Research Square

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Joint Association of Estimated Glucose Disposal Rate (eGDR) and Obesity-Related Indices with Frailty Incidence: A Nationwide Prospective Cohort Study

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Research Article

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Abstract

Background Estimated glucose disposal rate (eGDR) is a surrogate marker of insulin resistance. A Body Shape Index (ABSI), Body Roundness Index (BRI), Chinese Visceral Adiposity Index (CVAI), Conicity Index (CI), and Waist-to-Height Ratio (WHtR) are established obesity measures, each linked to frailty risk. However, the combined effect of eGDR and these indices on frailty remains unclear. Thus, this study assessed their independent and joint associations with frailty risk.

Methods Data for this study came from the China Health and Retirement Longitudinal Study (CHARLS). Using receiver operating characteristic (ROC) curve analysis, we determined the optimal cut-off values for eGDR and obesity-related indices and then dichotomized participants accordingly. Univariate and multivariable Cox proportional hazards models, as well as restricted cubic spline (RCS) analysis, were applied to examine the associations between eGDR, obesity-related indices, and frailty risk. Predictive performance was evaluated using ROC curves, net reclassification improvement (NRI), and integrated discrimination improvement (IDI). Additionally, we assessed interaction effects and conducted subgroup analyses.

Results We included 7,472 participants (49% male, 51% female). Low eGDR plus high obesity-related indices increased frailty risk versus high eGDR plus low indices. The hazard ratios (HRs) for high ABSI, BRI, CVAI, CI, and WHtR (each with low eGDR) were 1.94 (95% CI: 1.41–2.67), 2.30 (1.65–3.19), 2.20 (1.58–3.07), 1.95 (1.42–2.66), and 2.21 (1.59–3.08), respectively. Adding eGDR to obesity indices improved frailty prediction. The area under the curve (AUC) for ABSI, BRI, CVAI, CI, and WHtR combined with eGDR were 0.671 (0.642–0.700), 0.672 (0.643–0.700), 0.669 (0.640–0.698), 0.669 (0.640–0.698), and 0.670 (0.641–0.699). The NRI and IDI for these combinations were 0.132/0.005, 0.187/0.003, 0.137/0.003, 0.153/0.004, and 0.152/0.003 (all $P<0.05$). No additive interaction was found between eGDR and any obesity index.No multiplicative interaction was observed between eGDR and BRI, CVAI, or WHtR. However, significant negative multiplicative interactions were identified between eGDR and ABSI, as well as between eGDR and CI.

Conclusions Lower eGDR and higher obesity-related indices independently and jointly predict frailty risk.The joint associations of different obesity-related indices with eGDR varied.Their combined use helps identify individuals at high risk early.

Research insights

What is currently known about this topic?

1.As a surrogate marker of insulin resistance, eGDR is associated with frailty and its progression.

2.In middle-aged and older adults, obesity-related indices are associated with the risk of frailty.

3.The incidence of frailty increases in the older adult population.

What is the key research question?

Whether eGDR and obesity-related indices are independently and jointly associated with frailty risk.

What is new?

1.eGDR and obesity-related indices independently and jointly increase the risk of frailty.

2.Combining eGDR with obesity-related indices enhances the accuracy of frailty prediction.

3.A significant negative multiplicative interaction exists between ABSI, CI, and eGDR.

How might this study influence clinical practice?

Combining eGDR with obesity-related indices is expected to enable earlier screening of individuals at high risk of frailty in the general population.

Introduction

Frailty is a clinical syndrome characterized by reduced physiological reserve and increased vulnerability to stressors. Even minor stress can lead to marked deterioration in health status[1]. As population aging accelerates, frailty has become a major concern in geriatrics and public health. It is closely associated with increased care needs and healthcare resource utilization[2]. A systematic review of 61,500 community-dwelling older adults reported a weighted prevalence of 10.7% for frailty and 41.6% for prefrailty, indicating a substantial and widespread community burden of frailty[3].In China, nationally representative studies have shown that frailty is closely associated with an increased risk of cardiovascular disease. Longitudinal evidence further indicates significant associations between frailty and the progression of physical and mental multimorbidity, suggesting that its impact extends beyond a single disease domain[4–5]. More importantly, frailty is not merely a manifestation of aging but a distinct risk state that independently predicts adverse outcomes, including falls, disability, hospitalization, and mortality[6]. Therefore, early identification of frailty, along with targeted monitoring and intervention, is essential for reducing adverse health outcomes and alleviating the overall healthcare burden.

Insulin resistance (IR) refers to reduced responsiveness of target tissues (skeletal muscle, liver, and adipose tissue) to insulin. This results in impaired glucose utilization, inadequate suppression of hepatic glucose output, and dysregulated lipid metabolism. Fundamentally, IR reflects a disruption of systemic metabolic homeostasis[7].IR is associated not only with disturbances in glucose metabolism but also with increased disease burden, functional impairment, and higher disability risk. Therefore, it can be considered an important risk marker for adverse health outcomes in older adults[8].Moreover, individuals with persistently elevated IR levels are more likely to develop frailty, experience its progression, and develop cardiovascular disease. This suggests that IR may play a role in the long-term development and progression of frailty[9].For measuring IR, the hyperinsulinemic-euglycemic clamp technique allows quantitative assessment of whole-body insulin sensitivity and has long been regarded as the gold standard. However, due to its invasiveness and high implementation costs, large-scale clinical application of this technique is severely limited[10–11].In this context, the estimated glucose disposal rate (eGDR) has been proposed as a convenient surrogate marker that effectively reflects IR[12]. eGDR is calculated by integrating key clinical variables, including glycated hemoglobin (HbA1c), waist circumference (WC), and hypertension status[13]. Previous studies indicate that lower eGDR levels generally reflect more severe IR[14].IR is not an isolated metabolic abnormality. It is often accompanied by inflammation and cognitive decline, which collectively affect muscle function and overall physiological reserve in older adults. These processes thereby form a pathophysiological basis for frailty[15].Accordingly, eGDR, as a surrogate marker of IR, is considered to have a potential biological association with frailty.

Obesity, particularly abdominal obesity and visceral fat accumulation, is not mutually exclusive with frailty. Among middle-aged and older adults, increased visceral fat area is often associated with a higher risk of frailty and poorer physical performance[16]. Although body mass index(BMI) remains the most commonly used clinical indicator for obesity assessment, it cannot distinguish between fat and muscle components. It also fails to adequately reflect fat distribution characteristics. These limitations hinder its ability to identify frailty risk[17]. Given this shortcoming, obesity-related indices that combine waist circumference with height, weight, and other parameters have recently gained

increasing attention. These include the A Body Shape Index (ABSI), Body Roundness Index (BRI), Conicity Index (CI), and Waist-to-Height Ratio (WHtR). These indices reflect central obesity or body fat distribution better than BMI[18–19]. In relevant population studies, elevated ABSI is associated with a higher risk of frailty and demonstrates superior discriminative value compared to BMI[20]. Elevated BRI is also associated with a nonlinear increase in frailty risk[21]. CI, an indicator of abdominal fat accumulation, is positively correlated with frailty[19]. WHtR shows a stronger correlation with the frailty index than BMI does. This suggests that after height adjustment, waist circumference-related indices may be more suitable for frailty risk stratification[17].In Chinese populations, the Chinese Visceral Adiposity Index (CVAI) — a surrogate marker of visceral adiposity constructed from age, BMI, waist circumference, triglycerides, and high-density lipoprotein cholesterol — has been used to assess obesity-related outcomes such as diabetes, hypertension, and heart disease in middle-aged and older adults[22]. Therefore, examining frailty from the perspectives of abdominal obesity and visceral fat deposition has a solid theoretical basis. Furthermore, comparing the strength of associations between frailty and indices such as ABSI, BRI, CVAI, CI, and WHtR may help identify more suitable risk assessment indicators for middle-aged and older populations.

eGDR and obesity-related indices may influence frailty development through synergistic pathways. Therefore, using data from the China Health and Retirement Longitudinal Study (CHARLS), we examined their independent and joint associations with frailty risk. We also assessed interaction effects and performed subgroup analyses.

Method

Study design and populations

This study was based on data from the CHARLS, a national prospective cohort that systematically collected longitudinal data on multidimensional health indicators (including physiological, psychological, and socioeconomic parameters) from middle-aged and older adults aged 45 years and above. The baseline survey employed a multistage stratified probability sampling method, covering 150 counties/districts and 450 urban communities/villages across 28 provinces in China, ultimately enrolling 17,708 nationally representative participants.The baseline survey was conducted in 2011, with follow-ups every 2–3 years thereafter. Detailed information on the study design and cohort characteristics is available on the CHARLS official website[23]. All participants provided written informed consent. The study was approved by the Institutional Review Board of Peking University (IRB00001052-11015). The study adhered to the ethical principles of the Declaration of Helsinki and was conducted in strict accordance with the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines.

We analyzed data from the CHARLS study spanning 2011 to 2015. The following exclusion criteria were applied. First, 4,671 participants with missing or outlier values for eGDR and obesity-related indicators (height, weight, waist circumference, glycated hemoglobin, and hypertension) were excluded. Second, 4,178 participants with incomplete baseline characteristics were excluded. Third, 1,387 participants aged < 45 years or diagnosed with frailty at or before the baseline survey were excluded. After applying these criteria, 7,472 participants were included in the final analysis. Figure 1 presents the flowchart of participant inclusion and exclusion.

Assessment of eGDR

In this study, eGDR was used as a quantitative measure of IR, with its calculation formula integrating key metabolic parameters, including WC, HbA1c, and hypertension status. The formula is as follows:eGDR = 21.158 − 0.09 x WC(cm) − 3.407 x hypertension(yes = 1,no = 0) − 0.551 x HbA1c(%)[24].

Assessment of ABSI, BRI, CVAI, CI and WHtR

The obesity-related indices used in this analysis include ABSI, BRI, CVAI, CI, and WHtR. These indices are widely used as markers of obesity in epidemiological studies to predict disease risk[25]. Height was measured following standard procedures. Participants stood barefoot and upright, with their heads positioned in the Frankfurt plane. Body weight was measured using a calibrated electronic scale, with participants wearing only light clothing. Waist circumference was measured with participants in a natural standing position, using a soft tape measure placed horizontally around the navel. The calculation of CVAI additionally requires blood sampling to assess triglyceride (TG) and high-density lipoprotein cholesterol (HDL-C) levels. BMI is calculated as BMI = weight (kg) / height (m)² [26]. The formulas for calculating ABSI, BRI, CVAI, CI, and WHtR are as follows:

1. $ABSI = \frac{\mathrm{WC(m)}}{Height(m)^{1/2} \times BMI^{2/3}}$[27]
2. $BRI = 364.2 - 365.5\sqrt{1 - \left(\frac{(WC(m)/(2\pi))^2}{(0.5 \times Height(m))^2}\right)}$[28]
3. Males: $CVAI = -267.93 + 0.68 \times age + 0.03 \times BMI(kg/m^2) + 4.00 \times WC(cm) + 22.00 \times \log_{10} TG(mmol/l) - 16.32 \times HDL - C(mmol/l)$
   Females: $CVAI = -187.32 + 1.71 \times age + 4.32 \times BMI(kg/m^2) + 1.12 \times WC(cm) + 39.76 \times \log_{10} TG(mmol/l) - 11.66 \times HDL - C(mmol/l)$[29]
4. $CI = \frac{WC(m)}{0.109\sqrt{\frac{weight(kg)}{height(m)}}}$[30]
5. $WHtR = WC(cm)/Height(cm)$[31]

Assessment of frailty

In this study, the incidence of frailty served as the primary outcome and was treated as a binary variable. Frailty was evaluated with the Fried criteria, which comprise the following five components: unintentional weight loss, self-reported exhaustion, reduced grip strength, slow walking speed, and low physical activity level[32]. Using the Fried criteria, the CHARLS database, and previously established medical evidence, we developed a modified frailty assessment tool. Its validity has been confirmed across several studies[33]. This work employed the updated frailty diagnostic criteria, which encompass exhaustion, weakness, physical inactivity, weight loss, and slowness. The detailed evaluation process is outlined below:(1) **Exhaustion**: Exhaustion was deemed present when participants selected “Most or all of the time” or “Occasionally or a moderate amount of the time” in response to either of the Chinese-language questions from the Center for Epidemiologic Studies Depression Scale (CES-D): “I felt everything I did was an effort during last week” or “I could not get going during last week.” This measure was defined in the same manner as the original variable proposed by Fried et al[32].(2) **Weakness**: Weakness was assessed via the self-reported item: “having difficulty in lifting or carrying weights over 5 kg”[34].(3) **Low physical activity**: Low physical activity was defined as meeting neither of the following conditions during a typical week: engaging in any physical activity or walking for at least 10 minutes per session. This definition differs from the one originally introduced by Fried and colleagues[32]. Nevertheless, this same measure has been employed in a prior comparable study as an indicator of low physical activity [35]. (4) **Weight loss**: Unintentional weight reduction of ≥ 5 kg over the preceding year, or a current body mass index (BMI) ≤ 18.5 kg/m², was used to define weight loss [33]. Evidence indicates that weight loss predicts frailty more effectively than either BMI or caloric intake [36]. (5) **Slowness**: Slowness was deemed present when participants experienced difficulty walking 100 meters or climbing multiple flights of stairs without rest. This definition aligns with the approach taken in earlier research [34].In our study, frailty was defined as the presence of three or more of the five components described above.

Covariates

Covariates in this study included age, sex, household registration, education level, marital status, smoking status, alcohol consumption, BMI, hypertension, diabetes, and dyslipidemia. Household registration was categorized as agricultural or others. Education level was classified into three levels: primary school or below, secondary school, and college or above. Marital status was categorized as married or others. Smoking status was determined based on participants' self-reported history of tobacco use and categorized as smokers or never smokers. Alcohol consumption status was classified as drinkers or non-drinkers according to alcohol use behavior over the past year. Hypertension was defined as self-reported history of hypertension, systolic blood pressure ≥ 140 mmHg, diastolic blood pressure ≥ 90 mmHg, or current use of antihypertensive medication[37]. Diabetes was determined by fasting blood glucose (FBG) level ≥ 7.0 mmol/L, HbA1c ≥ 6.5%, current use of antidiabetic medication, or self-reported history of diabetes[38]. The diagnosis of dyslipidemia was based on self-reported history, use of lipid-lowering medications, or lipid measurements such as triglycerides (TG) ≥ 150 mg/dL, total cholesterol (TC) ≥ 240 mg/dL, high-density lipoprotein cholesterol (HDL-C) < 40 mg/dL, or low-density lipoprotein cholesterol (LDL-C) ≥ 160 mg/dL[39].

Statistical analysis

In this study, descriptive statistical methods were used to analyze the baseline characteristics of participants. Based on the Kolmogorov-Smirnov test, all continuous variables with non-normal distributions were summarized as medians and interquartile ranges (IQR). Differences in baseline characteristics across groups were compared using the Kruskal-Wallis test. Categorical variables were presented as counts and percentages, with between-group differences assessed by the chi-square test. The distribution characteristics of continuous independent variables were visualized using histograms. Participants were then divided into four groups based on the optimal cut-off values of eGDR and obesity-related indices derived from Receiver Operating Characteristic (ROC) curves: (1) high eGDR and low obesity-related indices; (2) low eGDR and low obesity-related indices; (3) high eGDR and high obesity-related indices; (4) low eGDR and high obesity-related indices.

Kaplan-Meier curves were used to estimate the cumulative incidence of frailty. The log-rank test was applied to assess differences between groups. After adjusting for covariates (age, sex, household registration, education level, marital status, smoking status, alcohol consumption, BMI, hypertension, diabetes, and dyslipidemia), we employed restricted cubic splines (RCS) to examine the dose-response relationships between eGDR, ABSI, BRI, CVAI, CI, WHtR, and frailty occurrence. Given no evidence of violation of the proportional hazards assumption, we fitted crude, partially adjusted, and fully adjusted Cox proportional hazards models. These models estimated the hazard ratios (HRs) and corresponding 95% confidence intervals (CIs) for frailty occurrence associated with eGDR, ABSI, BRI, CVAI, CI, WHtR, and their combination.Subsequently, interaction terms between eGDR and each obesity-related indicator were added to the Cox models to assess their multiplicative interaction. The additive-scale interaction was evaluated using three indices: (1) Relative excess risk due to interaction (RERI) quantifies the excess risk attributable to interaction by comparing the combined effect of two exposures with the sum of their individual effects. (2) Attributable proportion (AP) is the proportion of the risk resulting from combined exposure that is attributable to the interaction between the two exposures. (3) Synergy index (SI) is the ratio of the excess risk due to combined exposure to the sum of excess risks due to each individual exposure.

In addition, ROC curves were plotted to evaluate the predictive performance of eGDR and obesity-related indices for frailty risk. Simultaneously, to estimate their incremental predictive value, we calculated the net reclassification improvement (NRI) and integrated discrimination improvement (IDI).

We conducted subgroup analyses to investigate potential heterogeneity in the associations between eGDR, obesity-related indices, and frailty occurrence. For sensitivity analyses, we recalculated eGDR using the redefined hypertension criteria (≥ 130/80 mmHg) and excluded participants with non-fasting blood samples at baseline.

All statistical analyses were performed using R software, version 4.4.2. A two-sided P value < 0.05 was considered statistically significant.

Results

Baseline characteristics of participants

A total of 7,472 participants were included in this study, of whom 49% were male and 51% were female. Among the participants, the optimal cut-off values derived from ROC curves were 9.3378 for eGDR, 0.0866 for ABSI, 4.60816 for BRI, 92.91 for CVAI, 1.318 for CI, and 0.56 for WHtR.The distributions of eGDR and obesity-related indices are shown in Fig. 2. During a follow-up of up to 4 years, frailty occurred in 1,012 participants. Table 1 presents the baseline characteristics of participants stratified by frailty status. Compared with non-frail participants, those with frailty were older.Regarding anthropometric indicators, individuals with frailty had significantly lower height, body weight, and BMI, and these differences were statistically significant. Among the various obesity-related indices, frail individuals showed higher BRI, CI, and WHtR, whereas the difference in CVAI was not significant (p = 0.32). Although ABSI reached statistical significance, the median values of the two groups were almost identical, suggesting that the difference was primarily driven by the large sample size and lacked practical significance.Regarding metabolic status, eGDR levels were similar between the two groups (p = 0.11). Among biochemical indicators, frail individuals had slightly higher FBG and HbA1c (both p ≤ 0.001) as well as higher HDL-C (p = 0.010), whereas no statistically significant differences were observed in TC, TG, or LDL-C between the two groups. Supplementary **Tables S1–S11** present the baseline characteristics of participants stratified individually and jointly by eGDR and obesity-related indices.

Table 1
Baseline characteristics of the participants stratified by frailty

Characteristics	Overall	Non-frail	Frail	p-value
	N = 7,472	N = 6,460	N = 1,012	
Age,years (median(IQR))	58.00 (52.00, 65.00)	57.00 (51.00, 64.00)	61.00 (55.75, 69.00)	< 0.001
Age, n (%)				< 0.001
Age < 75	7,010 (93.8%)	6,109 (94.6%)	901 (89%)	
Age ≥ 75	462 (6.2%)	351 (5.4%)	111 (11%)	
Hukou, n (%)				< 0.001
Others	1,313 (18%)	1,177 (18%)	136 (13%)	
Agriculture	6,159 (82%)	5,283 (82%)	876 (87%)	
Gender, n (%)				< 0.001
Female	3,844 (51%)	3,177 (49%)	667 (66%)	
Male	3,628 (49%)	3,283 (51%)	345 (34%)	
Marry, n (%)				< 0.001
Others	824 (11%)	666 (10%)	158 (16%)	
Married	6,648 (89%)	5,794 (90%)	854 (84%)	
Education, n (%)				< 0.001
Elementary school and below	5,125 (68.6%)	4,286 (66.3%)	839 (82.9%)	
Secondary school	2,238 (29.9%)	2,067 (32%)	171 (16.9%)	
College and above	109 (1.5%)	107 (1.7%)	2 (0.2%)	
BMI, kg/m2 (median(IQR))	23.20 (20.97, 25.75)	23.27 (21.09, 25.74)	22.68 (20.14, 25.82)	< 0.001
Smoke, n (%)				< 0.001
No	4,462 (60%)	3,777 (58%)	685 (68%)	
Yes	3,010 (40%)	2,683 (42%)	327 (32%)	
Drink, n (%)				< 0.001
No	4,907 (66%)	4,120 (64%)	787 (78%)	
Yes	2,565 (34%)	2,340 (36%)	225 (22%)	
Hypertension, n (%)				0.002
No	4,477 (60%)	3,916 (61%)	561 (55%)	

Abbreviations:eGDR:estimated glucose disposal rate;ABSI:A body shape index;BRI:body roundness index;CVAI:Chinese visceral adiposity index;CI:conicity index;WHtR:waist–height ratio;Hukou:the system of household registration;BMI:body mass index;FBG:fasting blood glucose;HbA1c:glycated hemoglobin;TC:total cholesterol;TG:triglyceride;HDL:high density lipoprotein cholesterol;LDL:low density lipoprotein cholesterol

Characteristics	Overall N = 7,472	Non-frail N = 6,460	Frail N = 1,012	p-value
Yes	2,995 (40%)	2,544 (39%)	451 (45%)	
Diabetes, n (%)				< 0.001
No	6,260 (84%)	5,455 (84%)	805 (80%)	
Yes	1,212 (16%)	1,005 (16%)	207 (20%)	
Dyslipidemia, n (%)				0.47
No	3,911 (52%)	3,392 (53%)	519 (51%)	
Yes	3,561 (48%)	3,068 (47%)	493 (49%)	
Height, cm (Median(IQR))	158.00 (152.30, 164.40)	158.50 (152.80, 164.83)	155.00 (150.00, 160.20)	< 0.001
Weight, kg (Median(IQR))	58.20 (51.50, 65.80)	58.70 (52.10, 66.30)	54.90 (48.18, 63.02)	< 0.001
Waist, cm (Median(IQR))	85.00 (78.00, 92.00)	85.00 (78.27, 92.00)	84.20 (76.97, 92.00)	0.016
FBG, mg/dl (Median(IQR))	102.42 (94.50, 113.40)	102.24 (94.32, 113.04)	103.95 (95.04, 116.28)	< 0.001
HbA1c, mg/dl (Median(IQR))	5.10 (4.90, 5.40)	5.10 (4.90, 5.40)	5.20 (4.90, 5.50)	0.001
TC, mg/dl (Median(IQR))	190.98 (167.78, 215.34)	190.98 (167.40, 215.34)	191.37 (168.94, 217.27)	0.37
TG, mg/dl (Median(IQR))	105.32 (74.34, 153.99)	105.32 (74.34, 153.33)	105.32 (75.22, 153.99)	0.51
HDL, mg/dl (Median(IQR))	49.48 (40.59, 59.92)	49.10 (40.59, 59.92)	50.64 (41.37, 61.47)	0.010
LDL, mg/dl (Median(IQR))	114.43 (93.56, 137.63)	114.43 (93.56, 137.63)	114.63 (92.69, 137.24)	0.83
eGDR, Median(IQR)	9.92 (7.25, 11.06)	9.96 (7.26, 11.05)	9.39 (7.13, 11.09)	0.11
ABSI, Median(IQR)	0.08 (0.08, 0.09)	0.08 (0.08, 0.09)	0.08 (0.08, 0.09)	< 0.001
BRI, Median(IQR)	4.04 (3.23, 5.05)	4.01 (3.24, 5.02)	4.24 (3.22, 5.27)	0.007
CVAI, Median(IQR)	93.54 (67.85, 122.65)	93.04 (67.69, 122.38)	96.44 (68.18, 124.30)	0.32
CI, Median(IQR)	1.28 (1.23, 1.34)	1.28 (1.23, 1.34)	1.30 (1.23, 1.36)	< 0.001
WHtR, Median(IQR)	0.53 (0.49, 0.58)	0.53 (0.49, 0.58)	0.55 (0.49, 0.59)	0.007

Abbreviations:eGDR:estimated glucose disposal rate;ABSI:A body shape index;BRI:body roundness index;CVAI:Chinese visceral adiposity index;CI:conicity index;WHtR:waist–height ratio;Hukou:the system of household registration;BMI:body mass index;FBG:fasting blood glucose;HbA1c:glycated hemoglobin;TC:total cholesterol;TG:triglyceride;HDL:high density lipoprotein cholesterol;LDL:low density lipoprotein cholesterol

Associations of ABSI, BRI, CVAI, CI, WHtR, and eGDR with the incidence of frailty

First, the associations of eGDR and each obesity-related index with the risk of frailty were analyzed independently. Kaplan-Meier survival analysis showed that participants with high ABSI, BRI, CVAI, CI, WHtR or low eGDR had

significantly higher cumulative incidence of frailty (all log-rank P < 0.0001; **Fig. S1**). These findings were confirmed by Cox regression models.After adjusting for potential confounding variables (Model 3), participants with high levels of obesity-related indices had a significantly increased risk of frailty compared with those with low levels: ABSI (HR: 1.30, 95% CI: 1.13–1.50), BRI (HR: 1.48, 95% CI: 1.24–1.75), CVAI (HR: 1.35, 95% CI: 1.15–1.60), CI (HR: 1.24, 95% CI: 1.09–1.42), and WHtR (HR: 1.40, 95% CI: 1.18–1.66).Additionally, compared with high eGDR, participants with low eGDR had a 1.72-fold higher risk of frailty (95% CI: 1.28–2.32) (Table 2). RCS analysis based on Model 3 revealed nonlinear associations of ABSI, BRI, CVAI, CI, WHtR, and eGDR with frailty occurrence (ABSI: P for nonlinear = 0.034; BRI: P for nonlinear < 0.001; CVAI: P for nonlinear < 0.001; CI: P for nonlinear = 0.043; WHtR: P for nonlinear < 0.001; eGDR: P for nonlinear = 0.014) (**Fig. S2**).

We then explored the combined effect of obesity-related indices and eGDR on frailty risk. Kaplan-Meier survival analysis showed that participants with high obesity-related indices and low eGDR had the highest cumulative incidence of frailty, whereas those with low obesity-related indices and high eGDR had the lowest (all log-rank P < 0.0001) (Fig. 3).Furthermore, Cox regression analysis showed that after full adjustment, participants with high obesity-related indices and low eGDR had the greatest risk of frailty. Compared with those having low obesity-related indices and high eGDR, the risk increased by 1.94-fold for high ABSI combined with low eGDR (HR: 1.94, 95% CI: 1.41–2.67), by 2.30-fold for high BRI combined with low eGDR (HR: 2.30, 95% CI: 1.65–3.19), by 2.20-fold for high CVAI combined with low eGDR (HR: 2.20, 95% CI: 1.58–3.07), by 1.95-fold for high CI combined with low eGDR (HR: 1.95, 95% CI: 1.42–2.66), and by 2.21-fold for high WHtR combined with low eGDR (HR: 2.21, 95% CI: 1.59–3.08) (**Table S12**).Meanwhile, we also evaluated the associations of ABSI, BRI, CVAI, CI, WHtR, and eGDR with frailty risk, taking into account the effects of interaction terms (**Table S13**).

Table 2
Associations of ABSI,BRI,CVAI,CI,WHtR and eGDR with frailty

	Case	Crude		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
eGDR									
high eGDR	508(12.16%)	Ref		Ref		Ref		Ref	
low eGDR	504(15.31%)	1.30(1.15–1.47)	< 0.001	1.21(1.07–1.37)	0.002	1.31(1.15–1.49)	< 0.001	1.72(1.28–2.32)	< 0.001
ABSI									
low ABSI	700(11.9%)	Ref		Ref		Ref		Ref	
high ABSI	312(19.63%)	1.77(1.55–2.03)	< 0.001	1.48(1.29–1.70)	< 0.001	1.35(1.17–1.55)	< 0.001	1.30(1.13–1.50)	< 0.001
BRI									
low BRI	592(12.29%)	Ref		Ref		Ref		Ref	
high BRI	420(15.81%)	1.31(1.16–1.49)	< 0.001	1.09(0.96–1.24)	0.204	1.53(1.29–1.81)	< 0.001	1.48(1.24–1.75)	< 0.001
CVAI									
low CVAI	466(12.64%)	Ref		Ref		Ref		Ref	
high CVAI	546(14.42%)	1.17(1.03–1.32)	0.014	1.06(0.93–1.20)	0.395	1.42(1.21–1.66)	< 0.001	1.35(1.15–1.60)	< 0.001
CI									
low CI	588(11.89%)	Ref		Ref		Ref		Ref	
high CI	424(16.78%)	1.46(1.29–1.66)	< 0.001	1.25(1.10–1.42)	< 0.001	1.29(1.13–1.48)	< 0.001	1.24(1.09–1.42)	0.001
WHtR									
low WHtR	586(12.39%)	Ref		Ref		Ref		Ref	
high WHtR	426(15.52%)	1.27(1.13–1.44)	< 0.001	1.05(0.93–1.20)	0.432	1.45(1.22–1.72)	< 0.001	1.40(1.18–1.66)	< 0.001

Model1 adjusted for age and gender;Model2 adjusted for age,gender,hukou,education,marital status,smoking status,drinking status and BMI;Model3 adjusted for factors in model2 and history of hypertension,diabetes,dyslipidemia.

Abbreviations:eGDR:estimated glucose disposal rate;ABSI:A body shape index;BRI:body roundness index;CVAI:Chinese visceral adiposity index;CI:conicity index;WHtR:waist–height ratio

Predictive performance of ABSI, BRI, CVAI, CI, WHtR, and eGDR for frailty occurrence

The predictive performance of obesity-related indices and eGDR for frailty risk was assessed using ROC curve analysis, NRI, and IDI (**Fig. 4**; **Table S14**). When evaluated individually, BRI showed the highest AUC (0.668, 95% CI: 0.639–0.697), whereas CI demonstrated the best reclassification performance (NRI: 0.181, 95% CI: 0.103–0.249). Regarding integrated discrimination improvement, adding BRI or CVAI alone yielded significant IDI gains (all IDI: 0.002, 95% CI: 0.000–0.005).In the integrated modeling assessment, the combination of BRI and eGDR showed the highest diagnostic performance, achieving the highest AUC (0.672, 95% CI: 0.643–0.700) and a significant NRI (0.187, 95% CI: 0.081–0.240). The combination of ABSI and eGDR exhibited the highest IDI (0.005, 95% CI: 0.002–0.010). Overall, the BRI plus eGDR combination performed best in terms of AUC and NRI, whereas the ABSI plus eGDR combination yielded the greatest IDI gain. These results indicate that combining eGDR with obesity-related indices can more effectively improve the predictive value for frailty risk.

Interaction analyses between ABSI, BRI, CVAI, CI, WHtR, and eGDR

The potential additive and multiplicative effects of obesity-related indices and eGDR on frailty risk were evaluated through interaction analysis (**Table 3**). After full adjustment for potential confounders, we observed that the 95% confidence intervals for RERI and AP between eGDR and each obesity-related index crossed 0, and the 95% confidence interval for SI crossed 1.Furthermore, the 95% confidence intervals for the multiplicative effects of eGDR with BRI, CVAI, and WHtR crossed 1, whereas the multiplicative effects of eGDR with ABSI and CI were less than 1 and their 95% confidence intervals did not cross 1. These findings indicate no statistically significant additive interaction between each obesity-related index and eGDR on frailty occurrence.Meanwhile, no multiplicative interaction was observed between BRI, CVAI, or WHtR and eGDR, whereas a significant negative multiplicative interaction existed between ABSI or CI and eGDR, indicating that the relative risk upon combined exposure to the two factors was less than the expected multiplicative effect.

Table 3
Interaction between the ABSI,BRI,CVAI,CI,WHtR and eGDR on frailty

Interactive indices	Interactive effects (95% CI)		
	Model 1	Model 2	Model 3
eGDR and ABSI			
Additive effect			
RERI	**-0.40(-0.83,0.02)**	**-0.33(-0.73,0.07)**	**-0.33(-0.78,0.12)**
AP	**-0.25(-0.53,0.03)**	**-0.21(-0.48,0.06)**	**-0.17(-0.42,0.08)**
SI	**0.60(0.36,1.00)**	**0.64(0.37,1.08)**	**0.74(0.48,1.14)**
Multiplicative effect	**0.72(0.55,0.95)**	**0.75(0.57,0.98)**	**0.73(0.56,0.96)**
eGDR and BRI			
Additive effect			
RERI	**-0.11(-0.41,0.20)**	**0.11(-0.27,0.50)**	**0.17(-0.30,0.64)**
AP	**-0.09(-0.34,0.16)**	**0.06(-0.14,0.27)**	**0.08(-0.12,0.27)**
SI	**0.68(0.25,1.82)**	**1.16(0.69,1.92)**	**1.15(0.79,1.70)**
Multiplicative effect	**0.91(0.70,1.18)**	**0.99(0.76,1.30)**	**0.94(0.72,1.23)**
eGDR and CVAI			
Additive effect			
RERI	**-0.03(-0.33,0.26)**	**0.20(-0.14,0.55)**	**0.28(-0.17,0.72)**
AP	**-0.03(-0.28,0.22)**	**0.12(-0.08,0.31)**	**0.13(-0.06,0.31)**
SI	**0.86(0.25,2.98)**	**1.39(0.74,2.61)**	**1.30(0.84,2.00)**
Multiplicative effect	**0.97(0.75,1.26)**	**1.09(0.83,1.41)**	**1.04(0.80,1.36)**
eGDR and CI			
Additive effect			
RERI	**-0.39(-0.74,-0.03)**	**-0.26(-0.62,0.11)**	**-0.31(-0.74,0.11)**
AP	**-0.28(-0.55,-0.02)**	**-0.17(-0.41,0.08)**	**-0.16(-0.39,0.07)**
SI	**0.49(0.28,0.88)**	**0.68(0.41,1.13)**	**0.75(0.51,1.10)**
Multiplicative effect	**0.72(0.56,0.93)**	**0.79(0.61,1.02)**	**0.75(0.58,0.97)**
eGDR and WHtR			
Additive effect			

Model1 adjusted for age and gender;Model2 adjusted for age,gender,hukou,education,marital status,smoking status,drinking status and BMI;Model3 adjusted for factors in model2 and history of hypertension,diabetes,dyslipidemia.

Abbreviations: RERI: relative excess risk due to interaction;AP: proportion attributable to interaction; SI: synergy index;eGDR:estimated glucose disposal rate;ABSI:A body shape index;BRI:body roundness index;CVAI:Chinese visceral adiposity index;CI:conicity index;WHtR:waist–height ratio

Interactive indices	Interactive effects (95% CI)		
	Model 1	**Model 2**	**Model 3**
RERI	**-0.13(-0.43,0.18)**	**0.08(-0.30,0.45)**	**0.12(-0.33,0.57)**
AP	**-0.11(-0.36,0.15)**	**0.04(-0.17,0.25)**	**0.05(-0.14,0.25)**
SI	**0.61(0.21,1.73)**	**1.11(0.65,1.90)**	**1.11(0.75,1.64)**
Multiplicative effect	**0.90(0.69,1.16)**	**0.98(0.75,1.28)**	**0.93(0.71,1.21)**
Model1 adjusted for age and gender;Model2 adjusted for age,gender,hukou,education,marital status,smoking status,drinking status and BMI;Model3 adjusted for factors in model2 and history of hypertension,diabetes,dyslipidemia.			
Abbreviations: RERI: relative excess risk due to interaction;AP: proportion attributable to interaction; SI: synergy index;eGDR:estimated glucose disposal rate;ABSI:A body shape index;BRI:body roundness index;CVAI:Chinese visceral adiposity index;CI:conicity index;WHtR:waist–height ratio			

Subgroup analyses

We performed stratified analyses across different subgroups to evaluate the associations between eGDR and obesity-related indices and incident frailty (**Fig. S3–S7**). In most subgroups, the associations of the combined groupings of eGDR with ABSI, BRI, CVAI, CI, and WHtR with frailty risk were consistent with the main analysis results.Specifically, the combined grouping of eGDR and ABSI showed significant interactions with household registration (interaction p = 0.039) and alcohol consumption status (interaction p = 0.045). The combined grouping of eGDR and BRI showed significant interactions with marital status (interaction p = 0.038) and dyslipidemia (interaction p = 0.049).The combined grouping of eGDR and CVAI showed a significant interaction with alcohol consumption status (interaction p = 0.046). No significant interactions were observed for the other stratified variables (all interaction P > 0.05). Furthermore, no significant interactions were found in the subgroup analyses for the combined groupings of eGDR with CI or eGDR with WHtR.

Sensitivity analysis

To validate the robustness of the results, we performed two sensitivity analyses. After recalculating eGDR using the redefined hypertension criteria (≥130/80 mmHg), the associations of the combined groupings of eGDR and obesity-related indices with frailty risk remained consistent with the main results (**Fig. 5**). Furthermore, after excluding participants with non-fasting blood samples at baseline, re-analysis yielded similar results (**Fig. S8**).

Discussion

In this national longitudinal study of 7,472 middle-aged and older adults, we found that lower eGDR and higher obesity-related indices independently and jointly increased frailty risk. Second, RCS regression analysis (Model 3) revealed nonlinear associations between eGDR, each obesity-related index, and frailty occurrence. Furthermore, ROC curve, NRI, and IDI analyses indicated that combining eGDR with obesity-related indices improved frailty risk prediction. This combined approach provided higher predictive value than adding eGDR alone or any single obesity-related index alone to the model.Interaction analysis revealed a significant negative multiplicative interaction between eGDR and ABSI, as well as between eGDR and CI, indicating an antagonistic effect of their combined action. No multiplicative interaction was found between eGDR and BRI, CVAI, or WHtR. Additionally, no significant additive interaction was observed between eGDR and any obesity-related index. Subgroup and sensitivity analyses yielded results consistent with the main findings. Overall, these findings suggest that combining eGDR with obesity-related indices may facilitate early identification and prevention of frailty.

ABSI, BRI, CVAI, CI, and WHtR are simple anthropometric indices that reflect central obesity, visceral fat accumulation, and abnormal body fat distribution. In recent years, they have been widely used to assess obesity-related metabolic disorders and the risk of adverse health outcomes. Previous studies have shown that ABSI is independently associated with mortality risk and has a significant positive correlation with frailty occurrence, whereas BMI does not demonstrate the same predictive ability[40]. Furthermore, Jie Xu et al. analyzed data from 7,186 participants and found that higher BRI was closely associated with frailty occurrence in older adults[41].Meanwhile, Meng Chen et al. explored the relationship between CI and frailty in a study of 8,748 older American adults. They found that elevated CI was a reliable predictor of frailty prevalence in older men and was significantly associated with frailty occurrence[42]. Furthermore, a study by Aijun Song et al. demonstrated that compared with BMI, BRI, and WHT.5R (waist/height0.5), WHtR showed a stronger association with the frailty index. They also suggested that among waist-centered obesity measures, WHtR should be prioritized in frailty risk assessment and clinical intervention for older adults[43].Previous studies suggest that some obesity-related indices are associated with frailty or adverse aging outcomes. However, whether the discriminative ability of these indices for frailty risk is consistent remains to be compared and validated. In this study, higher levels of ABSI, BRI, CVAI, CI, and WHtR were all significantly associated with an increased risk of frailty, with BRI showing the strongest association. This finding suggests that abnormal obesity-related body fat distribution may promote frailty occurrence through multiple mechanisms.On the one hand, obesity promotes the secretion of reactive oxygen species and pro-inflammatory cytokines from adipose tissue. This induces chronic low-grade inflammation that damages skeletal muscle, reduces muscle mass and function, and ultimately leads to frailty[44-45]. On the other hand, obesity often involves increased intramuscular lipid deposition. This lipid infiltration impairs muscle function and reduces strength, thereby exacerbating physical frailty in older adults through related metabolic pathways, even without loss of muscle mass[44].

eGDR, composed of waist circumference, hypertension status, and glycated hemoglobin, is a simple indicator for assessing IR[46]. Multiple studies have shown that eGDR, as a measure of IR, is a reliable predictor of frailty risk. For example, Hui Tian et al. analyzed data from 6,722 Chinese adults and found that eGDR was negatively associated with frailty risk, whereas the triglyceride-glucose (TyG) index and the metabolic score for insulin resistance (METS-IR) were positively associated with frailty risk[47].Furthermore, in a 7-year follow-up study of 6,778 participants, Jiayu Sun et al. found that lower eGDR was associated with accelerated frailty progression in middle-aged and older Chinese adults. They also found that transitioning from low to high eGDR might mitigate this progression[48]. Additionally, Raúl F. Pérez-Tasigchana et al. reported in an analysis of 1,499 older participants that metabolic syndrome (MS) and IR were associated with an increased risk of frailty[49]. Meanwhile, Wentao Yang et al. investigated the relationship between eGDR and frailty in a study of 26,282 American participants and observed a significant negative association between eGDR and frailty[50]. Consistent with previous studies, the present study also found that lower eGDR levels were associated with a higher risk of frailty. One possible mechanism is that skeletal muscle, as the primary target tissue of insulin, is a key site of IR. IR reduces the sensitivity of skeletal muscle cells to insulin, thereby decreasing glucose uptake. This leads to reduced muscle strength and function, and consequently increases the risk of frailty development and progression[51-52]. Another possible mechanism is that IR promotes oxidative stress, which is closely associated with frailty[53].

As an independent risk factor for frailty, IR increases its risk through multiple pathways. First, IR exacerbates oxidative stress and inflammatory responses, thereby linking inflammation to frailty and increasing frailty risk[54]. Second, IR impairs skeletal muscle function, leading to decreased muscle strength and mass. This in turn aggravates frailty. Meanwhile, IR promotes inflammatory responses in adipose tissue, leading to sarcopenic obesity and further exacerbating frailty[55].Obesity itself is also an independent risk factor for frailty. Obesity, especially abdominal obesity, is associated with chronic inflammation because adipose tissue in the abdominal region tends to release more

inflammatory cytokines[56]. Chronic inflammation is a key factor in the development of frailty[57]. Moreover, the coexistence of general and abdominal obesity may exacerbate inflammatory responses, creating a pro-inflammatory environment that further leads to frailty[58].The above mechanisms indicate that both IR and obesity are related to frailty. Therefore, it is important to investigate surrogate markers of IR and obesity (e.g., eGDR and various obesity-related indices) and their associations with frailty. However, no study has comprehensively evaluated the combined effect of these markers on frailty. The present study found that low eGDR was consistently associated with a higher frailty risk than high eGDR, regardless of whether in the general population or among individuals with low or high levels of obesity-related indices.Similarly, high obesity-related indices were consistently associated with an increased frailty risk compared with low levels, regardless of whether in the overall population or among individuals with low or high eGDR. Previous studies have shown that IR, as indicated by low eGDR, not only disrupts glucose metabolism but also promotes sarcopenia, thereby exacerbating frailty[59].Meanwhile, lipid accumulation in the vascular endothelium can impair endothelial function and increase the risk of cardiovascular disease, which is also associated with frailty[60].In addition, this study found that the combined group of low eGDR and high obesity-related indices exhibited the highest frailty risk. Among these, the combined effect of BRI was stronger than that of ABSI, CVAI, CI, and WHtR. Compared with ABSI, CVAI, CI, and WHtR, BRI is an anthropometric index based on waist circumference and height, primarily designed to characterize body shape and fat distribution from the perspective of “body roundness”[61]. Previous studies have shown that BRI is closer to body fat percentage and visceral fat volume than traditional indicators, thus not only reflecting abdominal obesity but also characterizing visceral fat load to a certain extent[61].In contrast, ABSI is essentially a body shape index derived by adjusting waist circumference for BMI and height, emphasizing waist circumference deviation relative to body size[62]. CVAI integrates age, BMI, waist circumference, triglycerides, and HDL-C, more directly reflecting visceral fat accumulation and its associated metabolic dysfunction[63]. CI is primarily used to describe the degree of central fat distribution[64].Furthermore, although BRI and WHtR share substantial overlapping information and may even be considered a one-to-one nonlinear transformation of WHtR, BRI has the advantage of being able not only to express the degree of waist circumference deviation relative to height but also to provide a more intuitive geometric interpretation of body fat level and overall body composition status[61] [65].Meanwhile, BRI is associated with an increased risk of low muscle mass[66], suggesting that it may more sensitively identify the fat-muscle imbalance state closely related to frailty. Therefore, the stronger association observed for the combined eGDR and BRI group in this study may reflect their advantage in capturing visceral fat accumulation and adverse body composition remodeling.

This study showed that combined exposure to low eGDR and high obesity-related indices significantly increased frailty risk. This association exhibited heterogeneity across different population subgroups. Specifically, the combined effect of low eGDR and high ABSI was more pronounced among individuals with non-agricultural household registration and non-drinkers. We also found a statistically significant interaction of alcohol consumption status on the combined effect of eGDR and CVAI. Specifically, compared with drinkers, the impact of combined low eGDR and high CVAI exposure on frailty risk was more significant among non-drinkers.For example, a study by Juan J. Llibre Rodriguez et al. showed that the risk of frailty was higher in urban areas than in rural areas in China and India[67]. Furthermore, L. Seematter-Bagnoud et al. examined alcohol consumption and frailty in a study of 1,564 older adults. They found that even after adjusting for poor baseline health status, non-drinkers had a higher risk of frailty than drinkers. This finding likely reflects the healthy survivor effect among drinkers[68]. This is consistent with our results.Second, our results showed that the combined effect of low eGDR and high BRI was stronger among married individuals and those with dyslipidemia. This finding is partially consistent with existing evidence. For example, Reneilwe Given Mashaba et al. analyzed data from 546 participants and found that those with dyslipidemia had a significantly higher likelihood of frailty[69].Overall, these findings suggest that combining eGDR with obesity-related indices can help identify subgroups

at high risk of frailty at the population level. This provides a practical approach for early identification and targeted intervention.

To further explore the combined association of eGDR and obesity-related indices with frailty risk, we conducted interaction analysis. The results showed no significant additive interaction between eGDR and any obesity-related index in frailty occurrence. This indicates that their combined effect did not exceed the simple sum of their individual main effects. On the multiplicative scale, no significant interaction was observed between eGDR and BRI, CVAI, or WHtR. However, a significant negative multiplicative interaction existed between eGDR and ABSI, as well as between eGDR and CI. Specifically, when ABSI or CI was already high, the relative increase in frailty risk associated with low eGDR was attenuated. This suggests that the risk contributions of the two factors were not simply multiplicative.This indicates that the combined effect patterns of different obesity phenotypes and glucose metabolism abnormalities on frailty occurrence are not uniform. Studies have shown that adiponectin, an important adipokine secreted by adipose tissue, improves insulin sensitivity in major insulin target tissues such as skeletal muscle and the liver. It also participates in the regulation of energy metabolism and inflammatory responses. Therefore, adiponectin is considered a key protective molecule against IR[70]. The basis for these effects lies in its binding to adiponectin receptor 1 (AdipoR1) and adiponectin receptor 2 (AdipoR2), which further activates signaling pathways including adenosine monophosphate-activated protein kinase (AMPK), p38 mitogen-activated protein kinase (p38MAPK), and peroxisome proliferator-activated receptor alpha (PPARα).This,in turn, promotes fatty acid oxidation, inhibits hepatic glucose output, and improves overall metabolic homeostasis[71].More direct mechanistic studies have shown that the globular domain of adiponectin (gACRP30) rapidly activates AMPK in skeletal muscle.It also inhibits acetyl-CoA carboxylase (ACC) activity,reduces malonyl-CoA levels, and enhances glucose transport and fatty acid oxidation. These findings provide experimental evidence for the ameliorative effect of adiponectin on IR[72].Furthermore, review studies have indicated that adiponectin levels are negatively correlated with obesity, diabetes, and other insulin-resistant states.By enhancing the activity of AMPK and PPARα pathways in the liver and skeletal muscle,adiponectin helps maintain normal glucose and lipid metabolism and prevents the development of IR[73].In the context of obesity-related metabolic disorders such as diabetes,adiponectin is also considered to have the potential to further improve insulin sensitivity and delay target organ damage. This suggests that it is not only involved in the regulation of insulin resistance but may also possess certain therapeutic value[74].It should be noted that the negative multiplicative interaction observed in this study does not imply that the combined exposure is harmless.Rather, it more likely suggests effect overlap or diminished marginal gain.In other words,when high ABSI or CI is combined with low eGDR,the risk is indeed higher, but the magnitude of increase does not reach the level expected by multiplying the respective risk ratios of the two factors.Therefore, the negative multiplicative interaction does not alter the fact that individuals with low eGDR combined with high ABSI or CI have an overall higher risk.This finding suggests that frailty risk assessment should not rely on a single indicator.Rather, it should incorporate both glucose metabolism status and body fat distribution characteristics to improve the accuracy of high-risk population identification and avoid underestimating the risk in key intervention targets. No significant interaction was observed between BRI, CVAI,or WHtR and eGDR in the occurrence of frailty in this study.A possible explanation for this is that,although BRI, CVAI,and WHtR can each reflect central or visceral fat-related abnormalities from different perspectives[75-77],the relationships between these indices and the insulin resistance-related metabolic status reflected by eGDR may represent correlated or parallel risk dimensions rather than significantly modifying each other's effects.Therefore,in this study, their combined effect on frailty did not exhibit a statistical interaction that deviates significantly from what is expected under additive or multiplicative models.

To further test the robustness of the study findings,we conducted sensitivity analyses focusing on the definition of key covariates and participant inclusion criteria.First,we repeated the analysis after redefining hypertension using the threshold of ≥130/80 mmHg.Second, because non-fasting status may interfere with the assessment of metabolism-related indicators,we repeated the analysis after excluding non-fasting participants.The results of both

sensitivity analyses were consistent with the main analysis.This indicates that the associations between the combined groupings (eGDR with ABSI, BRI, CVAI, CI, and WHtR) and frailty risk are robust.

However,several limitations of this study should be noted.First, as an observational study,it may be subject to residual confounding from incompletely controlled factors such as psychological characteristics, household income,and physical activity.Therefore,causal relationships between eGDR,obesity-related indices, and frailty risk cannot be established.Second,we excluded individuals with missing or abnormal values for exposure factors,which may have introduced selection bias.Third, this study did not incorporate longitudinal changes in eGDR or obesity-related indices.This makes it difficult to fully characterize the long-term evolution of their combined exposure patterns.Fourth,the CHARLS target population is exclusively from China.Therefore,generalizing the findings to other countries may be limited.Further studies are needed to verify the applicability of these findings in populations with different cultural backgrounds.Finally,some variables (e.g.,smoking,alcohol consumption,and history of diabetes and hypertension) relied on self-reported data,which may introduce recall bias and the risk of inaccuracies.

Conclusion

Overall, both eGDR and obesity-related indices (ABSI, BRI, CVAI, CI, WHtR) are useful predictors of frailty occurrence, and their combined assessment can further improve risk identification. This study highlights the importance of integrating insulin resistance and body fat abnormalities in clinical and public health practice. The combined use of eGDR and obesity-related indices may enable earlier screening of high-risk individuals for frailty in the general population, provide a reference for subsequent monitoring and intervention, and thereby reduce the overall burden of frailty.

Abbreviations

eGDR Estimated glucose disposal rate

ABSI A body shape index

BRI Body roundness index

CVAI Chinese visceral adiposity index

CI Conicity index

WHtR Waist-to-height ratio

CHARLS China health and retirement longitudinal study

IR Insulin resistance

ROC Receiver operating characteristic

RCS Restricted cubic spline

AUC Area under the curve

NRI Net reclassification improvement

IDI Integrated discrimination improvement

RERI Relative excess risk due to interaction

AP Attributable proportion

SI Synergy index

HbA1c Glycated hemoglobin

WC Waist circumference

BMI body mass index

STROBE Strengthening the reporting of observational studies in epidemiology

TG Triglyceride

TC total cholesterol

FBG Fasting blood glucose

LDL-C Low-density lipoprotein cholesterol

HDL-C High-density lipoprotein cholesterol

TyG Triglyceride-glucose

WHT.5R Waist/height0.5

CES-D Epidemiologic studies-depression scale

METS-IR Metabolic score for insulin resistance

MS Metabolic syndrome

AdipoR1 Adiponectin receptor 1

AdipoR2 Adiponectin receptor 2

AMPK Adenosine monophosphate activated protein kinase

p38MAPK p38 mitogen activated protein kinase

PPARα Peroxisome proliferator activated receptor alpha

gACRP30 Globular domain of adiponectin

ACC CoA carboxylase

HR Hazard ratio

CI Confidence interval

IQR Interquartile range

Declarations

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Author contributions

DW conceived and designed the experiments and wrote the manuscript.QT and HC organized the data, and CL performed the analyses.JL and SY contributed to the data quality control and the finalization of the manuscript. All authors read and approved the final manuscript.

Ethics approval and consent to participate

This study involving human participants was reviewed and approved by the Ethics Review Committee of Peking University. Written informed consent was obtained from all participants prior to their inclusion in the study. The study adhered to the ethical principles of the Declaration of Helsinki and was conducted in strict accordance with the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines.

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Availability of data and materials

Online repositories(https://charls.pku.edu.cn/) contain the datasets used in this investigation. Registration as a user on the website would be needed to obtain the data. After registration is reviewed and approved, the data set could be downloaded following the provided instructions.

Consent for publication

Not applicable.

Competing interests

The authors declare no competing interests.

Clinical trial number

Not applicable.

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Figures

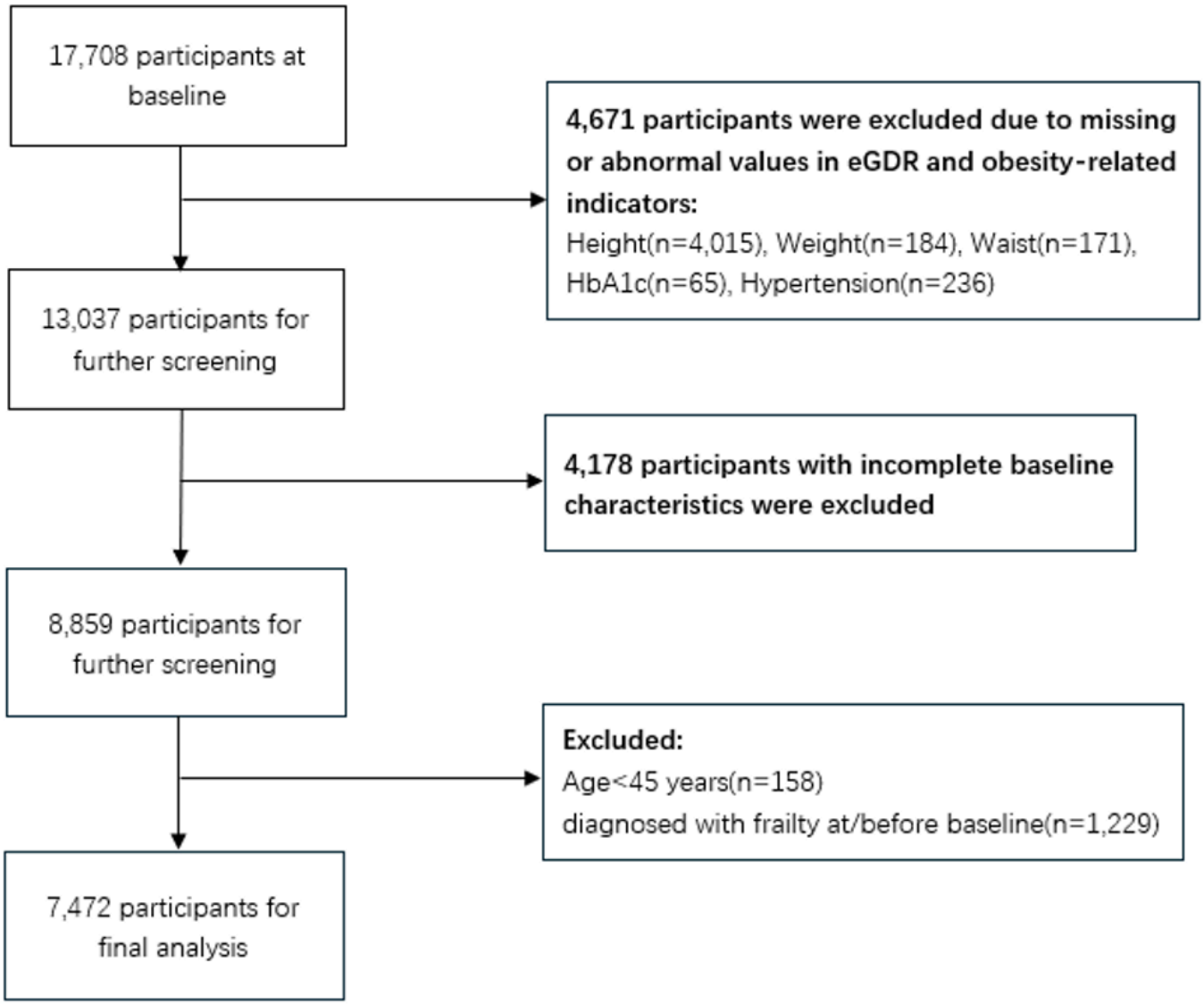


Figure 1

Flowchart illustrating the selection of the study population. Abbreviations: eGDR:estimated glucose disposal rate;HbA1c:glycated hemoglobin

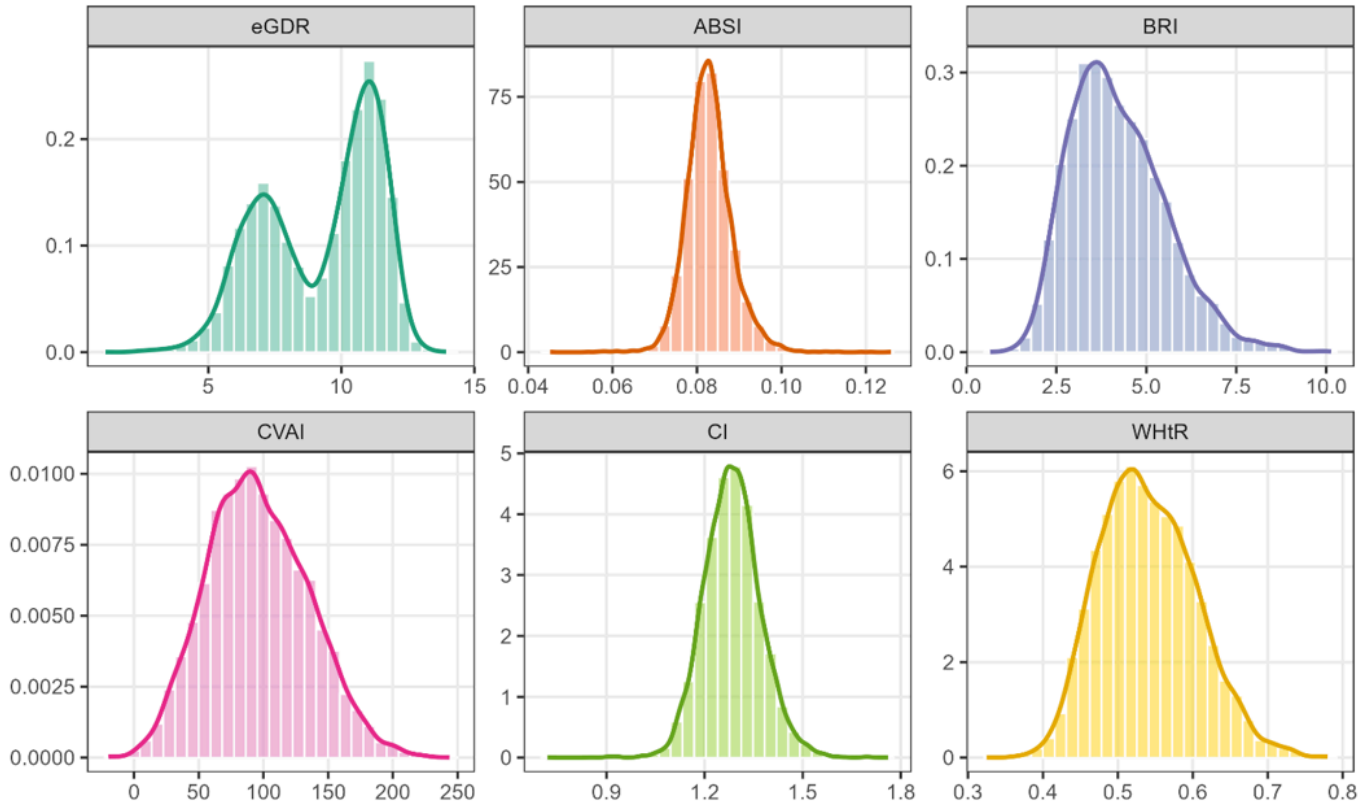


Figure 2

Distribution of eGDR and obesity-related indices.Abbreviations:eGDR:estimated glucose disposal rate;ABSI:A body shape index; BRI:body roundness index;CVAI:Chinese visceral adiposity index;CI:conicity index;WHtR:waist–height ratio

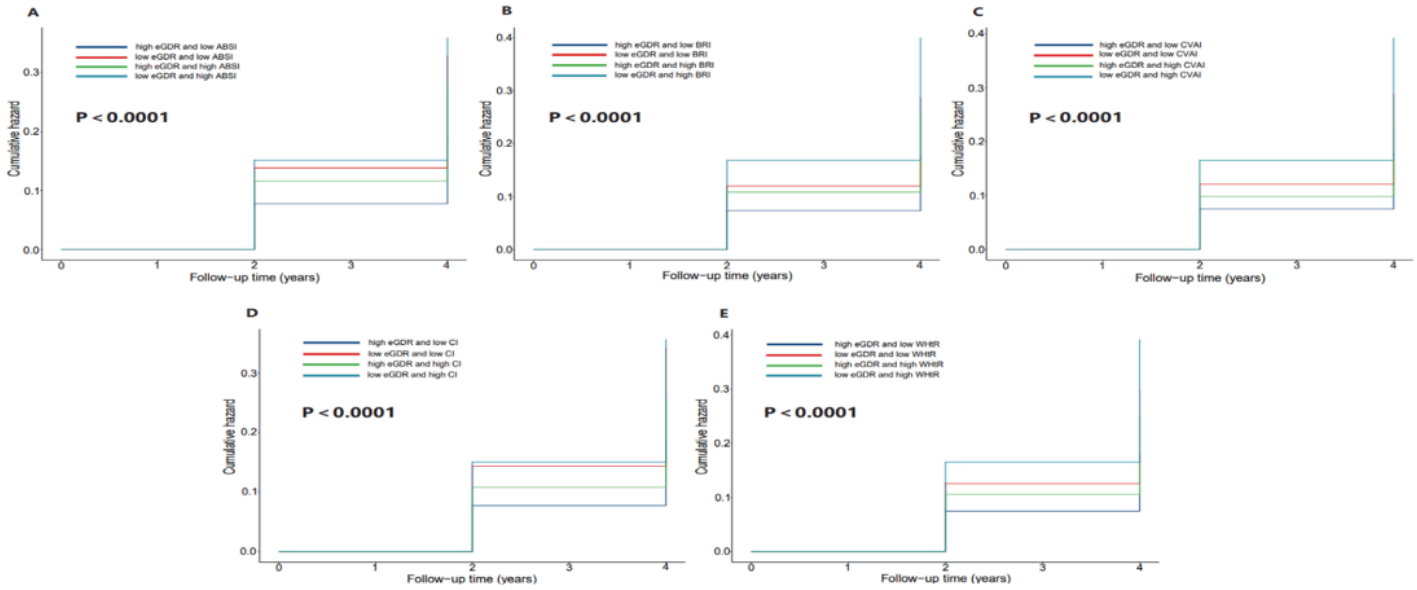


Figure 3

Kaplan–Meier plot of frailty incidence by eGDR and ABSI(A),eGDR and BRI(B),eGDR and CVAI(C),eGDR and CI(D),eGDR and WHtR(E).

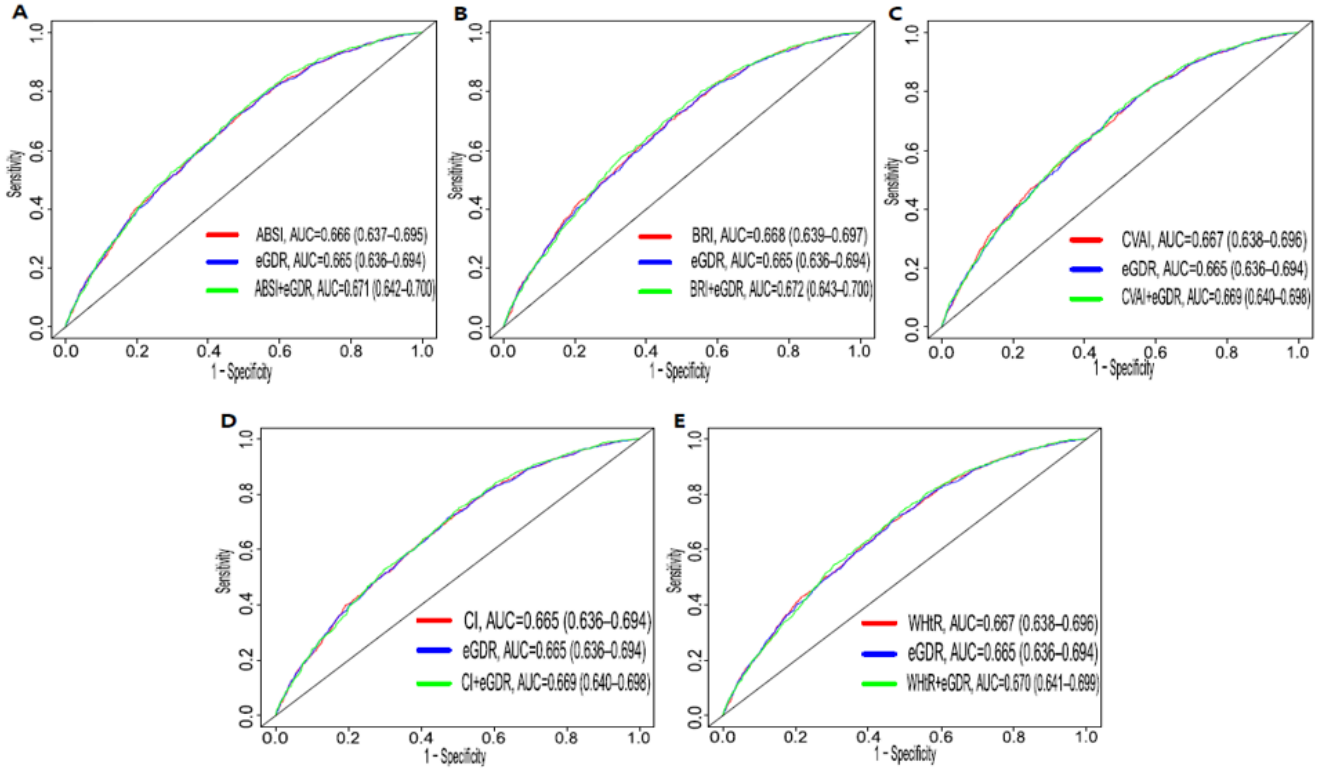


Figure 4

Receiver operating characteristic curves for ABSI(A),BRI(B),CVAI(C),CI(D),WHtR(E), alone and in combination with eGDR predicting frailty incidence based on Model3

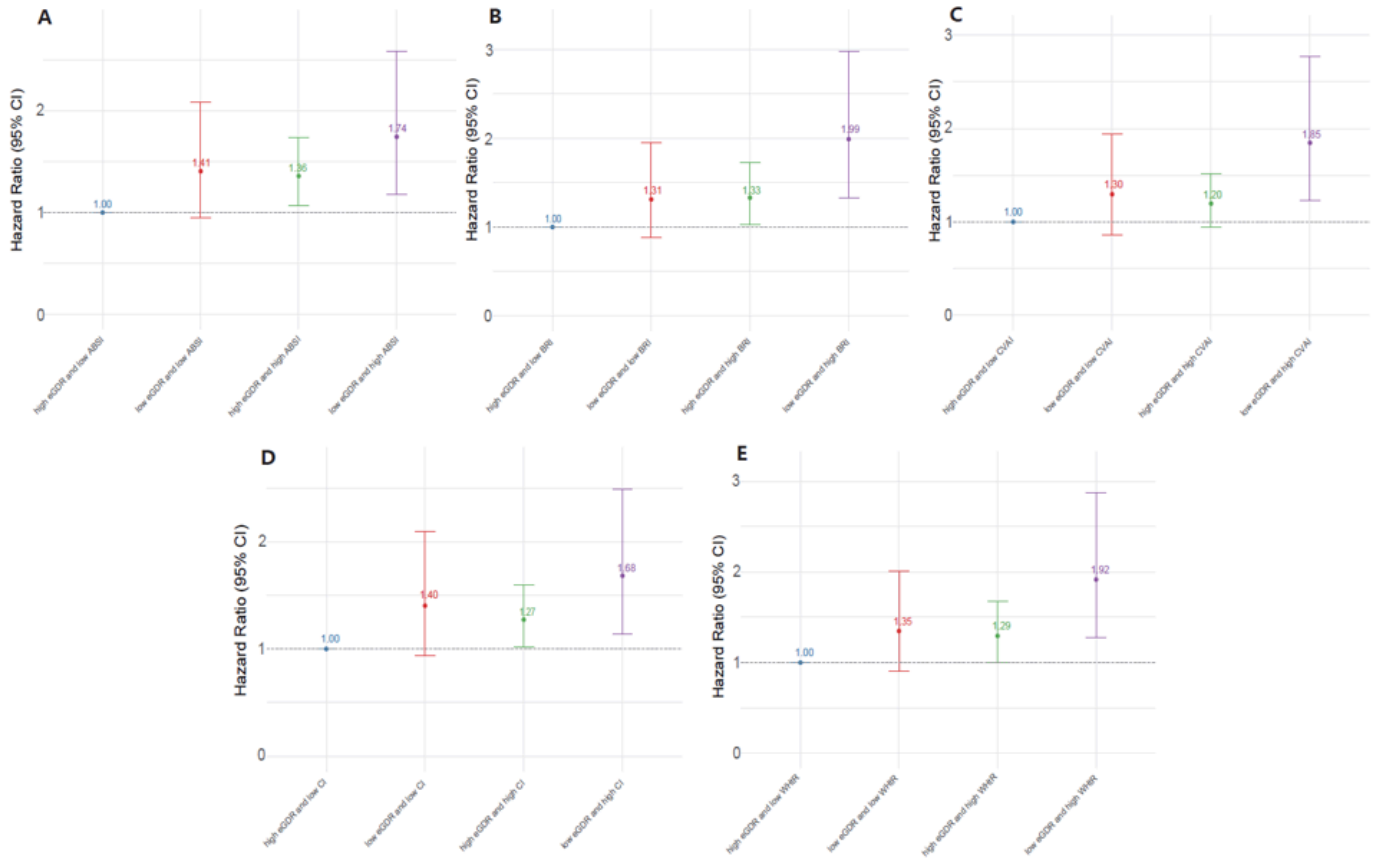


Figure 5

Sensitivity analysis of the combined effect of eGDR and obesity-related indices on frailty risk using the revised hypertension criteria (130/80 mmHg). (A)eGDR and ABSI;(B)eGDR and BRI;(C)eGDR and CVAI;(D)eGDR and CI;(E)eGDR and WHtR.The model was adjusted for age,gender,hukou,education,marital status,smoking status,drinking status,BMI,and history of hypertension,diabetes,dyslipidemia.

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