Association Between Dietary Carbohydrate Intake and Dietary Glycemic Index and Risk of Age-Related Cataract: A Meta-Analysis

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Purpose. To assess the association of dietary carbohydrate intake and dietary glycemic index (GI), and risk of age-related cataract (ARC), and quantitatively estimate their dose-response relationships.

Methods. We searched Medline, the Cochrane Library, Excerpta Medica database (EMBASE), Institute for Scientific Information (ISI) Science Citation Index, ISI Web of Knowledge, and China National Knowledge Infrastructure (CNKI) databases before October 2013. Two authors independently extracted data and assessed study quality. The random-effect model was used to calculate the pooled odds ratios (ORs). Dose-response analyses, subgroup analyses based on ARC subtypes, heterogeneity, and publication bias assessment were also carried out.

Results. Seven studies were included in our meta-analysis. The pooled ORs of ARC for the highest versus the lowest category of carbohydrate intake and GI were 1.18 (95% confidence interval [CI]: 1.01–1.38) and 1.15 (95% CI: 1.00–1.32), respectively. Further subgroup analyses based on ARC subtypes suggested a marginally significant association between higher carbohydrate intake and cortical cataract risk (OR: 1.37, 95% CI: 0.99–1.90), and a statistically significant association between higher GI and nuclear cataract risk (OR: 1.23, 95% CI: 1.03–1.46). In addition, a significant dose-response relationship was observed between carbohydrate intake and the risk of cortical cataract.

Conclusions. Our results indicate that higher dietary carbohydrate quantity and GI may be associated with the risk of cortical and nuclear cataract, respectively. The results should be interpreted cautiously and more studies are warranted to clarify this issue.

Keywords: dietary carbohydrate intake, glycemic index, age-related cataract, meta-analysis

Age-related cataract (ARC) remains the leading cause of blindness worldwide.[1] With the global aging of population, the prevalence of cataract is increasing rapidly. Although the lens extraction is usually available and effective, the growing need for cataract surgical resources imposes a heavy personal and societal economic burden.[2] Therefore, prevention through modifying known risk factors appears to offer the best way to the development of nonsurgical strategies for delaying or preventing cataract, which could not only enhance the quality of life for the elderly, but also reduce this enormous public health burden.

In recent years, various risk factors including age, diabetes, smoking, and exposure to UV-B light have been reported to play critical roles in cataract development.[3–5] There have been considerable evidence linking aberrant glucose metabolism to an increased cataract risk,[6–12] and several studies have investigated the possible associations between carbohydrate nutrition and cataract; however, the results of those trials, which examined the association between dietary carbohydrate and risk of various types of cataract in human were inconsistent.[13–19] The aim of our study was to evaluate the evidence from these studies on carbohydrate quantity and quality and the risk of ARC by summarizing it quantitatively with a meta-analysis approach.

Methods

Data Sources, Search Strategy, and Section Criteria

Systematic literature searches were conducted in six databases: Medline, the Cochrane Library, Excerpta Medica database (EMBASE), Institute for Scientific Information (ISI) Science Citation Index, ISI Web of Knowledge, and China National Knowledge Infrastructure (CNKI) up to October 2013. Search terms included "carbohydrate intake," "carbohydrate nutrition," "macronutrition intake," "dietary glycemic index," combined with "age-related cataract," "cataract," or "lens opacities." The references section of relevant reviews and original articles were also scanned for potential trials missed in the primary searches. Titles and abstracts of articles selected from the initial search were first scanned, and then full papers of potential eligible studies were reviewed. This meta-analysis was designed, conducted and reported according to the Preferred Reporting Items for Systematic Reviews and Meta-

Analyses (PRISMA) and Meta-analysis Of Observational Studies in Epidemiology (MOOSE) statements.[20,21]

We included articles if they met all the following criteria: (1) cross-sectional study, case-control, or cohort study published as an original article, (2) the study of interest was the dietary carbohydrate intake and/or dietary glycemic index (GI), (3) the outcome of interest was ARC, and (4) odds ratio (OR), relative risk (RR), or hazard ratios (HR) estimates and their 95% confidence intervals (CIs) were available or could be calculated. When there were overlapped or duplicated data, only the most recent data were included.

Data Extraction

Two reviewers (HW, HZ) independently extracted data using a standardized data extraction form. Any discrepancy was discussed and adjudicated by a third reviewer (PL) until a consensus was achieved. Information extracted from each article included the following items: first author, year of publication, country of origin (continent), type of study design, sample size, mean age, sex, outcomes definitions and grading, OR, RR, or HR, and corresponding 95% CIs for "the highest versus the lowest category of carbohydrate intake" and "the highest versus the lowest category of GI." If a study provided several risk estimates, the best adjusted estimate was extracted. The study quality was assessed using the Newcastle-Ottawa Scale.[22]

Statistical Analysis

We evaluated the association between dietary carbohydrate intake and dietary GI and ARC risk by pooling the results of the included studies. When factors of interest were estimated by greater than or equal to two studies, the pooled ORs and 95% CIs were calculated by a random-effect model, which considered both with-in and between-study variation. For each study, the most fully adjusted ORs for the highest versus the lowest category of carbohydrate intake and GI were used to calculate the pooled estimates. The extent of heterogeneity across studies was checked using the Q statistic and I^2 test.[23,24] P less than or equal to 0.1 and/or I^2 greater than 50% indicates significant heterogeneity. Moreover, we performed subgroup analyses based on ARC subtypes (cortical cataract, nuclear cataract, and posterior subcapsular cataract). Besides, subgroup analyses and sensitivity analyses were adopted to explain the potential heterogeneity.

We analyzed the dose-response relationship between dietary carbohydrate intake and dietary GI and ARC using linear, first-order, and second-order fractional polynomial regression of the inverse variance-weighted data to estimate a curve of best fit.[25] The best-fit curve was selected using decreased deviance compared with the reference model. Comparisons of curves to determine best fit were done using a χ^2 distribution.[25] We used generalized least squares (GLST) for trend estimation of summarized dose-response data.[26]

To assess the publication bias, funnel plots (i.e., plots of study results against precision) were constructed. The Egger's regression test was adopted to test the asymmetry of funnel plots ($P < 0.1$ was considered as statistically significant publication bias).[27] All analyses were conducted using Stata software (version 11.0; StataCorp, College Station, TX, USA), and the significance level was set to P less than 0.05.

Results

Literature Search

A flow diagram of our literature search is shown in Figure 1. After searching Medline, the Cochrane Library, EMBASE, ISI Science Citation Index, ISI Web of Knowledge, and CNKI, we identified 191 articles, 176 of which were excluded after first-pass review of abstracts and titles. After full-text review of the remaining 15 articles, eight articles were excluded for the following reasons: three articles were editorial, comment, or review but not original articles,[28–30] four studies did not evaluate carbohydrate intake or GI,[31–34] and one study did not report OR for the highest versus the lowest category of carbohydrate intake.[35] The remaining seven articles, including six population-based cohort studies[13–18] and one case-control study,[19] were included in the meta-analysis.

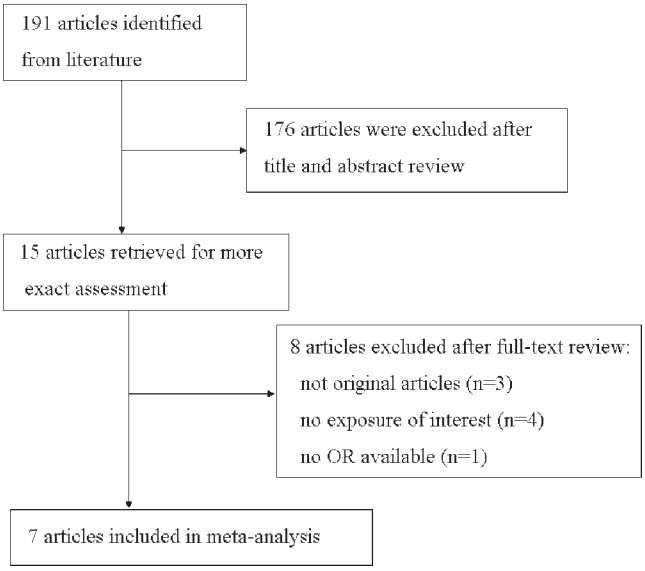

Figure 1. Selection of studies included in the meta-analysis.

Study Characteristics

A total of seven studies with 11,944 participants were included in our meta-analysis, as detailed in the Table. All articles were published between 2000 and 2012. Of these seven studies, three were conducted in the USA,[14,15,18] three in Australia,[13,16,17] and one in China.[19] One of the included studies was case-control study,[19] while the other six were based on cohort studies: two were cross-sectional analysis of baseline data from Blue Mountains Eye Study (BMES)[13] and Age-Related Eye Disease Study (AREDS)[15]; two reported the 5-[17] and 10-year[16] follow-up data of BMES; one analyzed the 14-year follow-up data from the Nutrition and Vision Project (NVP) of Nurses' Health Study (NHS)[14]; and the remaining one study assessed data from the Melbourne Visual Impairment Project (VIP) at the 5-year follow-up visit.[18] All seven studies reported the correlation between dietary carbohydrate intake and ARC risk, while five of them evaluated the association between dietary GI and ARC risk. Participants of the included studies were divided into different categories of three, four, and five according to their dietary carbohydrate intake or GI. Considering the difference in reporting the measurement of carbohydrate intake and GI, we used the highest versus lowest category to measure the association between carbohydrate intake and GI and risk of ARC. Not all the studies reported every subtype of ARC. Age-related cataracts ascertainment was all based on lens photography among the studies, while the definition and grading of cataract was based on different systems: the Wisconsin Cataract Grading System ($n = 3$)[13,16,17]; the Lens Opacities Classification System III ($n = 2$)[14,19]; the Age-Related Eye Disease Study System for Classifying Cataracts ($n = 1$),[15] and the Wilmer Cataract Grading System ($n = 1$).[18]

Table. Characteristics Reported in the Literatures Included in the Meta-Analysis

Reference	Age, y	Sex	No. of Participants	ARC Definition and Grading Cut-Points	ARC Subtypes	Measure/Range of Exposure	Adjusted Variables	Study Quality*
13	49–97	F/M	2900	The Wisconsin Cataract Grading System Cortical cataract: ≥5% cortical opacity; nuclear cataract: grade 4 or 5; posterior subcapsular cataract: any PSC present.	Nuclear Cortical Posterior Subcapsular	Carbohydrate (g/d): Q1–Q5 172.6 (Q1) 268.2 (Q5)	Age, sex, energy	8
14	53–73	F/M	417	LOCS III Nuclear opacities: grade ≥ 2.5; Cortical opacity: grade ≥ 1.0.	Nuclear Cortical	Carbohydrate (g/d):T1–T3 <185 (T1) ≥200 (T3) GI: T1–T3 <73.6 (T1) ≥75.9 (T3)	Age, BMI, summer sun exposure, daily alcohol intake, pack-years of smoking, duration of vitamin C supplement use	8
15	60–80	F/M	3377	AREDS-SCC Nuclear opacities: grade > 2.5; Cortical opacity: grade >0%.	Nuclear Cortical	Carbohydrate (g/d): lowest 25%, middle 50%, and highest 25% (F): <134.0 (lowest 25%) ≥176.1 (highest 25%) (M): <155.4 (lowest 25%) ≥202.3 (highest 25%) GI: lowest 25%, middle 50%, and highest 25% (F): <74.1 (lowest 25%) ≥80.7 (highest 25%) (M): <76.5 (lowest 25%) ≥82.1 (highest 25%)	Age, sex, education, race, BMI, daily alcohol intake, smoking status, sunlight exposure, dietary vitamin C intake, calorie intake, energy	8
17	≥49	F/M	1988	The Wisconsin Cataract Grading System Cortical cataract: ≥5% cortical opacity; nuclear cataract: grade 4 or 5; posterior subcapsular cataract: any PSC present.	Nuclear Cortical Posterior Subcapsular	Carbohydrate (g/d): Q1–Q5 188 (Q1) 284 (Q5)	Age, sex, diabetes, use of oral or inhaled corticosteroids, hypertension, BMI, alcohol and smoking history, myopia, dark brown iris color, sun-related skin damaged, IOP	8
16	≥49	F/M	933	The Wisconsin Cataract Grading System Cortical cataract: ≥5% cortical opacity; nuclear cataract: grade 4 or 5; posterior subcapsular cataract: any PSC present.	Nuclear Cortical Posterior Subcapsular	Carbohydrate (g/d): Q1–Q4 182 (Q1) 280 (Q4) GI: Q1–Q4 51.1 (Q1) 62.3 (Q4)	Age, sex, diabetes, cardiovascular disease, obesity, smoking, myopia, ever use of inhaled steroids	8
18	57.6 (mean age)	F/M	1609	The Wilmer Cataract Grading System Cortical cataract: 4/16 or greater opacity; nuclear cataract: Wilmer standard grade 2 or higher; posterior subcapsular cataract: PSC opacity ≥ 1 mm^2.	Nuclear Cortical	Carbohydrate (g/d): Q1–Q4 (F): 144.54 (Q1) 191.06 (Q4); (M): 229.74 (Q1) 170.21 (Q4) GI: Q1–Q4 (F): 47.45 (Q1) 49.74 (Q4) (M): 57.60 (Q1) 59.66 (Q4)	Age, sex, education, country of birth, BMI, daily alcohol intake, pack-years of smoking, sunlight exposure, AMD status, energy-adjusted dietary vitamin C, vitamin E, β-carotene, lutein/zeaxanthin intake, energy-adjusted linoleic acid, α-linolenic acid, eicosapentaenoic acid, docosahexaenoic acid, total fat intake	8

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TABLE. Continued

Reference	Age, y	Sex	No. of Participants	ARC Definition and Grading Cut-Points	ARC Subtypes	Measure/Range of Exposure	Adjusted Variables	Study Quality*
19	45–85	F/M	720	LOCS III Nuclear opacities: grade ≥4; cortical and posterior subcapsular opacity: grade ≥2.	Nuclear Cortical Posterior Subcapsular	Carbohydrate (g/d): Q1–Q4 Q1: the highest 25% Q4: the lowest 25%	Age, sex, smoking status, alcohol intake, hypertension, diabetes, BMI, family economic level	7

LOCS III, Lens Opacities Classification System III; AREDS-SCC, The Age-Related Eye Disease Study System for Classifying Cataracts; F, female; M, male.

* Study quality was judged based on the Newcastle-Ottawa Scale (range, 1–9 stars).

Besides, the grading cut-points for cataract definition varied among the studies. For participants with more than one type of cataract, three studies only used data of the most severely affected eye,[13,17,19] three studies excluded eyes with mixed cataracts,[14,15,18] and one study did not report the solution method.[16] Most studies provided risk estimates that were adjusted for age (all seven studies), sex (all seven studies), smoking (six studies), body mass index (BMI; five studies), and alcohol intake (five studies). Several studies were adjusted for diabetes (three studies), sun exposure (three studies), vitamin C intake (three studies), hypertension (two studies), myopia (two studies), and education (two studies).

Association Between Dietary Carbohydrate Intake and ARC Risk

The multivariable-adjusted ORs for each study and combination of all studies for the highest versus lowest category of carbohydrate intake are shown in Figure 2. We found that higher carbohydrate intake was significantly associated with increased risk of ARC (OR = 1.18, 95% CI: 1.01–1.38; I^2 = 41.7%; P = 0.033). In subgroup analyses, results from these studies on dietary carbohydrate intake in relation to cortical cataract, nuclear cataract, and posterior subcapsular cataract were inconsistent, with both inverse and positive relationship reported. Seven studies were included for the analysis of the association between carbohydrate intake and cortical cataract risk,[13–19] seven for carbohydrate intake and nuclear cataract risk,[13–19] and four for carbohydrate intake and posterior subcapsular cataract risk.[13,16,17,19] Results obtained revealed a marginally significant association between higher carbohydrate intake and cortical cataract risk (OR = 1.37, 95% CI: 0.99–1.90); however, no such association was found for higher carbohydrate intake with increased risk of nuclear cataract (OR = 1.04, 95% CI: 0.89–1.23) or posterior subcapsular cataract (OR = 1.27, 95% CI: 0.85–1.90).

Statistically significant heterogeneity was found in the studies of carbohydrate intake and cortical cataract (I^2 = 67.3%, P = 0.005), but not in the studies of nuclear cataract (I^2 = 0.0%; P = 0.749) and posterior subcapsular cataract (I^2 = 25.7%; P = 0.257). After removing the studies from BMES in Australian populations,[13,16,17] the heterogeneity was decreased (I^2 = 60.8%, P = 0.054) and stronger associations were found between carbohydrate intake and cortical cataract (OR = 1.97, 95% CI: 1.21–3.21). Furthermore, the estimate was unchanged for the remaining studies of nuclear cataract (OR = 1.02, 95% CI: 0.77–1.34) and posterior subcapsular cataract (OR = 1.24, 95% CI: 0.75–2.63).

Association Between Dietary GI and ARC Risk

Four studies assessed the correlation between dietary GI and ARC risk.[14–16,18] The multivariable-adjusted ORs for each study and combination of all studies for the highest versus the lowest category of GI are shown in Figure 3. We found that higher GI was significantly associated with increased risk of ARC (OR = 1.15, 95% CI: 1.00–1.32; I^2 = 13.1%; P = 0.325). Subgroup analyses were further conducted based on ARC subtype. As shown in Figure 3, all four studies analyzed the association between GI and cortical and nuclear cataract risk. Unlike carbohydrate intake, higher GI significantly increased the nuclear cataract risk by 23% (OR = 1.23, 95% CI: 1.03–1.46); however, no significantly increased risk was observed for cortical cataract (OR = 1.11, 95% CI: 0.81–1.52). In addition, there was statistically significant heterogeneity among studies assessing the association between GI and cortical cataract risk (I^2 = 54.6%; P = 0.086), but not in studies evaluating nuclear cataract risk (I^2 = 0.0%; P = 0.663). After

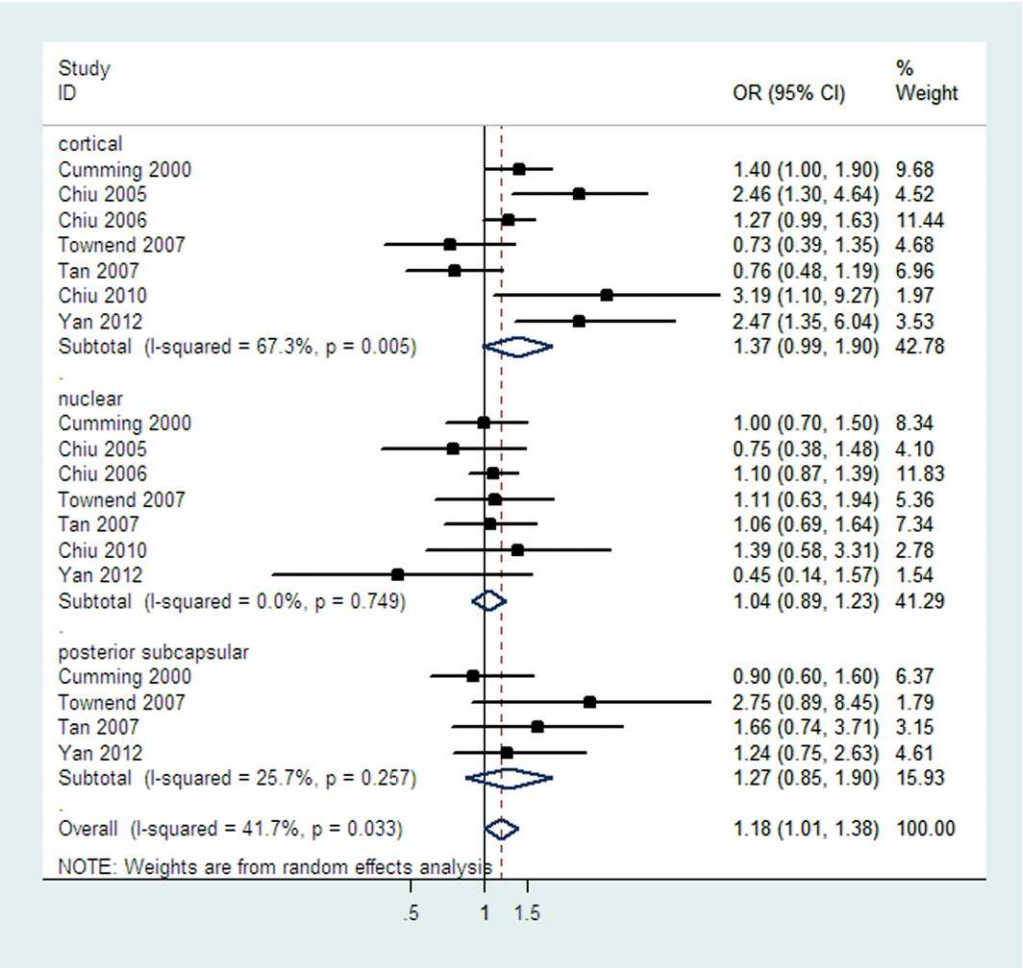

Figure 2. Pooled ORs of ARC and its subtypes for the highest versus the lowest category of carbohydrate intake.

excluding the study by Tan et al.,[16] no statically significant heterogeneity was found between GI and cortical cataract (OR = 0.99, 95% CI: 0.81–1.20; $I^2 = 0\%$; $P = 0.554$).

Dose-Response Meta-Analysis

Five studies were available for dose-response analysis,[13–15,18,19] and we identified a significant dose-response relationship between carbohydrate intake and the risk of cortical cataract (Fig. 4, $P = 0.03$). The fractional polynomial curve (Fig. 4B) indicated that carbohydrate intake might increase cortical cataract in an approximately linear manner (Fig. 4A). Best-fit curve is shown in Figure 4B, and the best-fit parameters, which were calculated by STATA software (StataCorp), were −5 and −4. In contrast, no clear dose-response relationship was observed between increased GI and risk of nuclear cataract ($P = 0.45$).

Publication Bias Analysis

Begg's funnel plot and Egger-weighted regression were applied and no significant publication bias was detected in our meta-analysis, as shown in Figure 5.

Discussion

The current meta-analysis summarizes the results of seven studies, including six population-based cohort studies[13–18] and one case-control study,[19] with a total of 11,944 participants. The results indicated that higher carbohydrate intake and GI significantly increase ARC risk. Interestingly, subgroup analyses based on ARC subtypes suggested a marginally significant association between higher carbohydrate intake and cortical cataract risk, while a statistically significant association between higher GI and nuclear cataract risk. Furthermore, a significant dose-response relationship was observed between carbohydrate intake and the risk of cortical cataract.

An association between carbohydrate nutrition and lens opacities is biologically plausible. Metabolic studies have shown that a high intake of carbohydrates can induce a rapid postprandial glucose response.[36,37] As compared with the rapid uptake of glucose and its subsequent decline to basal level in some cells and tissues, glucose is taken up relatively slow from plasma into the aqueous, through where it passes freely into the lens and is slowly turned over.[14] Prolonged exposure of the lens proteins to elevated glucose concentrations could cause polyol pathway disruption, lipid peroxidation, cross-linking, glycation, and glycation-mediated oxidation, which lead to increased osmotic and oxidative stress in the lens, and eventually opacification.[38–42] In addition, higher glycemic load was observed to be linked with higher plasma concentrations of the inflammatory marker C-reaction protein,[36] which may play an important role in the pathogenesis of ARC.[43] Animal studies also showed that higher concentrations of plasma glucose were associated with increased risk of cataract.[44]

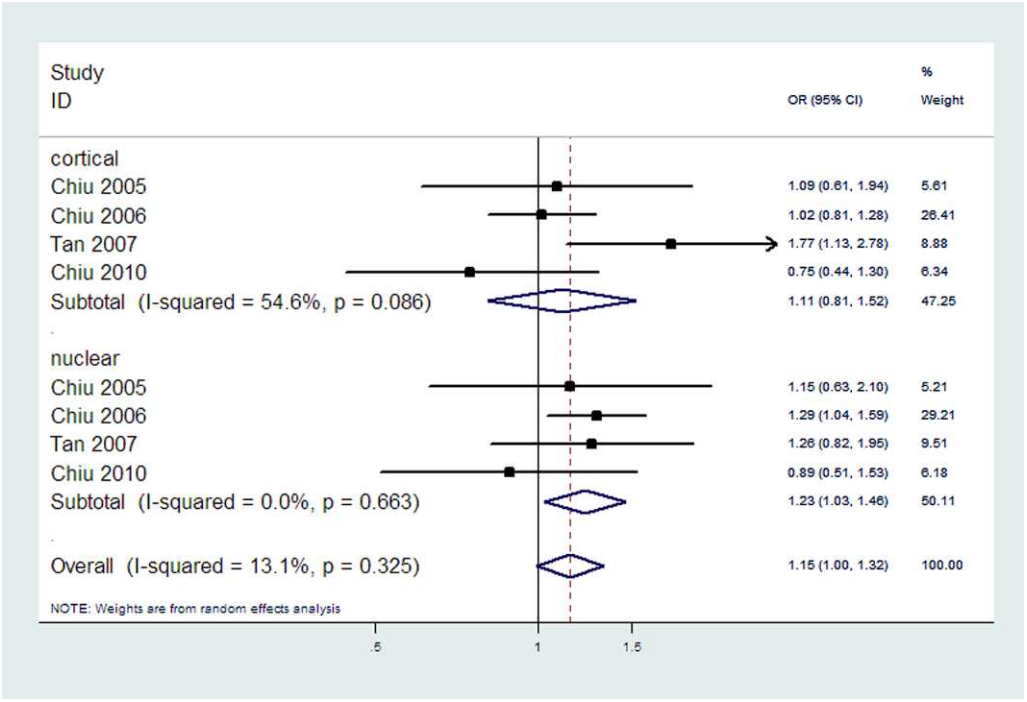

Figure 3. Pooled ORs of ARC and its subtypes for the highest versus the lowest category of GI.

However, the specific mechanisms underlying the association between carbohydrate intake and GI and cortical and nuclear cataract, respectively, remain to be clarified. It has been suggested that higher carbohydrate diets and plasma glucose concentrations might result in chronically enhanced exposure of lens cortex proteins to glucose,[14] and glucose concentrations remained higher in the cortex than in the nucleus of the lens.[45,46] In addition, the insoluble glycated lens proteins in diabetic cataract seemed to be located in the cortical region of lens.[47] Epidemiologic data also suggested that carbohydrate intake has a more consistent link with cortical cataract than with nuclear cataract.[3,10,11,48–50] These data supported our finding that higher carbohydrate intake might increase the risk of cortical cataract. In contrast, GI was shown to be associated with increased risk of nuclear cataract. Glycemic index, which is used to assess carbohydrate quality, was used to measure how fast a carbohydrate food can raise blood glucose.[15] Previous research indicated that after consuming higher GI diets, the peak postprandial blood glucose concentration is higher, and it takes a longer time to return to baseline blood glucose concentration.[51] Studies have shown that the postprandial rise in glucose is consistent with depression of serum antioxidants, that is, the higher the glycemia, the greater the postprandial depression of serum antioxidants.[52] These serum antioxidants including tocopherols, lutein, and vitamin C were reported to reduce the risk of incident nuclear cataract.[53–56] It has been suggested that because the nucleus of the lens, which contained considerably less antioxidant activity compared with the cortex, was significantly more susceptible to oxidation.[57] Therefore, it is

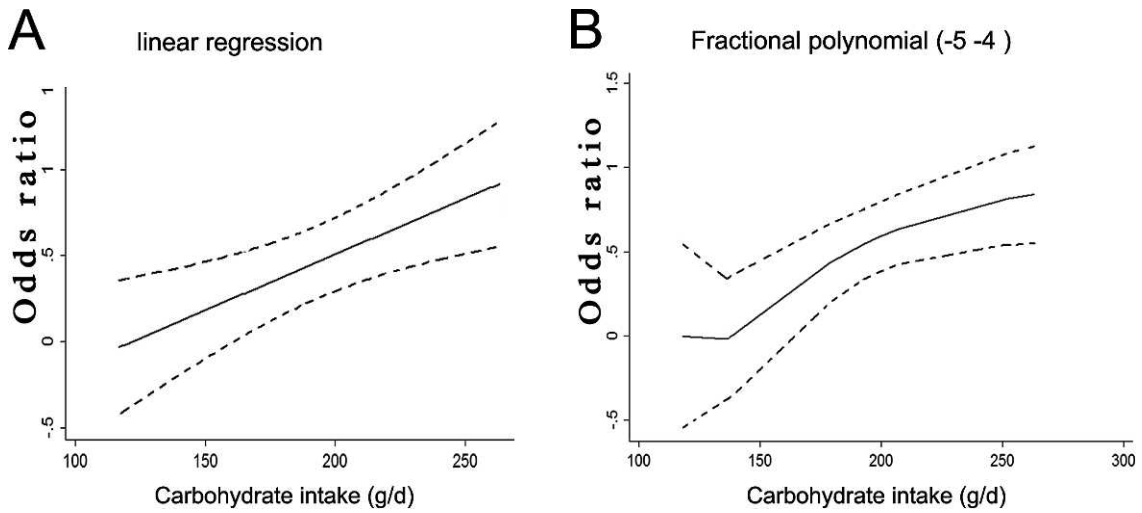

Figure 4. Dose-response analysis of the associations between carbohydrate intake and the risk of cortical cataract. (**A**) Linear regression curve. (**B**) Fractional polynomial curve. *Solid line*: pooled and fitted ORs; *dashed lines*: 95% CIs.

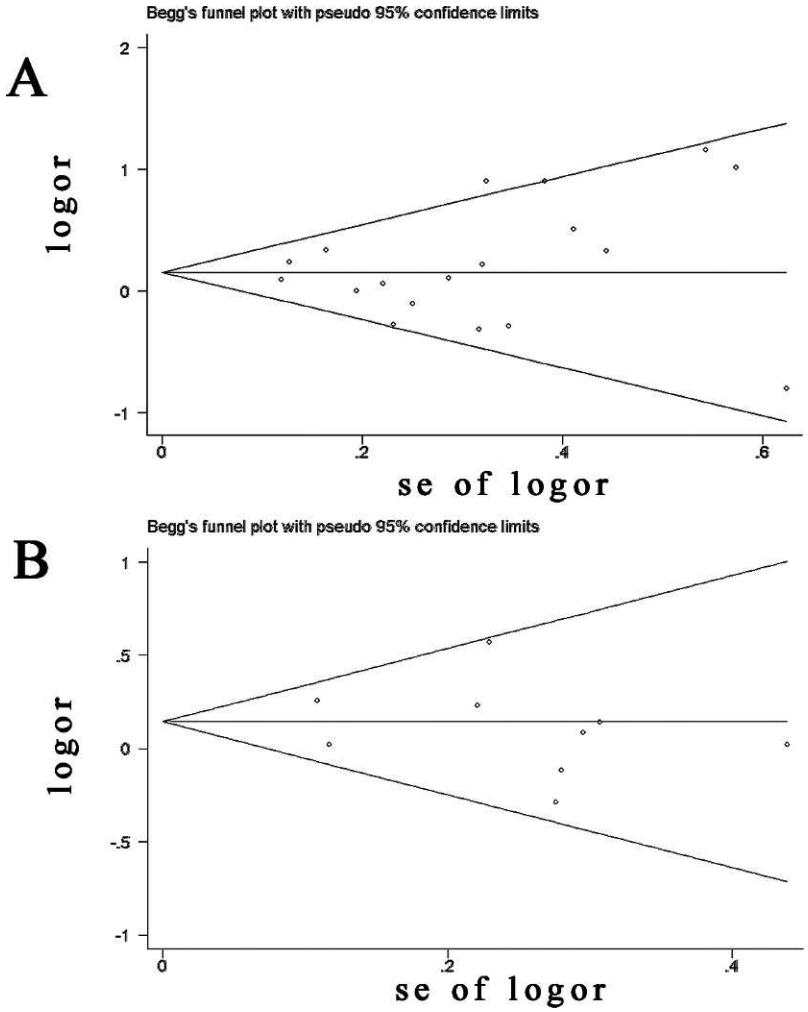

FIGURE 5. The funnel plots for the associations between carbohydrate intake (**A**) or GI (**B**) and cataract risk.

possible that higher GI diets, which could inhibit the serum antioxidants, may cause more oxidative damage in the nuclear tissue of lens than lower GI foods by exposing the tissue to glucose for longer time. However, the exact molecular mechanisms still need further investigation.

To determine the sources of heterogeneity is an important goal of meta-analysis. In the current study, significant heterogeneity was observed in the evaluation of the association between ARC and carbohydrate intake ($I^2 = 41.7\%$; $P = 0.033$). There were also significant heterogeneity in the assessment of the association between cortical cataract risk and carbohydrate intake ($I^2 = 67.3\%$; $P = 0.005$)/GI ($I^2 = 54.6\%$; $P = 0.086$). Subgroup and sensitivity analyses suggested that ARC subtype and individual study might contribute to the between-study heterogeneity. Other factors might also contribute to the heterogeneity, including the wide range of values for the cutoff points for the lowest and the highest categories for carbohydrate intake and GI level, the different cutoff points for cataract definition, various ages of the study population, different adjusting covariates, and the varied range of diet evaluation duration across the studies. A future individual participant data meta-analysis might help solve this problem.

Our study has several strengths. First, this is the first meta-analysis to assess the association between dietary carbohydrate intake and dietary GI and risk of ARC. Second, most of the included studies were of high methodological quality. Third, no publication bias was observed, which indicates that the entire pooled result may be unbiased. Finally, dose-response analyses were applied to assess the association between carbohydrate intake and cortical cataract risk, which further strengthened the association.

This meta-analysis, however, was limited in some aspects as well. First, the number of studies involved in the meta-analysis was not large enough, especially in subgroup analyses. Second, the included studies were limited to the United States, Australia, and China; therefore, the conclusions should be taken cautiously for other ethnic populations. Finally, the studies differed in their procedure for assessing ARC or its subtypes (Table). Measures of ARC, such as levels of lens opacity, introduce the potential of interobserver variation. Thus, this may have led to considerable variability in the conclusion of the present meta-analysis.

In conclusion, the present meta-analysis demonstrates that dietary carbohydrate intake and GI may be associated with increased risk of cortical and nuclear cataract, respectively. In addition, a significant dose-response relationship is observed between carbohydrate intake and cortical cataract risk. The results should be interpreted cautiously and more studies are warranted to clarify this issue. Carbohydrate nutrition represents one of the main dietary components for humans and ARC is still a great health burden, so further mechanistic studies and randomized trials would be warranted to develop preventive strategies according to these findings.

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