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Original Article

The association of estimated glucose disposal rate with white matter hyperintensities: A large prospective cohort study

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ABSTRACT

Background and objectives: Estimated glucose disposal rate (eGDR) is a novel and reliable marker of insulin resistance (IR), yet its association with white matter hyperintensities (WMH) remains unclear. This study investigates the relationship between eGDR and WMH in a cohort from the UK Biobank.

Methods: We included 34,789 participants without a history of stroke or dementia at baseline. WMH volume was estimated from T2-FLAIR brain magnetic resonance imaging (MRI) scans acquired in 2014, normalized to intracranial volume, and log-transformed. Multiple linear regression models were used to examine the association between eGDR and WMH volume. Additionally, restricted cubic spline (RCS) analysis was employed to explore the dose-response relationship between eGDR and WMH volume.

Results: Each 1-SD increase in eGDR was significantly associated with a reduction in WMH volume (β = -0.057; 95% CI: -0.062 to -0.051; $p < 0.001$). Compared to participants in the lowest eGDR quartile (Q1), those in quartiles Q2, Q3, and Q4 exhibited progressively lower WMH volumes, with β coefficients of -0.068 (95% CI: -0.097 to -0.039), -0.199 (95% CI: -0.228 to -0.169), and -0.295 (95% CI: -0.330 to -0.259), respectively (p for trend < 0.001). RCS analysis demonstrated a significant linear inverse relationship between eGDR and WMH volume (p for nonlinearity > 0.05). Subgroup analyses indicated consistent associations across most predefined groups.

Conclusion: Lower eGDR levels are associated with a greater burden of WMH, suggesting that eGDR may serve as a potential marker for predicting WMH burden in future clinical practice.

1. Introduction

Insulin resistance (IR) is a metabolic disorder characterized by reduced sensitivity of peripheral tissues to insulin, leading to disruptions in glucose metabolism [1]. This condition plays a critical role in the pathogenesis of various cardiovascular and cerebrovascular diseases, including stroke and cognitive decline, making it a key target for early detection and intervention [2]. Despite its clinical significance, current methods for assessing IR, such as the hyperinsulinemic-euglycemic clamp (HEC) and the homeostasis model assessment for insulin resistance (HOMA-IR), remain impractical for routine clinical use due to their complexity, invasiveness, and high cost [3,4]. These limitations

Abbreviations: BBB, Blood–Brain Barrier; BIANCA, Brain Intensity Abnormality Classification Algorithm; BMI, Body Mass Index; BP, Blood Pressure; BUN, Blood Urea Nitrogen; CI, Confidence Interval; CKD, Chronic Kidney Disease; CSVD, Cerebral Small Vessel Disease; CVD, Cardiovascular Disease; DBP, Diastolic Blood Pressure; eGDR, Estimated Glucose Disposal Rate; eGFR, Estimated Glomerular Filtration Rate; FBG, Fasting Blood Glucose; HbA1c, Glycosylated Hemoglobin A1c; HDL-C, High-Density Lipoprotein Cholesterol; HEC, Hyperinsulinemic–Euglycemic Clamp; HOMA-IR, Homeostasis Model Assessment for Insulin Resistance; hs-CRP, High-Sensitivity C-Reactive Protein; IR, Insulin Resistance; LDL-C, Low-Density Lipoprotein Cholesterol; MICE, Multiple Imputation by Chained Equations; MRI, Magnetic Resonance Imaging; RCS, Restricted Cubic Spline; SBP, Systolic Blood Pressure; SD, Standard Deviation; STROBE, Strengthening the Reporting of Observational Studies in Epidemiology; TC, Total Cholesterol; TDI, Townsend Deprivation Index; TG, Triglycerides; TyG, Triglyceride-Glucose Index; UA, Uric Acid; WC, Waist Circumference; WMH, White Matter Hyperintensities; T2-FLAIR, T2-weighted Fluid-Attenuated Inversion Recovery.

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highlight the need for more practical and accessible biomarkers of IR, which could be used in large-scale epidemiological studies and in clinical settings.

The estimated glucose disposal rate (eGDR) has emerged as a reliable, cost-effective, and non-invasive surrogate marker for IR. eGDR is calculated using easily accessible clinical parameters, including waist circumference (WC), blood pressure, and glycated hemoglobin (HbA1c) [5]. Previous studies have demonstrated that eGDR correlates well with insulin sensitivity and is associated with adverse health outcomes, including cardiovascular disease and stroke [5–9]. Due to its simplicity and practicality, eGDR presents a promising alternative to more invasive IR measurement techniques, especially in large-scale population studies and clinical practice.

White matter hyperintensities (WMH), visible as areas of increased signal intensity on brain magnetic resonance imaging (MRI) scans, are a hallmark of cerebral small vessel disease (CSVD). WMH are associated with an increased risk of stroke, cognitive decline, and vascular dementia, and they are believed to result from damage to small blood vessels in the brain [10,11]. This damage is exacerbated by risk factors such as hypertension, diabetes, and chronic inflammation. Insulin resistance has been implicated in the pathophysiology of CSVD through mechanisms such as endothelial dysfunction, inflammation, and vascular remodeling [12]. Although previous studies have linked IR with WMH burden, few large cohort studies have specifically explored the role of eGDR in the context of CSVD, particularly in the UK Biobank population.

Using data from the UK Biobank, a cohort of more than 500,000 individuals, this study investigated the association between eGDR and WMH volume. The richness of the dataset, which includes clinical, lifestyle, and imaging information, provides a unique opportunity to explore this link.This study aims to investigate the association between eGDR and WMH volume, filling a gap in the literature regarding the role of eGDR in relation to WMH, a key marker of CSVD. Ultimately, the findings of this study may provide important insights into the potential of eGDR as a non-invasive biomarker for early detection and intervention in individuals at risk for stroke and cognitive decline.

2. Methods

2.1. Study design and population

The UK Biobank is a large-scale, prospective, population-based cohort study that recruited approximately 500,000 participants aged 40 to 69 years across the United Kingdom from 2006 to 2010 [13]. Participants were invited to assessment centers located in England, Scotland, and Wales, where they provided written informed consent. Baseline assessments included the collection of biological samples (blood and urine), touchscreen questionnaires capturing lifestyle and medical history, and physical examinations measuring key health indicators such as height, weight, blood pressure (BP), and waist circumference (WC) [14]. From 2014 onwards, a subset of participants was invited to undergo the first wave of neuroimaging assessments, including brain MRI scans [15]. In 2016, the initiative was expanded to include an additional 100,000 participants for MRI assessments [16].

For this study, we initially identified 45,013 participants who had undergone the first wave of imaging assessments. However, participants with missing data on the eGDR (n = 3319) were excluded from the analysis. Additionally, to reduce potential confounding factors affecting the outcomes related to CSVD, we excluded participants with a prior history of dementia or stroke (n = 312). Further, we excluded individuals with missing data on key covariates essential for the analysis (n = 6593). After applying these inclusion and exclusion criteria, the final study cohort consisted of 34,789 participants. A flow chart summarizing the participant selection process is presented in Fig. 1. This study adhered to the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines.

2.2. Exposure

The primary exposure in this study was the eGDR, measured at baseline. eGDR is a composite indicator derived from HbA1c, hypertension status, and WC, serving as a proxy for IR. The eGDR was calculated using the formula: eGDR(mg/kg/min)=21.158−(hypertension×3.407)−(0.551×HbA1c[%])−(0.09×WC[cm]),where hypertension was coded as 0 (no hypertension) or 1 (hypertension) [17]. Hypertension was defined as meeting any of the following criteria: (1) self-reported history of hypertension; (2) use of antihypertensive medications; or (3) systolic blood pressure (SBP) ≥140 mmHg or diastolic blood pressure (DBP) ≥90 mmHg.

WC (cm) was measured by trained medical personnel using standardized protocols during the baseline examination. HbA1c levels, reflecting long-term blood glucose control, were measured via high-performance liquid chromatography.

2.3. Covariates

The covariates included demographic, lifestyle, and clinical characteristics. Demographic variables comprised age, sex, ethnicity, and the

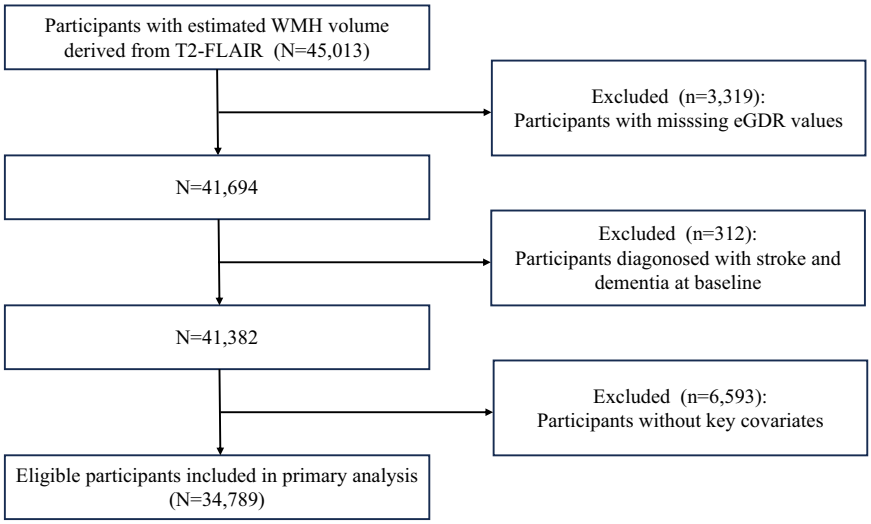

Fig. 1. Flow diagram of the participant selection process.

Townsend Deprivation Index (TDI). TDI is a composite score calculated based on unemployment rate, car ownership, home ownership, and household overcrowding, reflecting socioeconomic deprivation [18]. Lifestyle factors included smoking status (never, previous, or current) and drinking status (never, previous, or current).Baseline serum lipid profiles,high-sensitivity C-reactive protein (hs-CRP),blood urea nitrogen (BUN) and uric acid (UA) were measured using Beckman Coulter AU5800 analyzers [19]. Hemoglobin levels were measured using Beckman Coulter LH750 hematology analyzers.Diabetes was defined as a self-reported history of diabetes, the use of glucose-lowering medications,HbA1c levels exceeding 6.5 % or fasting blood glucose(FBG) exceeding 7.0 mmol/L [8]. Serum creatinine were measured by enzymatic analysis on a Beckman Coulter AU5400. Estimated glomerular filtration rate (eGFR) was calculated using the CKD-EPI equation, with chronic kidney disease (CKD) defined as an eGFR <60 mL/min/1.73 m^2 [19,20]. Body mass index (BMI) was calculated as weight in kilograms divided by height in meters squared, with obesity defined as a BMI of 30 kg/m^2 or higher [21].

2.4. Outcomes

In this study, we employed WMH volume as a biomarker to assess the burden of CSVD. WMH volume data were derived from T2-weighted fluid-attenuated inversion recovery (T2-FLAIR) MRI scans, which are particularly sensitive to white matter lesions, including hyperintensities associated with small vessel pathology [16]. The T2-FLAIR images were preprocessed and analyzed using a specialized image-processing pipeline developed by the UK Biobank. This pipeline utilized the Brain Intensity Abnormality Classification Algorithm (BIANCA), an automated, supervised tool designed to accurately segment and quantify the WMH regions in the brain, enabling precise estimation of total WMH volume [22]. The WMH volume data analyzed in this study were sourced from the first batch of head MRI scans available from the UK Biobank. To account for inter-individual differences in brain size, WMH volume was normalized to intracranial volume, yielding a standardized measure [16]. Finally, this normalized value was log-transformed to correct for its positively skewed distribution [16].

2.5. Statistical analysis

Based on eGDR values, participants were further classified into four quartiles (Q1–Q4). Continuous variables at baseline were presented as the mean ± standard deviation (SD), while categorical variables were expressed as frequencies and percentages. Differences between groups were evaluated using the Kruskal-Wallis rank sum test for continuous variables and Pearson's chi-square (χ^2) test for categorical variables. Linear regression models were employed to investigate the association between eGDR and WMH burden. Three models with varying levels of adjustment were constructed: Model 1 was unadjusted; Model 2 adjusted for age, sex, ethnicity, and TDI; and Model 3 further accounted for smoking status, drinking status, hemoglobin, total cholesterol (TC), triglycerides (TG), high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), BUN, UA, hs-CRP, diabetes, CKD, obesity,antihypertensive drugs use,antidiabetic drugs use. Restricted Cubic Spline (RCS) with four knots (at the 5th, 35th, 65th, and 95th percentiles) was applied to evaluate potential nonlinear relationships between eGDR and WMH volume. Subgroup analyses were conducted to assess whether factors such as age, sex, ethnicity and diabetes modified the observed associations for eGDR (both continuous and categorical) [8,9,23–25]. Multiple sensitivity analyses were performed to ensure the robustness of our findings. First, we redefined participants with baseline BP ≥130/80 mmHg as having hypertension and recalculated eGDR accordingly. Second, we repeated the analyses after excluding participants who were taking glucose-lowering or antihypertensive medications. Third, participants with FBG levels >7.0 mmol/L were excluded for further analysis. Fourthly, we excluded individuals with other diagnosed brain diseases **(Table S2)** to explore the findings in a more specific population.Fifth, multiple imputation of key covariates with missing data was conducted using the multiple imputation by chained equations (MICE) method (five imputations by chained equations, with estimates pooled according to Rubin's rules). Finally, within participants with diabetes, subgroup analyses stratified by the use of antidiabetic medications were performed to evaluate whether treatment status influenced the association between eGDR and WMH volume.

A two-tailed P-value <0.05 was considered statistically significant. All statistical analyses were performed using RStudio software (Version 4.3.1).

3. Results

3.1. Baseline characteristics

The baseline characteristics of participants stratified by eGDR quartiles are presented in Table 1 (Q1: 8.65 ± 0.74; Q2: 10.58 ± 0.69; Q3: 12.95 ± 0.47; Q4: 14.42 ± 0.47). A total of 34,789 participants with available brain imaging data were included in the final analysis. The mean age of the participants was 54.99 ± 7.53 years, and 48 % were female. Participants in higher eGDR quartiles were generally younger and exhibited lower levels of BUN and hs-CRP. Additionally, these participants had lower prevalence rates of obesity, diabetes, and use of antihypertensive and antidiabetic medications.

3.2. Association of eGDR and WMH volume

In the fully adjusted Model 3, each 1-SD increase in eGDR was associated with a significant reduction in WMH volume (β = −0.057; 95 % CI: −0.062 to −0.051; $p < 0.001$). Compared to participants in the lowest eGDR quartile (Q1), those in Q2 (β = −0.068; 95 % CI: −0.097 to −0.039; $p < 0.001$), Q3 (β = −0.199; 95 % CI: −0.228 to −0.169; $p < 0.001$), and Q4 (β = −0.295; 95 % CI: −0.330 to −0.259; $p < 0.001$) exhibited progressively lower WMH volumes, with a significant trend across quartiles (p for trend < 0.001) (Table 2). The dose-response relationship between eGDR and WMH volume is shown in Fig. 2. This linear relationship remained significant after full adjustment for covariates ($p < 0.001$, p for nonlinearity > 0.05), indicating a consistent inverse association between eGDR and WMH volume.

3.3. Subgroup analyses

Subgroup analyses were performed to assess whether the association between eGDR (both continuous and categorical) and WMH volume varied across predefined subgroups (Table 3 and Table 4). In most subgroups, the relationship remained consistent with the primary findings. Notably, the association between eGDR and WMH volume was significantly modified by age (interaction $p < 0.001$). For the categorical eGDR subgroup analysis, both age and sex significantly influenced the observed association (interaction $p < 0.001$). No significant interactions were observed between eGDR quartiles and other endpoints in the remaining subgroups. In both the continuous and categorical eGDR subgroup analyses, although the interaction with diabetes status was not statistically significant, we observed a suggestive trend indicating that eGDR may have a stronger predictive effect on WMH volume in non-diabetic individuals than in those with diabetes.

3.4. Sensitivity analyses

Multiple sensitivity analyses consistently supported the robustness of our findings. First, redefining hypertension as blood pressure ≥130/80 mmHg did not substantially alter the observed associations **(Table S3)**. Second, excluding participants taking antihypertensive or antidiabetic medications yielded similar results **(Table S4)**. Third, analyses restricted

Table 1
Baseline characteristics of participants stratified by quartiles of estimated glucose disposal rate.

Characteristics	Overall (n = 34,789)	Quartile 1 (n = 8699)	Quartile 2 (n = 8696)	Quartile 3 (n = 8698)	Quartile 4 (n = 8696)	P value
eGDR	11.65 ± 2.29	8.65 ± 0.74	10.58 ± 0.69	12.95 ± 0.47	14.42 ± 0.47	<0.001
Age (years)	54.99 ± 7.53	57.19 ± 7.05	56.67 ± 7.19	53.70 ± 7.47	52.39 ± 7.33	<0.001
Gender						<0.001
Female	18,234(52.4 %)	2099(24.1 %)	5103(58.7 %)	3380(38.9 %)	7652(88.0 %)	
Male	16,555(47.6 %)	6600(75.9 %)	3593(41.3 %)	5318(61.1 %)	1044(12.0 %)	
Race						0.15
White	33,813(97.2 %)	8475(97.4 %)	8461(97.3 %)	8453(97.2 %)	8424(96.9 %)	
Other	976(2.8 %)	224(2.6 %)	235(2.7 %)	245(2.8 %)	272(3.1 %)	<0.001
TDI	−1.89 ± 2.72	−1.86 ± 2.72	−1.99 ± 2.66	−1.85 ± 2.76	−1.87 ± 2.73	0.006
SBP(mmHg)	135.04 ± 17.65	148.15 ± 14.93	145.50 ± 16.04	125.79 ± 9.16	120.73 ± 10.49	<0.001
DBP(mmHg)	81.49 ± 9.89	88.77 ± 8.99	85.54 ± 8.83	77.53 ± 6.55	74.11 ± 7.07	<0.001
BMI(kg/m^2)	26.57 ± 4.19	30.11 ± 4.08	26.20 ± 3.91	26.74 ± 2.96	23.21 ± 2.35	<0.001
WC(cm)	87.90 ± 12.47	100.87 ± 8.33	85.65 ± 11.63	90.48 ± 5.81	74.59 ± 5.21	<0.001
Smoking status						<0.001
Never	21,208(61.0 %)	4724(54.3 %)	5336(61.4 %)	5340(61.4 %)	5808(66.8 %)	
Previous	11,427(32.8 %)	3461(39.8 %)	2882(33.1 %)	2711(31.2 %)	2373(27.3 %)	
Current	2154(6.2 %)	514(5.9 %)	478(5.5 %)	647(7.4 %)	515(5.9 %)	
Drinking status						0.002
Never	842(2.4 %)	170(2.0 %)	215(2.5 %)	203(2.3 %)	254(2.9 %)	
Previous	728(2.1 %)	187(2.1 %)	160(1.8 %)	193(2.2 %)	188(2.2 %)	
Current	33,219(95.5 %)	8342(95.9 %)	8321(95.7 %)	8302(95.4 %)	8254(94.9 %)	
FBG(mmol/L)	4.99 ± 0.94	5.22 ± 1.22	5.04 ± 0.91	4.89 ± 0.78	4.82 ± 0.72	<0.001
HbA1c(%)	5.35 ± 0.46	5.49 ± 0.60	5.36 ± 0.43	5.31 ± 0.38	5.24 ± 0.35	<0.001
TC(mmol/L)	5.73 ± 1.07	5.66 ± 1.15	5.85 ± 1.08	5.78 ± 1.03	5.64 ± 1.01	<0.001
TG(mmol/L)	1.64 ± 0.95	2.09 ± 1.09	1.62 ± 0.89	1.70 ± 0.92	1.16 ± 0.58	<0.001
HDL-C(mmol/L)	1.48 ± 0.38	1.29 ± 0.30	1.53 ± 0.39	1.40 ± 0.33	1.69 ± 0.36	<0.001
LDL-C(mmol/L)	3.59 ± 0.82	3.61 ± 0.88	3.65 ± 0.82	3.68 ± 0.79	3.41 ± 0.77	<0.001
BUN(mmol/L)	5.31 ± 1.23	5.52 ± 1.28	5.36 ± 1.23	5.33 ± 1.19	5.01 ± 1.16	<0.001
UA(μmol/L)	302.96 ± 77.35	353.87 ± 72.04	299.49 ± 73.10	311.88 ± 68.70	247.57 ± 55.03	<0.001
Serum creatinine(μmol/L)	72.25 ± 13.96	78.06 ± 14.48	71.05 ± 13.78	74.56 ± 13.37	65.35 ± 10.68	<0.001
hs-CRP(mg/L)	2.06 ± 3.59	2.72 ± 3.85	2.07 ± 3.54	2.02 ± 3.39	1.43 ± 3.43	<0.001
eGFR(ml/min/1.73m^2)	96.09 ± 13.59	91.39 ± 13.27	95.56 ± 13.21	95.78 ± 12.89	101.65 ± 12.97	<0.001
Hemoglobin(g/dL)	14.19 ± 1.22	14.81 ± 1.13	14.19 ± 1.15	14.34 ± 1.16	13.43 ± 1.02	<0.001
Obesity						<0.001
Yes	6325(18.2 %)	3828(44.0 %)	1322(15.2 %)	1126(12.9 %)	49(0.6 %)	
No	28,464(81.8 %)	4871(56.0 %)	7374(84.8 %)	7572(87.1 %)	8647(99.4 %)	
Diabetes						<0.001
Yes	1328(3.8 %)	747(8.6 %)	275(3.2 %)	193(2.2 %)	113(1.3 %)	
No	33,461(96.2 %)	7952(91.4 %)	8421(96.8 %)	8505(97.8 %)	8583(98.7 %)	
Antihypertensive drugs use						<0.001
Yes	5146(14.8 %)	3050(35.1 %)	1765(20.3 %)	198(2.3 %)	133(1.5 %)	
No	29,643(85.2 %)	5649(64.9 %)	6931(79.7 %)	8500(97.7 %)	8563(98.5 %)	
Antidiabetic drugs use						<0.001
Yes	594(1.7 %)	384(4.4 %)	103(1.2 %)	73(0.8 %)	34(0.4 %)	
No	34,195(98.3 %)	8315(95.6 %)	8593(98.8 %)	8625(99.2 %)	8662(99.6 %)	
WMH volume(mm^3)	5207.40 ± 6893.30	6950.43 ± 8283.92	6114.91 ± 7828.97	4258.22 ± 5375.97	3506.66 ± 4858.56	<0.001
Log-transformed normalized WMH volume	−6.18 ± 1.03	−5.83 ± 1.01	−6.00 ± 1.02	−6.34 ± 0.98	−6.54 ± 0.96	<0.001

eGDR: estimated glucose disposal rate;TDI: townsend deprivation index; BMI: body mass index; SBP: systolic blood pressure;DBP: diastolic blood pressure;WC:waist circumference;FBG: fasting blood glucose;HbA1c: glycosylated hemoglobin A1c;TC: total cholesterol;TG: triglycerides; HDL-C: high density lipoprotein cholesterol; LDL-C: low density lipoprotein cholesterol;BUN: blood urea nitrogen;Uric acid: UA;hs-CRP: high-sensitivity C-reactive protein;eGFR: estimated glomerular filtration rate;WMH: white matter hyperintensities.

Table 2
Associations between estimated glucose disposal rate and white matter hyperintensities volume.

eGDR	Model 1 β(95 % CI)	P value	Model 2 β(95 % CI)	P value	Model 3 β(95 % CI)	P value
Continuous						
Per SD increase	−0.124(−0.129,−0.120)	<0.001	−0.069(−0.074,−0.065)	<0.001	−0.057(−0.062,−0.051)	<0.001
Quartiles						
Q1	Ref		Ref		Ref	
Q2	−0.162(−0.192,−0.133)	<0.001	−0.126(−0.153,−0.099)	<0.001	−0.068(−0.097,−0.039)	<0.001
Q3	−0.502(−0.531,−0.472)	<0.001	−0.275(−0.301,−0.248)	<0.001	−0.199(−0.228,−0.169)	<0.001
Q4	−0.709(−0.738,−0.679)	<0.001	−0.393(−0.423,−0.363)	<0.001	−0.295(−0.330,−0.259)	<0.001
P for trend		<0.001		<0.001		<0.001

Model 1 was unadjusted;Model 2 adjusted for age, sex, ethnicity, and TDI; and Model 3 further accounted for smoking status, drinking status, hemoglobin, TC, TG, HDL-C, LDL-C, BUN, UA, hs-CRP, diabetes, CKD, obesity,antihypertensive drugs use,antidiabetic drugs use.

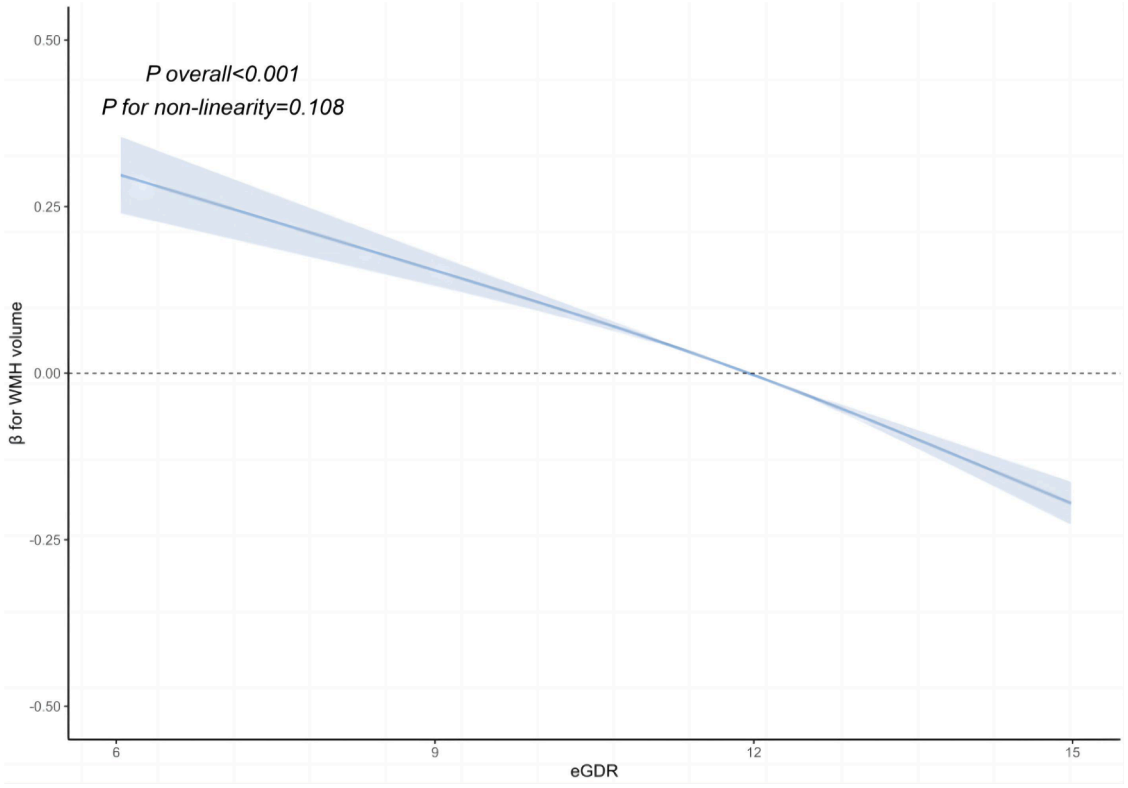

Fig. 2. Restricted cubic spline curves for white matter hyperintensities volume according to the estimated glucose disposal rate.
Adjusted by age, sex, ethnicity, TDI,smoking status, drinking status, hemoglobin, TC, TG, HDL-C, LDL-C, BUN, UA, hs-CRP, diabetes, CKD, obesity,antihypertensive drugs use,antidiabetic drugs use.

Table 3
Subgroup and interaction analysis of the association between estimated glucose disposal rate and white matter hyperintensities volume across various subgroups.

Variables[a]	β(95 % CI)	P for interaction
Age		**<0.001**
< 60	−0.082(−0.089,−0.075)	
≥ 60	−0.066(−0.076,−0.056)	
Sex		**0.698**
Male	−0.054(−0.062,−0.046)	
Female	−0.061(−0.069,−0.054)	
Race		**0.191**
White	−0.058(−0.063,−0.052)	
Others	−0.060(−0.090,−0.030)	
Diabetes		**0.470**
Yes	−0.044(−0.075,−0.014)	
No	−0.057(−0.063,−0.052)	

Adjusted variables included age, sex, ethnicity, TDI,smoking status, drinking status, hemoglobin, TC, TG, HDL-C, LDL-C, BUN, UA, hs-CRP, diabetes, CKD, obesity,antihypertensive drugs use,antidiabetic drugs use.

[a] Per SD increase.

to individuals with normal glycemic status reaffirmed the stability of the association **(Table S5)**. Fourth, excluding participants with other diagnosed brain diseases did not affect the significant relationship between eGDR and WMH volume **(Table S6)**.Fifth, multiple imputation of missing covariate data using the MICE method (five imputations by chained equations with estimates pooled according to Rubin's rules) produced results consistent with the primary analysis **(Table S7)**. Finally, in participants with diabetes, subgroup analyses stratified by glucose-lowering medication use showed that medication status did not modify the association between eGDR and WMH volume **(Table S8-S9)**. No evidence of interaction was observed for either continuous eGDR (p for interaction = 0.524) or categorical eGDR (p for interaction = 0.843), suggesting that the relationship between eGDR and WMH volume was not modified by glucose-lowering treatment.

4. Discussion

In this large prospective cohort of 34,789 participants, we found a significant inverse association between eGDR and WMH volume. RCS analyses further confirmed a linear relationship. Although age and sex were found to influence the relationship between eGDR and WMH, these factors did not significantly alter the primary conclusion, underscoring the robustness of our analysis.These observations suggest that eGDR could serve as an important predictor of WMH burden and a potential target for interventions aimed at mitigating disease progression.

An increasing body of evidence has linked IR to CSVD burden, suggesting that metabolic dysfunction can adversely affect brain microvascular health [12,26–30]. Several alternative markers of IR have been shown to correlate with white matter lesions.For instance, a cross-sectional study found that higher HOMA-IR levels correlated with altered white matter microstructural integrity in generally healthy adults [27]. Similarly, a study of 2615 cognitively normal middle-aged and older adults demonstrated a positive association between higher triglyceride-glucose (TyG) index levels and both silent brain infarcts and WMH volume [28]. Furthermore, among elderly patients with type 2 diabetes, an elevated TyG index has been identified as an independent risk factor for severe CSVD burden [31]. However, some studies have reported inconsistent findings. For example, a study of 4541 dementia-free older adults from rural China found that higher TyG index levels were associated with global brain atrophy (including reductions in total brain, gray matter, and white matter volumes) but not with WMH volume [32]. These discrepancies may be due to differences in study populations or methodologies, highlighting the complexity of the relationship between IR and CSVD.

The clinical utility of existing IR markers is limited [23]. HOMA-IR

Table 4
Subgroup and interaction analysis of the association between estimated glucose disposal rate (quartiles 1–4) and white matter hyperintensities volume across various subgroups.

Characteristics	eGDR				P interaction
	Q1	Q2	Q3	Q4	
Age					**<0.001**
<60	Ref	−0.127(−0.166,−0.087)	−0.313(−0.351,−0.274)	−0.446(−0.492,−0.400)	
≥60	Ref	−0.053(−0.101,−0.004)	−0.219(−0.272,−0.166)	−0.327(−0.393,−0.261)	
Sex					**<0.001**
Male	Ref	−0.125(−0.163,−0.087)	−0.219(−0.272,−0.166)	−0.327(−0.393,−0.261)	
Female	Ref	−0.023(−0.073,−0.028)	−0.184(−0.236,−0.131)	−0.263(−0.317,−0.208)	
Race					**0.259**
White	Ref	−0.072(−0.101,−0.043)	−0.199(−0.229,−0.169)	−0.304(−0.340,−0.269)	
Others	Ref	−0.209(−0.370,−0.048)	−0.313(−0.482,−0.145)	−0.390(−0.582,−0.199)	
Diabetes					**0.205**
Yes	Ref	−0.026(−0.165,−0.112)	−0.013(−0.178,0.152)	−0.175(−0.398,0.049)	
No	Ref	−0.073(−0.102,−0.043)	−0.205(−0.235,−0.174)	−0.301(−0.338,−0.265)	

Adjusted variables included age, sex, ethnicity, TDI,smoking status, drinking status, hemoglobin, TC, TG, HDL-C, LDL-C, BUN, UA, hs-CRP, diabetes, CKD, obesity, antihypertensive drugs use,antidiabetic drugs use.

requires fasting insulin, which is not routinely measured in non-diabetic populations [8,23]. The TyG index, although easier to calculate has shown inconsistent predictive performance across different metabolic settings [8,23]. By contrast, accumulating evidence suggests that eGDR outperforms the TyG index in predicting cardiovascular disease (CVD) risk, particularly among non-diabetic individuals [8,23]. Building on this rationale, our study extends these observations to the brain: we demonstrated that higher eGDR levels were independently and linearly associated with lower WMH volume. Taken together, these findings highlight eGDR as a practical and uniquely informative biomarker of IR, with potential value for capturing the impact of metabolic dysfunction on both cardiovascular and brain health.

Beyond its relationship with CSVD, eGDR has been recognized as a reliable and stable marker of IR, with demonstrated associations with various adverse outcomes,including CVD, post-stroke recovery, and depression [8,33,34]. For example, a study of 5512 Chinese adults found that lower eGDR levels were strongly associated with an increased risk of CVD in non-diabetic individuals, suggesting that eGDR is a useful tool for assessing cardiovascular risk even in the absence of overt diabetes [8]. Additionally, eGDR has been shown to predict post-stroke functional outcomes [33]. In a cohort of 6271 stroke patients, lower eGDR levels were linked to worse recovery, supporting its potential as a guide for clinical decisions in stroke management and rehabilitation [33]. Furthermore, eGDR has been found to predict mental health outcomes, with a study of 28,444 U.S. adults showing that lower eGDR levels were associated with a higher incidence of depression [34]. These findings highlight the broad-reaching implications of metabolic dysfunction, as captured by eGDR, on both physical and mental health, especially in conditions such as CVD and stroke.

Building on this body of evidence, our study expands the understanding of eGDR's role by demonstrating that it is not only associated with cardiovascular and mental health outcomes but also serves as a predictor of WMH burden. Specifically, our results suggest that lower eGDR levels, indicative of greater IR, may contribute to microvascular damage in the brain, thereby increasing the risk of CSVD. These findings position eGDR as a promising biomarker for evaluating brain health, offering valuable insights into the impact of metabolic dysfunction on cerebrovascular integrity.

A key strength of our study lies in its large sample size and the use of high-quality data from a well-characterized population-based cohort. Although our analysis was cross-sectional in nature, the exposure (eGDR) and outcome (WMH volume) were measured at different time points, which helps establish a temporal sequence between metabolic status and subsequent brain changes. In contrast to prior studies that were limited by small sample sizes or lacked detailed imaging data, our study design allowed for a more comprehensive and robust investigation of the association between IR and CSVD burden.Importantly, the inverse association between eGDR and WMH volume was consistent across both diabetic and non-diabetic participants. Although the interaction between diabetes status and eGDR was not statistically significant, our data suggest that non-diabetic individuals may experience a more pronounced impact of IR on WMH. This observation is in line with previous research, which has suggested that in the general population, eGDR is associated with an increased risk of CVD regardless of diabetes status, but the marker appears to be more sensitive in non-diabetic individuals [9]. This could be attributed to a "ceiling effect" in diabetic patients, where the presence of additional risk factors diminishes the sensitivity of eGDR as a risk marker [8,35,36]. The pathophysiology of WMH in diabetes is likely multifactorial, involving hyperglycemia-induced microangiopathy, advanced glycation end-products, and chronic inflammation, which could overshadow the contribution of IR as captured by eGDR [37]. In addition, the widespread use of glucose-lowering and antihypertensive therapies in diabetic individuals may attenuate the direct association between IR and WMH [38,39].

One possible mechanism underlying the association between IR and WMH is endothelial dysfunction [28,40,41]. IR disrupts phosphatidylinositol 3-kinase signaling pathways, impairing vascular homeostasis and increasing blood-brain barrier (BBB) permeability [42,43]. This allows inflammatory mediators and cytokines to infiltrate vessel walls and perivascular tissue, initiating or exacerbating CSVD development [44]. Furthermore, IR is linked to atherosclerosis, which promotes vascular inflammation and lipid metabolism dysregulation [42]. These processes can lead to cerebral hypoperfusion, microembolism, and small vessel damage [44]. Additionally, IR often coexists with metabolic disorders such as hypertension, diabetes, and obesity, all of which are established CSVD risk factors [45,46]. Our findings suggest that eGDR, as a marker of IR, may be useful in assessing the impact of metabolic dysfunction on brain health, particularly WMH burden.

Our findings highlight the potential value of eGDR as a practical and non-invasive biomarker for CSVD. In clinical settings, eGDR could be incorporated into multimodal risk assessment models to help identify individuals at higher risk of WMH burden and related outcomes, such as stroke or cognitive decline, even before clinical symptoms emerge. By stratifying patients according to eGDR levels, clinicians may be able to tailor preventive strategies, including earlier initiation of lifestyle modification or pharmacological interventions targeting IR and vascular risk factors. From a broader perspective, integrating eGDR into population-based screening tools could contribute to earlier detection of high-risk individuals, ultimately reducing disease burden.

Our study has several strengths that enhance its validity and clinical relevance. To our knowledge, this is the first study to examine the relationship between eGDR and WMH volume. A key strength of our study is the large sample size and the use of high-quality, standardized brain MRI data from the UK Biobank, enabling us to detect meaningful

associations between eGDR and white matter burden. Additionally, our study adjusted for a wide range of potential confounders, including demographic characteristics, lifestyle factors, and clinical conditions, which helps minimize bias and reduces the risk of reverse causality. These methodological strengths provide confidence in the robustness of our findings.

Despite these strengths, our study has several limitations. First, although the UK Biobank is a prospective cohort, the present analysis is essentially cross-sectional, and therefore no causal inference can be firmly established.Second, the cohort was composed predominantly of individuals of white ethnicity, which limits the generalizability of our findings to more diverse populations.Third,despite extensive adjustment, unmeasured factors—such as genetics, environment, or measurement variability—may still influence the association between eGDR and WMH.Fourth, we evaluated only baseline eGDR levels in relation to WMH burden, without considering dynamic changes in eGDR over time, which may provide additional insights into the long-term effects of insulin resistance on brain health.Finally, while we used WMH as the primary marker of CSVD, other neuroimaging biomarkers of CSVD, such as lacunar infarcts, cerebral microbleeds, or enlarged perivascular spaces, were not included in our analysis.Future studies incorporating multiple CSVD markers would provide a more comprehensive assessment.

5. Conclusion

Our study demonstrates a significant inverse association between eGDR and WMH volume, suggesting that eGDR may serve as a valuable marker for assessing IR-related brain health risks. Routine assessment of eGDR could support early risk stratification and inform preventive strategies to reduce WMH burden. Future research should validate these findings in more diverse populations, examine longitudinal changes in eGDR, and incorporate additional neuroimaging biomarkers to further elucidate the impact of IR on cerebral health.

Ethics approval and consent to participate

The UK Biobank study was approved by the North West Multicentre Research Ethics Committee (REC reference: 21/NW/0157). All participants have provided written informed consent.

Consent for publication

All authors read the manuscript and agreed to its publication.

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Data availability

The UK Biobank data are available online at https://www.ukbiobank.ac.uk. All qualified researchers are able to apply for data used for the health-related research. This research has been conducted using the UK Biobank Resource under Application Number 100,889.

Declaration of generative AI and AI-assisted technologies in the writing process

No generative AI or AI-assisted technologies were used in the writing of this manuscript.

CRediT authorship contribution statement

Han Wang: Visualization, Software, Methodology, Conceptualization. **Zhi-Ming Li:** Visualization, Validation, Methodology, Conceptualization. **Ben-Bo Xiong:** Software, Resources, Investigation. **Zi-Jie Wang:** Methodology, Investigation, Formal analysis. **Yi Qian:** Visualization, Validation, Resources, Data curation. **Xiao Hu:** Validation, Supervision, Resources. **Shan-Yu Zhang:** Visualization, Validation, Supervision. **Chu Chen:** Supervision, Project administration, Methodology. **Tian-Nan Yang:** Visualization, Validation, Supervision. **Qi Li:** Writing – original draft, Investigation, Funding acquisition.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.tjpad.2025.100464.

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