Serum Uric Acid Levels and Risk of Metabolic Syndrome: A Dose-Response Meta-Analysis of Prospective Studies

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Context: An excess circulating uric acid level, even within the normal range, is always comorbid with metabolic syndrome (MS), several of its components, and nonalcoholic fatty liver disease (NAFLD), which was regarded as hepatic manifestation of MS; however, these associations remain controversial.

Objective: This study aimed to quantitatively assess the relationship between the serum uric acid (SUA) levels and the MS/NAFLD risk.

Design: We searched for related prospective cohort studies including SUA as an exposure and MS/NAFLD as a result in MEDLINE (PubMed) and EMBASE databases up to January 31, 2015 and July 28, 2015, respectively. Pooled relative risks (RRs) and corresponding 95% confidence intervals (CIs) were extracted. A random-effects model was used to evaluate dose-response relationships.

Main Outcomes: On the basis of 11 studies (54 970 participants and 8719 MS cases), a combined RR of 1.72 (95% CI, 1.45–2.03; $P < .0001$) was observed for the highest SUA level category compared with the lowest SUA level category. Furthermore, based on nine studies (51 249 participants and 8265 MS cases), dose-response analysis suggested that each 1 mg/dL SUA increment was roughly linearly associated with the MS risk (RR, 1.30; 95% CI, 1.22–1.38; $P < .0001$). Beyond that, SUA level increased NAFLD risk (RR, 1.46; 95% CI, 1.31–1.63). Each 1 mg/dL SUA level increment led to 21% increase in the NAFLD risk.

Conclusions: This meta-analysis suggests that higher SUA levels led to an increased risk of MS regardless of the study characteristics, and were consistent with a linear dose-response relationship. In addition, SUA was also a causal factor for the NAFLD risk. **(*J Clin Endocrinol Metab* 100: 4198–4207, 2015)**

Metabolic syndrome (MS) is a cluster of interrelated components that is characterized as having three or more of the following conditions: central adiposity or higher waist circumference, high values of triglycerides, elevated blood pressure, impaired fasting glucose, and decreased high-density lipoprotein (HDL) cholesterol (1). MS is receiving greater attention from public health decision makers and physicians due to its association with an elevated incidence of future type 2 diabetes and other serious cardiovascular diseases. Determining the risk factors that increase the incidence of MS is urgently required for the early screening and prevention of MS.

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Abbreviations: CI, confidence interval; HDL, high-density lipoprotein; IR, insulin resistance; LTPA, leisure time physical activity; MOOSE, Meta-analysis of Observational Studies in Epidemiology; MS, metabolic syndrome; NADPH, nicotinamide adenine dinucleotide phosphate; NAFLD, nonalcoholic fatty liver disease; PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-analyses; RR, relative risk; SUA, serum uric acid; UA, uric acid.

An excess level of circulating uric acid (UA), the end product of the purine nucleosides degradation of and hepatic glycolysis, is always comorbid with type 2 diabetes (2, 3), as well as MS and several of its components, among children, adolescents, and adults. Recently, DeBosch et al (4) found new animal evidence suggesting that hyperuricemia per se disturbs normal metabolism and might lead to MS directly rather than indirectly via the enterocyte urate transporter Glut9 (encoded by the *SLC2A9* gene). Facchini et al (5) also demonstrated that the pathophysiological mechanism responsible for this association is insulin resistance (IR).

Recently, Carbone et al (6) have described the results from four longitudinal and 12 cross-sectional published studies (although these results could be subject to bias) regarding the association between SUA levels and the MS risk. However, the strength and the consistency of the quantitative relationship between the SUA level and MS remain unclear and inconclusive. More importantly, whether SUA independently contributes to the development of MS or is merely a byproduct of other processes that cause this disorder and whether SUA can act as a biomarker to predict the future development of MS remain controversial. So far no systematic review has been performed to evaluate the related studies to quantitatively assess the association between the SUA levels and the MS risk. This meta-analysis aimed to evaluate the strength and the shape of the quantitative association of the SUA levels with the MS risk based on prospective studies to assess the influence of study characteristics on this relationship, and to summarize the results in a systematic review. In addition, although nonalcoholic fatty liver disease (NAFLD) was regarded as a hepatic manifestation of MS (7), the relationship between SUA level and NAFLD risk still remained controversial (8–11). Therefore, the causality between SUA and NAFLD was also explored.

Materials and Methods

Data sources and searches

We complied with the Meta-analysis of Observational Studies in Epidemiology (MOOSE) (12) and the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) (13) protocols throughout the design, implementation, analysis, and reporting of our meta-analysis.

Three investigators (H.Y., C.Y., and X.L.) searched for related prospective cohort studies up to January 31, 2015/July 28, 2015 in MEDLINE (PubMed) and EMBASE databases examining the relationship between the SUA level and the MS/NAFLD risk, respectively.

Eligibility criteria

The included reports of the SUA concentrations and MS had to meet the following six criteria: 1) study of prospective cohort, 2) MS as a specific result, 3) baseline estimation of the SUA, 4) minimum follow-up duration of 1 year, 5) clear definition of MS corresponding to the incidence of MS, and 6) inclusion of data on relative risk (RR) with 95% confidence intervals (CIs) (or the minimum information necessary to calculate these values) for the association of MS with the SUA level. For every identified study, all subjects were free of MS at baseline according to MS diagnostic criteria and participated in the whole follow-up survey without missing SUA or variables used to define MS. Inclusion criteria for NAFLD were the same as MS (Supplemental Methods).

Data extraction and quality assessment

H.Y. and X.L. independently examined each eligible article and extracted the most completely adjusted RRs with 95% CIs according to a standardized data extraction process. The third investigator (C.Y.) was consulted to resolve discrepancies by consensus. We also performed a quality assessment according to the Newcastle-Ottawa criteria (14) for nonrandomized studies. Data extraction and quality assessment were described in detail in Supplemental Methods.

Statistical analysis

Multivariable-adjusted RRs and 95% CIs were used for the primary statistical analysis. The odds ratios and hazard ratios in each original study were assumed to provide accurate estimates of the risk ratios. Random-effects models introduced by DerSimonian and Laird (15) were applied for the incorporation of between-study heterogeneity and to obtain an overall RR for the highest SUA level category compared with the lowest SUA level category based on 11 studies (16–26). The same analysis was conducted with NAFLD based on three studies (8, 27, 28).

A secondary analysis was conducted to detect whether this link displays the dose-response effect if the primary analysis confirmed the significant link between the SUA level and the MS risk. To quantify the association between the SUA level and the MS risk, we estimated the RR of each 1 mg/dL SUA level increment for each study. Therefore, six studies (12 data points due to separate data for men and women) (17, 18, 21, 23, 25, 26) and three studies (three data points due to data only for men) (16, 19, 24) provided RRs for each SUA level category that were eligible for dose-response analysis using generalized least-squares trend estimation and variance-weighted least square regression model, respectively. For NAFLD, only one study provided enough information to calculate the RR of each 1 mg/dL SUA level increment. Once the dose-relationship between the SUA level and the MS risk was established, we further clarified whether this dose-response relationship was nonlinear or linear using a restricted cubic spline regression model. We first fitted the data to a fixed-effects potential nonlinearity model and then changed to a random-effects potential nonlinearity model if $P < .05$ for the goodness-of-fit/heterogeneity of the previous model. Briefly, a restricted cubic spline plot was used to reveal the potential nonlinearity between the SUA level and the MS risk, fitting a restricted cubic spline function at four points (at the fifth, 35th, 65th, and 95th percentiles), via generalized least-squares regression considering the relationship between each calculated RR for each 1 mg/dL SUA increment. In addition, we used a generalized

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linear model to test the relationship between the SUA level and the MS risk via a fixed/random-effects model. Then we combined the calculated study-specific estimates into a multivariate random-effects meta-analysis. We also calculated the *P* value for nonlinearity, linearity, and overall significance using the method of Greenland and Longnecker (29). The between-study heterogeneity was assessed using the I^2 statistic and the Cochran *Q* tests.

Stratified analyses and meta-regression were conducted considering the substantial effect of potentially significant covariates on between-study heterogeneity. Detailed information was in Supplemental Methods.

We performed the leave-one-out method for sensitivity analysis to evaluate each study and calculated a pooled estimate for the remaining studies. Sensitivity analyses were also performed with a fixed-effects model. Begg's test, Egger's test, and visual inspection of a funnel plot were used to evaluate publication bias. The potential effect of publication bias was assessed by the Duval and Tweedie (30) trim-and-fill method.

Two-sided tests were used, and $P < .05$ was regarded as statistically significant. Statistical analyses were conducted using Stata (version 12.0; StataCorp).

Results

Literature selection

Supplemental Figure 1 shows the flowchart of study selection and the literature search results. We included 11 publications that met our criteria for inclusion; all 11 studies (18 data points) could be used to compare the highest and lowest SUA level categories (16–26), and nine studies (15 data points) could be used to analyze the effect of each 1 mg/dL in the SUA level (16–19, 21, 23–26). Three studies could be used to compare the highest and lowest SUA level categories for NAFLD risk (8, 27, 28) and two studies (three data points) could be used to analyze the effect of each 1 mg/dL in the SUA level (8, 27).

Characteristics of the included studies

The 11 identified prospective studies (16–26) comprised a total of 54 970 participants and 8719 MS cases. The nine studies that provided adequate information for further dose-response analysis comprised 51 249 participants and 8265 MS cases (16–19, 21, 23–26) (Table 1). Table 1 includes all the 11 studies. The quality assessment of the identified studies showed an average score for all studies of 7.27; the score of each study was 6 or above (Supplemental Table 1). The three prospective studies comprised a total of 23 994 participants and 1022 NAFLD cases (Supplemental Table 2).

SUA levels and the risk of MS

First, the combined RR of incident MS of the highest SUA level category compared with the lowest SUA level

Table 1. Characteristics of the Identified Studies (n = 11) of Serum Uric Acid and Risk of Metabolic Syndrome

First Author	Year	Cohort Designation	Country	Diagnostic Criteria	Follow-Up, y	Age, Mean, y	Baseline SUA Level, Mean (SD), mg/dL	Men (%)	No. of Participants[a]	No. of Cases
Ryu S (16)	2007	UHS	Korea	NCEP ATP III	2.1	30–39	5.8	100	4779	708
Sui X (17)	2008	ACLS	United States	NCEP ATP III	5.7	43.7				
Men							6	100	8429	1120
Women							4.2	0	1260	44
Yang T (18)	2012	TwSHHH	China, Taiwan	UCS	5.41	41	6.2	45	3857	476
Men						41	7.14	100	1748	214
Women						41	5.42	0	2109	262
Wang JY (19)	2012	MJHSCT	China, Taiwan	IDF	2.7	12.9	6.9 (1.6)	100	613	19
Zhang Q (20)	2012	HMCSPH	China	CDS	6	54.05	6	100	2222	
Zhang ML (21)	2013	HECHD	China	IDF	3			40	7399	1190
Men						53	6.0 (1.1)	100	2957	776
Women						52	4.8 (1.0)	0	4442	749
Ferrara LA (22)	2014	SHS	United States	NCEP ATP III	4	32.7	5.2	41	1499	454
Nagahama K (23)	2014	OGHA	Japan	Japanese	4	48.7			5936	944
Men							6.4	100	3144	779
Women							4.6	0	2792	165
Lee JK (24)	2014	MHCP	Korea	IDF	5	44.6	6.00	100	14 906	2428
Oda E (25)	2014	MCCGS	Japan	NCEP ATP III	2.5			63		
Men						51.7	6.0	100	1606	177
Women						51.6	4.4	0	953	71
Babio N (26)	2015	PREDIMED	Spain	HIDF + AHLB	3.8	55–80	4.95	49	1511	753

Abbreviations: ACLS, Aerobics Center Longitudinal Study; CDS, Diabetes Branch of the Chinese Medical Association; HECHD, Health Examination Center of Heping District; HIDF+AHLB, Updated Harmonized Criteria of the International Diabetes Federation and the American Heart Association/National Heart, Lung, and Blood Institute; HMCSPH, Health Management Center of Shandong Provincial Hospital; IDF, The International Diabetes Federation criteria; MHCP, the Medical Health Check-up Program at the health promotion centre of a hospital in Seoul, Korea; MCCGS, Medical Check-up Center for general health screening (those who provided written informed consent); MJHSCT, the MJ Health Screening Center in Taiwan; NCEP ATP III, National Cholesterol Education Program Adult Treatment Panel Guideline III; OGHA, Okinawa General Health Association; PREDIMED, Prevención con DIeta MEDiterránea; SHS, The Strong Heart Study; TwSHHH, Taiwanese Survey on Prevalences of Hypertension, Hyperglycemia, and Hyperlipidemia; UCS, Unified criteria set by several major organizations (International Diabetes Federation Task Force on Epidemiology and Prevention; National Heart, Lung, and Blood Institute; American Heart Association; Word Heart Federation; International Atherosclerosis Society; and International Association for the Study of Obesity); UHS, University Hospital in Seoul, Korea.

[a] Number of participants included in the analysis in each study (not necessarily the number of participants at the beginning of each study).

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category was 1.72 (95% CI, 1.45–2.03; $P < .0001$) (Supplemental Figure 3A). Although significant heterogeneity across studies was found under the random-effects model, the primary results as such suggested a significantly positive association between the baseline SUA levels and the MS risk.

Second, we further conducted the dose-response meta-analysis to assess their correlation. Nine studies (15 data points) were considered to contain sufficient data for dose-response analysis and the RR for each 1 mg/dL SUA level increment was calculated. A forest plot containing study-specific RRs and 95% CIs as well as the combined pooled estimates of the increase in MS risk for each 1 mg/dL SUA level increment are presented in Figure 1. The pooled RR (95% CI) was 1.30 (1.22–1.38; $P < .0001$). This increment was found to be equivalent to the results of the highest SUA level compared with the lowest.

Heterogeneity and publication bias

The results of the RRs across studies (Q statistic, 48.74; I^2 statistic, 71%; 95% CI, 52–83%; $P < .001$) suggested that sampling variation was not the only cause of the high between-study heterogeneity and of the variation in the results. Regarding funnel plot asymmetry, the Begg's test ($P = .009$) and the Egger's regression test ($P = .092$) suggested the possibility of publication bias (Supplemental Figure 4, A and C). The existing publication bias was adjusted using the trim-and-fill method (30). The result suggested that two hypothetical negative unpublished prospective studies led to the generation of an asymmetric funnel plot. To achieve symmetry, we incorporated these two hypothetical studies. Although the relationship between the SUA level and the MS risk seemed to be slightly weakened (RR, 1.28; 95% CI, 1.21–1.36), the statistical significance of this relationship remained ($P < .0001$) (Supplemental Figure 4D).

Sensitivity analyses

We performed a sensitivity analysis to assess the extent of the influence of omitting individual studies on the pooled RR. The results suggested that no individual study dramatically influenced the pooled RRs, and the resulting RRs ranged from 1.26 (95% CI, 1.19–1.33) to 1.31 (95% CI, 1.23–1.40) per 1 mg/dL increment in the SUA levels. Furthermore, analysis using a fixed-effects model resulted in essentially identical results (RR, 1.30; 95% CI, 1.22–1.38) (Supplemental Figure 4B).

Stratified analyses

Stratified analyses and meta-regression were used to assess the potential modifiers of heterogeneity (Table 2).

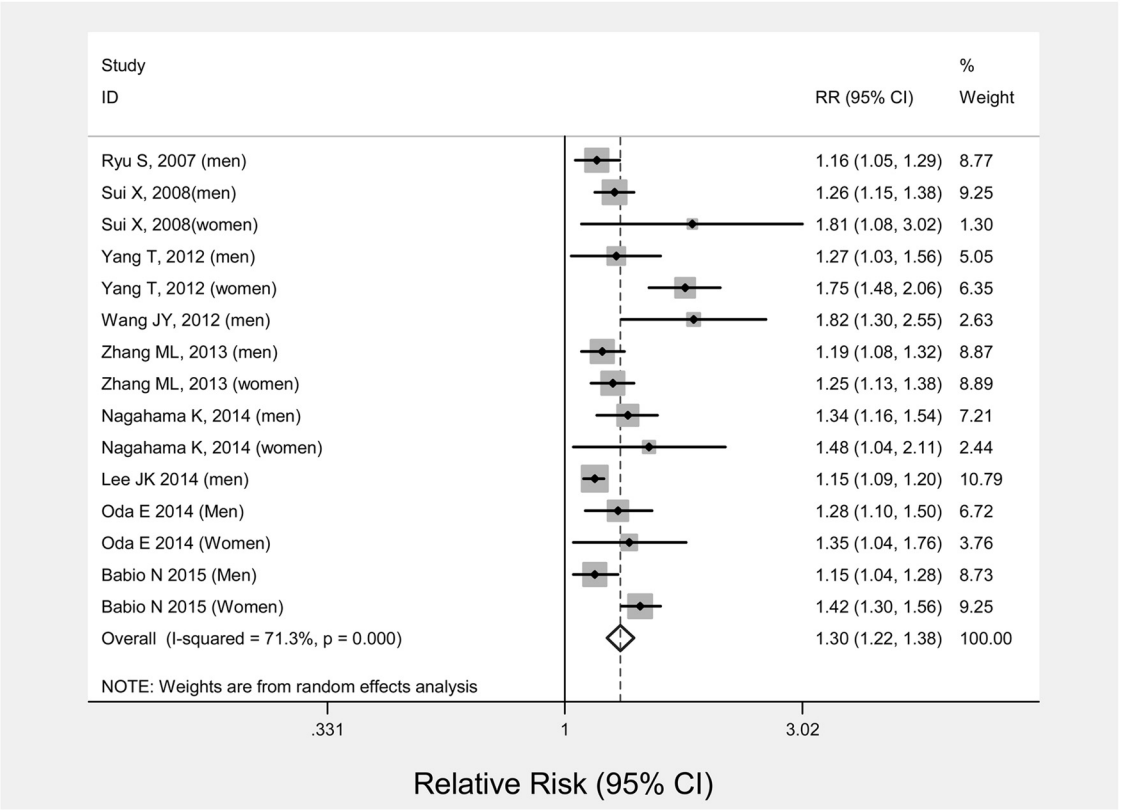

Figure 1. Overall RR with 95% CIs for the risk of MS for each 1 mg/dL increase in the SUA level. Fifteen data points are included from the nine studies. The area of each square stands for the weight of each study in the meta-analysis. The diamond shows the overall RR; the horizontal lines indicate the 95% CIs.

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Table 2. Stratified Meta-Analyses of the SUA Levels per 1 mg/dL Increment and the Risk of Metabolic Syndrome

Characteristic	Data points, No.	Pooled RR (95% CI)[c]	*P* Value for Heterogeneity	I^2 (95% CI), %	*P* Value for Meta-Regression[d]	Explanation of Heterogeneity, %
All studies	15[b]	1.30 (1.22–1.38)	<.001	71 (52–83)	<.0001	
Participant characteristics						
Country						
Asian	11	1.30 (1.20–1.40)	<.001	71 (47–84)	.969	−16.88
Non-Asian	4	1.30 (1.15–1.46)	.012	72 (22–90)		
Mean age, y						
<50	9	1.34 (1.21–1.49)	<.001	78 (58–88)	.45	−18.18
≥50	6	1.26 (1.17–1.36)	.049	55 (0–82)		
Sex						
Men	9	1.21 (1.16–1.28)	.078	43 (0–74)	.022	57.38
Women	6	1.44 (1.28–1.62)	.022	62 (7–84)		
Mean SUA level (mg/dL)						
≤5.5	8	1.35 (1.23–1.49)	.001	71 (41–86)	.243	10.5
>5.5	7	1.23 (1.15–1.31)	.058	51 (0–79)		
Study quality characteristics						
Adjustments						
Alcohol intake						
Yes	12	1.25 (1.18–1.31)	.008	57 (18–77)	.015	54.19
No	3	1.58 (1.25–1.99)	.041	69 (0–91)		
Smoking						
Yes	12	1.25 (1.18–1.31)	.008	57 (18–77)	.015	54.19
No	3	1.58 (1.25–1.99)	.041	69 (0–91)		
Physical activity						
Yes	8	1.23 (1.15–1.30)	.007	64 (22–83)	.031	31.08
No	7	1.45 (1.28–1.64)	.012	63 (17–84)		
Metabolic confounders[a]						
Sufficient	11	1.30 (1.22–1.39)	.013	55 (12–77)	.753	−12.99
Insufficient	4	1.29 (1.12–1.48)	<.001	87 (68–95)		
Study quality						
Score >7	8	1.26 (1.17–1.37)	.001	73 (45–87)	.402	−8.48
Score ≤7	7	1.34 (1.22–1.47)	.017	61 (11–83)		
Follow-up duration, y						
<5	10	1.28 (1.20–1.36)	.02	54 (7–78)	.651	−15.72
≥5.0	5	1.35 (1.16–1.57)	<.001	85 (67–93)		
Diagnostic criteria						
NCEP ATP III	5	1.24 (1.16–1.32)	.358	8 (0–81)		
Japanese	2	1.36 (1.19–1.55)	.609	0		
UCS	2	1.50 (1.10–2.05)	.018	82.2	.842	−16.52
IDF	4	1.22 (1.12–1.33)	.033	66 (0–88)		
HIDF+AHLB	2	1.28 (1.04–1.57)	.003	88.8		
Measure of association						
Risk ratio	1	1.16 (1.05–1.29)	NA	NA	.844	−15.13
Odds ratio	7	1.34 (1.22–1.47)	.017	61 (11–83)		
Hazard ratio	7	1.29 (1.17–1.41)	<.001	76 (50–89)		

Abbreviations: NA, not applicable; NCEP ATP III, National Cholesterol Education Program Adult Treatment Panel Guideline III; UCS, unified criteria set by several major organizations (International Diabetes Federation Task Force on Epidemiology and Prevention.

[a] Sufficient adjustment was defined as adjusting at lease three for more than three confounders (including body mass index, hypertension, fasting plasma glucose, HDL cholesterol, and triglycerides).

[b] Analysis based on nine studies and 15 data points, as men and women were included separately or different diagnostic criteria were used in the reported study.

[c] Pooled RRs of type 2 diabetes for each 1 mg/dL increase in the SUA level within the strata of each study characteristic are indicated.

[d] Represents the test for significance of the effect across strata.

Increased risk of MS with gradually elevated SUA level remained for all factors we proposed (ie, all RRs > 1). The positive association between the SUA levels and the MS risk was consistently found in both Asian (Korean, Japanese, and Chinese) and non-Asian (American and Spanish) populations. Adjustment for alcohol consumption, smoking, and physical activity, but not the metabolic factors, attenuated the relationship between the SUA level and the MS risk ($P = .015$, 0.015, and 0.031, respectively). In addition, sex ($P = .022$) altered this association, whereas the association did not substantially differ due to the effect of country, mean age, mean SUA level, study quality, measure of association, or the methodological quality measures mentioned above (follow-up duration and diagnostic criteria).

Linear dose-response analyses

Having confirmed this dose-response relationship, we assessed the potential nonlinearity of the relationship using a restricted cubic spline regression model. Although the random-effects model of nonlinearity was reasonable ($\chi^2 = 40.57$; $P < .001$) based on the assumption that a nonlinear relationship existed (Figure 2A), we further examined whether the dose-response relationship was nonlinear. Finally, we found that the

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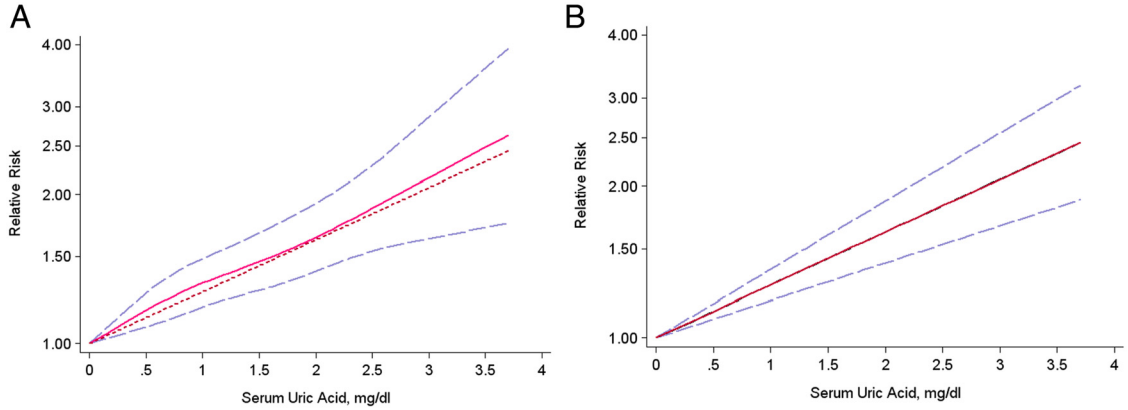

Figure 2. RR of MS for each SUA level increment according to a linear or nonlinear dose-response model. A, Nonlinear dose-response model based on restricted cubic splines for SUA concentrations at four points: the 5th, 35th, 65th, and 95th percentiles B, Linear dose-response model; *P* for the linear model <.001. The lines with long dashes stand for the point-wise 95% CIs for the fitted nonlinear trend (solid line). The lines with short dashes stand for the linear trend.

relationship between the SUA levels and the MS risk was linear ($\chi^2 = 0.84$; $P = .6555$). Therefore, a linear dose-response relationship was determined using random-effects analysis, and the results showed a significant positive linear relationship based on the restricted cubic spline regression model ($P < .001$ for linearity; Figure 2B). The overall RR per 1 mg/dL SUA level increment was 1.27 (95% CI,1.19–1.37) ($P < .001$). The model we used was reasonable ($\chi^2 = 44.33$; $P < .001$), and no significant heterogeneity between the identified studies was found ($Q = 36.68$; $P = .0619$).

Comparison with other risk factors for MS

Table 3 shows the comparison of other risk factors for MS based on published meta-analyses and systematic reviews (31–33). Interestingly, each 1 mg/dL SUA level increment had exactly the same effect as heavy smoking (≥ 20 cigarettes/d); this result verified the importance of SUA level increments. A higher level of leisure time physical activity (LTPA) and "responsible alcohol intake" (< 20 g/d for women and < 40 g/d for men) seemed to result in a reduced prevalence of MS.

Table 3. Comparison of Other Risk Factors of Metabolic Syndrome With SUA Level Increments

Risk Factor	RR (95% CI)	Effect on the RR for MS Relative to Each SUA Level Increment
High alcohol intake (31)		
Men		
0.1–39.9 g/d vs nondrinkers	0.75 (0.64–0.89)	−0.82
40–59.9 g/d vs nondrinkers	0.95 (0.83–1.09)	−0.15
≥ 60 g/d vs nondrinkers	0.99 (0.71–1.38)	−0.03
Women		
0–19.9 g/d vs nondrinkers	0.75 (0.64–0.89)	−0.82
20–39.9 g/d vs nondrinkers	0.81 (0.57–1.14)	−0.60
ND	ND	
Physical inactivity (LTPA) (33)		
All		
Moderate vs low	0.95 (0.91–1.00)	−0.15
High vs Low	0.80 (0.75–0.85)	−0.64
Men		
Moderate vs low	0.88 (0.81–0.97)	−0.36
High vs low	0.71 (0.63–0.80)	−0.98
Women		
Moderate vs low	0.99 (0.86–1.14)	−0.03
High vs low	0.68 (0.54–0.85)	−1.10
Active smoking (32)		
Men	1.34 (1.20–1.50)	0.83
Women	0.85 (0.60–1.21)	−0.46
Heavy smokers (≥20 cigarettes/d) vs nonsmokers	1.42 (1.27–1.59)	1.00
Light smokers (<20 cigarettes/d) vs nonsmokers	1.10 (0.90–1.35)	0.27
Former smoker vs nonsmokers in men	1.19 (1.00–1.42)	0.50

Abbreviation: ND, no data.

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SUA levels and the risk of NAFLD

The combined RR of incident NAFLD of the highest SUA level category compared with the lowest SUA level category was 1.46 (95% CI, 1.31–1.63; $P < .0001$) (Supplemental Figure 3B), which suggested a significantly positive association between the baseline SUA levels and the NAFLD risk. There was no obvious heterogeneity between the three studies ($I^2 = 25.1\%$; $P = .263$). Two studies (three points) included sufficient data for dose-response analysis and the result suggested that each 1 mg/dL SUA level increment resulted in 21% increase in the NAFLD risk (RR, 1.21; 95% CI, 1.03–1.41; $P = .021$).

Discussion

In this meta-analysis, we first summarized and quantified the relationship between the SUA level and the MS risk. Based on 11 prospective studies, 54 970 participants and 8719 MS cases displayed a pooled RR of 1.72 (95% CI, 1.45–2.03; $P < .0001$) of the highest SUA level category compared with the lowest SUA level category. Furthermore, dose-response analysis of nine studies, including 51 249 participants and 8265 MS cases, showed that 1 mg/dL increment in the SUA level led to a 30% increase in the risk of MS regardless of various study characteristics; our results were consistent with a linear dose-response relationship. In addition, 23 994 participants and 1022 NAFLD cases from three studies showed the combined RR of the NAFLD risk was 1.46 (95% CI, 1.31–1.63) of the highest SUA level category compared with the lowest SUA level category. Each 1 mg/dL SUA level increment led to 21% increase in the NAFLD risk (RR, 1.21; 95% CI, 1.03–1.41).The potential link between increased SUA levels and the MS risk has been mentioned by Carbone et al (6) based on a description of results for four longitudinal (16–19) and 12 cross-sectional studies. In this paper they just listed these 16 relative studies and described the results of these published studies. They also extracted all the RRs with 95% CIs but they did not analyze these data. Moreover, it is well known that only the prospective cohort instead of cross-sectional studies can determine the causality between the exposure factor (SUA) and the outcome (MS) and the extent of the correlation. Thus, Carbone et al's (6) work is not complete and even unconvincing. Our meta-analysis is the first study focused on high-quality prospective studies. Additional quantitative analyses have demonstrated that there is a significant positive linear dose-response association between the SUA level and the MS risk. Therefore, our meta-analysis had very important strengths compared with this review.

Pathological and epidemiological evidence has suggested that an elevated SUA level is related to lifestyle factors [in particular, drinking, physical activity, and smoking (34)] as well as several metabolic indices (high levels of blood pressure, body mass index, fasting plasma glucose, triglyceride, and low levels of HDL-C). Stratified and sensitivity analysis suggested a significant positive association even the analyses were limited to studies with sufficient adjustment for metabolic confounders or alcohol intake. A conclusion can be drawn regarding this analysis: the SUA level might independently predict the MS risk. Beside this, SUA levels taken as a significant factor in the prevalence and development of NAFLD.

Strengths and limitations

Our study had three noteworthy strengths. First, generalized least-squares trend estimation and variance-weighted least square regression model analyses allowed for the combination of comparable estimates and further clarified the dose-response association between the SUA levels and the MS risk. The consistency of the positive association between the SUA levels and the MS risk across the primary and secondary analyses, as well as our multiple stratified and sensitivity analyses, suggests that our conclusion did not depend on arbitrary decisions in our meta-analysis. Second, the results of the stratified and sensitivity analyses in our meta-analysis support that an elevated SUA level contributes to an increased MS risk. Third, this meta-analysis also determined a higher SUA level was a casual factor for an increase in risk of NAFLD, which was regarded as the hepatic manifestation of MS.

Our meta-analysis contained some limitations. First, residual confounding cannot be ruled out, although the adjusted RRs, the consistency of the results across various strata, and the sensitivity analysis results minimize this possibility. Second, publication bias is possible, and this factor affects the results of any meta-analysis. Based on the trim-and-fill adjustment method, the RR of MS for each 1 mg/dL SUA level increment was scaled downward by 0.02. Nevertheless, the relationship between the SUA level and the risk of MS remained statistically significant.

Heterogeneity in the study results

The results from the stratified meta-regression analysis are shown in Table 2. There was no significant influence on the study results due to participant characteristics, and the association tended to be stronger in women than in men. Regarding the study quality, the effect of adjustment for lifestyle factors (alcohol intake, smoking, and physical activity) was significant ($P = .015$, .015, and .031, respectively), which explained 54, 54, and 31% of the between-study heterogeneity, respectively.

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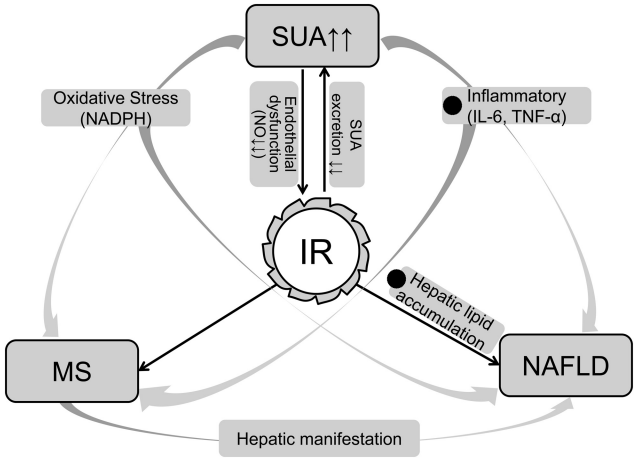

Figure 3. Mechanism of increased MS and NAFLD risk induced by elevated SUA level. The two black circle stands for the "two-hit" theory for causality between increased SUA level and higher NAFLD risk. ↑ ↑, increase; ↓ ↓, decrease.

Mechanisms

In humans, UA is generated at the end of purine metabolism via the activity of xanthine oxidase, which catalyzes the final two steps of UA conversion: from hypoxanthine to xanthine to UA (35). Currently, UA has been considered to perform multiple functions that affect cellular metabolism rather than being metabolically inert. Uric acid can act as a powerful scavenger of oxygen radicals (single oxygen peroxyl and hydroxyl radicals except for superoxide) to protect the erythrocyte membrane from lipid oxidation, can react with peroxynitrite to stabilize endothelial nitric oxide synthase activity, and can paradoxically function as a pro-oxidative and proinflammatory factor. This contradiction is due to its different functions inside cells (pro-oxidative effects mediated by a nicotinamide adenine dinucleotide phosphate [NADPH] oxidase-dependent pathway) compared with the soluble form in the extracellular milieu (antioxidant) (36).

The following mechanisms may explain SUA as a causal factor for both MS and NAFLD risk (Figure 3). Decreased renal UA excretion is the first such mechanism. The second mechanism is impaired endothelial function, which leads to decreased release of nitric oxide from endothelial cells (37). UA exacerbates IR by suppressing nitric oxide bioavailability. Conversely, hyperinsulinemia contributes to hyperuricemia by decreasing renal UA secretion and increasing the levels of UA-producing substrates (2). The third potential mechanism involves inflammation and the change in the oxidative status of adipocytes induced by UA, which results in MS (36). As for NAFLD, there was a two-hit theory that illustrated the mechanism regarding the causality between increased SUA and higher NAFLD risk. IR induced by elevated SUA led to hepatic lipid accumulation, which was the first hit in the development of NAFLD; and the second hit were NADPH oxidase system-dependent oxidative stress as well as the concurrent inflammatory process induced by IL-6 and TNF-α. Furthermore, NAFLD was a condition that not only related to MS closely but also served as hepatic manifestation, oxidative stress directly caused by SUA and inflammatory process might explain why high levels of SUA significantly increase NAFLD risk.

In addition, previous studies and our results have suggested that sex is a clearly important factor in the relationship between the SUA level and the MS risk. The difference in the SUA level resulting in hyperuricemia between men ($>$ 7.0 mg/dL) and women ($>$ 6.0 mg/dL) has been linked to the uricosuric effect of estrogens in women. However, the underlying mechanisms involved in the sex-specific association between the SUA concentration and the MS risk remain unclear and must be explored.

The strongest evidence supporting the contribution of SUA to MS/NAFLD has been reported by some studies based on animal models, which suggested that decreasing the SUA levels can prevent or reverse the development of MS (4, 38, 39) and NAFLD (40). However, there was only animal evidence that decreasing SUA levels benefited improvement of the features of MS and NAFLD, warranting well-designed intervention study in humans.

Conclusions

Our meta-analysis first summarized and quantified the dose-response association between the SUA level and the MS risk, indicating that elevated SUA level was a causal factor contributed to an increase risk of MS based on prospective studies of diverse populations. This association was confirmed to be a linear dose-response relationship. Each 1 mg/dL increase in the SUA level was associated with a 30% increase in the MS risk. At this point, pathologically and epidemiologically, MS risk has been demonstrated to be correlated with an elevated SUA concentration. More importantly, this dose-response relationship, the stability of this relationship among different populations, and the supportive findings of mechanistic studies suggest that SUA might be a useful predictor to facilitate its early prevention, diagnosis, and treatment in routine clinical practice. Regarding this point, high-quality evidence from randomized controlled trials is needed. Beyond that, we first summarized and showed the SUA level was a causal factor for the NAFLD risk which regarded as the hepatic manifestation of MS. Each 1 mg/dL SUA level increment led to 21% increase in the NAFLD risk.

Moreover, our findings have public health and lifestyle implications concerning the prevention of MS, such as

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reducing drinking, ceasing smoking, and increasing LTPA.

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