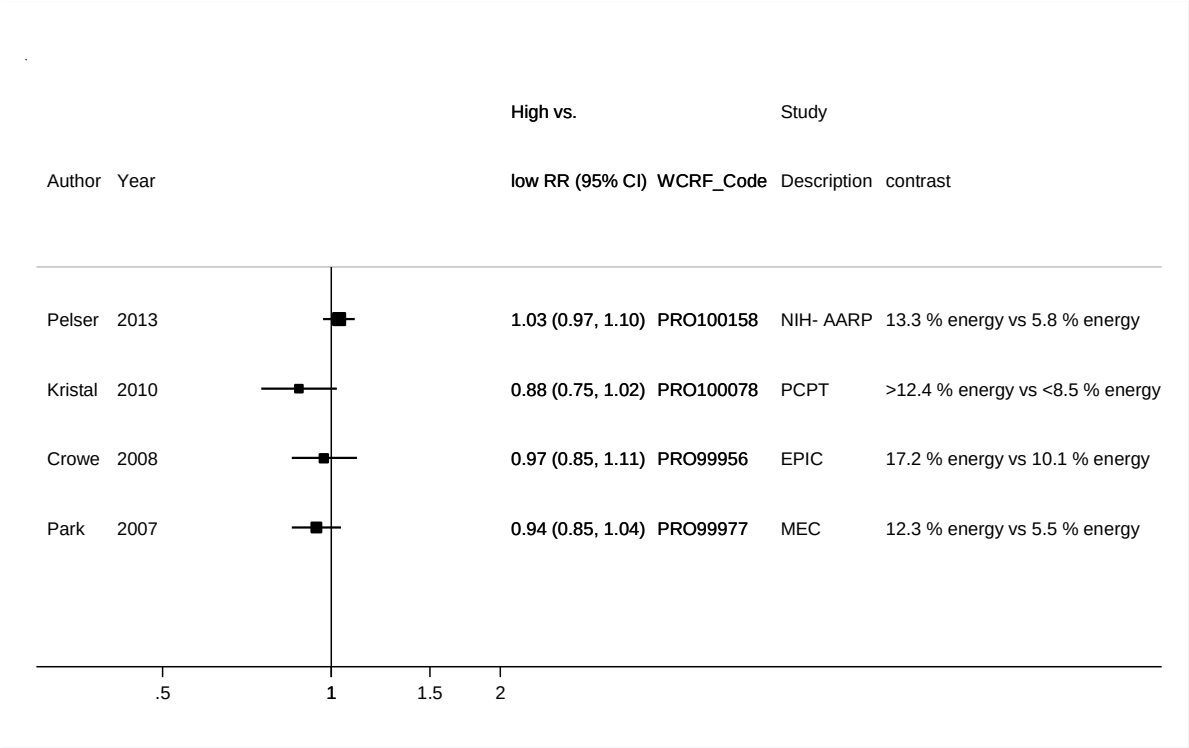


Figure 141 Dose-response meta-analysis of saturated fat and prostate cancer - per 5% increase in energy intake from saturated fat by cancer subtype

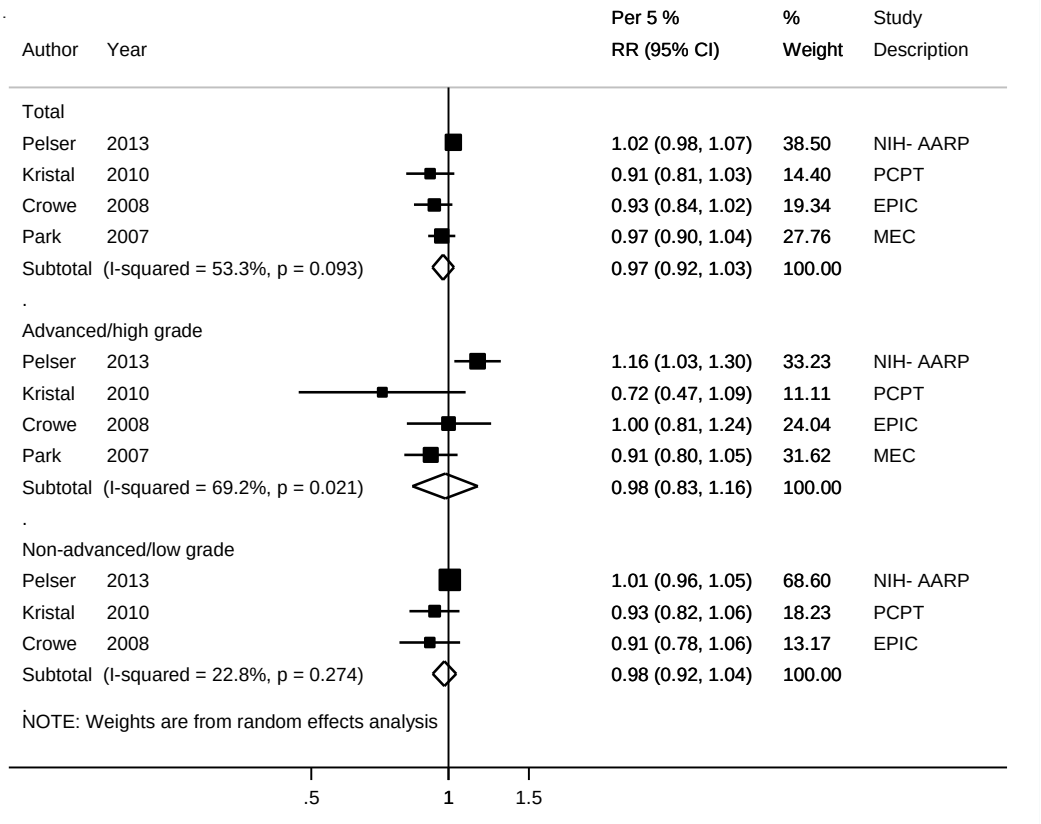


Figure 142 Funnel plot of % energy intake from saturated fat and prostate cancer

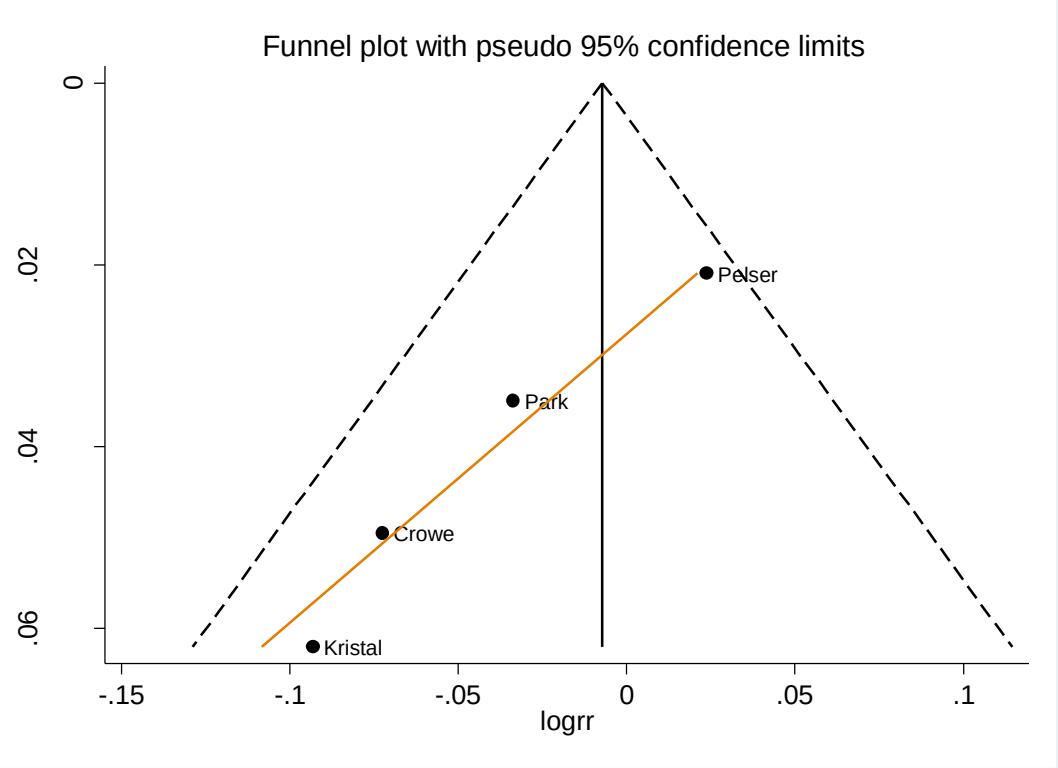
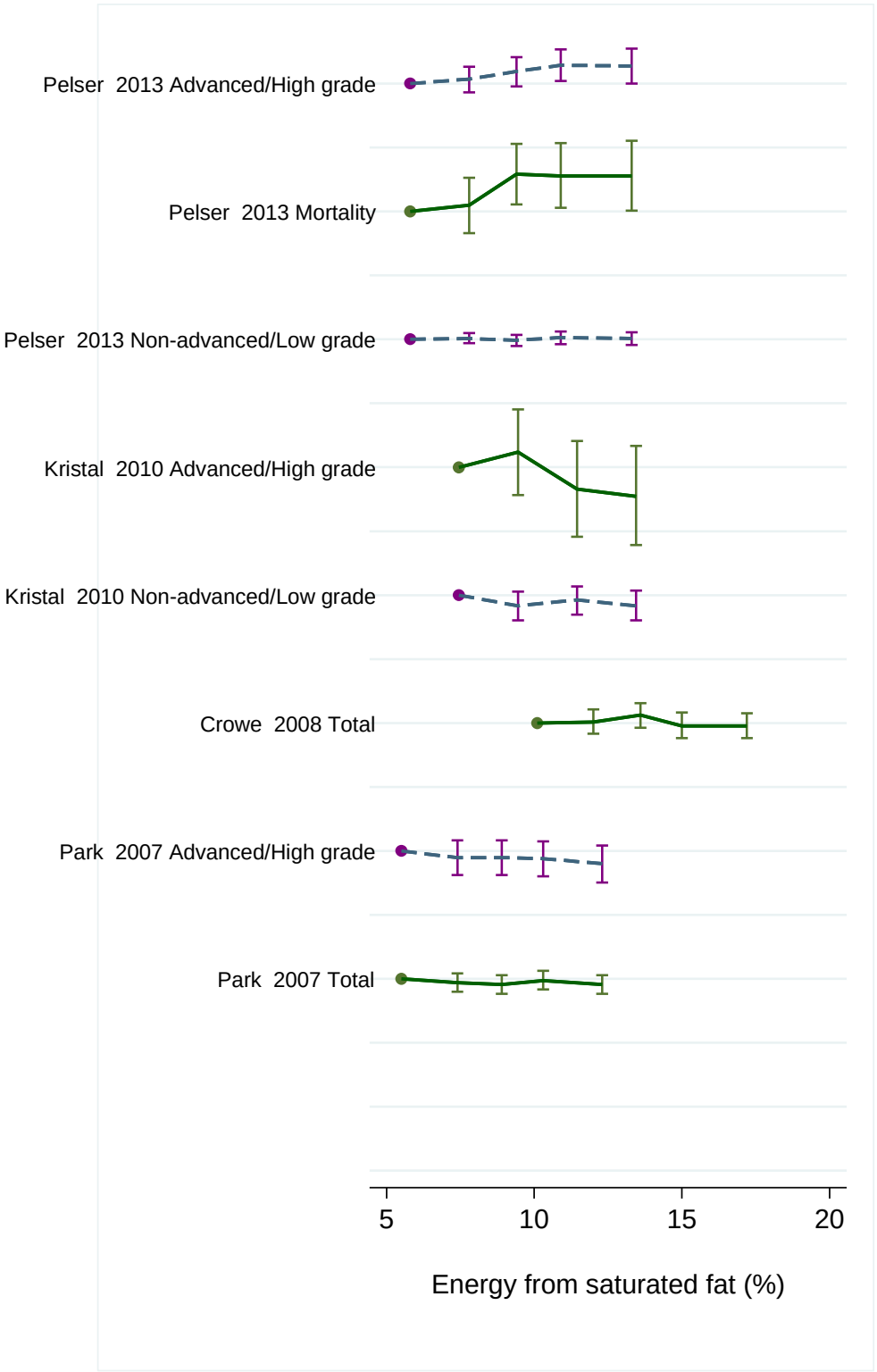


Figure 143 Dose-response graph of % energy intake from saturated fat and prostate cancer



5.2.3 Monounsaturated fatty acids

Methods

A total of 8 publications (8 cohort studies) were identified, 4 of which were identified during the Continuous Update Project. The unit used in the dose-response analysis was 10 g/day.

One study (Batty, 2011) investigated prostate cancer mortality. Cancer incidence was the outcome in all remaining studies.

Monounsaturated fat intake in kcal/day reported in Kristal et al, 2010 was converted to g/day, using a conversion factor of 9 kcal per 1g of fat. In this study, the RRs for low-grade (GS 2-7) and high-grade (GS 8-10) prostate cancers were combined before inclusion in the meta-analysis and high vs. low forest plots of total prostate cancer risk.

Advanced and high grade cancers were combined in an advanced/high grade subgroup and non-advanced, localised, and low grade were combined in non-advanced/low grade subgroup.

Main results

The summary RR per 10 g/day increase was 1.00 (95% CI 0.99-1.01; $I^2 = 0\%$; $p_{heterogeneity} = 0.47$) (all studies combined). There was no significant evidence of publication bias with Egger's test, p = 0.27.
The RR per 10 g per day was 0.98 (95% CI 0.89-1.07; $I^2=0\%$; $p_{heterogeneity} = 0.57$; n = 2) for non-advanced /low grade cancers and 1.12 (95% CI 0.94-1.34; $I^2 = 0\%$, $p_{heterogeneity} = 0.94$, n=4) for advanced/ high grade cancers.

Heterogeneity

Overall, there was no evidence of heterogeneity for all studies combined, $I^2 = 0\%$, $p_{heterogeneity} = 0.47$.

Comparison with the Second Expert Report

In the 2005 SLR the meta-analysis showed a significant positive association between intake of monounsaturated fatty acids and prostate cancer risk.

Published meta-analysis or pooled analysis

No published meta-analysis or pooled analysis was identified.

Table 128 Studies on monounsaturated fatty acid consumption identified in the CUP

Author, year	Country	Study name	Cases	Years of follow up	RR	LCI	UCI	Contrast
Batty, 2011	UK	Whitehall study, London	60	40 years	0.85	0.64	1.13	Per 12.3 g/d increase
					0.64	0.34	1.21	> 49.7 vs. < 40 g/day
Kristal, 2010	USA and Canada	Prostate Cancer Prevention Trial	1576	10 years max	1.02	0.73	1.42	GS 2-7 >352 vs. <170 kcal/day

			127		1.33	0.41	4.37	GS 8-10 > 352 vs. < 170 kcal/day
Wallström, 2007	Sweden	Malmö Diet and Cancer Study	817	11 years	1.01	0.80	1.29	45.1 vs. 29.6 g/day
Neuhouser, 2007	USA	The Carotene and Retinol Efficacy Trial	811	11 years	1.05	0.75	1.45	≥34.2 vs. < 19.4 g/day

Table 129 Overall evidence on monounsaturated fatty acid consumption and prostate cancer

	Summary of evidence
2005 SLR	Four studies were identified during the 2005 SLR. Three studies were included in the 2005 SLR meta-analysis. All studies reported no significant association between monounsaturated fat intake and prostate cancer.
Continuous Update Project	Four additional studies reported on monounsaturated fat and prostate cancer risk. All studies reported non-significant associations. No significant association was observed in the CUP meta-analysis.

Table 130 Summary of results of the dose response meta-analysis of monounsaturated fatty acid consumption and prostate cancer

Prostate cancer		
	SLR	CUP
Studies (n)	3	7
Cases (n)	993	4384
Increment unit used	Per 10g/day	Per 10 g/day
Overall RR (95%CI)	1.37 (1.10-1.70)	1.00 (0.99-1.01)
Heterogeneity (I^2,p-value)	0%, p = 0.71	0%, p = 0.47
Stratified analysis		
Advanced/high grade cancer		
Overall RR (95%CI)	1.20 (0.82-1.76)	1.12 (0.94-1.34)
Heterogeneity (I^2, p-value)	0%, p = 0.89, n = 2	0%, p = 0.94, n = 4
Non-advanced/low grade cancer*		
Overall RR (95%CI)		0.98 (0.89-1.07)
Heterogeneity (I^2,p-value)		0%, p = 0.57, n = 2

* No meta-analysis was conducted in the 2005 SLR.

Table 131 Inclusion/exclusion table for meta-analysis of monounsaturated fatty acid consumption and prostate cancer

WCRF code	Author	Year	Study design	Study name	Cancer outcome	2005 SLR	CUP dose-response meta-analysis	CUP HvL forest plot	Estimated values	Exclusion reasons
PRO100170	Batty	2011	Prospective Cohort study	Whitehall study, London	Mortality	No	Yes	Yes	Continuous RR rescaled per 10g/day increase Mid-exposure values	
PRO100078	Kristal	2010	Follow-up of subjects in finasteride trial	Prostate Cancer Prevention Trial	Incidence	No	Yes	Yes	Person years per quintile and mid-exposure values Conversion of kcal/day to g/day	
PRO99966	Wallström	2007	Prospective Cohort study	Malmö Diet and Cancer Study	Incidence	No	Yes	Yes	Person years per quintile	
PRO100002	Neuhouser	2007	Prospective Cohort study	Carotene and Retinol Efficacy Trial	Incidence	No	Yes	Yes	Person years per quintile and mid-exposure values	
PRO97676	Laaksonen	2004	Prospective Cohort study	Kuopio Ischaemic Heart Disease Risk Factor Study	Incidence	Yes	No	No		Only means
PRO01683	Schuurman	1999	Case-cohort study	Netherlands Cohort Study	Incidence	Yes	Yes	Yes		
PRO02242	Veierød	1997	Prospective Cohort study	Norway 1977-1983	Incidence	Yes	Yes	Yes	Person years per quintile	
PRO02875	Giovannucci	1993	Prospective Cohort study	Health Professionals Follow-up Study	Incidence/ mortality	Yes	Yes	Yes		

Figure 144 Highest versus lowest forest plot of monounsaturated fatty acid consumption and prostate cancer

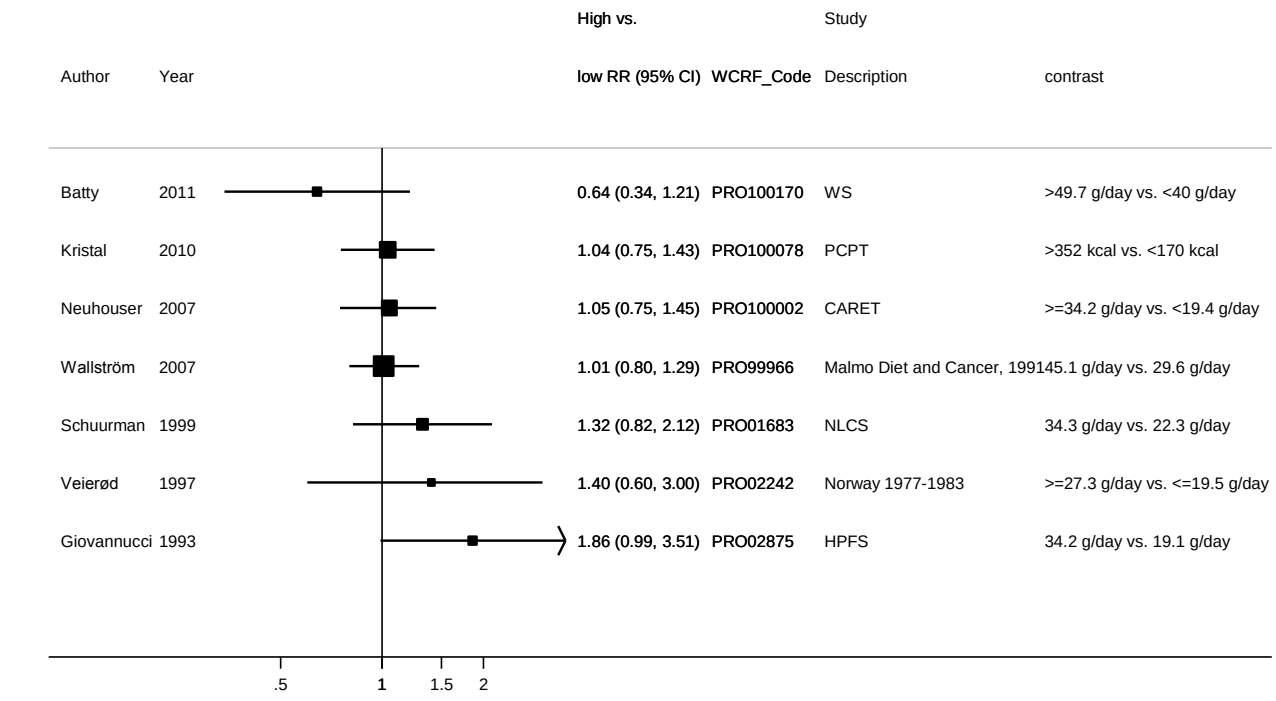
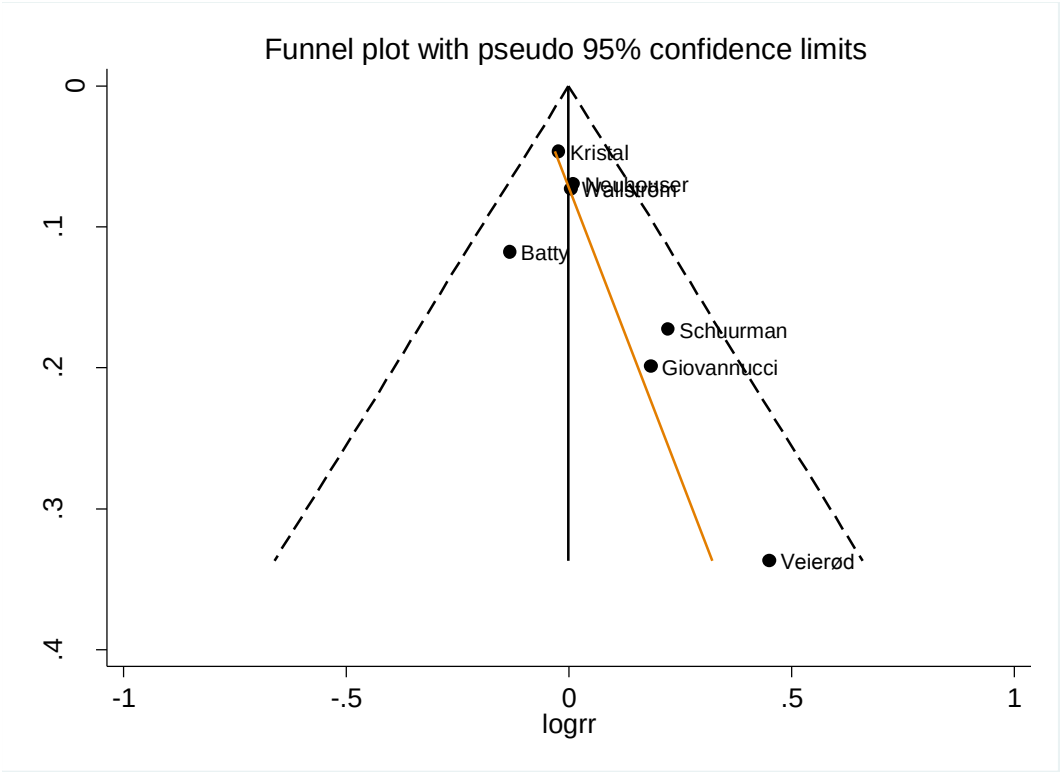


Figure 145 Funnel plot of monounsaturated fatty acid intake and prostate cancer



Egger's test p = 0.27

Figure 146 Dose-response graph of monounsaturated fatty acid and prostate cancer

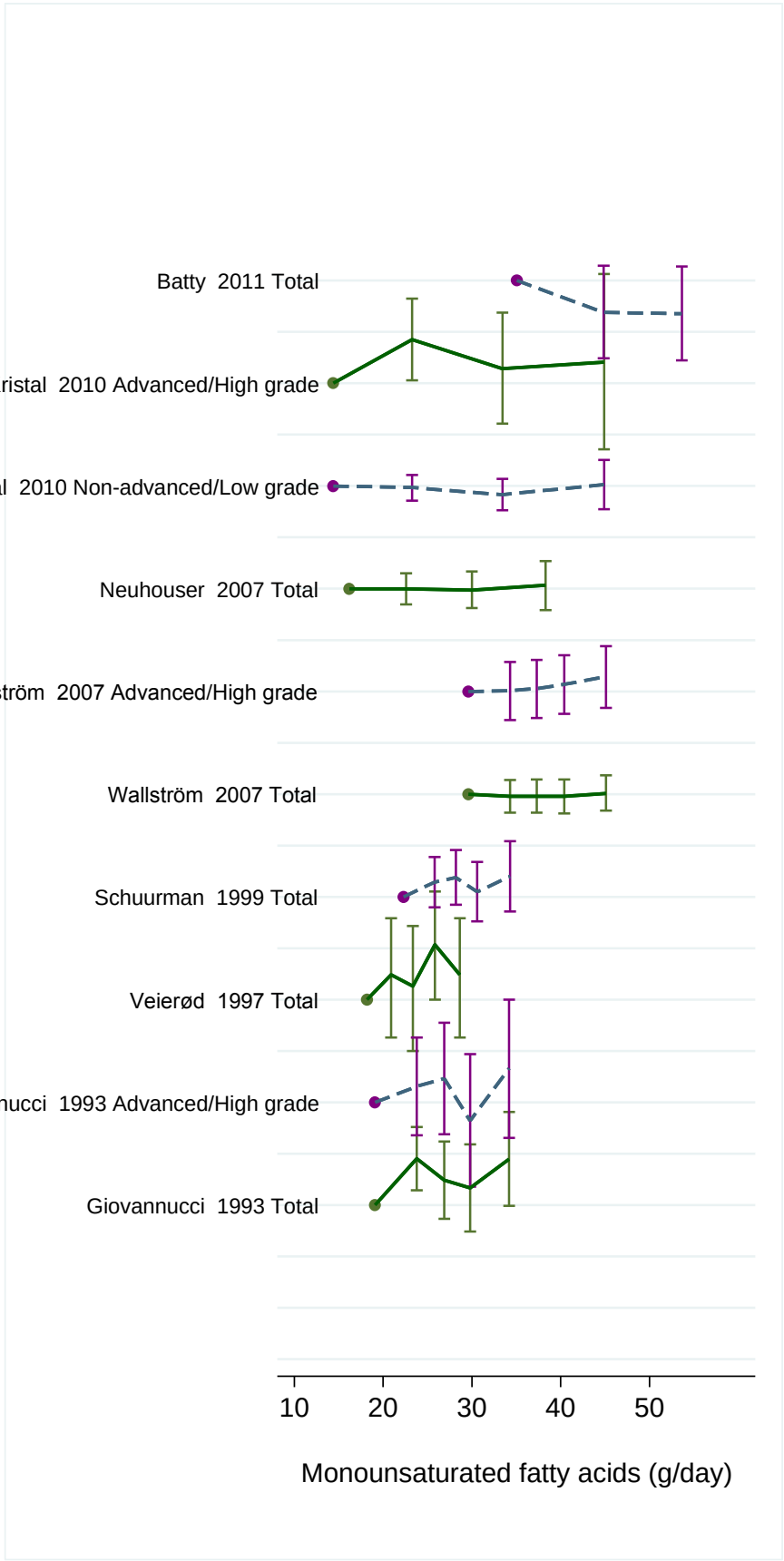
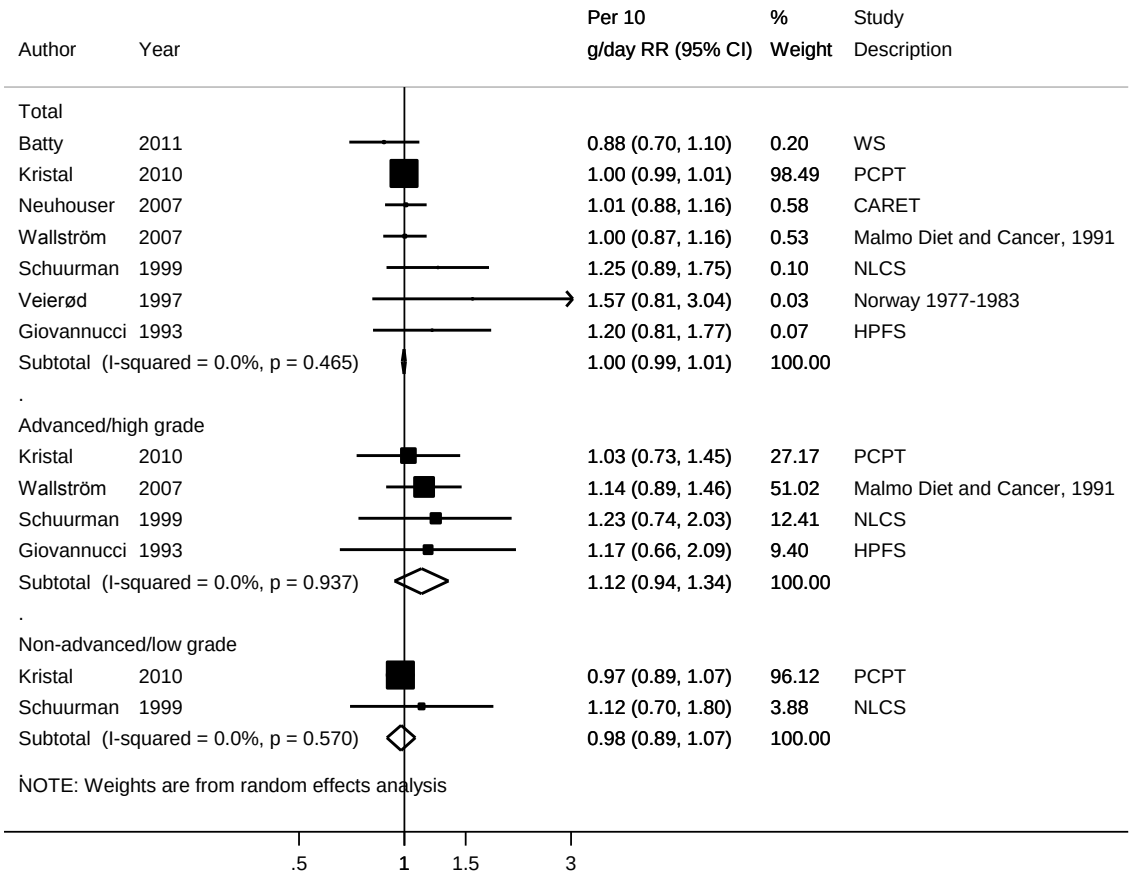


Figure 147 Dose-response meta-analysis of monounsaturated fatty acid intake and prostate cancer, per 10 g/day, stratified by cancer subtype.



5.2.4 Polyunsaturated fatty acids

Methods

Eight publications (eight cohort studies) were identified, five of which were identified during the Continuous Update Project. The unit used in the dose-response analysis was 10 g/day.

Polyunsaturated fat intake in kcal/day (Kristal et al, 2010) was converted to g/day, using 9 kcal per 1 g of fat.

One study (Batty et al, 2011) investigated prostate cancer mortality. Cancer incidence was the outcome in all remaining studies.

The RRs for low-grade (GS 2-7) and high-grade (GS 8-10) prostate cancers in Kristal et al (2010) were combined before inclusion in the dose-response meta-analysis and high vs. low forest plot of total prostate cancer risk.

In stratified analysis, advanced and high grade cancers were combined in an advanced/high grade subgroup and non-advanced, localised, and low grade were combined in non-advanced/low grade subgroup.

Main results

The summary RR per 10 g/day increase was 1.00 (95% CI 0.93-1.08; $I^2 = 2.6\%$; $p_{heterogeneity} = 0.41$) (all studies combined). There was no significant evidence of publication bias with Egger's test, p = 0.66.

The RR per 10 g per day was 0.96 (95% CI 0.86-1.07; $I^2 = 0\%$; $p_{heterogeneity} = 0.54$; n = 3) for non-advanced/low grade and 1.02 (95% CI 0.75-1.39; $I^2=68.9\%$; $p_{heterogeneity} = 0.02$; n = 4) for advanced/high grade cancer.

Heterogeneity

Low heterogeneity was observed, $I^2 = 2.6\%$, $p_{heterogeneity} = 0.41$.

Comparison with the Second Expert Report

In the 2005 SLR the meta-analysis on polyunsaturated fatty acids and prostate cancer showed a non-significant protective association.

Published meta-analysis or pooled analysis

No published meta-analysis or pooled analysis was identified.

Table 132 Studies on polyunsaturated fatty acid consumption identified in the CUP

Author, year	Country	Study name	Cases	Years of follow up	RR	LCI	UCI	Contrast
Agalliu, 2011	Canada	Canadian Study of Diet, Lifestyle, and Health	661	7.7 years	0.95	0.70	1.12	20.7 vs. 10.2 g/day
Batty, 2011	UK	Whitehall study, London	60	40 years	0.89	0.67	1.20	Per 2.8 g/day
					0.81	0.43	1.52	>8.7 vs. <6.8 g/day

Kristal, 2010	USA and Canada	Prostate Cancer Prevention Trial	1576	10 years max	0.88	0.68	1.15	GS 2-7 > 191 vs. < 93 kcal/day
			127		2.89	1.24	6.73	GS 8-10 > 191 vs. < 93 kcal/day
Wallström, 2007	Sweden	Malmö Diet and Cancer Study	817	11 years	1.05	0.84	1.30	23 vs. 12 g/day
Neuhouser, 2007	USA	The Carotene and Retinol Efficacy Trial	811	11 years	1.17	0.88	1.32	≥18.6 vs. <10.8 g/day

Table 133 Overall evidence on polyunsaturated fatty acid consumption and prostate cancer

	Summary of evidence
2005 SLR	Three studies were identified during the 2005 SLR. Two studies were included in the 2005 SLR meta-analysis. All studies reported no significant association between polyunsaturated fat intake and prostate cancer.
Continuous Update Project	Five additional studies reported on polyunsaturated fatty acid intake and prostate cancer risk. One study reported significant positive association with high grade cancer. No significant association was observed in the CUP meta-analysis.

Table 134 Summary of results of the dose response meta-analysis of polyunsaturated fatty acid consumption and prostate cancer

Prostate cancer		
	2005 SLR	CUP
Studies (n)	2	7
Cases (n)	714	4766
Increment unit used	Per 10 g/day	Per 10 g/day
Overall RR (95% CI)	0.98 (0.77-1.26)	1.00 (0.93-1.08)
Heterogeneity (I^2, p-value)	20.4%, p = 0.26	2.6%, p = 0.41
Stratified analysis		
Advanced/high grade cancer*		
Overall RR (95% CI)		1.02 (0.75-1.39)
Heterogeneity (I^2, p-value)		68.9%, p = 0.02, n = 4
Non-advanced/low grade cancer*		
Overal RR (95% CI)		0.96 (0.86-1.07)
Heterogeneity (I^2, p-value)		0%, p = 0.54, n = 3

* No meta-analysis was conducted in the 2005 SLR.

Table 135 Inclusion/exclusion table for meta-analysis of polyunsaturated fatty acid consumption and prostate cancer

WCRF code	Author	Year	Study design	Study name	Cancer outcome	2005 SLR	CUP dose-response meta-analysis	CUP HvL forest plot	Estimated values	Exclusion reasons
PRO100199	Agalliu	2011	Case-cohort study	Canadian Study of Diet, Lifestyle, and Health	Incidence	No	Yes	Yes	Person years per quintile	
PRO100170	Batty	2011	Prospective Cohort study	Whitehall study, London	Mortality	No	Yes	Yes	Continuous RR rescaled per 10g/day increase Mid-exposure values	
PRO100078	Kristal	2010	Follow-up of subjects in finasteride trial	Prostate Cancer Prevention Trial	Incidence	No	Yes	Yes	Person years per quintile and mid-exposure values Conversion of kcal/day to g/day	
PRO99966	Wallström	2007	Prospective Cohort study	Malmö Diet and Cancer Study	Incidence	No	Yes	Yes	Person years per quintile	
PRO100002	Neuhouser	2007	Prospective Cohort study	Carotene and Retinol Efficacy Trial	Incidence	No	Yes	Yes	Person years per quintile and mid-exposure values	
PRO97676	Laaksonen	2004	Prospective Cohort study	Kuopio Ischaemic Heart Disease Risk Factor Study	Incidence	Yes	No	No		Only means
PRO01683	Schuurman	1999	Case-cohort study	Netherlands Cohort Study	Incidence	Yes	Yes	Yes		
PRO02242	Veierød	1997	Prospective Cohort study	Norway 1977-1983	Incidence	Yes	Yes	Yes	Person years per quintile	

Figure 148 Highest versus lowest forest plot of polyunsaturated fatty acid consumption and prostate cancer

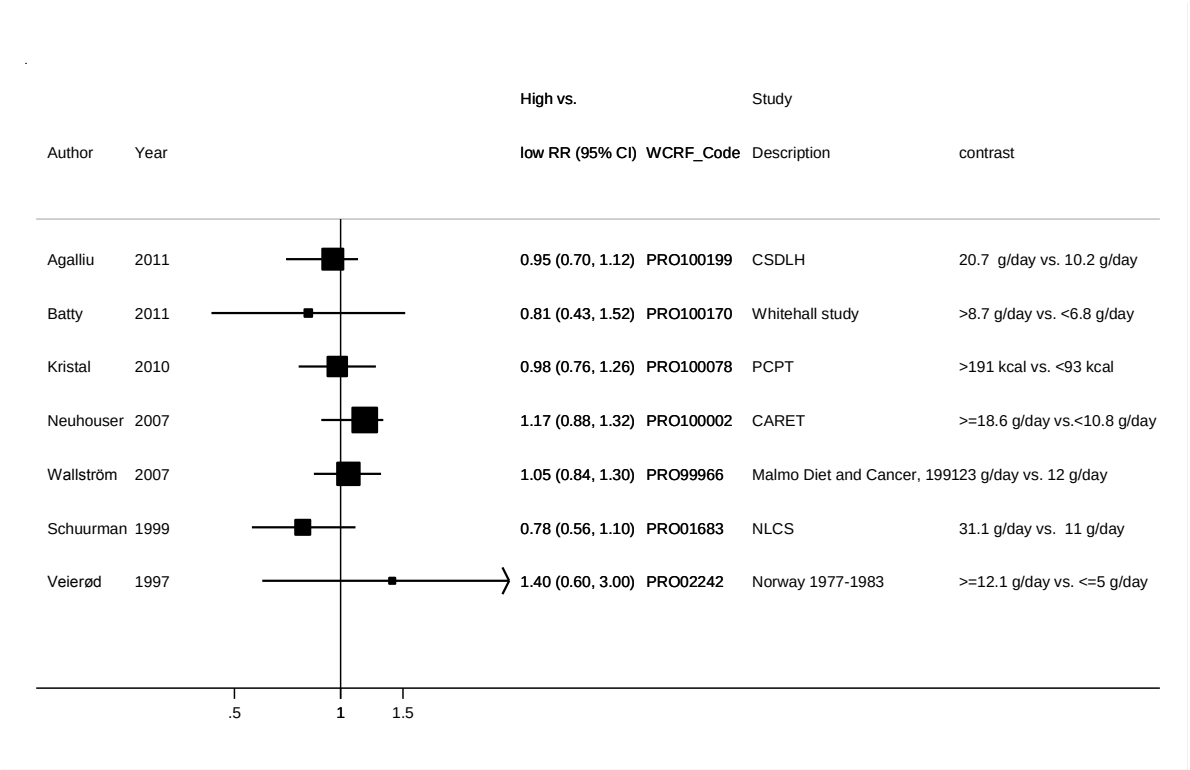


Figure 149 Dose-response meta-analysis of polyunsaturated fatty acid intake and prostate cancer, per 10 g/day, stratified by cancer subtype.

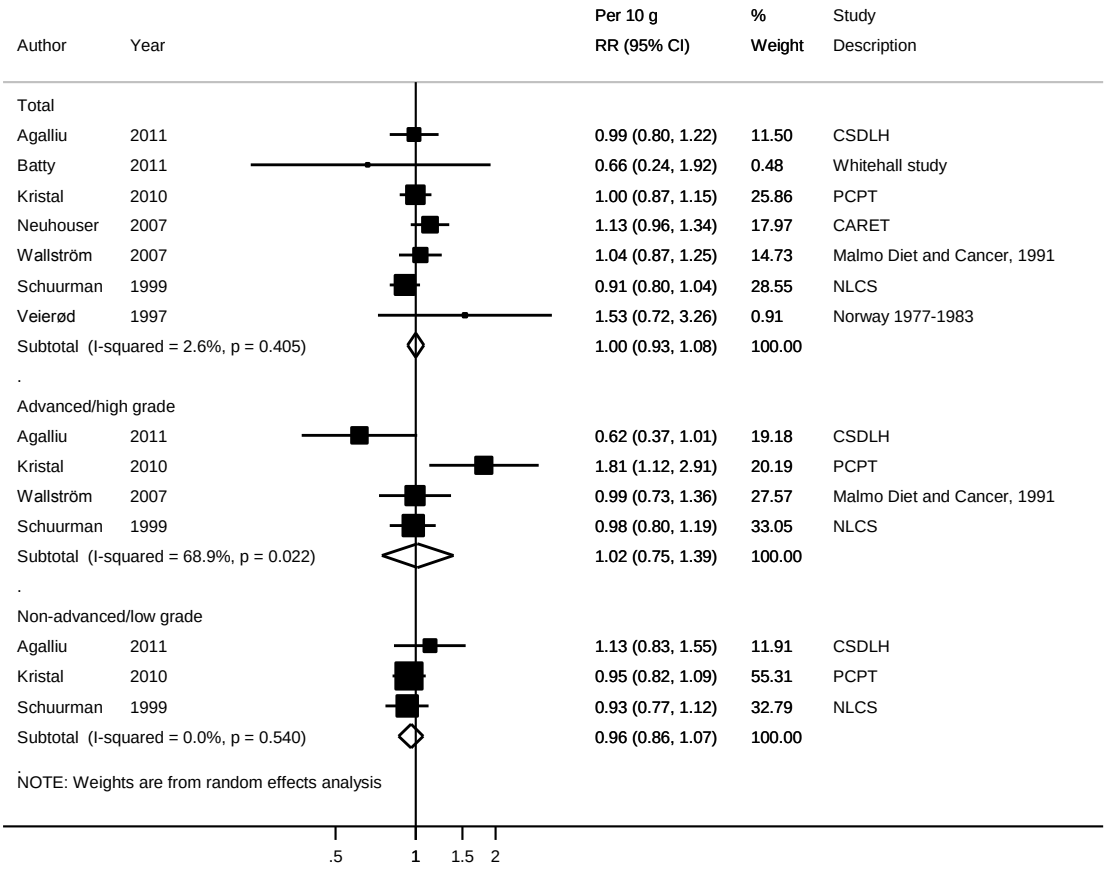
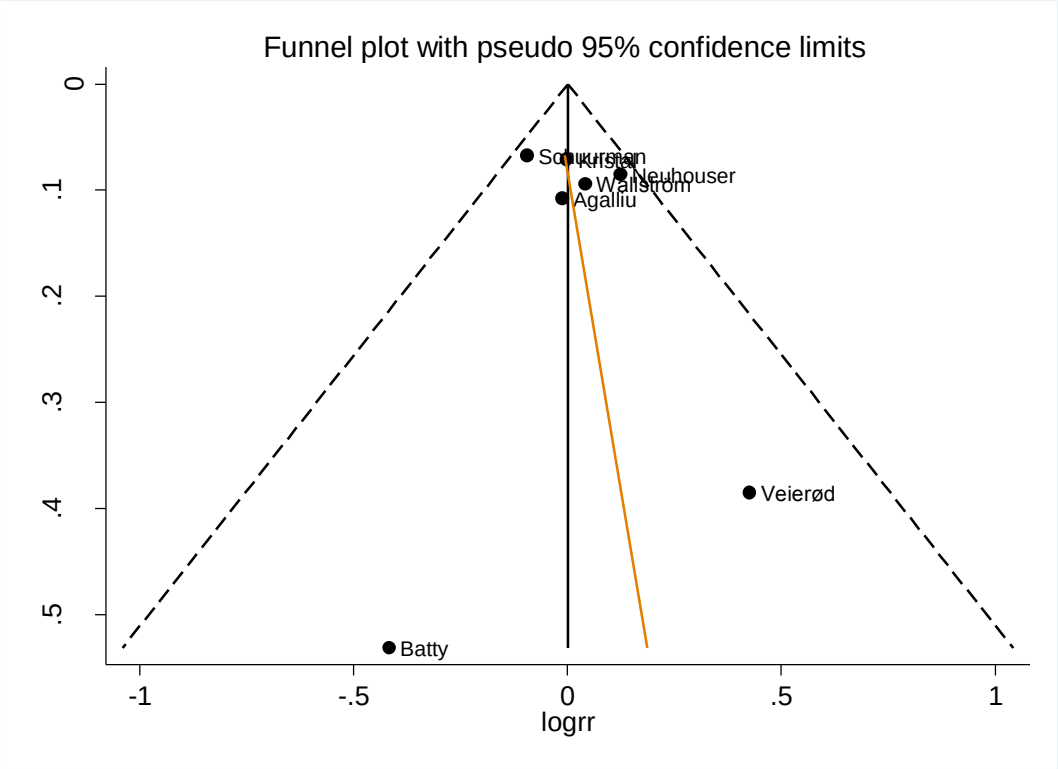
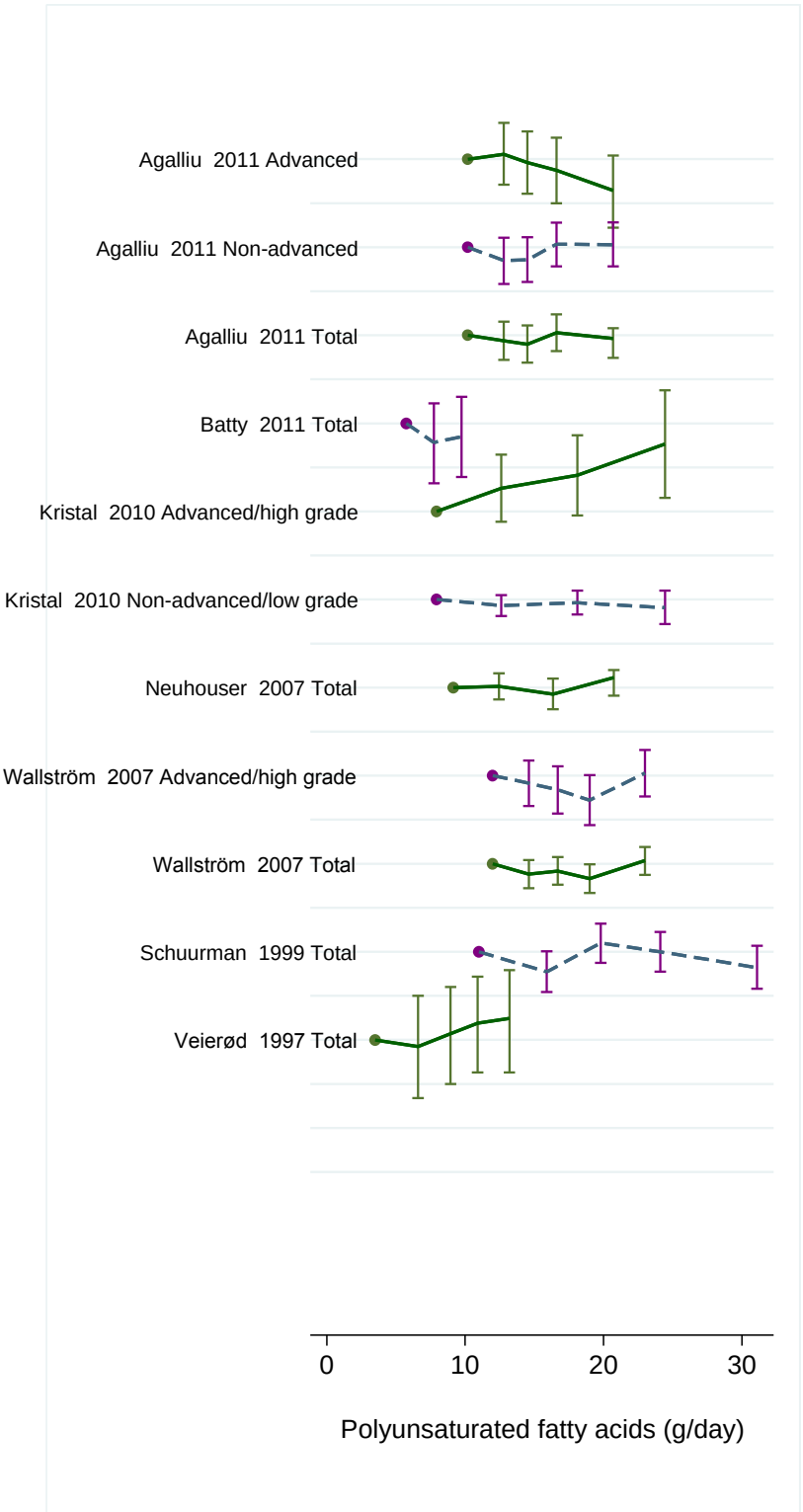


Figure 150 Funnel plot of polyunsaturated fatty acid intake and prostate cancer



Egger's test p = 0.66

Figure 151 Dose-response graph of polyunsaturated fatty acid and prostate cancer



5.2.4.1 α-linolenic fatty acids

Methods

Eleven publications (7 cohort studies) were identified, 5 of which were identified during the Continuous Update Project. The unit used in the dose-response analysis was 1 g/day.

Four publications from the HPFS cohort were identified in the SLR (Leitzmann et al, 2004; Platz et al, 2004c; Giovannucci et al, 1998b; Giovannucci et al, 1993) and one was identified during the CUP (Giovannucci et al, 2007). The most recent publication by Giovannucci et al, 2007 (3 544 cases) could not be used for dose-response meta-analysis due to missing confidence intervals and cases per category and was only used for high vs. low analysis. Leitzmann et al, 2004, Platz et al, 2004c and Giovannucci et al, 1998b were all excluded as a result of insufficient data. The HPFS publication by Giovannucci et al, 1993 (300 cases) was used in the dose-response meta-analysis. The HPFS is the only study that reported an increased risk of advanced prostate cancer in relation to higher alfa-linolenic fatty acids intake.

Pelser et al (2013) and Leitzmann et al (2004) reported intake of α-linolenic fatty acid as a percentage of total energy and Park et al (2007a) study reported in g/1000 kcal which could not be converted to g/day due to missing average energy intake per quintile of α-linolenic fatty acid. These studies were not used in the meta-analysis.

In order to conduct stratified analysis by prostate cancer type, GS $\geq$ 7 cancers were included in an advanced/high grade subgroup and GS < 7 cancers were included in non-advanced/low grade subgroup.

Main results

The summary RR per 1 g/day increase was 0.95 (95% CI 0.85-1.05; I^2 = 8.3%; $p_{heterogeneity}$ = 0.36). The RR per 1 g per day was 1.15 (95% CI 0.80-1.64; I^2 = 74.7%; $p_{heterogeneity}$ < 0.01; n = 4) for advanced/high grade and 0.85 (95% CI 0.68-1.05; I^2 = 0%; $p_{heterogeneity}$ = 0.85; n = 2) for non-advanced/low grade cancer.

Heterogeneity

Overall, there was no evidence of heterogeneity, I^2 = 8.3%, $p_{heterogeneity}$ = 0.36.

Comparison with the Second Expert Report

In the 2005 SLR the meta-analysis on α-linolenic fatty acid and prostate cancer showed a non-significant association.

Published meta-analysis or pooled analysis

A meta-analysis of five prospective studies found a summary RR of 0.95 (95% CI 0.84-1.09) comparing highest versus the lowest category of α-linolenic fatty acid intake (Carleton et al, 2013). All the studies included in the meta-analysis are in the Highest vs Lowest forest plot in the CUP SLR (Figure 150) that additionally includes two other studies.

Table 136 Studies on α-linolenic fatty acid consumption identified in the CUP

Author, year	Country	Study name	Cases	Years of follow up	Subgroup	RR	LCI	UCI	Contrast
Pelser, 2013	USA	NIH- AARP Diet and Health Study	2930	9 years	Advanced	1.17	1.04	1.31	0.88 vs. 0.41 % energy
			18934		Non-advanced	1.05	1.00	1.10	
			725		Fatal	1.13	0.89	1.43	
			21864		Pooled	1.07	1.02	1.12	
Giovannucci, 2007	USA	Health Professionals Follow-up Study	3544	16 years maximum	1.12		1.01	1.25	≥1.32 vs. <0.70 g/day
Park, 2007a	USA	Multiethnic Cohort Study	4404	8 years	0.92		0.84	1.02	1.07 vs. 0.55 g/1000 kcal
Wallström, 2007	Sweden	Malmö Diet and Cancer Study	817	11 years	0.92		0.73	1.15	2.7 vs. 1.4 g/day
Koralek, 2006	USA	PLCO Cancer Screening Trial	1898	5.1 years	0.94		0.81	1.09	1.75 vs. 1.09 g/day

Table 137 Overall evidence on α-linolenic fatty acid consumption and prostate cancer

	Summary of evidence
2005 SLR	Five studies were identified during the 2005 SLR. Three studies were included in the 2005 SLR meta-analysis. One study reported significant protective effect of α-linolenic acid.
Continuous Update Project	Five additional studies reported on α-linolenic acid and prostate cancer risk, two of which were included in the meta-analysis. Three studies reported non-significant inverse association, one study reported significant increase in risk. In Pelser, 2013 study significantly increased risk was restricted to non-fatal cases. A total of five studies were included in the meta-analysis. No significant association was observed in the CUP meta-analysis.

Table 138 Summary of results of the dose response meta-analysis of α-linolenic fatty acid consumption and prostate cancer

Prostate cancer		
	2005 SLR	CUP
Studies (n)	4	5
Cases (n)	1722	3977
Increment unit used	Per 1 g/day	Per 1 g/day
Overall RR (95% CI)	0.91 (0.76-1.09)	0.95 (0.85-1.05)
Heterogeneity (I^2, p-value)	19.8%, p = 0.29	8.3%, p = 0.36
Stratified analysis		
Advanced/high grade cancer		
Overall RR (95% CI)	1.92 (0.49-7.59)	1.15 (0.80-1.64)
Heterogeneity (I^2, p-value)	89.4%, p < 0.01, n = 2	74.7%, p < 0.01, n = 4
Non-advanced/low grade cancer*		
Overall RR (95% CI)		0.85 (0.68-1.05)
Heterogeneity (I^2, p-value)		0%, p = 0.85, n = 2

* No meta-analysis was conducted in the 2005 SLR.

Table 139 Inclusion/exclusion table for meta-analysis of α-linolenic fatty acid consumption and prostate cancer

WCRF code	Author	Year	Study design	Study name	Cancer outcome	2005 SLR	CUP dose-response meta-analysis	CUP HvL forest plot	Estimated values	Exclusion reasons
PRO100158	Pelser	2013	Prospective Cohort study	NIH- AARP Diet and Health Study	Incidence and mortality	No	No	Yes		Insufficient data
PRO99961	Giovannucci	2007	Prospective Cohort study	Health Professionals Follow-up Study	Incidence and mortality	No	No	Yes		Missing confidence intervals and cases per category; superseded by Giovannucci, 1993
PRO99977	Park	2007a	Prospective Cohort study	Multiethnic Cohort Study	Incidence	No	No	Yes		Insufficient data
PRO99966	Wallström	2007	Prospective Cohort study	Malmö Diet and Cancer Study	Incidence	No	Yes	Yes	Person years per quintile	
PRO99993	Koralek	2006	Prospective Cohort study	PLCO Cancer Screening Trial	Incidence	No	Yes	Yes	Person years per quintile	
PRO97679	Leitzmann	2004	Prospective Cohort study	Health Professionals Follow-up Study	Incidence	Yes	No	No		Insufficient data; superseded by Giovannucci, 1993;
PRO10575	Platz	2004c	Nested case control study	Health Professionals Follow-up Study	Incidence and mortality	Yes	No	No		Only means; superseded by Giovannucci, 1993;
PRO04076	Männistö	2003	Nested case control study	ATBC	Incidence	Yes	Yes	Yes	Person years per quintile	
PRO01683	Schuurman	1999	Case-cohort study	Netherlands Cohort Study	Incidence	Yes	Yes	Yes	Rescale of reported RR for continuous increase	
PRO02192	Giovannucci	1998b	Prospective Cohort study	Health Professionals Follow-up Study	Incidence and mortality	Yes	No	No		Two levels of exposure; advanced cancer only; superseded by Giovannucci, 1993;
PRO02875	Giovannucci	1993	Prospective Cohort study	Health Professionals Follow-up Study	Incidence and mortality	Yes	Yes	No		In H vs. L analysis superseded by Giovannucci, 2007 with more cases

Figure 152 Highest versus lowest forest plot of α-linolenic fatty acid consumption and prostate cancer

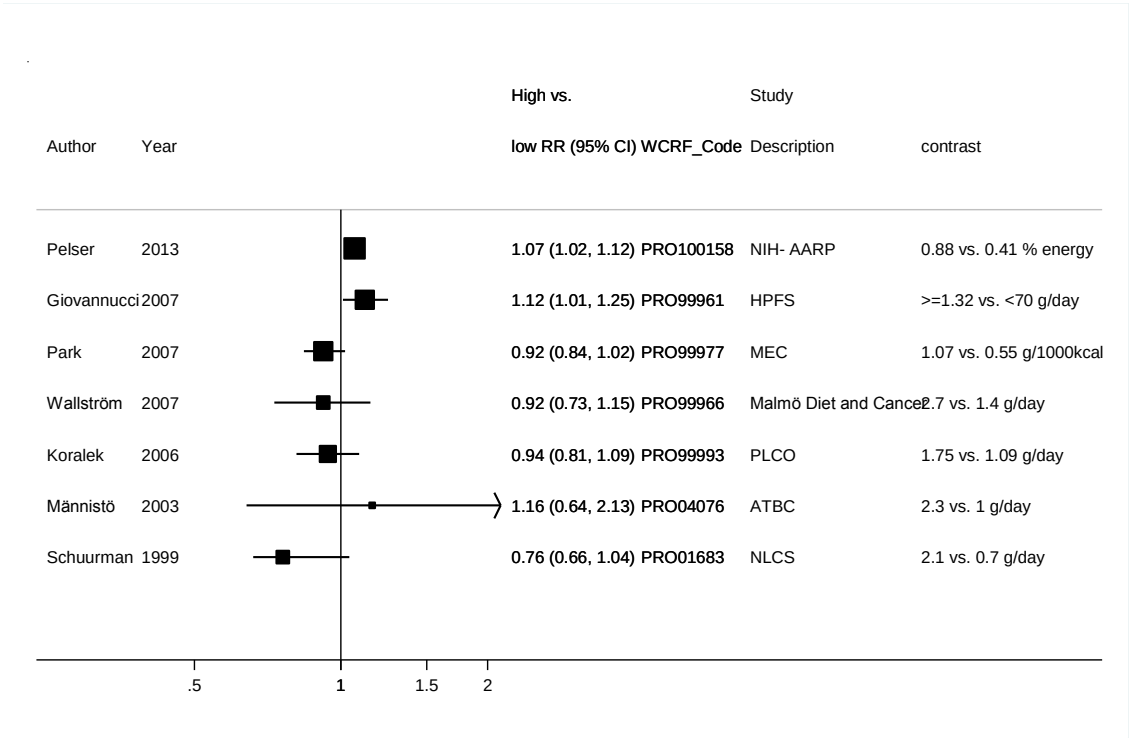


Figure 153 Dose-response meta-analysis of α-linolenic fatty acid intake and prostate cancer, per 1 g/day, stratified by cancer subtype

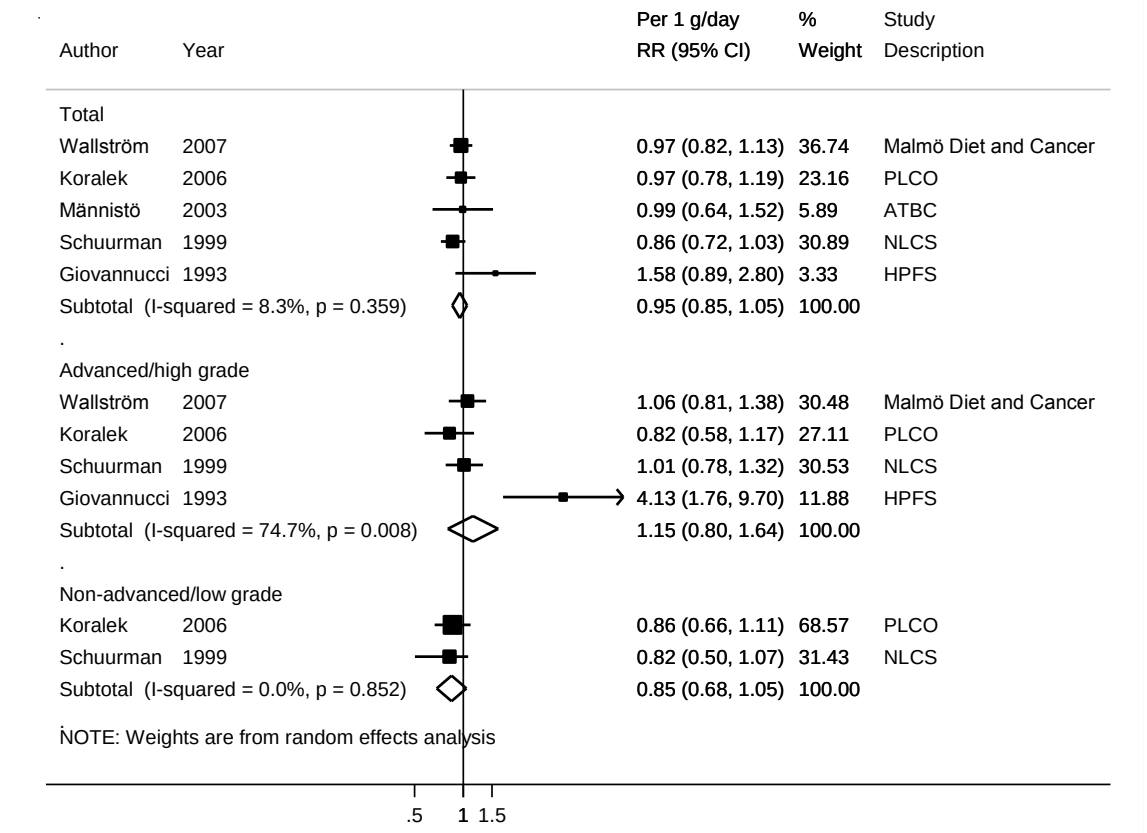
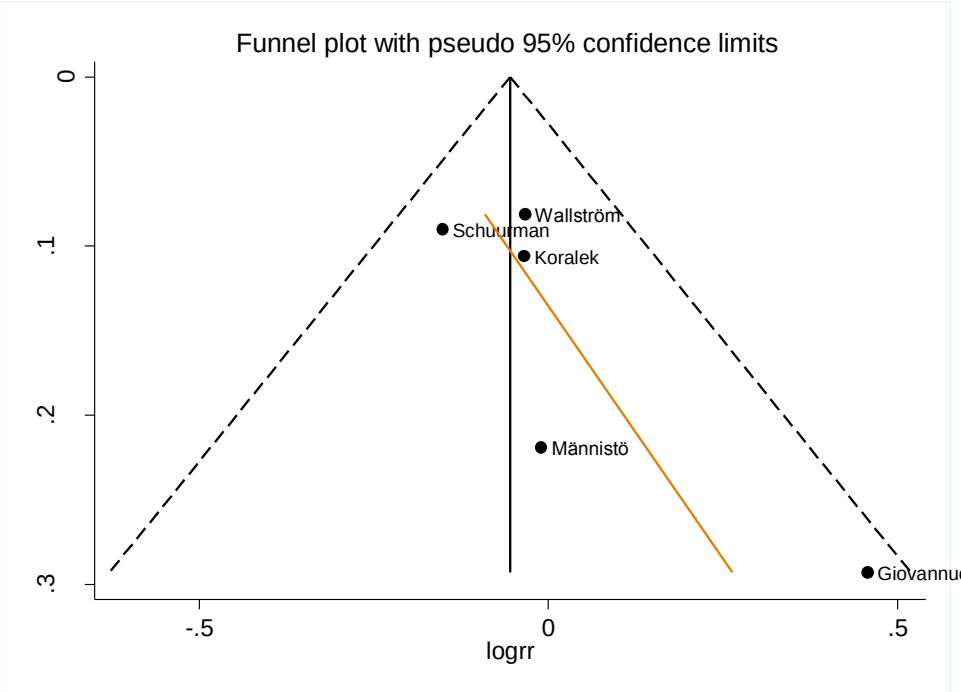
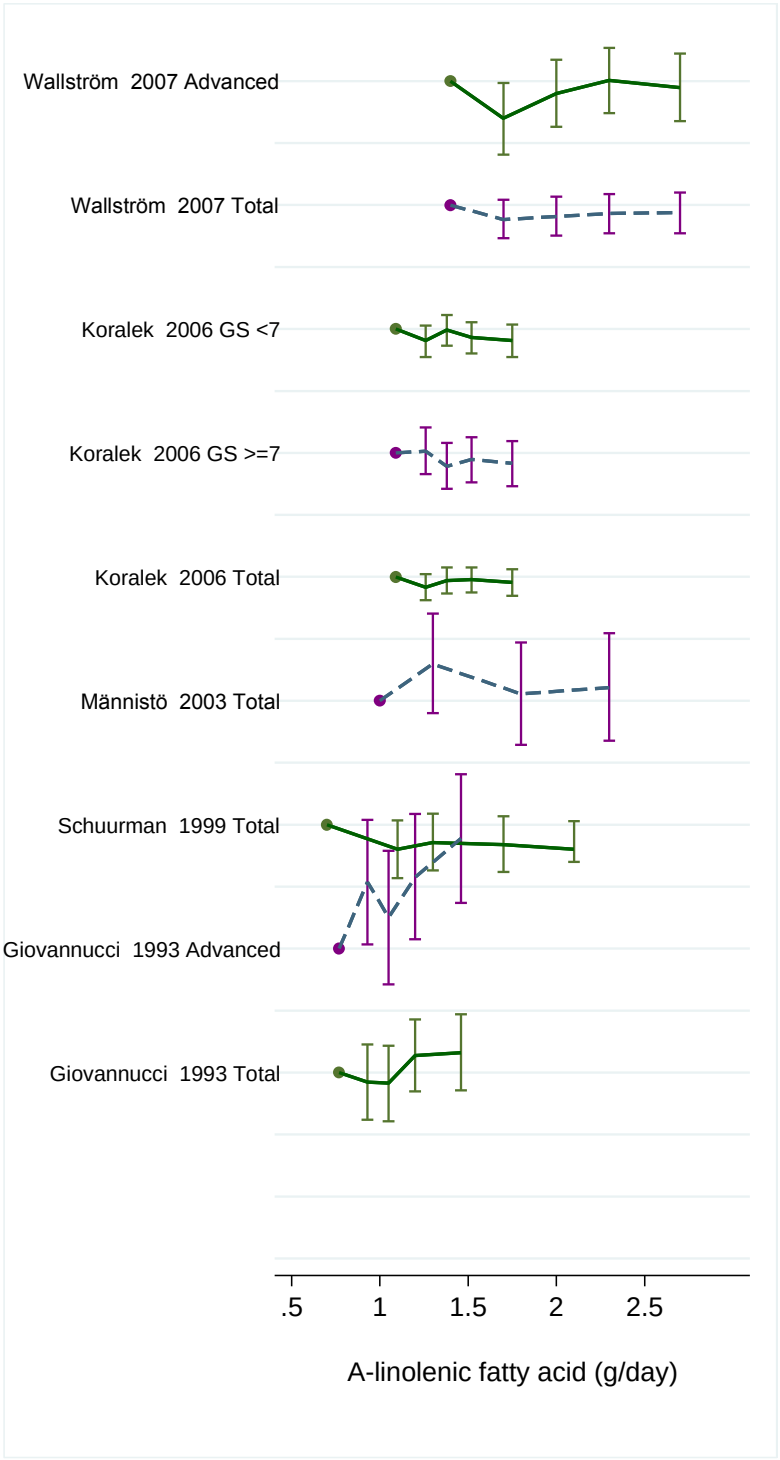


Figure 154 Funnel plot of α-linolenic fatty acid intake and prostate cancer



Egger's test p = 0.17

Figure 155 Dose-response graph of α-linolenic fatty acid and prostate cancer



5.2.4.1 Biomarkers of alpha-linolenic fatty acid

Methods

Eight publications (7 cohort studies) were identified, 5 of which were identified during the CUP. Six studies were included in the dose-response meta-analysis using an increment of 0.1%.

Four studies reported alpha-linolenic fatty acid as percentage of total fatty acids in serum (Brasky et al, 2011, Männistö 2003, and Harvei et al, 1997), one study was in plasma (Crowe et al, 2008), one in erythrocyte membrane (Park et al, 2009) and one in whole blood (Chavarro et al, 2007). All studies were combined together.

Stratified analysis by advanced/high grade cancers and non-advanced/low grade cancers were conducted. The advanced/high groups included tumours Gleason ≥ 8 (Brasky et al, 2011); regional or metastatics or Gleason ≥ 7 (Park et al, 2009) or T3, T4 and/or N1 and/or M1, or stage metastatic (Crowe et al, 2008b).

Brasky et al, 2011 reported risks for low and high grade prostate cancers separately. Risk estimates for cancer subgroups were combined for total cancer using Hamling's method.

Main results

The summary RR per 0.1% increase was 1.02 (95% CI 0.96-1.09; I^2=28.7%; $p_{heterogeneity}$ = 0.22) for all prostate cancer, 0.92 (95% CI 0.77-1.09; I^2 = 19.1%; $p_{heterogeneity}$ = 0.29; n = 3) for advanced/high grade and 1.03 (95% CI 0.92-1.15; I^2 = 0%; $p_{heterogeneity}$ = 0.40; n = 2) for non-advanced/low grade cancer.

In influence analysis, the summary RRs ranged from 1.01 (95% CI 0.94-1.09) when Chavarro et al, 2007 was omitted to 1.04 (95% CI 0.97-1.11) when Brasky et al, 2011 was omitted.

The Egger"s test of publication bias was not significant (p = 0.32)

Heterogeneity

Overall, there was low heterogeneity, I^2 = 28.7%, $p_{heterogeneity}$ = 0.22.

Comparison with the Second Expert Report

No meta-analysis was conducted in the 2005 SLR.

Published meta-analysis or pooled analysis

No pooled studies were identified. In a meta-analysis (Sorongon-Legaspi et al, 2013), the summary relative risk from five nested case-control studies was 1.19 (95% CI 0.95-1.50) with low heterogeneity (p = 0.33) for the comparison of the highest with the lowest categories of percentage of alpha-linolenic fatty acid.

Table 140 Studies on biomarkers of alpha-linolenic fatty acid identified in the CUP

Author, year	Country	Study name	Cases	Years of follow up	Subgroup	RR	LCI	UCI	Contrast
Cheng, 2013	USA	Carotene and Retinol Efficacy Trial	368	Maximum 20 years	Stage I-II Gleason score <7	0.99	0.7	1.41	≥ 0.12 vs. ≤ 0.09% of total serum phospholipids
			273		Stage III-IVGleason score ≥7	0.93	0.62	1.37	
Brasky, 2011	USA	Prostate Cancer Prevention Trial	1533	7 years	Low grade	0.92	0.75	1.13	> 0.18 vs. < 0.12% of total serum phospholipids
			125		High grade	0.64	0.38	1.11	
Park, 2009	USA	Multiethnic Cohort Study	376	1.9 years	Total	0.94	0.50	1.75	> 0.69 vs. ≤ 0.33% fatty acid composition in erythrocyte membranes
			102		Gleason score ≥7	0.60	0.17	2.14	> 0.59 vs. ≤ 0.38% fatty acid composition in erythrocyte membranes
Crowe, 2008b	Europe	European Prospective Investigation into Cancer and Nutrition	962	4.2 years	Total	1.06	0.75	1.50	0.36-2.63 vs. 0-0.18 mol% of plasma phospholipids
Chavarro, 2007	USA	Physicians' Health study	476	13 years	Total	1.31	0.89	1.95	0.54 vs. 0.24% of whole blood fatty acids

Table 141 Overall evidence on alpha-linolenic fatty acid and prostate cancer

	Summary of evidence
2005 SLR	Three studies were identified during the 2005 SLR, all showed non-significant results. No meta-analysis was conducted.
Continuous Update Project	Five additional studies reported on EPA fatty acid and prostate cancer risk, four of which were included in the meta-analysis. Three studies reported non-significant inverse association, two remaining studies reported non-significant increase in prostate cancer risk. A total of six studies were included in the meta-analysis. No association was observed in the CUP meta-analysis.

Table 142 Summary of results of the dose response meta-analysis of alpha-linolenic fatty acid and prostate cancer

Prostate cancer		
	2005 SLR*	CUP
Studies (n)		6
Cases (n)		3811
Increment unit used		Per 0.1% increase
Overall RR (95% CI)		1.02 (0.96-1.09)
Heterogeneity (I^2, p-value)		28.7%, p = 0.22
Stratified analysis		
Advanced/high grade cancer*		
Overall RR (95% CI)		0.92 (0.77-1.09)
Heterogeneity (I^2, p-value)		19.1%, p = 0.29, n = 3
Non-advanced/low grade cancer*		
Overall RR (95% CI)		1.03 (0.92-1.15)
Heterogeneity (I^2, p-value)		0%, p = 0.40, n = 2

* No meta-analysis was conducted in the 2005 SLR.

Table 143 Inclusion/exclusion table for meta-analysis of alpha-linolenic fatty acid and prostate cancer

WCRF code	Author	Year	Study design	Study name	Cancer outcome	2005 SLR	CUP dose-response meta-analysis	CUP HvL forest plot	Estimated values	Exclusion reasons
PRO100161	Cheng	2013	Nested case control study	Carotene and Retinol Efficacy Trial	Incidence	No	No	Yes		The percentage distribution of serum fatty acid concentration per each quartile are of a similar value
PRO100097	Brasky	2011	Nested case control study	Prostate Cancer Prevention Trial	Incidence	No	Yes	Yes	Mid-points of exposure categories, RRs for low and high grade cancer combined using Hamling's method	
PRO100213	Park	2009	Nested case control study	Multiethnic Cohort Study	Incidence	No	Yes	Yes	Mid-points of exposure categories	
PRO100030	Crowe	2008 b	Nested case control study	European Prospective Investigation into Cancer and Nutrition	Incidence	No	Yes	Yes	Cases and non-cases per quintile, mid-points of exposure categories	
PRO100027	Chavarro	2007	Nested case control study	Physicians' Health study	Incidence	No	Yes	Yes		
PRO04076	Männistö	2003	Nested case control study	ATBC	Incidence	Yes	Yes	Yes	Cases and non-cases per quintile	
PRO02352	Harvei	1997	Nested case control study	Norway 1973-1994	Incidence	Yes	Yes	Yes	Mid-points of exposure categories	
PRO02814	Gann	1994	Nested case control study	Physicians' Health study	Incidence	Yes	No	No		Superseded by Chavarro, 2007

Figure 156 Highest versus lowest forest plot of alpha-linolenic fatty acid and prostate cancer

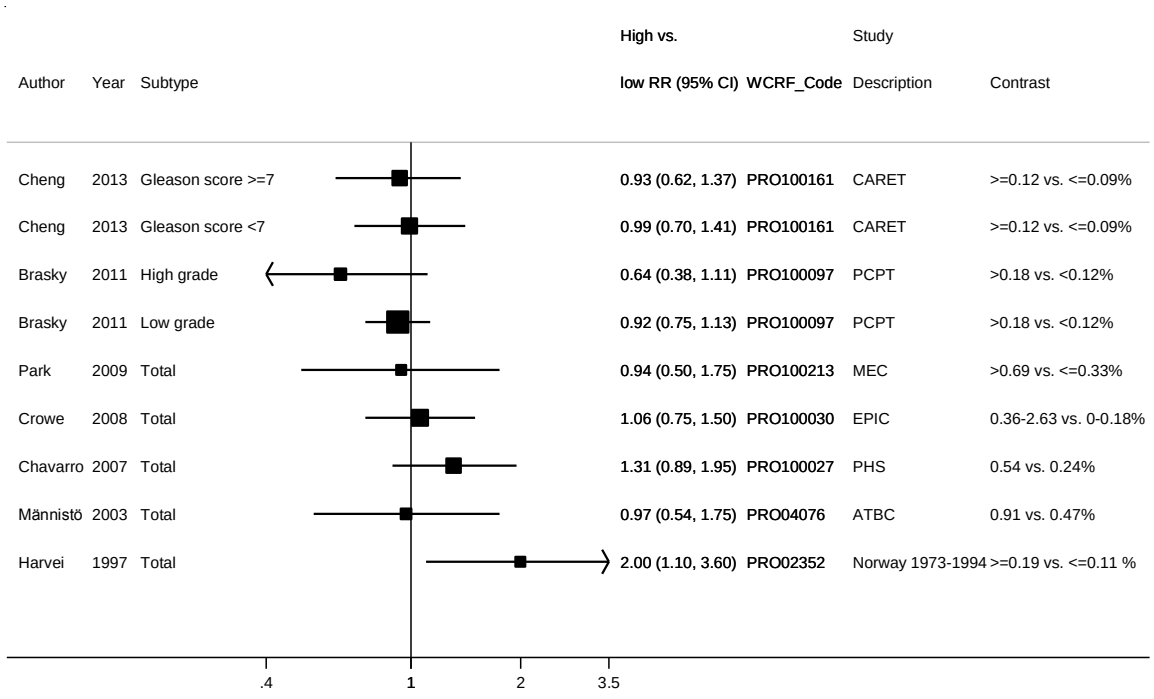


Figure 157 Dose-response meta-analysis of alpha-linolenic fatty acid and prostate cancer, per 0.1% increase, stratified by cancer subtype

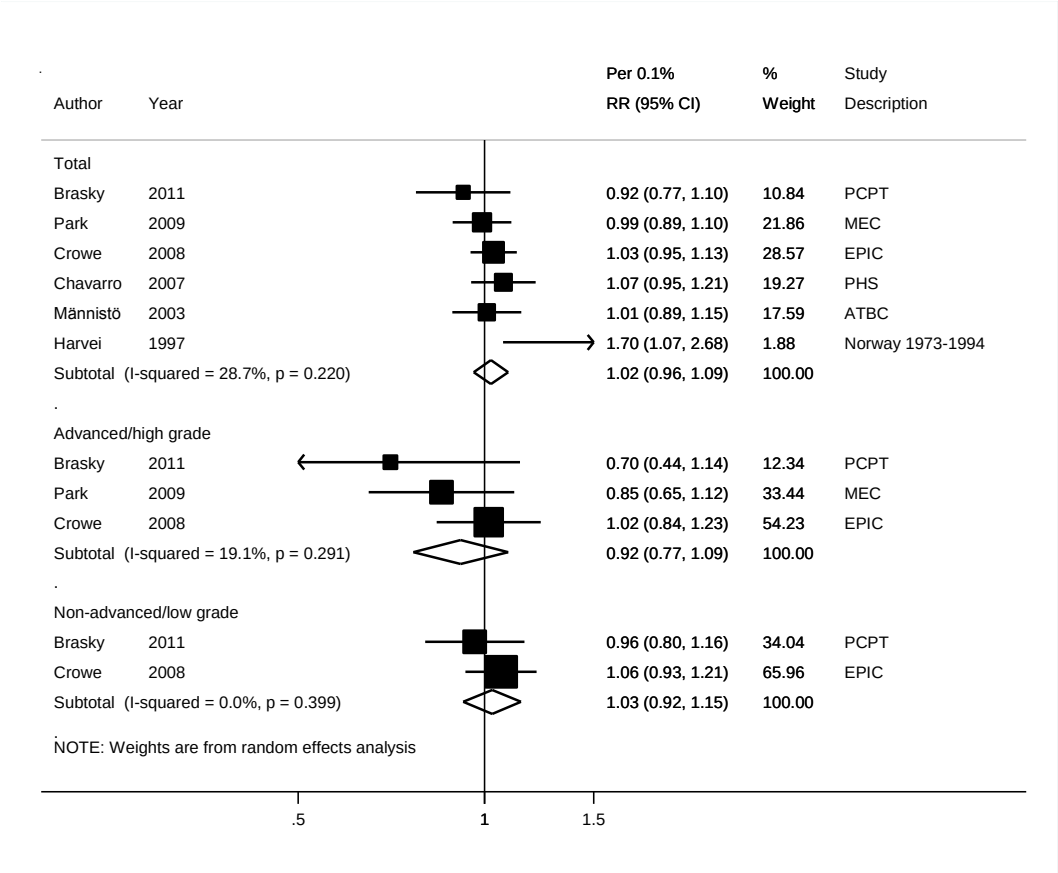
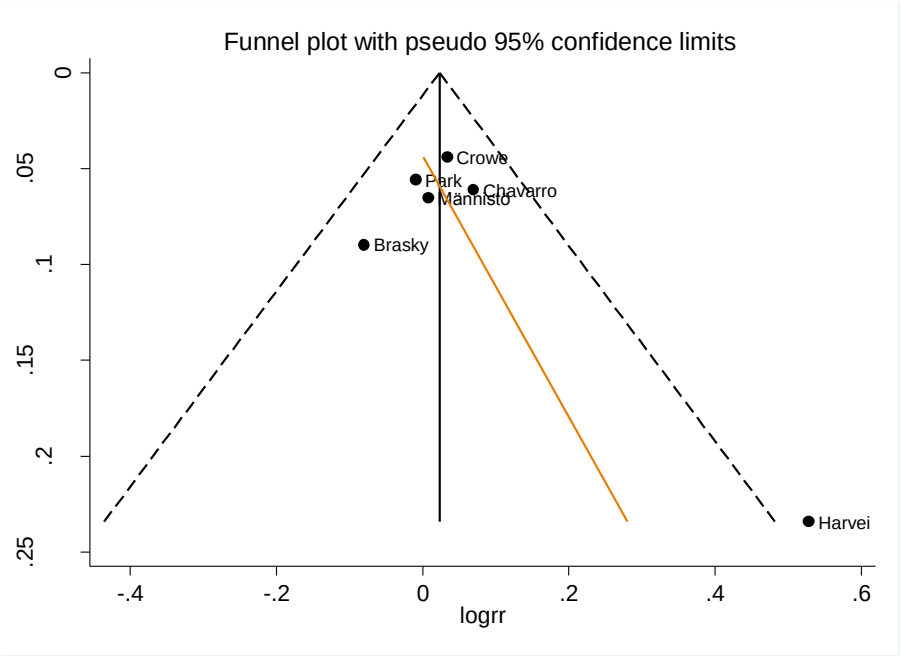
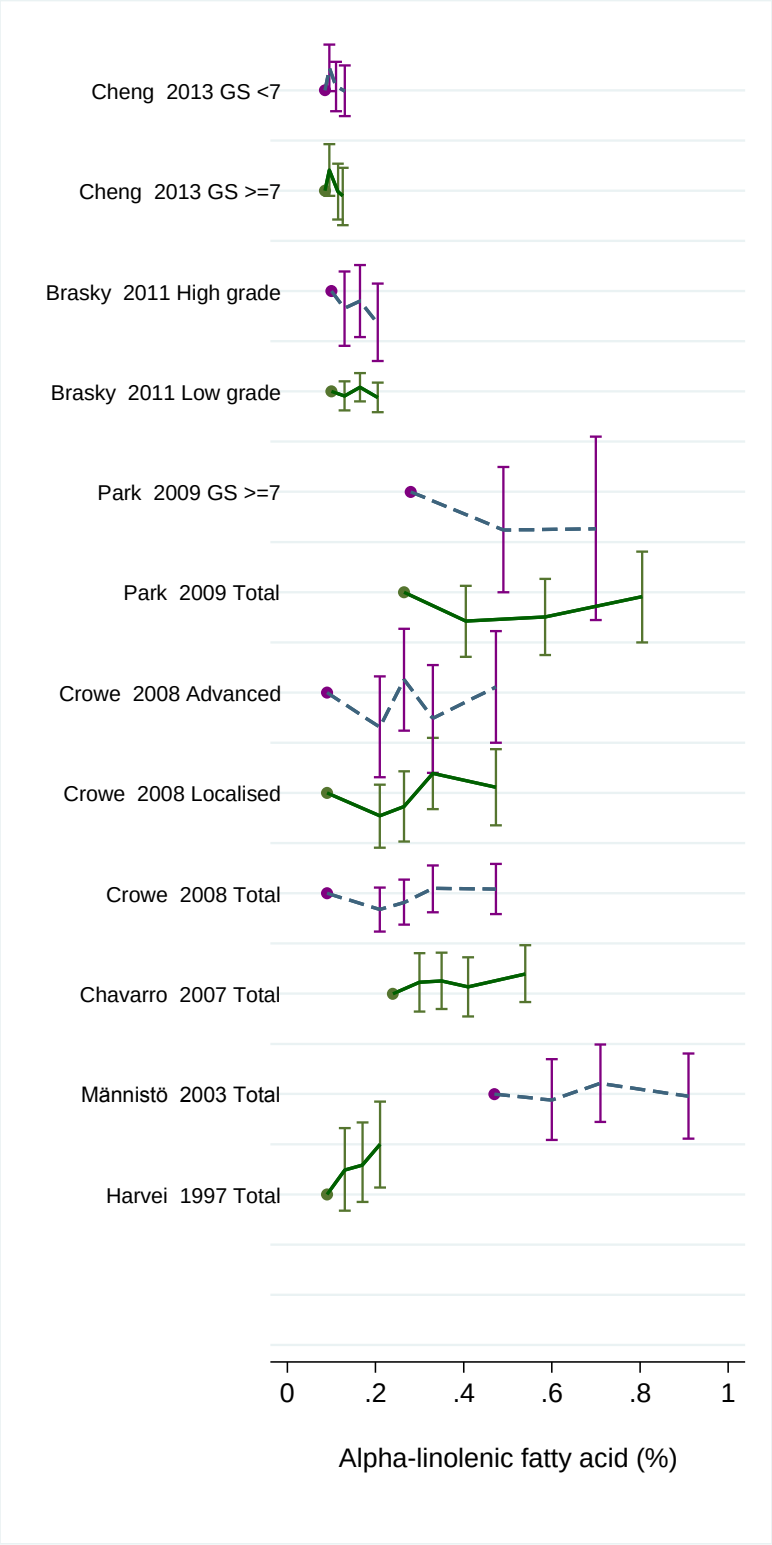


Figure 158 Funnel plot of alpha-linolenic fatty acid and prostate cancer



Egger's test p = 0.32

Figure 159 Dose-response graph of alpha-linolenic fatty acid and prostate cancer



5.2.4.1Biomarkers of EPA fatty acid

Methods

Eight publications (7 cohort studies) were identified, 5 of which were identified during the Continuous Update Project. The increment unit used in the dose-response analysis was 0.1%.

Five studies reported EPA fatty acid as percentage of total fatty acids in serum (Cheng et al, 2013, Brasky et al, 2011, Männistö 2003, and Harvei et al, 1997), one study in plasma (Crowe et al, 2008), one in erythrocyte membrane (Park et al, 2009) and one in whole blood (Chavarro et al, 2007). All studies were combined together.

Stratified analysis by advanced/high grade cancers and non advanced/low grade cancers were conducted. The advanced/high groups included tumours stage III/IV and Gleason ≥ 7 (Cheng et al, 2013); Gleason ≥ 8 (Brasky et al, 2011); regional or metastatics or Gleason ≥ 7 (Park et al, 2009) or T3, T4 and/or N1 and/or M1, or stage metastatic (Crowe et al, 2008b).

Brasky et al, 2011 and Cheng et al, 2013 reported risks for low grade, high grade and advanced/high grade-nonadvanced/low grade prostate cancers separately, respectively. Risk estimates for cancer subgroups were combined for total cancer using Hamling's method.

Main results

The summary RR per 0.1% increase was 1.00 (95% CI 0.99-1.01; I^2=21.2%; $p_{heterogeneity}$ = 0.27; n = 7) for all prostate cancer, 1.00 (95% CI 0.99-1.01; I^2 = 0%; $p_{heterogeneity}$ = 0.50; n = 4) for advanced/high grade and 1.00 (95% CI 1.00-1.01; I^2 = 0%; $p_{heterogeneity}$ = 0.96; n = 3) for non-advanced/low grade cancer. The summary RR did not change materially when studies were omitted in turn in the influence analysis.

The Egger's test of publication bias was not significant (p = 0.78)

Heterogeneity

Overall, there was low heterogeneity, I^2 = 21.2%, $p_{heterogeneity}$ = 0.27.

Comparison with the Second Expert Report

In the SLR, the meta-analysis of two nested case-control studies showed no significant association between serum or plasma EPA fatty acid and prostate cancer risk.

Published meta-analysis or pooled analysis

No pooled studies were identified. A meta-analysis had been published by Sorongon-Legaspi et al (2013). The summary relative risk from five prospective nested case-control studies for the comparison of the highest to the lowest category of biomarkers of EPA (per cent) was 1.03 (95% CI 0.76-1.40) with high heterogeneity (p = 0.07).

Table 144 Studies on EPA fatty acid identified in the CUP

Author, year	Country	Study name	Cases	Years of follow up	Subgroup	RR	LCI	UCI	Contrast
Cheng, 2013	USA	Carotene and Retinol Efficacy Trial	368	Maximum 20 years	Stage I-II Gleason score <7	1.07	0.75	1.52	≥ 0.75 vs. ≤ 0.42% of total serum phospholipids
			273		Stage III-IVGleason score ≥7	1.20	0.81	1.79	
Brasky, 2011	USA	Prostate Cancer Prevention Trial	1533	7 years	Low grade	1.01	0.83	1.24	> 0.74 vs. < 0.44 % of total serum phospholipids
			125		High grade	1.09	1.63	1.86	
Park, 2009	USA	Multiethnic Cohort Study	376	1.9 years	Total	1.11	0.73	1.67	> 0.77 vs. ≤ 0.41% fatty acid composition in erythrocyte membranes
			102		Gleason score >7	1.61	0.79	3.25	> 0.66 vs. ≤ 0.46% fatty acid composition in erythrocyte membranes
Crowe, 2008	Europe	European Prospective Investigation into Cancer and Nutrition	962	4.2 years	Total	1.31	0.96	1.81	1.95-9.49 vs. 0.16-0.80 mol% of plasma phospholipids
Chavarro, 2007	USA	Physicians' Health study	476	13 years	Total	0.57	0.36	0.92	2.36 vs. 1.28 % of whole blood fatty acids

Table 145 Overall evidence on EPA fatty acid and prostate cancer

	Summary of evidence

2005 SLR	Three studies were identified during the 2005 SLR, all showed non-significant results.
Continuous Update Project	Five additional studies reported on EPA fatty acid and prostate cancer risk, all of which were included in the meta-analysis. One study reported significant increase in cancer risk, all remaining studies reported non-significant increase in prostate cancer risk. Brasky, 2011 study reported a significant inverse association with high grade cancer. A total of seven studies were included in the meta-analysis. No significant association was observed in the CUP meta-analysis.

Table 146 Summary of results of the dose response meta-analysis of EPA fatty acid and prostate cancer

Prostate cancer		
	2005 SLR	CUP
Studies (n)	2	7
Cases (n)	318	4452
Increment unit used	Per 0.1% increase	Per 0.1% increase
Overall RR (95% CI)	1.00 (0.97-1.02)	1.00 (0.99-1.01)
Heterogeneity (I^2, p-value)	0%, p = 0.33	21.2%, p = 0.27
Stratified analysis		
Advanced/high grade cancer*		
Overall RR (95% CI)		1.00 (0.99-1.01)
Heterogeneity (I^2, p-value)		0%, p = 0.50, n = 4
Non-advanced/low grade cancer*		
Overall RR (95% CI)		1.00 (1.00-1.01)
Heterogeneity (I^2, p-value)		0%, p = 0.96, n = 3

* No meta-analysis was conducted in the 2005 SLR.

Table 147 Inclusion/exclusion table for meta-analysis of EPA fatty acid and prostate cancer

WCRF code	Author	Year	Study design	Study name	Cancer outcome	2005 SLR	CUP dose-response meta-analysis	CUP HvL forest plot	Estimated values	Exclusion reasons
PRO100161	Cheng	2013	Nested case control study	Carotene and Retinol Efficacy Trial	Incidence	No	Yes	Yes	Mid-points of exposure categories, RRs for Gleason score <7 and ≥7 cancer combined using Hamling's method	
PRO100097	Brasky	2011	Nested case control study	Prostate Cancer Prevention Trial	Incidence	No	Yes	Yes	Mid-points of exposure categories, RRs for low and high grade cancer combined using Hamling's method	
PRO100213	Park	2009	Nested case control study	Multiethnic Cohort Study	Incidence	No	Yes	Yes	Mid-points of exposure categories	
PRO100030	Crowe	2008 b	Nested case control study	European Prospective Investigation into Cancer and Nutrition	Incidence	No	Yes	Yes	Cases and non-cases per quintile, mid-points of exposure categories	
PRO100027	Chavarro	2007	Nested case control study	Physicians' Health study	Incidence	No	Yes	Yes		
PRO04076	Männistö	2003	Nested case control study	ATBC	Incidence	Yes	Yes	Yes	Cases and non-cases per quintile	
PRO02352	Harvei	1997	Nested case control study	Norway 1973-1994	Incidence	Yes	Yes	Yes	Mid-points of exposure categories	
PRO02814	Gann	1994	Nested case control study	Physicians' Health study	Incidence	Yes	No	No		Superseded by Chavarro, 2007

Figure 160 Highest versus lowest forest plot of EPA fatty acid and prostate cancer

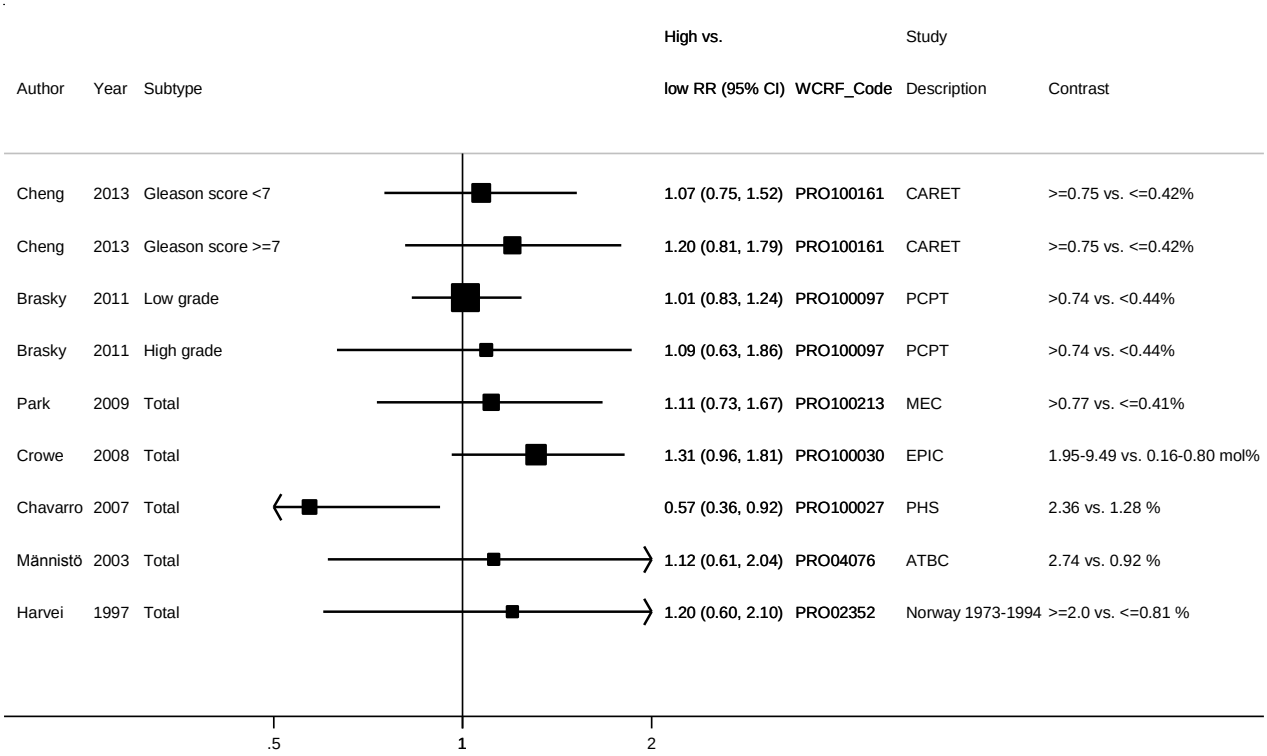


Figure 161 Dose-response meta-analysis of EPA fatty acid and prostate cancer, per 0.1% increase, stratified by cancer subtype

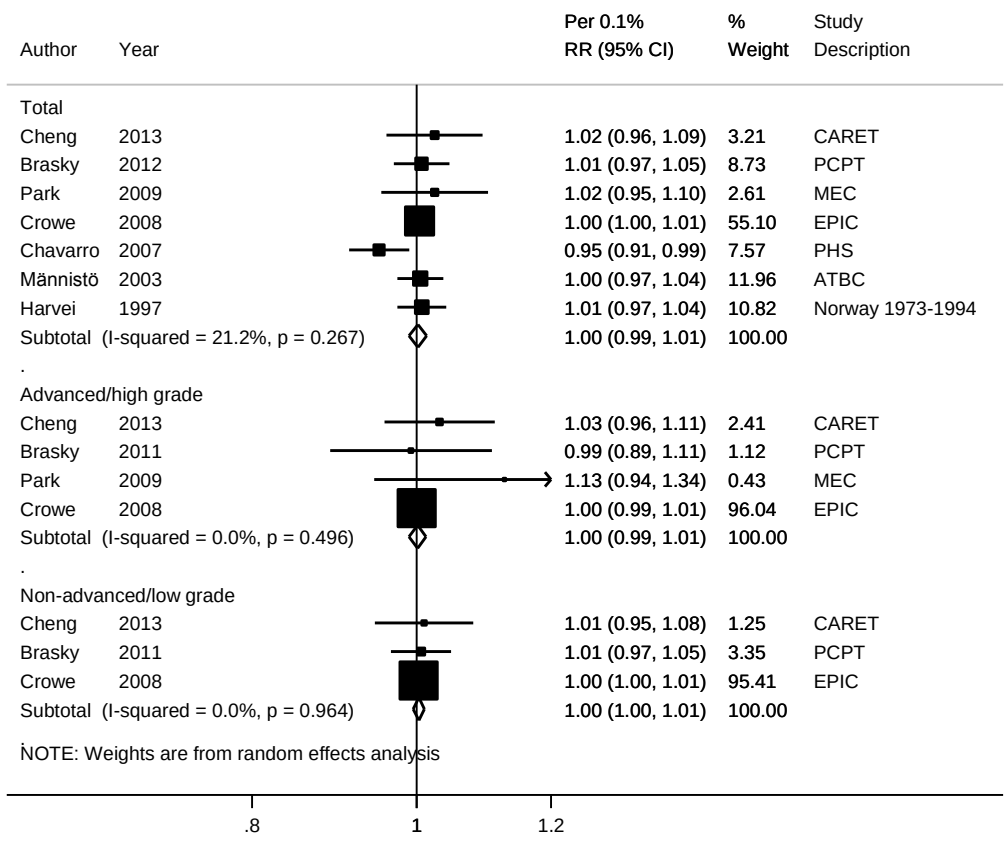
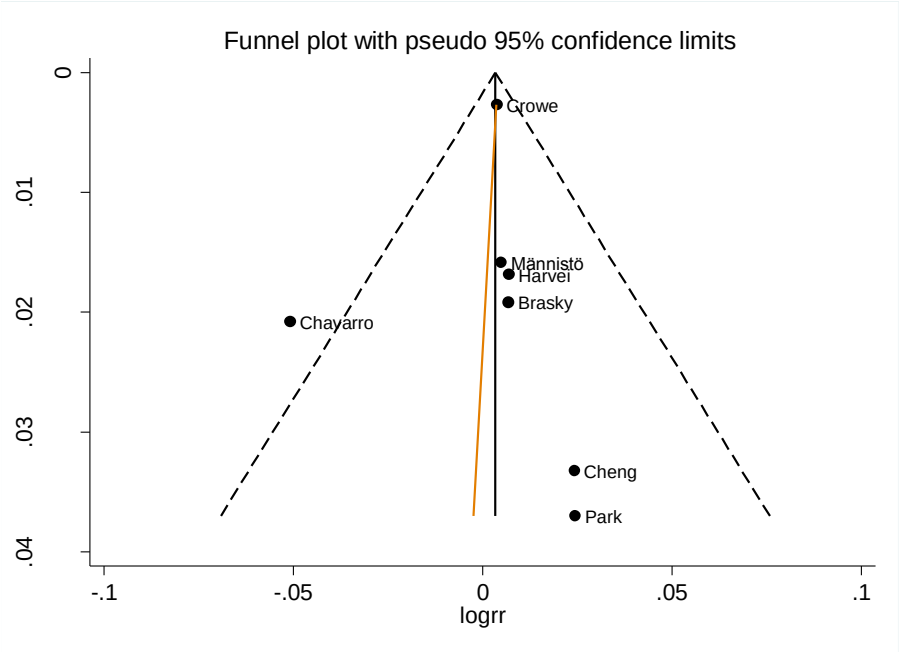
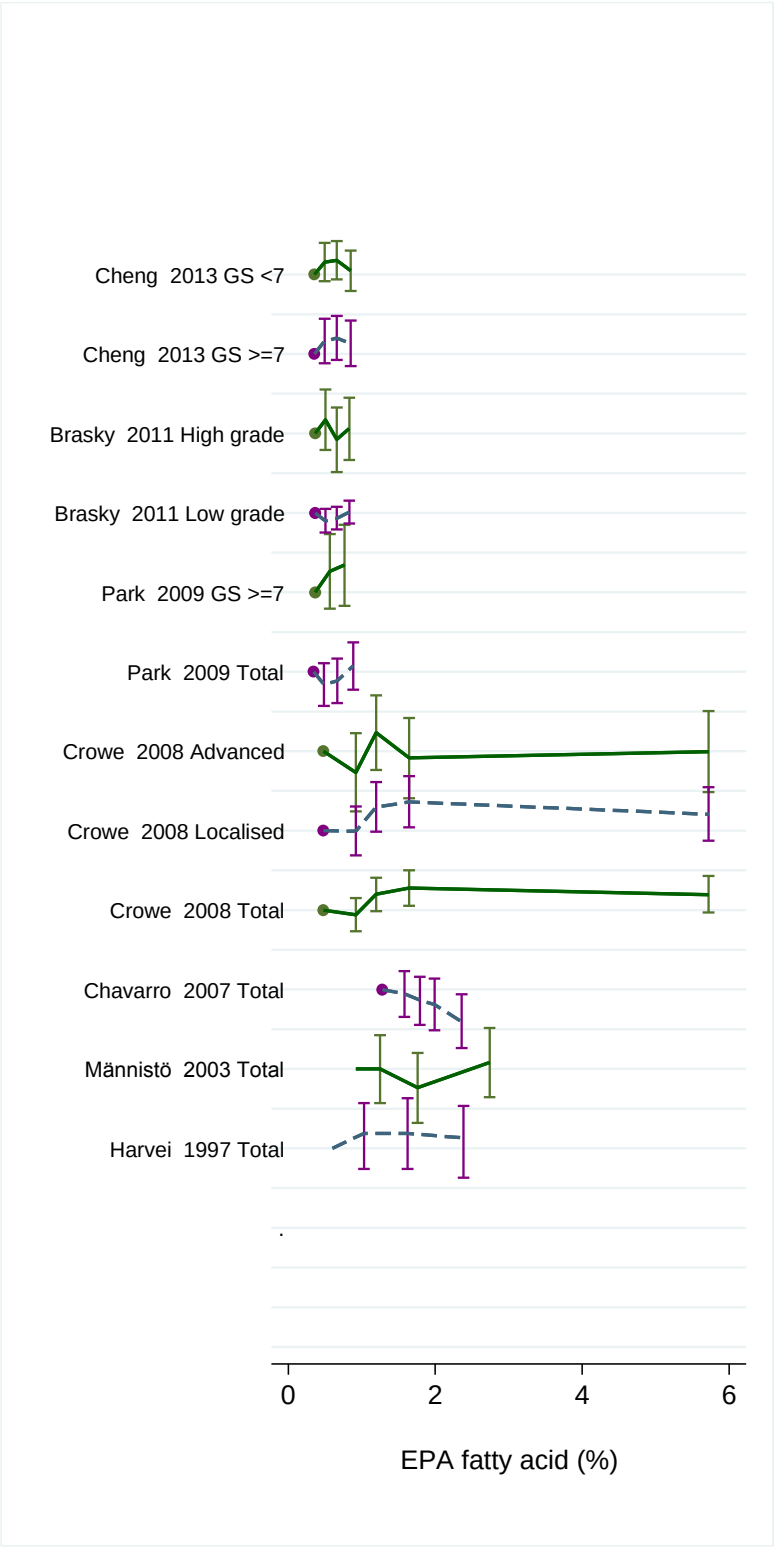


Figure 162 Funnel plot of EPA fatty acid and prostate cancer



Egger's test p = 0.78

Figure 163 Dose-response graph of EPA fatty acid and prostate cancer



5.2.4.1 Biomarkers of DHA fatty acid

Methods

Eight publications (7 cohort studies) were identified, 5 of which were identified during the Continuous Update Project. The increment unit used in the dose-response analysis was 0.5%. Four studies reported DHA fatty acid as percentage of total fatty acids in serum (Cheng et al, 2013, Brasky et al, 2011, Männistö 2003, and Harvei et al, 1997), one study in plasma (Crowe et al, 2008), one in erythrocyte membrane (Park et al, 2009) and one in whole blood (Chavarro et al, 2007). All studies were combined together.

Stratified analysis by advanced/high grade cancers and non advanced/low grade cancers were conducted. The advanced/high groups included tumours stage III/IV and Gleason ≥ 7 (Cheng et al, 2013); Gleason ≥ 8 (Brasky et al, 2011); regional or metastatics or Gleason ≥ 7 (Park et al, 2009) or T3, T4 and/or N1 and/or M1, or stage metastatic (Crowe et al, 2008b).

Brasky et al (2011) and Cheng et al (2013) reported risks for low grade, high grade and advanced/high grade-nonadvanced/low grade prostate cancers separately, respectively. Risk estimates for cancer subgroups were combined for total cancer using Hamling's method.

Main results

No significant associations were observed. The summary RR per 0.5% increase of DHA was 1.01 (95% CI 0.99-1.05, I^2 = 28.4%, $p_{heterogeneity}$ = 0.21, n = 7) for all prostate cancers, 1.07 (95% CI 0.92-1.25, I^2 = 93.3%, $p_{heterogeneity}$ < 0.001, n = 4) for advanced/high grade and 1.02 (95% CI 0.99-1.05, I^2 = 0%, $p_{heterogeneity}$ = 0.73, n = 3) for non-advanced/low grade cancer.

The Egger's test of publication bias was not significant (p=0.22)

One study of DHA fatty acids in serum reported lower values than the other studies (Männistö et al, 2003). After exclusion of this study the summary RR was 1.01 (95% CI 0.98-1.05). The summary RR did not change materially when studies were omitted in turn in the influence analysis. The summary RRs ranged from 1.01 (95% CI 0.96-1.05) when Crowe et al (2008) was omitted to 1.02 (95% CI 1.00-1.04) when Chavarro et al, 2007 was omitted.

Heterogeneity

Overall, there was low heterogeneity, I^2 = 28.4%, $p_{heterogeneity}$ = 0.21.

Comparison with the Second Expert Report

No meta-analysis was conducted in the 2005 SLR.

Published meta-analysis or pooled analysis

A meta-analysis had been published by Sorongon-Legaspi et al (2013). The summary relative risk from five prospective nested case-control studies for the comparison of the highest to the lowest category was 0.94 (95% CI 0.67-1.32) with significant heterogeneity (p = 0.02).

Table 148 Studies on serum DHA fatty acid identified in the CUP

Author, year	Country	Study name	Cases	Years of follow up	Subgroup	RR	LCI	UCI	Contrast
Cheng, 2013	USA	Carotene and Retinol Efficacy Trial	368	Maximum 20 years	Stage I-II Gleason score < 7	1.00	0.70	1.41	≥ 3.16 vs. ≤ 2.09 % of total serum phospholipids
			273		Stage III-IV Gleason score ≥ 7	1.10	0.74	1.63	
Brasky, 2011	USA	Prostate Cancer Prevention Trial	1533	7 years	Low grade	1.18	0.97	1.44	> 3.30 vs. < 2.26 % of total serum phospholipids
			125		High grade	2.5	1.34	4.65	
Park, 2009	USA	Multiethnic Cohort Study	376	1.9 years	Total	1.11	0.73	1.69	> 8 vs. ≤ 5.50 % fatty acid composition in erythrocyte membranes
			102		Gleason score ≥ 7	1.05	0.51	2.16	≥ 7.41 vs. ≤ 5.93 % fatty acid composition in erythrocyte membranes
Crowe, 2008b	Europe	European Prospective Investigation into Cancer and Nutrition	962	4.2 years	Total	1.39	1.02	1.9	5.34-10.37 vs. 1.62-3.34 mol% of plasma phospholipids
Chavarro, 2007	USA	Physicians' Health study	476	13 years	Total	0.60	0.39	0.93	3.37 vs. 1.42% of whole blood fatty acids

Table 149 Overall evidence on serum DHA fatty acid and prostate cancer

	Summary of evidence
2005 SLR	Three studies were identified during the 2005 SLR. No meta-analysis was performed. No statistically significant associations were reported.

Continuous Update Project	Five additional studies reported on DHA fatty acid and prostate cancer risk, all of which were included in the meta-analysis. One study reported significant inverse association, two studies reported significant increase in risk. In Brasky, 2011 study significantly increased risk was restricted to high grade cancer. All remaining studies found a non-significant increase in cancer risk with higher concentrations. A total of seven studies were included in the meta-analysis. No significant association was observed in the CUP meta-analysis.

Table 150 Summary of results of the dose response meta-analysis of DHA fatty acid and prostate cancer

Prostate cancer		
	2005 SLR*	CUP
Studies (n)		7
Cases (n)		4452
Increment unit used		Per 0.5% increase
Overall RR (95% CI)		1.01 (0.99-1.05)
Heterogeneity (I^2, p-value)		28.4%, p = 0.21
Stratified analysis		
Advanced/high grade cancer*		
Overall RR (95% CI)		1.07 (0.92-1.25)
Heterogeneity (I^2, p-value)		93.3%, p < 0.001, n = 4
Non-advanced/low grade cancer*		
Overall RR (95% CI)		1.02 (0.99-1.05)
Heterogeneity (I^2, p-value)		0%, p = 0.73, n = 3

* No meta-analysis was conducted in the 2005 SLR.

Table 151 Inclusion/exclusion table for meta-analysis of DHA fatty acid and prostate cancer

WCRF code	Author	Year	Study design	Study name	Cancer outcome	2005 SLR	CUP dose-response meta-analysis	CUP HvL forest plot	Estimated values	Exclusion reasons
PRO100161	Cheng	2013	Nested case control study	Carotene and Retinol Efficacy Trial	Incidence	No	Yes	Yes	Mid-points of exposure categories, RRs for aggressive (stage III/IV, Gleason >=7) and non-aggressive combined using Hamling's method	
PRO100097	Brasky	2011	Nested case control study	Prostate Cancer Prevention Trial	Incidence	No	Yes	Yes	Mid-points of exposure categories, RRs for low and high grade combined using Hamling's method	
PRO100213	Park	2009	Nested case control study	Multiethnic Cohort Study	Incidence	No	Yes	Yes	Mid-points of exposure categories	
PRO100030	Crowe	2008 b	Nested case control study	European Prospective Investigation into Cancer and Nutrition	Incidence	No	Yes	Yes	Cases and non-cases per quintile, mid-points of exposure categories	
PRO100027	Chavarro	2007	Nested case control study	Physicians' Health study	Incidence	No	Yes	Yes		
PRO04076	Männistö	2003	Nested case control study	ATBC	Incidence	Yes	Yes	Yes	Cases and non-cases per quintile	
PRO02352	Harvei	1997	Nested case control study	Norway 1973-1994	Incidence	Yes	Yes	Yes	Mid-points of exposure categories	
PRO02814	Gann	1994	Nested case control study	Physicians' Health study	Incidence	Yes	No	No		Superseded by Chavarro, 2007

Figure 164 Highest versus lowest forest plot of DHA fatty acid and prostate cancer

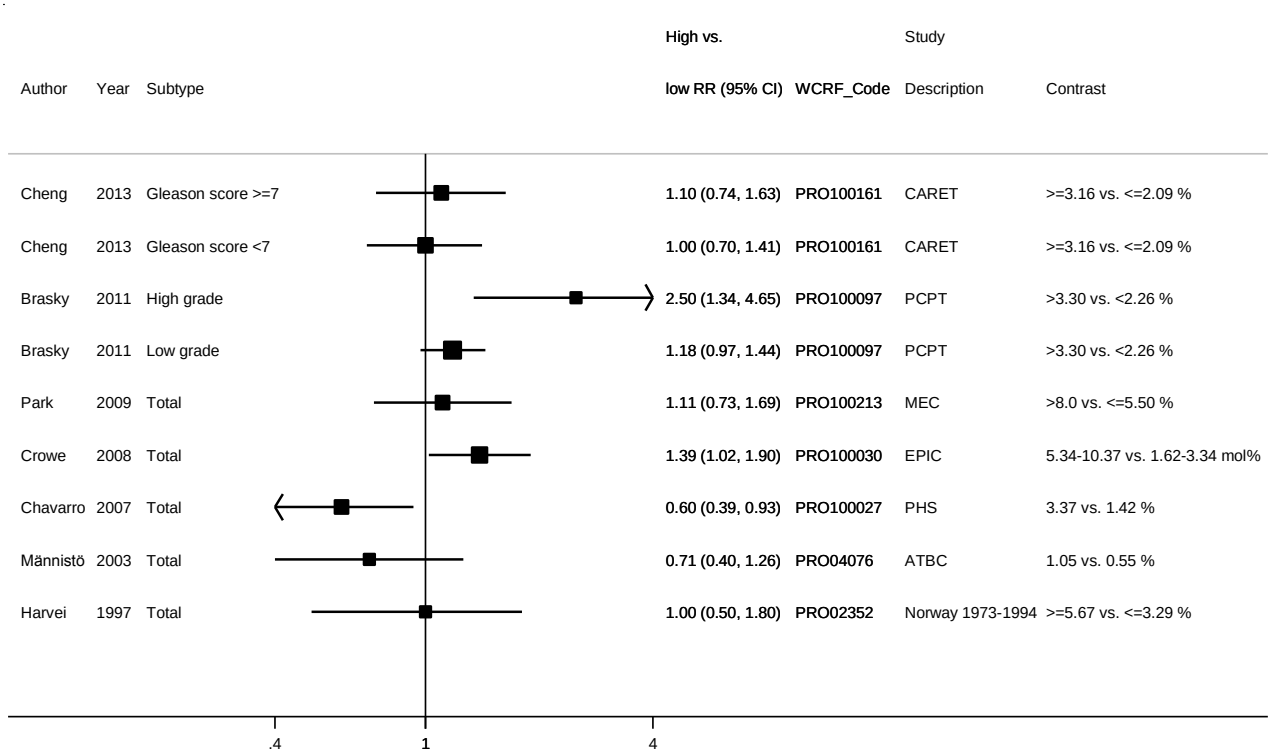


Figure 165 Dose-response meta-analysis of DHA fatty acid and prostate cancer, per 0.5% increase, stratified by cancer subtype

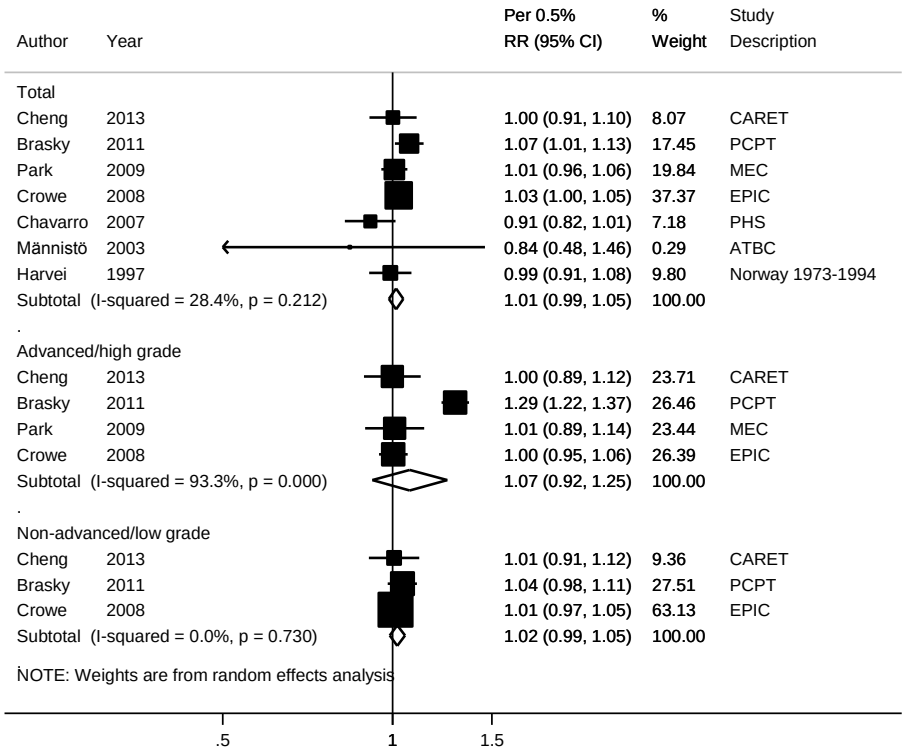
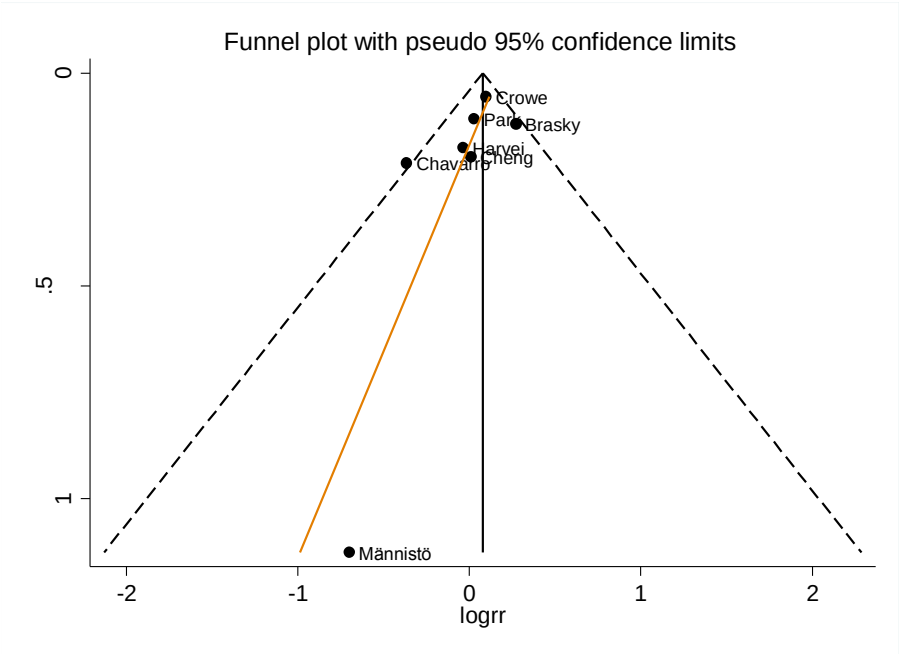
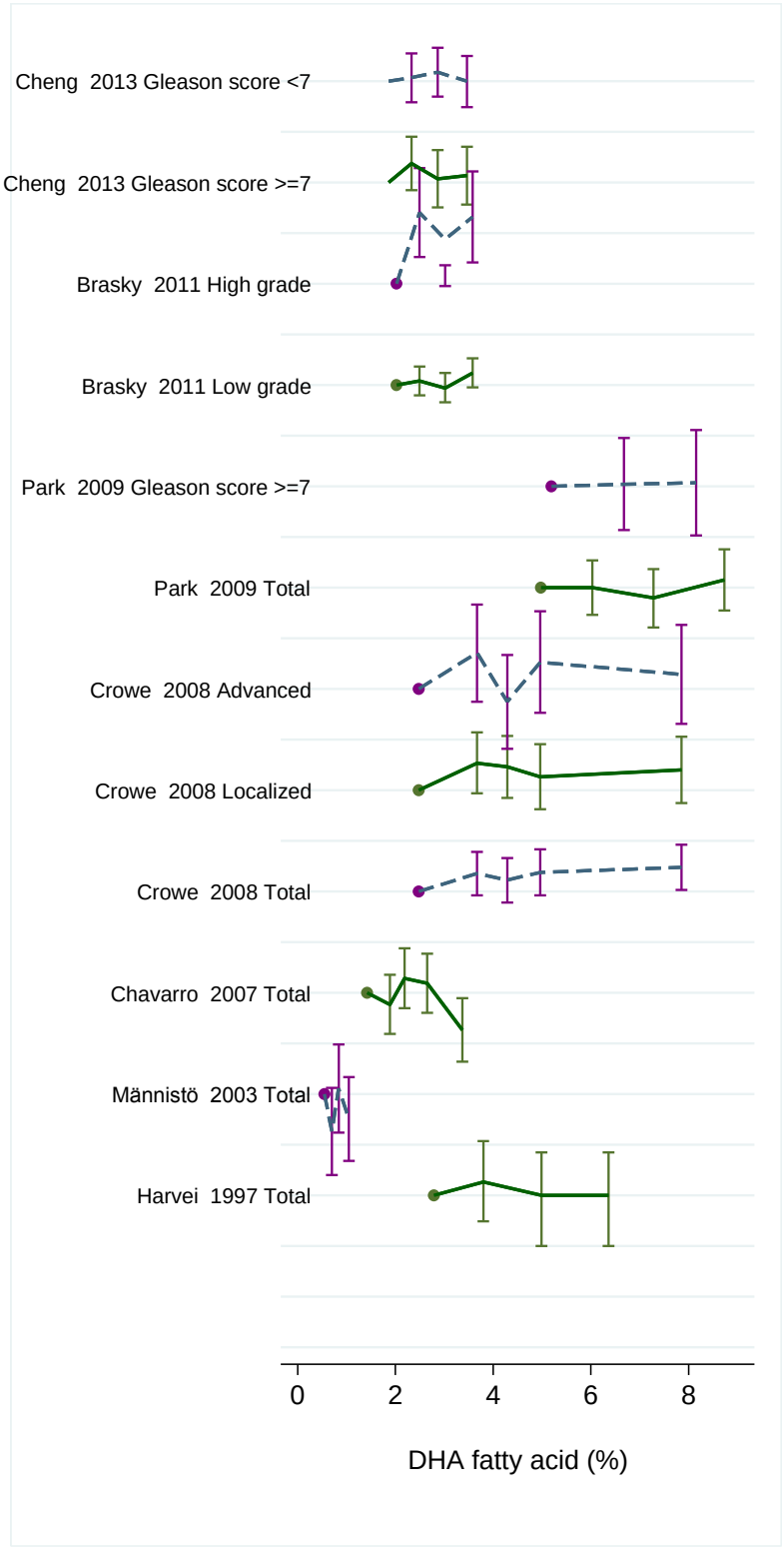


Figure 166 Funnel plot of DHA fatty acid and prostate cancer



Egger's test p = 0.22

Figure 167 Dose-response graph of DHA fatty acid and prostate cancer



5.2.4.1 Biomarkers of DPA fatty acid

Methods

Five publications (5 cohort studies) were identified, 4 of which were identified during the Continuous Update Project. The increment unit used in the dose-response analysis was 0.1%.

Two studies reported DPA fatty acid as percentage of total fatty acids in serum (Cheng et al, 2013, Harvei et al, 1997), one study in plasma (Crowe et al, 2008), one in erythrocyte membrane (Park et al, 2009) and one in whole blood (Chavarro et al, 2007). All studies were combined together.

Stratified analysis by advanced/high grade cancers and non-advanced/low grade cancers were conducted. The advanced/high groups included tumours stage III/IV and Gleason ≥ 7 (Cheng et al, 2013); regional or metastatics or Gleason ≥ 7 (Park et al, 2009) or T3, T4 and/or N1 and/or M1, or stage metastatic (Crowe et al, 2008b).

Cheng et al (2013) reported risks for stage I-II or GS <7 and stage III-IV or GS ≥7 prostate cancer separately. The two risk estimates for cancer subgroups were combined to obtain an estimate for total cancer using Hamling's method.

Main results

The summary RR per 0.1% increase of DPA was 0.96 (95% CI 0.92-1.00; I^2 = 50.7%; $p_{heterogeneity}$ = 0.09; n = 5) for all prostate cancers, 0.99 (95% CI 0.95-1.04; I^2 = 0%, $p_{heterogeneity}$ = 0.88; n = 3) for advanced/high grade and 0.98 (95% CI 0.94-1.02; I^2=0%; $p_{heterogeneity}$ = 0.67; n = 2) for non-advanced/low grade cancer.

In influence analysis, the summary RRs ranged from 0.94 (95% CI 0.89-0.99) when Crowe et al (2008) was omitted to 0.98 (95% CI 0.96-1.01) when Chavarro et al (2007) was omitted.

There was borderline statistical evidence of publication bias (Egger's test p = 0.05). The funnel plot shows that the two smaller studies are showing inverse associations that are stronger than expected by chance.

Heterogeneity

Overall, there was high heterogeneity, I^2 = 50.7%, $p_{heterogeneity}$ = 0.09.

Comparison with the Second Expert Report

No meta-analysis was conducted in the 2005 SLR.

Published meta-analysis or pooled analysis

No pooled studies were identified. A meta-analysis had been published by Sorongon-Legaspi et al (2013). The summary relative risk from four prospective nested case-control studies for the comparison of the highest to the lowest category was 0.77 (95% CI 0.61-0.99; p = 0.04) with no evidence of heterogeneity (p = 0.49).

Table 152 Studies on DPA fatty acid identified in the CUP

Author, year	Country	Study name	Cases	Years of follow up	Subgroup	RR	LCI	UCI	Contrast
Cheng, 2013	USA	Carotene and Retinol Efficacy Trial	368	Maximum 20 years	Gleason score < 7	0.89	0.64	1.24	≥ 0.91 vs. ≤ 0.71 % of total serum phospholipids
			273		Gleason score ≥ 7	0.91	0.63	1.32	
Park, 2009	USA	Multiethnic Cohort Study	376	1.9 years	Total	0.78	0.43	1.41	> 1.92 vs. ≤ 1.25 % fatty acid composition in erythrocyte membranes
			102		Gleason score ≥ 7	1.13	0.33	3.82	> 1.78 vs. ≤ 1.33 % fatty acid composition in erythrocyte membranes
Crowe, 2008b	Europe	European Prospective Investigation into Cancer and Nutrition	962	4.2 years	Total	0.95	0.65	1.39	1.45-2.59 vs. 0.44-0.98 mol% of plasma phospholipids
Chavarro, 2007	USA	Physicians' Health study	476	13 years	Total	0.60	0.38	0.93	1.19 vs. 0.77 % of whole blood fatty acids

Table 153 Overall evidence on DPA fatty acid and prostate cancer

	Summary of evidence
2005 SLR	One study was identified during the 2005 SLR. No statistically significant associations were reported.
Continuous Update Project	Four additional studies reported on DPA fatty acid and prostate cancer risk, all of which were included in the meta-analysis. Chavarro et al, 2007 reported significant inverse association for total cancer. All remaining studies found a non-significant inverse association except for Park et al, 2009 study where non-significantly increased risk was found for Gleason score ≥ 7 cancer. A total of five studies were included in the meta-analysis. A borderline inverse association was observed in the CUP meta-analysis.

Table 154 Summary of results of the dose response meta-analysis of DPA fatty acid and prostate cancer

Prostate cancer		
	2005 SLR*	CUP
Studies (n)		5

Cases (n)		2596
Increment unit used		Per 0.1% increase
Overall RR (95% CI)		0.96 (0.92-1.00)
Heterogeneity (I^2, p-value)		50.7%, p = 0.09
Stratified analysis		
Advanced/high grade cancer*		
Overall RR (95% CI)		0.99 (0.95-1.04)
Heterogeneity (I^2, p-value)		0 %, p = 0.88, n = 3
Non-advanced/low grade cancer*		
Overall RR (95% CI)		0.98 (0.94-1.02)
Heterogeneity (I^2, p-value)		0%, p = 0.67, n = 2

* No meta-analysis was conducted in the 2005 SLR.

Table 155 Inclusion/exclusion table for meta-analysis of DPA fatty acid and prostate cancer

WCRF code	Author	Year	Study design	Study name	Cancer outcome	2005 SLR	CUP dose-response meta-analysis	CUP HvL forest plot	Estimated values	Exclusion reasons
PRO100161	Cheng	2013	Nested case control study	Carotene and Retinol Efficacy Trial	Incidence	No	Yes	Yes	Mid-points of exposure categories, RRs for aggressive (stage III/IV, Gleason >=7) and non-aggressive combined using Hamling's method	
PRO100213	Park	2009	Nested case control study	Multiethnic Cohort Study	Incidence	No	Yes	Yes	Mid-points of exposure categories	
PRO100030	Crowe	2008 b	Nested case control study	European Prospective Investigation into Cancer and Nutrition	Incidence	No	Yes	Yes	Cases and non-cases per quintile, mid-points of exposure categories	
PRO100027	Chavarro	2007	Nested case control study	Physicians' Health study	Incidence	No	Yes	Yes		
PRO02352	Harvei	1997	Nested case control study	Norway 1973-1994	Incidence	Yes	Yes	Yes	Mid-points of exposure categories	

Figure 168 Highest versus lowest forest plot of DPA fatty acid and prostate cancer

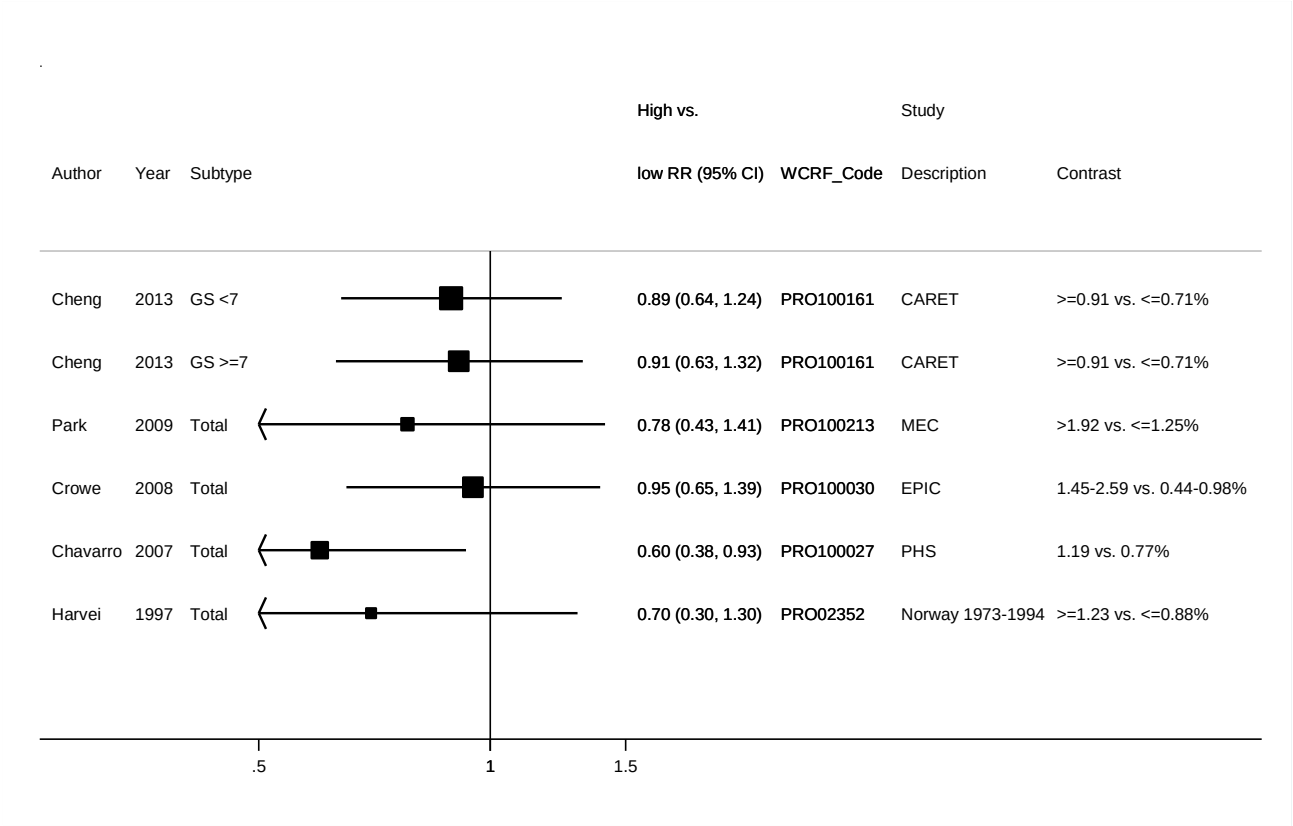


Figure 169 Dose-response meta-analysis of DPA fatty acid and prostate cancer, per 0.1% increase, stratified by cancer subtype

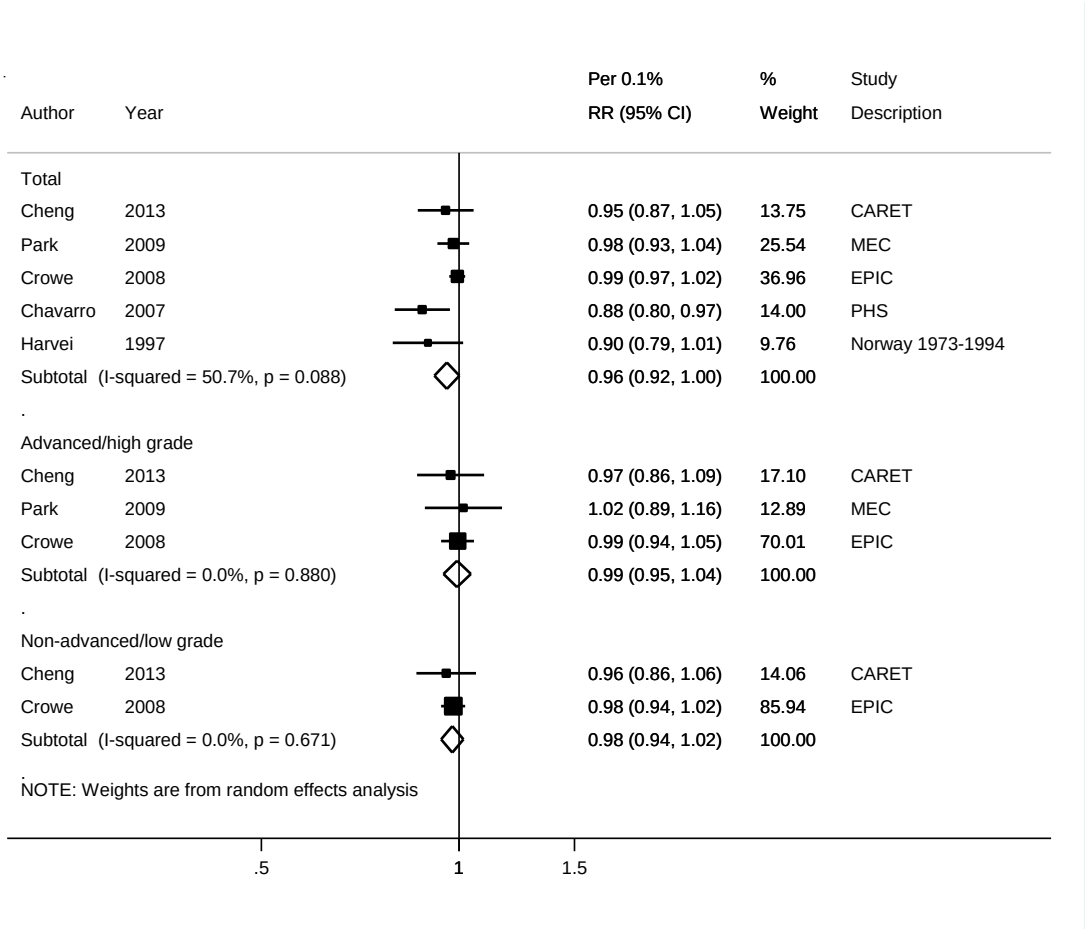
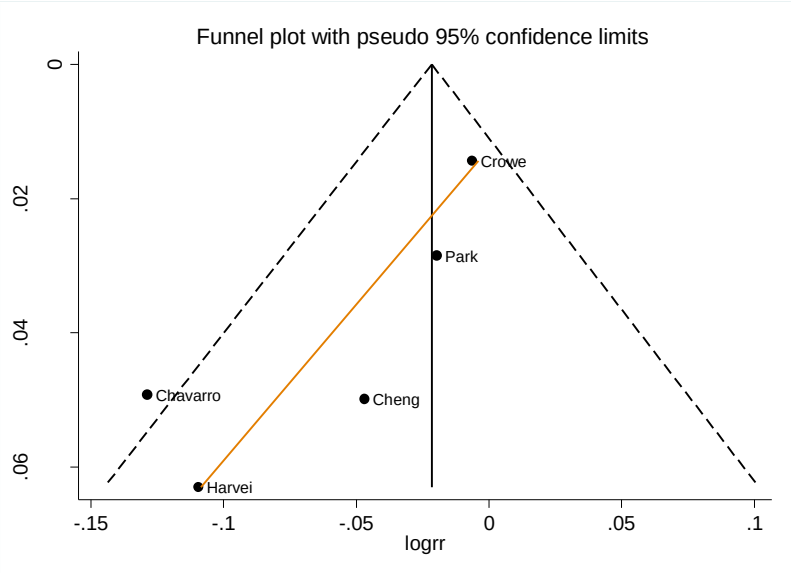
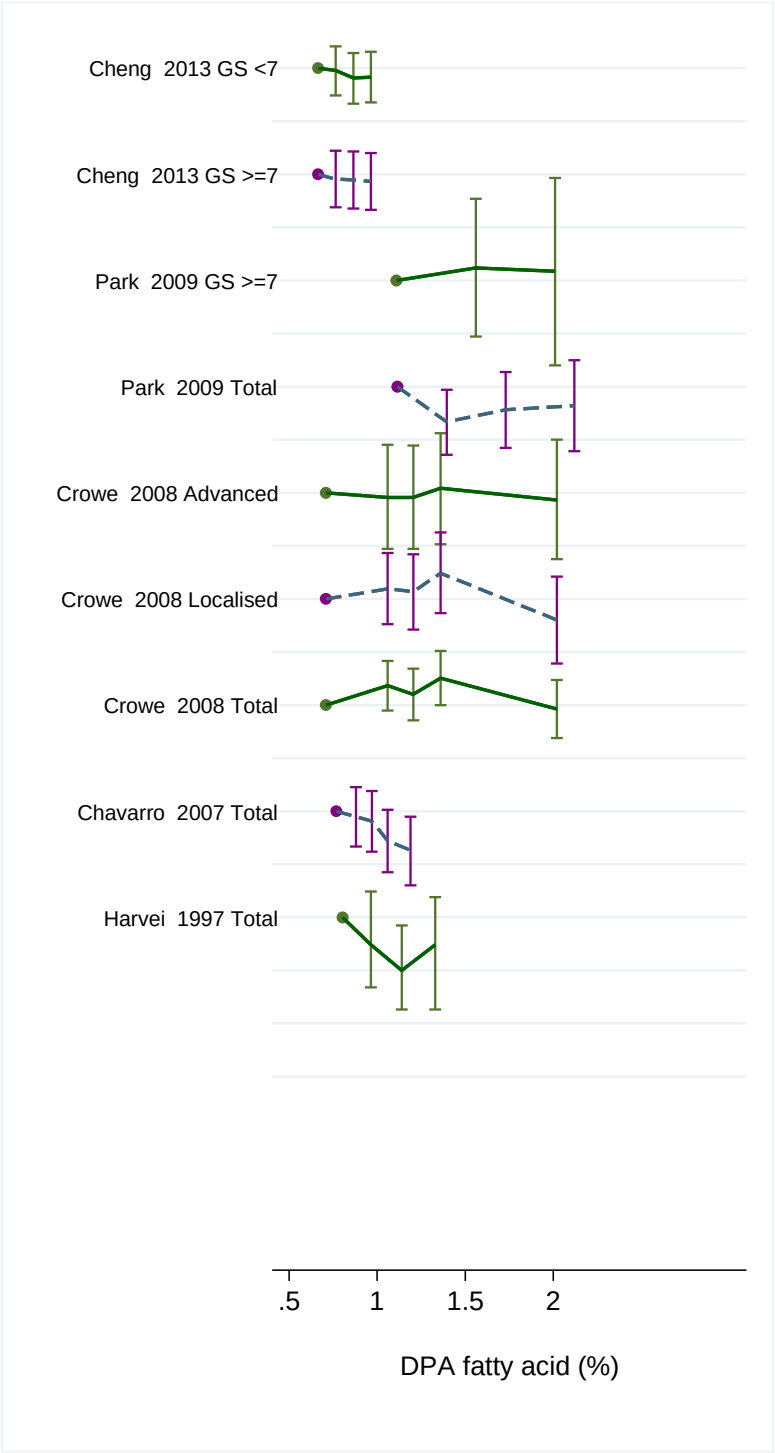


Figure 170 Funnel plot of DPA fatty acid and prostate cancer



Egger's test p = 0.05

Figure 171 Dose-response graph of DPA fatty acid and prostate cancer



5.5 Vitamins and Minerals

5.5.1.1 Serum retinol

Methods

Twenty publications from 18 cohort studies were identified; 7 publications from 6 studies were identified during the CUP. There are 2 publications from Alpha Tocopherol Beta Carotene Cancer Prevention study and 2 publications from the Maryland study. Dose-response analyses were conducted per 10 mcg/100 ml.

Two studies (Meyer et al, 2013; Karppi et al, 2012) reported serum retinol in μmol/l which was converted to mcg/100 ml by dividing the concentration in μmol/l by 0.03491.

One study (Eichholzer et al, 1999) compared the serum retinol in the lowest vs. highest quartiles which was recalculated to the highest vs. lowest, to be comparable with the other studies included in the high vs. low analysis, using the Hamling method (Hamling et al, 2008). From the studies included in the meta-analysis two studies (Mondul et al, 2011; Gill et al, 2009) reported on advanced/aggressive prostate cancer and one study reported on aggressive cancers (Schenk et al, 2009).

Overall, 11 cohort studies were included in the meta-analysis for total prostate cancer and 4 were included for advanced/aggressive prostate cancer.

Main results

The summary RR per 10 mcg/100 ml of serum retinol and total prostate cancer was 1.01 (95% CI 1.00-1.03, $I^2 = 28.9\%$, $p_{heterogeneity} = 0.17$). In influence analysis, the results were similar after omitting one study in each turn. When two studies with extreme high serum levels in the top category (Schenck et al, 2009; Gill et al, 2007) were excluded from the analysis, the RR per 10 mcg/100 ml was 1.02 (95% CI 1.01-1.03; $I^2 = 0\%$; $p_{heterogeneity} = 0.86$).

The RR per 10 mcg/100 ml was 1.00 (95% CI 0.97-1.04; $I^2=65.1\%$; $p_{heterogeneity} = 0.04$; n = 4) for advanced/aggressive cancers. The low number of studies did not allow exploration of the sources of the heterogeneity.

Heterogeneity

There was low heterogeneity ($I^2 = 28.9\%$; $p_{heterogeneity} = 0.17$). Egger'stest showed no evidence of publication bias (p = 0.17).

Comparison with the Second Expert Report

The meta-analysis on serum retinol and prostate cancer in the 2005 SLR showed a non-significant association

Published meta-analysis or pooled analysis

No published meta-analysis or pooled analysis was identified.

Table 156 Studies on serum retinol identified in the CUP

Author/year	Country	Study name	Cases	Years of follow-up	RR	LCI	UCI	Contrast
Meyer, 2013	Norway	Norway 1981-2006	2106	16.1 years	1.05	0.85	1.30	≥ 3.099 µmol/l vs. < 2.093 µmol/l
					1.09	0.97	1.21	Per µmol/l
Karppi, 2012	Finland	Kuopio Ischaemic Heart Disease Risk Factor Study	68	15 years	1.78	0.94	3.37	> 2.25 µmol/l vs. < 1.89 µmol/l
Mondul, 2011	Finland	Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study		417532 person-years	1.19	1.03	1.36	≥ 685 mcg/l vs. < 483 mcg/l
Gill, 2009	USA	Hawaii-Los Angeles Multiethnic Cohort (MEC) Study	467		1.05	0.70	1.58	163µg/dl vs. 83.5 µg/dl
Schenk, 2009	USA	Prostate, Lung, Colorectal, and Ovarian Cancer (PLCO) Screening Trial	692	8 years	0.80	0.57	1.11	≤ 262.6 ug/dl vs. ≥ 27.4 ug/dl
Ahn, 2008a	Finland	Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study	1111	12.3 years	1.14	0.98	1.33	> 632 ug/l vs. < 532 ug/l among those with no family history of prostate cancer
					2.54	1.74	3.72	> 632 ug/l vs. < 532 ug/l among those with family history of prostate cancer
Key, 2007	Europe	European Prospective Investigation into Cancer and Nutrition study	966	6 years	1.12	0.83	1.44	≥ 64.58 µg/dl vs. < 46.22 µg/dl

Table 157 Overall evidence on serum retinol and total prostate cancer

	Summary of evidence
2005 SLR	Thirteen publications (14 cohort studies) were identified during the 2005 SLR; five studies were included in the meta-analysis. One stuy showed a significant positive association.
Continuous Update Project	Seven new publications from 6 cohort studies were identified during the CUP. Overall, 11 studies were included in the meta-analysis. All except one study showed non-significant association. One study showed a positive association. A weak RR of borderline significance was obtained in the CUP meta-analysis.

Table 158 Summary of results of the dose-response meta-analysis of serum retinol and total prostate cancer

Total prostate cancer incidence and mortality		
	2005 SLR	CUP
Studies (n)	5	11
Cases (n)	1041	7168
Increment unit used	Per 10 mcg/100 ml	Per 10 mcg/100 ml
Overall RR (95% CI)	0.95 (0.76-1.22)	1.01 (1.00-1.03)
Heterogeneity (I^2, p-value)	I^2 = 93.9%, p = < 0.01	I^2 = 28.9%, p = 0.17
Stratified analysis		
Advanced/aggressive cancer		
Overall RR (95%CI)		1.00 (0.97-1.04)
Heterogeneity (I^2,p-value)		I^2 = 65.1%, p = 0.04, n = 4

Table 159 Inclusion/exclusion table for meta-analysis of serum retinol and total prostate cancer

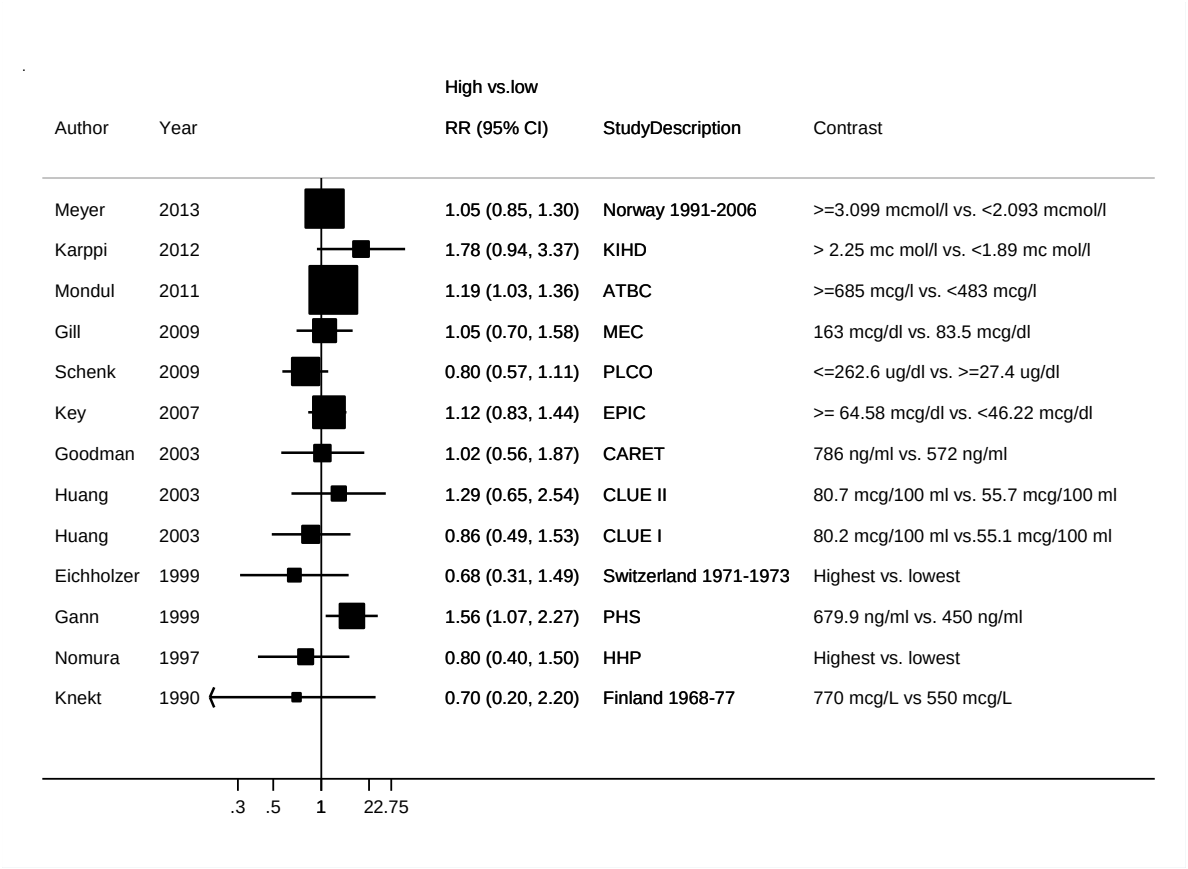
WCRF code	Author	Year	Study design	Study name	Cancer outcome	2005 SLR	CUP dose-response meta-analysis	CUP HvL forest plot	Estimated values	Exclusion reasons
PRO100166	Meyer	2013	Nested Case Control Study	Norway 1991-2006	Incidence	No	Yes	Yes	Mid-exposure values Conversion of μmol/l to μg/100ml	
PRO100165	Karppi	2012	Prospective Cohort Study	Kuopio Ischaemic Heart Disease Risk Factor Study	Incidence	No	Yes	Yes	Mid-exposure values Person years Conversion of μmol/l to μg/100ml	
PRO100092	Mondul	2011	Prospective Cohort Study	Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study	Incidence	No	Yes	Yes	Mid-exposure values	
PRO100044	Gill	2009	Nested Case Control Study	Hawaii-Los Angeles Multi-ethnic Cohort (MEC) Study	Incidence	No	Yes	Yes		
PRO100060	Schenk	2009	Nested Case Control Study	Prostate, Lung, Colorectal, and Ovarian Cancer (PLCO) Screening Trial	Incidence	No	Yes	Yes	Mid-exposure values	
PRO100022	Ahn	2008a	Prospective Cohort Study	Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study	Incidence	No	No	No		Only interactions data are shown Superseded by study of Mondul et al, 2011
PRO100008	Key	2007	Nested Case Control	European Prospective	Incidence	No	Yes	Yes	Mid-exposure values	

			Study	Investigation into Cancer and Nutrition study						
PRO00214	Goodman	2003	Nested Case Control Study	Carotene and Retinol Efficacy Trial	Incidence	Yes	Yes	Yes	Mid-exposure values	
PRO00526	Huang*	2003	Nested Case Control Study	USA Maryland 1974-1989 (Give us a CLUE to cancer; CLUE I &II)	Incidence	No	Yes	Yes	Mid-exposure values	
PRO01644	Eichholzer	2000	Prospective Cohort Study	Switzerland 1971-1973	Mortality	Yes	No	No		Only means are shown. Used Eichholzer 1999 instead
PRO01820	Gann	1999	Nested Case Control Study	Physician's Health Study	Incidence	Yes	Yes	Yes		
PRO01848	Eichholzer	1999	Prospective Cohort Study	Switzerland 1971-1973	Mortality	Yes	Yes	Yes	Person years Conversion of μmol/l to μg/100ml	
PRO02328	Nomura	1997	Nested Case Control Study	Honolulu Heart Program (Hawaii-USA)	Incidence	Yes	No	Yes		No quintile range
PRO06209	Criqui	1991	Nested Case Control Study	Lipid Research Clinics Prevalence and Follow-Up Study	Mortality	Yes	No	No		Only means are shown
PRO13415	Knekt	1990 b	Nested Case Control Study	Cancer Incidence Follow up of Finnish Mobile Clinic Health Examination Survey	Incidence	Yes	No	Yes		Only highest vs. lowest data

PRO93149	Hsing	1990a	Nested Case Control Study	USA Maryland 1974-1986	Incidence	Yes	No	No		Superseded by Huang 2003
PRO13426	Coates	1988	Nested Case Control Study	Washington State USA 1972-1984	Incidence	Yes	No	No		Only unadjusted results
PRO13478	Willett	1984	Nested Case Control Study	Hypertension Detection Follow-Up Programme	Mortality and incidence	Yes	No	No		Only means are shown
PRO10251	Peleg	1984	Nested Case Control Study	Evans County Cohort	Incidence	Yes	No	No		Only means are shown
PRO13467	Kark	1981	Nested Case Control Study	Evans County Cohort	Incidence	Yes	No	No		Only means are shown

*Huang, 2003 counted as 2 studies.

Figure 172 Highest versus lowest forest plot of serum retinol and total prostate cancer



*****In Eichholzer et al, 1999, the RR's were recalculated using Hamling method (Hamling et al, 2008).

Figure 173 Dose-response meta-analysis of serum retinol and total prostate cancer, per 10 mcg/100ml

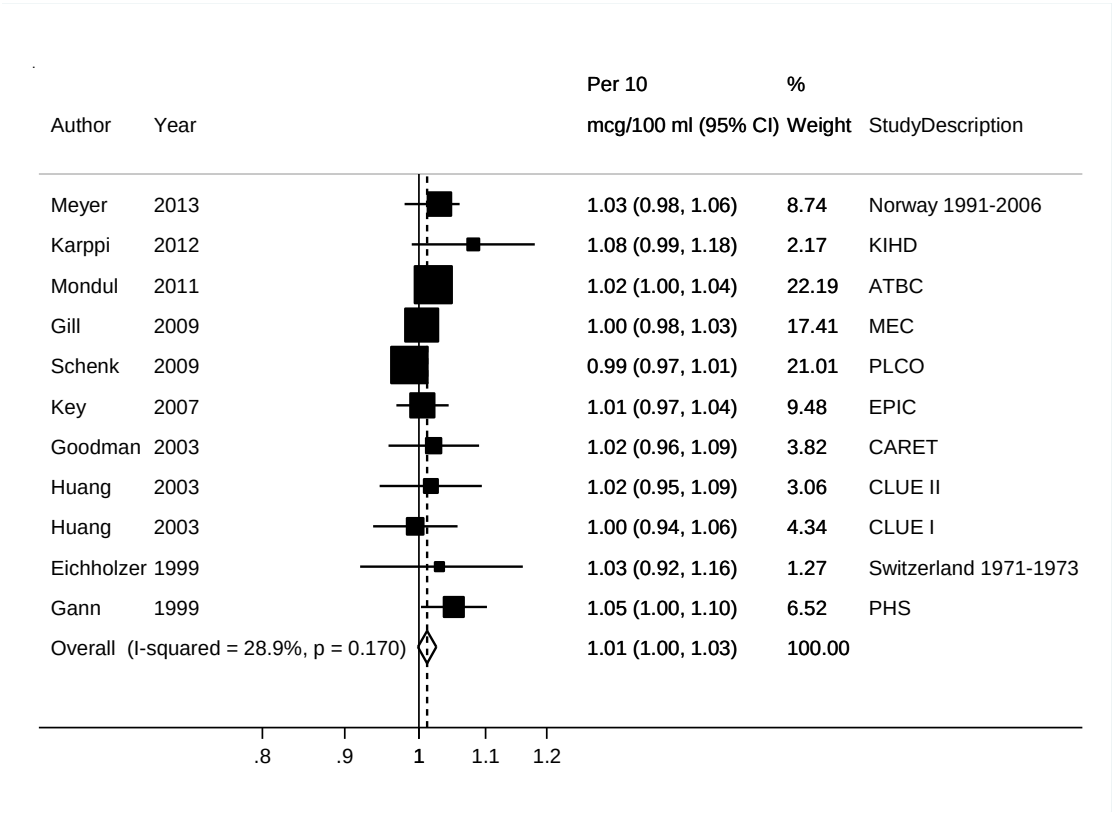
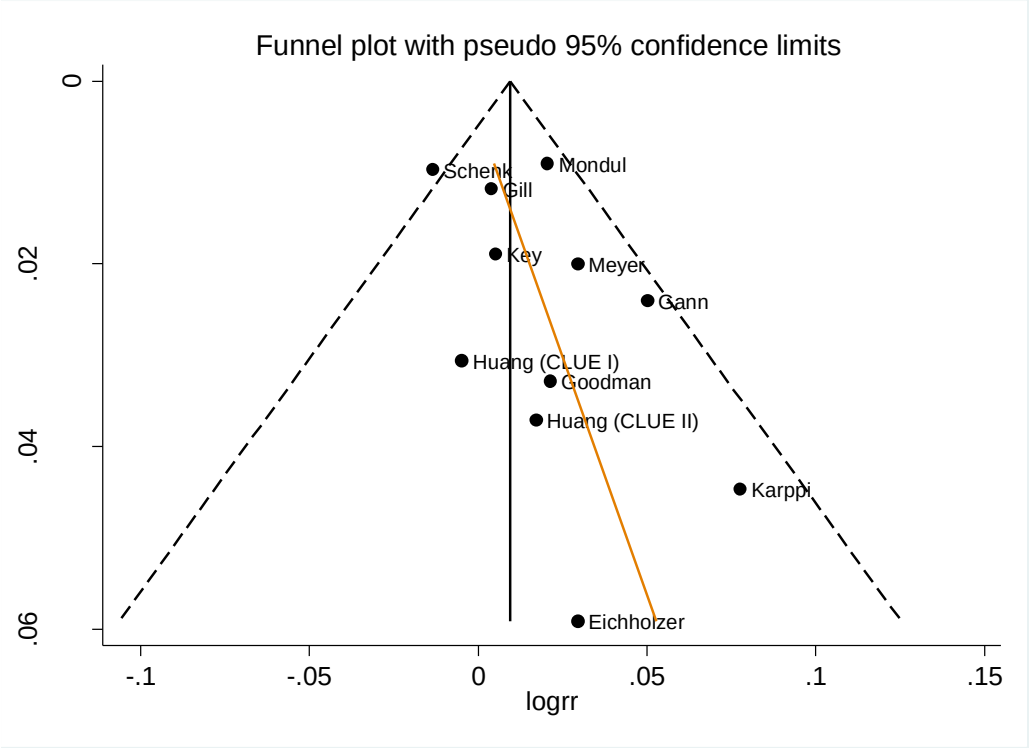


Figure 174 Funnel plot of serum retinol and total prostate cancer



Egger's test p = 0.17

Figure 175 Dose-response graph of serum retinol and prostate cancer

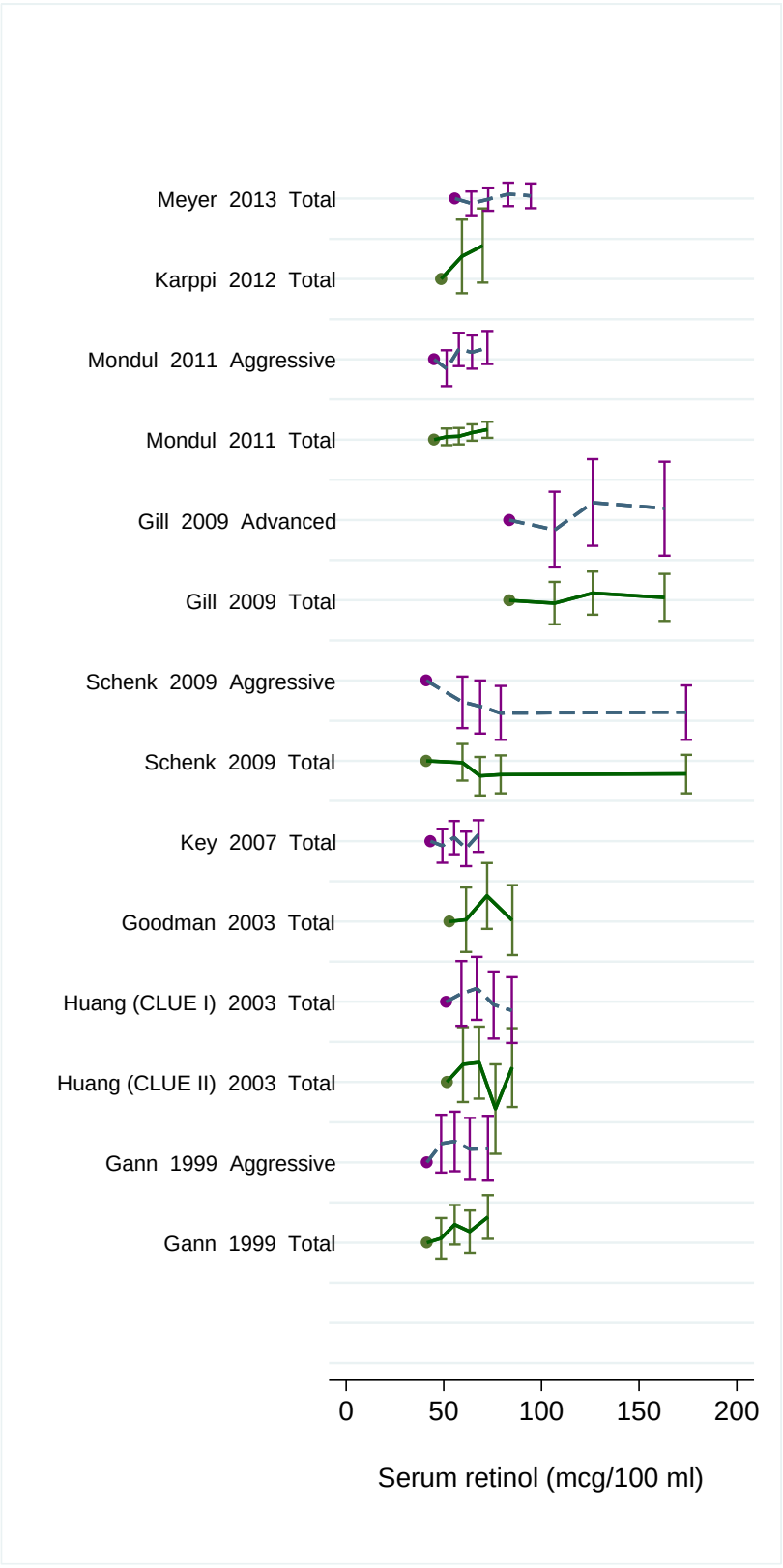
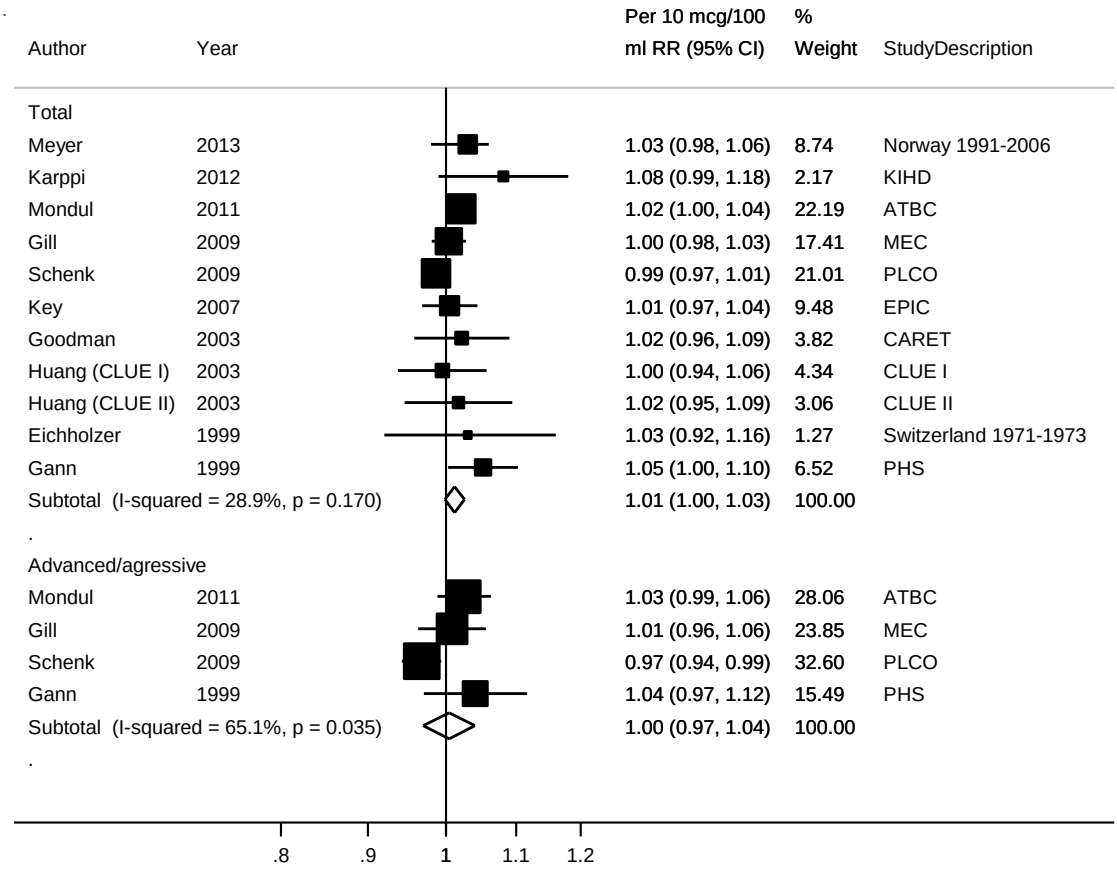


Figure 176 Dose-response meta-analysis of serum retinol and prostate cancer, per 10 mcg/100 ml stratified by cancer type



5.5.1.2 Dietary beta-carotene

Methods
Thirteen publications from 11 cohort studies were identified on dietary beta-carotene and prostate cancer, from which six studies were identified during the CUP. There are two publications from the Alpha Tocopherol Beta Carotene Cancer Prevention study and two from the Netherlands Cohort Study. Dose-response analyses were conducted for an increase of 700 mcg/day.

The Multi-ethnic Cohort (MEC) Study (Stram et al, 2006) reported the consumption of dietary beta-carotene in mcg/1000 kcal which was rescaled to mcg/day using the average energy intake provided in the same study by Sharma et al, 2013. For the Western Electric Study (Daviglus et al, 1996) the dietary beta-carotene intake in IU/day which was converted to mcg/day using IU/1.66 as equivalent to 1 mcg.

Overall, 10 cohort studies were included in dose-response analysis for total prostate cancer. No meta-analysis could be conducted on advanced or aggressive prostate cancer.

Main results
The summary RR of total prostate cancer per 700 mcg/day increase of dietary beta-carotene was 1.00 (95% CI 0.99-1.00; $I^2 = 0\%$; $p_{heterogeneity} = 0.92$).
In influence analysis the results were similar when the studies on mortality as outcome, were excluded from the analysis.

Heterogeneity
There was no evidence of heterogeneity ($I^2 = 0\%$, $p_{heterogeneity}=0.92$). Egger'stest showed no evidence of publication bias (p = 0.13).

Comparison with the Second Expert Report
In the 2005 SLR the meta-analysis on serum beta-carotene and prostate cancer showed a non-significant association.

Published meta-analysis or pooled analysis
No published meta-analysis or pooled analysis was identified.

Table 160 Studies on dietary beta-carotene identified in the CUP

Author/year	Country	Study name	Cases	Years of follow-up	RR	LCI	UCI	Contrast
Roswall, 2013	Denmark	Diet, Cancer and Health Cohort Study	1571	14.3 years	1.02	0.87	1.21	> 4650.2 µg/day vs. ≤ 1598.6 µg/day
					0.99	0.93	1.06	Per 5000 µg/day

Geybels, 2012	Netherlands	Netherlands Cohort Study	3451	17.3 years	0.96	0.82	1.13	4.5 mg/day vs. 1.6 mg/day
Batty, 2011	UK	Whitehall study	578	40 years	1.33	0.67	2.64	> 2403 µg/day vs. < 1082 µg/day
					1.01	0.79	1.30	Per 2665 µg/day
Ambrosini, 2008	Australia	Wittenoom Gorge, West Australian 1990-2004	97	12.7 years	0.96	0.58	1.61	> 4.6 mg/day vs. 0.1 mg/day
Kirsh, 2006	USA	Prostate, Lung, Colorectal, and Ovarian Cancer (PLCO) Screening Trial	1338	8 years	0.96	0.80	1.15	7744 µg/day vs. 2180 µg/day
Stram, 2006	USA	Hawaii-Los Angeles Multi-ethnic Cohort (MEC) Study	3922	>7 years	0.99	0.89	1.10	> 2822.1 µg/1000kcal vs. ≤998.2 µg/1000kcal

Table 161 Overall evidence on dietary beta-carotene and total prostate cancer

	Summary of evidence
2005 SLR	Seven studies were identified during the 2005 SLR; 6 were included in the meta-analysis. A non-significant association was found.
Continuous Update Project	Six additional studies were identified during the CUP. Overall, 10 studies were included in the meta-analysis. A non-significant association was found.

Table 162 Summary of results of the dose-response meta-analysis of dietary beta-carotene and total prostate cancer

Total prostate cancer incidence and mortality		
	2005 SLR	CUP
Studies (n)	6	10
Cases (n)	2101	12219
Increment unit used	Per 700 µg RDA/day	Per 700 µg/day
Overall RR (95% CI)	1.00 (0.99-1.01)	1.00 (0.99-1.00)
Heterogeneity (I^2, p-value)	I^2 = 0%, p = 0.99	I^2 = 0%, p = 0.92

Table 163 Inclusion/exclusion table for meta-analysis of dietary beta-carotene and total prostate cancer

WCRF code	Author	Year	Study design	Study name	Cancer outcome	2005 SLR	CUP dose-response meta-analysis	CUP HvL forest plot	Estimated values	Exclusion reasons
PRO100159	Roswall	2013	Prospective Cohort Study	Diet, Cancer and Health Cohort Study	Incidence	No	Yes	Yes	Mid-exposure values Person years	
PRO100198	Geybels	2012	Case-cohort Study	Netherlands Cohort Study	Incidence	No	Yes	Yes	Mid-exposure values	
PRO100170	Batty	2011	Prospective Cohort Study	Whitehall Study	Mortality	No	Yes	Yes	Mid-exposure values	
PRO99954	Ambrosini	2008	Nested Case Control Study	Wittenoom Gorge, West Australian 1990-2004	Incidence	No	Yes	Yes	Mid-exposure values	
PRO99992	Kirsh	2006	Prospective Cohort Study	Prostate, Lung, Colorectal, and Ovarian Cancer (PLCO) Screening Trial	Incidence and Mortality	No	Yes	Yes	Person years	
PRO99986	Stram	2006	Prospective Cohort Study	Hawaii-Los Angeles Multi-ethnic Cohort (MEC) Study	Incidence and Mortality	No	Yes	Yes	Person years Number of cases per quintiles Conversion of µg/ 1000 kcal to µg/day	
PRO00272	Woodson	2003	Nested Case Control Study	Alpha Tocopherol Beta Carotene Cancer	Incidence and Mortality	Yes	No	No		Only means are shown

				Prevention Study						
PRO00764	Schuurman	2002	Case-cohort Study	Netherlands Cohort Study	Incidence	Yes	No	No		Superseded by study of Geybels et al, 2012
PRO01034	Hirvonen	2001	Prospective Cohort Study	Alpha Tocopherol Beta Carotene Cancer Prevention Study	Incidence and Mortality	Yes	No	No		Only median is shown Supersede by Woodson et al, 2003 study
PRO02487	Daviglus	1996	Prospective Cohort Study	Western Electric Study	Incidence	Yes	Yes	Yes	Mid exposure values Conversion of IU to µg/day	
PRO02629	Giovannucci	1995	Prospective Cohort Study	Health Professionals Follow-up Study	Incidence	Yes	Yes	Yes	Mid exposure values	
PRO13404	Shibata	1992	Prospective Cohort Study	USA California 1981-1985	Incidence and Mortality	Yes	Yes	Yes	Person years	
PRO03129	Hsing	1990 b	Prospective Cohort Study	Lutheran Brotherhood Cohort Study	Mortality	Yes	Yes	Yes	Mid exposure values Person years Confidence intervals Number of cases per quartiles	

Figure 177 Highest versus lowest forest plot of dietary beta-carotene and total prostate cancer

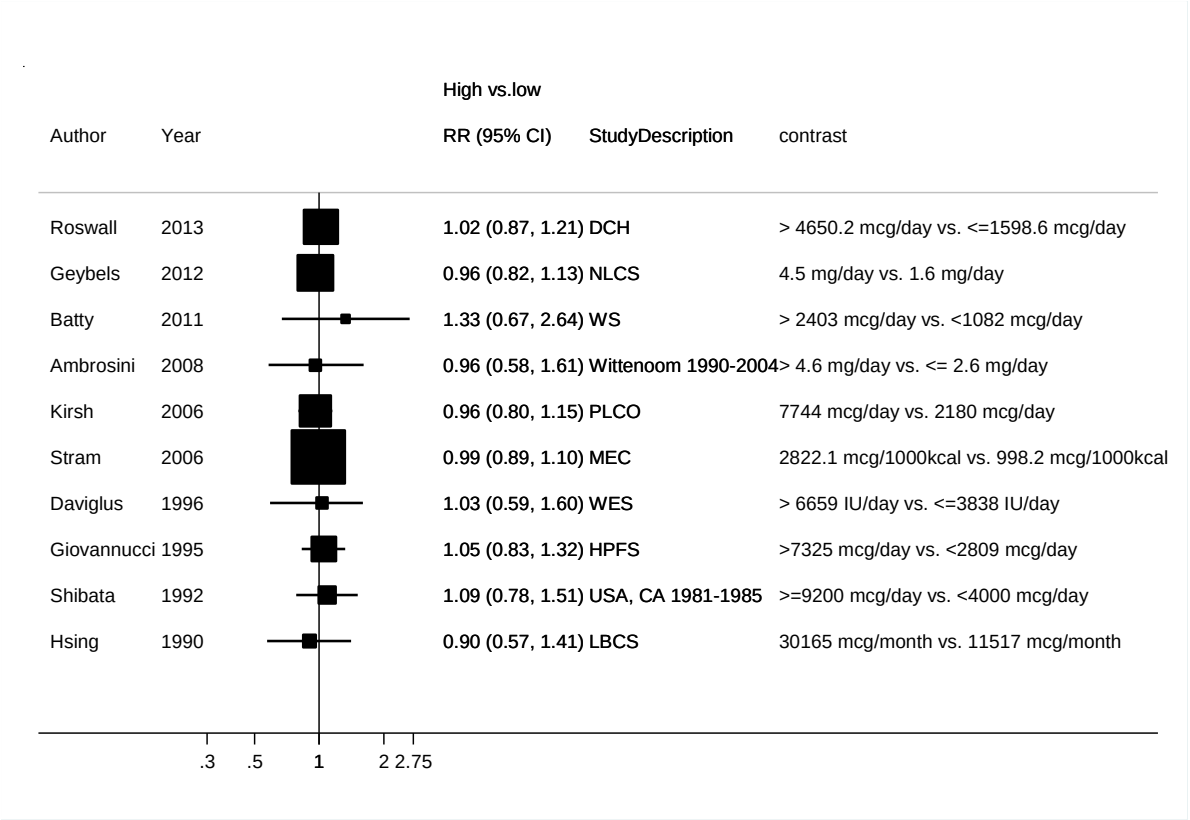


Figure 178 Dose-response meta-analysis of dietary beta-carotene and total prostate cancer, per 700 µg/day

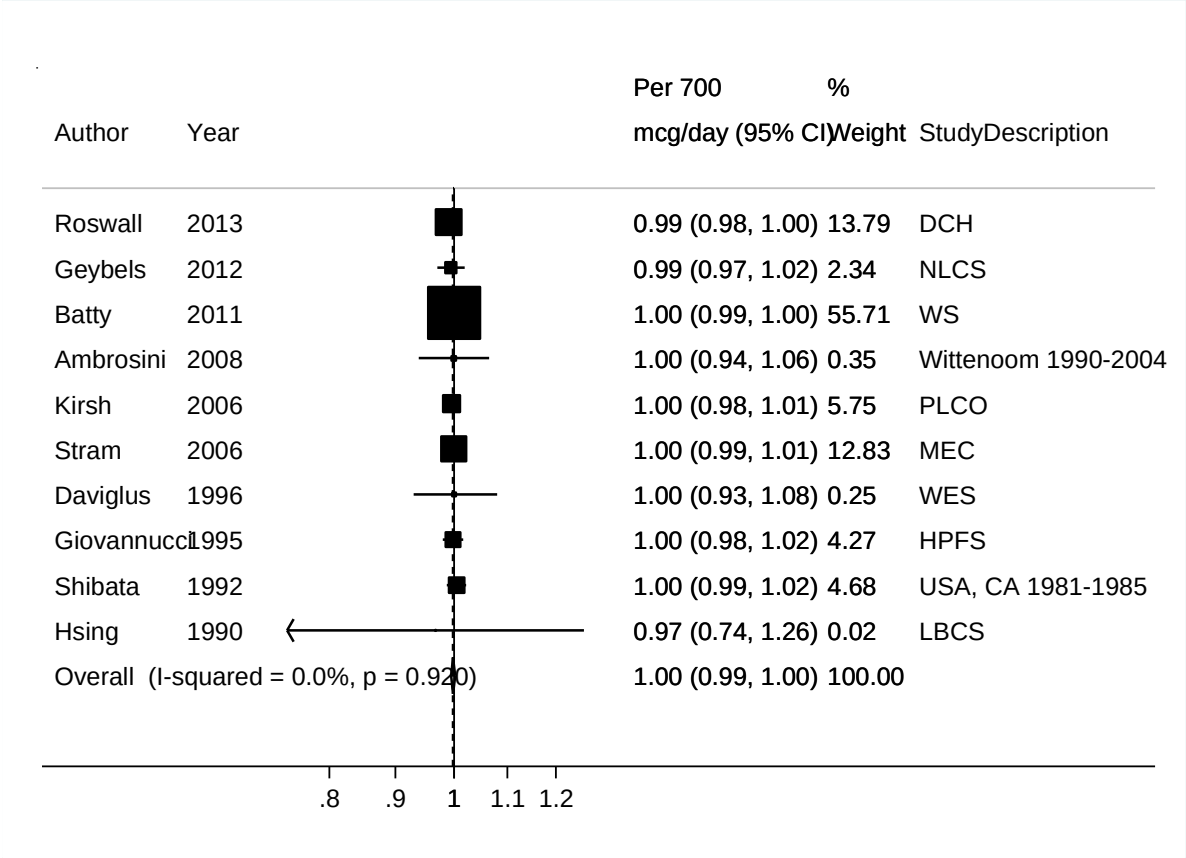
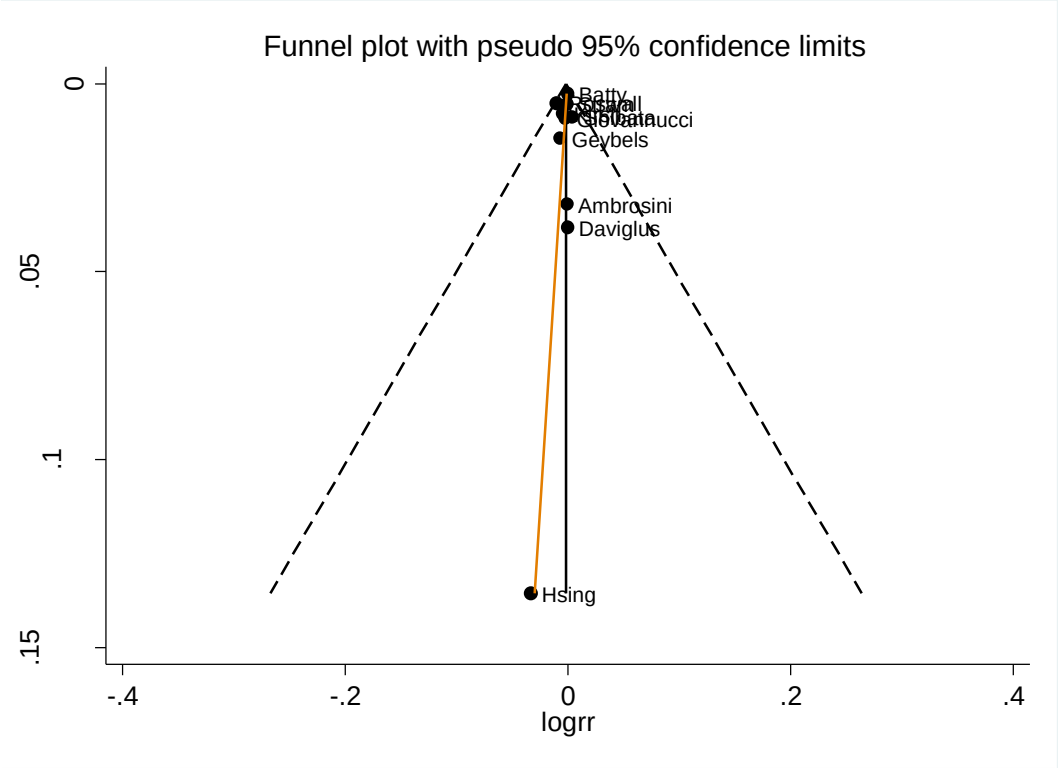
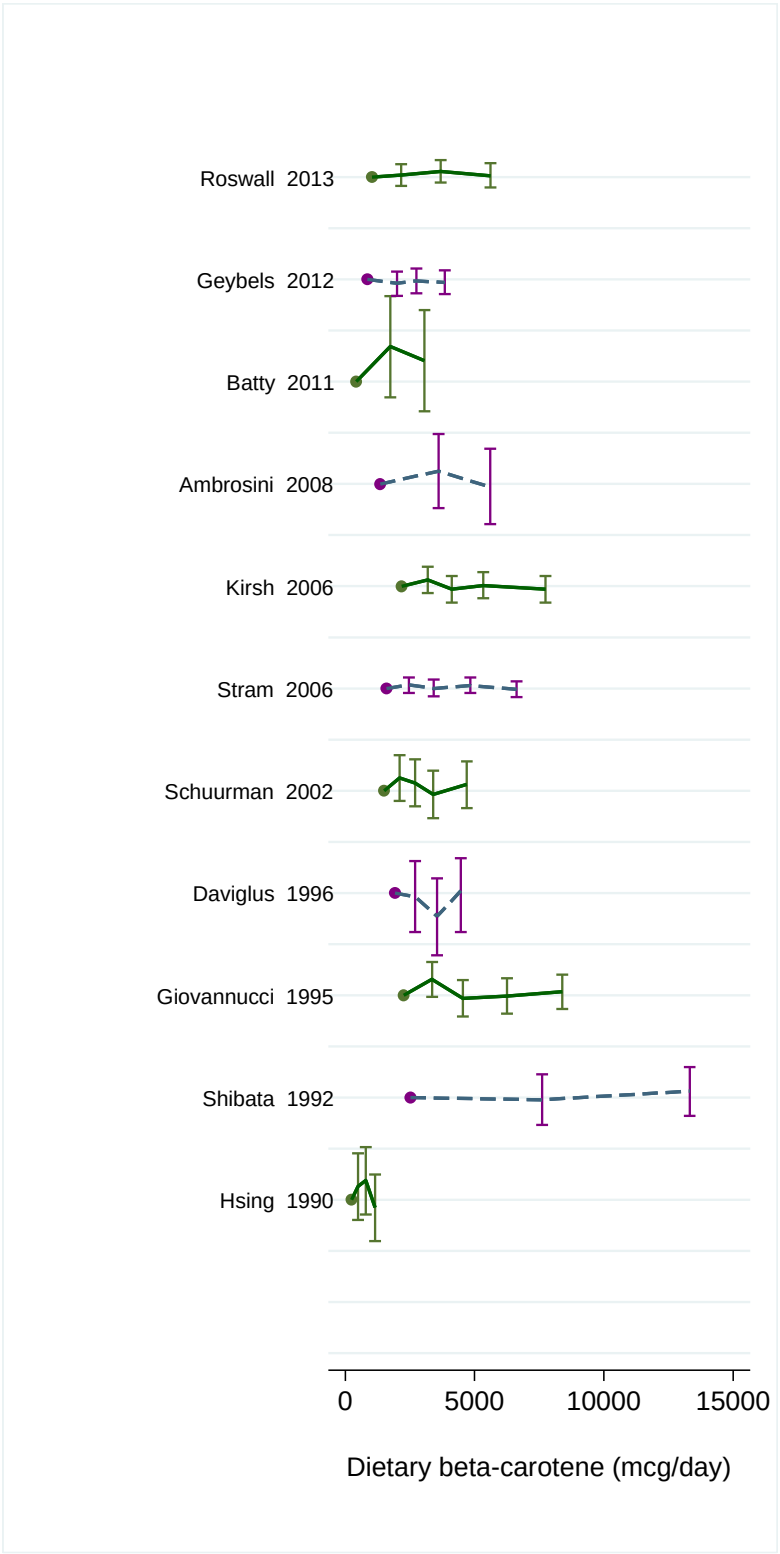


Figure 179 Funnel plot of dietary beta-carotene and total prostate cancer



Egger's test p = 0.13

Figure 180 Dose-response graph of dietary beta-carotene and prostate cancer



5.5.1.2 Supplemental beta-carotene

Methods

Five cohort studies were identified, three of them during the CUP.

Main results

No association of beta-carotene supplement and prostate cancer risk was observed in any of the identified studies.

Comparison with the Second Expert Report

There was substantial evidence of lack of protective effect and limited evidence to draw conclusions about a harmful effect of beta-carotene on prostate cancer.

Published meta-analysis or pooled analysis

A meta-analysis of three follow-up studies reported a RR of 1.18 (95% CI 0.61-2.30) (Stratton, 2011)

Table X Overall evidence on supplemental beta-carotene and prostate cancer

	Summary of evidence
2005 SLR	Two studies were identified. None reported significant associations.
Continuous Update Project	Three studies were identified. Only one reported an increased risk during follow-up in particpants of an intervention trial of beta-carotene in the intervention group, but only among people with family history of prostate cancer.

Table 164 Studies on supplemental beta-carotene identified in the CUP and SLR

Author, year	Country	Study name	Cases	Years of follow up	RR	LCI	UCI	Contrast
Roswall, 2013	Denmark	Diet, Cancer and Health cohort study	1571	14.3 years	1.17	0.56	2.41	>5615 vs. 0 mcg/day
					1.14	0.86	1.52	Per 5000 mcg/day
Ahn, 2008	Finland	Alpha-Tocpherol Beta-Carotene Cancer Prevention	1111	12.23 years	1.09	0.97	1.23	Yes (20 mg/day) with no family history of prostate cancer

		(ATBC)			1.98	1.37	1.86	No supplement with family history vs. no supplement and no family history of cancer
					2.02	1.42	2.88	Yes (20 mg/day) with family history of cancer vs. no supplement and no famiy history of cancer
Kirsh, 2006	USA	Prostate, Lung, Colorectal, and Ovarian (PLCO) Cancer Screening Trial	1338	8 years	0.82	0.65	1.04	≥2000 vs. 0 mcg/day
Wu, 2004	USA	Health Professionals Follow-up Study (HPFS)	450	~12 years	NA	-	-	Cases were more likely take beta-carotene supplements (24%) than controls (20%)
Cook 1999	USA	Physicians' Health Study	631	12 years	1.33	0.91	1.96	Highest vs. lowest
					1.33	0.74	2.37	Highest vs. lowest for aggressive prostate cancer
					1.00	0.56	1.76	Highest vs. lowest for non-aggressive prostate cancer

5.5.1.2 Serum alpha-carotene

Methods
Nine publications (9 studies) on serum alpha-carotene and prostate cancer were identified; three studies were identified during the CUP.

Overall, 7 cohort studies were included in dose-response analysis for total prostate cancer. Dose-response analyses were conducted per 10 mcg/100 ml. Two studies reported on advanced/aggressive prostate cancer (Peters et al, 2007; Gann et al, 1999). No meta-analysis could be conducted on advanced or aggressive prostate cancer.

Main results
The summary RR per 10 mcg/100 ml of serum alpha-carotene and prostate cancer risk was 1.06 (95% CI 0.94-1.21; $I^2 = 0\%$; $p_{heterogeneity} = 0.44$).

Heterogeneity
There was no heterogeneity ($I^2 = 0\%$; $p_{heterogeneity} = 0.44$). Egger's test showed no evidence of publication bias ($p = 0.64$).

Comparison with the Second Expert Report
In the 2005 SLR the meta-analysis on serum alpha-carotene and prostate cancer showed a non-significant inverse association.

Published meta-analysis or pooled analysis
No published meta-analysis or pooled analysis was identified.

Table 165 Studies on serum alpha-carotene identified in the CUP

Author/year	Country	Study name	Cases	Years of follow-up	RR	LCI	UCI	Contrast
Karppi, 2012	Finland	Kuopio Ischaemic Heart Disease Risk Factor Study	68	15 years	2.05	0.96	4.36	> 0.11 µmol /L vs. < 0.06 µmol/L
Key, 2007	Europe	European Prospective Investigation into Cancer and Nutrition	966	6 years	1.20	0.87	1.66	≥ 10.51 µg/dl vs. < 2.59 µg/dl
Peters, 2007	USA	Prostate, Lung, Colorectal, and Ovarian Cancer (PLCO) Screening Trial	692	1-8 years	1.18	0.85	1.64	16.6 µg/dl vs. 2.6 µg/dl

Table 166 Overall evidence on serum alpha-carotene and total prostate cancer

	Summary of evidence
2005 SLR	Seven cohorts (from 6 publications) were identified during the 2005 SLR; 5 studies were included in the meta-analysis. A non-significant association was found.
Continuous Update Project	Three new studies were identified during the CUP. Overall, seven studies were included in the meta-analysis, all showed non-significant associations. No significant association was observed in the CUP meta-analysis.

Table 167 Summary of results of the dose-response meta-analysis of serum alpha-carotene and total prostate cancer

Total prostate cancer incidence		
	2005 SLR	CUP
Studies (n)	5	7
Cases (n)	1249	2833
Increment unit used	Per 10 μg/100 ml	Per 10 μg/100 ml
Overall RR (95% CI)	0.87 (0.68-1.12)	1.06 (0.94-1.21)
Heterogeneity (I^2, p-value)	I^2 = 0%, p = 0.76	I^2 = 0%, p = 0.44

Table 168 Inclusion/exclusion table for meta-analysis of serum alpha-carotene and total prostate cancer

WCRF code	Author	Year	Study design	Study name	Cancer outcome	2005 SLR	CUP dose-response meta-analysis	CUP HvL forest plot	Estimated values	Exclusion reasons
PRO100165	Karppi	2012	Prospective Cohort Study	Kuopio Ischaemic Heart Disease Risk Factor Study	Incidence	No	Yes	Yes	Person-years Conversion of µmol /l to µg/100ml	
PRO100008	Key	2007	Nested Case Control Study	European Prospective Investigation into Cancer and Nutrition	Incidence	No	Yes	Yes	Mid exposure values	
PRO99969	Peters	2007	Nested Case Control Study	Prostate, Lung, Colorectal, and Ovarian Cancer (PLCO) Screening Trial	Incidence	No	Yes	Yes		
PRO03999	Wu	2004	Nested Case Control Study	Health Professionals Follow-up Study	Mortality and incidence	Yes	No	Yes		Only Medians are shown.
PRO00214	Goodman	2003	Nested Case Control Study	Beta-Carotene and Retinol Efficacy Trial	Incidence	Yes	Yes	Yes	Mid exposure values Number of cases per quartiles Conversion of ng/ml to µg/100ml	
PRO00526	Huang*	2003	Nested Case Control Study	USA Maryland 1974-1989 (Give us a CLUE to cancer; CLUE I &II)	Incidence	Yes	Yes	Yes	Mid exposure values	

PRO01820	Gann	1999	Nested Case Control Study	Physician's Health Study	Incidence	Yes	Yes	Yes		
PRO02328	Nomura	1997	Nested Case Control Study	Honolulu Heart Program (Hawaii, USA)	Incidence	Yes	No	Yes		No quintile range
PRO93149	Hsing	1990a	Nested Case Control Study	USA Maryland 1974-1986	Incidence	Yes	No	No		Superseded by study of Huang et al, 2003

*Huang, 2003 counted as 2 studies.

Figure 181 Highest versus lowest forest plot of serum alpha-carotene and total prostate cancer

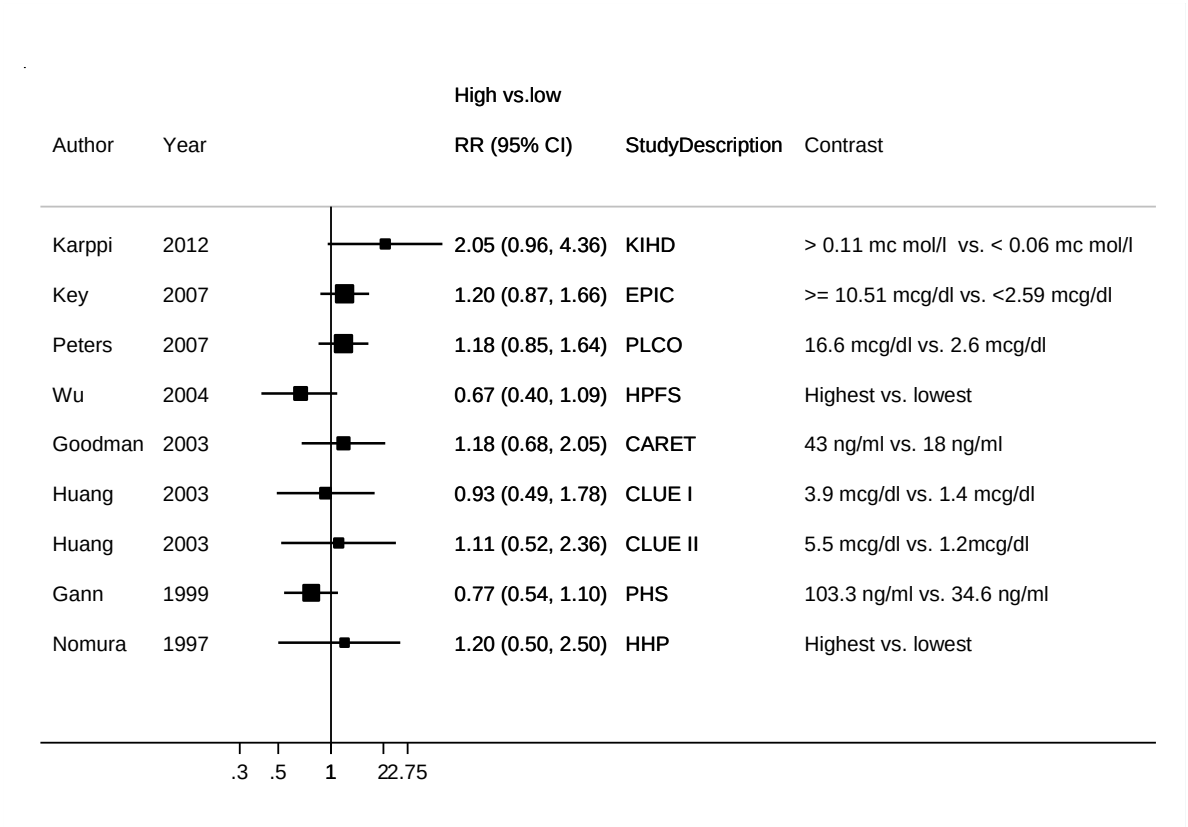


Figure 182 Dose-response meta-analysis of serum alpha-carotene and total prostate cancer, per 10 mcg/100ml

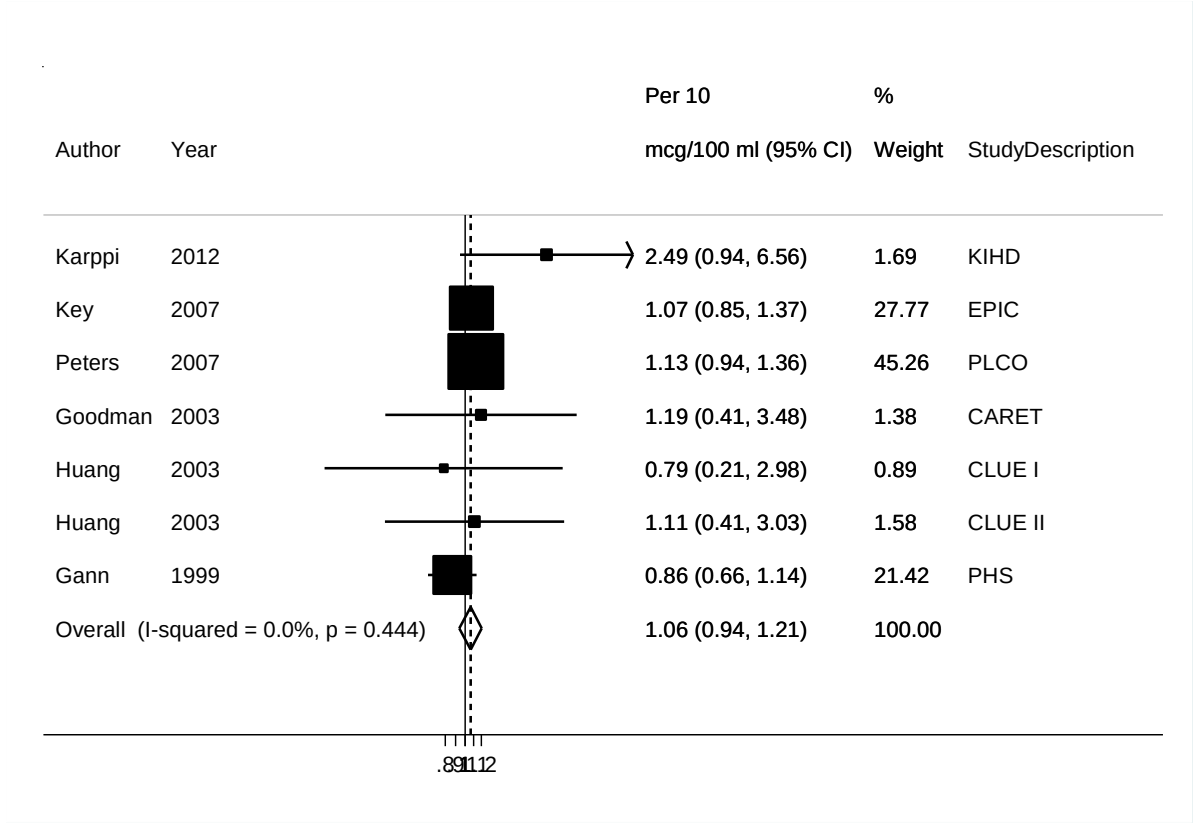


Figure 183 Funnel plot of serum alpha-carotene and total prostate cancer

Egger's test p = 0.64

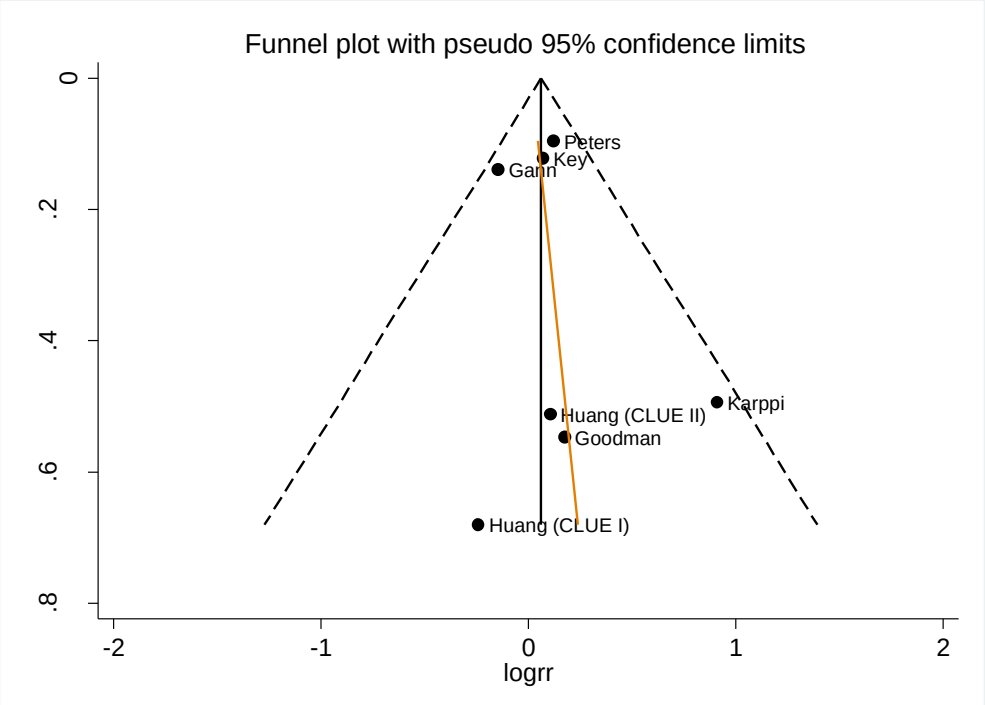
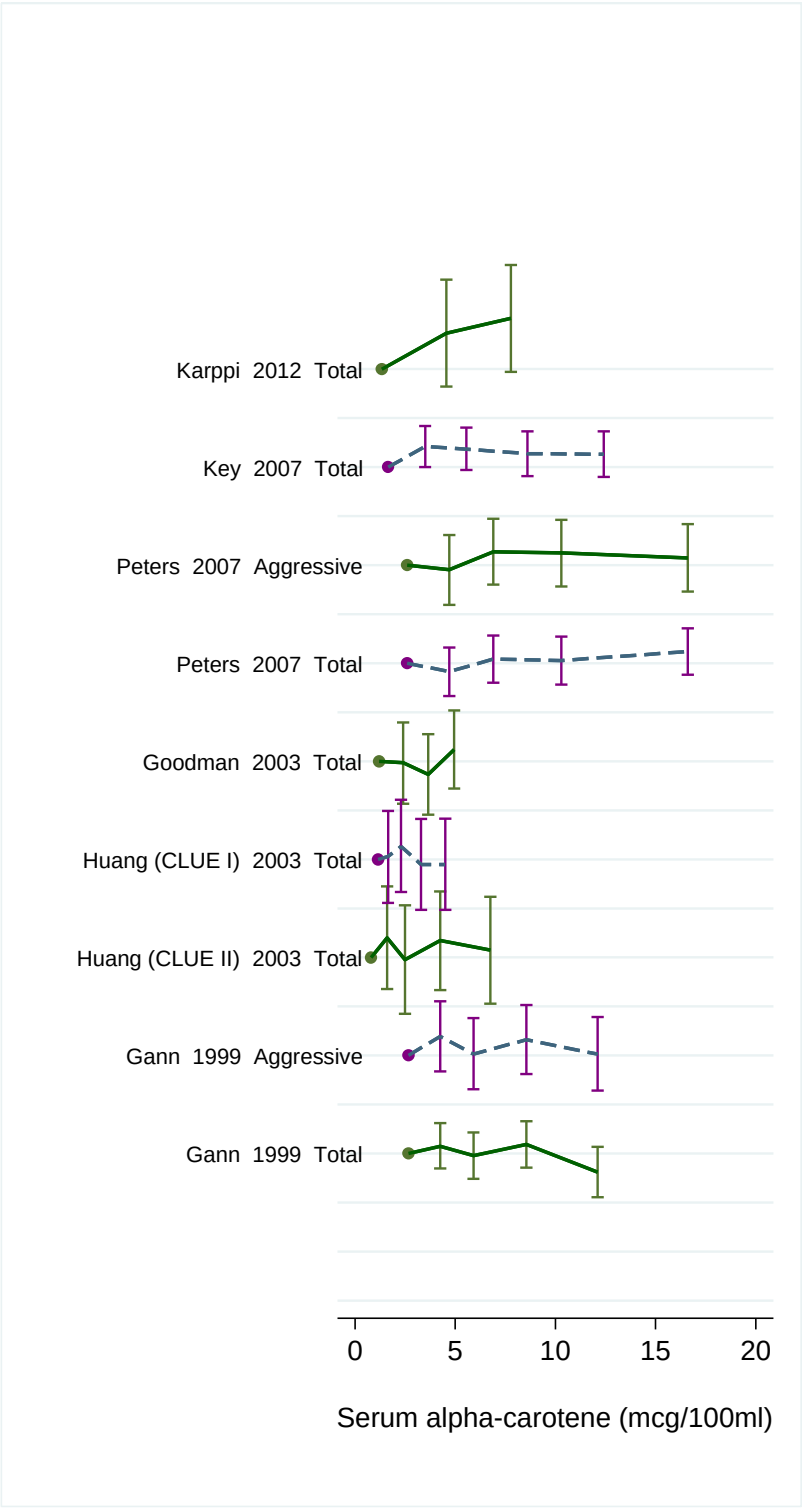


Figure 184 Dose-response graph of serum alpha-carotene and prostate cancer



5.5.1.2 Serum beta-carotene

Methods

Seventeen publications (14 cohort studies) on serum beta-carotene and prostate cancer were identified, six of them during the CUP. There were 3 publications from the Alpha Tocopherol Beta Carotene Cancer Prevention study and 3 publications from the Maryland study. Dose-response analyses were conducted per 10 mcg/100 ml.

The Kuopio Ischaemic Heart Disease Risk Factor Study (Karppi et al, 2012) and the study of Australia Mesothelioma Registry (Beilby et al, 2010), reported serum levels of beta-carotene in μmol/l which were converted to mcg/100 ml by dividing the concentration in μmol/l by 0.01863 (Switzer et al, 2005).

One study (Cook et al, 1999) used the highest quartile as referent category. The RR of the highest vs. lowest was estimated from the data using the Hamling method (Hamling et al, 2008).

From the studies included in the meta-analysis, one study reported on total, aggressive and non-aggressive prostate cancer (Cook et al, 1999), one study reported on total, aggressive (stage III or IV or Gleason score ≥ 7) and stage III and IV prostate cancer (Peters et al, 2007) and one study reported on total and advanced prostate cancer (Gill et al, 2009). Overall, 9 studies were included in the meta-analysis for serum beta-carotene and total prostate cancer.

Main results

The summary RR per 10 μg/100 ml of serum beta-carotene and total prostate cancer was 0.99 (95% CI 0.95-1.04;, $I^2 = 37.5\%$; $p_{heterogeneity} = 0.12$). The RR for advanced/high grade cancer per 10 mcg/100 ml increase was 0.97 (95% CI 0.85-1.12; n=639; $I^2 = 69.5\%$; $p_{heterogeneity} = 0.04$; n=3).

Heterogeneity

There was low heterogeneity ($I^2 = 37.5$ %; $p_{heterogeneity} = 0.12$). Egger'stest showed no evidence of publication bias (p = 0.47).

Comparison with the Second Expert Report

In the 2005 SLR the meta-analysis on serum beta-carotene and prostate cancer showed non-significant association.

Published meta-analysis or pooled analysis

No published meta-analysis or pooled analysis was identified.

Table 169 Studies on serum beta-carotene identified in the CUP

Author/year	Country	Study name	Cases	Years of follow-up	RR	LCI	UCI	Contrast
Karppi, 2012	Finland	Kuopio Ischaemic Heart Disease Risk Factor Study	68	15 years	2.29	1.12	4.66	> 0.40 µmol /l vs. < 0.25 µmol /l
Beilby, 2010	Australia	Australia Mesothelioma Registry	96	≈14 years	0.83	0.45	1.55	3.70 µmol /l vs. 0.10 µmol /l
					0.79	0.56	1.11	Per 1 log unit
Gill, 2009	USA	Multi-ethnic Cohort study of Diet and Cancer	467		0.81	0.55	1.18	59.7 µg/dl vs. 9.8 µg/dl
Ahn, 2008a	Finland	Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study	1111	12.3 years	0.99	0.85	1.15	> 234 ug/l vs. < 137 ug/l among those with no family history of prostate cancer
					2.16	1.44	3.25	> 234 ug/l vs. < 137 ug/l among those with family history of prostate cancer
Key, 2007	Europe	European Prospective Investigation into Cancer and Nutrition	966	6 years	0.92	0.66	1.28	≥ 27.28 µg/dl vs. < 8.21 µg/dl
Peters, 2007	USA	Prostate, Lung, Colorectal, and Ovarian Cancer (PLCO) Screening Trial	692	1-8 years	1.30	0.93	1.82	38.7 µg/dl vs. 6.1 µg/dl

Table 170 Overall evidence on serum beta-carotene and total prostate cancer

	Summary of evidence
2005 SLR	Eleven publications (10 cohort studies) were identified during the 2005 SLR; six studies were included in the meta-analysis. No significant association was found.
Continuous Update Project	Six new publications were identified during the CUP. Overall, 9 studies were included in the meta-analysis. No significant association was found.

Table 171 Summary of results of the dose-response meta-analysis of serum beta-carotene and total prostate cancer

Total prostate cancer incidence		
	2005 SLR	CUP
Studies (n)	6	9
Cases (n)	1499	3449
Increment unit used	Per 10 mcg/100 ml	Per 10 mcg/100 ml
Overall RR (95% CI)	1.00 (0.91-1.09)	0.99 (0.95-1.04)
Heterogeneity (I^2, p-value)	I^2 = 43.8%, p = 0.11	I^2 = 37.5%, p = 0.12
Stratified analysis		
Advanced/aggressive cancer		
Overall RR (95%CI)		0.97 (0.85-1.12)
Heterogeneity (I^2,p-value)		I^2 = 69.5%, p = 0.04, n = 3

Table 172 Inclusion/exclusion table for meta-analysis of serum beta-carotene and total prostate cancer

WCRF code	Author	Year	Study design	Study name	Cancer outcome	2005 SLR	CUP dose-response meta-analysis	CUP HvL forest plot	Estimated values	Exclusion reasons
PRO100165	Karppi	2012	Prospective Cohort Study	Kuopio Ischaemic Heart Disease Risk Factor Study	Incidence	No	Yes	Yes	Mid exposure values Person years Conversion of µmol /l to µg/100ml	
PRO100178	Beilby	2010	Nested Case Control Study	Australia Mesothelioma Registry	Incidence	No	Yes	Yes	Mid exposure values Conversion of µmol /l to µg/100ml	
PRO100044	Gill	2009	Nested Case Control Study	Multi-ethnic Cohort study of Diet and Cancer	Incidence	No	Yes	Yes		
PRO100022	Ahn**	2008a	Prospective Cohort Study	Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study	Incidence	No	No	No		Only interactions data are shown
PRO100008	Key	2007	Nested Case Control study	European Prospective Investigation into Cancer and Nutrition study	Incidence	No	Yes	Yes	Mid exposure values	
PRO99969	Peters	2007	Nested Case Control study	Prostate, Lung, Colorectal, and Ovarian Cancer (PLCO) Screening Trial	Incidence	No	Yes	Yes		
PRO97166	Meyer	2005	Prospective Cohort Study	SU.VI.MAX trial	Incidence	Yes	No	Yes		Only two categories of data

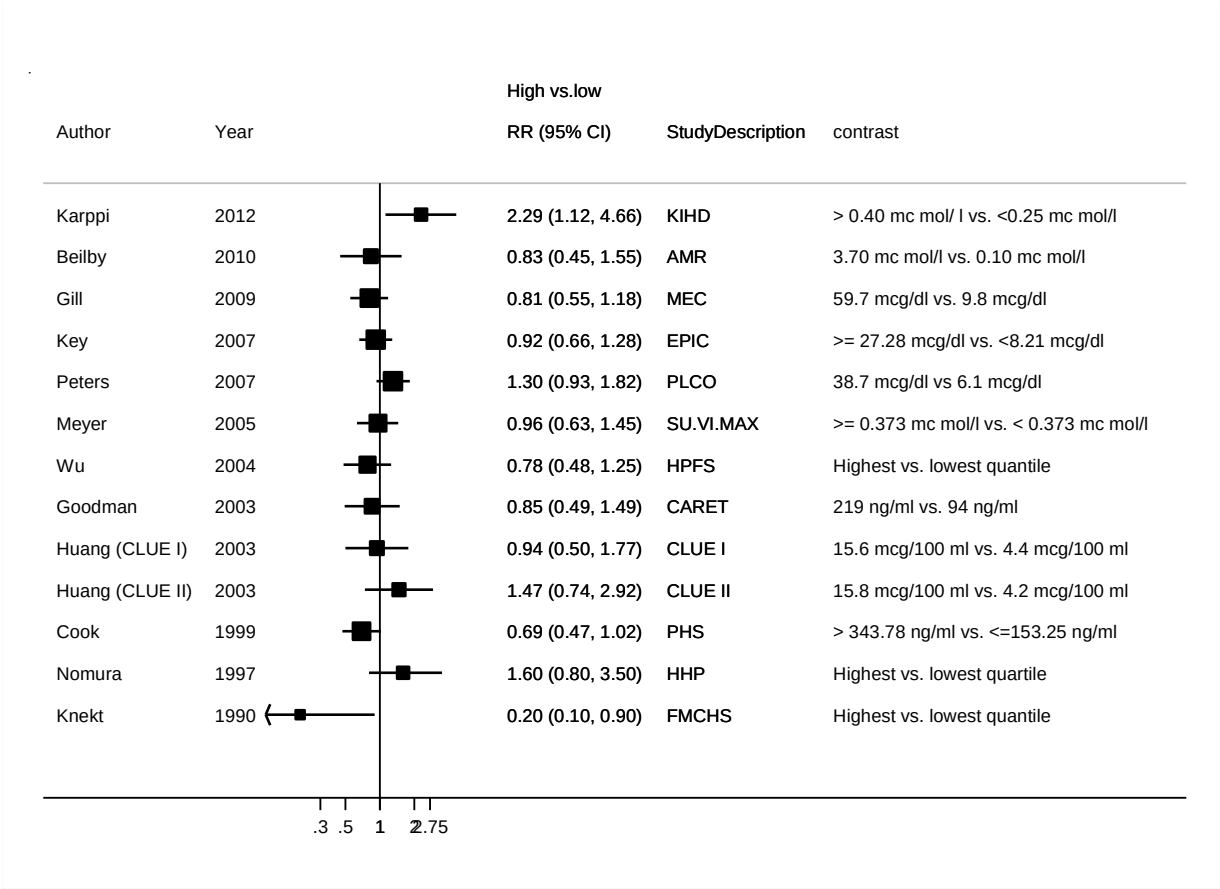
PRO97424	Weinstein**	2005	Nested Case Control Study	Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study	Incidence	Yes	No	No		Only means are shown
PRO03999	Wu	2004	Nested Case Control Study	Health Professional Follow up Study	Mortality and incidence	Yes	No	Yes		Only Medians are shown
PRO00526	Huang*	2003	Nested Case Control Study	USA Maryland 1974-1989 (Give us a CLUE to cancer; CLUE I &II)	Incidence	Yes	Yes	Yes	Mid exposure values	
PRO00214	Goodman	2003	Nested Case Control Study	Carotene and Retinol Efficacy Trial	Incidence	Yes	Yes	Yes	Mid exposure values Conversion of ng /ml to µg/100ml Number of cases per quartiles	-
PRO00272	Woodson**	2003	Nested Case Control Study	Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study	Mortality and incidence	Yes	No	No		Only means are shown
PRO01933	Cook	1999	Nested Case Control Study	Physician Health Study	Incidence	Yes	Yes	Yes	Mid exposure values Conversion of ng /ml to µg/100ml	
PRO02328	Nomura	1997	Nested Case Control Study	Honolulu Heart Program (Hawaii-USA)	Incidence	Yes	No	Yes		No quintile range
PRO13335	Comstock	1991	Nested Case Control Study	USA Maryland 1974-1975	Mortality and incidence	Yes	No	No		Superseded by study of Huang et al, 2003
PRO93149	Hsing	1990a	Nested Case Control Study	USA Maryland 1974-1986	Incidence	Yes	No	No		Superseded by study of Huang et al, 2003

PRO13415	Knekt	1990 b	Nested Case Control Study	Cancer Incidence Follow up of Finnish Mobile Clinic Health Examination Survey	Incidence	Yes	No	Yes		Only highest vs. lowest data Only means are shown

*Huang, 2003 counted as 2 studies.

** 3 publications of the ATBC study

Figure 185 Highest versus lowest forest plot of serum beta-carotene and total prostate cancer



*****In Cook et al, 1999, the RR's were recalculated using Hamling method (Hamling et al, 2008).

Figure 186 Dose-response meta-analysis of serum beta-carotene and total prostate cancer, per 10 mcg/100ml

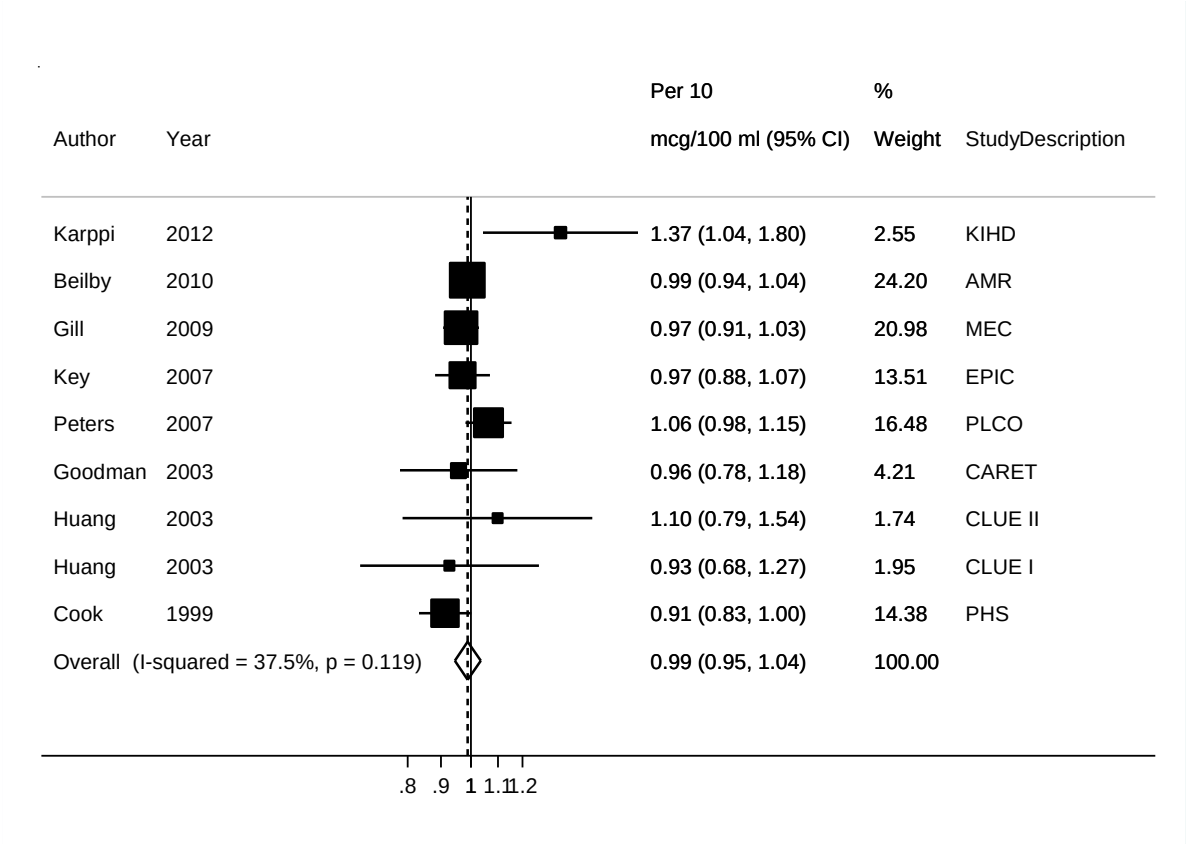


Figure 187 Funnel plot of serum beta-carotene and total prostate cancer

Egger's test p = 0.47

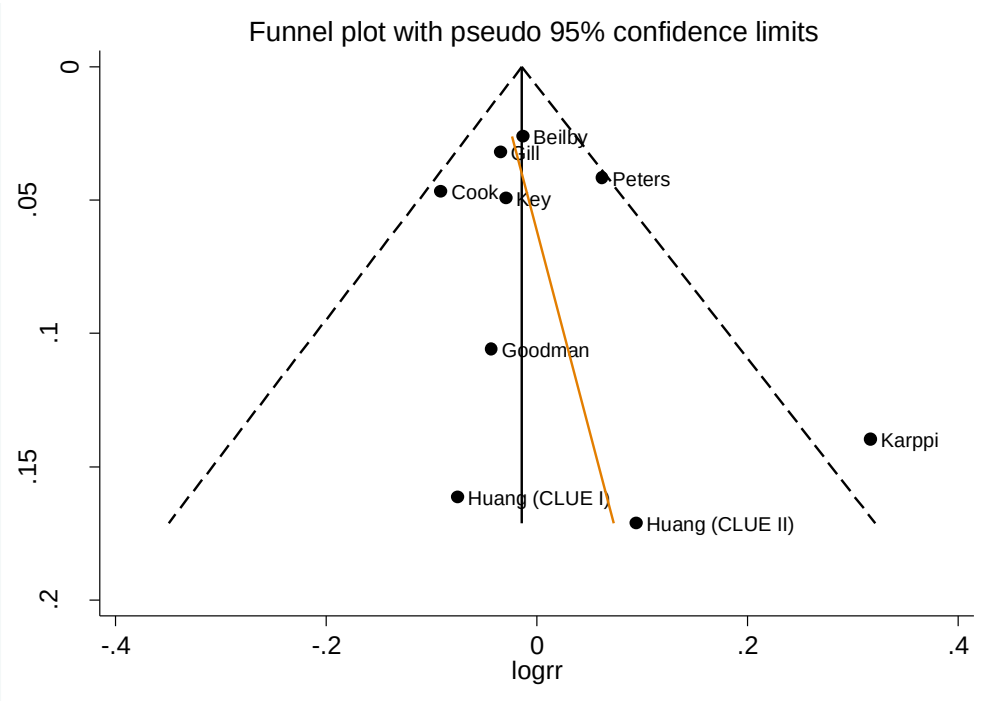


Figure 188 Dose-response graph of serum beta-carotene and prostate cancer

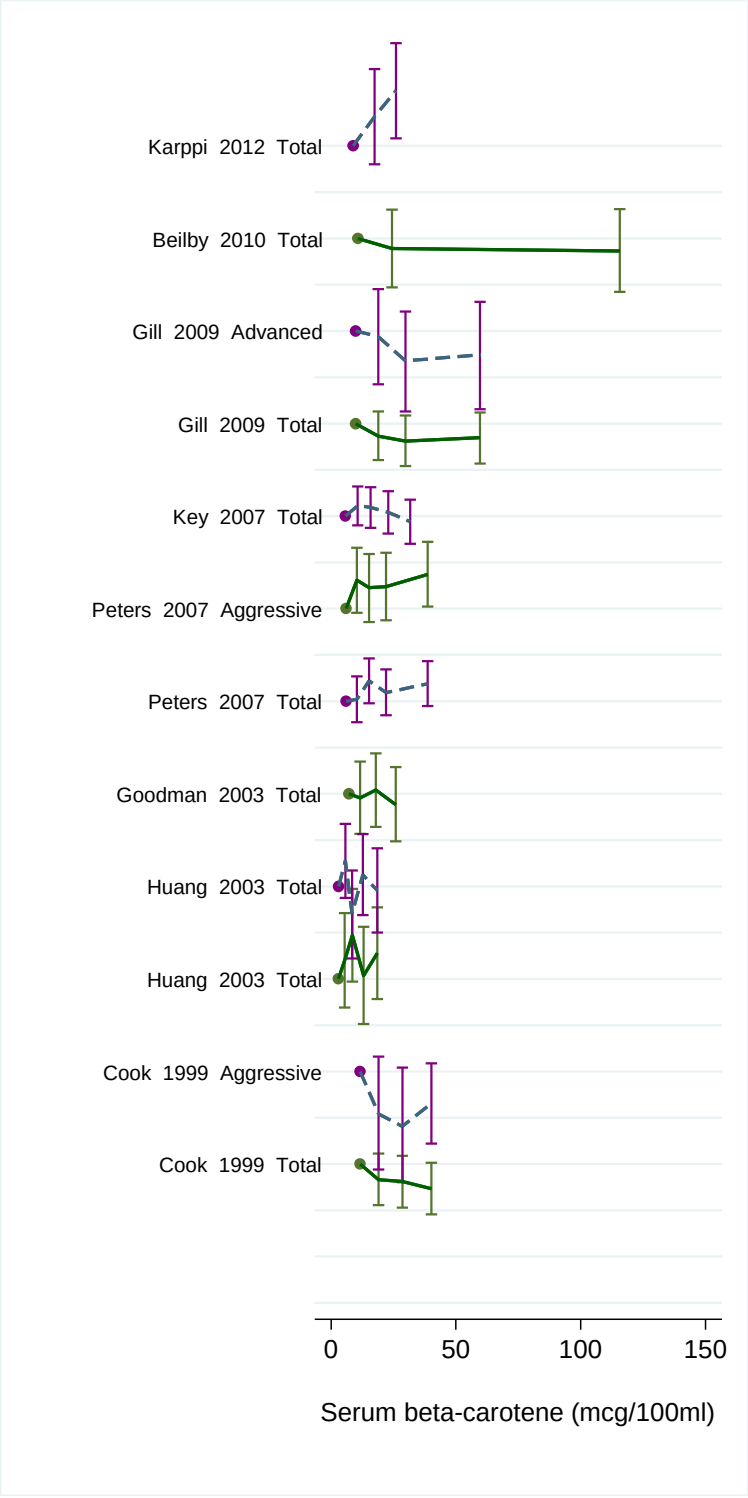
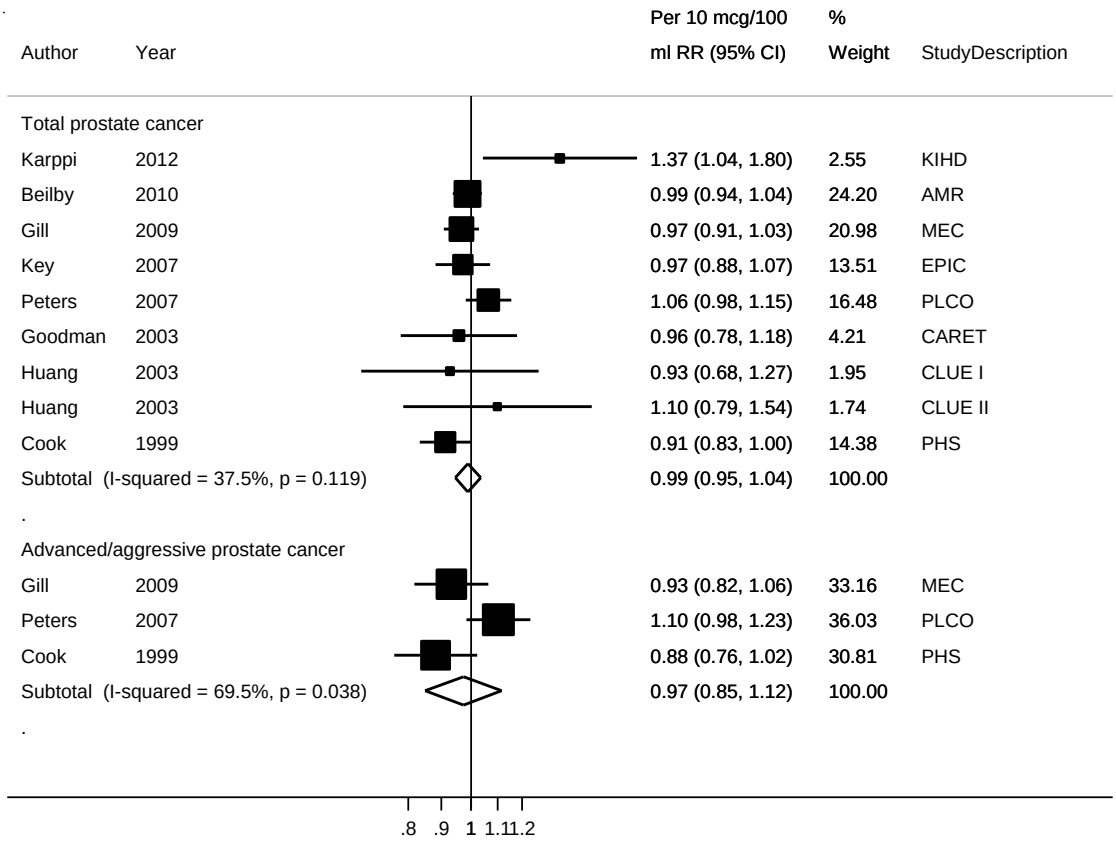


Figure 189 Dose-response meta-analysis of serum beta-carotene and prostate cancer, per 10 mcg/100ml stratified by cancer type



5.5.2 Dietary lycopene

Methods

Seven studies from twelve publications were identified. Five studies were identified in the CUP. The increment used in the dose-response analysis was 5 mg/day. One study (Stram et al, 2006) reported the intake of lycopene in micrograms per 1000 kcal/day, which was converted to mg/day using the median energy intake reported in another publication of the same study (Multiethnic Cohort Study). One study in Iowa farmers reported a very low dietary intake of lycopene (Parker et al, 1999).

From the studies included in the dose-response meta-analysis, two studies reported on total prostate cancer (Parker et al, 1999; Giovannucci et al, 2002), one each on total and aggressive prostate cancers (Schuurman et al, 2002), advanced and non-advanced prostate cancers (Kirsh et al, 2006a), total and non-localised or high-grade prostate cancers (Stram et al, 2006), Gleason score 2-7 and Gleason score 8-10 prostate cancers (Kristal et al, 2010), and total, non-advanced, advanced (Agalliu et al, 2011) and stage IV-only prostate cancers (Geybels et al, 2012). Advanced, aggressive, high grade and Gleason score 8-10 prostate cancer were combined into the advance/high grade subgroup and the non-advanced, localised, low grade, or Gleason score 2-7 prostate cancer were combined into non-advanced/low grade prostate cancers.

Main results

The summary RR per 5mg/day increase was 0.98 (95% CI 0.93-1.02; $I^2 = 34.2\%$; $p_{heterogeneity} = 0.17$; n = 7).

There was evidence of publication bias with Egger's test, p = 0.03. Visual inspection of the funnel plot suggests small studies on the right side of the funnel plot are missing. The small study on the left is an outlier with very low levels of dietary lycopene. In stratified analyses, the RR of advanced cancer per 5 mg/day was 1.03 (95% CI 0.81-1.29; $I^2 = 70.8\%$; $p_{heterogeneity} = 0.03$; n = 3) (Geybels et al, 2012; Agalliu et al, 2011; Kirsh et al, 2006a) and for high grade cancers it was 1.08 (95% CI 0.97-1.21; $I^2 = 0\%$; $p_{heterogeneity} = 0.49$; n = 25) (Kristal et al, 2010; Stram et al, 2006). The RR of nonadvanced cancer per 5 mg/day was 0.95 (95% CI: 0.89-1.02; $I^2=0\%$; $p_{heterogeneity} = 0.46$; n = 3).

There was evidence of non-linearity for total prostate cancer ($p < 0.01$), but not for advanced cancer ($p = 0.12$).

One of the studies assessed cumulative lycopene intake (Giovannucci et al, 2002). In this study, the highest versus lowest RR was 0.84 (95% CI 0.73-0.96; 18780 vs. 3415 mcg/day). All other studies have a single dietary assessment.

Heterogeneity

Overall, there was low evidence of heterogeneity, $I^2 = 34.2\%$, $p_{heterogeneity} = 0.17$.

Comparison with the Second Expert Report

In the 2005 SLR, foods containing lycopene (included both foods containing the constituent and foods which have lycopene added; mostly contained in tomatoes and tomato products) were considered a probable factor to decrease prostate cancer risk. The meta-analysis on dietary lycopene and prostate cancer showed a non-significant association.

Published meta-analysis or pooled analysis

A meta-analysis of 4 published randomised controlled trials (RCTs) identified no significant decrease in the incidence of benign prostatic hyperplasia (RR 0.95; 95% CI 0.63-1.44) or prostate cancer diagnosis (RR 0.92; 95% CI 0.66-1.29) between men randomised to receive lycopene and the comparison group. A meta-analysis of two studies showed a decrease in PSA levels in men diagnosed with prostate cancer, who received lycopene (mean difference= −1.58; 95% CI -2.61, -0.55) (Ilic et al, 2012).

The Cochrane collaboration published a review including 3 RCTs, with a total of 154 participants. The studies differed in design, type of participants and lycopene doses. The meta-analysis showed no statistical difference in PSA levels between men randomised to receive lycopene and the comparison group (MD -0.34; 95% CI -2.01-1.32). Only one study reported on the incidence of prostate cancer and it was 10% in the lycopene group versus 30% in control group. The blood levels of lycopene were not different in the group of men randomised to receive lycopene and the comparison group (MD 0.39 μg/mL; 95% CI 0.19-0.98 (Ilic et al, 2011).

Another meta-analysis of five cohort studies reported a RR of 0.93 (95% CI 0.86-1.01) for the highest versus the lowest dietary lycopene intake (Chen, 2013). A previous meta-analysis showed a RR for an increase of 12.7 mg/day of lycopene (the average content of one raw tomato serving of 200 g) of 0.95 (95% CI 0.89-1.26) for 7 case-control studies and 0.38 (95% CI 0.34-0.42) for 3 cohort studies (Etminam, 2004).

Table 173 Studies on dietary lycopene identified in the CUP

Author, year	Country	Study name	Cases	Years of follow up	RR	LCI	UCI	Contrast
Geybels, 2012	Netherlands	Netherlands Cohort Study	3451	17.3 years	1.10	0.94	1.30	1.7 vs. 0.2 mg/d
Agalliu, 2010	USA	Canadian Study of Diet, Lifestyle, and Health cohort	661	7.7 years	0.82	0.61	1.10	15871 vs. 2450.6 mcg/d
Kristal, 2010	USA and Canada	The Prostate Cancer Prevention Trial	1703	9 years	1.06	0.89	1.26	GS 2-7 >10,918 vs. < 3,999 mcg/d
					1.33	0.76	2.34	GS 8-10 > 10,918 vs. < 3,999 mcg/d
Stram, 2006	USA and Hawai	Multiethnic Cohort Study	3922	8 years	1.01	0.90	1.10	2018 vs. 752.5 mcg/1000 kcal
Kirsh, 2006a	USA	Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial	1338	4.2 years	0.95	0.79	1.13	17593 vs. 5,052 mcg/d

Table 174 Overall evidence on dietary lycopene and prostate cancer

	Summary of evidence
2005 SLR	Three studies were identified during the 2005 SLR and included in the meta-analysis. One study showed inverse association and the remaining reported non-significant associations.
Continuous Update Project	Five new studies were identified in the CUP, all showed a non-significant association. No significant association was observed in the CUP meta-analysis.

Table 175 Summary of results of the dose response meta-analysis of dietary lycopene and prostate cancer

Prostate cancer		
	2005 SLR	CUP
Studies (n)	3	7
Cases (n)	3204	14279
Increment unit used	Per 5 mg/day	Per 5 mg/day
Overall RR (95% CI)	0.97 (0.64-1.45)	0.98 (0.93-1.02)
Heterogeneity (I^2, p-value)	25.3%, p = 0.26	34.2%, p = 0.17
Stratified analysis		
Advanced		
Overall RR (95% CI)		1.03 (0.81-1.29)
Heterogeneity (I^2, p-value)		70.8%, p = 0.03, n = 3
High grade cancer		
Overall RR (95% CI)		0.98 (0.93-1.03)
Heterogeneity (I^2, p-value)		0%, p = 0.47, n = 4

Advanced/high grade cancer		
Overall RR (95% CI)		1.08 (0.97-1.21)
Heterogeneity (I^2, p-value)		0%, p = 0.49, n =2
Non-advanced cancer		
Overall RR (95% CI)		0.95 (0.89-1.02)
Heterogeneity (I^2, p-value)		0%, p = 0.46, n = 3

Table 176 Inclusion/exclusion table for meta-analysis of dietary lycopene and prostate cancer

WCRF code	Author	Year	Study design	Study name	Cancer outcome	2005 SLR	CUP dose-response meta-analysis	CUP HvL forest plot	Estimated values	Exclusion reasons	PSA
PRO	Geybels	2012	Case-cohort study	Netherlands Cohort Study	Incidence	No	Yes	Yes			No information on PSA testing
PRO100078	Kristal	2010	Nested case-control study	The Prostate Cancer Prevention Trial	Incidence	No	Yes	Yes	Mid-exposure values, conversion from mcg/day to mg/day		Study participants had PSA levels less than 3 ng/mL at study entry, there was annual screening (PSA plus DRE) during the 7 years of the trial, and determination of the presence or absence of disease was based on endpoint biopsies.
PRO100199	Agalliu	2011	Case-cohort study	Canadian Study of Diet, Lifestyle, and Health cohort	Incidence/ Mortality	No	Yes	Yes	Person-years, conversion from mcg/day to mg/day		Information on family history of prostatic cancer and screening for prostatic cancer by PSA or DRE was collected on 15% of all men (in later versions of the questionnaire only)
PRO99986	Stram	2006	Prospective Cohort study	Multiethnic Cohort Study	Incidence	No	Yes	Yes	Conversion from mcg/1000 kcal to mg/day		Adjusted by PSA use
PRO99965	Kirsh	2006 a	Prospective Cohort study	Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial	Incidence/ Mortality	No	Yes	Yes			Cancer screening study. Eligible participants had no more than one PSA test in the past 3 years; and were not participating in another screening or cancer prevention trial.
PRO99992	Kirsh	2006 b	Prospective Cohort study	Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial	Incidence/ Mortality	No	No	No		Superseded by Kirsh, 2006 PRO99965	
PRO10575	Platz	2004 c	Nested case-control study	Health Professionals Study	Incidence	Yes	No	No		Mean values used in 2005 SLR. Giovannucci 2002	

										was used	
PRO00940	Giovannucci	2002	Prospective Cohort study	Health Professionals Study	Incidence/ Mortality	Yes	Yes	Yes			Most men had PSA
PRO00764	Schuurman	2002	Case-cohort study	Netherlands Cohort Study	Incidence	Yes	Yes	Yes			PSA not common in the Netherlands by the time of the study and not expected as a confounder.
PRO01737	Parker	1999	Prospective Cohort study	Iowa's Farmers Study	Incidence	Yes	Yes	Yes	Mid-exposure values, conversion from mcg/day to mg/day		No data on PSA
PRO02058	Yoshizawa	1998	Nested case-control study	Health Professionals Study	Incidence	Yes	No	No		Mean values used in 2005 SLR, Superseded by Giovannucci, 2002	
PRO02629	Giovannucci	1995	Prospective Cohort study	Health Professionals Study	Incidence/ Mortality	Yes	No	No		Superseded by Giovannucci, 2002	

Figure 190 Highest versus lowest forest plot of dietary lycopene and prostate cancer

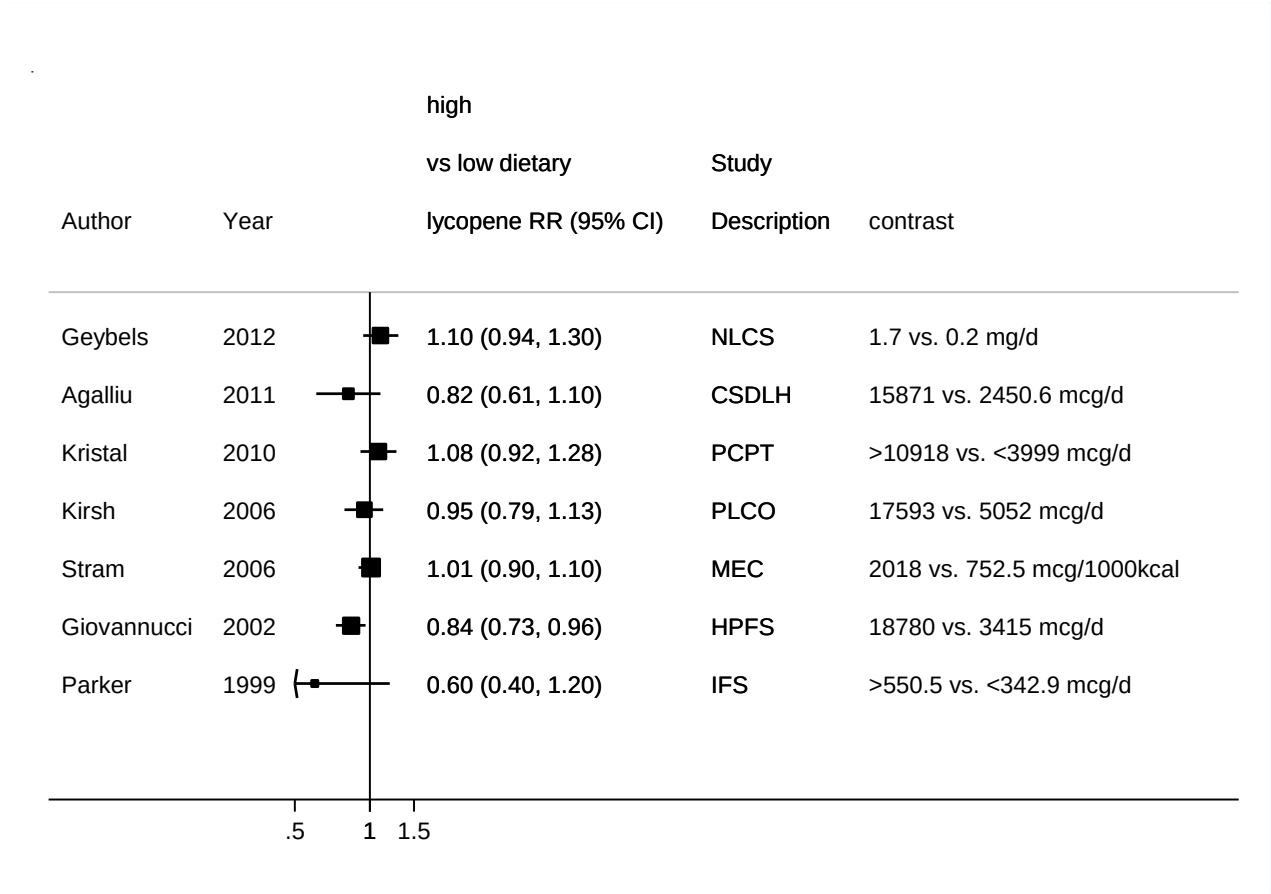
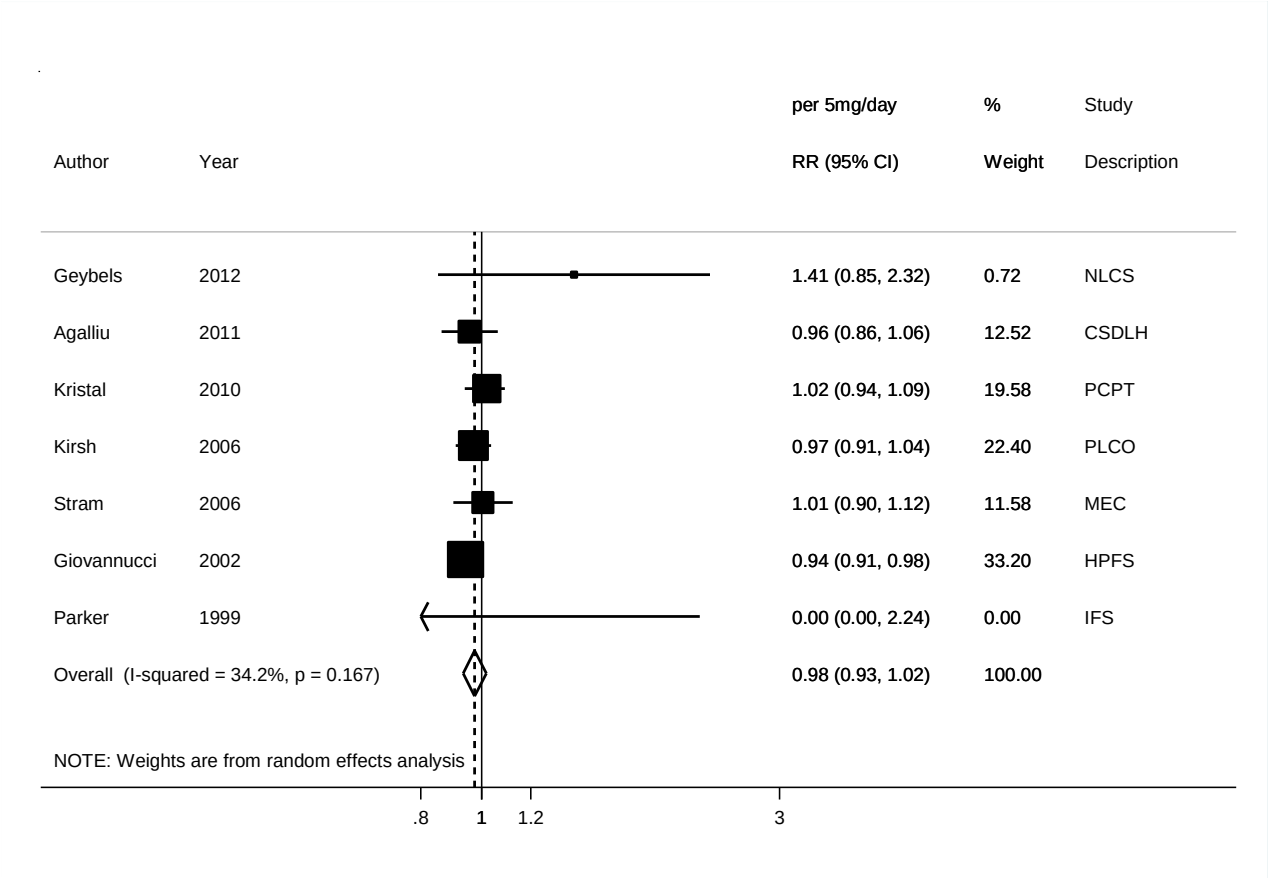
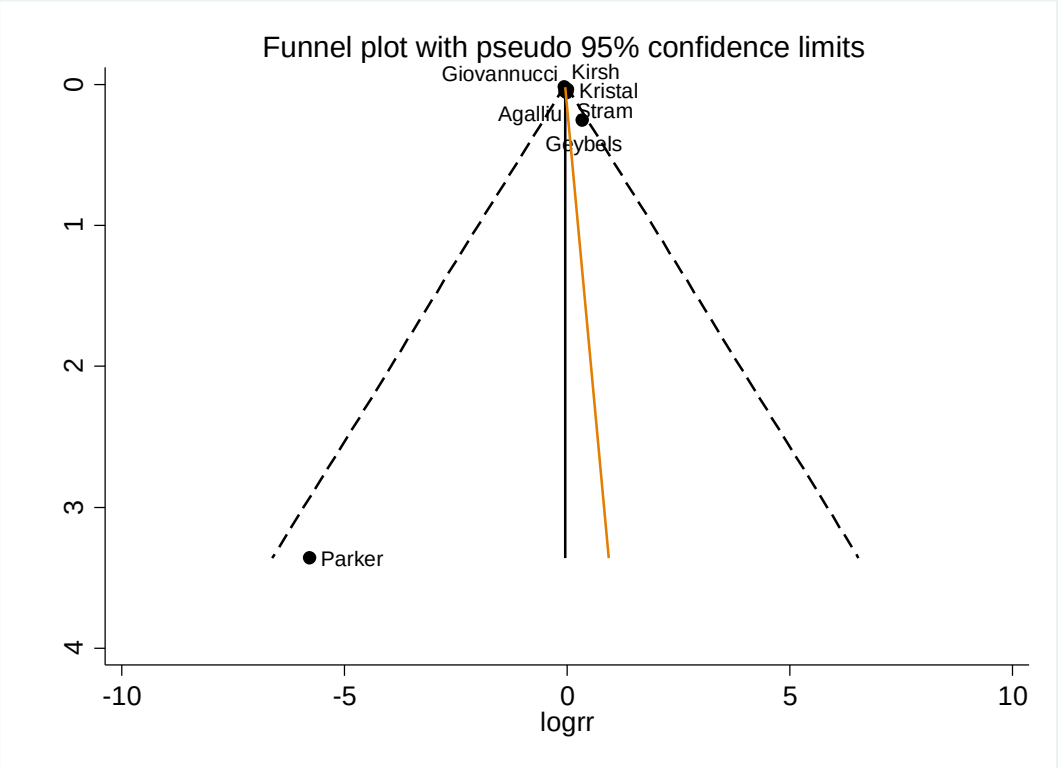


Figure 191 Dose-response meta-analysis of dietary lycopene and prostate cancer – per 5 mg/day



*Results very imprecise due to very small range of exposure in Parker et al, 1999

Figure 192 Funnel plot of dietary lycopene and prostate cancer



Egger's test p = 0.03

Figure 193 Dose-response graph of dietary lycopene and prostate cancer

Figure 194 Dose-response meta-analysis of dietary lycopene and prostate cancer, per 5 mg/day, stratified by prostate cancer type

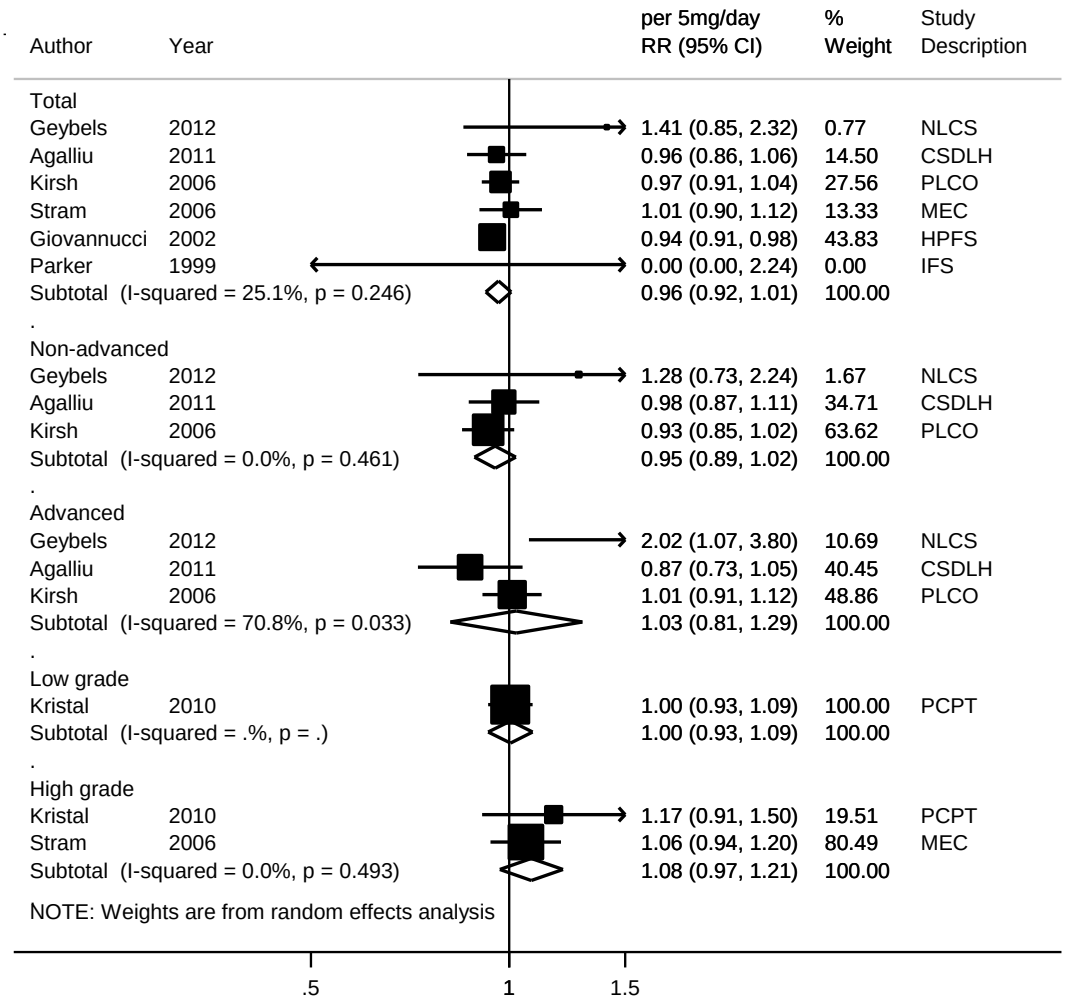
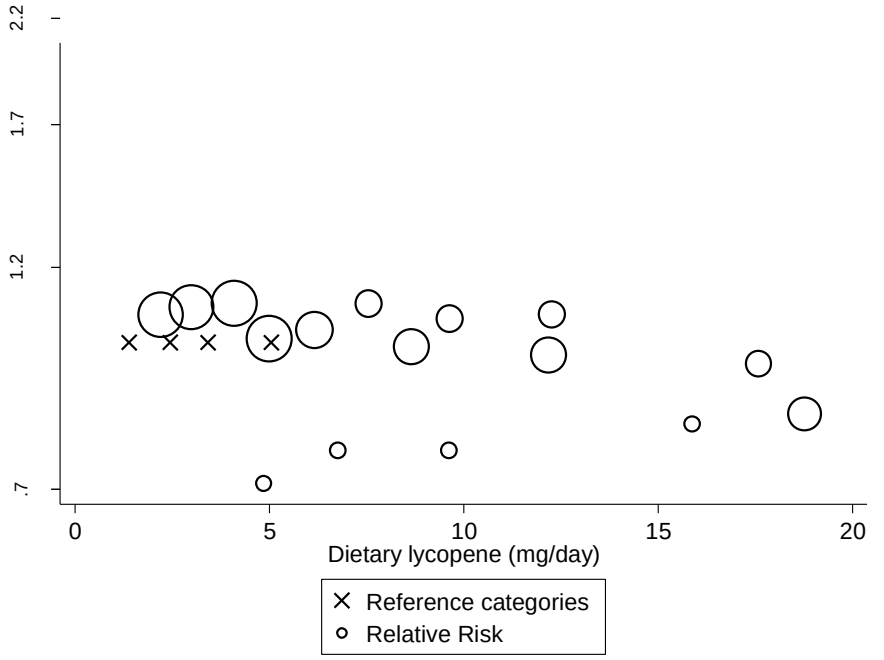


Figure 195 Non-linear dose-response analysis of dietary lycopene and total prostate cancer



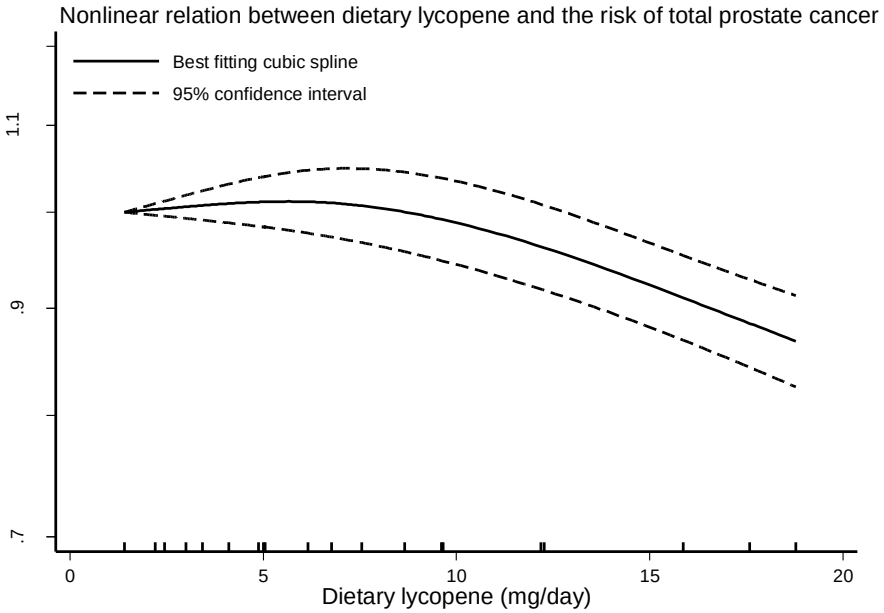


Table 177 Table with dietary lycopene values and corresponding RRs (95% CIs) for non-linear analysis of dietary lycopene and prostate cancer

Dietary Lycopene (mg/day)	RR (95% CI)
0	1
5	1.01 (0.98-1.03)
10	0.99 (0.95-1.03)
15	0.91 (0.86-0.95)

$p_{non\text{-}linearity} = 0.01$

5.5.2 Serum lycopene

Methods
Twelve studies from fourteen publications were identified, from which six studies were identified during the CUP. From the studies included in the dose-response meta-analysis: four studies reported on total prostate cancer (Goodman et al, 2003; Huang et al, 2003; Beilby et al, 2010; Karppi et al, 2012), one study on total, localised and advanced prostate cancer (Key et al, 2007), one on total and advanced prostate cancer (Gill et al, 2009), one on total, aggressive and stage III-IV prostate cancer (Peters et al, 2007) and one study on Gleason score 2-7 and Gleason score 8-10 prostate cancers (Kristal et al, 2011). Advanced, aggressive, high grade and Gleason score 8-10 prostate cancer were combined into advance/high grade prostate cancers and non-advanced, localised, low grade, Gleason score 2-7 prostate cancer were combined in non-advanced/low grade prostate cancers.

Main results
The summary RR per 10 mcg/dl was 0.99 (95% CI 0.96-1.01; I^2=0%; $p_{heterogeneity}$ = 0.65; n = 10). There was evidence of publication bias with Egger's test, p = 0.01. The asymmetry appears to be driven by the PLCO study (37.6 % weight in the dose-response meta-analysis). In a sensitivity analysis excluding the PLCO study, the Egger'stest p value was 0.11 and the combined RR estimate was 0.98 (95% CI 0.96-1.01). After exclusion of the PCPT study (Kristal, 2011) in which participants had frequent PSA tests, the combined RR estimate was 0.99 (95% CI 0.96-1.01; I^2 = 0%; $p_{heterogeneity}$ = 0.57). After exclusion of both studies (PCPT and PLCO), the RR estimate was 0.96 (95% CI 0.93-0.99; I^2=0 %; $p_{heterogeneity}$ = 0.99).

In analyses stratified by prostate cancer type, the RR per 10 mcg/dl was 0.98 (95% CI 0.93-1.03; I^2 = 61.2%; $p_{heterogeneity}$ = 0.04; n = 5) for advanced/high grade cancers and 1.00 (95% CI 0.95-1.06; I^2 = 0%; $p_{heterogeneity}$ = 0.43; n = 2) for non-advanced/low grade cancers. When the study by Kristal, 2011 on Gleason 7-10 was excluded, the RR per 10 mcg/dl for advanced cancers was 0.97 (95% CI 0.91-1.03; I^2 = 70.6%; $p_{heterogeneity}$ = 0.001; n = 4). There was evidence on a non-linear relationship between serum lycopene and total prostate cancer ($p < 0.01$), but not for advanced prostate cancer (p = 0.70). The non-linear dose-response relationship was driven by the extreme values of the PLCO study, with lycopene serum values higher than in the other studies and positive -although not statistically significant- associations reported for the two top quintiles of serum lycopene compared to the lowest.

Heterogeneity
Overall, there was low evidence of heterogeneity, I^2 = 0 %, $p_{heterogeneity}$ = 0.65.

Comparison with the Second Expert Report
In the 2005 SLR the overall result of the meta-analysis showed a non-significant association between serum lycopene and prostate cancer.

Published meta-analyses or pooled analyses
In a meta-analysis of nested case-control studies, the RR for the highest vs the lowest level of blood lycopene was 0.97 (95% CI 0.88-1.08; I^2 = 0%; p = 0.52) (Chen et al, 2013).

Table 178 Studies on serum lycopene identified in the CUP

Author, year	Country	Study name	Cases	Years of follow up	RR	LCI	UCI	Contrast
Karppi, 2012	Finland	Kuopio Ischaemic Heart Disease Risk Factor (KIHD) study	68	15 years	0.85	0.44	1.66	> 0.19 vs. < 0.08 µmol/l
Kristal, 2011	USA and Canada	The Prostate Cancer Prevention Trial	1683	9 years	0.91	0.72	1.14	GS 2-6 ≥ 46.6 vs. < 26.3 mcg/dl
					1.16	0.85	1.58	GS 7-10 ≥ 46.6 vs. < 26.3 mcg/dl
					1.20	0.71	2.04	GS 8-10 ≥46.6 vs. < 26.3 mcg/dl
Beilby, 2010	Australia	Wittenoom, Western Australia 1990	96	≈14 years	0.77	0.40	1.47	0.31–1.30 vs. 0-0.19 µmol/l
Gill, 2009	USA and Hawai	Multiethnic Cohort Study	467		0.78	0.53	1.14	65.6 vs. 22.0 mcg/dl
Peters, 2007	USA	Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial	692	8 years	1.14	0.82	1.58	108.4 vs. 30.5 mcg/dl
Key, 2007	Europe	EPIC	966	6 years	0.97	0.70	1.34	≥49.37 vs. <15.04 mcg/dl

Table 179 Overall evidence on serum lycopene and prostate cancer

	Summary of evidence
2005 SLR	Four studies could be included in the 2005 SLR meta-analysis. No significant associations were observed
Continuous Update Project	Five new studies were identified in the CUP, all showed non-significant results. No significant association was observed in the CUP meta-analysis.

Table 180 Summary of results of the dose response meta-analysis of serum lycopene and prostate cancer

Prostate cancer		
	2005 SLR	CUP
Studies (n)	4	10
Cases (n)	1107	4665
Increment unit used	Per 10 mcg/l	Per 10 mcg/dl
Overall RR (95% CI)	0.96 (0.93-1.00)	0.99 (0.96-1.01)
Heterogeneity (I^2, p-value)	0%, p = 0.92	0%, p = 0.65
Stratified analysis		
Advanced/high grade cancer		
Overall RR (95% CI)		0.98 (0.93-1.03)
Heterogeneity (I^2, p-value)		61.2%, p = 0.04, n = 5
Non-advanced/low grade cancer		
Overall RR (95% CI)		1.00 (0.95-1.06)
Heterogeneity (I^2, p-value)		0%, p = 0.43, n = 2

Table 181 Inclusion/exclusion table for meta-analysis of serum lycopene and prostate cancer

WCRF code	Author	Year	Study design	Study name	Cancer outcome	2005 SLR	CUP dose-response meta-analysis	CUP HvL forest plot	Estimated values	Exclusion reasons	PSA
PRO100165	Karppi	2012	Prospective Cohort Study	Kuopio Ischaemic Heart Disease Risk Factor (KIHD) study	Incidence	No	Yes	Yes	Mid-exposure values, conversion from memo/l to mcg/dl		No PSA info
PRO100091	Kristal	2011	Nested case-control study	The Prostate Cancer Prevention Trial	Incidence	No	Yes	Yes	Mid-exposure values		Study participants had PSA levels less than 3 ng/mL at study entry, there was annual screening (PSA plus DRE) during the 7 years of the trial, and determination of the presence or absence of disease was based on endpoint biopsies
PRO100178	Beilby	2010	Nested case-control study	Wittenoom, Western Australia 1990	Incidence	No	Yes	Yes	Mid-exposure values, conversion from memo/l to mcg/dl		Cancer registry. No PSA info.
PRO100044	Gill	2009	Prospective Cohort Study	Multiethnic Cohort Study	Incidence	No	Yes	Yes			When the analyses were restricted to control subjects with PSA values ≤4.0 ng/ml and their matched cases, the conclusions were unchanged (data not shown).
PRO99969	Peters	2007	Nested case-control study	Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial	Incidence	No	Yes	Yes			Nested case-control study limited to men randomized to the screening arm of the trial. These men were offered PSA screening at entry and annually for 5 years and digital rectal examination (DRE) at entry and annually for 3 years. Men with a positive PSA test (>4 ng/mL) or suspicious DRE suspicious were referred for prostate cancer diagnostic evaluation.
PRO100008	Key	2007	Nested case control study	EPIC	Incidence/ Mortality	No	Yes	Yes	Mid-exposure values		Data on PSA use not available
PRO03999	Wu	2004	Nested case-control study	Health Professionals Study	Incidence	Yes	No	Yes		No quintile range	The majority of cases diagnosis through PSA test
PRO10575	Platz	2004c	Nested case-control study	Health Professionals Study	Incidence	Yes	No	No		Insufficient data. Superseded by Wu, 2004	

PRO00214	Goodman	2003	Nested case-control study	Carotene and Retinol Efficacy Trial (CARET)	Incidence	Yes	Yes	Yes	Conversion from nag/ml to mcg/dl, person-years and cases per quintile		
PRO00526	Huang	2003	Case-cohort study	CLUE I and CLUE II*	Incidence	Yes	Yes	Yes	Mid-exposure values, person-years per quintile		The authors indicated they did not find evidence of overdiagnoses of early-stage prostate cancer by using PSA tests and digital rectal examinations.
PRO01820	Gann	1999	Case-cohort study	Physician's Health Study	Incidence	Yes	Yes	Yes			
PRO02328	Nomura	1997	Nested case-control study	Honolulu Heart Program	Incidence	Yes	No	Yes		No quintile range	
PRO13335	Comstock	1991	Case-cohort study	USA Maryland 1974-1975	Incidence	Yes	No	No		Superseded by Huang. 2003	
PRO93149	Hsing	1990a	Case-cohort study	USA Maryland 1974-1975	Incidence	Yes	No	No		Superseded by Huang 2003	

*Huang, 2003 counted as 2 studies.

Figure 196 Highest versus lowest forest plot of serum lycopene and prostate cancer

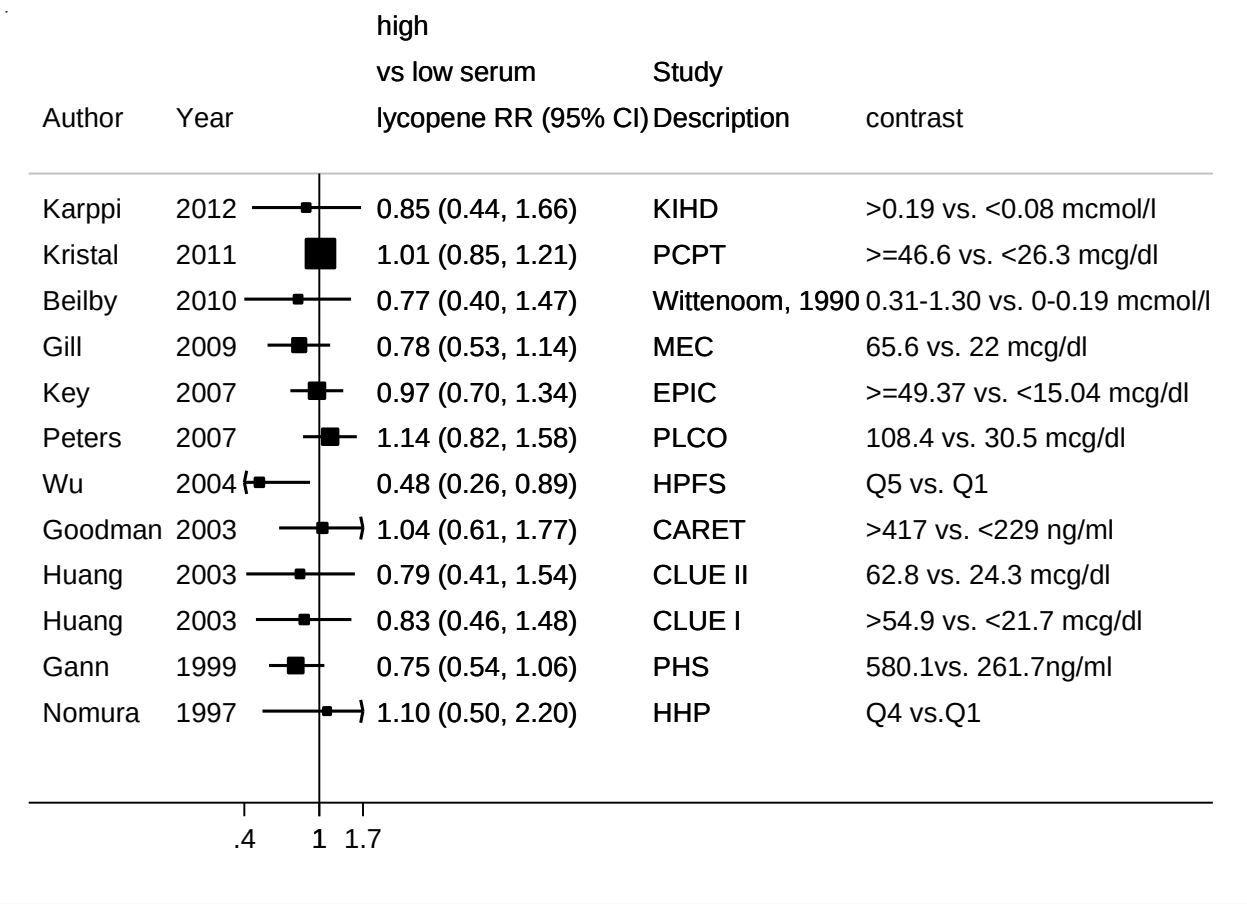


Figure 197 Dose-response meta-analysis of serum lycopene and prostate cancer – per 10 mcg/dl

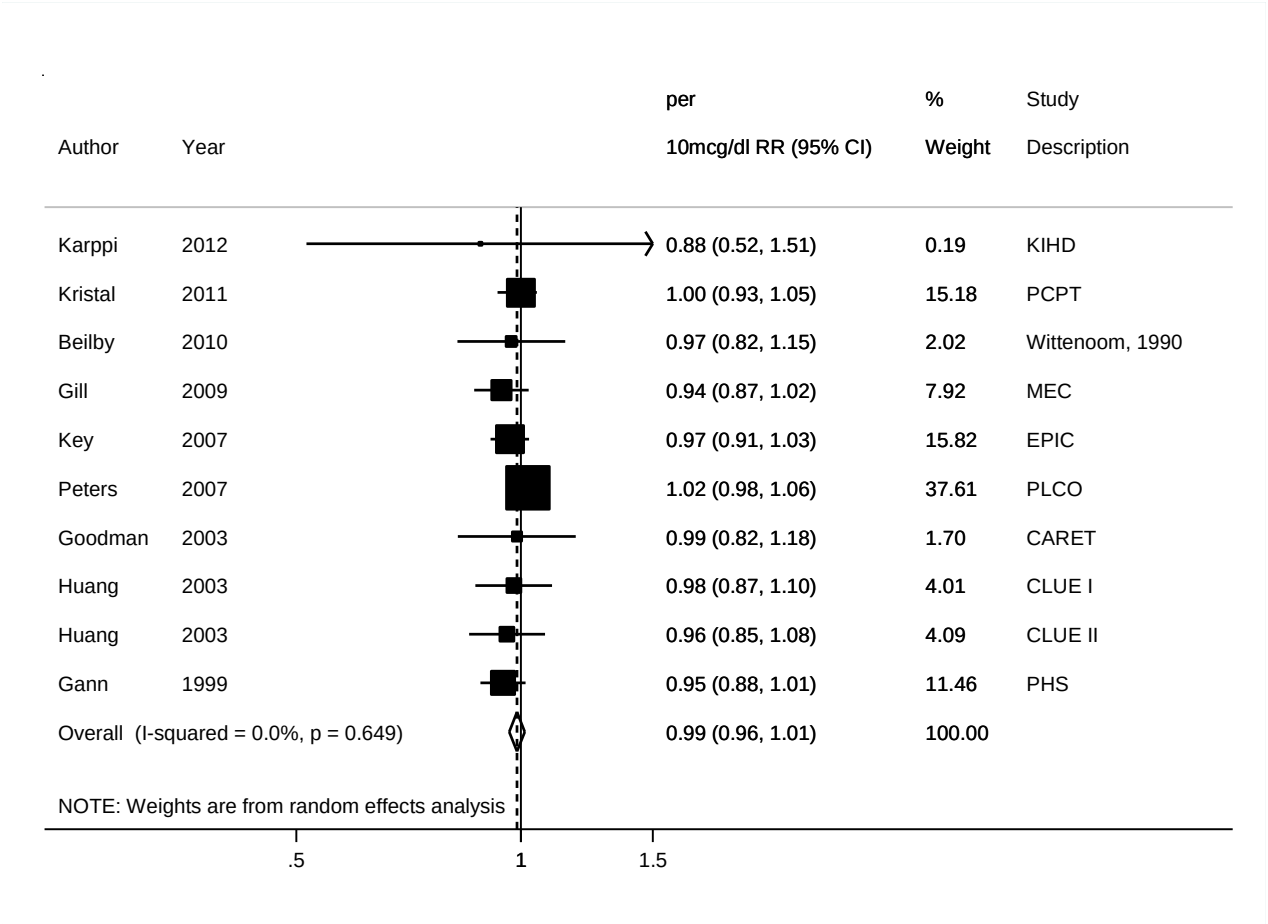
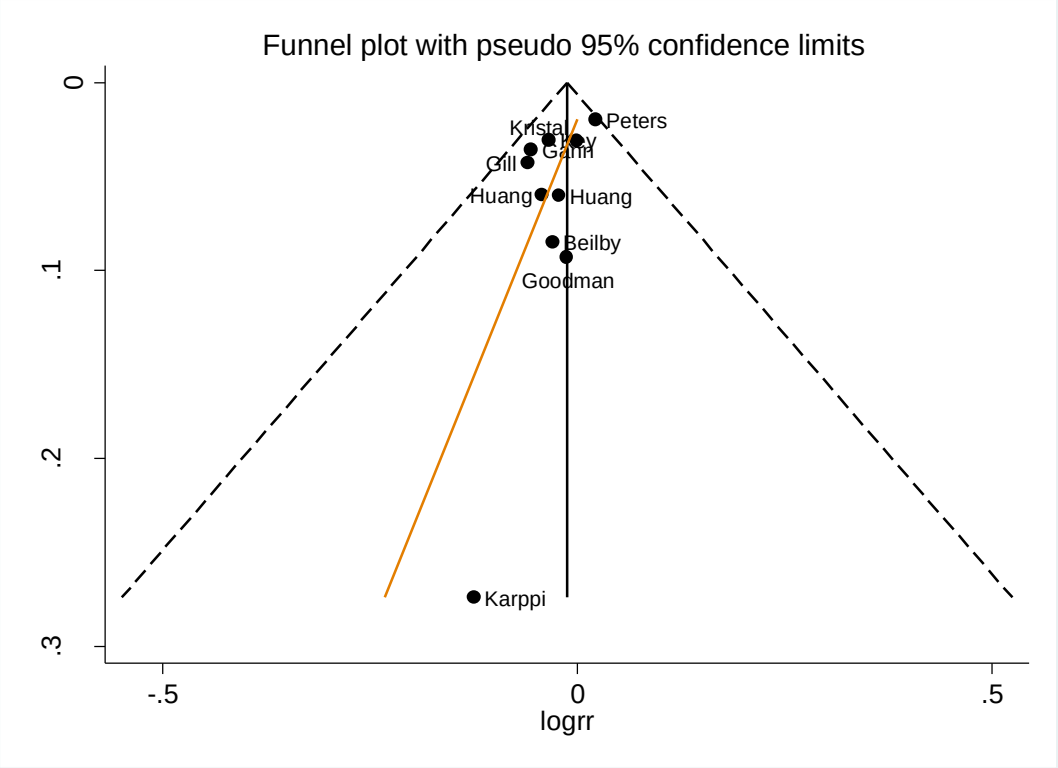


Figure 198 Funnel plot of serum lycopene and prostate cancer



Egger's test p = 0.01

Figure 199 Dose-response graph of serum lycopene and prostate cancer

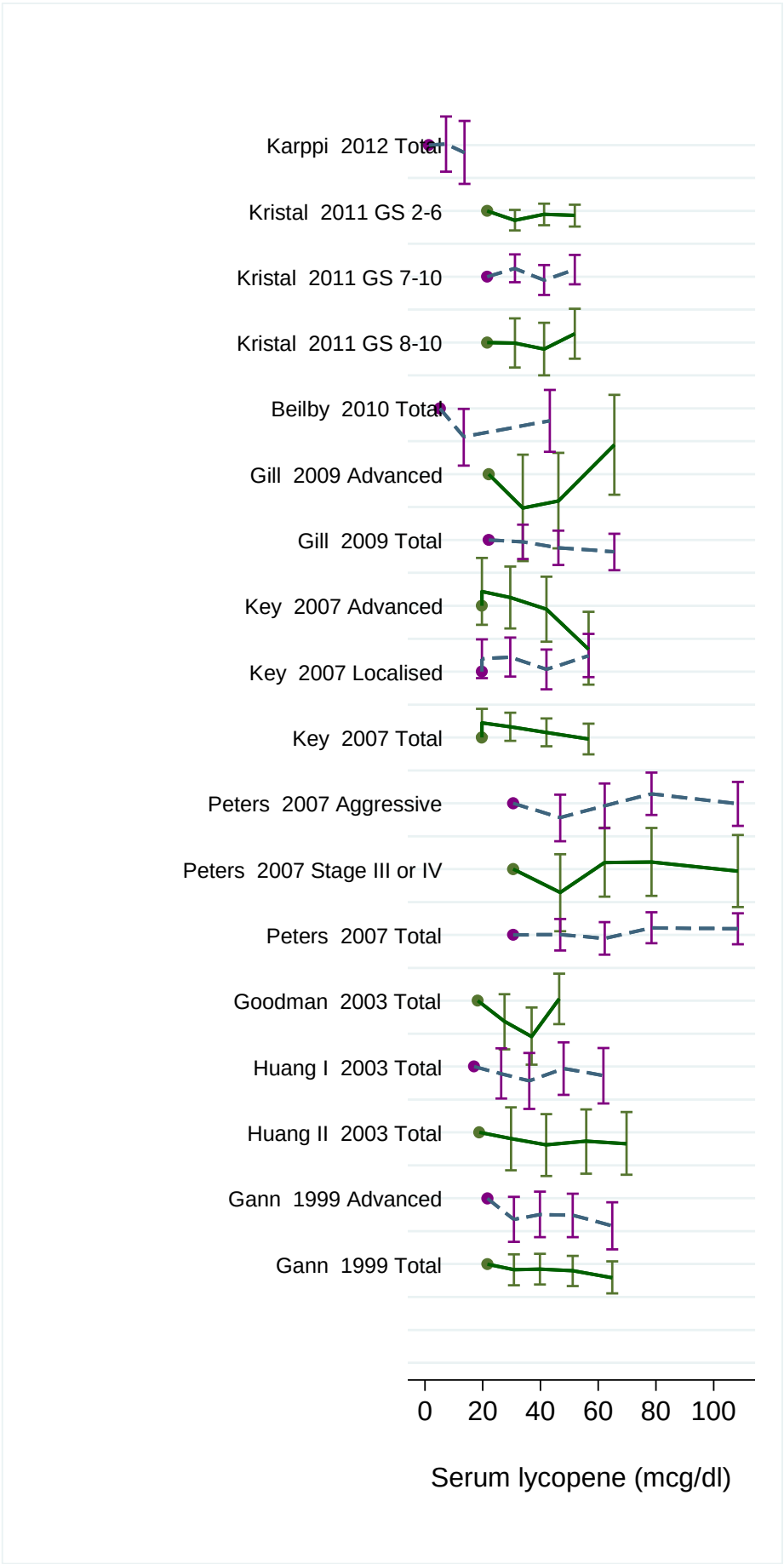


Figure 200 Dose-response meta-analysis of serum lycopene and prostate cancer, per 10 mcg/dl, stratified by prostate cancer type

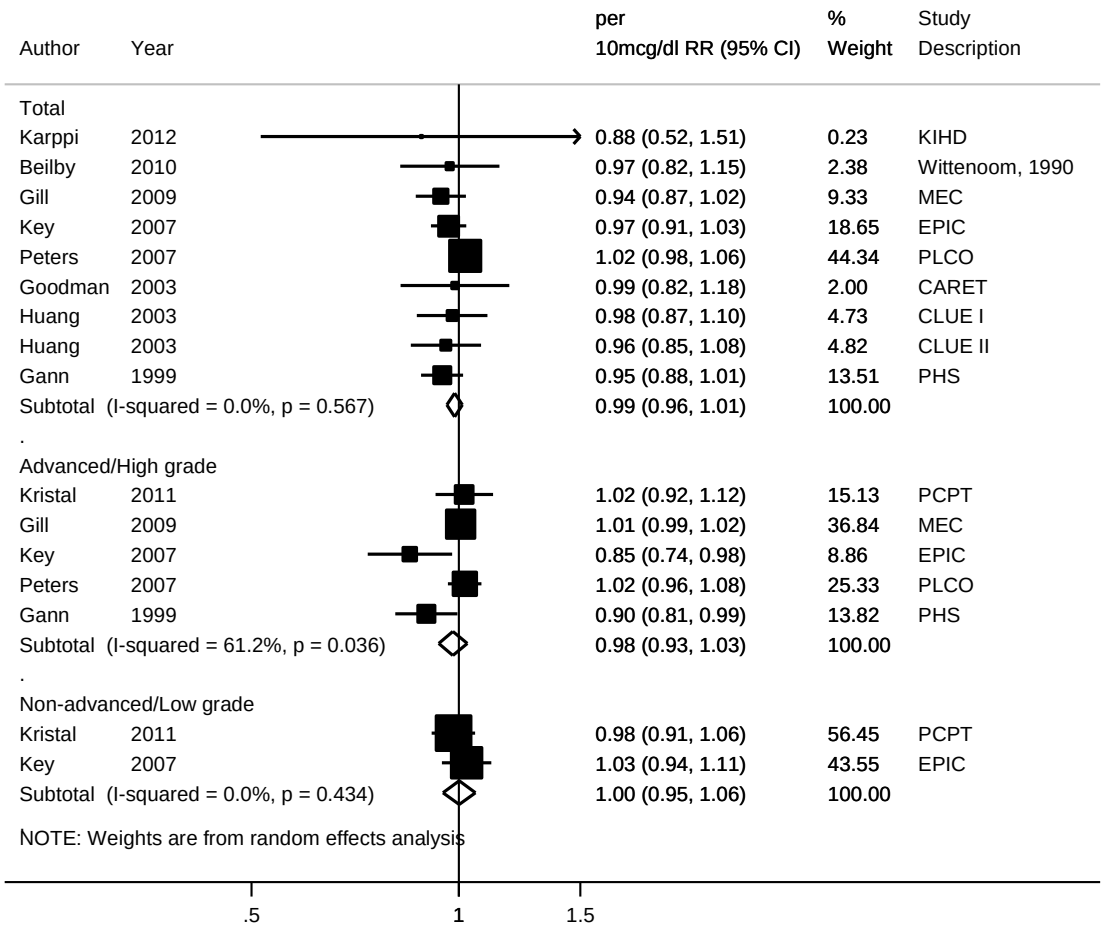
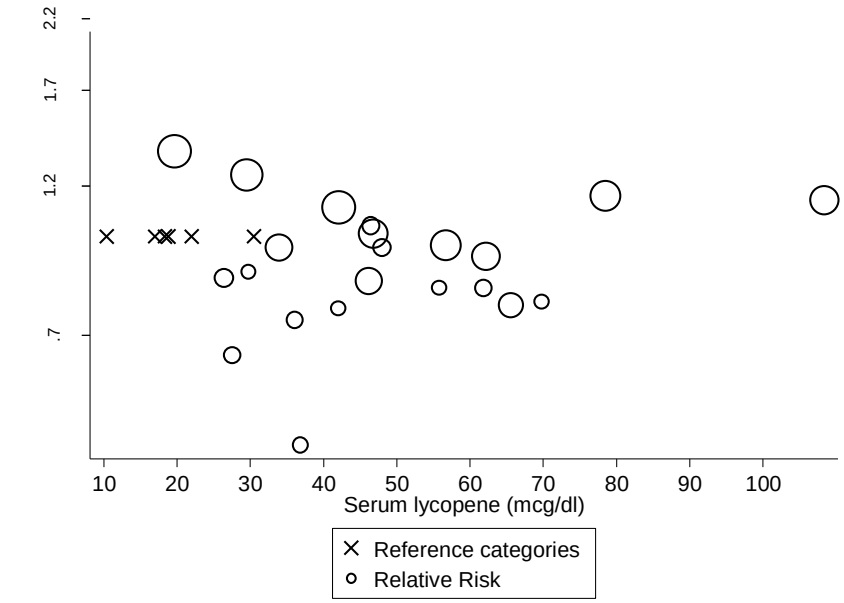


Figure 201 Non-linear dose-response analysis of serum lycopene and total prostate cancer



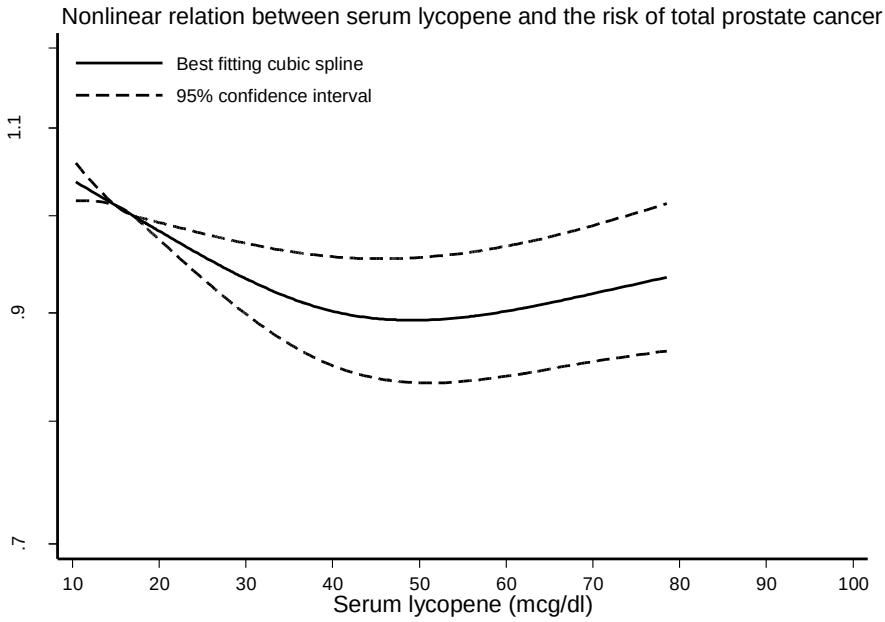


Table 182 Table with serum lycopene values and corresponding RRs (95% CIs) for non-linear analysis of serum lycopene and total prostate cancer

Serum lycopene (mcg/dl)	RR (95% CI)
17	1
30.5	0.93 (0.89-0.96)
55.8	0.89 (0.83-0.96)
78.5	0.94 (0.86-1.01)

$p_{non\text{-}linearity} = 0.001$

5.5.3 Serum folate

Methods
A total of 7 publications (7 cohort studies) of serum folate and prostate cancer were identified. Five of these publications were identified in the CUP. Dose-response meta-analysis was conducted per 5 nmol/L. A measurement unit of mcg/L was converted to nmol/L using a conversion factor of 2.265.

From the studies included in the dose-response meta-analysis, Collin et al (2010) reported on total, advanced and localised cancer. All remaining studies reported on total prostate cancer.

Rossi (2006) reported hazard ratios per unit of decrease of serum folate that was rescaled to an increase of 5 nmol/L. The hazard ratio was also recalculated for the inclusion in the highest vs. lowest forest plot.

Main results
The summary RR per 5 nmol/L increase was 1.01 (95% CI 1.00-1.02; $I^2 = 49.2\%$; $p_{heterogeneity} = 0.07$; n = 7). There was no evidence of publication bias with Egger's test, p = 0.31.

Heterogeneity
Overall, there was moderate evidence of heterogeneity, $I^2 = 49.2\%$, $p_{heterogeneity} = 0.07$.

Comparison with the Second Expert Report
In the 2005 SLR the meta-analysis on serum folate and prostate cancer showed non-significant association.

Published meta-analysis or pooled analysis
In a published pooled analysis of two randomised controlled trials and five prospective cohorts, the summary pooled multivariate RR of prostate cancer per 10 nmol/L serum folate increase was 1.11 (95% CI 0.96-1.28; p = 0.20) (Collin et al, 2010).

Table 183 Studies on serum folate identified in the CUP

Author, year	Country	Study name	Cases	Years of follow up	RR	LCI	UCI	Contrast
De Vogel, 2013	Norway	JANUS Serum Bank	3000	-	1.15	0.97	1.37	≥ 17.5 vs. < 10.9 nmol/L
Beilby, 2010	Australia	Australia Mesothelioma Registry	92	14 years maximum	1.09	0.48	2.46	6.30-45.1 vs. 1.50-3.80 µg/L
Collin, 2010	UK	Prostate testing for cancer and Treatment study	1461	8 years maximum	1.01	0.82	1.24	> 26.2 vs. < 10.8 nmol/L
Johansson, 2008	Europe	European Prospective Investigation into Cancer and Nutrition	855	7 years maximum	1.30	0.88	1.93	≥ 16.55 vs. < 4.82 nmol/L
Rossi, 2006	Australia	Busselton Health Survey, 1969	52 events	29 years	1.18	0.90	1.51	Per 2 µg/L decrease

Table 184 Overall evidence on serum folate and prostate cancer

	Summary of evidence
2005 SLR	Two studies were included in the 2005 SLR meta-analysis reporting no significant associations.
Continuous Update Project	Five new studies were identified in the CUP, all reported non-significant association towards increased risk of prostate cancer. Overall, seven studies were included in the meta-analysis. A weak RR of borderline significance was obtained in the CUP meta-analysis.

Table 185 Summary of results of the dose response meta-analysis of serum folate and prostate cancer

Prostate cancer		
	2005 SLR*	CUP
Studies (n)	2	7
Cases (n)	478	5938
Increment unit used	Per 10 nmol/L	Per 5 nmol/L
Overall RR (95%CI)	1.33 (0.87-2.05)	1.01 (1.00-1.02)
Heterogeneity (I^2,p-value)	0%, p = 0.71	49.2%, p = 0.07

* No stratified meta-analysis was conducted in the 2005 SLR.

Table 186 Inclusion/exclusion table for meta-analysis of serum folate and prostate cancer

WCRF code	Author	Year	Study design	Study name	Cancer outcome	2005 SLR	CUP dose-response meta-analysis	CUP HvL forest plot	Estimated values	Exclusion reasons
PRO100157	De Vogel	2013	Nested case control study	JANUS Serum Bank	Incidence	No	Yes	Yes	Midpoints	
PRO100178	Beilby	2010	Nested case control study	Australia Mesothelioma Registry	Incidence	No	Yes	Yes	Midpoints	
PRO100181	Collin	2010	Nested case control study	Prostate testing for cancer and Treatment (ProtecT) study	Incidence	No	Yes	Yes	Cases per quintile, midpoints	
PRO100029	Johansson	2008	Nested case control study	European Prospective Investigation into Cancer and Nutrition	Incidence	No	Yes	Yes	Midpoints	
PRO100043	Rossi	2006	Prospective cohort study	Busselton (Western Australia) Health Survey, 1969	Incidence/ mortality	No	Yes	No	Inverted HR and rescaled for a continuous increment	
PRO97481	Hultdin	2005	Nested case control study	Västerbotten Intervention Project (VIP) and the WHO Northern Sweden Monitoring Trends and Determinants of Cardiovascular Disease (MONICA) study	Incidence	Yes	Yes	Yes	Midpoints	
PRO00139	Weinstein	2003	Nested case control study	ATBC Study	Incidence	Yes	Yes	Yes	Midpoints	

Figure 202 Highest versus lowest forest plot of serum folate and prostate cancer

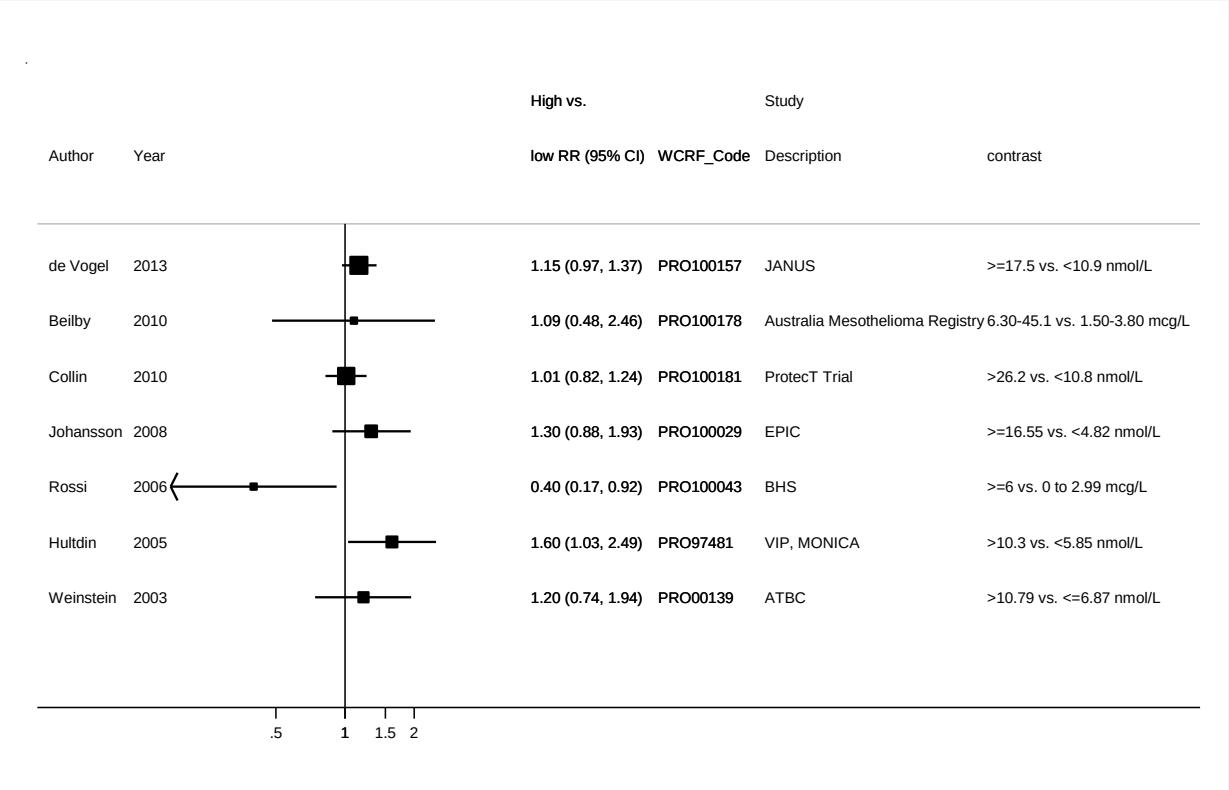


Figure 203 Dose-response meta-analysis of serum folate and prostate cancer - per 5 nmol/L

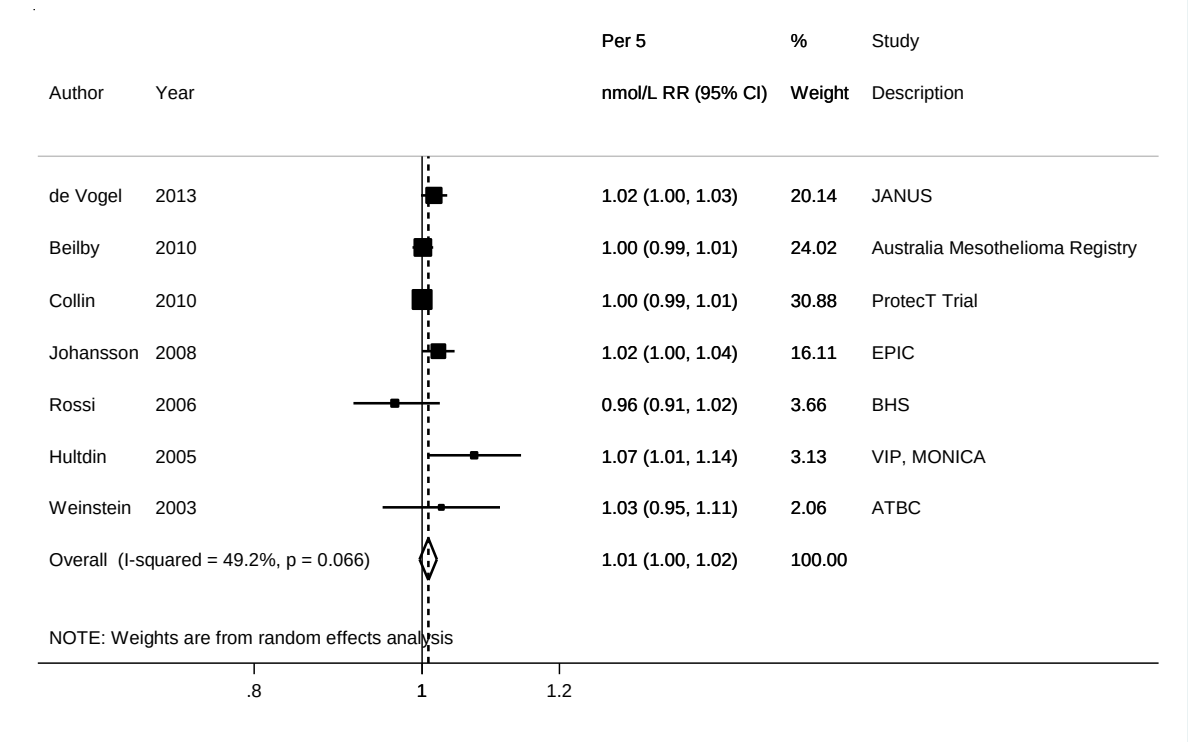
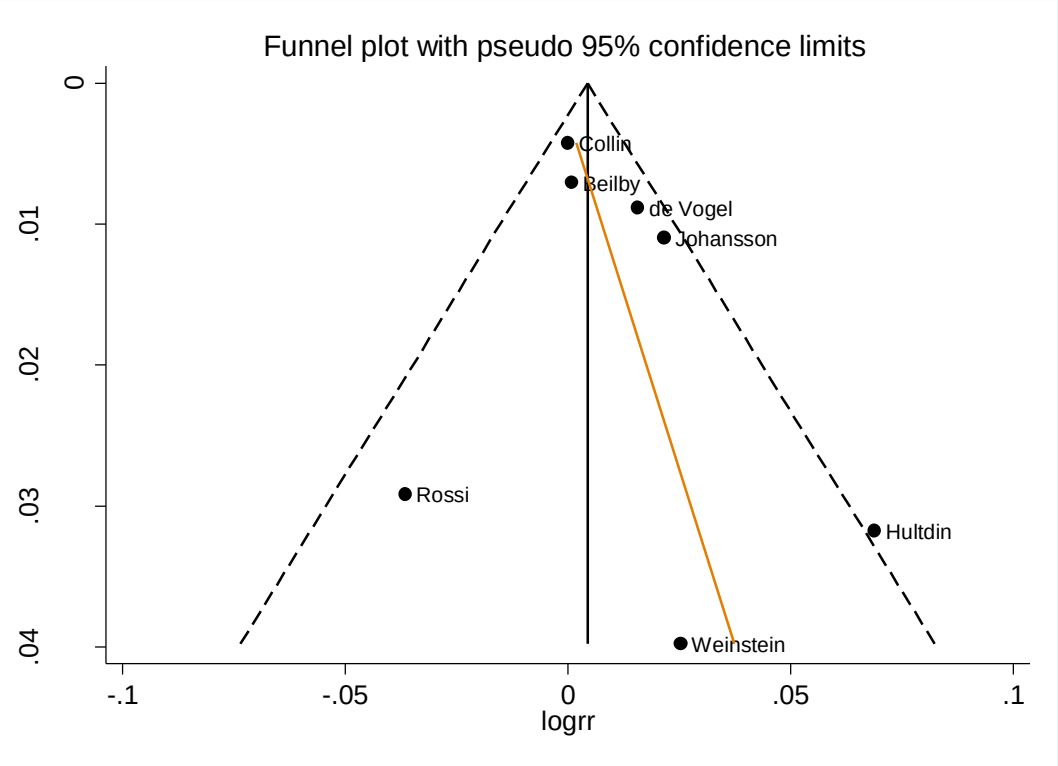
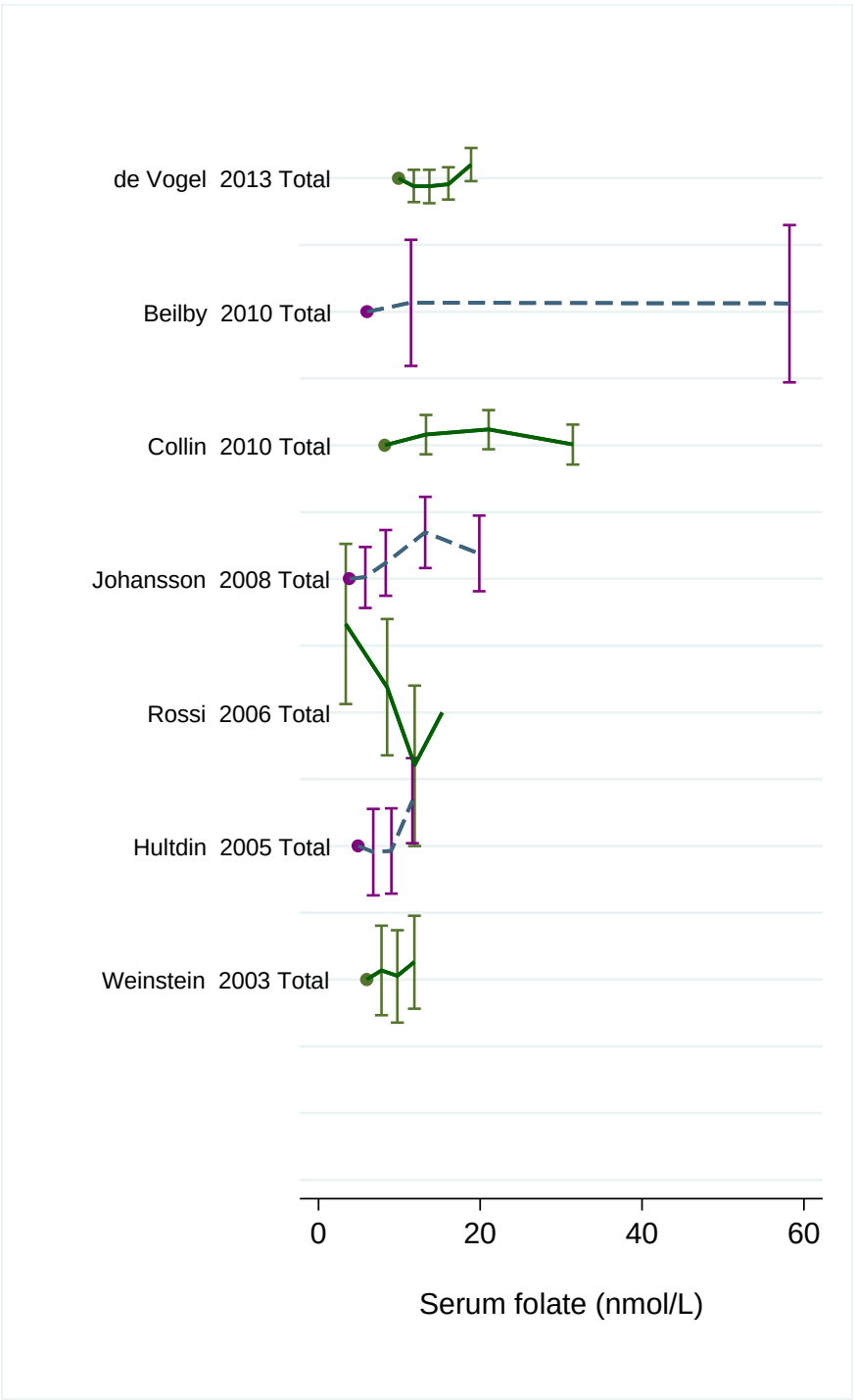


Figure 204 Funnel plot of serum folate and prostate cancer



Egger's test p = 0.31

Figure 205 Dose-response graph of serum folate and prostate cancer



5.5.9 Dietary vitamin C

Methods
A total of 11 publications including 9 cohort studies of dietary vitamin C and prostate cancer were identified. Five of these publications were identified in the CUP. Dose-response analysis was conducted per 40 mg/day increase. Two publications from ATBC cohort identified in the 2005 SLR (Woodson et al, 2003; Hirvonen et al, 2001) only reported mean values and could not be included in the analysis.

From the studies included in the dose-response meta-analysis: five studies reported on total prostate cancer (Roswall et al, 2013; Kirsh et al, 2006; Parker et al, 1999; Daviglus et al, 1996; Shibata et al, 1992), one reported on total, nonadvanced, advanced and stage IV prostate cancer (Geybels et al, 2012).

Kristal et al, 2010 study reported RR for low-grade (GS 2-7) and high-grade (GS 8-10) prostate cancer separately. Results were pooled in order to conduct a dose-response meta-analysis of total prostate cancer risk.

Main results
The summary RR per 40 mg/day increase was 1.02 (95% CI 0.98-1.05; $I^2 = 37.2\%$; $p_{heterogeneity} = 0.15$; n = 7). There was no evidence of publication bias with Egger's test, p = 0.15.

Heterogeneity
Overall, there was moderate evidence of heterogeneity, $I^2 = 37.2\%$, $p_{heterogeneity} = 0.15$.

Comparison with the Second Expert Report
In the 2005 SLR the meta-analysis on dietary vitamin C and prostate cancer showed non-significant association.

Published meta-analysis or pooled analysis
No published meta-analyses or pooled studies were identified.

Table 187 Studies on dietary vitamin C identified in the CUP

Author, year	Country	Study name	Cases	Years of follow up	RR	LCI	UCI	Contrast
Roswall, 2013	Denmark	Diet, Cancer and Health	1571	14.3 years	0.95	0.83	1.08	Per 100 mg/day increase
					0.92	0.77	1.09	> 121.5 vs. ≤ 70.6 mg/day
Geybels, 2012	The Netherland	Netherlands Cohort Study	3451	17.3 years	1.14	0.97	1.35	145.7 vs. 54.5 mg/day
Kristal, 2010	USA and Canada	The Prostate Cancer Prevention Trial	1703	10 years max	1.05	0.89	1.25	GS 2-7 > 179.1 vs. < 78.7 mg/day
					1.24	0.71	2.15	GS 8-10 > 179.1 vs. < 78.7 mg/day
Kirsh, 2006	USA	PLCO Cancer Screening Trial	1338	4.2 years	1.00	0.83	1.22	263 vs. 77 mg/day
Stram, 2006	USA	Multiethnic cohort study	3922	8 years	1.06	0.93	1.18	>106.4 vs. ≤ 37.9 mg/1000 kcal

Table 188 Overall evidence on dietary vitamin C and prostate cancer

	Summary of evidence
2005 SLR	Five studies were included in the 2005 SLR meta-analysis. One study reported a significant positive association between dietary vitamin C intake and the risk of prostate cancer.
Continuous Update Project	Five new studies were identified in the CUP. None of the studies reported significant associations. Seven studies were included in the meta-analysis and no significant association was found.

Table 189 Summary of results of the dose response meta-analysis of dietary vitamin C and prostate cancer

Prostate cancer		
	2005 SLR*	CUP
Studies (n)	5	7
Cases (n)	1260	8484
Increment unit used	Per 40 mg/day	Per 40 mg/day
Overall RR (95% CI)	1.06 (0.98-1.15)	1.02 (0.98-1.05)
Heterogeneity (I^2, p-value)	38.1%, p = 0.17	37.2%, p = 0.15

* No stratified meta-analysis was conducted in the 2005 SLR.

Table 190 Inclusion/exclusion table for meta-analysis of dietary vitamin C and prostate cancer

WCRF code	Author	Year	Study design	Study name	Cancer outcome	2005 SLR	CUP dose-response meta-analysis	CUP HvL forest plot	Estimated values	Exclusion reasons
PRO100159	Roswall	2013	Prospective cohort study	Diet, Cancer and Health	Incidence	No	Yes	Yes	Rescale of reported RR for continuous increase	
PRO100198	Geybels*	2012	Case cohort study	Netherlands Cohort Study	Incidence	No	Yes	Yes		
PRO100078	Kristal	2010	Nested case control study	The Prostate Cancer Prevention Trial	Incidence	No	Yes	Yes	Mid-exposure values	
PRO99992	Kirsh	2006b	Prospective cohort study	PLCO Cancer Screening Trial	Incidence	No	Yes	Yes	Person years per quintile	
PRO99986	Stram	2006	Prospective cohort study	Multiethnic cohort study	Incidence	No	No	Yes		Energy intake is not provided to convert mg/1000kcal
PRO00272	Woodson	2003	Nested case control study	ATBC Study	Incidence/mortality	Yes	No	No		Means only
PRO00764	Schuurman	2002	Case cohort study	Netherlands Cohort Study	Incidence	Yes	Yes	Yes		Superseded by Geybels, 2012
PRO01034	Hirvonen	2001	Prospective cohort study	ATBC Study	Incidence/mortality	Yes	No	No		Means only. Same study as Woodson 2003
PRO01737	Parker*	1999	Prospective cohort study	USA Iowa 1986/1989-1995	Incidence	Yes	Yes	Yes	Mid-exposure values,	
PRO02487	Daviglus	1996	Prospective cohort study	Western Electric Study	Incidence	Yes	Yes	Yes	Mid-exposure values	
PRO13404	Shibata	1992	Prospective cohort study	USA California 1981/1985-1989	Incidence	Yes	Yes	Yes	Mid-exposure values, person years per tertile	

*Age adjusted results.

Figure 206 Highest versus lowest forest plot of dietary vitamin C and prostate cancer

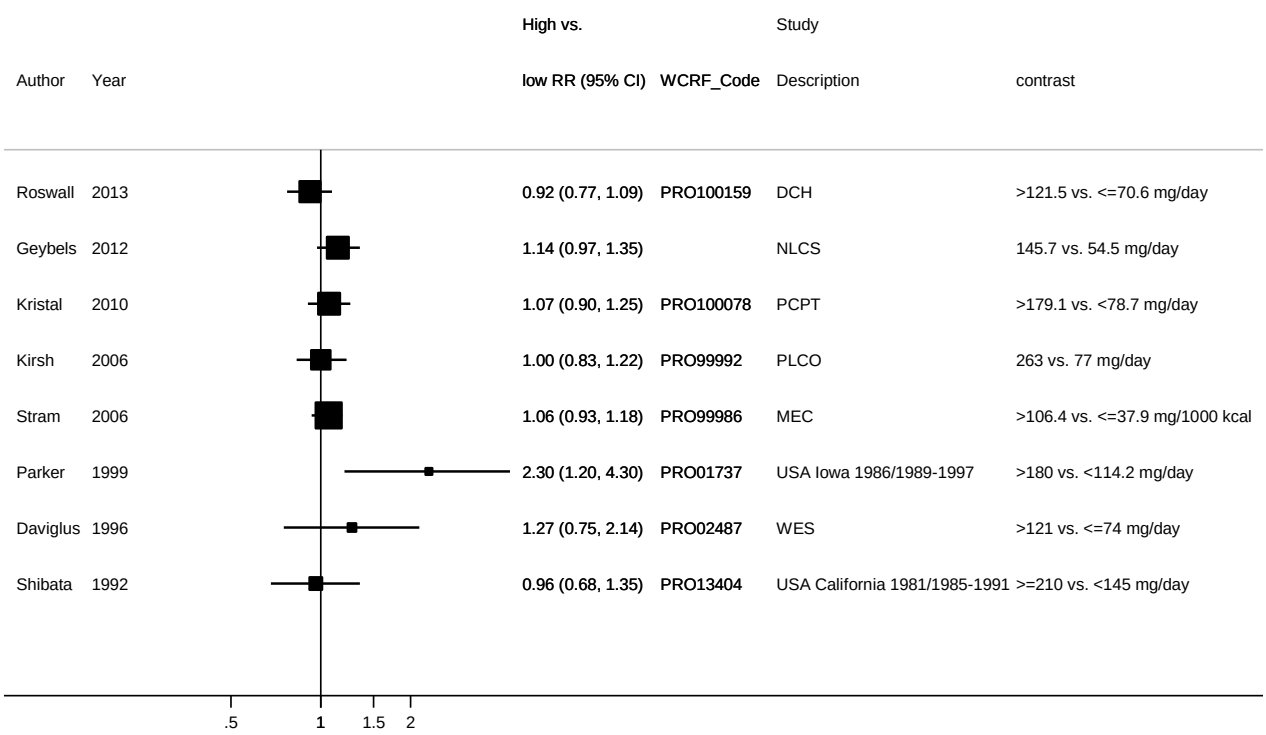


Figure 207 Dose-response meta-analysis of dietary vitamin C and prostate cancer - per 40 mg/day

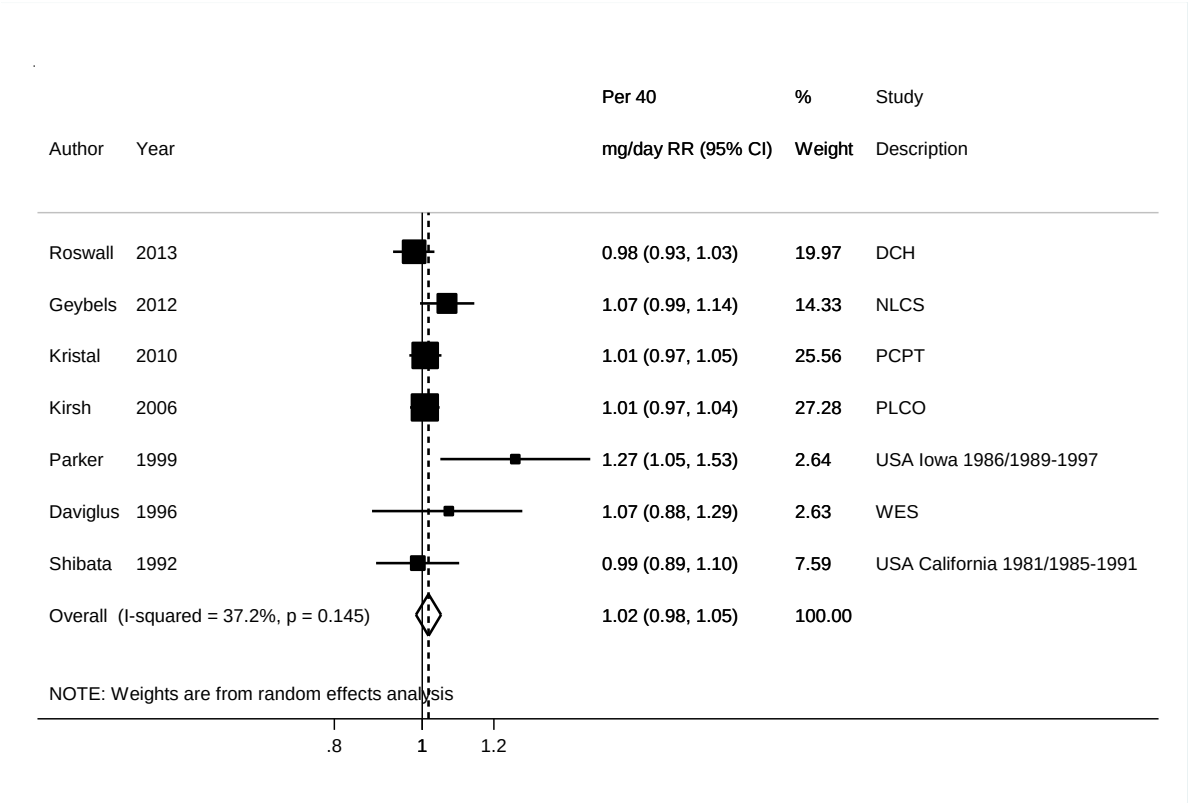
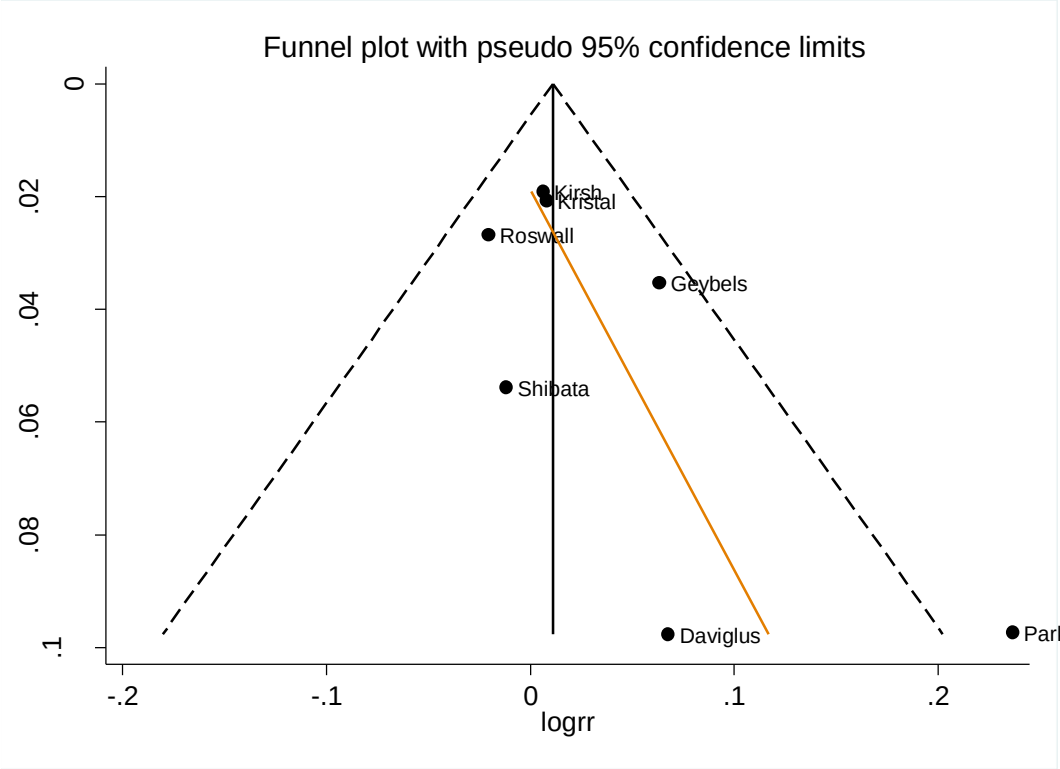
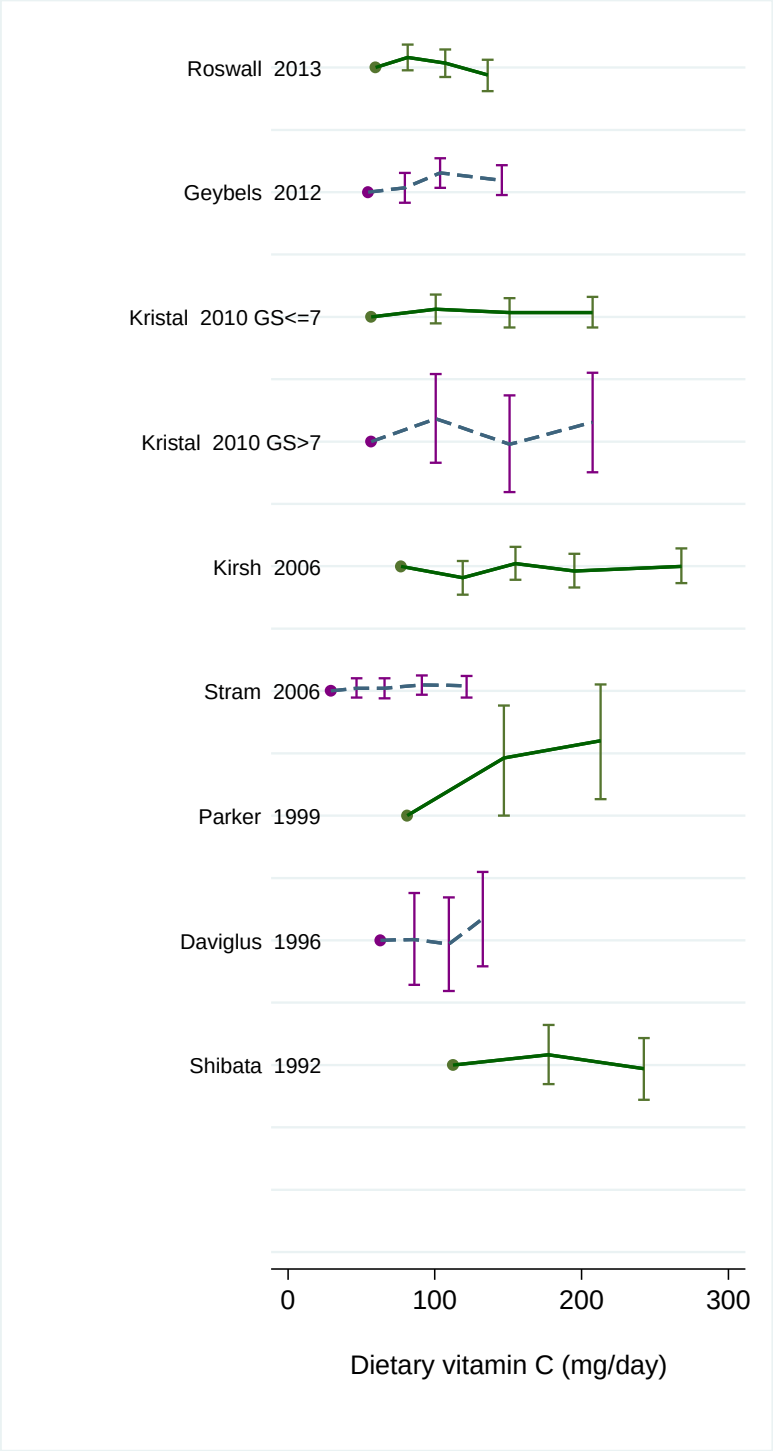


Figure 208 Funnel plot of dietary vitamin C and prostate cancer



Egger's test p = 0.15

Figure 209 Dose-response graph of dietary vitamin C and prostate cancer



5.5.10 Blood 25-hydroxy vitamin D

Methods

Twenty-four publications from nineteen studies were identified, from which 10 studies from 14 publications were identified in the CUP .Two studies were updated publications of studies identified in the 2005 SLR (HPFS and PHS) and one study was published twice during the CUP (ATBC study).

The increment unit used in the dose-response analysis was 30 nmol/l. From the studies included in the dose-response meta-analysis four studies were on plasma 25-hydroxy vitamin D and 13 were on serum 25-hydroxyvitamin D. Three studies previously identified in the 2005 SLR reported on plasma 1,25-hydroxy vitamin D and two studies reported on serum 1,25-hydroxy vitamin D. No new studies on 1,25-hydroxy vitamin D were identified.

From the studies included in the dose-response meta-analysis: nine studies included total prostate cancer (Braun et al, 1995; Nomura et al, 1998; Jacobs et al, 2004; Tuohimaa et al, 2004; Baron et al, 2005; Park et al, 2010; Albanes et al, 2011; Brändstedt et al, 2012; Ordonez et al, 2013), one included total and aggressive prostate cancer (Li et al, 2007), one study included total, advanced and unknown metastasis status prostate cancer (Meyer et al, 2013), one study included prostate cancer incidence, prostate cancer mortality, fatal, advanced and high grade (Shui et al, 2012), one study included Gleason score < 7 and Gleason score ≥ 7 prostate cancer (Barnett et al, 2010), one studied included total, localised, advanced, low and high grade prostate cancer (Travis et al, 2009) one studied included total, non-aggressive (Gleason sum <7 and stage <III), aggressive with lenient definition (Gleason sum ≥ 7 or stage III or IV), high stage aggressive (stage III or IV, any Gleason sum), high grade aggressive (Gleason sum ≥ 7, any stage) and aggressive disease with stringent definition (Gleason sum ≥ 8 or stage III or IV) (Ahn et al, 2008b) and one study total, aggressive Gleason score ≥ 7, less aggressive Gleason score < 7 prostate cancer (Platz et al, 2004). In order to conduct stratified analysis by prostate cancer type, advanced, aggressive, high grade and Gleason score ≥ 7 prostate cancer were combine in an advance/high grade subgroup and non-advanced, localised, low grade, Gleason score < 7 prostate cancer were combined in non-advanced/low grade subgroup.

Main results

The summary RR per 30nmol/l per day was 1.04 (95% CI 1.00-1.07; $I^2 = 0\%$; $p_{heterogeneity} = 0.50$; n = 17). There was no evidence of publication bias with Egger's test, p = 0.48. The RR for advanced/high grade cancers was 1.01(95% CI 0.93-1.10; $I^2 = 0\%$; $p_{heterogeneity} = 0.44$; n = 6) and for non-advanced/low grade was 1.04 (95% CI 0.97-1.13; $I^2 = 0\%$; $p_{heterogeneity} = 0.68$; n = 5). There was evidence of non-linearity in the association for total prostate cancer ($p<0.01$) and for advanced prostate cancer (p = 0.02). The curves suggest that individuals with higher blood 25-hydroxy vitamin D levels may be at higher risk of prostate cancer.

Heterogeneity

Overall, there was low evidence of heterogeneity, $I^2 = 0\%$, $p_{heterogeneity} = 0.50$.

Comparison with the Second Expert Report

In the 2005 SLR, the meta-analysis on blood 25-hydroxy vitamin D and prostate cancer showed a non-significant association.

Published meta-analysis or pooled analysis

A meta-analysis including 14 cohort/nested case–control studies investigated the association between 25(OH) D and total prostate cancer. This gave a total of 4,353 prostate cancer cases. There were 6 studies that included 871 aggressive prostate cancer cases. The summary random-effects OR estimate per 10 ng/mL increase in 25(OH) D was 1.04 (95% CI 0.99-1.10; p = 0.12; I^2 = 0%; p = 0.95). For aggressive prostate cancer, the summary random- effects OR per 10 ng/mL increase in 25(OH) D was 0.98 (0.84, 1.15; p = 0.78; I^2 = 32%; p = 0.19). Seven cohort/nested case–control studies investigated 1,25(OH)2 D. Overall, the summary random-effects OR estimate per 10 pg/mL increase in 1,25(OH)2 D was 1.00 (0.87, 1.14; p = 0.96,I^2 = 41%, p = 0.12) (Gilbert et al, 2011).

Table 191 Studies on 25-hydroxy vitamin D identified in the CUP

Author, year	Country	Study name	Cases	Years of follow up	RR	LCI	UCI	Contrast
Ordonez, 2013	Germany	ESTHER study	171	8 years	1.21	0.86	1.70	> 61.5 vs. 36.5-61.5 nmol/l
Meyer, 2013	Norway	Norway 1981-2006	2106	16.1 years	1.17	0.93	1.48	≥ 90 vs. 50-69 nmol/l
					1.13	1.02	1.25	Per 30 nmol/l
Brändstedt, 2012	Sweden	Malmö Diet and Cancer Study cohort	943	7.6 years	1.34	0.99	1.82	≥ 103 vs. ≤ 68 nmol/l
Shui, 2012	USA	Health Professionals Study	1260	18 years	1.07	0.86	1.34	Incidence Q4 vs. Q1
					0.44	0.24	0.79	Mortality Q4 vs. Q1
Albanes, 2011	Finland	ATBC	1000	12.6 years	1.16	0.73	1.86	> 75 vs. < 25 nmol/l
Freedman, 2010	USA	NHANES III	74	13.4 years	1.23	0.50	3.05	≥ 80 vs. < 50 nmol/L
Park, 2010	USA and Hawaii	Multiethnic Cohort Study	329	13 years	1.17	0.72	1.89	≥ 39.9 vs. < 22.9 ng/ml
Barnett, 2010	USA	Osteoporotic Fractures in Men (MrOS) study	297	5.3 years	1.20	0.81	1.78	35.2 vs. 15.5 ng/ml
Travis, 2009	Europe	EPIC	652	4.1 years	1.28	0.88	1.88	70.9-163.7 vs. 2.5-40.4 nmol/l
Ahn, 2008b	USA	PLCO	749	8 years	1.08	0.77	1.53	Q5 vs. Q1
Tuohimaa, 2007	Finland	Helsinki Heart Study	132	10.8 years	1.25	0.64	2.43	≥ 60 vs. < 40 nmol/l

Faupel-Badger, 2007	Finland	ATBC	296	19 years	0.89	0.49	1.62	> 23.98 vs. ≤ 14.79
Li, 2007	USA	Physician's Health Study	1066	18 years	1.01	0.71	1.44	Q1 vs. Q4
Giovannucci, 2006b	USA	Health Professionals Study	461 cases of advanced prostate	14 years	0.8	0.58	1.19	Per 25 nmol/l

Table 192 Overall evidence on 25-hydroxy vitamin D and prostate cancer

	Summary of evidence
2005 SLR	Eight studies were included in the 2005 SLR meta-analysis. All were non-significant.
Continuous Update Project	Ten new studies were identified in the CUP, all showed a non-significant increased risk for higher levels of 25-hydroxy vitamin D. One study reported a positive association with fatal cancers. A weak borderline positive association for total prostate cancers was observed in the CUP meta-analysis.

Table 193 Summary of results of the dose response meta-analysis of 25-hydroxy vitamin D and prostate cancer

Prostate cancer		
	2005 SLR	CUP
Studies (n)	8	17
Cases (n)	1581	7802
Increment unit used	Per 10 mcg/l	Per 30 nmol/l
Overall RR (95%CI)	1.01 (0.94-1.10)	1.04 (1.00-1.07)
Heterogeneity (I^2, p-value)	0%, p = 0.82	0%, p = 0.50
Stratified analysis		
Advanced/high grade cancer		
Overall RR (95%CI)		1.01 (0.93-1.10)
Heterogeneity (I^2, p-value)		0%, p = 0.44, n = 6
Non-advanced/low grade cancer		
Overall RR (95%CI)		1.04 (0.97-1.13)
Heterogeneity (I^2, p-value)		0%, p = 0.68, n = 5

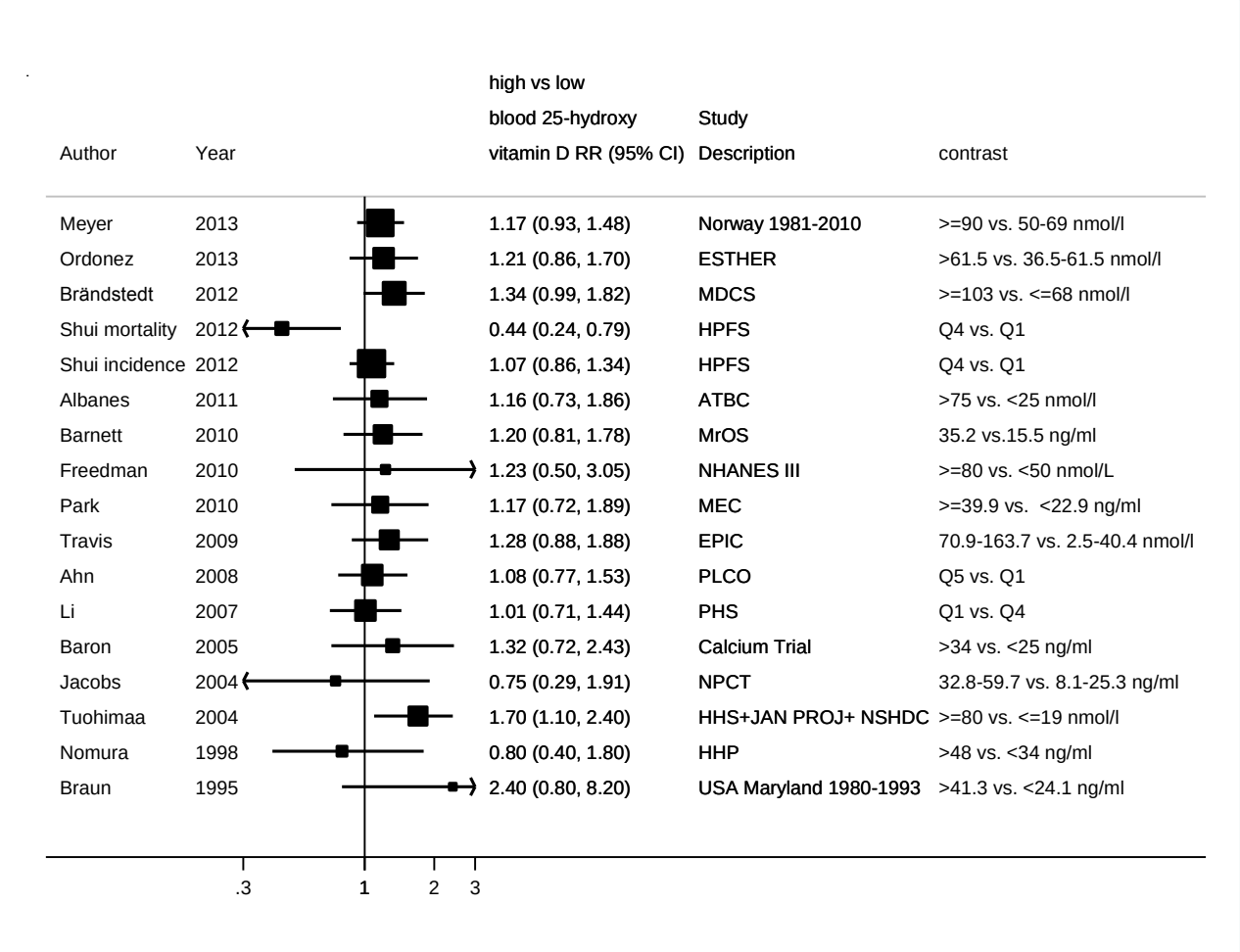
Table 194 Inclusion/exclusion table for meta-analysis of blood 25-hydroxy vitamin D and prostate cancer

WCRF code	Author	Year	Study design	Study name	Cancer outcome	2005 SLR	CUP dose-response meta-analysis	CUP HvL forest plot	Estimated values	Exclusion reasons
PRO100144	Ordonez	2013	Prospective Cohort study	ESTHER study, Germany	Incidence	No	Yes	Yes	Mid-exposure values, Person-years per quintile	
PRO100166	Meyer	2013	Nested case-control study	Norway 1981-2006	Incidence	No	Yes	Yes	Mid-exposure values	
PRO100154	Brändstedt	2012	Nested case-control study	Malmö Diet and Cancer Study cohort	Incidence	No	Yes	Yes	Mid-exposure values	
PRO100151	Shui	2012	Nested case-control study	Health Professionals Study	Incidence /Mortality	No	No	Yes		Quintile range missing, Platz, 2004 used in the dose-response analysis
PRO100175	Albanes	2011	Nested case-control study	ATBC	Incidence /Mortality	No	Yes	Yes	Mid-exposure values, conversion from ng/ml to nmol/l	
PRO100200	Freedman	2010	Prospective Cohort study	NHANES III	Mortality	No	No	Yes		Only two categories
PRO100179	Park	2010	Nested case-control study	Multiethnic Cohort Study	Incidence	No	Yes	Yes	Mid-exposure values, conversion from ng/ml to nmol/l	
PRO100180	Barnett	2010	Case-cohort study	Osteoporotic Fractures in Men (MrOS) study	Incidence	No	Yes	Yes	Conversion from ng/ml to nmol/l	
PRO100059	Travis	2009	Nested case-control study	EPIC	Incidence	No	Yes	Yes		
PRO99996	Ahn	2008b	Nested case-control study	PLCO	Incidence /Mortality	No	Yes	Yes	Mid-exposure values	
PRO100017	Tuohimaa	2007	Nested case-control study	Helsinki Heart Study	Incidence	No	No	No		Only reported interactions, Tuohimaa, 2004 was used instead
PRO100013	Faupel-	2007	Nested case-	ATBC	Incidence	No	No	No		Superseded by Albanes, 2011

	Badger		control study							
PRO99997	Li	2007	Nested case-control study	Physician's Health Study	Incidence	No	Yes	Yes	Conversion from ng/ml to nmol/l	
PRO99991	Giovannucci	2006b	Nested case-control study	Health Professionals Study	Mortality	No	No	No		Superseded by Shui, 2012
PRO97184	Baron	2005	Prospective Cohort study	Calcium Trial, USA	Incidence	Yes	Yes	Yes	Mid-exposure values, Conversion from ng/ml to nmol/l, person-years per quintile	
PRO00254	Tuohimaa	2004	Nested case-control study	HHS 81-82/ JAN PROJ 73/ NSHDC 85*	Incidence	Yes	Yes	Yes	Mid-exposure values	
PRO10575	Platz	2004c	Nested case-control study	Health Professionals Study	Incidence /Mortality	Yes	Yes	No	Conversion from ng/ml to nmol/l	
PRO97667	Jacobs	2004	Nested case-control study	Nutritional Prevention of Cancer Trial	Incidence	Yes	Yes	Yes	Mid-exposure values, conversion from ng/ml to nmol/l	
PRO01427	Ahonen	2000	Nested case-control study	Helsinki Heart Study	Incidence	Yes	No	No		Superseded by Tuohimaa, 2004
PRO02122	Ma	1998	Nested case-control study	Physician's Health Study	Incidence	Yes	No	No		Superseded by Li, 2007
PRO02014	Nomura	1998	Nested case-control study	Honolulu Heart Program	Incidence	Yes	Yes	Yes	Mid-exposure values, conversion from ng/ml to nmol/l	
PRO02492	Gann	1996	Nested case-control study	Physician's Health Study	Incidence	Yes	No	No		Superseded by Li, 2007
PRO02676	Braun	1995	Nested case-control study	USA Maryland 1980-1992	Incidence	Yes	Yes	Yes	Mid-exposure values, conversion from ng/ml to nmol/l	
PRO02868	Corder	1993	Nested case-control study	Kaiser Permanente Medical Care Program	Incidence	Yes	No	No		Identified in the 2005 SLR, not used due to insufficient data, reported in text there was no significant association between prostate cancer and blood vitamin D

***** Tuohimaa, 2004 counted as 3 studies.

Figure 210 Highest versus lowest forest plot of 25-hydroxy vitamin D and prostate cancer



For Ahn (2008) the quintile range used was 66.7-138 vs. 8-38.4 nmol/l for winter and spring-collected samples and 78.0-156.0 vs. 16.2-48.7 for summer and fall-collected samples.

For Li (2007) the quantile range used was 0 vs. 31.1 ng/ml for winter/spring-collected samples and 0 vs. 39.5 ng/ml for summer/fall-collected samples

Figure 211 Dose-response meta-analysis of 25-hydroxy vitamin D and prostate cancer – per 30 nmol/l

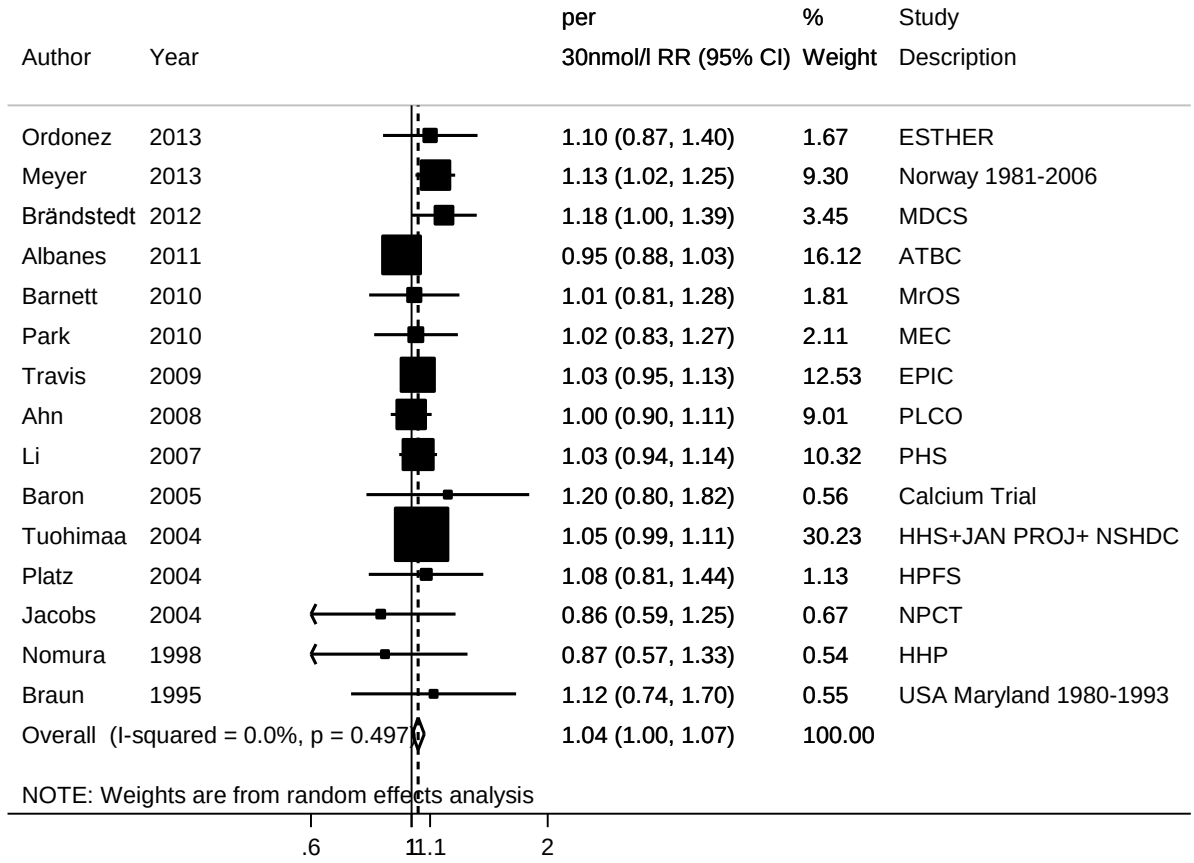
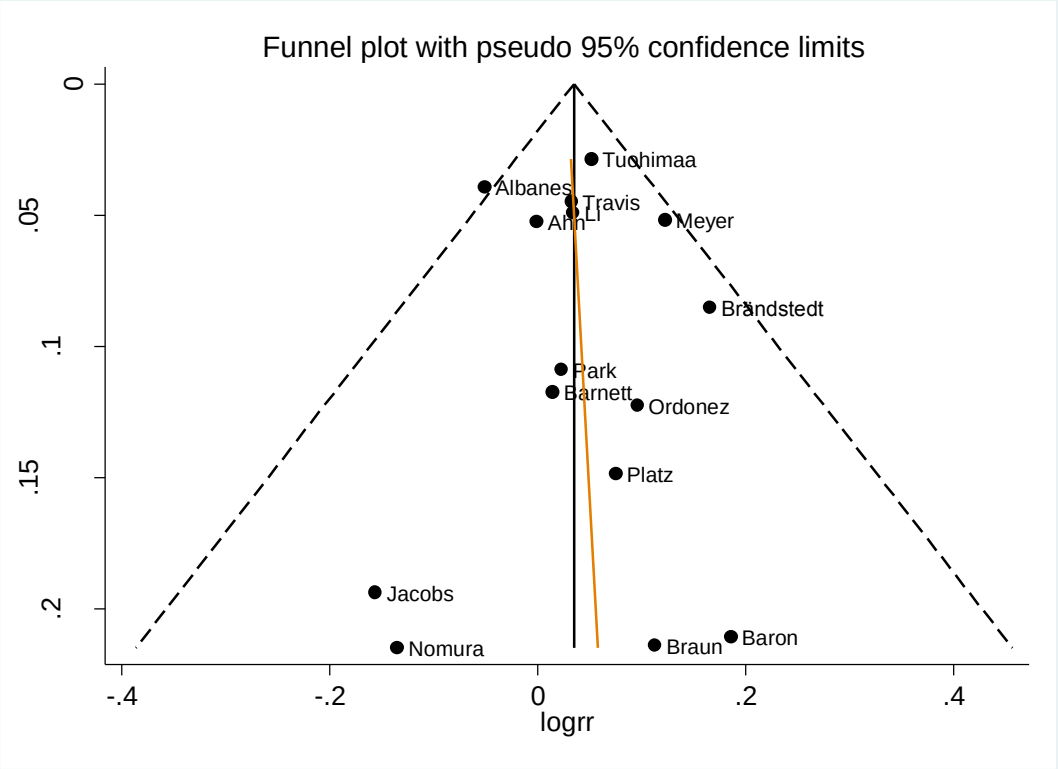


Figure 212 Funnel plot of 25-hydroxy vitamin D and prostate cancer



Egger's test p = 0.48

Figure 213 Dose-response graph of 25-hydroxy vitamin D and prostate cancer

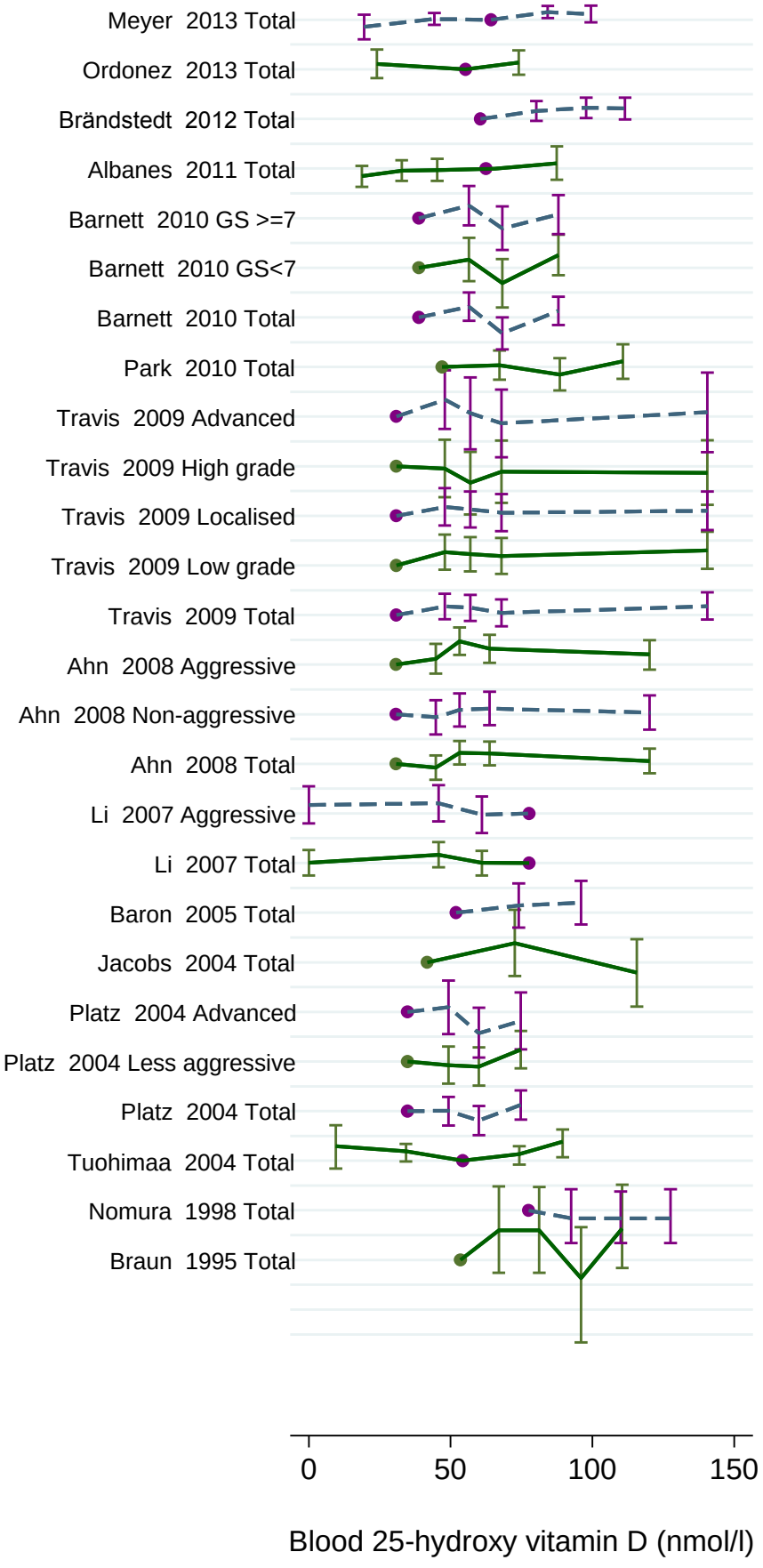


Figure 214 Dose-response meta-analysis of 25-hydroxy vitamin D and prostate cancer, per 30 nmol/l, stratified by prostate cancer type

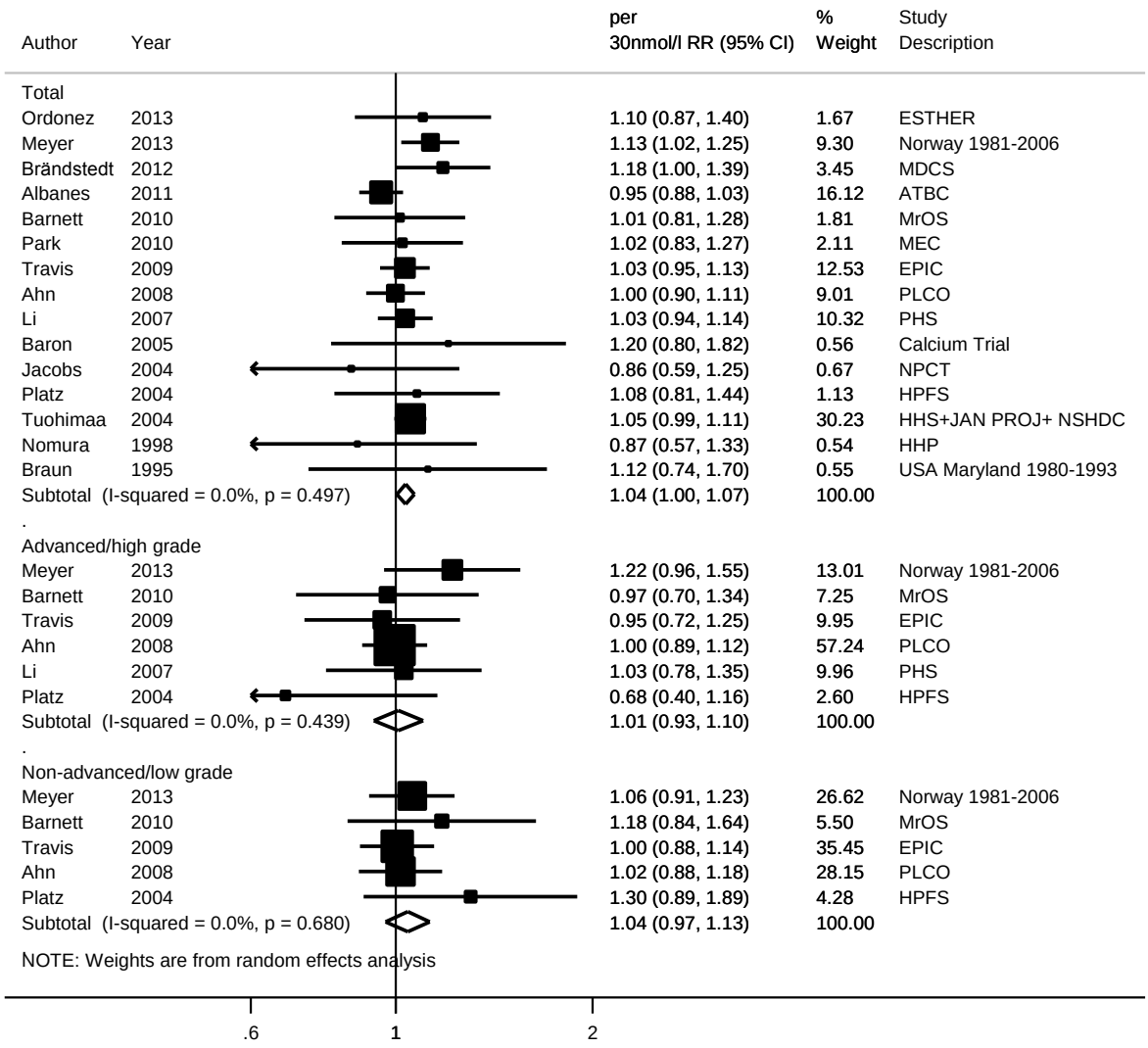
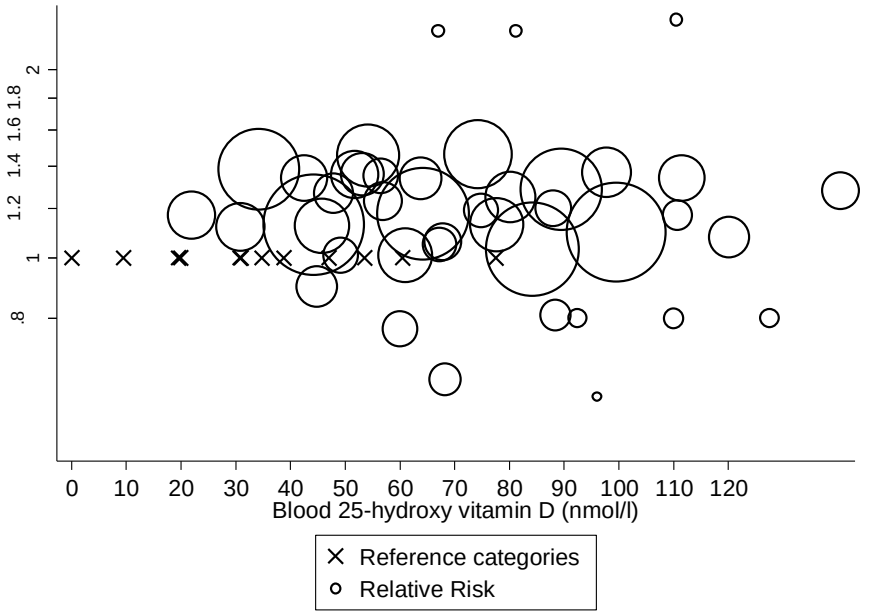


Figure 215 Non-linear dose-response analysis of 25-hydroxy vitamin D and total prostate cancer



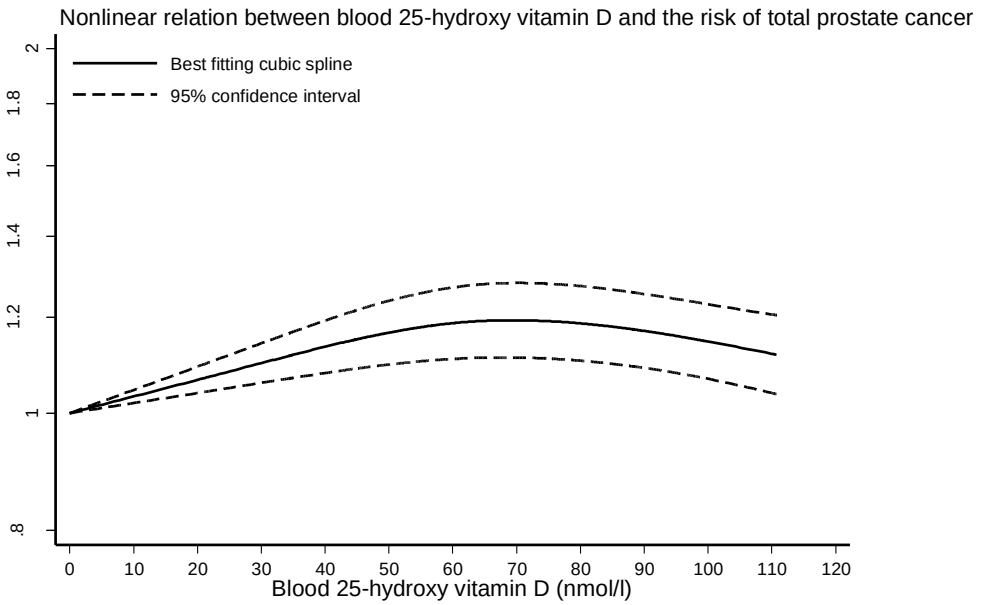
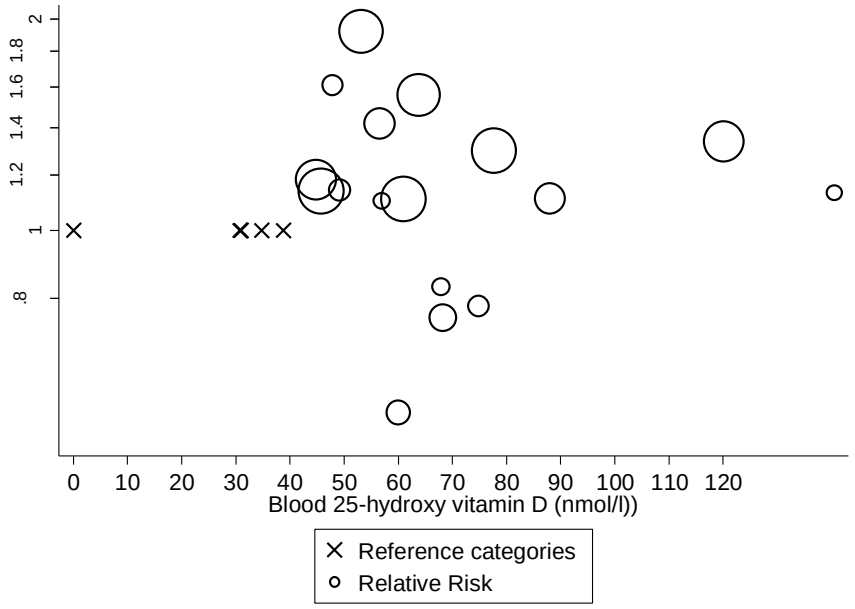


Table 195 Table with 25-hydroxy vitamin D values and corresponding RRs (95% CIs) for non-linear analysis of 25-hydroxy vitamin D and total prostate cancer

25-hydroxy vitamin D (nmol/l)	RR (95% CI)
0	1
30.8	1.10 (1.06-1.14)
60	1.18 (1.10-1.27)
92.5	1.16 (1.08-1.25)

$p_{non\text{-}linearity} < 0.01$

Figure 216 Non-linear dose-response analysis of 25-hydroxy vitamin D and advanced prostate cancer



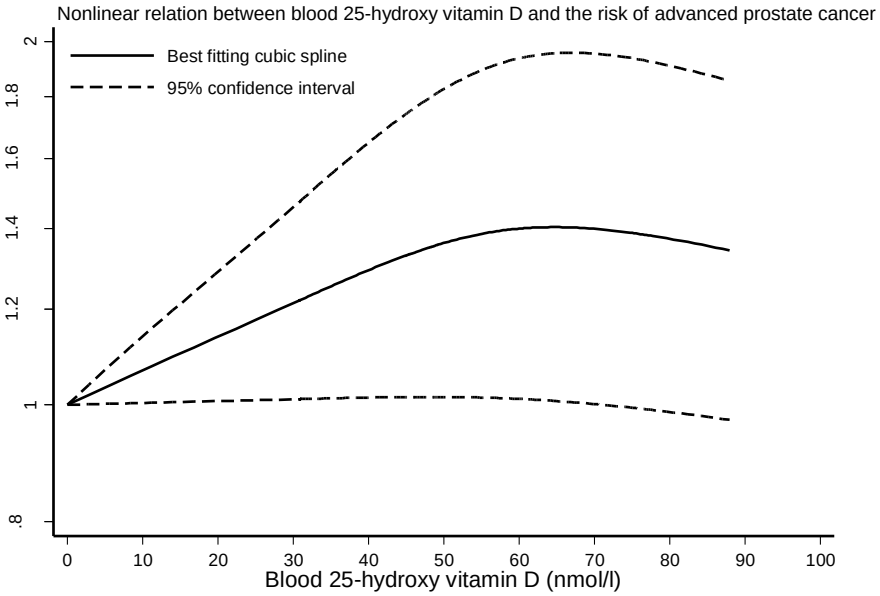


Table 196 Table with 25-hydroxy vitamin D values and corresponding RRs (95% CIs) for non-linear analysis of 25-hydroxy vitamin D and advanced prostate cancer

25-hydroxy vitamin D (nmol/l)	RR (95% CI)
0	1
30.8	1.22 (1.01-1.47)
60	1.39 (1.01-1.93)
88	1.34 (0.97-1.85)

$p_{non\text{-}linearity} = 0.02$

5.5.11 Dietary vitamin E

Methods
Nine publications from 6 cohort studies published on dietary vitamin E and prostate cancer; 5 were identified during the CUP. There are 3 publications from Alpha Tocopherol Beta Carotene Cancer Prevention study. Dose-response analyses were conducted per 10 mg/day.

The Multi-ethnic Cohort (MEC) Study (Stram et al, 2006) reported the intake of vitamin E in mg alpha-tocopherol equivalent per1000 kcal which was rescaled to mg/day using the average energy intake provided in the same study by Sharma et al, 2013.

Overall, 5 studies were included in the meta-analysis for total prostate cancer.

Main results
The summary RR per 10 mg/day of dietary vitamin E was 1.01 (95% CI 0.96-1.06; $I^2 = 20.4\%$; $p_{heterogeneity} = 0.29$). In influence analysis, the RR ranged from 1.02 (95% CI 0.98-1.07) to 0.99 (95% CI 0.93-1.06) after excluding the two studies (Kirsh et al, 2006; Stram et al, 2006) with incidence and mortality as outcome. No stratified analysis could be conducted.

Heterogeneity
There was low heterogeneity ($I^2 = 20.4\%$; $p_{heterogeneity} = 0.29$). Egger'stest showed no evidence of publication bias (p = 0.57).

Comparison with the Second Expert Report
No meta-analysis was conducted during the 2005 SLR.

Published meta-analysis or pooled analysis
No published meta-analyses or pooled studies were identified.

Table 197 Studies on dietary vitamin E identified in the CUP

Author/year	Country	Study name	Cases	Years of follow-up	RR	LCI	UCI	Contrast
Roswall, 2013	Denmark	Diet, Cancer and Health Cohort Study	1571	14.3 years	0.92	0.78	1.1	> 12 mg/day vs. ≤ 7.3 mg/day
					1.09	0.92	1.29	Per 10 mg/day
Geybels, 2012	Netherlands	Netherland Cohort Study	3451	17.3	1.08	0.92	1.27	22.4 mg/day vs. 7.7 mg/day
Peters, 2008	USA	VITamins And Lifestyle (VITAL) Study	830	≈4 years	0.90	0.70	1.2	≥ 17.1 mg alpha-TE/day vs. < 8.6 mg alpha-TE/day

Stram, 2006	USA	Hawaii-Los Angeles Multiethnic Cohort (MEC) Study	3922	≈ 7 years	1.07	0.97	1.19	> 6 mg vs. ≤ 3.9 mg alpha tocopherol equivalent/1000 kcal
Kirsh, 2006b	USA	Prostate, Lung, Colorectal, and Ovarian Cancer (PLCO) Screening Trial	1338	4.2 years	0.93	0.78	1.12	15.8 mg/day vs. 8.6 mg/day

Table 198 Overall evidence on dietary vitamin E and total prostate cancer

	Summary of evidence
2005 SLR	Four publications from 2 studies were identified during the 2005 SLR. No meta-analysis was conducted.
Continuous Update Project	Five new studies were identified during the CUP. Overall, 5 studies were included in the meta-analysis. A non-significant association was found.

Table 199 Summary of results of the dose-response meta-analysis of dietary vitamin E and total prostate cancer

Total prostate cancer incidence and mortality		
	2005 SLR*	CUP
Studies (n)	-	5
Cases (n)	-	11112
Increment unit used	-	Per 10 mg/day
Overall RR (95% CI)	-	1.01 (0.96-1.06)
Heterogeneity (I^2, p-value)	-	I^2 = 20.4%, p = 0.29

*No meta-analysis was conducted during the 2005 SLR.

Table 200 Inclusion/exclusion table for meta-analysis of dietary vitamin E and total prostate cancer

WCRF code	Author	Year	Study design	Study name	Cancer outcome	2005 SLR	CUP dose-response meta-analysis	CUP HvL forest plot	Estimated values	Exclusion reasons
PRO100159	Roswall	2013	Prospective Cohort Study	Diet, Cancer and Health Cohort Study	Incidence	No	Yes	Yes	Mid-exposure values Person years	
PRO100198	Geybels	2012	Case-cohort Study	Netherland Cohort Study	Incidence	No	Yes	Yes	Mid-exposure values	
PRO100182	Peters	2008	Prospective Cohort Study	VITamins And Lifestyle (VITAL) Study	Incidence	No	Yes	Yes	Mid-exposure values	
PRO99986	Stram	2006	Prospective Cohort Study	Hawaii-Los Angeles Multiethnic Cohort (MEC) Study	Mortality and incidence	No	Yes	Yes	Mid-exposure values Conversion of mg alpha toc equiv/1000 kcal to mg/day Person years Number of cases per quintiles	
PRO99992	Kirsh	2006 b	Prospective Cohort Study (Follow-up of screening arm in trial)	Prostate, Lung, Colorectal, and Ovarian Cancer (PLCO) Screening Trial	Mortality and incidence	No	Yes	Yes	Person years	
PRO97424	Weinstein	2005	Case-cohort Study	Alpha Tocopherol Beta Carotene Cancer Prevention Study	Incidence	Yes	No	No		Only means are shown.
PRO00764	Schuurman	2002	Case-cohort Study	Netherland Cohort Study	Incidence	Yes	No	No		Superseded by study of Geybels et al, 2012

PRO01034	Hirvonen	2001	Prospective Cohort Study	Alpha Tocopherol Beta Carotene Cancer Prevention Study	Mortality and incidence	Yes	No	No		Only means are shown. Superseded by study of Weinstein et al, 2005
PRO02143	Hartman	1998 b	Prospective Cohort Study	Alpha Tocopherol Beta Carotene Cancer Prevention Study	Mortality and incidence	Yes	No	No		Only means are shown. Superseded by study of Weinstein et al, 2005

Figure 217 Highest versus lowest forest plot of dietary vitamin E and total prostate cancer

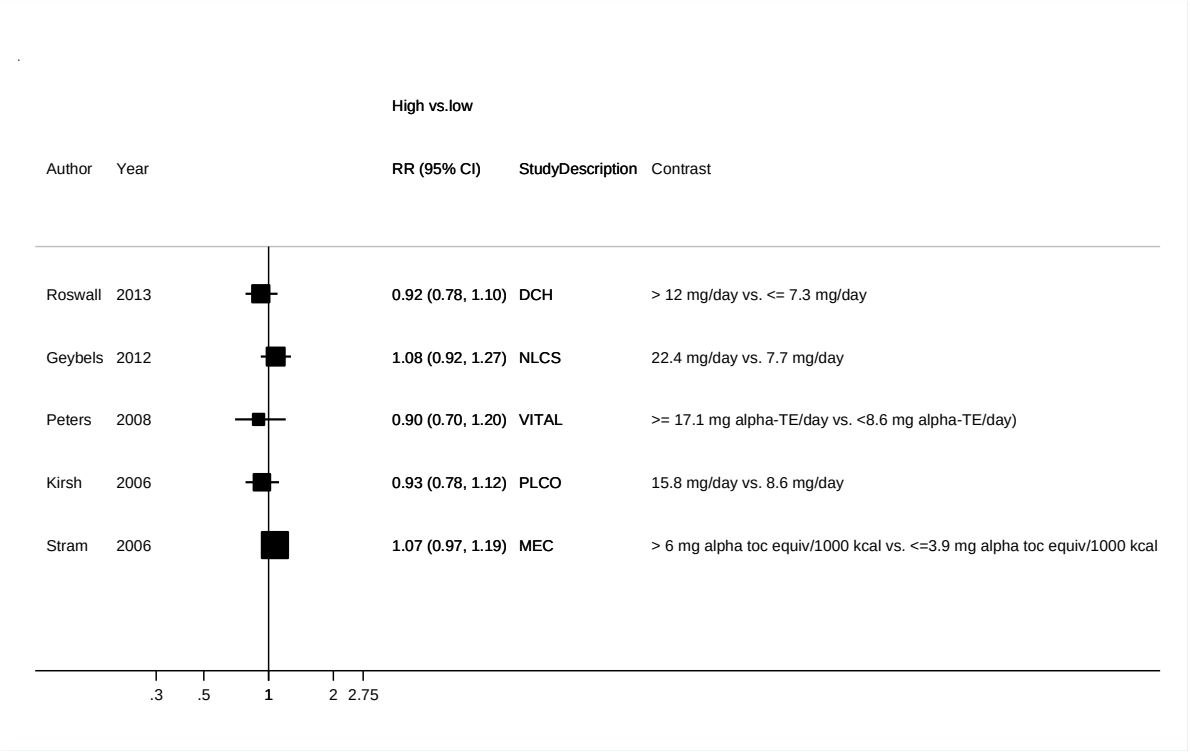


Figure 218 Dose-response meta-analysis of dietary vitamin E and total prostate cancer, per 10 mg/day

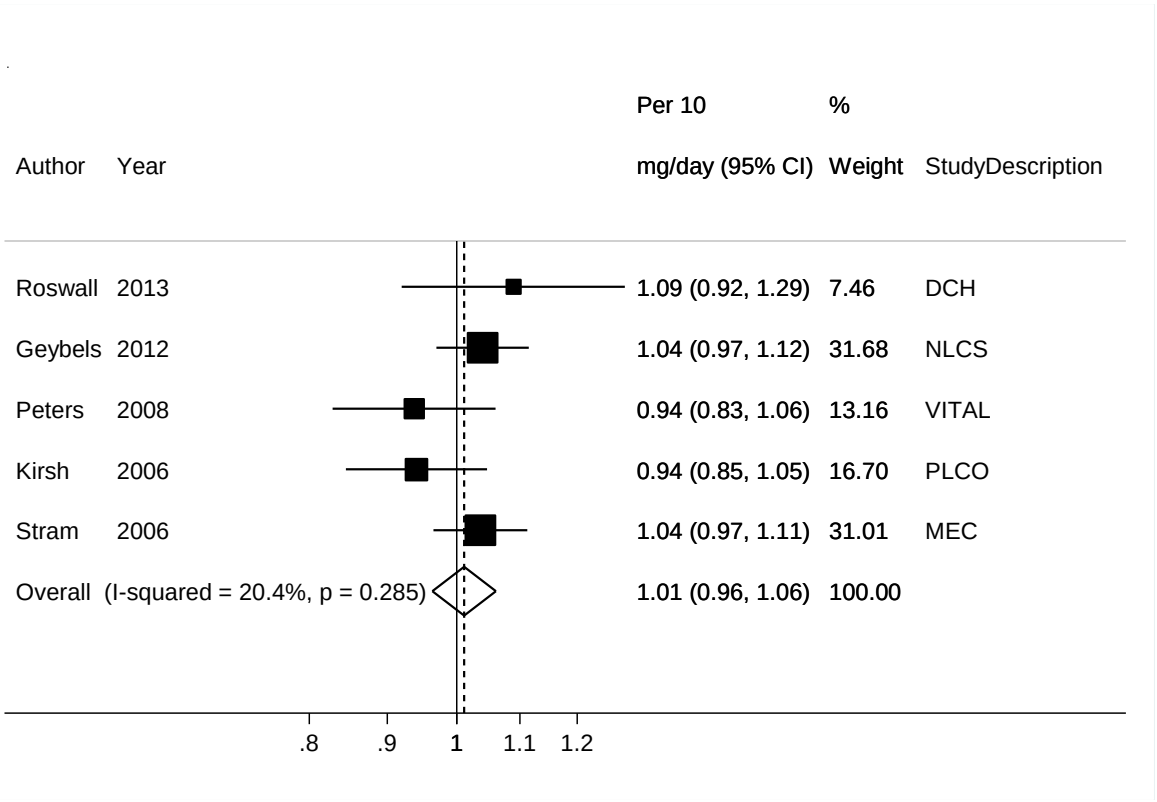
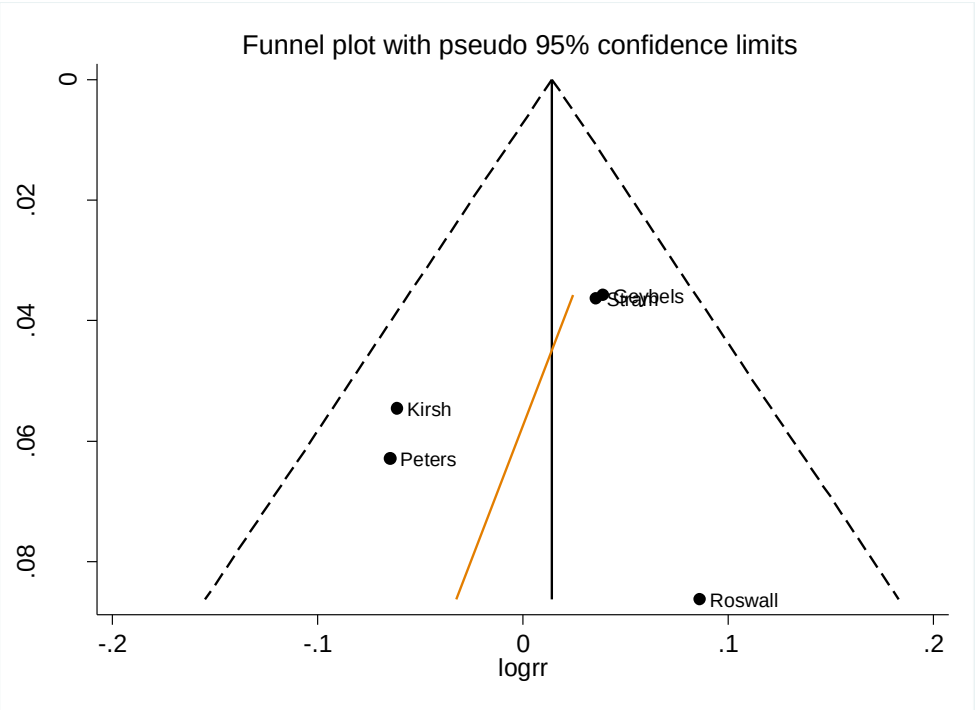
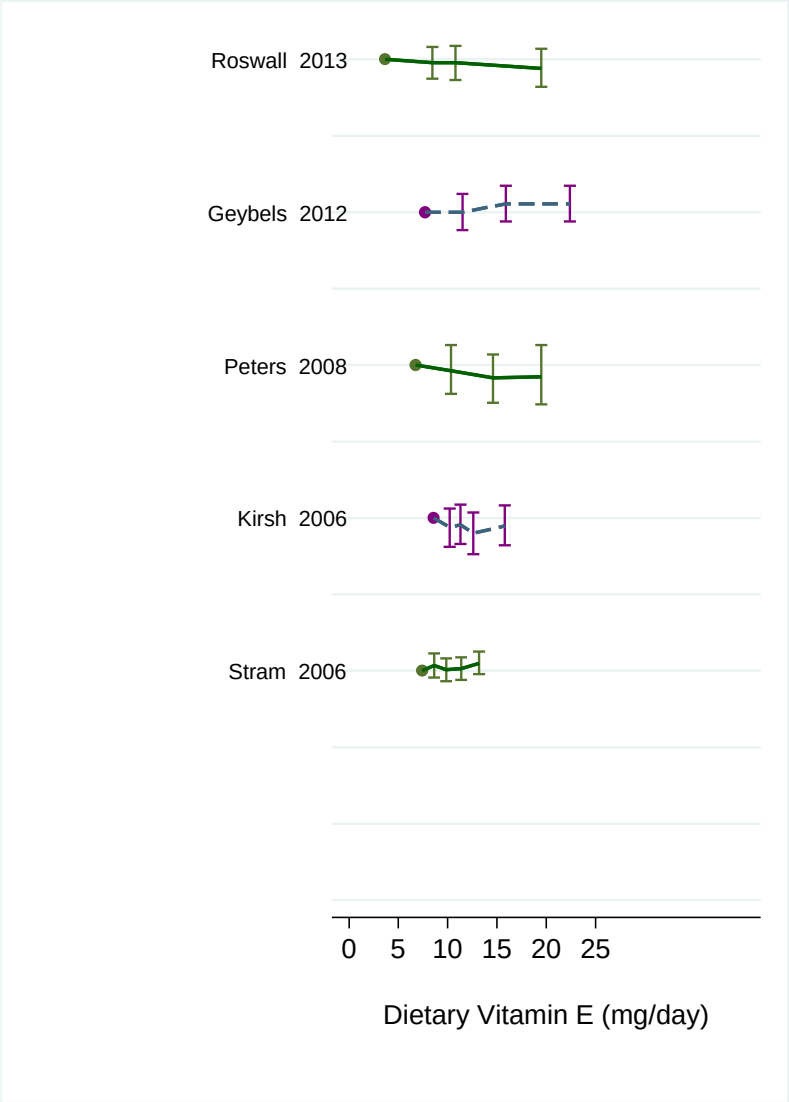


Figure 219 Funnel plot of dietary vitamin E and total prostate cancer



Egger's test p = 0.57

Figure 220 Dose-response graph of dietary vitamin E and prostate cancer



5.5.11 Vitamin E supplement

Methods

Twenty one publications from 14 studies published on vitamin E supplement and prostate cancer; 10 were identified during the CUP. There are 3 publications for Health Professionals Follow-up study, 3 publications for CLUE I and CLUE II studies, 2 publications for VITamins And Lifestyle (VITAL) Study 2 publications for National Institutes of Health (NIH)-AARP Diet and Health Study, 2 publications for Alpha Tocopherol Beta Carotene Cancer Prevention study, and 2 publications for Cancer Prevention Study II (CPS-II). Dose-response analyses were conducted per 100 IU/day.

Three studies (Roswall et al, 2013; Kristal et al, 2010; Gonzalez et al, 2009) reported supplement intake of vitamin E in mg per day that was converted to IU/day using 1 IU equals to 1.5 mg.

From the studies included in the meta-analysis, 7 studies (Roswall et al, 2013; Gonzalez et al, 2009; Chae et al, 2009; Iso et al, 2007; Stram et al, 2006; Stevens et al, 2005; Shibata et al, 1992) reported on total prostate cancer, three studies (Kirsh et al, 2006; Rodriguez et al, 2004; Shuurman et al, 2002) on total and advanced prostate cancer, one study (Wright et al, 2007) on total, advanced and localised prostate cancer, one study (Kristal et al, 2010) on high grade (Gleason score 8-10) and low grade (Gleason score 2-7) prostate cancer and one study (Chan et al, 1999) on total (non-stage A1), extra prostatic (stage C or D) and metastatic or fatal prostate cancer.

In the study of Kristal et al, 2010, the dose response estimates for high-grade (Gleason score 8-10) and low-grade (Gleason score 2-7) prostate cancer were combined before inclusion in the dose-response meta-analysis of total prostate cancer risk.

In stratified analysis by prostate cancer type, advanced and high grade (Gleason score 8-10) cancers were included in the advanced/high grade subgroup and low grade and localised cancers were included in non-advanced/low grade subgroup.

Overall, 7 studies were included in the meta-analysis for total prostate cancer, 5 studies for advanced/high grade prostate cancer and 2 studies for non-advanced/low grade prostate cancer.

Main results

The summary RR of prostate cancer per 100 IU/day of vitamin E supplement was 1.00 (95% CI 0.99-1.01; $I^2 = 0\%$; $p_{heterogeneity} = 0.54$). After stratification by prostate cancer type, the RR per 100 IU/day was 1.00 (95% CI 0.97-1.03; $I^2 = 30.1\%$; $p_{heterogeneity} = 0.22$; n = 5) for advanced/high grade cancers and 1.02 (95% CI 0.93-1.12; $I^2 = 31.6\%$; $p_{heterogeneity} = 0.23$; n = 2) for non-advanced/low grade cancers.
In influence analysis, the summary RR was 0.99 (95% CI 0.99-1.00) when restricting the analysis to studies on incident cancers.

Heterogeneity
There was no evidence of heterogeneity ($I^2 = 0\%$; $p_{heterogeneity} = 0.54$). Egger's test showed no evidence of publication bias (p = 0.64).

Comparison with the Second Expert Report
In the 2005 SLR the meta-analysis on vitamin E supplement and prostate cancer showed non-significant association.

Published meta-analysis or pooled analysis
No published meta-analyses or pooled studies were identified.

Table 201 Studies on vitamin E supplement identified in the CUP

Author/year	Country	Study name	Cases	Years of follow-up	RR	LCI	UCI	Contrast
Roswall, 2013	Denmark	Diet, Cancer and Health Cohort Study	1571	14.3years	0.94	0.75	1.19	≤ 10 mg/day vs. none
					0.99	0.98	1.01	Per 10 mg/day
Kristal, 2010	USA and Canada	The Prostate Cancer Prevention Trial	1576 Gleason Score 2-7	~ 9 years	1.08	0.96	1.23	> 30 mg/day vs. < 8 mg/day For Gleason score 2-7
			127 Gleason Score 8-10		1.21	0.82	1.78	> 30 mg/day vs. < 8 mg/day For Gleason score 8-10
Chae, 2009	USA	''Give us a CLUE to cancer and Heart Disease'' CLUE II	269	~ 13 years	1.01	0.72	1.41	Ever user vs. non-user
Gonzalez, 2009	USA	VITamins And Lifestyle (VITAL) Study	832	2-4 years	1.09	0.91	1.32	201-1500 mg/day vs. none in 10 years average

Peters, 2008	USA	VITamins And Lifestyle (VITAL) Study	830	~ 4 years	0.93	0.68	1.3	≥ 400 IU/day vs. none in organ confined cancers
					0.43	0.19	1.0	≥ 400 IU/day vs. none in advanced cancers
Iso, 2007	Japan	Japan Collaborative Cohort study for Evaluation of Cancer Risk	169	15 years	0.78	0.29	2.11	Use vs. non-use
Wright, 2007	USA	National Institutes of Health (NIH)-AARP Diet and Health Study	10241	5 years	0.97	0.87	1.07	≥ 800IU vs. 0 IU
Lawson, 2007	USA	National Institutes of Health (NIH)-AARP Diet and Health Study	10241	5 years	1.06	0.97	1.17	> 7 times/week vs. never
Kirsh, 2006b	USA	Prostate, Lung, Colorectal, and Ovarian Cancer (PLCO) Screening Trial	1338	8 years (4.2 average years)	0.97	0.83	1.13	> 400 IU vs. none
Stram, 2006	USA	Hawaii-Los Angeles Multi-ethnic Cohort (MEC) Study	3922	~ > 7 years	1.03	0.95	1.12	≥ 33.75 mg alpha-toc equiv/day vs. ≤ 33.75 mg alpha-toc equiv/day

Table 202 Overall evidence on vitamin E supplement and total prostate cancer

	Summary of evidence
2005 SLR	Eleven publications from 7 studies were identified during the 2005 SLR. Three studies were included in the meta-analysis. All showed non-significant association.
Continuous update	Ten new publications from 9 studies were identified during the CUP. Overall, seven studies were included in the meta-analysis. No significant association was found.

Table 203 Summary of results of the dose-response meta-analysis of vitamin E supplement and total prostate cancer

Total prostate cancer incidence and mortality		
	2005 SLR	Continuous Update Project
Studies (n)	3	7
Cases (n)	6385	21862
Increment unit used	100 IU/day	100 IU/day
Overall RR (95% CI)	1.00 (0.98-1.02)	1.00 (0.99-1.01)
Heterogeneity (I^2, p-value)	I^2 = 0%, p = 0.71	I^2 = 0%, p = 0.54
Stratified analysis		
Advanced/high grade cancer		
Overall RR (95%CI)		1.00 (0.97-1.03)
Heterogeneity (I^2,p-value)		30.1%, p = 0.22, n = 5
Non-advanced/low grade cancer		
Overall RR (95%CI)		1.02 (0.93-1.12)
Heterogeneity (I^2,p-value)		31.6%, p = 0.23, n = 2

Table 204 Inclusion/exclusion table for meta-analysis of vitamin E supplement and total prostate cancer

WCRF code	Author	Year	Study design	Study name	Cancer outcome	2005 SLR	CUP dose-response meta-analysis	CUP HvL forest plot	Estimated values	Exclusion reasons
PRO100159	Roswall	2013	Prospective Cohort Study	Diet, Cancer and Health Cohort Study	Incidence	No	Yes	Yes	Mid-exposure values Conversion of mg/day to IU/day Number of cases per quintiles Person years	
PRO100078	Kristal	2010	Prospective Cohort Study	The Prostate Cancer Prevention Trial	Incidence	No	Yes	Yes	Pooled high and low grade cancer subgroups Conversion of mg/day to IU/day	
PRO100074	Chae	2009	Nested Case Control Study	‘‘Give us a CLUE to cancer and Heart Disease’’ CLUE II	Incidence	No	No	Yes		Only two categories of data
PRO100066	Gonzalez	2009	Prospective Cohort Study	VITamins And Lifestyle (VITAL) Study	Mortality and incidence	No	Yes	Yes	Mid-exposure values Person-years Conversion of mg/day to IU/day	
PRO100182	Peters	2008	Prospective Cohort Study	VITamins And Lifestyle (VITAL) Study	Incidence	No	No	No		Superseded by Gonzalez et al, 2009
PRO100042	Iso	2007	Prospective Cohort Study	Japan Collaborative Cohort study for Evaluation of Cancer Risk	Mortality	No	No	Yes		Only two categories of data

PRO99994	Wright	2007	Prospective Cohort Study	National Institutes of Health (NIH)-AARP Diet and Health Study	Mortality and incidence	No	Yes	Yes		
PRO99999	Lawson	2007	Prospective Cohort Study	National Institutes of Health (NIH)-AARP Diet and Health Study	Mortality and incidence	No	No	No		Duplicate of Wright et al, 2007
PRO99992	Kirsh	2006 b	Prospective Cohort Study	Prostate, Lung, Colorectal, and Ovarian Cancer (PLCO) Screening Trial	Mortality and incidence	No	Yes	Yes	Mid-exposure values Person years	
PRO99986	Stram	2006	Prospective Cohort Study	Hawaii-Los Angeles Multiethnic Cohort (MEC) Study	Mortality and incidence	No	No	Yes		Missing number of cases in each category
PRO97424	Weinstein	2005	Nested Case Control Study	Alpha Tocopherol Beta Carotene Cancer Prevention	Incidence	Yes	No	No		Only number of users in cases and controls are shown. High vs. low reported by Hartman 1998
PRO97880	Stevens	2005	Prospective Cohort Study	Cancer Prevention Study II (CPS-II)	Mortality	Yes	No	No		Units were reported in times/month. Rodriguez et al, 2004 was used instead
PRO07981	Rodriguez	2004	Prospective Cohort Study	Cancer Prevention Study II (CPS-II)	Incidence	Yes	Yes	Yes	Mid exposure values	
PRO10700	Platz	2004 b	Nested Case Control Study	‘‘Give us a CLUE to cancer and Heart Disease’’ CLUE II	Incidence	Yes	No	No		Only percentages of users in cases and controls are shown Superseded by Chae et al, 2009

PRO10575	Platz	2004c	Nested Case Control Study	Health Professionals Follow-up study	Mortality and incidence	Yes	No	No		Only percentages of users in cases and controls are shown Chan 1999 used instead
PRO03999	Wu	2004	Nested Case Control Study	Health Professionals Follow-up Study	Mortality and incidence	Yes	No	No		Only number of users and non-users are shown Chan 1999 used instead
PRO00526	Huang	2003	Nested Case Control Study	USA Maryland 1974-1989 (Give us a CLUE to cancer; CLUE I &II)	Incidence	Yes	No	No		No RR available Superseded by Chae et al, 2009
PRO00764	Schuurman	2002	Case-cohort Study	Netherlands' Cohort Study	Incidence	Yes	No	Yes		Only data for users vs. non-users are shown
PRO02143	Hartman	1998 b	Prospective Cohort Study	Alpha Tocopherol Beta Carotene Cancer Prevention	Mortality and incidence	Yes	No	No		Only high vs. low results are shown.
PRO01939	Chan	1999	Prospective Cohort Study	Health Professionals Follow-up study	Mortality and incidence	Yes	Yes	Yes	Mid-exposure values	
PRO13404	Shibata	1992	Prospective Cohort Study	USA California 1981-1985	Mortality and incidence	Yes	No	Yes		Only data for users vs. non-users are shown

*Studies of Chae, 2009; Platz, 2004 and Huang, 2003 count as two cohort studies each.

Figure 221 Highest versus lowest forest plot of vitamin E supplement and total prostate cancer

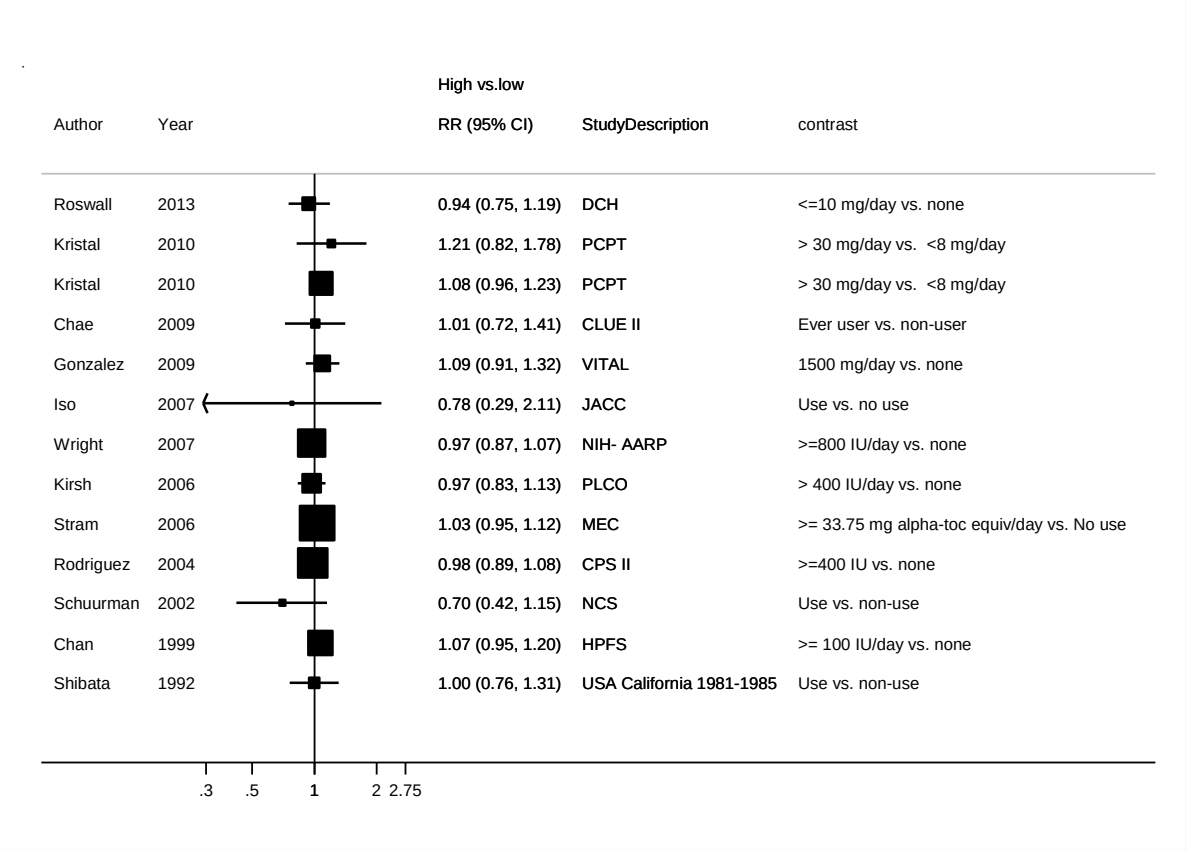


Figure 222 Dose-response meta-analysis of vitamin E supplement and total prostate cancer, per 100 IU/day

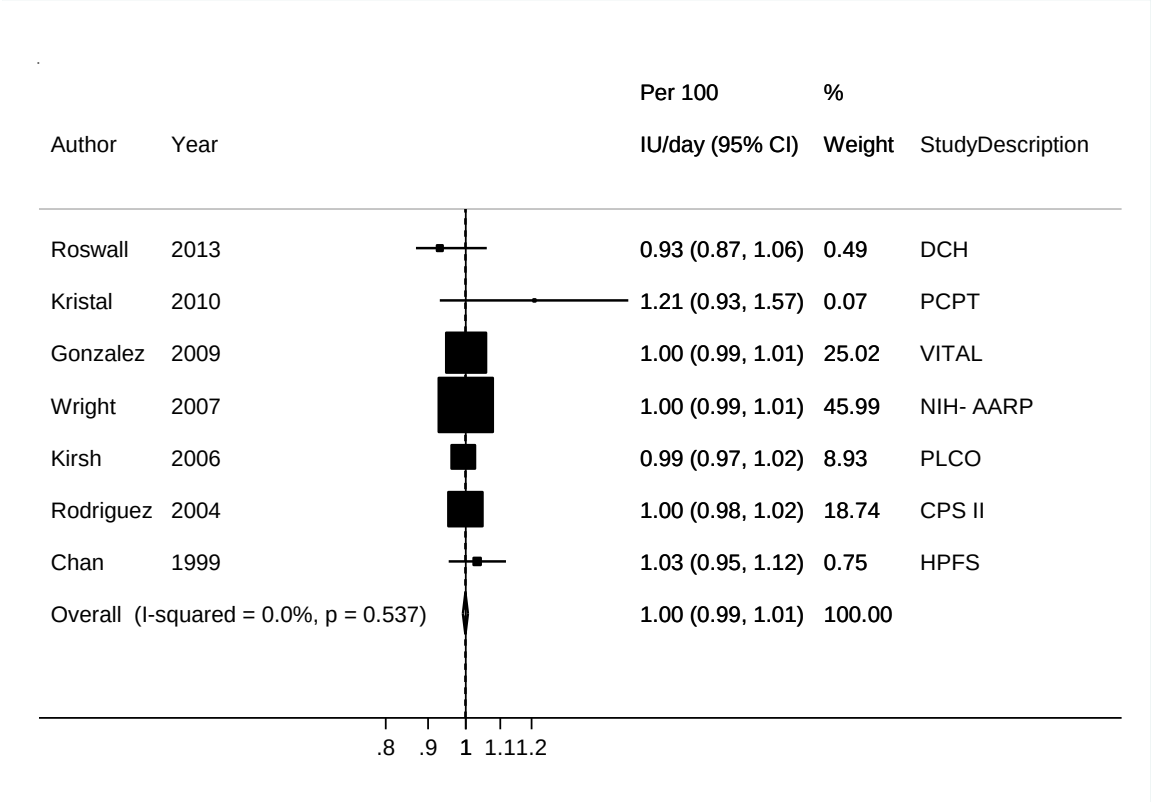
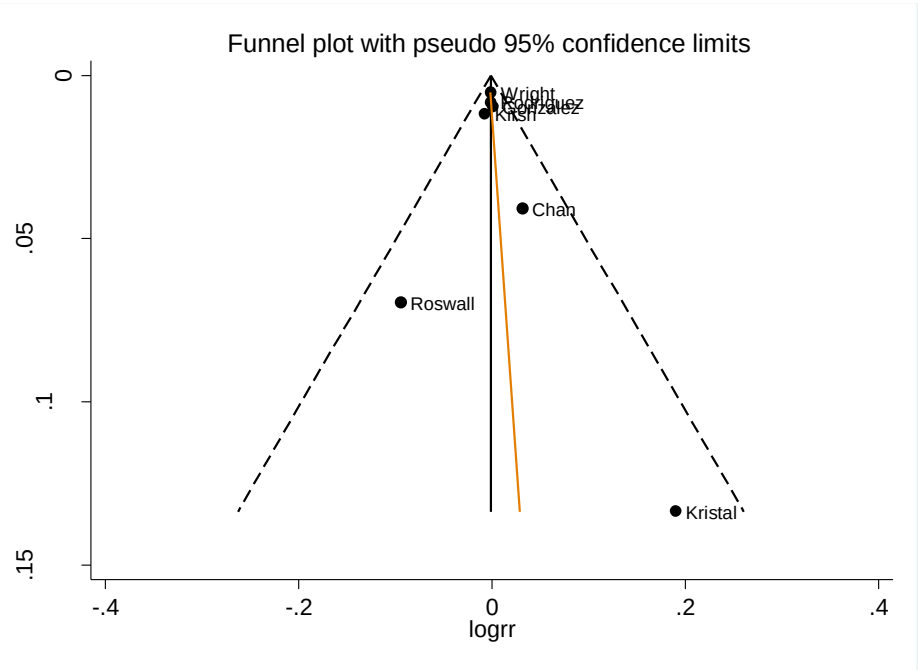


Figure 223 Funnel plot of vitamin E supplement and total prostate cancer



Egger's test p = 0.64

Figure 224 Dose-response graph of vitamin E supplement and prostate cancer

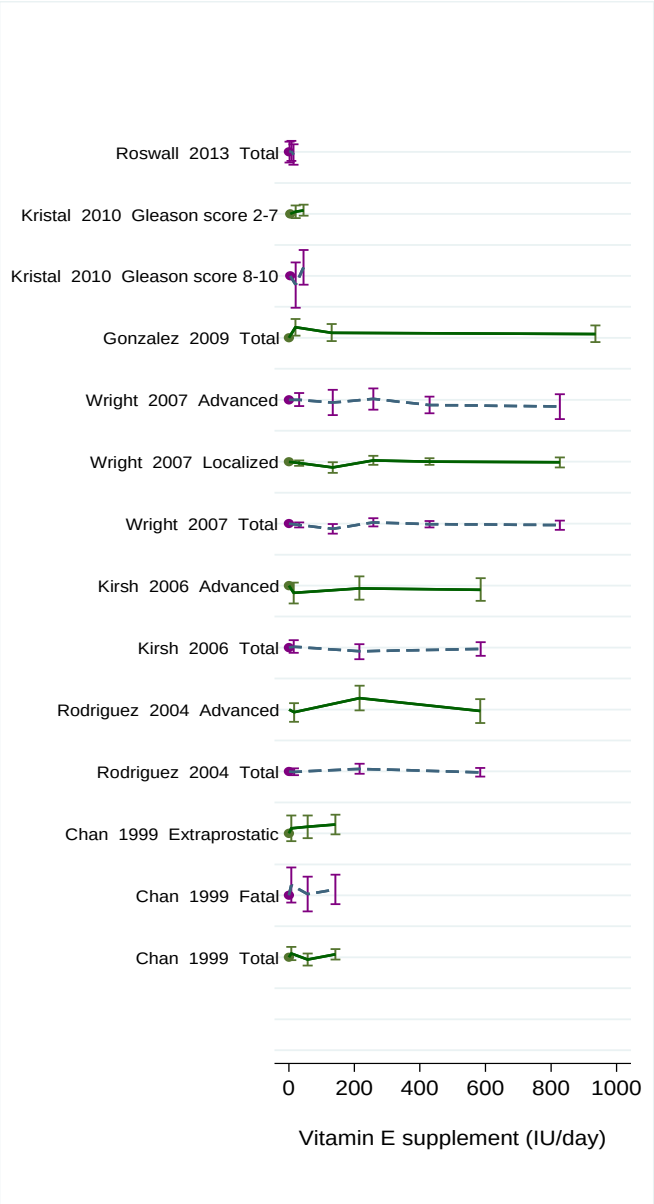
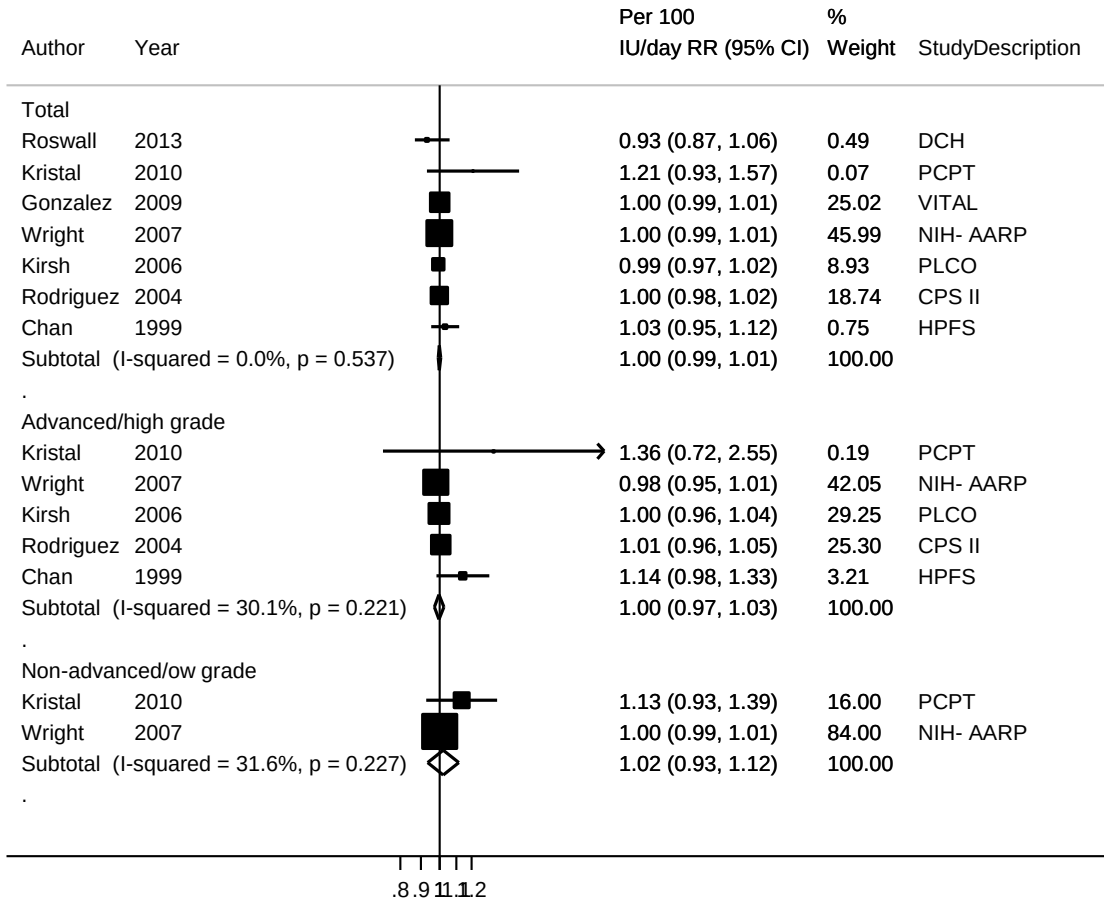


Figure 225 Dose-response meta-analysis of vitamin E supplement and advanced prostate cancer, per 100 IU/day



5.5.11 Dietary alpha-tocopherol

Methods

Four prospective studies on intake of alpha-tocopherol from diet were identified during the CUP. From these, two previous reports of one of the cohorts (ATBC follow-up) were identified during the 2005 SLR. There was not enough data to conduct new meta-analysis.

Main results.

None of the studies reported significant associations.

Comparison with the Second Expert Report

The two case-control studies identified in the 2005 SLR reported significant inverse associations.

Published meta-analysis or pooled analysis

No published meta-analyses or pooled studies on dietary alpha-tocopherol were identified.

Table 205 Overall evidence on alpha-tocopherol from diet and prostate cancer

	Summary of evidence
2005 SLR	Two case-control studies reported significant inverse associations. No association was observed in a cohort study
Continuous update Project	Four cohort studies in total had been published. None of them had reported significant associations

Table 206 Studies on dietary alpha-tocopherol identified in the CUP

Author, year	Country	Study name	Cases	Years of follow up	RR	LCI	UCI	Contrast
Peters, 2008	USA	VITamins And Lifestyle (VITAL)	830	~ 4 years	0.91	0.70	1.20	≥13.1 vs. <6.8 mg/day
Weinstein, 2007	Finland	Alpha-Tocopherol, Beta-Carotene Cancer Prevention (ATBC)	1732	19 years	1.12	0.79	1.59	13.01 vs. 6.96 mg/day
Wright, 2007	USA	NIH-AARP Diet and Health Study	10241	5 years	0.97	0.90	1.05	10 vs. 4.8 mg/day
Kirsh, 2006	USA	Prostate, Lung, Colorectal, and Ovarian (PLCO) Cancer Screening Trial	1338	8 years	0.92	0.77	1.10	12.6 vs. 6.1 mg/day

5.5.11 Serum alpha-tocopherol

Methods
Seventeen publications from 12 cohort studies were identified; 5 publications from 4 studies (3 new studies and 1 update from Alpha-Tocopherol, Beta-Carotene Cancer Prevention (ATBC) study) were identified during the CUP. There were 5 publications from ATBC study. Dose-response analyses were conducted per mg per litre.

From the studies included in the meta-analysis two studies (Weinstein et al, 2012; Weinstein et al, 2007) reported on total, advanced/aggressive and non-advanced/non-aggressive prostate cancer and one study reported on total and advanced prostate cancer (Gill et al, 2009).

Overall, 9 studies were included in the meta-analysis for total prostate cancer incidence and 4 studies were included for advanced/aggressive prostate cancer.

Main results
The summary RR per 1 mg/l of serum alpha-tocopherol and total prostate cancer was 0.99 (95% CI 0.98-1.00; $I^2 = 0\%$; $p_{heterogeneity} = 0.49$). The RR for advanced/high grade cancers per 1 mg/l increase of serum alpha tocopherol was 0.98 (95% CI 0.97-1.00; n= 948; $I^2 = 22.2\%$; $p_{heterogeneity} = 0.28$; n = 4).

Heterogeneity
There was no evidence of heterogeneity ($I^2 = 0\%$, $p_{heterogeneity} = 0.49$). Egger's test showed no evidence of publication bias (p = 0.67).

Comparison with the Second Expert Report
During the SLR, there was an evidence of a decrease in the risk of prostate cancer with an increase in serum alpha-tocopherol.

Published meta-analysis or pooled analysis
No published meta-analyses or pooled studies were identified.

Table 207 Studies on serum alpha-tocopherol identified in the CUP

Author/year	Country	Study name	Cases	Years of follow-up	RR	LCI	UCI	Contrast
Weinstein, 2012	USA	Prostate, Lung, Colorectal, and Ovarian Cancer (PLCO) Screening Trial	680	≈ 8 years	0.63	0.44	0.92	> 24.5mg/l vs. ≤ 12.3 mg/l
Gill, 2009	USA	Hawaii-Los Angeles Multiethnic Cohort (MEC) Study	467		0.95	0.65	1.41	2.51 mg/dl vs. 0.90 mg/dl
Ahn, 2008	Finland	Alpha-Tocopherol, Beta-Carotene Cancer Prevention (ATBC) Study	1111	12.3 years	0.96	0.80	1.15	> 12.9 mg/l vs. < 10.5 mg/l among those with no family history of prostate cancer
					1.26	0.72	2.20	> 12.9 mg/l vs. < 10.5 mg/l among those with family history of prostate cancer
Key, 2007	Europe	European Prospective Investigation into Cancer and Nutrition (EPIC) Study	966	6 years	0.82	0.61	1.11	≥ 680 µg /dl vs. < 1132 µg/dl
Weinstein, 2007	Finland	Alpha-Tocopherol, Beta-Carotene Cancer Prevention (ATBC) Study	1732	19 years	0.80	0.66	0.96	14.17 mg/l vs. 9.33 mg/l

Table 208 Overall evidence on serum alpha-tocopherol and total prostate cancer

SLR	Summary of evidence
2005 SLR	Twelve publications were identified during the SLR. Seven studies were included in the meta-analysis. There was no evidence of association.
Continuous Update Project	Five new publications were identified during the CUP. Overall, 9 studies were included in the meta-analysis. There was no evidence of association.

Table 209 Summary of results of the dose-response meta-analysis of serum alpha-tocopherol and total prostate cancer

Total prostate cancer incidence and mortality		
	Incidence and mortality	Incidence only
	SLR	CUP
Studies (n)	7	9
Cases (n)	1482	4989
Increment unit used	Per 1 mg/l	Per 1 mg/l
Overall RR (95% CI)	0.98 (0.97-1.00)	0.99 (0.98-1.00)
Heterogeneity (I^2, p-value)	I^2 = 0%, p=0.44	I^2 = 0%, p = 0.49
Stratified analysis		
Advanced/aggressive cancer		
Overall RR (95% CI)		0.98 (0.97-1.00)
Heterogeneity (I^2, p-value)		I^2 = 22.2%, p = 0.28, n = 4

Table 210 Inclusion/exclusion table for meta-analysis of serum alpha-tocopherol and total prostate cancer

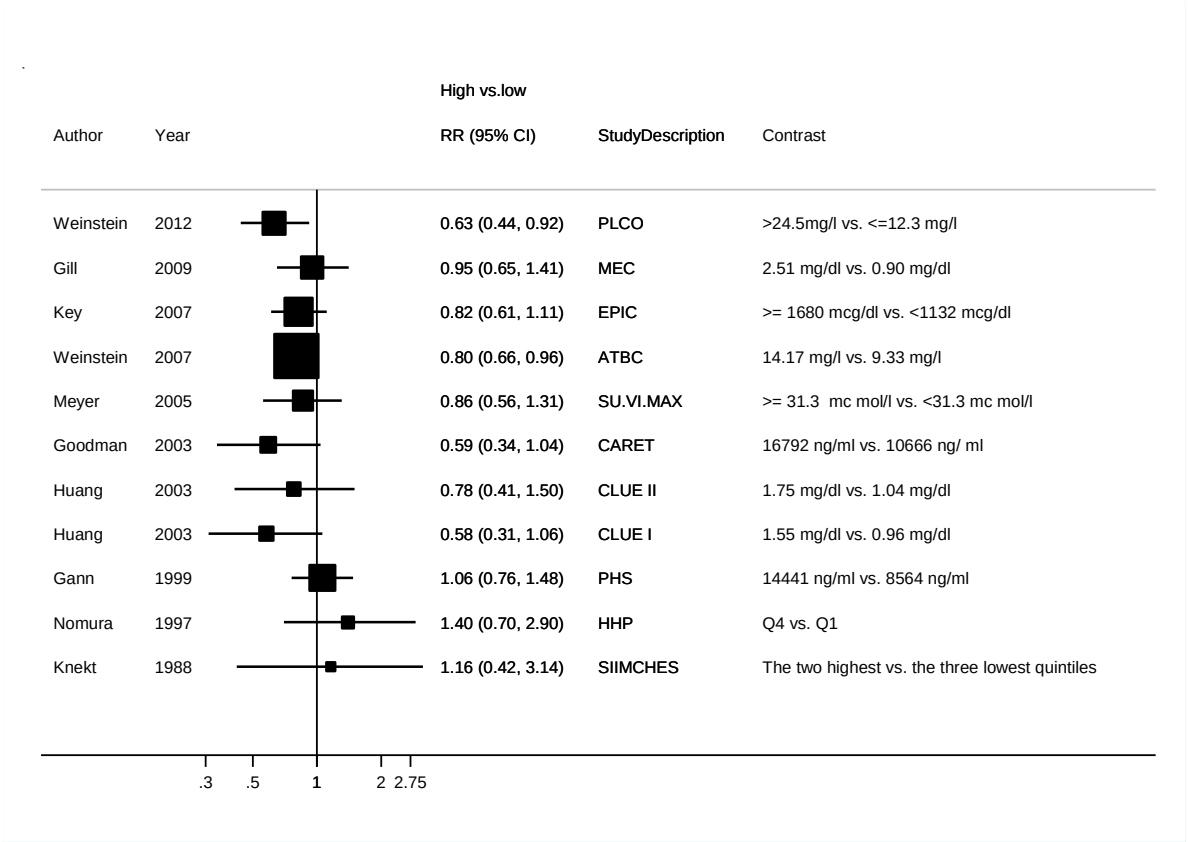
WCRF code	Author	Year	Study design	Study name	Cancer outcome	SLR	CUP dose-response meta-analysis	CUP HvL forest plot	Estimated values	Exclusion reasons
PRO100164	Weinstein	2012	Nested Case Control Study	Prostate, Lung, Colorectal, and Ovarian Cancer (PLCO) Screening Trial	Incidence	No	Yes	Yes		
PRO100044	Gill	2009	Nested Case Control Study	Hawaii-Los Angeles Multiethnic Cohort (MEC) Study	Incidence	No	Yes	Yes	Conversion of mg/dl to mg/l	
PRO100022	Ahn	2008a	Prospective Cohort Study	Alpha-Tocopherol, Beta-Carotene Cancer Prevention (ATBC) Study	Incidence	No	No	No		Only interaction data Duplicate of Weinstein et al, 2007
PRO100008	Key	2007	Nested Case Control Study	European Prospective Investigation into Cancer and Nutrition study	Incidence	No	Yes	Yes	Mid exposure values Conversion of µg /dl to mg/l	
PRO100040	Weinstein	2007	Prospective Cohort Study	Alpha-Tocopherol, Beta-Carotene Cancer Prevention (ATBC) Study	Incidence	No	Yes	Yes	Mid exposure values	
PRO97424	Weinstein	2005	Nested Case Control Study	Alpha-Tocopherol, Beta-Carotene Cancer Prevention (ATBC) Study	Incidence	Yes	No	No		Duplicate of Weinstein et al, 2007

PRO97166	Meyer	2005	Prospective Cohort Study	SU.VI.MAX Trial	Incidence	Yes	No	Yes		Only two categories of data
PRO97676	Laaksonen	2004	Prospective Cohort Study	Kuopio Ischaemic Heart Disease Risk Factor Study	Incidence	Yes	No	No		Only means are shown
PRO00214	Goodman	2003	Nested Case Control Study	Carotene and Retinol Efficacy Trial (CARET)	Incidence	Yes	Yes	Yes	Mid exposure values Conversion of ng /ml to mg/l Number of cases per quartiles	
PRO00272	Woodson	2003	Nested Case Control Study	Alpha-Tocopherol, Beta-Carotene Cancer Prevention (ATBC) Study	Mortality and incidence	Yes	No	No		Superseded by Weinstein et al, 2007 Only means are shown
PRO00526	Huang*	2003	Nested Case Control Study	USA Maryland 1974-1989 (Give us a CLUE to cancer; CLUE I &II)	Incidence	Yes	Yes	Yes	Mid exposure values Conversion of mg/dl to mg/l	
PRO01379	Helzlsouer	2002	Nested Case Control Study	CLUE II	Incidence	Yes	No	No		Superseded by Huang et al, 2003
PRO01820	Gann	1999	Nested Case Control Study	Physicians' Health Study	Incidence	Yes	Yes	Yes		
PRO02143	Hartman	1998 b	Prospective Cohort Study	Alpha-Tocopherol, Beta-Carotene Cancer Prevention (ATBC) Study	Mortality and incidence	Yes	No	No		Superseded by Weinstein et al, 2007
PRO02328	Nomura	1997	Nested Case Control Study	Honolulu Heart Program (Hawaii, USA)	Incidence	Yes	No	Yes		No quintile range
PRO13418	Knekt	1988	Historical Cohort Study	Social Insurance Institution's Mobile Clinic	Incidence	Yes	Yes	Yes	Mid-exposure values Confidence Intervals Number of cases for	

				Health Examination Survey					quintiles Person years of follow up	
PRO93149	Hsing	1990a	Nested Case Control Study	USA Maryland 1974-1986	Incidence	Yes	No	No		Superseded by Huang et al, 2003

*Huang, 2003 counted as 2 studies.

Figure 226 Highest versus lowest forest plot of serum alpha-tocopherol and total prostate cancer



In Knekt et al, 1988, the confidence intervals were estimated.

Figure 227 Dose-response meta-analysis of serum alpha-tocopherol and total prostate cancer, per 1mg/l

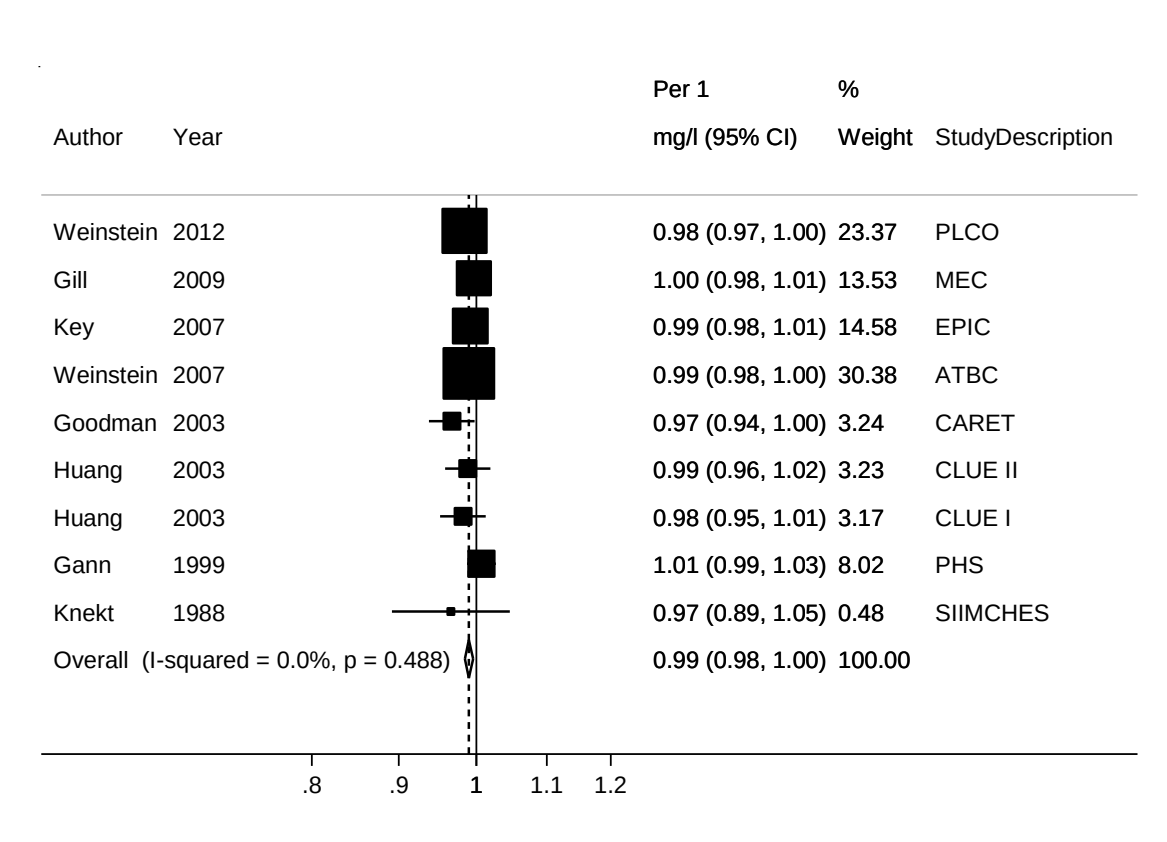
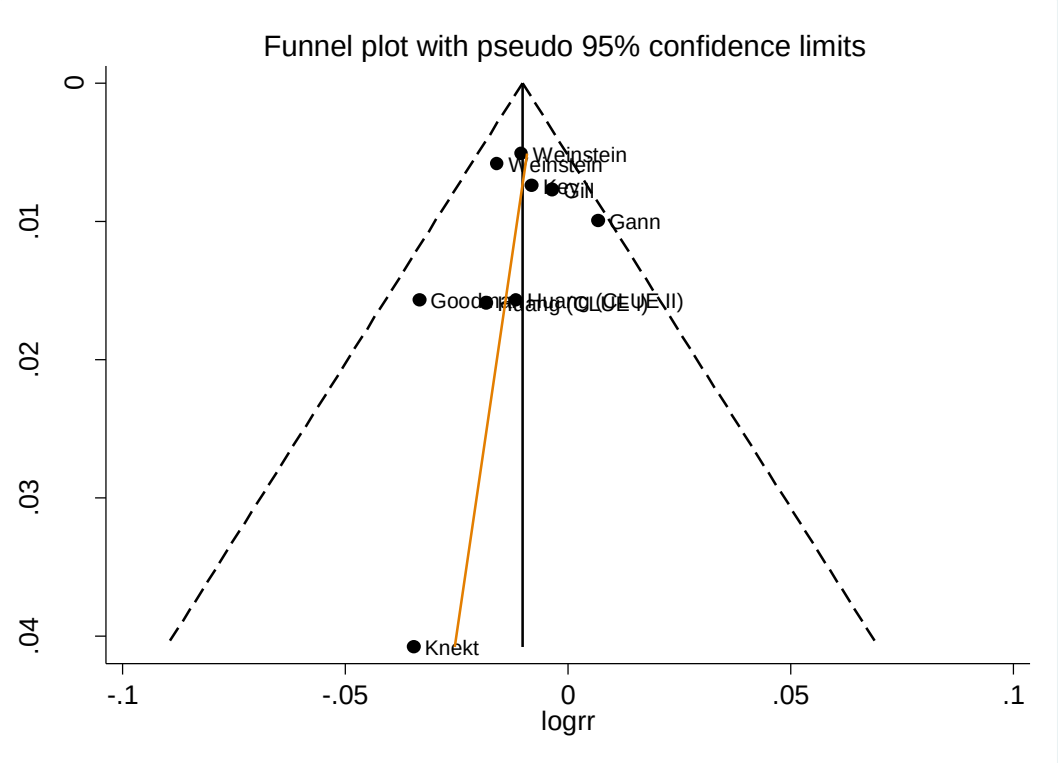


Figure 228 Funnel plot of serum alpha-tocopherol and total prostate cancer



Egger's test p = 0.67

Figure 229 Dose-response graph of serum alpha-tocopherol and prostate cancer

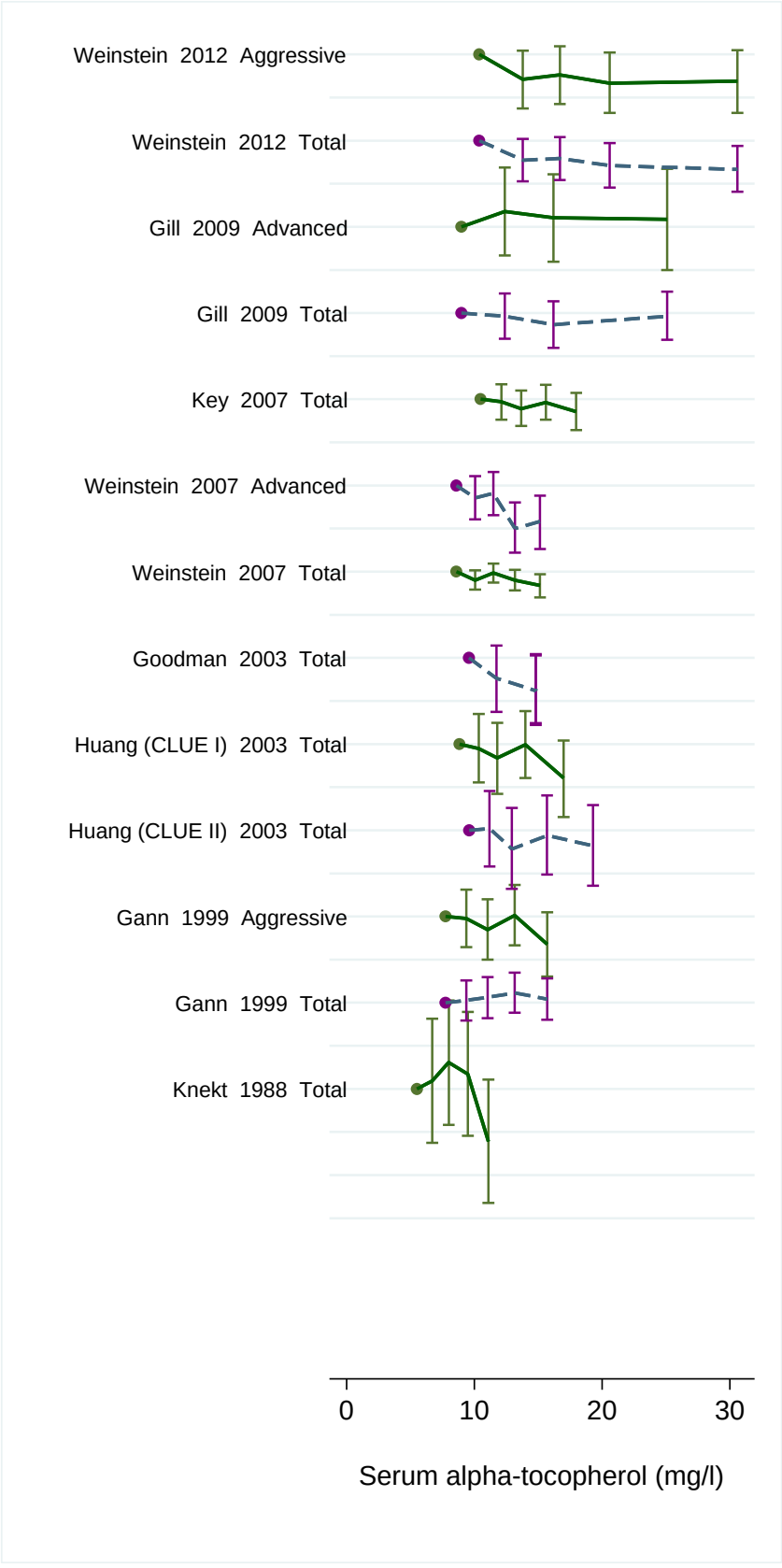
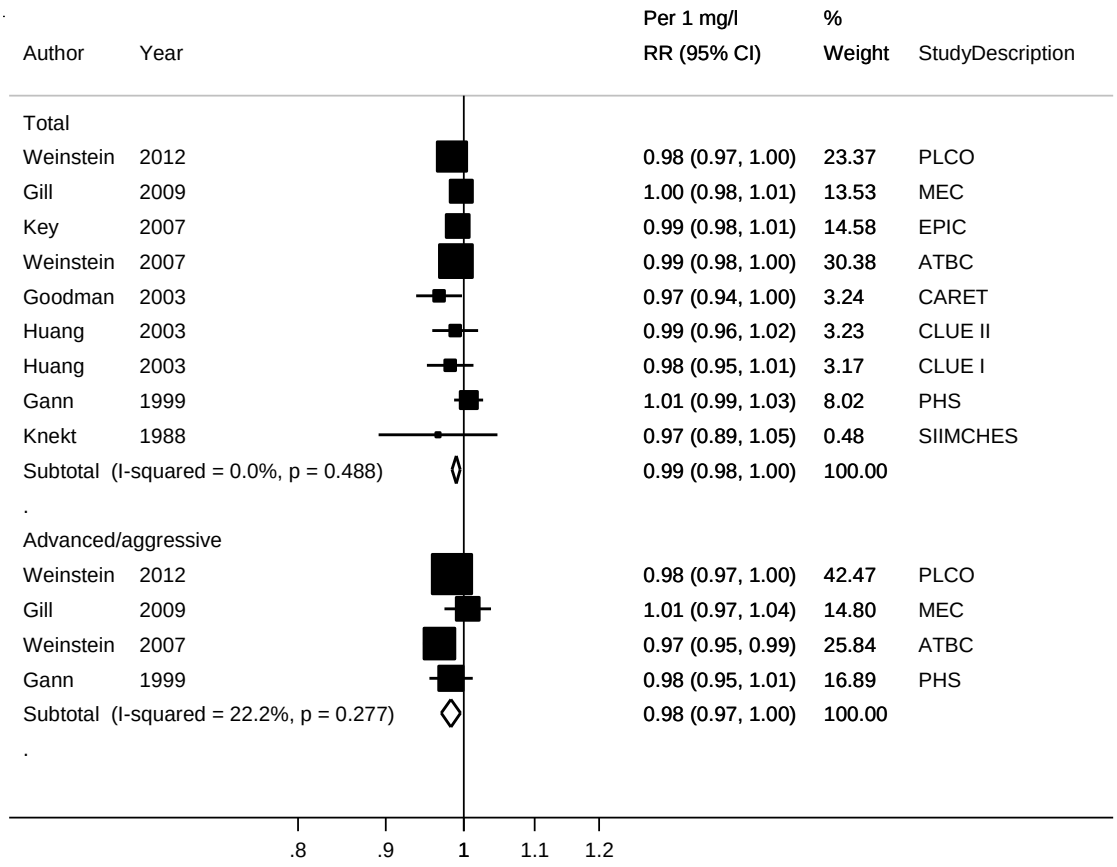


Figure 230 Dose-response meta-analysis of serum alpha-tocopherol and advanced prostate cancer, per 1 mg/l



5.5.11 Serum gamma-tocopherol

Methods
A total of 11 publications from 9 cohort studies were identified; 3 were identified during the CUP. Dose-response analyses were conducted per mg per litre.

From the studies included in the meta-analysis one study (Gill et al, 2009) reported on total and advanced prostate cancer and one study (Weinstein et al, 2012) reported on total, aggressive and non-aggressive prostate cancer.

Overall, 7 studies were included in the meta-analysis for total prostate cancer. No meta-analysis could be conducted on advanced or aggressive prostate cancer.

Main results
The summary RR per 1 mg/l of serum gamma-tocopherol and total prostate cancer was 0.97 (95% CI 0.91-1.04; I^2=52.1%; $p_{heterogeneity}$ = 0.05).

Heterogeneity
There was evidence of moderate heterogeneity (I^2=52.1%; $p_{heterogeneity}$ = 0.05). Egger'stest showed no evidence of publication bias (p = 0.06).

Comparison with the Second Expert Report
The meta-analysis on serum gamma tocopherol and prostate cancer during the SLR showed an overall a significant inverse association.

Published meta-analysis or pooled analysis
No published meta-analyses or pooled studies were identified.

Table 211 Studies on serum gamma-tocopherol identified in the CUP

Author/year	Country	Study name	Cases	Years of follow-up	RR	LCI	UCI	Contrast
Weinstein, 2012	USA	Prostate, Lung, Colorectal, and Ovarian Cancer (PLCO) Screening Trial	680	≈ 8 years	1.35	0.92	1.97	> 4.78 mg/l vs. ≤ 1.38 mg/l
Gill, 2009	USA	Hawaii-Los Angeles Multiethnic Cohort (MEC) Study	467		0.95	0.65	1.39	0.34 mg/dl vs. 0.06 mg/dl
Key, 2007	Europe	European Prospective Investigation into Cancer and Nutrition (EPIC) Study	966	6 years	1.33	0.93	1.90	≥ 161.11 mcg/dl vs. < 62.52 mcg/dl

Table 212 Overall evidence on serum gamma-tocopherol and total prostate cancer

SLR	Summary of evidence
2005 SLR	Eight publications were identified during the SLR; 6 were included in the meta-analysis. Non-significant inverse association was found.
Continuous Update Project	Three new studies were identified during the CUP; all of which were included in the meta-analysis. Overall, 7 studies were included in the meta-analysis. No significant inverse association was found.

Table 213 Summary of results of the dose-response meta-analysis of serum gamma-tocopherol and total prostate cancer

Total prostate cancer incidence		
	SLR	CUP
Studies (n)	6	7
Cases (n)	1324	2742
Increment unit used	Per 1 mg/l	Per 1 mg/l
Overall RR (95% CI)	0.90 (0.81-0.99)	0.97 (0.91-1.04)
Heterogeneity (I^2, p-value)	I^2 = 40.1%, p=0.14	I^2 = 52.1%, p = 0.05

Table 214 Inclusion/exclusion table for meta-analysis of serum gamma-tocopherol and total prostate 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
PRO100164	Weinstein	2012	Nested Case Control Study	Prostate, Lung, Colorectal, and Ovarian Cancer (PLCO) Screening Trial	Incidence	No	Yes	Yes		
PRO100044	Gill	2009	Nested Case Control Study	Hawaii-Los Angeles Multiethnic Cohort (MEC) Study	Incidence	No	Yes	Yes	Conversion of mg/dl to mg/l	
PRO100008	Key	2007	Nested Case Control Study	European Prospective Investigation into Cancer and Nutrition study	Incidence	No	Yes	Yes	Mid exposure values Conversion of µg /dl to mg/l	
PRO97424	Weinstein	2005	Nested Case Control Study	Alpha-Tocopherol, Beta-Carotene Cancer Prevention (ATBC) Study	Incidence	Yes	Yes	Yes	Mid exposure values Conversion of mg /dl to mg/l	
PRO00526	Huang*	2003	Nested Case Control Study	USA Maryland 1974-1989 (Give us a CLUE to cancer; CLUE I &II)	Incidence	Yes	Yes	Yes	Mid exposure values Conversion of mg/dl to mg/l	
PRO00214	Goodman	2003	Nested Case Control Study	Carotene and Retinol Efficacy Trial (CARET)	Incidence	Yes	Yes	Yes	Mid exposure values Conversion of ng /ml to mg/l Number of cases per quartiles	

PRO01379	Helzlsouer	2000	Nested Case Control Study	USA Maryland 1974-1989 (Give us a CLUE II)	Incidence	Yes	No	No		Superseded by Huang et al, 2003
PRO01820	Gann	1999	Nested Case Control Study	Physicians' Health Study	Incidence	Yes	No	No		Only unadjusted results
PRO02143	Hartman	1998 b	Prospective Cohort Study	Alpha-Tocopherol, Beta-Carotene Cancer Prevention (ATBC) Study	Mortality and incidence	Yes	No	No		Superseded by Weinstein et al, 2005
PRO02328	Nomura	1997	Nested Case Control Study	Honolulu Heart Program (Hawaii-USA)	Incidence	Yes	No	Yes		No quintile range
PRO93149	Hsing	1990a	Nested Case Control Study	USA Maryland 1974-1986	Incidence	Yes	No	No		Superseded by Huang et al, 2003

*Huang, 2003 counted as 2 studies.

Figure 231 Highest versus lowest forest plot of serum gamma-tocopherol and total prostate cancer

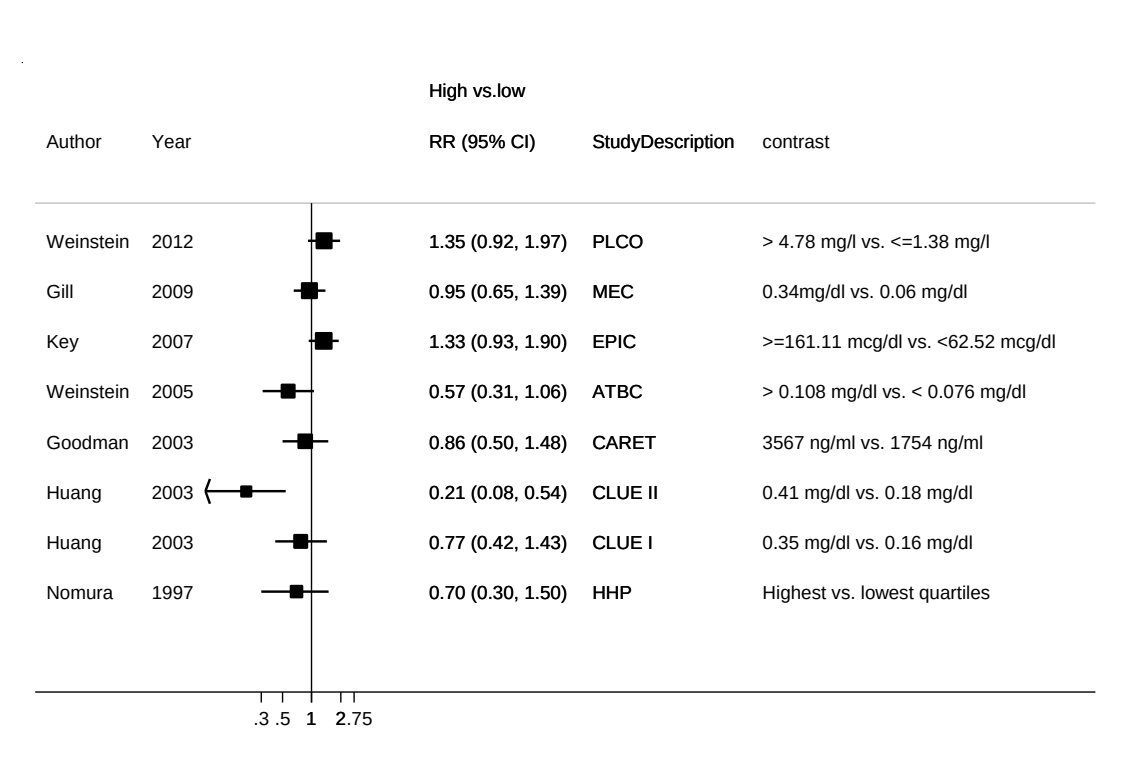


Figure 232 Dose-response meta-analysis of serum gamma-tocopherol and total prostate cancer, per 1mg/l

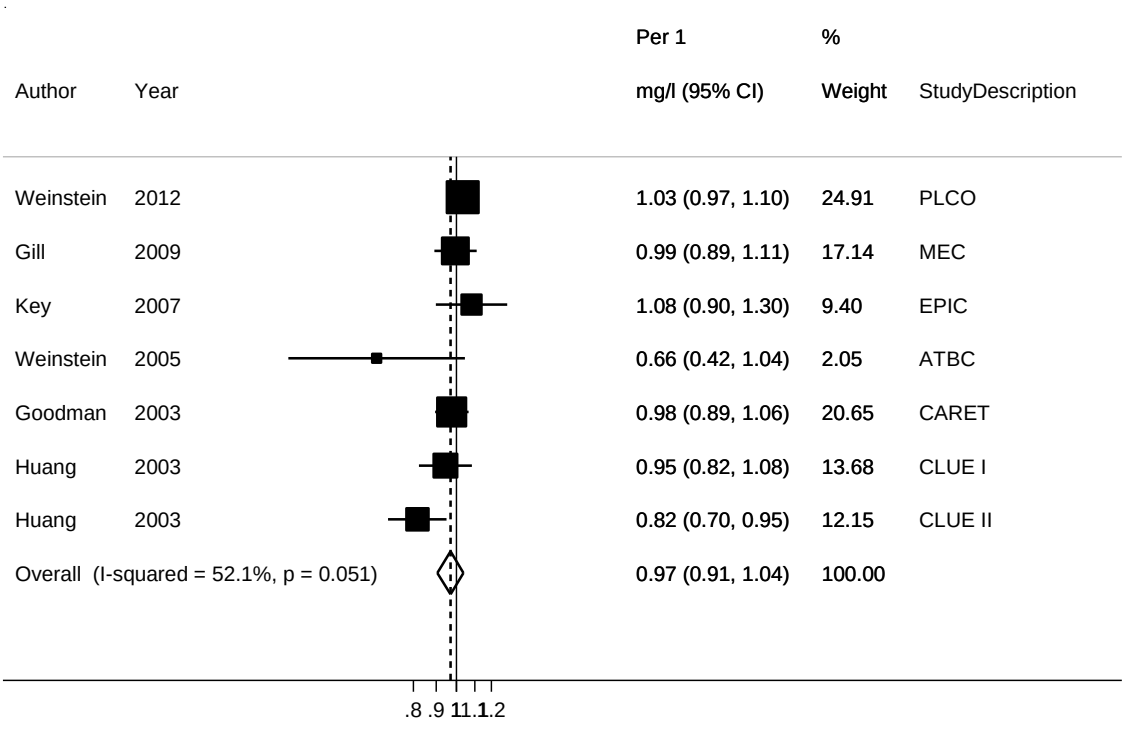
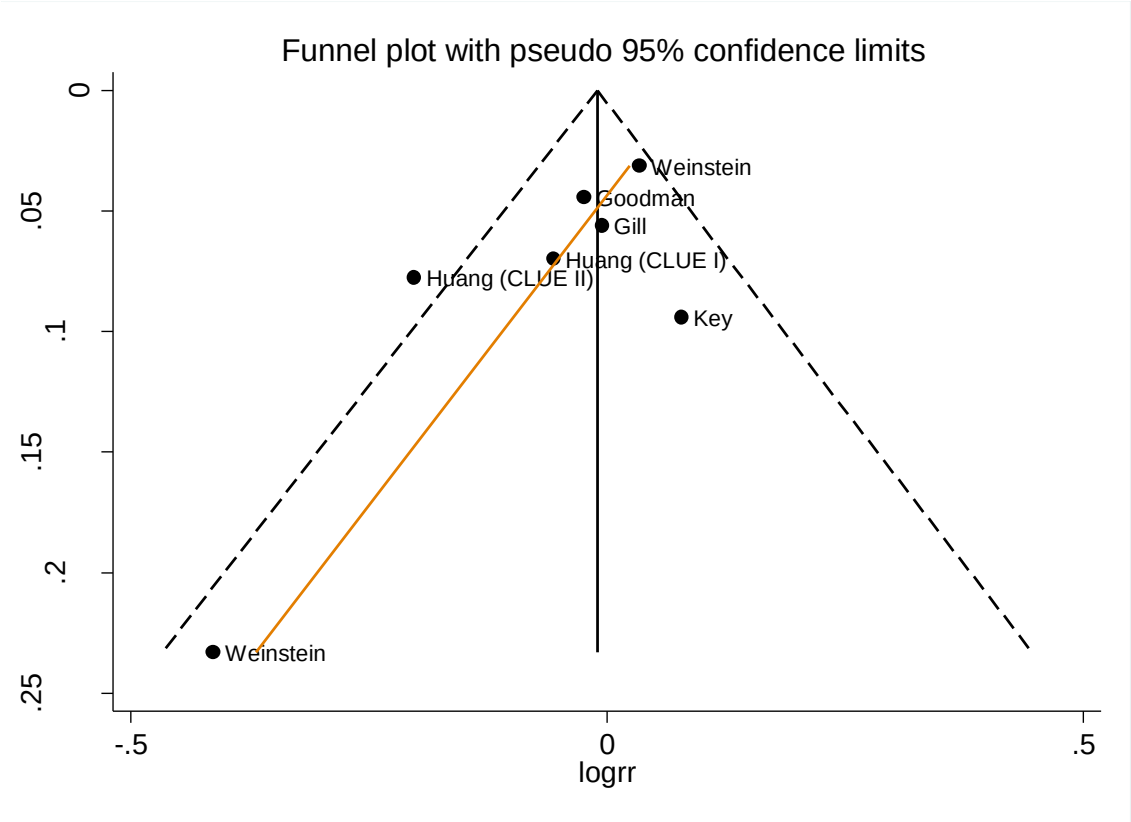
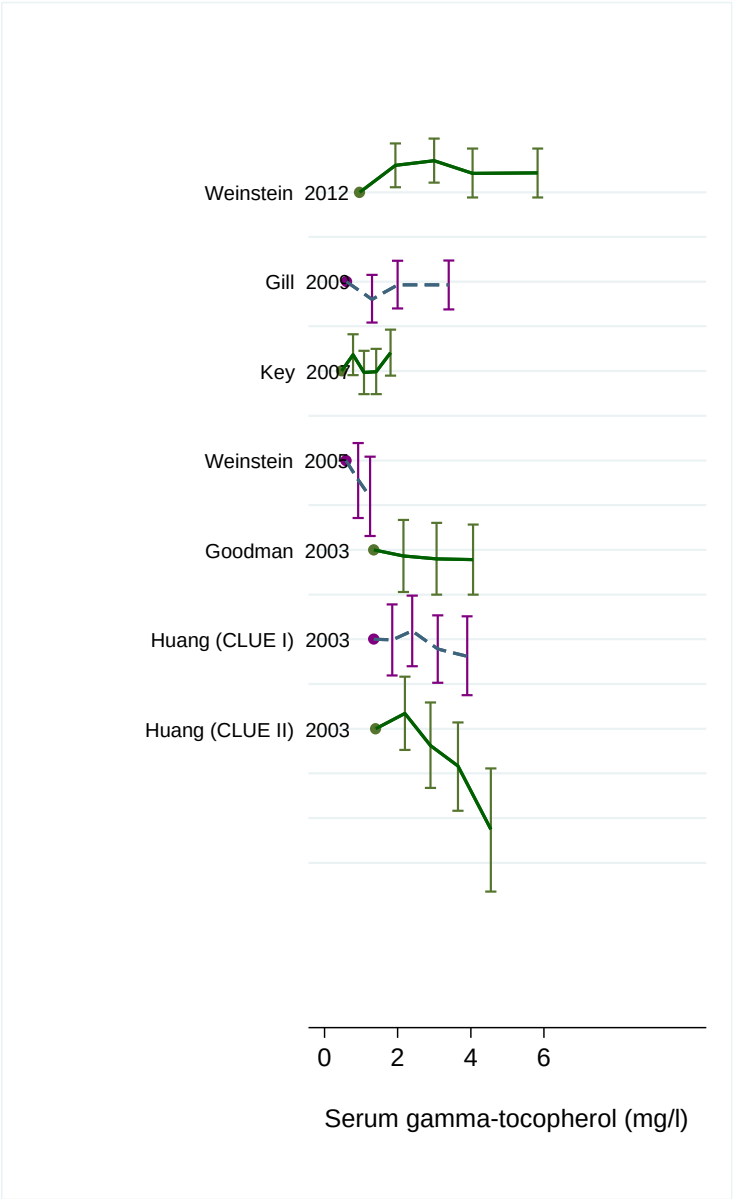


Figure 233 Funnel plot of serum gamma-tocopherol and total prostate cancer



Egger's test p = 0.06

Figure 234 Dose-response graph of serum gamma-tocopherol and prostate cancer



5.6.3 Total calcium

(See Appendix Studies on Calcium)

Methods

A total of 9 cohort studies (12 publications) have been published on total calcium (dietary and supplemental) and prostate cancer risk. Eight cohort studies (10 publications) were identified in the CUP. Dose-response analyses were conducted per 400 mg per day increase in total calcium intake.

Of the studies that were included in the dose-response analysis of total calcium and prostate cancer 9 studies reported on total prostate cancer: Rodriguez et al, 2003; Kesse et al, 2006; Giovannucci et al, 2006b; Rohrmann et al, 2007; Park et al, 2007; Ahn et al, 2007; Park et al, 2009; Kristal et al, 2010; and Butler et al, 2010. Five studies reported on non-advanced, low-stage, localised or non-aggressive prostate cancer: Giovannucci et al, 2006; Rohrmann et al, 2007; Park et al, 2007b (MEC); Park Y et al, 2007 (NIH-AARP Diet and Health Study); and Ahn et al, 2007. Seven studies reported on advanced, high-stage, aggressive, or Gleason score 8-10 prostate cancer; Rodriguez et al, 2003; Giovannucci et al, 2006b; Rohrmann et al, 2007; Park et al, 2007b (MEC); Park Yet al, 2007 (NIH-AARP Diet and Health Study); and Ahn et al, 2007; and Kristal et al, 2010. Two studies reported on fatal prostate cancer: Giovannucci et al, 2006b; and Park et al, 2010.

Main results

The summary RR per 400 mg/d increase in total calcium intake was 1.02 (95% CI 1.01-1.04; $I^2 = 12.2\%$; $p_{heterogeneity} = 0.33$; n = 9) for total prostate cancer. There was no indication of publication bias with Egger's test, p = 0.26. When stratified by outcome type the summary RR was 1.01 (95% CI 0.98-1.03; $I^2 = 28.7\%$; $p_{heterogeneity} = 0.22$; n = 6) for nonadvanced cancers, 1.03 (95% CI 0.99-1.07; $I^2 = 43.5\%$; $p_{heterogeneity}=0.10$; n = 7) for advanced cancers and 1.11 (95% CI 1.02-1.21; $I^2 = 0\%$; $p_{heterogeneity} = 0.33$; n = 2) for fatal cancers. There was evidence of nonlinearity, $p_{non\text{-}linearity} < 0.01$, with a flat curve up to approximately 1200 mg/d and an elevated risk with higher intakes.

Heterogeneity

There was little heterogeneity, $I^2 = 12.2\%$, $p_{heterogeneity} = 0.33$.

Conclusion from the Second Expert Report

In the SLR of the 2007 Expert Report the evidence relating total calcium to prostate cancer was too limited or inconsistent for a conclusion to be made.

Published meta-analyses

A meta-analysis of 5 cohort studies (4 on total calcium, one on dietary calcium, which were combined) reported a summary RR of 1.15 (95% CI 1.02-1.30) (Huncharek et al, 2009).

Table 215 Studies on total calcium identified in the CUP

Author/year	Country	Study name	Cases	Years of follow-up	RR	LCI	UCI	Contrast
Butler, 2010	Singapore	Singapore Chinese Health Study	298	7 years	1.25	0.89	1.74	659 vs. 211 mg/d
Kristal, 2010	USA	Prostate Cancer Prevention Trial	1703	7 years	1.17 0.46	0.97 0.24	1.42 0.89	> 1537 vs. <689 mg/d, Gleason score 2-7 > 1537 vs. < 689 mg/d, Gleason score 8-10
Park, 2009	USA	NIH-AARP Diet and Health Study	17189	8 years	1.03	0.98	1.08	1530 vs. 526 mg/d
Ahn, 2007	USA	PLCO Cancer Screening Trial	1910	8.9 years	0.89	0.66	1.19	≥ 2001 vs. ≤ 750 mg/d
Park Y, 2007	USA	NIH- AARP Diet and Health Study	10180	6 years	0.97	0.85	1.10	≥ 2000 mg vs. < 250 mg/d
Park, 2007b	USA	Multiethnic Cohort Study	4404	8 years	1.04	0.91	1.20	≥ 1301 vs. < 470 mg/d
Rohrmann, 2007	USA	CLUE II	199	13 years	0.99	0.70	1.41	≥ 957.58 vs. < 685.77 mg/d
Giovannucci, 2007	USA	Health Professionals Follow-up Study	2161	16 years				> 2000 vs. < 500 mg/d
					0.96	0.68	1.34	Organ confined
					1.98	1.04	3.78	Minimally extraprostatic
					1.91	1.20	3.03	Advanced
Kesse, 2006	France	SU.VI.MAX	69	7.7 years	2.43	1.05	5.62	> 1081 vs. < 725 mg/d
Giovannucci, 2006a	USA	Health Professionals Follow-up Study	3544	16 years	1.28	1.02	1.60	≥ 2000 vs. < 500 mg/d

Table 216 Overall evidence on total calcium and prostate cancer

	Summary of evidence
2005 SLR	Two prospective studies reported on total calcium intake and prostate cancer risk and both reported significant positive associations.
Continuous Update Project	Eight additional studies reported on total calcium intake and prostate cancer risk, of which two reported significant positive associations, one reported a significant inverse association in Gleason score 8-10 tumours, but no significant association in Gleason score 2-7 tumours, and the remaining studies reported no significant associations. A weak positive association was observed for total and fatal prostate cancers in the CUP meta-analysis

Table 217 Summary of results of the dose-response meta-analysis of total calcium and prostate cancer

Prostate cancer		
	2005 SLR	CUP
Studies (n)	2	9
Cases (n)	3880	33196
RR (95% CI)	1.08 (0.99-1.17)	1.02 (1.01-1.04)
Increment unit used	Per 1000 mg/day	Per 400 mg/day
Heterogeneity (I^2, p-value)	3.6%, p = 0.31	12.2%, p = 0.33
	Non advanced cancers	
Studies (n)	-	6
Cases (n)		2860
RR (95% CI)		1.01 (0.98-1.03)
Increment unit used		Per 400 mg/day
Heterogeneity (I^2, p-value)		28.7%, p = 0.22
	Advanced cancers	
Studies (n)	-	7
Cases (n)		16343
RR (95% CI)		1.03 (0.99-1.07)
Increment unit used		Per 400 mg/day
Heterogeneity (I^2, p-value)		43.5%, p = 0.10
	Fatal cancers	
Studies (n)	-	2
Cases (n)		490
RR (95% CI)		1.11 (1.02-1.21)
Increment unit used		Per 400 mg/day
Heterogeneity (I^2, p-value)		0%, p = 0.33

Table 218 Inclusion/exclusion table for meta-analysis of total calcium and prostate 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
PRO100079	Butler	2010	Prospective Cohort	Singapore Chinese Health Study	Incidence	No	Yes	Yes		
PRO100078	Kristal	2010	Prospective Cohort	Prostate Cancer Prevention Trial	Incidence	No	Yes	Yes		
PRO100146	Park	2009	Prospective Cohort	NIH-AARP Diet and Health Study	Incidence	No	Yes	Yes	Cases/person-years	
PRO100039	Ahn	2007	Prospective Cohort	PLCO Cancer Screening Trial	Incidence	No	Yes	Yes		
PRO100005	Park Y	2007	Prospective Cohort	NIH- AARP Diet and Health Study	Incidence	No	No	No		Overlap with Park et al, 2009 (PRO100146)
PRO99976	Park	2007b	Prospective Cohort	Multiethnic Cohort Study	Incidence	No	Yes	Yes	Mid-exposure values, person-years	
PRO99970	Rohrmann	2007	Prospective Cohort	CLUE II	Incidence	No	Yes	Yes	Mid-exposure values	
PRO99961	Giovannucci	2007	Prospective Cohort	Health Professionals Follow-up Study	Incidence	No	No	No		Overlap with Giovannucci et al, 2006 (PRO099968)
PRO99957	Kesse	2006	Prospective Cohort	SU.VI.MAX	Incidence	No	Yes	Yes	Mid-exposure values, person-years	
PRO99968	Giovannucci	2006a	Prospective Cohort	Health Professionals Follow-up Study	Incidence	No	Yes	Yes	Person-years	

PRO00127	Rodriguez	2003	Prospective Cohort	Cancer Prevention Study ll Nutrition Cohort	Incidence	Yes	Yes	Yes	Mid-exposure values	
PRO02192	Giovannucci	1998b	Prospective Cohort	Health Professionals Follow-up Study	Incidence	Yes	No	No		Overlap with Giovannucci et al, 2006 (PRO099968)

Figure 235 Highest versus lowest forest plot of total calcium and prostate cancer

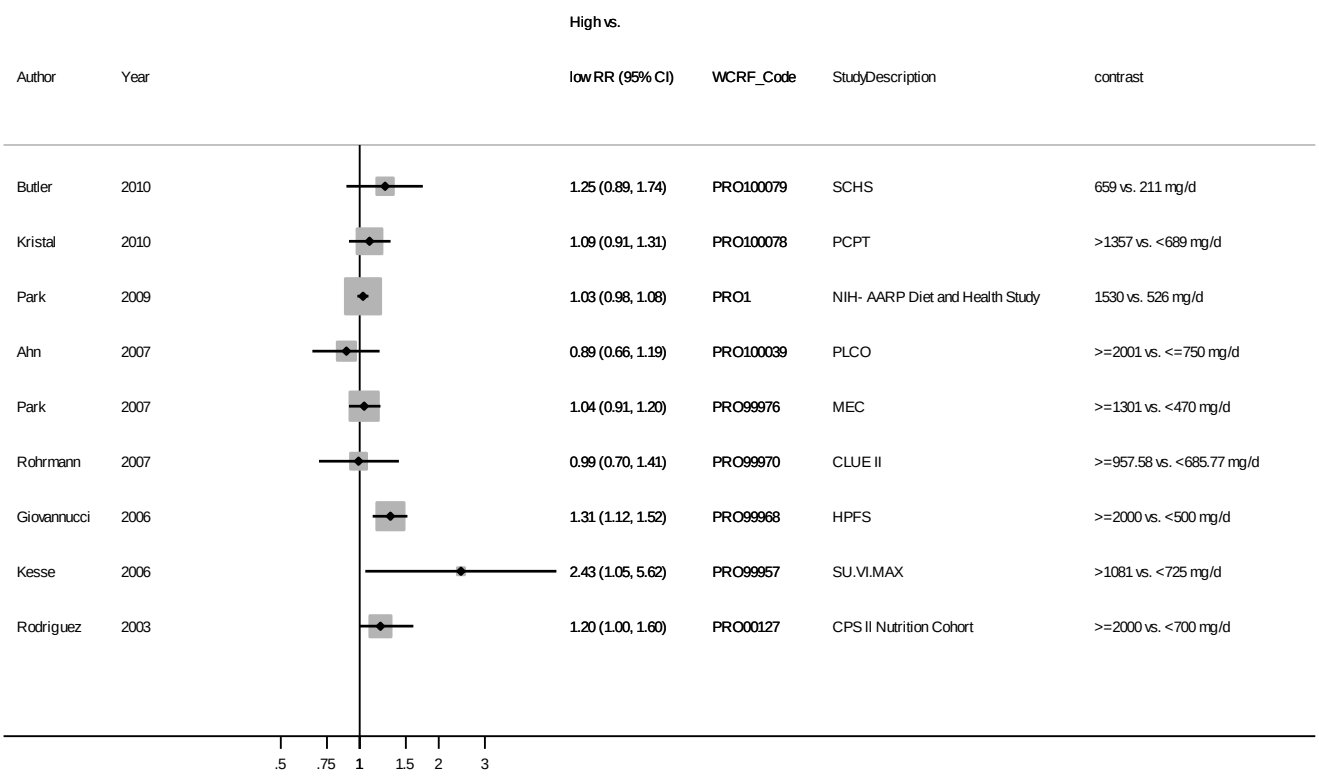


Figure 236 Dose-response meta-analysis of total calcium and prostate cancer, per 400 mg/day

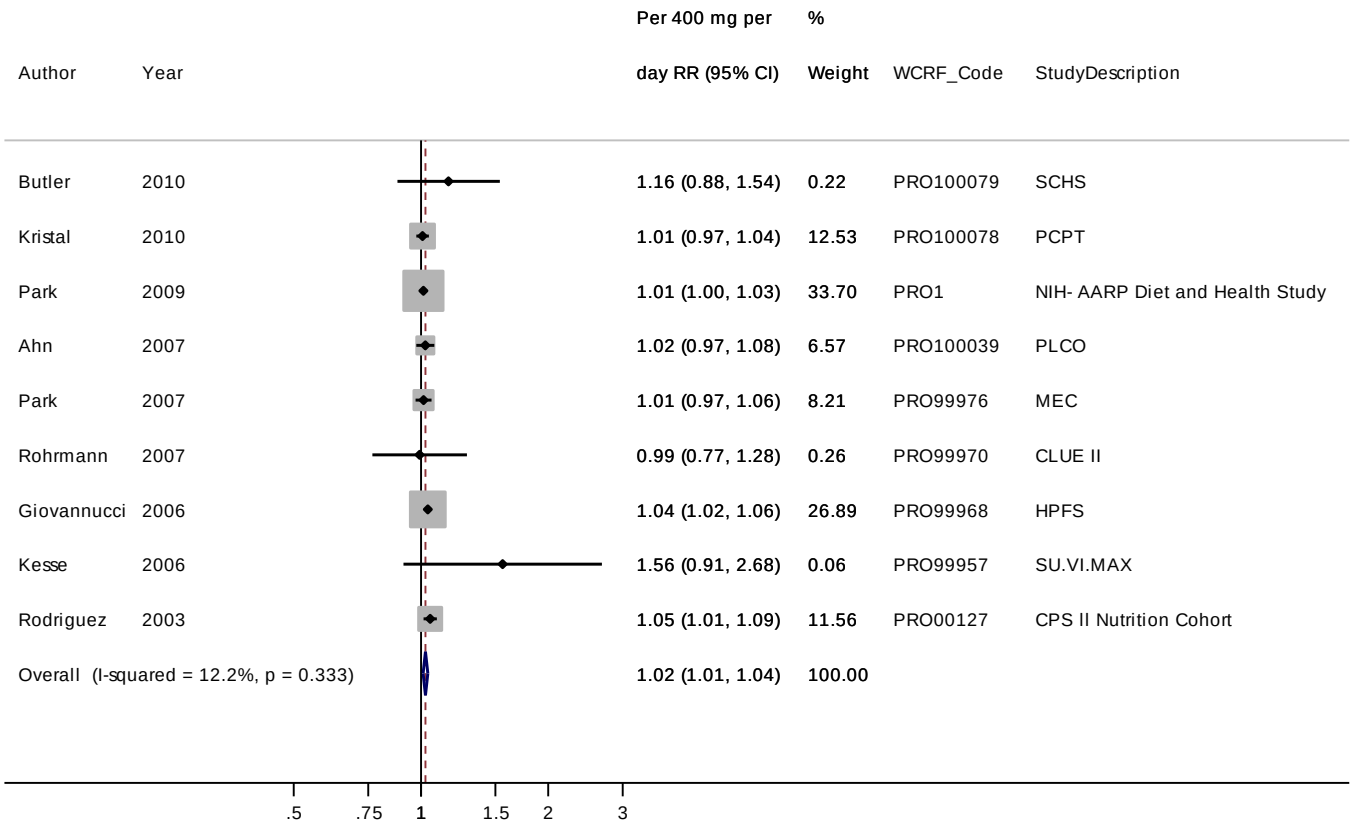
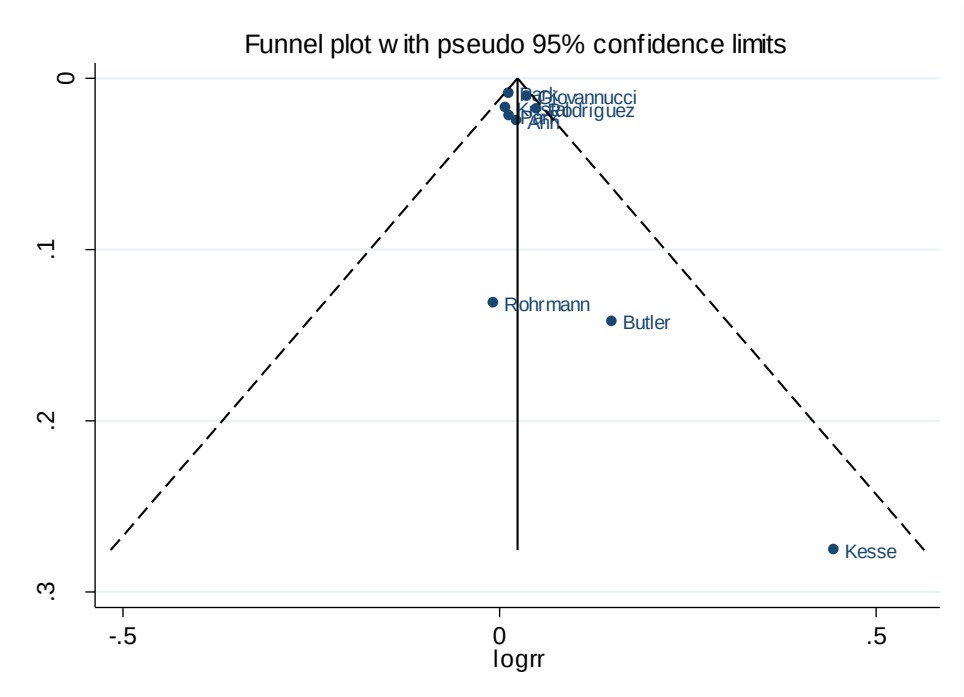


Figure 237 Funnel plot of total calcium and prostate cancer



Egger's test, p = 0.26

Figure 238 Dose-response graph of total calcium and total prostate cancer

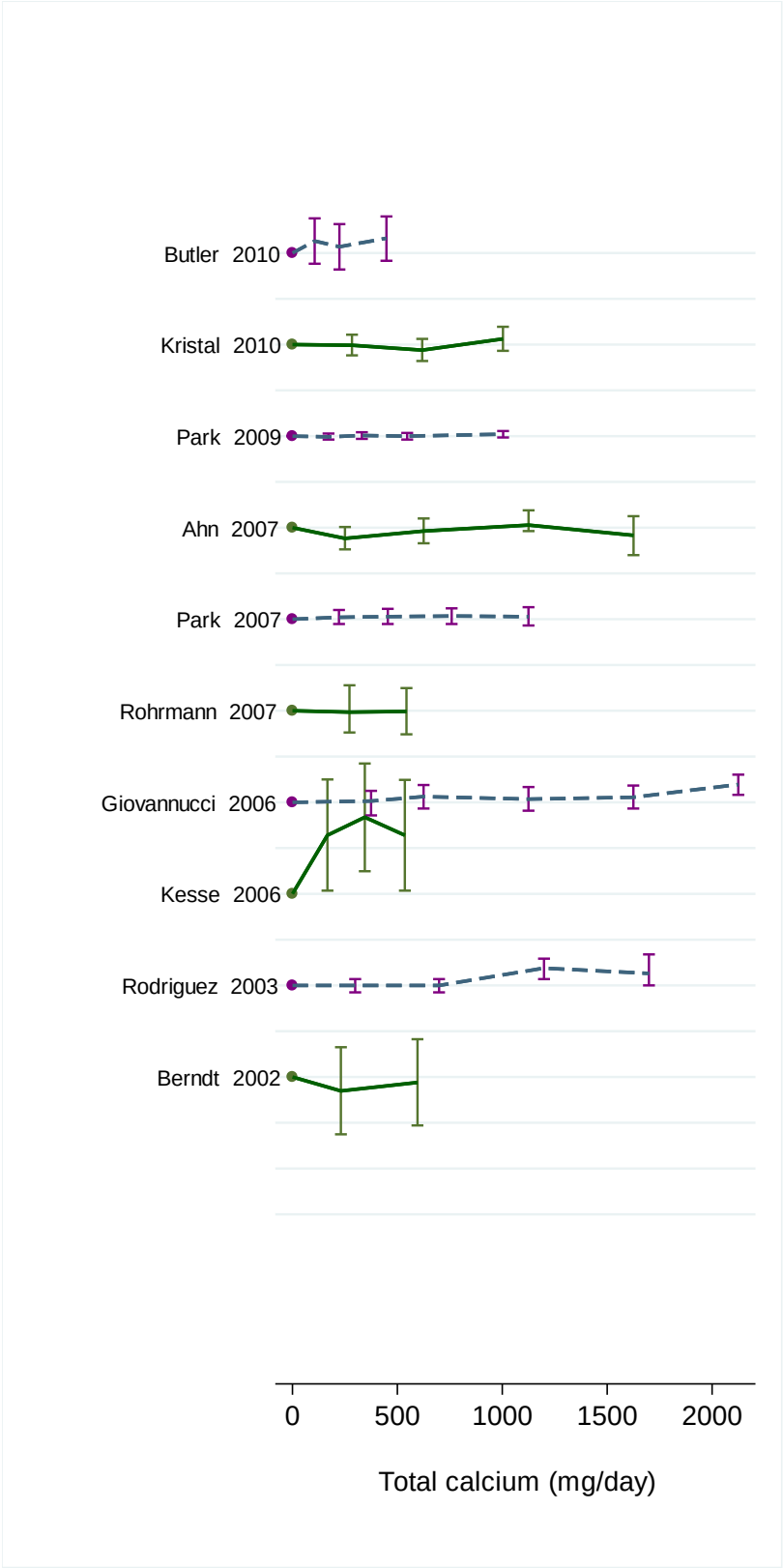


Figure 239 Dose-response meta-analysis of total calcium and prostate cancer, per 400 mg/day, stratified by outcome type

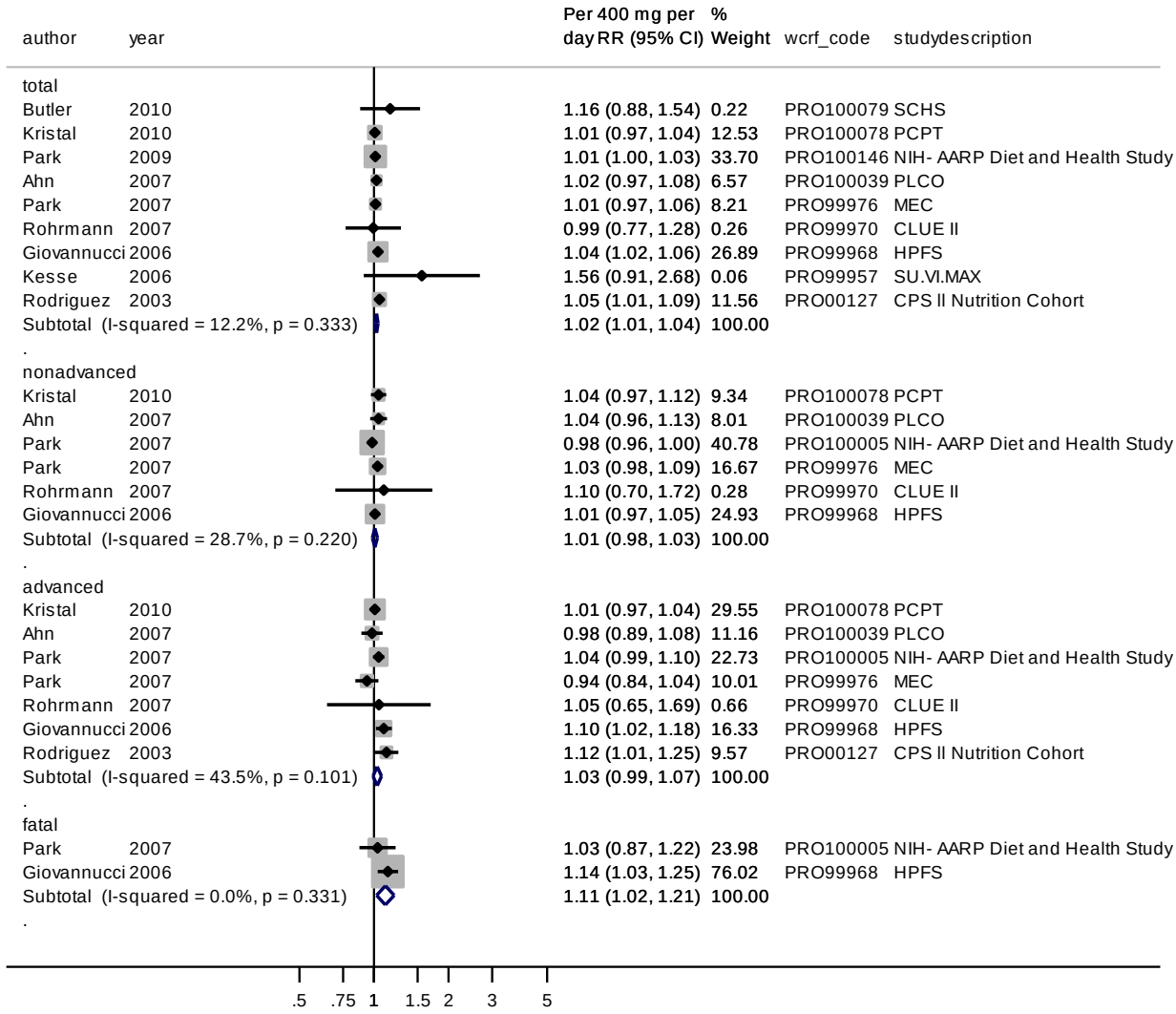


Figure 240 Non-linear dose-response analysis of total calcium intake and total prostate cancer

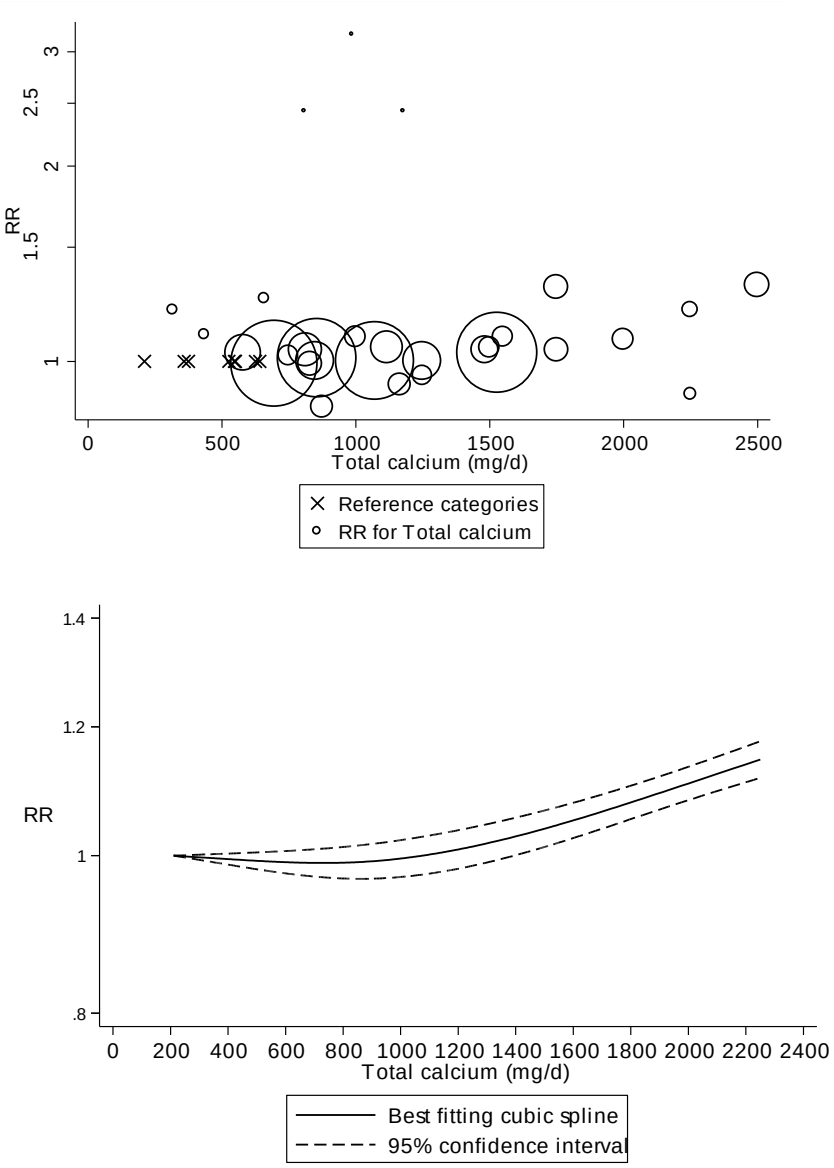


Table 219 Table with total calcium intake values and corresponding RRs (95% CIs) for non-linear analysis of total calcium intake and total prostate cancer

Total calcium intake (mg/day)	RR (95% CI)
211	1
526	0.99 (0.98-1.01)
1000	1.00 (0.97-1.02)
1251	1.01 (0.99-1.04)
1500	1.04 (1.01-1.07)
1751	1.07 (1.05-1.10)
2000	1.11 (1.08-1.13)
2251	1.15 (1.12-1.18)

$p_{non\text{-}linearity} < 0.01$

5.6.3 Dietary calcium

Methods
A total of 16 cohort studies (18 publications) have been published on dietary calcium and prostate cancer risk. Eleven studies were identified in the CUP. Dose-response analyses were conducted per 400 mg per day increase in dietary calcium intake.

Of the studies included in the dose-response analysis 15 studies reported on total prostate cancer: Schuurman et al, 1999b; Berndt et al, 2002; Rodriguez et al, 2003; Tseng et al, 2005; Baron et al, 2005; Severi et al, 2006; Park et al, 2007; Mitrou et al, 2007; Ahn et al, 2007; Kurahashi et al, 2008a; Allen et al, 2008; Park et al, 2009; Chae et al, 2009; Kristal et al, 2010; Butler et al, 2010. Eight studies reported on nonaggressive, nonadvanced, Gleason score 2-7 or localised prostate cancer; Schuurman et al, 1999, Severi et al, 2006; Park et al, 2007b; Mitrou et al, 2007; Ahn et al, 2007; Kurahashi et al, 2008a; Allen et al, 2008; Kristal et al, 2010. Ten studies reported on aggressive, advanced, Gleason score 8-10 prostate cancer: Schuurman et al, 1999; Rodriguez et al, 2003; Severi et al, 2006; Giovannucci et al, 2006b; Park et al, 2007b; Mitrou et al, 2007; Ahn et al, 2007; Kurahashi et al, 2008a; Allen et al, 2008; Kristal et al, 2010.

Main results
The summary RR per 400 mg/day increase in dietary calcium intake was 1.05 (95% CI 1.02-1.09; $I^2 = 49.1\%$; $p_{heterogeneity} = 0.02$; n = 15) for total prostate cancer. There was some indication of publication bias with Egger's test, p=0.11. There was evidence of nonlinearity, pnonlinearity<0.01. When stratified by outcome type the summary RR was 1.07 (95% CI 1.03-1.12; $I^2 = 7.4\%$; $p_{heterogeneity} = 0.37$; n = 8) for nonadvanced cancers and 1.02 (95% CI 0.93-1.12; $I^2 = 55.3\%$; $p_{heterogeneity} = 0.02$; n = 10) for advanced cancers.

Nine of the 13 studies published after 2003 provided some information of PSA test in the study populations. In the Prostate Cancer Prevention Trial (Kristal et al, 2010), all participants had PSA tests. Almost all diagnosed prostate cancers were local stage and screen-detected. No significant association of dietary or total calcium and advanced prostate cancer was observed. In the NIH-AARP, about 85% of the prostate cancers diagnosed were not advanced cancers. The analyses were adjusted for PSA testing (Park et al, 2009; Park et al, 2007). No significant association with dietary or supplemental calcium was observed; a significant inverse association of calcium from non-dairy sources with non advanced prostate cancer risk and of skim milk with advanced prostate cancers were observed. In the MEC, the authors could not control for PSA utilization. PSA utilization in the study population (questionnaire close to end of study follow-up) was related to higher calcium and milk intake and it could have acted as a confounding factor (Park et al, 2007). No significant association with calcium intake was observed. In the JPHC I&II, PSA based-detection of prostate cancers was 38%. A positive association with dairy foods was observed; a significant association with calcium intake was lost after multivariate adjustment (Kurahasi et al, 2008). In the nested case-control study in the CLUE II study (Chae et al, 2009), there was no appreciable difference in PSA test rate between cases and controls. The percentage of cancers with stage II-IV was 22% with 30% of the stage data missing in the study. No significant association with dietary calcium was observed. In the ATBC study (Mitrou et al, 2007) a large proportion of cases was diagnosed through clinical symptoms. Dietary calcium was positively associated with increased prostate cancer risk. No significant association with total dairy intake

remained after adjustment for calcium. Findings were similar by prostate cancer stage and grade.

In the HPFS (Giovannucci et al, 2006), PSA testing was slightly higher in men with higher calcium intake. Dietary calcium was significantly positively associated to advanced cancer but not related to non advanced cancers. The results were the same when the analyses were limited to men with a PSA test. In the NHANES I (Tseng et al, 2005), the results were similar in analysis stratified by year of diagnosis (before and after 1991, year from which PSA was more widely used). Calcium intake and low fat milk were positively associated to prostate cancer risk in this study. In the RCT on calcium supplementation, PSA values at study baseline were lower in the group randomised to calcium. Subsequent prostate cancer risk was not related to dietary calcium at baseline (Baron et al, 2005).

Heterogeneity

There was moderate heterogeneity, $I^2 = 49.1\%$, $p_{heterogeneity} = 0.02$ that was explained by one outlying study (Tseng et al, 2005), and when excluded the summary RR was 1.04 (95% CI 1.02-1.07; $I^2 = 12.7\%$; $p_{heterogeneity} = 0.32$; n = 14). The heterogeneity was not modified after exclusion of the PCPT study (Kristal et al, 2010) in which people underwent frequent PSA tests (RR for 400 mg of increase of dietary calcium 1.05; 95% CI 1.02-1.09; $I^2 = 55.4\%$; $p_{heterogeneity} = 0.006$). However, for advanced/high grade cancers the heterogeneity was reduced when the PCPT study (Kristal et al, 2010) that reported on Gleason 8-10 was excluded (RR 1.05; 95% CI 0.97-1.12; $I^2 = 35.7\%$; $p_{heterogeneity} = 0.13$). The heterogeneity was also reduced when the HPFS was excluded (RR 0.99; 95% CI 0.92-1.07; $I^2 = 35.5\%$ $p_{heterogeneity} = 0.13$).

Conclusion from the Second Expert Report

In the 2005 SLR it was stated the dietary calcium probably increases prostate cancer risk.

Published meta-analyses

A meta-analysis of 5 prospective studies reported a summary RR for total prostate cancer of 1.38 (95% CI 1.04-1.83) comparing high vs. low calcium intake, while for advanced prostate cancer the summary RR was 1.46 (95% CI 0.65-3.25) (Gao et al, 2005).

A meta-analysis of 5 cohort studies reported a summary RR of 1.15 (95% CI 1.02-1.30) for high vs. low calcium intake (Huncharek et al, 2009).

Table 220 Studies on dietary calcium identified in the CUP

Author/year	Country	Study name	Cases	Years of follow-up	RR	LCI	UCI	Contrast
Kristal, 2010	USA	Prostate Cancer Prevention Trial	1703 cases	7 years	1.27 0.43	1.02 0.21	1.57 0.89	> 1165 vs. < 598 mg/d, Gleason score 2-7 > 1165 vs.

								< 598 mg/d, Gleason score 8-10
Butler, 2010	Singapore	Singapore Chinese Health Study	298	11 years	1.23	0.88	1.72	651 vs. 210 mg/d
Park, 2009	USA	NIH-AARP Diet and Health Study	17189	8 years	1.04	0.98	1.09	1247 vs. 478 mg/d
Chae, 2009	USA	CLUE II	269	~14 years	1.08	0.66	1.75	≥ 878.7 vs. < 424.0 mg/d
Kurahashi, 2008a	Japan	JPHC study-cohort I and II	329	7.5 years	1.24	0.85	1.81	725.1 vs. 282.8 mg/d
Allen, 2008a	Ten European countries	European Prospective Investigation into Cancer and nutrition (EPIC)	2727	8.7 years	1.17	1.00	1.35	1320 vs. 780 mg/d
Park, 2007b	USA	Multiethnic Cohort Study	4404	8 years	1.02	0.87	1.19	≥ 1123 vs. < 417 mg/d
Mitrou, 2007	Finland	Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study	1267	17 years	1.63	1.27	2.10	≥ 2000 vs. < 1000 mg/d
Ahn, 2007	USA	PLCO Cancer Screening Trial	1910	8.9 years	1.22	0.83	1.79	≥ 2001 vs. ≤ 750 mg/d
Severi, 2006	Australia	The Melbourne collaborative cohort study	674	10.9 years	0.98	0.72	1.33	1238 vs. 507 mg/d
Giovannucci, 2006a	USA	Health Professionals Follow-up Study	3544	16 years	1.46	1.12	1.90	≥ 933 vs. < 585 mg/d, advanced cancers

Table 221 Overall evidence on dietary calcium and prostate cancer

	Summary of evidence
2005 SLR	Eight[1] studies reported on dietary calcium intake and prostate cancer risk, four of which reported positive associations and the remaining studies found no significant association.
Continuous Update Project	Eleven cohort studies reported on dietary calcium intake and prostate cancer and four of these reported increased risk. A significant association was observed for total and non advanced prostate cancer

[1] One of these studies (Chan et al, 2001, PRO01091) reported on dairy calcium intake and is not included in the analysis of dietary calcium in the present analysis.

Table 222 Summary of results of the dose-response meta-analysis of dietary calcium and prostate cancer

Prostate cancer		
	2005 SLR	CUP
Studies (n)	8	15
Cases (n)	7288	38749
RR (95% CI)	1.27 (1.09-1.48)	1.05 (1.02-1.09)
Increment unit used	Per 1000 mg/day	Per 400 mg/day
Heterogeneity (I^2, p-value)	46.4%, p = 0.07	49.1%, p = 0.02
	Non advanced cancers	
Studies (n)	-	8
Cases (n)		9048
RR (95% CI)		1.07 (1.03-1.12)
Increment unit used		per 400 mg/day
Heterogeneity (I^2, p-value)		7.4%, p = 0.37
	Advanced cancers	
Studies (n)	-	10
Cases (n)		3999
RR (95% CI)		1.02 (0.93-1.12)
Increment unit used		Per 400 mg/day
Heterogeneity (I^2, p-value)		55.3%, p = 0.02

Table 223 Inclusion/exclusion table for meta-analysis of dietary calcium and prostate 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
PRO100078	Kristal	2010	Prospective Cohort	Prostate Cancer Prevention Trial	Incidence	No	Yes	Yes	Mid-exposure values	
PRO100079	Butler	2010	Prospective Cohort	Singapore Chinese Health Study	Incidence	No	Yes	Yes	Person-years	
PRO100146	Park	2009	Prospective Cohort	NIH-AARP Diet and Health Study	Incidence	No	Yes	Yes	Cases/person-years	
PRO100074	Chae	2009	Nested case-control study	CLUE II	Incidence	No	Yes	Yes	Mid-exposure values	
PRO100000	Kurahashi	2008a	Prospective Cohort	JPHC study-cohort I and II	Incidence	No	Yes	Yes		
PRO99955	Allen	2008a	Prospective Cohort	European Prospective Investigation into Cancer and nutrition (EPIC)	Incidence	No	Yes	Yes	Person-years	
PRO99976	Park	2007b	Prospective Cohort	Multiethnic Cohort Study	Incidence	No	Yes	Yes	Mid-exposure values, person-years	
PRO99979	Mitrou	2007	Prospective Cohort	Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study	Incidence	No	Yes	Yes		
PRO100039	Ahn	2007	Prospective Cohort	PLCO Cancer Screening Trial	Incidence	No	Yes	Yes	Mid-exposure values, person-years	

PRO99990	Severi	2006	Prospective Cohort	The Melbourne collaborative cohort study	Incidence	No	Yes	Yes	Mid-exposure values, cases, person-years	
PRO99968	Giovannucci	2006a	Prospective Cohort	Health Professionals Follow-up Study	Incidence	No	Yes	Yes	Person-years	Included in analyses on advanced prostate cancers only
PRO97221	Tseng	2005	Prospective Cohort	NHANESI	Incidence	Yes	Yes	Yes		
PRO97184	Baron	2005	Prospective Cohort	Calcium Polyp Prevention Study	Incidence	Yes	Yes	Yes		
PRO00127	Rodriguez	2003	Prospective Cohort	Cancer Prevention Study ll Nutrition Cohort	Incidence	Yes	Yes	Yes	Mid-exposure values	
PRO00628	Berndt	2002	Prospective Cohort	Baltimore Longitudinal Study of Aging	Incidence	Yes	Yes	Yes		
PRO01426	Chan	2000	Prospective Cohort	Alpha Tocopherol Beta Carotene Cancer Prevention	Incidence	Yes	No	No		Overlap with Mitrou et al, 2007 (PRO99979)
PRO01759	Schuurman	1999b	Case cohort	Netherlands Cohort Study	Incidence	Yes	Yes	Yes		
PRO02192	Giovannucci	1998b	Prospective Cohort	Health Professionals Follow-up Study	Incidence	Yes	No	No		Overlap with Giovannucci et al, 2006 (PRO099968)

Figure 241 Highest versus lowest forest plot of dietary calcium and prostate cancer

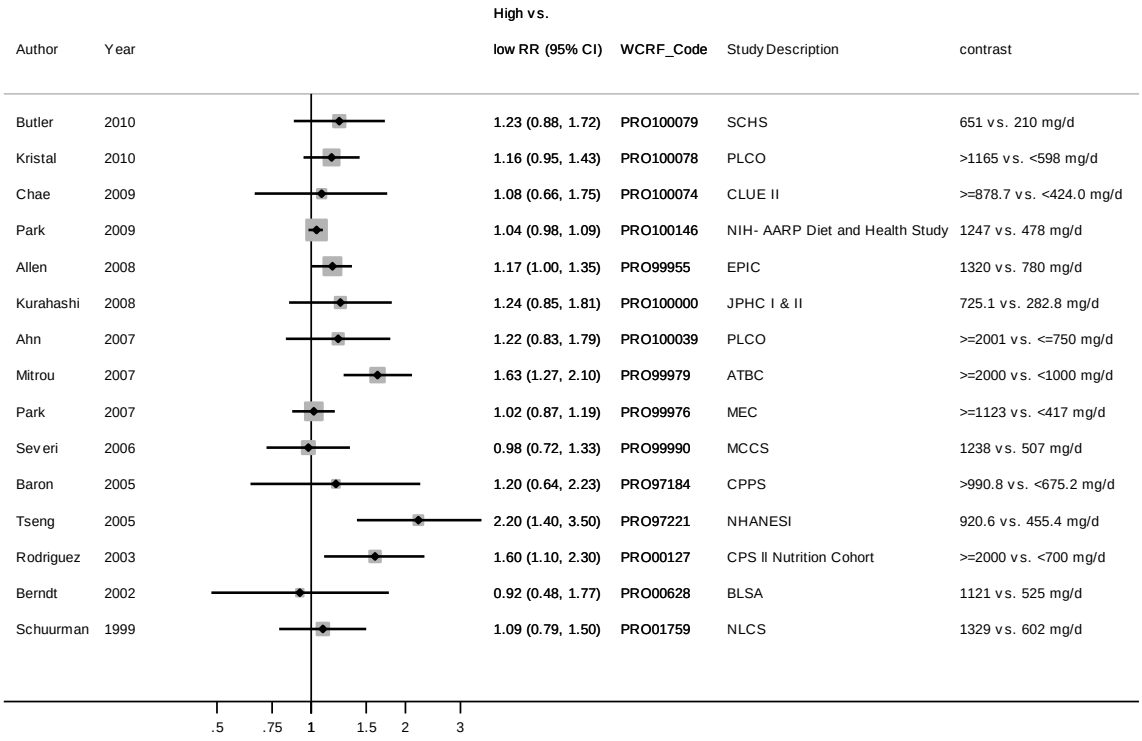


Figure 242 Dose-response meta-analysis of dietary calcium and prostate cancer, per 400 mg/day

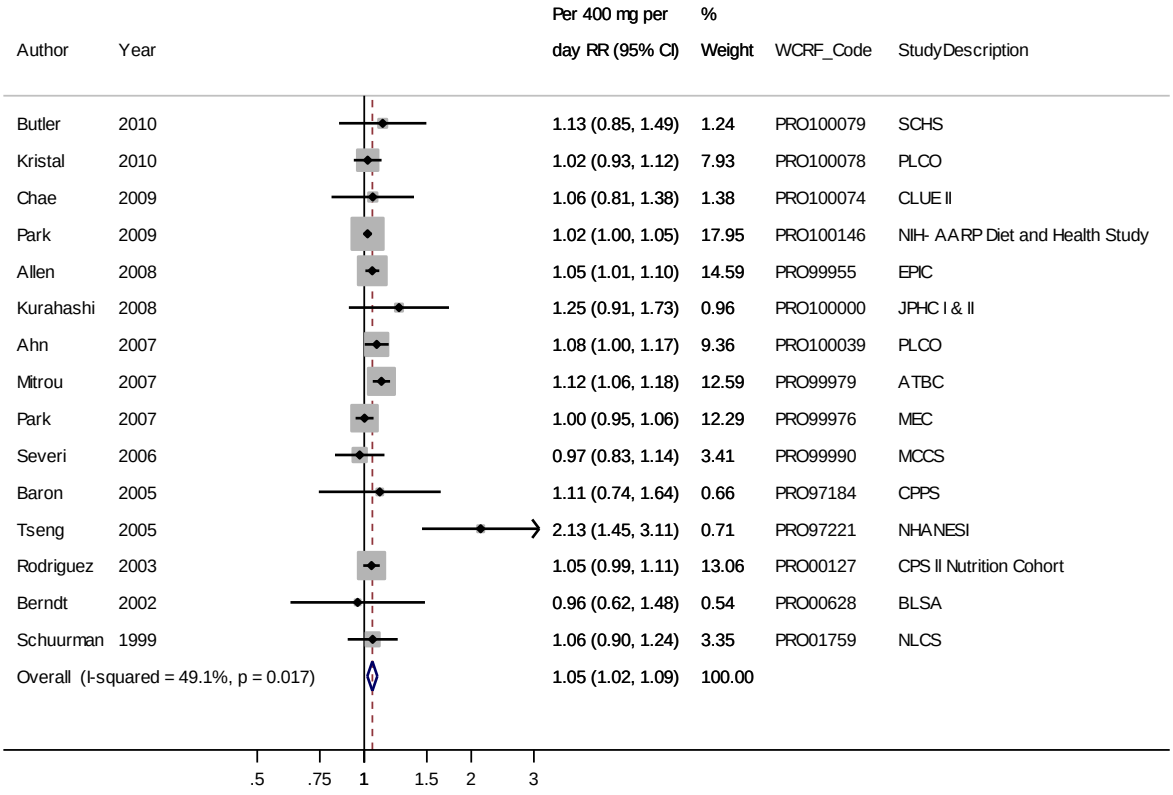
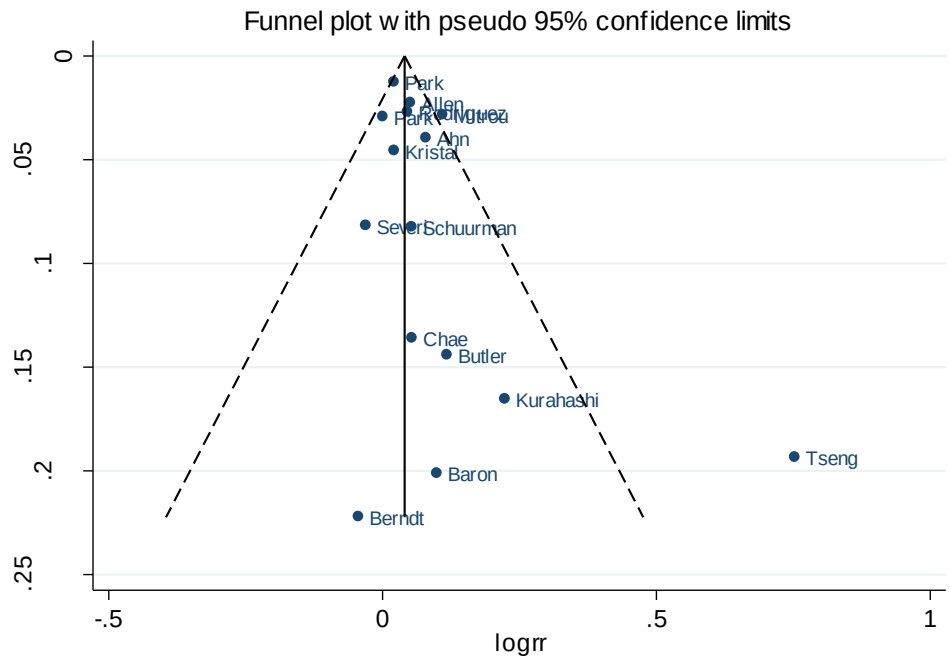


Figure 243 Funnel plot of dietary calcium and prostate cancer



Egger's test p = 0.11

Figure 244 Dose-response graph of dietary calcium and total prostate cancer

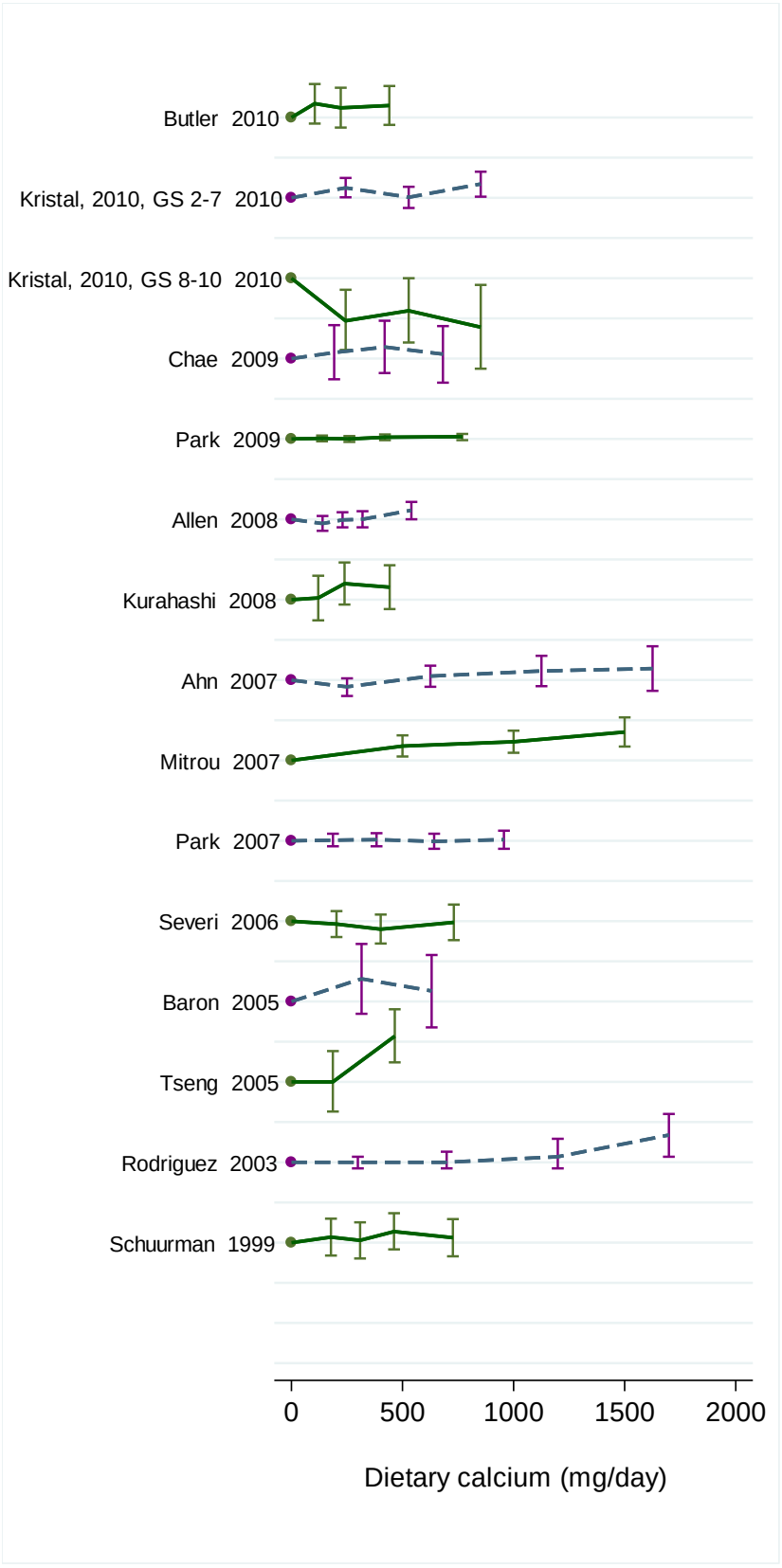


Figure 245 Dose-response meta-analysis of dietary calcium and prostate cancer, per 400 mg/day, stratified by outcome type

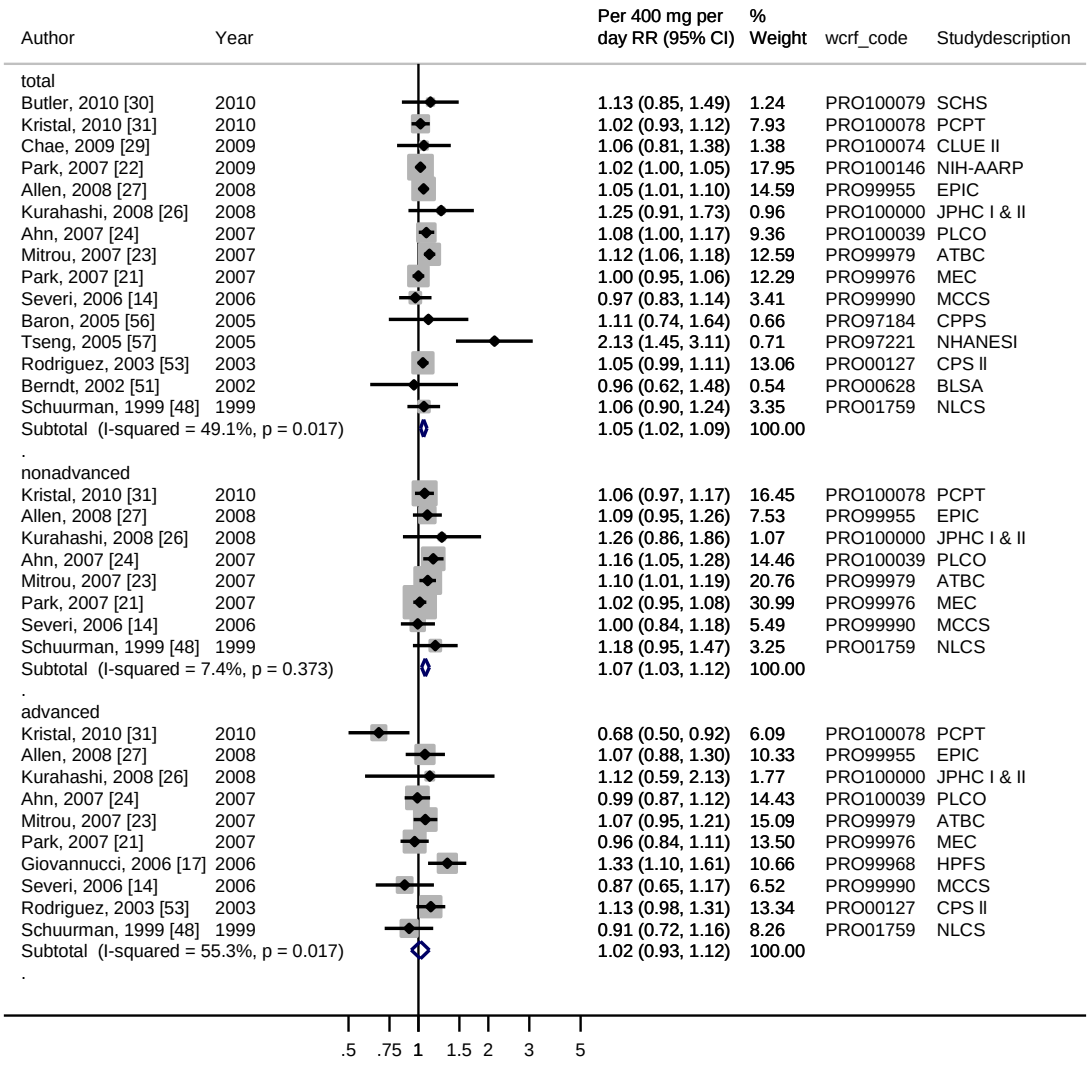


Figure 246 Non-linear dose-response analysis of dietary calcium intake and total prostate cancer

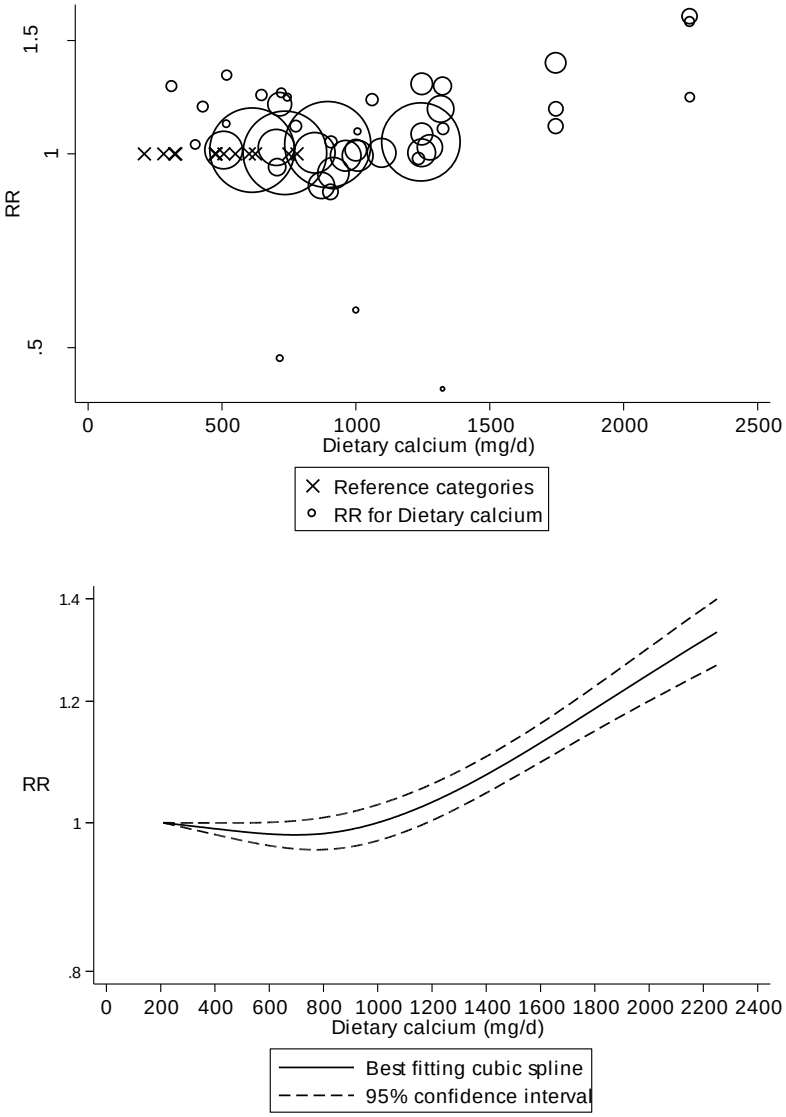


Table 224 Table with dietary calcium intake values and corresponding RRs (95% CIs) for non-linear analysis of dietary calcium intake and total prostate cancer

Dietary calcium intake (mg/day)	RR (95% CI)
210	1
507	0.99 (0.97-1.00)
1004	1.00 (0.97-1.03)
1238	1.04 (1.01-1.07)
1329	1.06 (1.03-1.09)
1750	1.17 (1.13-1.21)
2250	1.33 (1.27-1.40)

$p_{non\text{-}linearity} < 0.01$

5.6. 3 Supplemental calcium

Methods
A total of 9 cohort studies and one randomized clinical trial (12 publications) have been published on supplemental calcium prostate cancer risk up. Seven cohort studies (8 publications) were identified in the CUP. Dose-response analyses were conducted per 400 mg per day increase in supplemental calcium intake.

Of the studies that were included in the dose-response analysis of supplemental calcium and prostate cancer 4 studies reported on total prostate cancer: Park et al, 2007; Ahn et al, 2007; Park et al, 2009; Kristal et al, 2010. Four studies were included in the analysis of nonadvanced, nonaggressive, localised or Gleason score 8-10 prostate cancer: Park et al, 2007 (MEC); Park et al, 2007 (NIH-AARP Diet and Health Study); Ahn et al, 2007; Kristal et al, 2010. Five studies were included in the analysis of advanced, aggressive or Gleason score 2-7 prostate cancer: Giovannucci et al, 2006; Park et al, 2007 (MEC); Park et al, 2007 (NIH-AARP Diet and Health Study); Ahn et al, 2007; Kristal et al, 2010. Two studies were included in the analysis of fatal prostate cancer: Giovannucci et al, 2006; Park et al, 2007 (NIH-AARP Diet and Health Study).

Main results
The summary RR per 400 mg/d increase in supplemental calcium intake was 0.99 (95% CI 0.96-1.01; $I^2 = 0\%$; $p_{heterogeneity} = 0.63$; n = 4) for total prostate cancer. There was no indication of publication bias with Egger's test, p = 0.11. When stratified by outcome type the summary RR was 0.99 (95% CI 0.96-1.02; $I^2 = 0\%$; $p_{heterogeneity} = 0.44$; n = 4) for nonadvanced prostate cancer, 1.01 (95% CI 0.94-1.09; $I^2=16.6\%$; $p_{heterogeneity} = 0.31$) for advanced prostate cancer, and 1.29 (95% CI 1.08-1.54; $I^2 = 0\%$; $p_{heterogeneity} = 0.78$; n = 2) for fatal prostate cancer. There was no evidence of nonlinearity, $p_{non\text{-}linearity} = 0.63$.

Heterogeneity
There was no heterogeneity, $I^2 = 0\%$, $p_{heterogeneity} = 0.63$.

Conclusion from the Second Expert Report
In the SLR of the 2007 Expert Report the evidence relating supplemental calcium to prostate cancer was too limited or inconsistent for a conclusion to be made.

Published meta-analyses
None of the previous meta-analyses evaluated calcium from supplemental sources (Gao et al, 2006, Huncharek et al, 2009).

Table 225 Studies on supplemental calcium identified in the CUP

Author/year	Country	Study name	Cases	Years of follow-up	RR	LCI	UCI	Contrast
Kristal, 2010	USA	Prostate Cancer Prevention Trial	1703	7 years	0.77	0.46	1.32	> 199 vs. < 150 mg/d
Park, 2009	USA	NIH-AARP Diet and Health Study	17189	8 years	0.96	0.88	1.05	≥ 1000 vs. 0 mg/d
Ahn, 2007	USA	PLCO Cancer Screening Trial	1910	8.9 years	0.94	0.68	1.29	≥ 801 vs. 0 mg/d
Rohrmann, 2007	USA	CLUE II	199	13 years	0.86	0.62	1.19	Any vs. none
Park Y, 2007	USA	NIH- AARP Diet and Health Study	10180	6 years	1.00	0.88	1.13	≥ 1000 vs. 0 mg/d
Park, 2007b	USA	Multiethnic Cohort Study	4404	8 years	0.99	0.90	1.08	≥ 200 vs. 0 mg/d
Koh, 2006	USA	Harvard Alumni Health Study 1962-1966	815	10 years	1.05	0.84	1.31	Any vs. none
Giovannucci, 2006a	USA	Health Professionals Follow-up Study	3544	16 years	1.22 1.51	0.93 1.09	1.62 2.10	≥ 401 vs. 0 mg/d, advanced ≥ 401 vs. 0 mg/d, fatal

Table 226 Overall evidence on supplemental calcium and prostate cancer

	Summary of evidence
2005 SLR	Four studies reported on supplemental calcium and one found a borderline significant positive association, while the remaining studies found no significant association.
Continuous Update Project	Seven additional studies (8 publications) reported on supplemental calcium intake and prostate cancer risk, of which one reported a significant positive association only for fatal prostate cancer, while all the remaining studies reported no significant association. A significant association was observed only with fatal prostate cancers

Table 227 Summary of results of the dose-response meta-analysis of supplemental calcium and prostate cancer

Prostate cancer		
	2005 SLR	CUP
Studies (n)	-	4
Cases (n)		19412
RR (95% CI)		0.99 (0.96-1.01)
Increment unit used		Per 400 mg/day
Heterogeneity (I^2, p-value)		0%, p = 0.63
	Non advanced cancers	
Studies (n)	-	4
Cases (n)		14824
RR (95% CI)		0.99 (0.96-1.02)
Increment unit used		Per 400 mg/day
Heterogeneity (I^2, p-value)		0%, p = 0.44
	Advanced cancers	
Studies (n)	-	5
Cases (n)		3605
RR (95% CI)		1.01 (0.94-1.09)
Increment unit used		Per 400 mg/day
Heterogeneity (I^2, p-value)		16.6%, p = 0.31
	Fatal cancers	
Studies (n)	-	2
Cases (n)		490
RR (95% CI)		1.29 (1.08-1.54)
Increment unit used		Per 400 mg/day
Heterogeneity (I^2, p-value)		0%, p = 0.78

Table 228 Inclusion/exclusion table for meta-analysis of supplemental calcium and prostate 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
PRO100078	Kristal	2010	Prospective Cohort	Prostate Cancer Prevention Trial	Incidence	No	Yes	Yes		
PRO100146	Park	2009	Prospective Cohort	NIH-AARP Diet and Health Study	Incidence	No	Yes	Yes	Cases/person-years	
PRO100039	Ahn	2007	Prospective Cohort	PLCO Cancer Screening Trial	Incidence	No	Yes	Yes	Mid-exposure values, person-years	
PRO99970	Rohrmann	2007	Prospective Cohort	CLUE II	Incidence	No	No	Yes	Mid-exposure values	<3 categories
PRO100005	Park Y	2007	Prospective Cohort	NIH- AARP Diet and Health Study	Incidence	No	Yes	No		Surpassed by Park et al, 2009 (PRO100146) for total prostate cancer, but included for nonadvanced, advanced, and fatal cancers
PRO99976	Park	2007b	Prospective Cohort	Multiethnic Cohort Study	Incidence	No	Yes	Yes	Mid-exposure values, person-years	
PRO99962	Koh	2006	Prospective Cohort	Harvard Alumni Health Study 1962-1966	Incidence	No	No	Yes		<3 categories
PRO99968	Giovannucci	2006a	Prospective Cohort	Health Professionals Follow-up Study	Incidence	No	Yes	No	Person-years	Only included in analysis of advanced and fatal prostate cancer

PRO97221	Tseng	2005	Prospective Cohort	NHANESI	Incidence	Yes	No	Yes		<3 categories
PRO97184	Baron	2005	Randomized controlled trial	Calcium Polyp Prevention Study	Incidence	Yes	No	Yes		<3 categories
PRO10575	Platz	2004c	Nested case-control study	Health Professionals Follow-up Study	Incidence	Yes	No	No		Overlaps with Giovannucci 2006 No risk estimates
PRO00127	Rodriguez	2003	Prospective Cohort	Cancer Prevention Study ll Nutrition Cohort	Incidence	Yes	No	Yes		<3 categories

Figure 247 Highest versus lowest forest plot of supplemental calcium and prostate cancer

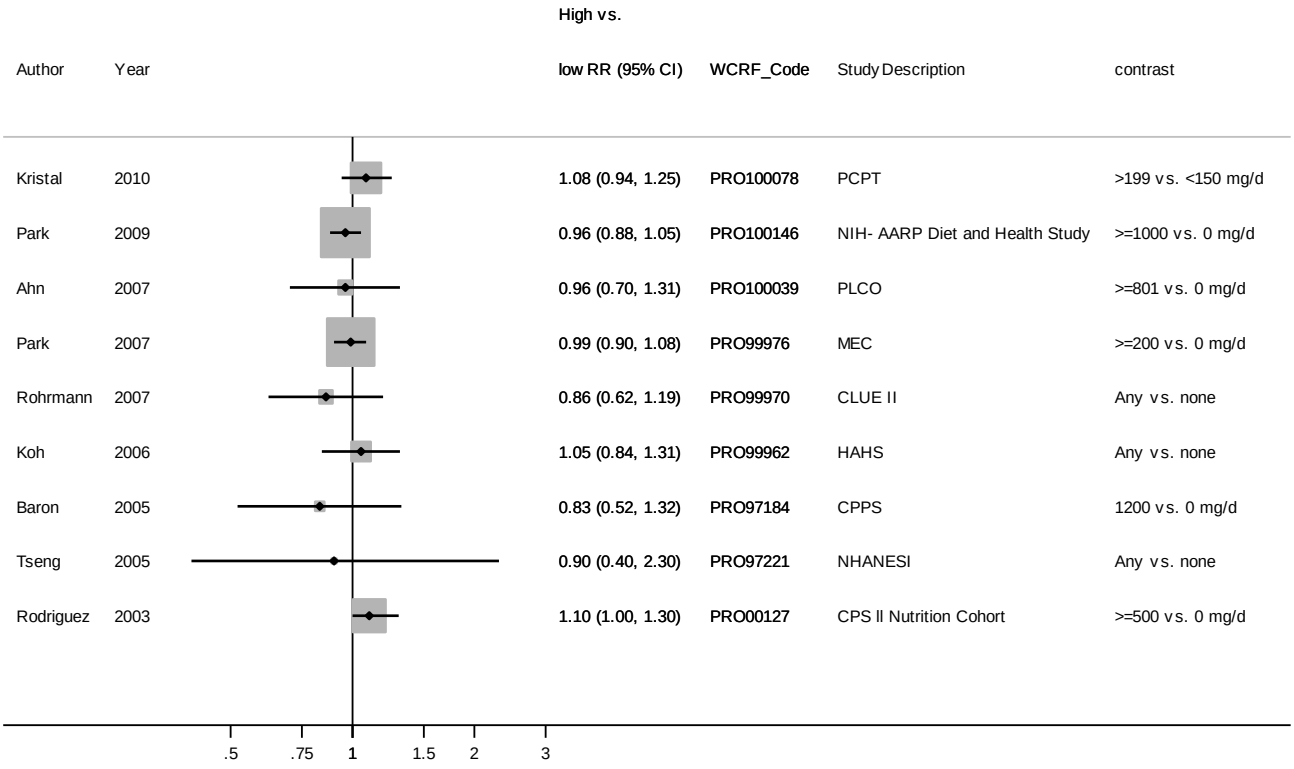


Figure 248 Dose-response meta-analysis of supplemental calcium and prostate cancer, per 400 mg/day

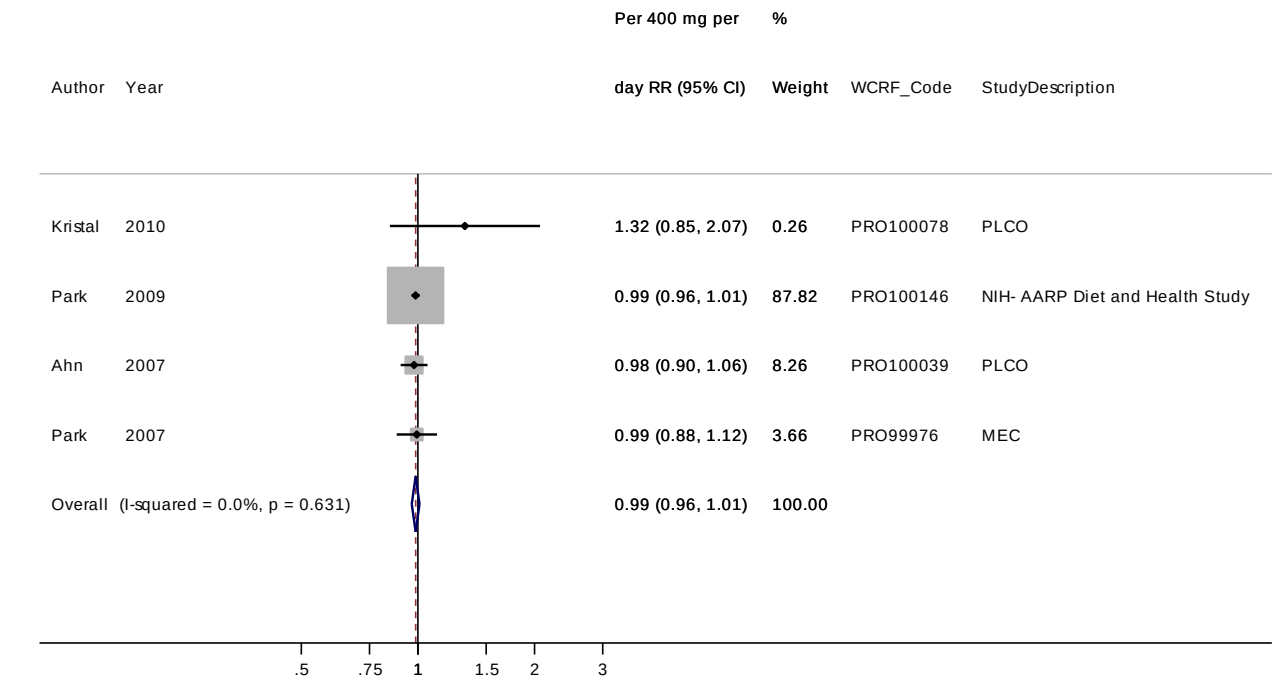


Figure 249 Dose-response graph of supplemental calcium and total prostate cancer

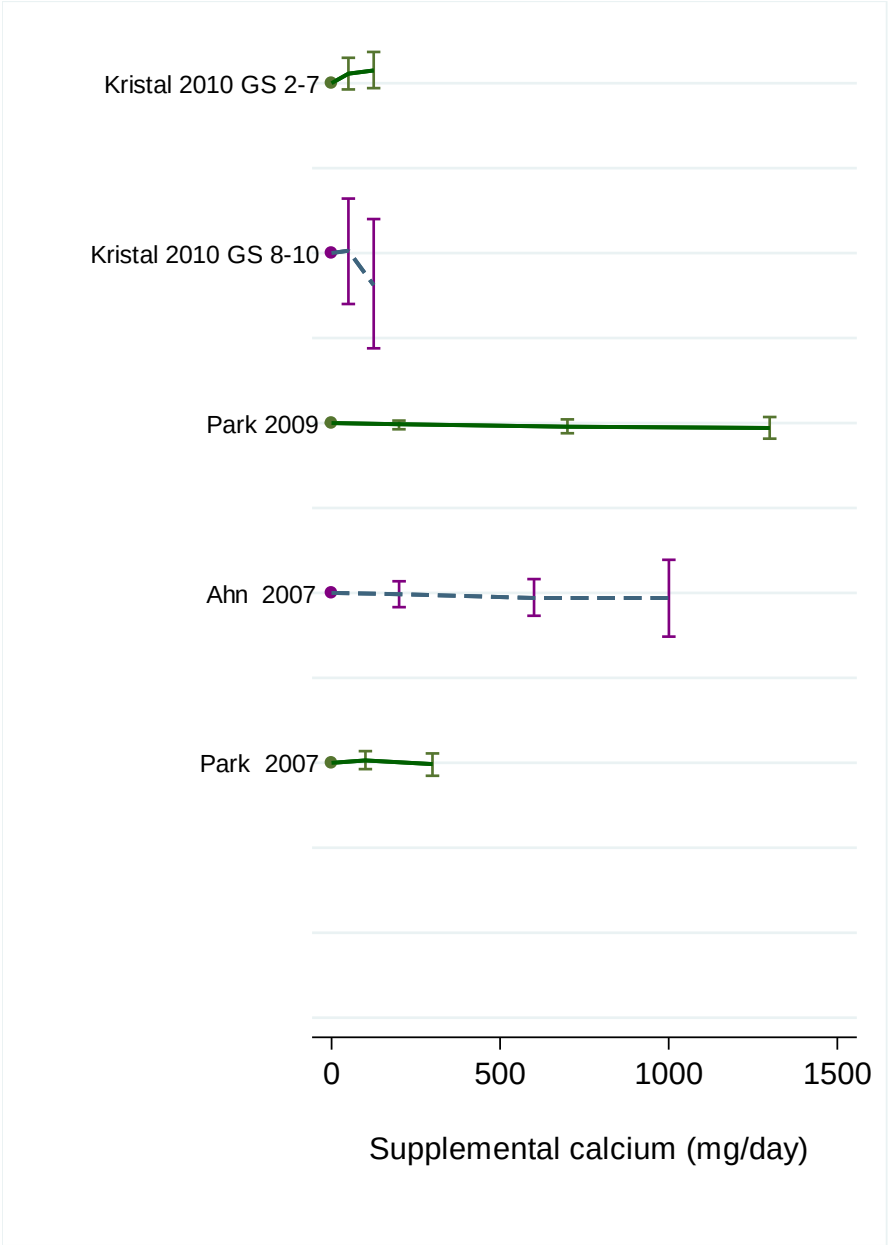
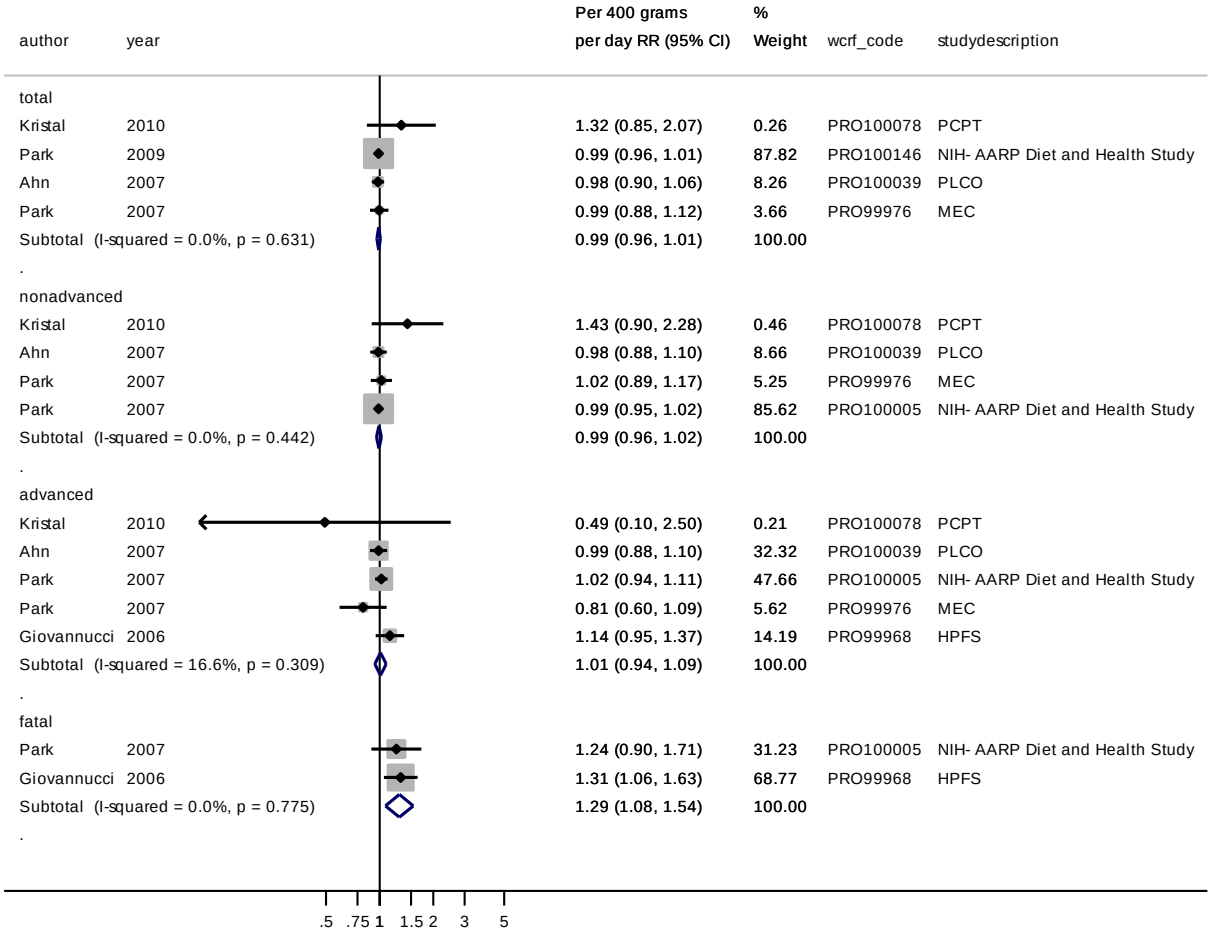


Figure 250 Dose-response meta-analysis of supplemental calcium and prostate cancer, per 400 mg/day, stratified by outcome type



5.6.3 Dairy calcium

Methods
A total of 7 cohort studies (8 publications) have been published on dairy calcium and prostate cancer risk. Seven studies (7 publications) were identified in the CUP. Dose-response analyses were conducted per 400 mg per day increase in dairy calcium intake.

All studies reported on total prostate cancer: Chan et al, 2001; Koh et al, 2006; Kesse et al, 2006; Park et al, 2007; Rohrmann et al, 2007; Mitrou et al, 2007; Allen et al, 2008 and Song et al, 2013. Two studies reported on nonadvanced or localised prostate cancer and on advanced prostate cancer cancer: Park Y et al, 2007 (NIH-AARP Diet and Health Study) and Allen et al, 2008a. Two studies reported on fatal prostate cancer: Park et al, 2007 and Koh et al, 2006.

Main results
The summary RR per 400 mg/d increase in dairy calcium intake was 1.06 (95% CI 1.02-1.09; $I^2 = 32.7\%$; $p_{heterogeneity} = 0.19$; n = 6). There was no indication of publication bias with Egger's test, p = 0.31. There was no evidence of non-linearity, $p_{non\text{-}linearity} = 0.37$. When stratified by outcome type the summary RR was 1.03 (95% CI 1.00-1.07; $I^2 = 0\%$; $p_{heterogeneity} = 0.82$; n = 2) for non advanced, 1.05 (95% CI 0.96-1.15; $I^2 = 0\%$; $p_{heterogeneity} = 0.99$; n = 2) for advanced and 1.05 (95% CI 0.69-1.60; $I^2 = 55.1\%$; $p_{heterogeneity} = 0.14$; n = 2) for fatal prostate cancer.

Heterogeneity
There was low heterogeneity, $I^2 = 32.7\%$, $p_{heterogeneity} = 0.19$.

Conclusion from the Second Expert Report

In the 2005 SLR the evidence relating dairy calcium to prostate cancer risk was not evaluated because of few studies.

Table 229 Studies on dairy calcium identified in the CUP

Author/year	Country	Study name	Cases	Years of follow-up	RR	LCI	UCI	Contrast
Song, 2013	USA	Physician's Health Study	2806	28 years	1.14	0.97	1.34	Quintile 5 vs. 1
Allen, 2008a	Ten European countries	European Prospective Investigation into Cancer and nutrition (EPIC)	2727	8.7 years	1.18	1.03	1.36	880 vs. 300 mg/d

Rohrmann, 2007	USA	CLUE II	199	13 years	1.08	0.76	1.54	Tertile 3 vs. 1
Park Y, 2007	USA	NIH- AARP Diet and Health Study	10180	6 years	1.06	0.99	1.14	≥ 800 vs. < 250 mg/d
Mitrou, 2007	Finland	Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study	1267	17 years	1.28	1.07	1.54	1613.7 vs. 565.8 mg/d
Koh, 2006	USA	Harvard Alumni Health Study 1962-1966	815	10 years	0.91	0.70	1.18	≥ 600 vs. < 199 mg/d
Kesse, 2006	France	SU.VI.MAX	69	7.7 years	2.90	1.15	7.31	> 696 vs. < 354 mg/d

Table 230 Overall evidence on dairy calcium and prostate cancer

	Summary of evidence
2005 SLR	One cohort study reported a statistically significant increased risk with higher dairy calcium intake.
Continuous Update Project	Seven studies were identified in the CUP and three of these found significant positive associations, while the remaining four studies found no significant association. A significant association was observed for total cancers

Table 231 Summary of results of the dose-response meta-analysis of dairy calcium and prostate cancer

Prostate cancer		
	2005 SLR	CUP
Studies (n)	-	6
Cases (n)	-	10493
RR (95% CI)	-	1.06 (1.02-1.09)
Increment unit used	-	Per 400 g/day
Heterogeneity (I^2, p-value)	-	32.7%, p = 0.19
	Advanced cancers	
Studies (n)	-	2
Cases (n)		1967
RR (95% CI)		1.05 (0.96-1.15)
Increment unit used		Per 400 mg/day
Heterogeneity (I^2, p-value)		0%, p = 0.99
	Non advanced cancers	
Studies (n)	-	2
Cases (n)		9885
RR (95% CI)		1.03 (1.00-1.07)
Increment unit used		per 400 mg/day
Heterogeneity (I^2, p-value)		0%, p = 0.82
	Fatal cancers	
Studies (n)	-	2
Cases (n)		277
RR (95% CI)		1.05 (0.69-1.60)
Increment unit used		per 400 mg/day
Heterogeneity (I^2, p-value)		55.1%, p = 0.14

Table 232 Inclusion/exclusion table for meta-analysis of dairy calcium and prostate 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
PRO100162	Song	2013	Prospective Cohort	Physician's Health Study	Incidence	No	No	Yes	Mid-exposure values	No quantities, Chan et al, 2001 (PRO01091) used instead
PRO99955	Allen	2008a	Prospective Cohort	European Prospective Investigation into Cancer and nutrition (EPIC)	Incidence	No	Yes	Yes	Person-years	
PRO99970	Rohrmann	2007	Prospective Cohort	CLUE II	Incidence	No	No	Yes		<3 categories
PRO100005	Park Y	2007	Prospective Cohort	NIH- AARP Diet and Health Study	Incidence	No	Yes	Yes	Mid-exposure values, person-years	
PRO99979	Mitrou	2007	Prospective Cohort	Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study	Incidence	No	Yes	Yes		
PRO99962	Koh	2006	Prospective Cohort	Harvard Alumni Health Study 1962-1966	Incidence	No	Yes	Yes	Mid-exposure values, person-years	
PRO99957	Kesse	2006	Prospective Cohort	SU.VI.MAX	Incidence	No	Yes	Yes	Mid-exposure values, person-years	
PRO01091	Chan	2001	Prospective Cohort	Physicians' Health Study	Incidence	Yes	Yes	No	Mid-exposure values, person-years	Overlap with Song et al, 2013 (PRO100162)

Figure 251 Highest versus lowest forest plot of dairy calcium and prostate cancer

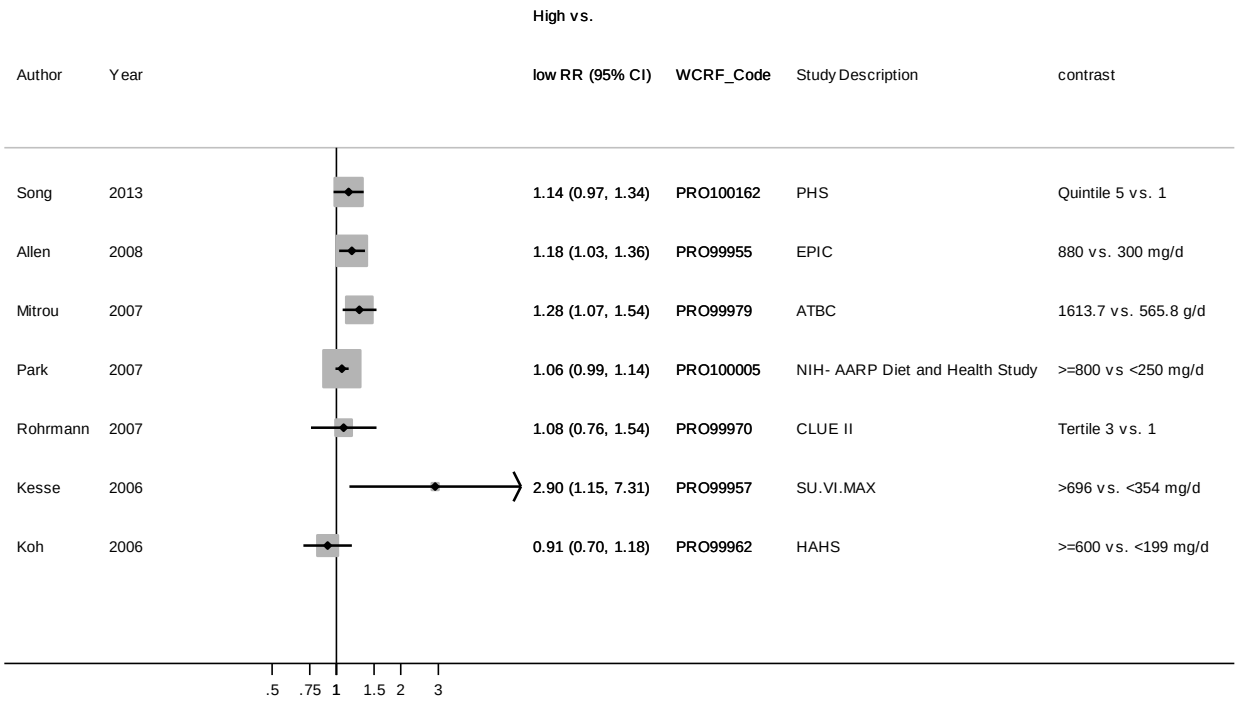


Figure 252 Dose-response meta-analysis of dairy calcium and prostate cancer, per 400 mg/day

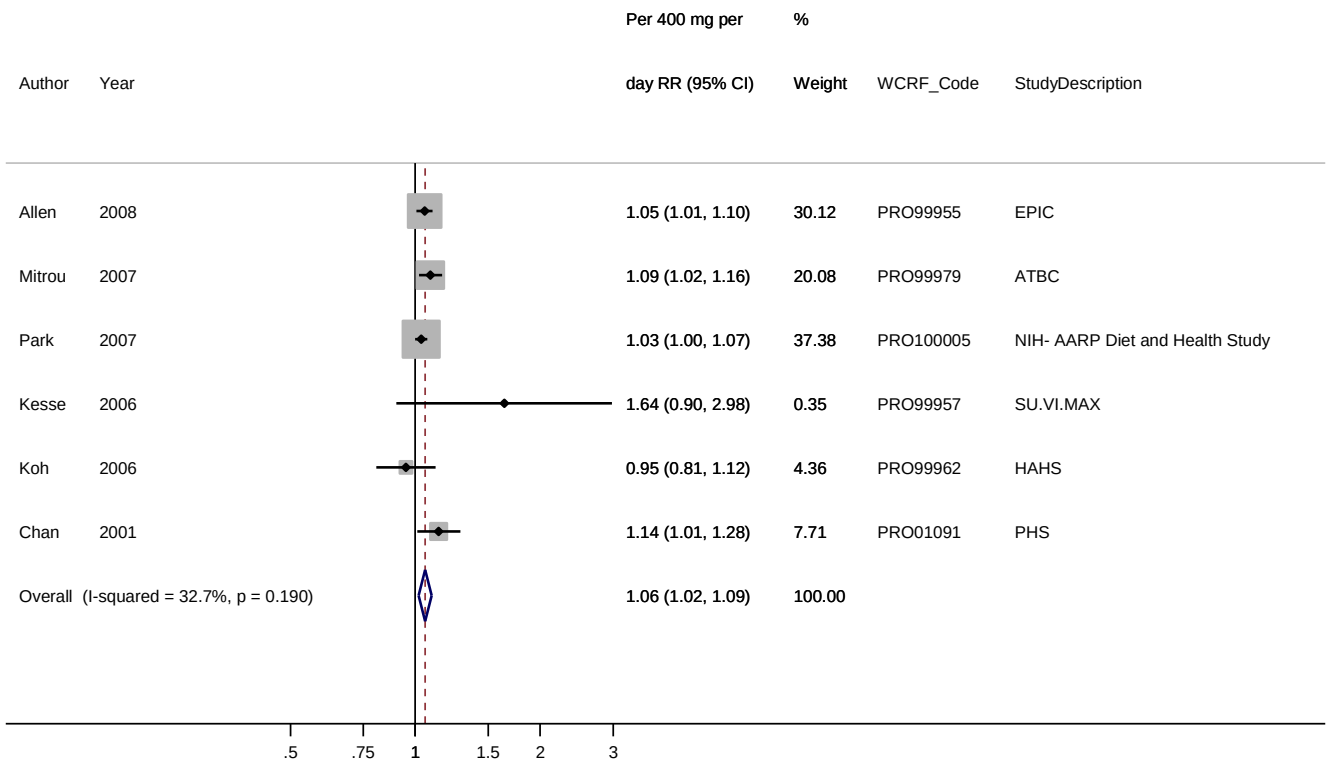
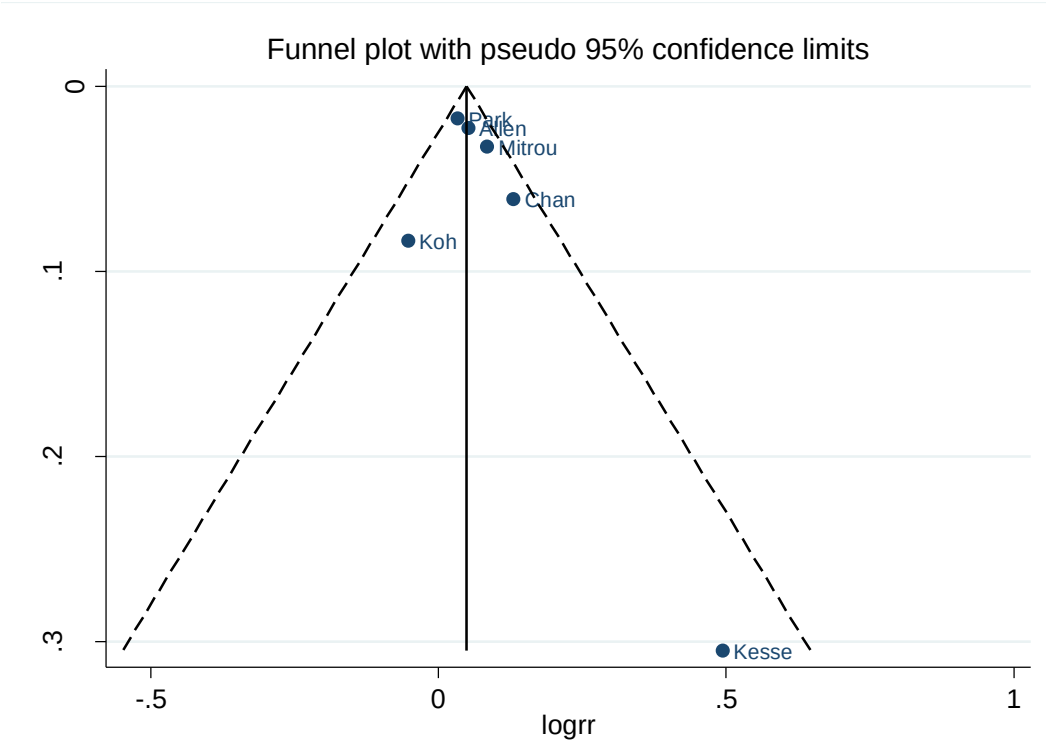


Figure 253 Funnel plot of dairy calcium and prostate cancer



Egger's test p = 0.31

Figure 254 Dose-response graph of dairy calcium and total prostate cancer

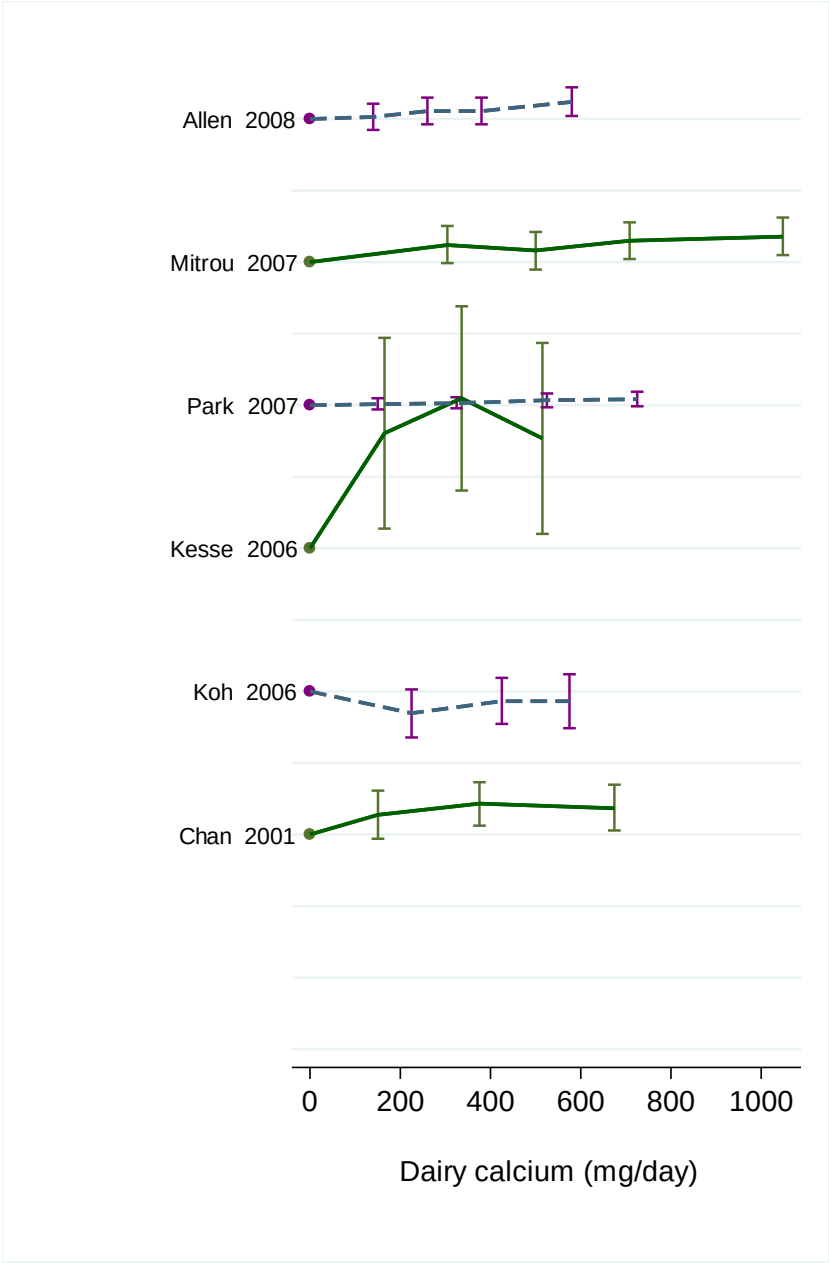
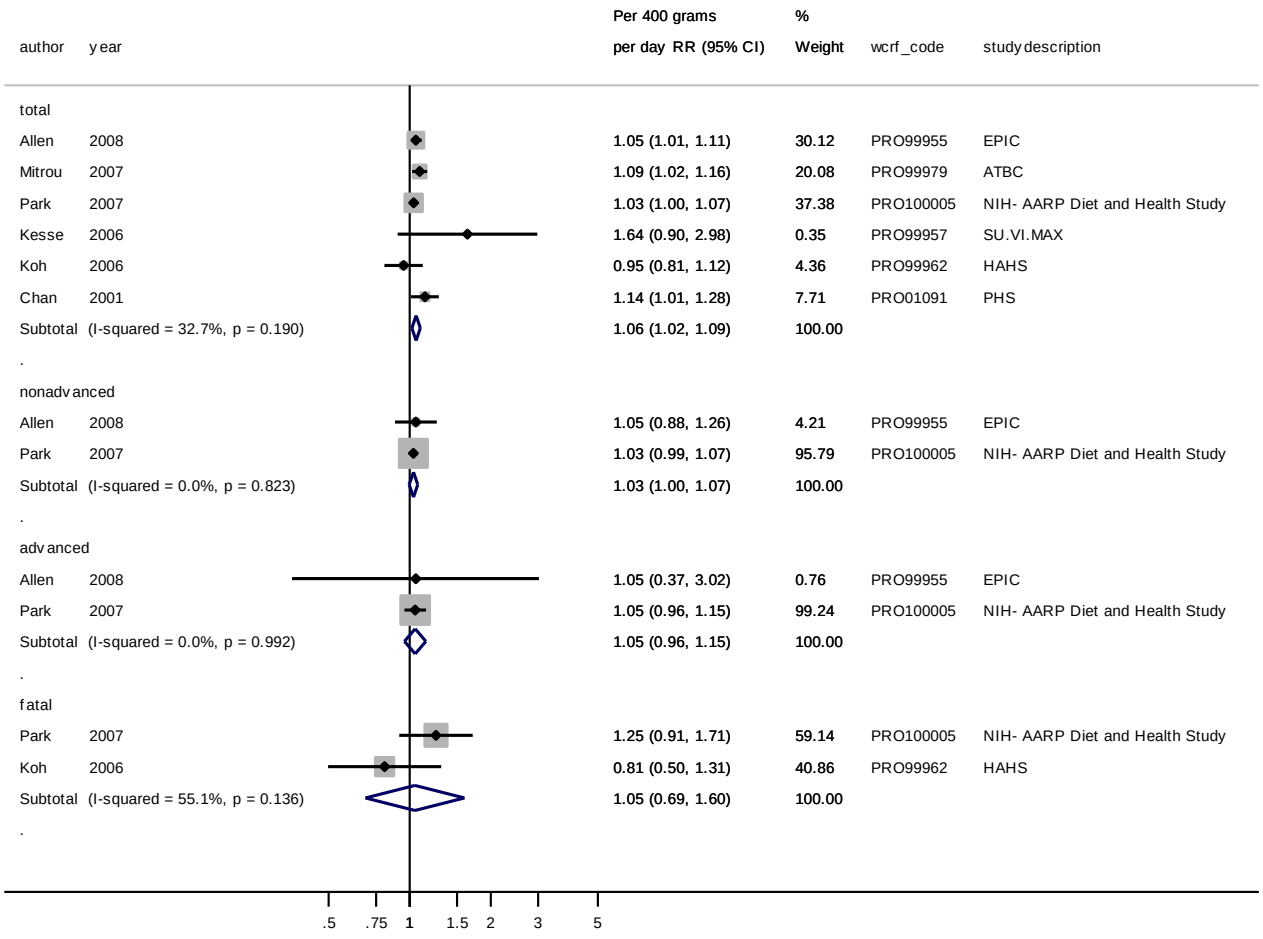


Figure 255 Dose-response meta-analysis of dairy calcium and prostate cancer, per 400 mg/day, stratified by outcome type



5.6.3 Nondairy calcium

Methods
A total of 4 cohort studies (4 publications) have been published on nondairy calcium prostate cancer risk. Three cohort studies were identified in the CUP. Dose-response analyses were conducted per 400 mg per day increase in nondairy calcium intake.

Of the studies that were included in the dose-response analysis of nondairy calcium and prostate cancer 4 studies reported on total prostate cancer: Tseng et al, 2005; Kesse et al, 2006; Park Y et al, 2007; Allen et al, 2008a. Two studies reported on non-advanced or localised prostate cancer and on advanced prostate cancer: Park Y et al, 2007 (NIH-AARP Diet and Health Study); and Allen et al, 2008a.

Main results
The summary RR per 400 mg/d increase in nondairy calcium intake was 0.97 (95% CI 0.90-1.04; $I^2 = 0\%$; $p_{heterogeneity} = 0.59$; n = 4) for total prostate cancer. There was no indication of publication bias with Egger's test, p = 0.92. When stratified by outcome type the summary RR was 0.97 (95% CI 0.79-1.20; $I^2 = 36.9\%$; $p_{heterogeneity} = 0.21$; n = 2) for nonadvanced cancers, 1.09 (95% CI 0.89-1.34; $I^2 = 0\%$; $p_{heterogeneity} = 0.95$) for advanced cancers. There was evidence of nonlinearity, $p_{non\text{-}linearity}<0.01$, with a slight non-significant positive association up to 400 mg/d, but a reduced risk at an intake of 700 mg/d.

Heterogeneity
There was no heterogeneity, $I^2 = 0\%$, $p_{heterogeneity} = 0.59$.

Conclusion from the Second Expert Report
In the SLR of the 2007 Expert Report the evidence relating nondairy calcium to prostate cancer was too limited or inconsistent for a conclusion to be made.

Published meta-analyses
None of the previous meta-analyses evaluated calcium from nondairy sources (Gao et al, 2006, Huncharek et al, 2009).

Table 233 Studies on nondairy calcium identified in the CUP

Author/year	Country	Study name	Cases	Years of follow-up	RR	LCI	UCI	Contrast
Allen, 2008a	10 European countries	European Prospective Investigation into Cancer and Nutrition	2727	8.7	1.04	0.90	1.19	Per 300 mg/d
Park Y, 2007	USA	NIH- AARP Diet and Health Study	10180	6 years	0.82	0.69	0.98	≥ 600 mg vs. < 250 mg/d
Kesse, 2006	France	SU.VI.MAX	69	7.7 years	1.12	0.60	2.11	> 440 vs. < 294 mg/d

Table 234 Overall evidence on nondairy calcium and prostate cancer

	Summary of evidence
2005 SLR	Only one study reported on nondairy calcium and found no significant association.
Continuous Update Project	Three additional studies reported on nondairy calcium intake and prostate cancer risk. No significant association was observed in the CUP meta-analysis.

Table 235 Summary of results of the dose-response meta-analysis of nondairy calcium and prostate cancer

Prostate cancer		
	2005 SLR	CUP
Studies (n)	-	4
Cases (n)		13107
RR (95% CI)		0.97 (0.90-1.04)
Increment unit used		Per 400 mg/d
Heterogeneity (I^2, p-value)		0%, p = 0.59
	Non advanced cancers	
Studies (n)	-	2
Cases (n)		9885
RR (95% CI)		0.97 (0.79-1.20)
Increment unit used		Per 400 mg/d
Heterogeneity (I^2, p-value)		36.9%, p = 0.21
	Advanced cancers	
Studies (n)	-	2
Cases (n)		1967
RR (95% CI)		1.09 (0.89-1.34)
Increment unit used		Per 400 mg/d
Heterogeneity (I^2, p-value)		0%, p = 0.95

Table 236 Inclusion/exclusion table for meta-analysis of nondairy calcium and prostate 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
PRO99955	Allen	2008a	Prospective Cohort	European Prospective Investigation into Cancer and nutrition (EPIC)	Incidence	No	Yes	Yes	Person-years	
PRO100005	Park Y	2007	Prospective Cohort	NIH- AARP Diet and Health Study	Incidence	No	Yes	Yes		
PRO99957	Kesse	2006	Prospective Cohort	SU.VI.MAX	Incidence	No	Yes	Yes	Mid-exposure values, person-years	
PRO97221	Tseng	2005	Prospective Cohort	NHANESI	Incidence	Yes	Yes	Yes		

Figure 256 Highest versus lowest forest plot of nondairy calcium and prostate cancer

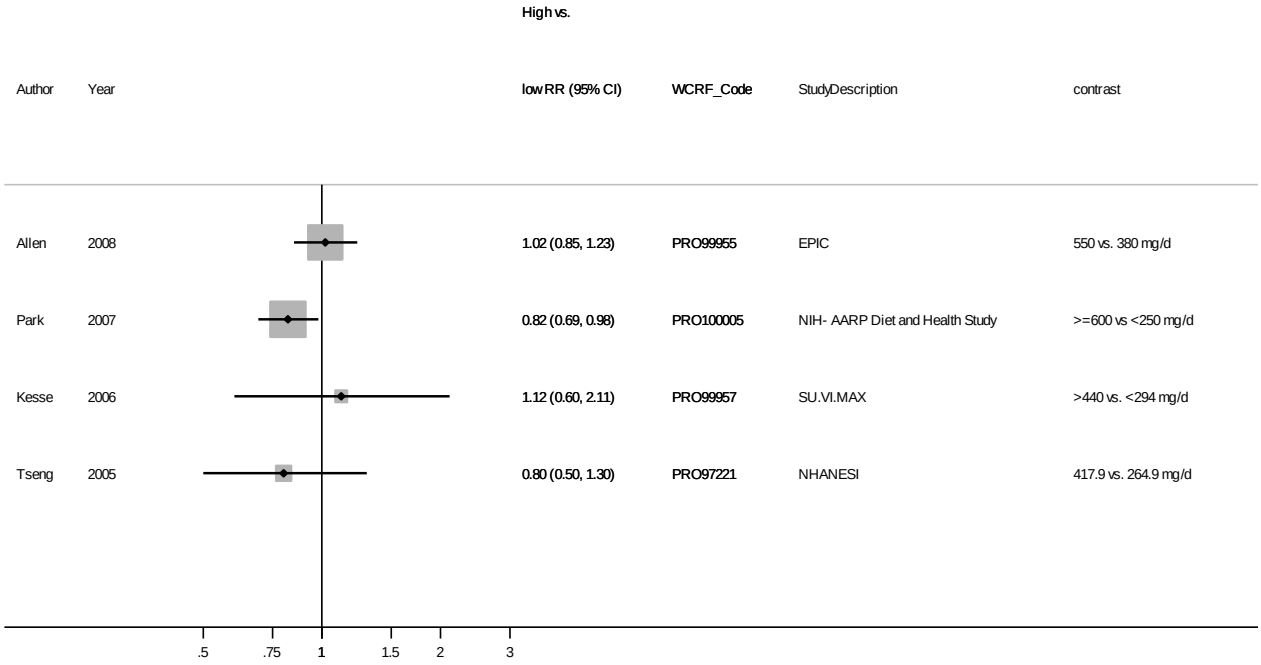


Figure 257 Dose-response meta-analysis of nondairy calcium and prostate cancer, per 400 mg/day

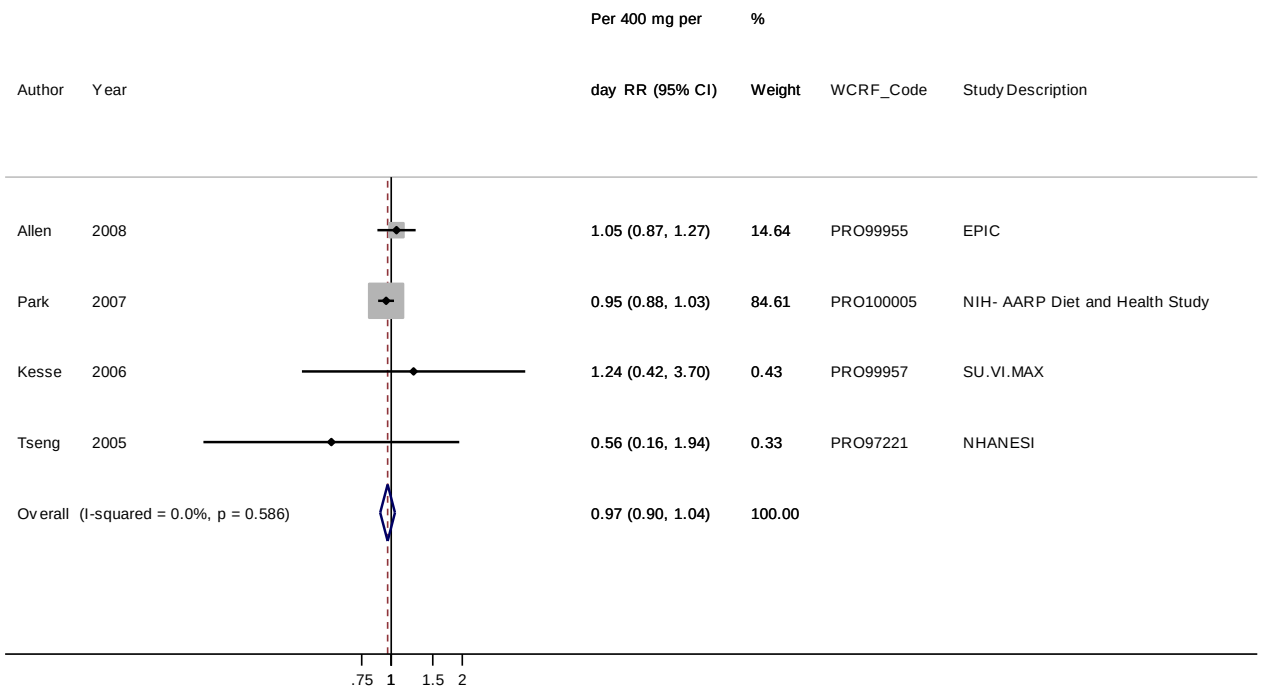
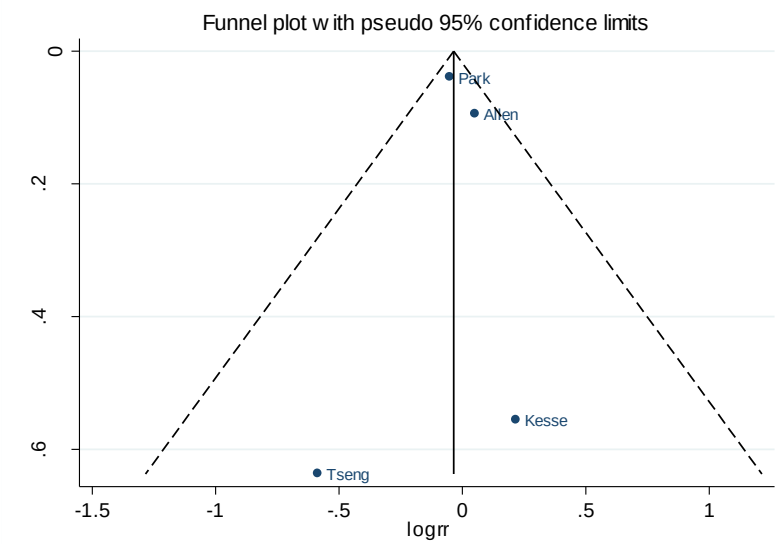


Figure 258 Funnel plot of nondairy calcium and prostate cancer



Egger's test, p = 0.92

Figure 259 Dose-response graph of nondairy calcium and prostate cancer

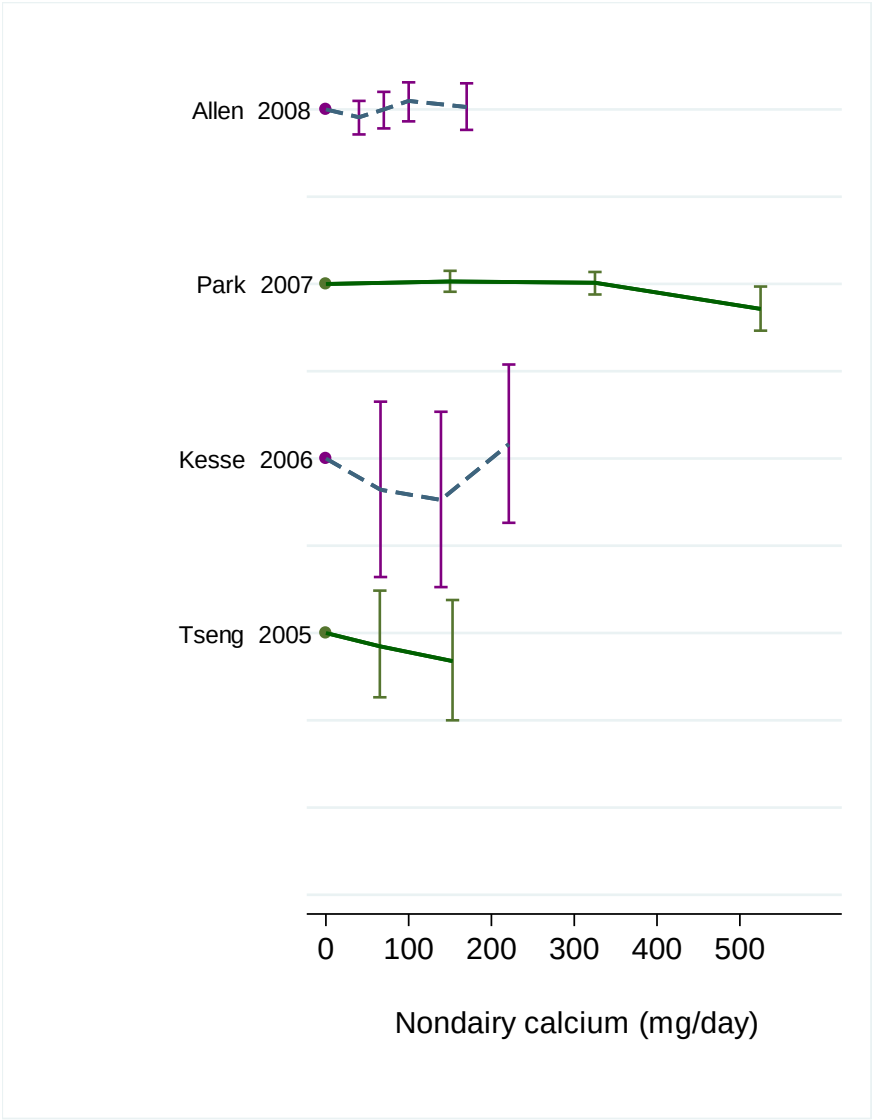


Figure 260 Dose-response meta-analysis of nondairy calcium and prostate cancer, per 400 mg/day, stratified by outcome type

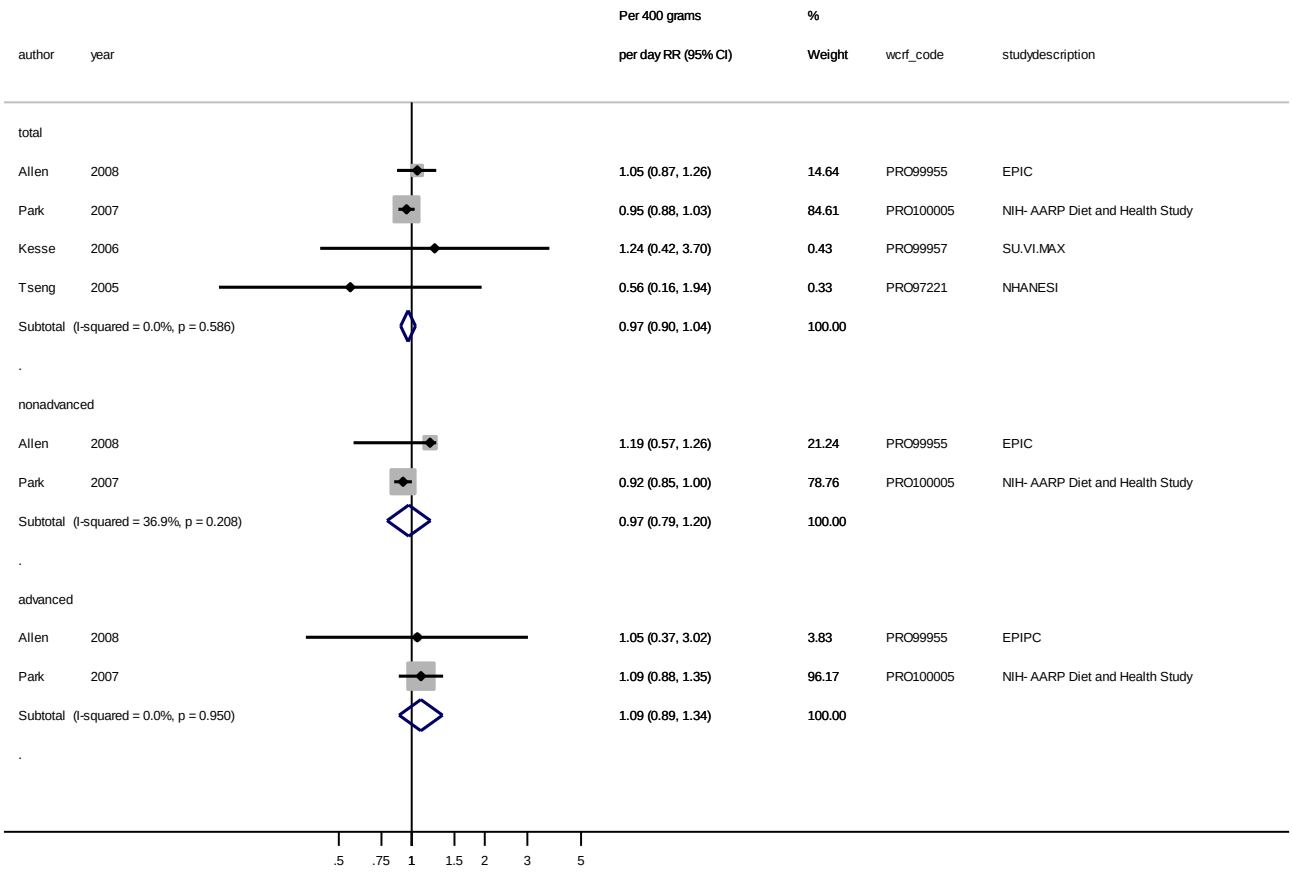


Figure 261 Non-linear dose-response analysis of nondairy calcium intake and total prostate cancer

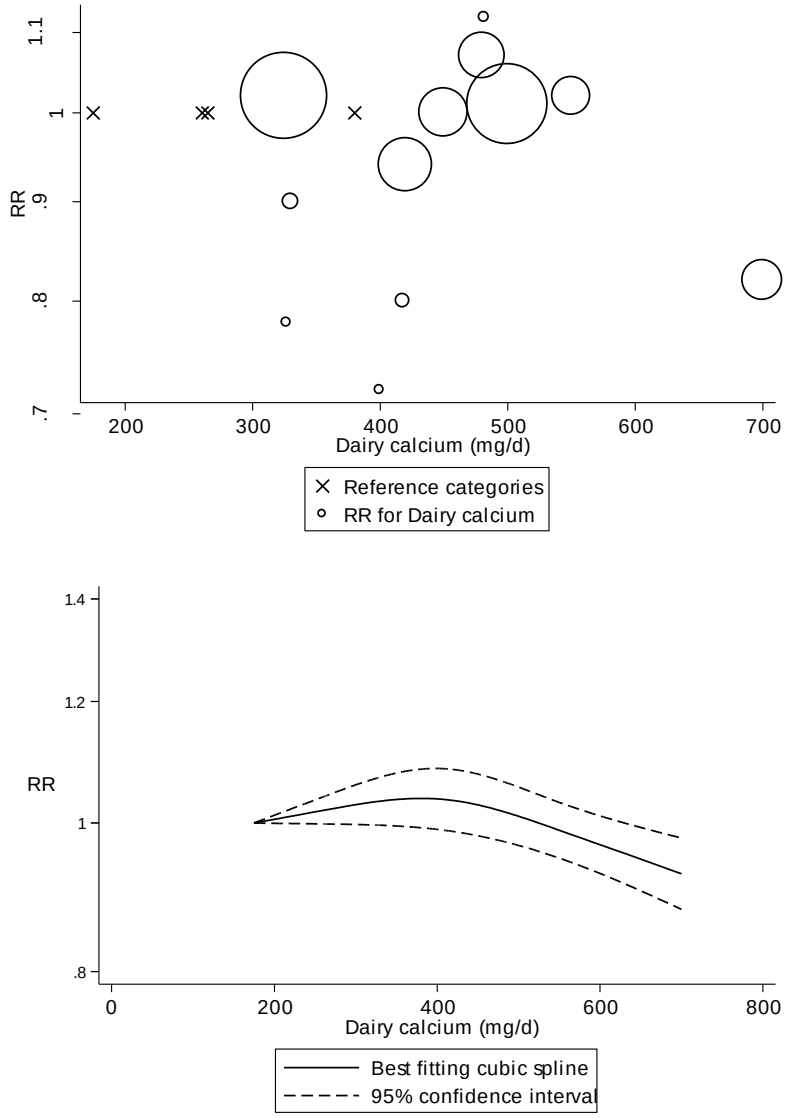


Table 237 Table with nondairy calcium intake values and corresponding RRs (95% CIs) for non-linear analysis of nondairy calcium intake and total prostate cancer

Nondairy calcium intake (mg/day)	RR (95% CI)
175	1
325	1.03 (1.00-1.07)
400	1.04 (0.99-1.09)
500	1.01 (0.97-1.06)
550	0.99 (0.95-1.03)
700	0.93 (0.88-0.98)

$p_{non\text{-}linearity} < 0.01$

5.6.4 Serum/ Plasma/toenail selenium

Methods
Seventeen studies were identified, four of which were identified during the CUP. Three studies were on plasma selenium (Allen, 2008; Li, 2004 and Brooks, 2001) and all the other studies were on serum selenium. The increment used in the dose-response analysis was 10 mcg/l.

From the studies included in the dose-response meta-analysis: two studies reported on total prostate cancer (Grundmark, 2011; Nomura 2000), one study included total and advanced prostate cancer (Gill, 2009), one study included total, advanced, low and high grade prostate cancer (Allen, 2008b), one study included total, advanced, non-advanced and stage III-IV prostate cancer (Peters, 2007), one study included total, localised and advanced prostate cancer (Li, 2004), and one study included Gleason score 2-7, Gleason score 8-10, early and advanced prostate cancer (Goodman, 2001).

Main results
The summary RR per 10 mcg/l was 0.95 (95% CI 0.91-1.00; $I^2 = 28.5\%$; pheterogeneity = 0.19; n = 9). There was evidence of publication bias with Egger's test, $p < 0.01$. The asymmetry in the funnel plot suggests small studies showing positive associations had not been published.
After stratification by prostate cancer type, the RR per10 mcg/l the RR was 0.95 (95% CI 0.89-1.00; $I^2 = 0\%$; $p_{heterogeneity} = 0.63$; n = 5; 1500 cases) for advanced/high grade cancers and 0.99 (95% CI 0.95-1.03; $I^2 = 0\%$; $p_{heterogeneity} = 0.89$; n = 4; 1879 cases) for non-advanced/low grade cancers.
There was a nonlinear dose response relationship for advanced prostate cancer (p=0.04) that showed a continuous decrease of risk with increasing levels of blood selenium in the range investigated. The RR of advanced prostate cancer was 0.72 (95% CI 0.60-0.86) at 95 mcg/l and was also significant for highest levels. No significant departure from linearity was observed for total prostate cancer (p = 0.11).

Heterogeneity
Overall, there was low evidence of heterogeneity, $I^2 = 28.5\%$, $p_{heterogeneity} = 0.19$.

Comparison with the Second Expert Report
In the SLR the meta-analysis on serum or plasma selenium and prostate cancer showed no significant association (RR per 10 mcg/l increase = 0.95; 95% CI 0.89-1.00).

Published meta-analysis or pooled analysis
A systematic review and meta-analysis reported a non-linear dose-response relationship between plasma/serum selenium and prostate cancer risk, using WCRF-CUP database with end date of search November 2010. Two studies included in the WCRF CUP were not included in this meta-analysis. In the nonlinear dose response analysis for prostate cancer including 7 case-control studies nested in cohorts and 2 case-control studies, the RRs were 0.85 (95% CI 0.74-0.97) at 135 ng/mL and 0.75 (95% CI 0.65, 0.86) at 170 ng/ml. Exclusion of the two case-control studies resulted in a similar result. The relation between plasma/serum selenium and advanced prostate cancer risk (6 nested case-control studies) showed a gradual reduction in risk with RRs of 0.60 (95% CI 0.45-0.81) at 135 ng/mL and 0.50 (95% CI 0.36, 0.68) at 170 ng/ml.
A U-shape relationship between toenail selenium and prostate cancer was observed (but only two nested case-control studies and one case-control). The RR was 0.29 (95% CI 0.14-0.61) with toenail selenium ranging from 0.85 to 0.94 mcg/g (Hurst, 2012).

The Cochrane group published a review of 14 studies, were the summary risk estimate

for highest vs lowest was 0.53 (95% CI 0.35-0.81), 3 studies for toenail levels and 0.81 (95% CI 0.68 to 0.97), 9 studies for blood levels (Dennert, 2012).

Table 238 Studies on plasma/serum selenium identified in the CUP

Author, year	Country	Study name	Cases	Years of follow up	RR	LCI	UCI	Contrast
Grundmark, 2011	Sweden	Uppsala Longitudinal Study of Adult Men (ULSAM)	208	34 years	0.83	0.60	1.16	> 81 vs. ≤ 70 mcg/l
Gill, 2009	USA and Hawai	Multiethnic Cohort Study	467		0.82	0.59	1.14	0.16 vs. 0.12 mcg/g
Allen, 2008b	Europe	EPIC	959	4 years	0.96	0.70	1.31	≥ 84.1 vs. < 62 mcg/l
Peters, 2007	USA	PLCO	724	8 years	0.84	0.62	1.14	≥158 to 253 vs. 50.5 to <126.8 ng/mL

Table 239 Overall evidence on plasma/serum selenium and prostate cancer

	Summary of evidence
2005 SLR	Nine studies were identified during the SLR and included in the meta-analysis. Overall there was a non-significant association between serum or plasma selenium and total prostate cancer. Serum or plasma selenium showed an inverse significant association with aggressive/advanced prostate cancer (2 studies included in the meta-analysis).
Continuous Update Project	Four new studies were identified in the CUP, all showed non-significant results. Weak inverse associations of borderline significance were observed in the CUP dose-response meta-analysis for total and advanced cancers

Table 240 Summary of results of the dose response meta-analysis of plasma/serum selenium and prostate cancer

Prostate cancer		
	SLR	CUP
Studies (n)	9	9
Cases (n)	1329	3559
Increment unit used	Per 10 mcg/l	Per 10 mcg/l
Overall RR (95% CI)	0.95 (0.89-1.00)	0.95 (0.91-1.00)
Heterogeneity (I^2, p-value)	58.3%, p = 0.01	28.5%, p = 0.19
Stratified analysis		
Advanced/high grade cancer		
Overall RR (95% CI)	0.87 (0.79-0.97)	0.95 (0.89-1.00)
Heterogeneity (I^2, p-value)	0%, p = 0.38, n = 2	0%, p = 0.63, n = 5
Non-advanced/low grade cancer		
Overall RR (95% CI)		0.99 (0.95-1.03)
Heterogeneity (I^2, p-value)		0%, p = 0.89, n = 4

Table 241 Inclusion/exclusion table for meta-analysis of plasma/serum selenium and prostate 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
PRO100105	Grundmark	2011	Prospective Cohort study	Uppsala Longitudinal Study of Adult Men (ULSAM)	Incidence	No	Yes	Yes		
PRO100044	Gill	2009	Prospective Cohort study	Multiethnic Cohort Study	Incidence	No	Yes	Yes	Conversion from mcg/g to mcg/l	
PRO100015	Allen	2008 b	Prospective Cohort study	EPIC	Incidence/ Mortality	No	Yes	Yes		
PRO99995	Peters	2007	Nested case-control study	Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial	Incidence/ Mortality	No	Yes	Yes		
PRO97166	Meyer	2005	Prospective Cohort study	SUVIMAX	Incidence	Yes	No	Yes		
PRO10545	Li	2004	Nested case-control study	Physician's Health Study	Incidence	Yes	Yes	Yes	Conversion from ppm to mcg/l	
PRO01079	Goodman	2001	Nested case-control study	Carotene and Retinol Efficacy Trial (CARET)	Incidence	Yes	Yes	Yes	Conversion from mcg/dl to mcg/l	
PRO01046	Brooks	2001	Nested case-control study	Baltimore Longitudinal Study of Aging BLSA	Incidence	Yes	Yes	Yes	Conversion from mcg/dl to mcg/l	
PRO01467	Nomura	2000	Nested case-control study	Honolulu Heart Program	Incidence	Yes	Yes	Yes		
PRO06209	Criqui	1991	Prospective Cohort study	Lipid Research Clinics Prevalence and Follow-Up Study	Incidence	Yes	No	No		Mean values used in SLR
PRO13425	Knekt	1990a	Nested case	FMCHS	Incidence	Yes	Yes	Yes	Confidence intervals	

			control study							
PRO10354	Ringstad	1988	Nested case control study	Tromso Heart Study	Incidence	Yes	No	No		Mean values used in SLR
PRO13426	Coates	1988	Nested case control study	Washington, 1972-1984	Incidence/ Mortality	Yes	No	No		No confidence intervals, only 13 cases
PRO13445	Virtamo	1987	Prospective Cohort study	Finland, 1959	Incidence	Yes	No	No		Mean values used in SLR
PRO13494	Peleg	1985	Prospective Cohort study	Georgia, USA Evans County Study project 1960-1981	Incidence/ Mortality	Yes	No	No		Only mean values
PRO13424	Salonen	1984	Nested case control study	Finland, 1972	Incidence/ Mortality	Yes	No	No		Mean values used in SLR
PRO03520	Willett	1983	Nested case control study	Hypertension Detection Follow-Up Programme	Incidence/ Mortality	Yes	No	No		Mean values used in SLR

Figure 262 Highest versus lowest forest plot of plasma/serum selenium and prostate cancer

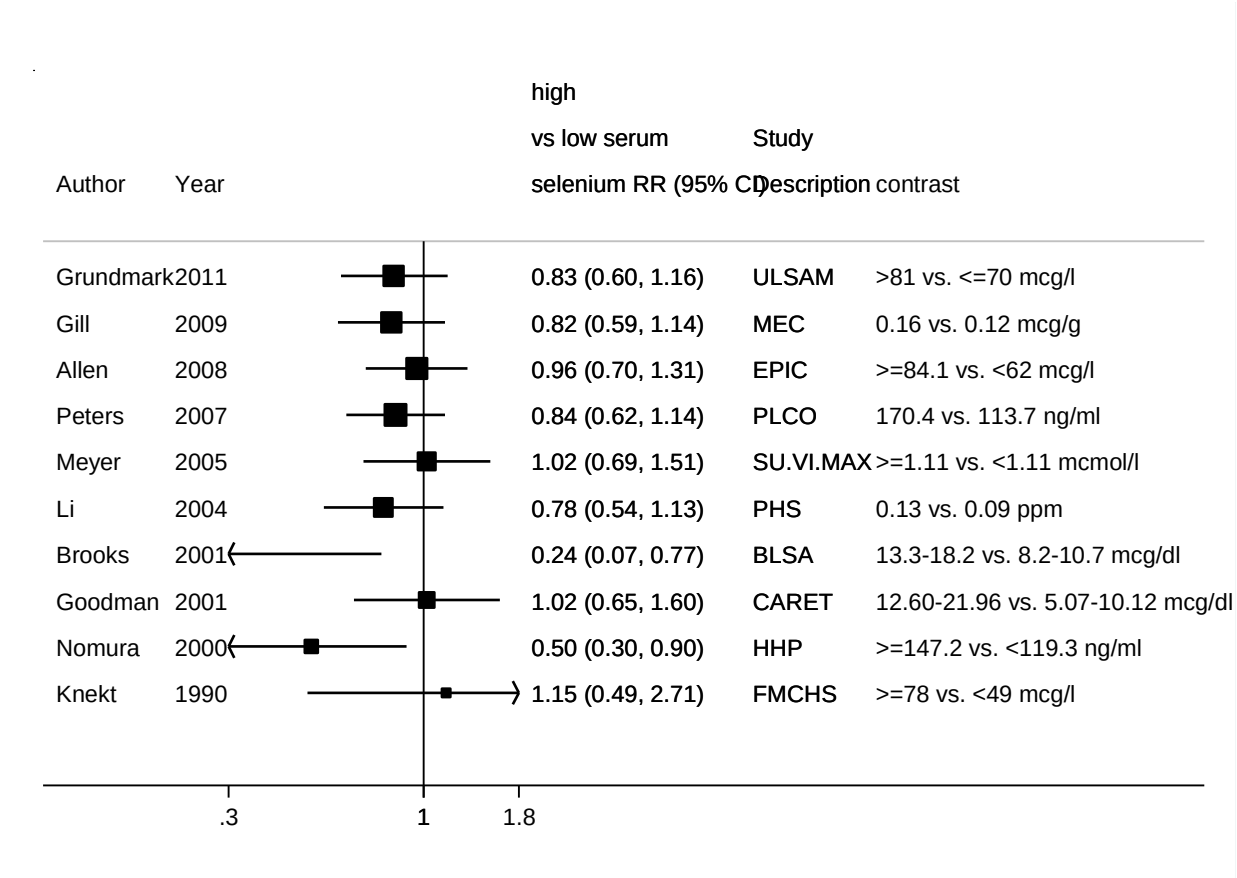


Figure 263 Dose-response meta-analysis of plasma/serum selenium and prostate cancer – per 10 mcg/l

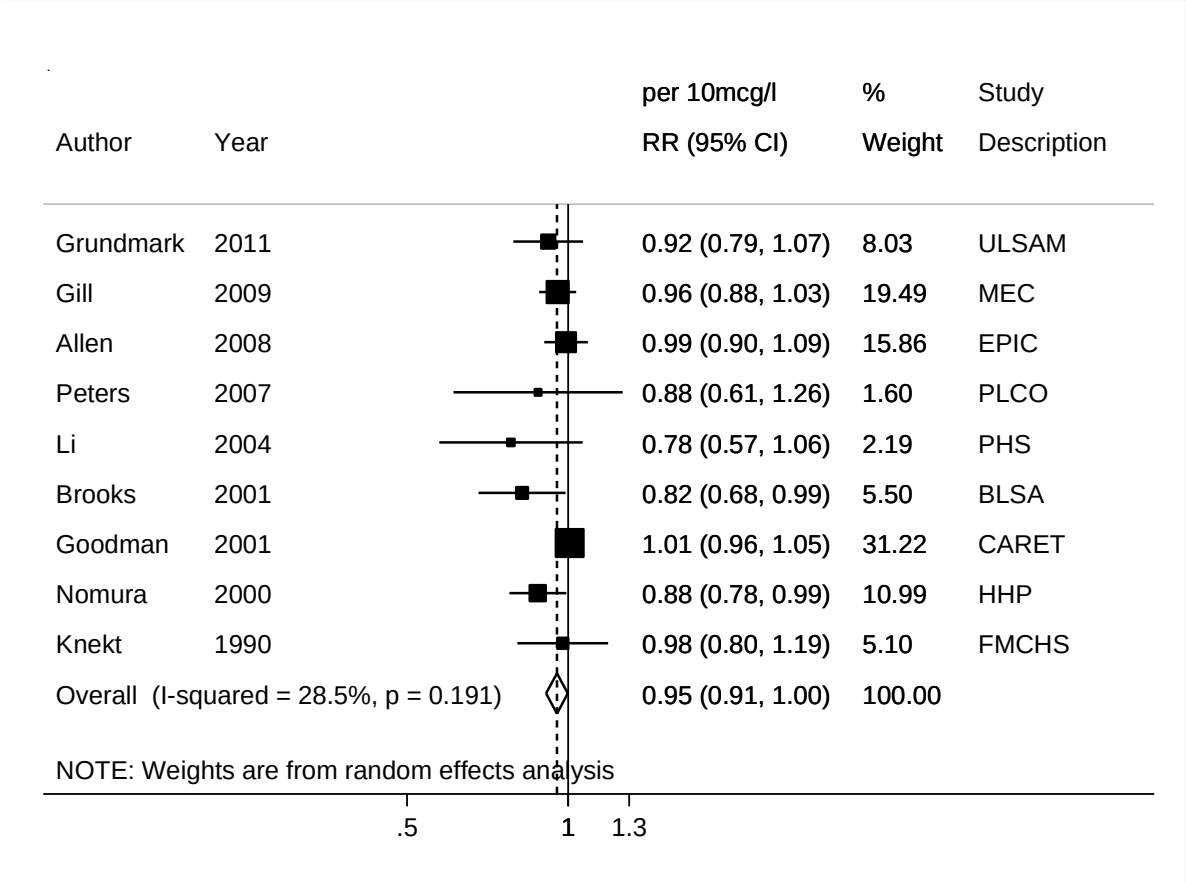
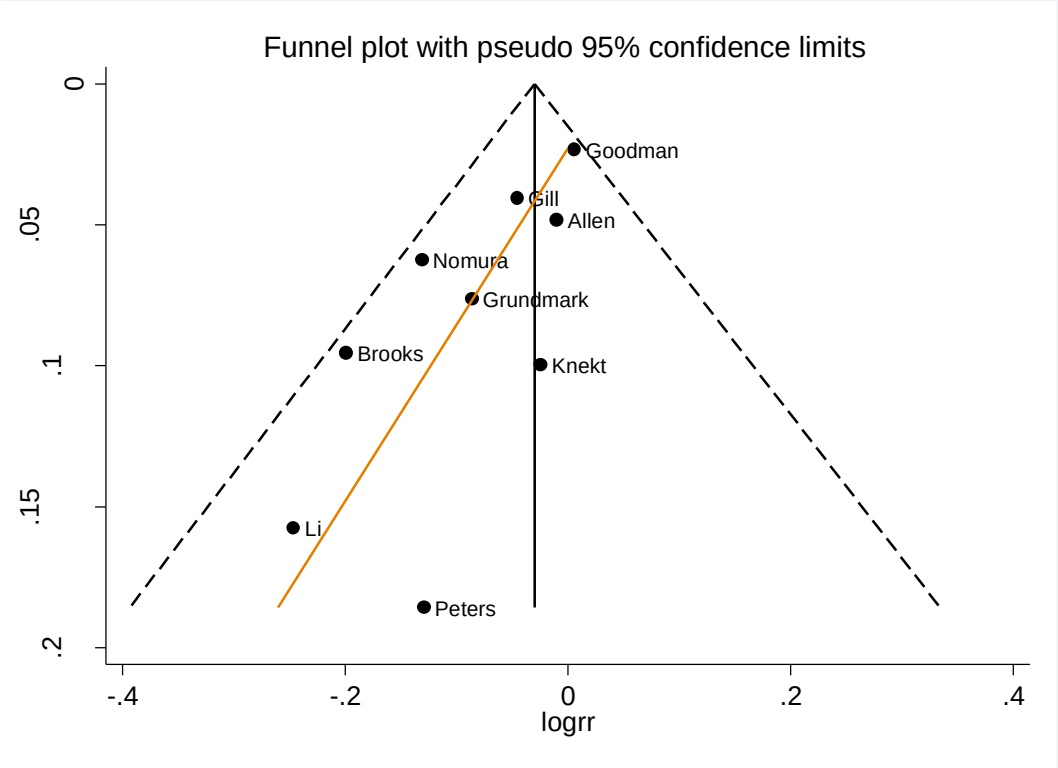


Figure 264 Funnel plot of plasma/serum selenium and prostate cancer



Egger's test p < 0.01

Figure 265 Dose-response graph of plasma/serum selenium and prostate cancer

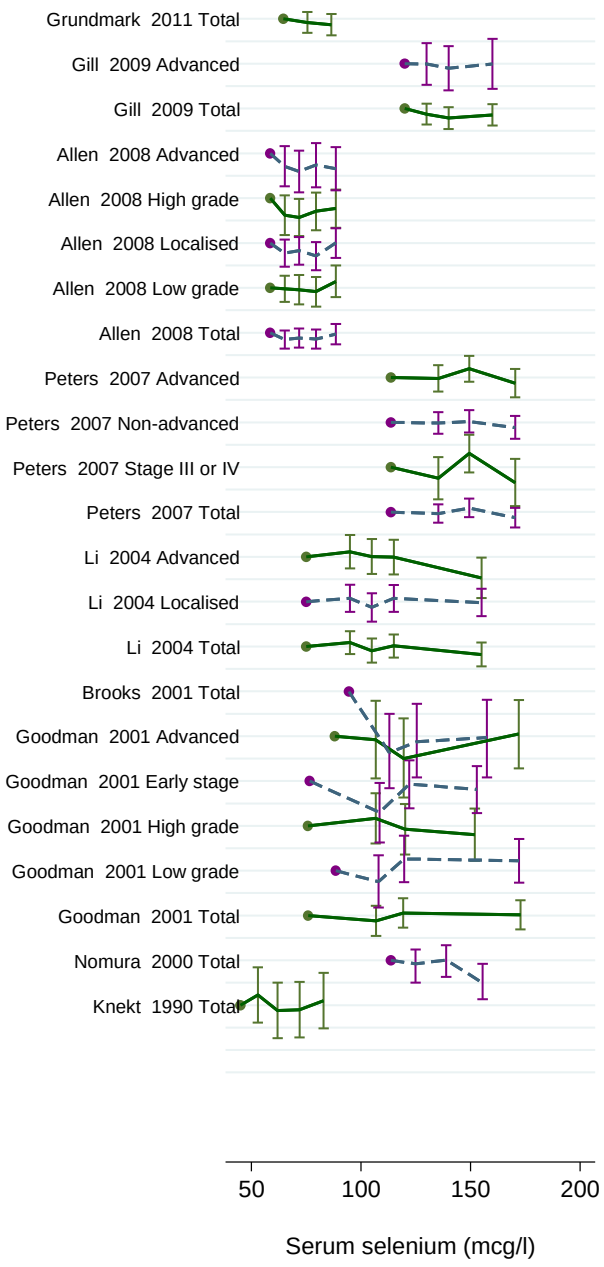


Figure 266 Dose-response meta-analysis of plasma/serum selenium and prostate cancer, per 10 mcg/l stratified by prostate cancer type

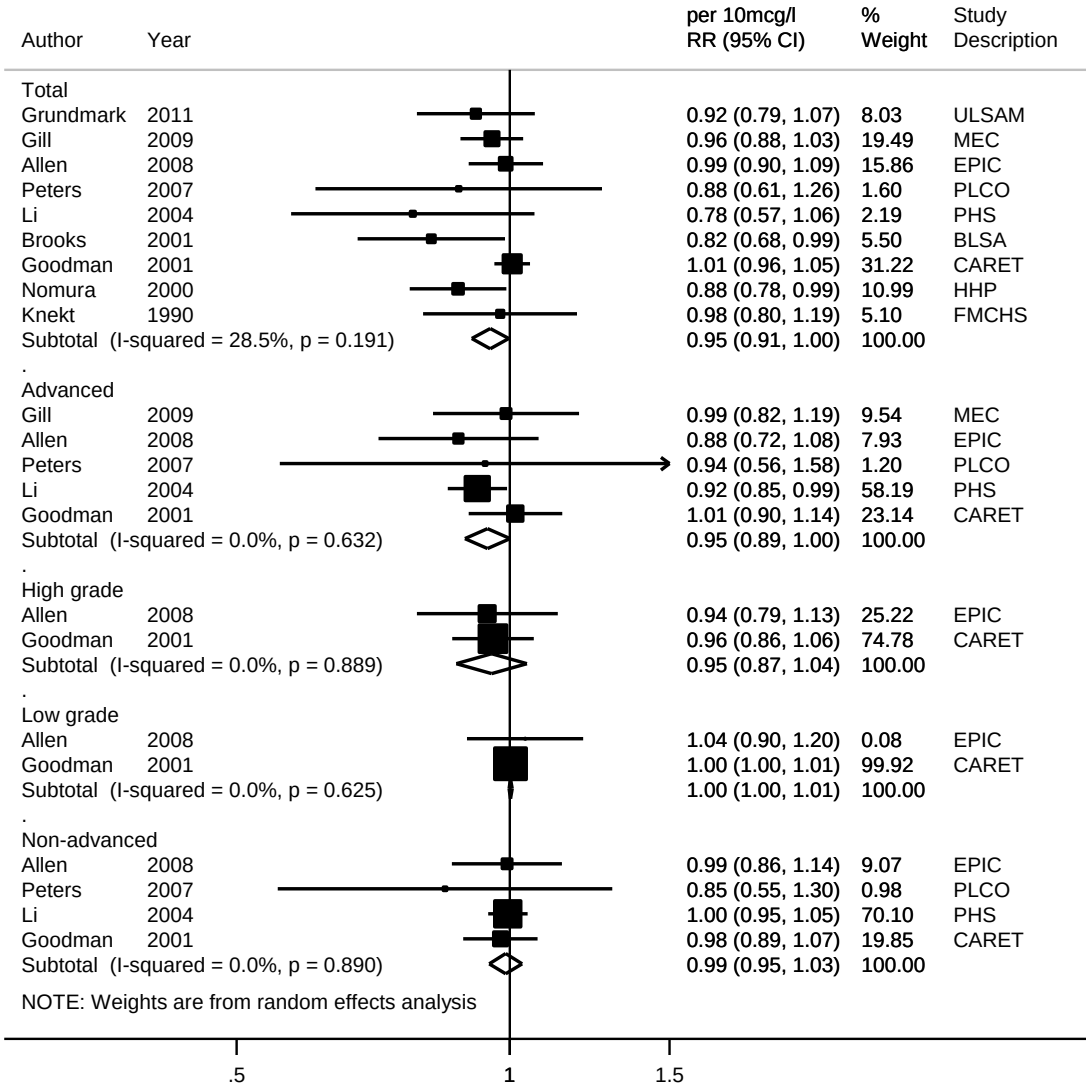
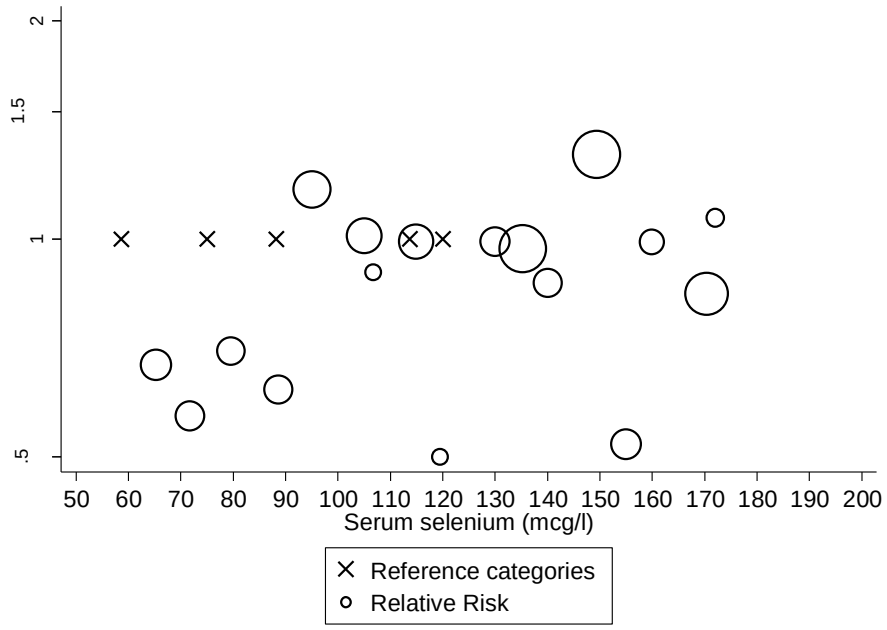


Figure 267 Non-linear dose-response analysis of plasma/serum selenium and advanced prostate cancer



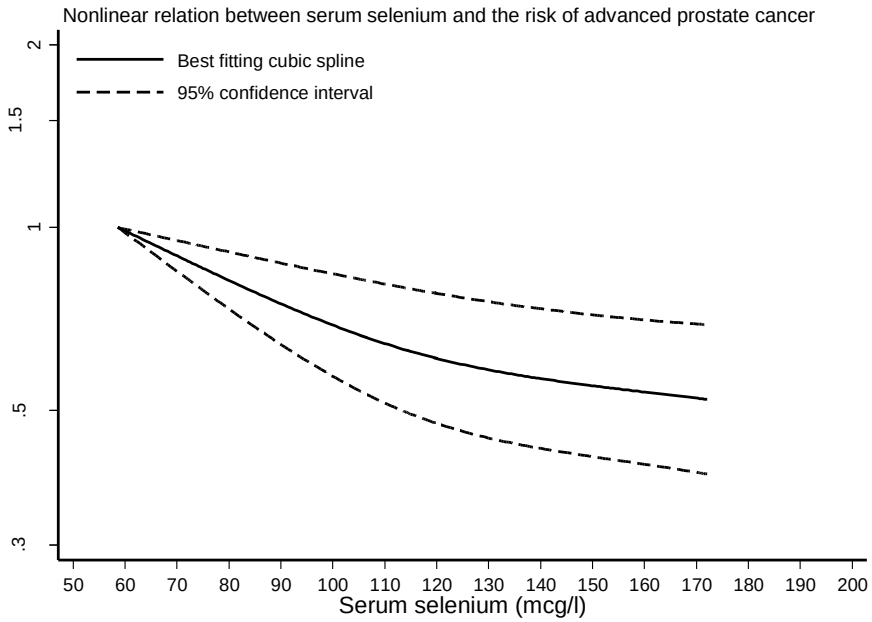


Table 242 Table with plasma/serum selenium values and corresponding RRs (95% CIs) for non-linear analysis of serum selenium and advanced prostate cancer

Serum selenium (mcg/l)	RR (95% CI)
58.65	1
95	0.72 (0.60-0.86)
120	0.61 (0.47-0.78)
160	0.53 (0.41-0.70)

$p_{non\text{-}linearity} = 0.04$

5.6.4 Selenium supplements

Methods
Five studies from 6 publications on selenium supplements and prostate cancer were identified from which four were identified during the CUP. Only three studies quantified the selenium supplements in mcg/day, the other studies only presented the use of supplements as a binary variable.

Main results
No meta-analysis was conducted. Two publications (Platz, 2004; Wu, 2004) of a nested case-control study in the HPFS reported that the percentage of selenium supplement users was similar in the cases and the controls. A study on the ATBC study reported borderline increased risk of prostate cancer in users of selenium supplements (HR for use vs non-use: 1.36; 95% CI 0.98-1.90) (Hartmann, 1988). Use of selenium supplements was not associated with prostate cancer in four cohort studies identified during the CUP.

Published meta-analysis or pooled analysis

A meta-analysis of one randomized controlled trial (SELECT-trial) and one case-control study reported a RR of 1.57 (95% CI 0.68-3.61; I^2 = 96%) (Stratton, 2011)

Table 243 Studies on selenium supplements identified in the CUP and the 2005 SLR

Author, year	Country	Study name	Cases	Years of follow up	RR	LCI	UCI	Contrast
Agalliu, 2010	USA	Canadian Study of Diet, Lifestyle, and Health cohort	661	7.7 years	0.76	0.43	1.33	105 vs. 0 µg/d
Kristal, 2010	USA	The Prostate Cancer Prevention Trial	1703	7 years	1.00	0.58	1.78	GS 2-7 > 30 vs. < 10 mcg/d
					1.06	0.89	1.25	GS 8-10 > 30 vs. < 10 mcg/d
Gonzalez, 2009	USA	VITAL study	832	3.5 years	1.10	0.92	1.35	22.51-400 vs. 0 10-yr avg. supplemental selenium (mcg/day)
Lawson, 2007	USA	NIH-AARP	10 241	5 years	1.02	0.91	1.14	>7 vs. 0 times/week
Platz, 2004	USA	Health Professionals Follow-up Study	460 cases/460 controls	Maximum 5 years	-	-	-	Supplement use: 7.6% in cases, 8.3% in controls p = 0.81
Wu, 2004	USA	Health Professionals Follow-up Study	450 cases/450 controls	Maximum 5 years	-	-	-	Supplement use: 73% in cases, 7.8% in controls

Hartmann, 1998	Finland	Follow-up of ATBC trial	317 cases	9 years	1.36	0.98	1.90	Use vs no use at baseline

6 Physical activity

6.1 Total physical activity

Methods

Nineteen publications from twelve studies were identified, from which 5studies from 6 publications were identified in the CUP; one study was an updated publication of a study identified in the 2005 SLR.

The wide variability in the methods of assessment of physical activity used did not allow doing dose-response analyses; only highest versus lowest analysis was performed.
There were ten studies which could be included in highest versus lowest analysis. One study (Crespo et al, 2008) on mortality was excluded from the analysis. From these nine studies, one study included total, localised, advanced and fatal prostate cancer (Orsini et al, 2009) and one study included total, metastatic and advanced prostate cancer (Giovannucci et al, 1998a).

Main results

The summary RR for the highest vs lowest level of physical activity was 0.97 (95% CI 0.90-1.04; $I^2 = 33.4\%$; $p_{heterogeneity} = 0.14$).

All studies, except two, one in Swedish men (Orsini et al, 2009) and one in NorthAmerica (Clarke et al, 2000), showed nonsignificant associations between total physical activity and total prostate cancer.

In the Swedish study, the significant inverse association was observed for advanced cancers – defined as regional or distant metastasis, Gleason ≥ 7 or PSA ≥ 100 ng/ml- (RR 0.75; 95% CI 0.58-0.98), and it was inverse but not significant for localized cancers. No association was observed for fatal cancers.

In the HPFS (Giovannucci et al, 1998a), no association was observed for overall, advanced (Stage C or D) and nonadvanced prostate cancers. Cases in stage A1 were excluded from the analyses.

In the NIH-AARP (Moore et al, 2009), the association of physical activity was not modified by PSA testing ($p < 0.05$). More than 80% and 70% of the participants reported having at least a rectal digital examination or a PSA test three years before study enrolment.

In the VITAL study (Gonzalez et al, 2009), a positive nonsignificant association was observed; Most of the participants (71.8 % of the non-cases) had PSA test two years before study enrolment and 84% of the cases has localized prostate cancer at diagnosis. Stratifed analyses were not conducted.

The remaining five studies, including Clarke et al, 2000 did not provide data on PSA testing, stage or Gleason score at diagnosis.

Comparison with the Second Expert Report

In the 2005 SLR, only a highest versus lowest analysis was conducted which showed inconsistent results.

The relationship between physical activity and prostate cancer was considered limited-no conclusion.

Published meta-analysis or pooled analysis

A meta-analysis consisted of 19 eligible cohort studies and 24 case-control studies reported a RR for the highest vs the lowest level of any type of physical activity of 0.90 (95% CI 0.84-0.95). The RR was 0.94 (95% CI 0.91-0.98) for cohort studies and 0.86 (95% CI 0.75-0.97) for case-control studies (Liu et al, 2011). No pooled analysis was identified

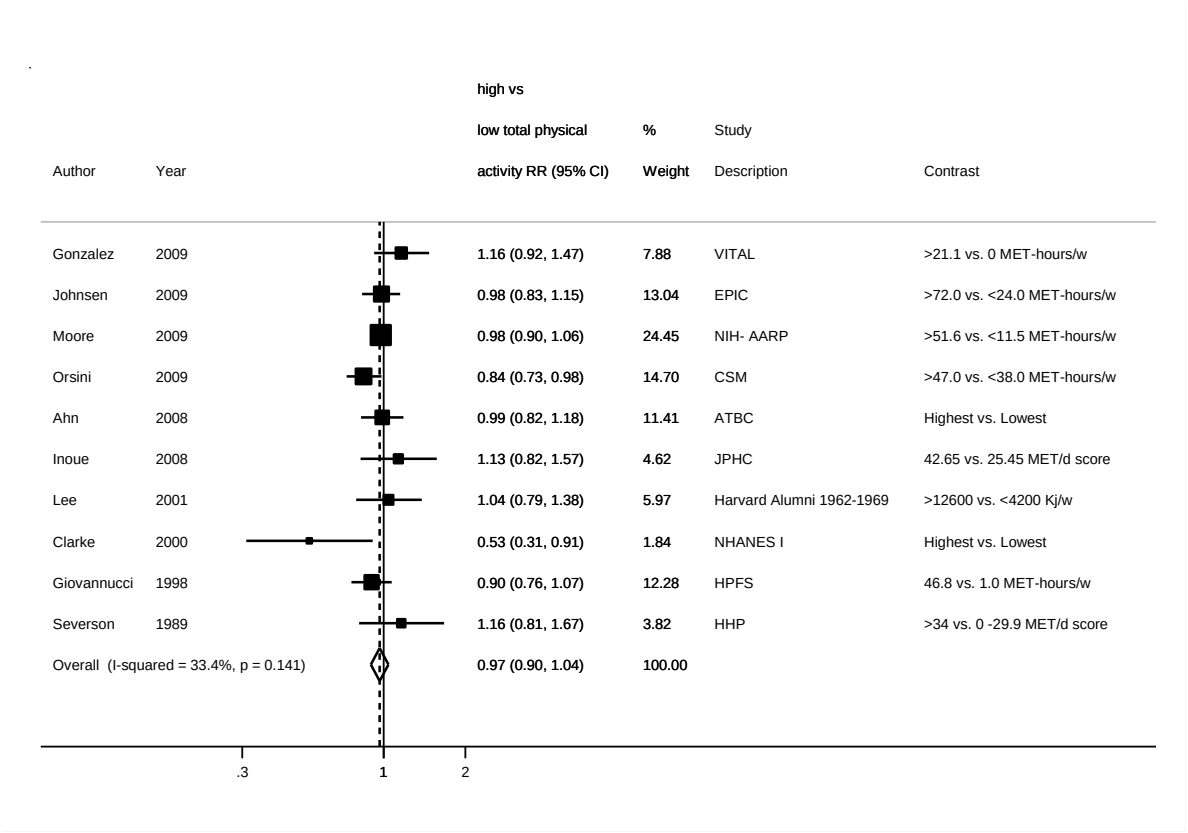
Table 244 Studies on total physical activity identified in the CUP

Author, year	Country	Study name	Cases	Years of follow up	RR	LCI	UCI	Contrast
Moore, 2009	USA	NIH- AARP study	9624	7 years	0.98	0.90	1.06	> 51.6 vs. < 11.5 MET-hours/w
Orsini, 2009	Sweden	Cohort of Swedish Men	2735	9 years	0.84	0.73	0.98	> 47.0 vs. > 38.0 MET-hours/w
Gonzalez, 2009	USA	VITAL study	832	3.5 years	1.16	0.92	1.47	> 21.1 vs. 0 MET-hours/w
Johnsen, 2009	Europe	EPIC study	2458	8.5 years	0.98	0.83	1.15	> 72.0 vs. < 24.0 MET-hours/w
Crespo, 2008	Puerto Rico	Puerto Rico Heart Health Program	167	7 years	1.19	0.75	1.90	> 37.0 vs. <2 7.0 MET/d score
Inuoe, 2008	Japan	Japan Public Health Centre based Prospective Study	4334	9 years	1.13	0.82	1.57	42.65 vs. 25.45 MET/d score
Ahn, 2008	Finland	ATBC study	1111	12.3 years	0.99	0.82	1.18	Highest vs. Lowest

Table 245 Inclusion/exclusion table for meta-analysis of total physical activity and prostate cancer

WCRF code	Author	Year	Study design	Study name	Cancer outcome	2005 SLR	CUP HvL forest plot	Screening, notes
PRO100046	Moore	2009	Prospective Cohort study	NIH- AARP	Incidence/ mortality	No	Yes	No evidence that RRs for moderate/vigorous intensity, light intensity and total activity differed according to PSA screening 3 years before enrolment (all Pinteraction>.05)
PRO100052	Orsini	2009	Prospective Cohort study	Cohort of Swedish Men	Incidence/ mortality	No	Yes	There is no official recommendation in Sweden on PSA testing as part of health check-ups or for screening purposes in men without lower urinary tract symptoms hence any bias that may be introduced by PSA is considered of limited relevance by the authors
PRO100066	Gonzalez	2009	Prospective Cohort study	VITAL	Incidence/ mortality	No	Yes	PSA use last 2 years >70% of participants. A positive association of prostate cancer with multivitamin use in this study may be attributed to bias due to correlation between multivitamin use and PSA screening.
PRO100073	Crespo	2008	Prospective Cohort study	Puerto Rico Heart Health Program	Mortality	No	No	Excluded, only study on mortality
PRO99983	Moore	2008	Prospective Cohort study	NIH- AARP	Incidence/ mortality	No	No	Excluded: superseded by Moore, 2009
PRO100111	Inuoe	2008	Prospective Cohort study	Japan Public Health Centre Study	Incidence	No	Yes	No data. This is a study with multiple cancers as endpoint
PRO100022	Ahn	2008	Prospective Cohort study	ATBC	Incidence	No	Yes	No association among men with no family history and nonsignificant risk increase in those with first-degree relative with prostate cancer (no significant interaction). Detection bias from screening appears unlikely: men with prostate family history had higher disease stage at diagnosis than men with no family history
PRO100035	Gonzalez	2007	Prospective Cohort study	VITAL	Incidence/ mortality	No	No	Excluded: superseded by Gonzalez, 2009
PRO99972	Littman	2006	Prospective Cohort study	VITAL	Incidence/ mortality	Yes	No	Excluded: superseded by Gonzalez, 2009
PRO97424	Weinstein	2005	Nested case-control study	ATBC	Incidence	Yes	No	Excluded: superseded by Ahn, 2008
PRO00964	Wolinsky	2002	Prospective Cohort study	Longitudinal study of ageing	Incidence	Yes	No	Excluded: only mean values
PRO01290	Lee	2001	Prospective Cohort study	Harvard Alumni Study	Incidence/ mortality	Yes	Yes	No data
PRO01468	Clarke	2000	Prospective Cohort study	NHANES I	Incidence/ mortality	Yes	Yes	No data
PRO01999	Giovannu-cci	1998 a	Prospective Cohort study	HPFS	Incidence/ mortality	Yes	Yes	Higher levels of physical activity were associated with a slightly higher frequency of digital rectal examination or PSA screening, but these differences were minor. Inverse association with vigorous activity persisted after men who did not have a PSA examination by 1994 were excluded RR = 0.45 for quintile 5 versus quintiles 1-4
PRO02766	Lee	1994	Prospective Cohort study	Harvard Alumni Study	Incidence/ mortality	Yes	No	Excluded: superseded by Lee, 2001
PRO03024	Lee	1992	Prospective Cohort study	Harvard Alumni Study	Incidence /mortality	Yes	No	Excluded: superseded by Lee, 2001
PRO03210	Severson	1989 a	Prospective Cohort study	HW USA 65-68) HHP	Incidence/ mortality	Yes	Yes	No data

Figure 268 Highest versus lowest forest plot of total physical activity and prostate cancer *



* In Ahn et al, 2008 physical activity was categorized based in combined occupational and leisure time activity with those sedentary in both activity types serving as the lowest level (high: more than once/week exercise in leisure time or moderate/heavy occupational activity; low: less than once/week exercise in leisure time and sedentary occupational activity).
In Clarke et al, 2000 the highest was much recreational activity and very active in the usual day aside recreational activity and low was none recreational physical activity and inactive in a usual day.

6.1.1.1 Occupational activity

Methods

Seventeen publications from fourteen studies were identified, from which 4 studies were identified in the CUP.

The wide variability in the methods of assessment of physical activity used did not allow doing dose-response analyses. Highest versus lowest analysis was performed. Thirteen 13 studies could be included in highest versus lowest analysis.

Main results

The overall estimate of the highest compared to the lowest level of occupational physical activity was 0.87 (95% CI 0.80-0.95).

In the EPIC study (Johnson et al, 2009) there was a significant inverse trend for advanced prostate cancer (defined as T3/T4, N1,2,3 or M1), but not for localised cancers; the test of interaction was not significant (p = 0.11). However, in the Swedish study (Orsini et al, 2009), the inverse association was observed for localized prostate cancer (RR 0.55; 95% CI 0.38-0.82; $p_{trend} < 0.001$) and it was inverse but not significant for advanced (> T2, NX-1, MX-1 or PSA > 100 or Gleason grade ≥ 7) and fatal cancers.

The remaining studies did not reported by stage of grade of the disease. In a Norwegian study (Nilsen et al, 2000) the analysis was repeated limiting follow-up up to 1992 to avoid biases due to differential PSA testing. The estimates were similar to those obtained with full follow-up.

Comparison with the Second Expert Report

In the 2005 SLR, only a highest versus lowest analysis was conducted on occupational physical activity and prostate cancer which showed inconsistent results.

Published meta-analysis or pooled analysis

A meta-analysis of 9 cohort studies reported a RR for highest vs lowest level of occupational physical activity of 0.91 (95% CI 0.87–0.95, $I^2 = 0\%$) (Liu et al, 2011). No pooled analysis was identified.

Table 246 Studies on occupational physical activity identified in the CUP

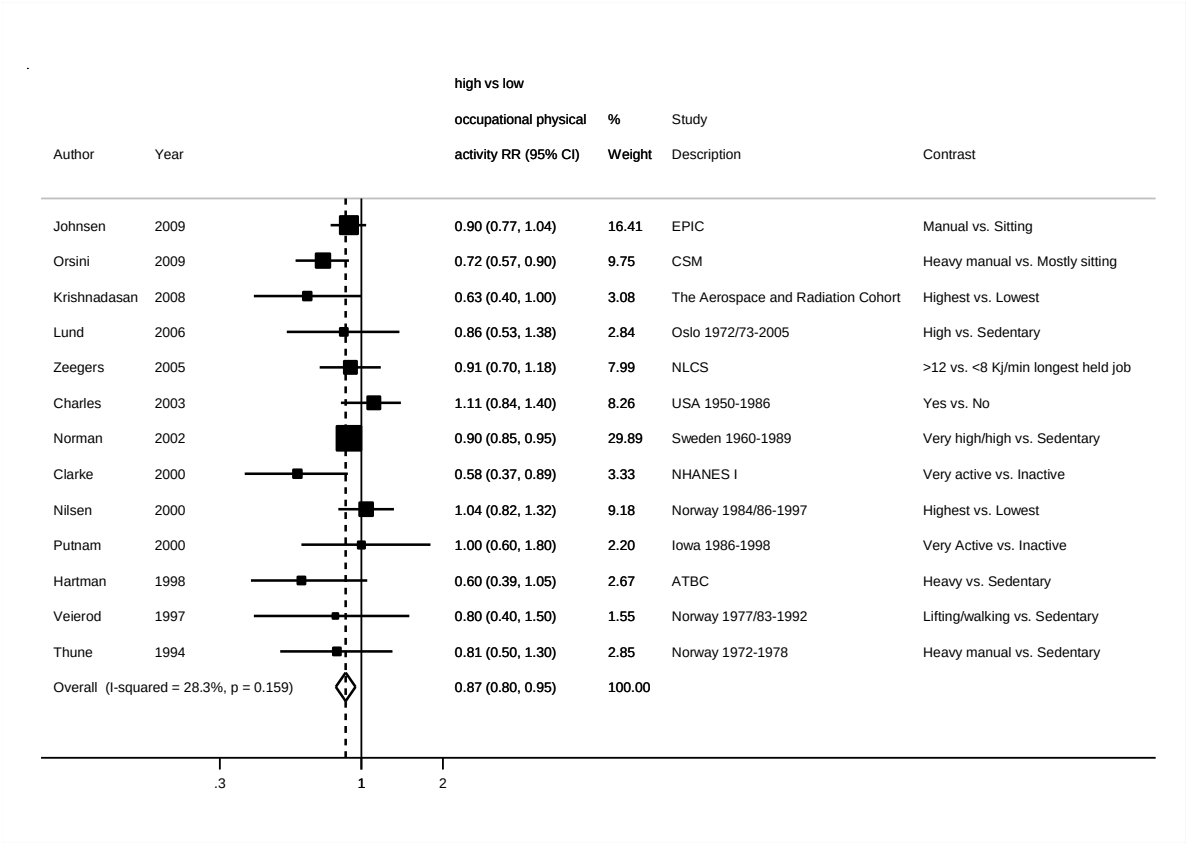
Author, year	Country	Study name	Cases	Years of follow up	RR	LCI	UCI	Contrast
Orsini, 2009	Sweden	Cohort of Swedish Men	2735	9 years	0.72	0.57	0.90	Heavy manual vs. mostly sitting
Johnsen, 2009	Europe	EPIC study	2458	8.5 years	0.90	0.77	1.04	Manual vs. Sitting

Krishnada-san, 2008	USA	The Aerospace and Radiation Cohort	392	11 years	0.63	0.40	1.00	Highest vs. Lowest
Lund Håheim, 2006	Norway	Oslo Cohort1972/73-1998	507	27 years	0.86	0.53	1.38	High vs. Sedentary

Table 247 Inclusion/exclusion table for meta-analysis of occupational physical activity and prostate cancer

WCRF code	Author	Year	Study design	Study name	Cancer outcome	2005 SLR	CUP HvL forest plot	Data on screening and notes
PRO100052	Orsini	2009	Prospective Cohort study	Cohort of Swedish Men	Incidence/ Mortality	No	Yes	There is no official recommendation in Sweden on PSA testing as part of health check-up or for screening purposes in men without lower urinary tract symptoms hence any bias that may be introduced by PSA is of limited relevance according to the authors
PRO100058	Johnsen	2009	Prospective Cohort study	EPIC	Incidence	No	Yes	Data on PSA testing were not available, but the rates of PSA testing across Europe seems to be low (6% in England and Wales,44 7% in the Netherlands, about 10% in Spain and 16% in Italy) compared to US rates of 57%
PRO100016	Krishnadasan	2008	Nested case-control study	The Aerospace and Radiation Cohort	Incidence	No	Yes	Workers with high occupational physical-activity levels were less likely to have reported family history of prostate cancer or have been screened regularly for prostate cancer, and were more likely to be African-American. Using Axelson's formula, the authors found unlikely that the observed reduced risk in highly active jobs was attributable to confounding (data not shown)
PRO100038	Lund	2006	Prospective Cohort study	Oslo Cohort1972/73-1998	Incidence	No	Yes	Screening of cardiovascular disease in 1972-1973. No data on PSA. 1,232 men participated in a randomized controlled trial on diet and smoking, and 785men in a randomized controlled trial on hypertension both over 5 years
PRO97122	Zeegers	2005	Prospective Cohort study	Netherlands Cohort Study	Incidence	Yes	Yes	No data on screening. No association with sitting hours/day per day at work. No association with combined occupational and nonoccupational physical activity (results not shown).
PRO00092	Charles	2003	Prospective Cohort study	Electric utilities workers study USA	Mortality	Yes	Yes	Mortality followed through 1988
PRO00947	Norman	2002	Prospective Cohort study	Sweden 1960-1989	Incidence/ Mortality	Yes	Yes	Follow-up until 1989. No association with prostate cancer mortality, no difference by age (more or less 70 years)
PRO01602	Nilsen	2000	Prospective Cohort study	Norway 1984/86 -1996	Incidence/ Mortality	Yes	Yes	RRs were similar in analysis restricted to follow-up to January 1993 to avoid potential bias due to differential PSA testing (460 cases, data not shown)
PRO01468	Clarke	2000	Prospective Cohort study	NHANES I	Incidence/ Mortality	Yes	Yes	No data
PRO01487	Putnam	2000	Prospective cohort study	Iowa's Men Study	Incidence/ Mortality	Yes	Yes	No data End of follow-up:1995
PRO01688	Nilsen	1999	Prospective Cohort study	Norway 1984/86-1993	Incidence/ Mortality	Yes	No	Excluded: superseded by Nilsen, 2000
PRO02180	Hartman	1998 a	Prospective Cohort study	ATBC	Incidence	Yes	Yes	Smokers and exposed to asbestos Nonsignificant RR reduction in workers who walked, and those who did lifting and walking but nonsignificant increase in heavy manual workers compared with sedentary workers
PRO02242	Veierod	1997	Prospective Cohort study	Norway 1977/1983-1992	Incidence/ Mortality	Yes	Yes	No data
PRO02604	Steenland	1995	Prospective Cohort study	NHANES I	Incidence/ Mortality	Yes	No	Excluded: superseded by Clarke, 2000
PRO02810	Hsing	1994	Prospective Cohort study	Shanghai, 1980-84	Incidence	No	No	Excluded, unadjusted SIR
PRO02744	Thune	1994	Prospective Cohort study	Norway 1972/1978-1991	Incidence/ Mortality	Yes	Yes	No data First year of follow-up excluded
PRO03201	Albanes,	1989	Prospective Cohort study	NHANES I	Incidence/ Mortality	Yes	No	Excluded, superseded by Clarke, 2000

Figure 269 Highest versus lowest forest plot of occupational physical activity and prostate cancer*



* In Krishnadasan, 2008, the lowest category was mainly sitting and the highest category was walking and light to heavy manual work. In Nilsen, 2000, the lowest category was almost never or infrequently worn out and high activity was often or nearly always worn out.
The RR (95% CI) in Norman, 2002 and Clarke 2002 were L vs H in the original publications and were recalculated using Hamling method for inclusion in the Figure

6.1.1.2 Recreational physical activity

Methods
Thirty publications from twenty-five studies were identified, from which 8 studies from 9 publications were identified in the CUP.

The wide variability in the methods of assessment of physical activity used did not allow doing dose-response analyses. Only highest versus lowest analysis was performed. Twenty-two studies could be included in highest versus lowest analysis. One cohort was on pesticide applicators (Alavanja et al, 2003).

Main results
Two studies were on mortality. The majority of the studies reported on recreational or leisure physical activity, one study was on cardiorespiratory fitness (Byun et al, 2011), another study was on walking and bicycling (Orsini et al, 2009), two studies were on exercise (Whittemore et al, 1984) or sport activities (Suzuki, 2007).
The summary RR (95% CI) for the highest vs the lowest comparisons were 0.89 (0.76-1.05) for fatal prostate cancers, 0.97 (0.90-1.04) for incident cases only and 0.97 (0.90-1.04) for studies that included fatal and incident cases.
One study on cardiorespiratory fitness (CRF) (Byun et al, 2011) showed an increased risk with higher CRF in particpants with cancer diagnosis before 1995 and no association in those diagnosed after that year. Incidence was defined by mail survey and this might have been a source of bias. Men with high CRF may be more likely to participate in the follow-up and in PSA screening and have an apparent increased risk of prostate cancer.

In the EPIC study (Johnsen et al, 2009) leisure time activity was not associated with risk of advanced, localized, high grade or low grade prostate cancer ($p < 0.35$ for stage, $p < 0.74$ for grade).
In a Swedish study (Orsini et al, 2009) cycling/walking was significantly inversely associated with advanced prostate cancer (defined as > T2, NX-1, MX-1 or PSA > 100 or Gleason grade ≥ 7; $p_{trend} < 0.001$) but the association was inverse but not significant for localised cancers.

In the Norwegian HUNT study (Nilsen et al, 2006), leisure time physical activity was inversely related to advanced prostate cancer (RR highest vs lowest frequency 0.66; 95% CI 0.44-0.99; $p_{trend} = 0.04$) but not will all cancers combined. In NHANES I (Patel et al, 2005), recreational physical activity was inversely related to aggressive cancers (stages III/ IV, Gleason ≥ 7 or grades 3 to 4 at diagnosis) but not to non aggressive cancers.
In a Dutch study (Zeegers et al, 2005) no association was observed both in advanced (stage T3-4, M0 or M1) and non advanced cancers. One study in Norway reported a suggestive inverse association in metastatic cancers (RR for the highest vs lowest frequency 0.65; 95% CI 0.40-1.06) (Nilsen et al, 2000).

Comparison with the Second Expert Report
In the 2005 SLR, the highest versus lowest meta-analysis on recreational physical activity and prostate cancer showed non-significant association.

Published meta-analysis or pooled analysis

A meta-analysis consisted of 19 eligible cohort studies reported a RR for the highest vs the lowest level of recreational physical activity of 0.95 (95% CI 0.90-1.00; I^2 = 15.1%) (Liu et al, 2011). No pooled analysis was identified.

Table 248 Studies on recreational physical activity identified in the CUP

Author, year	Country	Study name	Cases	Years of follow up	RR	LCI	UCI	Contrast
Batty, 2011	UK	Whitehall study	578	40 years	1.12	0.76	1.64	Active vs. none/inactive
Byun, 2011	USA	Aerobics Center Longitudinal Study	634	9.3 ±7.1 years	1.74	1.15	2.62	> 40 vs. < 19 % CRF level
Orsini, 2009	Sweden	Cohort of Swedish Men	2735	9 years	0.86	0.76	0.98	> 60 vs. 20-40 min/d
Johnsen, 2009	Europe	EPIC study	2458	8.5 years	1.01	0.88	1.16	> 72.0 vs. < 24.0 MET-hours/w
Yun, 2008	Korea	National Health Insurance Corporation (NHIC), Korea	305	6 years	0.91	0.72	1.14	Moderate/high vs. low
Suzuki, 2007	Japan	JACC study	124	≈23 years	1.18	0.74	1.86	< 1 vs. > 3 hours/w
Nilsen, 2006	Norway	HUNT study	957	17 years	1.01	0.81	1.27	≥ 4 vs. 0 times/w
Lund Håheim, 2006	Norway	Oslo Cohort1972/73-1998	507	27 years	0.45	0.17	1.22	High vs. Sedentary

Table 249 Inclusion/exclusion table for meta-analysis of recreational physical activity and prostate cancer

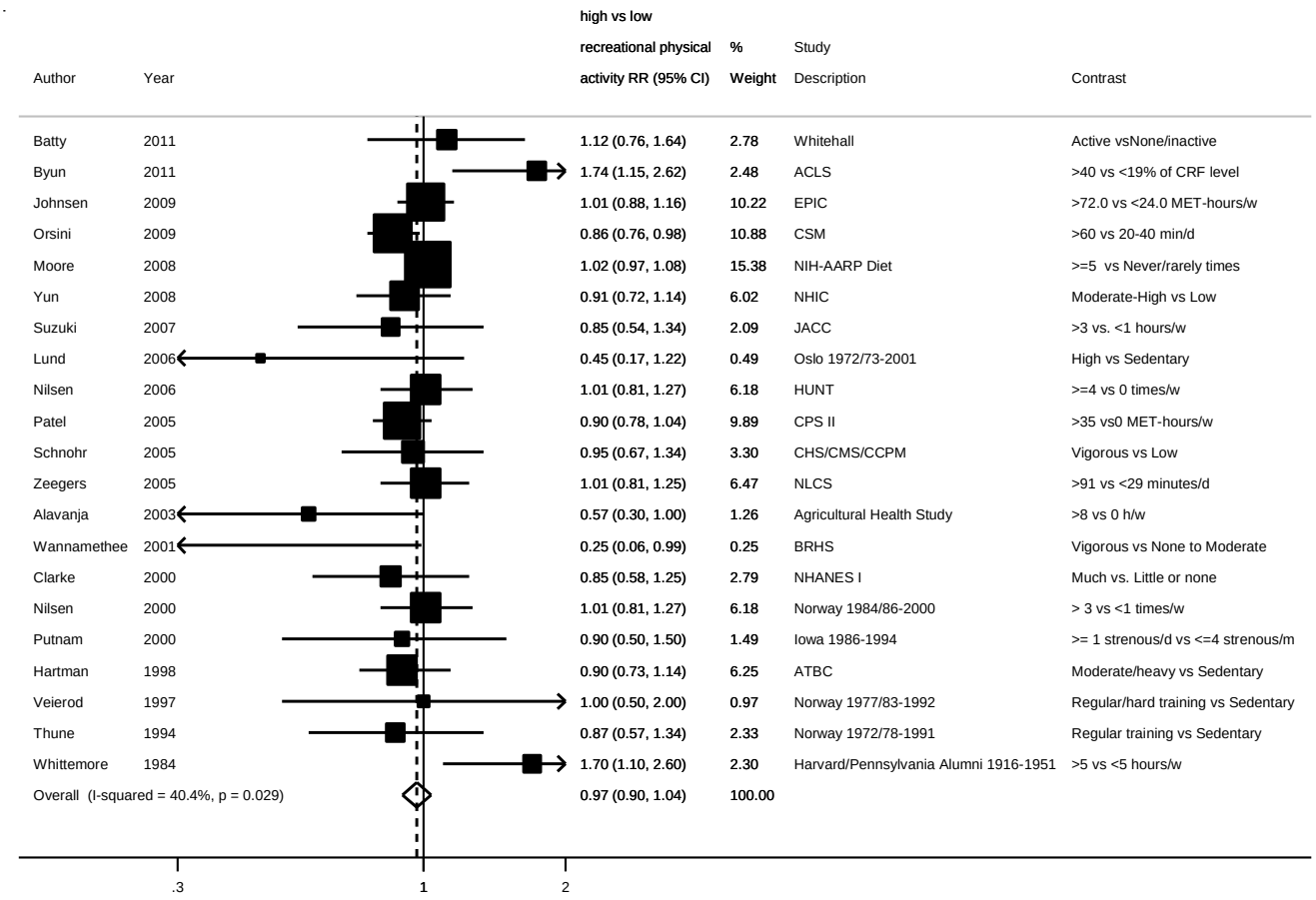
WCRF code	Author	Year	Study design	Study name	Cancer outcome	2005 SLR	CUP HvL forest plot	Screening, notes
PRO100170	Batty	2011	Prospective Cohort study	Whitehall study	Mortality	No	Yes	No data. Maximum follow-up of 40 years
PRO100171	Byun	2011	Prospective Cohort study	Aerobics Center Longitudinal Study	Incidence	No	Yes	In a subgroup of men with PSA test available (N = 3003), there was no significant association between Cardiorespiratory fitness (CRF) and prostate cancer (PrCA) without and with adjustment for PSA scores. Men with moderate or high CRF were more likely to revisit the clinic (49.3% vs. 34.3%), be screened for PSA (16.2% vs. 12.3%), and be diagnosed with PrCA (3.5% vs. 1.5%) compared to men who were in the low CRF level.
PRO100085	Batty	2010	Prospective Cohort study	Whitehall study	Mortality	No	No	Excluded, superseded by Batty, 2011
PRO100052	Orsini	2009	Prospective Cohort study	Cohort of Swedish Men	Incidence Mortality	No	Yes	There is no official recommendation in Sweden on PSA testing as part of health check-ups or for screening purposes in men without lower urinary tract symptoms hence any bias that may be introduced by PSA is of limited relevance in our data.
PRO100058	Johnsen	2009	Prospective Cohort study	EPIC study	Incidence	No	Yes	Data on PSA testing were not available, the rates of PSA testing across Europe seems to be low (6% in England and Wales,44 7% in the Netherlands,45 about 10% in Spain and 16% in Italy) compared to US rates of 57%
PRO100129	Yun	2008	Prospective Cohort study	National Health Insurance Corporation (NHIC), Korea	Incidence	No	Yes	No data, paper with multiple cancer outcomes
PRO99983	Moore	2008	Prospective Cohort study	NIH- AARP study	Incidence Mortality	No	Yes	Participants who engaged in high levels of physical activity were more likely to have had PSA screenings during the past three years. However, among men who had not undergone a PSA screening during the past three years, physical activity had no relation with total, advanced, or fatal prostate cancer. On the other hand, among men who had undergone a PSA test during the past three years, exercise at baseline was associated with a reduced risk of prostate cancer mortality (Ptrend = 0.05) and exercise during adolescence was associated with reduced risk of advanced prostate cancer (Ptrend = 0.01).
PRO100132	Suzuki	2007	Prospective Cohort study	JACC study	Mortality	No	Yes	No data, paper with multiple cancer outcomes
PRO99987	Nilsen	2006	Prospective Cohort study	HUNT study	Incidence Mortality	No	Yes	No data on PSA. However, in an analysis restricted to a period before PSA testing became prevalent (before 1993), the authors reported similar results as in the present study
PRO100038	Lund	2006	Prospective Cohort study	Oslo Cohort 1972/73-1998	Incidence	No	Yes	Screening of cardiovascular disease in 1972-1973. No data on PSA. 1,232 men participated in a randomized controlled trial on diet and smoking, and 785men in a randomized controlled trial on hypertension both over 5 years
PRO97344	Patel	2005	Prospective Cohort study	CPS II	Incidence Mortality	Yes	Yes	The age-adjusted percentage of men reporting PSA testing on the 1997 and/or the 1999 questionnaire was higher among active (81.3%) than inactive men (70.5%). However, in analysis restricted to the period with data on PSA (after 1997) physical activity was not associated with risk of aggressive prostate cancer but not with total prostate cancer
PRO98773	Schnohr	2005	Prospective Cohort study	The Copenhagen City Heart Study	Incidence Mortality	Yes	Yes	No data, paper on multiple cancers

PRO97122	Zeegers	2005	Prospective Cohort study	Netherlands Cohort Study	Incidence		Yes	No data
PRO97715	Zhu	2004	Nested case-control study	PHS	Incidence	Yes	No	Excluded, only mean values
PRO97676	Laak-sonen	2004	Prospective Cohort study	Kuopio Ischaemic Heart Disease Risk Factor Study	Incidence /Mortality	Yes	No	Excluded, only mean values
PRO00442	Alvanja	2003	Prospective Cohort study	Agricultural Health Study cohort	Incidence /Mortality	Yes	Yes	Pesticide applicators. End of follow-up:1999
PRO00515	Hsieh	2003	Prospective Cohort study	Baltimore Longitudinal Study of Ageing	Incidence	Yes	No	Excluded, only p-values
PRO01029	Wanna-methee	2001	Prospective Cohort study	BRHS British Regional Heart Study	Incidence / Mortality	Yes	Yes	No data, paper in multiple cancer outcomes
PRO01602	Nilsen	2000	Prospective Cohort study	Norway 1984/86 - 1996	Incidence / Mortality	Yes	Yes	RRs were similar in analysis restricted to follow-up to January 1993 to avoid potential bias due to differential PSA testing (460 cases, data not shown)
PRO01468	Clarke	2000	Prospective Cohort study	NHANES I	Incidence /Mortality	Yes	Yes	No data
PRO01487	Putnam	2000	Prospective cohort study	Iowa's Men Study	Incidence / Mortality	Yes	Yes	No data End of follow-up:1995
PRO12115	Davey	2000	Prospective Cohort study	Whitehall study	Mortality	Yes	No	Excluded, superseded by Batty, 2011
PRO01688	Nilsen	1999	Prospective Cohort study	Norway 1984/86-1993	Incidence / Mortality	Yes	No	Excluded, superseded by Nilsen, 2000
PRO02180	Hartman	1998 a	Prospective Cohort study	ATBC	Incidence	Yes	Yes	Among workers, leisure physical activity was inversely related to prostate cancer risk for all occupational levels, except heavy laborers
PRO02364	Cerhan	1997	Prospective Cohort study	Iowa's 65+ rural health study	Incidence / Mortality	Yes	No	Excluded, superseded by Putnam, 2000
PRO02242	Veierod	1997	Prospective Cohort study	Norway 1977/1983-1992	Incidence /Mortality	Yes	Yes	No data
PRO02518	Oliveira	1996	Prospective Cohort study	Aerobics Center Longitudinal Study	Incidence	Yes	No	Excluded, superseded by Byun , 2011
PRO02744	Thune	1994	Prospective Cohort study	Norway 1972/1978-1991	Incidence /Mortality	Yes	Yes	No data First year of follow-up excluded
PRO03201	Albanes,	1989	Prospective Cohort study	NHANES I	Incidence /Mortality	Yes	No	Excluded, superseded by Clarke, 2000

PRO13451	Garfinkel	1988	Prospective Cohort study	CPS II	Mortality	Yes	No	Excluded, superseded by Patel 2005
PRO03461	Whittemore	1984	Prospective Cohort study	HPAS Harvard 1916/1950 and Pennsylvania 1931/40 Alumni Study	Incidence /Mortality	Yes	Yes	No data

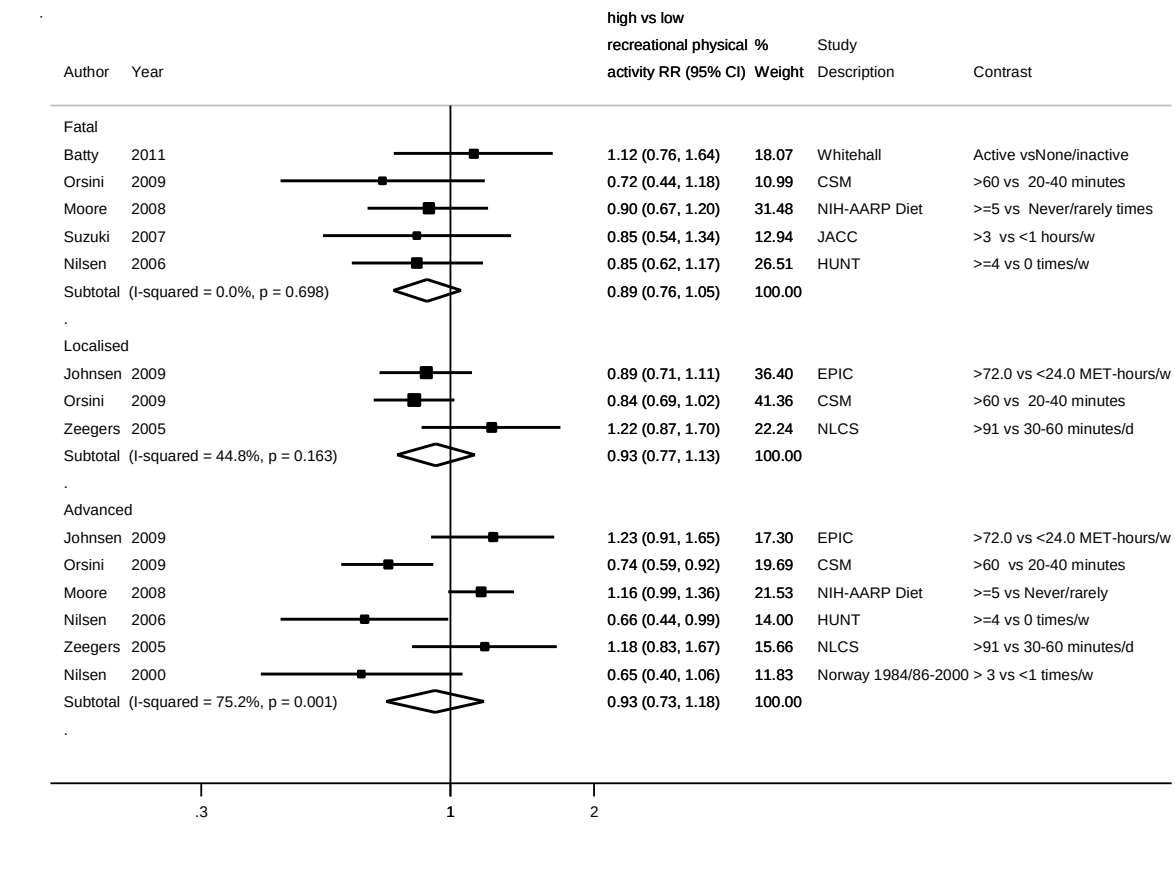
* Schnohr, 2005 counted as 3 studies.

Figure 270 Highest versus lowest forest plot of recreational physical activity and prostate cancer*



* In Yun, 2008, high/ was ≥ 2 times/week for ≥ 30 min/time or ≥ 5 times/week for < 30 min/time, and low was ≤ 4 times/week for < 30 min/time or ≤ 1 time/week for ≥ 30 min/time.
In Schnohr, 2005 vigorous was light physical activity> 4 hours per week or more vigorous physical activity 2–4 hours per week(brisk walking, fast cycling, heavy gardening, sports where you get sweaty or exhausted or highly vigorous physical activity) or regular heavy exercise or competitive sports several times per week. Low was defined as almost entirely sedentary (reading, TV, cinema) or light physical activity less than 2 hours per week.
In Wannamethee, 2001 vigorous was very frequent sporting exercise or frequent sporting exercise plus other recreational activities. Moderate was cycling or very frequent weekend recreational activies plus regular walking, or sporting activity once a week.
The RR (95% CI) in Suzuki, 2007 and Clarke 2002 were L vs H in the original publications and were recalculated using Hamling method for inclusion in the Figure.

Figure 271 Highest versus lowest forest plot of recreational physical activity and prostate cancer, by prostate cancer outcome



7 Energy balance

7.1 Energy intake

Methods

Twenty-four publications from seventeen studies were identified, from which seven studies from eight publications were identified in the CUP.

Eight studies were included in the CUP meta-analysis. The increment unit used in the dose-response analysis was 500 kcal/day. Non-linear dose response meta-analysis was not conducted as the dose-response graphs do not suggest a possible non-linear dose response.

One study reported on prostate cancer mortality (Smit et al, 2007); one study reported on total and advanced prostate cancer (Schuurman et al, 1999) before implementation of PSA in The Netherlands, with advanced cancers defined as stage T3-T4, regionally invasive or metastatic cancers. One study reported on any prostate cancer (including fatal cases) and reported associations also for advanced cancers (regionally invasive, metastatic and fatal) (Platz et al, 2003). One study reported analyses stratified by Gleason score (< 7 and ≥ 7) (Kristal et al,

2010) that were pooled using fixed effect models in these review for inclusion in the dose-response meta-analysis.

Stratified analyses were conducted for a subgroup including advanced cancer (Schuurman et al, 1999; Platz et al, 2003), fatal cancers (Smit et al, 2007) and cases with Gleason score ≥ 7 (Kristal et al, 2010)

Main results
The summary RR per 500 kcal/day was 1.00 (95% CI 0.98-1.02; $I^2 = 0.0\%$; $p_{heterogeneity} = 0.60$; n = 8). There was no evidence of publication bias with Egger's test, p = 0.69.

In stratified analysis, the RR of advanced, aggressive or fatal cancers was 1.01 (95% CI 0.95-1.08; $I^2 = 27.3\%$; $p_{heterogeneity} = 0.25$; n = 4) for an increase of 500 kcal/day.

Heterogeneity
Overall, there was no evidence of heterogeneity, $I^2 = 0\%$, $p_{heterogeneity} = 0.60$.

Comparison with the Second Expert Report

In the 2005 SLR, the summary RR for 500 kcal/day was 1.00 (95% CI 0.98-1.03). Seven studies were included in the meta-analysis. Outcomes were incidence or mortality. One study included prevalent cases and this study explained most of the observed heterogeneity ($I^2 = 50.7\%$; $p_{heterogeneity} = 0.05$).

Published meta-analysis or pooled analysis
No meta-analysis or pooled analysis was identified.

Table 250 Studies on energy intake identified in the CUP

Author, year	Country	Study name	Cases	Years of follow up	RR	LCI	UCI	Contrast
Lin, 2013	USA	NHANES III	61 (mortality)		0.59	0.15	2.29	Per log kcal/d
Kristal, 2010	USA	The Prostate Cancer Prevention Trial	1576 Gleason 2-7	9 years	1.07	0.92	1.25	> 2679 vs. < 1557 kcal/d
			127 Gleason 8-10		0.69	0.4	1.17	
Chae, 2009	USA	CLUE II	269	3 years	1.25 *	0.78	1.90	> 1861.8 vs. < 1107.8 kcal/d
Gonzalez, 2007/ Gonzalez, 2009	USA	VITAL	832	2-4 years	1.02	0.84	1.25	≥ 2700 vs. < 1658 kcal/d***
Giovannucci, 2007	USA	Health Professionals Follow-up Study	3,544	~16 years	1.00	0.88	1.13	> 2468 vs. < 1446.9 kcal/d
Smit, 2007	Puerto Rico	PR Heart Health Program	167 (mortality)	~41 years	1.24	0.81	1.90	> 2847 vs. <1770 kcal/d**
Iso, 2007	Japan	Japan Collaborative Cohort study	162 (mortality)	NA	1.63	1.00	2.67	No change vs. modified

*only adjusted for age and ethnicity
** data from 24 hours recall
***Age-adjusted

Table 251 Overall evidence on energy intake and prostate cancer

	Summary of evidence
2005 SLR	Eleven studies were identified in the 2007 SLR from which seven studies were included in the 2007 SLR meta-analysis (one included prevalent cases). Overall, no significant association was observed.
Continuous Update Project	Seven studies were identified in the CUP, all showed non-significant associations. No significant association was observed in the CUP meta-analysis.

Table 252 Summary of results of the dose response meta-analysis of energy intake and prostate cancer

Prostate cancer		
	2005 SLR	CUP
Studies (n)	7	8
Cases (n)	4385	6755
Increment unit used	Per 500 kcal/day	Per 500 kcal/day
Overall RR (95% CI)	1.01 (0.96-1.08)	1.00 (0.98-1.02)
Heterogeneity (I^2, p-value)	50.7%, p = 0.056	0.0%, p = 0.60
Stratified analysis		
Advanced/High grade/Fatal cancer		4
Overall RR (95% CI)		1.01 (0.95-1.08)
Heterogeneity (I^2, p-value)		27.3%, p = 0.25

Table 253 Inclusion/exclusion table for meta-analysis of energy intake and prostate cancer

WCRF code	Author	Year	Study design	Study name	Cancer outcome	2005 SLR	CUP dose-response meta-analysis	CUP HvL forest plot	Estimated values	Exclusions reasons
PRO100149	Lin	2013	Prospective Cohort	NHANES III	Mortality	No	No	No		Increment expressed in log unit. Cui, 2004 (PRO97049) was used in HvsL forest plot
PRO100078	Kristal	2010	Prospective Cohort	Prostate Cancer Prevention Trial	Incidence	No	Yes	Yes	Mid-exposure values. Pooled high and low Gleason score subgroups	
PRO100066	Gonzalez	2009	Prospective Cohort	Vitamins And Lifestyle Study	Incidence and mortality	No	Yes	Yes	Mid-exposure values	
PRO100074	Chae	2009	Nested Case Control	CLUE II	Incidence	No	Yes	Yes	Mid-exposure values	
PRO100019	Smit	2007	Prospective Cohort	Puerto Rico Health	Mortality	No	Yes	Yes	Mid-exposure values, number of cases per quantile	
PRO100035	Gonzalez	2007	Prospective Cohort	Vitamins And Lifestyle Study	Incidence and mortality	No	No	No		Same as Gonzalez, 2009 (PRO100066)
PRO100042	Iso	2007	Prospective Cohort	Japan Collaborative Cohort study	Mortality	No	No	No		Exposure is energy intake modification
PRO99961	Giovannucci	2007	Prospective Cohort	Health Professionals Follow-up Study	Incidence	No	No	No		No confidence intervals, no cases distribution. Platz, 2003 (PRO00174) was used instead
PRO97424	Weinstein	2005	Case Cohort	ATBC	Incidence	Yes	No	No		Only mean exposures reported. No measure of association.
PRO10700	Platz	2004b	Nested Case Control	CLUE ll	Incidence	Yes	No	No	Mid-exposure values	Superseded by Chae, 2009 (PRO100074)

PRO97049	Cui	2004	Nested Case Control	NHANES III	Incidence and prevalence	Yes	No	Yes		Energy intake (kcals) not reported
PRO97676	Laaksonen	2004	Prospective Cohort	Kuopio Ischaemic Heart Disease Risk Factor Study	Incidence	Yes	No	No		Only mean exposures reported. No measure of association.
PRO00174	Platz	2003	Prospective Cohort	Health Professionals Follow-up study	Incidence and mortality	Yes	Yes	Yes	Mid-exposure values	
PRO00272	Woodson	2003	Nested Case Control	ATBC	Incidence and mortality	Yes	No	No		Superseded by Weinstein, 2005 (PRO97424)
PRO00515	Hsieh	2003	Prospective Cohort	Baltimore Longitudinal Study of Aging	Incidence	Yes	No	No		Include prevalent cases
PRO01034	Hirvonen	2001	Prospective Cohort	ATBC	Incidence and mortality	Yes	No	No		Superseded by Weinstein, 2005 (PRO97424)
PRO01108	Dirx	2001	Nested Case Control	The Netherlands Cohort study	Incidence	Yes	No	No		Exposure was energy restriction early in life
PRO01426	Chan	2000	Prospective Cohort	ATBC	Incidence	Yes	Yes	Yes	Mid-exposure values	
PRO01683	Schuurman	1999	Nested Case Control	The Netherlands Cohort study	Incidence	Yes	Yes	Yes		
PRO02180	Hartman	1998a	Prospective Cohort	ATBC	Incidence	Yes	No	No		Superseded by Weinstein, 2005 (PRO97424)
PRO02242	Veierod	1997	Prospective Cohort	Norway 1977-1983	Incidence	Yes	Yes	Yes	Mid-exposure values	
PRO02582	Gronberg	1996	Nested Case Control	Sweden 1967-1970	Incidence and prevalence	Yes	No	No		Energy intake not quantified
PRO03125	Stemmermann	1990	Prospective Cohort	Honolulu Heart Program	Incidence and mortality	Yes	No	No		Only mean exposures reported. No measure of association.
PRO03210	Severson	1989b	Prospective Cohort	USA Hawaii 1965-1968	Incidence	Yes	Yes	Yes	Mid-exposure values	

Figure 272 Highest versus lowest forest plot of energy intake and prostate cancer

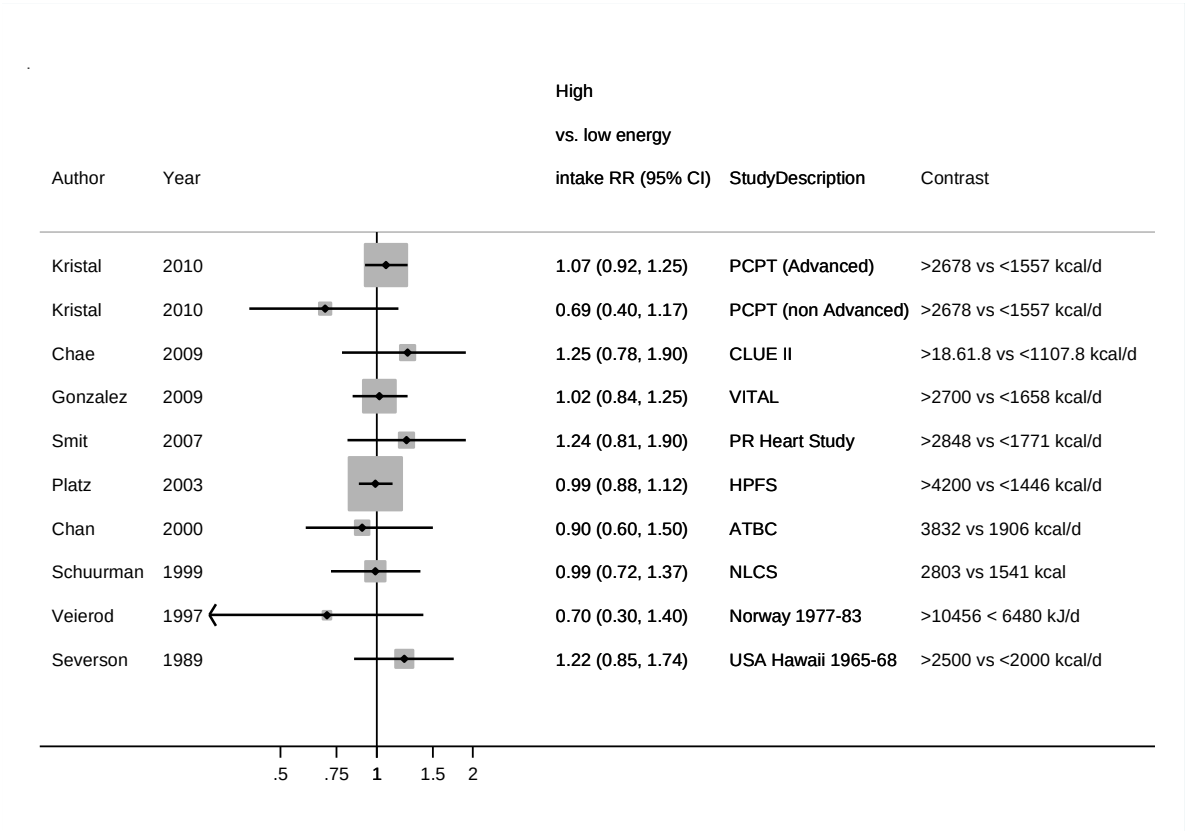


Figure 273 Dose-response meta-analysis of energy intake and prostate cancer – per 500 kcal/day

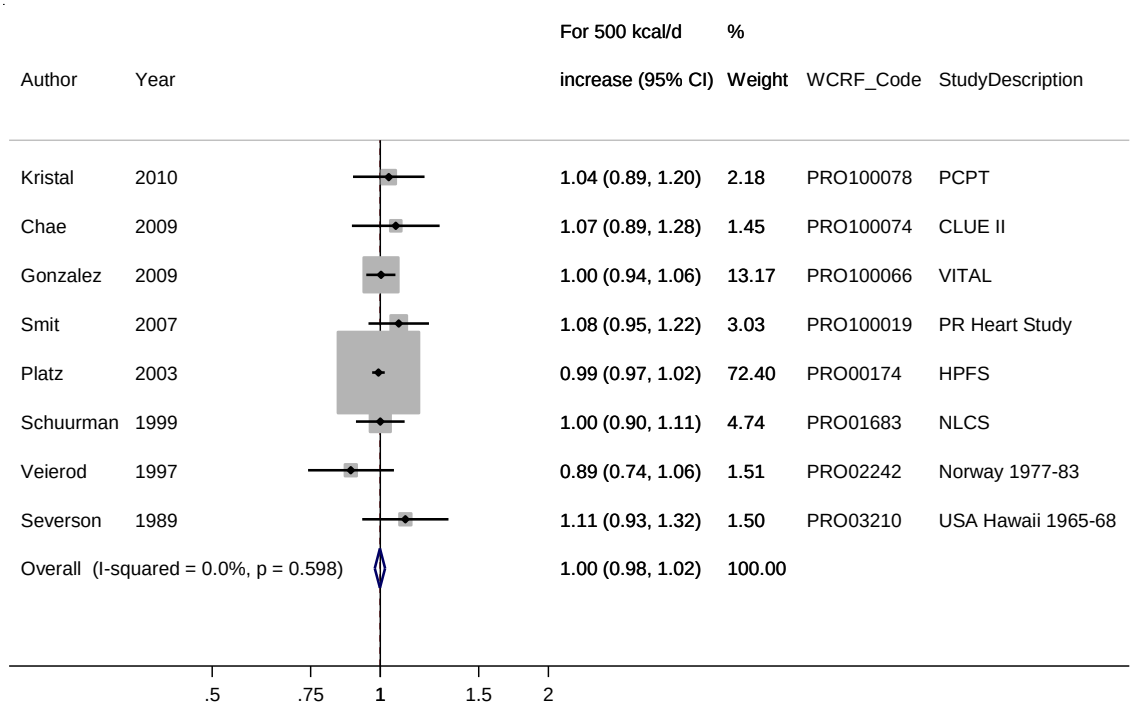
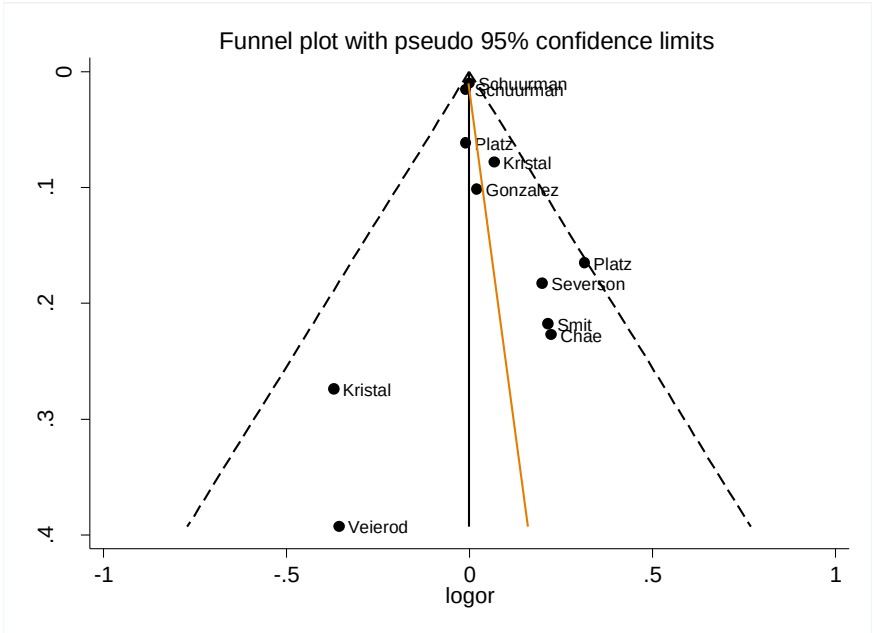


Figure 274 Funnel plot of energy intake and prostate cancer



Egger's test p = 0.69

Figure 275 Dose-response graph of energy intake and prostate cancer

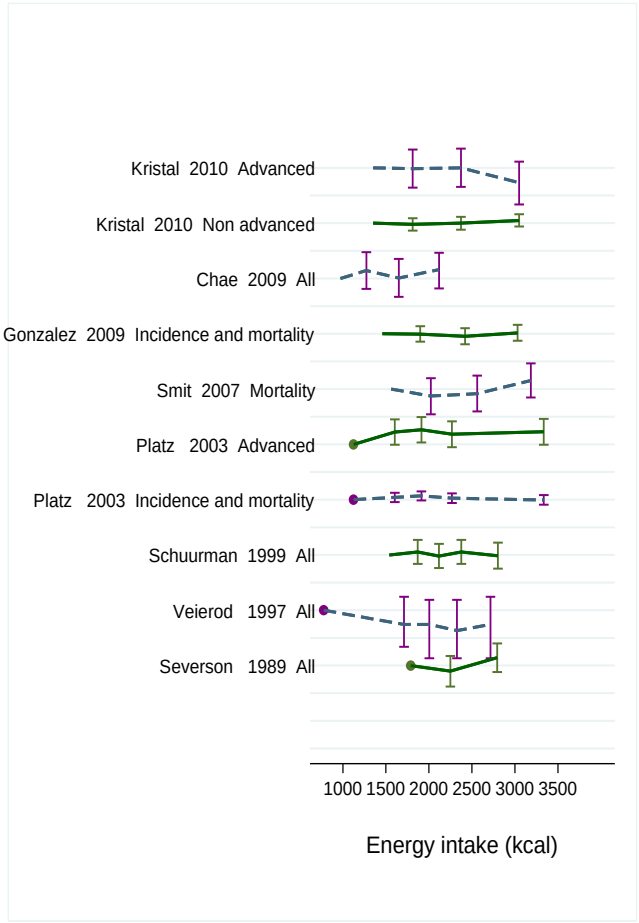
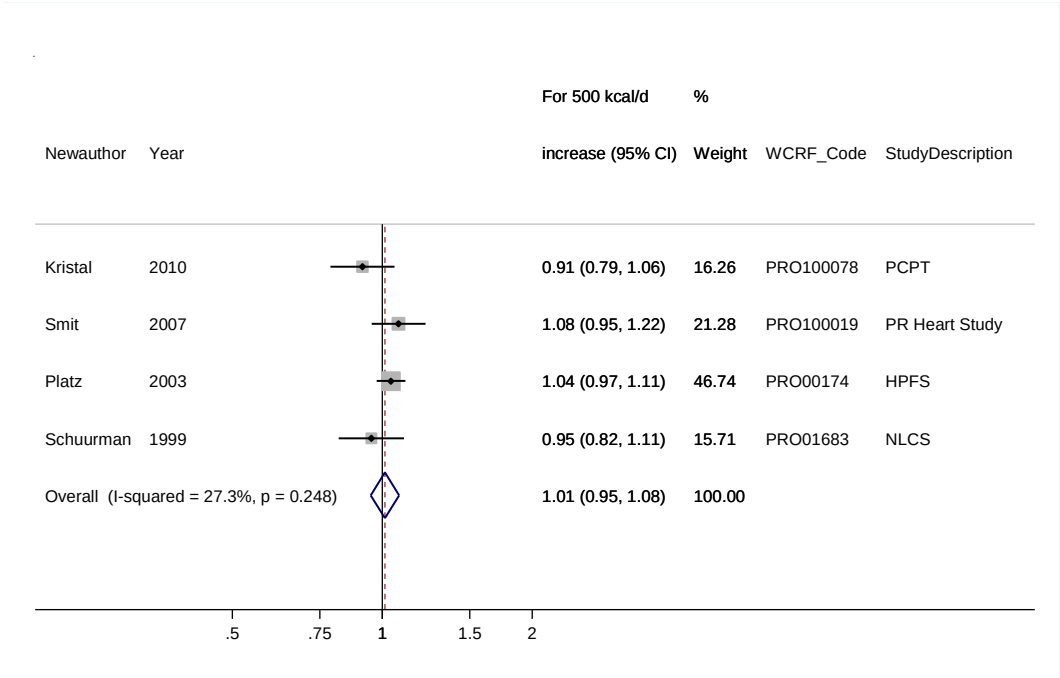


Figure 276 Dose-response meta-analysis of energy intake and advanced/aggressive/fatal prostate cancer, per 500 kcal/day



8 Anthropometry

8.1.1 BMI

Methods
Overall, 64 studies from 114 publications were identified. Thirty-two studies from 39 publications were identified during the CUP. Sixteen studies were new to the CUP, 16 studies had also published in the 2005 SLR.

Forty-five studies could be included in the dose-response meta-analysis on prostate cancer. The increment unit used in the analysis was 5 kg/m^2.

The Oslo Study (Lund Håheim et al, 2006) is a component study of Norway 1972-1978 (Thune et al, 1994). The MDC study (Wallström et al, 2009) is a component study of the EPIC study (Pischon et al, 2008). The Collaborative Cohort Study (Shafique et al, 2012b) is a component study of the Mid Span Study (Shafique et al, 2012a). HUNT2 is a follow-up study of HUNT 1 (Chamberlain et al, 2011; Martin et al, 2009; Lund Nilsen et al, 1999). NHEFS (Dehal et al, 2011) is a follow-up study of NHANES I (Clarke et al, 2000). There is an overlapping of populations in the studies of Lukanova et al, 2006, Hultdin et al, 2005, Stattin et al, 2004, and Stattin et al, 2001, and in Lundqvist et al, 2007, Jonsson et al, 2003, and Gronberg et al, 1996. Further twenty-one studies had multiple publications. One publication (Rodriguez et al, 2001) identified during the 2005 SLR included two cohort studies (CPS I and II).

Six studies – PHS (Li et al, 2004; Zhu et al, 2004; Gann et al, 1999; Gann et al, 1994); BLSA (Hsieh et al, 2003; Brooks et al, 2001); FMCHS (Heikkila et al, 1999); NPCT (Jacobs et al, 2004); KIHDRFS (Laaksonen, et al, 2004); and Sweden 1974-1982 (Persson-Moschos et al, 2000) identified in the 2005 SLR only reported mean exposure values and could not be included in the analysis. There were no new publications for these studies.

Another seven studies were not included in the analysis because of insufficient data. Two publications from HHP only reported mean exposure values (Nomura et al, 2000; Nomura et al, 1997) and another publication of the study only reported incident rates (Nomura et al, 1985). Seven publications from the ATBC study only reported mean exposure values (Weinstein et al, 2005; Woodson et al, 2003; Kikkinen et al, 2003; Mannisto et al, 2003; Hirvonen et al, 2001; Hartman et al, 1998a,b) and another publication of the study reported results on the interaction between family history and BMI in relation to breast cancer risk (Ahn et al, 2008). One publication from CARET reported mean exposure values (Lamharzi et al, 2003) and another publication reported only on the number of cases and non-cases per exposure category (King et al, 2005). ULSAM (Grundmark et al, 2011) only reported unadjusted results. The studies of Tulinius et al (1997), Hiatt et al (1994), and Whittemore et al (1985) reported no significant association.

For the linear dose-response meta-analysis, the BMI categories were included as defined by the studies. In some studies, the reference category was normal weight and underweight normal weight in other studies. When the lowermost BMI category was not used as reference category (usually the underweight group) this category was excluded from the linear dose-response meta-analysis. However, all the BMI categories were included in the non-linear dose-response meta-analysis, and the method of Hamling was used to recalculate the relative risks when the reference category was not the lowermost category (Bassett et al, 2012; Discacciati et al, 2011; Batty et al, 2011; Hernandez et al, 2009; Martin et al, 2009; Jee et al, 2008; Fujino et al, 2007; Lundqvist et al, 2007; Bradbury et al, 2005; Rodriguez et al, 2001; Engeland et al, 2003).

From the studies included in the dose-response meta-analysis, 22 studies reported on total prostate cancer (Van Kruijsdijk et al, 2013; Andreotti et al, 2010; Chae et al, 2009; Jee et al, 2008; Krishnadasan et al, 2008; Lundqvist et al, 2007; Lukanova et al, 2006; Samanic et al, 2006; Tande et al, 2006; Bradbury et al, 2005; Kuriyama et al, 2005; Rapp et al, 2005; Allen et al, 2004; Engeland et al, 2003; Lee et al, 2001; Fitzptrick et al, 2001; Habel et al, 2000; Veierod et al, 1997; Thune et al, 1994; Le Marchand et al, 1994; Mils et al, 1989; Thompson et al, 1989), four studies on total, advanced/aggressive, localised/non-aggressive, high grade, and low grade prostate cancer (Hernandez et al, 2009; Pischon et al, 2008; Rodrigues et al, 2007; Gong et al, 2006), one study on total, advanced/aggressive and high grade prostate cancer (Shafique et al, 2012), five studies on total, advanced/aggressive and localised/non-aggressive prostate cancer (Littman et al, 2007; Kurahashi et al, 2006; Putnam et al, 2000; Schuurman et al, 2000; Cerhan et al, 1997), two studies on total and advanced/aggressive prostate cancer (Baillargeon et al, 2006; Giovannucci et al, 1997), three studies on total, advanced/aggressive, localised/non-aggressive and fatal prostate cancer (Bassett et al, 2012; Martin et al, 2009; Wright et al, 2007), three studies on total, advanced/aggressive and fatal prostate cancer (Batty et al, 2011; Eichholzer et al, 2005; Gapstur et al, 2001), three studies on advanced/aggressive and fatal prostate cancer (Dehal et al, 2011; Fujino et al, 2007; Rodriguez et al, 2001), one study on advanced/aggressive, localised/non-aggressive and fatal prostate cancer (Discacciati et al, 2011) and one study on fatal prostate cancer (Calle et al, 2003).

Main results

The summary RR of prostate cancer per 5 kg/m^2 was 1.00 (95% CI 0.98-1.03; I^2 = 64.0%; $p_{heterogeneity}$ < 0.01; n = 45) (all studies combined). The Egger's test of publication bias was not significant (p = 0.74). The summary RR did not change materially when studies were omitted in turn in the influence analysis.

After stratification by prostate cancer type, the summary RRs per 5 kg/m^2 were 1.00 (95% CI 0.97-1.03; I^2 = 67.3%; $p_{heterogeneity}$ < 0.01; n = 39) for total prostate cancer (removing studies reporting on mortality), 1.08 (95% CI 1.04-1.12; I^2=18.8%; $p_{heterogeneity}$ = 0.21; n = 23) for advanced prostate cancer and 0.95 (95% CI 0.92-0.98, I^2=37.8%; $p_{heterogeneity}$ = 0.08; n = 14) for non-advanced prostate cancer. After stratification by prostate cancer grade, the summary RRs per 5 kg/m^2 were 1.08 (95% CI 1.01-1.15; I^2 = 16.7%; $p_{heterogeneity}$ = 0.31; n = 6) for high grade prostate cancer and 0.93 (95% CI 0.89-0.97; I^2 = 31.8%; $p_{heterogeneity}$ = 0.22; n = 4) for low grade prostate cancer. For prostate cancer mortality, the summary RR per 5 kg/m^2 was 1.11 (95% CI 1.06-1.17; I^2 = 19.6%; $p_{heterogeneity}$ = 0.25; n = 12).

There was evidence of non-linear relationship for total and non-advanced/low grade prostate cancer (both p < 0.01). The curves were of a slight inverted J-shaped that showed the highest increased risk at BMI of 25 kg/m^2. For advanced/high grade prostate cancer and prostate cancer mortality, there was no statistical evidence of departure from linearity (p = 0.75; p = 0.07 respectively).

Five studies explored whether PSA tests influenced the association of BMI with prostate cancer. None of the studies identified a modification of the association. Three of the studies reported lower proportion of screening or PSA testing in obese men.

In the MEC (Hernandez et al, 2009) history of PSA screening (45% of men screened) did not influence the association of BMI with prostate cancer risk. The proportion of screening was the lowest among underweight men and the highest among obese.
In the HPFS (Giovannucci et al, 2007), the association of BMI with total and advanced prostate cancers were similar for the subgroups defined by diagnosis before PSA-era and during PSA.

In the VITAL study (Littman et al, 2007), the associations of BMI at baseline with prostate cancer risk did not differ by PSA testing two years before diagnosis (72% of the participants has a PSA test).

In the Cancer Prevention Study II (Rodriguez et al, 2007), PSA screening (89% of the men) did not modify the association between BMI and prostate cancer. PSA screening was slightly lower among heavier men.

In the NIH-AARP study (Wright et al, 2007) no effect modification by PSA test or digital rectal examination within three years before baseline was observed (70% of men had PSA test). The study results were similar when restricting the analyses to men with PSA test before baseline. The proportion of PSA test use was slightly smaller in obese men.

In another American study, the results did not change after adjustment for PSA levels at baseline (Baillargeon et al, 2006).

Heterogeneity

There was evidence of high heterogeneity between studies of prostate cancer risk (I^2 = 64.0%; $p_{heterogeneity}$ < 0.01; n = 45, for all studies combined; I^2 = 67.3%; $p_{heterogeneity}$ < 0.01; n = 39, for total prostate cancer). However, only low and moderate heterogeneity was observed in the subgroup analysis by cancer type (I^2 = 18.8%; $p_{heterogeneity}$ = 0.21; n = 23, for advanced/high grade prostate cancer; I^2 = 37.8%; $p_{heterogeneity}$ = 0.08; n = 14 for non-advanced/low grade prostate cancer).

Comparison with the Second Expert Report

In the 2005 SLR, the meta-analysis on BMI and prostate cancer showed no significant association (RR per 5 kg/m^2 = 1.00; 95% CI 0.99-1.01).

Published meta-analysis or pooled analysis

The summary RRs per 5 kg/m^2 were 1.09 (95% CI 1.02-1.16; I^2 = 38.1 %; $p_{heterogeneity}$ = 0.08; n = 13) for advanced prostate cancer and 0.94 (95% CI 0.91-0.97; I^2 = 17.6%; $p_{heterogeneity}$ = 0.27; n = 12) for localised prostate cancer in a meta-analysis of prospective studies (Discacciati et al, 2012).

In a meta-analysis of studies with prostate cancer mortality as outcome, the summary RR was 1.15 (95%CI 1.06-1.25; I^2 = 59.0%; $p_{heterogeneity}$ = 0.03; 6 cohort studies) for an increase of 5 kg/m^2 (Cao et al, 2011)

In a dose-response meta-analysis, the summary RR of prostate cancer was 1.03 (95%CI 0.99-1.06; I^2 = 72.7%; $p_{heterogeneity}$ < 0.0001; n = 27) per 5 kg/m^2 (Renehan et al, 2008).

All the studies included in the published meta-analyses are included in the CUP review.

A pooling project with prostate cancer mortality as outcome, the Asia-Pacific Cohort Studies Collaboration (APCSC), reported a HR of 1.45 (95% CI 0.97-2.19) for BMI ≥ 30 versus 18.5-24.9 kg/m^2 and 1.18 (95% CI 0.96-1.44) per 5 kg/m^2 increase of BMI (278 deaths) (Parr et al, 2010). In another pooling project, the Prospective Studies Collaboration (Whitlock et al, 2009) the HR for prostate cancer mortality was 1.13 (95% CI 1.02-1.24) for an increase of 5 kg/m^2 of BMI

Table 254 Studies on BMI identified in the CUP

Author, year	Country	Study name	Cases	Years of follow up	RR	LCI	UCI	Contrast
van Kruijsdijk, 2013	Nether-lands	Second Manifestations of ARTerial disease (SMART) Study	91	5.5 years	0.79	0.64	0.97	Per 3.6 kg/m^2 increase
Lin, 2013	USA	National Health and Nutrition Examination Survey (NHANES III)	61	12.4 years	1.56	0.59	4.14	≥ 30 vs. < 25 kg/m^2
Shafique, 2012a	Scotland	Midspan study	650	293284 person-years	1.03	0.77	1.40	≥ 30 vs. < 25 kg/m^2
Shafique, 2012b	UK	The Collaborative Cohort Study	318	28 years	1.28	0.77	2.11	≥ 30 vs. < 25 kg/m^2
Bassett, 2012	Australia	The Melbourne collaborative cohort study (MCCS)	1374	15 years	0.96	0.80	1.15	≥ 30 vs. ≤ 24.9 kg/m^2
					1.06	0.97	1.17	Per 5 kg/m^2
Discacciati, 2011	Sweden	Vastmanland and Orebro, Sweden	2336	371792 person-years	0.69	0.52	0.92	≥ 30 vs. < 21 kg/m^2 for localised prostate cancer
					1.15	0.75	1.74	≥ 30 vs. < 21 kg/m^2 for advanced prostate cancer
					1.36	0.73	2.53	≥ 30 vs. < 21 kg/m^2 for fatal prostate cancer
Grundmark, 2011	Sweden	Uppsala Longitudinal Study of Adult Men (ULSAM)	208	31290 Person-years	1.03	0.73	1.46	≥ 26 vs. ≤ 23.4 kg/m^2

Dehal, 2011	USA	Nutrition Examination Survey Epidemiology Follow-up Study (NHEFS)	44	118998 Person -years	1.36	0.53	3.47	Obesity vs. normal weight
Batty, 2011	UK	Whitehall study (WS)	578	40 years	1.00	0.61	1.65	≥ 30 vs. < 18.5 kg/m^2
					1.04	0.94	1.14	Per 1 SD increase
Chamberlain , 2011	Norway	North-Trondelag Health Study (HUNT I&II)	649	9.3 years	0.87	0.68	1.12	44.32 vs. 16.28 kg/m^2 (HUNT I)
					0.97	0.87	1.08	per 1 SD (HUNT I)
					0.97	0.74	1.26	44.32 vs. 16.28 kg/m^2 (HUNT II)
					0.95	0.83	1.09	per 1 SD (HUNT II)
Andreotti, 2010	USA	Agricultural Health Study Cohort (AgriHSC)	1274	Over 10 years	0.91	0.66	1.26	≥ 35 vs. < 18.5 kg/m^2
					1.00	0.98	1.01	Per 1 kg/m^2 increase
Burton, 2010	UK	Glasgow Alumni Cohort study	111	49 years	1.43	0.68	3.00	> 25 vs. < 19 kg/m^2
					1.02	0.93	1.11	Per 1 kg/m^2 increase of early adulthood BMI
Stocks 2010	Sweden	Swedish Construction Workers Cohort (SCWC)	10002	22.2 years	1.05	0.97	1.12	≥ 27 vs. < 21.9 kg/m^2
Hernandez, 2009	USA	Multi-ethnic Cohort Study (MEC)	5554	9.6 years	0.94	0.85	1.05	≥ 30 vs. 18.5-24.9 kg/m^2
Wallström 2009	Sweden	Malmo Diet and Cancer Cohort Study (MDC Study)	817	11 years	1.06	0.84	1.33	Obese vs. underweight
					0.90	0.72	1.13	Highest vs. lowest
Martin, 2009	Norway	North-Trondelag Health Study (HUNT II)	797	9.3 years	0.87	0.69	1.11	≥ 30 vs. < 18.5 kg/m^2
					0.98	0.91	1.06	Per 3.5 kg/m^2 increase

Gonzalez, 2009	USA	Vitamins And Lifestyle Study (VITAL)	832	3.5 years	0.89	0.72	1.09	> 30 vs. 18.5-24.9 kg/m^2
Chae, 2009	USA	CLUE II	262		0.95	0.57	1.57	≥ 30 vs. < 24.9 kg/m^2
Inoue, 2009	Japan	JPHC	119	10.2 years	0.99	0.66	1.48	Overweight (≥ 25) vs. No overweight (< 25) kg/m^2
Davey Smith, 2009	Sweden	Swedish Intergeneratio nal Mortality Study	5810	50 years	1.00	0.97	1.03	per 1 SD increase
Krishnadasa, 2008	USA	The Aerospace and Radiation Cohort	362		2.00	1.00	4.20	≥3 0 vs. < 25 kg/m^2
Pischon, 2008	Europe	European Prospective Investigation into Cancer and Nutrition (EPIC)	2446	8.5 years	0.99	0.86	1.13	≥ 29.4 vs. < 23.6 kg/m^2
					0.96	0.90	1.02	Per 5 kg/m^2 increase
Jee, 2008	Korea	Korean National Health Insurance Corporation Study (KNHIC)	2569	10.8 years	1.39	0.90	2.17	≥ 30 vs. < 20 kg/m^2

Ahn, 2008	Finland	Alpha-Tocopherol, Beta-Carotene Cancer Prevention (ATBC) Study	1111	12.3 years	2.00	1.30	3.07	> 27.6 kg/m^2 and with family history of prostate cancer vs. < 24.6 kg/m^2 and without family history
Giovannucci, 2007	USA	Health Professionals Follow-up cohort Study (HPFS)	3544	673706 Person-years	1.02	0.76	1.36	Highest vs. lowest for organ confined prostate cancer
					0.91	0.48	1.72	Highest vs. lowest for minimally extraprostatic prostate cancer
					1.34	0.79	2.26	Highest vs. lowest for advanced prostate cancer
Littman, 2007	USA	Vitamins And Lifestyle Study (VITAL)	832		0.87	0.71	1.10	≥ 30 vs. < 25 kg/m^2
Lundqvist, 2007	Sweden, Finland	Sweden, Finland Co-twin study	1283	25.2 years	0.90	0.60	1.30	≥ 30 vs. 18.5-24.9 kg/m^2 (older cohort)
					1.00	0.98	1.02	Per 1 kg/m^2 increase (older cohort)
					1.30	0.70	2.20	≥ 30 vs. 18.5-24.9 kg/m^2 (younger cohort)

					1.00	0.97	1.04	Per 1 kg/m^2 increase (younger cohort)
Rodriguez, 2007	USA	Cancer Prevention Study II Nutrition Cohort Study (CPS II)	5252	11 years	0.91	0.75	1.12	≥ 35 vs. < 25 kg/m^2
Wright, 2007	USA	National Institutes of Health-AARP Diet and Health Study	9986	5 years	0.65	0.50	0.85	≥ 40 vs. < 25 kg/m^2
Gonzalez, 2007	USA	VITamins And Lifestyle (VITAL) Cohort Study	832	3.3 years	0.89	0.72	1.09	≥ 30 vs. 18.5-24.0 kg/m^2
Fujino, 2007	Japan	Japan Collaborative Cohort Study (JACC)	160		0.87	0.12	6.29	≥ 30 vs. < 18.5 kg/m^2
Kurahashi, 2006	Japan	Japan Public Health Centre-based Prospective Study (JPHC I and II)	311		1.24	0.92	1.67	≥ 25.0 vs. ≤ 21.9 kg/m^2
Gong, 2006	USA	Prostate Cancer Prevention Trial (PCPT)	1936		0.96	0.83	1.10	≥ 30 vs. < 25 kg/m^2
Lund Håheim, 2006	Norway	Oslo follow up study (Olso study)	507	27 years	1.02	1.00	1.06	Per 1 kg/m^2 increase
Tande, 2006	USA	ARIC Study	385	12.1 years	1.14	0.86	1.51	≥ 29.8 vs. ≤ 24.6 kg/m^2
Baillargeon, 2006	USA	San Antonio Center for Biomarkers of Risk of Prostate Cancer Cohort Study (SABOR study)	125	1.43 years	0.72	0.36	1.47	≥ 30 vs. < 25 kg/m^2

Lukanova, 2006	Sweden	Northern Sweden Health and Disease Cohort (NSHDC)	461	8.2 years	0.78	0.55	1.08	≥ 30 vs. 18.5-24.9 kg/m^2
Samanic, 2006	Sweden	Swedish Construction Workers Cohort (SCWC)	6691	19 years	1.09	0.99	1.19	≥ 30 vs. 25-29 kg/m^2
Rapp 2005	Austria	VHM&PP Study Cohort	1138	9.63 years	0.73	0.39	1.37	≥ 35 vs. 18.5-24.9 kg/m^2
Fitzpatrick 2001	USA	Cardiovascular Health Study	209	5.6 years	1.05	1.02	1.09	Per 1 kg/m^2
Severson 1988	USA	Hawaii, USA 1965-1968	174		1.33	0.92	1.92	≥ 25 vs. ≤ 22.49 kg/m^2

Table 255 Overall evidence on BMI and prostate cancer

	Summary of evidence
2005 SLR	Seventy three publications were identified during the 2005 SLR and a further two publications (Fitzpartick et al 2001; Severson et al, 1988) were found missing from this search. Thirty five studies (34 estimates) were included in the meta-analysis. Overall, no significant association was found. Thirteen studies reported a statistically non-significant inverse association; 16 studies reported a positive association, of which two were borderline significant associations and three were significant associations; and five studies reported no significant association.
Continuous Update Project	Thirty two studies from 39 publications were identified during the CUP. Overall, 45 studies were included in the meta-analysis. Five studies reported significant associations. The CUP meta-analysis found significant positive associations for advanced and high grade cancers.

Table 256 Summary of results of the dose response meta-analysis of BMI and prostate cancer

Prostate cancer		
	2005 SLR	CUP
Studies (n)	35	45
Cases (n)	58317	91486
Increment unit used	Per 5 kg/m^2	Per 5 kg/m^2
Overall RR (95% CI)	1.00 (0.99-1.01)	1.00 (0.98-1.03)
Heterogeneity (I^2, p-value)	67.0%, p < 0.01	64.0%, p < 0.01
Stratified analyses		
Total prostate cancer		
Overall RR (95% CI)		1.00 (0.97-1.03)
Heterogeneity (I^2, p-value)		67.3%, p < 0.01, n = 39
Fatal cancer		
Overall RR (95% CI)		1.11 (1.06-1.17)
Heterogeneity (I^2, p-value)		19.6%, p = 0.25, n = 12
Advanced/high grade cancer/fatal		
Overall RR (95% CI)	0.99 (0.96-1.01)	1.08 (1.04-1.12)
Heterogeneity (I^2, p-value)	0%, p = 0.57, n = 2	18.8%, p = 0.21, n = 23
Non-advanced/low grade cancer		
Overall RR (95% CI)		0.95 (0.92-0.98)
Heterogeneity (I^2, p-value)		37.8%, p = 0.08, n = 14
High grade cancer		
Overall RR (95% CI)		1.08 (1.01-1.15)
Heterogeneity (I^2, p-value)		16.7%, p = 0.31, n = 6
Low grade cancer		
Overall RR (95% CI)		0.93 (0.89-0.97)
Heterogeneity (I^2, p-value)		31.8%, p = 0.22, n = 4

Table 257 Inclusion/exclusion table for meta-analysis of BMI and prostate cancer

WCRF code	Author	Year	Study design	Study name	Cancer outcome	2005 SLR	CUP dose-response meta-analysis	CUP HvL forest plot	Estimated values	Exclusion reasons/remarks
PRO100186	van Kruijsdijk	2013	Prospective Cohort study in patients with manifest vascular disease	Second Manifestations of ARTerial disease (SMART) Study	Incidence	No	Yes	No		Dose-response results only
PRO100149	Lin	2013	Prospective Cohort study	National Health and Nutrition Examination Survey (NHANES III)	Mortality	No	No	Yes		Excluded from dose-response analysis - missing cases and non-cases per category
PRO100117	Shafique	2012a	Prospective Cohort study	Midspan study	Incidence, all and advanced/high grade cancers	No	Yes	Yes	Number of non-cases for categories, mid-exposure values	
PRO100136	Shafique	2012 b	Prospective Cohort study	The Collaborative Cohort Study	Incidence	No	No	No		Duplicate publication; component study of Midspan Studies Shafique 2012 (PRO100117); superseded
PRO100163	Bassett	2012	Prospective Cohort study	The Melbourne collaborative cohort study (MCCS)	Mortality and incidence, all, advanced/high grade,	No	Yes	Yes	Mid-exposure values; used the Hamling method to recalculate RRs with the lowermost category as reference for the non-	

					fatal cancers				linear analysis	
PRO100102	Discacciati	2011	Prospective Cohort Study	Va¨stmanland and O¨rebro, Sweden	Incidence, all, advanced/high grade, fatal cancers	No	Yes	Yes	Used the Hamling method to recalculate RRs with the lowermost category as reference for the non-linear analysis	Pooled results on advanced/localised prostate cancers for total prostate cancer
PRO100105	Grundmark	2011	Prospective Cohort Study	Uppsala Longitudinal Study of Adult Men (ULSAM)	Incidence	No	No	No		Unadjusted results
PRO100109	Dehal	2011	Prospective Cohort Study	Nutrition Examination Survey Epidemiology Follow-Up Study (NHEFS)	Mortality	No	Yes	Yes	Mid-exposure values	NHEFS is a follow-up study of NHANES I
PRO100170	Batty	2011	Prospective Cohort Study	Whitehall study	Mortality	No	Yes	Yes	Mid-exposure values; used the Hamling method to recalculate RRs with the lowermost category as reference for the non-linear analysis	
PRO100172	Chamberlain	2011	Prospective Cohort Study	North-Trondelag Health Study (HUNT I&II)	Incidence	No	No	No		Duplicate publication; superseded by Martin et al, 2009 (PRO100050) with more sufficient data
PRO100081	Andreotti	2010	Prospective Cohort Study	Agricultural Health Study Cohort (AgriHSC)	Incidence	No	Yes	Yes	Mid-exposure values	
PRO100083	Burton	2010	Prospective Cohort Study	Glasgow Alumni Cohort study	Mortality	No	No	No		BMI at early adulthood (a previous published

										article on the same study was used by 2005 SLR Okasha 2002 PRO00729)
PRO100193	Stocks	2010	Prospective Cohort Study	Swedish Construction Workers Cohort (SCWC)	Incidence, all, advanced/high grade, and fatal cancers	No	Yes	Yes	Mid-exposure values	
PRO100072	Hernandez	2009	Prospective Cohort Study	Multi-ethnic Cohort Study (MEC)	Incidence, all and advanced/high grade cancers	No	Yes	Yes	Mid-exposure values; used the Hamling method to recalculate RRs with the lowermost category as reference for the non-linear analysis	
PRO100047	Wallström	2009	Prospective Cohort Study	Malmo Diet and Cancer Cohort Study (MEC study)	Incidence	No	No	No		Duplicate publication; component study of Pischon et al, 2008 (PRO100036)
PRO100050	Martin	2009	Prospective Cohort Study	North-Trondelag Health Study (HUNT II)	Mortality and incidence, all and fatal cancers	No	Yes	Yes	Used the Hamling method to recalculate RRs with the lowermost category as reference for the non-linear analysis	Excluded from fatal cancer highest vs lowest plot – dose-response result only
PRO100066	Gonzalez	2009	Prospective Cohort Study	Vitamins And Lifestyle Study (VITAL)	Mortality and incidence	No	No	No		Duplicate publication; superseded by Littman et al, 2007 (PRO99973)

PRO100074	Chae	2009	Nested Case Control Study	CLUE II	Incidence	No	Yes	Yes	Mid-exposure values	
PRO100128	Inoue	2009	Prospective Cohort Study	Japan Public Health Centre-based Prospective Study (JPHC)	Incidence	No	No	No		Duplicate publication; superseded by Kurahashi et al, 2006 (PRO99964)
PRO100142	Davey Smith	2009	Prospective Cohort Study	Swedish Intergenerational Mortality Study	Mortality	No	No	No		Offspring conscription BMI
PRO100016	Krishnadasa	2008	Nested Case Control Study	The Aerospace and Radiation Cohort	Incidence	No	Yes	Yes	Mid-exposure values	
PRO100036	Pischon	2008	Prospective Cohort Study	European Prospective Investigation into Cancer and Nutrition (EPIC)	Mortality and incidence, all and advanced/high grade cancers	No	Yes	Yes		
PRO100133	Jee	2008	Prospective Cohort Study	Korean National Health Insurance Corporation Study (KNHIC)	Incidence	No	Yes	Yes	Mid-exposure values; used the Hamling method to recalculate RRs with the lowermost category as reference for the non-linear analysis	
PRO100022	Ahn	2008a	Prospective Cohort Study	Alpha-Tocopherol, Beta-Carotene Cancer Prevention (ATBC) Study	Incidence	No	No	No		Interaction between BMI and family history of cancer

PRO99961	Giovannucci	2007	Prospective Cohort Study	Health Professionals Follow-up Study (HPFS)	Incidence, all and advanced/high grade cancers	No	No	Yes		Duplicate publication; missing 95% CIs in all categories except for the uppermost category
PRO99973	Littman	2007	Prospective Cohort Study	Vitamins And Lifestyle Study (VITAL)	Mortality and incidence, all and advanced/high grade cancers	No	Yes	Yes	Mid-exposure values	
PRO100018	Lundqvist	2007	Prospective Cohort Study	Sweden, Finland Co-twin study	Mortality and incidence	No	Yes	Yes	Used the Hamling method to recalculate RRs with the lowermost category as reference for the non-linear analysis	Pooled results from the older and younger cohorts by a fixed-effect model; article also provided results from a co-twin control analysis
PRO99974	Rodriguez	2007	Prospective Cohort Study	Cancer Prevention Study II Nutrition Cohort Study (CPS II)	Mortality and incidence, all and advanced/high grade cancers	No	Yes	Yes	Mid-exposure values	
PRO100004	Wright	2007	Prospective Cohort Study	National Institutes of Health-AARP Diet and Health Study	Mortality and incidence, all, advanced/high grade, fatal cancers	No	Yes	Yes	Mid-exposure values	
PRO100035	Gonzalez	2007	Prospective Cohort Study	VITamins And Lifestyle (VITAL) Cohort Study	Mortality and incidence	No	No	No		Duplicate publication; superseded by

										Littman et al, 2007 (PRO99973)
PRO100130	Fujino	2007	Prospective Cohort Study	Japan Collaborative Cohort Study (JACC)	Mortality	No	Yes	Yes	Mid-exposure values; used the Hamling method to recalculate RRs with the lowermost category as reference for the non-linear analysis	
PRO99964	Kurahashi	2006	Prospective Cohort Study	Japan Public Health Centre-based Prospective Study (JPHC I and II)	Incidence, all and advanced/high grade cancers	No	Yes	Yes	Mid-exposure values	
PRO99985	Gong	2006	Observational study in a RCT follow-up	Prostate Cancer Prevention Trial (PCPT)	Incidence, all and advanced/high grade cancers	No	Yes	Yes	Cases and non-cases per quartile, mid-exposure values	
PRO100038	Lund Håheim	2006	Prospective Cohort Study	Oslo follow up study (Olso study)	Incidence	No	No	No		Duplicate publication; component study of Thune et al, 1994 (PRO02744)
PRO100041	Baillargeon	2006	Nested Case Control Study	San Antonio Center for Biomarkers of Risk of Prostate Cancer Cohort Study (SABOR study)	Incidence, all and advanced/high grade cancers	No	Yes	Yes	Mid-exposure values	
PRO100035	Lukanova	2006	Prospective Cohort Study	Northern Sweden Health and Disease Cohort (NSHDC)	Incidence	No	Yes	Yes	Mid-exposure values	

PRO100141	Samanic	2006	Prospective Cohort Study	Swedish Construction Workers Cohort (SCWC)	Incidence	No	No	No		Duplicate publication; superseded by Stocks 2010 (PRO100193)
PRO100194	Tande	2006	Prospective Cohort study	ARIC Study	Incidence	No	Yes	Yes	Mid-exposure values	
PRO100183	Rapp	2005	Prospective Cohort Study	VHM&PP Cohort Study	Incidence	No	Yes	Yes	Mid-exposure values	
PRO97481	Hultdin	2005	Case Cohort Study	VIP and MONICA	Incidence	Yes	No	No		Duplicate publication; mean exposure only; overlapped and superseded by Lukanova et al, 2006 (PRO100035)
PRO97881	Bradbury	2005	Nested Case Control Study	GPRD, UK study	Incidence	Yes	Yes	Yes	Mid-exposure values; used the Hamling method to recalculate RRs with the lowermost category as reference for the non-linear analysis	

PRO97224	King	2005	Nested Case Control Study	Beta-Carotene and Retinol Efficacy Trial **(**CARET)	Incidence	Yes	No	No		Number of cases and non-cases per category only
PRO97166	Meyer	2005	Prospective Cohort Study	SU.VI.MAX Trial	Incidence	Yes	No	Yes		Only high vs. low results are shown
PRO97288	Eichholzer	2005	Prospective Cohort Study	Basel Prospective Study	Mortality	Yes	Yes	No		Excluded from all highest vs lowest plots - dose-response results only
PRO99269	Kuriyama	2005	Prospective Cohort Study	Japan 1984	Incidence	Yes	Yes	Yes	Mid-exposure values	
PRO97424	Weinstein	2005	Case-cohort Study	Alpha-Tocopherol, Beta-Carotene Cancer Prevention (ATBC) Study	Incidence	Yes	No	No		Duplicate publication; mean exposure only, superseded by Ahn et al, 2008 (PRO100022)

PRO97149	Oh	2005	Prospective Cohort Study	Korean National Health Insurance Corporation Study (KNHIC)	Incidence	Yes	No	No		Duplicate publication; superseded by Jee et al, 2008 (PRO100133)
PRO03999	Wu	2004	Nested Case Control Study	Health Professionals Follow-Up Study (HPFS)	Mortality and incidence	Yes	No	No		Duplicate publication; superseded by Giovannucci et al, 2007 (PRO99961); cases and non-cases per BMI category only
PRO04004	Ozasa	2004	Nested Case Control Study	Japan Collaborative Cohort Study (JACC)	Mortality and incidence	Yes	No	No		Duplicate publication; results in text only – no significant association; superseded by Fujino, 2007 (PRO100130)
PRO10700	Platz	2004 b	Nested Case Control Study	CLUE II	Incidence	Yes	No	No		Duplicate publication; mean exposure only; superseded by Chae et al, 2009 (PRO100074)
PRO10575	Platz	2004c	Nested Case Control Study	Health Professionals Follow-Up Study (HPFS)	Mortality and incidence	Yes	No	No		Duplicate publication; mean exposure only, superseded by Giovannucci et al, 2007 (PRO99961)

PRO10545	Li	2004	Nested Case Control Study	Physician Health Study (PHS)	Incidence	Yes	No	No		Duplicate publication; mean exposure only; superseded by Zhu et al, 2004 (PRO97715)
PRO97049	Cui	2004	Nested case-Control Study	The National Health and Nutrition Examination Survey (NHANES III)	Incidence and prevalence	Yes	No	No		Duplicate publication; superseded by Lin, 2013 (PRO100149)
PRO97367	Allen	2004	Prospective Cohort Study	Life Span Study (LSS)	Incidence	Yes	Yes	Yes	Mid-exposure values	
PRO97667	Jacobs	2004	Nested Case Control Study	Nutritional Prevention of Cancer Trial (NPCT)	Incidence	Yes	No	No		Mean exposure only
PRO97676	Laaksonen	2004	Prospective Cohort Study	Kuopio Ischaemic Heart Disease Risk Factor Study (KIHDRFS)	Incidence	Yes	No	No		Mean exposure only

PRO97715	Zhu	2004	Case Cohort Study	Physician Health Study (PHS)	Incidence	Yes	No	No		Mean exposure only
PRO97316	Stattin	2004	Case Cohort Study	Northern Sweden Health and Disease Cohort (NSHDC)	Incidence	Yes	No	No		Duplicate publication; mean exposure only; overlapped and superseded by Lukanova et al, 2006 (PRO100035)
PRO99344	Jeffreys	2004	Historical Cohort Study	Boyd Orr Cohort	Mortality and incidence	Yes	No	No		Childhood BMI
PRO00337	Giovannucci	2003a	Prospective Cohort Study	Health Professionals Follow-up Study (HPFS)	Mortality and incidence	Yes	No	No		Duplicate publication; superseded by Giovannucci et al, 2007 (PRO99961)
PRO00515	Hsieh	2003	Prospective Cohort Study	Baltimore Longitudinal Study of Aging (BLSA)	Incidence and prevalence	Yes	No	No		Duplicate publication; mean exposure only; superseded by Brooks et al, 2001 (PRO01046)

PRO00302	Engeland	2003	Prospective Cohort Study	Norway 1963-1975	Mortality and incidence	Yes	Yes	Yes	Person-years per category; mid-exposure values; used the Hamling method to recalculate RRs with the lowermost category as reference for the non-linear analysis	
PRO00373	Jonsson	2003	Prospective Cohort Study	Swedish Twin Cohort 1886-1925	Mortality and incidence	Yes	No	No		Duplicate publication; component study of Lundqvist et al, 2007 (PRO100018)
PRO04077	MacInnis	2003	Prospective Cohort Study	Melbourne Collaborative Cohort Study (MCCS)	Incidence	Yes	No	No		Duplicate publication; superseded by Bassett et al, 2012 (PRO100163)
PRO00442	Alavanja	2003	Prospective Cohort Study	Agricultural Health Study Cohort (AgriHSC)	Incidence	Yes	No	No		Duplicate publication; no exposure values; superseded by Andreotti et al, 2010 (PRO100081)
PRO00448	Calle	2003	Prospective Cohort Study	Cancer Prevention Study (CPS II)	Mortality	Yes	Yes	No		Duplicate publication; prostate cancer deaths only (included in the prostate cancer mortality dose-response analysis and highest vs lowest plot); Rodriguez 2007 (PRO99974) was

										used in the total prostate cancer analysis and advanced/high grade/fatal cancers
PRO00272	Woodson	2003	Nested Case Control Study	Alpha Tocopherol Beta Carotene Cancer Prevention (ATBC)	Mortality and incidence	Yes	No	No		Duplicate publication; mean exposure only; superseded by Ahn et al, 2008 (PRO100022)
PRO00142	Kilkkinen	2003	Nested Case Control Study	Alpha Tocopherol Beta Carotene Cancer Prevention (ATBC)	Mortality and incidence	Yes	No	No		Duplicate publication; mean exposure only Superseded by Ahn et al, 2008 (PRO100022)
PRO00451	Lamharzi	2003	Nested Case Control Study	Beta-Carotene and Retinol Efficacy Trial (CARET)	Incidence	Yes	No	No		Duplicate publication; mean exposure only; superseded by King et al, 2005 (PRO97224)
PRO00526	Huang	2003	Nested Case Control Study	CLUE II	Incidence	Yes	No	No		Duplicate publication; superseded by Chae et al, 2009 (PRO100074)

PRO04076	Männistö	2003	Nested Case Control Study	Alpha Tocopherol Beta Carotene Cancer Prevention (ATBC)	Mortality and incidence	Yes	No	No		Duplicate publication; mean exposure only Superseded by Ahn et al, 2008 (PRO100022)
PRO00964	Wolinsky	2002	Prospective Cohort Study	Longitudinal Study on Aging (LSA)	Incidence and prevalence	Yes	No	Yes		Highest vs. lowest results only
PRO00755	Platz	2002	Nested Case Control Study	CLUE II	Incidence	Yes	No	No		Duplicate publication; mean exposure only; superseded by Chae et al, 2009 (PRO100074)
PRO00729	Okasha	2002	Historical Cohort Study	Glascow Alumni Cohort Study	Mortality	Yes	No	No		Duplicate publication; BMI at early adulthood (new article from the same study published by Burton et al, 2010 PRO100083)
PRO01034	Hirvonen	2001	Prospective Cohort Study	Alpha Tocopherol Beta Carotene Cancer Prevention (ATBC)	Mortality and incidence	Yes	No	No		Duplicate publication; mean exposure only Superseded by Ahn et al, 2008 (PRO100022)

PRO01232	Rodriguez	2001	Prospective Cohort Study	Cancer Prevention Study (CPS I & II)	Mortality	Yes	Yes	Yes	Mid-exposure values; used the Hamling method to recalculate RRs with the lowermost category as reference for the non-linear analysis	CPS I included in the analysis; CPS II superseded by Calle, 2003 (PRO00448)
PRO01290	Lee	2001	Prospective Cohort Study	Harvard Alumni Health Study 1962-1966	Mortality and incidence	Yes	Yes	Yes	Mid-exposure values	
PRO01094	Gapstur	2001	Prospective Cohort Study	The Chicago Heart Association Detection Project in Industry Cohort (CHAC)	Mortality	Yes	Yes	Yes		
PRO01046	Brooks	2001	Nested Case Control Study	Baltimore Longitudinal Study of Aging (BLSA)	Incidence	Yes	No	No		Mean exposure only
PRO01299	Stattin	2001	Nested Case Control Study	VIP and MONICA	Incidence	Yes	No	No		Duplicate publication; mean exposure only; overlapped and superseded by Lukanova et al, 2006 (PRO100035)

PRO100192	Fitzpatrick	2001	Prospective Cohort Study	Cardiovascular Health Study (CHS)	Incidence	No	Yes	No		Missed in the 2005 SLR; dose-response results only
PRO01468	Clarke	2000	Prospective Cohort Study	The National Health and Nutrition Examination Survey (NHANES)	Mortality and incidence	Yes	No	No		Duplicate publication; mean exposure only Superseded by Dehal et al, 2011 (PRO100109)
PRO01599	Habel	2000	Prospective Cohort Study	California, USA 1964-1973	Incidence	Yes	Yes	Yes	Cases and non-cases per quintile; mid-exposure values	
PRO01467	Nomura	2000	Nested Case Control Study	Honolulu Heart Program (HHP)	Incidence	Yes	No	No		Mean exposure only
PRO01379	Helzlsouer	2000	Nested Case Control Study	CLUE II	Incidence	Yes	No	No		Duplicate publication; superseded by Chae 2009 PRO100074

PRO13420	Persson-Moschos	2000	Nested Case Control Study	Sweden 1974-1982	Incidence	Yes	No	No		Mean exposure only
PRO01612	Schuurman	2000	Nested Case Control Study	Netherland Cohort Study (NLCS)	Incidence, all and advanced/high grade cancers	Yes	Yes	Yes		Excluded from advanced/high grade cancers highest vs lowest plot – dose-response result only
PRO01487	Putnam	2000	Prospective Cohort study	IW, USA 1986-1989	Incidence, all and advanced/high grade cancers	Yes	Yes	Yes	Mid-exposure values	
PRO01688	Lund Nilsen	1999	Prospective Cohort study	Norway 1984-1986/HUNT 1	Mortality and incidence	Yes	No	No		Duplicate publication; superseded by Martin et al, 2009 (PRO100050)
PRO01820	Gann	1999	Nested Case Control Study	Physician Health study (PHS)	Incidence	Yes	No	No		Duplicate publication; mean exposure only Superseded by Zhu et al, 2004 (PRO97715)
PRO01720	Heikkila	1999	Nested Case Control Study	Finnish Mobile Clinic Health Examination Survey (FMCHS)	Incidence	Yes	No	No		Mean exposure only

PRO02180	Hartman	1998a	Prospective Cohort study	Alpha Tocopherol Beta Carotene Cancer Prevention (ATBC)	Incidence	Yes	No	No		Duplicate publication; mean exposure only superseded by Ahn et al, 2008 (PRO100022)
PRO02058	Yoshizawa	1998	Nested Case Control Study	Health Professionals follow-up Study (HPFS)	Mortality and incidence	Yes	No	No		Duplicate publication; mean exposure only Superseded by Giovannucci et al, 2007 (PRO99961)
PRO02143	Hartman	1998 b	Prospective Cohort study	Alpha Tocopherol Beta Carotene Cancer Prevention (ATBC)	Mortality and incidence	Yes	No	No		Duplicate publication; mean exposure only; superseded by Ahn et al, 2008 (PRO100022)
PRO02314	Giovannucci	1997	Prospective Cohort study	Health Professionals Follow-up Study (HPFS)	Mortality and incidence, all and advanced/high grade cancers	Yes	Yes	No	Mid-exposure values	With sufficient data for a dose-response meta-analysis; Giovannucci 2007 PRO99961 has more cases and was included in the highest vs. lowest meta-analysis
PRO02242	Veierod	1997	Prospective Cohort study	Norway 1977-1983	Incidence	Yes	Yes	Yes	Person-years per category; mid-exposure values	

PRO02364	Cerhan	1997	Prospective Cohort study	Iowa 65+ Rural Health Study	Incidence, all and advanced/high grade cancers	Yes	Yes	Yes	Mid-exposure values	
PRO02254	Tulinius	1997	Prospective Cohort study	Icelandic Cardiovascular Risk Factor Study (ICRFS)	Incidence	Yes	No	No		Insufficient data - no significant association (P>0.1)
PRO02328	Nomura	1997	Nested Case Control Study	Honolulu Heart Program (HHP)	Incidence	Yes	No	No		Duplicate publication; mean exposure only; superseded by Nomura 2000 (PRO01467)
PRO02418	Guess	1997	Nested Case Control Study	California, USA 1964-1971	Incidence	Yes	No	No		Duplicate publication; mean exposure only; superseded by Habel et al, 2000 (PRO01599)
PRO02391	Andersson	1997	Historical Cohort Study	Sweden 1971-1975	Mortality and incidence	Yes	No	No		Duplicate publication; superseded by Stocks et al, 2010 (PRO100193)
PRO02582	Gronberg	1996	Nested Case Control Study	Sweden 1967-1970	Incidence and prevalence	Yes	No	No		Duplicate publication; superseded by Lundqvist et al, 2007 (PRO100018)

PRO02635	Gann	1995	Prospective Cohort study	Chicago Heart Association Cohort (CHAC)	Mortality	Yes	No	No		Duplicate publication; superseded by Gapstur et al, 2001
PRO02744	Thune	1994	Prospective Cohort study	Norway 1972-1978	Incidence	Yes	Yes	No		Dose-response results only
PRO02809	Chyou	1994	Prospective Cohort study	Hawaii, USA 1965-1968	Incidence	Yes	No	No		Duplicate publication; mean exposure only; superseded by Severson 1988 (PRO03225)
PRO02788	Le Marchand	1994	Prospective Cohort study	Hawaii, USA 1975-1980	Incidence	Yes	Yes	Yes	Cases and non-cases per quartile; mid-exposure values	
PRO02822	Hiatt	1994	Prospective Cohort study	California, USA 1979-1985	Incidence	Yes	No	No		Insufficient data – no significant association

PRO02814	Gann	1994	Nested Case Control Study	Physician's Health Study (PHS)	Mortality and incidence	Yes	No	No		Duplicate publication; mean exposure only; superseded by Zhu et al, 2004 (PRO97715)
PRO03165	Barrett-Connor	1990	Prospective Cohort study	USA California 1972-1974 (Lipid Research Clinic Prevalence Study)	Mortality and incidence	Yes	No	No		Duplicate publication; mean exposure only; superseded by Thompson et al, 1989 (PRO03216)
PRO03196	Mills	1989	Prospective Cohort study	Adventist Health Study (AHS)	Incidence	Yes	Yes	Yes	Mid-exposure values	
PRO03216	Thompson	1989	Prospective Cohort study	USA California 1972-1974 (Lipid Research Clinic Prevalence Study)	Mortality, incidence and prevalence	Yes	Yes	No		Dose-response results only
PRO03225	Severson	1988	Prospective Cohort study	USA Hawaii 1965-1968	Incidence	No	Yes	Yes	Mid-exposure values	Missed in the 2005 SLR

PRO03447	Nomura	1985	Prospective Cohort study	Honolulu Heart Program (HHP)	Incidence	Yes	No	No		Duplicate publication; insufficient data – incident rates only; superseded by Nomura, 2000 (PRO01467)
PRO03451	Whittemore	1985	Nested Case Control Study	Harvard and Pennsylvania Alumni Study 1916-1950	Mortality and incidence	Yes	No	No		Insufficient data - no significant association

Figure 277 Highest versus lowest forest plot of BMI and prostate cancer

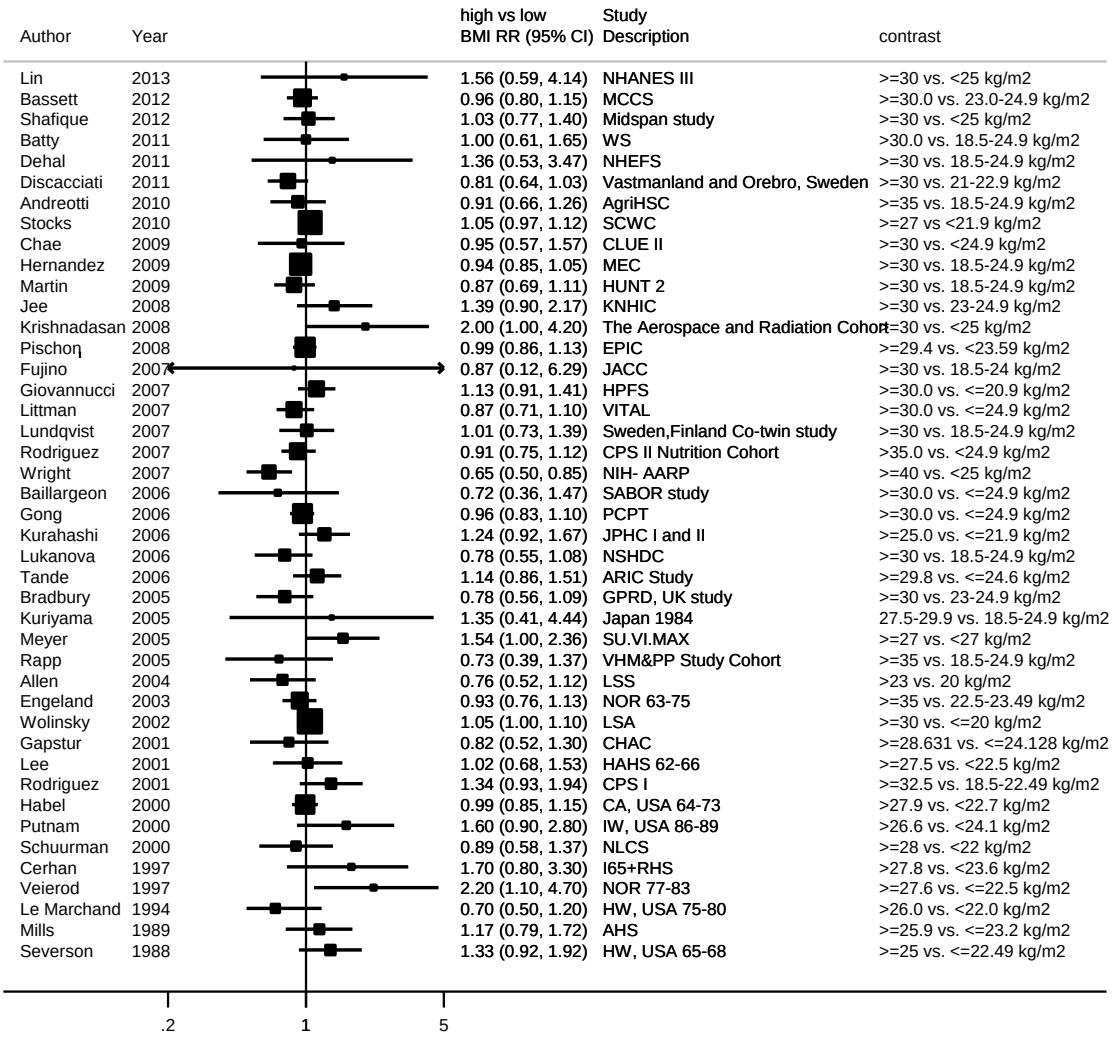


Figure 278 Dose-response meta-analysis of BMI and prostate cancer – per 5 kg/m^2

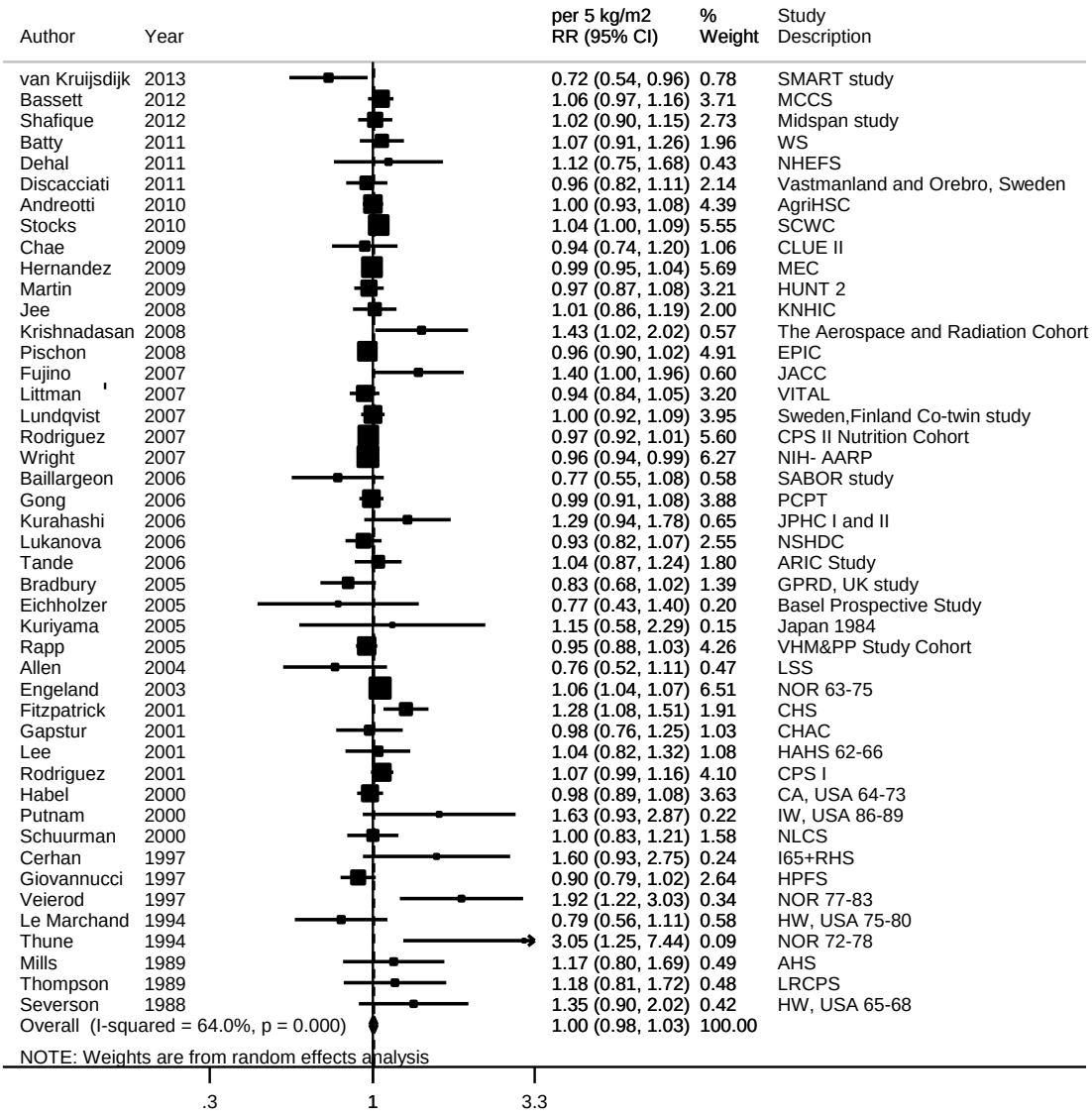
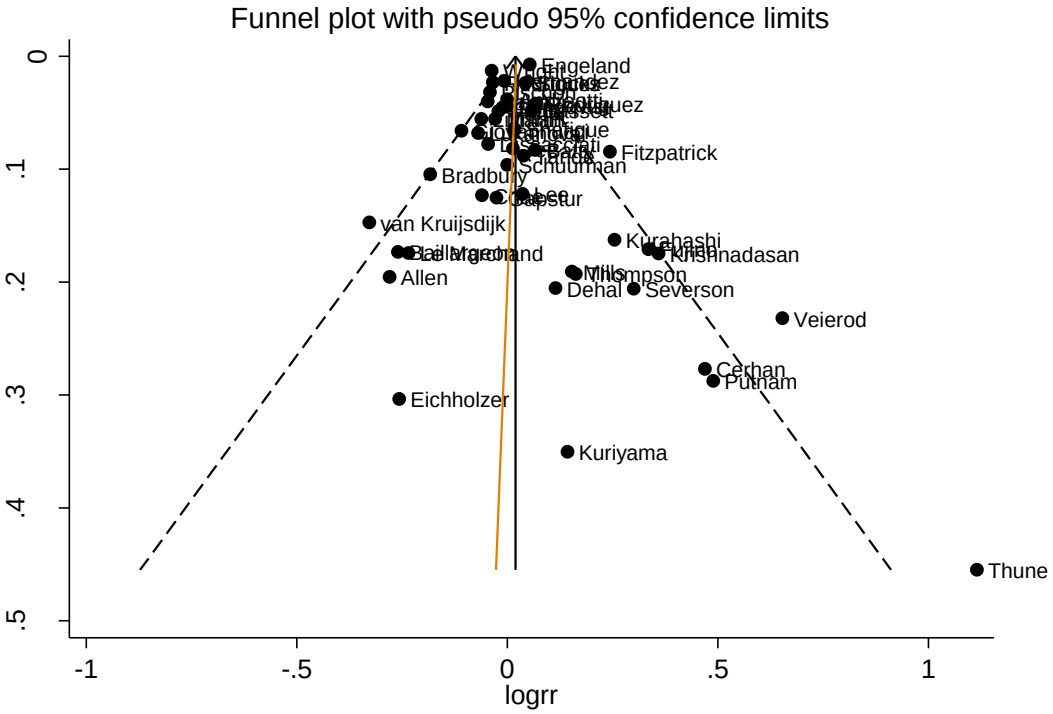
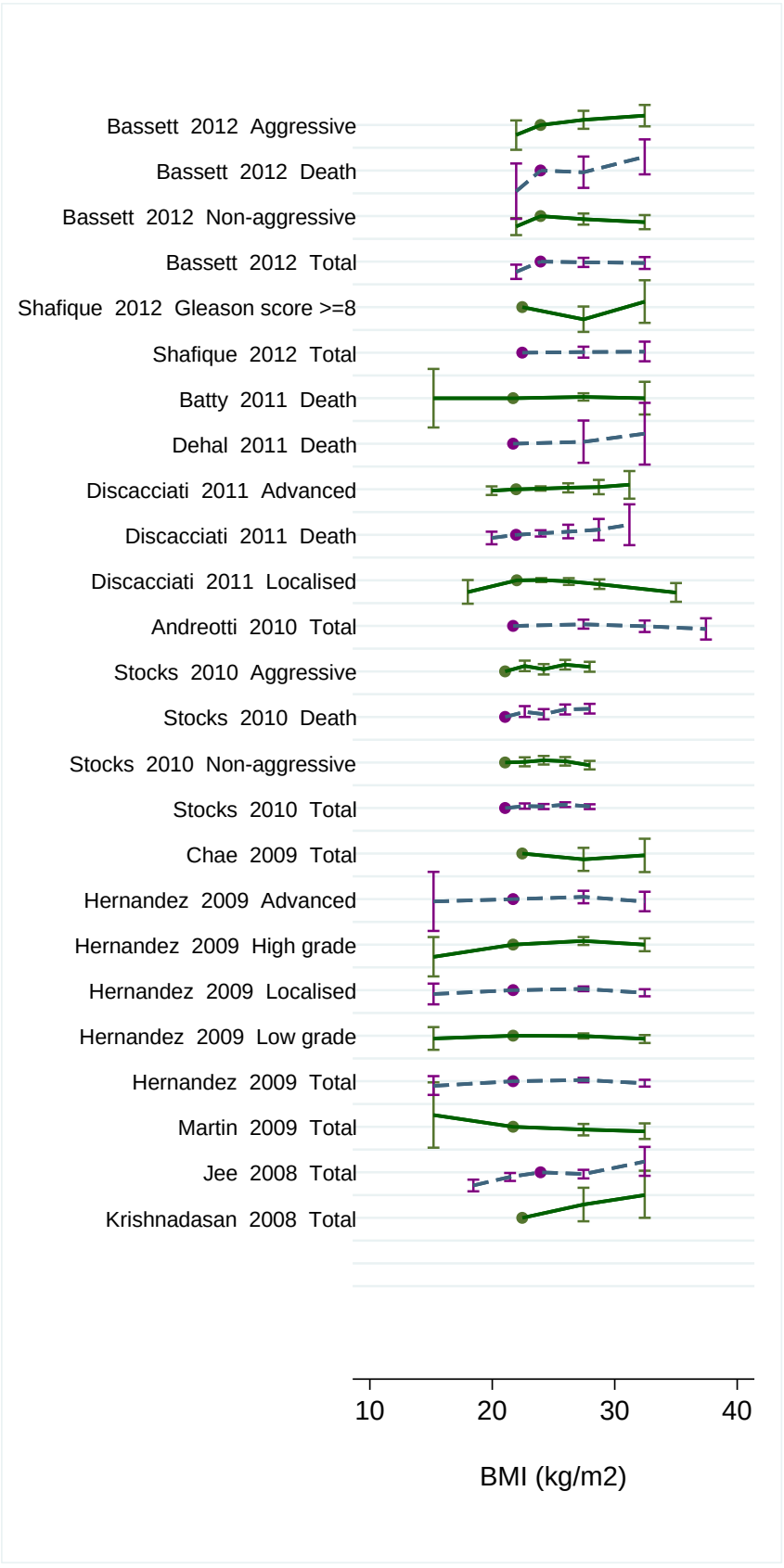


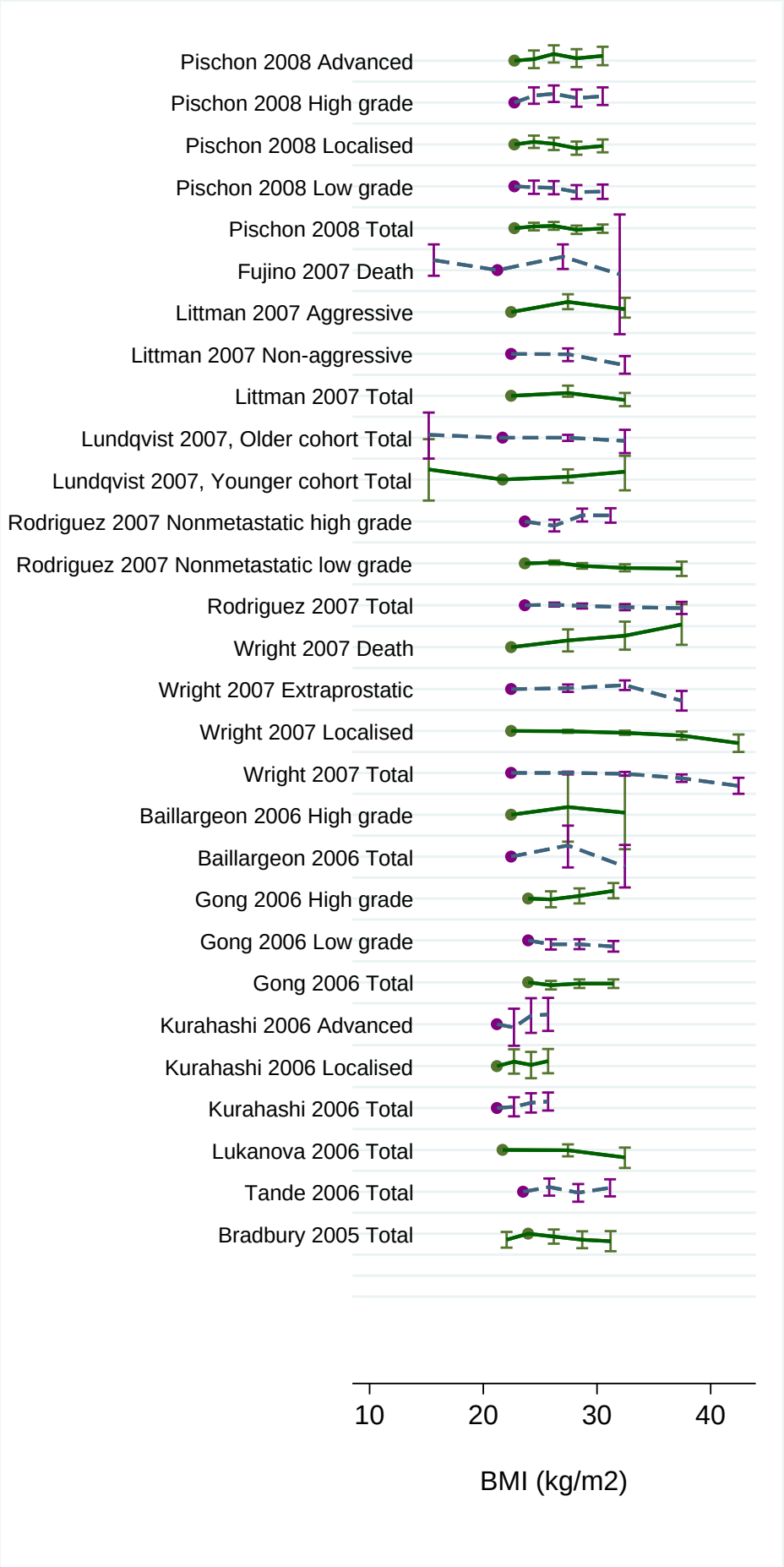
Figure 279 Funnel plot of BMI and prostate cancer



Egger's test p = 0.74

Figure 280 Dose-response graph of BMI and prostate cancer




Pischon 2008 Advanced
Pischon 2008 High grade
Pischon 2008 Localised
Pischon 2008 Low grade
Pischon 2008 Total
Fujino 2007 Death
Littman 2007 Aggressive
Littman 2007 Non-aggressive
Littman 2007 Total
Lundqvist 2007, Older cohort Total
Lundqvist 2007, Younger cohort Total
Rodriguez 2007 Nonmetastatic high grade
Rodriguez 2007 Nonmetastatic low grade
Rodriguez 2007 Total
Wright 2007 Death
Wright 2007 Extraprostatic
Wright 2007 Localised
Wright 2007 Total
Baillargeon 2006 High grade
Baillargeon 2006 Total
Gong 2006 High grade
Gong 2006 Low grade
Gong 2006 Total
Kurahashi 2006 Advanced
Kurahashi 2006 Localised
Kurahashi 2006 Total
Lukanova 2006 Total
Tande 2006 Total
Bradbury 2005 Total
10
20
30
40
BMI (kg/m2)

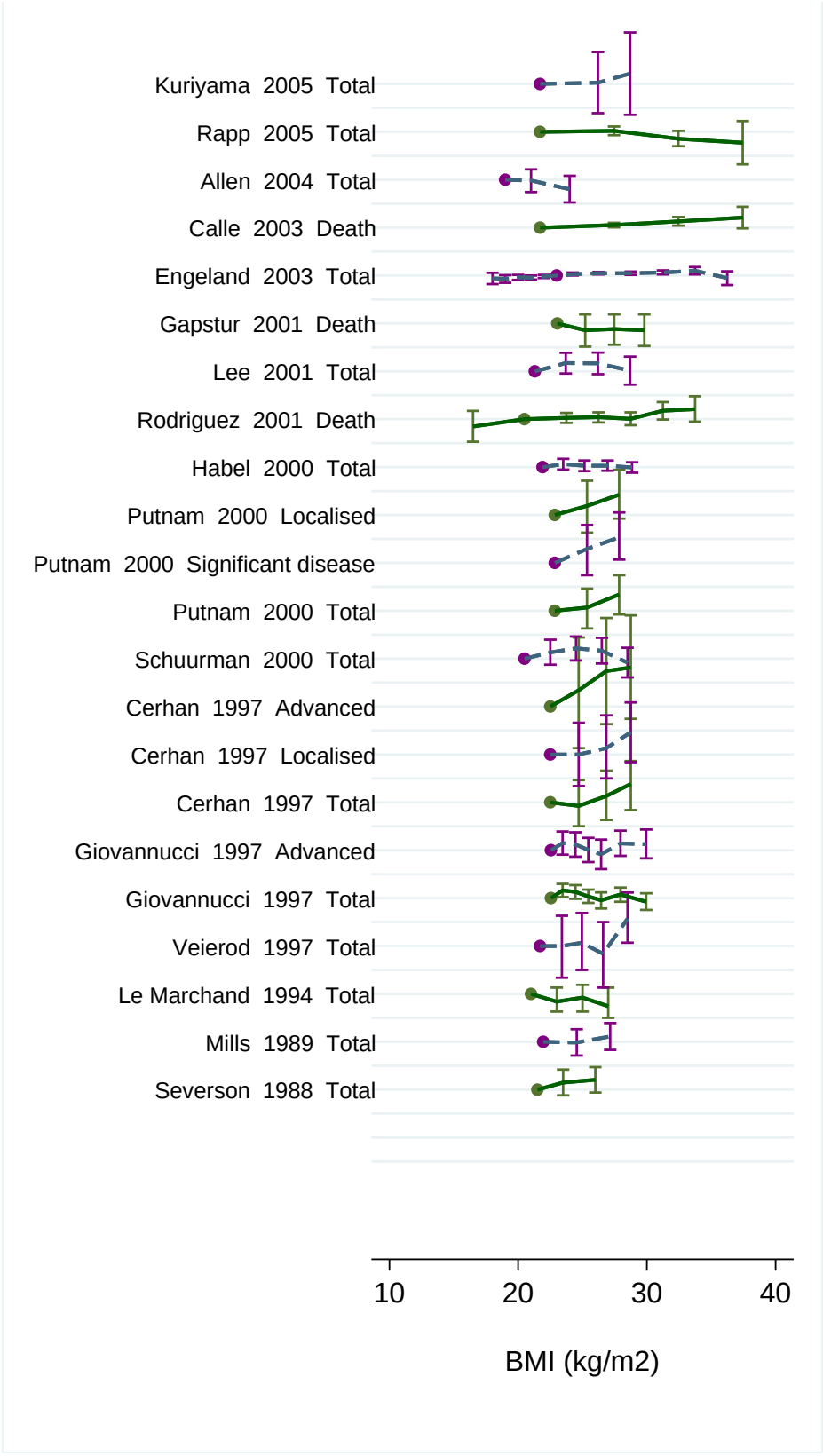

Kuriyama 2005 Total
Rapp 2005 Total
Allen 2004 Total
Calle 2003 Death
Engeland 2003 Total
Gapstur 2001 Death
Lee 2001 Total
Rodriguez 2001 Death
Habel 2000 Total
Putnam 2000 Localised
Putnam 2000 Significant disease
Putnam 2000 Total
Schuurman 2000 Total
Cerhan 1997 Advanced
Cerhan 1997 Localised
Cerhan 1997 Total
Giovannucci 1997 Advanced
Giovannucci 1997 Total
Veierod 1997 Total
Le Marchand 1994 Total
Mills 1989 Total
Severson 1988 Total
10
20
30
40
BMI (kg/m2)

Figure 281 Highest vs lowest forest plot of BMI for prostate cancer mortality

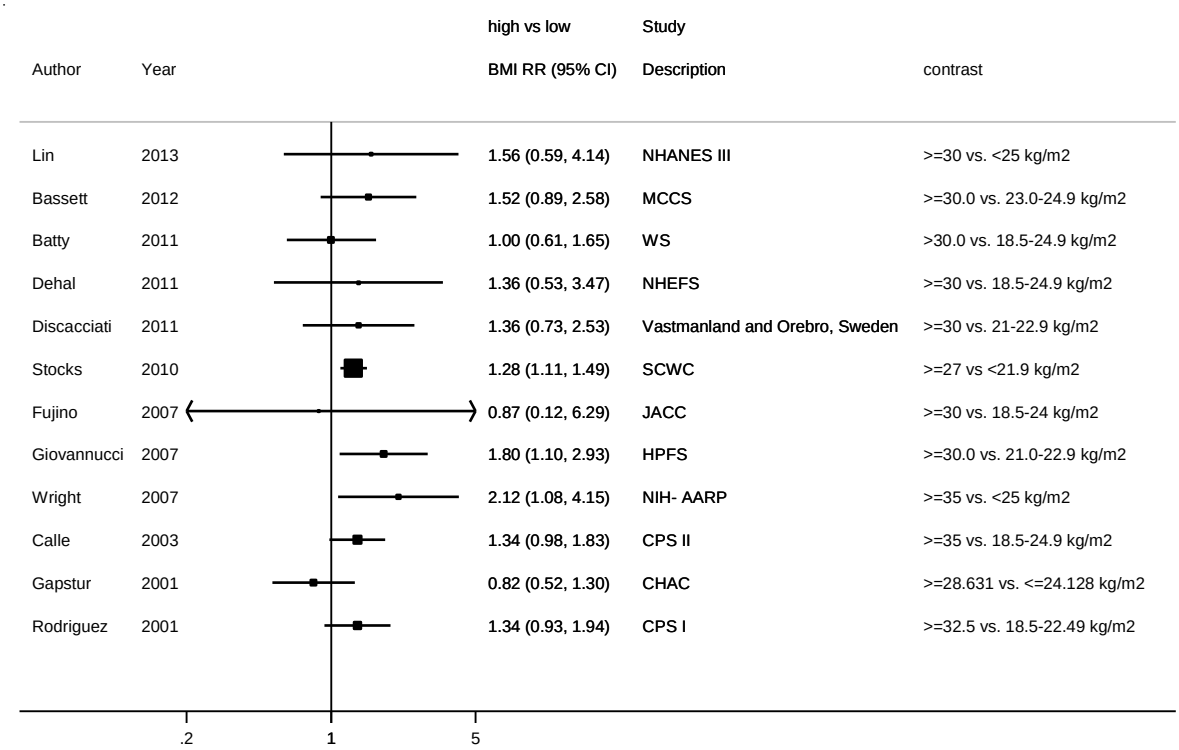


Figure 282 Dose-response meta-analysis of BMI and prostate cancer mortality – per 5 kg/m^2

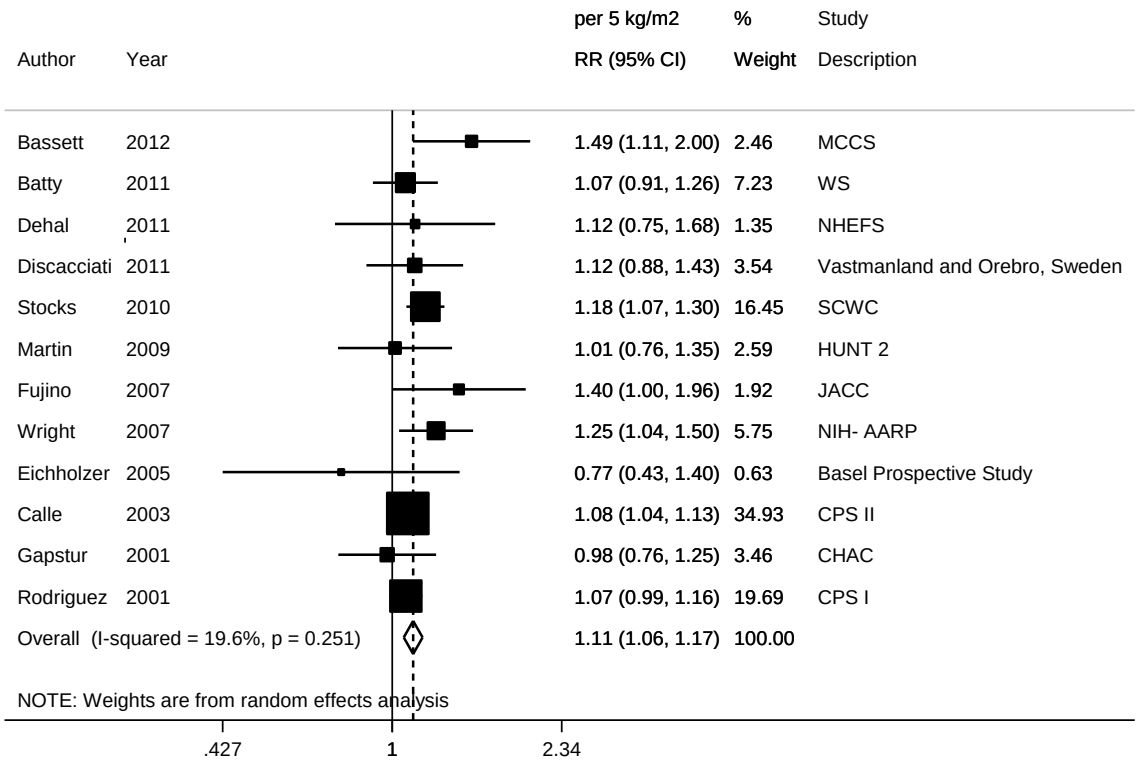


Figure 283 Dose-response meta-analysis of BMI and total prostate cancer (excluding studies on mortality) - per 5 kg/m^2

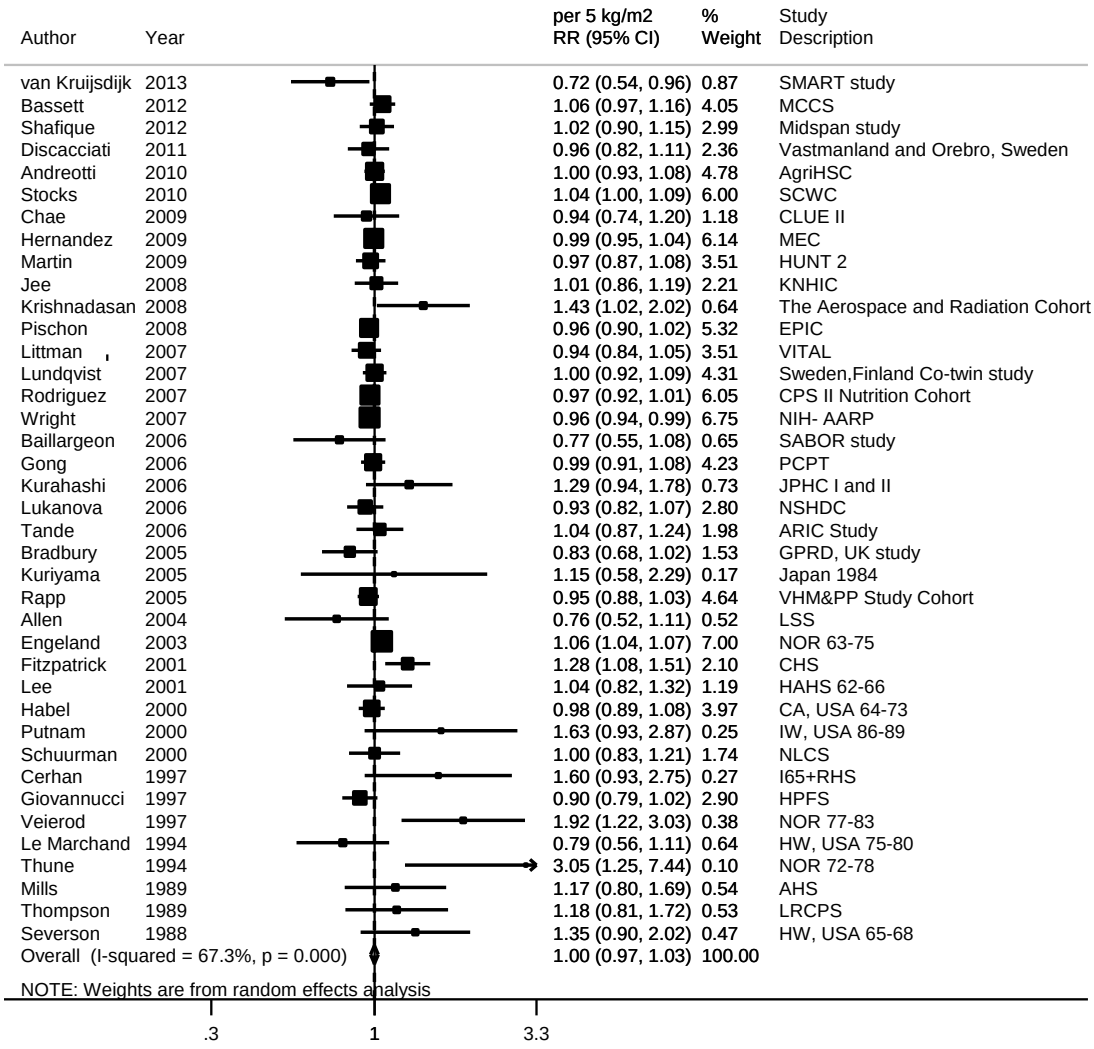


Figure 284 Highest vs lowest forest plot of BMI for advanced/high-grade/fatal prostate cancer

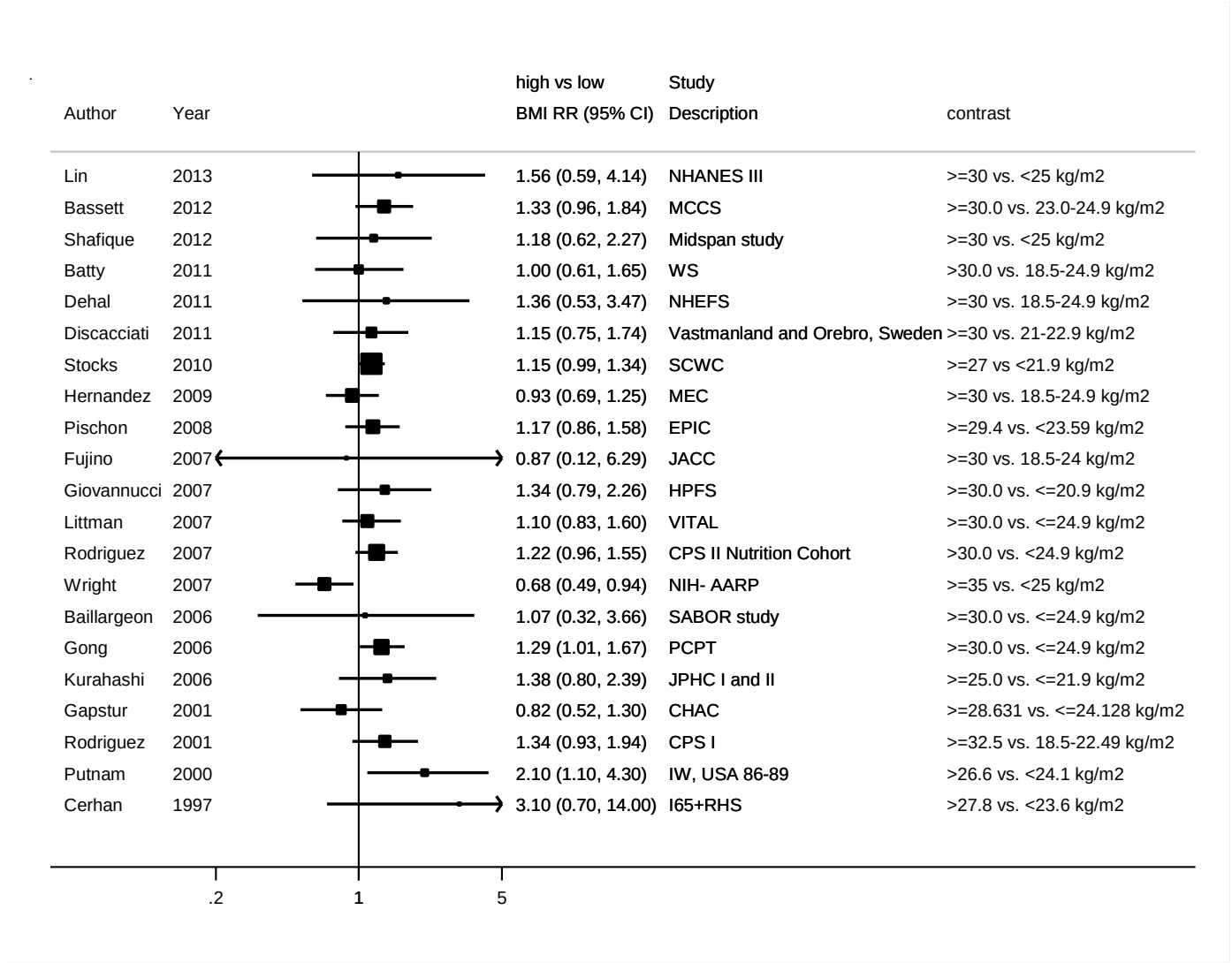


Figure 285 Dose-response meta-analysis of BMI and advanced/high grade/fatal and non-advanced prostate cancer – per 5 kg/m^2

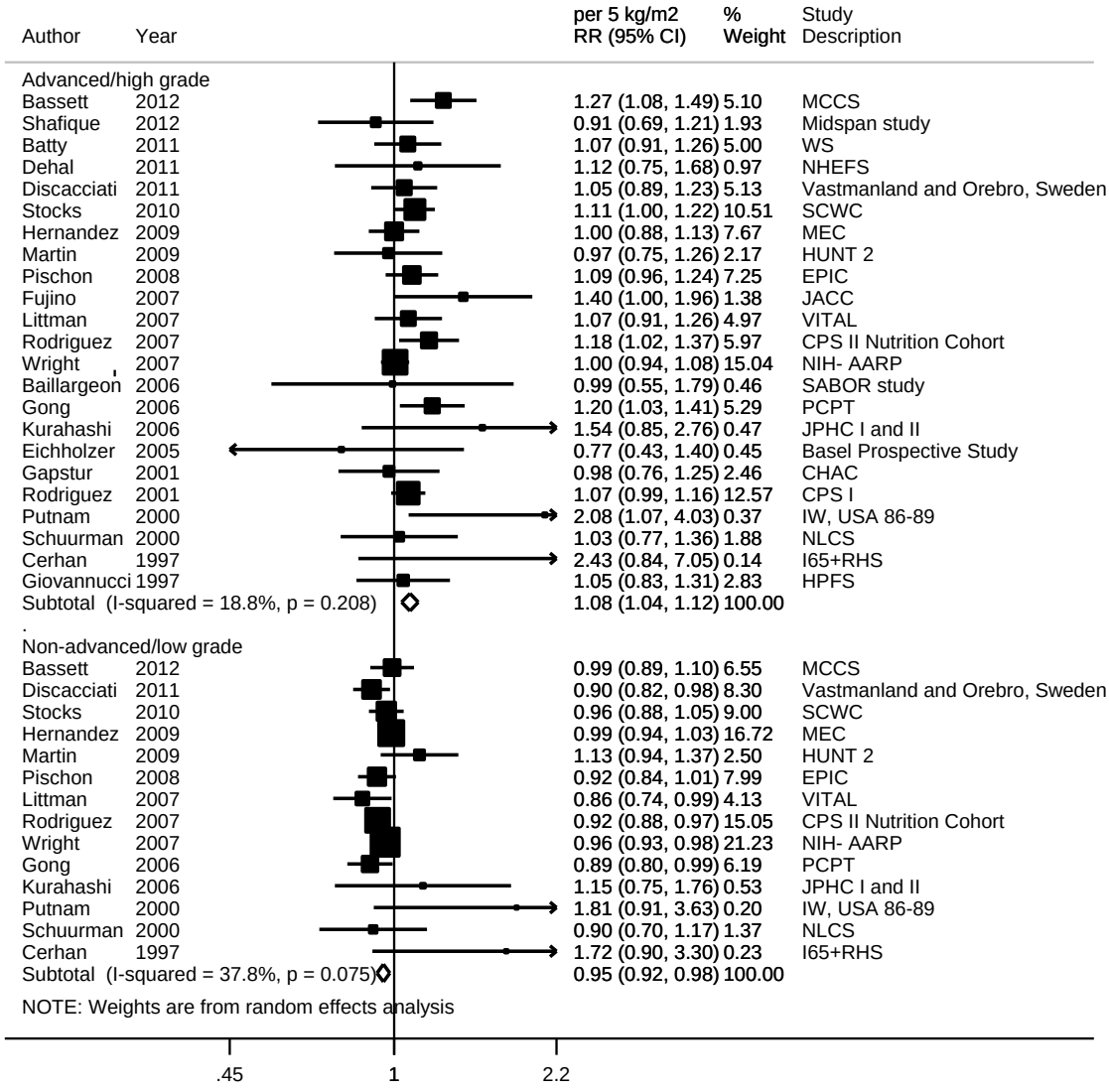


Figure 286 Dose-response meta-analysis of BMI and high/ low grade prostate cancer – per 5 kg/m^2

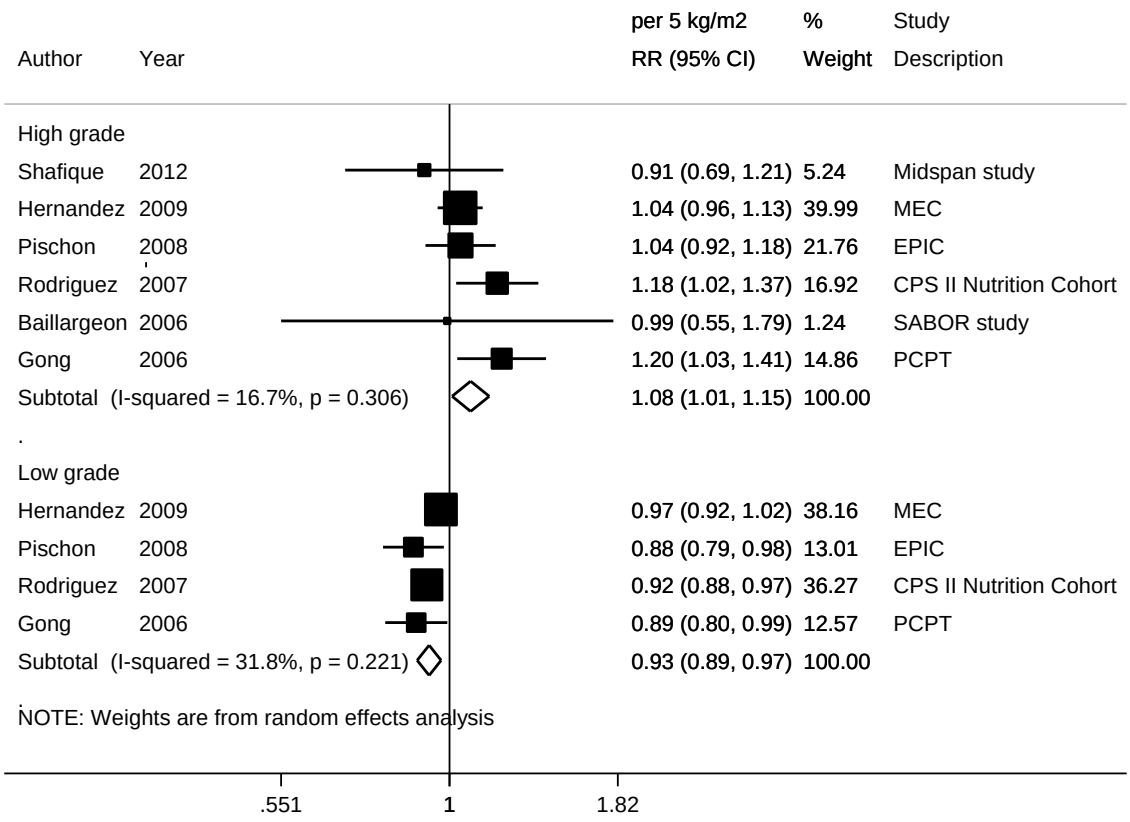
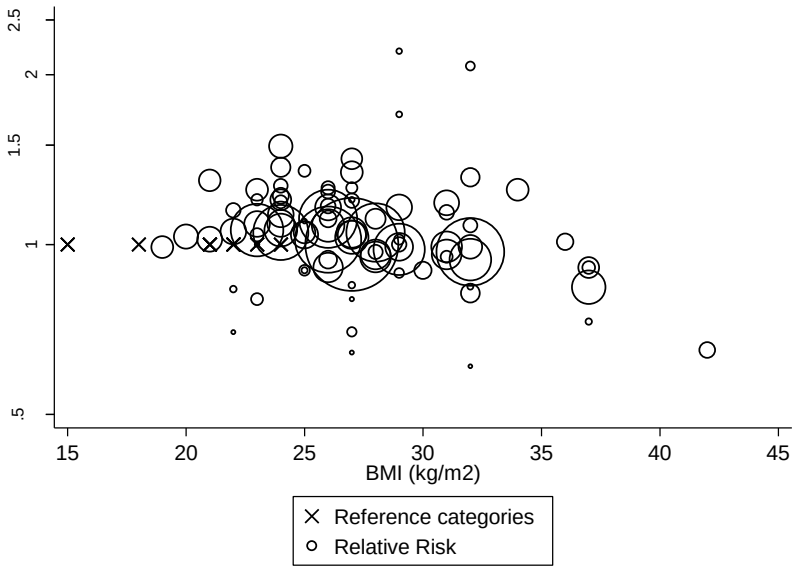


Figure 287 Non-linear dose-response analysis of BMI and total prostate cancer (excluding studies on mortality)



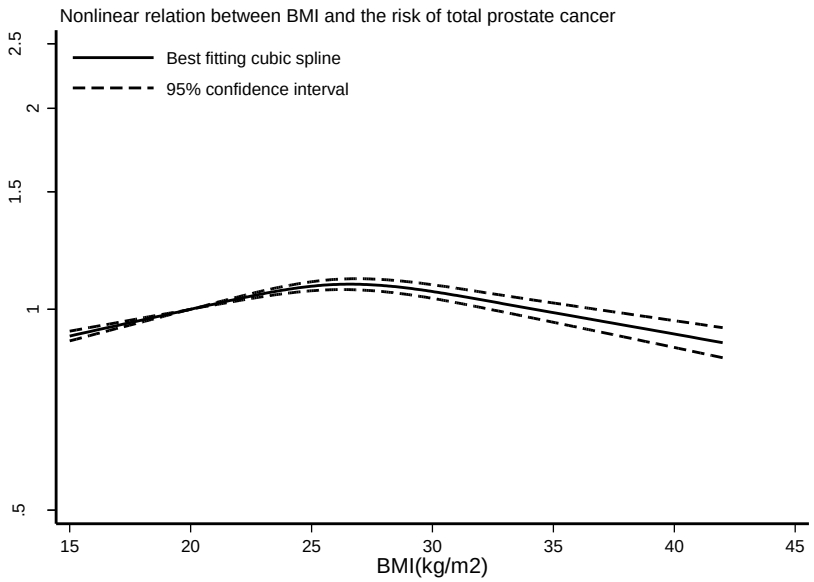
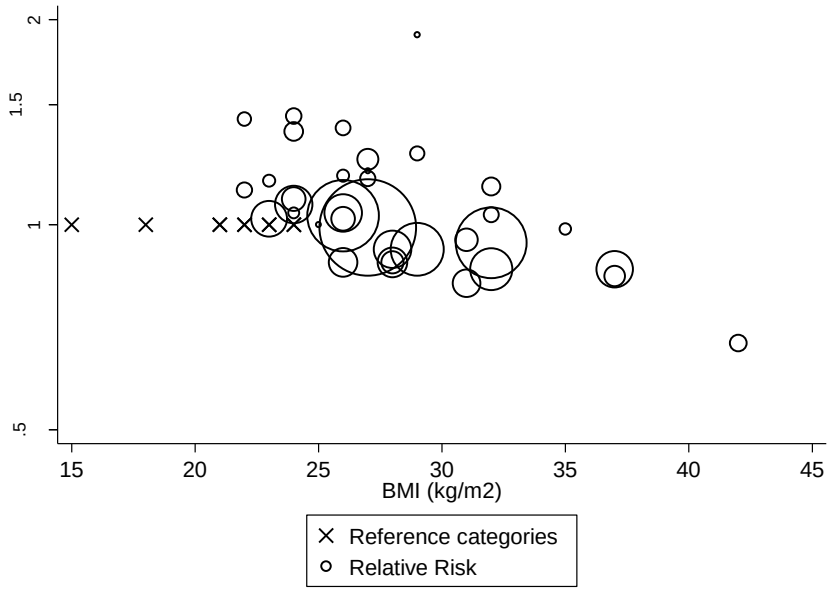


Table 258 Table with BMI values and corresponding RRs (95% CIs) for non-linear analysis of BMI and total prostate cancer

BMI (kg/m^2)	RR (95% CI)
15	0.91 (0.90-0.93)
20	1.00
25	1.08 (1.07-1.10)
30	1.06 (1.04-1.09)
36	0.97 (0.94-1.01)

$p_{non\text{-}linearity} < 0.01$

Figure 288 Non-linear dose-response analysis of BMI and non-advanced/low grade prostate cancer



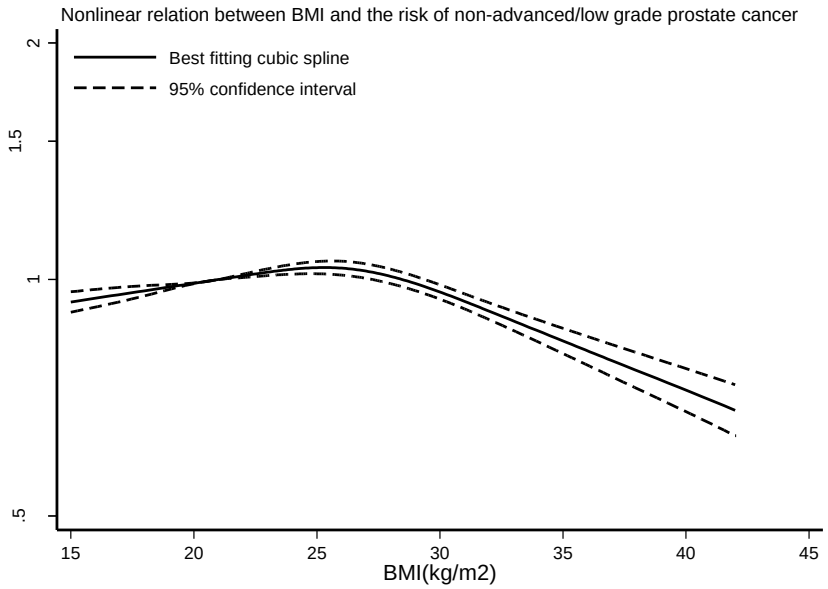


Table 259 Table with BMI values and corresponding RRs (95% CIs) for non-linear analysis of BMI and non-advanced/low grade prostate cancer

BMI (kg/m^2)	RR (95% CI)
15	0.94 (0.91-0.96)
21	1.00
25	1.04 (1.02-1.05)
31	0.94 (0.92-0.96)
37	0.79 (0.75-0.83)

$p_{non\text{-}linearity} < 0.01$

8.1.1 BMI at age 18-21

Methods
A total of 11 publications including 8 studies of BMI (at age 18-21) and prostate cancer were identified. Six publications of these were identified in the CUP. Dose-response analyses and stratified analyses of BMI (at age 18-21) and prostate cancer risk were conducted per 5 kg/m^2.

Results of BMIs for the following ages were combined for this meta-analysis: age 18 years (Bassett et al, 2012; Littman et al, 2007; Wright et al, 2007), 18.4 (Gray et al, 2012), 20 (Schuurman et al, 2000) and 21 years (Chae et al, 2009; Giovannucci et al, 1997). Two studies included category for underweight (BMI <18.5 kg/m^2) which was excluded in order to conduct a meta-analysis. After exclusion, only two levels of exposure remained in Hernandez et al, 2009 study which was only used for high vs. low analysis.

From the studies included in the dose-response meta-analysis: one study reported on total prostate cancer (Chae et al, 2009), two studies reported on total, nonaggressive and aggressive (Bassett et al, 2012; Littman et al, 2007), one study reported on total, localised and advanced (Schuurman et al, 2000), one study reported on total, advanced and metastatic (Giovannucci et al, 1997), one study reported on total, localised and extra prostatic cancer (Wright et al, 2007). Three studies investigated prostate cancer mortality (Bassett et al, 2012; Gray 2012; Wright et al, 2007). Cancer incidence was the outcome in all remaining studies. In order to conduct stratified analysis by prostate cancer type, aggressive, extra prostatic and advanced cancers were combined in an advanced/high grade subgroup and nonaggressive and localised were combined in non-advanced/low grade subgroup.

Main results
The summary RR per 5 kg/m^2 was 0.99 (95% CI 0.93-1.06; $I^2 = 27.4\%$; $p_{heterogeneity} = 0.22$; n = 7). There was no evidence of publication bias with Egger's test, p = 0.08.
After stratification by prostate cancer type, the RR per 5 kg/m^2 increase in BMI was 1.04 (95% CI: 0.86-1.25; $I^2 = 71.1\%$; $p_{heterogeneity} = 0.01$; n=5) for advanced/high grade prostate cancer and 1.00 (95% CI 0.86-1.16; $I^2 = 70.6\%$; $p_{heterogeneity} = 0.02$; n = 4) for non-advanced/low grade. The RR per 5 kg/m^2 increase was 1.13 (95% CI 0.93-1.37; $I^2 = 0\%$; $p_{heterogeneity} = 0.71$; n = 3) for prostate cancer mortality and 0.99 (95% CI 0.92-1.06; $I^2 = 34.5\%$; $p_{heterogeneity} = 0.18$; n = 6) for prostate cancer incidence.

Heterogeneity
Overall, there was low evidence of heterogeneity, $I^2 = 27.4\%$, $p_{heterogeneity} = 0.22$.

Comparison with the Second Expert Report
In the 2005 SLR, the meta-analysis on BMI (at age 18 or 20) and prostate cancer showed no significant association.

Published meta-analysis or pooled analysis
No published meta-analyses or pooled studies were identified.

Table 260 Studies on BMI (at age 18-21) identified in the CUP

Author, year	Country	Study name	Cases	Years of follow up	RR	LCI	UCI	Contrast
Bassett, 2012	Australia	The Melbourne Collaborative Cohort Study	1374	15 years	1.01	0.90	1.15	Per 5 kg/m^2 increase
					1.04	0.90	1.20	≥ 25 vs. 18.5 kg/m^2
Gray, 2012	USA	The Harvard Alumni Health Study	4790	56.5 years	1.11	1.05	1.17	Per 2.56 kg/m^2 increase
					1.37	0.98	1.93	> 23 vs. < 20 kg/m^2
Chae, 2009	USA	CLUE II	269	4 years max	1.19	0.42	3.34	≥ 30 vs. < 24.9 kg/m^2
Hernandez, 2009	USA and Hawaii	Multiethnic Cohort	5285	9.6 years	0.91	0.83	0.99	≥ 25 vs. < 18.5 kg/m^2
Littman, 2007	USA	Vitamins And Lifestyle Study	791	4 years	1.10	0.89	1.40	≥ 25 vs.< 21.5kg/m^2
Wright, 2007	USA	NIH- AARP Diet and Health Study	5436	5 years	0.93	0.84	1.02	≥25 vs. <18.5 kg/m^2

Table 261 Overall evidence on BMI (at age 18-21) and prostate cancer

	Summary of evidence
2005 SLR	Five studies were included in the 2005 SLR meta-analysis. All reported statistically non-significant results.
Continuous Update Project	Six new publications from 6 cohort studies were identified in the CUP, one of which reported significant positive association between BMI at age 18-21 and incidence of total prostate cancer. Two studies reported statistically significant inverse associations for total and localised prostate cancer. Overall, seven studies were included in this meta-analysis. No significant association was observed in the CUP meta-analysis.

Table 262 Summary of results of the dose response meta-analysis of BMI (at age 18-21) and prostate cancer

Prostate cancer		
	2005 SLR	CUP
Studies (n)	5	7
Cases (n)	2721	14475
Increment unit used	Per 5 kg/m^2	Per 5 kg/m^2
Overall RR (95% CI)	1.00 (0.97-1.01)	0.99 (0.93-1.06)
Heterogeneity (I^2, p-value)	26.8%, p = 0.24	27.4%, p = 0.22
Stratified analysis		
Advanced/high grade cancer*		
Overall RR (95% CI)		1.04 (0.86-1.25)
Heterogeneity (I^2, p-value)		71.1%, p = 0.01, n = 5
Non-advanced/low grade cancer*		
Overall RR (95% CI)		1.00 (0.86-1.16)
Heterogeneity (I^2, p-value)		70.6%, p = 0.02, n = 4
Incidence		
Overall RR (95% CI)	1.01 (0.98-1.05)	0.99 (0.92-1.06)
Heterogeneity (I^2, p-value)	26%, n=3	34.5%, p = 0.18, n = 6
	Incidence and mortality combined	**Mortality**
Overall RR (95% CI)	0.99 (0.97-1.00)	1.13 (0.93-1.37)
Heterogeneity (I^2, p-value)	73.9%, n = 2	0%, p = 0.71, n = 3

* No meta-analysis was conducted in the 2005 SLR.

Table 263 Inclusion/exclusion table for meta-analysis of BMI (at age 18-21) and prostate cancer

WCRF code	Author	Year	Study design	Study name	Cancer outcome	2005 SLR	CUP dose-response meta-analysis	CUP HvL forest plot	Estimated values	Exclusion reasons
PRO100163	Bassett	2012	Prospective cohort study	Melbourne Collaborative Cohort Study	Incidence/mortality	No	Yes	Yes		
PRO100189	Gray	2012	Prospective cohort study	Harvard Alumni Health Study	Mortality	No	Yes	Yes		
PRO100074	Chae	2009	Nested case control study	CLUE II	Incidence	No	Yes	Yes	Mid-exposure values	
PRO100072	Hernandez	2009	Prospective cohort study	Multiethnic Cohort Study	Incidence	No	No	Yes		Two levels of exposure only
PRO99973	Littman	2007	Prospective cohort study	Vitamins And Lifestyle Study	Incidence	No	Yes	Yes	Mid-exposure values, person years per category	
PRO100004	Wright	2007	Prospective cohort study	NIH- AARP Diet and Health Study	Incidence/mortality	No	Yes	Yes	New reference category, person years per category, Mid-exposure values	
PRO10700	Platz	2004b	Nested case control study	CLUE II	Incidence	Yes	No	No		Means only; superseded by Chae, 2009
PRO10575	Platz	2004c	Nested case control study	Health Professionals Follow-up Study	Incidence/mortality	Yes	No	No		Means only; superseded by Giovannucci, 1997
PRO00526	Huang	2003	Nested case control study	CLUE II	Incidence	Yes	No	No		Superseded by Chae, 2009
PRO01612	Schuurman	2000	Prospective cohort study	Netherlands Cohort Study	Incidence	Yes	Yes	Yes	Rescaled continuous estimate	
PRO02314	Giovannucci	1997	Prospective cohort study	Health Professionals Follow-up Study	Incidence	Yes	Yes	Yes	Mid-exposure values	

*Age adjusted.

Figure 289 Highest versus lowest forest plot of BMI (at age 18-21) and prostate cancer

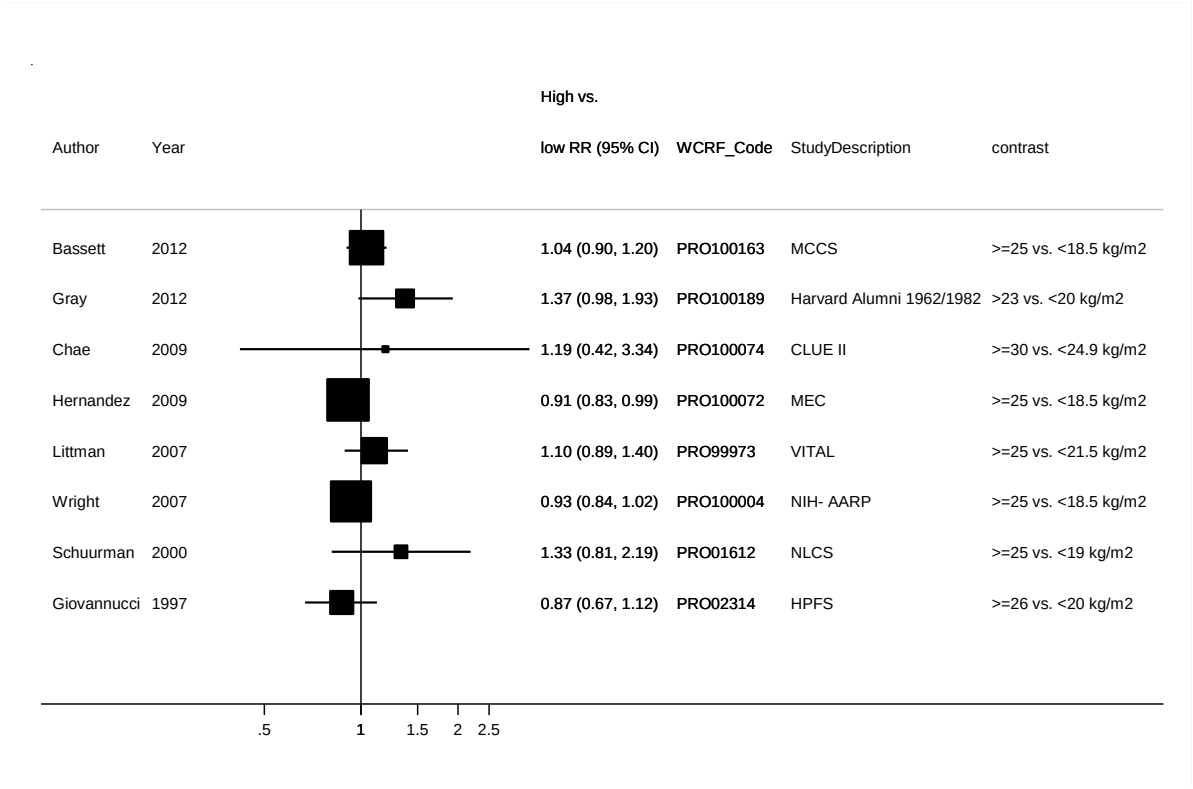


Figure 290 Dose-response meta-analysis of BMI (at age 18-21) and prostate cancer - per 5 kg/m^2

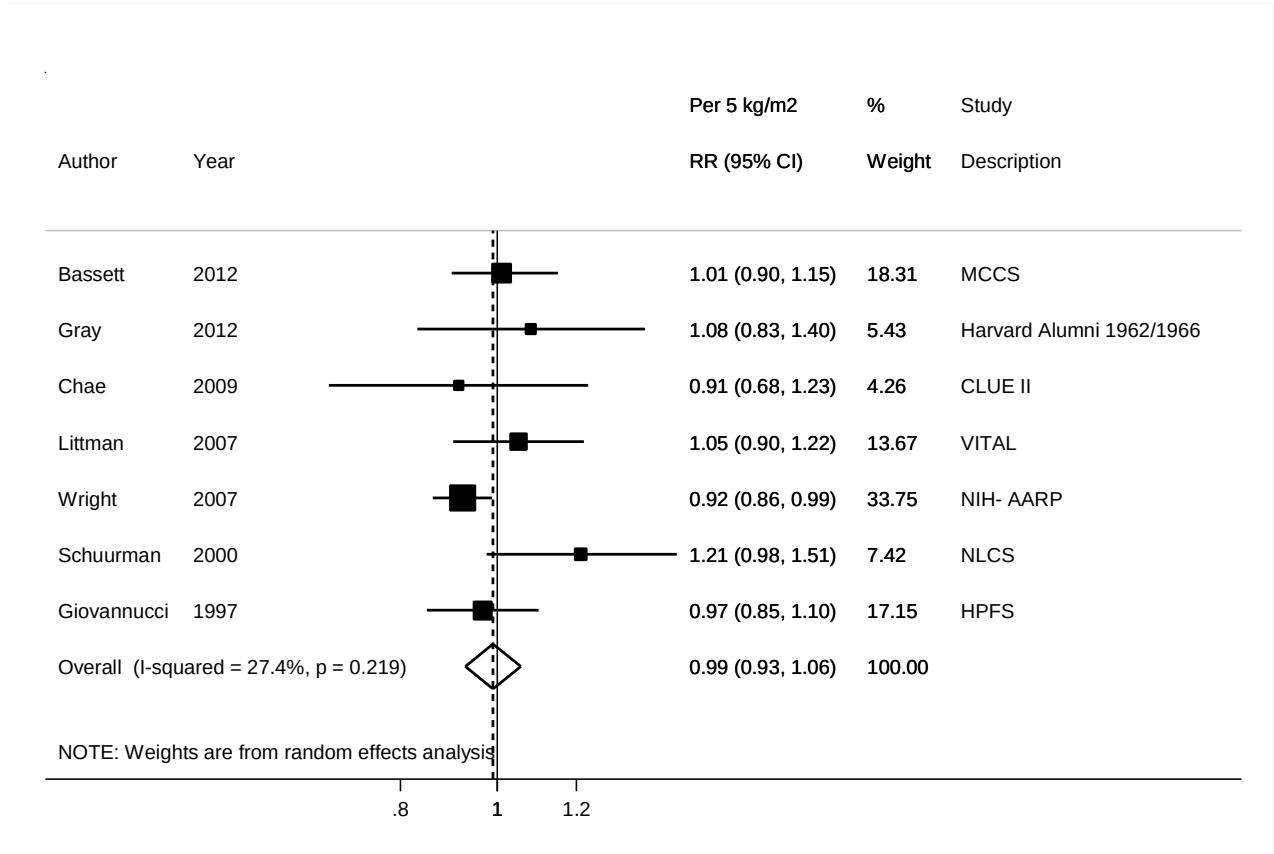
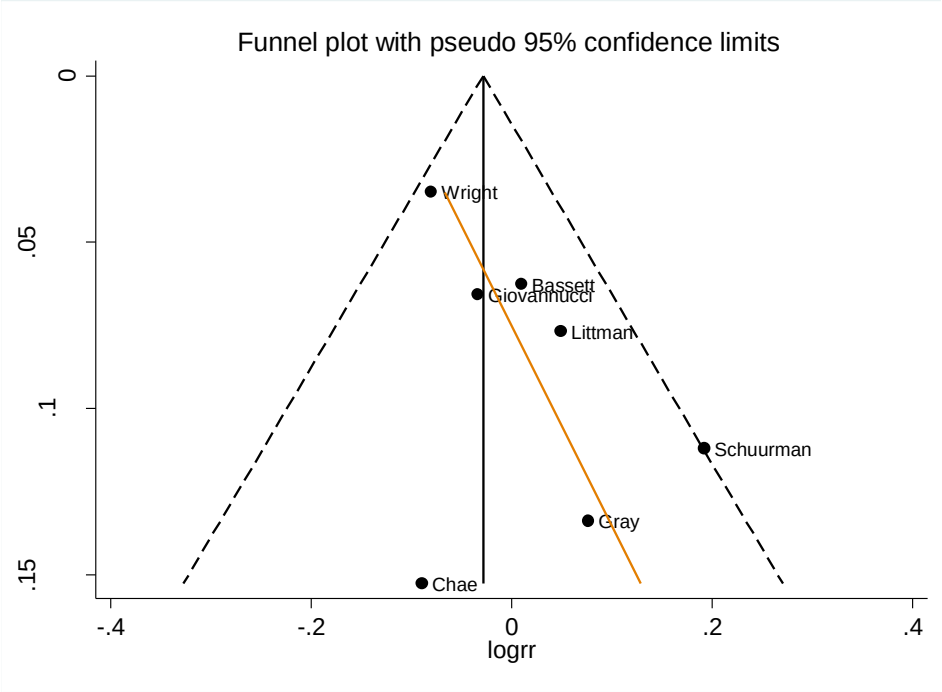


Figure 291 Funnel plot of BMI (at age 18-21) and prostate cancer



Egger's test p = 0.08

Figure 292 Dose-response graph of BMI (at age 18-21) and prostate cancer

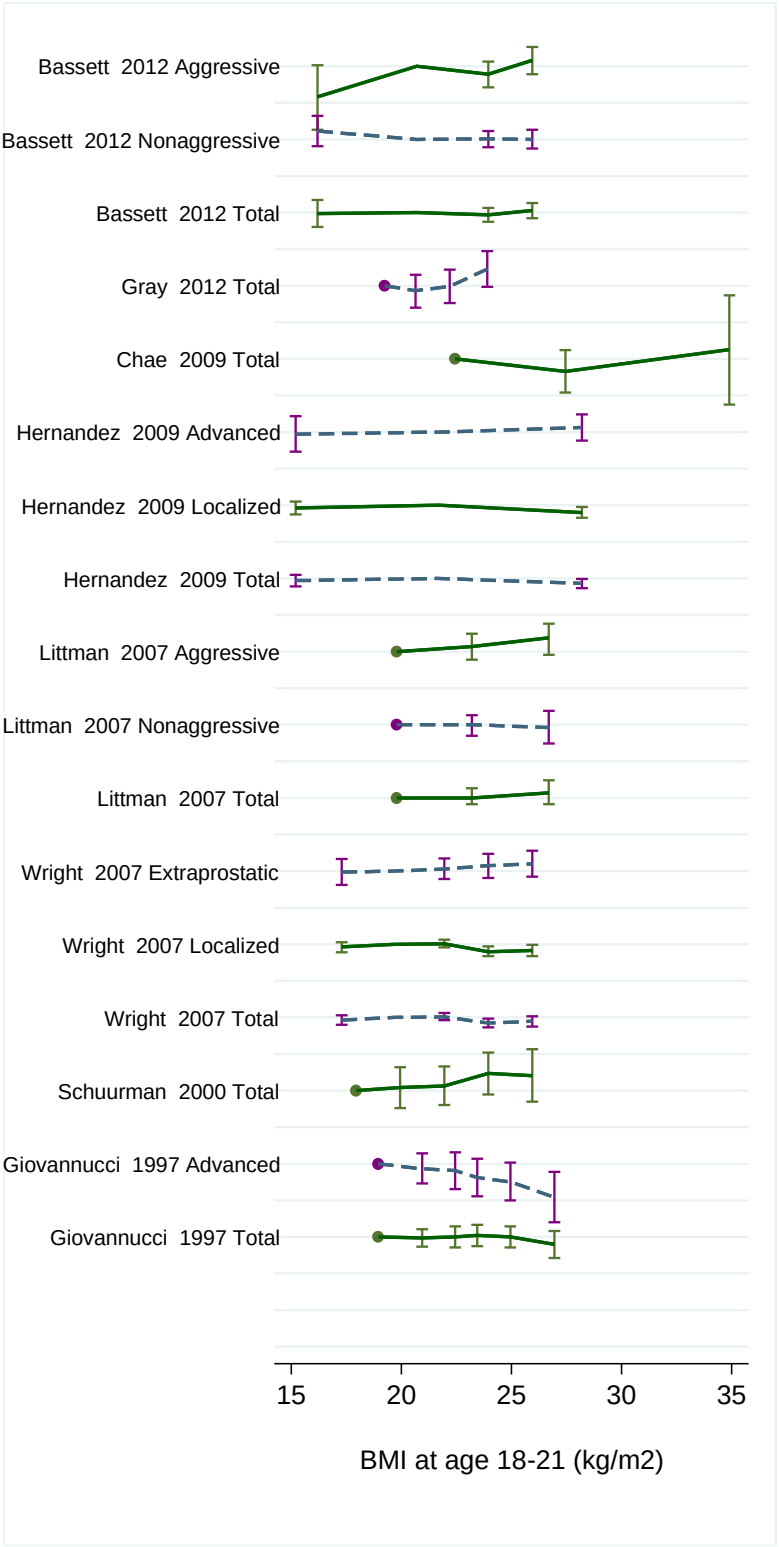


Figure 293 Dose-response meta-analysis of BMI (at age 18-21) and prostate cancer, per 5 kg/m^2, stratified by cancer subtype

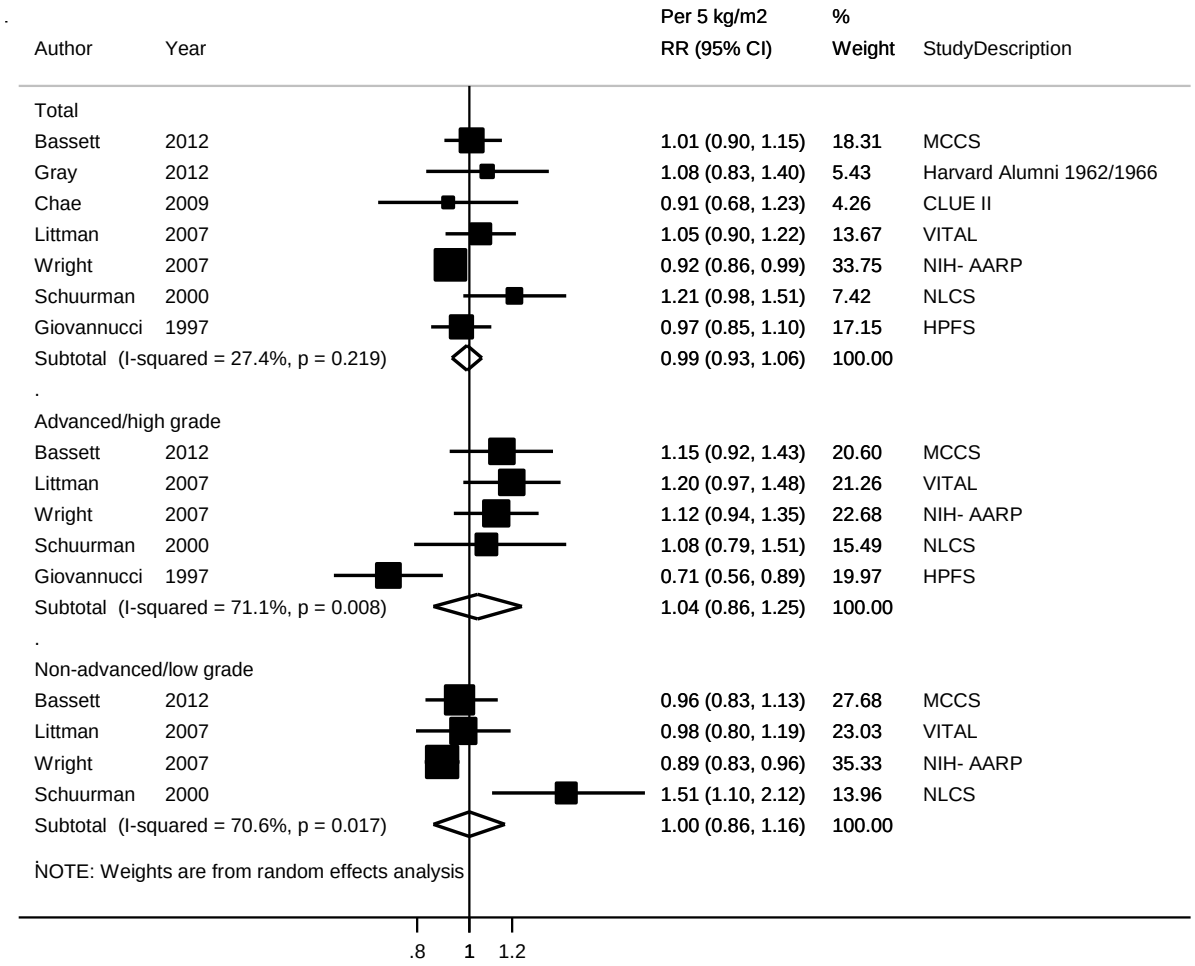
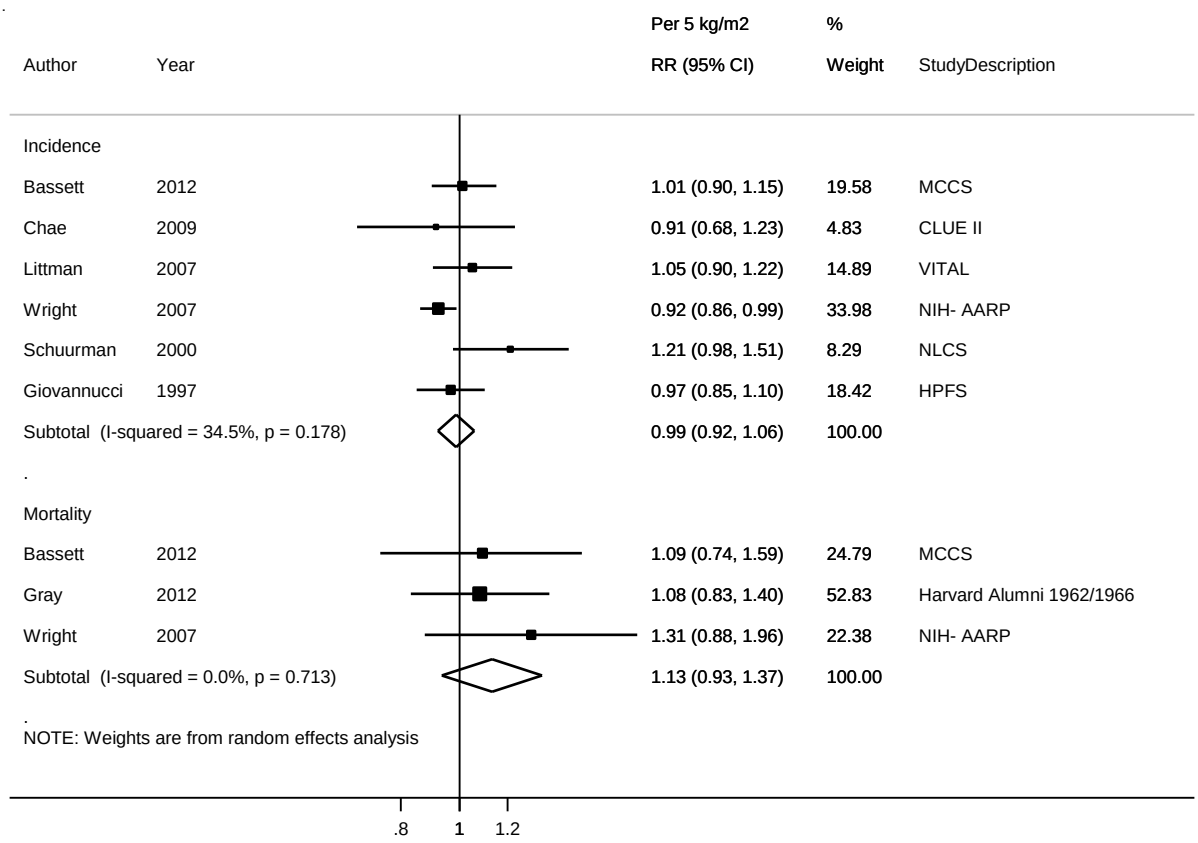


Figure 294 Dose-response meta-analysis of BMI (at age 18-21) and prostate cancer, per 5 kg/m^2, stratified by outcome



8.1.3 Weight

Methods
A total of 27 publications including 23 studies of weight and prostate cancer were identified. Seven publications of these were identified in the CUP. Dose-response analyses and stratified analyses of weight and prostate cancer risk were conducted per 5 kg weight.

From the studies included in the dose-response meta-analysis: eight studies reported on total prostate cancer (Fujino, 2007; Habel, 2000; Putnam, 2000; Nilsen, 1999; Andersson, 1997; Tulinius, 1997; Chyou, 1994; Whittemore, 1984), two reported on total, non-aggressive and aggressive prostate cancer (Bassett, 2012; Littman, 2007), one study reported on total, low grade and high grade cancer (Gong, 2006), one study reported on total, localised, advanced, low grade and high grade prostate cancer (Hernandez, 2009), one study reported on total, localised and extraprostatic prostate cancer (Wright, 2007), one study reported on total, localised, regional and distant stage cancer stratified by age (Le Marchand, 1994).

Three studies reported on incidence and mortality (Andersson, 1997; Wright 2007; Bassett, 2012), two reported on incidence and mortality combined (Nilsen, 1999; Whittemore, 1984), one reported on mortality only (Fujino, 2007) and all remaining studies reported on prostate cancer incidence.

In order to conduct stratified analysis by prostate cancer type, advanced, high grade, aggressive, and extraprostatic cancers were combined in an advanced/high grade subgroup and non-advanced, nonaggressive, localised, and low grade were combined in non-advanced/low grade subgroup.

Main results
The summary RR per 5 kg increase was 1.01 (95% CI 1.00-1.02; $I^2 = 35\%$; $p_{heterogeneity} = 0.1$, n = 14). There was no evidence of publication bias with Egger's test, p = 0.06.
After stratification by prostate cancer type, the RR per 5 kg increase in weight was 1.03 (95% CI 1.01-1.06; $I^2 = 0\%$; $p_{heterogeneity} = 0.45$; n = 5) for advanced/high grade prostate cancer and 0.99 (95% CI 0.97-1.00; $I^2 = 56.9\%$; $p_{heterogeneity} = 0.06$; n = 5) for non-advanced/low grade.
The RR for prostate cancer incidence and mortality per 5 kg increase in weight was 1.01 (95% CI 0.99-1.02; $I^2 = 46.5\%$; $p_{heterogeneity} = 0.05$; n = 11) and 1.09 (95% CI 1.04-1.14, $I^2 = 13\%$; $p_{heterogeneity} = 0.33$, n = 4), respectively.

Heterogeneity
Overall, there was low evidence of heterogeneity, $I^2 = 35\%$, $p_{heterogeneity} = 0.1$.

Comparison with the Second Expert Report
In the 2005 SLR, the evidence from adjusted cohort studies was suggestive of an increased prostate cancer risk with increasing weight.

Published meta-analysis or pooled analysis
No published meta-analyses or pooled studies were identified.

Table 264 Studies on weight identified in the CUP

Author, year	Country	Study name	Cases	Years of follow up	RR	LCI	UCI	Contrast
Bassett, 2012	Australia	The Melbourne Collaborative Cohort Study	1374	15 years	1.01	0.98	1.05	Incidence, per 5 kg increase
					1.03	0.87	1.21	Incidence, ≥ 87.6 vs. <73 kg
Chamberlain, 2011	Norway	HUNT (Nord-Trøndelag Health Study), Norway	649	9.3 years	0.96	0.85	1.08	HUNT-1 Per 6.2 kg increase
					0.95	0.83	1.09	HUNT-2 Per 6.2 kg increase
Hernandez, 2009	USA and Hawaii	Multiethnic Cohort	5554	9.6 years	1.00	0.90	1.12	≥ 194 vs. < 154 lbs
Fujino, 2007	Japan	Japan Collaborative Cohort Study	160	549584 person years	0.98	0.65	1.49	≥ 63 vs.< 55 kg
Littman, 2007	USA	Vitamins And Lifestyle Study	817	4 years	0.92	0.75	1.10	≥ 215 vs.< 173 lbs
Wright, 2007	USA	NIH- AARP Diet and Health Study	5725	5 years	0.91	0.82	1.00	Incidence, > 97.2 vs. ≤ 74.5kg
			89		2.19	1.00	4.78	Mortality, > 97.2 vs. ≤ 74.5 kg, P_{trend}=0.01
Gong, 2006	USA	The Prostate Cancer Prevention Trial	1936	7 years	1.06	0.92	1.23	≥ 95.3 vs. < 78.0 kg

Table 265 Overall evidence on weight and prostate cancer

	Summary of evidence
2005 SLR	Eight studies were included in the 2005 SLR meta-analysis. All were non-significant.
Continuous Update Project	Seven new publications from seven cohort studies were identified in the CUP. Two studies reported statistically significant increase in risk of prostate cancer mortality and one study of high grade prostate cancer, one study reported an inverse association for non aggressive prostate cancer and an increased risk of aggressive prostate cancer in highest vs. lowest weight measured at 45 years of age. Overall, fourteen studies were included in the meta-analysis. The CUP meta-analysis found a positive association for fatal prostate cancer and a weak positive association for advanced/high grade prostate cancer

Table 266 Summary of results of the dose response meta-analysis of weight and prostate cancer

Prostate cancer		
	2005 SLR	CUP
Studies (n)	14	14
Cases (n)	8242	22010
Increment unit used	Per 5 kg	Per 5 kg
Overall RR (95% CI)	1.01 (1.00-1.03)	1.01 (1.00-1.02)
Heterogeneity (I^2, p-value)	31.1%, p = 0.13	35%, p= 0.10
Stratified analysis		
Advanced/high grade cancer*		
Overall RR (95% CI)		1.03 (1.01-1.06)
Heterogeneity (I^2, p-value)		0%, p = 0.45, n = 5
Non-advanced/low grade cancer*		
Overall RR (95% CI)		0.99 (0.97-1.00)
Heterogeneity (I^2, p-value)		56.9%, p = 0.06, n = 5
Incidence		
Overall RR (95%CI)	1.01 (1.00-1.03)	1.01 (0.99-1.02)
Heterogeneity (I^2, p-value)		46.5%, p = 0.05, n =1 1
	Incidence and mortality combined	**Mortality**
Overall RR (95% CI)	1.00 (0.97-1.03)	1.09 (1.04-1.14)
Heterogeneity (I^2, p-value)		13%, p = 0.33, n = 4

* No meta-analysis was conducted in the 2005 SLR.

Table 267 Inclusion/exclusion table for meta-analysis of weight and prostate cancer

WCRF code	Author	Year	Study design	Study name	Cancer outcome	2005 SLR	CUP dose-response meta-analysis	CUP HvL forest plot	Estimated values	Exclusion reasons
PRO100163	Bassett	2012	Prospective cohort study	The Melbourne Collaborative Cohort Study	Incidence/mortality	No	Yes	Yes	Mid-exposure values	
PRO100172	Chamberlain	2011	Prospective cohort study	HUNT (Nord-Trøndelag Health Study), Norway	Incidence	No	No	No		Overlap with Nilsen, 1999
PRO100072	Hernandez	2009	Prospective cohort study	Multiethnic Cohort	Incidence	No	Yes	Yes	Person years per quintile, Mid-exposure values	
PRO100130	Fujino*	2007	Prospective cohort study	Japan Collaborative Cohort Study	Mortality	No	Yes	Yes	Mid-exposure values	
PRO99973	Littman	2007	Prospective cohort study	Vitamins And Lifestyle Study	Incidence	No	Yes	Yes	Converted lb to kg, Mid-exposure values, person years per quintile	
PRO100004	Wright	2007	Prospective cohort study	NIH- AARP Diet and Health Study	Incidence/mortality	No	Yes	Yes	Person years per quintile, Mid-exposure values	
PRO99985	Gong	2006	Observational study in a RCT follow-up	The Prostate Cancer Prevention Trial	Incidence	No	Yes	Yes	Cases, non-cases per quintile, Mid-exposure values	
PRO97424	Weinstein	2005	Case cohort	ATBC Study	Incidence	Yes	No	No		Means only
PRO10545	Li	2004	Nested case control study	Physicians' Health Study	Incidence	Yes	No	No		Means only

PRO97316	Stattin	2004	Case cohort	Northern Sweden Health and Disease Cohort	Incidence	Yes	No	No		Means only
PRO00302	Engeland	2003	Prospective cohort study	Norway 1963-2001	Incidence/mortality	Yes	No	Yes		Only two categories of exposure
PRO00451	Lamharzi	2003	Nested case control study	CARET	Incidence	Yes	No	No		Means only
PRO04077	MacInnis	2003	Prospective cohort study	The Melbourne Collaborative Cohort Study	Incidence	Yes	No	No		Superseded by Bassett, 2012
PRO01046	Brooks	2001	Nested case control study	Baltimore Longitudinal Study of Aging	Incidence	Yes	No	No		Means only
PRO01468	Clarke	2000	Prospective cohort study	NHANESI Epidemiologic Follow-up Study	Incidence/mortality	Yes	No	No		Means only
PRO01599	Habel	2000	Prospective cohort study	Kaiser Permanente Medical Care Program	Incidence	Yes	Yes	Yes	Converted lb to kg, person years per quintile	
PRO01487	Putnam	2000	Prospective cohort study	Iowa 1986-1995		Yes	Yes	Yes	Mid-exposure values	
PRO01612	Schuurman	2000	Nested case control study	Netherlands Cohort Study	Incidence	Yes	No	No		Means only
PRO01688	Nilsen*	1999	Prospective cohort study	HUNT (Nord-Trøndelag Health Study), Norway	Incidence/mortality	Yes	Yes	Yes	Mid-exposure values	
PRO02391	Andersson*	1997	Historical cohort	Swedish Construction Workers' Cohort Study	Incidence/mortality	Yes	Yes	Yes	Mid-exposure values	
PRO02364	Cerhan	1997	Prospective cohort study	Iowa 1982-1993	Incidence	Yes	No	No		Superseded by Putnam, 2000
PRO02254	Tulinius*	1997	Prospective cohort	Icelandic Cardiovascular Risk Factor Study	Incidence	Yes	Yes	No	Rescaled continuous estimate	Only continuous estimate

PRO02809	Chyou	1994	Prospective cohort study	USA Hawaii 1965-1992	Incidence	Yes	Yes	Yes	Person years per category, Mid-exposure values	
PRO02822	Hiatt	1994	Prospective cohort study	Kaiser Permanente Medical Care Program	Incidence	Yes	No	No		Superseded by Habel, 2000
PRO02788	Le Marchand	1994	Prospective cohort study	USA Hawaii 1975-1989	Incidence	Yes	Yes	Yes	Person years, 50^{th} quintile, Mid-exposure values	
PRO06325	Garfinkel	1986	Prospective cohort study	Cancer Prevention Study I	Mortality	Yes	No	No		No number of cases
PRO03461	Whittemore	1984	Case cohort	Harvard and Pennsylvania Alumni Study 1916-1950	Incidence/mortality	Yes	Yes	No	Converted lb to kg, rescaled continuous estimate	Only continuous estimate

*Age adjusted.

Figure 295 Highest versus lowest forest plot of weight and prostate cancer

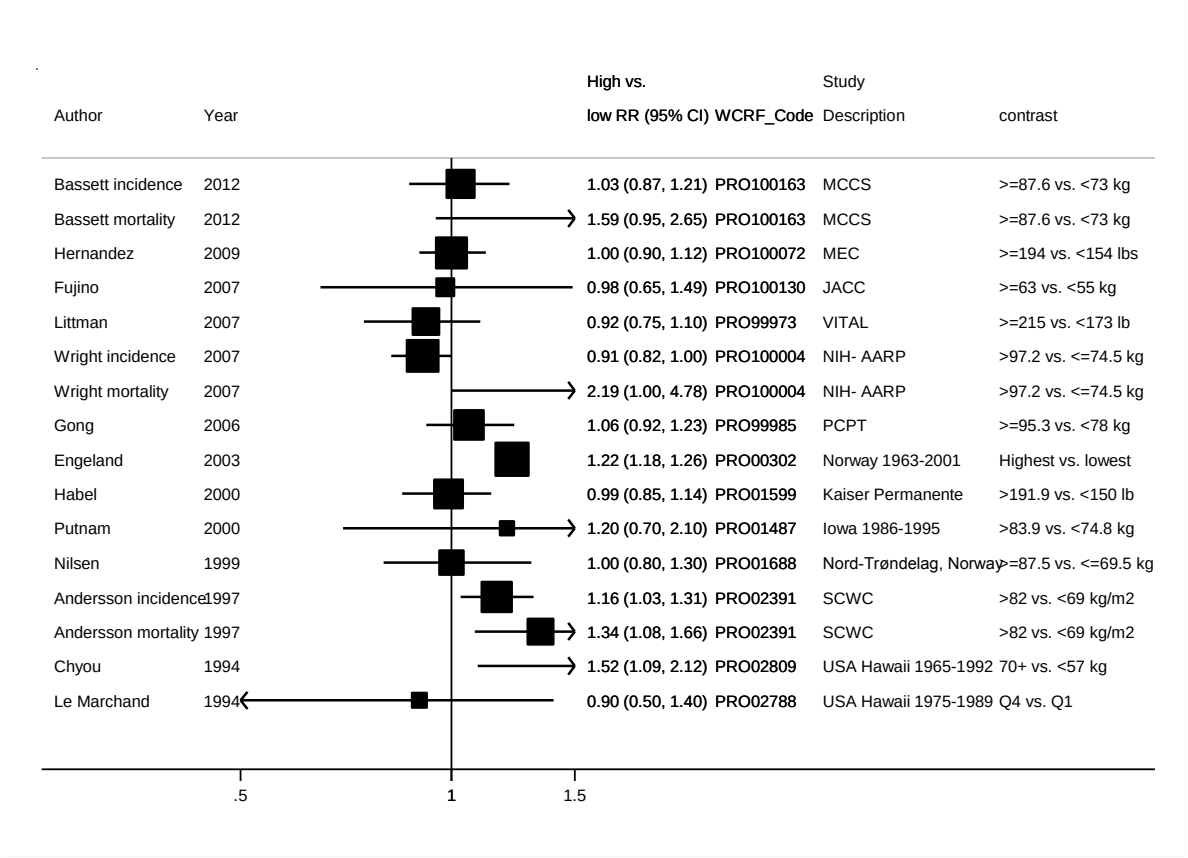


Figure 296 Dose-response meta-analysis of weight and prostate cancer - per 5 kg

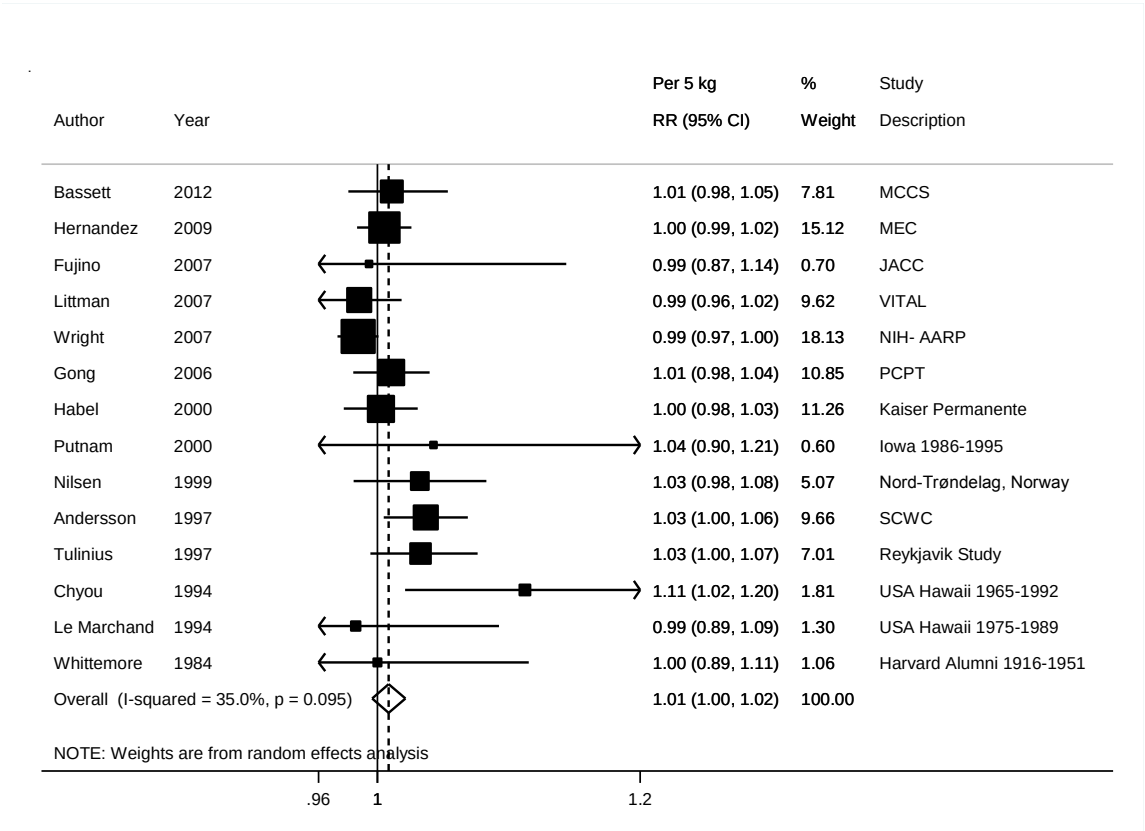
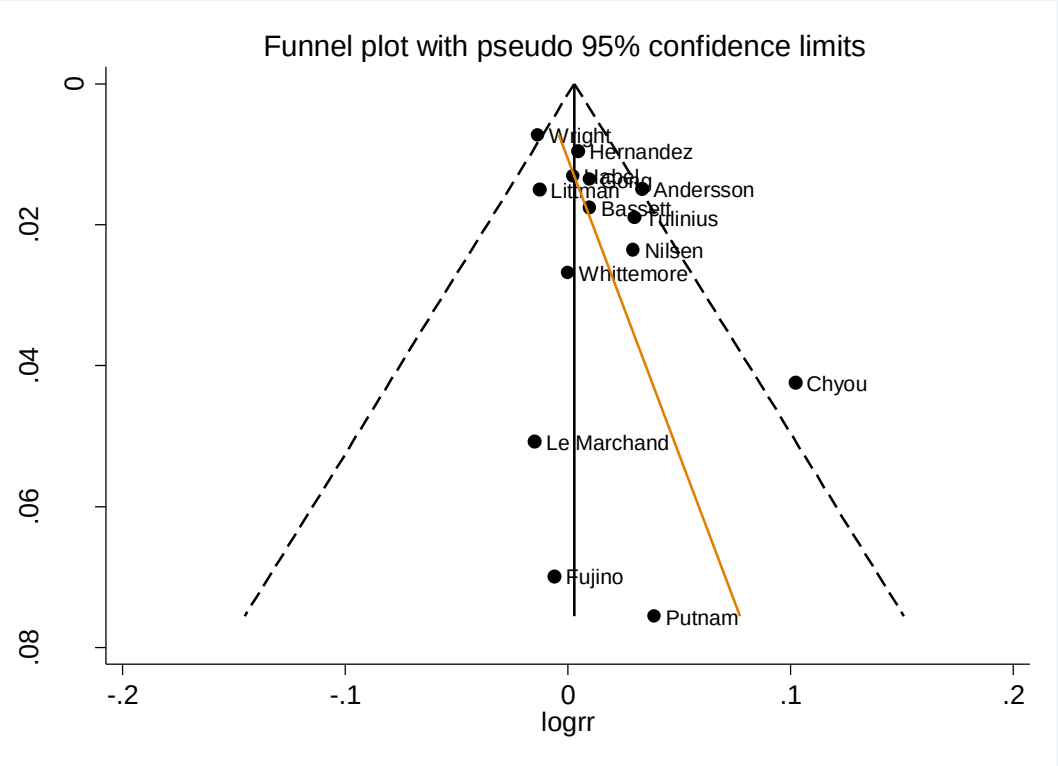


Figure 297 Funnel plot of weight and prostate cancer



Egger's test p = 0.06

Figure 298 Dose-response graph of weight and prostate cancer

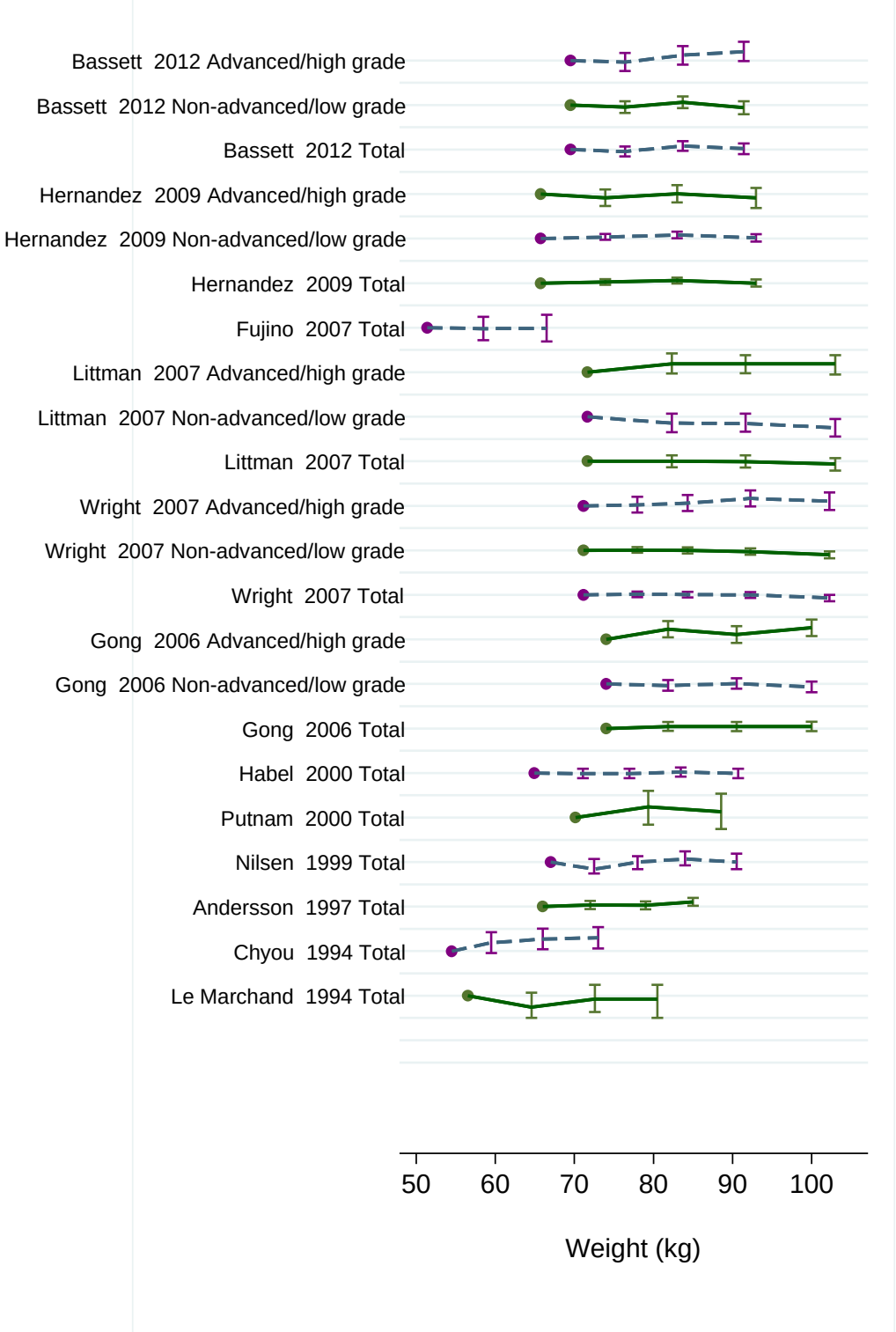


Figure 299 Dose-response meta-analysis of weight and prostate cancer, per 5 kg, stratified by cancer subtype

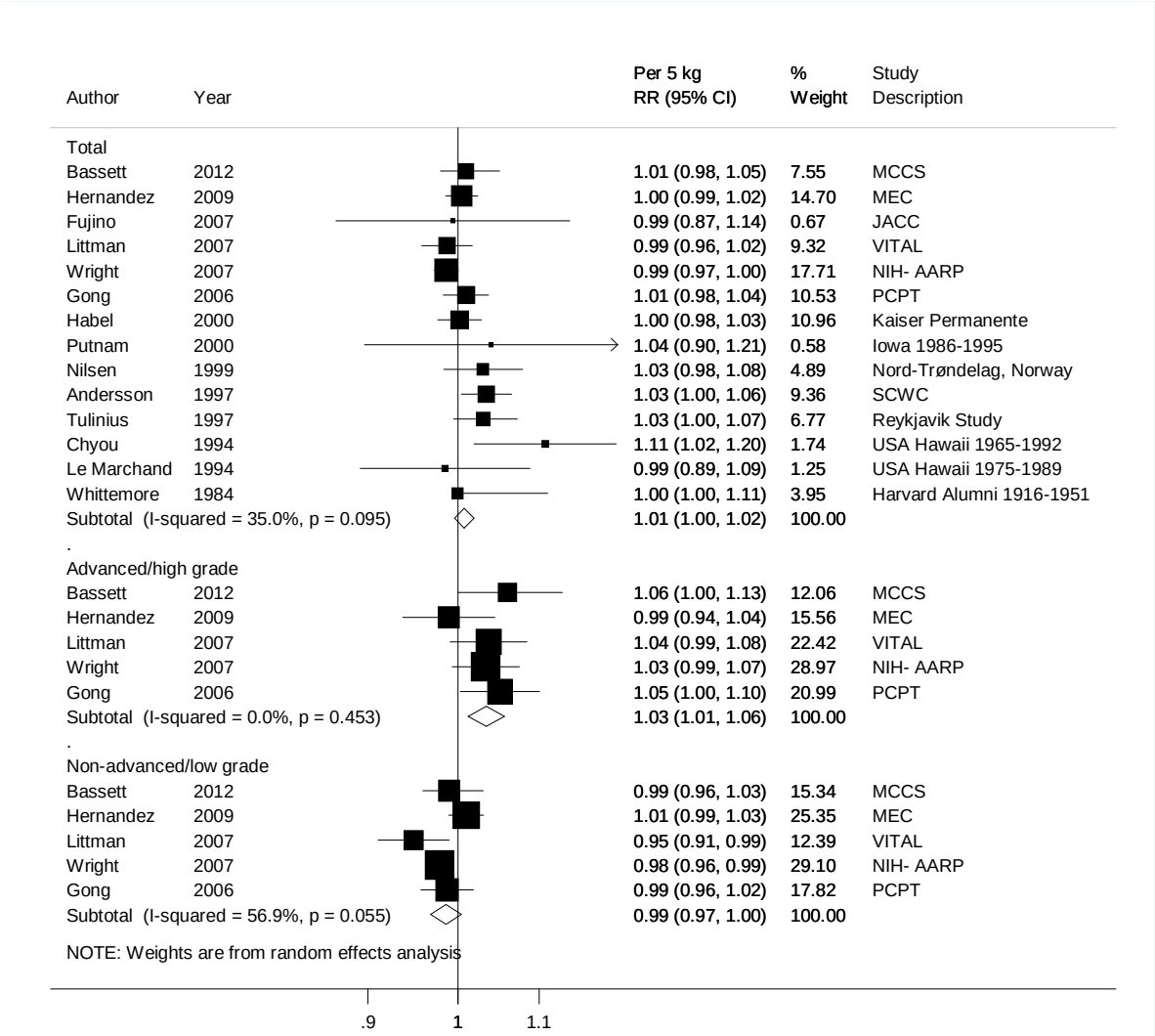
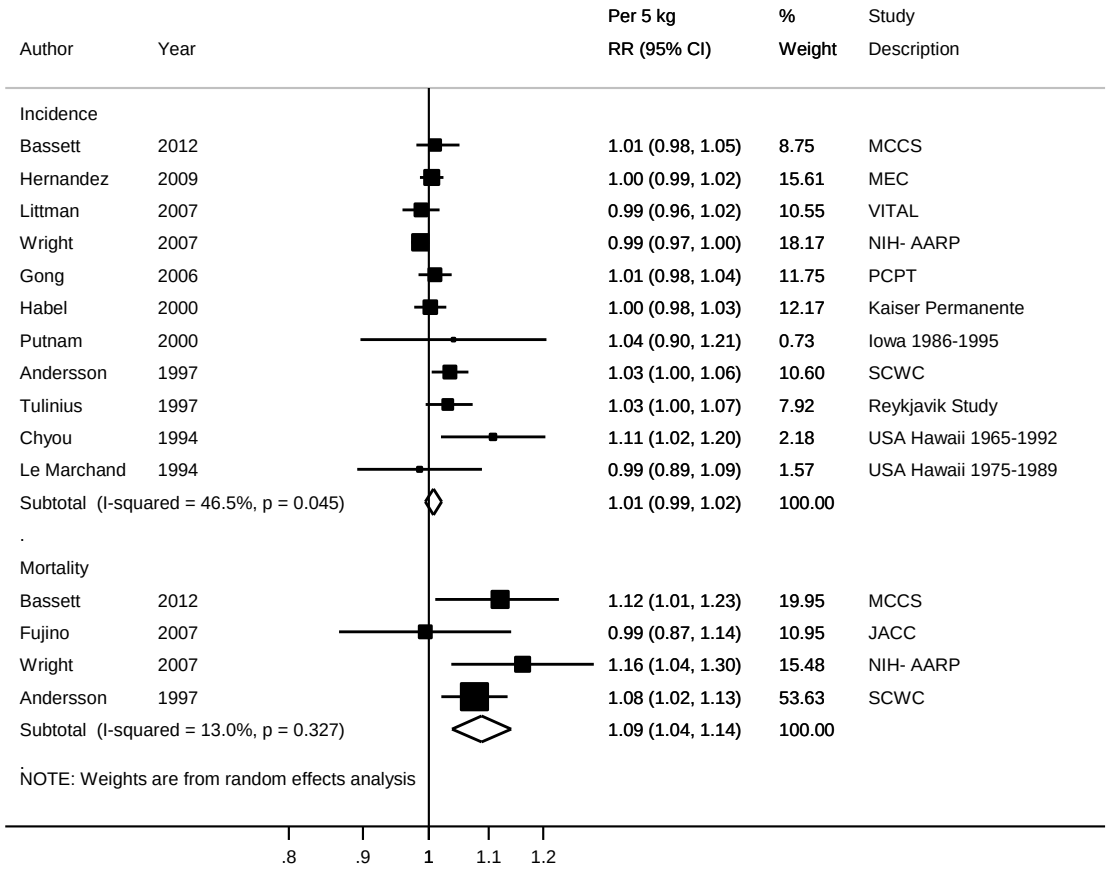


Figure 300 Dose-response meta-analysis of weight and prostate cancer, per 5 kg, stratified by outcome



8.2.1 Waist circumference

Methods
Eleven studies (from 12 publications) were identified, from which seven studies (eight publications) were identified during the CUP. Wallström et al (2009) is a component study of a multi-centered study (Pischon, 2008).

Nine studies could be included in the dose-response meta-analysis on prostate cancer. The increment unit used in the analysis was 10 cm. Five of the nine studies reported on total prostate cancer only (van Kruijsdijk, 2013; Baillargeon, 2006; Tande, 2006; Hubbard, 2004; Lee, 2001), one on total, localised, advanced, low grade, and high grade prostate cancers (Pischon, 2008), one on total, low grade, and high grade prostate cancers (Gong, 2006), one on total, localised, advanced, and fatal prostate cancers (Martin, 2009), one on total, low grade (Gleason 1-4), moderate grade (Gleason 5-7), and advanced (Gleason 8-10 and metastatic cases) prostate cancers (MacInnis, 2003).

A separate figure for all studies combined was not produced as there is no mortality study.

Main results
The summary RR per 10 cm was 1.00 (95% CI 0.97-1.03; $I^2 = 0\%$; $p_{heterogeneity} = 0.54$; n = 9) for prostate cancer risk. There was no evidence of publication bias with Egger's test, p=0.66.

After stratification by prostate cancer type, the summary RRs per 10 cm were 1.12 (95% CI 1.04-1.21; I^2=14.9%; $p_{heterogeneity} = 0.32$; n = 4) for advanced prostate cancer and 1.01 (95% CI 0.90-1.12; I^2=71.7%, $p_{heterogeneity} = 0.01$; n = 4) for non-advanced/low grade prostate cancer.

There was evidence of non-linearity relationship (p = 0.05), with the highest associated risk increase for prostate cancer at waist circumference of 95 cm.

Heterogeneity
There was no evidence of heterogeneity, $I^2 = 0\%$, $p_{heterogeneity} = 0.54$.

Comparison with the Second Expert Report
In the 2005 SLR, the meta-analysis on waist circumference and prostate cancer showed an overall non-significant positive association.

Published meta-analysis or pooled analysis
A meta-analysis published in 2006 observed a non-significant positive association (summary RR per 10 cm = 1.03; 95% CI 0.97-1.09) between waist circumference and the risk of prostate cancer (MacInnis, 2006). All four cohort studies included in this published review were included in the present report. Giovannucci et al (1997) was not included in the analysis because of missing data. No pooled analysis was identified.

Table 268 Studies on waist circumference identified in the CUP

Author, year	Country	Study name	Cases	Years of follow up	RR	LCI	UCI	Contrast
van Kruijsdijk, 2013	The Netherlands	SMART study	91	5.5 years	0.87	0.69	1.10	Per 10.6 cm
Grundmark, 2010	Sweden	ULSAM	237	30.3 years	1.31	0.83	2.08	> 102 vs. ≤ 102 cm
Martin, 2009	Norway	HUNT2	797	9.3 years	1.05	0.83	1.32	≥ 98 vs. ≤ 86 cm
					0.99	0.92	1.08	Per 9.4 cm
Wallström, 2009	Sweden	MDC study	817	11 years	1.00	0.80	1.26	≥ 102 vs. ≤ 85 cm
Pischon, 2008	Europe	EPIC	2446	8.5 years	0.99	0.86	1.14	≥ 103 vs. < 86 cm
					1.00	0.97	1.02	Per 5 cm
Baillargeon, 2006	USA	SABOR study	125	1.43 years	0.56	0.24	1.27	T3 vs. T1
Gong, 2006	USA	PCPT	832	3.3 years	0.93	0.81	1.18	≥ 108 vs. < 95 cm
Tande, 2006	USA	ARIC Study	385	12.1 years	0.92	0.68	1.24	≥ 105 vs. ≤ 90 cm

Table 269 Overall evidence on waist circumference and prostate cancer

	Summary of evidence
2005 SLR	Four prospective studies were identified during the 2005 SLR and all were included in the meta-analysis. Three studies observed a statistically non-significant positive association. One study reported no significant association.
Continuous Update Project	All seven (eight publications) prospective studies identified in the CUP showed non-significant results. One study reported a significant positive association for advanced prostate cancer. The CUP meta-analysis showed a significant positive association for advanced/high grade cancers only

Table 270 Summary of results of the dose response meta-analysis of waist circumference and prostate cancer

Prostate cancer		
	2005 SLR	CUP
Studies (n)	4	9
Cases (n)	2472	6883
Increment unit used	Per 10 cm	Per 10 cm
Overall RR (95% CI)	1.03 (0.98-1.08)	1.00 (0.97-1.03)
Heterogeneity (I^2, p-value)	10.0%, p = 0.34	0%, p = 0.54
Stratified analysis		
Advanced/high grade cancer		
Overall RR (95% CI)	1.04 (0.98-1.10)	1.12 (1.04-1.21)
Heterogeneity (I^2, p-value)	n = 1	14.9%, p = 0.32, n = 4
Non-advanced/low grade cancer		
Overall RR (95% CI)		1.01 (0.90-1.12)
Heterogeneity (I^2, p-value)		71.7%, p = 0.01, n = 4

Table 271 Inclusion/exclusion table for meta-analysis of waist circumference and prostate cancer

WCRF code	Author	Year	Study design	Study name	Cancer outcome	2005 SLR	CUP dose-response meta-analysis	CUP HvL forest plot	Estimated values	Exclusion reasons/remarks
PRO100186	van Kruijsdijk	2013	Prospective Cohort study	SMART study	Incidence	No	Yes	No		Dose-response result only
PRO100191	Grundmark	2010	Prospective Cohort study	ULSAM	Incidence/ Mortality	No	No	No		Unadjusted result
PRO100050	Martin	2009	Prospective Cohort study	HUNT 2 cohort	Incidence, all and advanced/high grade cancers	No	Yes	Yes		No categorical results by cancer types; excluded from advanced/high grade cancer highest vs lowest plot – dose-response result only
PRO100047	Wallström	2009	Prospective Cohort study	MDC study	Incidence all and advanced/high grade cancers	No	No	No		Superseded by Pischon, 2008; Component study of EPIC
PRO100036	Pischon	2008	Prospective Cohort study	EPIC	Incidence/ Mortality, all and advanced/high grade cancers	No	Yes	Yes		
PRO100041	Baillargeon	2006	Nested Case-Control study	SABOR study	Incidence	No	Yes	Yes	Number of cases and non-cases per tertile, exposure values	
PRO99985	Gong	2006	Observational study in a RCT follow-up	PCPT	Incidence, all and advanced/high grade cancers	No	Yes	Yes	Number of non-cases per quartile; mid-exposure values	
PRO100194	Tande	2006	Prospective Cohort study	ARIC Study	Incidence	No	Yes	Yes	Mid-exposure values	

PRO03985	Hubbard	2004	Prospective Cohort study	Baltimore Longitudinal Study of Aging	Incidence	Yes	Yes	Yes	Mid-exposure values	
PRO04077	MacInnis	2003	Prospective Cohort study	MCCS	Incidence, all and advanced/high grade cancers	Yes	Yes	No		Excluded from all highest vs lowest plots - dose-response result only
PRO01290	Lee	2001	Prospective Cohort study	Harvard Alumni Health Study 1962-1966	Incidence/ Mortality	Yes	Yes	Yes	Mid-exposure values	
PRO02314	Giovannucci	1997	Prospective Cohort study	HPFS	Incidence/ Mortality, all and advanced/high grade cancers	Yes	No	Yes		Excluded from prostate cancer and advanced/high grade cancers dose-response meta-analyses - missing 95% CIs, except for Q5 vs. Q1

Figure 301 Highest versus lowest forest plot of waist circumference and prostate cancer

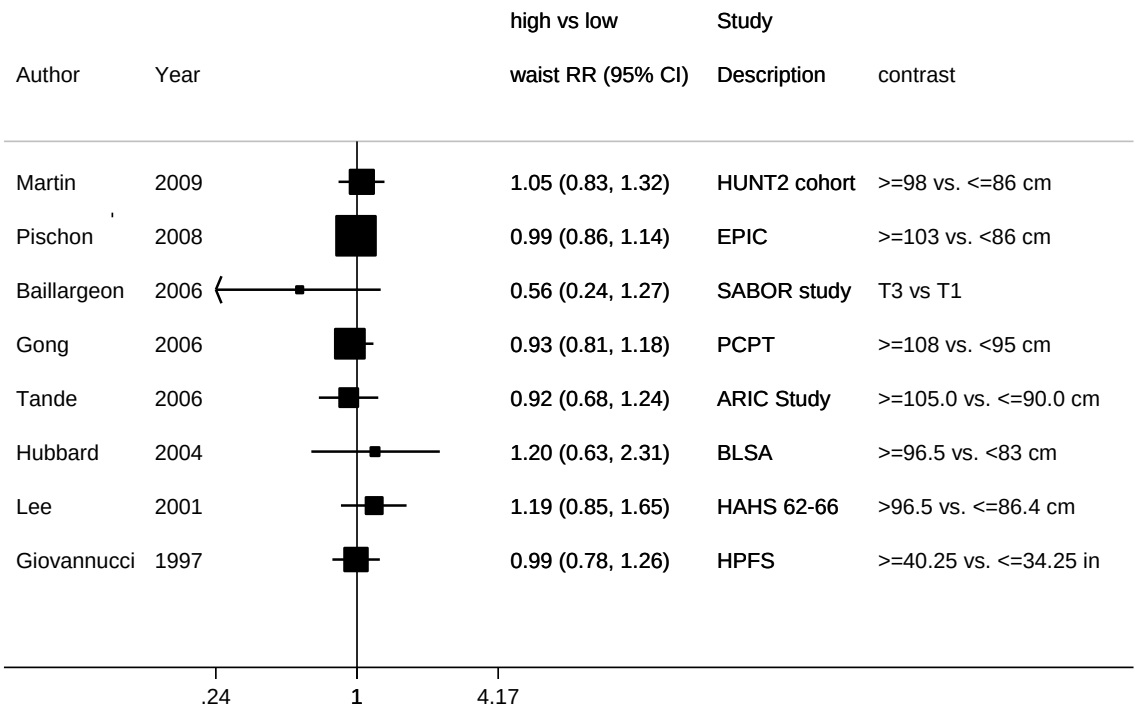


Figure 302 Dose-response meta-analysis of waist circumference and prostate cancer – per 10 cm

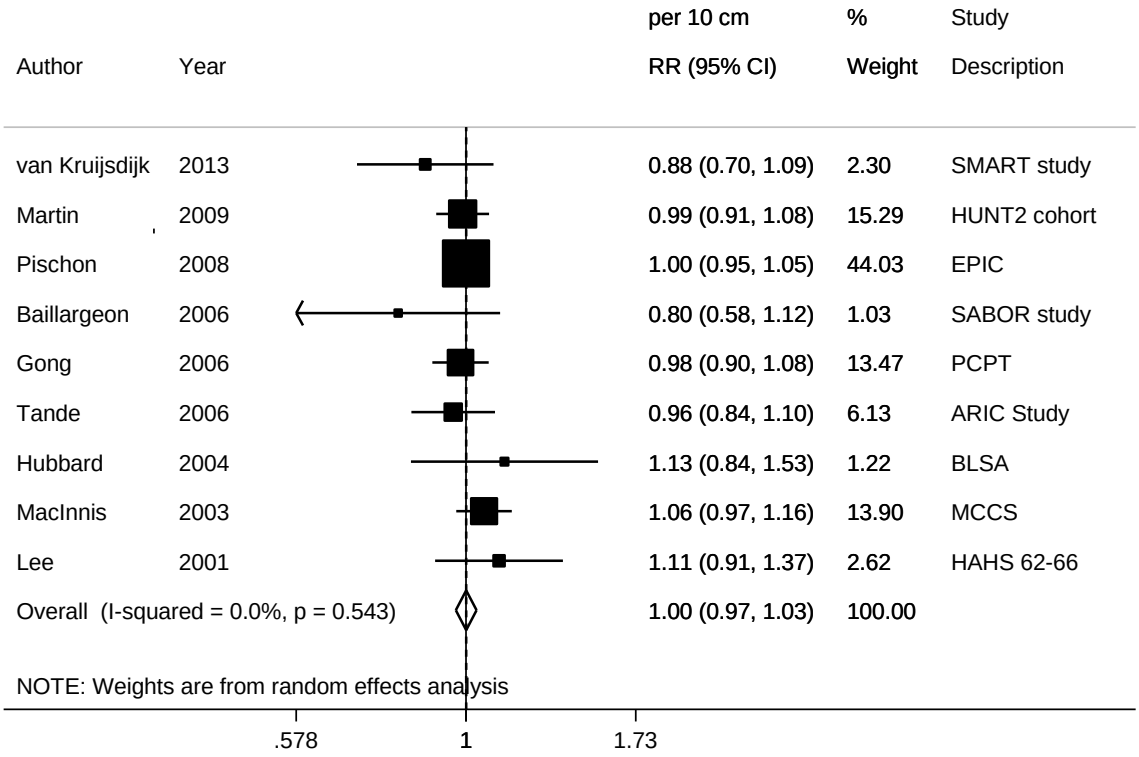
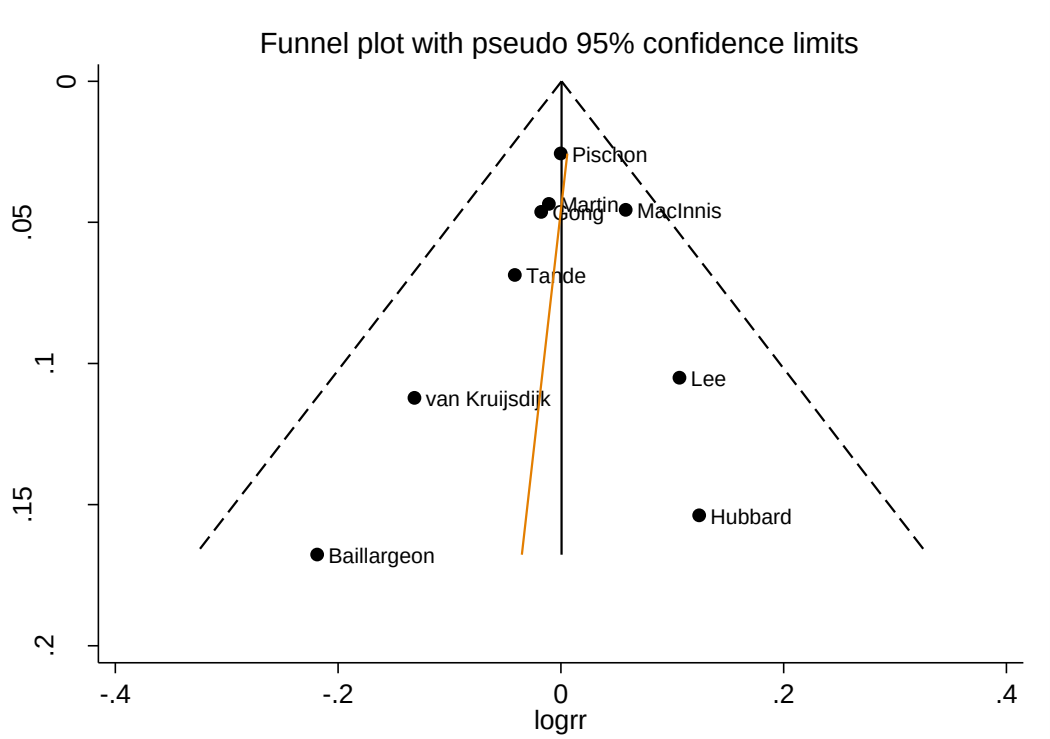


Figure 303 Funnel plot of waist circumference and prostate cancer



Egger's test p = 0.66

Figure 304 Dose-response graph of waist circumference and prostate cancer

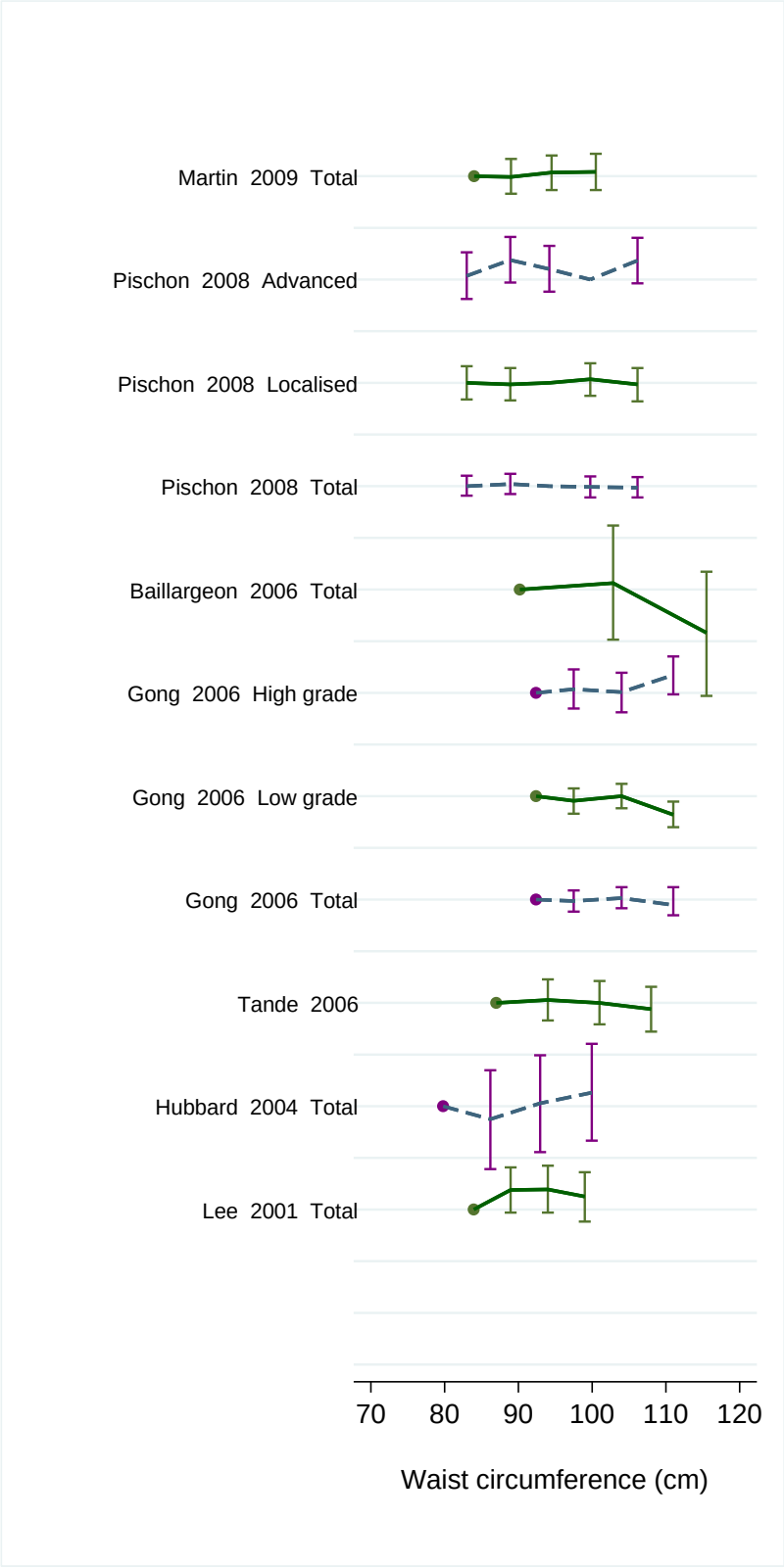


Figure 305 Highest vs lowest forest plot of waist circumference for advanced/high-grade prostate cancer

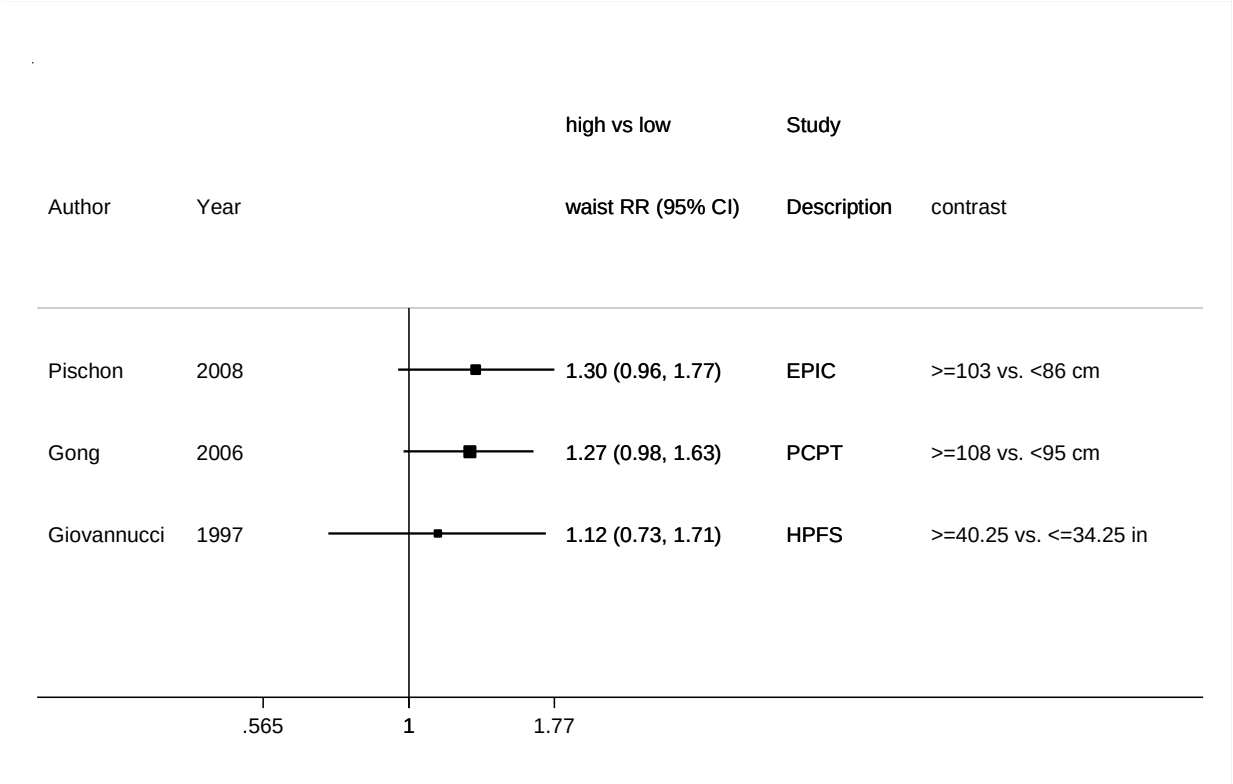


Figure 306 Dose-response meta-analysis of waist circumference and prostate cancer, per 10 cm, stratified by prostate cancer type

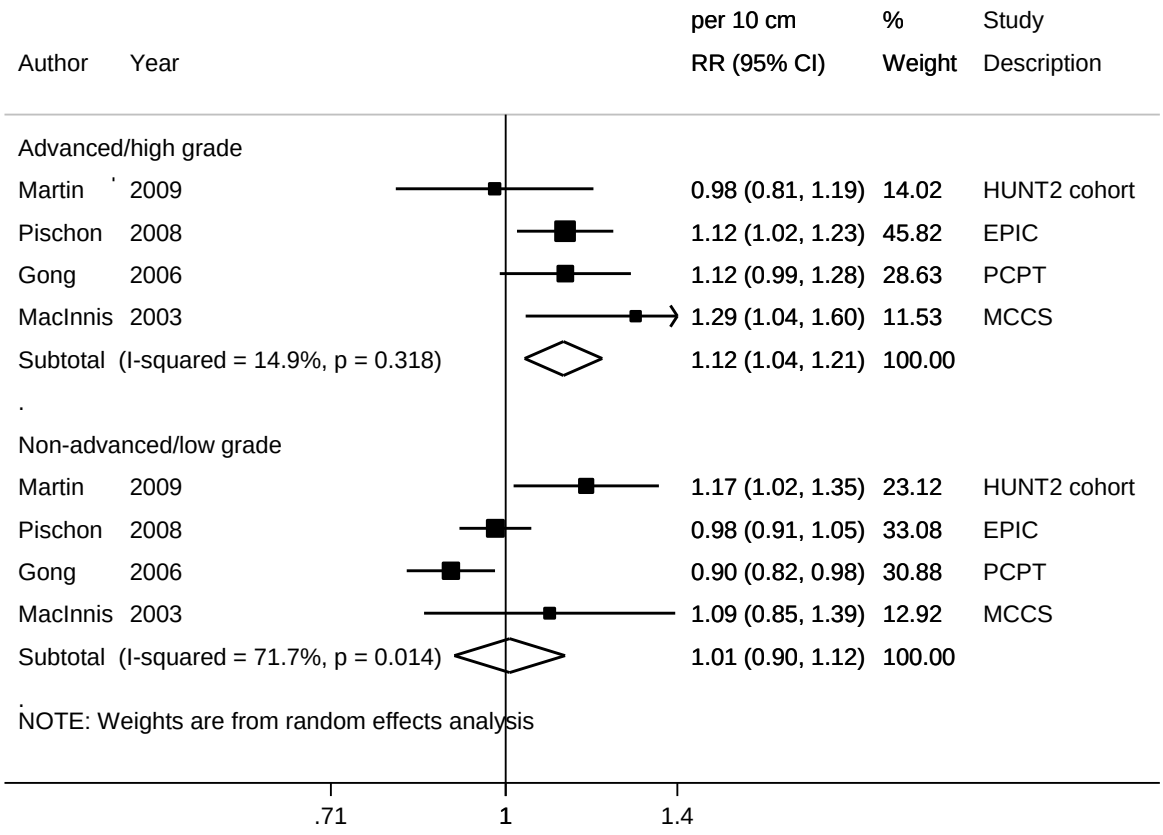
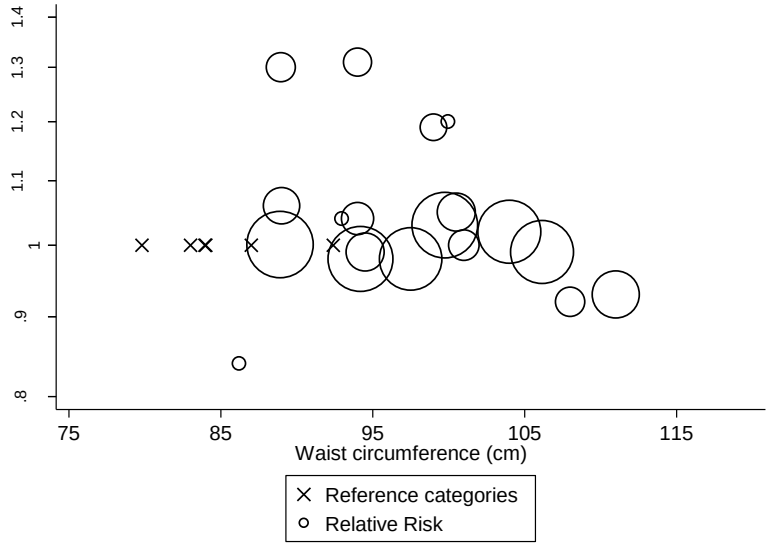


Figure 307 Non-linear dose-response analysis of waist circumference and prostate cancer



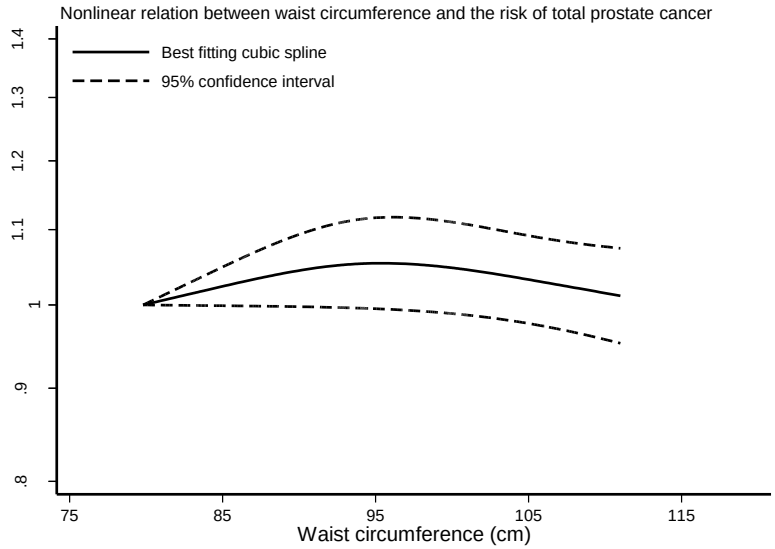


Table 272 Table with waist circumference values and corresponding RRs (95% CIs) for non-linear analysis of waist circumference and prostate cancer

WC (cm)	RR (95% CI)
79.8	1.00
88.9	1.04 (1.00-1.08)
94.5	1.05 (1.00-1.12)
100.5	1.05 (0.99-1.11)
111.0	1.01 (0.95-1.07)

$p_{non\text{-}linearity} = 0.05$

8.2.3 Waist to hip ratio

Methods
Six studies were identified, from which three studies were identified during the CUP.

Five studies could be included in the dose-response meta-analysis on prostate cancer. The increment unit used in the analysis was 0.1. One of the five studies reported on total prostate cancer only (Hubbard, 2004), one on total, localised, advanced, low grade, and high grade prostate cancers (Pischon, 2008), one on total, low grade, and high grade prostate cancers (Gong, 2006). One on total, localised, advanced, and fatal prostate cancers (Martin, 2009), one on total, low grade (Gleason 1-4), moderate grade (Gleason 5-7), and advanced (Gleason 8-10 and metastatic cases) prostate cancers (MacInnis, 2003).

A separate figure for all studies combined was not produced as there is no mortality study.
A non-linear dose-response analysis was not conducted as only four studies could be included. MacInnis et al (2003) reported linear dose-response results only.

Main results
The summary RR per 0.1 units was 1.01 (95% CI 0.96-1.06; $I^2 = 0\%$; $p_{heterogeneity} = 0.81$; n = 5) for prostate cancer risk. There was no evidence of publication bias with Egger's test, p = 0.34.

After stratification by prostate cancer type, the summary RRs per 0.1 units were 1.15 (95% CI 1.03-1.28; $I^2 = 0\%$; $p_{heterogeneity} = 0.63$; n = 4) for advanced/high grade prostate cancer and 0.99 (95% CI 0.90 1.09; $I^2=19.1\%$; $p_{heterogeneity} = 0.30$; n = 4) for non-advanced/low grade prostate cancer.

Heterogeneity
Overall, there was no evidence of heterogeneity, $I^2 = 0\%$, $p_{heterogeneity} = 0.81$.

Comparison with the Second Expert Report
In the 2005 SLR, the meta-analysis on waist to hip ratio and prostate cancer showed an overall non-significant positive association.

Published meta-analysis or pooled analysis
A meta-analysis published in 2006 observed a non-significant positive association (summary RR per 0.1 units 1.11, 95% CI 0.95-1.30; 3 cohort studies; 4 case-control studies) between waist to hip ratio and the risk of prostate cancer (MacInnis, 2006). All three cohort studies included in this published review were included in the present report. Giovannucci et al (1997) was not included in the analysis because of missing data. No pooled analysis was identified.

Table 273 Studies on waist to hip ratio identified in the CUP

Author, year	Country	Study name	Cases	Years of follow up	RR	LCI	UCI	Contrast
Martin, 2009	Norway	HUNT2	797	9.3 years	1.02	0.80	1.31	≥ 0.94 vs. ≤ 0.86
					0.99	0.92	1.07	Per 0.06 units
Pischon, 2008	Europe	EPIC	2446	8.5 years	1.01	0.88	1.15	≥ 0.99 vs. < 0.887
					1.02	0.95	1.10	Per 0.1 units
Gong, 2006	USA	Prostate Cancer Prevention Trial	832	3.3 years	0.98	0.80	1.22	≥1 vs. <0.9

Table 274 Overall evidence on waist to hip ratio and prostate cancer

	Summary of evidence
2005 SLR	Three prospective studies were identified during the 2005 SLR and all were included in the meta-analysis. All studies observed statistically non-significant results. One study reported an inverse association, one study reported a positive association, and one study reported no significant association.
Continuous Update Project	Three new prospective studies were identified in the CUP, all showed non-significant results. One study reported a significant positive association for advanced cancer. The CUP showed a significant positive association for advanced/high grade cancers.

Table 275 Summary of results of the dose response meta-analysis of waist to hip ratio and prostate cancer

Prostate cancer		
	2005 SLR	CUP
Studies (n)	3	5
Cases (n)	2033	5843
Increment unit used	Per 0.1 units	Per 0.1 units
Overall RR (95% CI)	1.02 (0.88-1.19)	1.01 (0.96-1.06)
Heterogeneity (I^2, p-value)	53.6%, p = 0.12	0%, p = 0.81
Stratified analysis		
Advanced/high grade cancer		
Overall RR (95% CI)	1.03 (0.93-1.14)	1.15 (1.03-1.28)
Heterogeneity (I^2, p-value)	n = 1	0%, p = 0.63, n = 4
Non-advanced/low grade cancer		
Overall RR (95%CI)		0.99 (0.90-1.09)
Heterogeneity (I^2, p-value)		19.1%, p = 0.30, n = 4

Table 276 Inclusion/exclusion table for meta-analysis of waist to hip ratio and prostate cancer

WCRF code	Author	Year	Study design	Study name	Cancer outcome	2005 SLR	CUP dose-response meta-analysis	CUP HvL forest plot	Estimated values	Exclusion reasons
PRO100050	Martin	2009	Prospective Cohort study	HUNT2	Incidence, all and advanced/high grade cancers	No	Yes	Yes		No categorical results by cancer types; excluded from advanced/high grade cancer highest vs lowest plot – dose-response result only
PRO100036	Pischon	2008	Prospective Cohort study	EPIC	Incidence/ Mortality, all and advanced/high grade cancers	No	Yes	Yes		
PRO99985	Gong	2006	Observational study in a RCT follow-up	PCPT	Incidence, all and advanced/high grade cancers	No	Yes	Yes	Number of non-cases per quartile	
PRO03985	Hubbard	2004	Prospective Cohort study	Baltimore Longitudinal Study of Aging	Incidence	Yes	Yes	Yes		
PRO04077	MacInnis	2003	Prospective Cohort study	MCCS	Incidence, all and advanced/high grade cancers	Yes	Yes	No		Excluded from all highest vs lowest plots - dose-response results only
PRO02314	Giovannucci	1997	Prospective Cohort study	HPFS	Incidence/ Mortality, all and advanced/high grade cancers	Yes	No	Yes		Excluded from all dose-response meta-analyses - missing 95% CIs, except for Q5 vs. Q1

Figure 308 Highest versus lowest forest plot of waist to hip ratio and prostate cancer

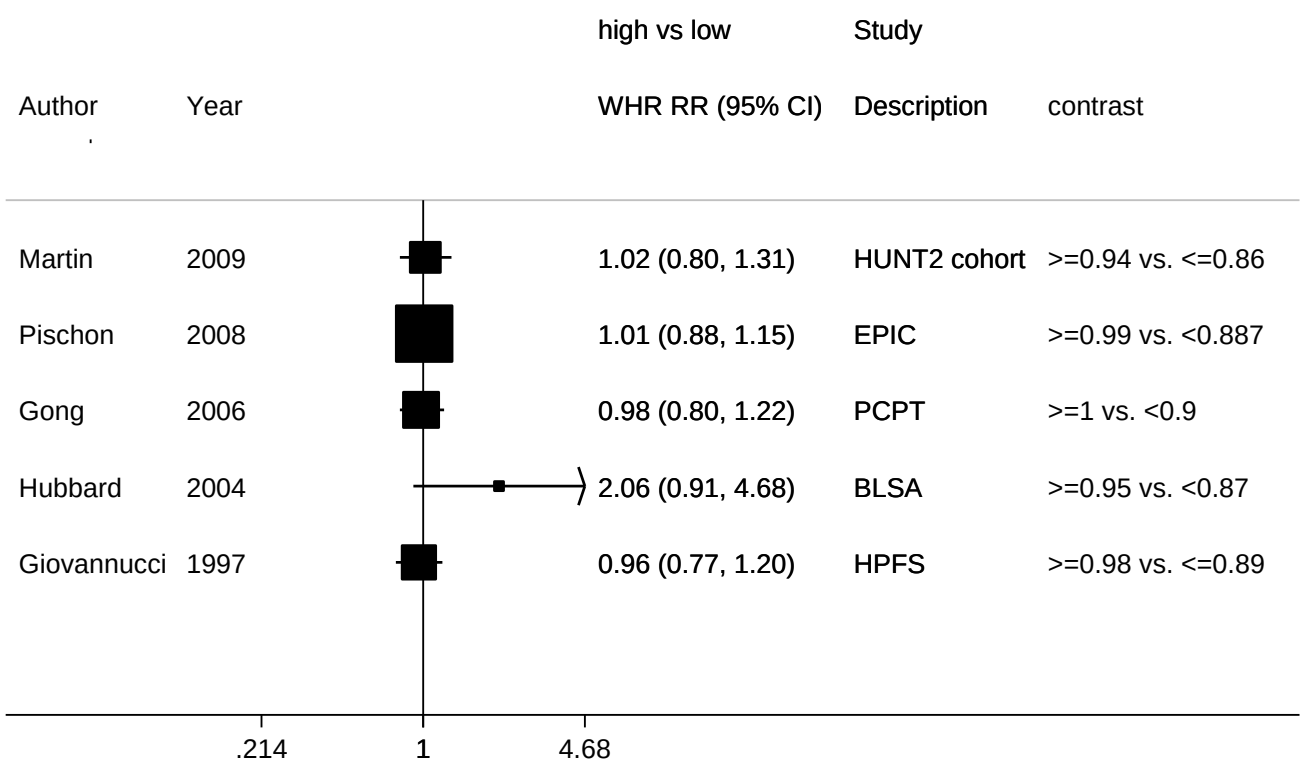


Figure 309 Dose-response meta-analysis of waist to hip ratio and prostate cancer – per 0.1 units

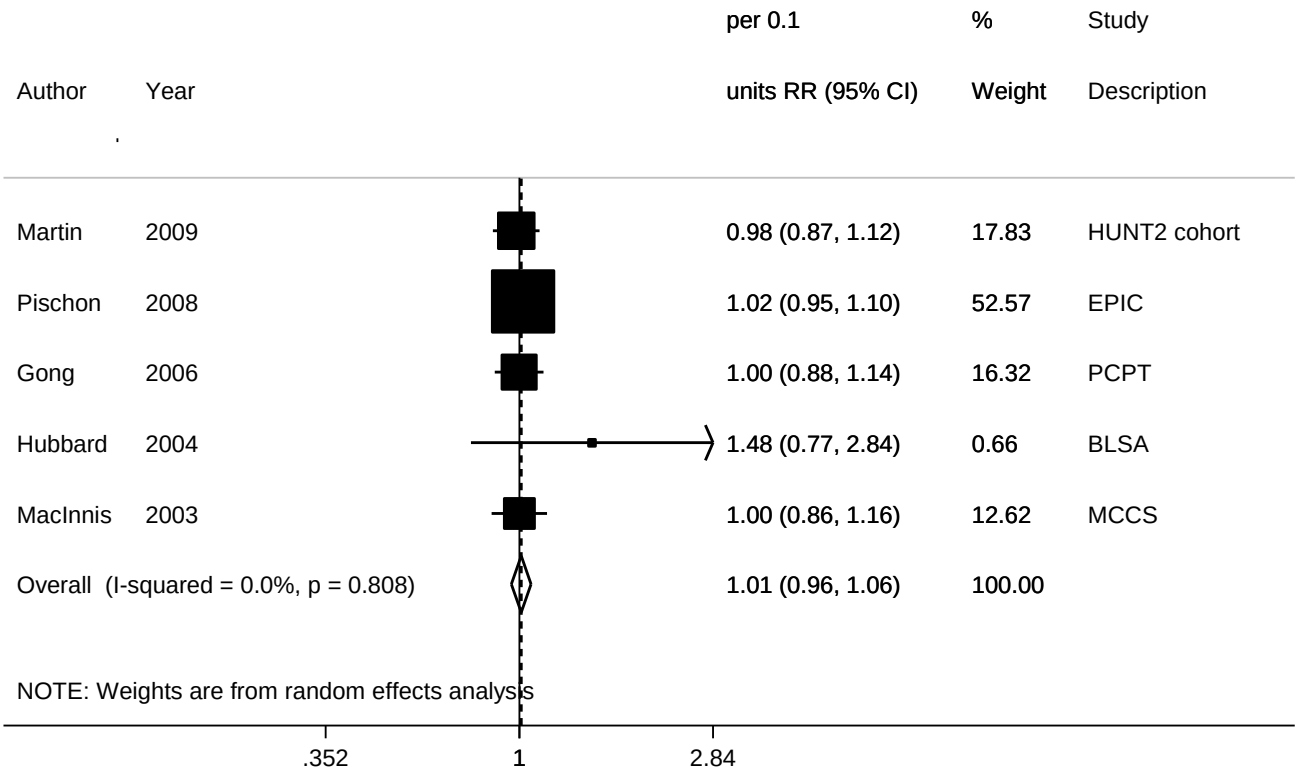
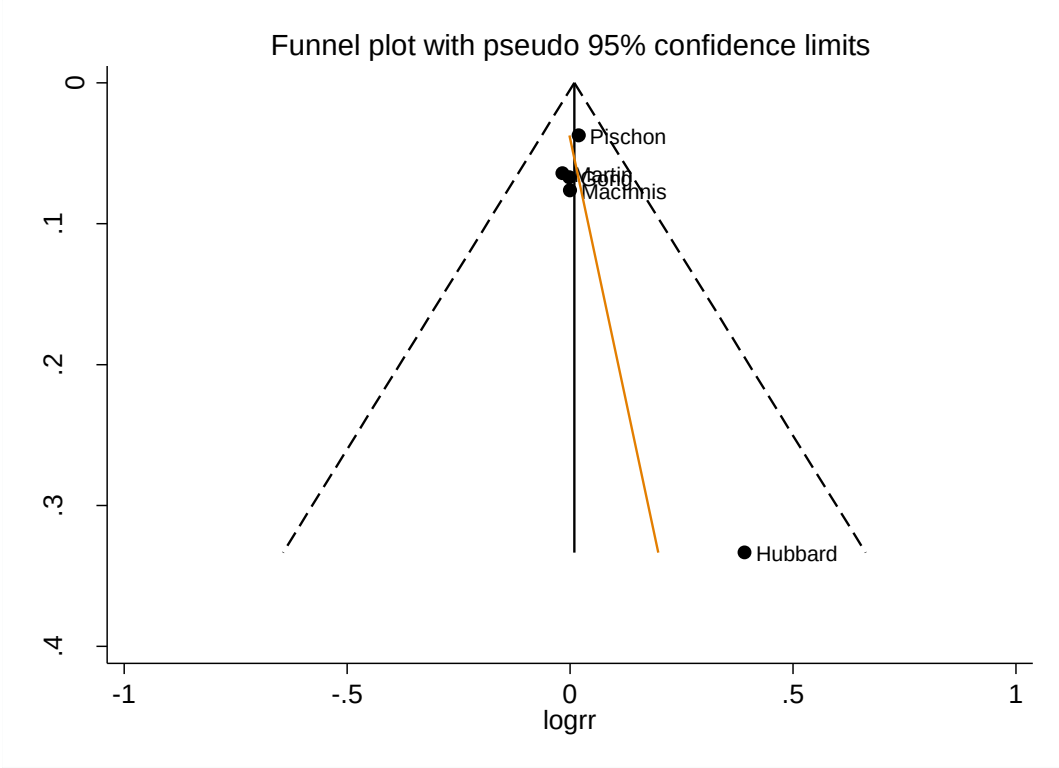


Figure 310 Funnel plot of waist to hip ratio and prostate cancer



Egger's test p = 0.34

Figure 311 Dose-response graph of waist to hip ratio and prostate cancer

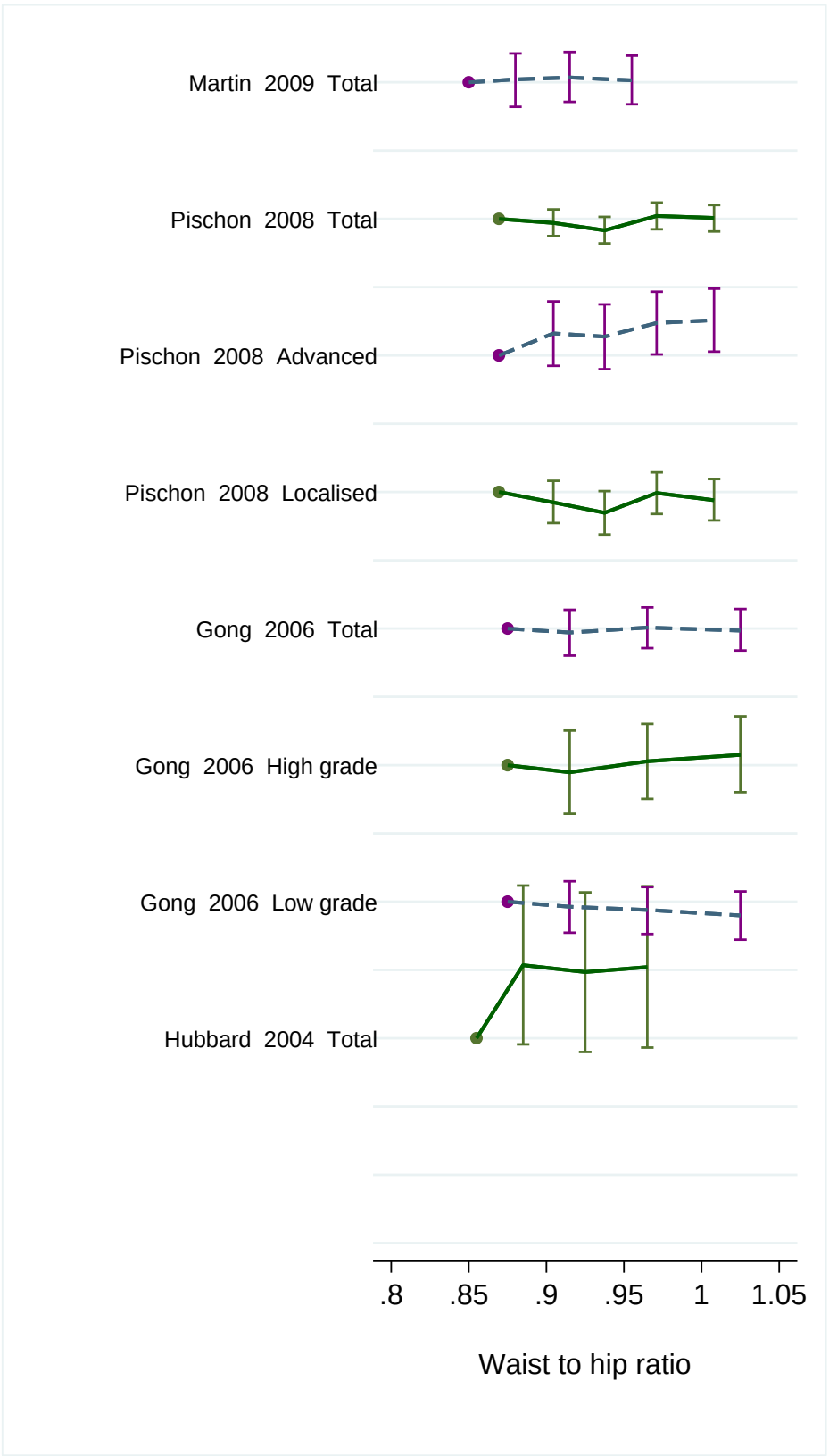


Figure 312 Highest vs lowest forest plot of waist to hip ratio for advanced/high-grade prostate cancer

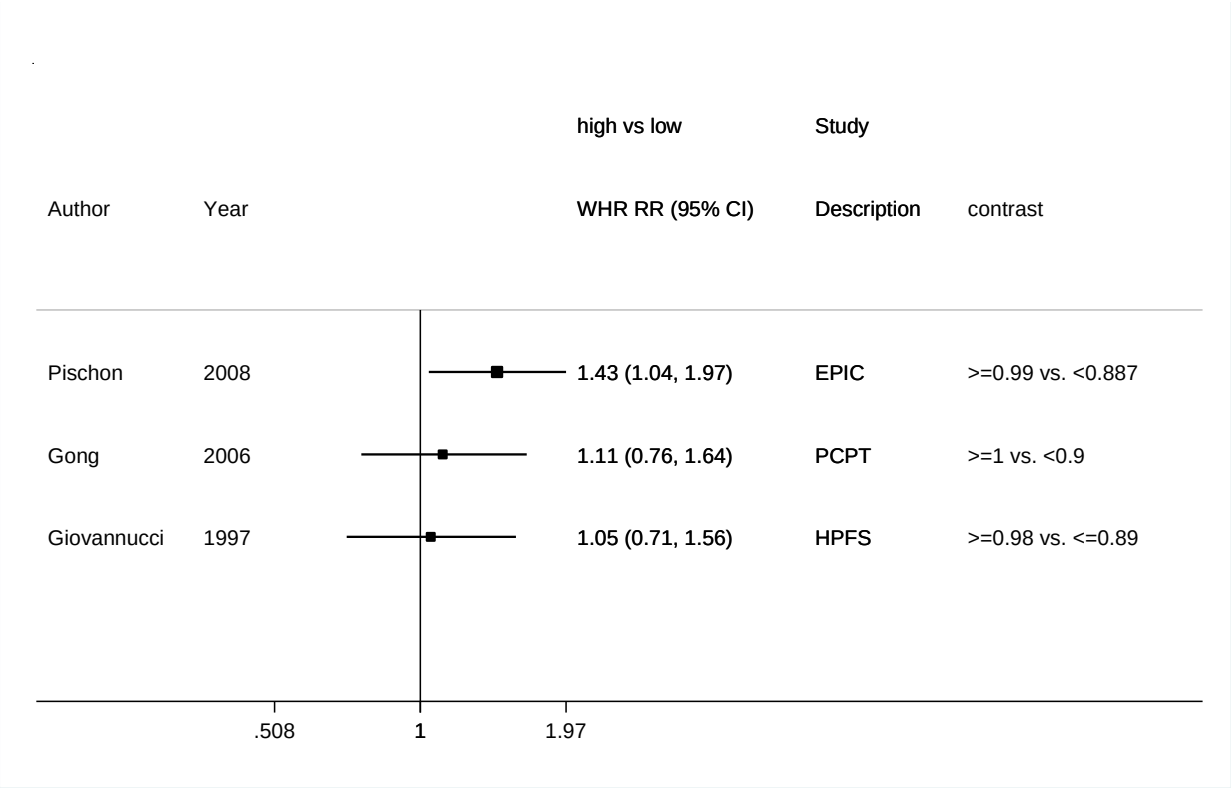
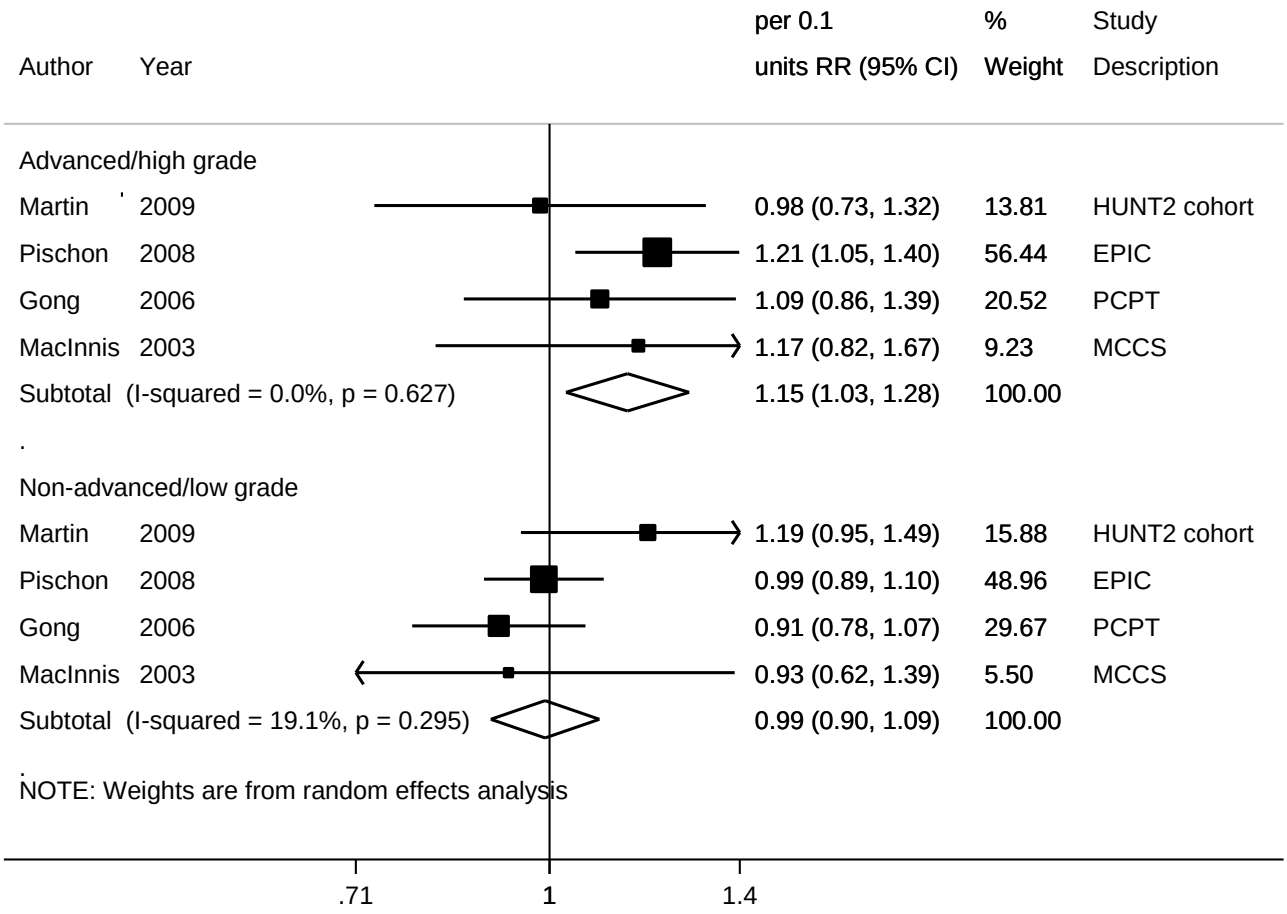


Figure 313 Dose-response meta-analysis of waist to hip ratio and prostate cancer, per 0.1 units, stratified by prostate cancer type



8.3.1 Height

Methods

Overall, 42 studies from 53 publications were identified. Seventeen studies from 20 publications were identified during the CUP. Eleven studies (12 publications) were new to the CUP.

Wallström et al (2009) is a component study of Pischon et al (2008). Four studies (ATBC, HPFS, MCCS, WS) (6 publications) had also published in the 2005 SLR. Lunqvist et al (2007) overlapped with Jonsson et al (2003) and Lund Håheim et al (2006) is a component study of Thune et al (1994).

In addition, the studies of CLUE II and PHS had published multiple articles during the 2005 SLR. One publication identified during the 2005 SLR has two studies (CPS I and II).

Seven studies – Harvard, USA 1880-1916 (Greenwald et al, 1974); Hawaii, USA 1965-1968 (Chyon et al, 1994); NHANES (Clarke et al, 2000); BLSA (Brooks et al, 2001); CARET (Lamharzi et al, 2003); VIP/MONICA (Stattin et al, 2004); CLUE II (Platz et al, 2002; Platz et al, 2004) identified in the 2005 SLR only reported mean exposure values and could not be included in the analysis. There were no new publications for these studies. In addition, the study of Hiatt et al (1994) (California, USA 1979-1985) was not included in the analysis.

Thirty-four studies could be included in the dose-response meta-analysis on prostate cancer. The increment unit used in the analysis was 5 cm. The method of Hamling was used to recalculate the RRs when the lowest height category was not used as a reference category (Engeland et al, 2003; Jonsson et al, 2003; Rodriguez et al, 2001).

From the studies included in the dose-response meta-analysis, 16 studies reported on total prostate cancer (Sung et al, 2009; Sequoia et al, 2006; Tande et al, 2006; Engeland et al, 2003; Gunnell et al, 2003; Jonsson et al, 2003; Davey Smith et al, 2000; Habel et al, 2000; Putnam et al, 2000; Cerhan et al, 1997; Hebert et al, 1997; Tulinius et al, 1997 Veierod et al, 1997; Le Marchand et al, 1994; Thune et al, 1994; Albanes et al, 1988), two studies on total, advanced/aggressive, localised/non-aggressive, high grade, and low grade prostate cancer (Hernandez et al, 2009; Pischon et al, 2008), five studies on total, advanced/aggressive, and localised/non-aggressive prostate cancer (Ahn et al, 2009a; Littman et al, 2007; Kurahashi et al, 2006; Schuurman et al, 2000; Lund Nilsen et al, 1999), two studies on total, non-aggressive/Gleason score < 7, aggressive/Gleason score ≥ 7, and fatal prostate cancer (Bassett et al, 2012; Stocks et al, 2010), one study on total, low grade, and high grade prostate cancer (Gong et al, 2006), two studies on total, and advanced/high grade prostate cancer (Shafique et al, 2012a; Giovannucci et al, 1997), one study on total and fatal prostate cancer (Andersson et al, 1997), and five studies on fatal cancer (Batty et al, 2011; Fujino et al, 2007; Freeman et al, 2001; Rodriguez et al, 2001 (CPS I/II)). Advanced, aggressive, high grade and fatal cancers were combined in a sub-group for separate meta-analysis.

Main results

The summary RR of prostate cancer per 5 cm was 1.04 (95% CI 1.03-1.05; $I^2 = 21.0\%$; $p_{heterogeneity} = 0.14$; n = 34) (all studies with different outcomes combined). The summary RR did not change materially when studies were omitted in turn in the influence analysis. The Egger's test of publication bias was not significant (p = 0.79) but the funnel plot suggests that a small study reporting a positive association is an outlier. For prostate cancer mortality, the summary RR per 5 cm was 1.04 (95% CI 1.01-1.06; $I^2 = 35.6\%$; $p_{heterogeneity} = 0.13$; n = 9).

After stratification by prostate cancer type, the summary RRs per 5 cm were 1.04 (95% CI 1.03-1.05; $I^2 = 20.5\%$; $p_{heterogeneity} = 0.17$; n = 28) for total prostate cancer (excluding studies reporting on

mortality), 1.04 (95% CI 1.02-1.06; I^2=46.7%; $p_{heterogeneity}$ = 0.01; n = 19) for advanced/high grade prostate cancer, and 1.03 (95% CI 1.01-1.05; I^2 = 19.4%; $p_{heterogeneity}$ = 0.27; n = 10) for non-advanced/low grade prostate cancer. After stratification by prostate cancer grade, the summary RRs per 5 cm were 1.01 (95% CI 0.96-1.06; I^2 = 45.2%; $p_{heterogeneity}$ = 0.12; n = 5) for high grade prostate cancer, and 1.02 (95% CI 0.98-1.07, I^2=64.7%; pheterogeneity = 0.04; n = 4) for low grade prostate cancer.

There was evidence of non-linearity relationship for total and advanced/high grade prostate cancers (p = 0.01 and p < 0.01 respectively), but not for non-advanced/low grade prostate cancer (p=0.20).

Heterogeneity

There was no evidence of heterogeneity between studies of prostate cancer risk (I^2 = 21.0%; $p_{heterogeneity}$ = 0.14; n = 34, all studies combined).

Comparison with the Second Expert Report

In the 2005 SLR, the meta-analysis on height and prostate cancer showed an overall non-significant positive association.

Published meta-analysis or pooled analysis

Thirty-one cohort studies were included in a dose-response meta-analysis (Zuccolo et al, 2008). The summary RR per 10 cm increase was 1.09 (95% CI 1.06-1.12; I^2 = 23.4%; $p_{heterogeneity}$ = 0.12). All the studies included in the meta-analysis are included in the CUP review, apart from the case-control study originated from the ProtecT trial (Zuccolo et al, 2008). The RR per 10 cm was 1.06 (95% CI 0.97-1.16) in this trial.

The Emerging Risk Factors Collaboration (ERFC, 2012) observed a HR of 1.07 (95% CI 1.02-1.11) per 6.5 cm increase in height in a pooled analysis that included 2818 prostate cancer deaths from 1,085,949 participants (121 prospective studies).

The Asia Pacific Cohort Studies Collaboration (APCSC) observed a HR of 1.06 (95% CI 0.95-1.18) per 6.0 cm increase in a pooled analysis that included 274 prostate cancer deaths from 506,648 Asian men (38 population-based cohort studies) (Batty et al, 2010).

Table 277 Studies on height identified in the CUP

Author, year	Country	Study name	Cases	Years of follow up	RR	LCI	UCI	Contrast
Bassett, 2012	Australia	MCCS	1374	15 years	1.04	0.88	1.23	≥ 177.6 vs. < 167.7 cm
					1.02	0.97	1.07	Per 5 cm
Shafique, 2012a	Scotland	Midspan study	650	293284 person-years	1.35	1.04	1.75	≥ 177.9 vs. ≤ 165.1 cm
Batty, 2011	UK	WS	578	40 years	1.37	1.09	1.74	> 1.78 vs. < 1.73 m
					1.11	1.01	1.22	Per 0.068 m
Stocks, 2010	Sweden	SCWC	10002	22.2 years	1.14	1.06	1.22	≥ 184.0 vs. ≤ 172.9 cm
Ahn, 2009a	USA	PLCO	2144	8.9	1.06	0.82	1.36	> 190 vs. ≤ 170 cm

				years	1.02	0.98	1.05	Per 5 cm
Hernandez, 2009	USA	MEC	5554	9.6 years	1.01	0.92	1.11	≥ 70 vs. < 66 in
Sung, 2009	Korea	Korean Cohort Study	1612	8.72 years	1.11	0.96	1.29	> 171.0 vs. 164.6-168.0 cm
					1.08	1.03	1.13	Per 5 cm
Wallström 2009	Sweden	MDC study (component of EPIC)	817	11 years	1.31	1.05	1.64	≥ 182 vs. ≤ 170 cm
Ahn 2008a	Finland	ATBC	1111	12.3 years	2.50	1.69	3.69	> 176 cm and with family history vs. < 171 cm and no family history
Pischon, 2008	Europe	EPIC	2446	8.5 years	1.04	0.91	1.20	≥ 180.5 vs. < 168 cm
					1.01	0.98	1.04	Per 5 cm
Fujino, 2007	Japan	JCCS	160		0.84	0.56	1.25	≥ 165 vs. < 160 cm
Giovannucci, 2007	USA	HPFS	3544	673706 person-years	1.05	0.88	1.27	≥ 72 vs. < 66 in
Littman, 2007	USA	VITAL	832	4 years (max)	1.30	1.10	1.60	≥ 73 vs. ≤ 68 in
Lundqvist, 2007	Sweden, Finland	Sweden, Finland Co-twin study	1284	25 years	1.00	0.90	1.20	Q4 vs. Q1
					1.03	0.97	1.09	Per 1 SD
Batty, 2006	UK	WS	434	35 years (max)	1.39	1.03	1.88	≥ 181 vs. ≤ 170.9 cm
Gong, 2006	USA	PCPT	1936	7 years	1.22	1.05	1.43	≥ 1.83 vs. < 1.72 m
Tande, 2006	USA	ARIC Study	385	12.1 years	0.92	0.69	1.22	≥ 180.0 vs. ≤ 170.0 cm
Kurahashi, 2006	Japan	JPHC I and II	311	13 (max)	1.08	0.73	1.59	≥ 168 vs. ≤ 159 cm
Lund Håheim, 2006	Norway	Oslo Study	507	27 years	1.00	0.99	1.02	Per 1 cm
Sequoia, 2006	Finland	ATBC	1346	14.1 years	1.14	0.96	1.35	179-200 vs. 136-168 cm
					1.08	0.99	1.18	Per 10 cm

Table 278 Overall evidence on height and prostate cancer

	Summary of evidence
2005 SLR	Thirty-one studies (33 publications) were identified during the 2005 SLR. Five of the 23 studies included in the meta-analysis observed statistically significant or borderline significant increased risk.
Continuous Update Project	Seventeen studies (11 new) from 20 publications were identified in the CUP. Five studies observed a significant increased risk for the highest versus lowest comparison. Thirteen studies reported on advanced prostate cancer and three observed a significant increased risk. The CUP meta-analysis showed a positive association for all prostate cancers and in most subgroups.

Table 279 Summary of results of the dose response meta-analysis of height and prostate cancer

Prostate cancer		
	2005 SLR	CUP
Studies (n)	23	34
Cases (n)	46729	79387
Increment unit used	Per 10 cm	Per 5 cm
Overall RR (95% CI)	1.02 (0.97-1.08)	1.04 (1.03-1.05)
Heterogeneity (I^2, p-value)	86.2%, p < 0.001	21.0%, p=0.14
Stratified analysis		
Total prostate cancer		
Overall RR (95% CI)		1.04 (1.03-1.05)
Heterogeneity (I^2, p-value)		20.5%, p = 0.17,n=28
Fatal cancer		
Overall RR (95% CI)	0.91 (0.73-1.13)	1.04 (1.01-1.06)
Heterogeneity (I^2, p-value)	-*, n = 5	35.6%, p = 0.13, n = 9
Advanced/high grade cancer		
Overall RR (95% CI)	0.91 (0.77-1.08)	1.04 (1.02-1.06)
Heterogeneity (I^2, p-value)	86.0%, p<0.01, n=7	46.7%, p = 0.01, n = 19
Non-advanced/low grade cancer		
Overall RR (95% CI)		1.03 (1.01-1.05)
Heterogeneity (I^2, p-value)		19.4%, p = 0.27, n = 10
High grade cancer		
Overall RR (95% CI)		1.01 (0.96-1.06)
Heterogeneity (I^2, p-value)		45.2%, p = 0.12, n = 5
Low grade cancer		
Overall RR (95% CI)		1.02 (0.98-1.07)
Heterogeneity (I^2, p-value)		64.7%, p = 0.04, n = 4

*Values not available

Table 280 Inclusion/exclusion table for meta-analysis of height and prostate cancer

WCRF code	Author	Year	Study design	Study name	Cancer outcome	2005 SLR	CUP dose-response meta-analysis	CUP HvL forest plot	Estimated values	Exclusion reasons/remarks
PRO100163	Bassett	2012	Prospective Cohort study	MCCS	Incidence/ Mortality	No	Yes	Yes		
PRO100117	Shafique	2012	Prospective Cohort study	Midspan study	Incidence	No	Yes	Yes	Mid-exposure values	
PRO100170	Batty	2011	Prospective Cohort study	WS	Mortality	No	Yes	Yes		
PRO100193	Stocks	2010	Prospective Cohort study	SCWC	Incidence	No	Yes	Yes	Mid-exposure values	
PRO100045	Ahn	2009 a	Prospective Cohort study	PLCO	Incidence/ Mortality	No	Yes	Yes		
PRO100072	Hernandez	2009	Prospective Cohort study	MEC	Incidence	No	Yes	Yes	Person-years per quartile; mid-exposure values	
PRO100054	Sung	2009	Prospective Cohort study	Korean Cohort Study	Incidence	No	Yes	Yes	Cases and person-years per quartile	
PRO100047	Wallström	2009	Prospective Cohort study	MDC study	Incidence	No	No	No		Duplicate publication; component study of Pischon, 2008; superseded
PRO100022	Ahn	2008 a	Prospective Cohort study	ATBC	Incidence	No	No	No		Duplicate publication; interaction between height and family history in relation to prostate cancer; superseded by Sequoia, 2006

PRO100036	Pischon	2008	Prospective Cohort study	EPIC	Incidence/ Mortality	No	Yes	Yes		
PRO100130	Fujino	2007	Prospective Cohort study	JACC	Mortality	No	Yes	Yes	Mid-exposure values	
PRO99961	Giovannucci	2007	Prospective Cohort study	HPFS	Incidence	No	No	Yes		Duplicate publication; two exposure categories only; included in H vs. L analysis – more cases than Giovannucci, 1997
PRO99973	Littman	2007	Prospective Cohort study	VITAL	Incidence/ Mortality	No	Yes	Yes	Mid-exposure values	
PRO100018	Lundqvist	2007	Prospective Cohort study	Sweden, Finland Co-twin study	Incidence/ Mortality	No	No	Yes		Duplicate publication; overlapped with Jonsson, 2003; included in H vs. L analysis - more number of cases; excluded in dose-response analysis - no exposure values and unknown value of increment
PRO100190	Batty	2006	Prospective Cohort study	WS	Mortality	No	No	No		Duplicate publication; superseded by Batty, 2011
PRO99985	Gong	2006	Observational study of a RCT follow-up	PCPT	Incidence	No	Yes	Yes	Cases and non-cases per quartile; mid-exposure values	
PRO99964	Kurahashi	2006	Prospective Cohort study	JPHC I and II	Incidence	No	Yes	Yes	Mid-exposure values	

PRO100038	Lund Håheim	2006	Prospective Cohort study	Norway, Oslo follow up study (Oslo Study)	Incidence	No	No	No		Duplicate publication; component study of Thune, 1994; superseded
PRO99971	Sequoia	2006	Prospective Cohort study	ATBC	Incidence	No	Yes	Yes		
PRO100194	Tande	2006	Prospective Cohort study	ARIC Study	Incidence	No	Yes	Yes	Mid-exposure values	
PRO97424	Weinstein	2005	Nested Case Control study	ATBC	Incidence	Yes	No	No		Duplicate publication ; superseded by Sequoia, 2006
PRO10545	Li	2004	Nested Case Control study	PHS	Incidence	Yes	No	No		Duplicate publication ; less number of cases; superseded by Hebert, 1997
PRO10700	Platz	2004 b	Nested Case Control study	CLUE ll	Incidence	Yes	No	No		Mean exposure only
PRO10575	Platz	2004 c	Nested Case Control study	HPFS	Incidence/ Mortality	Yes	No	No		Duplicate publication ; superseded by Giovannucci, 2007
PRO97316	Stattin	2004	Case Cohort Study	VIP/MONICA	Incidence	Yes	No	No		Mean exposure only
PRO00302	Engeland	2003	Prospective Cohort study	Norway 1963-1975	Incidence/ Mortality	Yes	Yes	Yes	Recalculated RRs with lowest category as reference using Hamling's method; mid-exposure values	
PRO97771	Gunnell	2003	Prospective Cohort study	Caerphilly Study	Incidence	Yes	Yes	No		Dose-response results only
PRO00373	Jonsson	2003	Prospective Cohort study	Sweden Twin Cohort 1886-1925	Incidence/ Mortality	Yes	Yes	No	Recalculated RRs with lowest category as reference using Hamling's method; mid-exposure values	Overlapped with Lundqvist, 2007; included in dose-response analysis – sufficient data

PRO00451	Lamharzi	2003	Nested Case Control study	CARET	Incidence	Yes	No	No		Mean exposure only
PRO04077	MacInnis	2003	Prospective Cohort study	MCCS	Incidence	Yes	No	No		Duplicate publication ; superseded by Bassett, 2012
PRO00755	Platz	2002	Nested Case Control study	CLUE ll	Incidence	Yes	No	No		Duplicate publication; superseded by Platz, 2004; mean exposure only
PRO01046	Brooks	2001	Nested Case Control study	BLSA	Incidence	Yes	No	No		Mean exposure only
PRO01344	Freeman	2001	Historical Cohort study	NHIS 86-94	Mortality	Yes	Yes	Yes		
PRO01232	Rodriguez	2001	Prospective Cohort study	CPS I	Mortality	Yes	Yes	Yes	Recalculated RRs with lowest category as reference using Hamling's method; mid-exposure values	
				CPS II	Mortality	No	Yes	Yes	Recalculated RRs with lowest category as reference using Hamling's method; mid-exposure values	CPS II missed in 2005 SLR
PRO01468	Clarke	2000	Prospective Cohort study	NHANES	Incidence/ Mortality	Yes	No	No		Mean exposure only
PRO01618	Davey Smith	2000	Prospective Cohort study	UK 72-76	Mortality	Yes	Yes	No		Dose-response results only
PRO01599	Habel	2000	Prospective Cohort study	California, USA 1964-1973	Incidence	Yes	Yes	Yes	Cases and person-years per quartile; mid-exposure values	
PRO01487	Putnam	2000	Prospective Cohort study	IW,USA 86-89	Incidence	Yes	Yes	Yes	Mid-exposure values	

PRO01612	Schuurman	2000	Case Cohort Study	NLCS	Incidence	Yes	Yes	Yes		
PRO01688	Lund Nilsen	1999	Prospective Cohort study	Norway 1984-1986/HUNT study	Incidence/ Mortality	Yes	Yes	Yes	Cases and person-years per quintile; mid-exposure values	
PRO02391	Andersson	1997	Historical Cohort study	Sweden 1971-1975	Incidence	Yes	Yes	Yes	Mid-exposure values	
PRO02364	Cerhan	1997	Prospective Cohort study	I65 + RHS	Incidence	Yes	Yes	Yes	Mid-exposure values	
PRO02314	Giovannucci	1997	Prospective Cohort study	HPFS	Incidence/ Mortality	Yes	Yes	No	Mid-exposure values	Exposure range missed in 2005 SLR; included in dose-response analysis – sufficient exposure data
PRO02326	Hebert	1997	Prospective Cohort study	PHS	Incidence	Yes	Yes	Yes	Estimated 95% CI from p-value	
PRO02254	Tulinius	1997	Prospective Cohort study	ICRFS	Incidence	Yes	Yes	No		Dose-response results only
PRO02242	Veierod	1997	Prospective Cohort study	Norway1977-1983	Incidence	Yes	Yes	Yes	Mid-exposure values	Same screening programme as Thune, 1994 but with different recruitment periods
PRO10195	Leon	1995	Prospective Cohort study	WS	Mortality	Yes	No	No		Duplicate publication; superseded by Batty, 2011
PRO02809	Chyou	1994	Prospective Cohort study	Hawaii, USA 1965-1968	Incidence	Yes	No	No		Mean exposure only

PRO02822	Hiatt	1994	Prospective Cohort study	California, USA 1979-1985	Incidence	Yes	No	No		Results in text only- No difference in height found between patients with prostate cancer and control subjects
PRO02788	Le Marchand	1994	Prospective Cohort study	Hawaii, USA 1975-1980	Incidence	Yes	Yes	Yes	Cases and person-years per quartile; exposure value at 50 percentile; mid-exposure values	
PRO02744	Thune	1994	Prospective Cohort study	Norway 1972-1978	Incidence	Yes	Yes	No	Mid-exposure values	Not overlap with other Norwegian screening programmes; dose-response results only
PRO13427	Albanes	1988	Prospective Cohort study	NHANES I 71-75	Incidence	Yes	Yes	Yes	Cases and person-years per quartile; mid-exposure values	
PRO03769	Greenwald	1974	Nested Case Control study	Harvard, USA 1880-1916	Mortality	Yes	No	No		Mean exposure only

Figure 314 Highest versus lowest forest plot of height and prostate cancer

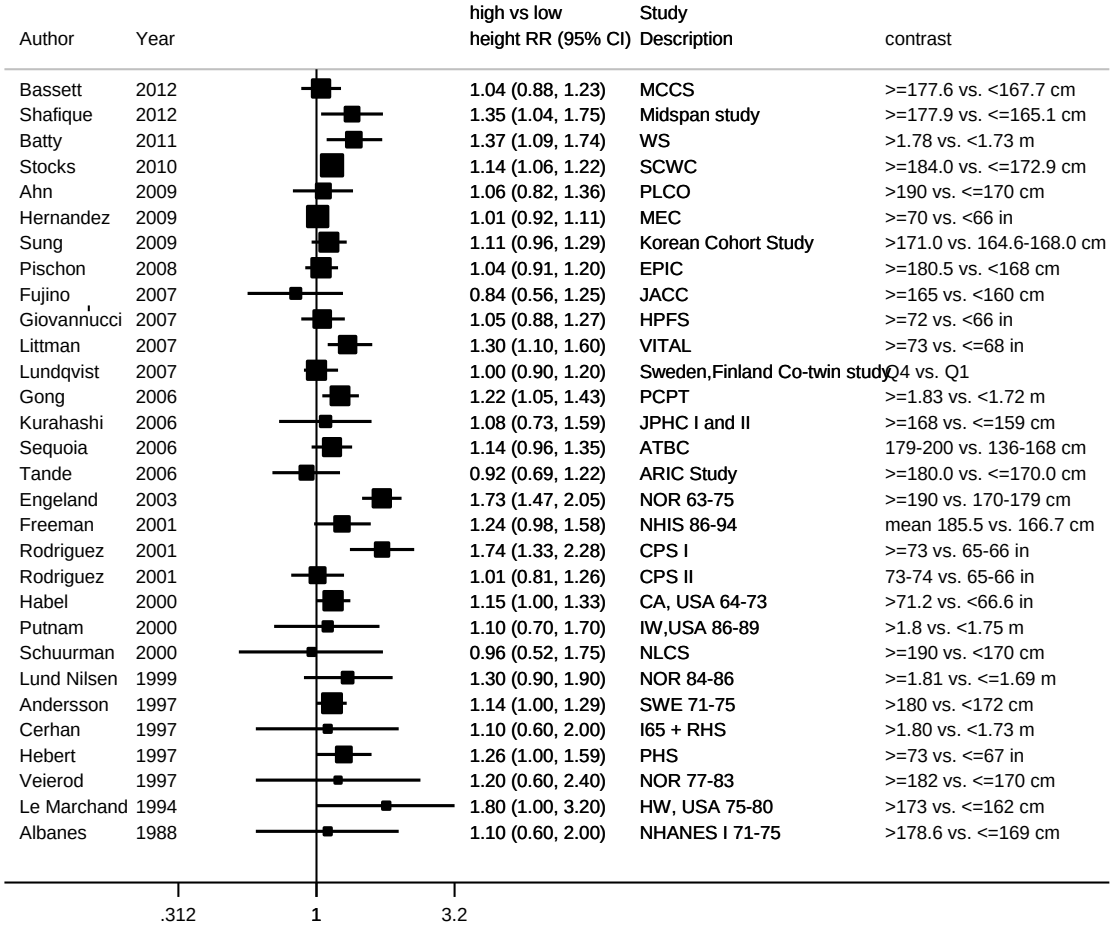


Figure 315 Dose-response meta-analysis of height and prostate cancer – per 5 cm

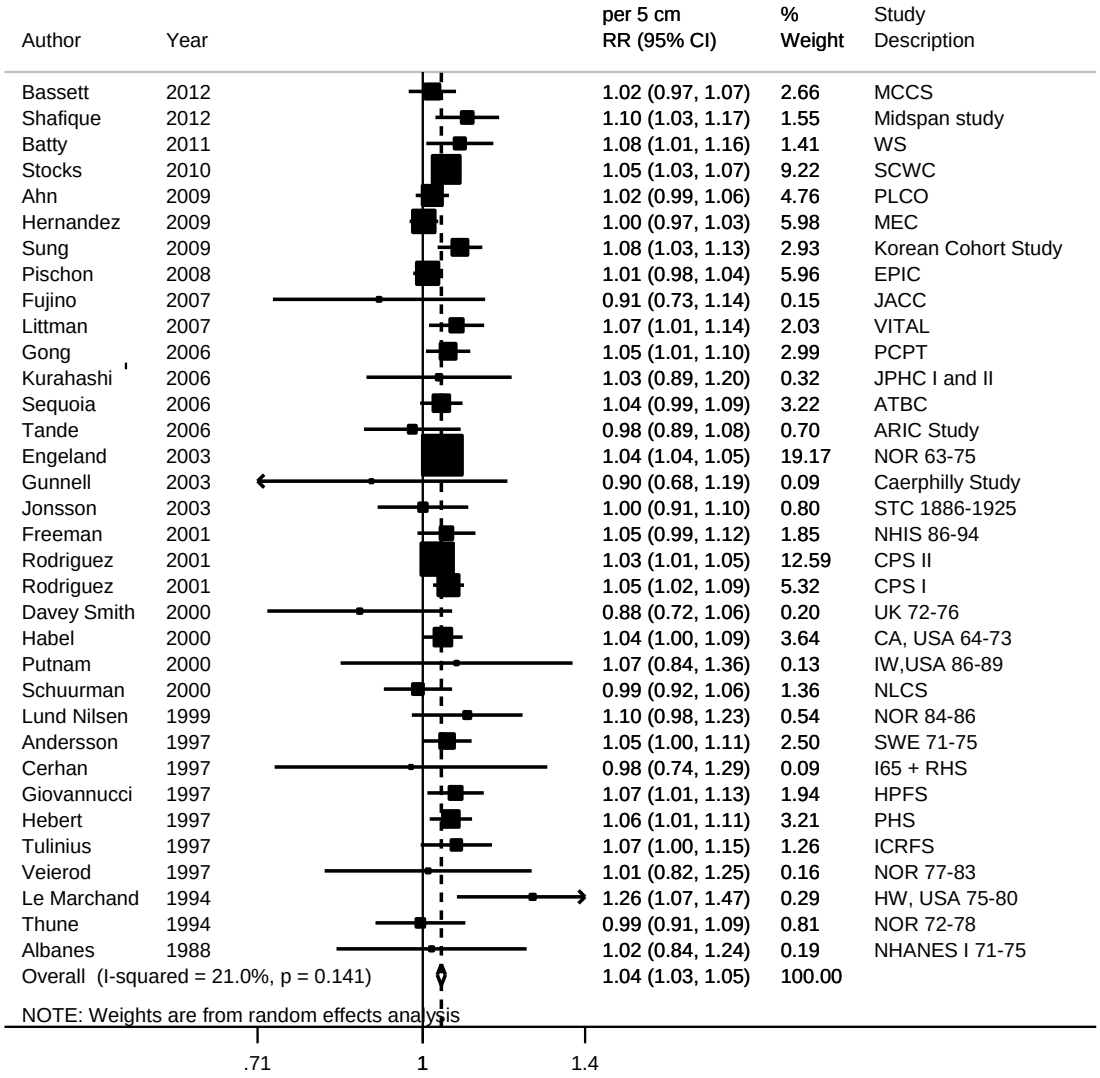
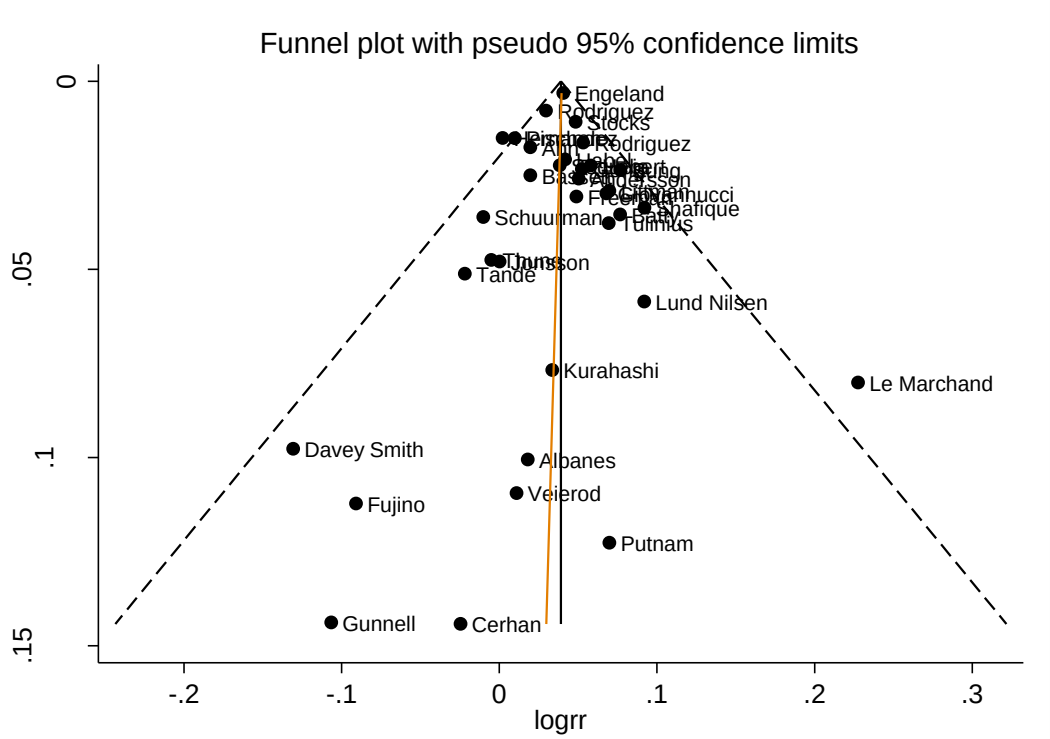
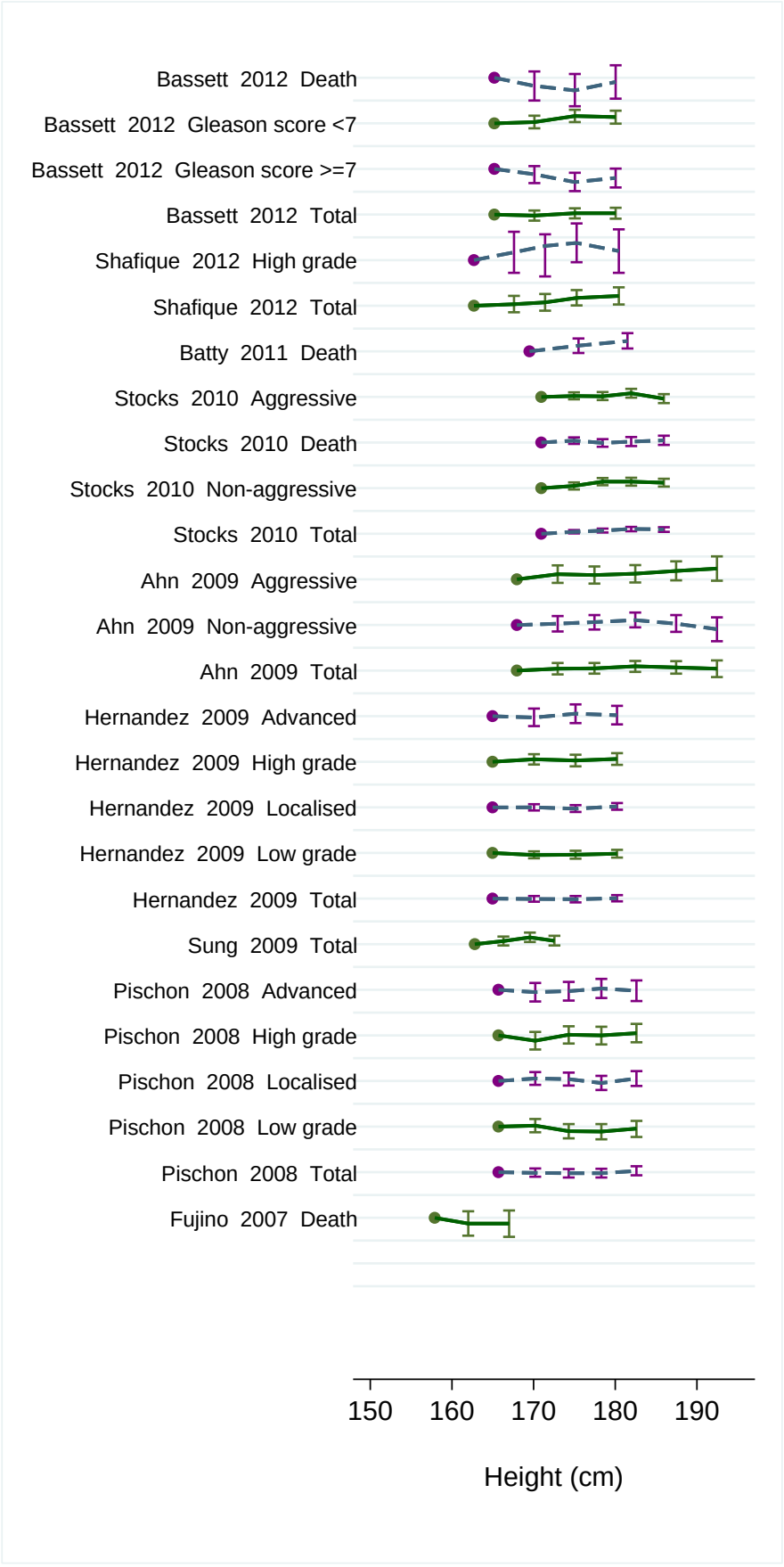


Figure 316 Funnel plot of height and prostate cancer



Egger's test p = 0.79

Figure 317 Dose-response graph of height and prostate cancer



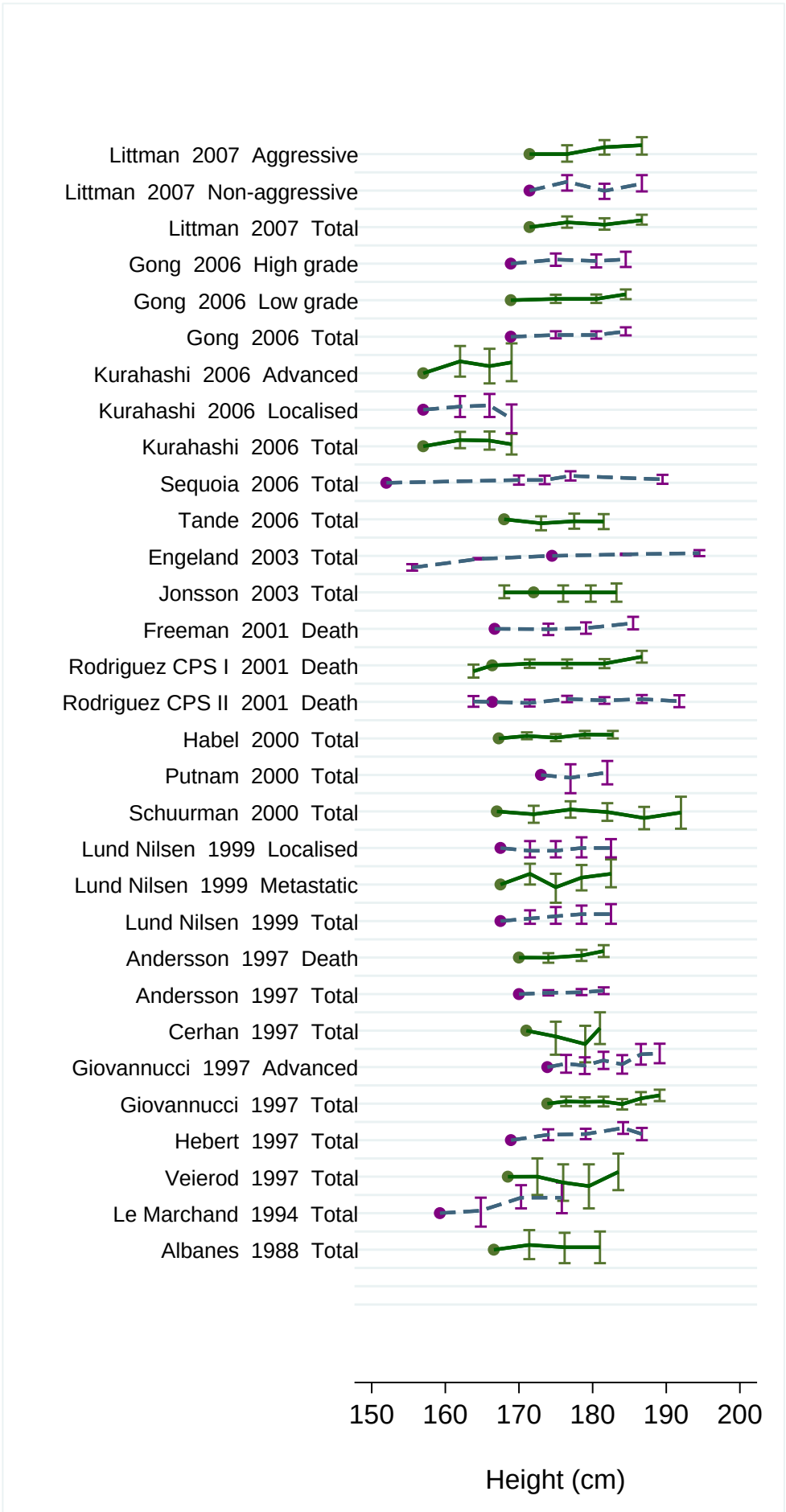

Littman 2007 Aggressive
Littman 2007 Non-aggressive
Littman 2007 Total
Gong 2006 High grade
Gong 2006 Low grade
Gong 2006 Total
Kurahashi 2006 Advanced
Kurahashi 2006 Localised
Kurahashi 2006 Total
Sequoia 2006 Total
Tande 2006 Total
Engeland 2003 Total
Jonsson 2003 Total
Freeman 2001 Death
Rodriguez CPS I 2001 Death
Rodriguez CPS II 2001 Death
Habel 2000 Total
Putnam 2000 Total
Schuurman 2000 Total
Lund Nilsen 1999 Localised
Lund Nilsen 1999 Metastatic
Lund Nilsen 1999 Total
Andersson 1997 Death
Andersson 1997 Total
Cerhan 1997 Total
Giovannucci 1997 Advanced
Giovannucci 1997 Total
Hebert 1997 Total
Veierod 1997 Total
Le Marchand 1994 Total
Albanes 1988 Total
150
160
170
180
190
200
Height (cm)

Figure 318 Dose-response meta-analysis of height and prostate cancer mortality– per 5 cm

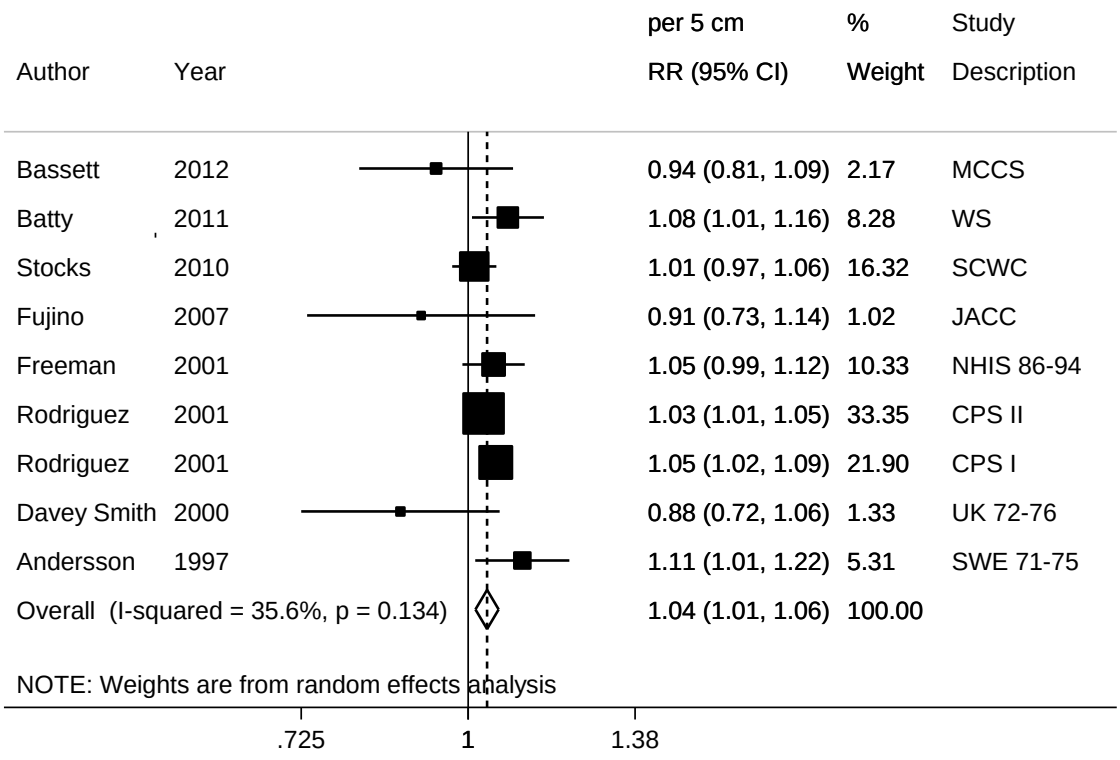


Figure 319 Dose-response meta-analysis of height and total prostate cancer – per 5 cm

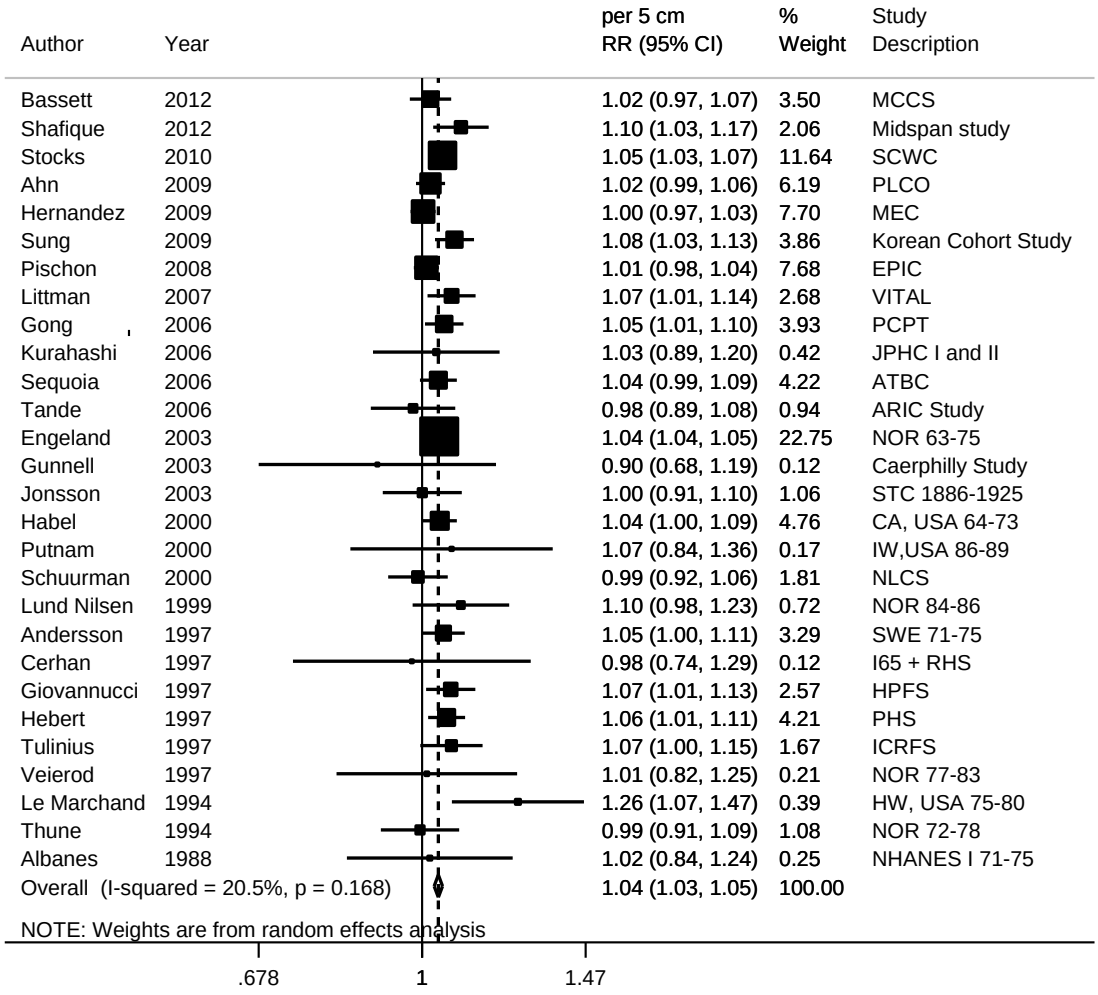


Figure 320 Dose-response meta-analysis of height and prostate cancer, per 5 cm, stratified by prostate cancer type

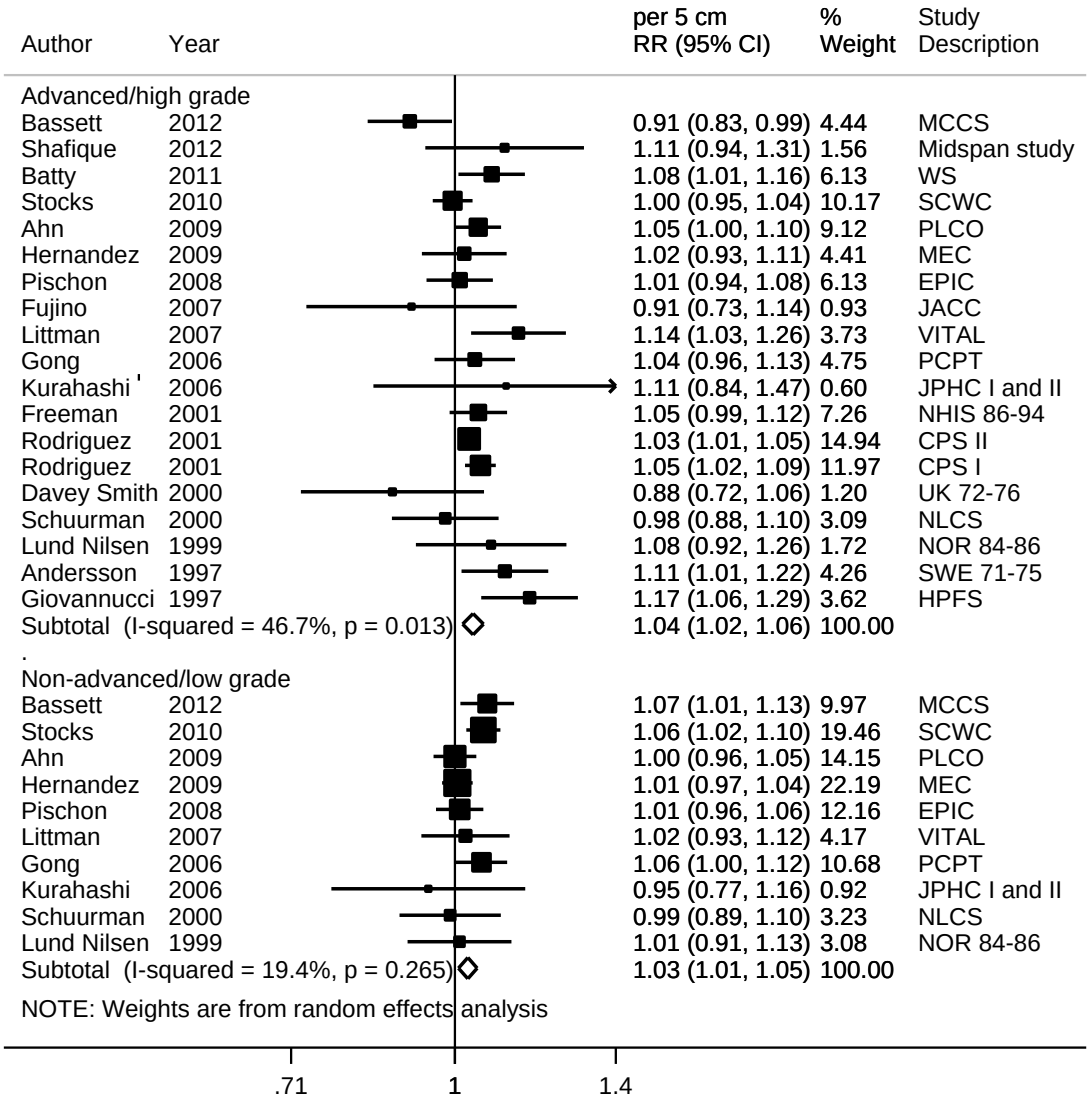


Figure 321 Dose-response meta-analysis of height and prostate cancer, per 5 cm, stratified by prostate cancer grade

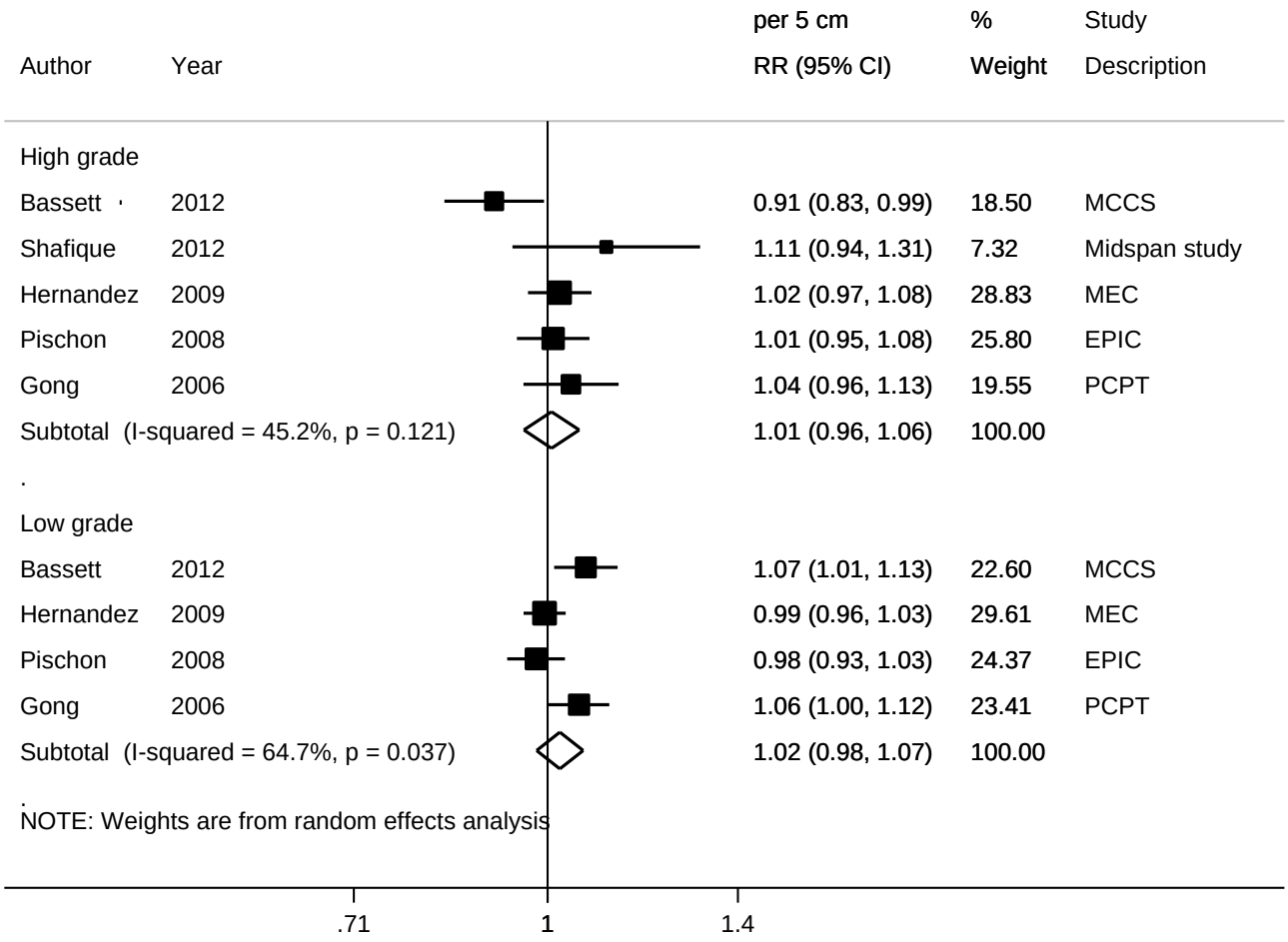
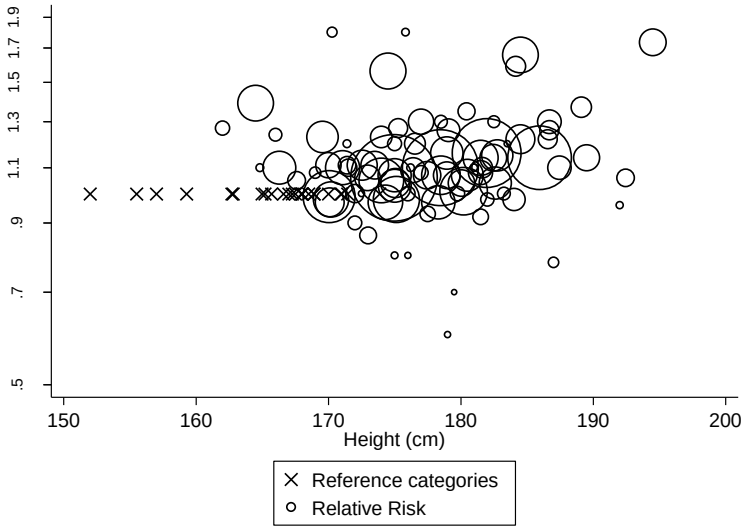


Figure 322 Non-linear dose-response analysis of height and total prostate cancer



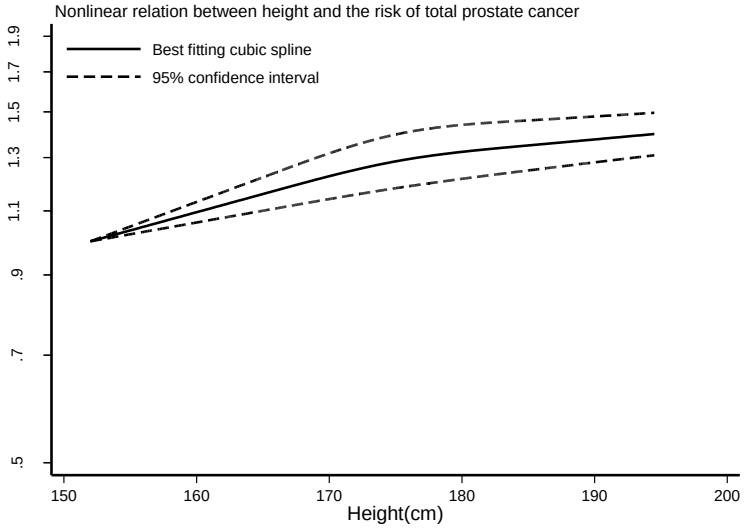
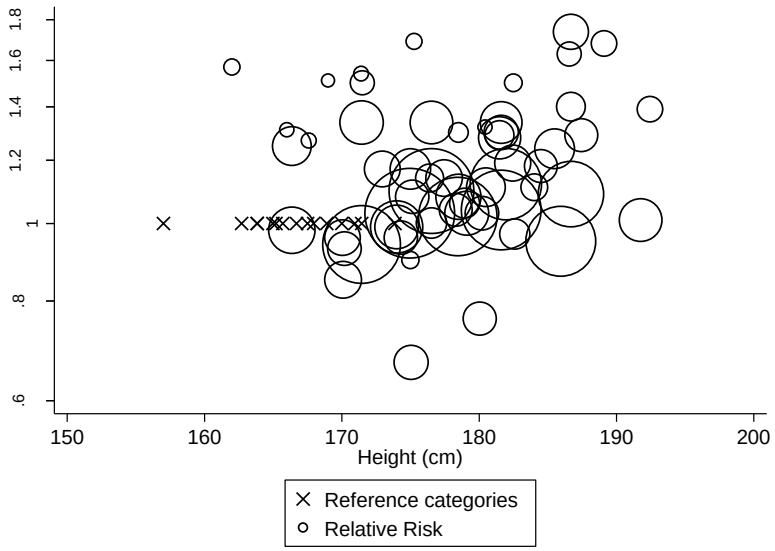


Table 281 Table with height values and corresponding RRs (95% CIs) for non-linear analysis of height and total prostate cancer

Height (cm)	RR (95% CI)
152.0	1
166.0	1.17 (1.11-1.24)
178.5	1.31 (1.21-1.43)
189.5	1.37 (1.28-1.48)

$p_{non\text{-}linearity} = 0.01$

Figure 323 Non-linear dose-response analysis of height and advanced/high grade prostate cancer



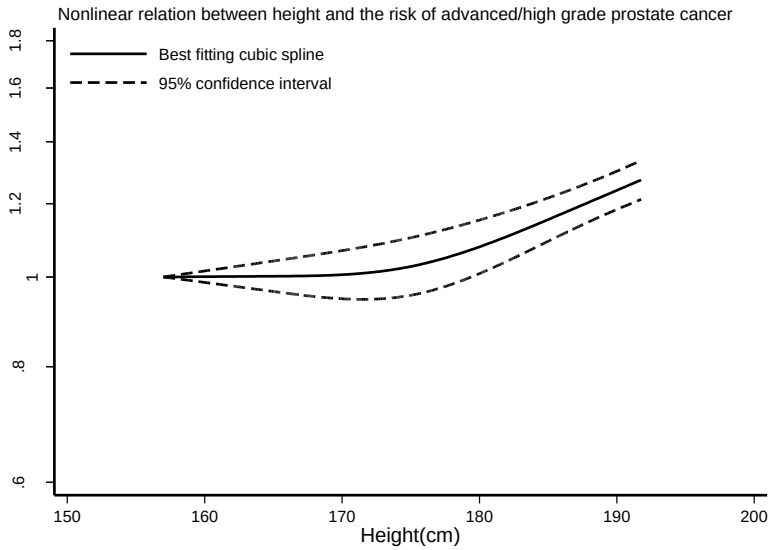


Table 282 Table with height values and corresponding RRs (95% CIs) for non-linear analysis of height and advanced/high grade prostate cancer

Height (cm)	RR (95%CI)
157.0	1
170.0	1.01 (0.95-1.07)
181.5	1.10 (1.03-1.17)
192.5	1.29 (1.22-1.35)

$p_{non\text{-}linearity} < 0.01$

8.4.1 Birth weight

Methods
Nine publications were identified, from which three studies were identified in the CUP and six studies were identified in the 2005 SLR.

For the dose-response analyses results were converted to a common scale of exposure level (grams). The increment unit used in the dose-response analysis was 500 grams.

Eight studies were included in the meta-analysis. Seven of the studies reported on prostate cancer (Platz, 1998; Ekbom, 2000; Nilsen, 2005; McCormack, 2005; Ahlgren, 2007; Eriksson, 2007; Cnattingius, 2009). Two studies investigated fatal prostate cancers (Ekbom, 1996; Eriksson, 2007), one study reported high grade prostate cancers (Platz, 1998) and one study on metastatic cancers (Nilsen, 2005).

High grade and metastatic cancers were combined in a subgroup of advanced/high grade

Main results
The summary RR per 500 g of increase of birth weight was 1.03 (95% CI 0.99-1.08; $I^2 = 0\%$; $p_{heterogeneity} = 0.64$; n = 8). After stratification by cancer outcome, the RR per 500 g of birth weight increase for total cancer (after removing the study reporting on mortality) was 1.03 (95% CI 0.99-1.08; $I^2 = 0\%$; $p_{heterogeneity} = 0.53$; n = 7), for advanced/high grade cancer the summary RR was 1.09 (95% CI 0.97-1.22; $I^2=0\%$; $p_{heterogeneity} = 0.56$; n = 2), and the summary RR for mortality was 1.09 (95% CI 0.96-1.25; $I^2 = 0\%$; $p_{heterogeneity} = 0.35$; n = 2).

Heterogeneity
Overall, there was no evidence of heterogeneity, $I^2 = 0\%$, $p_{heterogeneity} = 0.64$. There was no evidence of publication bias with Egger's test, p = 0.12.

Comparison with the Second Expert Report
In the 2005 SLR, the evidence on the association of birth weight and prostate cancer was considered as limited – no conclusion. The CUP meta-analysis show a non-significant association (RR 1.01; CI 95% 0.97-1.05).

Published meta-analysis or pooled analysis
No meta-analysis or pooled analysis was identified.

Table 283 Studies on birth weight identified in the CUP

Author, year	Country	Study name	Cases	Years of follow up	RR	LCI	UCI	Contrast
Cnattingius, 2009	Sweden	Swedish Twin Cohort	382	33 years	1.22	0.94	1.57	≥ 3000 g vs. < 2500 g
					1.25	0.96	1.62	Per 500 g increase
Ahlgren M, 2007	Denmark	Danish Birth Cohort	302	~ 35 years	1.06	0.85	1.32	Per 1000 g increase
Eriksson, 2007	Sweden	Goteborg study	120	~ 35 years	1.62	1.04	2.51	≥ 4250 vs. ≤ 3000 g
					1.24	0.91	1.68	Per 1000 g increase

Table 284 Overall evidence on birth weight and prostate cancer

	Summary of evidence
2005 SLR	Six studies were included in the 2005 SLR meta-analysis. All were non-significant. All showed no significant association. .
Continuous Update Project	Three new studies were identified in the CUP, all showed no significant association. No significant association was observed in the CUP meta-analysis.

Table 285 Summary of results of the dose response meta-analysis of birth weight and prostate cancer

Prostate cancer		
	SLR	CUP
Studies (n)	6	8
Cases (n)	2023	2827
Increment unit used	Per 454 g	Per 500 g
Overall RR (95% CI)	1.01 (0.98-1.05)	1.03 (0.99-1.08)
Heterogeneity (I^2, p-value)	0%, p = 0.76	0%, p = 0.64
Stratified analysis		
Advanced/high grade		
Overall RR (95% CI)	1.08 (1.00-1.17)	1.09 (0.97-1.22)
Heterogeneity (I^2, p-value)	0%, p = 0.79, n = 3 (one article on mortality, one on metastatic cancer and one on high stage)	0%, p = 0.56, n = 2
Mortality		
Overall RR (95% CI)		1.09 (0.96-1.25)
Heterogeneity (I^2, p-value)		0%, p = 0.35, n = 2

Table 286 Inclusion/exclusion table for meta-analysis of birth weight and prostate 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
PRO100068	Cnattingius	2009	Historical Cohort	Swedish Twin Cohort	Incidence	No	Yes	Yes	Rescale continuous values	
PRO100118	Ahlgren	2007	Historical Cohort	Danish Birth Cohort	Incidence	No	Yes	No	Rescale continuous values	
PRO99975	Eriksson	2007	Historical Cohort	Goteborg Study	Incidence /Mortality	No	Yes	Yes	Rescale continuous values	
PRO98949	McCormack	2005	Prospective Cohort	Uppsala Birth Study	Incidence	Yes	Yes	Yes	Rescale continuous values	
PRO97431	Nilsen	2005	Prospective Cohort	Trondheim Birth Cohort	Incidence /metastatic cancer	Yes	Yes	Yes	Mid-exposure values	
PRO01627	Ekbom	2000	Nested case-control study	Stockholm Birth Cohort	Incidence	Yes	Yes	No		
PRO02100	Platz	1998	Historical Cohort	Health Professionals Follow-up Study	Incidence	Yes	Yes	Yes	Mid-exposure values	
PRO02523	Ekbom	1996	Nested case-control study	Uppsala University Hospital Cohort	Mortality	Yes	Yes	No		
PRO02643	Tibblin	1995	Historical Cohort	Swedish 1913 Cohort	Incidence	Yes	No	No		No RR reported, only incidence per 1000-person-years

Figure 324 Highest versus lowest forest plot of birth weight and prostate cancer

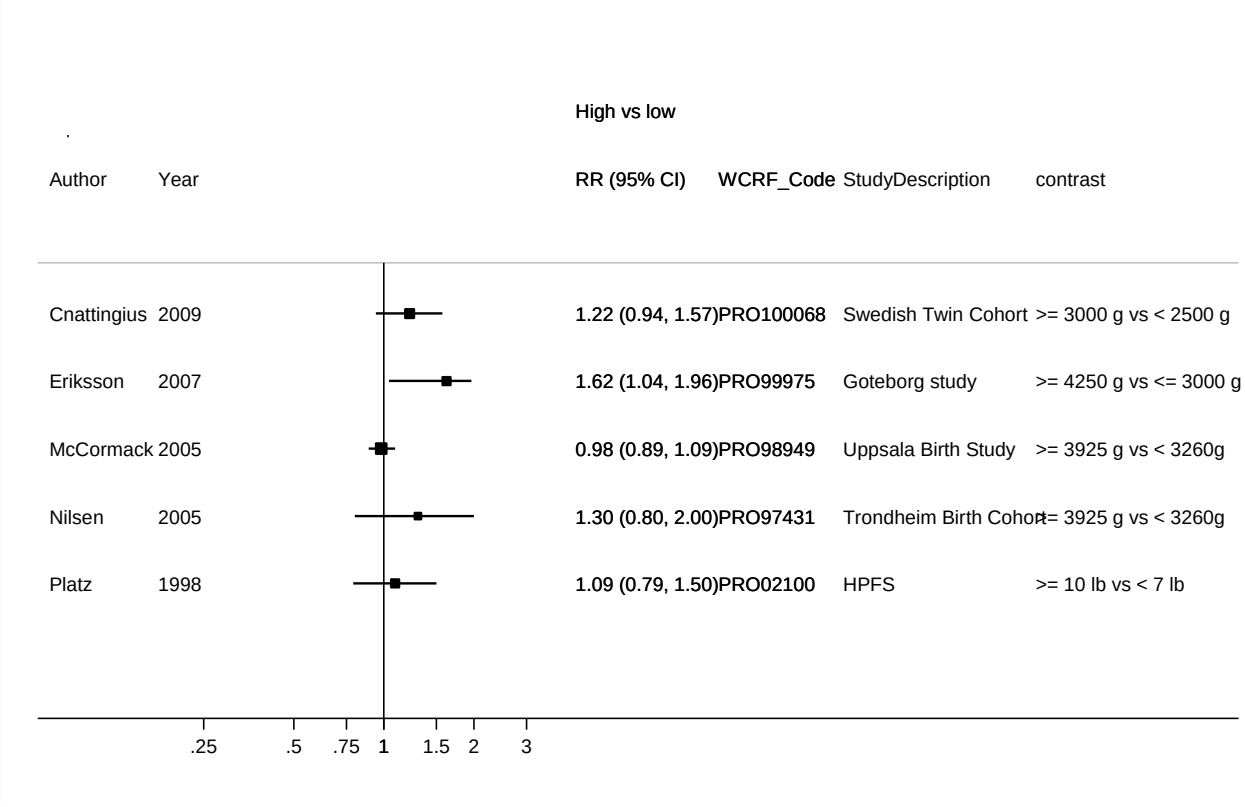


Figure 325 Dose-response meta-analysis of birth weight and prostate cancer – per 500 g

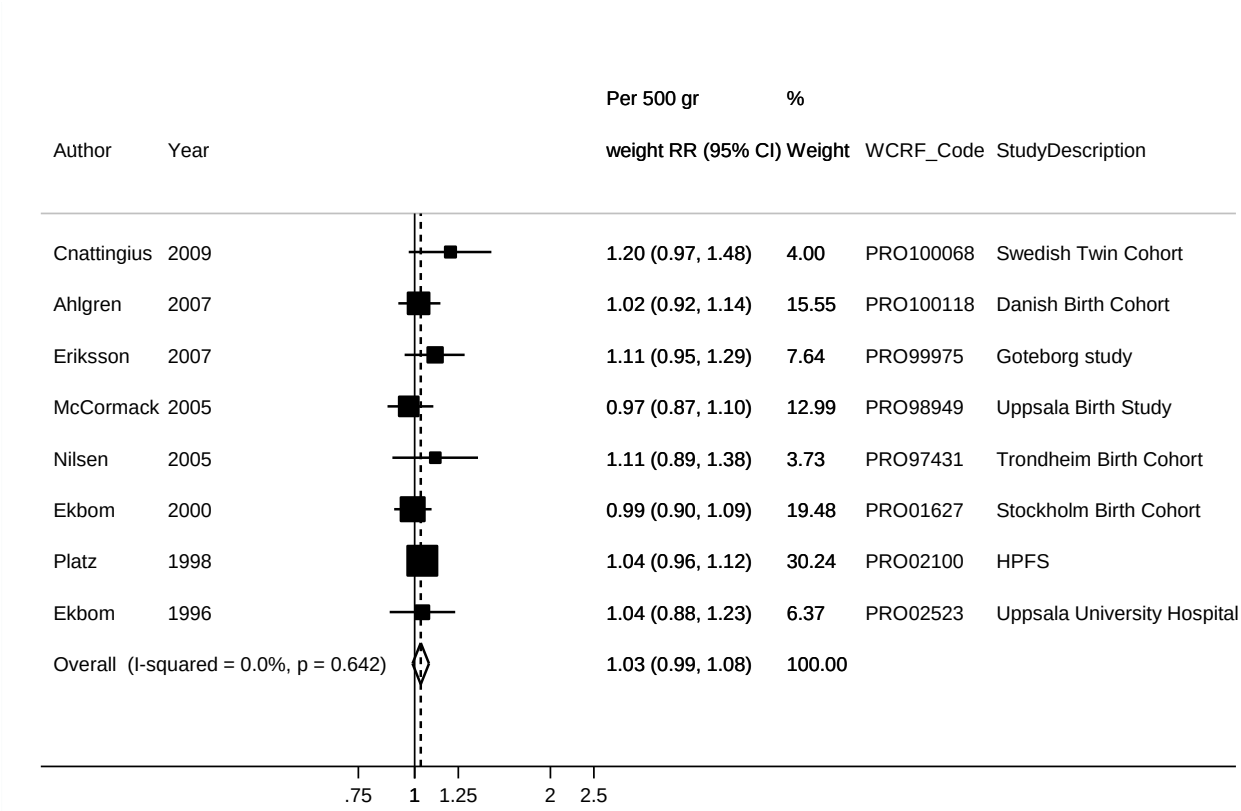
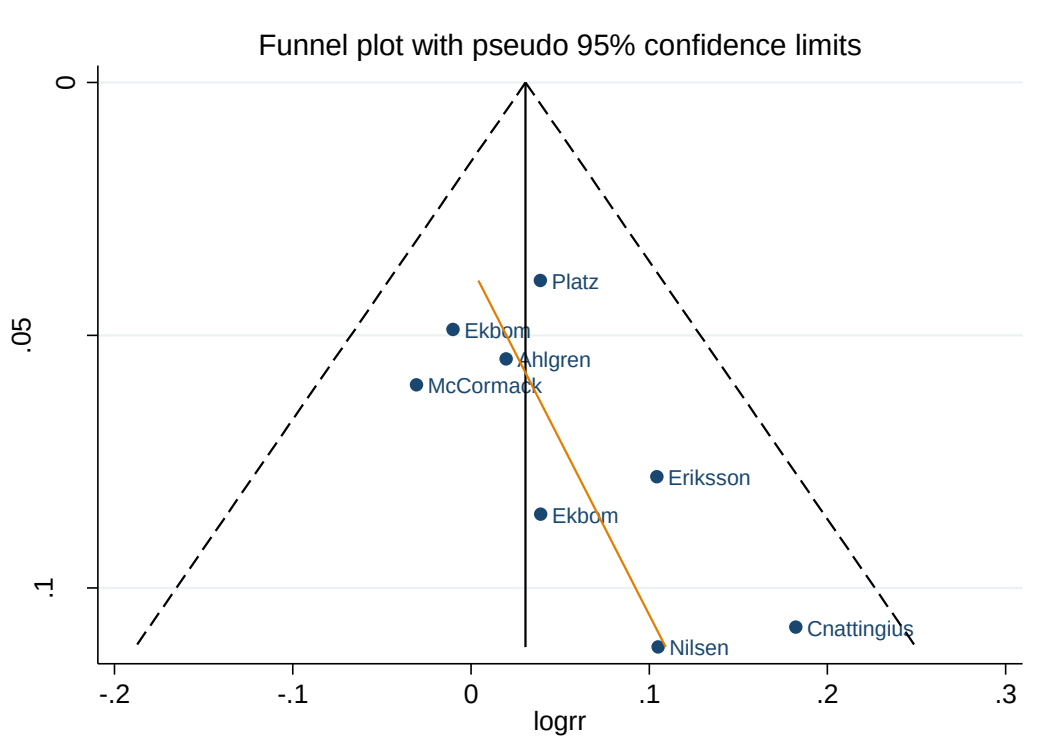


Figure 326 Funnel plot of birth weight and prostate cancer



Egger's test p = 0.12

Figure 327 Dose-response graph of birth weight and prostate cancer

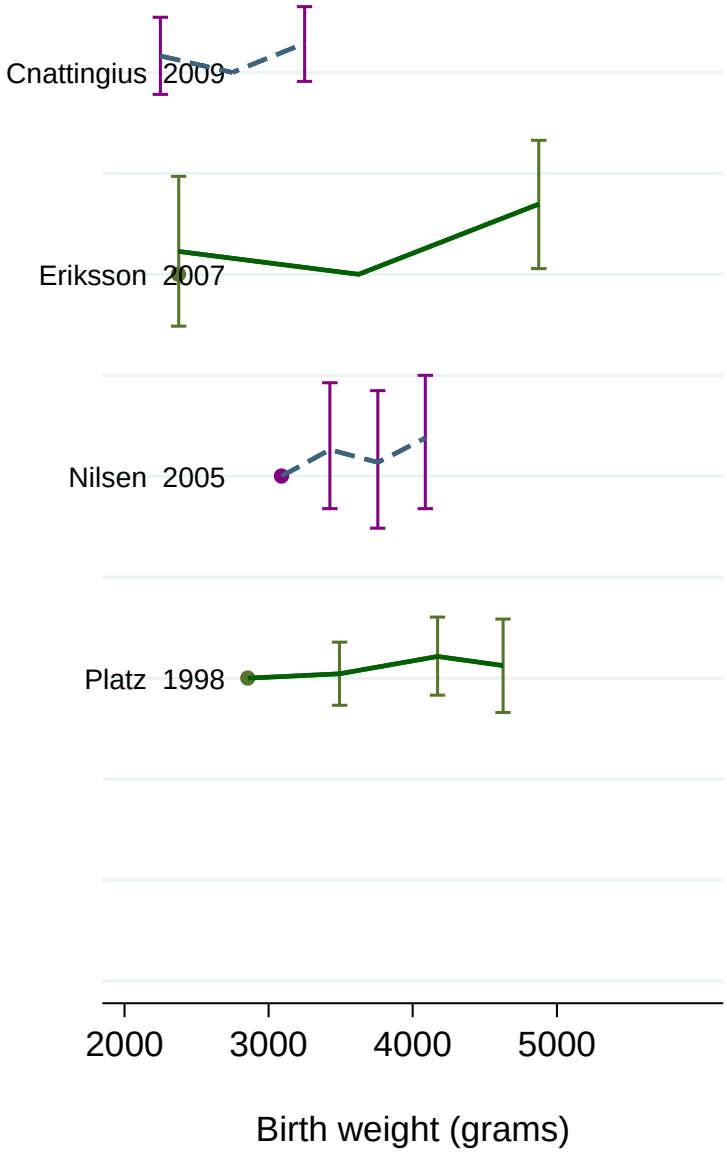
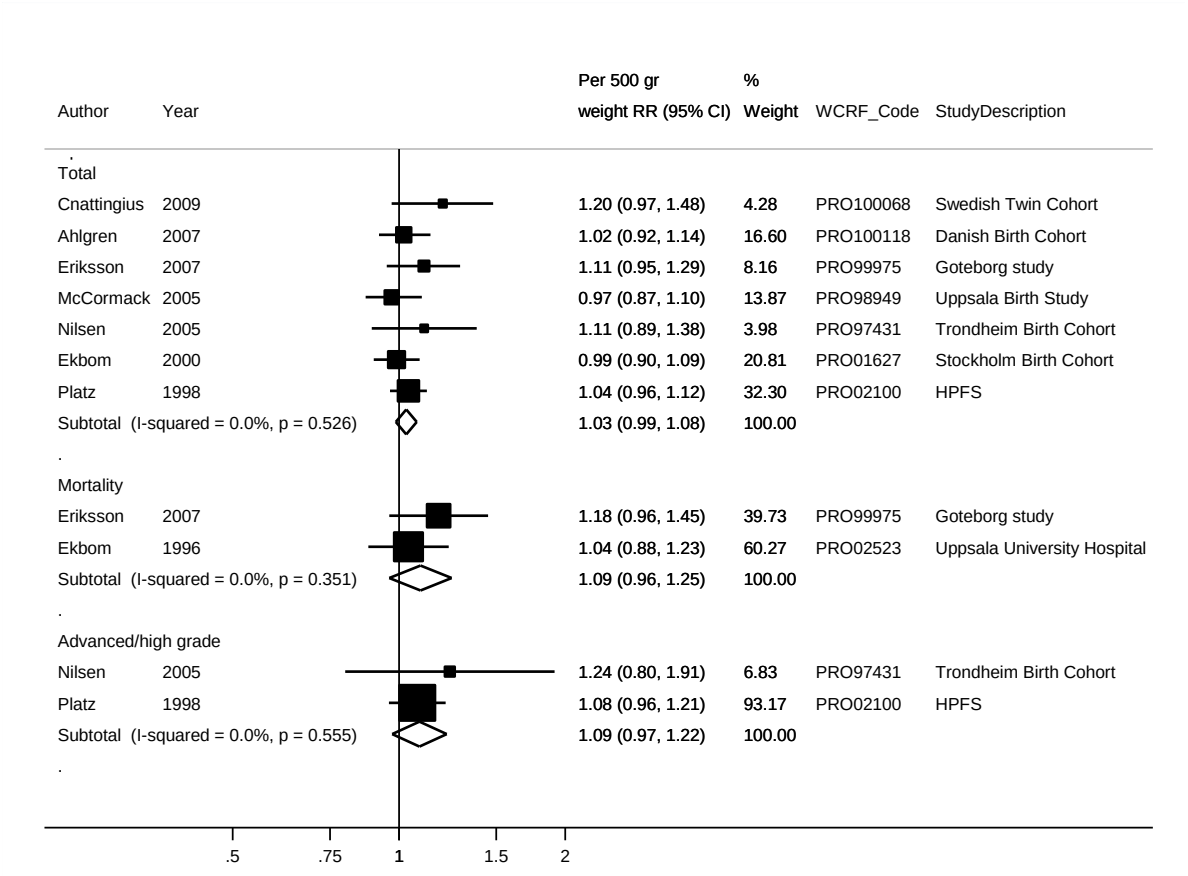


Figure 328 Dose-response meta-analysis of birth weight and prostate cancer, per 500 g, stratified by prostate cancer type



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Appendix.

a) Studies on calcium

Several studies investigated on calcium intake. The sources of calcium intake investigated by each study are indicated with a cross in the list below:

			Source of calcium				
Author/year	Country	Study name	Total	From diet	From supplements	From dairy foods	From non dairy foods
Song, 2013	USA	PHS				x	
Butler, 2010		SCHS	x	x			
Kristal, 2010	USA	PCPT	x	x	x		
Park, 2007, 2009	USA	NIH-AARP	x	x	x	x	x
Kurahashi, 2008	Japan	JPHC I and II		x			
Allen, 2008	Euroepan countries	EPIC		x		x	x
Rohrmann, 2007	USA	CLUE II	x	x	x	x	
Park, 2007	USA	MEC	x	x	x		
Mitrou, 2007	Finland	ATBC		x		x	
Ahn, 2007	USA	PLCO	x	x	x		
Severi, 2006	Australia	MCCS		x			
Koh, 2006	USA	Harvard Alumni Health Study 1962-1966			x	x	

Kesse, 2006	France	SU.VI.MAX	x			x	x
Giovannucci, 2007, 2006, 1998	USA	HPFS	x	x	x		
Tseng, 2005	USA	NHANESI	x			x	x
Rodriguez, 2003	USA	CPS II	x				
Berndt, 2002	USA	Baltimore Longitudinal Study of Aging	x				
Baron,2005	USA	RCT Ca		x	x		
Schuurman, 1999	Netherlands	NLCS	x				

b) Anthropometric characteristics investigated by each study

Several studies investigated BMI, height, waist circumference and waist-to-hip ratio. The antrhopoemtric characteristics investigated by each study are indicated with a cross in the list below:

			Anthropometric characteristic			
			BMI	Height	Waist	WHR
Hsieh 2003, Brooks 2001, Hubbard 2004	USA	BLSA	x	x	x	x
Gunnell 2003	UK	Caerphilly Study		x		
Fitzpatrick 2001	USA	CHS	x			
Tande 2006	USA	ARIC Study	x	x	x	
Ahn 2008, Weinstein 2005, Sequoia 2006	Finland	ATBC	x	x		
Eichholzer 2005	Switzerland	Basel Prospective Study	x			
Mills 1989	USA	AHS	x			

Andreotti 2010, Alavanja 2003	UK	AgriHSC	x			
Thompson 1989	USA	California 1972-1974	x			
King 2005, Lamharzi 2003	USA	CARET	x	x		
Gapstur 2001	USA	CARDIA	x			
Chae 2009, Platz, 2004, 2002; Huang 2003; Helzlsouer 2000	USA	CLUE II	x	x		
Rodriguez 2001	USA	CPS I	x	x		
Rodriguez 2007; Calle 2003	USA	CPS II	x	x		
Pischon 2008	European countries	EPIC	x	x	x	x
Burton 2010, Okasha 2002	UK	Glasgow Alumni Cohort study	x			
Bradbury	UK	GPRD	x			
Lee 2001	USA	Harvard Alumni Health Study 1962-1966	x		x	
Le Marchand 1994	USA	Hawaii, USA 1975-1980	x	x		
Giovannucci 2007, 2006, 2003, 1997; Wu 2004; Pltz 2004,	USA	HPFS	x	x	x	x
Chamberlain, 2011; Martin, 2009; Lund, 1999	UK	HUNT I&II	x	x	x	x
Cerhan 1997	USA	Iowa 65+ Rural Health Study	x	x		
Tulinius 1997	Iceland	ICRFS		x		
Putnam 2000	USA	IW, USA 1986-1989	x	x		
Fujino, 2007; Osaza, 2004	Japan	JACC	x	x		
Kuriyama, 2005	Japan	Japan 1984	x			

Inoue 2009, Kurahashi 2006	Japan	JPHC	x	x		
Laaksonen 2004	Japan	KIHDRFS	x			
Jee, 2008; Oh, 2005	Korea	KNHIC	x			
Hiatt 1994, Habel 2000	USA	KPMCP	x	x		
Sung 2009	Korea	Korean Cohort Study		x		
Allen 2004	Japan	Life Span Study (LSS)	x			
Wolinsky 2002	USA	Longitudinal Study on Aging (LSA)	x			
Bassett, 2012;MacInnis, 2003	Australia	MCCS	x	x	x	x
Hernandez, 2009	USA	MEC	x	x		
Shafique, 2012	UK	Midspan study	x	x		
Dehal, 2011; Albanes 1988	USA	NHANES I	x	x		
Cui, 2004	USA	NHANES III	x			
Wright, 2007	USA	NHI-AARP	x			
Freeman 2001	USA	NHIS 86-94		x		
Schuurman, 2000	Netherlands	NLCS	x	x		
Engeland, 2003	Norway	Norway 1963-1975	x	x		
Thune, 1994	Norway	Norway 1972-1978	x	x		
Veierod, 1997	Norway	Norway 1977-1983	x	x		
Jacobs, 2004	USA	NPC Trial	x			
Lukanova 2006, Stattin 2004, Hultdin 2005	Sweden	NSHDC	x			
Lund, 2006	Norway	Oslo follow up study	x	x		
Gong, 2006	USA	PCPT	x	x	x	x
Li, 2004; Zhu, 2004; Hebert 1997	USA	PHS	x	x		

Ahn 209	USA	PLCO		x	
Baillargeon	USA	SABOR	x		x
Stocks, 2010; Samanic, 2006	Sweden	SCWC	x	x	
van Kruijsdijk, 2013	Netherlands	SMART	x		x
Meyer 2005	France	SU.VI.MAX Trial	x		
Andersson 1997	Sweden	Sweden 1971-1975	x	x	
Gronberg 1996	Sweden	Sweden 1967-1970	x		
Lundqvist 2007; Johnson 2003	Sweden-Finland	Sweden, Finland Co-twin study	x	x	
Jonsson 2003	Sweden	Swedish Twin Cohort 1886-1925	x		
Discacciati, 2011	Sweden	Sweden	x		
Krishnadasan, 2008	USA	The Aerospace and Radiation Cohort	x		
Lin 2013, Grundmark, 2011	Sweden	ULSAM	x		x
Severson 1988	USA	USA Hawaii 1965-1968	x		
Rapp, 2005	Austria	VHM&PP Cohort	x		
Gonzalez, 2007, 2009; Littman, 2007;	USA	VITAL	x	x	
Batty 2011; Davey Smith, 2000, Leon 1995	UK	Whitehall study	x	x	