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RESEARCH ARTICLE

Serum uric acid and risk of incident diabetes in middle-aged and elderly Chinese adults: prospective cohort study

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Abstract **The association between serum uric acid and the risk of incident diabetes in Chinese adults remains unknown. This study aimed to investigate this association in a community-dwelling population aged ⩾ 40 years in Shanghai, China. Oral glucose tole3rance test was conducted during baseline and follow-up visits. Relative risk regression was utilized to examine the associations between baseline gender-specific serum uric acid levels and incident diabetes risk. A total of 613 (10.3%) incident diabetes cases were identified during the follow-up visit after 4.5 years. Fasting plasma glucose, postload glucose, and glycated hemoglobin A1c during the follow-up visit progressively increased across the sex-specific quartiles of serum uric acid (all *P*s < 0.05). The incidence rate of diabetes increased across the quartiles of serum uric acid (7.43%, 8.77%, 11.47%, and 13.43%). Multivariate adjusted regression analysis revealed that individuals in the highest quartile had 1.36-fold increased risk of diabetes compared with those in the lowest quartile of serum uric acid (odds ratio (95% confidence interval) = 1.36 (1.06 – 1.73)). Stratified analysis indicated that the association was only observed in women. Accordingly, serum uric acid was associated with the increased risk of incident diabetes among middle-aged and elderly Chinese women.**

Keywords incident diabetes; prospective study; uric acid

Introduction

The burden of diabetes mellitus is increasing. The global expense for diabetes in 2015 was 1.8% of the global gross domestic product [1]. Despite insights into the complex pathophysiology of diabetes, its early detection and life-threatening complications remain an ongoing challenge [2–4]. Uric acid is the end product of human purine nucleoside catabolism and is mainly synthesized from hypoxanthine and xanthine. Hyperinsulinemia causes high renal reabsorption of uric acid and increases its serum concentrations [4,5]. Although evidence revealed that an elevated uric acid level precedes the development of diabetes [3,6–12], the association between uric acid and diabetes remains controversial because several studies reported their inverse relationship [13,14]. Some works revealed a strong association between the serum uric acid levels and diabetes in women [6,15]. Understanding the relationship of uric acid level and diabetes is required to verify uric acid as a risk factor for diabetes.

We aimed to investigate the independent association between serum uric acid levels and future risk for incident type 2 diabetes in a well-established, population-based, prospective cohort.

Materials and methods

Subjects

The participants were recruited from an ongoing cohort study, and a detailed description of the study design was previously published [16–18]. Community-based residents

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from Jiading District, Shanghai, China were enrolled from March to August 2010. This study was composed of 10 375 aged 40 years or older participants who completed a comprehensive survey, which included a detailed questionnaire, anthropometric measurement, a standard 75-g oral glucose tolerance test (OGTT), and blood and urine collection. Han Chinese participants comprised 98.8% (n = 10 254) of the total population. From August 2014 to July 2015, all participants were invited to participate in an in-person follow-up visit. Among the 10 375 study participants, 1979 with diabetes and 61 with missing data of uric acid, blood pressure, glucose profiles at baseline were excluded. A total of 179 participants died, and 2191 did not follow up and thus were excluded from the analysis. A total of 5965 Han participants, including 2109 (35.36%) men and 3856 (64.64%) women, were included in the final analysis, and their average follow-up period was 4.5 years (Fig. 1). The baseline characteristics of dropouters and completers were compared using Student's t-test for continuous variables and χ^2 test for category variables in men and women (Supplementary Table S1). No significant differences were found between the groups in terms of uric acid and blood glucose profile (Ps > 0.05).

The study protocol was approved by the Institutional Review Board of Ruijin Hospital Affiliated to Shanghai Jiao Tong University School of Medicine. All participants provided written informed consent.

Data collection

All participants provided information on their socio-demographic characteristics, previous medical diseases, medications, and lifestyle factors (e.g., cigarette smoking, alcohol drinking, physical activity) through a standard questionnaire administered by trained physicians during baseline and follow-up visits. All staff received a detailed training program covering the study protocol and standard operation procedures, and only those who passed a site-based simulation assessment were allowed to participate in the study. Participants who regularly smoked cigarettes or consumed alcohol in the past six months were defined as current smokers or current drinkers [17]. Physical activity was estimated using the short form of the International Physical Activity Questionnaire with questions on frequency and duration of moderate and vigorous activities and walking [19]. Moderate and vigorous physical activity was defined as $\geqslant$ 150 min/week of moderate-intensity physical activity, or 75 min/week of vigorous-intensity aerobic physical activity, or an equivalent combination of moderate- and vigorous-intensity aerobic activities [20]. Body weight, height, and blood pressure were measured by trained study nurses using a standard protocol. Body weight and height were measured with participants wearing lightweight clothes and without shoes. Waist circumference was measured at the level of the umbilicus. Body mass index (BMI) was calculated as weight (kg) divided by height squared (m^2). After at least 5 min of rest, blood pressure was measured at a nondominant arm using an automated electronic device (OMRON Model HEM-752 FUZZY, Omron 131 Company, Dalian, China) [21]. After overnight fasting, venous blood samples were collected during baseline and follow-up visits. All participants underwent a 75-g OGTT in the morning,

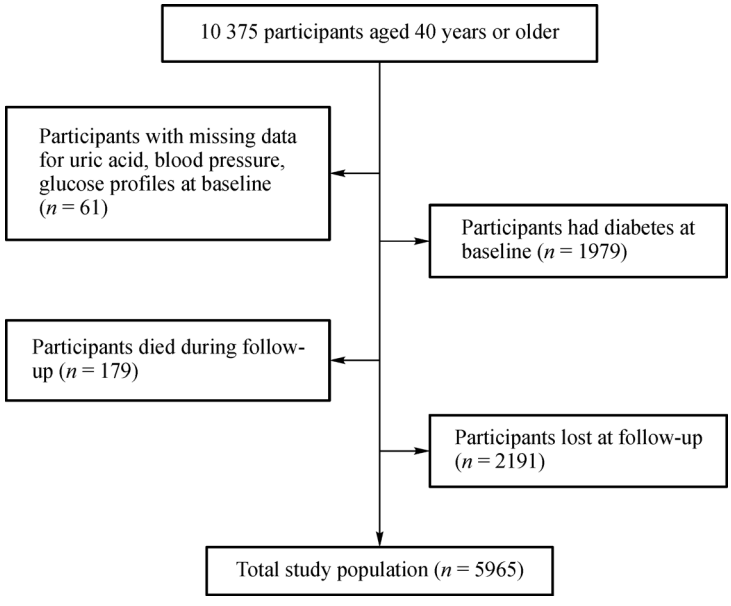

Fig. 1 Flowchart of the study participants.

with blood samples collected at 0 and 2 h to test fasting plasma glucose (FPG) and 2-h postload plasma glucose (PPG), respectively. FPG and PPG were determined via glucose oxidase method using an autoanalyzer (Modular P800; Roche, Basel, Switzerland). Glycated hemoglobin (HbA1c) level was determined through HPLC (BIO-RAD, Hercules, CA, USA). Serum uric acid, fasting serum insulin, triglycerides (TG), total cholesterol (TC), high-density lipoprotein cholesterol (HDL-c), low-density lipoprotein cholesterol (LDL-c), and creatinine were all determined by a chemiluminescence method using an autoanalyzer (Modular E170; Roche) [22]. Estimated glomerular filtration rate (eGFR) was assessed based on the Chronic Kidney Disease Epidemiology Collaboration formula for White/other (except Black) expressed in mililiters per minute per 1.73 m^2: (1) females: Cr $\leqslant$ 0.7 mg/dL, $eGFR = 144 \times (Cr/0.7)^{-0.329} \times (0.993)^{age}$; Cr $>$ 0.7 mg/dL, $eGFR = 144 \times (Cr/0.7)^{-1.209} \times (0.993)^{age}$; (2) males: Cr $\leqslant$ 0.9 mg/dL, $eGFR = 141 \times (Cr/0.9)^{-0.411} \times (0.993)^{age}$; Cr $>$ 0.9 mg/dL, $eGFR = 141 \times (Cr/0.9)^{-1.209} \times (0.993)^{age}$.

Definitions

Hypertension was defined as systolic blood pressure (SBP) $\geqslant$ 140 mmHg, and/or diastolic blood pressure (DBP) $\geqslant$ 90 mmHg, and/or self-reported previous diagnosis of hypertension by physicians, and/or taking antihypertensive medications [16].

Incident diabetes was defined as FPG $\geqslant$ 7.0 mmol/L, and/or 2-h PPG $\geqslant$ 11.1 mmol/L, and/or HbA1c $\geqslant$ 6.5%, and/or self-reported use of antidiabetic medication during follow-up among participants without diabetes at baseline [16].

Impaired glucose regulation (IGR) was defined as: 6.1 $\leqslant$ FPG $<$ 7.0 mmol/L, and/or 7.8 $\leqslant$ 2-h PPG $<$ 11.1 mmol/L, and/or 5.7 % $\leqslant$ HbA1c $<$ 6.5 %, without a history of diabetes [18].

Statistical analysis

Data were presented as mean $\pm$ standard deviation (SD) (medians) and interquartiles for continuous variables, or numbers (percentages) for categorical parameters. Baseline characteristics were described based on gender-specific quartiles. The analyses of continuous and categorical variables to assess differences among quartiles were determined through one-way ANOVA or χ^2 test.

Pearson's correlation test was used to analyze the correlation between serum uric acid concentrations (as continuous variable) at baseline and biochemistry measurements tested during baseline and follow-up visits.

Time-to-event analysis, such as Cox regression model, has assumptions, including proportional hazards and no tied data between event times [23]. In this study, glycemic measures were only obtained at two time points (baseline and follow-up visits). A high proportion of tied diabetes event times was identified in our data. Therefore, the Cox regression model was unsuitable for the analysis of cumulative diabetes.

Logistic regression model can be used to estimate the odds ratios of cumulative diabetes. However, the cumulative incidence of diabetes was high in our study, and odds ratio was not a good approximate for relative risk when the event rates were high. Therefore, relative risk regression was used for the analysis of cumulative diabetes in this study [23].

Relative risk regression was utilized to examine the associations between gender-specific serum uric acid categories at baseline and risk of incident diabetes [23,24]. Model 1 was unadjusted. Model 2 was adjusted in terms of age. Model 3 was adjusted in terms of gender, BMI, smoking status, drinking status, physical activity, educational attainment, and family history of diabetes. Model 4 was adjusted in terms of FPG, TC, TG, EGFR, and hypertension (no/yes). All adjusted confounders were measured during baseline examination. *P* values for trend were tested through the quartiles of serum uric acid treating it as an ordinal variable.

The relationship of serum uric acid quartiles and risk of diabetes was explored through stratified analyses in terms of age ($<$ 60 or $\geqslant$ 60 years), sex (male/female), BMI ($<$ 24 or $\geqslant$ 24), physically active (no/yes), current smoker (no/yes), current drinker (no/yes), hypertension (no/yes), high school or above educational attainment (no/yes), family history of diabetes (no/yes), and IGR (no/yes). The *P* value for interaction was calculated using a likelihood ratio test to compare the models with and without interaction terms.

All analyses were conducted on SAS version 9.2, and a two-tailed $P < 0.05$ was considered statistically significant.

Results

Baseline characteristics

The study included 5965 participants with a mean age of 57.6 $\pm$ 9.0 years, where 35.4% (n = 2109) were men. Among them, 54.4% (n = 3245) had IGR, and 45.6% (n = 2720) had normal glucose regulation. At baseline, the quartiles of serum uric acid were $<$ 212.2, 212.2–254.3, 254.3–305.6, $\geqslant$ 305.6 μmol/L for women, and $<$ 293, 293–345.2, 345.2–401.9, $\geqslant$ 401.9 μmol/L for men. A total of 548 (9.2%) participants (405 men and 143 women) had serum uric acid higher than 420 μmol/L.

The baseline characteristics of participants based on their gender-specific uric acid quartiles are shown in Table 1. Individuals with increased serum uric acid level appeared to be old, obese, current drinker, physically active, with family history of diabetes, and had

significantly high levels of blood pressure, blood glucose, HbA1c, TC, LDL-c, TGs, and low levels of eGFR, HDL-c (all *P*s < 0.05) (Table 1, Fig. 2).

Pearson's correlation analysis

The results of Pearson's correlation analysis showed that serum uric acid was positively correlated to FPG, 2-h PPG, HbA1c, TG, HDL-c and negatively correlated to eGFR ($P < 0.05$) at baseline and follow-up visits. Serum uric acid was not associated with serum TC and LDL-c at follow-up but was positively correlated with TC and LDL-c at baseline (Table 2).

Serum uric acid and the increased risk of incident diabetes

Relative risk regression analysis indicated that elevated serum uric acid was associated with increased risks of incident diabetes. As shown in Table 3, the rates of incident diabetes were 111 (7.43%), 131 (8.77%), 171 (11.47%), and 200 (13.43%) across the quartiles of serum uric acid levels ($P < 0.05$). Multivariate adjusted risk ratios (RRs) (95% confidence interval (CI)) of incident diabetes associated with serum uric acid were 1.00, 1.15 (0.90–1.46), 1.25 (0.99–1.58), and 1.36 (1.06–1.73) ($P < 0.05$) (Table 3).

Stratified analysis of the relationship of serum uric acid and incident diabetes

Stratified analysis was performed based on the demographic, lifestyle, and metabolic-related factors collected during baseline survey (Table 4). Multivarible-adjusted models suggested that the highest quartile of serum uric acid was significantly associated with increased risk of incident diabetes in participants aged < 60 (RR 1.58, 95% CI 1.13–2.21), female (RR 1.58, 95% CI 1.13–2.20), BMI $\geqslant 24$ (RR 1.60, 95% CI 1.20–2.15), physically inactive (RR 1.40, 95% CI 1.07–1.82), non-current smoker (RR 1.52, 95% CI 1.16–2.00), noncurrent drinker (RR 1.41, 95% CI 1.09–1.82), without hypertension (RR 1.60, 95% CI 1.04–2.45), with high school or above educational attainment (RR 1.76, 95% CI 1.004–3.08), without family history of diabetes (RR 1.33, 95% CI 1.02–1.73), and with IGR (RR 1.30, 95% CI 1.01–1.68) as compared with the lowest uric acid quartile.

The potential interactions of serum uric acid level with other risk factors in modifying the risk of incident diabetes were analyzed. As shown in Table 4, no significant interaction was found between serum uric acid levels, sex, physical activity, smoking status, drinking status, hypertension, and education attainment. A significant interaction was found between age, BMI, family history of diabetes, IGR, and serum uric acid (*P*s for interaction < 0.05).

Table 1 Baseline clinical and biochemical characteristics of participants stratified by using the sex-specific quartiles of serum uric acid levels

	Serum uric acid, μmol/L				P_{trend}
	Quartile 1	Quartile 2	Quartile 3	Quartile 4	
No. of participants, *n* (%)	1493 (25.06)	1493 (25.00)	1490 (25.01)	1489 (24.93)	
Age (year)	56.40±9.12	56.69±8.47	57.79±8.84	59.48±9.08	<0.0001
BMI (kg/m^2)	23.79±2.92	24.59±2.86	25.27±3.17	26.16±3.17	<0.0001
Waist circumference (cm)	78.07±8.13	80.78±7.90	82.85±8.66	85.14±8.26	<0.0001
Educational attainment (high school or above), *n* (%)	301 (20.23)	315 (21.23)	322 (21.68)	266 (17.97)	0.09
Current smoker, *n* (%)	316 (22.33)	291 (20.98)	295 (20.85)	257 (18.29)	0.20
Current drinker, *n* (%)	117 (8.22)	146 (10.45)	167 (11.79)	165 (11.69)	0.01
Physically active, *n* (%)	186 (12.49)	214 (14.38)	231 (15.55)	235 (15.80)	0.006
SBP (mmHg)	135.10±18.72	138.59±19.07	140.27±19.65	144.13±19.43	<0.0001
DBP (mmHg)	80.37±10.07	82.33±9.98	83.34±10.16	84.62±10.30	<0.0001
Family history of diabetes, *n* (%)	110 (7.39)	142 (9.54)	124 (8.34)	153 (10.28)	0.02
FPG (mmol/L)	5.03±0.55	5.07±0.54	5.11±0.56	5.16±0.56	<0.0001
2-h PPG (mmol/L)	6.23±1.59	6.50±1.66	6.74±1.73	7.14±1.79	<0.0001
HbA1c (%)	5.5 (5.3–5.7)	5.5 (5.3–5.7)	5.6 (5.3–5.8)	5.6 (5.4-5.8)	<0.0001
Fasting cholesterol (mmol/L)	5.14±0.93	5.33±0.92	5.35±0.98	5.53±1.08	<0.0001
Fasting HDL cholesterol (mmol/L)	1.44±0.34	1.36±0.31	1.32±0.30	1.27±0.31	<0.0001
Fasting LDL cholesterol (mmol/L)	3.01±0.80	3.19±0.80	3.22±0.85	3.33±0.89	<0.0001
Fasting TGs (mmol/L)	1.03 (0.78–1.41)	1.25 (0.94–1.76)	1.40 (1.03–1.93)	1.69 (1.24–2.38)	<0.0001
eGFR	103.87±9.09	101.70±9.37	98.90±9.99	94.27±13.40	<0.0001

Data are expressed as mean±SD or median (interquartile range) for continuous variables and number (proportion) for categorical variables.
The analyses of continuous and categorical variables to assess the differences among quartiles are determined through one-way ANOVA or χ^2 test.

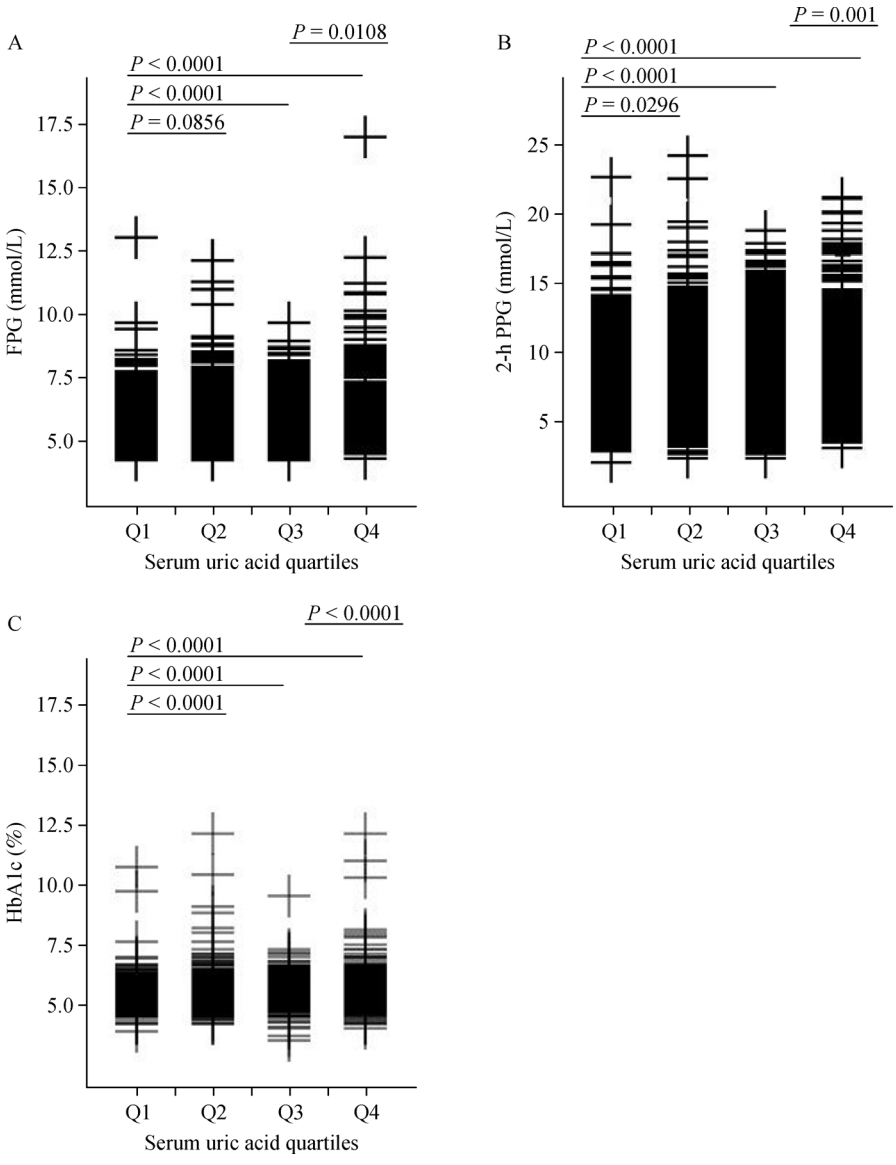

Fig. 2 Associations between FPG, 2-h PPG, and HbA1c levels at 4.5-year follow-up visit with baseline serum uric acid levels. (A) FPG levels at 4.5-year follow-up point based on uric acid quartiles at baseline. (B) 2-h PPG levels in 75-g OGTT at 4.5-year follow-up point based on uric acid quartiles at baseline. (C) HbA1c levels at 4.5-year follow-up point based on uric acid quartiles at baseline. Note: data are expressed as mean ± SD for FPG, 2-h PPG levels and median (interquartile range) for HbA1c levels.

Table 2 Pearson's correlation analysis for the relationship of baseline serum uric acid levels and biochemistry measurements at baseline and follow-up visits, respectively

	Baseline		Follow-up	
	R	*P* value	*R*	*P* value
FPG	0.089	<0.0001	0.102	<0.0001
2-h PPG	0.118	<0.0001	0.123	<0.0001
HbA1c	0.065	<0.0001	0.072	<0.0001
TGs	0.303	<0.0001	0.187	<0.0001
TC	0.039	0.003	−0.010	0.48
LDL cholesterol	0.050	0.0001	−0.015	0.29
HDL cholesterol	−0.268	<0.0001	−0.051	0.0002
eGFR	−0.361	<0.0001	−0.215	<0.0001

LDL, low-density lipoprotein; HDL, high-density lipoprotein.
Pearson's correlation test was used to analyze the correlation between serum uric acid concentrations (as continuous variable) at baseline and biochemistry measurements tested during baseline and follow-up visits.

Table 3 Relative risk (95% CI) of incident diabetes for baseline serum uric acid quartiles

	RR (95% CI)				P_{trend}
	Quartile 1	Quartile 2	Quartile 3	Quartile 4	
Cases/N	111/1493	131/1493	171/1490	200/1489	
Incidence of diabetes (%)	7.43	8.77	11.47	13.43	<0.0001
Model 1	1.00	1.18 (0.93–1.50)	1.54 (1.23–1.94)	1.81 (1.45–2.25)	<0.0001
Model 2	1.00	1.17 (0.92–1.50)	1.50 (1.20–1.89)	1.70 (1.36–2.13)	<0.0001
Model 3	1.00	1.12 (0.87–1.43)	1.26 (1.00–1.60)	1.30 (1.03–1.65)	<0.0001
Model 4	1.00	1.15 (0.90–1.46)	1.25 (0.99–1.58)	1.36 (1.06–1.73)	<0.0001

Model 1, unadjusted; Model 2, adjusted in terms of age; Model 3, adjusted in terms of gender, BMI, smoking status, drinking status, physical activity, educational attainment, family history of diabetes; Model 4, adjusted in terms of FPG, TC, TGs, eGFR, hypertension (Yes/No).
Relative risk regression was utilized to examine the associations between gender-specific serum uric acid categories at baseline and risk of incident diabetes.

Table 4 Subgroup analysis for the association between sex-specific serum uric acid levels and risk of incident diabetes

	Incidence of diabetes (%)	RR (95% CI)				P_{trend}	P for interaction
		Quartile 1	Quartile 2[a]	Quartile 3[a]	Quartile 4[a]		
Age (year)							
<60	8.81	1.00	1.23 (0.88–1.72)	1.44 (1.04–1.99)	1.58 (1.13–2.21)	<0.0001	0.03
⩾60	12.80	1.00	1.02 (0.71–1.46)	1.03 (0.73–1.45)	1.06 (0.75–1.49)	0.02	
Sex							
Male	11.43	1.00	1.01 (0.71–1.46)	1.001 (0.70–1.42)	1.06 (0.73–1.52)	0.10	0.68
Female	9.65	1.00	1.28 (0.92–1.79)	1.46 (1.06–2.01)	1.58 (1.13–2.20)	<0.0001	
BMI (kg/m^2)							
<24	6.70	1.00	1.01 (0.67–1.52)	1.16 (0.77–1.77)	1.06 (0.65–1.73)	0.54	0.0001
⩾24	12.61	1.00	1.29 (0.94–1.75)	1.41 (1.05–1.89)	1.60 (1.20–2.15)	<0.0001	
Physically active							
No	10.29	1.00	1.17 (0.90–1.52)	1.31 (1.01–1.68)	1.40 (1.07–1.82)	<0.0001	0.86
Yes	10.39	1.00	1.03 (0.53–1.98)	0.96 (0.52–1.78)	1.18 (0.66–2.12)	0.02	
Current smoker							
No	10.45	1.00	1.26 (0.95–1.66)	1.33 (1.01–1.74)	1.52 (1.16–2.00)	<0.0001	0.08
Yes	9.58	1.00	0.83 (0.48–1.43)	1.01 (0.62–1.64)	0.81 (0.46–1.42)	0.48	
Current drinker							
No	10.09	1.00	1.15 (0.89–1.49)	1.21 (0.94–1.55)	1.41 (1.09–1.82)	<0.0001	0.24
Yes	11.93	1.00	1.14 (0.53–2.49)	1.44 (0.75–2.76)	0.92 (0.44–1.93)	0.31	
Hypertension							
No	6.72	1.00	1.38 (0.92–2.06)	1.55 (1.03–2.32)	1.60 (1.04–2.45)	0.002	0.12
Yes	13.01	1.00	1.02 (0.75–1.38)	1.11 (0.84–1.47)	1.20 (0.90–1.60)	0.0009	
Highschool or above educational attainment							
No	10.29	1.00	1.11 (0.85–1.45)	1.23 (0.95–1.59)	1.29 (0.98–1.68)	<0.0001	0.25
Yes	9.97	1.00	1.48 (0.81–2.71)	1.43 (0.80–2.53)	1.76 (1.004–3.08)	<0.0001	
Family history of diabetes							
No	9.75	1.00	1.21 (0.93–1.56)	1.21 (0.94–1.56)	1.33 (1.02–1.73)	<0.0001	<0.0001
Yes	15.88	1.00	0.87 (0.44–1.75)	1.62 (0.88–3.00)	1.53 (0.83–2.81)	0.005	
IGR							
No	2.24	1.00	0.91 (0.44–1.89)	0.97 (0.45–2.08)	1.14 (0.48–2.72)	0.54	<0.0001
Yes	17.01	1.00	1.16 (0.90–1.51)	1.31 (1.02–1.68)	1.30 (1.01–1.68)	0.0001	

[a] Adjusted in terms of age, sex, BMI, hypertension (Yes/ No), smoking status, drinking status, educational attainment, physical activity, TC, TGs, FPG, eGFR, and family history of diabetes (except for strata).
Stratified analyses was utilized to examine the relationship of serum uric acid quartiles and risk of diabetes in terms of age (<60 or⩾60 years), sex (male/ female), BMI (<24 or⩾24), physically active (no/yes), current smoker (no/yes), current drinker (no/yes), hypertension (no/yes), high school or above educational attainment (no/yes), family history of diabetes (no/yes), and IGR (no/yes). The P value for interaction was calculated using a likelihood ratio test comparing the models with and without interaction terms.

Discussion

In this prospective study on middle-aged and elderly Chinese population, we observed that a high level of serum uric acid was associated with an increased risk of incident diabetes. Individuals in the third and the highest quartiles had significantly higher incidence of diabetes (7.43% vs. 11.47% and 13.43%, *P*s < 0.05) than those in the lowest quartile. A fully adjusted relative risk analysis revealed that individuals in the highest quartiles had 1.36-fold increased risk of incident diabetes compared with those in the lowest quartile of serum uric acid.

Our data were consistent with previous findings on the association between serum uric acid concentrations and incident risk of diabetes [3,6,8,15]. The Rotterdam Study showed that the risk of developing type 2 diabetes of patients in the highest quartile of uric acid is increased by 1.68 times compared with those in the first quartile. In addition, the association is weaker in men than in women, but no data were shown [8]. The results of Atherosclerosis Risk in Communities Study suggested that uric acid level is associated with diabetes after the adjustment for risk factors (HR 1.18, 95% CI 1.13–1.23), but subgroup analysis was not conducted [3]. Kivity *et al*. observed that uric acid is independently associated with diabetes outcome in women (HR 1.57, 95% CI 1.32–1.86) but not in men (HR 1.08, 95% CI 0.99–1.17) [15]. Liu *et al*. suggested that the changes in hyperuricemia, especially persistent hyperuricemia, are appropriate to reflect diabetes risk [11]. They defined diabetes on the basis of FPG level $\geqslant 7.0$ mmol/L or with the use of antidiabetic medication because of the lack of OGTT. Han *et al*. reported a temporal relationship of uric acid and future risk of diabetes by performing cross-lagged panel and mediation analysis in 17 044 subjects from Heilongjiang Province [10]. Among the participants, 7482 underwent OGTT. Wang *et al*. observed a U-shape relationship of FPG and serum uric acid levels in individuals with normal glucose tolerance [12]. Their cross-sectional design precluded a definitive conclusion about causality. However, none of the above studies has focused on the elderly Chinese population.

The gender difference of serum uric with chronic diseases has been reported by previous epidemiological studies. We performed data analysis using the established classification of a gender-specific quartile method to fully exclude the influence from the abovementioned gender difference [25]. Stratified analysis showed that the association between serum uric acid and increased risk of incident diabetes was statistically significant only in women. This observation was in accordance with previous cohort studies. Meisinger *et al*. reported that uric acid is associated with diabetes development in women (HR per 1 mmol/L increase was 2.05) [26]. Yamada *et al.* revealed that an elevated serum uric acid can predict impaired fasting glucose and type 2 diabetes in women [27]. Nakanishi *et al.* found a significant association between serum uric acid and risk of type 2 diabetes, impaired fasting glucose, and hypertension among male participants [28]. Serum uric acid is a metabolic difference between males and females possibly due to the difference of sex hormones [29]. The increased serum uric acid levels of postmenopausal women may result from menopause-related changes in metabolism [30]. Chou *et al.* reported that the association of serum uric acid level to insulin resistance and plasma glucose levels is stronger in females than in males [31]. Baseline serum uric acid was associated with glycemic markers at 4.5-year follow-up visit. We observed statistically significant but apparently insignificant increment of fasting glucose and HbA1c across the serum uric acid quartiles, whereas the increment of 2-h PPG was prominent. The three glucose indicators tended to increase across serum uric acid quartiles, and this result was consistent with sensitivity analysis (Supplementary Table S2) and our main findings.

The biological mechanisms underlying the association between serum uric acid and development of diabetes remain controversial [4,6,32]. A possible mechanism is that serum uric acid is associated with the induction of renal inflammatory and vascular changes by activating the NF-κB signaling [33]. Hyperuricemia can influence the endothelial dysfunction by stimulating the renin–angiotensin system and inhibiting neuronal nitric oxide (NO) system, thereby dysregulating the glucose uptake [34]. Fructose-induced uric acid generation causes mitochondrial oxidative stress that promotes fat accumulation that is independent of excessive caloric intake [32]. The mitochondrial oxidative stress in islet cells combined with the promotion of formation of fatty liver can lead to insulin resistance [32]. This condition plays an important role in the pathogenesis of type 2 diabetes and has been implicated in the underlying mechanism of hyperuricemia and incident diabetes. Insulin resistance damages the platelet and endothelium functions, leads to nitric oxide inhibition, and contributes to hyperinsulinemia and diabetes [35,36]. Conversely, hyperinsulinemia reduces the renal excretion of uric acid on the proximal tubular of the kidney, leading to hyperuricemia.

The strengths of this study were the large sample size, diagnosis of diabetes through OGTT and HbA1c measurement, priority of gender-specific quartile, and the ability to adjust for multiple confounders. However, we acknowledged some important limitations. First, the major limitation was the relatively short duration of follow-up (mean of 4.5 years). Second, the study participants only had one follow-up visit, and glycemic measures were obtained at only two time points (baseline and follow-up visits). These conditions could limit the accuracy of ascertainment of timing of diagnoses, especially diabetes. Third, eGFR was estimated using the Chronic Kidney

Disease Epidemiology Collaboration equation based on creatinine rather than direct measurement, possibly leading to some variability. Fourth, the possibility of residual confounding caused by unmeasured or poorly measured confounders, such as incident diabetes diagnosis timing, smoking status, alcohol consumption, and energy intake, could not be eliminated. Self-reported activity level with International Physical Activity Questionnaire was difficult to quantify for many low-income, low-literacy populations. Finally, the present study was performed in a middle-aged and elderly Chinese Han population. Thus, the results may not be applicable to the general population.

We observed that high serum uric acid level was associated with a significantly increased risk of incident diabetes among the middle-aged and elderly Chinese women. Serum uric acid reduction might prevent diabetes and cardiovascular diseases because uric acid levels are effectively and safely modifiable with treatment. These findings could be translated into large public health gains. Future investigations are needed for the causal interference and exact mechanism.

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Compliance with ethics guidelines

Di Cheng, Chunyan Hu, Rui Du, Hongyan Qi, Lin Lin, Xueyan Wu, Lina Ma, Kui Peng, Mian Li, Min Xu, Yu Xu, Yufang Bi, Weiqing Wang, Yuhong Chen, and Jieli Lu declare that they have no conflict of interest. All procedures followed were in accordance with the ethical standards of the Institutional Review Board of Ruijin Hospital Affiliated to Shanghai Jiao Tong University School of Medicine and with the *Helsinki Declaration* of 1975, as revised in 2000. Informed consent was obtained from all patients for being included in the study.

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