SUPPLEMENTARY DATA

Supplementary Table 1. Unweighted ARIC Visit 1 (1987-1989) Participant Characteristics Comparing Those Who Attended Versus Did Not Attend ARIC Visit 5 (N=15,792).

	Attended ARIC Visit 5 (n=6,538)	Did Not Attend ARIC Visit 5 (n=9,254)	P-Value*
Age (years), mean	52.1	55.6	<0.001
Female, %	58.8	52.6	<0.001
Race/field center, %			<0.001
Minneapolis, Minnesota whites	29.1	22.4	
Washington County, Maryland whites	26.8	24.0	
Forsyth County, North Carolina whites	20.3	23.8	
Forsyth County, North Carolina blacks	1.6	4.1	
Jackson, Mississippi blacks	21.7	25.0	
Education, %			<0.001
< High school	15.1	30.0	
High school, GED, or vocational school	41.5	40.0	
College, graduate, or professional school	43.2	29.8	
Smoking status, %			<0.001
Never	48.9	36.5	
Former	33.1	31.4	
Current	17.9	32.0	
Not reported	0.1	0.1	
Diabetes, %	6.0	16.2	<0.001
Hypertension, %	25.3	41.9	<0.001
Hyperlipidemia, %	22.7	28.7	<0.001
History of cardiovascular disease, %	1.9	7.1	<0.001
APOE ε4 Genotype, %			<0.001
0 APOE ε4 alleles	67.9	64.9	
1 or 2 APOE ε4 alleles	28.0	30.6	

*P-value represents t-test p-value for continuous variables and chi-square p-value for categorical variables.

Abbreviations: ARIC, Atherosclerosis Risk in Communities; GED, general education development; SD, standard deviation.

SUPPLEMENTARY DATA

Supplementary Table 2. Unweighted ARIC Visit 5 (2011-2013) Participant Characteristics Comparing Those Included Versus Excluded From Analyses Among ARIC Visit 5 Attendees, N=6,538.

	Excluded (n=4,825)	Included (n=1,713)	P-Value†
Age (years), mean	75.6	76.3	<0.001
Female, %	58.4	59.8	0.315
Race/field center, %			<0.001
Minneapolis, Minnesota whites	31.2	22.5	
Washington County, Maryland whites	26.9	26.2	
Forsyth County, North Carolina whites	19.3	23.6	
Forsyth County, North Carolina blacks	1.6	1.6	
Jackson, Mississippi blacks	20.1	26.0	
Education*, %			0.081
< High school	15.7	13.7	
High school, GED, or vocational school	41.5	41.4	
College, graduate, or professional school	42.6	45.0	
Smoking status, %			<0.001
Never	34.8	41.5	
Former	44.5	47.7	
Current	5.8	4.8	
Not reported	13.8	6.0	
Diabetes, %	32.6	31.0	0.784
HbA1c (%), mean	6.0	6.0	0.771
Hypertension, %	75.0	74.4	0.584
Hyperlipidemia, %	62.8	61.7	0.405
History of cardiovascular disease, %	17.2	8.5	<0.001
Atrial fibrillation, %	8.2	4.4	<0.001
APOE ε4 Genotype, %			0.845
0 APOE ε4 alleles	66.8	71.0	
1 or 2 APOE ε4 alleles	27.6	29.0	

*Assessed at ARIC visit 1 (1987-1989).

†P-value represents t-test p-value for continuous variables and chi-square p-value for categorical variables.

Abbreviations: ARIC, Atherosclerosis Risk in Communities; GED, general education development; HbA1c, glycated hemoglobin; SD, standard deviation.

SUPPLEMENTARY DATA

Supplementary Table 3. Weighted Adjusted* Cross-Sectional Associations of Pre-Diabetes/Undiagnosed Diabetes/Diagnosed Diabetes/HbA1c Categories with Brain MRI Parameters, ARIC Visit 5 (2011-2013), N=1713.

	No Diabetes	Pre-Diabetes	Undiagnosed Diabetes	Diagnosed Diabetes	
	HbA1c <5.7% (n=597)	HbA1c 5.7-< 6.5% (n=514)	HbA1c ≥6.5% (n=37)	HbA1c <7.0% (n=418)	HbA1c ≥7.0% (n=147)
Volumes**, β (95% CI)					
Total brain volume	0 (Reference)	0.01 (-0.05, 0.08)	0.05 (-0.08, 0.19)	-0.03 (-0.09, 0.03)	**-0.20 (-0.31, -0.10)**
Frontal lobe volume	0 (Reference)	0.03 (-0.05, 0.11)	0.12 (-0.08, 0.32)	-0.02 (-0.10, 0.06)	**-0.15 (-0.26, -0.04)**
Temporal lobe volume	0 (Reference)	0.02 (-0.06, 0.10)	0.10 (-0.05, 0.25)	0.00 (-0.09, 0.08)	**-0.16 (-0.30, -0.02)**
Occipital lobe volume	0 (Reference)	-0.04 (-0.14, 0.06)	-0.14 (-0.39, 0.10)	-0.03 (-0.13, 0.07)	**-0.21 (-0.35, -0.07)**
Parietal lobe volume	0 (Reference)	0.02 (-0.06, 0.10)	0.07 (-0.11, 0.26)	-0.02 (-0.11, 0.06)	**-0.16 -0.27, -0.04)**
Deep gray matter volume	0 (Reference)	0.05 (-0.06, 0.16)	-0.02 (-0.35, 0.31)	0.03 (-0.08, 0.13)	**-0.30 (-0.44, -0.15)**
Alzheimer disease signature region volume	0 (Reference)	0.01 (-0.07, 0.09)	0.07 (-0.12, 0.25)	-0.03 (-0.12, 0.06)	**-0.16 (-0.29, -0.03)**
Hippocampal volume	0 (Reference)	0.04 (-0.07, 0.15)	0.10 (-0.16, 0.35)	-0.01 (-0.12, 0.11)	**-0.22 (-0.40, -0.04)**
Markers of Subclinical Cerebrovascular Disease, OR (95% CI)					
Lobar microhemorrhages	1 (Reference)	1.62 (0.93, 2.80)	1.10 (0.30, 4.04)	0.90 (0.48, 1.70)	1.31 (0.58, 2.95)
Subcortical microhemorrhages	1 (Reference)	0.88 (0.60, 1.29)	**0.34 (0.13, 0.94)**	0.83 (0.55, 1.26)	1.07 (0.64, 1.79)
Cortical Infarcts	1 (Reference)	1.44 (0.86, 2.41)	0.94 (0.26, 3.41)	1.03 (0.60, 1.78)	1.13 (0.56, 2.27)
Lacunar infarcts	1 (Reference)	1.10 (0.74, 1.62)	**0.09 (0.01, 0.69)**	0.86 (0.57, 1.30)	1.70 (0.96, 3.02)
Log_2 WMH volume†, β (95% CI)	0 (Reference)	0.11 (-0.06, 0.28)	-0.23 (-0.69, 0.22)	0.04 (-0.13, 0.20)	**0.29 (0.05, 0.52)**

*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).

†Standard deviation units. Definition of 1 standard deviation: 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.

Bolded data represents p<0.05 compared to no diabetes and HbA1c <5.7%

SUPPLEMENTARY DATA

Supplementary Table 4. Weighted Adjusted* Cross-Sectional Associations of Pre-Diabetes/Diabetes/Fasting Glucose Categories with Brain MRI Parameters, ARIC Visit 5 (2011-2013), N=1639.

	No Diabetes	Pre-Diabetes	Diabetes	
	Fasting Glucose <100 mg/dl (n=427)	Fasting Glucose 100-<126 mg/dl (n=600)	Fasting Glucose <150 mg/dl (n=476)	Fasting Glucose ≥150 mg/dl (n=136)
Volumes†, β (95% CI)				
Total brain volume	0 (Reference)	-0.05 (-0.12, 0.01)	**-0.09 (-0.16, -0.02)**	**-0.15 (-0.25, -0.04)**
Frontal lobe volume	0 (Reference)	0.02 (-0.06, 0.10)	-0.05 (-0.13, 0.04)	-0.03 (-0.15, 0.09)
Temporal lobe volume	0 (Reference)	-0.02 (-0.10, 0.06)	-0.05 (-0.14, 0.04)	-0.09 (-0.22, 0.04)
Occipital lobe volume	0 (Reference)	-0.02 (-0.13, 0.08)	-0.06 (-0.18, 0.05)	-0.13 (-0.28, 0.02)
Parietal lobe volume	0 (Reference)	0.02 (-0.06, 0.10)	-0.03 (-0.12, 0.05)	-0.02 (-0.13, 0.10)
Deep gray matter volume	0 (Reference)	-0.03 (-0.15, 0.08)	-0.07 (-0.18, 0.05)	**-0.32 (-0.49, -0.15)**‡
Alzheimer disease signature region volume	0 (Reference)	0.00 (-0.09, 0.08)	-0.07 (-0.16, 0.02)	-0.04 (-0.17, 0.09)
Hippocampal volume	0 (Reference)	-0.06 (-0.17, 0.05)	-0.10 (-0.22, 0.02)	**-0.27 (-0.45, -0.10)**‡
Markers of Subclinical Cerebrovascular Disease, OR (95% CI)				
Lobar microhemorrhages	1 (Reference)	1.06 (0.63, 1.80)	0.58 (0.31, 1.11)	1.18 (0.59, 2.36)
Subcortical microhemorrhages	1 (Reference)	1.05 (0.71, 1.54)	0.88 (0.58, 1.34)	1.10 (0.64, 1.89)
Cortical Infarcts	1 (Reference)	1.22 (0.70, 2.14)	1.24 (0.69, 2.20)	1.18 (0.52, 2.67)
Lacunar infarcts	1 (Reference)	1.25 (0.82, 1.92)	0.98 (0.62, 1.54)	1.75 (0.93, 3.29)
Log_2 WMH volume†, β (95% CI)	0 (Reference)	0.10 (-0.08, 0.29)	0.10 (-0.08, 0.28)	0.10 (-0.14, 0.33)

*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).

†Standard deviation units. Definition of 1 standard deviation: 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.

Bolded data represents p<0.05 compared to no diabetes and fasting glucose <100 mg/dl.

‡P<0.05 for comparison of diabetes and fasting glucose ≥150 versus diabetes and fasting glucose <150 mg/dl.

SUPPLEMENTARY DATA

Supplementary Table 5. Weighted Participant Characteristics By Diabetes Duration Category Among those with Diabetes, ARIC Visit 5 (2011-2013), N=602.

	Diabetes Duration <10 Years (n=342)	Diabetes Duration ≥10 Years (n=260)	P-Value‖
Age (years), mean	75.0	75.9	0.041
Female, %	61.7	65.9	0.344
Race/field center, %			0.476
Minneapolis, Minnesota whites	26.0	21.2	
Washington County, Maryland whites	29.8	32.1	
Forsyth County, North Carolina whites	14.5	15.2	
Forsyth County, North Carolina blacks	1.7	4.3	
Jackson, Mississippi blacks	28.1	27.1	
Education*, %			0.395
< High school	15.7	20.2	
High school, GED, or vocational school	43.4	38.9	
College, graduate, or professional school	40.8	40.9	
Smoking status, %			0.562
Never	35.1	40.7	
Former	53.2	49.4	
Current	4.9	5.1	
Not reported	6.9	11.4	
Hypertension, %	81.6	87.5	0.100
Hyperlipidemia, %	64.1	78.0	0.002
History of cardiovascular disease, %	6.9	11.4	0.074
Atrial fibrillation, %	7.2	3.8	0.115
HbA1c (%), mean	6.3	6.9	<0.001
APOE ε4 Genotype, %			0.638
0 APOE ε4 alleles	73.9	71.9	
1 or 2 APOE ε4 alleles	26.1	28.1	
Volumes† (cm^3), mean			
Total brain volume	1011.7	992.6	<0.001
Frontal lobe	148.8	147.7	0.015
Temporal lobe	102.2	99.8	<0.001
Occipital lobe	40.3	39.6	0.006
Parietal lobe	105.5	103.5	<0.001
Deep gray matter‡	29.9	29.4	0.002
Alzheimer disease signature region§	59.1	58.0	0.001
Hippocampal	7.0	6.8	<0.001
Markers of Subclinical Cerebrovascular Disease			
Lobar microhemorrhages, %	6.1	6.6	0.810
Subcortical microhemorrhages, %	17.2	17.8	0.868
Cortical infarcts, %	6.9	10.7	0.130
Lacunar infarcts, %	10.7	23.0	<0.001
WMH volume† (cm^3), median	9.8	12.2	0.021

SUPPLEMENTARY DATA

*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.
||P-value represents t-test p-value for continuous variables and chi-square p-value for categorical variables.
Abbreviations: ARIC, Atherosclerosis Risk in Communities; GED, general education development; HbA1c, glycated hemoglobin; SD, standard deviation.

SUPPLEMENTARY DATA

Supplementary Table 6. Weighted Adjusted* Cross-Sectional Associations of Diabetes Duration Categories with Brain MRI Parameters Among Those with Undiagnosed and Diagnosed Diabetes, ARIC Visit 5 (2011-2013), N=602.

	Undiagnosed Diabetes (n=37)	Diagnosed Diabetes Duration <10 Years (n=305)	Diagnosed Diabetes Duration ≥10 Years (n=260)
Volumes†, β (95% CI)			
Total brain volume	0 (Reference)	-0.11 (-0.26, 0.03)	**-0.19 (-0.34, -0.05)**
Frontal lobe volume	0 (Reference)	**-0.23 (-0.43, -0.03)**	**-0.22 (-0.43, -0.02)**
Temporal lobe volume	0 (Reference)	-0.13 (-0.29, 0.04)	**-0.22 (-0.39, -0.05)**
Occipital lobe volume	0 (Reference)	0.07 (-0.18, 0.32)	0.02 (-0.23, 0.27)
Parietal lobe volume	0 (Reference)	-0.15 (-0.34, 0.04)	**-0.23 (-0.43, -0.04)**
Deep gray matter volume	0 (Reference)	-0.07 (-0.42, 0.27)	-0.11 (-0.46, 0.24)
Alzheimer disease signature region volume	0 (Reference)	-0.15 (-0.34, 0.05)	**-0.21 (-0.41, -0.01)**
Hippocampal volume	0 (Reference)	-0.13 (-0.40, 0.13)	-0.23 (-0.50, 0.03)
Vascular Pathology, OR (95% CI)			
Lobar microhemorrhages	1 (Reference)	1.08 (0.26, 4.47)	1.01 (0.25, 4.19)
Subcortical microhemorrhages	1 (Reference)	**3.13 (1.11, 8.88)**	**3.11 (1.09, 8.88)**
Cortical Infarcts	1 (Reference)	0.93 (0.26, 3.36)	1.36 (0.38, 4.92)
Lacunar infarcts	1 (Reference)	6.86 (0.84, 56.16)	**13.42 (1.62, 111.39)**
log2(WMH volume)†, β (95% CI)	0 (Reference)	0.22 (-0.19, 0.62)	0.40 (-0.02, 0.82)

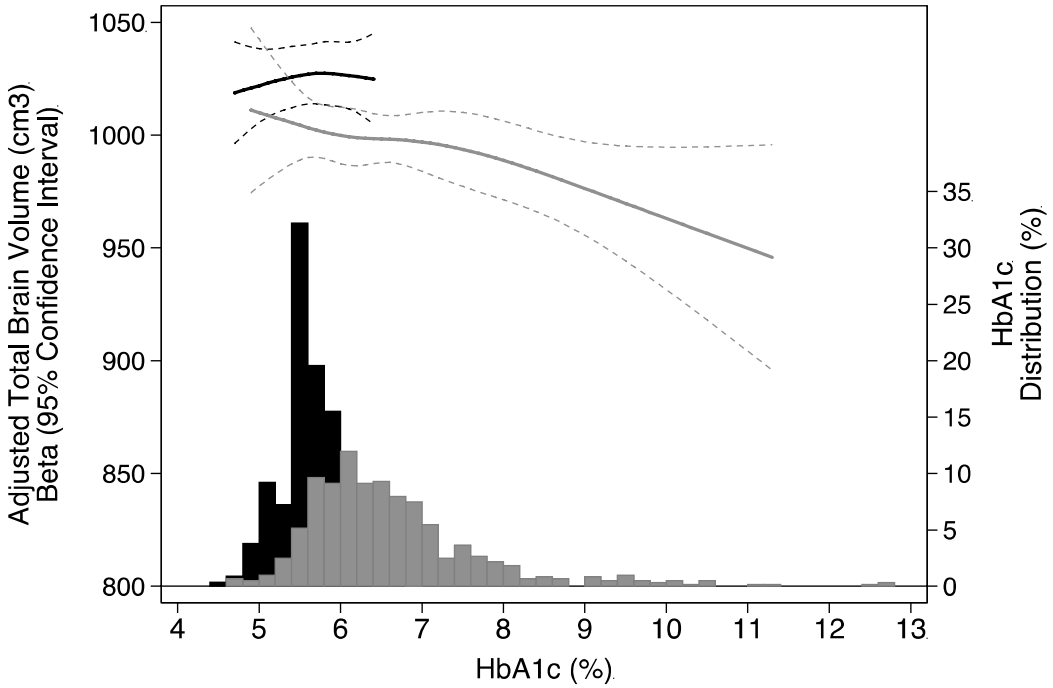
*Model adjusted for age, sex, race/field center, education, smoking status, hypertension, cardiovascular disease, APOE ε4 genotype, and total intracranial volume (when outcome is volume).

†Standard deviation units. Definition of 1 standard deviation: 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.

Bolded data represents $p<0.05$.

SUPPLEMENTARY DATA

Supplementary Figure 1. Weighted Adjusted* Restricted Cubic Spline Model Showing the βs (95% Confidence Intervals) for the Association of HbA1c with Total Brain Volume (cm^3), ARIC Visit 5 (2011-2013), N=1713.



The solid lines represent the βs and the dashed lines represent the 95% confidence intervals. Knots are at 5th, 35th, 65th, and 95th percentiles. Restricted cubic splines are centered at the 10th percentile and truncated at 0.5th and 99.5th percentile of the HbA1c distribution. Histogram shows the distribution of concentrations of HbA1c.

*Model adjusted for age, sex, race/field center, education, smoking status, hypertension, cardiovascular disease, APOE ε4 genotype, and total intracranial volume.