Association Between Hemoglobin A1c and Cerebral Microbleeds in Community-based Stroke-free Individuals: a Cross-sectional Study

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Abstract

Background: The association between hemoglobin 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 ischemic attack and whether it differs between individuals with and without diabetes mellitus.

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

Results: CMBs were detected in 119 (21.88%) individuals. HbA1c was independently associated with CMBs after adjustment (adjusted odds ratio [OR],1.51; 95% confidence interval [CI], 1.03–2.22). In 87 patients with diabetes mellitus, the multivariable logistic analysis showed that HbA1c was significantly associated with CMBs (adjusted OR, 1.67; 95% CI, 1.04–2.69), whereas in individuals without diabetes mellitus, no significant association was observed between HbA1c and CMBs (adjusted OR, 1.07; 95% CI, 0.50–2.30).

Conclusions: HbA1c is associated with CMBs in participants without stroke or transient ischemic attack, particularly in patients with diabetes mellitus. This finding suggests that the status of glycemic control warrants attention for the prevention of CMBs. It would be beneficial to manage HbA1c strictly to control the risk of CMBs, especially in patients with diabetes mellitus.

Introduction

Cerebral microbleeds (CMB), a neuroimaging marker of cerebral small vessel disease (CSVD), are characterized by small foci of blood cell leakage. (1, 2) CMBs can predict stroke and increase the risk of death from all causes. (3) 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, (4) several studies have suggested that patients with DM were more likely to have CMBs. (5-13) Hemoglobin A1c (HbA1c) has been recognized as a biomarker that reflects the long-term status of glycemic control in patients with DM, (14) reduction in HbA1c level can reduce the risk of microvascular diseases. (15) However, it is uncertain whether HbA1c contributes to the development of CMBs. Furthermore, most previous studies on the association between HbA1c and CMBs were focused more on hospital-based patients with stroke, (16, 17) few research have conducted in stroke-free populations.

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

Methods

Study population

All individuals were recruited from a community study of Cardio- and cerebrovascular Accident Monitoring, Epidemiology and caRe quAlity System (CAMERA), which aimed to investigate the cerebrovascular disease risk in a community-based population. (18) The present study specifically recruited individuals aged 18 to 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 tumors, (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, and (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 glycemic status, such as hemoglobinopathies or red blood cell disorders.

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 participant prior to participation.

Data collection

The individuals were face-to-face interviewed by trained coordinators who were blinded to the MRI data. General demographic characteristics, behavioral lifestyle, and medical history were collected through a questionnaire. Hypertension was defined as self-reported medical history or took medication treatment in the previous two weeks, DM was defined according to the American Diabetes Association criteria in 2022 (14) as fasting blood glucose (FBG) $\geq$ 7.0 mmol/L or HbA1c $\geq$ 6.5% or self-reported or use of oral hypoglycemic agents or insulin in the last two weeks, and dyslipidemia was defined as self-reported medical history or took medication treatment in the previous two weeks. Measurements of weight, height and blood pressure were performed by trained nurses. The body mass index was calculated as weight in kilograms divided by the square of the height in meters. The average of two measurements recorded in the right arm with a rest period of five minutes was used to determine systolic and diastolic blood pressure.

Measurement of hemoglobin 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 using a 3.0T MR scanner (Philips Achieva TX, Philips Healthcare, Best, The Netherlands) with a custom-designed 36-channel neurovascular coil. An SWI sequence was acquired using the following imaging parameters: fast field echo sequence repetition time, 24 ms; echo times, 5 ms, 10 ms, 15 ms, 20 ms; flip angle, 17°; field of view, 25.6 × 19.2 × 12.8 cm^3; slice thickness, 2 mm; in-plane resolution, 0.6 × 0.6 mm^2; and scan time, 4 min and 2 s.

The SWI images were interpreted by two observers (M. Yu and Y. Jia) 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 that were small (typically <5 mm to 10 mm), circular, and homogeneous (Figure 2). (1, 19) 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).

Cohen's κ values of inter- and intra-observer reliability in identifying the presence of CMBs were 0.94 and 0.99. The intraclass 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 both 0.94 and 0.99.

Statistical analyses

The normal distribution of the data was tested using the Kolmogorov–Smirnov test. Quantitative variables with normal distribution were presented as mean ± standard deviation, and variables with non-normal distribution were summarized as median and interquartile range. 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 the presence of CMBs by adjusting for potential confounders that were significant in univariate analysis ($P < 0.05$) and history of DM. Multinomial logistic regression was used for the association between HbA1c and the location of CMBs. The participants absent of CMB were used as a reference. Subgroup analysis of participants with and without DM was performed. A two-tailed P value < 0.05 was considered statistically significant. All statistical analyses were performed using SAS software version 9.4 (SAS Institute Inc., Cary, NC, USA).

Results

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 history of stroke or TIA (n = 50), a total of 544 individuals were finally included in the statistical analysis (Figure 1). The mean age of the individuals was 58.65 ± 13.66 years, 217 (39.89%) were male, and 87 (15.99%) with DM (Table 1). Of the 544 participants, 119 (21.88%) had at least one CMB. CMBs were more likely to locate in the lobar region (14.34%), followed by the deep brain or infratentorial regions (4.23%), and mixed regions (3.31%) (Table 2).

Compared to the participants absence of CMB, the individuals with CMBs were significantly older (67.34 ± 10.83 vs. 56.21 ± 13.38 years, $P = 0.006$), predominantly male (54.62% vs. 35.76%, $P < 0.001$), had higher HbA1c level (6.03 ± 0.93% vs. 5.73 ± 0.66%, $P < 0.001$), had greater proportions of history of smoke (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 of using antiplatelet agents (26.89% vs. 7.53%, $P < 0.001$), antihypertensive agents (43.70% vs. 25.88%, $P < 0.001$), and lipid-lowering drugs (36.13% vs. 24.00%, $P = 0.008$) , and had higher systolic pressure (132.61 ± 17.46 vs. 124.81 ± 15.64 mmHg, $P < 0.001$) and FBG level (5.21 ± 1.39 vs. 4.94 ± 0.93 mmol/L, $P = 0.047$).

In the subgroup analysis stratified by DM status, the presence of CMBs was higher in patients with DM than in individuals without DM (27.59% vs. 20.79%). Among the 87 patients with DM, 24 (27.59%) had CMBs, including 15 (17.24%) individuals with lobar CMBs, 6 (6.90%) individuals with deep or infratentorial CMBs, and 3 (3.45%) individuals with mixed CMBs. HbA1c level was significantly higher in individuals with CMBs compared to those without CMB in both the DM (7.37 ± 1.27% vs. 6.72 ± 1.00%, $P = 0.014$) and non-DM participants (5.69 ± 0.33% vs. 5.55 ± 0.36%, $P < 0.001$) (Table S1 in the Data Supplement).

Association between HbA1c and cerebral microbleeds

Significant association between the level of HbA1c and the presence of any CMB was found in multivariable logistic regression by adjusting for age, sex, and DM (OR, 1.55; 95% CI, 1.05–2.27, $P = 0.026$, Model 1, Table 3). After further adjustment for history of smoking, hypertension, AF, antiplatelet agents, antihypertensive agents, lipid-lowering drugs, 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 3).

Regarding the location of CMBs, HbA1c was significantly associated with deep or infratentorial CMBs (OR, 2.22; 95% CI, 1.21–4.07, $P = 0.010$, Model 2, Table 3), but not with CMBs in the lobar region (OR, 1.48; 95% CI, 0.93–2.35, $P = 0.097$, Model 2, Table 3).

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 4) and deep or infratentorial CMBs (OR, 2.67; 95% CI, 1.17–6.10, $P = 0.020$, Model 2, Table 4) in patients with DM. Among patients with DM, HbA1c levels were categorized into quartiles (quartile 1: HbA1c $\leq$ 6.2%, quartile 2: 6.2 < HbA1c $\leq$ 6.6%, quartile 3: 6.6 < HbA1c $\leq$ 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 S2 in the Data Supplement).

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 patients 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 might increase the risk of occurrence of CMBs in patients with DM.

The prevalence of CMBs in our study was 21.88%, which is higher than the result of the Taizhou study (18.51% (20)), but two-fold higher than that in the Shunyi study (10.6% (21)), 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 studies. The SWI in our study was more sensitive in detecting CMBs than the conventional T2*-weighted gradient-echo type echo planar 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 accelerates endothelial dysfunction and arterial stiffness and increases the risk of blood leakage into surrounding tissues. (9)

There was a significant association between HbA1c and CMBs in our study, which suggested an increase in CMBs risk with an increase in HbA1c level. Our findings were consistent with some previous studies. In a population-based study, Qiu et al (5) found that DM was significantly associated with CMBs (OR, 1.58; 95% CI, 1.04–2.39) in the AGES-Reykjavik study. Similarly, a systematic review (11) 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 patients with the DM, but not in the individuals without DM. In Finnish Diabetic Nephropathy study, CMBs were associated with the severity of diabetic retinopathy in patients with type 1 DM.(24) Lei et al(25) found that higher blood glucose levels (> 5.3mmol/L) are associated with deep or infratentorial CMBs, but not with lobar CMBs in patients with acute ischemic stroke. 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, (22) in which only 472 individuals were included and the prevalence of DM (7.8%) was relatively low. The Atherosclerosis Risk in Communities Neurocognitive Study (ARIC-NCS) also found that DM was not associated with either the lobar CMBs (OR, 1.33; 95% CI, 0.61–2.91) or subcortical CMBs (OR, 1.07; 95% CI, 0.65–1.76). (26) However, their average age was 75 years, and individuals with hypertension accounted for 62.6–84.2% in the ARIC-NCS study, which was higher than that in our study (mean age 58.65 ± 13.66 years, 32.54% hypertensive individuals), suggesting that hypertension may act as an important confounding factor. (26)

HbA1c reflects the cumulative glycemic history during the previous 3 months and has been a biomarker for long-term glycemic control in patients with DM. (14)There are several possible mechanisms explaining how DM increases the risk of CMBs. First, hyperglycemia can injure endothelial function by impairing endothelium-dependent vasorelaxation (27) and enhancing the production of mitochondrial reactive oxygen species (ROS), (28) leading to the formation and deposition of advanced glycation end products, (4) which are associated with the onset and progression of diabetes. (29) Second, the overproduction of ROS and increased glycosylation of hemoglobin due to the suppression of the oxygen-carrying capacity of hemoglobin lead to tissue hypoxia and microbleeds. (30) Third, high HbA1c level impairs myogenic response by diminishing the contractile capability of cerebral vascular smooth muscle cells. (28) 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, indicating the significant importance of glycemic control in stroke-free individuals. Second, compared to previous studies investigating the association between DM or fasting glucose and CMBs, (5-13, 16, 17, 22, 26, 31-36) HbA1c was used to investigate the association between glucose status and CMBs in the present study. This may provide a more reliable and precise association between long-term glycemic status and CMBs. Third, the use of SWI guaranteed the accurate detection of CMBs. (1) However, our study has some limitations. One limitation is that all individuals were recruited from the community, which may exist selection bias, and the sample size may not be sufficiently large. Second, only the association, but not the causal effect, between HbA1c and CMBs can be investigated based on this cross-sectional study. These findings should be further verified in future multicenter, large-scale, prospective cohort studies.

Conclusion

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

List Of Abbreviations

AF atrial fibrillation

ARISC-NCS Atherosclerosis Risk in Communities Neurocognitive Study

CAMERA Cardio- and cerebrovascular Accident Monitoring, Epidemiology and caRe quAlity System

CI confidence interval

CMB cerebral microbleed

CSVD cerebral small vessel disease

DICOM Digital Imaging and Communications in Medicine

DM diabetes mellitus

FBG fasting blood glucose

HbA1c hemoglobin A1c

LDL-C low-density lipoprotein-cholesterol

MRI magnetic resonance imaging

OR odds ratio

ROS reactive oxygen species

SWI susceptibility-weighted imaging

TIA transient ischemic attack

Declarations

Ethics approval and consent to participate

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 participant prior to participation.

Consent for publication

Not applicable.

Availability of data and materials

The datasets used and analysed during the current study are available from the corresponding author on reasonable request.

Competing interests

None.

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Authors' contributions

G. Liu and X. Zhao designed the study. M. Yu, D. Yang, G. Zhang, H. Qiao, H. Han, R. Shen, and Z. Ning contributed to the data collection. R. Zhang and Y. Jiang contributed to the data collection and management. M. Yu and Y. Jia interpreted the data. M. Yu performed the statistical analysis and drafted the manuscript. X. Zhao and G. Liu made critical revisions to the manuscript. All authors have read the manuscript and approved the submitted version.

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References

1. Greenberg SM, Vernooij MW, Cordonnier C, Viswanathan A, Al-Shahi Salman R, Warach S, et al; Microbleed Study Group. Cerebral microbleeds: a guide to detection and interpretation. Lancet Neurol. 2009;8(2):165-74.
2. Fazekas F, Kleinert R, Roob G, Kleinert G, Kapeller P, Schmidt R, et al. Histopathologic analysis of foci of signal loss on gradient-echo T2*-weighted MR images in patients with spontaneous intracerebral hemorrhage: evidence of microangiopathy-related microbleeds. AJNR Am J Neuroradiol. 1999;20(4):637-42.
3. Charidimou A, Shams S, Romero JR, Ding J, Veltkamp R, Horstmann S, et al. Clinical significance of cerebral microbleeds on MRI: A comprehensive meta-analysis of risk of intracerebral hemorrhage, ischemic stroke, mortality, and dementia in cohort studies (v1). Int J Stroke. 2018;13(5):454-68.
4. Rerkpattanapipat P, D'Agostino RB Jr, Link KM, Shahar E, Lima JA, Bluemke DA, et al. Location of arterial stiffening differs in those with impaired fasting glucose versus diabetes: implications for left ventricular hypertrophy from the Multi-Ethnic Study of Atherosclerosis. Diabetes. 2009;58(4):946-53.
5. Qiu C, Cotch MF, Sigurdsson S, Garcia M, Klein R, Jonasson F, et al. Retinal and cerebral microvascular signs and diabetes: the age, gene/environment susceptibility-Reykjavik study. Diabetes. 2008;57(6):1645-50.
6. Qiu C, Sigurdsson S, Zhang Q, Jonsdottir MK, Kjartansson O, Eiriksdottir G, et al. Diabetes, markers of brain pathology and cognitive function: the Age, Gene/Environment Susceptibility-Reykjavik Study. Ann Neurol. 2014;75(1):138-46.
7. Hara M, Yakushiji Y, Suzuyama K, Nishihara M, Eriguchi M, Noguchi T, et al. Synergistic effect of hypertension and smoking on the total small vessel disease score in healthy individuals: the Kashima scan study. Hypertens Res. 2019;42(11):1738-44.
8. Yakushiji Y, Charidimou A, Noguchi T, Nishihara M, Eriguchi M, Nanri Y, et al. Total Small Vessel Disease Score in Neurologically Healthy Japanese Adults in the Kashima Scan Study. Intern Med. 2018;57(2):189-96.

9. Caunca MR, Del Brutto V, Gardener H, Shah N, Dequatre-Ponchelle N, Cheung YK, et al. Cerebral Microbleeds, Vascular Risk Factors, and Magnetic Resonance Imaging Markers: The Northern Manhattan Study. J Am Heart Assoc. 2016;5(9):e003477.
10. Chen R, Ovbiagele B, Feng W. Diabetes and Stroke: Epidemiology, Pathophysiology, Pharmaceuticals and Outcomes. Am J Med Sci. 2016;351(4):380-6.
11. Cordonnier C, Al-Shahi Salman R, Wardlaw J. Spontaneous brain microbleeds: systematic review, subgroup analyses and standards for study design and reporting. Brain. 2007;130(Pt 8):1988-2003.
12. Shams S, Martola J, Granberg T, Li X, Shams M, Fereshtehnejad SM, et al. Cerebral microbleeds: different prevalence, topography, and risk factors depending on dementia diagnosis-the Karolinska Imaging Dementia Study. AJNR Am J Neuroradiol. 2015;36(4):661-6.
13. Saji N, Kimura K, Yagita Y, Uemura J, Aoki J, Sato T, et al. Deep Cerebral Microbleeds and Renal Dysfunction in Patients with Acute Lacunar Infarcts. J Stroke Cerebrovasc Dis. 2015;24(11):2572-9.
14. American Diabetes Association Professional Practice Committee; 2.Classification and Diagnosis of Diabetes: Standards of Medical Care in Diabetes-2022. Diabetes Care. 2022;45(Suppl.1):S17-S38.
15. Stratton IM, Adler AI, Neil HA, Matthews DR, Manley SE, Cull CA, et al. Association of glycaemia with macrovascular and microvascular complications of type 2 diabetes (UKPDS 35): prospective observational study. BMJ. 2000;321:405-12.
16. Kim BJ, Lee SH, Kang BS, Yoon BW, Roh JK. Diabetes increases large artery diseases, but not small artery diseases in the brain. Journal of Neurology. 2008;255(8):1176-81.
17. Heo SH, Lee SH, Kim BJ, Kang BS, Yoon BW. Does glycated hemoglobin have clinical significance in ischemic stroke patients? Clin Neurol Neurosurg. 2010;112(2):98-102.
18. Han H, Zhang R, Liu G, Qiao H, Chen Z, Liu Y, et al. Reduction of cerebral blood flow in community-based adults with subclinical cerebrovascular atherosclerosis: A 3.0T magnetic resonance imaging study. Neuroimage. 2019;188:302-8.
19. Haacke EM, Xu Y, Cheng YC, Reichenbach JR. Susceptibility weighted imaging (SWI). Magn Reson Med. 2004;52(3):612-8.
20. Li S, Fang F, Cui M, Jiang Y, Wang Y, Kong X, et al. Incidental findings on brain MRI among Chinese at the age of 55-65 years: the Taizhou Imaging Study. Sci Rep. 2019;9(1):464.
21. Han F, Zhai F, Wang Q, Zhou L, Ni J, Yao M, et al. Prevalence and Risk Factors of Cerebral Small Vessel Disease in a Chinese Population-Based Sample. J Stroke. 2018;20(2):239-46.
22. Jeerakathil T, Wolf PA, Beiser A, Hald JK, Au R, Kase CS, et al. Cerebral microbleeds: prevalence and associations with cardiovascular risk factors in the Framingham Study. Stroke. 2004;35(8):1831-5.
23. Del Brutto VJ, Zambrano M, Mera RM, Del Brutto OH. Population-Based Study of Cerebral Microbleeds in Stroke-Free Older Adults Living in Rural Ecuador: The Atahualpa Project. Stroke. 2015;46(7):1984-1986.
24. Eriksson MI, Summanen P, Gordin D, Forsblom C, Shams S, Liebkind R, et al. Cerebral small-vessel disease is associated with the severity of diabetic retinopathy in type 1 diabetes. BMJ Open Diabetes

Res Care. 2021;9(1):e002274.
25. Lei C, Zhong L, Ling Y, Chen T. Blood Glucose Levels Are Associated with Cerebral Microbleeds in Patients with Acute Ischaemic Stroke. Eur Neurol. 2018;80(3-4):187-92.
26. Schneider ALC, Selvin E, Sharrett AR, Griswold M, Coresh J, Jack Jr. CR, et al. Diabetes, Prediabetes, and Brain Volumes and Subclinical Cerebrovascular Disease on MRI: The Atherosclerosis Risk in Communities Neurocognitive Study (ARIC-NCS). Diabetes Care. 2017;40(11):1514-21.
27. Arrick DM, Sharpe GM, Sun H, Mayhan WG. nNOS-dependent reactivity of cerebral arterioles in Type 1 diabetes. Brain Research. 2007;1184:365-71.
28. Guo Y, Wang S, Liu Y, Fan L, Booz GW, Roman RJ, et al. Accelerated cerebral vascular injury in diabetes is associated with vascular smooth muscle cell dysfunction. GeroScience. 2020;42(2):547-61.
29. Ofosu FK, Elahi F, Daliri EB, Yeon SJ, Ham HJ, Kim JH, et al. Flavonoids in Decorticated Sorghum Grains Exert Antioxidant, Antidiabetic and Antiobesity Activities. Molecules. 2020;25(12):2854..
30. Martin D. S. KM, Grocott M. P., Mythen M. G. Concepts in hypoxia reborn. Crit Care. 2010;14(4):315.
31. Zhou JB, Tang XY, Han YP, Luo FQ, Cardoso MA, Qi L. Prediabetes and structural brain abnormalities: Evidence from observational studies. Diabetes Metab Res Rev. 2020;36(4):e3261.
32. van Agtmaal MJM, Houben AJHM, de Wit V, Henry RMA, Schaper NC, Dagnelie PC, et al. Prediabetes Is Associated With Structural Brain Abnormalities: The Maastricht Study. Diabetes Care. 2018;41(12):2535-43.
33. Brundel M, Reijmer YD, van Veluw SJ, Kuijf HJ, Luijten PR, Kappelle LJ, et al. Cerebral microvascular lesions on high-resolution 7-Tesla MRI in patients with type 2 diabetes. Diabetes. 2014;63(10):3523-9.
34. Moran C, Phan TG, Chen J, Blizzard L, Beare R, Venn A, et al. Brain atrophy in type 2 diabetes: regional distribution and influence on cognition. Diabetes Care. 2013;36(12):4036-42.
35. Shima H, Ishimura E, Naganuma T, Yamazaki T, Kobayashi I, Shidara K, et al. Cerebral microbleeds in predialysis patients with chronic kidney disease. Nephrol Dial Transplant. 2010;25(5):1554-9.
36. Emanuel AL, van Duinkerken E, Wattjes MP, Klein M, Barkhof F, Snoek FJ, et al. The presence of cerebral white matter lesions and lower skin microvascular perfusion predicts lower cognitive performance in type 1 diabetes patients with retinopathy but not in healthy controls-A longitudinal study. Microcirculation. 2019;26(3):e12530.

Tables

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 smoke	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 drugs	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/m^2)	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: FBG, fasting blood glucose; CMB, cerebral microbleed; HbA1c, glycosylated hemoglobin; HDL-C, high density lipoprotein-cholesterol; Hs-CRP, high sensitivity C-reactive protein; LDL-C, low density lipoprotein-cholesterol.

Table 2 Descriptive statistics stratified by CMB location in the 544 individuals

	Number, n (%)
Any CMB	119 (21.88)
Lobar CMBs	78 (14.34)
Deep brain or infratentorial CMBs	23 (4.23)
Mixed CMBs	18 (3.31)

Abbreviations: CMB, cerebral microbleed.

Lobar CMBs, the cortical gray or subcortical white matter; deep brain or infratentorial CMBs, basal ganglia, thalamus, white matter of the internal and external capsules, brainstem or cerebellum; mixed CMBs, both lobar CMBs and deep brain or infratentorial CMBs.

Table 3 Logistic regression analyses for the association between HbA1c and CMBs (HbA1c as 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)	2.22 (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)

Any lobar CMBs included lobar CMBs and mixed CMBs;

Any deep CMBs included deep or infratentorial CMBs and mixed CMBs;

Model 1 was adjusted for age, sex, diabetes mellitus; Model 2 was adjusted for age, sex, diabetes mellitus, history of smoke, hypertension, atrial fibrillation, antiplatelet agents, antihypertensive agents,

lipid-lowering drugs, and LDL-C.

Table 4 Logistic regression analyses for the association between HbA1c and CMBs of DM and non-DM individuals

	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)	1.003 (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 (0.43–10.69)
Any deep CMBs	3.07 (1.06–8.90)	1.17 (0.37–3.65)	1.17 (0.38–3.67)

Any lobar CMBs included lobar CMBs and mixed CMBs;

Any deep CMBs included deep or infratentorial CMBs and mixed CMBs;

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

Figures

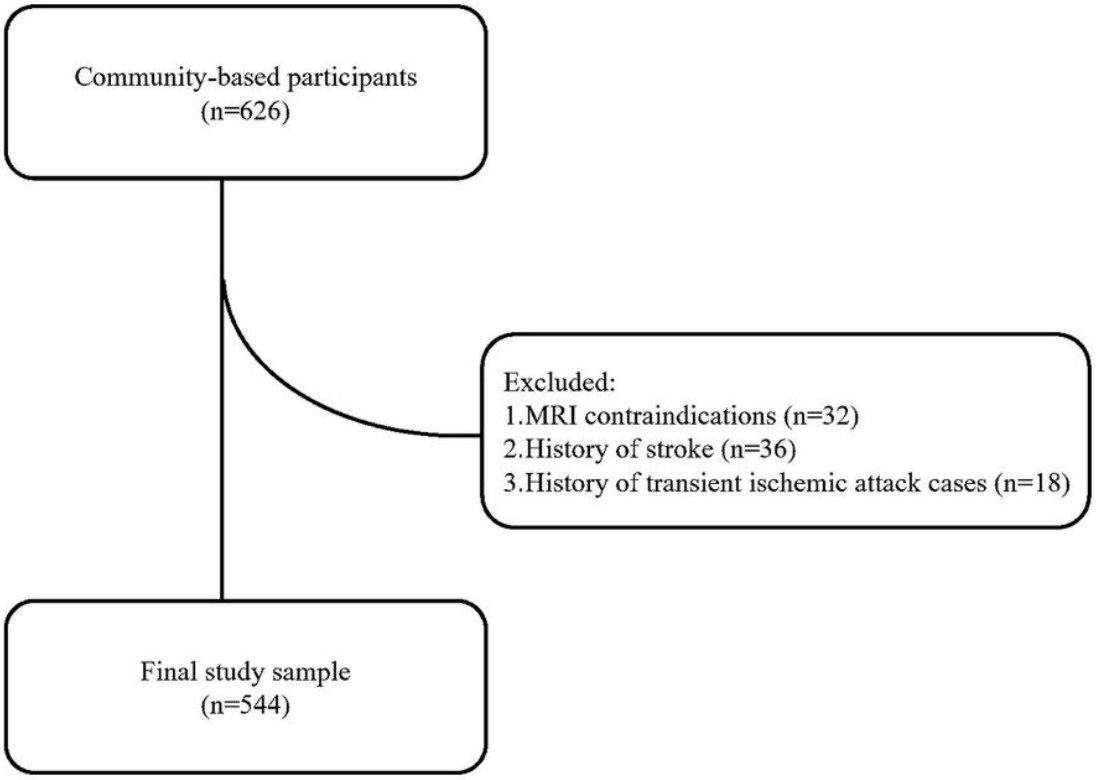

Figure 1

Flow diagram of inclusion and exclusion of the study

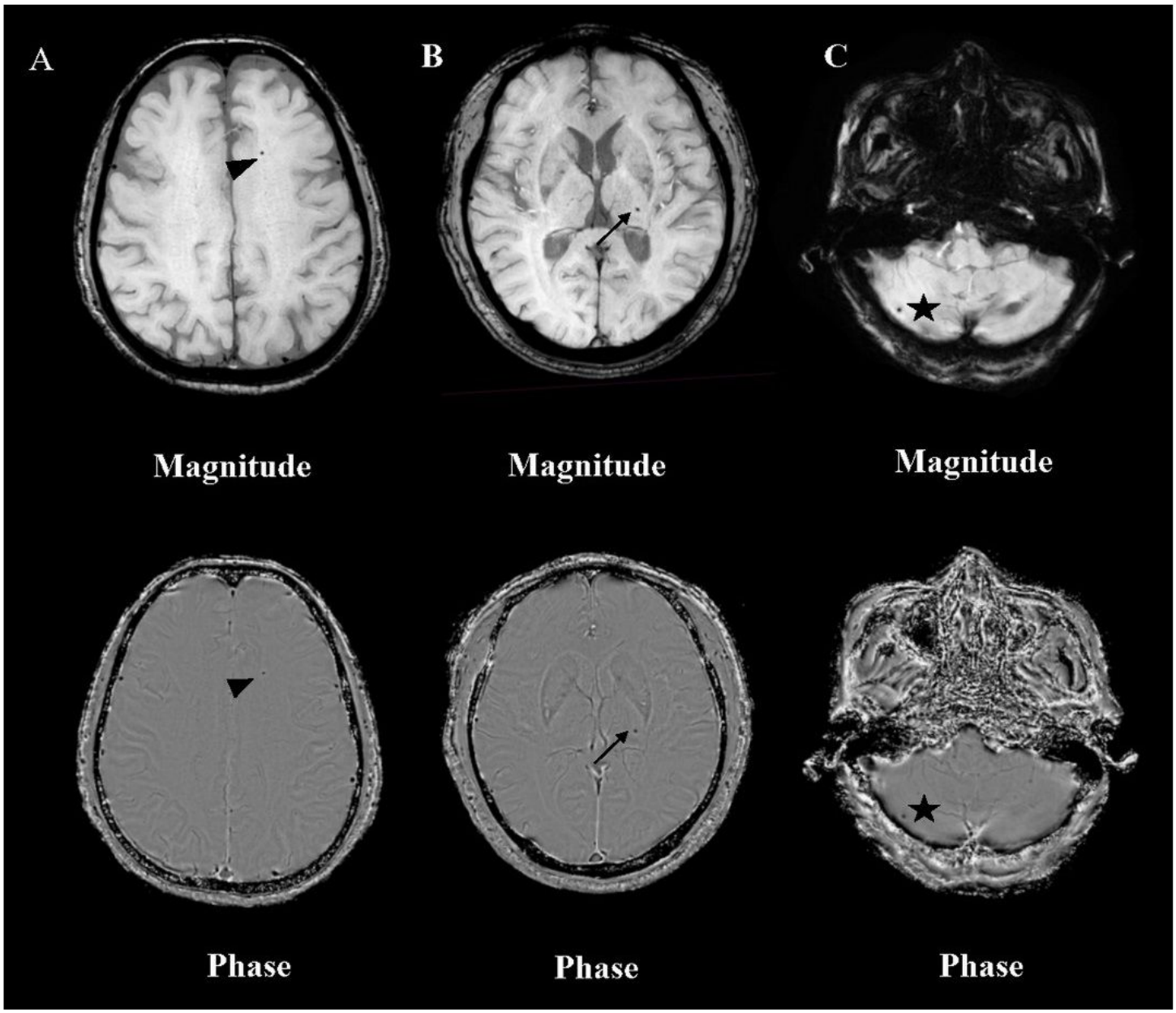

Figure 2

Examples of cerebral microbleeds (CMB) by location on SWI. Magnitude and phase are sequences for SWI. (A) Arrow heads indicate lobar CMB. (B) Arrow indicates deep brain CMB. (C) Star-shaped mark indicates infratentorial CMB.

Supplementary Files

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- SupplementalMaterial.docx