Carbohydrate intake and glycemic index in relation to the odds of early cortical and nuclear lens opacities[1–5]

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ABSTRACT

Background: Animal studies suggest a role for dietary carbohydrate in cataractogenesis. However, few published human studies have evaluated associations between carbohydrate nutrition and lens opacification.

Objective: Our objective was to test the hypothesis that long-term carbohydrate intake and dietary glycemic index are associated with the odds of early cortical and nuclear opacities.

Design: Subjects were 417 Boston-area members of the Nurses' Health Study cohort aged 53–73 y. Dietary information was based on an average from 5 semiquantitative food-frequency questionnaires collected over a 14-y period. Opacities were assessed by using the Lens Opacity Classification System III (LOCS III). We used eyes ($n = 711$) as the unit of analysis and generated odds ratios by using a generalized estimating approach to logistic regression to account for the lack of independence between the 2 eyes of each subject.

Results: After multivariate adjustment, the odds of cortical opacities (LOCS III $\geq$1.0) among women in the highest tertile of carbohydrate intake ($\geq$200 g/d) was 2.46 times (95% CI: 1.30, 4.64; P for trend = 0.005) that among women in the lowest tertile ($<$185 g/d). This association was not affected by adjustment for dietary glycemic index, which was not associated with early cortical opacities. Carbohydrate nutrition was not associated with the odds of nuclear opacities (LOCS III $\geq$2.5).

Conclusions: These data suggest that carbohydrate quantity, but not carbohydrate quality, is associated with early cortical opacities, and that neither the quantity nor the quality of dietary carbohydrate affects the risk of nuclear opacities in middle-aged women. *Am J Clin Nutr* 2005;81:1411–6.

KEY WORDS Cataract, lens, nutrition, carbohydrate, glycemic index, glycation, aging, stress, epidemiology, humans, risk factor

INTRODUCTION

Results of a nationwide survey of middle-aged and older Americans revealed that blindness is among the most feared age-related impairments (1). Cataract is the leading cause of blindness worldwide (2, 3). An estimated 20.5 million Americans aged $\geq$40 y (17.2% of that population) have cataract, 6.1 million (5.1%) have pseudophakia or aphakia, and it is predicted that those numbers will rise by 50% within 2 decades (4). Opacification, or lens clouding, begins months or even years before vision is affected. Consequently, strategies to prevent opacification hold promise for reducing this enormous public health burden.

There are 3 principal forms of age-related cataract. Nuclear and cortical opacities affect the center and adjacent peripheral tissue of the lens, respectively. Posterior subcapsular (PSC) opacities affect the posterior aspect of the lens. Age-related opacification is usually attributable to aggregation and precipitation of the normally well-ordered and soluble crystallin lens proteins, a phenomenon believed to result in part from cross-linking that occurs when amino groups react with open-chain sugars or glycolytic intermediates to form so-called advanced glycation end products (5). Despite the hypothesized role for sugars in cataractogenesis and considerable evidence linking aberrant glucose metabolism to cataract risk (6–17), only a few studies have examined the relation between dietary carbohydrate and cataract (18–22). To better understand the influence of carbohydrate nutrition on the early stages of cataractogenesis, we

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examined associations between long-term carbohydrate intake and dietary glycemic potential and the odds of different types of early lens opacities.

SUBJECTS AND METHODS

Study subjects

The characteristics of the participants and details of the methods have been described previously (23, 24). In brief, the Nutrition and Vision Project (NVP) is a subset of the Nurses' Health Study (NHS; 25). In 1993, 17 y after initiation of the NHS, 1717 women aged 53–73 y who resided in the Boston area, had both lenses intact, were free of diagnosed cancer other than nonmelanoma skin cancer, and had complete dietary data were identified from the NHS cohort. With the aim of enrolling 600 women into the NVP, we initially contacted these 1717 candidates via a letter that requested their participation. We received positive responses from 895 women (52%), and 603 of these volunteers were scheduled between April 1993 and August 1995 for data collection and lens evaluation. The most common reason for the failure to examine the remaining 292 volunteers was scheduling conflicts due to work and travel.

Assessment of lens status

Every NVP participant underwent a standardized eye examination, including ocular and medical history, Bailey-Lovie test of visual acuity, manifest refraction, external ocular examination, applanation tonometry, contrast sensitivity function, glare testing, and a slit-lamp examination of the anterior segment with an assessment of risk of angle-closure glaucoma. Pupils were dilated to a minimum of 6 mm. Ocular lens opacities are classified according to the region affected. The Nidek EAS 1000 camera (Hiroishi, Japan) was used to obtain digital black-and-white retroillumination images of the cortical zone of the lens. We also used a photographic slit-lamp (Carl Zeiss, Oberkochen, West Germany) and Ektachrome 200 film (Kodak, Rochester, NY) to take color film images for assessing nuclear opacity.

The Lens Opacities Classification System III (LOCS III; 26, 27) was used to measure the degree of lenticular opacification. Grades ranged from 0.1 to 5.9 for cortical and PSC opacities and from 0.1 to 6.9 for nuclear opacities. All images were evaluated in several grading sessions within a 2-mo period after all photographs and images were obtained. In vivo LOCS III grading of the extent of PSC opacification was also done at the slit-lamp. The examiners and graders were blind to the identity of the eye, as well as to the nutrient status of the volunteers. We considered eyes to have opacities if the LOCS III cortical grade was $\geq$1.0, the nuclear grade was $\geq$2.5, or the PSC grade was $\geq$0.5. These cutoffs represent early lens opacification and are not typically associated with symptoms such as reduced vision.

Assessment of nutrient intake

In 1980, a 61-item semiquantitative food-frequency questionnaire (FFQ) was incorporated into the NHS biennial questionnaire (25). The FFQ asked about usual dietary intakes over the previous year and classified them into 9 possible response categories, which ranged from "never or less than once per month" to "6 or more times per day." In addition, the 1980 questionnaire asked about vitamin supplement use and the duration of vitamin supplement use before 1980. A revised and expanded FFQ was administered in 1984, 1986, and 1990. The current version of the FFQ includes 126 food items and details of vitamin and mineral supplement use that collectively account for >90% of the total intake of the 70 nutrients measured by the questionnaire (28). The FFQ has been comprehensively validated in relation to both long-term diet records (28–30) and biochemical markers of nutrient status (31, 32). In addition to the FFQs routinely collected as part of the NHS, an FFQ was administered as part of the NVP examination. The combined data from the 5 FFQs were used to calculate nutrient intake from 1980 to the time of the NVP examination (1993–1995).

We used the dietary glycemic index (GI) to assess carbohydrate quality. Jenkins et al (33) introduced the concept of GI for individual foods to facilitate the identification of potentially clinically useful foods that result in relatively low glycemic responses. GI for foods is defined as the glycemic response (ie, the area under the glucose response curve up to 2 h) after consumption of a fixed amount of carbohydrate from a test food, relative to the glycemic response to a reference food. The GI values for foods in the FFQ were either derived from published values that used white bread as the reference food or imputed from GI values of comparable foods (34). The dietary GI 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 used as the weight. Another derivative measure, glycemic load, is a product of the dietary GI (quality) and total dietary carbohydrate intake (quantity). It assesses the total dietary glycemic effect and thus represents both the quality and quantity of dietary carbohydrate intake (35). Carbohydrate variables were adjusted for total energy with the use of the residuals method (36).

Defining nonnutritional variables

Information on known or suspected nonnutritional risk factors for cataract was collected from the biennial NHS questionnaires. For our analyses, cigarette pack-years (number of packs of cigarettes smoked per day $\times$ numbers of years of smoking); summertime sunlight exposure ($\geq$8 h/wk) as reported on the 1980 questionnaire; alcohol use and total fat intake calculated as the average from 5 FFQs collected between 1980 and 1993–1995; lifetime duration of use of multivitamins, vitamin C, and vitamin E, as determined from responses to questions on the 5 questionnaires; and body mass index (BMI; measured in kg/m^2) were considered as covariates. BMI was calculated from the height and weight reported on the 1980 questionnaire.

Statistical methods

We excluded women with a confirmed diagnosis of diabetes in 1990 or earlier ($n = 20$) or a history of cataract ($n = 72$). The study size was further reduced because of missing or unusable eye data ($n = 42$) and invalid data on total energy intake ($n = 8$) or covariates ($n = 6$). For maximal statistical power, we evaluated associations between indicators of carbohydrate nutrition and opacity by using eyes as the unit of analysis. We also excluded eyes with more than one type of opacity. The use of mixed opacities may reduce our power to detect associations with specific types of opacities, because the various opacities have multiple, but not necessarily mutually exclusive, etiologies. Thus, an additional 38 women were excluded because both of their eyes had mixed opacities ($n = 32$) or PSC opacities only ($n = 6$). Because there was a small number of eyes with pure PSC opacity

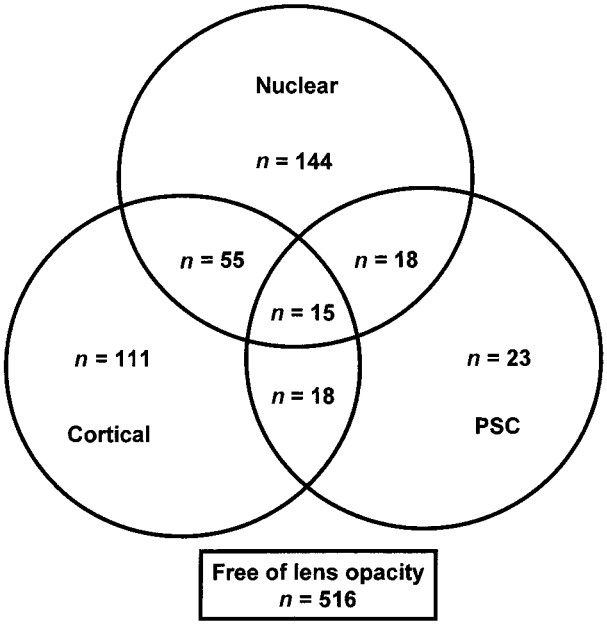

FIGURE 1. Distribution of eyes by presence of cortical, nuclear, and posterior subcapsular (PSC) opacities (Lens Opacity Classification System III ≥1.0, 2.5, and 0.5, respectively).

(12 eyes from the 6 women noted and 11 eyes from women with unilateral pure PSC opacities), those 23 eyes were also excluded from further analyses. Collectively, the remaining 417 women contributed 771 eyes to the analysis (**Figure 1**).

With the use of means ± SEs, medians (when values were not normally distributed), and proportions, we first described the included women in terms of demographic factors and potential confounders of associations between carbohydrate intake and dietary GI and cortical and nuclear opacity (2, 37, 38). We estimated odds ratios (ORs) relating carbohydrate intake and dietary GI to cortical and nuclear opacities by logistic regression analysis with the use of SAS PROC GENMOD (39). The procedure uses the generalized estimating equation to estimate the coefficients and to adjust the SEs of the model terms for the correlated data resulting from repeated measurements (both eyes) of the same person (40). The reference group for the eyes with cortical opacities ($n = 111$) and the eyes with nuclear opacities ($n = 144$) was the group of eyes with no opacities ($n = 516$).

Women were divided into tertile categories according to their dietary GI or total carbohydrate intake (average from 5 FFQs). For each variable, women in the bottom third of the distribution composed the referent category. The tertiles for carbohydrate intake were 185 g/d and 200 g/d. The tertiles for dietary GI were 73.6 and 75.9.

We estimated ORs from 2 models. Model 1 adjusted for age only. Model 2 further adjusted for BMI, summertime sun exposure, total alcohol intake, cigarette smoking, and duration of vitamin C supplement use. Additional covariates adjusted for in model 2 included a subset of potential confounders, ie, duration of multivitamin use, duration of vitamin E supplement use, and total fat intake. Exclusion of these 3 terms from the models resulted in only minor changes in the ORs.

To test for trends across total carbohydrate and dietary GI categories, we assigned the median value in each category to everyone within the category and then included this value as a continuous variable in the logistic regression models. The category medians were 173, 193, and 211 g/d for dietary carbohydrate, and 71.6, 74.8, and 77.6 for dietary GI. We used a P value <0.05 to denote significance, and all tests were two-sided.

RESULTS

The mean age of the women was 60.8 ± 0.25 y, and mean BMI was 24.1 ± 0.20. Almost 90% reported having spent ≥8 h/wk outdoors in the summer, and about the same proportion reported drinking alcohol (median intake: 5.4 g/d). Just under half the women reported vitamin C supplement use (median duration: 4 y), and 60.6% of the women reported a history of cigarette smoking (median: 22 pack-years). Mean carbohydrate intake was 192.2 ± 1.06 g/d, and mean dietary GI was 74.7 ± 0.16.

Although all of the covariates included in the multiple logistic regression models influenced the main effects, only a few were strongly associated with opacity after multivariate adjustment (**Table 1**). Specifically, the odds of nuclear opacity increased by 26% for each 1-y increase in age (OR: 1.26; 95% CI: 1.19, 1.32), but the association between age and cortical opacity was weak (OR: 1.04; 95% CI: 0.98, 1.09). Consistent with some, but not all, prior studies we observed an approximate doubling of the odds that both cortical (OR: 2.25; 95% CI: 1.03, 4.91) and nuclear (OR: 2.09; 95% CI: 0.91, 4.77) opacities were associated with a report of ≥8 h/wk of summertime sun exposure (37). Only the association with cortical opacity was significant. The odds of both nuclear and cortical opacities indicated no association with smoking. Finally, the odds of both nuclear (OR: 0.92; 95% CI: 0.87, 0.97) and cortical (OR: 0.95; 95% CI: 0.91, 0.99) opacities decreased significantly with each additional year of supplemental vitamin C use, as noted earlier (23, 24, 41).

In age- and multivariate-adjusted models, daily intake of ≥200 g carbohydrate was associated with odds of cortical opacity at least twice those of the consumption of <185 g carbohydrate/d (**Table 2**). Although the age-adjusted model revealed that increasing carbohydrate intake was associated with a marginally significant decrease in the odds of nuclear opacity, multivariate adjustment showed that this association was confounded by other factors. Dietary GI was not related to opacity. We did not report our findings from the glycemic load analysis for either type of opacity, because results were almost identical to those for total carbohydrate. This is not surprising, because the 2 measurements tend to be highly correlated. In our study, the correlation coefficient was 0.93 ($P < 0.001$).

DISCUSSION

In this study of apparently healthy, middle-aged women, long-term carbohydrate intake was positively associated with the odds of early cortical opacities but not with the odds of early nuclear opacities. Dietary GI did not relate to risk of either cortical or nuclear opacity.

Several lines of evidence support our observation of a positive association between carbohydrate intake and the odds of cortical opacities. As compared with the rapid, facilitated uptake of glucose and its subsequent decline to basal amounts in some cells and tissues, glucose is taken up more slowly from plasma into the aqueous humor, the fluid that provides nutrients to the lens (42, 43). Glucose then passes into the lens, where it is apparently only slowly turned over. Laboratory studies have shown that

TABLE 1
Characteristics and multivariate-adjusted odds ratios (OR) for the occurrence of cortical and nuclear lens opacities[1]

Variables	Unaffected[2] ($n = 516$)	Type of opacity[3] Cortical ($n = 111$)	OR (95% CI)	Nuclear ($n = 144$)	OR (95% CI)
Age (y)	59.56 ± 0.20[4]	60.03 ± 0.50	1.04 (0.98, 1.09)	64.19 ± 0.41	1.26 (1.19, 1.32)[5]
BMI (kg/m^2)	24.09 ± 0.18	24.14 ± 0.35	1.01 (0.96, 1.07)	23.89 ± 0.31	0.99 (0.93, 1.06)
Summertime sun exposure ≥8 h/wk (%)	86.63	91.89	2.25 (1.03, 4.91)[5]	91.67	2.09 (0.91, 4.77)
Alcohol intake			1.00 (0.97, 1.03)		1.02 (0.99, 1.05)
Drinkers (%)	89.15	84.68		91.67	
Median (g/d)	5.69	4.95		6.20	
Cigarette smoking			1.00 (0.99, 1.01)		1.00 (0.99, 1.01)
Smokers (%)	61.96	64.89		57.58	
Median (pack-year)	22.10	19.20		25.73	
Vitamin C supplement use			0.95 (0.91, 0.99)[5]		0.92 (0.87, 0.97)[5]
Users (%)	50.53	39.34		36.84	
Median duration (y)	4.00	3.00		4.00	

[1] Values are adjusted for age, BMI in 1980, summer sun exposure in 1980, daily alcohol intake, pack-years of smoking, duration of vitamin C supplement use, and energy-adjusted total carbohydrate intake. The unit of analysis was an eye ($n = 771$). LOCS III, Lens Opacities Classification System III.
[2] Reference group.
[3] Cortical opacity, LOCS III ≥1.0; nuclear opacity, LOCS III ≥2.5.
[4] $\bar{x}$ ± SE (all such values).
[5] $P < 0.05$.

prolonged exposure of lens proteins to elevated glucose concentrations results in extensive glycation, the consequences of which may include oxidation, cross-linking, aggregation, and precipitation of the modified lens proteins (44). Nuclear magnetic resonance studies indicate that glucose concentrations remain higher in the cortex than in the nucleus (45, 46). Thus, it would appear that higher carbohydrate intakes and plasma concentrations of glucose will result in chronically enhanced exposure of lens cortex proteins to glucose. In addition, enzyme activities involved in the metabolism of glucose decrease toward the center of the lens, which is consistent with higher concentrations of glucose and glucose transporters in the cortex than in the lens nucleus (47). These effects may result in enhanced cortical protein modification, precipitation, and cataract because the lens proteins are extremely long-lived, having half-lives of decades, and because opportunities for repair or removal and replacement are limited (2). The data are also consistent with in vivo evidence that the precipitation of glycated lens proteins in diabetic cataractogenesis is initiated in the cortical region (48). It is interesting that epidemiologic studies also show that carbohydrate metabolism and diabetes have more consistently been linked with cortical cataract than with nuclear opacities (11–16).

The data presented here can be compared with data from several prior studies. In the Blue Mountains Eye Study, risk

TABLE 2
Age- and multivariate-adjusted odds ratios (OR) relating total carbohydrate intake and dietary glycemic index among 417 Nutrition and Vision Project participants to cortical and nuclear opacity in the 771 eyes analyzed[1]

Dietary variable[2]	No opacity ($n = 516$) n	Cortical opacity ($n = 111$) n	Age-adjusted OR (95% CI)	Multivariate-adjusted OR (95% CI)	Nuclear opacity ($n = 144$) n	Age-adjusted OR (95% CI)	Multivariate-adjusted OR (95% CI)
Carbohydrate (g/d)							
< 185	186	23	1.0	1.0	53	1.0	1.0
185–200	162	38	1.95 (1.05, 3.62)	2.09 (1.11, 3.93)	44	0.81 (0.45, 1.44)	0.95 (0.51, 1.78)
≥ 200	168	50	2.30 (1.27, 4.17)	2.46 (1.30, 4.64)	47	0.58 (0.32, 1.06)	0.75 (0.38, 1.48)
P for trend			0.005	0.005		0.08	0.42
Glycemic index							
< 73.6	163	36	1.0	1.0	57	1.0	1.0
73.6–75.9	186	35	0.85 (0.47, 1.52)	0.81 (0.45, 1.45)	39	0.67 (0.37, 1.21)	0.61 (0.33, 1.14)
≥ 75.9	167	40	1.13 (0.65, 1.97)	1.09 (0.61, 1.94)	48	1.12 (0.63, 1.99)	1.15 (0.63, 2.10)
P for trend			0.69	0.79		0.79	0.74

[1] Values are adjusted for age, BMI in 1980, summer sun exposure in 1980, daily alcohol intake, pack-years of smoking and duration of vitamin C supplement use. Dietary glycemic index is the weighted average of glycemic index scores for each food item, with the amount of carbohydrate consumed from each food item as the weight. The unit of analysis was an eye. Cortical opacity, Lens Opacities Classification System (LOCS) III ≥1.0; nuclear opacities, LOCS III ≥2.5.
[2] Energy-adjusted by using the residuals method.

of cortical cataract was 40% higher in subjects whose daily carbohydrate intake exceeded 268.2 g (the fifth quintile) than it was in those with daily carbohydrate intake <172.6 g (the first quintile; $P < 0.05$), although the test for trend was not significant ($P = 0.12$) (18). Consistent with our findings, neither the Blue Mountains Eye Study nor the Beaver Dam Eye Study reported any significant association between carbohydrate intake and nuclear opacity (18, 19). Results of 2 studies (20, 22), including one based on the full NHS cohort (22), that found no significant relation between dietary carbohydrate and cataract extraction (primarily cataracts in the nuclear zone of the lens) also appear to be consistent with our findings, because nuclear cataracts represent most extracted cataracts (22). PSC cataracts are also overrepresented among extracted cataracts, whereas cortical cataracts compose only a small proportion of cataracts that are surgically removed. We were unable to assess the relation with PSC opacities because of small numbers.

Our study had several strengths. First, by recruiting participants from the NHS prospective cohort, we were able to relate previous long-term dietary exposures to opacity. Second, the possibility of recall bias was minimized by our exclusion of women previously diagnosed with cataract and by our use of early lens opacities as the endpoint. To elaborate, women with early lens opacities should not have been aware of them, because visual acuity was similar in nurses with and without opacities (data not shown). Third, confounding was controlled not only by multivariate adjustment and our exclusion of women with more than one type of opacity but also by the sample's homogeneity, which precluded substantial confounding by sex and race and minimized confounding by socioeconomic status. Although the degree to which our findings apply to men and members of other socioeconomic strata is unknown, mechanisms of cataractogenesis are not known to vary by sex or socioeconomic status. Our study did, however, also have some limitations. For example, because of inadequate power, we did not find a significant association between age and cortical opacity. The nonrepresentative nature of this subgroup of the NHS with regard to Americans in general might restrict the generalization of our results. The lack of serum or lens biomarkers also warrants further studies.

In summary, carbohydrate intake was positively associated with the odds of early cortical opacities in middle-aged women. Because carbohydrate foods represent the main energy source for humans, understanding the potentially harmful effects of a high-carbohydrate diet on the lens is important and worthy of further study.

C-JC, MSM, GR, PFJ, and AT participated in the data analysis and the writing of this manuscript. AT was responsible for the design and concept of the project, arranged for the various institutes to collaborate, and obtained funding. WW, SEH, and LTC participated in manuscript preparation and arranged for funding. LTC directed the collection of the ophthalmologic data. WW and SEH arranged for collection of the nutritional and personal health data used for these analyses. None of the authors had a conflict of interest.

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