ISSN: (Print) (Online) Journal homepage: <https://www.tandfonline.com/loi/bfsn20>

## Longitudinal association of dietary carbohydrate and the risk cardiovascular disease: a dose-response meta-analysis

Noushin Mohammadifard, Marjan Mansourian, Somayyeh Firouzi, Marzieh Taheri & Fahimeh Haghigatdoost

To cite this article: Noushin Mohammadifard, Marjan Mansourian, Somayyeh Firouzi, Marzieh Taheri & Fahimeh Haghigatdoost (2021): Longitudinal association of dietary carbohydrate and the risk cardiovascular disease: a dose-response meta-analysis, Critical Reviews in Food Science and Nutrition, DOI: [10.1080/10408398.2021.1900057](https://doi.org/10.1080/10408398.2021.1900057)

To link to this article: <https://doi.org/10.1080/10408398.2021.1900057>



[View supplementary material](#)



Published online: 19 Mar 2021.



[Submit your article to this journal](#)



Article views: 92



[View related articles](#)



CrossMark

[View Crossmark data](#)



REVIEW

## Longitudinal association of dietary carbohydrate and the risk cardiovascular disease: a dose-response meta-analysis

Noushin Mohammadifard<sup>a</sup> , Marjan Mansourian<sup>b</sup>, Somayyeh Firouzi<sup>c</sup>, Marzieh Taheri<sup>d</sup>, and Fahimeh Haghigatdoost<sup>e</sup>

<sup>a</sup>Isfahan Cardiovascular Research Center, Cardiovascular Research Institute, Isfahan University of Medical Sciences, Isfahan, Iran;

<sup>b</sup>Epidemiology and Biostatistics Department, Health School, Isfahan University of Medical Sciences, Isfahan, Iran; <sup>c</sup>Department of Dietetics, Grafton Base Hospital, Grafton, NSW, Australia; <sup>d</sup>Interventional Cardiology Research Center, Cardiovascular Research Institute, Isfahan University of Medical Sciences, Isfahan, Iran; <sup>e</sup>Hypertension Research Center, Cardiovascular Research Institute, Isfahan University of Medical Sciences, Isfahan, Iran

### ABSTRACT

Previous findings on the association of dietary carbohydrate with cardiovascular disease (CVD) events and mortality are inconsistent. We aimed to assess the relationship between dietary carbohydrate and the incidence of cardiovascular events and mortality. A comprehensive literature search of MEDLINE (PubMed), Scopus, ISI Web of Science, and EMBASE, was performed up to June 2019. Prospective cohort studies which examined dietary carbohydrate in relation to fatal and non-fatal myocardial infarction, fatal and non-fatal stroke, heart failure, and sudden cardiac death were included in our study. Summary HRs and 95% CIs were estimated using a random-effects model. A total of 19 cohort studies including 15,663,111 participants were identified. Combining 27 effect sizes with 1,577,225 CVD cases led to a significant association between dietary carbohydrate and total CVD events ( $HR = 1.05$ , 95% CI: 1.00, 1.10;  $I^2 = 38.5\%$ ), but no association was observed between dietary carbohydrate and CVD mortality ( $HR = 1.02$ ; 95% CI: 0.91, 1.14;  $I^2 = 27.1\%$ , derived from 8 effect sizes with 106,412 events), and CHD events ( $HR = 1.03$ , 95% CI: 0.98, 1.09;  $I^2 = 46.6\%$ , derived from 18 effect sizes with 1,549,281 events). Moreover, using 8 effect sizes with 6,829 cases, higher carbohydrate intake was associated with increased risk of stroke ( $HR = 1.13$ ; 95% CI: 1.01, 1.27;  $I^2 = 0.0\%$ ). In subgroup analysis by sex, higher carbohydrate intake increased the risk of total CVD events ( $HR: 1.10$ ; 95% CI: 1.03, 1.17;  $I^2 = 0.0\%$ ), and CHD ( $HR: 1.10$ ; 95% CI: 1.01, 1.20;  $I^2 = 15.0\%$ ), but not stroke and CVD mortality in women. No significant association was found in men. Low- to very-low-certainty evidence suggests that higher carbohydrate intake is directly but slightly associated with CVD and stroke risk, while no association was found for CHD and CVD mortality. We also found sex-specific associations.

### KEYWORDS

Carbohydrate; CVD; CHD; mortality; dose response meta-analysis

## Introduction

Cardiovascular diseases (CVD) are the first leading cause of mortality and disability worldwide (Yusuf et al. 2014; Lennon, Claussen, and Kuersteiner 2018). Over the last decades, investigators established a clear relationship between diet and CVD (Mozaffarian 2016). Nutritional behavior is one of the most important modifiable risk factors for CVD (Dalen and Devries 2014). Carbohydrates can play a major role in health outcomes, because they are the main source of energy intake in all communities (Blaak 2016). As decreasing carbohydrate intake may be associated with increased intake of saturated fatty acids (SFA), no current guideline exists to recommend low carbohydrate diet (Eckel et al. 2014), and the 2015–2020 dietary guidelines for Americans recommends that 45–65% of total daily energy intake should be met by carbohydrates (You 2015).

Some randomized clinical trials (RCTs) demonstrated an improvement in cardiovascular risk factors by a low carbohydrate diet (Foster et al. 2003; Gardner et al. 2007). However, these studies have not investigated whether it was the effect of low carbohydrate intake or the subsequent energy intake reduction (Hu et al. 2014), examined a small number of participants for a short duration and may have poor adherence with a high rate of attrition (Foster et al. 2003; Gardner et al. 2007). The Women's Health Initiative trial recently found no beneficial effects on CVD risk and total mortality in those who met 24% and 58% of their daily energy requirement from fat and carbohydrate compared with those with 35% and 48%, respectively (Prentice et al. 2017). Meta-analysis of the RCTs indicated that a low carbohydrate diet vs. a low fat diet decreased body weight and triglycerides, but increased LDL-C levels (Mansoor et al. 2016).

**CONTACT** Marzieh Taheri  [taheri2008.marzieh@gmail.com](mailto:taheri2008.marzieh@gmail.com)  Interventional Cardiology Research Center and Hypertension Research Center, Cardiovascular Research Institute, Isfahan University of Medical Sciences, Isfahan, Iran; Fahimeh Haghigatdoost  [f\\_haghigatdoost@yahoo.com](mailto:f_haghigatdoost@yahoo.com)  Interventional Cardiology Research Center and Hypertension Research Center, Cardiovascular Research Institute, Isfahan University of Medical Sciences, Isfahan, Iran.

 Supplemental data for this article can be accessed at <https://doi.org/10.1080/10408398.2021.1900057>.

Another meta-analysis of cohort studies illustrated that total SFA compared with total carbohydrate intake had no significant association with coronary heart disease (CHD) or CVD risk (Siri-Tarino et al. 2010). Recent evidence from Prospective Urban Rural Epidemiological study on more than 135,000 adults in 18 countries around the world indicated that high carbohydrate intake was associated with increased all-cause mortality risk, but not cardiovascular events (Dehghan et al. 2017).

Meta-analysis of prospective cohort studies showed that glycemic index and glycemic load were associated with increased CHD risk (Mirrahimi et al. 2012). However, to the best of our knowledge, there have been no meta-analysis of observational studies which has specifically examined the association between carbohydrate intake and the incidence of CVD events. Given that carbohydrates meet a wide range of daily energy intake in different populations, as well as Acceptable Macronutrient Distribution Ranges (AMDR) for carbohydrates, the associations may differ by the internal reference range for the studied populations. Moreover, the association between carbohydrates and cardiovascular diseases could depend on the foods that are replaced with or for carbohydrate. Therefore, due to the necessity of more evidence to help to guide recommendations in terms of optimal carbohydrate intake, we aimed to review and perform a dose-response meta-analysis on observational studies assessing the relationship between carbohydrate intake and cardiovascular risk.

## Methods

The search results reported the studies carried out up to June 2019. To find relevant articles searches were made in MEDLINE via PUBMED ([www.ncbi.nlm.nih.gov/pubmed/](http://www.ncbi.nlm.nih.gov/pubmed/)); National Library of Medicine, Bethesda, MD), Scopus, ISI Web of Science and Google Scholar. Searches were not restricted by language, but limited only to human studies. Three groups of medical subject headings (MeSH) and non-MeSH keywords were selected to search the databases: keyword group 1: “dietary carbohydrate”, “carbohydrate”; keyword group 2: “cardiovascular disease”, “heart failure”, “myocardial infarction”, “heart arrest”, “stroke”, “cardiovascular”, “heart disease”, “myocardial ischemia”, “coronary artery disease”, “coronary heart disease”, “atherosclerosis”, “hypertension”; and keyword group 3: “prospective”, “longitudinal”, “cohort”, “cohort studies”.

### Inclusion criteria

For the present systematic review and meta-analysis, we used: (1) prospective cohort studies, (2) studies reporting hazard ratio (HR) or risk ratio (RR) for CVD events (fatal and non-fatal myocardial infarction (MI), fatal and non-fatal stroke, heart failure, and sudden cardiac death) across the categories of carbohydrate intake and (3) studies conducted on adult populations aged  $\geq 18$  years. Three investigators (NM, FH and MT) screened the abstracts/titles and full texts of the articles that seemed to meet the inclusion criteria to

identify relevant articles, which were then retrieved for further screening. A reference list of related papers was also checked for any missing related articles. In the case of multiple publications from the same study, we only selected the most recent or informative.

### Exclusion criteria

We excluded: (1) studies evaluating only the glycemic index, glycemic load, any carbohydrate sources and carbohydrate score as a carbohydrate indicator, (2) prospective cohort studies that did not report hazard ratio (95% confidence interval) of carbohydrate intake, (3) papers reporting the results of the same studies, and (4) studies which were conducted among diabetic patients.

### Data extraction

The study characteristics included the last name of the first author, the year of publication, the country in which the study was carried out, the mean/range of subjects' age, the number of participants by sex, the study name, the mean carbohydrate intake (grams per day/percentage of daily energy or categorical based on tertiles, quartiles, quintiles or deciles), dietary assessment method, maximally-adjusted HRs or RRs and their 95% CIs and adjusted factors.

### Quality assessment

The Newcastle Ottawa Scale (NOS) for prospective cohort studies was applied to evaluate the quality of studies by two reviewers (MT and FH). (Wells et al. 2014) The NOS consists of three main domains (i.e. population selection, comparability, and outcome) and eight questions. The possible score achieved by cohort studies ranges from zero to nine.

### Statistical analysis

The criteria for meta-analysis were outcomes reported as proportional hazard ratios (HRs) or risk ratios (RRs) and 95% CIs. Q test and  $I^2$  statistic were used to evaluate the heterogeneity of studies. The level of significance was set to 0.05 for the Q test. When there was high heterogeneity between-studies ( $>50\%$ ), a random-effects model was used. Otherwise, the fixed-effect model was used. Moreover, subgroup analysis was performed to explore heterogeneity. Subgroup analyses were conducted on the basis of sex (male/female/both), adjustment for blood pressure (yes/no), adjustment for diabetes (yes/no), adjustment for family history of CVD (yes/no), adjustment for protein intake (yes/no), adjustment for fat intake (yes/no), and study duration ( $\geq$  median vs.  $\leq$  median). Between subgroup heterogeneity was tested using fixed effect model.

Sensitivity analysis was performed to determine the influence of each individual study on the pooled results by omitting each study. Publication bias was assessed by funnel plot. Begg's and Egger's tests were used to measure the possible publication bias.

Furthermore, a 1-stage fixed-effects dose-response meta-analysis with a restricted cubic spline between carbohydrate percentage of energy and risk of CVD events was performed using the method proposed by Xu and Doi (Xu and Doi 2018). The model uses the inverse variance weighted least squares regression with cluster robust error variances (REMR model). Restricted cubic splines with three knots at fixed percentiles of 10%, 50%, and 90% throughout the entire distribution of carbohydrate percentage of energy were used. This analysis was performed when there were at least three studies or subgroups of study for a CVD event and also for studies that reported a carbohydrate percentage of energy for at least two quantitative classifications. Statistical analyses were performed using Stata software (Version 14.0; StataCorp). The significance level was set as 0.05 (two-sided).

## Results

We retrieved 2485 articles from the literature search. After removing 938 duplicated studies, we reviewed 1547 and excluded 1391 papers which did not meet our inclusion criteria. The remaining 156 papers were identified for full text review. Of those, we excluded 137 studies due to lack of data on CVD events ( $n=72$ ), assessing glycemic index and load or carbohydrate score as independent variables ( $n=59$ ), examining only diabetic individuals ( $n=3$ ), and using a low carbohydrate diet ( $n=3$ ). Figure 1 shows the study selection process. Finally, 19 cohort studies (14, 17–34), with a total of 15,663,111 adults, were eligible for inclusion in our analysis.

Table 1 illustrates the characteristics of the 19 included prospective cohort studies in the systematic review. Briefly, the participants were aged 20 and over in these studies. The follow-up year ranged between 4 and 30 years. Six studies were conducted in the USA (Esrey, Joseph, and Grover 1996; Liu et al. 2000; Oh et al. 2005; Jakobsen et al. 2009; Li et al. 2015; AlEssa et al. 2018), eight in Europe (Beulens et al. 2007; Sieri et al. 2010; Burger et al. 2011; Wallström et al. 2012; Sieri et al. 2013; Simila et al. 2013; Sonestedt et al. 2015; Ho et al. 2020), four in Asia (Oba et al. 2010; Yu et al. 2013; Rebello et al. 2014; Yu et al. 2016), and one study was a multicenter study (Dehghan et al. 2017). The Prospective Urban Rural Epidemiology (PURE) study was carried out in 18 countries from five continents (Dehghan et al. 2017).

### Carbohydrate intake and CVD

In total, 19 studies with 27 effect sizes provided data on the association between highest and lowest intake of carbohydrate and total CVD events (14, 17–34). The pooled HR for the highest compared with the lowest level of carbohydrate intake was 1.05 (95% CI: 1.00, 1.10) (Table 2). The between-studies heterogeneity was significant ( $I^2 = 38.5\%$ ,  $P = 0.023$ ). The subgroup analysis based on sex was done to find the heterogeneity source (Figure 2A). We found an increase in the risk of CVD events by 10% (HR: 1.10; 95% CI: 1.03,

1.17) in women (Figure 2A) (Liu et al. 2000; Oh et al. 2005; Beulens et al. 2007; Jakobsen et al. 2009; Oba et al. 2010; Sieri et al. 2010; Burger et al. 2011; Wallström et al. 2012; Yu et al. 2013; Rebello et al. 2014; Li et al. 2015; Yu et al. 2016; AlEssa et al. 2018). Between-study heterogeneity disappeared in this subgroup analysis ( $I^2 = 0.0\%$ ,  $P = 0.563$ ). However, there was no significant association in men (Figure 2A) (Jakobsen et al. 2009; Oba et al. 2010; Sieri et al. 2010; Burger et al. 2011; Simila et al. 2013; Yu et al. 2013; Rebello et al. 2014; Li et al. 2015; AlEssa et al. 2018). No evidence of heterogeneity was found in men ( $I^2 = 38.5\%$ ,  $P = 0.111$ ). The pooled estimate from the linear dose-response of CVD risk was statistically non-significant 0.99 (95% CI: 0.99, 1.00) per unit (% of daily energy) increase in dietary carbohydrate in 9 studies, with the 55 effect sizes from all categories of carbohydrate intake (Oh et al. 2005; Wallström et al. 2012; Simila et al. 2013; Yu et al. 2013; Li et al. 2015; Sonestedt et al. 2015; Dehghan et al. 2017; AlEssa et al. 2018; Ho et al. 2020) (Figure 1A, supplementary material). There was also no significant nonlinear association between dietary carbohydrate and risk of CVD which were evaluated in nine studies with 55 HRs (HR: 1.01, 95% CI: 0.99, 1.01,  $P$ -nonlinearity = 0.092) (Oh et al. 2005; Wallström et al. 2012; Simila et al. 2013; Yu et al. 2013; Li et al. 2015; Sonestedt et al. 2015; Dehghan et al. 2017; AlEssa et al. 2018; Ho et al. 2020) (Figure 1A, supplementary material).

### Carbohydrate intake and CHD

We evaluated the association between carbohydrate intake and CHD with 18 HRs from 11 studies (Esrey, Joseph, and Grover 1996; Liu et al. 2000; Jakobsen et al. 2009; Sieri et al. 2010; Burger et al. 2011; Simila et al. 2013; Yu et al. 2013; Rebello et al. 2014; Li et al. 2015; Dehghan et al. 2017; AlEssa et al. 2018). The findings revealed no significant association between dietary carbohydrate and CHD events (HR = 1.03; 95% CI: 0.98, 1.09) (Figure 2B). The between-studies heterogeneity was significant ( $I^2 = 46.6\%$ ,  $P = 0.016$ ). Subgroup analysis based on sex (Table 2 and Figure 2C) showed that there was a significant association between carbohydrate intake and CHD in women (HR: 1.10; 95% CI: 1.01, 1.20) (Liu et al. 2000; Jakobsen et al. 2009; Sieri et al. 2010; Burger et al. 2011; Yu et al. 2013; Rebello et al. 2014; Li et al. 2015; AlEssa et al. 2018), but not men (Jakobsen et al. 2009; Sieri et al. 2010; Burger et al. 2011; Simila et al. 2013; Yu et al. 2013; Rebello et al. 2014; Li et al. 2015; AlEssa et al. 2018). There was no between-studies heterogeneity in women ( $I^2 = 15.0\%$ ,  $P = 0.312$ ). Sensitivity analysis was carried out and no significant change was observed after removing each study.

### Carbohydrate intake and stroke

The association of carbohydrate intake and stroke was examined with 8 effect sizes from 6 studies (Oh et al. 2005; Oba et al. 2010; Burger et al. 2011; Sieri et al. 2013; Yu et al. 2016; Dehghan et al. 2017). The pooled HR

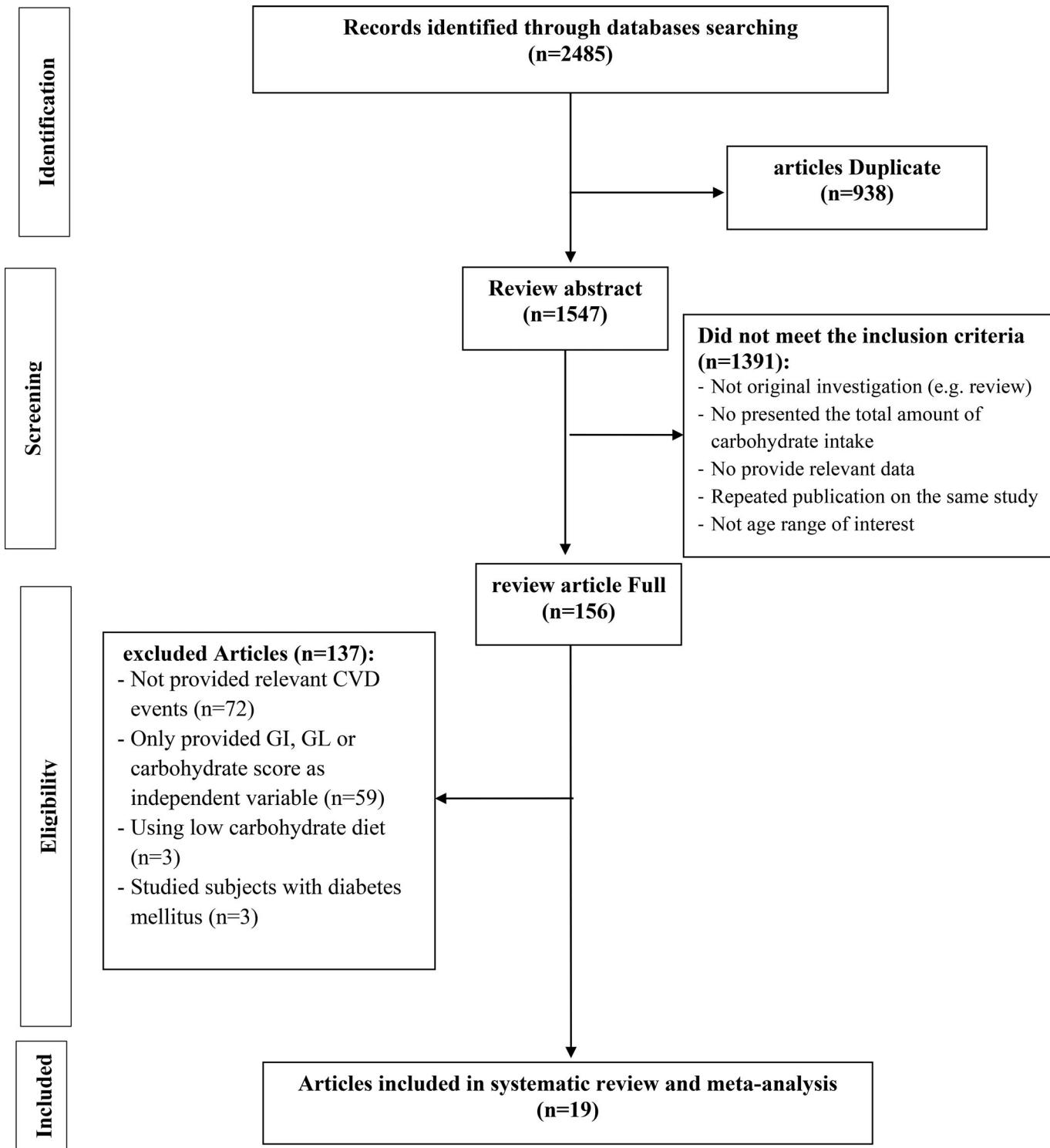


Figure 1. The flow chart of study selection.

obtained a significant 13% increase in stroke incidence by carbohydrate intake ( $HR = 1.13$ ; 95% CI: 1.01, 1.27). There was no evident heterogeneity between studies ( $I^2 = 0.0\%$ ,  $P = 0.617$ ) (Figure 2B). In subgroup analysis based on sex, a null association was observed in all subgroups (Table 2, Figure 2C). Sensitivity analysis revealed that excluding of four studies disappeared the significant association (Oh et al. 2005; Sieri et al. 2010; Yu et al. 2013; Dehghan et al. 2017).

#### Carbohydrate intake and CVD mortality

Combining of 8 HRs from 5 studies (Esrey, Joseph, and Grover 1996; Oba et al. 2010; Sieri et al. 2013; Rebello et al. 2014; Yu et al. 2016; Dehghan et al. 2017) provided no significant association between dietary carbohydrate and CVD mortality ( $HR = 1.02$ ; 95% CI: 0.91, 1.14) (Figure 2D). No evidence of between-study heterogeneity was indicated ( $I^2 = 27.1\%$ ,  $P = 0.212$ ). In subgroup

**Table 1.** Characteristics of studies included in the meta-analysis.

Study	Country	Age	Number of participants			Study name	Follow-up year	Dietary assessment method	Outcomes	Adjustment	Study quality score
			Men	women	Total						
Wallström et al. (2012)	Sweden	44–73	8139	12,535	20,674	Malmo Diet and Cancer Cohort	13.5	FFQ & Diet history (7-day)	CVD (fatal or non-fatal MI, CHD mortality, cerebral infarction, ischemic stroke)	Age, total energy intake, season, BMI, smoking, education, alcohol, SBP, antihypertensive treatment, antihyperlipidemic treatment, leisure time physical activity and energy-adjusted dietary fiber	8
Simila et al. (2013)	Finland	50–69	21,955	—	21,955	The Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study	19	FFQ	CHD (first acute non-fatal MI or CHD death)	Age, intervention group, smoking, BMI, physical activity, serum total and HDL-C, BP and intakes of energy, alcohol, total fat, protein, magnesium and potassium	9
AlEissa et al. (2018)	USA	M = 40–75 F = 30–55	51,529	121,701	173,230	NHS and HPES	M = 26 F = 28	FFQ	CHD, ischemic stroke	Age, BMI, family history of CHD, smoking, alcohol, physical activity, multivitamin use, aspirin use, vitamin E use, race, total energy, PUFA to SFA ratio and trans fat	8
Liu et al. (2000)	USA	38–63	—	75,521	75,521	NHS	10	FFQ	CHD (fatal and non-fatal MI)	Residual energy adjusted carbohydrate, age, BMI, smoking, alcohol, parental family history of MI before the age of 60 y, self-reported history of hypertension or history of high cholesterol, menopausal status, postmenopausal hormone replacement, aspirin use and use of multiple vitamin or vitamin E supplement, physical activity, protein intake, SFA intake, PUFA intake and trans fats intake, fiber intake, dietary vitamin E and folate intake and energy intake	8
Yu et al. (2016)	China	40–70	—	64,328	64,328	—	12	FFQ	Age, education, smoking, BMI, family history of	8	

(continued)

**Table 1.** Continued.

Study	Country	Age	Number of participants			Study name	Follow-up year	Dietary assessment method	Outcomes	Adjustment	Study quality score
			Men	women	Total						
Yu et al. (2013)	China	40–74	52,512	64,854	117,366	Shanghai Women's Health Study	M = 5.4 F = 9.8	FFQ	CHD	Age, education, income, smoking, alcohol intake, physical activity, WHR, history of hypertension, and disease history	8
Oh et al. (2005)	USA	30–55	—	78,779	78,779	NHS	18	FFQ	Stroke	Age, BMI, smoking, alcohol intake, parental history of MI, history of hypertension, hypercholesterolemia and diabetes	7
Jakobsen et al. (2009)	USA	47–61	—	—	344,696	AHS, ARIC, ATBC, FMC, GPS, NHS, HPS, IIHD, IWHS, VIP & WHS	4–10	FFQ or Diet history	CHD and CHD mortality	Intakes of MUFA, PUFA, trans fat, protein, glycemic carbohydrate, energy, smoking, BMI, education, alcohol intake and history of hypertension	8
Rebello et al. (2014)	China	45–74	455,504	17,753	63,257	The Singapore Chinese Health Study Cohort	18	FFQ	CHD mortality	Age, year of interview, father's dialect, and total energy intake, cigarette smoking, alcohol consumption, physical activity, sleep duration, education level, BMI, history of hypertension, and, for women only, menopausal status and hormone replacement therapy use, dietary	9

Sieri et al. (2013)	Italy	35–75	13,646	30,453	44,099	EPIC	10.9	FFQ	Stroke	Energy adjusted by residual method; age, sex, education, smoking, BMI, alcohol intake, non-alcohol energy intake, cereal fiber intake, SFA, MUFA, PUFA and physical activity	9
Sonenstedt et al. (2015)	Sweden	44–74	10,049	16,396	26,445	Malmö Diet and Cancer Study	14	Diet history	CVD (fatal or non-fatal MI, CHD and stroke)	Age, sex, season, diet method version, energy intake, BMI, smoking, alcohol intake, leisure-time physical activity and education	9
Beulens et al. (2007)	Netherlands	49–70	–	17,357	17,357	EPIC	7–11	FFQ	CVD	Age, hypertension, hypercholesterolemia, smoking, BMI, SBP, physical activity, menopausal status, hormone replacement therapy use, oral contraceptives use, alcohol intake, energy intake, energy-adjusted intake of vitamin E, protein, fiber, folate; SFA, MUFA and PUFA	8
Li et al. (2015)	USA	M = 40–75 F = 30–75	42,908	84,628	127,536	NHS and HPFS	NHS: >30 HPFS: 24	FFQ	Non-fatal MI and CHD mortality	Energy intake, the energy contribution from protein, cholesterol intake, alcohol intake, smoking, BMI, physical activity, use of vitamins and aspirin, family history of MI and diabetes, hypercholesterolemia and hypertension, intake of fruits and vegetables	7
Sieri et al. (2010)	Italy	35–74	15,171	32,578	47,749	EPICOR Study	7.9	FFQ	Fatal and non-fatal CHD	Non-alcohol energy intake, hypertension, smoking, education, alcohol intake, BMI, fiber intake and physical activity	8
Oba et al. (2010) Dehghan et al. (2017)	Japan Multicenteris	≥35 35–70	12,561	15,301	27,862 Overall (n = 335) China	Takayama study PURE	7 7.4	FFQ FFQ	Stroke mortality CVD events (fatal and non-fatal MI, stroke and heart failure)	Age Education, WHR, smoking, physical activity, diabetes, urban or rural	7 7

(continued)

Table 1. Continued.

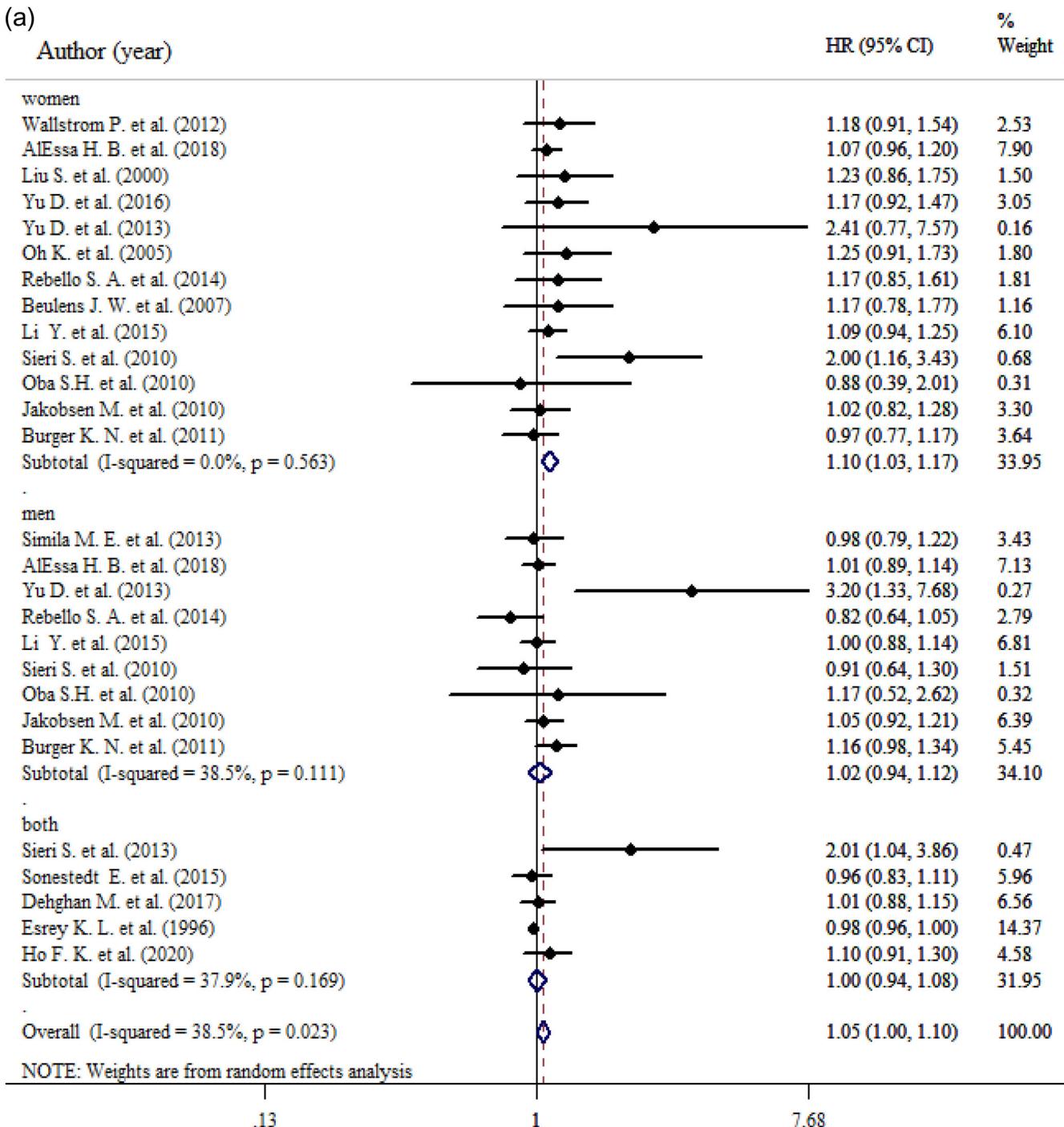
Study	Country	Age	Number of participants		Study name	Follow-up year	Dietary assessment method	Outcomes	Adjustment	Study quality score
			Men	women						
Burger et al. (2011)	Netherlands	21–64	8855	10,753	19,608	EPIC-MORGEN	11.9	FFQ	CHD, stroke	8
Erey, Joseph, and Grover (1996)	USA	Group 1—30–59y, group 2—60–79y	Group 1—2071 Group 2—282	Group 1—339 Group 2—621	Group 1—1854 Group 2—339	Group 1—3925 American Lipid Research Clinics Prevalence Follow-up Study	12.4	24-hour recall	CHD mortality	7
Ho et al. (2020)	UK	37–73 y	109,362	86,296	195,658	UK Biobank	10.6	24-hour recall	CVD	8

BMI: body mass index; CABG: coronary artery bypass grafting; CHD: coronary heart disease; CRP: C-reactive protein; CVD: cardiovascular disease; DBP: diastolic blood pressure; FFQ: food frequency questionnaire; HDL: high density lipoprotein; MI: myocardial infarction; MUFA: mono unsaturated fatty acid; PUFA: poly unsaturated fatty acid; SFA: saturated fatty acid; SBP: systolic blood pressure; WHR: waist circumference; WHR: waist to hip ratio.

**Table 2.** Hazard ratio and 95% confidence interval of carbohydrate intake and the risk of cardiovascular disease based on sex and events.

		N	HR (95%CI)	p- Heterogeneity between subgroups	$\chi^2$	Heterogeneity chi-squared	P-value (Heterogeneity test)	Egger	Begg	Ntrim	Trim HR	Trim
CVD	overall	27	1.05(1.00,1.10)		38.5%	42.28	0.023	T = 4.42, p < 0.001	Z = 1.83, p = 0.067	9	1.02 (0.97, 1.07)	Z = 0.69, p = 0.493
	Men	9	1.02(0.94,1.12)	0.002	38.5%	13.02	0.111					
	women	13	1.10(1.03,1.17)		0.0	10.6	0.563					
	both	5	1.00(0.94,1.08)		37.9%	6.44	0.169					
CHD	overall	18	1.03(0.98,1.09)		46.6%	31.84	0.016					
	Men	8	1.02(0.93,1.13)	0.011	49.5%	13.85	0.054					
	women	8	1.10(1.01,1.20)		15.0%	8.24	0.312					
	both	2	0.98(0.96,1.00)		0.0%	0.66	0.418					
Stroke	overall	8	1.13(1.01,1.27)		0.0	5.35	0.617					
	Men	2	1.04(0.75,1.46)	0.858	0.0	0.09	0.762					
	women	4	1.12(0.95,1.33)		0.0	2.05	0.562					
	both	2	1.37(0.79,2.39)		65.5%	2.90	0.088					
Mortality	overall	8	1.02(0.91,1.14)		27.1%	9.60	0.212					
	Men	2	0.85(0.67,1.07)	0.273	0.0	0.68	0.410					
	women	3	1.13(0.87,1.46)		0.0	0.40	0.818					
	both	3	1.11(0.88,1.40)		66.3	5.93	0.052					
Mortality	CHD	3	0.98(0.86,1.00)	0.138	37.0%	3.17	0.205					
	Stroke	4	1.26(0.90,1.77)		0.0	2.91	0.406					
CVD	CVD Type	CHD	18	1.03(0.98,1.09)	0.029	46.4%	31.84					
		Stroke	8	1.13(1.01,1.27)		0.0	5.35	0.016				
Duration	<=median(=11.7y)	14	1.14(1.03,1.27)	0.003	38.0	20.96	0.719					
	>median	13	1.00(0.97,1.02)		4.6	12.58	0.074					
Adj. HTN	Htn adj.	20	1.06(1.00,1.13)	0.336	46.7	35.62	0.040					
Adj. DM	No htn adj.	7	1.03(0.96,1.09)		0.0	5.74	0.012					
	DM adj.	10	1.07(0.98,1.16)	0.162	47.0	47.0	0.453					
	No DM adj.	17	1.04(0.98,1.09)		26.0	21.62	0.049					
Adj. family history	Yes	8	1.08(0.99,1.17)	0.025	36.0	21.62	0.156					
of CVD	No	19	1.03(0.98,1.09)		36.0	10.98	0.140					
Adj. protein	protein adj.	5	0.98(0.96,1.00)	0.003	31.6	26.31	0.093					
	No protein adj.	22	1.07(1.01,1.14)		0.0	2.86	0.581					
Adj. Fat	Fat adj.	17	1.05(0.99,1.11)	0.104	31.5	30.64	0.080					
	No Fat adj.	10	1.06(0.97,1.14)		43.7	28.43	0.028					
					19.7	11.21	0.261					

\*HR (95%CI): Hazard ratio (95% confidence interval); CVD: cardiovascular disease; CHD: coronary heart disease; HTN: hypertension; DM: diabetes mellitus.



**Figure 2.** Forest plots of the association between dietary carbohydrate and risk of cardiovascular disease by sex (A), CVD event (coronary heart disease and stroke) (B), CVD event and sex (C), and cardiovascular mortality by sex (D) in cohort studies. Diamonds represent pooled estimates from random-effects analysis.

analysis by sex, no significant association was illustrated in either men or women, or in both sexes (Figure 2D). Sensitivity analysis was performed and exclusion of any study at a time did not influence the overall estimate. In a subgroup analysis based on CVD events, neither CHD mortality nor stroke mortality was related to carbohydrate intake (Table 2). There were small but significant linear and non-linear associations between dietary carbohydrate and risk of CVD mortality which were evaluated in two studies with 3 HRs (linear: HR: 0.99, 95% CI: 0.99, 1.00, *P*-linearity =

0.031 and non-linear: HR: 1.02, 95% CI: 1.00, 1.04, *P*-nonlinearity = 0.042) (Rebello et al. 2014; Dehghan et al. 2017) (Figure 1B, supplementary material).

#### Sensitivity analysis and publication bias

The sensitivity analysis indicated that removing two studies (Sieri et al. 2010; Yu et al. 2013) removed the significance. We found an asymmetry in funnel plot (Figure 3) and Egger's (*P* = 0.067) and Egger's (*P* < 0.0001) tests illustrated evidence

(b)

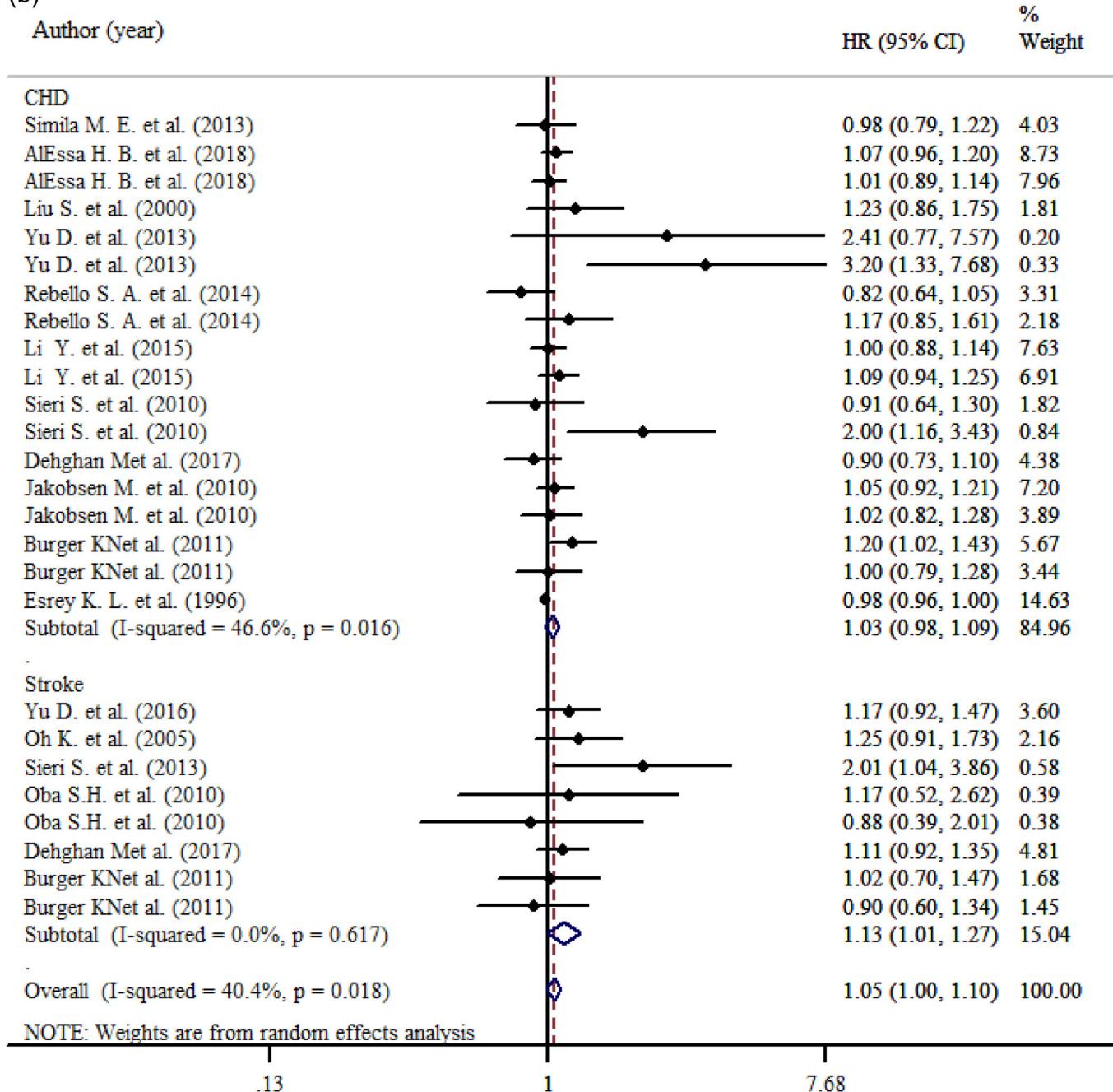


Figure 2. Continued.

of publication bias. Based on trim and fill analysis, 9 additional studies were required to balance the asymmetry (Table 2). Adjusted values based on trim and fill analysis also indicated a null association between dietary carbohydrate intake and a risk of CVD events (HR: 1.02; 95% CI: 0.97, 1.07).

We also performed further subgroup analysis based on follow-up duration, and adjustment for confounders including hypertension/blood pressure, diabetes mellitus, family history of CVD, dietary protein, and fat intake (Table 2). We found a higher risk for incident CVD events in studies with shorter follow-up duration or in those without adjustment for protein intake. The associations in other subgroups were statistically non-significant.

## Discussion

The current meta-analysis suggests that the association of total daily carbohydrate intake with CVD varies by the type of CVD event and sex. We found that higher carbohydrate intake was associated with a slight increase in the risk of CVD and stroke in the whole population, as well as CHD and CVD in women, without any significant association in men. The results of dose-response analysis also confirmed the null association between carbohydrate intake and CVD risk, except for the slightly, but unlikely clinically, significant linear and nonlinear association between carbohydrate intake and CVD mortality.

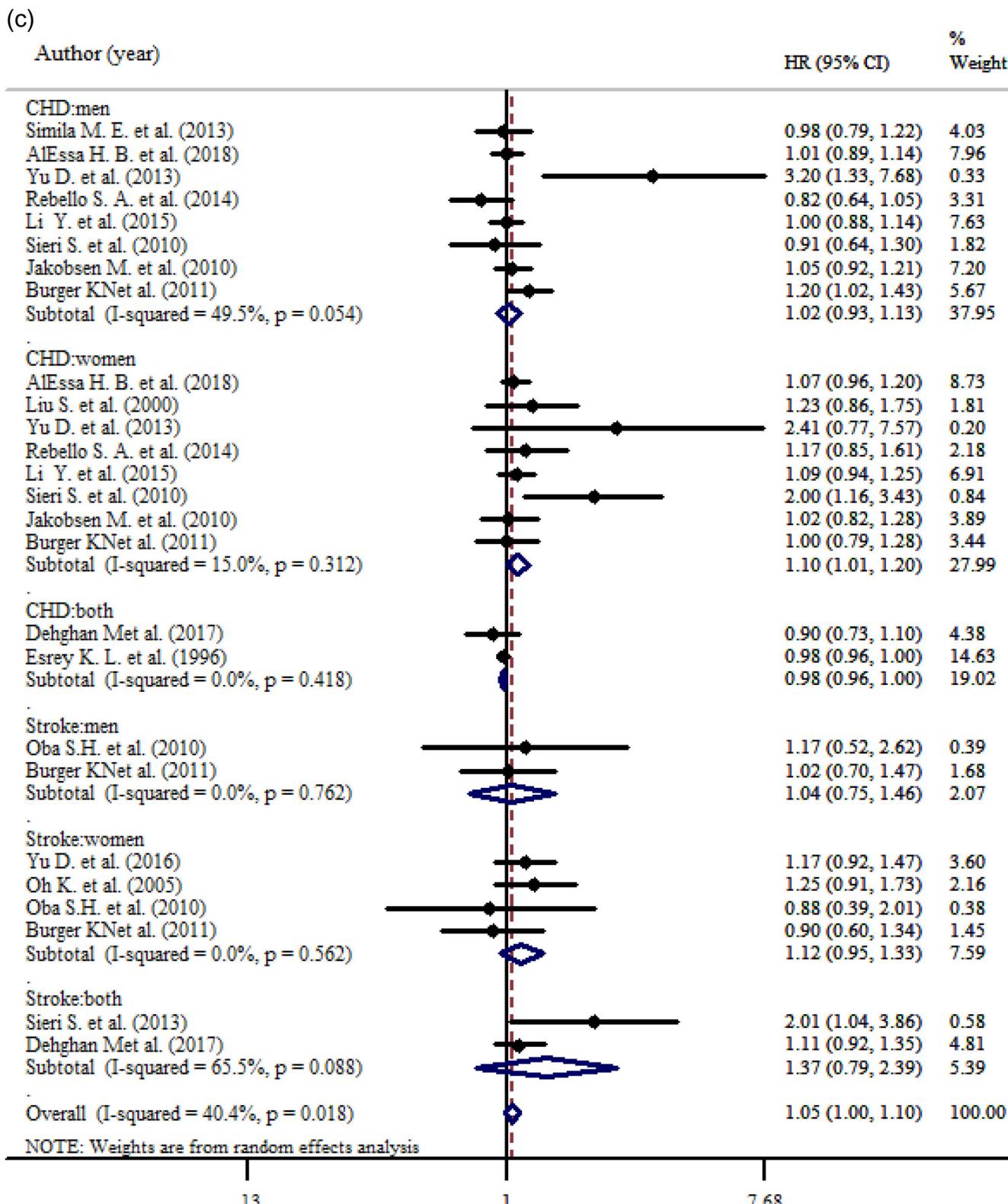


Figure 2. Continued.

The long-term effect of dietary carbohydrate quantity on health status is conflicting. Results from a current meta-analysis of prospective cohort studies revealed a U-shaped association between dietary carbohydrate and mortality, with minimal risk at the range from 50–55% carbohydrate intake (Seidelmann et al. 2018), whilst in another meta-analysis, despite a higher risk of all-cause mortality among

individuals with a low carbohydrate diet, no association was found for risk of CVD incidence and mortality (Noto et al. 2013). Nevertheless, this meta-analysis did not assess the risk of other CVD events rather than CVD incidence and mortality.

Determining the appropriate amounts of carbohydrate in diet has its own clinical implications. For example, although

(d)

Author (year)

	%
HR (95% CI)	Weight

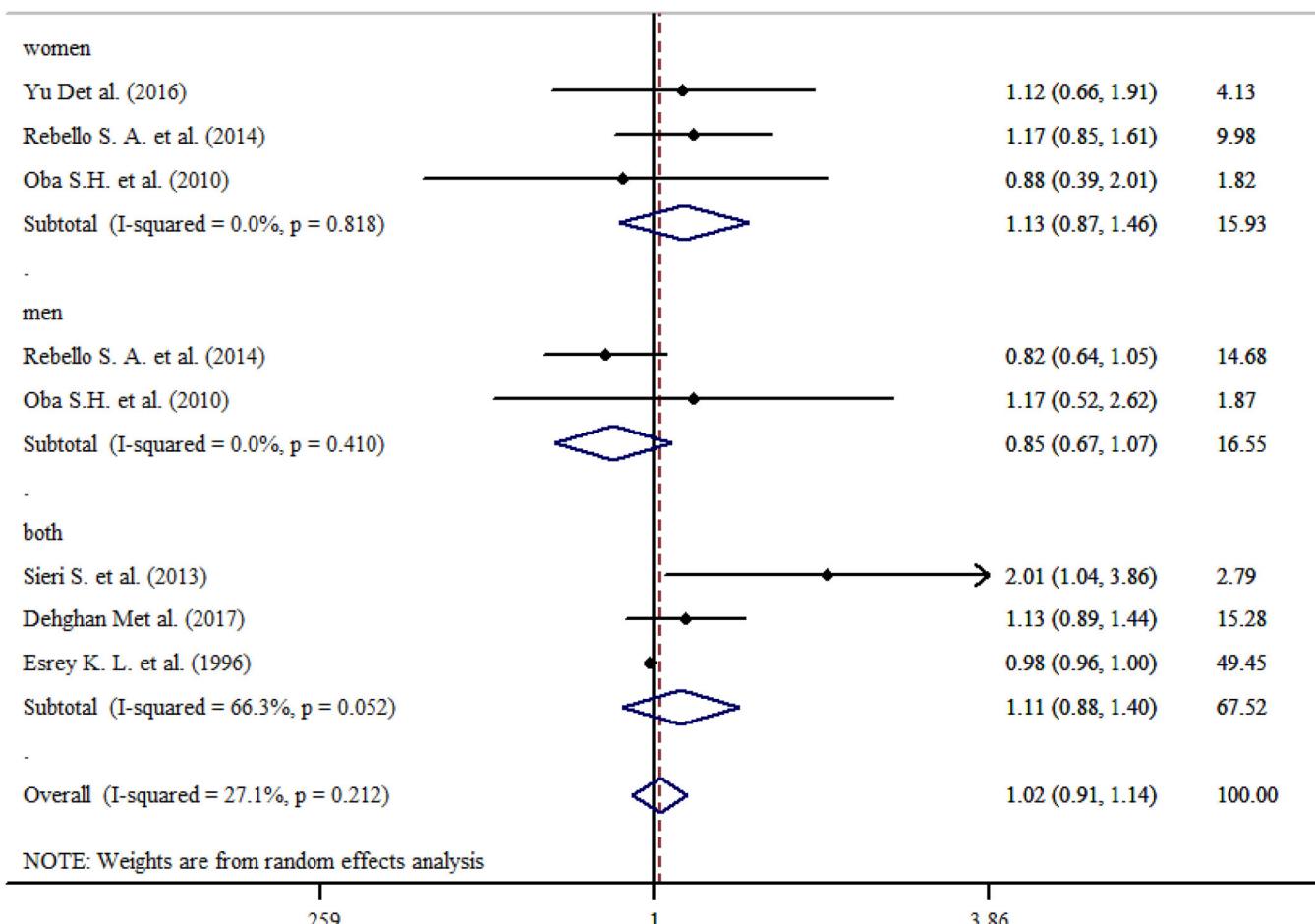


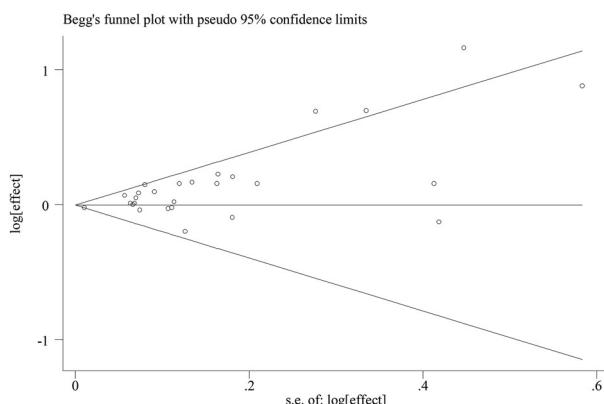
Figure 2. Continued.

dietary guidelines have recommended a diet low in SFA to reduce CHD risk, SFA did not increase the risk of CHD compared with carbohydrates in a meta-analysis (Siri-Tarino et al. 2010). Moreover, the PURE and Singapore Chinese Health Studies found no evidence of a greater risk of major CVD, stroke, myocardial infarction, and CVD mortality with increasing total daily carbohydrate intake (Rebello et al. 2014; Dehghan et al. 2017). However, in line with our results, the Shanghai Men's and Women's Health Study demonstrated a direct link between carbohydrate and risk of CHD incidence (Yu et al. 2013). Inconsistency between studies might be due, in part, to the evident differences in the prevalence of various risk factors, dietary composition, carbohydrate quality, and the main sources of protein intake in diverse populations (Seidelmann et al. 2018).

The lack of association between carbohydrate and CVD mortality in the current meta-analysis might be due to the low number of cases. Nevertheless, the direct link found for stroke and CVD may be related to the effect of higher post-prandial glycemia response on intermediate risk factors of stroke. This may induce the formation of advanced glycation end products, stimulate oxidative stress and inflammatory processes, and lead to dyslipidemia, causing endothelial

impairment and vessel dysfunction (Ludwig 2002; Goldin et al. 2006) and increasing the risk of stroke and CVD (Koska et al. 2018; Jenny et al. 2019; Xuan et al. 2019).

The null association found for carbohydrate and CVD in men are in agreement with the recent meta-analysis demonstrating no association between dietary glycemic index and mortality in men (Shahdadian et al. 2019). This might be related to the possible substitutes for dietary carbohydrate. For instance, in one study, replacing SFA with carbohydrate was associated with lower risk of mortality (Dominguez et al. 2018), and in another one, the substitution of red meat with vegetables and potato was associated with a decreased risk of MI (Wurtz et al. 2016), whereas the substitution of fatty fish with vegetables was associated with the increased risk of MI. Although refined sources of carbohydrate are the main source of carbohydrate in high-carbohydrate diets (Gross et al. 2004), decreasing carbohydrate is inevitably associated with increasing protein or fat, which might be provided by unhealthy sources such as red meat and SFA. Several studies support the null association for refined grains with metabolic diseases, but an increased risk for red and processed meat consumption (Liu et al. 2000; Oh et al. 2005; Oba et al. 2010; Rebello et al. 2014). Moreover, it is



**Figure 3.** Begg's funnel plot with pseudo 95% confidence limits.

worth mentioning that glycemic index and load are less useful indicators for carbohydrate quality rather than dietary fiber and whole grain; therefore, they should be considered in studies which aim to assess dietary carbohydrates in relation to non-communicable diseases (Reynolds et al. 2019). Another explanation for this difference might be different metabolic responses to dietary carbohydrate. Women have greater changes in serum glucose, triglyceride and HDL levels when consuming a high-carbohydrate diet in comparison with men, which leads to a greater risk of CVD in women (Knopp et al. 2006). Despite these explanations, the differences between men and women in this regard should be interpreted cautiously since it may not be an inherent difference by sex, but by gender. While sex refers to biological differences between men and women (i.e. hormones and body composition), gender determines how individuals behave, react, and communicate in different situations. Moreover, gender interacts with biological sex along with other social factors such as socioeconomic status and ethnicity, and thereby affects cardiovascular health (O'Neil et al. 2018). Nevertheless, in epidemiological studies, only the confounding role of biological sex, but not gender, has been taken into account.

Some of the limitations of our study merit consideration. First, the current analysis was performed on observational data; nevertheless, it should be kept in mind that it is difficult to examine the long-term effects of low carbohydrate diets on cardiovascular health using RCTs. Second, using different tools to assess dietary intakes with their own measurement errors may lead to misclassification of participants and dramatically influence the results. Third, even with extracting data for maximally-adjusted models, the confounding effect of residual and unknown confounders cannot be totally excluded. Fourth, we could not determine the effect of a low-carbohydrate diet when substituted with different macronutrients due to lack of data. Fifth, we could not perform dose-response analysis stratified by sex could not be assessed for the limited number of studies. Sixth, carbohydrate is predominantly provided by refined sources in low- and middle-income countries (Seidelmann et al. 2018); nevertheless, subgroup analysis based on countries was not possible since studies principally originated from high-income countries. Lastly, since our meta-analysis was

performed on cohort studies, our results have low to very-low certainty.

This is the first meta-analysis examining the quantity of carbohydrates in relation to the risk of CVD and stroke incidence and mortality. It includes mainly high-quality studies with a long follow-up duration, and large sample size, assessing multiple nations, and a wide range of carbohydrate intake. Moderate heterogeneity between studies also suggests a consistency between study results, and may suggest that variations, at least to some extent, are attributable to chance.

## Conclusion

Low- to very-low-certainty evidence revealed a slight positive link between carbohydrate intake and CVD and stroke. However, the association between carbohydrate and CVD and CHD was only significant in women, but not men. Further studies in low- and middle-income countries are required.

## Acknowledgements

The authors' responsibilities were as follows: NM was involved in the conception. NM, MT, and FH conducted the research and extracted data. MT and MM analyzed the data. NM, MT, SF, and FH wrote the manuscript. All authors read and approved the final manuscript, and they have no conflicts of interest.

## Disclosure statement

No conflicts of interest.

## Funding

This study was funded by Isfahan University of Medical Sciences.

## ORCID

Noushin Mohammadifard <http://orcid.org/0000-0003-1776-1060>

## References

- AlEssa, H. B., R. Cohen, V. S. Malik, S. N. Adebamowo, E. B. Rimm, J. E. Manson, W. C. Willett, and F. B. Hu. 2018. Carbohydrate quality and quantity and risk of coronary heart disease among US women and men. *The American Journal of Clinical Nutrition* 107 (2):257–67. doi: [10.1093/ajcn/nqx060](https://doi.org/10.1093/ajcn/nqx060).
- Beulens, J. W., L. M. de Bruijne, R. P. Stolk, P. H. Peeters, M. L. Bots, D. E. Grobbee, and Y. T. van der Schouw. 2007. High dietary glycemic load and glycemic index increase risk of cardiovascular disease among middle-aged women: A population-based follow-up study. *Journal of the American College of Cardiology* 50 (1):14–21. doi: [10.1016/j.jacc.2007.02.068](https://doi.org/10.1016/j.jacc.2007.02.068).
- Blaak, E. E. J. 2016. Carbohydrate quantity and quality and cardiometabolic risk. *Current Opinion in Clinical Nutrition and Metabolic Care* 19 (4):289–93. doi: [10.1097/MCO.0000000000000290](https://doi.org/10.1097/MCO.0000000000000290).
- Burger, K. N. J., J. W. J. Beulens, J. M. A. Boer, A. M. W. Spijkerman, and D. L. van der A. 2011. Dietary glycemic load and glycemic index and risk of coronary heart disease and stroke in Dutch men

- and women: The EPIC-MORGEN study. *PLoS One* 6 (10):e25955. doi: [10.1371/journal.pone.0025955](https://doi.org/10.1371/journal.pone.0025955).
- Dalen, J. E., and S. Devries. 2014. Diets to prevent coronary heart disease 1957–2013: What have we learned? *The American Journal of Medicine* 127 (5):364–9. doi: [10.1016/j.amjmed.2013.12.014](https://doi.org/10.1016/j.amjmed.2013.12.014).
- Dehghan, M., Mente, A. X. Zhang, S. Swaminathan, W. Li, V. and Mohan, R. 2017. Associations of fats and carbohydrate intake with cardiovascular disease and mortality in 18 countries from five continents (PURE): A prospective cohort study. *Lancet* 390 (10107): 2050–62.
- Dominguez, L. J., M. Bes-Rastrollo, F. J. Basterra-Gortari, A. Gea, M. Barbagallo, and M. A. Martinez-Gonzalez. 2018. Should we recommend reductions in saturated fat intake or in red/processed meat consumption? The SUN prospective cohort study. *Clinical Nutrition (Edinburgh, Scotland)* 37 (4):1389–98. doi: [10.1016/j.clnu.2017.06.013](https://doi.org/10.1016/j.clnu.2017.06.013).
- Eckel, R. H., J. M. Jakicic, J. D. Ard, J. M. de Jesus, N. Houston Miller, V. S. Hubbard, I.-M. Lee, A. H. Lichtenstein, C. M. Loria, B. E. Millen, et al. 2014. AHA/ACC guideline on lifestyle management to reduce cardiovascular risk: A report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. *Journal of the American College of Cardiology*. 63 (25 Part B):2960–84. doi: [10.1016/j.jacc.2013.11.003](https://doi.org/10.1016/j.jacc.2013.11.003).
- Esrey, K. L., L. Joseph, and S. A. Grover. 1996. Relationship between dietary intake and coronary heart disease mortality: Lipid research clinics prevalence follow-up study. *Journal of Clinical Epidemiology* 49 (2):211–6. doi: [10.1016/0895-4356\(95\)00066-6](https://doi.org/10.1016/0895-4356(95)00066-6).
- Foster, G. D., H. R. Wyatt, J. O. Hill, B. G. McGuckin, C. Brill, B. S. Mohammed, P. O. Szapary, D. J. Rader, J. S. Edman, S. Klein, et al. 2003. A randomized trial of a low-carbohydrate diet for obesity. *The New England Journal of Medicine* 348 (21):2082–90. doi: [10.1056/NEJMoa022207](https://doi.org/10.1056/NEJMoa022207).
- Gardner, C. D., A. Kiazyk, S. Alhassan, S. Kim, R. S. Stafford, R. R. Balise, H. C. Kraemer, and A. C. King. 2007. Comparison of the Atkins, Zone, Ornish, and LEARN diets for change in weight and related risk factors among overweight premenopausal women: The A TO Z Weight Loss Study: A randomized trial. *JAMA* 297 (9): 969–77. doi: [10.1001/jama.297.9.969](https://doi.org/10.1001/jama.297.9.969).
- Goldin, A., J. A. Beckman, A. M. Schmidt, and M. A. Creager. 2006. Advanced glycation end products: Sparking the development of diabetic vascular injury. *Circulation* 114 (6):597–605. doi: [10.1161/CIRCULATIONAHA.106.621854](https://doi.org/10.1161/CIRCULATIONAHA.106.621854).
- Gross, L. S., L. Li, E. S. Ford, and S. Liu. 2004. Increased consumption of refined carbohydrates and the epidemic of type 2 diabetes in the United States: An ecologic assessment. *The American Journal of Clinical Nutrition* 79 (5):774–9. doi: [10.1093/ajcn/79.5.774](https://doi.org/10.1093/ajcn/79.5.774).
- Ho, F. K., Gray, S. R. P. Welsh, F. Petermann-Rocha, H. Foster, H. Waddell, J., et al. 2020. Associations of fat and carbohydrate intake with cardiovascular disease and mortality: Prospective cohort study of UK Biobank participants. *BMJ* 368:m688.
- Hu, T., Bazzano, L. J. N. Metabolism, and C. Diseases. 2014. The low-carbohydrate diet and cardiovascular risk factors: Evidence from epidemiologic studies. *Nutrition, Metabolism, and Cardiovascular Diseases* 24 (4):337–43. doi: [10.1016/j.numecd.2013.12.008](https://doi.org/10.1016/j.numecd.2013.12.008).
- Jakobsen, M. U., E. J. O'Reilly, B. L. Heitmann, M. A. Pereira, K. Bälter, G. E. Fraser, U. Goldbourt, G. Hallmans, P. Knekt, S. Liu, et al. 2009. Major types of dietary fat and risk of coronary heart disease: A pooled analysis of 11 cohort studies. *The American Journal of Clinical Nutrition* 89 (5):1425–32. doi: [10.3945/ajcn.2008.27124](https://doi.org/10.3945/ajcn.2008.27124).
- Jenny, N. S., P. W. Callas, S. E. Judd, L. A. McClure, B. Kissela, N. A. Zakai, and M. Cushman. 2019. Inflammatory cytokines and ischemic stroke risk: The REGARDS cohort. *Neurology* 92 (20):e2375–e2384. doi: [10.1212/WNL.0000000000007416](https://doi.org/10.1212/WNL.0000000000007416).
- Knopp, R. H., P. Paramsothy, B. M. Retzlaff, B. Fish, C. Walden, A. Dowdy, C. Tsunehara, K. Aikawa, and M. C. Cheung. 2006. Sex differences in lipoprotein metabolism and dietary response: Basis in hormonal differences and implications for cardiovascular disease. *Current Cardiology Reports* 8 (6):452–9. doi: [10.1007/s11886-006-0104-0](https://doi.org/10.1007/s11886-006-0104-0).
- Koska, J., A. Saremi, S. Howell, G. Bahn, B. De Courten, H. Ginsberg, P. J. Beisswenger, and P. D. Reaven, VADT Investigators. 2018. Advanced glycation end products, oxidation products, and incident cardiovascular events in patients with type 2 diabetes. *Diabetes Care* 41 (3):570–6. doi: [10.2337/dc17-1740](https://doi.org/10.2337/dc17-1740).
- Lennon, R. P., K. A. Claussen, and K. A. Kuersteiner. 2018. State of the heart: An overview of the disease burden of cardiovascular disease from an epidemiologic perspective. *Primary Care* 45 (1):1–15. doi: [10.1016/j.pop.2017.11.001](https://doi.org/10.1016/j.pop.2017.11.001).
- Li, Y., A. Hruby, A. M. Bernstein, S. H. Ley, D. D. Wang, S. E. Chiuve, L. Sampson, K. M. Rexrode, E. B. Rimm, W. C. Willett, et al. 2015. Saturated fats compared with unsaturated fats and sources of carbohydrates in relation to risk of coronary heart disease: A prospective cohort study. *Journal of the American College of Cardiology*. 66 (14): 1538–48. doi: [10.1016/j.jacc.2015.07.055](https://doi.org/10.1016/j.jacc.2015.07.055).
- Liu, S., W. C. Willett, M. J. Stampfer, F. B. Hu, M. Franz, L. Sampson, C. H. Hennekens, and J. E. Manson. 2000. A prospective study of dietary glycemic load, carbohydrate intake, and risk of coronary heart disease in US women. *The American Journal of Clinical Nutrition* 71 (6):1455–61. doi: [10.1093/ajcn/71.6.1455](https://doi.org/10.1093/ajcn/71.6.1455).
- Ludwig, D. S. 2002. The glycemic index: Physiological mechanisms relating to obesity, diabetes, and cardiovascular disease. *JAMA* 287 (18):2414–23. doi: [10.1001/jama.287.18.2414](https://doi.org/10.1001/jama.287.18.2414).
- Mansoor, N., K. J. Vinknes, M. B. Veierød, and K. Retterstøl. 2016. Effects of low-carbohydrate diets v. low-fat diets on body weight and cardiovascular risk factors: A meta-analysis of randomised controlled trials. *British Journal of Nutrition* 115 (3):466–79. doi: [10.1017/S0007114515004699](https://doi.org/10.1017/S0007114515004699).
- Mirrahimi, A., R. J. de Souza, L. Chiavaroli, J. L. Sievenpiper, J. Beyene, A. J. Hanley, L. S., et al. 2012. Associations of glycemic index and load with coronary heart disease events: A systematic review and meta-analysis of prospective cohorts. *Journal of the American Heart Association*. 1 (5):e000752.
- Mozaffarian, D. J. C. 2016. Dietary and policy priorities for cardiovascular disease, diabetes, and obesity: A comprehensive review. *Circulation* 133 (2):187–225. doi: [10.1161/CIRCULATIONAHA.115.018585](https://doi.org/10.1161/CIRCULATIONAHA.115.018585).
- Noto, H., A. Goto, T. Tsujimoto, and M. Noda. 2013. Low-carbohydrate diets and all-cause mortality: A systematic review and meta-analysis of observational studies. *PLoS One* 8 (1):e55030. doi: [10.1371/journal.pone.0055030](https://doi.org/10.1371/journal.pone.0055030).
- Oba, S., C. Nagata, K. Nakamura, K. Fujii, T. Kawachi, N. Takatsuka, and H. Shimizu. 2010. Dietary glycemic index, glycemic load, and intake of carbohydrate and rice in relation to risk of mortality from stroke and its subtypes in Japanese men and women. *Metabolism: Clinical and Experimental* 59 (11):1574–82. doi: [10.1016/j.metabol.2010.02.004](https://doi.org/10.1016/j.metabol.2010.02.004).
- Oh, K., F. B. Hu, E. Cho, K. M. Rexrode, M. J. Stampfer, J. E. Manson, S. M. Liu, and W. C. Willett. 2005. Carbohydrate intake, glycemic index, glycemic load, and dietary fiber in relation to risk of stroke in women. *American Journal of Epidemiology* 161 (2):161–9. doi: [10.1093/aje/kwi026](https://doi.org/10.1093/aje/kwi026).
- O'Neil, A., A. J. Scovelle, A. J. Milner, and A. Kavanagh. 2018. Gender/sex as a social determinant of cardiovascular risk. *Circulation* 137 (8):854–64. doi: [10.1161/CIRCULATIONAHA.117.028595](https://doi.org/10.1161/CIRCULATIONAHA.117.028595).
- Prentice, R. L., A. K. Aragaki, L. Van Horn, C. A. Thomson, S. A. Beresford, J. Robinson, L. Snetselaar, G. L. Anderson, J. E. Manson, M. A. Allison, et al. 2017. Low-fat dietary pattern and cardiovascular disease: Results from the Women's Health Initiative randomized controlled trial. *The American Journal of Clinical Nutrition* 106 (1): 35–43. doi: [10.3945/ajcn.117.153270](https://doi.org/10.3945/ajcn.117.153270).
- Rebello, S. A., H. Koh, C. Chen, N. Naidoo, A. O. Odegaard, W. P. Koh, L. M. Butler, J. M. Yuan, and R. M. Van Dam. 2014. Amount, type, and sources of carbohydrates in relation to ischemic heart disease mortality in a Chinese population: A prospective cohort study. *The American Journal of Clinical Nutrition* 100 (1):53–64. doi: [10.3945/ajcn.113.076273](https://doi.org/10.3945/ajcn.113.076273).
- Reynolds, A., J. Mann, J. Cummings, N. Winter, E. Mete, and L. J. T. L. Te Morenga. 2019. Carbohydrate quality and human health: A

- series of systematic reviews and meta-analyses. *Lancet (London, England)* 393 (10170):434–45. doi: [10.1016/S0140-6736\(18\)31809-9](https://doi.org/10.1016/S0140-6736(18)31809-9).
- Seidelmann, S. B., B. Claggett, S. Cheng, M. Henglin, A. Shah, L. M. Steffen, A. R. Folsom, E. B. Rimm, W. C. Willett, S. D. Solomon, et al. 2018. Dietary carbohydrate intake and mortality: A prospective cohort study and meta-analysis. *The Lancet Public Health* 3 (9): e419–e428. doi: [10.1016/S2468-2667\(18\)30135-X](https://doi.org/10.1016/S2468-2667(18)30135-X).
- Shahdadian, F., P. Saneei, A. Milajerdi, and A. Esmaillzadeh. 2019. 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. *The American Journal of Clinical Nutrition* 110 (4):921–37. doi: [10.1093/ajcn/nqz061](https://doi.org/10.1093/ajcn/nqz061).
- Sieri, S., F. Brighenti, C. Agnoli, S. Grioni, G. Masala, B. Bendinelli, C. Sacerdote, F. Ricceri, R. Tumino, M. C. Giurdanella, et al. 2013. Dietary glycemic load and glycemic index and risk of cerebrovascular disease in the EPICOR cohort. *PLoS One* 8 (5):e62625. doi: [10.1371/journal.pone.0062625](https://doi.org/10.1371/journal.pone.0062625).
- Sieri, S., V. Krogh, F. Berrino, A. Evangelista, C. Agnoli, F. Brighenti, N. Pellegrini, D. Palli, G. Masala, C. Sacerdote, et al. 2010. Dietary glycemic load and index and risk of coronary heart disease in a large Italian cohort: The EPICOR study. *Archives of Internal Medicine* 170 (7):640–7. doi: [10.1001/archinternmed.2010.15](https://doi.org/10.1001/archinternmed.2010.15).
- Simila, M. E., J. P. Kontto, S. Mannisto, L. M. Valsta, and J. Virtamo. 2013. Glycaemic index, carbohydrate substitution for fat and risk of CHD in men. *The British Journal of Nutrition* 110 (9):1704–11. doi: [10.1017/S0007114513000858](https://doi.org/10.1017/S0007114513000858).
- Siri-Tarino, P. W., Q. Sun, F. B. Hu, and R. M. Krauss. 2010. Meta-analysis of prospective cohort studies evaluating the association of saturated fat with cardiovascular disease. *The American Journal of Clinical Nutrition* 91 (3):535–46. doi: [10.3945/ajcn.2009.27725](https://doi.org/10.3945/ajcn.2009.27725).
- Sonestedt, E., S. Hellstrand, C.-A. Schulz, P. Wallström, I. Drake, U. Ericson, B. Gullberg, B. Hedblad, and M. Orho-Melander. 2015. The association between carbohydrate-rich foods and risk of cardiovascular disease is not modified by genetic susceptibility to dyslipidemia as determined by 80 validated variants. *PLoS One* 10 (4): e0126104. doi: [10.1371/journal.pone.0126104](https://doi.org/10.1371/journal.pone.0126104).
- Wallström, P., E. Sonestedt, J. Hlebowicz, U. Ericson, I. Drake, M. Persson, B. Gullberg, B. Hedblad, and E. Wärffält. 2012. Dietary fiber and saturated fat intake associations with cardiovascular disease differ by sex in the Malmö diet and cancer cohort: A prospective study. *PLoS One*. 7 (2):e31637. doi: [10.1371/journal.pone.0031637](https://doi.org/10.1371/journal.pone.0031637).
- Wells, G., B. Shea, D. O’connell, J. Peterson, V. Welch, M. Losos, et al. 2014. The Newcastle-Ottawa Scale (NOS) for assessing the quality of nonrandomised studies in meta-analyses. [Internet].
- Wurtz, A. M., M. D. Hansen, A. Tjønneland, E. B. Rimm, E. B. Schmidt, K. Overvad, and M. U. Jakobsen. 2016. Substitution of meat and fish with vegetables or potatoes and risk of myocardial infarction. *The British Journal of Nutrition* 116 (9):1602–10. doi: [10.1017/S0007114516003500](https://doi.org/10.1017/S0007114516003500).
- Xu, C., and S. A. R. Doi. 2018. The robust error meta-regression method for dose-response meta-analysis. *International Journal of Evidence-Based Healthcare* 16 (3):138–44. doi: [10.1097/XEB.0000000000000132](https://doi.org/10.1097/XEB.0000000000000132).
- Xuan, Y., M. Bobak, A. Anusrti, E. H. J. M. Jansen, A. Pajak, A. Tamosiunas, K.-U. Saum, B. Hollecze, X. Gao, H. Brenner, et al. 2019. Association of serum markers of oxidative stress with myocardial infarction and stroke: Pooled results from four large European cohort studies. *European Journal of Epidemiology* 34 (5):471–81. doi: [10.1007/s10654-018-0457-x](https://doi.org/10.1007/s10654-018-0457-x).
- You, A. 2015. Dietary guidelines for Americans. US Department of Health and Human Services and US Department of Agriculture.
- Yu, D., X. O. Shu, H. Li, Y. B. Xiang, G. Yang, Y. T. Gao, W. Zheng, and X. Zhang. 2013. Dietary carbohydrates, refined grains, glycemic load, and risk of coronary heart disease in Chinese adults. *American Journal of Epidemiology* 178 (10):1542–9. doi: [10.1093/aje/kwt178](https://doi.org/10.1093/aje/kwt178).
- Yu, D., X. Zhang, X.-O. Shu, H. Cai, H. Li, D. Ding, Z. Hong, Y.-B. Xiang, Y.-T. Gao, W. Zheng, et al. 2016. Dietary glycemic index, glycemic load, and refined carbohydrates are associated with risk of stroke: A prospective cohort study in urban Chinese women. *The American Journal of Clinical Nutrition* 104 (5):1345–51. doi: [10.3945/ajcn.115.129379](https://doi.org/10.3945/ajcn.115.129379).
- Yusuf, S., S. Rangarajan, K. Teo, S. Islam, W. Li, L. Liu, J. Bo, Q. Lou, F. Lu, T. Liu, et al. 2014. Cardiovascular risk and events in 17 low-, middle-, and high-income countries. *New England Journal of Medicine* 371 (9):818–27. doi: [10.1056/NEJMoa1311890](https://doi.org/10.1056/NEJMoa1311890). Supplemental added to complete or make up a deficiency More (Definitions, Synonyms, Translation)