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SYSTEMATIC REVIEWS AND META-ANALYSES

Carbohydrate intake and risk of metabolic syndrome: A dose–response meta-analysis of observational studies

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KEYWORDS
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Dose–response analysis;
Meta-analysis;
Metabolic syndrome;
Observational study

Abstract *Background and aims:* Epidemiological association studies have reported inconsistent findings on the relationship between carbohydrate intake and risk of metabolic syndrome (MetS). Therefore, we aimed to conduct the first dose–response meta-analysis to investigate this effect.
Methods and results: A systematic search in PubMed and Web of Science databases from their inception to June 01, 2019, together with relevant literature scrutiny, was performed to identify related studies for inclusion into the meta-analysis. We calculated the odds ratios (ORs) with 95% confidence intervals (CIs) using a random effects model. Furthermore, subgroup, sensitivity, heterogeneity, and publication bias analyses were performed. This meta-analysis included 14 cross-sectional and four cohort studies, totaling 284,638 participants and 69,554 MetS cases. The highest versus the lowest carbohydrate intake values were associated with an increased risk of MetS (OR: 1.253, 95% CI: 1.147–1.368), with moderate heterogeneity (I^2 = 54.5%). Using dose–response analysis, we found a linear association between carbohydrate consumption and MetS risk with a corresponding OR of 1.026 (95% CI, 1.004–1.048) and with significant heterogeneity (I^2 = 82.0%) at 5% energy intake from carbohydrates. We have found similar results using subgroup analyses for major study characteristics and adjustment for confounders. Sensitivity analysis further enhanced the robustness of the results, and no publication bias was detected.
Conclusion: Carbohydrate intake is associated with an increased risk of developing MetS. Therefore, additional large prospective cohort studies are warranted to confirm our findings.

Introduction

Metabolic syndrome (MetS) represents a concurrence of interrelated metabolic disorders characterized by unregulated glucose metabolism and insulin levels, central obesity, mild dyslipidemia, and hypertension [1]. The prevalence of MetS is rapidly increasing worldwide. The overall prevalence of MetS in the United States increased from 32.9% in 2003–2004 to 34.7% in 2011–2012 [2]. A

Abbreviations: ATP III, National Cholesterol education Program Adult Treatment Panel III; BMI, body mass index; DR, Dietary record; FFQ, Food Frequency Questionnaire; IDF, International Diabetes Federation; MetS, Metabolic syndrome; MeSH, Medical Subject Heading; MOOSE, Meta-analysis Of Observational Studies in Epidemiology; SBP, systolic blood pressure; TC, total cholesterol; TG, serum triglyceride.

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similar high prevalence of MetS has also been observed in southern Iran [3], Brazil [4], China [5], and Middle Eastern countries [6]. Furthermore, previous studies have suggested that MetS is associated with the risk of coronary heart disease and other forms of cardiovascular atherosclerotic diseases (CVD), type 2 diabetes mellitus, and breast and colorectal cancers [7–9]. Because of these associated risks, MetS and its potential health consequences are currently considered an important public health concern, and controlling the development of MetS is therefore of great significance.

Environmental factors including urbanization and westernization can significantly affect the prevalence of MetS among various groups, and it is important to highlight the role of nutrition in clinical care advocacy, research, and policy [10].

Carbohydrates are a major macronutrient, and previous studies have investigated the associations between carbohydrate intake and MetS but have found inconsistent results [8,11–27]. For example, a cross-sectional study reported that the quantity of carbohydrate intake has a positive association with the risk of MetS in women with a body mass index (BMI) $\geq$25 kg/m^2 but not in women with a BMI$<$25 kg/m^2 and men [17]. In another cross-sectional study, carbohydrate intake appeared to be broadly unrelated to the prevalence of MetS [13].

Thus far, the role of carbohydrate intake with the risk of developing MetS has not been systematically reviewed, particularly by quantitative meta-analysis. Therefore, we performed a meta-analysis of observational studies to quantify the association between carbohydrate consumption and risk of MetS. Furthermore, we investigated the possible dose–response curves and formally assessed the potential causes of heterogeneity, which may lead to a deeper understanding of the nature of the associations between carbohydrate intake and MetS.

Methods

This study was performed following the Meta-analyses Of Observational Studies in Epidemiology (MOOSE) guidelines [28]. The study protocol was registered with PROSPERO (CRD42019130987).

Literature search

We searched PubMed and Web of Science databases for studies involving carbohydrate consumption and risk of MetS that were published from inception to June 01, 2019, to identify relevant publications. The following keywords and/or MeSH terms were searched: metabolic syndrome X or metabolic syndrome or syndrome X or insulin resistance syndrome or MetS and dietary carbohydrates or carbohydrates. No restrictions were applied. The references cited in the retrieved articles were checked to identify additional studies.

Study selection

Two independent reviewers carried out study selection and exclusion procedures. Studies were included if they met the following criteria: 1) use of any one of the observational study designs (e.g., as a cohort study, case–control study, or cross-sectional study); 2) the exposure of interest as carbohydrate intake; 3) reporting on the risk of MetS as the outcome of interest rather than only reporting on the risk of the MetS component; 4) reporting of the usable risk estimates (e.g., odds ratio [OR] or necessary data for calculation) between carbohydrate consumption and MetS; 5) focus on the general population (aged 18 years and above); 6) publication in the English language.

Studies were excluded if they met the following criteria: 1) lack of original data, comments, letters, and unpublished results; 2) reporting of risk estimates that could not be summarized; 3) not reporting on the actual carbohydrate intake (e.g., score of a low-carbohydrate diet); 4) failing to calculate the proportion of energy obtained from carbohydrate intake from the total energy (e.g., calculating the proportion of energy obtained from carbohydrate intake from the energy obtained from other three major energy-supplying nutrients); 5) focus on unhealthy populations.

Data abstraction and quality evaluation

Three reviewers independently extracted the following information of study characteristics from the included publications: authors, publication year, study region, study design, sample size (numbers of cases and non-cases), gender, age range or mean age of participants, method of dietary assessment, criteria for MetS definition, and factors adjusted in multivariable models. We also extracted the data of total dietary carbohydrate intake, which included all sugars/free sugars, and the data of maximally adjusted risk estimates for pooling analyses. Where necessary, we contacted the corresponding authors of the included studies to gather missing data.

Assessment was performed with the Newcastle Ottawa Scale (NOS) to evaluate the risk of bias in the cohort studies [29]. Each study was assigned scores on the basis of three criteria (selection, comparability, and outcomes), and we added a point to assess whether the data analysis used had an energy-adjusted residual or nutrient-density model [30]. The maximum score was ten, and the minimum score was zero. A score range of eight to ten was reflective of high methodological quality, a score range of four to seven indicated moderate quality, and a score range of four or less indicated low quality. A modified version of the National Institutes of Health Quality Assessment Tool for Observational Cohort and Cross-Sectional Studies was used for assessing the quality of the included cross-sectional studies [31]. This assessment was modified to

make it more relevant for cross-sectional research, resulting in the need to assess each article for 11 out of the 14 questions; therefore, study quality could range from 0 to 11. A score of 10 or 11 indicated good quality, a score range of 6–9 as fair quality, and a score below six as poor quality [32].

Statistical analysis

In this meta-analysis, risk ratio (RR) was considered equivalent to OR [33]. To assess the associations between carbohydrate intake and MetS risk, we used OR and its 95% confidence interval (CI) as a measure of effect size for all studies. We pooled the risk estimates of developing MetS from the highest versus the lowest values of carbohydrate intake using a random effects model. For studies that had not used the lowest category as a reference, the OR and its 95% CI were recalculated [34]. In cases where only separate ORs for men or women were available in the original report, we pooled sex-specific ORs using fixed effects models for subsequent meta-analysis where possible. This ensured that inter-study heterogeneity was not underestimated. We also pooled ORs specific for methods of dietary assessment using fixed effects models for subsequent meta-analysis when a study used different methods to assess carbohydrate intake, and we estimated OR separately.

For the dose–response meta-analysis, we first estimated the study-specific linear trends between exposure and outcome using the method described by Greenland and Longnecker [35]. The estimated linear trends were then pooled with a random-effects meta-analysis. For each study, the mean or median consumption level of each category of carbohydrate was assigned to each corresponding OR. When the lowest or highest categories were unbounded, we assumed the width of the category to be the same as that of the adjacent category when estimating themed points. In the studies conducted by Nabuco et al. [21] and Kim et al. [17], carbohydrate intake was measured in grams (a weight); these data were converted to a percentage of the total energy intake by multiplying by four and then dividing the mean daily total energy intake (1 g carbohydrate = ≈4 Kcal energy) [36]. In addition, we examined nonlinear associations between carbohydrate consumption and the risk of MetS using restricted cubic splines with 3 knots at fixed percentiles (10%, 50%, and 90%). For inclusion into the dose–response meta-analysis, the size of the risk effect should be provided for at least three quantitative categories of carbohydrate consumption and sufficient detail regarding the number of cases and participants or person-years for each category should be available.

Potential small study effects such as publication bias were evaluated by funnel plots and Egger's and Begg's tests. Heterogeneity was evaluated by calculating I^2 values [37], and we also reported the heterogeneity as low, moderate, and high with I^2 values of 25%, 50%, and 75%, respectively [38]. To assess the sources of heterogeneity among studies and test the robustness of the associations, we conducted subgroup analyses and sensitivity analyses, respectively.

Subgroup and meta-regression analyses were performed according to the study design (cross-sectional or cohort studies), location (Asian or non-Asian countries), number of cases (<600 or ≥600), sex (men or women), age range (adult, old people, or young adult), exposure measurement (Food Frequency Questionnaire (FFQ), dietary records [DR], 24 h recall, or others), MetS definition criteria (Adult Treatment Panel [ATP] III or other criteria), adjusted BMI, total energy intake, physical activity, smoking status, and drinking status (yes or no). For sensitivity analyses, we excluded each study in sequence. All data analyses were calculated using STATA/SE 11.0 software, and P values < 0.05 were considered as significant.

Results

Literature search

Fig. 1 illustrates the detailed literature screening processes. Briefly, 3,852 publications were identified from the two databases, after exclusion of duplications and papers that did not meet the inclusion criteria. We obtained 52 full-text articles of potentially relevant studies, and after the text was fully reviewed, we excluded 34 articles. Ha et al. [16] reported separate risks of MetS for different populations (American and Korean); therefore, this study was regarded as two independent reports. In total, 18 publications with 19 reports of 69,554 MetS cases were included in the final meta-analysis.

Characteristics of the included studies

The characteristics of the 18 publications (19 reports) are summarized in Table 1. The 18 included studies, which represented a total of 69,554 MetS cases and 215,084 noncases, were published between 2001 and 2018. Briefly, we included four cohort studies [12,14,15,20] and 14 cross-sectional studies [8,11,13,16–19,21–27]. Of these 19 reports, 11 were conducted in Asian countries [8,11,14–18,20,22–24] and eight were conducted in non-Asian countries [12,13,16,19,21,25–27]. Of these 18 studies, nine measured consumption of carbohydrates using a FFQ [13–15,17,18,20,23,26,27], seven by 24 h recall [8,16,21,22,24,25], one by FFQ and 24 h recall [11], and one by other methods [19]. With regard to MetS definition, 15 reports adopted the ATP III criteria or its adapted version [8,11,12,14,16–22,24,26,27], and the rest used alternative criteria [13,15,23,25]. All studies adjusted for age, except for one study, where the population were all born in 1946 and were therefore of the same age [12]. Most reports controlled for conventional risk factors including BMI

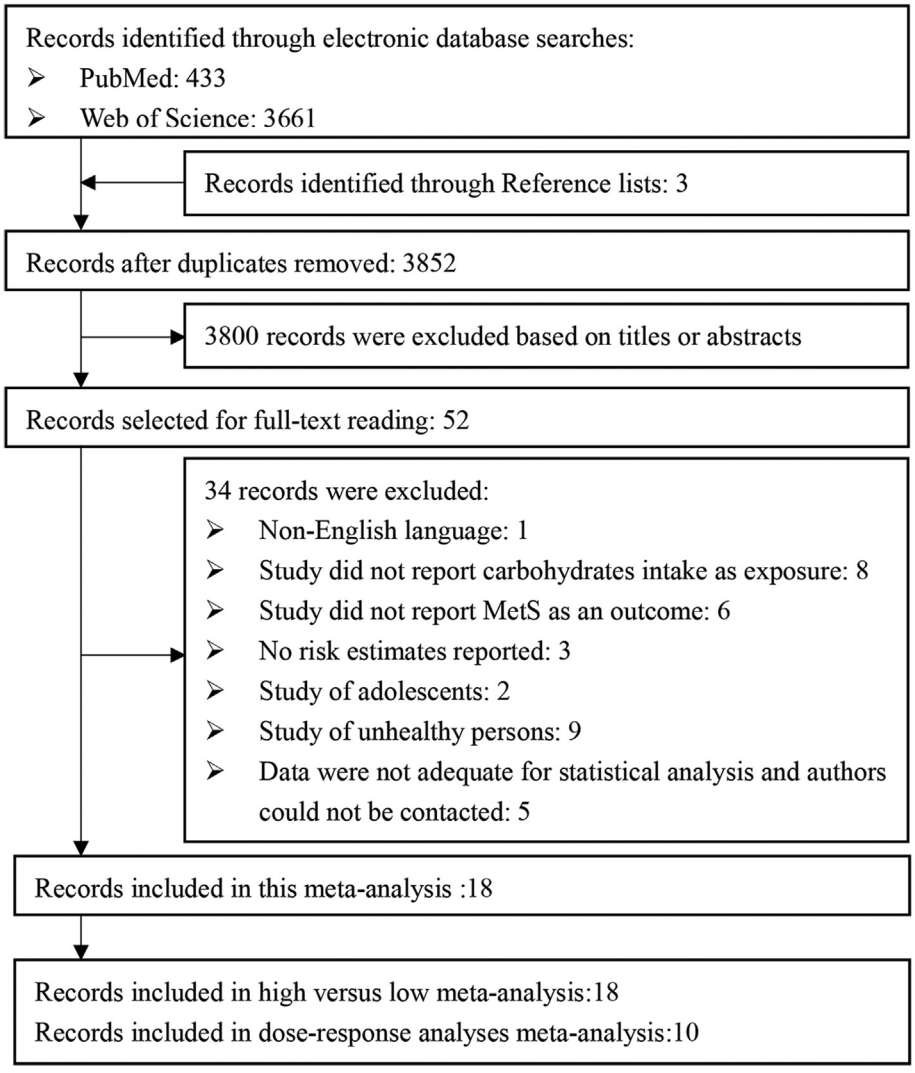

Figure 1 Flow diagram of the study search process.

(n = 11), cigarette smoking (n = 16), alcohol intake (n = 14), physical activity (n = 16), and total energy intake (n = 12).

A detailed quality assessment of the cohort studies is shown in Supplementary Tables 1 and 2. In general, one cross-sectional study and two cohort studies were of high quality.

High versus low meta-analysis

We included all 18 reports, and the pooled OR of MetS for the highest versus the lowest category of carbohydrate intake was 1.253 (95% CI, 1.147−1.368, Fig. 2), with moderate heterogeneity (I^2 = 54.5%, P = 0.003). There was no significant small study bias (Begg's test P = 0.102, Egger's test P = 0.276, Supplementary Fig. 1).

For different subgroup analyses, the associations between carbohydrate consumption and risk of MetS did not differ substantially by major study characteristics and adjustment for confounders. Furthermore, the results of meta-regression analysis demonstrated a significant heterogeneity between the stratified analysis by MetS definition, adjustment for BMI (P = 0.042), cigarette smoking (P = 0.028), and alcohol intake (P = 0.047), which indicated that these confounders may contribute to the heterogeneity of all studies in the pooled analysis (Table 2). Sensitivity analysis, performed by excluding each study in sequence, had no influence on the overall results (Supplementary Fig. 2).

Dose−response analyses

Ten reports were included for the dose−response meta-analysis of the association between carbohydrate consumption and risk of MetS. The pooled estimate of OR from the linear dose−response meta-analysis was 1.026 (95% CI, 1.004−1.048) per 5% of the energy from carbohydrate intake (Fig. 3). There was significant heterogeneity between the studies (I^2 = 82.0%, P = 0.000). We did not find a nonlinear association between carbohydrate intake and

Table 1 Baseline characteristics of the included studies.

Study (First author, year)	Location	Study design	Participants (MetS/total)	Men/Women	Age (years)	Exposure measurement	MetS definition	Adjustments
Ahn 2017 [11]	Korea	cross-sectional study	1643/10,286	3996/6290	19–65	24 h recall and FFQ	ATPIII	sex, age, BMI, residence area, education level, smoking and drinking status, physical activities, obesity
Almoosawi 2013 [12]	England	cohort study	390/1098	738/750	53	5-day estimated dietary records	ATPIII	daily total energy intake, sex, social occupation, region, smoking status, alcohol intake status, recreational physical activity
Brunner 2001 [13]	the UK	cross-sectional study	692/6343	4480/1863	39–62	FFQ	clustering of risk factors	age
Bruscato 2010 [25]	Brazil	cross-sectional study	91/284	0/284	≧60	24 h dietary recall	IDF	age, smoking, physical activity, education level, total energy intake, fiber intake in the diet
Carnethon 2004 [19]	the USA	cross-sectional study	575/4192	2323/1869	24.9 ± 3.6[a]	Diet history survey	ATP III	age, race, sex, crude fiber intake, education, BMI, physical activity, smoking status, alcohol intake, crude fiber intake, total fat intake, weight change from baseline to year, physical activity level
Cho 2017 [14]	Korea	cohort study	4744/5565	2696/2869	40–69	FFQ	ATP III	age, sex, BMI, income status, education status, smoking status, alcohol consumption status, physical activity level
Feng 2015 [15]	China	cohort study	369/2734	858/1876	20–74	FFQ	IDF	age, sex, BMI, smoking status, drink, physical activities, total energy, fat and fiber intake, SBP, TC, and TG
Ha (Korean) 2018 [16]	Korea	cross-sectional study	3450/20,515	8236/12,279	men: 40.6 ± 0.2, women: 41.5 ± 0.2[b]	24 h dietary recall	ATP III	age, alcohol consumption, body mass index, current smoking status, education level, family income, physical activity, survey period, total energy intake
Ha (US) 2018 [16]	the USA	cross-sectional study	612/3324	1669/1655	men: 38.4 ± 0.6, women: 39.8 ± 0.5[b]	24 h dietary recall	ATP III	age, alcohol consumption, body mass index, current smoking status, education, ethnicity, family income, physical activity, survey period, total energy intake
Kim 2008 [17]	Korea	cross-sectional study	276/910	340/570	≧20	FFQ	ATP III	age, smoking status, alcohol intake, education, family history of disease, BMI, physical activity, fiber intake, total energy intake
Kwon 2018 [8]	Korea	cross-sectional study	5825/15,582	6737/8845	20–64	24 h dietary recall	ATP III	age, BMI, current smoking, alcohol intake, regular exercise, total energy intake, protein intake, antidyslipidemia medication

Lee 2018 [18]	Korea	cross-sectional study	39,655/161,326	53,704/107,622	Urban: 51.34 ± 0.02[a], Rural: 53.95 ± 0.05[a]	FFQ	ATP III	age, residential area, household income, education level, alcohol, smoke, exercise, BMI, daily total energy intake
McKeown 2004 [27]	the USA	cross-sectional study	606/2384	1290/1544	30–62	FFQ	ATP III	sex, age, cigarette dose, total energy intake, alcohol intake, percentage saturated fat, percentage polyunsaturated fat, multivitamin use, physical activity
Mirmiran 2008 [20]	Iran	cohort study	72/410	184/226	18–74	FFQ	ATP III	age, sex, BMI, total calorie and food group intake, smoking, physical activity
Nabuco 2018 [21]	Brazil	cross-sectional study	54/245	0/245	≧60	24 h dietary recall	ATP III	chronological age, skeletal muscle mass, % body fat
Park 2017 [22]	Korea	cross-sectional study	8536/38,829	15,770/23,059	˃19	24 h dietary recall	ATP III	sex, age, BMI, residence area, education level, smoking status, alcohol consumption, physical activities, obesity
Shirani 2015 [23]	Iran	cross-sectional study	85/442	0/442	˃20	FFQ	IDF	age, family history of diabetes, family history of stroke, medication use, BMI
Song 2014 [24]	Korea	cross-sectional study	1124/6845	2631/4214	30–65	24 h dietary recall	ATP III	age, residence area, education level, smoking status, current alcohol intake, vigorous physical activity, total energy intake
Wannamethee 2006 [26]	the UK	cross-sectional study	755/2934	2934/0	40–79	FFQ	ATP III	age and each of BMI, dietary fat, and carbohydrates were fitted continuously; smoking; physical activity; alcohol intake; social class

Abbreviations: ATP III, National Cholesterol Education Program Adult Treatment Panel III; BMI, body mass index; FFQ, Food Frequency Questionnaire; IDF, International Diabetes Federation; MetS, metabolic syndrome; SBP, systolic blood pressure; TC, total cholesterol; TG, serum triglyceride.

[a] Mean ± SD.

[b] Mean ± SE.

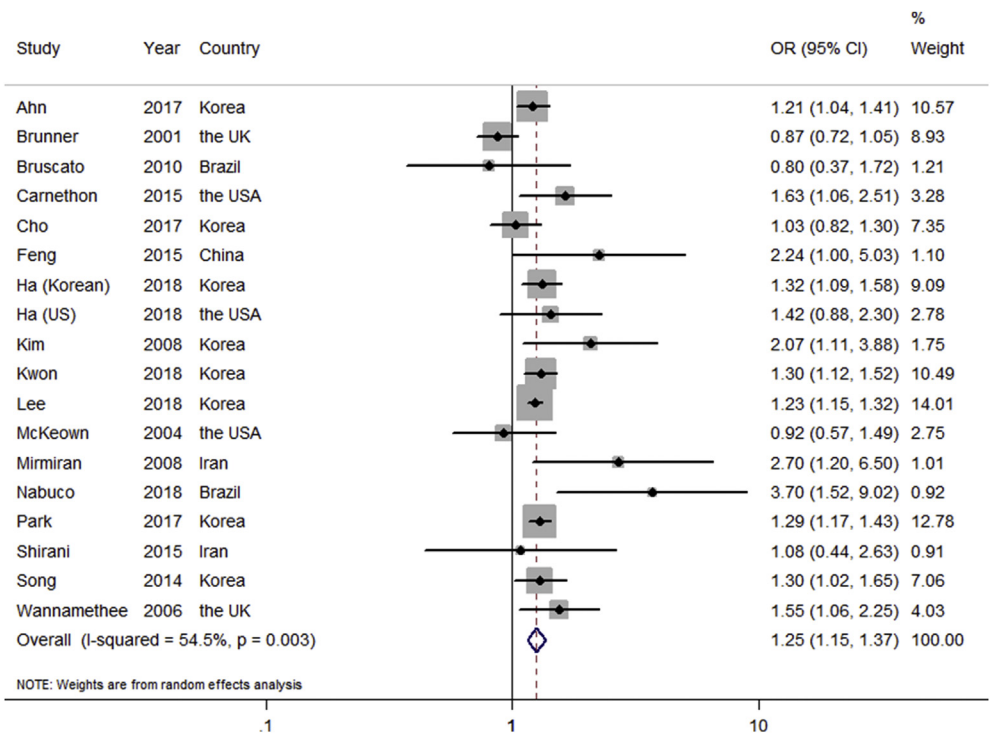

Figure 2 Forest plot (random effects model) of meta-analysis of carbohydrate consumption (highest vs. lowest category) and MetS risk. Squares indicate study-specific ORs (size of the square reflects the study-specific statistical weight), horizontal lines indicate 95% CIs, and diamond indicates the summary OR with its 95% CI.

risk of MetS ($P = 0.131$), and there was no potential for publication bias (Begg's test $P = 0.421$, Egger's test $P = 0.659$, Supplementary Fig. 3).

In subgroup analyses using exposure measurement methods, we found an inverse relationship between dietary carbohydrate intake and MetS with DR (OR, 0.840; 95% CI, 0.759–0.929) but not with other methods, which may be attributed to only one study being included. For other subgroup analyses, the associations between carbohydrate consumption and risk of MetS did not differ substantially in the major study characteristics and adjustment for confounders (Table 2). Univariate meta-regression analysis showed that no covariate had a significant impact on inter-study heterogeneity. Sensitivity analysis, performed by excluding each study in sequence, had no influence on the overall results (Supplementary Fig. 4).

Discussion

The findings of our meta-analyses reveal a positive association between consumption of carbohydrates and risk of MetS when comparing the highest category with the lowest. Moreover, we observed a linear dose–response association between carbohydrate intake and prevalence of MetS, with a 2.6% increase in the risk of MetS per 5% energy from carbohydrate intake.

In our meta-analysis, we found a positive association between carbohydrate intake and MetS in studies conducted in Asian countries but not in those conducted in non-Asian countries. This may be attributed to the different amounts of consumption and sources of carbohydrates among these studies. For example, the mean carbohydrate intake in the highest quintile was 56.29% of the total energy intake in a study carried out in the UK [23]. In contrast, this value was 80.15% in a study carried out in Korea [24]. Furthermore, a previous study has suggested that most participants from low-income and middle-income countries consume more refined sources (such as white rice and white bread) [39]. Taken together, these factors could explain the regional differences we found in the type of carbohydrate consumed. Therefore, when interpreting the results of this meta-analysis, location factors need to be considered.

We found that the heterogeneity was decreased when compared with the overall heterogeneity among studies using either the ATP III criteria or other criteria. For example, the International Diabetes Federation (IDF) was used to define MetS in a Chinese study [15] and ATP III was used in a Korean study [18], suggesting that different methods of defining MetS may account for the heterogeneity in the present study. However, a previous study suggested that although prevalence estimates for MetS were mostly similar in any given population regardless of the definition used, different individuals are identified; there is generally good concordance among all the MetS criteria [7]. However, the different aforementioned associations might be attributed to limited studies with alternative criteria to define MetS.

Table 2 Summary risk estimates of the associations between carbohydrate intake and MetS risk (highest versus lowest and dose–response analysis).

Factor	Highest versus lowest					Dose–response analysis				
	No. of studies	OR (95% CI)	Heterogeneity		Meta-regression analysis	No. of studies	OR (95% CI)	Heterogeneity		Meta-regression analysis
			I^2 (%)	P^*	$P^\dagger$			I^2 (%)	P^*	$P^\dagger$
Overall	18	1.253 (1.147,1.368)	54.5	0.003	–	10	1.026 (1.004,1.048)	82.0	0.000	–
Subgroup analyses										
Design										
Cross-sectional study	15	1.250 (1.146,1.364)	52.8	0.008	0.918	7	1.037 (1.012,1.062)	77.0	0.000	0.253
Cohort study	3	1.673 (0.840,3.334)	72.8	0.025		3	0.976 (0.893,1.066)	87.5	0.000	
Population										
Asian	11	1.260 (1.190,1.335)	15.1	0.300	0.479	6	1.021 (1.001,1.042)	68.9	0.007	0.543
Non-Asian	7	1.278 (0.930,1.755)	72.5	0.001		4	1.009 (0.953,1.069)	89.7	0.000	
No. of cases										
<600	9	1.247 (1.191,1.306)	0.0	0.557	0.558	5	1.033 (0.950,1.123)	86.2	0.000	0.775
≥600	9	1.539 (1.078,2.197)	72.6	0.000		5	1.014 (1.002,1.026)	49.7	0.094	
Sex										
Women	9	1.241 (1.028,1.498)	36.7	0.125	0.970	–	–	–	–	–
Men	7	1.283 (1.048,1.571)	59.6	0.021		–	–	–	–	–
Age range										
Adult	14	1.221 (1.122,1.328)	52.3	0.011	0.191	7	1.022 (1.004,1.040)	65.0	0.009	0.482
Old people	3	1.603 (0.802,3.201)	69.3	0.038		3	0.993 (0.910,1.084)	93.1	0.000	
Young adult	1	1.630 (1.059,2.508)	–	–		–	–	–	–	
Exposure										
FFQ	10	1.209 (1.030,1.418)	64.1	0.003	0.198	6	1.026 (1.000,1.053)	68.9	0.007	0.949
DR	–	–	–	–		1	0.840 (0.759,0.929)	–	–	
24 h-recall	7	1.293 (1.200,1.392)	7.2	0.375		3	1.042 (0.997,1.089)	89.3	0.000	
Others	1	1.630 (1.059,2.508)	–	–		–	–	–	–	–
MetS definition										
ATP III	14	1.283 (1.194,1.378)	34.3	0.100	0.013	9	1.027 (1.004,1.050)	83.9	0.000	0.796
Non-ATP III	4	1.036 (0.696,1.543)	43.0	0.153		1	1.003 (0.929,1.082)	–	–	
Adjusted BMI										
Yes	11	1.296 (1.219,1.378)	9.9	0.350	0.042	6	1.024 (1.004,1.044)	48.0	0.087	0.494
No	7	1.105 (0.912,1.340)	66.7	0.006		4	1.008 (0.954,1.065)	92.5	0.000	
Adjusted total energy intake										
Yes	11	1.300 (1.187,1.423)	23.2	0.223	0.287	5	1.019 (0.970,1.070)	82.7	0.000	0.840
No	7	1.193 (0.999,1.425)	73.7	0.001		5	1.030 (0.998,1.063)	85.1	0.000	
Adjusted physical activity										
Yes	15	1.269 (1.193,1.350)	19.9	0.232	2.42	8	1.018 (0.997,1.038)	76.9	0.000	0.574
No	3	1.407 (0.603,3.281)	79.7	0.007		2	1.054 (0.972,1.143)	74.7	0.047	
Adjusted smoking status										
Yes	15	1.269 (1.193,1.350)	19.9	0.232	0.028	8	1.018 (0.997,1.038)	76.9	0.000	0.574
No	3	1.407 (0.603,3.281)	79.7	0.007		2	1.054 (0.972,1.143)	74.7	0.047	
Adjusted drinking status										
Yes	13	1.262 (1.199,1.329)	7.7	0.369	0.047	8	1.014 (0.993,1.034)	77.9	0.000	0.322
No	5	1.399 (0.778,2.516)	74.9	0.003		3	1.064 (1.018,1.112)	50.4	0.133	

*P for heterogeneity within each subgroup. $P < 0.1$ indicates statistical significance.
†P for heterogeneity between subgroups with meta-regression. $P < 0.05$ indicates statistical significance.
Abbreviations: ATP III, National Cholesterol Education Program Adult Treatment Panel III; BMI, body mass index; DR, dietary records; FFQ, Food Frequency Questionnaire; IDF, International Diabetes Federation; MetS, metabolic syndrome.

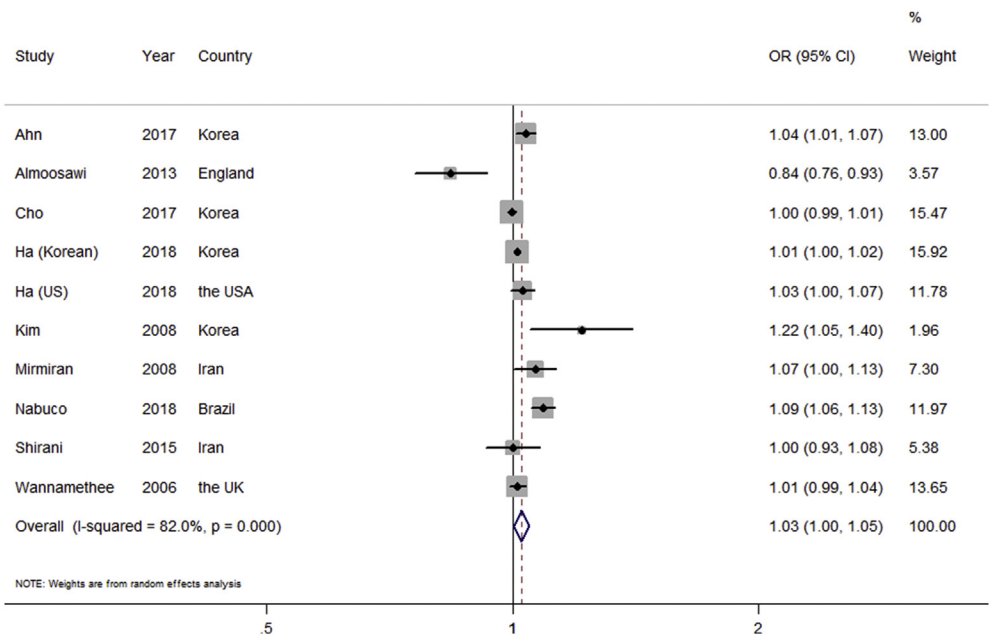

Figure 3 Forest plot (random effects model) of the meta-analysis of carbohydrate consumption (per 5% energy increment) and the risk of MetS. Squares indicate study-specific ORs (size of the square reflects the study-specific statistical weight), horizontal lines indicate 95% CIs, and diamond indicates the summary OR with its 95% CI.

Linear dose–response relationships were observed, with a 2.6% increase in the risk of MetS per 5% energy from carbohydrate intake. Seidelmann et al. reported that both high- and low-percentage carbohydrate diets were associated with an increase in total mortality, with minimal risk observed at 50–55% carbohydrate intake [40]. Therefore, we also observed nonlinear associations between carbohydrate consumption and the risk of MetS but not nonlinear association. This finding may be attributed to the different study designs (most were cross-sectional studies comparing all cohort studies including the Seidelmann et al. study) as well as outcomes of interest (MetS vs. mortality).

There are several plausible biological explanations for the associations between carbohydrate intake and MetS risk. First, the previous study demonstrated that long-term intake of carbohydrates that could be rapidly absorbed, such as glucose, may increase insulin resistance and demand for insulin; hence, the pancreas may become exhausted in terms of insulin production [41]. Second, metabolic regulation of insulin gene expression enables β-cells to maintain adequate stores of intracellular insulin to sustain the secretory demand. Glucose is the major physiological regulator of insulin gene expression [42]. Hence, excessive intake of carbohydrates can cause a high level of blood glucose, which contributes to insulin resistance and therefore influences glucose metabolism. A high-carbohydrate diet, which is common in Asian and less developed nations, tends to have refined sources (such as white rice and white bread) that have low fiber content; this type of diet may reflect poor food quality and confer a chronically high glycemic load that can lead to negative metabolic consequences [39,43,44]. Third, short-term benefits of low- and very low-carbohydrate diets, such as weight loss and improvement in blood pressure and blood lipid profile, have also been shown in normoglycemic individuals [45]. Therefore, there is an inverse association between low-carbohydrate diet and MetS.

Our work has several strengths. First, it is the first meta-analysis that aimed at assessing the association between carbohydrate consumption and MetS risk on the basis of the most comprehensive literature search to date. In addition, the association not only considered carbohydrate intake as a variable but also occurred in a dose–response manner. Second, we carried out numerous subgroup and sensitivity analyses to test the stability and reliability of our findings, which were generally consistent. Third, Egger's linear regression test indicated that the *P* value was not significant, and Begg's rank correlation test showed no publication bias, suggesting that results were not affected by publication bias.

We should not ignore the limitations of the current meta-analysis. First, the recall and selection bias cannot be eliminated owing to the observational nature of the studies included. Cohort studies are less susceptible to such bias, but only four cohort studies were included in the present meta-analysis. Therefore, this result should be interpreted with caution. Second, although a wide range of potential confounding factors have been adjusted for in the original studies, high carbohydrate intake may accompany dietary factors such as total energy intake, salt intake, saturated fat intake, and fiber intake, and some important confounding factors such as physical activities were not well controlled for in some studies. Therefore, residual confounding effects from other lifestyle factors cannot be excluded, which may cause inaccurate evaluations of their effects on the risk of MetS. Third, carbohydrates represent a single nutrient, and this therefore will

not reflect the interactions between multiple nutrients. However, carbohydrates are the main nutrient for energy production in humans, and their effect on the occurrence and development of disease conditions cannot be ignored. Therefore, dietary guidelines are still needed to recommend carbohydrate intake in the future. Finally, possible language bias could have occurred, as we excluded one non-English publication. As language limited us in determining the design details and statistical methodology, we were forced to exclude those articles even if they met all other inclusion criteria.

In conclusion, our findings suggest that dietary carbohydrate intake is associated with an increased risk of MetS. Considering the limitations of this meta-analysis, additional large, prospective studies and randomized controlled trials adjusted for more dietary factors and other confounding factors are warranted to verify our findings. Furthermore, a detailed classification of carbohydrates should be carried out to better understand their role in relation to MetS.

Author contributions

Author contributions are as follows: Zhao YH and Wu QJ contributed to the study design; Xia Y and Chang Q conducted literature search; Liu YS and Zhang JY extracted the data and conducted statistical analyses; Liu YS and Wu QJ wrote the first draft of the manuscript and edited the manuscript. All authors read and approved the final version of the manuscript.

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Conflicts of interest

The authors have nothing to disclose.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.numecd.2019.09.003.

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