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Association of uric acid to high-density lipoprotein cholesterol ratio with the presence or absence of hypertensive kidney function: results from the China Health and Retirement Longitudinal Study (CHARLS)

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Abstract

Objective Some studies have shown that uric acid (UA) to high-density lipoprotein (HDL-C) ratio (UHR), as an indicator of inflammation, is associated with metabolic syndrome and hypertension, but its relationship with decreased renal function is unclear. This study intends to analyze the relationship between UHR and decline in renal function.

Methods Data were obtained from the 2011–2015 data of the China Health and Aging Tracking Survey (CHARLS) of Peking University, and 7,198 study participants were included and followed up until 2015. The eGFR (Total glomerular filtration rate) was estimated according to the CKD-EPI [1] creatinine equation. eGFR ≥ 60mL/min/1.73 m^2 at baseline renal function was defined as normal renal function, and eGFR < 60mL/min/1.73 m^2 at baseline renal function was defined as chronic kidney disease; new-onset eGFR < 60mL/min/1.73 m^2 was defined as the occurrence of decline in renal function; in the chronic kidney disease population decrease in eGFR ≥ 5mL/min/1.73 m^2/year or 30% from baseline or admission to dialysis was defined as rapid progression of chronic kidney disease. eGFR slope was defined as the ratio of the difference between the final eGFR and the baseline eGFR over 4 years of follow-up. Binary logistic regression was used to analyze the relationship between UHR and renal function decline or progression, as well as linear regression and non-linear regression to clarify the relationship between UHR and GFR slope in hypertensive patients, and the correlation between UHR and CRP, and to assess the relationship between UHR levels and the risk of renal function decline in hypertensive people.

Results (1) Hypertension was a risk factor for the decline of renal function (OR: 1.34, $P = 0.03$); (2) UHR was a risk factor for the decline of renal function in the hypertensive population (OR: 1.32, $P = 0.02$), and with the increasing level of UHR, the risk of developing CKD (Chronic Kidney Disease) in hypertension was higher (P for trend = 0.03); (3) The subgroup analyses showed that there was no interaction between hypertension and age, cystatin C and hemoglobin

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did not interact with each other; (4), In the hypertensive population, the slope of UHR and eGFR showed a J-shaped correlation, with UHR > 7.6% as the cut-off point, and the slope of eGFR tended to increase with increasing UHR; in the non-hypertensive population UHR and eGFR showed a linear correlation, and the slope of the decline in eGFR was smaller than that of the hypertensive population; (5), After adjusting for confounders, UHR and CRP were positive correlation ($t = 3.56$, $P < 0.05$); (6) In the hypertensive population with normal CRP, the risk of decline in renal function increased accordingly with increasing UHR ($P = 0.003$). UHR did not show a correlation with CRP in the hypertensive population with abnormal CRP ($P = 0.24$).

Conclusion In the hypertensive population, elevated UHR is associated with an increased risk of decline in renal function; with UHR > 7.6% as the cut-off point, the slope of eGFR tended to increase with increasing UHR, and UHR can be used as an indicator for risk stratification of renal injury in the hypertensive population.

Keywords Chronic kidney disease (CKD), Hypertension, Uric acid to high-density lipoprotein ratio (UHR)

Presentation

Chronic kidney disease (CKD) is defined as decreased renal function (estimated glomerular filtration rate (eGFR) < 60mL/min/1.73 m^2 [2]) and or renal impairment lasting ≥ 3 months [3]. Chronic kidney disease (CKD) is a chronic, non-communicable disease worldwide that imposes a heavy socio-economic burden, and the Global Burden of Disease Study 2013 estimated that age-standardized mortality rates for CKD increased by 36.9% globally between 1990 and 2013, while mortality rates for CKD caused by hypertension increased by 29.4% [4]; Therefore, early identification of risk factors for declining renal function is critical.

The kidneys are protective against systemic inflammation, but they are highly susceptible to damage from pro-inflammatory cytokines and oxidative stress, as demonstrated in CKD and many other renal pathologies [5]. Risk factors for decreased renal function include traditional risk factors such as a long history of hypertension, diabetes, dyslipidemia, and smoking; and non-traditional risk factors such as vascular calcification and inflammation. Inflammation is important role in chronic diseases, regardless of traditional or non-traditional risk factors. Pro-inflammatory processes in the decline of renal function include a variety of infections, periodontal disease, oxidative stress due to accumulation of advanced glycosylation end products, metabolic acidosis, reduced cytokine clearance, insulin resistance, post-translational modification of blood-borne molecules (e.g., lipoproteins), and epigenetic factors [6]. Regulation of hormones and vasoactive molecules prevents damage caused by the physiological hypoxic environment within the renal medulla, which is destroyed during inflammation. In addition, chronic inflammation predisposes to intrarenal changes in the microvascular system that can lead to kidney injury [7]. Secondly, the renal tubules are the seat of many inflammatory cytokines, chemokines, and fibrosis mediators that are key to coping with renal injury. These markers are highly regulated; however, dysregulation can lead to maladaptive responses and repair as well as progression to CKD. Dysregulation can be caused by recurrent injuries such as diabetes mellitus, incomplete recovery from Acute Kidney Injury (AKI) and susceptibility to ischemia in the presence of inflammation and other mismatches in energy supply and demand [8]. There is no lack of inflammatory factors involved in the inflammatory process, including interleukin (IL)-1, IL-6 and tumor necrosis factor (TNF), NK-κB, interferon-γ (IFN-γ) and macrophage migration inhibitory factor (MIF).

From 2019 to date, UHR has emerged in the public eye as a brand new member of the inflammatory factors, proven to increase under inflammatory conditions [9], UHR is defined as the ratio of UA to HDL-C, and the most recent evidence in the medical literature suggests that UHR acts as a marker for chronic, low-grade inflammation in chronic diseases such as hypertension [10], fatty liver disease [11], and coronary artery disease [12] with chronic renal failure [13] as chronic, low-grade markers of inflammation. The diagnostic utility of UHR has been demonstrated, for example, in metabolic syndrome [14]. In hypertension, it has been shown that poor control of hypertension is associated with an elevated UHR [15]. In women of childbearing age, UHR was found to be positively associated with hypertension (OR > 1, $P < 0.001$) [16]. UHR in CKD, a study in China in 2022 explored for the first time the association between UHR on the reduction of eGFR and the risk of CKD in the general population, and found that the high value of UHR was positively associated with the risk of CKD in the normal population [13]. However, the relationship between UHR and the decline of renal function in hypertension is not yet known, and we would like to explore the relationship between UHR and the decline of renal function in hypertension through the China Health and Retirement Longitudinal Study (CHARLS) (Fig. 1 is a scatterplot of the distribution of eGFR versus UHR in hypertensive and non-hypertensive populations).

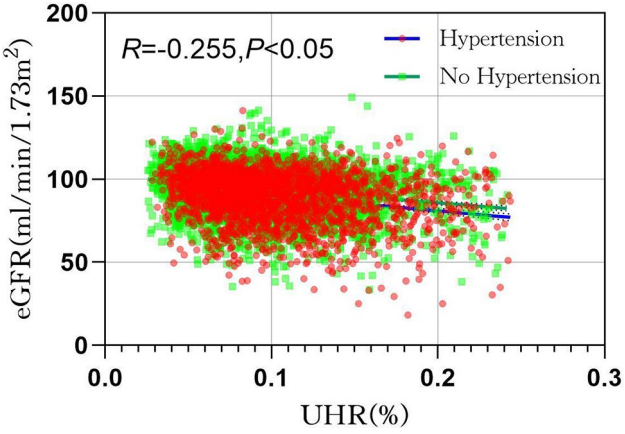

Fig. 1 Scatter plot of eGFR and UHR distribution in hypertensive and non-hypertensive populations

Patients and methods

Study design and population

The subjects of this study are from the China Health and Retirement Longitudinal Study (CHARLS), a longitudinal survey representative of China, which provides a high-quality public micro-database of social, economic, and health assessments of people aged 45 years or older through the collection of data and blood samples from professionals, and whose respondents are followed up every two years, with two follow-up cycles. Blood samples were collected. Baseline data were from 2011, and results were recorded in 2015. A total of 17,707 people were enrolled in this part of the study, removing a total of 10,223 people with no age, sex, no UHR ratio in one of the years, and no eGFR value could be calculated, 18 people with no information on hypertension and 191 people with outliers in the < 1% and > 99% quartiles of the baseline UHR, and 77 people with no information on diabetes, for a total of 7,198 people enrolled in this part of the study. Figure 2 shows the technology roadmap.

Sample collection

Blood samples were taken by a professional with an 8 ml fasting blood sample. Tests were performed within 1–2 h of sample collection, whole blood cell tests were analyzed by the local county CDC or town/rural health center that had undergone quality control, the rest of the blood specimens were stored and transported at 4 °C for subsequent hemoglobin testing, and the rest of the samples were transported at -20 °C and transported to the Chinese CDC in Beijing within 2 weeks, and stored at -80 °C until the CMU laboratory Perform analyses. Glycated hemoglobin was measured by borate affinity HPLC, blood glucose, total cholesterol, high-density lipoprotein, low-density lipoprotein and triglycerides by enzymatic colorimetric assay, urea nitrogen by urease enzyme-enhanced ultraviolet assay, uric acid by the UA Plus method, and cystatin C by particle-enhanced turbidimetry.

Clinical definition

In this study, the CKD-EPI creatinine equation was used to calculate female eGFR = 141/144 × min(SCr/κ)^(α) × (0.993)^(age), where 144 is for females and 141 is for males, SCr is serum creatinine, κ is 0.7 for females and 0.9 for males, α is -0.329 for females when SCr ≤ 0.7 mg/dL and −1.209 when SCr > -1.209 when SCr > 0.7 mg/dL; α was −0.411 for males with SCr ≤ 0.9 mg/dL and

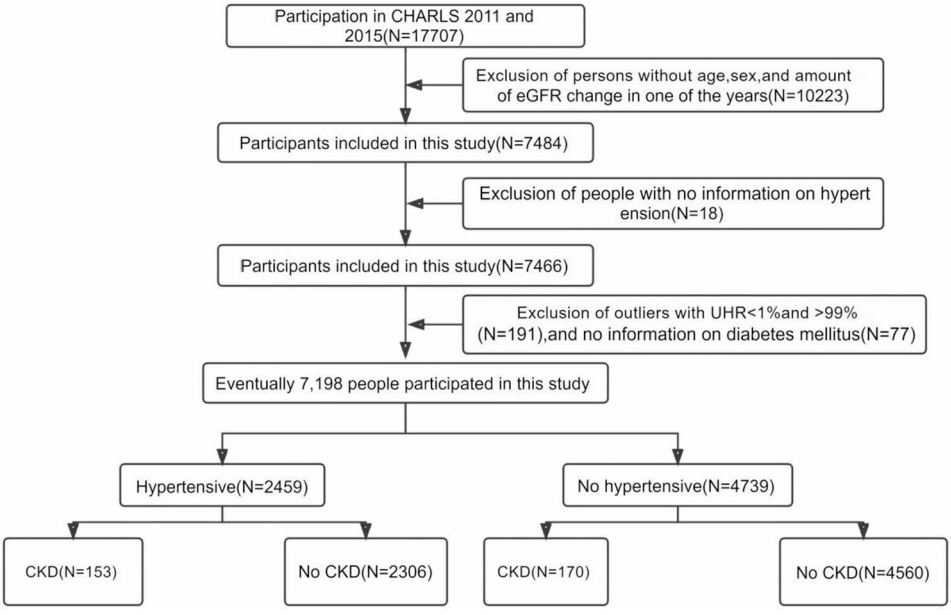

Fig. 2 Technology roadmap

– 1.209 for males when SCr > 0.9 mg/dL [1]. eGFR categories were defined as G1 ≥ 90, 60 ≤ G2 < 90, 30 ≤ G3 < 60, 15 ≤ G4 < 30, and G5 < 15. We defined the baseline renal function eGFR ≥ 60 mL/min/1.73 m^2 defined as normal renal function, and baseline renal function eGFR < 60 mL/min/1.73 m^2 defined as abnormal renal function, and compared with baseline renal function, a decrease in renal function in those with normal renal function at baseline was defined as eGFR < 60 mL/min/1.73 m^2, and a decrease in renal function in those with abnormal renal function was defined as Decrease in eGFR ≥ 5 mL/min/1.73 m^2/year or 30% from baseline.

Hypertension was defined as a mean systolic blood pressure (SBP) ≥ 140 mmHg and mean diastolic blood pressure (DBP) ≥ 90 mmHg measured three times on the left arm at 30 min' rest in a seated position or a self-reported history of hypertension and previous use of antihypertensive medication. Heart disease was defined as being informed by a physician of the presence of previous myocardial infarction, coronary heart disease, angina pectoris, congestive heart failure, and other heart conditions; stroke was defined as being diagnosed by a physician with their disease.

Dyslipidemia was defined as having been told by a doctor to have elevated cholesterol and triglycerides and lowered HDL cholesterol.

UHR was calculated as the ratio of SUA (mg/dL) to HDL-C (mg/dL). UHR was classified into four classes according to quartiles (U_1: UHR ≤ 6.45%; U_2: 6.45–8.54%; U_3: 8.54–11.51%; U_4: ≥ 11.51%).

Assessment of covariates

Medical history (diabetes or hyperglycemia, stroke and heart disease) and lifestyle information (alcohol consumption and smoking) were collected from all participants during face-to-face interviews with trained interviewers. Diabetes mellitus was defined as fasting blood glucose > 125 mg/dl, glycated hemoglobin > 6.5% and a previous diagnosis of diabetes mellitus, dyslipidemia, tumors, chronic lung disease, liver disease, arthritis or rheumatism, gastric disease, emotional and psychological abnormality, and asthma were defined as having been informed by a doctor about their medical history. Alcohol consumption was defined as more than one drink per month [17]. Smoking was defined as past and present history of smoking.

Statistical methods

We used SPSS 25.0 and R4.3.2 for statistical analyses and GraphPad Prism for plotting. Continuous variables were applied according to whether they were normally distributed as mean (standard deviation, SD) or median (interquartile range, IQR), while categorical variables showed frequencies and percentages. All participants were categorized according to their UHR quartiles and parametric tests were performed using the Kruskal-Wallis test, chi-square test, etc. as appropriate. Univariate and multivariate logistic regression analyses were used to estimate the relationship between levels of UHR for progression to CKD or progression of renal function in hypertensive patients. Model 1 was a crude analysis that did not adjust for confounders and clarified the association between hypertension and each quartile of UHR between new-onset CKD or CKD progression. Model 2 was adjusted for the most common confounding biases, namely age and sex. In addition, the full model was calculated based on further adjustments for the corresponding confounders (Model 3). The median was substituted as the level of UHR at each level, and the trend of the incremental UHR index was estimated, and the p-value was substituted as the trend. COX proportional risk regression was used to compare the cumulative risk between the CRP and UHR groups; R4.3.2 and SPSS25.0 were used for the statistical analyses. $P < 0.05$ was considered to be of statistically significant (two-sided).

Results

Participant characteristics

A total of 7198 CHARLS participants took part in this study. Baseline characteristics of all adults in this study (e.g., Table 1). Based on quartiles of UHR index values (U_1 to U_4), the prevalence of participants with renal insufficiency U_1, U_2, U_3, and U_4 in 2011 was: 0.73%, 1.76%, 2.22%, and 5.17%; and the prevalence of participants with renal insufficiency after 4 years of follow-up was: 3.59%, 4.84%, 5.39%, and 10.3%. We found that there was an increase of 2.9%, 3.0%, 3.2% and 5.1% in the 3 groups of UHR in the 2015 renal insufficiency cohort compared to the 2011 renal insufficiency cohort (e.g. Table 1). It can be seen that: the prevalence of CKD increased with increasing UHR levels. Meanwhile, combining with the baseline table of the population in 2011, it was found that: (1) In the male population, the proportion of UHR gradually increased with the increase of UHR level; (2) In metabolism-related factors such as hypertension, dyslipidemia, diabetes mellitus and hyperglycemia history, stroke, smoking and alcohol consumption, all of them showed a greater proportion with the increase of UHR, which is consistent with the results of previous studies.

Baseline characteristics of participants with and without hypertension are shown in Table 2. A total of 323 participants had new-onset renal insufficiency, with 153 subjects with hypertension developing renal insufficiency during follow-up and 170 subjects without hypertension developing renal insufficiency during follow-up.

From Table 3; Fig. 3, it can be seen that hypertension is a risk factor for the progression of renal function to CKD (OR: 1.34, $P = 0.03$), in addition to this,

Table 1 Baseline characteristics of participants by UHR Index

	U_1	U_2	U_3	U_4	*P* value
	N **= 1782**	***N*** **= 1819**	***N*** **= 1798**	***N*** **= 1799**	
Sex(male)	27.3%	40.2%	51.2%	62.0%	< 0.05
Hypertension	25.1%	30.8%	35.9%	44.8%	< 0.05
Dyslipidemia	5.7%	8.5%	10.3%	15.3%	< 0.05
Diabetes or High Blood Sugar	12.0%	13.3%	17.5%	23.7%	< 0.05
Chronic Lung diseases	9.5%	11.2%	10.1%	10.2%	0.39
Stroke	1.5%	1.9%	2.0%	2.9%	0.02
Heart disease	11.1%	11.8%	11.4%	14.8%	<0.05
Psychiatric Problems	1.8%	1.2%	1.3%	0.9%	0.16
Stomach or other Digestive system	26.9%	23.9%	22.5%	18.9%	<0.05
Asthma	3.5%	4.0%	3.2%	3.5%	0.63
Arthritis or Rheumatism	37.1%	35.0%	34.5%	33.0%	0.08
Drinking wine	22.3%	24.0%	24.5%	28.3%	<0.05
Smoking history	25.9%	35.3%	42.2%	49.2%	<0.05
Blood Urea Nitrogen (BUN) (mg/dl)	14.8 (12.3;17.8)	14.9 (12.4;18.2)	14.9 (12.5;17.8)	15.6 (13.2;18.7)	< 0.05
Creatinine (mg/dl)	0.68 (0.60;0.76)	0.72 (0.64;0.82)	0.78 (0.68;0.88)	0.85 (0.72;0.96)	< 0.05
Triglycerides (mg/dl)	80.5 (62.0;109.0)	95.6 (69.9;129.0)	114 (83.2;161.1)	154 (106.2;230.1)	< 0.05
Hdl Cholesterol (mg/dl)	63.4 (55.7;73.7)	53.4 (47.2;60.7)	45.6 (40.2;52.2)	37.1 (32.1;42.7)	<0.05
C-Reactive Protein (CRP) (mg/l)	0.68 (0.41;1.33)	0.92 (0.50;1.89)	1.09 (0.59;2.18)	1.45 (0.76;2.86)	< 0.05
Uric Acid (mg/dl)	3.30 (2.84;3.80)	3.97 (3.52;4.51)	4.50 (3.97;5.11)	5.38 (4.72;6.15)	< 0.05
Hemoglobin (g/dl)	13.8 (12.7;15.0)	14.1 (13.0;15.2)	14.4 (13.1;15.7)	14.8 (13.5;16.1)	< 0.05
Cystatin C (mg/l)	0.92 (0.82;1.04)	0.96 (0.84;1.10)	0.99 (0.87;1.13)	1.01 (0.89;1.18)	< 0.05
Age	58.0 (51.0;64.0)	58.0 (51.0;64.0)	58.0 (52.0;65.0)	59.0 (53.0;65.0)	< 0.05
Renal insufficiency2011	0.73%	1.76%	2.22%	5.17%	< 0.05
Renal insufficiency2015	3.59%	4.84%	5.39%	10.3%	< 0.05

U1:<6.45%, U2: 6.45%~8.54%; U38.54%~11.51%; U4: ≥11.51%

Pearson χ^2 test or Kruskal-Wallis test or multigroup ANOVA. Values are expressed as n (%), median (25th-75th percentile), mean ± SD

age, hemoglobin, blood creatinine and cystatin C are all risk factors for the development of CKD, with ORs of 1.05 (95%CI 1.04–1.07), 0.85 (95%CI 0.79–0.90), 3.89 (95%CI 1.75–8.62), and 1.85 (95%CI 1.12–3.07), with *P* less than 0.05.Subgroup analyses were performed for the potential risk factors for CKD. There was no statistically significant interaction between age and hypertension ($P = 0.84$,Fig. 4),and no statistically significant interaction between cystatin C and hypertension ($P = 0.40$, Fig. 5) as well as no interaction between hemoglobin and hypertension ($P = 0.23$, Fig. 6).

After adjusting for confounders such as age, sex, history of diabetes and hyperglycemia, dyslipidemia, emotional and psychological disorders, uric acid, cystatin C and hemoglobin, the risk of CKD in hypertensive patients with different levels of UHR was OR: 1.32 (95% CI 1.05–1.66, $P = 0.02$); as shown in Fig. 7A, the risk of CKD in hypertensive population increased with the rise of UHR; while there was no statistically significant relationship between different levels of UHR in non-hypertensive population and their progression to CKD ($P = 0.40$), as shown in Fig. 7B. CKD risk in the hypertensive population; while there was no statistically significant relationship between different levels of UHR and its progression to CKD in the non-hypertensive population ($P = 0.40$), as shown in Fig. 7B, the risk of progression to CKD with subsequent UHR also tended to increase in the non-hypertensive population, but it was not statistically significant. Combined with Tables 4 and 5, the relative risk of different levels of UHR in hypertensive versus non-hypertensive populations can be found.

UHR was found to increase the risk of progression to CKD in the hypertensive population in Table 6 model 1, while the OR for progression of renal function to renal insufficiency in hypertensive patients was found to be incremental at the level of UHR according to the fully corrected model (Table 5, model 3, *P* for trend = 0.033). The OR for new-onset CKD for U_2, U_3, and U_4, using U_1 as the reference, was 1.29 (95% CI 0.64–2.57), 1.99 (95% CI 1.04–3.79) and 1.95 (95% CI 1.01–3.74), respectively. Similarly, the relative risk of progression to CKD in the non-hypertensive population increased with increasing UHR, but it was not significantly trended (*P* for trend = 0.292).

Study II

We also analyzed the relationship between UHR and its slope in patients with and without hypertension, and we obtained Fig. 8, where it can be seen that the slope of GFR is greater in patients with hypertension compared to the

Table 2 Baseline graph of renal function with and without progression to CKD

	Not progressed to CKD	Progression to CKD	*P* value
	N = 6875	*N* = 323	
Sex(male)	45.1%	47.1%	0.50
Dyslipidemia	9.8%	13.2%	< 0.05
Diabetes or High Blood Sugar	16.4%	21.4%	0.02
Chronic Lung diseases	10.1%	12.7%	0.13
Hypertension	33.5%	47.4%	< 0.05
Liver diseases	3.9%	2.8%	0.33
Heart diseases	12.2%	14.3%	0.25
Stomach or other Digestive system	23.0%	24.5%	0.51
Stroke	2.0%	4.0%	< 0.05
Asthma	3.5%	5.3%	0.09
Arthritis or Rheumatism	34.6%	39.9%	0.051
Smoking history	38.0%	41.0%	0.29
Drinking wine	24.8%	24.1%	0.79
Psychiatric Problems	1.3%	1.2%	<0.05
Blood Urea Nitrogen (BUN) (mg/dl)	15.01 (12.52;18.07)	15.91 (13.44;19.35)	< 0.05
Creatinine (mg/dl)	0.75 (0.64;0.86)	0.87 (0.75;1.02)	< 0.05
Triglycerides (mg/dl)	105.32 (75.22;153.10)	114.17(80.54;163.73)	0.04
Hdl Cholesterol (mg/dl)	49.10 (40.59;59.92)	47.55(37.50;59.92)	0.03
C-Reactive Protein (CRP) (mg/l)	0.99 (0.53;2.07)	1.11 (0.70;2.74)	< 0.05
Uric Acid (mg/dl)	4.22 (3.52;5.05)	4.71 (3.87;5.51)	< 0.05
Hemoglobin (g/dl)	14.30 (13.10;15.60)	13.70 (12.70;14.90)	< 0.05
Cystatin C (mg/l)	0.96 (0.85;1.10)	1.16 (0.97;1.34)	< 0.05
Age	58.00 (51.00;64.00)	65.00 (59.00;72.00)	< 0.05
UHR	0.08 (0.06;0.11)	0.10 (0.07;0.15)	< 0.05
BMI	23.16 (21.02;25.87)	23.59(20.87;25.91)	0.59

Pearson χ^2 test or Kruskal-Wallis test

slope of GFR without hypertension; in order to further explore the effect of the progression of renal function in patients with hypertension, we compared those with a decrease in GFR in patients with hypertension with those without a decrease in GFR in patients without hypertension; of these, there were 1,583 people with a decrease in GFR in hypertension and a total of 4,739 people without a decrease in GFR in hypertension. people had a total of 1,583 and those without hypertensive GFR decline had a total of 4,739. Figure 8 shows the relationship between UHR and eGFR slope in the population with and without hypertension.

After adjusting for sex, history of diabetes or hyperglycemia, chronic lung disease, mood, psychological disorders, gastric disorders, uric acid, hemoglobin, cystatin C, C-reactive protein, blood creatinine, and high-density lipoprotein in the hypertensive population, we can find that the UHR correlated with the slope of the eGFR in a J-shape, with a statistically significant nonlinear P-value at 10% (Fig. 9); whereas, in the population without hypertension with the increase of UHR its GFR slope increased (Fig. 10); by comparing the two populations, we can find that the GFR slope in the hypertensive population was significantly larger than that in the non-hypertensive patients; and in the hypertensive population the GFR slope showed a trend of decreasing and then increasing as the UHR increased the GFR slope; combining with Fig. 9, it can be concluded that in the hypertensive patients after the UHR ≥ 7.6% the eGFR slope increased significantly.

Table 3 Risk ratio according to the presence or absence of progression to CKD

	P value	OR	95%CI	
			Low	Up
Hypertension	0.03	1.34	1.03	1.76
Dyslipidemia	0.13	1.36	0.92	2.02
Diabetes or High Blood Sugar	0.87	0.97	0.69	1.37
Stroke	0.25	1.47	0.77	2.81
Blood Urea Nitrogen (BUN) (mg/dl)	0.79	1.00	1.00	1.03
Triglycerides (mg/dl)	0.67	1.00	1.00	1.00
Hdl Cholesterol (mg/dl)	0.49	1.00	0.99	1.03
C-Reactive Protein (CRP) (mg/l)	0.23	0.99	0.96	1.01
Uric Acid (mg/dl)	0.21	0.86	0.69	1.09
Hemoglobin (g/dl)	< 0.05	0.85	0.79	0.90
Cystatin C (mg/l)	0.02	1.85	1.12	3.07
Age	< 0.05	1.05	1.04	1.07
Creatinine (mg/dl)	< 0.05	3.89	1.75	8.62

Compared with the traditional inflammatory factor CRP (Fig. 11), CRP showed a positive correlation with UHR by linear regression backward stepwise method (t = 3.56, $P < 0.05$), i.e. as CRP increased, UHR increased with it, after adjusting for a history of diabetes mellitus or hypertension, chronic lung disease, emotional, psychological and other disorders, urea nitrogen, blood creatinine, triglycerides, and cystatin C (e.g., Table 7).

In order to further clarify the relationship between UHR and CRP in hypertensive population, we classified CRP into high-level (CRP > 3 mg/dl), low-level group (CRP ≤ 3 mg/dl); high-level UHR (> 11%) and low-level group UHR (UHR ≤ 11%); and according to the above, we classified the hypertensive population into four groups: i.e., Group 1: Normal level of CRP with normal level of UHR; Group 2: high level of CRP with normal level of UHR; Group 3: normal level of CRP with high level of UHR; Group 4: high level of CRP with high level of UHR; in this way, the relationship between different levels of CRP and UHR was compared and a baseline table of the population was obtained according to the four groups

Characteristic	P value	OR	OR(95%CI)
Hypertension	0.03	1.34	1.34(1.03 to 1.76)
Dyslipidemia	0.13	1.36	1.36(0.92 to 2.02)
Diabetes or High Blood Sugar	0.87	0.97	0.97(0.69 to 1.37)
Stroke	0.25	1.47	1.47(0.77 to 2.81)
Blood Urea Nitrogen (BUN) (mg/dl)	0.79	1.00	1.00(1.00 to 1.03)
Triglycerides (mg/dl)	0.67	1.00	1.00(1.00 to 1.00)
Hdl Cholesterol (mg/dl)	0.49	1.00	1.00(0.99 to 1.03)
C-Reactive Protein (CRP) (mg/l)	0.23	0.99	0.99(0.96 to 1.01)
Uric Acid (mg/dl)	0.21	0.86	0.86(0.69 to 1.09)
Hemoglobin (g/dl)	<0.05	0.85	0.85(0.79 to 0.90)
Cystatin C (mg/l)	0.02	1.85	1.85(1.12 to 3.07)
Age	<0.05	1.05	1.05(1.04 to 1.07)
Creatinine (mg/dl)	<0.05	3.89	3.89(1.75 to 8.62)

Fig. 3 Risk ratios according to the presence or absence of CKD

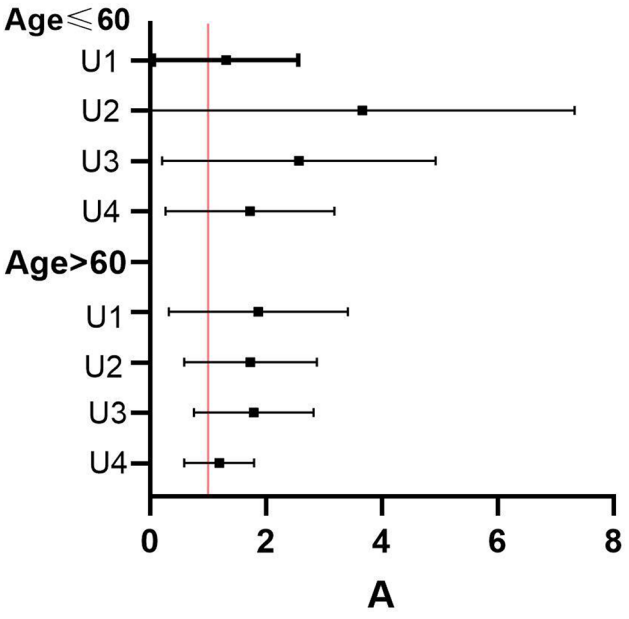

Fig. 4 Subgroup analysis of age and hypertension

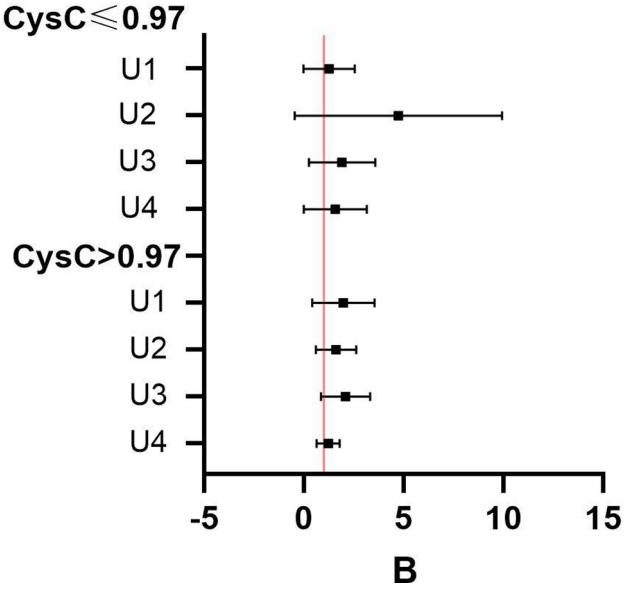

Fig. 5 Subgroups of cystatin C and hypertension

(Table 8). In the cohort study of hypertensive patients, 1314 (53.4%) had normal levels of CRP with UHR, 258 (10.5%) had high levels of CRP with normal levels of UHR, 646 (26.3%) had normal levels of CRP with high levels of UHR as well as 241 (9.8%) had not only an elevated CRP but also an elevated UHR. After 4 years of follow-up, there were 65 (42.5%), 17 (11.1%), 49 (32.0%) and 22 (14.4%) new CKDs in the 4 groups, respectively. We found that the prevalence of hypertension was higher in both high levels of CRP and high levels of UHR compared to group 1; the prevalence of hypertension was higher when the group with normal CRP and high levels of UHR was compared to the group with high levels of UHR and normal levels of UHR; and the prevalence was highest when both CRP and UHR were high (51.80%).

The risk of developing CKD was analyzed between UHR and different levels of CRP. It was found that in high levels of CRP, the risk of developing CKD in the hypertensive population was in a U-shape of decreasing and then increasing with increasing UHR, but the UHR was not statistically significant ($P = 0.24$); whereas in normal levels of CRP it showed a non-linear increase in the risk of new-onset CKD in hypertension with increasing levels of UHR ($P = 0.003$, P-non- linear: 0.004). Elevated CRP did not increase the incidence of CKD in hypertensive patients at either normal or high levels of UHR, so we can assume that UHR can be used to assess the risk of

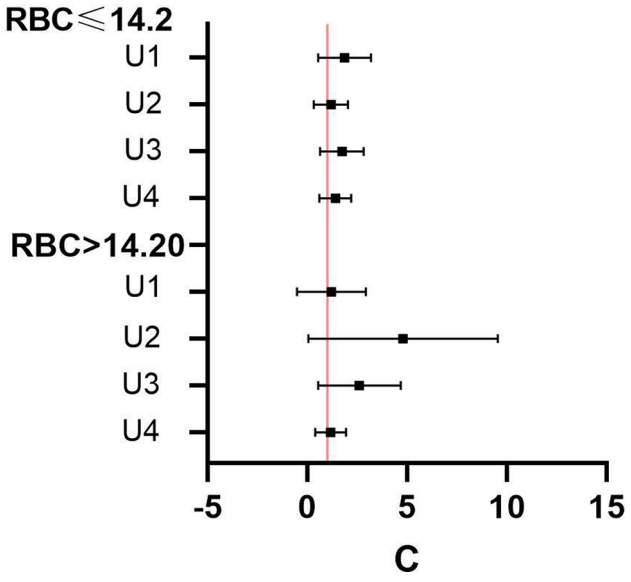

Fig. 6 Subgroup analysis of hemoglobin and hypertension

CKD in hypertensive patients when CRP is normal in the hypertensive population (Fig. 12).

Discussion

In this large cohort study of Chinese adults, we first found that the prevalence of chronic metabolism-related diseases such as hypertension, dyslipidemia, history of diabetes mellitus or hyperglycemia, stroke, cardiac disease, gastric or other digestive disorders, history of alcohol consumption, and history of smoking, all of which were similarly increased with the increase in UHR levels (all $P<0.005$), which was consistent with previous findings; among Chinese adults with hypertension, the risk of progression to CKD was J-shaped (trend $P=0.033$) with the increase in UHR. In Chinese adults with hypertension, the risk of progression to CKD was J-shaped with increasing UHR (trend $P=0.033$).

In contrast to previous studies, UHR is a new indicator of inflammation and metabolism, which has been demonstrated in a number of studies, such as a positive correlation with visceral adiposity in patients with type 2 diabetes mellitus [18], and as a marker for identifying

Table 4 Binary logistic backward stepwise method modeling in hypertensive population

	P value	OR	95%CI	
			Low	Up
UHR level	0.02	1.32	1.05	1.66
Age	< 0.05	1.05	1.03	1.08
Sex	0.46	1.17	0.77	1.77
Diabetes or High Blood Sugar	0.93	1.02	0.66	1.58
Dyslipidemia	0.15	1.46	0.91	2.33
Emotional, Nervous, or Psychiatric Problems	0.56	0.55	0.07	4.23
Uric Acid (mg/dl)	0.10	0.84	0.69	1.03
Hemoglobin (g/dl)	0.03	0.90	0.81	0.99
Cystatin C (mg/l)	< 0.05	4.21	2.19	8.12

Table 5 Binary logistic backward stepwise method modeling in non-hypertensive populations

	P value	OR	95%CI	
			Low	Up
UHR level	0.40	1.10	0.89	1.35
Sex	0.24	0.78	0.52	1.18
Age	< 0.05	1.05	1.03	1.07
Diabetes or High Blood Sugar	0.94	0.98	0.59	1.62
Dyslipidemia	0.51	1.27	0.63	2.59
Emotional, Nervous, or Psychiatric Problems	0.67	1.37	0.32	5.79
Uric Acid (mg/dl)	0.004	1.30	1.09	1.57
Hemoglobin (g/dl)	< 0.05	0.84	0.76	0.92
Cystatin C (mg/l)	0.02	1.90	1.12	3.24

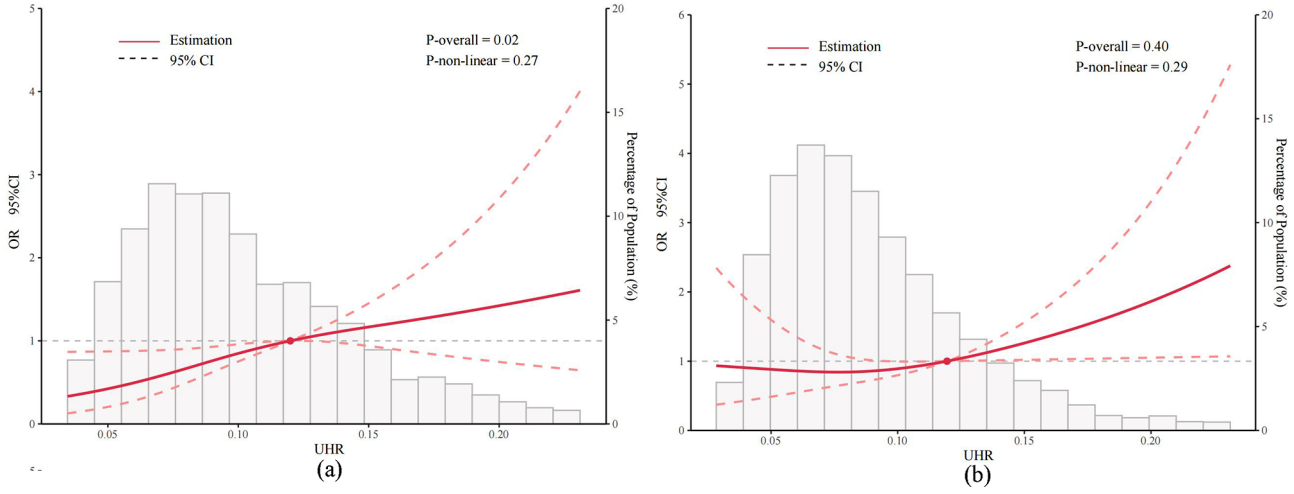

Fig. 7 **A** restricted cubic spline plot of UHR for new-onset CKD in the hypertensive population. **B** restricted cubic spline plot of UHR for new-onset CKD in the no hypertensive population

Table 6 Association between hypertension and new-onset CKD stratified by UHR index

	Quartile of UHR				
	Group 1	**Group 2**	**Group 3**	**Group 4**	***P* for trend**
Hypertensive	<6.86%	6.86%~9.08%	9.08%~12.32%	≥ 12.32%	
Model1	1.00	1.26(0.69–2.30)	1.75(1.00-3.07)	2.03(1.18–3.47)	0.004
Model2	1.00	1.16(0.63–2.14)	1.72(0.97–3.05)	1.94(1.11–3.38)	0.007
Model3	1.00	1.29 (0.64–2.57)	1.99 (1.04–3.79)	1.95 (1.01–3.74)	0.033
Non-hypertensive					
Model1	1.00	0.98(0.62–1.54)	1.04(0.66–1.65)	1.97(1.30–2.98)	< 0.05
Model2	1.00	1.01(0.64–1.61)	1.09(0.69–1.75)	2.07(1.35–3.19)	< 0.05
Model3	1.00	0.84(0.49–1.47)	0.96(0.54–1.71)	1.27(0.67–2.41)	0.292

Model 1: Unadjusted

Model 2: Adjusted for age and sex

Model 3: Based on age, sex, history of diabetes and hyperglycemia, dyslipidemia, emotional and psychological disorders, uric acid, cystatin C, and hemoglobin

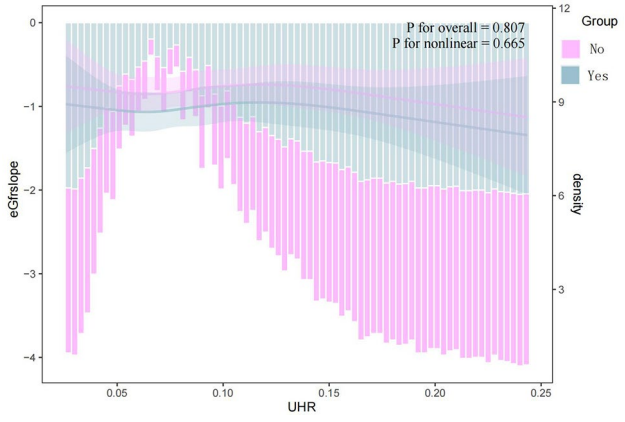

Fig. 8 Relationship between UHR and eGFR slope in patients with and without hypertension

Table 7 Relationship between CRP and UHR

	B	**Standard error**	**Beta**	**t**	***P***
UHR	16.92	4.75	0.10	3.56	<0.05
Diabetes or High Blood Sugar	1.81	0.39	0.11	4.70	<0.05
Chronic Lung diseases	1.08	0.49	0.05	2.21	0.03
Emotional, psychological and disease	-1.18	1.35	-0.02	-0.88	<0.05
Blood Urea Nitrogen (BUN) (mg/dl)	-0.11	0.04	-0.07	-2.86	<0.05
Creatinine (mg/dl)	-2.84	1.04	-0.09	-2.73	<0.05
Triglycerides (mg/dl)	-0.01	0.002	-0.08	-2.77	<0.05
Cystatin C (mg/l)	3.02	0.78	0.12	3.89	<0.05

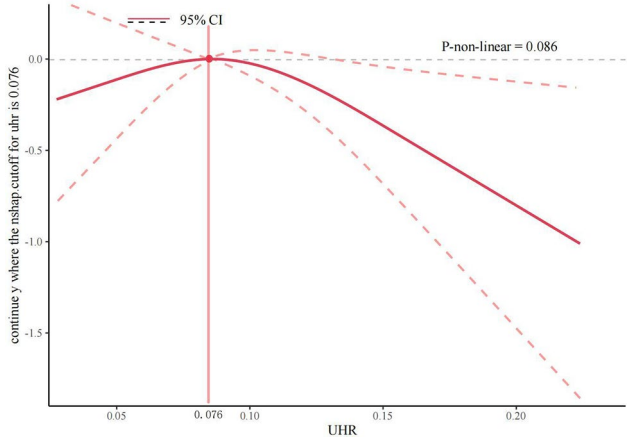

Fig. 9 Relationship between UHR and eGFR Slope in hypertensive population

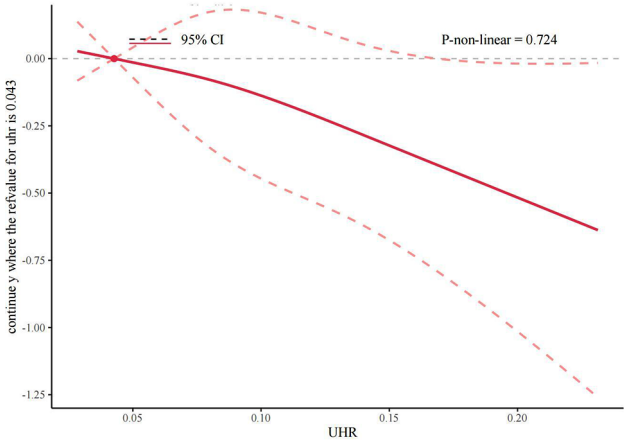

Fig. 10 Relationship Between UHR and eGFR Slope in a non-hypertensive population

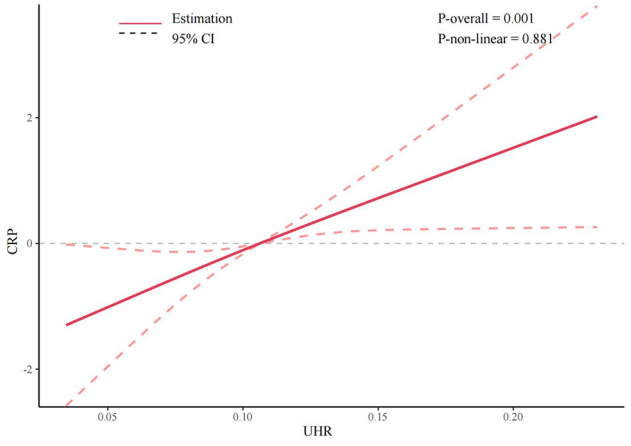

Fig. 11 Relationship between CRP and UHR

Table 8 Grouped according to UHR vs. CRP

	Group 1	Group 2	Group 3	Group 4	*P* value
	N = 4464	*N* = 703	*N* = 1566	*N* = 465	
Sex(male)	38.20%	42.40%	63.20%	56.30%	< 0.05
Hypertension	29.40%	36.70%	41.30%	51.80%	< 0.05
Dyslipidemia	7.91%	10.00%	14.00%	16.10%	< 0.05
Diabetes or High Blood Sugar	13.20%	19.30%	21.80%	27.30%	< 0.05
Chronic Lung diseases	9.79%	13.40%	8.70%	15.10%	< 0.05
Stroke	1.77%	2.00%	2.31%	3.88%	0.019
Asthma	3.35%	5.71%	3.01%	4.32%	0.007
Arthritis or Rheumatism	35.20%	36.80%	31.60%	40.20%	0.003
Blood Urea Nitrogen (BUN) (mg/dl)	15.0 (12.4;18.1)	14.3 (11.8;17.2)	15.7 (13.3;18.6)	15.3 (12.8;18.2)	< 0.05
Creatinine (mg/dl)	0.71 (0.62;0.82)	0.72 (0.63;0.82)	0.85 (0.72;0.96)	0.82 (0.71;0.98)	< 0.05
Triglycerides (mg/dl)	93.8 (69.0;133)	92.9 (69.0;133)	149.0(104;225)	148.0(102;219)	< 0.05
Hdl Cholesterol (mg/dl)	54.1 (46.4;63.8)	52.6 (45.6;61.5)	37.9 (32.9;43.7)	36.7 (32.1;42.9)	< 0.05
Creatinine (mg/dl)	0.73 (0.45;1.27)	5.42 (3.86;10.3)	1.06 (0.66;1.72)	5.09 (3.78;8.90)	< 0.05
Uric Acid (mg/dl)	3.87 (3.30;4.50)	4.00 (3.47;4.69)	5.32 (4.65;6.10)	5.28 (4.64;6.04)	< 0.05
Hemoglobin (g/dl)	14.1 (12.9;15.3)	14.1 (12.8;15.3)	14.8 (13.5;16.1)	14.6 (13.4;15.8)	< 0.05
Cystatin C (mg/l)	0.94(0.84;1.07)	1.02(0.89;1.16)	1.01(0.89;1.17)	1.04(0.89;1.25)	< 0.05
Age	57.0 (51.0;64.0)	60.0 (54.0;66.0)	58.0 (52.0;65.0)	60.0 (54.0;68.0)	< 0.05

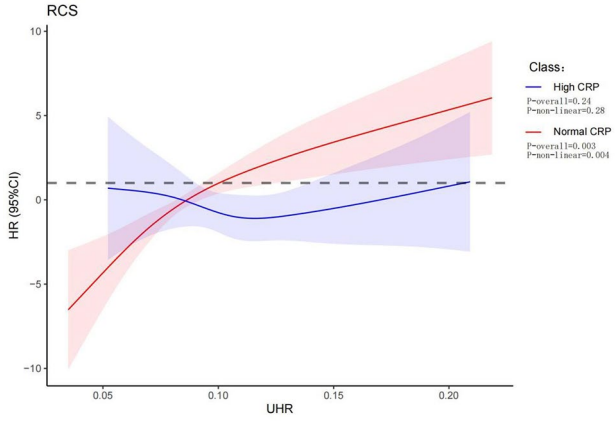

Fig. 12 Association between UHR and progression to renal insufficiency in groups with different levels of CRP in a hypertensive population

those at high risk of metabolic syndrome in non-diabetic men [19], and as a predictor of significant lesions in patients with single-vessel disease with moderate coronary stenosis [20], which suggests the presence of low-grade inflammation; in a previous study of UHR and CKD, which included urinary protein and eGFR as endpoint events, the influence of UHR on CKD has been demonstrated. are suggestive of the presence of low-grade inflammation; among previous studies of UHR and CKD [21], which included urinary protein and eGFR as endpoint events, etc., proved the involvement of UHR in the morbidity of the progression of CKD, and likewise we found that UHR can increase the risk of CKD, with a statistically significant difference ($P < 0.05$). However, compared to previous studies, we added the exploration between UHR and GFR slope in hypertensive population, which amplified the characteristics of CKD progression even more, and in turn, we found that UHR showed a J-type association rather than a positive correlation in GFR slope in hypertensive population. Lower levels of UHR (UHR < 7.6%) showed a decrease in GFR slope, while the GFR slope gradually increased after 7.6%, which included the increase and decrease of eGFR after 4 years of follow-up in the hypertensive population; this is different from the increasing prevalence of CKD and hypertension at the level of UHR; in combination with the relationship between the UHR and the slope of eGFR in the non-hypertensive population we found that UHR also increases the slope of eGFR decline, which in hypertensive populations may be related to the combined effects of hypertension and UHR. Previous studies have found no significant association of SUA in hypertensive patients taking antihypertensive medication and a U-shaped association in hypertensive patients not taking antihypertensive medication [22], With the development of China and the popularity of medication for basic diseases, almost more than 90% of our study population had taken antihypertensive medication, so we hypothesized that there was no significant association between hypertension and SUA in ours. Correlation analyses in a cross-sectional study including 62,957 Chinese adult men showed a positive correlation between systolic blood pressure and HDL-c (rho = 0.01, $P = 0.004$) and a negative correlation between diastolic blood pressure and HDL-c (rho = -0.02, $P < 0.01$) [23]; In our study about 5000 people had hypertension specific blood pressure values and about 130 people had high systolic and diastolic blood pressure (systolic blood pressure > 160 mmHg and diastolic blood pressure > 90 mmHg), it is reasonable to speculate that there may be a non-linear correlation between UHR and

systolic and diastolic blood pressure in hypertensive population. We therefore analyse the relationship between UHR and CKD progression in the hypertensive population and found a J-shaped correlation between UHR and the slope of eGFR in the hypertensive population. In the baseline characteristics of our study, we found that there was a large difference in age between those who had or had not developed CKD, considering the characteristics of the CHARLS database, i.e., the majority of the population was >45 years of age; it has been shown that the manifestation of SUA in hypertension varies in different age groups, with a positive correlation between SUA levels and the incidence of hypertension in < 55 years of age, and no correlation between SUA levels and the prevalence of hypertension in ≥ 55 years of age [24]; and a significant correlation was found in 7198 individuals in our study. In our study, only 127 out of 7198 people were < 45 years old, the rest were ≥ 45 years old, and the highest age was 93 years old; therefore, the above SUA performance could not explain the phenomenon that the slope of GFR decreased and then increased with the increase of UHR. We all know that eGFR also decreases with increasing age, but a large cohort study previously showed that the burden of CKD increased without considering age-related eGFR decline [25], so we excluded the age-related effect for the time being; subsequently, in 2023, UHR had an independent predictive role in diabetic nephropathy [10], and we speculated that UHR could not only be used as a predictor of diabetes mellitus, but also as a predictor of renal function. renal function, but also as a predictor of renal function in hypertension, which inspired our study. The combination of our results is that there is a strong statistical significance of cystatin C in both hypertensive and non-hypertensive populations, but there is no statistically significant relationship between UHR and CKD progression in non-hypertensive populations, and there is a statistically significant relationship between UHR and CKD progression in hypertensive populations. UHR may be better than cystatin C as a risk stratification for CKD progression in hypertensive population. CRP, a traditional inflammatory indicator, is highly expressed by many inflammatory cells (possibly macrophages) and endogenous renal cells (including tubular cells and endothelial cells) in renal diseases [26], and previous studies have shown that CRP activates Smad3 through ERK/p38 and TGF-β1 signaling pathways, promotes the activation of inflammation and accumulation of myeloid-derived suppressor cells and apoptosis, and inhibits autophagy and blocks the cell cycle, leading to the progression of AKI [27]. CRP single nucleotide polymorphism (SNP) rs2808630 has been associated with the development of CKD in African Americans and non-Hispanic blacks with hypertensive nephropathy. Meanwhile, CRP SNP rs2808630 was associated with albuminuria, an important risk factor for CKD progression [28]. It is highly likely that high CRP promotes inflammatory cell infiltration as well as the release of cytokines, chemokines, and TGF-β1 from diseased kidneys, leading to progressive renal inflammation and fibrosis [29], whereas the mechanism of CRP in CKD is likely to be consistent with that of mid- to pre-AKI (i.e., activation of Smad3 phosphorylation via the ERK/p38 and TGF-β1 signaling pathways), followed by a decrease in MCP-1 by increasing MCP-1 expression and decreasing Smad7 expression to induce renal inflammation by activating the NF-κB pathway activation [27]. From our study, we can see that CRP is a risk factor for the development of CKD in both hypertensive and non-hypertensive populations, and we can see from Fig. 11 that there is a linear correlation between UHR and CRP, i.e., as UHR rises CRP rises as well, and we speculate that UHR can be a predictor of progression to renal insufficiency in hypertensive patients, but because of the lack of our population However, because of the lack of CKD in our population, we need to validate this idea in the clinical CKD population at a later stage. Further looking at the relationship between UHR and CRP in the hypertensive population, we found that UHR was positively correlated with the risk of progression to CKD in the low-level CRP group, and it can also be hypothesized that UHR can be used as a predictor of the risk of progression to CKD in the hypertensive population when CRP is normal.

We hypothesized several potential mechanisms by which UHR would accelerate the progression of hypertension to CKD. First, previous studies have reported a positive correlation between higher SUA and prehypertension and hypertension in the Chinese population [30]. Animal studies have shown that mild hyperuricemia induces hypertension and renal injury in rats through stimulation of the renin-angiotensin system and inhibition of neuronal nitric oxide synthase (nNOS) [31], whereas nitric oxide (NO), as an endothelium-derived relaxing factor, is essential for maintaining blood pressure (BP) [32]. HDL consists of lipid and protein components, with the lipid fraction comprising the lipids that make up the lipid monolayer (mainly phosphatidylcholine) and surface lipids contained mainly in lipid rafts, including sphingolipids, such as ceramides, glycosidic amides, and sphingomyelins. HDL inhibits leukocyte adhesion molecules, proinflammatory factors, and monocytes, by translocation of lipids from peripheral blood and tissues to the liver [33, 34]. HDL inhibits leukocyte adhesion molecules, proinflammatory factors, monocyte activity and their differentiation into macrophages, thus exerting anti-arterial periarteriosclerosis, anti-inflammatory and antioxidant effects [35–37]. We do not know whether the mechanism of inflammatory action exerted by UHR, as the ratio of the dual inflammatory action factors of SUA

and HDL, is related to the two, so we look forward to subsequent studies to confirm this.

This study has several strengths. First, we linked UHR to the progression of renal function in a hypertensive population for the first time; second, we used a trend study to demonstrate a nonlinear correlation between UHR and progression to CKD in a hypertensive population, and further scaled up the slope of the GFR to explore the relationship between the GFR slope and UHR as a continuous variable. Third, we also correlated UHR with CRP, a traditional indicator of inflammation, and found a consistent inflammatory correlation, i.e., as UHR gets higher, UHR also gets higher. In the hypertensive population, when CRP is normal, the risk of CKD increases with higher UHR, which is not addressed by previous studies.

At the same time this study has some limitations. First, this is an observational analysis. Although adjustments were made for a range of chronic diseases and blood markers, social factors were not included in this study, and the results represent statistical relationships, not causality. Second, we only included renal function at baseline and endpoint events; multiple renal function tests for the eGFR slope would have been more accurate and would have allowed us to explore its progression over time. Third, urinary albumin is an important factor in CKD that was not documented in the present data, so we were not able to assess the relationship between UHR and urinary albumin in hypertensive patients progressing to CKD. Fourth, the population we included in the current study was predominantly over 45 years of age, which is not a good representation of the younger population. In conclusion, our study needs to be further refined and further demonstrated in future studies.

In conclusion, this study demonstrated that UHR is a risk factor for progression to CKD in hypertensive population and that there is a gradient of progression of renal function to CKD in hypertensive patients in terms of UHR grade; meanwhile, the progression of renal function was assessed using the GFR slope, and it was found that there was a J-type association between its slope and UHR in hypertensive population, whereas there was no significant relationship between GFR slope and UHR in the non-hypertensive population. In conclusion, in both hypertensive and non-hypertensive patients, finding risk factors for the progression of CKD and controlling or slowing down its progression is essential for both individual health and quality of life and for the economic burden on the family or the country.

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12882-024-03939-7.

Supplementary Material 1

Author contributions

Li Siying was mainly responsible for project design, data statistics and paper writing. Zhen Liu was mainly responsible for reviewing the quality of the article and guiding the content of the article. Lu Chen was responsible for designing the research program.

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Data availability

Details of the CHARLS data are available from http://charls.pku.edu.cn/pages/data/111/zh-cn.html.

Declarations

Ethics approval and consent to participate

All methods were performed in accordance with the Declaration of Helsinki. This work was fully compliant with Ethical Standards and approved by the Ethics Review Committee of Peking University (IRB 00001052–11015). Written informed consent for each participant was obtained prior to sample collection.

Consent for publication

Not applicable.

Recognize

We thank all participants in the CHARLES study team.

Competing interests

The authors declare no competing interests.

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