Clinical Nutrition 42 (2023) 1827–1838

Contents lists available at ScienceDirect

Clinical Nutrition

journal homepage: http://www.elsevier.com/locate/clnu

Meta-analyses

Dietary glycemic index, glycemic load and all-cause and cause-specific mortality: A meta-analysis of prospective cohort studies

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ARTICLE INFO

Article history:
Received 28 February 2023
Accepted 14 August 2023

Keywords:
Glycemic index
Glycemic load
All-cause mortality
CVD mortality
Cancer mortality
Meta-analysis

SUMMARY

Background & aims: The findings of previous studies investigating the association between dietary glycemic index, glycemic load, and the risk of mortality have been inconsistent. We performed a meta-analysis to evaluate this association.

Methods: A systematic search in PubMed and Web of Science databases was conducted to identify prospective cohort studies on dietary glycemic index and load with risk of mortality through January 2023. Study-specific relative risks (RR) were combined by using random effects models.

Results: Fifteen prospective cohort studies with a total of 527,650 participants and 48,598 all-cause and cause-specific deaths were included in the current meta-analysis. Pooled analyses indicated a higher risk of all-cause mortality (RR = 1.10, 95% CI: 1.00–1.20) and stroke mortality (RR = 1.30, 95% CI: 1.04–1.62) for the highest *versus* lowest levels of glycemic index. A significant non-linear association was found between glycemic index and mortality of all-causes (*P* for non-linearity = 0.02) and CVD (*P* for non-linearity <0.001), indicating increased risk at high levels of glycemic index (≥63.1 for all-cause mortality; ≥72.8 for CVD mortality). Glycemic load was positively associated with risk of CVD mortality (RR = 1.18, 95% CI: 1.09–1.27) and stroke mortality (RR = 1.30, 95% CI: 1.05–1.60) in the highest *versus* lowest meta-analysis. For cancer mortality, there was no significant association with glycemic index, but the association with glycemic load differed by sex.

Conclusions: Our results indicated that high glycemic index and glycemic load was associated with an increased risk of mortality from CVD and stroke. Further large prospective studies are warranted to provide definitive evidence in subgroups.

1. Introduction

The Glycemic index is defined as a percentage of the appropriate mean glucose tolerance test value after eating 50 g of carbohydrate, compared with a reference food [1]. In other words, the glycemic index is a qualitative indicator of the ability of carbohydrates to raise blood glucose levels [2]. According to the International Standards Organization (ISO) announcement in 2010, the cut points for glycemic index classification are high (glycemic index ≥70), medium (glycemic index 56–69), and low (glycemic index ≤55) [3]. The glycemic load is calculated by multiplying the glycemic index by the carbohydrate content of the food [2]. In the end, the glycemic load can be said to be an indicator that can represent not only the quality but also the quantity of carbohydrates. Both glycemic index and glycemic load may affect carbohydrate quality, along with dietary fiber, whole grains, and legumes [4]. There have been many studies examining the association between the quality of carbohydrates and the risk of chronic disease or mortality [4]. However, most studies were about the beneficial effect of dietary fiber and whole grains on health [5,6]. Relatively less attention has been given to glycemic index and glycemic load regarding the risk of non-communicable disease incidence and mortality. The glycemic index and glycemic load, which represent the quantity and quality of dietary carbohydrates, could influence mortality risk by affecting the risk of chronic diseases, including metabolic syndrome, diabetes, cardiovascular disease, and cancer [7]. Therefore, identifying the association between the glycemic index, glycemic load, and risk of mortality is crucial to improve public health by lowering the risk of premature death.

Findings from previous studies investigating the association between glycemic index or glycemic load and the risk of mortality

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https://doi.org/10.1016/j.clnu.2023.08.014

were not consistent [8–22]. Some studies found a positive association between glycemic index or glycemic load and the risk of total mortality [8–10,13,15,16,18]. Several other studies only suggested significant associations between glycemic index or glycemic load and the risk of mortality from specific causes [17,19,21]. The other studies failed to produce significant results regarding the association between glycemic index or glycemic load and the risk of mortality. There was a meta-analysis examining the association of glycemic index or glycemic load and the risk of mortality [23], but they included studies on subjects with disease. To explore the effect of glycemic index and load on the risk of mortality in healthy people, we conducted a systematic review and meta-analysis of prospective cohort studies on participants without disease.

2. Material and methods

2.1. Data sources and searches

We searched PubMed and ISI Web of Science databases to identify studies that examined the association between glycemic index or load and risk of mortality in English from inception to January 2023. The following keywords were used: "(glycemic index OR glycaemic index OR glycemic load OR glycaemic load) combined with (mortality OR death OR fatal OR survival)." The reference lists of the included articles were also reviewed manually to identify additional eligible studies. This meta-analysis was registered on PROSPERO (CRD42023397493).

2.2. Study selection

Published articles were included in this meta-analysis according to the following inclusion criteria: (1) prospective design; (2) the exposure of interest was dietary glycemic index or dietary glycemic load; (3) the outcome of interest was mortality; (4) they reported relative risks (RR) with related confidence intervals (CI). More than two articles from the same cohort were included in this meta-analysis because they provided mortality from different causes [8,12,15,19–21]. Studies involving patients with specific diseases were excluded.

2.3. Data extraction and quality assessment

Two authors (Y.K. and Y.J.) independently extracted relevant data according to the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) statement [24]. The information extracted from each article included last name of first author's, year of publication, cohort name, number of subjects and cases, age, sex, geographical region or country, period of follow-up, categories of dietary glycemic index or load, the RRs and 95% CIs for each category of dietary glycemic index or load, and adjusted variables. When articles reported several RRs, we selected RRs reflecting the greatest degree of adjustment for potential confounding factors.

The included study quality was evaluated by using the Newcastle–Ottawa quality assessment scale [25]. Two authors (Y.K. and Y.J.) independently assessed the quality of each study on three factors including selection of subjects, comparability of cohorts, and ascertainment of outcomes of interest. When a study achieved ten or more points (out of 13), it was considered high quality. Studies with points of 7–9 and a point of 6 or less were considered good and low quality, respectively. Any disagreements in data extraction and quality assessment were solved by reviewing the original articles and discussion.

2.4. Statistical analysis

The RRs from individual studies were combined using the DerSimonian and Laird [26] random effects models, which take both within- and between-study variations into account. When a study did not report the lowest glycemic index or glycemic load category as a reference, we recalculated the RR and its 95% CI [17]. The Pooled RRs were presented as forest plots. The heterogeneity among the studies was examined with the use of Cochran's Q test [27] and inconsistency was quantified through I^2 statistics [28]. To explore potential sources of heterogeneity, we performed subgroup analyses by sex and geographical region. Sensitivity analysis omitting one study at a time was conducted to assess the extent to which inferences can be influenced by a specific study. Publication bias was evaluated with Begg's [29] and Egger's regression asymmetry test [30] and funnel plot. The linear dose–response meta-analysis was performed using the 2-stage generalized least-squares trend estimation method to estimate the study-specific slope lines first and then acquire an overall average slope, with the use of the methods proposed by Greenland and Longnecker [31–33]. We assigned the median or mean value of the glycemic index and load for each category with reference to information reported in the original article. If a study used white bread as a reference food, the glycemic index and load value were multiplied by 0.71 to convert from the white bread scale to a glucose scale [34]. A potential non-linear association between dietary glycemic index and dietary glycemic load and risk of mortality was also examined using restricted cubic splines with 3 knots at fixed percentiles (10%, 50%, and 90%) throughout the whole distribution [35]. The P-value for non-linearity was obtained by testing the null hypothesis, in which the coefficient of the second spline is equal to zero. The P-values were two-tailed, and a P-value of less than 0.05 was considered statistically significant. All statistical analyses were conducted with Stata version 17.0 software (StataCorp, TX, USA).

3. Results

3.1. Study characteristics

Fifteen papers of twelve prospective cohort studies involving 527,650 subjects and 48,598 deaths from all-causes, 13,226 deaths from CVD, 14,614 deaths from cancer, and 2108 deaths from stroke were suitable for this meta-analysis [8–22] (Fig. 1). Detailed characteristics of studies included in meta-analysis were presented in Table 1. The largest cohort had 127,016 subjects [9], and the smallest had 1609 subjects [13], with an average cohort size of 63,819. Eleven papers provided effect sizes for dietary glycemic index and dietary glycemic load [8–13,15–17,19,22]. Four other papers reported effect sizes only for either dietary glycemic index [20,21] or dietary glycemic load [14,18]. The mean follow-up period was 12.9 years, and the duration of follow-up ranged from 4.7 years to 18.2 years. By geographic region, studies were from Europe [11,14,16,17,22] (five cohorts), Asia [8,10,12,15,19] (four cohorts), US [18] (one cohort), Oceania [13,20,21] (one cohort), and multicontinent [9] (one cohort). Age, smoking and energy intake were adjusted in all studies, and BMI [8,10–12,14–19,21,22] and alcohol consumption [8,10,11,15–20,22] were adjusted in most studies. The result of the quality assessment ranged from 9 to 12 showing a mean score of 10.7.

3.2. Glycemic index and mortality

Nine prospective cohort studies including 449,246 participants and 43,705 deaths were included in the meta-analysis for the

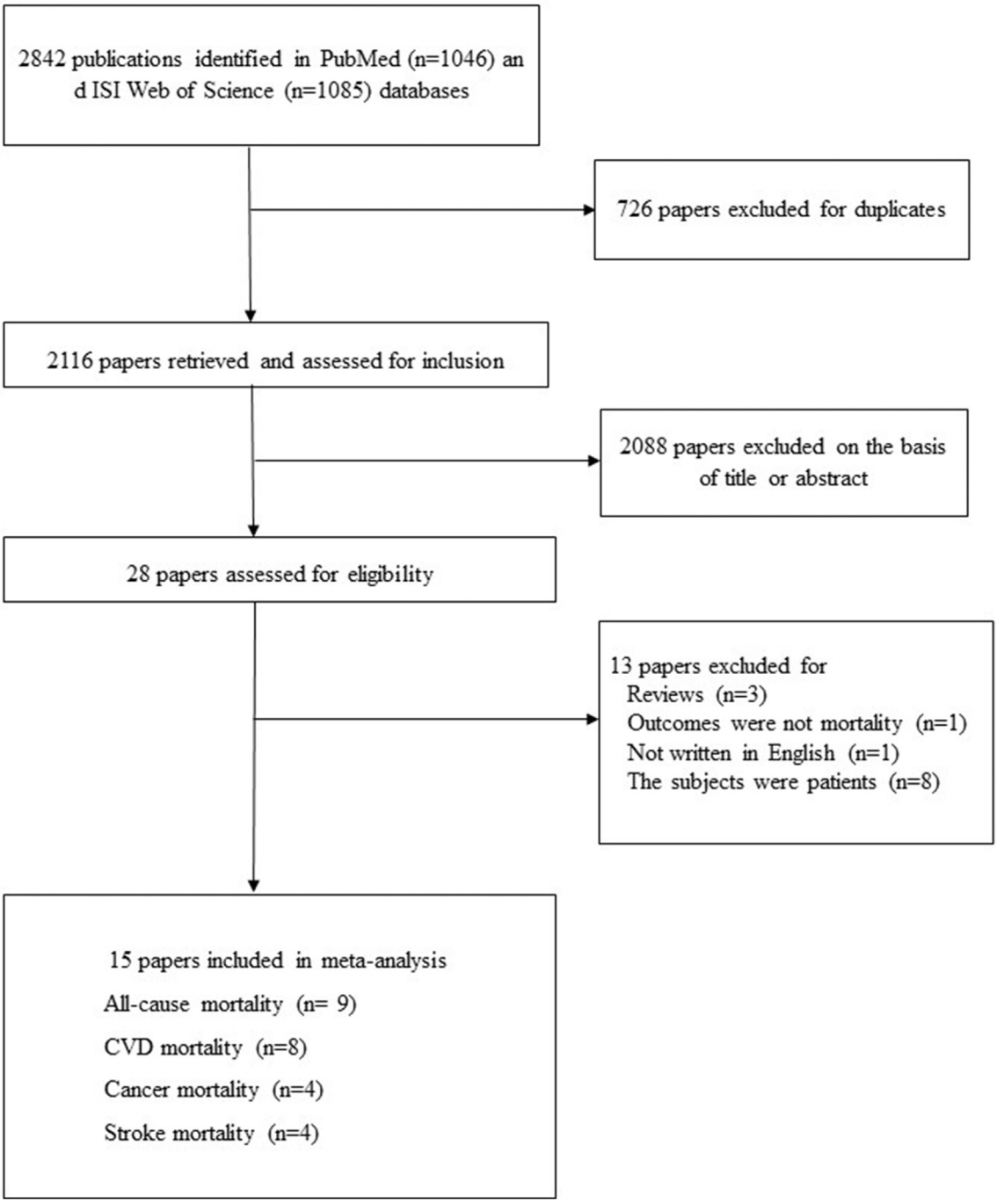

Fig. 1. Flow chart of study selection.

association between glycemic index and all-cause mortality [8–11,13,15,16,22]. The pooled RR for all-cause mortality the highest compared *with* lowest levels of glycemic index was 1.10 (95% CI: 1.00–1.20) showing significant heterogeneity among studies ($I^2 = 80.2\%$, $P < 0.001$) (Fig. 2). The heterogeneity decreased slightly ($I^2 = 62.0\%$, $P = 0.01$) when two studies targeted at Asian males [8,15] were excluded. By sex, an increased risk of all-cause mortality was observed in women (RR: 1.11, 95% CI: 1.05–1.18), unlike in men (RR: 0.99, 95% CI: 0.87–1.14) (Table 2). A dose–response meta-analysis showed a significant non-linear association between the glycemic index and all-cause mortality, with an RR greater than 1 on a glycemic index ≥63.1 (P for non-linearity = 0.02) (Fig. 3).

Eight prospective cohort studies including 405,271 participants and 13,226 deaths were included in meta-analysis for the association between glycemic index and CVD mortality [8–10,15,17,20,22]. The pooled RR for CVD mortality the highest compared with lowest levels of glycemic index was 1.16 (95% CI: 0.98–1.38) showing significant heterogeneity among studies ($I^2 = 81.3\%$, $P < 0.001$) (Fig. 4). The significant heterogeneity disappeared ($I^2 = 20.6\%$, $P = 0.26$) when one outlying study [17] was excluded. In the subgroup analyses by sex and geographical region, the positive association between glycemic index and CVD mortality was observed stronger in women and Asia (Table 2). Some evidence of non-linear association between the glycemic index and CVD

Table 1
Characteristics of studies included in the meta-analysis on glycemic index/glycemic load and mortality from all-causes, CVD, stroke and cancer.

First author, year	Country	Cohort name	Follow-up period	Age at baseline (years)	sex	Study size		Comparison of Exposure	Cause of death	Adjustment for covariates
						Subjects	No. of death			
Levitan, 2007 [22]	Sweden	Cohort of Swedish Men	8 y	45–79 y	Male	36,246	2959	GI Q4 vs. Q1 (82.9 vs. 73.0) GL Q4 vs. Q1 (250 vs. 180)	All-causes CVD	Age, BMI, physical activity, self-reported history of hypertension, family history of myocardial infarction before 60 y of age, use of aspirin, cigarette smoking, marital status, education, and quartiles of intake of total energy, carbohydrate, saturated fat, polyunsaturated fat, alcohol, and cereal fiber
Kaushik, 2009 [21]	Australia	Blue Mountains Eye Study	13 y	≥49	Male and female	2897	95	GI T3 vs. T1 (60.6 vs. 52.4)	Stroke	Age, sex, systolic blood pressure, diastolic blood pressure, antihypertensive medication use, BMI, smoking status, educational qualifications, fair or poor self-rated health, history of myocardial infarction and stroke, and presence of diabetes, intake of energy
Buyken, 2010 [20]	Australia	Blue Mountains Eye Study	13 y	≥49	Male	1245	151	GI T3 vs. T1 (61.6 vs. 53.8)	CVD	Age, energy, total fiber residuals, total fat intake, whether underweight, current smoking, use of corticosteroid drugs at baseline
					Female	1490	109	GI T3 vs. T1 (59.6 vs. 51.9)		Age, energy, total fiber residuals, alcohol consumption, current smoking, presence of diabetes at baseline
Oba, 2010 [19]	Japan	Takayama study	7 y	≥35	Male and female	27,862	247	GI Q4 vs. Q1 (70.2 vs. 58.2) GL Q4 vs. Q1 (219.6 vs. 193.1)	Stroke	Age, BMI, smoking status, physical activity, reported history of hypertension, education, intake of total energy, alcohol, dietary fiber, salt, total fat
Baer, 2011 [18]	United States	Nurses' Health Study	1986–2004 (18 y)	30–55 years	Female	50,112	4893	Per 41 of GI	All-causes CVD Cancer	Age, BMI, energy. Weight change since age 18years, height, smoking status, smoking amount/duration, physical activity, alcohol intake, nut consumption, polyunsaturated fat, cereal fiber, dietary cholesterol, systolic blood pressure, use of blood pressure medications, personal history of diabetes, parental MI before age 60 years, time since menopause
Grau, 2011 [17]	Denmark	Former Glostrup Population Studies	6-25 y	30–70	Male and female	1819	108	GI P95 vs. P5 GL P95 vs. P5	CVD	Age, total energy intake, BMI, energy-adjusted carbohydrate intake, energy-adjusted fat intake, energy-adjusted protein intake, energy-adjusted fibre intake, cohort, level of education, level of physical activity, smoking status

Castro-Quezada, 2014 [16]	Spain	PREDIMED study	4.7 y	55–80	Male and female	3583	123	GI Q4 vs. Q1 (63.1 vs. 52.1) GL Q4 vs. Q1 (144.4 vs. 91.9)	All-causes	Age, sex, recruitment center, intervention group, smoking, education, marital status, physical activity, BMI, self-reported history of cancer, arterial hypertension, dyslipidemia, and cardiovascular disease, total energy intake, alcohol intake, dietary fiber intake, saturated fatty acids, monounsaturated fatty acids
Nagata, 2014 [15]	Japan	Takayama study	16 y	≥35	Male and female	28,356	4616	GI Q4 vs. Q1 (69.9 vs. 57.4) GL Q4 vs. Q1 (258.5 vs.161.9)	All-causes CVD Cancer	Age, energy, height, BMI, physical activity, smoking status, education, marital status, histories of diabetes and hypertension, intakes of alcohol, saturated fat, polyunsaturated fat, salt, vegetables and fruits
Turati, 2015 [14]	Greece	EPIC Greek cohort study	10.4 y	20–86	Male and female	20,275	162	GL T3 vs. T1	CVD	Age, sex, education, BMI, physical activity, smoking status, arterial hypertension, and total energy intake without carbohydrates
Gopinath, 2016 [13]	Australia	Blue Mountains Eye Study	10 y	≥49	Male and female	1609	610	GI Q4 vs. Q1 GL Q4 vs. Q1	All-causes	Age, sex, marital status, living status, smoking, weight status, energy-adjusted total fiber intake
Yu, 2016 [12]	China	Shanghai Women's Health Study	12 y	40–70	Female	64,328	609	GI P90 vs. P10 (80 vs. 71) GL P90 vs. P10 (239 vs. 174)	Stroke	Age, education, cigarette smoking, BMI, family history of stroke, hypertension, and dyslipidemia, total energy intake, saturated fat intake, a partial diet quality score
Sieri, 2017 [11]	Italy	EPIC-Italy study	14.9 y	50.7, mean	Male and female	45,148	2460	GI Q5 vs. Q1 GL Q5 vs. Q1	All-causes	Age, sex, education, smoking status, BMI, alcohol intake, fibre intake, saturated fat intake, non-alcohol energy intake, physical activity
Huang, 2021 [10]	Japan	Japan Public Health Center-based Prospective Study	17.1 y	40–69	Male and female	72,783	12,448	GI Q4 vs. Q1 (67.2 vs. 54.6) GL Q4 vs. Q1 (165.6 vs. 145.0)	All-causes CVD Cancer Stroke	Age, sex, public health center, history of hypertension, BMI, physical activity, smoking status and intensity, alcohol consumption, intakes of total energy, salt, red and processed meat, and fish
Jenkins, 2021 [9]	Multicontinent	Prospective Urban Rural Epidemiological Study	9.5 y	35–70	Male and female	127,016	7382	GI Q5 vs. Q1 (64.6 vs. 54.0) GL Q5 vs. Q1 (332.3 vs. 96.6)	All-causes CVD Cancer	Age, sex, education, smoking, urban/rural location, income country, physical activity, waist hip ratio, statin, blood pressure medications, history of diabetes, fiber, whole grains, daily energy and center
Zhao, 2022 [8]	China	Shanghai Men's Health Study	12.8 y	40–74	Male	59,770	6004	GI Q4 vs. Q1 (76.7 vs. 65.3) GL Q4 vs. Q1 (265.0 vs. 183.6)	All-causes CVD Cancer	Age, energy, education, income, occupation, smoking status, alcohol intake, physical activity, Charlson comorbidity index
		Shanghai Women's Health Study	18.2 y		Female	74,735	7103	GI Q4 vs. Q1 (76.4 vs. 64.9) GL Q4 vs. Q1 (230.8 vs. 163.7)	All-causes CVD Cancer	Age, energy, education, income, occupation, smoking status, alcohol intake, physical activity, Charlson comorbidity index, menopause status

BMI, body mass index; GI, glycemic index; GL, glycemic load; PREDIMED, PREvención con DIeta MEDiterránea.
The cohort was in order of publication year, and in the case of the same year, it was listed in alphabetical order by author name.

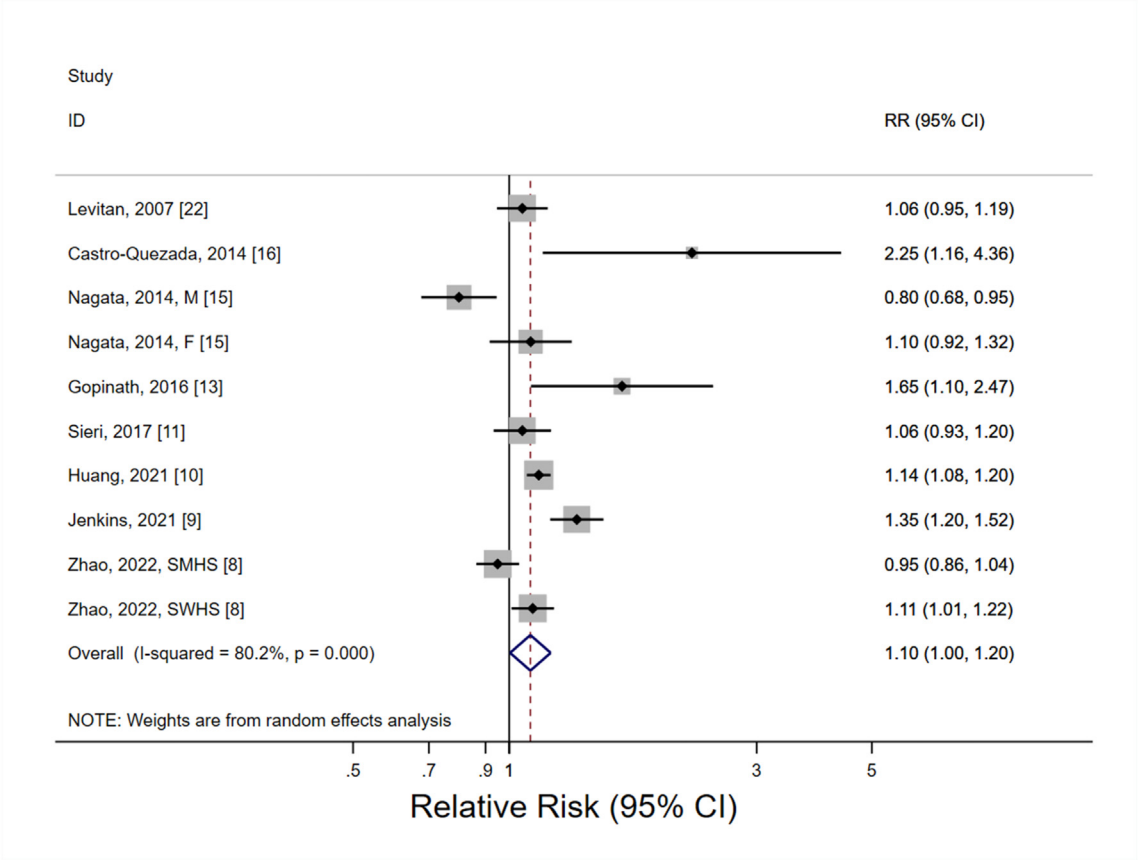

Fig. 2. Forest plots of the prospective cohort studies of all-cause mortality for high *versus* low glycemic index.

mortality was found (*P* for non-linearity <0.001) (Fig. 3). Significantly increased CVD mortality was observed, starting with a glycemic index of 72.8 or higher.

Four prospective cohort studies including 167,870 participants and 2108 deaths were included in meta-analysis for the association between glycemic index and stroke mortality [10,12,19,21]. The pooled RR for stroke mortality the highest compared with lowest levels of glycemic index was 1.30 (95% CI: 1.04–1.62) with no significant heterogeneity among studies (I^2 = 36.0%, P = 0.18) (Supplementary Fig. 1). We found no significant association between glycemic index and stroke mortality in linear (*P* for linearity = 0.13) and non-linear (*P* for non-linearity = 0.59) dose–response analysis.

Four prospective cohort studies including 235,644 participants and 12,253 deaths were included in meta-analysis for the association between glycemic index and cancer mortality [8,10,15]. The pooled RR for cancer mortality the highest compared with lowest levels of glycemic index was 1.00 (95% CI: 0.89–1.12) showing significant heterogeneity among studies (I^2 = 59.2%, P = 0.04) (Supplementary Fig. 2). The observed significant heterogeneity disappeared (I^2 = 31.0%, P = 0.23) when one study in Chinese men [8] was removed. There was no significant association between glycemic index and cancer mortality in linear (*P* for linearity = 0.65) and non-linear (*P* for non-linearity = 0.76) dose–response analysis.

3.3. Glycemic load and mortality

The association between glycemic load and all-cause mortality was evaluated in 10 prospective cohort studies including 499,358 participants and 48,598 deaths [8–11,13,15,16,18,22]. The pooled RR for the association of the highest compared with lowest levels of glycemic load with all-cause mortality was 1.02 (95% CI: 0.93–1.12) with significant heterogeneity among studies (I^2 = 77.3%, P < 0.001) (Fig. 5). The observed significant heterogeneity slightly decreased (I^2 = 66.7%, P = 0.001) when one study in Japanese men [15] was excluded. By sex, the positive association between glycemic load and all-cause mortality was observed in women (RR: 1.15, 95% CI: 1.09–1.22), not in men (RR: 0.92, 95% CI: 0.81–1.04) (*P* for difference = 0.04) (Table 3). There was no significant differences by geographic region (*P* for difference >0.2 in all comparisons) (Table 3). We did not find a linear (*P* for linearity = 0.48) or non-linear (*P* for non-linearity = 0.58) association between glycemic load and all-cause mortality (Fig. 6).

The association between glycemic load and CVD mortality was investigated in 9 prospective cohort studies including 472,923 participants and 12,966 deaths [8–10,14,15,17,18,22]. The pooled RR for the association of the highest compared with lowest levels of glycemic load with CVD mortality was 1.18 (95% CI: 1.09–1.27) with no significant heterogeneity (I^2 = 0.0%, P = 0.91) (Fig. 7). In the subgroup analysis by sex, a positive association between glycemic load and CVD mortality was similar in men (RR: 1.18, 95% CI: 1.05–1.32) and women (RR: 1.19, 95% CI: 1.07–1.32) (Table 3). By geographic region, the results from Asia showed significant positive association (RR: 1.20, 95% CI: 1.09–1.31) (Table 3). There was no significant non-linear association between glycemic load and CVD mortality (*P* for non-linearity = 0.63) (Fig. 6). The pooled RR of CVD mortality for a 50 increment in glycemic load was 1.03 (95% CI: 1.01–1.04), indicating linear association (Table 3).

The association between glycemic load and stroke mortality was investigated in 3 prospective cohort studies including 164,973 participants and 2013 deaths [10,12,19]. The pooled RR for the association of the highest compared with lowest levels of glycemic load with stroke mortality was 1.30 (95% CI: 1.05–1.60) with no

Table 2
Summary of pooled relative risks (RR) of mortality from all-causes, CVD, stroke and cancer for glycemic index.

	No. of studies	RR	95%CI	*P* for difference
All-cause mortality				
High *versus* low glycemic index				
All studies	9	1.10	1.00–1.20	
Stratified by sex				
Male	4	0.99	0.87–1.14	0.29
Female	3	1.11	1.05–1.18	
Stratified by geographical region				
Asia	4	1.02	0.91–1.14	
Europe	3	1.10	0.94–1.30	0.54[a], 0.25[a]
Oceania	1	1.65	1.10–2.47	0.16[a], 0.56[a]
Multicontinent	1	1.35	1.20–1.52	0.16[a], 0.36[a],
CVD mortality				
High *versus* low glycemic index				
All studies	8	1.16	0.98–1.38	
Stratified by sex				
Male	6	1.00	0.79–1.26	0.17
Female	5	1.40	1.06–1.85	
Stratified by geographical region				
Asia	4	1.21	1.08–1.35	
Europe	3	1.17	0.50–2.76	0.91[b], 0.65[b]
Oceania	1	1.03	0.74–1.43	0.60[b], 0.69[b]
Multicontinent	1	1.32	1.08–1.61	0.86[b], 0.82[b]
Stroke mortality				
High *versus* low glycemic index				
All studies	4	1.30	1.04–1.62	
Stratified by sex				
Male	2	1.16	0.62–2.19	0.996
Female	3	1.21	0.97–1.51	
Cancer mortality				
High *versus* low glycemic index				
All studies	4	1.00	0.89–1.12	
Stratified by sex				
Male	3	0.97	0.84–1.11	0.37
Female	3	1.07	0.94–1.22	

[a] *P* value difference in RRs of all-cause mortality for Europe *versus* Asia ($P = 0.54$), Oceania *versus* Europe ($P = 0.25$), Oceania *versus* Asia ($P = 0.16$), Mulicomtinent versus Oceania ($P = 0.56$), Multicontinent *versus* Asia ($P = 0.16$), and Multicontinent versus Europe ($P = 0.36$).
[b] *P* value difference in RRs of CVD mortality for Europe *versus* Asia ($P = 0.91$), Oceania *versus* Europe ($P = 0.65$), Oceania *versus* Asia ($P = 0.60$), Mulicomtinent *versus* Oceania ($P = 0.69$), Multicontinent *versus* Asia ($P = 0.86$), and Multicontinent *versus* Europe ($P = 0.82$).

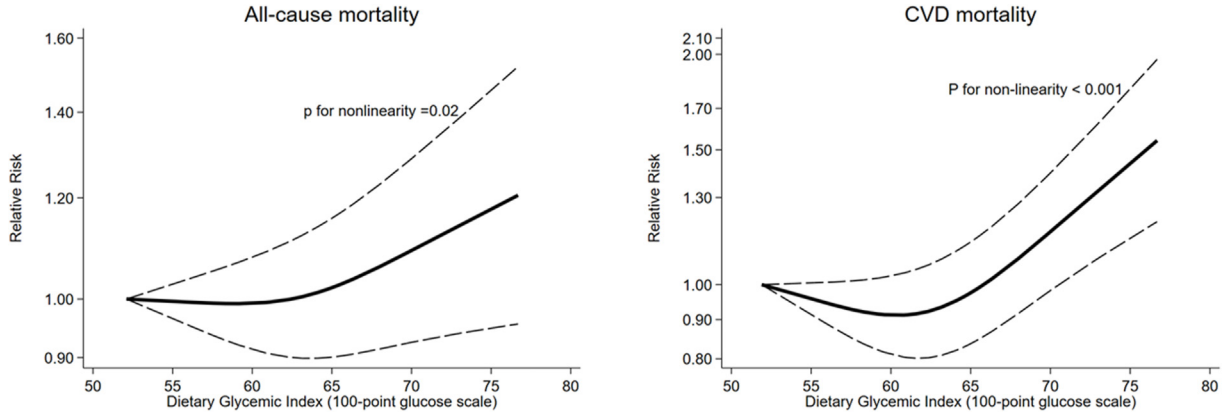

Fig. 3. Pooled dose–response association between glycemic index and mortality from all-causes and CVD. Solid lines represent relative risk (RR), dashed lines represent 95% confidence intervals.

significant heterogeneity ($I^2 = 0.0\%$, $P = 0.90$) (Supplementary Fig. 3). There was no linear (*P* for linearity = 0.73) or non-linear (*P* for non-linearity = 0.75) association between glycemic load and stroke mortality.

The association between glycemic load and cancer mortality was investigated in 5 prospective cohort studies including 285,756 participants and 14,614 deaths [8,10,15,18]. The pooled RR for the association of the highest compared with lowest levels of glycemic load with cancer mortality was 0.98 (95% CI: 0.85–1.12) with significant heterogeneity ($I^2 = 73.6\%$, $P = 0.002$) (Supplementary Fig. 4). The significant heterogeneity disappeared ($I^2 = 0.0\%$, $P = 0.57$) after removing two studies showing RR of more than 1 [8,18]. In the subgroup analysis by sex, an inverse association between glycemic load and cancer mortality was shown in men (RR: 0.88, 95% CI: 0.80–0.97), unlike women (RR: 1.11, 95% CI: 1.01–1.22) (*P* for difference = 0.02) (Table 3). We did not observe any linear (*P* for linearity = 0.22) or non-linear (*P* for non-linearity = 0.59) association between glycemic load and cancer mortality.

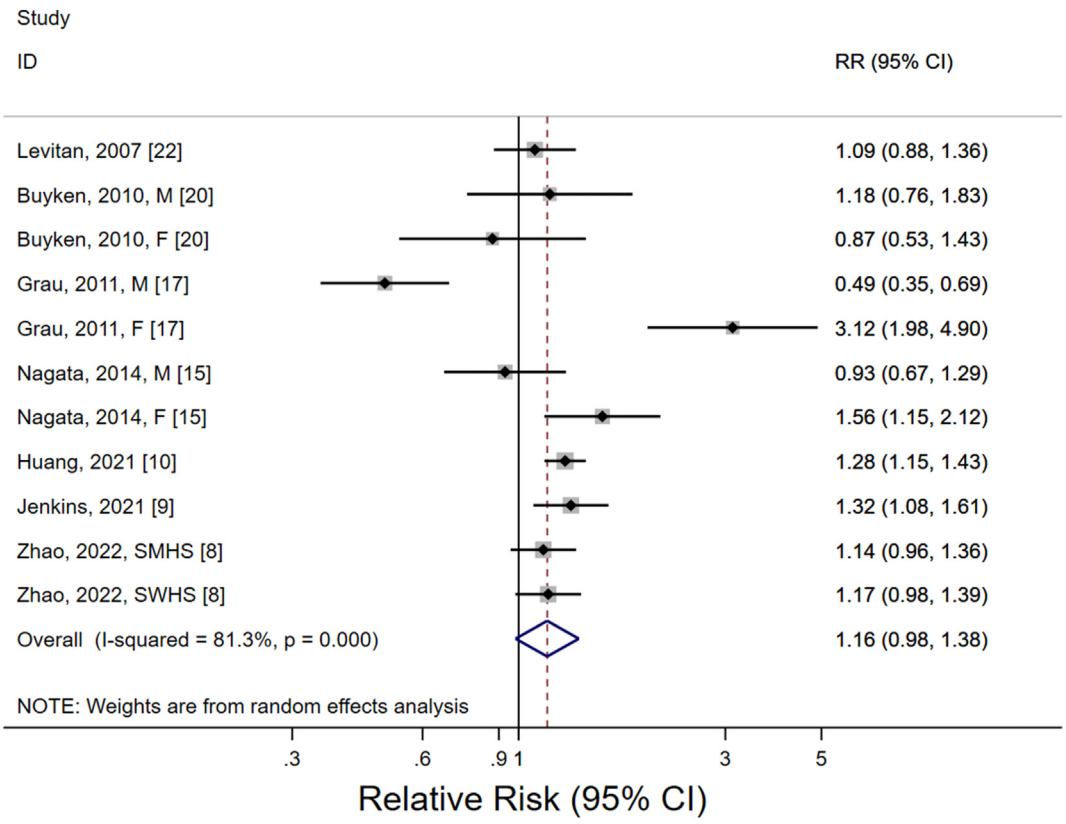

Fig. 4. Forest plots of the prospective cohort studies of CVD mortality for high *versus* low glycemic index.

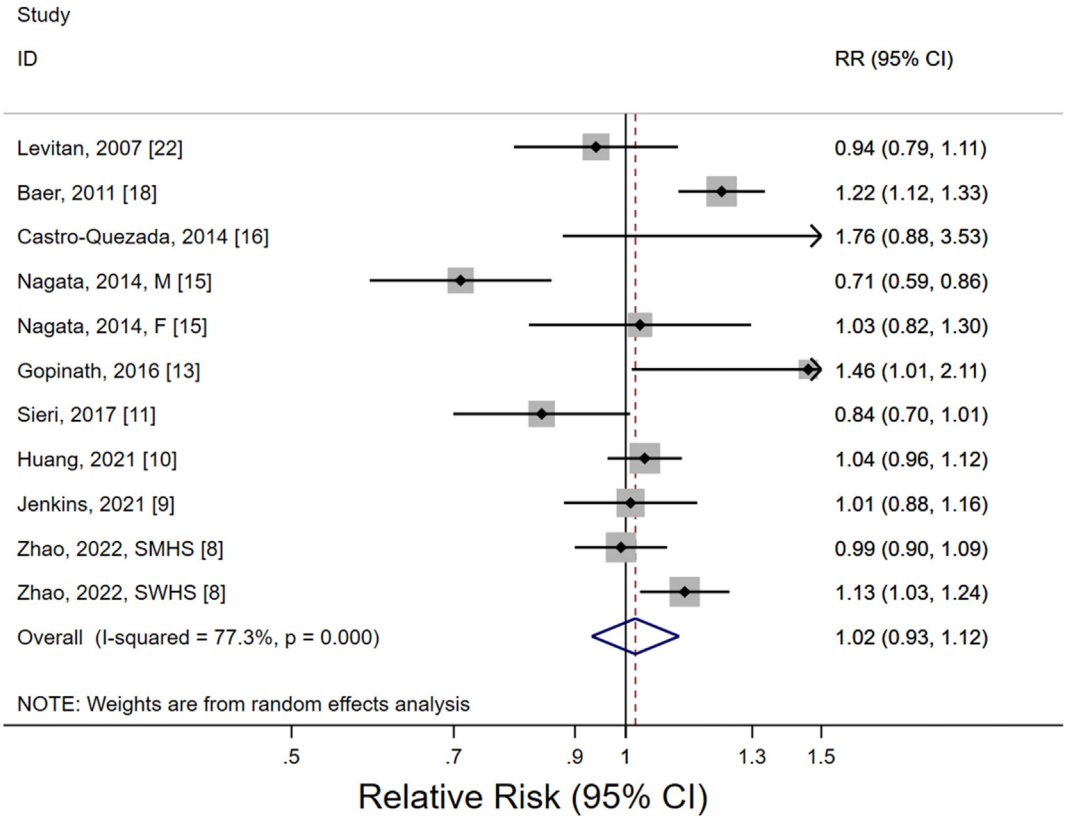

Fig. 5. Forest plots of the prospective cohort studies of all-cause mortality for high *versus* low glycemic load.

Table 3
Summary of pooled relative risks (RR) of mortality from all-causes, CVD, stroke and cancer for glycemic load.

	No. of studies	RR	95%CI	*P* for difference
All-cause mortality				
High *versus* low glycemic index				
All studies	10	1.02	0.93–1.12	
Stratified by sex				
Male	4	0.92	0.81–1.04	0.04
Female	4	1.15	1.09–1.22	
Stratified by geographical region				
Asia	4	0.99	0.88–1.11	
Europe	3	0.94	0.76–1.16	0.82[a], 0.19[a]
Oceania	1	1.46	1.01–2.11	0.20[a], 0.59[a]
United States	1	1.22	1.12–1.33	0.29[a], 0.28[a], 0.48[a]
Multicontinent	1	1.01	0.88–1.16	0.88[a], 0.78[a], 0.30[a]
CVD mortality				
High *versus* low glycemic index				
All studies	9	1.18	1.09–1.27	
Stratified by sex				
Male	6	1.18	1.05–1.32	0.91
Female	6	1.19	1.07–1.32	
Stratified by geographical region				
Asia	4	1.20	1.09–1.31	
Europe	3	1.14	0.93–1.40	0.69[b], 0.78[b]
United States	1	1.19	0.98–1.45	0.96[b], 0.78[b]
Multicontinent	1	1.09	0.86–1.38	0.49[b], 0.59[b]
Increment of 50 in glycemic load				
All studies	5	1.03	1.01–1.04	
Stroke mortality				
High *versus* low glycemic index				
All studies	3	1.30	1.05–1.60	
Stratified by sex				
Male	2	1.44	0.94–2.21	0.35
Female	3	1.18	0.90–1.56	
Cancer mortality				
High *versus* low glycemic index				
All studies	5	0.98	0.85–1.12	
Stratified by sex				
Male	3	0.88	0.80–0.97	0.02
Female	4	1.11	1.01–1.22	

[a] *P* value difference in RRs of all-cause mortality for Europe *versus* Asia ($P = 0.82$), Oceania *versus* Europe ($P = 0.19$), Oceania *versus* Asia ($P = 0.20$), United States *versus* Oceania ($P = 0.59$), United States *versus* Asia ($P = 0.29$), United States *versus* Europe ($P = 0.28$), United States *versus* Multicontinent ($P = 0.48$), Multicontinent *versus* Asia ($P = 0.88$), Multicontinent *versus* Europe ($P = 0.78$), and Multicontinent *versus* Oceania ($P = 0.30$).

[b] *P* value difference in RRs of CVD mortality for Europe *versus* Asia ($P = 0.69$), Multicontinent *versus* Europe ($P = 0.78$), United States *versus* Asia ($P = 0.96$), United States *versus* Europe ($P = 0.78$), Multicontinent *versus* Asia ($P = 0.49$), and United States *versus* Multicontinent ($P = 0.59$).

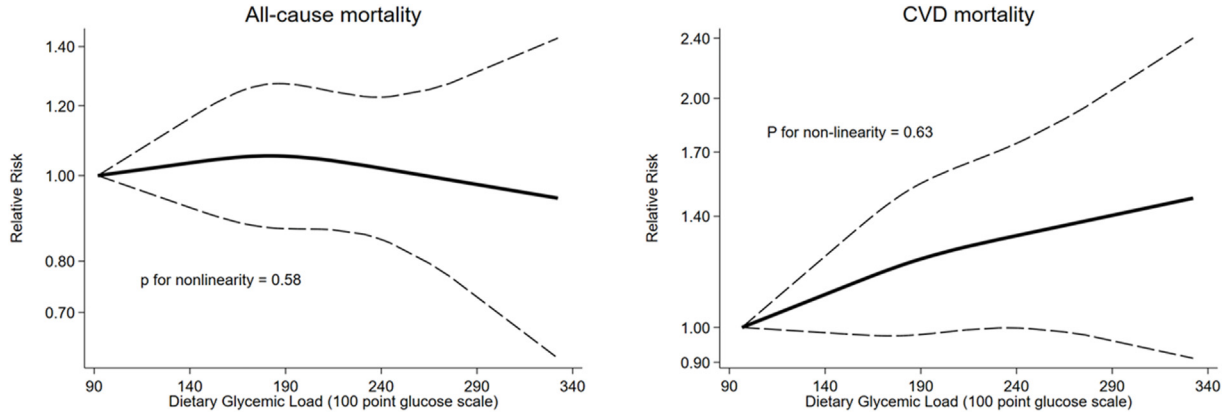

Fig. 6. Pooled dose–response association between glycemic load and mortality from all-causes and CVD. Solid lines represent relative risk (RR), dashed lines represent 95% confidence intervals.

3.3.1. Publication bias

We found no indication of publication bias for glycemic index and all-cause mortality (Begg's $p = 0.59$; Egger's $p = 0.79$), CVD mortality (Begg's $p = 0.64$; Egger's $p = 0.68$), stroke mortality (Begg's $p = 0.81$; Egger's $p = 0.83$), and cancer mortality (Begg's $p = 0.81$; Egger's $p = 0.53$). In addition, no evidence of publication bias was shown in the analysis for glycemic load and all-cause mortality (Begg's $p = 0.64$; Egger's $p = 0.64$), CVD mortality (Begg's $p = 0.21$; Egger's $p = 0.06$), stroke mortality (Begg's $p = 0.31$; Egger's $p = 0.16$), and cancer mortality (Begg's $p = 1.00$; Egger's $p = 0.41$).

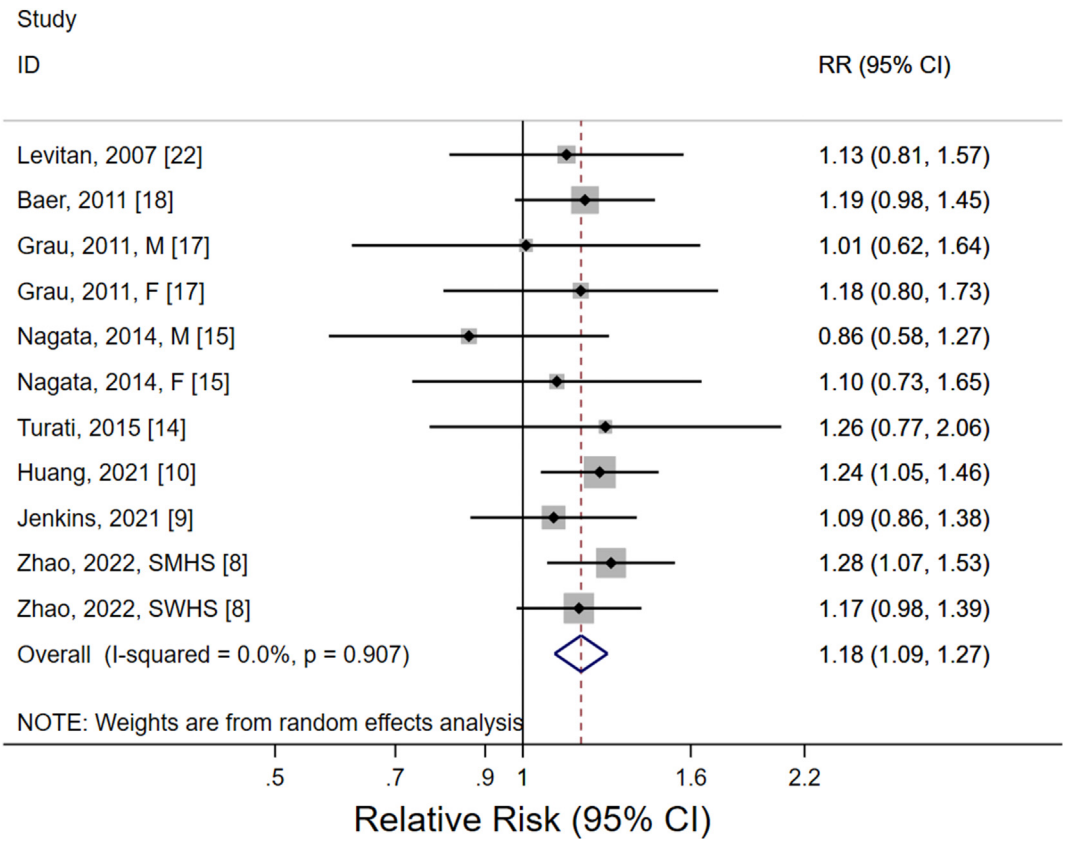

Fig. 7. Forest plots of the prospective cohort studies of CVD mortality for high *versus* low glycemic load.

4. Discussion

Findings from our meta-analysis of prospective cohort studies indicate higher mortality from all-causes (10% higher risk) and stroke (30% higher risk) in the comparison of high versus low glycemic index categories, and higher mortality from CVD (18% higher risk) and stroke (30% higher risk) in the comparison of high versus low glycemic load categories. There was a significant difference with sex for glycemic load and all-cause and cancer mortality, showing that high glycemic load was significantly associated with high risk of mortality from all-causes and cancer in women only. Further dose–response analyses showed significant non-linear associations of glycemic index and all-cause and CVD mortality.

Our results showing the increased risk of CVD mortality at high glycemic load were consistent with previous studies suggesting the positive association between glycemic load and risk of coronary heart disease. A meta-analysis including ten prospective cohort studies reported a 27% higher risk of coronary heart disease for the highest glycemic load quantile compared with the lowest [36]. The positive association between glycemic load and CVD mortality can be explained by various CVD risk factors which are affected by increased glycemic load. One randomized controlled trial including 244 women found that high glycemic load was associated with plasma C-reactive protein, a marker of systemic inflammation, which can increase the risk of ischemic heart disease [37]. On the other hand, meta-analyses of randomized controlled trials revealed that a low glycemic load diet could decrease BMI and fat mass and improve lipid profiles by reducing total and low density lipoprotein cholesterol in overweight or obese people [38,39]. A recent meta-analysis of 29 randomized controlled trials also showed that low glycemic index/load dietary patterns reduced other CVD risk factors, including HbA1c, fasting glucose, and systolic blood pressure in people with diabetes [40]. In addition, several observational studies have observed that a high glycemic load is associated with reduced high density lipoprotein cholesterol levels, which can reduce the risk of CVD [14]. Another piece of evidence to support the positive association between glycemic load and CVD is acarbose. Acarbose, the alpha-glucosidase inhibitor that effectively converts dietary carbohydrates to a low glycemic load form, has been observed to reduce the risk of CVD and hypertension in the randomized controlled trial in patients with impaired glucose tolerance [41].

Unlike glycemic load, the positive association between glycemic index and risk of CVD mortality was observed in women only. Our results on the glycemic index and risk of CVD mortality were not significant in overall population, but a 40% high risk of CVD mortality was found in women in the highest glycemic index category compared to the lowest. The difference by sex was also shown in the previous studies examining the association of glycemic index and CVD risk. According to a meta-analysis including ten studies, 26% increased risk of coronary heart disease was seen in women with high glycemic index [36]. On the other hand, there was a non-significant association between glycemic index and risk of coronary heart disease in men [36]. The reason for the sex-specific difference may be that women are more vulnerable to high glycemic index diets. A more significant increase in triglyceride levels and greater reduction in serum high-density lipoprotein were observed in women than men with a high dietary glycemic index [42]. Hypertriglyceridemia and a decrease in high-density lipoprotein cholesterol may carry an increased risk for CVD [43,44]. Our results of a dose–response meta-analysis of glycemic index and CVD mortality indicate an increased risk at glycemic indexes of 72.8 or higher

in the overall population. Therefore, CVD mortality of men may also be elevated by a high glycemic index. Further studies are required to identify the association between glycemic index and risk of CVD mortality.

Concerning stroke mortality, the association with the glycemic index or the glycemic load was found to have consistent results though a small number of studies were included in the analysis. Both glycemic index and load were observed to be positively associated with the risk of stroke mortality in the highest *versus* lowest meta-analysis. Diets with a high glycemic index may increase the risk of mortality from stroke by elevating the risk of diabetes [45] and glucose intolerance [19]. Accumulating evidence from observational studies showed that people with type 2 diabetes had a 76% higher risk of stroke compared with those without diabetes [46]. In addition, people with hyperglycemia had lower survival after an ischemic stroke than those with normal glycemia in both individuals with diabetes and without diabetes [47]. It can be speculated that a high glycemic index and load may increase the risk of stroke and worsen post-stroke outcomes, thereby increasing the risk of stroke mortality.

With regard to cancer mortality, the association with glycemic load showed conflicting results by sex in the current meta-analysis. In women, a positive association between glycemic load and risk of cancer mortality was observed, while a reduced risk of cancer mortality was found in men with a high glycemic index. It is speculated that these results were mostly derived from two studies involving large populations [8,18]. Previous observational studies on the association of glycemic load and the risk of cancer mostly reported non-significant results [48]. Hyperglycemia induced by high glycemic load could contribute to increase the risk of cancer through raising insulin-like growth factor-1 or causing inflammation or oxidative stress [49]. However, no association between hyperglycemia and the risk of cancer has been found in Mendelian randomization studies [50]. We also need to be cautious in interpreting the results because a relatively small number of studies were included in our meta-analysis on glycemic load and the risk of cancer mortality.

To the best of our knowledge, this is the first meta-analysis investigating the association between glycemic index and load and risk of all-cause and cause-specific mortality among people without disease. We included recent prospective cohort studies involving a large population [8–10], and thus the current meta-analysis has good statistical power for examining the association between glycemic index and load and risk of mortality from all-causes, CVD, cancer and stroke. In addition, the results can provide a preventive dietary strategy (i.e., for example, eating foods that raise blood glucose levels slowly rather than foods that raise blood glucose rapidly may be more beneficial to your health) to reduce premature death by examining the association between glycemic index and load and the risk of mortality in healthy people. There are some limitations that should be considered in this study. First, studies included in the meta-analysis differed in the cut-off levels of the glycemic index and load in the lowest and highest categories. However, we investigated changes in risk of mortality according to changes in glycemic index and load by performing a dose–response analysis as well as the highest *versus* lowest analysis. Second, most studies included in the meta-analysis assessed dietary intake using a food frequency questionnaire that was not specially designed to calculate the glycemic index and load. Also, dietary intakes that were self-reported through the food frequency questionnaire are likely to be misclassified. Fortunately, misclassification of dietary intake leads to null results, so the association between glycemic index and load and mortality risk is less likely to be overestimated. Lastly, observational studies have a problem with residual confounding, although many studies included in this meta-analysis adjusted potential confounders including BMI, smoking, energy intake, and alcohol consumption. Confounders can influence the results by leading the estimate to either increase or decrease, depending on the presence or absence of correlation [51]. Meanwhile, over-adjustment may also affect the results by reducing significant associations. Markers such as the contents of dietary fiber and whole grains influence the glycemic index [52]. Many studies included in this meta-analysis controlled for dietary fiber [9,13,16,18–20,22].

In conclusion, the current meta-analysis of prospective cohort studies indicated that high glycemic index and load was associated with an increased risk of mortality from CVD and stroke. Further well-designed large prospective cohort studies are warranted to provide more definitive evidence in subgroups.

Author's contributions

The authors' responsibilities were as follows— YK and YJ: Study concept and design; YK: data collection and statistical analysis; YK: writing—original draft; YJ: writing—review and editing; YJ: study supervision; YK and YJ: Interpretation of the data, critical revision of the paper for important intellectual content and approval of the final paper for submission; and all authors: read and approved the final manuscript.

Funding

This work was supported by the National Research Foundation of Korea, funded by the Ministry of Science, ICT and Future Planning (Grant number: NRF-2021R1F1A1050847). Funders had no role in the study design, data collection and analysis, decision to publish, or preparation of the manuscript.

Data availability

Data are available from the corresponding author upon reasonable request.

Conflicts of interest

The authors declare no potential conflicts of interest.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.clnu.2023.08.014.

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