



Serum uric acid as a risk factor of all-cause mortality and cardiovascular events among type 2 diabetes population: Meta-analysis of correlational evidence



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ABSTRACT

Aims: To explore the association between serum uric acid (SUA) level and the risk of cardiovascular complications and all-cause mortality rates among individuals with type 2 diabetes.

Methods: Web of Science and PubMed database were searched for studies reported associations between SUA level and cardiovascular complications and all-cause mortality among individuals with type 2 diabetes. Hazard ratios (HRs) were independently extracted by two investigators and synthesized through meta-analysis across selected studies.

Results: 6 (n = 11,750 patients), 4 (n = 3044 patients) and 2 studies (n = 7792 patients) were identified reporting associations between SUA level and all-cause mortality, coronary heart disease (CHD) and stroke respectively. HR for all-cause mortality, CHD, and stroke per 59 μmol/l increase was 1.06 (95% CI: 1.03, 1.09), 1.09 (95% CI: 0.94, 1.26) and 1.19 (95% CI: 1.08, 1.31), respectively.

Conclusions: Overall, the SUA level was associated with a higher risk of all-cause mortality and stroke. We found no significant association between SUA level and CHD among type 2 diabetes population.

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1. Introduction

The pandemic of diabetes is a threat to health across the world, with an estimation of 422 million adults (prevalence: 8.5%) living with

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diabetes in 2014, compared to 108 million (prevalence: 4.7%) in 1980.¹ According to a recent study conducted by Guariguata and colleagues,² this escalating trend would result in a diabetes population of 592 million by 2035.

Diabetes complications are known to be major causes of reduced quality of life, disability, and escalated economic burden. They also represent the leading cause of mortality in developed countries.^{3,4} Since a large proportion of diabetes patients will die of or experience cardiovascular disease (CVD), a particular emphasis has been placed on CVD risk factors management among diabetes patients by major health organizations including the World Health Organization, the Centers for Disease Control and Prevention, and the American Diabetes Association.^{5–7}

In the last decade, serum uric acid (SUA), a degradation metabolite of purines, has been widely identified as a possible risk factor for CVD.^{8,9} Recently, a direct association between elevated SUA level and progression speed of type 2 diabetes has been identified by multiple studies.^{10–12} Individuals with diabetes were often accompanied by a higher level of serum uric acid, compared with non-diabetes population.¹³ Considering the well-established association between diabetes and CVD risks, it became less clear if the traditional believed association between SUA and CVD is direct, or an indirect association, mediated by diabetes.

The evidence on the association between SUA and CVD exclusively among diabetes population was poorly synthesized. For example, studies have found a higher SUA level associated with increased morbidity of CVDs such as stroke and coronary heart disease (CHD) among diabetes population.^{14,15} Additionally, several cohort studies concluded that there was a statistically significant association between SUA and all-cause mortality among type 2 diabetic population.¹⁶ However, these findings were disputed by some other evidence. Recent studies found that SUA has no significant association with CVDs and all-cause mortality among diabetes population.^{17,18} These controversial findings might be attributable to the heterogeneity of sampling designs across studies.

Elevated SUA is a metabolic syndrome, which can disturb glucose uptake and intensify insulin resistance.¹⁹ Additionally, SUA could also inhibit nitric oxide bioavailability and induce endothelial dysfunction. This could lead to several cardiovascular complications and even CVD related death.^{20,21} To understand whether SUA level is associated with the escalation of cardiovascular events and all-cause mortality among type 2 diabetic population is important for secondary and tertiary prevention of cardiovascular outcomes.

Two meta-analysis have been conducted to evaluate the associations between elevated SUA and other complications among the population with type 2 diabetes.^{22,23} One systematic review study was conducted recently and identified major potential predictors including uric acid for chronic kidney diseases among patients with diabetes.²⁴ However, no published study of meta-analysis was conducted to investigate the association between SUA and the prognosis of specific cardiovascular complications and all-cause mortality among type 2 diabetes. Therefore, this study aims to conduct a meta-analysis to ascertain the effect of SUA on the progression of these complications and all-cause mortality among subjects with diabetes by integrating currently published studies.

2. Material and methods

This article followed the Meta-analysis Of Observational Studies in Epidemiology (MOOSE) Guidelines to report systematic reviews and conduct meta-analysis for observational studies.²⁵ MOOSE checklist was in Supplemental Table S1.

2.1. Data sources and searches

A systematic literature search was conducted using electronic databases the Web of Science and PubMed database from January 1980 to May 2019. Searching strategies in this literature review were done

using various combinations of terms related to “diabetes”, “serum uric acid”, “cardiovascular disease”, “all-cause mortality/death”, and “stroke”. Detailed information was showed in Supplemental materials (Supplemental Table S2). Studies were limited in English publications and human researches. Handling abstracts and unpublished studies were not included. References were checked manually for full text reviewed articles (only the included studies) to identify potentially eligible articles. There was no attempt to contact authors during the study period.

2.2. Study selection

The inclusion criteria in this meta-analysis were (1): targeted Type 2 diabetes population (2); included one or more outcomes (i.e. CVD, stroke, coronary heart/artery disease, and all-cause mortality) or a sufficiently close proxy (3); controlled for correlated cardio-metabolic variables, which may be confounding, such as blood pressure, weight, lipids, etc. (4); conducted a test of SUA concentration at baseline (5); reported adjusted Odds Ratio (OR) or Relative Risk/Hazard Ratio (RR/HR) (6); articles were written in English. The exclusion criteria were (1) studies included patients under 18 years old (2); studies included pregnant woman (3); reviews, commentary articles, and editorials (4); separately defined SUA level for male and female (5); sample limited to people with diabetes and a specific disease. If data of two or more articles were derived from the same study, we only included the most recent one in this analysis.

2.3. Data extraction

After removing all duplicated articles from two databases, potential titles and abstracts were screened manually. Full texts of potentially relevant studies were then retrieved and assessed to determine eligibility for inclusion according to established criteria detailed above. Data extraction for each study included first author's name, publication year, sample size, confounding variables, adjusted ORs and HRs (95% CI) for the association between SUA level and outcomes, numbers of target population and events in each SUA group if the article reported SUA levels in quantiles.

One investigator extracted data using a predefined extraction form and extraction checked by a different investigator. Disagreements were discussed in a group for consensus. Each study in this meta-analysis was assessed using Quality Assessment Tools from the National Institute of Health which includes a series of criteria to rate quality.²⁶

2.4. Data analysis

A data imputation process has been conducted to replace missing values with logical approximations based on other given data in the same study. Any uncertainties or discrepancies between the two reviewers were resolved through consensus or consultation with another reviewer. All the extracted ORs were transformed into HR, using the formula recommended by Grant²⁷:

$$HR \approx \frac{OR}{1-p+p \times OR}$$

(p denotes the incidence of the outcome in the non-exposed group).

The unit of HRs was standardized to a percentage per 59 $\mu\text{mol/l}$ SUA increase in each study to quantify the dose-response relationship between the baseline SUA level and the development of diabetic complications and all-cause mortality. Since the measurement to describe SUA were different across studies, all mg/dl or mmol/l uric acid concentrations were converted to units $\mu\text{mol/l}$, using conversion rate (1 mg/dl = 59.48 $\mu\text{mol/l}$, 1 mmol/l = 1000 $\mu\text{mol/l}$). For studies that reported the HRs by quantiles of SUA instead of unit SUA change, we transformed HRs of categories to HR of unit SUA increase for each study by using

similar method used in several studies about dose-response relationship based on data in each study of categories of SUA levels, number of events and participants in each group, adjusted HR and its corresponding 95% CI in each group.^{11,28,29} Heterogeneity was assessed using I^2 statistics, a value over 50% was considered a measure of severe heterogeneity.³⁰ If the test for heterogeneity was not significant, summary estimates of HRs or effect sizes and 95% CIs for the estimates were derived using a fixed-effects model; otherwise, a random-effects model was used.³¹ The meta-analysis was performed using Stata 15.1 software package.

Publication bias was not assessed because the number of trials (<10) was inadequate to properly examine a funnel plot or to use more advanced regression-based assessments.³²

3. Results

3.1. Literature search

The process of systematic literature screening is provided in Fig. 1. The initial literature search produced 1163 eligible articles after excluding duplications retrieved from PubMed and Web of Science databases for the years 1980–2019. After that, a title review was conducted, and 178 articles met the inclusion/exclusion criteria. Besides, a round of abstract review and a full-text review were conducted, from which 66 studies were excluded due to an irrelevant study population (not type 2 diabetes), and another set of 43 studies were excluded due to a lack of any designated outcomes. Twelve studies were identified as appropriate for data abstraction and synthesized. Among those studies, 6 of them reported the association between SUA level and all-cause mortality.^{16,17,33–36} Four evaluated whether SUA level independently predicts coronary heart/artery disease among type 2 diabetes population.^{14,18,37,38} Lehto et al.¹⁵ and Wang et al.³⁹ both found that elevated SUA level was associated with escalated risk of stroke in patients with type 2 diabetes.

3.2. Characteristics of the included studies

Table 1 summarizes the baseline patient characteristics and the design of studies on the association between SUA and corresponding outcomes. All 12 studies were published between 1998 and 2019; and they

all adjusted the covariates (e.g., hypertension, smoking status, etc.). For all-cause mortality, data from six cohort studies involving a total of 11,750 individuals with diabetes were pooled. The mean age ranged from 59.3 to 68.8 years old. Among these six studies, one was from Korea, one was from the United States, and the other four were from Italy. The four studies identified to examine coronary heart disease (CHD) outcomes related to SUA levels yielded a combined population of 3044 individuals with diabetes. One study was from Italy, and the other three were from Asia. The mean age ranged from 57.68 to 69 years old. The mean SUA level of subjects ranged from 307 to 398.55 $\mu\text{mol/l}$. For stroke, the two studies analyzed yielded an aggregate of 7792 patients. One group was from Finland, and the other was from China.

3.3. Result of meta-analysis

Three forest plots with HRs (95% CIs) and pooled estimated increased risks of diabetes complications and all-cause mortality with respect to per 59 $\mu\text{mol/l}$ increase in SUA are presented in Fig. 2, Fig. 3 and Fig. 4. As shown in Fig. 3, the random-effects model was applied because there was significant heterogeneity for the association between SUA level and risk of stroke.

Fig. 2 presents the HR of all-cause mortality per 59 $\mu\text{mol/l}$ increase in SUA level. Six studies were included ($n = 11,750$ patients), and the overall HR was estimated to be 1.06 (95% CI: 1.03–1.09). Fig. 3 presents the HR of CHD events per 59 $\mu\text{mol/l}$ increase in SUA level. Four studies were included ($n = 3044$ patients), and the overall HR was estimated to be 1.09 (95% CI: 0.94–1.26) from a random-effects model because of the statistically significant heterogeneity ($I^2 = 89.6\%$). We did not find obviously different results across different study designs in these four studies. Fig. 4 presents the HR of stroke per 59 $\mu\text{mol/l}$ increase in SUA level. Two studies were included ($n = 7792$ patients), and the overall HR was estimated to be 1.19 (95% CI: 1.08, 1.31). Although there was significant heterogeneity ($I^2 = 54.4\%$), only two studies were included in analysis and the number is too small to estimate the between-studies variance with any precision; therefore, the fixed-effects model was used as the only viable option in this case.⁴⁰ Since a low number of studies was reported for each outcome, no subgroup analyses were conducted.

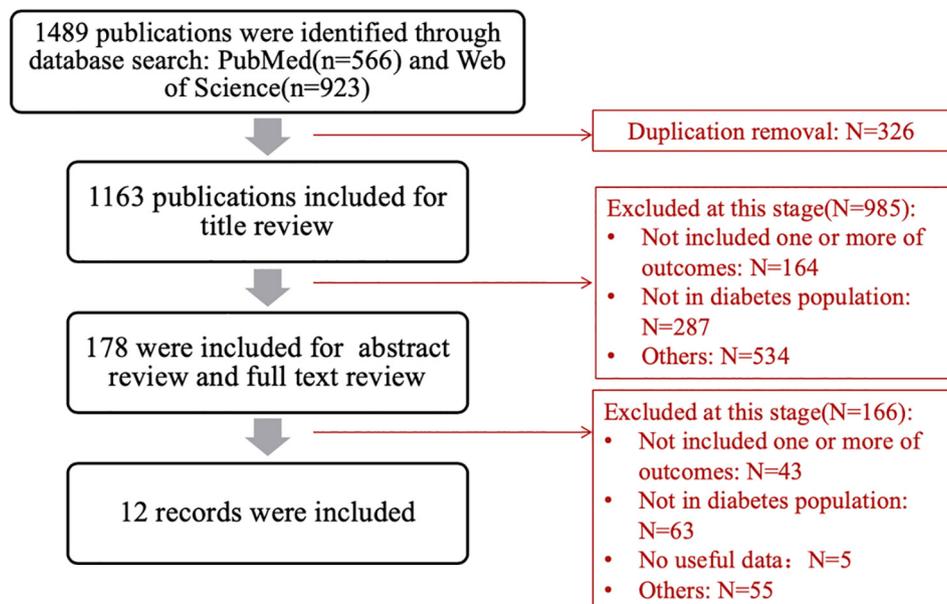


Fig. 1. Literature Screening Flow Chart.

Table 1
Summary of included studies.

Author	Year	Type	Population	Outcome	Mean age (years)/ Age range	Mean SUA/SUA range ($\mu\text{mol/l}$)	Adjustment	Number of patients	Quality score	Calculated HR/59 $\mu\text{mol/l}$ SUA
Jee ³³	2004	Cohort	Korean	All-cause Mortality	–	–	Yes	3200	11	1.09
Ioachimescu ¹⁶	2007	Cohort	American	All-cause Mortality	59.3 \pm 11.5	371.7 \pm 106.2	Yes	535	9	1.21
Zoppini ³⁴	2009	Cohort	Italian	All-cause Mortality	Tertile 1: 67 \pm 10 Tertile 2: 67 \pm 10 Tertile 3: 68 \pm 9	Tertile 1: 207 \pm 36 Tertile 2: 280 \pm 26 Tertile 3: 388 \pm 91	Yes	2726	12	1.04
Ong ¹⁷	2010	Cohort	Italian	All-cause Mortality	64.1 \pm 11.3	350 \pm 100	Yes	1268	11	1.03
Panero ³⁵	2012	Cohort	Italian	All-cause Mortality	68.8 \pm 10.6	321.79 \pm 99.33	Yes	1509	10	1.07
Lamacchia ³⁶	2017	Cohort	Italian	All-cause Mortality	Tertile 1: 60.5 \pm 9.3 Tertile 2: 61.4 \pm 9.4 Tertile 3: 62.8 \pm 9.6	Tertile 1: \leq 273.63 Tertile 2: 273.63–345.01 Tertile 3: >345.01	Yes	2512	9	1.04
Ito ³⁷	2011	Cross-Section	Japanese	CHD	64 \pm 12	307 \pm 81	Yes	1213	7	0.88
Chuengsamarn ¹⁴	2014	Cross-Section	Thai	CHD	57.8 \pm 13.4	392.60 \pm 124.92	Yes	608	7	1.21
Verdoia ¹⁸	2014	Case-Control	Italian	CHD	69 \pm 9.9	398.55 \pm 339.06	Yes	1173	7	0.99
Jayashankar ³⁸	2016	Case-Control	Indian	CHD	57.68 \pm 6.04	313.49 \pm 79.71	Yes	50	5	1.21
Lehto ¹⁵	1998	Cohort	Finnish	Stroke	45–64	–	Yes	1017	7	1.35
Wang ³⁹	2017	Cross-Section	Chinese	Stroke	52.23 \pm 6.07	299.79 \pm 88.80	Yes	6775	10	1.14

CHD: coronary heart disease; SUA: serum uric acid; HR: hazard ratio.

4. Discussion

Although previous studies have investigated the relationship between SUA and CVD or all-cause mortality risk in certain disease populations or the general population, to our best knowledge, this meta-analysis is the first to summarize the available evidence on the relationship between SUA level and the development of two major cardiovascular complications and all-cause mortality in individuals with type 2 diabetes. The majority of the included studies had adequate sample

sizes, follow-up lengths (cohort studies), and confounder adjustments. This systematic review provides a meta-analysis of 12 relevant studies involving a total of >22,000 individuals. The main findings suggested a significantly positive correlation with each 59 $\mu\text{mol/l}$ increase in SUA leading to a 6% increase in the risk of all-cause mortality and a 19% increase in the risk of stroke among individuals with a diagnosis of type 2 diabetes.

Within the population analyzed for this review, the association between increasing SUA levels and CHD did not reach statistical

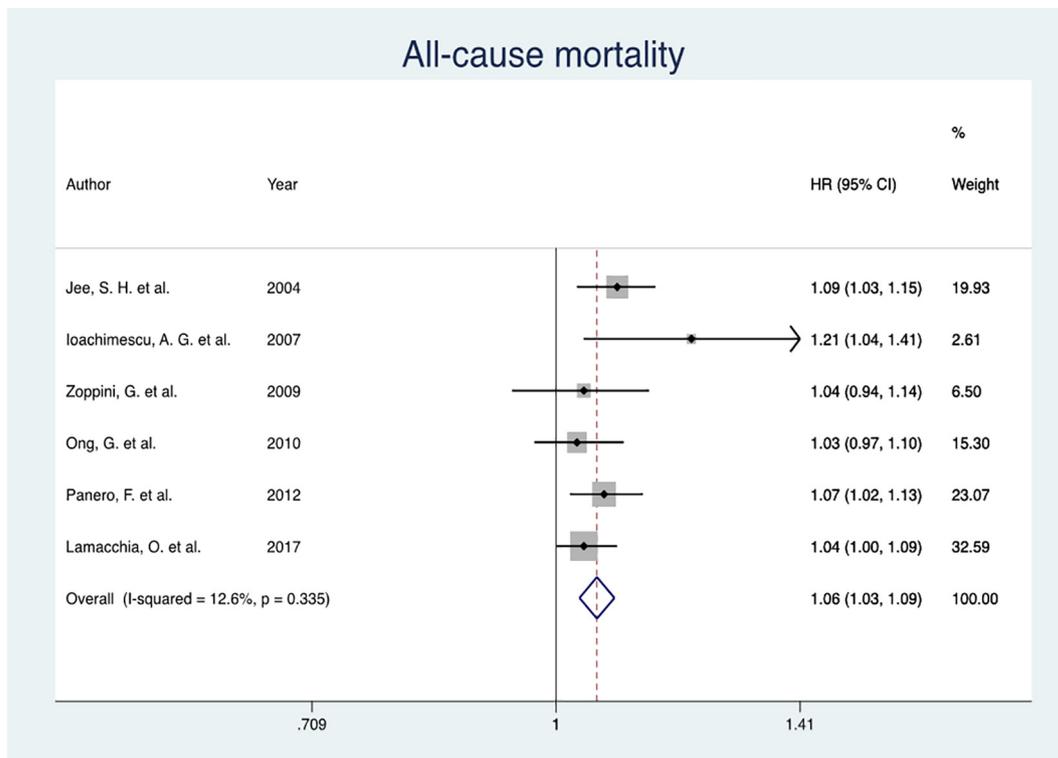


Fig. 2. Meta-analysis result of all-cause mortality studies.

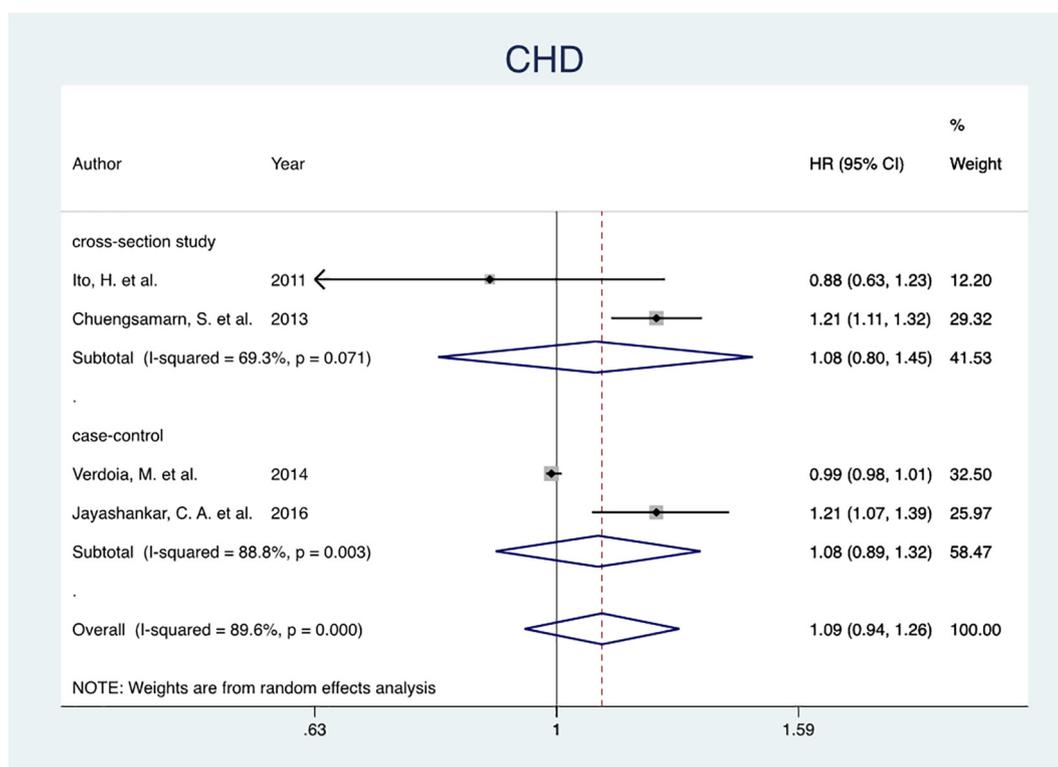


Fig. 3. Meta-analysis result of coronary heart disease (CHD) studies.

significance. While our results suggested that SUA may not be a major risk factor for CHD in this specific type 2 diabetes cohort, the findings from other groups indicated that SUA does play an important role in CHD risk in other populations. For example, one meta-analysis found that in patients with coronary heart disease, each 1 mg/ml SUA rise increased all-cause mortality by 20%.⁴¹ Additionally, another systematic

review found that hyperuricemia was associated with increased risk of CHD (adjusted RR 1.13; 95% CI 1.05–1.21) in the general population.⁴²

This analysis only included studies with type 2 diabetes population. There were some studies excluded because they included a sample population with both type 2 diabetes and one more disease. For example, one study concluded elevated SUA levels are

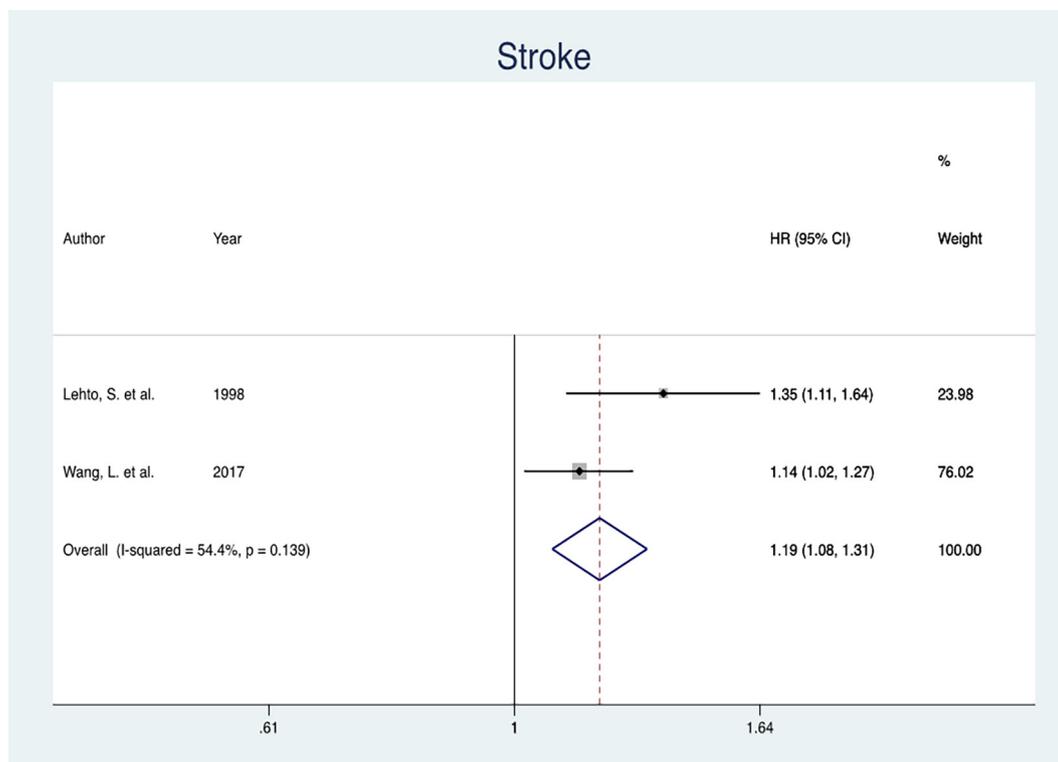


Fig. 4. Meta-analysis result of stroke studies.

significantly associated with 1-year all-cause mortality among the population with both type 2 diabetes and coronary artery disease.⁴³ We excluded these studies because our study aims to evaluate the effect of SUA level on the progression of CVD and all-cause mortality among the general diabetes population not the population with both diabetes and a specific disease. Therefore, results from this meta-analysis could be applied to diabetic population no matter whether they have other certain diseases.

The following limitations must be considered while interpreting the findings. First, our estimation on the HRs between SUA level and CHD, stroke, and mortality may suffer from publication bias. In other words, if positive findings are more likely to be published in this particular research topic, we may have overestimated the actual HRs in the general population. Second, we cannot determine whether the role of SUA on the risk of complications in type 2 diabetes population is a dose-response or a threshold effect.²⁸ Third, significant heterogeneity was observed, thus, random-effects models might provide studies with a small sample size a higher weight to decrease the influence of heterogeneity. Although we extracted adjusted associations from selected studies, not all studies control the same confounding factors which include cardio-metabolic variables, physical activities, diabetes-related variables, unhealthy behaviors, drug treatment, and et al. The variation of covariates across studies could also influence our estimation on pooled associations. Fourth, the limited number of articles included in the meta-analysis may limit the generalizability of the combined HRs. Especially, only two studies related stroke were included and they had different study designs. Future studies could include more studies and conduct meta-analysis separately for different study designs. We may not have identified some studies that were unpublished or published in other languages.

In this study, we only stressed the association between SUA level and macrovascular diseases. However, there were rising studies showed an association between high SUA level and microvascular diseases, such as retinopathy, nephropathy, and neuropathy.^{22,44,45} Previous meta-analysis has already concluded that elevated SUA is an independent risk factor for vascular complications and mortality in diabetes patients.²⁸ However, it synthesized studies of several vascular diseases of both macrovascular and microvascular diseases but not for a certain type of vascular disease.

5. Conclusions

This study emphasizes the importance of managing SUA levels to prevent all-cause mortality and stroke among type 2 diabetes population. SUA levels were found to be associated with a higher risk of all-cause mortality and stroke. However, among the identified type 2 diabetes population, there is no significant association between SUA level and CHD. It also raises concerns for a potentially neglected damage caused by a certain class of anti-diabetic drugs which has an impact on increasing SUA level. More work should be done to further elucidate the relationship between serum uric acid levels and anti-diabetic medications since this association could have global clinical implications in the management of diabetes patients.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.jdiacomp.2019.07.006>.

References

- World Health Organization. *Global report on diabetes*. 2016. (doi:ISBN 978 92 4 156525 7).
- Guariguata L, Whiting DR, Hambleton I, Beagley J, Linnenkamp U, Shaw JE. Global estimates of diabetes prevalence for 2013 and projections for 2035. *Diabetes Res Clin Pract* 2014 <https://doi.org/10.1016/j.diabres.2013.11.002>.
- Van Dieren S, Beulens JWJ, Van Der Schouw YT, Grobbee DE, Neal B. The global burden of diabetes and its complications: an emerging pandemic. *Eur J Cardiovasc Prev Rehabil* 2010 <https://doi.org/10.1097/01.hjr.0000368191.86614.5a>.
- Young BA, Lin E, Von Korff M, et al. Diabetes complications severity index and risk of mortality, hospitalization, and healthcare utilization. *Am J Manag Care* 2008;14(1):15-23.
- World Health Organization. *Prevention of cardiovascular disease guidelines for assessment and management of cardiovascular risk WHO library cataloguing-in-publication data*. 2007.
- Centers for Disease Control and Prevention. *National diabetes fact sheet: national estimates and general information on diabetes and prediabetes in the United States*. 2011. (Centers Dis Control Prev US Dep Heal Hum Serv. 2011. doi:Centers for Disease Control and Prevention. National diabetes fact sheet: national estimates and general information on diabetes and prediabetes in the United States, 2011. Atlanta, GA: U.S. Department of Health and Human Services, Centers for Disease Con).
10. Cardiovascular disease and risk management: standards of medical care in diabetes 2019. *Diabetes Care* 2019 <https://doi.org/10.2337/dc19S010>.
- Hayden MR, Tyagi SC. Uric acid: a new look at an old risk marker for cardiovascular disease, metabolic syndrome, and type 2 diabetes mellitus: the urate redox shuttle. *Nutr Metab* 2004 <https://doi.org/10.1186/1743-7075-1-10>.
- Verdecchia P, Schillaci G, Reboldi GP, Santusamio F, Porcellati C, Brunetti P. Relation between serum uric acid and risk of cardiovascular disease in essential hypertension: the PIUMA study. *Hypertension* 2000 <https://doi.org/10.1161/01.HYP.36.6.1072>.
- 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 <https://doi.org/10.1371/journal.pone.0056864>.
- Xu Y-L, Xu K-F, Bai J-L, et al. Elevation of serum uric acid and incidence of type 2 diabetes: a systematic review and meta-analysis. *Chronic Dis Transl Med* 2016 <https://doi.org/10.1016/j.cdtm.2016.09.003>.
- Kodama S, Saito K, Yachi Y, et al. Association between serum uric acid and development of type 2 diabetes. *Diabetes Care* 2009 <https://doi.org/10.2337/dc09-0288>.
- Hussain A, Latiwesh OB, Ali F, Younis MYG, Alammar JA. Effects of body mass index, glycemic control, and hypoglycemic drugs on serum uric acid levels in type 2 diabetic patients. *Cureus* 2018 <https://doi.org/10.7759/cureus.3158>.
- Chuengsamarn S, Rattanamongkolgul S, Jirawatnotai S. Association between serum uric acid level and microalbuminuria to chronic vascular complications in Thai patients with type 2 diabetes. *J Diabetes Complications* 2014;28(2):124-9.
- Lehto S, Niskanen L, Rönnemaa T, Laakso M. Serum uric acid is a strong predictor of stroke in patients with non-insulin-dependent diabetes mellitus. *Stroke* 1998 <https://doi.org/10.1161/01.STR.29.3.635>.
- Ioachimescu AG, Brennan DM, Hoar BM, Kashyap SR, Hoogwerf BJ. Serum uric acid, mortality and glucose control in patients with type 2 diabetes mellitus: a PreCIS database study. *Diabet Med* 2007 <https://doi.org/10.1111/j.1464-5491.2007.02302.x>.
- Ong G, Davis WA, Davis TME. Serum uric acid does not predict cardiovascular or all-cause mortality in type 2 diabetes: the Fremantle Diabetes Study. *Diabetologia* 2010 <https://doi.org/10.1007/s00125-010-1735-7>.
- Verdoia M, Barbieri L, Schaffer A, et al. Impact of diabetes on uric acid and its relationship with the extent of coronary artery disease and platelet aggregation: a single-centre cohort study. *Metabolism* 2014 <https://doi.org/10.1016/j.metabol.2014.01.010>.
- Tassone EJ, Cimellaro A, Peticone M, et al. Uric acid impairs insulin signaling by promoting ENPP1 binding to insulin receptor in human umbilical vein endothelial cells. *Front Endocrinol (Lausanne)* 2018 <https://doi.org/10.3389/fendo.2018.00098>.
- Puddu P, Puddu GM, Cravero E, Vizioli L, Muscari A. The relationships among hyperuricemia, endothelial dysfunction, and cardiovascular diseases: molecular mechanisms and clinical implications. *J Cardiol* 2012 <https://doi.org/10.1016/j.jicc.2012.01.013>.
- Khosla UM, Zharikov S, Finch JL, et al. Hyperuricemia induces endothelial dysfunction. *Kidney Int* 2005 <https://doi.org/10.1111/j.1523-1755.2005.00273.x>.
- Yu S, Chen Y, Hou X, et al. Serum uric acid levels and diabetic peripheral neuropathy in type 2 diabetes: a systematic review and meta-analysis. *Mol Neurobiol* 2016 <https://doi.org/10.1007/s12035-014-9075-0>.
- Du L, Ma J, Zhang X. Higher serum uric acid may contribute to cerebral infarction in patients with type 2 diabetes mellitus: a meta-analysis. *J Mol Neurosci* 2017 <https://doi.org/10.1007/s12031-016-0848-y>.
- Norris KC, Smoyer KE, Rolland C, Van Der Vaart J, Grubb EB. Albuminuria, serum creatinine, and estimated glomerular filtration rate as predictors of cardio-renal outcomes in patients with type 2 diabetes mellitus and kidney disease: a systematic literature review. *BMC Nephrol* 2018 <https://doi.org/10.1186/s12882-018-0821-9>.
- Stroup DF, Berlin JA, Morton SC, et al. Meta-analysis of observational studies in epidemiology: a proposal for reporting. *JAMA* 2000 <https://doi.org/10.1001/jama.283.15.2008>.
- Services UD of H and H. *Quality assessment tool for observational cohort and cross-sectional studies*. Bethesda, MD: Natl Institutes Heal Dep Heal Hum Serv.. 2014.
- Grant RL. Converting an odds ratio to a range of plausible relative risks for better communication of research findings. *BMJ* 2014 <https://doi.org/10.1136/bmj.f7450>.
- Xu Y, Zhu J, Gao L, et al. Hyperuricemia as an independent predictor of vascular complications and mortality in type 2 diabetes patients: a meta-analysis. *PLoS One* 2013 <https://doi.org/10.1371/journal.pone.0078206>.

29. Berlin JA, Longnecker MP, Greenland S. Meta-analysis of epidemiologic dose-response data. *Epidemiology* 1993<https://doi.org/10.1097/00001648-199305000-00005>.
30. Higgins JPT, Thompson SG. Quantifying heterogeneity in a meta-analysis. *Stat Med* 2002<https://doi.org/10.1002/sim.1186>.
31. DerSimonian R, Laird N. Meta-analysis in clinical trials revisited. *Contemp Clin Trials* 2015<https://doi.org/10.1016/j.cct.2015.09.002>.
32. Cochrane. 10.4.3.1 Recommendations on testing for funnel plot asymmetry. *Database* 2008<https://doi.org/10.1002/9780470712184.fmatter>.
33. Jee SH, Lee SYL, Kim MT. Serum uric acid and risk of death from cancer, cardiovascular disease or all causes in men. *Eur J Cardiovasc Prev Rehabil* 2014;11:185-91<https://doi.org/10.1097/01.hjr.0000130222.50258.22>.
34. Zoppini G, Targher G, Negri C, et al. Elevated serum uric acid concentrations independently predict cardiovascular mortality in type 2 diabetic patients. *Diabetes Care* 2009<https://doi.org/10.2337/dc09-0625>.
35. Panero F, Gruden G, Perotto M, et al. Uric acid is not an independent predictor of cardiovascular mortality in type 2 diabetes: a population-based study. *Atherosclerosis* 2012<https://doi.org/10.1016/j.atherosclerosis.2011.11.042>.
36. Lamacchia O, Fontana A, Pacilli A, et al. On the non-linear association between serum uric acid levels and all-cause mortality rate in patients with type 2 diabetes mellitus. *Atherosclerosis* 2017<https://doi.org/10.1016/j.atherosclerosis.2017.03.008>.
37. Ito H, Abe M, Mifune M, et al. Hyperuricemia is independently associated with coronary heart disease and renal dysfunction in patients with type 2 diabetes mellitus. *PLoS One* 2011<https://doi.org/10.1371/journal.pone.0027817>.
38. Jayashankar C, Andrews H, Vijayasarathi, et al. Serum uric acid and low-density lipoprotein cholesterol levels are independent predictors of coronary artery disease in Asian Indian patients with type 2 diabetes mellitus. *J Nat Sci Biol Med* 2016<https://doi.org/10.4103/0976-9668.184703>.
39. Wang L, Hu W, Miao D, et al. Relationship between serum uric acid and ischemic stroke in a large type 2 diabetes population in China: a cross-sectional study. *J Neurol Sci* 2017<https://doi.org/10.1016/j.jns.2017.03.023>.
40. Borenstein M, Hedges LV, Higgins JPT, Rothstein HR. A basic introduction to fixed-effect and random-effects models for meta-analysis. *Res Synth Methods* 2010<https://doi.org/10.1002/jrsm.12>.
41. Wang R, Song Y, Yan Y, Ding Z. Elevated serum uric acid and risk of cardiovascular or all-cause mortality in people with suspected or definite coronary artery disease: a meta-analysis. *Atherosclerosis* 2016<https://doi.org/10.1016/j.atherosclerosis.2016.10.006>.
42. Li M, Hu X, Fan Y, et al. Hyperuricemia and the risk for coronary heart disease morbidity and mortality a systematic review and dose-response meta-analysis. *Sci Rep* 2016<https://doi.org/10.1038/srep19520>.
43. Ndrepepa G, Braun S, King L, et al. Prognostic value of uric acid in patients with type 2 diabetes mellitus and coronary artery disease. *Clin Sci* 2012<https://doi.org/10.1042/cs20120336>.
44. Liang CC, Lin PC, Lee MY, et al. Association of serum uric acid concentration with diabetic retinopathy and albuminuria in Taiwanese patients with type 2 diabetes mellitus. *Int J Mol Sci* 2016<https://doi.org/10.3390/ijms17081248>.
45. Lytvyn Y, Perkins BA, Cherney DZI. Uric acid as a biomarker and a therapeutic target in diabetes. *Can J Diabetes* 2015<https://doi.org/10.1016/j.cjcd.2014.10.013>.