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ORIGINAL ARTICLE

Serum uric acid associates with the incidence of type 2 diabetes in a prospective cohort of middle-aged and elderly Chinese

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Abstract This study is to prospectively investigate the association between serum uric acid and the incidence of type 2 diabetes in middle-aged and elderly Chinese. This study consisted of 924 non-diabetic adults aged 40 years or older at baseline. Subjects who received antidiabetic therapies and those who responded positively to the 75-g oral glucose tolerance test according to the 1999 World Health Organization criteria were diagnosed as having type 2 diabetes. Ninety-eight subjects developed type 2 diabetes during the 3.5-year follow-up. The hazard ratio (HR) for incident diabetes was 1.50 [95% confidence interval (CI) 1.18–1.92] for the highest sex-specific quartile of serum uric acid compared with the lowest after controlling for confounders. Participants with hyperuricemia had an HR of 1.95 (95% CI 1.11–3.44) for incident diabetes compared with those without hyperuricemia. Compared with the lowest quartile, the highest quartile had an HR for incident diabetes of 2.45 (95% CI 1.39–4.33) in men and 1.39 (95% CI 1.04–1.84) in women after fully adjustment. Adding serum uric acid to a model of conventional risk factors for diabetes improved the area under the curve for prediction of type 2 diabetes by 5%. Serum uric acid was an independent predictor of incident type 2 diabetes in middle-aged and elderly Chinese.

Keywords Serum uric acid · Type 2 diabetes · Prospective study

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Introduction

Previous studies have demonstrated that hyperuricemia is associated with a wide range of morbidity status, including hypertension, metabolic syndrome, renal and cardiovascular diseases [1–4]. Experimental studies have shed light on the relationship between serum uric acid and glucose metabolism. Evidence shows that serum uric acid may play a role in insulin resistance through obstructing the bioactivity of nitric oxide [5], which is crucial for insulin-stimulated glucose uptake in skeletal muscle [6], and by promoting secretion of inflammatory factors and adipocytokine [7].

Positive association between serum uric acid and glucose metabolism has been reported in several cross-sectional studies [8–10]. However, prospective studies on the association of uric acid with incident type 2 diabetes are limited and the results are conflicting [11–15]. It was reported that higher level of serum uric acid was a risk factor for incident type 2 diabetes in the Netherlanders [11], and this association was confirmed in Americans [12]. On the other hand, it was found that uric acid was not associated with incident type 2 diabetes in Japanese [13]. In addition, a sex difference in the association between uric acid and type 2 diabetes was observed in Indians and Creole population and Japanese office workers [14, 15].

The purpose of this study was to investigate, in a prospective community-based cohort of Chinese aged 40 years

or older, whether higher levels of serum uric acid independently predict the incidence of type 2 diabetes.

Subjects and methods

Subjects

Subjects were recruited from Baoshan District in Shanghai, as reported previously [16, 17]. The study protocol was approved by the Institutional Review Board of Rui-Jin Hospital affiliated to Shanghai Jiao-tong University School of Medicine, and informed consent was obtained from each participant. In May of 2005, 1284 non-diabetic subjects aged 40 years or older were included in this study. Glucose metabolism status was determined by a simplified 75-g oral glucose tolerance test (OGTT, fasting and 2-h post-load blood sampling only). Standard questionnaire was used to collect the information on lifestyle, medical history and the use of medications. Anthropometric measurements were performed by experienced physicians. Blood and urine samples were collected from each participant for biochemical measurements.

In November of 2008, all the participants were invited to have a follow-up examination. Each participant was asked to undergo the same clinical and biochemical measurements as those at the baseline. A total of 944 subjects (73.5%) responded and participated in the follow-up examination. Participants with missing data on history of diabetes or OGTT ($n = 20$) at the follow-up visit were excluded, leaving 924 participants for the present analysis.

Clinical and biochemical measurements

Body weight and height were measured by experienced physicians. Body mass index (BMI) was calculated as body weight in kilograms divided by body height squared in meters. Blood pressure was measured on the non-dominant arm with an automated electronic sphygmomanometer (OMRON Model1 Plus, Omron Company, Kyoto, Japan) three times (averaged for analysis) consecutively with 1 min intervals after at least 5 min rest in a seated position.

Plasma glucose concentrations, serum concentrations of uric acid and creatinine, triglycerides, total cholesterol, high-density lipoprotein (HDL)-cholesterol and low-density lipoprotein (LDL)-cholesterol were measured by an autoanalyser (Beckman CX-7 Biochemical Autoanalyser, Brea, CA, USA). The white blood cell count was determined using an automated cell counter. Serum insulin concentration was measured using a radioimmunoassay (Sangon Company, Shanghai, China). Serum high sensitive C-reactive protein concentrations were measured using highly sensitive competitive immunoassay (antigens and antibodies from BioCheck, Foster City, CA, USA). The intra-assay and inter-assay coefficients of variation for high sensitive C-reactive protein concentration was 4.4 and 3.3%, respectively.

Definitions

Type 2 diabetes was determined by OGTT according to the 1999 World Health Organization criteria supplemented by a questionnaire during the follow-up examination. The participants were asked whether they had been diagnosed with diabetes; with a positive response, further information was collected on type of diabetes, time and place it was first diagnosed and whether by OGTT finally, therapeutic measurements performed and family history of diabetes. Subjects who received antidiabetic therapies and those who responded positively to OGTT as fasting plasma glucose (FPG) $\geq$ 7.0 mmol/l and/or 2-h post-challenge plasma glucose (PPG) $\geq$ 11.1 mmol/l were diagnosed as having type 2 diabetes. During the follow-up period, 98 subjects developed type 2 diabetes.

Hyperuricemia was defined as concentrations of serum uric acid great equal 360 μmol/l in women and 420 μmol/l in men. Insulin resistance was defined as index of homeostasis model assessment of insulin resistance (HOMA-IR) greater than 2.50.

Statistical analysis

SAS version 8.1 (SAS Institute, Cary, NC) was used for database management and statistical analysis. HOMA-IR was calculated as fasting insulin (μIU/ml) × fasting glucose (mmol/l)/22.5. Measurements (including HOMA-IR, fasting insulin, and high sensitive C-reactive protein) with a skewed distribution were normalized by logarithmic transformation before analysis. The one-way ANOVA (for continuous variables) and Chi-squared test (for categorical variables) were performed to analyze the statistical differences of the clinical and biochemical characteristics by diabetes status or sex-specific quartiles of serum uric acid. Linear regression analysis was used to test for trend of the association across the sex-specific quartiles of serum uric acid levels.

For each participant, person-years of follow-up were calculated from the date of enrollment in the study to the date of the incidence of type 2 diabetes or the date of follow-up visit, whichever occurred first. Cox proportional hazards analysis was used to evaluate the hazard ratios (HRs) and 95% confidence interval (CI) for sex-specific quartiles of serum uric acid levels, and further analyze the association between serum uric acid and incident diabetes in men and women separately. The sex-specific cutoff points for serum uric acid quartiles were: quartile 1: uric

acid <285 μmol/l in men and <197 μmol/l in women; quartile 2: 285–333 μmol/l in men and 197–246 μmol/l in women; quartile 3: 334–391 μmol/l in men and 247–295 μmol/l in women; quartile 4: 392–775 μmol/l in men and 296–580 μmol/l in women. The data were adjusted first for age and sex (Model 1), and further for BMI, family history of diabetes, smoking and alcohol drinking (Model 2). The data were additionally adjusted for the potential confounding variables, including systolic blood pressure, diastolic blood pressure, serum HDL-cholesterol, triglycerides, total cholesterol, FPG, fasting insulin and serum creatinine (Model 3) and were finally adjusted for white blood cell count and high sensitive C-reactive protein (Model 4). To investigate the potential interaction of insulin resistance and serum uric acid on the incidence of diabetes, we included the interaction term to the Cox hazards models. The serum uric acid levels were fitted as a continuous variable and HRs (95% CI) were computed for each 1-standard deviation (SD) increase of serum uric acid levels for the stratified analysis according to HOMA-IR (HOMA-IR $\leq$ vs. $>$ 2.50).

To measure the discriminative attribution of the uric acid, we used the receiver operating characteristic curve to calculate corresponding areas under the curve (AUC) for logistic regression models incorporating conventional risk factors (including age, sex, BMI, family history of diabetes, smoking and alcohol drinking) with and without inclusion of serum uric acid [18]. A P value of less than 0.05 was considered to be statistically significant.

Results

Characteristics of the participants

Baseline characteristics of the participants by diabetes status at 3.5-year follow-up are presented in Table 1. Participants who progressed to type 2 diabetes during the follow-up period had higher levels of BMI, systolic blood pressure, diastolic blood pressure and HOMA-IR, higher concentrations of FPG, 2-h PPG, fasting insulin, serum triglycerides and high sensitive C-reactive protein, and lower concentrations of HDL-cholesterol and creatinine than those who did not develop diabetes (all $P < 0.05$). Serum uric acid levels were significantly higher in the participants who developed type 2 diabetes than those who did not develop diabetes (unadjusted $P = 0.0005$, age, sex and BMI-adjusted $P = 0.0002$).

Baseline characteristics of participants by sex-specific quartiles of serum uric acid are presented in Table 2. Compared with those in the lowest quartile, participants in the highest quartile were older. Serum uric acid levels were positively associated with higher levels of BMI, systolic and diastolic blood pressures, higher concentrations of FPG, 2-h PPG, fasting insulin, total cholesterol, triglycerides, LDL-cholesterol and serum creatinine, and lower levels of HDL-cholesterol (all $P < 0.05$). Serum uric acid was positively correlated with HOMA-IR ($r = 0.14$, $P < 0.0001$) and the levels of HOMA-IR were significantly increased across sex-specific serum uric acid quartiles ($P < 0.0001$). Serum uric acid was positively correlated with chronic inflammatory markers such as high sensitive C-reactive protein ($r = 0.18$, $P < 0.0001$) and white blood cell count ($r = 0.11$, $P = 0.0008$) after adjusting for HOMA-IR, and high sensitive C-reactive protein was also significantly increased across serum uric acid quartiles ($P < 0.0001$).

Serum uric acid in association with incident type 2 diabetes

Cox regression analysis shows that elevated serum uric acid was significantly associated with an increased risk of type 2 diabetes (Table 3). The age- and sex-adjusted HRs (95% CI) for diabetes were 0.66 (0.34–1.30) for the second, 0.92 (0.66–1.28) for the third, and 1.40 (1.26–1.67) for the fourth quartile of serum uric acid, compared with the first quartile (P for trend <0.0001). Compared with the participants without hyperuricemia, those with hyperuricemia had 2.71-fold of increased risk for type 2 diabetes. This association was not substantially changed after further adjusting for BMI, family history of diabetes, smoking, alcohol drinking, systolic blood pressure, diastolic blood pressure, HDL-cholesterol, triglycerides, total cholesterol, FPG, fasting insulin, serum creatinine, white blood cell count and high sensitive C-reactive protein (Models 2, 3, and 4).

When analyzing the association between serum uric acid and incident diabetes in men and women separately, compared with the lowest quartile, the highest quartile of serum uric acid had an HR of 2.45 (95% CI 1.39–4.33) in men, and 1.39 (95% CI 1.04–1.84) in women, after fully adjustment.

Serum uric acid and the risk of incident type 2 diabetes by HOMA-IR

Among participants without insulin resistance (HOMA-IR $\leq$ 2.50), the HRs for incident diabetes with each 1-SD increase of serum uric acid levels were 1.45–1.58 in four multivariate regression models (all $P < 0.05$). In contrast, among those with insulin resistance (HOMA-IR $>$ 2.50), this association was no longer significant (all $P > 0.05$) in four models. The interaction between uric acid and HOMA-IR was significant in Model 1 and 2; however, the P values for interaction were no longer significant after

Table 1 Baseline characteristics of the participants by diabetes status at 3.5-year follow-up

	Incident diabetes $n = 98$	No diabetes $n = 826$	P value
Age (years)	61.6 ± 9.3	61.6 ± 9.1	0.99
Men n (%)	30 (30.6)	302 (36.6)	0.25
BMI (kg/m^2)	26.0 ± 3.2	24.8 ± 3.2	<0.001
Current smoking n (%)	12 (12.2)	113 (13.7)	0.69
Current alcohol drinking n (%)	13 (13.3)	99 (12.0)	0.71
Family history of diabetes n (%)	15 (15.3)	77 (9.3)	0.06
Systolic blood pressure (mmHg)	145 ± 25	136 ± 23	<0.001
Diastolic blood pressure (mmHg)	82 ± 11	79 ± 11	0.005
FPG (mmol/l)	6.1 ± 0.6	5.5 ± 0.6	<0.001
2-h PPG (mmol/l)	8.5 ± 1.8	6.8 ± 1.5	<0.001
Fasting insulin (mIU/l)	8.9 (4.1–14.9)	4.6 (2.3–8.0)	<0.001
HOMA-IR	2.3 (1.0–3.9)	1.1 (0.6–2.0)	<0.001
Total cholesterol (mmol/l)	4.8 ± 0.9	4.8 ± 0.9	0.98
Triglycerides (mmol/l)	1.5 (1.1–2.2)	1.2 (0.9–1.8)	<0.001
HDL-cholesterol (mmol/l)	1.3 ± 0.3	1.5 ± 0.4	<0.001
LDL-cholesterol (mmol/l)	2.7 ± 0.7	2.7 ± 0.7	0.90
High sensitive C-reactive protein (mg/l)	2.8 (1.2–6.2)	1.9 (0.8–4.0)	<0.001
White blood cell count ($\times 10^9$/l)	5.9 ± 1.4	5.7 ± 1.4	0.23
Serum creatinine (μmol/l)	62.6 ± 14.1	66.1 ± 15.3	0.03
Serum uric acid (μmol/l)	314.9 ± 97.8	280.4 ± 90.7	<0.001

Data are means ± SD or median (interquartile range) for skewed variables or number (proportion) for categorical variables. P values are for the ANOVA or Chi-square analyses

BMI body mass index, *FPG* fasting plasma glucose, *PPG* post-challenge plasma glucose, *HOMA-IR* homeostasis model assessment of insulin resistance, *HDL* high-density lipoprotein, *LDL* low-density lipoprotein

adjusting for systolic blood pressure, diastolic blood pressure, HDL-cholesterol, total cholesterol, triglycerides, FPG, fasting insulin, serum creatinine, white blood cell count and high sensitive C-reactive protein (Table 4).

Receiver operating characteristic curve for the incidence of type 2 diabetes

Figure 1 shows the receiver operating characteristic curves for the logistic regression model including conventional risk factors with and without the inclusion of serum uric acid. The AUC for the conventional model was 0.60 (95% CI 0.47–0.74, $P = 0.05$), and was increased to 0.65 (95% CI 0.54–0.77, $P = 0.02$) when the serum uric acid was added.

Discussion

In this prospective study, we found that serum uric acid was an independent predictor for the incidence of type 2 diabetes in middle-aged and elderly Chinese. Furthermore, our data indicated the association between serum uric acid and the incidence of type 2 diabetes was independent from insulin resistance, which plays an important role in the pathology of type 2 diabetes.

Several cross-sectional studies have indicated a positive relationship between uric acid and glucose metabolism in different populations [8–10]. However, the prospective studies of this association are limited and have presented inconsistent results. It was shown in a 6-year follow-up study among 2310 Japanese male adults that serum uric acid level was significantly associated with the risk of diabetes [15]. And this association was also confirmed in the Rotterdam Study, a 10-year follow-up study in the Netherlands population [11]. On the contrary, the Osaka Health Survey showed that the association between uric acid and type 2 diabetes was not significant after multivariate adjustment [13]. Moreover, a sex difference exists in this association in Indians and Creole population: the multivariate adjusted HRs (95% CI) for the development of diabetes with each 1-SD increment in serum uric acid were 1.14 (1.01–1.30) in Indian men and 1.37 (1.11–1.68) in Creole men, and they were 1.07 (0.95–1.22) and 1.01 (0.84–1.22), respectively, in Indians and Creole women [14]. We use sex-specific quartiles of serum uric acid in the analysis and further analyze the association by gender, and our results prospectively demonstrated that higher serum

Table 2 Baseline characteristics of the participants, according to sex-specific serum uric acid quartiles at baseline

	Sex-specific serum uric acid quartile				*P* value (trend across quartiles)
	1 (lowest)	2	3	4 (highest)	
n	227	235	229	233	–
Serum uric acid (μmol/l)	185.2 ± 46.8	251.9 ± 43.7	304.4 ± 47.4	489.5 ± 75.4	–
Age (years)	60.4 ± 9.3	60.3 ± 9.4	62.0 ± 8.6	63.8 ± 8.8	<0.001
BMI (kg/m^2)	23.9 ± 2.8	24.3 ± 3.1	25.2 ± 3.2	26.2 ± 3.2	<0.001
Current smoking *n* (%)	39 (17.2)	24 (10.2)	34 (14.9)	28 (12.0)	0.29
Current alcohol drinking *n* (%)	25 (11.0)	27 (11.5)	33 (14.4)	36 (15.5)	0.07
Family history of diabetes *n* (%)	22 (9.7)	22 (9.4)	26 (11.4)	22 (9.4)	0.89
Systolic blood pressure (mmHg)	132 ± 26	135 ± 22	138 ± 22	143 ± 24	<0.001
Diastolic blood pressure (mmHg)	77 ± 12	79 ± 11	80 ± 11	81 ± 12	<0.001
FPG (mmol/l)	5.5 ± 0.6	5.5 ± 0.6	5.6 ± 0.6	5.7 ± 0.6	<0.001
2-h PPG (mmol/l)	6.6 ± 1.6	6.7 ± 1.6	7.1 ± 1.5	7.7 ± 1.7	<0.001
Fasting insulin (mIU/l)	3.8 (2.2–7.1)	3.9 (1.9–6.6)	5.1 (2.2–9.0)	7.4 (3.3–12.8)	<0.001
HOMA-IR	0.9 (0.5–1.8)	0.9 (0.5–1.6)	1.3 (0.6–2.2)	1.8 (0.8–3.4)	<0.001
Total cholesterol (mmol/l)	4.7 ± 0.8	4.8 ± 0.9	4.9 ± 0.9	4.9 ± 0.9	0.004
Triglycerides (mmol/l)	1.0 (0.7–1.4)	1.1 (0.8–1.6)	1.4 (1.0–2.0)	1.5 (1.1–2.4)	<0.001
HDL-cholesterol (mmol/l)	1.6 ± 0.4	1.5 ± 0.4	1.4 ± 0.4	1.4 ± 0.4	<0.001
LDL-cholesterol (mmol/l)	2.7 ± 0.7	2.7 ± 0.7	2.8 ± 0.7	2.8 ± 0.8	0.04
High sensitive C-reactive protein (mg/l)	1.1 (0.5–2.5)	1.6 (0.7–4.0)	1.9 (1.0–3.7)	3.2 (1.7–6.3)	<0.001
White blood cell count (× 10^9/l)	5.7 ± 1.4	5.6 ± 1.4	5.9 ± 1.5	5.8 ± 1.3	0.09
Serum creatinine (μmol/l)	60.6 ± 15.1	62.9 ± 13.2	67.1 ± 14.2	72.1 ± 15.9	<0.001

Data are means ± SD or median (interquartile range) for skewed variables or number (proportion) for categorical variables. *P* values are for the ANOVA or Chi-square analyses

BMI body mass index, *FPG* fasting plasma glucose, *PPG* post-challenge plasma glucose, *HOMA-IR* homeostasis model assessment of insulin resistance, *HDL* high-density lipoprotein, *LDL* low-density lipoprotein

uric acid level was a predictor for incident type 2 diabetes in men and women, independent of a series of conventional risk factors, such as family history of diabetes, BMI, FPG and fasting insulin, blood pressure, cigarette smoking and serum creatinine, etc. We found the HR was much bigger in men (2.45, 95% CI 1.39–4.33) than in women (1.39, 95% CI 1.04–1.84) after fully adjusted, and that may depends on a higher basal level of serum uric acid in men than in women. Furthermore, the receiver operating characteristic curves showed that serum uric acid improved the AUC for prediction of type 2 diabetes beyond the contribution of conventional risk factors by 5%.

Previous studies have suggested that several potential mechanisms might account for the positive association between higher serum uric acid levels and type 2 diabetes. First, higher levels of serum uric acid take an important part in leading to endothelial dysfunction [19] and disturbing nitric oxide release from endothelial cells [5], a process that reduces the insulin-stimulated glucose intake in skeletal muscle. Second, serum uric acid, a strong oxidant in patients with metabolic syndrome [20], plays an important role in inducing inflammation and oxidative stress in adipocytes [7, 21], which are closely related to the occurrence of type 2 diabetes [22]. Finally, higher serum uric acid accounts for the increased renal glomerular pressure [23], a cause for glucose intolerance.

We found that a serum uric acid level of 392 μmol/l or greater in men or 296 μmol/l or greater in women had nearly 1.50-fold increased risk for incident type 2 diabetes independent of several confounders, including age, sex, BMI, family history of diabetes, smoking and alcohol drinking, systolic and diastolic blood pressure, HDL-cholesterol, total cholesterol, triglycerides, FPG, fasting insulin, serum creatinine, white blood cell count and high sensitive C-reactive protein. A possible explanation is that serum uric acid has dual function on health outcomes, and the end points depend on the balance of the two. At lower levels, serum uric acid is a potent endogenous antioxidant in the body and has anti-oxidative beneficial effects [24, 25]. On the other hand, at elevated levels, serum uric acid takes an important part as prooxidant on vascular cells and adipocytes [26], and can promote the secretion of several inflammatory mediators, including C-reactive protein and monocyte chemoattractant protein-1 [27, 28]. Thus at higher levels, its prooxidant function may overwhelm the antioxidant function, causing a series of endocrine

Table 3 Incidence rate and risk of incident type 2 diabetes in relation to increased serum uric acid at baseline

	Participants (cases)	Person-years (PY)	Crude rate per 1000 PY	HR (95% CI)			
				Model 1	Model 2	Model 3	Model 4
All participants ($n = 924$)							
Quartile 1	227 (21)	801.9	26.2	1.00 (Ref.)	1.00 (Ref.)	1.00 (Ref.)	1.00 (Ref.)
Quartile 2	235 (14)	828.6	16.9	0.66 (0.34–1.30)	0.62 (0.31–1.22)	1.04 (0.49–2.22)	0.97 (0.45–2.09)
Quartile 3	229 (15)	799.2	18.8	0.92 (0.66–1.28)	0.82 (0.58–1.16)	1.00 (0.67–1.49)	1.03 (0.69–1.56)
Quartile 4	233 (48)	809.1	59.3	1.40 (1.26–1.67)	1.36 (1.13–1.64)	1.57 (1.24–1.99)	1.50 (1.18–1.92)
P for trend	924 (98)	–	–	<0.001	<0.001	<0.001	0.001
With hyperuricemia versus without hyperuricemia				2.71 (1.65–4.43)	2.31 (1.39–3.82)	2.15 (1.23–3.75)	1.95 (1.11–3.44)
Men ($n = 332$)							
Quartile 1	81 (6)	287.6	20.9	1.00 (Ref.)	1.00 (Ref.)	1.00 (Ref.)	1.00 (Ref.)
Quartile 2	84 (5)	296.3	16.9	0.80 (0.24–2.64)	0.89 (0.26–2.99)	1.47 (0.37–5.87)	1.64 (0.39–6.92)
Quartile 3	83 (6)	293.7	20.4	0.95 (0.54–1.68)	0.89 (0.49–1.65)	1.63 (0.50–5.33)	2.13 (0.61–7.44)
Quartile 4	84 (13)	293.6	44.3	1.37 (1.00–1.89)	1.35 (1.00–1.94)	2.24 (1.30–3.86)	2.45 (1.39–4.33)
P for trend	332 (30)	–	–	0.048	0.167	0.008	0.002
Women ($n = 592$)							
Quartile 1	146 (15)	514.3	29.2	1.00 (Ref.)	1.00 (Ref.)	1.00 (Ref.)	1.00 (Ref.)
Quartile 2	151 (9)	532.2	16.9	0.59 (0.26–1.36)	0.53 (0.23-1.23)	0.84 (0.32–2.19)	0.97 (0.37–2.55)
Quartile 3	146 (9)	505.5	17.8	0.85 (0.55–1.31)	0.76 (0.49–1.19)	0.81 (0.48–1.37)	0.79 (0.47–1.34)
Quartile 4	149 (35)	515.6	67.9	1.41 (1.14–1.75)	1.35 (1.08–1.69)	1.38 (1.04–1.83)	1.39 (1.04–1.84)
P for trend	592 (68)	–	–	<0.001	0.001	0.039	0.052

HR hazard ratio; *CI* confidence interval; *Model 1* adjusted for age and sex; *Model 2* additionally adjusted for BMI, family history of diabetes, smoking and alcohol drinking; *Model 3* additionally adjusted for systolic blood pressure, diastolic blood pressure, HDL-cholesterol, total cholesterol, triglycerides, FPG, fasting insulin and serum creatinine; *Model 4* additionally adjusted for white blood cell count and high sensitive C-reactive protein

Table 4 Association of type 2 diabetes with each 1-SD increase of serum uric acid stratified by HOMA-IR

Model	HOMA-IR ≤ 2.50 ($n = 739$)		HOMA-IR > 2.50 ($n = 185$)		*P* value for interaction
	HR (95% CI)	*P*	HR (95% CI)	*P*	
1	1.58 (1.22–2.04)	<0.001	1.13 (0.85–1.50)	0.41	0.041
2	1.47 (1.12–2.00)	0.006	1.12 (0.83–1.53)	0.46	0.047
3	1.56 (1.14–2.13)	0.005	1.38 (0.98–1.93)	0.062	0.63
4	1.45 (1.06–1.99)	0.022	1.37 (0.96–1.95)	0.082	0.77

HR hazard ratio; *CI* confidence interval; *Model 1* adjusted for age and sex; *Model 2* additionally adjusted for BMI, family history of diabetes, smoking and alcohol drinking; *Model 3* additionally adjusted for systolic blood pressure, diastolic blood pressure, HDL-cholesterol, total cholesterol, triglycerides, FPG, fasting insulin and serum creatinine; *Model 4* additionally adjusted for white blood cell count and high sensitive C-reactive protein

disorders. It is important clinically, and since the assessment of uric acid is widely available and the medication to decrease serum uric acid is safe and inexpensive, the public health should attach importance to high serum uric acid.

To explore whether the association between serum uric acid and incident type 2 diabetes was modified by insulin resistance, we assessed the interaction of insulin resistance (assessed by HOMA-IR) and serum uric acid on the incidence of diabetes. The HOMA-IR is a well-validated measurement for insulin resistance and well correlated with reference techniques such as the euglycemic clamp (0.58–0.88), and it has been proved to be a robust clinical and epidemiological tool in descriptions of the pathophysiology of diabetes [29]. We found that the association between serum uric acid and type 2 diabetes was more predominant in participants without insulin resistance. However, the interaction between serum uric acid and insulin resistance was not significant after adjusting for

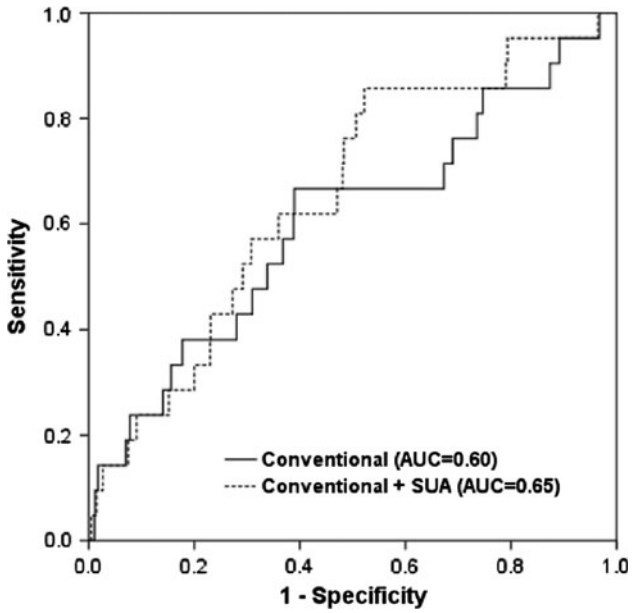

Fig. 1 Receiver operating characteristic curve for the incident of type 2 diabetes. The curves are based on logistic regression models including conventional risk factors (age, sex, BMI, family history of diabetes, smoking and alcohol drinking) with and without the inclusion of serum uric acid. The AUC for the conventional model was 0.60 (95% CI 0.47–0.74, $P = 0.05$), and was increased to 0.65 (95% CI 0.54–0.77, $P = 0.02$) when the serum uric acid was added. *SUA* serum uric acid

several potential confounders, including systolic blood pressure, diastolic blood pressure, HDL-cholesterol, total cholesterol, triglycerides, FPG, fasting insulin, serum creatinine, white blood cell count and high sensitive C-reactive protein. The result indicated that the prediction power of serum uric acid on the incidence of type 2 diabetes might be independent from insulin resistance, which plays an important role in the pathogenesis of type 2 diabetes [30]. In Model 4, the HRs and *P* values in the two groups were similar, which may indicate a role for oxidative processes independent of insulin resistance in subjects with insulin resistance cannot be excluded. This suggested that even in circumstance of insulin resistance, uric acid may have some oxidative activity additional to high sensitive C-reactive protein and atherogenic dyslipidemia.

A major strength of our study included the prospective nature of the analysis, which minimized the bias of reverse association. In addition, we have measured and carefully adjusted for a wide spectrum of known or potential confounders including lifestyle and biochemical factors in our analyses. However, several limitations in this study must be considered. First, residual confounding effects of unknown factors such as dietary intakes could not be ruled out in our study due to lack of detailed information, but we adjusted a serious of confounders such as age, sex, BMI, family history of diabetes, smoking and alcohol drinking, blood pressures, lipid profiles, plasma glucose, serum insulin, creatinine, white blood cell counts and hs-CRP to control the bias. Second, since the baseline serum uric acid concentrations were measured only once, the intra-individual variations might have potential effects on our results. However, the measurement variation would likely attenuate the associations toward null. Third, the analysis was restricted to Chinese. Further studies in other populations are warranted to validate our findings.

In conclusion, our results indicate that serum uric acid may be an independent predictor for the incidence of type 2 diabetes in middle-aged and elderly Chinese. Further research is needed to investigate the possible benefits of anti-hyperuricemic treatment for preventing type 2 diabetes and the associated complications.

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