Clinical Rheumatology (2020) 39:339–346
https://doi.org/10.1007/s10067-019-04790-0

ORIGINAL ARTICLE

Association between cumulative serum urate and development of diabetes type II: the Kailuan Study

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Received: 8 August 2019 / Revised: 8 September 2019 / Accepted: 21 September 2019 / Published online: 29 October 2019

Abstract

Objective To explore whether cumulative serum urate (cumSU) is correlated with diabetes type II mellitus incidence.

Methods In this study, we recruited individuals participating in all Kailuan health examinations from 2006 to 2013 without stroke, cancer, gestation, myocardial infarction, and diabetes type II diagnosis in the first three examinations. CumSU was calculated by multiplying the average serum urate concentration and the time between the two examinations (umol/L × year). CumSU levels were categorized into five groups: Q_1–Q_5. The effect of cumSU on diabetes type II incidence was estimated by logistic regression.

Results A total of 36,277 individuals (27,077 men and 9200 women) participated in the final analysis. The multivariate logistic regression model showed the odds ratios (95% confidence intervals) of diabetes type II from Q_1 to Q_5 were 1.00 (reference), 1.25 (1.00 to 1.56), 1.43 (1.15 to 1.79), 1.49 (1.18 to 1.87), and 1.80 (1.40 to 2.32), respectively. Multivariable odds ratios per 1-standard deviation increase in cumSU were 1.26 (1.17 to 1.37) in all populations, 1.20 (1.10 to 1.32) for men, and 1.52 (1.27 to 1.81) for women, respectively.

Conclusions CumSU is a significant risk factor for diabetes type II. Individuals with higher cumSU, especially women, are at a higher risk of diabetes type II independent of other known risk factors.

Key Points
- *Cumulative exposure to serum urate is a significant risk factor for diabetes type II.*
- *Individuals with higher cumSU, especially women, are at a higher risk of diabetes type II.*

Keywords Cumulative serum urate · Diabetes type II · Risk factors

Serum urate (SU), an end product of purine metabolism [1], correlates with many recognized cardiovascular risk factors [2] including age, male sex, hypertension, hypertriglyceridemia, obesity, insulin resistance, and metabolic syndrome [3–5]. However, the association between cumulative serum urate (cumSU) levels and diabetes type II mellitus is unclear. While some studies report a positive association between high SU levels and diabetes type II [5–9], others report either no association [10] or an inverse relationship [11]. Moreover, most studies examining the association between baseline SU and diabetes type II incidence have not investigated how cumSU affects blood sugar levels or diabetes type II incidence. We hypothesized that higher levels of cumSU are associated with greater incidence of diabetes type II mellitus.

We conducted this study in a large sample of Chinese adults to investigate the relationship between cumSU and diabetes type II mellitus incidence after adjusting for major confounders.

Yixuan Han and Yanying Liu contributed equally to this work.

Electronic supplementary material The online version of this article (https://doi.org/10.1007/s10067-019-04790-0) contains supplementary material, which is available to authorized users.

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Methods

Study design and population

The Kailuan Study [12] is a prospective cohort study conducted in the Kailuan community in Tangshan City, China. From June 2006 to October 2007, a total of 101,510 participants (81,110 men and 20,400 women) aged 18–98 years were recruited to participate in the Kailuan Study. They were subsequently followed-up in three subsequent visits in 2008–2009, 2010–2011, and 2012–2013. The current analysis is based on a subgroup of 36,277 individuals (27,077 men and 9200 women) with complete follow-up data available and without diabetes type II mellitus prior to their last visit (Fig. 1). Subjects diagnosed with myocardial infarction, stroke, cancer, or pregnancy during the visits were excluded.

Assessment of health metrics

Information on age, sex, disease history, medication (including insulin, oral hypoglycemic agents, diuretics, and antihypertensive drug use), physical activity, smoking, alcohol intake, and education was collected via questionnaires at baseline and each of the three follow-up visits. Height, weight, and blood pressure were examined by trained physician staff. All measurements were performed using standardized protocols described previously [12]. Blood samples were collected from the antecubital vein after overnight fasting. Fasting blood glucose was measured using the hexokinase/glucose-6-phosphate-dehydrogenase method. Total cholesterol and triglycerides were assessed enzymatically. High-density lipoprotein cholesterol and low-density lipoprotein cholesterol levels were determined using a direct test method (inter-assay coefficient of variation < 10%; Mind Bioengineering Co. Ltd.,

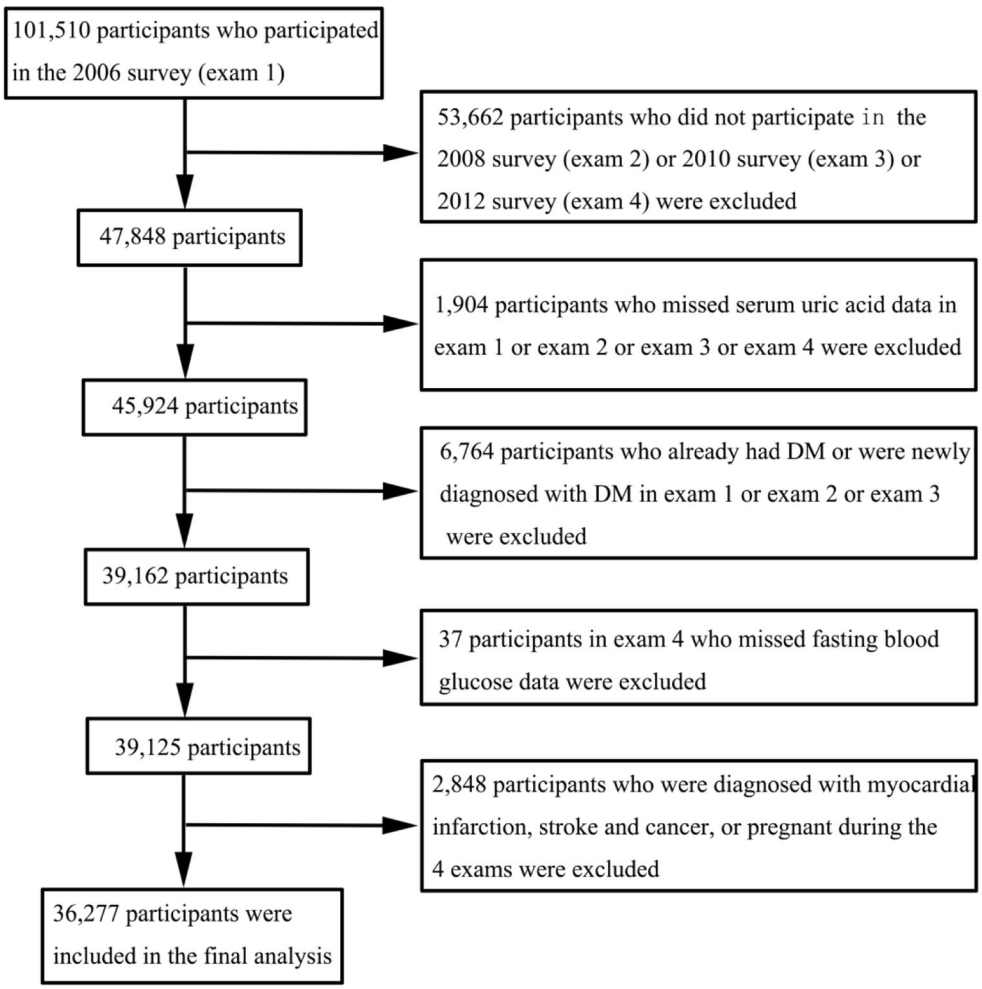

Fig. 1 Flow Chart Describing the Selection and Subsequent Loss of Participants: Selection of Kailuan Study Participants. The Kailuan Study: A prospective cohort study conducted in the Kailuan community in Tangshan City, China. The Time of the study: From June 2006 to October 2007. Study Population: 101,510 participants. They were subsequently followed-up in three subsequent visits in 2008–2009, 2010–2011, and 2012–2013. The current analysis is based on a subgroup of 36,277 individuals with complete follow-up data available and without diabetes mellitus prior to their last visit.

Shanghai, China). SU concentrations were determined using oxidase method. All biochemical variables were assessed at the central laboratory of Kailuan General Hospital with using a Hitachi autoanalyzer (Hitachi 747; Hitachi, Tokyo, Japan).

Diabetes type II is diagnosed as fasting glucose ≥ 7 mmol/L, or fasting glucose ≤ 7 mmol/L with the use of insulin or oral hypoglycemic agents. Systolic and diastolic blood pressures were averaged across 2 measurements. Hypertension was defined as a mean systolic blood pressure ≥ 140 mmHg and/or a mean diastolic blood pressure ≥ 90 mmHg, or a mean systolic blood pressure < 140 mmHg and/or a mean diastolic blood pressure < 90 mmHg after treatment. Estimated glomerular filtration rate (mL/min/1.73 m^2) was calculated by CKD-EPI. Body mass index was calculated as body weight (kg) divided by the square of body height (m^2). Smoking was defined as consumption of 1 cigarette every day for at least 1 year. Drinking was defined as consuming on average 100-mL wine (or alcohol content over 50%) per day for more than 1 year. Physical activity was defined as performing at least 30-min exercise more than 3 times a week. Education was defined as high school education level or above. Positive family history of diabetes type II means first-degree relative has been diagnosed with diabetes type II.

Cumulative serum urate

CumSU was defined as the summation of average SU for each pair of consecutive examinations multiplied by the time between these two consecutive visits in years:

$[((SU_1 + SU_2)/2) \times time_{1-2}] + [((SU_2 + SU_3)/2) \times time_{2-3}] + [((SU_3 + SU_4)/2) \times time_{3-4}]$, where SU_1, SU_2, SU_3, and SU_4 indicate SU at examinations 1 (baseline), 2, 3, and 4, respectively [13–16]. $Time_{1-2}$, $time_{2-3}$, and $time_{3-4}$ indicate the participant-specific time interval between consecutive examinations 1–4 in years. For men, CumSU was categorized in μmol/L × year as < 1499 (Q_1 group), 1499–1739 (Q_2 group), 1739–1971 (Q_3 group), 1971–2261 (Q_4 group), and ≥ 2261 (Q_5 group). For women, cumSU was categorized as < 1259 (Q_1 group), 1259–1435 (Q_2 group), 1435–1602 (Q_3 group), 1602–1841 (Q_4 group), and ≥ 1841 (Q_5 group).

Statistical analyses

Statistical analyses were performed with SPSS 13.0. Continuous variables were described as mean (standard deviation, SD). Comparison among different groups was analyzed by one-way analysis of variance. Categorical variables were described as percentages and were compared using chi-square tests (χ^2 tests). Logistic regression model was used to estimate the risk of diabetes type II with cumSU metrics. Odds ratios (ORs) and 95% confidence intervals (CIs) were calculated. We fitted three multivariate models. Model 1 is a univariate logistic regression analysis without adjustment. Model 2 is adjusted by baseline age and sex from model 1. Model 3 is adjusted by education level, physical activity, smoking, alcohol consumption, family history of diabetes type II, baseline hypertension, diuretics usage, body mass index, fasting blood glucose, SU, total cholesterol, triglycerides, and estimated glomerular filtration rate. Logistic regression analysis was used to evaluate the effect of one SD increase of cumSU on the new onset of diabetes type II. The significance level was set at $P < 0.05$.

Results

Data of population

Out of the 101,510 individuals participating in the baseline examination, 47,828 subjects underwent all 4 visits. The number of cases excluded due to diabetes type II diagnosis prior to the last visit was 6762. Moreover, 903, 1412, and 247 cases were excluded due to diagnosis of myocardial infarction, stroke, and cancer, respectively, during any visit. Two hundred eighty-six individuals were excluded due to pregnancy. We also excluded 1941 participants due to missing data of blood glucose and SU. The remaining 36,277 participants were included in the present study (Fig. 1). Among them, 9200 participants were women, and 27,077 cases were men. The mean age of the participants was 47.33 (11.48) years. For women, the average age was 46.88 (10.57) years. For men, the average age was 47.49 (11.77) years.

Baseline data among different groups

Q_1 group occupies 19.99% of all the subjects, whereas Q_2–Q_5 occupies 19.97%, 20.05%, 19.97%, and 20.02%, respectively. As compared with the baseline data obtained in 2006, there were significant differences in sex, age, hypertension, diuretics use, body mass index, fasting blood glucose, SU, total cholesterol, triglycerides, estimated glomerular filtration rate, family history of diabetes type II, smoking, alcohol intake, physical activity, and education among the 5 groups (Table 1, $P < 0.05$).

Incidence of new-onset diabetes type II among different groups

The incidence of new-onset diabetes type II in the last visit was 3.34%, with 1212 cases diagnosed during the last visit. In Q_1, Q_2, Q_3, Q_4, and Q_5, 166, 206, 239, 258, and 343 cases were diagnosed, respectively. The incidence of new-onset diabetes type II was 2.29%, 2.84%, 3.29%, 3.56%, and 4.72%, in Q_1–Q_5 groups, respectively. In the incidence of new-onset diabetes type II, men scored higher than women in the Q_1, Q_2,

Table 1 Baseline characteristics of the random subcohort by quintiles of the cumulative exposure of serum uric acid

	Q_1 ($n_1 = 7251$)	Q_2 ($n_2 = 7244$)	Q_3 ($n_3 = 7274$)	Q_4 ($n_4 = 7246$)	Q_5 ($n_5 = 7262$)	Overall ($n = 36,277$)	P
Male sex, *n* (%)	5412 (74.64)	5410 (74.68)	5425 (74.58)	5411 (74.68)	5419 (74.62)	27,077 (74.64)	1.000
Age (years)	44.87 ± 10.43	46.72 ± 10.89[a]	47.31 ± 11.21[ab]	48.24 ± 11.78[abc]	49.52 ± 12.46[abcd]	47.33 ± 11.48	< 0.001
Hypertension, *n* (%)	2662 (36.71)	2354 (32.50)	2384 (32.77)	2535 (34.98)	3021 (41.60)	12,956 (35.71)	< 0.001
Diuretics use, *n* (%)	13 (0.18)	17 (0.23)	39 (0.54)	80 (1.10)	134 (1.85)	263 (0.72)	< 0.001
BMI (kg/m^2)	24.25 ± 3.38	24.26 ± 3.26	24.65 ± 3.37[ab]	25.11 ± 3.30[abc]	25.99 ± 3.45[abcd]	24.85 ± 3.41	< 0.001
SU (umol/L)	218.44 ± 55.20	248.66 ± 58.35[a]	275.75 ± 58.11[ab]	306.31 ± 60.93[abc]	368.38 ± 80.23[abcd]	283.53 ± 81.50	< 0.001
FBG (mmol/L)	5.00 ± 0.67	5.05 ± 0.66[a]	5.01 ± 0.65[b]	4.99 ± 0.64[bc]	5.00 ± 0.64[b]	5.01 ± 0.65	< 0.001
TC (mmol/L)	4.55 ± 1.29	4.81 ± 1.12[a]	4.93 ± 1.01[ab]	4.99 ± 1.00[abc]	5.11 ± 1.07[abcd]	4.88 ± 1.12	< 0.001
TG (mmol/L)	1.52 ± 1.22	1.46 ± 1.16[a]	1.47 ± 1.16[a]	1.61 ± 1.31[abc]	1.91 ± 1.46[abcd]	1.59 ± 1.28	< 0.001
eGFR (mL/min per 1.73 m$^{2)}$	84.29 ± 29.11	87.61 ± 25.84[a]	86.95 ± 23.40[a]	84.85 ± 20.83[bc]	81.62 ± 22.42[abcd]	85.06 ± 24.58	< 0.001
Education, *n* (%)	1249 (17.22)	1609 (21.21)	1843 (25.34)	1977 (27.28)	2290 (31.53)	8968 (24.72)	< 0.001
Smoking, *n* (%)	1600 (22.07)	2219 (20.07)	2305 (31.69)	2304 (31.80)	2377 (32.73)	10,805 (29.78)	< 0.001
Drinking, *n* (%)	827 (11.41)	1136 (15.68)	1270 (17.46)	1360 (18.77)	1507 (20.75)	6100 (16.82)	< 0.001
DM-Fam, *n* (%)	260 (3.59)	356 (4.91)	384 (5.28)	364 (5.02)	425 (5.85)	1789 (4.93)	< 0.001
Physical, *n* (%)	578 (7.97)	754 (10.41)	958 (13.17)	1129 (15.58)	1260 (17.35)	4679 (12.90)	< 0.001

BMI, body mass index; *SU*, serum urate; *FBG*, fasting blood glucose; *TC*, total cholesterol; *TG*, triacylglycerol; *eGFR*, estimated glomerular filtration rate; *DM-Fam*, family history of diabetes. Q_1 quintile1, Q_2 quintile2, Q_3 quintile3, Q_4 quintile4, Q_5 quintile5. Compared with the first quintile group, [a] $P < 0.05$; Compared with the second quintile group, [b] $P < 0.05$; Compared with the third quintile group, [c] $P < 0.05$; Compared with the fourth quintile group, [d] $P < 0.05$

and Q_3 groups, while no differences between men and women in Q_4 and Q_5 groups were observed (Fig. 2).

Risk factor analysis to diabetes type II

As compared with Q_1 group, the odds ratio of new-onset diabetes type II incidence was 1.25, 1.45, 1.58, and 2.12 in Q_2, Q_3, Q_4, and Q_5 groups, respectively. After complete adjustment (model 3), OR in Q_2–Q_4 was slightly increased while OR in Q_5 group decreased from 2.12 to 1.80. The trend was more obvious for women than men. Multivariate adjusted ORs for the incidence of diabetes type II corresponding to a 1-S.D. increase in cumSU were 1.20 in men and 1.52 in women. We found a similar trend across age groups (Table 2).

Sensitivity analysis

To exclude the influence of hypertension and antihypertensive therapy on the association between cumSU and incidence of diabetes type II, a sensitivity analysis was performed after excluding 15,945 patients with hypertension. We found the association between cumSU and incidence of diabetes type II was unaffected (Table 3).

Discussion

Recently, hyperuricemia has been proposed as a novel risk factor for diabetes type II, but the results from epidemiologic studies have been mixed [5–11, 17–19] (Suppl. 1). From 2

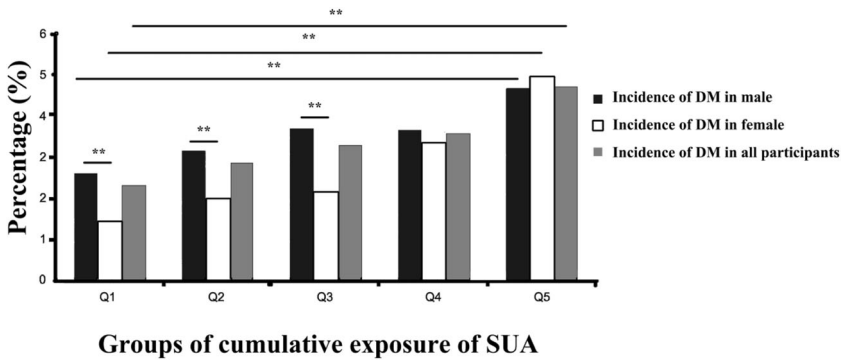

Fig. 2 Incidence of new-onset diabetes among different groups. SU, serum urate; DM, diabetes mellitus. $^{**}P < 0.05$

Table 2 Odds ratios and 95% confidence intervals of diabetes according to the time-weighted cumulative exposure of serum urate

	Group of cumulative exposure of serum uric acid								
	Q_1	Q_2	Q_3	Q_4	Q_5	SUA[#]	One SD increase	SUA*	*P*
Case number, *n* (%)	166 (2.29)	206 (2.84)	239 (3.29)	258 (3.56)	343 (4.72)				
Model 1*	1.00	1.25 (1.02, 1.54)[a]	1.45 (1.19, 1.77)[c]	1.58 (1.29, 1.92)[c]	2.12 (1.75, 2.55)[c]		1.29 (1.23, 1.36)		< 0.001
Model 2[†]	1.00	1.19 (0.97, 1.47)	1.36 (1.12, 1.67)[b]	1.45 (1.19, 1.77)[c]	1.89 (1.56, 2.28)[c]		1.25 (1.19, 1.32)		< 0.001
Model 3[‡]	1.00	1.25 (1.00, 1.56)[a]	1.43 (1.15, 1.79)[b]	1.49 (1.18, 1.87)[b]	1.80 (1.40, 2.32)[c]	1.00 (1.00, 1.00)	1.26 (1.17, 1.37)	1.00 (1.00, 1.00)[a]	< 0.001
Sex									
Women	26 (1.41)	36 (1.96)	39 (2.11)	61 (3.32)	91 (4.94)				
Model 1*	1.0	1.40 (0.84, 2.32)	1.50 (0.91, 2.48)	2.40 (1.51, 3.81)[c]	3.62 (2.33, 6.63)[c]		1.55 (1.40, 1.72)		< 0.001
Model 2[†]	1.0	1.33 (0.80, 2.21)	1.38 (0.83, 2.27)	2.04 (1.28, 3.26)[b]	2.60 (1.65, 4.09)[c]		1.38 (1.23, 1.54)		< 0.001
Model 3[‡]	1.0	1.19 (0.69, 2.06)	1.21 (0.70, 2.08)	1.89 (1.11, 3.20)[a]	2.40 (1.35, 4.27)[b]	1.00 (1.00, 1.00)	1.52 (1.27, 1.81)	1.00 (0.99, 1.00)[a]	< 0.001
Men	140 (2.59)	170 (3.14)	200 (3.69)	197 (3.64)	252 (4.65)				
Model 1*	1.00	1.22 (0.97, 1.53)	1.44 (1.16, 1.80)[b]	1.42 (1.14, 1.77)[b]	1.84 (1.49, 2.27)[c]		1.23 (1.16, 1.30)		< 0.001
Model 2[†]		1.17 (0.93, 1.47)	1.37 (1.10, 1.70)[b]	1.33 (1.07, 1.66)[a]	1.70 (1.38, 2.10)[c]		1.20 (1.13, 1.28)		< 0.001
Model 3[‡]		1.27 (1.00, 1.61)	1.48 (1.16, 1.89)[b]	1.39 (1.08, 1.80)[a]	1.64 (1.24, 2.19)[b]	1.00 (1.00, 1.00)	1.20 (1.10, 1.32)	1.00 (1.00, 1.00)	< 0.001
Age, year									
< 40	22 (0.99)	20 (1.11)	29 (1.59)	37 (2.12)	39 (2.50)				
Model 3[‡]	1.00	1.13 (0.60, 2.15)	1.61 (0.87, 2.99)	2.00 (1.08, 3.66)[a]	1.80 (0.90, 3.66)	1.00 (1.00, 1.00)	1.35 (1.09, 1.67)	1.00 (1.00, 1.00)	0.007
40 to 60	126 (2.81)	159 (3.42)	162 (3.53)	176 (3.96)	229 (5.26)				
Model 3[‡]	1.00	1.23 (0.96, 1.58)	1.29 (1.00, 1.67)	1.44 (1.11, 1.88)[b]	1.73 (1.29, 2.33)[c]	1.00 (1.00, 1.00)	1.28 (1.29, 2.33)	1.00 (1.00, 1.00)[a]	< 0.001
≥ 60	18 (3.22)	27 (3.42)	48 (5.55)	45 (4.28)	75 (5.56)				
Model 3[‡]	1.00	1.18 (0.64, 2.21)	1.87 (1.04, 3.36)[a]	1.55 (0.84, 2.85)	2.02 (1.03, 3.95)[a]	1.00 (1.00, 1.00)	1.12 (0.91, 1.36)	1.00 (1.00, 1.00)	0.283

cumSU, cumulative exposure of serum uric acid; *SD*, standard deviation; *SU*, serum urate. Q_1 quintile1, Q_2 quintile2, Q_3 quintile3, Q_4 quintile4, Q_5 quintile5

Model 1*: univariate logistic regression analysis without adjustment

Model 2[†]: adjusted for as model 1* plus age (years), sex

Model 3[‡]: adjusted for as model 2[†] plus education level, physical activity, smoking, drinking, family history of diabetes, hypertension, diuretics use, body mass index, serum uric acid, fasting blood glucose, total cholesterol, triacylglycerol, estimated glomerular filtration rate

[a] $P < 0.05$, [b] $P < 0.01$, [c] $P < 0.001$

SUA[#]: baseline uric acid when categorical logistic regression analysis is used

*SUA**: baseline uric acid when continuous variable logistic regression analysis is used

Table 3 Odds ratios and 95% confidence intervals of DM according to the time-weighted cumulative exposure of serum urate in non-hypertension population

	Group of cumulative exposure of serum urate								
	Q_1	Q_2	Q_3	Q_4	Q_5	SU[#]	One SD increase	SU*	*P*
Case number, *n* (%)	65 (1.60)	72 (1.77)	91 (2.24)	99 (2.42)	115 (2.83)				
Model 1*	1.00	1.11 (0.79, 1.55)	1.41 (1.02, 1.95)[a]	1.53 (1.11, 2.10)[b]	1.79 (1.32, 2.43)[c]		1.21 (1.11, 1.32)		< 0.001
Model 2[†]	1.00	1.06 (0.75, 1.48)	1.31 (0.95, 1.81)	1.40 (1.02, 1.92)[a]	1.61 (1.18, 2.20)[b]		1.19 (1.09, 1.30)		< 0.001
Model 3[‡]	1.00	1.11 (0.79, 1.58)	1.41 (1.00, 1.98)	1.54 (1.08, 2.19)[a]	1.74 (1.17, 2.58)[b]	1.00 (1.00, 1.00)	1.25 (1.11, 1.42)	1.00 (1.00, 1.00)	< 0.001
Sex									
Women	9 (0.76)	19 (1.63)	17 (1.44)	25 (2.13)	30 (2.58)				
Model 1*	1.00	2.14 (0.97, 4.75)	1.90 (0.84, 4.28)	2.81 (1.31, 6.05)[b]	3.40 (1.61, 7.19)[b]		1.34 (1.13, 1.60)[b]		0.001
Model 2[†]	1.00	2.03 (0.91, 4.51)	1.69 (0.75, 3.82)	2.41 (1.12, 5.20)[a]	2.35 (1.10, 5.05)[a]		1.16 (0.97, 1.38)		0.105
Model 3[‡]	1.00	1.92 (0.85, 4.35)	1.59 (0.68, 3.71)	2.41 (1.05, 5.53)[a]	2.82 (1.14, 6.93)[a]	1.00 (0.99, 1.00)[a]	1.35 (1.04, 1.75)[a]	1.00 (0.99, 1.00)[a]	0.026
Men	56 (1.95)	53 (1.84)	74 (2.59)	74 (2.56)	85 (2.96)				
Model 1*	1.00	0.94 (0.64, 1.37)	1.34 (0.94, 1.89)	1.32 (0.93, 1.87)	1.53 (1.09, 2.15)[a]		1.20 (1.08, 1.33)[c]		< 0.001
Model 2[†]	1.00	0.90 (0.62, 1.32)	1.26 (0.88, 1.79)	1.23 (0.87, 1.75)	1.44 (1.02, 2.03)[a]		1.18 (1.06, 1.31)[b]		0.002
Model 3[‡]	1.00	0.98 (0.66, 1.45)	1.38 (0.94, 2.02)	1.35 (0.91, 2.02)	1.48 (0.95, 2.31)	1.00 (1.00, 1.00)[a]	1.21 (1.05, 1.40)[b]	1.00 (1.00, 1.00)	0.009

cumSU, cumulative exposure of serum urate; *SD*, standard deviation; *SU*, serum urate

Q_1 quintile1, Q_2 quintile2, Q_3 quintile3, Q_4 quintile4, Q_5 quintile5

Model 1*, univariate logistic regression analysis without adjustment; Model 2[†], adjusted for as model 1* plus age (years), sex; Model 3[‡], adjusted for as model 2[†] plus education level, physical activity, smoking, drinking, family history of diabetes, hypertension, diuretics use, body mass index, serum uric acid, fasting blood glucose, total cholesterol, triacylglycerol, estimated glomerular filtration rate; SU*, baseline uric acid when continuous variable logistic regression analysis is used; SUA[#], baseline uric acid when categorical logistic regression analysis is used

[a] $P < 0.05$, [b] $P < 0.01$, [c] $P < 0.001$

generations of the Framingham Heart Study, Bhole et al. found that individuals with higher SU are at a higher future risk of diabetes type II independent of other known risk factors [6]. The results were consistent with subgroup analysis by sex and hypertension status. In contrast, it was found that higher SU levels were inversely associated with diabetes type II in a representative sample of adults [11].

Among all these studies, only a single-time SU was measured. This may not adequately reflect its longitudinal variation and cumulative burden. Therefore, to our knowledge, there is little information regarding how cumSU affects diabetes type II incidence. Summary measures of SU that capture both the duration and intensity could more accurately estimate the effects of these risk factors over several decades. As a result, we used cumSU to evaluate the association between SU and diabetes type II.

In our study, a higher cumSU grading significantly increased the risk of diabetes type II incidence. The result was consistent with subgroup analysis by sex and age. After total adjustment, the risk of diabetes type II increased with cumSU. The same trend was also found in a non-hypertension population, suggesting cumSU is an independent risk factor to diabetes type II. However, there was no correlation between baseline SU and new-onset diabetes type II. This means cumSU has higher prognostic ability than baseline UA.

We also found that elevation of one SD of cumSU was associated with increased risk of diabetes type II. Similarly, Juraschek et al. found that with each 1 mg/dL increase in SU, the hazard ratio of diabetes type II also increased [8]. Moreover, the association between SU and diabetes type II was stronger in women [20], which is consistent with our study. However, another study found multivariate adjusted HRs for the incidence of diabetes type II corresponding to a one SD increase in SU was more significantly increased in men than in women [21]. The reason needs to be further investigated.

The underlying role of SU in the deterioration of glucose metabolism is not clear. A possible explanation is that high SU levels regulate oxidative stress, inflammation, and enzymes associated with glucose and lipid metabolism primarily in the liver, adipose tissue, and skeletal muscle [22]. Through positive feedback, adipose tissue could produce and secrete additional SU through xanthine oxidoreductase [23]. Through altering glucose metabolism, hyperuricemia would decrease insulin sensitivity and lead to insulin resistance [5, 24]. In support of this, studies have shown that SU may be a true mediator of renal disease and progression, which correspondingly causes diabetes type II [25].

Our study has several major strengths. We first report the association of cumSU with diabetes type II. CumSU, in addition to single baseline SU, increases reliability due to sampling of additional time points. This parameter had never been correlated with disease outcome until now. Additionally, large sample size and a constant number of participants were other distinct advantages in this study.

Our investigation has several limitations. First, all participants came from the city of Tangshan and were employees or retirees of the Kailuan Group Company. This study population was not representative of the total Chinese population. Therefore, Chinese individuals with a different lifestyle or different mean education level were not adequately represented. Second, our study shows cumSU is more correlated with diabetes type II in women than in men, the association between cumSU and diabetes type II in the whole population may be underestimated due to the disproportionate ratio of women to men. Lastly, specific confounding variables like diet and antihyperuricemia medication were not analyzed.

In conclusion, higher cumSU increases the risk of diabetes type II. This association was stronger than that of single SU and the risk of diabetes type II. Therefore, when assessing the risk of diabetes type II, the role of cumSU should be taken into consideration, especially in women.

Acknowledgments We are grateful to the participants that were recruited in this study for their essential contribution.

Contributors YH, YL, XL, WY, YW, and PY participated in the study design, drafting of the manuscript, data collection, and statistical analysis. JW, YH, RS, HS, JW, WY, BL, NL, HS, WY, LL, and YH participated in data collection and statistical analysis. LC designed the study and gave final approval for the manuscript.

Compliance with ethical standards The study was approved by the Ethics Committees of Kailuan General Hospital following the guidelines outlined by the Helsinki Declaration. All subjects agreed to participate in this study and provided written informed consent.

Disclosures None.

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