

## Meta Analysis

# Elevation of serum uric acid and incidence of type 2 diabetes: A systematic review and meta-analysis

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Received 26 July 2016

Available online 2 November 2016

## Abstract

**Objective:** Recently, several cohort studies suggested a positive relationship between serum uric acid (SUA) and type 2 diabetes mellitus (T2DM), which is inconsistent with the results of functional research. Our aim was to further evaluate this correlation by conducting a systematic review.

**Methods:** Computerized literature searches of the Medline database, EMBASE database, and PubMed were used to evaluate the relationship between SUA and T2DM in cohort studies. Cochran's  $Q$  and  $I^2$  statistics were used to evaluate heterogeneity among studies, and pooled relative risk (RR) and odds ratio (OR) with 95% confidence intervals (CIs) were calculated using random-effects and fixed-effects models. The summary RR and OR of per 1 mg/ml-SUA increase were calculated separately because of their different epidemiological implications and calculation methods. Additionally, sensitivity analysis, stratified analysis, meta-regression, and multiple meta-regression were applied to investigate the heterogeneity among studies.

**Results:** A total of 970 articles were retrieved from the searches. Sixteen publications of cohort studies containing 61,714 participants were included. The pooled RR was 1.131 (95% CI: 1.084–1.179) with significant heterogeneity among studies ( $I^2 = 51.9\%$ ,  $P = 0.018$ ). Adjusted RR to evaluate the stability of the relationship between SUA and T2DM in the sensitivity analysis was similar (RR = 1.140, 95% CI: 1.087–1.197), with statistically significant heterogeneity ( $I^2 = 54.5\%$ ,  $P = 0.015$ ). Stratified analysis and meta-regression showed that the positive relationship remained irrespective of age, sex, region, and adjustment for confounding factors including body mass index, fasting blood glucose, systolic blood pressure, diastolic blood pressure, alcohol consumption, smoking, blood cholesterol, waist circumference, fatty liver, and drugs affecting SUA.

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Peer review under responsibility of Chinese Medical Association.



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<http://dx.doi.org/10.1016/j.cdtm.2016.09.003>

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**Conclusion:** Although SUA is independently associated with development of T2DM, insulin resistance increased as the baseline SUA concentration increased; thus, the correlation between SUA and T2DM requires further evaluation and the baseline insulin resistance status should also be considered.

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*Keywords:* Uric acid; Diabetes; Meta-analysis

## Introduction

In 2011, there were 366 million people with diabetes, and this number is expected to rise to 552 million by 2030.<sup>1</sup> The majority of the patients have type 2 diabetes mellitus (T2DM). The prevalence of T2DM has become a big public health challenge worldwide. Dietary recommendations and genetic counseling have been taken into consideration in preventing the development of T2DM.<sup>2,3</sup> However, identifying a high risk susceptible population and encouraging lifestyle modification is likely to be the most effective strategy of prevention. Therefore, great efforts have been made to gain insight into T2DM risk factors, including a strong family history of diabetes mellitus, age, obesity, physical inactivity, body mass index (BMI), alcohol intake, serum triglyceride concentration, uric acid concentration, and coronary heart disease.<sup>4–6</sup> Whether the above defined risk factors can be applicable to the global community however requires further investigation.<sup>7</sup>

Many recent epidemiologic evidences have been devoted to the relationship between serum uric acid (SUA) and T2DM. A meta-analysis of 11 studies reported in 2009 revealed a positive relationship between SUA and the development of T2DM<sup>8</sup> but with several limitations existed. First, the progression of T2DM frequently occurs with aging and metabolic syndrome (MS) factors. As a type of MS, increased SUA can also be accompanied with T2DM.<sup>9,10</sup> Second, several more factors, such as fasting blood glucose (FBG), 2-hour post prandial blood glucose (2 h-PBG), family history of diabetes, physical activity, and drugs affecting SUA at baseline, also participate in the progression and development of T2DM. Such factors can be confounding for evaluating the correlation between SUA and T2DM. No sufficient adjustment and/or objective quality assessment was made for these confounding factors in the studies that included in this meta-analysis. Third, a combination of risk ratios (*RRs*) and odds ratios (*ORs*) as indicators of *RR* could have overestimated the actual *RR*.

Recently, a variety of publications closely examining this association showed discordant results. Thus, the relationship between SUA and T2DM still remains controversial. This meta-analysis also included the most recent 5 studies since 2009 that indicated a positive relationship between SUA and T2DM, and then to better quantify this positive correlation a literature-based systematic review was performed.

## Methods

### *Data selection*

We conducted a computerized literature search of the Medline, EMBASE, and PubMed databases. The following algorithm was applied for both the Medical Subject Heading (MeSH) and the full text. The search strings were as follows: [(‘uric acid’ [mesh]) AND (‘type 2 diabetes’ [mesh])] AND [‘uric acid’ AND ‘type 2 diabetes’].

### *Inclusion and exclusion criteria*

Included articles were required to meet the following criteria: (1) inclusion of T2DM as a dominant outcome; (2) measurement of SUA concentration at baseline; (3) at baseline the participants did not have T2DM; (4) *RR* or *OR* and its corresponding 95% confidence interval (*CI*) or sufficient data to calculate them were provided. The articles were excluded if: (1) the outcome was not T2DM; (2) the baseline SUA level was not assessed; (3) *RRs* or *ORs* and its corresponding 95% *CI*s (or data to calculate them) were not given. If data from two or more articles were derived from the same subjects, only the most recent article was included in this analysis.

### *Data extraction*

Two researchers independently screened and assessed each of the potential titles, abstracts, and/or

full texts to determine the eligibility for inclusion. If any discrepancies occurred, a third investigator would make the definitive decision for the study eligibility and data extraction. Data extracted for this review included the first author's name, publication year, population studied, baseline SUA (mg/dl), age (years), percentage of men, sample size, number of cases, adjusted *RR* (95% *CI*), multivariable adjustment, cohort design, and duration of follow-up. Additionally, the original data of baseline 2h-PBG and the subsequent adjustments were requested from the authors of these primary articles included. Commitments or questionnaires for all of the participants were administered correspondingly in each study of this meta-analysis.

#### *Statistical analysis*

In the studies which the analyzed SUA level was defined as a categorical variable, the pooled *RR* could not be calculated directly from the different results of the SUA stratification analysis. To quantify the dose-response relationship between the baseline SUA level and the development of T2DM, the *RR* was calculated for the increment of 1 mg/dl SUA in each study. This method for trend estimation was supported by Berlin et al.<sup>11</sup> The logarithmic relative risk model is excellent whereas statistical properties of the linear relative risk model are unsuitable for categorical variables.<sup>11</sup> The midpoint in each category was estimated by the average of the lower and upper bound. If the highest or the lowest category was open-ended, the interval length at an open-ended would be assumed to be the same as the adjacent interval. The log *RR* or log *OR* from each study was calculated by converting the 95% *CI* to its natural logarithm (width of the *CI* divided by 3.92).<sup>12</sup> The estimates for men and women were synthesized into a combined value using a weighting method in each study to decrease the large heterogeneity across studies.

As the overestimated pooled *RR* is close to 1 and of little practical importance because the total incidence is relatively rare,<sup>8</sup> the *RRs* and *ORs* should be evaluated separately for the calculation and epidemiological significance because the two indexes are distinct, and this might be helpful to decrease the potential errors. In assessing heterogeneity among studies, Cochran *Q* and *I*<sup>2</sup> statistics were used.<sup>13</sup> For the *Q* statistic, a *P* value <0.10 was considered statistically significant for heterogeneity; for *I*<sup>2</sup>, a value >50% was considered a measure of severe heterogeneity. If *P* value <0.10 (*I*<sup>2</sup> value >50%), the random-effects model which

DerSimonian and Laird reported was used<sup>14,15</sup>; otherwise, the fix-effects model was conducted.

Sensitivity analysis to detect the source of heterogeneity was applied to calculate the overall homogeneity and effect size by excluding one study at a time. The most weighted article was removed from the analysis and a meta-analysis with the remaining articles was then conducted. Additionally, stratification analysis, meta-regression, and multiple meta-regression were used to assess a potential difference in distinct populations characterized by different features, such as gender, age, and geographical area. Only studies that provided *RRs* were used in the sensitivity analysis, stratification analysis, and meta-regression. A funnel plot and Egger's linear regression test were used to investigate any possible publication bias.<sup>16</sup> All the statistical analyses were performed using STATA version 10.0 (STATA, College Station, TX, USA). A two-tailed *P* value <0.05 was considered to be significant.

## **Results**

### *Included and excluded articles*

A total of 631 articles were retrieved from EMBASE and 441 articles from PubMed. After removing duplicates, 970 articles remained (Fig. 1) whilst 948 articles were then excluded based on their titles. Of the 22 articles remaining, 4 articles were excluded for reasons listed in Fig. 1. Eighteen articles were selected for further full-text review. Another 2 studies were excluded for the reasons presented in Fig. 1. Thus, a total of 16 studies published from January 1st 1975 to March 30th 2012 met the criteria for inclusion in this meta-analysis and systematic review.

Five studies (30%) reported risk prediction models for men and women separately, one of which provided data for men, women, and all of them together. Of the remaining 4 articles, weighted estimates for the general population were conducted to decrease the heterogeneity among studies. Data from two generations were shown in one of the studies. Ultimately, 16 publications including a total of 27 risk prediction models were statistically synthesized by meta-analysis.

### *Data request from the corresponding authors of included articles*

Subsequently, Wang et al replied and supplied a *RR* adjusted for fasting plasma glucose,<sup>17</sup> while the authors of other studies did not reply.

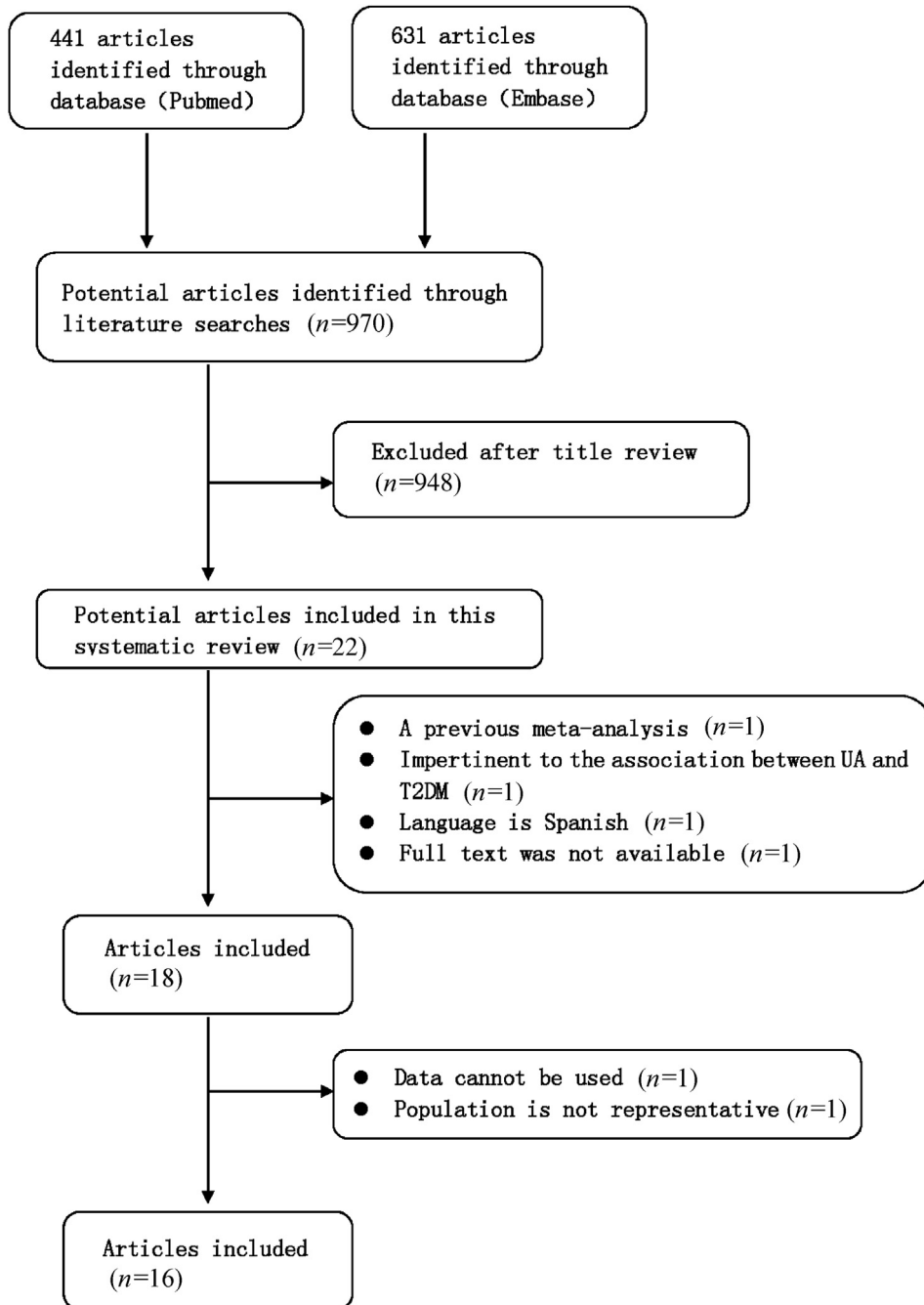


Fig. 1. Flow chart on the articles selection process. T2DM: type 2 diabetes mellitus; UA:uric acid.

### Characteristics of studies

Eight articles were prospective cohort studies and eight were historical cohort studies. Mean baseline SUA level of the subjects ranged from 4.0 to 8.0 mg/ml. Mean age at baseline ranged from 41 to 64 years.

Sample size per study ranged from 161 to 8688 and a total of 67,174 participants were included (Table 1). One study considered the effect of diuretic use, the other four adjusted for FBG, one of which only referring to blood glucose level. However, there was no study that considered both diuretic use and blood

Table 1  
Characteristics of included studies.

First author's name	Publication year	Cohort design	Mean baseline SUA, mg/dl	Mean age, years	Sample size, <i>n</i>	Number of cases	Adjusted RR (95% CI)	Multivariable adjustment
Medalie <sup>13</sup>	1975	H	4.8	49	8688	344	1.15 (0.99–1.32) <sup>a</sup>	Age, BMI, PVD, SBP, cholesterol, hemoglobin, born in Europe, education
Ohlson <sup>14</sup>	1988	H	5.3	50	766	47	1.27 (1.0–1.58) <sup>a</sup>	Glutamic pyruvic transaminase, blood glucose, BMI, Bilirubin, SBP, FHD
Perry <sup>15</sup>	1995	P	6.0	50	7577	194	1.15 (0.96–1.36) <sup>a</sup>	Age, BMI, prevalent coronary heart disease, physical activity, alcohol, smoking, SBP, high density lipoprotein cholesterol, heart rate
Chou <sup>16</sup>	1998	H	5.8	50	654	39	1.73 (1.17–2.57) <sup>b</sup>	NA
Taniguchi <sup>17</sup>	2001	P	5.2	41	6478	639	1.01 (0.94–1.09) <sup>a</sup>	Age, BMI, alcohol, smoking, physical activity, FBG, FHD Survey
Meisinger <sup>18</sup>	2002	H	5.7	52	3052	128	1.04 (0.91–1.20) <sup>a</sup>	NA
Men <sup>18</sup>			4.0	51	3114	85	1.60 (1.34–1.91) <sup>a</sup>	
Lin <sup>19</sup>	2004	H	8.0	49	293	27	0.85 (0.62–1.17) <sup>b</sup>	NA
Men <sup>19</sup>			7.1	55	161	21	1.46 (1.08–1.98) <sup>b</sup>	
Chien <sup>20</sup>	2008	H	5.6	54	2690	548	1.09 (1.01–1.17) <sup>a</sup>	Age, BMI, alcohol, exercise, marital status, education level, occupation, FHD, MS
Dehghan <sup>21</sup>	2008	P	5.4	Over 55	4536	462	1.09 (1.03–1.16) <sup>a</sup>	Age, sex, BMI, WC, SBP/DBP, HDL-cholesterol
Nan <sup>22</sup>	2008	H	6.6	41	1941	337	1.13 (1.05–1.23) <sup>a</sup>	cohort, serum creatinine, alcohol drinking, history of hypertension, FHD and ethnicity, fasting serum insulin
Men <sup>22</sup>			5.0	42	2318	379	1.04 (0.96–1.14) <sup>a</sup>	
Kramer <sup>23</sup>	2009	H	5.7	63.3 ± 8.6	566	55	1.63 (1.21–2.19) <sup>b</sup>	Age, sex, BMI, diuretic use, estimated glomerular filtration rate
Rathmann <sup>24</sup>	2009	P	5.1 ± 1.3	63.9 ± 5.4	887	93	1.70 (1.3–2.3) <sup>b</sup>	Age, sex
Men <sup>24</sup>			6.3 ± 1.3	63.4 ± 5.4	449	60	1.50 (1.1–2.2) <sup>b</sup>	
Women <sup>24</sup>			4.96 ± 1.3	62.9 ± 5.4	438	33	2.20 (1.3–3.9) <sup>b</sup>	
Bhole <sup>25</sup>	2010	P	4.3 ± 1.1	45	4883	641	1.20 (1.11–1.28) <sup>a</sup>	Age, sex, BMI, alcohol consumption, smoking, physical activity, hypertension, blood glucose level, blood cholesterol level, creatinine level, serum triglyceride level
Original <sup>25</sup>			5.7 ± 1.4	37	4292	497	1.15 (1.06–1.23) <sup>a</sup>	
Yamada <sup>26</sup>	2011	P	5.97 ± 1.21	48.4 ± 10.2	7114	576	1.00 (0.92–1.09) <sup>b</sup>	Age, BMI, FHD, hypertension, triglyceride, fatty liver, alcohol, smoking
Men <sup>26</sup>			4.27 ± 0.92	50.0 ± 9.1	5529	221	1.36 (1.17–1.58) <sup>b</sup>	
Women <sup>26</sup>	2011	P	4.78 ± 1.50	61.6	924	98	1.199 (1.033–1.391) <sup>a</sup>	Age, sex, BMI, FHD, smoking, alcohol, SBP/DBP, HDL-cholesterol, total cholesterol, triglyceride, FBG, fasting insulin, serum creatinine, white blood cell, high sensitive C-reactive protein
Tiange <sup>27</sup>			5.22 ± 1.33	45–64	711	68	1.426 (1.17–1.705) <sup>a</sup>	
Kai <sup>28</sup>	2011	P	5.22 ± 1.33	45–64	711	68	1.426 (1.17–1.705) <sup>a</sup>	BMI, PP, PPI, SBP, heart rate, FBG, WC, total cholesterol, HDL-C

SUA: serum uric acid; PVD: peripheral vascular disease; FHD: family history of diabetes; FBG: fasting blood glucose; HDL: high density lipoprotein; MS: metabolic syndrome; WC: waist circumference; BMI: body mass index; SBP/DBP: systolic/diastolic blood pressure; alcohol: alcohol consumption; PP: pulse pressure; PPI: pulse pressure index; NA: not available; H: Historical; P: Prospective.

<sup>a</sup>HR or RR; <sup>b</sup>Adjusted OR.

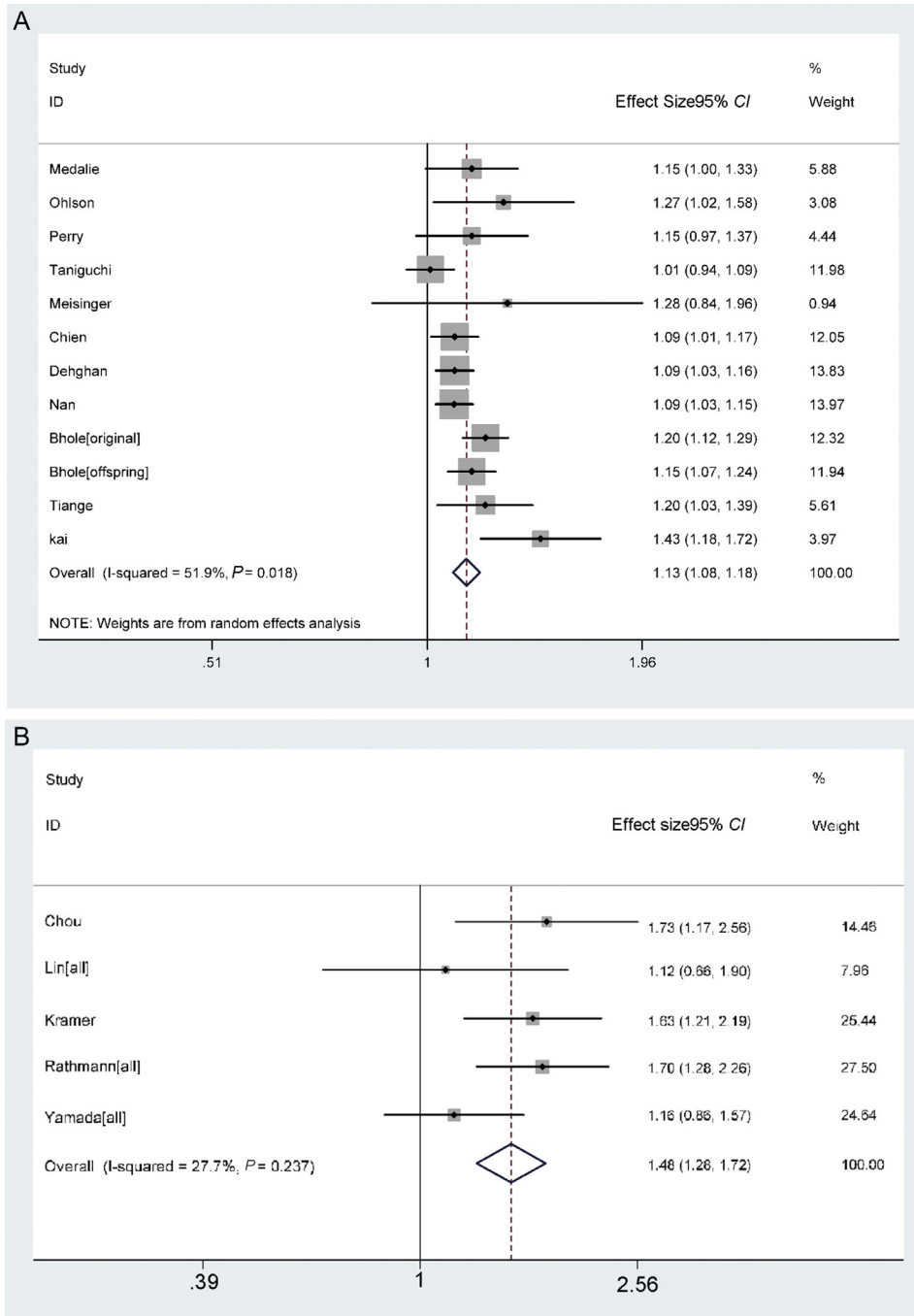


Fig. 2. Forest plot of risk of T2DM for each mg/dl increase in SUA. A. Overall RR (with corresponding 95% CIs) respectively for risk of type 2 diabetes for each mg/dl increase in SUA from random effect model. Diamonds are overall relative risk; Horizontal lines indicate 95% CIs. B. Overall OR (with corresponding 95% CIs) respectively for risk of type 2 diabetes for each mg/dl increase in SUA from fix effect model. Diamonds are overall relative risk; Horizontal lines indicate 95% CIs. T2DM: type 2 diabetes mellitus; SUA: serum uric acid.

Table 2  
Stratified and meta-regression analysis to explore the effects of study characteristics on T2DM.

Variable	Stratum	Studies (n)	RR	Tests for heterogeneity			Meta-regression
				Q	P	I <sup>2</sup> (%)	P
Sex	Male	7	1.078 (1.031–1.127)	10.21	0.116	41.2	0.151
	Female	3	1.328 (0.960–1.837)	20.98	<0.05	90.5	
Geographical area	Western	8	1.128 (1.094–1.163)	7.52	0.377	6.9	0.845
	Asia	4	1.141 (1.018–1.279)	13.99	0.004	77.9	
Age, years	<50	5	1.114 (1.048–1.185)	12.40	0.015	67.7	0.865
	50–60	5	1.204 (1.075–1.349)	8.16	0.086	51.0	
	≥60	2	1.115 (1.087–1.145)	1.36	0.244	26.5	
SUA, mg/dl	<5.5	8	1.159 (1.078–1.246)	20.9	0.004	66.5	0.832
	≥5.5	4	1.107 (1.066–1.150)	1.7	0.637	0.0	
Study design	Historical	5	1.104 (1.057–1.152)	2.67	0.614	0.0	0.759
	Prospective	7	1.145 (1.073–1.221)	19.82	0.003	69.7	
Follow-up, years	≤10	7	1.083 (1.046–1.122)	7.02	0.319	14.5	0.307
	>10	5	1.179 (1.100–1.264)	10.36	0.035	61.4	
Adjustment							
Family history of DM	Yes	5	1.080 (1.040–1.120)	7.27	0.122	45.0	0.131
	No	7	1.150 (1.109–1.192)	9.84	0.131	39.0	
Physical activity	Yes	6	1.124 (1.055–1.197)	13.44	0.094	46.9	0.661
	No	6	1.113 (1.072–1.156)	9.41	0.020	62.8	
FBG	Yes	5	1.166 (1.064–1.279)	12.34	0.001	78.1	0.485
	No	7	1.100 (1.063–1.138)	3.08	0.799	0.00	
BMI	Yes	10	1.139 (1.084–1.197)	21.6	0.01	58.3	0.633
	No	2	1.091 (1.030–1.156)	0.59	0.444	0.00	
SBP	Yes	9	1.137 (1.104–1.171)	13.56	0.094	41.0	0.077
	No	3	1.053 (1.000–1.109)	2.92	0.232	31.5	
Alcohol	Yes	7	1.115 (1.063–1.170)	13.6	0.034	55.9	0.314
	No	5	1.199 (1.076–1.336)	8.87	0.065	54.9	
Smoking	Yes	5	1.126 (1.082–1.172)	12.4	0.015	67.7	0.917
	No	7	1.126 (1.069–1.186)	10.08	0.122	40.4	
TC	Yes	7	1.152 (1.112–1.193)	9.87	0.13	39.2	0.074
	No	5	1.074 (1.034–1.115)	5.94	0.204	32.7	
WC	Yes	2	1.228 (0.945–1.595)	7.20	0.007	86.1	0.579
	No	10	1.115 (1.083–1.148)	15.66	0.074	42.5	

Summary relative risk for the relationship between uric acid and T2DM by gender, geographical area, adjustments (family history of DM, physical activity, FBG, BMI, SBP, alcohol, smoking, total cholesterol, waist circumference and so on), and meta regression analysis to explore the effects of study characteristics except the analytic stratification variable. Pooled *RRs* of T2DM for each 1 mg/dl increase in SUA within the strata of each study characteristic are indicated.

SUA: serum uric acid; DM: diabetes mellitus; FBG: fasting blood glucose; BMI: body mass index; SBP: systolic blood pressure; WC: waist circumference; TC: total cholesterol.

glucose level simultaneously. None of the risk measurements were adjusted for 2h-PBG or for other drugs that influenced SUA level such as allopurinol.

Mean follow-up duration ranged from 2.0 to 62.0 years with 9 articles conducted among the European population, and the other 7 articles were among the Asian population. Four articles included men only, while the rest articles included both men and women. Other relevant study characteristics are tabulated in [Table S1](#).

### Results of the meta-analysis

A forest plot with *RRs* (95% *CI*s) and pooled estimates of increased risk of T2DM with respect to per 1 mg/dl increase in SUA is presented in [Fig. 2](#). A

random-effects model showed that the pooled adjusted *RR* and its 95% *CI* was 1.131 (1.084–1.179), and the pooled adjusted *OR* and its 95% *CI* was 1.484 (1.278–1.723). Heterogeneity of *RR* and *OR* observed among these studies were 51.9% ( $Q = 22.86$ ,  $P = 0.018$ ) and 27.7% ( $Q = 5.53$ ,  $P < 0.237$ ). The pooled estimates were synthesized for men and women of each study separately and that significantly decreased the heterogeneity of *RR* among studies from 68.4% to 51.9% and of *OR* from 81.6% to 27.7%.

In the sensitivity analysis to evaluate the stability of the relationship between SUA and T2DM, the adjusted *RR* was still similar ( $RR = 1.140$ , 95% *CI*: 1.087–1.197), with evidence of statistically significant heterogeneity ( $P = 0.015$ ,  $I^2 = 54.5%$ ).



The studies were stratified by gender, geographic region, age, confounding factors, and other study properties relevant to study quality. For those with previously elevated SUA, the risk of having T2DM was attenuated by adjusting for all of the above factors (all pooled *RRs* were  $\geq 1$ ). The findings were similar irrespective of the physical activity ( $P = 0.661$ ) or family history of diabetics ( $P = 0.131$ ). Effect of diuretic use was considered in only one study ( $RR = 1.63$ ) (Table 2). In the multiple regression analysis of confounding factors for T2DM, the *P*-values of all variables included were  $>0.05$  (Table S2).

For young adults (18–30 years) without MS, each unit increase in SUA was associated with increased overall risk of type 2 diabetes ( $OR = 1.22$ , 95% *CI*: 1.07–1.38).<sup>18</sup> *RRs* for the development of diabetes corresponding to per mg/dl increase in SUA were 1.27 (1.06–1.52) in pre-menopausal women and 1.21 (1.09–1.35) in post-menopausal population respectively.<sup>19</sup> Whereas a relatively higher incidence of diabetes was found in post-menopausal hyperuricemic women compared with pre-menopausal women ( $OR = 3.88$ , 95% *CI*: 1.92–7.91).

### Publication bias

Significant funnel plot asymmetry for the relationship between uric acid and T2DM is shown in Fig. 3. *P*-value for Begg's regression test was less than 0.01, which indicates a high risk of publication bias.

### Discussion

This systematic review aimed to further qualify the relationship between SUA and the development of T2DM. Recently (since 2009) 5 related studies were

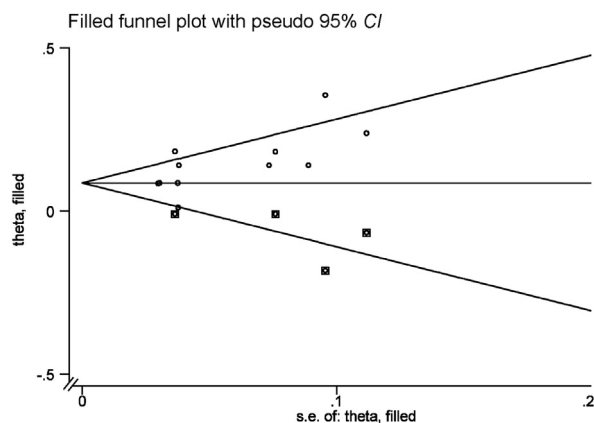


Fig. 3. Funnel plot of cohort studies to evaluate the relationship of serum uric acid and type 2 diabetes. Begg's regression test,  $P < 0.5$ .

published. The results of this meta-analysis indicated that each 1 mg/dl increase in SUA led to a 13.1% increase in the risk of T2DM (pooled *RR*) and a 48.4% increase in the risk of T2DM (pooled *OR*). Stratified analysis by age, gender, geographical area, SUA, study design, duration of follow-up, and confounding factors further indicated that SUA was positively related with T2DM. In addition, multiple meta-regression did not show these variables influenced the correlation between SUA and T2DM.

The results of the previous meta-analysis published in 2009 suggested that SUA was positively associated with the development of T2DM.<sup>8</sup> Several limitations of that meta-analysis have been discussed in the Introduction section of this manuscript. Given that those limitations might influence the accuracy of results, the methods in this study were thus improved. First, to decrease the bias due to the combination of *RRs* and *ORs*, here, the Meta-Analysis was conducted for *RRs* and *ORs* separately. The estimates for men and women from each study were synthesized by a weighting method and further combined afterwards. The heterogeneity of the *RR* among studies decreased from 68.4% to 51.9% and of the *OR* from 81.6% to 27.7%, which should provide a more reliable summary *RR*. We also have contacted the corresponding authors of each article for complementary information about the *RR* adjusted for FBG and 2h-PBG, as well as drugs affecting SUA concentration and other confounding factors. Despite few responses, more research should be conducted to sufficiently assess the relationship with the help of the authors of the articles included in this study.

Elevated SUA predicts T2DM not only among the young but also the elderly,<sup>18</sup> especially the pre-menopausal and post-menopausal women.<sup>20</sup> Costa et al.<sup>21</sup> described a positive association between SUA and the development of T2DM in 2002, but did not provide *RRs* or data to calculate such an association and thus, this article was not included in our meta-analysis. Metabolic risk factors, especially elevated SUA, are independent predictors of diabetes and impaired glucose tolerance (IGT) in Mauritian normoglycemic subjects over 5 years of follow-up.<sup>19</sup> However, this study provided the risk of diabetes and IGT together and thus it was not included in our meta-analysis either.<sup>22</sup> Even though a positive relationship between SUA and T2DM in these studies was presented, there is conflicting evidence on epidemiology and on biology, presented as follows.

It has been reported that the progression of T2DM frequently occurs with aging and MS factors and vice-



versa.<sup>9</sup> As a type of MS, the occurrence of SUA could also be paralleled by the development of T2DM. Thus, the possibility of a correlation rather than causation between SUA and T2DM should not be excluded. As Cook et al<sup>23</sup> reported, up to 8.0 mmol/L, a positive relationship was observed between serum glucose status and SUA concentrations whereas lower SUA levels were observed at higher levels of glucose. Therefore, an inverse V-shaped relationship should also be considered. In addition, lowering SUA concentration could prevent nephropathy in T2DM.<sup>24–26</sup> However, the effect of lowering SUA on the prevention and treatment of T2DM is still unknown.

Biologically, as a systemic marker of oxidative status, SUA is strongly linked to insulin resistance (a pathogenic mechanism of T2DM) by inhibiting the production of nitric oxide<sup>27</sup> or increasing the expression of C-reactive protein.<sup>28</sup> Such practice would activate platelet adhesiveness,<sup>29,30</sup> and induces endothelial dysfunction,<sup>31</sup> which blocks insulin-stimulated glucose uptake. On the contrary, other studies have reported that lowering SUA concentration might not be an effective strategy for restoring endothelial function<sup>32,33</sup> and might not lower the risk of development of T2DM. Additionally, Pfister et al<sup>34</sup> stated that SUA is not responsible for the development of T2DM and reported limited expectations that uric-acid-lowering drugs will be effective in the prevention of T2DM.

The underlying mechanism of T2DM included insulin resistance, hyperinsulinemia, and a variety of metabolic abnormalities, which also might increase SUA concentration. Hyperinsulinemia caused by insulin resistance is inversely related to 24 h urinary UA clearance<sup>35,36</sup>; insulin resistance can lead to an increase in SUA concentration by both reducing renal UA secretion by renal proximal tubular UA reabsorption enhancement in humans due to an active transport mechanism closely linked to the tubular reabsorption of sodium<sup>37–41</sup> and accumulating substrates for UA production.<sup>42</sup> Furthermore, two studies showed that homeostasis model assessment (HOMA) insulin resistance (HOMA-IR) increased as the concentration of SUA elevated at baseline. Chien et al<sup>43</sup> reported HOMA-IR was 1.48, 1.63, 1.77, 1.93, and 2.16 from the lowest to the highest quintile of SUA. Whereas Wang et al<sup>17</sup> reported HOMA-IR was 0.9, 0.9, 1.3, and 1.8 from the lowest to the highest quintile of SUA ( $P < 0.001$ ). Therefore, a correlation between SUA and T2DM should be considered.

Because of the conflicting results listed above, further quality assessment should be arranged. First, besides obesity, being female and elderly have been

mentioned to be major risk factors for the development of prediabetes and T2DM,<sup>44–46</sup> and all important confounding factors should be adjusted for including parental history of DM, physical activity, age, gender, BMI, drinking, and smoking, and especially FBG/PBG. Unfortunately, none of the included studies adjusted adequately for all of these factors. Second, several anti-hypertensive drugs including losartan and hydrochlorothiazide can increase SUA concentration. Hypertension patients with a higher SUA concentration who are taking these drugs should be excluded. There was only one included study<sup>47</sup> that adjusted for diuretic drugs and age, gender, BMI, and also estimated glomerular filtration rate. On the contrary, adjustment for blood pressure (BP) in 6 articles<sup>20,48–52</sup> has a risk of over-adjustment. Therefore, whether SUA is an innocent bystander or a cause for T2DM needs further exploration.

Although 4 studies<sup>19,20,51,53</sup> demonstrated that the association between SUA and DM was heterogeneous for men and women, the pooled analysis showed that the increased risk was similar for men and women. Further investigation into the probable different correlation of SUA and T2DM should be conducted between men and women instead of adjustment.

The main limitation of the present study is the statistical publication bias, because each publication step was inevitably affected by the factors of publication year, editors, authors, and the results found. According to the results of the meta-regression classified by the publication year, the reported relationship between SUA and T2DM was significantly different at each time. Studies with positive results are more likely to be accepted. The possibility that studies with negative results did not have the opportunity to be published should also be considered.

Next, the *RR* calculation for per 1 mg/dl increase in SUA to quantify the dose-response relationship between the baseline SUA level and incidence of T2DM may have overestimated the magnitude of any publication bias.<sup>8</sup>

In conclusion, the results of this meta-analysis indicate that SUA is independently associated with development of T2DM, both in men and women, in the elderly and the young, in pre-menopausal and post-menopausal women. Insulin resistance increased as baseline SUA concentration increased; thus, the correlation between SUA and T2DM should be further evaluated and baseline insulin resistance status should be considered. Therefore, more evidence of the epidemic etiology, mechanisms, and especially genetics are urgently needed to further clarify whether

the relationship between SUA and the development of T2DM is causal or simply a co-occurrence. In addition, studies investigating the effect of interventions to lower SUA concentrations in T2DM are warranted.

### Conflicts of interest

None declared in the conflict of interest statement.

### Acknowledgments

This work was supported by the Science & Technology Program of Jiangsu Province (Grant No. BE2009681) and the Priority Academic Program for the Development of Jiangsu Higher Education Institutions (Public Health and Preventive Medicine), and grants to X. Wu from the National Natural Science Foundation of China (81261120566), Jiangsu Province key medical personnel project (RC2011068) and 333 projects in the fourth phase of Jiangsu Province (BRA2015389).

### Appendix A. Supplementary data

Supplementary data related to this article can be found at <http://dx.doi.org/10.1016/j.cdtm.2016.09.003>.

### References

- Whiting DR, Guariguata L, Weil C, Shaw J. IDF diabetes atlas: global estimates of the prevalence of diabetes for 2011 and 2030. *Diabetes Res Clin Pract.* 2011;94:311–321.
- Carter P, Khunti K, Davies MJ. Dietary recommendations for the prevention of type 2 diabetes: what are they based on? *J Nutr Metab.* 2012;2012:847202.
- Waxler JL, O'Brien KE, Delahanty LM, et al. Genetic counseling as a tool for type 2 diabetes prevention: a genetic counseling framework for common polygenetic disorders. *J Genet Couns.* 2012;21:684–691.
- Bjorge T, Lukanova A, Tretli S, et al. Metabolic risk factors and ovarian cancer in the metabolic syndrome and cancer project. *Int J Epidemiol.* 2011;40:1667–1677.
- Morrell JS, Lofgren IE, Burke JD, Reilly RA. Metabolic syndrome, obesity, and related risk factors among college men and women. *J Am Coll Health.* 2012;60:82–89.
- Ding D, Chong S, Jalaludin B, Comino E, Bauman AE. Risk factors of incident type 2-diabetes mellitus over a 3-year follow-up: results from a large Australian sample. *Diabetes Res Clin Pract.* 2015;108:306–315.
- Lam DW, LeRoith D. The worldwide diabetes epidemic. *Curr Opin Endocrinol Diabetes Obes.* 2012;19:93–96.
- Kodama S, Saito K, Yachi Y, et al. Association between serum uric acid and development of type 2 diabetes. *Diabetes Care.* 2009;32:1737–1742.
- Goncalves JP, Oliveira A, Severo M, Santos AC, Lopes C. Cross-sectional and longitudinal associations between serum uric acid and metabolic syndrome. *Endocrine.* 2012;41:450–457.
- Chen D, Zhang H, Gao Y, et al. Cross-sectional and longitudinal associations between serum uric acid and metabolic syndrome: results from Fangchenggang area male health and examination survey in China. *Clin Chim Acta.* 2015;446:226–230.
- Berlin JA, Longnecker MP, Greenland S. Meta-analysis of epidemiologic dose-response data. *Epidemiology.* 1993;4:218–228.
- Jiang Y, Ben Q, Shen H, Lu W, Zhang Y, Zhu J. Diabetes mellitus and incidence and mortality of colorectal cancer: a systematic review and meta-analysis of cohort studies. *Eur J Epidemiol.* 2011;26:863–876.
- Whitehead A, Whitehead J. A general parametric approach to the meta-analysis of randomized clinical trials. *Stat Med.* 1991;10:1665–1677.
- DerSimonian R, Laird N. Meta-analysis in clinical trials. *Control Clin Trials.* 1986;7:177–188.
- DerSimonian R, Laird N. Meta-analysis in clinical trials revisited. *Contemp Clin Trials.* 2015;45:139–145.
- Egger M, Davey SG, Schneider M, Minder C. Bias in meta-analysis detected by a simple, graphical test. *BMJ.* 1997;315:629–634.
- Wang T, Bi Y, Xu M, et al. Serum uric acid associates with the incidence of type 2 diabetes in a prospective cohort of middle-aged and elderly Chinese. *Endocrine.* 2011;40:109–116.
- Bennett M, Pandya BJ, Krishnan E, et al. Hyperuricemia as an early marker for type 2 diabetes among young adults. *Arthritis Rheum-U.S.* 2009;60:2033.
- Nan H, Qiao Q, Soderberg S, et al. Serum uric acid and incident diabetes in Mauritian Indian and Creole populations. *Diabetes Res Clin Pract.* 2008;80:321–327.
- Lin KC, Tsai ST, Lin HY, Chou P. Different progressions of hyperglycemia and diabetes among hyperuricemic men and women in the Kinmen study. *J Rheumatol.* 2004;31:1159–1165.
- Costa A, Iguale I, Bedini J, Quinto L, Conget I. Uric acid concentration in subjects at risk of type 2 diabetes mellitus: relationship to components of the metabolic syndrome. *Metabolism.* 2002;51:372–375.
- Boyko EJ, de Courten M, Zimmet PZ, Chitson P, Tuomilehto J, Alberti KG. Features of the metabolic syndrome predict higher risk of diabetes and impaired glucose tolerance: a prospective study in Mauritius. *Diabetes Care.* 2000;23:1242–1248.
- Cook DG, Shaper AG, Thelle DS, Whitehead TP. Serum uric acid, serum glucose and diabetes: relationships in a population study. *Postgrad Med J.* 1986;62:1001–1006.
- Doria A, Krolewski AS. Diabetes: lowering serum uric acid levels to prevent kidney failure. *Nat Rev Nephrol.* 2011;7:495–496.
- Kosugi T, Nakayama T, Heinig M, et al. Effect of lowering uric acid on renal disease in the type 2 diabetic db/db mice. *Am J Physiol Renal Physiol.* 2009;297:F481–F488.
- Maahs DM, Caramori L, Cherney DZ, et al. Uric acid lowering to prevent kidney function loss in diabetes: the preventing early renal function loss (PERL) allopurinol study. *Curr Diab Rep.* 2013;13:550–559.
- Khosla UM, Zharikov S, Finch JL, et al. Hyperuricemia induces endothelial dysfunction. *Kidney Int.* 2005;67:1739–1742.
- Kang DH, Park SK, Lee IK, Johnson RJ. Uric acid-induced C-reactive protein expression: implication on cell proliferation and

- nitric oxide production of human vascular cells. *J Am Soc Nephrol*. 2005;16:3553–3562.
29. Alderman M, Redfern JS. [Serum uric acid – a cardiovascular risk factor?]. *Ther Umsch*. 2004;61:547–552 [in German].
  30. Gagliardi AC, Miname MH, Santos RD. Uric acid: a marker of increased cardiovascular risk. *Atherosclerosis*. 2009;202:11–17.
  31. Hong Q, Qi K, Feng Z, et al. Hyperuricemia induces endothelial dysfunction via mitochondrial Na<sup>+</sup>/Ca<sup>2+</sup> exchanger-mediated mitochondrial calcium overload. *Cell Calcium*. 2012;51:402–410.
  32. Waring WS, McKnight JA, Webb DJ, Maxwell SR. Lowering serum urate does not improve endothelial function in patients with type 2 diabetes. *Diabetologia*. 2007;50:2572–2579.
  33. Wun YT, Chan CS, Lui CS. Hyperuricaemia in type 2 diabetes mellitus. *Diabetes Nutr Metab*. 1999;12:286–291.
  34. Pfister R, Barnes D, Luben R, et al. No evidence for a causal link between uric acid and type 2 diabetes: a Mendelian randomisation approach. *Diabetologia*. 2011;54:2561–2569.
  35. Facchini F, Chen YD, Hollenbeck CB, Reaven GM. Relationship between resistance to insulin-mediated glucose uptake, urinary uric acid clearance, and plasma uric acid concentration. *JAMA*. 1991;266:3008–3011.
  36. de Oliveira EP, Burini RC. High plasma uric acid concentration: causes and consequences. *Diabetol Metab Syndr*. 2012;4:12.
  37. Muscelli E, Natali A, Bianchi S, et al. Effect of insulin on renal sodium and uric acid handling in essential hypertension. *Am J Hypertens*. 1996;9:746–752.
  38. Quinones GA, Natali A, Baldi S, et al. Effect of insulin on uric acid excretion in humans. *Am J Physiol*. 1995;268:E1–E5.
  39. Cappuccio FP, Strazzullo P, Farinaro E, Trevisan M. Uric acid metabolism and tubular sodium handling. Results from a population-based study. *JAMA*. 1993;270:354–359.
  40. Perez-Ruiz F, Aniel-Quiroga MA, Herrero-Beites AM, Chinchilla SP, Erauskin GG, Merriman T. Renal clearance of uric acid is linked to insulin resistance and lower excretion of sodium in gout patients. *Rheumatol Int*. 2015;35:1519–1524.
  41. Nakamura M, Satoh N, Suzuki M, et al. Stimulatory effect of insulin on renal proximal tubule sodium transport is preserved in type 2 diabetes with nephropathy. *Biochem Biophys Res Commun*. 2015;461:154–158.
  42. Fox IH. Metabolic basis for disorders of purine nucleotide degradation. *Metabolism*. 1981;30:616–634.
  43. Chien KL, Chen MF, Hsu HC, et al. Plasma uric acid and the risk of type 2 diabetes in a Chinese community. *Clin Chem*. 2008;54:310–316.
  44. Gomez-Ambrosi J, Silva C, Galofre JC, et al. Body adiposity and type 2 diabetes: increased risk with a high body fat percentage even having a normal BMI. *Obesity (Silver Spring)*. 2011;19:1439–1444.
  45. He YH, Jiang GX, Yang Y, et al. Obesity and its associations with hypertension and type 2 diabetes among Chinese adults age 40 years and over. *Nutrition*. 2009;25:1143–1149.
  46. Nayak BS, Butcher DM, Bujhawan S, et al. Association of low serum creatinine, abnormal lipid profile, gender, age and ethnicity with type 2 diabetes mellitus in Trinidad and Tobago. *Diabetes Res Clin Pract*. 2011;91:342–347.
  47. Kramer CK, von Muhlen D, Jassal SK, Barrett-Connor E. Serum uric acid levels improve prediction of incident type 2 diabetes in individuals with impaired fasting glucose: the Rancho Bernardo Study. *Diabetes Care*. 2009;32:1272–1273.
  48. Perry IJ, Wannamethee SG, Walker MK, Thomson AG, Whincup PH, Shaper AG. Prospective study of risk factors for development of non-insulin dependent diabetes in middle aged British men. *BMJ*. 1995;310:560–564.
  49. Dehghan A, van Hoek M, Sijbrands EJ, Hofman A, Witteman JC. High serum uric acid as a novel risk factor for type 2 diabetes. *Diabetes Care*. 2008;31:361–362.
  50. Bhole V, Choi JW, Kim SW, de Vera M, Choi H. Serum uric acid levels and the risk of type 2 diabetes: a prospective study. *Am J Med*. 2010;123:957–961.
  51. Yamada T, Fukatsu M, Suzuki S, Wada T, Joh T. Elevated serum uric acid predicts impaired fasting glucose and type 2 diabetes only among Japanese women undergoing health checkups. *Diabetes Metab*. 2011;37:252–258.
  52. Wu K, Chen XP, Gao Y, Zhang X, Li LX, Wan LY. [Predictive value of serum uric acid on type 2 diabetes mellitus]. *Zhonghua Liu Xing Bing Xue Za Zhi*. 2011;32:1153–1157.
  53. Meisinger C, Thorand B, Schneider A, Stieber J, Doring A, Lowel H. Sex differences in risk factors for incident type 2 diabetes mellitus: the MONICA Augsburg cohort study. *Arch Intern Med*. 2002;162:82–89.

Edited by Wei-Zhu Liu