Prediabetes Is Associated With Structural Brain Abnormalities

Prediabetes Is Associated With Structural Brain Abnormalities: The Maastricht Study

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OBJECTIVE

Structural brain abnormalities are key risk factors for brain diseases, such as dementia, stroke, and depression, in type 2 diabetes. It is unknown whether structural brain abnormalities already occur in prediabetes. Therefore, we investigated whether both prediabetes and type 2 diabetes are associated with lacunar infarcts (LIs), white matter hyperintensities (WMHs), cerebral microbleeds (CMBs), and brain atrophy.

RESEARCH DESIGN and METHODS

We used data from 2,228 participants (1,373 with normal glucose metabolism [NGM], 347 with prediabetes, and 508 with type 2 diabetes (oversampled); mean age 59.2 ± 8.2 years; 48.3% women) of the Maastricht Study, a population-based cohort study. Diabetes status was determined with an oral glucose tolerance test. Brain imaging was performed with 3 Tesla MRI. Results were analyzed with multivariable logistic and linear regression analyses.

RESULTS

Prediabetes and type 2 diabetes were associated with the presence of LIs (odds ratio 1.61 [95% CI 0.98–2.63] and 1.67 [1.04–2.68], respectively; P_{trend} = 0.027), larger WMH (β 0.07 log10-transformed mL [log-mL] [95% CI 0.00–0.15] and 0.21 log-mL [0.14–0.28], respectively; P_{trend} <0.001), and smaller white matter volumes (β −4.0 mL [−7.3 to −0.6] and −7.2 mL [−10.4 to −4.0], respectively; P_{trend} <0.001) compared with NGM. Prediabetes was not associated with gray matter volumes or the presence of CMBs.

CONCLUSIONS

Prediabetes is associated with structural brain abnormalities, with further deterioration in type 2 diabetes. These results indicate that, in middle-aged populations, structural brain abnormalities already occur in prediabetes, which may suggest that the treatment of early dysglycemia may contribute to the prevention of brain diseases.

Structural brain abnormalities are thought to be an important pathway through which type 2 diabetes causes brain diseases (1). Indeed, there is extensive evidence that type 2 diabetes is associated with an increased risk of brain diseases, such as stroke, dementia, and depression (1–9), and of structural brain abnormalities on MRI, such as lacunar infarcts (LIs), white matter hyperintensities (WMHs), and brain atrophy (10), which in turn are associated with an increased risk of stroke, dementia, and depression (11–13).

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Whether prediabetes (defined as impaired fasting glucose or impaired glucose tolerance [14]) is also associated with an increased risk of structural brain abnormalities and brain diseases is not clear (15). However, this appears to be a distinct possibility because structural brain abnormalities in type 2 diabetes are thought to be, to an important extent, of micro- and macrovascular origin (16–19) and because (extracranial) micro- and macrovascular dysfunction has been shown to be present not only in type 2 diabetes but also in prediabetes (the so-called ticking clock hypothesis) (20–22). In contrast to this hypothesis, the Atherosclerosis Risk in Communities Neurocognitive Study (ARIC-NCS) recently reported no associations of prediabetes with LIs, WMHs, cerebral microbleeds (CMBs), or smaller brain volumes in an elderly study population (23). However, the development of structural brain abnormalities may start at middle age (24), and no studies have investigated this in a middle-aged population. It is important to know whether prediabetes is associated with structural brain abnormalities, as this would add to the accumulating evidence that prediabetes is not a benign state (25–27). In addition, this would imply that prediabetes provides a window of opportunity for the prevention of brain diseases in type 2 diabetes.

Therefore, we investigated whether prediabetes and continuous measures of hyperglycemia (glycated hemoglobin [HbA_{1c}] and fasting and 2-h plasma glucose from an oral glucose tolerance test [OGTT]) are associated with structural brain abnormalities. In addition, we investigated whether any such associations were independent of cardiovascular risk factors, such as hypertension, as cardiovascular risk factors are an important alternative explanation for any association between (pre)diabetes and structural brain abnormalities.

RESEARCH DESIGN AND METHODS

Study Population and Design

We used data from the Maastricht Study, an observational population-based cohort study. The rationale and methodology have previously been described (28). In brief, the study focuses on the etiology, pathophysiology, complications, and comorbidities of type 2 diabetes and is characterized by an extensive phenotyping approach. Eligible for participation were all individuals aged between 40 and 75 years and living in the southern part of the Netherlands. Participants were recruited through mass media campaigns, the municipal registries, and the regional Diabetes Patient Registry via mailings. Recruitment was stratified according to known type 2 diabetes status, with an oversampling of individuals with type 2 diabetes for reasons of efficiency. The present report includes cross-sectional data from 3,451 participants, who completed the baseline survey between November 2010 and September 2013. The examinations of each participant were performed within a time window of 3 months. MRI measurements were implemented from December 2013 onward until February 2017 and were available in 2,313 of 3,451 participants. Eleven MRI scans were excluded owing to pathology (n = 2), metal artifacts (n = 1), or insufficient scan quality (n = 8). Participants with type 1 diabetes or other types of diabetes (n = 27) were excluded from the analysis. In the remaining 2,275 participants, complete data on covariates were available in 2,228 participants (Supplementary Fig. 1). The study has been approved by the institutional medical ethics committee (NL31329.068.10) and the Minister of Health, Welfare and Sport of the Netherlands (permit 131088-105234-PG). All participants gave written informed consent.

Diabetes Status

For determination of (pre)diabetes status, all participants, except those who used insulin, underwent a standardized 2-h 75-g OGTT after an overnight fast. For safety reasons, participants with a fasting glucose level >11.0 mmol/L, as determined by a fingerprick, did not undergo the OGTT (n = 42). For these individuals, fasting glucose level and information about diabetes medication use were used to determine diabetes status. Diabetes status was defined according to the World Health Organization 2006 criteria as normal glucose metabolism (NGM), prediabetes (impaired fasting glucose [6.1–7.0 mmol/L] or impaired glucose tolerance [2-h postdose OGTT glucose 7.8–11.1 mmol/L]), or type 2 diabetes (fasting plasma glucose ≥7.1, 2-h postdose OGTT glucose >11.1, or the use of diabetes medication) (14). Individuals without type 1 diabetes on diabetes medication were classified as having type 2 diabetes (28).

Measures of Glycemia

Venous fasting and postload plasma glucose levels were measured by the enzymatic hexokinase method on two automatic analyzers (the Synchron LX20 [Beckman Coulter Inc.] for samples obtained between November 2010 and April 2012 and the cobas 6000 [Roche Diagnostics, Mannheim, Germany] for samples obtained thereafter). HbA_{1c} was determined by ion-exchange high-performance liquid chromatography (28).

Brain MRI

Brain MRI was performed on a 3 Tesla (3T) MRI scanner (MAGNETOM Prismafit Syngo MR D13D; Siemens Healthcare, Erlangen, Germany) by use of a 64-element head coil for parallel imaging. The MRI protocol consisted of a three-dimensional T1-weighted (T1) sequence (repetition time/echo time/inversion time 2,300/2.98/900 ms, 1.00 mm cubic voxel, 176 continuous slices, matrix size of 240 × 250, and reconstructed matrix size of 512 × 51), a T2-weighted fluid-attenuated inversion recovery (FLAIR) (repetition time/echo time/inversion time 5,000/394/1,800 ms, 0.98 × 0.98 × 1.26 mm acquisition voxel and 0.49 × 0.49 × 1.00 mm reconstructed voxel, 176 continuous slices, acquisition matrix size of 250 × 250, and reconstructed matrix size of 512 × 51), and a gradient recalled echo (GRE) pulse sequence with susceptibility-weighted imaging (SWI). Contraindications for MRI assessments were the presence of a cardiac pacemaker or implantable cardioverter defibrillator, neurostimulator, nondetachable insulin pump, metallic vascular clips or stents in the head, cochlear implant, metal-containing intrauterine device, metal splinters or shrapnel, dentures with magnetic clip, an inside bracket, pregnancy, epilepsy, and claustrophobia. The protocols for MRI acquisition and analysis were in line with the current STRIVE (STandards for ReportIng Vascular changes on nEuroimaging) V1 imaging standards (29).

Measurements of Markers of Cerebral Small-Vessel Disease

T2-weighted FLAIR and T1 images were used to identify WMHs (30). WMHs identified were summed to assess total

WMH burden in milliliters. Periventricular WMHs (pWMHs) were automatically defined as WMHs <3 mm and deep cortical WMH (dWMHs) as WMHs ≥3 mm from the cerebrospinal fluid (CSF) (31). This method has a small chance of misclassification of juxtacortical WMHs, which are relatively uncommon (32), as pWMHs. LIs were defined as focal lesions of ≥3 and <15 mm in size with a signal intensity similar to that of CSF on all sequences and a hyperintense rim on T2 and FLAIR images (29). CMBs were rated on three-dimensional T2* GRE imaging with SWI by use of the Microbleed Anatomical Rating Scale (33) and were defined as focal lesions of ≥2 and ≤10 mm in size with a hypointense signal on T2* GRE and SWI images (29). The number and location of LIs and CMBs were rated manually by three neuroradiologists. The intraclass correlation coefficient (95% CI) for the three raters based on 50 randomly selected scans was 0.84 (0.74–0.91) and 0.83 (0.72–0.90) for the presence of LIs and CMBs, respectively.

Measurements of Brain Volumes

T1 images and T2-weighted FLAIR images were analyzed by use of an ISO-13485:2012–certified, automated method (which included visual inspection) (30,34). T1 images were segmented into gray matter, white matter, and CSF volumes (1 voxel = 1.00 mm^3 = 0.001 mL) (34). Intracranial volume was calculated as the sum of gray matter, white matter (including WMH volume), and CSF volumes.

General Characteristics and Covariates

As previously described (28), educational level (low, intermediate, high), smoking status (never, current, former) and history of cardiovascular disease were assessed by questionnaires. Medication use was assessed in a medication interview where generic name, dose, and frequency were registered. We measured weight, height, BMI, waist circumference, blood pressure (measured in office and via ambulatory 24-h blood pressure monitoring at home [WatchBP 03; Microlife AG, Widnau, Switzerland]), serum creatinine, 24-h urinary albumin excretion (twice), and plasma lipid profile as previously described (28). Estimated glomerular filtration rate (in mL/min/1.73 m^2) was calculated with the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation based on both serum creatinine and serum cystatin C (35).

Statistical Analysis

All statistical analyses were performed by use of the Statistical Package for Social Sciences (version 22.0; IBM, Chicago, IL). General characteristics of the study population were presented as mean ± SD, as median (interquartile range), or as percentages and were evaluated by ANOVA (continuous variables with a normal distribution) or χ^2 tests (categorical variables). We used multiple linear regression analysis to investigate the association of (pre)diabetes status, HbA_{1c}, fasting plasma glucose, or 2-h postload glucose levels with WMH, white matter, gray matter, and CSF volumes and logistic regression analysis to investigate the association with LIs (yes/no) and CMBs (yes/no). For linear trend analyses, the categorical variable glucose metabolism status (NGM = 0, prediabetes = 1, and type 2 diabetes = 2) was used in the regression models. For assessment of regression coefficients per glucose metabolism group, analyses with dummy variables for prediabetes and type 2 diabetes were used. Model 1 was adjusted for age, sex, and the time between the baseline and MRI measurement. Model 2 was additionally adjusted for BMI, smoking status, total–to–HDL cholesterol ratio, serum triglycerides, eGFR, office systolic blood pressure, and educational level. For analyses of total, dWMH, pWMH, white matter, and gray matter volumes, additional adjustment for intracranial volume was included for model 1. Skewed variables (WMH, dWMH, and pWMH volumes) were log10 transformed. A P value <0.05 was considered statistically significant. Interaction terms (e.g., prediabetes * sex, type 2 diabetes * sex, or HbA_{1c} * sex) were incorporated in the regression models to test for interaction among, on the one hand, prediabetes, type 2 diabetes, and measures of hyperglycemia and, on the other hand, age and sex, on structural brain abnormalities. A $P_{interaction}$ <0.10 was considered statistically significant.

RESULTS

General Characteristics of the Study Population

Table 1 shows the general characteristics of the study population, stratified by (pre)diabetes status. The study population consisted of 2,228 participants; 1,373 participants had NGM, 347 had prediabetes, and 508 had type 2 diabetes. The mean age was 59.2 ± 8.2 years, and 48.3% were women. Participants with prediabetes and type 2 diabetes were more likely to be older, less likely to be female, more likely to have an adverse cardiovascular risk profile, more likely to be current smokers, and more likely to have a low educational level (Table 1). Individuals who underwent MRI were more likely to be younger, were less likely to have type 2 diabetes, were less likely to be current smokers, and were less likely to have a low educational level compared with the study population that did not undergo MRI (Supplementary Table 1).

Prediabetes and Structural Brain Abnormalities

After full adjustment, prediabetes and type 2 diabetes were significantly associated with the presence of LIs (odds ratio [OR] 1.61 [95% CI 0.98–2.63] and 1.67 [1.04–2.68], respectively; P_{trend} = 0.027) (Table 2) and larger volumes of WMHs (β 0.07 log10-transformed mL [log-mL] [95% CI 0.00–0.15] and 0.22 log-mL [0.16–0.29], respectively; P_{trend} <0.001) (Table 2) compared with NGM. In addition, both prediabetes and type 2 diabetes were significantly associated with larger volumes of dWMHs (β 0.07 log-mL [−0.01 to 0.15] and 0.16 log-mL [0.08–0.24], respectively; P_{trend} <0.001) and pWMHs (β 0.06 log-mL [−0.01 to 0.13] and 0.20 log-mL [0.14–0.27], respectively; P_{trend} <0.001). The regression coefficients of prediabetes with WMH volume were approximately one-third to one-half that of the type 2 diabetes coefficient, which suggests a continuous association from NGM to prediabetes to diabetes. No associations of prediabetes or type 2 diabetes were found with the presence of CMBs (OR 0.85 [95% CI 0.57–1.27] and 1.14 [0.80–1.62], respectively; P_{trend} = 0.567) (Table 2).

After full adjustment, prediabetes and type 2 diabetes were significantly associated with smaller white matter volumes compared with NGM (β −4.0 mL [95% CI −7.3 to −0.6] and −7.2 mL [−10.4 to −4.0], respectively; P_{trend} < 0.001). The regression coefficient of prediabetes with white matter volume was approximately one-half that of the

Table 1—General characteristics of the study population

	NGM (n = 1,373)	Prediabetes (n = 347)	Type 2 diabetes (n = 508)	P_{trend}
Demographics				
Age (years)	57.6 ± 8.1	61.1 ± 7.6	62.5 ± 7.5	<0.001
Sex (% female)	55.6	44.5	31.1	<0.001
Glucose metabolism				
Fasting glucose (mmol/L)	5.2 ± 0.4	5.9 ± 0.6	7.4 ± 1.2	<0.001
2-h postload glucose (mmol/L)*	5.4 ± 1.1	8.1 ± 1.8	14.1 ± 4.1	<0.001
HbA_{1c} (%)	5.4 ± 0.3	5.7 ± 0.4	6.6 ± 0.6	<0.001
HbA_{1c} (mmol/mol)	36.1 ± 3.7	38.6 ± 4.4	48.1 ± 7.0	<0.001
Cardiovascular risk factors				
BMI (kg/m^2)	25.4 ± 3.5	27.3 ± 4.0	28.9 ± 4.5	<0.001
Systolic BP (mmHg)	130.7 ± 16.8	136.2 ± 16.3	139.5 ± 16.3	<0.001
Diastolic BP (mmHg)	75.3 ± 9.9	77.5 ± 9.6	77.8 ± 9.4	<0.001
Hypertension (%)	38.9	60.1	81.5	<0.001
Total–to–HDL cholesterol ratio	3.6 ± 1.2	3.9 ± 1.2	3.7 ± 1.2	<0.001
Triglycerides (mmol/L)	1.2 ± 0.7	1.6 ± 1.0	1.7 ± 0.9	<0.001
eGFR (mL/min/1.73 m^2)	90.5 ± 13.0	87.0 ± 13.7	85.8 ± 16.3	<0.001
History of CVD (%)	8.7	11.4	20.9	<0.001
Medication use (%)				
Antihypertension medication	20.5	39.6	69.9	<0.001
Lipid-modifying medication	14.7	29.8	71.9	<0.001
Lifestyle factors (%)				
Smoking, never/former/current	40.9/47.8/11.3	30.1/59.5/11.3	32.5/54.7/12.8	0.001
Educational level, low/medium/high	25.2/28.3/46.5	32.7/30.9/36.4	41.3/30.1/28.5	<0.001
Markers of cerebral small-vessel disease				
LIs present (%)†	4.1	7.9	9.0	<0.001
Total WMH (mL)	0.17 (0.05–0.52)	0.27 (0.07–1.12)	0.40 (0.15–1.31)	<0.001
dWMH (mL)	0.04 (0.01–0.15)	0.08 (0.01–0.30)	0.09 (0.02–0.40)	<0.001
pWMH (mL)	0.20 (0.05–0.73)	0.30 (0.09–0.90)	0.12 (0.04–0.37)	<0.001
CMBs present (%)‡	10.9	12.3	15.8	0.020
Brain volumes (mL)				
White matter	479.6 ± 59.5	468.3 ± 62.6	466.0 ± 60.0	<0.001
Gray matter	666.6 ± 58.8	654.3 ± 62.9	648.0 ± 61.6	<0.001
CSF	247.2 ± 45.8	257.2 ± 50.0	268.8 ± 50.4	<0.001
Intracranial	1,394.1 ± 133.9	1,381.1 ± 146.2	1,384.7 ± 131.7	0.148
MRI lag time (years)	2.4 ± 1.3	2.4 ± 1.3	2.4 ± 1.3	0.608

Data are presented as means ± SD or median (interquartile range) unless otherwise indicated and are stratified for (pre)diabetes status: NGM, prediabetes, or type 2 diabetes. BP, blood pressure; CVD, cardiovascular disease; eGFR, estimated glomerular filtration rate. *2-h postload glucose values were available in n = 2,111. †Data on LIs were available in n = 2,190. ‡Data on CMBs were available in n = 2,149.

type 2 diabetes coefficient, which suggests a continuous association from NGM to prediabetes to diabetes. In addition, prediabetes and type 2 diabetes were significantly associated with larger CSF volumes compared with NGM (β 3.9 mL [0.8–7.6] and 12.5 mL [9.0–16.1], respectively; P_{trend} <0.001). Prediabetes was not associated with gray matter volumes, while type 2 diabetes was associated with lower gray matter volumes, compared with NGM (β −0.4 mL [−3.7 to 2.8] and −6.2 mL [−9.4 to −3.1], respectively; P_{trend} < 0.001) (Fig. 1 and Table 2).

Continuous Measures of Hyperglycemia and Structural Brain Abnormalities

After full adjustment, HbA_{1c}, fasting plasma glucose, and 2-h postload glucose levels were associated with the presence of LIs (OR 1.28 [95% CI 1.09–1.50], P = 0.002; 1.22 [1.03–1.44], P = 0.020; and 1.21 [1.01–1.44], P = 0.039, per SD, respectively) (Table 3) and higher volumes of WMHs, dWMHs, and pWMHs (standardized β for WMH 0.09 [95% CI 0.05–0.13], P < 0.001; 0.11 [0.07–0.15], P < 0.001; and 0.11 [0.07–0.15], P < 0.001, respectively) (Table 3). In addition, HbA_{1c}, fasting plasma glucose, and 2-h postload glucose levels were associated with lower white matter and gray matter and higher CSF volumes (standardized β for white matter −0.02 [−0.04 to 0.00], P = 0.032; −0.03 [−0.05 to −0.01], P = 0.007; and −0.04 [−0.06 to −0.02], P < 0.001; for gray matter −0.04 [−0.06 to −0.02], P < 0.001; −0.04 [−0.06 to −0.02], P = 0.001; and −0.02 [−0.04 to 0.00], P = 0.035; and for CSF 0.07 [0.05–0.10], P < 0.001; 0.08 [0.05–0.11], P < 0.001; and 0.07 [0.05–0.10], P < 0.001, respectively). No associations of HbA_{1c}, fasting plasma glucose, or 2-h postload glucose levels were found with the presence of CMBs (OR 1.04 [95% CI 0.90–1.20], P = 0.580; 1.03 [0.89–1.19], P = 0.668; and 0.98 [0.84–1.13], P = 0.743, per SD, respectively). Scatterplots with regression lines of continuous measures of hyperglycemia with WMH volume are provided in Supplementary Fig. 2.

Additional Analyses

When we used volumes in percentage of intracranial volume, instead of volumes in milliliters and corrected for intracranial volume, associations of prediabetes and type 2 diabetes, HbA_{1c}, fasting glucose, and 2-h postload glucose with structural

Table 2—Multivariable-adjusted differences in structural brain abnormalities among individuals with prediabetes and individuals with type 2 diabetes, as compared to individuals with NGM

	Prediabetes	Type 2 diabetes	P_{trend}
Markers of cerebral small-vessel disease			
LIs (yes/no), OR (95% CI)			
Model 1	1.62 (1.00–2.64)	1.71 (1.11–2.63)	0.012
Model 2	1.61 (0.98–2.63)	1.67 (1.04–2.68)	0.027
Total WMH volume (log-mL), β (95% CI)			
Model 1	0.08 (0.00–0.15)	0.22 (0.16–0.29)	<0.001
Model 2	0.07 (0.00–0.15)	0.21 (0.14–0.28)	<0.001
dWMH volume (log-mL), β (95% CI)			
Model 1	0.08 (0.00–0.16)	0.17 (0.10–0.24)	<0.001
Model 2	0.07 (−0.01–0.15)	0.16 (0.08–0.24)	<0.001
pWMH volume (log-mL), β (95% CI)			
Model 1	0.07 (0.00–0.14)	0.22 (0.16–0.28)	<0.001
Model 2	0.06 (−0.01–0.13)	0.20 (0.14–0.27)	<0.001
CMBs (yes/no), OR (95% CI)			
Model 1	0.85 (0.57–1.26)	1.17 (0.85–1.26)	0.433
Model 2	0.85 (0.57–1.27)	1.14 (0.80–1.62)	0.567
Brain volumes			
White matter volume (mL), β (95% CI)			
Model 1	−3.2 (−6.5 to 0.1)	−6.1 (−9.0 to −3.1)	<0.001
Model 2	−4.0 (−7.3 to −0.6)	−7.2 (−10.4 to −4.0)	<0.001
Gray matter volume (mL), β (95% CI)			
Model 1	−1.1 (−4.4 to 2.1)	−8.2 (−11.1 to −5.3)	<0.001
Model 2	−0.4 (−3.7 to 2.8)	−6.2 (−9.4 to −3.1)	<0.001
CSF (mL), β (95% CI)			
Model 1	3.9 (0.3–7.6)	13.4 (10.1–16.7)	<0.001
Model 2	3.9 (0.8–7.6)	12.5 (9.0–16.1)	<0.001

Associations of prediabetes and type 2 diabetes with structural brain abnormalities in the study population. ORs with 95% CI represent the risk of the presence of LIs or CMBs, and regression coefficients indicate the mean difference with 95% CI in total WMH, dWMH, and pWMH volumes or white matter, gray matter, and CSF volumes of participants with prediabetes or type 2 diabetes compared with NGM. Model 1: adjusted for age, sex, intracranial volume (only for analyses with WMH, white matter, gray matter, and CSF) and time between baseline and MRI measurements. Model 2: model 1 adjustments with additional adjustment for BMI, smoking status, total–to–HDL cholesterol ratio, office systolic blood pressure, estimated glomerular filtration rate, and educational level.

brain abnormalities remained similar (Supplementary Tables 2 and 3). When we replaced office with 24-h ambulatory systolic blood pressure in the models, or added blood pressure–lowering and lipid-modifying medication to the models, associations remained similar (Supplementary Tables 4 and 5). Furthermore, when we additionally adjusted for eGFR <60 mL/min/1.73 m^2 and urinary albumin excretion >30 mg/24 h, associations did not materially change (Supplementary Tables 6 and 7). When we used HbA_{1c} to assess glucose metabolism status (NGM HbA_{1c} <5.7%, prediabetes HbA_{1c} 5.7–6.5%, and type 2 diabetes HbA_{1c} ≥6.5%), associations did not materially change (Supplementary Table 8). In addition, when we excluded participants with evidence of a brain infarct on MRI (n = 42 [data not shown]) or participants with an MRI lag time >1.0 years (n = 1,333) (Supplementary Table 9), associations remained similar. Finally, associations among prediabetes, type 2 diabetes, and measures of glycemia did not differ significantly between men and women ($P_{interaction}$ >0.10).

CONCLUSIONS

This study demonstrates that prediabetes, as well as continuous measures of hyperglycemia (HbA_{1c} and fasting and 2-h postload plasma glucose levels), is associated with structural brain abnormalities (cerebral small-vessel disease and brain atrophy), independent of major cardiovascular risk factors. To put these results into perspective, the structural brain abnormalities observed were comparable with 2.1 years of brain aging in prediabetes and 5.9 years in type 2 diabetes. This study therefore provides further evidence that prediabetes is not a benign state (25,36) and stresses that prediabetes provides an opportunity for the prevention of brain diseases.

This large population-based study shows that prediabetes and continuous measures of hyperglycemia are associated with LIs, WMHs, and brain atrophy. Thus, our findings are consistent with the concept that the associations between glycemia and structural brain abnormalities are of a continuous nature. In contrast to our findings, the ARIC-NCS study recently reported no associations of prediabetes with LIs, WMHs, CMBs, or smaller brain volumes (23). This may be explained by differences in study population, since the ARIC-NCS study population was ~16 years older compared with our study population, while there is evidence to suggest that the effects of cardiovascular risk factors (including hyperglycemia) on structural brain abnormalities are most profound in middle-aged individuals (24,37). In addition, the ARIC-NCS study determined prediabetes status based on HbA_{1c} levels only, whereas we determined prediabetes status based on both an OGTT and HbA_{1c} levels (Table 2 and Supplementary Table 8). Previous studies reported a higher prevalence of LIs and smaller white and gray matter volumes in type 2 diabetes (10) as well as (mostly nonsignificant) associations of prediabetes, HbA_{1c}, and fasting plasma glucose with brain volumes (15,38–48).

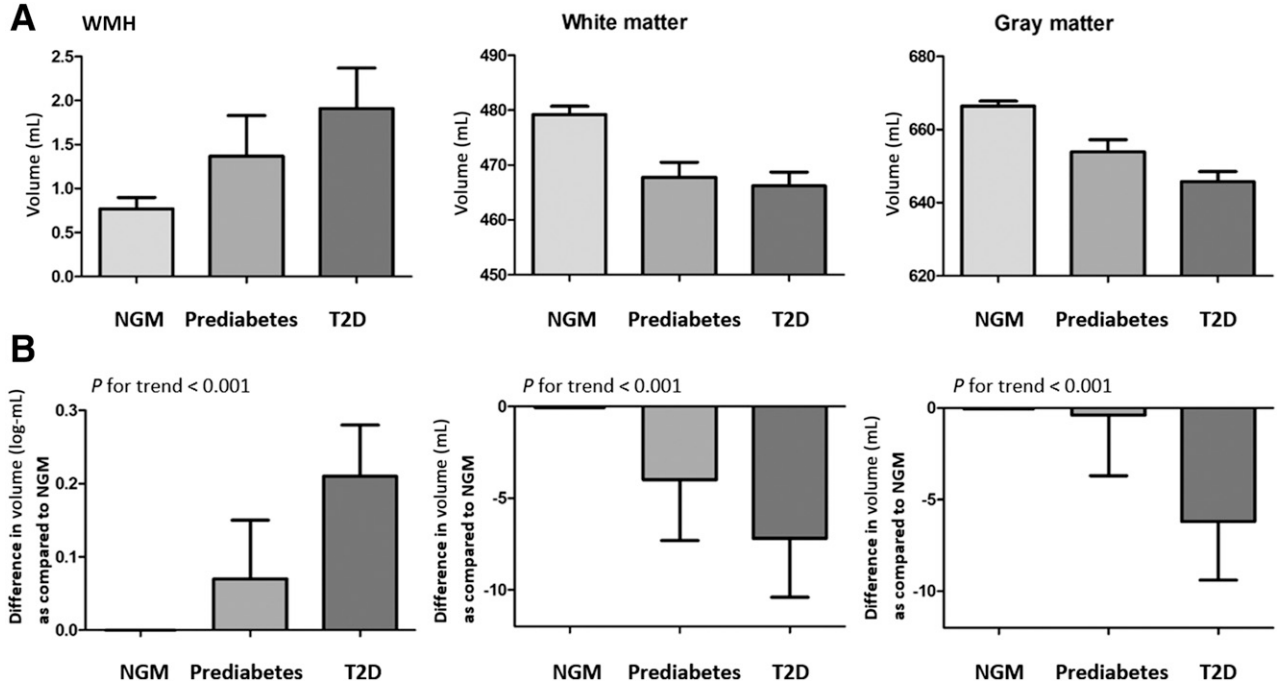

Figure 1—*A*: Mean volumes, adjusted for intracranial volume, of WMHs, white matter, and gray matter in individuals with NGM, individuals with prediabetes, and individuals with type 2 diabetes (T2D). *B*: Fully adjusted differences in volumes in participants with prediabetes and participants with type 2 diabetes compared with NGM. Data are presented as mean with 95% CI.

Importantly, and in contrast to previous studies (10,15,38–48), we used 3T MRI with SWI and GRE sequences, which increased sensitivity to detect structural brain abnormalities compared with 1.5T MRI without SWI (49,50). In addition, we showed that our findings were independent of a broad array of cardiovascular risk factors. We used linear trend analyses to test for a graded increase in structural brain abnormalities from NGM to prediabetes to type 2 diabetes. Indeed, the increase in structural brain abnormalities in prediabetes was approximately one-third to one-half that in type 2 diabetes (Table 3 and Fig. 1). In addition, the interpretation of a graded increase is supported by the significant associations of continuous measures of glycemia with structural brain abnormalities. We attribute the lack of statistical significance of the association between prediabetes and gray matter volumes to a type 2 statistical error because power in between-group comparisons is reduced compared with trend analyses. We found no associations of prediabetes, type 2 diabetes, or continuous measures of hyperglycemia with CMBs, which is in line with previous studies (51,52).

The associations of prediabetes and continuous measures of hyperglycemia with structural brain abnormalities can be explained by several, not mutually exclusive, mechanisms (53). First, hyperglycemia is associated with generalized, including cerebral, microcirculatory endothelial dysfunction (22), which in turn may lead to cerebral perfusion deficits, resulting in chronic ischemia of the brain tissue (54,55). Chronic ischemia can induce structural abnormalities in cerebral white matter, which are visualized as WMHs on MRI (54–61). The brain is particularly susceptible to such perfusion deficits, as it has a high energy demand but no reserve energy capacity. Moreover, the cerebral endothelium and blood-brain barrier are vulnerable to oxidative stress, which can occur as a result of hyperglycemia-associated increased production of reactive oxygen species and limited antioxidant defenses in the brain (62–65). Blood-brain barrier disruption, in turn, can lead to vessel wall thickening, disorganization and breakdown of the cerebral microcirculation, and enlargement of perivascular spaces, edema, and tissue damage, which can contribute to structural brain abnormalities (65,66). Second, hyperglycemia may directly induce neurodegeneration (glucotoxicity) through the polyol, hexosamine, and advanced glycation end product pathways; oxidative stress; and inflammation (67–69). Third, cerebral insulin resistance may impair regional glucose metabolism and disrupt the intracellular release, and extracellular clearance, of β-amyloid and thus contribute to neurodegeneration and brain atrophy. In addition, cerebral microvascular endothelial dysfunction and blood-brain barrier disruption may reduce insulin transport to brain parenchyma and thus further enhance cerebral insulin resistance (70,71).

Strengths of our study include its population-based design with oversampling of participants with type 2 diabetes, which enabled an accurate comparison of individuals with prediabetes compared with individuals with type 2 diabetes; the use of 3T MRI, which has a high sensitivity to detect WMHs (49), and the use of SWI, which has a high sensitivity to detect CMBs (50); the use of fully automated brain segmentation and WMH detection, which is the preferred technique for investigating brain anatomy (72); the use of HbA_{1c} levels and an OGTT to accurately characterize glucose metabolism; and the extensive assessment of potential confounders. Our study also has limitations. First, we used cross-sectional data; therefore, we cannot exclude reverse causality. In view of previous research (10), it is likely that hyperglycemia can cause structural

Table 3—Multivariable-adjusted associations of HbA_{1c}, fasting glucose, and 2-h postload glucose levels with structural brain abnormalities

	HbA_{1c}	*P*	Fasting glucose	*P*	2-h postload glucose	*P*
Markers of cerebral small-vessel disease						
LIs (yes/no), OR (95% CI)						
Model 1	1.28 (1.11–1.49)	0.001	1.22 (1.05–1.42)	0.009	1.19 (1.00–1.40)	0.047
Model 2	1.28 (1.09–1.50)	0.002	1.22 (1.03–1.44)	0.020	1.21 (1.01–1.44)	0.039
Total WMH volume (log-mL), β (95% CI)						
Model 1	0.10 (0.07–0.14)	<0.001	0.12 (0.08–0.15)	<0.001	0.12 (0.08–0.15)	<0.001
Model 2	0.09 (0.05–0.13)	<0.001	0.11 (0.07–0.15)	<0.001	0.11 (0.07–0.15)	<0.001
dWMH volume (log-mL), β (95% CI)						
Model 1	0.07 (0.03–0.11)	0.001	0.09 (0.05–0.12)	<0.001	0.07 (0.03–0.11)	<0.001
Model 2	0.06 (0.01–0.10)	0.008	0.08 (0.04–0.12)	<0.001	0.06 (0.02–0.11)	0.003
pWMH volume (log-mL), β (95% CI)						
Model 1	0.11 (0.08–0.15)	<0.001	0.13 (0.09–0.16)	<0.001	0.13 (0.09–0.17)	<0.001
Model 2	0.10 (0.06–0.14)	<0.001	0.12 (0.08–0.16)	<0.001	0.12 (0.08–0.16)	<0.001
CMBs (yes/no), OR (95% CI)						
Model 1	1.05 (0.92–1.19)	0.479	1.04 (0.91–1.19)	0.574	0.97 (0.85–1.11)	0.668
Model 2	1.04 (0.90–1.20)	0.580	1.03 (0.89–1.19)	0.668	0.98 (0.84–1.13)	0.743
Brain volumes						
White matter volume (mL), β (95% CI)						
Model 1	−0.02 (−0.04 to 0.00)	0.052	−0.03 (−0.05 to −0.01)	0.016	−0.04 (−0.06 to −0.02)	0.001
Model 2	−0.02 (−0.04 to 0.00)	0.032	−0.03 (−0.05 to −0.01)	0.007	−0.04 (−0.06 to −0.02)	<0.001
Gray matter volume (mL), β (95% CI)						
Model 1	−0.05 (−0.07 to −0.04)	<0.001	−0.05 (−0.07 to −0.03)	<0.001	−0.03 (−0.05 to −0.01)	0.004
Model 2	−0.04 (−0.06 to −0.02)	<0.001	−0.04 (−0.06 to −0.02)	0.001	−0.02 (−0.04 to 0.00)	0.035
CSF (mL), β (95% CI)						
Model 1	0.09 (0.06–0.11)	<0.001	0.09 (0.06–0.11)	<0.001	0.08 (0.05–0.10)	<0.001
Model 2	0.07 (0.05–0.10)	<0.001	0.08 (0.05–0.11)	<0.001	0.07 (0.05–0.10)	<0.001

Associations between continuous measures of glycemia and structural brain abnormalities in the study population. ORs with 95% CI represent the risk of the presence of LIs or CMBs, and standardized β and 95% CIs indicate the mean difference in WMH, dWMH, and pWMH volumes or white matter, gray matter, and CSF volumes per SD increase in HbA_{1c}, fasting plasma glucose, or 2-h postload glucose. Model 1: adjustment for age, sex, intracranial volume, and time between baseline and MRI measurements. Model 2: model 1 adjustments plus additional adjustment for BMI, smoking status, total–to–HDL cholesterol ratio, office systolic blood pressure, estimated glomerular filtration rate, and educational level.

brain abnormalities. However, the brain can directly regulate the glucose metabolism (73–75). Structural brain abnormalities may disrupt, or be a marker of disruption of, local signaling pathways, which may impair brain regulation of glucose metabolism (76). Thus, the associations we observed may be bidirectional. Second, the time passed between biochemical and MRI measurements might have influenced the associations observed; however, we adjusted for this in all analyses, which, moreover, did not significantly influence the results. In addition, we performed additional analyses in which participants with a MRI lag time >1.0 year were excluded, which did not substantially affect our results. Third, our study population was intensively treated with regard to cardiovascular risk factors, was mainly of Caucasian race, and was aged 40–75 years. This should be considered when extrapolating our findings to other populations. Fourth, although we adjusted for major potential confounders, including cardiovascular risk factors, we cannot fully exclude the possibility of residual confounding by variables not included in these analyses.

In conclusion, we showed, in a general population, that prediabetes and continuous measures of hyperglycemia are associated with structural brain abnormalities, independent of major cardiovascular risk factors. These findings support the concept that cerebrovascular and neurodegenerative abnormalities can already be observed in the prediabetes phase, prior to the diagnosis of type 2 diabetes, and contribute to the cerebral complications of type 2 diabetes and prediabetes, such as stroke, dementia, and depression. Our study supports the concept that treatment of prediabetes should be considered for the prevention of complications of type 2 diabetes (77), including structural brain abnormalities and brain disease.

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