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The mediating role of systolic blood pressure in the association between estimated glucose disposal rate and renal prognosis: a nationwide prospective cohort study

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Abstract

Aim: Despite the well-documented pathogenic role of insulin resistance (IR) and hypertension in nephropathy progression, the prognostic value of the estimated glucose disposal rate (eGDR) for incident renal dysfunction remains unclear. This population-based longitudinal analysis specifically examined the eGDR-renal dysfunction relationship in middle-aged and elderly populations, with a particular focus on the potential mediating role of systolic blood pressure (SBP) based on a nationwide longitudinal study.

Methods: Utilizing data from 8,136 participants in the China Health and Retirement Longitudinal Study (CHARLS, 2011-2015), we conducted multivariable-adjusted logistic regression analyses combined with a restricted cubic spline model to assess the association between eGDR and incident renal dysfunction. Mediation analysis was

employed to assess the proportion of the association mediated by SBP in this relationship.

Results: Over a median follow-up period of 4 years, 2,223 participants developed renal dysfunction. Both eGDR and SBP were significantly and independently associated with incident renal dysfunction. The odds ratio (OR) for eGDR was 0.73 (95%CI: 0.58-0.92), while the OR for SBP was 1.20 (95%CI: 1.05-1.38). Restricted cubic spline analysis identified critical thresholds, with eGDR levels below 11.6 mg/kg/min and SBP levels above 125 mmHg being associated with a higher risk of renal dysfunction. Mediation analysis further demonstrated that SBP acted as a significant mediator in the relationship between eGDR and renal dysfunction, accounting for 42.6% of the total effect (95%CI: 19.9%-86.7%).

Conclusion: This prospective cohort study identifies eGDR as an independent predictor of renal dysfunction, with nearly half of its effect mediated by SBP. These findings highlight the potential benefit of integrated management strategies targeting both insulin sensitivity and blood pressure control to reduce the risk of renal dysfunction in aging populations.

Keywords: Estimated glucose disposal rate, renal dysfunction, systolic blood pressure, mediation effects, insulin resistance

INTRODUCTION

Chronic kidney disease (CKD) constitutes a pivotal driver of global health disparities, acting as both a direct contributor to mortality and a catalyst for cardiovascular morbidity[1]. According to Global Burden of Disease metrics, CKD affected an estimated 843.6 million individuals worldwide and was responsible for 3.1 million deaths and 41.5 million disability-adjusted life years in 2019[2]. The growing global health challenge posed by CKD necessitates the systematic identification of modifiable risk factors associated with early-stage renal dysfunction progression. Such efforts are essential for the timely implementation of evidence-based prevention strategies aimed at slowing disease progression and reducing associated morbidity.

Recent studies have highlighted insulin resistance (IR) as a key contributor to declining renal function[3]. Improving insulin sensitivity has been proposed as a potential strategy to preserve renal function and mitigate CKD risk[4]. Described in DeFronzo's seminal 1979 publication, the hyperinsulinemic-euglycemic clamp (HEC) maintains its position as the criterion standard for quantifying insulin sensitivity through physiological glucose disposal rates[5]; however, its requirement for continuous insulin/glucose infusions, specialized personnel, and prolonged monitoring precludes widespread application in population-level research. The estimated glucose disposal rate (eGDR) derived from anthropometric (waist circumference), glycemic [hemoglobin A1c (HbA1c) levels], and hemodynamic (hypertension status) determinants has emerged as a clinically operational proxy to quantify IR dynamics, circumventing invasive methodologies. Previous studies have confirmed that eGDR is strongly associated with metabolic syndrome[6], and predicts cardiovascular events and mortality in patients with diabetes[7]. Emerging evidence suggests a potential link between eGDR and renal dysfunction in diabetic populations; however, its association with renal outcomes in the general population remains inconclusive. In particular, studies exploring the relationship between eGDR and renal dysfunction among middle-aged and older adults in China are limited and have reported inconsistent findings[8].

Hypertension and IR are closely interrelated conditions that significantly affect kidney function[9,10]. Recent epidemiological studies have consistently demonstrated an association between blood pressure (BP) and IR across diverse populations. For instance, Zhang *et al.* revealed through Mendelian randomization studies that genetically determined IR increases the risk of developing hypertension[11]. Similarly, Zeng *et al.*

highlighted a nonlinear relationship between both systolic blood pressure (SBP) and diastolic blood pressure (DBP) and IR in U.S. adults[12]. Our prior study demonstrated that IR significantly mediates the association between obesity and hypertension among middle-aged and older Chinese adults[13]. These findings highlight the bidirectional relationship between IR and elevated BP, both of which contribute to renal function deterioration. However, few studies have investigated the complex interplay between BP, IR, and renal dysfunction.

Therefore, this longitudinal cohort study investigated the temporal relationship between IR (quantified using the eGDR formula) and progressive renal dysfunction in a nationally representative sample of Chinese adults aged ≥ 45 years. Employing causal mediation modeling, we further elucidated the mediating role of SBP within this biological pathway.

METHODS

Study cohort

This investigation was embedded within the China Health and Retirement Longitudinal Study (CHARLS; a nationally representative cohort), a population-based prospective cohort study systematically tracking the multidimensional health dynamics of community-dwelling Chinese residents (https://charls.pku.edu.cn/en/)[14]. Baseline data were collected in 2011, enrolling 17,708 participants from over 10,000 households across 150 counties and 450 villages. Follow-up assessments are conducted biennially, and the study design has been described in detail elsewhere[15-17]. For this analysis, baseline data were derived from the 2011 wave, with follow-up data from 2013 and 2015. Initially, all participants from the 2011 CHARLS cohort (n = 17,708) were included. Participants meeting any of the following exclusion criteria were excluded: (1) incomplete demographic documentation (age < 45 years, sex data missing; n = 1,722) or absence of essential serum biomarkers (n = 4,552); (2) baseline eGFR < 60 mL/min/1.73 m^2 (n = 967); (3) longitudinal tracking failure during 2013-2015 surveillance cycles (n = 2,331). A total of 8,136 participants meeting the inclusion criteria were included in the final study population after applying pre-specified exclusion criteria. A flowchart detailing the study selection process is shown in Figure 1. All procedures in the CHARLS investigation were conducted in compliance with the ethical standards established by Peking University's review board (Ethics ID: IRB00001052-11015), with legally valid informed consent obtained in written form from each participant.

Laboratory evaluation and anthropometric data

BP measurements were obtained with a calibrated mercury sphygmomanometer. Following an overnight fast, morning venous blood specimens were collected, immediately aliquoted, and cryopreserved at -80 °C for subsequent analysis. Standardized laboratory protocols were employed to quantify metabolic parameters: [lipid profile total cholesterol (TC), triglycerides (TG), high-density lipoprotein cholesterol (HDL-C), and low-density lipoprotein cholesterol (LDL-C)], glucose homeostasis markers (fasting glucose, hemoglobin A1c HbA1c), renal function indices [blood urea nitrogen (BUN), uric acid (UA), cystatin C (CysC), serum creatinine (Scr)], and inflammatory biomarkers [C-reactive protein (CRP)]. The following indices were calculated:

1. eGDR: 21.16-0.09 × waist circumference - 3.407 × hypertension - 0.551 × HbA1c[18-20]. (waist circumference measured in centimeters; hypertension is a binary variable (1 if hypertension is present, 0 if not); HbA1c is the percentage of glycated hemoglobin.)
2. eGFR (CKD-EPI creatinine equation)[21]:

For males:

If Scr ≤ 0.7 mg/dL: $eGFR = 144 \times (Scr/0.7)^{-0.329} \times (0.993)^{age}$

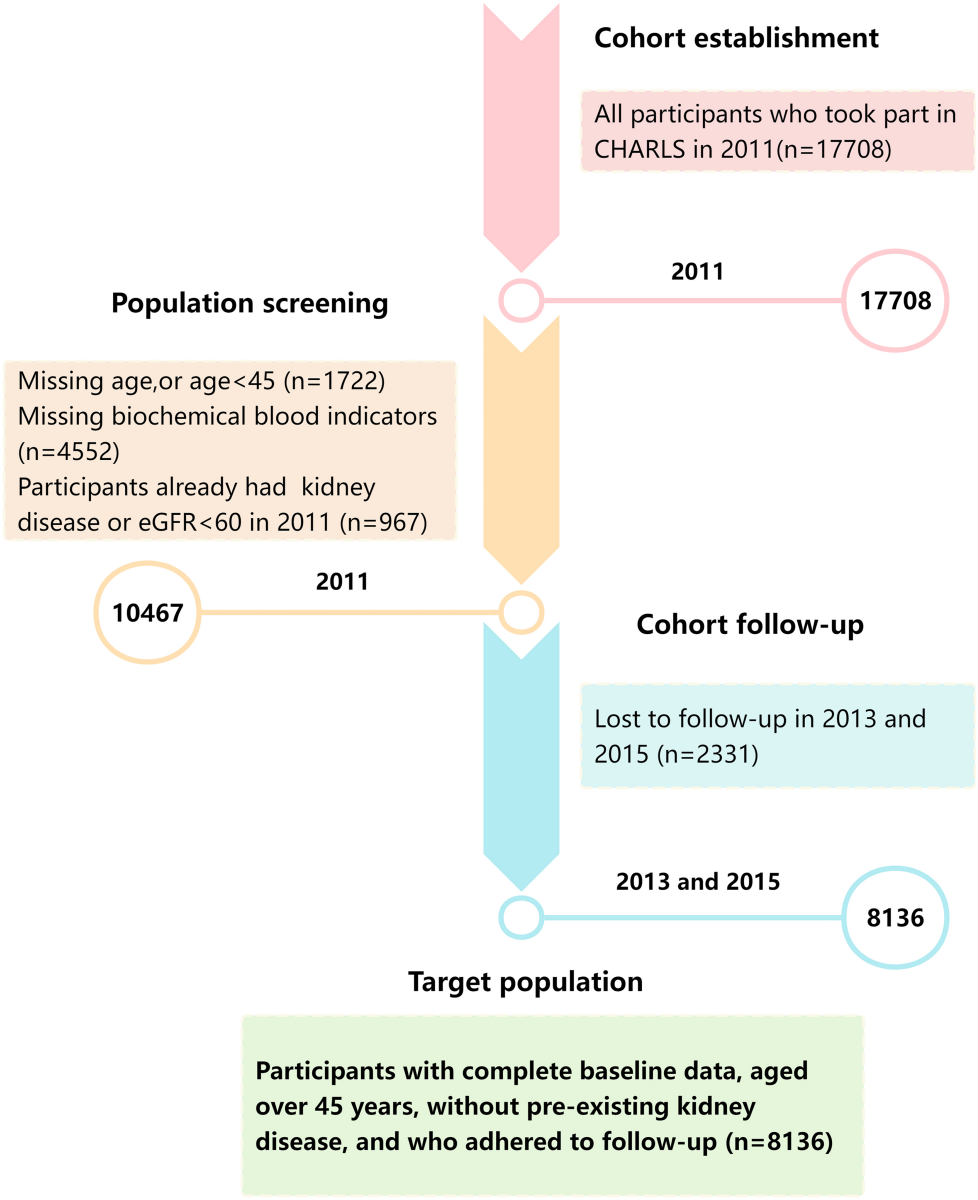

Figure 1. Study Flowchart. A total of 8,136 participants were included according to the inclusion and exclusion criteria.

If Scr > 0.7 mg/dL: eGFR = $144 \times (Scr/0.7)^{-1.209} \times (0.993)^{age}$
For females:
If Scr ≤ 0.9 mg/dL: eGFR = $144 \times (Scr/0.9)^{-0.411} \times (0.993)^{age}$
If Scr > 0.9 mg/dL: eGFR = $144 \times (Scr/0.9)^{-1.209} \times (0.993)^{age}$

(Scr is the serum creatinine level in mg/dL. Age is in years.)
3. BMI: weight (kg) / height^2 (m^2).
4. CVAI (Chinese visceral adiposity index) (Sex-specific formulas):
For males:
CVAI = -267.93 + 0.68 × Age + 0.03 × BMI + 4.00 × WC + 22.00 × lgTG-16.32 × HDL-C
For females:

CVAI = -187.32 + 1.71 × Age + 4.23 × BMI + 1.12 × WC + 39.76 × lgTG-11.66 × HDL-C
(Age in years; WC in cm; TG and HDL-C in mmol/L)

Definitions

Renal dysfunction was defined using the following criteria[22-24]:

(1) eGFR < 60 mL/min/1.73 m^2;
(2) a 50% decrease in eGFR;
(3) a doubling of baseline creatinine levels.

Hypertension diagnosis required either SBP/DBP ≥ 140/90 mmHg on two consecutive readings or current antihypertensive pharmacotherapy usage. Diabetes was identified based on a self-reported history of diabetes or the use of antidiabetic medications. Dyslipidemia was determined through self-reported diagnosis.

Statistical analyses

Continuous data distributions were characterized using parametric (mean ± standard deviation) and non-parametric [median (interquartile range)] descriptors according to normality testing. Comparative analyses utilized non-parametric Wilcoxon tests for skewed distributions and chi-square contingency testing for categorical comparisons. Three-tiered logistic regression models examined eGDR-SBP-renal dysfunction relationships: Model 1 adjusted for age and sex; Model 2 further adjusted for education level, marital status, and comorbidities (hypertension, diabetes, cardiac disease); Model 3 additionally adjusted for smoking and alcohol consumption.

Nonlinear dose-response relationships were investigated using restricted cubic spline regression with Akaike Information Criterion (AIC)-optimized knot placement (3-5 knots). Causal mediation pathways were quantified through counterfactual framework analysis, evaluating SBP's proportion-mediated effect between eGDR and renal dysfunction. The total effect was partitioned into direct and indirect effects, with the latter quantifying the mediated pathway through SBP. Specifically, the indirect effect was calculated as the product of (a) the effect of eGDR on SBP and (b) the effect of SBP on renal dysfunction. The mediation proportion was expressed as (indirect effect / total effect) × 100%. The total effect (c) was defined as the sum of the direct effect (c') and the indirect effect (a × b). Estimates were derived using 5,000 bootstrap resamples to ensure robust inference. All models were adjusted for sociodemographic factors (age, sex, education level, marital status), clinical comorbidities (hypertension, diabetes, cardiac disease), and lifestyle behaviors (smoking status, alcohol consumption). Missing data on covariates were addressed via multiple imputation. Subgroup analyses were conducted by stratifying participants according to sex, marital status, substance use, and comorbidity history. Statistical computations were conducted using the *R* software (version 4.2.1). The threshold for statistical significance was defined as a two-tailed α-level of 0.05.

RESULTS

Baseline characteristics of participants

Before baseline comparison analysis, we conducted a comparative analysis of the included and excluded subjects [Supplementary Table 1] to check for selection bias. The results revealed no significant differences in key demographic and clinical characteristics, indicating that excluding these cases did not introduce systematic bias.

Table 1. Demographics and baseline characteristics of subjects in 2011

Characteristic	Overall *N* = 8,136	Renal dysfunction		*P*
		No *N* = 5,913	Yes *N* = 2,223	
Age (year)	58 (52, 65)	58 (51, 64)	60 (53, 67)	< 0.001
Gender (male, %)	3,754 (46.1%)	2,621 (44.3%)	1,133 (51.0%)	< 0.001
Education level (*n*, %)				0.357
Below primary school	3,858 (47.5%)	2,788 (47.2%)	1,070 (48.2%)	
Primary or middle school	1,811 (22.3%)	1,328 (22.5%)	483 (21.8%)	
High school	1,662 (20.5%)	1,227 (20.8%)	435 (19.6%)	
College or above	791 (9.7%)	560 (9.5%)	231 (10.4%)	
Marital status (married, %)	7,228 (88.9%)	5,305 (89.8%)	1,923 (86.5%)	< 0.001
History of diseases				
Hypertension (*n*, %)	2,222 (27.6%)	1,482 (25.3%)	740 (33.5%)	< 0.001
Diabetes (*n*, %)	540 (6.7%)	334 (5.7%)	206 (9.4%)	< 0.001
Dyslipidemia (*n*, %)	1,084 (13.5%)	631 (10.8%)	453 (20.6%)	< 0.001
Current smoking (*n*, %)	2,640 (32.6%)	1,924 (32.6%)	716 (32.3%)	0.772
Alcohol consumption (*n*, %)	2,347 (29.4%)	1,681 (28.9%)	666 (30.8%)	0.096
SBP (mmHg)	126 (113, 141)	125 (113, 140)	128 (114, 145)	< 0.001
DBP (mmHg)	74 (67, 83)	74 (67, 83)	75 (67, 84)	0.048
Pulse (beats/min)	72 (65, 79)	72 (65, 79)	72 (65, 79)	0.937
BMI (kg/m^2)	23.2 (21.0, 25.9)	23.3 (21.1, 25.9)	23.1 (20.9, 25.9)	0.122
CVAI	100 (78, 126)	100 (77, 125)	101 (78, 128)	0.050
Blood glucose (mmol/L)	102 (95, 113)	102 (95, 113)	102 (94, 114)	0.965
BUN (mg/dL)	15.1 (12.5, 18.1)	14.9 (12.4, 17.8)	15.8 (13.2, 19.0)	< 0.001
Serum creatinine (mg/dL)	0.75 (0.64, 0.87)	0.75 (0.64, 0.86)	0.78 (0.66, 0.94)	< 0.001
UA (mg/dL)	4.40 ± 1.20	4.34 ± 1.21	4.56 ± 1.15	< 0.001
CsyC (mg/dL)	1.00 (0.90, 1.04)	1.00 (0.89, 1.03)	1.00 (0.99, 1.09)	< 0.001
CRP (mg/L)	2.57 ± 6.65	2.54 ± 7.16	2.65 ± 5.06	0.440
TC (mg/dL)	190 (167, 215)	190 (166, 215)	190 (168, 215)	0.411
TG (mg/dL)	106 (75, 157)	106 (75, 155)	108 (77, 162)	0.044
HDL-C (mg/dL)	49 (40, 60)	49 (40, 60)	49 (40, 60)	0.548
LDL-C (mg/dL)	114 (93, 136)	114 (93, 137)	114 (92, 136)	0.542
HbA1c (%)	5.10 (4.90, 5.40)	5.10 (4.90, 5.40)	5.10 (4.90, 5.40)	0.509
eGDR	9.73 ± 1.96	9.78 ± 1.98	9.59 ± 1.91	< 0.001

Normally distributed variables are expressed as mean ± standard deviation, and non-normally distributed variables are expressed as median (interquartile range). All other values are expressed as averages or standard deviations. The Wilcoxon rank sum test or Pearson chi-square test is used to test variables with non-normal distribution. SBP: Systolic blood pressure; DBP: diastolic blood pressure; BMI: body mass index; CVAI: Chinese visceral adiposity index; BUN: blood urea nitrogen; UA: uric acid; CysC: cystatin C; CRP: C-reactive protein; TC: total cholesterol; TG: triglyceride; HDL-C: high-density lipoprotein cholesterol; LDL-C: low-density lipoprotein cholesterol; HbA1c: glycosylated hemoglobin type A1c; eGDR: estimated glucose disposal rate.

Among the 8,136 participants included in the study, 2,223 (27.3%) experienced renal dysfunction [Table 1]. At baseline, individuals with renal dysfunction were slightly older, more likely to be male, and had a lower proportion of married individuals compared to those without renal dysfunction. The prevalence of hypertension, diabetes, and heart disease was significantly higher in the renal dysfunction group. BP levels were also higher among participants with renal dysfunction. Notably, the eGDR was significantly lower in participants who developed renal dysfunction (9.78 ± 1.98 *vs.* 9.59 ± 1.91, $P < 0.001$).

Association between SBP, eGDR index and the incidence of renal dysfunction

Before conducting the mediation analysis, we evaluate potential mediating variables to determine whether they satisfy the criteria for mediators. The results of the multivariate correlation with eGDR indicated that BUN and eGDR were not correlated, indicating that BUN is not suitable as a mediator [Supplementary Table 2]. Additionally, due to the nonlinear relationships between eGDR and variables such as Scr, CysC, BMI, and CVAI, these variables were excluded from the mediation analysis [Supplementary Table 3].

Table 2 summarizes the longitudinal associations between eGDR and SBP with renal dysfunction. After adjusting for age, gender, education level, marital status, comorbidities, smoking, and alcohol consumption, SBP was shown to have a persistent independent association with renal dysfunction. Specifically, each unit increase in SBP was associated with a 20% increased risk of renal dysfunction (OR = 1.20, 95%CI: 1.05-1.38; $P = 0.010$). Regarding eGDR quartiles, compared to the lowest quartile (Q1), the risk of renal dysfunction was significantly higher in Q2 (OR = 2.11, 95%CI: 1.70-2.62; $P < 0.001$), whereas Q4 demonstrated a significantly lower risk (OR = 0.73, 95%CI: 0.58-0.92; $P = 0.009$). A significant downward trend in renal dysfunction risk was observed across increasing eGDR quartiles (P for trend < 0.001).

After adjusting for multiple variables, restricted cubic spline analysis showed that an eGDR below the threshold of 11.6 mg/kg/min was associated with a substantially increased risk of renal dysfunction [Figure 2A]. Similarly, an SBP threshold of 125 mmHg emerged as an inflection point, above which the risk of renal dysfunction notably increased [Figure 2B].

Mediation analysis of eGDR, SBP and renal dysfunction

Mediation analysis was performed to examine the role of SBP in the relationship between eGDR and renal dysfunction. The total effect of eGDR on renal dysfunction was modest but statistically significant (c = -0.021, 95%CI: -0.031 to -0.011; $P < 0.001$). SBP was identified as a significant mediator, with an indirect effect of -0.009 (95%CI: -0.013 to -0.0045; $P < 0.001$), accounting for 42.6% (95%CI: 19.9% to 86.7%) of the total effect. After adjustment for SBP, the direct effect of eGDR on renal dysfunction remained significant (c' = -0.012) [Table 3 and Figure 3].

In addition to SBP, other variables such as age, TG, UA, diabetes, and hyperlipemia also showed significant indirect effects. Age mediated 29.0% (95%CI: 16.8% to 52.8%) of the total effect, TG 17.1% (95%CI: 6.2% to 38.6%), UA 26.7% (95%CI: 15.7% to 52.7%), diabetes 51.3% (95%CI: 30.6% to 78.8%), and hyperlipemia 30.0% (95%CI: 11.2% to 51.6%). Variables such as DBP, CRP, hypertension, and marital status did not demonstrate significant indirect effects in the mediation analysis [Table 3].

Subgroup analysis

Figure 4 displays the results of subgroup analyses stratified by gender, marital status, and smoking history. Significant associations between eGDR and renal dysfunction were observed among participants with alcohol consumption and in those with diabetes. In addition, no significant interactions were identified between eGDR and most subgroup variables (all P for interaction > 0.05), except for marital status. A significant interaction was observed with marital status (P for interaction = 0.004), suggesting a potential modifying effect of this variable on the relationship between eGDR and renal dysfunction. To further clarify whether marital status affects the mediating role of SBP in eGDR and renal function, subjects were divided into different subgroups according to marital status for mediating analysis, and the results show that SBP's mediating effect remains consistent in the single subgroup, while the direct effect of eGDR on renal function decline was not significant in the married subgroup [Supplementary Table 4].

Table 2. Association between SBP, eGDR and renal dysfunction

Characteristic	Model 1		Model 2		Model 3	
	OR (95%CI)	*P*	OR (95%CI)	*P*	OR (95%CI)	*P*
SBP	1.09 (1.03, 1.15)	0.001	1.08 (1.03, 1.14)	0.003	1.20 (1.05, 1.38)	0.010
eGDR quartile groups						
Q1	-		-		-	
Q2	2.01 (1.76, 2.30)	< 0.001	1.98 (1.60, 2.44)	< 0.001	2.11 (1.70, 2.62)	< 0.001
Q3	0.78 (0.67, 0.90)	< 0.001	0.78 (0.62, 0.97)	0.026	0.84 (0.67, 1.06)	0.149
Q4	0.77 (0.66, 0.89)	< 0.001	0.67 (0.54, 0.84)	< 0.001	0.73 (0.58, 0.92)	0.009
P for trend		< 0.001		< 0.001		< 0.001

Model 1: Age and gender were adjusted; Model 2: Age, gender, education level, marital status, and comorbidities (hypertension, diabetes and heart diseases) were adjusted; Model 3: Age, gender, education level, marital status, comorbidities (hypertension, diabetes and heart diseases) and smoking and alcohol consumption were adjusted. Q1: eGDR ≤ 9.12; Q2: 9.12 < eGDR ≤ 9.83; Q3: 9.83 < eGDR ≤ 11.04; Q4: GDR > 11.04. SBP: Systolic blood pressure; eGDR: estimated glucose disposal rate; OR: odds ratio; CI: confidence interval.

Table 3. Mediation analysis for the associations between eGDR, SBP and renal dysfunction

Independent variable	Mediator	Total effect (c)		Indirect effect (a × b)		Direct effect (c′)		Proportion mediated, % (95%CI)
		β (95%CI)	*P* value	β (95%CI)	*P* value	β (95%CI)	*P* value	
eGDR	SBP	-0.021 (-0.031, -0.011)	< 0.001	-0.009 (-0.013, -0.005)	< 0.001	-0.012 (-0.023, -0.001)	0.032	42.6 (19.9, 86.7)
eGDR	DBP	-0.011 (-0.017, -0.005)	< 0.001	-0.001 (-0.003, 0.001)	0.500	-0.010 (-0.017, -0.005)	< 0.001	7.7 (-16.3, 30.4)
eGDR	Age	-0.010 (-0.017, -0.005)	< 0.001	-0.003 (-0.004, -0.002)	< 0.001	-0.008 (-0.014, -0.002)	< 0.001	29.0 (16.8, 52.8)
eGDR	TG	-0.011 (-0.017, -0.006)	< 0.001	-0.002 (-0.003, -0.001)	< 0.001	-0.009 (-0.015, -0.004)	< 0.001	17.1 (6.2, 38.6)
eGDR	UA	-0.011 (-0.017, -0.006)	< 0.001	-0.003 (-0.004, -0.002)	< 0.001	-0.008 (-0.014, -0.003)	< 0.001	26.7 (15.7, 52.7)
eGDR	CRP	-0.011 (-0.017, -0.006)	< 0.001	-0.000 (-0.000, 0.001)	0.540	-0.0111 (-0.017, -0.005)	< 0.001	0.7 (-1.7, 3.3)
eGDR	Hypertension	0.008 (0.001, 0.013)	0.020	-0.001 (-0.002, 0.001)	0.300	-0.010 (-0.016, -0.005)	< 0.001	6.3 (-6.1, 22.8)
eGDR	Diabetes	-0.016 (-0.022, -0.009)	< 0.001	-0.008 (-0.012, -0.005)	< 0.001	-0.008 (-0.013, -0.002)	0.020	51.3 (30.6, 78.8)
eGDR	Hyperlipemia	-0.013 (-0.018, -0.007)	< 0.001	-0.004 (-0.006, 0.001)	0.020	-0.009 (-0.015, -0.004)	< 0.001	30.0 (11.2, 51.6)
eGDR	Marital status	-0.020 (-0.031, -0.010)	< 0.001	-0.001 (-0.001, 0.000)	0.100	-0.019 (-0.030, -0.010)	< 0.001	2.5 (-0.4, 8.0)

CI: Confidence interval; SBP: systolic blood pressure; UA: uric acid; CRP: C-reactive protein; TG: triglyceride; eGDR: estimated glucose disposal rate; DBP: diastolic blood pressure.

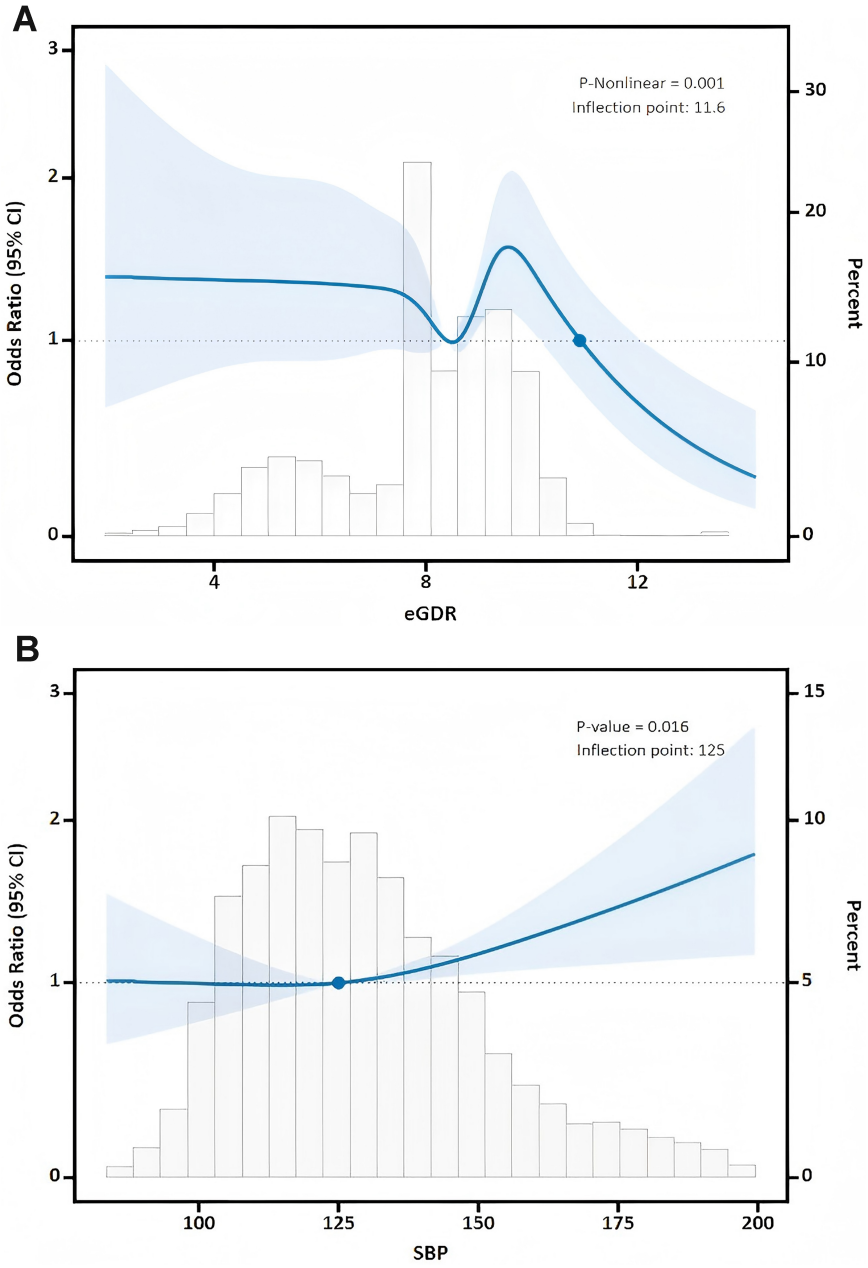

Figure 2. The correlations of eGDR or SBP with follow-up renal outcome events. (A) Association between multivariable adjusted odds ratios for renal outcome events with eGDR; (B) Association between multivariable adjusted odds ratios for renal outcome events with SBP. SBP: Systolic blood pressure; eGDR: estimated glucose disposal rate.

DISCUSSION

Utilizing a national population-based cohort study, our investigation demonstrated an inverse correlation between eGDR and renal dysfunction, with lower eGDR values showing significant associations with increased risks of detrimental renal outcomes. Notably, mediation analysis revealed that SBP exerts a significant mediating effect in the relationship between eGDR and renal dysfunction. This study provides strong evidence of the interplay between IR and hypertension in renal prognosis, underscoring the importance of addressing these metabolic and cardiovascular factors in managing renal health in the aging Chinese population.

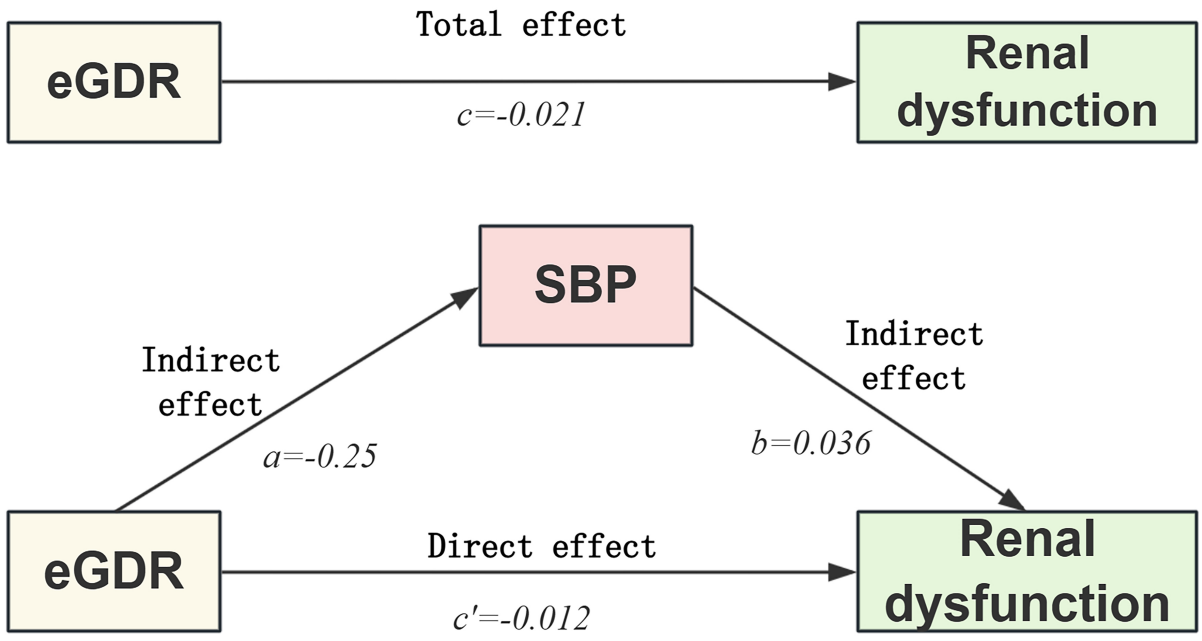

Figure 3. Mediation analysis of SBP in the association between eGDR and renal dysfunction. The total effect was partitioned into direct and indirect effects, with the latter quantifying the mediated pathway through SBP. Specifically, the indirect effect was calculated as the product of (a) the effect of eGDR on SBP and (b) the effect of SBP on renal dysfunction. The mediation proportion was expressed as (indirect effect/total effect) × 100%. The total effect (c) was defined as the sum of the direct effect (c′) and the indirect effect (a × b). SBP: Systolic blood pressure; eGDR: estimated glucose disposal rate.

In recent years, eGDR has emerged as a key surrogate marker for IR and a valuable predictor of renal outcomes. A longitudinal analysis from the DCCT/EDIC cohort reported that reduced eGDR levels below the 5.6 mg/kg/min threshold demonstrated significant predictive value for proteinuria development in 1,441 patients with type 1 diabetes (T1DM)[8] Similarly, an Italian study involving 15,773 patients with type 2 diabetes confirmed the predictive value of eGDR for renal function decline[25]. A cross-sectional study of 200 patients with T1DM in Lithuania found a higher prevalence of microalbuminuria and diabetic nephropathy in those with eGDR values below 6.4 mg/kg/min[26]. Additionally, in a cohort of 2,151 patients, individuals with eGDR < 4 mg/kg/min demonstrated a significantly higher risk of nephropathy compared to those with eGDR ≥ 8 mg/kg/min[20]. However, not all studies have observed this relationship. For example, a pooled analysis by Ebert *et al.*[27]. involving 13,026 T2DM patients found no association between eGDR and renal prognosis. Similarly, a cross-sectional study of 165 T1DM patients without cardiac, renal, or ocular complications reported no association between eGDR and albumin-to-creatinine ratio[28]. Our study, using the data from the nationally representative CHARLS cohort, demonstrated a significant association between lower eGDR levels and increased risk of renal dysfunction among the middle-aged and elderly population.

Both IR and hypertension are well-known risk factors for renal function decline, and their coexistence significantly amplifies this risk. IR, a hallmark of T2DM, contributes to the occurrence and progression of hypertension. Previous research has shown that hypertension increases the risk of diabetic nephropathy. Wu *et al.* found that diabetic patients with hypertension had a 1.78-fold higher risk of developing CKD compared to normotensive individuals[29]. A meta-analysis of 27 studies reported a 1.67-fold increased risk of diabetic nephropathy in diabetic patients with hypertension compared to those without[30]. Our study builds upon these findings by elucidating the mediating role of SBP in the relationship between eGDR and renal dysfunction. Specifically, SBP accounted for 42.6% of the total effect of eGDR on renal dysfunction, indicating that hypertension partially explains the link between IR and renal prognosis.

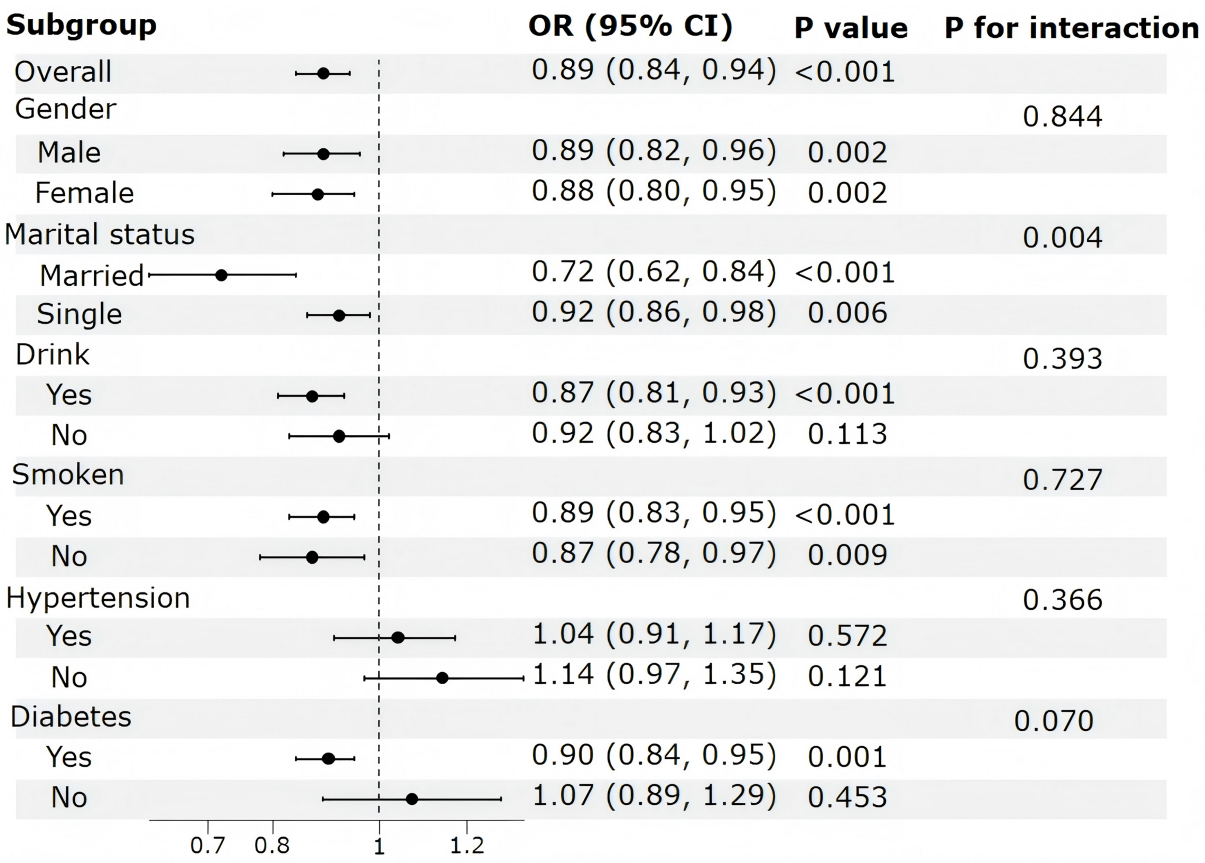

Figure 4. Association between eGDR and renal dysfunction in different subgroups. Subgroup analysis stratified by gender, marital status, and history of smoking showed the robustness of the results. Significant associations between eGDR and renal events were observed in participants with a history of drinking and diabetes. No interaction was observed between the eGDR index and any of the subgroup variables (all *P* for interaction > 0.05) except marital status (*P* for interaction = 0.004). OR: Odds ratio; eGDR: estimated glucose disposal rate.

The association between IR and hypertension has been well documented. In a study of 4,717 Brazilian adults, IR was shown to increase the risk of developing hypertension[31]. Similarly, in a cohort of 10,810 participants, a positive linear relationship was observed between SBP and HOMA-IR in individuals with prediabetes and normal glucose levels[32]. Mechanistically, hyperinsulinemia that occurs under IR is prone to lead to the activation of the sympathetic nervous system and the renin-angiotensin-aldosterone system (RAAS), promoting sodium retention, water retention, and vasoconstriction. Additionally, IR may influence vascular smooth muscle tone by increasing intracellular calcium levels, contributing to vasoconstriction[33,34]. Furthermore, shared risk factors such as obesity, dyslipidemia, and chronic inflammation may underlie both IR and hypertension, complicating the interplay between these conditions[35].

Although SBP emerged as the predominant mediator in our analysis, other factors also contributed to the relationship between eGDR and renal dysfunction. Age mediated 29.0% of the total effect, suggesting that the adverse impact of IR on renal function may be more pronounced in older individuals. Scr, CysC, uric

acid, and triglycerides - known markers of renal prognosis - also demonstrated significant mediating effects in this study, enriching our understanding of the biological pathways linking IR to renal dysfunction. Furthermore, hyperlipidemia and diabetes history mediated 30.0% and 51.3% of the total effect, respectively. This finding aligns with previous research, including a 10-year prospective cohort study by Huh *et al.*, which identified a close association between metabolic syndrome and CKD[36].

The subgroup results of this study suggested that there was an interaction between marital status and eGDR, and marital status affected the direct effect of eGDR on renal dysfunction in the mediation analysis. This interaction may work through two interrelated pathways: lifestyle behavior and self-awareness/management. First, marital relationships often shape health-promoting behaviors that directly influence eGDR. Cohabitation or spousal support is associated with improved adherence to dietary modifications (e.g., reduced carbohydrate intake) and physical activity regimens, both critical for maintaining insulin sensitivity. A systematic review study suggests that family support is associated with lower HbA1c in men, which facilitates blood glucose detection and control[37]. Second, partner and family support can help the early prevention and treatment of the disease. A recent study shows that family and partners play an important and positive role in patients' cognition and self-management of the disease, and are of great value in delaying the progression of renal function in patients with early CKD[38].

This study provides some guidance for clinical practice. Our findings indicate that eGDR < 11.6 mg/kg/min is tied to higher renal dysfunction risk, with systolic BP acting as a mediator. Clinicians can use eGDR to spot high-risk patients early, especially those below this threshold yet with normal renal function. For these patients, closer monitoring and early intervention may delay or prevent renal dysfunction. BP control, via lifestyle changes or medications like ACEIs/ARBs, is crucial for prevention, particularly in low-eGDR patients. Treatment should be individualized based on eGDR and systolic BP levels. Regular monitoring of renal function and BP in low-eGDR patients is advised, and a multidisciplinary approach can enhance management. Our results suggest incorporating eGDR testing and personalized strategies based on eGDR/BP could delay disease progression. Further research is needed to refine eGDR's application in kidney disease diagnosis/treatment.

The major strength of this study lies in the use of a nationally representative sample from the CHARLS cohort, which allowed us to comprehensively examine the relationship between insulin sensitivity, as measured by eGDR, and renal outcomes in the general middle-aged and elderly Chinese population. However, this study has several limitations. Although we adjusted for several potential confounders, residual confounding from unmeasured factors, such as environmental influences and psychological stress, cannot be excluded. Additionally, future research should consider age differences, as our study focused on adults aged 45 and older, but this relationship may also exist in younger people, who have different metabolic profiles and risk thresholds. Racial diversity is another factor, as genetic, lifestyle, and environmental differences across races can affect the relationship between eGDR, BP, and renal dysfunction. Additionally, regional differences in healthcare, diet, and environmental exposure between rural and urban populations, as well as socioeconomic variations, may influence renal dysfunction and should be investigated in future studies. Lastly, the absence of proteinuria and hematuria data may affect the accuracy of risk stratification, as these parameters are key biomarkers of renal injury, and these variables should be included in future studies.

Conclusion

In this nationally representative longitudinal cohort study, we identified a significant inverse association between eGDR and renal dysfunction, with our analyses providing statistical evidence suggesting that SBP

may act as a potential mediator in this relationship. These findings enhance our understanding of how IR contributes to adverse renal outcomes and underscore the importance of addressing both metabolic and cardiovascular risk factors in the prevention and management of renal disease.

DECLARATIONS

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Authors' contributions

Conceived and designed the study: Wang Y, Niu ZJ
Conducted the research: Niu ZJ
Performed data analysis and drafted the manuscript: Niu ZJ, Yan MY
Contributed to critical revisions of the manuscript: Wang Y, Cui Y, Tian PX
Read and approved the final manuscript: Niu ZJ, Yan MY, Cui Y, Dou M, Tian PX, Wang Y

Availability of data and materials

The datasets used and analyzed during the current study are available from the corresponding authors upon reasonable request.

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Conflicts of interest

Wang Y is a Junior Editorial Board member of the journal *Metabolism and Target Organ Damage*. Wang Y was not involved in any steps of the editorial process, including reviewer selection, manuscript handling, and decision making. The other authors declared that there are no conflicts of interest.

Ethical approval and consent to participate

All procedures in the CHARLS investigation were conducted in compliance with the ethical standards established by Peking University's review board (Ethics ID: IRB00001052-11015), with legally valid informed consent obtained in written form from each participant.

Consent for publication

Not applicable.

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