RESEARCH ARTICLE

Association between haemoglobin A1c and cerebral microbleeds in community-based stroke-free individuals: A cross-sectional study

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Abstract
Aims: The association between haemoglobin A1c (HbA1c) and cerebral microbleeds (CMBs) remains unclear. We aimed to investigate the association between HbA1c and CMBs in community-based individuals without stroke or transient ischaemic attack (TIA) and whether the association differs between individuals with and without diabetes mellitus (DM).

Materials and Methods: All individuals were recruited from a community in Beijing, China, from January 2015 to September 2019. All individuals completed a questionnaire and underwent blood tests and brain magnetic resonance imaging. A susceptibility-weighted imaging sequence was acquired to detect CMBs, which were defined as small, round and low-signal lesions with <10 mm diameter. The association between HbA1c and CMBs was analysed using multivariable logistic regression adjusted for demographics, medical history and blood sample test results. Subgroup analyses stratified by history of DM were performed.

Results: Of 544 recruited individuals, 119 (21.88%) had CMBs. HbA1c was independently associated with CMBs (odds ratio [OR], 1.51; 95% confidence interval [CI], 1.03–2.22). In 87 individuals with DM, multivariable logistic analysis showed that HbA1c was significantly associated with CMBs (OR, 1.67; 95% CI, 1.04–2.69), whereas in individuals without DM, no significant association was observed between HbA1c and CMBs (OR, 1.07; 95% CI, 0.50–2.30).

Conclusions: HbA1c was associated with CMBs in individuals without stroke or TIA, particularly in individuals with DM, suggesting that the status of glycaemic control warrants attention for the prevention of CMBs. It would be beneficial to manage HbA1c specifically to control the risk of CMBs, especially in individuals with DM.

Keywords: cerebral microbleeds, diabetes mellitus, haemoglobin A1c, susceptibility-weighted imaging

Abbreviations: AF, atrial fibrillation; CI, confidence interval; CMB, cerebral microbleed; CSVD, cerebral small vessel disease; DM, diabetes mellitus; FBG, fasting blood glucose; HbA1c, haemoglobin A1c; LDL-C, low-density lipoprotein-cholesterol; MRI, magnetic resonance imaging; OR, odds ratio; SWI, susceptibility-weighted imaging; TIA, transient ischaemic attack.
INTRODUCTION

Cerebral microbleeds (CMBs), a neuroimaging marker of cerebral small vessel disease (CSVD), are characterised by small foci of blood cell leakage. CMBs can predict stroke and increase the risk of death from all causes. Therefore, it is critical to identify the risk factors for CMBs and facilitate the primary prevention of cerebrovascular diseases.

Increasing evidence has shown that diabetes mellitus (DM) can damage microvessels, and several studies have suggested that patients with DM are more likely to have CMBs. Haemoglobin A1c (HbA1c) has been recognised as a biomarker that reflects the long-term status of glycaemic control in patients with DM, and reduction in HbA1c levels can reduce the risk of microvascular diseases. However, it is unclear whether HbA1c contributes to the development of CMBs. Furthermore, most of the previous studies on the association between HbA1c and CMBs focused more on hospital-based patients with stroke. However, few studies have been conducted in stroke-free populations.

The present study aimed to investigate the association between HbA1c levels and CMBs in individuals free of stroke or transient ischaemic attack (TIA) and whether the association varies between individuals with and without DM.

MATERIALS AND METHODS

Study population

All individuals were recruited from a community study known as Cardio- and cerebrovascular Accident Monitoring, Epidemiology, and caRe quAlity System (CAMERA), which aimed to investigate the cerebrovascular disease risk in a community-based population. The present study specifically recruited individuals aged 18–85 years who participated in the CAMERA study from January 2015 to September 2019. Individuals with the following conditions were excluded from this study: (1) known malignant tumours; (2) severe clinical conditions (heart failure, hepatic failure or renal failure); (3) stenting therapy history; (4) contraindications to magnetic resonance imaging (MRI); (5) pregnancy; (6) absence of susceptibility-weighted imaging (SWI) images or MRI with poor image quality; (7) history of stroke or TIA (the purpose of excluding patients with stroke or TIA is to avoid overestimating the prevalence of CMBs); and (8) unsuitability for HbA1c in the assessment of glycaemic status, such as haemoglobinopathies or red blood cell disorders.

We did not exclude individuals on medication or therapy affecting platelet counts, and prothrombin time or partial thromboplastin time was not tested in our study population.

Data collection

The individuals were interviewed face-to-face by trained coordinators who were blinded to the MRI data. General demographic characteristics, behavioural lifestyle and medical history were collected through a questionnaire. Hypertension was defined as self-reported medical history or having taken hypertension agents in the previous 2 weeks. DM was defined according to the American Diabetes Association criteria in 2022 as fasting blood glucose (FBG) ≥ 7.0 mmol/l or HbA1c ≥ 6.5% or self-reported or use of oral hypoglycemic agents or insulin in the last 2 weeks. Dyslipidaemia was defined as self-reported medical history or having taken lipid lowering agents in the previous 2 weeks. Measurements of weight, height and blood pressure were performed by trained nurses. Body mass index was calculated as the weight in kilograms divided by the square of the height in metres. The average of two measurements recorded in the right arm with a rest period of 5 minutes was used to determine the systolic and diastolic blood pressure.

Measurement of haemoglobin A1c (HbA1c) and other biochemical parameters

The following fasting blood sample parameters were evaluated: HbA1c, FBG, low-density lipoprotein-cholesterol (LDL-C), high-density lipoprotein-cholesterol and high-sensitivity C-reactive protein. All measurements were conducted in the central laboratory of the Beijing Tiantan Hospital.

Magnetic resonance imaging protocol and image analysis

Brain MRI was performed on a 3.0T MR scanner (Philips Achieva TX, Philips Healthcare, Best, The Netherlands) with a custom-designed 36-channel neurovascular coil. The SWI sequence was acquired using the following imaging parameters: fast field echo sequence; repetition time, 24 ms; echo times, 5 ms, 10 ms, 15 and 20 ms; flip angle, 17°; field of view, 25.6 × 19.2 × 12.8 cm²; slice thickness, 2 mm; in-plane resolution, 0.6 × 0.6 mm²; and scan time, 4 min and 2 s.

The SWI images were interpreted by two observers (M. Y. and Y. J.) experienced in neuroimaging using a Digital Imaging and Communications in Medicine (DICOM) viewer (RadiAnt DICOM Viewer, Medixant, Poznan, Poland). CMBs were defined as hypointense entities ordinarily observed on SWI which were small (<10 mm), circular and homogeneous (Figure 1). The following characteristics of CMBs were evaluated: (1) presence or absence; (2) number of CMB lesions; and (3) location of CMB lesions, including lobar CMB (cortex or subcortical white matter), deep brain or infratentorial (basal ganglia, thalamus, white matter of the internal and external capsules, brainstem or cerebellum) and mixed CMBs (both lobar CMB and deep brain or infratentorial CMB).

Reproducibility study

The MR images of 40 individuals were randomly selected for the intra-observer and inter-observer reproducibility study. Two observers blinded to clinical information independently evaluated the
presence and number of CMBs on SWI images. One observer interpreted the SWI images again after a time interval of 3 months for the purpose of minimising memory bias.

### 2.6 Statistical analyses

The normal distribution of the data was determined using the Kolmogorov–Smirnov test. Quantitative variables with normal distribution were presented as mean ± standard deviation, and variables with non-normal distribution were summarised as median and interquartile ranges. Qualitative data were described as frequencies and percentages. Quantitative data were compared using an independent *t*-test (normal distribution) or Wilcoxon test (non-normal distribution). Qualitative data were compared using the Chi-square test, and Fisher’s exact test was used if ≤20% of the expected cell counts were less than five. Multivariable logistic regression was performed to estimate the odds ratio (OR) and corresponding 95% confidence interval (CI) of HbA1c in discriminating the presence of CMBs by adjusting for potential confounders which were significant in univariate analysis (*p* < 0.05) and a history of DM. Multinomial logistic regression was used for assessing the association between HbA1c and the location of CMBs. The individuals without CMB were used as a reference. A subgroup analysis of individuals with and without DM was performed. Cohen’s kappa analysis was utilised to determine the intra-observer and inter-observer agreement in identifying the presence of CMBs. The intraclass correlation coefficient was calculated to determine the intra-observer and inter-observer agreement in evaluating the number of CMBs. A two-tailed *p* value < 0.05 was considered statistically significant.

### 3 RESULTS

#### 3.1 General characteristics of the study population

In total, 626 individuals were recruited from the Tsinghua community in the CAMERA study between January 2015 and September 2019. After excluding individuals who had MRI contraindications (*n* = 32) or a history of stroke or TIA (*n* = 50), a total of 544 individuals were finally included in the statistical analysis (Figure 2). Of 544 individuals, the mean age was 58.65 ± 13.66 years, 217 (39.89%) are male and 87 (15.99%) had DM (Table 1). Of the 544 participants, 119 (21.88%) had at least one CMB. CMBs were more likely to be located in the lobar region (14.34%), followed by the deep brain or infratentorial regions (4.23%) and mixed regions (3.31%) (Table S1 in the Supplementary Material 1).

Compared to the individuals without CMBs, those with CMBs were significantly older (67.34 ± 10.83 years vs. 56.21 ± 13.38 years, *p* = 0.006); predominantly male (54.62% vs. 35.76%, *p* < 0.001); had higher HbA1c levels (6.03 ± 0.93% vs. 5.73 ± 0.66%, *p* < 0.001); had greater proportions with history of smoking (21.01% vs. 12.00%, *p* = 0.012), hypertension (48.74% vs. 28.00%, *p* < 0.001) and atrial fibrillation (AF) (6.72% vs. 1.88%, *p* = 0.011); had higher percentages using antiplatelet agents (26.89% vs. 7.53%, *p* < 0.001), antihypertensive agents (43.70% vs. 25.88%, *p* < 0.001) and lipid lowering agents (36.13% vs. 24.00%, *p* = 0.008) and had higher systolic
pressure (132.61 ± 17.46 mmHg vs. 124.81 ± 15.64 mmHg, \( p < 0.001 \)) and FBG levels (5.21 ± 1.39 mmol/L vs. 4.94 ± 0.93 mmol/L, \( p = 0.047 \)). Only one participant (0.18%) was taking an anticoagulant, which was warfarin.

In the subgroup analysis stratified by DM status, the prevalence of CMBs was higher in individuals with DM than those without DM (27.59% vs. 20.79%). Among the 87 individuals with DM, 24 (27.59%) had CMBs, including 15 (17.24%) with lobar CMBs, 6 (6.90%) with deep or infratentorial CMBs and 3 (3.45%) with mixed CMBs. HbA1c levels were significantly higher in individuals with CMBs compared to those without CMBs in both the DM (7.37 ± 1.27% vs. 6.72 ± 1.00%, \( p = 0.014 \)) and non-DM individuals (5.69 ± 0.33% vs. 5.55 ± 0.36%, \( p < 0.001 \)) (Table S2 in Supplementary Material 1).

### 3.2 Association between HbA1c and cerebral microbleeds

A significant association between the level of HbA1c and the presence of any CMB was found in multivariable logistic regression after adjusting for age, sex and DM (OR, 1.55; 95% CI, 1.05–2.27, \( p = 0.026 \), Model 1, Table 2). After further adjustment for a history of smoking, hypertension, AF, antplatelet agents, antihypertensive agents, lipid lowering agents and LDL-C, the association between HbA1c and the presence of any CMB remained statistically significant (OR, 1.51; 95% CI, 1.03–2.22, \( p = 0.036 \), Model 2, Table 2).

Regarding the location of CMBs, HbA1c was significantly associated with deep or infratentorial CMBs (OR, 2.21; 95% CI, 1.21–4.07, \( p = 0.010 \), Model 2, Table 2), but not with CMBs in the lobar region (OR, 1.48; 95% CI, 0.93–2.35, \( p = 0.097 \), Model 2, Table 2).

In the subgroup analysis, HbA1c was significantly associated with any CMB (OR, 1.67; 95% CI, 1.04–2.69, \( p = 0.033 \), Model 2, Table 3) and deep or infratentorial CMBs (OR, 2.67; 95% CI, 1.17–6.10, \( p = 0.020 \), Model 2, Table 3) in individuals with DM. Among individuals with DM, HbA1c levels were categorised into quartiles (quartile 1: HbA1c ≤ 6.2%, quartile 2: 6.2 < HbA1c ≤ 6.6%, quartile 3: 6.6 < HbA1c ≤ 7.2% and quartile 4: HbA1c > 7.2%). HbA1c > 7.2% was significantly associated with any CMB (OR, 6.13; 95% CI, 1.27–29.49, \( p = 0.020 \), Model 2) (Table S3 in Supplementary Material 1).

### 4 REPRODUCIBILITY

Cohen’s \( \kappa \) values of inter- and intra-observer reliability in identifying the presence of CMBs were 0.94 and 0.99, respectively. The intra-class correlation coefficients of inter-observer and intra-observer reliability in evaluating the number of CMBs were 0.96 and 0.99, respectively. Cohen’s \( \kappa \) values of inter-observer and intra-observer reliability in assessing the location of CMBs were 0.94 and 0.99, respectively.

### 5 DISCUSSION

This study investigated the association between HbA1c levels and CMBs in community individuals without stroke or TIA. We found that HbA1c was significantly associated with CMBs after adjusting for potential confounders. In the subgroup analysis, HbA1c was significantly associated with CMBs in individuals with DM, whereas this association was not statistically significant in individuals without DM. Our findings indicate that the association between HbA1c and CMBs was more pronounced in individuals with high blood glucose levels, suggesting that poor blood glucose control may increase the risk of CMBs in individuals with DM.

The prevalence of CMBs in our study was 21.88%, which is higher than the result of the Taizhou study (18.51%\(^{23}\)) and two-fold higher than that of the Shunyi study (10.6%\(^{22}\)), both of which were Chinese community-based studies. Such variations in the prevalence of CMBs may be owing to inconsistent imaging techniques for detecting CMBs or the range of individuals’ ages among different locations.
studies. The SWI utilised in our study was more sensitive in detecting CMBs than the conventional T2*-weighted gradient-echo imaging used in the Taizhou study. The average age in our study (58.65 ± 13.66 years) was slightly higher than that in the Shunyi cohort (55.6 ± 9.3 years). Elderly adults were more likely to have CMBs, 20,22,23 because aging could accelerate the endothelial

| TABLE 1 Characteristics of individuals stratified by CMB presence |
|---------------------------------------------------------------|
| Total (n = 544) | CMB present (n = 119) | CMB absent (n = 425) | p value |
|----------------|----------------------|---------------------|--------|
| Age (years)    | 58.65 ± 13.66        | 67.34 ± 10.83       | 56.21 ± 13.38 | 0.006 |
| Sex (male)     | 217 (39.89)          | 65 (54.62)          | 152 (35.76) | <0.001 |
| History of smoking | 76 (13.97)        | 25 (21.01)          | 51 (12.00) | 0.012 |
| Alcohol consumption | 246 (45.22)       | 52 (43.70)          | 194 (45.65) | 0.706 |
| Medical history |                        |                     |         |
| Diabetes mellitus | 87 (15.99)         | 24 (20.17)          | 63 (14.82) | 0.160 |
| Hypertension    | 177 (32.54)         | 58 (48.74)          | 119 (28.00) | <0.001 |
| Dyslipidemia    | 269 (49.45)         | 60 (50.42)          | 209 (49.18) | 0.810 |
| Atrial fibrillation | 16 (2.94)         | 8 (6.72)            | 8 (1.88) | 0.011 |
| History of medication |              |                     |         |
| Antiplatelet agents | 64 (11.76)       | 32 (26.89)          | 32 (7.53) | <0.001 |
| Antihypertensive agents | 162 (29.78)     | 52 (43.70)          | 110 (25.88) | <0.001 |
| Lipid lowering agents | 145 (26.65)     | 43 (36.13)          | 102 (24.00) | 0.008 |
| Oral hypoglycemic agents or insulin | 58 (10.66) | 18 (15.13)          | 40 (9.41) | 0.074 |
| Physical examination |                  |                     |         |
| BMI (kg/m²)    | 24.30 ± 3.38        | 24.62 ± 3.59        | 24.21 ± 3.32 | 0.245 |
| Systolic blood pressure (/mmHg) | 126.50 ± 16.35   | 132.61 ± 17.46     | 124.81 ± 15.64 | <0.001 |
| Diastolic blood pressure (/mmHg) | 75.27 ± 9.39   | 75.45 ± 9.45       | 75.22 ± 9.38 | 0.820 |
| Laboratory examination |                 |                     |         |
| HbA1c (%)      | 5.79 ± 0.73         | 6.03 ± 0.93         | 5.73 ± 0.66 | 0.001 |
| FBG (mmol/L)   | 5.00 ± 1.05         | 5.21 ± 1.39         | 4.94 ± 0.93 | 0.047 |
| LDL-C (mmol/L) | 2.95 ± 0.84         | 2.81 ± 0.75         | 2.99 ± 0.86 | 0.038 |
| HDL-C (mmol/L) | 1.48 ± 0.37         | 1.46 ± 0.36         | 1.48 ± 0.38 | 0.527 |
| Hs-CRP (mg/L)  | 0.90 (0.50, 1.70)   | 0.90 (0.53, 1.90)   | 0.8 (0.50, 1.70) | 0.346 |

Abbreviations: CMB, cerebral microbleed; FBG, fasting blood glucose; HbA1c, glycosylated haemoglobin; HDL-C, high density lipoprotein-cholesterol; Hs-CRP, high sensitivity C-reactive protein; LDL-C, low density lipoprotein-cholesterol.

| TABLE 2 Logistic regression analyses for the association between HbA1c and CMBs (HbA1c as a quantitative variable) |
|---------------------------------------------------------------|
| Unadjusted OR (95% CI) | Model 1 OR (95% CI) | Model 2 OR (95% CI) |
|-------------------------|---------------------|---------------------|
| Any CMB                 | 1.63 (1.26–2.11)    | 1.55 (1.05–2.27)    | 1.51 (1.03–2.22) |
| Lobar CMBs              | 1.61 (1.20–2.17)    | 1.54 (0.98–2.41)    | 1.48 (0.93–2.35) |
| Any lobar CMBs          | 1.52 (1.14–2.01)    | 1.35 (0.88–2.07)    | 1.29 (0.83–2.00) |
| Deep or infratentorial CMBs | 2.07 (1.42–3.04) | 2.29 (1.26–4.16)    | 2.21 (1.21–4.07) |
| Any deep CMBs          | 1.70 (1.20–2.41)    | 1.60 (0.95–2.68)    | 1.54 (0.92–2.58) |

Note: Model 1 was adjusted for age, sex and diabetes mellitus; Model 2 was adjusted for age, sex, diabetes mellitus, history of smoking, hypertension, atrial fibrillation, antplatelet agents, antihypertensive agents, lipid lowering agents and LDL-C.

Abbreviations: CI, confidence interval; CMB, cerebral microbleed; HbA1c, glycosylated haemoglobin; HDL-C, low density lipoprotein-cholesterol; OR, odds ratio.

aAny lobar CMBs included lobar CMBs and mixed CMBs.

bAny deep CMBs included deep or infratentorial CMBs and mixed CMBs.
dysfunction and arterial stiffness and increase the risk of blood leakage into surrounding tissues. There was a significant association between HbA1c and CMBs in our study, suggesting an elevated HbA1c level increases the risk of CMBs. Our findings are consistent with some previous studies. Qiu et al. found that DM was significantly associated with CMBs (OR, 1.58; 95% CI, 1.04–2.39) in the population-based AGES-Reykjavik study. Similarly, a systematic review (OR, 1.58; 95% CI, 1.04–2.39) in the population-based AGES-Reykjavik study. Similarly, a systematic review revealed that DM was associated with CMBs in neurologically healthy adults (OR, 2.2; 95% CI, 1.2–4.2). In our subgroup analysis, such an association can only be found in individuals with DM, but not in the individuals without DM. In the Finnish Diabetic Nephropathy study, CMBs were found to be associated with the severity of diabetic nephropathy in patients with Type 1 DM. As for location of CMBs, we found that HbA1c was associated with deep or infratentorial CMBs but not with lobar CMBs. Similarly, Lei et al. found that higher blood glucose levels (>5.3 mmol/L) are associated with deep or infratentorial CMBs, but not with lobar CMBs in patients with acute ischaemic stroke. CMBs appear to correspond to distinct aetiologies in different regions, although the precise mechanism of CMB formation is complicated. Deep or infratentorial CMBs were typically caused by hypertension, whereas lobar CMBs were commonly caused by cerebral amyloid angiopathy. Our findings indicate that HbA1c-associated CMBs are more likely to be associated with hypertension than cerebral amyloid angiopathy. However, several studies have reported inconsistent results. No significant association was found between DM and CMBs (OR, 0.35; 95% CI, 0.04–2.75) in the Framingham Offspring and Cohort Study, in which only 472 individuals were included and the prevalence of DM (7.8%) was relatively low. The Atherosclerosis Risk in Communities Neurocognitive Study also found that DM was not associated with either lobar CMBs (OR, 1.33; 95% CI, 0.61–2.91) or subcortical CMBs (OR, 1.07; 95% CI, 0.65–1.76). However, their average age was 75 years, and individuals with hypertension accounted for 62.6%–84.2% in the Atherosclerosis Risk in Communities Neurocognitive Study, which was higher than that in our study (mean age of 58.65 ± 13.66 years; 32.54% of individuals had hypertension), suggesting that hypertension may act as an important confounding factor.

HbA1c reflects the cumulative glycaemic history during the previous 3 months and has become a biomarker for long-term glycaemic control in patients with DM. Several possible mechanisms explain how DM increases the risk of CMBs. First, hyperglycemia can injure endothelial function by impairing endothelium-dependent vasorelaxation and enhancing the production of mitochondrial reactive oxygen species (ROS), leading to the formation and deposition of advanced glycation end products, which are associated with the onset and progression of diabetes. Second, the overproduction of ROS and increased glycosylation of haemoglobin due to the suppression of the oxygen-carrying capacity of haemoglobin lead to tissue hypoxia and microbleeds. Third, high HbA1c levels impair myogenic response by diminishing the contractile capability of cerebral vascular smooth muscle cells. After the arteriole loses tension, the elasticity of the vessel wall decreases, and cerebral blood flow is enhanced with transient hypertension, leading to vascular rupture and CMB formation.

The major strengths of our study are as follows: First, our participants were recruited from a community without stroke or TIA, resulting in a lower prevalence of CMBs (12.9%) compared to previous studies with higher prevalence (46.3–84.2%). Second, the present study included 1569 participants with a mean age of 62.6 years, which is consistent with the mean age of the population-based AGES-Reykjavik study. However, their average age was 75 years, and individuals with hypertension accounted for 62.6%–84.2% in the Atherosclerosis Risk in Communities Neurocognitive Study, which was higher than that in our study (mean age of 58.65 ± 13.66 years; 32.54% of individuals had hypertension), suggesting that hypertension may act as an important confounding factor.

Note: Subgroup analysis: Model 1 was adjusted for age, sex; Model 2 was adjusted for age, sex, history of smoking, hypertension, atrial fibrillation, antiplatelet agents, antihypertensive agents, lipid lowering agents, and LDL-C.

Abbreviations: CI, confidence interval; CMB, cerebral microbleed; DM, diabetes mellitus; HbA1c, glycosylated haemoglobin; LDL-C, low density lipoprotein-cholesterol; OR, odds ratio.

|                  | Unadjusted OR (95% CI) | Model 1 OR (95% CI) | Model 2 OR (95% CI) |
|------------------|------------------------|---------------------|---------------------|
| **DM patients**  |                        |                     |                     |
| Any CMB          | 1.66 (1.08–2.56)        | 1.64 (1.05–2.55)    | 1.67 (1.04–2.69)    |
| Lobar CMBs       | 1.68 (1.01–2.79)        | 1.59 (0.94–2.69)    | 1.52 (0.83–2.76)    |
| Any lobar CMBs   | 1.47 (0.91–2.38)        | 1.40 (0.85–2.31)    | 1.35 (0.78–2.35)    |
| Deep or infratentorial CMBs | 2.36 (1.23–4.54) | 2.43 (1.24–4.76) | 2.67 (1.17–6.10) |
| Any deep CMBs    | 1.72 (0.97–3.05)        | 1.71 (0.96–3.06)    | 1.81 (0.95–3.46)    |
| **Non-DM patients** |                       |                     |                     |
| Any CMB          | 3.12 (1.59–6.12)        | 1.18 (0.56–2.50)    | 1.07 (0.50–2.30)    |
| Lobar CMBs       | 3.16 (1.43–6.98)        | 1.18 (0.50–2.83)    | 1.004 (0.41–2.47)   |
| Any lobar CMBs   | 2.89 (1.40–5.95)        | 1.05 (0.48–2.34)    | 0.92 (0.41–2.07)    |
| Deep or infratentorial CMBs | 4.53 (1.06–19.31) | 2.06 (0.42–10.04) | 2.16 (0.44–10.70) |
| Any deep CMBs    | 3.07 (1.06–8.90)        | 1.17 (0.37–3.65)    | 1.17 (0.38–3.68)    |
indicating the significant importance of glycaemic control in stroke-free individuals. Second, compared to previous studies investigating the association between history of DM or fasting glucose and CMBs, HbA1c was used to investigate the association between glycaemic status and CMBs. Third, the use of SWI guaranteed the accurate detection of CMBs. However, our study has some limitations. First, unmeasured variables may have residual confounding effects on our findings. A potential confounding effect from anticoagulant use could not be adjusted in the analysis because only one participant in our study used an anticoagulant, which was warfarin. Second, only the association, but not a causal effect, between HbA1c and CMBs can be investigated based on this cross-sectional study. Third, all individuals were recruited from the community, which may indicate a possible selection bias. Despite a moderate sample size of 544 individuals, the findings may not be more representative than those inferred from a larger sample size. These findings should be further verified in future multicentre, large-scale, prospective cohort studies.

6 | CONCLUSION

In our study, HbA1c was associated with CMBs in participants without stroke or TIA, particularly in individuals with DM. This finding suggests that the status of glycaemic control warrants attention for the prevention of CMBs.

AUTHOR CONTRIBUTIONS

Yongjun Wang, Gaifen Liu and Xihai Zhao designed the study. Miaoxin Yu, Dandan Yang, Guihao Zhang, Huiyu Qiao, Hualu Han, Rui Shen and Zihan Ning contributed to the data collection. Runhua Zhang and Yong Jiang contributed to the data collection and management. Miaoxin Yu and Yanan Jia interpreted the data. Miaoxin Yu performed the statistical analysis and drafted the manuscript. Xihai Zhao and Gaifen Liu made critical revisions to the manuscript. All authors have read the manuscript and approved the submitted version.

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CONFLICT OF INTEREST

The author declares that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author Gaifen Liu, upon reasonable request.

ETHICS STATEMENT

The study protocol was approved by the Institutional Review Board of Beijing Tiantan Hospital (approval number: KY2014-005-02), and written consent was obtained from each individual prior to participation.

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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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