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RESEARCH ARTICLE

# Diabetes mellitus exacerbates changes in white matter hyperintensity shapes and volume: A longitudinal study

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## Abstract

**INTRODUCTION:** Although white matter hyperintensity (WMH) can progress over time, little is known about the underlying mechanisms. In addition, type 2 diabetes mellitus (T2DM) exacerbates the accumulation of WMH. Here we aimed to investigate longitudinal changes in WMH shapes and volume in older adults with and without T2DM.

**METHODS:** Participants underwent baseline and follow-up magnetic resonance imaging (MRI). WMH volume and shape markers were automatically assessed. We compared WMH volume and shape markers at baseline and follow-up.

**RESULTS:** A total of 200 participants were included at baseline and 181 at follow-up. The mean age ± SD of our study participants was 69.86 ± 6.03 years; 79 (39.90%) had a history of diabetes mellitus (T2DM) and 73 (36.50%) were male. For shape markers, participants with T2DM showed more complex periventricular (eccentricity, $p = 0.027$) and deep WMH shape markers (fractal dimension, $p = 0.002$) than participants without T2DM. At baseline, there were no statistically significant differences ($p > 0.05$) in WMH volume when participants with T2DM were compared to participants without T2DM. At follow-up, a more complex shape of periventricular/confluent WMH on follow-up (concavity index, $p = 0.005$; inverse sphericity index, $p = 0.001$). In addition, total ($p < 0.001$), periventricular ($p < 0.001$), and deep ($p = 0.001$) WMH volumes increased significantly.

**DISCUSSION:** A more irregular shape of periventricular and deep WMH and higher WMH volumes were associated with T2DM participants. These findings suggest that WMH shape markers may be useful in determining prognosis for cerebral small vessel disease and aid in future preventive treatments.

KEYWORDS
cerebral small vessel disease, diabetes mellitus, magnetic resonance imaging, shape markers, white matter hyperintensity

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**Highlights**

- Patients with diabetes mellitus have more irregular white matter hyperintensity (WMH) shapes and increased WMH volumes.
- Diabetes mellitus exacerbates the changes in WMH shapes and volumes
- WMH shape markers might have the potential to aid in future preventive treatments and prevent clinical deterioration.

## 1 | BACKGROUND

Dementia and cognitive decline are caused by cerebral small vessel disease (SVD).[1,2] Common structural cerebral imaging structures include white matter hyperintensities (WMHs), lacunes, perivascular spaces (PVSs), and cerebral microbleeds (CMBs). SVD symptoms usually begin as minor abnormalities that gradually worsen over several decades. It is possible to slow SVD pathophysiology by implementing lifestyle interventions in populations at risk at an early stage.[3,4] Currently, it is impossible to accurately identify individuals with SVD who have an increased risk at an early stage. It is necessary to develop more sensitive and specific biomarkers.

In older adults, WMHs are common and result from acquired diseases[1]; it is notable that WMH is a radiological indicator of SVD.[1] The presence of WMHs is associated with cognitive decline and dementia,[1,5–7] but not everyone with WMHs will experience cognitive decline or dementia.[6] There is a challenge in identifying individuals with specific WMH patterns who are at risk of cognitive decline or dementia. WMH volume is a crude, but commonly used, marker that does not allow for such differentiation. Recent studies have also investigated WMH type and shape as promising novel markers that may provide a more comprehensive understanding of WMHs than volume alone. A previous study analyzed the burden or volume of periventricular and deep WMHs (DWMHs) in community-dwelling older adults, finding that periventricular WMHs are more closely associated than DWMHs with cognitive decline.[6] This finding is likely influenced by the volume of periventricular WMHs, which are usually larger than DWMHs. Little attention has been paid to WMH type and shape to date. Previous post-mortem histopathological studies have found that WMH shape is associated with underlying pathologies.[6,8] According to these studies, confluent WMH that had a more irregular shape led to more severe parenchymal changes than periventricular WMH that had a mild, smooth appearance.

Based on magnetic resonance imaging (MRI)–based WMH shape markers, we hypothesized that different underlying SVD pathologies result in different WMH shapes. Recent studies have shown that WMH shape was associated with long-term risk of stroke and dementia and increased mortality in patients with increased vascular risk.[9,10] However, longitudinal changes in community-dwelling older adults remain underexplored.

Diabetes mellitus (DM) is a chronic vascular risk factor for white matter change. Accumulating studies have shown the impact of type 2 DM (T2DM) on the white matter microstructure and shapes in older adults.[11,12] It is suggested that T2DM can be a target for intervention because it may induce changes in vascular integrity and function and brain structure. At present no studies have reported how T2DM is associated with WMH shapes as quantified from the periventricular and deep regions. To be able to move toward using WMH shapes as biomarkers for T2DM changes in cerebrovascular diseases, it is imperative to explore this.

We therefore aimed to investigate longitudinal changes in WMH shape and volume in community-dwelling older adults. The prevalence of WMHs among patients with diabetes has also been shown to be higher than that among individuals without diabetes.[13,14] In addition, we stratified our study cohort into older adults with and without a history of T2DM, a vascular condition known to be associated with an increased burden of WMH[15] and dementia,[16,17] and evaluated their WMH volume and shape marker changes.

## 2 | METHODS

### 2.1 | Participants

This study is based on data from the Alzheimer's Disease Neuroimaging Initiative (ADNI) database (www.adni.loni.usc.edu) established in 2003, led by Michael W. Weiner. The multicenter ADNI study aims to identify and develop clinical, imaging, genetic, and biochemical biomarkers for AD diagnosis and prognosis. ADNI sites obtained approval from the institutional review boards and informed consent from participants or authorized representatives following the Declaration of Helsinki. Our study cohort included cognitively normal controls without psychological and neurological disorders. Participants with baseline 3.0 Tesla fluid-attenuated inversion recovery (FLAIR) and T1-weighted high-resolution images were obtained from the ADNI cohort.

At baseline, questionnaires were used to assess age, sex, and education level. Diabetes mellitus was defined as a self-reported diabetes history, use of anti-diabetic medication, or fasting blood glucose level >7.0 mmol/L. Hypertension was defined as self-reported or use of antihypertensive medication or measured systolic blood pressure >140 mmHg and/or diastolic blood pressure >90 mmHg. A mercury sphygmomanometer was used to measure systolic and diastolic blood pressure, and their mean was calculated.

## 2.2 | APOE status

As reported previously, apolipoprotein E (*APOE*) genotyping was extracted from the ADNI database for all participants. As part of the *APOE* analysis, individuals were grouped according to how many ε4 alleles they carried (none, one, or two).

## 2.3 | Neuropsychological examination

All participants received the Mini-Mental State Examination (MMSE) and Montreal Cognitive Assessment (MoCA); these are brief dementia screening tools with a total score of 30 and a higher score indicates better cognition.

## 2.4 | MR imaging

All detailed acquisition steps for the FLAIR and T1 images are available at the ADNI website (www.adni.loni.usc.edu/methods). Initially, WMHs were automatically segmented using the FLAIR images by the lesion prediction algorithm (LPA)[18] as implemented in the LST toolbox version 3.0.0 (www.statistical-modelling.de/lst.html) for Statistical Parametric Mapping (SPM) 12 (Wellcome Trust Center for Neuroimaging, London, UK). The result was a lesion probability map, and a threshold of 0.1 was set to produce binary WMH masks. Then, T1-weighted images were registered to FLAIR space and used to create a brain mask that excludes brain regions where WMHs should not appear, and a distance-to-ventricle mask that defined the regions around the lateral ventricles at 3 mm with FSL.[19]

We classified segmented WMHs into periventricular WMHs (PWMHs) and deep WMHs (or DWMHs) according to previous research.[10] PWMHs were defined as lesions located within a 3 mm distance from the lateral ventricular wall, regardless of their extension into the white matter. In contrast, we identified DWMHs as lesions being at a minimum distance of 3 mm from the lateral ventricular edge. WMH volume calculation included only lesions with more than five voxels. The process of WMH segmentation and location classification is displayed in Figure 1. Table S1 shows an overview of the shape markers.

To calculate the shape features of WMHs, the masks were transformed to standard Montreal Neurological Institute (MNI)152 atlas space by registering a T1-weighted image to MNI and applying the transformation parameters. These parameters, including convexity, inverse sphericity index, eccentricity, concavity index, and fractal dimension were assessed based on previous reports.[20,21] The inverse sphericity index measures the deviation of a lesion's shape from a spherical form. A value close to 1 indicates a shape that is nearly spherical.[22] Eccentricity measures the elongation of a lesion, defined as the ratio of the minor axis of a lesion by its major axis. Similarly, a value close to 1 suggests a more spherical lesion.[23] Convexity was obtained by dividing the convex hull surface area by the lesions' surface area. As a measure of roughness, the concavity index was calculated based on solidity and convexity. Fractal dimension (FD) was calculated using the box-counting technique. WMH clusters of less than 10 voxels were excluded as shape features cannot be accurately calculated due to the collinearity or coplanarity of voxels. Mean values per WMH shape marker were calculated per participant. For periventricular WMH, convexity, inverse sphericity index, eccentricity, and concavity index were assessed; for DWMH, eccentricity and fractal dimension were assessed. Volumes of PWMHs, DWMHs, and total WMHs were calculated within the shape pipeline.

The characteristics of the participants and clinical information were blinded by the researchers. After MR images were processed, visual quality checks were carried out. Currently, given the absence of a standardized protocol for computing shape markers of WMHs, and to enhance the reproducibility of our study, all scripts used for imaging processing of MRI data in this research are made available at https://github.com/LuuuXG/WMH_segmentation_scripts.

### RESEARCH IN CONTEXT

1. **Systematic review**: PubMed was used to search the literature by the authors. A previous study showed that patients with diabetes mellitus (DM) have irregular white matter hyperintensity (WMH) shapes; however, little is known about the longitudinal WMH shape changes in patients with DM.
2. **Interpretation**: Older adults with DM have more irregular WMH shapes and increased WMH volumes than those without DM. DM exacerbates the irregularity of WMH shapes and accumulation of WMH volume.
3. **Future direction**: These findings suggest that WMH shape markers may help determine patient prognoses and guide future preventive treatments.

## 2.5 | Statistical analysis

To compare the demographics and clinical characteristics between the two groups, an independent *t*-test was performed for continuous variables, and chi-square tests were performed for categorical variables.

Linear regression analyses were used to investigate the differences in WMH volume and shape markers between participants with and without T2DM at baseline. Linear regression analyses were also used to explore the WMH changes at baseline and follow-up. All analyses were adjusted for age, gender, status and level of education. The analyses for WMH volumes were additionally adjusted for total intracranial volume; for WMHs, shape features were additionally adjusted for natural log-transformed total WMH volume (% intracranial volume) to test if the changes were independent of WMH volume. All statistical analyses were conducted in R Studio using R version 4.2.1; *p*-values less than 0.05 were considered statistically significant.

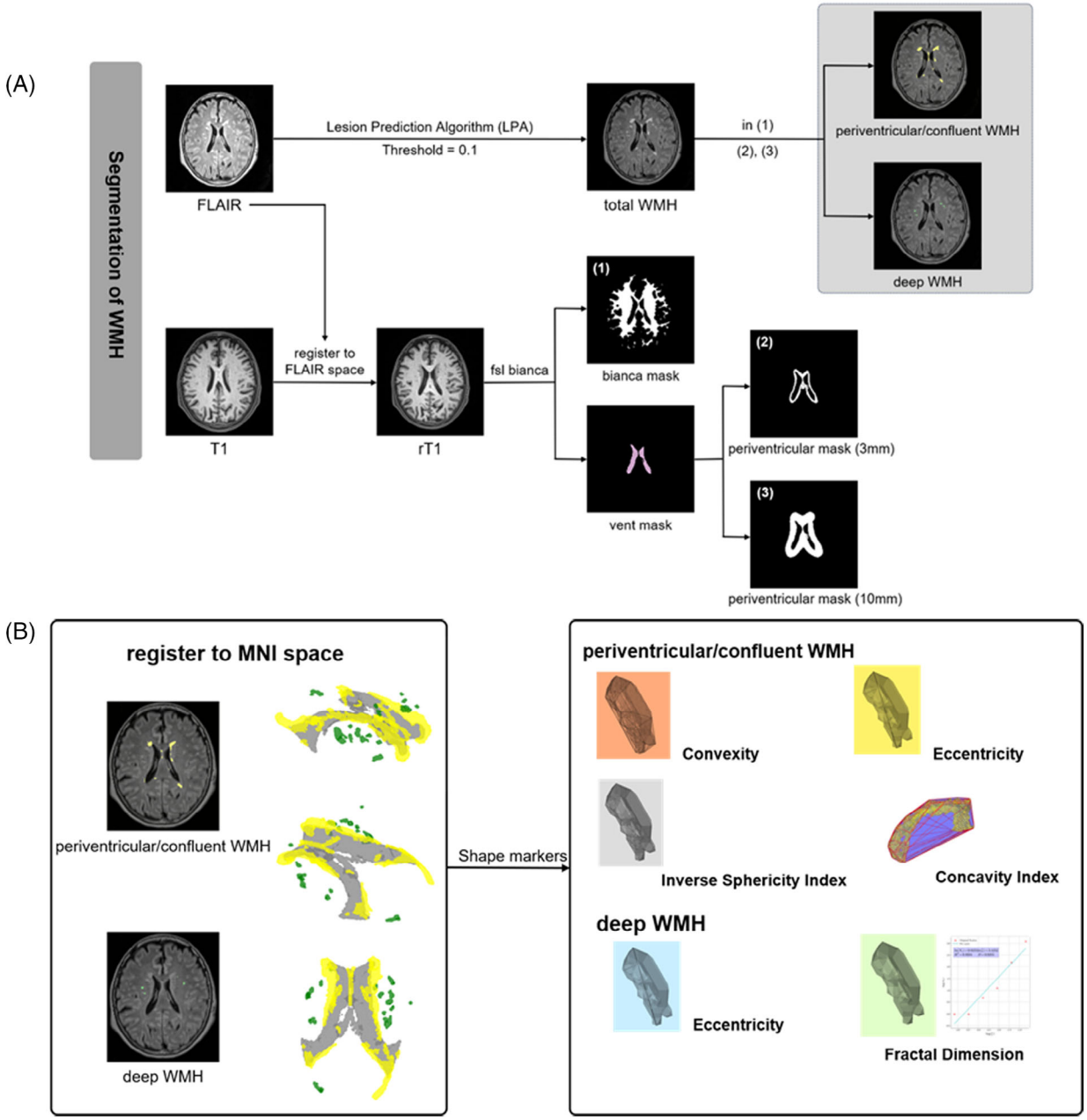


**FIGURE 1** Segmentation and shape features of WMHs. (A) Shows the methodological sequence of segmenting WMHs into PWMHs and DWMHs. (B) Shows the shape features used in quantifying the WMHs in the PWMHs and DWMHs. DWMH, deep WMH; PWMH, periventricular WMH; WMH, white matter hyperintensity.

## 3 | RESULTS

At baseline, 200 participants were included in the study, and all participants were invited for a follow-up visit. Of the 200 participants, 181 participants followed up. All participants included in our final data analysis underwent three-dimensional (3D) FLAIR and 3D T1-weighted imaging.

Table 1 shows the demographics and clinical information of our study participants. At baseline, the mean age ± SD of our study participants was 69.86 ± 6.03 years; 79 (39.90%) had a history of diabetes mellitus and 73 (36.50%) were male.

Participants with T2DM were older compared to participants without T2DM at baseline as shown in Table S2. There was no significant difference in gender or other clinical parameters.

At baseline, there were no statistically significant differences in WMH volume when participants with T2DM were compared to participants without T2DM, as shown in Figure 2 (total WMH, $p = 0.343$; PWMH, $p = 0.397$; DWMH, $p = 0.158$). For shape markers, participants with T2DM showed a more complex periventricular (eccentricity, $p = 0.027$) and DWMH shape markers (fractal dimension, $p = 0.002$) compared to participants without T2DM.

**TABLE 1** Baseline characteristics and clinical information of our study participants.

| | *N* = 200 |
|---|---|
| Age, years, mean (SD) | 69.86 ± 6.03 |
| Time to follow-up, mean (SD) | 1.96 ± 0.90 |
| Males, *n* (%) | 73 (36.50%) |
| Diabetes mellitus, *n* (%) | 79 (39.90%) |
| Hypertension, *n* (%) | 67 (33.50%) |
| Hyperlipidemia, *n* (%) | 48 (24.74%) |
| Height, mean (SD) | 109.69 ± 49.49 |
| Weight, mean (SD) | 143.49 ± 54.30 |
| SBP, mmHg, mean (SD) | 134.03 ± 15.73 |
| DBP, mmHg, mean (SD) | 76.25 ± 9.35 |
| Education, years, mean (SD) | 17 [16, 18] |
| MMSE score | 29 [29, 30] |
| MoCA, score | 27 [25, 28] |
| *APOE* ε4, n (%) | |
| 0 | 113 (59.79) |
| 1 | 69 (36.51) |
| 2 | 7 (3.70) |
| CSF parameters | |
| Aß40 | 1810 [1439, 21310] |
| Aß42 | 1150 [834, 1653] |
| Aß42/Aß40 | 0.07 [0.05, 0.09] |
| tau | 210 [169, 260] |
| p-tau | 18 [15, 25] |

Abbreviations: Aß, amyloid beta; *APOE*, apolipoprotein E gene; CSF, cerebrospinal fluid; DBP, diastolic blood pressure; MMSE, Mini-Mental State Examination; MoCA, Montreal Cognitive Assessment; SD, standard deviation; SBP, systolic blood pressure.

At follow-up, total ($p < 0.001$), PWMH ($p < 0.001$) and DWMH ($p = 0.001$) volumes increased significantly in all participants. In addition, we found a more complex shape of periventricular/confluent WMH on follow-up (concavity index, $p = 0.005$; inverse sphericity index, $p = 0.001$) in all participants. No significant differences were seen on DWMH markers on follow-up (all $p > 0.05$). Figure 2 and Table S3 show the baseline and follow-up WMH volumes and shape markers of our study participants.

Figure 3 shows the baseline and follow-up WMH volumes and shape makers in participants with and without T2DM. An increase was seen in the total WMH ($p = 0.051$) and PWMH ($p = 0.067$), and a significant increase was seen in the DWMH volume ($p = 0.034$) when participants with T2DM were compared with participants without T2DM. Similarly, DWMH shape markers still differed between the two groups (fractal dimension, $p < 0.001$). Significant difference remained the same after additionally adjusting for *APOE* genotype.

## 4 | DISCUSSION

Early identification of AD high-risk individuals is crucial for implementing timely intervention and managing the disease effectively. WMH, a common radiological indicator of SVD, contributes to AD. In this study, we found a more irregular shape of periventricular/confluent WMH on follow-up in our study participants. Similarly, total, periventricular/confluent, and deep WMH volumes increased significantly on follow-up. In T2DM participants, DWMH volumes increased and DWMH shapes differed on follow-up.

Our study accentuates the importance of diabetic health to improve brain health outcomes. Cross-sectional studies[24,25] have shown the association of diabetes and WMH volume; in addition, there is a growing body of evidence indicates that DM exacerbates WMH accumulation.[15,25] On baseline analysis, significant differences were not seen in WMH volume when participants with T2DM were compared to NODM (no DM) participants; on follow-up, we showed that participants with T2DM had higher WMH volumes compared to NODM, which is in line with previous studies.

There is increasing evidence that shows that T2DM is closely related to SVD, which is a key factor for initiation of WMH. A recent report[21] showed that patients with T2DM had irregular PWMH and DWMH shapes compared to NODM. Although the underlying mechanisms of T2DM and WMHs are still unknown, Del Bene et al.[14] emphasized the relationship between the association of T2DM and WMHs. Our baseline analysis showed that participants with T2DM had more complex PWMH and DWMH shapes compared to NODM, which is in line with previous reports. WMH shapes can be affected by T2DM, since it affects cerebral blood flow and endothelial function, aggravating atherosclerosis and ultimately changing WMH shapes.[26] Several pathways and mechanisms are involved in the development of WMHs in T2DM, which may interact and promote each other. Diabetes can impact the brain through a variety of mechanisms, most prominent among them being chronic hyperglycemia, which can cause oxidative stress and inflammation, which in turn can damage the brain's neurovascular unit.[27,28] In turn, dysfunction of the blood–brain barrier permeability may lead to changes in the brain microvasculature and over time, to WMH[29] which is in line with our study. There is, however, a need for further investigation and understanding of the drivers of WMHs in T2DM.

According to previous studies,[9,30,31] WMH shape facilitates a more detailed characterization of WMH by helping to quantify the heterogeneity of WMH associated with underlying pathologies. Distinct WMH shape patterns were shown previously to be associated with increased long-term stroke, dementia risk, and mortality.[9,30] In the current study, we showed that PWMH and DWMH shape markers deteriorated over time. Similarly, we found that deterioration of WMH shape markers in participants with T2DM was more severe compared to participants without T2DM, suggesting that T2DM exacerbates the complexity of WMH shapes over time. T2DM causes atherosclerosis in the cerebral microcirculation. Long-term T2DM is associated with severe atherosclerosis, the principal cause of chronic cerebral

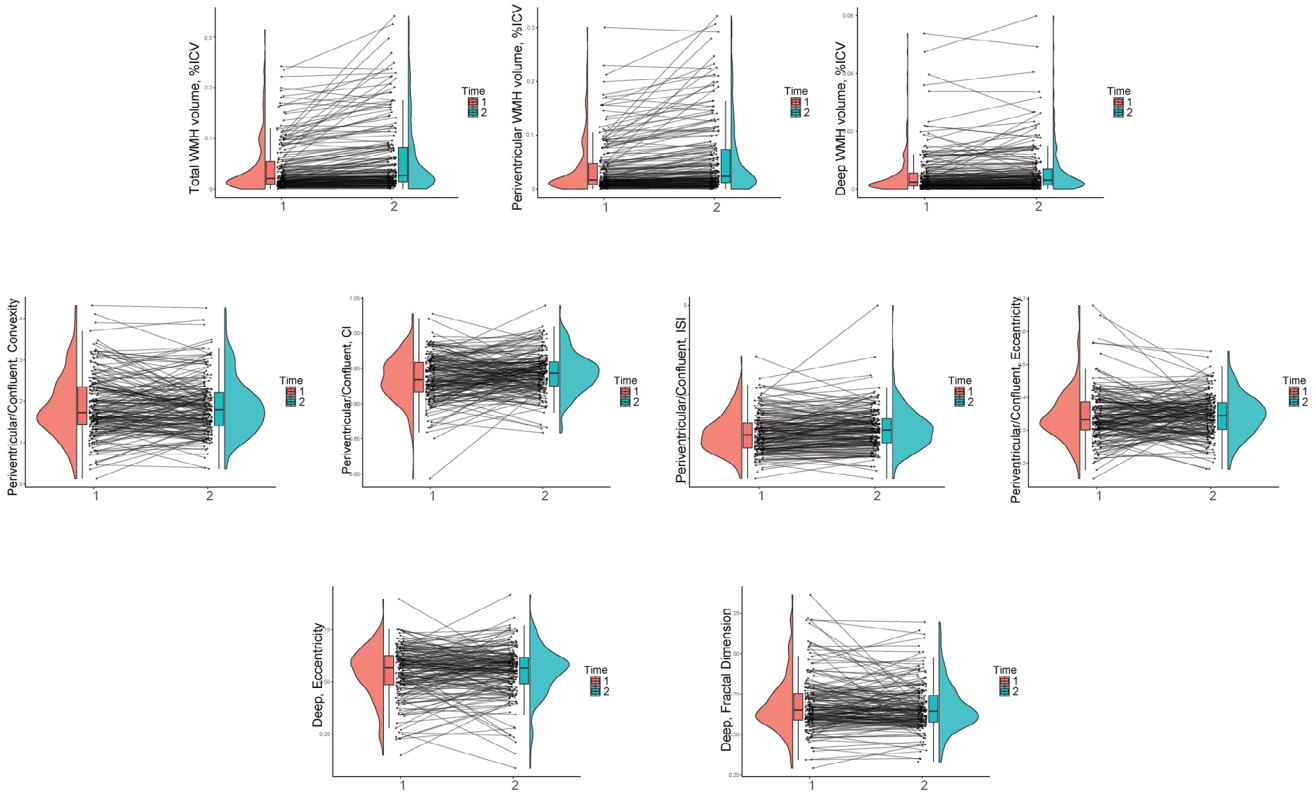


**FIGURE 2** Comparison of baseline and longitudinal WMH volume and shape markers in the study cohort. WMH, white matter hyperintensity.

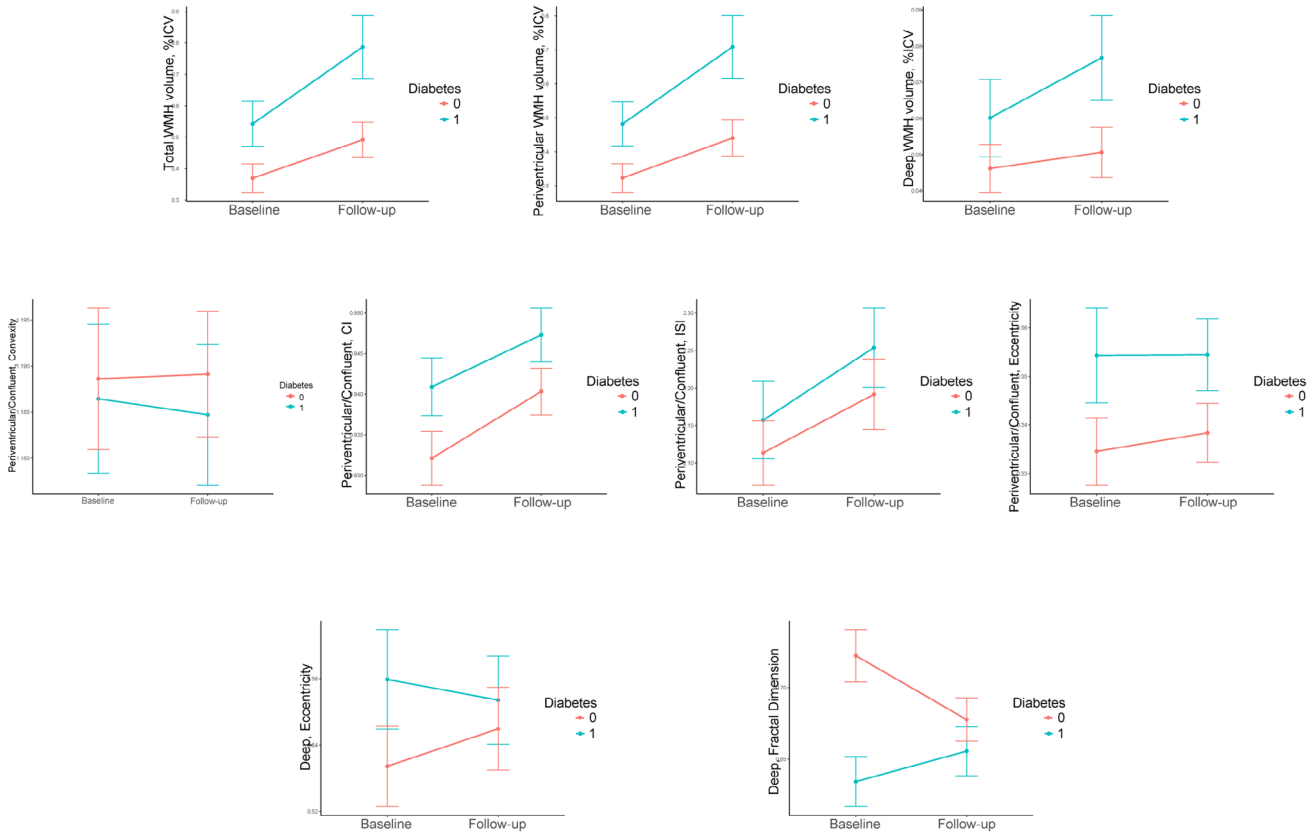


**FIGURE 3** Comparison of baseline and longitudinal WMH volume and shape markers in participants with and without type 2 diabetes mellitus. WMH, white matter hyperintensity.

ischemia. Severe atherosclerosis can lead to decreased cerebral blood flow and cause diffuse cerebral insufficiency and demyelination of WM, ultimately resulting in changes in WMH shapes. The current findings strengthen the hypothesis that longitudinal changes in older adults can be assayed by MRI-based WMH shape markers.

WMH shape may be a suitable additional marker next to WMH volume to describe longitudinal WMH changes in older adults. Variations in WMH shape patterns are likely to reflect the heterogeneous nature of WMH pathologies, as reported previously.[10,31] A key contributing factor to white matter damage is hypoperfusion, since SVD affects the cerebral vessels.[6,32] PWMHs and DWMHs are vulnerable to hypoperfusion[6]; thus hypoxic and/or ischemic changes in these areas may reflect distinct WMH shape patterns.

Based on the findings in our current study, there is evidence that WMH shape has additional diagnostic value compared to WMH volume alone, which is in line with previous studies.[10,33] For the identification of patients at risk of cerebral disorders, the shape of WMH could be used as a non-invasive independent marker in conjunction with other markers of SVD. Individuals at risk of cerebral disorders could undergo lifestyle changes to limit SVD progression in older adults. Although characteristic pathological features of the diabetic brain have not yet been identified, vascular compromise is common in the elderly and is accompanied by damage to WM pathways. Age and hypertension are the most consistent predictors of WMHs,[34,35] although some studies indicate that diabetes increases WMH risk.[15,36,37] The increased WMH volumes and irregular WMH shapes, presumably accompanied by unidentified clinical variables, may account, at least in part, for diabetic WMH changes ultimately leading to cerebral disorders. Our findings add to the notion that DM may be associated with WMH exacerbations. Future research is warranted to investigate whether it may be a possible target for SVD prevention or treatment.

The strengths of this study are the longitudinal study design of older adults in which we used quantitative WMH volume measurements. We would like to acknowledge some limitations in our study. Our study participants consisted of participants without cerebral disorders, which may limit the generalizability of the results. Data-driven approaches have been used to classify WMHs of potentially different origins, and future studies may employ such classifications to better understand WMH changes in older adults. In addition to prior studies, WMH shape metrics have also been selected based on previous studies. However, the reliability of these parameters requires further verification, particularly concerning the accuracy of calculating lesions with small volumes. Currently, *APOE* genotype and hypertension are considered to be risk factors for WMH.[13] However, not all participants enrolled in our study had their *APOE* genotype and blood pressure examination performed or recorded, so these covariates were not included in our statistical analysis. Neuropsychological examination was not performed on all participants. Future studies may be needed to evaluate the association between neuropsychological measures and WMH metrics in older adults.

In conclusion, we found that WMH shape is a promising marker in addition to WMH volume concerning assessing the WMH changes over time. A more irregular shape of PWMHs and DWMHs and higher WMH volumes were associated with individuals with T2DM. These findings suggest that WMH shape markers may be useful in determining SVD prognosis and may aid in future preventive treatments.

## AUTHOR CONTRIBUTIONS

*Study concept and design*: Shihao Xu, Zhen Wang, Zhipeng Su, and Wenjun Wu. *Data acquisition*: Zhen Wang, Zhipeng Su, Yan Wang, Jiahui Chen, and Zhiming Pan. *Data analysis and interpretation*: Shihao Xu, Zhen Wang, Zhipeng Su, and Wenjun Wu. *Drafting of the manuscript*: Shihao Xu, Zhen Wang, and Zhipeng Su. *Critical review of manuscript*: Shihao Xu, Zhen Wang, and Zhipeng Su. All authors approved this version of the manuscript.

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## CONFLICT OF INTEREST STATEMENT

The authors declare that they have no conflicts of interest. Author disclosures are available in the Supporting Information.

## DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on request from the corresponding author.

## CONSENT STATEMENT

All participants provided written informed consent before enrolling in the study.

## ETHICS STATEMENT

The First Affiliated Hospital of Wenzhou Medical University Ethics Committee approved the study (Ethics number KY2021-153).

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## SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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