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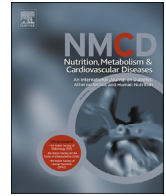
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Distinct hyperuricemia trajectories are associated with different risks of incident diabetes: A prospective cohort study

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Abstract *Background and aim:* Conflicting results suggest a link between serum uric acid and diabetes and previous studies ignored the effect of continuous exposure of serum uric acid on diabetes risk. This study aims to characterize hyperuricemia trajectories in middle-aged adults and to examine its potential impact on diabetes risk, considering the role of obesity, dyslipidemia, and hypertension.
Methods and results: The cohort included 9192 participants who were free of diabetes before 2013. The hyperuricemia trajectories during 2009—2013 were identified by latent class growth models. Incident diabetes during 2014—2018 was used as the outcome. Modified Poisson regression models were used to assess the association of trajectories with diabetes. Furthermore, marginal structural models were used to estimate the mediating effects of the relationship between hyperuricemia trajectories and diabetes. We identified three discrete hyperuricemia trajectories: high-increasing (n = 5794), moderate-stable (n = 2049), and low-stable (n = 1349). During 5 years of follow-up, we documented 379 incident diabetes cases. Compared with the low-stable pattern, the high-increasing pattern had a higher risk of developing diabetes (RR, 1.42; 95% CI: 1.09—1.84). In addition, the percentages of total effect between the high-increasing hyperuricemia pattern and diabetes mediated by obesity, dyslipidemia, and hypertension were 24.41%, 18.26%, and 6.29%. However, the moderate-stable pattern was not associated with an increased risk of diabetes.
Conclusions: These results indicate that the high-increasing hyperuricemia trajectory is significantly associated with an increased risk of diabetes. Furthermore, obesity, dyslipidemia, and hypertension play mediating roles in the relationship between the high-increasing hyperuricemia pattern and increased diabetes risk.

1. Introduction

Diabetes increases the risk of cardiovascular diseases, burden of death, and costs [1–4]. The early detection of modifiable risk factors that prevent diabetes is top public health priorities. Previously, numerous studies have shown that uric acid is a risk factor for diabetes, whereas controversial results also exist [5–12]. Given the global burden of hyperuricemia, understanding the effect of hyperuricemia on diabetes is of critical importance [13].

It is worth noting that most previous studies focused on serum uric acid (SUA) in a single or limited number of measurements, ignoring the potential effect of continuous exposure of SUA on diabetes risk. Recent studies reported an increased risk of incident diabetes with short-term (2-year) SUA gain [14,15]. SUA levels are relatively unstable due to its biorhythm, diet, and exercise [16]. Thus the trajectories of hyperuricemia over time may reflect long-term exposure that is more relevant to diabetes risk. Nevertheless, the effect of long-term hyperuricemia changing patterns on diabetes incidence has not been well described so far.

In addition, the strong association between uric acid and body mass index (BMI) has been documented before [17,18]. Several studies also reported that SUA−diabetes association was largely weakened by BMI [19,20]. Furthermore, a cohort study demonstrated the temporal relationship between hyperuricemia and obesity, and its association with increased risk of type 2 diabetes [21]. More recently, clinical and epidemiological studies also suggested that SUA was associated with the development of dyslipidemia and hypertension [22−25]. Relying on the studies above, we hypothesized that metabolism factors including obesity, dyslipidemia, and hypertension might act as mediators in the causal pathway from SUA to diabetes. However, these hypotheses have not been well explored.

In the present study, we aimed to identify distinct hyperuricemia changing trajectories which show the possibility of hyperuricemia in the general population, access the association of hyperuricemia trajectories with incident diabetes, and determine the potential mediating factors in the relation between hyperuricemia trajectories and future risk of diabetes.

2. Methods

2.1. Study cohort

The Beijing Health Management Cohort (BHMC) study is a prospective dynamic cohort study designed to investigate the progression from health to metabolic disorders in individuals from urban areas of northeast China. A total of 14,402 participants were identified in the current study based on the number of measurements of SUA levels (at least 3 times) during the exposure period (from January 2009 to December 2013). Data for incident diabetes were collected during the follow-up period (from January 2014 to December 2018) (Fig. 1). We excluded 1701 participants with diabetes and 1093 participants with stroke, cancer, or cardiovascular disease in or prior to December 2013. We further excluded 2416 participants lost to follow-up by December 2018. Finally, the total number of participants who were eligible for the present study was 9192. The study protocol was approved by the Ethics Committee of Capital Medical University, and written informed consent was provided by all participants.

2.2. Assessment of SUA

Fasting blood samples were collected in the morning after 12 h overnight fast and transfused into vacuum tubes containing EDTA from 7:00 to 9:00 a.m. The SUA level was measured by enzymatic methods using a chemistry analyzer (Beckman LX 20, America). Information regarding the current treatment of elevated SUA was extracted from participants' internal medical summaries. Hyperuricemia was defined as SUA level greater than 7 mg/dL for males and SUA level greater than 6 mg/dL for females or treatment with the SUA-lowering agent. The hyperuricemia trajectories from 2009 to 2013 were the primary exposure of the current study. Furthermore, four indicators were used to access SUA variability from 2009 to 2013, including standard deviation (SD), coefficient of variation (CV), coefficient of variation independent of the mean (VIM) [26] and average successive variability (ASV) [27] (see Supplementary Information Part 1).

2.3. Assessment of covariates

Height and weight were measured in light clothes, without shoes, by trained research assistants. BMI was calculated as weight (kg) divided by height (m) squared. Three recordings of blood pressure after 5 min of rest in a sitting position with the use of an electronic sphygmomanometer were recorded in all participants. Blood pressures used for data analyses were calculated as the mean of the last two measurements. Blood samples were collected from participants after an overnight fast of at least 12 h and shipped to the central laboratory of the hospital. SUA, fasting plasma glucose (FPG), total cholesterol (TC), high-density lipoprotein cholesterol (HDLC), low-density lipoprotein cholesterol (LDLC), and triglycerides (TG) were measured
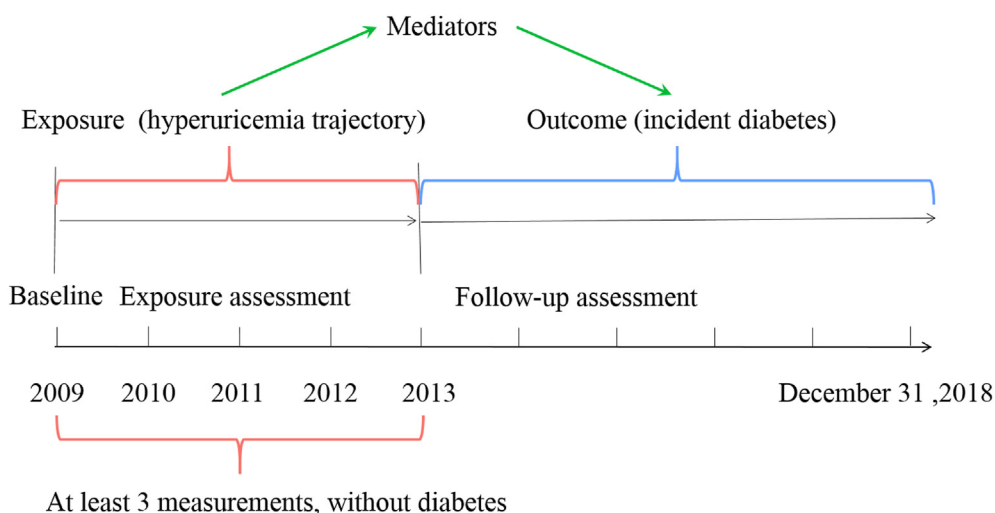
Figure 1 Schematic diagram of study design.

by enzymatic methods using a chemistry analyzer (Beckman LX 20, America). Estimated glomerular filtration rate (eGFR) was calculated by glomerular filtration rate estimating equation for Chinese [28].

Family history of diabetes and information regarding lifestyle factors, including educational level, physical activity, smoking status, and alcohol intake status were collected from each participant using a questionnaire as previously described [14]. Physical activity level was classified as low (<1 time per week), moderate (1−2 times per week), or high (≥3 times per week, each time lasting more than 30 min). Participants were defined as smokers if they reported having smoked ≥100 cigarettes in their lifetime [29]. Participants were defined as drinkers if they reported having consumed alcohol ≥12 times in the preceding year [30].

2.4. Mediator and outcome

Mediators included obesity, hypertension, and dyslipidemia. Obesity was defined as having a mean BMI during the exposure period higher than 28 kg/m^2 based on Asian criteria [31]. Hypertension was defined as systolic blood pressure (SBP) ≥140 mmHg or diastolic blood pressure (DBP) ≥90 mmHg or use of any antihypertensive medication or self-reported history of hypertension according to the JNC-7 criteria [32]. The diagnostic criteria for dyslipidemia were mean TC ≥ 6.2 mmol/L, TG ≥ 2.3 mmol/L, LDLC ≥ 4.1 mmol/L, or HDLC < 1.0 mmol/L during the exposure period [33].

The outcome was incident diabetes during follow-up period in this study. The diagnosis of diabetes referred to the American Diabetes Association, including fasting glucose ≥7.0 mmol/L, HbA1c ≥ 6.5%, or the use of any antidiabetic medication or self-reported diagnosis history of diabetes [34]. In the absence of unequivocal hyperglycemia, diagnosis requires two abnormal test results from the same sample or in two separate samples. The glucose hexokinase method was used to measure fasting blood samples.

2.5. Statistical methods

Latent class growth models (LCGM) were used to ascertain hyperuricemia trajectory groups using the SAS PROC TRAJ with a LOGIT model [35]. We investigated multiple LCGMs with different trajectory shapes including linear and nonlinear parameters. According to the starting values calculated from the first group model, we changed group count from 2 to 5, then used repeated trajectory analysis to identify the latent classes. The following criteria determined the shapes and the optimal number of groups: (1) using the lowest Bayesian information criterion; (2) Including at least 2% of the participants in each group. In our study, the optimal fitting model was cubic trajectories of 3 groups. Kruskal Wallis tests and Chi-square tests were applied to test the difference of baseline characteristics among different trajectory groups.

We applied modified Poisson regression analyses to assess the relative risk (RR) and 95% confidence interval (CI) of diabetes by the trajectory groups of hyperuricemia [36]: model 1 was adjusted for age and sex; model 2 was extra adjusted for BMI, educational level, physical activity, smoking status, alcohol intake status, and family history of diabetes at baseline; model 3 was adjusted for the covariates in model 2 plus SBP, DBP, TC, TG, HDLC, LDLC, and eGFR at baseline.

Basing on a counterfactual framework, the mediation analysis using marginal structure model (MMSM) was developed to obtain unbiased estimates of the direct and indirect effects. Therefore, the MMSM was used to decompose the effect of hyperuricemia trajectories on an increased risk of diabetes into nature indirect effect mediated through mediator variables and the remaining nature direct effect in this study [37]. Once marginal structural models were fitted, a modified Poisson regression model was used to gain RR estimates of natural direct and indirect effects.

2.6. Sensitivity analysis

To test whether the potential association between hyperuricemia trajectories and diabetes risk was independent of hyperuricemia status at baseline or last visit, we further adjusted for hyperuricemia status in 2009 or 2013. To examine the effect of variability in SUA concentrations, we further adjusted the SUA variability. To explore whether the effects of hyperuricemia trajectories on diabetes risk were further explained by the change of BMI, we adjusted for the change of BMI during the exposure period in the models. To simulate the random assignment of different hyperuricemia trajectory groups, we performed 1:1 propensity score matching method without replacement according to Caliper Matching for this study [38]. Furthermore , we used the standardized mean differences to measure the differences of covariates between before and after matching, a value below 0.1 represented a meaningful balance (see Supplementary Information Part 2). To evaluate if the mediating effects of mediators in the association between hyperuricemia trajectories and diabetes were robust, we re-estimated the mediating effect by sequentially dropping one confounding variable at a time when computing the predicted values for the mediator in MMSM.

All statistical analyses were performed using SAS software version 9.4 (SAS Institute, Chicago, IL, USA) and R (version 4.0.0), and $P < 0.05$ was considered to represent statistical significance.

3. Results

According to the characteristics of their hyperuricemia status changes during this 5-year exposure period, we divided 9192 subjects into three different hyperuricemia trajectory groups, namely the "low-stable" trajectory, the "moderate-stable" trajectory and the "high-increasing" trajectory. As shown in Fig. 2, 56.1% of the participants were in a low-stable trajectory state, and they maintained a low SUA level throughout the exposure period without hyperuricemia. 28.4% of the participants were in a moderate-stable trajectory state, who maintained a medium probability of hyperuricemia. 15.5% of participants had a high-increasing trajectory, starting with a moderate probability of hyperuricemia and then a rapidly increasing probability of hyperuricemia during a 5-year exposure period. Compared with participants in the low-stable pattern, participants in the other groups were more likely to be men, drinkers, and smokers, had higher age, BMI, and concurrent cardiovascular risk factors (Table 1).

Table 2 showed the adjusted RRs of incident diabetes associated with hyperuricemia trajectories. After adjusting for potential confounders, we observed that participants in the high-increasing group had 1.42 times (95% CI: 1.09−1.84) greater risk of developing diabetes than those in the low-stable group. However, there was no significant increase in the risk of diabetes in the moderate-stable group (RR, 1.08; 95% CI: 0.84−1.38). On the basis of model 3 confounding factor adjustment, we adjusted the hyperuricemia status in 2009 and 2013, respectively, then discovered similar results. Meanwhile, adjustment for SD, CV, VIM, or ASV of uric acid levels during exposure respectively, showed that the association between the high-increasing group and diabetes risk remained significant. Further adjustment for the changes in BMI during exposure did not materially change the results.

There were significant differences in the propensity score distribution between the high-increasing group and
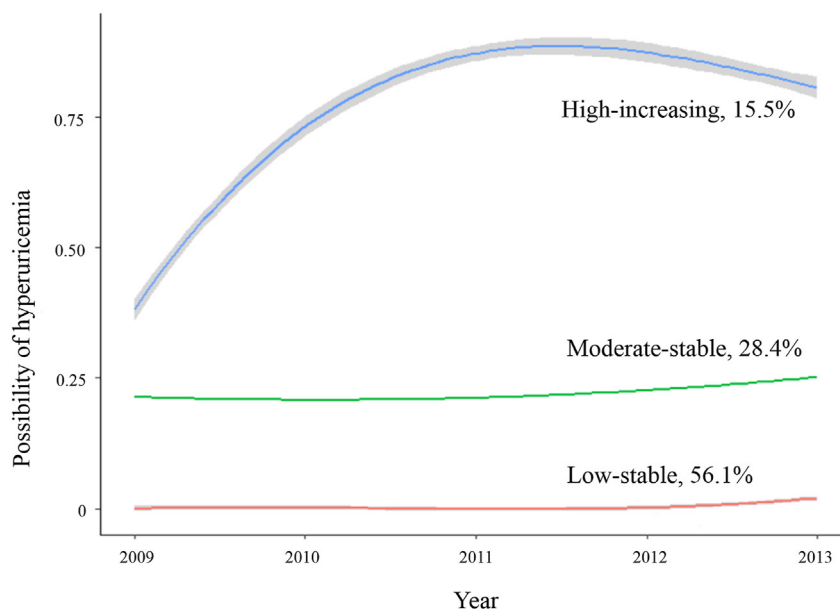

Figure 2   Trajectories of hyperuricemia status during the exposure period.

Table 1 Baseline characteristics of study participants, stratified according to hyperuricemia trajectories.

Baseline characteristic	Low-stable (n = 5794)	Moderate- stable (n = 2049)	High- increasing (n = 1349)	Overall (n = 9192)
Male (n, %)	3336 (57.58)	1645 (80.28)	1196 (88.66)	6177 (67.2)
Age (years)	47.6 ± 12.6	49.2 ± 14.1	49.5 ± 14.3	48.3 ± 13.3*
BMI (kg/m^2)	24.5 ± 3.2	26.1 ± 3.22	27.0 ± 3.19	25.2 ± 3.38*
SBP (mm Hg)	120 ± 15.9	126 ± 15.4	128 ± 14.7	123 ± 16.0*
DBP (mm Hg)	69.9 ± 10.3	73.6 ± 10.5	75.1 ± 10.8	71.5 ± 10.6*
TC (mmol/L)	4.71 ± 0.86	4.84 ± 0.93	4.87 ± 0.94	4.76 ± 0.89*
TG (mmol/L)	1.37 ± 1.03	1.86 ± 1.48	2.15 ± 1.65	1.59 ± 1.29*
HDLC (mmol/L)	1.36 ± 0.35	1.23 ± 0.32	1.16 ± 0.28	1.30 ± 0.34*
LDLC (mmol/L)	3.06 ± 0.79	3.20 ± 0.84	3.24 ± 0.82	3.12 ± 0.81*
eGFR (mL/min/1.73 m^2)	101.0 ± 20.5	94.9 ± 19.4	90.2 ± 19.2	97.8 ± 20.5*
SUA (mg/dL)	4.97 ± 1.00	6.53 ± 0.95	7.78 ± 1.11	5.73 ± 1.46*
High school or higher education (n, %)	5505 (95.01)	1951 (95.22)	1276 (94.59)	8732 (95)
Physical activity (n, %)				
Low	1589 (27.42)	590 (28.79)	410 (30.39)	2589 (28.17)
Moderate	3604 (62.20)	1248 (60.91)	779 (57.75)	5631 (61.26)
High	601 (10.37)	211 (10.30)	160 (11.86)	972 (10.57)
Smoking status (n, %)	559 (9.65)	225 (10.98)	186 (13.79)	970 (10.55)*
Drinking status (n, %)	1118 (19.30)	434 (21.18)	361 (26.76)	1913 (20.81)*
Family history of diabetes (%)	482 (8.32)	177 (8.64)	128 (9.49)	787 (8.56)

*P value for the difference of variables between the hyperuricemia trajectories<0.05.
Data were presented as mean (standard deviation) or number (%).
The abbreviations of the variables: BMI = body mass index; SBP = systolic blood pressure; DBP = diastolic blood pressure; TC = total cholesterol; TG = triglycerides; HDLC = high-density lipoprotein cholesterol; LDLC = low-density lipoprotein cholesterol; eGFR = estimated glomerular filtration rate; SUA = serum uric acid.

Table 2 Risk of diabetes, according to trajectories of hyperuricemia status.

Variable	Low-stable	Moderate-stable	High-increasing
Total	5794	2049	1349
Diabetes (n,%)	185 (3.19)	98 (4.78)	96 (7.12)
Model 1[a]	Reference	1.37 (1.07, 1.75)	1.99 (1.55, 2.56)
Model 2[b]	Reference	1.14 (0.89, 1.46)	1.50 (1.16, 1.95)
Model 3[c]	Reference	1.08 (0.84, 1.38)	1.42 (1.09, 1.84)
Sensitivity analysis			
Sensitivity analysis 1[d]	Reference	1.15 (0.87, 1.53)	1.61 (1.13, 2.29)
Sensitivity analysis 2[e]	Reference	1.18 (0.91, 1.53)	1.52 (1.16, 1.99)
Sensitivity analysis 3[f]	Reference	1.15 (0.89, 1.47)	1.43 (1.11, 1.86)
Sensitivity analysis 4[g]	Reference	1.12 (0.87, 1.45)	1.45 (1.11, 1.88)
Sensitivity analysis 5[h]	Reference	1.18 (0.92, 1.53)	1.52 (1.16, 1.99)
Sensitivity analysis 6[i]	Reference	1.14 (0.87, 1.50)	1.60 (1.07, 2.39)
Sensitivity analysis 7[j]	Reference	1.07 (0.83, 1.36)	1.40 (1.08, 1.82)

Data were relative risks (RRs) and 95% confidence intervals (CIs).
[a] Adjusted for age, sex at baseline.
[b] Adjusted for variables in model 1 as well as education level, smoking, alcohol consumption, physical activity, family history of diabetes and body mass index at baseline.
[c] Adjusted for variables in model 2 as well as systolic blood pressure, diastolic blood pressure, total cholesterol, triglycerides, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol and estimated glomerular filtration rate at baseline.
[d] Adjusted for variables in model 3 as well as hyperuricemia status in 2009.
[e] Adjusted for variables in model 3 as well as standard deviation of uric acid levels during the exposure period.
[f] Adjusted for variables in model 3 as well as coefficient of variation of uric acid levels during the exposure period.
[g] Adjusted for variables in model 3 as well as coefficient of variation independent of mean of uric acid levels during the exposure period.
[h] Adjusted for variables in model 3 as well as average successive variability of uric acid levels during the exposure period.
[i] Adjusted for variables in model 3 as well as hyperuricemia status in 2013.
[j] Adjusted for variables in model 3 as well as the change of body mass index during the exposure period.

the low-stable group. After matching, the propensity score distribution overlapped together without significant differences (Fig. 3). In the propensity score matching sample (1277 vs. 1277), the standardized mean differences in baseline characteristics between the two groups were smaller than 0.1, and the baseline characteristics of the two groups were comparable (see Supplementary Information Part 3 Fig. S1). In 2554 propensity score matching samples, participants in the high-increasing group had higher risk of developing diabetes compared with participants in the
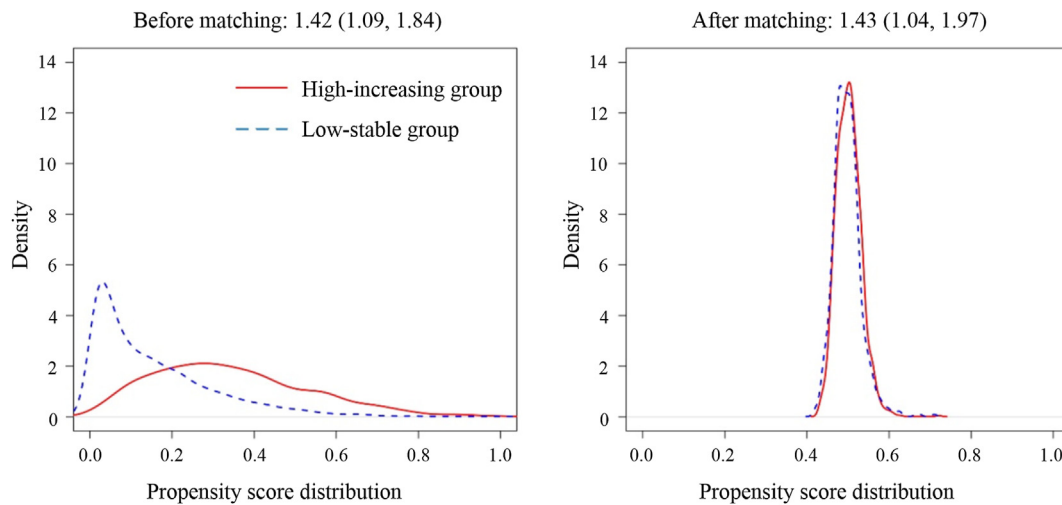
Figure 3 Propensity score distribution between high-increasing hyperuricemia group and low-stable hyperuricemia group.

low-stable group, and the corresponding RR was 1.43 (95% CI: 1.04, 1.97).

Table S1 (see Supplementary Information Part 3) showed that stratified by gender, participants in the high-increasing group had a higher risk of developing diabetes in females (RR, 2.53; 95% CI: 1.40−4.55) rather than in males (RR, 1.28; 95% CI: 0.96−1.70) comparing with those in the low-stability group (P for interaction: 0.02). In addition, participants in the high-increasing group had a higher risk of developing diabetes in the older group (RR, 1.52; 95% CI: 1.10−2.11).

To estimate the mediating effect, we first established a statistical model of obesity with diabetes and hyperuricemia trajectories using the marginal structure method. The prevalence of obesity was significantly higher among the high-increasing group (31.58%) than the low-stable group (10.37%). Under the comparison of the two groups, the obesity risk in the high-increasing group was 3.04 times higher than in the low-stable group. Furthermore, the result showed that obesity was also closely related to

diabetes. After adjustment for hyperuricemia trajectories and other potential confounders, participants in the obesity group experienced a higher risk of diabetes (RR, 1.97; 95% CI: 1.57−2.45).

In order to evaluate the mediating effect, the marginal structural models were used to evaluate the mediating effect of obesity among the relationship between hyperuricemia trajectories and diabetes (Table 3, Fig. 4). Among the high-increasing group, the 54% increased risk of diabetes could be decomposed into a direct natural RR of 1.42 (95% CI: 1.09−1.84), and an indirect obesity mediated RR of 1.12 (95% CI 1.08−1.16). Almost 24.41% of the total effect of high-increasing hyperuricemia pattern on the increased risk of diabetes was mediated by obesity.

In addition, the association between high-increasing hyperuricemia pattern and diabetes mediated by hypertension and dyslipidemia with an indirect RR of 1.02 (95% CI: 1.01, 1.04) and 1.09 (95% CI: 1.05, 1.12). The percentages of the total effect mediated by hypertension and dyslipidemia were estimated at 6.29% and 18.26% (Fig. 4).

Table 3 Direct, and indirect effect of trajectories of hyperuricemia on Diabetes.

Variable		Low-stable	Moderate-stable	High-increasing
Obesity[a]	Natural direct effect	Reference	1.08 (0.84, 1.38)	1.42 (1.09, 1.84)
	Natural indirect effect	Reference	1.07 (1.04, 1.09)	1.12 (1.08, 1.16)
Hypertension[b]	Natural direct effect	Reference	1.07 (0.84, 1.37)	1.43 (1.10, 1.85)
	Natural indirect effect	Reference	1.02 (1.01, 1.03)	1.02 (1.01, 1.04)
Dyslipidemia[c]	Natural direct effect	Reference	1.09 (0.85, 1.39)	1.45 (1.11, 1.89)
	Natural indirect effect	Reference	1.06 (1.03, 1.08)	1.09 (1.05, 1.12)

Data were relative risks (RRs) and 95% confidence intervals (CIs).

[a] Adjusted for age, sex, education level, smoking, alcohol consumption, physical activity, family history of diabetes, systolic blood pressure, diastolic blood pressure, total cholesterol, triglycerides, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol and estimated glomerular filtration rate at baseline.

[b] Adjusted for age, sex, education level, smoking, alcohol consumption, physical activity, family history of diabetes, body mass index, total cholesterol, triglycerides, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol and estimated glomerular filtration rate at baseline.

[c] Adjusted for age, sex, education level, smoking, alcohol consumption, physical activity, family history of diabetes, body mass index, systolic blood pressure, diastolic blood pressure and estimated glomerular filtration rate at baseline.
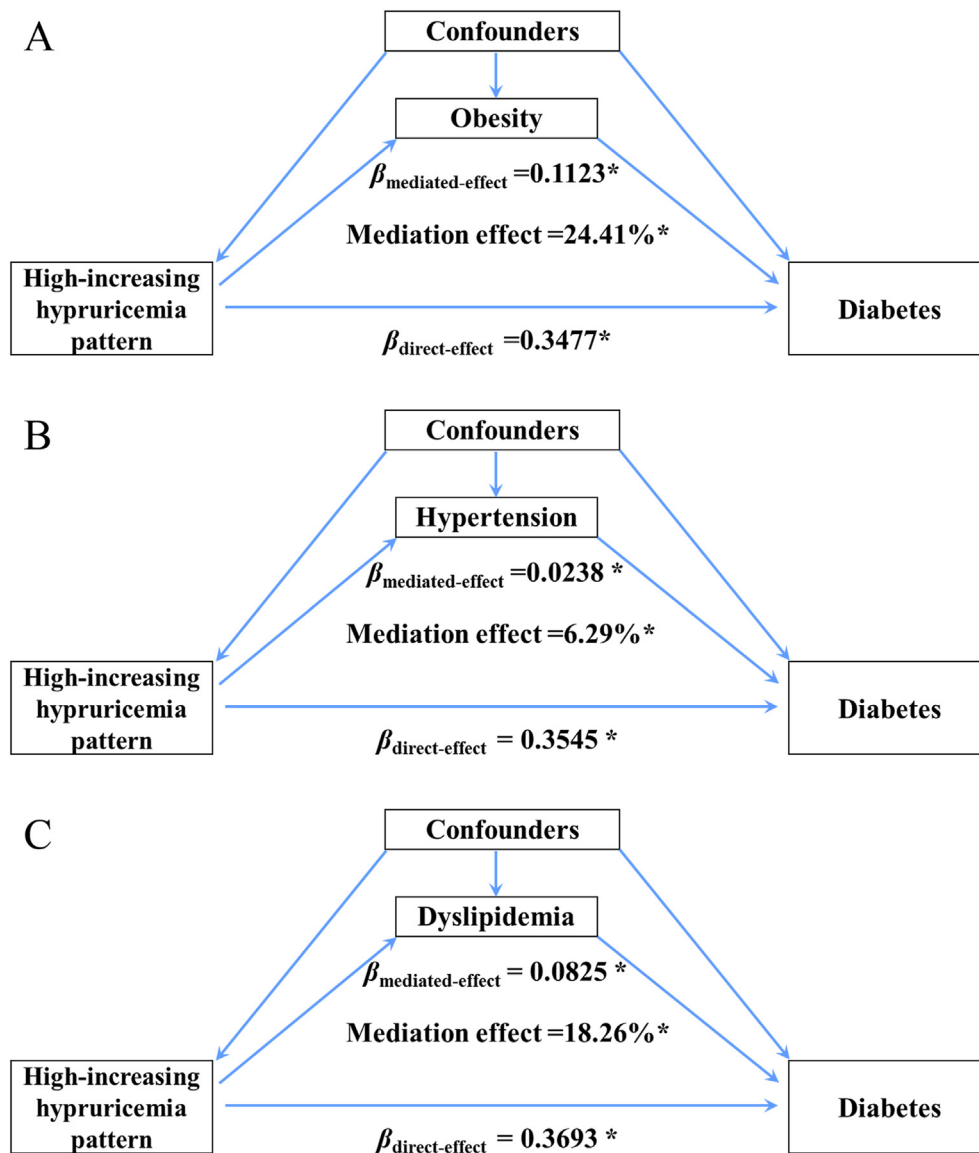
Figure 4 Direct, and indirect effects of hyperuricemia trajectory on diabetes mediated by obesity (A), hypertension (B), and dyslipidemia (C).

In the sensitivity analyses, we excluded one confounding variable sequentially at a time when computing the predicted values for the mediator in MMSM. We observed very little change in the mediating effect of mediators among the relationship between hyperuricemia trajectories and diabetes (see Supplementary Information Part 3 Table S2-S4).

4. Discussion

In this prospective study of 9192 adults, we identified 3 distinct hyperuricemia trajectories over a 5-year span. Participants in the hyperuricemia high-increasing pattern, as compared with those in the low-stable pattern, had a higher risk for diabetes during 5 years of follow-up. Furthermore, obesity, hypertension, and dyslipidemia partially mediated the association between high-increasing hyperuricemia trajectory and future risk of diabetes.

In recent decades, the prevalence of diabetes has increased substantially in the world. Diabetes affects about 463 million adults, a number expected to rise to 700 million by 2045 worldwide [39]. The Global Burden of Disease study estimated there were 1.02 million deaths worldwide from Type 2 diabetes in 2017, representing a 43% increase from 2007 [4]. The rising prevalence of diabetes has placed a heavy burden on patients and health care systems worldwide.

Moreover, human consumption of foods that are rich in purines, high in added sucrose, and high in fructose corn syrup have increased dramatically recently. As the main component of added sugar, fructose, therefore leads to a significant increase in SUA [40]. SUA has been proposed as a potential predictive marker for the risk of developing diabetes in primary care based on 1) the strong, graded association between baseline SUA and diabetes [41], 2) the

time sequence from SUA to diabetes [21], and 3) the feasible and inexpensive nature of its measurement in routine medical examination. Therefore, prospective cohort and clinical trials are needed to evaluate the significance of uric acid levels in relation to the long-term risk of diabetes.

Previous studies, which were generally based on a single SUA assessment, generated conflicting results on the association between SUA and diabetes risk. For example, a cohort study in Italy found that a 1-SD increase of baseline SUA was associated with a 26% increased risk of new-onset impaired fasting glucose and a 29% increased risk of new-onset diabetes mellitus [5]. Moreover, a longitudinal study of people who were older than 65 years suggested that subjects in high-level groups of SUA had a higher chance to have diabetes [7]. This evidence was also replicated in the Japanese [8], Korean [9], Dutch [10], and American [8] populations. However, a Mendelian randomization study reported that uric acid concentration was not causally related to an increased risk of diabetes [11]. Because of the variability of SUA, one measurement of SUA at baseline may be temporary and may underestimate the true association between SUA and diabetes risk. A recent study demonstrated that the persistent presence of hyperuricemia was associated with an increased risk of diabetes after adjusting for other diabetic risk factors [14]. However, the relationship between long-term changes in hyperuricemia and the potential risk for diabetes has been less well researched. Furthermore, considering potential heterogeneity in changes in SUA levels among individuals, hyperuricemia trajectories may reflect the potential hyperuricemia dynamic changing patterns [24].

To our knowledge, this is the first study to assess the potential impacts of hyperuricemia trajectories on diabetes risk. Notably, we identified a high-increasing hyperuricemia growth trajectory with a proportion of 15.5%. Our analyses showed that participants in the high-increasing pattern were subsequently associated with higher (RR, 1.42; 95% CI: 1.09−1.84) diabetes risk, compared with those who experienced a low-stable trajectory. The group-based trajectory could divided subjects into subgroups by the average and variability of SUA progression [42]. Thus subjects in each subgroup would follow similar SUA trajectories that cluster together, while different subgroups would exhibit distinctly population heterogeneity in longitudinal changes in SUA levels rather than a single measurement of SUA. For example, participants with the high-increasing pattern had a higher risk of developing diabetes than did those with the moderate-stable pattern, although they had a similar possibility of hyperuricemia at the beginning of the exposure period.

In addition, our results found that approximately 25% of participants with new-onset diabetes experienced a rapid increase in the possibility of hyperuricemia before the onset of diabetes. These findings link the long-term existence of hyperuricemia with diabetes risk rather than single or short term hyperuricemia, which may benefit the understanding of the knowledge base and the prevention of diabetes.

Previous evidence has suggested that uric acid and BMI probably influence glucose metabolism through stimulating hepatic lipogenesis [43] and inducing the generation of inflammatory cytokines and nonesterified fatty acids that lead to insulin resistance [44,45]. This notion is supported by several observational studies. The US National Health and Nutrition Examination Survey found that adiposity factors could mediate the association between SUA and glucose/insulin homeostasis [46]. Similarly, a study in Thailand reported every 1 mg/dL increase in SUA was associated with the increased waist circumference and then was significantly associated with an increase in FPG by 0.082 mg/dL [47].

However, the medication role of adiposity factors in SUA and diabetes in the above studies was hampered by the cross-sectional study design and the possibility of confounding factors. Basing on the marginal structure models, this longitudinal study broke down a total effect into a so-called natural direct and indirect effect, regardless of the underlying bias due to confounding. Our result reported that approximately 24.41% of the total effect of high-increasing hyperuricemia pattern on the increased risk of diabetes was mediated through obesity. The current study thus adds to evidence suggesting that hyperuricemia indirectly contributes to the development of diabetes through obesity.

Furthermore, this study first detected that dyslipidemia and hypertension partially mediated the association between high-increasing hyperuricemia pattern and diabetes. The biological mechanisms of these mediation effects have not been understood. Cell and animal studies have suggested that uric acid could induce systemic hypertension through stimulating the epithelial sodium channel in the distal nephron with a consequent decrease in renal sodium excretion [48] and stimulates triglyceride accumulation within hepatocytes through the cleavage and nuclear translocation of the sterol regulatory element-binding by increasing hepatocyte endoplasmic reticulum stress [49]. Both dyslipidemia and hypertension have been reported to be associated with diabetes through inducing insulin resistance and beta-cell dysfunction as described in previous studies [50,51]. Our results suggest that the effect of the high-increasing hyperuricemia pattern on diabetes might be partially through the existence of dyslipidemia and hypertension. These hypotheses should be investigated and further explored.

Our study has several strengths. It is the first to evaluate the relationship between hyperuricemia trajectories and the risk of diabetes in Chinese urban adults, which can help to identify high-risk groups for diabetes. The second strength is that the study provides evidence for potential roles of metabolism factors including obesity, dyslipidemia, and hypertension in the association between hyperuricemia trajectories and diabetes. Finally, the prospective cohort study design and long follow-up period help the determination of the true relationship between hyperuricemia trajectories and diabetes.

However, several limitations need to be addressed. Firstly, the diet was identified as a risk factor for hyperuricemia and diabetes; however nutritional factors were not measured, which may confound the association between hyperuricemia trajectories and diabetes risk. Secondly, as a mediator, obesity was defined as having a mean BMI during the exposure period higher than 28 kg/m^2 based on Asian criteria, which may inflate the proportion of diabetes risk mediated through obesity. Although we performed mediation analysis using marginal structural models, more advanced causal inference methods involving the repeatedly measured mediator variables are needed in the future. Finally, this study was conducted using a sample of the Beijing population, and therefore our findings have limited generalizability to other populations.

5. Conclusions

The current study identified three discrete hyperuricemia trajectories and found that the high-increasing pattern was significantly associated with the subsequent risk of developing diabetes. Monitoring hyperuricemia trajectories may provide an important approach to identify a population with a higher risk of diabetes. In addition, our study is the first to evaluate the mediating roles of metabolism factors in the association between hyperuricemia trajectories and diabetes based on prospective cohort data. Our findings suggest that a noteworthy portion of the increased risk of diabetes among individuals with high-increasing hyperuricemia pattern is mediated through obesity, dyslipidemia, and hypertension. This information may help in understanding the complicated association between hyperuricemia and the risk of diabetes. Future researches are needed to confirm these findings.

Author contribution

X.G. and J.L. contributed to the conception or design of the work. H.P., L.T., Y.L., M.G., X.L., S.C., X.T., J.Z., and Y.L. contributed to the acquisition, analysis, or interpretation of data for the work. J.L. drafted the manuscript. X.W. and X.Y. critically revised the manuscript. All authors gave final approval and agreed to be accountable for all aspects of work ensuring integrity and accuracy.

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Ethics approval

All procedures performed in studies involving human participants were in accordance with the principles of the Declaration of Helsinki. The study protocol was approved by the Ethics Committee of Capital Medical University.

Consent to participate

Informed consent was obtained from all individual participants included in the study.

Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Declaration of competing interest

The authors declared they do not have anything to disclose regarding conflict of interest with respect to this manuscript.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.numecd.2023.02.018.

References

[1] Rosengren A, Dikaiou P. Cardiovascular outcomes in type 1 and type 2 diabetes. Diabetologia 2023. https://doi.org/10.1007/s00125-022-05857-5.

[2] Cole JB, Florez JC. Genetics of diabetes mellitus and diabetes complications. Nat Rev Nephrol 2020. https://doi.org/10.1038/s41581-020-0278-5.

[3] Kehlenbrink S, Smith J, Ansbro É, et al. The burden of diabetes and use of diabetes care in humanitarian crises in low-income and middle-income countries. Lancet Diabetes Endocrinol 2019. https://doi.org/10.1016/S2213-8587(19)30082-8.

[4] Collaborators GCOD. Global, regional, and national age-sex-specific mortality for 282 causes of death in 195 countries and territories, 1980-2017: a systematic analysis for the Global Burden of Disease Study 2017. Lancet 2018. https://doi.org/10.1016/S0140-6736(18)32203-7.

[5] Bombelli M, Quarti-trevano F, Tadic M, et al. Uric acid and risk of new-onset metabolic syndrome, impaired fasting glucose and diabetes mellitus in a general Italian population. J Hypertens 2018; 36(7):1492−8. https://doi.org/10.1097/HJH.0000000000001721.

[6] Zhou C, Liu M, Zhang Z, et al. Positive association of serum uric acid with new-onset diabetes in Chinese women with hypertension in a retrospective analysis of the China Stroke Primary Prevention Trial. Diabetes Obes Metab 2020. https://doi.org/10.1111/dom.14072.

[7] Chang JB, Chen Y-L, Hung Y-J, et al. The role of uric acid for predicting future metabolic syndrome and type 2 diabetes in older people. J Nutr Health Aging 2017;21(3):329−35. https://doi.org/10.1007/s12603-016-0749-3.

[8] Nakanishi N, Okamoto M, Yoshida H, et al. Serum uric acid and risk for development of hypertension and impaired fasting glucose or type II diabetes in Japanese male office workers. Eur J Epidemiol 2003;18(6):523−30. https://doi.org/10.1023/a:1024600905574.

[9] Lee SH, Kim K-M, Kim K-N. Combined effect of serum gamma-glutamyltransferase and uric acid on incidence of diabetes mellitus: A longitudinal study. Medicine 2017;96(19):e6901. https://doi.org/10.1097/MD.0000000000006901.

[10] Dehghan A, Van Hoek M, Sijbrands EJ, et al. High serum uric acid as a novel risk factor for type 2 diabetes. Diabetes Care 2008. https://doi.org/10.2337/dc07-1276.

[11] Sluijs I, Holmes M, Yt VDS, et al. A Mendelian randomization study of circulating uric acid and type 2 diabetes. Diabetes 2015. https://doi.org/10.2337/db14-0742.

[12] Li X, Meng X, Gao X, et al. Elevated serum xanthine oxidase activity is associated with the development of type 2 diabetes: a prospective cohort study. Diabetes Care 2018. https://doi.org/10.2337/dc17-1434.

[13] Liu R, Han C, Wu D, et al. Prevalence of hyperuricemia and gout in mainland China from 2000 to 2014: a systematic review and meta-analysis. BioMed Res Int 2015. https://doi.org/10.1155/2015/762820.

[14] Liu J, Tao L, Zhao Z, et al. Two-year changes in hyperuricemia and risk of diabetes: a five-year prospective cohort study. J Diabetes Res 2018. https://doi.org/10.1155/2018/6905720.

[15] Su H, Liu T, Li Y, et al. Serum uric acid and its change with the risk of type 2 diabetes: a prospective study in China. Primary Care Diabetes 2021. https://doi.org/10.1016/j.pcd.2021.06.010.

[16] Maiuolo J, Oppedisano F, Gratteri S, et al. Regulation of uric acid metabolism and excretion. Int J Cardiol 2016;213:8−14. https://doi.org/10.1016/j.ijcard.2015.08.109.

[17] Ishizaka N, Ishizaka Y, Toda A, et al. Changes in waist circumference and body mass index in relation to changes in serum uric acid in Japanese individuals. J Rheumatol 2010;37(2):410−6. https://doi.org/10.3899/jrheum.090736.

[18] Tanaka K, Ogata S, Tanaka H, et al. The relationship between body mass index and uric acid: a study on Japanese adult twins. Environ Health Prev Med 2015. https://doi.org/10.1007/s12199-015-0473-3.

[19] Pölönen P, Jawahar Deen A, Leinonen HM, et al. Nrf2 and SQSTM1/p62 jointly contribute to mesenchymal transition and invasion in glioblastoma. Oncogene 2019. https://doi.org/10.1038/s41388-019-0956-6.

[20] Norvik JV, Storhaug HM, Ytrehus K, et al. Overweight modifies the longitudinal association between uric acid and some components of the metabolic syndrome: the Tromsø Study. BMC Cardiovasc Disord 2016;16:1−9. https://doi.org/10.1186/s12872-016-0265-8.

[21] Han T, Meng X, Shan R, et al. Temporal relationship between hyperuricemia and obesity, and its association with future risk of type 2 diabetes. Int J Obes 2018;42(7):1336−44. https://doi.org/10.1038/s41366-018-0074-5.

[22] Chen S, Yang H, Chen Y, et al. Association between serum uric acid levels and dyslipidemia in Chinese adults: a cross-sectional study and further meta-analysis. Medicine 2020. https://doi.org/10.1097/MD.0000000000019088.

[23] Kansui Y, Matsumura K, Morinaga Y, et al. Impact of serum uric acid on incident hypertension in a worksite population of Japanese men. J Hypertens 2018;36(7):1499−505. https://doi.org/10.1097/HJH.0000000000001743.

[24] Ma H, Wang X, Guo X, et al. Distinct uric acid trajectories are associated with different risks of incident hypertension in middle-aged adults. Mayo Clin Proc 2019. https://doi.org/10.1016/j.mayocp.2018.08.042.

[25] Sharaf El Din UAA, Salem MM, Abdulazim DO. Uric acid in the pathogenesis of metabolic, renal, and cardiovascular diseases: a review. J Adv Res 2017. https://doi.org/10.1016/j.jare.2016.11.004.

[26] Rothwell PM, Howard SC, Dolan E, et al. Effects of beta blockers and calcium-channel blockers on within-individual variability in blood pressure and risk of stroke. Lancet Neurol 2010. https://doi.org/10.1016/S1474-4422(10)70066-1.

[27] Lim Y-M, Yang P-S, Jang E, et al. Body mass index variability and long-term risk of new-onset atrial fibrillation in the general population: a Korean nationwide cohort study. Mayo Clin Proc 2019. https://doi.org/10.1016/j.mayocp.2018.10.019.

[28] Ma Y-C, Zuo L, Chen J-H, et al. Modified glomerular filtration rate estimating equation for Chinese patients with chronic kidney disease. J Am Soc Nephrol : JASN (J Am Soc Nephrol) 2006;17(10): 2937−44. https://doi.org/10.1681/ASN.2006040368.

[29] Liao Y, Xie L, Chen X, et al. Sleep quality in cigarette smokers and nonsmokers: findings from the general population in central China. BMC Publ Health 2019. https://doi.org/10.1186/s12889-019-6929-4.

[30] Moore Aa, Giuli L, Gould R, et al. Alcohol use, comorbidity, and mortality. J Am Geriatr Soc 2006. https://doi.org/10.1111/j.1532-5415.2006.00728.x.

[31] Chen C, Lu FC, Department of Disease Control Ministry of Health, PR China. The guidelines for prevention and control of overweight and obesity in Chinese adults. Biomed Environ Sci 2004;17(Suppl):1−36.

[32] Chobanian Av, Bakris Gl, Black Hr, et al. Seventh report of the joint national committee on prevention, detection, evaluation, and treatment of high blood pressure. Hypertension 2003. https://doi.org/10.1161/01.HYP.0000107251.49515.c2.

[33] Pan L, Yang Z, Wu Y, et al. The prevalence, awareness, treatment and control of dyslipidemia among adults in China. Atherosclerosis 2016. https://doi.org/10.1016/j.atherosclerosis.2016.02.006.

[34] American Diabetes Association. Standards of medical care in diabetes-2022 abridged for primary care providers. Clin Diabetes 2022. https://doi.org/10.2337/cd22-as01.

[35] Jones B, Nagin D, Roeder K. A SAS procedure based on mixture models for estimating developmental trajectories. Socio Methods Res 2001. https://doi.org/10.1177/0049124101029003005.

[36] Yelland LN, Salter AB, Ryan P. Performance of the modified Poisson regression approach for estimating relative risks from clustered prospective data. Am J Epidemiol 2011;174(8):984−92. https://doi.org/10.1093/aje/kwr183.

[37] Lange T, Vansteelandt S, Bekaert M. A simple unified approach for estimating natural direct and indirect effects. Am J Epidemiol 2012. https://doi.org/10.1093/aje/kwr525.

[38] Sekhon J. Multivariate and propensity score matching software with automated balance optimization: the matching package for R. J Stat Software 2011. https://doi.org/10.18637/jss.v042.i07.

[39] Saeedi P, Petersohn I, Salpea P, et al. Global and regional diabetes prevalence estimates for 2019 and projections for 2030 and 2045: results from the international diabetes federation diabetes atlas, 9 edition. Diabetes Res Clin Pract 2019. https://doi.org/10.1016/j.diabres.2019.107843.

[40] Nakagawa T, Johnson RJ, Andres-Hernando A, et al. Fructose production and metabolism in the kidney. J Am Soc Nephrol : JASN (J Am Soc Nephrol) 2020. https://doi.org/10.1681/ASN.2019101015.

[41] Lv Q, Meng XF, He FF, et al. High serum uric acid and increased risk of type 2 diabetes: a systemic review and meta-analysis of prospective cohort studies. PLoS One 2013;8(2):e56864. https://doi.org/10.1371/journal.pone.0056864.

[42] Nguena Nguefack HL, Pagé MG, Katz J, et al. Trajectory modelling techniques useful to epidemiological research: a comparative narrative review of approaches. Clin Epidemiol 2020. https://doi.org/10.2147/CLEP.S265287.

[43] Lanaspa MA, Sanchez-Lozada LG, Choi Y-J, et al. Uric acid induces hepatic steatosis by generation of mitochondrial oxidative stress: potential role in fructose-dependent and -independent fatty liver. J Biol Chem 2012;287(48):40732−44. https://doi.org/10.1074/jbc.M112.399899.

[44] Sánchez-Lozada LG, Lanaspa MA, Cristóbal-García M, et al. Uric acid-induced endothelial dysfunction is associated with mitochondrial alterations and decreased intracellular ATP concentrations. Nephron Exp Nephrol 2012. https://doi.org/10.1159/000345509.

[45] Tanica L, Pedro M-V, Fred P, et al. Elevated serum uric acid is associated with high circulating inflammatory cytokines in the population-based colaus study. PLoS One 2011;6(5):e19901. https://doi.org/10.1371/journal.pone.0019901.

[46] Mazidi M, Katsiki N, Mikhailidis DP, et al. The link between insulin resistance parameters and serum uric acid is mediated by adiposity. Atherosclerosis 2018. https://doi.org/10.1016/j.atherosclerosis.2017.12.033.

[47] Thunyarat A, Dumrongrat L, Sangsulee T, et al. Direct and indirect effects of serum uric acid on blood sugar levels in patients with

prediabetes: a mediation analysis. J Diabetes Res 2017;2017:6830671. https://doi.org/10.1155/2017/6830671.

[48] Xu W, Huang Y, Li L, et al. Hyperuricemia induces hypertension through activation of renal epithelial sodium channel (ENaC). Metab Clin Exp 2016. https://doi.org/10.1016/j.metabol.2015.10.026.

[49] Choi Y-J, Shin H-S, Choi HS, et al. Uric acid induces fat accumulation via generation of endoplasmic reticulum stress and SREBP-1c activation in hepatocytes. Lab Investig J Tech Methods Pathol 2014. https://doi.org/10.1038/labinvest.2014.98.

[50] Tsimihodimos V, Gonzalez-Villalpando C, Meigs JB, et al. Hypertension and diabetes mellitus: coprediction and time trajectories. Hypertension 2018. https://doi.org/10.1161/HYPERTENSIONAHA.117.10546.

[51] Tangvarasittichai S. Oxidative stress, insulin resistance, dyslipidemia and type 2 diabetes mellitus. World J Diabetes 2015. https://doi.org/10.4239/wjd.v6.i3.456.