



The Effects of Cardiometabolic Factors on the Association Between Serum Uric Acid and Chronic Kidney Disease in Chinese Middle-Aged and Older Population: A Mediation Analysis

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Introduction: To explore whether dyslipidemia, hyperglycemia or hypertension has mediating effect on the association between serum uric acid (SUA) and the development of chronic kidney disease (CKD).

Methods: We conducted a mediation analysis to explore the potential mediating effects of systolic blood pressure (SBP), diastolic blood pressure (DBP), blood glucose, triglyceride (TG), total cholesterol (TC), high-density lipoprotein cholesterol (HDL-C) and low-density lipoprotein cholesterol (LDL-C) on the association between SUA and estimated glomerular filtration rate (eGFR). The data were obtained from China Health and Retirement Longitudinal Study (CHARLS), covering 5,762 individuals.

Results: SUA had a negative dose-response total effect on eGFR (β -3.11, 95% CI -3.40 to -2.82, P -value<0.001). The linear regression between SUA and seven potential mediators indicated that blood glucose (β 0.80, 95% CI 0.18 to 1.42, P -value=0.012), TG (β 10.01, 95% CI 8.22 to 11.79, P -value<0.001), TC (β 2.64, 95% CI 1.83 to 3.45, P -value<0.001), HDL-C (β -0.27, 95% CI -0.52 to -0.02, P -value=0.034) and LDL-C (β 1.15, 95% CI 0.49 to 1.80, P -value=0.001) all had significant dose-response association with SUA, but SBP and DBP showed no significant association with SUA. In terms of the association between potential mediators and eGFR, only TG (β 0.003, 95% CI -0.001 to 0.01, P -value=0.117) and HDL-C (β 0.01, 95% CI -0.02 to 0.04, P -value=0.444) did not have significant linear association with eGFR. The linear regression showed that SUA was directly associated with eGFR (P -value<0.001).

Conclusions: This study supported that the association between SUA and the risk of CKD was not mediated by hypertension, hyperglycemia or dyslipidemia.

Keywords: mediation analysis, serum uric acid, chronic kidney disease, cardiometabolic factors, dyslipidemia, hypertension, hyperglycemia

INTRODUCTION

Chronic kidney disease (CKD), characterized by ongoing and irreversible damage of the renal parenchyma which leads to chronic deterioration of renal function (1), is mainly reflected by decline of estimated glomerular filtration rate (eGFR) (2). CKD has been recognized as a rapidly growing worldwide public health problem (3), especially in developing countries (3, 4).

In recent years, serum uric acid (SUA), the end product of purine metabolism in humans (5), has gradually been considered as a risk factor of CKD (6–11). There are many potential mechanisms behind this, such as the activation of the renin-angiotensin system (RAS) (12, 13), the proliferation of the vascular smooth muscle cells (VSMC) through Cyclooxygenase-2 (COX-2) dependent pathway (13), and direct fibrogenic effect on renal cells (13).

Existing evidence has suggested that elevated SUA concentration may play a role in the development of CKD (7, 8), which may be mediated by cardiometabolic factors. SUA has been reported to be associated with the pathogenesis of dyslipidemia (7), diabetes (14) and hypertension (15) which are also the risk factors of CKD (16), and these risk factors usually coexist and could influence each other (17). However, limited studies have examined the mediating effect of such cardiometabolic factors on the association between SUA and CKD; therefore, whether dyslipidemia, hyperglycemia or

hypertension has mediating effect on the association between SUA and the development of CKD remains unclear.

This population-based study used nationally representative survey data to explore whether hyperglycemia, hypertension or dyslipidemia has mediating effect on the association between SUA and CKD in Chinese middle-aged and older population.

METHODS

Database and Study Population

The China Health and Retirement Longitudinal Study (CHARLS) was a nationally representative longitudinal survey among the population aged 45 years and older in China. This survey was carried out every two or three years. To date, there have been four surveys conducted in 2011 (visit 1), 2013 (visit 2), 2015 (visit 3) and 2018 (visit 4), respectively. Blood sample data were collected at visit 1 and visit 3. Detailed information about this survey is available elsewhere (18). This study was approved by the Ethical Review Committee of Peking University (IRB00001052-11015), and written informed consent was obtained from each participant.

Participants with available blood sample data at visit 1 were included in this study. We excluded the participants younger than 45 years old at baseline, those were not followed at visit 3,

TABLE 1 | Characteristics of participants at baseline.

Characteristics	Overall	Female	Male	P-value
Participants, n (%)	5,762	3,132	2,630	
Age (years, SD)	58.84 (9.13)	58.43 (9.23)	59.31 (8.98)	<0.001
Smoking, n (%)				<0.001
Current/former	2,209 (37.84)	237 (7.16)	1,972 (73.12)	
Drinking, n (%)				<0.001
Current/former	2,201 (38.99)	455 (13.52)	1,746 (68.29)	
BMI (kg/m²), n (%)				<0.001
Underweight (<18.5 kg/m ²)	326 (5.21)	169 (4.70)	157 (5.79)	
Normal (≥18.5–24 kg/m ²)	2,905 (48.69)	1,404 (42.65)	1,501 (55.61)	
Overweight (≥24–28 kg/m ²)	1,754 (32.79)	1,044 (36.67)	710 (28.34)	
Obesity (≥28 kg/m ²)	753 (13.31)	499 (15.98)	254 (10.26)	
SUA (mg/dL, SD)	4.53 (1.31)	4.11 (1.06)	5.02 (1.39)	<0.001
SBP (mmHg)	130.65 (20.92)	131.07 (22.07)	130.15 (19.51)	0.118
DBP (mmHg)	76.06 (11.92)	75.91 (11.86)	76.22 (11.99)	0.359
Blood glucose (mg/dL, SD)	108.86 (33.41)	108.51 (31.55)	109.26 (35.42)	0.396
TG (mg/dL, SD)	131.03 (87.96)	137.37 (87.72)	123.75 (87.70)	<0.001
TC (mg/dL, SD)	192.15 (38.46)	196.76 (38.41)	186.84 (37.83)	<0.001
HDL-C (mg/dL, SD)	49.57 (15.17)	49.90 (14.55)	49.19 (15.85)	0.073
LDL-C (mg/dL, SD)	116.28 (34.68)	119.30 (34.77)	112.80 (34.25)	<0.001
eGFR (mL/min per 1.73 m², SD)	92.34 (14.55)	92.69 (14.47)	91.93 (14.62)	<0.050

SD, standard deviation; BMI, body mass index; SUA, serum uric acid; SBP, systolic blood pressure; DBP, diastolic blood pressure; TG, triglyceride; TC, total cholesterol; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; eGFR, estimated glomerular filtration rate. There were 20, 21, 24, 724, 724, 10, 29, 5, 13 and 11 individuals with missing information in smoking, drinking, BMI, SBP, DBP, blood glucose, TG, TC, LDL-C and eGFR, respectively.

those lacked SUA data at visit 1 or creatine data at visit 3, and those did not have a blood test in fasting state at visit 1 or visit 3. Participants with hypouricemia [i.e., SUA < 2 mg/dL for both sexes (19)] at baseline were excluded as well.

Exposure and Outcome Assessment

The exposure variable was baseline SUA. In this study, the outcome considered in this study was eGFR (mL/min per 1.73 m²) which was estimated using the CKD-EPI creatinine equation (2009): $141 \times \min(\text{Scr}/\kappa, 1)^\alpha \times \max(\text{Scr}/\kappa, 1)^{-1.209} \times 0.993 \text{Age} [\times 1.018 \text{ if female}] [\times 1.159 \text{ if black}]$, where Scr is serum creatinine, 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 (20).

Covariate Assessment

The covariates considered in this study were as follows: age (years), sex (male, female), smoking (never, current/former), drinking (never, current/former), body mass index (BMI, kg/m²) (21, 22),

and medication use (i.e., medication treatment for hypertension, hyperglycemia and dyslipidemia). BMI was calculated by dividing weight (kg) by the square of height (m) and BMI was categorized into four levels (underweight: <18.5 kg/m², normal: ≥18.5–24 kg/m², overweight: ≥24–28 kg/m², obesity: ≥28 kg/m² (23).

Potential Mediators

The selected potential mediators were systolic blood pressure (SBP), diastolic blood pressure (DBP), blood glucose, triglyceride (TG), total cholesterol (TC), high-density lipoprotein cholesterol (HDL-C) and low-density lipoprotein cholesterol (LDL-C), since previous studies reported the association between SUA with hypertension, hyperglycemia or dyslipidemia (7, 14, 15) and the association between hypertension, hyperglycemia or dyslipidemia with CKD (16). All potential mediators was measured at visit 3.

Statistical Analysis

Comparisons of baseline demographic characteristics or clinical features between sexes were performed by Student t test for

TABLE 2 | The mediating effects of cardiometabolic factors on the association between SUA and eGFR.

Step	Effect	β (95% CI)	P-value
Total effect: association between SUA and eGFR			
	SUA	-3.11 (-3.40 to -2.82)	<0.001
Mediation analysis			
Step 1: association between SUA and potential mediators			
	SBP	-0.25 (-0.64 to 0.14)	0.214
	DBP	0.02 (-0.20 to 0.25)	0.841
	Blood glucose	0.80 (0.18 to 1.42)	0.012
	TG	10.01 (8.22 to 11.79)	<0.001
	TC	2.64 (1.83 to 3.45)	<0.001
	HDL-C	-0.27 (-0.52 to -0.02)	0.034
	LDL-C	1.15 (0.49 to 1.80)	0.001
Step 2: association between potential mediators and eGFR			
	SBP	0.05 (0.03 to 0.07)	<0.001
	DBP	0.06 (0.03 to 0.10)	<0.001
	Blood glucose	0.03 (0.01 to 0.04)	<0.001
	TG	0.003 (-0.001 to 0.01)	0.117
	TC	-0.01 (-0.02 to -0.0001)	0.047
	HDL-C	0.01 (-0.02 to 0.04)	0.444
	LDL-C	-0.02 (-0.03 to -0.01)	<0.001
Step 3 (direct effect): association between SUA and eGFR that excluded the effects of potential mediators			
	SBP	-3.05 (-3.35 to -2.76)	<0.001
	DBP	-3.07 (-3.36 to -2.77)	<0.001
	Blood glucose	-3.14 (-3.43 to -2.85)	<0.001
	TG	-3.20 (-3.49 to -2.90)	<0.001
	TC	-3.09 (-3.39 to -2.80)	<0.001
	HDL-C	-3.10 (-3.39 to -2.80)	<0.001
	LDL-C	-3.08 (-3.37 to -2.78)	<0.001
Indirect effect (caused by each of the mediators)			
	SBP	-0.01 (-0.05 to 0.02)	0.509
	DBP	0.002 (-0.03 to 0.03)	0.918
	Blood glucose	0.02 (-0.01 to 0.06)	0.109
	TG	0.10 (0.03 to 0.17)	0.003
	TC	-0.003 (-0.05 to 0.04)	0.856
	HDL-C	-0.001 (-0.01 to 0.01)	0.878
	LDL-C	-0.02 (-0.05 to 0.01)	0.158

SUA, serum uric acid; eGFR, estimated glomerular filtration rate; SBP, systolic blood pressure; DBP, diastolic blood pressure; TG, triglyceride; TC, total cholesterol; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol.

All logistic regressions were adjusted for age, sex, smoking, drinking, medication treatment for hypertension, diabetes or dyslipidemia, and body mass index level. The bold values represent statistically significant effects.

continuous variables, and Pearson chi-squared test for categorical variables.

Before examination of the possible mediating effects of the seven potential mediators on the association between SUA and eGFR, we evaluated the total effect of SUA on eGFR over five-year period. A multivariable linear regression model adjusted for age, sex, smoking, drinking and BMI level (underweight: <18.5 kg/m², normal: ≥18.5–24 kg/m², overweight: ≥24–28 kg/m², obesity: ≥28 kg/m²) was used, with SUA analyzed as a continuous variable.

We followed standard procedures for mediation analysis, using three main steps to do a series of linear regressions adjusted for age, sex, smoking, drinking, BMI level and medication treatment for hypertension, hyperglycemia or dyslipidemia (24). In the first step, the association between SUA and a range of potential mediators was examined. In the second step, the effect of each potential mediator on eGFR was evaluated. In the third step, the potential mediators and baseline SUA were all included in linear regression to examine whether

SUA has a direct or indirect effect on eGFR. The indirect effect between SUA and eGFR caused by the potential mediators was evaluated using khb program in Stata version 15.0 (25). Subgroup analyses by sex (male, female) were performed.

The inverse probability weighting method was adopted to take non-response rate into consideration. The individuals with missing data in some variables were not considered in the analyses including the corresponding variables. All statistical analyses were performed by Stata version 15.0 (StataCorp, College Station, TX, USA). Two-sided P-value less than 0.05 was set as the statistically significant level.

RESULTS

Baseline Characteristics

This study included 5,762 participants, with 3,132 females and 2,630 males. Males were more likely to be older, smokers,

TABLE 3 | The mediating effects of cardiometabolic factors on the association between SUA and eGFR in males.

Step	Effect	β (95% CI)	P-value
Total effect: association between SUA and eGFR			
	SUA	-2.71 (-3.09 to -2.34)	<0.001
Mediation analysis			
Step 1: association between SUA and potential mediators			
	SBP	-0.03 (-0.54 to 0.48)	0.898
	DBP	0.20 (-0.10 to 0.51)	0.184
	Blood glucose	0.90 (0.10 to 1.70)	0.028
	TG	6.41 (4.21 to 8.61)	<0.001
	TC	2.50 (1.50 to 3.51)	<0.001
	HDL-C	0.07 (-0.27 to 0.42)	0.675
	LDL-C	1.40 (0.56 to 2.24)	0.001
Step 2: association between potential mediators and eGFR			
	SBP	0.02 (-0.01 to 0.05)	0.107
	DBP	0.03 (-0.02 to 0.08)	0.179
	Blood glucose	0.02 (0.003 to 0.04)	0.023
	TG	0.01 (-0.0002 to 0.01)	0.059
	TC	-0.02 (-0.03 to -0.003)	0.021
	HDL-C	0.004 (-0.04 to 0.05)	0.844
	LDL-C	-0.04 (-0.05 to -0.02)	<0.001
Step 3 (direct effect): association between SUA and eGFR that excluded the effects of potential mediators			
	SBP	-2.69 (-3.07 to -2.32)	<0.001
	DBP	-2.70 (-3.08 to -2.33)	<0.001
	Blood glucose	-2.76 (-3.13 to -2.38)	<0.001
	TG	-2.78 (-3.15 to -2.40)	<0.001
	TC	-2.68 (-3.06 to -2.30)	<0.001
	HDL-C	-2.70 (-3.08 to -2.32)	<0.001
	LDL-C	-2.66 (-3.03 to -2.28)	<0.001
Indirect effect (caused by each of the mediators)			
	SBP	-0.001 (-0.02 to 0.02)	0.941
	DBP	0.01 (-0.02 to 0.04)	0.533
	Blood glucose	0.02 (-0.02 to 0.06)	0.229
	TG	0.08 (0.01 to 0.15)	0.035
	TC	-0.02 (-0.07 to 0.04)	0.490
	HDL-C	0.001 (-0.004 to 0.01)	0.841
	LDL-C	-0.04 (-0.09 to 0.01)	0.112

SUA, serum uric acid; eGFR, estimated glomerular filtration rate; SBP, systolic blood pressure; DBP, diastolic blood pressure; TG, triglyceride; TC, total cholesterol; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol.

All logistic regressions were adjusted for age, sex, smoking, drinking, medication treatment for hypertension, diabetes or dyslipidemia, and body mass index level. The bold values represent statistically significant effects.

drinkers, lower in BMI, TG, TC, LDL-C and eGFR, and, higher in SUA (Table 1). There were no significant differences in SBP, DBP, blood glucose, and HDL-C between two sexes.

Total Effect of SUA on eGFR

After adjustment for age, sex, smoking, drinking and BMI level, there was a negative dose-response relationship of SUA and eGFR (β -3.11, 95% CI -3.40 to -2.82, Table 2). Repeating the linear regressions in different sexes, such a dose-response relationship was still significant in males (β -2.71, 95% CI -3.09 to -2.34, Table 3) and females (β -3.67, 95% CI -4.14 to -3.21, Table 4).

Test of Mediation

Evaluating the association between SUA and seven potential mediators, blood glucose (β 0.80, 95% CI 0.18 to 1.42), TG (β 10.01, 95% CI 8.22 to 11.79), TC (β 2.64, 95% CI 1.83 to 3.45) and LDL-C (β 1.15, 95% CI 0.49 to 1.80) all had significant positive dose-response relationship with SUA, while HDL-C had

negative dose-response relationship with SUA (β -0.27, 95% CI -0.52 to -0.02, Table 2 and Figure 1).

In terms of the association between potential mediators and eGFR, only TG (β 0.003, 95% CI -0.001 to 0.01) and HDL-C (β 0.01, 95% CI -0.02 to 0.04) did not have significant linear association with eGFR. There were significant positive dose-response relationships between SBP (β 0.05, 95% CI 0.03 to 0.07), DBP (β 0.06, 95% CI 0.03 to 0.10), blood glucose (β 0.03, 95% CI 0.01 to 0.04) and eGFR. Also, there were significant negative dose-response relationships between TC (β -0.01, 95% CI -0.02 to -0.0001) or LDL-C (β -0.02, 95% CI -0.03 to -0.01) and eGFR.

The linear regression including both the potential mediators and SUA showed that SUA was directly associated with eGFR (P -value<0.001). However, except for TG, the indirect effects of other potential mediators were all non-significant. Although the indirect effect of TG was significant, it was opposite to the total effect; therefore, TG was not a mediator of the association between SUA and eGFR. Stratified by different sexes, similar results were observed (Tables 3 and 4).

TABLE 4 | The mediating effects of cardiometabolic factors on the association between SUA and eGFR in females.

Step	Effect	β (95% CI)	P-value
Total effect: association between SUA and eGFR			
	SUA	-3.67 (-4.14 to -3.21)	<0.001
Mediation analysis			
Step 1: association between SUA and potential mediators			
	SBP	-0.63 (-1.24 to -0.01)	0.046
	DBP	-0.24 (-0.59 to 0.11)	0.181
	Blood glucose	0.51 (-0.47 to 1.49)	0.306
	TG	14.72 (11.8 to 17.63)	<0.001
	TC	2.85 (1.53 to 4.16)	<0.001
	HDL-C	-0.68 (-1.05 to -0.31)	<0.001
	LDL-C	0.79 (-0.26 to 1.83)	0.142
Step 2: association between potential mediators and eGFR			
	SBP	0.08 (0.05 to 0.10)	<0.001
	DBP	0.09 (0.04 to 0.14)	<0.001
	Blood glucose	0.03 (0.01 to 0.05)	<0.001
	TG	0.002 (0.004 to 0.01)	0.537
	TC	-0.005 (-0.02 to 0.01)	0.471
	HDL-C	0.02 (-0.03 to 0.06)	0.475
	LDL-C	-0.01 (-0.03 to 0.01)	0.208
Step 3 (direct effect): association between SUA and eGFR that excluded the effects of potential mediators			
	SBP	-3.58 (-4.05 to -3.11)	<0.001
	DBP	-3.60 (-4.07 to -3.12)	<0.001
	Blood glucose	-3.69 (-4.16 to -3.23)	<0.001
	TG	-3.82 (-4.29 to -3.35)	<0.001
	TC	-3.68 (-4.15 to -3.21)	<0.001
	HDL-C	-3.68 (-4.15 to -3.21)	<0.001
	LDL-C	-3.67 (-4.14 to -3.20)	<0.001
Indirect effect (caused by each of the mediators)			
	SBP	-0.04 (-0.14 to 0.05)	0.372
	DBP	-0.02 (-0.07 to 0.04)	0.494
	Blood glucose	0.02 (-0.03 to 0.06)	0.448
	TG	0.14 (0.03 to 0.26)	0.016
	TC	0.01 (-0.05 to 0.07)	0.809
	HDL-C	0.004 (-0.04 to 0.05)	0.863
	LDL-C	-0.01 (-0.03 to 0.02)	0.622

SUA, serum uric acid; eGFR, estimated glomerular filtration rate; SBP, systolic blood pressure; DBP, diastolic blood pressure; TG, triglyceride; TC, total cholesterol; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol. All logistic regressions were adjusted for age, sex, smoking, drinking, medication treatment for hypertension, diabetes or dyslipidemia, and body mass index level. The bold values represent statistically significant effects.

DISCUSSION

This national population-based study supported a direct association between SUA and the development of CKD, with no mediating effect of dyslipidemia, hypertension or hyperglycemia. The potential mechanisms for the direct effect of SUA are as follows. First, RAS would be activated by high-level SUA (26), thereby increasing the glomerular pressure and generating direct fibrogenic effect on renal cells which could lead to kidney disease (27). Second, an animal study indicated SUA could stimulate the proliferation of VSMC by uric acid-mediated COX-2 dependent pathway, thereby inducing preglomerular vasculopathy, vascular injury and renal dysfunction (28). Third, SUA probably had a direct effect on renal tubular cells through the induction of phenotypic transition of cultured renal tubular cells (i.e., epithelial-to-mesenchymal transition, EMT) (29), and EMT is an important contributor to the pathogenesis of renal fibrosis (30). Fourth, SUA may also induce CKD *via* the decrease of NO production and induction of oxidative stress (28).

As hypertension, hyperglycemia and dyslipidemia are risk factors of CKD (16) and also related to high-level SUA (7), it is possible that the association between SUA and CKD could be explained by the mediating effect of these cardiometabolic risk factors. However, the result of the mediation analysis indicated that there was no mediating effect of hypertension, hyperglycemia or dyslipidemia on the association between SUA and CKD. The possible explanations are as follows.

First, although high-level SUA could increase the risk of hypertension, hyperglycemia and dyslipidemia, the strong direct damage effect of SUA on CKD may be more potent than the effect of hypertension, hyperglycemia or dyslipidemia on renal function in the initial stage of CKD. Also, the sample size in our study can ensure us to exclude the contribution of each mediator to the indirect effect, which only made up less than 5% of the total effect. Second, the marker of early renal damage from hyperglycemia and hypertension is microalbuminuria (31, 32), and only with disease progressing, high-level blood pressure and high-level blood glucose could cause obvious damage to eGFR. The study period in our study was only five years; therefore, the effect of hypertension or hyperglycemia on the decline of eGFR may be weak in the initial stage of CKD.

The significant relationship between SUA and the development of hyperglycemia observed in this study was consistent with previous studies (14, 33, 34). The positive association between SUA and hyperglycemia can be explained by nitric oxide reduction induced by hyperuricemia (35). The decrease of nitric oxide lowers insulin-stimulated glucose intake in skeletal muscle and prompts insulin resistance (36), thereby leading to hyperglycemia. The association between SUA and the development of dyslipidemia found in this study was also consistent with some previous studies (7, 34). However, other studies indicated that there was no relationship between SUA and the development of dyslipidemia (37, 38). Therefore, the role of SUA in the pathogenesis of dyslipidemia is still controversial and future work in this regard is warranted.

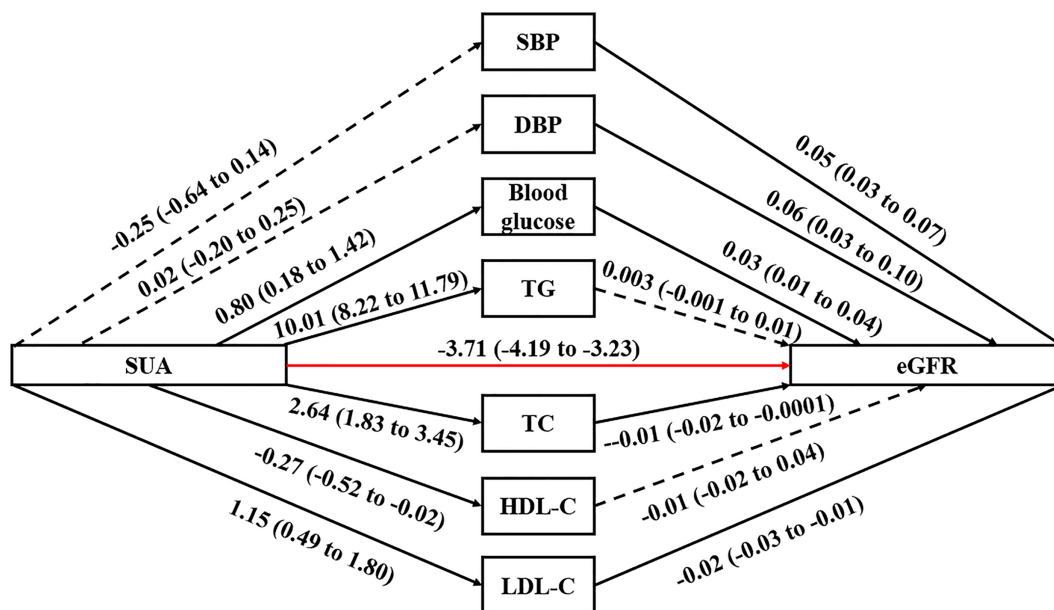


FIGURE 1 | Path diagram for mediational model. SUA, serum uric acid; eGFR, estimated glomerular filtration rate; SBP, systolic blood pressure; DBP, diastolic blood pressure; TG, triglyceride; TC, total cholesterol; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol. The solid arrows represent a significant effect, and the dashed arrow represents a nonsignificant effect. The red arrow represents the association between SUA and eGFR that excluded the effects of the seven potential mediators. The regression linear coefficient β and 95% CIs are positioned beside each arrow.

We also observed the positive relationships between SBP, DBP or blood glucose and eGFR. This phenomenon could be explained by glomerular hyperfiltration in initial stage of hypertension and hyperglycemia (13, 39, 40), since the glomerular hyperfiltration in those with hyperglycemia and hypertension may be caused by improper vasodilation of afferent arteriole (39) and increased glomerular hydraulic pressure, respectively (41). It was noticeable that there was no significant dose-response relationship between HDL-C and eGFR. One study suggested that lower HDL-C was related to higher eGFR in individuals without kidney disease (42). One explanation is that individuals with high-level HDL-C may also have high-level TC and high-level LDL-C which are also negatively associated with eGFR as observed in our study and other previous studies (43, 44). Therefore, HDL-C may not have a protective effect on kidney function. However, another study reported that HDL-C was critical for the protection against renal dysfunction (45). Also, it was found that high-level HDL-C was not related to reduced mortality risk in individuals with kidney dysfunction (46). These conflicting results probably indicated that the effect of HDL-C could be heterogeneous; therefore, the mechanisms of how HDL-C influence the development of CKD remains unclear.

This longitudinal study utilized the nationally representative data to explore whether SUA has a direct effect on the development of CKD among Chinese middle-aged and older population. But this study still has limitations. First, no data on albuminuria were included, which is an important factor for the definition of CKD. However, the definition of CKD using eGFR < 60 mL/min per 1.73 m² is well-accepted and acknowledged in population-based studies (47, 48). Second, in CHARLS, the identification of hyperglycemia and hypertension depended on not only the data from blood test and physical examination, but also self-reported physician diagnosis. But according to previous validation studies, the self-reports of common chronic diseases were accurate and well-accepted (49, 50). In addition, many published high-quality studies based on CHARLS also used such self-reported physician diagnosis, which confirmed the reliability and accuracy of the data.

CONCLUSIONS

This study supported that the association between SUA and the risk of CKD was not mediated by hypertension, hyperglycemia

or dyslipidemia. These findings highlight the important role of SUA as a risk factor for CKD. Therefore, it is necessary to regularly measure SUA in order to circumvent the manifestation of CKD and its progression into end-stage renal disease.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

This study was approved by the Ethical Review Committee of Peking University (IRB00001052-11015). The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

SW, XL, and YS conceived and designed the study. LX and LL acquired the data. LX, HS, SZ, SW, LL, XL, and YS interpreted and analyzed the data. LX and HS drafted the manuscript. SZ, SW, XL, and YS reviewed the manuscript for important intellectual content critically. All authors contributed to the article and approved the submitted version.

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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 a potential conflict of interest.

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