Dietary carbohydrate and the progression of age-related macular degeneration: a prospective study from the Age-Related Eye Disease Study[1–4]

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ABSTRACT

Background: Cross-sectional studies indicate that diets that provide a higher dietary glycemic index (dGI) are associated with a greater risk of age-related macular degeneration (AMD). No prospective studies have addressed this issue.

Objective: The objective was to prospectively evaluate the effect of baseline dGI on the progression of AMD.

Design: dGI was calculated as the weighted average of GIs from foods and was evaluated as being above or below the sex median (women: 77.9; men: 79.3) for 3977 participants aged 55–80 y (58% women) in the Age-Related Eye Disease Study. The 7232 eligible eyes without advanced AMD were classified into 1 of 3 AMD categories: group 1 (nonextensive small drusen), group 2 (intermediate drusen, extensive small drusen, or pigmentary abnormalities), or group 3 (large drusen or extensive intermediate drusen). With the use of multifailure Cox proportional-hazards regression, we modeled the time to the maximal progression to evaluate the relation between dGI and the risk of AMD.

Results: Overall, the multivariate-adjusted risk of progression over 8 y of follow-up ($\bar{x}$: 5.4 y) was significantly higher (risk ratio: 1.10; 95% CI: 1.00, 1.20; $P = 0.047$) in the high-dGI group than in the low-dGI group. The risk of progression for groups 1, 2, and 3 eyes was 5%, 8%, and 17% greater, respectively (P for trend < 0.001). The latter gives an estimate that 7.8% of new advanced AMD cases would be prevented in 5 y if people consumed the low-dGI diet.

Conclusion: Persons at risk of AMD progression, especially those at high risk of advanced AMD, may benefit from consuming a smaller amount of refined carbohydrates. *Am J Clin Nutr* 2007; 86:1210–8.

KEY WORDS Retina, nutrition, carbohydrate, diabetes, sugar, glycation, inflammation, aging, stress, epidemiology

INTRODUCTION

Age-related macular degeneration (AMD) is the major cause of legal blindness (defined as best corrected visual acuity of 20/200 or worse in the better eye) in North American, Australian, and Western European populations (1). In the United States alone, AMD was estimated to account for over 426,000 cases of legal blindness in 2000 (2). It is estimated that the number of people having visually impairing AMD will double and reach 3 million by 2020 (3), and the related socioeconomic burden, which is now greater than ever, will continue to grow. This burden will probably be exacerbated by the epidemics of dietary carbohydrate-related disorders, such as obesity, the metabolic syndrome, and diabetes (4). The multifactorial etiology of this disease has impeded the discovery of a single intervention that slows its progression. Therefore, prevention through the modification of known risk factors appears to offer the greatest promise to address this emerging personal and public health issue. Among known risk factors, dietary intervention may be one of the most practical and cost-effective solutions (5).

Data from the Age-Related Eye Disease Study (AREDS) of the National Eye Institute of the National Institutes of Health (Bethesda, MD) suggested that elderly persons at high risk of developing blinding AMD and without contraindications such as smoking should consider taking antioxidants plus zinc (6). It was estimated that the potential effect on the public health of this intervention in the United States would be the prevention of 25% (329 ,000 cases) of advanced AMD and any associated vision loss in 5 y (7). The limited efficacy of this intervention warrants further studies to identify additional prevention strategies. Surprisingly, only limited attention has been given to elucidating the relations between the risk of AMD and dietary carbohydrate, which is the most important energy source of human physiology. The quality of carbohydrate foods in diets measured by dietary

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glycemic index (dGI) has been related to the risk of many age-related diseases, including diabetes, cardiovascular disease, and cancer (8). Glycemic index (GI) values for each food item have been suggested as being useful to consumers in helping them to choose foods to reduce their risk of these diseases (9).

Cross-sectional data from the Nutrition and Vision Project of the Nurses' Health Study (10) and the AREDS (4) indicate that dGI is associated with the risk of all degrees of AMD, and it has been estimated that 20% of prevalent cases of advanced AMD may be prevented if dGI was reduced below the median (4). However, no prospective study has addressed this issue. In the present study, by using the eye data from the AREDS, we had the unique opportunity to evaluate the relative contribution of dGI to the progression of different stages of AMD in nondiabetic individuals followed for 8 y ($\bar{}$: 5.4 y). The results provided the first prospective evidence to support the hypothesis that dietary carbohydrate is associated with the risk of age-related eye diseases (4, 10–12). The potential effect of the finding on the public health was also estimated.

SUBJECTS AND METHODS

Age-Related Eye Disease Study population

AREDS is a long-term, multicenter, prospective study dedicated to assessing the clinical course, prognosis, risk factors, and prevention strategy of both AMD and cataract (13). The protocol was approved by a Data and Safety Monitoring Committee and by the institutional review boards of the 11 participating ophthalmic centers before initiation of the study. Written informed consent was obtained from participants before enrollment. All participants were required to have ≥1 eye with a visual acuity of 20/32 or better, and the lens and vitreous had to be sufficiently clear to allow good-quality retinal photographs that would permit identification and quantification of small drusen. In addition, ≥1 eye of each participant was to be free of eye disease that could complicate assessment of AMD or lens opacity progression (eg, optic atrophy and acute uveitis), and that eye could not have had previous ocular surgery (except cataract surgery and unilateral photocoagulation for AMD). Finally, potential participants were excluded for illness or disorders that would make long-term follow-up or compliance with the study protocol unlikely or difficult. A total of 4757 participants, aged 55-80 y at recruitment, were enrolled from November 1992 to January 1998.

Procedures

Data on possible risk factors for AMD were obtained from a baseline general physical and ophthalmic examination, a detailed questionnaire on basic characteristics and demographic data, and a validated (N Kurinij et al, unpublished observations, 1998) food-frequency questionnaire (FFQ).

Photographs were scheduled at baseline, at the 2-y visit, and annually thereafter during the 8 y of follow-up. Stereoscopic fundus photographs of the macula were graded at an ophthalmic photograph reading center, where the various lesions associated with AMD were assessed according to the AREDS AMD Classification System (14). The AREDS AMD Classification System showed satisfactory reliability for detecting the onset of advanced AMD and moderate-to-substantial agreement on various abnormalities across the AMD spectrum (14). Eyes were classified into 1 of 5 groups (*see* below) according to the size and extent of drusen, presence of geographic atrophy, and neovascular changes of AMD (14). The 5 groups, numbered serially and based on increasing severity of drusen or type of AMD, were defined as follows: group 1 (no drusen), eyes had no drusen or nonextensive small drusen; group 2 (intermediate drusen), eyes had ≥1 intermediate drusen, extensive small drusen, or pigment abnormalities associated with AMD; group 3 (large drusen), eyes had ≥1 large drusen or extensive intermediate drusen; group 4 (geographic atrophy), eyes had geographic atrophy; and group 5 (neovascular), eyes had choroidal neovascularization or retinal pigment epithelium detachment.

Study subjects

The recruitment scheme of the present study is shown in **Figure 1**. Of the available 4757 subjects at baseline, we first excluded 398 persons with diabetes at baseline; 161 persons with missing nutritional, nonnutritional, and ophthalmologic covariates; 99 persons with invalid calorie intake (valid intake range is 400-3000 kcal/d for women and 600-3500 kcal/d for men; 4); and 122 persons lost to follow-up. This left 7232 eyes at risk of progression at baseline, including 2697 eyes in group 1, 1781 eyes in group 2, and 2754 eyes in group 3, from 3977 persons; 722 persons contributed only one eye, because the fellow eyes in groups 4 and 5 ($n = 722$) at baseline were excluded. They were excluded because they were considered as the end stage of AMD and thus not at risk of progression.

Assessment of outcomes

We considered the time to the first maximal AMD progression of studied eyes during the study period. Progression for a study eye was defined by a more advanced AMD category (*see* Procedures) than the baseline grade. With the following exception, analyses of progression to either neovascular AMD or central geographic atrophy are without regard to progression to the other. The analysis of progression to central geographic atrophy (definitely involving the center of the macula or questionably involving the center but definitely present proximally, on the basis of a reading of the center reports) did not count as central geographic atrophy when it occurred in an eye that also exhibited subretinal fibrosis at the same visit.

An "event" of AMD progression was defined as the occurrence of the first maximal AMD progression in one eye at a single visit. Every eye contributed at most one event, and therefore each person had either no event, 1 event, or, at most, 2 events. For example, for an eye (assuming the right eye) of a person with a progression sequence of 2→2→2→3→2→3→3→3, we considered that the outcome occurred at visit 4 (the first maximal progression from group 2 at baseline into group 3). Assuming that this person had 2 eyes at risk of progression and that the other eye (assuming the left eye) of this person had a sequence of 2→2→3→3→2→3→3→3, we identified this person as having 2 events, 1 at visit 4 (right eye) and 1 at visit 3 (left eye). In this case, the left-eye event is the first event and the right-eye event is the second event. For people with events in both eyes at the same time point, we ordered the right-eye event as the first event and the left-eye event as the second event. We also performed an analysis in which we ordered the left-eye event as the first event and the right-eye event as the second event. The results were similar and thus are not shown here.

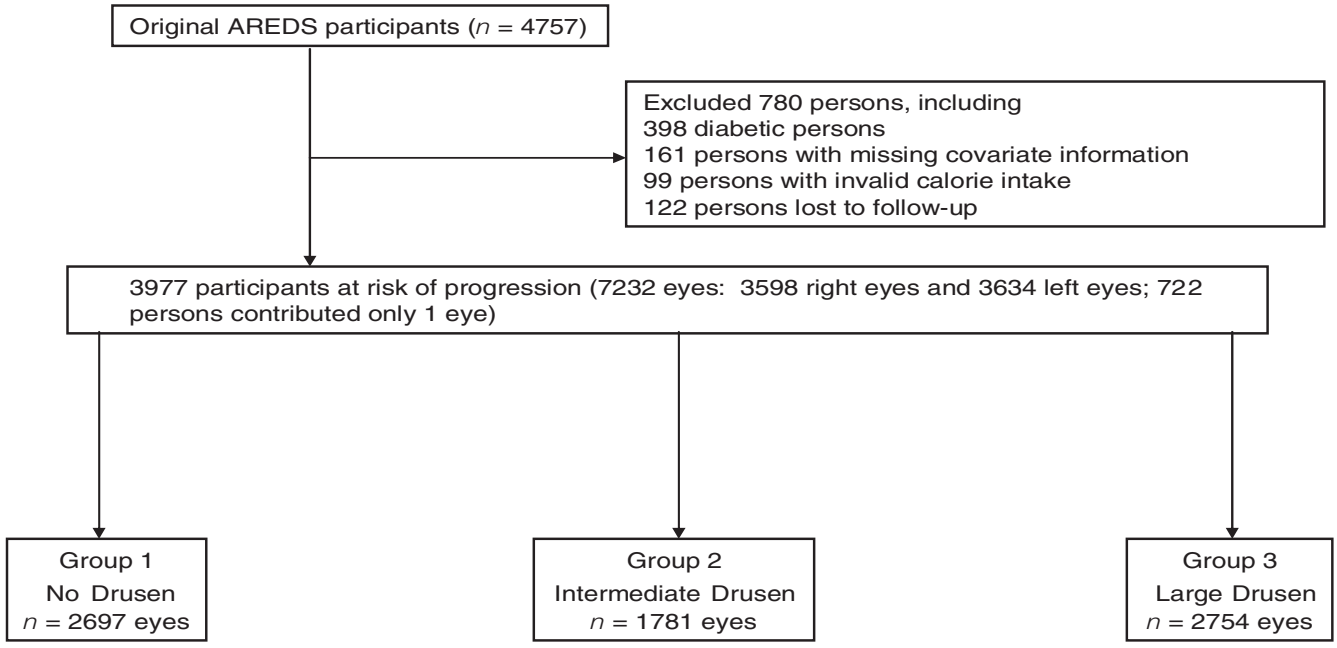

FIGURE 1. Flow chart describing the disposition of subjects at risk of age-related macular degeneration (AMD) progression from the Age-Related Eye Disease Study (AREDS). AMD was classified by the AREDS AMD Classification System as follows: group 1, no drusen; group 2, intermediate drusen; group 3, large drusen. Eyes in groups 4 (geographic atrophy) and 5 (neovascularization) at baseline were excluded from the present analysis because they were considered to be at the end stage of AMD and thus were not at risk of progression.

Assessment of dietary carbohydrate variables

The previously mentioned validated FFQ, which was a 90-item modified Block FFQ, was administered to the AREDS participants at baseline. The FFQ collected information about usual dietary intakes over the previous year and classified them into 9 possible response categories, ranging from "never or less than once per month" to "2 or more times per day." The daily total carbohydrate intake of an individual was calculated by summing the product of the frequency, serving size, and carbohydrate content per serving from individual food items derived from the nutrition database of the Nutrition Coordinating Center at the University of Minnesota. The FFQ was validated in relation to 24-h recall by use of a subset of the AREDS volunteers ($n = 192$). Correlations for energy and carbohydrate intakes between the 24-h recall and the FFQ were 0.51 ($P < 0.001$) and 0.56 ($P < 0.001$), respectively (N Kurinij et al, unpublished observation, 1998).

The GI is a physiologic measure of the glycemic quality of carbohydrate-containing foods (15). It was devised to measure how fast a food raises blood glucose and is defined as the ratio of the area under curve of 2-h blood glucose curves from the same amount (50 g) of available carbohydrate from test food compared with reference food (pure glucose or white bread; 15). The GI values for foods in the FFQ were either derived from published values by using white bread as the reference food or imputed from GI values of comparable foods (16). 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 [Σ ($GI_i \times W_i$)/W] (17), where GI_i is the glycemic index of an individual food, W is the weight of total carbohydrate, and W_i is the weight of available carbohydrate of individual food. The fiber content was subtracted from the carbohydrate content. Carbohydrate and other nutritional variables were adjusted for total energy intake by using the residuals method (18).

Defining potential covariates

The following were considered as potential covariates in the present analyses: age, sex, education level (college graduate, some college, or high school or less), race (white or other), body mass index (computed from weight and height; kg/m^2), smoking status (ever or never), alcohol intake (g/d), sunlight exposure (h/d; 19) hypertension history, baseline AMD classification, lens opacity, refractive error (hyperopic or myopic), and energy-adjusted dietary variables, including total carbohydrate, fat, lutein and zeaxanthin, folic acid, niacin, riboflavin, thiamin, β-carotene, vitamin C, vitamin E, and zinc intakes.

Statistical analysis

To maximize power, we used eyes as the unit of analysis and identified eyes with nonadvanced AMD lesions (groups 1, 2, and 3; *see* Procedures) at baseline as the at-risk set for progression. We first described baseline characteristics by dGI status (evaluated as being above or below the sex median; women: 77.9; men: 79.3). Chi-square and Wilcoxon's 2-sample tests were used to examine the difference of characteristic distributions between the high- and low-dGI groups. AMD outcome and time to the first maximal progression were used to calculate baseline AMD grade-specific crude risk ratios (RRs) and 95% CIs for high compared with low dGI. We estimated cumulative survival functions for high- and low-dGI groups according to the method of Kaplan and Meier (product limit estimators). Because the tails of the estimated survival curves are usually unreliable, we calculated the survival curves only up to 96 mo of follow-up. SAS PROC LIFETEST software (version 9.1; SAS Institute, Cary, NC) was used to compute the survival function for each group, and the log-rank test was used to compare the 2 distributions.

We calculated multivariate-adjusted RRs and 95% CIs that related dGI to subsequent maximal AMD progression during the

follow-up period by Cox regression by using SAS PROC PHREG software (version 9.1). The models were adjusted for age, sex, baseline AMD grade, those baseline characteristics that were significantly different between the high- and low-dGI groups in any AMD category (*see* **Table 1** and **Table 2**), and energy-adjusted dietary variables: total carbohydrate, fat, lutein and zeaxanthin, folic acid, niacin, riboflavin, β-carotene, vitamin C, vitamin E, and zinc intakes. Three multifailure survival methods—the Andersen-Gill (AG) method (20), the Wei-Lin-Weissfeld (WLW) method (21), and the Prentice-Williams-Peterson (PWP) method (22)— all of which are generalized forms of the Cox proportional-hazards model (*see* Table 2), were applied to the data to account for the lack of independence between 2 eyes from the same individual. In the present study, multifailure meant that an event can occur in 0, 1, or 2 eyes. The AG method was used to estimate the global (overall; unstratified) effects of dGI. Because both the WLW and PWP methods analyze repeated events by stratification according to their order of occurrence, they were used to estimate the ordered event-specific risk associated with dGI. The results from both WLW and PWP methods are similar; thus, only the WLW results are shown in Table 2.

To evaluate whether there was a positive relation between baseline AMD grade and dGI-associated RRs (Table 2), we related the RR to baseline AMD grade in a multivariate linear regression by using SAS PROC MIXED with REPEATED statement software (version 9.1). The *P* value for trend was derived from the *P* value for the regression coefficient of baseline AMD grade.

Group 3 eyes are especially interesting clinically because they are at high risk of developing advanced AMD. Therefore, we also analyzed the dose-response relation between group 3 eyes and dGI (**Figure 2**). To test for trends across dGI quintiles, we assigned the median value in each category to everyone within the category and then included this as a continuous variable in the Cox regression models. We used $P < 0.05$ to denote statistical significance, and all tests were 2-sided.

RESULTS

The distribution of characteristics of the 7232 at-risk eyes is shown in Table 1. The distributions of age, sex, smoking status, sunlight exposure, lens opacity, and AREDS treatment were not significantly different between high- and low-dGI groups. In general, the high-dGI subgroup was more likely to be nonwhite and less educated than was the low-dGI subgroup. The high-dGI subgroup was more likely to have higher body mass index than was the low-dGI subgroup in group 2 and in the overall sample at baseline, but not in groups 1 and 3. Whereas the high-dGI subgroup was more likely to have hypertension than was the low-dGI subgroup in the overall sample, there was no distributional difference between the high- and low-dGI subgroups in groups 1, 2, and 3. As for refractive error, the high-dGI subgroup was more likely to have hyperopia in the overall sample and in group 2; there was no distributional difference between the high- and low-dGI subgroups in groups 1 and 3.

At the end of the present study, 35.2% of eyes in the low-dGI subgroup (1299 of 3691) and 37.1% of eyes in the high-dGI subgroup (1314 of 3541) had progression (ie, developed an event; **Table 3**). Most of the progression cases during the study period were one-grade progressions, eg, 1→2, 2→3, 3→4, or 3→5. For example, in group 2 at baseline, in the high-dGI subgroup, there were 335 events (eyes), and of these 335 events, 281 progressed into group 3. Therefore, 83.9% (281/335) were one-grade (2→3) progression. The mean follow-up time was 65.1 mo (5.4 y). The high-dGI subgroup had a higher risk of progression than did the low-dGI subgroup across group 1 through group 3 as well as in the overall sample. In addition, the higher the baseline AMD grade, the higher the crude RR (95% CI): 1.04 (0.92, 1.18), 1.09 (0.93, 1.26), and 1.14 (1.00, 1.29), respectively, and 1.08 (1.00, 1.17) for the overall sample.

The 2 Kaplan-Meier survival curves showed a gradual bifurcated pattern, which indicated no profound violation of the proportional hazard assumption for the further application of Cox regression models, and a lower progression rate in the low-dGI group than in the high-dGI group (**Figure 3**). The estimated proportion with progression at the end of the study was 43.5% in the low-dGI group and 48.0% in the high-dGI group. The survival distributions for the 2 dGI groups were significantly different ($P = 0.018$, log-rank test).

The multivariate-adjusted RRs derived from the Cox proportional-hazards models are shown in Table 2. Overall, the risk of progression was significantly higher in the high-dGI group than in the low-dGI group (RR: 1.10; 95% CI: 1.00, 1.20; $P = 0.047$). When we examined the data by baseline AMD categories, we found results very similar to the crude estimates, which showed that the more advanced the AMD grade at baseline, the higher the dGI-associated risk of progression (*P* for trend < 0.001); there was a 17%, 8%, and 5% greater risk for groups 3, 2, and 1 eyes, respectively. The point estimate was significant only for group 3 (RR: 1.17; 95% CI: 1.01, 1.36; $P = 0.041$). In the stratification analyses, the WLW and PWP methods gave comparable results (data not shown). The event-specific RRs suggested that dGI was more strongly associated with second-event risk than with first-event risk in groups 2 and 3 and in the overall sample, but not in group 1. Of the participants with 2 group 3 eyes, the risk of progression in the fellow eye after the first event was 30% ($P = 0.088$) greater in the high-dGI group than in the low-dGI group; the more advanced the baseline AMD grade, the higher the dGI-associated risk of progression for second events (*P* for trend < 0.001).

Analyses in those at high risk of developing advanced AMD (group 3 at baseline) showed a significant dose-response relation (*P* for trend = 0.011) with dGI. There is a nearly 40% greater risk for the highest 20% of dGI than for the lowest 20% (RR: 1.39; 95% CI: 1.08, 1.79; $P = 0.012$; Figure 2).

DISCUSSION

In the present study, we show for the first time that people who consume diets that consist of greater amounts of refined carbohydrate are at greater risk of AMD progression than are those whose diets contain smaller amounts of refined carbohydrate. Moreover, the higher the baseline AMD grade, the higher the greater dGI-associated risk. The data support and extend our prior cross-sectional observations that the consumption of foods that provide high rapid increases in blood sugar may confer additional risk of progression of AMD (4, 10). To evaluate this issue in the present prospective study, we used a multifailure Cox regression to model the time to repeated events (ie, events in one or both eyes) in an individual, and we applied 3 different approaches to estimate global and, through stratification by the

TABLE 1
Baseline characteristics by dietary glycemic index (dGI) status and age-related macular degeneration (AMD) group[1]

	AMD group and dGI status							
	Group 1: no drusen		Group 2: intermediate drusen		Group 3: large drusen		Overall	
	High (n = 1270)	Low (n = 1427)	High (n = 865)	Low (n = 916)	High (n = 1406)	Low (n = 1348)	High (n = 3541)	Low (n = 3691)
Age (range: 55–80 y)								
<65 y [n (%)]	407 (32.05)	420 (29.43)	204 (23.58)	222 (24.24)	244 (17.35)	259 (19.21)	855 (24.15)	901 (24.41)
65–71 y [n (%)]	538 (42.36)	622 (43.59)	369 (42.66)	386 (42.14)	521 (37.06)	477 (35.39)	1428 (40.33)	1485 (40.23)
≥71 y [n (%)]	325 (25.59)	385 (26.98)	292 (33.76)	308 (33.62)	641 (45.59)	612 (45.40)	1258 (35.53)	1305 (35.36)
P^2	0.33		0.95		0.40		0.97	
Race [n (%)]								
White	1184 (93.23)	1379 (96.64)	810 (93.64)	888 (96.94)	1359 (96.66)	1329 (98.59)	3353 (94.69)	3596 (97.43)
Other	86 (6.77)	48 (3.36)	55 (6.36)	28 (3.06)	47 (3.34)	19 (1.41)	188 (5.31)	95 (2.57)
P^2	< 0.001		0.001		< 0.001		< 0.001	
Sex [n (%)]								
Female	715 (56.30)	823 (57.67)	517 (59.77)	544 (59.39)	816 (58.04)	784 (58.16)	2048 (57.84)	2151 (58.28)
Male	555 (43.70)	604 (42.33)	348 (40.23)	372 (40.61)	590 (41.96)	564 (41.84)	1493 (42.16)	1540 (41.72)
P^2	0.47		0.87		0.95		0.70	
Education [n (%)]								
College graduate	422 (33.23)	681 (47.72)	267 (30.87)	399 (43.56)	366 (26.03)	507 (37.61)	1055 (29.79)	1587 (43.00)
Some college	398 (31.34)	413 (28.94)	238 (27.51)	271 (29.59)	441 (31.37)	424 (31.45)	1077 (30.42)	1108 (30.02)
High school or less	450 (35.43)	333 (23.34)	360 (41.62)	246 (26.86)	599 (42.60)	417 (30.93)	1409 (39.79)	996 (26.98)
P^2	< 0.001		< 0.001		< 0.001		< 0.001	
Smoking status [n (%)]								
Yes	655 (51.57)	687 (48.14)	447 (51.68)	469 (51.20)	823 (58.53)	775 (57.49)	1925 (54.36)	1931 (52.32)
No	615 (48.43)	740 (51.86)	418 (48.32)	447 (48.80)	583 (41.47)	573 (42.51)	1616 (45.64)	1760 (47.68)
P^2	0.08		0.84		0.58		0.08	
Alcohol intake [median (g/d)]	0.96	1.44	0.89	1.38	0.89	1.74	0.89	1.52
P^3	0.1		0.04		< 0.001		< 0.001	
BMI (kg/m^2)								
<23.6 (bottom 20%)	286 (22.52)	315 (22.07)	174 (20.12)	202 (22.05)	285 (20.27)	266 (19.73)	745 (21.04)	783 (21.21)
23.6–31 (middle 60%)	752 (59.21)	863 (60.48)	530 (61.27)	588 (64.19)	824 (58.61)	828 (61.42)	2106 (59.47)	2279 (61.74)
≥31 (top 20%)	232 (18.27)	249 (17.45)	161 (18.61)	126 (13.76)	297 (21.12)	254 (18.84)	690 (19.49)	629 (17.04)
P^2	0.78		0.02		0.25		0.02	
Sunlight exposure (h/d)								
<0.22 (bottom 20%)	275 (21.65)	284 (19.90)	151 (17.46)	161 (17.58)	284 (20.20)	268 (19.88)	710 (20.05)	713 (19.32)
0.22–1.65 (middle 60%)	760 (59.84)	877 (61.46)	534 (61.73)	579 (63.21)	838 (59.60)	799 (59.27)	2132 (60.21)	2255 (61.09)
≥1.65 (top 20%)	235 (18.50)	266 (18.64)	180 (20.81)	176 (19.21)	284 (20.20)	281 (20.85)	699 (19.74)	723 (19.59)
P^2	0.52		0.70		0.91		0.69	
Hypertension [n (%)]								
Yes	444 (34.96)	457 (32.03)	327 (37.80)	324 (35.37)	578 (41.11)	514 (38.13)	1349 (38.10)	1295 (35.09)
No	826 (65.04)	970 (67.97)	538 (62.20)	592 (64.63)	828 (58.89)	834 (61.87)	2192 (61.90)	2396 (64.91)
P^2	0.11		0.29		0.11		0.008	
Lens opacity [n (%)]								
Yes	221 (17.40)	268 (18.78)	182 (21.04)	179 (19.54)	386 (27.45)	377 (27.97)	789 (22.28)	824 (22.32)
No	1049 (82.60)	1159 (81.22)	683 (78.96)	737 (80.46)	1020 (72.55)	971 (72.03)	2752 (77.72)	2867 (77.68)
P^2	0.35		0.43		0.76		0.97	
Refractive error [n (%)]								
Hyperopic	1012 (79.69)	1126 (78.91)	706 (81.62)	689 (75.22)	1135 (80.73)	1059 (78.56)	2853 (80.57)	2874 (77.87)
Myopic	258 (20.31)	301 (21.09)	159 (18.38)	227 (24.78)	271 (19.27)	289 (21.44)	688 (19.43)	817 (22.13)
P^2	0.62		0.001		0.16		0.005	
AREDS treatment [n (%)]								
Placebo	584 (45.98)	606 (42.47)	221 (25.55)	247 (26.97)	322 (22.90)	365 (27.08)	1127 (31.83)	1218 (33.00)
Antioxidants alone	506 (39.84)	606 (42.47)	206 (23.82)	252 (27.51)	366 (26.03)	325 (24.11)	1078 (30.44)	1183 (32.05)
Zinc alone	98 (7.72)	106 (7.43)	233 (26.94)	203 (22.16)	357 (25.39)	331 (24.55)	688 (19.43)	640 (17.34)
Antioxidants plus zinc	82 (6.46)	109 (7.64)	205 (23.70)	214 (23.36)	361 (25.68)	327 (24.26)	648 (18.30)	650 (17.61)
P^2	0.22		0.08		0.09		0.07	

[1] AMD groups were classified according to the criteria of the Age-Related Eye Disease Study (AREDS) AMD Classification System. High and low dGI were defined as values above or below the sex median cutoffs (women: 77.9; men: 79.3). The n shown is equal to 100% for that column.
[2] Chi-square tests compared the characteristic distributions between the high- and low-dGI groups.
[3] Wilcoxon's 2-sample tests compared the characteristic distributions between the high- and low-dGI groups.

TABLE 2
Global and occurrence order–specific risk ratios (and 95% CIs) comparing high and low dietary glycemic index (dGI) in the progression of age-related macular degeneration (AMD) by baseline AMD classifications from Cox proportional-hazards analysis[1]

	Baseline AMD classification				
Model[2]	Group 1: no drusen (n = 2697)	Group 2: intermediate drusen (n = 1781)	Group 3: large drusen (n = 2754)	P for trend	Overall (n = 7232)
Global model (AG)	1.05 (0.91, 1.22)	1.08 (0.91, 1.30)	1.17 (1.01, 1.36)	< 0.001	1.10 (1.00, 1.20)
Event-specific model (WLW)					
First event[3]	1.09 (0.92, 1.29)	1.06 (0.87, 1.29)	1.10 (0.92, 1.31)	NA[4]	1.07 (0.97, 1.19)
Second event[3]	0.97 (0.73, 1.29)	1.15 (0.75, 1.75)	1.30 (0.96, 1.76)	< 0.001	1.11 (0.90, 1.35)

[1] AG, Andersen-Gill method; WLW, Wei-Lin-Weissfeld method. AMD groups were classified according to the Age-Related Eye Disease Study AMD Classification System. High and low dGI were defined as values above or below the sex median cutoffs (women: 77.9; men: 79.3). A total of 7232 eyes, including 3691 eyes in the low-dGI category and 3541 eyes in the high-dGI category, from groups 1, 2, and 3 at baseline were considered to be at risk of progression. Eyes in groups 4 and 5 at baseline were excluded from the present analysis because they were considered to be at the end stage of AMD and thus not at risk of progression. The time to the first maximal AMD progression of studied eyes during the study period was analyzed. Progression for a study eye was defined by a more advanced AMD category than the baseline grade.

[2] The AG approach models the repeated AMD progressions for each person as separate observations, with the risk set not constrained by the number of events occurring within a person, and uses a robust sandwich covariance matrix structure for the within-subject correlation to compensate the assumption of independence among multiple observations per person over time. It uses a common baseline hazard function for all events and estimates a global parameter for dGI. In the WLW method, repeated events are stratified according to their order of occurrence, and the marginal analysis of each repeated observation is performed separately by using a Cox proportional-hazards model without imposing any dependence structure in the model. An event-specific hazard is estimated by stratified analysis that allows a separate hazard for each event. All models were adjusted for age, sex, race, education, alcohol intake, BMI, hypertension history, refractive error, baseline AMD grade (only in the overall analysis), and energy-adjusted dietary variables, including total carbohydrate, fat, lutein and zeaxanthin, folic acid, niacin, riboflavin, β-carotene, vitamin C, vitamin E, and zinc intakes.

[3] An "event" of AMD progression was defined as the occurrence of the first maximal AMD progression in one eye at a single visit. Every eye contributed ≤1 event; therefore, each person had either 0, 1, or ≤2 events.

[4] NA, not applicable.

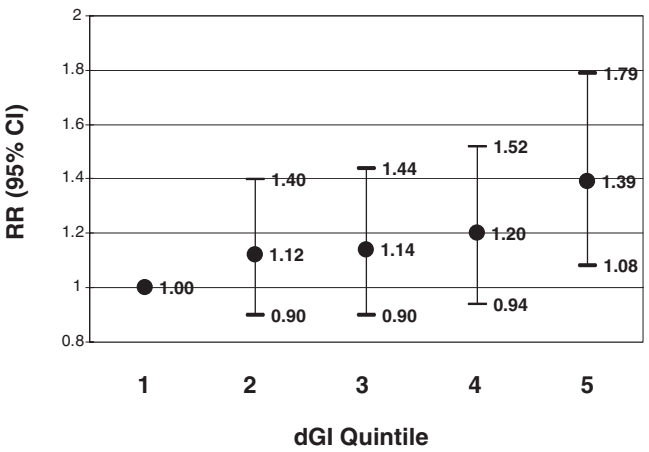

FIGURE 2. Dose-response relation between dietary glycemic index (dGI) and the risk of developing advanced age-related macular degeneration (AMD) in large drusen at baseline, expressed as risk ratios (RRs) and 95% CIs. The quintiles (median cutoffs) for dGI were 73.6, 76.6, 79.1, and 81.7 for women and 75.7, 78.3, 80.3, and 82.8 for men. According to the Age-Related Eye Disease Study AMD Classification System, group 3 (large drusen or extensive intermediate drusen, n = 2754) includes eyes that had ≥1 large drusen or extensive intermediate drusen. Advanced AMD includes eyes in group 4 (geographic atrophy) or group 5 (neovascularization). The time to the first advanced AMD progression of studied eyes during the study period was analyzed. With the use of the Andersen-Gill method of estimating the indicators (RRs and 95% CIs) for dGI, the Cox regression model was adjusted for age, sex, race, education, alcohol intake, BMI, hypertension history, refractive error, and energy-adjusted dietary variables, including total carbohydrate, fat, lutein and zeaxanthin, folic acid, niacin, riboflavin, β-carotene, vitamin C, vitamin E, and zinc intake. P for trend = 0.011.

order of outcome occurrence, event-specific effects of dGI. In the stratification analysis, in which we compared the results from modeling the time to first events with the results from modeling the time to second events across earlier and later stages of AMD, we gained further support of the finding from global (unstratified) analysis that dGI may play a somewhat more important role in the later stages than in the earlier stages of early AMD progression. This result implies that persons with more advanced early AMD lesions would benefit more by consuming low-dGI diets than would those with earlier stages of early AMD lesions. The data also suggest that the existing early AMD lesions would accelerate the dGI-associated AMD progression.

Possible mechanisms

The current data strengthen our previous hypothesis that AMD may share etiologies and risk factors with several major systemic disorders, including obesity, diabetes, and cardiovascular disease (4). Previous cross-sectional studies (4, 10) and the present analysis (data not shown) have consistently not found a relation between total carbohydrate intake and risk of AMD. The use of total carbohydrate intake as a marker, however, does not take into account the glycemic or other adverse effects of different forms of carbohydrates. As we noted previously (4, 10), dGI may affect the risk of AMD through multiple pathways. It is hypothesized that high-GI diets allow higher concentrations of available glucose to enter cells during the postprandial period, which results in chronically high oxidative stress, whereas low-GI diets, but not low-carbohydrate diets, appear to be beneficial in reducing such oxidative stress (23). Therefore, it is possible that high-GI

TABLE 3
Outcome and duration of follow-up by baseline dietary glycemic index (dGI) categories and age-related macular degeneration (AMD) classification[1]

	AMD group and dGI status							
	Group 1: no drusen		Group 2: intermediate drusen		Group 3: large drusen		Overall	
	High (n = 1270)	Low (n = 1427)	High (n = 865)	Low (n = 916)	High (n = 1406)	Low (n = 1348)	High (n = 3541)	Low (n = 3691)
Outcome at follow-up [n (%)]								
Group 1	785 (61.81)	895 (62.72)	—	—	—	—	785 (22.17)	895 (24.25)
Group 2	421 (33.15)	456 (31.96)	530 (61.27)	578 (63.10)	—	—	951 (26.86)	1034 (28.01)
Group 3	60 (4.72)	70 (4.91)	281 (32.49)	282 (30.79)	912 (64.86)	919 (68.18)	1253 (35.39)	1271 (34.44)
Group 4[2]	0 (0.00)	2 (0.14)	16 (1.85)	19 (2.07)	213 (15.15)	189 (14.02)	229 (6.47)	210 (5.69)
Group 5[3]	4 (0.31)	4 (0.28)	38 (4.39)	37 (4.04)	281 (19.99)	240 (17.80)	323 (9.12)	281 (7.61)
Progression [n (%)]								
No	785 (61.81)	895 (62.72)	53 (61.27)	578 (63.10)	912 (64.86)	919 (68.18)	2227 (62.89)	2392 (64.81)
Yes	485 (38.19)	532 (37.28)	335 (38.73)	338 (36.90)	494 (35.14)	429 (31.82)	1314 (37.11)	1299 (35.19)
Duration of follow-up by outcome (eye-months)								
Group 1	58 672	68 139	—	—	—	—	58 672	68 139
Group 2	20 573	22 577	39 894	44 897	—	—	60 467	67 474
Group 3	3038	3192	11 320	10 944	68 545	69 397	82 903	83 533
Group 4[2]	0	125	765	1057	10 911	9293	11 676	10 475
Group 5[3]	154	222	1560	1749	12 069	11 565	13 783	13 536
Total eye-months	82 437	94 255	53 539	58 647	91 525	90 255	227 501	24 3157
Crude progression rate (95% CI)[4]	5.88 (5.37, 6.43)	5.64 (5.17, 6.14)	6.26 (5.60, 6.96)	5.76 (5.17, 6.41)	5.40 (4.93, 5.90)	4.75 (4.31, 5.22)	5.78 (5.47, 6.10)	5.34 (5.06, 5.64)
Crude RD (95% CI)[5]	0.24 (−0.47, 0.95)		0.49 (−0.42, 1.40)		0.64 (−0.01, 1.30)		0.43 (0.01, 0.86)	
Crude RR (95% CI)[5]	1.04 (0.92, 1.18)		1.09 (0.93, 1.26)		1.14 (1.00, 1.29)		1.08 (1.00, 1.17)	

[1] RR, risk ratio; RD, rate difference. High and low dGI were defined as values above or below the sex median cutoffs (women: 77.9; men: 79.3). The n shown is equal to 100% for that column. AMD groups were classified according to the Age-Related Eye Disease Study AMD Classification System. The time to the first maximal AMD progression of studied eyes during the study period was analyzed. Progression for a study eye was defined by a more advanced AMD category than the baseline grade.

[2] Geographic atrophy.

[3] Neovascularization.

[4] Overall values in these groups (high- plus low-dGI) are as follows: 5.76 (5.41, 61.2) for group 1, 6.00 (5.55, 6.47) for group 2, 5.08 (4.76, 5.42) for group 3, and 5.55 (5.34, 5.77) for the groups overall.

[5] Data were derived by comparing the risk of high- and low-dGI groups. RDs were derived by subtracting the rate of the low-dGI group from the rate of the high-dGI group. RRs were derived by dividing the rate of the high-dGI group by the rate of the low-dGI group.

diets may result in enhanced glycation, the formation of advanced glycation end products, glycoxidation, and subsequent inflammatory and angiogenic responses in the development of AMD (24–26). In addition, compensatory hyperlipidemia in the late postprandial stage after the consumption of high-GI foods (8, 27, 28) and the insulin-like growth factor axis, which has been linked to dGI and age-related diseases (29, 30), may play certain roles in the pathogenesis of AMD.

With the use of the data from the present epidemiologic study, we were also able to glean insights into the role of dGI in the development of AMD. Although the crude rate for group 2 AMD is the highest among the 3 baseline AMD groups, the rate differences and RRs between high dGI and low dGI suggest that a history of consuming a high-dGI diet may play a more important role in the later stages than in the earlier stages of AMD progression (Tables 2 and 3). In addition, we found, in the event-specific analyses, that dGI played a more important role in the second events in the later stages (Table 2). Because individuals with bilateral AMD progression (ie, individuals having a second event) may represent those who were more susceptible to AMD progression, this finding implies that the interaction between AMD susceptibility and dGI affects the risk of AMD progression, whereas dGI plays a more important role in the later stages. Further studies are needed to clarify the detailed mechanisms.

Strengths and limitations

Compared with the cross-sectional features of the previous studies (4, 10), the prospective design of the present study reduces the possibility of biased recall of diet, and it also clarifies the temporality of causation because all data on food intake were collected before the baseline and follow-up eye examinations. Furthermore, the graded eye data were classified by graders who were blinded to the nutrition data in the present study. Although GI values are generally reproducible from place to place, there are some variations in published GI values for apparently similar foods (17). For those foods, we chose the GI of the most popular American food item in our compilation (12). It is unlikely that the nondifferential misclassification in dGI compilation of the present study could explain the findings because the compilers were blinded to the ophthalmic data. In addition, detailed data for each eye and multifailure statistical approaches offer a unique opportunity for exploring the relative contribution of dGI in different stages of AMD progression and providing a more nuanced picture of the dGI effect.

As in all observational studies, there were limitations in the way the data in the present study were collected. Because participants attended eye examinations at scheduled annual visits, most of the vision-nonimpairing progression was detected at

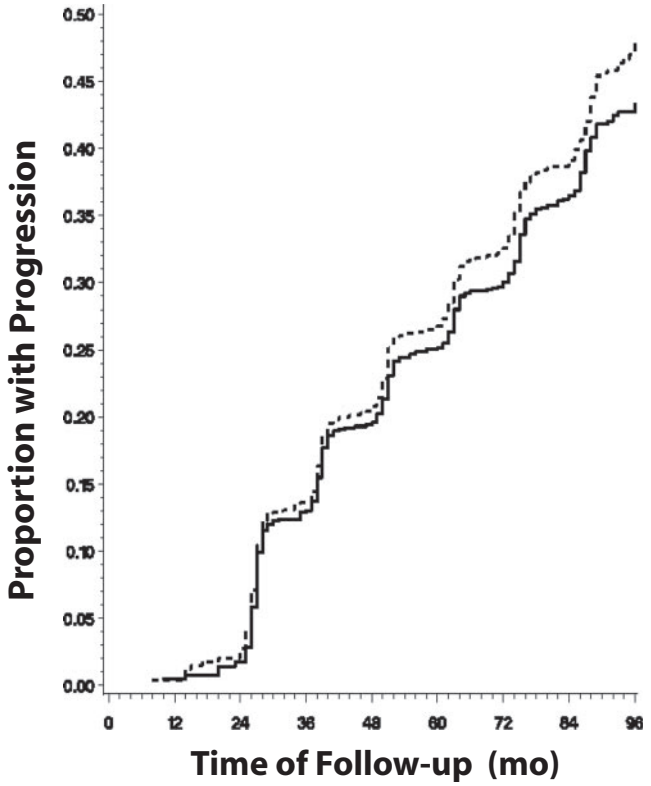

FIGURE 3. Kaplan-Meier analysis of time to age-related macular degeneration (AMD) progression in high (——)- and low (——)-dietary glycemic index (dGI) categories (dGI values were evaluated by using the sex median cutoffs: 77.9 for women and 79.3 for men). The time to the first maximal AMD progression of studied eyes during the study period was analyzed. Progression for a study eye was defined by a more advanced AMD category than the baseline grade according to the Age-Related Eye Disease Study AMD Classification System: group 1, no drusen; group 2, intermediate drusen; group 3, large drusen; group 4, geographic atrophy; and group 5, neovascularization. A total of 7232 eyes, including 3691 eyes in the low-dGI category and 3541 eyes in the high-dGI category from groups 1, 2, and 3 at baseline, were considered to be at risk of progression. Eyes in groups 4 and 5 at baseline were excluded from the present analysis because they were considered to be in the end stage of AMD and thus not at risk of progression. $P = 0.0182$, log-rank test.

these time points. Therefore, more events were identified at annual scheduled follow-up visits and fewer events were identified between follow-up visits (Figure 2). The exact time of progression was difficult to ascertain, because most of the vision-nonimpairing progression could not be known until the eye examination was performed. However, there is no reason to believe that the vision-nonimpairing progression would have occurred differentially between the high- and low-dGI groups, because the high response rate during the follow-up period (>97%) has balanced the detection of events and excluded bias from differential participation. By examining the cumulative hazard plot for detection of progression (Figure 3), one can see that, as expected, major "steps" occurred at scheduled annual time points. However, the increments of progression were indistinguishable between the high- and low-dGI groups, which suggested that the effect of dGI should not be unduly biased by the limitation of ascertaining exact progression time.

In the present study, dietary information was collected by use of an FFQ at baseline recruitment. There may be a concern about dietary change over the study period. Intuitively, short-term recall or diet records may seem to provide better measures. However, because such records are generally unrepresentative of usual intake and are expensive to obtain, they are usually used in the validation or calibration of other methods of dietary assessment that are more practical for epidemiologic studies, such as has been done in the present study (N Kurinij et al, unpublished observations, 1998). Because diets tend to be reasonably correlated from year to year, information derived from FFQs is considered to be more practical and valid for measuring long-term dietary intake in epidemiologic studies (31). Furthermore, at the time of the present study, there were no prior studies that related dietary carbohydrate to AMD. Thus, it is unlikely that the participants would have modified their diets on the basis of such relations. Multiple measurements during the study period (eg, annual FFQ administration) will be an advantage in future studies.

Another concern may be uncontrolled potential and residual confounders, of which physical activity, diabetes, and socioeconomic status may be the most interesting. In the Beaver Dam Eye Study, an active lifestyle was suggested to have a protective effect on the incidence of exudative AMD, but not on early AMD or geographic atrophy (32). However, studies have suggested that physical activity is more likely to be a synergistic factor, but not a confounder for physical activity, in the protective effect of low-dGI diets on cardiovascular diseases (33), which have been suggested to share common etiologies and risk factors with AMD (27). Furthermore, by using isocaloric (energy-adjusted) nutrient variables, we also diminished the effect of variation in factors other than the nutrient per se, such as body size, physical activity, and metabolic efficiency (18). As for diabetes status, although we controlled its potential confounding by excluding subjects′ with diabetes at baseline, newly developed cases during the follow-up period may raise a concern. However, the concern should be largely alleviated because we tried to evaluate its influence by including those baseline diabetic subjects in the analyses and found that the findings were the same (data not shown). The influence of socioeconomic status, which may influence accessibility to health care and may be an important factor in determining disease progression, should be minimized for several reasons. First, by the inclusion of "education level" in the models, the confounding effect was at least partially controlled. Second and more important, because AREDS is a trial with a high follow-up rate (>97%), it is unlikely that the results were distorted by differential participation, as discussed above.

Public health implication

The present data extend the concern about the the current diet in the United States, in which carbohydrates mainly consist of highly processed and refined grains. As in our cross-sectional investigations (4, 10), the present findings are applicable to the majority of the healthy elderly population. Robust results from both the WLW and PWP methods indicated that high-dGI diets are associated with a greater risk of AMD progression, especially for those with more advanced disease (large drusen or extensive intermediate drusen). For those at high risk of advanced AMD (group 3 participants at baseline), the results of the present study (Table 2) showed that high-dGI diets increased the risk of developing advanced AMD by 17%. With the use of these data, we estimated that reducing dGI for the upper 50% of the elderly population may reduce 7.8% of new advanced AMD cases in 5 y by using the following calculation:

$$\text{Population-attributable fraction} = P_x(\text{RR} - 1)/[P_x(\text{RR} - 1) + 1] = (0.5 \times 0.17)/[(0.5 \times 0.17) + 1] = 7.8\% \quad (1)$$

where P_x is the proportion of exposure in the population (4, 34). The efficacy of such low-dGI diets warrants randomized controlled clinical trials.

In conclusion, the prospective data in the present study indicate that poor dietary carbohydrate quality as defined by dGI, but not quantity, increases the risk of AMD progression in persons with early AMD, especially those at the later stages. The data also suggest a potential modifiable dietary factor that may be protective against developing AMD and any accompanying vision loss.

The authors' responsibilities were as follows—C-JC: analysis design, data analysis, intellectual input, and drafting of the manuscript; AT: drafting of the manuscript and intellectual input in terms of study topic choice: RCM and GG: data collection, data analyses, and proofreading of the manuscript; and RK: drafting of the manuscript. None of the authors had any conflict of interest.

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