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Correlation Between Blood Glucose Level and Cerebral Small Vessel Disease Markers in Neurologically Asymptomatic, Nondiabetic Individuals

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ABSTRACT

Objectives: Cerebral small vascular disease (CSVD) is not rare in neurologically asymptomatic individuals. Glucose control and insulin resistance (IR) may be its risk factors. We aimed to explore the relationship between CSVD markers, glucose control, and IR in neurologically asymptomatic, nondiabetic individuals.

Methods: A total of 412 participants from the annual physical examinations population in our hospital who underwent brain magnetic resonance imaging from May 2019 to June 2021 were enrolled. We collected clinical data and blood test indices and calculated the triglyceride-glucose (TyG) index. CSVD markers were assessed, including lacunes, white matter hyperintensities (WMH), enlarged perivascular spaces (EPVS), cerebral microbleeds (CMBs), and the total CSVD score. Correlations between CSVD markers, clinical variables, and blood test parameters were analyzed.

Results: The median age of our group was 70.32 ± 10.27 years (45–103 years). The prevalence of asymptomatic CSVD was 43.7%. Lacunes were present in 8.3%, periventricular WMH (PVWMH) in 65.3%, deep WMH (DWMH) in 64.1%, EPVS in 87.4%, and CMBs in 31.3% of individuals. Glycated hemoglobin A1c (HbA1c) varied between PVWMH subgroups ($p = 0.043$). Fasting blood glucose (FBG) was higher in individuals with deep CMBs than in those without deep CMBs ($p = 0.012$). FBG was an independent risk factor for deep CMBs after controlling for multiple variables. However, the TyG index was not associated with CSVD markers.

Conclusions: The prevalence of neurologically asymptomatic CSVD is common in the nondiabetic population. It may be beneficial for middle-aged and elderly people to pay attention to their blood glucose levels.

1 | Background

Cerebral small vascular disease (CSVD) represents a group of pathological processes with various etiologies affecting the small arteries, arterioles, venules, and capillaries in the brain [1]. CSVD has negative effects on the daily life of middle-aged and elderly people and is thought to be among the main causes of stroke and cognitive impairment [1–3]. Furthermore, CSVD could manifest as gait disorders, such as Parkinsonism, bladder dysfunction, mood disorders, and epilepsy [1–3]. In neurologically asymptomatic individuals, CSVD is not rare and is receiving increasing attention. Asymptomatic CSVD refers to neuroimaging evidence of CSVD prior to the development of clinical symptoms [2]. These CSVD markers mainly include

lacunes, white matter hyperintensities (WMH), enlarged perivascular spaces (EPVS), and cerebral microbleeds (CMBs) [2]. In addition, the total CSVD score has been considered a more complete estimate of the overall impact of CSVD on the brain, potentially being superior to separately measuring only one or two features [4, 5].

Previous studies have already demonstrated that hyperglycemia (glycated hemoglobin [HbA1c] and fasting glucose levels) correlated with the risk of stroke in diabetics. However, the association between glucose control level and CSVD is limited in nondiabetics. In addition, insulin resistance (IR) is defined as an impairment in insulin-mediated control of glucose metabolism in tissues [6]. IR has been identified as a risk factor for numerous diseases, including type 2 diabetes (DM), metabolic syndrome, and ischemic stroke [7–9]. The triglyceride-glucose index (TyG) has been proposed as a critical marker for IR, which is associated with several metabolic syndrome, cardiovascular, and cerebrovascular diseases [10]. The impact of IR on CSVD in neurologically asymptomatic individuals also remains unclear, especially in the nondiabetic population.

A more comprehensive understanding of the mechanism of CSVD, particularly in the preclinical stages in a healthy population, will play a critical role in effective prevention in the future. In this study, our objective was to investigate whether glucose control and insulin resistance are associated with CSVD markers in neurologically asymptomatic, nondiabetic individuals. Our findings may assist us in identifying effective predictors to recognize high-risk groups of CSVD.

2 | Methods

2.1 | Subjects and Clinical Assessments

There is a fixed population who undergo annual physical examinations in our hospital, taking blood tests and brain magnetic resonance imaging (MRI) scans. We enrolled neurologically asymptomatic, nondiabetic individuals aged 45 years or more from this population in this study from May 2019 to June 2021. We excluded participants that had a history of cerebrovascular disease (stroke, transient ischemic attacks, or cerebral hemorrhage), dementia (a Mini-Mental State Examination score < 24), severe depression, anxiety, metabolic encephalopathy, poisoning, infection, or severe medical diseases. Our study was approved by a local ethics committee (2022BJYYEC-340-01), and written informed consent was obtained from each participant after a detailed description of the study was provided.

We collected the clinical information, including age, sex ratio, and body mass index (BMI). Vascular risk factors were also recorded, including hypertension (HTN), hyperlipidemia (HL), coronary heart disease (CHD), atrial fibrillation (AF), smoking status, and history of severe intracranial vascular stenosis and occlusion. Blood samples were drawn in the morning after an overnight fast and measured the level of fasting blood glucose (FBG), glycated hemoglobin A1c (HbA1c), total cholesterol (TC), triglyceride (TG), high density lipoprotein cholesterol (HDL-C), low density lipoprotein cholesterol (LDL-C), white blood cell, hemoglobin, blood platelet, and serum creatinine (sCr). The triglyceride-glucose (TyG) index was calculated using the log scale of [fasting TG (mg/dL) × fasting glucose (mg/dL)/2] [11]. We divided the study group according to the TyG index quartiles as follows: Q1 ≤ 8.22 (≤ 25th percentile]; Q2: 8.23–8.54 (26 to 50th percentile]; Q3: 8.55–8.88 (51 to 75th percentile]; and Q4 ≥ 8.89 (≥ 76th percentile].

2.2 | MR Image Acquisition

All MRI examinations were performed using a 3.0 T MRI scanner (SIGNA Pioneer). Sequences consisted of T1-weighted [repetition time/echo time (TR/TE) = 2082/25 ms, field of view (FOV) = 24 cm × 24 cm, matrix = 512 × 512, and 5 mm slice thickness, and 1.5 mm slice gap], T2-weighted imaging (T2WI, TR/TE = 5873/129 ms; FOV = 24 cm × 24 cm, matrix = 512 × 512, 5 mm slice thickness, and 1.5 mm slice gap), fluid-attenuated inversion recovery (FLAIR; TR/TE = 8400/96 ms; FOV = 24 cm × 24 cm, matrix = 512 × 512, and 5 mm slice thickness, and 1.5 mm slice gap), and susceptibility weighted imaging (SWI; TR/TE = 40/22 ms; flip angle (FA) = 15°, FOV = 24 cm × 24 cm, matrix = 512 × 512, and 2 mm slice thickness without slice gap).

2.3 | MRI Analysis

CSVD markers were assessed by two trained investigators blinded to the participants' clinical information, including lacunes, periventricular and deep WMH (PVWMH and DWMH), EPVS, and CMBs. Lacunes were defined as round or ovoid cerebrospinal fluid-filled cavities in the basal ganglia or white matter, usually 3–15 mm [12, 13]. PVWMH and DWMH lesions were assessed using the Fazekas scale from 0 to 3 [14]. PVWMHs were graded as 0 = absence, 1 = "caps" or pencil-thin lining, 2 = smooth "halo" and 3 = irregular PVWMH extending into the deep white matter. DWMHs were defined as 0 = absence, 1 = punctate foci, 2 = beginning confluence of foci, 3 = large confluent areas [14]. EPVS refered to punctate hyperintensities on T2WI in the basal ganglia and were rated as follows: 0 = no EPVS, 1 = < 10 EPVS, 2 = 11–20 EPVS, 3 = 21–40 EPVS, and 4 = > 40 EPVS [15]. CMBs are well-defined, round hypointensities, ≤ 10 mm on SWI images [13]. In addition, we calculated the total CSVD score ranging from 0 to 4 [4]. One point was added for each of the following: ≥ 1 lacunes, ≥ 1 CMBs, high-grade WMH (Fazekas score = 3 in PVWMH or ≥ 2 in DWMH), and moderate-to-severe EPVS (> 10 in the basal ganglia) [4].

2.4 | Statistics

Statistical analyses were performed using the Statistical Package for the Social Sciences (SPSS) software (version 26.0). The characteristics were compared according to the TyG index quartiles using the chi-square test, a one-way analysis of variance, or the Kruskal–Wallis test. Analysis of variance (ANOVA) and post hoc tests were used to compare the differences between different grades of CSVD subgroups. Binary logistic regression and multivariate ordered logistic regression analysis were carried out between CSVD markers and multiple variables, including clinical factors and blood index. Multivariate linear regression

analysis was performed between the TyG index and multiple variables, including clinical parameters and CSVD imaging markers. Statistically significant was set at $p < 0.050$.

3 | Results

3.1 | Clinical Characteristics

From May 2019 to June 2021, 607 individuals aged 45 years or more admitted to our hospital were assessed. Of them, 109 individuals with DM, 46 individuals with a history of stroke, nine individuals with dementia, three individuals with severe anxiety or depression, and 28 individuals with incomplete clinical information were excluded from this study. Finally, a total of 412 individuals with nondiabetes were enrolled in this cross-sectional retrospective study. All participants had complete clinical, laboratory, and brain MRI data.

The median age of the 412 individuals was 70.32 ± 10.27 years (45–103 years); 61.2% were male. In our population, 299 individuals (72.6%) aged 65 years or over, and 86 individuals (20.9%) aged 80 years or over. Among cases, 222 individuals (53.9%) had hypertension, 310 individuals (75.2%) had dyslipidemia, 96 individuals (23.3%) had coronary heart disease, 19 individuals (4.6%) had atrial fibrillation, and 50 individuals (12.1%) had severe intracranial vascular stenosis and occlusion. Other detailed characteristics are presented in Table 1.

The prevalence of asymptomatic CSVD in our study was 43.7%. Lacunes were present in 8.3%, PVWMH in 65.3%, DWMH in 64.1%, EPVS in 87.4%, and CMBs in 31.3% of individuals. For the total CSVD burden, 232 individuals (56.3%) had no markers of CSVD, and 4 individuals (1.0%) presented with all four markers (Table 2). The median TyG index, HbA1c, and FBG were 8.57 ± 0.48, 5.62 ± 0.42 (%), and 5.52 ± 0.57 (mmol/L), respectively.

TABLE 1 | Demographic data of the study population.

	All (n = 412)
Age (years)	70.32 ± 10.27
Male	252 (61.2%)
BMI	24.97 ± 2.89
Hypertension	222 (53.9%)
Hyperlipidemia	310 (75.2%)
Coronary heart disease	96 (23.3%)
Atrial fibrillation	19 (4.6%)
Current smoking	28 (6.8%)
Drinking	38 (9.2%)
HGB	144.8 ± 16.31
WBC	5.51 ± 1.39
PLT	192.73 ± 47.06
HbA1c (%)	5.62 ± 0.42 (4.33–7.58)
sCr (μmol/L)	85.43 ± 16.36
FBG (mmol/L)	5.52 ± 0.57 (3.92–9.12)
TC (mmol/L)	4.17 ± 0.93
TG (mmol/L)	1.34 ± 0.70
HDL (mmol/L)	1.35 ± 0.34
LDL (mmol/L)	2.70 ± 0.87
TyG index	8.57 ± 0.48 (7.36–10.21)

Note: Data are expressed as *n* (%), or mean ± SD (range).
Abbreviations: BMI, body mass index; FBG, fasting blood glucose; HbA1c, glycated hemoglobin A1c; HBG, hemoglobin; HDL-C, high density lipoprotein cholesterol; LDL-C, low density lipoprotein cholesterol (LDL-C); PLT, blood platelet; sCr, serum creatinine; TC, total cholesterol; TG, triglyceride; TyG index, the triglyceride-glucose index; WBC, white blood cell.

TABLE 2 | CSVD Neuroimaging characteristics of the participants.

	All (n = 412)
Lacunes (%)	34 (8.3)
PVWMH	
None (%)	143 (34.7)
Mild (%)	187 (45.4)
Moderate (%)	67 (16.3)
Severe (%)	15 (3.6)
DWMH	
None (%)	148 (35.9)
Mild (%)	239 (58.0)
Moderate (%)	24 (5.8)
Severe (%)	1 (0.2)
EPVS	
None (%)	52 (12.6)
Mild (%)	284 (68.9)
Moderate (%)	58 (14.1)
Severe (%)	18 (4.4)
CMBs	129 (31.3)
Cortex (%)	99 (24.0)
Deep (%)	51 (12.4)
Total CSVD score	
0 (%)	232 (56.3)
1 (%)	120 (29.1)
2 (%)	34 (8.3)
3 (%)	22 (5.3)
4 (%)	4 (1.0)

Abbreviations: CMBs, cerebral microbleeds; CSVD, cerebral small vessel disease; DWMH, deep white matter hyperintensities; EPVS, enlarged perivascular spaces; PVWMH, periventricular white matter hyperintensities.

3.2 | Differences Between Four TyG Index Groups

Four TyG index groups differed in BMI ($p < 0.001$), hypertension ($p < 0.001$), and hyperlipidemia ($p < 0.001$). There were no significant differences in age, sex ratio, rate of coronary heart disease, atrial fibrillation, current smoking, drinking status, and proportion of severe intracranial vascular stenosis and occlusion between the four groups. The Q4 TyG index quartile group had the highest BMI. For laboratory characteristics, HbA1, FBG, TC, TG, and LDL-C were highest in the fourth TyG index quartile group. As to CSVD markers, there were no significant differences in lacunes, PVWMH, DWMH, EPVS, CMBs, and total CSVD score between these four groups (all $p > 0.05$) (Table 3).

3.3 | Differences in Clinical Parameters and Blood Index Between CSVD Subgroups

Individuals with lacunes ($n = 34$) showed older age ($p < 0.001$) and higher HTN rate ($p = 0.016$) than those without lacunes ($n = 378$). Individuals with CMBs ($n = 129$) exhibited older age ($p < 0.001$), higher HTN ($p = 0.025$) and AF ($p = 0.045$) rate than those without CMBs ($n = 283$). Individuals with cortical CMBs ($n = 99$) showed older age than those without cortical CMBs ($n = 313$) ($p = 0.002$). Individuals with deep CMBs ($n = 51$) exhibited older age ($p < 0.001$), higher HTN rate ($p = 0.011$), and higher drinking rate ($p = 0.026$) compared with those without deep CMBs ($n = 361$). Different PVWMH subgroups differed in HTN rate ($p = 0.002$) and CHD rate ($p = 0.009$). DWMH subgroups showed different HTN rate ($p = 0.010$). Moreover, there were also significant differences in HTN rate ($p < 0.001$) and drinking rate ($p = 0.003$) between EPVS subgroups. However, different CSVD subgroups did not differ in proportion of severe intracranial vascular stenosis and occlusion.

HbA1c ($p = 0.043$), HDL-C ($p = 0.047$), and LDL-C ($p = 0.012$) levels differed between different PVWMH grades groups. There were also significant differences in TC ($p = 0.009$) and LDL-C ($p = 0.014$) between different DWMH grades groups.

TABLE 3 | Clinical characteristics of the study group according to TyG index quartiles.

	TyG index quartiles				
	Q1 (≤8.22)	**Q2 (8.23–8.54)**	**Q3 (8.55–8.88)**	**Q4 (≥8.89)**	***p***
n	103	103	103	103	—
Age (years)	72.50 ± 9.92	69.83 ± 11.16	69.21 ± 9.46	69.74 ± 10.29	0.094
Male (%)	63.1	64.1	64.1	53.4	0.088
BMI	23.75 ± 2.77	24.74 ± 2.80	25.56 ± 2.89	25.83 ± 2.67	< 0.001*
Hypertension (%)	39.8	46.6	64.1	65.0	< 0.001*
Hyperlipidemia (%)	60.2	74.8	79.6	86.4	< 0.001*
Coronary heart disease (%)	24.3	20.4	25.2	23.3	0.859
Atrial fibrillation (%)	5.8	3.9	4.9	3.9	0.895
Current smoking (%)	3.9	4.9	8.7	9.7	0.263
Drinking (%)	5.8	10.7	5.8	14.6	0.085
HbA1c (%)	5.49 ± 0.33	5.60 ± 0.40	5.66 ± 0.43	5.73 ± 0.45	< 0.001*
FBG (mmol/L)	5.25 ± 0.46	5.44 ± 0.48	5.58 ± 0.50	5.84 ± 0.67	< 0.001*
TC (mmol/L)	3.90 ± 0.83	4.24 ± 0.87	4.13 ± 0.90	4.41 ± 1.03	0.001*
TG (mmol/L)	0.72 ± 0.12	1.03 ± 0.13	1.37 ± 0.18	2.23 ± 0.80	< 0.001*
HDL (mmol/L)	1.55 ± 0.36	1.43 ± 0.32	1.28 ± 0.28	1.15 ± 0.23	< 0.001*
LDL (mmol/L)	2.40 ± 0.72	2.80 ± 0.87	2.75 ± 0.84	2.85 ± 0.97	0.001*
Lacunes (%)	9.7	5.8	6.8	10.7	0.536
PVWMH (%)	9.4	5.6	6.6	10.4	0.369
DWMH (%)	73.8	67.0	56.3	59.2	0.200
EPVS (%)	88.3	85.4	86.4	89.3	0.768
CMBs (%)	33.0	28.2	31.1	33.0	0.860
Total CSVD score	0.77 (0–3)	0.53 (0–4)	0.61 (0–3)	0.66 (0–4)	0.217

Note: Data are expressed as *n* (%), or mean ± SD (range).
Abbreviations: BMI, body mass index; CMBs, cerebral microbleeds; CSVD, cerebral small vessel disease; DWMH, deep white matter hyperintensities; EPVS, enlarged perivascular spaces; FBG, fasting blood glucose; HbA1c, glycated hemoglobin A1c; HDL-C, high density lipoprotein cholesterol; LDL-C, low density lipoprotein cholesterol (LDL-C); PVWMH, periventricular white matter hyperintensities; TC, total cholesterol; TG, triglyceride. *$p < 0.05$.

TC ($p = 0.010$) and LDL-C ($p = 0.004$) differed between different EPVS grades groups. Individuals with cortical CMBs showed lower TC ($p = 0.032$) and lower LDL-C ($p = 0.020$) levels than those without cortical CMBs. FBG was higher in individuals with deep CMBs compared with those without deep CMBs ($p = 0.012$) (Figure 1). There was a significant difference in LDL-C ($p = 0.029$) between five total CSVD burden groups. However, the TyG index did not differ between groups with different grades of lacunes, WMHs, CMBs, EPVS, and total CSVD burden.

3.4 | Correlation Between CSVD Markers and Its Risk Factors

In logistic regressions, all CSVD markers were associated with increasing age. Binary logistic regression showed that higher FBG along with older age were independent risk factors for deep CMBs, after controlling for sex ratio, BMI, vascular risk factors, HbA1c, and blood lipid. After adding the proportion of severe intracranial vascular stenosis and occlusion to the independent variable, the association between deep CMBs and higher FBG was still statistically significant. However, other CSVD imaging markers did not correlate with blood glucose levels (Table 4). In addition, the TyG index was not associated with CSVD imaging markers in this study.

3.5 | Correlation Between the TyG Index and Its Risk Factors

Multiple linear regression analysis revealed that the TyG index correlated with BMI, HTN, HL, FBG, TC, TG, and LDL-C levels. However, no significant association was found between the TyG index and CSVD markers (Table 5).

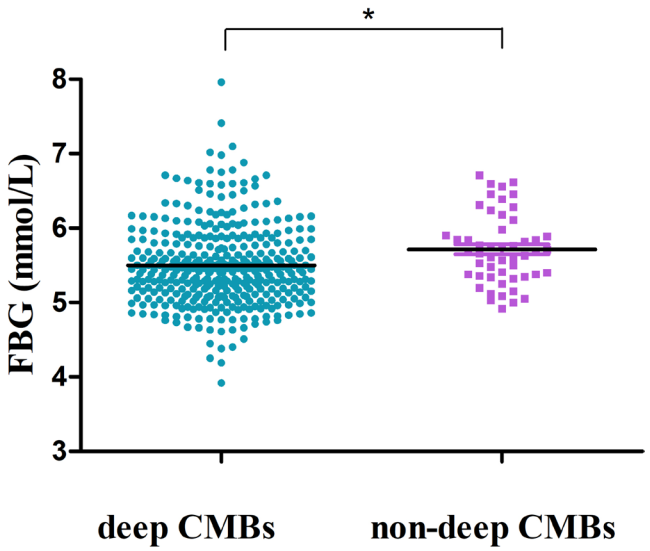

FIGURE 1 | Differences in FBG between individuals with deep CMBs and without deep CMBs. *$p \leq 0.050$. CMBs, cerebral microbleeds; FBG, fasting blood glucose.

4 | Discussion

In this study, we found that 43.7% of nondiabetic individuals had asymptomatic CSVD in the middle-aged and elderly population. All CSVD markers related to increasing age. Furthermore, we observed an association between HbA1c and PVWMH, and between FBG and deep CMBs. To our knowledge, this is the first study revealing the correlation between glucose level and cerebral microbleeds in neurologically asymptomatic, nondiabetic individuals.

The majority of the population in our study was elderly (median age: 70.32 ± 10.27 years). Among cases, 299 individuals (72.6%) aged 65 years or over, and 86 individuals (20.9%) aged 80 years or older. More than half the population in our study had vascular risk factors. In addition, we used SWI to assess cerebral microbleeds, which was more sensitive than T2*-weighted MRI. Hence, our findings support that CSVD is common in middle-aged and elderly people and thus requires more attention.

The association between CSVD and diabetes (DM) was observed in previous work. Lacunes and WMH were found to be more common in the DM group than in the impaired glucose tolerance and control groups [16]. As to neurologically asymptomatic individuals, previous studies also revealed that glucose levels and the marker of insulin resistance (IR) were correlated with CSVD markers, including silent brain infarcts and WMH [17–19]. However, another study found that there was no association between glycemic control and CSVD in neurologically asymptomatic individuals with type 1 diabetes [20]. Their results remain controversial. Our findings supported the correlation between glucose level and deep cerebral microbleeds in neurologically asymptomatic, nondiabetic individuals. Our study had a large sample size and complete clinical and neuroimaging data from a fixed population who undergo annual physical examinations. It helps us to screen risk factors for CSVD in the preclinical stage. Up to now, the association between higher blood glucose level and cerebral microbleeds was not clear. Previous studies indicated that higher blood glucose levels may accelerate cellular and molecular aging processes, aggravate oxidative stress, and endothelial dysfunction, and then lead to increased microvascular fragility. Microvascular fragility was related to the rupture of small intracerebral vessels, which was known as CMBs. Therefore, we speculated that in neurologically asymptomatic, nondiabetic individuals, higher glucose levels could aggravate cellular aging and microvascular fragility [21, 22]. Furthermore, high glucose levels could induce damage to the endothelium, blood–brain barrier alterations, and vascular inflammation. Vascular inflammation was related to small vascular disease, especially among patients with stroke [23]. Moreover, hyperglycemia could induce alterations in vascular tissue that potentially promote atherosclerosis [24], which may also be correlated with deep CMBs. Therefore, it suggests that it may be beneficial to pay attention to the blood glucose levels in middle-aged and elderly populations.

As to IR, TyG index was found to be related to EPVS, WMH, and lacunes in the nondiabetic population or community-dwelling subjects [25–29]. Furthermore, Yang et al. indicated that insulin resistance index (HOMA-IR) was positively associated with the total CSVD score [30]. However, in our study, we did not find the relationship between IR (TyG index) and CSVD markers. We speculated that one of the reasons was related to the

TABLE 4 | Logistic regression of factors associated with CSVD markers.

	Deep CMBs		Cortical CMBs	
	Multivariable adjusted		Multivariable adjusted	
	OR (95% CI)	*p*	OR (95% CI)	*p*
Age	1.07 (1.04–1.10)	< 0.001*	1.03 (1.01–1.06)	0.004*
FBG	1.66 (1.03–2.68)	0.036*	—	0.829
HbA1c	—	0.682	—	0.442
TyG index	—	0.327	—	0.425
TC	—	0.686	—	0.781
TG	—	0.410	—	0.427
HDL-C	—	0.225	—	0.480
LDL-C	—	0.433	—	0.051
	Total CMBs		**Lacunes**	
	Multivariable adjusted		Multivariable adjusted	
	OR (95% CI)	*p*	OR (95% CI)	*p*
Age	1.06 (1.03–1.08)	< 0.001*	1.07 (1.04–1.11)	< 0.001*
FBG	—	0.720	—	0.627
HbA1c	—	0.582	—	0.186
TyG index	—	0.376	—	0.449
TC	—	0.585	—	0.288
TG	—	0.462	—	0.237
HDL-C	—	0.771	—	0.096
LDL-C	—	0.696	—	0.308
	PVWMH		**DWMH**	
	Multivariable adjusted		Multivariable adjusted	
	OR (95% CI)	*p*	OR (95% CI)	*p*
Age	1.10 (1.08–1.13)	< 0.001*	1.06 (1.03–1.08)	< 0.001*
FBG	0.82 (0.52–1.30)	0.406	1.07 (0.66–1.73)	0.789
HbA1c	1.52 (0.89–2.60)	0.126	1.27 (0.72–2.25)	0.414
TyG index	0.58 (0.14–2.32)	0.440	0.23 (0.05–1.02)	0.053
TC	1.30 (0.62–2.7)	0.490	0.70 (0.32–1.56)	0.389
TG	1.46 (0.60–3.52)	0.399	1.65 (0.64–4.24)	0.298
HDL-C	1.41 (0.60–3.31)	0.433	1.13 (0.45–2.86)	0.791
LDL-C	0.70 (0.33–1.47)	0.345	1.28 (0.58–2.86)	0.542
	EPVS		**CSVD burden**	
	Multivariable adjusted		Multivariable adjusted	
	OR (95% CI)	*p*	OR (95% CI)	*p*
Age	1.07 (1.05–1.1)	< 0.001*	1.09 (1.07–1.12)	< 0.001*
FBG	0.82 (0.50–1.35)	0.437	0.88 (0.55–1.42)	0.613
HbA1c	1.22 (0.67–2.22)	0.507	0.96 (0.55–1.67)	0.887

(Continues)

TABLE 4 | (Continued)

	EPVS		CSVD burden	
	Multivariable adjusted		Multivariable adjusted	
	OR (95% CI)	*p*	OR (95% CI)	*p*
TyG index	0.85 (0.18–3.92)	0.833	1.16 (0.28–4.91)	0.838
TC	0.82 (0.38–1.78)	0.612	0.70 (0.33–1.45)	0.334
TG	1.50 (0.57–3.93)	0.407	1.24 (0.50–3.04)	0.642
HDL-C	1.36 (0.54–3.43)	0.509	1.54 (0.65–3.66)	0.330
LDL-C	0.87 (0.40–1.92)	0.737	1.14 (0.54–2.4)	0.732

Abbreviations: FBG, fasting blood glucose; HbA1c, glycated hemoglobin A1c; HDL-C, high density lipoprotein cholesterol; LDL-C, low density lipoprotein cholesterol (LDL-C); TC, total cholesterol; TG, triglyceride; TyG index, the triglyceride-glucose index.
*Adjusted for sex ratio, BMI, current smoking, HTN, HL, CHD, and AF.

TABLE 5 | Multiple linear regression analysis between possible predictors and TyG index.

	B	*β*	*T*	*p*	95% CI
Age	−0.001	−0.023	−1.297	0.195	−0.003–0.000
Sex	0.014	0.009	0.549	0.583	−0.037–0.065
BMI	0.008	0.047	2.881	0.004*	0.002–0.013
HTN	0.046	0.049	3.006	0.003*	0.016–0.076
HL	0.052	0.047	3.126	0.002*	0.019–0.085
CHD	0.012	0.010	0.684	0.494	−0.022–0.045
AF	0.030	0.013	0.875	0.382	−0.037–0.096
Current smoking	0.037	0.020	1.338	0.182	−0.017–0.092
Lacunes	−0.030	−0.018	−0.802	0.423	−0.104–0.044
PVWMH	−0.003	−0.005	−0.241	0.809	−0.027–0.021
DWMH	−0.026	−0.031	−1.721	0.086	−0.055–0.004
EPVS	−0.003	−0.005	−0.201	0.841	−0.037–0.030
CMBs	−0.020	−0.019	−0.400	0.689	−0.117–0.078
Cortical CMBs	0.008	0.007	0.196	0.845	−0.072–0.088
Deep CMBs	0.007	0.005	0.205	0.837	−0.063–0.078
CSVD burden	0.018	0.034	0.766	0.444	−0.028–0.064
HbA1c	0.028	0.025	1.453	0.147	−0.010–0.067
FBG	0.177	0.214	12.817	< 0.001*	0.150–0.204
TC	−0.076	−0.149	−2.894	0.004*	−0.128 to −0.024
TG	0.579	0.858	43.327	< 0.001*	0.552–0.605
HDL-C	−0.019	−0.014	−0.615	0.539	−0.080–0.042
LDL-C	0.110	0.200	4.171	< 0.001*	0.058–0.161

Abbreviations: AF, atrial fibrillation; BMI, body mass index; CHD, coronary heart disease; CMBs, cerebral microbleeds; CSVD, cerebral small vessel disease; DWMH, deep white matter hyperintensities; EPVS, enlarged perivascular spaces; FBG, fasting blood glucose; HbA1c, glycated hemoglobin A1c; HDL-C, high density lipoprotein cholesterol; HL, hyperlipidemia; HTN, hypertension; LDL-C, low density lipoprotein cholesterol; PVWMH, periventricular white matter hyperintensities; TC, total cholesterol; TG, triglyceride; TyG index, the triglyceride-glucose index. *$p < 0.05$.

methodological differences. We used TyG index to assess insulin resistance, while HOMA-IR was used in their study. Moreover, the participants in this study are neurologically asymptomatic, nondiabetic individuals, and the proportion of insulin resistance is low, which may not cause significant neuroimaging changes and statistical differences. In the future, we will expand the

sample size to further observe the correlation between insulin resistance indicators and clinical conditions. There were some limitations in this study. Firstly, this is a cross-sectional study. Further larger sample size and prospective studies are needed to validate our findings. Secondly, TyG index was used to assess IR, instead of the homeostatic model assessment for insulin resistance (HOMA- IR). We could utilize other useful and straightforward indicators of IR state to investigate the relationship between IR and CSVD markers during subsequent physical examinations. Finally, the findings might only be applicable to certain Asian populations, so we should be more careful to generalize the conclusion.

5 | Conclusions

Our study has revealed that CSVD was very common and provided evidence supporting the relationship between blood glucose levels and CSVD risk in neurologically asymptomatic, nondiabetic middle-aged and elderly populations. It may be beneficial for healthy people to pay attention to blood glucose levels. The correlation between insulin resistance and CSVD in these groups needs more investigation in the future.

Author Contributions

X.M., F.L., and Y.L. contributed to the conception and design of the study. X.M., L.Q., J.C., W.D., J.H., and A.S. collected the clinical data. X.M. performed the imaging and statistical analysis, and wrote the first draft of the manuscript. Y.L. revised the manuscript. All authors approved the final version of the manuscript.

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Ethics Statement

All procedures performed in studies involving human participants were in accordance with the Declaration of Helsinki and its later amendments or comparable ethical standards. The study was approved by Beijing Hospital ethics committee (2022BJYYEC-340-01).

Consent

All participants were informed about the objectives of the research and signed separate informed consent forms.

Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

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

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