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Interaction Effect of Estimated Pulse Wave Velocity and Serum Klotho Level on Chronic Kidney Disease

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Keywords: chronic kidney disease | cross-sectional study | estimated pulse wave velocity | Klotho | NHANES

ABSTRACT

Objectives: Older individuals usually have greater arterial stiffness, lower serum Klotho levels and a greater incidence of chronic kidney disease (CKD). The current study aimed to evaluate the interaction effect of estimated pulse wave velocity (ePWV) and serum Klotho levels on CKD in Americans.

Methods: Data from the National Health and Nutrition Examination Survey database from 2007 to 2016 were used. Participants with data for the assessment of ePWV and serum Klotho and for the assessment of CKD were enrolled. The associations between ePWV and serum Klotho levels were analyzed via restricted cubic spline analysis and a linear regression model. The associations between exposure factors and CKD prevalence were assessed via a logistic regression model. Subgroup analysis was performed for each confounding factor to assess the robustness of the results.

Results: This study enrolled 13,273 participants, 3859 of whom were CKD patients. CKD patients had higher ePWV (9.66 ± 1.75 m/s vs. 8.48 ± 1.64 m/s, $p < 0.001$) and lower levels of serum Klotho (816.35 ± 290.47 pg/mL vs. 869.87 ± 315.87 pg/mL, $p < 0.001$). A significant negative linear association was found between ePWV and serum Klotho. According to the fully adjusted model, a significant interaction effect between ePWV and serum Klotho was observed on the risk of CKD ($p < 0.001$). Compared with individuals with a lower ePWV and higher serum Klotho, individuals with an increased ePWV and lower serum Klotho had a significantly elevated risk of CKD (OR: 1.847, 95% confidence interval: 1.467–2.325; $p < 0.001$). The subgroup analysis revealed that the results were robust.

Abbreviations: AA, associate of arts; ACR, (urinary) albumin/creatinine ratio; BMI, body mass index; cfPWV, carotid-femoral PWV; CI, confidence interval; CKD, chronic kidney disease; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; ePWV, estimated pulse wave velocity; GED, general education development; HDL, high-density lipoprotein; MAP, mean arterial pressure; NHANES, National Health and Nutrition Examination Survey; OR, odds ratio; SBP, systolic blood pressure; SD, standard deviation; STROBE, Strengthening the Reporting of Observational Studies in Epidemiology.

Peilin Zou and Jiajun Li contributed equally to this work.

Conclusions: The study demonstrated significant interaction effect of ePWV and serum Klotho on the prevalence of CKD. Individuals with increased ePWV and decreased serum Klotho levels had the highest risk of CKD. The assessment of the combination of ePWV and serum Klotho for CKD management should be considered routine in clinical practice.

1 | Introduction

With the aging of populations worldwide, the prevalence of chronic diseases, such as heart failure, cognitive impairment, and chronic kidney disease (CKD), is increasing annually worldwide. CKD is defined as the impairment of kidney function or structure of prolonged duration exceeding 3 months, leading to cardiovascular diseases (CVDs), the need for dialysis or kidney transplantation, or even death. There is a bidirectional association between CKD and aging. The prevalence of CKD increases with age, and CKD can also promote biological aging via several mechanisms. Owing to the progressive aging of the population worldwide, CKD is predicted to be the 5th most common cause of mortality worldwide by 2040 and the second leading cause of mortality by the end of this century in aging countries [1]. These conditions are related to high prevalence, high costs, and poor outcomes [2]. The identification of predictors for the prevalence and development of CKD is highly important for its prevention and treatment, which may help achieve healthy aging in older individuals.

The kidney, as an organ with low arteriolar resistance and requiring high blood flow, is easily damaged by arterial stiffening due to elevated microvascular pressure coupled with an enhanced pulse wave [3]. Arterial stiffness increases with age, and atherosclerosis is the most characteristic manifestation of vascular aging [4]. The assessment of pulse wave velocity (PWV) is a tangible and straightforward modality for quantifying arterial stiffness. Several studies have reported that elevated carotid-femoral PWV (cfPWV) is associated with a decline in the renal function of CKD patients [5, 6] and progression to end-stage kidney disease [7]. The estimated PWV (ePWV), which is considered to be a proxy of the cfPWV [8], is calculated on the basis of age and blood pressure. The ePWV was similar to the measured cfPWV for major cardiovascular events [9]. It is suitable for large-scale investigations and routine or even daily monitoring because of its nearly zero cost, especially when the PWV cannot be measured by equipment. Unfortunately, there is currently a lack of evidence regarding the association between ePWV and CKD.

Serum Klotho is highly expressed in the kidney and is considered an aging suppressor [10]. It is a transmembrane and soluble circulating protein [11]. The level of serum Klotho is associated with multiple diseases, including CKD [12], CVD [13], diabetes [14], and all-cause mortality [15]. It has been reported that in the early stages of CKD, a reduction in the serum soluble Klotho level commences [16], exhibiting a positive association with the estimated glomerular filtration rate (eGFR) and an inverse link with the incidence of CKD, particularly in elderly, obese, and diabetic populations [17]. Moreover, Klotho is considered a biomarker for healthy aging [18] and a valuable potential therapeutic target for aging-related diseases [19]. Interestingly, the levels of serum Klotho exhibited an inverse association with the aortic-brachial PWV (baPWV) in patients who received dialysis [20].

Considering the potential associations among ePWV, soluble serum Klotho and CKD, in this study, we hypothesized that elevated ePWV might be associated with a high risk of CKD and that an interaction between ePWV and serum Klotho might exist. This interactive correlation may indicate that individuals with high ePWV, especially those with decreased levels of serum Klotho, may suffer from CKD. This study, on the basis of a nationwide investigation, provides evidence for the accurate prediction and evaluation of CKD and novel insight into the prevention and treatment of CKD.

2 | Methods

The results were reported in accordance with the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines.

2.1 | Study Design and Population

Over 100,000 individuals participated in this cross-sectional annual survey, the National Health and Nutrition Examination Survey (NHANES), from 1999 to 2023 in the U.S. These participants participated in data collection only once during the period 1999–2023. This survey recruited participants via a complicated probability sampling strategy and conducted biological sample testing, physical examinations, and standardized interviews to gather relevant data. This study was approved by the Ethics Review Committee of the National Center for Health Statistics. For the purpose of the current study, we enrolled participants from five cycles of the NHANES, namely, 2007–2008, 2009–2010, 2011–2012, 2013–2014, and 2015–2016, owing to the availability of data regarding the level of serum Klotho. We excluded individuals without data to assess the presence of CKD ($n = 18{,}885$), the level of serum Klotho ($n = 28{,}563$) or the ePWV ($n = 1817$). Finally, we included 13,273 participants for further analysis (Figure S1).

2.2 | Assessment of the ePWV and Serum Klotho Concentration

A qualified examiner took the participants' blood pressure after they had rested quietly in a seated position for 5 min, according to the American Heart Association's blood pressure measurement technique [21]. Using the equation derived from the Reference Values for Arterial Stiffness Collaboration [22], the ePWV was calculated from age and mean blood pressure (MBP), which was calculated on the basis of systolic blood pressure (SBP) and diastolic blood pressure (DBP). In accordance with previously published studies [22, 23], the MBP was calculated via Algorithm (1):

$$\mathrm{MBP} = \mathrm{DBP} + [0.4 \times (\mathrm{SBP} - \mathrm{DBP})] \quad (1)$$

The ePWV was calculated via Algorithm (2):

$$\begin{aligned} ePWV = {} & 9.587 - (0.402 \times age) + \left[4.560 \times 0.001 \times \left(age^2\right)\right] \\ & - \left[2.621 \times 0.00001 \times \left(age^2\right) \times MBP\right] \\ & + (3.176 \times 0.001 \times age \times MBP) - (1.832 \times 0.01 \times MBP) \end{aligned} \quad (2)$$

The level of serum Klotho was assessed via a Human Soluble Serum Klotho Assay Kit (Immuno-Biological Laboratories Co. Ltd.) based on fresh-frozen blood samples. The average result from two tests of each sample served as the final value. The test was repeated when the quality control sample yielded results exceeding two standard deviations (SDs) from the specified target value.

2.3 | Ascertainment of CKD

The estimated glomerular filtration rate (eGFR) was calculated according to the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI):

$$eGFR = 141 \times \min\left(\frac{Scr}{\kappa}, 1\right)^{\alpha} \times \max\left(\frac{Scr}{\kappa}\right)^{-1.209} \times 0.993^{Age} \times 1.018\ [\text{if female}] \times 1.159\ [\text{if black}]$$

in which Scr is the serum creatinine in mg/dL, κ is 0.7 for females and 0.9 for males, α is −0.329 for females and −0.411 for males, min is the minimum of Scr/κ or 1, and max is the maximum of Scr/κ or 1. The eGFR units are mL/min/1.73 m^2 [24]. The urinary albumin–creatinine ratio (ACR) was calculated via the following equation: ACR (mg/g) = urinary albumin (mg/dL)/urinary creatinine (g/dL). Renal impairment was defined as the presence of albuminuria and was characterized by an ACR equal to or exceeding 30 mg/g. According to the KDIGO guidelines, CKD is classified into five stages on the basis of the eGFR and/or evidence of kidney damage [25].

2.4 | Covariates

The demographic variables included age, sex (categorical, male and female), race (categorical, other Hispanic, non-Hispanic Black, Mexican American, non-Hispanic White, and Other), education level (categorical, less than 9th grade, 9–11th grade, high School Grade/GED or Equivalent, some college or AA degree and college graduate or above), marital status (categorical, married, widowed, divorced, separated, never married and with partner), and the ratio of income poverty (categorical, <5 and ≥ 5). The income–poverty ratio was determined by dividing family income by the poverty limits for the size of the family, as well as the applicable year and state. The examination variables included body mass index (BMI) (categorical, <24 kg/m^2 as normal, ≥ 24 kg/m^2 as abnormal), which was computed by weight (kg) divided by height squared (m^2), and MAP (mmHg, calculated as (SBP + 2 × DBP)/3). The laboratory data included triglyceride levels, serum creatinine levels, total serum cholesterol levels, hemoglobin levels, high-density lipoprotein (HDL) levels, and glycohemoglobin levels. The questionnaire variables included smoking status (categorical, yes and no) and alcohol consumption status (categorical, yes and no). Hypertension was defined as high BP in participants who were told by a doctor. Diabetes status was defined as the patient who took insulin, took diabetic pills to lower blood sugar, was told by a doctor that they had "diabetes or sugar diabetes" when they were not pregnant, had glycohemoglobin > 6.5%, had a fasting glucose > 7 mmol/L or had a 2-h glucose (OGTT) > 11.1 mmol/L.

2.5 | Statistical Analysis

In the NHANES database, weighted analysis was performed on all the data by using WTMEC2YR, SDMVPSU, and SDMVSTRA as weighted variables. Continuous variables are presented as the means (plus SDs). Categorical variables are presented as numbers (composition ratios (%)). The characteristics of participants with or without CKD or participants with different ePWV values were compared via Student's *t*-test or analysis of variance, and the chi-square test was used for continuous variables and categorical variables, respectively. The associations between ePWV and serum Klotho levels were assessed via restricted cubic spline (RCS) analysis and a linear regression model. The associations between exposure factors and the risk of CKD were assessed via logistic regression models. In each model, the ePWV and serum Klotho level were classified as high or low according to the median of each variable, and we calculated odds ratios (ORs) with 95% confidence intervals (CIs). The interaction between ePWV and serum Klotho was tested with an interaction model. We also assessed the associations between the combination of ePWV and serum Klotho and CKD, in which the combination of low ePWV and high serum Klotho was used as the reference. Subgroup analysis was performed for each confounding factor to assess the robustness of the results.

All the statistical analyses were performed by using R 4.3.1. $p < 0.05$ was considered to indicate statistical significance.

3 | Results

3.1 | Characteristics of the Enrolled Individuals

This study enrolled 13,273 individuals, 3859 of whom were considered to suffer from CKD. As presented in Table 1, CKD patients were more likely to be male (73.33% vs. 38.59%, $p < 0.001$), smokers (55.82% vs. 45.83%, $p < 0.001$), alcohol abusers (69.94% vs. 65.25%, $p < 0.001$), hypertension patients (60.82% vs. 40.47%, $p < 0.001$), and diabetes patients (38.33% vs. 19.48%, $p < 0.001$). CKD patients were more likely in terms of age (62.62 ± 10.43 vs. 55.71 ± 10.36, $p < 0.001$), BMI (30.27 ± 6.68 kg/m^2 vs. 29.50 ± 6.65 kg/m^2, $p < 0.001$), MAP (91.64 ± 13.47 mmHg vs. 89.24 ± 11.07 mmHg, $p < 0.001$), triglycerides (2.01 ± 1.47 mmol/L vs. 1.85 ± 1.61 mmol/L, $p < 0.001$), Scr (1.19 ± 0.79 mg/dL vs. 0.81 ± 0.16 mg/dL, $p < 0.001$), and hemoglobin (14.17 ± 1.66 g/dL vs. 13.95 ± 1.43 g/dL, $p < 0.001$), glycohemoglobin (6.29% ± 1.51% vs. 5.84% ± 1.00%, $p < 0.001$) and ACR (159.41 ± 655.28 mg/g vs. 8.70 ± 5.70 mg/g, $p < 0.001$) and total serum cholesterol (4.94 ± 1.19 mmol/L vs. 5.23 ± 1.07 mmol/L, $p < 0.001$), HDL (1.28 ± 0.42 mmol/L vs. 1.41 ± 0.43 mmol/L, $p < 0.001$). Moreover, a lower percentage of CKD patients had received higher education (48.64% with university higher education vs. 50.87%, $p < 0.001$) or high income (16.48% vs. 19.40%, $p < 0.001$). Importantly, CKD patients had a greater ePWV (9.66 ± 1.75 m/s

TABLE 1 | Characteristics of individuals with or without chronic kidney disease (from the NHANES database of the population surveyed from 2007 to 2016).

	CKD ($n = 3859$)	Non-CKD ($n = 9414$)	p
Age	62.62 (10.43)	55.71 (10.36)	< 0.001
Sex, male (%)	2830 (73.33%)	3633 (38.59%)	< 0.001
Race			
Mexican American	510 (13.22%)	1596 (16.95%)	< 0.001
Other Hispanic	404 (10.46%)	1122 (11.92%)	
Non-Hispanic White	1755 (45.48%)	3999 (42.48%)	
Non-Hispanic Black	865 (22.42%)	1754 (18.63%)	
Other race	325 (8.42%)	943 (10.02%)	
Education level			
Less Than 9th Grade	561 (14.54%)	1227 (13.03%)	< 0.001
9–11th Grade (includes 12th grade with no diploma)	602 (15.60%)	1325 (14.07%)	
High school Grad/GED or equivalent	877 (22.73%)	2069 (21.98%)	
Some college or AA degree	1000 (25.91%)	2595 (27.57%)	
College graduate or above	816 (21.15%)	2194 (23.31%)	
Smoke (yes, %)	2154 (55.82%)	4314 (45.83%)	< 0.001
Alcohol (yes, %)	2699 (69.94%)	6143 (65.25%)	< 0.001
Hypertension (yes, %)	2347 (60.82%)	3810 (40.47%)	< 0.001
Diabetes (yes, %)	1479 (38.33%)	1834 (19.48%)	< 0.001
BMI (kg/m^2)	30.27 (6.68)	29.50 (6.65)	< 0.001
Mean arterial pressure (mm Hg)	91.64 (13.47)	89.24 (11.07)	< 0.001
Triglyceride (mmol/L)	2.01 (1.47)	1.85 (1.61)	< 0.001
Serum creatinine (mg/dL)	1.19 (0.79)	0.81 (0.16)	< 0.001
Serum total cholesterol (mmol/L)	4.94 (1.19)	5.23 (1.07)	< 0.001
Hemoglobin (g/dL)	14.17 (1.66)	13.95 (1.43)	< 0.001
HDL (mmol/L)	1.28 (0.42)	1.41 (0.43)	< 0.001
Glycohemoglobin (%)	6.29 (1.51)	5.84 (1.00)	< 0.001
ACR (mg/g)	159.41 (655.28)	8.70 (5.70)	< 0.001
Serum Klotho (pg/ml)	816.35 (290.47)	869.87 (315.87)	< 0.001
ePWV (m/s)	9.66 (1.75)	8.48 (1.64)	< 0.001
Ratio of family income to poverty			
≥ 5	636 (16.48%)	1826 (19.40%)	< 0.001
< 5	2925 (75.80%)	6819 (72.43%)	

Abbreviations: AA, associate of arts; ACR, (urinary) albumin/creatinine ratio; BMI, body mass index; ePWV, estimated pulse wave velocity; GED, general education development; HDL, high-density lipoprotein.

vs. 8.48 ± 1.64 m/s, $p < 0.001$) and lower serum Klotho level (816.35 ± 290.47 vs. 869.87 ± 315.87, $p < 0.001$).

Interestingly, similar results were found in individuals with higher ePWV (Table S1). Notably, individuals with higher ePWV also had lower serum Klotho levels (821.95 ± 283.58 pg/mL, $p < 0.001$). After fully adjusting for confounding factors, RCS analysis revealed a significant linear association between ePWV and serum Klotho (Figure 1, $p_{overall} = 0.010$, $p_{nonlinearity} = 0.040$). According to the fully adjusted linear regression model, a significant linear relationship was also found between ePWV and serum Klotho (β: −1.400; 95% CI: −2.000 to −1.731; $p < 0.001$).

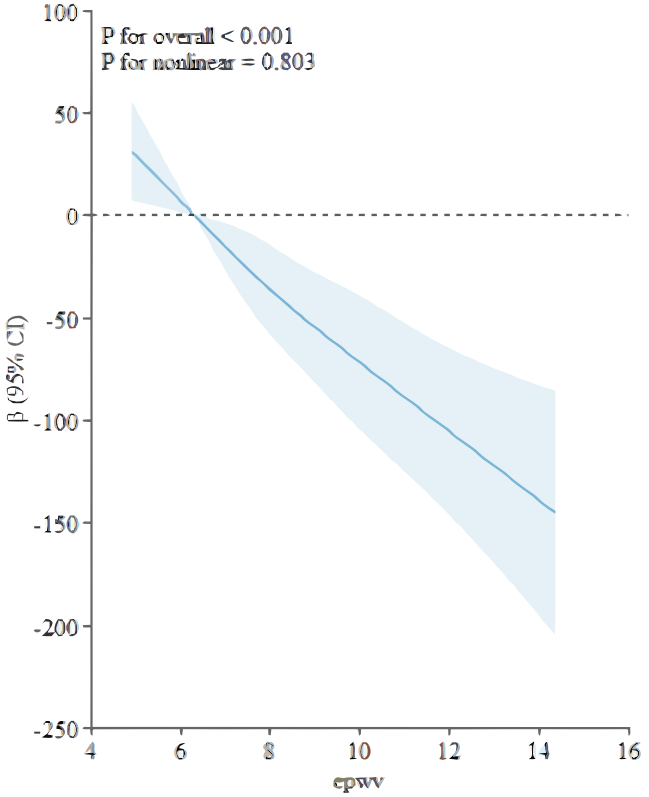

FIGURE 1 | Restricted cubic spline analysis for the correlation between the estimated pulse wave velocity and serum Klotho level after adjusting for all enrolled confounding factors.

3.2 | The Correlation and Interaction Effects of ePWV and Serum Klotho on the Risk of CKD

Although both increased ePWV and decreased serum Klotho were significantly associated with an elevated risk of CKD, only the association between ePWV and CKD remained significant in Model 3 (Table 2). A significant interaction effect between ePWV and serum Klotho was observed on the risk of CKD among all three models ($p < 0.001$). Interestingly, according to the fully adjusted model with mutual adjustment, both the ePWV ($p < 0.001$) and the serum Klotho level ($p = 0.029$) were significantly associated with CKD.

The results of RCS analysis demonstrated a linear association between ePWV and the prevalence of CKD (Figure S2A) and a nonlinear association between the serum Klotho level and the prevalence of CKD (Figure S2B).

3.3 | The Combination of ePWV and Serum Klotho for the Prediction of CKD Risk

Compared with individuals with a lower ePWV and a higher serum Klotho, individuals with an increased ePWV and a decreased serum Klotho had a significantly greater risk of CKD according to all three models, including the fully adjusted model (Table 3, model 1, OR = 3.715, 95% CI: 3.179–4.342, $p < 0.001$; model 2, OR = 2.169, 95% CI: 1.770–2.659, $p < 0.001$; model 3: OR = 1.847, 95% CI: 1.467–2.325, $p < 0.001$).

TABLE 2 | Logistic regression models of the associations between ePWV and the level of serum Klotho and the risk of CKD (from the NHANES database of the population surveyed from 2007 to 2016).

		Model 1			Model 2			Model 3			Model 4	
		OR (95% CI)	*p*	*p* for interaction	OR (95% CI)	*p*	*p* for interaction	OR (95% CI)	*p*	*p* for interaction	OR (95% CI)	*p*
ePWV	Low	Ref		< 0.001	Ref		< 0.001	Ref		< 0.001		
	High	3.030 (2.733–3.359)	< 0.001		2.355 (1.948–2.846)	< 0.001		1.612 (1.327–1.959)	< 0.001		2.029 (1.634–2.520)	< 0.001
Klotho	Low	Ref			Ref			Ref				
	High	0.789 (0.699–0.890)	< 0.001		1.085 (0.919–1.281)	0.328		0.848 (0.746–0.964)	0.013		1.099 (0.925–1.305)	0.277

Note: Model 1 was a crude model without adjusting for confounding factors. Model 2 was adjusted for sex, age, and BMI. Model 3 was adjusted for the variables of Model 2 plus race, mean arterial pressure, education level, the ratio of family income to poverty, marital status, smoking status, drinking state, diabetes state, hypertension state, triglycerides, total serum cholesterol, hemoglobin, and HDL. Model 4 is a mutually adjusted model based on Model 3. The levels of ePWV and klotho are classified as "high" or "low" on the basis of the median value of each variable.
Abbreviations: CI, confidence interval; CKD, chronic kidney disease; ePWV, estimated pulse wave velocity; OR, odds ratio.

TABLE 3 | Logistic regression models of the associations between the combination of ePWV and the level of serum Klotho and the risk of CKD (from the NHANES database of the population surveyed from 2007 to 2016).

	Model 1		Model 2		Model 3	
	OR (95% Cl)	*p*	OR (95% Cl)	*p*	OR (95% Cl)	*p*
High-Klotho, low-ePWV	Ref		Ref		Ref	
Low-Klotho, low-ePWV	1.027 (0.870–1.212)	0.750	0.921 (0.781–1.088)	0.328	0.910 (0.766–1.081)	0.277
High-Klotho, high-ePWV	2.480 (2.151–2.859)	<0.001	1.496 (1.230–1.819)	<0.001	1.251 (1.000–1.564)	0.050
Low-Klotho, high-ePWV	3.715 (3.179–4.342)	<0.001	2.169 (1.770–2.659)	<0.001	1.847 (1.467–2.325)	<0.001

Note: Model 1 was a crude model without adjusting for confounding factors. Model 2 was adjusted for sex, age, and BMI. Model 3 was adjusted for the variables of Model 2 plus race, mean arterial pressure, education level, the ratio of family income to poverty, marital status, smoking status, drinking state, diabetes state, hypertension state, triglycerides, total serum cholesterol, hemoglobin, and HDL. The levels of ePWV and klotho are classified as "high" or "low" on the basis of the median value of each variable.
Abbreviations: CI, confidence interval; CKD, chronic kidney disease; ePWV, estimated pulse wave velocity; OR, odds ratio.

3.4 | Secondary Analyses

In the subgroup analysis, the continuous variables were classified as high or low according to the median of each variable when used as stratification variables. The associations between increased ePWV and decreased serum Klotho and the risk of CKD remained robust in most subgroups in the stratified analyses, except for subgroups with different races, diabetes status, marital status, mean arterial pressure and poverty status (Table S2).

4 | Discussion

According to the results of the present nationwide cross-sectional study of 13,273 individuals from the NHANES database from 2007 to 2016, there was a significant interaction effect between ePWV and serum Klotho on the risk of CKD. An increased ePWV and decreased serum Klotho were associated with a greater risk of CKD.

In our study, all confounding factors, including age, BMI, race, triglyceride, serum creatinine, total serum cholesterol, hemoglobin, HDL, urine albumin, urine creatinine, glycohemoglobin, ACR, smoking status, drinking status, the ratio of family income to poverty, education level, diabetes status, and hypertension status, were different among patients with different ePWV and individuals with or without CKD. After adjusting for these confounders, increased ePWV was still significantly associated with a greater risk of CKD. Similar to cfPWV, elevated ePWV is also associated with arterial stiffness [26]. Reports suggest that elevated ePWV can predict major cardiovascular events independently of systematic coronary risk evaluation, the Framingham risk score and cfPWV, indicating the unique predictive value of ePWV for cardiovascular diseases [9]. Elevated ePWV is also associated with a greater risk of in-hospital and 1 year mortality in CKD patients [27]. Owing to the need for an extended examination time, well-trained personnel, and an expensive apparatus, the cfPWV may not be available under all circumstances, where the ePWV can be regarded as a suitable substitute [26]. Owing to the need for a high flow rate of blood, the vascular resistance of the kidney is relatively low, increasing the vulnerability of the kidney to the pulsatile aspects of blood flow and blood pressure [7]. In detail, the pressure from pulse wave can penetrate deeply into the microvasculature of the kidney [28], leading to the loss of renal function and proteinuria caused by damage to the glomerulus [29]. A prospective study reported that increased BP is involved in initiating renal damage and progressive loss of renal function [30]. Moreover, independent of brachial BP, arterial stiffness may lead to incident heart failure in nondialyzed CKD patients [31] and lead to adverse cardiovascular outcomes and even death in patients with end-stage renal disease [32]. Unfortunately, no evidence has been established for the association between ePWV and the risk of CKD. According to the results of our study, attention should be given to the risk of CKD in individuals with increased ePWV. Considering the convenience and accessibility of ePWV assessment, it can be considered a daily routine monitor for CKD and cardiovascular events. Moreover, the increase in ePWV is more pronounced in the elderly population, making it particularly important to assess and monitor ePWV in older individuals.

As a single-pass transmembrane protein, serum Klotho is expressed primarily in the kidney. Serum Klotho deficiency is a common feature of both CKD and aging [33, 34]. Klotho, which has been recognized as a gene involved in the aging process in mammals for more than 30 years, is strongly correlated with aging. Klotho exerts its antiaging effects through various mechanisms, including the suppression of the insulin/IGF-1 signaling pathway, the inhibition of Wnt signaling, and the reduction of oxidative stress. These pathways are closely associated with the cellular aging process. Additionally, Klotho plays a role in maintaining calcium and phosphate homeostasis, which are vital for cellular and systemic aging [35]. Klotho-deficient mice present cardiovascular pathologies, notably cardiac fibrosis, cardiac hypertrophy, and vascular calcification [11, 36–38]. Amelioration of cardiovascular damage is observed after restoration of renal klotho expression and the level of serum soluble Klotho in Klotho-deficient animal models [12, 37–39]. In clinical studies, serum Klotho downregulation represents more than just an early indicator of renal damage. Serum Klotho downregulation is also a key complication of CKD and could exert a pathogenic influence on the progression of CKD [38]. As a therapeutic agent, recombinant Klotho can reduce vascular calcification and fibrosis in CKD, thereby preventing the progression of cardiovascular disease [40]. Moreover, a study indicated

that restoring Klotho levels or function could be beneficial in slowing the aging process in CKD patients [41]. Similar to other studies [17], we also reported that the serum level of Klotho was negatively associated with the risk of CKD. Notably, after we adjusted for all the included confounders, we detected a significant negative linear association between ePWV and serum Klotho. Currently, no studies have explored the relationship between Klotho and ePWV. Klotho, a circulating protein primarily secreted by the kidneys, is intrinsically linked to kidney function [42], and the association between arterial stiffness and CKD is inseparable. Our research revealed a linear relationship between Klotho and ePWV, which may be partially explained by the associations among Klotho, ePWV, and CKD. Future studies are needed to investigate and clarify the direct relationship and underlying mechanisms between Klotho and arterial stiffness.

In our study, we identified a significant interaction effect between ePWV and serum Klotho levels in modulating the risk of CKD. Notably, individuals presenting with both an elevated ePWV and reduced serum Klotho levels were found to be at the highest risk for CKD, a relationship that has not been previously documented in the literature. Previous studies have separately demonstrated the predictive capacity of PWV for CKD progression and composite outcomes [43], as well as the role of Klotho in CKD pathophysiology [44]. However, the combined impact of these factors on CKD remains unexplored. Our study firstly revealed that ePWV was also associated with a high risk of CKD. Moreover, our findings underscore a novel and critical interaction between vascular stiffness and the protective factor Klotho in the pathogenesis of CKD, suggesting that the interplay between these biomarkers may be pivotal in predicting disease onset and progression. Moreover, in the subgroup analysis, the combination of the ePWV and the serum Klotho level still had significant predictive value for the risk of CKD. These results emphasize the value of serum Klotho for accurate prediction of CKD in individuals with arterial stiffness. In addition, populations with increased ePWV and decreased serum Klotho levels, such as male individuals and older individuals, presented a greater risk of CKD in some subgroups. Notably, diabetes and hypertension are well-known risk factors for the development and progression of CKD, whereas our study revealed that increased ePWV and decreased serum Klotho were significantly associated with a greater risk of CKD in individuals without diabetes or hypertension. These results further emphasize the necessity of assessing the combination of ePWV and serum Klotho in individuals who are traditionally considered to have a low CKD risk. Future research should focus on exploring these subgroups to better understand the detailed associations and risks within each subgroup.

4.1 | Limitations

Some limitations of our study should be noted. First, some confounding factors, such as the level of serum fibroblast growth factor, which is reported to influence the level of serum Klotho, were not assessed because of the lack of relevant results. In addition, the lack of a history of drug use for the treatment of CKD may bias the ascertainment of CKD. Second, we excluded many individuals because of the lack of data for the assessment of ePWV, serum Klotho and CKD prevalence, which could introduce potential bias. Third, owing to the inherent limitations of the cross-sectional design, the causal relationships between ePWV or serum Klotho and CKD could not be assessed, and these associations should be further assessed on the basis of longitudinal evidence. Although the representation of the entire population in the USA and the utilization of weighted analysis guarantees a high level of external validity, the interpretation of the results should consider ethnic and regional differences and age groups (in addition to 40–79 years old). Moreover, since ePWV is calculated on the basis of blood pressure and age rather than via direct measurement, there is potential for bias when it is used to assess arterial stiffness. Unlike cfPWV or baPWV, which are directly measured, ePWV may not fully and accurately assess arterial stiffness. We hope that the NHANES study can introduce more precise indicators in the future.

5 | Conclusion

Our study demonstrated significant interaction effect of ePWV and serum Klotho on the prevalence of CKD. Individuals with increased ePWV and decreased serum Klotho levels had the highest risk of CKD. The assessment of the combination of ePWV and serum Klotho should be considered routine in clinical practice.

Author Contributions

P.Z. and J.L. collected and analyzed the data, conducted the analysis and drafted the manuscript; Y.Z. reviewed and edited the manuscript; L.C. assisted in conceptualization, methodology, and validation; J.L., M.L. and N.H. collected the data; L.Z., H.G. and C.Z. conceived the study and reviewed the manuscript. All the authors mentioned above made substantial contributions to the content of the paper and approved the final version of the manuscript. All the authors have read and approved the final version of the manuscript and agree with the order of presentation of the authors.

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Ethics Statement

The authors have nothing to report.

Consent

The authors have nothing to report.

Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

The datasets generated during and/or analyzed during the current study are available on the website of the NHANES datasets 2007–2016 repository, https://wwwn.cdc.gov/nchs/nhanes.

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Supporting Information

Additional supporting information can be found online in the Supporting Information section.