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Asymmetric U-shaped relationship between blood glucose and white matter lesions: results of a cross-sectional study

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Abstract

Background Elderly individuals are susceptible to the accrual of White Matter Lesions (WMLs), a subcategory of cerebral small-vessel disease. WMLs are strongly linked to an increased risk of strokes, intracerebral hemorrhages, and dementia. While the relationship between blood glucose levels and the development of WMLs has been investigated in previous studies, the findings remain inconsistent. Some evidence suggests that glucose dysregulation, including both hypo- and hyperglycemia, may contribute to WML formation through mechanisms such as endothelial dysfunction and chronic inflammation. However, other studies report no significant correlation. This inconsistency underscores the need for further investigation.

Methods In this investigation, the primary data were derived from a predictive mathematical model designed to estimate WMLs based on parameters obtained from routine medical examinations, with head MRI scans serving as the reference standard for WML diagnosis and quantification. We leveraged multivariable logistic regression analysis to scrutinize the relationship between blood glucose concentrations and WMLs. Additionally, we employed a restricted cubic spline regression model to investigate a potential non-linear relationship between these variables.

Results There were 1904 participants who underwent medical check-ups which included a head MRI. Generally, the relationship between blood glucose levels and white matter lesions followed an asymmetric U-shaped curve (P for non-linearity = 0.004). A consistent finding was that compared to the individuals in the 2nd and 3rd quartiles (95 to 107 mg/dl), the 1st quartile (OR, 1.71; 95% CI: 1.26–2.30) and 4th quartile (OR, 1.57; 95%CI: 1.12–2.20) had white matter lesions were significantly higher.

Conclusion An asymmetric U-shaped relationship exists between blood glucose and WMLs, with the lowest risk occurring at 95–107 mg/dl. Management of blood glucose can help prevent the occurrence and development of WMLs. However, the study's cross-sectional design limits causal inference, and the reliance on pre-existing data constrained the availability of variables.

Keywords Blood glucose, White matter lesions, Cerebral small vessel disease, Asymmetric U-shaped relationship

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Introduction

White matter lesions (WMLs), a hallmark of cerebral small vessel disease (SVD), are common in older adults and are strongly associated with an increased risk of stroke, vascular dementia, depression, and gait disturbances [1, 2]. WMLs are typically identified on magnetic resonance imaging (MRI) as hyperintense regions on T2-weighted or FLAIR sequences, reflecting underlying pathologies such as. demyelination, axonal loss, and gliosis [2, 3]. Numerous studies have unequivocally linked WMLs to recurrent strokes, increased severity, and poor prognoses [4–6]. While the clinical significance of WMLs is well established, their pathogenesis remains incompletely understood, and modifiable risk factors are still being actively investigated.

In recent years, substantial research has focused on the manifestation and progression of WMLs, aiming to identify risk factors contributing to their development and presence [1, 7]. Multiple studies have confirmed associations between WML prevalence and factors such as age, hypertension, diabetes mellitus (DM), and a history of stroke or myocardial infarction [8–10]. Among these potential contributors, glucose dysregulation-including both hypo-and hyperglycemia-has emerged as a critical yet understudied factor. Current evidence suggests that abnormal glucose levels may influence WML development through mechanisms such as endothelial dysfunction, chronic inflammation, and impaired cerebral autoregulation. However, findings across studies remain inconsistent: while some report significant associations between glucose dysregulation and WML burden [6, 7], others find no clear link [11]. Furthermore, most studies focus on categorical distinctions (e.g., diabetes versus non-diabetes) rather than examining the continuous relationship between blood glucose levels and WMLs, leaving a critical gap in our understanding of how varying glucose levels impact brain health across the glycemic spectrum.

By investigating this continuous relationship, our study aims to address this gap and provide new insights into the role of glucose homeostasis in WML development. Identifying glucose dysregulation as a potential modifiable risk factor could have significant implications for prevention and intervention strategies targeting cerebrovascular health. To explore this relationship, we conducted a post-hoc analysis using data from a study that developed a discriminant model to predict WMLs. The data were obtained from a medical check-up program spanning April 1, 2016, to October 31, 2017.

Methods

Data source

The data for this study was sourced from the Dryad Digital Repository (https://doi.org/10.5061/dryad.73bh2q8). Detailed information about this cohort is described in the original study publication [12]. Data from the original study has been authorized for use on the dryad Web site by the authors [12]. Our analysis of Dryad data Package for a secondary hypothesis adhered to Dryad's Terms of Service and respected the author's rights. The original study received approval from the ethical review committee of Shin Takeo Hospital [12]. We report this study following the guidelines of Enhancing the Reporting of Observational Studies in Epidemiology.

Study population

The original dataset consisted of a total 1904 patients recruited at a single-center comprehensive medical examination in Japan from April 2016 to October 2017. All patients were subjected to head MRI, blood tests, and relevant questionnaires during the examination period. T1-weighted imaging (T1WI), T2-weighted imaging (T2WI), and fluid-attenuated inversion recovery (FLAIR) sequences were performed on the MRI of the head. WMLs were defined as lesions exhibiting hyperintense signals on T2-weighted and FLAIR images, while appearing iso-intense or slightly hypointense on T1-weighted images.

Baseline variables

Baseline blood glucose

As part of a comprehensive medical examination, the patient's fasting blood glucose level was measured using biochemical testing [12].

Covariates

The following data on the basic characteristics of the patient were collected: demographic characteristics such as age, gender, body mass index (BMI), and mean arterial pressure (MAP); chronic comorbidities such as metabolic syndrome, smoking habit, drinking habit, drinking volume, diabetes mellitus, arterial hypertension, hyperlipidemia; routine laboratory sampling included low-density lipoprotein cholesterol (LDL), high-density lipoprotein cholesterol (HDL), LH ratio (ratio of LDL to HDL), triglyceride (TG), hemoglobin A1c (HbA1c). The number of carotid plaques and the carotid plaque score (PS) was calculated for each patient by ultrasonography. Carotid plaque score (PS) was the summation of the maximum thickness values of all plaques with an intima-media thickness greater than 1.1 mm in both the left and right carotid arteries [12].

Outcome

The outcome of this study was the presence of WMLs in the brain confirmed by head MRI which was monitored from 1 April 2016 to 31 October 2017.

Statistical analysis

All patients were subjected to a descriptive analysis. To describe the distribution of continuous variables, we used the mean and standard deviation (SD), while for skewed variables, we used the median and interquartile range (IQR). Numeric and percentage values were used to express the categorical variables. A chi-square or Fisher's Exact test was utilized to determine differences between groups for categorical variables, while a one-way ANOVA and Kruskal-Wallis test were employed for normally distributed and non-normal continuous variables, respectively. The relationship between blood glucose and WMLs was determined using multivariate logistic regression analysis, resulting in odds ratios (OR) and 95% confidence intervals (95% CI). There was no adjustment to Model (I) Age and gender adjustments were made to Model (II) Model III was further adjusted for BS, HDL, plaque number, HbA1c, MAP, smoking, drinking, metabolic syndrome, LDL, PS, TG, LH, BMI, and application of cholesterol-lowering drugs, antihypertensive drugs, and insulin. To assess a potentially nonlinear relationship between blood glucose and WMLs with adjustments for covariates in model III, a regression analysis using restricted cubic splines (RCS) with four knots (5th, 35th, 65th, and 95th percentiles of blood glucose) was performed [13]. To address the potential impact of covariate imbalance on blood glucose levels, a propensity score weighting approach was applied. Multinomial propensity scores were estimated by applying generalized boosted machine-learning models [14], with the specific calculation process carried out using the R package 'twang' [15]. The estimated propensity scores included all covariates from Model (III) To reduce bias caused by confounding, the weighted cohort was generated using the inverse probability weighting (IPW) method [16]. After weighting, covariate balance was assessed using standardized mean differences (SMDs), with SMD values less than 0.2 considered indicative of sufficient balance. Statistical analyses were conducted using R software (version 4.4.1; http://www.r-project.org, The R Foundation). A two-tail ed test was performed, and p-values less than 0.05 were considered statistically significant.

Results

Participant characteristics

Out of the original cohort, we identified a total of 1,904 cases, consisting of 988 males and 916 females, average age: 56.4 ± 11.5 years [12]. Table 1 displays the characteristics of participants divided into quartiles of blood glucose. The results show that participants with higher blood glucose levels were more likely to be older females who smoked and had a higher BMI, PS, MAP, TG, HbA1c, and greater use of cholesterol-lowering drugs, antihypertensive drugs, and insulin. They also had lower levels of HDL.

Association of blood glucose and WMLs

Tables 2 and 3 present a comparison of the results from univariate and multivariate logistic regression models. In the multivariate model, which was adjusted for all covariates in Table 1, several non-linear relationships were observed between categorizing blood glucose and WMLs. The group of people with blood glucose levels of 95–107 (mg/dl) had the lowest incidence of WMLs. The cubic simulation curve of blood glucose and WMLs, demonstrated in Fig. 1, followed an asymmetric U-shaped with the nadir at around 100 mg/dl (P value for nonlinearity = 0.004). Moreover, after considering potential confounders, an asymmetric U-shaped relationship between blood glucose and WMLs was observed through quartile analysis. Compared to the Q2 group (95–100 mg/dl), adjusted odds ratios (ORs) for Q1 (95 mg/dl), Q3 (101–107 mg/dl), and Q4 (> 107 mg/dl) were 1.49 (95% CI, 1.10-2.00), 1.0 (95% CI, 0.74–1.36), and 1.53 (95% CI, 1.10–2.12), respectively (Table 2). Participants in both the first and fourth quartiles of blood glucose were at higher risk of WMLs compared to those in the intermediate quartiles. Moreover, Fig. 2 showed that the asymmetric U-shaped relationship persisted in Models I, II and III.

Other risk factors for the incidence of WMLs

Table 3 presents the results of univariate logistic and multivariable logistic regression analyses conducted to identify the risk factors for WMLs. Using univariate binary logistic regression, we found that WMLs were related to age, BS, gender, HDL, plaque number, HbA1c, MAP, PS, smoking, drinking, metabolic syndrome, and application of cholesterol-lowering drugs, antihypertensive drugs, insulin, but not to LDL, TG, LH, or BMI. The multivariate logistic regression analysis found that BS, age, gender, HDL, MAP, metabolic syndrome, and application of antihypertensive drugs were independent risk factors for WMLs. The outcome indicated that age ≧ 60 years (OR = 4.915; 95% CI, 3.87–6.242; $P < 0.001$), female (OR = 1.446; 95% CI, 1.093–1.914; $P = 0.010$), HDL (OR = 1.024; 95% CI, 1.006–1.042; $P = 0.009$), MAP(OR = 1.018; 95% CI, 1.009–1.027; $P < 0.001$), and application of antihypertensive drugs (OR = 1.798; 95% CI, 1.33–2.432; $P < 0.001$) was significantly associated with a higher incidence of WMLs after adjusting for other covariates.

Stratified analyses based on additional variables

A stratified analysis was conducted to evaluate the potential effects of modifications on the relation between blood glucose and WMLs in several subgroups. The results

Table 1 Baseline characteristics of participants

Covariates	Total	Baseline blood glucose (mg/dl)				*P*-value
		< 95	95–100	101–107	> 107	
	(*n* = 1904)	1(*n* = 457)	2(*n* = 494)	3(*n* = 434)	4(*n* = 519)	
Age(years), n(%)						< 0.001
20–59	1050(55.1)	282(61.7)	296(59.9)	246(56.7)	226(43.5)	
≥60	854(44.9)	175(38.3)	198(40.1)	188(43.3)	293(56.5)	
Gender, n(%)						< 0.001
Female	988(51.9)	153(33.5)	233(47.2)	261(60.1)	341(65.7)	
Male	916(48.1)	304(66.5)	261(52.8)	173(39.9)	178(34.3)	
PS	1.1 ± 2.0	0.8 ± 1.7	0.9 ± 1.8	0.9 ± 1.8	1.7 ± 2.4	< 0.001
LDL(mg/dl)	120.9 ± 30.4	118.3 ± 29.0	120.6 ± 29.8	123.2 ± 31.7	121.4 ± 31.1	0.107
HDL(mg/dl)	61.1 ± 15.4	65.0 ± 15.8	62.7 ± 15.9	60.8 ± 14.8	56.5 ± 13.8	< 0.001
TG(mg/dl)	111.8 ± 99.8	89.1 ± 54.3	95.4 ± 53.0	119.9 ± 140.9	140.7 ± 114.5	< 0.001
Plaque, M(IQR)	0.0(0.0,1.0)	0.0(0.0,1.0)	0.0(0.0,1.0)	0.0(0.0,1.0)	0.0(0.0,2.0)	< 0.001
LH	2.1 ± 0.8	1.9 ± 0.7	2.1 ± 0.7	2.2 ± 0.8	2.3 ± 0.8	< 0.001
HbA1c(%)	5.8 ± 0.6	5.5 ± 0.3	5.6 ± 0.3	5.7 ± 0.3	6.3 ± 0.9	< 0.001
BMI(kg/m^2)	23.2 ± 3.4	21.8 ± 3.0	22.6 ± 2.9	23.4 ± 3.2	24.7 ± 3.7	< 0.001
MAP(mmHg)	90.5 ± 13.3	86.4 ± 12.7	89.3 ± 12.6	91.7 ± 13.5	94.4 ± 13.2	< 0.001
Smoking, n(%)						0.741
No	1568(82.4)	382(83.6)	407(82.4)	359(82.7)	420(80.9)	
Yes	336(17.6)	75(16.4)	87(17.6)	75(17.3)	99(19.1)	
Amount of drink, n(%)						< 0.001
< 180ML/day	1224(64.3)	331(72.4)	334(67.6)	257(59.2)	302(58.2)	
180ML-360ML/day	467(24.5)	86(18.8)	110(22.3)	124(28.6)	147(28.3)	
360ML-540ML/day	158(8.3)	29(6.3)	38(7.7)	38(8.8)	53(10.2)	
> 540ML/day	55(2.9)	11(2.4)	12(2.4)	15(3.5)	17(3.3)	
Cholesterol-lowering drugs, n(%)						< 0.001
No	1589(83.5)	408(89.3)	438(88.7)	367(84.6)	376(72.4)	
Yes	315(16.5)	49(10.7)	56(11.3)	67(15.4)	143(27.6)	
Drink habit, n(%)						< 0.001
Rarely drink	796(41.8)	218(47.7)	231(46.8)	160(36.9)	187(36)	
Sometimes	565(29.7)	154(33.7)	137(27.7)	130(30)	144(27.7)	
Everyday	543(28.5)	85(18.6)	126(25.5)	144(33.2)	188(36.2)	
Insulin, n(%)						< 0.001
No	1765(92.7)	454(99.3)	489(99)	423(97.5)	399(76.9)	
Yes	139(7.3)	3(0.7)	5(1)	11(2.5)	120(23.1)	
Metabolic syndrome, n(%)						< 0.001
No	1429(75.1)	413(90.4)	418(84.6)	321(74)	277(53.4)	
Reserve	196(10.3)	33(7.2)	49(9.9)	69(15.9)	45(8.7)	
Yes	279(14.7)	11(2.4)	27(5.5)	44(10.1)	197(38)	
Antihypertensive drugs, n(%)						< 0.001
No	1442(75.7)	391(85.6)	407(82.4)	334(77)	310(59.7)	
Yes	462(24.3)	66(14.4)	87(17.6)	100(23)	209(40.3)	

Abbreviations: IQR, interquartile range; SD, standard deviation; PS, carotid plaque score; LDH, low-density lipoprotein cholesterol; HDL, high-density lipoprotein cholesterol; TG, triglyceride; HbA1c, hemoglobin A1c; LH, ratio of LDL to HDL; BMI, body mass index; MAP, mean arterial pressure; Plaque N, plaque number

[a] Variables are presented as mean ± SD, median (IQR) or n (%)

of stratified analyses were consistent, after stratifying by age, gender, metabolic syndrome, smoking, MAP, HbA1c, drinking, TG, BMI and antihypertensive drugs, no significant interactions were found in any subgroup. (*P* interaction > 0.05) (Table S1).

Inverse probability treatment weighting to control confounding factors

We combined the Q2 and Q3 groups (quartiles 2–3, 95 to 107 mg/dl) because their risks were similar. The balance of other covariates has been markedly increased between groups after the propensity score weighting, as illustrated in Table S2. Supplementary Figure S1 implies that post inverse probability weighting, the Standardised Mean

Table 2 Relationship between blood glucose and WMLs

Variables Blood glucose	Total (*n*)	WML *n*(%)	Model I OR(95% CI)	*P*-value	Model II OR(95% CI)	*P*-value	Model III OR(95% CI)	*P*-value
<95(mg/dl)	457	248 (54.3)	1.31 (1.01–1.69)	0.039	1.47 (1.09-2.00)	0.012	1.49 (1.10-2.00)	0.009
95–100(mg/dl)	494	235 (47.6)	1.00(Ref)		1.00(Ref)		1.00(Ref)	
101–107(mg/dl)	434	216 (49.8)	1.09 (0.84–1.41)	0.504	1.03 (0.76–1.39)	0.841	1.00 (0.74–1.36)	0.990
>107(mg/dl)	519	345 (66.5)	2.19 (1.7–2.82)	< 0.001	1.67 (1.24–2.25)	0.001	1.53 (1.10–2.21)	0.011
p for trend			< 0.001		0.316		0.964	

Model I, No adjustment. Model II, Adjusted for age and gender. Model III, Adjusted for age, gender, carotid plaque score, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, triglyceride, ratio of LDL to HDL, body mass index, mean arterial pressure, plaque number, amount of drink, cholesterol-lowering drugs, drink habit, insulin, metabolic syndrome and antihypertensive drugs

Table 3 Univariate logistic and multivariable logistic regression models evaluating the association between blood glucose and WMLs

Variable	Univariate logistic analysis	*P*-value	Multivariable logistic analysis	*P*-value
	OR (95%CI)		OR (95%CI)	
BS <95(mg/dl)	1.308 (1.013–1.688)	0.039	1.493 (1.106–2.014)	0.009
BS 95–100(mg/dl)	1(Ref)		1(Ref)	
BS 101–107(mg/dl)	1.092 (0.844–1.414)	0.504	0.999 (0.736–1.357)	0.995
BS >107(mg/dl)	2.185 (1.695–2.816)	< 0.001	1.499 (1.068–2.102)	0.0192
Age(years)	7.45 (6.04–9.189)	< 0.001	4.915 (3.87–6.242)	< 0.001
Gender, n(%)	1.542 (1.286–1.85)	< 0.001	1.446 (1.093–1.914)	0.010
PS	1.36 (1.276–1.45)	< 0.001	1.003 (0.809–1.244)	0.977
LDL(mg/dl)	1.002 (0.999–1.005)	0.109	0.999 (0.989–1.008)	0.771
HDL(mg/dl)	1.013 (1.007–1.019)	< 0.001	1.024 (1.006–1.042)	0.009
TG	0.999 (0.998-1)	0.146	1 (0.998–1.001)	0.778
Plaque, M(IQR)	1.782 (1.592–1.995)	< 0.001	1.326 (0.888–1.982)	0.168
LH	0.894 (0.793–1.006)	0.064	1.334 (0.794–2.244)	0.276
HbA1c(%)	1.917 (1.578–2.328)	< 0.001	1.06 (0.838–1.342)	0.627
BMI(kg/m^2)	1.004 (0.978–1.031)	0.774	0.977 (0.937–1.02)	0.289
MAP(mmHg)	1.024 (1.017–1.032)	< 0.001	1.018 (1.009–1.027)	< 0.001
smoking, n(%)	0.517 (0.407–0.657)	< 0.001	0.854 (0.631–1.156)	0.306
Amount of drink < 180ML/day	1(Ref)		1(Ref)	
Amount of drink (180ML-360ML/day)	0.679 (0.548–0.842)	< 0.001	0.869 (0.634–1.19)	0.380
Amount of drink (360ML-540ML/day)	0.543 (0.388–0.758)	< 0.001	0.738 (0.475–1.149)	0.179
Amount of drink > 540ML/day	0.583 (0.339–1.004)	0.052	1.038 (0.537–2.009)	0.911
Cholesterol-lowering drugs, n(%)	2.726 (2.08–3.571)	< 0.001	1.359 (0.964–1.917)	0.080
Drink habit(Rarely drink), n(%)	1(Ref)		1(Ref)	
Drink habit(Sometimes), n(%)	0.783 (0.63–0.973)	0.0274	1.274 (0.957–1.695)	0.097
Drink habit(Everyday), n(%)	0.775 (0.622–0.965)	0.022	1.113 (0.791–1.567)	0.538
Insulin, n(%)	2.955 (1.969–4.434)	< 0.001	1.141 (0.645–2.021)	0.650
Metabolic syndrome(No), n(%)	1(Ref)		1(Ref)	
Metabolic syndrome(Reserve), n(%)	1.371 (1.012–1.858)	0.042	1.868 (1.254–2.784)	0.002
Metabolic syndrome(Yes), n(%)	1.822 (1.392–2.385)	< 0.001	1.296 (0.855–1.963)	0.222
Antihypertensive drugs, n(%)	3.52 (2.773–4.467)	< 0.001	1.798 (1.33–2.432)	< 0.001

Abbreviations: BS, blood glucose; PS, carotid plaque score; LDH, low-density lipoprotein cholesterol; HDL, high-density lipoprotein cholesterol; TG, triglyceride; HbA1c, hemoglobin A1c; LH, ratio of LDL to HDL; BMI, body mass index; MAP, mean arterial pressure; Plaque N, plaque number; OR, odds ratio; CI, confidence interval; Ref, reference

Differences (SMD) for all variables fall below 0.2. Propensity score-weighted logistic models without or with adjustment covariates showed an asymmetric U-shaped association between BS and WMLs. As compared with the Q2-Q3 group, the adjusted OR were 1.71 (95% CI: 1.26–2.30) in the Q1 and 1.57 (95% CI:1.12–2.20) in the Q4 (Table 4).

Discussion

In this cross-sectional exploration involving Japanese adults, we initially revealed that both elevated and diminished blood glucose levels were correlated with an augmented risk of WMLs. Intriguingly, we discovered an asymmetric U-shaped association between blood glucose and WMLs, which is highly relevant for clinical and public health practices. The decrease in incidence for

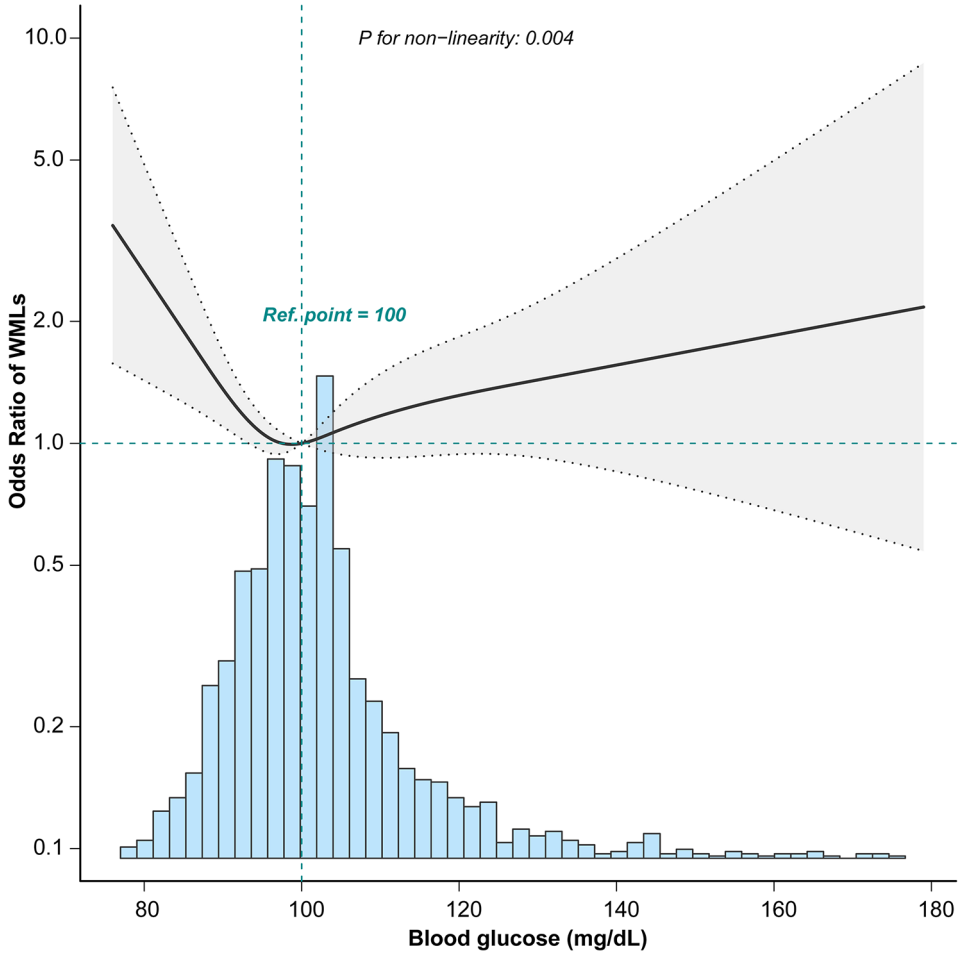

Fig. 1 Smoothing curve for the relationship between blood glucose and white matter lesions. Adjusted for age, gender, carotid plaque score, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, triglyceride, ratio of LDL to HDL, body mass index, mean arterial pressure, plaque number, amount of drink, cholesterol-lowering drugs, drink habit, insulin, metabolic syndrome and antihypertensive drugs. Only 99% of the data is shown

WMLs bottomed out approximately within the range of 95–107 mg/dl. Consequently, when blood glucose levels were compared to those in the 2–3 quartiles (95 to 107 mg/dl), participants in the first quartile had significantly higher risks of white matter lesions (adjusted OR, 1.5; 95% CI: 1.11–2.02) as well as the fourth quartile (adjusted OR, 1.5; 95% CI: 1.07–2.11). These conclusions remained consistent following adjustment for confounding elements via propensity score weighting. This finding suggests that maintaining blood glucose within this optimal range may serve as an important preventative measure to mitigate WMLs and their associated complications. For instance, patients with glucose levels in these extreme ranges may require closer clinical monitoring to prevent neurological damage. However, further longitudinal studies are needed to determine causality and validate these thresholds.

According to stratified analyses, the relationship between blood glucose and WMLs remains robust. A retrospective assessment of 93 patients revealed that diabetic individuals had larger volumes and counts of WMLs ($P = 0.0001$). Furthermore, a stepwise logistic regression model identified diabetes as the only significant factor associated with WMLs ($P = 0.0001$), supporting our findings [17].The Swedish National Study on Aging and Care, implementing a cohort study of prospectively accumulated longitudinal data ($n = 2746$), inferred that DM is linked with both a more extensive volume of white matter hyperintensities and a swift accumulation thereof [11]. Studies on type 2 diabetes and WMLs suggest that individuals with diabetes are more likely to exhibit brain structural abnormalities, including reduced grey matter volume, enlarged lateral ventricles, and significant cerebral tissue loss [18–20]. These findings reinforce the importance of glycemic control, not only for preventing the vascular complications of diabetes but also for preserving structural and functional brain integrity.

There are several possible explanations for our findings. Currently, it is generally accepted that WMLs are

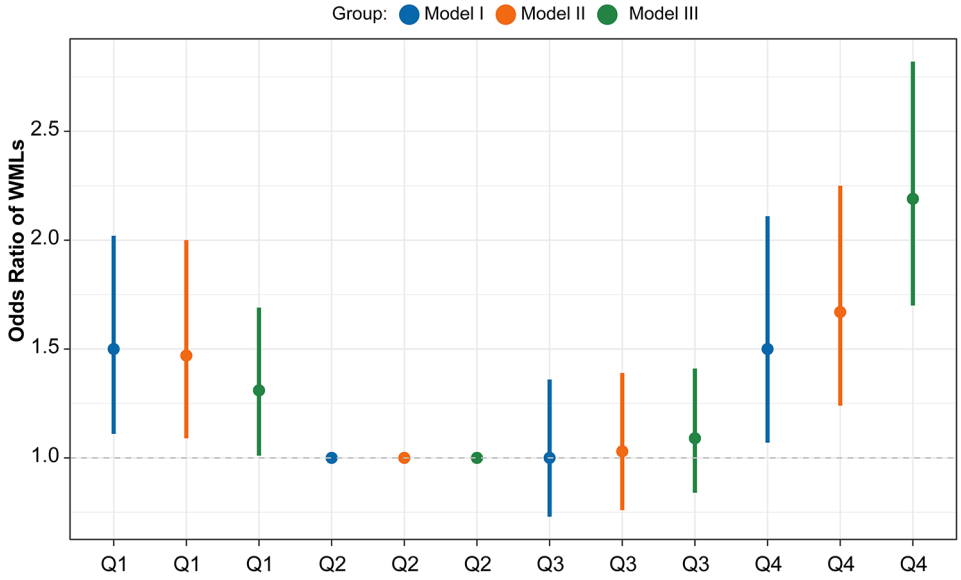

Fig. 2 The relationship between blood glucose and risk of white matter lesions in various models. Model I, No adjustment. Model II, Adjusted for age and gender. Model III, Adjusted for age, gender, carotid plaque score, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, triglyceride, ratio of LDL to HDL, body mass index, mean arterial pressure, plaque number, amount of drink, cholesterol-lowering drugs, drink habit, insulin, metabolic syndrome and antihypertensive drugs

Table 4 Propensity score weighting logistic models to control the impact of covariate imbalance in blood glucose groups[a]

Blood glucose(mg/dl)	Crude OR(95% CI)	Adjusted OR(95% CI)	*P*-value
Q1 (<95 mg/dl)	1.26(1.00-1.57)	1.71(1.26–2.30)	0.001
Q2-Q3 (95-107 mg/dl)	Ref	Ref	
Q4 (>107 mg/dl)	2.1(1.68–2.62)	1.57(1.12–2.20)	0.008

[a] Adjusted for age, gender, carotid plaque score, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, triglyceride, ratio of LDL to HDL, body mass index, mean arterial pressure, plaque number, amount of drink, cholesterol-lowering drugs, drink habit, insulin, metabolic syndrome and antihypertensive drugs

Abbreviations: Q, quartiles; OR, odds ratio; CI, confidence interval; Ref: reference

primarily caused by cerebral ischemia or hypoperfusion, disruption of the blood-brain barrier, venous collagenosis, and genetic factors [21, 22]. Specifically, hyperglycemia causes vascular damage by the inflammatory response, oxidative stress, atherosclerosis and endothelial dysfunction. The result of hyperglycemia is an increase in capillary permeability, a decrease in cerebral blood flow, and an impaired blood-brain barrier which may contribute to the formation of WMLs [23, 24]. This aligns with the observed association between elevated blood glucose levels and WMLs in our study, as chronic hyperglycemia may lead to progressive microvascular injury and subsequent white matter damage. Conversely, hypoglycemia can lead to white matter lesions (WMLs) by causing neuronal energy depletion and metabolic dysfunction, ultimately impairing neural activity, structural integrity, and resulting in neuronal demise [25, 26]. This mechanism could explain the increased risk of WMLs observed in individuals with very low blood glucose levels in our analysis. Certain studies have posited that rats undergoing hypoglycaemic comas display pathological modifications, encompassing edema and degeneration of white matter, particularly within the pallidum, internal capsule, and corpus callosum [27]. Furthermore, it has been documented that patients suffering from severe hypoglycemia present anomalous signals within the white matter as observed through diffusion-weighted magnetic resonance imaging (DWI) [28, 29]. Animal studies provide useful mechanistic insights but have limited translatability to humans due to differences in glucose metabolism and the complexity of human vascular-neuronal interactions. Human-based studies are essential to validate these mechanisms and their clinical relevance [26]. Our findings further revealed an asymmetry in the U-shaped relationship between blood glucose levels and WML risk, wherein deviations below the optimal glucose range were associated with a disproportionately greater increase in WML risk compared to equivalent deviations above the optimal range. This asymmetry highlights the markedly detrimental effects of hypoglycemia on white matter integrity. Clinically, this distinction is significant as it underscores the potential dangers of overly aggressive glucose-lowering strategies, particularly in older adults or individuals with a history of cerebrovascular disease [30, 31]. These findings suggest that maintaining blood glucose within an optimal range, rather than pursuing excessively low targets, may be a more effective approach for minimizing WML risk and preserving white matter health.

Echoing the findings of previous investigations, we discerned that age [32], female gender [33], metabolic syndrome [34], and hypertension emerged as risk factors for WMLs [35]. Our exploration also unveiled an association between High-Density Lipoprotein (HDL) and WMLs in multivariable logistic regression analysis. Contrarily, another study found lower HDL-Cholesterol (HDL-C) did not independently pose a risk factor for WMLs [34]; this discrepancy may be explained by variations in sample size, population demographics, or differences in study methodologies, such as imaging techniques or statistical adjustments. This discrepancy indicates that the relationship between HDL levels and WMLs may be influenced by other factors, such as inflammation or oxidative stress, which warrant further investigation.

The non-linear relationship between glucose concentrations and WMLs is not yet fully understood. Our study aimed to assess the continuous association between blood glucose and WMLs, leading to several novel findings. First, we identified an asymmetric U-shaped relationship, showing that both hyperglycemia and hypoglycemia harm white matter integrity, with the lowest risk observed at 95–107 mg/dl. Second, these findings underscore the importance of this glycemic range as a potential therapeutic target to reduce white matter damage. Finally, the robustness of our results, supported by sensitivity analyses, suggests that this association is unlikely due to confounding alone. However, further longitudinal and mechanistic studies are needed to confirm these hypotheses.

This study has several limitations that should be noted. First, the cross-sectional design restricts the ability to infer a causal relationship between blood glucose levels and white matter lesions (WMLs). Additionally, reliance on existing data limited the availability of certain variables for analysis. Second, although we adjusted for multiple covariates, unmeasured confounders, such as diet, physical activity, and genetic predispositions, may still be present. These factors could independently influence both blood glucose levels and the risk of developing WMLs. Third, this study was based on a single-center cohort in Japan, where cultural and dietary factors, such as a high-carbohydrate diet (e.g., rice) and fish- and vegetable-rich patterns, may influence glycemic levels and their association with WMLs. The study's single-center design also limits its applicability to other populations with different genetic, environmental, or healthcare factors, and the lack of external validation further hampers the generalizability of the findings. Finally, the use of a publicly available dataset specific to the Japanese population may limit the generalizability of our findings to other populations. These limitations underscore the need for future multi-center or international longitudinal studies to confirm and expand upon these findings. However, diverse methodologies, including non-linear relationship testing and sensitivity analysis, were adopted to corroborate this association. Given these constraints, there is a pressing need for further exploration to unravel the underlying mechanisms and potential therapeutic interventions for this intricate condition.

Conclusion

Our investigation affirms the existence of an asymmetric U-shaped relationship between blood glucose levels and WMLs, with a lowest risk noted at 95–107 mg/dl. This illustrates the criticality of monitoring and maintaining optimal glycemic levels to mitigate the risk of WML, potentially reducing the incidence of several associated neurological disorders.

Abbreviations

WMLs	White matter lesions
MRI	Magnetic resonance imaging
BS	Blood glucose
DM	Diabetes mellitus
RCS	Restricted cubic splines
BMI	Body mass index
MAP	Mean arterial pressure
DWI	Diffusion-weighted imaging
LDL	Lipoprotein cholesterol
HDL	High-density lipoprotein cholesterol
TG	Triglyceride
HbA1c	Hemoglobin A1c
PS	Plaque score
IPW	Inverse probability weighting
SMD	Standardised mean differences

Supplementary Information

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Supplementary Material 1

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Not applicable.

Author contributions

J.F. was instrumental in the conceptualization and design of the study. Y.Z. was responsible for data collection and carried out the initial analyses. Q.C. managed the literature searches, provided summaries of previous research studies, and contributed substantially to the interpretation of the findings, N.L. was responsible for the creation of figures and tables in the manuscript. Lastly, D.L.took charge of drafting and finalizing the manuscript, ensuring all aspects of the study were accurately represented. All authors have reviewed, edited, and approved the final version of the manuscript.

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Data availability

No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate

The original study received approval from the ethical review committee of Shin Takeo Hospital, thus eliminating the necessity for further ethical review in this manuscript. The original researchers have secured informed consent from

all participants and/or their legal guardians. We affirm that all methodologies employed in our research conformed to the pertinent guidelines and regulations.

Consent for publication
Not applicable.

Competing interests
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