Diabetes, Prediabetes, and Brain Volumes and Subclinical Cerebrovascular Disease on MRI: The Atherosclerosis Risk in Communities Neurocognitive Study (ARIC-NCS)

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EPIDEMIOLOGY/HEALTH SERVICES RESEARCH

OBJECTIVE

To examine the associations of prediabetes, diabetes, and diabetes severity (as assessed by HbA_{1c} and diabetes duration) with brain volumes and vascular pathology on brain MRI and to assess whether the associations of diabetes with brain volumes are mediated by brain vascular pathology.

RESEARCH DESIGN AND METHODS

Cross-sectional study of 1,713 participants in the Atherosclerosis Risk in Communities Neurocognitive Study (ARIC-NCS) (mean age 75 years, 60% female, 27% black, 30% prediabetes, and 35% diabetes) who underwent 3T brain MRI scans in 2011–2013. Participants were categorized by diabetes-HbA_{1c} status as without diabetes (<5.7% [reference]), with prediabetes (5.7 to <6.5%), and with diabetes ([defined as prior diagnosis or HbA_{1c} ≥6.5%] <7.0% vs. ≥7.0%), with further stratification by diabetes duration (<10 vs. ≥10 years).

RESULTS

In adjusted analyses, compared with participants without diabetes and HbA_{1c} <5.7%, participants with prediabetes and those with diabetes and HbA_{1c} <7.0% did not have significantly different brain volumes or vascular pathology (all $P > 0.05$), but those with diabetes and HbA_{1c} ≥7.0% had smaller total brain volume (β −0.20 SDs, 95% CI −0.31, −0.09), smaller regional brain volumes (including frontal, temporal, occipital, and parietal lobes; deep gray matter; Alzheimer disease signature region; and hippocampus [all $P < 0.05$]), and increased burden of white matter hyperintensities (WMH) ($P = 0.016$). Among participants with diabetes, those with HbA_{1c} ≥7.0% had smaller total and regional brain volumes and an increased burden of WMH (all $P < 0.05$) compared with those with HbA_{1c} <7.0%. Similarly, participants with longer duration of diabetes (≥10 years) had smaller brain volumes and higher burden of lacunes (all $P < 0.05$) than those with a diabetes duration <10 years. We found no evidence for mediation by WMH in associations of diabetes with smaller brain volumes by structural equation models (all $P > 0.05$).

CONCLUSIONS

More-severe diabetes (defined by higher HbA_{1c} and longer disease duration) but not prediabetes or less-severe diabetes was associated with smaller brain volumes and an increased burden of brain vascular pathology. No evidence was found that associations of diabetes with smaller brain volumes are mediated by brain vascular pathology, suggesting that other mechanisms may be responsible for these associations.

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Diabetes and prediabetes are associated with accelerated cognitive decline (1), and diabetes is associated with an approximately twofold increased risk of dementia (2). Subclinical brain pathology, as defined by small vessel disease (lacunar infarcts, white matter hyperintensities [WMH], and microhemorrhages), large vessel disease (cortical infarcts), and smaller brain volumes also are associated with an increased risk of cognitive decline and dementia (3–7). The mechanisms by which diabetes contributes to accelerated cognitive decline and dementia are not fully understood, but contributions of hyperglycemia to both cerebrovascular disease and primary neurodegenerative disease have been suggested in the literature, although results are inconsistent (2,8). Given that diabetes is a vascular risk factor, brain atrophy among individuals with diabetes may be driven by increased cerebrovascular disease. Brain magnetic resonance imaging (MRI) provides a noninvasive opportunity to study associations of hyperglycemia with small vessel disease (lacunar infarcts, WMH, microhemorrhages), large vessel disease (cortical infarcts), and brain volumes (9). The Standards for Reporting Vascular Changes on Neuroimaging statement supports brain MRI as a good surrogate marker of large and small vessel disease (9); the goal of this statement is to provide standardized definitions for vascular lesions and brain volumes. The existing body of literature on the topic of hyperglycemia with MRI findings has important limitations, including a lack of rigorous assessments of both diabetes status and brain MRI markers of subclinical cerebrovascular disease and total and regional brain volumes within the same study population. Furthermore, few prior studies evaluated the associations of prediabetes (10) and indices of diabetes severity (e.g., glycated hemoglobin [HbA_{1c}], disease duration) (11,12) with brain MRI measures.

The community-based Atherosclerosis Risk in Communities Neurocognitive Study (ARIC-NCS) of older individuals (mean age 75 years, range 67–90 years) provides a unique opportunity to examine the associations of prediabetes and diabetes with total and regional brain volumes and cerebrovascular pathology, including cortical infarcts, lacunar infarcts, lobar microhemorrhages, subcortical microhemorrhages, and WMH volume, on brain MRI. We hypothesized that older adults with prediabetes and diabetes have smaller total and regional brain volumes and increased burden of subclinical cerebrovascular disease compared with older individuals with normoglycemia. We also hypothesized that among individuals with diabetes, those with more-severe disease (as measured by higher HbA_{1c} and longer disease duration) have smaller brain volumes and an increased burden of subclinical cerebrovascular disease than those with better glycemic control and shorter disease duration. Furthermore, we hypothesized that the associations of prediabetes and diabetes with smaller brain volumes is mediated by cerebrovascular disease.

RESEARCH DESIGN AND METHODS

Study Population

The ARIC Study is an ongoing, community-based prospective cohort study of 15,792 middle-aged adults (age 45–64 years at baseline) recruited from four U.S. communities: Washington County, Maryland; Forsyth County, North Carolina; the suburbs of Minneapolis, Minnesota; and Jackson, Mississippi (13). Participants were initially seen at four in-person visits that occurred ~3 years apart from 1987 to 1989 for visit 1 through 1996 to 1998 for visit 4. A fifth visit was conducted from 2011 to 2013 and was attended by 6,538 participants. Supplementary Table 1 shows the baseline (1987–1989) characteristics of ARIC participants, comparing those who attended versus those who did not attend ARIC visit 5. A subsample of participants who attended visit 5 was selected for brain MRI scans (14). Briefly, selection criteria for a visit 5 brain MRI scan were absence of MRI contraindications and any one of the following: *1*) prior participation in the ARIC brain MRI ancillary study (15), *2*) evidence of cognitive impairment at visit 5 (low Mini-Mental State Examination score [<21 for whites and <19 for blacks] or both low visit 5 domain *z* scores on two or more cognitive domains [< −1.5 SD; domains of memory, executive function, language] and cognitive decline on the Delayed Word Recall Test, the Digit Symbol Substitution Test, or the Word Fluency Test [defined as visit 5 score − highest previous score <20th percentile on one or more tests or <10th percentile on two or more tests]), or *3*) a random sample of participants without evidence of cognitive impairment at visit 5. In total, 1,978 participants underwent visit 5 brain MRI scans. Of these, we excluded 80 participants with clinical neurologic disease (multiple sclerosis, stroke, surgery/radiation to skull/brain, brain tumor), 53 with incomplete MRI data or poor image quality, 32 with missing data on diabetes status or HbA_{1c}, and 100 with missing covariates included in our statistical models, leaving a total of 1,713 participants included in the current analysis. Supplementary Table 2 shows characteristics of ARIC visit 5 participants compared with those included and excluded from the current analysis.

The ARIC Study has been approved by the institutional review boards at all participating institutions. All participants gave written informed consent at each study visit.

Diabetes Definition and Measurement of HbA_{1c} and Fasting Glucose

Diabetes was defined by a self-reported physician diagnosis, diabetes medication use assessed at study visits and on annual follow-up telephone calls, or an HbA_{1c} ≥6.5% measured at ARIC visit 5 (2011–2013). Diabetes duration was dichotomized as <10 years versus ≥10 years. In sensitivity analyses, we created a separate category for undiagnosed diabetes (defined as no physician diagnosis and no diabetes medication use with an HbA_{1c} ≥6.5%).

HbA_{1c} was measured at visit 5 (2011–2013). Whole-blood samples were assayed for HbA_{1c} measurement by using high-performance liquid chromatography (G7 HPLC Analyzer; Tosoh Bioscience, South San Francisco, CA). HbA_{1c} was categorized by using cut points defined in the American Diabetes Association clinical practice recommendations (16,17): <5.7% (without diabetes), 5.7 to <6.5% (prediabetes), and <7.0% and ≥7.0% (diabetes).

In sensitivity analyses, we also defined prediabetes/diabetes categories by using fasting glucose: <100 mg/dL (without diabetes), 100 to <126 mg/dL (prediabetes), and <150 and ≥150 mg/dL (with diabetes) (16). Fasting glucose was measured by hexokinase method in a subset of participants who fasted at least 8 h (*n* = 1,639).

Brain MRI Protocol and Image Analysis

The ARIC visit 5 (2011–2013) brain MRI scans were performed by using four 3T scanners (Maryland: Siemens Verio;

North Carolina: Siemens Skyra; Minnesota: Siemens Trio; Mississippi: Siemens Skyra). The following sequences were obtained: localizer, magnetization-prepared rapid gradient-echo MP-RAGE (1.2-mm slices), axial gradient recalled echo T2-weighted imaging (T2*GRE) (4-mm slices), axial T2 fluid-attenuated inversion recovery (FLAIR) (5-mm slices), field mapping (3-mm slices), and axial diffusion tenor images (2.7-mm slices for Skyra and Verio scanners and 3-mm slices for Trio scanner). Brain volumes were measured on MP-RAGE sequences using image analysis software (FreeSurfer; http://surfer.nmr.mgh.harvard.edu) (18), WMH volume and infarcts were assessed on T2 FLAIR sequences, and microhemorrhages were assessed on T2*GRE sequences. WMH burden was measured quantitatively by using an algorithm developed at the Mayo Clinic in Rochester, Minnesota (19). Lacunar infarcts were defined as subcortical T2 FLAIR lesions with central hypointensity $>$3 mm and hyperintensity $\leq$20 mm in maximum dimension located in the caudate, lenticular nucleus, internal capsule, thalamus, brainstem, deep cerebellar white matter, centrum semiovale, or corona radiata (9,20). Cortical infarcts were defined as T2 FLAIR lesions of $>$20 mm in minimum diameter (21). Microhemorrhages were lesions on T2*GRE sequences of $\leq$5 mm in maximum diameter and were divided into lobar and subcortical microhemorrhages (9).

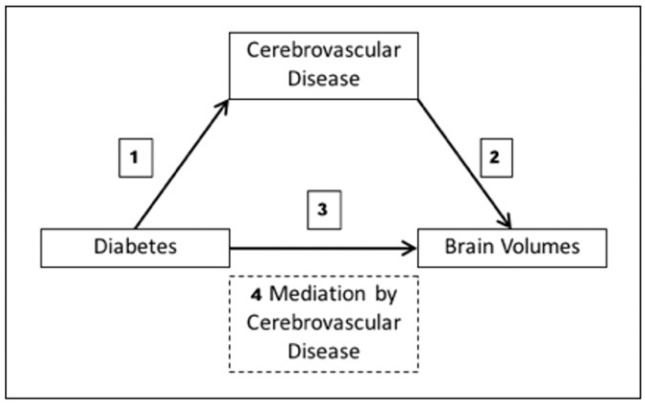
The following brain volumes were used as outcomes in our analyses: total brain volume, lobar volumes (frontal, parietal, temporal, and occipital), deep gray subcortical structure volume (defined as the total volume of the thalamus, caudate, putamen, and globus pallidum), total volume of an Alzheimer disease signature region (defined as the total volume of parahippocampal, entorhinal, and inferior parietal lobules; hippocampus; precuneus; and cuneus) (22), and hippocampal volume.

Statistical Analysis

Characteristics of the study population at visit 5 (2011–2013) are shown by diabetes-HbA_{1c} category. To compare across diabetes-HbA_{1c} categories, *t* tests or *P* values for linear trend were used to compare means for continuous variables, and χ^2 tests were used to compare proportions for categorical variables. Adjusted linear and logistic regression models were used to assess the associations of diabetes-HbA_{1c} categories with brain volumes and subclinical cerebrovascular disease. All analyses incorporated sampling weights to account for the ARIC brain MRI sampling strategy; therefore, all analyses represent an estimation of associations in the entire ARIC visit 5 (2011–2013) population. In linear regression analyses for brain volumes, each brain volume was scaled on the basis of its SD to facilitate comparison of the magnitude of association across brain regions. WMH volume was log base 2 ($\log_2$) transformed for normality. In analyses stratified by diagnosed diabetes status (defined by self-reported physician diagnosis or medication use), we also modeled the association of continuous HbA_{1c} with total brain volume by using a restricted cubic spline with four knots placed at the 5th, 35th, 65th, and 95th percentiles (23). Secondary analyses were done to investigate associations of HbA_{1c} and diabetes duration categories with brain volumes and markers of subclinical cerebrovascular disease among participants with diabetes (*n* = 602).

To assess whether associations of diabetes with smaller brain volumes are mediated by cerebrovascular disease, we used mediation pathway methods (24). In this analysis, we examined relationships between diabetes and MRI markers of cerebrovascular disease (path 1 in Fig. 1*A*), between MRI markers of cerebrovascular disease and brain volumes (path 2 in Fig. 1*A*), and between diabetes and brain volumes (path 3 in Fig. 1*A*). Finally, we assessed whether relationships between diabetes and brain volumes were attenuated when also adjusted for MRI markers of cerebrovascular disease. We formally calculated mediation estimates from indirect effects (the difference between estimates obtained when looking at the associations of diabetes with brain volumes [total effect; path 3] and estimates obtained when further adjusted for cerebrovascular disease

A



B

	Unmediated Associations (Base Model) β (95% CI)	Base Model + WMH β (95% CI)	Mediation Estimate β (95% CI)
Total brain volume	**-0.044 (-0.067, -0.021)**	**-0.041 (-0.063, -0.018)**	-0.003 (-0.008, 0.001)
Frontal lobe volume	**-0.041 (-0.070, -0.011)**	**-0.036 (-0.065, -0.007)**	-0.005 (-0.010, 0.000)
Temporal lobe volume	**-0.036 (-0.067, -0.004)**	-0.028 (-0.060, 0.003)	-0.007 (-0.015, 0.001)
Occipital lobe volume	**-0.050 (-0.084, -0.017)**	**-0.046 (-0.079, -0.012)**	-0.005 (-0.010, 0.001)
Parietal lobe volume	**-0.053 (-0.082, -0.024)**	**-0.050 (-0.078, -0.021)**	-0.004 (-0.008, 0.000)
Deep gray matter volume	**-0.052 (-0.091, -0.013)**	**-0.060 (-0.098, -0.022)**	0.008 (-0.001, 0.017)
Alzheimer disease signature region volume	**-0.041 (-0.072, -0.010)**	**-0.037 (-0.068, -0.006)**	-0.004 (-0.008, 0.000)
Hippocampal volume	-0.025 (-0.068, 0.017)	-0.020 (-0.062, 0.022)	-0.005 (-0.012, 0.001)

Figure 1—Boldface data represent significance at the $P < 0.05$ level. Mediation model to assess whether the associations of diabetes with brain volumes are mediated by cerebrovascular disease. *A*: If mediation by brain vascular pathology is present, paths 1–3 should be significantly associated and path 3 should be attenuated when also adjusted for the potential mediation (path 4). *B*: Weighted models adjusted for age, sex, race/field center, education, smoking status, hypertension, cardiovascular disease, APOE ε4 genotype, and total intracranial volume.

[direct effects, path 4] by using structural equation models when significant associations were seen for paths 1, 2, and 3 [Fig. 1]) (24).

All covariates used in the regression models were assessed at visit 5 (2011–2013) unless otherwise specified. Covariates were age (years), sex (male, female), race/field center (Maryland whites; Minnesota whites; North Carolina whites; North Carolina blacks; Mississippi blacks), education (less than high school, high school or equivalent, college or graduate or professional school as assessed at visit 1 [1987–1989]), cigarette smoking status (current, former, never, not reported), hypertension (systolic blood pressure ≥140 mmHg, diastolic blood pressure ≥90 mmHg by self-report of physician diagnosis or hypertension medication use), cardiovascular disease (history of coronary artery disease, myocardial infarction, coronary artery bypass surgery, and/or angioplasty, including previous reviewer-adjudicated events during ARIC follow-up), and total intracranial volume (in cubic centimeters; included in models where outcome is volume).

All reported *P* values were based on two-sided tests, and $P < 0.05$ was considered statistically significant. Analyses were performed with Stata/SE 13 software (StataCorp, College Station, TX).

RESULTS

Study Population Characteristics

Overall, the mean age of participants was 75 years, 60% were women, 27% were black, 30% had prediabetes (HbA_{1c} 5.7 to <6.5%), and 35% had diabetes. Compared with participants without diabetes and HbA_{1c} <5.7%, those with prediabetes (HbA_{1c} 5.7 to <6.5%) were of similar age (75.2 vs. 75.0 years; $P = 0.551$), were more likely to be black (24% vs. 11%; $P < 0.001$), have less than a high school education (11% vs. 7%; $P = 0.017$), and have hypertension (71% vs. 63%; $P = 0.012$) (Table 1). Among participants with diabetes, those with HbA_{1c} <7.0% versus ≥7.0% were of similar age (75.4 vs. 75.1 years; $P = 0.481$), but those with diabetes and HbA_{1c} ≥7.0% were more likely to be black (39% vs. 28%; $P = 0.020$) and to have less than a high school education (23% vs. 16%; $P = 0.031$) and were more likely to have a longer duration of diabetes (12 vs. 8 years; $P < 0.001$).

Associations of Prediabetes/Diabetes-HbA_{1c} Categories With Brain Volumes and Markers of Subclinical Cerebrovascular Disease

Compared with participants without diabetes and HbA_{1c} <5.7%, those with diabetes and HbA_{1c} ≥7.0% had smaller total brain volume (β −0.20 SDs; 95% CI −0.31, −0.09) and smaller regional brain volumes, including frontal, temporal, occipital, and parietal lobes; deep gray matter; Alzheimer disease signature region; and hippocampus (all $P < 0.05$) (Table 2). Compared with participants with diabetes and HbA_{1c} <7.0%, those with diabetes and HbA_{1c} ≥7.0% had smaller total brain volume ($P < 0.001$), frontal lobe volume ($P = 0.012$), temporal lobe volume ($P = 0.012$), occipital lobe volume ($P = 0.008$), parietal lobe volume ($P = 0.015$), deep gray matter volume ($P < 0.001$), Alzheimer disease signature region volume (0.031), and hippocampal volume ($P = 0.016$). Both participants with diabetes and HbA_{1c} <7.0% and those with prediabetes (HbA_{1c} 5.7 to <6.5%) had similar total and regional brain volumes compared with participants without diabetes and HbA_{1c} <5.7% (all $P > 0.05$). The continuous association of HbA_{1c} (stratified by self-reported diabetes status) with total brain volume is shown in Supplementary Fig. 1. In sensitivity analyses, adding a separate category for individuals with undiagnosed diabetes (Supplementary Table 3), compared with participants without diabetes and HbA_{1c} <5.7%, those with undiagnosed diabetes ($n = 37$) had similar brain volumes (all $P > 0.05$).

No differences in the presence of lobar microhemorrhages, subcortical microhemorrhages, cortical infarcts, and lacunar infarcts were observed among the diabetes-HbA_{1c} categories (all $P > 0.05$) (Table 2). Compared with participants without diabetes and HbA_{1c} <5.7%, those with diabetes and HbA_{1c} ≥7.0% had increased WMH volume ($P = 0.016$). The WMH volume among participants with diabetes and HbA_{1c} ≥7.0% was also significantly greater than among those with diabetes and HbA_{1c} <7.0% ($P = 0.017$).

In sensitivity analyses wherein prediabetes/diabetes categories were defined by fasting glucose among 1,639 participants who fasted at least 8 h, results overall were similar in pattern to the main analyses that used HbA_{1c} but were attenuated (Supplementary Table 4). Compared with participants without diabetes and fasting glucose <100 mg/dL, those with prediabetes (fasting glucose 100 to <126 mg/dL) had similar brain volumes and markers of cerebrovascular disease (all $P > 0.05$), whereas those with diabetes and fasting glucose <150 mg/dL had smaller total brain volume (β −0.09 SDs; 95% CI −0.16, −0.02), and those with diabetes and fasting glucose ≥150 mg/dL had smaller total brain volume (β −0.15 SDs; 95% CI −0.25, −0.04), deep gray matter volume (β −0.32 SDs; 95% CI −0.49, −0.15), and hippocampal volume (β −0.27 SDs; 95% CI −0.45, −0.10).

Associations of Diabetes Duration Categories With Brain Volumes and Markers of Subclinical Cerebrovascular Disease Among Participants With Diabetes

The characteristics of the 602 participants with diabetes are shown stratified by diabetes duration category in Supplementary Table 5. Those with diabetes duration ≥10 years were older than those with diabetes duration <10 years (75.9 vs. 75.0 years; $P = 0.041$) but were similar in terms of race and sex (all $P > 0.05$). Compared with participants with diabetes duration <10 years, those with diabetes duration ≥10 years has smaller adjusted total brain volume (β −0.13 SDs; 95% CI −0.20, −0.05) and smaller temporal lobe (β −0.14 SDs; 95% CI −0.24, −0.03), parietal lobe (β −0.11 SDs; 95% CI −0.21, −0.01), and hippocampal (β −0.16 SDs; 95% CI −0.30, −0.02) volumes (Table 3). Participants with diabetes duration ≥10 years also had a 2.44 times increased odds (95% CI 1.46, 4.05) of lacunar infarcts compared with those with diabetes duration <10 years (Table 3). In sensitivity analyses, adding a separate category for individuals with undiagnosed diabetes ($n = 37$) (Supplementary Table 6), compared with participants with diagnosed diabetes, those with diagnosed diabetes and duration <10 years had smaller frontal lobe volumes (β −0.23 SDs; 95% CI −0.43, −0.03) and a 3.13 times increased odds (95% CI 1.11, 8.88) of subcortical microhemorrhages. Those with diagnosed diabetes and duration ≥10 years had smaller total brain; frontal, temporal, and parietal lobe; and Alzheimer disease signature

Table 1—Weighted participant characteristics by diabetes and HbA_{1c} category, ARIC visit 5 (2011–2013) (n = 1,713)

	No diabetes (HbA_{1c} <5.7%)	Prediabetes (HbA_{1c} 5.7 to <6.5%)	Diabetes		P value‖
			HbA_{1c} <7.0%	HbA_{1c} ≥7.0%	
Patients (n)	597	514	448	154	
Mean age (years)	75.0	75.2	75.4	75.1	0.654
Female sex (%)	59.7	61.7	64.4	60.4	0.595
Race/field center (%)					<0.001
White/Minneapolis, MN	35.1	29.4	25.4	19.6	
White/Washington County, MD	29.1	21.4	31.1	29.6	
White/Forsyth County, NC	25.1	25.1	15.6	12.0	
Black/Forsyth County, NC	0.3	1.8	3.3	1.0	
Black/Jackson, MS	10.5	22.3	24.5	37.9	
Education* (%)					<0.001
Less than high school	6.6	10.6	15.8	23.0	
High school, GED, or vocational school	40.0	40.3	40.6	44.8	
College or graduate or professional school	53.4	49.1	43.6	32.2	
Smoking status (%)					0.417
Never	44.6	42.8	36.7	39.5	
Former	47.2	46.2	52.1	50.1	
Current	3.3	5.9	5.3	4.1	
Not reported	4.9	5.1	5.9	6.3	
Hypertension (%)	62.6	71.4	84.2	83.3	<0.001
Hyperlipidemia (%)	51.8	60.5	68.8	73.0	<0.001
History of cardiovascular disease (%)	5.2	8.4	8.8	8.4	0.127
Atrial fibrillation (%)	4.0	2.8	6.3	4.3	0.124
Mean diabetes duration (years)	–	–	8.2	12.1	<0.001
APOE ε4 genotype (%)					0.763
0 alleles	71.2	73.8	73.7	71.1	
1 or 2 alleles	28.8	26.2	26.3	28.9	
Mean volume† (cm^3)					
Total brain	1,030.1	1,027.8	1,021.4	1,003.4	<0.001
Frontal lobe	152.3	152.2	150.8	148.4	<0.001
Temporal lobe	103.8	103.6	102.8	101.1	<0.001
Occipital lobe	41.7	41.0	40.8	39.6	<0.001
Parietal lobe	108.4	107.7	106.6	104.4	<0.001
Deep gray matter‡	30.1	30.3	30.2	29.3	<0.001
Alzheimer disease signature region§	60.5	60.1	59.6	58.5	<0.001
Hippocampus	7.0	7.1	7.0	6.8	<0.001
Markers of subclinical cerebrovascular disease (%)					
Lobar microhemorrhages	6.2	9.9	5.6	8.3	0.089
Subcortical microhemorrhages	17.8	17.7	16.1	21.7	0.621
Cortical infarcts	7.2	10.8	8.2	9.4	0.260
Lacunar infarcts	14.4	16.8	13.3	23.4	0.067
Median WMH volume† (cm^3)	9.7	10.2	10.4	12.9	0.026

GED, general education development. ‖P value represents P linear trend across the median of HbA_{1c} levels for each diabetes and HbA_{1c} category for continuous variables and represents the χ^2 P value for categorical variables. *Assessed at ARIC visit 1 (1987–1989). †Adjusted for total intracranial volume. ‡Defined as thalamus + putamen + caudate + globus pallidus. §Defined as hippocampus + parahippocampal + entorhinal + inferior parietal lobule + precuneus + cuneus.

region volumes and an increased odds of subcortical microhemorrhages and lacunes compared with the individuals with undiagnosed diabetes (all $P < 0.05$).

Mediation Analyses

As shown in Table 2, the diabetes and HbA_{1c} ≥7.0% category was associated with smaller total and regional brain volumes (path 3 in Fig. 1*A*) and with increased WMH burden but not with any other marker of subclinical cerebrovascular disease (path 1 in Fig. 1*A*). Additional analyses showed that WMH burden was significantly associated with

Table 2—Weighted adjusted* cross-sectional associations of diabetes and HbA_{1c} categories with brain MRI parameters, ARIC visit 5 (2011–2013) (*n* = 1,713)

	No diabetes (HbA_{1c} <5.7%)	Prediabetes (HbA_{1c} 5.7 to <6.5%)	Diabetes	
			HbA_{1c} <7.0%	HbA_{1c} ≥7.0%
Patients (*n*)	597	514	448	154
Volumes†, β (95% CI)				
Total brain	0 (Reference)	0.01 (−0.05, 0.08)	−0.02 (−0.08, 0.04)	**−0.20 (−0.31, −0.09)‡**
Frontal lobe	0 (Reference)	0.03 (−0.05, 0.11)	−0.01 (−0.09, 0.07)	**−0.15 (−0.26, −0.04)‡**
Temporal lobe	0 (Reference)	0.02 (−0.06, 0.10)	0.01 (−0.07, 0.09)	**−0.16 (−0.29, −0.02)‡**
Occipital lobe	0 (Reference)	−0.04 (−0.14, 0.06)	−0.03 (−0.14, 0.07)	**−0.22 (−0.36, −0.08)‡**
Parietal lobe	0 (Reference)	0.02 (−0.06, 0.10)	−0.02 (−0.10, 0.06)	**−0.15 (−0.26, −0.04)‡**
Deep gray matter	0 (Reference)	0.05 (−0.06, 0.16)	0.02 (−0.08, 0.13)	**−0.28 (−0.42, −0.14)‡**
Alzheimer disease signature region	0 (Reference)	0.01 (−0.07, 0.09)	−0.02 (−0.11, 0.06)	**−0.16 (−0.28, −0.03)‡**
Hippocampus	0 (Reference)	0.04 (−0.07, 0.15)	0.00 (−0.11, 0.12)	**−0.21 (−0.38, −0.03)‡**
Markers of subclinical cerebrovascular disease, OR (95% CI)				
Lobar microhemorrhages	1 (Reference)	1.62 (0.93, 2.80)	0.91 (0.49, 1.68)	1.33 (0.61, 2.91)
Subcortical microhemorrhages	1 (Reference)	0.88 (0.60, 1.29)	0.78 (0.52, 1.18)	1.07 (0.65, 1.76)
Cortical infarcts	1 (Reference)	1.44 (0.86, 2.41)	1.02 (0.60, 1.75)	1.13 (0.57, 2.25)
Lacunar infarcts	1 (Reference)	1.10 (0.74, 1.62)	0.80 (0.53, 1.21)	1.61 (0.91, 2.83)
Log_2 WMH volume†, β (95% CI)	0 (Reference)	0.11 (−0.06, 0.29)	0.01 (−0.15, 0.17)	**0.29 (0.05, 0.52)‡**

Boldface data represent $P < 0.05$ compared with no diabetes and HbA_{1c} <5.7%. *Model adjusted for age, sex, race/field center, education, smoking status, hypertension, cardiovascular disease, APOE ε4 genotype, and total intracranial volume (when outcome is volume). †SD units. Definition of 1 SD: total brain volume 108.1 cm^3, frontal lobe volume 16.0 cm^3, temporal lobe volume 11.7 cm^3, occipital lobe volume 5.5 cm^3, parietal lobe volume 12.6 cm^3, deep gray matter volume 4.3 cm^3, Alzheimer disease signature region volume 7.0 cm^3, hippocampal volume 1.0 cm^3. ‡$P < 0.05$ for comparison of diabetes and HbA_{1c} ≥7.0% vs. diabetes and HbA_{1c} <7.0%.

all total and regional brain volumes (all $P < 0.05$) (path 2 in Fig. 1*A*). Therefore, we assessed by using structural equation models whether associations of diabetes with smaller brain volumes were mediated by WMH burden (Fig. 1*B*). We did not find any evidence at the $P < 0.05$ level that associations of diabetes and HbA_{1c} ≥7.0% with smaller brain volumes were mediated by WMH burden (all *P* values for indirect effects 0.072–0.081) (Fig. 1*B*).

CONCLUSIONS

In this community-based population, we found that ARIC-NCS participants with diabetes with HbA_{1c} ≥7.0% have smaller total and regional brain volumes and an increased burden of WMH, but those with prediabetes (HbA_{1c} 5.7 to <6.5%) and diabetes with HbA_{1c} <7.0% have brain volumes and markers of subclinical cerebrovascular disease similar to those without diabetes. Furthermore, among participants with diabetes, those with more-severe disease (as measured by higher HbA_{1c} and longer disease duration)

Table 3—Weighted adjusted* cross-sectional associations of diabetes duration categories with brain MRI parameters among participants with diabetes, ARIC visit 5 (2011–2013) (*n* = 602)

	Diabetes duration <10 years (*n* = 342)	Diabetes duration ≥10 years (*n* = 260)
Volumes†, β (95% CI)		
Total brain	0 (Reference)	**−0.13 (−0.20, −0.05)**
Frontal lobe	0 (Reference)	−0.04 (−0.15, 0.06)
Temporal lobe	0 (Reference)	**−0.14 (−0.24, −0.03)**
Occipital lobe	0 (Reference)	−0.08 (−0.20, 0.04)
Parietal lobe	0 (Reference)	**−0.11 (−0.21, −0.01)**
Deep gray matter	0 (Reference)	−0.12 (−0.25, 0.02)
Alzheimer disease signature region	0 (Reference)	−0.10 (−0.20, 0.01)
Hippocampus	0 (Reference)	**−0.16 (−0.30, −0.02)**
Markers of subclinical cerebrovascular disease, OR (95% CI)		
Lobar microhemorrhages	1 (Reference)	1.03 (0.50, 2.12)
Subcortical microhemorrhages	1 (Reference)	1.13 (0.69, 1.85)
Cortical infarcts	1 (Reference)	1.47 (0.76, 2.85)
Lacunar infarcts	1 (Reference)	**2.44 (1.46, 4.05)**
Log_2 WMH volume†, β (95% CI)	0 (Reference)	0.18 (−0.03, 0.39)

Boldface data represent $P < 0.05$. *Model adjusted for age, sex, race/field center, education, smoking status, hypertension, cardiovascular disease, APOE ε4 genotype, and total intracranial volume (when outcome is volume). †SD units. Definition of 1 SD: total brain volume 108.1 cm^3, frontal lobe volume 16.0 cm^3, temporal lobe volume 11.7 cm^3, occipital lobe volume 5.5 cm^3, parietal lobe volume 12.6 cm^3, deep gray matter volume 4.3 cm^3, Alzheimer disease signature region volume 7.0 cm^3, hippocampal volume 1.0 cm^3.

had smaller total and regional brain volumes and an increased burden of cerebrovascular disease compared with those with lower HbA_{1c} and shorter disease duration. However, we found no evidence that associations of diabetes with smaller brain volumes are mediated by cerebrovascular disease.

The findings of this study extend the current literature that suggests that diabetes is strongly associated with brain volume loss (11,25–27). Global brain volume loss (11,25–27) has been consistently reported, but associations of diabetes with smaller specific brain regions have been less robust (27,28). Similar to prior studies, the current results show that compared with individuals without diabetes, those with diabetes have smaller total brain volume (11,25–27) and regional brain volumes, including frontal and occipital lobes, deep gray matter, and the hippocampus (25,27). Furthermore, the current study suggests that greater severity of disease (as measured by HbA_{1c} and diabetes duration) is associated with smaller total and regional brain volumes. These results are consistent with some prior studies that have included measures of disease severity (11,12) but not others (28). The current study found that participants with prediabetes and those with diabetes and HbA_{1c} <7.0% had total and regional brain volumes similar to those without diabetes, suggesting that the effects of diabetes on brain volumes are primarily driven by disease severity (higher HbA_{1c} and longer duration). Mechanisms whereby diabetes may contribute to brain volume loss include accelerated amyloid-β and hyperphosphorylated tau deposition as a result of hyperglycemia (29). Another possible mechanism involves pancreatic amyloid (amylin) infiltration of the brain, which then promotes amyloid-β deposition (29). Few studies have specifically looked at associations of prediabetes (defined by HbA_{1c} and/or fasting glucose) with brain volumes. The Second Manifestations of Arterial Disease-Magnetic Resonance study reported associations of metabolic syndrome with smaller total brain volume (10); however, similar to the current study, the individual component of impaired glucose metabolism (prediabetes) was not associated with smaller total brain volume compared with normoglycemia.

Studies of diabetes with small vessel ischemic disease have shown inconsistent results, particularly for WMH (30,31), whereas associations of diabetes with lacunes have been slightly more consistent (32–35). One review on the topic of the association of diabetes with WMH (30) suggested that the inconsistencies across studies may be partially due to the advent of higher-resolution imaging and improved methodology to measure volumes of markers of cerebrovascular disease because the authors observed more significant associations between diabetes and WMH in studies that used quantitative volumetric MRI techniques versus those that used dichotomous or ordinal rating scales for WMH burden. Indeed, we used 3T MRI scanners with volumetric assessment of WMH burden and found significantly increased WMH burden among participants with diabetes, especially among those with more-severe disease as assessed by higher HbA_{1c}, compared with those without diabetes. The introduction of higher-resolution MRI has also allowed for the assessment of microhemorrhages. Similar to prior studies (36–38), we did not find significant associations of diabetes with either lobar or subcortical microhemorrhages.

Taken together, in contrast to prior work suggesting little or no association of diabetes with small vessel disease (11,31), the current results suggest that diabetes is associated with both lower brain volumes and increased cerebrovascular pathology (WMH and lacunes). However, we did not see evidence for mediation by markers of subclinical cerebrovascular disease in the associations between diabetes and smaller brain volumes. These findings have important implications for mechanisms underlying the observed associations of diabetes with both accelerated cognitive decline (1) and increased risk of dementia (2) and suggest that diabetes may lead to a higher prevalence of subclinical cerebrovascular disease and smaller brain volumes through independent mechanisms. In contrast to the current findings in diabetes, prior work in the entire ARIC-NCS cohort (39) found that relationships between markers of cerebrovascular disease on MRI and cognitive function are mediated by a process that affects brain volumes (perhaps microinfarcts not consistently visible by MRI), suggesting that cerebrovascular disease and brain volumes may have shared underlying pathophysiological mechanisms. Although our mediation analyses were not significant at the $P < 0.05$ level, the P values for mediation ranged from 0.072 to 0.081, suggesting that this study was underpowered to assess mediation effects. These mediation analyses should be interpreted with caution, and future studies should also investigate mediation by cerebrovascular disease in the associations of diabetes with brain volumes in larger populations.

Strengths of this study include a detailed assessment of covariates, diabetes, and indices of diabetes severity, including HbA_{1c} and diabetes duration, and >1,700 participants with brain MRI data. The current brain MRI data were obtained from 3T scanners and included total and regional brain volumes as well as microhemorrhages, cortical and lacunar infarcts, and WMH volumes. The study was limited by the inability to evaluate within-person changes in brain volumes and markers of subclinical cerebrovascular disease over time. Another important limitation of this cross-sectional study is the possibility of reverse causation, with participants with cognitive impairment and presumably smaller brain volumes and increased cerebrovascular disease being less compliant with medications and diet, which could then lead to poorer glycemic control. However, reverse causation is an unlikely explanation for the results given supporting evidence from prospective studies of diabetes and brain volumes and cerebrovascular disease showing associations with increased brain atrophy and increased burden of cerebrovascular lesions over time (14).

In conclusion, in this community-based population of ARIC-NCS participants, diabetes, but not prediabetes, was associated with smaller brain volumes. Furthermore, participants with more-severe diabetes (as assessed by higher HbA_{1c} and longer disease duration) had smaller brain volumes and an increased burden of WMH and lacunes than those with less-severe disease. We found no evidence that associations of diabetes with smaller brain volumes were mediated by cerebrovascular disease, suggesting that other mechanisms may be responsible for these associations. These findings have implications for mechanisms underlying the observed associations of diabetes with both accelerated cognitive decline and increased risk of

dementia, suggesting that both brain atrophy and small vessel ischemic disease may independently contribute, but additional prospective studies are needed to look directly at both cognitive function and brain imaging findings among individuals with and without diabetes over time.

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Author Contributions. A.L.C.S. performed the data analysis, contributed to the discussion, and wrote the manuscript. E.S., A.R.S., M.G., J.C., C.R.J., D.K., and T.M. contributed to the discussion and reviewed and edited the manuscript. R.F.G. performed the data analysis, contributed to the discussion, and reviewed and edited the manuscript. A.L.C.S. and R.F.G. are the guarantors of this work and, as such, had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

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