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Association between estimated glucose disposal rate and prediction of cardiovascular disease risk among individuals with cardiovascular-kidney-metabolic syndrome stage 0–3: a nationwide prospective cohort study

Jing Tian[1], Hu Chen[2], Yan Luo[1], Zhen Zhang[1], Shiqiang Xiong[1,3*] and Hanxiong Liu[1*]

Abstract

Background Insulin resistance is a crucial factor in the development of cardiovascular diseases (CVD), yet the relationship between the estimated glucose disposal rate (eGDR), an index reflecting insulin resistance, and the risk of new-onset CVD among individuals with cardiovascular-kidney-metabolic (CKM) syndrome stage 0–3 remains underexplored, and large-scale prospective cohort studies are needed to clarify this relationship.

Methods All data for this study were extracted from the China Health and Retirement Longitudinal Study (CHARLS). The primary outcome was the incidence of new-onset CVD (including heart diseases (HD) and stroke) during the follow-up period (from 2013 to 2020). Multivariable logistic regression models were applied to elucidate the relationship between the eGDR and the risk of developing CVD. The restricted cubic splines (RCS), mediation analysis, and stratified analyses were also employed.

Results This study included 6752 participants, of whom 1495 (22%) developed CVD. Odds ratios and 95% confidence intervals from lowest eGDR level (<7.37 mg/kg/min) to highest eGDR level (≥ 11.16 mg/kg/min) were 1.00 (reference), 0.81 (0.68, 0.96), 0.72 (0.58, 0.88), and 0.74 (0.58, 0.94) respectively, for the occurrence of CVD; 1.00 (reference), 0.81 (0.67,0.97), 0.72 (0.57,0.90), and 0.75 (0.58,0.97) respectively, for the occurrence of HD; 1.00 (reference), 0.91 (0.74,1.12), 0.80 (0.62,1.04), and 0.71 (0.52,0.97) respectively, for the occurrence of stroke after adjusting for all potential covariates. The RCS analysis discovered an approximately inverse "L" correlation between eGDR and the occurrence of CVD and HD across all individuals with CKM syndrome stages 0–3 (All *P* for overall < 0.001, All *P* for nonlinear = 0.005), while there was a negative linear correlation between eGDR and the risk of new-onset stroke (*P* for overall = 0.026, *P* for

*Correspondence:
Shiqiang Xiong
xionglliu@163.com
Hanxiong Liu
lhanx@126.com

Full list of author information is available at the end of the article

nonlinear = 0.098). Furthermore, the proportions mediated through BMI were 41.98%, 43.05%, and 43.23% for CVD, HD and stroke, respectively. No significant interactions were found.

Conclusions The eGDR was a novel indicator of new-onset CVD in individuals with CKM syndrome stages 0–3, with BMI serving as a partial mediator in the association between eGDR and CVD risk. Addressing insulin resistance may represent a viable strategy for reducing the risk of CVD in this population.

Keywords Estimated glucose disposal rate, Cardiovascular diseases, Cardiovascular-kidney-metabolic syndrome, Insulin resistance, CHARLS

Introduction

Cardiovascular diseases (CVD), diabetes mellitus, and chronic kidney disease remain the leading causes of mortality worldwide, in which overweight/obesity is a shared risk factor [1, 2]. Overweight/obesity, hyperglycemia, hypertension, dyslipidemia, chronic kidney disease, and cardiovascular disease are common comorbidities in the population, with multidirectional associations among these conditions [3, 4, 5, 6]. To further investigate pathophysiological interactions of metabolic risk factors (such as obesity, diabetes) renal, and cardiac, the President of the American Heart Association provides a framework for cardiovascular-kidney-metabolic (CKM) [7]. A study from the National Health and Nutrition Examination Survey from 2011 to 2020 showed a prevalence of CKM stages 0–3 at about 91.8%, and the prevalence of each stage did not change significantly with the study period [8]. Poor CKM health leads to premature death, greater risk of CVD, heightened healthcare burden and decreased quality of life [7, 9]. However, there are fewer studies on the early identification of indicators of future CVD risk in individuals with CKM stage 0–3.

Insulin resistance (IR) is defined as an impaired response to insulin stimulation, which leads to abnormalities in glucose and lipid metabolism [10]. Earlier research revealed that IR is crucial in the development of CKM [7]. The hyperinsulinemic-euglycemic clamp is widely regarded as the gold standard for assessing IR [11]. However, the method of measurement is invasive and expensive and therefore unable to be widely used in clinical settings. Previous studies have shown that the estimated glucose disposal rate (eGDR), comprising glycated hemoglobin A1c (HbA1c), a history of hypertension, and waist circumference (WC), is a convenient approach to assessing IR and decreasing levels of eGDR are associated with worsened IR [12]. Additionally, previous studies have demonstrated that the eGDR has greater accuracy compared with the gold standard [13]. The eGDR is markedly superior in predicting coronary atherosclerosis when compared to the elements of the eGDR and other markers of insulin resistance (including the Homeostasis model assessment of insulin resistance (HOMA-IR) and triglyceride-glucose index) [14]. Substantial evidence suggests that a high level of eGDR decreases the risk of atherosclerotic cardiovascular disease, coronary heart disease, myocardial infarction, stroke, all-cause, and CVD mortality [13, 15]. However, little is known about the relationship between eGDR and the risk of CVD among patients with CKM syndrome stage 0–3.

Hence, considering the vital role of CKM syndrome in the occurrence and development of CVD, the relationship between eGDR and the occurrence of CVD across individuals with CKM syndrome stage 0–3 deserves to be investigated. This study may assist in deepening the understanding of CKM and justify early integrative interventions to ease the threat of CVD on the population.

Materials and methods

Study design and participants

The China Health and Retirement Longitudinal Study (CHARLS) is a nationally representative longitudinal survey of Chinese residents aged 45 and over, with participants selected through a multi-stage, stratified probability sampling method. The survey is designed to gather comprehensive data on middle-aged and older adults and to address the challenges of population aging. The CHARLS program launched with a national baseline survey (wave 1) in 2011–2012 and conducted five surveys through 2020 (wave 2 in 2013, wave 3 in 2015, wave 4 in 2018, and wave 5 in 2020), recruiting a total of 17,708 participants from 10,257 households covering 450 villages across 150 counties or districts in China [16]. Ethical approval for the CHARLS study was obtained from the Ethics Review Board of Peking University (IRB00001052-11015), and each participant gave informed written consent before being involved in the study. Conducted in line with the principles of the Declaration of Helsinki, the study also adhered to the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines [17].

The flow diagram (Fig. 1) presents the inclusion and exclusion criteria for this study. Participants meeting any of the following criteria were also excluded: (1) lack of age information ($n = 9$); (2) those aged under 45 years old ($n = 477$); (3) participants lacking information on CVD ($n = 240$); (4) participants who had CVD at baseline ($n = 2721$); (5) participants with missing waist measurement ($n = 3027$); (6) participants with missing glycated hemoglobin A1c (HbA1c) measurement ($n = 1326$); (7)

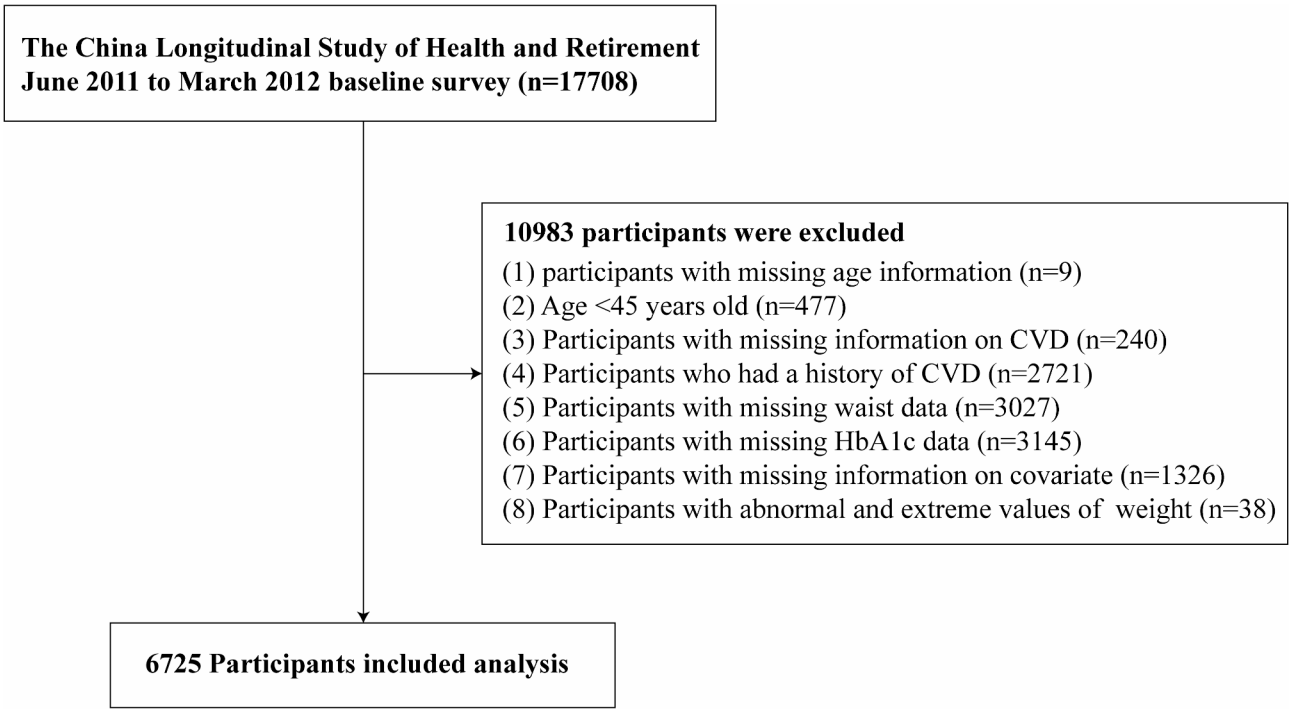

Fig. 1 Flow chart of the study participants
CVD cardiovascular diseases; *HbA1c* glycated hemoglobin A1c

participants lacking information on covariates ($n = 1326$); (8) participants with abnormal and extreme values of weight ($n = 38$). Finally, 6725 participants were enrolled in the present study.

Assessment of exposure

The calculation for eGDR (mg/kg/min), as previously described, is: eGDR = 21.158- (0.09*WC) - (3.407*HT) -(0.551*HbA1c), with WC representing waist circumference in centimeters, HT indicating hypertension status (1 for yes, 0 for no), and HbA1c denoting the percentage of HbA1c [13, 18]. Trained examiners collected body measurements (including height, weight, and WC) from all participants [16]. The definition of hypertension included the use of medications for high blood pressure, a self-reported diagnosis from a physician, or an average systolic blood pressure of at least 140 mmHg or diastolic blood pressure of at least 90 mmHg from three consecutive measurements. HbA1c was obtained by testing whole blood samples collected. HbA1c measurements were performed at the Youanmen Center for Clinical Laboratory of Capital Medical University. Assays use a High Performance Liquid Chromatography (HPLC) system.

Assessment of outcome

The study primarily aimed to observe the occurrence of CVD, which was a composite event including heart diseases (HD) and stroke. The incidence of HD is established by the following question: "Have you been diagnosed by a doctor with heart disease, coronary artery disease, angina, congestive heart failure, or any other heart problem? Likewise, the development of a stroke is confirmed by the question, "Have you been diagnosed with a stroke by a doctor? CVD was identified as self-reported HD and stroke. If a participant stated a heart disease or stroke in the previous wave of surveys, the condition of CVD needed to be reconfirmed in the next wave of surveys. If individuals refused a previous self-reported diagnosis of HD or stroke, these inconsistencies were rectified by retrospective methods. The confirmation of CVD in this study was consistent with our previous studies using CHARLS [19].

Definition of CKM syndrome stage 0–3

According to the AHA Presidential Advisory Statement on CKM Syndrome, CKM syndrome is classified as stages 0 to 3 [7]. The stages are as follows: stage 0 has no risk factors for CKM syndrome; Stage 1 is defined by excess adiposity or dysfunction; Stage 2 comprises metabolic risk factors or chronic kidney disease (CKD); and Stage 3 includes subclinical cardiovascular disease. In this categorization, stage G4 or G5 CKD, which is considered very high-risk, and a high 10-year CVD risk as estimated by the Framingham Risk Score were regarded as equivalent risks for subclinical CVD [20]. The Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) formula was used to compute estimating glomerular

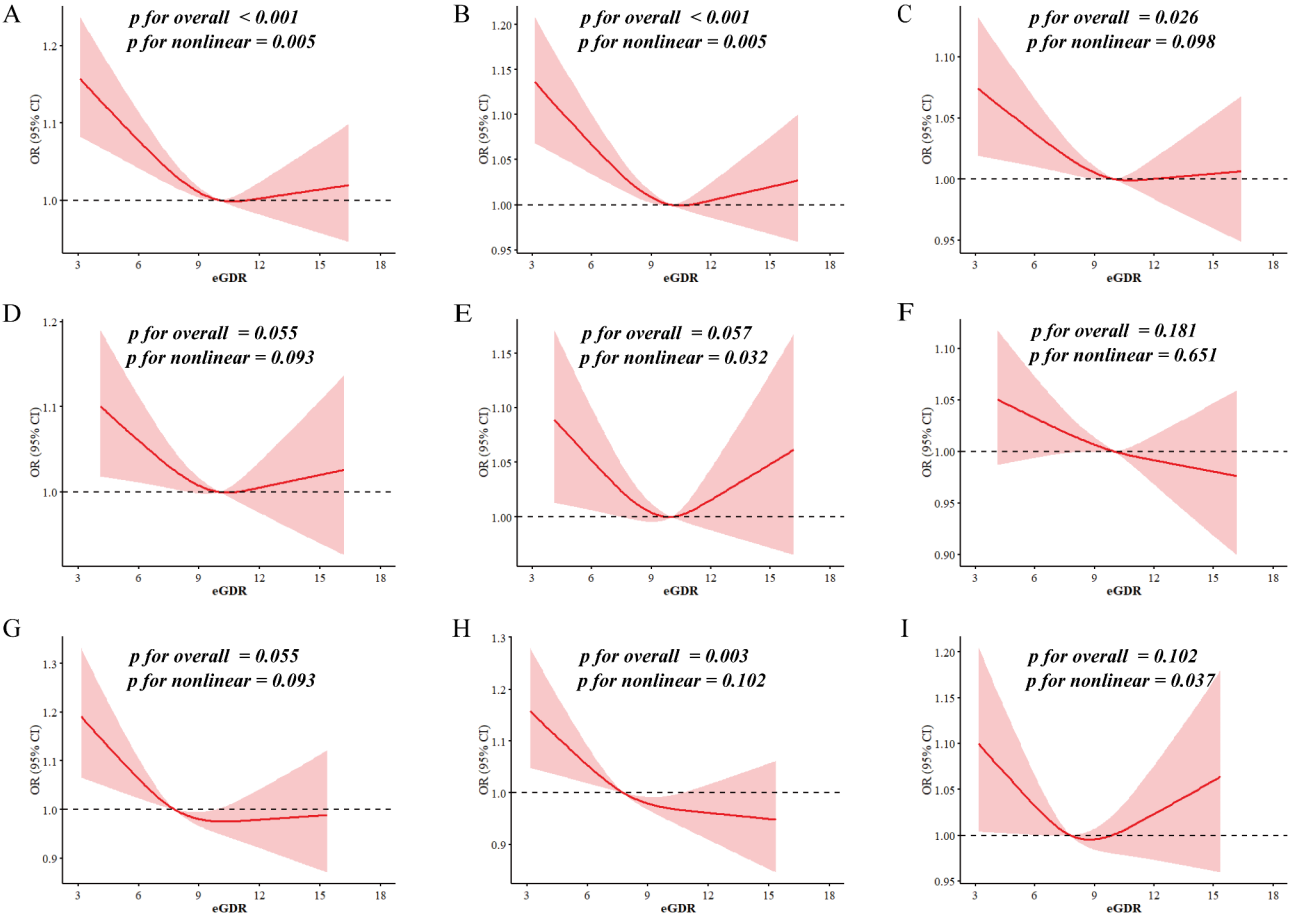

Fig. 2 Restricted cubic spline curve for the association between the eGDR and outcome. **A**, **B**, and **C** indicate the relationship between eGDR and the risk of new-onset CVD, HD, and stroke among individuals with CKM stages 0–3, respectively. **D**, **E**, and **F** indicate the relationship between eGDR and the risk of new-onset CVD, HD, and stroke among individuals with CKM stage 2, respectively. **G**, **H**, and **I** indicate the relationship between eGDR and the risk of new-onset CVD, HD, and stroke among individuals with CKM stage 3, respectively. Red lines represent the odds ratio, and red areas represent 95% confidence intervals. The model was adjusted for age, sex, race, BMI, hukou, marital status, education levels, alcohol use, smoking status, the coexistence of diseases (diabetes, dyslipidemia, depression, cancer, and sleep problems), SBP, DBP, eGFR, TG, HDL-c, LDL-c, CRP, UA, and HGB. The restricted cubic spline regression models were conducted with 3 knots at the 10th, 50th, and 90th percentiles of eGDR and the risk of new-onset CVD (including heart diseases and stroke)
eGDR estimated glucose disposal rate; *CVD* Cardiovascular diseases; *HD* heart diseases; *CKM* Cardiovascular-Kidney-Metabolic; *BMI* body mass index; *SBP* systolic blood pressure; *DBP* diastolic blood pressure; *eGFR* estimation of glomerular filtration rate; *TG* triglyceride; *HDL-c* high-density lipoprotein cholesterol; *LDL-c* low-density lipoprotein cholesterol; *CRP* C-reactive protein; *UA* uric acid; *HGB* Hemoglobin

filtration rate (eGFR) [21], which was then classified into CKD stages according to the Kidney Disease Improvement Global Outcomes (KDIGO) [7].

Assessment of covariates

Potential confounders, including various demographic and health-related factors, were sourced from the CHARLS database. This comprehensive information includes details such as age, sex (male/female), body mass index (BMI), systolic blood pressure (SBP), diastolic blood pressure (DBP), Hukou status (a household record that officially identifies a person as a permanent resident of an area) is divided into agricultural and other hukou (including urban and unified hukou), marital status (married/others), education levels (elementary school or below/middle school/high school or above), alcohol consumption (Participants who did not drink more than 12 times in the past 12 months were categorized as never drinkers, while current drinkers were defined as those who drank more than 12 times in the past 12 months), smoking status (individuals who had smoked fewer than 100 cigarettes throughout their lifetime were classified as never smokers, while those who had smoked 100 or more cigarettes but had quit were regarded as current smokers.), and disease status (including diabetes mellitus, dyslipidemia, cancer, depression, and sleep problems). Diabetes is identified through self-reported diagnosis, the use of insulin or oral hypoglycemic agents, fasting blood glucose (FBG) ≥ 126 mg/dL, or HbA1c level ≥ 6.5%, while prediabetes is determined by having FBG between 100 mg/dL and 125 mg/dL, or HbA1c between 5.7% and 6.4% [22]. Dyslipidemia can be defined by meeting any

of the following: (1) self-reported dyslipidemia; (2) currently taking lipid-lowering medications; and (3) laboratory lipid tests and detailed diagnostic criteria are readily available [23]. The 10-item short form of the Center for Epidemiologic Studies Depression Scale (CESD-10) was employed to evaluate depression, and those who scored ≥ 10 were deemed to have depressive symptoms [24]. Sleep quality was evaluated by inquiring about the average number of hours slept each night during the previous month. In 2015, the National Sleep Foundation suggested that adults aged 18–64 years should sleep for 7 to 9 h daily, while those aged 65 and above should aim for 7 to 8 h [25]. Sleep duration that does not meet the recommendations represents a sleep disorder. Laboratory tests such as triglyceride (TG), total cholesterol (TC), high-density lipoprotein cholesterol (HDL-c), low-density lipoprotein cholesterol (LDL-c), blood urea nitrogen (BUN), serum creatinine (Scr), C-reactive protein (CRP), uric acid (UA), and hemoglobin (HGB) were also collected.

Statistical analysis

Data normality was tested by the Shapiro–Wilk test. Non-normally distributed Continuous variables were expressed as the median with interquartile range (IQR), while categorical variables appeared as the frequency with percentage (%). Baseline characteristics among the groups were analyzed using the Kruskal-Wallis H test or the Wilcoxon rank-sum test for continuous variables, and the chi-squared test or Fisher's exact test for categorical variables.

To examine the odds ratios (OR) and 95% confidence intervals (CI) regarding the association between eGDR and the risk of primary and secondary outcomes, multivariate logistic regression models were employed. Univariate logistic regression analyses were employed to estimate the relationship between variables and the incidence of cardiovascular disease. Clinically significant factors from previous studies and variables with *P* values ≤ 0.10 in univariate logistic regression analyses were included in multivariate logistic regression analyses. Four models were developed to account for potential confounding factors. The crude model was unadjusted; Model 1 was only adjusted for age, sex, race, BMI, hukou, marital status, and education levels; Model 2 further adjusted (from Model 1) for alcohol use, smoking status, the coexistence of diseases (diabetes, dyslipidemia, depression, cancer, and sleep problems). Model 3 was further adjusted (from Model 2) for SBP, DBP, eGFR, TG, HDL-c, LDL-c, CRP, UA, and HGB. In the multicollinearity test (Table S1), we established the variance inflation factors for each variable in the analysis, with all being less than 5, meaning that no significant multicollinearity exists [26]. Besides, to determine whether there was a nonlinear dose-response relationship between eGDR and the risk of outcomes after multivariable adjustment, restricted cubic spline curves (RCS) with three knots at the 10th, 50th, and 90th percentiles were applied to individuals with CKM syndrome stages 0 to 3, CKM stage 2, and CKM stage 3, respectively.

Mediation analysis was used to quantify the extent to which BMI mediated the relationship between eGDR and primary and secondary outcomes. Specifically, we employed logistics regression to analyze the outcome and linear regression for the mediator. We used residual correlation plots to assess normality and linearity. The mediated proportion was obtained as the difference between the estimated total effect size and the estimated direct effect size divided by the estimated total effect size. The significance of the mediating effect was assessed through the examination of 1000 bootstrap samples.

Stratified analyses and potential interactions applied to stratify age (< 60 years old or ≥ 60 years old), sex (male or female), BMI (< 23 kg/m2 or ≥ 23 kg/m2), smoking status (never smoker or current smoker), drinking status (non-drinker or current drinker), dyslipidemia (no or yes), diabetes mellitus (no or prediabetes/diabetes), and CKM stage (stage 0–2 or stage 3). All statistical analyses were conducted using R software version 4.3.2 (http://www.R-project.org/). A two-tailed *P* value < 0.05 was considered statistically significant.

Results

Baseline characteristics of the study participants

Of the 17,708 people surveyed at baseline between June 2011 and March 2012, 6752 were recruited for analysis. Of these, 48% were male and 52% female. The median (IQR) for age, BMI, and WC for all participants were 58 (51,62), 23.0 (20.8,25.5), and 84 (78,91) respectively. Participants were categorized according to eGDR quartiles (Q) as shown in Table 1. Participants with higher eGDR quartiles were likely to be younger, female, married, agriculture hukou, less educated, have lower BMI, WC, SBP, DBP, WBC, HGB, CRP, FBG, TC, TG, LDL-c, UA, Scr, fewer comorbidities (such as hypertension, diabetes, and dyslipidemia), and lower new-onset CVD (including new-onset HD and new-onset stroke). Conversely, HDL-c and eGFR were significantly higher. History of smoking and alcohol consumption, along with depression symptoms were statistically significant among the groups; however, no significant differences were found in the history of cancer, sleep problems, platelet (PLT), and BUN.

Table S2 provides a comprehensive overview of baseline characteristics according to the occurrence of CVD, revealing no significant differences in hukou, marital status, education levels, smoking status, history of cancer, PLT, BUN, Scr, UA, and HGB ($P > 0.05$). The overall

Table 1 Baseline characteristics of individuals classified by quartiles of the eGDR

Characteristic	Overall (*n* = 6,725)	Q1 (< 7.37) (*n* = 1,689)	Q2 (7.37,10.04) (*n* = 1,677)	Q3 (10.04,11.16) (*n* = 1,692)	Q4 (≥ 11.16) (*n* = 1,667)	*P* value [a]
Age, years	58 (51, 64)	60 (54, 66)	59 (53, 66)	56 (49, 62)	57 (51, 63)	**< 0.001**
Sex						**0.003**
Male	3,228 (48.00%)	746 (44.17%)	817 (48.72%)	828 (48.94%)	837 (50.21%)	
Female	3,497 (52.00%)	943 (58.83%)	860 (51.28%)	864 (51.06%)	830 (49.79%)	
Hukou						**< 0.001**
Agriculture	5,739 (85.34%)	1,377 (81.53%)	1,413 (84.26%)	1,454 (85.93%)	1,495 (89.68%)	
Others	986 (14.66%)	312 (18.47%)	264 (15.74%)	238 (14.07%)	172 (10.32%)	
Marital status						**< 0.001**
Married	6,028 (89.64%)	1,504 (89.05%)	1,450 (86.46%)	1,566 (92.55%)	1,508 (90.46%)	
Others	697 (10.36%)	185 (10.95%)	227 (13.54%)	126 (7.45%)	159 (9.54%)	
Education levels						**0.002**
Elementary school or below	4,686 (69.68%)	1,200 (71.05%)	1,199 (71.50%)	1,113 (65.78%)	1,174 (70.43%)	
Middle school	1,366 (20.31%)	318 (18.83%)	330 (19.68%)	399 (23.58%)	319 (19.14%)	
High school or above	673 (10.01%)	171 (10.12%)	148 (8.83%)	180 (10.64%)	174 (10.44%)	
BMI, kg/m^2	23.0 (20.8, 25.5)	25.7 (23.6, 28.0)	23.2 (20.8, 26.2)	23.2 (21.7, 24.7)	20.5 (19.1, 21.9)	**< 0.001**
Waist, cm	84 (78, 91)	93 (88, 98)	84 (78, 95)	85 (82, 88)	75 (71, 78)	**< 0.001**
SBP, mmHg	127 (114, 142)	146 (137, 160)	133 (121, 148)	118 (110, 127)	116 (108, 126)	**< 0.001**
DBP, mmHg	75 (67, 83)	84 (76, 92)	78 (71, 86)	70 (64, 77)	69 (63, 75)	**< 0.001**
Smoking status						**< 0.001**
Never	4,038 (60.04%)	1,090 (65.54%)	984 (58.68%)	1,021 (60.34%)	943 (56.57%)	
Current	2,687 (39.96%)	599 (35.46%)	693 (41.32%)	671 (39.66%)	724 (43.43%)	
Drinking status						**0.013**
Never	4,913 (73.06%)	1,285 (76.08%)	1,201 (71.62%)	1,224 (72.34%)	1,203 (72.17%)	
Current	1,812 (26.94%)	404 (23.92%)	476 (28.38%)	468 (27.66%)	464 (27.83%)	
Hypertension						**< 0.001**
No	4,095 (60.89%)	10 (0.59%)	764 (45.56%)	1,689 (99.82%)	1,632 (97.90%)	
Yes	2,630 (39.11%)	1,679 (99.41%)	913 (54.44%)	3 (0.18%)	35 (2.10%)	
Diabetes						**< 0.001**
No	2,715 (40.37%)	462 (27.35%)	596 (35.54%)	740 (43.74%)	917 (55.01%)	
Prediabetes/ diabetes	4,010 (59.63%)	1,227 (72.65%)	1,081 (64.46%)	952 (56.25%)	750 (44.99%)	
Dyslipidemia						**< 0.001**
No	2,077 (30.88%)	286 (16.93%)	501 (29.87%)	539 (31.86%)	751 (45.05%)	
Yes	4,648 (69.12%)	1,403 (83.07%)	1,176 (70.13%)	1,153 (68.14%)	916 (54.95%)	
Cancer						0.617
No	6,668 (99.15%)	1,674 (99.11%)	1,662 (99.11%)	1,675 (99.00%)	1,657 (99.40%)	
Yes	57 (0.85%)	15 (0.89%)	15 (0.89%)	17 (1.00%)	10 (0.60%)	
depression						**0.012**
No	4,345 (64.61%)	1,114 (65.95%)	1,070 (63.80%)	1,130 (66.78%)	1,031 (61.85%)	

Table 1 (continued)

Characteristic	Overall (*n* = 6,725)	Q1 (< 7.37) (*n* = 1,689)	Q2 (7.37,10.04) (*n* = 1,677)	Q3 (10.04,11.16) (*n* = 1,692)	Q4 (≥ 11.16) (*n* = 1,667)	*P* value [a]
Yes	2,380 (35.39%)	575 (34.04%)	607 (36.20%)	562 (33.22%)	636 (38.15%)	
CVD						**< 0.001**
No	5,230 (77.77%)	1,157 (68.50%)	1,294 (77.16%)	1,385 (81.86%)	1,394 (83.62%)	
Yes	1,495 (22.23%)	532 (31.50%)	383 (22.84%)	307 (18.14%)	273 (16.38%)	
Sleep problems						0.203
No	3,018 (44.88%)	750 (44.40%)	721 (42.99%)	785 (46.39%)	762 (45.71%)	
Yes	3,707 (55.12%)	939 (55.60%)	956 (57.01%)	907 (53.61%)	905 (54.29%)	
Heart diseases						**< 0.001**
Yes	1,178 (17.52%)	408 (24.16%)	296 (17.65%)	249 (14.72%)	225 (13.50%)	
No	5,547 (82.48%)	1,281 (75.84%)	1,381 (82.35%)	1,443 (85.28%)	1,442 (86.50%)	
Stroke						**< 0.001**
Yes	823 (12.24%)	298 (17.64%)	221 (13.18%)	171 (10.11%)	133 (7.98%)	
No	5,902 (87.76%)	1,391 (82.36%)	1,456 (86.82%)	1,521 (89.89%)	1,534 (92.02%)	
WBC[b],(×10^9/L)	6.00 (4.99, 7.21)	6.20 (5.20, 7.50)	6.00 (5.00, 7.20)	5.90 (4.90, 7.20)	5.70 (4.70, 6.90)	**< 0.001**
PLT[b],(×10^9/L)	207 (162, 255)	208 (165, 259)	206 (159, 255)	208 (160, 255)	205 (162, 250)	0.178
BUN[b], mg/dl	15.2 (12.5, 18.2)	15.2 (12.7, 18.2)	15.2 (12.6, 18.3)	15.2 (12.5, 18.2)	15.1 (12.5, 18.2)	0.822
FBG, mg/dl	102 (94, 113)	106 (98, 120)	103 (96, 116)	101 (94, 110)	98 (92, 107)	**< 0.001**
Scr, mg/dl	0.76 (0.64, 0.88)	0.77 (0.67, 0.89)	0.76 (0.66, 0.88)	0.75 (0.64, 0.87)	0.75 (0.63, 0.86)	**< 0.001**
TC, mg/dl	191 (167, 215)	198 (173, 225)	191 (170, 216)	190 (166, 215)	182 (161, 207)	**< 0.001**
TG, mg/dl	104 (74, 152)	129 (92, 189)	107 (75, 159)	100 (73, 143)	86 (64, 121)	**< 0.001**
HDL-c, mg/dl	49 (41, 60)	46 (38, 54)	49 (40, 60)	50 (41, 60)	55 (45, 65)	**< 0.001**
LDL-c, mg/dl	114 (93, 137)	119 (97, 145)	114 (93, 137)	114 (93, 137)	108 (89, 130)	**< 0.001**
CRP, mg/l	1.01 (0.54, 2.08)	1.43 (0.75, 2.79)	1.06 (0.56, 2.14)	0.89 (0.52, 1.83)	0.74 (0.43, 1.48)	**< 0.001**
HbA1c,%	5.10 (4.90, 5.40)	5.30 (5.00, 5.60)	5.20 (4.90, 5.50)	5.10 (4.90, 5.40)	5.00 (4.80, 5.20)	**< 0.001**
UA, mg/dl	4.28 (3.56, 5.13)	4.57 (3.78, 5.47)	4.37 (3.59, 5.23)	4.18 (3.52, 4.95)	4.07 (3.40, 4.84)	**< 0.001**
HGB, g/dl	14.20 (13.00, 15.50)	14.50 (13.30, 15.80)	14.30 (13.10, 15.60)	14.20 (13.00, 15.50)	13.90 (12.70, 15.10)	**< 0.001**
eGFR	95 (85, 103)	93 (82, 100)	94 (83, 102)	97 (87, 104)	97 (88, 104)	**< 0.001**
eGDR	10.03 (7.36, 11.15)	6.45 (5.91, 6.94)	8.48 (7.84, 9.49)	10.68 (10.39, 10.92)	11.66 (11.39, 11.99)	**< 0.001**
CKM stage						**< 0.001**
0	420 (6.25%)	0 (0.00%)	0 (0.00%)	73 (4.31%)	347 (20.82%)	
1	688 (10.23%)	0 (0.00%)	89 (5.31%)	351 (20.74%)	248 (14.88%)	
2	3,439 (51.14%)	787 (46.60%)	938 (55.93%)	956 (56.50%)	758 (45.47%)	
3	2,178 (32.39%)	902 (53.40%)	650 (38.76%)	312 (18.44%)	314 (18.44%)	

Data are presented as the median(interquartile range) or number (%), as appropriate

[a] P value was based on the Kruskal-Wallis H test, Pearson's Chi-squared test, or Fisher's exact test where appropriate

[b] Missing data: 4 for white blood cells; 1 for platelet; 1 for blood urea nitrogen

BMI body mass index, *CVD* Cardiovascular diseases, *SBP* systolic blood pressure, *DBP* diastolic blood pressure, *WBC* white blood cell, *PLT* platelet, *BUN* blood urea nitrogen, *FBG* fasting blood glucose, *Scr* Serum creatinine, *TC* total cholesterol, *TG* triglyceride, *HDL-c* high-density lipoprotein cholesterol, *LDL-c* low-density lipoprotein cholesterol, *CRP* C-reactive protein, *HbA1c* glycosylated hemoglobin A1c, *UA* uric acid, *HGB* Hemoglobin, *eGFR* estimation of glomerular filtration rate, *eGDR* estimated glucose disposal rate, *CKM* Cardiovascular-Kidney-Metabolic

prevalence rates of hypertension, hyperglycemia, and dyslipidemia were 39%, 60%, and 69% respectively. Compared with participants without CVD, participants with new-onset CVD were older, female, had higher BMI, WC, SBP, and DBP, tended to have a history of alcohol consumption and comorbidities (hypertension, hyperglycemia, dyslipidemia, sleep problems, and depression), and had a higher prevalence of new-onset HD, new-onset stroke, and CKM stage 3, and higher WBC, CRP, TG, TC, LDL-c, FBG, and HbA1c, but there was lower HDL-c, eGFR, and eGDR.

Relationship between the eGDR and outcome in participants with CKM syndrome stages 0–3

During follow-up between 2013 and 2020, a total of 1495 (22%) participants developed CVD, including 1178 from new-onset HD, and 823 from new-onset stroke. Multivariable logistic regression models were utilized to estimate the relationship between the eGDR and the risk of primary and secondary outcomes, as presented in Table 2. After full multivariable adjustment in Model 3, eGDR was inversely linked to the risk of new-onset CVD, new-onset HD, and new-onset stroke. The eGDR was transformed from a continuous variable to a categorical variable based on quartiles. Compared with Q1, Q4 had a decreased risk of new-onset CVD (OR = 0.43, 95% CI: 0.36–0.50), new-onset HD (OR = 0.64, 95% CI: 0.50–0.81), and new-onset stroke (OR = 0.64, 95% CI: 0.50–0.81) in the unadjusted model. The negative association of eGDR with the incidence of CVD, HD, and stroke remained steady after adjusting for age, sex, BMI, hukou, marital status, and education level in Model 1. In Model 2, eGDR was inversely linked to the risk of new-onset CVD and new-onset HD compared with Q1; for stroke, although no significant difference was found in Q2, a negative relationship was still observed in Q3 and Q4. OR and 95% CI from Q1 to Q4 were 1.00 (reference), 0.81 (0.68, 0.96), 0.72 (0.58, 0.88), and 0.74 (0.58, 0.94) respectively, for the occurrence of CVD; 1.00 (reference), 0.81 (0.67,0.97), 0.72 (0.57,0.90), and 0.75 (0.58,0.97) respectively, for the occurrence of HD; 1.00 (reference), 0.91 (0.74,1.12), 0.80 (0.62,1.04), and 0.71 (0.52,0.97) respectively, for the occurrence of stroke after adjusting for all potential covariates. Moreover, the findings revealed that the risk of new-onset CVD, HD, and stroke decreased with increasing eGDR (from Q1 to Q4) (P for trend < 0.05). After adjusting for all covariates in all individuals with CKM syndrome stages 0–3, the RCS curves showed an approximately inverse "L" correlation between eGDR and occurrence of CVD and HD (All P for overall < 0.001, All P for nonlinear = 0.005) (Fig. 2A and B), while there was a negative linear correlation between eGDR and the risk of new-onset stroke (P for overall = 0.026, P for nonlinear = 0.098) (Fig. 2 C). In participants with CKM syndrome stage 2, eGDR exhibited a negative linear relationship with the risk of new-onset CVD (P for overall = 0.055, P for nonlinear = 0.093) (Fig. 2D), new-onset stroke (P for overall = 0.181, P for nonlinear = 0.651) (Fig. 2F), and a U-shaped relationship with the risk of new-onset HD (P for overall = 0.057, P for nonlinear = 0.032) (Fig. 2E). Among participants with CKM stage 3, eGDR displayed a decreasing linear relation with the risk of new-onset CVD (P for overall = 0.055, P for nonlinear = 0.093) (Fig. 2G) and HD (P for overall = 0.003, P for nonlinear = 0.102) (Fig. 2H), while exhibiting a U-shaped correlation with the risk of new-onset stroke (P for overall = 0.102, P for nonlinear = 0.037) (Fig. 2I).

Mediation analysis

Mediation analyses revealed that BMI partially mediated the association between eGDR and outcome (Fig. 3). Specifically, in the unadjusted model, the indirect effects of eGDR mediated by BMI were found to be associated with CVD, HD, and stroke, accounting for 19.22%, 28.01%, and 16.58%, respectively. In the fully adjusted model, the proportions mediated through BMI were 41.98%, 43.05%, and 43.23% for CVD, HD, and stroke, respectively.

Subgroup analyses

To further assess the association between eGDR and the risk of CVD, HD, and stroke, several subgroup analyses and interactions were performed. The analyses were stratified by age, sex, BMI, smoking status, alcohol consumption, dyslipidemia, diabetes mellitus, and CKM stage. The results of the stratified analysis are shown in Table 3 and Table S3-S4. After adjusting for multiple factors, there was no significant interaction between the aforementioned subgroup characteristics and eGDR quantile for CVD, HD, and stroke (P for interaction > 0.05).

Discussion

In this prospective, nationwide longitudinal cohort study of participants aged 45 years and older with CKM syndrome stage 0–3 in China, a significantly inverse relationship between eGDR and the risk of new onset of CVD and HD was found after full adjustment for potential confounders, and participants with highest eGDR level (≥ 11.16 mg/kg/min) had a 29% lower risk of new-onset stroke. Moreover, the RCS regression analysis demonstrated a nearly L-shaped negative correlation between eGDR and the incidence of CVD and HD, with a negative linear relation to the risk of new-onset stroke. In addition, BMI partially mediated the association between eGDR and the risk of new-onset CVD, new-onset HD, and new-onset stroke. Subgroup analyses for varying demographic and clinical features further confirmed the reliability of our findings. The results of the study suggested that

Table 2 Association between the eGDR and outcome in participants with CKM syndrome stages 0–3

Characteristics	Crude model		Model 1		Model 2		Model 3	
	OR(95%CI)	*P*	OR(95%CI)	*P*	OR(95%CI)	*P*	OR(95%CI)	*P*
CVD								
eGDR(continuous)	0.86(0.84–0.88)	< 0.001	0.91(0.88–0.93)	< 0.001	0.92(0.89–0.95)	< 0.001	0.94(0.90–0.97)	< 0.001
eGDR quartiles								
Q1	Reference	—	Reference	—	Reference	—	Reference	—
Q2	0.64(0.55–0.75)	< 0.001	0.75(0.64–0.88)	< 0.001	0.77(0.65–0.91)	0.002	0.81(0.68–0.96)	0.017
Q3	0.48(0.41–0.57)	< 0.001	0.61(0.51–0.73)	< 0.001	0.64(0.54–0.77)	< 0.001	0.72(0.58–0.88)	0.002
Q4	0.43(0.36–0.50)	< 0.001	0.61(0.50–0.74)	< 0.001	0.65(0.53–0.80)	< 0.001	0.74(0.58–0.94)	0.014
P for trend		< 0.001		< 0.001		< 0.001		0.009
Heart disease								
eGDR(continuous)	0.88(0.86–0.91)	< 0.001	0.93(0.90–0.96)	< 0.001	0.94(0.91–0.97)	< 0.001	0.94(0.90–0.98)	0.004
eGDR quartiles								
Q1	Reference	—	Reference	—	Reference	—	Reference	—
Q2	0.67(0.57–0.80)	< 0.001	0.79(0.66–0.94)	0.008	0.80(0.67–0.96)	0.016	0.81(0.67–0.97)	0.026
Q3	0.54(0.45–0.64)	< 0.001	0.68(0.56–0.82)	< 0.001	0.71(0.58–0.86)	< 0.001	0.72(0.57–0.90)	0.004
Q4	0.49(0.41–0.59)	< 0.001	0.70(0.56–0.87)	0.002	0.73(0.59–0.92)	0.007	0.75(0.58–0.97)	0.029
P for trend		< 0.001		< 0.001		0.004		0.022
Stroke								
eGDR(continuous)	0.86(0.83–0.89)	< 0.001	0.90(0.87–0.94)	< 0.001	0.92(0.88–0.95)	< 0.001	0.95(0.90–0.99)	0.031
eGDR quartiles								
Q1	Reference	—	Reference	—	Reference	—	Reference	—
Q2	0.71(0.59–0.86)	< 0.001	0.80(0.66–0.98)	0.028	0.83(0.68–1.02)	0.074	0.91(0.74–1.12)	0.384
Q3	0.52(0.43–0.64)	< 0.001	0.63(0.50–0.78)	< 0.001	0.67(0.54–0.84)	< 0.001	0.80(0.62–1.04)	0.102
Q4	0.40(0.32–0.50)	< 0.001	0.53(0.41–0.69)	< 0.001	0.59(0.45–0.76)	< 0.001	0.71(0.52–0.97)	0.030
P for trend		< 0.001		< 0.001		< 0.001		0.025

Data are presented as OR(95%CI) and *P* value

Crude model: unadjusted;

Model 1: age, sex, body mass index, hukou, marital status, education levels were adjusted;

Model 2: age, sex, body mass index, hukou, marital status, education levels, smoking status, drinking status, diabetes, dyslipidemia, depression, cancer, and sleep problems were adjusted

Model 3: age, sex, body mass index, hukou, marital status, education levels, smoking status, drinking status, diabetes, dyslipidemia, depression, cancer, sleep problems, SBP, DBP, eGFR, TG, HDL-c, LDL-c, CRP, UA, and HGB were adjusted

eGDR estimated glucose disposal rate, *CKM* Cardiovascular-Kidney-Metabolic, *CVD* Cardiovascular diseases, *SBP* systolic blood pressure, *DBP* diastolic blood pressure, *eGFR* estimation of glomerular filtration rate, *TG* triglyceride, *HDL-c* high-density lipoprotein cholesterol, *LDL-c* low-density lipoprotein cholesterol, *CRP* C-reactive protein, *UA* uric acid, *HGB* Hemoglobin, *OR* Odds ratio, *CI* confidence interval

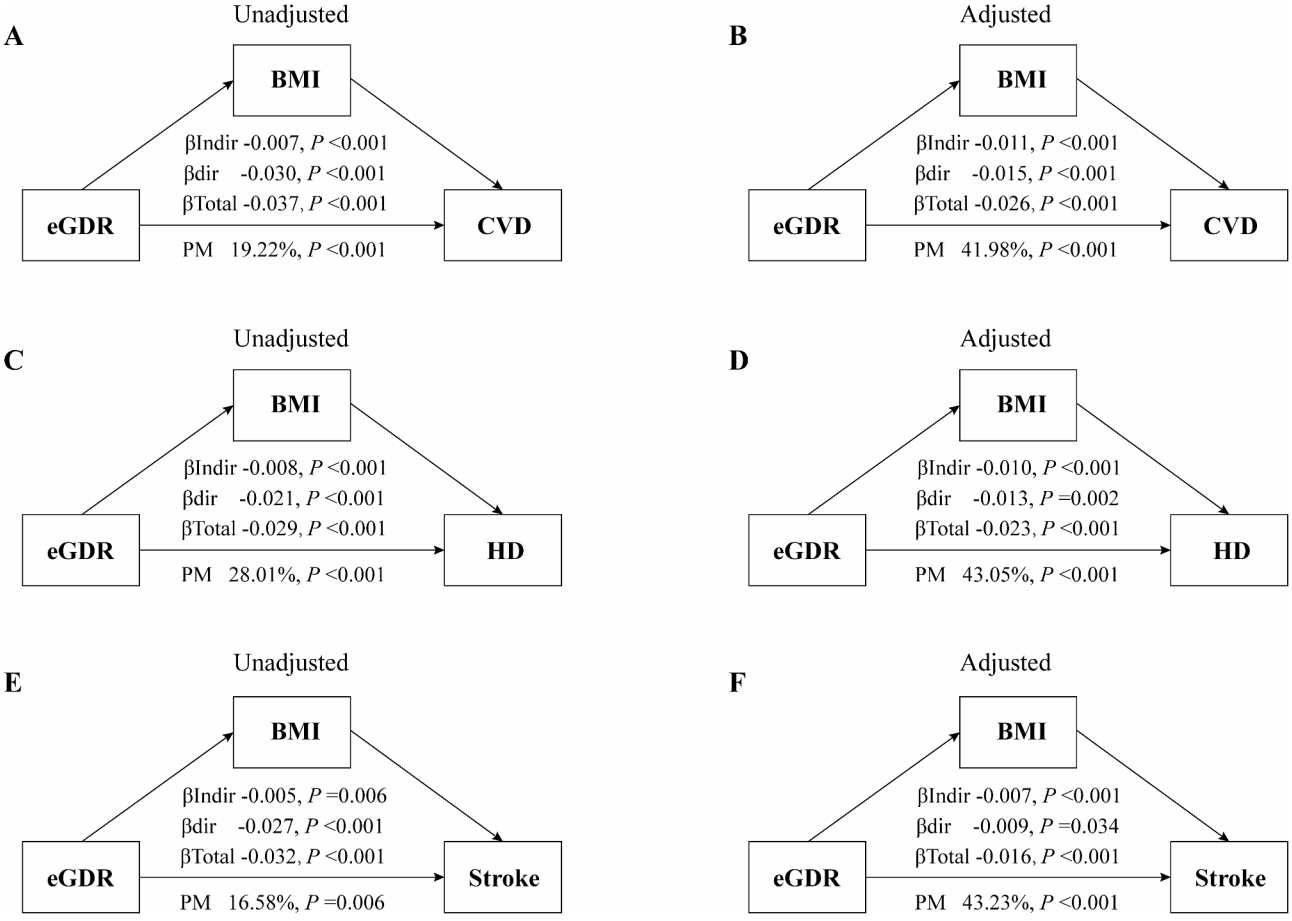

Fig. 3 BMI mediated the effect of eGDR and new-onset CVD, HD, and stroke in different adjusted models
BMI body mass index; *eGDR* estimated glucose disposal rate; *CVD* Cardiovascular diseases; HD heart diseases; *βIndir* Beta coefficients of Indirect effect; βdir Beta coefficients of direct effect; βtotal Beta coefficients of Total effect; PM proportion mediated

eGDR contributed to the early identification and prediction of individuals at high risk of CVD (including HD and stroke), with weight management and improvement of IR being critical to alleviating the risk of CVD [7].

WC is a powerful anthropometric parameter for the assessment of central obesity and visceral fat, which are strongly linked to IR [27, 28]. A meta-analysis revealed that increased fasting insulin concentrations or the HOMA-IR were connected with an increased risk of suffering from hypertension in the general population [29]. A Mendelian randomization analysis by Georgakis MK et al. found that increased HbA1c levels were connected with a high risk of ischemic stroke, especially large-artery and small-vessel stroke [30]. The eGDR, a composite of WC, history of hypertension, and HbA1c was considered a credible biomarker of IR, and the eGDR had concordance with the gold standard, the hyperinsulinemic-euglycemic clamp test [13]. The results of this study are well in line with other studies displaying the relationship between eGDR and the risk of CVD. Previous studies have suggested higher levels of eGDR are correlated with a lower risk of developing CVD (including stroke) in the general population or non-diabetic adults with CKD [31, 32]. A meta-analysis of five studies involving 19,960 individuals by Sun et al. indicated that elevated eGDR reduced the incidence of CVD and all-cause mortality among individuals with type 1 diabetes [33]. Similarly, a cross-sectional study involving 4725 Americans from the National Health and Nutrition Examination Survey (NHANES) showed that low eGDR (representing insulin resistance) increased the occurrence of CVD among participants with prediabetes and this relationship was linear [34]. In addition, a prospective cohort study from CHARLS enrolling 5512 non-diabetic participants demonstrated that per one standard deviation increment in eGDR decreased the risk of CVD, HD, and stroke by 17%, 13%, and 30%, respectively, and that obesity played a mediating role in the association between eGDR and the risk of CVD and HD [35]. It was notable that when eGDR increased to a certain level, the risk of CVD increased, which might be associated with underweight/wasting or sarcopenia [36, 37].

Table 3 Subgroup analysis for the association between eGDR and the risk of new-onset CVD among individuals with CKM syndrome stages 0–3

Subgroups	Event/Total	OR(95%CI)	*P* value	*P* for interaction
Age, years				0.089
< 60				
Q1	248/835	1.00	Reference	
Q2	184/881	0.76(0.59–0.97)	0.025	
Q3	171/1123	0.59(0.45–0.79)	< 0.001	
Q4	143/1025	0.64(0.45–0.89)	0.008	
≥ 60				
Q1	284/854	1.00	Reference	
Q2	199/796	0.86(0.68–1.10)	0.233	
Q3	136/569	0.86(0.63–1.17)	0.334	
Q4	130/642	0.84(0.60–1.18)	0.311	
Sex				0.164
Male				
Q1	229/746	1.00	Reference	
Q2	168/817	0.72(0.56–0.94)	0.014	
Q3	133/828	0.65(0.48–0.90)	0.008	
Q4	118/837	0.61(0.43–0.88)	0.008	
Female				
Q1	303/943	1.00	Reference	
Q2	215/860	0.89(0.70–1.12)	0.305	
Q3	174/864	0.76(0.57-1.00)	0.053	
Q4	155/830	0.85(0.61–1.17)	0.309	
BMI, Kg/m^2				0.109
< 23				
Q1	85/295	1.00	Reference	
Q2	180/811	0.75(0.55–1.03)	0.069	
Q3	139/766	0.68(0.47–0.98)	0.039	
Q4	233/1460	0.58(0.41–0.83)	0.003	
≥ 23				
Q1	447/1394	1.00	Reference	
Q2	203/866	0.75(0.60–0.93)	0.009	
Q3	168/926	0.59(0.46–0.76)	< 0.001	
Q4	40/207	0.65(0.43–0.96)	0.034	
Smoking status				0.950
Never smoker				
Q1	345/1090	1.00	Reference	
Q2	228/984	0.84(0.67–1.04)	0.114	
Q3	193/1021	0.77(0.59–0.99)	0.048	
Q4	157/943	0.81(0.59–1.10)	0.170	
Current smoker				
Q1	187/599	1.00	Reference	
Q2	155/693	0.77(0.58–1.02)	0.069	
Q3	114/671	0.65(0.46–0.91)	0.013	
Q4	116/724	0.65(0.44–0.96)	0.030	
Alcohol consumption				0.106
Non-drinker				
Q1	419/1285	1.00	Reference	
Q2	284/1201	0.85(0.70–1.04)	0.107	
Q3	220/1224	0.73(0.57–0.94)	0.013	
Q4	216/1203	0.90(0.68–1.19)	0.462	
drinker				
Q1	113/404	1.00	Reference	

Table 3 (continued)

Subgroups	Event/Total	OR(95%CI)	*P* value	*P* for interaction
Q2	99/476	0.72(0.51–1.02)	0.065	
Q3	87/468	0.66(0.44–0.99)	0.048	
Q4	57/464	0.40(0.24–0.65)	< 0.001	
Dyslipidemia				0.188
No				
Q1	76/286	1.00	Reference	
Q2	94/501	0.77(0.53–1.13)	0.174	
Q3	92/539	0.81(0.52–1.26)	0.349	
Q4	94/751	0.62(0.38–1.01)	0.052	
Yes				
Q1	456/1403	1.00	Reference	
Q2	289/1176	0.83(0.68-1.00)	0.054	
Q3	215/1153	0.68(0.53–0.86)	0.002	
Q4	179/916	0.81(0.61–1.06)	0.129	
Diabetes mellitus				0.374
No				
Q1	130/462	1.00	Reference	
Q2	132/596	0.92(0.67–1.25)	0.571	
Q3	134/740	0.82(0.58–1.17)	0.280	
Q4	143/917	0.84(0.56–1.25)	0.391	
prediabetes/diabetes				
Q1	402/1227	1.00	Reference	
Q2	251/1081	0.76(0.62–0.93)	0.009	
Q3	173/952	0.65(0.50–0.84)	0.001	
Q4	130/750	0.68(0.50–0.91)	0.011	
CKM stage				0.842
Stage 0–2				
Q1	233/787	1.00	Reference	
Q2	233/1027	0.86(0.68–1.08)	0.191	
Q3	246/1380	0.77(0.59-1.00)	0.054	
Q4	212/1353	0.80(0.59–1.09)	0.158	
Stage 3				
Q1	299/902	1.00	Reference	
Q2	150/650	0.76(0.58–0.99)	0.043	
Q3	61/312	0.65(0.45–0.95)	0.027	
Q4	61/314	0.73(0.48–1.10)	0.131	

The results were adjusted for all covariates except the corresponding stratification variable

eGDR estimated glucose disposal rate, *CVD* Cardiovascular diseases, *CKM* Cardiovascular-Kidney-Metabolic, *BMI* body mass index, *OR* odds ratio, *CI* confidence interval

The exact underlying mechanisms contributing to the occurrence of CVD among CKM stage 0–3 via IR remain unclear, and several potential pathways are worthy of consideration. Firstly, IR disturbed the balance of phosphatidylinositol 3-kinase (PI3K)-Akt and mitogen-activated protein kinase (MAPK) signaling pathways, which subsequently caused vascular smooth muscle cell proliferation and vasoconstriction, exacerbating vascular stiffness, blood pressure, and inflammation [38, 39, 40]. In addition, IR not only evoked endothelial dysfunction, foam cell formation, and vulnerable plaque formation, promoting the development of atherosclerosis, but also decreased permeability of the microcirculation [39, 41, 42]. Secondly, Insulin resistance is frequently accompanied by hyperglycemia, hypertension, disorders of lipid metabolism (including increased TG levels, decreased HDL-c, and elevated concentrations of small-particle LDL-c and free fatty acids), and abnormalities in visceral fat distribution (such as the heart and liver), all of which are risk factors for the development of CVD [43, 44, 45]. These factors lead to lipotoxicity and glucotoxicity in vascular endothelial cells, increased reactive oxygen species in organelles such as mitochondria, endoplasmic reticulum, and lysosomes, as well as an increased formation of advanced glycation end-products, which further result in vascular endothelial cell injury and infiltration

of inflammatory cells and inflammatory factors in cardiomyocytes, which leads to arterial stiffness, plaque instability, and myocardial remodeling [46, 47, 48]. Furthermore, IR induced chronic low-grade inflammation, which was characterized by a decrease in anti-inflammatory markers (such as adiponectin) and an increase in pro-inflammatory cytokines (such as tumor necrosis factor-α, interleukin-1, interleukin-6, and leptin), further impairing vascular endothelial cell function promoting atherosclerotic CVD [38, 47, 49, 50, 51]. Thirdly, IR influenced platelet adhesion, activation, and aggregation, which led to cardiovascular disease by arterial stenosis or thromboembolism [39, 52]. Last, IR is connected with increased sympathetic nervous system activity, activation of the renin-angiotensin-aldosterone system, inappropriate renal sodium handling, and impaired cardiac autonomic function, all of which heighten cardiac and renal burdens and thus contribute to the risk of CVD [40, 53].

Although the exact time to diagnosis of cardiovascular disease events was not obtained in this study, the data for this study were derived from CHARLS, which is a prospective national cohort study with substantial and reliable medical data. In addition, this study provided a comprehensive control for potential confounders, including demographic factors, lifestyle behaviors, and pre-existing health conditions. However, the present study still exhibited several limitations. First, while this study revealed associations between the eGDR and the risk of new-onset CVD, causality cannot be determined. Second, due to data limitations, it is still possible that residual confounders (such as dietary status and energy intake, physical activity, family income, and occupation) were not adequately considered in the present study. Future studies should continue to investigate the interaction of eGDR with other cardiovascular risk factors and validate its predictive value in different populations. Third, although parameters (such as height, weight, and WC) were measured by specialized equipment and trained individuals, measurement error and variability among the surveyors are inevitable. Fourth, in this study, CVD was ascertained based on self-reported physician diagnosis information, which might lead to classification bias. However, previous studies have demonstrated that self-reports are generally consistent with medical records and the misreports are not systematic, indicating that the potential misclassification bias is minor [19, 37, 54]. Fifth, it is impossible to evaluate the direct effects of insulin secretion and hyperinsulinemia on CVD risk as we lack direct measurements of insulin levels. Sixth, the impact of dynamic changes in eGDR on the risk of new-onset CVD among individuals with CKM 0–3 is unknown, and future trajectory analyses might be utilized to further validate the relationship. Seventh, the medical history (such as self-reported CVD and Self-reported dyslipidemia) was acquired by a standardized questionnaire and might be subject to recall bias. This is an unavoidable issue. Additionally, although the rate of loss to follow-up in this study was acceptable, the occurrence of competing events (such as death due to CVD) probably underestimated the relationship between eGDR and CVD. Last, although the findings are suitable for the middle-aged and elderly population in China, they are not likely to be directly replicable to non-Chinese populations or younger individuals.

Conclusion

The eGDR was a novel indicator of new-onset CVD in individuals with CKM syndrome stages 0–3, with BMI serving as a partial mediator in the association between eGDR and CVD risk. Addressing insulin resistance may represent a viable strategy for reducing the risk of CVD in this population.

Abbreviations

CVD	Cardiovascular diseases
CKM	Cardiovascular-kidney-metabolic
IR	Insulin resistance
eGDR	estimated glucose disposal rate
HbA1c	Hemoglobin A1c
WC	Waist circumference
HOMA-IR	Homeostasis model assessment of insulin resistance
CHARLS	China Health and Retirement Longitudinal Study
STROBE	Strengthening the Reporting of Observational Studies in Epidemiology
HT	Hypertension
HPLC	High Performance Liquid Chromatography
HD	Heart diseases
CKD	Chronic kidney disease
CKD-EPI	Chronic Kidney Disease Epidemiology Collaboration
eGFR	estimating glomerular filtration rate
KDIGO	Kidney Disease Improvement Global Outcomes
BMI	Body mass index
SBP	Systolic blood pressure
DBP	Diastolic blood pressure
FBG	Fasting blood glucose
CESD-10	10-item short form of the Center for Epidemiologic Studies Depression Scale
TG	Triglyceride
TC	Total cholesterol
HDL-c	High-density lipoprotein cholesterol
LDL-c	Low-density lipoprotein cholesterol
BUN	Blood urea nitrogen
Scr	Serum creatinine
CRP	C-reactive protein
UA	Uric acid
HGB	Hemoglobin
IQR	Interquartile range
OR	Odds ratios
CI	Confidence interval
RCS	Restricted cubic splines
Q	Quartiles
PLT	Platelet
NHANES	National Health and Nutrition Examination Survey
PI3K-Akt	Phosphatidylinositol 3-kinase PI3K-Akt
MAPK	Mitogen-activated protein kinase

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s13098-025-01626-7 .

Supplementary Material 1

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Author contributions
JT: Conceptualization, Methodology, Software, Data curation, Visualization, Validation, Formal analysis, Writing – original draft, and Writing – review & editing. HC: Data curation, Visualization, Formal analysis, Writing – original draft, Writing – review & editing, and Funding acquisition. YL: Writing – original draft, and Writing – review & editing. ZZ: Methodology, and Writing – review & editing. SX: Conceptualization, Methodology, Data curation, Formal analysis, Writing – review & editing, and Funding acquisition. HL: Supervision, Methodology, Data curation, Formal analysis, Writing – review & editing, and Funding acquisition. All authors read and approved the final manuscript.

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Data availability
Data supporting the results of this study are available from the China Health and Retirement Longitudinal Study (CHARLS) repository. The data can be accessed by registering and submitting a request through the official CHARLS website at http://charls.pku.edu.cn.

Declarations

Ethics approval and consent to participate
The data used in this study were approved by the Biomedical Ethics Review Board of Peking University (approval number: IRB00001052-11015). Written informed consent was gained from all participants. All human research methods described in the manuscript were in accordance with national laws and the 1964 Declaration of Helsinki and its later amendments.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

Author details
[1]Department of Cardiology, College of Medicine, Southwest Jiaotong University, Affiliated Hospital of Southwest Jiaotong University, The Third People's Hospital of Chengdu, Chengdu, Sichuan 610031, China
[2]Department of Cardiology, Mianyang Central Hospital, School of Medicine, University of Electronic Science and Technology of China, Mianyang, Sichuan, China
[3]Institute of Biomedical Engineering, Key Laboratory of Advanced Technologies of Materials, Ministry of Education, Southwest Jiaotong University, Chengdu, Sichuan, China

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