Glycemic Index, Retinal Vascular Caliber, and Stroke Mortality

Shweta Kaushik, BMed(Hons), MPH; Jie Jin Wang, MMed, PhD; Tien Y. Wong, MD, MPH, PhD; Victoria Flood, MPH, PhD; Alan Barclay, BSc, Grad Dip Dietetics; Jennie Brand-Miller, PhD, FAIFST; Paul Mitchell, MD, PhD

Background and Purpose—It is unclear whether diets with high glycemic index (GI) and low cereal fiber (CF) are associated with greater risk of stroke. We aimed to assess the relationship between dietary GI and CF content, retinal microvasculature changes, and stroke-related mortality.

Methods—The study consisted of a population-based cohort, 49+ years, examined at baseline (1992 to 1994). At baseline, participants completed validated food frequency questionnaires. Mean GI was calculated using an Australian database. Retinal arteriolar and venular diameters were measured from photographs. Mortality data were derived using the Australian National Death Index.

Results—Over 13 years, 95 of 2897 participants (3.5%) died from stroke. Increasing GI (hazard ratio, 1.91; 95% CI, 1.01 to 3.47, highest versus lowest tertile) and decreasing CF (hazard ratio, 2.13; 95% CI, 1.19 to 3.80, lowest versus highest tertile) predicted greater risk of stroke death adjusting for multiple stroke risk factors. Persons consuming food in the highest GI tertile and lowest CF tertile had a 5-fold increased risk of stroke death (hazard ratio, 5.06; 95% CI, 1.67 to 15.22). Increasing GI and decreasing CF were also associated with retinal venular caliber widening (P<0.01). Adjustment for retinal venular caliber attenuated stroke death risk associated with high GI by 50% but did not affect the risk associated with low CF consumption.

Conclusions—High-GI and low-CF diets predict greater stroke mortality and wider retinal venular caliber. The association between a high-GI diet and stroke death was partly explained by GI effects on retinal venular caliber, suggesting that a high-GI diet may produce deleterious anatomic changes in the microvasculature. (Stroke. 2009;40:206-212.)

Key Words: carbohydrate ■ diet ■ epidemiology ■ glycemic index ■ microcirculation ■ retinal vessels

There is increasing evidence that postprandial or postchallenge glycemia is an important, independent risk factor for stroke.1 Dietary glycemic index (GI) is a commonly used marker of the postprandial blood glucose response. This index ranks carbohydrates according to their effect on blood glucose.2 Only a few studies have examined the relationship of GI and risk of stroke,3–5 and pathophysiological mechanisms underlying this potential association are unclear. It has been postulated that high-GI diets might lead to small vessel dysfunction, an important precursor of stroke and other cardiovascular diseases.3,6–9 The formation of advanced glycation end products, glycemia-induced oxidative stress, or the effects of inflammatory intermediaries have all been proposed as possible factors mediating the effects of higher GI on small vessels.6,10–13

The retinal microvasculature shares similar anatomic, physiological, and embryological characteristics with the cerebral vasculature.14,15 Quantitative measurement of retinal microvascular changes is now possible using reproducible, computer-assisted methods to examine retinal photographs.16 Population-based studies further showed that subtle retinal vascular caliber changes (particularly narrower arterioles and wider venules) independently predicted stroke and stroke death.17–20 Thus, studying the association of GI and retinal microvascular changes may provide insights into potential effects of postprandial blood glucose response on the microvasculature.

We investigated the associations of GI with stroke-related mortality and retinal microvascular caliber in an older Australian cohort. We aimed to test the hypothesis that retinal microvascular changes may partly explain the reported association between high-GI foods and stroke mortality. We also examined associations with dietary cereal fiber (CF) given its strong interrelationship with GI.

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From the Centre for Vision Research, Department of Ophthalmology and Westmead Millennium Institute (S.K., J.J.W., V.F., P.M.), University of Sydney, Sydney, Australia; the Centre for Eye Research Australia (J.J.W., T.Y.W.), University of Melbourne, Melbourne, Australia; the Human Nutrition Unit, Department of Molecular and Microbial Biosciences (V.F., A.B., J.B.-M.), University of Sydney, Sydney, Australia; and the Department of Ophthalmology (T.Y.W.), National University of Singapore, Singapore.

Correspondence to Paul Mitchell, MD, PhD, Centre for Vision Research, Department of Ophthalmology, Westmead Millennium Institute, University of Sydney, Westmead Hospital, Hawkesbury Road, Westmead, NSW Australia, 2145. E-mail paul_mitchell@wmi.usyd.edu.au

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Methods

Study Population
The Blue Mountains Eye Study (BMES) is a population-based cohort study of vision, common eye diseases, and other health outcomes in an urban, predominantly white population aged 49 years or older. The 1992 to 1994 baseline study examined 3654 eligible residents of 2 postcodes of the Blue Mountains region west of Sydney, Australia (82.4% response). Subsequent 5- and 10-year examinations of this cohort were conducted.21,22 The study adhered to the Helsinki Declaration recommendations and was approved by the Sydney West Area Health Service Human Research Ethics Committee. Written, informed consent was obtained from all participants.

Retinal Photography
Detailed methods of grading the caliber of retinal arterioles and venules are described elsewhere.23 In brief, at the baseline examination, 30° photographs of the macular, optic disc, and other retinal fields of both eyes were taken, after pupil dilation, using a Zeiss FF3 fundus camera (Zeiss, Oberkochen, Germany). We used methods developed by the University of Wisconsin–Madison24 to measure the internal caliber of retinal arterioles and venules from digitized photographs. These were then summarized using established formulas25 that account for branching patterns and combine individual vessel calibers into summary indices, reflecting the mean arteriolar and venular calibers, respectively, of each eye.

Dietary Data
A standardized interview and examination was performed and participants completed a detailed food frequency questionnaire (FFQ). This had 145 items, modified for the Australian diet and vernacular, from a Willett questionnaire26 incorporating a 9-category frequency scale and standard portion size estimates. This FFQ had reasonable concurrent validity when validated against 4-day weighed food records collected on 3 occasions in 1 year.27 The validation yielded an energy-adjusted Spearman coefficient of 0.82 between self-reported and weighed food records and correctly classified 85% to within one quintile difference for dietary fiber. The corresponding coefficient for GI was 0.57 and correct classification of subjects to within one quintile difference for GI was 74%.28 Dietary intakes were estimated using Australian Tables of Food Composition (NUTTAB 90)29 and published GI values using the glucose/100 scale.29 Additional GI data were obtained from the Sydney University GI Research Service (SU/GIRS) online database (www.glycemindex.com). In total, 88.9% of GI values were obtained from published values and 11.1% were interpolated from similar food items. The consumption of breakfast cereals, collected in the FFQ, was used to enhance accuracy of the GI calculations.

An overall GI value for each participant’s diet was calculated by summing the weighted GI of individual foods in the diet. The weighting was proportional to the contribution of individual foods to total carbohydrate intake. We also extracted data on total fiber intake as well as the fiber contribution from cereals, vegetables, and fruits. The FFQ was attempted and returned by 3267 participants at baseline (89.4%) with 2897 (88.7% of those attempting the FFQ, 79.3% of total participants) having sufficiently complete and plausible FFQ data for analysis. Subjects were excluded when more than 12 FFQ questions were missing, if an entire page was blank, or if daily energy intakes were <2500 kJ or >18 000 kJ.27,30

Demographic, Lifestyle, and Dietary Variables
The interview included questions about medical history, including physician-diagnosed history of stroke and myocardial infarction, and lifestyle factors such as smoking. Higher educational achievement was defined as attainment of educational qualifications (certificate, diploma, or degree) after secondary schooling. A single measure of systolic blood pressure and diastolic blood pressure using a mercury sphygmomanometer was recorded from the first and fifth Korotkoff sounds. Body mass index was calculated as weight (kg)/height (m)2. Fasting blood samples were processed the same day for hemoglobin, white cell and platelet counts, glucose, total cholesterol, triglycerides, high-density lipoprotein-cholesterol, and fibrinogen levels by the Institute of Clinical Pathology, Westmead Hospital.

Stroke Mortality
Mortality data since baseline (13 years) were obtained by data linkage with the Australian National Death Index in December 2005. The sensitivity and specificity of Australian National Death Index data has been estimated to be 93.7% and 100% for all-cause deaths, respectively, and 92.5% and 89.6%, respectively, for cardiovascular deaths.31,32 Stroke deaths (thrombotic, hemorrhagic) included the following International Classification of Diseases, 9th Revision codes (430.0 to 438.9) and International Classification of Diseases, 10th Revision codes (I60.0 to I69.9) when listed as any cause of death. No validity data on stroke-related deaths were previously reported.

Statistical Methods
Statistical analyses were performed using SAS Version 9.1 (SAS Institute, Cary, NC). The associations between dietary variables and retinal vessel caliber data are cross-sectional, whereas the mortality associations are longitudinal.

Subject intakes were divided into tertiles by their mean dietary GI or fiber intake. Dietary GI and fiber variables were adjusted for total energy intake using the Willett residual method.33 This method was also used to assess the effect of nutritional variables on retinal arteriolar or venular caliber independent of fellow vessel influences; venule-adjusted arteriolar caliber was defined using linear regression with venular caliber as the independent variable and arteriolar caliber the dependent variable by calculating residuals and adding these to the expected mean arteriolar caliber. Arteriole-adjusted venular caliber was similarly defined. The resulting adjusted caliber variables represent the nonshared variance of each vessel measurement, respectively.34–36

Cox proportional hazards regression was used to assess hazard ratios (HRs) with 95% CIs for tertile of mean GI or CF consumption on 13-year stroke-related mortality after adjusting for age, gender, systolic blood pressure and diastolic blood pressure, body mass index, smoking status, educational qualifications, fair or poor self-rated health, history of myocardial infarction and stroke, and presence of diabetes. The proportional hazards assumption was tested for GI or CF variables with stroke mortality and no violations were detected. Participants lost to follow-up were treated as censored.

To determine the individual and joint effects of GI and CF on the risk of stroke, we stratified the population into 3 groups by unhealthy versus healthy dietary intakes of these 2 measures. First, persons in both the lowest tertile of GI and the highest tertile of CF were considered healthy by both measures (“both healthy”). Second, persons in either the lowest tertile of GI or the highest tertile of CF, but not both, were considered healthy in only one measure (“either healthy”). Third, persons positioned in both the highest tertile of GI and the lowest tertile of CF were considered to have “both unhealthy” categories. We assessed the HR of stroke for the “both unhealthy” and “either healthy” categories compared with the “both healthy” category. The remaining 3 groups of participants were excluded from this analysis: those in the middle tertiles of both, those in middle tertile of cereal fiber and highest tertile of glycemic index, and those in the middle tertile of glycemic index and lowest tertile of cereal fiber.

To investigate whether retinal venular caliber is an intermediate marker on the pathway among GI, CF, and stroke risk, we included retinal venular caliber in the Cox regression models to assess whether the effect size was attenuated. We also evaluated synergy using the Rothman synergy index (S)37 to determine if the joint effects from GI and CF on the risk of stroke death or wider retinal venular caliber exceeded the sum of effects from each factor alone.

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S_{ab} = \frac{(RR_{ab} - 1)}{(RR_a + RR_b - 2)}
\]
RR_4 is the relative risk of the joint exposure group; RR_3 and RR_1 are relative risks for exposure to GI or CF, respectively. The synergy index represents the ratio of increased risk due to joint exposure (with synergistic effect) to the sum of increased risks due to each exposure alone.

The mean venule-adjusted arteriolar caliber and arteriole-adjusted venular caliber for GI or CF tertile was assessed using analysis of covariance. The lowest tertile of GI and highest tertile of fiber consumption were the reference categories. Finally, we used logistic models to assess interactions between fiber consumption and GI in their effects on the retinal microvascularity using the widest venular quintile as the outcome variable.

Three analysis of covariance models were constructed: Model 1 adjusted for age, gender, systolic blood pressure and diastolic blood pressure, body mass index, smoking, educational qualifications, fair or poor self-rated health, diabetes mellitus, history of coronary heart disease, and total vegetable, saturated fat, and fish consumption. Model 2 was adjusted for variables in Model 1 plus the nutrient variables, vitamins C and E, β-carotene, zinc, and folate replacing the vegetable variable. Model 3 additionally adjusted for white cell count, hemoglobin, and fibrinogen when the dependent variable was mean venular caliber.38–41

**Results**

Of the 3654 baseline participants, 2897 participants with FFQs sufficiently complete and plausible were included for analysis. For the retinal vessel analysis, a further 185 participants were excluded due to missing retinal photographs or poor photographic images precluding vessel measurement or with retinal diseases confounding measurement of retinal vessel caliber. Participants without usable FFQ data were more likely to be older (mean age 69.3 years versus 65.3 years) or current smokers (17.7% versus 14.2%) than those with usable FFQs. Among those completing the FFQ, mean venule-adjusted arteriolar caliber was 187.3 μm and mean arteriole-adjusted venular caliber was 225.0 μm.

Over the 13 years, a total of 1297 participants had died (35.5% of the original cohort) by December 2005 with 139 of these recorded as stroke-related deaths (3.8%). After accounting for persons with available FFQ data, 95 stroke-related deaths (3.8%) are included in this report.

Table 1 demonstrates the baseline characteristics of the population by GI tertiles. Male gender, fair or poor self-rated health, educational qualifications, white cell count, current smoking, and the consumption of vegetables, fish, and several nutrients differed between GI strata.

Table 2 demonstrates that higher mean dietary GI and lower CF consumption at baseline was associated with greater 13-year stroke-related mortality. After adjusting for age, gender, systolic blood pressure and diastolic blood pressure, body mass index, smoking status, educational qualifications, fair or poor self-rated health, history of myocardial infarction and stroke, and presence of diabetes, the HR of stroke-related death for persons with diets in the highest tertile of GI was 1.91 (95% CI, 1.01 to 3.47) compared with those with diets in the 2 lower tertiles. The HR for the lowest tertile of CF consumption was 2.13 (95% CI, 1.19 to 3.80) compared with the 2 higher tertiles. We found no relationship between total, vegetable, or fruit fiber and risk of stroke-related death.

Joint effects of GI and CF on stroke-related death is shown in Table 2. The group with unhealthy diet in either category (either highest tertile of GI or lowest tertile of CF) had a near doubling of risk for stroke death compared with the group with healthy diet in both categories. The group with unhealthy diet in both categories had a 5-fold increased risk for stroke death (Table 2). The synergy index was 2, suggesting a substantial excess risk of stroke death attributable to joint exposure to both high-GI and low-CF diet.

We found no relationship among total carbohydrate consumption (excluding nondigestible fiber), glycemic load, and stroke mortality (data not shown). There was also no relationship demonstrated among GI (T3 versus remainder; HR, 0.91; 95% CI, 0.70 to 1.17), CF (T1 versus remainder; HR, 0.94; 95% CI, 0.73 to 1.22), and the 13-year incidence of coronary heart disease mortality, suggesting some specificity of the observed associations with stroke-related death (Table 2). However, we also found a higher risk of all-cause mortality in persons with both a high-GI and low-CF diet (HR, 1.48; 95% CI, 1.11 to 1.98).

Table 3 shows the mean arteriolar and venular caliber by mean dietary GI and CF consumption after adjusting for multiple potential confounding variables. Higher mean dietary GI was associated with narrower mean arteriolar caliber (P trend=0.22) but wider mean venular caliber (P for
Lower CF consumption was associated with significantly narrower arteriolar caliber ($P_{trend}=0.002$) and wider venular caliber ($P_{trend}=0.001$). These associations persisted after replacing vegetable consumption with micronutrients in Model 2 or after further control for hemoglobin and fibrinogen in Model 3. Stratifying by the presence of hypertension or diabetes did not alter these relationships.

We found a statistical interaction between the effects of mean dietary GI and CF on venular caliber ($P_{interaction}=0.002$; Table 4). Participants with both a high-GI and low-CF diet had 2-fold greater odds of being in the widest category of retinal venular caliber. A synergy index of 1.50 suggested a greater effect of these 2 factors on wider venular caliber when jointly present.
particularly susceptible to high levels of postprandial glycemia because endothelial cells are unable to regulate glucose transport across the cell membrane. Inflammation or reduced antioxidant capacity from hyperglycemia could also mediate endothelial dysfunction.

Recent studies found no relationship between high-GI diets and cardiovascular mortality similar to our findings. Levitan et al reported a relationship between hemorrhagic stroke and high GI. This could not be confirmed in our study because of the relatively small number of participants with hemorrhagic stroke on International Classification of Diseases classification (n=9).

We showed that diets low in CF were associated with adverse changes not only in retinal venular caliber, but also in retinal arteriolar caliber. Many studies have shown that consumption of wholegrain cereals (CF being an important constituent) is inversely associated with cardiovascular disease and results in modest blood pressure reductions. However, we did not observe any attenuation of the magnitude of stroke risk after accounting for retinal venular caliber in our statistical models suggesting that its associations with risk of stroke-related death and with microvascular changes are independent.

The different pattern of diet relationships between arteriolar and venular caliber (ie, healthy diets associated with narrower arterioles but wider venules) may represent different pathogenic processes affecting arterioles and venules. Wider venules, for example, have been observed in association with inflammatory factors and endothelial dysfunction in contrast to arteriolar caliber, which is principally affected by hypertension.

Strengths of this study include its well-defined urban population, use of a validated food questionnaire to collect dietary information, and detailed questionnaires that permitted careful assessment of potential confounding variables. The retinal vessel grading was masked with good intragrader reliability. Measurement error in the assessment of dietary factors was collected long before stroke death events occurred. Participants may have altered their fiber consumption after diagnosis with hypertension or cardiovascular disease, but they would have been less likely to have altered the GI of their diets, because there was little publicity about the potential benefits of lower GI diet during the period 1992 to 1994. An important limitation of our study is the cross-sectional nature of the associations of GI and vessel caliber.
Despite our best efforts to control for socioeconomic and lifestyle variables, incomplete control for confounding effect from unmeasured social factors may have occurred. Residual confounding, however, seems unlikely to have had a major influence on our findings given their internal consistency, i.e., different patterns of dietary associations were observed (e.g., CF, but not total or fruit fiber, was associated with stroke), that would be difficult to explain by confounding from unmeasured lifestyle factors. Finally, the relatively low sensitivity and specificity of death certificate data could have tended to misclassify some stroke deaths, but this would likely only result in an underestimation of the association.

It should be recognized that the retinal vessel caliber differences observed between the lowest and highest categories of dietary GI and CF were modest (the between-person variation was 16.8 μm in arteriolar caliber and 16.3 μm in venular caliber). It has been shown, however, that even such a small reduction in retinal arteriolar caliber can be associated with moderate changes in blood pressure; for example, each 10 mm Hg increase in systolic blood pressure was associated with a 1.1 μm reduction in arteriolar caliber. Confirmation of our results in similar population-based studies such as those in the United States and the Netherlands would strengthen these findings.

In conclusion, we showed that diets with high GI and low CF content predicted greater stroke mortality. These diets were also associated with wider retinal venular caliber, an intermediate microvascular marker of stroke. The increased risk of stroke mortality associated with high-GI diets was attenuated by 50% after accounting for variations in retinal venular caliber. Although microvascular changes are known to precede cardiovascular events, our findings indicate that the deleterious cerebrovascular effects from high-GI diets could operate partly by anatomic effects on the cerebral microvasculature.

Disclosures
J.B.-M. is a coauthor of The New Glucose Revolution book series, the director of a not-for-profit GI-based food endorsement program in Australia, and manages the University of Sydney GI testing service. A.B. 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.

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