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Association between eGDR and accelerated aging: the mediating role of ePWV

Shaoyan Lu[1†], Yu-Jun Xiong[2†], Xiang-Da Meng[3†], Da-Ming Shao[4] and Tian Lv[5*]

Abstract

Objective This study examines the association between estimated glucose disposal rate (eGDR) and accelerated aging in middle-aged and older adults, with a focus on the mediating role of estimated pulse wave velocity (ePWV).

Methods Data from the 2011 wave of the China Health and Retirement Longitudinal Study (CHARLS) were analyzed, including middle-aged and older participants. Biological age was estimated using the Klemera-Doubal method, and accelerated aging was defined as the difference between biological and chronological age. The eGDR was calculated based on waist circumference, hypertension status, and HbA1c levels, while ePWV was estimated using mean blood pressure and age. Logistic regression models assessed the relationship between baseline eGDR, ePWV, and accelerated aging, adjusting for confounders.

Results A total of 8,529 participants (mean age 59.31 years) were included. A significant inverse association was found between eGDR and accelerated aging. Participants with the lowest eGDR quartile had an 81% higher risk of accelerated aging compared to those in the highest quartile (OR = 0.19, 95% CI 0.17–0.22, $P < 0.001$). Mediation analysis showed that ePWV mediated 12.90% of the relationship between eGDR and accelerated aging (95% CI 9.20%–16.60%).

Conclusion Reduced insulin sensitivity, indicated by low eGDR, is a significant risk factor for accelerated aging. Vascular aging, measured by ePWV, mediates part of this relationship. These findings highlight the importance of monitoring insulin sensitivity and vascular health to mitigate aging and age-related health risks.

Keywords Aging, eGDR, ePWV, CHARLS, Mediating effect

Introduction

Accelerated aging is a growing public health concern, strongly associated with increased morbidity, functional decline, and mortality, particularly in older adults [1]. Unlike chronological aging, which is purely time-dependent, biological aging reflects the cumulative burden of physiological and metabolic stressors, making it a more precise indicator of health span and longevity [2]. Identifying key determinants of accelerated aging is crucial for developing early interventions to mitigate age-related health risks. Emerging evidence suggests that metabolic dysfunction and vascular impairment play pivotal roles in aging acceleration, with insulin resistance (IR) and arterial stiffness serving as critical contributors [3, 4].

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Estimated glucose disposal rate (eGDR), an indicator of insulin sensitivity, has emerged as a novel biomarker associated with metabolic health and cardiovascular risk. Insulin resistance (IR), defined as the need for higher doses of insulin to achieve a normal physiological response, has been linked to an increased risk of stroke through mechanisms such as atherosclerosis [5]. Clinically, the euglycemic-hyperinsulinemic clamp is the gold standard for assessing IR, while the homeostasis model assessment of insulin resistance (HOMA-IR) serves as a widely accepted surrogate [6, 7]. Due to the high cost and complexity of these methods, noninvasive alternatives, such as the estimated glucose disposal rate (eGDR), are gaining attention. Research has supported the utility of eGDR as a reliable surrogate indicator of insulin resistance, with lower eGDR levels being significantly associated with increased mortality among individuals with diabetes [8]. Additionally, eGDR has been identified as a predictor of adverse cardiovascular outcomes, including stroke [9].

Arterial stiffness, measured by estimated pulse wave velocity (ePWV), is another key determinant of biological aging [10, 11]. Vascular aging, characterized by reduced arterial elasticity, contributes to impaired perfusion, increased cardiac workload, and heightened susceptibility to age-related disease [12]. EPWV, an effective surrogate for directly measured pulse wave velocity, has been validated as a strong predictor of cardiovascular outcomes and overall mortality [13]. Notably, IR and arterial stiffness are interrelated, as insulin resistance exacerbates vascular dysfunction through endothelial damage and chronic low-grade inflammation [14].

Despite growing recognition of the individual effects of eGDR and ePWV on aging, their mechanistic interactions remain underexplored. Given their fundamental roles in metabolic and vascular health, further investigation into their associations with accelerated aging is essential. Leveraging data from the China Health and Retirement Longitudinal Study (CHARLS), this study aims to examine the relationships between eGDR, ePWV, and accelerated aging, providing insights that could inform strategies to promote healthy aging and reduce age-related disease burden.

Materials and methods

Study design and participants

This study is a secondary analysis of the China Health and Retirement Longitudinal Study (CHARLS), a national, population-based cohort targeting Chinese adults aged 45 and above (http://charls.pku.edu.cn/). The sample was drawn from 150 counties or districts and 450 villages across 28 provinces in China, spanning the period from 2011 to 2020 [15].

For our analysis, we utilized data from waves 1 of CHARLS in 2011. Wave 1 in 2011 included 17,705 participants; individuals without eGDR and biological age related data were excluded. The exclusion criteria for this study included participants with missing data on key variables such as educational attainment, alcohol consumption status, hemoglobin levels, smoking status, diabetes mellitus diagnosis, residential status, uric acid levels, heart disease-related information, and other missing covariate data. These exclusions were necessary to ensure the integrity and completeness of the dataset, allowing for more accurate and reliable statistical analysis (Fig. 1).

Assessment of eGDR and ePWV

In the current study, estimated glucose disposal rate (eGDR, mg/kg/min) was calculated using a previously established formula: eGDR = 21.158—(0.09 * WC)—(3.407 * HT)—(0.551 * HbA1c), where WC represents waist circumference (cm), HT is hypertension status (yes = 1, no = 0), and HbA1c is the glycated hemoglobin level (% DCCT). Waist circumference was measured at the natural waist position [7]. The ePWV was calculated based on the mean blood pressure (MBP) and age using the following formula: $ePWV = 9.587 - 0.402 * age + 4.560 * 10^{-3} * age^2 - 2.621 * 10^{-5} * age^2 * MBP + 3.176 * 10^{-3} * age * MBP - 1.832 * 10^{-2} * MBP$ [16, 17].

Determination of biological age and definition of accelerated aging

We estimated composite biological age using the Klemera and Doubal Method (KDM), incorporating biomarkers such as creatinine, high-sensitivity C-reactive protein, total cholesterol, triglycerides, glycosylated hemoglobin, urea nitrogen, platelets, and systolic blood pressure [18]. The calculation followed algorithms established in prior research [19]. Accelerated aging, a widely accepted indicator of systemic biological wear and tear, was quantified as the residual (biological age—chronological age). This approach allows for the identification of individuals whose biological systems exhibit age-related changes at a pace faster than the population average for their age, which has been linked to increased risk of age-associated diseases and mortality [20].

Covariate

According to prior research and clinical experts, potentially confounding and modifying variables were identified as follow: age, sex (male or female), residence (urban, rural), education (less than high school, high school or above), marital status (married, non-married), waist and hand strength. Clinical indicators such as uric acid, hemoglobin, blood lipids and glucose were measured in

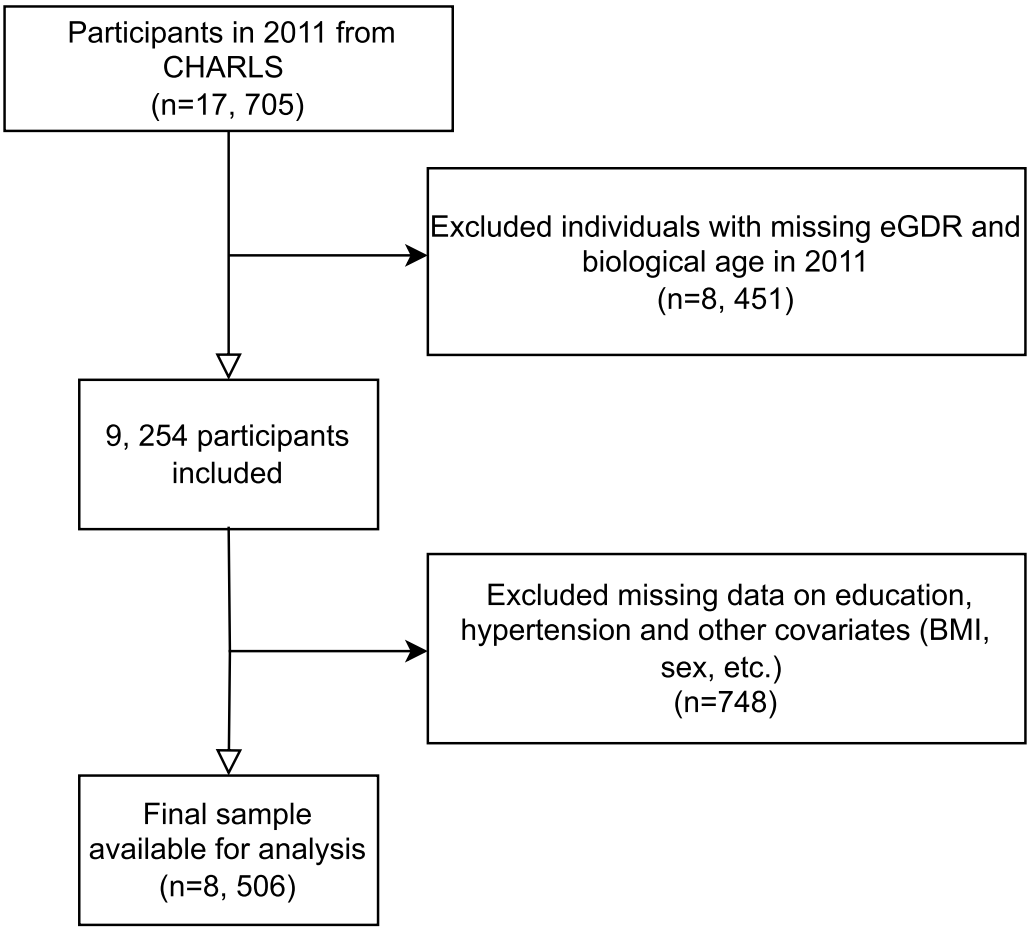

Fig. 1 Flowchart of participant screening

the laboratory. Heart disease, dyslipidemia, hypertension, diabetes mellitus, Center for Epidemiologic Studies Short Depression Scale -10 (CESD-10) score and depression evaluation were evaluated through a standardized questionnaire that inquired whether participants had ever been diagnosed by a doctor with these conditions [21, 22]. Alcohol drinking and smoking status were classified into two distinct categories as ever/present or never [23, 24].

Statistical analysis

Data were presented as means and standard deviations (SDs) for continuous variables with normal distributions and as medians with interquartile ranges for those that were non-normally distributed. Categorical variables were described as frequencies with percentages. Baseline characteristics between groups were compared using the chi-squared test, analysis of variance (ANOVA), or the Kruskal–Wallis rank-sum test, depending on the type of data [25].

Multivariable-adjusted logistic regression analyses were used to estimate odds ratios (ORs) and 95% confidence intervals (CIs) for outcomes associated with eGDR (Table 2). Three models were developed: Unadjusted model as Model 0; Model 1 adjusted for sex, smoke, alcohol drink, creatinine and residence; Model 2 included the adjustments from Model 1 plus dyslipidemia, depression, diabetes mellitus, hand strength, ePWV, uric acid, BMI. Additionally, the potential nonlinear connections between eGDR and accelerated aging were explored using restricted cubic spline (RCS) curves. These curves were positioned at specific percentiles (10%, 50%, and 90%) within the eGDR distribution (Fig. 2).

A mediation analysis was conducted to evaluate the direct and indirect effects between eGDR and accelerated aging through elevated ePWV by bootstrap (Fig. 3). All statistical analyses were performed using R software (version 4.2.1). Multiple imputations were conducted with the 'charlsR' package. Mediation analysis utilized the 'mediation' package. A two-sided *P*-value of <0.05 was considered statistically significant [26].

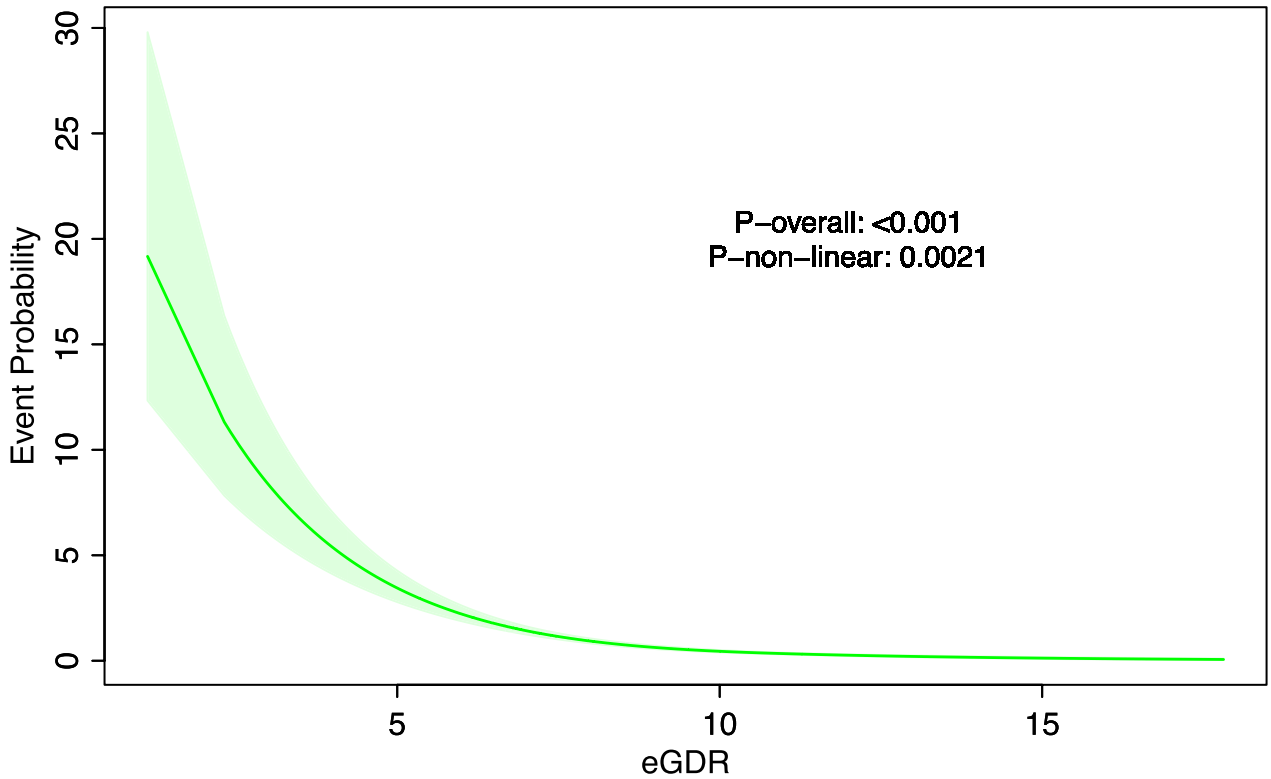

Fig. 2 Restricted cubic spline (RCS) for the association between eGDR with the risks of accelerated aging

Results

Study participants and baseline characteristics

The final cohort consisted of 8529 adults, with 3717 classified as having accelerated aging (Table 1). The mean age was 59.31 ± 9.25 years, and 47.02% of participants were male. Compared to the decelerated aging group, individuals with accelerated aging were more likely to be male and have a higher BMI, hemoglobin, blood glucose, creatinine, uric acid, total cholesterol, low-density lipoprotein cholesterol, triglycerides, and HbA1c levels. Additionally, they had a higher prevalence of dyslipidemia, smoking, alcohol consumption, hypertension, and diabetes mellitus, along with lower eGDR values ($P < 0.001$). Residence distribution also differed significantly, with a lower proportion of individuals with accelerated aging living in rural areas.

Correlation between eGDR and accelerated aging

The association between eGDR and accelerated aging was further explored using restricted cubic spline (RCS) analysis, as depicted in Fig. 2. The results indicated a significant inverse non-linear relationship between eGDR and the risk of accelerated aging (P overall < 0.001, P non-linear = 0.0021). This association remained robust after adjusting for sex, smoking, alcohol consumption, creatinine, residence, dyslipidemia, depression, diabetes mellitus, hand strength, ePWV, uric acid, and BMI.

Associations of eGDR with accelerated aging by multiple logistic regression

A multivariable logistic regression analysis was performed to investigate the association between eGDR and accelerated aging, treating eGDR both as a continuous variable and a categorical variable divided into quartiles, as shown in Table 2. When analyzed as a continuous variable, higher eGDR was significantly associated with a lower risk of accelerated aging in the unadjusted model (Model 0) (OR = 0.69, 95% CI 0.68–0.71, $P < 0.001$). This inverse relationship remained robust after adjusting for sex, smoking, alcohol consumption, creatinine, and residence in Model 1 (OR = 0.66, 95% CI 0.64–0.67, $P < 0.001$) and persisted in the fully adjusted model (Model 2), which further accounted for dyslipidemia, depression, diabetes mellitus, hand strength, ePWV, uric acid, and BMI (OR = 0.70, 95% CI 0.68–0.72, $P < 0.001$).

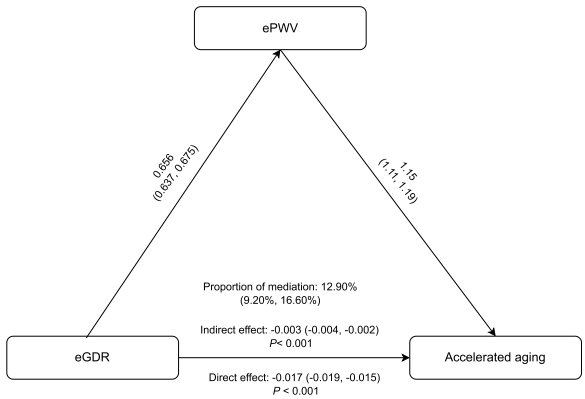

Fig. 3 Mediation analyses of ePWV and eGDR on accelerated aging

When categorized into quartiles, individuals in the third quartile (Q3) of eGDR had significantly lower odds of accelerated aging compared to those in the lowest quartile (Q1) across all models. In Model 0, participants in Q3 had an 81% lower risk of accelerated aging (OR = 0.19, 95% CI 0.17–0.22, $P < 0.001$). This association remained significant in Model 1 (OR = 0.15, 95% CI 0.13–0.17, $P < 0.001$) and Model 2 (OR = 0.20, 95% CI 0.17–0.24, $P < 0.001$), reinforcing the strong protective effect of higher eGDR against accelerated aging.

Mediation analyses of eGDR of ePWV on accelerated aging

Figure 3 illustrated the mediation effects between eGDR, ePWV, and accelerated aging. ePWV significantly mediated 12.90% (95% CI 9.20%-16.60%) of the association between eGDR and accelerated aging.

Discussion

Our study provides strong evidence of an inverse association between eGDR and accelerated aging, suggesting that insulin resistance plays a critical role in the aging process. Insulin resistance is a key driver of metabolic dysfunction, contributing to chronic inflammation, oxidative stress, and endothelial dysfunction, all of which accelerate biological aging [27–29]. Prior research has linked lower eGDR levels to increased risks of cardiovascular disease, frailty, and mortality, reinforcing its relevance as a biomarker of aging. The non-linear relationship observed in our study indicates that even moderate declines in insulin sensitivity can substantially increase the risk of accelerated aging, underscoring the importance of early metabolic intervention.

The association between eGDR and aging is further supported by several cohort studies that have demonstrated a direct link between insulin resistance and biological aging markers. Yang et al. reported a positive correlation between HOMA-IR and biological aging [30]. Epidemiological studies in humans suggest that insulin has a pro-aging effect. While insulin resistance generally increases with age, centenarians tend to maintain normal glucose tolerance, lower fasting insulin levels, and higher insulin sensitivity compared to adults over 75 years old [31]. Mechanistically, insulin resistance disrupts glucose metabolism, leading to systemic metabolic inflexibility, increased oxidative damage, and heightened cellular senescence [32]. These disruptions compromise tissue repair and regeneration, leading to premature aging at both the cellular and systemic levels.

Our mediation analysis further highlights the role of vascular aging, as measured by ePWV, in the relationship between eGDR and accelerated aging. Arterial stiffness is a hallmark of vascular aging and is closely associated with increased cardiovascular morbidity, cognitive decline, and mortality [33]. Insulin resistance contributes to vascular dysfunction through multiple mechanisms, including impaired nitric oxide bioavailability, increased oxidative stress, and chronic low-grade inflammation [34–36]. Additionally, hyperinsulinemia promotes the accumulation of advanced glycation end products, leading to collagen cross-linking and reduced arterial elasticity [37]. In our study, ePWV mediated approximately 12.90% of the association between eGDR and accelerated aging, suggesting that vascular impairment serves as a key pathway through which metabolic dysfunction accelerates biological aging.

These findings are consistent with previous research demonstrating the interplay between metabolic and vascular aging. Animal studies have shown that insulin resistance exacerbates vascular calcification and extracellular matrix remodeling, leading to increased arterial stiffness and impaired organ perfusion [38]. Similarly, human cohort studies have reported that individuals with lower insulin sensitivity exhibit greater arterial stiffness and a higher prevalence of age-related diseases [39]. Given that both eGDR and ePWV are modifiable factors, interventions targeting insulin sensitivity and vascular health may offer effective strategies to slow the aging process. Lifestyle modifications, including regular physical activity, dietary improvements, and weight management, have been shown to enhance insulin sensitivity and reduce arterial stiffness [40]. Pharmacological approaches, such as metformin and SGLT2 inhibitors, may also play a role in mitigating the adverse effects of insulin resistance on aging [41, 42].

Our study has several strengths and limitations. We leveraged a large, nationally representative cohort from CHARLS, ensuring robust statistical power and generalizability within middle-aged and older Chinese populations. Additionally, we employed validated metrics for both insulin sensitivity (eGDR) and vascular aging

Table 1 Baseline characteristics of participants

	Overall (n = 8, 529)	***Accelerated Aging*** **(n = 3, 717)**	***Decelerated Aging*** **(n = 4, 812)**	***P*** **value**
Age (years)	59.31 ± 9.25	59.16 ± 9.09	59.43 ± 9.36	0.180
Sex (Male %)	4010 (47.02)	2183(58.73)	1827(37.97)	< 0.0001
Marital status				
Married	7539 (88.39)	3303 (88.86)	4236 (88.03)	0.250
Non-married	990 (11.61)	414 (11.14)	576 (11.97)	
BMI (kg/m^2)	23.53 ± 3.89	24.18 ± 3.97	23.03 ± 3.74	< 0.0001
Hemoglobin (g/dL)	14.37 ± 2.21	14.80 ± 2.36	14.05 ± 2.02	< 0.0001
Education (%)				
Less Than High School	7696(90.23)	3334(89.70)	4362(90.65)	0.150
High School or above	833 (9.77)	383(10.30)	450 (9.35)	
Residence				
Rural	5558(65.17)	2328(62.63)	3230(67.12)	< 0.001
Urban	2971(34.83)	1389(37.37)	1582(32.88)	
Glucose (mg/dL)	110.36 ± 36.73	117.30 ± 46.75	105.00 ± 25.26	< 0.001
Creatinine (mg/dL)	0.78 ± 0.21	0.87 ± 0.25	0.72 ± 0.15	< 0.001
Uric acid (mg/dL)	4.45 ± 1.25	4.86 ± 1.32	4.14 ± 1.10	< 0.001
Dyslipidemia (yes%)	797 (9.34)	396(10.65)	401 (8.33)	< 0.001
TC (mg/dL)	193.56 ± 38.29	198.66 ± 38.98	189.63 ± 37.27	< 0.001
HDL-C (mg/dL)	51.21 ± 15.25	50.98 ± 15.61	51.39 ± 14.97	0.220
LDL-C (mg/dL)	116.65 ± 35.05	120.60 ± 36.62	113.60 ± 33.47	< 0.001
TG (mg/dL)	131.26 ± 93.69	135.79 ± 102.21	127.76 ± 86.39	< 0.001
Smoke (%)	2618(30.70)	1364(36.70)	1254(26.06)	< 0.001
Alcohol drink (%)	2817(33.03)	1415(38.07)	1402(29.14)	< 0.001
eGDR	9.26 ± 2.31	8.27 ± 2.26	10.03 ± 2.04	< 0.001
Biological Age (years)	58.84 ± 10.04	62.47 ± 9.59	56.03 ± 9.46	< 0.001
HbA1c (%)	5.27 ± 0.81	5.48 ± 1.04	5.11 ± 0.51	< 0.001
Waist (cm)	84.36 ± 12.67	86.43 ± 12.70	82.76 ± 12.41	< 0.001
ePWV (m/s)	9.57 ± 1.91	10.16 ± 1.88	9.11 ± 1.81	< 0.001
Hand strength (kg)	31.20 ± 10.44	33.20 ± 11.02	29.65 ± 9.69	< 0.001
Hypertension (%)	2169(25.43)	1365(36.72)	804(16.71)	< 0.001
Diabetes Mellitus (%)	1246(14.61)	792(21.31)	454 (9.43)	< 0.001
Heart disease = yes (%)	974(11.42)	439(11.81)	535(11.12)	0.340
CESD-10 score	8.53 ± 6.36	8.00 ± 6.21	8.94 ± 6.45	< 0.001
Depression (%)	3262(38.25)	1302(35.03)	1960(40.73)	< 0.001

BMI body mass index, *TC* total cholesterol, *HDL* high-density lipoprotein, *LDL* low-density lipoprotein, *TG* triglycerides, *eGDR* estimated glucose disposal rate, *HbA1c* glycated hemoglobin, *ePWV* estimated pulse wave velocity, *CESD-10* Center for Epidemiologic Studies Short Depression Scale -10

(ePWV), allowing for a comprehensive assessment of their roles in accelerated aging. Our use of mediation analysis provided novel insights into the indirect effects of metabolic dysfunction on aging through vascular pathways, highlighting potential targets for intervention. However, the cross-sectional nature of our study prevents the establishment of causal relationships between eGDR, ePWV, and accelerated aging. Future longitudinal studies are needed to confirm these associations and explore the temporal dynamics of metabolic and vascular aging. Moreover, our analysis was limited to a Chinese population in a limited year, which may restrict the generalizability of our findings to other ethnic groups with different genetic backgrounds, lifestyles, and healthcare systems. Additionally, the analysis was restricted to individuals aged 45 years and older using data from the CHARLS. While this focus on an aging Chinese population is appropriate for understanding risk factors relevant to this demographic, it may limit the external validity of our findings. Genetic backgrounds, dietary habits, and environmental exposures—such as sodium intake, levels of physical activity, and air pollution—vary substantially

Table 2 Risk classification of Accelerated Aging based on eGDR by Multiple Logistic Regression analysis

	Model 0	Model 1[a]	Model 2[b]
eGDR	0.69(0.68,0.71) ***	0.66 (0.64, 0.67) ***	0.70 (0.68, 0.72) ***
Q1	ref	ref	ref
Q2	0.52 (0.46,0.59) ***	0.47 (0.41, 0.54) ***	0.54 (0.46, 0.62) ***
Q3	0.19 (0.17,0.22) ***	0.15 (0.13, 0.17) ***	0.20 (0.17, 0.24) ***
Q4	0.14 (0.12,0.15) ***	0.10 (0.09, 0.12) ***	0.15 (0.12, 0.18) ***

[a] Model 1 adjusted for sex, smoke, alcohol drink, creatinine, residence

[b] Model 2 adjusted for sex, smoke, drink, creatinine, residence, dyslipidemia, depression, diabetes mellitus, hand strength, ePWV, uric acid, BMI

*** *P* < 0.001

across populations and could influence insulin sensitivity and biological aging trajectories. For example, East Asian populations tend to exhibit higher visceral fat accumulation and different metabolic responses compared to Western populations, potentially affecting the observed associations between eGDR and aging. Therefore, replication of our findings in ethnically and geographically diverse cohorts is essential to assess their broader applicability.

Conclusion

Our study underscores the strong association between eGDR and accelerated aging, with ePWV acting as a significant mediator in this relationship. These findings highlight the interconnected nature of metabolic and vascular aging, reinforcing the need for comprehensive strategies to maintain insulin sensitivity and vascular health. Future research should focus on elucidating the molecular mechanisms underlying these associations and exploring potential therapeutic interventions to promote healthy aging. Longitudinal studies and interventional trials will be essential to validate our findings and further investigate the clinical implications of targeting insulin resistance and arterial stiffness in aging populations.

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Author contributions

SYL and LT conceived and designed the study, acquired the data and drafted the manuscript; DMS analyzed the data; YJX and XDM contributed to the interpretation of the results and critical revision of the manuscript for important intellectual content; SYL developed the software and provided technical support. TL had the primary responsibility for final content. All authors have read and approved the final manuscript. The authors reported no conflicts of interest.

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None.

Availability of data and materials

The datasets used and/or analyzed in this research are publicly accessible or can be obtained from the corresponding author upon reasonable request at http://charls.pku.edu.cn/en.

Declarations

Ethics approval and consent to participate

The CHARLS study adhered to the ethical principles outlined in the Declaration of Helsinki and received approval from the Institutional Review Board of Peking University (IRB00001052-11015). The research involving human participants was approved by the Ethics Committee of Peking University. Written informed consent was obtained from all patients/participants prior to their involvement in the study.

Consent for publication

Not applicable.

Competing interests

The authors declare no competing interests.

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