Dietary Carbohydrate in Relation to Cortical and Nuclear Lens Opacities in the Melbourne Visual Impairment Project

Chung-Jung Chiu,¹ Luba Robman,² Catherine Anne McCarty,^{2,3} Bickol Nanjan Mukesh,² Allison Hodge,⁴ Hugh Ringland Taylor,² and Allen Taylor¹

PURPOSE. In vitro and in vivo animal studies suggest that dietary carbohydrates play a role in cataractogenesis. Few epidemiologic studies have been conducted to evaluate this association. The objective of this study was to examine the cross-sectional associations between total carbohydrate intake, dietary glycemic index (dGI), and the risk of cortical and nuclear cataracts.

METHODS. After excluding 864 persons from 2473 eligible participants, 1609 eligible nondiabetic participants (mean age, 57.6 years, 55.9% female) in the Melbourne Visual Impairment Project (VIP) were enrolled. Dietary information derived from a semiquantitative food-frequency questionnaire and cataract status graded by the Wilmer protocol (cortical cataract: opacity $\geq 4/16$; nuclear cataract grade ≥ 2) were collected. With the use of the generalized estimating approach to logistic regression to account for the lack of independence between the eyes of an individual, the associations between dietary carbohydrates and risk of cataract in eyes with no or a single type (pure) of cataract were examined.

RESULTS. Multivariate adjustment showed that pure cortical cataract (197 eyes) was significantly associated with total carbohydrate intake (odds ratio [OR] comparing the highest quartile with the lowest quartile = 3.19, 95% confidence interval [CI] = 1.10–9.27; $P_{\text{trend}} = 0.017$). The OR for nuclear cataract

(366 eyes) comparing the third quartile of dGI with the first quartile (OR = 1.64, 95% CI = 1.02–2.65) was significant, but there was not a consistent dose-response association ($P_{\text{trend}} = 0.75$).

CONCLUSIONS. Carbohydrate intake may be optimized to prolong eye lens function. Because of the high proportion of subjects with missing covariates, these results warrant further study. (*Invest Ophthalmol Vis Sci.* 2010;51:2897–2905) DOI: 10.1167/iovs.08-2824

Cataract remains the leading cause of visual impairment in the world.¹ In less-developed countries cataract often results in blindness. Although in developed countries cataract surgery is usually available and effective, it imposes a heavy personal and societal economic burden.² With the aging of the population, the situation will be exacerbated. Therefore, prevention through modifying known risk factors appears to offer the best approach to this major personal and public health issue. Dietary intervention may be one of the most practical and cost-effective solutions if appropriate risk factors are identified.^{3,4} The overall impression from the many observational studies is that antioxidant intake can be optimized to prolong eye lens function,⁵ but large-scale intervention trials showed mixed results.^{5–12} Thus, it is critical to identify and research additional prevention strategies.

Considerable evidence has linked aberrant glucose metabolism or diabetes to cataract risk, and in vitro and in vivo animal studies also suggest that carbohydrates play an important role in cataractogenesis.^{13–15} However, only limited attention has been given to elucidating relations between risk of cataract and dietary carbohydrate intake in humans.^{16–22} Our previous investigations in the Nutrition and Vision Project (NVP) of the Nurses' Health Study (NHS)²⁰ and the Age-Related Eye Disease Study (AREDS) of the National Eye Institute (NEI), National Institutes of Health (NIH)²¹ suggest that dietary carbohydrate is associated with the risk of both cortical and nuclear cataracts, which together account for more than 80% of cataract cases.²³ The glycemic index (GI) was devised to measure how fast a carbohydrate-containing food can raise blood glucose. All dietary constituents can be integrated to obtain a dietary GI (dGI), which can be used as a measure of quality and pattern of dietary carbohydrate. The result can be distinguished from the simple measure of total carbohydrate intake (grams per day).

In this cross-sectional analysis of data from the Melbourne Visual Impairment Project (VIP) at the 5-year follow-up visit,²⁴ we examined the relationship between two aspects of carbohydrate nutrition—total carbohydrate intake and dGI—and the prevalence of cortical and nuclear cataracts in an older Australian population.

From the ¹Jean Mayer U.S. Department of Agriculture Human Nutrition Research Center on Aging at Tufts University, Boston, Massachusetts; the ²Centre for Eye Research Australia and the ⁴Department of Medicine, University of Melbourne, Melbourne, Victoria, Australia; and the ³Marshfield Medical Research Foundation, Marshfield Clinic, Marshfield, Wisconsin.

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Corresponding author: Allen Taylor, Jean Mayer USDA Human Nutrition Research Center on Aging at Tufts University, 711 Washington Street, Boston, MA 02111; allen.taylor@tufts.edu.

METHODS

VIP Study Population

The Melbourne VIP is a population-based, prospective study established to assess the clinical course, prognosis, risk factors, and prevention strategy for eye disease.²⁴ The protocol was approved by the Human Research and Ethics Committee of the Royal Victorian Eye and Ear Hospital and conformed to the Declaration of Helsinki for research involving human subjects. Informed consent was obtained from participants before enrollment. Eligible participants were recruited via a household census from the permanent residents in nine pairs of census collector districts randomly selected from the Melbourne Statistical Division. A total of 3271 participants, aged over 40 years at baseline recruitment, were enrolled from 1992 to 1994. Data on possible risk factors for cataract were obtained from a baseline general physical examination, ophthalmic photography, a detailed questionnaire on basic characteristics and demographic data at the time of the household census. From 1997 through 1999, all participants were traced, and those still living in the selected areas were invited to return to locally established test sites for a 5-year follow-up examination. Reported deaths were confirmed through the National Death Index at the Australian Institute for Health and Welfare in Canberra. The follow-up examinations were attended by 2594 participants and involved the same protocol as was used at baseline. In addition, a validated food-frequency questionnaire (FFQ) was administered.²⁵

Ophthalmic Procedures

Similar standardized ophthalmic examinations were conducted at baseline and the 5-year follow-up visits. Presenting and best corrected visual acuity was measured with a 4-m logMAR chart. Visual field assessment was performed with a visual field perimeter (Humphrey

Field Analyzer, 24-2 Fastpac statistical program; Carl Zeiss Meditec, Inc., Dublin, CA). Intraocular pressure was measured with a handheld tonometer (Tonopen; Oculab, Glendale, CA) and confirmed by a Goldmann applanation tonometer.

A slit lamp biomicroscopic examination was performed after pupil dilation to a minimum of 6 mm with tropicamide and phenylephrine. Lens opacities were graded clinically at the time of the examination and subsequently from photographs according to the Wilmer cataract grading system.²⁶ The cortex was assessed on retroillumination, and the nucleus was assessed with a slit lamp. Cortical cataract was defined as 4/16 or greater opacity, nuclear cataract was defined as Wilmer standard grade 2 or higher, and posterior subcapsular (PSC) cataract was defined as PSC opacity ≥ 1 mm².

Photographs were graded by two research assistants at both baseline and follow-up, and discrepancies were adjudicated by an independent reviewer. The measurement error associated with photographic grading of the lens was determined by regading a sample of baseline photographs at follow-up.²⁷ Clinical grades were used when photographic grades were not available. Photographic grades were available for more than 80% of the cohort for the three types of cataract. The agreement between clinical opacity and photographic grades was 0.86, 0.89, and 0.73 for cortical, nuclear, and PSC, cataract, respectively. These coefficients indicate good agreement for all three types of opacity.²⁸

Study Subjects

Figure 1 shows the recruitment scheme of participants from the VIP and the distribution of specific cataract types in the present study. Prior diagnosis of diabetes was determined with a comprehensive interview performed at the test site.²⁴ The questions relating to diabetes have been validated and used by Welborn et al.^{29,30} Of the available

FIGURE 1. Flow chart describing recruitment of subjects and distribution of studied eyes by presence of cortical, nuclear, and PSC cataracts from the Melbourne VIP. Cataract was graded according to the Wilmer protocol. Cortical cataract was defined as 4/16 or greater opacity. Nuclear cataract was defined as Wilmer standard grade 2 or higher. PSC cataract was defined as PSC opacity ≥ 1 mm². The eyes were classified as presenting cataract on the basis of that event occurring in either eye, regardless of the status of the fellow eye at baseline or follow-up examination.

TABLE 1. Characteristics of Participants and Nonparticipants from the Visual Impairment Project

Variable	Participants (<i>n</i> = 1609)	Excluded (<i>n</i> = 864)	<i>P</i>
Age (y), mean $\pm$ SE	57.61 $\pm$ 0.26	58.12 $\pm$ 0.40	0.28*
Sex, male	44.13%	45.60%	0.50†
Non-Australian birth	38.28%	49.25% (<i>n</i> = 863)‡	<0.0001†
Education, less than college	83.90%	87.08% (<i>n</i> = 836)‡	0.037†
Body mass index, median, kg/m ²	25.27	25.60 (<i>n</i> = 325)‡	0.18§
Sunlight exposure, median	0.640	0.638 (<i>n</i> = 781)‡	0.048§
Smoking, median pack-years	0.10	0.60 (<i>n</i> = 857)‡	0.091§
Ever smoked	50.2%	51.9%	
Alcohol consumption, median drinks/day	1.00	1.00 (<i>n</i> = 854)‡	0.34§
Hypertension	26.97%	23.31% (<i>n</i> = 858)‡	0.048†
Macular degeneration	23.68%	21.30%	0.19†

* Two-sided *t*-tests.

† Two-sided Fisher's exact tests.

‡ Number of persons for whom the information on the variable was available.

§ Two-sided Wilcoxon two-sample tests.

|| AMD was defined as the presence of any macular degeneration lesions in either eye at baseline or follow-up examinations during the Melbourne Visual Impairment Project, using the International Age-Related Macular Degeneration Classification System. If status was unknown, AMD was considered to be absent.

2594 participants at the follow-up visit, we identified and excluded the 121 diabetic persons, because diabetes is a strong confounder of the associations that were of interest to us. An additional 864 persons were excluded from the remaining 2473 eligible participants. These include 797 persons with missing covariates (the majority [*n* = 457] of which were due to missing data on BMI), 40 with invalid calorie intake (valid intake ranging from 400 to 3,000 calories (1,674–12,552 kJ) for the women and 600 to 3,500 calories (2,510–14,644 kJ) for the men, and 27 with bilateral missing cataract data. As a result, 3217 eyes of 1609 persons were included, with 1 person contributing only one eye. For maximum statistical power, we evaluated associations between indicators of carbohydrate nutrition and cataract with eyes used as the unit of analysis. Only eyes with pure cataract (with only one type of cataract) were used as cases, and those without any type of cataract were controls (see the Statistical Methods section). By using eyes as the unit, we considered and categorized every eye independently (i.e., without reference to the type of opacity or opacity grade in the fellow eye). The 189 eyes with mixed cataracts were not used, because the various cataracts may have had multiple but not necessarily mutually exclusive etiologies, and because using mixed cataracts may have reduce our power to detect associations with specific types of cataracts. The 2948 eyes composed of 197 eyes with pure cortical cataract, 366 eyes with pure nuclear cataract, and 2385 eyes without any type of cataract came from 1550 participants; 152 participants contributed only one eye.

Assessment of Dietary Variables

The semiquantitative FFQ administered at the follow-up examination (1997–1999) was developed and validated by the Cancer Council of Victoria (CCV) Australia for use in the ethnically diverse Australian population.²⁵ It includes 74 food items in four categories, with 10 frequency options for each, ranging from *never* to *three or more times daily*, and three questions on alcohol intake. Participants were asked to identify usual portion sizes from a series of photographs in the FFQ and to select the frequency of consumption for each food over the past year. The daily nutrient intake of an individual was calculated by summing the products of the frequency, portion size, and nutrient composition data for each food item. Nutrient composition data were derived from NUTTAB,³¹ an Australian fatty acid database (RMIT) and U.S. Department of Agriculture carotenoid tables.³²

We assessed carbohydrate quality by using the GI, as previously described.³³ Jenkins et al.³⁴ developed the GI to facilitate identification of potentially clinically useful foods that result in relatively low glycemic responses. The GI for foods is defined as the glycemic response

(i.e., the area under the glucose response curve up to 2 hours) after consumption of a fixed amount of carbohydrate from a test food, relative to the glycemic response to a reference food. The GIs for foods in the FFQ were derived either from published values, with glucose as the reference food, or imputed from GI values of comparable foods.³⁵ The dGI for each subject was calculated as the weighted average of the GI scores for each food item, with the amount of carbohydrate consumed from each food item as the weight: $[\sum (GI_i \times W_i)/W]$.³⁶

Defining Covariates

For our analyses, age, sex, education level, country of birth, body mass index (BMI; kilograms weight/height in meters squared), hypertension history, presence of AMD, alcohol intake (grams per day), smoking in pack-years, sunlight exposure (hours per day),³⁷ dietary vitamin C (milligrams per day), vitamin E (milligrams per day), β -carotene (micrograms per day), lutein and zeaxanthin (micrograms per day), zinc (milligrams per day), total fat (grams per day), linoleic acid (grams per day), α -linolenic acid (grams per day), eicosapentaenoic acid (EPA; grams per day), docosahexaenoic acid (DHA; grams per day), total carbohydrate intake (grams per day), and dGI were the covariates. All nutrient variables were adjusted for total energy intake using the residual method.³⁸

Statistical Methods

To determine whether the 864 excluded eligible persons were different from the 1609 participants (Fig. 1), we used means, medians (when values were not normally distributed), or proportions (for categorical variables), as appropriate, to compare participants and nonparticipants in terms of basic characteristics, including age, sex, education level, country of birth, BMI, hypertension history, presence of AMD, alcohol intake, pack-years smoked, and sunlight exposure (Table 1).

We estimated odds ratios (ORs) relating carbohydrate intake and dGI to cortical and nuclear cataract by logistic regression analysis (PROC GENMOD; SAS, ver. 9.1; SAS Institute Inc, Cary, NC). The procedure uses the generalized estimating equation (GEE) method to estimate the coefficients and adjust the standard errors of the model terms for the correlated data resulting from repeated measurements (both eyes) on the same individual.³⁹ The comparison group for the eyes with cortical cataract (*n* = 197) and the eyes with nuclear cataract (*n* = 366) was the group of eyes with no cataract (*n* = 2385; Fig. 1). Participants were divided into quartile categories according to their dGI or total carbohydrate intake. For each variable, participants in the lowest 25% of the distribution comprised the referent category. The

TABLE 2. Multivariate-Adjusted OR (95% CI) Relating Total Carbohydrate Intake and dGI to Cortical Cataract

Dietary Variables*	Cortical Cataract Prevalence† n (%)		Multivariate-Adjusted OR and 95% CI‡			
	No Cataract (n = 2385)	Pure Cortical Cataract (n = 197)	Adjusted for Nondietary Variables OR (95% CI)	Adjusted for Nondietary and Micronutrient Variables OR (95% CI)	Adjusted for Nondietary and Fat Variables OR (95% CI)	Adjusted for Nondietary and All Dietary Variables OR (95% CI)
Quartiles of carbohydrate intake (g/d)						
Q1	633 (26.54)	43 (21.83)	1	1	1	1
Q2	577 (24.19)	49 (24.87)	1.00 (0.60–1.67)	1.13 (0.67–1.92)	1.40 (0.79–2.46)	1.65 (0.88–3.09)
Q3	572 (23.98)	56 (28.43)	1.10 (0.65–1.86)	1.35 (0.77–2.36)	1.93 (0.94–3.96)	2.44 (1.06–5.63)
Q4	603 (25.28)	49 (24.87)	0.99 (0.58–1.67)	1.27 (0.73–2.19)	2.43 (0.97–6.10)	3.19 (1.10–9.27)
P	0.38§		0.94	0.30	0.033	0.017
Quartiles of dGI¶						
Q1	593 (24.86)	53 (26.90)	1	1	1	1
Q2	606 (25.41)	56 (28.43)	0.93 (0.57–1.52)	0.93 (0.57–1.53)	0.90 (0.55–1.48)	0.90 (0.55–1.47)
Q3	576 (24.15)	43 (21.83)	0.95 (0.56–1.59)	0.91 (0.53–1.57)	0.92 (0.55–1.56)	0.90 (0.53–1.54)
Q4	610 (25.58)	45 (22.84)	0.81 (0.49–1.33)	0.77 (0.44–1.33)	0.76 (0.45–1.27)	0.75 (0.44–1.30)
P		0.59§	0.44	0.35	0.33	0.34

* Dietary variables were energy-adjusted by using the residuals method. Participants were divided into quartile categories according to dGI or total carbohydrate intake. For each variable, participants in the lowest 25% of the distribution comprised the referent category. The cutoff for total carbohydrate intake was 153.89, 168.59, and 181.64 g/d in the women and 181.86, 199.13, and 214.92 g/d in the men. The cutoffs for dGI were 49.20, 52.17, and 55.34 in the women and 51.36, 54.46, and 57.26 in the men.

† Cortical cataract was defined as Wilmer cortical opacity grade 2 or greater (4/16 or more of pupil circumference). The unit of analysis was the eye; n (%) refers to the number (percentage) of eyes in the category.

‡ Nondietary variables included age, sex, education, country of birth, BMI, daily alcohol intake, pack-years of smoking, sunlight exposure, and AMD status. Micronutrient variables included energy-adjusted dietary vitamin C, vitamin E, β -carotene, zinc, and lutein/zeaxanthin intake. Fat variables included energy-adjusted linoleic acid, α -linolenic acid, eicosapentaenoic acid, docosahexaenoic acid, and total fat intake. All models were mutually adjusted for energy-adjusted dGI or total carbohydrate intake. Dietary variables included micronutrient variables and fat variables. *No opacity* comprised the control group. The results derived from further adjusting for dietary protein in the model were similar—that is, a significant association between cortical cataract and total carbohydrate intake was noted ($P_{\text{trend}} = 0.013$); the ORs (95% CI) adjusted for nondietary and all dietary variables (including protein) were 1 (referent), 1.74 (0.87–3.45), 2.61 (1.08–6.31), and 3.50 (1.12–10.97) for the quartile categories, respectively.

§ Derived from χ^2 test of independence between total carbohydrate intake or dGI categories and cortical cataract.

|| Derived from the test for trend across categories of total carbohydrate intake or dGI. The test for trend was assessed by using the median within each category as a continuous variable. The medians for total carbohydrate intake categories were 144.54 g/d, 160.81 g/d, 174.52 g/d and 191.06 g/d for the women and 170.21 g/d, 190.69 g/d, 206.95 g/d and 229.74 g/d for the men. The medians for dGI categories were 47.45, 50.73, 53.62 and 57.60 for the women and 49.74, 52.76, 55.80 and 59.66 for the men.

¶ The weighted average of the GI scores for each food item, with the amount of carbohydrate consumed from each food item as the weight.

cutoffs for total carbohydrate intake were 153.89, 168.59, and 181.64 g/d for the women and 181.86, 199.13, and 214.92 g/d for the men. The cutoffs for dGI were 49.20, 52.17, and 55.34 for the women and 51.36, 54.46, and 57.26 for the men. To evaluate the confounding effects from different covariates in the multivariate analysis, we grouped covariates into three groups: nondietary variables, micronutrient variables, and fat variables. The nondietary variables include age, sex, education, country of birth, BMI, daily alcohol intake, pack-years of smoking, sunlight exposure, and AMD status. The micronutrient variables were energy-adjusted dietary vitamin C, vitamin E, β -carotene, zinc, and lutein/zeaxanthin intake. The fat variables include energy-adjusted linoleic acid, α -linolenic acid, EPA, DHA, and total fat intake. All models were mutually adjusted for energy-adjusted dGI or total carbohydrate intake. We estimated ORs from four models. Model 1 adjusted for the nondietary group only. Model 2 further adjusted for micronutrient variables. The fat variables were included in model 3. In model 4, the full model, all nondietary and dietary variables were included.

To test for trends across total carbohydrate and dGI categories, we assigned the median value in each category to everyone within the category and then included it as a continuous variable in the logistic regression models. The medians for total carbohydrate intake categories were 144.54, 160.81, 174.52, and 191.06 g/d for the women and 170.21, 190.69, 206.95, and 229.74 g/d for the men. The medians for dGI categories were 47.45, 50.73, 53.62, and 57.60 for the women and 49.74, 52.76, 55.80, and 59.66 for the men.

We set the significance level at $P < 0.05$.

RESULTS

In the comparison with the 1609 participants, the 864 excluded eligible persons were more likely not to have been born in Australia ($P < 0.001$), were less likely to have a college education ($P = 0.037$), had less sunlight exposure ($P = 0.048$), and were less likely to have a history of hypertension ($P = 0.048$; Table 1). They were similar in terms of age, sex, BMI, daily alcohol consumption, and history of AMD.

In the multivariate analysis of total carbohydrate intake (Table 2), adjusted for either nondietary variables alone or for nondietary plus micronutrient variables, we did not find a significant association between total carbohydrate intake and the risk of cortical cataract. However, in the model adjusted for fat and nondietary variables, we found a positive relationship between total carbohydrate intake and risk of cortical cataract (OR for the highest quartile = 2.43, 95% confidence interval [CI] = 0.97–6.10; $P = 0.06$, $P_{\text{trend}} = 0.033$). This result implies that the association between total carbohydrate intake and risk of cortical cataract was confounded by dietary fat intake in our study sample. In the model adjusted for all dietary and nondietary variables, the relationship remained and became somewhat stronger (OR for the highest quartile = 3.19, 95% CI = 1.10–9.27; $P_{\text{trend}} = 0.017$).

There were significant negative correlations between intakes of total carbohydrate and total fat ($r = -0.32$, $P <$

TABLE 3. Multivariate-Adjusted OR (95% CI) Relating Total Carbohydrate Intake and dGI to Nuclear Cataract

Dietary Variables*	Nuclear Cataract Prevalence† <i>n</i> (%)		Multivariate-Adjusted OR and 95% CI‡			
	No Cataract (<i>n</i> = 2385)	Pure Nuclear Cataract (<i>n</i> = 366)	Adjusted for Nondietary Variables OR (95% CI)	Adjusted for Nondietary and Micronutrient Variables OR (95% CI)	Adjusted for Nondietary and Fat Variables OR (95% CI)	Adjusted for Nondietary and All Dietary Variables OR (95% CI)
Quartiles of carbohydrate intake (g/d)						
Q1	633 (26.54)	73 (19.95)	1	1	1	1
Q2	577 (24.19)	98 (26.78)	1.14 (0.71–1.84)	1.25 (0.77–2.05)	1.21 (0.72–2.04)	1.29 (0.74–2.23)
Q3	572 (23.98)	101 (27.60)	1.12 (0.68–1.83)	1.31 (0.77–2.21)	1.21 (0.64–2.27)	1.35 (0.69–2.67)
Q4	603 (25.28)	94 (25.68)	1.08 (0.66–1.76)	1.32 (0.78–2.22)	1.22 (0.55–2.69)	1.39 (0.58–3.31)
<i>P</i>		0.047§	0.84	0.35	0.72	0.56
Quartiles of dGI¶						
Q1	593 (24.86)	85 (23.22)	1	1	1	1
Q2	606 (25.41)	80 (21.86)	0.81 (0.50–1.30)	0.83 (0.51–1.34)	0.80 (0.49–1.28)	0.81 (0.50–1.32)
Q3	576 (24.15)	111 (30.33)	1.61 (1.03–2.51)	1.66 (1.04–2.64)	1.56 (0.99–2.46)	1.64 (1.02–2.65)
Q4	610 (25.58)	90 (24.59)	0.91 (0.57–1.47)	0.93 (0.55–1.59)	0.86 (0.52–1.41)	0.89 (0.51–1.53)
<i>P</i>		0.075§	0.72	0.62	0.91	0.75

* Information on dietary variables is given in Table 2.

† Nuclear cataract was defined as Wilmer nuclear opacity standard grade 2.0 or greater. The unit of analysis was the eye; *n* (%) refers to the number (percentage) of eyes in the category.

‡ Results were adjusted for dietary and nondietary variables. Nondietary, micronutrient, and fat variables are as described in Table 2. All models were mutually adjusted for energy-adjusted dGI or total carbohydrate intake. Dietary variables included micronutrient variables and fat variables. *No opacity* comprised the control group. The results derived from further adjusting dietary protein intake in the model were similar—that is, except for a sporadically significant OR (95% CI) of 1.65 (1.02–2.67) at the third quartile category of dGI, no association between nuclear cataract and dGI was found ($P_{\text{trend}} = 0.75$); the ORs (95% CI) adjusted for nondietary and all dietary variables (including protein) were 1 (referent), 0.82 (0.51–1.33), 1.65 (1.02–2.67), and 0.89 (0.52–1.53) for the quartile categories, respectively.

§ Derived from χ^2 test of independence between total carbohydrate intake or dGI categories and nuclear cataract.

|| Derived from the test for trend across categories of total carbohydrate intake or dietary GI. The test for trend was assessed by using the median within each category as a continuous variable. The medians for total carbohydrate intake and dGI categories are as in Table 2.

¶ Weighted average of the GI scores for each food item, with the amount of carbohydrate consumed from each food item as the weight.

0.0001), linoleic acid ($r = -0.064$, $P = 0.01$), α -linolenic acid ($r = -0.12$, $P < 0.0001$), EPA ($r = -0.11$, $P < 0.0001$), and DHA ($r = -0.13$, $P < 0.0001$). Among these fat variables, only total fat intake was significantly associated with the risk of cortical cataract (multivariate OR = 1.04, 95% CI = 1.01–1.08). However, we did not find a significant interaction between total carbohydrate and fat intakes ($P = 0.91$).

In the analysis of dGI and risk of cortical cataract, we did not find significant associations (Table 2).

For nuclear cataract, the P values of the χ^2 tests of independence with total carbohydrate intake and dGI are 0.047 and 0.075, respectively, suggesting an association between nuclear cataract and dietary carbohydrate (Table 3). However, in the multivariate analysis (Table 3) there were no significant relationships between total carbohydrate intake and risk of nuclear cataract in any of the models. In the analysis of dGI, compared with the lowest quartile, the third quartile showed an increased risk of nuclear cataract (OR = 1.64, 95% CI = 1.02–2.65, adjusted for dietary and nondietary variables). No significant trend across dGI quartiles was found.

To evaluate the impact of missing BMI data on our results, we also analyzed the data by not selecting for the presence of BMI data. Similar results were noted, which indicates that the conclusion is not changed even when those without BMI data are included in the analysis. The ORs (95% CI) for the quartile categories for the association between cortical cataract and total carbohydrate intake were 1.29 (0.71–2.35), 2.02 (0.94–4.33), and 2.71 (0.99–7.41), respectively, with $P_{\text{trend}} = 0.0213$.

To further evaluate the impact of diabetic status on our findings, we also analyzed the data by including diabetic participants and adjusting for diabetic status in the multivariate

logistic models. The results were similar and would not change our conclusion. The ORs (95% CI) for the quartile categories for the association between cortical cataract and total carbohydrate intake were 1.43 (0.79–2.61), 2.09 (0.94–4.63), and 2.50 (0.88–7.07), respectively, with $P = 0.0312$ for trend.

We used mixed-opacity definitions and reanalyzed the data (Table 4). Unlike in the pure opacity analysis (Tables 2, 3), the types of cataract by the mixed-opacity definitions were defined without reference to the presence of other types of cataract. The mixed results showed similar patterns and trends to the results obtained when pure opacities were used, consistent with our experience in analyzing data from the NVP of the NHS and the AREDS,^{20,21} in which use of pure opacity in data analysis increased statistical power.

There may be concern that excluding eyes with mixed opacity will result in the exclusion of eyes with the most severe opacity and thus affect the observed associations. To evaluate for this bias, instead of using pure-opacity definitions, we defined cataract without regard to other types of opacity (i.e., mixed opacity) to examine the association between cortical opacity and total carbohydrate intake. No significant association was found at the cutoff points of 4/16, 6/16, and 8/16 for cortical opacity. A marginally significant trend suggested a positive association at the cutoff point of 2/16; the ORs (95% CI) per quartile categories for the association between cortical cataract and total carbohydrate intake were 1.20 (0.72–2.00), 1.76 (0.91–3.39), and 2.12 (0.86–5.26), respectively, with $P_{\text{trend}} = 0.0534$. These results implied that the observed association is mainly with earlier stages of cortical opacity.

TABLE 4. Multivariate-Adjusted OR (95% CI) Relating Total Carbohydrate Intake and dGI to Mixed Cataract

Dietary Variables*	Cataract Prevalence† <i>n</i> (%)		Multivariate-Adjusted OR (95% CI)‡
	No Cataract	Cataract	
Cortical Cataract			
Quartiles of carbohydrate intake (g/d)			
Q1	633 (26.54)	69 (21.36)	1
Q2	577 (24.19)	89 (27.55)	1.53 (0.88–2.65)
Q3	572 (23.98)	88 (27.24)	1.74 (0.83–3.68)
Q4	603 (25.28)	77 (23.84)	2.13 (0.78–5.80)
<i>P</i>	0.13§		0.11
Quartiles of dGI¶			
Q1	593 (24.86)	76 (23.53)	1
Q2	606 (25.41)	92 (28.48)	1.01 (0.65–1.56)
Q3	576 (24.15)	77 (23.84)	1.14 (0.72–1.80)
Q4	610 (25.58)	78 (24.15)	0.83 (0.51–1.35)
<i>P</i>	0.69§		0.55
Nuclear Cataract			
Quartiles of carbohydrate intake (g/d)			
Q1	633 (26.54)	100 (19.05)	1
Q2	577 (24.19)	147 (28.00)	1.15 (0.69–1.93)
Q3	572 (23.98)	149 (28.38)	1.17 (0.62–2.20)
Q4	603 (25.28)	129 (24.57)	1.08 (0.47–2.52)
<i>P</i>	0.001§		0.98
Quartiles of dGI¶			
Q1	593 (24.86)	118 (22.48)	1
Q2	606 (25.41)	121 (23.05)	0.84 (0.54–1.31)
Q3	576 (24.15)	158 (30.10)	1.66 (1.06–2.61)
Q4	610 (25.58)	128 (24.38)	0.91 (0.55–1.51)
<i>P</i>	0.04§		0.68

* Information on dietary variables is given in Table 2.

† No cataract, *n* = 2385. Cortical cataract (*n* = 323) was defined as Wilmer cortical opacity grade 2 or greater (4/16 or more of pupil circumference). Nuclear cataract (*n* = 525) was defined as Wilmer nuclear opacity standard grade 2 or greater. Types of cataract were defined without reference to the presence of other types of cataract. The unit of analysis was the eye; *n* (%) refers to the number (percentage) of eyes in the category.

‡ Results were adjusted for nondietary and all dietary variables. Nondietary, micronutrient, and fat variables are as described in Table 2. All models were mutually adjusted for energy-adjusted dGI or total carbohydrate intake. Dietary variables included micronutrient variables and fat variables. No opacity comprised the control group.

§ Derived from χ^2 test of independence between total carbohydrate intake or dGI categories and cataract.

|| Derived from the test for trend across categories of total carbohydrate intake or dGI. The test for trend was assessed by using the median within each category as a continuous variable. The medians for total carbohydrate intake and dGI categories are as in Table 2.

¶ The weighted average of the GI scores for each food item, with the amount of carbohydrate consumed from each food item as the weight.

DISCUSSION

Results from the present cross-sectional analysis are consistent with the epidemiologic data showing that there is a positive relation between total carbohydrate intake and risk of cortical cataract (Fig. 2A).^{16,20–22} Despite the difference across studies in the period covered by dietary questionnaires, and the cutoff points for defining cortical opacities, similar findings have been reported in three other studies in U.S. as well as Australian populations, including the NVP of the NHS, the AREDS, and the baseline Blue Mountains Eye Study (BMES).^{16,20,21} The baseline BMES,¹⁶ the AREDS,²¹ and the present study evaluated short-term diet (the past year), whereas the NVP study evaluated long-term diet (previous 14 years).²⁰ The baseline BMES and the present study used cutoff points for cortical opacities that were comparable to the cutoff point used for moderate cortical opacities in the AREDS,^{16,21} whereas in the NVP a cutoff point

for cortical opacities was used that was similar to that for mild cortical opacities in the AREDS.

In several studies, researchers tried to relate dietary carbohydrate to nuclear cataract (Fig. 2B) or cataract extraction (Fig. 2C).^{17–19,21} Neither the NVP nor the full NHS found an association between dGI and nuclear cataract, but they had different end points: early opacities in the NVP and cataract extraction in the full NHS.^{19,20} Because both dGI and cataract have been related to major systemic diseases or mortality,^{40–49} using late stages of cataract as an end point may increase the possibility of survival bias.²¹ Also, cataract extraction is performed at highly variable extents of opacification. In contrast, AREDS found a positive association between dGI and nuclear cataract.²¹ In the present study, we found only an increased risk of nuclear cataract in the third quartile of dGI compared with the first quartile, without a significant dose-response relationship. Although similar end points for nuclear cataract, comparable to

FIGURE 2. Literature relating dietary carbohydrate to cataract.

those for mild nuclear opacities in the AREDS, were used in the NVP and the present study, differences between studies in the sample size, study design, and participants' ethnic backgrounds may explain the difference in findings. These factors may also explain the inconsistent findings for cortical cataract between the 10-year follow-up in the BMES and other studies, including the baseline results in the BMES, per se.^{16,19–22} In the 10-year follow-up in the BMES, the investigators found that poorer dietary carbohydrate quality (high dGI), but not quantity, predicted incident cortical cataract.²² In the baseline BMES, GI was not examined, although the top quintile of total carbohydrate intake had increased OR for cortical cataract. Thus, findings at baseline and in the 10-year follow-up in the BMES indicate that dietary carbohydrate affects the risk of cortical cataract, but this inconsistency needs further clarification.

Whereas the risk of cortical opacity has been related to total carbohydrate intake, there has been no report of a significant association between total carbohydrate intake and nuclear cataract. This corroborates our prior hypotheses that there are etiologic differences between nuclear and cortical cataract.^{20,21} However, specific mechanisms involved in different tissues and diseases may vary and remain to be clarified.

Our study had several strengths. First, by recruiting participants from a well-characterized cohort, we were able to use the standardized procedures for collection of risk factor information and classification of lens opacity. Second, it is unlikely

that participants with high carbohydrate or dGI diets were more likely to be identified as cases, because lens opacity grading was performed by graders masked to our nutrition data. Third, although the onset of visual symptoms resulting from lens opacities may affect the dietary reporting, it is unlikely that the participants would have modified their dietary carbohydrate reports based on such relations, because at the time of this study there were no prior studies that showed associations between dietary carbohydrate and lens opacities. Fourth, in our dGI compilation, we chose the GI of Australian food items for apparently similar foods in the international table of GI and glycemic load values.^{33,35} It is unlikely that nondifferential misclassification in our dGI compilation could explain our findings, because dietary analysis was conducted independent of ophthalmic data. Finally, using eyes as the unit of analysis not only increased our statistical power but also allowed us to control confounding by excluding eyes with more than one type of opacity, because different types of cataract may have different risk factors.

It is unlikely that characteristics associated with poor use of services confounded the carbohydrate–cataract associations in the VIP cohort because, first, the prevalence of cataract surgery for both cortical and nuclear cataract in the VIP cohort was less than 10%.^{27,28} Second, in our multivariate analysis, we found that education level, which is one of the important characteristics associated with poor use of services, did not confound the associations of our interest. Third, our current findings

support previous hypotheses that the mechanisms of cataractogenesis do not vary by sex or socioeconomic status, since we did not find significant interactions with these variables.^{20,21}

In our confounder analysis, total fat intake was significantly associated with the risk of cortical cataract. However, because fat factors are subcomponents of one another and the various variables in the model depend on the question to be addressed,⁵⁰ clearly the potential association between fat intake and cataract deserves further study.^{51,52}

The high proportion (30.7%) of participants with missing covariates and missing BMI data accounted for most of these (21.7%) may raise concerns that should be addressed in further studies.

In summary, this study adds additional support to the nascent body of epidemiologic evidence that dietary carbohydrate intake is a modifiable risk factor for the prevention of cataract. Further mechanistic studies and randomized trials would be helpful for developing therapeutic and preventive strategies to address this global epidemic.

References

- Congdon NG, Friedman DS, Lietman T. Important causes of visual impairment in the world today. *JAMA*. 2003;290:2057-2060.
- Taylor HR, Vu HT, Keeffe JE. Visual acuity thresholds for cataract surgery and the changing Australian population. *Arch Ophthalmol*. 2006;124:1750-1753.
- Chiu CJ, Taylor A. Nutritional antioxidants and age-related cataract and maculopathy. *Exp Eye Res*. 2007;84:229-245.
- Taylor A, ed. *Nutritional and Environmental Influences on the Risk for Cataract*. New York: CRC Press; 1999.
- Age-Related Eye Disease Study Research Group. A randomized, placebo-controlled, clinical trial of high-dose supplementation with vitamins C and E and beta carotene for age-related cataract and vision loss: AREDS report no. 9. *Arch Ophthalmol*. 2001;119:1439-1452.
- McNeil JJ, Robman L, Tikellis G, Sinclair MI, McCarty CA, Taylor HR. Vitamin E supplementation and cataract: randomized controlled trial. *Ophthalmology*. 2004;111:75-84.
- Teikari JM, Rautalahti M, Haukka J, et al. Incidence of cataract operations in Finnish male smokers unaffected by a tocopherol or b carotene supplements. *J Epidemiol Community Health*. 1998;52:468-472.
- Christen W, Glynn R, Sperduto R, Chew E, Buring J. Age-related cataract in a randomized trial of beta-carotene in women. *Ophthalmic Epidemiol*. 2004;11:401-412.
- Sperduto RD, Hu TS, Milton RC, et al. The Linxian cataract studies: two nutrition intervention trials. *Arch Ophthalmol*. 1993;111:1246-1253.
- Christen WG, Manson JE, Glynn RJ, et al. A randomized trial of beta carotene and age-related cataract in US physicians. *Arch Ophthalmol*. 2003;121:372-378.
- Chylack LT Jr, Brown NP, Bron A, et al. The Roche European American Cataract Trial (REACT): a randomized clinical trial to investigate the efficacy of an oral antioxidant micronutrient mixture to slow progression of age-related cataract. *Ophthalmic Epidemiol*. 2002;9:49-80.
- Clinical Trial of Nutritional Supplements and Age-Related Cataract Study Group, Maraini G, Sperduto RD, et al. A randomized, double-masked, placebo-controlled clinical trial of multivitamin supplementation for age-related lens opacities: clinical trial of nutritional supplements and age-related cataract report no. 3. *Ophthalmology*. 2008;115:599-607.e1.
- Tessier F, Obrenovich M, Monnier VM. Structure and mechanism of formation of human lens fluorophore LM-1: relationship to vesperlysine A and the advanced Maillard reaction in aging, diabetes, and cataractogenesis. *J Biol Chem*. 1999;274:20796-20804.
- Taylor A, Lipman RD, Jahngen-Hodge J, et al. Dietary calorie restriction in the Emory mouse: effects on lifespan, eye lens cataract prevalence and progression, levels of ascorbate, glutathione, glucose, and glycohemoglobin, tail collagen breaktime, DNA and RNA oxidation, skin integrity, fecundity, and cancer. *Mech Ageing Dev*. 1995;79:33-57.
- Stitt AW. The Maillard Reaction in Eye Diseases. *Ann NY Acad Sci*. 2005;1043:582-597.
- Cumming RG, Mitchell P, Smith W. Diet and cataract: the Blue Mountains Eye Study. *Ophthalmology*. 2000;107:450-456.
- Mares-Perlman JA, Brady WE, Klein BE, et al. Diet and nuclear lens opacities. *Am J Epidemiol*. 1995;141:322-334.
- Tavani A, Negri E, La Vecchia C. Food and nutrient intake and risk of cataract. *Ann Epidemiol*. 1996;6:41-46.
- Schaumberg DA, Liu S, Seddon JM, Willett WC, Hankinson SE. Dietary glycemic load and risk of age-related cataract. *Am J Clin Nutr*. 2004;80:489-95.
- Chiu CJ, Morris MS, Rogers G, et al. Carbohydrate intake and glycemic index in relation to the odds of early cortical and nuclear lens opacities. *Am J Clin Nutr*. 2005;81:1411-1416.
- Chiu CJ, Milton RC, Gensler G, Taylor A. Dietary carbohydrate and glycemic index in relation to cortical and nuclear lens opacities in the Age-Related Eye Disease Study. *Am J Clin Nutr*. 2006;83:1177-1184.
- Tan J, Wang JJ, Flood V, et al. Carbohydrate nutrition, glycemic index, and the 10-y incidence of cataract. *Am J Clin Nutr*. 2007;86:1502-1508.
- Rochtchina E, Mukesh BN, Wang JJ, McCarty CA, Taylor HR, Mitchell P. Projected prevalence of age-related cataract and cataract surgery in Australia for the years 2001 and 2021: pooled data from two population-based surveys. *Clin Exp Ophthalmol*. 2003;31:233-236.
- Livingston PM, Carson CA, Stanislavsky YL, Lee SE, Guest CS, Taylor HR. Methods for a population-based study of eye disease: the Melbourne Visual Impairment Project. *Ophthalmic Epidemiol*. 1994;1:139-148.
- Ireland P, Jolley D, Giles G. Development of the Melbourne FFQ: a food frequency questionnaire for use in an Australian prospective study involving an ethnically diverse cohort. *Asia Pacific J Clin Nutr*. 1994;3:19-31.
- Taylor HR, West SK. A simple system for the clinical grading of lens opacities. *Lens Res*. 1988;5:139-148.
- McCarty CA, Mukesh BN, Dimitrov PN, Taylor HR. Incidence and progression of cataract in the Melbourne Visual Impairment Project. *Am J Ophthalmol*. 2003;136:10-17.
- McCarty CA, Mukesh BN, Fu CL, Taylor HR. The epidemiology of cataract in Australia. *Am J Ophthalmol*. 1999;128:446-465.
- Welborn TA, Glatthaar C, Whittall D, Bennett S. An estimate of diabetes prevalence from a national population sample: a male excess. *Med J Aust*. 1989;150:78-81.
- Welborn TA, Knuiman MW, Bartholomew HC, Whittall DE. 1989-90 National Health Survey: prevalence of self-reported diabetes in Australia. *Med J Aust*. 1995;163:129-132.
- Lewis J, Milligan G, Hunt A. *NUTTAB95 Nutrient Data Table for Use in Australia*. Canberra: Australian Government Publishing Service; 1995.
- Holden JM, Eldridge AL, Beecher GR, et al. Carotenoid content of U.S. Foods: an update of the database. *J Food Comp*. 1999;12:169-196.
- Hodge AM, English DR, O'Dea K, Giles GG. Glycemic index and dietary fiber and the risk of type 2 diabetes. *Diabetes Care*. 2004;27:2701-2706.
- Jenkins DJ, Wolever TM, Taylor RH. Glycemic index of foods: a physiological basis for carbohydrate exchange. *Am J Clin Nutr*. 1981;34:362-366.
- Foster-Powell K, Holt SH, Brand-Miller JC. International table of glycemic index and glycemic load values: 2002. *Am J Clin Nutr*. 2002;76:5-56.
- Wolever TM, Nguyen PM, Chiasson JL, et al. Determinants of diet glycemic index calculated retrospectively from diet records of 342 individuals with non-insulin-dependent diabetes mellitus. *Am J Clin Nutr*. 1994;59:1265-1269.
- McCarty CA, Lee SE, Livingston PM, Bissinella M, Taylor HR. Ocular exposure to UV-B in sunlight: the Melbourne visual impairment project model. *Bull World Health Organ*. 1996;74:353-360.

38. Willett W, Stampfer MJ. Total energy intake: implications for epidemiologic analyses. *Am J Epidemiol*. 1986;124:17-27.
39. Zeger SL, Liang KY. Longitudinal data analysis for discrete and continuous outcomes. *Biometrics*. 1986;42:121-130.
40. Augustin LS, Franceschi S, Jenkins DJ, Kendall CW, La Vecchia C. Glycemic index in chronic disease: a review. *Eur J Clin Nutr*. 2002;56:1049-1071.
41. Jenkins DJA, Kendall CWC, Augustin LSA, et al. Glycemic index: overview of implications in health and disease. *Am J Clin Nutr*. 2002;76(suppl):266S-273S.
42. Minassian DC, Mehra V, Johnson GJ. Mortality and cataract: findings from a population-based longitudinal study. *Bull World Health Organ*. 1992;70:219-223.
43. Thompson JR, Sparrow JM, Gibson JM, Rosenthal AR. Cataract and survival in an elderly nondiabetic population. *Arch Ophthalmol*. 1993;111:675-679.
44. Klein R, Klein BE, Moss SE. Age-related eye disease and survival: the Beaver Dam Eye Study. *Arch Ophthalmol*. 1995;113:333-339.
45. Knudsen EB, Baggesen K, Naeser K. Mortality and causes of mortality among cataract-extracted patients: a 10-year follow-up. *Acta Ophthalmol Scand*. 1999;77:99-102.
46. Hu FB, Hankinson SE, Stampfer MJ, et al. Prospective study of cataract extraction and risk of coronary heart disease in women. *Am J Epidemiol*. 2001;153:875-881.
47. Hennis A, Wu SY, Li X, Nemesure B, Leske MC. Lens opacities and mortality: the Barbados Eye Studies. *Ophthalmology*. 2001;108:498-504.
48. Clemons TE, Kurinij N, Sperduto RD, AREDs Research Group. Associations of mortality with ocular disorders and an intervention of high-dose antioxidants and zinc in the Age-Related Eye Disease Study: AREDs Report No. 13. *Arch Ophthalmol*. 2004;122:716-726.
49. McCarty CA, Nanjan MB, Taylor HR. Vision impairment predicts 5 year mortality. *Br J Ophthalmol*. 2001;85:322-326.
50. Willett WC. *Nutritional Epidemiology*. 2nd ed. New York: Oxford University Press; 1998.
51. Lu M, Taylor A, Chylack LTJ, et al. Dietary fat intake and early age-related lens opacities. *Am J Clin Nutr*. 2005;81:773-779.
52. Lu M, Cho E, Taylor A, Hankinson SE, Willett WC, Jacques PF. Prospective study of dietary fat and risk of cataract extraction among US Women. *Am J Epidemiol*. 2005;161:948-959.