Dietary glycemic index and the risk of age-related macular degeneration

Shweta Kaushik, Jie Jin Wang, Victoria Flood, Jennifer Sue Ling Tan, Alan W Barclay, Tien Y Wong, Jennie Brand-Miller, and Paul Mitchell

ABSTRACT

Background: Dietary factors are known risk factors for age-related macular degeneration (AMD)—the leading cause of visual loss among persons aged ≥65 y. High-glycemic-index diets have been hypothesized as a risk factor for AMD, but prospective data are unavailable.

Objective: The objective was to examine the association between dietary glycemic index and the 10-y incidence of AMD in the Blue Mountain Eye Study population.

Design: This was a population-based cohort study with 3654 participants (≥49 y) examined at baseline (1992–1994); 2335 patients were reexamined after 5 y and 1952 after 10 y. The Wisconsin System was used to grade 10-y incident early and late AMD from retinal photographs. A food-frequency questionnaire was used to collect dietary information at baseline, and an Australian database was used to calculate the mean glycemic index.

Results: Over 10 y, 208 of 1810 persons (cumulative incidence: 11.1%) developed early AMD. After age, smoking, other risk factors, and dietary constituents were adjusted for, a higher mean dietary glycemic index was associated with an increased 10-y risk of early AMD in a comparison of quartiles 1 and 4 (relative risk (RR): 1.77; 95% CI: 1.13, 2.78; P for trend = 0.03). Conversely, a greater consumption of cereal fiber (RR: 0.68; 95% CI: 0.44, 1.04; P for trend = 0.05) and breads and cereals (predominantly lower glycemic index foods such as oatmeal) (RR: 0.67; 95% CI: 0.44, 1.02; P for trend = 0.03) was associated with a reduced risk of incident early AMD. No relation was observed with late AMD.

Conclusions: A high-glycemic-index diet is a risk factor for early AMD—the recognized precursor of sight-threatening late AMD. Low-glycemic-index foods such as oatmeal may protect against early AMD.

INTRODUCTION

Age-related macular degeneration (AMD) affects >10% of persons aged ≥50 y and is the most frequent cause of incurable blindness in the United States and elsewhere (1–3). AMD has early and late forms; early AMD is the precursor for sight-threatening late AMD. Dietary factors have long been implicated as possible risk factors for AMD. The Age-Related Eye Disease Study (AREDS) has shown that high-dose zinc and antioxidant supplementation have reduced the progression from early to late AMD (4, 5). However, few clinical trials have investigated the primary prevention of early AMD, and their findings have been equivocal (6, 7).

Dietary glycemic index (GI) is commonly used to characterize the postprandial blood glucose response to the consumption of carbohydrates, which is now recognized as an important factor for cardiovascular disease (8, 9). The GI ranks carbohydrate quality from 0 (low glycemic response) to 100 (high glycemic response) on the basis of the blood glucose response 2 h after the consumption of 50 g of a carbohydrate food relative to the response after the consumption of 50 g of glucose (10). The index therefore provides a global summary measure of the rate of digestion and absorption of that carbohydrate food. Diets with a high GI are associated with an increased risk of coronary heart disease, stroke, and type 2 diabetes (11–14).

It is unknown whether high-GI diets are associated with risk of AMD. Two cross-sectional studies reported an association between dietary consumption of carbohydrates with higher GIs and AMD (15, 16), but prospective studies are lacking. In this population-based prospective cohort study, we examined the associations of dietary GI and long-term risk of AMD. We specifically investigated the independent effect of dietary fiber intake, given known interrelations between GI and fiber, (17) and also investigated food groups that could underlie potential associations.

SUBJECTS AND METHODS

Study population

We conducted a population-based cohort study of vision, common eye diseases, and other health outcomes in an urban, predominantly white population aged ≥49 y in the Blue Mountains, Australia. The Blue Mountains Eye Study population has been described previously (18). The study was approved by the University of Sydney Human Research Ethics Committee.

Participants

Two cross-sectional studies reported an association between dietary consumption of carbohydrates with higher GIs and AMD (15, 16), but prospective studies are lacking. In this population-based prospective cohort study, we examined the associations of dietary GI and long-term risk of AMD. We specifically investigated the independent effect of dietary fiber intake, given known interrelations between GI and fiber, (17) and also investigated food groups that could underlie potential associations.
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Assessment of confounders

The interview included questions about past medical history, including physician-diagnosed history of stroke or myocardial infarction, and lifestyle factors such as smoking. Higher educational achievement was defined as attainment of qualifications (certificate, diploma, or degree) after leaving school. A single measure of systolic and diastolic blood pressure was recorded with the use of a mercury sphygmomanometer from the first and fifth Korotkoff sounds. Mean arterial blood pressure was defined as \( 0.33 \times \text{systolic blood pressure} + 0.67 \times \text{diastolic blood pressure} \). Body mass index (BMI) was calculated as weight (kg)/height squared (m). Diabetes was defined on the basis of either past history of diabetes and current diabetes treatment or a fasting plasma glucose concentration \( \geq 7.0 \text{ mmol/L} \) at examination according to the World Health Organization diabetes classification (26). Fasting blood samples were processed on the same day for white cell count, total cholesterol, and HDL cholesterol by the Institute of Clinical Pathology and Medical Research, Westmead Hospital.

Statistical methods

Statistical analyses were performed by using SAS (version 9: SAS Institute, Cary, NC). We examined the association between baseline mean dietary GI, consumption of carbohydrates and fiber, and specific foods and the 10-y incidence of both early and late AMD. GI, carbohydrate, and fiber variables were adjusted for total energy intake by using the Willett residual method (28). Subject intakes were divided into quartiles for GI, macronutrients, and food groups.
Person-specific incidence rates were calculated by using Kaplan-Meier product-limit survival estimates to incorporate information from the 5- and 10-y examinations. Cumulative incidence was estimated by subtracting the Kaplan-Meier estimate from one and expressed as a percentage. Discrete linear logistic models were used to assess relations between dietary variables and incident early or late AMD at either of the 2 follow-up time points. The following potential confounders were considered: age, sex, mean arterial blood pressure, BMI, smoking, HDL cholesterol, post–secondary school qualifications, past history of coronary heart disease or stroke, and consumption of fish, total vegetables, fruit, and total fat. Micronutrient variables, vitamins C and E, β-carotene, zinc, lutein, zeaxanthin, and folate replaced total vegetables, fruit, and total fat in alternative models. Relative risks (RRs) and 95% CIs are presented.

RESULTS

Over the 10-y period, incident early AMD developed in 208 of 1810 persons at risk (cumulative incidence: 11.1%) and late AMD developed in 54 of 1913 persons at risk (cumulative incidence: 2.8%). The mean (± SD) energy-adjusted GI of foods consumed in this population was 56.6 ± 4.5 in persons without diabetes. Participants with incident (early and late) AMD were older and more likely to be male at baseline than were those without AMD (Table 1).

The characteristics of the population are shown by GI quartiles in Table 2. Male sex, qualification level, smoking status, HDL cholesterol concentration, white blood cell count, and consumption of vegetables, fish, macronutrients, and micronutrients differed across these quartiles. Correlations between dietary variables were moderate to low (−0.2 to 0.4).

The associations between mean dietary GI, cereal fiber, consumption of breads and cereals, and the 10-y incidence of indistinct soft drusen and pigmentary abnormalities—the 2 cardinal signs of early AMD—are shown in Table 4. The highest compared with the lowest quartile of mean dietary GI at the baseline examination predicted a 68% higher 10-y risk of indistinct soft drusen (P for trend = 0.04). The highest compared with the lowest quartile of cereal fiber (P for trend = 0.01) and breads and cereal consumption (P for trend = 0.04) predicted a 39% and 47% reduction, respectively, in the 10-y risk of indistinct soft drusen. A relatively similar reduction (by 39% or 31%) in the 10-y risk of retinal pigmentary abnormalities was predicted by the highest quartile of cereal fiber (P for trend = 0.04) and breads and cereal consumption (P for trend = 0.04).

We further examined dietary composition in the breads and cereals group. The highest mean intakes within this group were mostly of relatively low-GI foods such as oatmeal and wholemeal/mixed-grain bread. For example, the daily mean consumption of oatmeal (x: 60.3 g/d) was substantially greater than the

### Table 1

Baseline characteristics of the study sample (n = 2641)†

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Incident age-related macular degeneration (n = 262)</th>
<th>No incident age-related macular degeneration (n = 2379)</th>
<th>P value‡</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (y)</td>
<td>66.7 ± 7.7</td>
<td>63.1 ± 8.2</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Male sex (%)</td>
<td>44.3</td>
<td>37.0</td>
<td>0.04</td>
</tr>
<tr>
<td>Mean arterial blood pressure (mm Hg)</td>
<td>104.8 ± 11.9</td>
<td>103.6 ± 11.9</td>
<td>0.13</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>26.0 ± 4.1</td>
<td>26.4 ± 4.5</td>
<td>0.22</td>
</tr>
<tr>
<td>Current smoker (%)</td>
<td>12.7</td>
<td>10.5</td>
<td>0.36</td>
</tr>
<tr>
<td>History of coronary heart disease (%)</td>
<td>13.2</td>
<td>17.4</td>
<td>0.09</td>
</tr>
<tr>
<td>History of stroke (%)</td>
<td>2.5</td>
<td>5.0</td>
<td>0.03</td>
</tr>
<tr>
<td>Fasting serum cholesterol (mmol/L)</td>
<td>6.1 ± 1.0</td>
<td>6.0 ± 1.1</td>
<td>0.72</td>
</tr>
<tr>
<td>Consumption of fish (g/d)</td>
<td>25.3 ± 24.5</td>
<td>27.7 ± 27.4</td>
<td>0.23</td>
</tr>
<tr>
<td>Zinc (mg/d)</td>
<td>12.0 ± 0.2</td>
<td>11.8 ± 0.1</td>
<td>0.24</td>
</tr>
<tr>
<td>Vitamin C (mg/d)</td>
<td>337.1 ± 25.9</td>
<td>346.1 ± 9.3</td>
<td>0.74</td>
</tr>
<tr>
<td>Vitamin E (mg/d)</td>
<td>50.2 ± 7.5</td>
<td>38.4 ± 2.7</td>
<td>0.14</td>
</tr>
<tr>
<td>β-Carotene (µg/d)</td>
<td>7641.5 ± 303.9</td>
<td>7409.5 ± 109.2</td>
<td>0.47</td>
</tr>
<tr>
<td>Lutein and zeaxanthin (µg/d)</td>
<td>827.7 ± 11.5</td>
<td>833.8 ± 32.1</td>
<td>0.86</td>
</tr>
</tbody>
</table>

† Data are expressed as means ± SD unless otherwise indicated.
‡ Incident age-related macular degeneration includes both early and late forms.
§ Chi-square and t tests were used to assess differences between persons with and without incident age-related macular degeneration.
mean consumption of other breakfast cereals (x̄: 32.9 g/d). Similarly, the mean consumption of whole-meal/mixed-grain bread (x̄: 48.0 g/d) was greater than for white bread—a relatively high-GI food (x̄: 23.1 g/d).

Overall carbohydrate consumption was not associated with the incidence of early AMD or its component lesions. No significant relations were found between total carbohydrate intake and the incidence of early AMD or its components. No significant associations were found between the mean dietary GI of foods consumed, cereal fiber, carbohydrates, and the 10-y incidence of late AMD (data not shown).

**DISCUSSION**

Diet is one of few modifiable risk factors for AMD, the major cause of blindness among elderly persons in the United States. In this prospective population-based study, we showed that diets with a higher GI were associated with an increased 10-y risk of early AMD and its key component lesion, indistinct soft drusen. Conversely, greater consumption of cereal fiber was associated with a reduced risk of early AMD and its components. We identified specific food groups that might underlie these relations, i.e., breads and cereals. These associations were independent of smoking and traditional AMD risk factors.

The calculated GI of carbohydrates is commonly used to determine its “dietary value,” because carbohydrates are critical macronutrients that influence insulin secretion and postprandial glycemia, now known to be important factors in the pathogenesis of diabetes and cardiovascular disease. Consistent with this hypothesis, we found no association between total consumption of carbohydrates and risk of early AMD, which suggested that it is not the quantity of carbohydrates per se but possibly their postprandial effects that are important.

Our results are based on the exclusion of persons with diabetes. Analysis of the entire cohort attenuated the significance level of findings. It is likely that the inclusion of persons with diabetes led to some misclassification in GI, which tended to bias our results toward the null. Persons with diabetes are likely to have unpredictable glycemic responses, which makes it difficult to classify these subjects on the basis of glycemic values extrapolated from persons without diabetes.

To the best of our knowledge, only 2 studies, both of which were cross-sectional, have examined this relation. The Nurses’ Health Study found that the mean dietary GI was related to pigmentary abnormalities but not to drusen (15). However, we found no significant prospective association between GI and long-term risk of pigmentary abnormalities. The reasons for the difference in findings with our study are unclear, although one reason may have been the different study methods, particularly different AMD definitions, used. Analysis of AREDS data showed a relation between large drusen and the highest quintile of GI as well as a positive relation between mean GI and an increasing severity of disease (16).
Our findings have a sound biological basis. Early signs of AMD, such as soft drusen, may result from oxidative damage in the light- and oxygen-rich milieu of the retina (29) or from inflammation and activation of the complement cascade (30, 31). It is possible that either or both of these 2 pathogenic mechanisms may be activated by higher-GI diets. Normal levels of glycemia tend to depress plasma antioxidant capacity (32) and hyperglycemia has been shown to generate oxidative stress (33–36). In diabetes, the oxidative stress generated by hyperglycemia has been shown to activate all pathways leading to diabetes complications, including the polyclonal and hexosamine pathways, the formation of advanced glycation end products, and the activation of protein kinase C (33). For AMD, it seems likely that oxidative stress results in protein modifications that contribute to the development of drusen (37, 38). In relation to inflammation, a recent study showed that a high-glycemic-load diet predicted higher concentrations of C-reactive protein—an inflammatory mediator also found in drusen (30, 39).

Evidence of a role for advanced glycosylation end products (AGEs) in AMD pathobiology is also accumulating. AGEs are important pathological byproducts of hyperglycemia and have been found to accumulate in the outer retina with increasing age (40). Higher AGE concentrations are found in persons with AMD and are also a component of drusen (40). It is thought that the vascular endothelium is exquisitely sensitive to hyperglycemia because of its inability to control glucose transport across the membrane (33). AGEs accumulate in the endothelium and contribute to both endothelial dysfunction and permeability, a mechanism proposed for the increased risk of stroke in persons consuming high-GI diets (41). Recent studies have shown links between stroke, cardiovascular disease, and AMD; one of the possible mechanisms may be hyperglycemia-induced damage to the vascular endothelium (42, 43).

We showed that cereal fiber consumption reduced the long-term risk of early AMD. To our knowledge, this association has not been investigated previously. Cereal fiber can also reduce the glycemic response to subsequent meals by a second-meal effect (44). Lower levels of postprandial glycemia may thus represent a common mechanism for the beneficial effects observed from both GI and cereal fiber.

The strengths of our study include its prospective nature, long-term follow-up of a stable population-based sample, reasonable follow-up time, use of high-quality stereoscopic retinal photography with validated grading to assess macular conditions (including side-by-side comparisons of the baseline and follow-up examination photographs), and reliable categorization of the GI of a wide range of Australian foods, which contrasts with other studies in which this index was largely extrapolated (25).

Our study had several limitations. We had insufficient power to show relations between mean GI and the incidence of late AMD. A relatively high proportion of participants with missing FFQ data were likely to be older and current smokers. This may explain the lack of baseline differences between participants with and without incident AMD, because the missing data might have diluted the associations observed since smokers and older persons were more likely to have AMD.

Because healthy behaviors, such as not smoking and greater fruit and vegetable consumption, were associated with diets with a lower mean GI in our study (Table 1), the overall GI of foods...
TABLE 4
Multivariate-adjusted associations between mean dietary glycemic index, cereal fiber, and breads and cereals and the 10-y incidence of the 2 hallmark lesions of early age-related macular degeneration (n = 2641)

<table>
<thead>
<tr>
<th>Variable (median)</th>
<th>No. at risk</th>
<th>Cases</th>
<th>Cumulative incidence</th>
<th>Relative risk (95% CI)</th>
<th>Relative risk (95% CI)</th>
<th>No. at risk</th>
<th>Cases</th>
<th>Cumulative incidence</th>
<th>Relative risk (95% CI)</th>
<th>Relative risk (95% CI)</th>
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<tbody>
<tr>
<td>Mean dietary glycemic index</td>
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<tr>
<td>Q1 (51.9)</td>
<td>477</td>
<td>37</td>
<td>9.0</td>
<td>1</td>
<td>1</td>
<td>447</td>
<td>84</td>
<td>22.2</td>
<td>0.99 (0.72, 1.35)</td>
<td>1.01 (0.72, 1.41)</td>
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<tr>
<td>Q2 (55.2)</td>
<td>462</td>
<td>45</td>
<td>11.3</td>
<td>1.38 (0.89, 2.13)</td>
<td>1.33 (0.83, 2.12)</td>
<td>431</td>
<td>83</td>
<td>22.8</td>
<td>0.95 (0.68, 1.31)</td>
<td>0.98 (0.69, 1.38)</td>
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<tr>
<td>Q3 (57.7)</td>
<td>459</td>
<td>44</td>
<td>10.9</td>
<td>1.31 (0.83, 2.08)</td>
<td>1.41 (0.87, 2.27)</td>
<td>435</td>
<td>80</td>
<td>22.6</td>
<td>0.95 (0.68, 1.31)</td>
<td>0.98 (0.69, 1.38)</td>
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<tr>
<td>Q4 (61.3)</td>
<td>423</td>
<td>47</td>
<td>14.1</td>
<td>1.67 (1.07, 2.63)</td>
<td>1.68 (1.03, 2.74)</td>
<td>393</td>
<td>77</td>
<td>23.7</td>
<td>1.05 (0.75, 1.46)</td>
<td>1.08 (0.75, 1.55)</td>
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<td>P for trend</td>
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<td>Q1 (2.8 g)</td>
<td>415</td>
<td>48</td>
<td>14.4</td>
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<td>1</td>
<td>388</td>
<td>92</td>
<td>29.3</td>
<td>1</td>
<td>1</td>
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<td>Q2 (5.3 g)</td>
<td>452</td>
<td>46</td>
<td>12.3</td>
<td>0.72 (0.47, 1.10)</td>
<td>0.75 (0.48, 1.16)</td>
<td>420</td>
<td>60</td>
<td>17.1</td>
<td>0.51 (0.36, 0.72)</td>
<td>0.49 (0.34, 0.70)</td>
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<td>Q3 (7.8 g)</td>
<td>472</td>
<td>36</td>
<td>8.8</td>
<td>0.51 (0.32, 0.79)</td>
<td>0.51 (0.32, 0.82)</td>
<td>452</td>
<td>82</td>
<td>22.7</td>
<td>0.66 (0.48, 0.90)</td>
<td>0.69 (0.50, 0.96)</td>
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<tr>
<td>Q4 (12.3 g)</td>
<td>482</td>
<td>43</td>
<td>10.1</td>
<td>0.64 (0.42, 0.97)</td>
<td>0.61 (0.39, 0.96)</td>
<td>446</td>
<td>84</td>
<td>22.8</td>
<td>0.62 (0.45, 0.85)</td>
<td>0.61 (0.43, 0.85)</td>
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<tr>
<td>Mean breads and cereals</td>
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<tr>
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<td>14.9</td>
<td>1</td>
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<td>47</td>
<td>12.1</td>
<td>0.81 (0.54, 1.23)</td>
<td>0.81 (0.53, 1.24)</td>
<td>422</td>
<td>80</td>
<td>22.7</td>
<td>0.74 (0.54, 1.03)</td>
<td>0.75 (0.53, 1.05)</td>
</tr>
<tr>
<td>Q3 (231.8 g)</td>
<td>492</td>
<td>35</td>
<td>8.4</td>
<td>0.58 (0.37, 0.88)</td>
<td>0.60 (0.38, 0.95)</td>
<td>465</td>
<td>78</td>
<td>20.5</td>
<td>0.72 (0.52, 0.99)</td>
<td>0.71 (0.50, 0.99)</td>
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<tr>
<td>Q4 (376.0 g)</td>
<td>462</td>
<td>39</td>
<td>10.5</td>
<td>0.57 (0.37, 0.88)</td>
<td>0.53 (0.33, 0.83)</td>
<td>432</td>
<td>80</td>
<td>21.5</td>
<td>0.69 (0.50, 0.95)</td>
<td>0.69 (0.49, 0.97)</td>
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<tr>
<td>P for trend</td>
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<td>0.04</td>
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<thead>
<tr>
<th>Variable (median)</th>
<th>No. at risk</th>
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1 The glycemic index and cereal fiber were energy-adjusted. The data exclude persons with diabetes. Discrete linear logistic regression used to assess the relative risk of the 10-y incidence of the component lesions of early AMD.

2 Also includes the relatively fewer cases of reticular drusen.

3 Adjusted for age and sex.

4 Additional adjustment for mean arterial blood pressure, BMI, smoking, HDL cholesterol, qualification level, history of myocardial infarction or stroke, fish consumption, and total vegetable, fruit, and total fat (energy-adjusted) intakes. Micronutrient variables, vitamins C and E, β-carotene, zinc, lutein, zeaxanthin, and folate replaced total vegetables and total fat in alternative models, but the results were similar.

5 Highest mean intakes within the breads and cereals group were mostly from foods with a relatively low glycemic index, such as oatmeal.

consumed by individuals may be a marker for healthy dietary and lifestyle patterns rather than be representative of a causal pathway. Persons consume a combination of various foods simultaneously, but not in isolation. However our analyses address the associations of AMD with food components in relative isolation, with adjustment for energy and only a limited number of other food elements and lifestyle factors. Additionally, people potentially change their diets over time, and our dietary data, collected at one point in time, likely suffer from a range of measurement errors. It remains a challenge to nutritional epidemiologists to summarize and group patterns of dietary intake and also cover all aspects of diet. Currently, there are no widely accepted approaches in this regard. We attempted to address some of these issues by controlling for many dietary and lifestyle factors in the analysis. We also excluded persons who were likely to have modified their diets, such as persons with diabetes, who may also have unpredictable glycemic responses to similar foods compared with the general population. We believe that our study findings need to be validated by future studies using better approaches to eliminate potential residual confounding effects. Support for our study findings at this stage, however, arises from the consistency of the findings across the 3 studies that include both cross-sectional and longitudinal observations—the present study and 2 others (15, 16).

Finally, in our population, a higher GI was associated with an increase in stroke-related mortality (although not all-cause or coronary heart disease mortality). Although survival bias could have diluted our results, this effect is likely to be relatively modest because the number of stroke deaths was small (n = 95). Early AMD is the major predictor of progression to late AMD, and few effective preventive or therapeutic strategies that target these early signs are available (29, 45, 46). Primary prevention of early AMD lesions will substantially reduce the number of persons who develop sight-threatening late AMD. Whereas antioxidant supplements may delay progression from early to late AMD (5), the findings of other randomized controlled trials on the primary prevention of early AMD have been equivocal (6, 7). Our study, therefore, has potential implications for the prevention of early AMD in the population.

In summary, we showed that a diet with a high mean GI is a risk factor for early AMD. Conversely, specific foods, such as cereal fiber, may reduce the risk of early AMD. Our findings require replication in prospective studies in other populations. AMD is currently responsible for ~14 million cases of blindness or severe visual impairment worldwide (47). Given its significant public health impact, recommendations to consume lower-GI diets may help prevent AMD on a population-wide basis.

The authors’ responsibilities were as follows—PM, JJW, and SK: study concept and design; PM, JJW, VF, and AWB: data acquisition; SK: data analysis and draft of manuscript; SK, PM, and JJW: data interpretation; PM, JJW, VF, JB-M, TYW, JSLT, and AWB: critical revision of the manuscript for important intellectual content; PM, JJW, and VF: statistical expertise; and PM and JJW: funding.
REFERENCES


