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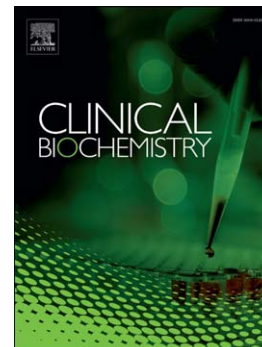
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PII: S0009-9120(15)00588-3
DOI: doi: [10.1016/j.clinbiochem.2015.12.010](https://doi.org/10.1016/j.clinbiochem.2015.12.010)
Reference: CLB 9201

To appear in: *Clinical Biochemistry*

Received date: 22 September 2015
Revised date: 25 December 2015
Accepted date: 26 December 2015



Please cite this article as: Zhou Yongjing, Wei Feifei, Fan Yu, High serum uric acid and risk of nonalcoholic fatty liver disease: a systematic review and meta-analysis, *Clinical Biochemistry* (2015), doi: [10.1016/j.clinbiochem.2015.12.010](https://doi.org/10.1016/j.clinbiochem.2015.12.010)

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High serum uric acid and risk of nonalcoholic fatty liver disease: a systematic review and meta-analysis

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Running title: Uric acid and risk of NAFLD

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Abstract

Objectives: Emerging evidence connects serum uric acid (SUA) levels to nonalcoholic fatty liver disease (NAFLD). The objective of this study was to systematically evaluate the association between SUA levels and risk of NAFLD by conducting a meta-analysis of available observational studies.

Design and methods: We searched for relevant studies in PubMed, Embase, China National Knowledge Infrastructure, and Wanfang databases until October 2014. All observational studies that evaluated SUA levels and NAFLD risks were included. Pooled adjusted odds ratio (OR) and corresponding 95% confidence intervals (CI) were calculated comparing the highest to lowest SUA category.

Results: Four cross-sectional studies, two prospective studies, and three retrospective studies involving 55,573 participants were identified. In overall risk estimates, the pooled OR of NAFLD occurrence was 1.92 (95% CI: 1.59–2.31) comparing the highest to lowest SUA levels in a random effect model. Subgroup analysis showed that high SUA levels increased the risk of NAFLD in cross-sectional studies (OR: 2.18; 95% CI: 1.58–3.03), retrospective studies (OR 1.82; 95% CI: 1.43–2.33), and prospective studies (OR 1.43; 95% CI: 1.20–1.71). The risk of NAFLD seemed more pronounced among women (OR 1.85; 95% CI: 1.43–2.38) than among men (OR 1.56; 95% CI: 1.30–1.86).

Conclusion: This meta-analysis suggests that increased SUA level is associated with an exacerbated risk of NAFLD. This increased risk is probably independent of conventional NAFLD risk factors.

Keywords: Serum uric acid; nonalcoholic fatty liver disease; meta-analysis.

Introduction

Non-alcoholic fatty liver disease (NAFLD) is one of the most common chronic liver diseases worldwide, affecting 20% to 30% of the general population [1] and up to 46% of the middle-aged group in Western countries [2]. The prevalence of ultrasonographic steatosis in Chinese populations is >30% [3]. NAFLD that includes simple steatosis and non-alcoholic steatohepatitis (NASH) that may lead to hepatocellular carcinoma [4] is identified as a hepatic manifestation of the metabolic syndrome linked to obesity [5, 6].

Uric acid is an end-product of purine metabolism in humans [7]. Increased serum uric acid (SUA) levels have been associated with metabolic syndrome [8-11], type 2 diabetes [12, 13], insulin resistance [14], and chronic kidney disease [15-17]. Numerous studies [18-27] have indicated that increased SUA levels were associated with the occurrence of NAFLD. Specially, elevated SUA levels even in a normal range also increased NAFLD risk [23]. However, whether SUA levels are an independent risk factor of NAFLD remains controversial.

To the best of our knowledge, no previous meta-analysis has specifically investigated the association between increased SUA levels and risk of NAFLD. This study aimed to evaluate the association between SUA levels and NAFLD risk in a general population by conducting a meta-analysis.

Methods

Data sources and searches

This meta-analysis was conducted with the checklist of the Meta-Analysis of Observational Studies in Epidemiology [28]. A comprehensive literature search was conducted on literature published through October 2014 using the PubMed, Embase, China National Knowledge Infrastructure, and Wanfang databases. The following search keywords were used: uric acid OR hyperuricemia OR urate and NAFLD/non-alcoholic fatty liver disease OR NASH/non-alcoholic steatohepatitis OR fatty liver OR liver enzymes and observational study OR prospective study OR retrospective study OR cross-sectional study OR case-control study. Moreover, we also manually searched the reference lists of selected articles to identify potential additional studies. Two authors

(Y Fan and FF Wei) independently judged the study eligibility with 100% agreement.

Study selection

Inclusion criteria were as follows: 1) observational studies that enrolled the general population with sample sizes more than 1,000; 2) data regarding SUA levels and NAFLD risk were provided; and 3) study provided adjusted hazard ratios (HR) or odds ratio (OR) with 95% confidence interval (CI) for NAFLD risk comparing the highest to lowest SUA levels. NAFLD was diagnosed on the basis of liver histology, radiology, and biochemistry [29]. Studies were excluded if 1) the study design was a review, editorial, abstract, or unpublished article; 2) studies enrolling less than 1,000 subjects; 3) fatty liver disease was caused by alcohol consumption (>30 g/day for males, >20 g/day for females), and 4) participants suffered from viral hepatitis, drug-induced, immunological, or hereditary liver diseases, and other serious diseases.

Data extraction and quality assessment

All data were extracted independently by two authors (YJ Zhou and FF Wei) using a standardized form. The following data were extracted: basic characteristics of each study (first author's surname, year of publication, design, and geographic regions), participant information (gender, mean age, or age range of participants), category of SUA level comparison, NAFLD definition, adjusted HR or OR with corresponding 95% CI, and adjustment for confounders. Discrepancies were resolved by a third author (YJ Zhou). The quality of the selected studies was assessed by two authors (YJ Zhou and FF Wei) using a 22-item Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) score [30].

Data synthesis and analysis

Data analyses used the most fully adjusted risk estimate. We pooled the risk estimate comparing the highest to lowest SUA category. Cochran Q chi-square statistic (significance level of $P < 0.10$) and I^2 statistic (significance level of $I^2 < 50\%$) were used to evaluate heterogeneity across studies. We selected a random effect model to pool the overall OR because of anticipated heterogeneity among studies. Begg's rank correlation test [31] and Egger's linear regression test (significance level of $P < 0.10$) [32] were conducted to assess the extent of potential publication bias. Finally, sensitivity analysis was performed by sequentially omitting one study in each cycle to evaluate result stability. Meta-analyses were conducted using STATA statistical software version 12.0 (STATA Corp. LP, College Station, TX, USA). A p -value < 0.05 was considered

statistically significant.

Results

Study characteristics

Using the search strategy and predefined inclusion criteria, nine studies [18-26] involving 55,573 participants were ultimately included in this meta-analysis. The detailed study selection process is presented in Figure 1. The characteristics of the included studies are listed in Table 1. Of the 9 articles, 4 were cross-sectional studies [23-26], 2 were prospective studies [20, 22], and 3 were retrospective studies [18, 19, 21]. The included studies were published between 2010 and 2013. The sample size of each study ranged from 1,440 to 10,732 subjects. In general, the overall quality of the included studies was moderate to good (range from 16 to 20) based on the on the STROBE score (supplemental Table S1).

Association of SUA levels with NAFLD

In the overall analysis of the 9 included studies, the pooled multivariate OR for NAFLD occurrence was 1.92 (95% CI: 1.59–2.31) comparing the highest to lowest SUA levels in a random effect model (Figure 2). A significant heterogeneity across studies was detected ($I^2 = 78.5\%$; $P < 0.001$). No evidence of publication bias was found based on the Begg's rank correlation test ($P = 0.125$) or Egger's linear regression test ($P = 0.225$). Subgroup analyses revealed that the pooled OR was 1.43 (95% CI: 1.20–1.71) in 2 prospective studies [20, 22], 1.82 (95% CI: 1.43–2.33) in 3 retrospective studies [18, 19, 21], and 2.18 (95% CI: 1.58–3.03) in 4 cross-sectional studies [23-26].

Gender difference in high SUA levels and NAFLD occurrence

Six studies [19, 21-24, 26] showed increased SUA levels and NAFLD occurrence based on gender (Figure 3). Of these 6 studies, 4 investigated both genders [19, 21, 23, 26] and 2 evaluated men only [22, 24]. Pooled gender-specific OR estimates of NAFLD occurrence in men and women were 1.56 (95% CI: 1.30–1.86) and 1.85 (95% CI: 1.43–2.38), respectively. Substantial heterogeneity was found in men ($I^2 = 51.35\%$; $P = 0.068$) but not in women ($I^2 = 33.3\%$; $P = 0.213$).

Sensitivity analyses

Sensitivity analyses results of our primary outcome showed minimal changes in magnitude

and direction of the pooled OR when any of the studies were omitted from the meta-analysis (Figure 4).

Discussion

This meta-analysis suggests that the highest SUA subjects have an approximately 2-fold higher risk of NAFLD as defined by ultrasonography. The risk may be independent of age, gender, and obesity (as estimated by BMI and waist circumference). Among subjects with increased SUA levels, women likely showed a greater risk of NAFLD than men.

The role of SUA as a potential risk factor of NAFLD has been investigated. To our knowledge, this is the first meta-analysis to investigate the association of SUA levels and NAFLD. Subgroup analysis revealed that the relationship between SUA levels and NAFLD occurrence was not affected by study design. The pooled OR from cross-sectional or retrospective studies was in close agreement with those from prospective studies. However, the risk appeared to be more pronounced in cross-sectional studies (OR = 2.18) than in prospective studies (OR = 1.42). Increased SUA levels likely exhibited a stronger impact on NAFLD in women. This trend is consistent with gender-specific data from the outcome of coronary heart disease in women [33]. These differences can be partly explained by different SUA levels between men and women, high prevalence of metabolic syndrome, and higher homeostasis model assessment of insulin resistance values found in women [34].

In line with these included studies, other studies did not satisfy the inclusion criteria also dealing with this issue. In a cross-sectional study [35] involving 8,925 participants, hyperuricemia defined by SUA level $> 420 \mu\text{mol/L}$ in men and SUA level $> 360 \mu\text{mol/L}$ in women was associated with an increased risk of NAFLD (OR=1.29; 95% CI=1.07–1.56). In a case-control study [36] with 60 consecutive patients, the highest SUA level (5.4 mg/dl to 8.9 mg/dl) is an independent predictor of NAFLD (risk ratio=9.14; 95% CI=3.48–24.0). These findings are in overall accordance with the results of our study.

The standard criteria of NAFLD diagnosis [29] include liver histology, radiology, and biochemistry; other competing causes of steatosis are excluded. Liver biopsy is considered as a standard of NAFLD diagnosis. In the original studies of our meta-analysis, all of the included studies only used ultrasound to identify NAFLD cases. Hyperuricemia defined as SUA

level > 7 mg/dl in men and SUA level > 6 mg/dl in women was independently associated with the histological severity of steatosis, lobular inflammation, and NAFLD activity score of 166 patients with NAFLD [37]. Another recent publication [38] showed that hyperuricemia was a common finding in patients with NAFLD and independently associated with early histological findings. These findings suggested that SUA level was not only associated with NAFLD occurrence but also closely correlated with the severity of NAFLD.

Several underlying mechanisms may help to explain the association between SUA levels and NAFLD risk. Metabolic disturbances might be a link between SUA levels and risk of NAFLD. Increased SUA levels lead to endothelial dysfunction [39], oxidative stress [40-42], insulin resistance [43], and inflammation [44, 45]. Inflammation is a potential link between NAFLD and insulin resistance [46, 47]. Insulin resistance decreases renal secretion of uric acid [48] and subsequent increases SUA levels. All these factors could contribute to the occurrence and development of NAFLD.

This meta-analysis has several potential limitations. First, most of the included studies applied a cross-sectional or retrospective design. Selection biases in these studies cannot be excluded. Second, liver biopsy is considered as the standard of NAFLD diagnosis. Despite these advantages, all of the original studies applied ultrasonographic examination to identify NAFLD cases; these studies were not sufficiently sensitive to detect mild steatosis. However, ultrasonography is the most widely used method to diagnose NAFLD because the overall sensitivity and specificity of this technique in detecting hepatic steatosis are acceptable [49]. Third, many of the included studies did not adjust for other potentially important confounders, such as BMI, glomerular filtration rate, and serum insulin that may affect SUA levels [50]. Lack of adjustment for these confounders may lead to overestimation of risk estimates. Fourth, a substantial degree of heterogeneity among cross-sectional studies ($I^2 = 86.0\%$) or overall studies ($I^2 = 78.5\%$) reduced the reliability of our results. The diversity in cut-off levels of SUA levels and a wide range of the subjects' age across studies partly contributed to the high heterogeneity of the pooled risk estimates. Finally, our study cannot answer the question of whether SUA level can be used as a marker of NAFLD; thus, future studies should be conducted to evaluate the predictive value of SUA in NAFLD.

In conclusion, this meta-analysis indicates that increased SUA levels are independently

associated with NAFLD occurrence regardless of gender, age, obesity, and metabolic syndrome. This risk seems more pronounced in women than in men. These findings suggest that pharmacological intervention of SUA disorder may reduce the occurrence of NAFLD and attenuate the severity and progression. However, further well-designed prospective studies should be conducted to clarify the cause–effect relationship between uric acid and NAFLD.

Author Contributions:

Yongjing Zhou and Feifei Wei extracted the data, performed statistical analysis, and drafted the manuscript. Yu Fan contributed to the conception and design, interpretation of data, and revised the manuscript.

Conflict of interest

Not declared.

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Figure legends

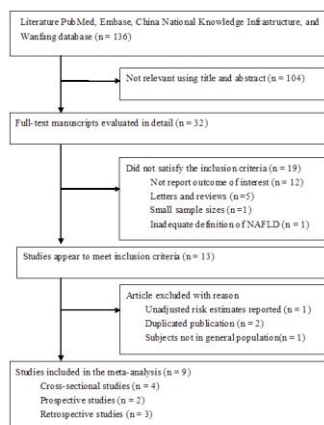
Figure 1 Flow diagram of studies identified and selected.

Figure 2 Odds ratio with 95% confidence interval of non-alcoholic fatty liver disease risk comparing the highest to the lowest serum uric acid category in a random effect model.

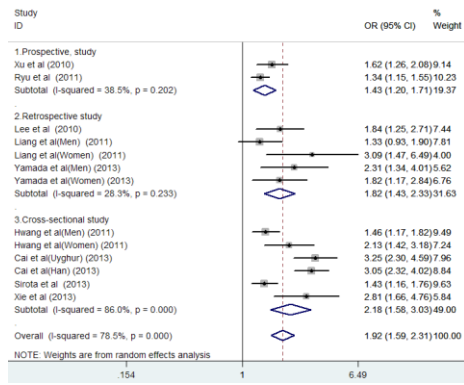
Figure 3 Gender-specific Odds ratio with 95% confidence interval of non-alcoholic fatty liver disease risk comparing the highest to the lowest serum uric acid category in a random effect model.

Figure 4 Odds ratio with 95% confidence interval of non-alcoholic fatty liver disease risk comparing the highest to the lowest serum uric acid levels by omitting each study from the included studies.

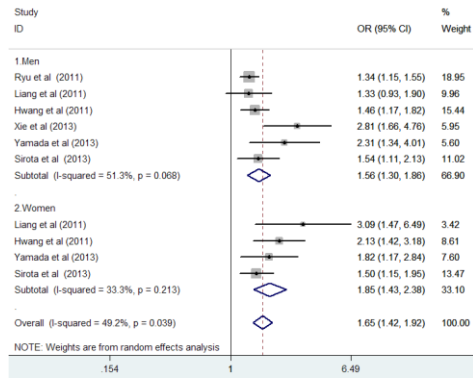
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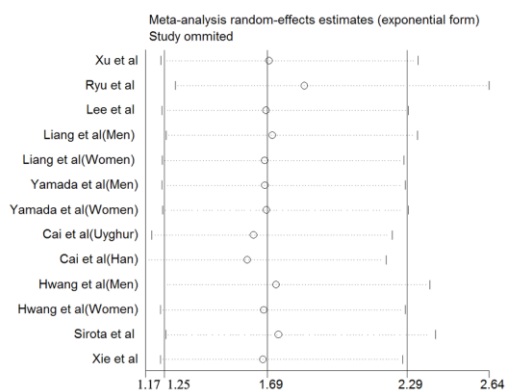


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Table 1 - Summary of basic character of the included studies

Study/year	Region	Design	Subjects (% women)	Age/range Mean (SD)	Comparison	NAFLD definition	Ever OR
Lee et al 2010 [18]	Korea	Retrospective study	4,954 (49.5)	40.0(5.9)	Highest quintile vs. lowest quintile ≥ 5.9 mg/dl vs. < 3.9 mg/dl.	NAFLD was diagnosed based on the findings of ultrasonography	Total 1.84
Yamada et al 2010 [19]	Japan	Retrospective study	4,118 (74.7)	51.4 \pm 11.2 M; 51.8 \pm 9.2 F	Highest quintile vs. lowest quintile ≥ 6.50 mg/dl vs. < 5.0 mg/dl in M and ≥ 4.9 mg/dl vs. ≤ 3.7 mg/dl in F	NAFLD was diagnosed by characteristic echo patterns	Total 2.31 1.82
Xu et al 2010 [20]	China	Population-based prospective study	6,890 (34.8)	44.4 (12.7)	Highest quintile vs. lowest quintile ≥ 410 μ mol/l vs. ≤ 295 μ mol/l in M and ≥ 299 μ mol/l vs. ≤ 205 μ mol/l in F	NAFLD was diagnosed by abdominal ultrasound following exclusion of alcohol consumption, viral, or autoimmune liver disease	Total 1.62
Liang et al 2011 [21]	China	Retrospective study	2,074 (30.2)	20-86	Highest quintile vs. lowest quintile ≥ 395 μ mol/l vs. ≤ 302.5 μ mol/l in M and ≥ 298.6 μ mol/l vs. ≤ 218.6 μ mol/l in F.	NAFLD was diagnosed by characteristic echo patterns	Total 1.33 3.09
Ryu et al 2011 [22]	Korea	Prospective, study	5,741 (0)	30-59	Highest quintile vs. lowest quintile ≥ 6.5 mg/dl vs. < 5.2 mg/dl.	NAFLD was diagnosed by characteristic echo patterns	Total 1.34
Hwang et al 2011 [23]	Korea	Cross-sectional study	9,019(48.6)	>20	Highest quintile vs. lowest quintile ≥ 6.4 mg/dl vs. ≤ 5.1 mg/dl in M and ≥ 4.6 mg/dl vs. ≤ 3.1 mg/dl in F	NAFLD was diagnosed by characteristic echo patterns	Total 1.46 2.13
Xie et al 2013[24]	China	Cross-sectional study	1,440 (0)	29-44	Highest quintile vs. lowest quintile $\geq 490.4 \pm 3.0$ μ mol/l vs. $< 288.3 \pm 1.8$ μ mol/l.	NAFLD was diagnosed by abdominal ultrasound without alcohol consumption, viral, or autoimmune liver disease	Total 2.81
Cai et al 2013 [25]	China	Cross-sectional study	4,157 (Uyghur); 6,448 (Han)	43.24 \pm 12.91 42.24 \pm 12.91	Highest quintile vs. lowest quintile ≥ 417 μ mol/l vs. ≤ 281.68 μ mol/l in M and ≥ 357 μ mol/l vs. ≤ 194 μ mol/l in F	NAFLD was diagnosed by characteristic echo patterns	Total 3.25 3.05
Sirota et al 2013 [26]	USA	Cross-sectional study	10,732 (52.7)	20-74	Highest vs. lowest > 6.9 mg/dl vs. ≤ 5.2 mg/dl in men and > 5.3 mg/dl vs. ≤ 3.7 mg/dl in women.	NAFLD presence were defined by ultrasonographic detection of steatosis in the absence of other liver diseases	Total 1.43 1.54 1.50

Abbreviations: M, male; F, female; BMI, body mass index; HR, hazard ratios; OR, odds ratio; SBP, systolic blood pressure; DBP, diastolic blood pressure; DM, diabetes mellitus; TC, total cholesterol; GGT, gamma-glutamyltransferase; LDL, low-density lipoprotein; HDL, high-density lipoprotein; MS, metabolic syndrome; CRP, C-Reactive protein; ALT, alanine aminotransferase; AST, aspartate aminotransferase; eGFR, estimated glomerular filtration rate; HOMA-IR: homeostasis model assessment of insulin resistance.

Highlight

Conflicting results have been reported on SUA levels and risk of NAFLD.

To evaluate high SUA levels and NAFLD risk by conducting a meta-analysis.

Elevated SUA levels are independently associated with NAFLD occurrence.

This risk seems more pronounced in women than in men.

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