Title:

The Association between Serum Uric Acid and Development of Type 2 Diabetes Mellitus. A Meta-Analysis

Running title: Uric Acid and Type 2 Diabetes

Keywords: Uric acid, Type 2 diabetes, Meta-analysis

Authors

Satoru Kodama, MD, PhD, Kazumi Saito, MD, PhD, Yoko Yachi, RD, Mihoko Asumi, MS, Ayumi Sugawara, RD[1], Kumiko Totsuka, RD, Aki Saito, RD, and Hirohito Sone MD, PhD, FACP[1]

Affiliation

Department of Endocrinology and Metabolism, University of Tsukuba Mito Medical Center, Ibaraki, Japan

Correspondence:

Hirohito Sone, MD, PhD, FACP. Department of Endocrinology and Metabolism, University of Tsukuba Mito Medical Center, 3-2-7 Miya-machi, Mito, Ibaraki, Japan (310-0015)
(hsone@md.tsukuba.ac.jp)

Word Count: 2840 words (including Abstract about 247 words)

Abstract

Objective

To systematically evaluate the association between serum uric acid (SUA) level and subsequent development of type 2 diabetes (T2DM)

Research Design and Methods

We searched MEDLINE (1966 to 2009 Mar 31) and EMBASE (1980 to 2009 Mar 31) for observational cohort studies examining the association between SUA and the risk of T2DM by manual literature search. Relative risks (RRs) for each 1 mg/dl increase in SUA were pooled by using a random-effects model. The studies included were stratified into subgroups representing different study characteristics, and meta-regression analyses were performed to investigate the effect of these characteristics on the association between SUA and T2DM risk.

Results

The search yielded 11 cohort studies (42,834 participants) that reported 3305 incident cases of T2DM during follow-up periods ranging from 2.0 to 13.5 years. The pooled RR of a 1 mg/dl increase in SUA was 1.17 (95% confidence interval (CI) 1.09–1.25). Study results were consistently significant (i.e. greater than 1) across characteristics of participants and study design. Publication bias was both visually and statistically suggested (*P*=0.03 for Egger's test, 0.06). Adjustment for publication bias attenuated the pooled RR per mg/dl increase in SUA (RR, 1.11; 95% CI, 1.03-1.20), but the association remained statistically significant (*P*=0.009).

Conclusions

The current meta-analysis suggests that SUA level is positively associated with the development of T2DM regardless of various study characteristics. Further research should attempt to determine whether it is effective to utilize SUA level as a predictor of T2DM for its primary prevention.

Introduction

Identifying risk factors for the development of type 2 diabetes (T2DM) is essential for its early screening and prevention. Serum uric acid (SUA) level has been suggested to be associated with risk of T2DM. Biologically, uric acid (UA) plays an important role in worsening of insulin resistance (IR) in animal models by inhibiting the bioavailability of nitric oxide, which is essential for insulin-stimulated glucose uptake (1). However, hyperinsulinemia as a consequence of IR causes an increase in SUA concentration by both reducing renal UA secretion (2) and accumulating substrates for UA production (3). Therefore, it remains controversial whether SUA is independently associated with the development of T2DM. The aim of our meta-analysis was to summarize the association between SUA level and risk of T2DM derived from previously published cohort studies and to examine the effect of study characteristics on this association.

Research Design and Methods

Search Strategy

The meta-analysis was fundamentally conducted according to the checklist of the Meta-analysis of Observational Studies in Epidemiology (4). We performed a systematic literature search of MEDLINE (1966 to 2009 Mar 31) and EMBASE (1980 to 2009 Mar 31) for observational cohort studies examining the association between SUA level and risk of T2DM. The keywords were related to SUA (combined exploded version of the Medical Subject Headings [MeSH] [*uric acid*] and the following text words [*hyperuricemia* OR (*Acid* AND *Uric*) OR *Trioxopurine* OR *Trihydroxypurine* OR *Urate* OR *gout* OR *gouts*]) and T2DM (combined unexploded version of MeSH [*diabetes mellitus* or *diabetes mellitus*, *type 2*] and the following

text words [*Hyperglycemias* OR *Hyperglycemia* OR (*Diabetes Mellitus* AND (*Type 2* OR *Type II* OR *Ketosis Resistant* OR *Ketosis-Resistant* OR *Maturity Onset* OR *Maturity-Onset* OR *Noninsulin Dependent* OR *Non Insulin Dependent* OR *Non-Insulin-Dependent* OR *Slow Onset* OR *Slow-Onset* OR *Stable* OR *Adult Onset* OR *Adult-Onset*)) OR *MODY* OR *NIDDM*]).

Included papers had to meet the following criteria: (1) prospective or historical cohort study; (2) inclusion of T2DM as a specified outcome; (3) baseline assessment of SUA level; and (4) inclusion of data on relative risk (RR), which is generally expressed as the odds ratio in a historical cohort study or the risk ratio in a prospective cohort study, and its corresponding 95% confidence intervals (CIs) (or data to calculate them) for T2DM associated with SUA level. When two or more studies were conducted using the same subjects, the study that included the most recently updated data was selected.

Data Abstraction

The data that we abstracted included the first author's name, year of publication, country of origin, cohort design (i.e., prospective or historical cohort), methods for ascertaining diabetes, mean follow-up duration, mean or midpoint of participants' age, proportion of men, baseline SUA level, number of participants and events, and adjusted variables. Odds and risk ratios were combined as indicators of RR, based on the assumption that the odds ratio is an approximation of the risk ratio; this assumption has some limitations, however, especially when the outcome of interest is common (5).

If a study provided several RRs, such as unadjusted and adjusted RRs, the most completely adjusted RR was used. Each RR was transformed to its natural logarithm (log RR), and its corresponding 95% confidence interval (95% CI) or *P* value was used to calculate the standard

error (SE) for each log RR. Two of our investigators independently reviewed each published paper and extracted the relevant information. Any disagreement was resolved by consensus.

Data synthesis

To quantify the dose-response relationship between the baseline SUA level and risk of T2DM, we calculated the RR for each 1 mg/dl increase in SUA in each study. For studies that analyzed SUA level not as a continuous but as a categorical variable (i.e., studies where subjects were categorized based on SUA level and RRs for the development of T2DM according to SUA level were reported), we used the method for trend estimation supported by Berlin et al. and Orsini et al. (6, 7). This method is particularly useful when the full data are not available. It enables us to correct for covariance between risk estimates from the same study and to estimate the corrected linear trend using generalized least squares if data on the adjusted RR and the number of participants (or person-time) and cases for each category are provided.

When the mean SUA level was not reported, the range's midpoint in each category was used, except for the lowest and highest category, for which the mean SUA level was estimated by assuming normality of SUA distribution, which is the same method as used in a previously published meta-analysis (8). Each log RR was pooled by using a random-effects model (9). The overall RR and its 95% CI could be calculated by exponentiation of the pooled log RR. We assessed heterogeneity of RRs across studies using both I-squared and Q statistics (10).

Sensitivity analyses

The studies included were stratified by key factors related to cohort design (i.e., prospective or historical cohort) and other study properties related to study quality and participant

characteristics that were identified a priori. Study quality was assessed according to the method of ascertainment of diabetes (whether blood measurements, or reports by participants or physicians or both), mean follow-up duration (>8 years or ≤8 years) and inclusion of adjustment for the following potentially important confounding variables: alcohol intake (Yes or No) and metabolic profile (sufficient or insufficient). We regarded the adjustment for metabolic variables as sufficient when the risk estimate was adjusted for more than three factors among obesity, hypertension (or systolic blood pressure), fasting plasma glucose, HDL-cholesterol and triglyceride. We identified country of origin (Asian or Western countries), mean age (>50 years or ≤50 years), sex (whether men only, women only, or both men and women) and mean SUA level (>5.5 mg/dl or ≤5.5 mg/dl) as possible participant characteristics. We calculated the pooled RR within the strata of each study characteristic, and meta-regression analyses were conducted to assess the effects of these study characteristics on the T2DM risk and incremental increase in SUA level.

The possibility of publication bias was assessed by the Begg's and the Egger's tests (11, 12), and visual inspection of a funnel plot. We also performed the Duval and Tweedie "trim and fill" procedure (13) to further assess the possible effect of publication bias in our meta-analysis. This method considers the possibility of hypothetical "missing" studies that might exist, imputes their RRs, and recalculates a pooled RR that incorporates the hypothetical missing studies as though they actually existed. Data were analyzed by using STATA software version 10 (STATA Corp., College Station, TX, USA). $P<0.05$ was considered as statistically significant except for the test of publication bias, in which the level of significance is $P<0.10$ (14).

Results

Literature Search

Of 1258 citation retrieved by the search strategy, 1225 citations were excluded after a first screening based on titles and abstracts, leaving 33 articles for full-text review. Manual searching of the reference lists of these articles identified 8 additional articles. Of the total of 41 articles for full-text review, 30 articles were excluded for the following reasons: 1) case-control studies (6 studies); 2) clinical trials (3 studies); 3) risk estimates of the association of T2DM with SUA level were not reported (9 studies); 4) pre-specified outcome did not include T2DM (5 studies); sufficient data to estimate the RR of T2DM and its corresponding SE per incremental increase in UA were not provided (4 studies); 5) data reported were updated by more recent studies (3 studies). Eleven studies (15-25) met the inclusion criteria. Three studies investigated men and women separately. Finally, 14 cohorts involving a total of 42,834 participants and 3305 incident cases were included in our analyses.

Study Characteristics

Characteristics of the eleven included studies are shown in **Table 1**. Three studies (17, 19, 23) were prospective cohort and 8 (15, 16, 18, 20-22, 24, 25) were historical cohort. The selected studies were published between 1975 and 2009, and the number of subjects per study ranged from 250 to 8688. Mean SUA level of subjects ranged from 4.0 to 8.0 mg/dl and mean age ranged from 41 to 63 years except for one study (23), in which data on mean age (over 55 years) were not available. Four studies (15-17, 19) included men only, and seven (18-21, 23-25) included both women and men. Six studies (15, 18, 19, 21, 22, 24) were conducted in Asian countries and five (16, 17, 20, 23, 25) in Western countries. Mean follow-up duration ranged

from 2.0 to 13.5 years.

Regarding methods for ascertaining diabetes, four studies (18, 19, 22, 25) used blood measurements only, two (17, 20) used reports by participants and/or physicians only, and five (15, 16, 21, 23, 24) used both. Risk measures were adjusted for alcohol intake in 5 studies (17, 19, 20, 22, 24), and the adjustment for sufficient metabolic variables was sufficient in 5 studies (18, 21-24). A few risk estimates were adjusted for smoking status (3 studies) (17, 19, 20), family history of diabetes (4 studies) (16, 20, 22, 24) and fasting insulin concentration (3 studies) (18, 21, 24) . Only two studies (21, 24) considered the effect of serum creatinine, and one study considered the effect of diuretic use (25). None of risk measurements was adjusted for other drugs that influence SUA level such as alloprinol.

Overall and stratified analyses

Figure 1 shows a forest plot with RRs and 95% CIs and pooled estimates for the reduction in risk of T2DM for each mg/dl increase in SUA. The pooled crude RR (95% CI) was 1.17 (1.19-1.25). There was evidence of statistical heterogeneity of RRs across studies (Q statistic, 50.4; I-squared statistic, 74.2%; P<0.001).

Table 2 shows findings of the stratified and meta-regression analysis to explore the effects of study characteristics. An increased risk of T2DM associated with an incremental increase in SUA was consistently found within all strata of each study characteristic (i.e., all pooled RRs were greater than 1). There were no significant differences in the pooled risk estimates between cohort design (pooled RR [95% CI] of 1.22 [1.10-1.36] for historical cohort and 1.10 [1.01-1.20] for prospective cohort, P=0.36). The influence of participant characteristics on the study results was not significant. Adjustment for alcohol intake attenuated the association

between SUA and T2DM risk (*P*=0.02), whereas the effect of sufficient adjustment for metabolic variables was not significant (*P*=0.46).

Test of publication bias

Visual inspection of the funnel plot revealed asymmetry (see online **Appendix A**). This raises the possibility of publication bias, which was statistically supported by the Egger's test (*P*=0.06). We decided to adjust for this publication bias using the trim and fill method (13). According to this method, it was suggested that there were 3 hypothetical negative unpublished cohorts that distorted the symmetry of the funnel plot. When these cohorts were incorporated to produce a hypothetically symmetrical funnel plot, the association between SUA and T2DM was modestly attenuated (RR, 1.10, 95% CI, 1.03-1.20) but remained statistically significant (*P*=0.009).

Conclusions

Our meta-analysis is the first to summarize the quantitative relationship between SUA levels and risk of T2DM, indicating that each 1 mg/dl increase in SUA resulted in a 17% increase in the risk of T2DM. **Table 3** compares other risk factors of T2DM, established from meta-analysis or systematic review (26-29), with SUA. Interestingly, the effect of a 1-mg/dl increment in SUA has been found to be comparable to a 1-kg/m^2 increment in BMI.

Pathologically and epidemiologically, it has been indicated that elevated SUA concentration is correlated with lifestyle factors (high alcohol intake (30) in particular) and various metabolic profiles (especially high values of BMI, blood pressure, FPG and triglycerides,

and low HDL cholesterol values (31, 32), which are typically considered to be diagnostic criteria for metabolic syndrome (MetS) (33)), leading to a drastic increase in the risk of T2DM (31, 34). Therefore, it is possible to establish whether the observed positive association between SUA level and risk of T2DM is non-causal. Our sensitivity analysis indicated that a significant association was observed if analyses were limited to studies that included adjustment for alcohol intake or sufficient metabolic confounders (i.e., more than three metabolic confounders among BMI, fasting plasma glucose, hypertension (or systolic blood pressure), HDL cholesterol and triglycerides), although the adjustment weakened the association. Therefore, the results of this analysis strongly suggest that SUA is an independent predictor of the development of T2DM. Therefore, these findings suggest that there are both non-causal and causal associations between SUA level and the risk of T2DM.

The limitations of this meta-analysis must be considered. First, the overall effect estimated by the current analysis might be inaccurate due to the statistically significant publication bias. According to the results of the compensatory trim and fill method, the overall RR of T2DM for each 1 mg/dl SUA increase should be scaled downward by 0.07 to adjust for publication bias. However, this method may overestimate the magnitude of any publication bias (35). Moreover, this method did not change the statistical significance of the association between SUA level and development of T2DM. Therefore, the effect of adjustment for publication bias was probably modest. Second, the odds and risk ratios were combined as indicators of RR. The odds ratio overestimates the risk ratio, especially when the outcome of interest is common. It is possible that this method could distort the overall and stratified analyses within cohort design. The overestimation is, however, of little practical importance and can be ignored as long as the pooled risk ratio is near to 1 and the total incidence is relatively rare (less than 10%), as they were in our

meta-analysis (5). Third, in the sensitivity analysis, the statistical power might be insufficient to explain the source of the large study heterogeneity because of the small number of data units within strata. For example, there was a substantially larger increase in the risk of elevated SUA for development of T2DM observed in Western countries (RR, 1.27) as compared with Asian countries (RR, 1.09) and for women (RR, 1.28) as compared with men (RR, 1.09). Although these differences were statistically insignificant, we cannot exclude the possibility of the influence of race or gender on the association between SUA level and T2DM. This issue might be solved by a patient-level meta-analysis, which would be beyond the current meta-analysis. Fourth, there were few studies that included a consideration of significant confounders influencing SUA level, such as serum creatinine and drugs (e.g., diuretic agents or alloprinol). These confounders could contribute to modification of the association between SUA and risk of T2DM. Fifth, we thought it was too early to determine whether there is a cut-off level in SUA to increase or reduce the risk of development of T2DM because of both the limited number of studies that used SUA level as a categorical variable and provided RR data for each category and the variation in methods of how SUA levels in each subject were categorized. Therefore, we cannot rule out the possibility that SUA level has a threshold effect on the risk of T2DM rather than a dose-response effect.

In conclusion, our meta-analysis suggests that SUA level is independently associated with the development of T2DM. It is possible that these findings are the first step to utilizing SUA, which has been suggested to be a risk factor for T2 DM, in primary care medical practice. Further research should attempt to investigate whether SUA would be useful for predicting T2DM with respect to the prevention of T2DM; for example, studies should aim to specify the population for

which the SUA level is especially important and to determine the SUA threshold for increased risk of T2DM.

Acknowledgment: H.S. and S. K. are recipients of a Grant-in-Aid for Scientific Research and Postdoctoral Research Fellowship respectively, both from the Japan Society for the Promotion of Science (JSPS), Japan Cardiovascular Research Foundation and Ministry of Health Labor and Welfare, Japan. These research organizations providing funding support did not have any role in the design or conduct of the study.

References

1. Khosla UM, Zharikov S, Finch JL, Nakagawa T, Roncal C, Mu W, Krotova K, Block ER, Prabhakar S, Johnson RJ: Hyperuricemia induces endothelial dysfunction. *Kidney Int* 67:1739-1742, 2005

2. Quinones Galvan A, Natali A, Baldi S, Frascerra S, Sanna G, Ciociaro D, Ferrannini E: Effect of insulin on uric acid excretion in humans. *Am J Physiol* 268:E1-5, 1995

3. Fox IH: Metabolic basis for disorders of purine nucleotide degradation. *Metabolism* 30:616-634, 1981

4. Stroup DF, Berlin JA, Morton SC, Olkin I, Williamson GD, Rennie D, Moher D, Becker BJ, Sipe TA, Thacker SB: Meta-analysis of observational studies in epidemiology: a proposal for reporting. Meta-analysis Of Observational Studies in Epidemiology (MOOSE) group. *JAMA* 283:2008-2012, 2000

5. Zhang J, Yu KF: What's the relative risk? A method of correcting the odds ratio in cohort studies of common outcomes. *JAMA* 280:1690-1691, 1998

6. Berlin JA, Longnecker MP, Greenland S: Meta-analysis of epidemiologic dose-response data. *Epidemiology* 4:218-228, 1993

7. Orsini N, Bellocco R, Greenland S: Generalized least squares for trend estimation of summarized dose-response data. *Stata Journal* 6:40-57, 2006

8. Danesh J, Collins R, Appleby P, Peto R: Association of fibrinogen, C-reactive protein, albumin, or leukocyte count with coronary heart disease: meta-analyses of prospective studies. *JAMA* 279:1477-1482, 1998

9. DerSimonian R, Laird N: Meta-analysis in clinical trials. *Control Clin Trials* 7:177-188, 1986

10. Higgins JP, Thompson SG: Quantifying heterogeneity in a meta-analysis. *Stat Med* 21:1539-1558, 2002

11. Begg CB, Mazumdar M: Operating characteristics of a rank correlation test for publication bias. *Biometrics* 50:1088-1101, 1994

12. Egger M, Davey Smith G, Schneider M, Minder C: Bias in meta-analysis detected by a simple, graphical test. *BMJ* 315:629-634, 1997

13. Duval S, Tweedie R: Trim and fill: A simple funnel-plot-based method of testing and adjusting for publication bias in meta-analysis. *Biometrics* 56:455-463, 2000

14. Sterne JA, Gavaghan D, Egger M: Publication and related bias in meta-analysis: power of statistical tests and prevalence in the literature. *J Clin Epidemiol* 53:1119-1129, 2000

15. Medalie JH, Papier CM, Goldbourt U, Herman JB: Major factors in the development of diabetes mellitus in 10,000 men. *Arch Intern Med* 135:811-817, 1975

16. Ohlson LO, Larsson B, Bjorntorp P, Eriksson H, Svardsudd K, Welin L, Tibblin G, Wilhelmsen L: Risk factors for type 2 (non-insulin-dependent) diabetes mellitus. Thirteen and one-half years of follow-up of the participants in a study of Swedish men born in 1913. *Diabetologia* 31:798-805, 1988

17. 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* 310:560-564, 1995

18. Chou P, Li CL, Wu GS, Tsai ST: Progression to type 2 diabetes among high-risk groups in Kin-Chen, Kinmen. Exploring the natural history of type 2 diabetes. *Diabetes Care* 21:1183-1187, 1998

19. Taniguchi Y, Hayashi T, Tsumura K, Endo G, Fujii S, Okada K: Serum uric acid and the risk for hypertension and Type 2 diabetes in Japanese men: The Osaka Health Survey. *J Hypertens* 19:1209-1215, 2001

20. 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* 162:82-89, 2002

21. 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* 31:1159-1165, 2004

22. Chien KL, Chen MF, Hsu HC, Chang WT, Su TC, Lee YT, Hu FB: Plasma uric acid and the risk of type 2 diabetes in a Chinese community. *Clin Chem* 54:310-316, 2008

23. 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* 31:361-362, 2008

24. Nan H, Qiao Q, Soderberg S, Pitkaniemi J, Zimmet P, Shaw J, Alberti G, Uusitalo U, Pauvaday V, Chitson P, Tuomilehto J: Serum uric acid and incident diabetes in Mauritian Indian and Creole populations. *Diabetes Res Clin Pract* 80:321-327, 2008

25. 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

26. Vazquez G, Duval S, Jacobs DR, Jr., Silventoinen K: Comparison of body mass index, waist circumference, and waist/hip ratio in predicting incident diabetes: a meta-analysis. *Epidemiol Rev* 29:115-128, 2007

27. Jeon CY, Lokken RP, Hu FB, van Dam RM: Physical activity of moderate intensity and risk of type 2 diabetes: a systematic review. *Diabetes Care* 30:744-752, 2007

28. Willi C, Bodenmann P, Ghali WA, Faris PD, Cornuz J: Active smoking and the risk of type 2

diabetes: a systematic review and meta-analysis. *JAMA* 298:2654-2664, 2007
29. Howard AA, Arnsten JH, Gourevitch MN: Effect of alcohol consumption on diabetes mellitus: a systematic review. *Ann Intern Med* 140:211-219, 2004
30. Liberopoulos EN, Miltiadous GA, Elisaf MS: Alcohol intake, serum uric acid concentrations, and risk of gout. *Lancet* 364:246-247; author reply 247, 2004
31. Klein BE, Klein R, Lee KE: Components of the metabolic syndrome and risk of cardiovascular disease and diabetes in Beaver Dam. *Diabetes Care* 25:1790-1794, 2002
32. Yoo TW, Sung KC, Shin HS, Kim BJ, Kim BS, Kang JH, Lee MH, Park JR, Kim H, Rhee EJ, Lee WY, Kim SW, Ryu SH, Keum DG: Relationship between serum uric acid concentration and insulin resistance and metabolic syndrome. *Circ J* 69:928-933, 2005
33. Tsouli SG, Liberopoulos EN, Mikhailidis DP, Athyros VG, Elisaf MS: Elevated serum uric acid levels in metabolic syndrome: an active component or an innocent bystander? *Metabolism* 55:1293-1301, 2006
34. Laaksonen DE, Lakka HM, Niskanen LK, Kaplan GA, Salonen JT, Lakka TA: Metabolic syndrome and development of diabetes mellitus: application and validation of recently suggested definitions of the metabolic syndrome in a prospective cohort study. *Am J Epidemiol* 156:1070-1077, 2002
35. High false positive rate for trim and fill method [article online], 2000, Available from http://bmj.bmjjournals.com/cgi/eletters/320/7249/1574#8757

Table 1 Characteristics of studies included in meta-analysis

First Author	Year	Cohort designation	Population	Follow-up (years)	*Diabetes ascertainment	Baseline SUA (mg/dl)	Age (years)	%Men	**No. participants	No. cases	Cohort Design
Medalie (15)	1975	IIHDS	Israel	5.0	both	4.8	49	100	8688	344	H
Ohlson (16)	1988	SMB	Sweden	13.5	both	5.3	50	100	766	47	H
Perry (17)	1995	BRHS	British	12.8	report	6.0	50	100	7577	194	P
Chou (18)	1998	KS	China	2.0	measure	5.8	50	52	654	39	H
Taniguchi (19)	2001	OHS	Japan	9.5	measure	5.2	41	100	6478	639	P
Meisinger (20) [men]	2002	MONIKA	Germany	7.6	report	5.7	52	100	3052	128	H
[women]						4.0	51	0	3114	85	H
Lin (21) [men]	2004	KS	China	7.0	both	8.0	49	100	293	27	H
[women]						7.1	55	0	161	21	H
Chien (22)	2008	CSCCC	China	9.0	measure	5.6	54	43	2690	548	H
Dehghan (23)	2008	RS	Neitherland	10.1	both	5.4	over 55	NA	4536	462	P
Nan (24) [men]	2008	MNCDS	Mauritius	8.2	both	6.6	41	100	1941	337	H
[women]						5.0	42	0	2318	379	H
Kraemer(25)	2009	UC	USA	13.0	measure	5.7	63	41	566	55	H

Abbreviations: IIHDS, Israel Ischemic Heart Disease Study; SMB, The Study of Men Born in 1913; BRHS, British Regional Heart Study; KS, The Kinmen Study; OHS, The Osaka Health Study; MONIKA, MONIKA-Augsberg Cohort Study; JAPF: Japan Arteriosclerosis Prevention Fund; CSCCC, Chin-Shan Community Cardiovascular Center;

RS, The Rotterdam Study; MNCDS, Mauritius Non-Communicable Diseases Surveys; UC; University of California; SUA, serum uric acid; SD, standard deviation; %Men, percentage of men; H, historical cohort; P, prospective cohort; NA: not available

* "measure" means using blood measurements, "report" means using reports by participants or physicians, and "both" means using both blood measurements and reports by participants or physicians

** Number of participants included in the analysis in each study (not necessarily the number of participants at the beginning of each study)

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

Study Characteristics	No. of cohorts	*Pooled relative risk [95% CI]	*P* value of meta-regression†
study design			
Historical cohort	10	1.22 [1.10; 1.36]	0.55
Prospective cohort	4	1.10 [1.01; 1.20]	
Indicators of participants characteristics			
Country			
Asia	8	1.09 [1.04; 1.21]	0.10
Western	6	1.27 [1.12; 1.44]	
Mean age			
≤50	8	1.12 [1.04; 1.19]	0.14
>50	6	1.26 [1.11; 1.44]	
Sex			
men only	7	1.09 [1.02; 1.16]	0.09
women only	4	1.28 [1.08; 1.51]	0.31
both men and women	3	1.40 [0.98; 2.00]	
Mean SUA level			
≤5.5 mg/dl	6	1.18 [1.15; 1.32]	0.98
>5.5 mg/dl	8	1.16 [1.05; 1.28]	
Indicators of study quality			
Study adjustment for alcohol intake			
No	9	1.27 [1.13; 1.43]	0.02
yes	5	1.07 [1.02; 1.12]	
Metabolic confounders**			
insufficient	8	1.21 [1.09; 1.34]	0.46
sufficient	6	1.11 [1.02; 1.21]	
Follow-up duration			
≤8 years	6	1.25 [1.03; 1.51]	0.37
>8 years	8	1.13 [1.05; 1.20]	
Diabetes ascertainment			
blood measurements only	4	1.18 [1.02; 1.37]	0.81
report only	3	1.24 [0.96; 1.59]	0.64
both	7	1.14 [1.06; 1.23]	

* Pooled relative risks of type 2 diabetes for each 1 mg/dl increase in serum uric acid (SUA) within the strata of each study characteristics are indicated

Abbreviation: CI, confidence interval

** If the relative risks were adjusted for more than 3 confounders (among body mass index, fasting plasma glucose, hypertension (or systolic blood pressure), HDL cholesterol and triglycerides), they were regarded as "sufficient"; otherwise, they were regarded as "insufficient".

† Represents the test for significance of the effect across strata

Table 3 Comparison of other risk factors of type 2 diabetes mellitus with incremental increase in serum uric acid (SUA)

Risk factor	Relative risk	How much of mg/dl in SUA is the relative risk comparable to?
Obesity (26)		
body mass index (per kg/m^2)	1.16	1.0
waist circumference (per cm)	1.06	0.4
High alcohol intake (29)		
>3 drinks/day vs. 1 to 3 drinks/day	1.43	2.3
Physical inactivity (27)		
the lowest vs. the highest level of moderate-intensity physical activity*	**1.20	1.2
Smoking (28)		
heavy smokers (≥20 cigarettes/day) vs. non-smokers	1.61	3.1
light smokers (<20 cigarettes/day) vs. non-smokers	1.29	1.7
former smoker vs. non-smokers	1.23	1.4

* Typically, no walking vs. ≥2.5 hours/week brisk walking

** This relative risk is adjusted for body mass index.

Figure Legends

Figure 1. Overall relative risk (RR) (with corresponding 95% confidence intervals (CIs) in parentheses) for risk of type 2 diabetes for each mg/dl increase in serum uric acid. The area of each square is proportional to study weight. Diamond indicates overall RR; horizontal lines indicate 95%CIs.