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Association between estimated glucose disposal rate and future cardiovascular disease risk across glucose metabolism status: a prospective cohort study

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Abstract

Background Cardiovascular disease (CVD) remains a major global health challenge, particularly affected by glucose metabolism status. However, the relationship between estimated glucose disposal rate (eGDR) and future CVD risk across different glucose metabolism status remains unclear.

Methods We analyzed data from the China Health and Retirement Longitudinal Study (2011–2020) of participants aged ≥ 45 years. The eGDR was calculated using waist circumference, hypertension status, and HbA1c levels. CVD events (stroke or cardiac events) were the outcome. Participants were categorized by glucose metabolism status (normoglycemia, prediabetes, diabetes). Cox proportional hazards models and restricted cubic splines were used to assess associations and potential non-linear relationships.

Results Among 7,828 participants (52.84% male, mean age 59.01 ± 9.21 years) followed for an average of 8.29 years, 1,944 participants (24.83%) developed CVD. Higher eGDR was inversely associated with CVD risk across all glucose metabolism states. Below the inflection points (11.77, 11.15, and 11.56 mg/kg/min for normoglycemia, prediabetes, and diabetes, respectively), each 1-unit increase in eGDR reduced CVD risk by 14% (HR = 0.86, 95%CI: 0.83–0.89), 10% (HR = 0.90, 95%CI: 0.86–0.93), and 14% (HR = 0.86, 95%CI: 0.81–0.91), respectively.

Conclusion The eGDR demonstrates a potentially non-linear inverse association with future CVD risk across different glucose metabolism states.

Keywords Cardiovascular disease, Estimated glucose disposal rate, Glucose metabolism status, Cohort study, Stroke

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Introduction

Cardiovascular disease (CVD) remains a significant global health challenge, with its prevalence continuing to rise across various demographics and regions [1, 2]. Recent studies indicate that CVD is responsible for a substantial portion of global morbidity and mortality, affecting nearly half a billion individuals worldwide [3, 4]. The World Health Organization (WHO) recognizes CVD as one of the leading causes of death, accounting for more than 40% of global mortality [5–8]. The prevalence of CVD is particularly alarming in low- and middle-income countries, where it is exacerbated by increasing rates of risk factors such as hypertension, diabetes, and obesity [9, 10].

Diabetes, prediabetes, and normoglycemia are critical states in the continuum of glucose regulation that significantly influence cardiovascular risk [11, 12]. Diabetes itself is a significant risk factor for cardiovascular morbidity and mortality [13, 14]. Moreover, a growing body of research indicates that prediabetes is associated with an increased risk of CVD [15, 16]. Interestingly, those with diabetes or prediabetes are not the only ones at risk for CVD. Research has consistently demonstrated that even individuals classified as normoglycemic can experience heightened cardiovascular risks due to underlying metabolic disturbances [17–19]. This paradox is explained by insulin resistance (IR), which often precedes detectable glycemic abnormalities and induces chronic inflammation while activating pathological molecular pathways conducive to CVD development [20, 21]. These mechanisms establish a critical link between subtle metabolic dysfunction and cardiovascular risk even without overt dysglycemia [20, 21]. Even though they might not exhibit obvious signs of diabetes, these individuals' cardiovascular health has to be closely watched and evaluated.

IR represents a critical physiological state underlying various metabolic disorders and CVD [22]. Metabolic syndrome (MetS), characterized by a cluster of cardiometabolic risk factors including abdominal obesity, dyslipidemia, hyperglycemia, and hypertension, shares IR as its common pathophysiological foundation and has been consistently associated with increased CVD risk [23]. The estimated glucose disposal rate (eGDR) includes waist circumference (WC), hypertension, and Hemoglobin A1c (HbA1c), integrates key components of MetS, serves as a practical measure of IR, and is associated with diabetes [24–27]. Moreover, eGDR has been validated against the euglycemic hyperinsulinemic clamp technique, which is considered the gold standard for measuring insulin sensitivity [24, 28]. According to several earlier studies, eGDR was substantially linked to CVD in the general population, CVD under circadian rhythm and various metabolic states, CVD in people without diabetes, stroke in the general population, and stroke in diabetes people [26, 29–33]. However, little is known about the precise relationships between eGDR and CVD in the general population over different glucose metabolism status, especially in persons with prediabetes or normoglycemia. There is a need for a more thorough examination because the existing literature only provides a limited understanding of this relationship.

Based on data from the China Health and Retirement Longitudinal Study (CHARLS), we sought to assess the relationship between eGDR and risk of CVD (stroke or cardiac events) in individuals with glucose metabolism status, given the importance of this condition in the development of CVD.

Methods

Data source and study population

All participants in this prospective study were drawn from the CHARLS, a nationwide cohort that was established in 2011. The cohort focuses on middle-aged and elderly Chinese citizens who are 45 years of age or older [34]. In order to determine their health condition, the participants are tracked down once every two to three years. Five follow-up survey waves have been conducted thus far, with data being gathered in 2011, 2013, 2015, 2018, and 2020. The specific research procedures have been previously outlined [34]. The CHARLS study was approved by the Peking University Institutional Review Board (IRB00001052-11015) and all participants provided written informed consent.

CVD incidence increases markedly with age, particularly in middle-aged and older adults [1, 2, 35, 36]. The CHARLS has been used successfully in previous published studies examining the relationship between eGDR and CVD in this middle-aged and elderly specific population [26, 30, 31]. In the flowchart (Fig. 1), the inclusion and exclusion criteria are specified: (i) participants younger than 45 or with missing data. (ii) participants with CVD or missing baseline information. (iii) participants who had less than two years of follow-up. (iv) participants lacking data on WC, hypertension, and HbA1c. (v) participants with extreme eGDR values that are more or less than three standard deviations from the mean. Consequently, the study included a total of 7,828 individuals.

Data collection

The information collected for this study includes: (i) Data on demographics: gender, age, marital status, living place, and education level. (ii) Lifestyle-related information: smoking status, drinking status, self-report hypertension, self-report diabetes. (iii) Physical dimensions: height, weight, WC, systolic blood pressure (SBP), and diastolic blood pressure (DBP). (iv) Lab test results: triglyceride (TG), total cholesterol (TC), high-density lipoprotein

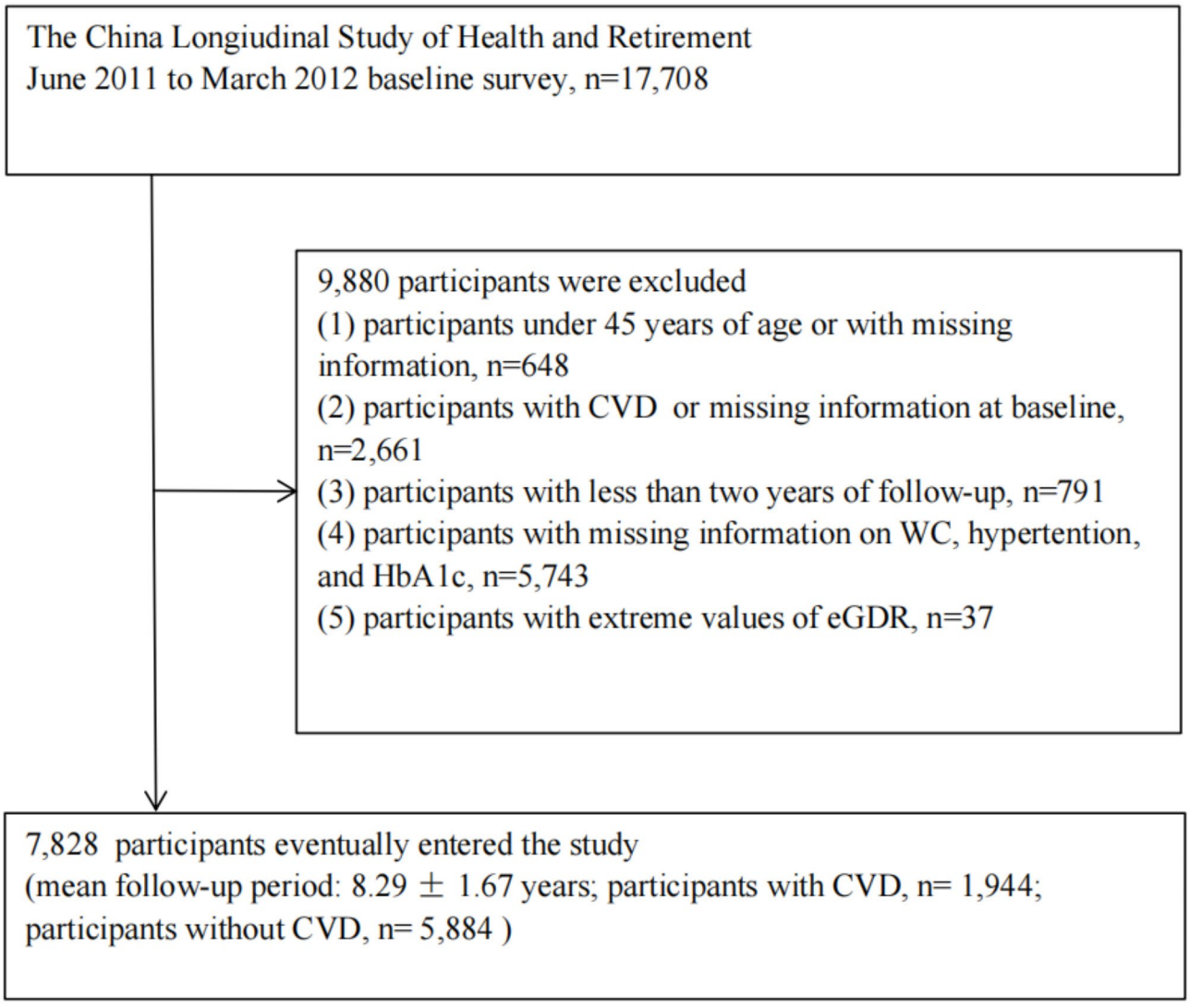

Fig. 1 The flowchart of study participants

cholesterol (HDL-c), low-density lipoprotein cholesterol (LDL-c), uric acid (UA), serum creatinine (Scr), blood urea nitrogen (BUN), Hemoglobin A1c (HbA1C), fasting plasma glucose (FPG), C-reactive protein (CRP), White blood cell (WBC), platelets.

Variables

eGDR

The present study utilized the earlier established formula to calculate the eGDR (mg/kg/min) [24]:

$$eGDR = 21.158 - (0.09 * WC) - (3.407 * hypertension) - (0.551 * HbA1c)$$

[WC = waist circumference (cm), hypertension (yes = 1/no = 0), and HbA1c = HbA1c (%)]

A diagnosis of hypertension was determined by either a self-reported physician diagnosis or SBP/DBP of at least 140/90 mmHg [37].

Glucose metabolism status

Diabetes was determined by an FPG level of 126 mg/dl or higher, an HbA1c of 6.5% or more, and/or a self-reported diagnosis from a doctor [11]. Prediabetes was identified by an FPG ranging from 100 to 125 mg/dL or an HbA1c between 5.7% and 6.4% [11]. Those without prediabetes or diabetes were identified as having normoglycemia [11].

Outcomes of the study

CVD diagnosis

The investigation focused on the incidence of CVD over the follow-up period (2013, 2015, 2018, and 2020). To gather past CVD diagnoses (cardiac events or stroke), a standardized question, "Have you been diagnosed

with heart failure, coronary heart disease, angina, heart attack, or other heart problems by a doctor?" or "Have you been diagnosed with stroke by a doctor?" was used. This is consistent with earlier, related research [38, 39]. The CHARLS study team adopted strict quality control techniques for data recording and verification to assure the trustworthiness of the data [34].

Missing data handling

In the total sample of 7,828 participants, the missing data were as follows: smoking status (1, 0.01%), drinking status (6, 0.08%), BMI (60, 0.77%), FBG (117, 1.49%), CRP (103, 1.32%), WBC (156, 1.99%), platelets (153, 1.95%), BUN (104, 1.33%), Scr (120, 1.53%), TG (108, 1.38%), HDL-c (103, 1.32%), LDL-c (118, 1.51%), and UA (103, 1.32%). Missing covariate data were addressed using multiple imputations [40]. Missing data analysis was conducted with the assumption that the data was missing at random [41].

Statistical analysis

Baseline characteristics across eGDR quartiles were compared using one-way analysis of variance (ANOVA) or Kruskal-Wallis tests for continuous variables, depending on their distribution patterns. Categorical variables were compared using chi-square tests.

The selection of confounding factors was based on two criteria: variables that induced changes in effect estimates exceeding 10% or demonstrated association with the outcome [42]. TC was excluded due to collinearity concerns (Supplementary Table S1). Based on clinical relevance and previous literature, the final set of confounding variables included demographic characteristics (gender, age, living place, education level, marital status), lifestyle factors (drinking status, smoking status), inflammatory markers (CRP, WBC, platelets), and metabolic parameters (FBG, BUN, Scr, UA, TG, HDL-c, LDL-c, BMI).

The association between eGDR and CVD risk was evaluated using Cox proportional hazards regression models, generating hazard ratios (HRs) with corresponding 95% confidence intervals (CIs). Three models with progressive adjustment were established: a non-adjusted model; Adjust I model (incorporating age and gender); and Adjust II model (including gender, age, living place, education level, marital status, drinking status, smoking status, CRP, WBC, platelets, FBG, BUN, Scr, UA, TG, HDL-c, LDL-c, BMI). The potential nonlinear relationship between eGDR and CVD risk was examined through restricted cubic spline (RCS) models, while two-piecewise linear regression models were applied to identify inflection points using log-likelihood ratio tests [43]. Threshold effect analyses were conducted within glucose metabolism subgroups to determine specific eGDR inflection points. To explore potential effect modifications, stratified analyses were performed across various subgroups (gender, age, BMI, smoking status, drinking status, and glucose metabolism status), with formal testing of interaction terms. The robustness of the findings to unmeasured confounding was assessed using E-value calculations [44].

Statistical analyses were performed using R software (version 4.2.0) and EmpowerStats (version 4.2), with all results reported in accordance with the STROBE guidelines [42]. Statistical significance was defined as a two-sided P-value less than 0.05.

Results

Characteristics

The study included 7,828 subjects (52.84% male) with an average age of 59.01 ± 9.21 years (Table 1). Figure 2 demonstrates that eGDR has a normal distribution, with a mean value of 9.41 ± 2.21 mg/kg/min. At baseline, 41.58% of participants had normoglycemia, 42.91% had prediabetes, and 15.51% had diabetes. During an average follow-up of 8.29 ± 1.67 years, the total CVD prevalence was 24.83%. From eGDR quartiles Q1 to Q4, BMI, WC, HbA1c, FBG, CRP, TC, TG, and LDL-c decreased, whereas HDL-c increased (all $P < 0.001$). The prevalence of CVD fell across quartiles, from 35.22 to 18.07% (Table 1).

Multivariate analyses

In the fully adjusted model (Adjust II), increased eGDR was significantly associated with lower risk of CVD across all glucose metabolism status (Table 2). For each 1 mg/kg/min increment in eGDR, the CVD risk decreased by 13% in normoglycemia group (HR = 0.87, 95%CI: 0.84–0.90), 8% in prediabetes group (HR = 0.92, 95%CI: 0.89–0.95), and 12% in diabetes group (HR = 0.88, 95%CI: 0.83–0.92). When analyzed by quartiles, participants in the highest eGDR quartile showed significantly reduced risks compared with the lowest quartile (normoglycemia: HR = 0.46, 95%CI: 0.37–0.57; prediabetes: HR = 0.65, 95%CI: 0.53–0.80; diabetes: HR = 0.43, 95%CI: 0.28–0.68) (Table 2).

Nonlinear analyses

The association between eGDR and CVD risk was examined using RCS analyses, stratified by glucose metabolism status (Fig. 3). The dose-response curves revealed inverse associations across all glycemic states, with distinct inflection points observed in normoglycemic, prediabetic, and diabetic populations (Fig. 3).

Threshold effect analysis revealed non-linear associations between eGDR and CVD risk across all glucose metabolism status (Table 3). A significant infection point was observed at eGDR = 11.77, 11.15, and 11.56 mg/kg/min for normoglycemia, prediabetes, and diabetes

Table 1 Characteristics of study participants according to eGDR quartiles

Variable	Overall	eGDR quartile (mg/kg/min)				*P* value
		Q1(2.67–7.42)	Q2(7.42–10.09)	Q3(10.09–11.17)	Q4(11.17–16.18)	
N	7828	1956	1957	1956	1959	
Age, years	59.01 ± 9.21	60.95 ± 9.36	59.91 ± 9.45	57.20 ± 8.50	57.98 ± 9.00	< 0.001
Gender						< 0.001
Male	4136 (52.84%)	1110 (56.75%)	1036 (52.94%)	1002 (51.23%)	988 (50.43%)	
Female	3692 (47.16%)	846 (43.25%)	921 (47.06%)	954 (48.77%)	971 (49.57%)	
Living place						< 0.001
Urban	2597 (33.18%)	772 (39.47%)	664 (33.93%)	632 (32.31%)	529 (27.00%)	
Rural	5231 (66.82%)	1184 (60.53%)	1293 (66.07%)	1324 (67.69%)	1430 (73.00%)	
Education level						0.001
Below primary school	3817 (48.76%)	981 (50.15%)	973 (49.72%)	879 (44.94%)	984 (50.23%)	
Primary school	1695 (21.65%)	419 (21.42%)	443 (22.64%)	414 (21.17%)	419 (21.39%)	
Middle school	1559 (19.92%)	380 (19.43%)	367 (18.75%)	450 (23.01%)	362 (18.48%)	
High school or above	757 (9.67%)	176 (9.00%)	174 (8.89%)	213 (10.89%)	194 (9.90%)	
Married	6912 (88.30%)	1694 (86.61%)	1690 (86.36%)	1785 (91.26%)	1743 (88.97%)	< 0.001
Smoking status	3089 (39.47%)	692 (35.38%)	777 (39.72%)	780 (39.88%)	840 (42.88%)	< 0.001
Drinking status	3092 (39.53%)	766 (39.18%)	794 (40.61%)	752 (38.49%)	780 (39.84%)	0.566
BMI, kg/m^2	23.03 (20.78–25.58)	25.63 (23.52–27.93)	23.61 (20.93–26.50)	23.15 (21.58–24.60)	20.42 (19.03–21.90)	< 0.001
WC, cm	84.16 ± 11.67	93.33 ± 7.38	86.36 ± 10.76	84.79 ± 4.16	72.17 ± 11.14	< 0.001
HbA1c, %	5.25 ± 0.79	5.49 ± 1.06	5.35 ± 0.94	5.16 ± 0.41	4.99 ± 0.42	< 0.001
FPG, mg/dl	109.57 ± 35.50	119.57 ± 48.11	114.37 ± 42.48	103.34 ± 18.19	101.00 ± 18.89	< 0.001
CRP, mg/dl	1.00 (0.54–2.09)	1.41 (0.74–2.78)	1.06 (0.57–2.12)	0.89 (0.51–1.80)	0.74 (0.43–1.53)	< 0.001
WBC (×10^9/L)	6.24 ± 1.89	6.50 ± 1.98	6.24 ± 1.81	6.20 ± 1.86	6.04 ± 1.89	< 0.001
Platelets (×10^9/L)	212.00 ± 72.55	214.64 ± 72.79	212.09 ± 75.55	210.94 ± 70.24	210.32 ± 71.45	0.264
BUN, mg/dl	15.74 ± 4.47	15.80 ± 4.51	15.84 ± 4.64	15.62 ± 4.40	15.71 ± 4.31	0.431
Scr, mg/dL	0.78 ± 0.23	0.80 ± 0.32	0.78 ± 0.20	0.77 ± 0.18	0.76 ± 0.16	< 0.001
TC, mg/dl	193.55 ± 38.42	201.33 ± 40.23	194.47 ± 37.64	192.32 ± 38.21	186.08 ± 35.97	< 0.001
TG, mg/dl	104.43 (74.34-152.22)	130.10 (90.27-188.51)	107.08 (76.11–159.30)	99.12 (73.46–141.60)	85.85 (63.72-121.69)	< 0.001
HDL-c, mg/dl	51.56 ± 15.32	47.12 ± 13.94	50.99 ± 15.71	51.91 ± 14.63	56.24 ± 15.55	< 0.001
LDL-c, mg/dl	116.25 ± 34.64	121.05 ± 36.98	116.18 ± 34.64	116.75 ± 34.24	111.03 ± 31.80	< 0.001
UA, mg/dl	4.44 ± 1.24	4.69 ± 1.31	4.51 ± 1.26	4.32 ± 1.17	4.22 ± 1.17	< 0.001
Baseline Hypertension	2951 (37.70%)	1943 (99.34%)	966 (49.36%)	2 (0.10%)	40 (2.04%)	< 0.001
eGDR (mg/kg/min)	9.41 ± 2.21	6.35 ± 0.82	8.76 ± 0.87	10.68 ± 0.30	11.84 ± 0.78	< 0.001
Follow-up time, years	8.29 ± 1.67	7.96 ± 1.93	8.24 ± 1.73	8.44 ± 1.49	8.52 ± 1.42	< 0.001
Baseline Glucose metabolism status						< 0.001
Normoglycemia	3255 (41.58%)	579 (29.60%)	701 (35.82%)	897 (45.86%)	1078 (55.03%)	
Prediabetes	3359 (42.91%)	868 (44.38%)	882 (45.07%)	871 (44.53%)	738 (37.67%)	
Diabetes	1214 (15.51%)	509 (26.02%)	374 (19.11%)	188 (9.61%)	143 (7.30%)	
CVD						< 0.001
No	5884 (75.17%)	1267 (64.78%)	1458 (74.50%)	1554 (79.45%)	1605 (81.93%)	
Yes	1944 (24.83%)	689 (35.22%)	499 (25.50%)	402 (20.55%)	354 (18.07%)	

Data are presented as mean ± standard deviation, median (interquartile range) or number (percentage)

groups, respectively. Below the threshold, eGDR showed a strong protective effect against CVD risk. Specifically, each 1-unit increment of eGDR reduced CVD risk by 14% in the normoglycemia group (HR = 0.86, 95%CI: 0.83–0.89, $P < 0.0001$), 10% in the prediabetes group (HR = 0.90, 95%CI: 0.86–0.93, $P < 0.0001$), and 14% in the diabetes group (HR = 0.86, 95%CI: 0.81–0.91, $P < 0.0001$) (Table 3).

We used E-values to determine the robustness of potential unmeasured confounders in the data, and our findings were consistent until an unmeasured confounder had an HR larger than 1.41.

Subgroup analyses

Stratified analyses were performed to evaluate the consistency of the association between eGDR and CVD risk

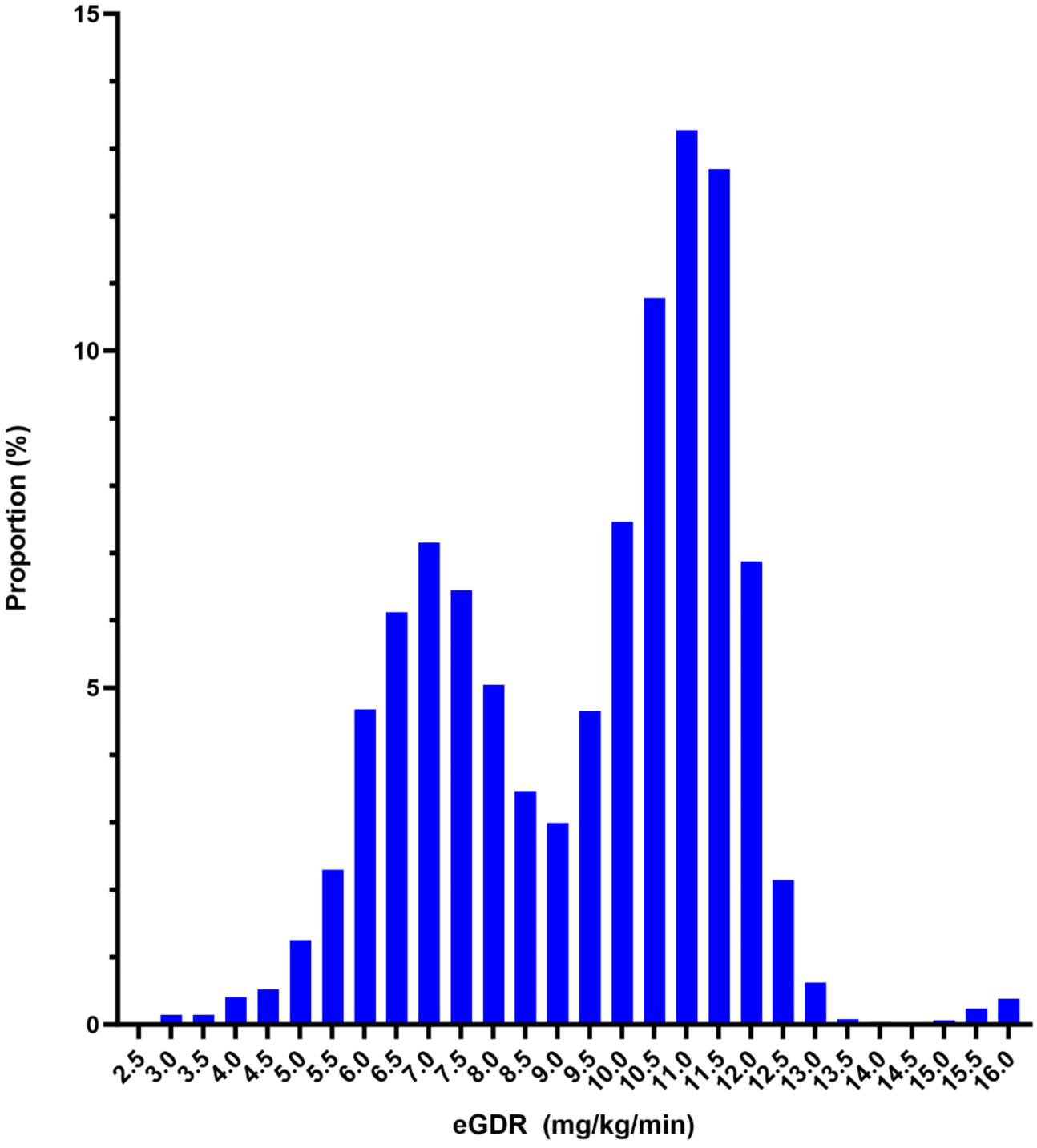

Fig. 2 Distribution of eGDR in the study population

across different subgroups (Table 4). The protective effect of eGDR against CVD was remarkably consistent across gender, age, drinking status, smoking status, BMI, and glucose metabolism status (Table 4).

Discussion

In this large-scale prospective cohort study of 7,828 participants aged ≥ 45 years with an average follow-up of 8.29 years, we investigated a significant inverse association between eGDR and CVD risk, with distinct threshold effects across glucose metabolism states. Below the identified thresholds (11.77, 11.15, and 11.56 mg/kg/min for

Table 2 Relationship between eGDR and CVD risk across different glucose metabolism status

Exposure	Non-adjusted HR (95% CI) *P* value	Adjust I HR (95% CI) *P* value	Adjust II HR (95% CI) *P* value
Normoglycemia			
eGDR (mg/kg/min)	0.86 (0.83, 0.89) < 0.0001	0.87 (0.84, 0.90) < 0.0001	0.87 (0.84, 0.90) < 0.0001
eGDR quartile (mg/kg/min)			
Q1	1.0	1.0	1.0
Q2	0.76 (0.62, 0.94) 0.0090	0.77 (0.63, 0.94) 0.0115	0.78 (0.63, 0.95) 0.0152
Q3	0.56 (0.46, 0.69) < 0.0001	0.59 (0.48, 0.73) < 0.0001	0.59 (0.48, 0.73) < 0.0001
Q4	0.44 (0.36, 0.54) < 0.0001	0.46 (0.37, 0.57) < 0.0001	0.46 (0.37, 0.57) < 0.0001
P for trend	< 0.0001	< 0.0001	< 0.0001
Prediabetes			
eGDR (mg/kg/min)	0.90 (0.87, 0.93) < 0.0001	0.92 (0.89, 0.95) < 0.0001	0.92 (0.89, 0.95) < 0.0001
eGDR quartile (mg/kg/min)			
Q1	1.0	1.0	1.0
Q2	0.74 (0.62, 0.88) 0.0006	0.78 (0.65, 0.92) 0.0043	0.77 (0.65, 0.92) 0.0036
Q3	0.59 (0.49, 0.71) < 0.0001	0.66 (0.54, 0.79) < 0.0001	0.66 (0.55, 0.80) < 0.0001
Q4	0.60 (0.49, 0.73) < 0.0001	0.65 (0.53, 0.79) < 0.0001	0.65 (0.53, 0.80) < 0.0001
P for trend	< 0.0001	< 0.0001	< 0.0001
Diabetes			
eGDR (mg/kg/min)	0.85 (0.81, 0.89) < 0.0001	0.85 (0.81, 0.89) < 0.0001	0.88 (0.83, 0.92) < 0.0001
eGDR quartile (mg/kg/min)			
Q1	1.0	1.0	1.0
Q2	0.54 (0.42, 0.69) < 0.0001	0.54 (0.42, 0.70) < 0.0001	0.58 (0.44, 0.75) < 0.0001
Q3	0.43 (0.30, 0.61) < 0.0001	0.44 (0.31, 0.63) < 0.0001	0.50 (0.35, 0.73) 0.0002
Q4	0.34 (0.22, 0.51) < 0.0001	0.35 (0.23, 0.53) < 0.0001	0.43 (0.28, 0.68) 0.0003
P for trend	< 0.0001	< 0.0001	< 0.0001
Total			
eGDR (mg/kg/min)	0.88 (0.86, 0.89) < 0.0001	0.89 (0.87, 0.90) < 0.0001	0.89 (0.87, 0.91) < 0.0001
eGDR quartile (mg/kg/min)			
Q1	1.0	1.0	1.0
Q2	0.70 (0.62, 0.78) < 0.0001	0.71 (0.64, 0.80) < 0.0001	0.72 (0.64, 0.81) < 0.0001
Q3	0.55 (0.48, 0.62) < 0.0001	0.59 (0.52, 0.67) < 0.0001	0.59 (0.52, 0.67) < 0.0001
Q4	0.48 (0.42, 0.54) < 0.0001	0.51 (0.44, 0.58) < 0.0001	0.52 (0.45, 0.59) < 0.0001
P for trend	< 0.0001	< 0.0001	< 0.0001

Non-adjusted model was conducted without adjustment

Adjust I model was adjusted for gender and age

Adjust II model was adjusted for gender, age, living place, education level, marital status, drinking status, smoking status, CRP, WBC, platelets, FPG, BUN, Scr, UA, TG, HDL-c, LDL-c, BMI

normoglycemia, prediabetes, and diabetes, respectively), each 1 mg/kg/min increase in eGDR was associated with reduced CVD risk by 14% in the normoglycemia group (HR = 0.86, 95%CI: 0.83–0.89), 10% in the prediabetes group (HR = 0.90, 95%CI: 0.86–0.93), and 14% in the diabetes group (HR = 0.86, 95%CI: 0.81–0.91).

Markers of IR, including Homeostatic Model Assessment of β-cell function (HOMA-β), Quantitative Insulin Sensitivity Check Index (QUICKI), and Triglyceride-Glucose (TyG) index, have demonstrated significant associations with CVD [45–47]. The eGDR, comprising WC, hypertension status, and HbA1c, provides a comprehensive assessment of IR that incorporates both laboratory values and clinical parameters [25–27]. Compared to other IR indices, eGDR offers several advantages for CVD risk assessment in clinical practice: it integrates multiple metabolic components rather than relying solely on glucose and insulin measurements (as with HOMA-β and QUICKI) [45–47]; it captures both glycemic parameters and central adiposity, which independently influence cardiovascular risk [24]. Furthermore, the eGDR includes more complete metabolic markers and valid CVD risk assessments across different glucose metabolism statuses [26, 30–33], which is better than individual metabolic markers such as WC or HbA1c alone [26].

These findings align with several recent studies on eGDR and CVD risk. Zhang et al. [31] reported a significant inverse association between eGDR and CVD risk in non-diabetic individuals (HR = 0.86, 95%CI: 0.83–0.89), matching our normoglycemia group findings. Similar

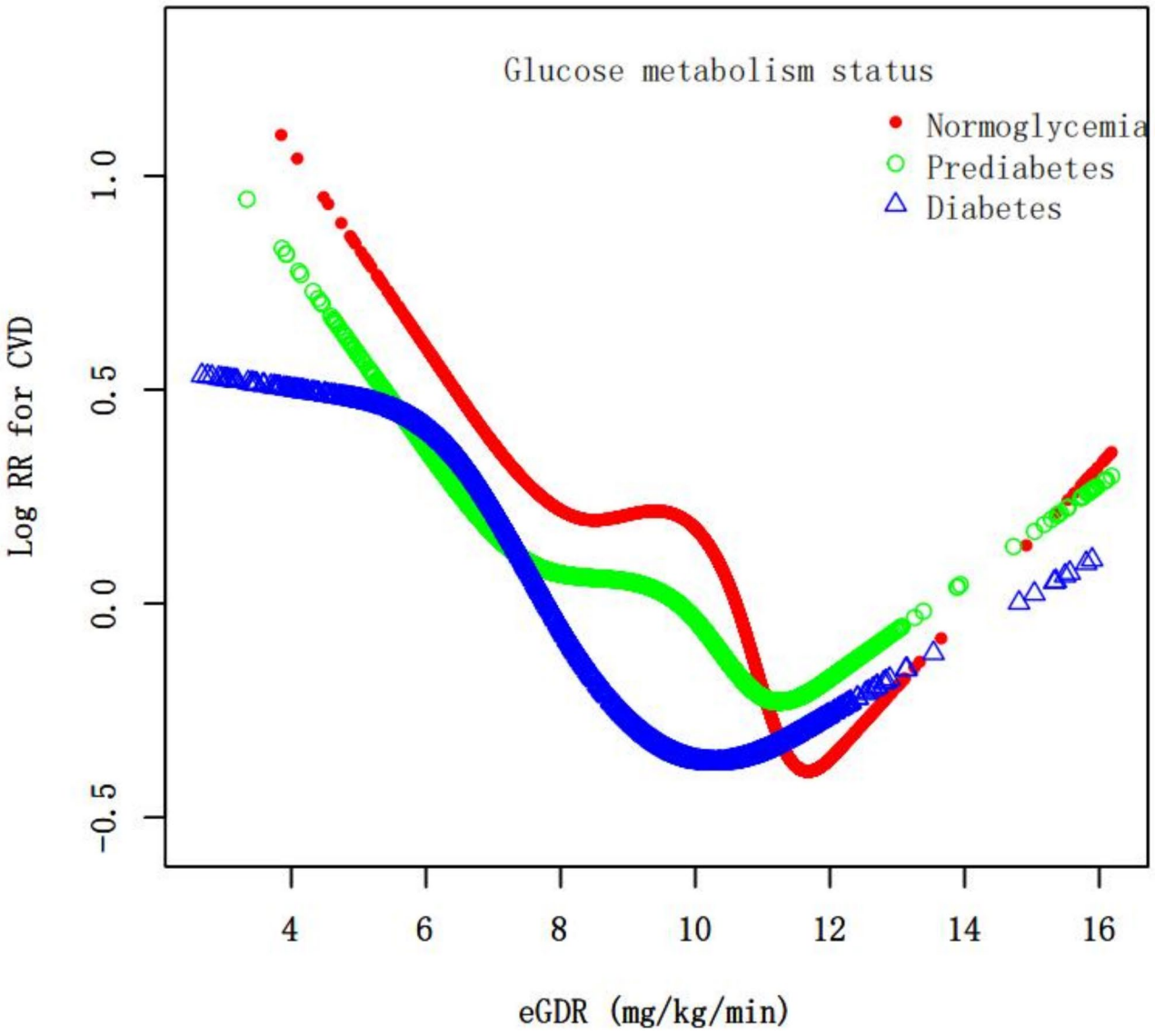

Fig. 3 Non-linear associations between eGDR and CVD risk stratified by glucose metabolism status. The association was evaluated using RCS models. Models were adjusted for gender, age, living place, education level, marital status, drinking status, smoking status, CRP, WBC, platelets, FPG, BUN, Scr, UA, TG, HDL-c, LDL-c, BMI

Table 3 Threshold effect analysis of eGDR on CVD risk stratified by glucose metabolism status

Model	Normoglycemia HR (95% CI) *P* value	Prediabetes HR (95% CI) *P* value	Diabetes HR (95% CI) *P* value
One-line linear regression			
One-line effect	0.87 (0.84, 0.90) < 0.0001	0.92 (0.89, 0.95) < 0.0001	0.88 (0.83, 0.92) < 0.0001
Two-piecewise regression			
Infection points of eGDR (mg/kg/min)	11.77	11.15	11.56
< Infection points	0.86 (0.83, 0.89) < 0.0001	0.90 (0.86, 0.93) < 0.0001	0.86 (0.81, 0.91) < 0.0001
≥ Infection points	1.13 (0.92, 1.37) 0.2409	1.10 (0.97, 1.26) 0.1423	1.29 (0.99, 1.69) 0.0564
P for log-likelihood ratio test	0.025	0.010	0.015

Models were adjusted for gender, age, living place, education level, marital status, drinking status, smoking status, CRP, WBC, platelets, FPG, BUN, Scr, UA, TG, HDL-c, LDL-c, BMI

Table 4 Stratified analyses of the association between eGDR and CVD risk

Subgroup	*N*	HR (95% CI) *P* value	*P* for interaction
Gender			0.3112
Male	4136	0.88 (0.86, 0.91) < 0.0001	
Female	3692	0.87 (0.84, 0.90) < 0.0001	
Age, years			0.1171
45–53	2379	0.86 (0.82, 0.90) < 0.0001	
54–61	2634	0.89 (0.85, 0.92) < 0.0001	
62–101	2815	0.90 (0.87, 0.93) < 0.0001	
Drinking status			0.3231
No	4734	0.87 (0.85, 0.90) < 0.0001	
Yes	3094	0.89 (0.86, 0.92) < 0.0001	
Smoking status			0.9103
No	4738	0.88 (0.86, 0.90) < 0.0001	
Yes	3090	0.87 (0.84, 0.90) < 0.0001	
Glucose metabolism status			0.0712
Normoglycemia	3255	0.86 (0.83, 0.89) < 0.0001	
Prediabetes	3359	0.90 (0.87, 0.93) < 0.0001	
Diabetes	1214	0.86 (0.82, 0.90) < 0.0001	
BMI, kg/m^2			0.9815
<24	4741	0.89 (0.86, 0.92) < 0.0001	
≥24	3087	0.89 (0.86, 0.92) < 0.0001	

Models were adjusted for gender, age, living place, education level, marital status, drinking status, smoking status, CRP, WBC, platelets, FPG, BUN, Scr, UA, TG, HDL-c, LDL-c, and BMI, except for stratified variables

results were found by Ren et al. [26] using CHARLS data (HR = 0.89, 95%CI: 0.85–0.93) and Zabala et al. [32] in type 2 diabetes patients (HR = 0.85, 95%CI: 0.82–0.89), which corresponds to our diabetes group results (HR = 0.86, 95%CI: 0.81–0.91). These studies consistently demonstrate that higher eGDR protects against CVD risk. Despite similarities, our study offers distinct advantages and methodological differences. For instance, Zhang et al. [31] specifically focused on non-diabetic individuals, whereas our study explored the relationship between eGDR and CVD risk across all glucose metabolism states, including normoglycemia, prediabetes, and diabetes, providing a more comprehensive perspective. Compared to Ren et al. [26], we employed advanced methods such as RCS and threshold effect analysis, which enabled us to identify specific eGDR inflection points (11.77, 11.15, and 11.56 mg/kg/min). Additionally, while Zabala et al. [32] concentrated on stroke risk in type 2 diabetes, our study included both stroke and cardiac events, allowing for a broader assessment of CVD risk.

Decreased eGDR is associated with increased CVD across the spectrum of glucose metabolism, with distinct pathophysiological mechanisms in different glycemic states. Lower eGDR reflects greater IR [24], which triggers adverse cardiovascular effects varying by glycemic status. In normoglycemic individuals, reduced eGDR indicates subclinical IR, leading to early endothelial dysfunction through impaired nitric oxide bioavailability and inflammatory changes [21, 48], exacerbated by dysregulated adipokine production and oxidative stress [49]. In prediabetes, IR combines with mild hyperglycemia to intensify endothelial dysfunction through increased oxidative stress and pro-inflammatory cytokines [50, 51]. The mechanism is most prominent in diabetes, where severe IR and chronic hyperglycemia synergistically enhance cardiovascular risk through oxidative stress-mediated pathways, advanced glycation end-products accumulation, and severe endothelial dysfunction [52, 53]. With additional complications of dyslipidemia and pro-thrombotic states [54], eGDR is important for cardiovascular risk stratification across different glycemic states [55].

Multivariate analysis demonstrated significant CVD risk reductions of 11%, 8%, and 12% per unit increase in eGDR for normoglycemic, prediabetic, and diabetic populations, respectively (P for trend < 0.0001). Stratified analyses across demographic and clinical subgroups confirmed the robustness of these associations (all P for interaction > 0.05). The non-linear analysis identified distinct eGDR inflection points (11.77, 11.15, and 11.56 mg/kg/min for normoglycemia, prediabetes, and diabetes, respectively), with each unit increase below these thresholds demonstrating similar cardiovascular protective effects (14% risk reduction in normoglycemic and diabetic groups, 10% in prediabetes). The consistency of these associations across the glucose metabolism spectrum might suggest a meaningful role of eGDR in cardiovascular health. The slightly attenuated protective effect observed in prediabetes could possibly reflect the distinct pathophysiological features of this transitional state, characterized by progressive β-cell dysfunction, altered incretin responses, and specific patterns of IR [56–58], alongside unique inflammatory profiles and oxidative stress patterns [59, 60].

These findings may have several potential implications for cardiovascular health management. First, identifying glycemic status-specific thresholds might provide reference points for CVD risk assessment. Second, the observed association between eGDR and CVD risk, regardless of glycemic status, could suggest the importance of eGDR in cardiovascular health. Third, the relatively consistent protective effects may indicate that higher eGDR levels could be associated with cardiovascular benefits across all glycemic states. The persistence of these associations throughout different glucose metabolism states appears to support a potential role of eGDR in CVD protection, which might warrant consideration independent of glucose metabolism status. Clinically, patients with lower eGDR levels warrant higher surveillance and more aggressive preventive interventions, regardless of their glycemic status. These strategies might

target the key components of eGDR: WC, BP and HbA1c. This comprehensive approach could more effectively reduce CVD risk in these vulnerable patients.

Strengths and limitations

This investigation exhibited several strengths. The analysis utilized a large, nationally representative cohort with extended follow-up (mean 8.29 years), enhancing result reliability and generalizability. The relationship between eGDR and CVD risk was comprehensively examined across different glucose metabolism states using RCS and threshold effect analysis, to identify non-linear associations and specific inflection points. The methodological robustness was demonstrated through comprehensive confounder adjustment and consistent findings across stratified analyses. Additionally, the calculated E-value indicated strong resistance to potential unmeasured confounding, further supporting the validity of the findings.

Several limitations warrant consideration in this study. First, CVD outcomes relied solely on self-reported information through standardized questionnaires without clinical verification, potentially introducing recall bias and event misclassification. Second, our analysis lacked specificity in cerebrovascular event classification, as we did not differentiate between types of stroke, limiting the precision of our findings. Third, despite our comprehensive adjusted model, we omitted important clinical variables that significantly differed among eGDR groups, particularly baseline hypertension and CVD history, which may restrict the generalizability of our results to patients with pre-existing CVD. Future research should address these limitations through objective outcome verification, more precise stroke classification, and inclusion of all relevant clinical covariates in statistical analyses.

Conclusions

This large-scale prospective cohort study of 7,828 participants aged ≥ 45 years with an average follow-up of 8.29 years demonstrates a significant non-linear inverse association between eGDR and CVD risk across different glucose metabolism states, with distinct threshold effects identified for normoglycemia (11.77 mg/kg/min), prediabetes (11.15 mg/kg/min), and diabetes (11.56 mg/kg/min). Below these thresholds, each unit increase in eGDR showed consistent cardiovascular protective effects. These findings underscore the potential importance of eGDR for cardiovascular risk assessment, regardless of glucose metabolism status. The consistent protective effects observed across glycemic states suggest that maintaining higher eGDR levels might be beneficial for cardiovascular health in all populations. Future studies should focus on validating these non-linear relationships between eGDR and CVD risk across different age groups and ethnic populations.

Abbreviations

eGDR	Estimated glucose disposal rate
BMI	Body mass index
WC	Waist circumference
HbA1c	Hemoglobin A1c
FBG	Fasting blood glucose
CRP	C-reactive protein
WBC	White blood cell
BUN	Blood urea nitrogen
Scr	Serum creatinine
TC	Total cholesterol
TG	Triglycerides
HDL-c	High-density lipoprotein cholesterol
LDL-c	Low-density lipoprotein cholesterol
UA	Uric acid
CVD	Cardiovascular disease

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s13098-025-01697-6.

Supplementary Material 1

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Author contributions

Xiaomin Liang conceptualized, designed the study and wrote the original draft. Kai Lai, Xiaohong Li and Di Ren were responsible for data curation, conducted the formal analysis, and developed the methodology. Shuiqing Gui, Zemao Xing, and Ying Li were responsible for project administration and supervision. All authors read and approved the final manuscript.

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Data availability

The data used in this study are publicly available from the CHARLS database (http://charls.pku.edu.cn/).

Declarations

Ethics approval and consent to participate

The CHARLS study was approved by the Peking University Institutional Review Board (IRB00001052-11015) and all participants provided written informed consent.

Consent for publication

Not applicable.

Competing interests

The authors declare no competing interests.

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