Retinal Microvascular Signs And Cognitive Ability In Elderly People With Type 2 Diabetes

Retinal Microvascular Abnormalities and Cognitive Impairment in Middle-Aged Persons

The Atherosclerosis Risk in Communities Study

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Background and Purpose—Cerebral microvascular disease has been hypothesized to contribute to cognitive impairment, but few clinical data are available. Here, we examine the relation of retinal microvascular abnormalities with cognitive function in middle-aged persons free of stroke.

Methods—The Atherosclerosis Risk in Communities Study is a population-based study with examinations every 3 years from 1987 through 1998. At visit 3, when participants were 51 to 70 years of age, retinal photographs were obtained and evaluated for retinal microvascular abnormalities according to standardized protocols. Cognitive function was assessed with standardized tests (Delayed Word Recall Test, Digit Symbol Subtest, and Word Fluency Test) at visits 2 and 4 and averaged for analysis. Persons with stroke or taking central nervous system–relevant medications were excluded, leaving 8734 with data for this study.

Results—After education, diabetes mellitus, blood pressure, carotid intima-media thickness, and other risk factors were controlled for, retinopathy was associated with lower cognitive test scores. The adjusted odds ratios for persons with Delayed Word Recall scores 2 SD or lower than the mean were 2.60 [95% confidence interval (CI), 1.30 to 2.91] for any retinopathy, 3.00 (95% CI, 1.81 to 4.98) for microaneurysms, 3.39 (95% CI, 1.99 to 5.78) for retinal hemorrhage, and 3.07 (95% CI, 1.53 to 6.17) for soft exudates. Results were similar for the other 2 cognitive tests and in people with and without diabetes and hypertension.

Conclusions—Retinopathy is independently associated with poorer cognitive function in middle-aged persons without stroke, suggesting that cerebral microvascular disease may contribute to the development of cognitive impairment. **(*Stroke*. 2002;33:1487-1492.)**

Key Words: cognitive disorders ■ dementia, vascular ■ hypertension ■ retina ■ retinal diseases

Although cognitive impairment is an important cause of morbidity in elderly persons, its pathogenesis remains poorly understood.[1] Cerebral microvascular disease has been hypothesized to contribute to the development of vascular cognitive impairment[2,3] and to modify the risk and course of Alzheimer's disease.[4–7] In support of such a hypothesis, associations of cognitive impairment with a number of microvascular risk factors such as hypertension,[8–10] diabetes mellitus,[10,11] cigarette smoking,[12] and inflammation[13] have been described. Additionally, pathological studies have demonstrated cerebral microvascular alterations (eg, tortuosity and narrowing of arterioles) among the characteristic degenerative changes associated with dementia.[14–18]

Nevertheless, few clinical data are available to support an association between microvascular disease and cognitive impairment, particularly in the general population. In part, the reason is that the cerebral microcirculation is difficult to evaluate outside highly specialized settings.[19,20] The retinal arterioles provide a unique opportunity to study the consequences of cerebral microvascular disease because they can be viewed noninvasively and because their anatomy, physiology, and embryology are similar to those of cerebral arterioles.[21] Retinal microvascular abnormalities related to aging, hypertension, and other processes have therefore been suggested to reflect similar pathology in the cerebral microcirculation.[22]

Received December 12, 2001; final revision received February 4, 2002; accepted February 20, 2002.

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Stroke **is available at http://www.strokeaha.org** **DOI: 10.1161/01.STR.0000016789.56668.43**

In the Atherosclerosis Risk in Communities (ARIC) study, retinal photographs were obtained of participants at the third visit and graded for retinal microvascular characteristics according to standardized methods.[23] We have previously reported that retinal microvascular abnormalities were related to concurrently measured blood pressure and were independently related to past blood pressure[24] and various markers of inflammation and endothelial dysfunction.[25] We have also shown that retinal abnormalities predict stroke independently of traditional risk factors.[26]

The purpose of the present study is to examine the association between retinal microvascular abnormalities and cognitive impairment in middle-aged persons free of stroke in the ARIC study.

Methods

Study Population

The ARIC study included 15 792 women and men 45 to 64 years of age at recruitment in 1987 through 1989.[27] Population samples were selected from 4 US communities: Forsyth County, North Carolina; Jackson, Miss (blacks only); suburbs of Minneapolis, Minn; and Washington County, Maryland.[27] Of those examined at baseline (visit 1), 92.9% of survivors returned for the visit 2 examination 3 years later, 86.2% of survivors returned for the visit 3 examination 6 years from baseline, and 80.5% of survivors returned for the visit 4 examination 9 years from baseline.

Retinal photographs of each participant were taken at visit 3.[23] Of the 12 887 who returned for visit 3, we excluded 38 whose race was neither black nor white, 42 black residents in Minneapolis and Maryland, and 174 who did not participate at visit 2. We then excluded 2919 who were using central nervous system–relevant medications (ie, antipsychotics, antidepressants, anxiolytics, narcotic analgesics, anticonvulsants, and antineoplastic agents) and 265 with a history of stroke up to visit 4, leaving 9623 eligible for these analyses. Of these, 9 had missing blood pressure data, 162 had no retinal photographs, and 544 had ungradable photographs, leaving 8734 who provided data for this study. Characteristics of participants with and without gradable retinal photographs have been previously reported.[25] Persons with gradable photographs were younger and more likely to be white but did not differ by sex or smoking status.

Retinal Grading and Definitions

The retinal photography procedure has previously been described in detail.[23] Briefly, photographs of the retina were taken of 1 randomly selected eye after 5 minutes of dark adaptation. Trained and certified graders, masked to participant characteristics, evaluated the photographic slides for microvascular abnormalities using standardized protocols. Any retinopathy was defined as present if any of the following lesions were detected: microaneurysms, retinal hemorrhages (blot or flame shaped), soft exudates, hard exudates, macular edema, intraretinal microvascular abnormalities, venous beading, new vessels at the disc or elsewhere, vitreous hemorrhage, disc swelling, or laser photocoagulation scars.[23] Similarly, arteriovenous nicking and focal arteriolar narrowing were defined as present if graded definite or probable. Generalized arteriolar narrowing was quantified via a computer-assisted technique. The photographs were digitized by a high-resolution scanner, and the diameters of individual arterioles and venules coursing through a specified zone surrounding the optic disc were measured and summarized as the arteriole-to-venule ratio (AVR). A smaller AVR represents narrower arterioles (because venular diameters vary little),[23] and generalized arteriolar narrowing was defined as the lowest 20th percentile of the sample AVR distribution.[26] As previously reported, intragrader and intergrader κ statistics ranged from 0.61 to 1.00, respectively, for retinopathy, arteriovenous nicking, and focal arteriolar narrowing.[23] For AVR, intragrader and intergrader reliability coefficients were 0.84 and 0.79, respectively.

Cognitive Function Tests

Assessment of cognitive function in the ARIC study is described in detail elsewhere.[10,13] All participants at visits 2 and 4 had the following 3 neuropsychological tests: the Delayed Word Recall Test,[28] the Digit Symbol Subtest of the Wechsler Adult Intelligence Scale–Revised,[29] and the Word Fluency Test of the Multilingual Aphasia Examination.[30] Trained interviewers administered these tests in a standardized order during 1 session in a quiet room.

The Delayed Word Recall Test is an evaluation of verbal learning and recent memory that requires the person to recall 10 common nouns after a 5-minute interval during which another psychometric test is given.[28] Test scores ranged from 0 to 10 words recalled. Test-retest reliability coefficient over 6 months has been reported to be 0.75 in normal elderly individuals.[28]

The Digit Symbol Subtest is a paper-and-pencil task requiring timed translation of numbers[1–9] to symbols with a key. The test measures psychomotor performance and is relatively unaffected by intellectual ability, memory, or learning.[29] It appears to be a sensitive indicator of brain damage, but it is not useful in localizing a lesion.[31] The test is scored as the number of numbers translated to symbols correctly within 90 seconds, up to a possible maximum of 93. Test-retest reliability coefficient over 2 to 5 weeks has been reported to be 0.82 in middle-aged persons.[29]

The Word Fluency Test requires the participant to generate as many words as possible beginning with the letters F, A, and S in 60 seconds for each letter. The test is particularly sensitive to damage in the frontal lobes of the brain.[30] The score is the total number of words generated. Test-retest reliability coefficient based on an alternate test form has been reported to be 0.82.[30]

Definition of Other Variables

Participants underwent standardized cardiovascular assessment at each visit.[32] Blood pressure was taken with a random-zero sphygmomanometer, and the mean of the last 2 measurements was used. Mean arterial blood pressure was computed as two thirds of the diastolic value plus one third of the systolic value, and the average of this over the first 3 exams (ie, 6-year mean arterial blood pressure) was included as a covariate in the assessment of the independence of retinal abnormalities with cognitive impairment.[26] Education, occupation, diabetes and hypertension history, cigarette smoking, and alcohol consumption were ascertained from examiner-administered questionnaire. Diabetes mellitus was defined as fasting glucose $\geq$7.0 mmol/L, nonfasting glucose $\geq$11.1 mmol/L, or a self-reported history of physician-diagnosed diabetes or treatment for diabetes. Hypertension was defined as systolic blood pressure $\geq$140 mm Hg, diastolic blood pressure $\geq$90 mm Hg, or use of antihypertensive medication during the previous 2 weeks. Average internal carotid intima-media wall thickness (IMT) was obtained from standardized B-mode ultrasonograms.[32] Blood collection and processing for total plasma cholesterol, high-density lipoprotein (HDL) cholesterol, and triglycerides are described elsewhere.[32] All covariates were based on visit 3 data, except for education and occupation (visit 1), carotid artery IMT (visit 2), and mean arterial blood pressure (average of visits 1 through 3).

Statistical Analysis

Cognitive function scores in the ARIC population were distributed approximately normally and were treated as continuous variables in the analysis.[10,13] We evaluated associations of retinal lesions at visit 3 to cognitive test scores that were averaged over visits 2 and 4 among participants who attended all 3 examinations (n=7526). We additionally evaluated retinal associations to cognitive test scores of visits 2 (n=8694) and 4 (n=7552) separately (results were similar and not presented).

We used analysis of covariance to compare the mean cognitive test scores in persons with and without a specific retinal lesion, adjusting for age, sex, race, field center, education (attended grade school or less, attended but did not graduate from high school, graduated from high school, attended vocational school, attended college, attended graduate school), and occupation (professional or manager, other). In

TABLE 1. Baseline Characteristics of Study Population by Presence of Retinopathy

	Adjusted Means or %*		
	Retinopathy Absent (n=8143)	Retinopathy Present (n=590)	P†
Age, y	53.7	54.5	<0.001
Men, %	48.1	49.0	0.65
Black, %	27.3	29.9	<0.001
High school graduate, %	81.8	79.3	0.12
Professional/manager, %	26.2	21.3	0.008
Diabetes, %	7.0	34.0	<0.001
Fasting glucose, mmol/L	5.68	7.84	<0.001
Hypertension, %	29.0	39.7	<0.001
Mean arterial blood pressure, mm Hg	88.6	90.0	0.003
Total plasma cholesterol, mmol/L	5.55	5.51	0.45
HDL cholesterol, mmol/L	1.34	1.27	<0.001
Total triglycerides, mmol/L	1.42	1.63	<0.001
Cigarette smoking (current), %	21.7	23.0	0.46
Alcohol use (current), %	60.6	56.8	0.05
Alcohol use (past), %	15.9	17.8	0.23

*Means and proportions adjusted for age, sex, race, and field center (except for age, men, and black, which are unadjusted for age, sex and race, respectively).

†*P*-value represents difference in adjusted means or proportions between persons with and without any retinopathy.

multivariate models, we further adjusted for diabetes (yes/no), fasting glucose (mmol/L), hypertension (yes/no), 6-year mean arterial blood pressure (mm Hg), carotid artery IMT (mm), fasting total cholesterol, HDL cholesterol and triglycerides (mmol/L), cigarette smoking (ever/never), and alcohol consumption (ever/never).

To evaluate the retinal associations with extremes in cognitive scores,[33] we defined cognitive impairment as scores 2 SD or lower than the mean scores with the following cutoffs: Delayed Word Recall Test, ≤4; Digit Symbol Subtest, ≤20; and Word Fluency Test, ≤11. For each test, we used logistic regression models to determine the odds of cognitive impairment associated with specific retinal lesions, adjusting for potential confounders.

Results

A comparison of characteristics between persons with and without any retinopathy in the study population is shown in Table 1. Persons with any retinopathy were older, more likely to be black, and less likely to have a professional or managerial occupation. After adjustment for age, sex, race, and field center, persons with retinopathy were more likely to have diabetes and higher fasting glucose levels, hypertension and higher mean arterial blood pressure, and lower HDL cholesterol but higher triglyceride levels.

The means (SD) of the average cognitive scores of visits 2 and 4 were as follows: 6.48 (1.3) for Delayed Word Recall, 45.7 (12.8) for Digit Symbol Subtest, and 34.1 (11.6) for Word Fluency Test. After adjustment for age, sex, race, field center, education, and occupation, mean scores of all 3 tests were significantly lower in persons with any retinopathy, microaneurysm, retinal hemorrhage, and soft exudates compared with persons without these lesions (data not shown). Adjustment for diabetes, hypertension, carotid IMT, and other vascular risk factors did not substantially alter these relations (Table 2).

Results of logistic regression models for cognitive impairment are shown in Table 3. After adjustment, persons with any retinopathy, microaneurysms, retinal hemorrhage, and soft exudates were to 1.4 to 4.1 times more likely to have cognitive impairment than persons without these lesions.

We repeated analyses in persons with and without hypertension and diabetes separately because these conditions are

TABLE 2. Multivariable-Adjusted Mean Cognitive Function Tests Scores by Presence of Retinal Microvascular Abnormalities

			Delayed Word Recall			Digit Symbol Subtest			Word Fluency Test		
		n*	Mean†	SE	P‡	Mean†	SE	P‡	Mean†	SE	P‡
Any retinopathy	Present	429	6.49	0.06	0.001	44.8	0.44	0.02	33.1	0.49	0.02
	Absent	6798	6.70	0.01		45.8	0.11		34.2	0.12	
Microaneurysm	Present	219	6.34	0.09	<0.001	44.6	0.65	0.03	32.8	0.71	0.03
	Absent	6686	6.71	0.02		46.1	0.11		34.3	0.12	
Retinal hemorrhage	Present	190	6.36	0.09	<0.001	44.5	0.69	0.05	32.6	0.76	0.04
	Absent	7015	6.70	0.01		45.9	0.11		34.2	0.12	
Soft exudates	Present	90	6.28	0.13	0.002	42.5	1.01	0.001	31.4	1.10	0.01
	Absent	7249	6.69	0.01		45.9	0.11		34.2	0.12	
Arteriovenous nicking	Present	972	6.67	0.04	0.52	45.6	0.29	0.36	33.5	0.32	0.03
	Absent	6340	6.69	0.02		45.9	0.12		34.3	0.13	
Focal arteriolar narrowing	Present	1050	6.79	0.04	0.02	46.3	0.29	0.16	34.3	0.32	0.75
	Absent	6129	6.69	0.02		45.9	0.12		34.2	0.13	
Generalized arteriolar narrowing	Present	1300	6.68	0.03	0.40	46.1	0.25	0.49	34.3	0.29	0.82
	Absent	5433	6.71	0.02		46.3	0.12		34.4	0.14	

*Number of persons with and without a specific retinal lesion.

†Mean adjusted for age, sex, race, field center, education, occupation, diabetes, fasting glucose, hypertension, mean arterial blood pressure of visits 1 through 3, carotid IMT, cigarette smoking, alcohol consumption, fasting total and HDL cholesterol levels, and triglyceride levels.

‡*P* represents difference in means by presence of retinal lesion.

TABLE 3. Multivariable-Adjusted Odds Ratios for Cognitive Impairment* in Association With Retinal Microvascular Abnormalities

	Odds Ratio (95% Confidence Interval)†		
	Delayed Word Recall (n=299/7494‡)	Digit Symbol Subtest (n=260/7468‡)	Word Fluency Test (n=145/7479‡)
Any retinopathy	2.60 (1.70–3.99)	1.91 (1.04–3.49)	2.03 (1.07–3.86)
Microaneurysm	3.00 (1.81–4.98)	2.04 (1.00–4.15)	1.62 (0.74–3.54)
Retinal hemorrhage	3.39 (1.99–5.78)	1.99 (0.94–4.20)	4.10 (1.90–8.86)
Soft exudates	3.07 (1.53–6.17)	1.40 (0.54–3.66)	2.27 (0.85–6.06)
Arteriovenous nicking	1.15 (0.81–1.62)	1.14 (0.71–1.84)	1.32 (0.81–2.14)
Focal arteriolar narrowing	0.60 (0.40–0.91)	1.31 (0.80–2.15)	1.24 (0.76–2.03)
Generalized arteriolar narrowing	1.10 (0.80–1.49)	1.08 (0.69–1.69)	1.37 (0.88–2.12)

*Cognitive impairment defined as 2 SD or lower from the mean cognitive test scores with the following cutoffs: ≤4 for Delayed Word Recall, ≤20 for Digit Symbol Subtest, and ≤11 for Word Fluency Test.

†Odds ratio (95% confidence interval) for cognitive impairment in association with a specific retinal lesion adjusted for age, sex, race, field center, education, occupation, diabetes, fasting glucose, hypertension and mean arterial blood pressure averaged over visits 1 through 3, carotid IMT, cigarette smoking, alcohol consumption, fasting total and HDL cholesterol levels, and triglyceride levels.

‡Number of persons with cognitive impairment/number at risk.

known to influence retinopathy and cognitive function. The overall pattern of associations was similar (Results based on Delayed Word Recall scores are presented in Table 4). Formal tests of interaction for hypertension and diabetes status in the whole sample by inclusion of cross-product terms (eg, any retinopathy times hypertension) in the logistic regression models did not reveal significant interaction ($P>0.20$ for all terms).

Results were generally similar in analyses repeated separately for demographic subgroups stratified by age (51 to 60 years, 61 to 70 years), sex, and race (data not shown). Finally, we attempted to analyze the retinal associations with the 6-year change in cognitive tests scores from visits 2 to 4 (ie, difference in scores between visits 2 and 4). However, the change in scores was minimal in this middle-aged population (eg, change in score for the Delayed Word Recall was <10% of the SD of the mean score).

Discussion

In this population-based study of middle-aged people free of stroke, various manifestations of retinal microvascular disease, determined by standardized grading of retinal photographs, were related to cognitive impairment, determined by neuropsychological tests administered in a standardized setting. For all 3 cognitive tests, persons with any retinopathy, microaneurysms, retinal hemorrhage, and soft exudates had significantly lower mean cognitive test scores and were 1.4 to 4.1 times more likely to have the lower extremes in these scores (cognitive impairment) than persons without these lesions, independent of diabetes, blood pressure, carotid IMT, and other vascular risk factors. These associations were seen in persons with and without diabetes and hypertension.

Our study provides further insights into the pathogenesis of cognitive impairment. Although cerebral microvascular disease has been hypothesized to contribute to cognitive impair-

TABLE 4. Multivariable-Adjusted Odds Ratios for Cognitive Impairment* (Based on Delayed Word Recall Scores) in Association With Retinal Microvascular Abnormalities by Hypertension and Diabetes Status

	Odds Ratio (95% Confidence Interval)†			
	Hypertension (n=133/2737‡)	No Hypertension (n=166/4757‡)	Diabetes (n=59/950‡)	No Diabetes (n=240/6541‡)
Any retinopathy	2.65 (1.52, 4.60)	2.59 (1.29, 5.19)	2.20 (1.09, 4.41)	2.58 (1.48, 4.49)
Microaneurysm	2.53 (1.30, 4.91)	3.00 (1.81, 4.98)	2.75 (1.32, 5.72)	2.60 (1.24, 5.48)
Retinal hemorrhage	4.69 (2.49, 8.81)	3.39 (1.99, 5.78)	3.59 (1.70, 7.59)	2.70 (1.16, 6.27)
Soft exudates	3.63 (1.59, 8.30)	3.07 (1.53, 6.17)	1.92 (0.74, 5.04)	5.07 (1.87, 13.77)
Arteriovenous nicking	1.17 (0.73, 1.88)	1.15 (0.81, 1.62)	1.63 (0.75, 3.51)	1.05 (0.71, 1.56)
Focal arteriolar narrowing	0.73 (0.44, 1.22)	0.60 (0.40, 0.91)	0.98 (0.44, 2.19)	0.52 (0.32, 0.84)
Generalized arteriolar narrowing	1.45 (0.95, 2.23)	0.80 (0.50, 1.31)	0.61 (0.27, 1.37)	1.26 (0.89, 1.77)

*Cognitive impairment defined as 2 SD or lower from the mean Delayed Word Recall scores (score of ≤4).

†Odds ratio (95% confidence interval) for cognitive impairment in association with a specific retinal lesion adjusted for age, sex, race, field center, education, occupation, diabetes, fasting glucose, hypertension, mean arterial blood pressure averaged over visits 1 through 3, carotid IMT, cigarette smoking, alcohol consumption, fasting total and HDL cholesterol levels, and triglyceride levels.

‡Number of persons with cognitive impairment/number at risk.

ment,[4–6] data to support such a hypothesis are sparse. Some histopathological studies show Alzheimer's disease to be associated with numerous structural and physiological alterations of the cerebral microvasculature, including cerebral arteriolar narrowing,[14] arteriolar tortuosity,[15] capillary microaneurysms,[17] endothelial cell dysfunction,[14] and breakdown of the blood-brain barrier.[16] One theory is that these anatomic alterations lead to abnormal microvascular flow patterns, impairment in the delivery of nutrients to susceptible neurons, reactive astrocytosis, and finally formation of plaques and neurofibrillary tangles characteristic of severe dementia.[6] However, because diseases of the cerebral microcirculation are difficult to assess in vivo, the retinal microvasculature provides a useful noninvasive approach to study the consequences of cerebral microvascular disease. Retinal microvascular abnormalities related to aging and hypertension have been reported to correlate closely with pathological changes in the cerebral microcirculation among stroke decedents[34] and have been found in epidemiological studies to be associated with clinical stroke,[26,35,36] lacunar infarct,[37] and cerebral white-matter lesions.[38] Thus, our study supports the hypothesis that cerebral microvascular disease may play an important role in the development of cognitive impairment.

Additionally, these findings offer clues to the specific pathophysiological processes that occur in the cerebral microcirculation of persons with cognitive impairment. The retinal lesions that were related most consistently to lower cognitive scores (eg, microaneurysm, retinal hemorrhages) are indicators of more severe retinal microvascular disease and are usually seen when there is a breakdown in the blood-retinal barrier.[21,22] In contrast, other retinal characteristics such as arteriovenous nicking and arteriolar narrowing, which reflect milder microvascular changes,[21,22] appear to be related weakly to cognitive impairment. We have also previously shown that incident stroke was more strongly related to retinopathy (multivariable-adjusted relative risk, 2.6) than arteriovenous nicking (multivariable-adjusted relative risk, 1.6) and arteriolar narrowing (multivariable-adjusted relative risk, 1.2).[26] Thus, the association with retinopathy but not with arteriovenous nicking and arteriolar narrowing suggests that disruption of the blood-brain barrier of the cerebral microcirculation may be an important pathological feature in the development of stroke and cognitive impairment.[16]

From a clinical perspective, these data provide additional evidence that cognitive impairment may have a vascular component and may therefore be amenable to treatment and preventive strategies targeted at vascular diseases.[39] It is less clear that retinal lesions provide useful independent information regarding risk of cognitive impairment and dementia. Retinopathy is infrequent in the general population, and the retinal assessment in the ARIC study was performed with standardized photographic grading. In addition, differences in cognitive function scores between persons with and without retinopathy were small although statistically significant. Nevertheless, modest deficits detected in midlife may reflect risk of future dementia.[39]

Limitations of this study should be mentioned. First, because retinal and cognitive assessments were at different study visits, we could compare only retinal microvascular data collected at visit 3 with the average of cognitive tests scores 3 years before (visit 2) and after (visit 4) the retinal examination. This makes it difficult to distinguish clearly cause and effect, although it seems unlikely that cognitive function affects the development of retinal microvascular lesions. Second, selection bias may have obscured some relevant associations and enhanced others. For example, if persons with retinal abnormalities with cognitive impairment were more likely excluded because of ungradable photographs (or other reasons), the observed associations would be falsely attenuated. Finally, visual acuity data were not available, and biases could result if those who could not optimally perform the cognitive tests had visual impairment. However, retinal microvascular changes evaluated in this study are not known to be an important cause of visual impairment.[40]

In conclusion, we found that in middle-aged persons without stroke, signs of retinal microvascular disease are independently associated with lower cognitive function. The associations suggest that cerebral microvascular disease may be important in the pathogenesis of cognitive impairment. Longitudinal data may clarify the temporal sequence of these associations and the eventual clinical significance of these small, early cognitive function changes.

Acknowledgments

This study was supported by contracts N01-HC-35125, N01-HC-35126, N01-HC-55015, N01-HC-55016, N01-HC-55018, N01-HC-55019, N01-HC-55020, N01-HC-55021, and N01-HC-55022 from the National Heart, Lung, and Blood Institute, Bethesda, Md. Additional support was provided by the American Diabetes Association and National University of Singapore (Dr Wong). We thank the staff and participants in the ARIC study for their important contributions.

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