

Dietary glycemic index and the risk of age-related macular degeneration¹⁻³

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: 14.1%) 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. *Am J Clin Nutr* 2008;88:1104–10.

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,

¹ From the Centre for Vision Research, Department of Ophthalmology and Westmead Millennium Institute, University of Sydney, Sydney, Australia (SK, JJW, VF, JSLT, and PM); the Centre for Eye Research Australia, University of Melbourne, Australia (JJW and TYW); the Human Nutrition Unit, Department of Molecular and Microbial Biosciences, University of Sydney, Sydney, Australia (VF, AWB, and JB-M); and the Department of Ophthalmology, National University of Singapore, Singapore, Republic of Singapore (TYW).

² Supported by the Australian National Health and Medical Research Council.

³ Reprints not available. Address correspondence to P Mitchell, Department of Ophthalmology, University of Sydney, Centre for Vision Research, Westmead Millennium Institute, Westmead Hospital, Hawkesbury Road, Westmead, NSW Australia, 2145. E-mail: paul_mitchell@wmi.usyd.edu.au.

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west of Sydney, Australia (Blue Mountain Eye Study). At baseline in 1992–1994, 3654 participants (82.4% response) were examined (18, 19). Participants were examined every 5 y; 2335 (75.1% of survivors) at the second examination in 1997–1999, and 1952 (76.5% of survivors) at the third in 2002–2004. The study complied with recommendations of the Helsinki Declaration and was approved by the Sydney West Area Health Service Human Research Ethics Committee. Written informed consent was obtained from all participants.

AMD definition

At each visit, 30° stereoscopic retinal photographs of the macula and other retinal fields of both eyes were taken, as described previously (18). Details of the photographic grading for AMD lesions were reported previously (18), which closely followed the Wisconsin Age-Related Maculopathy Grading System (20). All photographs taken at each examination had an initial masked grading. Assessments of inter- and intragrader reliability showed good agreement (18). Side-by-side grading of the baseline and 5-y photographs (21) and of the baseline and 10-y photographs was then performed for participants with any AMD lesions identified at either follow-up examination.

Early AMD was defined, in the absence of late AMD, as presence at the macula of either 1) large ($>125 \mu\text{m}$ diameter) indistinct soft (or reticular) drusen or 2) both large distinct soft drusen and retinal pigmentary abnormalities (hyperpigmentation or hypopigmentation) (18, 22). Late AMD was defined to include either neovascular AMD or geographic atrophy—the 2 late-stage lesions described in the International AMD classification (22). All late AMD cases detected from each examination were adjudicated and confirmed by a retinal specialist (PM).

Incident early AMD was defined by new appearance of early AMD lesions at follow-up examinations (1). Participants with either distinct soft drusen or retinal pigmentary abnormalities at the baseline examination, but not both, who went on to develop complementary lesions that together made up early AMD were included as incident early AMD cases (1). Incident indistinct soft drusen or incident retinal pigmentary abnormalities were defined similarly among persons without early or late AMD. Incident late AMD was defined by the new appearance at follow-up of neovascular AMD or geographic atrophy.

Dietary assessment

A standardized interview and examination were performed, and participants completed a detailed 145-item food-frequency questionnaire (FFQ) modified for the Australian diet and vernacular from a Willett questionnaire (23), which incorporated a 9-category frequency scale and standard portion size estimates. This FFQ had reasonable concurrent validity when validated against 4-d weighed food records collected on 3 occasions in 1 y ($n = 79$) (24).

GI data were obtained from the Sydney University Glycemic Index Research Service (SUGiRS) online database (www.glycemicindex.com) and published values (25). In total, 88.9% of GI values were obtained from published values, and 11.1% were interpolated from similar food items. An overall GI value for each participant's diet was calculated by summing the weighted GI of individual foods in the diet, with the weighting proportional to the contribution of individual foods to total carbohydrate intake. We also extracted data on the fiber contribution from both breads and cereals.

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 $\text{weight (kg)} / \text{height squared (m)}$. 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.

Study sample

The baseline cohort consisted of 3654 predominantly white participants who were aged ≥ 49 y, 43.3% of whom were men. At the 10-y follow-up examinations, there were 1952 participants: 1103 (30.2% of original cohort) of the participants had died, 375 (10.3%) had moved from the study area, and 224 (6.1%) refused to participate. Retinal photographs were obtained for both eyes in 98%, or for at least one eye in 99%, of the baseline and 5-y participants (21) and for both eyes in 85% (1649/1952), or for at least one eye in 87% (1689/1952), of the 10-y participants. Those lost to follow-up tended to be younger, to have a lower socioeconomic status, and to smoke, but were less likely to have coronary heart disease (21).

The FFQ was attempted and returned by 3267 baseline participants (89.4%); 2897 (79.3% of total participants) had sufficiently complete and plausible FFQ data for analysis. Subjects were excluded if >12 questions were missing, if an entire page remained blank, or if daily energy intakes were $<2500 \text{ kJ}$ or $>18\,000 \text{ kJ}$ (24, 27). Participants without usable FFQ data were more likely to be older (mean age: 69.3 y compared with 65.3 y) or current smokers (17.7% compared with 14.2%) than were those with usable FFQs.

We initially conducted the analyses in the whole cohort and then excluded persons with diabetes on the basis that the GI of persons with diabetes is likely to be misclassified because of their unpredictable glycemic responses. The baseline study sample thus consisted of 2641 participants (72.3%) who had reliable dietary assessment data, had gradable fundus photographs, had participated in at least one follow-up examination, and did not have diabetes.

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: 14.1%) and late AMD developed in 54 of 1913 persons at risk (cumulative incidence: 3.7%). The mean (\pm 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 early AMD in persons without diabetes are shown in Table 3. Subjects with the highest compared with the lowest quartile of mean dietary GI at baseline had a 77% higher 10-y risk of early AMD (P for trend = 0.02). This increased risk was unchanged by

including cereal fiber in the model. On the other hand, subjects consuming the highest compared with the lowest quartile of cereal fiber had a 68% reduction in their 10-y risk of early AMD (P for trend = 0.05). A similar reduction in risk of early AMD was evident for an increasing consumption of breads and cereals (P for trend = 0.03).

Analysis of the entire cohort (inclusion of persons with diabetes) produced similar but borderline significant findings. Furthermore, inclusion of the white blood cell count in the statistical models attenuated the observed effect sizes, likely because of the reduced number because $\approx 20\%$ of the participants did not have this blood test performed. Stratification by age showed that in persons younger than 70 y (at the baseline examination), the relation between early AMD and GI (quartile 4 versus quartile 1, 78% increased risk of early AMD) or cereal fiber (quartile 4 compared with quartile 1: 54% reduced risk of early AMD) was strengthened and remained significant. In persons aged >70 y, the results were markedly attenuated, with no trends demonstrated, and became nonsignificant.

Multivariate-adjusted 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 (\bar{x} : 60.3 g/d) was substantially greater than the

TABLE 1

Baseline characteristics of the study sample ($n = 2641$)¹

Characteristics	Incident age-related macular degeneration ² ($n = 262$)	No incident age-related macular degeneration ² ($n = 2379$)	P value ³
Age (y)	68.7 ± 7.7	63.1 ± 8.2	<0.0001
Male sex (%)	44.3	37.0	0.04
Mean arterial blood pressure (mm Hg)	104.8 ± 11.9	103.6 ± 11.9	0.13
BMI (kg/m ²)	26.0 ± 4.1	26.4 ± 4.5	0.22
Current smoker (%)	12.7	10.5	0.36
History of coronary heart disease (%)	13.2	17.4	0.09
History of stroke (%)	2.5	5.0	0.03
Fasting serum cholesterol (mmol/L)	6.1 ± 1.0	6.0 ± 1.1	0.72
Consumption of fish (g/d)	25.3 ± 24.5	27.7 ± 27.4	0.23
Zinc (mg/d)	12.0 ± 0.2	11.8 ± 0.1	0.24
Vitamin C (mg/d)	337.1 ± 25.9	346.1 ± 9.3	0.74
Vitamin E (mg/d)	50.2 ± 7.5	38.4 ± 2.7	0.14
β -Carotene (μ g/d)	7641.5 ± 303.9	7409.5 ± 109.2	0.47
Lutein and zeaxanthin (μ g/d)	827.7 ± 11.5	833.8 ± 32.1	0.86

¹ Data are expressed as means \pm SD unless otherwise indicated.

² Incident age-related macular degeneration includes both early and late forms.

³ Chi-square and t tests were used to assess differences between persons with and without incident age-related macular degeneration.

TABLE 2

Factors associated with age-related macular degeneration at the baseline Blue Mountains Eye Study examination by mean dietary glyceemic index quartiles ($n = 2641$)¹

Characteristics	Glyceemic index quartile				<i>P</i> value ²
	1 (51.8 ± 2.5)	2 (55.2 ± 0.8)	3 (57.7 ± 0.8)	4 (61.4 ± 2.8)	
No. of subjects	646	664	662	669	
Age (y)	64.0 ± 9.3	65.5 ± 9.2	65.0 ± 9.1	65.0 ± 9.6	0.11
Male sex (%)	29.8	39.4	47.1	59.4	<0.001
Post-secondary school qualifications (%) ³	55.9	52.9	47.6	43.2	<0.001
Mean arterial blood pressure (mm Hg)	102 ± 12.2	103 ± 12.3	104 ± 12.3	103 ± 12.1	0.12
BMI (kg/m ²)	25.7 ± 4.5	25.7 ± 4.3	25.7 ± 4.8	25.4 ± 4.6	0.57
Current smoker (%)	9.34	11.0	14.2	22.4	<0.001
History of coronary heart disease (%)	14.7	16.0	13.4	15.7	0.94
History of stroke (%)	3.56	4.80	5.49	4.12	0.50
Fasting serum cholesterol (mmol/L)	6.10 ± 1.1	6.00 ± 1.0	6.00 ± 1.0	5.90 ± 1.1	0.14
Fasting HDL cholesterol (mmol/L)	1.40 ± 0.4	1.40 ± 0.4	1.30 ± 0.4	1.30 ± 0.5	0.02
White blood cell count (×10 ⁹)	6.10 ± 1.7	6.25 ± 1.7	6.20 ± 1.7	6.40 ± 1.8	<0.001
Consumption of					
Vegetables (g/d)	434 ± 198	428 ± 191	410 ± 180	363 ± 214	0.03
Fish (g/d)	30.9 ± 30.2	30.7 ± 31.0	25.7 ± 26.2	22.4 ± 21.6	<0.001
Dietary intake of ⁴					
Total fat (g/d)	74.8 ± 15.1	77.6 ± 14.2	77.1 ± 13.5	75.9 ± 13.0	0.27
Total fiber (g/d)	31.7 ± 9.4	28.8 ± 8.2	25.9 ± 7.1	22.4 ± 6.8	<0.001
Vitamin E (mg/d)	9.60 ± 141	8.53 ± 122	7.69 ± 93	7.14 ± 88	<0.001
Vitamin C (mg/d)	256 ± 477	222 ± 355	191 ± 354	156 ± 296	<0.001
β-Carotene (μg/d)	7435 ± 4982	7161 ± 4282	6462 ± 4167	5799 ± 4340	<0.001
Zinc (mg/d)	12.3 ± 2.3	11.9 ± 2.1	11.4 ± 2.2	11.0 ± 2.3	<0.001
Lutein and zeaxanthin (μg/d)	883 ± 537	778 ± 471	713 ± 485	587 ± 414	<0.001
Folate (μg/d)	392 ± 315	357 ± 180	337 ± 366	317 ± 197	<0.001

¹ Data are expressed as means ± SD unless otherwise indicated. The glyceemic index was energy-adjusted.

² Chi-square test and ANCOVA were used to assess trends across quartiles. *P* for trend across categories <0.05.

³ Any postschool qualification (eg, trade certificate, diploma, and degree).

⁴ Antioxidant amounts include both diet (energy-adjusted) and supplements; total fat and fiber were energy-adjusted.

mean consumption of other breakfast cereals (\bar{x} : 32.9 g/d). Similarly, the mean consumption of whole-meal/mixed-grain bread (\bar{x} : 48.0 g/d) was greater than for white bread—a relatively high-GI food (\bar{x} : 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 dietary fiber and its separate vegetable fiber or fruit fiber components or between individual vegetable or fruit consumption and the incidence of early AMD or its component lesions. 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, ie, 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 glyceemic responses, which makes it difficult to classify these subjects on the basis of glyceemic 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).

TABLE 3

Multivariate-adjusted associations between mean dietary glycemic index, cereal fiber, and breads and cereals and the 10-y incidence of early age-related macular degeneration ($n = 2641$)¹

Variable (median)	Early age-related macular degeneration					
	No. at risk	Cases	Cumulative incidence	Relative risk (95% CI) ²	Relative risk (95% CI) ³	Relative risk (95% CI) ⁴
Mean dietary glycemic index						
Q1 (51.9)	473	43	10.3	1	1	1
Q2 (55.2)	459	55	13.9	1.30 (0.85, 1.97)	1.39 (0.91, 2.14)	1.40 (0.91, 2.14)
Q3 (57.7)	455	52	13.4	1.39 (0.93, 2.09)	1.43 (0.92, 2.22)	1.40 (0.90, 2.18)
Q4 (61.3)	423	58	17.4	1.70 (1.15, 2.64)	1.77 (1.13, 2.78)	1.67 (1.06, 2.64)
<i>P</i> for trend	—	—	—	0.02	0.02	0.04
Mean cereal fiber						
Q1 (2.8 g)	412	51	15.4	1	1	NA
Q2 (5.3 g)	448	55	15.0	0.87 (0.59, 1.30)	0.88 (0.59, 1.33)	—
Q3 (7.8 g)	472	53	13.0	0.73 (0.49, 1.10)	0.75 (0.49, 1.14)	—
Q4 (12.3 g)	478	49	11.6	0.71 (0.47, 1.06)	0.68 (0.44, 1.04)	—
<i>P</i> for trend	—	—	—	0.07	0.05	—
Mean breads and cereals ⁵						
Q1 (82.6 g)	413	55	16.1	1	1	NA
Q2 (150.5 g)	446	57	15.0	0.92 (0.62, 1.36)	0.94 (0.63, 1.41)	—
Q3 (231.8 g)	491	46	11.1	0.72 (0.48, 1.08)	0.75 (0.49, 1.14)	—
Q4 (376.0 g)	460	50	12.7	0.68 (0.46, 1.01)	0.67 (0.44, 1.02)	—
<i>P</i> for trend	—	—	—	0.03	0.03	—

¹ The glycemic index and cereal fiber were energy-adjusted. The data exclude persons with diabetes. Discrete linear logistic regression was used to assess the relative risk of 10-y incident early AMD. NA, not available; Q, quartile.

² Adjusted for age and sex.

³ 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.

⁴ Additional adjustment for cereal fiber.

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

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 polyol 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 ($n = 2641$)¹

Variable (median)	Indistinct soft drusen ²					Pigmentary abnormalities				
	No. at risk	Cases	Cumulative incidence	Relative risk (95% CI) ³	Relative risk (95% CI) ⁴	No. at risk	Cases	Cumulative incidence	Relative risk (95% CI) ³	Relative risk (95% CI) ⁴
Mean dietary glycemic index										
Q1 (51.9)	477	37	9.0	1	1	447	84	22.2	1	1
Q2 (55.2)	462	45	11.3	1.38 (0.89, 2.13)	1.33 (0.83, 2.12)	431	83	22.8	0.99 (0.72, 1.35)	1.01 (0.72, 1.41)
Q3 (57.7)	459	44	10.9	1.31 (0.83, 2.08)	1.41 (0.87, 2.27)	435	80	22.6	0.95 (0.68, 1.31)	0.98 (0.69, 1.38)
Q4 (61.3)	423	47	14.1	1.67 (1.07, 2.63)	1.68 (1.03, 2.74)	393	77	23.7	1.05 (0.75, 1.46)	1.08 (0.75, 1.55)
<i>P</i> for trend				0.04	0.04				0.89	0.75
Mean cereal fiber										
Q1 (2.8 g)	415	48	14.4	1	1	388	92	29.3	1	1
Q2 (5.3 g)	452	46	12.3	0.72 (0.47, 1.10)	0.75 (0.48, 1.16)	420	60	17.1	0.51 (0.36, 0.72)	0.49 (0.34, 0.70)
Q3 (7.8 g)	472	36	8.8	0.51 (0.32, 0.79)	0.51 (0.32, 0.82)	452	88	22.7	0.66 (0.48, 0.90)	0.69 (0.50, 0.96)
Q4 (12.3 g)	482	43	10.1	0.64 (0.42, 0.97)	0.61 (0.39, 0.96)	446	84	22.8	0.62 (0.45, 0.85)	0.61 (0.43, 0.85)
<i>P</i> for trend				0.02	0.01				0.02	0.04
Mean breads and cereals ⁵										
Q1 (82.6 g)	416	52	14.9	1	1	387	86	27.1	1	1
Q2 (150.5 g)	451	47	12.1	0.81 (0.54, 1.23)	0.81 (0.53, 1.24)	422	80	22.7	0.74 (0.54, 1.03)	0.75 (0.53, 1.05)
Q3 (231.8 g)	492	35	8.4	0.58 (0.37, 0.91)	0.60 (0.38, 0.95)	465	78	20.5	0.72 (0.52, 0.99)	0.71 (0.50, 0.99)
Q4 (376.0 g)	462	39	10	0.57 (0.37, 0.88)	0.53 (0.33, 0.83)	432	80	21.5	0.69 (0.50, 0.95)	0.69 (0.49, 0.97)
<i>P</i> for trend				0.08	0.04				0.04	0.04

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.



JBM is a coauthor of *The New Glucose Revolution* book series (Hodder and Stoughton, New York, NY), is the Director of a not-for-profit GI-based food endorsement program in Australia, and manages the University of Sydney GI testing service. AB is a coauthor of one of these books: *Diabetes & Pre-diabetes Handbook* and is a consultant to a not-for-profit GI-based food endorsement program in Australia. None of the other authors had a conflict of interest to declare. All authors declare their independence from the funding body (The Australian National Health and Medical Research Council), which had no role in the study design, the collection, analysis, the interpretation of the data, the writing of the report, or the decision to submit the paper for publication.

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