The Cross-sectional and Longitudinal Associations of Diabetic Retinopathy With Cognitive Function and Brain MRI Findings: The Action to Control Cardiovascular Risk in Diabetes (ACCORD) Trial

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OBJECTIVE

Longitudinal evidence linking diabetic retinopathy with changes in brain structure and cognition is sparse. We used data from the Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial to determine whether diabetic retinopathy at baseline predicted changes in brain structure or cognition 40 months later.

RESEARCH DESIGN AND METHODS

Participants from the ACCORD-MIND and ACCORD-Eye substudies were included in analyses of cognition (n = 1,862) and MRI-derived brain variables (n = 432). Retinopathy was categorized as none, mild nonproliferative, or moderate/severe. Tests of cognition included the Mini-Mental State Examination (MMSE), Digit Symbol Substitution Test (DSST), Rey Auditory Verbal Learning Test, and Stroop test. Primary brain outcomes were gray matter and abnormal white matter volumes.

RESULTS

Baseline retinopathy was associated with lower gray matter volume (adjusted means of 470, 466, and 461 cm^3 for none, mild, and moderate/severe retinopathy, respectively; P = 0.03). Baseline retinopathy also predicted a greater change in MMSE and DSST scores at 40 months in each retinopathy category (MMSE: −0.20, −0.57, and −0.42, respectively [P = 0.04]; DSST: −1.30, −1.84, and −2.89, respectively [P = 0.01]).

CONCLUSIONS

Diabetic retinopathy is associated with future cognitive decline in people with type 2 diabetes. Although diabetic retinopathy is not a perfect proxy for diabetes-related brain and cognitive decline, patients with type 2 diabetes and retinopathy represent a subgroup at higher risk for future cognitive decline.

PATHOPHYSIOLOGY/COMPLICATIONS

Brain imaging studies suggest that type 2 diabetes–related microvascular disease may affect the central nervous system in addition to its effects on other organs, such as the eye and kidney. Histopathological evidence indicates that microvascular disease in the brain can lead to white matter lesions (WMLs) visible with MRI of the brain (1), and risk for them is often increased by type 2 diabetes (2–6). Type 2 diabetes also has recently been associated with lower brain volume, particularly gray matter volume (7–9).

The association between diabetic retinopathy and changes in brain tissue is of particular interest because retinal and cerebral small vessels have similar anatomy, physiology, and embryology (10). Increased severity of retinopathy is associated with increased severity of cardiovascular outcomes (11). In addition, the preponderance of evidence suggests diabetic retinopathy is associated with increased WML burden (3,12–14), although variation exists. While cross-sectional studies support a correlation between diabetic retinopathy and WMLs (2,3,6,15), diabetic retinopathy and brain atrophy (16), diabetic retinopathy and psychomotor speed (17,18), and psychomotor speed and WMLs (5,19,20), longitudinal evidence demonstrating the assumed sequence of disease development, for example, vascular damage of eye and brain followed by cognitive decline, is lacking.

Using Action to Control Cardiovascular Risk in Diabetes (ACCORD) data, in which a subset of participants received longitudinal measurements of diabetic retinopathy, cognition, and MRI variables, we analyzed the *1*) cross-sectional associations between diabetic retinopathy and evidence of brain microvascular disease and *2*) determined whether baseline presence or severity of diabetic retinopathy predicts 20- or 40-month changes in cognitive performance or brain microvascular disease.

RESEARCH DESIGN AND METHODS

Participants

Data presented here include two subsets of ACCORD subjects. Analyses of associations between diabetic retinopathy and cognition include 1,862 participants who enrolled in both the ACCORD-Eye and ACCORD-MIND substudies (described below). Analyses with MRI variables included 432 participants who took part in both the ACCORD-Eye study and the MRI substudy of the ACCORD-MIND. For longitudinal analysis, 1,842 participants had complete data for all time points and 361 had complete data for MRI analyses. The design and inclusion/exclusion criteria of each study are briefly described below (Fig. 1).

The ACCORD trial (21) was a multicenter randomized trial examining the effects of intensive glycemic control, blood pressure, and lipids on cardiovascular disease events. The 10,251 ACCORD participants were aged 40–79 years, had poorly controlled type 2 diabetes ($HbA_{1c} > 7.5\%$ [58.5 mmol/mol]), and had or were at high risk for cardiovascular disease.

The design of the ACCORD-Eye trial has been previously described in detail (22). The ACCORD-Eye sample comprised 3,472 participants who did not report previous vitrectomy or photocoagulation surgery for proliferative diabetic retinopathy at baseline and who completed fundus photography of 7 standard stereoscopic fields and underwent standardized eye examinations by an ophthalmologist or optometrist at baseline. The photographs were evaluated by certified personnel using a standard protocol at the Fundus Photograph Reading Center at the University of Wisconsin (Madison, WI). The graders were masked to all medical information and treatment allocation and used the modified Early Treatment Diabetic Retinopathy Study (ETDRS) final diabetic retinopathy severity scale for persons, a standardized method for assessing diabetic retinopathy and its progression (22).

ACCORD-MIND included a subset of 2,977 ACCORD participants who completed a 30-min cognitive testing battery, 614 of whom also had useable scans from the MRI substudy (23,24). Six of the seven clinical center networks participated in the MIND substudy. ACCORD-MIND had visits at three time points: baseline, 20 months, and 40 months. MRI of the brain was completed at baseline and the 40-month time point. Brain MRI scans were evaluated at the ACCORD-MIND MRI Reading Center located in the Department of Radiology at the University of Pennsylvania School of Medicine (Philadelphia, PA).

All participants provided written informed consent. All protocols were approved by the board governing National Institutes of Health intramural research and the local institutional review board at each center. The study was performed in accordance with the Declaration of Helsinki.

Data Acquisition

Retinopathy Measures

ACCORD-Eye participants were evaluated for progression of diabetic retinopathy at baseline and year 4 through standardized eye examinations and fundus photography of seven standard stereoscopic fields. The eye examination assessed visual acuity, the anterior segment, and the fundus after dilation. In addition, the entire ACCORD cohort had visual acuity assessments at their clinical sites following a standardized protocol that used a logarithmic visual acuity chart (the ETDRS chart) at baseline, which was used to adjust for visual acuity in cognitive analyses. The entire

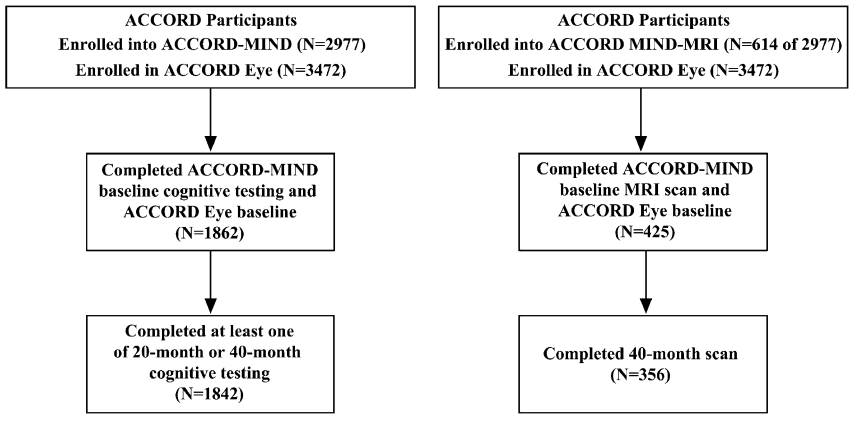

Figure 1—Diagram of subject selection for the current analysis.

ACCORD cohort also answered questions about laser photocoagulation, vitrectomy, and cataract surgery at each annual visit (22). The severity of diabetic retinopathy at baseline was classified by the ETDRS with 12 sublevels. The 12 sublevels were subsequently grouped as either no retinopathy (ETDRS level 10); mild nonproliferative diabetic retinopathy (NPDR) (levels 15–20); moderate NPDR (levels 35–43); or severe retinopathy (i.e., severe NPDR, proliferative retinopathy, or laser therapy or vitrectomy at baseline [levels above 47]) (25). For this analysis, moderate and severe retinopathy categories were pooled because of the relatively small number of participants in the severe category.

Neuropsychological Tests

Cognitive measures were collected at baseline, 20 months, and 40 months. The test battery for cognitive function included the Mini-Mental State Exam (MMSE), the Digit Symbol Substitution Test (DSST), the Rey Auditory Verbal Learning Test (RAVLT), and the modified Stroop test. The MMSE is an assessment of global cognitive function (26); scores range from 0–30, and it is widely used in clinical practice and research to assess for dementia. The DSST, a test of psychomotor speed (27), was measured as the number of correctly completed cells. The RAVLT, a measure of memory (28), was reported as the average number of words recalled (0 to 15) over the immediate, short, and delayed recall trials. The modified Stroop test, a measure of executive functioning (29), was reported as the interference score; a higher score indicates worse function. The MMSE, DSST, and Stroop all require visual functioning; accordingly, statistical model 2 included adjustment for baseline visual acuity.

MRI Measures

MRI scans were acquired at baseline and the 40-month time point. Two MRI measures were used to reflect microvascular disease in the brain. Abnormal white matter volume (described below) was comprised largely of WMLs believed to be of microvascular origin (1). In addition, total gray matter volume was used because evidence suggests that gray matter atrophy may also be a consequence of brain microvascular disease (4). The MRI protocol (24) was standardized across sites and acquired images appropriate for estimating gray matter and white matter tissue volumes. The MRI data were collected using the following sequences run on 1.5-Tesla scanners: 3-dimensional, fast, spoiled, gradient-echo T_1-weighted images (repetition time [TR] = 21 ms, flip angle = 30°, echo time [TE] = 8 ms, voxel size = 1.5 × 0.9 × 0.9 mm) used to determine brain volumes and morphology, and 2-dimensional, axial, fast, spin-echo fluid-attenuated inversion recovery (FLAIR) (TR = 8000 ms, inversion time = 2000 ms, TE = 100 ms) and proton density/T_2-weighted (TR = 3200 ms, $TE_{1,2}$ = 27 and 120 ms) sequences with a voxel size of 3.0 × 0.9 × 0.9 mm to study pathology. Quality control was performed in accordance with the American College of Radiology's MRI quality control program and has been described in detail previously (23,24).

Volumes were estimated using previously described automated methods (30,31). First, a digital anatomic atlas/registration computer algorithm was used to classify the brain into 92 anatomical regions of interest (ROIs) identified as gray matter, white matter, or cerebrospinal fluid (CSF). These ROIs were organized into an anatomically hierarchical system that was collapsed into three anatomic ROIs: total brain, total gray matter, and total white matter structures. Gray matter and white matter then were categorized as being normal or abnormal using an automated multispectral computer program. Tissue was classified as normal or abnormal using the following steps: T_1-weighted volumetric MRI scans were preprocessed according to a standardized protocol for alignment, removal of extracerebral tissue, and segmentation of brain parenchyma into gray matter, white matter, and CSF. Following additional preprocessing steps, including histogram standardization and coregistration, the lesion segmentation component of the algorithm was applied, based on local signal features extracted from coregistered multiparametric MRI sequences (e.g., T_1, proton density, T_2, and FLAIR). A support vector machine classifier was first trained on expert-defined small vessel ischemic disease (SVID) lesions in 45 ACCORD-MIND cases and then was used to classify SVID in new cases. For algorithm training purposes, SVID was operationally defined as a nonmass lesion having FLAIR signal greater than normal gray matter in a vascular distribution. Regional volumetric measurements were obtained via an automated computer-based template warping method that summed the number of respective voxels falling within each anatomic region. The MRI variables are total brain; normal, abnormal, and total gray matter; and normal, abnormal, and total white matter volumes. Here we present results from abnormal white matter and total gray matter volume because these variables have previously been associated with diabetes (2–8). Abnormal white matter comprises both regions of diffuse small-vessel disease and focal white matter hyperintensities surrounding these changes. Total brain volume was computed by summing gray and white matter volumes. Total intracranial volume (ICV) was calculated to estimate head size by summing gray matter, white matter, and CSF volumes.

Statistical Methods

Means and SDs are reported for continuous variables; numbers and percentages are reported for categorical variables. Cross-sectional analyses of MRI measures were done using baseline measurements. Because of the skewness of the distribution, abnormal white matter volume was log transformed after adding 0.1 to all original measurements to account for those with a volume equal to 0.

Two linear regression models were fit to evaluate cross-sectional associations between baseline diabetic retinopathy and cognitive function. Model 1 adjusted for age, sex, ethnicity, education, smoking, and geographic region. Model 2 built on this by further adjusting for duration of diabetes, HbA_{1c}, HDL, triglycerides, systolic blood pressure, use of antihypertensive medication, depression, alcohol use, presence of neuropathy, and visual acuity.

The longitudinal association of baseline diabetic retinopathy with changes in cognitive function was assessed with mixed effects ANCOVA models that incorporated both the 20-month and 40-month outcome measures. A visit effect and a visit by diabetic retinopathy group interaction effect are included in all models. Model 1 adjusted for age, sex, ethnicity, education, smoking, geographic region,

and treatment assignment. Model 2 added duration of diabetes, HbA_{1c}, HDL, triglycerides, systolic blood pressure, use of antihypertensive medication, depression, alcohol use, presence of neuropathy, and baseline visual acuity.

Two linear regression models also were fit to test potential cross-sectional associations between baseline diabetic retinopathy and the four MRI measures (total brain, gray matter, white matter, and abnormal white matter volumes). Model 1 adjusted for ICV, age, sex, ethnicity, education, smoking, and geographic region. Model 2 further adjusted for duration of diabetes, HbA_{1c}, HDL, triglycerides, systolic blood pressure, use of antihypertensive medication depression, alcohol use, and presence of neuropathy. Because abnormal white matter was log transformed, means were obtained by back transformation.

Linear regression analyses relating baseline diabetic retinopathy to the change in the four MRI measures was performed using a 40-month change score (i.e., the 40-month measure minus the baseline measure). For the analysis of change, both baseline and follow-up abnormal white matter were log transformed before calculating the change score. Model 1 adjusted for ICV, age, sex, ethnicity, education, smoking, geographic region, and treatment assignment. Model 2 further adjusted for duration of diabetes, HbA_{1c}, HDL, triglycerides, systolic blood pressure, use of antihypertensive medication, depression, alcohol use, and presence of neuropathy.

The association between a $\geq$3-point change in ETDRS score at the 48-month time point and 40-month changes in cognition and MRI volumes were investigated using the same two statistical models and linear regression analyses.

RESULTS

Baseline characteristics for the study participants included in these analyses are shown in column 1 of Table 1. Columns 2 and 3 show characteristics of subjects without (n = 1,430) and with (n = 432) MRI. These are compared with the rest of the ACCORD cohort in column 4.

Cross-sectional Associations at Baseline

Table 2 presents adjusted mean values for each cognitive variable for the three categories of retinopathy from minimally and maximally adjusted models. At baseline, participants with moderate/severe diabetic retinopathy had lower DSST scores than those with no or mild retinopathy after adjusting for demographics and lifestyle factors in model 1; adjusted means were 47.8 (none), 48.1 (mild), and 46.2 (moderate/severe) (P = 0.03). Further adjustment using model 2 for vascular and diabetes risk factors, depression, and visual acuity eliminated this effect. Scores on the MMSE, RAVLT, and Stroop task were not significantly associated with diabetic retinopathy at baseline in model 1 or model 2 (Table 2).

Table 3 presents results of cross-sectional analyses of diabetic retinopathy and total brain, gray, white, and abnormal white matter volumes. At baseline, diabetic retinopathy was associated with abnormal white matter after adjusting for demographics, lifestyle factors, and ICV. Compared with those without diabetic retinopathy, individuals with mild NPDR and moderate/severe NPDR/proliferative diabetic retinopathy had a greater volume of abnormal white matter (adjusted means were 0.81 [none], 1.04 [mild], and 1.16 cm^3 [moderate/severe]; P = 0.02) using model 1. After further adjusting for vascular and diabetes risk factors using model 2, the association was no longer significant. Additional analysis was performed to investigate the relative contributions of vascular and diabetes risk factors to this analysis. The inclusion of vascular risk factors, particularly systolic blood pressure, was responsible for the drop in significance (Supplementary Table 1).

In addition, the presence and severity of diabetic retinopathy was associated with less gray matter volume (470, 467, and 462 cm^3 [no, mild, and moderate/severe NPDR, respectively]; P = 0.02) after adjusting for demographics, lifestyle factors, and ICV (model 1; Table 3). This association remained statistically significant after adjusting for vascular and diabetes risk factors in model 2. Expressed as a percent of ICV, the gray matter represented 41.1%, 40.9%, and 40.4% of ICV.

Associations Between Baseline Diabetic Retinopathy and Change in Cognition and MRI Variables

The next analyses addressed the question of whether diabetic retinopathy at baseline predicted increases in abnormal white matter or decreases in gray matter volume or cognitive scores over 40 months of follow-up. Cognitive data are presented for 20- and 40-month time points (n = 1,842). Imaging data were not collected at the 20-month time point, so all imaging data are from the 40-month time point (n = 361).

Baseline diabetic retinopathy was associated with more rapid 40-month declines in DSST and MMSE when adjusting for demographics and lifestyle factors in model 1 (Table 4). Moreover, increasing severity of diabetic retinopathy was associated with increased amounts of decline in DSST performance ($-$1.30, $-$1.76, and $-$2.81 for no, mild, and moderate/severe NPDR, respectively; P = 0.003). The associations remained virtually unchanged after further adjusting for vascular and diabetes risk factors, depression, and visual acuity using model 2. Baseline diabetic retinopathy was not associated with changes in RAVLT summary score and Stroop, and no significant association was observed between baseline diabetic retinopathy and 20-month changes in cognitive scores. No significant associations were observed between baseline diabetic retinopathy and changes in total brain volume, gray matter volume, or white matter volume over 40 months using either statistical model (Table 5).

Associations Between Change in Retinopathy and Change in Cognition and MRI Variables

The previous analyses focused on the relationship between the presence of retinopathy at baseline and the progression of brain atrophy, WMLs, and cognitive decline. It is possible, however, that the effects of developing retinopathy are different than the effects of persistent retinopathy on cognitive and brain outcomes. The results of these analyses were very similar to those of the main analyses. There were no associations between development of retinopathy and measured brain imaging variables, but modest associations were present with cognitive variables (Supplementary Table 2).

CONCLUSIONS

This longitudinal study provides new evidence that diabetic retinopathy is

Table 1—Cognition-related characteristics of the current study population (participating in both the ACCORD-MIND and ACCORD-Eye substudies)

Characteristics	ACCORD-MIND/Eye study			Eligible for ACCORD-MIND/Eye
	Total (*n* = 1,862)	Without MRI (*n* = 1,430)	With MRI (*n* = 432)	(*n* = 6,968)
Age, years	62.3 ± 5.7	62.2 ± 5.8	62.4 ± 5.6	61.9 ± 7.0
Female sex	817 (43.9)	647 (45.2)	170 (39.4)	3092 (44.4)
Education				
<High school	220 (11.8)	189 (13.2)	31 (7.2)	1,120 (16.1%)
High school graduate/GED	444 (23.8)	347 (24.3)	97 (22.5)	1,855 (26.6%)
Some college/technical school	678 (36.4)	522 (36.5)	156 (36.1)	2,130 (30.6%)
College graduate or higher	520 (27.9)	372 (26.0)	148 (34.3)	1,857 (26.7)
Race/ethnicity				
African American	300 (16.1)	233 (16.3)	67 (15.5)	1,189 (17.1)
White	1,350 (72.5)	1,034 (72.3)	316 (73.1)	4,195 (60.2)
Hispanic	118 (6.3)	91 (6.4)	27 (6.3)	529 (7.6)
Other	94 (5.0)	72 (5.0)	22 (5.1)	1,055 (15.1)
Network				
Canada	235 (12.6)	235 (16.4)	0 (0.0)	1,273 (18.3)
Western U.S.	351 (18.9)	351 (24.5)	0 (0.0)	1,392 (20.0)
Minnesota/Iowa	414 (22.2)	214 (15.0)	200 (46.3)	827 (11.9)
Ohio/Michigan	264 (14.2)	188 (13.1)	76 (17.6)	1,308 (18.8)
Northeastern U.S.	194 (10.4)	137 (9.6)	57 (13.2)	1,027 (14.7)
Southeastern U.S.	404 (21.7)	305 (21.3)	99 (22.9)	1,141 (16.4)
Smoking status				
Never	812 (43.6)	622 (43.5)	190 (44.0)	3,103 (44.6)
Former	831 (44.6)	649 (45.4)	182 (42.1)	2,898 (41.6)
Current	219 (11.8)	159 (11.1)	60 (13.9)	957 (13.8)
Systolic blood pressure	135.1 ± 17.6	135.1 ± 17.5	135.0 ± 17.9	137.3 ± 17.1
Antihypertensive medications	1,579 (84.8)	1,209 (84.5)	370 (85.6)	5,870 (84.2)
Duration of diabetes	9.7 ± 6.8	9.9 ± 6.9	9.3 ± 6.4	11.0 ± 7.8
HbA_{1c} (mmol/mol)	67.2 ± 10.9	67.2 ± 12.0	65.0 ± 9.8	67.2 ± 12.0
HbA_{1c} (%)	8.3 ± 1.0	8.3 ± 1.1	8.1 ± 0.09	8.3 ± 1.1
Triglycerides	193.5 ± 150.0	193.4 ± 155.0	194.0 ± 132.1	192.1 ± 152.6
HDL cholesterol				
Women	47.2 ± 12.0	46.9 ± 12.0	48.2 ± 12.2	47.0 ± 12.7
Men	38.8 ± 9.3	38.5 ± 9.3	39.8 ± 9.2	38.6 ± 9.7
Visual acuity†	75.7 ± 10.1	75.5 ± 10.3	76.4 ± 9.4	72.9 ± 12.8
Depression (PHQ score >10)	267 (14.3)	216 (15.1)	51 (11.8)	
Baseline DSST	54.4 ± 15.6	54.1 ± 15.5	55.1 ± 15.7	
Baseline RAVLT	7.5 ± 2.4	7.6 ± 2.5	7.5 ± 2.4	
Baseline Stroop	30.2 ± 16.2	31.2 ± 15.2	30.2 ± 16.2	
Baseline MMSE	27.6 ± 2.4	27.5 ± 2.5	27.9 ± 2.2	

Data presented are mean ± SD or *n* (%). †75 Letters is a visual acuity of 20/30. GED, General Educational Development; PHQ, Patient Health Questionnaire.

associated with future cognitive decline in persons with type 2 diabetes and confirms the finding from the Edinburgh Type 2 Diabetes Study derived from cross-sectional data that lifetime cognitive decline is associated with diabetic retinopathy (32). We found that the presence of diabetic retinopathy, independent of visual acuity, predicts greater declines in global cognitive function measured with the MMSE and that the magnitude of decline in processing speed measured with the DSST increased with increasing severity of baseline diabetic retinopathy. The association with psychomotor speed is consistent with prior cross-sectional findings in community-based samples of middle-aged (18) and older adults (17), as well as prospective studies of a community-based sample of middle-aged adults (33) and patients with type 1 diabetes (34) showing that retinopathy with different etiologies predicted a subsequent decline in psychomotor speed. This study extends these findings to patients with type 2 diabetes. To our knowledge, this is the first time a prospective association between diabetic retinopathy and global cognitive function has been noted in a type 2 diabetes cohort (35).

We also observed a cross-sectional association at baseline between diabetic retinopathy and gray matter volume. This finding supports the idea that cerebral atrophy partly explains the predictive ability of diabetic retinopathy for future cognitive declines and is in

Table 2—Cross-sectional association of diabetic retinopathy with cognitive function and brain volumes

	MMSE		DSST		RAVLT summary score		Stroop	
	Adjusted mean (95% CI)	*P* value*	Adjusted mean (95% CI)	*P* value*	Adjusted mean (95% CI)	*P* value*	Adjusted mean (95% CI)	*P* value*
Model 1†								
None	26.7 (26.5–27.0)	0.38	47.8 (46.4–49.1)	0.03	7.3 (7.1–7.6)	0.13	31.7 (30.1–33.3)	0.29
Mild NPDR	26.7 (26.3–27.0)		48.1 (46.3–49.9)		7.1 (6.8–7.4)		32.5 (30.4–34.6)	
Moderate and severe NPDR, PDR	26.6 (26.3–26.9)		46.2 (44.7–47.7)		7.1 (6.8–7.4)		32.9 (31.1–34.6)	
Model 2‡								
None	26.7 (26.4–27.1)	0.50	48.3 (46.3–50.3)	0.65	7.5 (7.1–7.8)	0.35	31.8 (29.5–34.1)	0.66
Mild NPDR	26.7 (26.2–27.0)		49.0 (46.7–51.3)		7.3 (6.9–7.7)		32.6 (29.9–35.3)	
Moderate and severe NPDR, PDR	26.6 (26.2–27.0)		48.2 (46.0–50.3)		7.3 (6.9–7.7)		32.4 (29.8–34.9)	

*The *P* values represent a test for overall equality of means. †Model 1 includes the variables age, sex, ethnicity, education, smoking, and geographic region. ‡Model 2 includes the model 1 variables as well as diabetes duration, HbA_{1c}, HDL, triglycerides, systolic blood pressure, use of antihypertensive medication, depression, alcohol use, neuropathy, and visual acuity. PDR, proliferative diabetic retinopathy.

accord with a recent observation from the Age, Gene/Environment Susceptibility–Reykjavik study that the association between diabetes and executive function is mediated by brain atrophy (36). Because gray matter volume included both cortical and subcortical gray matter, this concurs with previous observations of a cross-sectional association between diabetic retinopathy and cortical atrophy in a cohort of middle-aged and older adults (4), as well as an association between diabetic retinopathy and ventricular enlargement in a community-based sample of middle-aged adults (37). However, the fact that adjustment for cardiovascular factors attenuated the association between diabetic retinopathy and abnormal white matter does not mean that retinopathy is not an important predictor of white matter disease; rather, the relationship was largely accounted for by cardiovascular risk factors that are known to contribute to both diseases. In particular, adjusting for systolic blood pressure greatly reduced the association between diabetic retinopathy and abnormal white matter (Supplementary Table 1). Given that DSST performance is linked with WMLs (38), it is interesting to note that the association between diabetic retinopathy and the DSST at baseline also was reduced to nonsignificance after adjusting for cardiovascular factors.

The results of this analysis support recent findings reported by Crosby-Nwaobi and colleagues (39), who examined the association between the MMSE and retinopathy in a cohort of 380 patients from an eye screening program. Although they concluded that diabetic retinopathy did not predict MMSE score, they compared patients with proliferative diabetic retinopathy with a combined group with no retinopathy or nonproliferative retinopathy; their sensitivity analysis showed that those with mild retinopathy had more cognitive impairment than those with no retinopathy. In the ACCORD data presented here, presence of diabetic retinopathy was associated with lower MMSE score, but severity of retinopathy was not. This was virtually unaltered by adjustment for cardiovascular factors. In contrast, worse DSST performance, which is known to be associated with hypertension and WMLs (5,19,20), was associated with severity of diabetic retinopathy and attenuated by adjustment for cardiovascular risk factors.

The lack of longitudinal association with MRI variables should be interpreted with caution. Because fewer

Table 3—Cross-sectional association of diabetic retinopathy with brain volumes

	Total brain volume		Gray matter volume		White matter volume		Abnormal white matter	
	Adjusted mean (95% CI)	*P* value*	Adjusted mean (95% CI)	*P* value*	Adjusted mean (95% CI)	*P* value*	Adjusted mean (95% CI)	*P* value*
Model 1†								
None	935 (932–938)	0.10	470 (467–474)	0.02	464 (462–468)	0.48	0.81 (0.70–0.93)	0.01
Mild NPDR	936 (929–941)		467 (461–474)		467 (462–473)		1.04 (0.79–1.35)	
Moderate and severe NPDR, PDR	929 (924–934)		462 (457–467)		467 (463–471)		1.16 (0.94–1.43)	
Model 2‡								
None	934 (931–938)	0.18	470 (467–474)	0.02	464 (461–467)	0.50	0.86 (0.74 –1.00)	0.40
Mild NPDR	933 (927–939)		466 (459–472)		467 (461–472)		0.97 (0.74–1.25)	
Moderate and severe NPDR, PDR	928 (923–933)		461 (456–466)		467 (462–472)		1.04 (0.83–1.31)	

*The *P* values represent a test for overall equality of means. †Model 1 includes the variables ICV, age, sex, ethnicity, education, smoking, and geographic region. ‡Model 2 includes the model 1 variables as well as diabetes duration, HbA_{1c}, HDL, triglycerides, systolic blood pressure, use of antihypertensive medication, depression, alcohol use, and neuropathy. PDR, proliferative diabetic retinopathy.

Table 4—Longitudinal association of diabetic retinopathy at baseline with change in cognitive function

	MMSE		DSST		RAVLT summary score		Stroop	
	Adjusted mean (95% CI)	*P* value*	Adjusted mean (95% CI)	*P* value*	Adjusted mean (95% CI)	*P* value*	Adjusted mean (95% CI)	*P* value*
20-Month change								
Model 1†								
None	−0.03 (−0.18 to 0.11)	0.42	−1.14 (−1.65 to −0.63)	0.51	0.39 (0.27–0.51)	0.71	−0.80 (−1.68 to −0.08)	0.86
Mild NPDR	−0.17 (−0.43 to 0.08)		−1.11 (−2.01 to −0.21)		0.29 (0.08–0.50)		−0.42 (−1.98 to 1.15)	
Moderate and severe NPDR, PDR	−0.18 (−0.37 to 0.02)		−1.62 (−2.32 to −0.93)		0.39 (0.23–0.56)		−0.44 (−1.64 to 0.76)	
Model 2‡								
None	−0.02 (−0.17 to 0.14)	0.45	−1.14 (−1.66 to −0.57)	0.59	0.35 (0.23–0.48)	0.42	−0.70 (−1.65 to 0.26)	0.93
Mild NPDR	−0.14 (−0.41 to 0.12)		−1.12 (−2.07 to −0.22)		0.27 (0.05–0.48)		−0.42 (−2.04 to 1.20)	
Moderate and severe NPDR, PDR	−0.19 (−0.40 to 0.03)		−1.61 (−2.37 to −0.85)		0.45 (0.27–0.63)		−0.83 (−2.15 to 0.50)	
40-Month change								
Model 1								
None	−0.20 (−0.35 to −0.05)	0.04	−1.30 (−1.82 to −0.78)	0.003	0.45 (0.33–0.57)	0.41	−0.39 (−1.28 to 0.51)	0.65
Mild NPDR	−0.54 (−0.80 to −0.28)		−1.76 (−2.67 to −0.84)		0.41 (0.20–0.62)		−0.08 (−1.67 to 1.51)	
Moderate and severe NPDR, PDR	−0.41 (−0.61 to −0.21)		−2.81 (−3.52 to −2.11)		0.57 (0.41–0.73)		0.33 (−0.89 to 1.55)	
Model 2								
None	−0.20 (−0.35 to −0.04)	0.04	−1.30 (−1.86 to −0.75)	0.01	0.41 (0.28–0.54)	0.19	−0.29 (−1.27 to 0.67)	0.89
Mild NPDR	−0.57 (−0.84 to −0.31)		−1.84 (−2.78 to −0.89)		0.39 (0.18–0.61)		0.01 (−1.64 to 1.65)	
Moderate and severe NPDR, PDR	−0.42 (−0.64 to −0.20)		−2.89 (−3.67 to −2.12)		0.61 (0.43–0.79)		0.11 (−1.24 to 1.46)	

*The *P* values represent an overall test for equality of means. †Model 1 includes the variables age, sex, ethnicity, education, smoking, geographic region, and treatment assignment. ‡Model 2 includes model 1 variables as well as diabetes duration, HbA_{1c}, HDL, triglycerides, systolic blood pressure, use of antihypertensive medication, depression, alcohol use, neuropathy, and visual acuity. PDR, proliferative diabetic retinopathy.

subjects who had both MRI and eye data collected were available, tests for association between diabetic retinopathy and cognition (n = 1,862) likely have greater power than tests with MRI variables (n = 432). It is also possible that the longitudinal association we observed between diabetic retinopathy and cognition could be driven by regional changes in brain volume or lesion load that are not apparent using whole-brain averages, or that brain changes are evident only in the subset of participants who showed accelerated cognitive decline (40). Another point worth considering is that the average age of patients in this cohort was approximately 62 years; associations with both cognitive function and brain findings might be stronger in an older cohort. Finally, we tested a number of different associations but did not correct *P* values for multiple testing, so significance values should be interpreted with that in mind. Future studies can investigate these alternatives.

At this time, a number of studies have examined the relationship between retinopathy and cognition and retinopathy and cerebrovascular disease. Two fundamental clinical questions are at the heart of these articles: *1*) Should physicians consider diabetic retinopathy to be an indicator that patients are at higher risk for cognitive decline and adjust their practice accordingly? and *2*) Can physicians use diabetic retinopathy as a proxy for cerebrovascular damage to the brain? We observed that the presence of diabetic retinopathy at baseline predicted greater decline in performance on the DSST and, more marginally, on the MMSE. The magnitude of changes would not likely impair activities of daily living in the short term but suggests that patients who have diabetic retinopathy are at higher risk for cognitive decline. It is less clear whether diabetic retinopathy adequately serves as a proxy for cerebrovascular damage to the brain. While it may be true that diabetic retinopathy signals greater risk for increased abnormal white matter volume and decreased gray matter volume, the reverse—that lack of retinopathy implies lack of risk—is not necessarily true. This is clear when looking at frequency tables of retinopathy by level of white matter disease, such as those from the Atherosclerosis Risk in

Communities (ARIC) study (6) and Cardiovascular Health Study (CHS) (3). In our data set, 50% of people in the highest quartile of abnormal white matter had no diabetic retinopathy (Supplementary Table 3) but are likely still at risk for cerebrovascular-related cognitive decline. These observations underscore the need for monitoring of cognitive function to become a routine part of clinical practice, particularly for older adults and those with diabetes.

Table 5—Longitudinal association of diabetic retinopathy at baseline with change in brain volumes

	Total brain volume		Gray matter volume		White matter volume		Abnormal white matter	
	Adjusted mean (95% CI)	*P* value*	Adjusted mean (95% CI)	*P* value*	Adjusted mean (95% CI)	*P* value*	Adjusted mean (95% CI)	*P* value*
Model 1†								
None	−14.85 (−17.03 to −12.67)	0.30	−19.21 (−22.07 to −16.35)	0.75	4.40 (1.52–7.28)	0.83	1.93 (1.80–2.06)	0.05
Mild NPDR	−18.11 (−22.32 to −13.91)		−21.54 (−27.02 to −16.07)		3.33 (−2.18 to 8.84)		1.61 (1.41–1.83)	
Moderate and severe NPDR, PDR	−17.02 (−20.26 to −13.79)		−20.11 (−24.35 to −15.88)		2.89 (−1.37 to 7.16)		1.79 (1.62–1.98)	
Model 2‡								
None	−14.66 (−17.02 to −12.31)	0.25	−19.79 (−22.88 to −16.70)	0.91	5.13 (1.98–8.28)	0.49	1.93 (1.80–2.10)	0.06
Mild NPDR	−18.24 (−22.56 to −13.93)		−20.93 (−26.61 to −15.26)		2.69 (−3.09 to 847)		1.61 (1.41–1.85)	
Moderate and severe NPDR, PDR	−17.60 (−21.17 to −14.03)		−19.28 (−23.97 to −14.59)		1.67 (−3.10 to 6.45)		1.79 (1.60–2.00)	

*The *P* values represent an overall test for equality of means. †Model 1 includes the variables ICV, age, sex, ethnicity, education, smoking, geographic region, and treatment assignment. ‡Model 2 includes the model 1 variables as well as diabetes duration, HbA_{1c}, HDL, triglycerides, systolic blood pressure, use of antihypertensive medication, depression, alcohol use, and neuropathy. PDR, proliferative diabetic retinopathy.

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