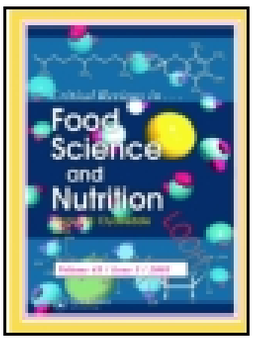

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REVIEW

Dietary glycemic index, glycemic load, and chronic disease: an umbrella review of meta-analyses of prospective cohort studies

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ABSTRACT

We aimed to present a comprehensive review of the association of dietary glycemic index (GI) and load (GL) with the risk of chronic disease. Published meta-analyses of prospective observational studies evaluating the association of dietary GI and GL with risk of chronic disease were identified by a search in PubMed and Scopus to November, 2020. Summary relative risks (SRRs) were recalculated using random-effects models. The certainty of evidence was rated by the GRADE approach. Eighteen meta-analyses of prospective cohort studies, reporting 19 SRRs for dietary GI and 17 SRRs for dietary GL were identified. There was a positive association between dietary GI and the risk of type 2 diabetes, coronary heart disease, and colorectal, breast, and bladder cancers, as well as between dietary GL and the risk of coronary heart disease, type 2 diabetes, and stroke. With regard to cancers at other sites, there was no significant association. The certainty of evidence ranged from very low to low. Although by GRADE classification no associations were rated stronger than low, they were classified as one grade higher when the NutriGrade system was used. Further research is needed to add evidence for the relation of dietary GI and GL with cancer risk.

KEYWORDS

Carbohydrates; cardiovascular disease; cohort studies; coronary heart disease; glycemic index; glycemic load; meta-analysis; mortality; neoplasms

Introduction

Dietary carbohydrates are the main energy source (Jequier 1994), and have the largest impact on postprandial blood glucose levels (Brand-Miller 2004). It is proposed that both quality and quantity of carbohydrates consumed in the human diet have important health outcomes (Ludwig et al. 2018).

In 1981, the concept of glycaemic index (GI) was introduced as an attempt to measure the quality of dietary carbohydrates, especially for the treatment of diabetes (Jenkins et al. 1981). It is a scale, where the reference food (glucose or white bread) is given the value of 100, and reflects the degree of postprandial glycaemic response to carbohydrates in different foods indexed to a reference carbohydrate, first as glucose and later as white bread (Wolever et al. 1991). Accordingly, carbohydrates with low ($\leq$55) or high ($\geq$70) GI values on the glucose scale can cause lower or greater raises in blood glucose levels, respectively. However, the quantity of carbohydrate is also an important factor in determining the blood glucose response. The glycaemic load (GL) combines both the quality and quantity of carbohydrates and reflects the GI of a food and its carbohydrate content (Salmeron et al. 1997).

Given the effects of dietary carbohydrates on energy intake and blood glucose levels, it has been suggested that diets with high GI and GL values may be associated with a higher risk of chronic disease including type 2 diabetes (T2D) and cardiovascular disease (CVD) (Brand-Miller 2003; Ludwig 2002). A number of important meta-analyses of observational studies have already been undertaken of the association of dietary GI/GL with the risk of chronic disease (Bhupathiraju et al. 2014; Gnagnarella et al. 2008; Mirrahimi et al. 2012). However, the association of GI with any health related outcome has been questioned by one of the most recently published meta-analysis (Reynolds et al. 2019). We have therefore undertaken a comprehensive review with a focus on the strength of the evidence, the accuracy of the estimates, as well as the degree of the methodological quality of the data in our systematic review and meta-analysis (Schwingshackl et al. 2016).

Umbrella reviews have been recently used to present a relatively comprehensive understanding of published meta-analyses on a specific topic (Aromataris et al. 2015). Reviewing the published meta-analyses and rating the

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strength of their evidence, evaluating their methodological quality, and assessment of the accuracy of their estimates may help present more reliable evidence of the association of dietary components with the risk of chronic disease. Umbrella reviews can also help clarify whether the results of the published meta-analyses are unbiased. Thus, we aimed to perform an umbrella review of meta-analyses of prospective cohort studies evaluating the association of dietary GI and GL with the risk of chronic disease.

Methods

Systematic search

Two authors (SS and AJ) carried out a systematic literature search according to the Preferred Reporting Items for Systematic Reviews and Meta-analyses: the PRISMA statement (Moher et al. 2009). The systematic search was performed in PubMed and Scopus databases to November, 2020 for potential relevant meta-analyses of prospective cohort studies evaluating the association of dietary GI or GL with the risk of any chronic disease. The literature search was supplemented by screening of the reference lists of all relevant reviews and meta-analyses. The complete search strategy is provided in Supplementary Table 1.

Selection of meta-analyses

Studies with the following criteria were considered eligible for inclusion in the present umbrella review: 1) meta-analyses of prospective cohort studies that were conducted in in the general population aged 18 years or older; 2) assessed dietary intakes by a standard dietary assessment tool (e.g. food frequency questionnaires, diet history, 24 hour dietary recalls, and dietary records) and reported dietary GI and/or GL as exposure; 3) considered the incidence of any chronic disease including T2D, CVD, neurological disorders, total and site-specific cancers, all-cause and cause-specific mortality, etc. as outcomes; and 4) reported multivariable adjusted summary risk estimate and corresponding 95% confidence intervals for each outcome.

Primary studies and studies with no summary risk estimate (e.g. narrative reviews and systematic reviews without meta-analysis) were excluded. If more than one meta-analysis was found for a given outcome (for example, dietary GI and T2D), the study with the largest number of primary prospective cohort studies was selected (Neuenschwander et al. 2019).

Data extraction

Two authors (AJ and SS) independently extracted the following data from eligible meta-analyses: first author's name, publication year, exposure, number of primary prospective cohort studies included in the analysis, number of participants/case, and type of comparison (high *v* low or dose-response meta-analysis). We also extracted the following data from primary prospective cohort studies included in each meta-analysis: first author's name, year of publication, exposure, number of participants/cases, maximally adjusted relative risks and their corresponding 95% confidence intervals (CIs), and confounding variables that were included in the analyses. Disagreement was resolved by consensus.

Assessment of methodological quality

We used the assessment of multiple systematic reviews (AMSTAR) tool for evaluating the methodological quality of each published meta-analysis that were included in our umbrella review (Shea et al. 2007; Shea et al. 2009). This scale ranges from zero to 11, and evaluates the methodological quality of published meta-analyses. Accordingly, meta-analyses with $\geq$ 8 points were rated high quality, and meta-analyses with 4-7 points and $\leq$ 3 points were rated moderate and low quality, respectively (Sharif et al. 2013).

Risk of bias assessment

The quality of primary prospective cohort studies included in each meta-analysis was assessed by two independent reviewers (AJ and SS). Risk of bias assessment was performed by the use of the Newcastle Ottawa Scale (Wells et al. 2014).

Grading of the evidence

The certainty of the evidence was assessed by the use of the GRADE tool (Guyatt et al. 2008). This tool grades the evidence as high, moderate, low, or very low quality. Observational studies such as prospective cohort studies start as low-quality evidence that can be downgraded or upgraded on the basis of pre-specified criteria. The criteria used to downgrade evidence include study limitations, inconsistency, indirectness, imprecision, and publication bias. The criteria used to upgrade the quality of evidence include a large magnitude of association, a dose–response gradient, and attenuation by plausible confounding.

We also applied the NutriGrade scale for evaluating the quality of evidence (Schwingshackl et al. 2016). This score is a tool to judge the meta-evidence of randomized controlled trials and cohort studies in nutrition research and considers nutrition-specific aspects such as dietary assessment methods and diet-associated biomarkers. This score includes eight components including: 1) risk of bias, study quality, or study limitations; 2) precision of the estimate; 3) heterogeneity; 4) directness; 5) publication bias; 6) funding bias; 7) effect size; and 8) dose-response association. The score ranges from zero to 10. According to this method, the strength of the evidence obtained by published meta-analyses was categorized as very low (0-3.99), low (4-5.99), moderate (6-7.99), and high ($\geq$8). We used both GRADE and NutriGrade scales to rate the strength/quality of the evidence. However, our final conclusions in this study have been formulated on the basis of the GRADE approach.

Statistical analysis

For each outcome, we extracted maximally adjusted relative risks and their 95%CIs from each primary prospective cohort study included in selected meta-analyses. Then, we recalculated summary relative risk (SRR) and its corresponding 95% CI by using the DerSimonian and Laird random-effects model (DerSimonian and Laird 1986). Because some of the included meta-analyses used a fixed-effects model to combine primary effect sizes, we used this approach to standardize SRRs across all meta-analyses (Neuenschwander et al. 2019). In addition, with the use of this approach, we obtained sufficient information for the evaluation of the quality of the evidence (including τ^2, I^2, and publication bias).

For published meta-analyses that included separate risk estimates based on sex or other subgroups from a given primary study, we combined subgroup-specific estimates using a fixed-effects model and used the combined effect size for our analyses. For published meta-analyses that combined prospective cohorts, retrospective observational studies (e.g, case-control or retrospective cohort studies) and cross-sectional studies in their analyses, we excluded cross-sectional and retrospective studies and recalculated SRRs using the results from prospective cohort studies only. Primary studies with unadjusted risk estimates were also excluded. In addition, primary studies included in each published meta-analysis that were conducted in patients with specific disease or primary studies that assessed cancer survival were excluded from the analyses to ensure that all studies had prospective design and were conducted in the general population. In each meta-analysis, we evaluated between-study heterogeneity by using the I^2 statistic and its 95%CI (Higgins et al. 2003). Because I^2 is dependent on the study size, we also calculated τ^2, which is independent of study size (Riley, Higgins, and Deeks 2011). We evaluated potential publication bias using Egger's test (Egger et al. 1997). All analyses were conducted with Stata 13.

Results

The initial systematic search identified 3759 records. We reviewed titles and abstracts of all retrieved articles and ultimately, 36 published meta-analyses of observational studies were identified (Aune et al. 2012a; Aune et al. 2012b; Barclay et al. 2008; Bhupathiraju et al. 2014; Cai et al. 2019; Cai et al. 2015; Choi, Giovannucci, and Lee 2012; Dong and Qin 2011; Dong et al. 2011; Dong et al. 2012; Fan et al. 2012; Galeone et al. 2013; Gnagnarella et al. 2008; Greenwood et al. 2013; Hardy, Garvin, and Xu 2020; Livesey and Livesey 2019; Livesey et al. 2013; Livesey et al. 2019; Ma, Liu, and Song 2012; Mirrahimi et al. 2012; Mulholland et al. 2008; Mullie et al. 2016; Nagle et al. 2013; Rossi et al. 2015; Sadeghi et al. 2020a, 2020b; Salari-Moghaddam et al. 2019; Schlesinger et al. 2017; Shahdadian et al. 2019; Turati et al. 2019; Turati et al. 2015; Wang et al. 2015; Wu et al. 2014; Xu et al. 2019; Ye et al. 2017; Zhu et al. 2020). For the purpose of the present umbrella review, we selected those with the largest number of primary prospective cohort studies (Neuenschwander et al. 2019) and thus, 18 meta-analyses, reporting 19 SRRs for dietary GI and 17 SRRs for dietary GL obtained from 79 primary prospective cohort studies were considered eligible for the analyses (Barclay et al. 2008; Bhupathiraju et al. 2014; Cai et al. 2019; Cai et al. 2015; Choi, Giovannucci, and Lee 2012; Fan et al. 2012; Hardy, Garvin, and Xu 2020; Livesey et al. 2019; Rossi et al. 2015; Sadeghi et al. 2020a, 2020b; Salari-Moghaddam et al. 2019; Shahdadian et al. 2019; Turati et al. 2019; Turati et al. 2015; Wu et al. 2014; Xu et al. 2019; Zhu et al. 2020). Reasons for excluding studies are presented in Figure 1.

Published meta-analyses included in our review reported the following events as their outcome of interest: all-cause and CVD mortality (Shahdadian et al. 2019), coronary heart disease (CHD, GI) (Fan et al. 2012), CHD (GL) (Hardy, Garvin, and Xu 2020), stroke (GI) (Cai et al. 2015), stroke (GL) (Rossi et al. 2015), T2D (GI) (Livesey et al. 2019), T2D (GL) (Bhupathiraju et al. 2014), depression (Salari-Moghaddam et al. 2019), age-related cataract (Wu et al. 2014), gallbladder disease (Barclay et al. 2008), prostate cancer (Sadeghi et al. 2020b), breast cancer (Choi, Giovannucci, and Lee 2012), ovarian cancer (Turati et al. 2015), endometrial (GI) and lung cancers (Turati et al. 2019), endometrial cancer (GL) (Sadeghi et al. 2020a), renal cell carcinoma (Xu et al. 2019), bladder cancer (Zhu et al. 2020), and liver, gastric, pancreatic, and colorectal cancers (Cai et al. 2019). The general characteristics of the published meta-analyses included in the present review are provided in Supplementary Table 2.

For all-cause and CVD mortality, depression, renal cell carcinoma, bladder cancer, lung cancer, and gallbladder disease we found one published meta-analysis. For other outcomes, we found more than one published meta-analyses in relation to dietary GI and GL. Published meta-analyses with the same outcome reported similar SRRs, except for colorectal cancer, for which a published meta-analysis in 2012 reported null associations for both GI and GL (Aune et al. 2012a), but two recent meta-analyses with larger number of studies reported significant positive associations (Cai et al. 2019; Choi, Giovannucci, and Lee 2012). There were $\geq$10 primary prospective cohort studies available for the analyses of T2D, CHD, colorectal and breast cancers; and 5-9 primary prospective cohort studies for the analyses of stroke, all-cause mortality, and prostate, endometrial, and pancreatic cancers. For other outcomes, <5 primary prospective cohort studies were available for the analyses. All primary studies included in published meta-analyses reported multivariable relative risks. Of 79 primary studies included in the eligible meta-analyses, 90% (n = 71) controlled for age, 86% (n = 68) controlled for sex, 82% (n = 65) for energy intake and body mass index, 75% (n = 59) for alcohol intake and smoking status, and 62% (n = 49) for physical activity in their multivariable analyses.

Methodological quality

We used the validated AMSTAR tool (Shea et al. 2007; Shea et al. 2009) to assess the methodological quality of included meta-analyses. The overall AMSTAR score for each meta-analysis is presented in Supplementary Table 2, and detailed

Table 1. Summary relative risk with 95%CI and strength of the evidence for association of dietary glycemic index and the risk of chronic disease.

Outcome	Number of primary studies	Number of cases	Comparison	Summary relative risk (95%CI)	Quality of evidence (GRADE)	Reasons for downgrading/ upgrading the evidence (GRADE)	Quality of evidence (NutriGrade)
Gallbladder disease	2	7581	High vs low	1.26 (1.11, 1.40)	Low	None	Moderate
Bladder cancer	2	1315	High vs low	1.26 (1.08, 1.46)	Low	None	Moderate
Type 2 diabetes	15	34,841	Per 10-unit	1.18 (1.07, 1.29)	Low	Downgraded for inconsistency	Moderate
Coronary heart disease	10	7137	High vs low	1.14 (1.05, 1.24)	Low	None	Moderate
Colorectal cancer	12	14,108	High vs low	1.08 (1.01, 1.16)	Low	None	Moderate
Breast cancer	11	25,917	High vs low	1.06 (1.01, 1.11)	Low	None	Moderate
Stroke	7	3046	High vs low	1.07 (0.97, 1.19)	Low	None	Low
Prostate cancer	5	15,949	High vs low	0.98 (0.94, 1.03)	Low	None	Low
Endometrial cancer	7	4011	High vs low	1.00 (0.91, 1.10)	Low	None	Low
Pancreatic cancer	8	3097	High vs low	1.02 (0.90, 1.16)	Low	None	Low
Gastric cancer	3	869	High vs low	0.92 (0.57, 1.50)	Very low	Downgraded for inconsistency and imprecision	Low
Liver cancer	4	984	High vs low	1.04 (0.83, 1.32)	Very low	Downgraded for imprecision	Low
Renal cell carcinoma	2	1315	High vs low	0.99 (0.81, 1.17)	Very low	Downgraded for inconsistency	Low
All-cause mortality	5	10,768	High vs low	1.10 (0.94, 1.30)	Very low	Downgraded for serious risk of bias, inconsistency and imprecision	Very low
Depression	2	5412	High vs low	1.06 (0.72, 1.39)	Very low	Downgraded for serious risk of bias, inconsistency, indirectness and imprecision	Very low
Age-related cataract	3	643	High vs low	1.02 (0.82, 1.22)	Very low	Downgraded for imprecision	Very low
Cardiovascular mortality	4	2582	High vs low	1.03 (0.90, 1.17)	Very low	Downgraded for serious risk of bias	Very low
Ovarian cancer	2	739	High vs low	0.94 (0.74, 1.19)	Very low	Downgraded for imprecision	Very low
Lung cancer	2	1312	High vs low	0.98 (0.70, 1.36)	Very low	Downgraded for imprecision, indirectness and inconsistency	Very low

scores are presented in Supplementary Table 3. All meta-analyses assigned a score of ≥6. Of 18 included meta-analyses, 14 meta-analyses were conducted with a high quality approach (≥8 points), and another four ones were performed with a moderate quality method (6 and 7 points). The main reasons for lower AMSTAR scores were due to the fact that included meta-analyses did not provide a list of excluded studies and did not consider the scientific quality of primary studies in preparing their conclusions and recommendations.

Certainty of evidence (GRADE)

GI results

Detailed GRADE and NutriGrade scores for included meta-analyses are provided in Supplementary Tables 4 and 5, respectively. On the basis of the GRADE approach, we did not find high- or moderate-certainty evidence for the relation of dietary GI with disease risks. We found significant positive associations for CHD, T2D, gallbladder disease, and colorectal, breast and bladder cancers, but the certainty of the evidence was rated low (Table 1). For all-cause and CVD mortality, age-related cataract, depression, stroke, and prostate, pancreatic, liver, gastric, renal cell, ovarian, lung and endometrial cancers, the associations were not significant and the certainty of the evidence was rated low or very low (Table 1). The main reasons for downgrading the evidence were imprecision (n = 7), inconsistency (n = 6), and serious risk of bias (n = 3).

GL results

For GL, we found a significant positive association between dietary GL and the risk of CHD (Table 2). Highest compared with the lowest category of dietary GL was associated with a 20% higher risk of CHD (SRRs: 1.20, 95%CI: 1.08, 1.33). The certainty of the evidence was rated very low by the use of the GRADE approach (serious inconsistency). In addition, we found significant positive associations between dietary GL and the risk of T2D, stroke and gallbladder disease, but the certainty of the evidence was rated low (Table 2). For other outcomes, the certainty of the evidence was rated very low and the associations were not significant. The main reasons for downgrading the certainty of evidence were imprecision (n = 10), inconsistency (n = 7), and serious risk of bias (n = 2). Detailed GRADE and NutriGrade scores for each outcome are provided in Supplementary Tables 5 and 6, respectively. Although by GRADE classification no associations were rated stronger than low, they were classified as one grade higher when the NutriGrade system was used. This change in status was seen for diabetes, cardiovascular disease, certain cancers and notably gallbladder disease for both GI and GL (Tables 1 and 2).

Publication bias

The results for publication bias are presented in Supplementary Table 2. There was some evidence of publication bias ($p < 0.05$) for the association of dietary GL with the risk of colorectal cancer. No evidence of publication bias was detected for the association of dietary GI and GL with other outcomes.

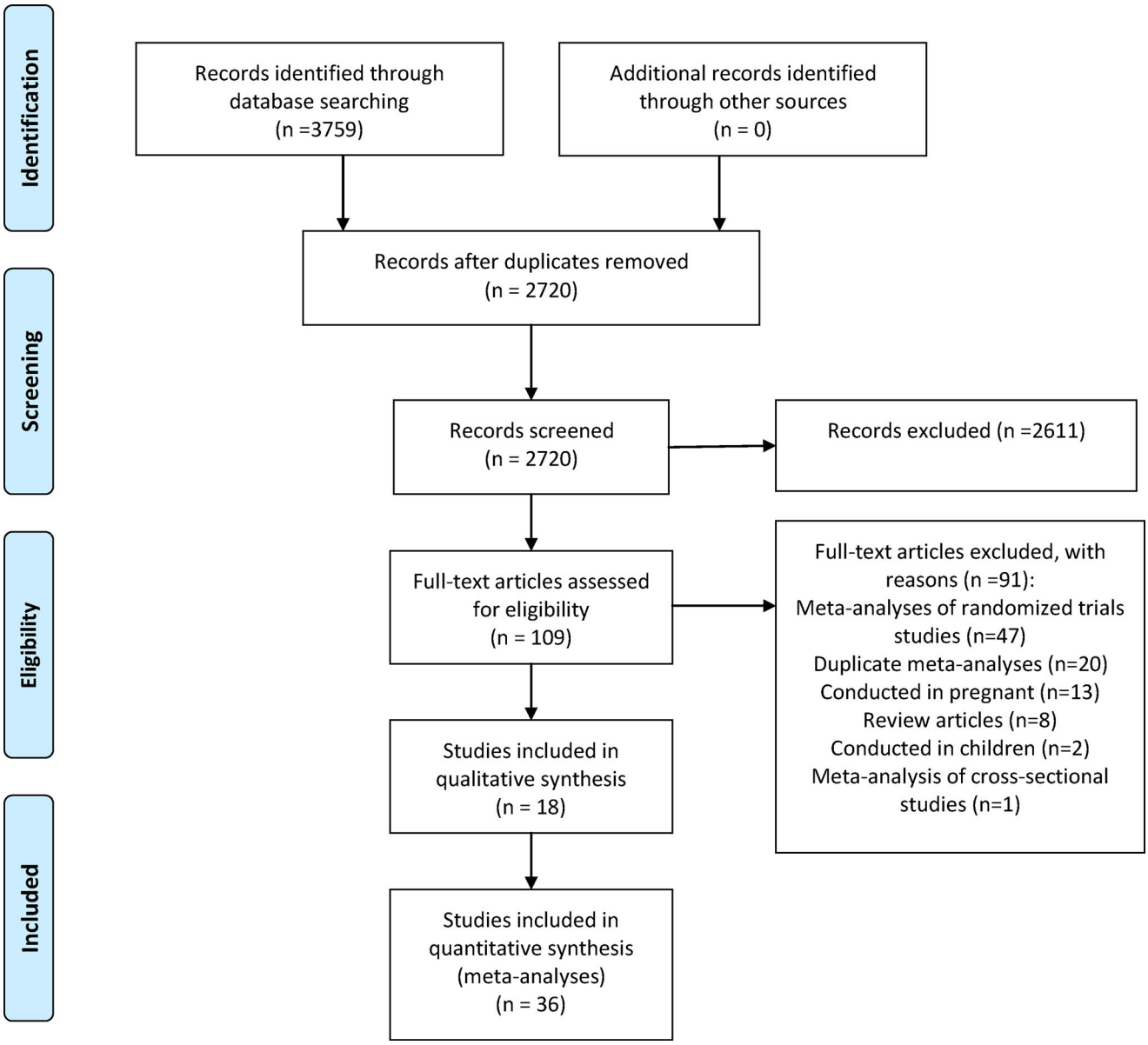

Figure 1. Literature search and study selection process.

Discussion

In this umbrella review of meta-analyses of prospective cohort studies, we presented a comprehensive assessment of the association of dietary GI and GL with the risk of chronic disease in the general population. We excluded retrospective and cross-sectional studies, and assessed the certainty of the evidence obtained by published meta-analyses. In addition, we evaluated the methodological quality of meta-analyses included in this review. We included 18 meta-analyses of prospective cohort studies, reporting 36 SRRs (19 SRRs for GI and 17 SRRs for GL) from 79 primary prospective cohort studies.

For GI, the results demonstrated that there were significant positive associations between higher dietary GI and the risk of T2D, CHD, gallbladder disease, and colorectal, breast and bladder cancers. The certainty of the evidence was rated low for these outcomes. For other outcomes, there were no significant associations and the certainty of the evidence was rated very low. For GL, low-certainty evidence suggested significant and positive associations for T2D, stroke, and gallbladder disease. There was also very low certainty evidence for the positive association of dietary GL and CHD. For other outcomes, the associations were not significant and the certainty of the evidence was rated very low.

We used AMSTAR score to evaluate the methodological accuracy of published meta-analyses. The results demonstrated that three meta-analyses were performed with a moderate quality method, and the remainders were conducted with a high quality approach. The main reasons for lower AMSTAR scores were due to the fact that included meta-analyses did not consider the scientific quality of primary studies in preparing their conclusions and recommendations. Of 18 published meta-analyses included in this review, 14 meta-analyses assessed the quality of primary studies with the use of the Newcastle Ottawa Scale (Stang 2010), one meta-analysis used its own criteria (Fan et al. 2012), and two meta-analyses did not assess the quality of primary studies (Rossi et al. 2015; Turati et al. 2015). Only

Table 2. Summary relative risk with 95%CI and strength of the evidence for association of dietary glycemic load and the risk of chronic disease.

Outcome	Number of primary studies	Number of cases	Comparison	Summary relative risk (95%CI)	Quality of evidence (GRADE)	Reasons for downgrading/ upgrading the evidence (GRADE)	Quality of evidence (NutriGrade)
Gallbladder disease	2	7581	High vs low	1.41 (1.25, 1.60)	Low	None	Moderate
Stroke	7	3255	High vs low	1.21 (1.05, 1.40)	Low	None	Moderate
Type 2 diabetes	14	46,115	High vs low	1.11 (1.05, 1.17)	Low	None	Moderate
Prostate cancer	5	15,949	High vs low	0.96 (0.89, 1.03)	Low	None	Low
Breast cancer	11	25,917	High vs low	1.05 (0.96, 1.14)	Very low	Downgraded for inconsistency	Moderate
Coronary heart disease	12	11,078	High vs low	1.20 (1.08, 1.33)	Very low	Downgraded for inconsistency	Low
Colorectal cancer	14	16,810	High vs low	0.98 (0.90, 1.07)	Very low	Downgraded for publication bias	Low
Endometrial cancer	8	4678	High vs low	1.10 (0.91, 1.33)	Very low	Downgraded for inconsistency and imprecision	Low
Gastric cancer	3	869	High vs low	0.77 (0.54, 1.09)	Very low	Downgraded for imprecision	Low
Liver cancer	4	984	High vs low	1.03 (0.76, 1.38)	Very low	Downgraded for imprecision	Low
Pancreatic cancer	9	3277	High vs low	0.90 (0.75, 1.07)	Very low	Downgraded for imprecision	Low
Bladder cancer	2	1315	High vs low	1.01 (0.78, 1.31)	Very low	Downgraded for imprecision	Low
Cardiovascular mortality	4	2582	High vs low	1.06 (0.89, 1.27)	Very low	Downgraded for serious risk of bias and imprecision	Very low
All-cause mortality	5	10,768	High vs low	0.97 (0.80, 1.18)	Very low	Downgraded for serious risk of bias, imprecision, inconsistency and publication bias	Very low
Renal cell carcinoma	2	1315	High vs low	0.78 (0.38, 1.17)	Very low	Downgraded for inconsistency and imprecision	Very low
Ovarian cancer	2	739	High vs low	0.94 (0.37, 3.26)	Very low	Downgraded for inconsistency and imprecision	Very low
Lung cancer	2	1312	High vs low	0.96 (0.75, 1.22)	Very low	Downgraded for imprecision, indirectness and inconsistency	Very low

one meta-analysis on the association of dietary GI/GL and depression (Salari-Moghaddam et al. 2019) evaluated the strength of the evidence with the use of the GRADE approach (Guyatt et al. 2008).

With regard to CVD, our umbrella review demonstrated that higher dietary GI was associated with a higher risk of CHD, and higher dietary GL values may increase the risk of CHD and stroke. For T2D, both high GI and GL values were associated with a higher risk. Our results regarding the association of dietary glycemic indices with the risk of CVD are in line with those of a published meta-analysis of prospective cohort studies which suggested a strong evidence for the relation of dietary glycemic index and load with the risk of CHD (Mente et al. 2009).

Diets with high GI and GL values can exacerbate postprandial hyperglycemia (Pawlak, Kushner, and Ludwig 2004), and thereby may increase the risk of CVD and T2D. There is evidence that consumption of diets with high GI values may induce low-grade systemic inflammation and thereby, may increase levels of biomarkers of systemic inflammation (Wolever et al. 2008). A recent meta-analysis of randomized controlled trials suggested that diets with low GI and GL values may have anti-inflammatory properties (Buyken et al. 2014). It has also been shown that lower dietary GI is associated with lower dietary inflammatory index score, which reflects the inflammatory potential of diet (Kim et al. 2017). Pharmalogic reduction of inflammation with lower C-reactive protein levels has been shown to reduce the risk of CVD (Ridker et al. 2005) and may be part of the mechanism by which low GI diets reduce the risk of CVD. In this respect, it is of interest that higher GI diets have been related to low HDL-C levels as a negative acute phase protein (Jenkins et al. 2008).

Diets with higher GI and GL values were also associated with unfavorable cardiometabolic abnormalities including dyslipidemia (Liu et al. 2001) and insulin resistance (Runchey et al. 2012). A meta-analysis of randomized controlled trials indicated that lower dietary glycemic index and load may significantly reduce blood pressure in healthy individuals (Evans et al. 2017), a strong risk factor for both CVD and T2D. On the other hand, intake of low GI diets can reduce energy intake and obesity in adults (Youn et al. 2012). A prospective investigation in European countries indicated that consumption of high GI diets may lead to a modest increase in waist circumference (Du et al. 2009) and thereby, may be a risk factor for abdominal adiposity. Furthermore, diets with greater dietary glycemic indices may increase CVD risk through negative effects on oxidative stress (Hu et al. 2006) and vascular and endothelial functions (Lavi et al. 2009). Finally, long-term consumption of diets with high GL and GI and subsequent prolonged hyperglycemia may lead to β-cells failure (Pawlak, Kushner, and Ludwig 2004).

With regard to cancer risk, low-certainty evidence suggested that higher dietary GI was significantly associated with a higher risk of colorectal, breast and bladder cancers. Regarding cancers for other sites, there were no significant associations and the certainty of the evidence was rated very low. However, the number of primary studies for those cancers with nonsignificant associations was very low. Exception was pancreatic cancer, for which the analysis of eight prospective cohort studies showed a nonsignificant association. For dietary GL, we did not find significant associations between higher dietary GL and the risk of cancers at any site.

We also evaluated the quality/strength of the evidence using NutriGrade score. This score is a tool to judge the meta-evidence of randomized controlled trials and cohort studies in nutrition research and considers nutrition-specific aspects such as dietary assessment methods and diet-associated biomarkers. The results indicated that, for most

outcomes, the strength of the evidence was upgraded by one level when we used NutriGrade score to rate the quality of the evidence. It is worth mentioning that there is concern that the GRADE system may benefit from some further developments to adequately capture cohort studies especially in nutrition (Katz et al. 2019; Qian et al. 2020). Therefore, we have also compared GRADE and NutriGrade systems designed for nutritional studies. There are some important differences between GRADE and NutriGrade approaches which may explain the observed differences. For example, in GRADE scale, the strength of the evidence for prospective cohort studies starts as low-quality evidence. The strength of the evidence is then downgraded to very low when there are shortcomings such as serious risk of bias, inconsistency, indirectness, imprecision, and publication bias. However, in the NutriGrade scale, the quality/strength of the evidence for an association could be high despite possible shortcomings (e.g., high heterogeneity and indication for publication bias) if the meta-analysis scores the maximum amount of points for the other items (Neuenschwander et al. 2019). Further research is needed to compare these two approaches to rate the quality of the evidence obtained by meta-analyses of prospective cohort studies in nutrition research.

This review has several strengths. We performed an umbrella review of meta-analyses of prospective cohort studies and presented a summary of all published meta-analyses. We summarized existing evidence regarding health outcomes of diets with high GI and GL values. We evaluated the certainty of the evidence, as well as the methodological quality of published meta-analyses. We excluded retrospective and cross-sectional studies, as well as studies that were conducted in diseased populations. In this umbrella review, all published meta-analyses reported forest plots and therefore, we were able to recalculate SRRs for all outcomes with the use of a random-effects meta-analysis.

However, limitations should be noted. First, we included meta-analyses of prospective cohort studies and therefore, the results are subject to confounding. However, of 72 prospective cohort studies used in this review, 90% controlled for age, 86% controlled for sex, 82% controlled for energy intake and body mass index, and 75% controlled for smoking status and alcohol drinking. Second, we did not evaluate the associations in different subgroups, for example in each sex separately. A published meta-analysis of prospective cohort studies found significant positive association between dietary GL and the risk of CHD, with significant association in women but not in men (Fan et al. 2012). Thus, potential sex differences in the associations need to be further explored. Geographical location may be another potential confounder. Dietary habits vary substantially in different geographical locations and thereby, contribution of dietary components to the GL may be different in different regions. For instance, white bread and potatoes are the two major contributors to the GL in Western countries (Levitan et al. 2007; Liu et al. 2002), while white rice is the major contributor in Asian populations (Oba et al. 2010). Third, of 36 SRRs reported in this umbrella review, There were <5 primary studies available for 18 SRRs, 5-9 primary studies for 10 SRRs, and ≥ 10 studies for 8 SRRs. For example, only two prospective cohort studies were available for the analyses of gallbladder disease, renal cell carcinoma and ovarian, bladder and lung cancers, three for gastric cancer, and four for CVD mortality and liver cancer. Thus, further well-performed prospective cohort studies are needed to investigate the association of diets with high GI and GL values with risk of chronic disease. Finally, of 18 included meta-analyses with 36 SRRs, only one meta-analysis (dietary GI and T2D) performed dose-response meta-analysis. According to the GRADE approach, the certainty of the evidence can be upgraded by one level when there was evidence of a significant dose-response association. Thus, future meta-analyses should test potential dose-response associations when evaluating the association of dietary GI and GL with disease risks.

Conclusions

The present study reviewed published meta-analyses of prospective cohort studies on the association of dietary GI and GL with the risk of chronic disease and found significant positive associations between dietary GI and the risk of CHD, T2D, gallbladder disease, and colorectal, breast and bladder cancers. There was also positive associations between dietary GL and the risk of T2D, CHD, gallbladder disease, and stroke. The certainty of the evidence was rated from very low to low. Further well-designed prospective cohort studies are needed to test the association between glycemic properties of the diet with cancer risk.

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