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Association of estimated glucose disposal rate with metabolic syndrome prevalence and mortality risks: a population-based study

Xiaoli Chen[1,2], Aihua Li[1,2] and Qilin Ma[1,2*]

Abstract

Background Insulin resistance (IR) is a central pathophysiological factor in metabolic syndrome (MetS) and an essential driver of cardiovascular disease (CVD) and mortality. The estimated glucose disposal rate (eGDR) is a reliable marker of IR and has been associated with CVD prognosis. This study aims to examine the relationship between eGDR, MetS, and their predictive roles in clinical outcomes.

Methods Data from the NHANES (2001–2018) were utilized, with a cross-sectional design applied to evaluate the association between eGDR and MetS prevalence, and a cohort design employed for mortality follow-up. Weighted logistic regression models were used to examine the association between eGDR and MetS. Weighted Cox proportional hazard models were applied to assess the link between eGDR and both all-cause and CVD mortality. To examine the non-linear associations between the eGDR, MetS, and mortality outcomes, restricted cubic spline (RCS) analysis was applied. Additionally, the predictive performance of eGDR, and other IR indices (TyG, HOMA-IR), for mortality was assessed using the C-statistic.

Results A robust negative association between eGDR and MetS prevalence was found, following full covariate adjustment ($p < 0.001$). The core findings were consistent across subgroups (all $p < 0.001$). Cox regression analysis indicated that in individuals with MetS, each standard deviation (SD) increment in eGDR was associated with an 11% and 18% decrement in the risk of all-cause and CVD mortality, respectively. RCS analysis displayed a non-linear association between eGDR and MetS prevalence, while a linear association between eGDR and mortality. The C-statistic showed that eGDR, compared to the TyG index and HOMA-IR, significantly improved predictive power for all-cause mortality ($p = 0.007$).

Conclusion eGDR is strongly associated with MetS and predicts all-cause and CVD mortality in individuals with MetS. Compared to TyG and HOMA-IR, eGDR offers superior predictive value for all-cause mortality, highlighting its potential as a useful tool in clinical risk assessment.

Keywords Insulin resistance, Metabolic syndrome, Estimated glucose disposal rate, NHANES, Mortality

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Introduction

Metabolic syndrome (MetS) is a complex clinical condition defined by the coexistence of several metabolic abnormalities, including hypertension (HTN), central obesity, impaired glucose metabolism, and dyslipidemia [1, 2]. The incidence of MetS among U.S. adults was 33% from 2003 to 2012, rising to 34.7% by 2016, according to data from the National Health and Nutrition Examination Survey (NHANES) [3, 4],. The clustering of MetS components substantially raises the risk of developing chronic conditions like chronic kidney disease (CKD) and cardiovascular disease (CVD), which in turn contribute to premature mortality [5, 6]. Individuals with MetS have more than double the risk of developing CVD and dying from it [6]. Given its increasing prevalence worldwide and its well-established role as a predictor of all-cause and CVD mortality [7], MetS has become a critical public health challenge. However, identifying reliable prognostic biomarkers and developing personalized follow-up strategies for MetS patients remain substantial challenges.

Insulin resistance (IR) is a key characteristic of MetS, indicating the reduced efficiency of insulin in facilitating glucose uptake and utilization [8, 9]. IR is recognized as a risk factor for both microvascular and macrovascular complications. While the hyperinsulinemic-euglycemic clamp is regarded as the gold standard for measuring insulin sensitivity, offering the most accurate measure of IR [10, 11]. However, its invasive nature and high cost restrict its clinical applicability. As alternatives, the homeostasis model assessment of insulin resistance (HOMA-IR) [12]and the triglyceride-glucose (TyG) index [13] are commonly used for screening IR. However, the value of HOMA-IR, which is based on fasting glucose and insulin levels, can be influenced by insulin administration, particularly in diabetic patients, which may limit its accuracy in certain populations [12]. The TyG index has been associated with MetS and its outcomes, but it may not fully capture the complexities of IR, especially when considering key MetS components like central obesity and HTN [14, 15]. In this context, the estimated glucose disposal rate (eGDR), an emerging tool for assessing IR, calculated from waist circumference (WC), HTN, and glycosylated hemoglobin A1c (HbA1c), may offer a more comprehensive approach. Initially applied to evaluate IR in patients with type 1 diabetes mellitus (T1DM) [16], eGDR has since been shown to be associated with stroke, diabetic kidney disease, and mortality in patients with type 2 diabetes mellitus (T2DM) [17, 18]. Recently, eGDR has been identified as a predictor of long-term mortality in both non-diabetic individuals [19] and the elderly [20]. Notably, in older adults, the association between eGDR and all-cause mortality is partially mediated by arterial stiffness, as measured by brachial-ankle pulse wave velocity (baPWV) [20]. However, the relationship between eGDR, MetS, and both mortality outcomes remains inadequately explored.

The aim of this study was to examine the association between eGDR and MetS prevalence and to assess the relationship between eGDR and all-cause and CVD mortality in individuals with and without MetS. Additionally, the predictive performance of eGDR, TyG, and HOMA-IR for mortality outcomes was assessed using the C-statistic.

Methods

Study design and participants

The NHANES program employs a rigorous sampling methodology to select a representative cohort from the U.S. population, conducting biennial assessments of health and nutritional status across individuals nationwide. The study protocol was approved by the Ethics Review Committee of the NCHS, and all participants provided written informed consent prior to enrollment. As such, no additional ethical approval was needed for this analysis. This study included data from 91,351 individuals across 9 cycles of the NHANES, spanning from 2001 to 2018. Exclusion criteria included: (1) individuals aged under 20 years ($n = 41,150$) and pregnant ($n = 1,258$); (2) missing data on the eGDR record ($n = 7,945$); (3) missing data on MetS diagnosis ($n = 21,480$); (4) lack of follow-up information ($n = 26$); and (5) missing data on covariates or sample weights ($n = 3,055$). After applying these criteria, 16,437 participants were included in the final analysis. A flowchart of participant selection is provided in Fig. S1.

Exposure and outcome variables

The eGDR, employed as the exposure variable, was calculated using the formula: 21.158 - (0.09 × WC [cm]) - (3.407 × HTN status [1 = yes, 0 = no]) - (0.551 × HbA1c in %), which serves as a measure of IR [16, 19]. Based on the quartiles of the eGDR index, participants were divided into four groups (Q1, Q2, Q3, Q4). The primary outcomes evaluated included Mets status, all-cause mortality, and CVD mortality. MetS was diagnosed if at least three of the following criteria were present [2]: (1) WC > 102 cm in men or > 88 cm in women; (2) high-density lipoprotein cholesterol (HDL-C) < 40 mg/dL in males or < 50 mg/dL in females; (3) blood pressure (BP) > 130/85 mmHg or use of antihypertensive medications; (4) fasting blood glucose (FBG) > 100 mg/dL or taking diabetes medication; (5) plasma triglycerides (TG) > 150 mg/dL. In addition, we further examined the association between eGDR and all-cause or CVD mortality in individuals with and without MetS. Follow-up and endpoint data for participants were obtained by matching their records to the National Death Index (NDI) up to December 31, 2019.

CVD mortality was defined based on the following ICD-10 codes: I00–I09, I11, I13, I20–I51, and I60–I69.

Covariate

Standardized questionnaires were applied to gather sociodemographic and lifestyle information from participants, including age, sex (male, female), race (Mexican American, Black, White, and Other), educational attainment (below high school, high school or equivalent, and above high school), family income-to-poverty ratio (PIR) (< 1, 1-2.99, ≥ 3), marital status (married or living with a partner, other), smoking status (never, former, and current), and drinking habits (none, low-to-moderate, heavy). Clinical biomarkers, including total cholesterol (TC), albumin (ALB), blood urea nitrogen (BUN), aspartate aminotransferase (AST), alanine aminotransferase (ALT), uric acid (UA), and estimated glomerular filtration rate (eGFR), were measured using standardized laboratory protocols. CVD status was defined based on self-reported diagnoses of coronary heart disease (CHD), congestive heart failure (CHF), myocardial infarction (MI), stroke, or angina, as confirmed by a healthcare professional [21].

Statistical analysis

Statistical analyses followed CDC guidelines [22], incorporating the relevant NHANES sample weights and accounting for the complex, multistage survey structure. Continuous variables are summarized as median (interquartile range) and compared using the Wilcoxon rank-sum test. Categorical variables are presented as counts (weighted proportions) and analyzed with the weighted chi-square test. The relationship between eGDR and MetS was investigated using weighted univariable and multivariable logistic regression across three distinct models. Kaplan–Meier (K-M) curves illustrate the mortality rates across eGDR groups, with comparisons made using the log-rank test. Furthermore, univariable and multivariable Cox proportional hazard models were used to examine the association between eGDR and all-cause and CVD mortality in participants with or without MetS. Restricted cubic spline (RCS) curves were used to evaluate further the nonlinear relationships between eGDR and MetS, as well as between eGDR and all-cause and CVD mortality. Stratification and interaction analyses were conducted to assess the association between eGDR, MetS prevalence, and mortality across subgroups, including age (< 60, ≥ 60), sex, race, PIR, body mass index (BMI, kg/m^2) (< 25, 25-29.99, ≥ 30), educational attainment, smoking status, and alcohol consumption. In addition, we assessed the predictive value of the original model and models incorporating eGDR, as well as other IR indices (TyG index, HOMA-IR), which have previously been identified as predictors of Mets and its outcomes [14, 15, 23]. Model performance was compared using Harrell's C-index [24]. To further evaluate the additional predictive power beyond the basic models, the Net Reclassification Improvement (NRI) index was calculated.

All statistical analyses were conducted using R software (version 4.4.1). A two-sided p-value < 0.05 was considered significant for two-group comparisons, while for multiple-group comparisons, Bonferroni correction was applied, setting the threshold at $p = 0.017$ (0.05/3).

Results

Baseline characteristics

This study included 16,437 participants, weighted to represent a population of 184,376,625 individuals, with 48.9% males and 51.1% females. Baseline characteristics of individuals, stratified by the presence or absence of MetS, are summarized in Table 1. Approximately 6342 participants (35%) had MetS. Participants with MetS were generally older, predominantly White, and more likely to be married or living with a partner. They also had lower educational attainment and PIR. A higher proportion had a history of CVD, were former smokers, and were nondrinkers. Additionally, these individuals exhibited elevated levels of BMI, WC, TC, TG, LDL, HbA1c, FBG, ALT, AST, BUN, UA, and serum creatinine, as well as lower eGDR, HDL, ALB, and eGFR (all p-values < 0.05). In addition, baseline characteristics of all participants, as well as those with and without MetS, stratified by eGDR quartiles, are provided in Tables S1, S2, and S3.

Relationships between eGDR with MetS

Logistic regression analysis revealed a strong negative association between eGDR and MetS prevalence. After full covariate adjustment, individuals in higher quartiles of eGDR exhibited a significantly lower prevalence of MetS compared to the reference group (Q1). Specifically, the odds ratios (OR) for MetS prevalence were 0.66 (95% CI: 0.64–0.67) in Q2, 0.56 (95% CI: 0.55–0.58) in Q3, and 0.47 (95% CI: 0.46–0.48) in Q4, all with p-values < 0.001 and a trend p-value < 0.001(Table 2). The analysis of eGDR as a continuous predictor revealed that each standard deviation (SD) increase was associated with a 25% reduction in MetS prevalence (OR = 0.75, 95% CI: 0.74–0.76, $p < 0.001$) (Table 2). RCS analysis revealed a nonlinear association between eGDR and MetS, with a sharp increase in MetS prevalence when eGDR decreased (p for nonlinearity < 0.0001) (Fig. 1).

Figure 2 presents the results of subgroup analyses on the association between eGDR (as a continuous variable) and MetS, stratified by age, sex, race, education level, PIR, smoking and drinking status, and BMI. The findings were consistent across all subgroups (all $p < 0.001$). Furthermore, the interaction analysis revealed statistically

Table 1 Baseline characteristics of included participants stratified by with or without MetS

Characteristic	Total (*n* = 16,437)	Without MetS (*n* = 10,095)	With MetS (*n* = 6,342)	*P*-value
Age, years	46 (33, 59)	41 (30, 54)	54 (43, 65)	< 0.001
Sex				0.9
Male	8,155 (48.9%)	5,118 (48.8%)	3,037 (49.0%)	
Female	8,282 (51.1%)	4,977 (51.2%)	3,305 (51.0%)	
Race				< 0.001
Mexican American	2,698 (7.9%)	1,570 (7.8%)	1,128 (8.1%)	
Black	3,169 (10.7%)	2,014 (11.2%)	1,155 (9.9%)	
White	7,627 (69.6%)	4,563 (68.3%)	3,064 (71.9%)	
Other	2,943 (11.8%)	1,948 (12.7%)	995 (10.1%)	
Education levels				< 0.001
Under high school	1,707 (5.3%)	857 (4.5%)	850 (6.9%)	
High school or equivalent	6,090 (34.2%)	3,502 (31.4%)	2,588 (39.5%)	
Above high school	8,640 (60.4%)	5,736 (64.2%)	2,904 (53.6%)	
PIR				< 0.001
< 1	3,193 (13.4%)	1,873 (12.9%)	1,320 (14.3%)	
1-2.99	6,925 (36.4%)	4,071 (34.9%)	2,854 (39.1%)	
≥ 3	6,319 (50.2%)	4,151 (52.2%)	2,168 (46.6%)	
Marital status				0.007
Married or living with a partner	10,133 (64.9%)	6,154 (63.9%)	3,979 (66.8%)	
Other	6,304 (35.1%)	3,941 (36.1%)	2,363 (33.2%)	
Smoking status				< 0.001
Never smoker	8,905 (53.8%)	5,754 (56.2%)	3,151 (49.6%)	
Former smoker	4,183 (25.4%)	2,217 (22.4%)	1,966 (30.8%)	
Current smoker	3,349 (20.8%)	2,124 (21.4%)	1,225 (19.6%)	
Drinking status				< 0.001
Nondrinker	5,787 (29.0%)	3,182 (25.8%)	2,605 (35.0%)	
Low-to-moderate drinker	5,388 (35.4%)	3,411 (35.9%)	1,977 (34.4%)	
Heavy drinker	5,262 (35.6%)	3,502 (38.3%)	1,760 (30.5%)	
BMI, kg/m^2	27.7 (24.0, 32.1)	25.6 (22.8, 29.1)	31.5 (28.3, 36.2)	< 0.001
BMI category				< 0.001
Normal weight (< 25)	4,921 (31.4%)	4,417 (44.7%)	504 (7.1%)	
Overweight (25-29.99)	5,575 (33.4%)	3,555 (34.9%)	2,020 (30.7%)	
Obesity (≥ 30)	5,941 (35.2%)	2,123 (20.4%)	3,818 (62.2%)	
WC, cm	97.1 (86.8, 108.3)	91.1 (82.5, 100.1)	108.2 (100.1, 118.0)	< 0.001
TC, mg/dL	190.0 (165.0, 217.0)	189.0 (164.0, 214.0)	194.0 (167.0, 224.0)	< 0.001
TG, mg/dL	102.0 (71.0, 150.0)	86.0 (63.0, 117.0)	155.0 (106.0, 205.0)	< 0.001
LDL, mg/dL	112.0 (90.0, 137.0)	111.0 (90.0, 134.0)	115.0 (92.0, 140.0)	< 0.001
HDL, mg/dL	52.0 (43.0, 63.0)	56.0 (47.0, 67.0)	44.0 (38.0, 52.0)	< 0.001
HbA1c, %	5.40 (5.20, 5.70)	5.30 (5.10, 5.50)	5.60 (5.40, 6.10)	< 0.001
Fast glucose, mg/dL	99.0 (92.0, 107.0)	95.0 (90.0, 100.4)	107.4 (101.0, 120.0)	< 0.001
ALB, g/L	43.0 (40.0, 45.0)	43.0 (41.0, 45.0)	42.0 (40.0, 44.0)	< 0.001
ALT, U/L	21.0 (16.0, 28.0)	20.0 (16.0, 26.0)	24.0 (18.0, 32.0)	< 0.001
AST, U/L	22.0 (19.0, 27.0)	22.0 (19.0, 26.0)	23.0 (19.0, 28.0)	< 0.001
BUN, mg/dL	13.0 (10.0, 16.0)	12.0 (10.0, 15.0)	13.0 (11.0, 17.0)	< 0.001
UA, mg/dL	5.4 (4.5, 6.3)	5.1 (4.3, 6.0)	5.9 (5.0, 6.8)	< 0.001
Serum creatinine, mg/dl	0.85 (0.72, 1.00)	0.84 (0.72, 1.00)	0.87 (0.73, 1.00)	< 0.001
eGFR, $ml/min/1.73m^2$	98.7 (84.0, 111.4)	101.3 (87.6, 114.0)	93.5 (77.6, 106.5)	< 0.001
eGDR	8.57 (5.85, 10.19)	9.67 (8.01, 10.70)	5.41 (4.19, 7.48)	< 0.001
CVD	1,772 (8.4%)	665 (5.0%)	1,107 (14.6%)	< 0.001

Table 1 (continued)

Characteristic	Total (*n* = 16,437)	Without MetS (*n* = 10,095)	With MetS (*n* = 6,342)	*P*-value
All-cause mortality	2,142 (9.2%)	1,006 (6.6%)	1,136 (13.9%)	< 0.001
CVD mortality	683 (2.7%)	314 (1.9%)	369 (4.4%)	< 0.001

PIR: family income-to-poverty ratio, BMI: body mass index, WC: waist circumference, TC: total cholesterol, TG: triglyceride, LDL: low-density lipoprotein cholesterol, HDL: high-density lipoprotein cholesterol, HbA1c: glycated hemoglobin A1c, ALB: albumin, ALT: alanine aminotransferase, AST: aspartate aminotransferase, BUN: blood urea nitrogen, UA: uric acid, eGFR: estimated glomerular filtration rate, CVD: cardiovascular diseases

Data are presented as median (interquartile range) or counts (weighted proportions)

Table 2 Associations between eGDR and the prevalence of MetS

MetS	Model 1		Model 2		Model 3	
	OR (95% CI)	*p*-value	OR (95% CI)	*p*-value	OR (95% CI)	*p*-value
eGDR continues						
Per SD increase	0.74 (0.73, 0.74)	< 0.001	0.74 (0.73, 0.74)	< 0.001	0.75 (0.74, 0.76)	< 0.001
eGDR quartiles						
Q1	Ref		Ref		Ref	
Q2	0.65 (0.63, 0.66)	< 0.001	0.65 (0.63, 0.66)	< 0.001	0.66 (0.64, 0.67)	< 0.001
Q3	0.54 (0.53, 0.55)	< 0.001	0.55 (0.53, 0.56)	< 0.001	0.56 (0.55, 0.58)	< 0.001
Q4	0.44 (0.43, 0.44)	< 0.001	0.44 (0.43, 0.45)	< 0.001	0.47 (0.46, 0.48)	< 0.001
P for trend		< 0.001		< 0.001		< 0.001

OR, Odd Ratio; 95%CI, 95% Confidence interval

Model 1: No covariates were adjusted

Model 2: Age, gender, race, and family income poverty ratio were adjusted

Model 3: Age, gender, race, family income poverty ratio, education level, marital status, smoking status, drinking status, TC, ALB, ALT, AST, BUN, UA, eGFR, and CVD were adjusted

significant variability in the relationship between eGDR and MetS across subgroups stratified by age, race, PIR, smoking status, and BMI ($p < 0.05$). However, the magnitude of these differences was modest, suggesting that the statistical significance may have been influenced by the large sample size (Fig. 2).

Associations of eGDR with all-cause and cardiovascular mortality in individuals with and without MetS

Over a mean follow-up of 8.62 years, a total of 1,136 (13.9%) deaths were recorded in the MetS population, with 369 (4.4%) attributed to CVD. All-cause mortality rates among MetS patients were 346 (17.3%), 318 (15.7%), 313 (16%), and 159 (7.6%) across eGDR quartiles, respectively. Additionally, K-M survival analysis revealed that MetS patients in the highest eGDR quartile had significantly better overall and CVD survival compared to those in the lowest quartiles (both Log-rank $p < 0.001$) (Fig. 3A, B). The results of the weighted multivariable Cox regression analysis demonstrated that individuals in the highest quartile of eGDR had a significantly reduced risk of both all-cause and CVD mortality compared to those in the lowest quartile in individuals with MetS (HR = 0.74, 95% CI: 0.58–0.93; HR = 0.56, 95% CI: 0.36–0.87, respectively; $p < 0.017$) (Table 3). However, the P for trend across quartiles was not statistically significant, which may be attributed to smaller effect sizes in the intermediate quartiles (Q2 and Q3). Furthermore, each SD increment in eGDR, treated as a continuous variable, was associated with an 11% and 18% reduction in the risk of all-cause and CVD mortality, respectively, after adjusting for relevant covariates (both, $p < 0.05$) (Table 3). The results of the RCS analysis demonstrated a linear relationship between eGDR and all-cause and CVD mortality, with a dose-response effect (p for nonlinearity > 0.05). As eGDR decreased, the risk of both outcomes increased (Fig. 3C, D).

Additionally, we assessed the impact of eGDR on all-cause and CVD mortality in individuals without MetS. Cox regression analysis demonstrated that while the P for trend across eGDR quartiles was statistically significant ($p = 0.026$), none of the individual quartiles (Q2, Q3, or Q4) showed a significant association with all-cause mortality compared to Q1 (all $p > 0.05$). Additionally, no significant association was observed when eGDR was modeled as a continuous variable (Table S4). However, eGDR was identified as a significant predictor of CVD mortality. Compared to individuals in the lowest quartile, those in the highest quartiles had a 58% reduced risk of CVD mortality (HR = 0.42, 95%CI: 0.22–0.83, $p = 0.013$). Furthermore, for each SD increase in eGDR, the risk of CVD mortality decreased by 27% ($p < 0.05$) (Table S4). RCS analysis revealed a linear association between eGDR and CVD mortality in the absence of MetS (Fig. S2).

Stratified analyses demonstrated inconsistent relationships between eGDR and all-cause and CVD mortality across different groups within the MetS population

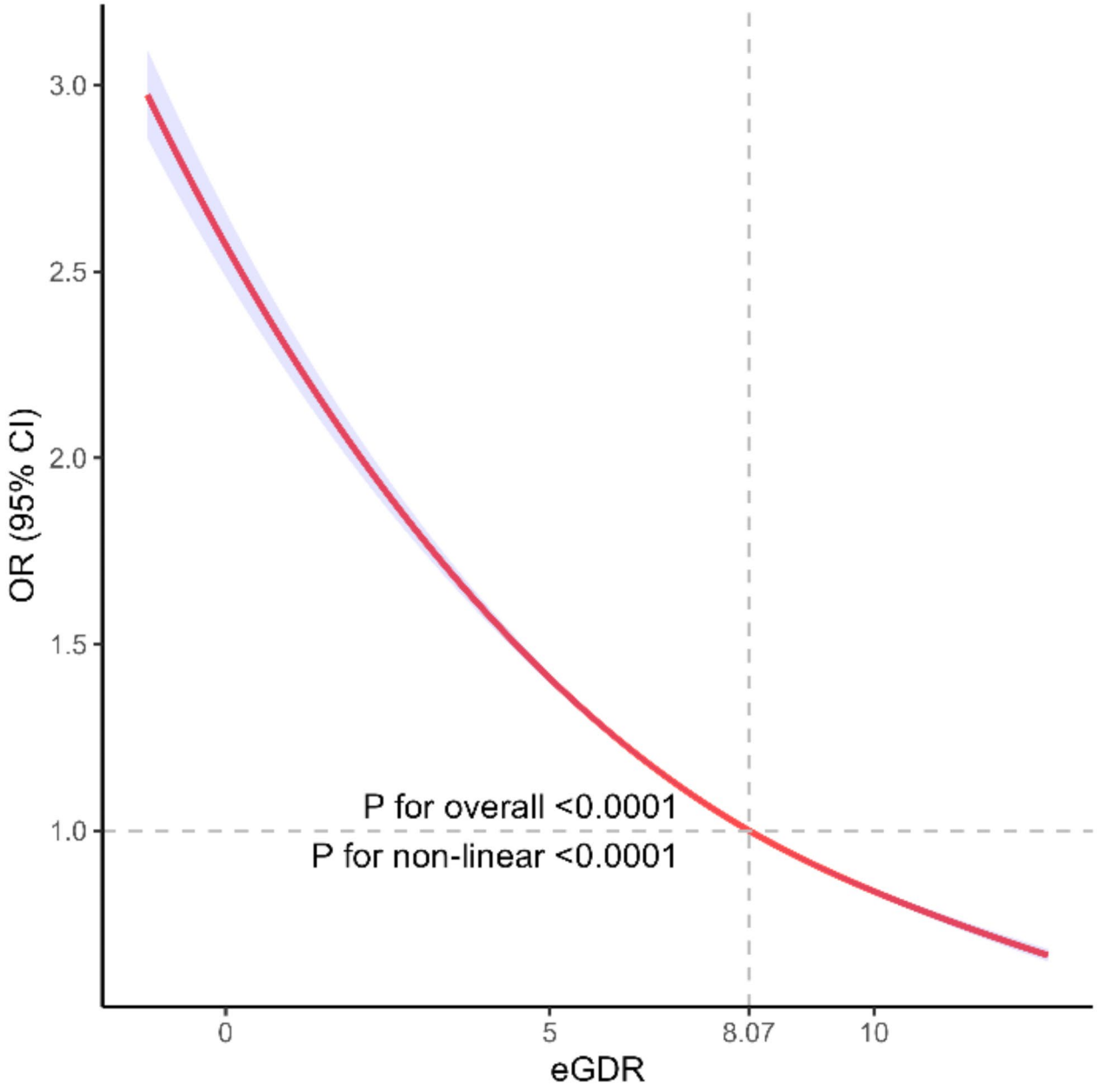

Fig. 1 Restricted cubic spline curve for the association between eGDR and the prevalence of Mets.Red lines represent references for odds ratios, and blue areas represent 95% confidence intervals. The model was adjusted for age, gender, race, family income poverty ratio, education level, marital status, smoking status, drinking status, TC, ALB, ALT, AST, BUN, UA, eGFR, and CVD

(Fig. 4). Stratified analyses showed that the association between eGDR and all-cause mortality was generally consistent across most subgroups within the MetS population, including age, sex, race, education levels, smoking status, and drinking status (all p for interaction > 0.05). However, significant interactions were detected for PIR and BMI categories (p for interaction < 0.05). Specifically, the association was more pronounced among individuals with PIR < 3 or BMI ≥ 30 (Fig. 4a). For CVD mortality, a significant interaction with BMI was observed (p for interaction = 0.04), where the association was evident only among individuals with BMI ≥ 30. Associations in other subgroups remained consistent (p for interaction > 0.05) (Fig. 4b).

In individuals without MetS, stratified and interaction analyses demonstrated no significant interactions across any subgroup (all p for interaction > 0.05), as presented in Fig. S3.

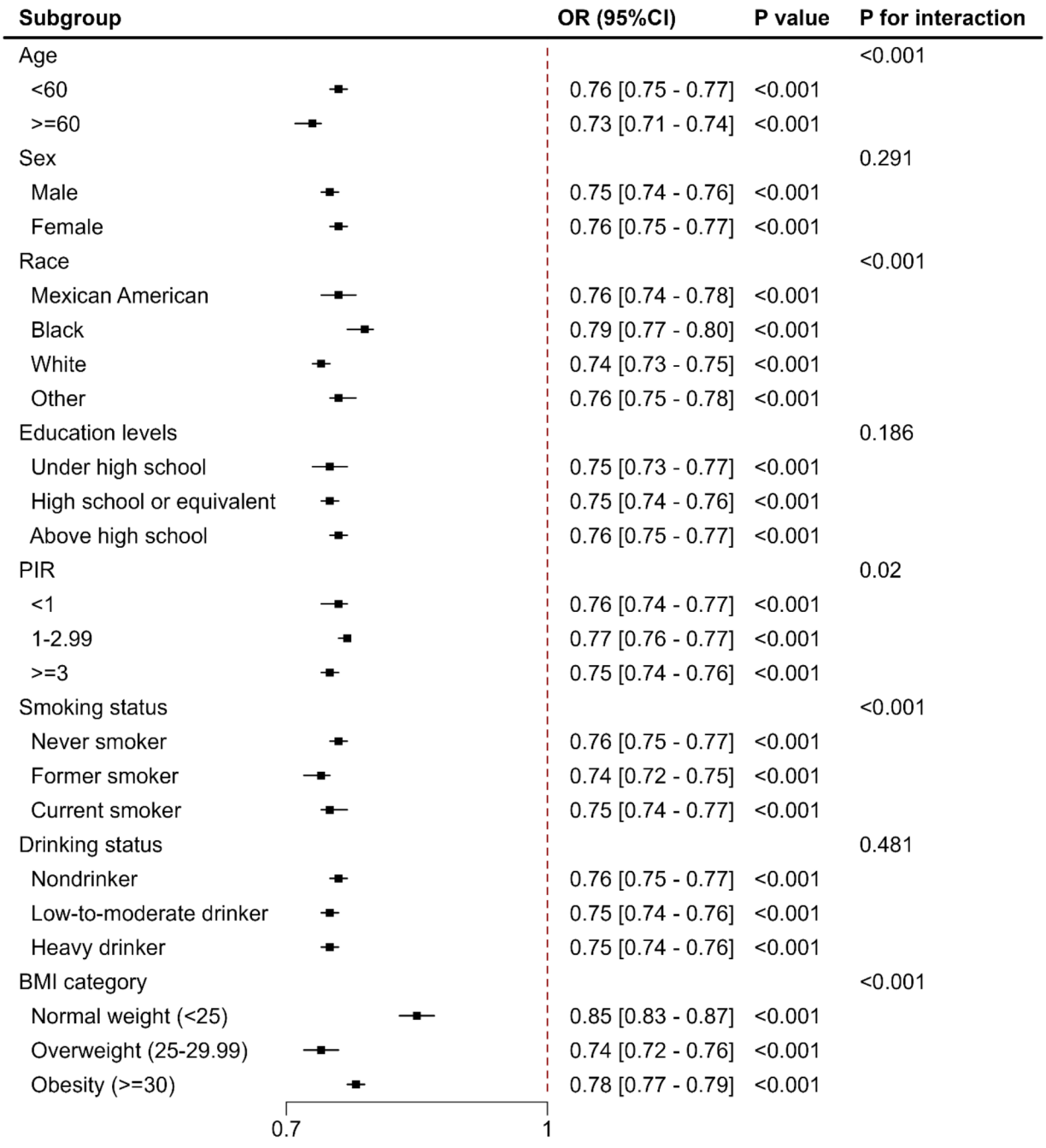

Fig. 2 Subgroup analysis of the association between eGDR and MetS
Adjusted for age, gender, race, family income poverty ratio, education level, marital status, smoking status, drinking status, TC, ALB, ALT, AST, BUN, UA, eGFR, and CVD. OR: odds ratio, CI: confidence interval

Incremental predictive value of eGDR

The eGDR significantly improved predictive power for all-cause mortality ($p = 0.007$), whereas no significant improvement was observed for CVD mortality ($p = 0.116$) when compared to the original model. Furthermore, neither the TyG index nor HOMA-IR demonstrated superior predictive performance for either outcome ($p > 0.05$) (Table 4). Notably, the NRI analysis revealed significant

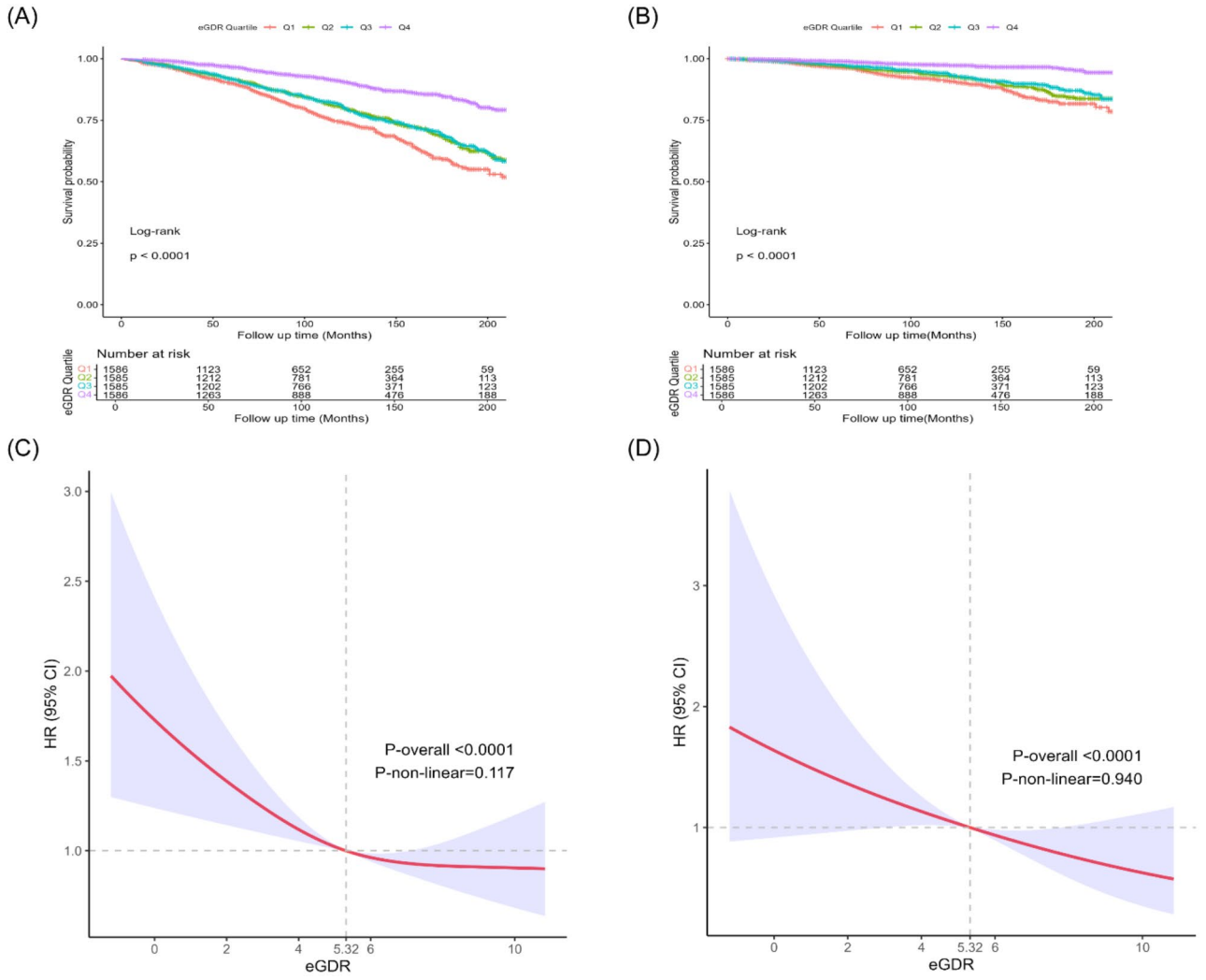

Fig. 3 Kaplan–Meier survival analysis of eGDR quartiles with all-cause mortality (**A**) and CVD mortality (**B**) in the MetS population. Restricted cubic spline analysis of the association between eGDR and all-cause (**C**) and CVD (**D**) mortality. Red lines represent references for hazard ratios, and blue areas represent 95% confidence intervals. The model was adjusted for age, gender, race, family income poverty ratio, education level, marital status, smoking status, drinking status, TC, ALB, ALT, AST, BUN, UA, eGFR, and CVD

reclassification improvements for all models in both all-cause and CVD mortality predictions (all $p < 0.05$).

Discussion

In the present study, we examined the relationship between the eGDR and the prevalence of MetS, as well as its association with all-cause and CVD mortality in individuals with and without MetS, utilizing data from the NHANES. The key findings are as follows: (1) A significant association was observed between eGDR and MetS prevalence, with RCS analysis revealing a non-linear relationship characterized by a sharp increase in MetS prevalence as eGDR decreased. (2) In individuals with MetS, eGDR was markedly associated with both all-cause and CVD mortality, exhibiting a linear relationship. (3) In contrast, among individuals without MetS, eGDR was only associated with CVD mortality, emphasizing the specific role of IR in cardiovascular risk. (4) C-statistic analysis showed that eGDR significantly improved the predictive accuracy for all-cause mortality in the MetS population, highlighting its potential as a valuable tool for clinical risk stratification compared to other IR indices, such as HOMA-IR and TyG. Collectively, these findings underscore the potential of eGDR as a reliable marker for identifying individuals at high risk of mortality in MetS populations, and highlight its role in improving long-term mortality prediction.

IR is a key pathophysiological driver of MetS and contributes to its development through multiple mechanisms, including disturbances in glucose and lipid homeostasis, endothelial dysfunction, and chronic low-grade inflammation. These processes collectively elevate

Table 3 Associations between eGDR and risk of all-cause and CVD mortality in the MetS population

	Model 1		Model 2		Model 3	
	HR (95% CI)	***p*-value**	**HR (95% CI)**	***p*-value**	**HR (95% CI)**	***p*-value**
All-cause mortality						
eGDR continues						
Per SD increase	0.69 (0.64, 0.74)	< 0.001	0.81 (0.74, 0.89)	< 0.001	0.89 (0.81, 0.98)	0.019
eGDR quartiles						
Q1	Ref		Ref		Ref	
Q2	0.78 (0.65, 0.92)	0.004	0.69 (0.58, 0.83)	< 0.001	0.79 (0.65, 0.96)	0.016
Q3	0.78 (0.64, 0.96)	0.020	0.79 (0.65, 0.97)	0.025	0.95 (0.77, 1.18)	0.655
Q4	0.32 (0.25, 0.41)	< 0.001	0.61 (0.48, 0.77)	< 0.001	0.74 (0.58, 0.93)	0.012
P for trend		< 0.001		< 0.001		0.088
CVD mortality						
eGDR continues						
Per SD increase	0.61 (0.54, 0.68)	< 0.001	0.70 (0.59, 0.83)	< 0.001	0.82 (0.72, 1.00)	0.048
eGDR quartiles						
Q1	Ref		Ref		Ref	
Q2	0.72 (0.53, 0.97)	0.033	0.63 (0.47, 0.84)	0.002	0.78 (0.56, 1.08)	0.134
Q3	0.70 (0.50, 0.98)	0.038	0.72 (0.50, 1.03)	0.074	0.98 (0.68, 1.40)	0.901
Q4	0.19 (0.12, 0.29)	< 0.001	0.39 (0.26, 0.58)	< 0.001	0.56 (0.36, 0.87)	0.010
P for trend		< 0.001		< 0.001		0.089

HR, Hazard Ratio; 95%CI, 95% Confidence interval

Model 1: No covariates were adjusted

Model 2: Age, gender, race, and family income poverty ratio were adjusted

Model 3: Age, gender, race, family income poverty ratio, education level, marital status, smoking status, drinking status, TC, ALB, ALT, AST, BUN, UA, eGFR, and CVD were adjusted

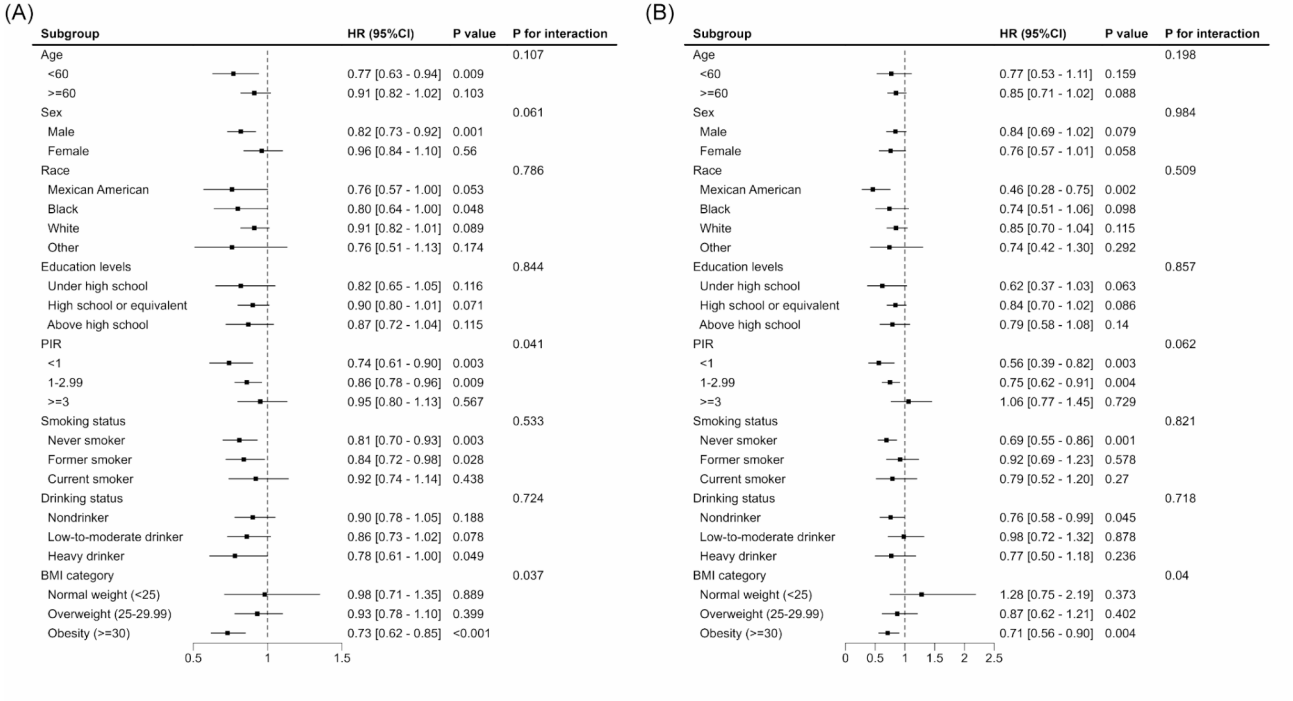

Fig. 4 Subgroup analysis of the association between eGDR and all-cause (B) and CVD mortality among individuals with MetS. Adjusted for age, gender, race, family income poverty ratio, education level, marital status, smoking status, drinking status, TC, ALB, ALT, AST, BUN, UA, eGFR, and CVD. HR: Hazard Ratio, CI: confidence interval

Table 4 Evaluation of model discrimination and risk reclassification for all-cause and cardiovascular mortality

Model	C-statistic (95%CI)	ΔC (95%CI)	*P*-value	NRI (95% CI)	*P*-value
All-cause mortality					
Basic model	0.824 (0.811, 0.836)	Ref		Ref	
Basic model + eGDR	0.825 (0.813, 0.837)	0.0014 (0.0004, 0.0024)	0.007	0.114 (0.056, 0.174)	< 0.001
Basic model + TyG	0.824 (0.812, 0.836)	0.0005 (-0.0004, 0.0013)	0.257	0.106 (0.055, 0.156)	< 0.001
Basic model + HOMA_IR	0.825 (0.812, 0.837)	0.0010 (-0.0001, 0.0020)	0.066	0.107 (0.062, 0.151)	< 0.001
CVD mortality					
Basic model	0.861 (0.842–0.880)	Ref		Ref	
Basic model + eGDR	0.863 (0.844–0.881)	0.0016 (-0.0004, 0.0035)	0.116	0.205 (0.109, 0.297)	< 0.001
Basic model + TyG	0.862 (0.844–0.881)	0.0009 (-0.0012, 0.0031)	0.397	0.114 (0.032, 0.200)	0.009
Basic model + HOMA_IR	0.862 (0.843–0.881)	0.0005 (-0.0007, 0.0017)	0.441	0.136 (0.065, 0.206)	< 0.001

Basic Model: Age, gender, race, family income poverty ratio, education level, marital status, smoking status, drinking status, TC, ALB, ALT, AST, BUN, UA, eGFR, and CVD were adjusted

the risk of cardiovascular and metabolic morbidity and mortality. IR impairs the ability of adipocytes to effectively take up glucose and store fat, leading to increased lipolysis and elevated levels of free fatty acids (FFAs) [9]. Visceral adipocytes, particularly, release FFAs during lipolysis, promoting hepatic fat accumulation and enhancing glucose production through gluconeogenesis, further exacerbating IR [25]. Prolonged elevated levels of FFAs lead to compensatory hyperinsulinemia to maintain normal blood glucose levels. However, sustained high FFAs can impair pancreatic β-cell function, ultimately contributing to the onset of diabetes [9]. Additionally, elevated FFAs stimulate the increased synthesis of TG and cholesterol esters, leading to increased production of triglyceride-rich low-density lipoproteins (VLDLs). VLDLs activate cholesterol ester transfer protein (CETP), which transfers TG to HDL, reducing HDL levels and contributing to atherogenic dyslipidemia a hallmark of IR and MetS [26]. IR can impair both vasoconstriction and diastolic function, contributing to endothelial dysfunction in the peripheral vasculature, and promoting the development of HTN [27, 28]. This process is primarily driven by diminished endothelial nitric oxide (NO) production and increased reactive oxygen species (ROS), both of which exacerbate vascular dysfunction [29]. Additionally, enhanced sympathetic nervous system activity and renin-mediated sodium retention further exacerbate vascular impairments, promoting the onset of HTN. Elevated plasma angiotensin II levels are commonly observed in obesity and IR [30]. Furthermore, research suggests that IR is associated with diminished levels of vascular endothelial growth factor (VEGF), a key mediator of vascular health, highlighting the complex interplay between metabolic dysregulation and vascular integrity [31, 32]. IR has been linked to the amplification of systemic inflammation [33]. Interleukin-6 (IL-6) activates various tissues, including vascular smooth muscle cells (VSMCs) and endothelial cells, driving the expression of vascular cell adhesion molecules (VCAMs) and stimulating local renin-angiotensin system (RAS) pathways [34]. Moreover, IR contributes to increased serum viscosity, promotes a prothrombotic environment, and enhances the release of pro-inflammatory cytokines from adipose tissue [35]. These factors collectively contribute to the progression of vascular atherosclerosis and dysfunction, significantly elevating the risks of CVD.

Given the complex interplay between IR and various pathophysiological mechanisms, early detection of individuals at risk for cardiovascular and metabolic disorders is crucial. eGDR, a non-invasive and efficient marker of IR, has been linked to complications such as retinopathy and nephropathy in young individuals with T1D [36], as well as clinical outcomes in patients with DM [17, 19]. In large cohorts of CKD patients without DM, higher eGDR levels were associated with a reduced risk of CVD and mortality [37]. Additionally, lower eGDR is independently associated with increased CVD risk and mortality in both the general population and non-diabetes [19, 38, 39]. These findings emphasize the utility of eGDR as a reliable tool for detecting individuals at high risk, irrespective of their glucose tolerance levels. In this study, eGDR shows promise as a valuable tool for identifying individuals at high risk of developing MetS and its associated complications. Our results demonstrate a significant negative association between eGDR and MetS prevalence. Stratification and interaction analyses revealed consistent findings across various subgroups, with significant interactions observed for age, race, PIR, smoking status, and BMI. Additionally, Cox regression and RCS analyses revealed a linear relationship between eGDR and mortality outcomes in the MetS population, with a significant increase in the risks of both all-cause and CVD mortality at lower eGDR levels. A significant interaction between eGDR and BMI was observed by stratification and interaction analyses, particularly in overweight individuals. The interaction between BMI and eGDR may be attributed to the fact that excess body fat, especially visceral

fat, exacerbates IR, inflammation, and endothelial dysfunction [40, 41]. These factors, in turn, increase the risk of adverse cardiovascular and metabolic outcomes. Therefore, eGDR may serve as a more robust predictor of mortality in obese individuals, where the presence of obesity amplifies the pathological effects of IR. Finally, we assessed the predictive performance of eGDR in comparison with other IR indices, including the TyG index and HOMA-IR, within the context of MetS and its associated mortality risks. Using Harrell's C-index, we found that the inclusion of eGDR significantly improved the model's predictive power for all-cause mortality ($p = 0.007$), highlighting its substantial prognostic value in identifying individuals at elevated risk. However, no significant improvement was observed in CVD mortality ($p = 0.116$), likely due to the small number of CVD deaths (369 cases, 4.4%). A larger sample size may be necessary to fully evaluate eGDR's predictive potential for CVD-specific mortality. In contrast, neither the TyG index nor HOMA-IR demonstrated superior predictive performance for either all-cause or CVD mortality ($p > 0.05$), which suggests that these IR indices may not offer additional value in predicting long-term mortality outcomes in this cohort. This finding underscores the potential of eGDR as a more effective tool for risk stratification in MetS patients, particularly in relation to overall survival.

Several strengths of the present study merit attention. First, the study utilizes an extensive, nationally representative sample of U.S. adults, and the application of sampling weights enhances the reliability and statistical power of the results. Moreover, data collection followed standardized procedures, minimizing the potential for selection bias. Given that IR is a long-term process, the relatively long follow-up period (mean: 8.62 years) strengthens the assessment of its impact on cardiovascular prognosis, offering valuable insights into its prognostic value. Another key strength lies in the comparison of eGDR with other widely used IR markers, such as the TyG index and HOMA-IR. This comparative analysis provides valuable insights into the relative predictive power of eGDR for mortality outcomes, further advancing our understanding of its clinical utility. However, several limitations should be acknowledged. First, The cross-sectional nature of the NHANES dataset limits the ability to draw definitive causal inferences. While the longitudinal analysis of mortality outcomes helps establish associations, the study cannot conclusively determine the directionality of these relationships. Second, although we adjusted for a wide range of potential confounders, residual confounding from unmeasured variables cannot be fully excluded. Third, the study's reliance on a single measurement of eGDR and its associated indices, while providing valuable insights, does not account for potential fluctuations over time, which may affect the accuracy of long-term risk predictions. Finally, the study was limited to the U.S. population because it relied on data from the NHANES database, which exclusively collects information on U.S. residents. As a result, the generalizability of our findings to other populations may be limited.

Conclusion

This study highlights the significant association between eGDR and the prevalence of MetS, as well as its predictive value for long-term mortality outcomes, particularly CVD mortality, in both MetS and non-MetS populations. Our findings suggest that eGDR is a valuable tool for assessing mortality risk and may provide superior predictive power compared to other IR markers such as the TyG index and HOMA-IR. Further studies are needed to validate these findings in diverse populations and assess the full potential of eGDR in clinical practice.

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12933-025-02599-7 .

Supplementary Material 1

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Author contributions

Xiaoli Chen conceived the research and interpreted the results. Xiaoli Chen and Aihua Li conducted the data collection and analysis. Xiaoli Chen drafted the manuscript, which was revised by Qilin Ma. All authors approved the final version of the manuscript.

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Availability of data and materials

No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate

Ethics approval for this study was granted by the Committee on Human Research at the University of California, San Francisco.

Consent for publication

Not applicable.

Competing interests

The authors declare no competing interests.

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