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Carbohydrates, glycemic index, glycemic load, sugars and breast cancer risk: a systematic review and dose-response meta-analysis of prospective studies

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Abstract

Context: The investigation of dose-response associations between carbohydrates, glycemic index (GI), glycemic load (GL) and risk of breast cancer stratified by menopausal status, hormone receptor status and body mass index (BMI) remains inconclusive.

Objective: A systematic review and dose-response meta-analyses was conducted to investigate these associations.

Data sources: As part of the World Cancer Research Fund/American Institute for Cancer Research Continuous Update Project, we searched PubMed for relevant studies on these associations, up to May 2015.

Study selection: Prospective studies reporting associations on intake of carbohydrates, GI, GL and breast cancer risk were included.

Data extraction: Two investigators independently extracted data from included studies.

***Data synthesis*:** Random-effects models were used to summarize relative risks (RRs) and 95% confidence intervals (CIs). Heterogeneity between subgroups, including menopausal status, hormone receptor status and body mass index (BMI) was explored using meta-regression. Nineteen publications were included. The summary RRs (95%CIs) for breast cancer were 1.04 (1.00-1.07) per 10 units/d for GI, 1.01 (0.98-1.04) per 50units/d for GL, and 1.00 (0.96-1.05) per 50g/d for carbohydrates, respectively. For GI, the association appeared slightly stronger among postmenopausal [summary RR (95%CI): 1.06 (1.02-1.10) per 10units/d)] than premenopausal women, though the difference was not statistically significant ($p_{heterogeneity}$=0.15). GL and carbohydrates were positively associated with breast cancer among postmenopausal women with estrogen-negative tumours [summary

RRs (95%CIs): 1.28 (1.08-1.52) for GL and 1.13 (1.02-1.25) for carbohydrates)]. No differences in BMI were detected.

Conclusions: Menopausal and hormone receptor status, but not BMI might be potential influencing factors for the associations between carbohydrates, GI, GL and breast cancer.

Introduction

Breast cancer is the most common cancer among women worldwide with an estimated 1.67 million new cancer cases diagnosed in 2012.[1] Many risk factors have been identified, including older age, hormonal and reproductive factors, and modifiable lifestyle factors.[2-4] Evidence is available that obesity, type 2 diabetes and possibly insulin resistance are related to increased risk of postmenopausal breast cancer as well.[4-8]

Thus, recently, there has been growing interest in the association between intake of foods related to glucose and insulin metabolism, and risk of breast cancer. Studies investigating the association between intake of total carbohydrates, or specific types of carbohydrates (such as total sugars or specific sugars), and breast cancer reported contradicting results,[9-21] and so far, no meta-analysis on this topic is available. Furthermore, it has been shown that the effect of different carbohydrates on post-prandial blood sugar concentration varies. Several meta-analyses investigated the association between diets with high glycemic index (GI) and glycemic load (GL) – markers of carbohydrate quality – and risk of breast cancer.[22-28] While findings of some meta-analyses indicated that breast cancer risk was moderately increased for GI [22, 25, 26] and GL [24], other studies failed to reach statistical significance for GI [23, 24, 27, 28] or GL,[22, 23, 25-28] respectively.

These studies have performed high versus low meta-analysis and little is known about the dose-response relation between GI, GL and breast cancer risk. Furthermore, studies that have stratified their analyses by menopausal status did not report differences for GI for pre- and postmenopausal women, whereas the association for GL and breast cancer seemed to be stronger in premenopausal women than in postmenopausal women.[23, 25, 26, 28] Only the most recent meta-analysis investigated

the associations between GI, GL and breast cancer stratified by estrogen-receptor (ER) status of the tumor and indicated a potential positive association only in women with estrogen-receptor-negative (ER-) status,[28] whereas evidence on stratification by other hormone receptor status, such as progesterone receptors (PR) is lacking. In addition, that most recent meta-analysis did not include the cohorts of the National Institutes of Health-American Association of Retired Persons Diet and Health Study (NIH-AARP),[29] the Women's health study (WHS),[30] and did not include the most recent reports with updated information of the Nurses' Health Study (NHS) II,[17] and the European Prospective Investigation into Cancer and Nutrition (EPIC) study.[16] Moreover, controversial findings have been reported by individual studies whether excess body weight as measured by body mass index (BMI) influences the carbohydrate-, GI-, or GL-breast cancer associations.[12, 13, 15, 17, 31] But so far, evidence is lacking that summarize these findings.

Therefore, our aims were twofold. First, we performed a systematic review and dose-response meta-analysis of prospective studies to investigate the shape and the magnitude of the associations between dietary factors related to glucose metabolism, including intake of carbohydrates, GI, GL, and specific types of carbohydrates and risk of breast cancer. Second, we investigated whether these associations differed by menopausal status, hormone receptor status and BMI, respectively.

Methods

This report was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement.[32]

Search strategy

Several databases, including, PubMed, Embase, CAB Abstracts, ISI Web of Science, BIOSIS, Latin American and Caribbean Center on Health Sciences Information, Cochrane library, Cumulative Index to Nursing and Allied Health Literature, The Allied and Complementary Medicine Database, National Research Register and In Process Medline, were searched up to December 2005 by several reviewers at Istituto Nazionale Tumori, Milan for the WCRF/AICR Second Expert Report (http://wcrf.org/int/research-we-fund/continuous-update-project-cup). All the relevant prospective studies were identified by the PubMed searches and therefore a change in the protocol was made and only PubMed was used for the updated searches from January 2006 up to May 2015. The literature search was carried out following a predefined protocol, which includes all the details of the search terms and has been published online (http://www.wcrf.org/sites/default/files/protocol_breast_cancer_2008.pdf). Reference lists of relevant papers and reviews were hand-searched to identify any other potentially relevant papers.

Study selection

The PICOS (Participants, Intervention Comparators, Outcomes, Study Design) criteria are presented in **Table 1**. The criteria for inclusion were as follows: I) investigation of the association between dietary intake of carbohydrates, GI, GL, specific types of carbohydrates (total and specific sugars, including fructose, sucrose, glucose, lactose, maltose and added sugars), and incidence of breast cancer, II) prospective study design, including cohort, case-cohort, or nested case-control studies, as well as follow-up studies of randomized clinical trials, and III) reported adjusted risk estimates (including relative risk (RR), hazard ratio (HR), or odds ratio

(OR) and the corresponding 95% confidence intervals (CIs)) for the association between carbohydrates, GI, GL or specific types of carbohydrates (total and specific sugars), and breast cancers. If multiple articles were published for the same study, we included the newest publication providing the largest number of cases. Two studies were only included in subgroups analyses.[33, 34] Studies were excluded if they did not provide enough data on the exposure (no quantification of the exposure were reported or only high vs. low analyses were shown),[35-39] or they assessed GI, GL or carbohydrates in childhood or adolescence.[40, 41]

Data extraction

The following information were extracted: first author's last name, year of publication, country where the study was conducted, study name, study design, age, specific characteristics of the study population, study size, number of cases, duration of follow-up, dietary assessment method, exposure (carbohydrates, GI, GL, total and specific sugars), quantity of intake, RRs and 95% CIs from the models with most number of confounder adjustments, and variables adjusted for in analyses.

Statistical methods

We conducted dose-response meta-analyses to summarize the association between carbohydrates, GI, GL, specific sugars, and breast cancer, by using random-effects models.[42] The linear dose-response trends (when not provided) were computed from the natural logarithm of the RRs and 95% CI across categories of intake of carbohydrates, specific sugars, GI, or GL, respectively, using the method by Greenland and Longnecker.[43] This method requires information on the RR with the respective 95% CI, the distribution of cases, person-years or non-cases, and the

quantified exposure value for at least three exposure categories. For studies that did not report on cases or persons-years/ non-cases per category, the total numbers were divided by the number of quantiles. For example, when the total number of person-years was reported, and the exposure was expressed as quintiles, the total number of person-years was divided by five. Means or medians of intake were assigned to each category. When only the range of the category was reported, we estimated the midpoint between the lower and upper limit. When a category was open-ended (uppermost or lowermost intake categories), we assumed that the range was the same as the adjacent category. When studies reported dietary intake as g/1000 kcal/d or % of energy/d, we converted the intake into g/d if appropriate information was available in the study.[17, 18] Based on previous reports, the summary RRs of the dose-response meta-analyses are presented for an increment per 50 g/d for carbohydrates,[44] 10 units/d for GI,[45] 50 units/d for GL,[45] and 10 g/d for sugar, or specific sugar,[20] respectively. We investigated whether there was a non-linear dose-response relation between carbohydrates, GI, GL, specific carbohydrates, and breast cancer risk using restricted cubic spline regression models with three knots at the 10th, 50th and 90th percentile, and a likelihood ratio test was used to evaluate non-linearity.[46, 47]

First, we examined the dietary factors with breast cancer risk (any, pre-, and postmenopausal breast cancer). We combined an overall RR for studies that reported findings separately for pre- and postmenopausal women using fixed-effect meta-analysis. Most studies have assessed premenopausal status only once (at baseline). Thus, we also stratified the analyses among premenopausal women by the time of assessment of premenopausal status (assessed at exposure vs. assessed at breast cancer diagnosis). Second, we stratified our meta-analyses by hormone receptor status, including ER (ER+ and ER-), PR (PR+ and PR-), and combinations of ER and

PR because it has been suggested that risk associations between carbohydrates, GI, GL and breast cancer might vary between this different tumour types. The Hamling's methods was used to combine RRs (95% CI) for different subtypes if required.[48] For example, when a study reported on the combination of hormone receptor status only (ER+/PR+ and ER+/PR-), we combined the two individual estimates to one single estimate (ER+). We performed these analyses for all breast cancers and among postmenopausal women, information among premenopausal women was limited. Third, we investigated whether excess body weight may influence the association between carbohydrates, GI, GL and breast cancer (all, and pre- and postmenopausal breast cancer separately) by stratifying the analyses by BMI (<25 vs ≥25 kg/m^2), as defined by the studies. Therefore, we included the study by Lajous et al. (E3N, the French cohort in EPIC)[33] because stratified analysis by BMI for the associations between carbohydrates, GI, GL and breast cancer were not available in the total EPIC cohort.[16]

Heterogeneity between studies was evaluated by the percentage of total variation in risk estimates explained by between-study variation (I^2 statistics).[49] Sources of heterogeneity were explored by subgroup analyses, including geographic area (Europe, North America, Asia-Pacific), duration of follow-up (<10 y, ≥10 y), number of cases (<1500, ≥1500), reference food for measuring GI and GL (glucose, white bread, combination of glucose and white bread), and adjustment for possible confounders, including hormone replacement therapy (HRT) use, parity, age at first birth, age at menopause, age at menarche, oral contraceptive use, education, physical activity, smoking, alcohol intake, family history of breast cancer, and history of breast disease. All the studies included in our meta-analysis adjusted for age, BMI and total

energy intake. Differences between subgroups were assessed using meta-regression analysis.[49]

Publication bias was visually explored by checking funnel plots for asymmetry and by applying Egger's test.[50]

A two-tailed p-value of <0.05 was considered as statistical significant. All analyses were performed using Stata 13.0 software (StataCorp, College Station, TX, USA).

Results

We identified 15 prospective studies (19 publications) on carbohydrates, GI, GL, total sugar and/or fructose intake and risk of breast cancer (**Figure 1** and **Table 2**). Out of these studies, ten studies were from Northern America, four from Europe and one from Asia-Pacific (**Table 2**).

Carbohydrates

In total, eleven prospective studies were included in the dose-response meta-analysis on carbohydrates (range: 112.3-343.5 g/d) and risk of breast cancer, including 30,275 cases among 892,403 participants.[9-17, 19, 21] There was no evidence of an association between intake of carbohydrates and risk of breast cancer [summary RR (95% CI) per 50 g/d: 1.00 (0.96-1.05); **Figure 2A**]. Statistically significant heterogeneity was observed between the studies (I^2=57% and $p_{heterogeneity}$=0.01), mainly driven by some smaller and earlier studies.[9-11, 21] No significant associations were observed in pre- and postmenopausal women (**Figure 2B** and **Table 3**). In total, four studies reported on the association between carbohydrates and breast cancer stratified by hormone receptor status.[15, 16, 19, 34] Carbohydrate intake was positively

associated to increased risk of ER- breast cancers [summary RR (95% CI) per 50 g/d: 1.11 (1.02-1.21); **Table 3** but not with ER+ breast cancer ($p_{heterogeneity}$ between ER- and ER+ receptor types=0.03). The same pattern was observed when the analysis was restricted to postmenopausal women only (**Table 3**).

Among the three studies stratified the results by BMI,[12, 14, 33] we found no significant heterogeneity between normal and overweight women ($p_{heterogeneity}$ between BMI<25 and BMI≥25 kg/m^2=0.32; **Table 3**).

In further subgroup analyses, neither geographic area, duration of follow-up, number of cases, nor adjustment for confounders modified the association between carbohydrates and breast cancer (**Table 3** and **Supplemental Table 2**).

There was statistical indication of a non-linear relation between carbohydrates intake and risk of breast cancer, however associations were weak ($p_{non\text{-}linearity}$=0.02; **Figure 2C**). There was no statistical evidence of publication bias (Egger's test: p=0.99). The funnel plot shows a small study reporting a strong positive association,[11] and two small studies reporting strong inverse associations (**Supplemental Figure 1A**).[9, 21]

Glycemic index

We identified ten studies that were eligible for dose-response meta-analysis on dietary GI (range 47.8-98.0 units/d) and risk of breast cancer, including 36,900 cases among 1,102,422 women.[12-17, 19, 29, 51, 52] Out of these, five studies used glucose,[14, 17, 19, 29, 51] three studies white bread,[12, 15, 52] and two studies glucose and white bread[13, 16] as reference food for the calculation of GI.

The summary RR (95% CI) per 10 units GI/d was 1.04 (95% CI: 1.00–1.07), with no statistically significant heterogeneity between the studies (I^2=27%; $p_{heterogeneity}$=0.19) (**Figure 3A**).

The association between GI and breast cancer was statistically significant in postmenopausal [summary RR (95%CI): 1.06 (1.02-1.10)], but not in premenopausal women [summary RR (95%CI): 1.01 (0.93-1.10)] (**Figure 3B**). However, this difference was not statistically significant (p=0.15) (**Table 3**). There was no evidence of heterogeneity between timing of assessment of premenopausal status (assessed at exposure vs. at diagnosis: $p_{heterogeneity}$=0.50; **Table 3**).

In total, only four studies investigated the association between GI and risk of breast cancer stratified by hormonal receptor status.[15-17, 19] In our meta-analysis no clear pattern emerged. A positive association was observed for ER+/PR- breast cancer, but the association was not statistically significant [summary RR (95%CI): 1.29 (0.96-1.73)] and there was no statistically significant difference between the subgroups ($p_{heterogeneity}$=0.20) (**Table 3**). For postmenopausal breast cancer, the association was slightly stronger for ER- and/or PR- breast cancers, but findings were not significant and no statistically significant differences between the subgroups were detected (**Table 3**).

Overall five studies examined the association between GI and breast cancer stratified by BMI.[12, 13, 17, 33, 51] There was no evidence of a difference by BMI, overall or among pre- and postmenopausal women (**Table 3**). In addition, five other studies reported that the association between GI and breast cancer was not modified by BMI (data not shown in the publications).[15, 16, 19, 29, 52]

When we stratified our meta-analysis by geographic area, duration of follow-up, number of cases or assessment of GI, we did not detect any differences by strata

(**Table 3**). In addition, we examined whether the inclusion of important confounders could affect our results, but findings did not change substantially (**Supplemental Table 2**).

There was no evidence for a non-linear association between GI and breast cancer risk ($p_{non\text{-}linearity}$= 0.32; **Figure 3C**). The curve showed a significant increase of breast cancer risk with increasing units of GI. There was no statistical evidence of publication bias (Egger's test: p=0.37), but the funnel plot shows asymmetry driven by one small study[51] (**Supplemental Figure 1B**).

Glycemic load

We included eleven studies, based on 37,846 cases among 1,140,868 women, investigating the association between GL (range: 52.9-239.4 units/d) and breast cancer in our dose-response meta-analysis.[12, 13, 15-17, 19, 29, 30, 51-53] Six studies used glucose,[14, 17, 19, 29, 30, 51] three studies white bread,[12, 15, 52] and two studies glucose and white bread[13, 16] as reference food for the calculation of GI.

Overall, there was no association between GL and breast cancer [summary RR (95% CI) per 50 units/d: 1.01 (95% CI: 0.98–1.04)]. There was suggestion of heterogeneity between the studies (I^2=43%; $p_{heterogeneity}$ = 0.07) (**Figure 4A**).

There was no evidence of differences by menopausal status (**Figure 4B** and **Table 3)**, or by timing of assessment of premenopausal status (**Table 3**). After stratification by hormonal receptor status (n=3 studies)[15, 16, 19], GL became a statistically significant risk factor for breast cancer among women with ER-, or ER-/PR- tumours [summary RR (95% CI) per 50 units/d: 1.20 (95% CI: 1.05-1.38), or 1.19 (95% CI: 1.02-1.38), respectively; **Table 3**]. Statistically significant differences between postmenopausal women with ER- compared to ER+ tumours were observed

[summary RR (95% CI) per 50 units/d: 1.28 (95% CI: 1.08–1.52), $p_{heterogeneity}$ between ER- and ER+ receptor types=0.05; **Table 3**].

Six studies reported associations stratified by BMI,[12, 13, 15, 17, 33, 51] and no differences by BMI were detected (**Table 3**). In four other studies there was no modification by BMI level (data not shown in the publications), [16, 19, 29, 30, 52] . One study found an increased risk of breast cancer in women with a BMI <25 kg/m^2 [RR (95% /CI) for the highest versus lowest quintile of GL: 1.26 (1.06-1.50)], but not in women with a BMI ≥25 kg/m^2 [RR (95%CI): 1.08 (0.88-1.33)].[15]

We did not observe any differences between geographic areas, duration of follow-up, number of cases and assessment of GL (**Table 3**). In addition, no differences between studies adjusting or not adjusting for main confounders were present (**Supplemental Table 2**).

There was indication of a non-linear association between GL and breast cancer risk ($p_{non\text{-}linearity}$=0.04; **Supplemental Figure 4C**), indicating no association at low score levels and positive association from GL values above approximately 150 units/d. There was no statistical evidence of publication bias (Egger's test: p=0.28); the funnel plot shows asymmetry driven by one study[51] (**Supplemental Figure 1C**).

Sugars

We identified four studies, including 12,414 breast cancer cases among 384,651 participants, on total sugar intake (defined as intrinsic sugars; range: 44.5-155.4 g/d) and risk of breast cancer.[13, 18, 19, 21] The summary RR per 10g /d was 0.99 (0.98-1.01, I^2=53%, $p_{heterogeneity}$=0.10) (**Figure 5A**), and no indication of a non-linear relation between sugar intake and risk of breast cancer was observed ($p_{non\text{-}linearity}$=0.24;

Figure 5B). There was no statistical significant evidence of publication bias (Egger's test: p=0.21; **Supplemental Figure 1D**), however only four studies were included.

For fructose intake (range: 8.5-64.2 g/d) and risk of breast cancer risk, three studies, including 11,542 cases among 352,627 women were identified.[18-20] The summary RR per 10 g/d was 0.99 (0.96-1.01, I^2=14%, $p_{heterogeneity}$=0.31) (**Figure 6A**). There was a suggestion of a non-linear positive association between fructose intake and breast cancer ($p_{non\text{-}linearity}$<0.001), with a change of the direction of the association from amounts of 40 g/d (**Figure 6B**). We did not observe statistical significant evidence of publication bias (Egger's test: p=0.73; **Supplemental Figure 1E**), however only three studies were included.

Few studies investigated the associations between other types of sugars, including sucrose,[18, 20] glucose,[20] lactose,[20] maltose,[20] or added sugars[18, 19] and risk of breast cancer. There were not enough studies to conduct meta-analyses on these specific subtypes of sugars and breast cancer; however, none of the studies have reported a statistically significant association.

Discussion

In our dose-response meta-analysis of prospective studies, the risk of breast cancer was increased by 6% in postmenopausal women for each increment of 10 units/d of GI and no risk increase was observed in premenopausal women, but the difference was not statistically significant. Overall, a limited number of studies suggests that the positive association is mainly with ER- and PR- breast cancer tumours, but no statistically significant result was observed. GL and carbohydrates were not related to increased risk of breast cancer in pre- and postmenopausal women. However, higher risk of breast cancer with higher GL and carbohydrate intake

levels were observed among women with hormone receptor ER- status. The associations between carbohydrates, GI, GL and pre- and postmenopausal breast cancer were not modified by BMI.

Our findings are comparable to findings of previous meta-analyses that reported a weak increased risk of breast cancer for higher GI levels in postmenopausal women,[23, 25, 26, 28] whereas other meta-analyses did not show.[22-24, 27] However, previous meta-analyses have focused on high vs. low analysis only and to our knowledge our meta-analysis is the first that investigated the dose-response association, and explored potential non-linear relations; our findings suggested that the association was linear. We did not find any evidence of differences between hormone receptor status for the association on GI and breast cancer, but a suggestive stronger association was observed for women with hormone receptor negative tumours. However, the number of studies was limited and more studies are needed before a conclusion can be drawn.

GL was not related to risk of pre- and postmenopausal breast cancer in our meta-analysis. The results of previous high vs. low meta-analyses are inconsistent; some reported a positive association,[24, 28] other did not report a significant relation.[22, 23, 25-27] After stratification by hormonal receptor status, the association became significant for women with ER- and ER-/PR- tumours.

To our knowledge, our meta-analysis is the first on carbohydrates and risk of breast cancer and we did not detect an association for pre- and post-menopausal breast cancers. However, similar to GL, a positive association was observed for women with ER- tumours. We did not detect an association between intake of total sugar or fructose with breast cancer risk. These findings should be carefully interpreted because number of studies was limited and we could not perform stratified

352 analysis by menopausal status, or hormone receptor status, respectively. Only one
353 study reported on fructose intake and risk of breast cancer by hormone receptor status
354 and findings indicated a weak positive association in ER+ tumours [RR (95% CI): 1.06
355 (0.96-1.18)], and an inverse association for ER- tumours [RR (95% CI): 0.84 (0.67-
356 1.06)], however, findings were not statically significant.[20]

357 Our results for the relation of GI and GL with breast cancer are slightly
358 inconsistent: for women with ER- tumours the association was stronger for GL than
359 for GI. GI and GL are both measurements of carbohydrate quality. The GI compares
360 the postprandial glucose response to a fixed amount of 50 grams of the carbohydrates
361 from different foods with that of a reference food. Because different foods vary
362 considerably in carbohydrate content, the amount that needs to be eaten to provide
363 50 grams of carbohydrate differs substantially for different foods. The GL therefore
364 takes into account both the GI and the total carbohydrate content of the food. The GL
365 has been shown to be a stronger predictor for postprandial glycemia and insulin
366 response compared to GI,[54, 55] which might explain our observation.

367 In postmenopausal women, both GI and GL were positively related to ER-
368 breast cancers, but the association was significant only for GL. It has been indicated
369 that diets high in GI/GL might be associated with hyperinsulinemia,[56, 57] insulin-like
370 growth factors (IGF-I),[58] type 2 diabetes,[44] and inflammatory biomarkers,[59] which also
371 play a role in breast cancer carcinogenesis, [6-8, 60, 61] and might be a potential
372 explanation for the association between GL (and GI) and risk of ER- breast cancers.
373 The pathological mechanisms remain unclear. A pooled analysis reported that IGF-I
374 was positively associated with ER+, but not with ER- tumours.[58] In contrast to these
375 findings, our meta-analysis pointed out that the association between diet - related to
376 glucose metabolism - and breast cancer risk is more relevant in hormone-independent

breast cancer, while hormone-dependent breast cancer might be more strongly influenced by hormonal risk factors.[62, 63] However, the number of studies investigating associations between GI, GL, carbohydrates, and sugars with risk of breast cancer by hormone receptor status was limited, and more studies are needed to draw a definite conclusion.

Our meta-analysis has several strengths. First, to our knowledge, this is the first systematic review and meta-analysis summarizing the evidence on the dose-response association of carbohydrate, sugar and fructose intake and risk of breast cancer. In addition, previous meta-analyses on GI, GL and breast cancer only reported high vs. low analyses and so far, did not o conduct linear or non-linear dose-response analyses. Second, our meta-analyses included a larger number of women than the previous studies on this topic (about one million women, including approximately 37,000 breast cancer cases), which enabled us to stratify the analyses by potential modifying factors, including menopausal status, hormone receptor status, and BMI. Third, we only included prospective studies in our meta-analysis to avoid recall bias from retrospective case-control studies, and this may also have led to less potential for selection bias in our meta-analysis.

Our meta-analysis has some limitations that also need to be considered. First, a diet high in carbohydrates, GI, GL or sugars may accompany with other behavioural and dietary factors, such as low physical activity, smoking, overweight and obesity, excess intake of total energy, and alcohol intake. However, in our meta-analyses findings did not change substantially in subgroup analyses that included studies with and without adjustment for these factors. Moreover, we did not find any differences of associations between normal- and overweight pre- and postmenopausal women. Second, measurement error of diet cannot be ruled out. The reliability of the GI has

been discussed in previous studies, which have shown that intra- and inter-individual variability in glycaemic response for single foods exists,[64, 65] and it is not only driven by methodological factors such as sample size, number of repeat measures and sampling time, but also by individual biological factors including age, BMI, blood lipids, CRP, and particularly by glycated haemoglobin (HbA1c) and insulin index.[64] In addition, ~~and~~ FFQs are not specifically designed to measure GI and GL, which might have attenuated our results. However, positive associations between GI, GL and other chronic diseases (e.g. type 2 diabetes) were identified using information on GI and GL from similar databases and similar FFQs.[44, 66] Moreover, dietary information was assessed at baseline and we have no information on change in dietary behaviour over time, which could have influenced our results. However, because of the prospective design of the studies any changes in diet after baseline would most likely have tended to attenuate the observed associations. Finally, our results that hormone receptor status of the tumours might affect the association between carbohydrates and GL and risk of breast cancer should be interpreted with caution because of the limited numbers of studies available. Thus, it is important to investigate whether exogenous hormones, such as the use of HRT can affect these associations as well and in our meta-analysis, we could not stratify for HRT use because data was limited. Only one study investigated the association between GI and risk of breast cancer stratified by HRT use, and reported a stronger association for HRT users [summary RR (95%CI): 2.15 (1.16-4.00)] compared to never users [summary RR (95%CI): 1.58 (0.79-3.18)] by comparing high versus low values of GI.[13]

In conclusion, in our meta-analysis, GI showed a weak positive linear association with risk of postmenopausal breast cancer, but the difference between menopausal status was not statistically significant. GL and carbohydrates were

associated with increased risk of breast cancer only among women with hormone receptor negative tumours, particularly ER-. Further studies on GI, GL, carbohydrates, sugar intake and risk of breast cancer, accounting for menopausal status, hormone receptor status, excess body weight, and HRT use are needed.

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Declaration of Interest

There were no conflict of interests for any authors.

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Table 1: Description of the PICOS criteria used in the meta-analysis

Parameter	Inclusion criteria
Population	Women without breast cancer at baseline
Intervention/exposures	Dietary intake of carbohydrates, GI, GL, specific types of carbohydrates (total and specific sugars, including fructose, sucrose, glucose, lactose, maltose and added sugars)
Comparison	Dose-response relation
Outcomes	Breast cancer
Type of study	Prospective studies: cohort, case-cohort and nested case-control studies, and follow-up studies of randomized clinical trials

Table 2: Study characteristics of prospective studies included in the meta-analysis on intake of carbohydrates, sugars, GI, GL and breast cancer risk

First Author, Year, Country	**Study name, design, age, other characteristics**	**Study size, Number of cases**	**Follow-up**	**Dietary assessment**	**Carbohydrates** Comparison RR (95% CI)	**GI** Comparison RR (95% CI)	**GL** Comparison RR (95% CI)	**Sugars** Comparison RR (95% CI)
Farvid,[17] 2014, USA	Nurses' Health Study, Prospective cohort study, (NHS) II, 27-44 y	90,488, 2,833	20 y	Validated FFQ in early adulthood, 137 food items	59.2 vs 40.6 % of energy All: 0.88 (0.78-0.99) Premenopausal: 0.88 (0.75-1.03) Postmenopausal: 0.87 (0.70-1.08) Converted into gram per d	57.9 vs 49.7 units/d All: 1.03 (0.91-1.16) Premenopausal: 1.05 (0.90-1.23) Postmenopausal: 1.08 (0.87-1.35) BMI <25 (at age 18y): 1.04 (0.92-1.18) BMI ≥25 (at age 18y): 1.12 (0.68-1.85) ER+/PR+: 1.09 (0.93-1.28) ER-/PR-: 0.95 (0.69-1.30)	149 vs 96 units/d All: 0.94 (0.83-1.06) Premenopausal: 0.93 (0.79-1.09) Postmenopausal: 0.95 (0.76-1.18) BMI <25 (at age 18y): 0.94 (0.83-1.06) BMI ≥25 (at age 18y): 1.19 (0.70-2.03)	
Romieu,[16] 2012, Europe	European Prospective Investigation into Cancer and Nutrition (EPIC) study, Prospective cohort study, 35-70 y	334,849, 11,576	11.5 y	Validated FFQ, diet history, 7-d food diary (depending on the cohort)	>244.1 vs <185.3 g/d All: 1.04 (0.96-1.12) Premenopausal: 1.01 (0.87-1.17) Postmenopausal: 1.01 (0.87-1.17) ER- 1.24 (1.02-1.52) ER-/PR- 1.33 (1.05-1.67)	>58.9 vs <52.7 units/d All: 1.05 (0.99-1.12) Premenopausal: 1.02 (0.90-1.16) Postmenopausal: 1.07 (0.99-1.17) ER- 1.04 (0.88-1.24) ER-/PR- 1.04 (0.86-1.26)	>137.8 vs <101.8 units/d All: 1.07 (1.00-1.14) Premenopausal: 1.04 (0.91-1.20) Postmenopausal: 1.09 (0.99-1.20) ER- 1.16 (0.96-1.41) ER-/PR- 1.17 (0.94-1.46)	

					ER+ 0.95 (0.86-1.06) ER- & postm. 1.41 (1.05-1.89) ER-/PR- & postm. 1.62 (1.15-2.30) ER+ & postm. 0.98 (0.85-1.13) ER-/PR-/ HER2- 1.26 (0.75-2.11) ER-/PR-/ HER2+ 1.67 (0.93-2.98)	ER+ 1.01 (0.93-1.10) ER- & postm. 1.21 (0.93-1.56) ER-/PR- & postm. 1.23 (0.92-1.65) ER+ & postm. 1.01 (0.90-1.14) ER-/PR-/ HER2- 1.03 (0.65-1.65) ER-/PR-/ HER2+ 1.48 (0.87-2.52)	ER+ 1.01 (0.93-1.11) ER- & postm. 1.36 (1.02-1.82) ER-/PR- & postm. 1.48 (1.07-2.05) ER+ & postm. 1.00 (0.87-1.14) ER-/PR-/ HER2- 1.35 (0.83-2.19) ER-/PR-/ HER2+ 1.35 (0.83-2.19)	
Tasevska,[18] 2012 USA	National Institutes of Health-American Association of Retired Persons (NIH-AARP) Diet and Health Study, Prospective cohort study, 50-71 years	179,990, 4,793	7.2 y	Validated semi-quantitative FFQ, 124 food items				Total sugars: 91.5 vs 38.7 g/1000 kcal 0.96 (0.85-1.08) Added sugars: 11.0 vs 2.4 tsp/1000 kcal 1.01 (0.91-1.12) Total fructose: 40.6 vs 14.8 g/1000 kcal 0.93 (0.84-1.04) Sucrose: 37.5 vs 13.6 g/1000 kcal 1.02 (0.93-1.13)
Shikany,[19] 2011, USA	Women's Health Initiative (WHI), Follow-up of a randomized controlled trial and prospective cohort study, 50-79 y, postmenopausal	148,767, 6,098	8 y	Validated FFQ, 122 food items	Available CHO: >305.7 vs <112.3 g/d All: 0.95 (0.80-1.14) ER+/PR+: 0.99 (0.77-1.27) ER+/PR-:	>57.0 vs <47.8 units/d All: 1.01 (0.91-1.12) ER+/PR+: 1.05 (0.90-1.22) ER+/PR-: 1.01 (0.71-1.43)	>150.4 vs <52.9 units/d All: 1.08 (0.92-1.29) ER+/PR+: 0.81 (0.63-1.04) ER+/PR-: 0.60 (0.33-1.09)	Total sugars: >155.4 vs <48.5g/d 1.06 (0.92-1.21) Added sugars: >85.2 vs <18.1 g/d 1.01 (0.89-1.16) Fructose: >35.0 vs <8.5 g/d 1.07 (0.95-1.21)

					0.75 (0.42-1.34) ER-/PR-: 1.33 (0.75-2.38)	ER-/PR-: 1.07 (0.74-1.52)	ER-/PR-: 1.68 (0.93-3.02)
George,[29] 2009, USA	National Institutes of Health-American Association of Retired Persons (NIH-AARP) Diet and Health Study, Prospective cohort study, 50-71 years postmenopausal	183,535, 5,478	6.9 y	Validated semi-quantitative FFQ, 124 food items		56.6-83.9 vs 33.6-50.4 units/d 1.05 (0.97-1.15)	135.3-583.7 vs 4.6-66.9 units/d 0.96 (0.81-1.12)
Larsson,[15] 2009, Sweden	Swedish Mammography Cohort (SMC), Prospective cohort study, mean 54 y, Screening program, postmenopausal	61,433, 2,952	17.4 y	Validated FFQ, 67 food items	≥246 vs <211 g/d All: 1.09 (0.95-1.25) ER+/PR+: 1.08 (0.88-1.33) ER+/PR-: 1.34 (0.93-1.94) ER-/PR-: 1.14 (0.73-1.79)	≥83.4 vs <75.8 units/d All: 1.08 (0.96-1.21) ER+/PR+: 0.89 (0.74-1.06) ER+/PR-: 1.44 (1.06-1.97) ER-/PR-: 1.29 (0.85-1.96)	≥200 vs <164 units/d All: 1.13 (1.00-1.29) ER+/PR+: 0.94 (0.77-1.13) ER+/PR-: 1.81 (1.29-2.53) ER-/PR-: 1.23 (0.79-1.90) BMI <25: 1.26 (1.06-1.50) BMI ≥25: 1.08 (0.88-1.33) BMI <25& ER+/PR- 2.03 (1.35-3.06) BMI ≥25& ER+/PR- 1.80 (0.92-3.53)
Wen,[14] 2009, China	Shangai Women's Health Study (SWHS), Prospective cohort study, 40-70 y	73.328, 616	7.4 y	Validated FFQ, 77 food items	343.5 vs 257.5 g/d All: 1.22 (0.94-1.58) Premenopausal: 2.01 (1.26-3.19)	76.8 vs 63.9 units/d All: 1.03 (0.79-1.34) Premenopausal:	239.4 vs 163.8 units/d All: 1.07 (0.82-1.39) Premenopausal:

					Postmenopausal: 0.98 (0.72-1.34) BMI <25: 1.09 (0.90-1.31) BMI ≥25: 1.06 (0.85-1.31) BMI <25 & prem.: 1.54 (1.10-2.16) BMI ≥25 & prem: 1.71 (1.05-2.80)	1.19 (0.73-1.94) Postmenopausal: 0.96 (0.70-1.31)	1.53 (0.96-2.45) Postmenopausal: 0.91 (0.67-1.25)	
Lajous,[33] 2008, France	E3N- European Prospective Investigation into Cancer and Nutrition (EPIC) study -France, Prospective cohort study, 42-72 y, postmenopausal	1,812, 62,739	9 y	Dietary history	BMI <25 & postm.: 1.04 (0.89-1.20) BMI ≥25 & postm.: 1.07 (0.77-1.49) only included in subgroups analysis	BMI <25 & postm.: 1.09 (0.93-1.28) BMI ≥25 & postm.: 1.35 (1.00-1.82) only included in subgroups analysis	BMI <25 & postm.: 1.08 (0.92-1.28) BMI ≥25 & postm.: 1.22 (0.90-1.67) only included in subgroups analysis	
Sieri,[51] 2007, Italy	Hormones and Diet in the Etiology of Breast Cancer" (ORDET) study, Prospective cohort study, 34-70 y,	8,926, 289	11.5 y	Semi-quantitative FFQ, 107 food items	Not included in meta-analysis: CHO reported per 5 %energy	>57.5 vs <53.5 units/d All: 1.57 (1.04-2.36) Premenopausal: 1.82 (1.01-3.27) Postmenopausal: 1.12 (0.62-2.02) BMI <25: 2.22 (1.18-4.19) BMI ≥25: 1.11 (0.64-1.94)	>133.7vs <103.2 units/d All: 2.53 (1.54-4.16) Premenopausal: 3.89 (1.81-8.34) Postmenopausal: 1.67 (0.80-3.46) BMI <25: 5.79 (2.60-12.9) BMI ≥25: 1.31 (0.66-2.61)	
Nielsen,[20] 2005, Denmark	Diet, Cancer and Health (DCH) study, Prospective cohort study, 50-65 y, postmenopausal	23,870, 634	6.6 y	Validated FFQ, 192 food items	Not included for CHO: overlap with Romieu, 2012	Not included for GI: overlap with Romieu, 2012	Not included for GL: overlap with Romieu, 2012	**Glucose:** per 50 g/d All: 1.06 (0.79-1.42) ER+: 1.05 (0.91-1.21) ER-:

								0.86 (0.64-1.16) **Fructose** per 10 g/d All: 0.99 (0.81-1.20) ER+: 1.06 (0.96-1.18) ER-: 0.84 (0.67-1.06) **Sucrose** per 10 g/d All: 1.01 (0.94-1.08) ER+: 1.01 (0.95-1.07) ER-: 1.05 (0.94-1.16) **Maltose** per 2 g/d All: 1.02 (0.88-1.18) ER+: 1.04 (0.90-1.20) ER-: 1.03 (0.78-1.38) **Lactose** per 10 g/d All: 1.04 (0.98-1.10) ER+: 1.04 (0.97-1.11) ER-: 1.07 (0.95-1.22)
Silvera,[13] 2005, Canada	Canadian National Breast Screening Study (CNBSS), Prospective cohort study, 40-59y, Screening program	49,111, 1,450	16.6 y	Validated FFQ, 69 food items	>249 vs <143 g/d All: 0.93 (0.70-1.22)	>96 vs <60 units/d All: 0.88 (0.63-1.22) Premenopausal: 0.78 (0.52-1.16) Postmenopausal:	>175 vs <119 units/d All: 0.95 (0.79-1.14) Premenopausal: 0.96 (0.76-1.22)	Total sugars: >103 vs <52 g/d All: 0.88 (0.70-1.12)

						1.87 (1.18-2.97) BMI <25 & prem.: 0.89 (0.54-1.45) BMI ≥25 & prem.: 0.62 (0.32-1.23) BMI <25 & postm.: 1.99 (1.06-9.72) BMI ≥25 & postm.: 1.57 (0.78-3.13)	Postmenopausal: 1.08 (0.82-1.41) BMI <25 & prem.: 1.01 (0.76-1.35) BMI ≥25 & prem.: 0.85 (0.55-1.31) BMI <25 & postm.: 0.97 (0.68-1.39) BMI ≥25 & postm.: 1.22 (0.82-1.82)
Holmes,[12] 2004, USA	Nurses' Health Study (NHS), Prospective cohort study, 35-55 y, Registered nurses	88,678, 4,092	18 y	Validated semi-quantitative FFQ, 61 food items	240 vs 159 g/d All: 0.97 (0.87-1.08) Premenopausal: 0.98 (0.78-1.23) Postmenopausal: 0.96 (0.84-1.09) BMI <25 & prem.: 1.20 (0.89-1.61) BMI ≥25 & prem.: 0.72 (0.48-1.07) BMI <25 & postm.: 0.95 (0.78-1.15) BMI ≥25 & postm.: 0.96 (0.80-1.17)	81 vs <9 units/d All: 1.08 (0.97-1.19) Premenopausal: 1.02 (0.82-1.28) Postmenopausal: 1.15 (1.02-1.30) BMI <25 & prem.: 1.06 (0.79-1.42) BMI ≥25 & prem.: 0.83 (0.57-1.22) BMI <25 & postm.: 1.28 (1.08-1.53) BMI ≥25 & postm.: 1.05 (0.87-1.26)	186 vs 116 units/d All: 0.98 (0.87-1.11) Premenopausal: 0.87 (0.70-1.12) Postmenopausal: 1.03 (0.90-1.16) BMI <25 & prem.: 1.01 (0.75-1.35) BMI ≥25 & prem.: 0.68 (0.45-1.03) BMI <25 & postm.: 1.06 (0.87-1.28) BMI ≥25 & postm.: 0.97 (0.80-1.18)
Higginbotham,[30] 2004, USA	Women's health study (WHS), Prospective cohort study (based on randomized controlled trial), ≥ 45 y	38,446, 897	6.8 y	Validated semi-quantitative FFQ, 131 food items		Q5 vs Q1 (no quantity) Not included in dose-response meta-analysis	143 vs. 92 units/d All: 1.01 (0.76-1.35) Premenopausal: 1.27 (0.79-2.03) Postmenopausal: 0.90 (0.63-1.31)
Jonas,[52] 2003, USA	Cancer Prevention Study (CPS) II Nutrition Cohort, Prospective cohort study,	70,888, 1,442	5 y	Validated semi-quantitative		85 vs 65 units/d 1.03 (0.87-1.22)	147 vs 83 units/d 0.90 (0.76-1.08)

	50-74 y, postmenopausal			FFQ, 68 food items		
Sieri,[21] 2002, Italy	"Hormones and Diet in the Etiology of Breast Cancer" (ORDET) study, Nested case-control study, 41-70 y, postmenopausal	214 controls, 56 cases	5.5 y	semi-quantitative FFQ, 107 food items	217.6-303.4 vs <190.2 g/d 0.73 (0.33–1.59)	Total sugars: 72.9–141.0 g vs. <54.3 g/d 0.34 (0.11–1.03)
Kushi,[34] 1995, USA	Iowa Women's Health Study (IWHS), Prospective cohort study, 55-69 y, postmenopausal	34,388, 262	6 y	Validated semi-quantitative FFQ, 127 food items (same used 1984 in Nurses Health Study)	≥225 vs <198 g/d ER+/PR+: 0.79 (0.60-0.79) ER+/PR-: 0.78 (0.44-1.39) ER-/PR+: 3.82(0.76-19.19) ER-/PR-: 0.60 (0.31-1.14) Unknown 0.98 (0.72-1.35)	
Barrett-Connor,[11] 1993, USA	Rancho Bernardo, Prospective cohort study, 40-79 y	590, 15	15 y	24h recall	per 66 g/d 1.93 (1.18-3.16)	
Kushi,[10] 1992 USA	Iowa Women's Health Study (IWHS), Prospective cohort study, 55-69 y, postmenopausal	34,388, 459	4 y	Validated semi-quantitative FFQ, 127 food items (same used 1984 in Nurses Health Study)	≥252.7 vs <181 g/d 1.16 (0.72-1.86)	
Knekt,[9] 1990, Finland	Social Insurance Institution's Mobile Clinic Health Examination Survey, Prospective cohort study, 20-69 y	3,988, 54	20 y	Dietary history method	≥278 vs ≤207 g/d 0.40 (0.16–1.00)	

Table 3. Summary relative risks (RR) and 95% confidence intervals (95% CI) of dose-response meta-analyses of carbohydrates, GI, GL and breast cancer by subgroups.

	Carbohydrates (per 50 g/d)					GI (per 10 units/d)					GL (per 50 units/d)				
	Summary RR (95% CI)	n	I^2 (%)	p_{within}[a]	$p_{between}$[b]	Summary RR (95% CI)	n	I^2 (%)	p_{within}[a]	$p_{between}$[b]	Summary RR (95% CI)	n	I^2 (%)	p_{within}[a]	$p_{between}$[b]
All studies	1.00 (0.96-1.05)	11	57.3	.009	-	1.04 (1.00-1.07)	10	27.2	.194	-	1.01 (0.98-1.04)	11	42.7	.065	
Menopausal status															
Premenopausal	1.03 (0.91-1.17)	4	76.1	.006	.999	1.01 (0.93-1.10)	6	34.0	.181	.150	1.07 (0.92-1.24)	7	72.0	.002	.671
Postmenopausal	1.00 (0.95-1.06)	9	44.9	.069		1.06 (1.02-1.10)	10	19.2	.266		1.02 (0.99-1.06)	11	3.5	.409	
Time of assessment of premenopausal status[c]															
At exposure	0.96 (0.90-1.02)	2	0	.400	.444	0.99 (0.89-1.11)	4	42.9	.154	.502	1.04 (0.88-1.23)	5	66.9	.017	.968
At cancer diagnosis	1.22 (0.75-1.98)	2	89.7	.002		1.08 (0.89-1.29)	2	18.1	.269		1.15 (0.70-1.88)	2	89.1	.002	
Hormone receptor status															
All															
estrogen receptor (ER)															
ER+	0.97 (0.93-1.01)	4	17.7	.302	.029	1.04 (0.97-1.12)	4		.911	.882	0.99 (0.95-1.02)	3	53.6	.116	.055
ER-	1.11 (1.02-1.21)	4	0	.820		1.03 (0.90-1.18)	4		.870		1.20 (1.05-1.38)	3	0	.976	
progesterone receptor (PR)											.849				
PR+	0.97 (0.92-1.03)	3	0	.525	.427	1.02 (0.91-1.14)	3		.234	.849	0.91 (0.83-1.00)	2	0	.487	.182
PR-	1.04 (0.90-1.21)	4	63.8	.040		1.03 (0.89-1.20)	4		.577		1.05 (0.96-1.14)	3	72.9	.025	
combinations															
ER+/PR+	0.93 (0.81-1.06)	3	73.2	.024		1.02 (0.91-1.14)	3		.234		0.91 (0.83-1.00)	2	0	.487	
ER+/PR-	1.05 (0.78-1.40)	3	62.2	.071	.379	1.29 (0.96-1.73)	2		.188	.200	1.16 (0.54-2.51)	2	92.8	.000	.591
ER-/PR-	1.09 (0.96-1.24)	4	32.5	.218		1.01 (0.88-1.17)	4		.822		1.19 (1.02-1.38)	3	0	.987	
ER-/PR+	2.99 (0.75-11.89)	1	-	-		-	-		-		-	-	-	-	
Postmenopausal [d]															
estrogen receptor (ER)															
ER+	0.98 (0.93-1.04)	4	23.8	.269	.047	1.02 (0.93-1.13)	3	0	.938	.311	0.99 (0.95-1.03)	3	53.8	.115	.046
ER-	1.13 (1.02-1.25)	4	0	.530		1.16 (0.96-1.40)	3	0	.864		1.28 (1.08-1.52)	3	0	.589	
progesterone receptor (PR)															
PR+	0.97 (0.92-1.03)	3	0	.525	.464	0.99 (0.85-1.15)	2	48.5	.164	.353	0.91 (0.83-1.00)	2	0	.487	.292
PR-	1.06 (0.86-1.31)	4	70.6	.017		1.19 (0.92-1.54)	2	0	.579		1.08 (0.96-1.21)	3	82.6	.003	
combinations															
ER+/PR+	0.93 (0.81-1.06)	3	73.2	.024		0.99 (0.85-1.15)	2	48.5	.164	.214	0.91 (0.95-1.03)	2	0	.487	
ER+/PR-	1.05 (0.78-1.40)	3	62.2	.071	.391	1.29 (0.96-1.73)	2	42.2	.188		1.16 (0.54-2.51)	2	92.8	.000	.503
ER-/PR-	1.10 (0.91-1.34)	4	53.9	.089		1.15 (0.94-1.39)	3	0	.950		1.29 (1.08-1.54)	3	0	.494	
ER-/PR+	2.99 (0.75-11.89)	1	-	-		-	-	-	-		-	-	-	-	
BMI, kg/m²															
All															
< 25	1.02 (0.96-1.08)	3	0	.803	.315	1.08 (0.99-1.17)	5	52.5	.077	.644	1.02 (0.99-1.04)	6	80.7	.000	.985
≥ 25	0.97 (0.90-1.04)	3	0	.509		1.03 (0.97-1.11)	5	0	.442		1.01 (0.99-1.02)	6	0	.515	

Premenopausal women															
< 25	1.11 (0.94-1.32)	2	0	.326	.703	0.98 (0.89-1.08)	2	0	.472	.323	0.99 (0.86-1.15)	2	0	.579	.939
≥ 25	1.06 (0.55-2.02)	2	80.4	.024		0.88 (0.97-1.20)	2	0	.849		0.79 (0.65-0.97)	2	0	.325	
Postmenopausal women															
< 25	1.01 (0.94-1.07)	2	0	.539	.839	1.15 (1.01-1.32)	3	71.9	.029	.705	1.01 (0.99-1.03)	4	39.9	.172	.942
≥ 25	0.99 (0.91-1.09)	2	0	.725		1.11 (1.02-1.20)	3	0	.683		1.01 (1.00-1.03)	4	0	.394	
Geographic area															
Europe	0.94 (0.80-1.10)	4	72.9	.011	.707	1.07 (0.99-1.17)	3	27.2	.194	.456	1.16 (0.96-1.40)	3	82.4	.003	.414
North America	0.99 (0.94-1.04)	6	51.9	.605		1.02 (0.98-1.06)	6	20.4	.280		1.00 (0.99-1.01)	7	0	.820	
Asia-Pacific	1.07 (0.92-1.25)	1	-	-		0.97 (0.81-1.18)	1	-	-		1.05 (0.89-1.24)	1	-	-	
Assessment of GI and GL															
Glucose	-	-	-	-	-	1.03 (0.96-1.10)	5	23.4	.265	.767	1.02 (0.93-1.11)	6	61.9	.022	.991
White Bread	-	-	-	-		1.05 (1.00-1.11)	3	3.4	.355		1.02 (0.96-1.08)	3	42.7	.159	
Glucose/ white bread	-	-	-	-		1.02 (0.94-1.11)	2	76.9	.037		1.01 (0.97-1.06)	2	0	.501	
Duration of follow-up															
<10 years of follow-up	1.00 (0.96-1.04)	3	0	.509	.675	1.02 (0.97-1.07)	4	0	.642	.547	1.00 (0.96-1.05)	5	0	.732	.825
≥10 years of follow-up	0.99 (0.93-1.06)	8	68.1	.003		1.05 (0.99-1.11)	6	51.3	.068		1.02 (0.96-1.07)	6	67.6	.009	
Number of cases															
<1500	1.00 (0.84-1.19)	6	71.0	.004	.925	1.00 (0.93-1.07)	4	36.2	.195	.056	1.04 (0.91-1.19)	5	63.5	.027	.984
≥1500	1.00 (0.96-1.03)	5	34.6	.191		1.06 (1.02-1.09)	6	0	.753		1.01 (0.98-1.04)	6	22.8	.263	

BMI, body mass index; CI, confidence interval; ER, oestrogen receptor; GI, glycemic index; GL, glycemic load; n, number of studies; PR, progesterone receptor; RR, relative risk

[a] p_{within}, p for heterogeneity within each subgroup

[b] $p_{between,}$ p for heterogeneity between subgroups with meta-regression

[c] only among studies including premenopausal women

[d] for premenopausal women: no data available

Figure 1: Flow chart of study selection: search period June 1st 2008-April 30th 2015.

Figure 2: Intake of carbohydrates and breast cancer. (A) Dose-response analysis per 50 g/day for any breast cancer, (B) by menopausal status, and (C) non-linear dose-response analysis.

Figure 3: Glycemic index and breast cancer. (A) Dose-response analysis per 10 units/day for any breast cancer, (B) by menopausal status, and (C) non-linear dose-response analysis.

Figure 4: Glycemic load and breast cancer. (A) Dose-response analysis per 50 g/day for any breast cancer, (B) by menopausal status, and (C) non-linear dose-response analysis.

Figure 5: Intake of total sugars and breast cancer. (A) Dose-response analysis per 10 g/day for any breast cancer, and (B) non-linear dose-response analysis.

Figure 6: Intake of fructose and breast cancer. (A) Dose-response analysis per 10 g/day for any breast cancer, and (B) non-linear dose-response analysis.

Figure 1

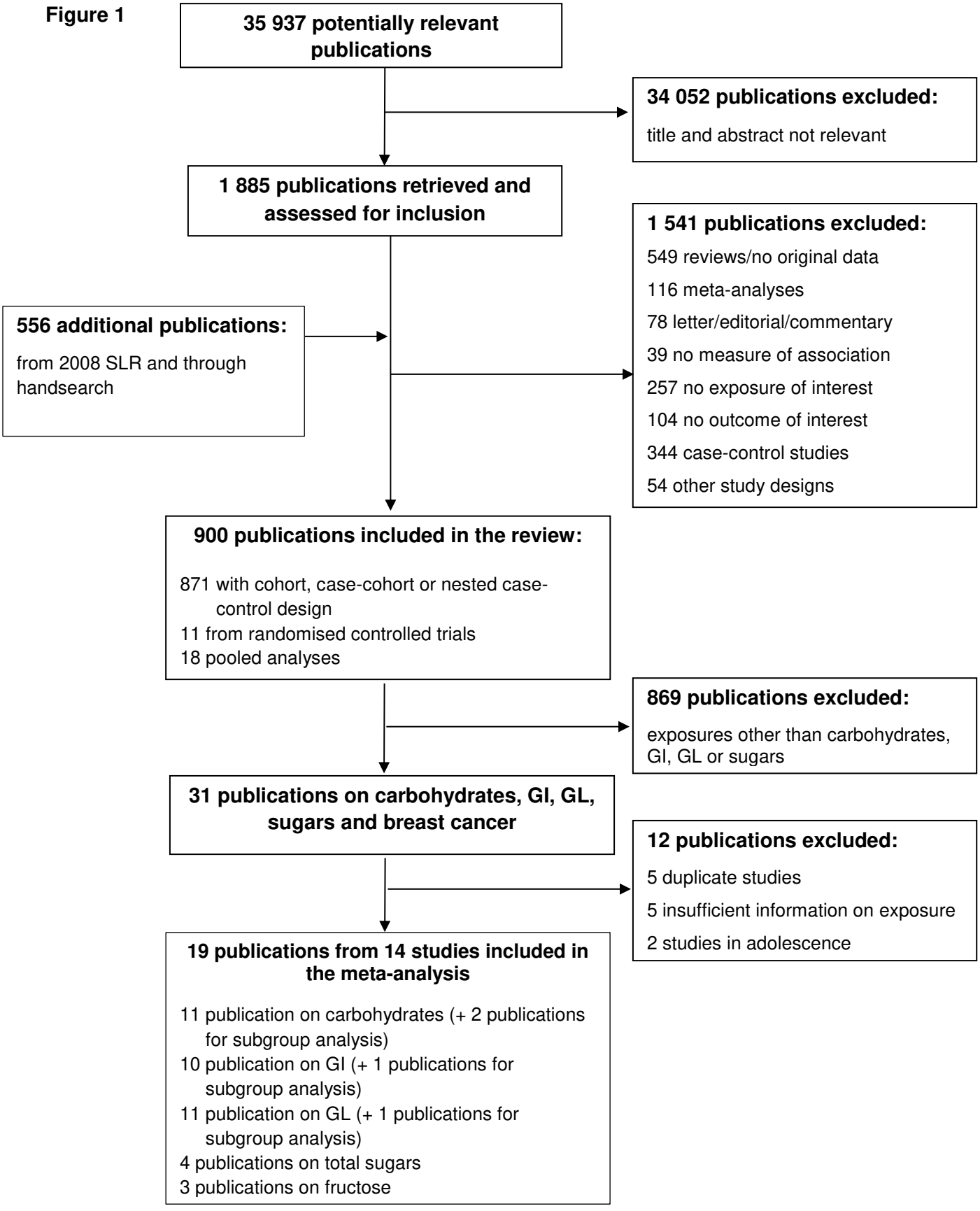
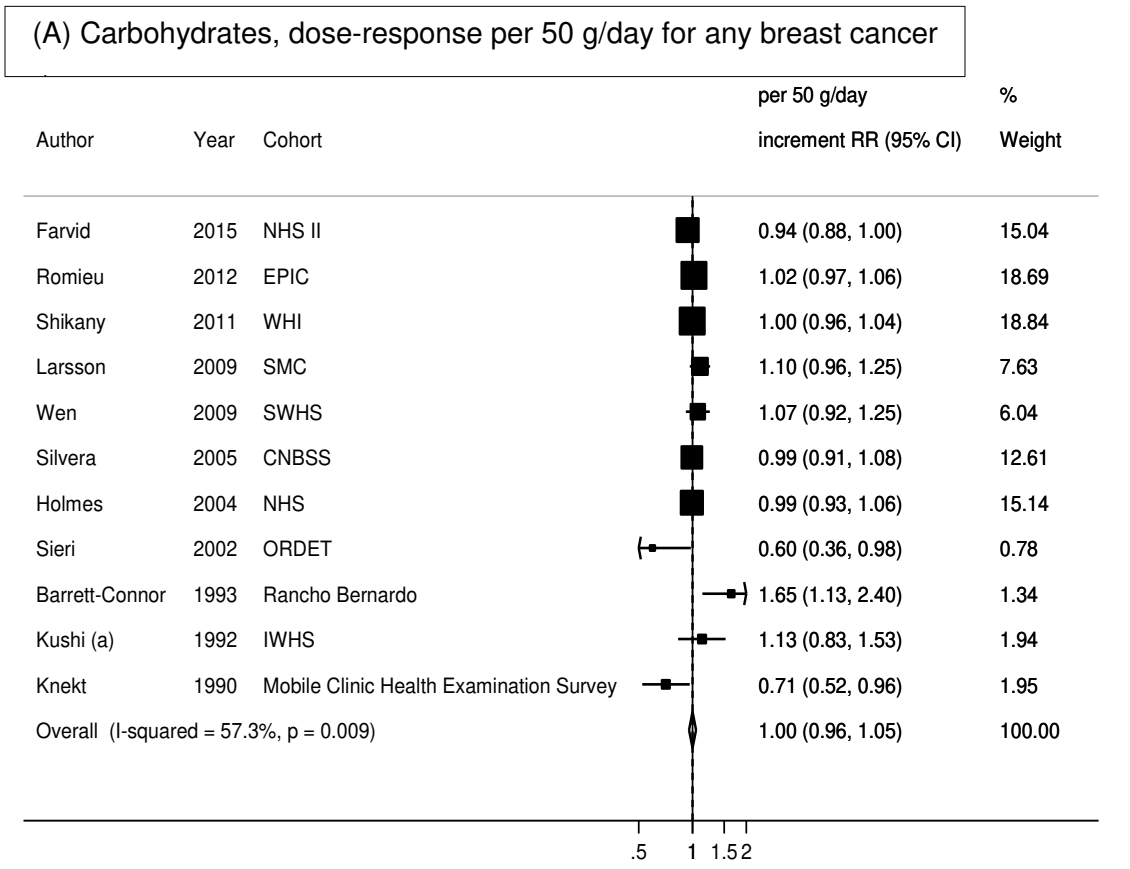
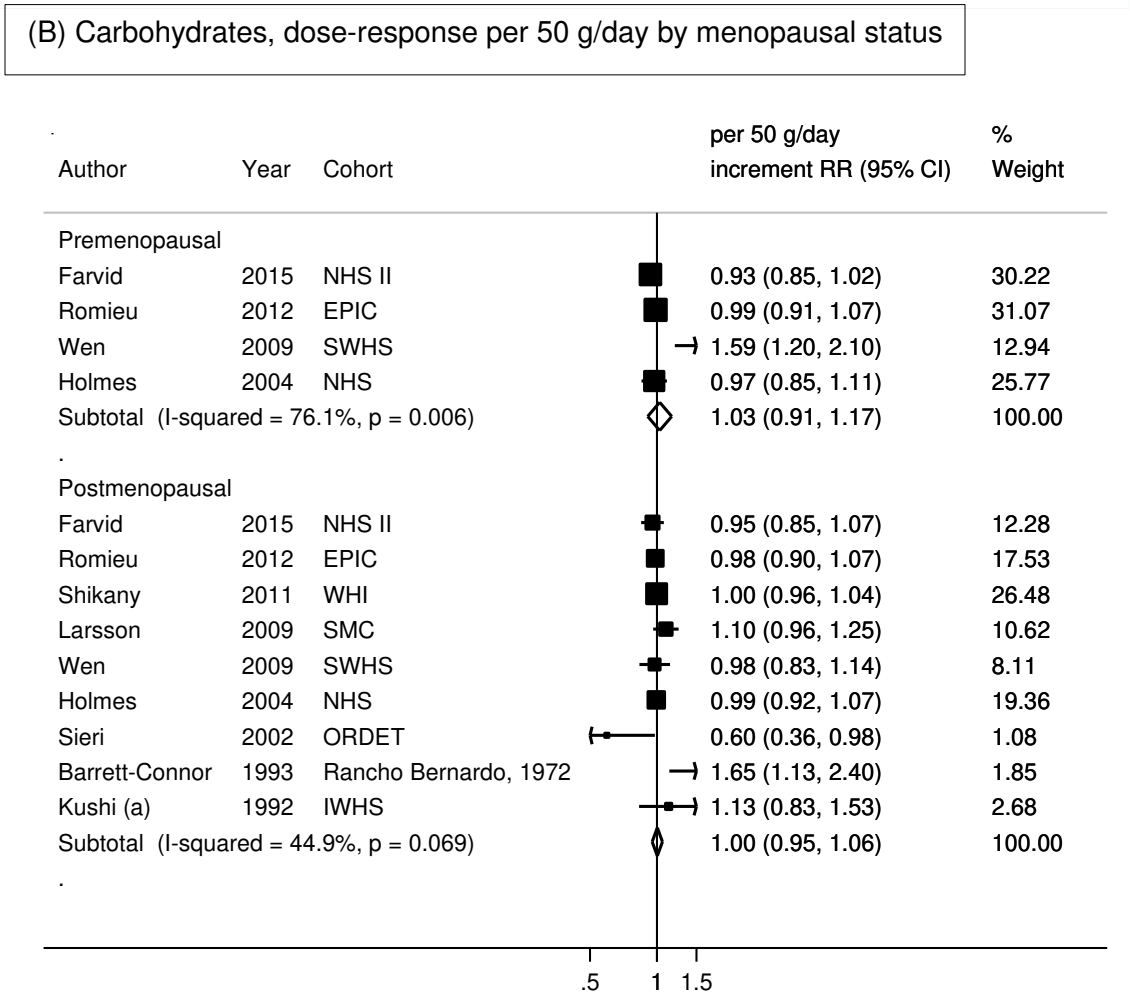

35 937 potentially relevant publications
34 052 publications excluded:
title and abstract not relevant
1 885 publications retrieved and assessed for inclusion
1 541 publications excluded:
549 reviews/no original data
116 meta-analyses
78 letter/editorial/commentary
39 no measure of association
257 no exposure of interest
104 no outcome of interest
344 case-control studies
54 other study designs
556 additional publications:
from 2008 SLR and through handsearch
900 publications included in the review:
871 with cohort, case-cohort or nested case-control design
11 from randomised controlled trials
18 pooled analyses
869 publications excluded:
exposures other than carbohydrates, GI, GL or sugars
31 publications on carbohydrates, GI, GL, sugars and breast cancer
12 publications excluded:
5 duplicate studies
5 insufficient information on exposure
2 studies in adolescence
19 publications from 14 studies included in the meta-analysis
11 publication on carbohydrates (+ 2 publications for subgroup analysis)
10 publication on GI (+ 1 publications for subgroup analysis)
11 publication on GL (+ 1 publications for subgroup analysis)
4 publications on total sugars
3 publications on fructose

Figure 2


(A) Carbohydrates, dose-response per 50 g/day for any breast cancer
Author
Year
Cohort
per 50 g/day increment RR (95% CI)
% Weight
Farvid 2015 NHS II 0.94 (0.88, 1.00) 15.04
Romieu 2012 EPIC 1.02 (0.97, 1.06) 18.69
Shikany 2011 WHI 1.00 (0.96, 1.04) 18.84
Larsson 2009 SMC 1.10 (0.96, 1.25) 7.63
Wen 2009 SWHS 1.07 (0.92, 1.25) 6.04
Silvera 2005 CNBSS 0.99 (0.91, 1.08) 12.61
Holmes 2004 NHS 0.99 (0.93, 1.06) 15.14
Sieri 2002 ORDET 0.60 (0.36, 0.98) 0.78
Barrett-Connor 1993 Rancho Bernardo 1.65 (1.13, 2.40) 1.34
Kushi (a) 1992 IWHS 1.13 (0.83, 1.53) 1.94
Knekt 1990 Mobile Clinic Health Examination Survey 0.71 (0.52, 0.96) 1.95
Overall (I-squared = 57.3%, p = 0.009) 1.00 (0.96, 1.05) 100.00
.5
1
1.5
2


(B) Carbohydrates, dose-response per 50 g/day by menopausal status
Author
Year
Cohort
per 50 g/day increment RR (95% CI)
% Weight
Premenopausal
Farvid 2015 NHS II 0.93 (0.85, 1.02) 30.22
Romieu 2012 EPIC 0.99 (0.91, 1.07) 31.07
Wen 2009 SWHS 1.59 (1.20, 2.10) 12.94
Holmes 2004 NHS 0.97 (0.85, 1.11) 25.77
Subtotal (I-squared = 76.1%, p = 0.006) 1.03 (0.91, 1.17) 100.00
Postmenopausal
Farvid 2015 NHS II 0.95 (0.85, 1.07) 12.28
Romieu 2012 EPIC 0.98 (0.90, 1.07) 17.53
Shikany 2011 WHI 1.00 (0.96, 1.04) 26.48
Larsson 2009 SMC 1.10 (0.96, 1.25) 10.62
Wen 2009 SWHS 0.98 (0.83, 1.14) 8.11
Holmes 2004 NHS 0.99 (0.92, 1.07) 19.36
Sieri 2002 ORDET 0.60 (0.36, 0.98) 1.08
Barrett-Connor 1993 Rancho Bernardo, 1972 1.65 (1.13, 2.40) 1.85
Kushi (a) 1992 IWHS 1.13 (0.83, 1.53) 2.68
Subtotal (I-squared = 44.9%, p = 0.069) 1.00 (0.95, 1.06) 100.00
.5
1
1.5

(C) Carbohydrates, non-linear dose-response

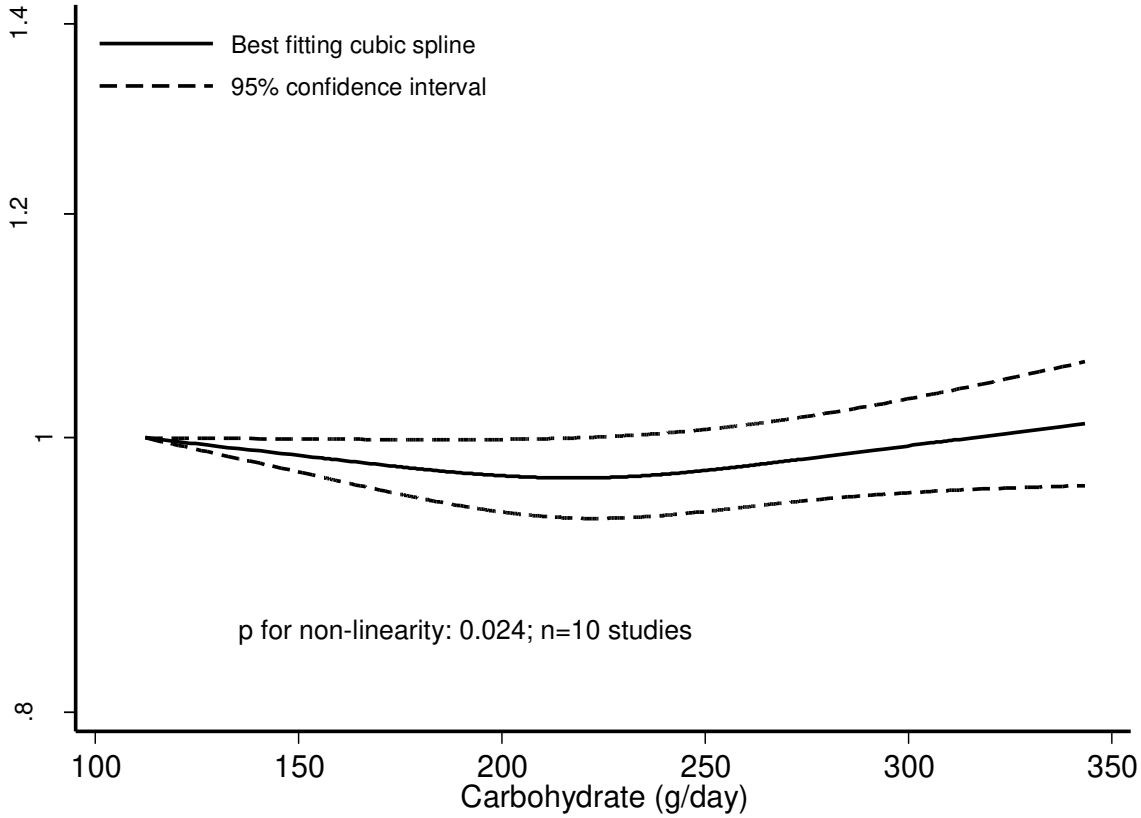
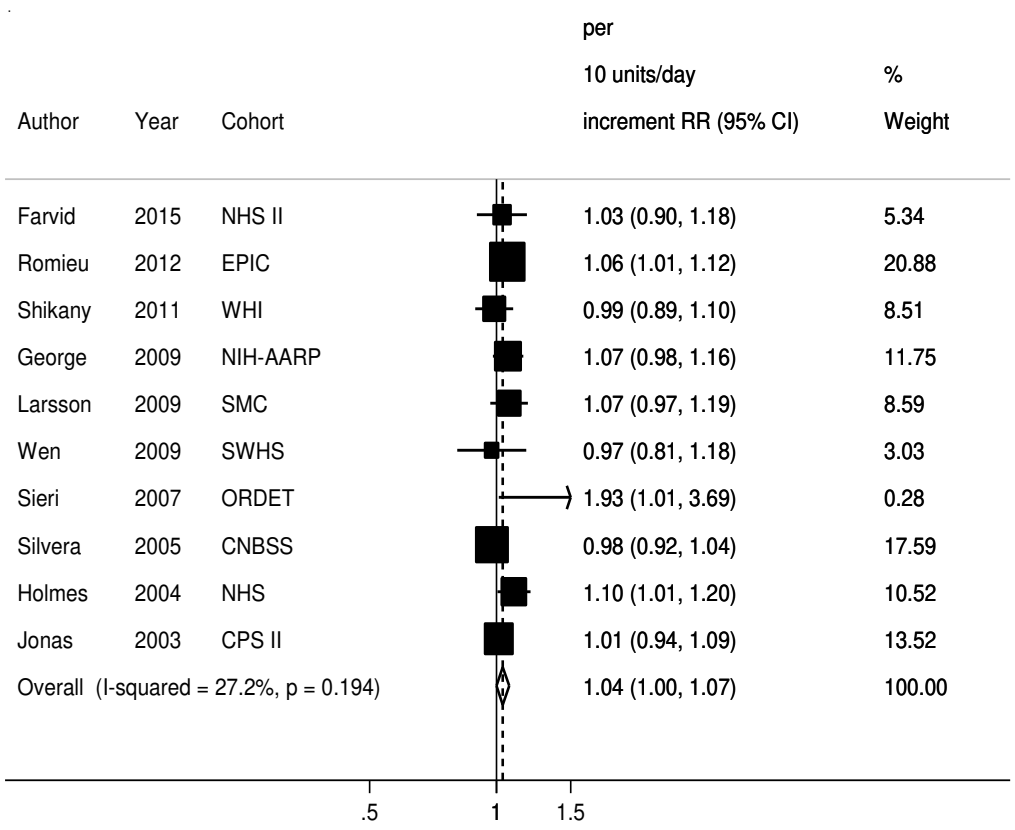
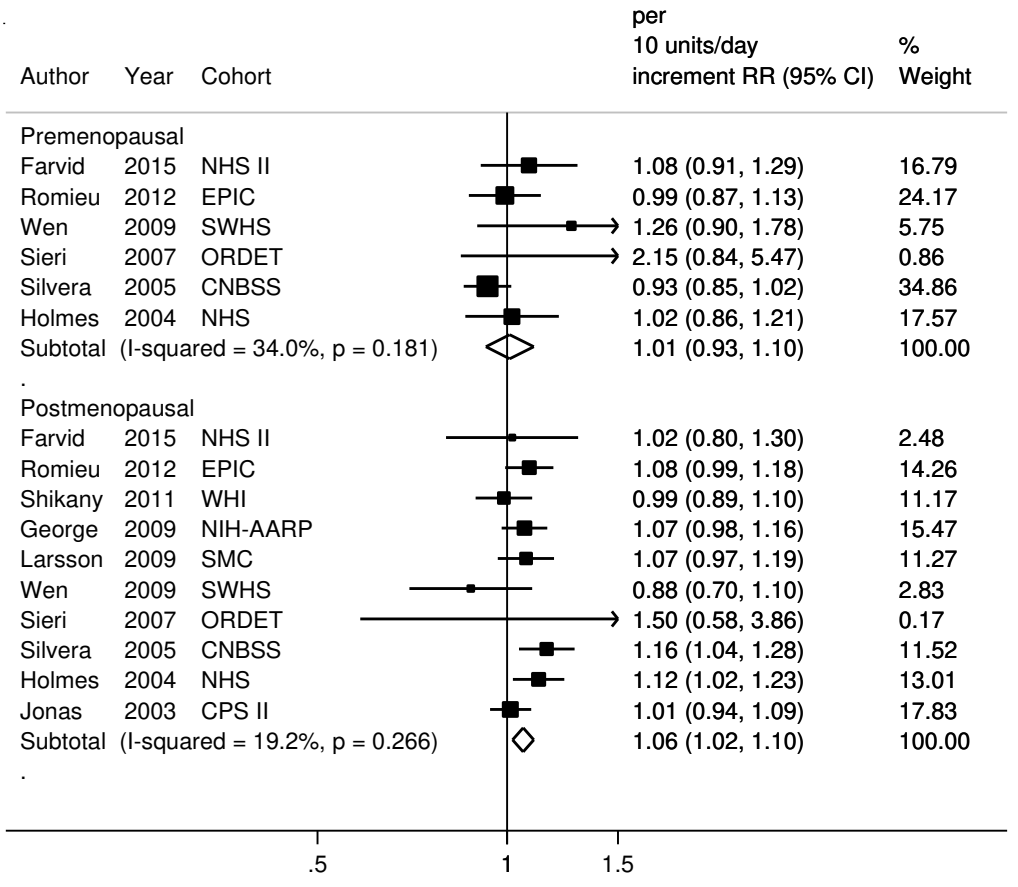


Figure 3

(A) Glycemic index, dose-response per 10 units/day for any breast cancer



(B) Glycemic index, dose-response per 10 units/day by menopausal status



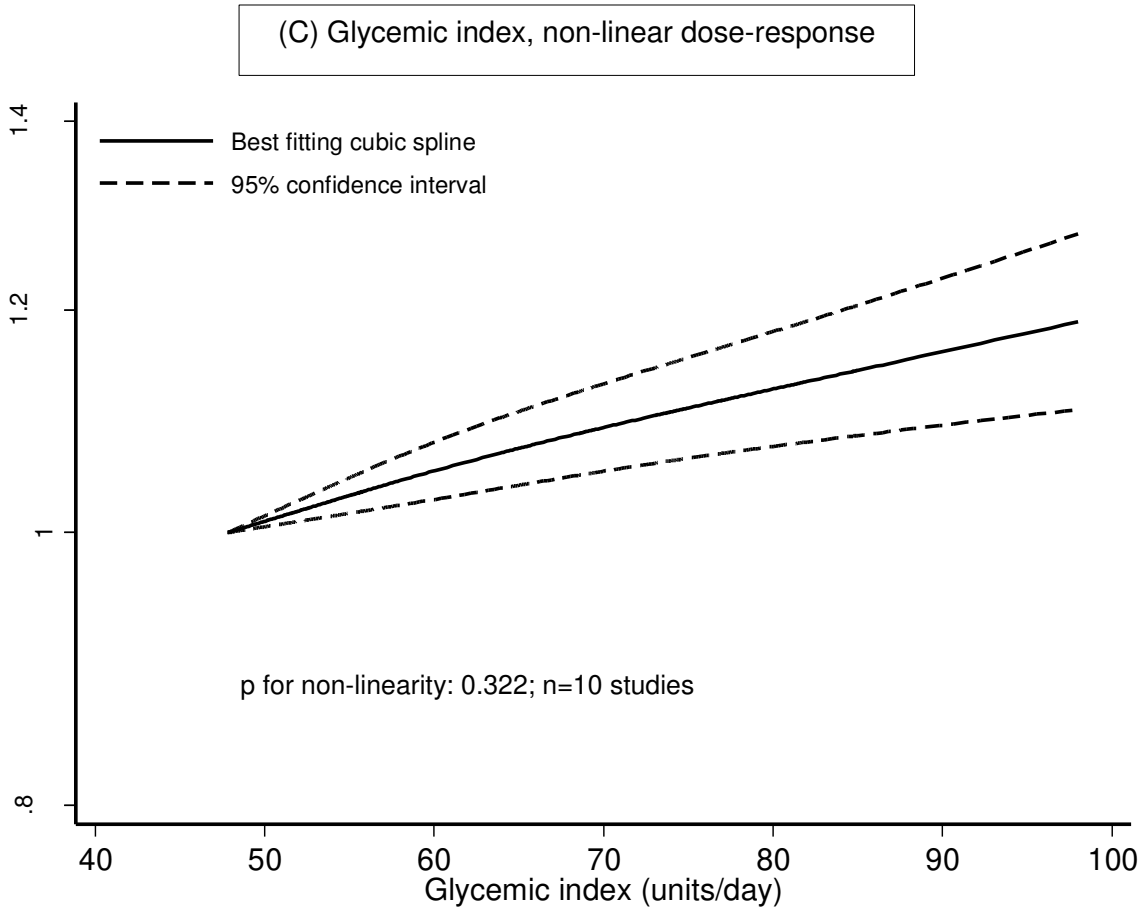
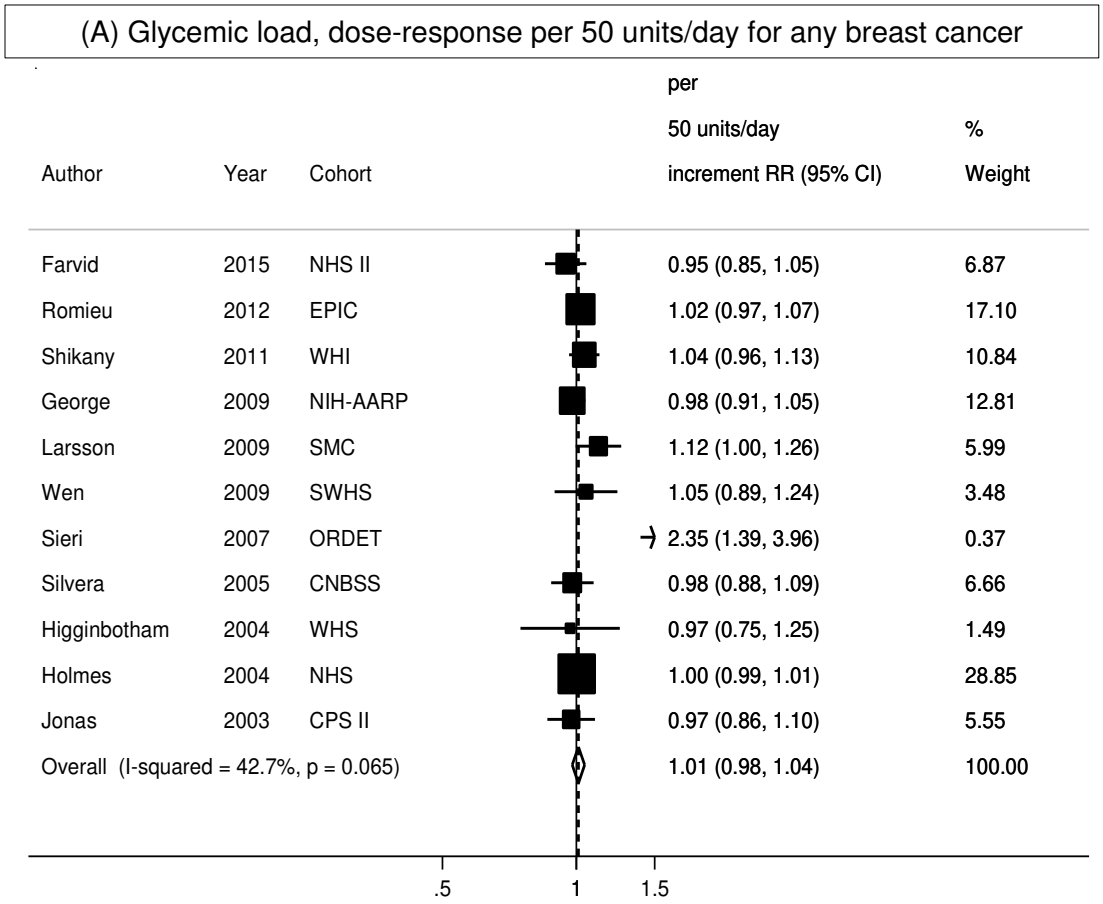
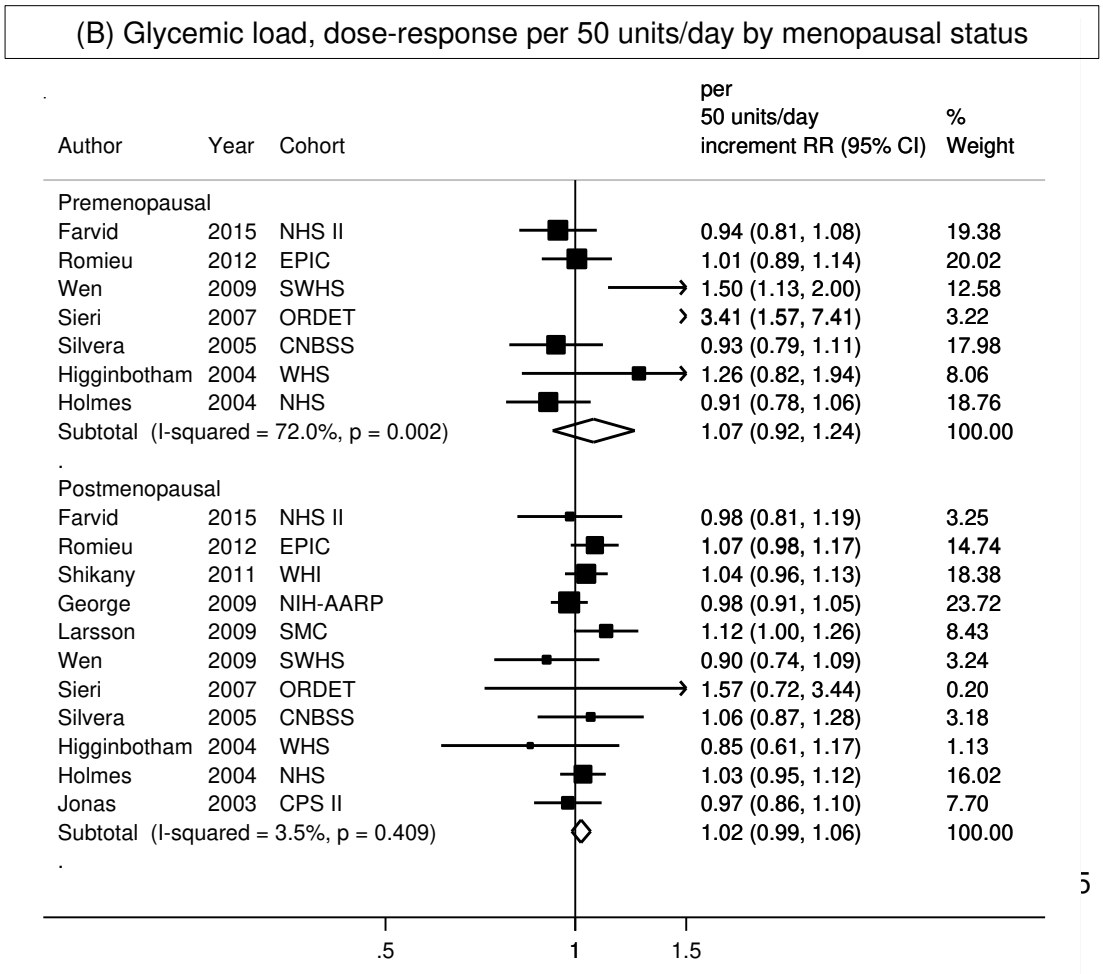

(C) Glycemic index, non-linear dose-response
Best fitting cubic spline
95% confidence interval
p for non-linearity: 0.322; n=10 studies
1.4
1.2
1
.8
40
50
60
70
80
90
100
Glycemic index (units/day)

Figure 4


(A) Glycemic load, dose-response per 50 units/day for any breast cancer
Author
Year
Cohort
per 50 units/day increment RR (95% CI)
% Weight
Farvid 2015 NHS II 0.95 (0.85, 1.05) 6.87
Romieu 2012 EPIC 1.02 (0.97, 1.07) 17.10
Shikany 2011 WHI 1.04 (0.96, 1.13) 10.84
George 2009 NIH-AARP 0.98 (0.91, 1.05) 12.81
Larsson 2009 SMC 1.12 (1.00, 1.26) 5.99
Wen 2009 SWHS 1.05 (0.89, 1.24) 3.48
Sieri 2007 ORDET 2.35 (1.39, 3.96) 0.37
Silvera 2005 CNBSS 0.98 (0.88, 1.09) 6.66
Higginbotham 2004 WHS 0.97 (0.75, 1.25) 1.49
Holmes 2004 NHS 1.00 (0.99, 1.01) 28.85
Jonas 2003 CPS II 0.97 (0.86, 1.10) 5.55
Overall (I-squared = 42.7%, p = 0.065) 1.01 (0.98, 1.04) 100.00
.5
1
1.5


(B) Glycemic load, dose-response per 50 units/day by menopausal status
Author
Year
Cohort
per 50 units/day increment RR (95% CI)
% Weight
Premenopausal
Farvid 2015 NHS II 0.94 (0.81, 1.08) 19.38
Romieu 2012 EPIC 1.01 (0.89, 1.14) 20.02
Wen 2009 SWHS 1.50 (1.13, 2.00) 12.58
Sieri 2007 ORDET 3.41 (1.57, 7.41) 3.22
Silvera 2005 CNBSS 0.93 (0.79, 1.11) 17.98
Higginbotham 2004 WHS 1.26 (0.82, 1.94) 8.06
Holmes 2004 NHS 0.91 (0.78, 1.06) 18.76
Subtotal (I-squared = 72.0%, p = 0.002) 1.07 (0.92, 1.24) 100.00
Postmenopausal
Farvid 2015 NHS II 0.98 (0.81, 1.19) 3.25
Romieu 2012 EPIC 1.07 (0.98, 1.17) 14.74
Shikany 2011 WHI 1.04 (0.96, 1.13) 18.38
George 2009 NIH-AARP 0.98 (0.91, 1.05) 23.72
Larsson 2009 SMC 1.12 (1.00, 1.26) 8.43
Wen 2009 SWHS 0.90 (0.74, 1.09) 3.24
Sieri 2007 ORDET 1.57 (0.72, 3.44) 0.20
Silvera 2005 CNBSS 1.06 (0.87, 1.28) 3.18
Higginbotham 2004 WHS 0.85 (0.61, 1.17) 1.13
Holmes 2004 NHS 1.03 (0.95, 1.12) 16.02
Jonas 2003 CPS II 0.97 (0.86, 1.10) 7.70
Subtotal (I-squared = 3.5%, p = 0.409) 1.02 (0.99, 1.06) 100.00
.5
1
1.5

(C) Glycemic load, non-linear dose-response

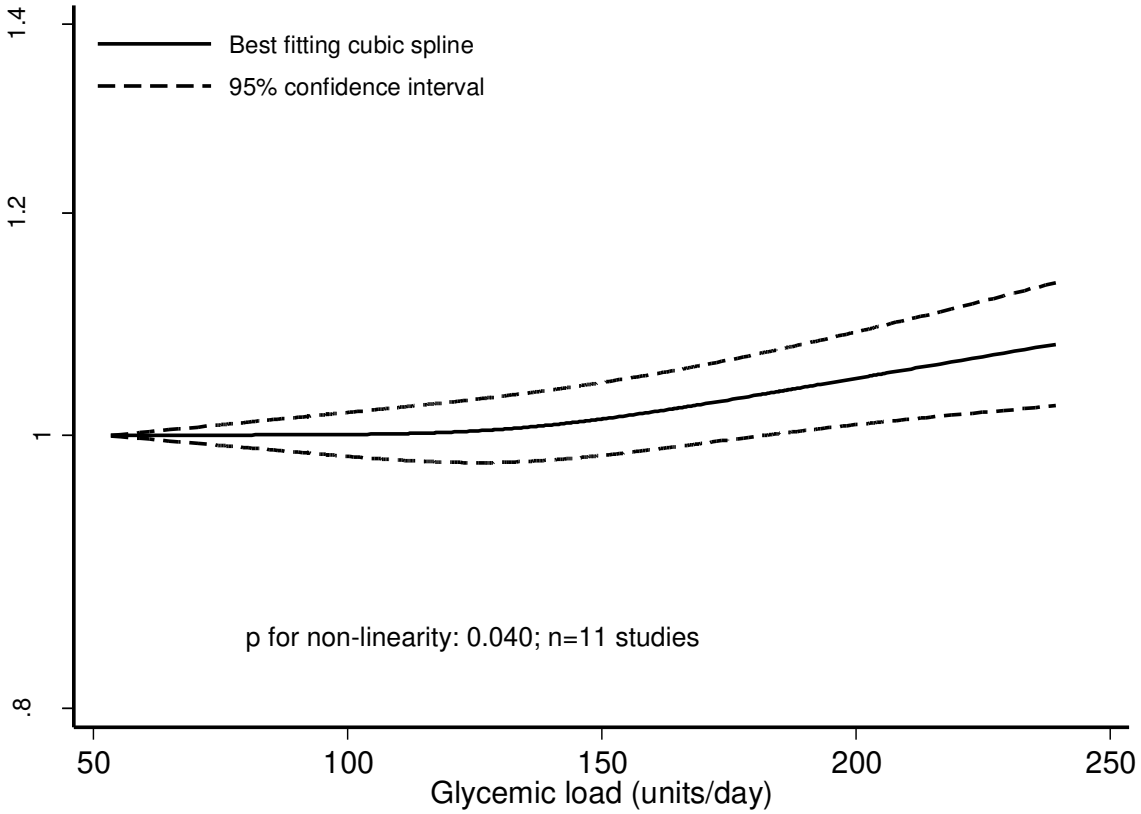


Figure 5

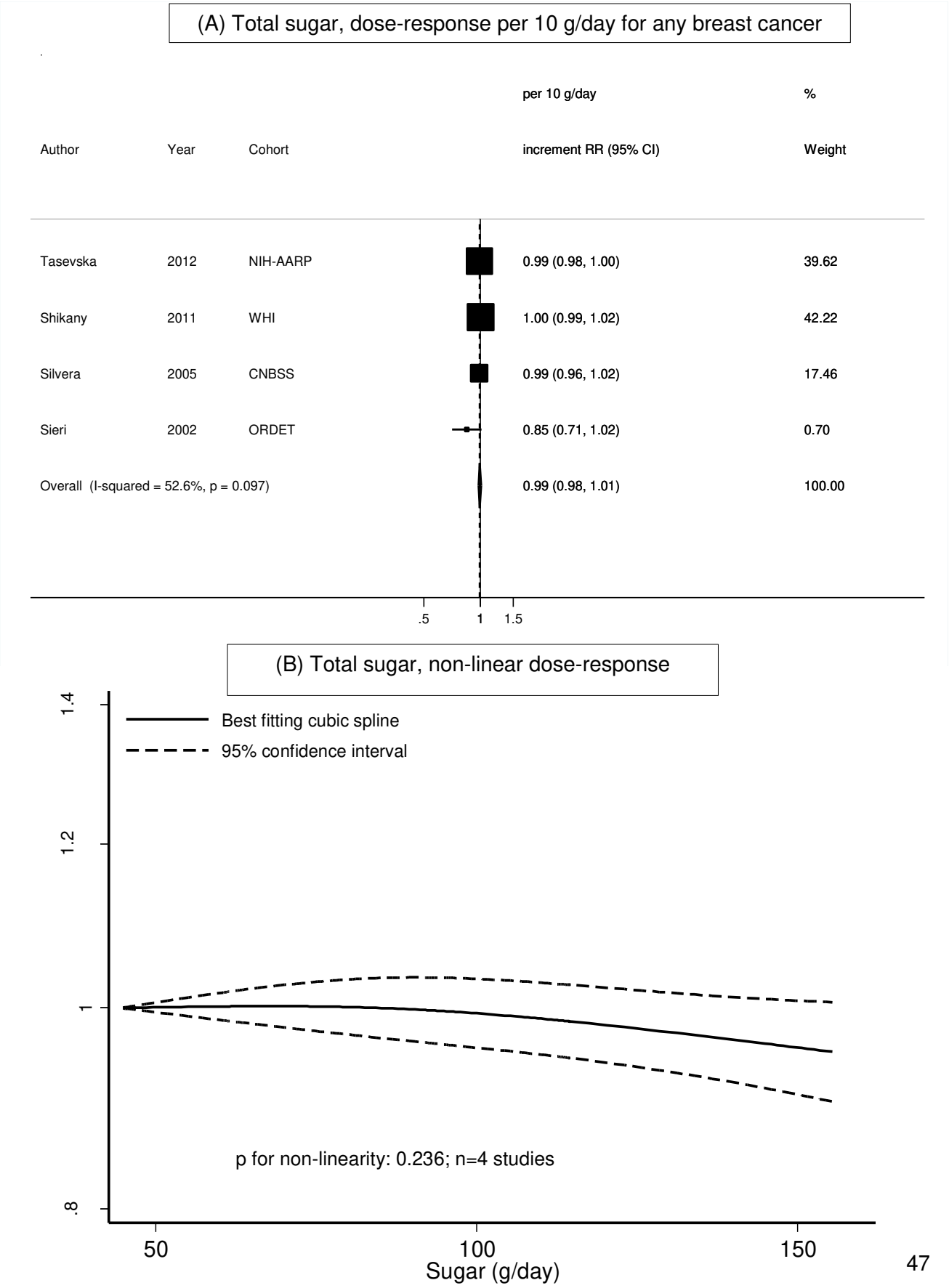
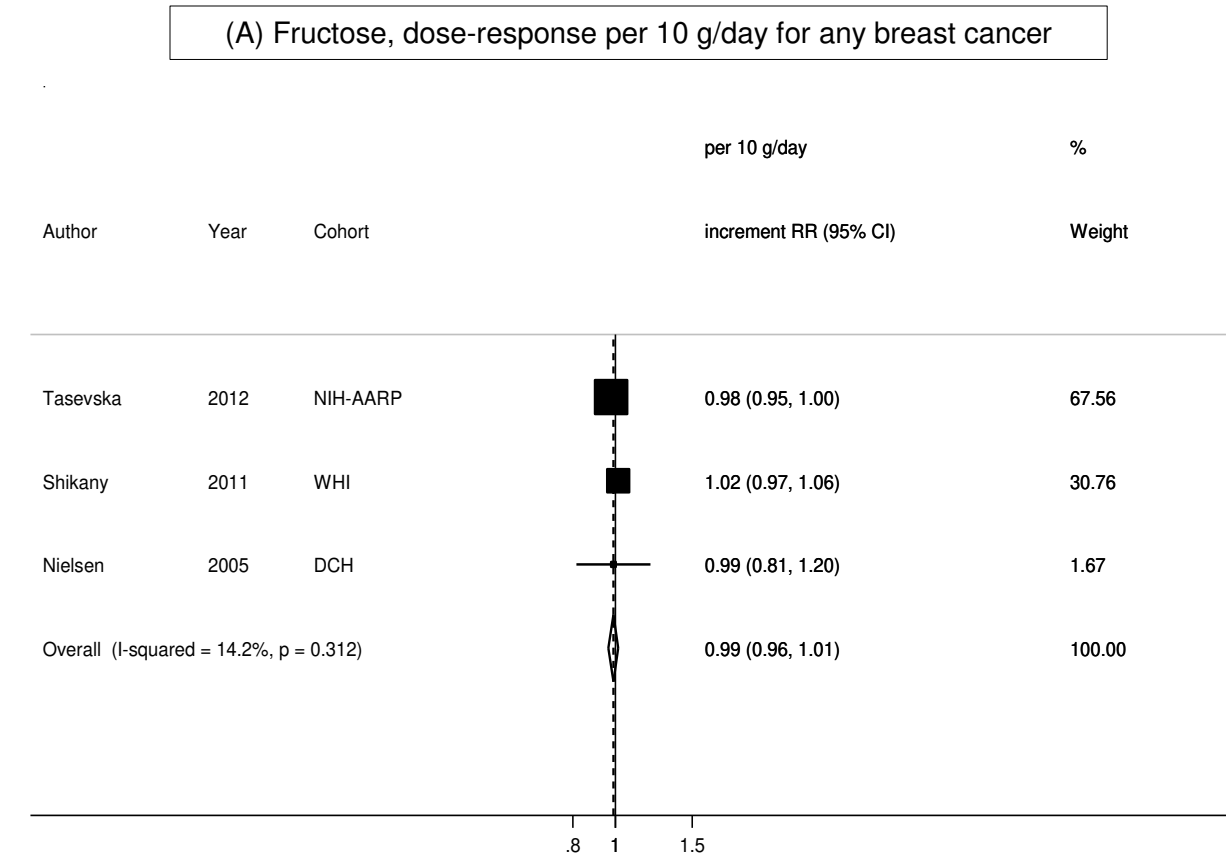
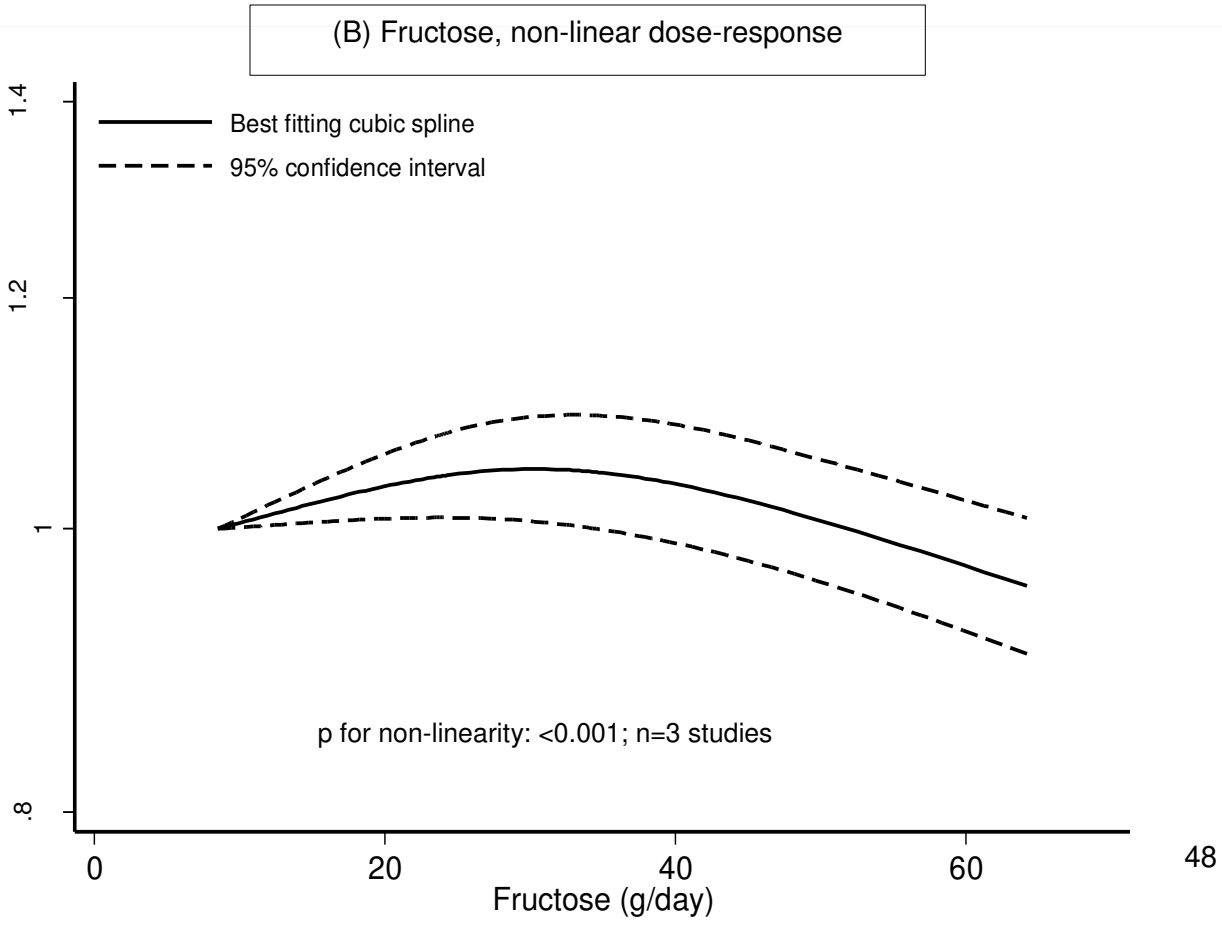

(A) Total sugar, dose-response per 10 g/day for any breast cancer
per 10 g/day
%
Author
Year
Cohort
increment RR (95% CI)
Weight
Tasevska 2012 NIH-AARP 0.99 (0.98, 1.00) 39.62
Shikany 2011 WHI 1.00 (0.99, 1.02) 42.22
Silvera 2005 CNBSS 0.99 (0.96, 1.02) 17.46
Sieri 2002 ORDET 0.85 (0.71, 1.02) 0.70
Overall (I-squared = 52.6%, p = 0.097) 0.99 (0.98, 1.01) 100.00
.5
1
1.5
(B) Total sugar, non-linear dose-response
Best fitting cubic spline
95% confidence interval
1.4
1.2
1
.8
p for non-linearity: 0.236; n=4 studies
50
100
150
Sugar (g/day)

Figure 6


(A) Fructose, dose-response per 10 g/day for any breast cancer
per 10 g/day
%
Author
Year
Cohort
increment RR (95% CI)
Weight
Tasevska 2012 NIH-AARP 0.98 (0.95, 1.00) 67.56
Shikany 2011 WHI 1.02 (0.97, 1.06) 30.76
Nielsen 2005 DCH 0.99 (0.81, 1.20) 1.67
Overall (I-squared = 14.2%, p = 0.312) 0.99 (0.96, 1.01) 100.00
.8
1
1.5


(B) Fructose, non-linear dose-response
Best fitting cubic spline
95% confidence interval
1.4
1.2
1
.8
p for non-linearity: <0.001; n=3 studies
0
20
40
60
Fructose (g/day)