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Association between the cumulative estimated glucose disposal rate and incident cardiovascular disease in individuals over the age of 50 years and without diabetes: data from two large cohorts in China and the United States

Jin Zhang[1,2†], Ziyi Sun[1,2†], Yufei Li[2,3], Yuhan Yang[1,2], Wenjie Liu[1,2], Mengwen Huang[1] and Kuiwu Yao[4*]

Abstract

Background The estimated glucose disposal rate (eGDR) has been linked to incident cardiovascular disease (CVD) in individuals without diabetes. However, few studies have accounted for long-term cumulative eGDR exposure.

Objective The aim of this study was to explore whether long-term cumulative eGDR was independently associated with incident CVD in individuals over the age of 50 years and without diabetes.

Methods This study used data from the China Health and Retirement Longitudinal Study (CHARLS) and Health and Retirement Study (HRS). The cumulative eGDR was calculated as the summation of the average eGDR for each pair of consecutive examinations multiplied by the time between these two consecutive visits, in years. The outcome was incident CVD. Cox proportional hazards regression models and restricted cubic spline (RCS) regression models were used to evaluate the association between cumulative eGDR and incident CVD.

Results A total of 2430 participants from CHARLS and 2008 participants from HRS were included in the analysis. The median age of the participants in CHARLS at baseline was 59 years [IQR: 55–65 years], and 1205 (49.59%) were men. The median age of the participants in HRS at baseline was 64 years [IQR: 57–70 years], and 705 (35.11%) were men. The RCS regression model showed a negative and linear association between the cumulative eGDR and incidence of CVD (CHARLS: $P<0.001$, P for nonlinearity = 0.248; HRS: $P=0.013$, P for nonlinearity = 0.121). After multivariate adjustment, the higher levels of cumulative eGDR were independently associated with a lower risk of CVD (per SD, CHARLS: HR: 0.802, 95% CI: 0.716–0.898, HRS: HR: 0.791, 95% CI: 0.665–0.940, pooled analysis: HR: 0.799, 95% CI: 0.726–0.878).

†Jin Zhang and Ziyi Sun contributed equally.

*Correspondence:
Kuiwu Yao
yaokuiwu@126.com

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

Conclusions A lower level of cumulative eGDR was associated with an increased risk of incident CVD in individuals over the age of 50 years and without diabetes. Continuous monitoring of cumulative eGDR exposure over time, based on consideration of traditional risk factors, may prove beneficial for the early identification and intervention of individuals at high risk of CVD. In regions with limited healthcare resources, among individuals with limited ability to access, process, and understand health information and services, cumulative eGDR may offer improved clinical applicability.

Keywords eGDR, Cardiovascular disease, Cumulative exposure, Cohort study

Background

Cardiovascular disease (CVD) is the leading cause of mortality and morbidity worldwide and is a serious threat to population health and increases healthcare expenditures [1–4]. Especially in low- and middle-income countries, CVD imposes a significant socioeconomic and health burden [3–5]. According to a 2023 World Heart Federation report, the number of deaths attributable to CVD increased worldwide from 12.1 million in 1990 to 20.5 million in 2021 [5]. It is predicted that by 2050, 45 million adults will be affected by CVD [1]. Compared with downstream treatment, upstream prevention requires more attention [5, 6]. With the aging of the population, there is an urgent need to enhance the prevention and early intervention of CVD.

Insulin resistance (IR) has been demonstrated to be a principal risk factor for CVD [7–9]. The estimated glucose disposal rate (eGDR) is one of the indices used to assess IR. In comparison to the invasive, complex, time-consuming, and costly operation of the hyperinsulinemic-euglycemic clamp, which represents the gold standard method for measuring insulin sensitivity, eGDR is a relatively simple, convenient, and low-cost method of assessing IR, which makes it a more suitable choice for large-scale, daily clinical use [10]. Compared to homeostasis model assessment of insulin resistance (HOMA-IR), eGDR performs better in predicting all-cause mortality and cardiovascular mortality [11]. In comparison to triglyceride-glucose (TyG), eGDR incorporates both clinical and laboratory indices, providing a more comprehensive, stable, and continuous assessment [12, 13]. Furthermore, studies have demonstrated that eGDR is a reliable indicator of IR when compared to hyperinsulinemic-euglycemic clamp [14]. Hence, eGDR has the potential to become a valuable tool in clinical practice, particularly in regions where medical resources are limited.

Previous studies have shown that eGDR has different sensitivity for CVD risk prediction in diabetic and non-diabetic populations, and eGDR appears to be more sensitive in predicting CVD in non-diabetic patients [13, 15]. In addition, considering the potential effect of adverse lifestyle and environmental factors in the diabetic population, which may influence the incidence of CVD and thus affect the study results, this study focused on the individuals without diabetes. Recent studies have demonstrated that the eGDR can be used to predict the incidence of CVD with increased sensitivity in individuals without diabetes [15–17]. However, eGDR is a dynamic state over time, and a single measurement may not be sufficient to reflect the cumulative burden of eGDR. Previous studies have demonstrated that cumulative exposure to cardiovascular risk factors is an effective predictor of the risk of adverse long-term cardiovascular outcomes and mortality, independent of baseline risk factor levels, and assessment at baseline alone is insufficient to reflect the longitudinal associations between cumulative exposure and cardiovascular outcomes over time [12, 18, 19]. Most published studies considered only eGDR levels at a single time point, with minimal attention paid to cumulative exposures. There is currently a dearth of published studies investigating the association between cumulative eGDR and the incidence of CVD in individuals over the age of 50 years and without diabetes. Accordingly, this study used longitudinal data from two nationwide representative surveys to evaluate the association between the cumulative eGDR and incident CVD in individuals over the age of 50 years and without diabetes.

Methods

Data sources and study population

Data were obtained from the China Health and Retirement Longitudinal Study (CHARLS) and Health and Retirement Study (HRS), two nationally representative cohorts conducted in individuals aged 45 years and older in China and in individuals over the age of 50 years in the United States, respectively. For further details regarding the design of the two cohorts, please refer to the Additional file 1. In particular, biomarkers for HRS were collected from half of the sample in 2006, 2010, and 2014, and from the other half of the sample in 2008, 2012, and 2016 [20]. CHARLS and HRS were approved by the Institutional Review Board of Peking University and the Institutional Review Board of the University of Michigan Health Sciences and the National Institute on Aging, respectively [20–22]. Informed consent was obtained from all study participants. In this study, the baseline was established using data from wave 1 (2011–2012) of CHARLS and wave 8 (2006)/wave 9 (2008) of HRS. The cumulative eGDR was evaluated using data from wave

1 (2011–2012) and wave 3 (2015) of CHARLS and wave 8 (2006)/wave 9 (2008), wave 10 (2010)/wave 11 (2012), and wave 12 (2014)/wave 13 (2016) of HRS. Subsequent follow-up surveys were employed to monitor the incidence of CVD until the final follow-up surveys, namely wave 4 to wave 5 (2018–2020) for CHARLS and wave 13 to wave 15 (2016–2020)/wave 14 to wave 15 (2018–2020) for HRS. Participants were excluded if they met any of the following criteria: (1) with incomplete data on eGDR; (2) with diabetes mellitus (DM) or missing DM information; (3) with CVD or missing CVD information; (4) age ≤ 50 years at baseline or with missing age information; (5) without CVD follow-up data.

Data assessment and definitions

Definitions of the cumulative eGDR

The eGDR was calculated as previously described [14, 16] according to the following formula: eGDR = 21.158 - (0.09 * WC) -(3.407 * HTN) - (0.551 * HbA1c) [WC = waist circumference (cm), HTN = hypertension (yes = 1/no = 0), and HbA1c = glycosylated hemoglobin (%)]. In the original study by Williams et al., WC was also tested with a comparable association as for waist-to-hip ratio [14, 23]. The WC was measured at the umbilical level, with the subject standing upright, breathing normally, and the WC was wrapped horizontally around the subject's navel. During the measurement and recording process, the subject was instructed to temporarily suspend their respiration [24, 25]. HTN was defined as a diagnosis by a physician or use of hypertension medications, or with an average systolic blood pressure (SBP) ≥ 140 mmHg or an average diastolic blood pressure (DBP) ≥ 90 mmHg [26–28]. HbA1c was measured in CHARLS as a whole blood sample and in HRS as a dried blood spot, released into the NHANES equivalent assay scale [22, 29]. Details of the collection, storage, transport, preservation and testing of samples from the two cohorts can be found elsewhere [20, 22]. As previous studies described [28, 30], the cumulative eGDR was defined as the summation of the average eGDR for each pair of consecutive examinations multiplied by the time between these two consecutive visits, in years: In the CHARLS, cumulative eGDR = $(eGDR_{vistit1} + eGDR_{vistit2})/2*(time_{1-2})$. In the HRS, cumulative eGDR = $(eGDR_{vistit1} + eGDR_{vistit2})/2*(time_{1-2}) + (eGDR_{vistit2} + eGDR_{vistit3})/2*(time_{2-3})$. $eGDR_{vistit1}$, $eGDR_{vistit2}$, $eGDR_{vistit3}$ indicated the eGDR at the first, second and third examinations, respectively, and $time_{1-2}$ and $time_{2-3}$ indicate the participant-specific time intervals between consecutive visits in years. The time of examination of the two cohorts was presented in Additional file 1 (Fig.S1).

Ascertainment of CVD and follow-up

The outcome of this study was incident CVD. In accordance with previous studies [31–34], CVD was ascertained in CHARLS and HRS based on the self-reported physician-diagnosed heart disease (heart attack, coronary heart disease, angina, congestive heart failure, or other heart problems) or stroke. In each wave of the two cohorts, participants were asked, "Has a doctor told you that you have had a heart attack, coronary heart disease, angina, congestive heart failure, or other heart problems?" " Has a doctor told you that you have had a stroke?" Those who reported being diagnosed with heart disease or stroke were considered to have CVD.

The follow-up was initiated from wave 3 (2015) of CHARLS and wave 12 (2014)/wave 13 (2016) of HRS, respectively. The endpoint of follow-up was at the first occurrence of CVD or the censoring date, whichever came first, with the censoring date being the date of the last survey in which each participant was interviewed [35]. Ideally, the last survey was wave 5 (2020) of CHARLS and wave 15 (2020) of HRS, respectively.

Covariates

Covariates included age, gender, marital status, residence type, educational level, smoking status, alcohol drinking status, dyslipidemia, lipid-lowering therapy, and use of hypertension medications. In this study, marital status was classified as married and others. Residence type was classified as rural and urban. Educational level was classified into three groups: middle school or below, high school or vocational school, and college or above. Smoking status was classified as never and ever. Ever smokers included former and current smokers. Similarly, alcohol drinking status was classified as never and ever. Dyslipidemia was defined as total cholesterol (TC) ≥ 240 mg/dL, triglycerides (TG) ≥ 150 mg/dL, low-density lipoprotein cholesterol ≥ 160 mg/dL, high-density lipoprotein cholesterol (HDL-C) < 40 mg/dL, self-reported dyslipidemia or lipid-lowering therapy [27, 28, 36]. Diabetes was defined as fasting glucose ≥ 126 mg/dL, HbA1c ≥ 6.5%, self-reported physician diagnosis or use of any hypoglycemic medication [28, 37].

Statistical analysis

Categorical variables were expressed as counts (percentage) and compared using the chi-squared tests. Continuous variables were presented as mean ± standard deviations and compared using the Analysis of Variance (ANOVA) test when normally distributed and shown as median (interquartile range [IQR]) and compared using the Mann-Whitney U test when nonnormally distributed. The participants were divided into four groups according to quartiles relative to cumulative eGDR level. Kaplan-Meier curves and log-rank tests were used to

illustrate and compare the cumulative incidence rates of CVD in the four groups. The association between cumulative eGDR and incident CVD in the four groups were evaluated using the Cox proportional hazards regression models. Based on the literature review, three models were estimated: Model 1 adjusted for age and gender; Model 2 adjusted for age, gender, marital status, residence type, educational level, smoking status, and alcohol drinking status; Model 3 adjusted for age, gender, marital status, residence type, educational level, smoking status, alcohol drinking status, dyslipidemia, lipid-lowering therapy and use of hypertension medications. The pooled estimates were calculated using random-effect meta-analyses as previously used [38–40]. The heterogeneity of β values across the cohorts was evaluated by Cochran's Q test and I^2 statistic. We also used restricted cubic spline (RCS) regression models to explore the potential nonlinear association of the cumulative eGDR and incident CVD. We fit restricted cubic spline models with 3–5 nodes and then selected the model with the smallest Akaike information criterion (AIC) to determine the number of nodes. Additionally, we performed subgroup and interaction analyses to investigate whether the association between the cumulative eGDR and incident CVD varied according to different factors (gender, smoking status, alcohol drinking status, and obesity). Missing data were assumed to be missing at random and therefore were imputed with multivariate imputation by chained equation (MICE) package. Sensitivity analyses were performed to calculate eGDR using BMI instead of WC. $eGDR_{BMI}$ = 19.02 - (0.22 * BMI) - (3.26 * HTN) - (0.61 * HbA1c) [BMI = body mass index (kg/m^2), HTN = hypertension (yes = 1/no = 0), and HbA1c = HbA1c (%)] [41]. In addition, to account for the competing risk between incident CVD and all-cause mortality, the Fine-Gray model was fitted to assess the association between cumulative eGDR and incident CVD. Moreover, using the C-index, net reclassification index, and integrated discrimination improvement, we evaluated the predictive performance improvement of adding cumulative eGDR to the basic model, and compared it to the basic model and single eGDR, and the basic model and TyG related indices. Significance was indicated by two-sided p values less than 0.05. All statistical analyses were performed using IBM SPSS (version 27.0), Stata (version 16.0), and R (version 4.2.0).

Results

Characteristics of participants

A total of 2430 participants from CHARLS and 2008 participants from HRS were included for analysis. The participant screening flowchart was presented in Fig. 1. Details of the screening of participants in each cohort were provided in Additional file 1 (Fig.S2A and Fig.S2B). The median age of participants in CHARLS at baseline was 59 years [IQR: 55–65 years], and 1205 (49.59%) were men. The median age of participants in HRS at baseline was 64 years [IQR: 57–70 years], and 705 (35.11%) were men. Based on quartiles of the cumulative eGDR, the baseline characteristics of participants in each group were presented in Tables 1 and 2. Comparison of baseline characteristics between participants included and excluded from analysis in each cohort were presented in Additional file 1 (Table S1 and Table S2).

Association between the cumulative eGDR and incident CVD

In total, 406 (16.71%) participants in CHARLS developed CVD during follow-up between wave 3 (2015) and wave 5 (2020), and 246 (12.25%) participants in HRS developed CVD during follow-up between wave 12 (2014)/wave 13 (2016) and wave 15 (2020). Kaplan-Meier analysis showed that participants in Quartile 4 had significantly lower cumulative incidence rates of CVD (CHARLS: log-rank $P < 0.001$, HRS: log-rank $P < 0.001$) (Additional file 1: Fig.S3A, Fig.S3B). The association between the cumulative eGDR classified by quartiles and incident CVD was presented in Table 3. After multiple adjustments, compared with Quartile 1, the risk of CVD was significantly lower in Quartile 4 (pooled HR: 0.551, 95% CI: 0.421–0.722). In CHARLS, after adjusting for potential confounders in Model 3, compared with Quartile 1, the risk of CVD was significantly lower in Quartile 3 (HR: 0.626, 95% CI: 0.459–0.853) and Quartile 4 (HR: 0.587, 95% CI: 0.428–0.806). In HRS, after adjustment for all potential confounders in Model 3, compared with Quartile 1, the risk of CVD was significantly lower in Quartile 4 (HR: 0.469, 95% CI: 0.282–0.782). The RCS regression model showed a negative, linear association between the cumulative eGDR and incidence of CVD in with or without adjusting for covariates (Adjusted covariates in Model 3: CHARLS: $P < 0.001$, P for nonlinearity = 0.248; HRS: $P = 0.013$, P for nonlinearity = 0.121). (Figure 2A, B, C and D). In the fully adjusted model, higher levels of cumulative eGDR were independently associated with a lower risk of CVD (per SD, pooled analysis: HR: 0.799, 95% CI: 0.726–0.878, CHARLS: HR: 0.802, 95% CI: 0.716–0.898, HRS: HR: 0.791, 95% CI: 0.665–0.940).

Subgroup analyses and sensitivity analyses

The association of the cumulative eGDR with incident CVD risk stratified by different factors (age, gender, smoking status, alcohol drinking status, and obesity), respectively. As shown in Additional file 1 (Table S3), subgroups did not have significant interactions. Sensitivity analyses yielded congruent results when the analyses calculated eGDR using BMI instead of WC. (Additional file 1: Figure 2A, B, C and D, Table S4). When accounting

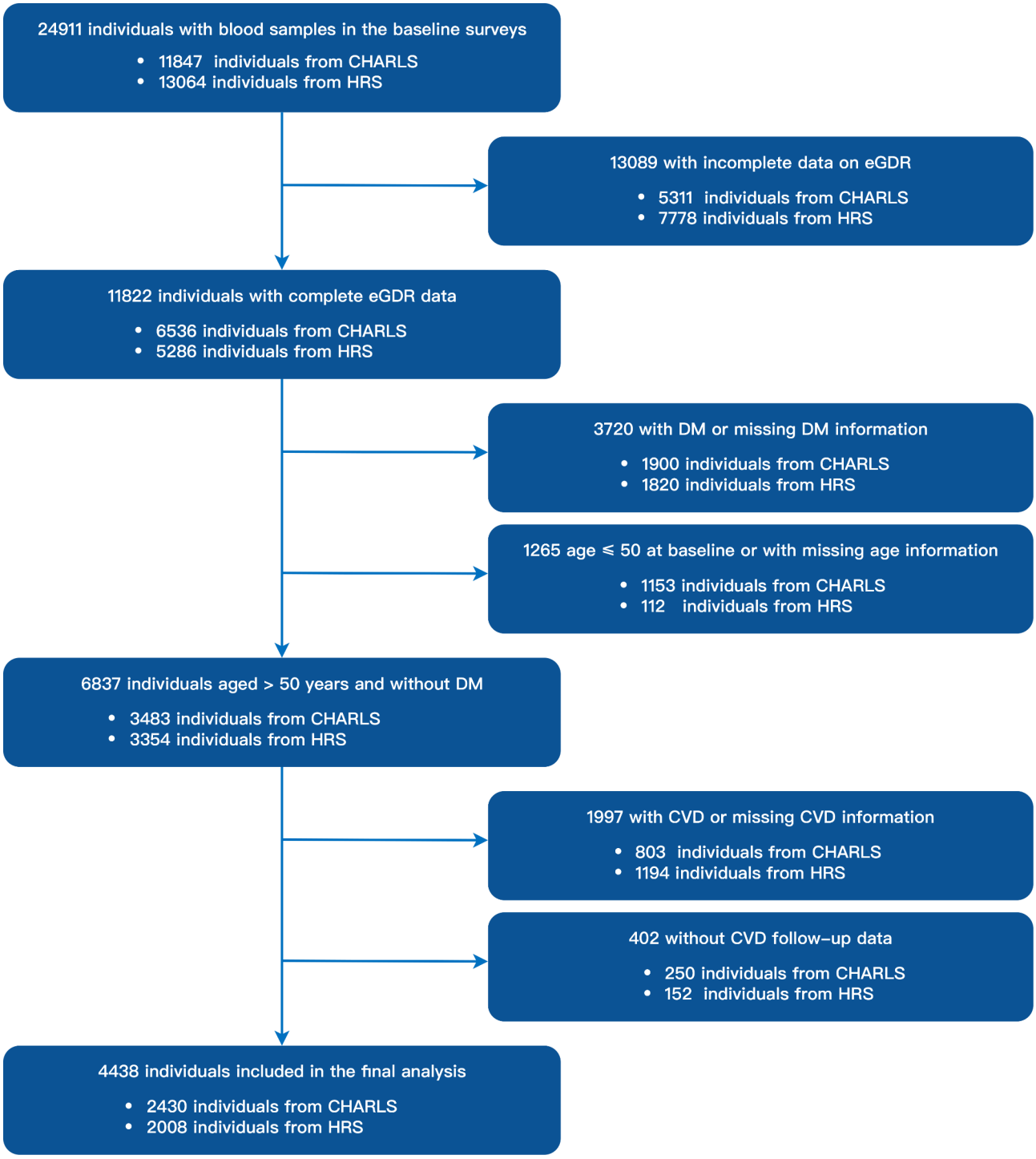

Fig. 1 Flowchart of the study population

for competing risk by all-cause mortality, consistent results were observed, as shown in Additional file 1 (Table S5).

Predictive performance

Based on the literature review and covariates in Model 3, the basic models were constructed (including age, gender, marital status, residence type, educational level, smoking status, alcohol drinking status, dyslipidemia, lipid-lowering therapy, use of hypertension medications, TC, and HDL-C). Compared with the basic model, adding the cumulative eGDR optimized the predictive ability by the C-index (CHARLS: 0.613 vs. 0.600, $P<0.001$; HRS: 0.674 vs. 0.667, $P=0.019$). Additionally, compared

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

Characteristics	Total (*n* = 2430)	Quartile 1 (*n* = 607)	Quartile 2 (*n* = 608)	Quartile 3 (*n* = 608)	Quartile 4 (*n* = 607)
Age, years	59.00 [55.00, 65.00]	61.00 [56.00, 66.50]	60.00 [56.00, 66.00]	58.00 [55.00, 63.00]	59.00 [55.00, 64.00]
Gender, n(%)					
Male	1205 (49.59)	278 (45.80)	306 (50.33)	306 (50.33)	315 (51.89)
Female	1225 (50.41)	329 (54.20)	302 (49.67)	302 (49.67)	292 (48.11)
Marital status, n(%)					
Married	2091 (86.05)	513 (84.51)	517 (85.03)	525 (86.35)	536 (88.30)
Others	339 (13.95)	94 (15.49)	91 (14.97)	83 (13.65)	71 (11.70)
Residence type, n(%)					
Rural	1715 (70.58)	398 (65.57)	418 (68.75)	430 (70.72)	469 (77.27)
Urban	715 (29.42)	209 (34.43)	190 (31.25)	178 (29.28)	138 (22.73)
Educational level, n(%)					
Middle school or below	2251 (92.63)	565 (93.08)	569 (93.59)	560 (92.11)	557 (91.76)
High school or vocational school	166 (6.83)	39 (6.43)	38 (6.25)	45 (7.40)	44 (7.25)
College or above	13 (0.53)	3 (0.49)	1 (0.16)	3 (0.49)	6 (0.99)
Smoking status, n(%)					
Ever	1008 (41.48)	232 (38.22)	255 (41.94)	255 (41.94)	266 (43.82)
Never	1422 (58.52)	375 (61.78)	353 (58.06)	353 (58.06)	341 (56.18)
Alcohol drinking status, n(%)					
Ever	1058 (43.54)	263 (43.33)	258 (42.43)	266 (43.75)	271 (44.65)
Never	1372 (56.46)	344 (56.67)	350 (57.57)	342 (56.25)	336 (55.35)
Hypertension, n(%)	814 (33.50)	577 (95.06)	210 (34.54)	22 (3.62)	5 (0.82)
Dyslipidemia, n(%)	998 (41.07)	345 (56.84)	259 (42.60)	223 (36.68)	171 (28.17)
Lipid-lowering therapy, n (%)	61 (2.51)	29 (4.78)	13 (2.14)	13 (2.14)	6 (0.99)
Hypertension medications, n (%)	293 (12.06)	248 (40.86)	45 (7.40)	0 (0.00)	0 (0.00)
Waist circumference, cm	83.00 (76.80, 90.00)	89.80 (83.60, 96.60)	85.00 (77.95, 93.00)	83.50 (80.00, 87.43)	75.00 (71.00, 78.15)
Body mass index, kg/m^2	22.38 (20.42, 24.65)	24.39 (22.41, 27.06)	22.92 (20.79, 25.55)	22.68 (21.09, 24.15)	20.08 (18.89, 21.52)
Systolic blood pressure, mm Hg	124.50 (112.50, 138.50)	145.00 (133.00, 157.00)	129.00 (118.50, 141.00)	116.50 (108.00, 126.00)	114.50 (106.00, 123.00)
Diastolic blood pressure, mm Hg	73.00 (66.00, 81.00)	83.00 (74.50, 90.00)	74.50 (68.00, 82.50)	69.50 (64.00, 75.00)	67.50 (61.50, 73.50)
Total cholesterol, mg/dL	190.59 (167.40, 214.47)	197.94 (173.78, 221.52)	191.75 (170.10, 215.05)	187.50 (164.98, 212.63)	184.02 (164.31, 206.06)
High-density lipoprotein cholesterol, mg/dL	51.03 (42.62, 61.47)	47.17 (39.43, 56.83)	49.87 (41.75, 61.08)	50.64 (43.20, 59.92)	55.67 (46.78, 66.50)
Glycosylated hemoglobin, %	5.10 (4.80, 5.30)	5.10 (4.90, 5.40)	5.10 (4.80, 5.30)	5.10 (4.90, 5.30)	5.00 (4.80, 5.30)

Missing data: 20 for dyslipidemia, 36 for lipid-lowering therapy, 2 for hypertension medications, 17 for body mass index, 12 for systolic blood pressure, 13 for diastolic blood pressure, 56 for total cholesterol, and 51 for high-density lipoprotein cholesterol

with the basic model and HTN, adding the cumulative eGDR optimized the predictive ability by the C-index (CHARLS: 0.613 vs. 0.602, $P < 0.001$; HRS: 0.674 vs. 0.669, $P < 0.001$). However, the predictive ability by the C-index did not show consistent results when cumulative eGDR was added in the two cohorts compared to adding eGDR at baseline (CHARLS: 0.613 vs. 0.603, $P < 0.001$; HRS: 0.674 vs. 0.676, $P = 0.022$). (Additional file 1: Table S6). In the CHARLS cohort, the addition of cumulative eGDR optimized the predictive ability by the C-index compared to the basic model with the addition of TyG related indices, including cumulative TyG (0.613 vs. 0.602, $P < 0.001$), cumulative TyG-BMI (0.613 vs. 0.605, $P < 0.001$), cumulative TyG-WC (0.613 vs. 0.603, $P < 0.001$), and cumulative TyG combined with waist-to-height ratio (TyG-WHtR) (0.613 vs. 0.601, $P < 0.001$). (Additional file 1: Table S7).

Discussion

In this study, we explored the association between cumulative eGDR and incident CVD in individuals over the age of 50 years and without diabetes. Our results showed that a lower level of cumulative eGDR was associated with an increased risk of incident CVD in individuals over the age of 50 years and without diabetes. Our findings suggested

Table 2 Baseline characteristics of HRS individuals classified by quartiles of the cumulative eGDR

Characteristics	Total ($n=2008$)	Quartile 1 ($n=502$)	Quartile 2 ($n=502$)	Quartile 3 ($n=502$)	Quartile 4 ($n=502$)
Age, years	64.00 [57.00, 70.00]	65.00 [58.00, 71.00]	65.00 [58.00, 71.00]	64.00 [57.00, 70.00]	60.00 [55.00, 67.00]
Gender, n(%)					
Male	705 (35.11)	238 (47.41)	181 (36.06)	167 (33.27)	119 (23.71)
Female	1303 (64.89)	264 (52.59)	321 (63.94)	335 (66.73)	383 (76.29)
Marital status, n(%)					
Married	1422 (70.82)	355 (70.72)	343 (68.33)	356 (70.92)	368 (73.31)
Others	586 (29.18)	147 (29.28)	159 (31.67)	146 (29.08)	134 (26.69)
Residence type, n(%)					
Rural	664 (33.07)	174 (34.66)	176 (35.06)	163 (32.47)	151 (30.08)
Urban	1344 (66.93)	328 (65.34)	326 (64.94)	339 (67.53)	351 (69.92)
Educational level, n(%)					
Middle school or below	228 (11.35)	81 (16.14)	62 (12.35)	52 (10.36)	33 (6.57)
High school or vocational school	1165 (58.02)	286 (56.97)	305 (60.76)	297 (59.16)	277 (55.18)
College or above	615 (30.63)	135 (26.89)	135 (26.89)	153 (30.48)	192 (38.25)
Smoking status, n(%)					
Ever	993 (49.45)	271 (53.98)	242 (48.21)	245 (48.80)	235 (46.81)
Never	1015 (50.55)	231 (46.02)	260 (51.79)	257 (51.20)	267 (53.19)
Alcohol drinking status, n(%)					
Ever	1276 (63.55)	304 (60.56)	309 (61.55)	333 (66.33)	330 (65.74)
Never	732 (36.45)	198 (39.44)	193 (38.45)	169 (33.67)	172 (34.26)
Hypertension, n(%)	1061 (52.84)	466 (92.83)	398 (79.28)	175 (34.86)	22 (4.38)
Dyslipidemia, n(%)	1921 (95.67)	487 (97.01)	487 (97.01)	481 (95.82)	466 (92.83)
Lipid-lowering therapy, n (%)	535 (26.64)	181 (36.06)	163 (32.47)	110 (21.91)	81 (16.14)
Hypertension medications, n (%)	708 (35.26)	345 (68.73)	278 (55.38)	83 (16.53)	2 (0.40)
Waist circumference, cm	96.52 (86.36, 104.78)	109.22 (102.87, 116.84)	95.25 (89.54, 100.33)	93.98 (82.55, 104.14)	86.36 (78.74, 93.35)
Body mass index, kg/m^2	27.73 (24.78, 31.40)	32.34 (29.61, 36.44)	27.37 (25.49, 30.14)	26.83 (24.13, 30.20)	24.78 (22.76, 27.04)
Systolic blood pressure, mm Hg	125.50 (114.50, 138.50)	133.50 (122.50, 146.88)	131.50 (119.12, 143.00)	125.00 (115.50, 135.50)	114.00 (106.00, 124.38)
Diastolic blood pressure, mm Hg	79.50 (72.50, 86.50)	83.50 (76.00, 91.38)	82.50 (76.00, 88.50)	78.50 (72.50, 85.50)	74.00 (68.00, 79.50)
Total cholesterol, mg/dL	207.71 (180.76, 236.13)	199.39 (175.98, 230.74)	208.44 (184.17, 230.71)	209.67 (185.92, 238.67)	210.60 (183.11, 243.09)
High-density lipoprotein cholesterol, mg/dL	56.64 (45.44, 70.08)	49.92 (41.54, 60.95)	57.76 (47.81, 70.08)	56.64 (46.56, 70.08)	63.77 (50.85, 75.68)
Glycosylated hemoglobin, %	5.46 (5.22, 5.70)	5.47 (5.24, 5.80)	5.46 (5.22, 5.69)	5.46 (5.22, 5.70)	5.36 (5.11, 5.69)

Missing data: 4 for residence type, 18 for smoking status, 610 for dyslipidemia, 1 for hypertension medications, 37 for body mass index, 41 for systolic blood pressure, 42 for diastolic blood pressure, 69 for total cholesterol, and 343 for high-density lipoprotein cholesterol

that monitoring cumulative eGDR exposure over time, based on consideration of traditional risk factors, may prove beneficial for early identification of individuals at high risk of CVD, leading to early targeted interventions. In addition, this simple, convenient, and low-cost tool is easily accessible in regions with limited healthcare resources and may offer improved clinical applicability for individuals with limited ability to access, process, and understand health information and services.

IR is an independent risk factor for CVD [42, 43]. eGDR was first developed by Katherine V. Williams based on data from the euglycemic-hyperinsulinemic clamp study in 24 patients with type 1 diabetes mellitus (T1DM), which correlated well with euglycemic-hyperinsulinemic clamp measured IR [14]. Previous studies of eGDR concentrated on vascular complications and prognosis in patients with diabetes and showed that eGDR is strongly associated with microvascular and macrovascular complications [23, 41, 44–48]. Studies have extended the eGDR application population to individuals without diabetes. The results of a cross-sectional study revealed that eGDR improves the identification of prevalent ischemic heart disease in the rural general population, with a high prevalence of ischemic heart disease in individuals with lower eGDR [17]. A

Table 3 Association between the cumulative eGDR and incident CVD

	CHARLS						HRS						Pooled analysis									
	Model 1		Model 2		Model 3		Model 1		Model 2		Model 3		Model 1				Model 2				Model 3			
	HR 95%CI	P value	HR 95%CI	P value	HR 95%CI	P value	HR 95%CI	P value	HR 95%CI	P value	HR 95%CI	P value	HR 95%CI	P value[a]	I^2, %	P value[b]	HR 95%CI	P value[a]	I^2, %	P value[b]	HR 95%CI	P value[a]	I^2, %	P value[b]
Quartile 1	Reference		Reference		Reference		Reference		Reference		Reference		Reference				Reference				Reference			
Quartile 2	0.836 (0.651–1.072)	0.158	0.836 (0.651–1.073)	0.159	0.881 (0.673–1.155)	0.359	0.792 (0.574–1.092)	0.155	0.801 (0.580–1.104)	0.175	0.864 (0.623–1.197)	0.379	0.819 (0.673–0.998)	0.047	0.0	0.795	0.823 (0.675–1.002)	0.053	0.0	0.837	0.874 (0.710–1.076)	0.205	0.0	0.928
Quartile 3	0.585 (0.443–0.774)	< 0.001	0.583 (0.441–0.772)	< 0.0001	0.626 (0.459–0.853)	0.003	0.761 (0.548–1.058)	0.104	0.778 (0.559–1.083)	0.137	0.987 (0.679–1.436)	0.947	0.657 (0.509–0.849)	0.001	30.0	0.232	0.664 (0.501–0.880)	0.004	41.3	0.192	0.776 (0.497–1.212)	0.265	70.3	0.066
Quartile 4	0.548 (0.413–0.727)	< 0.001	0.541 (0.407–0.719)	< 0.001	0.587 (0.428–0.806)	< 0.001	0.336 (0.215–0.524)	< 0.001	0.339 (0.217–0.530)	< 0.001	0.469 (0.282–0.782)	0.004	0.443 (0.275–0.712)	0.001	69.7	0.069	0.443 (0.281–0.697)	< 0.001	66.6	0.084	0.551 (0.421–0.722)	< 0.001	0.0	0.464
Per SD change	0.785 (0.713–0.864)	< 0.001	0.781 (0.710–0.860)	< 0.001	0.802 (0.716–0.898)	< 0.001	0.703 (0.611–0.808)	< 0.001	0.707 (0.614–0.813)	< 0.001	0.791 (0.665–0.940)	0.008	0.752 (0.677–0.836)	< 0.001	38.5	0.202	0.753 (0.686–0.827)	< 0.001	24.1	0.251	0.799 (0.726–0.878)	< 0.001	0.0	0.896

Model 1 adjusted for age and gender; Model 2 adjusted for age, gender, marital status, residence type, educational level, smoking status, and alcohol drinking status; Model 3 adjusted for age, gender, marital status, residence type, educational level, smoking status, alcohol drinking status, dyslipidemia, lipid-lowering therapy, and use of hypertension medications.

P value[a] For the pooled HR 95%CI.

P value[b] For the I^2 statistic

cohort study indicated that eGDR was negatively and linearly associated with incident CVD in the general population, and the association was significant in participants with and without diabetes, with a 16% decreased risk of CVD for each 1-SD increase of eGDR (HRs: 0.84, 95% CI: 0.79–0.88) [15]. A study of prediabetic adults in the United States showed that lower eGDR is associated with an increased risk of all-cause and CVD mortality, with prediabetic adults with eGDR < 4 mg/kg/min having a 358% increased risk of CVD compared to prediabetic adults with eGDR ≥ 8 mg/kg/min [49]. A retrospective study suggested that lower eGDR was a risk factor for major adverse cardiovascular events in patients with non-ST-segment elevation acute coronary syndrome and non-diabetes, and the incidence of major adverse cardiovascular events was significantly higher in the lower eGDR group than in the higher eGDR group (HR: 1.337, 95% CI: 1.201–1.488, $P < 0.001$) [50]. Previously, it has been shown that eGDR can improve the ability to predict the risk of CVD among individuals without diabetes, with an incremental predictive value [16], further confirming the reliability of eGDR as an assessment of CVD risk in individuals without diabetes. Our study found that cumulative eGDR had a negative linear relationship with the risk of CVD in individuals over 50 years of age and without diabetes. This finding was consistent with previously observed associations between eGDR and CVD among individuals without diabetes. In addition, we calculated long-term cumulative exposures, and used data from two nationally representative cohorts, increasing the external and internal validity of our study. The strength of risk factor associations varies over the life course and generally decreases with age [51]. However, the incidence of IR is significantly higher in the elderly than in the young, and the predictive value of eGDR may be more important in the elderly population, where it has been shown to be an independent predictor of all-cause mortality in the elderly [52]. Studies suggested that eGDR is more sensitive in predicting cardiovascular events in non-diabetic populations [13, 15]. Considering the different sensitivity of eGDR for CVD risk prediction in diabetic and non-diabetic populations, the potential effect of adverse lifestyle and environmental factors in the diabetic population, and the relationship of estrogen with metabolic regulation, which may influence the incidence of CVD [15], our study was conducted in individuals over the age of 50 years and without diabetes, and the results suggested that monitoring eGDR based on consideration of traditional risk factors may facilitate early identification and intervention in individuals at high risk of CVD.

An increasing number of studies are now considering the role of cumulative effects in disease risk [26, 28, 36, 53]. Cumulative exposure to CVD risk factors has been shown to predict the risk of long-term adverse CVD outcomes and mortality independent of baseline risk factor

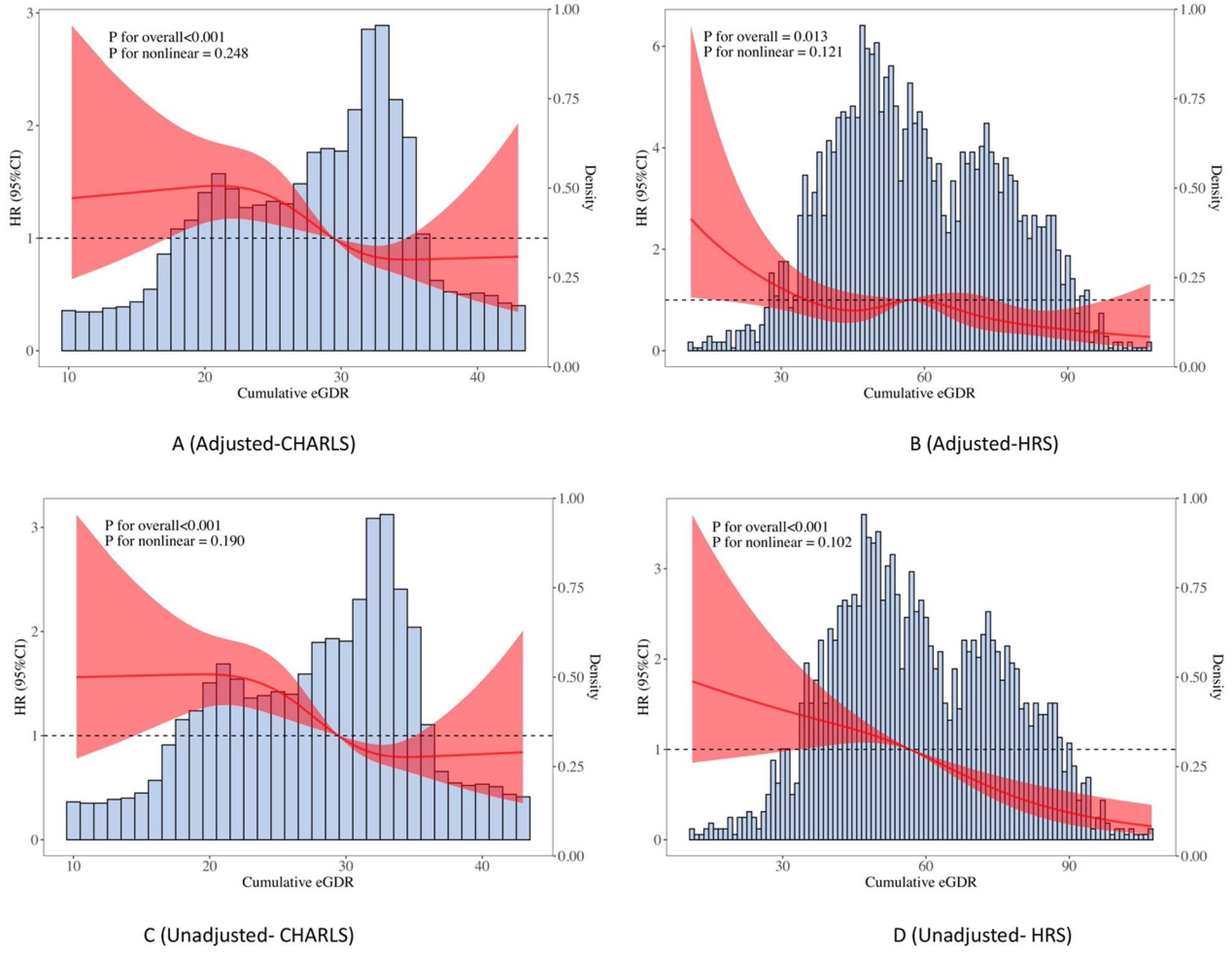

Fig. 2 Restricted cubic spline curves for incident CVD according to the cumulative eGDR. The adjusted model adjusted age, gender, marital status, residence type, educational level, smoking status, alcohol drinking status, dyslipidemia, lipid-lowering therapy, and use of hypertension medications

levels, and assessment at baseline alone does not reflect the longitudinal associations between cumulative exposure over time and CVD outcomes [12, 18, 19]. These findings serve as a reminder of the value of dynamic monitoring of CVD risk factors, taking into account the extent and cumulative duration of risk factor exposure. Previously, a study found that a higher decline in eGDR was associated with a 19% risk of CVD, and the use of changes in eGDR is valuable in evaluating the risk of stroke [54]. Similarly, our study considered long-term cumulative exposure to eGDR and showed that cumulative eGDR was associated with incident CVD, and a lower level of cumulative eGDR was associated with an increased risk of incident CVD, indicating that dynamic monitoring of eGDR may be useful in identifying individuals at high risk of CVD and targeting interventions as early as possible.

The TyG index, which is often used as a surrogate measure of IR, has been shown in many studies to be associated with CVD outcomes in different populations [55]. However, using the TyG index alone to predict cardiovascular prognosis may be insufficient because its formula includes only fasting plasma glucose and TG and does not incorporate other indicators such as HTN and central obesity, which are closely associated with IR and cardiovascular prognosis [13]. Previous studies have shown that compared with the TyG index and HOMA-IR, the eGDR shows excellent predictive value in all-cause mortality and cardiovascular mortality [11]. In non-diabetic participants, the predictive value of the eGDR for CVD incidence was superior to that of the TyG index [16]. Similarly, among individuals over the age of 50 years and without diabetes from the CHARLS cohort, the addition of cumulative eGDR optimized the predictive ability of incident CVD by the C-index compared to the basic model with the addition of cumulative TyG. Difference in CVD incidence rates was observed between the two cohorts. Moreover, a comparison was conducted regarding the predictive ability of adding cumulative eGDR versus eGDR at baseline to the basic model for CVD risk.

Interestingly, the predictive performance was diametrically opposed in the two cohort populations. In these two representative cohorts, Chinese elders had a lower education level and a higher proportion of rural population relative to those in the United States, and had correspondingly lower health literacy [56]. Previous studies have shown that China is less advanced in the epidemiological transition, but due to inadequate treatment and poor control, the actual population levels are worse for blood pressure levels and not so different for lipid levels [57]. Chinese elders thus may have limited ability to access, process, and understand health information and services, and they may be less likely to receive treatment and make corresponding changes in their lives, with an increased vulnerability to incident CVD. Therefore, dynamic monitoring of eGDR may be useful in identifying individuals at high risk of CVD and targeting interventions as early as possible, especially among individuals with limited ability to access, process, and understand health information and services.

Obesity is associated with IR [58]. WC reflects central obesity, which is a typical IR condition and is strongly associated with CVD and adverse cardiovascular outcomes [59]. A study on eGDR and stroke risk used WQS regression to analyze the contribution of eGDR components and showed that WC and HTN were the main contributors [54]. Zhang et al. showed that obesity played an important mediating role in the association between eGDR and CVD [16]. The above results proved that weight loss plays an important role in CVD prevention, suggesting that the popularization of obesity-related knowledge should be strengthened and individuals should be encouraged to eat a reasonable diet, increase physical activity, and adopt a healthy lifestyle to reduce the risk of obesity. A Swedish cohort study found that low eGDR was associated with an increased risk of stroke and death in patients with type 2 diabetes mellitus (T2DM), with the relative attributable risk of HTN being the most important [48]. IR appears to act synergistically with HTN to increase the risk of poor prognosis [60], suggesting the importance of treating HTN to improve risky prognosis. A study by Katherine V. Williams et al. mentioned that subjects with poor glycemic control (HbA1c > 11.4%) were excluded from the study when the eGDR was developed and therefore the importance of HbA1c in the eGDR scoring may have been underestimated, whereas optimizing glycemic control remains a key clinical priority given the known impact of improved glycemic control on risk prognosis [14]. Notably, a study further analyzed the association between eGDR components and complications and showed that the eGDR as a whole had the strongest correlation with complications, highlighting the unique value of the eGDR as a comprehensive IR marker in risk stratification compared to using each of its metrics in isolation [41].

The strengths of this study are its unique broad population coverage with two national cohorts, the CHARLS, which represents the middle-aged and elderly population in China, and the HRS, which represents the elderly population in the United States, and the long follow-up period with high external and internal validity. eGDR is a comprehensive IR marker that is simple, easy to obtain, low-cost, universally available, stable, and reliable. Based on the consideration of traditional risk factors, the use of eGDR in large-scale population screening and through long-term monitoring of cumulative eGDR levels, among middle-aged and elderly populations without diabetes may help to identify individuals at high risk of CVD and to implement more targeted preventive or therapeutic measures as early as possible. Cumulative eGDR may offer better clinical applicability for individuals with limited ability to access, process, and understand health information and services in regions with limited and inadequate healthcare resources.

However, there are some limitations: (1) Similar to other studies, CVD was defined as self-reporting heart disease and stroke, which might lead to potential misclassification. (2) The CVD outcome was a composite outcome of hard clinical endpoints combined with nonspecific clinical endpoints such as "angina", which may obscure the relative contribution of each component to the overall CVD risk, making it difficult to pinpoint the most critical factors driving the outcome. (3) Only small part of the initial cohort population was included in the study due to missingness of data etc., this may exhibit ascertainment bias. (4) Although our model was adjusted for covariates, it could not eliminate the effect of unmeasured confounders on our results, which is a common problem in observational studies. Therefore, future studies should include more biomarkers and clinical variables to assess the relationship between cumulative eGDR and CVD more comprehensively.

Conclusions

In this study, we found that a lower level of cumulative eGDR was associated with an increased risk of incident CVD in individuals over the age of 50 years and without diabetes. Continuous monitoring of cumulative eGDR exposure over time, based on consideration of traditional risk factors, may prove beneficial for the early identification and intervention of individuals at high risk of CVD. In regions with limited healthcare resources, among individuals with limited ability to access, process and understand health information and services, the cumulative eGDR, with its advantages of convenience, efficacy and economic feasibility, may offer improved clinical applicability.

Abbreviations

AIC	Akaike information criterion
BMI	Body mass index
CHARLS	China Health and Retirement Longitudinal Study
CVD	Cardiovascular disease
DBP	Diastolic blood pressure
eGDR	Estimated glucose disposal rate
HbA1c	Glycosylated hemoglobin
HDL-C	High-density lipoprotein cholesterol
HOMA-IR	Homeostasis model assessment of insulin resistance
HRS	Health and Retirement Study
HTN	Hypertension
IR	Insulin resistance
RCS	Restricted cubic spline
SBP	Systolic blood pressure
T1DM	Type 1 diabetes mellitus
T2DM	Type 2 diabetes mellitus
TC	Total cholesterol
TG	Triglycerides
TyG	Triglyceride-glucose
WC	Waist circumference

Supplementary Information

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Supplementary Material 1

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Author contributions

JZ, ZS and KY conceived the study. JZ, ZS, and YL prepared and analyzed the data. JZ and YY carried out literature search. JZ, ZS, YL, YY, WL and MH interpreted the results. JZ and ZS drafted the manuscript. All authors read and approved the final manuscript.

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Data availability

The dataset was based on the CHARLS and HRS, which is publicly available and can be obtained by visiting their web sites (CHARLS: https://charls.pku.edu.cn/; HRS: https://hrs.isr.umich.edu).

Declarations

Ethics approval and consent to participate

Ethical approval for the CHARLS was granted by the Institutional Review Board at Peking University. The HRS was approved by the Institutional Review Board at the University of Michigan and the National Institute on Aging. Informed consent was obtained from all study participants.

Consent for publication

Not applicable.

Competing interests

The authors declare no competing interests.

Author details

[1]Guang'anmen Hospital, China Academy of Chinese Medical Sciences, Beijing, China
[2]Graduate School, Beijing University of Chinese Medicine, Beijing, China
[3]Centre for Evidence-Based Chinese Medicine, Beijing University of Chinese Medicine, Beijing, China
[4]China Academy of Chinese Medical Sciences, Beijing, China

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