BMJ Open

Association of uric acid with the decline in estimated glomerular filtration rate in middle-aged and elderly populations: evidence based on the China Health and Retirement Longitudinal Study

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To cite: Liu P, Liang Y, Cui S, *et al*. Association of uric acid with the decline in estimated glomerular filtration rate in middle-aged and elderly populations: evidence based on the China Health and Retirement Longitudinal Study. *BMJ Open* 2023;**13**:e071771. doi:10.1136/bmjopen-2023-071771

► Prepublication history and additional supplemental material for this paper are available online. To view these files, please visit the journal online (http://dx.doi.org/10.1136/bmjopen-2023-071771).

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Received 12 January 2023
Accepted 12 April 2023

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ABSTRACT

Objective Whether uric acid (UA) has an effect on renal function remains controversial. We aimed to investigate the association between serum UA with the decline in estimated glomerular filtration rate (eGFR) in middle-aged and elderly populations in the China Health and Retirement Longitudinal Study (CHARLS).

Design Longitudinal cohort study.

Setting This was a second analysis of a public dataset (CHARLS).

Participants In this study, 4538 middle-aged and elderly individuals were screened after removing individuals younger than 45 years old, with kidney disease, malignant tumour and missing values.

Outcome measures Blood tests were performed both in 2011 and 2015. Decline in eGFR was defined as an eGFR decrease of more than 25% or deterioration of the eGFR stage during the 4-year follow-up period. Logistic models corrected for multiple covariables were used to analyse the association of UA with the decline in eGFR.

Results The median (IQR) concentrations of serum UA grouped by quartiles were 3.1 (0.6), 3.9 (0.3), 4.6 (0.4) and 5.7 (1.0) mg/dL, respectively. After multivariable adjustment, the OR of the decline in eGFR was higher for quartile 2 (3.5–<4.2 mg/dL: OR 1.44; 95% CI 1.07 to 1.64; p<0.01), quartile 3 (4.2–<5.0 mg/dL: OR 1.72; 95% CI 1.36 to 2.18; p<0.001) and quartile 4 (≥5.0 mg/dL: OR 2.04; 95% CI 1.58 to 2.63; p<0.001) when compared with quartile 1 (<3.5 mg/dL), and the p value for the trend was <0.001.

Conclusions Over a 4-year follow-up period, we found that elevated UA was associated with a decline in eGFR in the middle-aged and elderly individuals with normal renal function.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ High-quality data from nationally representative cohort were used to examine the association between uric acid (UA) and the decline in estimated glomerular filtration rate (eGFR) in middle-aged and elderly populations.
⇒ Interaction test was use in the stratified group to further observe the association between UA levels and the decline in eGFR.
⇒ The lack of duplicate blood tests made the baseline data less robust and reliable.
⇒ Data on urinary protein, renal imaging, as well as renal pathology, were lacking in China Health and Retirement Longitudinal Study, which might create bias in the statistical results.
⇒ The rate of missing visit was high during the follow-up period, which would cause selection bias.

INTRODUCTION

The prevalence of chronic kidney disease (CKD) is approximately 13.4% (11.7%–15.1%) worldwide, and there are more than 100 million individuals with CKD in China.[1] CKD inevitably imposes a substantial disease burden on patients, concomitant with the increased incidence of end-stage renal disease (ESRD), cardiovascular events and deaths.[1 2] Clearly, early detection of risk factors for CKD is particularly important, as timely intervention of the corresponding risk factors could reduce CKD incidence, improve people's living quality, and relieve the medical and economic burden on society.[3]

It is universally recognised by clinicians that hypertension, diabetes mellitus (DM), chronic heart disease, obesity, smoking and long-term use of non-steroidal anti-inflammatory drugs can lead to renal impairment.[4 5] However, clinicians may face a dilemma over whether the elevated levels of uric acid (UA), a kind of end product of nucleic acid metabolism, can cause glomerular filtration rate (GFR) deterioration. In some special clinical situations, such as in patients with tumour lysis syndrome, the serum UA increases sharply in a short period of time, resulting in numerous UA crystals that may lead to renal tubule obstruction and acute kidney injury.[6] Meanwhile, renal lesions induced by UA crystals also

increase the risk and progression of CKD.[7] Additionally, the proposed mechanisms of renal impairment involve an imbalance between pro-oxidative and antioxidative factors, activation of the renin–angiotensin–aldosterone system, endothelial dysfunction and smooth muscle cell proliferation, which are independent of UA crystals.[7–12] However, some researchers believe that the increase of serum UA is secondary to kidney damage. When subtle kidney lesions occur, the increase of serum UA precedes the increase of serum creatinine (Scr), which means that using elevated UA to predict the decline in GFR evaluated by Scr might be neither appropriate nor feasible.[13] Regarding clinical studies, some prospective cohort studies revealed that elevated serum UA was associated with adverse renal events, including the onset of CKD, CKD deterioration and ESRD occurrence.[14–18] On the other hand, some researchers did not find the association between UA and progression of CKD.[19–21] As noted above, the effect of UA on renal function remains controversial. Moreover, most studies have found a relationship between serum UA and adverse kidney incidence in patients with CKD. In general, studies investigating the association between serum UA and decline in estimated GFR (eGFR) in individuals without CKD are lacking, especially in the context of the Chinese population. Therefore, the current controversy and dearth of information on this subject deserve further study.

The China Health and Retirement Longitudinal Study (CHARLS) is a prospective cohort study, which conducted a nationwide sampling survey to assess the social, economic, behavioural, psychological, and health performance of the middle-aged and elderly individuals.[22 23] The CHARLS completed the baseline survey in 2011, and again collected blood samples from the population during the follow-up study in 2015. The purpose of this study was to investigate the relationship between serum UA levels and the decline in eGFR in this 4-year follow-up cohort study.

METHODS

Study population

The data in this study came from the CHARLS, a publicly available cohort of health, economic, and health for middle-aged and older adults.[22 23] The individuals of the cohort completed baseline surveys in 2011 (wave 1), followed up every 2–3 years thereafter, and a second follow-up survey in 2015 (wave 3). In this study, we used wave 1 and wave 3 data which contained blood analysis results.

There was a total of 17 708 individuals in the baseline survey (wave 1). Individuals were excluded according to the following exclusion criteria: (1) no blood analysis; (2) non-fasting blood analysis; (3) missing eGFR data; (4) kidney disease reported by clinicians or eGFR less than 60 min/L/1.73 m^2; (5) having malignant tumours; (6) younger than 45 years old. A total of 9112 individuals were included after the initial screening. We found that among those 9112 individuals, 3435 (33.4%) individuals with missing values were excluded from wave 1. In order to make full use of the data, we excluded individuals with missing values exceeding five variables and filled in the remaining missing values with multiple imputation. Eventually, 7769 participants were retained in wave 1. We then excluded individuals who had no follow-up data, without blood analysis, no fasting blood sample or without eGFR results in wave 3. The detailed study population screening process is shown in figure 1.

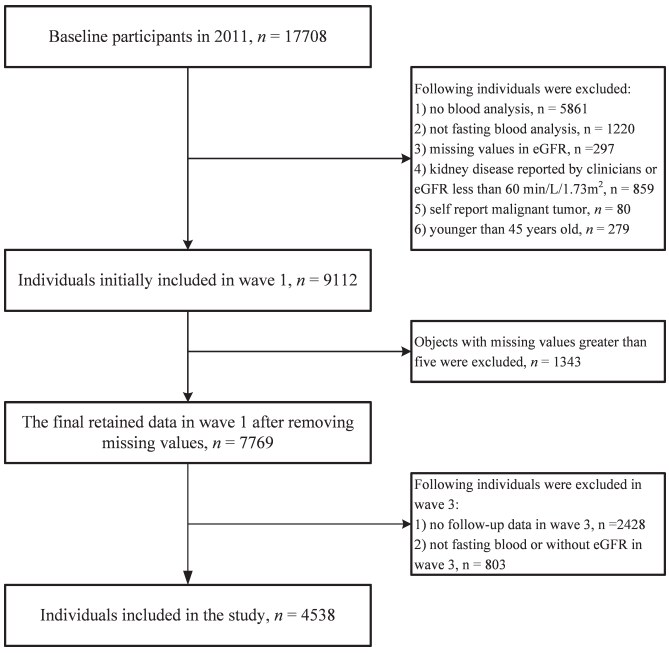

Figure 1 Flow chart of participant selection. eGFR, estimated glomerular filtration rate.

Blood sample data

The detailed description of the blood sample collection, processing, transportation and storage is given elsewhere.[22 24] Briefly, the venous blood samples were collected by staff from local Chinese Center for Disease Control and Prevention (CDC) stations. Then, the collected blood samples were sent to the local CDC and Beijing CDC laboratories, under low temperature storage, for analysis. White blood cells (WBCs), haemoglobin and platelet counts were measured on automated analysers available at county CDC stations or town/village health centre. High-sensitivity C reactive protein (hs-CRP), glycosylated haemoglobin (HbA1c), a lipid panel, glucose, blood urea nitrogen (BUN), creatinine and UA were assessed at the Youanmen Center for Clinical Laboratory of Capital Medical University (Beijing, China), which had excellent performance during annual evaluation by External Quality Assurance Program organised by the National Center for Clinical Laboratories.

In the baseline (wave 1) blood examination, glucose and lipid panels, including total cholesterol, high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol and triglyceride (TG), were measured by

enzymatic colorimetric test. The hs-CRP was measured by immunoturbidimetric assay; HbA1c was assessed by boronated affinity high-performance liquid chromatography; BUN was determined by an enzymatic ultraviolet spectrophotometric method using urease; Scr was measured using a rate-blanked and compensated Jaffe creatinine method; UA was measured using the UA Plus method. The Scr measurement method used in wave 3 was consistent with that used in wave 1.

Study outcome

The GFR was evaluated using the Chronic Kidney Disease Epidemiology Collaboration equation based on Scr proposed in 2012.[25] Due to the lack of urinary protein markers and limited follow-up duration, this study used a decline in eGFR as the endpoint event to identify early renal impairment in individuals without CKD. The decline in eGFR was defined as an eGFR decrease of more than 25% or a deterioration of the eGFR stage.[26]

Covariates

Baseline covariates (wave 1) included in this study were the following: sex (female vs male), age, marital status (married with spouse present vs other marital status), education level (middle school and below vs high school and above), smoking status (ever vs never), drinking status (ever vs never), residence (rural region vs urban region), height, weight, waist circumference, body mass index (BMI), dominant hand grip strength (HGS), systolic blood pressure (SBP), diastolic blood pressure (DBP), eGFR, self-reported diseases (high blood pressure (BP), DM, blood lipid abnormality, heart disease, and rheumatism or arthritis) as well as the modern medicine treatment for the aforementioned diseases. Resting BP was measured for each participant three times every 45–60 s with an Omron HEM-7112 sphygmomanometer (Omron Co, Dalian, China). The mean of the latter two measurements of BP was used. Age was divided into two groups according to whether it was under or over 60 years old. Other marital status included married but not living with spouse, separated, divorced, widowed or never married. BMI was the body mass (weight) divided by the square of the body height. The HGS was categorised into two groups according to the IQR by sex (group 1: the lower quartile; group 2: the upper three quartiles). The eGFR was also divided into two groups (group 1: eGFR 60–89 mL/min/1.73 m^2 vs group 2: eGFR ≥90 mL/min/1.73 m^2). Self-reported diseases were those that had been diagnosed by a physician. Hypertension was defined as SBP ≥140 mm Hg, and/or DBP ≥90 mm Hg, and/or self-reported hypertriton, and/or medicine therapy for hypertension. Any of the following conditions can be diagnosed with DM: (1) fasting blood glucose ≥126 mg/dL; (2) HbA1c ≥6.5%; (3) a self-reported history of diabetes; (4) hypoglycaemic therapy using modern medicines. Dyslipidaemia was defined as fasting TG ≥150 mg/dL, or HDL-C ≤40 mg/dL, or diagnosed as dyslipidaemia and treated. Heart disease included heart attack, coronary heart disease, angina, congestive heart failure or other heart problems.

Statistical methods

Characteristics were expressed as median (IQR) for continuous variables and the number of participants (percentage) for categorical variables. The statistical analysis of the differences in population grouped by quartiles of serum UA was performed by $\chi 2$ test for categorical data and Kruskal-Wallis test for continuous data. Before developing the logical model, we converted the continuous independent variables that had no linear relationship with the logit-transformed dependent variable into classified variables. Univariate analysis was performed to compare the difference between the eGFR decline and the non-eGFR decline groups to limit the number of confounding variables. In addition, for continuous independent variables, we conducted a collinearity test by using variance inflation factors. The association between elevated serum UA and decline in eGFR was estimated using logistic models before and after calibration for age group, sex, marital status, smoking status, education level, residential location, BMI, eGFR group, hypertension, antihypertensive therapy, DM, hypoglycaemic therapy, dyslipidaemia, therapy for dyslipidaemia, self-reported heart disease and therapy for heart disease. In addition, we performed sensitivity analysis by potential modifiers of the association between elevated serum UA and decline in eGFR, and interaction test in the stratified group. P<0.05 (two-sided test) was considered to be statistically significant. All data analyses were performed using the Stata/MP V.16 software (StataCorp, College Station, Texas, USA).

Patient and public involvement

The data of this study were anonymised. Patients and the public were not involved in the design or conduct, or reporting, or dissemination plans of the study.

RESULTS

Study participants and baseline characteristics

The participant screening process was precisely depicted in figure 1. We included 7769 participants at baseline (wave 1) and 4538 eligible individuals were eventually selected at follow-up (wave 3). The characteristics of the participants included in the study were compared with those included in the baseline and excluded after the follow-up period, and the comparison is shown in online supplemental table 1.

The characteristics of the 4538 participants are presented by quartiles of UA in table 1. After a 4-year follow-up period, the decline in eGFR occurred in 184 (16.2%), 232 (20.4%), 237 (20.9%) and 232 (20.4%) participants in quartile 1, quartile 2, quartile 3 and quartile 4 groups, respectively. The median (IQR) concentrations of serum UA among the four groups were 3.1 (0.6), 3.9 (0.3), 4.6 (0.4), and 5.7 (1.0) mg/dL, respectively. The participants with higher serum UA had the following

Table 1 Population characteristics by quartiles of serum uric acid

	Q1 (<3.5 mg/dL) (n=1133)	Q2 (3.5–4.2 mg/dL) (n=1136)	Q3 (4.2–5.0 mg/dL) (n=1134)	Q4 (≥5.0 mg/dL) (n=1135)	P value
Demographic and biomarker indicators					
Age (years)	57 (11)	58 (12)	58 (12)	59 (12)	<0.001
45~59	779 (68.8)	705 (62.1)	678 (59.8)	614 (54.1)	<0.001
60~	354 (31.2)	431 (37.9)	456 (40.2)	521 (45.9)	
Female, n (%)	901 (79.5)	743 (65.4)	524 (46.2)	326 (28.7)	<0.001
Married with spouse, n (%)	957 (84.5)	960 (84.5)	957 (84.3)	990 (87.2)	0.16
Education, n (%)					
Middle school and below	867 (76.5)	844 (74.3)	762 (67.2)	750 (66.1)	<0.001
High school and above	266 (23.5)	292 (25.7)	372 (32.8)	385 (33.9)	
Ever drink, n (%)	271 (23.9)	349 (30.7)	480 (42.3)	660 (58.2)	<0.001
Ever smoke, n (%)	253 (22.3)	347 (30.6)	475 (41.9)	626 (55.2)	<0.001
Rural region, n (%)	799 (70.5)	769 (67.7)	764 (67.4)	680 (59.9)	<0.001
Height (m)	1.55 (0.10)	1.56 (0.11)	1.59 (0.12)	1.61 (0.11)	<0.001
Weight (kg)	55.6 (13.4)	57.1 (13.4)	58.8 (15.1)	61.7 (14.8)	<0.001
Waist (cm)	83.4 (12.6)	85.0 (12.4)	85.0 (13.8)	87.0 (15.0)	<0.001
Body mass index (kg/m^2)	23.0 (4.6)	23.2 (4.8)	23.3 (4.8)	23.7 (4.8)	<0.001
HGS (kg)	28.0 (11.0)	29.9 (12.5)	32.0 (13.5)	35.8 (14.5)	<0.001
HGS group, n (%)					
The low quarter of HGS	307 (27.1)	305 (26.9)	278 (24.5)	265 (23.4)	0.11
The upper three quarters of HGS	826 (72.9)	831 (73.1)	856 (75.5)	870 (76.6)	
Systolic blood pressure (mm Hg)	123 (26)	125 (27)	127 (27)	130 (26)	<0.001
Diastolic blood pressure (mm Hg)	73 (15)	74 (15)	75 (16)	77 (16)	<0.001
Blood examinations					
WBCs (×10^9/L)	5.7 (2.3)	5.8 (2.1)	6.0 (2.2)	6.2 (2.3)	<0.001
Haemoglobin (g/L)	137 (22)	142 (22)	145 (23)	148 (24)	<0.001
Platelet (×10^9/L)	219 (91)	208 (92)	208 (94)	201 (92)	<0.001
Blood urea nitrogen (mg/dL)	13.7 (4.6)	14.7 (5.6)	15.1 (5.3)	16.1 (5.5)	<0.001
Fasting glucose (mg/dL)	101 (14)	102 (15)	102 (15)	103 (16)	<0.001
GHbA1c (%)	5.1 (0.4)	5.1 (0.5)	5.2 (0.5)	5.2 (0.5)	<0.01
eGFR (mL/min/1.73 m^2)	100 (12)	97 (14)	94 (17)	89 (19)	<0.001
eGFR group, n (%)					
60~89 mL/min/1.73 m^2	185 (16.3)	296 (26.1)	424 (37.4)	603 (53.1)	<0.001
90~ mL/min/1.73 m^2	948 (83.7)	840 (79.4)	710 (62.6)	532 (46.9)	
Total cholesterol (mg/dL)	187 (46)	192 (47)	191 (48)	195 (46)	<0.001
Triglyceride (mg/dL)	96 (65)	103 (65)	105 (78)	109 (86)	<0.001
HDL cholesterol (mg/dL)	51 (19)	50 (19)	49 (19)	46 (19)	<0.001
LDL cholesterol (mg/dL)	114 (42)	116 (44)	115 (43)	117 (46)	0.13
hs-CRP (mg/L)	0.77 (0.83)	0.92 (1.10)	0.99 (1.30)	1.07 (1.44)	<0.001
Uric acid (mg/dL)	3.1 (0.6)	3.9 (0.3)	4.6 (0.4)	5.7 (1.0)	<0.001
Disease states and corresponding medications					
Hypertension, n (%)	371 (32.7)	440 (38.7)	483 (42.6)	583 (51.4)	<0.001
Antihypertensive therapy, n (%)	149 (13.2)	204 (18.0)	216 (19.1)	295 (26.0)	<0.001
Diabetes mellitus, n (%)	176 (15.5)	172 (15.1)	168 (14.8)	200 (17.6)	0.25

Continued

Table 1 Continued

	Q1 (<3.5 mg/dL) (n=1133)	Q2 (3.5–4.2 mg/dL) (n=1136)	Q3 (4.2–5.0 mg/dL) (n=1134)	Q4 (≥5.0 mg/dL) (n=1135)	P value
Hypoglycaemic therapy, n (%)	57 (5.0)	29 (2.6)	27 (2.4)	40 (3.5)	0.001
Dyslipidaemia, n (%)	612 (54.0)	690 (60.7)	717 (63.2)	763 (67.2)	<0.001
Therapy for dyslipidaemia, n (%)	60 (5.3)	51 (4.5)	65 (5.7)	73 (6.4)	0.23
Self-reported heart disease, n (%)	122 (10.8)	132 (11.6)	128 (11.3)	152 (13.4)	0.24
Therapy for heart disease, n (%)	72 (6.4)	78 (6.9)	78 (6.9)	95 (8.4)	0.27
Self-report rheumatism or arthritis, n (%)	389 (34.3)	383 (33.7)	398 (35.1)	378 (33.3)	0.82
Therapy for rheumatism or arthritis, n (%)	173 (15.3)	154 (13.6)	170 (15.0)	125 (11.0)	0.01
Outcomes, n (%)					
eGFR decline ≥25%	43 (3.8)	57 (5.0)	70 (6.2)	61 (5.4)	0.08
Deterioration of eGFR stage	182 (16.1)	228 (20.1)	231 (20.4)	231 (20.2)	0.02
Decline in eGFR	184 (16.2)	232 (20.4)	237 (20.9)	232 (20.4)	0.02

Data are n (%) or median (IQR).
The HGS was grouped according to the IQR by sex.
eGFR, estimated glomerular filtration rate; GHbA1c, glycosylated haemoglobin A1c; HDL, high-density lipoprotein; HGS, hand grip strength; hs-CRP, high-sensitivity C reactive protein; LDL, low-density lipoprotein; WBCs, white blood cells.

characteristics: were older; had lower eGFR; percentages of female and percentages of individuals with rural residence; had higher education level; percentages of individuals who ever drink and ever smoke; height; weight; BMI; waist circumference; HGS; SBP; DBP; WBC; haemoglobin; BUN; fasting glucose; hs-CRP; percentages of hypertension; antihypertensive therapy rate; prevalence of dyslipidaemia and prevalence of self-reported heart disease.

Association between serum UA and decline in eGFR

The results of univariate analysis are shown in online supplemental table 2. As shown in table 2, after adjustment for age group, sex, marital status, smoking status, education level, residential location, BMI, eGFR group, hypertension, antihypertensive therapy, DM, hypoglycaemic therapy, dyslipidaemia, therapy for dyslipidaemia, self-reported heart disease and therapy for heart disease, the risk of decline in eGFR was higher for quartile 2 (3.5–<4.2 mg/dL: OR 1.44; 95% CI 1.07 to 1.64; p<0.01), quartile 3 (4.2–<5.0 mg/dL: OR 1.72; 95% CI 1.36 to 2.18; p<0.001) and quartile 4 (≥5.0 mg/dL: OR 2.04; 95% CI 1.58 to 2.63; p<0.001) compared with quartile 1 (<3.5 mg/dL), and p for the trend was <0.001.

Sensitivity analysis by potential modifiers

We performed stratified analysis to evaluate the association between the decline in eGFR and serum UA (quartile 1 vs quartiles 2–4) in age group, sex, residential location, education level, smoking status, eGFR group, BMI group, DM, hypertension, self-reported heart disease and dyslipidaemia (table 3). The tendency in each subgroup was almost consistent with the overall tendency (all p for interaction>0.05) except for subgroup of eGFR: 60–89 mL/min/1.73 m^2, DM and self-reported heart disease (p>0.05). Although p values were more than

Table 2 Serum uric acid and the OR of the decline in eGFR stratified by quartiles

Variable	Q1	Q2	Q3	Q4	P for trend
Uric acid					
Participants, no	1133	1136	1134	1135	
Median, mg/dL	3.1	3.9	4.6	5.7	
Events, no (ratio)*	184 (16.2)	232 (20.4)	237 (20.9)	232 (20.4)	
Crude model	1.00 (ref)	1.32 (1.07, 1.64)	1.36 (1.10, 1.67)	1.33 (1.07, 1.64)	0.02
Adjusted model†	1.00 (ref)	1.44 (1.15, 1.81)	1.72 (1.36, 2.18)	2.04 (1.58, 2.63)	<0.001

*Incidence of the decline in eGFR during the follow-up.
†Adjusted for age group, sex, marital status, smoking status, education, residential location, body mass index, eGFR group, hypertension, antihypertensive therapy, diabetes mellitus, hypoglycaemic therapy, dyslipidaemia, therapy for dyslipidaemia, self-report heart disease and therapy for heart disease.
eGFR, estimated glomerular filtration rate.

Table 3 Stratified analyses by potential modifiers of the association between serum uric acid and the decline in eGFR

Subgroup category	Events (rate)*	Adjusted OR (95% CI)	Subgroup category	Events (rate)*	Adjusted OR (95% CI)	P value for interaction
Age, years			Age, years			0.51
45–59			≥60			
Q1	94 (12.1)	Ref	Q1	90 (25.4)	Ref	
Q2–4	307 (15.4)	1.59 (1.22, 2.08)	Q2–4	90 (28.0)	1.77 (1.71, 2.39)	
Sex			Sex			0.38
Men			Women			
Q1	40 (17.2)	Ref	Q1	144 (16.0)	Ref	
Q2–4	394 (21.7)	1.89 (1.28, 2.78)	Q2–4	307 (19.3)	1.55 (1.23, 1.96)	
Residential location			Residential location			0.20
Rural area			Urban area			
Q1	139 (17.4)	Ref	Q1	45 (13.5)	Ref	
Q2–4	471 (21.3)	1.57 (1.24, 1.98)	Q2–4	230 (19.3)	1.94 (1.31, 2.87)	
Education			Education			0.66
Elementary school or below			Middle school or above			
Q1	145 (14.7)	Ref	Q1	39 (14.7)	Ref	
Q2–4	540 (21.7)	1.67 (1.33, 2.10)	Q2–4	191 (18.2)	1.51 (1.00, 2.29)	
Ever smoke			Ever smoke			0.34
Yes			No			
Q1	42 (11.7)	Ref	Q1	142 (16.1)	Ref	
Q2–4	316 (21.8)	2.04 (1.37, 3.02)	Q2–4	385 (19.7)	1.51 (1.20, 1.91)	
eGFR, mL/min/1.73 m^2			eGFR, mL/min/1.73 m^2			0.84
60–89			≥90			
Q1	12 (6.5)	Ref	Q1	172 (18.1)	Ref	
Q2–4	140 (10.6)	1.51 (0.79, 2.85)	Q2–4	561 (27.0)	1.66 (1.34, 2.05)	
BMI, kg/m^2			BMI, kg/m^2			0.65
<24			>24			
Q1	121 (17.6)	Ref	Q1	63 (14.2)	Ref	
Q2–4	420 (21.9)	1.62 (1.25, 2.09)	Q2–4	281 (18.9)	1.74 (1.26, 2.42)	
Diabetes mellitus			Diabetes mellitus			0.84
Yes			No			
Q1	28 (15.9)	Ref	Q1	156 (16.3)	Ref	
Q2–4	106 (19.6)	1.55 (0.93, 2.58)	Q2–4	595 (20.8)	1.64 (1.32, 2.04)	
Hypertension			Hypertension			0.44
Yes			No			
Q1	70 (18.9)	Ref	Q1	114 (15.0)	Ref	
Q2–4	353 (23.4)	1.72 (1.25, 2.36)	Q2–4	348 (18.3)	1.65 (1.27, 2.14)	
Self-reported heart disease			Self-reported heart disease			0.94
Yes			No			
Q1	22 (18.0)	Ref	Q1	162 (16.0)	Ref	
Q2–4	89 (21.6)	1.55 (0.86, 2.78)	Q2–4	612 (20.5)	1.64 (1.33, 2.04)	
Dyslipidaemia			Dyslipidaemia			0.74
Yes			No			
Q1	95 (15.5)	Ref	Q1	89 (17.1)	Ref	
Q2–4	434 (20.0)	1.64 (1.26, 2.15)	Q2–4	267 (21.6)	1.65 (1.23, 2.23)	

The model was adjusted, if not stratified, for age group, sex, marital status, smoking status, education, residential location, body mass index, eGFR group, hypertension, antihypertensive therapy, diabetes mellitus, hypoglycaemic therapy, dyslipidaemia, therapy for dyslipidaemia, self-report heart disease and therapy for heart disease.
*Incidence rate of the GFR decline during the follow-up.
BMI, body mass index; eGFR, estimated glomerular filtration rate.

0.05 in those subgroups, the OR of decline in eGFR was higher in elevated UA group (quartile 1 vs quartiles 2–4).

DISCUSSIONS

In the 4-year representative nationwide cohort (CHARLS), we found that elevated UA levels were associated with the decline in eGFR in middle-aged and elderly Chinese populations with normal renal function, and higher UA levels implied a higher risk of decline in eGFR.

Although the association between UA and adverse renal events has been evaluated in numerous previous studies, to date, no consistent results have been obtained. Several cohort studies from Western countries, such as the USA, Italy and Australia, appeared to demonstrate that increased UA levels were associated with adverse renal events.[15 17 27–29] Similarly, some prospective cohort studies from East Asian countries indicated that elevated serum UA levels were associated with decreased renal function, increased CKD incidence or ESRD onset.[18 30–34] Although the endpoints of the above-mentioned studies were slightly different from those in this study, all these studies indicated that hyperuricaemia could lead to renal impairment, which is basically consistent with this study. What is noteworthy is that some studies obtained a UA cut-off point to predict kidney outcome, which was based on an L-shaped relationship between the UA and adverse renal events.[14 18 27 35] In addition, a study by Wang *et al*, including 94 422 participants from Taiwan, found that serum UA level and the occurrence of CKD exhibited a J-shaped relationship, such that, when serum UA was greater than 7.3 mg/dL or less than 2.0 mg/dL, the CKD risk increased.[16] Also, a cross-sectional study based on data from 90 143 participants from Japan reported that hypouricaemia was associated with kidney disease.[36] In this study, we did not observe a J-shaped relationship between a decline in eGFR and UA levels, which might be due to too few individuals with hypouricaemia. However, some prospective cohort studies did not find a significant association between increased and adverse kidney events.[14 20 21] In a Japanese cohort of 48 177 individuals, hyperuricaemia did not serve as an independent predictor for ESRD in males after correcting multiple confounders.[14] Furthermore, several studies showed that the relationship between elevated UA and CKD progression disappeared after adjustment of other risk factors.[20 21] Regarding the population with DM, a cross-sectional study by Rosolowsky *et al* reported that in individuals with DM, high serum UA levels were associated with decreased eGFR.[37] Zoppini *et al* conducted a prospective cohort study in patients with DM and found that elevated UA levels increased the risk of CKD incidence.[17] In the subgroup analysis in this study, no significant association was found between the decline in eGFR and increased blood UA in the population with diabetes. A possible explanation for these discrepant findings may lie in the different outcomes and follow-up times used in these studies. In a prospective cohort with 411 participants with hypertension, Hung *et al* found that elevated UA level was associated with decreased renal function.[31] In this study, we observed a similar trend in the population with or without hypertension. In summary, although the association between elevated UA level and the decline in eGFR remains unclear, the CHARLS dataset provided an opportunity to examine the association between serum UA levels and the decline in eGFR in middle-aged and older adults, with correction for multiple covariates and many subgroup analyses.

The effect of UA on kidney function is complicated. The most widely accepted mechanism is that crystal deposition occurs in kidney when serum UA exceeds 7 mg/dL.[38] Other mechanisms include oxidative stress, endothelial dysfunction, renal fibrosis and inflammation, which would lead to DNA damage, enzyme inactivation, cell apoptosis, glomerulosclerosis, interstitial fibrosis, hyperfiltration and inflammatory response activation, eventually causing GFR deterioration or onset of urine protein.[38 39] Pathologically, UA seems to cause renal impairment through multiple pathways. However, two recently published high-quality randomised controlled trials (RCTs) found that UA-lowering therapy could not confer significant renal benefit in patients with CKD.[40 41] Therefore, the causal relationship between elevated UA and CKD is still a matter of further research. Importantly, the aforementioned RCTs were conducted with UA-lowering therapy in a population with CKD stages 2–4 and could not determine whether the population with normal renal function would benefit from such UA-lowering therapy. In this study, we found that elevated UA levels were associated with the decline in eGFR. However, whether early intervention in a healthy population with hyperuricaemia could benefit the kidney function still needs further study.

There were some limitations in this study. First, the lack of duplicate blood tests made the baseline data less robust and reliable. Second, data on urinary protein, renal imaging, as well as renal pathology, were lacking in CHARLS, which might create bias in the statistical results. Third, we did not consider the CKD occurrence as a study outcome in this study due to the lack of urinary protein data. Fourth, the rate of missing visit was high during the follow-up period, which would cause selection bias (online supplemental table 1).

CONCLUSIONS

Over a 4-year follow-up period, we observed that elevated UA levels were associated with a decline in eGFR in the middle-aged and elderly individuals without CKD. Early UA-lowering therapy in the population with hyperuricaemia with normal renal function might delay the deterioration of renal function. However, certainly, this inference needs to be further confirmed by RCT studies.

Acknowledgements The authors are grateful to the China Health and Retirement Longitudinal Study (CHARLS) team for providing the data.

Contributors PL, YL and SC—analysis and interpretation of data and preparation of the manuscript. KH and XS—data cleaning. LL and YL—study concept and

design of the manuscript. ML and YL—preparation and critical review of the manuscript. ML—responsible for the overall content as the guarantor. All authors read, provided feedback and approved the final manuscript.

Funding This work was supported by joint grants from the City and University (College) of Guangzhou Science and Technology Bureau (SL2022A03J01092).

Competing interests None declared.

Patient and public involvement The data of this study were anonymized. Patients and the public were not involved in the design or conduct, or reporting, or dissemination plans of the study.

Patient consent for publication Not required.

Ethics approval This study involves human participants and the Medical Ethics Review Committee of Peking University approved this study, and all participants provided written informed consent before participating. The IRB approval number for the main household survey, including anthropometrics, was IRB00001052-11015; the IRB approval number for biomarker collection was IRB00001052-11014. This study was a secondary analysis of a public dataset and did not require ethics approval again.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement Data are available upon reasonable request. CHARLS data of the study will be available to investigators at the CHARLS website (http://charls.pku.edu.cn/en).

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Association of uric acid with the decline in estimated glomerular filtration rate in middle-aged and elderly populations: evidence based on the China Health and Retirement Longitudinal Study

Supplemental Table 1. Baseline characteristics of participants included and excluded in the study

Characteristics	participants included in baseline (n=7769)	participants included in the baseline and excluded after follow-up (n=3231)	participants included in the study (n=4538)	*P*-value
Demographic and biomarker indicators				
Age (years)	58 (52~65)	58 (52~66)	58 (52~64)	0.51
45~59	4370 (56.2)	1,797 (55.6)	2,573 (56.7)	0.34
60~	3399 (43.8)	1,434 (44.4)	1,965 (43.3)	
Female [*n* (%)]	4170 (53.7)	1676 (51.9)	2494 (55.0)	<0.01
Married with spouse [*n* (%)]	6490 (83.5)	2626 (81.3)	3864 (85.2)	<0.001
Education				
Middle school and below [*n* (%)]	5471 (70.4)	2248 (69.6)	3223 (71.0)	0.17
High school and above [*n* (%)]	2298 (29.6)	983 (30.4)	1315 (29.0)	
Ever drink [*n* (%)]	3032 (39.0)	1272 (39.4)	1760 (38.8)	0.60
Ever smoke [*n* (%)]	3010 (38.7)	1309 (40.5)	1701 (37.5)	<0.01
Rural region [*n* (%)]	5021 (64.6)	2009 (62.2)	3012 (66.4)	<0.001
Height (m)	1.58 (1.52~ 1.64)	1.58 (1.52~1.64)	1.58 (1.52~1.64)	0.72
Weight (kg)	57.8 (51.0~65.7)	57.3 (50.3~65.2)	58.2 (51.4~65.9)	<0.01
Waist (cm)	84.9 (78.0~92.0)	84.0 (77.4~91.2)	85.0 (78.6~92.3)	<0.01
Body mass index (kg/m^2)	23.1 (20.9~25.8)	22.9 (20.6~25.6)	23.3 (21.1~25.9)	<0.001
HGS (kg)	31.0 (25.0~39.0)	30.5 (24.5~39.0)	31.0 (25.0~39.0)	0.74
HGS group [*n* (%)]				
The low quarter of HGS	1955 (25.2)	882 (27.3)	1073 (23.6)	<0.001
The upper three quarters of HGS	5814 (74.8)	2349 (72.7)	3465 (76.4)	
Systolic blood pressure (mmHg)	126 (114~141)	127 (115~141)	126 (114~141)	0.19
Diastolic blood pressure (mmHg)	75 (67~83)	75 (67~83)	74 (67~83)	0.36
Blood examination				
WBCs (×10^9/L)	5.9 (5.0~7.2)	6.0 (5.0~7.3)	5.9 (5.0~7.2)	0.08
Hemoglobin (mg/dL)	14.2 (13.1~15.5)	14.2 (13.0~15.5)	14.3 (13.1~15.5)	0.82
Platelet (×10^9/L)	207 (163~254)	204 (160~251)	209 (164~257)	<0.01
Blood urea nitrogen (mg/dL)	15.0 (12.5~18.0)	15.0 (12.5~18.0)	14.9 (12.5~17.9)	0.23
Fasting glucose (mg/dL)	101.7 (94.5~110.2)	101.5 (94.3~110.5)	101.9 (94.9~109.8)	0.20
GHbA1c (%)	5.1 (4.9~5.4)	5.1 (4.9~5.4)	5.1 (4.9~5.4)	0.89
Total cholesterol (mg/dL)	191.0 (168.6~215.3)	191.0 (168.6~214.9)	191.6 (168.6~215.7)	0.35
Triglyceride (mg/dL)	102.7 (74.3~145.1)	101.8 (74.3~144.3)	103.5 (74.3~146.0)	0.36
HDL cholesterol (mg/dL)	49.5 (40.6~59.9)	50.0 (41.0~60.3)	49.1 (40.6~59.5)	0.12
LDL cholesterol (mg/dL)	115.2 (94.3~138.0)	115.2 (94.7~138.0)	115.6 (94.3~138.0)	0.71
hs-CRP (mg/L)	0.94 (0.55~1.74)	0.95 (0.56~1.75)	0.92 (0.54~1.73)	0.24
Uric acid (mg/dL)	4.3 (3.6~5.1)	4.4 (3.6~5.2)	4.2 (3.5~5.0)	<0.001
Q1	1937 (24.9)	733 (22.7)	1204 (26.5)	<0.001
Q2	1941 (25.0)	764 (23.6)	1177 (26.0)	

Q3	1947 (25.1)	862 (26.7)	1085 (23.9)	
Q4	1944 (25.0)	872 (27.0)	1072 (23.6)	
eGFR (mL/min/1.73m^2)	95.0 (85.1~102.5)	93.8 (83.5~102.0)	95.9 (86.3~102.7)	<0.001
60~89 mL/min/1.73m^2	2780 (35.8)	1272 (39.4)	1,508 (33.2)	<0.001
90~ mL/min/1.73m^2	4989 (64.2)	1959 (60.6)	3,030 (66.8)	
Disease states and corresponding medications				
Hypertension [*n* (%)]	3180 (40.9)	1303 (40.3)	1877 (41.4)	0.36
Antihypertensive therapy [*n* (%)]	1470 (18.9)	606 (18.8)	864 (19.0)	0.75
Diabetes mellitus [*n* (%)]	1256 (16.2)	540 (16.7)	716 (15.8)	0.27
Hypoglycemic therapy [*n* (%)]	267 (3.4)	114 (3.6)	153 (3.4)	0.74
Heart disease [*n* (%)]	892 (11.5)	358 (11.1)	534 (11.8)	0.35
Therapy for heart disease [n (%)]	543 (7.0)	220 (6.8)	323 (7.1)	0.60
Dyslipidemia [n (%)]	4702 (60.5)	1920 (59.4)	2782 (61.3)	0.10
Therapy for dyslipidemia [n (%)]	363 (4.7)	114 (3.5)	249 (5.5)	<0.001
Rheumatism [n (%)]	2653 (34.2)	1105 (34.2)	1548 (34.1)	0.94
Therapy for rheumatism [n (%)]	1021 (13.1)	399 (12.4)	622 (13.7)	0.08

Data are *n* (%) or median (interquartile range); HGS: handgrip strength; WBCs: white blood cell; GHbA1c: glycosylated hemoglobin A1c; HDL: high-density lipoprotein; LDL: low-density lipoprotein; hs-CRP: high-sensitivity C-reactive protein; eGFR: estimated glomerular filtration rate.

The Mann-Whitney U test was for continuous variables and $\chi 2$ test was for categorical variables between Group 1 and Group 2 respectively.

Supplemental Table 2. Univariate analysis of variables between eGFR decline group and non-eGFR decline group

Variables	Coef.	95% Conf. Interval	*P*-value
Demographic and biomarker indicators			
Age (years)			
45~59	ref		
60~	0.808	0.659 to 0.957	<0.001
Sex			
Female	ref		
Male	0.200	0.053 to 0.347	0.01
Married with spouse [*n* (%)]	0.298	0.103 to 0.493	<0.01
Education			
Middle school and below [n (%)]	ref		
High school and above [*n* (%)]	-0.185	-0.351 to -0.019	0.03
Ever drink [*n* (%)]	0.058	-0.093 to 0.208	0.45
Ever smoke [*n* (%)]	0.156	0.006 to 0.306	0.04
Rural region [*n* (%)]	0.144	-0.014 to 0.302	0.07
Height (m)	-0.198	-1.083 to 0.688	0.66
Weight (kg)	-0.011	-0.018 to -0.004	<0.01
Waist (cm)	-0.005	-0.013 to 0.002	0.19
Body mass index (kg/m^2)	-0.036	-0.056 to -0.015	<0.01
HGS group			

The low quarter of HGS	ref		
The upper three quarters of HGS	-0.143	-0.308 to 0.022	0.09
Systolic blood pressure (mmHg)	0.008	0.005 to 0.012	<0.001
Diastolic blood pressure (mmHg)	0.001	-0.006 to 0.007	0.88
Blood examinations			
WBC (10^9/L)	0.014	-0.027 to 0.055	0.51
Hemoglobin (mg/dL)	-0.062	-0.099 to -0.024	<0.01
Platelet (10^9/L)	-0.001	-0.002 to 0.001	0.11
Blood urea nitrogen (mg/dL)	0.012	-0.005 to 0.030	0.16
Fasting glucose (mg/dL)	-0.004	-0.009 to 0.001	0.10
GHbA1c (%)	0.018	-0.151 to 0.187	0.83
eGFR group (mL/min/1.73m^2)			
60~89	ref		
90~	1.046	0.859 to 1.233	<0.001
Total cholesterol (mg/dL)	-0.002	-0.004 to -0.001	0.04
Triglyceride (mg/dL)	-0.001	-0.002 to -0.001	0.03
HDL cholesterol (mg/dL)	-0.001	-0.005 to 0.004	0.84
LDL cholesterol (mg/dL)	-0.002	-0.004 to 0.001	0.08
hs-CRP (mg/L)	0.037	-0.019 to 0.093	0.20
Uric acid (mg/dL)	0.046	-0.015 to 0.108	0.14
Uric acid group			
Q1	ref		
Q2	0.280	0.067 to 0.494	0.01
Q3	0.309	0.096 to 0.523	<0.01
Q4	0.281	0.068 to 0.495	0.01
Disease states and corresponding medications			
Hypertension [*n* (%)]	0.325	0.178 to 0.473	<0.001
Antihypertensive therapy [*n* (%)]	0.298	0.120 to 0.476	<0.01
Diabetes mellitus [*n* (%)]	-0.060	-0.264 to 0.144	0.56
Hypoglycemic therapy [*n* (%)]	0.007	-0.399 to 0.413	0.97
Heart disease [*n* (%)]	0.091	-0.132 to 0.314	0.43
Therapy for heart disease [n (%)]	0.259	-0.137 to 0.527	0.06
Dyslipidemia [n (%)]	0.264	-0.038 to 0.566	0.09
Therapy for dyslipidemia [n (%)]	-0.080	-0.230 to 0.07	0.30
Rheumatism [n (%)]	0.057	-0.097 to 0.211	0.47
Therapy for rheumatism [n (%)]	0.168	-0.038 to 0.374	0.11

HGS: handgrip strength; WBC: white blood cell; GHbA1c: glycosylated hemoglobin A1c; eGFR: estimated glomerular filtration rate; HDL: high density lipoprotein; LDL: low density lipoprotein; hs-CRP: high-sensitivity C-reactive protein.

The hand grip strength was grouped according to the interquartile range by sex. The lower quarter of the grip strength was group 1, and the upper three quarters were group 2. Serum uric acid is divided into Q1, Q2, Q3 and Q4 groups by one-quarter percentile.