Dietary glycemic index and carbohydrate in relation to early age-related macular degeneration

Chung-Jung Chiu, Larry D Hubbard, Jane Armstrong, Gail Rogers, Paul F Jacques, Leo T Chylack Jr, Susan E Hankinson, Walter C Willett, and Allen Taylor

ABSTRACT

Background: Several dietary factors have been linked to age-related maculopathy (ARM), the early form of age-related macular degeneration, and there is reason to think that dietary carbohydrate may play a role in the development of ARM.

Objective: The purpose of the present study was to examine the relation between dietary carbohydrate quality, as measured by dietary glycemic index (GI) or total carbohydrate intake, and ARM.

Design: From the Nurses’ Health Study, 1036 eyes from 526 Boston-area participants without a previous ARM diagnosis were included in the present study. The presence and degree of ARM were classified by the Age-Related Eye Diseases Study system. Long-term dietary information was based on data from an average of 4 food-frequency questionnaires collected over a 10-y period before the assessment of ARM. With eyes as the unit of analysis, we used a generalized estimating approach to logistic regression to estimate the odds ratios for ARM in a manner that accounted for the lack of independence between the 2 eyes from the same subject.

Results: After multivariate adjustment, dietary GI was related to ARM (specifically to retinal pigmentary abnormalities), whereas total carbohydrate intake was not. The odds ratio for ARM being in the highest tertile of dietary GI (≥77.0) versus the lowest (<74.6) was 2.71 (95% CI: 1.24, 5.93; P for trend = 0.01). Neither dietary GI nor total carbohydrate intake was related to drusen.

Conclusion: Our results suggest that dietary GI may be an independent risk factor for ARM. Am J Clin Nutr 2006;83:880–6.

KEY WORDS Age-related macular degeneration, retina, maculopathy, nutrition, vision, carbohydrate, glycemic index, glycation, aging, epidemiology, risk factor, food-frequency questionnaire, drusen, pigment abnormalities

INTRODUCTION

The macula is located in the center of the retina, where light is converted into electrical impulses before transmission to the brain. The macula enables us to see fine detail and is critical to central vision. Age-related macular degeneration (AMD) is one of the leading causes of irreversible vision loss in Americans 40 y of age and older (1). The prevalence of AMD in this segment of the US population is estimated to be 1.47%, with 1.75 million persons having some manifestation of AMD. The prevalence increases dramatically with age and is >10% among persons older than 80 y (2). Within the next 2 decades, as the number of elderly Americans increases, it is anticipated that the number of AMD cases will increase by 50% to 3 million (2). With no effective therapy for AMD (3), the related social and medical burden will continue to increase. Prevention remains the best approach for addressing this public health issue, and dietary modifications may provide one of the most cost-effective strategies. Several dietary factors have been linked to AMD (4–7).

However, to our knowledge, the association between AMD and dietary carbohydrate has not been evaluated. This association is particularly interesting because the retina has among the highest supplies of blood and nutrients, including glucose, and the retina is dependent on adequate glucose delivery from the systemic circulation to maintain its physiologic function (8). Because glucose stores in the retina are negligible, it appears that glucose metabolism is efficient in the retina. Appropriately, the role of glucose in age-related diseases, including AMD (9, 10), is now receiving considerable attention because of the potentially adverse effects of sustained high concentrations of glucose or glucose spike and age-related inefficiencies or improper metabolism, including the formation of advanced glycation end products and their sequelae. Thus, studies have shown that advanced

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glycation end products accumulate in drusen with age and occur at higher concentrations in patients with AMD (11, 12).

To better understand whether the amount or the quality of dietary carbohydrate may influence the risk of early AMD, referred to as age-related maculopathy (ARM), we examined associations between long-term carbohydrate intake and dietary glycemic index (GI), respectively, and the risk of ARM in a substudy of the Nurses’ Health Study (NHS) called the Nutrition and Vision Project (NVP).

SUBJECTS AND METHODS

Subjects

The NVP, a substudy of the NHS in participants residing in the Boston area, is a collaborative project between Tufts and Harvard Universities (13, 14). In 1993, a total of 1707 women aged 53–73 y, with both lenses intact, with no diagnosis of cancer other than nonmelanoma skin cancer, and with complete dietary data were identified from the NHS cohort with the aim of enrolling 600 women into the NVP. The 1707 candidates were initially contacted by letter to obtain their consent to participate in the NVP. We received positive responses from 730 women (43%), and 603 (83%) of these volunteers were scheduled between April 1993 and August 1995 to undergo baseline data collection, including retina evaluation. The most common reasons for failure to examine nurses who expressed interest in participating (n = 127) were scheduling conflicts due to work and travel. There were few notable differences between participants (n = 603) and nonparticipants (n = 1104) (15). All procedures were approved by the Tufts—New England Medical Center Institutional Review Board and the Brigham and Women’s Hospital Human Research Committee.

We excluded those with missing retinal data in both eyes (n = 5), invalid calorie intakes (daily energy intakes outside the range 800–3500 kcal; n = 11), missing covariates (n = 36), and confirmed diagnoses of diabetes in 1990 or earlier (n = 25). Diabetic women were excluded to avoid the potential confounding and modification effects on the association of interest. This left 526 women in the present study. None of the participants had been diagnosed with ARM at baseline.

Assessment of ARM

A standardized ophthalmic examination, including ocular and medical history, Bailey Lovie test of visual acuity and manifest refraction, external ocular examination, applanation tonometry, contrast sensitivity function and glare testing, and a slit-lamp examination of the anterior segment with an assessment of risk for angle closure glaucoma was administered to every NVP participant. Pupils were dilated to a minimum of 6 mm. Stereoscopic color fundus photographs of the macula were taken with a Topcon TRC 50X fundus camera (35-degree setting). At the Fundus Photograph Reading Center (University of Wisconsin, Madison, WI) the images were evaluated for the presence and severity of ARM on the basis of the Age-Related Eye Diseases Study (AREDS) classification (16).

Drusen were assessed with respect to size of individual drusen, cumulative area, and appearance (hard or soft), as described previously in AREDS (16). In brief, the largest drusen diameter and total drusen area were considered as defining the size and extent of drusen, respectively. Drusen size was classified into 3 drusen diameter categories relative to the size of the standardized optic disc (17). The disc diameter (DD), is set at 1500 μm by historical convention. This is equivalent to an area of 1.77 × 10⁶ μm². Thus, small, intermediate, and large drusen have diameters of <63 μm (1/24 DD), ≥63 μm to <125 μm, and ≥125 μm (1/12 DD), respectively. Under the AREDS scheme, small drusen were considered to be “extensive” when their cumulative area (total drusen area within 2 DD of the center of the macula) was at least that of AREDS standard circle C-1 (with a diameter of 1/12 DD). This corresponds to ≈15 small drusen as observed in stereo photographs and ≈5–10 small drusen observed by ophthalmoscopic examination. Intermediate drusen were considered to be “extensive” if any soft indistinct drusen were present and when the total area occupied by them was equivalent to the area that would be occupied by 20 drusen, each with a diameter of 100 μm. This would be equivalent to 1.57 × 10⁶ μm². If no soft indistinct drusen were present, intermediate drusen were considered to be “extensive” when they occupied area equivalent to ≥1/5 disc area (≈65 100-μm diameter drusen or equivalent to 5.11 × 10³ μm²). Other features of ARM are specified in detail in the AREDS grading protocol (16).

Eyes were divided into 3 groups according to the size and extent of drusen and presence of ARM. In the “Unaffected group” are eyes with no drusen or only nonextensive small drusen. To qualify for the “Drusen group,” the eye had to have one or more Intermediate drusen (including nonextensive intermediate drusen or extensive small drusen) or Large drusen (including large drusen or extensive intermediate drusen) and no pigmentary abnormalities characteristic of ARM. To qualify for the “ARM group,” the eye had to have pigmentary abnormalities, with or without drusen. Eyes presenting with both drusen and ARM were classified into the ARM group. Only 7 eyes had lesions other than drusen and pigmentary abnormalities. Of these, 3 had retinal detachments, 2 had geographic atrophy (GA), 1 had subretinal fibrosis, and 1 had retinal detachment, hard exudates, and subretinal fibrosis. To preserve the homogeneity of the outcome, these eyes were excluded from analysis. Of the 7 eliminated eyes, 3 were graded as advanced (1 of the 2 with GA, the 1 with subretinal fibrosis, and the 1 with retinal detachment, hard exudates, and subretinal fibrosis). The remaining 1036 eyes were from 526 women. Sixteen women contributed only one eye.

To describe the characteristics of these women, each woman was classified into one group based on the grading of both of her eyes. We included in the Unaffected group women with both eyes free of drusen and ARM or women with only nonextensive small drusen in one eye or both eyes. We included in the Drusen group, women without ARM but with one or more of the following: 1) nonextensive intermediate or extensive small drusen (collectively called Intermediate drusen) or 2) large drusen or extensive intermediate drusen (collectively called Large drusen). Women with ARM, or drusen and ARM, in at least one eye were classified into ARM group.

Assessment of nutrition intake

In 1980, a 61-item semiquantitative food-frequency questionnaire (FFQ) was incorporated into the NHS biennial questionnaires (14). The FFQ collected information 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.” Additionally, the 1980
questionnaire collected information on vitamin supplement use and the duration of vitamin supplement use before 1980. The FFQ was revised and expanded in 1984, 1986, and 1990. The present version of the FFQ includes 126 food items and details of vitamin and mineral supplement use that collectively account for >90% of the intake of the 70 nutrients measured by the questionnaire. The FFQ has been comprehensively validated in relation to long-term diet records (18, 19), biochemical markers of nutrient status (20, 21), and individual carbohydrate foods (22). In addition to the FFQs routinely collected as part of the NHS, an additional FFQ was administered as part of the NVP at baseline recruitment (1993–1995). The 4 FFQs, including the 1984, 1986, and 1990 FFQs from the NHS and the NVP baseline FFQ, were used to assess the dietary information. Participants were assigned the mean values for dietary variables, which were determined by averaging values from the 4 FFQs. We did not use the 1980 FFQ, because a more detailed assessment of carbohydrate intake was first undertaken in 1984.

We assessed carbohydrate quality using the GI. Jenkins et al (23) introduced the concept of GI to facilitate the identification of foods that result in relatively low glycemic responses. The GI for a food is defined as the glycemic response (ie, the incremental 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 with the use of white bread as the reference food or imputed from GI values of comparable foods (24). 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 as the weight. The dietary GI values determined for this subcohort of the NHS are comparable with the dietary GI values for the whole NHS (25) and with dietary GI values for other cohorts (26). All dietary variables were energy-adjusted by using the residuals method (27).

Defining nonnutritional variables

Information on known or suspected nonnutritional risk factors for AMD was collected from the biennial NHS questionnaires. For our analyses, age, history of hypertension (yes or no), pack-years of cigarettes smoked (ie, the number of packs of cigarettes smoked per day × the numbers of years of smoking), average alcohol intake, reported summertime sunlight exposure (≥8 h/wk) as reported on the 1980 questionnaire, and body mass index (BMI; calculated in kg/m² from height and weight as reported on the 1984 questionnaire) were considered as covariates.

Statistical methods

Of 526 women available for the present study, we identified 252 women affected with drusen or ARM in at least one eye. As previously described (see Assessment of ARM), we divided the women into 3 groups: Unaffected group (n = 274), Drusen group (n = 189), and ARM group (n = 63). We first compared the means ± SEs, medians, or proportions of covariates between the unaffected group (n = 274) and the drusen group (n = 189) or ARM group (n = 63). Wilcoxon’s two-sample test was used in place of the two-sample t test when the normality assumption was questionable. P values were adjusted by Bonferroni correction.

To evaluate the association between dietary carbohydrate and ARM, we used 1036 available eyes to model the odds of the ARM-related lesions by logistic regression with the SAS GENMOD procedure (28). The generalized estimating equation approach was used to estimate the regression coefficients (29). This procedure adjusts the SEs of regression coefficient estimates for correlated data derived from the use of both eyes of the same individual. Women were divided into 3 categories according to the tertiles of their dietary GI or total carbohydrate intake. Women in the second and third tertile categories were compared with women in the first tertile category. We used 3 models to evaluate the association between dietary GI and total carbohydrate intake and the odds of drusen and ARM. Model 1 included the energy-adjusted carbohydrate variables, either dietary GI or total carbohydrate intake, and age. Model 2 further adjusted for potential confounders, including BMI, alcohol intake, pack-years of cigarettes smoked, hypertension, outdoor sunlight exposure in the summer, and total fat, vitamin C, vitamin E, β-carotene, zinc, and calorie intakes. These covariates had been related to risk for ARM in prior studies (5–7, 30, 31). Model 3 was created to evaluate the independent effect of quantity and quality of dietary carbohydrate. In this model, total carbohydrate intake and dietary GI were simultaneously included along with the other covariates from model 2.

To test for trends across nutrient tertile categories, we assigned the median value in each category to everyone within the category and then included this median variable as a continuous factor in the logistic regression models. We used a P value < 0.05 for significance in the present analyses, and all tests were two-sided. All analyses were performed in SAS (version 8.02; SAS Institute Inc, Cary, NC).

RESULTS

Of the 526 women available for analysis, 274, 189, and 63 women qualified for the Unaffected, Drusen, and ARM groups, respectively (Table 1). Women in the Drusen group did not differ significantly from women in the Unaffected group with respect to age, BMI, summer sunlight exposure, alcohol drinking, pack-years of cigarettes smoked, hypertension, dietary GI, total carbohydrate intake, and calorie intake. In comparison, women in the ARM group were significantly older (P = 0.04) and had a marginally higher dietary GI (P = 0.08), but they did not differ from women in the Unaffected group with respect to the other variables noted above.

One thousand and thirty-six eyes, including 273 eyes with drusen, 71 eyes with pigmented abnormalities characteristic of ARM, and 692 eyes without lesions were available (Table 2). Neither dietary GI nor total carbohydrate intake was associated with drusen. There was also no association between dietary carbohydrate variables and either extensive intermediate or large drusen (Large drusen; n = 60) or small extensive or nonextensive intermediate drusen (Intermediate drusen; n = 213) (data not shown). In contrast, dietary GI was significantly and positively associated with ARM. The age-adjusted (model 1) and multivariate-adjusted (model 2) ORs for the third tertile category of dietary GI were >2-fold higher. The mutual adjustment of total carbohydrate intake and dietary GI in the model (model 3) did not substantially affect the ORs for either association with ARM. The OR for the third tertile category of dietary GI was 2.71.
TABLE 1
Characteristics of women by the absence or presence of drusen or age-related maculopathy (ARM) in the 3 subject groups

<table>
<thead>
<tr>
<th>Variables</th>
<th>Unaffected group (n = 274)</th>
<th>Drusen group (n = 189)</th>
<th><strong>p</strong></th>
<th>ARM group (n = 63)</th>
<th><strong>p</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (y)</td>
<td>61.3 ± 0.32</td>
<td>61.7 ± 0.44</td>
<td>0.98</td>
<td>63.0 ± 0.66</td>
<td>0.04</td>
</tr>
<tr>
<td>BMI in 1984 (kg/m²)</td>
<td>25.1 ± 0.27</td>
<td>24.8 ± 0.32</td>
<td>0.92</td>
<td>24.9 ± 0.60</td>
<td>NS</td>
</tr>
<tr>
<td>Alcohol intake (g)</td>
<td>3.6</td>
<td>3.1</td>
<td>NS</td>
<td>4.9</td>
<td>NS</td>
</tr>
<tr>
<td>Pack-years of cigarettes smoked (y)</td>
<td>5.6</td>
<td>2.8</td>
<td>NS</td>
<td>7.0</td>
<td>0.74</td>
</tr>
<tr>
<td>Outdoors in the summer</td>
<td>88.7</td>
<td>90.0</td>
<td>NS</td>
<td>84.1</td>
<td>0.64</td>
</tr>
<tr>
<td>Hypertension (%)</td>
<td>27.4</td>
<td>29.6</td>
<td>NS</td>
<td>38.1</td>
<td>0.18</td>
</tr>
<tr>
<td>Energy-adjusted dietary intake</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total carbohydrate (g)</td>
<td>198.5 ± 1.30</td>
<td>202.1 ± 1.34</td>
<td>0.10</td>
<td>202.6 ± 2.28</td>
<td>0.34</td>
</tr>
<tr>
<td>Glycemic index</td>
<td>75.4 ± 0.19</td>
<td>75.8 ± 0.23</td>
<td>0.32</td>
<td>76.3 ± 0.39</td>
<td>0.08</td>
</tr>
<tr>
<td>Total energy intake (kcal)</td>
<td>1794.0 ± 24.86</td>
<td>1794.4 ± 29.56</td>
<td>NS</td>
<td>1698.0 ± 43.87</td>
<td>0.18</td>
</tr>
</tbody>
</table>

1 Unaffected group: both eyes free of drusen and ARM or only nonextensive small drusen in one or both eyes; Drusen group: women without ARM who had one or more of the following: 1) nonextensive intermediate or extensive small drusen (Intermediate drusen) or 2) large drusen or extensive intermediate drusen (Large drusen). ARM group, women with ARM, or drusen and ARM, in at least one eye.

2 Derived from the t test or Wilcoxon’s test for the difference between women with and those without drusen or ARM. All P values were adjusted by Bonferroni correction.

3 All values are x ± SE.

4 All values are medians.

5 The 1984, 1986, 1990, and Nutrition and Vision Project baseline food-frequency questionnaires were used to calculate the energy-adjusted dietary averages.

6 Derived with the use of white bread as the reference.

(95% CI: 1.24, 5.93; P for trend = 0.01). Total carbohydrate intake was not associated with the risk of ARM.

Of the 7 eliminated eyes with ARM, other than pigmented abnormalities, 4 were graded as early (see Assessment of ARM). We also separately examined the results for all early ARM ( Intermediate drusen, respectively, and carbohydrate variables to reflect intake earlier in life than is represented by the average from the 4 FFQs, but the findings did not change. We also analyzed the data using extensive intermediate or large drusen (Large drusen) along with pigmented abnormalities as early ARM cases, because some studies include both categories as cases of early ARM (32, 33). Similar, but attenuated, findings were seen and this association was primarily due to the positive association between pigmented abnormalities and dietary GI, because we did not find any associations between extensive intermediate or large drusen (Large drusen) and carbohydrate variables (data not shown).

DISCUSSION

Our results showed that retinal pigment abnormalities characteristic of ARM are positively associated with long-term dietary GI in the NVP cohort, and this association is independent of total carbohydrate intake and currently known or suspected risk factors. According to our data, when total carbohydrate intake was held constant, there was a more than 2-fold higher odds for ARM in participants with dietary GI in the highest versus lowest third of the study sample.

In the present study, no association was found between drusen and the dietary carbohydrate variables considered here. This may appear surprising because ARM is often accompanied by drusen at diagnosis, and all forms of drusen examined appear to have similar carbohydrate components (34, 35). In addition, several studies reported that advanced glycation end products accumulate in drusen with age and occur at a higher concentration in patients with AMD (11, 12). We also analyzed the data by assigning small nonextensive drusen to the Drusen group rather than to the Unaffected group and by using 1984 carbohydrate variables to reflect intake earlier in life than is represented by the average from the 4 FFQs, but the findings did not change (data not shown). There was no association between Large drusen and Intermediate drusen, respectively, and carbohydrate variables (data not shown). Our failure to find an association, if it does exist, may imply that carbohydrate exposure before the time in life when the dietary data were collected could have been responsible for drusen formation. This is suggested in reports that drusen occur as early as age 50 y (30). In addition, we classified drusen by human grading of color fundus photographs (16). This scheme was developed to provide clinical reliability (36), but it may be insensitive to detecting the very earliest stages of drusen (37). Thus, the “unaffected” eyes may contain early stage drusen, which results in diminished power to detect the association. In our previous study, derived from the same cohort (38), long-term carbohydrate intake was associated with the odds of cortical lens opacities. Moreover, cataracts have been identified as a potential risk factor for ARM in some studies (31, 39). In the present analyses, we also examined the results with further adjustment for the presence of lens opacity in the multivariate analyses (data not shown). The status of lens opacity did not substantially change or confound our findings.

Although the detailed mechanism that explains the association between dietary GI and ARM remains to be elucidated, prior studies indicate that several hyperglycemia-mediated pathways could at least partially explain this pathologic process (8). These pathways include glycation and glycoxidation (or oxidation of glycated moieties), oxidative stress, activation of protein kinase C, direct toxic effects of glucose on the retinal pigment epithelium and capillary endothelium of blood retinal barrier,
and associated inflammatory and angiogenic responses (11, 40–44). Notably, a high-GI diet has been proposed to play a role in exacerbating the proinflammatory process (45), and it is plausible that hyperglycemia-mediated damage occurs below the diabetic threshold (46).

To anticipate limitations of this study, we considered several sources of bias that could account for the observed association between dietary GI and ARM. Several aspects of this study argue against such bias. First, it is unlikely that women with high-GI diets are more likely to be identified as having ARM because our retinal classifications were performed in an independent center by graders to whom our nutrition data were masked. In addition, at study onset, none of the participants had been diagnosed with ARM. Second, although the onset of visual symptoms resulting from ARM might affect dietary reporting, visual acuity was similar in the Unaffected, Drusen, and ARM groups (data not shown) because of the early nature of these lesions. Third, at the time of this study, there were no prior studies that related dietary carbohydrate to ARM. Thus, it is unlikely that the participants would have modified their diets based on such relations. For these reasons, family history of ARM is unlikely to have confounded our results. Fourth, dietary data were collected over a period of 10 years, a period of time that may have predated the macular lesions. Fifth, because the dietary data were collected well in advance of eye examinations, it is unlikely that there could have been any change in dietary behavior elicited by recruitment into this study. Nevertheless, although we adjusted for known and suspected risk factors in our analyses, confounding by unknown risk factors remains a possibility and it is possible that inadequate control of confounders may account for the observed association. It is useful to note that the definition of dietary GI is based on an arithmetic sum of GIs of individual foods. It does not account for the possible effects of other nutrients on the digestion, absorption, and metabolism of carbohydrate. Thus, it may be an imperfect index for the glycemic effect of a mixed meal. Finally, chance may have accounted for some type I errors, particularly given that we evaluated several nutrients in our analyses. Further studies are needed to confirm the observed association.

**TABLE 2**

<table>
<thead>
<tr>
<th>Energy-adjusted variable</th>
<th>Tertiles for GI²,³</th>
<th>P for trend</th>
<th>Tertiles for total carbohydrate intake (g)⁴</th>
<th>P for trend</th>
</tr>
</thead>
<tbody>
<tr>
<td>Drusen group</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cases: unaffected</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>OR</td>
<td>1.00</td>
<td>0.92</td>
<td>1.15</td>
<td>0.52</td>
</tr>
<tr>
<td>95% CI</td>
<td>(0.61, 1.39)</td>
<td>(0.77, 1.72)</td>
<td>(0.63, 1.40)</td>
<td>(0.90, 1.99)</td>
</tr>
<tr>
<td>Model 2⁶</td>
<td>1.00</td>
<td>0.94</td>
<td>1.19</td>
<td>0.45</td>
</tr>
<tr>
<td>95% CI</td>
<td>(0.62, 1.43)</td>
<td>(0.78, 1.81)</td>
<td>(0.54, 1.45)</td>
<td>(0.61, 2.16)</td>
</tr>
<tr>
<td>Model 3⁷</td>
<td>1.00</td>
<td>0.87</td>
<td>1.06</td>
<td>0.83</td>
</tr>
<tr>
<td>95% CI</td>
<td>(0.57, 1.33)</td>
<td>(0.68, 1.63)</td>
<td>(0.53, 1.43)</td>
<td>(0.57, 2.06)</td>
</tr>
<tr>
<td>ARM group</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cases: unaffected</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>OR</td>
<td>1.00</td>
<td>1.25</td>
<td>2.14</td>
<td>0.03</td>
</tr>
<tr>
<td>95% CI</td>
<td>(0.59, 2.61)</td>
<td>(1.10, 4.15)</td>
<td>(0.82, 3.26)</td>
<td>(0.88, 3.56)</td>
</tr>
<tr>
<td>Model 2⁶</td>
<td>1.00</td>
<td>1.64</td>
<td>2.56</td>
<td>0.007</td>
</tr>
<tr>
<td>95% CI</td>
<td>(0.75, 3.58)</td>
<td>(1.28, 5.12)</td>
<td>(0.71, 3.97)</td>
<td>(0.60, 6.31)</td>
</tr>
<tr>
<td>Model 3⁷</td>
<td>1.00</td>
<td>1.70</td>
<td>2.71</td>
<td>0.01</td>
</tr>
<tr>
<td>95% CI</td>
<td>(0.76, 3.80)</td>
<td>(1.24, 5.93)</td>
<td>(0.66, 3.74)</td>
<td>(0.47, 5.29)</td>
</tr>
</tbody>
</table>

**¹** Unaffected group: eye has no drusen or only nonextensive small drusen. Drusen group: eye has one or more Intermediate drusen (including nonextensive intermediate drusen or extensive small drusen) or Large drusen (including large drusen or extensive intermediate drusen). ARM group: eye has pigmentary abnormalities associated with ARM. A total of 1036 eyes from 526 women were used because 16 women contributed only one eye.

**²** Derived with the use of white bread as the reference.

**³** The tertiles for dietary GI were 74.6 and 77.0 and the category medians were 72.8, 75.9, and 78.4.

**⁴** The tertiles for total carbohydrate intake were 193.8 and 208.1 g/d and the category medians were 183.4, 201.2, and 216.4 g/d.

**⁵** Age-adjusted logistic analyses.

**⁶** Multivariate-adjusted logistic analyses including age, BMI (in kg/m²) in 1984, alcohol intake, pack-years of cigarettes smoked, hypertension, and outdoor in the summer ≥ 8 h/wk in 1980, and total fat, calorie, vitamin C, vitamin E, β-carotene, and zinc intakes.

**⁷** Multivariate-adjusted logistic analyses (model 2 plus dietary GI or total carbohydrate intake).
In conclusion, our results suggest a new ARM risk factor: dietary GI. Although our data cannot establish that the observed association is causal, they indicate a new direction for further studies. The results of such studies may ultimately prove helpful in preventing or delaying the onset of ARM and its related disability and costs.

All coauthors contributed substantially to this manuscript. C-JC, LDH, PFJ, LTC, WCW, SEH, and AT were responsible for the design and concept of the project. C-JC, GR, PFJ, and AT participated in the data analysis and writing of the manuscript. AT conceived of the project, arranged for the various institutes to collaborate, and obtained funding. WCW, SEH, and LTC helped prepare the manuscript and arranged for the funding. LDH and JA directed the collection of the ophthalmologic data. WCW and SEH arranged for the collection of the nutritional and personal health data. None of the authors had a conflict of interest.

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