



Reduced white matter microstructural integrity in prediabetes and diabetes: A population-based study

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Summary

Background White matter (WM) microstructural abnormalities have been observed in diabetes. However, evidence of prediabetes is currently lacking. This study aims to investigate the WM integrity in prediabetes and diabetes. We also assess the association of WM abnormalities with glucose metabolism status and continuous glucose measures.

Methods The WM integrity was analyzed using cross-sectional baseline data from a population-based Polyvascular Evaluation for Cognitive Impairment and vascular Events (PRECISE) study. The cohort, including a total of 2218 cases with the mean age of 61.3 ± 6.6 years and 54.1% female, consisted of 1205 prediabetes which are categorized into two subgroups (a group of 254 prediabetes with combined impaired fasting glucose (IFG) and impaired glucose tolerance (IGT) and the other group of 951 prediabetes without combined IFG/IGT), 504 diabetes, and 509 normal control subjects. Alterations of WM integrity were determined by diffusion tensor imaging along with tract-based spatial statistics analysis to compare diffusion metrics on WM skeletons between groups. The mixed-effects multivariate linear regression models were used to assess the association between WM microstructural alterations and glucose status.

Findings Microstructural abnormalities distributed in local WM tracts in prediabetes with combined IFG/IGT and spread widely in diabetes. These WM abnormalities are associated with higher glucose measures.

Interpretation Our findings suggest that WM microstructural abnormalities are already present at the prediabetes with combined IFG/IGT stage. Preventative strategies should begin early to maintain normal glucose metabolism and avert further destruction of WM integrity.

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Research in context

Evidence before this study

White matter microstructural abnormalities have been suggested as an important biomarker in diabetes. Previous studies utilizing diffusion tensor imaging have reported that white matter microstructural abnormalities were observed in diabetes. These abnormalities spread widely and were mainly located in commissural fibers, association fibers, and projection fibers, potentially contributing to neurobehavioral disorders. In contrast, evidence for white matter microstructural abnormalities in prediabetes is limited.

Added value of this study

We explored white matter microstructural abnormalities in diabetes, especially in prediabetes. Prediabetes is further categorized into subgroups with or without combined IFG/IGT. In this study, we observed white matter microstructural reductions at the local regions in prediabetes with combined IFG/IGT although no abnormalities were found in the whole prediabetes group. These abnormalities deteriorated when the disease progressed into the diabetes stage. Further, the white matter microstructural disruptions were associated with derangement of glucose metabolism.

Implications of all the available evidence

White matter microstructural reductions associated with abnormal glucose metabolism present at the prediabetic stage, specifically in prediabetes with combined IFG/IGT. The findings suggest that targeting the abnormalities by early glycemia intervention strategies may prevent a spectrum of diabetes-induced neurological disorders.

Introduction

Diabetes is a metabolic disorder with high and growing prevalence globally. The prevalence of diabetes in China has rapidly increased from 0.67% in 1980 to 10.4% in 2013, which brings a significant economic burden.^{1,2} Numerous studies suggest that diabetes contributed to a range of neurological disorders including stroke,³ dementia,⁴ depression,⁵ among others.^{6–8} Diabetes increases the burden of cerebral small vessel disease (SVD),^{9–11} manifested in the form of white matter (WM) abnormalities.^{12,13} A number of studies have observed macrostructural neuroimaging markers in diabetes including WM hyperintensities (WMH), WM lesions volume, and lacunes.^{10,14,15} In fact, WM microstructural abnormalities have been suggested as an important biomarker and considered in association with the etiology of diabetes-induced neurological disorders.^{16–18} Diffusion tensor imaging (DTI) is a sensitive and noninvasive tool for studying WM microstructural

integrity in living humans.¹⁹ It has been used in patients with diabetes. Alterations of diffusion metrics can reflect the changes in WM microstructural integrity. For example, decreased fractional anisotropy (FA) and increased mean diffusivity (MD) may occur as a result of demyelination or axonal damage of WM,^{20,21} which have been observed in diabetes.^{16,22–25} A population-based study has reported that individuals with diabetes displayed worse microstructural abnormalities of WM in the association tracts and forceps minor.²⁶ Despite these findings, investigations of the microstructural integrity of WM in prediabetes remain limited. Prediabetes refers to individuals whose glucose levels do not meet the criteria for diabetes but are higher than the normal level.²⁷ Prediabetes is considered a high-risk state for development of diabetes.²⁸ Recently, macrostructural abnormalities such as larger WM lesion volumes, more WMH, and abnormal WM network connectivity have been reported in prediabetes.^{13,29,30} Meanwhile, several studies suggest that microvascular dysfunction such as SVD was present in prediabetes,^{31,32} implicating that a reduction in microstructural integrity of WM might already occur in the prediabetes stage. However, there is only limited evidence in support of this notion.³³

It is critical to establish at what stage disruption of WM microstructural integrity begins. A previous study has reported that approximately 25% of individuals transitioned from early metabolic abnormalities, including impaired fasting glucose (IFG) and impaired glucose tolerance (IGT), to diabetes within 3–5 years, and about 70% of individuals with prediabetes eventually developed diabetes.³⁴ However, the heterogeneity of IFG and IGT in pathogenesis contributes to different rates in development of diabetes. Individuals with isolated IFG predominantly develop hepatic insulin resistance, whereas individuals with isolated IGT have normal to slightly reduced hepatic insulin sensitivity and develop moderate to severe muscle insulin resistance. Not surprisingly, individuals with combined IFG and IGT manifest both of these. Therefore, prediabetes with both IFG and IGT nearly double the rate of developing diabetes compared with those with just single metabolic abnormalities,^{35,36} and they were the high-risk population of prediabetes.^{36–38} Based on these findings, we separated prediabetes into two subgroups, i.e., prediabetes with combined IFG/IGT and prediabetes without combined IFG/IGT, to investigate at which stage of prediabetes WM microstructural abnormalities could be detected.

In this study, we report a detailed examination of WM microstructural abnormalities in the whole prediabetes, subgroups of prediabetes (prediabetes with or without combined IFG/IGT) and diabetes by DTI and tract-based spatial statistics (TBSS) analysis in a large population-based cohort. TBSS is an automated, observer-independent approach to examine the integrity of WM tracts on a voxel-wise basis. We also examined

whether WM microstructural disruption is associated with the status of glucose metabolism and continuous glucose measurements including fasting plasma glucose (FPG), 2-h post-load glucose, and glycated hemoglobin (HbA_{1c}).

Methods

Study population and design

We used data from the baseline (wave 1) assessment in the Polyvascular Evaluation for Cognitive Impairment and vaScular Events (PRECISE) study, which is known as a population-based prospective cohort study with a comprehensive evaluation of multiterritorial artery stenosis and plaque using advanced vascular imaging techniques and prospective collection of vascular events and cognitive assessments. Rationale and methodology of the study have been described previously.³⁹ Eligible for participation were all community-dwelling adults with ages between 50 and 75 years, with cluster sampled from six villages and four communities in Lishui city, China. The present report included cross-sectional data from 3067 participants who completed the baseline assessment between May 2017 and September 2019. MRI measurements were available in 2376 of 3067 participants. Of these, 156 participants were excluded owing to severe head motion ($n = 118$) and incomplete MRI data ($n = 38$). Complete clinical data were available from 2218 participants in the remaining 2220 participants (Figure 1).

Ethics

The PRECISE study was approved by the ethics committee at Beijing Tiantan Hospital (IRB approval number: KY2017-010-01) and Lishui Hospital (IRB approval number: 2016-42). All participants provided written informed consent before enrolling in the study. The trial was registered at ClinicalTrials.gov (NCT03178448).

Assessment of prediabetes and diabetes

For all participants, fasting blood samples were assayed for FPG and HbA_{1c} measurements. For those without a history of diabetes, a standardized oral glucose tolerance test (OGTT) (2-h 75-g) was performed. Participants with a history of diabetes or treated by hypoglycemic agents or insulin did not undergo the OGTT. Instead, the diabetic status was determined by the levels of FPG and HbA_{1c} and medication information in these individuals. All sampling and detection were centralized and completed in Lishui City Central Hospital. Fasting glucose and post-load glucose were measured by the enzymatic hexokinase method on two automatic analyzers (Abbott Architect C16000 and Abbott Architect I2000). HbA_{1c} was measured by an ion-exchange chromatography

method on an automatic analyzer (Tosoh INDIA HLC-723GB).

According to the diagnostic criteria recommended by American Diabetes Association (ADA) 2019,²⁷ diabetes was identified as self-reported diabetes previously diagnosis of diabetes by a physician, current use of anti-diabetic agents or FPG ≥ 7.0 mmol/L or 2-h post-load glucose ≥ 11.1 mmol/L or HbA_{1c} $\geq 6.5\%$ (48 mmol/mol). Prediabetes was defined as FPG ≥ 5.6 – 6.9 mmol/L or 2-h post-load glucose ≥ 7.8 – 11.0 mmol/L or HbA_{1c} ≥ 5.7 – 6.4% (39–47 mmol/mol). The remaining participants were considered normal glucose metabolism (NGM). Insolated IFG was defined by an elevated FPG concentration with a normal 2-h post-load glucose level. Insolated IGT was defined by an elevated 2-h post-load glucose concentration with a normal FPG level. Combined IFG/IGT was defined by fulfilling both criteria.³⁵ Participants with prediabetes were further separated into two subgroups: one subgroup with combined IFG/IGT regardless of HbA_{1c} level (hereafter called prediabetes with combined IFG/IGT) and the other subgroup consisting of the remaining participants, termed prediabetes without combined IFG/IGT (Supplementary Figure 1).

Image acquisition

MRI was performed on a 3.0 Tesla MRI scanner (Ingenia 3.0T, Philips, Best, The Netherlands). DTI data were acquired using a diffusion-sensitized spin-echo sequence with the following scan parameters: TR = 3500 ms, TE = 90 ms, 32 diffusion weighted directions with a b value of 1000 s/mm², and a single image with a b value of 0 s/mm², slice thickness = 2.5mm, no interslice gap, slices = 56, matrix size = 128 × 128, SENSE in-plane acceleration = 2, and voxel size = 2.5 × 2.5 × 2.5 mm³.

DTI image preprocessing

DTI processing was performed using FMRIB's Diffusion Toolbox of FMRI's Software Library (FSL, version 6.0.5, www.fmrib.ox.ac.uk/fsl/). First, FSL's "eddy_correct" (affine registration) command was applied to compensate eddy-current-induced and motion-related distortions. Second, the values of FA and MD were calculated by fitting a diffusion tensor model at each voxel.^{40,41}

TBSS statistical analysis

Voxel-wise statistical analysis of the images was performed by TBSS to determine group differences in WM microstructure.⁴² Briefly, FSL's nonlinear image registration algorithm was used to align all subjects' FA images into FMRIB58_FA template in Montreal Neurological Institute standard space. The mean of all aligned FA images was created, followed by creation of a

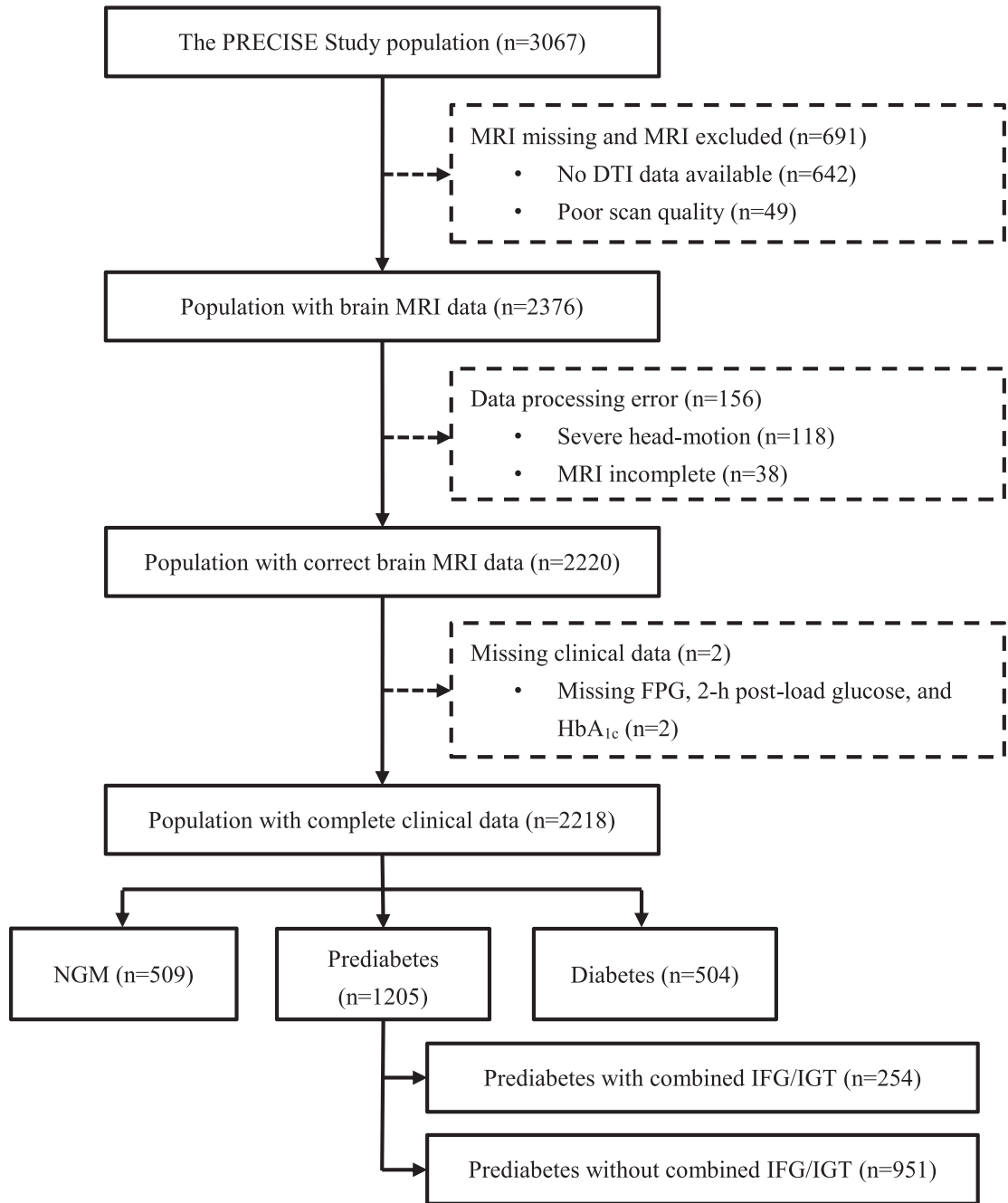


Figure 1. Flowchart of the study population.

NGM, normal glucose metabolism; FPG, fasting plasma glucose; IFG, impaired fasting glucose; IGT, impaired glucose tolerance.

skeletonized mean FA image by applying “thinning” (non-maximum-suppression perpendicular to the local tract structure). The threshold of the FA skeleton was 0.2 to include only white matter. Next, each subject’s FA image was projected onto the skeleton by filling the skeleton with FA values from the nearest relevant tract center. The maximum value in the subject’s FA image was obtained by searching perpendicular to the local

skeleton structure in each skeleton voxel. Finally, differences in the whole brain WM at the voxel level between (pre)diabetes groups and NGM group, including prediabetes and NGM, prediabetes with combined IFG/IGT subgroup and NGM, prediabetes without combined IFG/IGT subgroup and NGM, diabetes and NGM in which NGM served as the reference group, were analyzed using a nonparametric permutation-based

inference tool (FSL's "randomize"). The number of permutations was set to 5000 and was corrected using both threshold-free cluster enhancement (TFCE) and family-wise error (FWE) multiple comparison methods ($P < 0.05$ was considered statistically significant). Age and gender were added as covariates. Individual non-linear warps and skeleton projection of FA images were used to project MD onto the skeleton. The statistical methods for MD values were similar to the FA analysis.

The abnormal WM skeleton regions with statistically significant differences compared with NGM in TBSS analysis were labeled with reference to John Hopkins University (JHU) WM atlas (ICBM_DTI_81)⁴³ (Supplementary Table 1). The voxel numbers in the damaged area within different JHU regions were calculated and computed to obtain the percentage of damage voxel numbers (damaged voxels in JHU_{*i*}/total voxels in JHU_{*i*}, *i* means the *i*th JHU region). To obviate circular analysis,⁴⁴ the top five JHU regions with the largest percentage of damaged voxel numbers in diabetes were regarded as the regions of interest (ROIs). Finally, the mean values of FA and MD were computed in the whole white matter skeleton (hereafter called global FA values and global MD values) and the five JHU ROIs' skeletons.

Statistical analysis

Clinical characteristics of the participants were presented as mean \pm SD or median with interquartile range for continuous variables, and as percentages for categorical variables. Clinical characteristics were compared between glycemic metabolic groups by ANOVA for continuous variables with a normal distribution, Kruskal–Wallis test for continuous variables with skewed distribution, and Pearson's Chi-Square test for categorical variables. $P < 0.05$ was considered significant. Bonferroni corrected for all multiple comparisons.

The mixed-effects multivariate linear regression models were used to investigate the association of glucose metabolism status with the global FA(MD) and the ROIs' FA(MD) values, with glucose metabolism status as the fixed effect and communities as the random effect. All data were standardized before regression. To test for a linear trend of alterations of FA(MD) values over glucose status, the status of categorical variable glucose metabolism (NGM = 0, prediabetes without combined IFG/IGT = 1; prediabetes with combined IFG/IGT = 2; diabetes = 3) were used in the mixed-effects multivariate linear regression models. To assess regression coefficients per glucose metabolism status, analyses were adjusted for potential confounders, including age (years), sex (male or female), and educational level (illiteracy, elementary school, middle or high school, college or above) (model 1). Additional factors for adjustment included body mass index (continuous), hypertension (self-reported hypertension previously diagnosed

by a physician or current use of antihypertensive agents or systolic blood pressure ≥ 140 mm Hg or diastolic blood pressure ≥ 90 mm Hg), hyperlipidemia (yes or no), eGFR (continuous), history of stroke (yes or no), history of heart disease (yes or no), smoking (never, current or quit), and the use of lipid-modifying medication (yes or no) and antihypertension medication (yes or no) (model 2) (details of the clinical measurements performed see Supplementary Methods). The Linear mixed-effects models were used to investigate the potential association of continuous clinical glucose measures (FPG, 2-h post-load glucose, and HbA_{1c}) with the global FA(MD) and ROIs' FA(MD) values. Assessment of regression coefficients were adjusted for potential confounders described in model 1 and model 2. For multiple statistical tests, false discovery rate (FDR) correction with alpha = 0.05 was performed. $P < 0.05$ was considered statistically significant. Furthermore, a Wilcoxon rank sum test was performed to compare the differences in WMH volumes between (pre)diabetes groups and the control group (NGM). Pearson correlation analysis was carried out to examine the potential relationship between the global diffusion metrics (global FA and MD values) and total WMH volumes (details see Supplementary Methods). Statistical analyses were all performed using SAS 9.4 (SAS Institute Inc, Cary, NC).

Role of the funding source

The funders played no role in the study design, the collection, analysis, or interpretation of data, nor the preparation, or approval of the manuscript for publication.

Results

General characteristics of the study population

The study population consisted a total of 2218 participants. Individuals included in the study population had general characteristics similar to subjects who were excluded, and they were more likely to live in the community, have slightly higher fasting glucose and HbA_{1c} level, and have a higher education level. The study population included 509 (23.0%) NGM, 1205 (54.3%) prediabetes and 504 (22.7%) diabetes. The mean age was 61.3 \pm 6.6 years, and 54.1% were women (Supplementary Table 2). Compared with NGM, Participants with prediabetes and diabetes were older, more often had an adverse cardiovascular risk profile, and have larger WMH volume (Table 1). Participants in prediabetes with combined IFG/IGT (254 participants) were more likely to have an adverse cardiovascular risk profile and have larger WMH volume compared with prediabetes without combined IFG/IGT (951 participants) and NGM. Of 504 participants with diabetes, only 263 participants who were newly diagnosed diabetes performed OGTT and obtained 2-h post-load glucose data. The

	NGM (n = 509)	Prediabetes (n = 1205)	Diabetes (n = 504)	P
Demographics				
Age (years)	59.8±6.1	61.3±6.5 ^A	63.1±6.8 ^{B,C}	<0.001
Sex (% female)	53.2	54.3	54.6	0.90
Community/Village (% community)	63.1	61.7	66.1	0.24
Ethnicity (% Han)	96.1	96.1	97.6	0.27
Glucose metabolism				
Fasting glucose (mmol/L)	5.1±0.3	5.6±0.5 ^A	7.8±2.4 ^{B,C}	<0.001
2-h post-load glucose (mmol/L) *	6.0±1.1	7.3±1.7 ^A	12.8±3.6 ^{B,C}	<0.001
HbA _{1c} (%)	5.4±0.2	5.8±0.3 ^A	7.1±1.4 ^{B,C}	<0.001
HbA _{1c} (mmol/mol)	35.4±2.6	39.4±3.4 ^A	54.3±15.1 ^{B,C}	<0.001
Cardiovascular risk factors				
BMI (kg/m ²)	23.2±2.7	24.0±3.0 ^A	24.7±3.2 ^{B,C}	<0.001
Systolic BP (mmHg)	124.5±15.7	129.8±15.5 ^A	135.2±16.9 ^{B,C}	<0.001
Diastolic BP (mmHg)	73.4±8.5	75.7±9.0 ^A	76.8±8.6 ^B	<0.001
Hypertension (%)	30.3	42.7 ^A	60.9 ^{B,C}	<0.001
Total-to-HDL cholesterol ratio	3.9±1.1	4.1±1.1 ^A	4.2±1.1 ^B	<0.001
Triglycerides (mmol/L)	1.5±1.1	1.8±1.2 ^A	2.1±1.5 ^{B,C}	<0.001
Hyperlipidemia (%)	35.4	43.5 ^A	54.2 ^{B,C}	<0.001
eGFR (mL/min/1.73 m ²)	103.0±11.0	101.1±12.7	101.7±13.3	0.05
History of stroke (%)	2.4	2.3	3.6	0.31
History of heart disease (%)	5.7	8.8	11.9 ^B	0.002
Medication use (%)				
Lipid-lowering	1.8	4.1	8.5 ^{B,C}	<0.001
Antihypertensive	17.5	25.6 ^A	38.9 ^{B,C}	<0.001
Diabetes treatment (%)	–	–	43.5	–
Insulin	–	–	8.3	–
Oral hypoglycemic agents	–	–	37.5	–
Lifestyle factors (%)				
Smoking, never/current/quit	64.4/23.0/12.6	69.1/19.5/11.4	67.7/16.7/15.7	0.02
Education, illiteracy or elementary school / middle or high school / college or above	36.1/55.0/8.8	40.8/51.4/7.8	44.0/48.6/7.3	0.15
WMH volume (log cm ³) #	−0.0±1.8	0.2±1.7 ^A	0.6±1.7 ^{B,C}	<0.001

Table 1: Clinical characteristics of participants.
 Data are presented as means ± SD or percentage.
 * 2-h post-load glucose values were available in n = 1977. #WMH volume values were available in n = 2217.
^A prediabetes vs. NGM, *P* < 0.017;
^B diabetes vs. NGM, *P* < 0.017;
^C diabetes vs. prediabetes, *P* < 0.017 (Bonferroni corrected).
 BMI, body mass index; BP, blood pressure; HDL, high-density lipoproteins; eGFR, estimated glomerular filtration rate; WMH, white matter hyperintensity.

remaining 241 participants had a history of diabetes in which 17.4% of participants were treated with insulin and 78.4% of participants were treated with oral hypoglycemic agents (Supplementary Table 3).

TBSS statistical results

TBSS statistical analyses showed no significant differences between the whole group of prediabetes and NGM. However, a significant decrease of FA and a significant increase of MD were found in restricted WM tracts in prediabetes with combined IFG/IGT subgroup as compared with NGM (permutation test, *P* < 0.05, FWE corrected) (Figure 2a). Decreased FA was mainly observed

in the bilateral anterior corona radiata (ACR) and the right side of superior longitudinal fasciculus (SLF), posterior corona radiata (PCR), and anterior limb of internal capsule (ALIC). Increased MD was mainly observed in the right side of external capsule (EC), ACR, ALIC, SLF, and superior corona radiata (SCR) (Supplementary Table 4 for a complete listing of results). No significant differences were found between prediabetes without combined IFG/IGT and NGM in all diffusion metrics.

Voxel-wise TBSS statistical analyses revealed a significant decrease of FA and a significant increase of MD in widespread WM tracts in individuals with diabetes compared with NGM (permutation test, *P* < 0.05, FWE corrected) (Figure 2b). Compared with prediabetes with

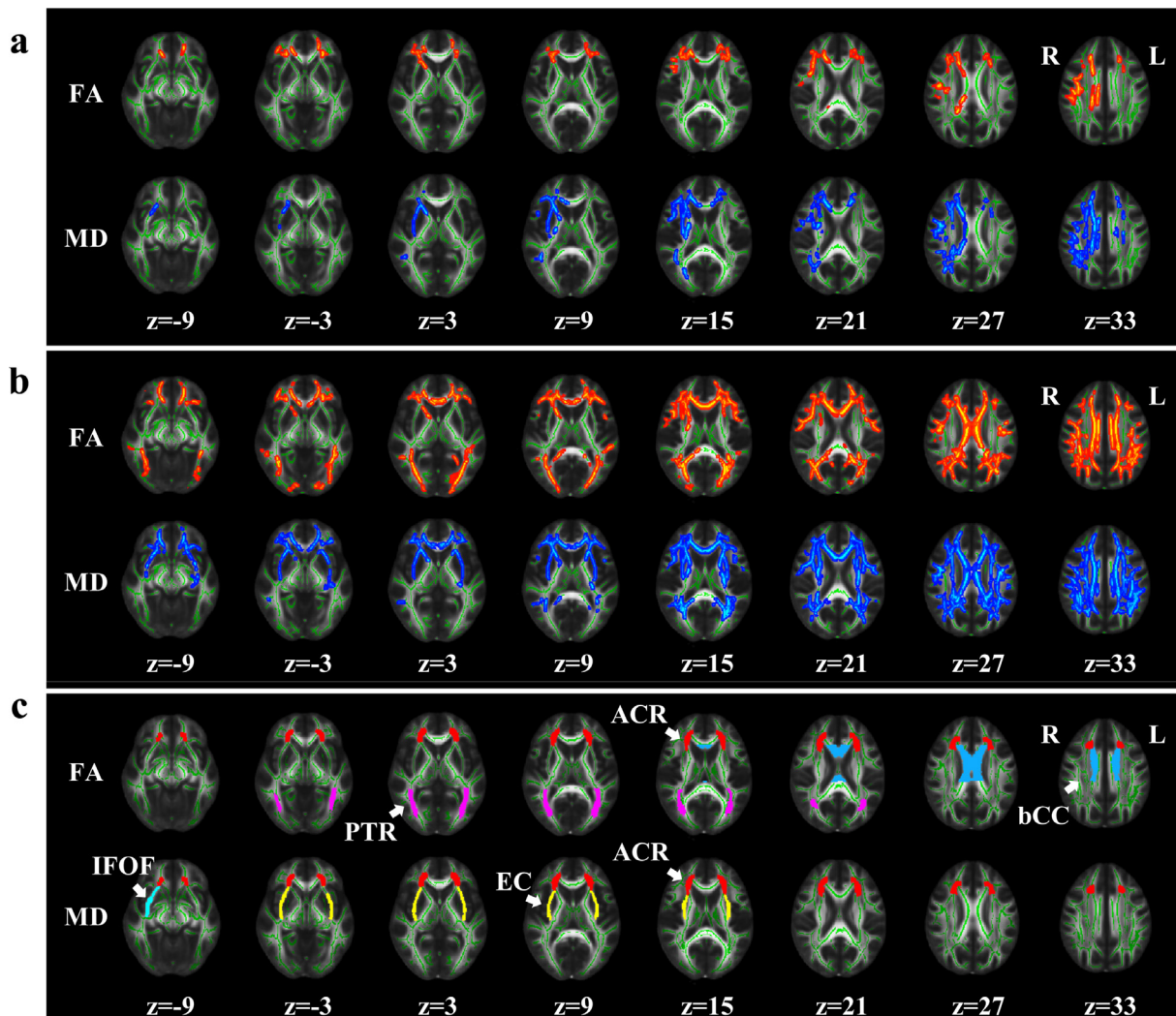


Figure 2. (a) Differences in TBSS analysis results of FA and MD in prediabetes with combined IFG/IGT subgroup relative to normal glucose metabolism (NGM). (b) Differences in TBSS analysis results of FA and MD in diabetes relative to NGM. Red-yellow (thickened for better visibility) regions represent tracts with decreased FA (permutation test, $P < 0.05$, FWE corrected); and blue-light-blue (thickened for better visibility) regions represent tracts with increased MD (permutation test, $P < 0.05$, FWE corrected). (c) The ROIs of FA and MD images in diabetes were labeled with reference to JHU atlas and shown in different colors. Results are overlaid on the mean FA skeleton (green) and Montreal Neurological Institute 152-FA template (gray).

FA, fraction anisotropy; MD, mean diffusivity; bCC, body of corpus callosum; ACR, anterior corona radiata; PTR, posterior thalamic radiation (include optic radiation); EC, external capsule; IFOF, inferior fronto-occipital fasciculus; R, right; L, left.

combined IFG/IGT, decreased FA spread to a wider area that was mainly involved in the regions including the body of corpus callosum (bCC), the bilateral ACR, and posterior thalamic radiation (PTR). Increased MD mainly spread to the bilateral ACR, EC and the right IFOF. These abnormal regions in FA and MD images had the largest percentage of damaged voxel numbers and were considered as the mainly damaged ROIs (Figure 2c) (Supplementary Table 4 for a complete listing of results).

Associations of glucose metabolism status with diffusion metrics

After full adjustment, prediabetes without combined IFG/IGT, prediabetes with combined IFG/IGT and diabetes were significantly associated with lower FA values in bCC, the bilateral ACR and PTR (all $P_{\text{trend}} < 0.05$, linear mixed model, FDR corrected), higher global MD values ($P_{\text{trend}} < 0.05$, linear mixed model), and higher MD value in the right EC and IFOF ($P_{\text{trend}} < 0.05$, linear mixed model, FDR corrected) compared with NGM.

	Prediabetes without combined IFG/IGT	Prediabetes with combined IFG/IGT	Diabetes	P_{trend}	P_{trend} (FDR)
FA_Global, β (95% CI)					
Model 1	0.03 (-0.08, 0.13)	-0.05 (-0.19, 0.09)	-0.09 (-0.21, 0.03)	0.05	-
Model 2	0.02 (-0.08, 0.12)	-0.04 (-0.18, 0.11)	-0.08 (-0.2, 0.04)	0.11	-
FA_bCC, β (95% CI)					
Model 1	0.004 (-0.09, 0.10)	-0.06 (-0.19, 0.08)	-0.22 (-0.33, -0.11)	<0.001	<0.001
Model 2	0.01 (-0.09, 0.10)	-0.05 (-0.18, 0.09)	-0.21 (-0.33, -0.09)	<0.001	<0.001
FA_ACR.R, β (95% CI)					
Model 1	-0.01 (-0.10, 0.09)	-0.13 (-0.26, 0.01)	-0.11 (-0.22, 0.01)	<0.001	<0.001
Model 2	-0.02 (-0.11, 0.08)	-0.14 (-0.28, -0.006)	-0.12 (-0.24, -0.004)	0.01	0.02
FA_ACR.L, β (95% CI)					
Model 1	-0.01 (-0.10, 0.09)	-0.16 (-0.29, -0.02)	-0.17 (-0.28, -0.06)	<0.001	<0.001
Model 2	-0.002 (-0.10, 0.09)	-0.13 (-0.26, 0.01)	-0.14 (-0.26, -0.03)	0.004	0.01
FA_PTR.R, β (95% CI)					
Model 1	-0.03 (-0.14, 0.07)	-0.05 (-0.19, 0.09)	-0.18 (-0.30, -0.07)	0.002	0.002
Model 2	-0.02 (-0.12, 0.08)	-0.005 (-0.15, 0.14)	-0.14 (-0.26, -0.02)	0.03	0.03
FA_PTR.L, β (95% CI)					
Model 1	-0.004 (-0.11, 0.10)	-0.08 (-0.22, 0.06)	-0.18 (-0.30, -0.06)	<0.001	<0.001
Model 2	0.01 (-0.10, 0.11)	-0.04 (-0.19, 0.1)	-0.14 (-0.26, -0.02)	0.01	0.02
MD_Global, β (95% CI)					
Model 1	-0.04 (-0.13, 0.05)	0.07 (-0.06, 0.20)	0.13 (0.02, 0.23)	0.003	-
Model 2	-0.04 (-0.13, 0.05)	0.04 (-0.09, 0.16)	0.09 (-0.01, 0.20)	0.02	-
MD_ACR.R, β (95% CI)					
Model 1	0.05 (-0.05, 0.15)	0.13 (0, 0.27)	0.20 (0.08, 0.31)	<0.001	<0.001
Model 2	0.02 (-0.08, 0.11)	0.04 (-0.09, 0.18)	0.11 (-0.01, 0.22)	0.05	0.07
MD_ACR.L, β (95% CI)					
Model 1	0.05 (-0.04, 0.15)	0.12 (-0.02, 0.26)	0.15 (0.04, 0.27)	0.01	0.01
Model 2	0.03 (-0.06, 0.13)	0.06 (-0.08, 0.19)	0.09 (-0.03, 0.20)	0.14	0.14
MD_EC.R, β (95% CI)					
Model 1	0.02 (-0.07, 0.12)	0.19 (0.06, 0.32)	0.17 (0.06, 0.28)	<0.001	<0.001
Model 2	0.0001 (-0.09, 0.09)	0.11 (-0.02, 0.24)	0.08 (-0.03, 0.19)	0.05	0.07
MD_EC.R, β (95% CI)					
Model 1	0.01 (-0.08, 0.10)	0.17 (0.04, 0.29)	0.18 (0.08, 0.28)	<0.001	<0.001
Model 2	-0.001 (-0.09, 0.09)	0.11 (-0.01, 0.24)	0.12 (0.02, 0.23)	0.005	0.02
MD_IFOF.R, β (95% CI)					
Model 1	0.002 (-0.09, 0.10)	0.13 (-0.01, 0.26)	0.14 (0.03, 0.25)	0.002	0.003
Model 2	-0.001 (-0.10, 0.09)	0.10 (-0.03, 0.24)	0.12 (0, 0.23)	0.01	0.03

Table 2: Multivariable-adjusted differences in FA and MD values among individuals with prediabetes and diabetes, as compared to NGM.

FA(MD)_Global indicated the mean FA(MD) values in the whole white matter skeleton. Model 1: adjustment for age, sex, and education level. Model 2: model 1 additionally adjusted for BMI, hypertension, hyperlipidemia, eGFR, history of stroke, history of heart disease, smoking, and the use of lipid-modifying medication and antihypertension medication. Boldface type indicated $P_{trend} < 0.05$ (linear mixed analyses) and P_{trend} (FDR) < 0.05 (linear mixed analyses, FDR corrected).

FDR, false discovery rate; IFG, impaired fasting glucose; IGT, impaired glucose tolerance; FA, fractional anisotropy; MD, mean diffusivity, eGFR, estimated glomerular filtration rate; bCC, body of corpus callosum; ACR, anterior corona radiata; PTR, posterior thalamic radiation (include optic radiation); EC, external capsule; IFOF, inferior fronto-occipital fasciculus; R, right; L, left.

The regression coefficients of FA values in bCC, the left ACR and PTR were reduced gradually from prediabetes without combined IFG/IGT to diabetes. Conversely, the regression coefficients of the global MD value and the MD value in the right EC and IFOF were increased gradually from prediabetes without combined IFG/IGT to diabetes. No associations were found in glucose metabolism status with the alterations of global FA value, and the MD values in the bilateral ACR and the right EC after full adjustments (Table 2).

Associations of continuous clinical glucose measures with diffusion metrics

After full adjustments, FPG and HbA_{1c} levels were associated with lower global FA values ($\beta = -0.15$ [95% CI: -0.09 to -0.01], $P < 0.05$, and $\beta = -0.05$ [95% CI: -0.09 to -0.01], $P < 0.05$, respectively, linear mixed model) and lower FA values in bCC, the bilateral ACR and PTR (all $P < 0.05$, linear mixed model, FDR corrected). No associations were found between the 2-h post-load glucose levels and the alterations of all FA values. No

	FPG			2-h post-load glucose*			HbA _{1c}		
	β (95% CI)	P	P (FDR)	β (95% CI)	P	P (FDR)	β (95% CI)	P	P (FDR)
FA_Global									
Model 1	-0.05 (-0.09, -0.02)	0.01	-	0.02 (-0.02, 0.06)	0.40	-	-0.05 (-0.09, -0.01)	0.01	-
Model 2	-0.05 (-0.09, -0.01)	0.02	-	0.02 (-0.02, 0.06)	0.31	-	-0.05 (-0.09, -0.01)	0.02	-
FA_bCC									
Model 1	-0.10 (-0.14, -0.07)	<0.001	<0.001	-0.03 (-0.07, 0.01)	0.14	0.23	-0.09 (-0.13, -0.05)	<0.001	<0.001
Model 2	-0.10 (-0.14, -0.06)	<0.001	<0.001	-0.03 (-0.07, 0.01)	0.17	0.47	-0.09 (-0.12, -0.05)	<0.001	<0.001
FA_ACR.R									
Model 1	-0.06 (-0.10, -0.03)	0.001	0.001	-0.04 (-0.08, 0)	0.08	0.21	-0.07 (-0.11, -0.03)	<0.001	<0.001
Model 2	-0.05 (-0.09, -0.01)	0.02	0.02	-0.02 (-0.06, 0.02)	0.32	0.54	-0.06 (-0.10, -0.02)	0.004	0.005
FA_ACRL									
Model 1	-0.07 (-0.11, -0.03)	<0.001	<0.001	-0.04 (-0.08, 0)	0.08	0.21	-0.07 (-0.11, -0.03)	<0.001	<0.001
Model 2	-0.06 (-0.09, -0.02)	0.005	0.01	-0.03 (-0.07, 0.01)	0.19	0.47	-0.06 (-0.10, -0.02)	0.002	0.003
FA_PTR.R									
Model 1	-0.06 (-0.10, -0.02)	0.003	0.003	-0.01 (-0.05, 0.03)	0.63	0.63	-0.07 (-0.11, -0.03)	<0.001	<0.001
Model 2	-0.04 (-0.08, 0)	0.04	0.04	0.01 (-0.04, 0.05)	0.82	0.96	-0.06 (-0.10, -0.02)	0.005	0.005
FA_PTR.L									
Model 1	-0.07 (-0.11, -0.03)	<0.001	<0.001	-0.01 (-0.05, 0.03)	0.62	0.63	-0.08 (-0.12, -0.04)	<0.001	<0.001
Model 2	-0.06 (-0.10, -0.02)	0.01	0.01	0.001 (-0.04, 0.04)	0.96	0.96	-0.07 (-0.11, -0.03)	0.001	0.003
MD_Global									
Model 1	0.04 (0.01, 0.08)	0.02	-	0.01 (-0.03, 0.05)	0.63	-	0.04 (0.01, 0.08)	0.02	-
Model 2	0.03 (-0.01, 0.06)	0.11	-	0 (-0.04, 0.04)	1.00	-	0.04 (0, 0.07)	0.05	-
MD_ACR.R									
Model 1	0.04 (0.01, 0.08)	0.02	0.04	0.02 (-0.02, 0.06)	0.29	0.08	0.04 (0, 0.08)	0.04	0.10
Model 2	0.01 (-0.02, 0.05)	0.46	0.76	-0.01 (-0.05, 0.03)	0.65	0.72	0.01 (-0.02, 0.05)	0.46	0.76
MD_ACRL									
Model 1	0.02 (-0.02, 0.06)	0.23	0.23	0.01 (-0.03, 0.05)	0.70	0.08	0.02 (-0.01, 0.06)	0.22	0.22
Model 2	0 (-0.04, 0.04)	0.97	0.99	-0.01 (-0.06, 0.03)	0.49	0.72	0.01 (-0.03, 0.04)	0.77	0.96
MD_EC.R									
Model 1	0.03 (-0.01, 0.07)	0.11	0.14	0.04 (0, 0.08)	0.06	0.08	0.02 (-0.01, 0.06)	0.21	0.22
Model 2	0 (-0.04, 0.04)	0.99	0.99	0.01 (-0.03, 0.05)	0.72	0.72	0 (-0.04, 0.04)	0.98	0.98
MD_EC.L									
Model 1	0.04 (0.01, 0.08)	0.02	0.04	0.03 (-0.01, 0.07)	0.09	0.08	0.03 (0, 0.07)	0.07	0.12
Model 2	0.02 (-0.01, 0.06)	0.22	0.55	0.01 (-0.02, 0.05)	0.51	0.72	0.02 (-0.02, 0.05)	0.36	0.76
MD_IFOF.R									
Model 1	0.05 (0.01, 0.09)	0.01	0.04	0 (-0.04, 0.04)	1.00	0.08	0.04 (0, 0.08)	0.03	0.10
Model 2	0.04 (0, 0.08)	0.04	0.22	-0.01 (-0.05, 0.03)	0.53	0.72	0.04 (0, 0.08)	0.05	0.25

Table 3: Multivariable-adjusted associations of FPG, 2-h post-load glucose, and HbA_{1c} levels with FA and MD values.

FA(MD)_Global indicated the mean FA(MD) values in the whole white matter skeleton. *2-h post-load glucose values were available in n = 1977. Model 1: adjustment for age, sex, and education level. Model 2: model 1 additionally adjusted for BMI, hypertension, hyperlipidemia, eGFR, history of stroke, history of heart disease, smoking, and the use of lipid-modifying medication and antihypertension medication. Boldface type indicated $P < 0.05$ (linear mixed model) and P (FDR) < 0.05 (linear mixed model, FDR corrected).

FDR, false discovery rate; IFG, impaired fasting glucose; IGT, impaired glucose tolerance; FA, fractional anisotropy; MD, mean diffusivity; eGFR, estimated glomerular filtration rate; bCC, body of corpus callosum; ACR, anterior corona radiata; PTR, posterior thalamic radiation (include optic radiation); EC, external capsule; IFOF, inferior fronto-occipital fasciculus; R, right; L, left.

associations were found between glucose measures and alterations of all MD values after full adjustments (Table 3).

Additional analyses: WMH volumes and diffusion metrics

The total WMH volumes in prediabetes with combined IFG/IGT subgroup and diabetes group were significantly

larger than those in the NGM group ($P < 0.05$, Wilcoxon rank sum test, FDR corrected), whereas no differences were found in prediabetes without combined IFG/IGT subgroup compared with the NGM group (Supplementary Figure 2a and Supplementary Figure 2b). The global FA values were negatively correlated with the WMH volumes ($r = -0.3701$, $P < 0.001$, Pearson correlation, Supplementary Figure 2c). In contrast, the global MD values

were positively correlated with the WMH volumes ($r = 0.5161$, $P < 0.001$, Pearson correlation, Supplementary Figure 2d).

Discussion

This population-based study showed reduced WM microstructural integrity in both prediabetes with combined IFG/IGT and diabetes, which was distributed at the specific local regions and involved in a wide range of the brain, respectively. Meanwhile, the damaged microstructural regions deteriorated significantly as prediabetes progressed to diabetes. These WM microstructural abnormalities were associated with higher clinical glucose measures including FPG and HbA_{1c}.

We investigated microstructural abnormalities of WM in the brain by DTI, a sensitive tool detecting directional diffusion of water molecules in tissues. In fibrous tissues such as WM, water diffusion is relatively unimpeded in the directions parallel to the fiber. However, it is highly restricted and hindered in the directions perpendicular to the fiber. Therefore, the diffusion in WM is anisotropic. MD and FA are two sensitive diffusion metrics used to measure the average movement and anisotropy of water molecules in WM.⁴⁵ Water diffusion is altered by impairment in WM microstructure due to ischemia, demyelination, axonal damage, inflammation, and edema.⁴⁶ A number of studies have shown that decreased FA and increased MD could indicate represented a lower WM microstructural integrity.^{47,48} FA and MD have been considered important composite metrics in measurements of WM microstructural abnormalities. In particular, FA is highly sensitive to microstructural changes.⁴⁵

In this study, we showed that WM microstructural abnormalities were already present in prediabetes, evidenced by decreased FA and increased MD values. Specifically, the reduced WM integrity was detected in prediabetes with combined IFG/IGT, suggesting that the prediabetes subgroup is at high risk for progression to diabetes. We also detected widespread WM microstructural abnormalities in diabetes. Compared with diabetes, disruption of WM microstructural integrity in prediabetes with combined IFG/IGT was located in specific local WM regions. We found that the damage regions were not prominent in the corpus callosum (CC), a principal commissural WM bundle connecting the left and right cerebral hemisphere,⁴⁹ suggesting that abnormal glucose metabolism mainly influences intra-hemispheres in prediabetes with combined IFG/IGT. Interestingly, we also found that the regions with reduced WM integrity tended to right-lateralize. Previous studies have reported that glucose metabolism was relatively higher in the right dorsal mesio-anterior cerebellum, lateral frontal and widespread temporal regions, insula and medial globus pallidus.^{50,51} Meanwhile, the

right hemisphere has a larger overall blood supply than the left hemisphere,⁵² thereby more prone to damage by hyperglycemia. Our results might provide evidence of neuroimaging to support the previous findings. However, the studies of cerebral metabolic asymmetries in prediabetes and diabetes are currently limited, and the precise pathogenic mechanisms remain to be determined. Our studies revealed that microstructural abnormalities of WM spread more widely with the development of diabetes. CC was one of the most severe damage regions in diabetes. Adverse effects of abnormal glucose metabolism might gradually spread from intra-hemispheres to inter-hemispheres, eventually causing a wide distribution of diabetes-induced WM microstructural abnormalities in a large part of the brain. These results were consistent with the previous studies.^{16,26,53} Moreover, the damaged WM regions were also in line with the view that diabetes contributes to neurological disorders. Diabetes-related markers of SVD, such as WMH and lacunes, are associated with neurological disorders (such as cognitive disorders,⁵⁴ mood disturbances⁵⁵) and gait problems,⁵⁶ which are well-recognized clinical expressions of SVD.⁵⁷ Our study showed severely damaged WM tracts in diabetes that have been related to these clinical abnormalities. For example, PTR is associated with the processing speed,⁵⁸ EC is associated with executive dysfunction,¹⁶ ACR, IFOF, and CC are associated with the depressive symptoms;⁵⁹ and CC damage is also associated with a lower gait velocity.⁶⁰ More importantly, we found that disruptions of the WM integrity appeared already in the same regions in prediabetes with combined IFG/IGT, indicating that the functional abnormalities might result from early alterations of WM microstructure which would be difficult to detect by clinical scales because of extremely mild symptoms.

The current study showed that the WM microstructural abnormalities were associated with glucose metabolism status (prediabetes without combined IFG/IGT, prediabetes with combined IFG/IGT, and diabetes) and continuous measures of hyperglycemia including FPG and HbA_{1c}, independent from cardiovascular risk factors, smoking status, and the use of medication. The associations were more likely to be reflected in the sensitive FA value. These findings indicate that deterioration of WM tracts becomes more pronounced in the progression from prediabetes to diabetes. Although TBSS analysis revealed no significant differences between prediabetes without combined IFG/IGT subgroup and NGM, the glucose metabolism status were continuously associated with the gradual decrease of FA values and the gradual increase of MD values. The interpretation of a graded reduction of WM integrity was indeed supported by the significant associations of continuous measures of glycemia with WM microstructural abnormalities. These results implicate that WM tracts might begin to be disrupted in the stage of prediabetes,

although abnormalities of WM microstructure were too mild to be detected in the stage of prediabetes without combined IFG/IGT. While a significant reduction of WM integrity was observed in the stage of prediabetes with combined IFG/IGT. These findings provided further evidence that prediabetes was not a benign state,^{28,61} and prediabetes with combined IFG/IGT was the high-risk population in prediabetes.^{35–38} Compared with prediabetes without combined IFG/IGT, prediabetes with combined IFG/IGT was at a higher risk and indicated worse glucose metabolism and possibly longer duration of the metabolic abnormality, likely leading to deleterious consequences in terms of SVD, inflammation, and oxidative stress.⁶² Presumably, the pathological changes (SVD or inflammation, *etc.*) related to abnormal glucose metabolism had been present for some time in the stage of prediabetes with combined IFG/IGT, reflecting on local WM microstructural abnormalities. Further, the total WMH volumes of the brain, a macrostructural biomarker, were correlated with lower global FA and higher global MD values, which showed similar results in this study. Larger WMH volumes have been observed in the stage of prediabetes with combined IFG/IGT, but not prediabetes without combined IFG/IGT. Therefore, the stage of prediabetes with combined IFG/IGT should be of higher concern.

The associations between clinical glucose measures and WM microstructural abnormalities can be explained by several possible mechanisms. Hyperglycemia is associated with a broad impairment of microvascular function including brain microvascular.³² It might contribute to inflammatory and hypoperfusion, resulting in chronic ischemia in the brain.⁶³ Meanwhile, hyperglycemia-induced increased oxidative stress is a major cause of endothelial dysfunction and blood-brain barrier disruption. Endothelial dysfunction can promote both pro-inflammatory and pro-coagulant states while blood-brain barrier disruption can lead to thickening and disorganization of the small blood vessel wall.^{64,65} Furthermore, diabetes is additionally atherogenic.⁹ All these pathogenic factors and pathways likely contribute to further dysregulation of blood supply in the brain. A previous study has reported that the brain consumes approximately 50% of all glucose.⁶⁶ Therefore, the brain is very sensitive to insufficient blood supply which could contribute to WM abnormalities.⁶² Disruption of WM microstructural integrity (ischemia, demyelination, axonal damage, inflammation or edema, *etc.*)⁴⁶ is most likely caused by a combination of hyperglycemia-induced inflammation, hypoperfusion, oxidative stress, endothelial dysfunction, and blood-brain barrier disruption.⁶² The results of associations between reduction of WM microstructural integrity and continuous glucose measures are in agreement with the previous findings that macrostructural abnormalities of the brain including WMH were associated with the continuous measures of hyperglycemia.²⁹ In contrast to the observations

of macrostructural abnormalities, we found no significant associations between WM microstructural abnormalities and 2-h post-load glucose after adjustments with cardiovascular risk factors and medication use. We attributed this to the possibility that OGTT was not performed in participants with a history of diabetes, resulting in the lack of nearly half of 2-h post-load glucose data.

Strengths of this study include a large population-based study reasonably representing the general population. The prevalence of prediabetes (54.3%) and diabetes (22.7%) in PRECISE study was similar to the prevalence reported in the nationwide population-based surveys³⁹ (45.8% prediabetes and 20.2% diabetes in 2013,⁶⁷ and 47.6% prediabetes and 23.9% diabetes in 2018⁶⁸ in the age group of 60–69). This study used new diagnostic criteria for prediabetes and diabetes, such as HbA_{1c}.²⁷ We do, however, acknowledge some limitations. First, not all participants from the cohort were included in the study because of missing DTI data caused by several reasons, including contraindications for an MRI scan and poor scan quality. Individuals included in the study population had general characteristics similar to subjects who were excluded, but they still exist subtle differences in the living environment and living habits between them. We have considered these factors as confounders in the regression models. Second, the DTI data in this study had only one phase encoding direction and did not use the AP + PA dual polarity phase encoding method for better distortion correction, which may have some limitations in DTI preprocessing.⁶⁹ However, the DTI acquisition in this study used a parallel acceleration (SENSE = 2, which reduces the distortion by a factor of 2) to mitigate distortion.⁷⁰ We have also added the AP + PA dual polarity phase encoding DTI scan in the follow-up of the PRECISE study. Third, participants with a history of diabetes lacked the 2-h post-load glucose data because OGTT was not performed in these participants. Therefore, associations between diffusion metrics and 2-h post-load glucose were only analyzed in prediabetes and newly diagnosed diabetes cases. Finally, the results are based on a Chinese community cohort and need to be validated in other populations.

In conclusion, we demonstrated that reduced WM microstructural integrity was present in the stage of prediabetes with combined IFG/IGT and became more severe in diabetes. These WM microstructural abnormalities were associated with glucose metabolism derangement and were independent of major cardiovascular risk factors and medication use. This finding suggested that impairment of WM microstructure may occur slowly during the process of prediabetes to diabetes, with the stage of prediabetes with combined IFG/IGT being the key turning point. Consequently, strategies to maintain normal glucose metabolism should begin early, prior to the stage of prediabetes with

combined IFG/IGT, to protect the integrity of WM microstructure. Early glycemia interventions in an appropriate stage may provide a more efficient strategy in the prevention of neurological disorders.

Contributors

J.J. and T.L. conceptualized and designed the study. Y.Z. contributed to data analysis and the writing of the manuscript. Y.P. contributed to the statistical analysis. X.C., J.J., T.L., Y.P., and P.S.S. contributed to the critical revision of the report. T.W., Y.W., J.J., Y.P., X.C., Z.Z., Z.L., X.M., H.L., and S.W. contributed to the data acquisition. Y.Z. and C.L. contributed to the quality control of data. Y.W., T.W., and T.L. approved the final version of the manuscript. W.Z., Z.Z., C.L., J.C., Z.W., H.N., and W. W. contributed to the discussion and interpretation of the data. J.J., Y.P., T.L., and Yongjun Wang verified the quality and accuracy of research, and clinical data. T.L., T.W., and Yongjun Wang are the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. All authors read and approved the final version of the manuscript.

Data sharing statement

All datasets generated or analyzed in the current study are available from the corresponding author on reasonable request.

Declaration of interests

The authors declare that they have no conflict of interest.

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Supplementary materials

Supplementary material associated with this article can be found in the online version at doi:10.1016/j.ebiom.2022.104144.

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