Journal of Health Care Communications
ISSN: 2472-1654
Open access Research Article

Multiplicative and Additive Interactions of Hyperuricemia and Hypertension on the Risk of Chronic Kidney Disease: Evidence from a Prospective Population-based Cohort Study

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ABSTRACT

Objective: To investigate the association between hyperuricemia (HUA) and the risk of Chronic Kidney Disease (CKD) in the Jinchang cohort and the interaction between HUA and hypertension on the risk of CKD, in order to provide a scientific basis for the prevention and treatment of CKD.

Methods: Based on the Jinchang cohort, a Cox regression model was applied to investigate the association between HUA and the risk of CKD using the non-HUA population as a reference, and *HR* values (95% *CI*) were calculated. According to the baseline age (<45 years, 45 years-64 years, ≥ 65 years), gender (male, female), BMI (<24.0 $kg.m^{-2}$, 24.0 $kg.m^{-2}$-27.9 $kg.m^{-2}$, ≥ 28.0 $kg.m^{-2}$), smoking (no, yes, quit smoking), alcohol consumption (no, yes, quit drinking, the study population diabetes (no, yes) hypertension (no, yes) and occupation (worker, other) were analyzed by subgroups. The product term of HUA and hypertension was also added to the Cox regression model to test whether there was a multiplicative interaction between the association of HUA and hypertension with the risk of developing CKD. The additive interaction between HUA and hypertension on the risk of developing CKD was examined using SAS macros, and the relative excess risk due to interaction (*RERI*), attributable proportion due to interaction (*AP*), and The results showed that after adjusting for the confounding factors, the H-risk ratio was higher than the *RERI*.

Results: After adjusting for confounders, there was an association between HUA and the risk of developing CKD, with the risk of CKD in the HUA population being 1.28 times higher than in the non-HUA population (HR=1.28, 95% *CI*:1.12-1.47). This association was more pronounced in the age ≥ 65 years, female, BMI <24 $kg.m^{-2}$, ex-smoker, worker, non-diabetic and hypertensive populations. The interaction results showed a positive multiplicative and additive interaction between HUA and hypertension on the risk of developing CKD. The product term INTM (95% *CI*) for HUA and hypertension was 1.33 (1.01-1.77); the additive interaction evaluation indexes *RERI* (95% *CI*), AP (95% *CI*), and SI (95% *CI*) were 0.64 (0.21-1.07), 0.27 (0.11-0.43), and 1.93 (1.16-3.19), respectively.

Conclusion: HUA is a risk factor for the development of CKD and has a synergistic effect with hypertension on the development of CKD. For the early prevention and treatment of CKD, the focus should be on and intervention for those with HUA combined with hypertension, so that the limited health resources and funds can be used rationally to the maximum extent.

Keywords: Hyperuricemia; Chronic kidney disease; Interaction; Cohort study

Received:	04-December-2023	**Manuscript No:**	IPJHCC-23-18503
Editor assigned:	06-December-2023	**PreQC No:**	IPJHCC-23-18503 (PQ)
Reviewed:	20-December-2023	**QC No:**	IPJHCC-23-18503
Revised:	25-December-2023	**Manuscript No:**	IPJHCC-23-18503 (R)
Published:	01-January-2024	**DOI:**	10.36846/2472-1654-8.6.8060

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Citation Ma Z, Hu X, Hu P, Shi J, Wang Y, et al. (2023) Multiplicative and Additive Interactions of Hyperuricemia and Hypertension on the Risk of Chronic Kidney Disease: Evidence from a Prospective Population-based Cohort Study. J Healthc Commun. 8:8060.

INTRODUCTION

Chronic Kidney Disease (CKD) is defined as a glomerular filtration rate (GFR) <60 mL min^{-1} 1.73 m^{-2} or the presence of one or more markers of renal injury for at least 3 months, which include albuminuria, abnormal urine sedimentation, and histological or structural abnormalities of the kidney [1]. Research shows that the global prevalence of CKD and the number of people with disabilities and deaths caused by CKD are increasing year by year. In 2017, the global total prevalence of CKD was 9.1%, and the number of CKD patients reached nearly 700 million, more than the number of patients with diabetes, osteoarthritis, chronic obstructive pulmonary disease, asthma or depression, and one third of the patients are in China and India [2,3]. Research has shown that from 1990 to 2017, the global all-age mortality rate of CKD increased by 41.5%. In 2017, 1.2 million people worldwide died from CKD, and the ranking of causes of death has also increased from 17th in 1990 to 12th [2]. CKD is also one of the urgent public health issues to be addressed in China. Research shows that the prevalence rate of CKD in China was 10.8% in 2009, and 8.2% in 2018-2019 [4]. From the prevalence rate, although the prevalence rate of CKD in China has declined over the past decade, the awareness rate of CKD is still very low, only 10%. Among CKD patients receiving treatment, the control rate of hypertension, diabetes and dyslipidemia is very low, 24.5%, 42.3% and 31.5% respectively [5]. Although the etiology of CKD is not yet clear, identifying risk factors for CKD and intervening can help prevent its occurrence or delay its progression, thereby reducing the risk of death and reducing the burden of CKD disease [6]. Research has shown that HUA can not only predict the risk of cardiovascular disease and metabolic syndrome, but also be an independent risk factor for CKD, and the risk of CKD increases with the increase of sUA [7-9].

Importantly, the occurrence and progression of CKD are the result of the long-term accumulation of multiple etiologies and risk factors, which can act independently or jointly on the body, producing synergistic or antagonistic effects [10]. For example, a cohort study in Taiwan, China shows that the association between HUA and sUA and CKD is stronger in women, and both HUA and sUA have a positive multiplicative interaction with gender on CKD [11]. A cohort study in the Netherlands showed that the association between sUA and the decrease in CKD and eGFR was more pronounced in hypertensive populations [12], and there was a positive multiplicative interaction between sUA and hypertension on the occurrence of CKD and the decrease in eGFR. However, the above studies only explored the multiplicative interaction between HUA or sUA and gender, hypertension, and did not further analyze whether there is an additive interaction. Moreover, research on the interaction between HUA and other related factors on the onset of CKD is still very limited. Therefore, this study is based on the Jinchang queue platform and uses the SAS interaction macro to explore the interaction between HUA and hypertension on the risk of CKD, providing scientific basis for the prevention and treatment of CKD [13].

MATERIALS AND METHODS

Study Design and Participants

The participants were all drawn from the Jinchang cohort [14-16], an ongoing prospective cohort study in Jinchang City, Gansu Province, China, based on the biennial physical examination of all employees of Jinchuan Nonferrous Metals Company (JNMC). From June 2011 to December 2013, a total of 48,001 participants completed the cohort baseline survey, and 33,355 participants completed the first round of follow-up survey from January 2014 to December 2015, with a median follow-up time of 2.2 years.

From the 33355 study subjects who completed the first round of follow-up, 179 cases of self-reported kidney disease, 1560 cases of missing CKD diagnostic information at baseline and follow-up, 1128 cases of baseline CKD patients, 146 cases of baseline malignant tumors, 179 cases of baseline gout patients, and 1741 cases of missing sUA at baseline and follow-up were excluded from the baseline epidemiological survey. Finally, 28422 study subjects were included.

Data Collection

The research data used in this study were derived from the Jinchang cohort baseline survey and the first round of follow-up surveys, including epidemiological questionnaires, physical examinations, and clinical biochemical examinations. Our research team designed the standardized and structured epidemiological questionnaires to collect basic socio-demographic information (age, gender, education, occupation, etc.), behavioral characteristics (smoking, drinking, exercise, etc.), and medical history of the participants. Uniformly trained interviewers conducted the questionnaire survey through one-on-one and face-to-face interviews. During the survey, it was ensured that the respondents clearly understood the content of the questionnaire, avoiding inducing questions, and cross-checking was conducted after completing the survey.

The physical examination and clinical biochemical examination were completed by the clinical staff of the Workers' Hospital of the Jinchuan Company, including height, weight, blood pressure, and various clinical biochemical indexes. Height and weight were measured by a computerized body scale (SK-X80/TCS-160D-W/H, Sonka, China) when the participants took off their shoes and wore light clothes. Body mass index (BMI) was calculated as weight in kilograms divided by height in meters squared ($kg.m^{-2}$). The blood pressure in a sitting position was measured by an electronic sphygmomanometer (BP750, AMpall, Seoul, Korea) three times continuously after at least 10 minutes of rest, and the average values were taken. Before venous blood collection, all participants were instructed to fast for at least 8 h. The clinical biochemical examination was detected by an automatic biochemical analyzer (Hitachi 7600-020, Kyoto, Japan), mainly including serum creatinine (Scr), sUA, total cholesterol (TC), fasting plasma glucose (FPG), triglyceride (TG), high-density lipoprotein cholesterol (HDL-C), and low-density lipoprotein cholesterol (LDL-C).

Study Outcomes and Related Definitions

CKD was defined in this study as the presence of abnormal glomerular filtration rate (eGFR <60 mL min^{-1} 1.73 m^{-2}) or proteinuria (urine dipstick reading ≥ 1+), of which eGFR was estimated according to the Chronic Kidney Disease Epidemiology Collaboration equation (CKD-EPI), based on Scr, age, and gender [1,17].

Covariates

Smokers were those who smoked at least one cigarette a day for more than 6 months, and non-smokers were those who never smoked or who smoked occasionally but did not meet the definition of a smoker. Ex-smokers were those who used to smoke but had not smoked for more than 6 months. Drinkers were those who drank liquor or other spirits, wine or other fruit wine, beer, and other alcohol at least once a week for more than 6 months, and non-drinkers were those who never drank or drank occasionally but did not meet the definition of drinkers. Ex-drinkers were those who used to drink but had not drunk for more than 6 months. Physical exercise was divided into three types: No, occasionally, and often exercise. Occasionally exercise was defined as exercise less than 3 times a week and exercise more than 30 minutes on average, and often exercise was considered as exercise at least 3 times a week for more than 30 minutes each time. Hypertension was defined as self-reported physician-diagnosed hypertension or definite clinical records of hypertension or blood pressure 140/90 mm Hg (1 mm Hg=0.133 kPa) [18]. Diabetes was defined as self-reported physician diagnosis of diabetes or definite clinical records of diabetes or fasting blood glucose ≥ 7.0 mmol/L [19].

Statistical Analysis

Participants' baseline characteristics were presented as means ± standard deviation (SD) for continuous variables and numbers (percentages) for categorical variables. Comparison of continuous variables between groups using the Student's t-test and chi-squared test for categorical variables. Hazard ratios (*HRs*) with 95% confidence intervals (95% *CI*s) were calculated to estimate the associations between HUA at baseline with new-onset CKD by using Cox proportional hazards regression models. None of the covariates were adjusted for Model 1, covariates that were included in Model 2 were those that altered the hazard ratios for the effect of CKD by more than 5% in and Analysis, and all of the covariates were in the form of categorical variables. Finally, the covariates included in Model 2 were age (<45 years, 45 years-64 years, 65 years), gender (male, female), BMI (<24.0 $kg.m^{-2}$, 24.0 $kg.m^{-2}$-27.9 $kg.m^{-2}$, 28 $kg.m^{-2}$), smoking status (non-smoker, smoker, ex-smoker), drinking status (non-drinker, drinker, ex-drinker), diabetes (no, yes), hypertension (no, yes), TG (1.20 mmol/L, 1.21 mmol/L-2.00 mmol/L, 2.01 mmol/L) at baseline. Stratified analyses were performed according to age, gender, BMI, smoking and drinking status, occupation, diabetes, and hypertension. Likelihood ratio tests were used to investigate interactions.

SAS macro was used to examine the additive and multiplicative interactions of CKD and related factors on the risk of HUA [13]. relative excess risk due to interaction (*RERI*), attributable proportion due to interaction, relative excess risk due to interaction (*RERI*), attributable proportion due to interaction, AP), synergy index (SI). Where, *RERI* represents the relative risk attributable to additive interaction, AP represents the proportion of the total effect attributable to additive interaction when two factors are present at the same time, and SI represents the ratio of the effect when two factors are present at the same time to the sum of the independent effects of two factors. If the confidence interval for *RERI* and AP does not contain 0, and the confidence interval for SI does not contain 1, then there is an additive interaction [20,21]. All statistical analyses were performed with SAS program, version 9.4 (SAS Institute Inc., Cary, NC, USA) and R software (R Foundation for Statistical Computing), version 4.3.2. All statistical tests were two-sided, and P <0.05 was considered statistically significant.

RESULTS

Baseline Characteristics of the Study Population

As shown in **Table 1**, a total of 28,422 subjects were included in the second part of the study, of which 61.70% were males, and the proportion of people <45 years old was the highest, reaching 52.13%. Except for occupation and diabetes, there were statistically significant differences in baseline characteristics between the patients with HUA and the non-HUA population. Among them, there were statistically significant differences in age, education level, smoking, drinking and physical exercise between HUA group and non-HUA group (all P<0.05). In addition, the proportion of men and hypertension in HUA group was higher than that in non-HUA group, and the difference was statistically significant (all P<0.05). The levels of BMI, SBP, DBP, FPG, TC, TG and LDL-C in HUA population were higher than those in non-HUA population. HDL-C was lower than that of non-HUA population, and the differences were statistically significant (all P<0.05).

Table 1: Baseline characteristics of study participants, stratified by HUA

Variables	Total population (N=28,422)	HUA (N=3869)	Non-HUA (N=24,553)	P value
		Age (years), N (%)		
<45	14,816 (52.13)	2023 (52.29)	12,793 (52.10)	<0.001
45-64	10,833 (38.11)	1407 (36.37)	9426 (38.39)	
≥ 65	2773 (9.76)	439 (11.34)	2334 (9.51)	
		BMI ($kg.m^{-2}$), N (%)		
<24.0	15,407 (54.21)	1677 (43.34)	13,730 (55.92)	
24.0-27.9	10,503 (36.95)	1649 (42.62)	8854 (36.06)	<0.001
≥ 28.0	2512 (8.84)	543 (14.04)	1969 (8.02)	
Male, N (%)	17,536 (61.70)	3189 (82.42)	14,347 (58.43)	<0.001

		Education, N (%)		
Junior high school or below	11,103 (39.06)	1381 (35.69)	9722 (39.60)	<0.001
High school	7776 (27.36)	1077 (27.84)	6699 (27.28)	
Junior college	5669 (19.95)	812 (20.99)	4857 (19.78)	
Bachelor's degree or above	3874 (13.63)	599 (15.48)	3275 (13.34)	
		Occupation, N (%)		
Front-line worker	21,983 (77.35)	2961 (76.53)	19,022 (77.47)	0.193
White-collar worker	6439 (22.65)	908 (23.47)	5531 (22.53)	
		Smoking status, N (%)		
Non-smoker	15,459 (54.39)	1534 (39.65)	13,925 (56.71)	<0.001
Smoker	10,565 (37.17)	1889 (48.82)	8676 (35.34)	
Ex-smoker	2398 (8.44)	446 (11.53)	1952 (7.95)	
		Drinking status, N (%)		
Non-drinker	21,128 (74.34)	2375 (61.39)	18,753 (76.38)	<0.001
Drinker	6022 (21.19)	1263 (32.64)	4759 (19.38)	
Ex-drinker	1272 (4.47)	231 (5.97)	1041 (4.24)	
		Physical exercise, N (%)		
No	3854 (13.56)	542 (14.01)	3312 (13.49)	Baseline
Occasionally	11,233 (39.52)	1601 (41.38)	9632 (39.23)	Baseline
Often	13,335 (46.92)	1726 (44.61)	11,609 (47.28)	Baseline
Diabetes, N (%)	1947 (6.85)	280 (7.24)	1667 (6.79)	0.306
Hypertension, N (%)	8286 (29.15)	1604 (41.46)	6682 (27.21)	<0.001
TC (mmol/L), Mean ± SD	4.70 ± 0.89	4.88 ± 0.94	4.67 ± 0.88	<0.001
TG (mmol/L), Mean ± SD	1.50 (1.10, 2.30)	2.10 (1.50, 3.10)	1.50 (1.00, 2.10)	<0.001
HDL-C (mmol/L), Mean ± SD	1.37 ± 0.35	1.25 ± 0.32	1.39 ± 0.35	<0.001
LDL-C (mmol/L), Mean ± SD	3.05 ± 0.74	3.14 ± 0.75	3.04 ± 0.73	<0.001

Data were presented as means ± SD for continuous variables with normal distribution, M (P25, P75) for continuous variables with skewed distribution, and numbers (percentages) for categorical variables. Differences between groups were compared using the Student's t-test for continuous variables with normal distribution, Wilcoxon rank-sum test for continuous variables with skewed distribution, and Chi-squared test for categorical variables. HUA, hyperuricemia; BMI, body mass index. TC, total cholesterol; TG, triglyceride; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol

Association between HUA and Risk of New-onset CKD

After adjusting for possible confounders, Cox regression showed an association between HUA, and the risk of developing CKD, with a 0.28-fold increase in the risk of developing CKD in the baseline HUA population compared with the non-HUA population (*HR*=1.28, 95% *CI*:1.12-1.47), as shown in **Table 2**.

Table 2: Associations between HUA at baseline with new-onset CKD

	N	No of Events (%)	Model 1		Model 2	
			HR (95% *CI*)	P value	*HR* (95% *CI*)	P value
Non-HUA	24,553	933 (3.80%)	1.00 (Ref)		1.00 (Ref)	
HUA	3869	279 (7.21%)	1.70 (1.48-1.93)	<0.001	1.28 (1.12-1.47)	<0.001

Model 1 was not adjusted for any covariates. Model 2 was adjusted for age (<45 years, 45 years-64 years, ≥ 65 years), gender (male, female), BMI (<24.0 kg.m^{-2}, 24.0 kg.m^{-2}-27.9 kg.m^{-2}, ≥ 28 kg.m^{-2}), smoking status (non-smoker, smoker, ex-smoker), drinking status (non-drinker, drinker, ex-drinker), diabetes (no, yes), hypertension (no, yes), TG (≤ 1.20 mmol/L, 1.21 mmol/L-2.00 mmol/L, ≥ 2.01 mmol/L) at baseline. CKD, chronic kidney disease; HUA, hyperuricemia; HR, hazard ratio; CI, confidence interval.

According to the baseline age of the study subjects (<45 years, 45-64 years, ≥ 65 years), sex (male, female), BMI (<24.0 kg.m^{-2}, 24.0 kg.m^{-2}-27.9 kg.m^{-2}, ≥ 28.0 kg.m^{-2}), smoking (no, yes, quit), and alcohol consumption (no, yes, quit), diabetes (no, yes) and hypertension (no, yes) were analysed in subgroups, and after adjusting for possible confounders, Cox regression showed that the association between HUA and the risk of developing CKD was more pronounced in the age ≥ 65 years, female, BMI <24 kg.m^{-2}, quit smoking, workers, non-diabetic and hypertensive populations, with *HR* (95% *CI*) 1.63 (1.25-2.11), 1.55 (1.13-2.13), 1.37 (1.10-1.71), 1.54 (1.10-2.14), 1.30 (1.11-1.52), 1.31 (1.12-1.53), and 1.45 (1.22-1.73), respectively. In addition, there was a multiplicative interaction between the associations of HUA and hypertension with the risk of developing CKD (P<0.05), and no multiplicative interactions were observed between the associations of HUA and other subgroups of categorical variables with the risk of developing CKD (all P>0.05) (**Figure 1**).

Analysis of the Combined Effect of HUA and Hypertension on the Risk of Developing CKD

As shown in **Table 3**, after adjusting for confounders, the risk of CKD in the baseline non-HUA and hypertensive, HUA and non-hypertensive, and HUA and hypertensive populations was 1.60 times (HR=1.60, 95% *CI*:1.39-1.83), 1.09 times (HR=1.09, 95% *CI*:0.87-1.37), 1.09 (HR=1.09, 95% *CI*:0.87-2.37), and 2.32 (HR=2.32, 95% *CI*:1.94-2.79) times.

Table 3: The joint effect of HUA and HTN on the risk of CKD

	HTN	N	*HR* (95% *CI*)	P value
Non-HUA	No	17871	1	
	Yes	6682	1.60 (1.39-1.83)	<0.001
HUA	No	2265	1.09 (0.87-1.37)	0.458
	Yes	1604	2.32 (1.94-2.79)	<0.001

HRs (95% *CI*) was adjusted for age (<45 years, 45 years-64 years, ≥ 65 years), gender (male, female), BMI (<24.0 kg.m^{-2}, 24.0 kg.m^{-2}-27.9 kg.m^{-2}, ≥ 28 kg.m^{-2}), smoking status (non-smoker, smoker, ex-smoker), drinking status (non-drinker, drinker, ex-drinker), diabetes (no, yes), TG (≤1.20 mmol/L, 1.21 mol/L-2.00 mmol/L, ≥ 2.01 mmol/L) at baseline. CKD, chronic kidney disease; HUA, hyperuricemia; HTN, hypertension; HR, Hazard Ratio; CI, Confidence Interval.

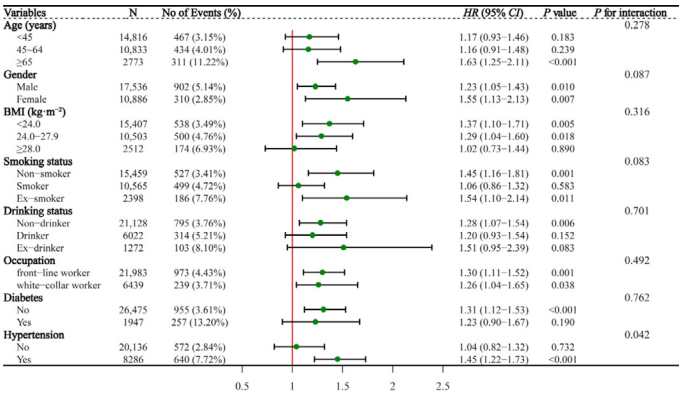

Figure 1: Stratified associations between HUA and new-onset CKD by age, gender, BMI, smoking status, drinking status, occupation, diabetes, and hypertension

Analysis of the Interaction between HUA and Hypertension on the Risk of Developing CKD

As shown in **Table 4**, after adjusting for confounders, there was a positive multiplicative and additive interaction between HUA and hypertension on the risk of developing CKD, and the percentage of the additive interaction was 27%; the product term INTM (95% *CI*) of HUA and hypertension was 1.33 (1.01-1.77); and the evaluators of the additive interaction, the *RERI* (95% *CI*), AP (95% *CI*), and SI (95% *CI*) were 0.64 (0.21-1.07), 0.27 (0.11-0.43), and 1.93 (1.16-3.19), respectively (**Figure 2**).

Table 4: Estimates of multiplicative and additive interaction of HUA and HTN on the risk of CKD

	Estimate	95% *CI*	P value
INTM	1.33	1.01-1.77	0.042
RERI	0.64	0.21-1.07	0.004
AP	0.27	0.11-0.43	<0.001
SI	1.93	1.16-3.19	0.011

Estimates was adjusted for age (<45 years, 45 years-64 years, ≥ 65 years), gender (male, female), BMI (<24.0 kg.m^{-2}, 24.0 kg.m^{-2}-27.9 kg.m^{-2}, ≥ 28 kg.m^{-2}), smoking status (non-smoker, smoker, ex-smoker), drinking status (non-drinker, drinker, ex-drinker), diabetes (no, yes), TG (≤ 1.20 mmol/L, 1.21 mmol/L-2.00 mmol/L, ≥ 2.01 mmol/L) at baseline. CKD, chronic kidney disease; HUA, hyperuricemia; HTN, hypertension; CI, confidence interval; INTM, interaction multiplicative; *RERI*, relative excess risk due to interaction; AP, attributable proportion due to interaction; SI, synergy index.

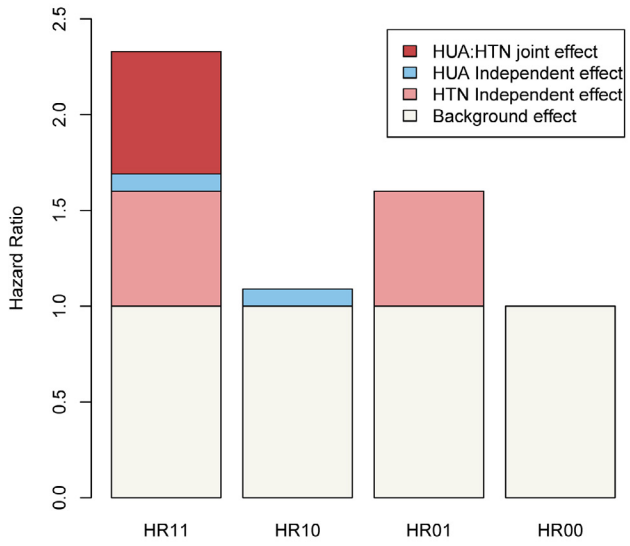

Figure 2: Schematic diagram of the interaction between HUA and hypertension on the risk of developing CKD

DISCUSSION

Studies have found that uric acid can lead to kidney injury by forming urate crystals that obstruct renal tubules, inducing proliferation of vascular smooth muscle cells and reduction of endothelial NO [22,23], and activating the renin-angiotensin-aldosterone system to cause an increase in blood pressure; furthermore, elevated levels of uric acid promote medial thickening of small pre-glomerular arterioles, which is directly correlated with glomerular capillary pressure [24]. Such small arterial changes in the kidney may lead to ischaemia and hypoxia, which are the strongest triggers of tubule-interstitial fibrosis [25]. Experimental studies have shown that hyperuricaemia accelerates the deterioration of renal function through high systemic blood pressure and cyclooxygenase-mediated thromboxane-induced vascular disease [26]. In addition, renal inflammation occurring in the context of hyperuricaemia plays a key role. Urate-induced stimulation of NLRP3 inflammatory vesicles and release of interleukin-1 β promotes chemokine signalling in proximal tubular cells, leading to tubular injury and proteinuria. Uric acid also induces

Toll-like receptor-dependent activation of renal mesangial cells, increases local expression of chemokines, promotes epithelial mesenchymal transition in renal tubular cells by decreasing E-calmodulin expression and increases fibronectin synthesis by up-regulating lysyl oxidase in renal tubular epithelial cells [27-30]. These alterations simultaneously promote intrarenal inflammation, interstitial fibrosis, and CKD. These mechanisms provide a biologically plausible explanation for the results of the association between HUA and the risk of developing CKD in this study. The results of this study showed that the risk of CKD in the baseline HUA population was increased by 0.28-fold compared with that in the non-HUA population (HR=1.28, 95% *CI*:1.12-1.47). Therefore, the management of HUA and sUA should be emphasised in the prevention and control of CKD, and the active treatment of HUA and control of sUA levels are beneficial in preventing the development of CKD as well as delaying the decline of eGFR.

The results of a cohort study in the Netherlands showed that the association between sUA and CKD and eGFR decline was stronger in hypertensive populations compared to non-hypertensive populations, and that there was a multiplicative interaction between sUA and hypertension on both the occurrence of CKD and the decline in eGFR [12]. However, this study did not further investigate whether there was an additive interaction between sUA and hypertension on the development of CKD. In the present study, it was found that there was not only a positive multiplicative interaction but also a positive additive interaction between HUA and hypertension on the development of CKD, with the percentage of additive interaction being 27%. The existence of this interaction may be due to the mutual influence of HUA and hypertension and their promotion of each other, resulting in the study subjects being more prone to develop CKD when HUA and hypertension coexist. Studies based on the Gusau cohort have shown that hyperuricaemia may contribute to the development of hypertension by causing microalbuminuria [31,32]. Harrison et al. proposed a secondary “strike” model to explain the mechanism of uric acid-induced hypertension [33,34]. The first “hit” is the activation of the renin-angiotensin-aldosterone system and the inhibition of nitric oxide synthesis, which promotes endothelial dysfunction, vascular smooth muscle cell proliferation, and sodium reabsorption, leading to a moderate but sustained increase in systemic blood pressure. The second “hit” involves the immune system. Uric acid released in response to hypertension-induced damage can be recognised as a dangerous molecule by pattern recognition receptors. Downstream signalling from these receptors leads to dendritic cell maturation and activation of resting T-cells, but it also triggers inflammatory vesicles and induces the secretion of pro-inflammatory cytokines. This pro-inflammatory environment simultaneously expands extracellular fluid volume and increases vascular resistance, which further promotes systemic hypertension. Correspondingly, hyperuricaemia is also common in patients with essential hypertension and the use of thiazide diuretics increases serum uric acid levels in hypertensive patients [35]. The above mechanisms may partly explain the fact that the effect of HUA and hypertension when co-existing is greater than the effect of HUA alone, i.e., there is a synergistic effect of HUA and hypertension on the risk of developing CKD.

The study has a large sample size, collects relatively comprehensive information, and adjusts for confounding factors as much as possible in the regression analyses, making the results highly credible. However, there are also some shortcomings. Firstly, this study only included data from the baseline and first follow-up surveys of the Jinchang cohort, and the follow-up period was relatively short and limited to the Jinchang cohort population, which restricted the extrapolation of the results. Therefore, the results still need to be further validated in a multi-centre, large-scale cohort. In addition, as an observational study, although this study adjusted for confounders as much as possible, it still could not avoid the interference of residual confounding. Finally, considering that the study population was already exposed to CKD risk factors such as heavy metals at the time of the baseline investigation, a quantitative assessment of metal exposure will help to further elucidate the pathogenesis of CKD.

CONCLUSION

In summary, HUA is a risk factor for the development of CKD, and there is a synergistic effect with hypertension on the development of CKD. According to the results of this study, for the early prevention and diagnosis of CKD, attention and intervention should be focused on those with HUA combined with hypertension, so that the limited health resources and funds can be utilized to the greatest extent reasonably. In addition, the results of this study will also help to further explore the mechanism of HUA leading to the development of CKD and provide new ideas for the scientific prevention and treatment of CKD.

AUTHOR CONTRIBUTIONS

Z.M. conceived and drafted the original manuscript. X.H., P.H. analyzed the data and performed the statistical analysis. J.S., Y.W., Y.T., H.L., F.X. and M.N. collected and cleaned the data. X.H. designed the analytic strategy and revised the manuscript for intellectual content. All authors have read and agreed to the published version of the manuscript.

FUNDING

This work was supported by the Natural Science Foundation of Gansu Province (20JR10RA599).

INSTITUTIONAL REVIEW BOARD STATEMENT

This study involving human participants was in accordance with the Helsinki Declaration of 1964 and its later amendments or comparable ethical standards. The Ethics Committee of the School of Public Health of Lanzhou University approved this study (Ethical Approved Code: 2015-01).

INFORMED CONSENT STATEMENT

All participants signed informed consent.

DATA AVAILABILITY STATEMENT

The data underlying this article cannot be shared publicly due to data protection reasons. The data will be shared upon reasonable request to the corresponding author.

ACKNOWLEDGEMENT

We would like to sincerely thank all of the participants and researchers from Jinchang Nonferrous Metal Company, the Worker's Hospital of JNMC, and Lanzhou University in the Jinchang Cohort Study for their contributions and collaboration.

CONFLICT OF INTEREST

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as potential conflicts of interest.

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