**See corresponding editorial on page 803 and article on page 891.**

# Dietary glycemic index, glycemic load, and risk of mortality from all causes and cardiovascular diseases: a systematic review and dose-response meta-analysis of prospective cohort studies

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**ABSTRACT**

**Background:** Previous findings on the association of dietary glycemic index (GI) and glycemic load (GL) with mortality are conflicting.

**Objectives:** The aim of this study was to summarize earlier findings on the association between dietary GI and GL and the risk of cardiovascular disease (CVD) and all-cause mortality.

**Methods:** A comprehensive literature search was performed of electronic databases, including MEDLINE (PubMed), Scopus, ISI Web of Science, EMBASE, and Google scholar, up to September 2018. Prospective cohort studies that reported GI and GL as the exposure and all-cause or CVD mortality as the outcome were included in the analysis. The random-effects model was used to estimate pooled RR and 95% CIs of all-cause and CVD mortality.

**Results:** Eighteen cohort studies with a total of 251,497 participants, reporting 14,774 cases of all-cause mortality and 3658 cases of CVD mortality, were included in the present analysis. No significant association was found between dietary GI and all-cause mortality (RR: 1.07; 95% CI: 0.96, 1.19) and CVD mortality (RR: 1.02; 95% CI: 0.87, 1.20). In addition, dietary GL was not associated with all-cause mortality (RR: 1.08; 95% CI: 0.93, 1.27) or CVD mortality (RR: 1.07; 95% CI: 0.92, 1.25). However, the highest dietary GI, in comparison to the lowest one, significantly increased the risk of all-cause mortality in women (RR: 1.17; 95% CI: 1.02, 1.35). No evidence for a nonlinear association between dietary GI or GL and all-cause and CVD mortality was found ($P > 0.05$).

**Conclusions:** This meta-analysis of prospective cohort studies showed no significant association between either dietary GI or GL and all-cause and CVD mortality in men, but a positive association of GI with all-cause mortality in women. *Am J Clin Nutr* 2019;110:921–937.

**Keywords:** glycemic index, glycemic load, all-causes mortality, CVD mortality, meta-analysis

## Introduction

Noncommunicable diseases (NCDs) are the leading cause of death worldwide and NCD deaths are projected to rise from 38 million in 2012 to 52 million by 2030 (1). Among chronic NCDs, cardiovascular disease (CVD) plays an important role in mortality and is responsible for 46.2% of NCD deaths (1, 2). In particular, a large portion of premature deaths (death at age <75 y) are from CVD (1–3). Therefore, developing effective preventive strategies to reduce mortality, especially from CVD, is needed.

Several modifiable factors, such as smoking, physical inactivity, BMI, and dietary patterns are related to mortality from CVD and other causes (4–8). Some previous studies have shown hyperglycemia or poor glycemic control to be a useful predictor

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Supplemental Table 1 and Supplemental Figures 1–12 are available from the "Supplementary data" link in the online posting of the article and from the same link in the online table of contents at https://academic.oup.com/ajcn/.

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Abbreviations used: CHD, coronary heart disease; CVD, cardiovascular disease; FFQ, food-frequency questionnaire; GI, glycemic index; GL, glycemic load; NCD, noncommunicable disease.

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of CVD morbidity and mortality (9, 10). The quality and quantity of dietary carbohydrate are 2 important factors that influence various NCDs such as CVD, metabolic syndrome, diabetes, and cancer (11, 12). The ability of dietary carbohydrates to enhance postprandial plasma glucose is different and depends on their structure and added viscous fiber (13, 14). The glycemic index (GI) ranks the nature of carbohydrates in foods and is defined as the incremental area under the plasma glucose curve after consumption of 50 g test carbohydrate, compared with a reference food (14). Glycemic load (GL) is a qualitative and quantitative index computed by multiplying GI by the carbohydrate content of the food (g/100 g or 1000 kJ edible food) (15).

A meta-analysis of prospective cohort studies revealed that high GI and GL diets were significantly associated with the increased risk of coronary heart disease (CHD) events, fatal and nonfatal, in women, but not in men (16). There is a growing body of epidemiologic studies on dietary GI and GL and mortality from CVD (17–20); however, findings are inconsistent in various populations and there is no comprehensive assessment. Findings on the role of dietary GI and GL in all-cause mortality are conflicting (17, 18, 21, 22). A number of studies have indicated an association between dietary GI or GL, and mortality from all causes, CVD, or CHD (21–23), but other studies found no evidence to support this hypothesis (18, 24, 25). In addition, whether there is a gender disparity on the association of dietary GI and GL with the risk of mortality is not clear. For instance, in a cohort study, the highest level of dietary GI in comparison to the lowest one was associated with a 20% reduced risk of all-cause mortality in men, but not in women (17). Due to these inconsistent findings, we aimed to conduct a systematic review and meta-analysis on the association of dietary GI and GL and risk of CVD and all-cause mortality. We hypothesized that dietary GI and GL might play a role in the incidence of all-cause and CVD mortality in healthy and unhealthy adults.

## Methods

### Search strategy

A comprehensive literature search was conducted of the electronic MEDLINE (PubMed), Scopus, ISI Web of Science, EMBASE, and Google scholar databases, up to September 2018, with no limitation in language or time of publication. The search terms we used were ("Glycemic Index"[Mesh] OR "Glycemic load"[TIAB] OR "Glycaemic index"[TIAB] OR "Glycaemic load"[TIAB] OR "carbohydrate quality"[TIAB]) AND (Mortality [TW] OR Death [TW] OR fatal [TW] OR Survival [TW]) AND ("observational study"[TIAB] OR "prospective study"[TIAB] OR "longitudinal study"[TIAB] OR "cohort study"[TIAB] OR "incidence study"[TIAB] OR "concurrent study"[TIAB]). The search was limited to humans. Duplicate citations were removed. We conformed to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines (26) in reporting this systematic review and meta-analysis. This study was registered at PROSPERO as CRD42018106266. The article selection was carried out independently by 2 investigators (FS and PS) and any disagreement was resolved by consultation with the principal investigator (AE). The full text of articles eligible for inclusion was obtained to extract the required data.

### Inclusion criteria

Published studies that met the following criteria were included: *1*) prospective cohort studies; *2*) conducted in adults; *3*) considered GI or GL as the exposure and all-cause or CVD mortality as the outcomes; and *4*) reported RR or HR with corresponding 95% CIs for the association of GI or GL with mortality from all causes or CVD.

### Excluded studies

The eligible articles included 2 reports from the European Prospective Investigation into Cancer and Nutrition cohort. Because 1 report was for an Italian population and the other was from a Greek community (25, 27), there was no overlap between these 2 study populations. The studies by Nagata et al. (17) and Oba et al. (24) used the same study population; Nagata et al. had reported CVD mortality, whereas the components of CVD mortality were separately reported by Oba et al.; therefore, the extracted RRs were included in 2 separate meta-analyses for mortality from CVD and stroke. Three reports from the Blue Mountains Eye Study were included in the current meta-analysis (20, 23, 28), because different causes of mortality were reported in these investigations. The study of Gopinath et al. (28) reported the risk for all-cause mortality, whereas the study of Buyken et al. (20) considered mortality from CVD, and the one by Kaushik et al. (23) investigated mortality from components of CVD, including stroke and CHD, separately. Levitan et al. published 2 studies, in 2007 and 2009, from the Cohort of Swedish Men (29, 30); one of these investigations was conducted on a healthy population and the other was done on individuals who were hospitalized for CVD; as there was no overlap between populations of these studies, both were included in our analysis. The cohort in the study by Li et al. (31) that followed cases of cancer for mortality was included in the analysis.

### Data extraction

We extracted the following data from each eligible article: first author's name, cohort name, health status of population, country, age range or mean age, sex, sample size, person years, length of follow-up, method of outcome assessment, level of dietary exposure used for comparison, number of deaths, RRs or HRs and their 95% CIs, median value of GI and GL in all categories, adjustments for covariates, characteristics of dietary intake assessment tools including type of dietary assessment tool, number of items in the questionnaires, correlation coefficients for carbohydrates in the validation studies, administration of dietary assessment tool and its interval, and source of GI values. Data extraction was conducted independently by 2 researchers (FS and PS) and any disagreements were resolved by consultation with the principal investigator (AE).

### Assessment of the quality of studies

The quality of included studies was evaluated according to the Newcastle-Ottawa Scale for cohort studies (32). The Newcastle-Ottawa Scale assigns a maximum of 9 points to each study: 4 for selection, 2 for comparability, and 3 for assessment of outcomes. In the current analysis, when a study got more than median points, it was considered as relatively high quality; otherwise it was deemed to be of low quality. Any discrepancies were resolved by discussion. Results from a quality assessment of studies included in the meta-analysis are presented in **Supplemental Table 1**.

### Statistical analysis

Reported RRs and HRs (and their 95% CIs) were used to calculate log RR and its standard error. Using a random-effects model that takes between-study variation into account, the overall effect size was calculated. Between-study heterogeneity was assessed through the use of Cochran's $Q$ test and $I^2$. In cases of significant between-study heterogeneity, we used subgroup analysis to explore possible sources of heterogeneity. Between-subgroup heterogeneity was examined through a fixed-effects model. Sensitivity analysis was done to examine the extent to which inferences might depend on a particular study. Publication bias was assessed by visual inspection of funnel plots. Formal statistical assessment of funnel plot asymmetry was done by Begg's test and Egger's regression asymmetry test. A dose-response meta-analysis was performed to examine the trend of RR/HR estimates across dietary GI and GL categories through the use of the method proposed by Greenland and Longnecker (33) and Orsini et al. (34). The open-ended categories were assumed as the same width as the neighboring categories. In cases of studies that used white bread to report values of GI and GL, the white bread scale was converted to a glucose scale, based on a conversion rate of 0.71. The potential nonlinear association between GI or GL and risk of mortality from all-causes and CVD was evaluated by a 2-stage random-effects dose-response meta-analysis that used a restricted cubic spline with 3 knots at fixed percentiles, 10%, 50%, and 90% throughout the whole distribution (35, 36). First, the restricted cubic spline model was estimated by generalized least-square regression (34), then a multivariate random-effects dose-response model was considered for combining the specific estimates of included studies (37). Statistical analyses were conducted with STATA version 14 (STATA Corp.). $P$ values $<0.05$ were considered statistically significant.

## Results

### Results of the literature search

The primary search of 4 databases yielded 1629 articles. The study selection process is illustrated in **Figure 1**. The titles and abstracts of articles were screened and the full text of 43 papers was carefully assessed based on inclusion and exclusion criteria. Seventeen articles met the inclusion criteria and were included. In addition, 1 study was found based on a manual check of the reference lists of included studies and was eligible for inclusion. Hence, 18 articles were finally considered eligible for inclusion in the present analysis.

### Study characteristics

Detailed characteristics of the eligible studies are summarized in **Table 1**. Among 18 included studies published between 2007 and 2018, 4 were carried out in United States (22, 31, 38, 39), 7 in European countries (18, 19, 21, 25, 27, 29, 30), 4 in Australia (20, 23, 28, 40), 2 in Japan (17, 24), and the last 1 in China (41). The age range of 251,497 participants was between 18 and 86 y. A total of 1,636,044 person-years were reported by 6 studies; the other 12 studies did not report person-years. Thirteen studies included both males and females; 3 investigations were conducted on female populations (39–41) and 2 on male populations (29, 30). The median GI and GL varied from 45 to 82.9 and from 86 to 285, respectively. Two studies reported means ± SDs for GI and GL and 1 study did not determine the values of GI and GL in quartiles. The follow-up duration was $<$10 y in 10 investigations and $\geq$10 y in 8 other studies. All included studies applied record linkage for assessment of mortality as the outcome. Among eligible studies, 11 were performed in healthy populations; the other 7 investigations were conducted in patients with ovarian cancer, esophageal adenocarcinoma and gastric cardia adenocarcinoma, breast cancer, colon cancer, head and neck carcinoma, diabetes mellitus, and hospitalized for CVD. Dietary intakes were evaluated in most studies with the use of validated food-frequency questionnaires (FFQs), although 1 study used a 7-d diet record or diet history interviews (19). The detailed characteristics of the dietary assessment tools are illustrated in **Table 2**. Most studies made adjustment for energy intake, except 1 study (39). Other adjustments in studies included age ($n$ = 10), BMI ($n$ = 13), physical activity ($n$ = 12), smoking status ($n$ = 14), education ($n$ = 10), history of diabetes ($n$ = 3), history of hypertension ($n$ = 6), intake of alcohol ($n$ = 8), saturated fat ($n$ = 8), polyunsaturated fat ($n$ = 4), monounsaturated fat ($n$ = 2), and fiber ($n$ = 6).

Out of 18 studies, 12 and 9 examined the relation of GI with all-cause and CVD (stroke, CHD, or total CVD) mortality, respectively. These studies reported a total of 14,774 cases of all-cause mortality, 3496 cases of CVD mortality, and 951 cases of stroke mortality. Multivariable adjusted HRs for highest compared with lowest level of dietary GI were between 0.78 and 2.25 for all-cause mortality, 0.79 and 1.56 for CVD mortality, and 0.78 and 2.09 for stroke mortality. In addition, the number of studies that provided data on association of GL with all-cause and CVD mortality were 12 and 8 studies, respectively, with total deaths of 14,774, 3236, and 856 for all causes, CVD, and stroke, respectively. The upper and lower limit of adjusted HRs for highest compared with lowest level of dietary GL were 0.71 and 2.10 for all-cause mortality, 0.86 and 1.20 for CVD mortality, and 1 and 1.33 for stroke mortality. With regard to the quality of the studies, 3 had a score of 8 (17, 19, 41) and the other 15 had a score of $\leq$7.

### Glycemic index and all-cause mortality

Twelve RRs from 11 studies provided data on GI and all-cause mortality and were included in this analysis. The pooled RR for highest compared with lowest level of GI was 1.07; however, this effect size was not statistically significant (95% CI: 0.96, 1.19) (**Figure 2**). The between-studies heterogeneity was significant

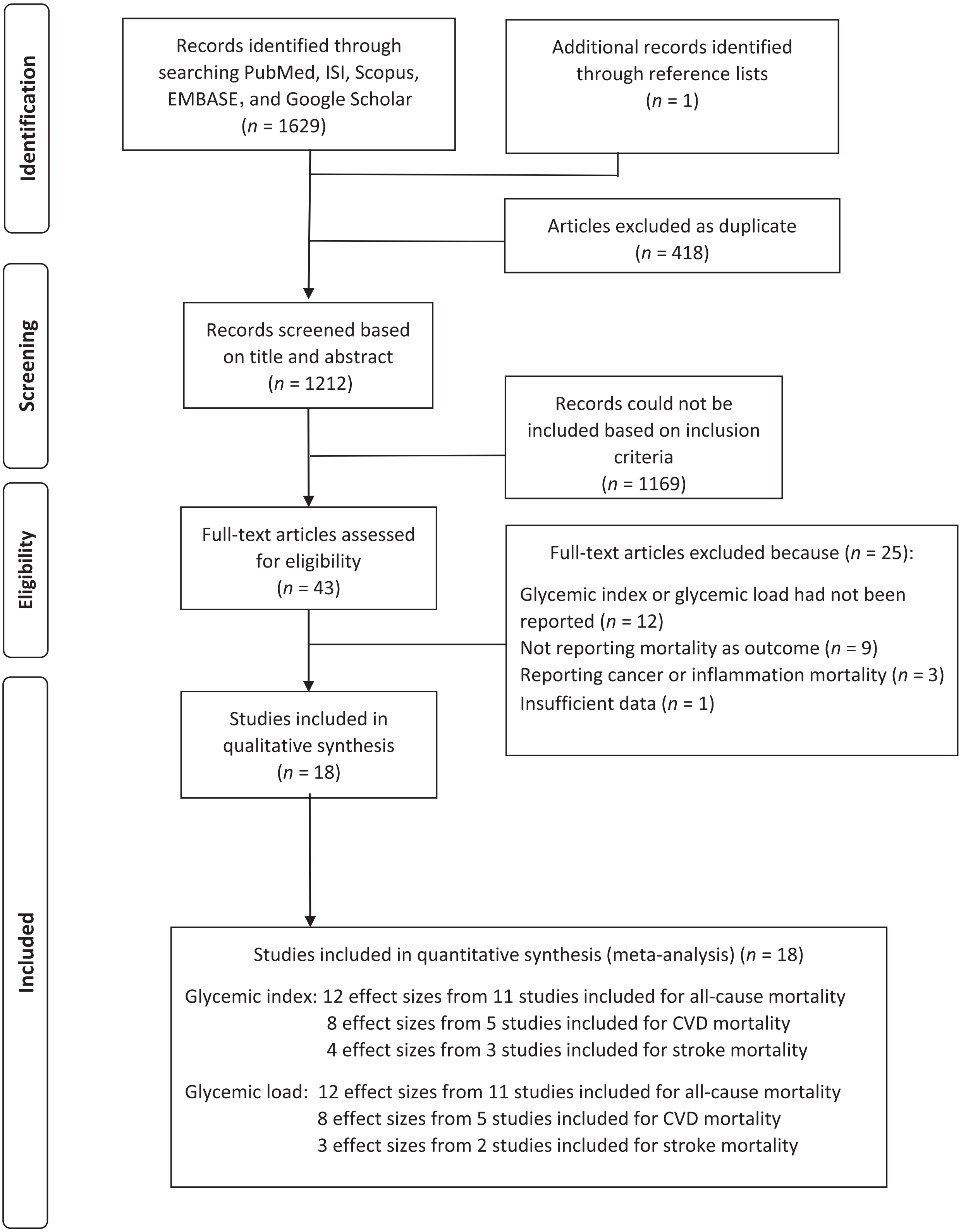

**FIGURE 1** The flow diagram of study selection.

($I^2 = 59.9\%$, $P = 0.004$). To find the source of heterogeneity, we conducted subgroup analysis based on gender (Figure 2), geographic region, quality score, follow-up duration, alcohol consumption, correlations for carbohydrate intake in validation studies, and health status of study participants. The results are illustrated in **Table 3**. The highest GI, in comparison to the lowest level, elevated the risk of all-cause mortality in females by 17% (RR: 1.17; 95% CI: 1.02, 1.35); no significant differences were shown in other subgroups. Between-study heterogeneity was not completely removed by these subgroup analyses. The pooled estimate from the linear dose-response meta-analysis was 1.00 (95% CI: 0.99, 1.01) per 1 unit increase in the dietary GI (**Supplemental Figure 1**). Five studies, with 24 effect sizes, were included in the nonlinear dose-response analysis on GI and all-cause mortality (17, 21, 22, 31, 40). Six studies that had not reported GI values or number of cases in each category of GI were not included in this analysis (27–30, 38, 39). We found no evidence of a nonlinear association between dietary GI and all-cause mortality ($P$-nonlinearity = 0.74) (**Supplemental Figure 2**). Findings from the sensitivity analysis revealed that none of the studies significantly influenced the overall effect. In addition, exclusion of studies conducted on patients (22, 29, 31, 38–40) did not significantly alter the findings (RR = 1.09; 95% CI: 0.93, 1.28) (**Supplemental Figure 3**). There was no evidence of publication bias for GI and all-cause mortality (Begg's test = 0.07 and Egger's test = 0.18) (**Supplemental Figure 4**).

### GI and CVD mortality

The association between GI and CVD mortality was examined in 5 investigations and 8 effect sizes were included in the analysis. Overall, no significant association was found between GI and CVD mortality (RR = 1.02; 95% CI: 0.87, 1.20) (**Figure 3**). No evidence of heterogeneity was found ($I^2 = 45.2\%$, $P = 0.078$). Subgroup analysis was carried out based on gender (Figure 3), diet assessment tools, quality score, follow-up duration, alcohol consumption, correlations for carbohydrate in validation studies, and health status of participants, and no significant association was observed in subgroups (Table 3). We did not find a linear dose-response association between GI and CVD mortality (pooled RR: 1.00; 95% CI: 0.98, 1.02) (**Supplemental Figure 5**). Ten effect sizes from 2 studies were used for nonlinear dose-response analysis (17, 20); studies that did not report data for number of cases with CVD mortality in each category of dietary GI were not considered in this analysis (19, 29, 30). Nonlinear dose-response analysis revealed that there was no significant association between dietary GI and CVD mortality ($P$-nonlinearity = 0.72) (**Supplemental Figure 6**). Sensitivity analysis was carried out and no significant change was observed after removing each study. No significant publication bias was found (Begg's test = 0.46 and Egger's test = 0.94) (Supplemental Figure 4).

### GL and all-cause mortality

Overall, 11 studies evaluated the association of GL with all-cause mortality, and the pooled RR obtained from 12 effect sizes did not show a significant association (RR = 1.08; 95% CI: 0.93, 1.27) (**Figure 4**). Because of the significant heterogeneity between studies ($I^2 = 72.3\%$, $P < 0.001$), subgroup analysis was conducted based on gender (Figure 4), geographic region, quality score, follow-up duration, alcohol consumption, correlations for carbohydrates in validation study, and health status of subjects. Subgroup analysis based on alcohol consumption revealed that subjects with the highest dietary GL, who did not consume alcohol, had a greater risk for all-cause mortality than those with the lowest GL (RR: 1.28; 95% CI: 1.01, 1.62) (Table 3). Removing studies that were conducted on patients (22, 29, 31, 38–40) did not significantly influence our findings (RR = 0.97; 95% CI: 0.80, 1.17) (**Supplemental Figure 7**). The dose-response analysis indicated no significant association between dietary GL and all-cause mortality (pooled RR: 1.00; 95% CI: 0.99, 1.00) (**Supplemental Figure 8**). The nonlinear analysis for dietary GL and all-cause mortality was done based on 5 studies that provided 24 effect sizes (17, 21, 22, 31, 40). Because of insufficient data for dietary GL or number of cases in each category of GL, 5 studies were not included in this analysis (27–30, 38, 39). In this nonlinear dose-response analysis, an increment in dietary GL was not associated with risk of all-cause mortality ($P$-nonlinearity = 0.97) (**Supplemental Figure 9**). Sensitivity analysis was performed, and overall effect did not change after sequentially excluding 1 study at a time. Findings from Begg's and Egger's tests (Begg's test = 0.01 and Egger's test = 0.01) rejected our null hypothesis about publication bias (Supplemental Figure 4).

### GL and CVD mortality

A total of 8 RRs from 5 studies were included in the analysis for the association between highest and lowest levels of GL and risk of CVD mortality. Overall RR for the association of highest compared with lowest level of GL with CVD mortality was not significant (RR = 1.07; 95% CI: 0.92, 1.25) (**Figure 5**). Although no between-study heterogeneity was observed ($I^2 = 0.0\%$, $P = 0.89$), we conducted subgroup analysis according to gender (Figure 5), diet assessment tools, quality score, follow-up duration, alcohol consumption, correlations for carbohydrates in validation study, and health status of subjects (Table 3). The findings in the subgroup analysis were not different from the main analysis. No statistically significant linear dose-response trend for the association of dietary GL and CVD mortality was found (pooled RR: 1.00; 95% CI: 0.99, 1.00) (**Supplemental Figure 10**). For nonlinear dose-response analysis of dietary GL and mortality from CVD, 10 effect sizes from 2 studies were included (17, 25). Three studies that did not provide sufficient data for dose-response analysis were not included (19, 29, 30). No nonlinear dose-response association was found between GL and CVD mortality ($P$-nonlinearity = 0.64) (**Supplemental Figure 11**). Sensitivity analysis was performed and exclusion of any study at a time did not influence the overall estimate. Publication bias was evaluated by Begg's test and Egger's test and the results were not significant (Begg's test = 0.62 and Egger's test = 0.27) (Supplemental Figure 4). In addition, the pooled RRs for association of GI and GL with stroke mortality are presented in **Supplemental Figure 12**. Overall, dietary GI and GL were not associated with risk of stroke mortality.

**TABLE 1** Main characteristics of prospective studies examining the association of GI with all-cause, CVD, cancer, and inflammation-related mortality[1]

| First author and year (ref.) | Cohort name | Country/region | Health status/representative of general population | Age range/ mean age | Sex | Sample size | Person-year | Duration of follow-up, y | Outcome assessment | Cases | Outcome | OR or RR or HR (95% CI) | Comparison[2] | Score | Adjustments[3] |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Arthur 2018 (38) | University of Michigan Head and Neck Specialized Program of Research Excellence (UM HN-SPORE) | Michigan | Patient (head and neck cancer)/no | 60.9 | M/F | 414 | NR | 5 | Social Security Death Index, yearly survey updates, notification from family or medical record reviews | 70 | All-cause mortality | 0.78 (0.42, 1.47) | GI high vs low (56 vs. 49) | 6 | 1, 2, 6, 15, 35, 60, 63 |
|  |  |  |  |  |  |  |  |  |  |  |  | 2.10 (1.15, 3.83) | GL high vs. low (145 vs. 102) |  |  |
| Sieri 2017 (27) | European Prospective Investigation into Cancer and Nutrition (EPIC)-Italy cohort | Italy | Healthy/yes | 50 | M/F | 45,148 | NR | 14.9 | Obtained from mortality databases. Causes of death were coded according to the ICD, 10th Revision | 2,460 | All-cause mortality | 1.06 (0.93, 1.20) | GI Q5 vs. Q1 (57.4 vs. 50) | 7 | 1, 4, 5, 6, 7, 11, 12, 16, 18, 62 |
|  |  |  |  |  |  |  |  |  |  |  |  | 0.84 (0.70, 1.01) | GL Q5 vs. Q1 (235.2 vs. 86) |  |  |
| Li 2017 (31) | — | USA | Patients (esophageal and gastric cardia adenocarcinoma)/no | 30–79 | M/F | 1029 (cases with esophageal adenocarcinoma and gastric cardia adenocarcinoma) | — | 7.5 and 10.75 | National Death Index | 434 | Overall mortality in esophageal adenocarcinoma | 0.97 (0.72, 1.33) | GI Q5 vs. Q1 (≥63.64 vs. <57.40) | 6 | 1, 2, 7, 61 |
|  |  |  |  |  |  |  |  |  |  |  |  | 1.24 (0.82, 1.87) | GL Q5 vs. Q1 (≥196.57 vs. <96.51) |  |  |
|  |  |  |  |  |  |  |  |  |  | 450 | Overall mortality in gastric cardia adenocarcinoma | 1.01 (0.75, 1.37) | GI Q5 vs. Q1 (≥63.64 vs. <57.40) |  |  |
|  |  |  |  |  |  |  |  |  |  |  |  | 0.73 (0.49, 1.08) | GL Q5 vs. Q1 (≥196.57 vs. <96.51) |  |  |
| Playdon 2017 (40) | Australian ovarian cancer study | Australia | Patients (ovarian cancer)/no | 18–79 | F | 811 | NR | 5.9 ± 3.8 | Medical record review and Australian NDI | 547 | All-cause mortality | 1.28 (1.01, 1.65) | GI Q4 vs. Q1 (55.1 vs. 45) | 6 | 1, 2, 4, 5, 6, 56, 57, 58, 59 |
|  |  |  |  |  |  |  |  |  |  |  |  | 1.12 (0.87, 1.44) | GL Q4 vs. Q1 (142 vs. 93) |  |  |
| Gopinath 2016 (28) | Blue Mountains Eye Study (BMES) | Australia | Healthy/yes | ≥49 | M/F | 1609 | NR | 10 | Australian NDI | 610 | All-cause mortality | 1.65 (1.10, 2.47) | GI Q4 vs. Q1 (NR) | 6 | 1, 2, 6, 8, 18, 53, 54, 55 |
|  |  |  |  |  |  |  |  |  |  |  |  | 1.46 (1.01, 2.10) | GL Q4 vs. Q1 (NR) |  |  |
| Yu 2016 (41) | Shanghai Women's Health Study (SWHS) population-based, prospective cohort study | China | Healthy/yes | 40–70 | F | 64,328 | 956,144 | 12 | ICD-9, code 430–438 | 609 | Stroke mortality | 1.15 (0.85, 1.56) | GI P90 vs. P10 (80 vs 71) | 8 | 1, 4, 6, 7, 10, 12, 50, 51, 52 |
|  |  |  |  |  |  |  |  |  |  |  |  | 1.33 (0.86, 2.08) | GL P90 vs. P10 (239 vs. 174) |  |  |
| Turati 2015 (25) | European Prospective Investigation into Cancer and Nutrition (EPIC) Greek cohort study | Greece | Healthy/yes | 20–86 | M/F | 20,275 | 193,563 | 10.4 | ICD-10 | 162 | CHD mortality | 1.26 (0.77, 2.06) | GL T3 vs. T1 (103 vs. 91) | 7 | 1, 4, 5, 6, 7, 10, 18, 46 |

(*Continued*)

**TABLE 1** (*Continued*)

| First author and year (ref.) | Cohort name | Country/region | Health status/representative of general population | Age range/ mean age | Sex | Sample size | Person-year | Duration of follow-up, y | Outcome assessment | Cases | Outcome | OR or RR or HR (95% CI) | Comparison[2] | Score | Adjustments[3] |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | M | 8246 | | | | 112 | CHD mortality | 1.07 (0.60, 1.91) | GL T3 vs. T1 (147.1 vs. 112.9) | | |
| | | | | | F | 12,029 | | | | 50 | CHD mortality | 1.81 (0.70, 4.63) | GL T3 vs. T1 (118.9 vs. 92.7) | | |
| Nagata 2014 (17) | Takayama study | Japan | Healthy/yes | ≥35 | M | 12,953 | 409,198 | 14.4 | Residential or family registers, ICD-10 | 2,499 | All-cause mortality | 0.80 (0.68, 0.95) | GI Q4 vs. Q1 (69.7 vs. 56.4) | 8 | 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15 |
| | | | | | | | | | | 665 | CVD mortality | 0.93 (0.67, 1.28) | | | |
| | | | | | | | | | | 2,499 | All-cause mortality | 0.71 (0.59, 0.86) | GL Q4 vs. Q1 (275.9 vs. 169.6) | | |
| | | | | | | | | | | 665 | CVD mortality | 0.86 (0.58, 1.27) | | | |
| | | | | | F | 15,403 | | | | 2,117 | All-cause mortality | 1.10 (0.91, 1.31) | GI Q4 vs. Q1 (70.1 vs. 58.3) | | |
| | | | | | | | | | | 764 | CVD mortality | 1.56 (1.15, 2.13) | | | |
| | | | | | | | | | | 2,117 | All-cause mortality | 1.03 (0.82, 1.30) | GL Q4 vs. Q1 (241.1 vs. 154.1) | | |
| | | | | | | | | | | 764 | CVD mortality | 1.10 (0.73, 1.64) | | | |
| Castro-Quezada 2014 (21) | PREDIMED study (Population at high cardiovascular risk) | Spain | Healthy/yes | 55–80 | M/F | 3583 | 15,555 | 4.7 | Family, NDI | 123 | All-cause mortality | 2.25 (1.16, 4.36) | GI Q4 vs. Q1 (63.1 vs. 52.1) | 5 | 1, 4, 5, 11, 12, 16, 17 |
| | | | | | | | | | | 123 | All-cause mortality | 1.76 (0.88, 3.54) | GL Q4 vs. Q1 (144.4 vs. 91.9) | | |
| Meyerhardt 2012 (22) | National Cancer Institute–sponsored Cancer and Leukemia Group B (CALGB) | Boston, MA and Durham, NC | Patient (stage III colon cancer)/no | 21–85 | M/F | 1011 | NR[4] | 7.8 | CALGB statistical center | 305 | All-cause mortality | 1.23 (0.83, 1.82) | GI Q5 vs. Q1 (58.2 vs. 51.1) | 5 | 1, 2, 4, 5, 18, 19, 20, 21, 22, 23, 24 |
| | | | | | | | | | | 305 | All-cause mortality | 1.74 (1.20, 2.51) | GL Q5 vs. Q1 (172 vs. 112.1) | | |
| Burger 2012 (18) | EPIC (European Prospective Investigation into Cancer and Nutrition) | European countries | Patient (individuals with diabetes mellitus)/no | 57.4 ± 6.7 | M/F | 6192 | 56,969 | 9.2 | ICD-10 | 791 | All-cause mortality | 0.99 (0.91, 1.07) | Per 1 SD of GI (3.9) | 6 | 1, 4, 5, 6, 7, 11, 12, 13, 16, 17, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34 |
| | | | | | | | | | | 306 | CVD mortality | 0.96 (0.85, 1.10) | | | |
| | | | | | | | | | | 791 | All-cause mortality | 1.01 (0.89, 1.14) | Per 1 SD of GL (22) | | |
| | | | | | | | | | | 306 | CVD mortality | 0.95 (0.78, 1.15) | | | |
| Belle 2011 (39) | HEAL (Health, Eating, Activity, and Lifestyle) prospective cohort study | New Mexico, Los Angeles county, Western Washington state | Patient (breast cancer)/no | 55.3 ± 10.6 | F | 688 | 4,615 | 6.7 | Medical record, SEER registry data, self-reported | 106 | All-cause mortality | 1.40 (0.78, 2.50) | GI Q4 vs. Q1 (53.8 vs. 48.3)[4] | 5 | 5, 35 |
| | | | | | | | | | | 106 | All-cause mortality | 0.95(0.53, 1.70) | GL Q4 vs. Q1 (92 vs. 69.7) | | 1, 16, 35 |
| Grau 2011 (19) | Former Glostrup population studied | Denmark | Healthy/yes | 30–70 | M | 1819 | NR | 6–25 | National register of cause of death and patients | | CVD mortality | 0.79 (0.56, 1.11) | GI P95 vs. P50; GL P95 vs. P50 | 8 | 1, 2, 4, 5, 6, 7, 11, 12, 49. 48 just for GI |
| | | | | | | 1885 | | | | | CVD mortality | 1.03 (0.63, 1.67) | | | |
| | | | | | F | 1811 | | | | 108 | CVD mortality | 1.06 (0.68, 1.68) | GI P95 vs. P50 | | |
| | | | | | | | | | | 108 | CVD mortality | 1.20 (0.82, 1.77) | GL P95 vs. P50 | | |
| Buyken 2010 (20) | Blue Mountains Eye Study (BMES) | Australia | Healthy/yes | ≥49 | M | 1245 | NR | 13 | NDI, family members | 151 | CVD mortality | 1.18 (0.76, 1.83) | GI T3 vs. T1 (61.6 vs. 53.8) | 7 | 1, 2, 6, 16, 36, 37, 38 |
| | | | | | F | 1490 | | | | 109 | CVD mortality | 0.87 (0.53, 1.43) | GI T3 vs. T1 (59.6 vs. 51.9) | | 1, 2, 6, 9, 11, 16 |

(*Continued*)

**TABLE 1** (*Continued*)

| First author and year (ref.) | Cohort name | Country/region | Health status/representative of general population | Age range/mean age | Sex | Sample size | Person-year | Duration of follow-up, y | Outcome assessment | Cases | Outcome | OR or RR or HR (95% CI) | Comparison[2] | Score | Adjustments[3] |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Oba 2010 (24) | Takayama study | Japan | Healthy/yes | ≥35 | M | 12,561 | NR | 7 | Ministry of Internal Affairs and Communication, national vital statics, ICD | 120 | Stroke mortality | 0.78 (0.41, 1.47) | GI Q4 vs. Q1 (70.3 vs. 58.0)[5] | 6 | For death from stroke: 1, 2, 4, 5, 6, 7, 10, 11, 14, 16, 36; otherwise just for 2 |
| | | | | | | | | | | 48 | Death from hemorrhagic stroke | 0.90 (0.42, 1.94) | | | |
| | | | | | | | | | | 60 | Death from ischemic stroke | 0.91 (0.43, 1.92) | | | |
| | | | | | | | | | | 120 | Death from stroke | 1.00 (0.47, 2.15) | GL Q4 vs. Q1 (237.2 vs. 202.8) | | |
| | | | | | | | | | | 48 | Death from hemorrhagic stroke | 0.86 (0.43, 1.73) | | | |
| | | | | | | | | | | 60 | Death from ischemic stroke | 0.92 (0.47, 1.83) | | | |
| | | | | | F | 15,301 | | | | 127 | Stroke mortality | 2.09 (1.01, 4.31) | GI Q4 vs. Q1 (70.0 vs. 58.3)[3] | | |
| | | | | | | | | | | 46 | Death from hemorrhagic stroke | 2.10 (0.82, 5.39) | | | |
| | | | | | | | | | | 69 | Death from ischemic stroke | 2.45 (1.01, 5.92) | | | |
| | | | | | | | | | | 127 | Death from stroke | 1.17 (0.51, 2.68) | GL Q4 vs. Q1 (201.9 vs. 183.4) | | |
| | | | | | | | | | | 46 | Death from hemorrhagic stroke | 2.30 (0.90, 5.88) | | | |
| | | | | | | | | | | 69 | Death from ischemic stroke | 1.59 (0.70, 3.65) | | | |
| Kaushik 2009 (23) | Blue Mountains Eye Study (BMES) | Australia | Healthy/yes | ≥49 | M/F | 2897 | NR | 13 | Australian NDI | 95 | Stroke mortality | 1.91 (1.01, 3.47) | GI T3 vs. T1 (60.6 vs. 52.4) | 6 | 1, 2, 4, 6, 7, 9, 18, 39, 40, 41, 42 |
| | | | | | | | | | | NR | CHD mortality | 0.91 (0.70, 1.78) | | | |
| Levitan 2009 (29) | Cohort of Swedish men | Sweden | Patient (hospitalized for CVD)/no | 45–79 | M | 4617 | NR | 6 | Swedish cause of death and health registers | 608 | CVD mortality | 0.86 (0.67, 1.10) | GI Q4 vs. Q1 (82.9 vs. 72.8) | 7 | 1, 4, 5, 6, 9, 10, 11, 12, 13, 23, 43, 44, 45 |
| | | | | | | | | 8 | | 1303 | All-cause mortality | 1.00(0.85, 1.19) | | | |
| | | | | | | | | 6 | | 608 | CVD mortality | 1.02 (0.70, 1.49) | GL Q4 vs. Q1 (285 vs. 184) | | |
| | | | | | | | | 8 | | 1303 | All-cause mortality | 1.15 (0.89, 1.49) | | | |
| Levitan 2007 (30) | Cohort of Swedish men | Sweden | Healthy/yes | 45–79 | M | 36,246 | NR | 6 | Swedish death registers | 785 | CVD mortality | 1.09 (0.88, 1.36) | GI Q4 vs. Q1 (82.9 vs. 73) | 7 | 1, 4, 5, 6, 7, 8, 10, 11, 12, 13, 23, 43, 44, 47 |
| | | | | | | | | 8 | | 2959 | All-cause mortality | 1.06 (0.95, 1.19) | | | |
| | | | | | | | | 6 | | 785 | CVD mortality | 1.13 (0.81, 1.56) | GL Q4 vs. Q1 (250 vs. 180) | | |
| | | | | | | | | 8 | | 2959 | All-cause mortality | 0.94 (0.79, 1.11) | | | |

[1] CHD, coronary heart disease; CVD, cardiovascular disease; F, female; GI, glycemic index; GL glycemic load; ICD; International Classification of Diseases; M, male; NDI, National Death Index; NR, not reported; Q, quartile; ref, reference; T, tertile.

[2] All values are medians, unless stated otherwise.

[3] Adjusted for: 1, intake of energy; 2, age; 3, height; 4, BMI; 5, physical activity; 6, smoking status; 7, education; 8, marital status; 9, history of diabetes; 10, history of hypertension; 11, intake of alcohol; 12, saturated fat; 13, polyunsaturated fat; 14, salt; 15, vegetables and fruits; 16, fiber intake; 17, monounsaturated fat; 18, sex; 19, depth of invasion through bowel wall; 20, number of positive lymph nodes; 21, baseline performance status; 22, treatment group; 23, cereal fiber; 24, time-varying dietary pattern; 25, smoking duration; 26, weighed food record; 27, menopausal status; 28, hormone replacement therapy use; 29, diabetes duration; 30, insulin use; 31, glycated hemoglobin; 32, energy-adjusted nutrients; 33, vitamin C; 34, energy-adjusted carbohydrate intake; 35, tumor stage, treatment, and tamoxifen use; 36, total fat intake; 37, whether underweight; 38, use of corticosteroid drugs at baseline; 39, systolic blood pressure and diastolic blood pressure; 40, antihypertensive medication use; 41, fair or poor self-rated health; 42, history of myocardial infarction and stroke; 43, family history of myocardial infarction before the age of 60 y; 44, aspirin use; 45, protein; 46, Mediterranean Diet score; 47, carbohydrate; 48, energy-adjusted carbohydrate, fat, protein, and fiber intake; 49, cohort; 50, family history of stroke; 51, history of dyslipidemia; 52, partial diet quality score; 53, living status; 54, weight status; 55, energy-adjusted total fiber intake; 56, International Federation of Gynecology and Obstetrics stage; 57, amount of residual disease; 58, grade; 59, tumor subtype; 60, tumor location; 61, study indicator; 62, nonalcohol energy intake; 63, human papilloma virus status.

[4] IQR.

[5] Mean.

**TABLE 2** Characteristics of dietary intakes assessment tools as an exposure[1]

| First author and year (ref.) | Dietary assessment method | FFQ items | Validated FFQ in study population | Correlation coefficient for carbohydrate | Validity reference | Number of times assessed | Assessment interval, y | Reference food for GI |
|---|---|---|---|---|---|---|---|---|
| Arthur 2018 (38) | FFQ | 131 | Validated | 0.65[2,3] | Dietary record | Twice | 1 | NR |
| Sieri 2017 (27) | FFQ | 47 dishes or food items | Validated | Male 0.52[2,3]<br>Female 0.54[2,3] | 24-h recall | At baseline | — | Glucose |
| Li 2017 (31) | FFQ | 104,124 | NR | NR | NR | At baseline | — | NR |
| Playdon 2017 (40) | FFQ | 135 | Validated | Overall = 0.37[2,4]<br>Male = 0.52[2,4]<br>Female = 0.27[2,4] | WFR | At baseline | — | NR |
| Gopinath 2016 (28) | FFQ | 145 | Validated | 0.62[2,3] | WFR | At baseline | — | Glucose |
| Yu 2016 (41) | FFQ | 77 | Validated | 0.66[5] | 24-h recall | Twice | 2–3 | Glucose |
| Turati 2015 (25) | FFQ | 150 | Validated | Male<br>Mono- and disaccharides = 0.35[3]<br>Polysaccharides = 0.36[3]<br>Female<br>Mono and disaccharides = 0.35[3]<br>Polysaccharides = 0.32[3] | 24-h recall | At baseline | — | Glucose |
| Nagata 2014 (17) | FFQ | 169 | Validated | Male 0.39[2,3]<br>Female 0.50[2,3] | Dietary record | At baseline | — | Glucose |
| Castro -Quezada 2014 (21) | FFQ | 137 | Validated | 0.56[2,3] | Dietary record | Each year during follow-up | 1 | Glucose |
| Meyerhardt 2012 (22) | FFQ | 131 | NR | 0.44[2,5] | Dietary record | Twice | NA | White bread |
| Burger 2012 (18) | Country-specific questionnaires: quantitative dietary questionnaire with individual portion size or semiquantitative FFQ | — | Validated | Male 0.40–0.84<br>Female 0.46–0.78<br>GI = 0.62[2]<br>GL = 0.6[2] | 24-h recall | At baseline | – | Glucose |
| Belle 2011 (39) | Women's Health InitiativeFFQ | 122 items; 19 adjusted questions; 4 summary questions | NR | 0.67[2,3] | Dietary record/recall | At baseline | — | NR |
| Grau 2011 (19) | 7-d diet record or diet history interviews | — | — | — | — | At baseline | — | White bread |
| Buyken 2010 (20) | FFQ | 145 | Validated | 0.62[2,3] | WFR | At baseline | — | glucose |
| Oba 2010 (24) | FFQ | 169 | Validated | Male 0.39[2,3]<br>Female 0.50[2,3] | Dietary record | At baseline | — | Glucose |
| Kaushik 2009 (23) | FFQ | 145 | Validated | 0.57[2,3] | WFR | At baseline | — | Glucose |
| Levitan 2009 (29) | FFQ | 96 | Validated | 0.76[2,3] | Dietary record | At baseline | — | White bread |
| Levitan 2007 (30) | FFQ | 96 | Validated | 0.76[2,3] | Dietary record | At baseline | — | White bread |

[1] FFQ, food-frequency questionnaire; GI, glycemic index; NR, not reported; ref, reference; WFR, weighed food record.
[2] Energy adjusted.
[3] Deattenuated.
[4] Spearman correlation coefficient.
[5] Pearson correlation coefficient.

**TABLE 3** Results of subgroup analysis for GI and GL and risk of all-cause and CVD mortality[1]

| | No. of effect sizes | RR (95% CI) | *P* within[2] | $I^2$ (%) | *P* between[3] |
|---|---|---|---|---|---|
| Subgroup analyses for GI and all-cause mortality | | | | | |
| Gender | | | | | 0.069 |
| Male | 3 | 0.95 (0.81, 1.13) | 0.023 | 73.6 | |
| Female | 3 | 1.17 (1.02, 1.35) | 0.517 | 0.0 | |
| Both | 6 | 1.15 (0.93, 1.43) | 0.021 | 62.2 | |
| US vs. non-US | | | | | 0.504 |
| US | 4 | 1.01 (0.81, 1.26) | 0.279 | 21.9 | |
| Non-US | 8 | 1.09 (0.96, 1.23) | 0.002 | 69.8 | |
| Quality score[4] | | | | | 0.037 |
| Scores ≤ median (7) | 10 | 1.11 (0.99, 1.23) | 0.053 | 46.2 | |
| Scores > median (7) | 2 | 0.94 (0.69, 1.28) | 0.012 | 84.3 | |
| Duration of follow-up, y | | | | | 0.415 |
| <10 | 8 | 1.09 (0.96, 1.23) | 0.092 | 42.9 | |
| ≥10 | 4 | 1.06 (0.86, 1.30) | 0.002 | 79.3 | |
| Alcohol consumption | | | | | 0.200 |
| Yes | 6 | 1.03 (0.91, 1.16) | 0.010 | 66.9 | |
| No | 6 | 1.17 (0.94, 1.45) | 0.058 | 53.3 | |
| Correlation between FFQ and carbohydrate | | | | | 0.281 |
| <0.55 | 5 | 1.05 (0.90, 1.24) | 0.010 | 69.8 | |
| ≥0.55 | 6 | 1.17 (0.96, 1.41) | 0.040 | 57.1 | |
| Not reported | 1 | 0.90 (0.73, 1.12) | — | — | |
| Health condition | | | | | 0.951 |
| Healthy | 6 | 1.09 (0.93, 1.28) | 0.001 | 75.3 | |
| Patients | 6 | 1.06 (0.92, 1.22) | 0.206 | 30.6 | |
| Subgroup analyses for GI and CVD mortality | | | | | |
| Gender | | | | | 0.045 |
| Male | 5 | 0.96 (0.84, 1.09) | 0.380 | 4.7 | |
| Female | 3 | 1.18 (0.82, 1.69) | 0.103 | 56.0 | |
| Quality score[4] | | | | | 0.517 |
| Scores ≤ median (7) | 4 | 0.99 (0.86, 1.15) | 0.413 | 0.0 | |
| Scores > median (7) | 4 | 1.05 (0.77, 1.44) | 0.023 | 68.4 | |
| Diet assessment | | | | | 0.229 |
| FFQ | 6 | 1.06 (0.88, 1.28) | 0.067 | 51.4 | |
| Questionnaire or recall | 2 | 0.88 (0.67, 1.16) | 0.310 | 3.2 | |
| Duration of follow-up, y | | | | | 0.502 |
| <10 | 2 | 0.98 (0.77, 1.23) | 0.159 | 49.6 | |
| ≥10 | 6 | 1.05 (0.84, 1.31) | 0.066 | 51.7 | |
| Alcohol consumption | | | | | 0.514 |
| Yes | 7 | 1.01 (0.85, 1.20) | 0.055 | 51.4 | |
| No | 1 | 1.18 (0.76, 1.83) | — | — | |
| Correlation between FFQ and carbohydrate | | | | | 0.155 |
| <0.55 | 2 | 1.21 (0.73, 2.00) | 0.023 | 80.6 | |
| ≥0.55 | 4 | 0.99 (0.86, 1.15) | 0.413 | 0.0 | |
| Not reported | 2 | 0.88 (0.67, 1.16) | 0.310 | 3.2 | |
| Health condition | | | | | 0.122 |
| Healthy | 7 | 1.06 (0.89, 1.26) | 0.110 | 42.2 | |
| Patients | 1 | 0.86 (0.67, 1.10) | — | — | |
| Subgroup analyses for GL and all-cause mortality | | | | | |
| Gender | | | | | 0.051 |
| Male | 3 | 0.91 (0.70, 1.17) | 0.008 | 79.4 | |
| Female | 3 | 1.06 (0.90, 1.25) | 0.827 | 0.0 | |
| Both | 6 | 1.31 (0.95, 1.80) | <0.001 | 78.9 | |
| US vs. non-US | | | | | 0.017 |
| US | 4 | 1.32 (0.88, 1.98) | 0.014 | 71.9 | |
| Non-US | 8 | 1.01 (0.86, 1.18) | 0.001 | 70.1 | |
| Quality score[4] | | | | | 0.006 |
| Scores ≤ median (7) | 10 | 1.15 (0.97, 1.36) | 0.002 | 65.7 | |
| Scores > median (7) | 2 | 0.85 (0.59, 1.22) | 0.014 | 83.3 | |
| Duration of follow-up, y | | | | | 0.004 |
| <10 | 8 | 1.18 (0.98, 1.41) | 0.018 | 58.7 | |
| ≥10 | 4 | 0.94 (0.73, 1.21) | 0.002 | 79.1 | |

(*Continued*)

**TABLE 3** (*Continued*)

| | No. of effect sizes | RR (95% CI) | $P$ within[2] | $I^2$ (%) | $P$ between[3] |
|---|---|---|---|---|---|
| Alcohol consumption | | | | | 0.009 |
| Yes | 6 | 0.94 (0.80, 1.11) | 0.009 | 67.2 | |
| No | 6 | 1.28 (1.01, 1.62) | 0.034 | 58.4 | |
| Correlation between FFQ and carbohydrate | | | | | 0.095 |
| <0.55 | 5 | 1.00 (0.78, 1.29) | <0.001 | 82.6 | |
| ≥0.55 | 6 | 1.23 (0.97, 1.56) | 0.033 | 58.8 | |
| Not reported | 1 | 0.94 (0.71, 1.25) | — | — | |
| Health condition | | | | | 0.001 |
| Healthy | 6 | 0.97 (0.80, 1.17) | 0.002 | 72.9 | |
| Patients | 6 | 1.22 (0.98, 1.50) | 0.051 | 54.5 | |
| Subgroup analyses for GL and CVD mortality | | | | | |
| Gender | | | | | 0.343 |
| Male | 5 | 1.02 (0.85, 1.23) | 0.889 | 0.0 | |
| Female | 3 | 1.19 (0.91, 1.56) | 0.637 | 0.0 | |
| Quality score[4] | | | | | 0.676 |
| Scores ≤ median (7) | 4 | 1.11 (0.89, 1.39) | 0.741 | 0.0 | |
| Scores > median (7) | 4 | 1.04 (0.85, 1.28) | 0.680 | 0.0 | |
| Diet assessment | | | | | 0.690 |
| FFQ | 6 | 1.05 (0.89, 1.25) | 0.770 | 0.0 | |
| Questionnaire or recall | 2 | 1.13 (0.84, 1.53) | 0.630 | 0.0 | |
| Duration of follow-up, y | | | | | 0.938 |
| <10 | 2 | 1.08 (0.84, 1.39) | 0.688 | 0.0 | |
| ≥10 | 6 | 1.07 (0.88, 1.29) | 0.736 | 0.0 | |
| Alcohol consumption | | | | | 0.557 |
| Yes | 6 | 1.06 (0.90, 1.24) | 0.886 | 0.0 | |
| No | 2 | 1.24 (0.75, 2.02) | 0.352 | 0.0 | |
| Correlation between FFQ and carbohydrate | | | | | 0.887 |
| <0.55 | 4 | 1.03 (0.81, 1.31) | 0.512 | 0.0 | |
| ≥0.55 | 2 | 1.08 (0.84, 1.39) | 0.688 | 0.0 | |
| Not reported | 2 | 1.13 (0.84, 1.53) | 0.630 | 0.0 | |
| Health condition | | | | | 0.774 |
| Healthy | 7 | 1.08 (0.92, 1.28) | 0.827 | 0.0 | |
| Patients | 1 | 1.02 (0.70, 1.49) | — | — | |

[1] CVD, cardiovascular disease; FFQ, food-frequency questionnaire; GI, glycemic index; GL, glycemic load.
[2] *P*-heterogeneity, within subgroup.
[3] *P*-heterogeneity, between subgroups.
[4] Quality scores were according to Newcastle-Ottawa Scale criteria (32).

## Discussion

In this meta-analysis, we found no significant association between either GI or GL with mortality from all causes and from CVD. However, a positive significant association has been quantified between GI and all-cause mortality in women. Other results did not vary by gender, diet assessment tools, quality score, follow-up duration, and geographic region. In addition, no evidence for nonlinear dose-response association between dietary GI or GL and mortality from all causes and CVD was found. To the best of our knowledge, this is the first meta-analysis which has quantitatively assessed the association of dietary GI and GL with all-cause and CVD mortality.

Although the current study did not demonstrate significant associations between both GI and GL with mortality from all causes and CVD, a number of previous meta-analyses found significant associations between GI and GL with some NCDs. One dose-response analysis showed that high GI and GL diet increase risk of type 2 diabetes as a leading cause of death, and the effect of GI was greater than that of GL (42). In addition, Barclay et al. (43) investigated the association of GI and GL with chronic diseases. Although this mentioned study suggested that high dietary GI and GL increased the risk of combined chronic diseases and diabetes, no significant association was observed between GI and GL with stroke, endometrial cancer, and digestive tract cancers. Furthermore, high GI elevated the risk of heart diseases and breast cancer; but dietary GL was not associated with these diseases. Another study reported a positive association between GI and GL and risk of CHD in women (44). Also, high dietary GL increased risk of stroke, whereas GI had no effect on stroke and death-related stroke. In other words, in contrast to previous studies, the investigation highlighted the effect of GL more than GI on stroke risk (44). In our study the highest level of GI, compared with the lowest one, increased the risk of all-cause mortality in women but not in men; but dietary GL had no relation with mortality. There are inconsistent findings regarding the effect of GI and GL on NCDs and deaths. In other words, a number of studies suggested that the association between mortality and GI is stronger than that between mortality and GL. The complex and heterogeneous nature of GL justified the weaker effect of GL on postprandial glycemia compared with

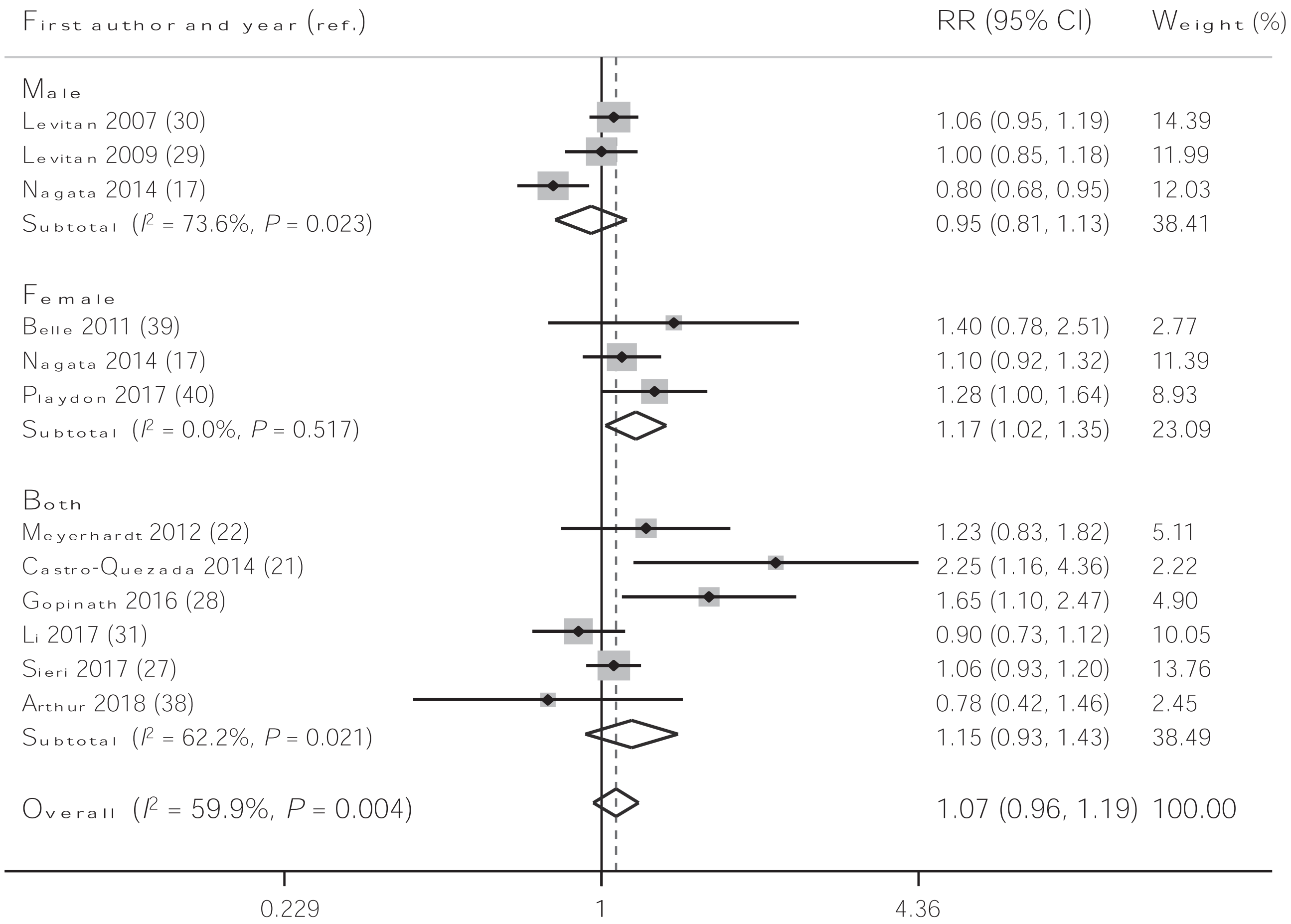

**FIGURE 2** Forest plots of the association between GI and risk of all-cause mortality in cohort studies. GI, glycemic index; ref, reference. The area of each square is proportional to the inverse of the variance of the RR. Horizontal lines represent 95% CIs. Diamonds represent pooled estimates from random-effects analysis.

GI (45). However, 1 study assumed that GL represented a broad aspect of dietary glycemic characteristics and had a greater effect than GI on diseases and mortality (44). Although the current analysis revealed a significant association between dietary GI and risk of all-cause mortality in women, it should be considered that this subgroup included only 3 RRs with a small sample size. The gender-modified effect can be explained by the greater elevation in serum triglyceride and greater reduction in serum HDL in women than men in response to a high dietary GI. In addition, after consumption of a high GI or GL diet, women have more elevated levels of blood glucose than men do. This may subsequently lead to a greater risk of NCDs (46–48). It should also be noted that the observations on the association between dietary GI/GL and risk of all-cause mortality in men were heterogeneous.

Three earlier meta-analyses have reported that diets with a high GI and GL were associated with an increased risk of incident CVDs and CHD, in particular in women (16, 49, 50). Mirrahimi et al. (16) reported that individuals with the greatest dietary GI and GL had 11% and 27% increased risk of incident CHD, respectively, compared with those with the lowest dietary GI and GL ($n$ = 240,936, CHD events = 6940). Another meta-analysis, covering 220,050 people, revealed that high dietary GI and GL was associated with an increased risk of CHD only in women (49). The same conclusions were reached in the study by Ma et al. (50). Therefore, we did not include studies that examined dietary GI/GL in relation to the incidence of these conditions; rather we focused on mortality as the main outcome of interest in the current meta-analysis. We failed to find any significant association between dietary GI and GL and CVD mortality, either in men or among women. The small number of included studies in this regard might provide an explanation for this finding. One randomized crossover-controlled feeding trial suggested that a low GI diet compared with a high GI diet did not improve the CVD risk factors (51), which is in line with our findings. Another randomized clinical trial reported that low dietary GI decreased inflammatory risk markers that might play a role in inflammatory-related mortality (52). Several meta-analyses showed that high GI and GL diets might increase the risk of cancers (53–55), but 1 meta-analysis of 14 cohort studies did not report any significant association between high GI or GL and colorectal cancer (56). In addition, an overview of the literature suggested

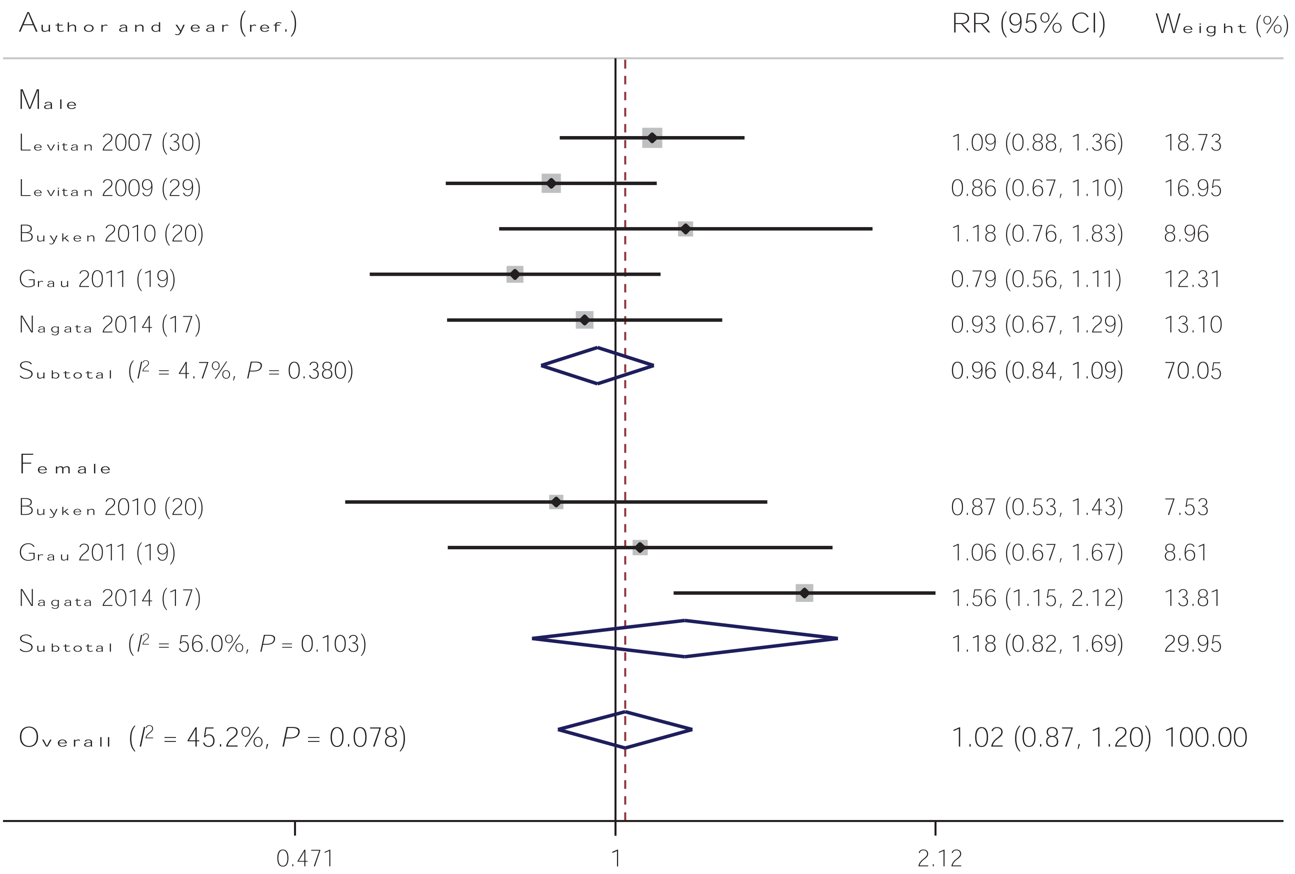

**FIGURE 3** Forest plots of the association between GI and risk of CVD mortality. CVD, cardiovascular disease; GI, glycemic index; ref, reference. The area of each square is proportional to the inverse of the variance of the RR. Horizontal lines represent 95% CIs. Diamonds represent pooled estimates from random-effects analysis.

that the effect of high GI and GL on increasing cancer risk is small or moderate (57), in agreement with the findings of the present study.

In contrast with this study, other studies suggested that consumption of low GI and GL diets might have beneficial effects on health status, such as useful effects on carbohydrate and lipid metabolism, and result in preventing the onset of CVD, diabetes mellitus, and cancers (58–60). The approaches taken to reduce overall GI differ between studies. A low glycemic response might be provided by replacing carbohydrates with proteins or fats or by addition of proteins and fats. In these cases, regulation of energy intake is important. A high-protein diet might increase the risk of CVD, because high-protein diets contain high amounts of saturated fatty acids (61). In addition, high-fat diets might be involved in the occurrence of overweight and obesity that can result in insulin resistance and hyperglycemia (62). Earlier studies have suggested the need to consider the source, type, and amount of carbohydrates in dietary recommendations to achieve a favorable glycemic response.

Although most previous studies recommended the use of low dietary GI and GL in the prevention and management of NCDs (42, 43), the application of these dietary indices in disease prevention and control is controversial due to differences in dietary patterns and quality (63, 64). Findings from previous studies on the link between GI/GL and diet composition have also been inconsistent (65–67). Some prior studies have reported that a high dietary GI and GL might contain both unfavorable and favorable aspects of dietary patterns (68). In addition, Azadbakht et al. (69) reported that dietary GI was inversely associated and GL was directly associated with diet quality. However, insufficient micronutrient intake is more probable in high GI diets, whereas a high GL diet is associated with nutrient adequacy.

Increasing the risk of chronic diseases through consumption of high GI and GL diets is a possible mechanism associated with CVD and all-cause mortality. A high GI diet results in rapid absorption of glucose and subsequently in increases in insulin secretion that encourage uptake of glucose by muscle and adipose tissue. Postprandial hyperglycemia from a high GI meal increases secretion of the gut hormones glucagon-like peptide 1 and glucose-dependent insulinotropic polypeptide. These hormones stimulate secretion of insulin from pancreatic $\beta$ cells and inhibit release of glucagon from $\alpha$ cells. A high insulin to glucagon ratio results in increasing anabolic pathways, such as glycogenesis and lipogenesis, and suppression of lipolysis and gluconeogenesis. These changes in metabolism result in chronic diseases such as obesity, CVD, and diabetes. In addition, hyperglycemia escalates oxidation of lipids, proteins, and DNA, which causes inflammation and reduces antioxidant capacity. These changes may be related to high blood pressure, formation

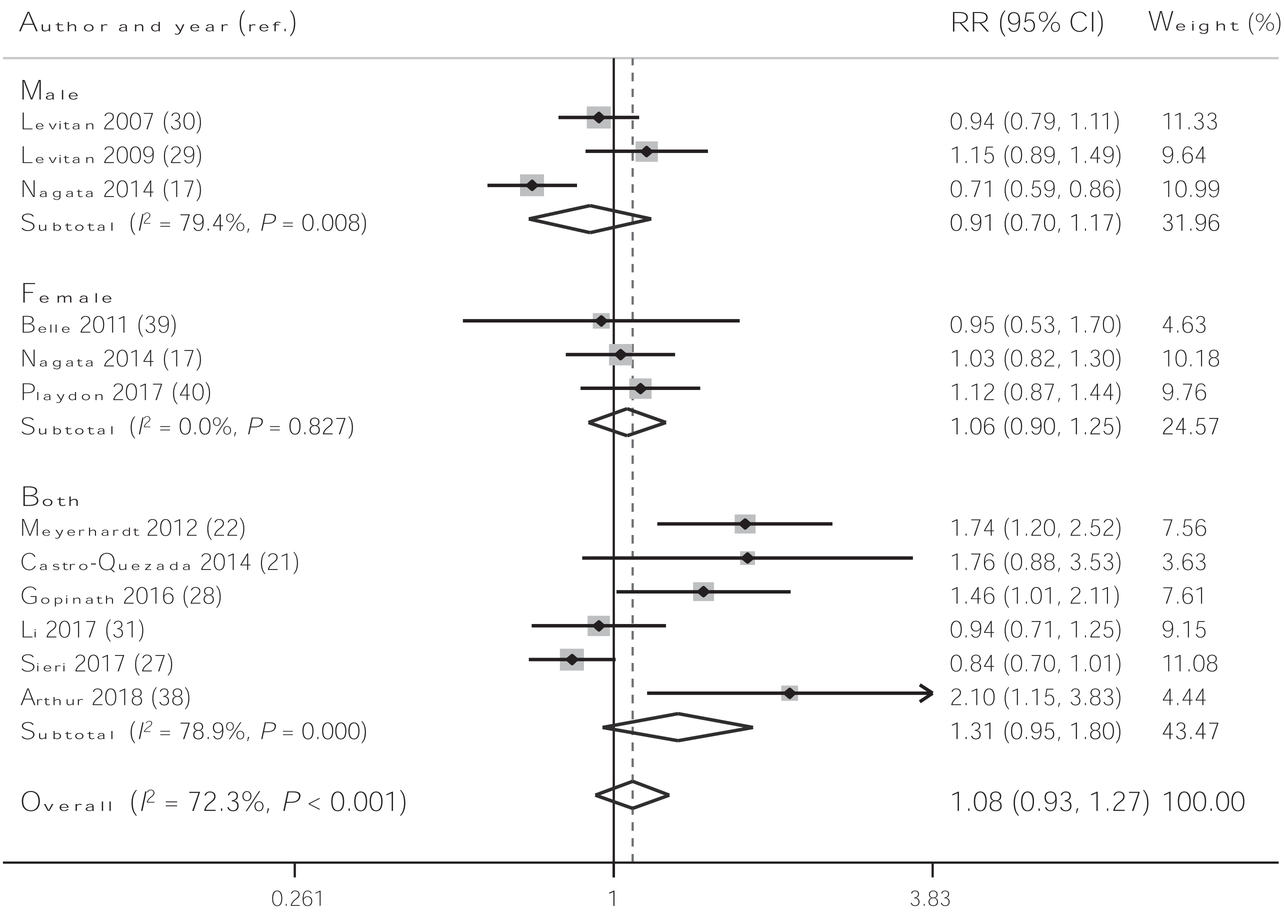

**FIGURE 4** Forest plots of the association between GL and risk of all-cause mortality. GL, glycemic load; ref, reference. The area of each square is proportional to the inverse of the variance of the RR. Horizontal lines represent 95% CIs. Diamonds represent pooled estimates from random-effects analysis..

of blood clots, and ultimately to an increase in CVD and CVD mortality.

The protective relation of dietary GI or GL against incidence of chronic diseases and subsequently mortality would be more important and notable in subjects with overweight, obesity, diabetes, and metabolic syndrome compared with healthy subjects. In other words, the effect of dietary GI or GL on mortality may not be seen in normometabolic populations (70–72). In the current meta-analysis, most included studies were conducted on apparently healthy populations and this might explain the null association between dietary GI or GL and mortality. However, when we performed subgroup analyses based on health conditions of study subjects, the findings were the same for both healthy and unhealthy participants.

Alcohol consumption might confound the effect of dietary GI and GL on mortality from CVD and all causes. There is still a question as to whether alcohol intake promotes cancer deaths, rather than CVD deaths. Available studies are not sufficient to investigate the confounding role of alcohol consumption on the association between dietary GI and GL and mortality.

The between-study heterogeneity might be explained by alcohol consumption, age of subjects, and accuracy of FFQs in assessment of carbohydrate intake, GI or GL. Dietary instruments that showed poor correlations between their measures of nutrient exposure and dietary records, as the gold standard, would inevitably result in a poor correlation between exposure and incident disease resulting in profound bias toward null association.

Among included studies, 8 investigations had used valid FFQs for assessment of dietary carbohydrate (correlation coefficient of >0.55 for carbohydrate intake between the FFQ and gold standard). Following Brunner et al. (73), we considered 0.5 as a good correlation coefficient for a valid FFQ. However, several previous valuable studies with correlations of <0.55 have still shown significant associations with the outcome. Therefore, it seems that even FFQs with correlation coefficients of <0.55 are valid instruments for assessing long-term dietary carbohydrate intake. For instance, the ARIC study and the pancreatic cancer study used an FFQ with an energy-adjusted correlation coefficient of 0.45 for total carbohydrate intake, compared with weighed food records (74, 75). In addition, the study by Mayer-Davis et al. (76) used an FFQ with an energy-adjusted correlation of only 0.37. All these investigators suggested that their FFQs were able to correctly rank individuals according to dietary GI and GL. These investigations showed significant relations between dietary GI/GL and the outcome. Another point that needs to be considered is that only 11 studies out of the 18 included in the current analysis were done on a representative sample of general population, and the remaining 7 studies were conducted on groups of patients. Although a subgroup analysis based on

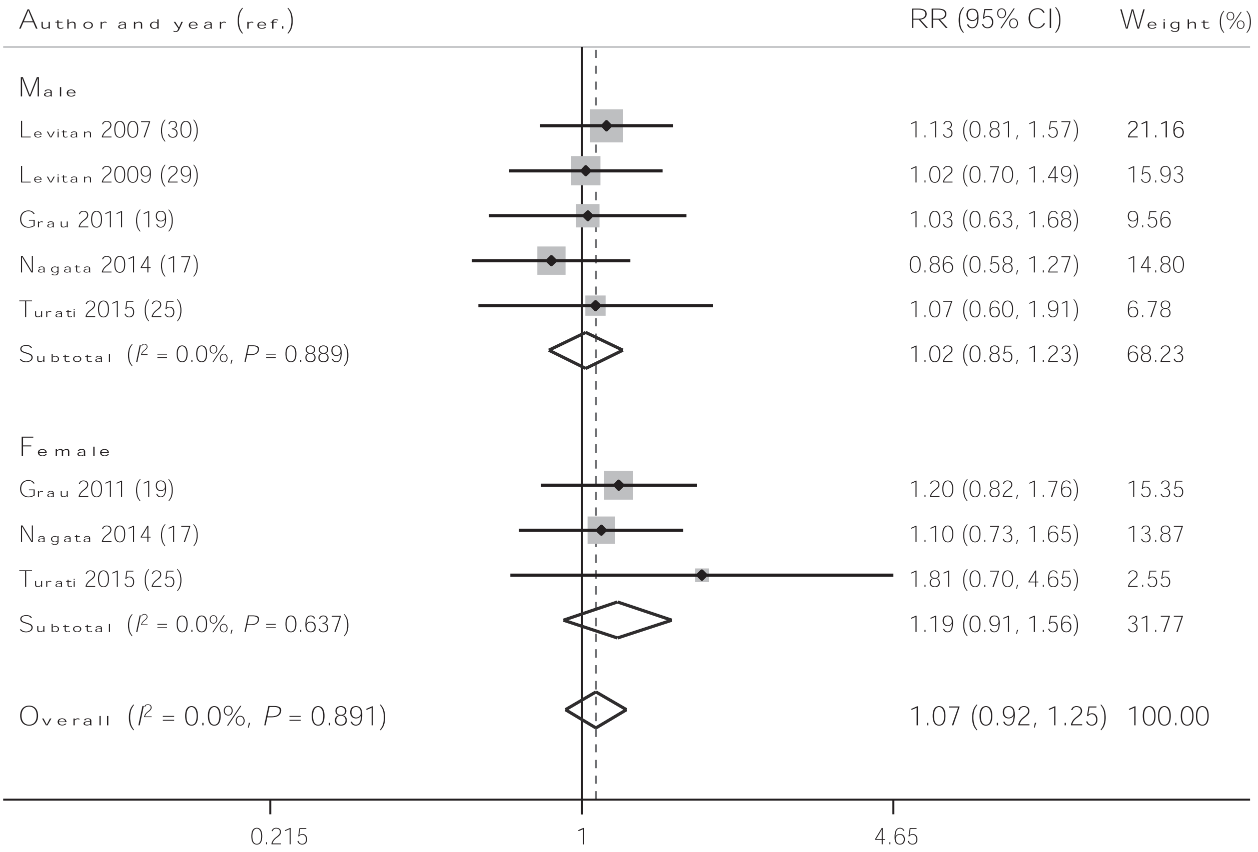

**FIGURE 5** Forest plots of the association between GL and risk of CVD mortality. CVD, cardiovascular disease; GL, glycemic load; ref, reference. The area of each square is proportional to the inverse of the variance of the RR. Horizontal lines represent 95% CIs. Diamonds represent pooled estimates from random-effects analysis.

a quality score of studies included in the current analysis was conducted, both high- and low-quality studies showed similar results.

The current meta-analysis has some strengths. The included studies had prospective cohort designs that reduce the risk of recall and selection bias. Also, most of the studies included in meta-analysis made adjustments for important confounders. However, some limitations should be considered. The cutoff range of GI and GL between the lowest and the highest levels differed between the studies. In addition, most of studies used FFQs for assessment of dietary intake and these FFQs were not specifically designed for calculating GI and GL. Moreover, self-reported dietary intakes could increase the risk of misclassification bias. Furthermore, the included studies did not note the frequency of meals, which could affect blood glucose concentration, and the analysis was not stratified according to the BMI, which might influence mortality risk. Also, because of the limited number of studies, evaluation of mortality from CHD and stroke was not possible. In addition, as few studies had reported correlations of $\geq$0.5 for dietary carbohydrates between the FFQ and the gold standard method, we were unable to limit the analysis to studies with a correlation of >0.5. Several included studies did not separately report the associations in males and females. Finally, between-study heterogeneity was not completely eliminated after subgroup analyses.

In conclusion, this meta-analysis of prospective cohort studies showed no significant association between either dietary GI or GL and mortality from all causes and CVD in men but a positive association of GI with all-cause mortality in women. Further studies with a prospective design are required to confirm these findings.

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