Relation of Dysglycemia to Structural Brain Changes in a Multiethnic Elderly Cohort

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OBJECTIVES: Abnormally high glucose levels (dysglycemia) increase with age. Epidemiological studies suggest that dysglycemia is a risk factor for cognitive impairment but the underlying pathophysiological mechanisms remain unclear. The objective of this study was to examine the relation of dysglycemia clinical categories (normal glucose tolerance (NGT), pre-diabetes, undiagnosed diabetes, known diabetes) with brain structure in older adults. We also assessed the relation between dysglycemia and cognitive performance.

DESIGN: Cross-sectional and longitudinal cohort study.

SETTING: Northern Manhattan (Washington Heights, Hamilton Heights, and Inwood).

PARTICIPANTS: Medicare recipients 65 years and older.

MEASUREMENTS: Dysglycemia categories were based on HBA1c or history of type 2 diabetes (diabetes). Brain structure (brain infarcts, white matter hyperintensities (WMH) volume, total gray matter volume, total white matter volume, total hippocampus volume) was assessed with brain magnetic resonance imaging; cognitive function (memory, language and visuospatial function, speed) was assessed with a validated neuropsychological battery.

RESULTS: Dysglycemia, defined with HbA1c as a continuous variable or categorically as pre-diabetes and diabetes, was associated with a higher number of brain infarcts, WMH volume and decreased total white matter, gray matter and hippocampus volumes cross-sectionally, and a significant decline in gray matter volume longitudinally. Dysglycemia was also associated with lower performance in language, speed and visuospatial function although these associations were attenuated when adjusted for education, APOE-ε4, ethnic group and vascular risk factors.

CONCLUSION: Our results suggest that dysglycemia affects brain structure and cognition even in elderly survivors, evidenced by higher cerebrovascular disease, lower white and gray matter volume, and worse language and visuospatial function and cognitive speed. **J Am Geriatr Soc 2016.**

Key words: dysglycemia; structural brain changes; cognition

Dysglycemia, defined as the presence of type 2 diabetes (diabetes) or pre-diabetes, is one of the most common public health problems in the United States. According to 2011 prevalence data from the Centers for Disease Control and Prevention (CDC), diabetes affects 25.8 million people in the United States, corresponding to 8.3% of the total U.S. population, while 79 million have pre-diabetes, more than a quarter of the U.S. population.[1] This problem is more common in the elderly, the group also at highest risk for cognitive impairment. In 2010, 26.9% of the population 65 years and older had diabetes, another 50% of elderly had pre-diabetes as measured by fasting glucose or hemoglobin A1c (HBA1c) levels and the prevalence of diabetes and pre-diabetes is trending upward.[2] An estimated 5.2 million Americans have late-onset Alzheimer's disease (LOAD) with an annual incidence rate increasing from 1% at ages 60 years to 8% at ages 85 years and older.[3]

Epidemiological studies suggest that diabetes, and several diabetes-related factors are risk factors for cognitive decline,[4] mild cognitive impairment (MCI),[5] and dementia,[6] but the underlying structural correlates and pathophysiological mechanisms remain unclear. Diabetes is related to a higher risk of cerebrovascular disease,[7] including high white matter hyperintensities (WMH) volume,[8] and infarcts. A limitation of most epidemiological studies examining this question is that persons without diabetes

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are treated as having normal glycemia, without taking into account whether they have undiagnosed diabetes or pre-diabetes. This can potentially attenuate the association between diabetes and cognition outcomes because pre-diabetes and undiagnosed diabetes may also be associated with brain structure and cognitive abnormalities.

The objective of the current study was to examine the relation of dysglycemia with various structural brain changes in a cohort of 618 nondemented elderly from the multiethnic Washington Heights Inwood Columbia Aging Project (WHICAP). In secondary analyses, we also assessed the relation between dysglycemia and cognitive performance in this brain-imaging sample.

METHODS

Subjects

The sample for this analysis was subjects from WHICAP who underwent brain imaging, were assessed for dysglycemia by testing for HbA1c or based on clinical records, and did not have dementia at the time of brain imaging.

Participants were selected from a cohort participating in the prospective study of aging and dementia in Medicare recipients, 65 years and older and residing in northern Manhattan. The cohort was recruited in two waves, in 1992 and 1999, and followed up at regular intervals of 18 to 24 months. The sampling strategies and recruitment outcomes have been described in detail.[9] Magnetic resonance imaging (MRI) was obtained in 769 participants. Participants were deemed eligible for MRI if they did not meet criteria for dementia at the visit (2002–2004) before the second follow-up (2005–2007), when brain imaging was performed. Of the 769 persons with MRI, 52 were excluded due to dementia at the time of MRI, and 99 due to no information on dysglycemia variables (diabetes history, HbA1c). The final sample comprised 618 nondemented participants, of whom 292 had a follow-up MRI conducted approximately 4 years (2 follow-up intervals) later (Figure 1). Recruitment, informed consent, and study procedures were approved by the institutional review boards of Columbia University Medical Center and Columbia University Health Sciences and the New York State Psychiatric Institute.

Measures of Dysglycemia and Other Covariates

HbA1C was measured by boronate affinity chromatography with the Primus CLC 385 (Primus, Kansas City, MO). "Dysglycemia" categories were defined based on HBA1C levels following American Diabetes Association guidelines[10] as follows: (1) normal glucose tolerance (NGT; HbA1c < 5.7%); (2) pre-diabetes (HbA1c 5.7–6.49%); (3) undiagnosed diabetes (HbA1c of 6.5% or higher); (4) known diabetes. Known diabetes was defined by self-report at baseline and at each follow-up interval and by the use of disease-specific medications. At baseline, all participants were also asked whether or not they had a history of hypertension any time during their life. If affirmative, they were asked whether or not they were under treatment and the specific type of treatment. Blood pressure was also recorded at each visit. The blood pressure cuff was placed on the right arm while the individual was seated, and a recording was obtained every 3 minutes over 9 minutes. The third measurement was recorded in the database. Values above 140 mm Hg (systolic) and 90 mm Hg (diastolic) were used as criteria for hypertension. Body mass index (BMI) was calculated using the formula BMI = mass (kg)/(height (m))^2. Fasting plasma total cholesterol and triglyceride levels were determined using standard techniques. High-density lipoprotein cholesterol (HDL-C) levels were determined after precipitation of apolipoprotein B containing lipoproteins with phosphotungstic acid. Low-density lipoprotein cholesterol was recalculated using the formula of Friedewald et al.[11] Non-HDL cholesterol levels were calculated using the following formula: non-HDL-C = total cholesterol − HDL-C. At baseline, all participants were asked if they had ever been treated with statins. For assessment of smoking habit, a trigger question asked whether or not the individual ever smoked at least 1 cigarette per day for a period of 1 year or more. If the answer to the trigger question was no, the subject was classified as a nonsmoker and no further

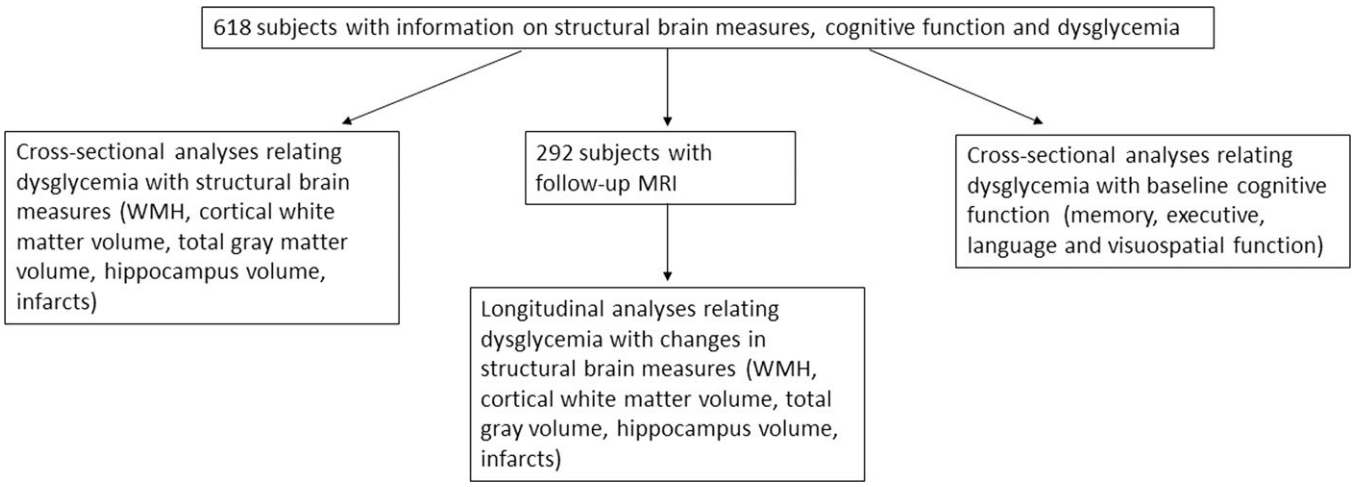

Figure 1. Project flow.

questions were asked. Participants who answered the question affirmatively were classified as current smokers if they were still smoking or past smokers if they had quit smoking. Current and past smokers were additionally asked at what age they began smoking and how many cigarettes on average they had smoked or still smoked per day. Past smokers were also asked at what age they stopped smoking. APOE genotypes were determined as described by Hixson and Vernier[12] with slight modification. We classified persons as homozygous or heterozygous for the APOE $\varepsilon 4$ allele or as not having any $\varepsilon 4$ allele.

MRI Protocol

Scan acquisition was performed on a 1.5T Philips Intera scanner at Columbia University Medical Center. T1-weighted (TR = 20 ms, TE = 2.1 ms, FOV 240 cm, 256 × 160 matrix, 1.3 mm slice thickness) and T2-weighted fluid attenuated inversion recovery (FLAIR; TR = 11,000 ms, TE = 144.0 ms, inversion time = 2,800, FOV 25 cm, 2 nex, 256 × 192 matrix with 3 mm slice thickness) images were acquired in the axial orientation. Scan acquisition sequence parameters were identical for the second MRI scan, which was performed on the same scanner.

Total gray matter, total white matter, hippocampus, and total intracranial volumes were derived with FreeSurfer version 5.1 (http://surfer.nmr.mgh.harvard.edu/) applied to the T1-weighetd MRI scans. Each segmented image was visually inspected by an expert operator and manually corrected if necessary. Volumes from left and right hippocampi were averaged to yield a single hippocampal volume measurement.

Regional WMH volumes were derived as described previously.[13] Briefly, FLAIR images were skull stripped, a Gaussian curve was fit to map the voxel intensity values, and values falling above 3.0 SD the image mean were labeled as WMH. Labeled images were inspected and corrected manually in the event of false positive or false negative labels.

The presence or absence of brain infarction on MRI was determined using all available images, as previously described.[14] Only lesions ≥3 mm qualified for consideration as brain infarcts.

Clinical Assessment

At each follow-up evaluation, each participant underwent an assessment of medical history, a physical/neurological examination, and a neuropsychological battery that included measures of memory, orientation, language, abstract reasoning, and visuospatial ability. Memory was evaluated using the multiple choice version of the Benton Visual Retention Test[15] and the seven subtests of the Selective Reminding Test:[16] total recall, long-term recall, long-term storage, continuous long-term storage, words recalled on last trial, delayed recall, and delayed recognition. Orientation was evaluated using parts of the modified Mini-Mental State Examination.[17] Language was assessed using the Boston Naming Test,[18] the Controlled Word Association Test,[19] category naming, and the Complex Ideational Material and Phrase Repetition subtests from the Boston Diagnostic Aphasia Evaluation.[20] Abstract Reasoning was evaluated using WAIS-R Similarities subtest,[21] and the non-verbal Identities and Oddities subtest of the Mattis Dementia Rating Scale.[22] Visuospatial ability was examined using the Rosen Drawing Test,[23] and a matching version of the Benton Visual Retention Test.[15] This neuropsychological test battery has established norms for the same community and has been shown to effectively distinguish between normal aging and dementia.[24]

Statistical Methods

Included in the final analytic sample were the 618 nondemented subjects with brain imaging data. First, we evaluated the distributions of HbA1c levels, dysglycemia, other vascular risk factors, demographic variables, and clinical characteristics at baseline using analysis of variance (ANOVA) for continuous variables and χ^2 test for categorical variables. Then, logistic regression and analysis of covariance (ANCOVA) models were used to relate HbA1c levels and dysglycemia categories with structural brain measures adjusting first for intracranial volume only (Model 1), then in addition for age and sex (Model 2), education, ethnic group and APOE genotype (Model 3), and finally hypertension, smoking, BMI, and HDL levels (Model 4). Using linear mixed models we assessed the longitudinal effect of dysglycemia on available repeated measures of structural brain changes (WMH, cortical white matter volume, total gray volume, and hippocampus volume).

For the analyses relating dysglycemia with cognitive function, we constructed a composite score for each cognitive domain using factor analysis. Specific tests included in each composite were for the memory domain the total recall, delayed recall, and delayed recognition subtests from the Selective Reminding Test, for the language domain the modified 15-item Boston Naming Test total score, Letter Fluency total, Category Fluency total, Similarities subtest of the Wechsler Adult Intelligence Scale – Revised, Boston Diagnostic Aphasia Evaluation Repetition and Comprehension subtests, for processing speed/executive functioning Color Trails 1 and 2, and for visuospatial abilities the recognition and matching tests from the Benton Visual Retention Test, the Rosen Drawing Test, and Identities/Oddities subtests of the Mattis Dementia Rating Scale. Invariance analyses showed that these measures are assessing similar constructs across English and Spanish speakers.

We then conducted ANCOVA analyses relating HbA1c levels and dysglycemia categories with the derived factor scores at baseline first performing crude models and then adjusting in a stepwise fashion for age, sex, education, ethnic group, APOE genotype, hypertension, smoking, BMI, and HDL levels. To assess a modification of APOE genotype on these associations conducted analyses including an interaction term for APOE genotype and dysglycemia in the models. All data analysis was performed using SPSS version 21.

RESULTS

Table 1 shows the characteristics of the data set for the whole sample and across dysglycemia categories. Out of the 618 subjects included in this analysis, 115 had normal glucose tolerance (NGT), 224 had pre-diabetes, 81 subjects

Table 1. Comparison of Baseline Characteristics for the Whole Sample and Across Dysglycemia Categories. Comparisons for Continuous Variables Was Conducted Using Analysis of Variance, and Chi-Squared Was Used for Categorical Outcomes

Characteristic[b]	All (n = 618)	NGT (n = 115)	Pre-Diabetes (n = 224)	Undiagnosed Diabetes (n = 81)	Known Diabetes (n = 198)
Age	80.0 (5.4)	79.8 (5.4)	80.6 (5.6)	79.8 (5.4)	79.6 (5.1)
Female, n (%)	428 (69.3)	76 (66.1)	159 (71.0)	55 (67.9)	138 (69.7)
Education	10.6 (4.8)	12.1 (4.7)	10.7 (4.9)	10.0 (4.6)[a]	9.7 (4.7)[a]
Ethnic group, n (%)					
White	168 (27.2)	51 (44.3)	66 (29.5)[a]	16 (19.8)[a]	35 (17.7)[a]
Black	202 (32.7)	28 (24.3)	62 (27.7)[a]	35 (43.2)[a]	77 (38.9)[a]
Hispanic	238 (38.5)	34 (29.6)	93 (41.5)[a]	30 (37.0)[a]	81 (40.9)[a]
Weight (pounds)	157.9 (34.1)	146.6 (31.9)	151.9 (31.5)	161.9 (35.7)[a]	169.6 (33.8)[a]
Height (cm)	161.1 (9.9)	161.4 (10.4)	160.8 (9.5)	161.3 (9.3)	161.1 (10.7)
BMI	27.7 (5.6)	25.5 (4.7)	26.6 (4.9)	28.4 (5.8)[a]	29.9 (6.0)[a]
APOE 4, n (%)	146 (23.6)	29 (25.2)	57 (25.4)	22 (27.2)	38 (19.2)
Diabetes, n (%)	198 (32.0)	–	–	–	198 (32.0)
HbA1c	6.5 (1.2)	5.4 (0.2)	6.1 (0.2)[a]	7.0 (0.6)[a]	7.5 (1.6)[a]
Hypertension, n (%)	546 (88.4)	91 (79.2)	194 (86.6)	70 (86.4)	191 (96.4)[a]
Non-HDL	128.9 (36.1)	131.4 (33.8)	131.7 (32.8)	135.6 (35.8)	121.1 (40.3)[a]
HDL	57.6 (16.9)	63.3 (17.8)	58.6 (16.5)	55.8 (15.4)	53.5 (16.7)[a]
Systolic BP	142.4 (21.7)	139.6 (23.8)	142.3 (21.9)	141.9 (18.4)	144.3 (21.4)
Smoking, n (%)	312 (50.5)	72 (62.6)	107 (47.8)[a]	36 (44.4)[a]	99 (49.0)[a]
Memory score	0.06 (0.78)	0.15 (0.84)	0.03 (0.77)	0.08 (0.75)	0.01 (0.77)
Executive score	0.10 (1.13)	0.39 (0.94)	0.12 (1.19)[a]	0.02 (1.13)[a]	−0.05 (1.12)[a]
Language score	0.26 (0.67)	0.42 (0.69)	0.31 (0.67)[a]	0.20 (0.60)[a]	0.12 (0.68)[a]
Visuospatial score	0.26 (0.61)	0.44 (0.60)	0.28 (0.62)[a]	0.23 (0.50)[a]	0.14 (0.61)[a]
Infarcts, n (%)	200 (31.0)	37 (31.4)	66 (28.3)	23 (27.7)	74 (35.1)
White matter hyperintensities	8.5 (10.5)	7.6 (9.6)	7.9 (9.7)	11.2 (13.7)	8.5 (10.0)
Total gray matter volume	535,159.6 (50,782.6)	553,703.9 (61,334.6)	541,412.2 (46,802.3)	534,264.1 (41,596.9)[a]	514,316.4 (44,688.4)[a]
Total white matter volume	396,059.7 (52,354.8)	412,060.9 (63,956.0)	400,916.9 (53,170.4)	401,267.9 (37,885.3)	375,901.0 (41,953.3)[a]
Hippocampal volume	6,670.6 (860.8)	6,784.6 (1,043.0)	6,746.9 (854.4)	6,632.6 (724.5)	6,510.5 (771.8)
Intracranial volume	1,303,967.1 (155,245.0)	1,356,590.6 (167,875.7)	1,309,562.3 (151,701.5)	1,297,898.0 (141,741.2)	1,269,556.0 (148,689.8)[a]

[a]Significant vs. persons with normal glucose tolerance (NGT).
[b]Numbers represent mean (SD) unless otherwise indicated.

had undiagnosed diabetes, and 198 had known diabetes. Compared to persons with NGT, persons with dysglycemia were less educated, more often black or Caribbean Hispanic, had higher levels of non-HDL-C and lower levels of HDL-C, had a higher BMI, had more often hypertension, and were less often smokers. On brain MRI, persons with dysglycemia showed lower cortical gray matter, cortical white matter, and intracranial brain volumes than persons with NGT. On neuropsychological testing, dysglycemia was associated with lower performance on executive function, language function, and speed.

In analyses relating dysglycemia categories to measures of brain structure, presence of dysglycemia was associated with a higher number of brain infarcts, volume of WMH, and decreased cortical white matter and gray matter volumes in all models performed (Table 2). In addition, known diabetes was associated with decreased hippocampus volume in the fully adjusted model. When using continuous levels of HbA1c as the predictor variable restricting the sample to persons without diabetes, results were consistent: higher levels of HbA1c were associated with an increased volume of WMH, and there were trends towards an association with lower gray matter and hippocampus volumes in the fully adjusted model (Table 2). In longitudinal analyses, dysglycemia was associated with a significant decline in total gray matter volume ($P = .04$; Figure 2A) that was worse for persons with NGT. While there was no significant difference in the rate of change in total hippocampus or total white matter volume over time, the slopes of change were parallel and separate across dysglycemia categories with appreciable lower volumes in persons with diabetes and pre-diabetes as compared with those with NGT (Figure 2B,C). There was no change in WMH volume over follow-up (Figure 2D), but the dysglycemia categories showed persistently higher WMH as compared with persons with NGT. When assessing possible interaction of these associations with APOE genotype, for none of the outcomes interaction terms were significant (Table S1).

Table 2. Results from Multivariable Models Examining the Cross-Sectional Relation of HbA1c Levels and Dysglycemia Categories to Brain Structure Measures. Linear Regression Models Were Used for All Outcomes Except Infarcts, for Which Logistic Regression Was Used

	Model 1			Model 2			Model 3			Model 4		
	Beta	**SE**	***P***	**Beta**	**SE**	***P***	**Beta**	**SE**	***P***	**Beta**	**SE**	***P***
Presence of Infarcts	**OR**	**95% CI**	***P***	**OR**	**95% CI**	***P***	**OR**	**95% CI**	***P***	**OR**	**95% CI**	***P***
HbA1c continuous	1.03	0.77–1.39	.81	1.02	0.75–1.37	.89	1.01	0.74–1.37	.91	0.96	0.68–1.34	.82
Known diabetes	1.34	0.81–2.19	.24	1.28	0.78–2.10	.32	1.34	0.79–2.27	.26	1.17	0.64–2.14	.60
Undiagnosed diabetes	0.96	0.51–1.80	.90	0.91	0.48–1.73	.79	0.93	0.48–1.79	.83	0.92	0.45–1.87	.83
Pre-diabetes	0.92	0.56–1.50	.74	0.90	0.55–1.48	.69	0.94	0.56–1.56	.82	0.79	0.45–1.38	.41
NGT	ref	ref	ref	ref	ref	ref	ref	ref	ref	ref	ref	ref
Number of Infarcts												
HbA1c continuous	0.01	0.06	.77	0.01	0.06	.77	0.02	0.07	.70	−0.01	0.06	.94
Known diabetes	0.30	0.13	.02	0.29	0.13	.03	0.32	0.14	.02	0.39	0.16	.01
Undiagnosed diabetes	−0.03	.17	.82	−0.05	0.17	.75	−0.01	0.17	.92	0.05	0.18	.75
Pre-diabetes	−0.06	.13	.63	−0.07	0.13	.58	−0.03	0.14	.81	−0.01	0.14	.89
NGT	ref	ref	ref	ref	ref	ref	ref	ref	ref	ref	ref	ref
WHI												
HbA1c continuous	0.12	0.05	.02	0.12	0.05	.01	0.12	0.05	.02	0.13	0.05	.01
Known diabetes	0.11	0.08	.21	0.13	0.08	.12	0.11	0.08	.21	0.12	0.09	.19
Undiagnosed diabetes	0.22	0.10	.02	0.24	0.10	.01	0.19	0.10	.04	0.21	0.10	.04
Pre-diabetes	0.08	0.08	.30	0.07	0.08	.34	0.08	0.08	.26	0.09	0.08	.25
NGT	ref	ref	ref	ref	ref	ref	ref	ref	ref	ref	ref	ref
Cortical White Matter Volume												
HbA1c continuous	−2,272.14	4,211.70	.59	−2,767.90	4,112.41	.50	−3,015.86	4,196.86	.47	−3,229.08	4,498.28	.47
Known diabetes	−14,994.23	6,180.31	.01	−16,328.29	6,115.73	.008	−14,617.85	6,400.05	.02	−12,068.02	7,097.68	.09
Undiagnosed diabetes	−131.44	7,285.55	.98	−1,356.19	7,194.74	.85	832.36	7,368.44	.91	1,928.95	7,895.34	.80
Pre-diabetes	−1,291.98	5,806.45	.82	−1,106.48	5,717.18	.84	−255.21	5,790.24	.96	137.05	6,248.04	.98
NGT	ref	ref	ref	ref	ref	ref	ref	ref	ref	ref	ref	ref
Total Gray Volume												
HbA1c continuous	−4,076.14	3,250.25	.21	−4,819.65	2,983.14	.10	−5,016.86	3,020.89	.09	−6,118.22	3,172.79	.05
Known diabetes	−16,592.17	5,119.89	.001	−19,375.01	4,758.23	<.0001	−17,535.02	4,969.88	<.0001	−19,074.56	5,340.42	<.0001
Undiagnosed diabetes	−7,957.34	6,035.50	.18	−10,502.05	5,597.72	.06	−8,460.54	5,721.87	.14	−9,802.54	5,940.60	.10
Pre-diabetes	−1,681.04	4,810.18	.72	−1,411.10	4,448.14	.75	−1,104.79	4,496.34	.80	−1,846.03	4,701.14	.69
NGT	ref	ref	ref	ref	ref	ref	ref	ref	ref	ref	ref	ref
Total Hippocampus Volume												
HbA1c continuous	−18.96	36.91	.60	−32.78	34.60	.34	−38.64	35.45	.27	−61.28	36.56	.09
Known diabetes	−97.56	138.8	.48	−136.45	129.90	.29	−170.44	136.52	.21	−328.53	148.56	.02
Undiagnosed diabetes	−63.04	163.66	.70	−99.01	152.82	.51	−119.27	157.18	.44	−227.44	165.26	.17
Pre-diabetes	44.46	130.44	.73	53.04	121.43	.66	35.56	123.51	.77	−19.24	130.78	.88
NGT	ref	ref	ref	ref	ref	ref	ref	ref	ref	ref	ref	ref

Model 1 = adjusted for intracranial volume; Model 2 = adjusted for intracranial volume, age, sex; Model 3 = adjusted for intracranial volume, age, sex, education, ethnic group, APOE; Model 4 = adjusted for intracranial volume, age, sex, education, ethnic group, APOE, hypertension, smoking, BMI, HDL.

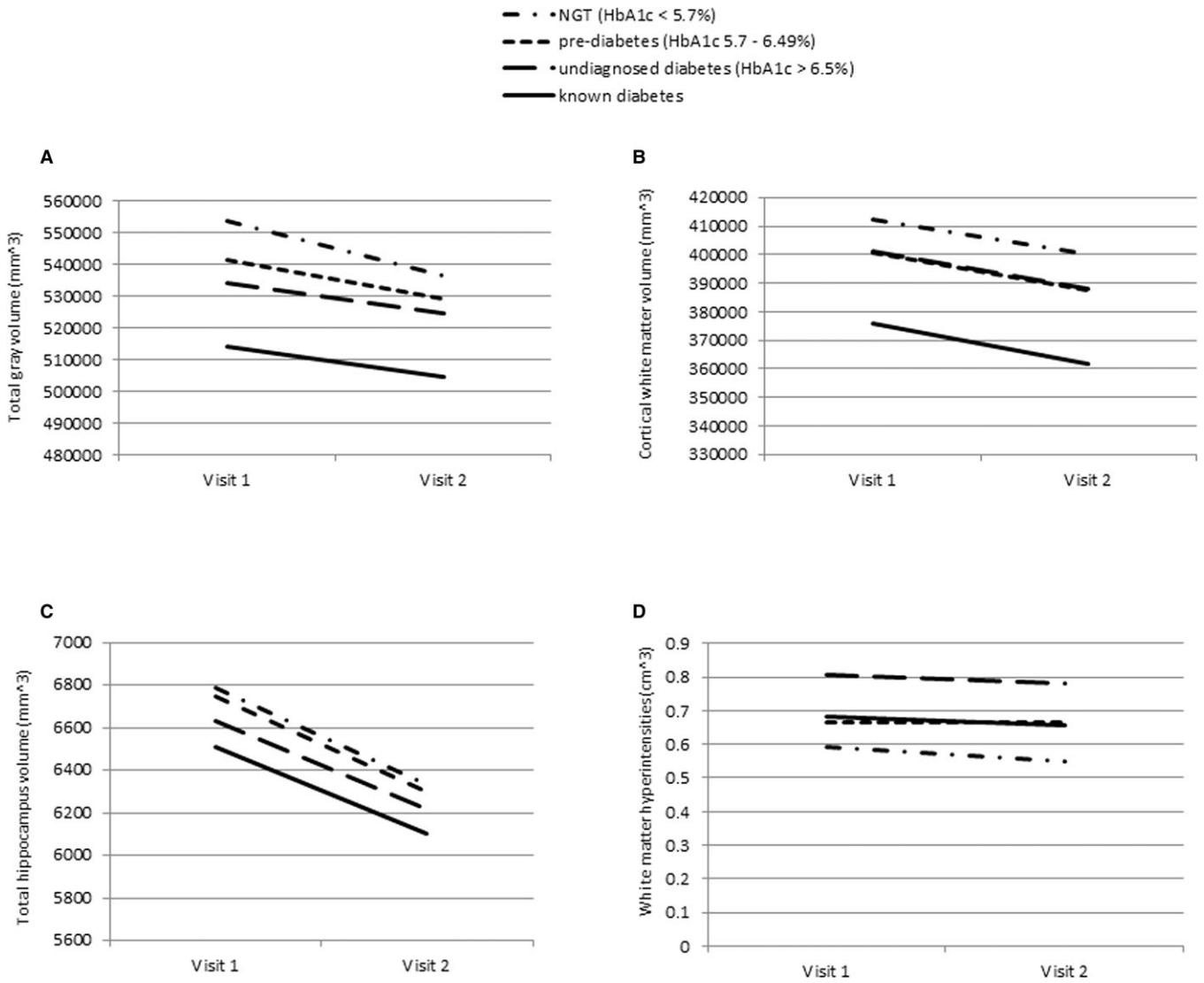

Figure 2. Mean value of structural brain changes at MRI visits 1 and 2 by dysglycemia category. (A) Total gray volume. (B) Cortical white matter volume. (C) Total hippocampus volume. (D) Volume of WHI.

In analyses relating dysglycemia to cognitive function, both pre-diabetes and diabetes as well as higher HbA1c levels were associated with lower performance in language, speed and visuospatial function in crude models and models adjusted for age and sex. In models adjusted for education, ethnic group, APOEe4 genotype or vascular risk factors, these associations were attenuated (Table 3).

DISCUSSION

In this study of elderly ethnically diverse community dwellers, presence of dysglycemia (diabetes, undiagnosed diabetes, and pre-diabetes) or higher HBA1c levels was associated with a higher number of brain infarcts, WMH volume and decreased total white matter, gray matter volumes and hippocampus volume in cross-sectional analyses, and a significant decline in gray matter volume in longitudinal analyses. In addition, dysglycemia was associated with lower performance in language, speed and visuospatial function although these associations were attenuated when adjusting for education, APOE genotype, ethnic group or vascular risk factors.

Many studies have shown associations of diabetes with cognitive decline,[25] mild cognitive impairment,[26] LOAD[27,28] and vascular dementia,[29] which predominantly used a history of diabetes as the predictor variable. The continuum of dysglycemia has also been shown to be related to a higher risk of cognitive decline[30] and dementia.[31] However, there is a paucity of data assessing brain structure and cognition as a function of long-term changes in glucose control and pre-diabetic stages, particularly in very old adults, as represented in our sample. Our observations are important because the impact of pre-diabetes and diabetes in very old adults is a matter of debate.[32]

Our findings are consistent with previous longitudinal studies reporting an association between diabetes and structural brain changes. In the Framingham Offspring Study midlife diabetes was associated with an annual increase in temporal horn volume,[33] hippocampal atrophy, and brain infarcts.[34] In the Atherosclerosis in Communities cohort[35] and the Leukoaraiosis and DISability in the

Table 3. Results from Multivariable Linear Regression Models Examining the Cross-Sectional Relation of HbA1c Levels and Dysglycemia Categories to Cognitive Performance

	Model 1			Model 2			Model 3			Model 4		
	Beta	SE	*P*	Beta	SE	*P*	Beta	SE	*P*	Beta	SE	*P*
Memory												
HbA1c continuous	−0.07	0.06	.27	−0.06	0.05	.28	−0.01	0.05	.82	−0.02	0.05	.69
Known diabetes	−0.15	0.09	.11	−0.16	0.08	.06	0.03	0.08	.73	0.01	0.09	.84
Undiagnosed diabetes	−0.07	0.11	.53	−0.07	0.11	.50	0.10	0.10	.31	0.11	0.11	.29
Pre-diabetes	−0.12	0.09	.18	−0.09	0.08	.26	−0.004	0.08	.96	0.01	0.08	.88
NGT	ref	ref	ref	ref	ref	ref	ref	ref	ref	ref	ref	ref
Language												
HbA1c continuous	−0.11	0.05	.02	−0.10	0.04	.02	−0.02	0.03	.46	−0.01	0.03	.79
Known diabetes	−0.30	0.08	<.0001	−0.31	0.07	<.0001	−0.06	0.06	.29	−0.04	0.06	.54
Undiagnosed diabetes	−0.22	0.09	.02	−0.22	0.09	.01	0.008	0.07	.91	0.04	0.07	.57
Pre-diabetes	−0.11	0.07	.15	−0.08	0.07	.27	0.05	0.05	.34	0.08	0.06	.17
NGT	ref	ref	ref	ref	ref	ref	ref	ref	ref	ref	ref	ref
Speed												
HbA1c continuous	−0.22	0.08	.01	−0.20	0.08	.01	−0.08	0.07	.23	−0.09	0.07	.23
Known diabetes	−0.44	0.14	.002	−0.46	0.13	.001	−0.21	0.12	.10	−0.21	0.13	.12
Undiagnosed diabetes	−0.36	0.17	.03	−0.34	0.16	.03	−0.09	0.15	.51	−0.11	0.15	.45
Pre-diabetes	−0.26	0.13	.05	−0.22	0.13	.09	−0.02	0.12	.83	−0.01	0.12	.89
NGT	ref	ref	ref	ref	ref	ref	ref	ref	ref	ref	ref	ref
Visuospatial												
HbA1c continuous	−0.09	0.04	.04	−0.08	0.04	.05	−0.01	0.03	.63	−0.01	0.03	.69
Known diabetes	−0.29	0.07	<.0001	−0.30	0.07	<.0001	−0.09	0.05	.09	−0.09	0.06	.14
Undiagnosed diabetes	−0.22	0.08	.02	−0.19	0.08	.02	−0.008	0.06	.91	−0.005	0.07	.94
Pre-diabetes	−0.15	0.07	.02	−0.12	0.06	.05	−0.008	0.05	.87	0.004	0.05	.94
NGT	ref	ref	ref	ref	ref	ref	ref	ref	ref	ref	ref	ref

Model 1 = crude; Model 2 = adjusted for age, sex; Model 3 = adjusted for age, sex, education, ethnic group, APOE; Model 4 = adjusted for age, sex, education, ethnic group, APOE-ε4, hypertension, smoking, body mass index, high-density lipoprotein.

Elderly Study[35] midlife diabetes was associated with reduced brain volume or brain atrophy. In the Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial[36] midlife diabetes was associated with brain volume loss, particularly in the gray matter. Persons with diabetes have been reported to have more brain atrophy compared with persons with diabetes and have higher WMH,[37] representative of neurodegeneration and small vessel cerebrovascular disease, respectively. We found that the associations between dysglycemia and white matter hyperintensities, cortical white matter volume, total gray volume, and total hippocampus volume were independent of APOE genotype. Some studies have found that the association between diabetes and cognitive outcomes is strongest among persons with the APOE-ε4 allele[38,39] but this finding is not consistent,[40] and was not supported by our findings (see Tables S1A–C).

Dysglycemia, cognitive impairment, and structural brain changes may have common underlying risk factors such as older age, which could confound the observed associations. However, our results are in line with the notion that dysglycemia may affect cognition through both vascular and neurodegenerative pathways. Dysglycemia is known to be a risk factor for cerebrovascular disease.[41] Strokes, ascertained by clinical history or as brain infarcts on MRI are related to a higher risk of dementia including LOAD.[42] While the mechanisms for this association are not clear, pathology studies have demonstrated that the presence of amyloid plaques is lower in brains of persons with dementia who also have infarcts[43] suggesting that the presence of infarcts lowers the threshold of amyloid in the brain necessary to cause dementia. White matter hyperintensities are related to a higher risk of cognitive impairment,[44] but the pathological underpinnings and etiological factors related to WMH are still not fully understood. There is a lot of evidence that WMH are ischemic in origin in the same way that infarcts are[45] and have what can be thought of as surrogate markers of cerebrovascular disease.[45] However, recent evidence also shows that WMH are common in LOAD and may be related to cerebral amyloid angiopathy.[46]

We found that dysglycemia is related to reduced gray matter volume, a surrogate of neurodegeneration. The medial temporal lobe (including the hippocampus and parahippocampus), the first region to be affected by neurofibrillary tangles and amyloid plaques as well as the greatest loss of neurons in AD,[47] most consistently exhibits decreased gray-matter volume in AD and MCI.[48] A study based on the Alzheimer's Disease Neuroimaging Initiative (ADNI) data set has demonstrated that gray-matter atrophy reflects clinically defined disease stages better than CSF (Cerebrospinal Fluid) biomarkers (such as Aβ and total tau).[49]

While a relation of dysglycemia with cerebrovascular markers is not surprising, neurodegeneration is also a plausible mechanism linking dysglycemia and brain atrophy. Hyperinsulinemia[50] and advanced glycation end products (AGE)[51] may link dysglycemia and neurodegeneration. One of our primary exposures, HbA1C, is the most

common example of AGE. HbA1c is a form of hemoglobin bound by glucose through the non-enzymatic glycation pathway, and is the primary measure of prolonged (8–12 weeks) average ambient plasma glucose concentration in the circulation as well as an AGE.

Our results were stronger in cross-sectional analyses compared with longitudinal analyses. However, there was a clear separation in slopes for brain structure variables suggesting a detrimental association with dysglycemia. While we cannot exclude the possibility that people who developed relatively smaller brains—for example due to low lower socioeconomic status or poor nutrition—may be more likely to develop diabetes and poor cognition, these findings are in line with the notion that the effect of dysglycemia on brain structure occurred earlier in the lifespan and might have stabilized to a level of change similar to the general population. The same observation was made for cognitive decline. This observation has been previously reported for both changes in cognitive performance and brain structure.[37,52]

Our study has several strengths. First, our cohort is community-based. Second, the diagnosis of dysglycemia was based on HbA1c levels reflecting a more stable measure of long-term glucose concentration in the circulation than blood glucose levels and allowing us to ascertain undiagnosed diabetes or glucose intolerance. Third, we had measures of structural brain changes from two timepoints allowing us to explore the longitudinal effect of pre-diabetes on changes in volumetric measures. Fourth, the cohort includes a high proportion of Hispanic and African-American participants, who have been significantly underrepresented in previous studies on pre-diabetes/diabetes and structural MRI measures or cognition, and who are at a higher risk of both dysglycemia and cognitive impairment. Fifth, we had concurrent comprehensive brain imaging and cognitive performance data. Finally, measures for multiple potential confounders were carefully recorded and adjusted for in the analyses.

Limitations of our study include that we only had one measurement of HBA1c levels which can lead to measurement error and ignores past glycemia trajectories. First, measurement error could have resulted in underestimation of the associations of dysglycemia with changes in volumetric measures in longitudinal analyses. Second, it would be interesting to examine lifetime cumulative or midlife effects of dysglycemia, but we only had a measure from the time of brain imaging and no information on how long the subjects have had diabetes and what has been the status of their overall glycemic control. Although we controlled for a wide variety of potential confounders, we cannot rule out the possibility of residual confounding (i.e., distortion remaining after controlling for confounders). Dysglycemia may be a marker of lower education and lower socioeconomic status, which in turn is related to a higher risk of cognitive impairment.[53]

It is important to point out that our findings are generalizable to relatively very old community dwelling persons without dementia. The main clinical implication of our findings is that dysglycemia may impact brain structure and cognition even in very old persons, suggesting that dysglycemia should not be considered "benign" in this age group and the need for interventions may be assessed.

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SUPPORTING INFORMATION

Additional Supporting Information may be found in the online version of this article:

Table S1. Results from linear regression models including an interaction term for HBA1C levels (A) and dysglycemia categories (B) with APOE genotype in relation to the outcomes.

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