Cardiovascular Diabetology

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Associations of estimated glucose disposal rate with frailty progression: results from two prospective cohorts

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Abstract

Background Frailty is a common geriatric syndrome associated with many adverse health outcomes. Identifying the risk factors of frailty is crucial and the insulin resistance (IR) is considered as a potential target. The estimated glucose disposal rate (eGDR) is a simple and reliable surrogate marker of IR. Associations of eGDR with frailty have not been explored. This study aimed to investigate the associations of eGDR with frailty progression.

Methods We used data from two prospective cohorts of the China Health and Retirement Longitudinal Study (CHARLS) and Health and Retirement Study (HRS). The eGDR was calculated as follows: eGDR (mg/kg/min) = 21.158 − (0.09×waist circumference) − (3.407×hypertension) − (0.551×glycosylated hemoglobin A_{1c}) [waist circumference (cm), hypertension (yes = 1/no = 0), and glycosylated hemoglobin A_{1c} (%)]. Participants were divided into three categories by tertiles of eGDR. Frailty index (FI) was calculated every two years and used to assess the degree of frailty which ranged from 0 to 100. Frailty progression was assessed by repeated measurements of FI during follow-up. Linear mixed-effect models were used to analyze the associations of eGDR with frailty progression.

Results 8872 participants from CHARLS (mean age: 58.9 years, female: 53.3%) and 5864 participants from HRS (mean age: 67.0 years, female: 59.0%) were included. The median follow-up periods were 7.0 years in the CHARLS and 12.8 years in the HRS, respectively. Compared to participants with lower tertile (T1) of eGDR, those with upper tertile (T3) of eGDR showed decelerated FI progression (CHARLS, β: -0.294, 95%CI -0.390 to -0.198, $P < 0.001$; HRS, β: -0.378, 95%CI -0.474 to -0.281, $P < 0.001$). Continuous eGDR was also associated with FI progression for significant deceleration in FI progression with per 1 SD increase in eGDR (CHARLS, β: -0.142, 95%CI -0.181 to -0.103, $P < 0.001$; HRS, β: -0.170, 95%CI -0.209 to -0.130, $P < 0.001$). These associations were still observed after excluding baseline frail participants. Furthermore, the associations of eGDR with FI progression were consistent among participants with and without diabetes.

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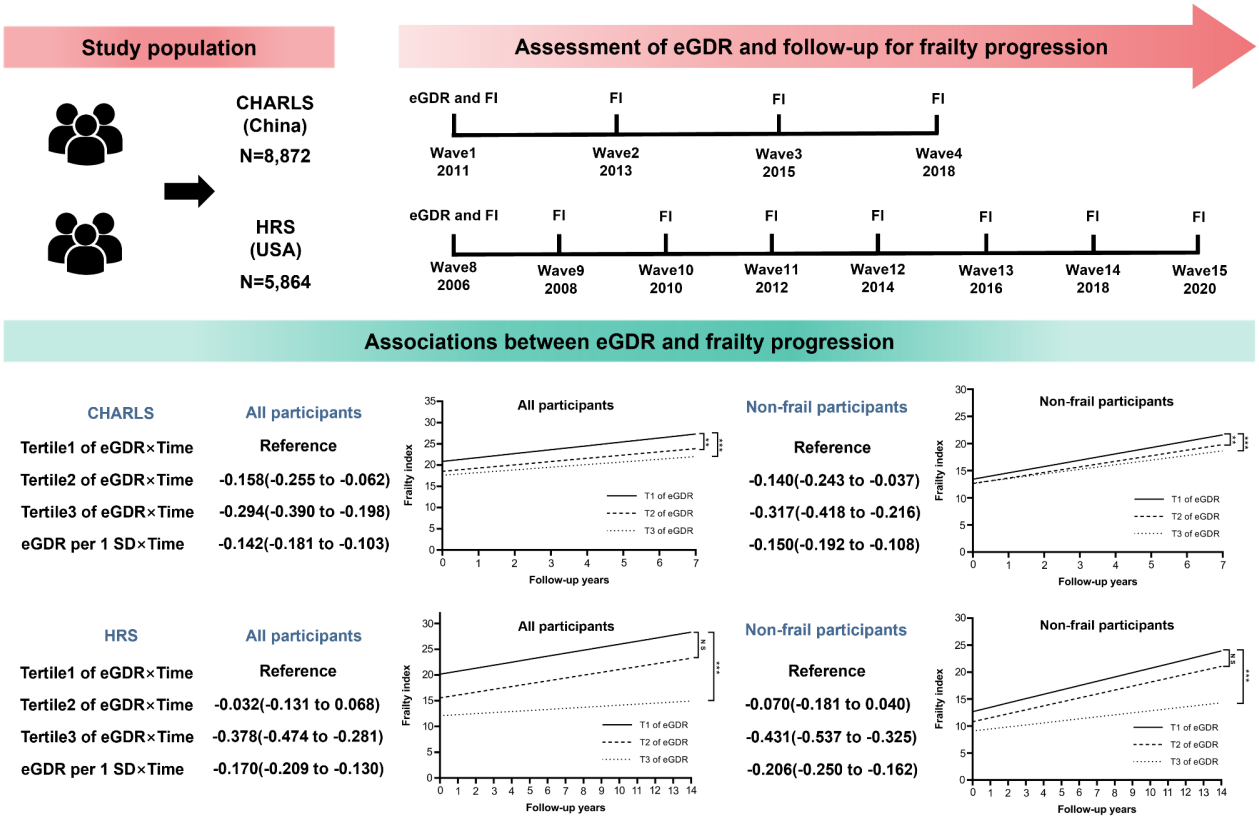
Conclusion Regardless of diabetes or not, a higher level of eGDR was associated with the decelerated frailty progression. Our findings highlight the role of eGDR in frailty progression and recommend taking effective interventions to improve eGDR for preventing frailty progression.

Graphical abstract The estimated glucose disposal rate and frailty progression. CHARLS, China Health and Retirement Longitudinal Study; HRS, Health and Retirement Study; eGDR, the estimated glucose disposal rate; FI, frailty index.



Keywords Insulin resistance, Estimated glucose disposal rate, Frailty, Diabetes, Epidemiology

Introduction

With the rapid increase in the old adults, frailty, a common geriatric syndrome, is becoming a major health burden [1]. Epidemiologic surveys showed that the prevalence of frailty ranged from 10.7 to 36.4% in community-dwelling older adults [2, 3]. The health care costs associated with frailty also increased year by year [1]. Frailty is a complex, non-specific clinical condition characterized by the loss of biological reserves in multiple organ systems, and increased vulnerability to various stressors [4]. A widely used method to assess frailty is the frailty index (FI). FI is defined as the accumulation of age-related health deficits, which is developed by Rockwood and colleagues [5]. It is well known that increased FI is associated with elevated risks of many adverse health outcomes, such as falls [6], cardiovascular disease (CVD) [7], chronic liver diseases [8], and all-cause mortality [9]. However, recent studies found that frailty was dynamic and could be reversed by effective interventions, while the reversion of frailty would reduce the risks of adverse health outcomes [1, 10–13]. Therefore, it is crucial to identify the risk factors of frailty, which provides the opportunity to perform targeted prevention and intervention at a specific time window. Recently, insulin resistance (IR) is considered as a potential risk factor of frailty [14].

IR plays an important role in the activation of chronic inflammation, which may reduce the insulin sensitivity in skeletal muscle cells and lead to the energy metabolic disorders. This may be a potential physiological mechanisms of frailty development [15–17]. The hyperinsulinemic-euglycemic (HIEG) clamp is the gold standard for measuring IR, yet its invasive nature and high costs render it impractical for widespread application in clinical

practice and large population cohorts [18]. Therefore, some alternative indicators are developed to measure IR, including the homeostasis model assessment for insulin resistance (HOMA-IR), triglyceride glucose (TyG) index and estimated glucose disposal rate (eGDR) [19–21]. However, the calculation of HOMA-IR is based on the fasting plasma glucose and insulin, which are not routinely tested for general populations [22]. The sensitivity and specificity of TyG are not satisfying in some conditions [23–26]. In comparison with HOMA-IR and TyG, eGDR is a more accessible and reliable alternative indicator of IR, and its accuracy in measuring IR is similar with the HIEG [20, 27–30]. Assessing the association of eGDR with frailty progression could further clarify the relationship between IR and frailty, and will provide crucial evidence for the necessity to conduct interventions on eGDR in frailty progression. Therefore, it is urgent to investigate the association of eGDR with FI progression. Furthermore, whether the effects of eGDR on frailty progression are consistent among individuals with or without diabetes also remain to be elucidated.

To fill these knowledge gaps, we used data from two prospective cohorts of China Health and Retirement Longitudinal Study (CHARLS) and Health and Retirement Study (HRS). We aimed to investigate the associations of eGDR with frailty progression among middle-age and old adults. In addition, we also examined the above associations among individuals with or without diabetes.

Methods

Study design and population

This study used data from the CHARLS and HRS cohorts, which were prospective, nationally representative cohorts conducted in China and the USA, respectively [31, 32]. Detailed study designs of both cohorts were described in Supplemental Methods. In the CHARLS, data from wave 1 (2011) to wave 4 (2018) were used, with wave 1 as the baseline. In the HRS, data from wave 8 (2006) to wave 15 (2020) were used, with wave 8 as the baseline. The CHARLS and HRS were approved by Ethics Review Committees of Peking University and the University of Michigan, respectively. Each participant provided the informed consent in both cohorts.

The selection process of the study population was shown in Fig. 1. Firstly, 17,139 participants from the CHARLS and 17,938 participants from the HRS were recruited. We then excluded 19,266 participants with missing data on eGDR and 217 participants with missing data on FI at the baseline. The remaining 15,535 participants (9351 from the CHARLS and 6184 from the HRS) were included for the analyses of eGDR and baseline frailty. In addition, we further excluded 799 participants without the reassessment of FI since the baseline, remaining 14,736 participants (8872 from the CHARLS and 5864 from the HRS) for the analyses of eGDR and frailty progression.

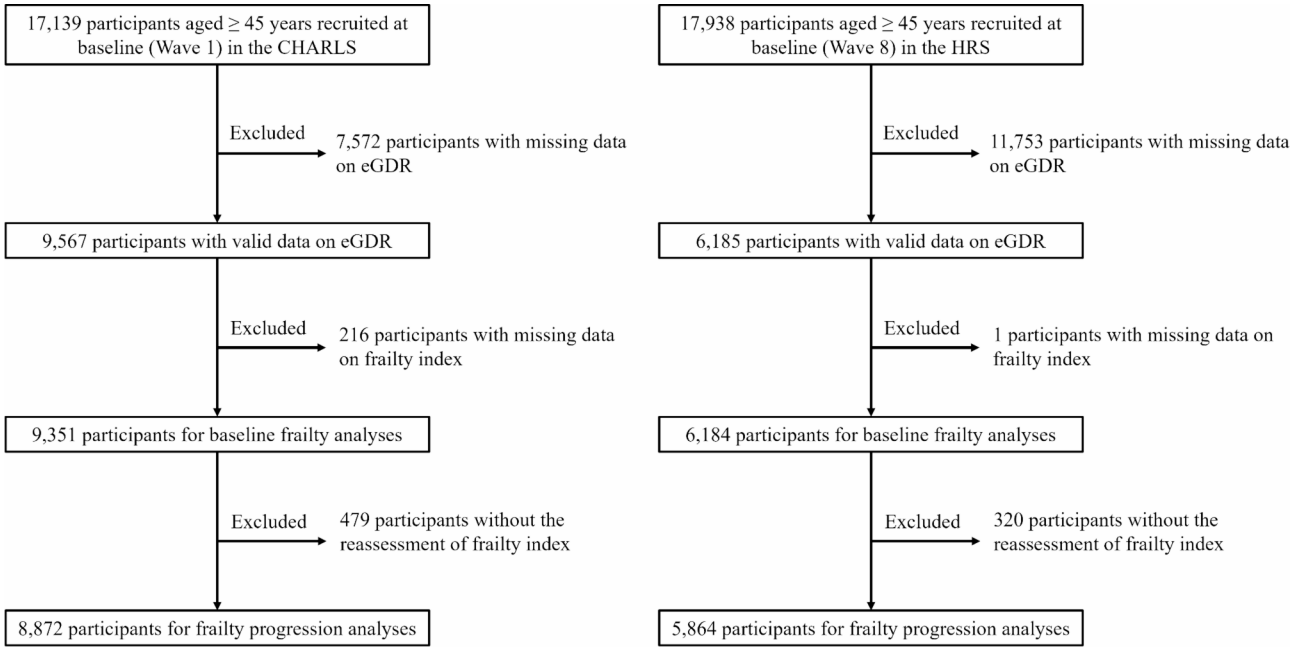


Fig. 1 Selection process of the study population. CHARLS, China Health and Retirement Longitudinal Study; HRS, Health and Retirement Study; eGDR, the estimated glucose disposal rate

Definition of eGDR

The eGDR was calculated by the following formula: eGDR (mg/kg/min) = 21.158– (0.09 × WC)– (3.407 × hypertension)– (0.551 × HbA_{1c}) [WC (cm), hypertension (yes = 1/ no = 0), and HbA_{1c} (%)]. Besides the continuous eGDR, we divided eGDR into three tertiles (T1, lower tertile of eGDR; T2, middle tertile of eGDR; T3, upper tertile of eGDR) [20].

In both cohorts, participants were asked to stand and measure the waist circumference (WC) at the navel using a tape measure [33, 34]. The glycosylated hemoglobin A_{1c} (HbA_{1c}) were measured using overnight fasting of venous blood samples by boronated affinity liquid chromatography in the CHARLS (https://charls.charlsdata.com/pages/data/111/en.html). In the HRS, HbA1c was measured by dried blood spots (DBSs) [35]. Hypertension was defined as the self-reported physician-diagnosed hypertension, and/or using any antihypertensive drugs, and/or measured blood pressure (BP) ≥ 140/90 mmHg at baseline.

Assessment of frailty

This study assessed frailty by the FI, which was defined as the accumulation of age-related health deficits. We constructed the FI following standard procedures established previously [13, 36, 37]. According to the data from CHARLS and HRS, 31 items were selected to construct the FI, including variables of disease (excluding hypertension), symptom, physical function, disability, depression, and cognition (Supplemental Table 1). Items 1–29 were grouped into 0 (absence of the deficit) or 1 (presence of the deficit) based on the specific cut-off value. Item 30 (memory test score) and item 31 (orientation test score) were continuous variables ranging from 0 to 1, and the higher values indicated the worse cognitive ability. For each participant, the FI was calculated as the sum of current health deficits divided by the total number of item and multiplied by 100. In this study, we allowed a 10% missing rate on the items of FI, then adjusted denominator when calculating the FI. For example, if two items were missing, the denominator were adjusted from 31 to 29 [37]. Therefore, the FI was a continuous variable ranging from 0 to 100, and a higher FI indicated a higher level of frailty. According to previous studies, frailty was defined as FI ≥ 25 [9, 13]. In the CHARLS and HRS, the FI was calculated at baseline and each wave of the follow-up. Frailty progression was assessed according to the repeated measurements of FI.

Covariates

The covariates included age, sex, education, marital status, smoking status, drinking status, physical activity, BMI, total cholesterol (TC), and C-reactive protein (CRP). For the consistency between CHARLS and HRS, education was divided into three levels: below high school, high school, and college or above. Marital status was classified into two categories: married or partnered and other marital status (separated, divorced, unmarried, or widowed). Smoking status was categorized as current smokers and non-current smokers (never or former smokers). Drinking status was categorized as current drinkers and non-current drinkers (never or former drinkers). Physical activity level was divided into four categories: vigorous (vigorous activity more than once a week), moderate (moderate activity more than once a week), light (light activity more than once a week), and inactive (the rest). BMI was calculated as the weight (kg) divided by the square of height (m^2).

Statistical analyses

In descriptive statistics, one-way ANOVA or Kruskal-Wallis rank sum tests were performed to compare the continuous variables, and Chi-square tests were conducted to compare the categorical variables. Continuous variables were expressed as the mean (standard deviation [SD]) or median (interquartile range [IQR]). Categorical variables were expressed as the number (percentage).

Linear-regression models were used to analyze the associations of eGDR (tertiles and continuous) with baseline frailty. Regression coefficients (β) and 95% confidence intervals (95%CI) were calculated. Model 1 was unadjusted. Model 2 was multivariable-adjusted controlling for age, sex, education level, marital status, smoking status, drinking status, physical activity, BMI, TC, and CRP. Linear mixed-effect models were used to analyze the associations of eGDR (tertiles and continuous) with frailty progression. In the linear mixed-effect models, outcome variables (Y) included all available repeated measurements of FI (including baseline FI). The time was defined as the actual time from baseline to the time point receiving the measurement of FI. The eGDR (continuous and tertiles), time, interaction of eGDR (continuous and tertiles) and time, and the same covariates used in the linear regression models were included as the exposure variables (X) for fixed effects. The regression coefficients of eGDR reflected the average difference in baseline FI for each SD increase in eGDR (if continuous) or compared to the reference category (if tertiles). The regression coefficients of time indicated the overall change rate of FI during follow-up (annual FI change). The regression coefficients of interaction terms (eGDR and time) indicated the average differences in FI change rates during follow-up (additional annual FI changes) for each SD increase in eGDR (if continuous) or compared to the reference category (if tertiles). For random effects, random intercept and slope were included to account for inter-individual differences at baseline and during follow-up, respectively. The assumed covariance structures between random effects were Cholesky decompositions.

In analyses of eGDR tertiles, the lower tertile (T1) was used as the reference. The trend test was conducted by assigning the tertile as a continuous variable [38, 39]. In analyses of continuous eGDR, results were presented as the changes with each SD increase of baseline eGDR. Moreover, we further examined the associations of eGDR with frailty and its progression among participants with and without diabetes. Diabetes was defined as the self-reported physician-diagnosis diabetes, and/or using any hypoglycemic drugs, and/or fasting blood glucose (FBG) ≥ 7.0 mmol/L, and/or the glycosylated hemoglobin A_{1c} (HbA_{1c}) level ≥ 6.5% at the baseline. The associations of eGDR with frailty progression were analyze again after excluding baseline frail participants. The missing rates of covariates were presented in Supplemental Tables 2, 3. The missing data of covariates were imputed by the multiple imputation with chained equation, which was described in Supplemental Methods.

Several sensitivity analyses were conducted to examine the robustness of our results: (1) using another definition of hypertension (130/80 mmHg) to calculate $eGDR_{130}$; (3) using the new FI (30 items) after removing the diabetes item from original FI items (31 items) to avoid the potential overlap of eGDR criteria with diabetes; (4) additionally adjusting for the use of antihypertensive, antidiabetic and antihyperlipidemic drugs in CHARLS, and the use of antihypertensive and antidiabetic drugs in HRS (the information of using antihyperlipidemic drugs was not available in HRS), respectively; (5) additionally adjusting for heart disease, stroke, and chronic kidney disease in CHARLS, and heart disease, stroke in HRS (the information of chronic kidney disease was not available in HRS), respectively; (6) excluding participants with missing data on covariates; (7) excluding participants with any missing data on FI items; (8) adding the interactions of covariates and time to the original models. In addition, stratified analyses were conducted by age (< 60, ≥ 60), sex, and obesity status. All statistical analyses were performed by R software (Version 4.1.3), and a two-tailed P values < 0.05 was defined as statistically significant.

Results

Baseline characteristics of the study population

Based on the inclusion and exclusion criteria, 9351 participants from the CHARLS (mean age: 59.2 years, female: 53.1%) and 6184 participants from the HRS (mean age: 67.4 years, female: 58.6%) were finally included for analyses of eGDR and baseline frailty. Table 1 shows the baseline characteristics of these participants stratified by tertiles of eGDR. In the CHARLS, participants with upper tertile (T1) of eGDR have the highest age and proportion of female, followed by middle tertile (T2) of eGDR and lower tertile (T3) of eGDR. While in the HRS, participants with T2 of eGDR have the highest age, followed by T1 of eGDR and T3 of eGDR. Participants with T3 of eGDR have the highest proportion of female, followed by T2 of eGDR and T1 of eGDR. In both cohorts, participants with T3 of eGDR have the highest proportion of married or partnered, the highest education and physical activity levels, and the lowest BMI, WC, SBP, HbA1c, CRP, and FI levels, followed by T2 of eGDR and T1 of eGDR.

After further exclusion, 8872 participants from CHARLS (mean age: 58.9 years, female: 53.3%) and 5864 participants from HRS (mean age: 67.0 years, female: 59.0%) were included for analyses of eGDR and frailty progression. The baseline characteristics were similar (Table 2).

Associations of eGDR with baseline frailty

The associations of eGDR with baseline FI are summarized in Table 3. After adjusting for covariates, when compared to the T1 of eGDR, the T3 of eGDR had significantly lower FI (CHARLS, β: -2.289, 95%CI -2.995 to -1.583, P < 0.001; HRS, β: -3.021, 95%CI -3.873 to -2.168, P < 0.001), then followed by the T2 of eGDR (CHARLS, β: -1.540, 95%CI -2.169 to -0.912, P < 0.001; HRS, β: -1.999, 95%CI -2.788 to -1.211, P < 0.001). The trend tests showed that there were decreasing trends of baseline FI with increasing eGDR in CHARLS and HRS (both P for trend < 0.001). Continuous eGDR was also associated with baseline FI for significant decrease in baseline FI with per 1 SD increase in eGDR (CHARLS, β: -1.146, 95%CI -1.435 to -0.857, P < 0.001; HRS, β: -1.683, 95%CI -2.068 to -1.298, P < 0.001).

When stratified by the diabetes status, non-diabetic participants with T3 of eGDR had significantly lower FI (CHARLS, β: -1.985, 95%CI -2.747 to -1.224, P < 0.001; HRS, β: -1.472, 95%CI -2.414 to -0.530, P = 0.002) as compared to those with T1 of eGDR. In the CHARLS, diabetic participants with middle tertile (T2) of eGDR also had significantly lower FI (β: -2.050, 95%CI -3.568 to -0.531, P = 0.008) with reference to T1 of eGDR. In the HRS, diabetic participants with T3 of eGDR had marginally significant lower FI (β: -2.079, 95%CI -4.396 to 0.238, P = 0.079) as compared to T1 of eGDR. When eGDR was continuous variable, non-diabetic participants with higher eGDR had significantly lower FI (CHARLS, β: -0.849, 95%CI -1.173 to -0.524, P < 0.001; HRS, β: -0.819, 95%CI -1.237 to -0.401, P < 0.001), and the similar results were also found in diabetic participants (CHARLS, β: -1.299, 95%CI -1.995 to -0.602, P < 0.001; HRS, β: -1.410, 95%CI -2.447 to -0.372, P = 0.008).

Associations of eGDR with frailty progression

Table 4 shows the associations of eGDR with FI progression among all participants. In both cohorts, when compared to participants with T1 of eGDR, those with T3 of

Table 1 Baseline characteristics of participants for baseline frailty analyses

Variables	CHARLS (*n* = 9351)				HRS (*n* = 6184)			
	T1 of eGDR	T2 of eGDR	T3 of eGDR	*P*-value	T1 of eGDR	T2 of eGDR	T3 of eGDR	*P*-value
Number	3086	3086	3179	-	2041	2044	2099	-
Age, mean (SD), years	61.0 (9.3)	58.8 (9.3)	57.9 (9.0)	< 0.001	67.7 (9.4)	69.3 (10.5)	65.1 (10.4)	< 0.001
Sex, n (%)								
Male	1354 (43.9)	1430 (46.3)	1598 (50.3)	< 0.001	1045 (51.2)	778 (38.1)	737 (35.1)	< 0.001
Female	1732 (56.1)	1656 (53.7)	1581 (49.7)		996 (48.8)	1266 (61.9)	1362 (64.9)	
Marital status, n (%)								
Married or partnered	2633 (85.3)	2709 (87.8)	2848 (89.6)	< 0.001	1976 (96.8)	1985 (97.1)	2041 (97.2)	0.713
Other marital status	453 (14.7)	377 (12.2)	331 (10.4)		65 (3.2)	59 (2.9)	58 (2.8)	
Education, n (%)								
Below high school	2214 (71.7)	2147 (69.6)	2244 (70.6)	0.363	611 (29.9)	498 (24.4)	357 (17.0)	< 0.001
High school	579 (18.8)	639 (20.7)	620 (19.5)		656 (32.1)	661 (32.3)	626 (29.8)	
College or above	293 (9.5)	300 (9.7)	315 (9.9)		774 (37.9)	885 (43.3)	1116 (53.2)	
Smoking status, n (%)								
Non-current smokers	1953 (63.3)	1874 (60.7)	1797 (56.5)	< 0.001	1805 (88.4)	1765 (86.4)	1760 (83.8)	< 0.001
Current smokers	1133 (36.7)	1212 (39.3)	1382 (43.5)		236 (11.6)	279 (13.6)	339 (16.2)	
Drinking status, n (%)								
Non-current drinkers	1912 (62.0)	1880 (60.9)	1898 (59.7)	0.188	1087 (53.3)	982 (48.0)	875 (41.7)	< 0.001
Current drinkers	1174 (38.0)	1206 (39.1)	1281 (40.3)		954 (46.7)	1062 (52.0)	1224 (58.3)	
Physical activity, n (%)								
Inactive	428 (13.9)	359 (11.6)	267 (8.4)	< 0.001	129 (6.3)	77 (3.8)	55 (2.6)	< 0.001
Light	869 (28.2)	706 (22.9)	664 (20.9)		346 (17.0)	264 (12.9)	182 (8.7)	
Moderate	931 (30.2)	959 (31.1)	932 (29.3)		944 (46.3)	930 (45.5)	885 (42.2)	
Vigorous	858 (27.8)	1062 (34.4)	1316 (41.4)		622 (30.5)	773 (37.8)	977 (46.5)	
BMI, mean (SD), kg/m^2	25.6 (3.8)	23.9 (3.7)	21.2 (3.0)	< 0.001	34.2 (5.5)	27.5 (4.4)	26.3 (4.4)	< 0.001
WC, median (Q1-Q3), cm	91.2 (86.1–97.8)	87.8 (79.6–93.0)	77.2 (73.0–81.0)	< 0.001	112.4 (107.3-120.7)	95.3 (89.5–99.7)	91.4 (81.3-100.3)	< 0.001
SBP, mean (SD), mmHg	147.3 (20.3)	128.4 (19.3)	117.5 (12.7)	< 0.001	137.5 (20.9)	136.5 (20.7)	119.5 (14.7)	< 0.001
HbA_{1c}, mean (SD), %	5.49 (1.08)	5.29 (0.75)	5.03 (0.42)	< 0.001	6.23 (1.14)	5.72 (0.67)	5.57 (0.49)	< 0.001
TC, mean (SD), mmol/L	5.18 (1.05)	5.01 (0.98)	4.83 (0.97)	< 0.001	3.31 (0.69)	3.40 (0.72)	3.49 (0.70)	< 0.001
CRP, median (Q1-Q3), mg/L	1.4 (0.7–2.8)	1.0 (0.6–2.1)	0.8 (0.5–1.7)	< 0.001	1.6 (0.7–3.3)	1.0 (0.5–2.2)	0.8 (0.4–1.8)	< 0.001
FI, median (Q1-Q3)	18.2 (11.5–28.7)	15.8 (9.4–25.7)	15.5 (9.2–24.0)	< 0.001	17.7 (9.5–28.2)	12.7 (6.3–22.2)	9.0 (4.7–17.8)	< 0.001

T1 was the lower tertile, T2 was the middle tertile, and T3 was the upper tertile. In the CHARLS, T1 of eGDR ≤ 7.71, 7.71 < T2 of eGDR ≤ 10.72, T3 of eGDR > 10.72. In the HRS, T1 of eGDR ≤ 5.29, 5.29 < T2 of eGDR ≤ 7.46, T3 of eGDR > 7.46

CHARLS, China Health and Retirement Longitudinal Study; HRS, Health and Retirement Study; eGDR, the estimated glucose disposal rate; BMI, body mass index; WC, waist circumference; SBP, systolic blood pressure; HbA_{1c}, glycated hemoglobin A_{1c}; TC, total cholesterol; CRP, C-reactive protein; FI, frailty index; SD, standard deviation; IQR, interquartile range

eGDR showed significantly decelerated FI progression (CHARLS, β: -0.294, 95%CI -0.390 to -0.198, $P < 0.001$; HRS, β: -0.378, 95%CI -0.474 to -0.281, $P < 0.001$). For participants with T2 of eGDR, the significantly decelerated FI progression was only found in the CHARLS (β: -0.158, 95%CI -0.255 to -0.062, $P = 0.001$). The trend tests illustrated that there were decelerating trends of FI progression with the elevated eGDR in the CHARLS and HRS (both P for trend < 0.001). Similarly, continuous eGDR was also associated with decelerated FI progression (CHARLS, β: -0.142, 95%CI -0.181 to -0.103, $P < 0.001$; HRS, β: -0.170, 95%CI -0.209 to -0.130, $P < 0.001$). After excluding participants with frailty at baseline (Table 5), associations between T3 of eGDR and decelerated FI progression were still observed (CHARLS, β: -0.317, 95%CI -0.418 to -0.216, $P < 0.001$; HRS, β: -0.431, 95%CI -0.537 to -0.325, $P < 0.001$). Meanwhile, participants with per 1 SD increment of eGDR were also associated with decelerated FI progression (CHARLS, β: -0.150, 95%CI -0.192 to -0.108, $P < 0.001$; HRS, β: -0.206, 95%CI -0.250 to -0.162, $P < 0.001$).

When stratified by the diabetes status, the associations between eGDR and decelerated FI progression remained consistent (Table 4). Non-diabetic participants with T3 of eGDR presented a slower FI progression than those with T1 of eGDR (CHARLS, β: -0.221, 95%CI -0.326 to -0.117, $P < 0.001$; HRS, β: -0.323, 95%CI -0.433 to -0.212, $P < 0.001$). Similar associations were also observed among

Table 2 Baseline characteristics of participants for frailty progression analyses

Variables	CHARLS (*n* = 8872)				HRS (*n* = 5864)			
	T1 of eGDR	T2 of eGDR	T3 of eGDR	*P*-value	T1 of eGDR	T2 of eGDR	T3 of eGDR	*P*-value
Number	2928	2930	3014		1940	1930	1994	
Age, mean (SD), years	60.5 (8.9)	58.5 (9.0)	57.6 (8.7)	< 0.001	67.5 (9.3)	68.9 (10.4)	64.7 (10.1)	< 0.001
Sex, n (%)								
Male	1285 (43.9)	1344 (45.9)	1512 (50.2)	< 0.001	992 (51.1)	721 (37.4)	692 (34.7)	< 0.001
Female	1643 (56.1)	1586 (54.1)	1502 (49.8)		948 (48.9)	1209 (62.6)	1302 (65.3)	
Marital status, n (%)								
Married or partnered	2531 (86.4)	2595 (88.6)	2713 (90.0)	< 0.001	1879 (96.9)	1875 (97.2)	1940 (97.3)	0.708
Other marital status	397 (13.6)	335 (11.4)	301 (10.0)		61 (3.1)	55 (2.8)	54 (2.7)	
Education, n (%)								
Below high school	2090 (71.4)	2026 (69.1)	2112 (70.1)	0.440	568 (29.3)	458 (23.7)	327 (16.4)	< 0.001
High school	559 (19.1)	611 (20.9)	601 (19.9)		625 (32.2)	625 (32.4)	596 (29.9)	
College or above	279 (9.5)	293 (10.0)	301 (10.0)		747 (38.5)	847 (43.9)	1071 (53.7)	
Smoking status, n (%)								
Non-current smokers	1864 (63.7)	1798 (61.4)	1707 (56.6)	< 0.001	1720 (88.7)	1674 (86.7)	1674 (84.0)	< 0.001
Current smokers	1064 (36.3)	1132 (38.6)	1307 (43.4)		220 (11.3)	256 (13.3)	320 (16.0)	
Drinking status, n (%)								
Non-current drinkers	1822 (62.2)	1784 (60.9)	1794 (59.5)	0.102	1016 (52.4)	915 (47.4)	817 (41.0)	< 0.001
Current drinkers	1106 (37.8)	1146 (39.1)	1220 (40.5)		924 (47.6)	1015 (52.6)	1177 (59.0)	
Physical activity, n (%)								
Inactive	390 (13.3)	328 (11.2)	245 (8.1)	< 0.001	105 (5.4)	62 (3.2)	40 (2.0)	< 0.001
Light	798 (27.3)	665 (22.7)	625 (20.7)		331 (17.1)	239 (12.4)	160 (8.0)	
Moderate	903 (30.8)	910 (31.1)	896 (29.7)		905 (46.6)	885 (45.9)	843 (42.3)	
Vigorous	837 (28.6)	1027 (35.1)	1248 (41.4)		599 (30.9)	744 (38.5)	951 (47.7)	
BMI, mean (SD), kg/m^2	25.7 (3.9)	23.9 (3.7)	21.2 (2.9)	< 0.001	34.3 (5.5)	27.7 (4.4)	26.4 (4.4)	< 0.001
WC, median (Q1-Q3), cm	91.0 (86.0-97.6)	87.9 (80.0–93.0)	77.2 (73.0-80.8)	< 0.001	112.4 (107.3-120.7)	95.3 (89.5-100.3)	92.1 (81.3-100.3)	< 0.001
SBP, mean (SD), mmHg	147.0 (20.2)	127.7 (19.0)	117.4 (12.6)	< 0.001	137.4 (20.7)	136.5 (20.6)	119.3 (14.5)	< 0.001
HbA_{1c}, mean (SD), %	5.48 (1.06)	5.30 (0.76)	5.03 (0.42)	< 0.001	6.21 (1.12)	5.71 (0.66)	5.56 (0.49)	< 0.001
TC, mean (SD), mmol/L	5.18 (1.04)	5.02 (0.98)	4.84 (0.96)	< 0.001	3.31 (0.69)	3.41 (0.72)	3.49 (0.70)	< 0.001
CRP, median (Q1-Q3), mg/L	1.4 (0.7–2.7)	1.0 (0.6-2.0)	0.8 (0.5–1.6)	< 0.001	1.6 (0.7–3.3)	1.0 (0.5–2.2)	0.8 (0.4–1.7)	< 0.001
FI, median (Q1-Q3)	18.1 (11.3–28.1)	15.7 (9.4–25.3)	15.3 (9.2–23.4)	< 0.001	17.4 (9.0-27.4)	12.3 (6.0-21.6)	8.6 (4.5–17.3)	< 0.001

T1 was the lower tertile, T2 was the middle tertile, and T3 was the upper tertile. In the CHARLS, T1 of eGDR ≤ 7.75, 7.75 < T2 of eGDR ≤ 10.74, T3 of eGDR > 10.74. In the HRS, T1 of eGDR ≤ 5.29, 5.29 < T2 of eGDR ≤ 7.47, T3 of eGDR > 7.47

CHARLS, China Health and Retirement Longitudinal Study; HRS, Health and Retirement Study; eGDR, the estimated glucose disposal rate; BMI, body mass index; WC, waist circumference; SBP, systolic blood pressure; HbA_{1c}, glycated hemoglobin A_{1c}; TC, total cholesterol; CRP, C-reactive protein; FI, frailty index; SD, standard deviation; IQR, interquartile range

diabetic participants (CHARLS, β: -0.575, 95%CI -0.861 to -0.290, $P < 0.001$; HRS, β: -0.365, 95%CI -0.679 to -0.052, $P = 0.023$). For continuous eGDR, the increment of eGDR was associated with the decelerated FI progression among participants without diabetes in both cohorts (CHARLS, β: -0.108, 95%CI -0.153 to -0.063, $P < 0.001$; HRS, β: -0.175, 95%CI -0.221 to -0.130, $P < 0.001$) and participants with diabetes in the CHARLS (β: -0.228, 95%CI -0.324 to -0.133, $P < 0.001$). After further excluding baseline frail participants (Table 5), the T3 of eGDR also had associations with the decelerated FI progression among participants with diabetes (CHARLS, β: -0.685, 95%CI -1.005 to -0.366, $P < 0.001$; HRS, β: -0.556, 95%CI -0.922 to -0.191, $P = 0.003$) and without diabetes (CHARLS, β: -0.239, 95%CI -0.347 to -0.130, $P < 0.001$; HRS, β: -0.336, 95%CI -0.454 to -0.219, $P < 0.001$). In both cohorts, the continuous eGDR was associated with decelerated FI progression among participants with diabetes (CHARLS, β: -0.247, 95%CI -0.356 to -0.138, $P < 0.001$; HRS, β: -0.159, 95%CI -0.306 to -0.013, $P = 0.033$) and without diabetes (CHARLS, β: -0.115, 95%CI -0.161 to -0.068, $P < 0.001$; HRS, β: -0.186, 95%CI -0.235 to -0.138, $P < 0.001$). Figures 2 and 3 show the predicted FI trajectories by three tertiles of eGDR among all participants and non-frail participants, respectively.

Table 3 Associations of eGDR with baseline FI

Variables	CHARLS (*n* = 9351)					HRS (*n* = 6184)				
	N	Model 1		Model 2		*N*	Model 1		Model 2	
		β (95% CI)	*P* value	β (95% CI)	*P* value		β (95% CI)	*P* value	β (95% CI)	*P* value
All participants										
T1 of eGDR	3086	[Reference]	—	[Reference]	—	2041	[Reference]	—	[Reference]	—
T2 of eGDR	3086	-2.449(-3.099 to -1.800)	< 0.001	-1.540(-2.169 to -0.912)	< 0.001	2044	-4.639(-5.421 to -3.858)	< 0.001	-1.999(-2.788 to -1.211)	< 0.001
T3 of eGDR	3179	-3.549(-4.194 to -2.905)	< 0.001	-2.289(-2.995 to -1.583)	< 0.001	2099	-8.050(-8.827 to -7.273)	< 0.001	-3.021(-3.873 to -2.168)	< 0.001
Trend test			< 0.001		< 0.001			< 0.001		< 0.001
eGDR per 1 SD	9351	-1.672(-1.935 to -1.408)	< 0.001	-1.146(-1.435 to -0.857)	< 0.001	6184	-3.816(-4.131 to -3.501)	< 0.001	-1.683(-2.068 to -1.298)	< 0.001
Participants without diabetes										
T1 of eGDR	2260	[Reference]	—	[Reference]	—	1179	[Reference]	—	[Reference]	—
T2 of eGDR	2566	-1.915(-2.635 to -1.195)	< 0.001	-1.146(-1.838 to -0.454)	0.001	1709	-2.223(-3.094 to -1.351)	< 0.001	-0.700(-1.584 to 0.184)	0.121
T3 of eGDR	2919	-2.912(-3.612 to -2.213)	< 0.001	-1.985(-2.747 to -1.224)	< 0.001	1940	-4.949(-5.799 to -4.099)	< 0.001	-1.472(-2.414 to -0.530)	0.002
Trend test			< 0.001		< 0.001			< 0.001		0.001
eGDR per 1 SD	7745	-1.346(-1.644 to -1.047)	< 0.001	-0.849(-1.173 to -0.524)	< 0.001	4828	-2.424(-2.775 to -2.072)	< 0.001	-0.819(-1.237 to -0.401)	< 0.001
Participants with diabetes										
T1 of eGDR	826	[Reference]	—	[Reference]	—	862	[Reference]	—	[Reference]	—
T2 of eGDR	520	-3.102(-4.642 to -1.561)	< 0.001	-2.050(-3.568 to -0.531)	0.008	335	-3.634(-5.461 to -1.807)	< 0.001	-1.087(-2.880 to 0.707)	0.235
T3 of eGDR	260	-3.030(-4.987 to -1.073)	0.002	-1.585(-3.640 to 0.469)	0.131	159	-7.196(-9.645 to -4.747)	< 0.001	-2.079(-4.396 to 0.238)	0.079
Trend test			< 0.001		0.034			< 0.001		0.062
eGDR per 1 SD	1606	-1.720(-2.368 to -1.072)	< 0.001	-1.299(-1.995 to -0.602)	< 0.001	1356	-3.920(-4.802 to -3.038)	< 0.001	-1.410(-2.447 to -0.372)	0.008

T1 was the lower tertile, T2 was the middle tertile, and T3 was the upper tertile. In the CHARLS, T1 of eGDR ≤ 7.71, 7.71 < T2 of eGDR ≤ 10.72, T3 of eGDR > 10.72. In the HRS, T1 of eGDR ≤ 5.29, 5.29 < T2 of eGDR ≤ 7.46, T3 of eGDR > 7.46

The results of eGDR per 1 SD was presented as the decrease in baseline FI with per 1 SD increase in eGDR

Model 1 was unadjusted; Model 2 was adjusted for age, sex, education, marital status, smoking status, drinking status, physical activity, BMI, total cholesterol, and C-reactive protein

eGDR, the estimated glucose disposal rate; FI, frailty index; CHARLS, China Health and Retirement Longitudinal Study; HRS, Health and Retirement Study; CI, confidence interval; SD, standard deviation

Sensitivity analyses

When using the $eGDR_{130}$ constructed by another definition of hypertension (130/80 mmHg), a higher level of $eGDR_{130}$ was still associated with lower baseline FI and slower FI progression, which was consistent with the main analyses (Supplemental Tables 4–5). Our results were also consistent when using the new FI (30 items) after removing the diabetes item from the original FI (31 items) (Supplemental Tables 6–7). Moreover, the associations of eGDR with baseline FI and FI progression were not materially changed after further adjusting for the uses of drugs (Supplemental Tables 8–9), further adjusting for heart disease, stroke, and chronic kidney disease (Supplemental Tables 10–11), excluding the participants with missing data on covariates (Supplemental Tables 12–13), excluding the participants with any missing data on FI items (Supplemental Tables 14–15), or adding the interactions of covariates and time to the models (Supplemental Table 16). In the stratified analyses by age, sex, and obesity status, similar results were also found (Supplemental Tables 17–22).

Discussion

In this study with two prospective cohorts, we found significant associations of eGDR with baseline frailty and frailty progression. A higher level of eGDR was associated with lower baseline FI and slower FI progression. The associations of eGDR with FI progression were still observed after excluding baseline frail participants. When stratified by the diabetes status, the above associations were also consistent among participants with and without diabetes.

Previous studies have revealed that HOMA-IR and TyG-index were positively associated with frailty

Table 4 Associations of eGDR with FI progression

Variables	CHARLS (*n* = 8872)					HRS (*n* = 5864)				
	N	Model 1		Model 2		*N*	Model 1		Model 2	
		β (95% CI)	*P* value	β (95% CI)	*P* value		β (95% CI)	*P* value	β (95% CI)	*P* value
All participants										
Time, years		1.081(1.013 to 1.150)	< 0.001	1.079(1.011 to 1.148)	< 0.001		1.234(1.164 to 1.304)	< 0.001	1.212(1.142 to 1.282)	< 0.001
T1 of eGDR×Time	2928	[Reference]	—	[Reference]	—	1940	[Reference]	—	[Reference]	—
T2 of eGDR×Time	2930	-0.161(-0.257 to -0.064)	0.001	-0.158(-0.255 to -0.062)	0.001	1930	-0.030(-0.130 to 0.070)	0.556	-0.032(-0.131 to 0.068)	0.534
T3 of eGDR×Time	3014	-0.296(-0.392 to -0.200)	< 0.001	-0.294(-0.390 to -0.198)	< 0.001	1994	-0.379(-0.476 to -0.282)	< 0.001	-0.378(-0.474 to -0.281)	< 0.001
Trend test			< 0.001		< 0.001			< 0.001		< 0.001
eGDR per 1 SD×Time	8872	-0.143(-0.182 to -0.104)	< 0.001	-0.142(-0.181 to -0.103)	< 0.001	5864	-0.172(-0.211 to -0.132)	< 0.001	-0.170(-0.209 to -0.130)	< 0.001
Participants without diabetes										
Time, years		1.016(0.937 to 1.094)	< 0.001	1.014(0.935 to 1.093)	< 0.001		1.170(1.082 to 1.259)	< 0.001	1.151(1.063 to 1.239)	< 0.001
T1 of eGDR×Time	2164	[Reference]	—	[Reference]	—	1137	[Reference]	—	[Reference]	—
T2 of eGDR×Time	2442	-0.117(-0.225 to -0.009)	0.033	-0.114(-0.222 to -0.007)	0.037	1629	-0.003(-0.119 to 0.112)	0.954	-0.010(-0.124 to 0.105)	0.869
T3 of eGDR×Time	2774	-0.223(-0.328 to -0.119)	< 0.001	-0.221(-0.326 to -0.117)	< 0.001	1854	-0.318(-0.429 to -0.207)	< 0.001	-0.323(-0.433 to -0.212)	< 0.001
Trend test			< 0.001		< 0.001			< 0.001		< 0.001
eGDR per 1 SD×Time	7380	-0.109(-0.153 to -0.064)	< 0.001	-0.108(-0.153 to -0.063)	< 0.001	4620	-0.175(-0.221 to -0.129)	< 0.001	-0.175(-0.221 to -0.130)	< 0.001
Participants with diabetes										
Time, years		1.277(1.133 to 1.421)	< 0.001	1.274(1.130 to 1.418)	< 0.001		1.307(1.186 to 1.429)	< 0.001	1.298(1.176 to 1.419)	< 0.001
T1 of eGDR×Time	764	[Reference]	—	[Reference]	—	803	[Reference]	—	[Reference]	—
T2 of eGDR×Time	488	-0.242(-0.470 to -0.014)	0.037	-0.241(-0.468 to -0.013)	0.038	301	0.116(-0.123 to 0.354)	0.342	0.115(-0.123 to 0.354)	0.342
T3 of eGDR×Time	240	-0.578(-0.864 to -0.292)	< 0.001	-0.575(-0.861 to -0.290)	< 0.001	140	-0.365(-0.678 to -0.052)	0.023	-0.365(-0.679 to -0.052)	0.023
Trend test			< 0.001		< 0.001			0.145		0.144
eGDR per 1 SD×Time	1492	-0.229(-0.325 to -0.134)	< 0.001	-0.228(-0.324 to -0.133)	< 0.001	1244	-0.018(-0.133 to 0.098)	0.762	-0.019(-0.134 to 0.097)	0.752

T1 was the lower tertile, T2 was the middle tertile, and T3 was the upper tertile. In the CHARLS, T1 of eGDR ≤ 7.75, 7.75 < T2 of eGDR ≤ 10.74, T3 of eGDR > 10.74. In the HRS, T1 of eGDR ≤ 5.29, 5.29 < T2 of eGDR ≤ 7.47, T3 of eGDR > 7.47

The results of eGDR per 1 SD×Time was presented as the deceleration in FI progression with per 1 SD increase in eGDR

Model 1 was unadjusted; Model 2 was adjusted for age, sex, education, marital status, smoking status, drinking status, physical activity, BMI, total cholesterol, and C-reactive protein. eGDR, the estimated glucose disposal rate; FI, frailty index; CHARLS, China Health and Retirement Longitudinal Study; HRS, Health and Retirement Study; CI, confidence interval; SD, standard deviation

progression [15, 40–42]. However, compared to HOMA-IR and TyG-index, eGDR was a more accessible and reliable IR alternative indicator. The association of eGDR with frailty progression was not investigated before. Our study filled this knowledge gap and found that a higher level of eGDR was associated with lower baseline FI and slower FI progression. When striated by diabetes status, these associations still persisted among participants with and without diabetes in the CHARLS. In the HRS, the association of eGDR with FI progression was not observed in the diabetic participants. However, this association became significant after excluding the baseline frail participants. We supposed that individuals with diabetes were more prone to frailty, unable to further observe the development of frailty, which known as the ceiling effect [36] (Table 5).

While the endocrine system is considered to play a crucial role in the development of frailty, including through complex interactions with the brain, immune system, and skeletal muscle [14], the mechanisms between IR and frailty remain unclear. Some studies suggested that IR and frailty may share the mechanisms of systemic inflammation, oxidative stress, and declining muscle function [43–45]. IR is usually accompanied by elevated production of pro-inflammatory cytokines and the activation of chronic inflammation, which can lead to enhanced

Table 5 Associations of eGDR with FI progression among baseline non-frail participants

Variables	CHARLS (*n* = 6528)					HRS (*n* = 4683)				
	N	Model 1		Model 2		*N*	Model 1		Model 2	
		β (95% CI)	*P* value	β (95% CI)	*P* value		β (95% CI)	*P* value	β (95% CI)	*P* value
All participants										
Time, years		1.257(1.182 to 1.332)	< 0.001	1.254(1.180 to 1.329)	< 0.001		1.290(1.209 to 1.370)	< 0.001	1.276(1.196 to 1.356)	< 0.001
T1 of eGDR×Time	2003	[Reference]	—	[Reference]	—	1371	[Reference]	—	[Reference]	—
T2 of eGDR×Time	2169	-0.140(-0.243 to -0.037)	0.008	-0.140(-0.243 to -0.037)	0.008	1555	-0.064(-0.175 to 0.047)	0.257	-0.070(-0.181 to 0.040)	0.212
T3 of eGDR×Time	2356	-0.319(-0.420 to -0.218)	< 0.001	-0.317(-0.418 to -0.216)	< 0.001	1757	-0.427(-0.533 to -0.321)	< 0.001	-0.431(-0.537 to -0.325)	< 0.001
Trend test			< 0.001		< 0.001			< 0.001		< 0.001
eGDR per 1 SD×Time	6528	-0.151(-0.193 to -0.109)	< 0.001	-0.150(-0.192 to -0.108)	< 0.001	4683	-0.204(-0.248 to -0.160)	< 0.001	-0.206(-0.250 to -0.162)	< 0.001
Participants without diabetes										
Time, years		1.186(1.102 to 1.269)	< 0.001	1.184(1.101 to 1.268)	< 0.001		1.185(1.090 to 1.281)	< 0.001	1.173(1.078 to 1.268)	< 0.001
T1 of eGDR×Time	1547	[Reference]	—	[Reference]	—	916	[Reference]	—	[Reference]	—
T2 of eGDR×Time	1823	-0.102(-0.216 to 0.011)	0.077	-0.103(-0.216 to 0.011)	0.076	1356	0.009(-0.115 to 0.133)	0.890	0.001(-0.122 to 0.124)	0.988
T3 of eGDR×Time	2186	-0.240(-0.348 to -0.131)	< 0.001	-0.239(-0.347 to -0.130)	< 0.001	1653	-0.330(-0.448 to -0.212)	< 0.001	-0.336(-0.454 to -0.219)	< 0.001
Trend test			< 0.001		< 0.001			< 0.001		< 0.001
eGDR per 1 SD×Time	5556	-0.115(-0.162 to -0.069)	< 0.001	-0.115(-0.161 to -0.068)	< 0.001	3925	-0.184(-0.232 to -0.135)	< 0.001	-0.186(-0.235 to -0.138)	< 0.001
Participants with diabetes										
Time, years		1.517(1.346 to 1.688)	< 0.001	1.511(1.340 to 1.681)	< 0.001		1.509(1.351 to 1.667)	< 0.001	1.497(1.339 to 1.655)	< 0.001
T1 of eGDR×Time	456	[Reference]	—	[Reference]	—	455	[Reference]	—	[Reference]	—
T2 of eGDR×Time	346	-0.217(-0.474 to 0.040)	0.099	-0.220(-0.477 to 0.037)	0.095	199	-0.078(-0.371 to 0.215)	0.603	-0.077(-0.370 to 0.216)	0.607
T3 of eGDR×Time	170	-0.688(-1.008 to -0.369)	< 0.001	-0.685(-1.005 to -0.366)	< 0.001	104	-0.556(-0.922 to -0.191)	0.003	-0.556(-0.922 to -0.191)	0.003
Trend test			< 0.001		< 0.001			0.007		0.007
eGDR per 1 SD×Time	972	-0.246(-0.356 to -0.137)	< 0.001	-0.247(-0.356 to -0.138)	< 0.001	758	-0.157(-0.304 to -0.010)	0.036	-0.159(-0.306 to -0.013)	0.033

Non-frail participants were defined as participants with baseline frailty index < 25. T1 was the lower tertile, T2 was the middle tertile, and T3 was the upper tertile. In the CHARLS, T1 of eGDR ≤ 7.75, 7.75 < T2 of eGDR ≤ 10.74, T3 of eGDR > 10.74. In the HRS, T1 of eGDR ≤ 5.29, 5.29 < T2 of eGDR ≤ 7.47, T3 of eGDR > 7.47

The results of eGDR per 1 SD×Time was presented as the deceleration in FI progression with per 1 SD increase in eGDR

Model 1 was unadjusted; Model 2 was adjusted for age, sex, education, marital status, smoking status, drinking status, physical activity, BMI, total cholesterol, and C-reactive protein. eGDR, the estimated glucose disposal rate; FI, frailty index; CHARLS, China Health and Retirement Longitudinal Study; HRS, Health and Retirement Study; CI, confidence interval; SD, standard deviation

glycogenesis, inhibition of β-oxidation, increased free fatty acids, and accumulation of TC in skeletal muscle and the liver [46–48]. In addition, as one of the major target tissues for insulin action, skeletal muscle is a primary site where insulin resistance occurs [49]. IR reduces the sensitivity of skeletal muscle cells to insulin, thereby decreasing glucose uptake [49]. Therefore, IR is associated with a decline in muscle strength and function, which may potentially trigger the onset and progression of frailty.

Our findings have important clinical and public health implications. In the clinical practice, clinicians should pay attention to the eGDR levels among diabetic participants for delaying frailty progression. However, frailty is a common geriatric syndrome, which may occur among non-diabetic participants with aging [50]. Therefore, in the public health practice, it is necessary for non-diabetic participants to pay attention to their eGDR levels as early as possible for preventing the rapid frailty progression in the future. In addition, recent studies found that increased exercise and intake of dietary fiber were positively associated with eGDR [51, 52], indicating that these interventions, such as exercise and intake of dietary fiber, may also be effective for improving eGDR levels to delay the frailty progression.

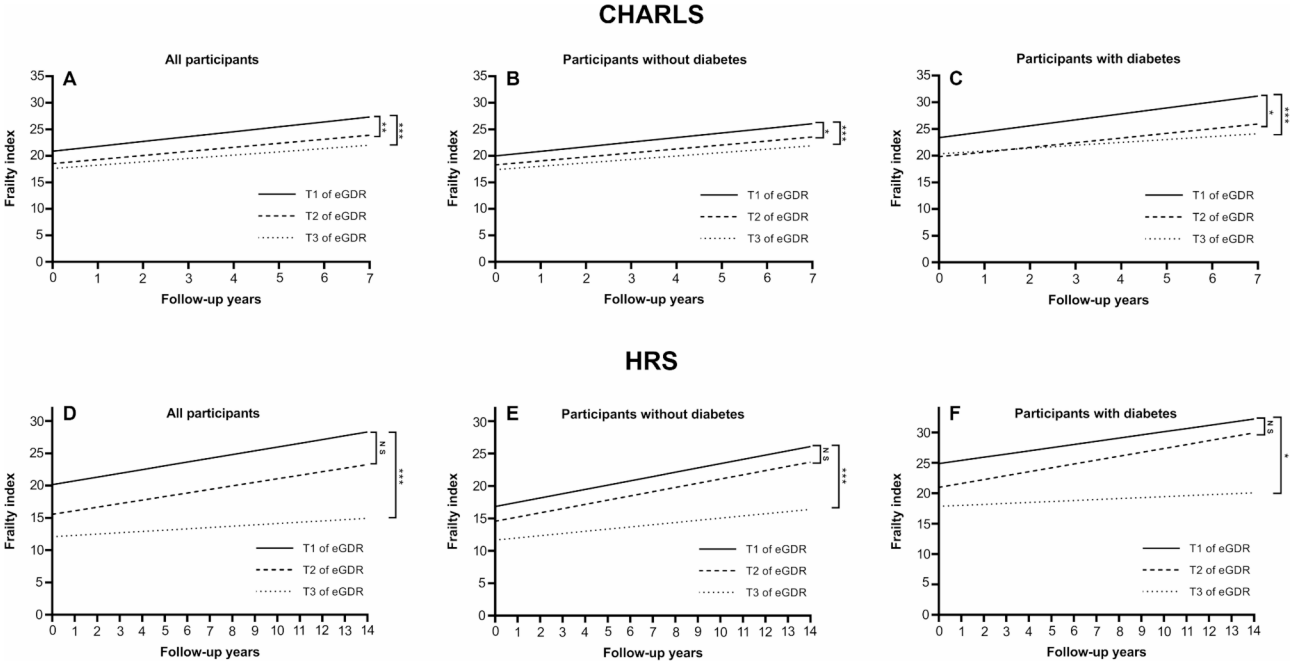


Fig. 2 Predicted FI trajectories by three tertiles of eGDR among all participants. **A**, all participants in the CHARLS; **B**, participants without diabetes in the CHARLS; **C**, participants with diabetes in the CHARLS; **D**, all participants in the HRS; **E**, participants without diabetes in the HRS; **F**, participants with diabetes in the HRS. The intercept of each line represented the level of baseline FI and the slope of each line represented the level of FI progression. T1 was the lower tertile, T2 was the middle tertile, and T3 was the upper tertile. In the CHARLS, T1 of eGDR ≤ 7.75, 7.75 < T2 of eGDR ≤ 10.74, T3 of eGDR > 10.74. In the HRS, T1 of eGDR ≤ 5.29, 5.29 < T2 of eGDR ≤ 7.47, T3 of eGDR > 7.47. CHARLS, China Health and Retirement Longitudinal Study; HRS, Health and Retirement Study; eGDR, the estimated glucose disposal rate; NS, not significant ($P \geq 0.05$); *, $0.01 \leq P < 0.05$; **, $0.001 \leq P < 0.01$; ***, $P < 0.001$

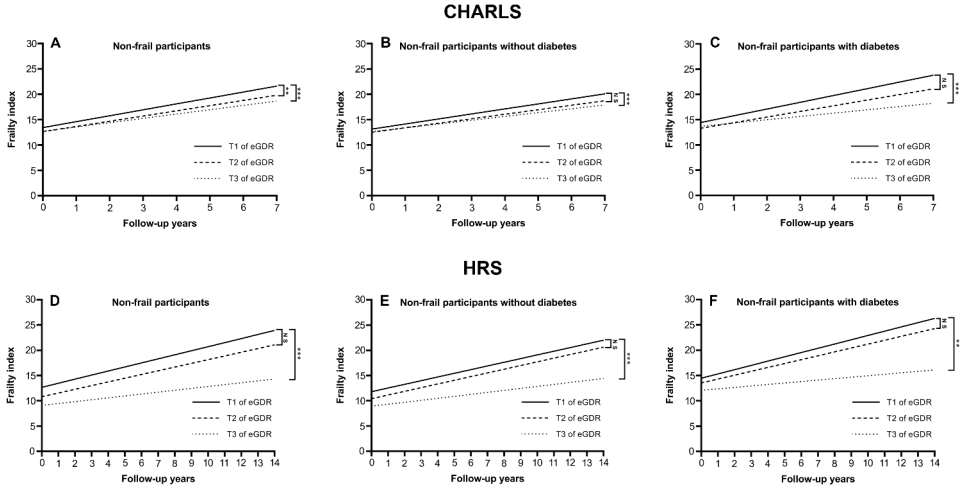


Fig. 3 Predicted FI trajectories by three tertiles of eGDR among non-frail participants. **A**, non-frail participants in the CHARLS; **B**, non-frail participants without diabetes in the CHARLS; **C**, non-frail participants with diabetes in the CHARLS; **D**, non-frail participants in the HRS; **E**, non-frail participants without diabetes in the HRS; **F**, non-frail participants with diabetes in the HRS. The intercept of each line represented the level of baseline FI and the slope of each line represented the level of FI progression. T1 was the lower tertile, T2 was the middle tertile, and T3 was the upper tertile. In the CHARLS, T1 of eGDR ≤ 7.75, 7.75 < T2 of eGDR ≤ 10.74, T3 of eGDR > 10.74. In the HRS, T1 of eGDR ≤ 5.29, 5.29 < T2 of eGDR ≤ 7.47, T3 of eGDR > 7.47. CHARLS, China Health and Retirement Longitudinal Study; HRS, Health and Retirement Study; eGDR, the estimated glucose disposal rate; NS, not significant ($P \geq 0.05$); *, $0.01 \leq P < 0.05$; **, $0.001 \leq P < 0.01$; ***, $P < 0.001$

There are several advantages in this study. As far as we know, this is the first study to explore the associations of eGDR with frailty progression. This study involved two prospective cohorts from different ethnicities, which had large samples size and rigorous study design. Our findings were consistent across both cohorts, indicating the generality of our results. The robustness of our results was also ensured by diverse sensitivity analyses.

However, this study also has several limitations. First, our study was observational, the causation could not be inferred. Second, the current definition of hypertension is controversial, we therefore performed a sensitivity analysis to redefine $eGDR_{130}$ using another definition of hypertension (130/80 mmHg). The results were consistent with the main analysis (Supplemental Tables 4–5). Third, the selection bias may exist, total of 799 (5.1%) participants were excluded because losing follow-up. The baseline characteristics of included and excluded participants were compared, showing the selection bias (Supplemental Tables 23–24). However, the rate of losing follow-up was relatively low, indicating the selection bias could be small. Finally, while we controlled various covariates, other residual confounding or unmeasured variables may remain, such as diet and genetic susceptibility.

Conclusion

Regardless of diabetes or not, a higher level of eGDR was associated with the decelerated frailty progression. Our findings highlight the role of eGDR in frailty progression and recommend taking effective interventions to improve eGDR for preventing frailty progression.

Abbreviations

IR	Insulin resistance
eGDR	The estimated glucose disposal rate
FI	Frailty index
CVD	Cardiovascular disease
CVD	Waist circumference
BMI	Body mass index
HRS	Health and Retirement Study
CHARLS	China Health and Retirement Longitudinal Study
HIEG	Hyperinsulinemic-euglycemic
HOMA-IR	Homeostasis model assessment for insulin resistance
TyG-BMI	Triglyceride glucose-body mass index
BP	Blood pressure
SBP	Systolic blood pressure
FBG	Fasting blood glucose
HbA_{1c}	Glycosylated hemoglobin A_{1c}
HbA1c	Total cholesterol
CRP	C-reactive protein
SD	Standard deviation
IQR	Interquartile range
CI	Confidence interval

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12933-025-02650-7 .

Supplementary Material 1

Acknowledgements

All authors thank the original data collectors, depositors, copyright holders, and funders of China Health and Retirement Longitudinal Study, Health and Retirement Study.

Author contributions

ZW, JZ, DH, and HH conceptualized this study. ZW, SX, and SD analyzed the data. ZW, JZ, DH did literature review and interpreted the result. ZW wrote the manuscript. JZ, ZS, SC, DH, and HH provided revision of the manuscript. All authors read and approved the final manuscript for publication.

Funding

This work was supported by the National Natural Science Foundation of China (No. 82000404) and a grant from the Natural Science Funds of Zhejiang Province, China (Project No. LQ21H020003).

Data availability

No datasets were generated or analysed during the current study.

Declarations

Competing interests

The authors declare no competing interests.

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Received: 31 December 2024 / Accepted: 14 February 2025
Published online: 19 February 2025

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