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The relationship between serum uric acid and clustering of cardiovascular disease risk factors, renal disorders among Shanghai population

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3 **The relationship between serum uric acid and clustering of cardiovascular disease risk factors,**
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6 **renal disorders among Shanghai population**
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ABSTRACT

Objectives To estimate the current prevalence of cardiovascular disease risk factors (CRFs) and renal disorders across serum uric acid (SUA) quartiles, and evaluate the relationships between SUA and CRFs, renal diseases in Shanghai population.

Study design Observational, cross-sectional study.

Setting Data were obtained from physical checkups of local residents at three hospitals in Shanghai.

Participants Residents were invited to take part in physical checkups at three hospitals and provided informed consents. Exclusion criteria were diseases that resemble cancer, hepatic disease and other coexisting illnesses including autoimmune kidney diseases, renal artery stenosis, individuals unable to provide complete information. There are 27176 individuals in our study.

Primary and secondary outcome measures Hyperuricemia was defined as serum uric acid ≥ 7 mg/dL in males and ≥ 6 mg/dL in females. The subjects were divided into gender-specific quartiles. We estimate the current prevalence of cardiovascular disease risk factors (CRFs) and renal disorders across serum uric acid (SUA) quartiles. The relationships between SUA and CRFs, renal disorders at different gender were evaluated with logistic regression analysis.

Results: There was a significant increase in the prevalence of major CRFs and renal diseases across SUA quartiles in separate analysis among men and women (all P -trend <0.001). After multiple adjustment, hyperuricemia positively connected with overweight/obesity, hypertension, dyslipidemia, renal insufficiency, albuminuria, acid urine, nephrolithiasis, but negatively connected with diabetes mellitus and alkaline urine (all $P<0.05$). Women had a stronger association between hyperuricemia and clustered CVD (cardiovascular disease) risk factors, CKD than men.

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3 **Conclusions:** In Shanghai population, concomitant with the elevated level of serum uric acid, the
4 prevalence rate of CRFs and renal diseases was rising. Hyperuricemia was significantly associated with
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6 CVD risk factors and renal disorders. Therefore, target inhibition of SUA level may have potential to
7
8 become an effective therapy in alleviating risks of CVDs and renal disorders, especially in females.
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13 **KEY WORDS:** Serum uric acid, CVD risk factors, renal disorders
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16 17 18 **ARTICLE SUMMARY**

19 20 **Article focus**

- 21 ● The current prevalence of cardiovascular disease risk factors (CRFs) and renal diseases across serum
22 uric acid (SUA) quartiles.
- 23 ● The relationships between SUA and CRFs, renal disorders in Shanghai population.
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30 31 **Key messages**

- 32 ● In Shanghai population, concomitant with the elevated level of serum uric acid, the prevalence rate of
33 CRFs and renal diseases was rising.
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37 ● Hyperuricemia was significantly associated with CVD risk factors and renal disorders, especially in
38 females.
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43 44 **Strengths and limitations of this study**

- 45 ● We conducted a multi-center study with large sample size which ensured sufficient power in
46 obtaining the accurate prevalent rate of cardiovascular disease risk factors (CRFs) and renal diseases
47 and analyzing the relationship between SUA and CRFs, renal disorders across SUA quartiles.
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51 ● The relationship was analyzed in both sexes and we got a solid conclusion about the differences
52 between men and women.
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- It was a cross-section study and the results could not establish causative relationships between hyperuricemia and CRFs clustering and renal diseases. Future follow-up studies are required for more accurate evaluation of these relationships.
- The data were from three medical centers' databases that lacks details in smoking, drinking, lifestyles and thus this might affect the deviations of some clinical outcomes.

INTRODUCTION

Uric acid (UA) is the final degradation product of purine metabolism in the liver, muscles and intestines¹. A high level of serum uric acid (SUA) is correlated with multiple disorders such as metabolic syndrome, cardiovascular disease as well as kidney diseases²⁻⁶. The association between hyperuricemia and CVD risk factors has been widely focused since the last century⁷. There are various risk factors involved in CVDs, including age, sex, obesity, hypertension, diabetes mellitus, dyslipidemia, family history, smoking, depression and so on⁸⁻¹². Numerous indexes of CVDs risk factors were closely associated with increased serum uric acid, such as body mass index (BMI), cholesterol, triglyceride, low-density lipoprotein (LDL), and high-density lipoprotein (HDL), systolic blood pressure (SBP), diastolic blood pressure (DBP), fasting plasma glucose (FPG)^{5 13-20}. However, the relationship between hyperuricemia and cardiovascular disease risk factors (CRFs) at different gender of Shanghai population has not been well studied. And the data from multiple clinical centers in China are extremely limited. In this study, we evaluated the prevalence of major CRFs (obesity, hypertension, diabetes mellitus, dyslipidemia) across SUA quartiles and analyzed the association of these factors with SUA level respectively in both men and women.

It has been documented that 70% of the daily UA production is excreted by the kidney²¹. UA tends to crystalize in low urine pH. Hyperuricemia reduces urine pH, and increases the risk of formation of

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3 urate stones²². Although early clinical studies did not find the association of UA with renal abnormalities
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6²³⁻²⁷, recent research indicated that serum uric acid level could predict the development of albuminuria²⁸.

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8 A prospective study demonstrated that high serum uric acid level is an independent risk factor for
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10 estimated glomerular filtrate rate (eGFR) decline²⁹. However, whether UA is a cause or an association to
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12 renal diseases is a question that still waits for further investigations. Thus, we assessed the prevalence of
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14 renal diseases across SUA quartiles, and the relationship between serum uric acid and renal disorders in
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16 Shanghai population.
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19 20 **METHODS**

21 22 **Study population**

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24 The permanent residents aged between 16-98 years who participated in the health checkups during the
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26 period from January 2015 and December 2015 of three medical centers Shanghai East Hospital Affiliated
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28 to Tongji University School of Medicine, Pudong New District Gongli Hospital and Baoshan Branch of
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30 Shanghai First People's Hospital were invited in the study. After excluding subjects with incomplete data,
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32 cancer, hepatic disease or other coexisting illnesses including autoimmune kidney diseases, renal artery
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34 stenosis, 27176 participants were enrolled in our study.
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39 40 **The primary outcomes**

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42 Hyperuricemia was defined as serum uric acid ≥ 7 mg/dL in males and ≥ 6 mg/dL in females or current use
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44 of uric acid (UA)-lowering drugs³⁰. SUA was determined using the uricase-peroxidase method.
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47 48 **Study definitions**

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50 Body mass index (BMI) was calculated as weight in kilograms divided by height in squared meters.
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52 According to WHO guidelines for the Asian Pacific population, normal weight was defined as $18.5 \leq \text{BMI}$
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54 < 24.0 kg/m², overweight was defined as $24.0 \leq \text{BMI} < 28.0$ kg/m², obesity was defined as $\text{BMI} \geq 28.0$
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3 kg/m², underweight was defined as BMI <18.5 kg/m² ³¹. Blood pressure measurements were taken
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5 according to the Joint National Committee VII criteria (JNC VII)³². Normal BP was defined as having
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7 SBP<120 mmHg and DBP<80 mmHg. Pre-hypertension was defined as having SBP of 120–139 mmHg
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9 and/or DBP of 80–89 mmHg. Grade 1 hypertension was defined as having SBP of 140–159 mmHg
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11 and/or DBP of 90–99 mmHg. Grade 2 or grade 3 hypertension was defined as SBP ≥160 mmHg and/or
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13 DBP ≥100 mmHg³². According to the Chinese adult dyslipidemia prevention guide (2007 edition),
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15 individuals with a fasting TC ≥6.22 mmol/L, TG ≥2.26 mmol/L, HDL-C<1.04 mmol/L, and/or
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17 LDL-C>4.14 mmol/L, or currently undergoing pharmacologic treatment were defined as the dyslipidemia
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19 ³³. T2D was defined based on World Health Organization (WHO) 1999 diagnostic criteria as fasting plasma
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21 glucose ≥7.0mmol/l or 2-h plasma glucose ≥11.1mmol/l, impaired fasting glucose (IFG) was defined as
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23 6.1 mmol/l ≤ FPG < 7.0 mmol/l, and normal condition was defined as FPG <6.1 mmol/l³⁴. The eGFR was
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25 calculated using Modification of Diet in Renal Disease (MDRD) formula ³⁵: 186×[serum creatinine (mg/
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27 dl)]-1.154×(age)-0.203×[0.742 (if female)]. According to the Kidney Disease Outcomes Quality Initiative
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29 (KDOQI) clinical practice guideline, estimated glomerular filtration rate (eGFR) <60 mL/min/1.73 m²,
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31 proteinuria and hematuria were defined as markers of CKD³⁶. Urine proteinuria were recorded as negative
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33 (-), trace, 1+, 2+ and 3+. Albuminuria was defined as ≥1+.

44 45 **Data collection**

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47 The subjects participating in the study attended to the medical center in the morning after overnight
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49 fasting for at least 12 hours. After 5 minutes resting, sitting blood pressure was measured in right arm by
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51 a trained medical staff using an electronic blood pressure monitor. The resting BP was measured three
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53 times with five minutes intervals between them, and then the averages were calculated, which were used
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3 for further analysis. Blood samples were obtained on their arrival at the medical center and fasting
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5 glucose (FPG) were measured by the hexokinase method, total cholesterol, low-density
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7 lipoprotein-cholesterol (LDL-C), high-density lipoprotein-cholesterol (HDL-C), triglyceride, blood urea
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9 nitrogen (BUN), creatinine, serum uric acid were measured in an automated bio-analyzer (Hitachi, Tokyo,
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11 Japan). Midstream urine specimen was collected for urinary analysis by the dipstick method. Urine pH
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13 and proteinuria were recorded as categorical data.
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18 After blood and urine sampling, basic characteristics and medical history were collected by medical
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20 staff. Anthropometric measurements including height and body weight were obtained according to a
21
22 standardized protocol. Renal ultrasonography scanning was performed and measured by an experienced
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24 radiologist using GE LOGIQ P5 scanner (GE Healthcare, Milwaukee, SUA) who was blinded to the
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26 subjects' medical information.
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32 **Patient and public involvement**

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34 No patient was involved in the design or conduct of the study, but the results of the study will be shared
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36 to patients coming for follow-up.
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40 **Statistical analysis**

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42 We divided the subjects into gender-specific quartiles [males (M): Q1 ≤ 4.9, Q2: 5.0-5.9, Q3: 6.0-6.9, Q4
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44 ≥ 7.0 mg/dL; females (F): Q1 ≤ 3.9, Q2: 4.0-4.9, Q3: 5.0-5.9, Q4 ≥ 6.0mg/dL] according to serum uric
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46 acid level. Continuous variables with a normal distribution were presented as the mean ± standard
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48 deviation. Categorical variables were described by frequency and percentage. Analysis of variance
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50 (ANOVA) was used to calculate the differences between continuous variables. Chi-square test was used
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52 for comparisons of categorical variables among groups. Pearson's correlation test was used to assess the
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3 association between serum UA level and various clinical parameters. Multivariable logistic regression
4 analysis (unadjusted and full-adjusted) was used to calculate the odds ratio for hyperuricemia according
5 to different status of clinical parameters. Furthermore, multivariable logistic regression analysis (multiple
6 adjusted models) was used to examine the association between related diseases and the SUA categories of
7 Q2 or greater compared to the lowest SUA category. The association between hyperuricemia and
8 clustered CVD risk factors had been calculated. Statistical analyses were performed by IBM SPSS
9 statistics version 20.0 (SPSS, Chicago, IL, USA). Statistical significance was set at *P*-values of <0.05.

20 RESULTS

23 Clinical characteristics of participants in quartiles of serum uric acid level.

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25 A total of 27,176 participants with mean age 48.88 ± 15.48 years, and 15300 (56.3%) men and 11876
26 (43.7%) women completed in the study. The prevalence rates of hyperuricemia of men and women were
27 22.3 % (95% confidence intervals 20.9–23.7%) and 11.1% (9.4–12.8%), respectively. Female individuals
28 with higher level of SUA were older than the age of males. With increasing quartiles of SUA, participants
29 had more CVDs risk factors (obesity, hypertension, dyslipidemia) and renal diseases (chronic kidney
30 disease, nephrolithiasis), as well as elevated levels of body mass index, systolic blood pressure, diastolic
31 blood pressure, total cholesterol, triglyceride, low density lipoprotein cholesterol, creatinine, blood urea
32 nitrogen (BUN), and decreased levels of high density lipoprotein cholesterol, estimated glomerular
33 filtration rate in both men and women (Table 1, all *P* values for trend <0.001).

50 The prevalence of CVD risk factors, renal diseases in quartiles of serum uric acid level

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52 As demonstrated in Figure 1, there was a significant increase in the prevalence of cardiovascular disease
53 risk factors and renal disorders across SUA quartiles in men and women (all *P* value for trend <0.001). In
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3 the male hyperuricemia individuals, the prevalence rates of obesity, hypertension, diabetes mellitus,
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6 dyslipidemia, chronic kidney disease and nephrolithiasis were 23.8% (95% CI, 20.9-26.7%), 35.7%
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8 (33.0-38.4%), 4.9% (1.6-8.2%), 54.3% (52.0-56.6%), 7.0% (3.8-10.2%) and 18.6% (15.6-21.6%)
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10 respectively. In the female hyperuricemia individuals, the prevalence rates of obesity, hypertension,
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13 diabetes mellitus, dyslipidemia, chronic kidney disease and nephrolithiasis were 23.8% (19.1-28.5%),
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15 43.2% (39.1-47.3%), 10.0% (4.9-15.1%), 45.8% (41.8-49.8%), 12.9% (7.9-17.9%) and 16.9%
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17 (12.0-21.8%) respectively.
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23 **The correlation between serum uric acid and various clinical parameters**

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25 We used Pearson's correlation analysis to investigate the relationships and the results were shown in
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27 Table 2. In men, the level of serum uric acid was positively correlated with BMI, SBP, DBP, TC, TG,
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29 LDL-C, and negatively correlated with age, FPG, HDL-C and eGFR (all P values<0.001). In women, the
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31 level of serum uric acid was positively correlated with age, BMI, SBP, DBP, FPG, TC, TG, LDL-C, and
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33 negatively correlated with HDL-C and eGFR (all P values<0.001).
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40 **The association between hyperuricemia and the clinical outcome**

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42 Multivariable logistic regression models (unadjusted and full-adjusted) were analyzed and the results
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44 were shown in Table 3 with the odds ratio for hyperuricemia according to different clinical outcome. We
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46 found that after adjustment for confounders, increased levels of BMI, BP, triglyceride, LDL-C,
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48 albuminuria all are positively related to increased odds ratio of hyperuricemia. Renal insufficiency, acid
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50 urine, nephrolithiasis also positively correlated with hyperuricemia, however, FPG and alkaline urine
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52 negatively correlated with hyperuricemia in both gender (all P values<0.05). These results suggested that
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3 the individuals with overweight/obesity, hypertension, dyslipidemia, renal insufficiency, massive
4 albuminuria, acid urine, nephrolithiasis were more susceptible to hyperuricemia in both men and women.
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10 **The relationship between different levels of serum uric acid and CVDs risk factors, renal disorders**

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12 Multivariable logistic regression analysis (multiple adjusted models) was studied and the results were
13 shown in Table 4. The odd ratio for obesity, hypertension, diabetes mellitus, dyslipidemia, chronic kidney
14 disease, nephrolithiasis in the highest SUA quartile was 3.115 (95% CI 2.604–3.727, $P < 0.001$, model 3),
15 1.290 (95% CI 1.136–1.465, $P < 0.001$, model 3), 0.205 (95% CI 0.165–0.255, $P < 0.001$, model 3), 2.503
16 (95% CI 2.226–2.815, $P < 0.001$, model 3), 6.962 (95% CI 4.921–9.851, $P < 0.001$, model 3), 1.480 (95%
17 CI 1.272–1.722, $P < 0.001$, model 3) compared with that in the lowest SUA quartile, respectively, in men.
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28 The data in table 5 were multivariable logistic regression analysis in women and the odd ratio for
29 obesity, hypertension, diabetes mellitus, dyslipidemia, chronic kidney disease, nephrolithiasis in the
30 highest SUA quartile was 3.755 (95% CI 2.956–4.769, $P < 0.001$, model 3), 1.287 (95% CI 1.075–1.539,
31 $P = 0.006$, model 3), 0.514 (95% CI 0.377–0.701, $P < 0.001$, model 3), 3.675 (95% CI 3.114–4.336, P
32 < 0.001 , model 3), 11.508 (95% CI 7.242–18.288, $P < 0.001$, model 3), 1.239 (95% CI 1.008–1.522, P
33 $= 0.042$, model 3) compared with that in the lowest SUA quartile, respectively.
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43 From multivariable logistic regression analysis in men and women we concluded that hyperuricemia
44 positively correlated with obesity, hypertension, dyslipidemia, chronic kidney disease, nephrolithiasis, but
45 negatively correlated with diabetes mellitus (all $P < 0.05$) in both gender. Furthermore, females had
46 stronger association between hyperuricemia and chronic kidney disease than males.
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55 **The association between hyperuricemia and clustered CVD risk factors.**

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Multivariable logistic regression was analyzed for hyperuricemia and clustered CVD risk factors, the results were shown in Table 6. After adjustment for age, compared with the group of zero CVD risk factor reference group, the odd ratio for group of ≥ 3 CVD risk factors was 3.804 (95% CI 3.252–4.450, $P < 0.001$), 6.265 (95% CI 4.945–7.938, $P < 0.001$) in men and women, respectively. The individuals with more CVD risk factors were associated with the higher ORs of hyperuricemia both in men and women (P for trend < 0.001). Furthermore, females had a stronger association of hyperuricemia with clustered CVD risk factors than males.

DISCUSSION

In present study, we found that increasing prevalence of CVD risk factors and renal disorders was predominantly associated with increased SUA level in Shanghai population. Moreover, our results demonstrated that the level of uric acid correlated negatively with age in men, but positively with the age in women. The gender-related differences between serum uric acid level and age could be resulted from sex hormones³⁷. One of the interesting findings in our investigation was that the higher level of SUA was positively correlated with the higher prevalence rates of diabetes mellitus in women, but inversely correlated with that in men. Further, the Pearson's correlation analysis demonstrated that the level of SUA positively correlated with fasting plasma glucose in women, but negatively in men, which may be due to the differences in lifestyles, occupations and sex hormones between men and women. However, multivariable logistic regression analysis after adjustment of confounding factors showed inverse association of serum uric acid with diabetes mellitus in both men and women, and this is probably due to the presence of high level of blood glucose which promotes renal excretion of serum uric acid. It has been indicated that hyperglycaemia worsens the function of beta cells and deteriorates glycemic control, which

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3 gradually elevates the rate of renal glomerular filtration.³⁸The hyperfiltration due to multiple kidney
4 disorders will lead to increase of the excretion of uric acid, and it will be more susceptible to diabetic
5 nephropathy with decreasing eGFR³⁹.
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10 Based on our data, hyperuricemia had a remarkable association with cardiovascular disease risk
11 factors and renal disorders. The more CVD risk factors individuals had, the higher ORs of hyperuricemia
12 were observed in both genders. There were numerous mechanisms involved in the close association
13 between serum uric acid and CVDs^{20 40-42} Uric acid stimulates platelet-derived growth factor receptor β
14 (PDGFR β) phosphorylation, leading to vascular smooth muscle cell (VSMC) proliferation⁴⁰. Uric acid
15 increases oxidative stress and stimulates the activation of renin-angiotensin system, resulting in the
16 senescence and apoptosis of human umbilical vein endothelial cells (HUVECs)⁴¹. Uric acid also can
17 cause mitochondrial alterations and decreased intracellular ATP production and subsequently result in
18 endothelial dysfunction in human aortic endothelial cells (HAECs)⁴². A large quantity of animal
19 experiments and human epidemiological documents indicated that SUA-lowering treatment was beneficial
20 for cardiovascular diseases^{20 43-45}.
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37 On the other hand, the related mechanisms in the link between hyperuricemia and chronic kidney
38 disease (CKD) were not well investigated. It was demonstrated that 70% of urate eliminated occurs in the
39 kidneys, and decreased eGFR would result in elevated levels of SUA⁴⁶. However, uric acid could induce
40 oxidative stress, trigger activation of RAAS and inflammation, cause endothelial dysfunction, and thus
41 subsequently lead to decline of eGFR^{42 47 48}. The persistent high level of SUA predicts the high risk of
42 developing CKD⁴⁹. There was a marked association of SUA with albuminuria in patients with renal
43 insufficiency⁵⁰. Our study were in consistent with many prospective studies^{29 51 52}, showing that SUA is
44 a significant risk factor for CKD and proteinuria, which is independent of confounders of CRFs. We
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3 further demonstrated that hyperuricemia significantly correlated with acid urine and nephrolithiasis,
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6 which was confirmed by the prevalence rates of chronic kidney disease and nephrolithiasis across the
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8 SUA levels.
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10 **CONCLUSION**

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13 In summary, our data demonstrated that the increasing prevalent rate of CRFs and renal disorders were
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15 significantly correlated with the elevated level of serum uric acid. Hyperuricemia was remarkably linked
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17 with CVD-related risk factors and kidney diseases. Furthermore, a close correlation between
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19 hyperuricemia and clustered CVD risk factors, CKD was observed in females than in males. Thus,
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21 decreasing SUA level may become a potential therapeutic treatment in preventing or delaying the
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23 multiple risks of CVDs and renal diseases, especially in women.
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33
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36 for their assistance in completing this project.
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40 **Author Contributions** M.T., N.L., S.Z., Y.S. and Y.Z. performed the statistical analysis and wrote the
41
42 manuscript; M.T., X.M., X.P., Y.C., H.G. and Y.S. participated in the data collection; M.T., N.L., S.Z.
43
44 and Y.Z. contributed to discussion; M.T., and N.L. participated in the design of the study and edited the
45
46 manuscript. All authors have read and approved the final manuscript. The corresponding author had full
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48 access to all the data in the study and had final responsibility for the decision to submit for publication.
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9

10 **Competing interests** None declared.

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13 **Patient consent** Obtained.

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16 **Ethics approval and consent to participate**

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18 This study was approved by the Human Research Ethics Committee of Shanghai East Hospital Affiliated to
19
20 Tongji University School of Medicine, the Human Research Ethics Committee of Pudong New District
21
22 Gongli Hospital and the Human Research Ethics Committee of Baoshan Branch of Shanghai First People's
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24 Hospital. All methods were performed in compliance with Good Clinical Practice (GCP) guidelines and the
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26 Declaration of Helsinki. Written informed consent was obtained from each participant before data
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28 collection.
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33 **Provenance and peer review** Not commissioned; externally peer reviewed.

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35 **Data sharing statement** The data sets generated and analysed during the current study are available from
36
37 the corresponding author upon reasonable request.
38
39

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Figure legend

Figure 1. Prevalence of major CVD risk factors, renal diseases in different levels of serum uric acid.

Prevalence of obesity(A), hypertension(B), diabetes mellitus(C), dyslipidemia(D), chronic kidney disease (E) and nephrolithiasis(F) in different levels of serum uric acid. The gender-specific quartiles of uric acid (mg/dL), Q1:males (M) ≤ 4.9 , females (F) ≤ 3.9 ; Q2: M 5.0-5.9, F 4.0-4.9; Q3: M 6.0-6.9, F 5.0-5.9; Q4: M ≥ 7.0 , F ≥ 6.0 .

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Table 1. Clinical characteristics of participants in quartiles of serum uric acid level.

	Men (n=15300)					Women (n=11876)				
	Q1 ≤4.9mg/dl	Q2 5.0-5.9mg/dl	Q3 6.0-6.9mg/dl	Q4 ≥7.0mg/dl	P-value for trend	Q1 ≤3.9mg/dl	Q2 4.0-4.9mg/dl	Q3 5.0-5.9mg/dl	Q4 ≥6.0mg/dl	P-value for trend
N(%)	2929(19.1%)	4720(30.8%)	4236(27.7%)	3415(22.3%)	-	3355(28.3%)	4553(38.3%)	2645(22.3%)	1323(11.1%)	-
Comorbidities										
Obesity (n, %)	194(6.6%)	450(9.5%)	620(14.6%)	814(23.8%)	< 0.001	133(4.0%)	364(8.0%)	380(14.4%)	315(23.8%)	< 0.001
Hypertension (n, %)	809(27.6%)	1215(25.7%)	1289(30.4%)	1220(35.7%)	< 0.001	554(16.5%)	1013(22.2%)	785(29.7%)	572(43.2%)	< 0.001
Diabetes mellitus (n, %)	351(12.0%)	306(6.5%)	224(5.3%)	168(4.9%)	< 0.001	125(3.7%)	170(3.7%)	154(5.8%)	132(10.0%)	< 0.001
Dyslipidemia (n, %)	735(25.1%)	1567(33.2%)	1732(40.9%)	1854(54.3%)	< 0.001	394(11.7%)	866(19.0%)	782(29.6%)	606(45.8%)	< 0.001
Chronic kidney disease (n, %)	48(1.6%)	114(2.4%)	138(3.3%)	238(7.0%)	< 0.001	25(0.7%)	78(1.7%)	105(4.0%)	171(12.9%)	< 0.001
Nephrolithiasis (n, %)	384(13.1%)	717(15.2%)	653(15.4%)	634(18.6%)	< 0.001	368(11.0%)	484(10.6%)	372(14.1%)	224(16.9%)	< 0.001
Biochemical variables										
Age	50.08±15.49	48.00±15.57	47.24±15.62	47.31±15.76	< 0.001	46.78±14.02	48.79±14.88	52.14±15.44	57.79±15.34	< 0.001
BMI (kg/m ²)	23.29±3.06	24.11±3.07	24.81±3.14	25.96±3.25	< 0.001	22.14±3.00	23.10±3.31	24.32±3.53	25.66±3.93	< 0.001
SBP (mmHg)	126.61±18.21	126.22±17.42	127.70±18.10	130.24±18.18	< 0.001	120.26±18.26	123.37±19.28	128.36±20.48	135.02±21.25	< 0.001
DBP (mmHg)	78.98±11.54	78.74±11.09	80.16±11.82	81.71±11.85	< 0.001	73.23±10.52	74.98±10.99	77.16±11.25	79.02±11.87	< 0.001
FPG (mmol/L)	5.65±1.87	5.36±1.35	5.33±1.21	5.33±1.07	< 0.001	5.08±1.22	5.12±1.12	5.29±1.22	5.57±1.28	< 0.001
TC (mmol/L)	4.52±0.88	4.58±0.86	4.71±0.89	4.87±0.91	< 0.001	4.64±0.91	4.82±0.93	5.00±0.94	5.17±1.04	< 0.001
TG (mmol/L)	1.28±1.27	1.45±1.14	1.72±1.46	2.14±1.71	< 0.001	0.96±0.59	1.19±0.76	1.46±0.98	1.97±1.61	< 0.001
HDL-C (mmol/L)	1.32±0.31	1.25±0.28	1.22±0.28	1.17±0.26	< 0.001	1.59±0.35	1.50±0.34	1.42±0.32	1.31±0.31	< 0.001
LDL-C (mmol/L)	2.77±0.76	2.88±0.76	2.95±0.77	3.04±0.81	< 0.001	2.71±0.77	2.89±0.79	3.07±0.81	3.11±0.86	< 0.001
eGFR (ml/(min*1.73m ²))	92.46±20.66	89.41±19.32	87.74±19.50	84.85±20.04	< 0.001	100.14±23.03	97.08±23.89	93.16±23.98	85.54±25.15	< 0.001
Cr (umol / L)	80.90±18.37	83.61±14.59	85.39±14.70	88.94±22.63	< 0.001	62.18±10.80	63.83±12.03	65.68±13.25	71.34±28.69	< 0.001
BUN (mmol/L)	5.19±1.31	5.26±1.22	5.31±1.25	5.43±1.56	< 0.001	4.57±1.20	4.84±1.23	5.11±1.27	5.55±1.82	< 0.001

Date are expressed as the mean±SE, percentages. Abbreviations: BMI: body mass index, SBP: systolic blood pressure, DBP: diastolic blood pressure, FPG: fasting plasma glucose, TC: total cholesterol, TG: triglyceride, HDL-C: high density lipoprotein cholesterol, LDL-C: low density lipoprotein cholesterol, eGFR: estimated glomerular filtration rate. Cr: creatinine, BUN: blood urea nitrogen.

Table 2. Correlation coefficients between serum uric acid and various parameters.

Variable	Men		Women		Total	
	r	P-value	r	P-value	r	P-value
Age	-0.059	< 0.001	0.227	< 0.001	0.014	0.020
BMI (kg/m ²)	0.289	< 0.001	0.327	< 0.001	0.343	< 0.001
SBP (mmHg)	0.075	< 0.001	0.234	< 0.001	0.158	< 0.001
DBP (mmHg)	0.091	< 0.001	0.166	< 0.001	0.197	< 0.001
FPG (mmol/L)	-0.072	< 0.001	0.124	< 0.001	0.039	< 0.001
TC (mmol/L)	0.148	< 0.001	0.185	< 0.001	0.091	< 0.001
TG (mmol/L)	0.221	< 0.001	0.326	< 0.001	0.290	< 0.001
HDL-C (mmol/L)	-0.177	< 0.001	-0.263	< 0.001	-0.357	< 0.001
LDL-C (mmol/L)	0.120	< 0.001	0.181	< 0.001	0.127	< 0.001
eGFR (ml/(min*1.73m ²))	-0.140	< 0.001	-0.194	< 0.001	-0.219	< 0.001

Abbreviations: BMI: body mass index, SBP: systolic blood pressure, DBP: diastolic blood pressure, FPG: fasting plasma glucose, TC: total cholesterol, TG: triglyceride, HDL-C: high density lipoprotein cholesterol, LDL-C: low density lipoprotein cholesterol, eGFR: estimated glomerular filtration rate.

Table 3. The odds ratio for hyperuricemia according to different status of parameters of men and women.

	Men				Women			
	Unadjusted		Full-adjusted		Unadjusted		Full-adjusted	
	OR (95%CI)	P-value	OR (95%CI)	P-value	OR (95%CI)	P-value	OR (95%CI)	P-value
BMI (kg/m ²)								
18.5 ≤BMI<24.0 (Ref.)								
BMI<18.5	0.502 (0.337-0.747)	0.001	0.558 (0.374-0.835)	0.004	0.502 (0.322-0.784)	0.002	0.636 (0.403-1.005)	0.052
24.0≤BMI<28.0	2.165 (1.978-2.368)	< 0.001	1.878 (1.707-2.065)	< 0.001	2.732 (2.392-3.121)	< 0.001	1.906 (1.649-2.203)	< 0.001
BMI≥28.0	3.972 (2.548-4.448)	< 0.001	3.102 (2.745-3.507)	< 0.001	5.077 (4.323-5.962)	< 0.001	3.126 (2.611-3.743)	< 0.001
Blood pressure (mmHg)								
Normotensive (Ref.)								
Pre-HT	1.304 (1.185-1.436)	< 0.001	1.138 (1.028-1.260)	0.013	1.958 (1.682-2.280)	< 0.001	1.129 (0.953-1.337)	0.159
Grade1 HT	1.663 (1.493-1.853)	< 0.001	1.350 (1.195-1.525)	< 0.001	3.321 (2.825-3.903)	< 0.001	1.328 (1.094-1.612)	0.004
Grade2/3 HT	1.716 (1.491-1.976)	< 0.001	1.393 (1.186-1.635)	< 0.001	4.887 (4.018-5.945)	< 0.001	1.480 (1.162-1.885)	0.002
FPG (mmol/L)								
FPG<6.1 (Ref.)								
6.1≤FPG<7	1.188 (1.026-1.375)	0.021	0.921 (0.785-1.081)	0.313	2.612 (2.126-3.209)	< 0.001	1.221 (0.972-1.535)	0.087
FPG≥7	0.655 (0.552-0.776)	< 0.001	0.410 (0.340-0.495)	< 0.001	2.673 (2.179-3.278)	< 0.001	0.793 (0.624-1.009)	0.059
Cholesterol (mmol/L)								
TC≤6.22 (Ref.)								
TC>6.22	1.885 (1.610-2.207)	< 0.001	1.072 (0.874-1.315)	0.502	2.044 (1.722-2.426)	< 0.001	1.070 (0.835-1.372)	0.591
Triglyceride (mmol/L)								
TG≤2.26 (Ref.)								
TG>2.26	2.881 (2.636-3.148)	< 0.001	2.242 (2.029-2.477)	< 0.001	4.603 (4.994-5.305)	< 0.001	2.513 (2.129-2.967)	< 0.001
HDL-C (mmol/L)								
HDL-C≥1.04 (Ref.)								
HDL-C<1.04	1.651 (1.519-1.795)	< 0.001	1.097 (0.999-1.205)	0.054	3.404 (2.898-3.999)	< 0.001	1.929 (1.601-2.324)	< 0.001
LDL-C (mmol/L)								
LDL-C≤4.14 (Ref.)								
LDL-C>4.14	1.737 (1.506-2.003)	< 0.001	1.522 (1.271-1.822)	< 0.001	1.871 (1.556-2.251)	< 0.001	1.299 (1.002-1.686)	0.049
eGFR (ml/(min*1.73m ²))								
eGFR≥90 (Ref.)								
60≤eGFR<89	1.175 (1.084-1.273)	< 0.001	1.351 (1.235-1.477)	< 0.001	1.672 (1.479-1.891)	< 0.001	1.580 (1.377-1.814)	< 0.001
eGFR≤59	3.185 (2.657-3.818)	< 0.001	4.461 (3.621-5.496)	< 0.001	9.569 (7.633-11.949)	< 0.001	6.453 (4.982-8.356)	< 0.001
Albuminuria								
-/+ (Ref.)								
+	1.256 (0.888-1.775)	0.198	0.899 (0.615-1.314)	0.584	6.020 (3.995-9.072)	< 0.001	2.899 (1.791-4.694)	< 0.001
++	2.123 (1.464-3.078)	< 0.001	1.392 (0.923-2.100)	0.115	3.203 (1.882-5.449)	< 0.001	1.521 (0.824-2.807)	0.180
+++	3.166 (1.990-5.036)	< 0.001	2.335 (1.393-3.913)	0.001	10.837 (6.108-19.225)	< 0.001	4.634 (2.399-8.953)	< 0.001
Urinary pH								
6≤pH≤7 (Ref.)								
pH<6	1.490 (1.375-1.615)	< 0.001	1.602 (1.464-1.752)	< 0.001	2.108 (1.875-2.371)	< 0.001	1.839 (1.613-2.098)	< 0.001
pH>7	0.534 (0.415-0.688)	< 0.001	0.581 (0.447-0.754)	< 0.001	0.653 (0.466-0.915)	0.013	0.741 (0.521-1.053)	0.094
Nephrolithiasis								
No (Ref.)								
Yes	1.317 (1.191-1.455)	< 0.001	1.250 (1.121-1.392)	< 0.001	1.553 (1.330-1.815)	< 0.001	1.214 (1.021-1.443)	0.028

Abbreviations: BMI: body mass index, FPG: fasting plasma glucose, TC: total cholesterol, TG: triglyceride, HDL-C: high density lipoprotein cholesterol, LDL-C: low density lipoprotein cholesterol, eGFR: estimated glomerular filtration rate. Blood pressure (mmHg): normotensive: SBP<120 and DBP<80; pre-HT: SBP of 120-139 and/or DBP of 80-89; Grade1 HT: SBP of 140-159 and/or DBP of 90-99; Grade2/3 HT: SBP≥160 and/or DBP≥100

Table 4. The association between SUA and Obesity, hypertension, Diabetes mellitus, Dyslipidemia, CKD, Nephrolithiasis in men.

	Q1	Q2			Q3			Q4		
	-	OR	95%CI	P-value	OR	95%CI	P-value	OR	95%CI	P-value
Obesity										
Model1	1(Ref.)	1.487	1.248-1.772	< 0.001	2.420	2.044-2.866	< 0.001	4.418	3.743-5.214	< 0.001
Model2 ^a	1(Ref.)	1.355	1.130-1.625	0.001	1.955	1.637-2.334	< 0.001	3.102	2.600-3.701	< 0.001
Model3 ¹	1(Ref.)	1.362	1.135-1.635	0.001	1.971	1.649-2.356	< 0.001	3.115	2.604-3.727	< 0.001
Hypertension										
Model1	1(Ref.)	0.999	0.895-1.115	0.981	1.351	1.209-1.509	< 0.001	1.769	1.577-1.983	< 0.001
Model2 ^b	1(Ref.)	0.934	0.832-1.048	0.246	1.146	1.019-1.289	0.023	1.266	1.118-1.434	< 0.001
Model3 ²	1(Ref.)	0.940	0.838-1.056	0.298	1.164	1.034-1.310	0.012	1.290	1.136-1.465	< 0.001
Diabetes mellitus										
Model1	1(Ref.)	0.539	0.457-0.636	< 0.001	0.445	0.372-0.531	< 0.001	0.407	0.335-0.495	< 0.001
Model2 ^c	1(Ref.)	0.434	0.366-0.516	< 0.001	0.289	0.239-0.349	< 0.001	0.210	0.170-0.259	< 0.001
Model3 ³	1(Ref.)	0.442	0.371-0.526	< 0.001	0.293	0.241-0.356	< 0.001	0.205	0.165-0.255	< 0.001
Dyslipidemia										
Model1	1(Ref.)	1.510	1.361-1.674	< 0.001	2.116	1.907-2.348	< 0.001	3.639	3.267-4.053	< 0.001
Model2 ^d	1(Ref.)	1.428	1.282-1.592	< 0.001	1.812	1.624-2.023	< 0.001	2.675	2.385-3.002	< 0.001
Model3 ⁴	1(Ref.)	1.408	1.262-1.570	< 0.001	1.755	1.571-1.961	< 0.001	2.503	2.226-2.815	< 0.001
Chronic kidney disease										
Model1	1(Ref.)	1.698	1.199-2.404	0.003	2.458	1.749-3.454	< 0.001	5.883	4.254-8.136	< 0.001
Model2 ^e	1(Ref.)	1.895	1.329-2.700	< 0.001	2.745	1.935-3.896	< 0.001	6.800	4.829-9.576	< 0.001
Model3 ⁵	1(Ref.)	1.894	1.325-2.707	< 0.001	2.795	1.966-3.975	< 0.001	6.962	4.921-9.851	< 0.001
Nephrolithiasis										
Model1	1(Ref.)	1.248	1.090-1.428	0.001	1.292	1.126-1.482	< 0.001	1.619	1.409-1.861	< 0.001
Model2 ^f	1(Ref.)	1.163	1.015-1.334	0.030	1.150	0.999-1.324	0.052	1.346	1.162-1.560	< 0.001
Model3 ⁶	1(Ref.)	1.225	1.067-1.406	0.004	1.229	1.065-1.418	0.005	1.480	1.272-1.722	< 0.001

Model 1: adjusted for age

^aModel 2: adjusted for variables included in model1 and SBP, DBP, FPG, TC, TG, HDL-C, LDL-C; ^bModel2: adjusted for variables included in model1 and BMI, FPG, TC, TG, HDL-C, LDL-C; ^cModel2: adjusted for variables included in model1 and BMI, SBP, DBP, FPG; ^dModel2: adjusted for variables included in model1 and BMI, SBP, DBP, FPG, TC, TG, HDL-C, LDL-C; ^eModel2: adjusted for variables included in model1 and BMI, SBP, DBP, FPG, TC, TG, HDL-C, LDL-C; ^fModel2: adjusted for variables included in model1 and BMI, SBP, DBP, FPG, TC, TG, HDL-C, LDL-C.

¹Model 3: adjusted for variables included in model2^a and eGFR, urine Ph, albuminuria, nephrolithiasis; ²Model 3: adjusted for variables included in model2^b and eGFR, urine Ph, albuminuria, nephrolithiasis; ³Model 3: adjusted for variables included in model2^c and eGFR, urine Ph, albuminuria, nephrolithiasis; ⁴Model 3: adjusted for variables included in model2^d and eGFR, urine Ph, albuminuria, nephrolithiasis; ⁵Model 3: adjusted for variables included in model2^e and urine Ph, albuminuria, nephrolithiasis; ⁶Model 3: adjusted for variables included in model2^f and eGFR, urine Ph, albuminuria.

Abbreviations: BMI: body mass index, SBP: systolic blood pressure, DBP: diastolic blood pressure, FPG: fasting plasma glucose, TC: total cholesterol, TG: triglyceride, HDL-C: high density lipoprotein cholesterol, LDL-C: low density lipoprotein cholesterol, eGFR: estimated glomerular filtration rate.

Table 5. The association between SUA and Obesity, hypertension, Diabetes mellitus, Dyslipidemia, CKD, Nephrolithiasis in women.

	Q1	Q2			Q3			Q4		
	-	OR	95%CI	P-value	OR	95%CI	P-value	OR	95%CI	P-value
Obesity										
Model1	1(Ref.)	2.000	1.630-2.455	< 0.001	3.568	2.902-4.387	< 0.001	5.837	4.687-7.269	< 0.001
Model2 ^a	1(Ref.)	1.652	1.338-2.041	< 0.001	2.453	1.976-3.045	< 0.001	3.560	2.818-4.497	< 0.001
Model3 ¹	1(Ref.)	1.679	1.358-2.076	< 0.001	2.498	2.008-3.107	< 0.001	3.755	2.956-4.769	< 0.001
Hypertension										
Model1	1(Ref.)	1.285	1.133-1.457	< 0.001	1.565	1.365-1.794	< 0.001	2.109	1.799-2.472	< 0.001
Model2 ^b	1(Ref.)	1.110	0.972-1.267	0.123	1.120	0.967-1.298	0.130	1.244	1.045-1.480	0.014
Model3 ²	1(Ref.)	1.127	0.987-1.287	0.078	1.161	1.001-1.347	0.049	1.287	1.075-1.539	0.006
Diabetes mellitus										
Model1	1(Ref.)	0.868	0.683-1.104	0.249	1.146	0.893-1.469	0.284	1.536	1.178-2.004	0.002
Model2 ^c	1(Ref.)	0.614	0.477-0.791	< 0.001	0.609	0.466-0.797	< 0.001	0.588	0.437-0.791	< 0.001
Model3 ³	1(Ref.)	0.596	0.462-0.770	< 0.001	0.566	0.431-0.744	< 0.001	0.514	0.377-0.701	< 0.001
Dyslipidemia										
Model1	1(Ref.)	1.670	1.466-1.903	< 0.001	2.735	2.385-3.136	< 0.001	4.761	4.075-5.561	< 0.001
Model2 ^d	1(Ref.)	1.583	1.386-1.809	< 0.001	2.385	2.071-2.747	< 0.001	3.836	3.265-4.508	< 0.001
Model3 ⁴	1(Ref.)	1.575	1.378-1.800	< 0.001	2.318	2.010-2.673	< 0.001	3.675	3.114-4.336	< 0.001
Chronic kidney disease										
Model1	1(Ref.)	1.962	1.241-3.102	0.004	3.676	2.353-5.745	< 0.001	9.740	6.306-15.045	< 0.001
Model2 ^e	1(Ref.)	2.092	1.317-3.322	0.002	4.096	2.591-6.475	< 0.001	11.510	7.282-18.193	< 0.001
Model3 ⁵	1(Ref.)	2.051	1.291-3.260	0.002	4.189	2.645-6.634	< 0.001	11.508	7.242-18.288	< 0.001
Nephrolithiasis										
Model1	1(Ref.)	0.922	0.798-1.065	0.268	1.183	1.012-1.383	0.035	1.312	1.090-1.580	0.004
Model2 ^f	1(Ref.)	0.853	0.736-0.988	0.034	1.022	0.868-1.203	0.797	1.034	0.847-1.262	0.742
Model3 ⁶	1(Ref.)	0.889	0.766-1.032	0.123	1.111	0.940-1.313	0.216	1.239	1.008-1.522	0.042

Model 1: adjusted for age

^aModel 2: adjusted for variables included in model1 and SBP, DBP, FPG, TC, TG, HDL-C, LDL-C; ^bModel2: adjusted for variables included in model1 and BMI, FPG, TC, TG, HDL-C, LDL-C; ^cModel2: adjusted for variables included in model1 and BMI, SBP, DBP, FPG; ^dModel2: adjusted for variables included in model1 and BMI, SBP, DBP, FPG, TC, TG, HDL-C, LDL-C; ^eModel2: adjusted for variables included in model1 and BMI, SBP, DBP, FPG, TC, TG, HDL-C, LDL-C; ^fModel2: adjusted for variables included in model1 and BMI, SBP, DBP, FPG, TC, TG, HDL-C, LDL-C.

¹Model 3: adjusted for variables included in model2^a and eGFR, urine Ph, albuminuria, nephrolithiasis; ²Model 3: adjusted for variables included in model2^b and eGFR, urine Ph, albuminuria, nephrolithiasis; ³Model 3: adjusted for variables included in model2^c and eGFR, urine Ph, albuminuria, nephrolithiasis; ⁴Model 3: adjusted for variables included in model2^d and eGFR, urine Ph, albuminuria, nephrolithiasis; ⁵Model 3: adjusted for variables included in model2^e and urine Ph, albuminuria, nephrolithiasis; ⁶Model 3: adjusted for variables included in model2^f and eGFR, urine Ph, albuminuria.

Abbreviations: BMI: body mass index, SBP: systolic blood pressure, DBP: diastolic blood pressure, FPG: fasting plasma glucose, TC: total cholesterol, TG: triglyceride, HDL-C: high density lipoprotein cholesterol, LDL-C: low density lipoprotein cholesterol, eGFR: estimated glomerular filtration rate.

Table 6. The association between hyperuricemia and clustered CVD risk factors.

Clustered CVD risk factors	Men						Women					
	Unadjusted			Age-adjusted			Unadjusted			Age-adjusted		
	OR	95%CI	P-value	OR	95%CI	P-value	OR	95%CI	P-value	OR	95%CI	P-value
0	Ref.											
1	1.948	1.774-2.140	< 0.001	2.119	1.926-2.332	< 0.001	3.337	2.887-3.856	< 0.001	2.642	2.266-3.081	< 0.001
2	2.977	2.671-3.318	< 0.001	3.390	3.029-3.794	< 0.001	6.116	5.199-7.195	< 0.001	4.447	3.728-5.304	< 0.001
≥3	3.343	2.867-3.897	< 0.001	3.804	3.252-4.450	< 0.001	8.848	7.070-11.075	< 0.001	6.265	4.945-7.938	< 0.001
p value for trend	< 0.001			< 0.001			< 0.001			< 0.001		

Clustered CVD risk factors included obesity, hypertension, diabetes mellitus, dyslipidemia

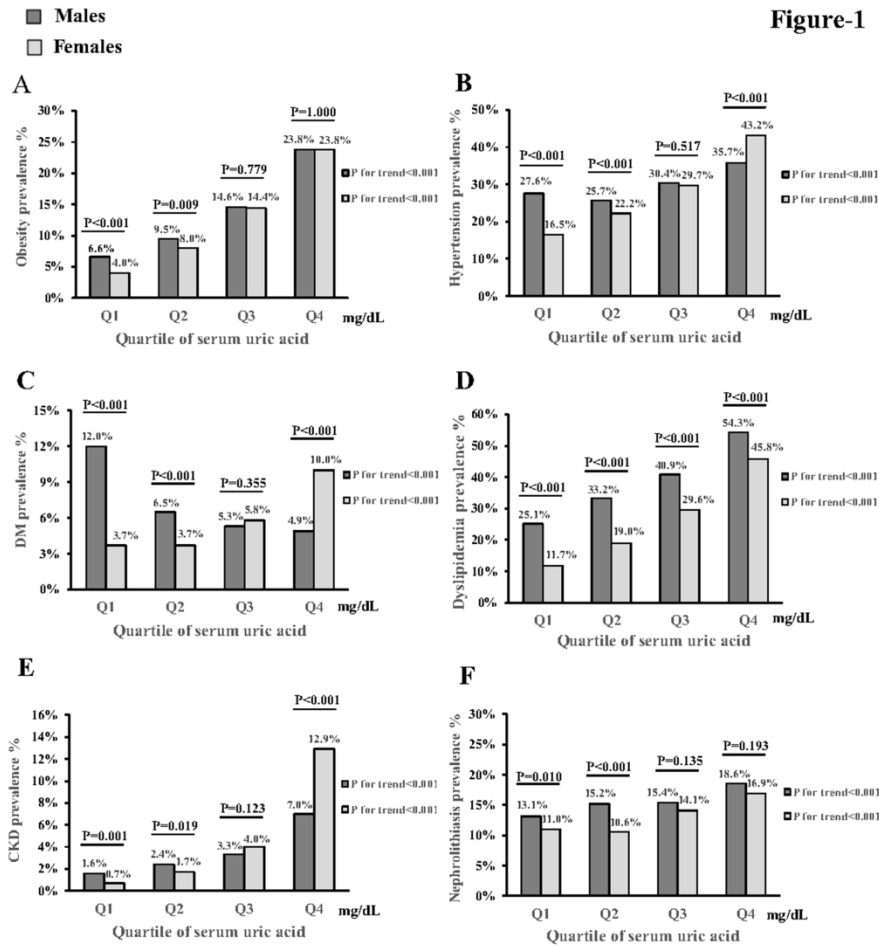


Figure 1. Prevalence of major CVD risk factors, renal diseases in different levels of serum uric acid. Prevalence of obesity(A), hypertension(B), diabetes mellitus(C), dyslipidemia(D), chronic kidney disease (E) and nephrolithiasis(F) in different levels of serum uric acid. The gender-specific quartiles of uric acid (mg/dL), Q1:males (M) ≤ 4.9 , females (F) ≤ 3.9 ; Q2: M 5.0-5.9, F 4.0-4.9; Q3: M 6.0-6.9, F 5.0-5.9; Q4: M ≥ 7.0 , F ≥ 6.0 .

190x254mm (300 x 300 DPI)

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The relationship between serum uric acid and clustering of cardiovascular disease risk factors, renal disorders among Shanghai population: a multi-center and cross-sectional study

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4 1 **The relationship between serum uric acid and clustering of cardiovascular disease risk factors,**
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7 2 **renal disorders among Shanghai population: a multi-center and cross-sectional study**

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ABSTRACT

Objectives To estimate the current prevalence of cardiovascular disease risk factors (CRFs) and renal disorders across serum uric acid (SUA) quartiles, and evaluate the relationships between SUA and CRFs, renal diseases in Shanghai population.

Study design Observational, cross-sectional study.

Setting Data were obtained from physical checkups of local residents at three hospitals in Shanghai.

Participants Residents were invited to take part in physical checkups and provided informed consents.

Exclusion criteria were diseases that resemble cancer, hepatic disease and other coexisting illnesses including autoimmune kidney diseases, renal artery stenosis, individuals treated with xanthine oxidase inhibitors and without complete information. There are 27176 individuals in our study.

Primary and secondary outcome measures Hyperuricemia was defined as SUA ≥ 7 mg/dL in males and ≥ 6 mg/dL in females or taking xanthine oxidase inhibitors. Subjects were divided into gender-specific quartiles. We estimate the prevalence of CRFs and renal disorders across SUA quartiles. The relationships between SUA and CRFs, renal disorders at different gender were evaluated with logistic regression analysis.

Results: There was a significant increase in the prevalence of major CRFs and renal diseases across SUA quartiles in separate analysis among men and women (all P -trend <0.001). After multiple adjustment, hyperuricemia positively correlated with obesity (Male OR=3.115, $P<0.001$; Female OR=3.755, $P<0.001$), hypertension (Male OR=1.290, $P<0.001$; Female OR=1.287, $P=0.006$), dyslipidemia (Male OR=2.503, $P<0.001$; Female OR=3.675, $P<0.001$), chronic kidney disease (Male OR=6.962, $P<0.001$; Female OR=11.508, $P<0.001$), nephrolithiasis (Male OR=1.480, $P<0.001$; Female OR=1.239, $P=0.042$),

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4 43 but negatively correlated with diabetes mellitus ((Male OR=0.205, $P<0.001$; Female OR=0.514,
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7 44 $P<0.001$)). Women had a stronger association between hyperuricemia and clustered CRFs as well as
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10 45 CKD than men.

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12 46 **Conclusions:** In Shanghai population, concomitant with the elevated level of SUA, the prevalence of
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15 47 CRFs and renal diseases was rising. Hyperuricemia was significantly associated with CRFs and renal
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18 48 disorders, especially in females.

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20 49 **KEY WORDS:** Serum uric acid, cardiovascular disease risk factors, renal disorders
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23 50 24 25 26 51 **ARTICLE SUMMARY**

27 28 29 52 **Article focus**

- 30
31 53 ● The current prevalence of cardiovascular disease risk factors (CRFs) and renal diseases across serum
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34 54 uric acid (SUA) quartiles.
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37 55 ● The relationships between SUA and CRFs, renal disorders in Shanghai population.
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39 56 **Key messages**

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42 57 ● In Shanghai population, concomitant with the elevated level of serum uric acid, the prevalence rate of
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45 58 CRFs and renal diseases was rising.
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48 59 ● Hyperuricemia was significantly associated with cardiovascular disease (CVD) risk factors and renal
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50 60 disorders, especially in females.
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52 53 61 **Strengths and limitations of this study**

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56 62 ● There is a strict exclusion criteria based on medical histories and laboratory findings.
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58 63 ● We conducted a multi-center study with large sample size which ensured sufficient power in
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4 64 obtaining the accurate prevalent rate of CRFs and renal diseases and analyzing the relationship
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7 65 between SUA and CRFs, renal disorders across SUA quartiles.
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10 66 ● The relationship was analyzed in both sexes and we got a solid conclusion about the differences
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12 67 between men and women.
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15 68 ● It was a cross-section study and the results could not establish causative relationships between
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18 69 hyperuricemia and CRFs clustering and renal diseases.
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20 70 ● The data were from three medical centers' databases that lacked details in waist circumference,
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23 71 HOMA-IR (homeostasis model assessment of insulin resistance), smoking, drinking, lifestyles, diet
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26 72 and pharmacotherapy, which might affect the deviations of some clinical outcomes.
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INTRODUCTION

Uric acid (UA) is the final degradation product of purine metabolism in the liver, muscles and intestines.¹ A high level of serum uric acid (SUA) is correlated with multiple disorders such as metabolic syndrome, cardiovascular disease as well as kidney diseases.²⁻⁴ The association between hyperuricemia and CVD risk factors has been widely focused since the last century.⁵ There are various risk factors involved in CVDs, including age, sex, obesity, hypertension, diabetes mellitus, dyslipidemia, family history, smoking, depression and so on.⁶⁻⁸ Numerous indexes of CVDs risk factors were closely associated with increased serum uric acid, such as body mass index (BMI), cholesterol, triglyceride, low-density lipoprotein (LDL), and high-density lipoprotein (HDL), systolic blood pressure (SBP), diastolic blood pressure (DBP), fasting plasma glucose (FPG).⁶⁻⁹ However, the relationship between hyperuricemia and cardiovascular disease risk factors (CRFs) at different gender of Shanghai population has not been well studied. And the data from multiple clinical centers in China are extremely limited. In this study, we evaluated the prevalence of major CRFs (obesity, hypertension, diabetes mellitus, dyslipidemia) across SUA quartiles and analyzed the association of these factors with SUA level respectively in both men and women.

It has been documented that 70% of the daily UA production is excreted by the kidney.¹⁰ UA tends to crystallize in low urine pH. Hyperuricemia reduces urine pH, and increases the risk of formation of urate stones.¹¹ Recent research indicated that serum uric acid level could predict the development of albuminuria.¹²⁻¹³ And elevated serum uric acid level was significantly associated with estimated glomerular filtrate rate (eGFR) decline.¹⁴⁻¹⁵ However, whether UA is a cause or an association to renal diseases is a question that still waits for further investigations. Thus, we assessed the prevalence of renal

diseases across SUA quartiles, and the relationship between serum uric acid and renal disorders in Shanghai population.

METHODS

Study population

The permanent residents aged between 16-98 years who participated in the health checkups during the period from January 2015 and December 2015 of three medical centers Shanghai East Hospital Affiliated to Tongji University School of Medicine, Pudong New District Gongli Hospital and Baoshan Branch of Shanghai First People's Hospital were invited in the study. After excluding subjects with incomplete data, cancer, hepatic disease or other coexisting illnesses including autoimmune kidney diseases, renal artery stenosis and subjects treated with xanthine oxidase inhibitors, 27176 participants were enrolled in our study.

The primary outcomes

Hyperuricemia was defined as serum uric acid ≥ 7 mg/dL in males and ≥ 6 mg/dL in females or current use of xanthine oxidase inhibitors.¹⁶ SUA was determined using the uricase-peroxidase method.

Study definitions

Body mass index (BMI) was calculated as weight in kilograms divided by height in squared meters. According to WHO guidelines for the Asian Pacific population, normal weight was defined as $18.5 \leq \text{BMI} < 24.0$ kg/m², overweight was defined as $24.0 \leq \text{BMI} < 28.0$ kg/m², obesity was defined as $\text{BMI} \geq 28.0$ kg/m², underweight was defined as $\text{BMI} < 18.5$ kg/m².¹⁷ Blood pressure measurements were taken according to the Joint National Committee VII criteria (JNC VII).¹⁸ Normal BP was defined as having SBP < 120 mmHg and DBP < 80 mmHg. Pre-hypertension was defined as having SBP of 120–139 mmHg

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4126 and/or DBP of 80–89 mmHg. Grade 1 hypertension was defined as having SBP of 140–159 mmHg
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7127 and/or DBP of 90–99 mmHg. Grade 2 or grade 3 hypertension was defined as SBP \geq 160 mmHg and/or
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10128 DBP \geq 100 mmHg.¹⁸ According to the Chinese adult dyslipidemia prevention guide (2007 edition),
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1229 individuals with a fasting TC \geq 6.22 mmol/L, TG \geq 2.26 mmol/L, HDL-C $<$ 1.04 mmol/L, and/or
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1530 LDL-C $>$ 4.14 mmol/L, or currently undergoing pharmacologic treatment were defined as the
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1831 dyslipidemia.¹⁹ T2D was defined based on World Health Organization (WHO) 1999 diagnostic criteria
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2032 as fasting plasma glucose \geq 7.0mmol/l or 2-h plasma glucose \geq 11.1mmol/l, impaired fasting glucose (IFG)
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2333 was defined as 6.1 mmol/l \leq FPG $<$ 7.0 mmol/l, and normal condition was defined as FPG $<$ 6.1 mmol/l.²⁰
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2634 The eGFR was calculated using Modification of Diet in Renal Disease (MDRD) formula²¹: $186 \times [\text{serum}$
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2935 creatinine (mg/ dl)] $^{-1.154} \times (\text{age})^{-0.203} \times [0.742 \text{ (if female)}]$. According to the Kidney Disease Outcomes
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3136 Quality Initiative (KDOQI) clinical practice guideline, estimated glomerular filtration rate (eGFR) $<$ 60
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3437 mL/min/1.73 m², proteinuria and hematuria were defined as markers of CKD.²² Urine proteinuria were
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3738 recorded as negative (-), trace, 1+, 2+ and 3+. Albuminuria was defined as \geq 1+.

41 4240 **Data collection**

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4541 The subjects participating in the study attended to the medical center in the morning after overnight
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4842 fasting for at least 12 hours. After 5 minutes resting, sitting blood pressure was measured in right arm by
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5043 a trained medical staff using an electronic blood pressure monitor. The resting BP was measured three
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5344 times with five minutes intervals between them, and then the averages were calculated, which were used
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5645 for further analysis. Blood samples were obtained on their arrival at the medical center and fasting
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5846 glucose (FPG) were measured by the hexokinase method, total cholesterol, low-density
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lipoprotein-cholesterol (LDL-C), high-density lipoprotein-cholesterol (HDL-C), triglyceride, blood urea nitrogen (BUN), creatinine, serum uric acid were measured in an automated bio-analyzer (Hitachi, Tokyo, Japan). Midstream urine specimen was collected for urinary analysis by the dipstick method. Urine pH and proteinuria were recorded as categorical data. Laboratory reagents were purchased from Nanjing Jiancheng Bioengineering Institute (Nanjing, China).

After blood and urine sampling, basic characteristics and medical history were collected by medical staff. Anthropometric measurements including height and body weight were obtained according to a standardized protocol. Renal ultrasonography scanning was performed and measured by an experienced radiologist using GE LOGIQ P5 scanner (GE Healthcare, Milwaukee, SUA) who was blinded to the subjects' medical information.

Patient and public involvement

No patient was involved in the design or conduct of the study, but the results of the study will be shared to patients coming for follow-up.

Statistical analysis

We divided the subjects into gender-specific quartiles [males (M): Q1 \leq 4.9, Q2: 5.0-5.9, Q3: 6.0-6.9, Q4 \geq 7.0 mg/dL; females (F): Q1 \leq 3.9, Q2: 4.0-4.9, Q3: 5.0-5.9, Q4 \geq 6.0mg/dL] according to serum uric acid level. The continuous variables are reported in means \pm SD and categorical variables are presented in percentages. In case of nonparametric data distribution medians with inter quartile range (IQR) are presented. The univariate analysis of variance (ANOVA) was used to measure the data among the groups or a Kruskal-Wallis test in case of nonparametric data distribution. Differences between groups for

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4 169 proportions were tested with a chi-square test. If the results show differences between the groups, the
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7 170 post-hoc tests would be done. As for the post-hoc test, we used least significance difference (LSD) test if
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10 171 the variance was homogeneous, and we used Tamhane's T2 test if not. Correlations were Pearson's or
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12 172 Spearman's depending on the distribution of the data. In the present study, SUA, age, BMI, SBP, DBP,
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15 173 FPG, TC, TG, HDL-C, LDL-C, eGFR were normally distributed. Thus, Pearson's correlation was used
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18 174 among these variables. If Pearson's correlation analysis was statistically significant, multiple linear
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20 175 regression analysis was performed to determine the association of SUA with various independent
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23 176 variables. We analyzed the multiple collinearity by calculating the correlation coefficient matrix,
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26 177 tolerance and variance inflation factor of independent variables. Multivariable logistic regression analysis
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29 178 (unadjusted and full-adjusted) was used to calculate the odds ratio for hyperuricemia according to
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31 179 different status of clinical parameters. Furthermore, multivariable logistic regression analysis (multiple
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34 180 adjusted models) was used to examine the association between related diseases and the SUA categories of
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37 181 Q2 or greater compared to the lowest SUA category. The association between hyperuricemia and
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40 182 clustered CVD risk factors had been calculated. Statistical analyses were performed by IBM SPSS
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43 183 statistics version 20.0 (SPSS, Chicago, IL, USA). Statistical significance was set at *P*-values of <0.05.
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45 184 RESULTS

47 185 Clinical characteristics of participants in quartiles of serum uric acid level.

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50 186 A total of 27,176 participants with mean age 48.88 ± 15.48 years, and 15300 (56.3%) men and 11876
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53 187 (43.7%) women completed in the study. The prevalence rates of hyperuricemia of men and women were
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56 188 22.3 % (95% confidence intervals (CI) 21.7–23.0%) and 11.1% (10.6–11.7%), respectively. Female
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58 189 individuals with higher level of SUA were older than the age of males. With increasing quartiles of SUA,
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4 190 participants had more CVDs risk factors (obesity, hypertension, dyslipidemia) and renal diseases (chronic
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7 191 kidney disease, nephrolithiasis), as well as elevated levels of body mass index, systolic blood pressure,
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10 192 diastolic blood pressure, total cholesterol, triglyceride, low density lipoprotein cholesterol, creatinine,
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12 193 blood urea nitrogen (BUN), and decreased levels of high density lipoprotein cholesterol, estimated
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15 194 glomerular filtration rate in both men and women (Table 1, all *P* values for trend <0.001).

196 **The prevalence of CVD risk factors, renal diseases in quartiles of serum uric acid level**

197 As demonstrated in Figure 1, there was a significant increase in the prevalence of cardiovascular disease
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26 198 risk factors and renal disorders across SUA quartiles in men and women (all *P* value for trend <0.001). In
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29 199 the male hyperuricemia individuals, the prevalence rates of obesity, hypertension, diabetes mellitus,
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31 200 dyslipidemia, chronic kidney disease and nephrolithiasis were 23.8% (95% CI, 22.4-25.3%), 35.7%
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34 201 (34.1-37.3%), 4.9% (4.2-5.6%), 54.3% (52.6-56.0%), 7.0% (6.1-7.8%) and 18.6% (17.3-19.9%)
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37 202 respectively. In the female hyperuricemia individuals, the prevalence rates of obesity, hypertension,
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40 203 diabetes mellitus, dyslipidemia, chronic kidney disease and nephrolithiasis were 23.8% (21.5-26.1%),
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42 204 43.2% (40.6-45.9%), 10.0% (8.4-11.6%), 45.8% (43.1-48.5%), 12.9% (11.1-14.7%) and 16.9%
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45 205 (14.9-19.0%) , respectively.

206 207 **The correlation between serum uric acid and various clinical parameters**

208 In the present study, SUA, age, BMI, SBP, DBP, FPG, TC, TG, HDL-C, LDL-C, eGFR were normally
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56 209 distributed. Thus, we used Pearson's correlation analysis to investigate the relationships and the results
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59 210 were shown in Table 2. In men, the level of serum uric acid was positively correlated with BMI, SBP,
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DBP, TC, TG, LDL-C, and negatively correlated with age, FPG, HDL-C and eGFR (all P values <0.001).

In women, the level of serum uric acid was positively correlated with age, BMI, SBP, DBP, FPG, TC, TG, LDL-C, and negatively correlated with HDL-C and eGFR (all P values <0.001).

Multiple linear regression analysis in Table 3 showed that adjusting for various factors, serum uric acid was still positively correlated with BMI, SBP, TC, TG, negatively correlated with age, FPG, HDL-C and eGFR in males (all P values <0.001). Serum uric acid was positively correlated with BMI, SBP, TC, TG, negatively correlated with FPG, HDL-C and eGFR in females (all P values <0.001 , except FPG P values=0.002).

The association between hyperuricemia and the clinical outcome

Multivariable logistic regression models (unadjusted and full-adjusted) were analyzed and the results were shown in Table 4 with the odds ratio (OR) for hyperuricemia according to different clinical outcome. We found that after adjustment for confounders, increased levels of BMI, BP, triglyceride, LDL-C, albuminuria all are positively related to increased odds ratio of hyperuricemia. Renal insufficiency, acid urine, nephrolithiasis also positively correlated with hyperuricemia, however, FPG and alkaline urine negatively correlated with hyperuricemia in both gender (all P values <0.05). These results suggested that the individuals with overweight/obesity, hypertension, dyslipidemia, renal insufficiency, massive albuminuria, acid urine, nephrolithiasis were more susceptible to hyperuricemia in both men and women.

The relationship between different levels of serum uric acid and CVDs risk factors, renal disorders

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4231 Multivariable logistic regression analysis (multiple adjusted models) was studied and the results were
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7232 shown in Table 5. The odd ratio for obesity, hypertension, diabetes mellitus, dyslipidemia, chronic kidney
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10233 disease, nephrolithiasis in the highest SUA quartile was 3.115 (95% CI 2.604–3.727, $P < 0.001$, model 3),
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1234 1.290 (95% CI 1.136–1.465, $P < 0.001$, model 3), 0.205 (95% CI 0.165–0.255, $P < 0.001$, model 3), 2.503
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1535 (95% CI 2.226–2.815, $P < 0.001$, model 3), 6.962 (95% CI 4.921–9.851, $P < 0.001$, model 3), 1.480 (95%
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1836 CI 1.272–1.722, $P < 0.001$, model 3) compared with that in the lowest SUA quartile, respectively, in men.

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20237 The data in Table 6 were multivariable logistic regression analysis in women and the odd ratio for
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2338 obesity, hypertension, diabetes mellitus, dyslipidemia, chronic kidney disease, nephrolithiasis in the
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2639 highest SUA quartile was 3.755 (95% CI 2.956–4.769, $P < 0.001$, model 3), 1.287 (95% CI 1.075–1.539,
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2940 $P = 0.006$, model 3), 0.514 (95% CI 0.377–0.701, $P < 0.001$, model 3), 3.675 (95% CI 3.114–4.336, P
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3141 < 0.001 , model 3), 11.508 (95% CI 7.242–18.288, $P < 0.001$, model 3), 1.239 (95% CI 1.008–1.522, P
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3442 $= 0.042$, model 3) compared with that in the lowest SUA quartile, respectively.

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3743 From multivariable logistic regression analysis in men and women we concluded that hyperuricemia
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4044 positively correlated with obesity, hypertension, dyslipidemia, chronic kidney disease, nephrolithiasis, but
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4245 negatively correlated with diabetes mellitus (all $P < 0.05$) in both gender. Furthermore, females had
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4546 stronger association between hyperuricemia and chronic kidney disease than males.

46 47 48 49 5048 **The association between hyperuricemia and clustered CVD risk factors.**

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5349 Multivariable logistic regression was analyzed for hyperuricemia and clustered CVD risk factors, the
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5650 results were shown in Table 7. After adjustment for age, compared with the group of zero CVD risk
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5951 factor reference group, the odd ratio for group of ≥ 3 CVD risk factors was 3.804 (95% CI 3.252–4.450, P
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4 252 <0.001), 6.265 (95% CI 4.945–7.938, $P < 0.001$) in men and women, respectively. The individuals with
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7 253 more CVD risk factors were associated with the higher ORs of hyperuricemia both in men and women (P
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9 254 for trend <0.001). Furthermore, females had a stronger association of hyperuricemia with clustered CVD
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12 255 risk factors than males.
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17 257 **DISCUSSION**

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20 258 In the present study, we found that increasing prevalence of CVD risk factors and renal disorders was
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23 259 predominantly associated with increased SUA levels in Shanghai population. According to our
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26 260 multi-center epidemiologic study of 27176 subjects, the prevalence of hyperuricemia in Shanghai was
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29 261 17.4% (95%CI 17.0%-17.9%), 22.3% (21.7–23.0%) in men and 11.1% (10.6–11.7%) in women. This is
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31 262 higher than the prevalence of hyperuricemia among nationwide Chinese adults between year 2009 and
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34 263 2010 (8.4%),²³ and close to the developed countries, such as United States (21.4 %) and Japan (25.8 %).
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37 264 ^{24 25} Along with the rapid economic development of Shanghai, the consumption of purine-rich food and
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40 265 alcohol is increasing. Meanwhile, obesity and aging population is rising. The change of lifestyle, dietary
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42 266 habit and population attributed to this phenomenon. The gender-related differences between serum uric
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45 267 acid level and age could be resulted from sex hormones. Estrogen promoted urinary uric acid excretion.²⁶
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48 268 Obesity is probably the major risk factor for CVD. Obesity accompanied by increased waist
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50 269 circumference, hyperinsulinemia and dyslipidemia. The most frequent manifestation of glucose
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53 270 metabolism in obese population is hyperinsulinemia, a compensatory mechanism, whereas fasting
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56 271 glucose remains normal.²⁷ It is likely that the presence of insulin resistance and hyperinsulinemia
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58 272 facilitates renal tubular cells to reabsorb sodium coupling with urate.²⁸ This may be the reason why
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4273 obesity is accompanied by hyperuricemia. And our data are also in agreement with the result from two
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7274 retrospective studies in youths.^{29 30}
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10 Hypertension is another important risk factor for CVD. Recently, Borghi C et al. found that SUA
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1276 levels were significantly higher in untreated and poorly controlled hypertensive patients in comparison to
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1577 normotensive controls and well-controlled hypertensive patients.³¹⁻³³ Our data were in accordance with
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1878 Borghi C's results. After adjustment of confounding factors, hypertension was still significantly
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2179 associated with hyperuricemia. The odd ratio for hypertension in the highest SUA quartile was 1.290
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2380 (95% CI 1.136–1.465, $P < 0.001$) in men, 1.287 (95% CI 1.075–1.539, $P < 0.001$) in women. Future
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2681 follow-up studies and randomized clinical trials are required for investigating the causative relationships
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2982 between urate and blood pressure. However, animal studies had showed that high level of uric acid
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3183 caused high blood pressure, which was mediated by activation of renal and systemic
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3484 renin-angiotensin-aldosterone systems (RAAS), oxidative stress, vascular insulin resistance and loss of
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3785 endothelial nitric oxide.^{34 35}
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40 One of the interesting findings in our investigation was that the higher level of SUA was positively
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4287 correlated with the higher prevalence rates of diabetes mellitus in women, but inversely correlated with
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4588 that in men (Figure 1). The Pearson's correlation analysis demonstrated that the level of SUA positively
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4889 correlated with fasting plasma glucose in women, but negatively in men. However, the coefficients of
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5090 determination of the models were low. The obtained P values below 0.001 may attributed to the effect of
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5391 the big sample size. So we further adopted multiple linear regression and multivariable logistic regression
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5692 analysis for association of various variable with serum uric acid. After adjustment of confounding factors,
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5893 results of multivariable logistic regression showed that inverse association of serum uric acid with
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4 294 diabetes mellitus in both men and women. The odd ratio for diabetes mellitus in the highest SUA quartile
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7 295 was 0.205 (95% CI 0.165–0.255, $P < 0.001$) in men, 0.514 (95% CI 0.377–0.701, $P < 0.001$) in women.
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10 296 This also confirmed by multiple linear regression analysis. We speculated that this phenomenon is
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12 297 probably due to the presence of high level of blood glucose which promotes renal excretion of serum uric
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15 298 acid. It has been indicated that hyperglycaemia worsens the function of beta cells and deteriorates
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18 299 glycemic control, which gradually elevates the rate of renal glomerular filtration.³⁶ The hyperfiltration
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20 300 due to multiple kidney disorders will lead to increased excretion of uric acid, and will be more susceptible
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23 301 to diabetic nephropathy with decreasing eGFR.³⁷
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26 302 Based on our data, hyperuricemia had a remarkable association with cardiovascular disease risk
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29 303 factors and renal disorders. The more CVD risk factors individuals had, the higher ORs of hyperuricemia
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31 304 were observed in both genders, especially in women. This was consistent with Borghi C's studies that
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34 305 SUA were associated with cardiovascular risk score, and the results supported an independent association
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37 306 between SUA and cardiovascular disease.^{3 38} There were numerous mechanisms involved in the close
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40 307 association between serum uric acid and CVDs.³⁹⁻⁴² Uric acid stimulates platelet-derived growth factor
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42 308 receptor β (PDGFR β) phosphorylation, leading to vascular smooth muscle cell (VSMC) proliferation.³⁹
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45 309 Uric acid increases oxidative stress and stimulates the activation of renin-angiotensin system, resulting in
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48 310 the senescence and apoptosis of human umbilical vein endothelial cells (HUVECs).⁴⁰ Uric acid also can
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51 311 cause mitochondrial alterations and decreased intracellular ATP production and subsequently result in
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53 312 endothelial dysfunction in human aortic endothelial cells (HAECs).⁴¹ A large quantity of animal
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56 313 experiments and human epidemiological documents indicated that SUA-lowering treatment was beneficial
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59 314 for cardiovascular diseases.⁴³⁻⁴⁷
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4315 On the other hand, the related mechanisms in the link between hyperuricemia and chronic kidney
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7316 disease (CKD) were not well investigated. It was demonstrated that 70% of urate eliminated occurs in the
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317 kidneys, and decreased eGFR would result in elevated levels of SUA.⁴⁸ However, uric acid could induce
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318 oxidative stress, trigger activation of RAAS and inflammation, cause endothelial dysfunction, and thus
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1319 subsequently lead to decline of eGFR.^{35 49 50} The persistent high level of SUA predicts the high risk of
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1820 developing CKD.⁵¹ There was a marked association of SUA with albuminuria in patients with renal
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321 insufficiency.⁵² Our study were in consistent with many prospective studies,^{14 53 54} showing that SUA is a
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2322 significant risk factor for CKD and proteinuria, which is independent of confounders of CRFs. We further
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2623 demonstrated that hyperuricemia significantly correlated with acid urine and nephrolithiasis, which was
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324 confirmed by the prevalence rates of chronic kidney disease and nephrolithiasis across the SUA levels.
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3125 This study has some limitations that need to be mentioned. First, it was a cross-section study and the
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3326 results could not establish causative relationships between hyperuricemia and CRFs clustering and renal
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3727 diseases. Future follow-up studies are required for more accurate evaluation of these relationships.
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328 Second, the data were from three medical centers' databases that lacked details in waist circumference,
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4229 HOMA-IR, smoking, drinking, lifestyles, diet and pharmacotherapy, which might affect the deviations of
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4530 some clinical outcomes. Nonetheless, the strengths of our study included its strict exclusion criteria based
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331 on medical histories and laboratory findings. And we conducted a multi-center study with large sample
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5032 size which ensured sufficient parameters and accurate results. The relationship was analyzed in both
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5333 sexes and a solid conclusion about the differences between men and women was gained.
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334 56 57 58335 **CONCLUSION** 59 60

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In summary, our data demonstrated that the increasing prevalent rate of CRFs and renal disorders were significantly correlated with the elevated level of serum uric acid. Hyperuricemia was remarkably linked with CVD-related risk factors and kidney disease, especially in females.

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Competing interests None declared.

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4359 **Patient consent** Obtained.
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7360 **Ethics approval and consent to participate**
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10361 This study was approved by the Human Research Ethics Committee of Shanghai East Hospital Affiliated
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12362 to Tongji University School of Medicine, the Human Research Ethics Committee of Pudong New District
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15363 Gongli Hospital and the Human Research Ethics Committee of Baoshan Branch of Shanghai First
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18364 People's Hospital. All methods were performed in compliance with Good Clinical Practice (GCP)
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20365 guidelines and the Declaration of Helsinki. Written informed consent was obtained from each participant
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23366 before data collection.
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26367 **Provenance and peer review** Not commissioned; externally peer reviewed.
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29368 **Data sharing statement** The data sets generated and analysed during the current study are available
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31369 from the corresponding author upon reasonable request.
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Figure legend

Figure 1. Prevalence of major CVD risk factors, renal diseases in different levels of serum uric acid.

Prevalence of obesity(A), hypertension(B), diabetes mellitus(C), dyslipidemia(D), chronic kidney disease

(E) and nephrolithiasis(F) in different levels of serum uric acid. The gender-specific quartiles of uric acid

(mg/dL), Q1: males (M) ≤ 4.9 , females (F) ≤ 3.9 ; Q2: M 5.0-5.9, F 4.0-4.9; Q3: M 6.0-6.9, F 5.0-5.9; Q4:

M ≥ 7.0 , F ≥ 6.0 .

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Table 1. Clinical characteristics of participants in quartiles of serum uric acid level.

	Men (n=15300)					Women (n=11876)				
	Q1 ≤4.9mg/dl	Q2 5.0-5.9mg/dl	Q3 6.0-6.9mg/dl	Q4 ≥7.0mg/dl	P-value for trend	Q1 ≤3.9mg/dl	Q2 4.0-4.9mg/dl	Q3 5.0-5.9mg/dl	Q4 ≥6.0mg/dl	P-value for trend
N(%)	2929(19.1%)	4720(30.8%)	4236(27.7%)	3415(22.3%)	-	3355(28.3%)	4553(38.3%)	2645(22.3%)	1323(11.1%)	-
Comorbidities										
Obesity (n, %)	194(6.6%)	450(9.5%)***	620(14.6%)***	814(23.8%)***	< 0.001	133(4.0%)	364(8.0%)***	380(14.4%)***	315(23.8%)***	< 0.001
Hypertension (n, %)	809(27.6%)	1215(25.7%)	1289(30.4%)*	1220(35.7%)***	< 0.001	554(16.5%)	1013(22.2%)***	785(29.7%)***	572(43.2%)***	< 0.001
Diabetes mellitus (n, %)	351(12.0%)	306(6.5%)***	224(5.3%)***	168(4.9%)***	< 0.001	125(3.7%)	170(3.7%)	154(5.8%)***	132(10.0%)***	< 0.001
Dyslipidemia (n, %)	735(25.1%)	1567(33.2%)***	1732(40.9%)***	1854(54.3%)***	< 0.001	394(11.7%)	866(19.0%)***	782(29.6%)***	606(45.8%)***	< 0.001
Chronic kidney disease (n, %)	48(1.6%)	114(2.4%)*	138(3.3%)***	238(7.0%)***	< 0.001	25(0.7%)	78(1.7%)***	105(4.0%)***	171(12.9%)***	< 0.001
Nephrolithiasis (n, %)	384(13.1%)	717(15.2%)*	653(15.4%)*	634(18.6%)***	< 0.001	368(11.0%)	484(10.6%)	372(14.1%)***	224(16.9%)***	< 0.001
Biochemical variables										
Age	50.08±15.49	48.00±15.57***	47.24±15.62***	47.31±15.76***	< 0.001	46.78±14.02	48.79±14.88***	52.14±15.44***	57.79±15.34***	< 0.001
BMI (kg/m ²)	23.29±3.06	24.11±3.07***	24.81±3.14***	25.96±3.25***	< 0.001	22.14±3.00	23.10±3.31***	24.32±3.53***	25.66±3.93***	< 0.001
SBP (mmHg)	126.61±18.21	126.22±17.42	127.70±18.10*	130.24±18.18***	< 0.001	120.26±18.26	123.37±19.28***	128.36±20.48***	135.02±21.25***	< 0.001
DBP (mmHg)	78.98±11.54	78.74±11.09	80.16±11.82***	81.71±11.85***	< 0.001	73.23±10.52	74.98±10.99***	77.16±11.25***	79.02±11.87***	< 0.001
FPG (mmol/L)	5.65±1.87	5.36±1.35***	5.33±1.21***	5.33±1.07***	< 0.001	5.08±1.22	5.12±1.12	5.29±1.22***	5.57±1.28***	< 0.001
TC (mmol/L)	4.52±0.88	4.58±0.86**	4.71±0.89***	4.87±0.91***	< 0.001	4.64±0.91	4.82±0.93***	5.00±0.94***	5.17±1.04***	< 0.001
TG (mmol/L)	1.28±1.27	1.45±1.14***	1.72±1.46***	2.14±1.71***	< 0.001	0.96±0.59	1.19±0.76***	1.46±0.98***	1.97±1.61***	< 0.001
HDL-C (mmol/L)	1.32±0.31	1.25±0.28***	1.22±0.28***	1.17±0.26***	< 0.001	1.59±0.35	1.50±0.34***	1.42±0.32***	1.31±0.31***	< 0.001
LDL-C (mmol/L)	2.77±0.76	2.88±0.76***	2.95±0.77***	3.04±0.81***	< 0.001	2.71±0.77	2.89±0.79***	3.07±0.81***	3.11±0.86***	< 0.001
eGFR (ml/(min*1.73m ²))	92.46±20.66	89.41±19.32***	87.74±19.50***	84.85±20.04***	< 0.001	100.14±23.03	97.08±23.89***	93.16±23.98***	85.54±25.15***	< 0.001
Cr (umol / L)	80.90±18.37	83.61±14.59***	85.39±14.70***	88.94±22.63***	< 0.001	62.18±10.80	63.83±12.03***	65.68±13.25***	71.34±28.69***	< 0.001
BUN (mmol/L)	5.19±1.31	5.26±1.22*	5.31±1.25***	5.43±1.56***	< 0.001	4.57±1.20	4.84±1.23***	5.11±1.27***	5.55±1.82***	< 0.001

The continuous variables are reported in means±SD and categorical variables are presented in percentages. In case of nonparametric data distribution medians with inter quartile range (IQR) are presented. Abbreviations: BMI: body mass index, SBP: systolic blood pressure, DBP: diastolic blood pressure, FPG: fasting plasma glucose, TC: total cholesterol, TG: triglyceride, HDL-C: high density lipoprotein cholesterol, LDL-C: low density lipoprotein cholesterol, eGFR: estimated glomerular filtration rate. Cr: creatinine, BUN: blood urea nitrogen. *P < 0.05, **P < 0.01, ***P < 0.001 vs. the group of Q1. Using the least significance difference (LSD) method if the variance is equal or the Tamhane's T2 method if the variance is not equal, using Kruskal-Wallis test in case of nonparametric data distribution.

Table 2. Correlation coefficients between serum uric acid and various parameters.

Variable	Men		Women		Total	
	r	P-value	r	P-value	r	P-value
Age	-0.059	< 0.001	0.227	< 0.001	0.014	0.020
BMI (kg/m ²)	0.289	< 0.001	0.327	< 0.001	0.343	< 0.001
SBP (mmHg)	0.075	< 0.001	0.234	< 0.001	0.158	< 0.001
DBP (mmHg)	0.091	< 0.001	0.166	< 0.001	0.197	< 0.001
FPG (mmol/L)	-0.072	< 0.001	0.124	< 0.001	0.039	< 0.001
TC (mmol/L)	0.148	< 0.001	0.185	< 0.001	0.091	< 0.001
TG (mmol/L)	0.221	< 0.001	0.326	< 0.001	0.290	< 0.001
HDL-C (mmol/L)	-0.177	< 0.001	-0.263	< 0.001	-0.357	< 0.001
LDL-C (mmol/L)	0.120	< 0.001	0.181	< 0.001	0.127	< 0.001
eGFR (ml/(min*1.73m ²))	-0.140	< 0.001	-0.194	< 0.001	-0.219	< 0.001

Abbreviations: BMI: body mass index, SBP: systolic blood pressure, DBP: diastolic blood pressure, FPG: fasting plasma glucose, TC: total cholesterol, TG: triglyceride, HDL-C: high density lipoprotein cholesterol, LDL-C: low density lipoprotein cholesterol, eGFR: estimated glomerular filtration rate.

Table 3. Multiple linear regression analysis for association of various independent variable with serum uric acid (dependent variable)

Variable	Men		Women		Total	
	<i>St B</i>	<i>P</i> -value	<i>St B</i>	<i>P</i> -value	<i>St B</i>	<i>P</i> -value
Age	-0.125	< 0.001			-0.139	< 0.001
BMI (kg/m ²)	0.214	< 0.001	0.188	< 0.001	0.195	< 0.001
SBP (mmHg)	0.060	< 0.001	0.054	< 0.001	0.087	< 0.001
FPG (mmol/L)	-0.122	< 0.001	-0.027	0.002	-0.059	< 0.001
TC (mmol/L)	0.103	< 0.001	0.111	< 0.001	0.090	< 0.001
TG (mmol/L)	0.114	< 0.001	0.146	< 0.001	0.107	< 0.001
HDL-C (mmol/L)	-0.085	< 0.001	-0.171	< 0.001	-0.254	< 0.001
eGFR (ml/(min*1.73m ²))	-0.153	< 0.001	-0.147	< 0.001	-0.208	< 0.001

Multicollinearity analysis showed that SBP and DBP highly correlate with each other, so do TC and LDL-C. And backward elimination was adopted for multiple linear regression to identify independent variables which have most impact on dependent variables. Finally, Independent variables DBP and LDL-C were removed in male and in total. Independent variables DBP, LDL-C and age were removed in female.

Abbreviations: BMI: body mass index, SBP: systolic blood pressure, DBP: diastolic blood pressure, FPG: fasting plasma glucose, TC: total cholesterol, TG: triglyceride, HDL-C: high density lipoprotein cholesterol, LDL-C: low density lipoprotein cholesterol, eGFR: estimated glomerular filtration rate. Standardized beta coefficients (*St B*) refer to how many standard deviations a dependent variable will change per standard deviation increase in the predictor variable.

Table 4. The odds ratio for hyperuricemia according to different status of parameters of men and women.

	Men				Women			
	Unadjusted		Full-adjusted		Unadjusted		Full-adjusted	
	OR (95%CI)	P-value	OR (95%CI)	P-value	OR (95%CI)	P-value	OR (95%CI)	P-value
BMI (kg/m ²)								
18.5 ≤BMI<24.0 (Ref.)								
BMI<18.5	0.502 (0.337-0.747)	0.001	0.558 (0.374-0.835)	0.004	0.502 (0.322-0.784)	0.002	0.636 (0.403-1.005)	0.052
24.0≤BMI<28.0	2.165 (1.978-2.368)	< 0.001	1.878 (1.707-2.065)	< 0.001	2.732 (2.392-3.121)	< 0.001	1.906 (1.649-2.203)	< 0.001
BMI≥28.0	3.972 (2.548-4.448)	< 0.001	3.102 (2.745-3.507)	< 0.001	5.077 (4.323-5.962)	< 0.001	3.126 (2.611-3.743)	< 0.001
Blood pressure (mmHg)								
Normotensive (Ref.)								
Pre-HT	1.304 (1.185-1.436)	< 0.001	1.138 (1.028-1.260)	0.013	1.958 (1.682-2.280)	< 0.001	1.129 (0.953-1.337)	0.159
Grade1 HT	1.663 (1.493-1.853)	< 0.001	1.350 (1.195-1.525)	< 0.001	3.321 (2.825-3.903)	< 0.001	1.328 (1.094-1.612)	0.004
Grade2/3 HT	1.716 (1.491-1.976)	< 0.001	1.393 (1.186-1.635)	< 0.001	4.887 (4.018-5.945)	< 0.001	1.480 (1.162-1.885)	0.002
FPG (mmol/L)								
FPG<6.1 (Ref.)								
6.1≤FPG<7	1.188 (1.026-1.375)	0.021	0.921 (0.785-1.081)	0.313	2.612 (2.126-3.209)	< 0.001	1.221 (0.972-1.535)	0.087
FPG≥7	0.655 (0.552-0.776)	< 0.001	0.410 (0.340-0.495)	< 0.001	2.673 (2.179-3.278)	< 0.001	0.793 (0.624-1.009)	0.059
Cholesterol (mmol/L)								
TC≤6.22 (Ref.)								
TC>6.22	1.885 (1.610-2.207)	< 0.001	1.072 (0.874-1.315)	0.502	2.044 (1.722-2.426)	< 0.001	1.070 (0.835-1.372)	0.591
Triglyceride (mmol/L)								
TG≤2.26 (Ref.)								
TG>2.26	2.881 (2.636-3.148)	< 0.001	2.242 (2.029-2.477)	< 0.001	4.603 (4.994-5.305)	< 0.001	2.513 (2.129-2.967)	< 0.001
HDL-C (mmol/L)								
HDL-C≥1.04 (Ref.)								
HDL-C<1.04	1.651 (1.519-1.795)	< 0.001	1.097 (0.999-1.205)	0.054	3.404 (2.898-3.999)	< 0.001	1.929 (1.601-2.324)	< 0.001
LDL-C (mmol/L)								
LDL-C≤4.14 (Ref.)								
LDL-C>4.14	1.737 (1.506-2.003)	< 0.001	1.522 (1.271-1.822)	< 0.001	1.871 (1.556-2.251)	< 0.001	1.299 (1.002-1.686)	0.049
eGFR (ml/(min*1.73m ²))								
eGFR≥90 (Ref.)								
60≤eGFR<89	1.175 (1.084-1.273)	< 0.001	1.351 (1.235-1.477)	< 0.001	1.672 (1.479-1.891)	< 0.001	1.580 (1.377-1.814)	< 0.001
eGFR≤59	3.185 (2.657-3.818)	< 0.001	4.461 (3.621-5.496)	< 0.001	9.569 (7.633-11.949)	< 0.001	6.453 (4.982-8.356)	< 0.001
Albuminuria								
-/+ (Ref.)								
+	1.256 (0.888-1.775)	0.198	0.899 (0.615-1.314)	0.584	6.020 (3.995-9.072)	< 0.001	2.899 (1.791-4.694)	< 0.001
++	2.123 (1.464-3.078)	< 0.001	1.392 (0.923-2.100)	0.115	3.203 (1.882-5.449)	< 0.001	1.521 (0.824-2.807)	0.180
+++	3.166 (1.990-5.036)	< 0.001	2.335 (1.393-3.913)	0.001	10.837 (6.108-19.225)	< 0.001	4.634 (2.399-8.953)	< 0.001
Urinary pH								
6≤pH<7 (Ref.)								
pH<6	1.490 (1.375-1.615)	< 0.001	1.602 (1.464-1.752)	< 0.001	2.108 (1.875-2.371)	< 0.001	1.839 (1.613-2.098)	< 0.001
pH>7	0.534 (0.415-0.688)	< 0.001	0.581 (0.447-0.754)	< 0.001	0.653 (0.466-0.915)	0.013	0.741 (0.521-1.053)	0.094
Nephrolithiasis								
No (Ref.)								
Yes	1.317 (1.191-1.455)	< 0.001	1.250 (1.121-1.392)	< 0.001	1.553 (1.330-1.815)	< 0.001	1.214 (1.021-1.443)	0.028

Abbreviations: BMI: body mass index, FPG: fasting plasma glucose, TC: total cholesterol, TG: triglyceride, HDL-C: high density lipoprotein cholesterol, LDL-C: low density lipoprotein cholesterol, eGFR: estimated glomerular filtration rate. Blood pressure (mmHg): normotensive: SBP<120 and DBP<80; pre-HT: SBP of 120-139 and/or DBP of 80-89; Grade1 HT: SBP of 140-159 and/or DBP of 90-99; Grade2/3 HT: SBP≥160 and/or DBP≥100

Table 5. The association between SUA and Obesity, hypertension, Diabetes mellitus, Dyslipidemia, CKD, Nephrolithiasis in men.

	Q1	Q2			Q3			Q4		
	-	OR	95%CI	P-value	OR	95%CI	P-value	OR	95%CI	P-value
Obesity										
Model1	1(Ref.)	1.487	1.248-1.772	< 0.001	2.420	2.044-2.866	< 0.001	4.418	3.743-5.214	< 0.001
Model2 ^a	1(Ref.)	1.355	1.130-1.625	0.001	1.955	1.637-2.334	< 0.001	3.102	2.600-3.701	< 0.001
Model3 ¹	1(Ref.)	1.362	1.135-1.635	0.001	1.971	1.649-2.356	< 0.001	3.115	2.604-3.727	< 0.001
Hypertension										
Model1	1(Ref.)	0.999	0.895-1.115	0.981	1.351	1.209-1.509	< 0.001	1.769	1.577-1.983	< 0.001
Model2 ^b	1(Ref.)	0.934	0.832-1.048	0.246	1.146	1.019-1.289	0.023	1.266	1.118-1.434	< 0.001
Model3 ²	1(Ref.)	0.940	0.838-1.056	0.298	1.164	1.034-1.310	0.012	1.290	1.136-1.465	< 0.001
Diabetes mellitus										
Model1	1(Ref.)	0.539	0.457-0.636	< 0.001	0.445	0.372-0.531	< 0.001	0.407	0.335-0.495	< 0.001
Model2 ^c	1(Ref.)	0.434	0.366-0.516	< 0.001	0.289	0.239-0.349	< 0.001	0.210	0.170-0.259	< 0.001
Model3 ³	1(Ref.)	0.442	0.371-0.526	< 0.001	0.293	0.241-0.356	< 0.001	0.205	0.165-0.255	< 0.001
Dyslipidemia										
Model1	1(Ref.)	1.510	1.361-1.674	< 0.001	2.116	1.907-2.348	< 0.001	3.639	3.267-4.053	< 0.001
Model2 ^d	1(Ref.)	1.428	1.282-1.592	< 0.001	1.812	1.624-2.023	< 0.001	2.675	2.385-3.002	< 0.001
Model3 ⁴	1(Ref.)	1.408	1.262-1.570	< 0.001	1.755	1.571-1.961	< 0.001	2.503	2.226-2.815	< 0.001
Chronic kidney disease										
Model1	1(Ref.)	1.698	1.199-2.404	0.003	2.458	1.749-3.454	< 0.001	5.883	4.254-8.136	< 0.001
Model2 ^e	1(Ref.)	1.895	1.329-2.700	< 0.001	2.745	1.935-3.896	< 0.001	6.800	4.829-9.576	< 0.001
Model3 ⁵	1(Ref.)	1.894	1.325-2.707	< 0.001	2.795	1.966-3.975	< 0.001	6.962	4.921-9.851	< 0.001
Nephrolithiasis										
Model1	1(Ref.)	1.248	1.090-1.428	0.001	1.292	1.126-1.482	< 0.001	1.619	1.409-1.861	< 0.001
Model2 ^f	1(Ref.)	1.163	1.015-1.334	0.030	1.150	0.999-1.324	0.052	1.346	1.162-1.560	< 0.001
Model3 ⁶	1(Ref.)	1.225	1.067-1.406	0.004	1.229	1.065-1.418	0.005	1.480	1.272-1.722	< 0.001

Model 1: adjusted for age

^aModel 2: adjusted for variables included in model1 and SBP, DBP, FPG, TC, TG, HDL-C, LDL-C; ^bModel2: adjusted for variables included in model1 and BMI, FPG, TC, TG, HDL-C, LDL-C; ^cModel2: adjusted for variables included in model1 and BMI, SBP, DBP, TC, TG, HDL-C, LDL-C; ^dModel2: adjusted for variables included in model1 and BMI, SBP, DBP, FPG; ^eModel2: adjusted for variables included in model1 and BMI, SBP, DBP, FPG, TC, TG, HDL-C, LDL-C; ^fModel2: adjusted for variables included in model1 and BMI, SBP, DBP, FPG, TC, TG, HDL-C, LDL-C.

¹Model 3: adjusted for variables included in model2^a and eGFR, urine Ph, albuminuria, nephrolithiasis; ²Model 3: adjusted for variables included in model2^b and eGFR, urine Ph, albuminuria, nephrolithiasis; ³Model 3: adjusted for variables included in model2^c and eGFR, urine Ph, albuminuria, nephrolithiasis; ⁴Model 3: adjusted for variables included in model2^d and eGFR, urine Ph, albuminuria, nephrolithiasis; ⁵Model 3: adjusted for variables included in model2^e and urine Ph, albuminuria, nephrolithiasis; ⁶Model 3: adjusted for variables included in model2^f and eGFR, urine Ph, albuminuria.

Abbreviations: BMI: body mass index, SBP: systolic blood pressure, DBP: diastolic blood pressure, FPG: fasting plasma glucose, TC: total cholesterol, TG: triglyceride, HDL-C: high density lipoprotein cholesterol, LDL-C: low density lipoprotein cholesterol, eGFR: estimated glomerular filtration rate.

Table 6. The association between SUA and Obesity, hypertension, Diabetes mellitus, Dyslipidemia, CKD, Nephrolithiasis in women.

	Q1	Q2			Q3			Q4		
	-	OR	95%CI	P-value	OR	95%CI	P-value	OR	95%CI	P-value
Obesity										
Model1	1(Ref.)	2.000	1.630-2.455	< 0.001	3.568	2.902-4.387	< 0.001	5.837	4.687-7.269	< 0.001
Model2 ^a	1(Ref.)	1.652	1.338-2.041	< 0.001	2.453	1.976-3.045	< 0.001	3.560	2.818-4.497	< 0.001
Model3 ¹	1(Ref.)	1.679	1.358-2.076	< 0.001	2.498	2.008-3.107	< 0.001	3.755	2.956-4.769	< 0.001
Hypertension										
Model1	1(Ref.)	1.285	1.133-1.457	< 0.001	1.565	1.365-1.794	< 0.001	2.109	1.799-2.472	< 0.001
Model2 ^b	1(Ref.)	1.110	0.972-1.267	0.123	1.120	0.967-1.298	0.130	1.244	1.045-1.480	0.014
Model3 ²	1(Ref.)	1.127	0.987-1.287	0.078	1.161	1.001-1.347	0.049	1.287	1.075-1.539	0.006
Diabetes mellitus										
Model1	1(Ref.)	0.868	0.683-1.104	0.249	1.146	0.893-1.469	0.284	1.536	1.178-2.004	0.002
Model2 ^c	1(Ref.)	0.614	0.477-0.791	< 0.001	0.609	0.466-0.797	< 0.001	0.588	0.437-0.791	< 0.001
Model3 ³	1(Ref.)	0.596	0.462-0.770	< 0.001	0.566	0.431-0.744	< 0.001	0.514	0.377-0.701	< 0.001
Dyslipidemia										
Model1	1(Ref.)	1.670	1.466-1.903	< 0.001	2.735	2.385-3.136	< 0.001	4.761	4.075-5.561	< 0.001
Model2 ^d	1(Ref.)	1.583	1.386-1.809	< 0.001	2.385	2.071-2.747	< 0.001	3.836	3.265-4.508	< 0.001
Model3 ⁴	1(Ref.)	1.575	1.378-1.800	< 0.001	2.318	2.010-2.673	< 0.001	3.675	3.114-4.336	< 0.001
Chronic kidney disease										
Model1	1(Ref.)	1.962	1.241-3.102	0.004	3.676	2.353-5.745	< 0.001	9.740	6.306-15.045	< 0.001
Model2 ^e	1(Ref.)	2.092	1.317-3.322	0.002	4.096	2.591-6.475	< 0.001	11.510	7.282-18.193	< 0.001
Model3 ⁵	1(Ref.)	2.051	1.291-3.260	0.002	4.189	2.645-6.634	< 0.001	11.508	7.242-18.288	< 0.001
Nephrolithiasis										
Model1	1(Ref.)	0.922	0.798-1.065	0.268	1.183	1.012-1.383	0.035	1.312	1.090-1.580	0.004
Model2 ^f	1(Ref.)	0.853	0.736-0.988	0.034	1.022	0.868-1.203	0.797	1.034	0.847-1.262	0.742
Model3 ⁶	1(Ref.)	0.889	0.766-1.032	0.123	1.111	0.940-1.313	0.216	1.239	1.008-1.522	0.042

Model 1: adjusted for age

^aModel 2: adjusted for variables included in model1 and SBP, DBP, FPG, TC, TG, HDL-C, LDL-C; ^bModel2: adjusted for variables included in model1 and BMI, FPG, TC, TG, HDL-C, LDL-C; ^cModel2: adjusted for variables included in model1 and BMI, SBP, DBP, TC, TG, HDL-C, LDL-C; ^dModel2: adjusted for variables included in model1 and BMI, SBP, DBP, FPG; ^eModel2: adjusted for variables included in model1 and BMI, SBP, DBP, FPG, TC, TG, HDL-C, LDL-C; ^fModel2: adjusted for variables included in model1 and BMI, SBP, DBP, FPG, TC, TG, HDL-C, LDL-C.

¹Model 3: adjusted for variables included in model2^a and eGFR, urine Ph, albuminuria, nephrolithiasis; ²Model 3: adjusted for variables included in model2^b and eGFR, urine Ph, albuminuria, nephrolithiasis; ³Model 3: adjusted for variables included in model2^c and eGFR, urine Ph, albuminuria, nephrolithiasis; ⁴Model 3: adjusted for variables included in model2^d and eGFR, urine Ph, albuminuria, nephrolithiasis; ⁵Model 3: adjusted for variables included in model2^e and urine Ph, albuminuria, nephrolithiasis; ⁶Model 3: adjusted for variables included in model2^f and eGFR, urine Ph, albuminuria.

Abbreviations: BMI: body mass index, SBP: systolic blood pressure, DBP: diastolic blood pressure, FPG: fasting plasma glucose, TC: total cholesterol, TG: triglyceride, HDL-C: high density lipoprotein cholesterol, LDL-C: low density lipoprotein cholesterol, eGFR: estimated glomerular filtration rate.

Table 7. The association between hyperuricemia and clustered CVD risk factors.

Clustered CVD risk factors	Men						Women					
	Unadjusted			Age-adjusted			Unadjusted			Age-adjusted		
	OR	95%CI	<i>P</i> -value	OR	95%CI	<i>P</i> -value	OR	95%CI	<i>P</i> -value	OR	95%CI	<i>P</i> -value
0	Ref.											
1	1.948	1.774-2.140	< 0.001	2.119	1.926-2.332	< 0.001	3.337	2.887-3.856	< 0.001	2.642	2.266-3.081	< 0.001
2	2.977	2.671-3.318	< 0.001	3.390	3.029-3.794	< 0.001	6.116	5.199-7.195	< 0.001	4.447	3.728-5.304	< 0.001
≥3	3.343	2.867-3.897	< 0.001	3.804	3.252-4.450	< 0.001	8.848	7.070-11.075	< 0.001	6.265	4.945-7.938	< 0.001
<i>P</i> value for trend			< 0.001			< 0.001			< 0.001			< 0.001

Clustered CVD risk factors included obesity, hypertension, diabetes mellitus, dyslipidemia

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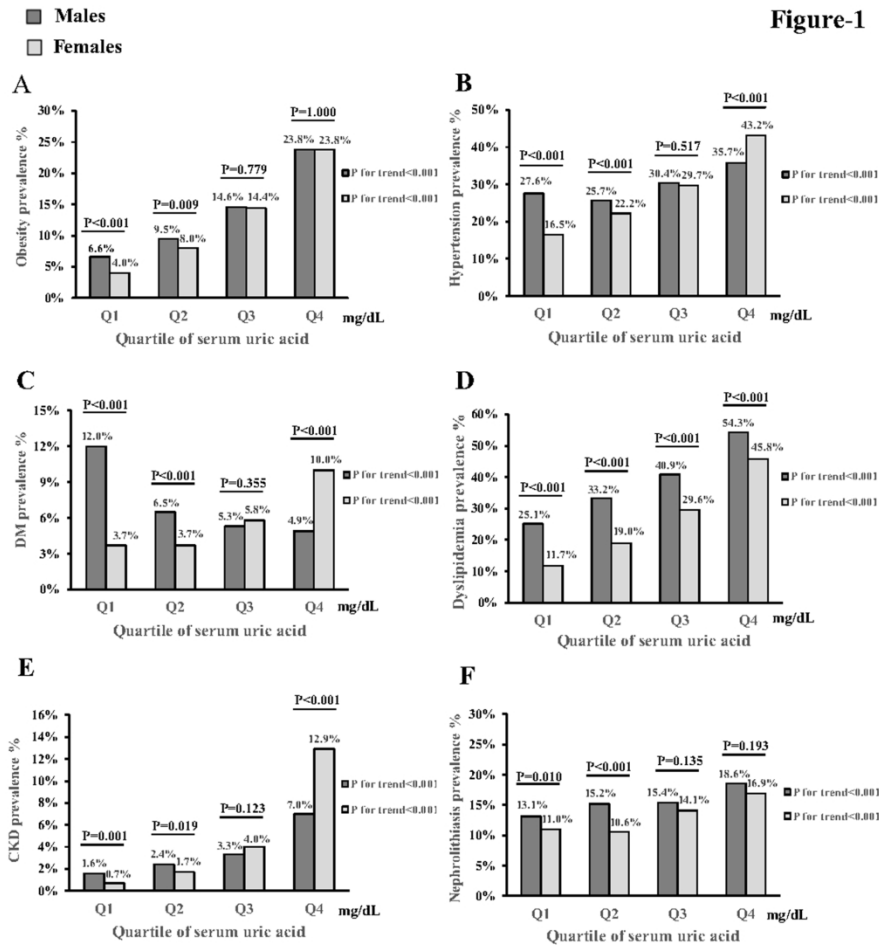


Figure 1. Prevalence of major CVD risk factors, renal diseases in different levels of serum uric acid. Prevalence of obesity(A), hypertension(B), diabetes mellitus(C), dyslipidemia(D), chronic kidney disease (E) and nephrolithiasis(F) in different levels of serum uric acid. The gender-specific quartiles of uric acid (mg/dL), Q1: males (M) ≤ 4.9 , females (F) ≤ 3.9 ; Q2: M 5.0-5.9, F 4.0-4.9; Q3: M 6.0-6.9, F 5.0-5.9; Q4: M ≥ 7.0 , F ≥ 6.0 .

190x254mm (300 x 300 DPI)

STROBE Statement—Checklist of items that should be included in reports of *cross-sectional studies*

	Item No	Recommendation
Title and abstract	1	<p>(a) The relationship between serum uric acid and clustering of cardiovascular disease risk factors, renal disorders among Shanghai population: a multi-center and cross-sectional study</p> <p>(b) Objectives To estimate the current prevalence of cardiovascular disease risk factors (CRFs) and renal disorders across serum uric acid (SUA) quartiles, and evaluate the relationships between SUA and CRFs, renal diseases in Shanghai population. Study design Observational, cross-sectional study. Setting Data were obtained from physical checkups of local residents at three hospitals in Shanghai. Participants Residents were invited to take part in physical checkups and provided informed consents. Exclusion criteria were diseases that resemble cancer, hepatic disease and other coexisting illnesses including autoimmune kidney diseases, renal artery stenosis, individuals treated with xanthine oxidase inhibitors and without complete information. There are 27176 individuals in our study. Primary and secondary outcome measures Hyperuricemia was defined as SUA ≥ 7 mg/dL in males and ≥ 6 mg/dL in females or taking xanthine oxidase inhibitors. Subjects were divided into gender-specific quartiles. We estimate the prevalence of CRFs and renal disorders across SUA quartiles. The relationships between SUA and CRFs, renal disorders at different gender were evaluated with logistic regression analysis. Results: There was a significant increase in the prevalence of major CRFs and renal diseases across SUA quartiles in separate analysis among men and women (all P-trend<0.001). After multiple adjustment, hyperuricemia positively connected with obesity (Male OR=3.115, $P<0.001$; Female OR=3.755, $P<0.001$), hypertension (Male OR=1.290, $P<0.001$; Female OR=1.287, $P=0.006$), dyslipidemia (Male OR=2.503, $P<0.001$; Female OR=3.675, $P<0.001$), chronic kidney disease (Male OR=6.962, $P<0.001$; Female OR=11.508, $P<0.001$), nephrolithiasis (Male OR=1.480, $P<0.001$; Female OR=1.239, $P=0.042$), but negatively connected with diabetes mellitus ((Male OR=0.205, $P<0.001$; Female OR=0.514, $P<0.001$)). Women had a stronger association between hyperuricemia and clustered CRFs, CKD than men. Conclusions: In Shanghai population, concomitant with the elevated level of SUA, the prevalence of CRFs and renal diseases was rising. Hyperuricemia was significantly associated with CRFs and renal disorders, especially in females.</p>
Introduction		
Background/rationale	2	The relationship between hyperuricemia and cardiovascular disease risk factors (CRFs) at different gender of Shanghai population has not been well studied. And the data from multiple clinical centers in China are extremely limited. Whether serum uric acid (SUA) is a cause or an association to renal diseases is a question that still waits for further investigations. Thus, we estimate the current prevalence of CRFs and renal disorders across SUA quartiles, and evaluate the relationships between SUA and CRFs, renal diseases in Shanghai population.
Objectives	3	To estimate the current prevalence of cardiovascular disease risk factors (CRFs) and renal disorders across serum uric acid (SUA) quartiles, and evaluate the relationships between SUA and CRFs, renal diseases in Shanghai population.
Methods		
Study design	4	Observational, cross-sectional study
Setting	5	Data were obtained from physical checkups of local residents at three hospitals in

Shanghai during the period from January 2015 and December 2015.		
Participants	6	Residents were invited to take part in physical checkups and provided informed consents. Exclusion criteria were diseases that resemble cancer, hepatic disease and other coexisting illnesses including autoimmune kidney diseases, renal artery stenosis, individuals treated with xanthine oxidase inhibitors and without complete information. There are 27176 individuals in our study.
Variables	7	Hyperuricemia was defined as serum uric acid ≥ 7 mg/dL in males and ≥ 6 mg/dL in females or current use of xanthine oxidase inhibitors. SUA was determined using the uricase-peroxidase method. Body mass index (BMI) was calculated as weight in kilograms divided by height in squared meters. According to WHO guidelines for the Asian Pacific population, normal weight was defined as $18.5 \leq \text{BMI} < 24.0$ kg/m ² , overweight was defined as $24.0 \leq \text{BMI} < 28.0$ kg/m ² , obesity was defined as BMI ≥ 28.0 kg/m ² , underweight was defined as BMI < 18.5 kg/m ² . Blood pressure measurements were taken according to the Joint National Committee VII criteria (JNC VII). Normal BP was defined as having SBP < 120 mmHg and DBP < 80 mmHg. Pre-hypertension was defined as having SBP of 120–139 mmHg and/or DBP of 80–89 mmHg. Grade 1 hypertension was defined as having SBP of 140–159 mmHg and/or DBP of 90–99 mmHg. Grade 2 or grade 3 hypertension was defined as SBP ≥ 160 mmHg and/or DBP ≥ 100 mmHg. According to the Chinese adult dyslipidemia prevention guide (2007 edition), individuals with a fasting TC ≥ 6.22 mmol/L, TG ≥ 2.26 mmol/L, HDL-C < 1.04 mmol/L, and/or LDL-C > 4.14 mmol/L, or currently undergoing pharmacologic treatment were defined as the dyslipidemia. T2D was defined based on World Health Organization (WHO) 1999 diagnostic criteria as fasting plasma glucose ≥ 7.0 mmol/l or 2-h plasma glucose ≥ 11.1 mmol/l, impaired fasting glucose (IFG) was defined as $6.1 \text{ mmol/l} \leq \text{FPG} < 7.0 \text{ mmol/l}$, and normal condition was defined as $\text{FPG} < 6.1 \text{ mmol/l}$. The eGFR was calculated using Modification of Diet in Renal Disease (MDRD) formula: $186 \times [\text{serum creatinine (mg/dl)}]^{-1.154} \times (\text{age})^{-0.203} \times [0.742 \text{ (if female)}]$. According to the Kidney Disease Outcomes Quality Initiative (KDOQI) clinical practice guideline, estimated glomerular filtration rate (eGFR) $< 60 \text{ mL/min/1.73 m}^2$, proteinuria and hematuria were defined as markers of CKD. Urine proteinuria were recorded as negative (–), trace, 1+, 2+ and 3+. Albuminuria was defined as $\geq 1+$.
Data sources/ measurement	8*	The permanent residents aged between 16-98 years who participated in the health checkups during the period from January 2015 and December 2015 of three medical centers Shanghai East Hospital Affiliated to Tongji University School of Medicine, Pudong New District Gongli Hospital and Baoshan Branch of Shanghai First People's Hospital were invited in the study. We divided the subjects into gender-specific quartiles [males (M): Q1 ≤ 4.9 , Q2: 5.0-5.9, Q3: 6.0-6.9, Q4 ≥ 7.0 mg/dL; females (F): Q1 ≤ 3.9 , Q2: 4.0-4.9, Q3: 5.0-5.9, Q4 ≥ 6.0 mg/dL] according to serum uric acid level.
Bias	9	We conducted a multi-center study with large sample size to reduce selection bias. We set a strict exclusion criteria based on medical histories and laboratory findings to reduce information bias.
Study size	10	There are 27176 individuals in our study.
Quantitative variables	11	The continuous variables are reported in means \pm SD and categorical variables are presented in percentages. In case of nonparametric data distribution medians with inter quartile range (IQR) are presented. The univariate analysis of variance (ANOVA) was used to measure the data among the groups or a Kruskal-Wallis test in case of nonparametric data distribution. Differences between groups for proportions were

tested with a chi-square test. If the results show differences between the groups, the post-hoc tests would be done. As for the post-hoc test, we used least significance difference (LSD) test if the variance was homogeneous, and we used Tamhane's T2 test if not.

Statistical methods	12	Correlations were Pearson's or Spearman's depending on the distribution of the data. In the present study, SUA, age, BMI, SBP, DBP, FPG, TC, TG, HDL-C, LDL-C, eGFR were normally distributed. Thus, Pearson's correlation was used among these variables. If Pearson's correlation analysis was statistically significant, multiple linear regression analysis was performed to determine the association of SUA with various independent variables. We analyzed the multiple collinearity by calculating the correlation coefficient matrix, tolerance and variance inflation factor of independent variables. Multivariable logistic regression analysis (unadjusted and full-adjusted) was used to calculate the odds ratio for hyperuricemia according to different status of clinical parameters. Furthermore, multivariable logistic regression analysis (multiple adjusted models) was used to examine the association between related diseases and the SUA categories of Q2 or greater compared to the lowest SUA category. The association between hyperuricemia and clustered CVD risk factors had been calculated. Statistical analyses were performed by IBM SPSS statistics version 20.0 (SPSS, Chicago, IL, USA). Statistical significance was set at P -values of <0.05 .
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Results

Participants	13*	After excluding subjects with incomplete data, cancer, hepatic disease or other coexisting illnesses including autoimmune kidney diseases, renal artery stenosis and subjects treated with xanthine oxidase inhibitors, 27176 participants were enrolled in our study.
Descriptive data	14*	According to our multi-center epidemiologic study of 27176 subjects, the prevalence of hyperuricemia in Shanghai was 17.4% (95%CI 17.0%-17.9%), 22.3% (21.7–23.0%) in men and 11.1% (10.6–11.7%) in women.
Outcome data	15*	In the male hyperuricemia individuals, the prevalence rates of obesity, hypertension, diabetes mellitus, dyslipidemia, chronic kidney disease and nephrolithiasis were 23.8% (95% CI, 22.4-25.3%), 35.7% (34.1-37.3%), 4.9% (4.2-5.6%), 54.3% (52.6-56.0%), 7.0% (6.1-7.8%) and 18.6% (17.3-19.9%) respectively. In the female hyperuricemia individuals, the prevalence rates of obesity, hypertension, diabetes mellitus, dyslipidemia, chronic kidney disease and nephrolithiasis were 23.8% (21.5-26.1%), 43.2% (40.6-45.9%), 10.0% (8.4-11.6%), 45.8% (43.1-48.5%), 12.9% (11.1-14.7%) and 16.9% (14.9-19.0%) respectively.
Main results	16	Multivariable logistic regression analysis (multiple adjusted models) was studied and the results were shown in Table 5. The odd ratio for obesity, hypertension, diabetes mellitus, dyslipidemia, chronic kidney disease, nephrolithiasis in the highest SUA quartile was 3.115 (95% CI 2.604–3.727, $P < 0.001$, model 3), 1.290 (95% CI 1.136–1.465, $P < 0.001$, model 3), 0.205 (95% CI 0.165–0.255, $P < 0.001$, model 3), 2.503 (95% CI 2.226–2.815, $P < 0.001$, model 3), 6.962 (95% CI 4.921–9.851, $P < 0.001$, model 3), 1.480 (95% CI 1.272–1.722, $P < 0.001$, model 3) compared with that in the lowest SUA quartile, respectively, in men. The data in Table 6 were multivariable logistic regression analysis in women and the odd ratio for obesity, hypertension, diabetes mellitus, dyslipidemia, chronic kidney disease, nephrolithiasis in the highest SUA quartile was 3.755 (95% CI 2.956–4.769, $P < 0.001$, model 3), 1.287 (95% CI 1.075–1.539, $P = 0.006$, model 3), 0.514 (95% CI 0.377–0.701, $P < 0.001$, model 3), 3.675 (95% CI 3.114–4.336, $P < 0.001$, model 3), 11.508 (95% CI 7.242–18.288, P

<0.001, model 3), 1.239 (95% CI 1.008–1.522, $P=0.042$, model 3) compared with that in the lowest SUA quartile, respectively.

Other analyses	17	Multivariable logistic regression was analyzed for hyperuricemia and clustered CVD risk factors, the results were shown in Table 7. After adjustment for age, compared with the group of zero CVD risk factor reference group, the odd ratio for group of ≥ 3 CVD risk factors was 3.804 (95% CI 3.252–4.450, $P < 0.001$), 6.265 (95% CI 4.945–7.938, $P < 0.001$) in men and women, respectively. The individuals with more CVD risk factors were associated with the higher ORs of hyperuricemia both in men and women (P for trend < 0.001). Furthermore, females had a stronger association of hyperuricemia with clustered CVD risk factors than males.
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Discussion

Key results	18	In summary, our data demonstrated that the increasing prevalent rate of CRFs and renal disorders were significantly correlated with the elevated level of serum uric acid. Hyperuricemia was remarkably linked with CVD-related risk factors and kidney diseases. Furthermore, a close correlation between hyperuricemia and clustered CVD risk factors, CKD was observed in females than in males.
Limitations	19	This study has some limitations that need to be mentioned. First, it was a cross-section study and the results could not establish causative relationships between hyperuricemia and CRFs clustering and renal diseases. Second, the data were from three medical centers' databases that lacked details in waist circumference, HOMA-IR, smoking, drinking, lifestyles, diet and pharmacotherapy, which might affect the deviations of some clinical outcomes.
Interpretation	20	It was a cross-section study and the results could not establish causative relationships between hyperuricemia and CRFs clustering and renal diseases. Future follow-up studies are required for more accurate evaluation of these relationships.
Generalisability	21	In Shanghai population, concomitant with the elevated level of serum uric acid, the prevalence of CRFs and renal diseases was rising. Hyperuricemia was significantly associated with CVD risk factors and renal disorders. Therefore, target inhibition of SUA level may have potential to become an effective therapy in alleviating risks of CVDs and renal disorders, especially in females.

Other information

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*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at <http://www.plosmedicine.org/>, Annals of Internal Medicine at <http://www.annals.org/>, and Epidemiology at <http://www.epidem.com/>). Information on the STROBE Initiative is available at www.strobe-statement.org.

BMJ Open

The relationship between serum uric acid and clustering of cardiovascular disease risk factors, renal disorders among Shanghai population: a multi-center and cross-sectional study

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4 1 **The relationship between serum uric acid and clustering of cardiovascular disease risk factors,**
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7 2 **renal disorders among Shanghai population: a multi-center and cross-sectional study**

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ABSTRACT

Objectives To estimate the current prevalence of cardiovascular disease risk factors (CRFs) and renal disorders across serum uric acid (SUA) quartiles, and evaluate the relationships between SUA and CRFs, renal diseases in Shanghai population.

Study design Observational, cross-sectional study.

Setting Data were obtained from physical checkups of local residents at three hospitals in Shanghai.

Participants Residents were invited to take part in physical checkups and provided informed consents.

Exclusion criteria were diseases that resemble cancer, hepatic disease and other coexisting illnesses including autoimmune kidney diseases, renal artery stenosis, individuals treated with xanthine oxidase inhibitors and without complete information. There are 26768 individuals in our study.

Primary and secondary outcome measures Hyperuricemia was defined as SUA ≥ 7 mg/dL in males and ≥ 6 mg/dL in females or taking xanthine oxidase inhibitors. Subjects were divided into gender-specific quartiles. We estimate the prevalence of CRFs and renal disorders across SUA quartiles. The relationships between SUA and CRFs, renal disorders at different gender were evaluated with logistic regression analysis.

Results: There was a significant increase in the prevalence of major CRFs and renal diseases across SUA quartiles in separate analysis among men and women (all P -trend <0.001). After multiple adjustment, hyperuricemia positively correlated with obesity (Male OR=3.165, $P<0.001$; Female OR=3.776, $P<0.001$), hypertension (Male OR=1.341, $P<0.001$; Female OR=1.289, $P=0.006$), dyslipidemia (Male OR=2.490, $P<0.001$; Female OR=3.614, $P<0.001$), chronic kidney disease (Male OR=7.081, $P<0.001$; Female OR=11.571, $P<0.001$), nephrolithiasis (Male OR=1.469, $P<0.001$; Female OR=1.242, $P=0.041$),

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4 43 but negatively correlated with diabetes mellitus (Male OR=0.206, $P<0.001$; Female OR=0.524, $P<0.001$).
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7 44 Women had a stronger association between hyperuricemia and clustered CRFs as well as CKD than men.
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10 45 **Conclusions:** In Shanghai population, concomitant with the elevated level of SUA, the prevalence of
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12 46 CRFs and renal diseases was rising. Hyperuricemia was significantly associated with CRFs and renal
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15 47 disorders, especially in females.
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18 48 **KEY WORDS:** Serum uric acid, cardiovascular disease risk factors, renal disorders
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23 50 **ARTICLE SUMMARY**

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26 51 **Article focus**

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28 52 ● The current prevalence of cardiovascular disease risk factors (CRFs) and renal diseases across serum
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31 53 uric acid (SUA) quartiles.
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- 34 54 ● The relationships between SUA and CRFs, renal disorders in Shanghai population.
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37 55 **Key messages**

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39 56 ● In Shanghai population, concomitant with the elevated level of serum uric acid, the prevalence rate of
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42 57 CRFs and renal diseases was rising.
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- 45 58 ● Hyperuricemia was significantly associated with cardiovascular disease (CVD) risk factors and renal
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48 59 disorders, especially in females.
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50 60 **Strengths and limitations of this study**

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- 53 61 ● There is a strict exclusion criteria based on medical histories and laboratory findings.
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- 56 62 ● We conducted a multi-center study with large sample size which ensured sufficient power in
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4 63 obtaining the accurate prevalent rate of CRFs and renal diseases and analyzing the relationship
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7 64 between SUA and CRFs, renal disorders across SUA quartiles.
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10 65 ● The relationship was analyzed in both sexes and we got a solid conclusion about the differences
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12 66 between men and women.
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15 67 ● It was a cross-section study and the results could not establish causative relationships between
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17 68 hyperuricemia and CRFs clustering and renal diseases.
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20 69 ● The data were from three medical centers' databases that lacked details in waist circumference,
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23 70 HOMA-IR (homeostasis model assessment of insulin resistance), smoking, drinking, lifestyles, diet
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26 71 and pharmacotherapy, which might affect the deviations of some clinical outcomes.
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INTRODUCTION

Uric acid (UA) is the final degradation product of purine metabolism in the liver, muscles and intestines.¹ A high level of serum uric acid (SUA) is correlated with multiple disorders such as metabolic syndrome, cardiovascular disease as well as kidney diseases.²⁻⁴ The association between hyperuricemia and CVD risk factors has been widely focused since the last century.⁵ There are various risk factors involved in CVDs, including age, sex, obesity, hypertension, diabetes mellitus, dyslipidemia, family history, smoking, depression and so on.⁶⁻⁸ Numerous indexes of CVDs risk factors were closely associated with increased serum uric acid, such as body mass index (BMI), cholesterol, triglyceride, low-density lipoprotein (LDL), and high-density lipoprotein (HDL), systolic blood pressure (SBP), diastolic blood pressure (DBP), fasting plasma glucose (FPG).⁶⁻⁹ However, the relationship between hyperuricemia and cardiovascular disease risk factors (CRFs) at different gender of Shanghai population has not been well studied. And the data from multiple clinical centers in China are extremely limited. In this study, we evaluated the prevalence of major CRFs (obesity, hypertension, diabetes mellitus, dyslipidemia) across SUA quartiles and analyzed the association of these factors with SUA level respectively in both men and women.

It has been documented that 70% of the daily UA production is excreted by the kidney.¹⁰ UA tends to crystallize in low urine pH. Hyperuricemia reduces urine pH, and increases the risk of formation of urate stones.¹¹ Recent research indicated that serum uric acid level could predict the development of albuminuria.¹²⁻¹³ And elevated serum uric acid level was significantly associated with estimated glomerular filtrate rate (eGFR) decline.¹⁴⁻¹⁵ However, whether UA is a cause or an association to renal diseases is a question that still waits for further investigations. Thus, we assessed the prevalence of renal

diseases across SUA quartiles, and the relationship between serum uric acid and renal disorders in Shanghai population.

METHODS

Study population

The permanent residents aged between 16-98 years who participated in the health checkups during the period from January 2015 and December 2015 of three medical centers Shanghai East Hospital Affiliated to Tongji University School of Medicine, Pudong New District Gongli Hospital and Baoshan Branch of Shanghai First People's Hospital were invited in the study. After excluding subjects with incomplete data, cancer, hepatic disease or other coexisting illnesses including autoimmune kidney diseases, renal artery stenosis and subjects treated with xanthine oxidase inhibitors, 26768 participants were enrolled in our study.

The primary outcomes

Hyperuricemia was defined as serum uric acid ≥ 7 mg/dL in males and ≥ 6 mg/dL in females or current use of xanthine oxidase inhibitors.¹⁶ SUA was determined using the uricase-peroxidase method.

Study definitions

Body mass index (BMI) was calculated as weight in kilograms divided by height in squared meters. According to WHO guidelines for the Asian Pacific population, normal weight was defined as $18.5 \leq \text{BMI} < 24.0$ kg/m², overweight was defined as $24.0 \leq \text{BMI} < 28.0$ kg/m², obesity was defined as $\text{BMI} \geq 28.0$ kg/m², underweight was defined as $\text{BMI} < 18.5$ kg/m².¹⁷ Blood pressure measurements were taken according to the Joint National Committee VII criteria (JNC VII).¹⁸ Normal BP was defined as having SBP < 120 mmHg and DBP < 80 mmHg. Pre-hypertension was defined as having SBP of 120–139 mmHg

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4125 and/or DBP of 80–89 mmHg. Grade 1 hypertension was defined as having SBP of 140–159 mmHg
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7126 and/or DBP of 90–99 mmHg. Grade 2 or grade 3 hypertension was defined as SBP \geq 160 mmHg and/or
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1027 DBP \geq 100 mmHg.¹⁸ According to the Chinese adult dyslipidemia prevention guide (2007 edition),
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1228 individuals with a fasting TC \geq 6.22 mmol/L, TG \geq 2.26 mmol/L, HDL-C $<$ 1.04 mmol/L, and/or
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1529 LDL-C $>$ 4.14 mmol/L, or currently undergoing pharmacologic treatment were defined as the
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1830 dyslipidemia.¹⁹ T2D was defined based on World Health Organization (WHO) 1999 diagnostic criteria
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2031 as fasting plasma glucose \geq 7.0mmol/l or 2-h plasma glucose \geq 11.1mmol/l, impaired fasting glucose (IFG)
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2332 was defined as 6.1 mmol/l \leq FPG $<$ 7.0 mmol/l, and normal condition was defined as FPG $<$ 6.1 mmol/l.²⁰
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2633 The eGFR was calculated using Modification of Diet in Renal Disease (MDRD) formula²¹: $186 \times [\text{serum}$
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2934 creatinine (mg/ dl)] $^{-1.154} \times (\text{age})^{-0.203} \times [0.742 \text{ (if female)}]$. According to the Kidney Disease Outcomes
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3135 Quality Initiative (KDOQI) clinical practice guideline, estimated glomerular filtration rate (eGFR) $<$ 60
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3436 mL/min/1.73 m², proteinuria and hematuria were defined as markers of CKD.²² Urine proteinuria were
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3737 recorded as negative (-), trace, 1+, 2+ and 3+. Albuminuria was defined as \geq 1+.

38 39 40 41 4239 **Data collection**

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4540 The subjects participating in the study attended to the medical center in the morning after overnight
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4841 fasting for at least 12 hours. After 5 minutes resting, sitting blood pressure was measured in right arm by
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5042 a trained medical staff using an electronic blood pressure monitor. The resting BP was measured three
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5343 times with five minutes intervals between them, and then the averages were calculated, which were used
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5644 for further analysis. Blood samples were obtained on their arrival at the medical center and fasting
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5845 glucose (FPG) were measured by the hexokinase method, total cholesterol, low-density
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lipoprotein-cholesterol (LDL-C), high-density lipoprotein-cholesterol (HDL-C), triglyceride, blood urea nitrogen (BUN), creatinine, serum uric acid were measured in an automated bio-analyzer (Hitachi, Tokyo, Japan). Midstream urine specimen was collected for urinary analysis by the dipstick method. Urine pH and proteinuria were recorded as categorical data. Laboratory reagents were purchased from Nanjing Jiancheng Bioengineering Institute (Nanjing, China).

After blood and urine sampling, basic characteristics and medical history were collected by medical staff. Anthropometric measurements including height and body weight were obtained according to a standardized protocol. Renal ultrasonography scanning was performed and measured by an experienced radiologist using GE LOGIQ P5 scanner (GE Healthcare, Milwaukee, SUA) who was blinded to the subjects' medical information.

Patient and public involvement

No patient was involved in the design or conduct of the study, but the results of the study will be shared to patients coming for follow-up.

Statistical analysis

We divided the subjects into gender-specific quartiles [males (M): Q1 \leq 4.9, Q2: 5.0-5.9, Q3: 6.0-6.9, Q4 \geq 7.0 mg/dL; females (F): Q1 \leq 3.9, Q2: 4.0-4.9, Q3: 5.0-5.9, Q4 \geq 6.0mg/dL] according to serum uric acid level. Distribution of variables was evaluated by the Kolmogorov Smirnov test and homogeneity of variance was assessed by the Levene test. The normal distributed data are reported in means \pm SD. Skewed or non-normal distributed data are presented in medians with inter quartile range (IQR). Categorical variables are showed in percentages. The univariate analysis of variance (ANOVA) was used to analyze

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the differences among groups' means in case of normal data distribution or after logarithmic normalization in case of skewed data (if appropriate). Kruskal-Wallis test was used to analyze the differences among groups' medians in case of nonparametric data distribution. Differences between groups for proportions were tested with chi-square tests. If the results show differences between the groups, the post-hoc tests would be done. As for the post-hoc test of normally distributed data, we used least significance difference (LSD) test if the variance was homogeneous, and we used Tamhane's T2 test if not. The post-hoc test of non-normally distributed data was compared using Kruskal-Wallis test. As for the post-hoc test of categorical variables, we used chi-square tests. Correlations were Pearson's or Spearman's depending on the distribution of the data. In the present study, SUA, age, BMI, SBP, DBP, FPG, TC, TG, HDL-C, LDL-C, eGFR were normally distributed. Thus, Pearson's correlation was used among these variables. If Pearson's correlation analysis was statistically significant, multiple linear regression analysis was performed to determine the association of SUA with various independent variables. We analyzed the multiple collinearity by calculating the correlation coefficient matrix, tolerance and variance inflation factor of independent variables. Multivariable logistic regression analysis (unadjusted and full-adjusted) was used to calculate the odds ratio for hyperuricemia according to different status of clinical parameters. Furthermore, multivariable logistic regression analysis (multiple adjusted models) was used to examine the association between related diseases and the SUA categories of Q2 or greater compared to the lowest SUA category. The association between hyperuricemia and clustered CVD risk factors had been calculated. Statistical analyses were performed by IBM SPSS statistics version 20.0 (SPSS, Chicago, IL, USA). Statistical significance was set at P -values of <0.05 .

RESULTS

Clinical characteristics of participants in quartiles of serum uric acid level.

A total of 26768 participants with mean age 48.93 ± 15.47 years, and 15041 (56.2%) men and 11727 (43.8%) women completed in the study. The prevalence rates of hyperuricemia of men and women were 22.2 % (95% confidence intervals (CI) 21.5–22.9%) and 10.8% (10.3–11.4%), respectively. Female individuals with higher level of SUA were older than the age of males. With increasing quartiles of SUA, participants had more CVDs risk factors (obesity, hypertension, dyslipidemia) and renal diseases (chronic kidney disease, nephrolithiasis), as well as elevated levels of body mass index, systolic blood pressure, diastolic blood pressure, total cholesterol, triglyceride, low density lipoprotein cholesterol, creatinine, blood urea nitrogen (BUN), and decreased levels of high density lipoprotein cholesterol, estimated glomerular filtration rate in both men and women (Table 1, all *P* values for trend <0.001).

The prevalence of CVD risk factors, renal diseases in quartiles of serum uric acid level

As demonstrated in Figure 1, there was a significant increase in the prevalence of cardiovascular disease risk factors and renal disorders across SUA quartiles in men and women (all *P* value for trend <0.001). In the male hyperuricemia individuals, the prevalence rates of obesity, hypertension, diabetes mellitus, dyslipidemia, chronic kidney disease and nephrolithiasis were 24.1% (95% CI, 22.6-25.5%), 36.5% (34.9-38.2%), 4.9% (4.2-5.7%), 54.4% (52.7-56.1%), 6.9% (6.1-7.8%) and 18.6% (17.3-19.9%) respectively. In the female hyperuricemia individuals, the prevalence rates of obesity, hypertension, diabetes mellitus, dyslipidemia, chronic kidney disease and nephrolithiasis were 24.0% (21.6-26.3%), 43.2% (40.5-46.0%), 10.2% (8.6-11.9%), 45.5% (42.8-48.3%), 12.8% (11.0-14.7%) and 16.9% (14.8-19.0%) , respectively.

The correlation between serum uric acid and various clinical parameters

In the present study, SUA, age, BMI, SBP, DBP, FPG, TC, TG, HDL-C, LDL-C, eGFR were normally distributed. Thus, we used Pearson's correlation analysis to investigate the relationships and the results were shown in Table 2. In men, the level of serum uric acid was positively correlated with BMI, SBP, DBP, TC, TG, LDL-C, and negatively correlated with age, FPG, HDL-C and eGFR (all P values < 0.001). In women, the level of serum uric acid was positively correlated with age, BMI, SBP, DBP, FPG, TC, TG, LDL-C, and negatively correlated with HDL-C and eGFR (all P values < 0.001).

Multiple linear regression analysis in Table 3 showed that adjusting for various factors, serum uric acid was still positively correlated with BMI, SBP, TC, TG, negatively correlated with age, FPG, HDL-C and eGFR in males (all P values < 0.001). Serum uric acid was positively correlated with BMI, SBP, TC, TG, negatively correlated with FPG, HDL-C and eGFR in females (all P values < 0.001, except FPG P values = 0.003).

The association between hyperuricemia and the clinical outcome

Multivariable logistic regression models (unadjusted and full-adjusted) were analyzed and the results were shown in Table 4 with the odds ratio (OR) for hyperuricemia according to different clinical outcome. We found that after adjustment for confounders, increased levels of BMI, BP, triglyceride, LDL-C and albuminuria and decreased levels of HDL-C all are positively related to increased odds ratio of hyperuricemia. Renal insufficiency, acid urine, nephrolithiasis also positively correlated with hyperuricemia, however, FPG and alkaline urine negatively correlated with hyperuricemia in both gender

(all P values<0.05). These results suggested that the individuals with overweight/obesity, hypertension, dyslipidemia, renal insufficiency, massive albuminuria, acid urine, nephrolithiasis were more susceptible to hyperuricemia in both men and women.

The relationship between different levels of serum uric acid and CVDs risk factors, renal disorders

Multivariable logistic regression analysis (multiple adjusted models) was studied and the results were shown in Table 5. The odd ratio for obesity, hypertension, diabetes mellitus, dyslipidemia, chronic kidney disease, nephrolithiasis in the highest SUA quartile was 3.165 (95% CI 2.644-3.790, P <0.001, model 3), 1.341 (95% CI 1.181-1.524, P <0.001, model 3), 0.206 (95% CI 0.165-0.257, P <0.001, model 3), 2.490 (95% CI 2.213–2.801, P <0.001, model 3), 7.081 (95% CI 4.985-10.058, P <0.001, model 3), 1.469 (95% CI 1.261–1.710, P <0.001, model 3) compared with that in the lowest SUA quartile, respectively, in men.

The data in Table 6 were multivariable logistic regression analysis in women and the odd ratio for obesity, hypertension, diabetes mellitus, dyslipidemia, chronic kidney disease, nephrolithiasis in the highest SUA quartile was 3.776 (95% CI 2.969-4.802, P <0.001, model 3), 1.289 (95% CI 1.076-1.545, P =0.006, model 3), 0.524 (95% CI 0.384-0.715, P <0.001, model 3), 3.614 (95% CI 3.058-4.272, P <0.001, model 3), 11.571 (95% CI 7.267-18.423, P <0.001, model 3), 1.242 (95% CI 1.009-1.530, P =0.041, model 3) compared with that in the lowest SUA quartile, respectively.

From multivariable logistic regression analysis in men and women we concluded that hyperuricemia positively correlated with obesity, hypertension, dyslipidemia, chronic kidney disease, nephrolithiasis, but negatively correlated with diabetes mellitus (all P <0.05) in both gender. Furthermore, females had stronger association between hyperuricemia and chronic kidney disease than males.

The association between hyperuricemia and clustered CVD risk factors.

Multivariable logistic regression was analyzed for hyperuricemia and clustered CVD risk factors, the results were shown in Table 7. After adjustment for age, compared with the group of zero CVD risk factor reference group, the odd ratio for group of ≥ 3 CVD risk factors was 3.889 (95% CI 3.322-4.552, $P < 0.001$), 6.270 (95% CI 4.936-7.964, $P < 0.001$) in men and women, respectively. The individuals with more CVD risk factors were associated with the higher ORs of hyperuricemia both in men and women (P for trend < 0.001). Furthermore, females had a stronger association of hyperuricemia with clustered CVD risk factors than males.

DISCUSSION

In the present study, we found that increasing prevalence of CVD risk factors and renal disorders was predominantly associated with increased SUA levels in Shanghai population. According to our multi-center epidemiologic study of 26768 subjects, the prevalence of hyperuricemia in Shanghai was 17.2% (95%CI 16.8%-17.7%), 22.2% (21.5–22.9%) in men and 10.8% (10.3–11.4%) in women. This is higher than the prevalence of hyperuricemia among nationwide Chinese adults between year 2009 and 2010 (8.4%),²³ and close to the developed countries, such as United States (21.4 %) and Japan (25.8 %).^{24 25} Along with the rapid economic development of Shanghai, the consumption of purine-rich food and alcohol is increasing. Meanwhile, obesity and aging population is rising. The change of lifestyle, dietary habit and population attributed to this phenomenon. The gender-related differences between serum uric acid level and age could be resulted from sex hormones. Estrogen promoted urinary uric acid excretion.²⁶

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4273 Obesity is probably the major risk factor for CVD. Obesity accompanied by increased waist
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7274 circumference, hyperinsulinemia and dyslipidemia. The most frequent manifestation of glucose
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10275 metabolism in obese population is hyperinsulinemia, a compensatory mechanism, whereas fasting
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1276 glucose remains normal.²⁷ It is likely that the presence of insulin resistance and hyperinsulinemia
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1577 facilitates renal tubular cells to reabsorb sodium coupling with urate.²⁸ This may be the reason why
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1878 obesity is accompanied by hyperuricemia. And our data are also in agreement with the result from two
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2179 retrospective studies in youths.^{29 30}

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2380 Hypertension is another important risk factor for CVD. Recently, Borghi C et al. found that SUA
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2681 levels were significantly higher in untreated and poorly controlled hypertensive patients in comparison to
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2982 normotensive controls and well-controlled hypertensive patients.³¹⁻³³ Our data were in accordance with
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3183 Borghi C's results. After adjustment of confounding factors, hypertension was still significantly
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3484 associated with hyperuricemia. The odd ratio for hypertension in the highest SUA quartile was 1.341
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3785 (95% CI 1.181-1.524, $P < 0.001$) in men, 1.289 (95% CI 1.076-1.545, $P = 0.006$) in women. Future
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4086 follow-up studies and randomized clinical trials are required for investigating the causative relationships
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4287 between urate and blood pressure. However, animal studies had showed that high level of uric acid
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4588 caused high blood pressure, which was mediated by activation of renal and systemic
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4889 renin-angiotensin-aldosterone systems (RAAS), oxidative stress, vascular insulin resistance and loss of
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5090 endothelial nitric oxide.^{34 35}

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5391 One of the interesting findings in our investigation was that the higher level of SUA was positively
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5692 correlated with the higher prevalence rates of diabetes mellitus in women, but inversely correlated with
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5893 that in men (Figure 1). The Pearson's correlation analysis demonstrated that the level of SUA positively
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4294 correlated with fasting plasma glucose in women, but negatively in men. However, the coefficients of
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7295 determination of the models were low. The obtained P values below 0.001 may attributed to the effect of
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10296 the big sample size. So we further adopted multiple linear regression and multivariable logistic regression
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12297 analysis for association of various variable with serum uric acid. After adjustment of confounding factors,
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15298 results of multivariable logistic regression showed that inverse association of serum uric acid with
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18299 diabetes mellitus in both men and women. The odd ratio for diabetes mellitus in the highest SUA quartile
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20300 was 0.206 (95% CI 0.165–0.257, $P < 0.001$) in men, 0.524 (95% CI 0.384–0.715, $P < 0.001$) in women.
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23301 This also confirmed by multiple linear regression analysis. We speculated that this phenomenon is
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26302 probably due to the presence of high level of blood glucose which promotes renal excretion of serum uric
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29303 acid. It has been indicated that hyperglycaemia worsens the function of beta cells and deteriorates
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31304 glycemic control, which gradually elevates the rate of renal glomerular filtration.³⁶ The hyperfiltration
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34305 due to multiple kidney disorders will lead to increased excretion of uric acid, and will be more susceptible
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37306 to diabetic nephropathy with decreasing eGFR.³⁷

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39307 Based on our data, hyperuricemia had a remarkable association with cardiovascular disease risk
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42308 factors and renal disorders. The more CVD risk factors individuals had, the higher ORs of hyperuricemia
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45309 were observed in both genders, especially in women. This was consistent with Borghi C's studies that
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48310 SUA were associated with cardiovascular risk score, and the results supported an independent association
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51311 between SUA and cardiovascular disease.^{3 38} There were numerous mechanisms involved in the close
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53312 association between serum uric acid and CVDs.³⁹⁻⁴² Uric acid stimulates platelet-derived growth factor
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56313 receptor β (PDGFR β) phosphorylation, leading to vascular smooth muscle cell (VSMC) proliferation.³⁹
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58314 Uric acid increases oxidative stress and stimulates the activation of renin-angiotensin system, resulting in
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4315 the senescence and apoptosis of human umbilical vein endothelial cells (HUVECs).⁴⁰ Uric acid also can
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7316 cause mitochondrial alterations and decreased intracellular ATP production and subsequently result in
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10317 endothelial dysfunction in human aortic endothelial cells (HAECs).⁴¹ A large quantity of animal
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1218 experiments and human epidemiological documents indicated that SUA-lowering treatment was beneficial
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1319 for cardiovascular diseases.⁴³⁻⁴⁷

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1820 On the other hand, the related mechanisms in the link between hyperuricemia and chronic kidney
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20321 disease (CKD) were not well investigated. It was demonstrated that 70% of urate eliminated occurs in the
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2322 kidneys, and decreased eGFR would result in elevated levels of SUA.⁴⁸ However, uric acid could induce
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2623 oxidative stress, trigger activation of RAAS and inflammation, cause endothelial dysfunction, and thus
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29324 subsequently lead to decline of eGFR.^{35 49 50} The persistent high level of SUA predicts the high risk of
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31325 developing CKD.⁵¹ There was a marked association of SUA with albuminuria in patients with renal
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3426 insufficiency.⁵² Our study were in consistent with many prospective studies,^{14 53 54} showing that SUA is a
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3727 significant risk factor for CKD and proteinuria, which is independent of confounders of CRFs. We further
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39328 demonstrated that hyperuricemia significantly correlated with acid urine and nephrolithiasis, which was
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4229 confirmed by the prevalence rates of chronic kidney disease and nephrolithiasis across the SUA levels.
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4530 This study has some limitations that need to be mentioned. First, it was a cross-section study and the
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48331 results could not establish causative relationships between hyperuricemia and CRFs clustering and renal
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50332 diseases. Future follow-up studies are required for more accurate evaluation of these relationships.
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5333 Second, the data were from three medical centers' databases that lacked details in waist circumference,
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56334 HOMA-IR, smoking, drinking, lifestyles, diet and pharmacotherapy, which might affect the deviations of
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58335 some clinical outcomes. Nonetheless, the strengths of our study included its strict exclusion criteria based
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4336 on medical histories and laboratory findings. And we conducted a multi-center study with large sample
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7337 size which ensured sufficient parameters and accurate results. The relationship was analyzed in both
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10338 sexes and a solid conclusion about the differences between men and women was gained.

1340 CONCLUSION

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1841 In summary, our data demonstrated that the increasing prevalent rate of CRFs and renal disorders
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21342 were significantly correlated with the elevated level of serum uric acid. Hyperuricemia was remarkably
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2343 linked with CVD-related risk factors and kidney disease, especially in females.

28
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4551 and Y.Z. contributed to discussion; M.T., and N.L. participated in the design of the study and edited the
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4852 manuscript. All authors have read and approved the final manuscript. The corresponding author had full
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5153 access to all the data in the study and had final responsibility for the decision to submit for publication.

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12 362
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24
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28 368 Gongli Hospital and the Human Research Ethics Committee of Baoshan Branch of Shanghai First
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31 369 People's Hospital. All methods were performed in compliance with Good Clinical Practice (GCP)
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33 370 guidelines and the Declaration of Helsinki. Written informed consent was obtained from each participant
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36 371 before data collection.
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42 373 **Data sharing statement** The data sets generated and analysed during the current study are available
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44 374 from the corresponding author upon reasonable request.
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4 517 **Figure legend**

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6 518 Figure 1. Prevalence of major CVD risk factors, renal diseases in different levels of serum uric acid.

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9 519 Prevalence of obesity(A), hypertension(B), diabetes mellitus(C), dyslipidemia(D), chronic kidney disease

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12 520 (E) and nephrolithiasis(F) in different levels of serum uric acid. The gender-specific quartiles of uric acid

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14 521 (mg/dL), Q1: males (M) ≤ 4.9 , females (F) ≤ 3.9 ; Q2: M 5.0-5.9, F 4.0-4.9; Q3: M 6.0-6.9, F 5.0-5.9; Q4:

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17 522 $M \geq 7.0$, $F \geq 6.0$.

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Table 1. Clinical characteristics of participants in quartiles of serum uric acid level.

	Men (n=15041)					Women (n=11727)				
	Q1 ≤4.9mg/dl	Q2 5.0-5.9mg/dl	Q3 6.0-6.9mg/dl	Q4 ≥7.0mg/dl	P-value for trend	Q1 ≤3.9mg/dl	Q2 4.0-4.9mg/dl	Q3 5.0-5.9mg/dl	Q4 ≥6.0mg/dl	P-value for trend
N(%)	2924(19.4%)	4617(30.7%)	4160(27.7%)	3340(22.2%)	-	3346(28.5%)	4509(38.4%)	2600(22.2%)	1272(10.8%)	-
Comorbidities										
Obesity (n, %)	192(6.6%)	446(9.7%)***	615(14.8%)***	804(24.1%)***	< 0.001	133(4.0%)	363(8.1%)***	380(14.6%)***	305(24.0%)***	< 0.001
Hypertension (n, %)	809(27.7%)	1215(26.3%)	1288(31.0%)**	1220(36.5%)***	< 0.001	554(16.6%)	1013(22.5%)***	785(30.2%)***	550(43.2%)***	< 0.001
Diabetes mellitus (n, %)	348(11.9%)	301(6.5%)***	222(5.3%)***	165(4.9%)***	< 0.001	125(3.7%)	170(3.8%)	153(5.9%)***	130(10.2%)***	< 0.001
Dyslipidemia (n, %)	735(25.1%)	1535(33.2%)***	1706(41.0%)***	1816(54.4%)***	< 0.001	394(11.8%)	861(19.1%)***	769(29.6%)***	579(45.5%)***	< 0.001
Chronic kidney disease (n, %)	47(1.6%)	114(2.5%)*	136(3.3%)***	232(6.9%)***	< 0.001	25(0.7%)	78(1.7%)***	105(4.0%)***	163(12.8%)***	< 0.001
Nephrolithiasis (n, %)	384(13.1%)	703(15.2%)*	642(15.4%)**	621(18.6%)***	< 0.001	368(11.0%)	484(10.7%)	367(14.1%)***	215(16.9%)***	< 0.001
Biochemical variables										
Age	50.06±15.49	48.05±15.59***	47.33±15.58***	47.34±15.74***	< 0.001	46.81±14.02	48.88±14.89***	52.23±15.43***	57.86±15.28***	< 0.001
BMI (kg/m ²)	23.29±3.06	24.11±3.08***	24.83±3.13***	25.98±3.26***	< 0.001	22.15±3.00	23.12±3.31***	24.34±3.54***	25.66±3.96***	< 0.001
SBP (mmHg)	126.60±18.21	126.31±17.54	128.12±17.92***	130.44±18.29***	< 0.001	120.32±18.24	123.59±19.23***	128.63±20.49***	135.29±21.14***	< 0.001
DBP (mmHg)	78.98±11.55	78.78±11.21	80.58±11.44***	81.85±11.95***	< 0.001	73.26±10.52	75.14±10.92***	77.38±11.22***	79.17±10.95***	< 0.001
FPG (mmol/L)	5.65±1.87	5.36±1.34***	5.33±1.21***	5.34±1.07***	< 0.001	5.08±1.22	5.13±1.13	5.30±1.22***	5.58±1.30***	< 0.001
TC (mmol/L)	4.52±0.88	4.58±0.86**	4.71±0.89***	4.87±0.91***	< 0.001	4.64±0.91	4.82±0.93***	5.00±0.94***	5.17±1.03***	< 0.001
TG (mmol/L)	1.28±1.27	1.45±1.15***	1.73±1.47***	2.15±1.72***	< 0.001	0.97±0.59	1.19±0.77***	1.47±0.99***	1.97±1.63***	< 0.001
HDL-C (mmol/L)	1.32±0.31	1.25±0.28***	1.22±0.28***	1.17±0.26***	< 0.001	1.59±0.35	1.50±0.34***	1.41±0.32***	1.32±0.31***	< 0.001
LDL-C (mmol/L)	2.77±0.76	2.88±0.76***	2.95±0.77***	3.04±0.82***	< 0.001	2.71±0.77	2.90±0.79***	3.07±0.82***	3.12±0.85***	< 0.001
eGFR (ml/(min*1.73m ²))	92.47±20.66	89.39±19.32***	87.66±19.50***	84.86±20.13***	< 0.001	100.15±23.04	97.08±23.93***	93.09±24.03***	85.59±25.04***	< 0.001
Cr (umol / L)	80.89±18.37	83.62±14.63***	85.43±14.69***	88.96±22.80***	< 0.001	62.18±10.80	63.82±12.04***	65.72±13.29***	71.24±28.89***	< 0.001
BUN (mmol/L)	5.19±1.31	5.26±1.22*	5.31±1.24***	5.44±1.57***	< 0.001	4.57±1.20	4.84±1.23***	5.11±1.27***	5.54±1.77***	< 0.001

The continuous variables are reported in means±SD and categorical variables are presented in percentages. In case of nonparametric data distribution medians with inter quartile range (IQR) are presented. Abbreviations: BMI: body mass index, SBP: systolic blood pressure, DBP: diastolic blood pressure, FPG: fasting plasma glucose, TC: total cholesterol, TG: triglyceride, HDL-C: high density lipoprotein cholesterol, LDL-C: low density lipoprotein cholesterol, eGFR: estimated glomerular filtration rate. Cr: creatinine, BUN: blood urea nitrogen. *P < 0.05, **P < 0.01, ***P < 0.001 vs. the group of Q1. As for the post-hoc test of normally distributed data, we used least significance difference (LSD) test if the variance was homogeneous, and we used Tamhane's T2 test if not. Non-normally distributed data was compared using Kruskal-Wallis test. As for the post-hoc test of categorical variables, we used chi-square tests.

Table 2. Correlation coefficients between serum uric acid and various parameters.

Variable	Men		Women		Total	
	r	P-value	r	P-value	r	P-value
Age	-0.059	< 0.001	0.226	< 0.001	0.014	0.025
BMI (kg/m ²)	0.291	< 0.001	0.326	< 0.001	0.344	< 0.001
SBP (mmHg)	0.080	< 0.001	0.237	< 0.001	0.161	< 0.001
DBP (mmHg)	0.097	< 0.001	0.174	< 0.001	0.204	< 0.001
FPG (mmol/L)	-0.071	< 0.001	0.125	< 0.001	0.040	< 0.001
TC (mmol/L)	0.148	< 0.001	0.186	< 0.001	0.091	< 0.001
TG (mmol/L)	0.222	< 0.001	0.325	< 0.001	0.290	< 0.001
HDL-C (mmol/L)	-0.177	< 0.001	-0.260	< 0.001	-0.356	< 0.001
LDL-C (mmol/L)	0.119	< 0.001	0.181	< 0.001	0.126	< 0.001
eGFR (ml/(min*1.73m ²))	-0.140	< 0.001	-0.192	< 0.001	-0.219	< 0.001

Abbreviations: BMI: body mass index, SBP: systolic blood pressure, DBP: diastolic blood pressure, FPG: fasting plasma glucose, TC: total cholesterol, TG: triglyceride, HDL-C: high density lipoprotein cholesterol, LDL-C: low density lipoprotein cholesterol, eGFR: estimated glomerular filtration rate.

Table 3. Multiple linear regression analysis for association of various independent variable with serum uric acid (dependent variable)

Variable	Men		Women		Total	
	<i>St B</i>	<i>P</i> -value	<i>St B</i>	<i>P</i> -value	<i>St B</i>	<i>P</i> -value
Age	-0.127	< 0.001			-0.142	< 0.001
BMI (kg/m ²)	0.215	< 0.001	0.188	< 0.001	0.195	< 0.001
SBP (mmHg)	0.066	< 0.001	0.059	< 0.001	0.092	< 0.001
FPG (mmol/L)	-0.122	< 0.001	-0.027	0.003	-0.059	< 0.001
TC (mmol/L)	0.101	< 0.001	0.110	< 0.001	0.089	< 0.001
TG (mmol/L)	0.114	< 0.001	0.147	< 0.001	0.108	< 0.001
HDL-C (mmol/L)	-0.084	< 0.001	-0.168	< 0.001	-0.252	< 0.001
eGFR (ml/(min*1.73m ²))	-0.154	< 0.001	-0.145	< 0.001	-0.208	< 0.001

Multicollinearity analysis showed that SBP and DBP highly correlate with each other, so do TC and LDL-C. And backward elimination was adopted for multiple linear regression to identify independent variables which have most impact on dependent variables. Finally, Independent variables DBP and LDL-C were removed in male and in total. Independent variables DBP, LDL-C and age were removed in female.

Abbreviations: BMI: body mass index, SBP: systolic blood pressure, DBP: diastolic blood pressure, FPG: fasting plasma glucose, TC: total cholesterol, TG: triglyceride, HDL-C: high density lipoprotein cholesterol, LDL-C: low density lipoprotein cholesterol, eGFR: estimated glomerular filtration rate. Standardized beta coefficients (*St B*) refer to how many standard deviations a dependent variable will change per standard deviation increase in the predictor variable.

Table 4. The odds ratio for hyperuricemia according to different status of parameters of men and women.

	Men				Women			
	Unadjusted		Full-adjusted		Unadjusted		Full-adjusted	
	OR (95%CI)	P-value	OR (95%CI)	P-value	OR (95%CI)	P-value	OR (95%CI)	P-value
BMI (kg/m ²)								
18.5 ≤BMI<24.0 (Ref.)								
BMI<18.5	0.495 (0.330-0.743)	0.001	0.544 (0.361-0.818)	0.003	0.495 (0.313-0.781)	0.002	0.618 (0.388-0.985)	0.043
24.0≤BMI<28.0	2.154 (1.967-2.360)	< 0.001	1.857 (1.687-2.044)	< 0.001	2.688 (2.347-3.078)	< 0.001	1.926 (1.663-2.230)	< 0.001
BMI≥28.0	3.983 (3.554-4.463)	< 0.001	3.231 (2.858-3.652)	< 0.001	5.037 (4.279-5.928)	< 0.001	3.148 (2.623-3.778)	< 0.001
Blood pressure (mmHg)								
Normotensive (Ref.)								
Pre-HT	1.288 (1.168-1.420)	< 0.001	1.047 (0.945-1.161)	0.378	2.017 (1.726-2.356)	< 0.001	1.259 (1.065-1.488)	0.007
Grade1 HT	1.673 (1.500-1.866)	< 0.001	1.160 (1.031-1.306)	0.013	3.481 (2.954-4.102)	< 0.001	1.580 (1.313-1.900)	< 0.001
Grade2/3 HT	1.728 (1.500-1.990)	< 0.001	1.140 (0.977-1.331)	0.096	4.568 (3.725-5.600)	< 0.001	1.615 (1.276-2.044)	< 0.001
FPG (mmol/L)								
FPG<6.1 (Ref.)								
6.1≤FPG<7	1.192 (1.029-1.381)	0.019	0.825 (0.704-0.966)	0.017	2.588 (2.098-3.192)	< 0.001	1.282 (1.017-1.615)	0.035
FPG≥7	0.655 (0.552-0.777)	< 0.001	0.368 (0.306-0.444)	< 0.001	2.723 (2.217-3.344)	< 0.001	0.848 (0.665-1.081)	0.183
Cholesterol (mmol/L)								
TC≤6.22 (Ref.)								
TC>6.22	1.908 (1.629-2.235)	< 0.001	1.075 (0.877-1.318)	0.488	2.027 (1.702-2.413)	< 0.001	1.086 (0.843-1.399)	0.523
Triglyceride (mmol/L)								
TG≤2.26 (Ref.)								
TG>2.26	2.868 (2.622-3.137)	< 0.001	2.286 (2.069-2.527)	< 0.001	4.564 (3.950-5.272)	< 0.001	2.529 (2.137-2.994)	< 0.001
HDL-C (mmol/L)								
HDL-C≥1.04 (Ref.)								
HDL-C<1.04	1.653 (1.519-1.799)	< 0.001	1.102 (1.002-1.211)	0.044	3.271 (2.773-3.859)	< 0.001	1.829 (1.511-2.212)	< 0.001
LDL-C (mmol/L)								
LDL-C≤4.14 (Ref.)								
LDL-C>4.14	1.742 (1.509-2.011)	< 0.001	1.502 (1.253-1.801)	< 0.001	1.884 (1.561-2.272)	< 0.001	1.327 (1.018-1.730)	0.037
eGFR (ml/(min*1.73m ²))								
eGFR≥90 (Ref.)								
60≤eGFR<89	1.175 (1.084-1.275)	< 0.001	1.230 (1.127-1.342)	< 0.001	1.699 (1.499-1.926)	< 0.001	1.716 (1.498-1.966)	< 0.001
eGFR≤59	3.157 (2.629-3.792)	< 0.001	3.213 (2.634-3.921)	< 0.001	9.473 (7.561-11.868)	< 0.001	7.563 (5.894-9.706)	< 0.001
Albuminuria								
-/+ (Ref.)								
+	1.264 (0.895-1.787)	0.184	0.922 (0.633-1.344)	0.674	5.830 (3.827-8.882)	< 0.001	2.951 (1.798-4.843)	< 0.001
++	2.138 (1.474-3.101)	< 0.001	1.354 (0.902-2.032)	0.144	3.183 (1.849-5.482)	< 0.001	1.549 (0.825-2.908)	0.173
+++	3.188 (2.004-5.073)	< 0.001	2.223 (1.332-3.707)	0.002	10.317 (5.758-18.486)	< 0.001	4.699 (2.395-9.219)	< 0.001
Urinary pH								
6≤pH<7 (Ref.)								
pH<6	1.509 (1.391-1.637)	< 0.001	1.522 (1.392-1.663)	< 0.001	2.083 (1.848-2.347)	< 0.001	1.900 (1.665-2.169)	< 0.001
pH>7	0.556 (0.432-0.716)	< 0.001	0.612 (0.472-0.795)	< 0.001	0.638 (0.451-0.901)	0.011	0.728 (0.508-1.043)	0.084
Nephrolithiasis								
No (Ref.)								
Yes	1.317 (1.191-1.457)	< 0.001	1.163 (1.044-1.295)	0.006	1.541 (1.315-1.806)	< 0.001	1.253 (1.051-1.494)	0.012

Abbreviations: BMI: body mass index, FPG: fasting plasma glucose, TC: total cholesterol, TG: triglyceride, HDL-C: high density lipoprotein cholesterol, LDL-C: low density lipoprotein cholesterol, eGFR: estimated glomerular filtration rate. Blood pressure (mmHg): normotensive: SBP<120 and DBP<80; pre-HT: SBP of 120-139 and/or DBP of 80-89; Grade1 HT: SBP of 140-159 and/or DBP of 90-99; Grade2/3 HT: SBP≥160 and/or DBP≥100

Table 5. The association between SUA and Obesity, hypertension, Diabetes mellitus, Dyslipidemia, CKD, Nephrolithiasis in men.

	Q1	Q2			Q3			Q4		
	-	OR	95%CI	P-value	OR	95%CI	P-value	OR	95%CI	P-value
Obesity										
Model1	1(Ref.)	1.523	1.277-1.816	< 0.001	2.472	2.086-2.929	< 0.001	4.517	3.824-5.337	< 0.001
Model2 ^a	1(Ref.)	1.384	1.153-1.662	< 0.001	1.975	1.653-2.359	< 0.001	3.156	2.643-3.768	< 0.001
Model3 ¹	1(Ref.)	1.392	1.159-1.672	< 0.001	1.991	1.664-2.382	< 0.001	3.165	2.644-3.790	< 0.001
Hypertension										
Model1	1(Ref.)	1.027	0.920-1.147	0.635	1.381	1.236-1.543	< 0.001	1.834	1.635-2.058	< 0.001
Model2 ^b	1(Ref.)	0.961	0.856-1.079	0.501	1.169	1.039-1.315	0.009	1.314	1.159-1.489	< 0.001
Model3 ²	1(Ref.)	0.968	0.862-1.087	0.582	1.188	1.055-1.338	0.004	1.341	1.181-1.524	< 0.001
Diabetes mellitus										
Model1	1(Ref.)	0.545	0.462-0.643	< 0.001	0.451	0.377-0.540	< 0.001	0.412	0.338-0.501	< 0.001
Model2 ^c	1(Ref.)	0.439	0.369-0.521	< 0.001	0.292	0.241-0.353	< 0.001	0.212	0.171-0.262	< 0.001
Model3 ³	1(Ref.)	0.446	0.374-0.532	< 0.001	0.296	0.244-0.360	< 0.001	0.206	0.165-0.257	< 0.001
Dyslipidemia										
Model1	1(Ref.)	1.510	1.361-1.675	< 0.001	2.122	1.912-2.355	< 0.001	3.645	3.271-4.061	< 0.001
Model2 ^d	1(Ref.)	1.425	1.278-1.589	< 0.001	1.800	1.612-2.009	< 0.001	2.665	2.374-2.992	< 0.001
Model3 ⁴	1(Ref.)	1.404	1.259-1.566	< 0.001	1.742	1.559-1.947	< 0.001	2.490	2.213-2.801	< 0.001
Chronic kidney disease										
Model1	1(Ref.)	1.762	1.241-2.502	0.002	2.514	1.784-3.544	< 0.001	5.980	4.309-8.299	< 0.001
Model2 ^e	1(Ref.)	1.966	1.376-2.810	< 0.001	2.800	1.966-3.987	< 0.001	6.913	4.890-9.771	< 0.001
Model3 ⁵	1(Ref.)	1.965	1.371-2.817	< 0.001	2.851	1.998-4.068	< 0.001	7.081	4.985-10.058	< 0.001
Nephrolithiasis										
Model1	1(Ref.)	1.246	1.089-1.427	0.001	1.288	1.122-1.478	< 0.001	1.616	1.406-1.859	< 0.001
Model2 ^f	1(Ref.)	1.161	1.012-1.331	0.033	1.142	0.992-1.316	0.065	1.338	1.154-1.552	< 0.001
Model3 ⁶	1(Ref.)	1.222	1.064-1.404	0.005	1.221	1.058-1.409	0.006	1.469	1.261-1.710	< 0.001

Model 1: adjusted for age

^aModel 2: adjusted for variables included in model1 and SBP, DBP, FPG, TC, TG, HDL-C, LDL-C; ^bModel2: adjusted for variables included in model1 and BMI, FPG, TC, TG, HDL-C, LDL-C; ^cModel2: adjusted for variables included in model1 and BMI, SBP, DBP, TC, TG, HDL-C, LDL-C; ^dModel2: adjusted for variables included in model1 and BMI, SBP, DBP, FPG; ^eModel2: adjusted for variables included in model1 and BMI, SBP, DBP, FPG, TC, TG, HDL-C, LDL-C; ^fModel2: adjusted for variables included in model1 and BMI, SBP, DBP, FPG, TC, TG, HDL-C, LDL-C.

¹Model 3: adjusted for variables included in model2^a and eGFR, urine Ph, albuminuria, nephrolithiasis; ²Model 3: adjusted for variables included in model2^b and eGFR, urine Ph, albuminuria, nephrolithiasis; ³Model 3: adjusted for variables included in model2^c and eGFR, urine Ph, albuminuria, nephrolithiasis; ⁴Model 3: adjusted for variables included in model2^d and eGFR, urine Ph, albuminuria, nephrolithiasis; ⁵Model 3: adjusted for variables included in model2^e and urine Ph, albuminuria, nephrolithiasis; ⁶Model 3: adjusted for variables included in model2^f and eGFR, urine Ph, albuminuria.

Abbreviations: BMI: body mass index, SBP: systolic blood pressure, DBP: diastolic blood pressure, FPG: fasting plasma glucose, TC: total cholesterol, TG: triglyceride, HDL-C: high density lipoprotein cholesterol, LDL-C: low density lipoprotein cholesterol, eGFR: estimated glomerular filtration rate.

Table 6. The association between SUA and Obesity, hypertension, Diabetes mellitus, Dyslipidemia, CKD, Nephrolithiasis in women.

	Q1	Q2			Q3			Q4		
	-	OR	95%CI	P-value	OR	95%CI	P-value	OR	95%CI	P-value
Obesity										
Model1	1(Ref.)	2.006	1.635-2.462	< 0.001	3.626	2.949-4.458	< 0.001	5.874	4.710-7.325	< 0.001
Model2 ^a	1(Ref.)	1.652	1.337-2.042	< 0.001	2.480	1.997-3.079	< 0.001	3.594	2.841-4.546	< 0.001
Model3 ¹	1(Ref.)	1.677	1.356-2.074	< 0.001	2.522	2.027-3.138	< 0.001	3.776	2.969-4.802	< 0.001
Hypertension										
Model1	1(Ref.)	1.291	1.139-1.465	< 0.001	1.597	1.392-1.831	< 0.001	2.091	1.780-2.455	< 0.001
Model2 ^b	1(Ref.)	1.117	0.978-1.275	0.103	1.146	0.989-1.327	0.070	1.240	1.040-1.479	0.016
Model3 ²	1(Ref.)	1.134	0.993-1.296	0.064	1.189	1.024-1.381	0.023	1.289	1.076-1.545	0.006
Diabetes mellitus										
Model1	1(Ref.)	0.872	0.686-1.108	0.262	1.152	0.898-1.478	0.265	1.578	1.208-2.061	0.001
Model2 ^c	1(Ref.)	0.616	0.478-0.793	< 0.001	0.609	0.466-0.797	< 0.001	0.601	0.446-0.809	0.001
Model3 ³	1(Ref.)	0.597	0.462-0.771	< 0.001	0.564	0.428-0.742	< 0.001	0.524	0.384-0.715	< 0.001
Dyslipidemia										
Model1	1(Ref.)	1.669	1.464-1.902	< 0.001	2.720	2.370-3.120	< 0.001	4.675	3.995-5.471	< 0.001
Model2 ^d	1(Ref.)	1.580	1.382-1.805	< 0.001	2.365	2.052-2.725	< 0.001	3.768	3.201-4.436	< 0.001
Model3 ⁴	1(Ref.)	1.570	1.374-1.795	< 0.001	2.298	1.991-2.652	< 0.001	3.614	3.058-4.272	< 0.001
Chronic kidney disease										
Model1	1(Ref.)	1.967	1.244-3.109	0.004	3.719	2.380-5.812	< 0.001	9.603	6.208-14.857	< 0.001
Model2 ^e	1(Ref.)	2.107	1.327-3.346	0.002	4.177	2.641-6.608	< 0.001	11.434	7.220-18.108	< 0.001
Model3 ⁵	1(Ref.)	2.065	1.299-3.283	0.002	4.295	2.711-6.807	< 0.001	11.571	7.267-18.423	< 0.001
Nephrolithiasis										
Model1	1(Ref.)	0.928	0.803-1.072	0.311	1.184	1.012-1.385	0.035	1.308	1.084-1.578	0.005
Model2 ^f	1(Ref.)	0.860	0.743-0.997	0.045	1.026	0.870-1.209	0.762	1.037	0.848-1.269	0.723
Model3 ⁶	1(Ref.)	0.897	0.773-1.041	0.153	1.117	0.944-1.321	0.196	1.242	1.009-1.530	0.041

Model 1: adjusted for age

^aModel 2: adjusted for variables included in model1 and SBP, DBP, FPG, TC, TG, HDL-C, LDL-C; ^bModel2: adjusted for variables included in model1 and BMI, FPG, TC, TG, HDL-C, LDL-C; ^cModel2: adjusted for variables included in model1 and BMI, SBP, DBP, TC, TG, HDL-C, LDL-C; ^dModel2: adjusted for variables included in model1 and BMI, SBP, DBP, FPG; ^eModel2: adjusted for variables included in model1 and BMI, SBP, DBP, FPG, TC, TG, HDL-C, LDL-C; ^fModel2: adjusted for variables included in model1 and BMI, SBP, DBP, FPG, TC, TG, HDL-C, LDL-C.

¹Model 3: adjusted for variables included in model2^a and eGFR, urine Ph, albuminuria, nephrolithiasis; ²Model 3: adjusted for variables included in model2^b and eGFR, urine Ph, albuminuria, nephrolithiasis; ³Model 3: adjusted for variables included in model2^c and eGFR, urine Ph, albuminuria, nephrolithiasis; ⁴Model 3: adjusted for variables included in model2^d and eGFR, urine Ph, albuminuria, nephrolithiasis; ⁵Model 3: adjusted for variables included in model2^e and urine Ph, albuminuria, nephrolithiasis; ⁶Model 3: adjusted for variables included in model2^f and eGFR, urine Ph, albuminuria.

Abbreviations: BMI: body mass index, SBP: systolic blood pressure, DBP: diastolic blood pressure, FPG: fasting plasma glucose, TC: total cholesterol, TG: triglyceride, HDL-C: high density lipoprotein cholesterol, LDL-C: low density lipoprotein cholesterol, eGFR: estimated glomerular filtration rate.

Table 7. The association between hyperuricemia and clustered CVD risk factors.

Clustered CVD risk factors	Men						Women					
	Unadjusted			Age-adjusted			Unadjusted			Age-adjusted		
	OR	95%CI	<i>P</i> -value	OR	95%CI	<i>P</i> -value	OR	95%CI	<i>P</i> -value	OR	95%CI	<i>P</i> -value
0	Ref.											
1	1.959	1.781-2.155	< 0.001	2.140	1.941-2.359	< 0.001	3.314	2.861-3.839	< 0.001	2.614	2.236-3.057	< 0.001
2	3.010	2.697-3.358	< 0.001	3.441	3.071-3.856	< 0.001	5.974	5.062-7.049	< 0.001	4.325	3.614-5.177	< 0.001
≥3	3.403	2.917-3.971	< 0.001	3.889	3.322-4.552	< 0.001	8.889	7.086-11.149	< 0.001	6.270	4.936-7.964	< 0.001
<i>P</i> value for trend			< 0.001			< 0.001			< 0.001			< 0.001

Clustered CVD risk factors included obesity, hypertension, diabetes mellitus, dyslipidemia

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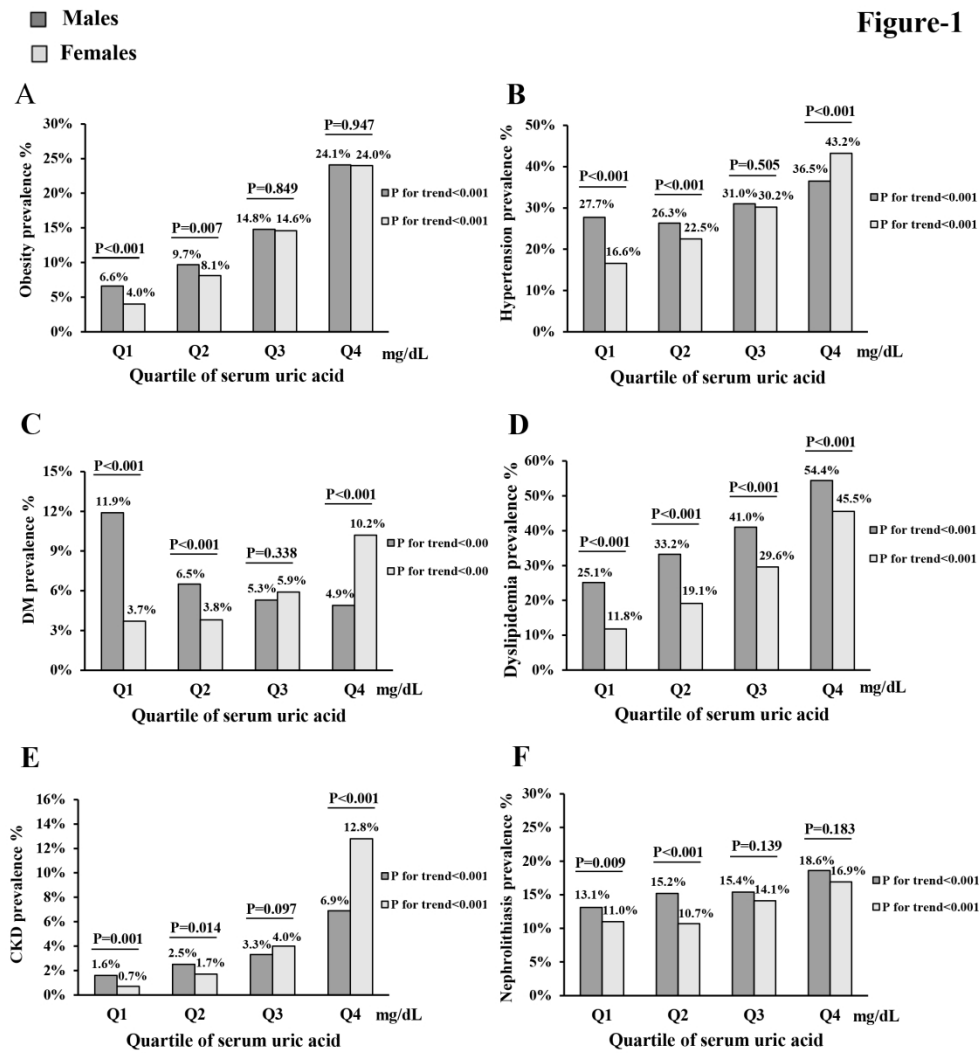


Figure legend

Figure 1. Prevalence of major CVD risk factors, renal diseases in different levels of serum uric acid. Prevalence of obesity(A), hypertension(B), diabetes mellitus(C), dyslipidemia(D), chronic kidney disease (E) and nephrolithiasis(F) in different levels of serum uric acid. The gender-specific quartiles of uric acid (mg/dL), Q1: males (M) ≤ 4.9 , females (F) ≤ 3.9 ; Q2: M 5.0-5.9, F 4.0-4.9; Q3: M 6.0-6.9, F 5.0-5.9; Q4: M ≥ 7.0 , F ≥ 6.0 .

STROBE Statement—Checklist of items that should be included in reports of *cross-sectional studies*

	Item No	Recommendation
Title and abstract	1	<p>(a) The relationship between serum uric acid and clustering of cardiovascular disease risk factors, renal disorders among Shanghai population: a multi-center and cross-sectional study</p> <p>(b) Objectives To estimate the current prevalence of cardiovascular disease risk factors (CRFs) and renal disorders across serum uric acid (SUA) quartiles, and evaluate the relationships between SUA and CRFs, renal diseases in Shanghai population. Study design Observational, cross-sectional study. Setting Data were obtained from physical checkups of local residents at three hospitals in Shanghai. Participants Residents were invited to take part in physical checkups and provided informed consents. Exclusion criteria were diseases that resemble cancer, hepatic disease and other coexisting illnesses including autoimmune kidney diseases, renal artery stenosis, individuals treated with xanthine oxidase inhibitors and without complete information. There are 26768 individuals in our study. Primary and secondary outcome measures Hyperuricemia was defined as SUA ≥ 7 mg/dL in males and ≥ 6 mg/dL in females or taking xanthine oxidase inhibitors. Subjects were divided into gender-specific quartiles. We estimate the prevalence of CRFs and renal disorders across SUA quartiles. The relationships between SUA and CRFs, renal disorders at different gender were evaluated with logistic regression analysis. Results: There was a significant increase in the prevalence of major CRFs and renal diseases across SUA quartiles in separate analysis among men and women (all P-trend<0.001). After multiple adjustment, hyperuricemia positively correlated with obesity (Male OR=3.165, $P<0.001$; Female OR=3.776, $P<0.001$), hypertension (Male OR=1.341, $P<0.001$; Female OR=1.289, $P=0.006$), dyslipidemia (Male OR=2.490, $P<0.001$; Female OR=3.614, $P<0.001$), chronic kidney disease (Male OR=7.081, $P<0.001$; Female OR=11.571, $P<0.001$), nephrolithiasis (Male OR=1.469, $P<0.001$; Female OR=1.242, $P=0.041$), but negatively correlated with diabetes mellitus (Male OR=0.206, $P<0.001$; Female OR=0.524, $P<0.001$). Women had a stronger association between hyperuricemia and clustered CRFs as well as CKD than men. Conclusions: In Shanghai population, concomitant with the elevated level of SUA, the prevalence of CRFs and renal diseases was rising. Hyperuricemia was significantly associated with CRFs and renal disorders, especially in females.</p>
Introduction		
Background/rationale	2	The relationship between hyperuricemia and cardiovascular disease risk factors (CRFs) at different gender of Shanghai population has not been well studied. And the data from multiple clinical centers in China are extremely limited. Whether serum uric acid (SUA) is a cause or an association to renal diseases is a question that still waits for further investigations. Thus, we estimate the current prevalence of CRFs and renal disorders across SUA quartiles, and evaluate the relationships between SUA and CRFs, renal diseases in Shanghai population.
Objectives	3	To estimate the current prevalence of cardiovascular disease risk factors (CRFs) and renal disorders across serum uric acid (SUA) quartiles, and evaluate the relationships between SUA and CRFs, renal diseases in Shanghai population.
Methods		
Study design	4	Observational, cross-sectional study
Setting	5	Data were obtained from physical checkups of local residents at three hospitals in

Shanghai during the period from January 2015 and December 2015.		
Participants	6	Residents were invited to take part in physical checkups and provided informed consents. Exclusion criteria were diseases that resemble cancer, hepatic disease and other coexisting illnesses including autoimmune kidney diseases, renal artery stenosis, individuals treated with xanthine oxidase inhibitors and without complete information. There are 26768 individuals in our study.
Variables	7	Hyperuricemia was defined as serum uric acid ≥ 7 mg/dL in males and ≥ 6 mg/dL in females or current use of xanthine oxidase inhibitors. SUA was determined using the uricase-peroxidase method. Body mass index (BMI) was calculated as weight in kilograms divided by height in squared meters. According to WHO guidelines for the Asian Pacific population, normal weight was defined as $18.5 \leq \text{BMI} < 24.0$ kg/m ² , overweight was defined as $24.0 \leq \text{BMI} < 28.0$ kg/m ² , obesity was defined as BMI ≥ 28.0 kg/m ² , underweight was defined as BMI < 18.5 kg/m ² . Blood pressure measurements were taken according to the Joint National Committee VII criteria (JNC VII). Normal BP was defined as having SBP < 120 mmHg and DBP < 80 mmHg. Pre-hypertension was defined as having SBP of 120–139 mmHg and/or DBP of 80–89 mmHg. Grade 1 hypertension was defined as having SBP of 140–159 mmHg and/or DBP of 90–99 mmHg. Grade 2 or grade 3 hypertension was defined as SBP ≥ 160 mmHg and/or DBP ≥ 100 mmHg. According to the Chinese adult dyslipidemia prevention guide (2007 edition), individuals with a fasting TC ≥ 6.22 mmol/L, TG ≥ 2.26 mmol/L, HDL-C < 1.04 mmol/L, and/or LDL-C > 4.14 mmol/L, or currently undergoing pharmacologic treatment were defined as the dyslipidemia. T2D was defined based on World Health Organization (WHO) 1999 diagnostic criteria as fasting plasma glucose ≥ 7.0 mmol/l or 2-h plasma glucose ≥ 11.1 mmol/l, impaired fasting glucose (IFG) was defined as $6.1 \text{ mmol/l} \leq \text{FPG} < 7.0 \text{ mmol/l}$, and normal condition was defined as $\text{FPG} < 6.1 \text{ mmol/l}$. The eGFR was calculated using Modification of Diet in Renal Disease (MDRD) formula: $186 \times [\text{serum creatinine (mg/dl)}]^{-1.154} \times (\text{age})^{-0.203} \times [0.742 \text{ (if female)}]$. According to the Kidney Disease Outcomes Quality Initiative (KDOQI) clinical practice guideline, estimated glomerular filtration rate (eGFR) $< 60 \text{ mL/min/1.73 m}^2$, proteinuria and hematuria were defined as markers of CKD. Urine proteinuria were recorded as negative (–), trace, 1+, 2+ and 3+. Albuminuria was defined as $\geq 1+$.
Data sources/ measurement	8*	The permanent residents aged between 16-98 years who participated in the health checkups during the period from January 2015 and December 2015 of three medical centers Shanghai East Hospital Affiliated to Tongji University School of Medicine, Pudong New District Gongli Hospital and Baoshan Branch of Shanghai First People's Hospital were invited in the study. We divided the subjects into gender-specific quartiles [males (M): Q1 ≤ 4.9 , Q2: 5.0-5.9, Q3: 6.0-6.9, Q4 ≥ 7.0 mg/dL; females (F): Q1 ≤ 3.9 , Q2: 4.0-4.9, Q3: 5.0-5.9, Q4 ≥ 6.0 mg/dL] according to serum uric acid level.
Bias	9	We conducted a multi-center study with large sample size to reduce selection bias. We set a strict exclusion criteria based on medical histories and laboratory findings to reduce information bias.
Study size	10	There are 26768 individuals in our study.
Quantitative variables	11	The continuous variables are reported in means \pm SD and categorical variables are presented in percentages. In case of nonparametric data distribution medians with inter quartile range (IQR) are presented. The univariate analysis of variance (ANOVA) was used to measure the data among the groups or a Kruskal-Wallis test in case of nonparametric data distribution. Differences between groups for proportions were

tested with a chi-square test. If the results show differences between the groups, the post-hoc tests would be done. As for the post-hoc test of normally distributed data, we used least significance difference (LSD) test if the variance was homogeneous, and we used Tamhane's T2 test if not. The post-hoc test of non-normally distributed data was compared using Kruskal-Wallis test. As for the post-hoc test of categorical variables, we used chi-square tests.

Statistical methods	12	Correlations were Pearson's or Spearman's depending on the distribution of the data. In the present study, SUA, age, BMI, SBP, DBP, FPG, TC, TG, HDL-C, LDL-C, eGFR were normally distributed. Thus, Pearson's correlation was used among these variables. If Pearson's correlation analysis was statistically significant, multiple linear regression analysis was performed to determine the association of SUA with various independent variables. We analyzed the multiple collinearity by calculating the correlation coefficient matrix, tolerance and variance inflation factor of independent variables. Multivariable logistic regression analysis (unadjusted and full-adjusted) was used to calculate the odds ratio for hyperuricemia according to different status of clinical parameters. Furthermore, multivariable logistic regression analysis (multiple adjusted models) was used to examine the association between related diseases and the SUA categories of Q2 or greater compared to the lowest SUA category. The association between hyperuricemia and clustered CVD risk factors had been calculated. Statistical analyses were performed by IBM SPSS statistics version 20.0 (SPSS, Chicago, IL, USA). Statistical significance was set at <i>P</i> -values of <0.05.
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Results

Participants	13*	After excluding subjects with incomplete data, cancer, hepatic disease or other coexisting illnesses including autoimmune kidney diseases, renal artery stenosis and subjects treated with xanthine oxidase inhibitors, 26768 participants were enrolled in our study.
Descriptive data	14*	According to our multi-center epidemiologic study of 26768 subjects, the prevalence of hyperuricemia in Shanghai was 17.2% (95%CI 16.8%-17.7%), 22.2% (21.5–22.9%) in men and 10.8% (10.3–11.4%) in women.
Outcome data	15*	In the male hyperuricemia individuals, the prevalence rates of obesity, hypertension, diabetes mellitus, dyslipidemia, chronic kidney disease and nephrolithiasis were 24.1% (95% CI, 22.6-25.5%), 36.5% (34.9-38.2%), 4.9% (4.2-5.7%), 54.4% (52.7-56.1%), 6.9% (6.1-7.8%) and 18.6% (17.3-19.9%) respectively. In the female hyperuricemia individuals, the prevalence rates of obesity, hypertension, diabetes mellitus, dyslipidemia, chronic kidney disease and nephrolithiasis were 24.0% (21.6-26.3%), 43.2% (40.5-46.0%), 10.2% (8.6-11.9%), 45.5% (42.8-48.3%), 12.8% (11.0-14.7%) and 16.9% (14.8-19.0%) , respectively.
Main results	16	Multivariable logistic regression analysis (multiple adjusted models) was studied and the results were shown in Table 5. The odd ratio for obesity, hypertension, diabetes mellitus, dyslipidemia, chronic kidney disease, nephrolithiasis in the highest SUA quartile was 3.165 (95% CI 2.644-3.790, <i>P</i> <0.001, model 3) , 1.341 (95% CI 1.181-1.524, <i>P</i> <0.001, model 3), 0.206 (95% CI 0.165-0.257, <i>P</i> <0.001, model 3), 2.490 (95% CI 2.213–2.801, <i>P</i> <0.001, model 3), 7.081 (95% CI 4.985-10.058, <i>P</i> <0.001, model 3), 1.469 (95% CI 1.261–1.710, <i>P</i> <0.001, model 3) compared with that in the lowest SUA quartile, respectively, in men. The data in Table 6 were multivariable logistic regression analysis in women and the odd ratio for obesity, hypertension, diabetes mellitus, dyslipidemia, chronic kidney disease, nephrolithiasis in the highest SUA quartile was 3.776 (95% CI 2.969-4.802, <i>P</i> <0.001, model 3), 1.289 (95% CI

1.076-1.545, $P = 0.006$, model 3), 0.524 (95% CI 0.384-0.715, $P < 0.001$, model 3), 3.614 (95% CI 3.058-4.272, $P < 0.001$, model 3), 11.571 (95% CI 7.267-18.423, $P < 0.001$, model 3), 1.242 (95% CI 1.009-1.530, $P = 0.041$, model 3) compared with that in the lowest SUA quartile, respectively.

Other analyses	17	Multivariable logistic regression was analyzed for hyperuricemia and clustered CVD risk factors, the results were shown in Table 7. After adjustment for age, compared with the group of zero CVD risk factor reference group, the odd ratio for group of ≥ 3 CVD risk factors was 3.889 (95% CI 3.322-4.552, $P < 0.001$), 6.270 (95% CI 4.936-7.964, $P < 0.001$) in men and women, respectively. The individuals with more CVD risk factors were associated with the higher ORs of hyperuricemia both in men and women (P for trend < 0.001). Furthermore, females had a stronger association of hyperuricemia with clustered CVD risk factors than males.
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Discussion

Key results	18	In summary, our data demonstrated that the increasing prevalent rate of CRFs and renal disorders were significantly correlated with the elevated level of serum uric acid. Hyperuricemia was remarkably linked with CVD-related risk factors and kidney diseases. Furthermore, a close correlation between hyperuricemia and clustered CVD risk factors, CKD was observed in females than in males.
Limitations	19	This study has some limitations that need to be mentioned. First, it was a cross-section study and the results could not establish causative relationships between hyperuricemia and CRFs clustering and renal diseases. Second, the data were from three medical centers' databases that lacked details in waist circumference, HOMA-IR, smoking, drinking, lifestyles, diet and pharmacotherapy, which might affect the deviations of some clinical outcomes.
Interpretation	20	It was a cross-section study and the results could not establish causative relationships between hyperuricemia and CRFs clustering and renal diseases. Future follow-up studies are required for more accurate evaluation of these relationships.
Generalisability	21	In Shanghai population, concomitant with the elevated level of serum uric acid, the prevalence of CRFs and renal diseases was rising. Hyperuricemia was significantly associated with CVD risk factors and renal disorders. Therefore, target inhibition of SUA level may have potential to become an effective therapy in alleviating risks of CVDs and renal disorders, especially in females.

Other information

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*Give information separately for exposed and unexposed groups.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at <http://www.plosmedicine.org/>, Annals of Internal Medicine at <http://www.annals.org/>, and Epidemiology at <http://www.epidem.com/>). Information on the STROBE Initiative is available at www.strobe-statement.org.